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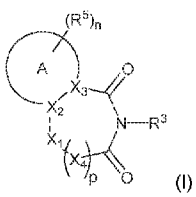
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(54) Title: COMPOUNDS AND COMPOSITIONS FOR THE TREATMENT OF CORONAVIRAL RELATED DISEASES



(I)

(57) Abstract: Provided herein are compounds of formula (I) and compositions for treating, managing or preventing coronaviral related diseases. In particular, provided herein are cyclic dione compounds which are inhibitors of SARS-CoV-2 main protease ($M^{Pro}$), pharmaceutical compositions comprising such compounds, method for synthesizing such compounds and methods of using such compounds and compositions for the treatment, management or prevention of coronaviral related diseases.

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# COMPOUNDS AND COMPOSITIONS FOR THE TREATMENT OF CORONAVIRAL RELATED DISEASES

## FIELD OF THE INVENTION

The present invention relates to compounds and compositions for the treatment, management and/or prevention of coronaviral related diseases. In particular, the present invention relates to compounds which are inhibitors of SARS-CoV-2 main protease ($M^{pro}$), to pharmaceutical compositions comprising such compounds, to methods for synthesizing such compounds and to methods of using such compounds and compositions for the treatment, management or prevention of coronaviral related diseases.

## BACKGROUND OF THE INVENTION

SARS-CoV-2 is a single positive-stranded RNA virus belonging to the genus Coronavirus β. The SARS-CoV-2 genome is about 30 kb in length, has untranslated regions (UTR) at both ends, and at least 6 complete open reading frame genes (ORF). Of these ORF's, ORF 1a/b directly encodes two polyproteins: polyprotein 1a (pp1a) and polyprotein 1ab (pp1ab). These polypeptides are cleaved by the main protease ($M^{pro}$), also known as 3C-like protease (3CLpro), and the papain-like protease (PLpro) into 16 non-structural proteins (nsps). These nsps play key roles in the production of subgenomic RNA, which encodes four major structural proteins, namely surface spike glycoprotein (S), envelope protein (E), membrane protein (M) and Nucleocapsid protein (N). Thus $M^{pro}$ plays a vital role in the replication cycle of SARS-CoV-2. Therefore, inhibiting the activity of $M^{pro}$ would block viral replication and may provide an effective therapeutic approach for the treatment of COVID-19, the disease caused by SARS-CoV-2, or for diseases caused by other beta-coronaviruses.

The identification of $M^{pro}$ inhibitors has been the subject of several reports. Most of these inhibitors are peptidomimetics, and typically come from previously studied protease inhibitors Dai, W. et al. (2020) Structure-based design of antiviral drug candidates targeting the SARS-CoV-2 main protease. Science, 368(6497), 1331–1335; Zhang, L., et al. (2020) Crystal structure of SARS-CoV-2 main protease provides a basis for design of improved a-ketoamide inhibitors. Science, 368(6489), 409–412; Ma, C. et al. (2020) Boceprevir, GC-376, and calpain inhibitors II, XII inhibit SARS-CoV-2 viral replication by targeting the viral main protease. Cell Research, 30(8), 678–692; Jin, Z. et al. (2020) Structure of Mpro from SARS-CoV-2 and discovery of its inhibitors. Nature, 582(7811), 289–293).

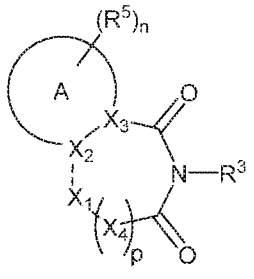
A peptidomimetic originally developed for SARS-CoV virus is currently in the clinic as an intravenous treatment for Covid-19 (Hoffman, R. L. et al. (2020). Discovery of Ketone-Based Covalent Inhibitors of Coronavirus 3CL Proteases for the Potential Therapeutic Treatment of COVID-19. Journal of Medicinal Chemistry, 63(21), 12725–12747).

A smaller number of publications describes non-peptidic small molecule inhibitors (Riva, L.

et al. (2020). Discovery of SARS-CoV-2 antiviral drugs through large-scale compound repurposing. Nature, 586(7827), 113–119; Ghahremanpour, M. M. et al. (2020). Identification of 14 Known Drugs as Inhibitors of the Main Protease of SARS-CoV-2. ACS Med Chem Lett, 11, 2526; Guenther, S. et al. (2021) X-ray screening identifies active site and allosteric inhibitors of SARS-CoV-2 main protease. Science. https://doi.org/10.1126/science.abf7945; Douangamath, A. et al. (2020). Crystallographic and electrophilic fragment screening of the SARS-CoV-2 main protease. Nature Communications, 11(1):5047, however there continues to be a need for effective treatments of diseases caused by beta-coronaviruses, especially COVID-19.

## SUMMARY OF THE INVENTION

In one aspect the invention therefore provides a compound of the Formula (I), or a pharmaceutically acceptable salt thereof,




(I)

wherein:

the dashed line between $X_1$ and $X_2$ is a single bond or a double bond;

$X_1$ is $NR^1$, N, $C(R^{2a})_2$, $CR^{2a}$, O, $C=C(R^{2a})_2$, $CR^{2a}R^{2b}$, a spiro attached 4 to 6 membered heterocycloalkyl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$, O, C(=O), S and $S(=O)_2$, or a spiro attached $C_3$-$C_8$cycloalkyl, and wherein the heterocycloalkyl and $C_3$-$C_8$cycloalkyl are unsubstituted or are substituted with 1 or 2 OH groups;

$X_2$ is N, C or CH;

$X_3$ is N, C or CH;

$X_4$ is $C(R^{2a})_2$ or $C=C(R^{2a})_2$;

$R^1$ is H, $C_1$-$C_6$alkyl, $C_3$-$C_8$cycloalkyl, 4 to 7 membered heterocycloalkyl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$, O and S, a $C_1$-$C_6$alkyl substituted with one or more $R^{12}$ or a $C_1$-$C_6$alkenyl substituted with one or more $R^{12}$, and wherein the cycloalkyl and heterocycloalkyl are unsubstituted or the cycloalkyl and heterocycloalkyl are substituted with 1 or 2 substituents independently selected from the group consisting of CN, -C(=O)OH, $NH_2$, OH, $C_1$-$C_6$haloalkyl, $C_1$-$C_6$alkyl or $C_1$-$C_6$alkyl substituted with -C(=O)OH, -OH, CN or $NH_2$;

each $R^{2a}$ is independently selected from the group consisting of H, CN, $NH_2$, $C_1$-$C_6$alkyl and $C_1$-$C_6$alkyl substituted with -C(=O)OH, -OH, CN or $NH_2$;

$R^{2b}$ is H, $C_1$-$C_6$alkyl, $C_3$-$C_8$cycloalkyl or 4 to 7 membered heterocycloalkyl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$, O and S, and wherein the $C_3$-$C_8$cycloalkyl and heterocycloalkyl are unsubstituted or the $C_3$-$C_8$cycloalkyl and heterocycloalkyl are substituted with 1, 2, 3 or 4 substituents independently selected from the group consisting of $C_1$-$C_6$alkyl, OH and $-N(R^7)_2$;

$R^3$ is selected from the group consisting of:

i) $-(CH_2)_{0-6}CHR^{13}R^{14}$;

ii) benzyl which is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

iii) a 6 membered heteroaryl with an attachment point at a carbon atom ring member and a N heteroatom as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 6 membered heteroaryl has 0, 1 or 2 additional N heteroatoms as ring members, and wherein the 6 membered heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

iv) a 10 membered bicyclic heteroaryl with an attachment point at a carbon atom ring member and a N heteroatom as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 10 membered bicyclic heteroaryl has 0, 1, 2 or 3 additional N heteroatoms as ring members, and wherein the 10 membered bicyclic heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

v) a 10 membered bicyclic heteroaryl with an attachment point at a carbon atom ring member and a N heteroatom as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 10 membered bicyclic heteroaryl further has 0, 1, 2, 3, or 4 ring members each independently selected from N, O and S, and wherein the 10 membered bicyclic heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

vi) a 9 membered bicyclic heteroaryl with an attachment point at a carbon atom ring member and a N heteroatom as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 9 membered bicyclic heteroaryl has 0, 1, 2, 3 or 4 additional N heteroatoms as ring members, and wherein the 9 membered bicyclic heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

vii) a 9 membered bicyclic heteroaryl with an attachment point at a carbon atom ring member and a N heteroatom as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 9 membered bicyclic heteroaryl further has 0, 1, 2, 3, or 4 ring members each independently selected from N, $NR^6$, O and S, and wherein the 9 membered bicyclic heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

viii) a 5 or 6 membered heterocycloalkyl with an attachment point at a carbon atom ring member and a $NR^6$ as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 5 or 6 membered heterocycloalkyl further has 0, 1, or 2 ring members each independently selected from N, $NR^6$, O and S, and wherein the 5 or 6 membered heterocycloalkyl is unsubstituted, substituted with 1 or 2 oxo, or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo;

ix) a 5 or 6 membered heterocyclyl with an attachment point at a carbon atom ring member and a $NR^6$ as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 5 or 6 membered heterocyclyl further has 0, 1, or 2 ring members each independently selected from N, $NR^6$, O and S, and wherein the 5 or 6 membered heterocyclyl is unsubstituted, substituted with 1 or 2 oxo, or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo;

x) a 9 or 10 membered bicyclic heterocyclyl with an attachment point at a carbon atom ring member and a $NR^6$ as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 9 or 10 membered heterocyclyl further has 0, 1, 2, 3, or 4 ring members each independently selected from N, $NR^6$, O and S, and wherein the 9 or 10 membered heterocyclyl is unsubstituted, substituted with 1 or 2 oxo, or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo;

xi) a 9 or 10 membered bicyclic heterocyclyl with an attachment point at a carbon atom ring member and a O heteroatom as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 9 or 10 membered heterocyclyl further has 0, 1, 2, 3, or 4 ring members each independently selected from N, $NR^6$, O and S, and wherein the 9 or 10 membered heterocyclyl is unsubstituted, substituted with 1 or 2 oxo, or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo;

xii) a 6 membered heteroaryl wherein 1, 2 or 3 ring members are each independently selected from N, O and S, and wherein the 6 membered heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

xiii) a 9 or 10 membered bicyclic heteroaryl wherein 1, 2, 3, 4 or 5 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 9 or 10 membered bicyclic heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

xiv) a 5 or 6 membered heterocycloalkyl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 5 or 6

membered heterocycloalkyl is unsubstituted, substituted with 1 or 2 oxo, or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo;

xv) a 5 or 6 membered heterocyclyl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 5 or 6 membered heterocyclyl is unsubstituted, substituted with 1 or 2 oxo, or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo;

xvi) a 6 membered heterocyclyl with an attachment point at a carbon atom ring member and a carbon atom as a ring member which is substituted with oxo and located at a beta (β) position relative to the attachment point, wherein the 6 membered heterocyclyl further has 1 or 2 ring members each independently selected from N, $NR^6$, O and S, and wherein the 6 membered heterocyclyl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with an oxo;

xvii) a 9 or 10 membered bicyclic heterocyclyl wherein 1, 2, 3, 4 or 5 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 9 or 10 membered bicyclic heterocyclyl is unsubstituted, substituted with 1 or 2 oxo, or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo;

and

xviii) a 10 membered bicyclic heterocyclyl with an attachment point at a carbon atom ring member and a carbon atom as a ring member which is substituted with oxo and located at a beta (β) position relative to the attachment point, wherein the 10 membered heterocyclyl further has 1, 2, 3, or 4 ring members each independently selected from N, $NR^6$, O and S, and wherein the 10 membered heterocyclyl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with an oxo;

Ring A is selected from the group consisting of:

i) phenyl;

ii) a 5 or 6 membered heteroaryl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S;

iii) $C_5$-$C_6$cycloalkenyl;

iv) 5 or 6 membered heterocyclyl wherein 1, 2 or 3 ring members are each independently selected from W, Y and Z, wherein W is $X_2$, $NR^6$, O, S, S=O or $S(=O)_2$, $X_2$ is N; Y is $NR^6$, O, S, S=O or $S(=O)_2$ and Z is $NR^6$, O or S, and wherein the 5 or 6 membered heterocyclyl is optionally substituted with oxo;

v) a 9 or 10 membered bicyclic heterocyclyl wherein 1, 2, 3, 4 or 5 ring members are each independently selected from N, $NR^6$, O and S;

vi) a 5 or 6 membered heterocycloalkyl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S and wherein the 5 or 6 membered heterocycloalkyl is optionally substituted with oxo;

and

vii) a 9 or 10 membered bicyclic heteroaryl wherein 1, 2, 3, 4 or 5 ring members are each independently selected from N, O and S;

each $R^4$ is independently selected from the group consisting of H, $-C(=O)N(R^7)_2$, $-C(=O)OH$, $-N(R^7)_2$, -CN, -OH, $-S(=O)_2R^6$, $-S(=O)_2N(R^7)_2$, $-C(=O)NR^7R^6$,  , $C_1$-$C_6$alkyl, halo, phenyl, $C_3$-$C_8$cycloalkyl, 4 to 6 membered heterocycloalkyl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S, 5 or 6 membered heteroaryl wherein 1, 2 or 3 ring members are each independently selected from N, O and S, and $C_1$-$C_6$alkyl substituted with $NH_2$, CN or OH, and wherein the phenyl, heterocycloalkyl and heteroaryl are unsubstituted or are substituted with 1 or 2 OH groups;

each $R^5$ is independently selected from the group consisting of -OH, $-NR^7R^8$, -NR6C(=O)C2-C6alkenyl, $-SF_5$, $-C(=O)N(R^7)_2$, $C_1$-$C_6$alkyl, $C_1$-$C_6$haloalkyl, halo, $C_1$-$C_6$haloalkoxy, $C_1$-$C_6$alkoxy, $C_3$-$C_8$cycloalkyl, 4 to 6 membered heterocycloalkyl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S, a 5 or 6 membered heteroaryl wherein 1, 2 or 3 ring members are each independently selected from N, O and S, and a $C_1$-$C_6$alkyl substituted with CN, $NH_2$ or OH, and wherein the cycloalkyl and heterocycloalkyl are unsubstituted or are substituted with 1, 2, 3 or 4 $R^9$;

each $R^6$ is independently selected from the group consisting of H, $C_1$-$C_6$alkyl, $-S(=O)_2N(R^7)_2$, $-C(=O)N(R^7)_2$ and $C_1$-$C_6$alkyl substituted with –OH, $-OR^7$, CN or –C(=O)OH;

each $R^7$ is independently selected from the group consisting of H and $C_1$-$C_6$alkyl;

$R^8$ is H, $C_1$-$C_6$alkyl, $C_3$-$C_8$cycloalkyl or 4 to 6 membered heterocycloalkyl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S, and wherein the cycloalkyl and heterocycloalkyl are unsubstituted or are substituted with 1, 2, 3 or 4 $R^9$;

each $R^9$ is independently selected from the group consisting of halo, $NR^{10}R^{11}$, $-C(=O)OH$, $-C(=O)N(R^7)_2$ and $C_1$-$C_6$alkyl substituted with -OH or $-N(R^7)_2$;

$R^{10}$ is H or $C_1$-$C_6$alkyl;

$R^{11}$ is H, $C_1$-$C_6$alkyl or $-S(=O)_2C_1$-$C_6$alkyl;

each $R^{12}$ is independently selected from the group consisting of CN, $NH_2$, -OH, $-C(=O)OH$, $-C(=O)OR^{10}$, $-C(=O)N(R^7)_2$, $-C_1$-$C_6$alkoxy, $C_1$-$C_6$alkyl, halo, $C_1$-$C_6$haloalkyl,

$C_3$-$C_8$cycloalkyl, a 5 or a 6 membered heteroaryl wherein 1, 2, 3, or 4 ring members are each independently selected from N, $NR^6$, O and S, and a 3 to 6 membered heterocycloalkyl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$, O and S, and wherein the cycloalkyl, heteroaryl and heterocycloalkyl are unsubstituted or are substituted with 1, 2 or 3 substituents independently selected from the group consisting of CN, -C(=O)OH, $NH_2$, OH, halo and $C_1$-$C_6$alkyl;

$R^{13}$ is H, -C(=O)N($R^7$)$_2$, or a 5 or 6 membered heteroaryl wherein 1, 2 3 or 4 ring members are each independently selected from N, $NR^6$, O and S;

$R^{14}$ is selected from the group consisting of

i) a 5 or 6 membered heterocyclyl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 5 or 6 membered heterocyclyl is unsubstituted, substituted with 1 or 2 oxo or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo;

and

ii) a 5 or a 6 membered heteroaryl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 5 or a 6 membered heteroaryl is unsubstituted, or is substituted with 1, 2, 3 or 4 $R^4$;

p is 0, 1 or 2, and

n is 0, 1, 2, 3 or 4.

Another aspect of the present invention is a pharmaceutical composition comprising a therapeutically effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers.

Another aspect of the present invention is a pharmaceutical composition comprising a compound of the invention, or a pharmaceutically acceptable salt, and one or more pharmaceutically acceptable carriers.

In another aspect, the invention provides a method\s for treating, preventing and/or managing a coronaviral-related disease or disorder, wherein the method comprises administering to a subject in need of such treatment, prevention or management a therapeutically or prophylactically effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof. In certain embodiments the coronaviral-related disease are COVID-19, other acute respiratory syndromes, non-respiratory coronavirus syndromes and post-infectious coronavirus syndromes.

In another aspect, the invention provides a method\s for treating, preventing and/or managing a coronaviral-related disease or disorder, wherein the method comprises administering to a subject in need of such treatment, prevention or management a compound of the invention, or a pharmaceutically acceptable salt thereof. In certain embodiments the coronaviral-related disease is COVID-19.

In another aspect, the invention provides use of a compound of of the invention, or a

pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment, prevention and/or management of a coronalviral-related disease or disorder.

In another aspect, the invention provides use of a compound of the invention, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment, prevention and/or management of COVID-19.

In another aspect, the invention provides the use of a compound of the invention, or a pharmaceutically acceptable salt thereof, in the treatment, prevention and/or management of a coronalviral-related disease or disorder.

In another aspect, the invention provides the use of a compound of the invention, or a pharmaceutically acceptable salt thereof, in the treatment, prevention and/or management of COVID-19.

In another aspect, the invention provides a compound of the invention, or a pharmaceutically acceptable salt thereof, for use in the treatment, prevention and/or management of a coronalviral-related disease or disorder.

In another aspect, the invention provides a compound of the invention, or a pharmaceutically acceptable salt thereof, for use in the treatment, prevention and/or management of COVID-19.

In another aspect, the invention provides kits comprising a compound of the invention for treating, preventing and/or managing a coronaviral-related disease.

In another aspect, the invention provides kits comprising a compound of the invention for treating, preventing and/or managing COVID-19.

In another aspect, the invention provides combinations for the treatment, prevention and/or management of a coronaviral related disease, wherein a compound of the invention is used in combination with one or more other active agents. In certain embodiments the active agent(s) is selected froma neutralizing antibody and an antiviral agent. In ceratin embodiments the active agent(s) is selected froma neutralizing antibody, an antiviral agent and other agents selected from alvelestat, Lenzilumab, Octagam, Remestemcel-L, RPH-104 + olokizumab, Bucillamine, CD24FC (MK-7110), Tradipitant, Ifenprodil, Tocilizumab, Leronlimab, Fenretinide, ATYR-1923, CYTO-205, APN-01, and Ampion. In certain embodiments, the neutralizing antibody is selected from Bamlanivimab, bamlanivimab + etesevimab, bamlanivimab + VIR-7831, REGN-COV2, VIR-7831, AZD7442, Regdanvimab/CT-P59, ABP-300, , COVI-AM/STI-2020, VIR-7832, SAB-185, JS016/etesevimab, C-135LS/C-144LS, BRII-196, BRII-198, SCTA-01, MW-33, DXP593, HFB-30132A, ADG20, COVI-GUARD (STI-1499) and convalescent plasma, and the antiviral agents is selected from remdesivir, Avigan/favipiravir, EIDD-2801/molnupiravir, AT-527, PF-00835231, PF-07321332, Ensovibep/DARPins, galidesivir, lopinavir-ritonavir, Virazole (ribavirin), levovir, elsulfavirine, thimerosal, UNI91103, silmitasertib/CX-4945, RBT-9, AT-301, Traneurocin/Neurosivir, Opaganib, ABX-464, SNG001, alisporivir, nafamostat mesylate, Vidofludimus/IMU-838, Emvododstat/PTC299, Brequinar, ATR-002, maraviroc.

In another aspect, the invention provides combinations for the treatment, prevention and/or management of a coronaviral related disease, wherein a compound of the invention is used in combination with remdesivir (also known as 2-ethylbutyl ((((2R,3S,4R,5R)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)-L-alaninate).

In another aspect, the invention provides combinations for the treatment, prevention and/or management of a coronaviral related disease, wherein a compound of the invention is used in combination with an antibody selected from ABBV 47D11, ABP-300, ADG20, Bamlanivimab + VIR-7831, Bamlanivimab+etesevimab, BRII196 + BRII198, C-135LS/C-144LS, Convalescent Plasma, COR-101, CT-P63, DXP593, Etesevimab (JS016), Evusheld/AZD-7442, HFB-30132A, IBIO123, IN-006, JMB2002, LY-CoV1404, Ly-CovMab, MAD0004J08, MW-33, REGEN-COV/Ronapreve, Regkirona/Regdanvimab, SAB-185, SCTA-01, STI-2099/COVIDROPS, TY027, VIR-7832 (GSK4182136), Xevudy/Sotrovimab and XVR011.

In another aspect, the invention provides combinations for the treatment, prevention and/or management of a coronaviral related disease, wherein a compound of the invention is used in combination with an antiviral agent selected from ABX-464, alisporivir, alvelestat, ANA-001, Apabetalone, Arakoda (Tafenoquine), ASC-09 + ritonavir, ASC11, AT-100, AT-301, AT-527 (Bemnifosubuvir), AT-H201, ATR-002, boceprivir, brequinar, Bucillamine, Camostat (DWJ1248), Camostat mesylate, Carrimycin, DC-402234 (FB2001), Ebeselen (SPI-1005), EDP-235, Elsulfavirine, Ensitrelvir/S-217622, Ensovibep, Favipiravir, FP-025, Galidesivir, Gamunex-C, Lagevrio/Molnupiravir, LAU-7b, Levovir, lopinavir-ritonavir, maraviroc, Masitinib, nafamostat mesylate, Narsoplimab, Neumifil, Neurosivir, Opaganib, Paxlovid/PF-07321332, PBI-0451, Pentarlandir, PF-07304814, PJS-539, Plitidepsin, Proxalutamide, PTC299 (emvododstat), RBT-9, RESP301, ribavirin, ritonavir, Silmitasertib, SLV213, SNG001, Thimerosal, Tollovir, Trabedersen (OT-101), Traneurocin, UNI91103, Upamostat, Veklury, Vidofludimus and Virazole (ribavirin).

In another aspect, the invention provides combinations for the treatment, prevention and/or management of a coronaviral related disease, wherein a compound of the invention is used in combination with Actemra/RoActemra, Ampion, APN-01 (alunacedase alfa), ATR-002, ATYR-1923, CYTO-205, Fenretinide (LAU-7b), Lenzilumab, Leronlimab, Octagam, Olumiant +/- Veklury , Remestemcel-L, RPH-104 + olokizumab, sarilumab , tocilizumab or Tradipitant.

## DETAILED DESCRIPTION

Definitions

The term “alkyl,” as used herein, refers to a fully saturated branched or straight hydrocarbon chain. In certain embodiments an alkyl group is a "$C_1$-$C_2$alkyl", "$C_1$-$C_3$alkyl", "$C_1$-$C_4$alkyl", "$C_1$-$C_5$alkyl", "$C_1$-$C_6$alkyl", "$C_1$-$C_7$alkyl", "$C_1$-$C_8$alkyl", "$C_1$-$C_9$alkyl" or "$C_1$-$C_{10}$alkyl", wherein the terms "$C_1$-$C_2$alkyl", "$C_1$-$C_3$alkyl", "$C_1$-$C_4$alkyl", "$C_1$-$C_5$alkyl", "$C_1$-$C_6$alkyl", "$C_1$-$C_7$alkyl", "$C_1$-$C_8$alkyl", "$C_1$-

$C_9$alkyl" and "$C_1$-$C_{10}$alkyl", as used herein, refer to an alkyl group containing at least 1, and at most 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms, respectively. Non-limiting examples of alkyl groups include methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, sec-butyl, *tert*-butyl, *n*-pentyl, isopentyl, neopentyl, *n*-hexyl, 3-methylhexyl, 2,2- dimethylpentyl, 2,3-dimethylpentyl, *n*-heptyl, *n*-octyl, *n*-nonyl and *n*-decyl.

The term “alkenyl,” as used herein, refers to a partially saturated branched or straight hydrocarbon chain having one more double bonds. In certain embodiments an alkenyl group is a "$C_2$-$C_3$alkenyl", "$C_2$-$C_4$alkenyl", "$C_2$-$C_5$alkenyl", "$C_2$-$C_6$alkenyl", "$C_2$-$C_7$alkenyl", "$C_2$-$C_8$alkenyl", "$C_2$-$C_9$alkenyl" or "$C_2$-$C_{10}$alkenyl", wherein the terms "$C_2$-$C_3$alkenyl", "$C_2$-$C_4$alkenyl", "$C_2$-$C_5$alkenyl", "$C_2$-$C_6$alkenyl", "$C_2$-$C_7$alkenyl", "$C_2$-$C_8$alkenyl", "$C_2$-$C_9$alkenyl" and "$C_2$-$C_{10}$alkenyl", as used herein, refer to an alkenyl group containing at least 2, and at most 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms, respectively. Non-limiting examples of alkenyl groups include ethenyl, *n*-propenyl, isopropenyl, *n*-butenyl, isobutenyl, sec-butenyl, *tert*-butenyl, *n*-pentenyl, isopentenyl, *n*-hexenyl, *n*-heptenyl, *n*-octenyl, *n*-nonenyl and *n*-decenyl.

The term "alkoxy", as used herein, refers to -O-alkyl or-alkyl-O-, wherein "alkyl" is as defined herein. In certain embodiments an alkoxy group is a "$C_1$-$C_2$alkoxy", "$C_1$-$C_3$alkoxy", "$C_1$-$C_4$alkoxy", "$C_1$-$C_5$alkoxy", "$C_1$-$C_6$alkoxy", "$C_1$-$C_7$alkoxy", "$C_1$-$C_8$alkoxy", "$C_1$-$C_9$alkoxy" or "$C_1$-$C_{10}$alkoxy", wherein the terms "$C_1$-$C_3$alkoxy", "$C_1$-$C_4$alkoxy", "$C_1$-$C_5$alkoxy", "$C_1$-$C_6$alkoxy", "$C_1$-$C_7$alkoxy", "$C_1$-$C_8$alkoxy", "$C_1$-$C_9$alkoxy" and "$C_1$-$C_{10}$alkoxy", as used herein refer to -O-$C_1$-$C_2$alkyl, -O-$C_1$-$C_3$alkyl, -O-$C_1$-$C_4$alkyl, -O-$C_1$-$C_5$alkyl, -O-$C_1$-$C_6$alkyl, -O-$C_1$-$C_7$alkyl, -O-$C_1$-$C_8$alkyl, -O-$C_1$-$C_9$alkyl or –O-$C_1$-$C_{10}$alkyl, respectively. Non-limiting examples of "alkoxy" groups include methoxy, ethoxy, *n*-propoxy, isopropoxy, *n*-butoxy, isobutoxy, sec-butoxy, *tert*-butoxy, *n*-pentoxy, isopentoxy, hexoxy, heptoxy, octoxy, nonoxy and decoxy.

The term “$C_3$-$C_8$cycloalkyl” as used herein, refers to a fully saturated, monocyclic hydrocarbon ring system having 3 to 8 carbon atoms as ring members. Non-limiting examples of such “$C_3$-$C_8$cycloalkyl” groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

The term "$C_5$-$C_6$cycloalkenyl" as used herein, refers to a partially saturated (but not aromatic), monocyclic hydrocarbon ring system having 5 to 6 carbon atoms as ring members. Non-limiting examples of "$C_5$-$C_6$cycloalkenyl", as used herein, include cyclopent-1-enyl, cyclopenta-1,3-dienyl, cyclohex-1-enyl and cyclohexa-1,3-dienyl.

The term "$C_1$-$C_6$alkyl-phenyl" as used herein, refer to a $C_1$-$C_6$alkyl as defined above which is substituted with a phenyl group. Non-limiting example of a $C_1$-$C_6$alkyl-phenyl is benzyl.

The term “haloalkyl” as used herein, refers to an alkyl group as defined herein, wherein at least one of the hydrogen atoms of the alkyl is replaced by a halo group (as defined herein). The haloalkyl can be monohaloalkyl, dihaloalkyl, trihaloalkyl, or polyhaloalkyl including perhaloalkyl. A monohaloalkyl can have one iodo, bromo, chloro or fluoro within the alkyl group. Dihaloalkyl and polyhaloalkyl groups can have two or more of the same halo atoms or a combination of

different halo groups within the alkyl. Typically the polyhaloalkyl contains up to 6, or 4, or 3, or 2 halo groups. Non-limiting examples of haloalkyl include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl. A perhalo-alkyl refers to an alkyl having all hydrogen atoms replaced with halo atoms, e.g., trifluoromethyl. Preferred haloalkyl groups, unless specified otherwise, include monofluoro-, difluoro- and trifluoro- substituted methyl and ethyl groups, e.g. $CF_3$, $CHF_2$, $CH_2F$, $CH_2CHF_2$ and $CH_2CF_3$.

The term "$C_1$-$C_6$haloalkyl" as used herein, refers to the respective "$C_1$-$C_6$alkyl", as defined herein, wherein at least one of the hydrogen atoms of the "$C_1$-$C_6$alkyl" is replaced by a halo group (as defined herein). The $C_1$-$C_6$haloalkyl groups can be mono$C_1$-$C_6$haloalkyl, wherein such $C_1$-$C_6$haloalkyl groups have one iodo, one bromo, one chloro or one fluoro. Additionally, the $C_1$-$C_6$haloalkyl groups can be di$C_1$-$C_6$haloalkyl wherein such $C_1$-$C_6$haloalkyl groups can have two halo atoms independently selected from iodo, bromo, chloro or fluoro. Furthermore, the $C_1$-$C_6$haloalkyl groups can be poly$C_1$-$C_6$haloalkyl wherein such $C_1$-$C_6$haloalkyl groups can have two or more of the same halo atoms or a combination of two or more different halo atoms. Such poly$C_1$-$C_6$haloalkyl can be perhalo$C_1$-$C_6$haloalkyl where all the hydrogen atoms of the respective $C_1$-$C_6$alkyl have been replaced with halo atoms and the halo atoms can be the same or a combination of different halo atoms. Non-limiting examples of "$C_1$-$C_6$haloalkyl" groups include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, fluoroethyl, difluoroethyl, trifluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl.

The term “haloalkoxy” as used herein, refers to the group –O-haloalkyl wherein the term "haloalkyl" is as defined herein. Non-limiting examples of haloalkoxy include fluoromethoxy, difluoromethoxy, trifluoromethoxy, chloromethoxy, dichloromethoxy, trichloromethoxy, pentafluoroethoxy, heptafluoropropoxy, difluorochloromethoxy, dichlorofluoromethoxy, difluoroethoxy, difluoropropoxy, dichloroethoxy and dichloropropoxy. A perhalo-alkoxy refers to an alkoxy having all hydrogen atoms replaced with halo atoms, e.g., trifluoromethoxy. Preferred haloalkoxy groups, unless specified otherwise, include monofluoro-, difluoro- and trifluoro- substituted methoxy and ethoxygroups, e.g. $-OCF_3$, $-OCHF_2$, $-OCH_2F$, $-OCH_2CHF_2$ and $-OCH_2CF_3$.

The term "$C_1$-$C_6$haloalkoxy" as used herein, refers to the group –O-$C_1$-$C_6$haloalkyl, wherein the term $C_1$-$C_6$haloalkyl is as defined herein. Non-limiting examples of "$C_1$-$C_6$haloalkoxy" groups include fluoromethoxy, difluoromethoxy, trifluoromethoxy, chloromethoxy, dichloromethoxy, trichloromethoxy, pentafluoroethoxy, heptafluoropropoxy, difluorochloromethoxy, dichlorofluoromethoxy, fluoroethoxy, difluoroethoxy, trifluoroethoxy, difluoropropoxy, dichloroethoxy and dichloropropoxy.

The terms "halogen” or “halo” as used herein, refer to fluoro (F), chloro (Cl), bromo (Br) and

iodo (I).

The term “heteroatoms”, as used herein, refers to nitrogen (N), oxygen (O) or sulfur (S) atoms.

The term “heteroaryl,” as used herein, refers to an aromatic ring system containing one or more heteroatoms which may be the same or different. The term “heteroaryl,” as used herein, also refers to an aromatic ring system having one or more ring members which are each independently selected from N, $NR^6$, O and S, where $R^6$ is as defined herein. Heteroaryl groups may be monocyclic ring systems or fused bicyclic ring systems. Monocyclic heteroaryl rings have from 5 to 6 ring atoms. Bicyclic heteroaryl rings have from 7 to 12 ring member atoms. Bicyclic heteroaryl rings include those ring systems wherein a heteroaryl ring is fused to a phenyl ring. Non-limiting examples of heteroaryl groups, as used herein, include benzofuranyl, benzo[c]thiophenyl, benzothiophenyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, cinnolinyl, furazanyl, furyl, imidazolyl, indolyl, indolizinyl, indazolyl, isoindolyl, isoquinolinyl, isoxazolyl, isothiazolyl, oxazolyl, oxaindolyl, oxadiazolyl (including 1,3,4-oxadiazolyl and 1,2,4-oxadiazolyl), purinyl, pyrazolyl, pyrrolyl, phthalazinyl, pyridyl (including 2-, 3-, and 4-pyridyl), pyridazinyl, pyrazinyl, pyrimidinyl, quinoxalinyl, quinolinyl, quinazolinyl, tetrazinyl, tetrazolyl, tetrazolo[1,5-a]pyridinyl, thiazolyl, thiadiazolyl (including 1,3,4-thiadiazolyl), thienyl, triazinyl, and triazolyl.

The term "5 or 6 membered heteroaryl", as used herein, refers to an aromatic, 5 or 6 membered monocyclic ring system wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S, where $R^6$ is as defined herein. Non-limiting examples of such 5 or 6 membered heteroaryl groups, as used herein, include furyl, imidazolyl, isoxazolyl, isothiazolyl, oxazolyl, pyrrolyl, pyrazolyl, thiadiazolyl, thiazolyl, thienyl, triazolyl, tetrazolyl, pyridyl (including 2-, 3-, and 4-pyridyl), pyridazinyl, pyrazinyl and pyrimidinyl. In certain embodiments, the term "5 or 6 membered heteroaryl", as used herein, also refers to an aromatic, 5 or 6 membered monocyclic ring system wherein 1, 2, or 3 ring members are each independently selected from N, $NR^6$, O and S, where $R^6$ is as defined herein. Non-limiting examples of such 5 or 6 membered heteroaryl groups, as used herein, include furyl, imidazolyl, isoxazolyl, isothiazolyl, oxazolyl, pyrrolyl, pyrazolyl, thiadiazolyl, thiazolyl, thienyl, triazolyl, pyridyl (including 2-, 3-, and 4-pyridyl), pyridazinyl, pyrazinyl and pyrimidinyl.

The term "6 membered heteroaryl", as used herein, refers to an aromatic, 6 membered monocyclic ring system wherein 1, 2 or 3 ring members are each independently selected from N, O and S. Non-limiting examples of such 6 membered heteroaryl groups, as used herein, include pyridyl (including 2-, 3-, and 4-pyridyl), pyridazinyl, pyrazinyl and pyrimidinyl.

The term "5 membered heteroaryl", as used herein, refers to an aromatic, 5 membered monocyclic ring system wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S, where $R^6$ is as defined herein. Non-limiting examples of such 5 membered heteroaryl groups, as used herein, include furyl, imidazolyl, isoxazolyl, isothiazolyl, oxazolyl, pyrrolyl, pyrazolyl, thiadiazolyl, thiazolyl, thienyl, triazolyl and tetrazolyl. In certain embodiments,

the term "5 membered heteroaryl", as used herein, also refers to an aromatic, 5 membered monocyclic ring system wherein 1, 2, or 3 ring members are each independently selected from N, $NR^6$, O and S, where $R^6$ is as defined herein. Non-limiting examples of such 5 membered heteroaryl groups, as used herein, include furyl, imidazolyl, isoxazolyl, isothiazolyl, oxazolyl, pyrrolyl, pyrazolyl, thiadiazolyl, thiazolyl, thienyl and triazolyl.

The term "9 or 10 membered bicyclic heteroaryl", as used herein, refers to a 9 or 10 membered fused, bicyclic aromatic ring system wherein 1, 2, 3, 4 or 5 ring members are each independently selected from N, $NR^6$, O and S, where $R^6$ is as defined herein. Non-limiting examples of such bicyclic heteroaryl groups, as used herein, include indolyl, quinolinyl, isoquinolinyl, indazolyl, purinyl, phthalazinyl, naphthyridinyl, quinazolinyl, cinnolinyl, thieno[2,3-*b*]furanyl, 1*H*-pyrazolo[4,3-*d*]-oxazolyl, imidazo[2,1-*b*] thiazolyl, imidazo[1,2-c]pyrimidinyl, imidazo[1,2-a]pyrazinyl, imidazo[1,2-a]pyridinyl, pyrazolo[1,5-a]pyrazinyl, pyrazino[2,3-*d*]pyridazinyl, imidazo[1,2-*b*][1,2,4]triazinyl, benzoxazolyl, benzimidazolyl, imidazopyridinyl, benzo[c]isoxazolyl and benzothiazolyl.

The term "4 to 7 membered heterocycloalkyl" as used herein, refers to a 4 to 7 membered, saturated hydrocarbon ring wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O or S, where $R^6$ is as defined herein. The heterocycloalkyl group can be attached to another group at a nitrogen or a carbon atom. Non-limiting examples of 4 to 6 membered heterocycloalkyl groups, as used herein, include azetadinyl (which includes azetadin-1-yl, azetadin-2-yl and azetadin-3-yl), oxetanyl (which includes oxetan-2-yl, oxetan-3-yl and oxetan-4-yl), thietanyl (which includes thietan-2-yl, thietan-3-yl and thietan-4-yl), pyrrolidinyl (which includes pyrrolidin-1-yl, pyrrolidin-2-yl, pyrrolidin-3-yl, pyrrolidin-4-yl and pyrrolidin-5-yl), tetrahydrofuranyl (which includes tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrofuran-4-yl and tetrahydrofuran-5-yl), tetrahydrothienyl (which includes tetrahydrothien-2-yl, tetrahydrothien-3-yl, tetrahydrothien-4-yl and tetrahydrothien-5-yl), piperidinyl (which includes piperidin-1-yl, piperidin-2-yl, piperidin-3-yl, piperidin-4-yl, piperidin-5-yl and piperidin-6-yl), tetrahydropyranyl (which includes tetrahydropyran-2-yl, tetrahydropyran-3-yl, tetrahydropyran-4-yl, tetrahydropyran-5-yl and tetrahydropyran-6-yl), tetrahydrothiopyranyl (which includes tetrahydrothiopyran-2-yl, tetrahydrothiopyran-3-yl, tetrahydrothiopyran-4-yl, tetrahydrothiopyran-5-yl and tetrahydrothiopyran-6-yl), piperazinyl (which includes piperazin-1-yl, piperazin-2-yl, piperazin-3-yl, piperazin-4-yl, piperazin-5-yl and piperazin-6-yl), morpholinyl (which includes morpholin-2-yl, morpholin-3-yl, morpholin-4-yl, morpholin-5-yl and morpholin-6-yl), thiomorpholinyl (which includes thiomorpholin-2-yl, thiomorpholin-3-yl, thiomorpholin-4-yl, thiomorpholin-5-yl and thiomorpholin-6-yl), oxathianyl (which includes oxathian-2-yl, oxathian-3-yl, oxathian-5-yl and oxathian-6-yl), dithianyl (which includes dithian-2-yl, dithian-3-yl, dithian-5-yl and dithian-6-yl), dioxolanyl (which includes dioxolan-2-yl, dioxolan-4-yl and dioxolan-5-yl), thioxanyl (which includes thioxan-2-yl, thioxan-3-yl, thioxan-4-yl and thioxan-5-yl), dithiolanyl (which includes dithiolan-2-yl, dithiolan-4-yl and dithiolan-5-yl), and pyrazolidinyl (which includes

pyrazolidin-1-yl, pyrazolidin-2-yl, pyrazolidin-3-yl, pyrazolidin-4-yl and pyrazolidin-5-yl), azepanyl, diazepanyl, triazepanyl, ozazepanyl, oxadiazepanyl, oxepanyl, thiepanyl, thiazepanyl and thiadiazepanyl.

The term "3 to 6 membered heterocycloalkyl" as used herein, refers to a 3 to 6 membered, saturated hydrocarbon ring wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$, O or S, where $R^6$ is as defined herein. The heterocycloalkyl group can be attached to another group at a nitrogen or a carbon atom. Non-limiting examples of 3 to 6 membered heterocycloalkyl groups, as used herein, include oxiranyl, aziridinyl, thiiranyl, azetadinyl (which includes azetadin-1-yl, azetadin-2-yl and azetadin-3-yl), oxetanyl (which includes oxetan-2-yl, oxetan-3-yl and oxetan-4-yl), thietanyl (which includes thietan-2-yl, thietan-3-yl and thietan-4-yl), pyrrolidinyl (which includes pyrrolidin-1-yl, pyrrolidin-2-yl, pyrrolidin-3-yl, pyrrolidin-4-yl and pyrrolidin-5-yl), tetrahydrofuranyl (which includes tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrofuran-4-yl and tetrahydrofuran-5-yl), tetrahydrothienyl (which includes tetrahydrothien-2-yl, tetrahydrothien-3-yl, tetrahydrothien-4-yl and tetrahydrothien-5-yl), piperidinyl (which includes piperidin-1-yl, piperidin-2-yl, piperidin-3-yl, piperidin-4-yl, piperidin-5-yl and piperidin-6-yl), tetrahydropyranyl (which includes tetrahydropyran-2-yl, tetrahydropyran-3-yl, tetrahydropyran-4-yl, tetrahydropyran-5-yl and tetrahydropyran-6-yl), tetrahydrothiopyranyl (which includes tetrahydrothiopyran-2-yl, tetrahydrothiopyran-3-yl, tetrahydrothiopyran-4-yl, tetrahydrothiopyran-5-yl and tetrahydrothiopyran-6-yl), piperazinyl (which includes piperazin-1-yl, piperazin-2-yl, piperazin-3-yl, piperazin-4-yl, piperazin-5-yl and piperazin-6-yl), morpholinyl (which includes morpholin-2-yl, morpholin-3-yl, morpholin-4-yl, morpholin-5-yl and morpholin-6-yl), thiomorpholinyl (which includes thiomorpholin-2-yl, thiomorpholin-3-yl, thiomorpholin-4-yl, thiomorpholin-5-yl and thiomorpholin-6-yl), oxathianyl (which includes oxathian-2-yl, oxathian-3-yl, oxathian-5-yl and oxathian-6-yl), dithianyl (which includes dithian-2-yl, dithian-3-yl, dithian-5-yl and dithian-6-yl), dioxolanyl (which includes dioxolan-2-yl, dioxolan-4-yl and dioxolan-5-yl), thioxanyl (which includes thioxan-2-yl, thioxan-3-yl, thioxan-4-yl and thioxan-5-yl), dithiolanyl (which includes dithiolan-2-yl, dithiolan-4-yl and dithiolan-5-yl), pyrazolidinyl (which includes pyrazolidin-1-yl, pyrazolidin-2-yl, pyrazolidin-3-yl, pyrazolidin-4-yl and pyrazolidin-5-yl), hexahydropyridazinyl and hexahydropyrimidinyl.

The term "4 to 6 membered heterocycloalkyl" as used herein, refers to a 4 to 6 membered, saturated hydrocarbon ring wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O or S, where $R^6$ is as defined herein. The heterocycloalkyl group can be attached to another group at a nitrogen or a carbon atom. Non-limiting examples of 4 to 6 membered heterocycloalkyl groups, as used herein, include azetadinyl (which includes azetadin-1-yl, azetadin-2-yl and azetadin-3-yl), oxetanyl (which includes oxetan-2-yl, oxetan-3-yl and oxetan-4-yl), thietanyl (which includes thietan-2-yl, thietan-3-yl and thietan-4-yl), pyrrolidinyl (which includes pyrrolidin-1-yl, pyrrolidin-2-yl, pyrrolidin-3-yl, pyrrolidin-4-yl and pyrrolidin-5-yl), tetrahydrofuranyl (which includes tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrofuran-4-yl

and tetrahydrofuran-5-yl), tetrahydrothienyl (which includes tetrahydrothien-2-yl, tetrahydrothien-3-yl, tetrahydrothien-4-yl and tetrahydrothien-5-yl), piperidinyl (which includes piperidin-1-yl, piperidin-2-yl, piperidin-3-yl, piperidin-4-yl, piperidin-5-yl and piperidin-6-yl), tetrahydropyranyl (which includes tetrahydropyran-2-yl, tetrahydropyran-3-yl, tetrahydropyran-4-yl, tetrahydropyran-5-yl and tetrahydropyran-6-yl), tetrahydrothiopyranyl (which includes tetrahydrothiopyran-2-yl, tetrahydrothiopyran-3-yl, tetrahydrothiopyran-4-yl, tetrahydrothiopyran-5-yl and tetrahydrothiopyran-6-yl), piperazinyl (which includes piperazin-1-yl, piperazin-2-yl, piperazin-3-yl, piperazin-4-yl, piperazin-5-yl and piperazin-6-yl), morpholinyl (which includes morpholin-2-yl, morpholin-3-yl, morpholin-4-yl, morpholin-5-yl and morpholin-6-yl), thiomorpholinyl (which includes thiomorpholin-2-yl, thiomorpholin-3-yl, thiomorpholin-4-yl, thiomorpholin-5-yl and thiomorpholin-6-yl), oxathianyl (which includes oxathian-2-yl, oxathian-3-yl, oxathian-5-yl and oxathian-6-yl), dithianyl (which includes dithian-2-yl, dithian-3-yl, dithian-5-yl and dithian-6-yl), dioxolanyl (which includes dioxolan-2-yl, dioxolan-4-yl and dioxolan-5-yl), thioxanyl (which includes thioxan-2-yl, thioxan-3-yl, thioxan-4-yl and thioxan-5-yl), dithiolanyl (which includes dithiolan-2-yl, dithiolan-4-yl and dithiolan-5-yl), pyrazolidinyl (which includes pyrazolidin-1-yl, pyrazolidin-2-yl, pyrazolidin-3-yl, pyrazolidin-4-yl and pyrazolidin-5-yl), hexahydropyridazinyl and hexahydropyrimidinyl.

The term "5 or 6 membered heterocycloalkyl" as used herein, refers to a 5 or 6 membered, saturated hydrocarbon ring wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O or S, where $R^6$ is as defined herein. The heterocycloalkyl group can be attached to another group at a nitrogen or a carbon atom. Non-limiting examples of 5 or 6 membered heterocycloalkyl groups, as used herein, include pyrrolidinyl (which includes pyrrolidin-1-yl, pyrrolidin-2-yl, pyrrolidin-3-yl, pyrrolidin-4-yl and pyrrolidin-5-yl), tetrahydrofuranyl (which includes tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrofuran-4-yl and tetrahydrofuran-5-yl), tetrahydrothienyl (which includes tetrahydrothien-2-yl, tetrahydrothien-3-yl, tetrahydrothien-4-yl and tetrahydrothien-5-yl), piperidinyl (which includes piperidin-1-yl, piperidin-2-yl, piperidin-3-yl, piperidin-4-yl, piperidin-5-yl and piperidin-6-yl), tetrahydropyranyl (which includes tetrahydropyran-2-yl, tetrahydropyran-3-yl, tetrahydropyran-4-yl, tetrahydropyran-5-yl and tetrahydropyran-6-yl), tetrahydrothiopyranyl (which includes tetrahydrothiopyran-2-yl, tetrahydrothiopyran-3-yl, tetrahydrothiopyran-4-yl, tetrahydrothiopyran-5-yl and tetrahydrothiopyran-6-yl), piperazinyl (which includes piperazin-1-yl, piperazin-2-yl, piperazin-3-yl, piperazin-4-yl, piperazin-5-yl and piperazin-6-yl), morpholinyl (which includes morpholin-2-yl, morpholin-3-yl, morpholin-4-yl, morpholin-5-yl and morpholin-6-yl), thiomorpholinyl (which includes thiomorpholin-2-yl, thiomorpholin-3-yl, thiomorpholin-4-yl, thiomorpholin-5-yl and thiomorpholin-6-yl), oxathianyl (which includes oxathian-2-yl, oxathian-3-yl, oxathian-5-yl and oxathian-6-yl), dithianyl (which includes dithian-2-yl, dithian-3-yl, dithian-5-yl and dithian-6-yl), dioxolanyl (which includes dioxolan-2-yl, dioxolan-4-yl and dioxolan-5-yl), thioxanyl (which includes thioxan-2-yl, thioxan-3-yl, thioxan-4-yl and thioxan-5-yl), dithiolanyl (which includes

dithiolan-2-yl, dithiolan-4-yl and dithiolan-5-yl), pyrazolidinyl (which includes pyrazolidin-1-yl, pyrazolidin-2-yl, pyrazolidin-3-yl, pyrazolidin-4-yl and pyrazolidin-5-yl), hexahydropyridazinyl and hexahydropyrimidinyl.

The term "6 membered heterocycloalkyl" as used herein, refers to a 6 membered, saturated hydrocarbon ring wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O or S, where $R^6$ is as defined herein. The heterocycloalkyl group can be attached to another group at a nitrogen or a carbon atom. Non-limiting examples of 6 membered heterocycloalkyl groups, as used herein, include piperidinyl (which includes piperidin-1-yl, piperidin-2-yl, piperidin-3-yl, piperidin-4-yl, piperidin-5-yl and piperidin-6-yl), tetrahydropyranyl (which includes tetrahydropyran-2-yl, tetrahydropyran-3-yl, tetrahydropyran-4-yl, tetrahydropyran-5-yl and tetrahydropyran-6-yl), tetrahydrothiopyranyl (which includes tetrahydrothiopyran-2-yl, tetrahydrothiopyran-3-yl, tetrahydrothiopyran-4-yl, tetrahydrothiopyran-5-yl and tetrahydrothiopyran-6-yl), piperazinyl (which includes piperazin-1-yl, piperazin-2-yl, piperazin-3-yl, piperazin-4-yl, piperazin-5-yl and piperazin-6-yl), morpholinyl (which includes morpholin-2-yl, morpholin-3-yl, morpholin-4-yl, morpholin-5-yl and morpholin-6-yl), thiomorpholinyl (which includes thiomorpholin-2-yl, thiomorpholin-3-yl, thiomorpholin-4-yl, thiomorpholin-5-yl and thiomorpholin-6-yl), oxathianyl (which includes oxathian-2-yl, oxathian-3-yl, oxathian-5-yl and oxathian-6-yl), dithianyl (which includes dithian-2-yl, dithian-3-yl, dithian-5-yl and dithian-6-yl), thioxanyl (which includes thioxan-2-yl, thioxan-3-yl, thioxan-4-yl and thioxan-5-yl), hexahydropyridazinyl and hexahydropyrimidinyl.

The term "3 membered heterocycloalkyl" as used herein, refers to a 3 membered, saturated hydrocarbon ring wherein 1or 2 ring members are each independently selected from N, $NR^6$, O or S, where $R^6$ is as defined herein. The heterocycloalkyl group can be attached to another group at a nitrogen or a carbon atom. Non-limiting examples of 3 membered heterocycloalkyl groups, as used herein, include oxiranyl, aziridinyl and thiiranyl.

The term "5 or 6 membered heterocyclyl" as used herein, refers to a partially saturated (but not aromatic) 5 or 6 membered monocyclic ring system wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$, O or S, where $R^6$ is as defined herein. In certain embodiments the term "5 or 6 membered heterocyclyl" as used herein, also refers to a partially saturated 5 or 6 membered monocyclic ring system wherein 1, 2 or 3 ring members are each independently selected from W, Y and Z, wherein W is $X_2$, $NR^6$, O, S, S=O or $S(=O)_2$, $X_2$ is N; Y is $NR^6$, O, S, S=O or $S(=O)_2$ and Z is $NR^6$, O or S, and wherein the 5 or 6 membered heterocyclyl is optionally substituted with oxo. The 5 or 6 membered heterocyclyl group can be attached to another group at a nitrogen or a carbon atom. Non-limiting examples of 5 or 6 membered heterocyclyl groups, as used herein, include 1,2-dihydropyridinyl and 2,3-dihydro-1H-pyrrolyl.

The term "6 membered heterocyclyl" as used herein, refers to a partially saturated (but not aromatic) 6 membered monocyclic ring system wherein 1, 2 or 3 ring members are each

independently selected from N, $NR^6$, O or S, where $R^6$ is as defined herein. In certain embodiments the term "6 membered heterocyclyl" as used herein, also refers to a partially saturated 6 membered monocyclic ring system wherein 1, 2 or 3 ring members are each independently selected from W, Y and Z, wherein W is $X_2$, $NR^6$, O, S, S=O or $S(=O)_2$, $X_2$ is N; Y is $NR^6$, O, S, S=O or $S(=O)_2$ and Z is $NR^6$, O or S, and wherein the 6 membered heterocyclyl is optionally substituted with oxo. The 6 membered heterocyclyl group can be attached to another group at a nitrogen or a carbon atom. Non-limiting examples of membered heterocyclyl groups, as used herein, include 1,2-dihydropyridinyl.

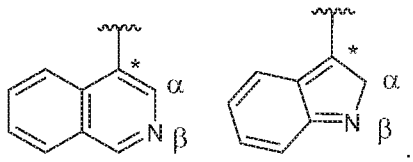
The term "5 membered heterocyclyl" as used herein, refers to a partially saturated (but not aromatic) 5 membered monocyclic ring system wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$, O or S, where $R^6$ is as defined herein. In certain embodiments the term "5 membered heterocyclyl" as used herein, also refers to a partially saturated 5 membered monocyclic ring system wherein 1, 2 or 3 ring members are each independently selected from W, Y and Z, wherein W is $X_2$, $NR^6$, O, S, S=O or $S(=O)_2$, $X_2$ is N; Y is $NR^6$, O, S, S=O or $S(=O)_2$ and Z is $NR^6$, O or S, and wherein the 5 membered heterocyclyl is optionally substituted with oxo. The 5 membered heterocyclyl group can be attached to another group at a nitrogen or a carbon atom. Non-limiting examples of 5 membered heterocyclyl groups, as used herein, include 2,3-dihydro-1H-pyrrolyl.

The term "9 or 10 membered bicyclic heterocyclyl" as used herein, refers to a partially saturated (but not aromatic) 9 or 10 membered bicyclic ring system wherein 1, 2, 3, 4 or 5 ring members are each independently selected from N, $NR^6$, O or S, where $R^6$ is as defined herein. The $C_5$-$C_6$heterocycloalkenyl group can be attached to another group at a nitrogen or a carbon atom. Non-limiting examples of 9 or 10 membered bicyclic heterocyclyl groups, as used herein, include isochromanyl, 1,2-dihydroquinolinyl, 3a,7a-dihydro-1H-pyrrolo[2,3-c]pyridinyl and 3a,7a-dihydro-1H-indazolyl.

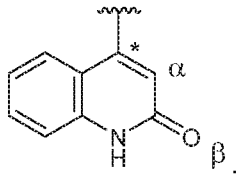
The term "oxo", as used herein, refers to the group =O.

The term "spiro attached", as used herein, refers to the attachment of one ring system to another ring system via one carbon aton common to both rings.

The term "located at a beta (β) position relative to the attachment point", as used herein, refers to the location of a heteroatom or substituent relative to the point of attachment of $R^3$ to the rest of the molecule. By way of example, in the structures below the N hetero atom is located at the beta (β) position relative to the attachment point indicated by the asterix (*)




Similarly, in the structure below the carbon atom which is a ring member substituted with oxo is located at the beta (β) position relative to the attachment point indicated by the asterix (*)



The term “isomers”, as used herein, refers to different compounds that have the same molecular formula but differ in arrangement and configuration of the atoms. Also as used herein, the term “an optical isomer” or “a stereoisomer” refers to any of the various stereo isomeric configurations which may exist for a given compound of the present invention and includes geometric isomers. It is understood that a substituent may be attached at a chiral center of a carbon atom. The term "chiral" refers to molecules which have the property of non-superimposability on their mirror image partner, while the term "achiral" refers to molecules which are superimposable on their mirror image partner. Therefore, the invention includes enantiomers, diastereomers or racemates of the compound. “Enantiomers” are a pair of stereoisomers that are non- superimposable mirror images of each other. A 1:1 mixture of a pair of enantiomers is a "racemic” mixture. The term is used to designate a racemic mixture where appropriate. "Diastereoisomers” are stereoisomers that have at least two asymmetric atoms, but which are not mirror-images of each other. The absolute stereochemistry can be specified according to the Cahn- Ingold- Prelog R-S system. When a compound is a pure enantiomer the stereochemistry at each chiral carbon may be specified by either *R* or *S*. Resolved compounds whose absolute configuration is unknown can be designated (+) or (-) depending on the direction (dextro- or levorotatory) which they rotate plane polarized light at the wavelength of the sodium D line. Certain compounds described herein contain one or more asymmetric centers or axes and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (*R*)- or (*S*)-. The absolute stereochemistry of atropisomers can be assigned either as *M* or *P* according to the “helicity” rule of Prelog and Helmchen.

The term "pharmaceutically acceptable carrier", as used herein, includes any and all solvents, dispersion media, coatings, surfactants, antioxidants, preservatives (e.g., antibacterial agents, antifungal agents), isotonic agents, absorption delaying agents, salts, preservatives, drug stabilizers, binders, excipients, disintegration agents, lubricants, sweetening agents, flavoring agents, dyes, and the like and combinations thereof, as would be known to those skilled in the art (see, for example, Remington's Pharmaceutical Sciences, 18th Ed. Mack Printing Company, 1990, pp. 1289- 1329). Except insofar as any conventional carrier is incompatible with the active ingredient, its use in the therapeutic or pharmaceutical compositions is contemplated.

The term “coronaviral related disease” means a disease caused by a member of the Coronavirus family (i.e., may belong to the Coronaviridae family). Coronaviruses (CoV) are positive-stranded RNA viruses with a crown-like appearance under an electron microscope due

to the presence of spike glycoproteins on the envelope. Any member of the coronavirus family (e.g., those belonging to the alphacoronavirus, betacoronavirus, deltacoronavirus, or gammacoronavirus genuses) that have a respiratory component are contemplated in the methods and uses described herein. As a non-limiting set of examples, the respiratory virus could be a betacoronavirus such as severe acute respiratory syndrome-related coronavirus (SARS-CoV), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), Middle East respiratory syndrome related coronavirus (MERS-CoV), OC43 and HKU1, or an alphacoronavirus such as 229E and NL63. The respiratory virus could also be a coronavirus other than SARS-CoV, SARS-CoV-2, MERS-CoV, OC43, HKU1, 229E or NL63. Patients infected with SARS-CoV-2 present with a wide range of clinical severity varying from asymptomatic to a severe form of interstitial pneumonia, which may progress towards acute respiratory distress syndrome (ARDS), a severe form of acute lung injury (ALI), a form of diffuse alveolar injury, and is a serious lung condition that causes low blood oxygenation and respiratory failure and/or multi organ failure (MOF), associated symptoms and death. The clinical symptoms of COVID-19 patients include fever, cough, fatigue, loss of smell, and shortness of breath within 2-14 days after exposure. SARS-CoV-2 uses the same receptor as SARS-CoV, angiotensin-converting enzyme 2 (ACE2), and mainly spreads through the respiratory tract. Cytokine profiling of patients with severe COVID-19 demonstrates elevated levels of interleukin (IL)-2, IL-7, IL-6, IL-1, granulocyte-colony stimulating factor, interferon-γ inducible protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1-α and tumor necrosis factor-α.

The terms “inhibit”, "inhibition" or “inhibiting”, as used herein, refers to the reduction or suppression of a given condition, symptom, or disorder, or disease, or a significant decrease in the baseline activity of a biological activity or process.

The term “subject” as used herein may refer to an animal. The animal may be a mammal. A subject also refers to for example, primates (e.g., humans, male or female), cows, sheep, goats, horses, dogs, cats, rabbits, rats, mice, fish, birds and the like. In certain embodiments, the subject is a primate. In yet other embodiments, the subject is a human. Except when noted, the terms “patient” or “subject” are used herein interchangeably.

As used herein, the terms “treat,” “treating,” or “treatment” of any disease or disorder refers in one embodiment, to ameliorating the disease or disorder (i.e., slowing or arresting or reducing the development of the disease or at least one of the clinical symptoms thereof). In another embodiment, “treat,” “treating,” or “treatment” refers to alleviating or ameliorating at least one physical parameter including those which may not be discernible by the patient. In yet another embodiment, “treat,” “treating,” or “treatment” refers to modulating the disease or disorder, either physically, (e.g., stabilization of a discernible symptom), physiologically, (e.g., stabilization of a physical parameter), or both.

As used herein, the term “prevent”, “preventing" or “prevention” of any disease or disorder

refers to the prophylactic treatment of the disease or disorder; or delaying the onset or progression of the disease or disorder.

As used herein, the expression “substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo” means the group is substituted with 1, 2, 3 or 4 $R^4$ or the group is substituted with 1, 2, 3 or 4 $R^4$ and is substituted with 1 or 2 oxo.

As used herein, the expression “optionally substituted with oxo” means the group is unsubstituted or is substituted oxo.

As used herein, and unless otherwise indicated, the terms "manage," "managing," and "management" encompass preventing the recurrence of the specified disease or disorder in a patient who has already suffered from the disease or disorder, and/or lengthening the time that a patient who has suffered from the disease or disorder remains in remission. The terms encompass modulating the threshold, development and/or duration of the disease or disorder, or changing the way that a patient responds to the disease or disorder.

The term "a therapeutically effective amount" of a compound of the present invention refers to an amount of the compound of the present invention that will elicit the biological or medical response of a subject, for example, reduction or inhibition of an enzyme or a protein activity, or ameliorate symptoms, manage a condition, alleviate conditions, slow or delay disease progression, or prevent a disease. In one non-limiting embodiment, the term “a therapeutically effective amount” refers to the amount of the compound of the present invention that, when administered to a subject, is effective to (1) at least partially alleviating, inhibiting, preventing managing and/or ameliorating a condition, or a disorder or a disease (i) mediated by SARS-CoV-2 main protease ($M^{pro}$), or (ii) associated with or mediated by SARS-CoV-2 main protease ($M^{pro}$) activity, or (iii) characterized by activity (normal or abnormal) of SARS-CoV-2 main protease ($M^{pro}$); or (2) reducing or inhibiting the activity of SARS-CoV-2 main protease ($M^{pro}$). In another non-limiting embodiment, the term “a therapeutically effective amount” refers to the amount of the compound of the present invention that, when administered to a cell, or a tissue, or a non-cellular biological material, or a medium, is effective to at least partially reducing or inhibiting the activity of SARS-CoV-2 main protease (Mpro).

The term “co-administer” refers to the presence of two active agents in the blood of an individual. Active agents that are co-administered can be concurrently or sequentially delivered.

As used herein, the term "a," "an," "the” and similar terms used in the context of the present invention (especially in the context of the claims) are to be construed to cover both the singular and plural unless otherwise indicated herein or clearly contradicted by the context.

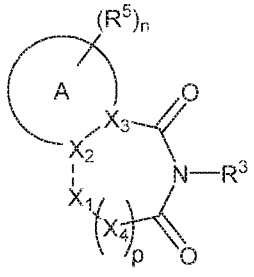
Unless specified otherwise, the terms “compound of the invention”, “compounds of the invention”, “compound of the present invention” or “compounds of the present invention” refers to a compound or compounds of Formula (I), or subformulae thereof such as Formula (I-a), (Formula (I-a), Formula (I-b), Formula (I-c), Formula (I-d), Formula (I-e), Formula (I-f), Formula (I-g), Formula (I-h), Formula (I-i), Formula (I-j), Formula (I-k), Formula (I-l), Formula (I-m),

Formula (I-n), Formula (I-o), Formula (I-p), Formula (I-q), Formula (I-r), Formula (I-s), Formula (I-t), Formula (I-u), Formula (I-v), Formula (I-w), Formula (I-x), Formula (I-y), Formula (I-z), Formula (I-aa), Formula (I-ab), Formula (I-ac), Formula (I-ad), Formula (I-ae), Formula (I-af), Formula (I-ag), Formula (I-ah), Formula (I-ai), Formula (I-aj), Formula (I-ak), Formula (I-al), Formula (I-am), Formula (I-an), Formula (I-ao), Formula (I-ap), Formula (I-aq), Formula (I-ar), Formula (I-as), Formula (I-at), Formula (I-au), Formula (I-av), Formula (I-aw), Formula (I-ax), Formula (I-ay), Formula (I-az), Formula (I-aaa), Formula (I-aab), Formula (I-aac), Formula (I-ba), Formula (I-bb), Formula (I-bc), Formula (I-bd), Formula (I-be), Formula (I-bf), Formula (I-bg), Formula (I-bh), Formula (I-bi), Formula (I-bj), Formula (I-bk), Formula (I-bl), Formula (I-bm), Formula (I-bn), Formula (I-bo), Formula (I-bp), Formula (I-bq), Formula (I-br), and Formula (I-bs), and exemplified compounds, and salts thereof, as well as all stereoisomers (including atropisomers, diastereoisomers and enantiomers) thereof.

Various enumerated embodiments of the present invention are described herein. It will be recognized that features specified in each embodiment may be combined with other specified features to provide further embodiments of the present invention.

Compounds of the Invention

The invention provides compounds of Formula (I), or a pharmaceutical acceptable salt or stereoisomer thereof,



(I)

wherein:

the dashed line between $X_1$ and $X_2$ is a single bond or a double bond;

$X_1$ is $NR^1$, N, $C(R^{2a})_2$, $CR^{2a}$, O, $C=C(R^{2a})_2$, $CR^{2a}R^{2b}$, a spiro attached 4 to 6 membered heterocycloalkyl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$, O, C(=O), S and $S(=O)_2$, or a spiro attached $C_3$-$C_8$cycloalkyl, and wherein the heterocycloalkyl and $C_3$-$C_8$cycloalkyl are unsubstituted or are substituted with 1 or 2 OH groups;

$X_2$ is N, C or CH;

$X_3$ is N, C or CH;

$X_4$ is $C(R^{2a})_2$ or $C=C(R^{2a})_2$;

$R^1$ is H, $C_1$-$C_6$alkyl, $C_3$-$C_8$cycloalkyl, 4 to 7 membered heterocycloalkyl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$, O and S, $C_1$-$C_6$alkyl substituted with one or more $R^{12}$ or $C_1$-$C_6$alkenyl substituted with one or more $R^{12}$,

and wherein the cycloalkyl and heterocycloalkyl are unsubstituted or the cycloalkyl and heterocycloalkyl are substituted with 1 or 2 substituents independently selected from the group consisting of CN, -C(=O)OH, $NH_2$, OH, $C_1$-$C_6$haloalkyl, $C_1$-$C_6$alkyl or $C_1$-$C_6$alkyl substituted with -C(=O)OH, -OH, CN or $NH_2$;

each $R^{2a}$ is independently selected from the group consisting of H, CN, $NH_2$, $C_1$-$C_6$alkyl and $C_1$-$C_6$alkyl substituted with -C(=O)OH, -OH, CN or $NH_2$;

$R^{2b}$ is H, $C_1$-$C_6$alkyl, $C_3$-$C_8$cycloalkyl or 4 to 7 membered heterocycloalkyl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$, O and S, and wherein the $C_3$-$C_8$cycloalkyl and heterocycloalkyl are unsubstituted or the $C_3$-$C_8$cycloalkyl and heterocycloalkyl are substituted with 1, 2, 3 or 4 substituents independently selected from the group consisting of $C_1$-$C_6$alkyl, OH and -$N(R^7)_2$;

$R^3$ is selected from the group consisting of:

i) -$(CH_2)_{0\text{-}6}CHR^{13}R^{14}$;

ii) benzyl which is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

iii) a 6 membered heteroaryl with an attachment point at a carbon atom ring member and a N heteroatom as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 6 membered heteroaryl has 0, 1 or 2 additional N heteroatoms as ring members, and wherein the 6 membered heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

iv) a 10 membered bicyclic heteroaryl with an attachment point at a carbon atom ring member and a N heteroatom as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 10 membered bicyclic heteroaryl has 0, 1, 2 or 3 additional N heteroatoms as ring members, and wherein the 10 membered bicyclic heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

v) a 10 membered bicyclic heteroaryl with an attachment point at a carbon atom ring member and a N heteroatom as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 10 membered bicyclic heteroaryl further has 0, 1, 2, 3, or 4 ring members each independently selected from N, O and S, and wherein the 10 membered bicyclic heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

vi) a 9 membered bicyclic heteroaryl with an attachment point at a carbon atom ring member and a N heteroatom as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 9 membered bicyclic heteroaryl has 0, 1, 2, 3 or 4 additional N heteroatoms as ring members, and wherein the 9 membered bicyclic heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

vii) a 9 membered bicyclic heteroaryl with an attachment point at a carbon atom ring member and a N heteroatom as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 9 membered bicyclic heteroaryl further has 0, 1, 2, 3, or 4 ring members each independently selected from N, $NR^6$, O and S, and wherein the 9 membered bicyclic heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

viii) a 5 or 6 membered heterocycloalkyl with an attachment point at a carbon atom ring member and a $NR^6$ as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 5 or 6 membered heterocycloalkyl further has 0, 1, or 2 ring members each independently selected from N, $NR^6$, O and S, and wherein the 5 or 6 membered heterocycloalkyl is unsubstituted, substituted with 1 or 2 oxo, or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo;

ix) a 5 or 6 membered heterocyclyl with an attachment point at a carbon atom ring member and a $NR^6$ as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 5 or 6 membered heterocyclyl further has 0, 1, or 2 ring members each independently selected from N, $NR^6$, O and S, and wherein the 5 or 6 membered heterocyclyl is unsubstituted, substituted with 1 or 2 oxo, or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo;

x) a 9 or 10 membered bicyclic heterocyclyl with an attachment point at a carbon atom ring member and a $NR^6$ as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 9 or 10 membered heterocyclyl further has 0, 1, 2, 3, or 4 ring members each independently selected from N, $NR^6$, O and S, and wherein the 9 or 10 membered heterocyclyl is unsubstituted, substituted with 1 or 2 oxo, or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo;

xi) a 9 or 10 membered bicyclic heterocyclyl with an attachment point at a carbon atom ring member and a O heteroatom as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 9 or 10 membered heterocyclyl further has 0, 1, 2, 3, or 4 ring members each independently selected from N, $NR^6$, O and S, and wherein the 9 or 10 membered heterocyclyl is unsubstituted, substituted with 1 or 2 oxo, or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo;

xii) a 6 membered heteroaryl wherein 1, 2 or 3 ring members are each independently selected from N, O and S, and wherein the 6 membered heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

xiii) a 9 or 10 membered bicyclic heteroaryl wherein 1, 2, 3, 4 or 5 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 9 or 10 membered bicyclic heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

xiv) a 5 or 6 membered heterocycloalkyl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 5 or 6 membered heterocycloalkyl is unsubstituted, substituted with 1 or 2 oxo, or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo;

xv) a 5 or 6 membered heterocyclyl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 5 or 6 membered heterocyclyl is unsubstituted, substituted with 1 or 2 oxo, or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo;

xvi) a 6 membered heterocyclyl with an attachment point at a carbon atom ring member and a carbon atom as a ring member which is substituted with oxo and located at a beta (β) position relative to the attachment point, wherein the 6 membered heterocyclyl further has 1 or 2 ring members each independently selected from N, $NR^6$, O and S, and wherein the 6 membered heterocyclyl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with an oxo;

xvii) a 9 or 10 membered bicyclic heterocyclyl wherein 1, 2, 3, 4 or 5 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 9 or 10 membered bicyclic heterocyclyl is unsubstituted, substituted with 1 or 2 oxo, or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo;

xviii) a 10 membered bicyclic heterocyclyl with an attachment point at a carbon atom ring member and a carbon atom as a ring member which is substituted with oxo and located at a beta (β) position relative to the attachment point, wherein the 10 membered heterocyclyl further has 1, 2, 3, or 4 ring members each independently selected from N, $NR^6$, O and S, and wherein the 10 membered heterocyclyl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with an oxo;

Ring A is selected from the group consisting of:

i) phenyl;

ii) a 5 or 6 membered heteroaryl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S;

iii) $C_5$-$C_6$cycloalkenyl;

iv) 5 or 6 membered heterocyclyl wherein 1, 2 or 3 ring members are each independently selected from W, Y and Z, wherein W is $X_2$, $NR^6$, O, S, S=O or

$S(=O)_2$, $X_2$ is N; Y is $NR^6$, O, S, S=O or $S(=O)_2$ and Z is $NR^6$, O or S, and wherein the 5 or 6 membered heterocyclyl is optionally substituted with oxo;

v) a 9 or 10 membered bicyclic heterocyclyl wherein 1, 2, 3, 4 or 5 ring members are each independently selected from N, $NR^6$, O and S;

vi) a 5 or 6 membered heterocycloalkyl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S and wherein the 5 or 6 membered heterocycloalkyl is optionally substituted with oxo;

and

vii) a 9 or 10 membered bicyclic heteroaryl wherein 1, 2, 3, 4 or 5 ring members are each independently selected from N, O and S;

each $R^4$ is independently selected from the group consisting of H, $-C(=O)N(R^7)_2$, $-C(=O)OH$, $-N(R^7)_2$, -CN, -OH, $-S(=O)_2R^6$, $-S(=O)_2N(R^7)_2$, $-C(=O)NR^7R^6$,  , $C_1$-$C_6$alkyl, halo, phenyl, $C_3$-$C_8$cycloalkyl, 4 to 6 membered heterocycloalkyl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S, 5 or 6 membered heteroaryl wherein 1, 2 or 3 ring members are each independently selected from N, O and S, and $C_1$-$C_6$alkyl substituted with $NH_2$, CN or OH, and wherein the phenyl, heterocycloalkyl and heteroaryl are unsubstituted or are substituted with 1 or 2 OH groups;

each $R^5$ is independently selected from the group consisting of -OH, $-NR^7R^8$, -NR6C(=O)C2-C6alkenyl, $-SF_5$, $-C(=O)N(R^7)_2$, $C_1$-$C_6$alkyl, $C_1$-$C_6$haloalkyl, halo, $C_1$-$C_6$haloalkoxy, $C_1$-$C_6$alkoxy, $C_3$-$C_8$cycloalkyl, 4 to 6 membered heterocycloalkyl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S, a 5 or 6 membered heteroaryl wherein 1, 2 or 3 ring members are each independently selected from N, O and S, and $C_1$-$C_6$alkyl substituted with CN, $NH_2$ or OH, and wherein the cycloalkyl and heterocycloalkyl are unsubstituted or are substituted with 1, 2, 3 or 4 $R^9$;

each $R^6$ is independently selected from the group consisting of H, $C_1$-$C_6$alkyl, $-S(=O)_2N(R^7)_2$, $-C(=O)N(R^7)_2$ and $C_1$-$C_6$alkyl substituted with –OH, $-OR^7$, CN or –C(=O)OH;

each $R^7$ is independently selected from the group consisting of H and $C_1$-$C_6$alkyl;

$R^8$ is H, $C_1$-$C_6$alkyl, $C_3$-$C_8$cycloalkyl or 4 to 6 membered heterocycloalkyl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S, and wherein the cycloalkyl and heterocycloalkyl are unsubstituted or are substituted with 1, 2, 3 or 4 $R^9$;

each $R^9$ is independently selected from the group consisting of halo, $NR^{10}R^{11}$, $-C(=O)OH$, $-C(=O)N(R^7)_2$ and $C_1$-$C_6$alkyl substituted with -OH or $-N(R^7)_2$;

$R^{10}$ is H or $C_1$-$C_6$alkyl;

$R^{11}$ is H, $C_1$-$C_6$alkyl or -S(=O)$_2$$C_1$-$C_6$alkyl;

each $R^{12}$ is independently selected from the group consisting of CN, $NH_2$, -OH, -C(=O)OH, -C(=O)O$R^{10}$, -C(=O)N($R^7$)$_2$, -C(=O)C(=O)OH, $C_1$-$C_6$alkoxy, $C_1$-$C_6$alkyl, halo, $C_1$-$C_6$haloalkyl, $C_3$-$C_8$cycloalkyl, a 5 or a 6 membered heteroaryl wherein 1, 2, 3, or 4 ring members are each independently selected from N, $NR^6$, O and S, and a 3 to 6 membered heterocycloalkyl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$, O and S, and wherein the cycloalkyl, heteroaryl and heterocycloalkyl are unsubstituted or are substituted with 1, 2 or 3 substituents independently selected from the group consisting of CN, -C(=O)OH, $NH_2$, OH, halo and $C_1$-$C_6$alkyl;

$R^{13}$ is H, -C(=O)N($R^7$)$_2$, or a 5 or 6 membered heteroaryl wherein 1, 2 3 or 4 ring members are each independently selected from N, $NR^6$, O and S;

$R^{14}$ is selected from the group consisting of

i) a 5 or 6 membered heterocyclyl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 5 or 6 membered heterocyclyl is unsubstituted, substituted with 1 or 2 oxo or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo;

and

ii) a 5 or a 6 membered heteroaryl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 5 or a 6 membered heteroaryl is unsubstituted, or is substituted with 1, 2, 3 or 4 $R^4$;

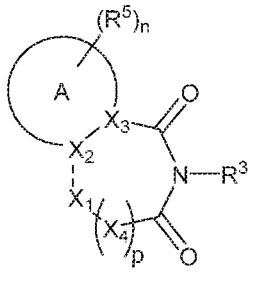
p is 0, 1 or 2, and

n is 0, 1, 2, 3 or 4.

Various embodiments of the compounds of the invention are described herein. It will be recognized that features specified in each embodiment may be combined with other specified features to provide further embodiments. The following enumerated embodiments are representative of the compounds of Formula (I) of the invention.

**Embodiment 1.** A compound of Formula (I), or a pharmaceutically acceptable salt or stereoisomer thereof, as described above in the Summary of the Invention.

**Embodiment 2.** A compound of Formula (I), or a pharmaceutically acceptable salt or stereoisomer thereof,



(I)

wherein:

the dashed line between $X_1$ and $X_2$ is a single bond or a double bond;

$X_1$ is $NR^1$, N, $C(R^{2a})_2$, $CR^{2a}$, O, $C=C(R^{2a})_2$, $CR^{2a}R^{2b}$, a spiro attached 4 to 6 membered heterocycloalkyl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$, O, C(=O), S and $S(=O)_2$, or a spiro attached $C_3$-$C_8$cycloalkyl, and wherein the heterocycloalkyl and $C_3$-$C_8$cycloalkyl are unsubstituted or are substituted with 1 or 2 OH groups;

$X_2$ is N, C or CH;

$X_3$ is N, C or CH;

$X_4$ is $C(R^{2a})_2$ or $C=C(R^{2a})_2$;

$R^1$ is H, $C_1$-$C_6$alkyl, $C_3$-$C_8$cycloalkyl, 4 to 7 membered heterocycloalkyl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$, O and S, $C_1$-$C_6$alkyl substituted with one or more $R^{12}$ or $C_1$-$C_6$alkenyl substituted with one or more $R^{12}$, and wherein the cycloalkyl and heterocycloalkyl are unsubstituted or the cycloalkyl and heterocycloalkyl are substituted with 1 or 2 substituents independently selected from the group consisting of CN, -C(=O)OH, $NH_2$, OH, $C_1$-$C_6$haloalkyl, $C_1$-$C_6$alkyl or $C_1$-$C_6$alkyl substituted with -C(=O)OH, -OH, CN or $NH_2$;

each $R^{2a}$ is independently selected from the group consisting of H, CN, $NH_2$, $C_1$-$C_6$alkyl and $C_1$-$C_6$alkyl substituted with -C(=O)OH, -OH, CN or $NH_2$;

$R^{2b}$ is H, $C_1$-$C_6$alkyl, $C_3$-$C_8$cycloalkyl or 4 to 7 membered heterocycloalkyl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$, O and S, and wherein the $C_3$-$C_8$cycloalkyl and heterocycloalkyl are unsubstituted or the $C_3$-$C_8$cycloalkyl and heterocycloalkyl are substituted with 1, 2, 3 or 4 substituents independently selected from the group consisting of $C_1$-$C_6$alkyl, OH and $-N(R^7)_2$;

$R^3$ is selected from the group consisting of:

i) $-(CH_2)_{0\text{-}6}CHR^{13}R^{14}$;

ii) benzyl which is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

iii) a 6 membered heteroaryl with an attachment point at a carbon atom ring member and a N heteroatom as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 6 membered heteroaryl

has 0, 1 or 2 additional N heteroatoms as ring members, and wherein the 6 membered heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

iv) a 10 membered bicyclic heteroaryl with an attachment point at a carbon atom ring member and a N heteroatom as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 10 membered bicyclic heteroaryl has 0, 1, 2 or 3 additional N heteroatoms as ring members, and wherein the 10 membered bicyclic heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

v) a 10 membered bicyclic heteroaryl with an attachment point at a carbon atom ring member and a N heteroatom as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 10 membered bicyclic heteroaryl further has 0, 1, 2, 3, or 4 ring members each independently selected from N, O and S, and wherein the 10 membered bicyclic heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

vi) a 9 membered bicyclic heteroaryl with an attachment point at a carbon atom ring member and a N heteroatom as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 9 membered bicyclic heteroaryl has 0, 1, 2, 3 or 4 additional N heteroatoms as ring members, and wherein the 9 membered bicyclic heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

vii) a 9 membered bicyclic heteroaryl with an attachment point at a carbon atom ring member and a N heteroatom as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 9 membered bicyclic heteroaryl further has 0, 1, 2, 3, or 4 ring members each independently selected from N, $NR^6$, O and S, and wherein the 9 membered bicyclic heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

viii) a 5 or 6 membered heterocycloalkyl with an attachment point at a carbon atom ring member and a $NR^6$ as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 5 or 6 membered heterocycloalkyl further has 0, 1, or 2 ring members each independently selected from N, $NR^6$, O and S, and wherein the 5 or 6 membered heterocycloalkyl is unsubstituted, substituted with 1 or 2 oxo, or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo;

ix) a 5 or 6 membered heterocyclyl with an attachment point at a carbon atom ring member and a $NR^6$ as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 5 or 6 membered heterocyclyl further has 0, 1, or 2 ring members each independently selected

from N, $NR^6$, O and S, and wherein the 5 or 6 membered heterocyclyl is unsubstituted, substituted with 1 or 2 oxo, or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo;

x) a 9 or 10 membered bicyclic heterocyclyl with an attachment point at a carbon atom ring member and a $NR^6$ as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 9 or 10 membered heterocyclyl further has 0, 1, 2, 3, or 4 ring members each independently selected from N, $NR^6$, O and S, and wherein the 9 or 10 membered heterocyclyl is unsubstituted, substituted with 1 or 2 oxo, or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo;

xi) a 9 or 10 membered bicyclic heterocyclyl with an attachment point at a carbon atom ring member and a O heteroatom as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 9 or 10 membered heterocyclyl further has 0, 1, 2, 3, or 4 ring members each independently selected from N, $NR^6$, O and S, and wherein the 9 or 10 membered heterocyclyl is unsubstituted, substituted with 1 or 2 oxo, or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo;

xii) a 6 membered heteroaryl wherein 1, 2 or 3 ring members are each independently selected from N, O and S, and wherein the 6 membered heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

xiii) a 9 or 10 membered bicyclic heteroaryl wherein 1, 2, 3, 4 or 5 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 9 or 10 membered bicyclic heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

xiv) a 5 or 6 membered heterocycloalkyl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 5 or 6 membered heterocycloalkyl is unsubstituted, substituted with 1 or 2 oxo, or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo;

xv) a 5 or 6 membered heterocyclyl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 5 or 6 membered heterocyclyl is unsubstituted, substituted with 1 or 2 oxo, or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo;

xvi) a 6 membered heterocyclyl with an attachment point at a carbon atom ring member and a carbon atom as a ring member which is substituted with oxo and located at a beta (β) position relative to the attachment point, wherein the 6 membered heterocyclyl further has 1 or 2 ring members each independently selected from N, $NR^6$, O and S, and wherein the 6 membered

heterocyclyl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with an oxo;

xvii) a 9 or 10 membered bicyclic heterocyclyl wherein 1, 2, 3, 4 or 5 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 9 or 10 membered bicyclic heterocyclyl is unsubstituted, substituted with 1 or 2 oxo, or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo;

xviii) a 10 membered bicyclic heterocyclyl with an attachment point at a carbon atom ring member and a carbon atom as a ring member which is substituted with oxo and located at a beta (β) position relative to the attachment point, wherein the 10 membered heterocyclyl further has 1, 2, 3, or 4 ring members each independently selected from N, $NR^6$, O and S, and wherein the 10 membered heterocyclyl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with an oxo;

Ring A is selected from the group consisting of:

i) phenyl;

ii) a 5 or 6 membered heteroaryl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S;

iii) $C_5$-$C_6$cycloalkenyl;

iv) 5 or 6 membered heterocyclyl wherein 1, 2 or 3 ring members are each independently selected from W, Y and Z, wherein W is $X_2$, $NR^6$, O, S, S=O or $S(=O)_2$, $X_2$ is N; Y is $NR^6$, O, S, S=O or $S(=O)_2$ and Z is $NR^6$, O or S, and wherein the 5 or 6 membered heterocyclyl is optionally substituted with oxo;

v) a 9 or 10 membered bicyclic heterocyclyl wherein 1, 2, 3, 4 or 5 ring members are each independently selected from N, $NR^6$, O and S;

vi) a 5 or 6 membered heterocycloalkyl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S and wherein the 5 or 6 membered heterocycloalkyl is optionally substituted with oxo;

and

vii) a 9 or 10 membered bicyclic heteroaryl wherein 1, 2, 3, 4 or 5 ring members are each independently selected from N, O and S;

each $R^4$ is independently selected from the group consisting of H, $-C(=O)N(R^7)_2$, $-C(=O)OH$, $-N(R^7)_2$, -CN, -OH, $-S(=O)_2R^6$, $-S(=O)_2N(R^7)_2$,  , $C_1$-$C_6$alkyl, halo, phenyl, $C_3$-$C_8$cycloalkyl, 4 to 6 membered heterocycloalkyl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S, 5 or 6 membered heteroaryl wherein 1, 2 or 3 ring members are each independently selected from N,

O and S, and $C_1$-$C_6$alkyl substituted with $NH_2$, CN or OH, and wherein the phenyl, heterocycloalkyl and heteroaryl are unsubstituted or are substituted with 1 or 2 OH groups;

each $R^5$ is independently selected from the group consisting of -OH, -$NR^7R^8$, -NR6C(=O)C2-C6alkenyl, -$SF_5$, -$C(=O)N(R^7)_2$, $C_1$-$C_6$alkyl, $C_1$-$C_6$haloalkyl, halo, $C_1$-$C_6$haloalkoxy, $C_1$-$C_6$alkoxy, $C_3$-$C_8$cycloalkyl, 4 to 6 membered heterocycloalkyl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S, a 5 or 6 membered heteroaryl wherein 1, 2 or 3 ring members are each independently selected from N, O and S, and $C_1$-$C_6$alkyl substituted with CN, $NH_2$ or OH, and wherein the cycloalkyl and heterocycloalkyl are unsubstituted or are substituted with 1, 2, 3 or 4 $R^9$;

each $R^6$ is independently selected from the group consisting of H, $C_1$-$C_6$alkyl, -$S(=O)_2N(R^7)_2$, -$C(=O)N(R^7)_2$ and $C_1$-$C_6$alkyl substituted with –OH, CN or –C(=O)OH;

each $R^7$ is independently selected from the group consisting of H and $C_1$-$C_6$alkyl;

$R^8$ is H, $C_1$-$C_6$alkyl, $C_3$-$C_8$cycloalkyl or 4 to 6 membered heterocycloalkyl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S, and wherein the cycloalkyl and heterocycloalkyl are unsubstituted or are substituted with 1, 2, 3 or 4 $R^9$;

each $R^9$ is independently selected from the group consisting of $NR^{10}R^{11}$, -$C(=O)N(R^7)_2$ and $C_1$-$C_6$alkyl substituted with -OH or -$N(R^7)_2$;

$R^{10}$ is H or $C_1$-$C_6$alkyl;

$R^{11}$ is H, $C_1$-$C_6$alkyl or -$S(=O)_2C_1$-$C_6$alkyl;

each $R^{12}$ is independently selected from the group consisting of CN, $NH_2$, -OH, -C(=O)OH, -$C(=O)N(R^7)_2$, -C(=O)C(=O)OH, $C_1$-$C_6$alkoxy, halo, $C_1$-$C_6$haloalkyl, $C_3$-$C_8$cycloalkyl, a 5 or a 6 membered heteroaryl wherein 1, 2, 3, or 4 ring members are each independently selected from N, $NR^6$, O and S, and a 3 to 6 membered heterocycloalkyl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$, O and S, and wherein the cycloalkyl, heteroaryl and heterocycloalkyl are unsubstituted or are substituted with 1, 2 or 3 substituents independently selected from the group consisting of CN, -C(=O)OH, $NH_2$, OH and $C_1$-$C_6$alkyl;

$R^{13}$ is H, -$C(=O)N(R^7)_2$, or a 5 or 6 membered heteroaryl wherein 1, 2 3 or 4 ring members are each independently selected from N, $NR^6$, O and S;

$R^{14}$ is selected from the group consisting of

i) a 5 or 6 membered heterocyclyl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 5 or 6 membered heterocyclyl is unsubstituted, substituted with 1 or 2 oxo or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo; and

ii) a 5 or a 6 membered heteroaryl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 5 or a 6 membered heteroaryl is unsubstituted, or is substituted with 1, 2, 3 or 4 $R^4$;

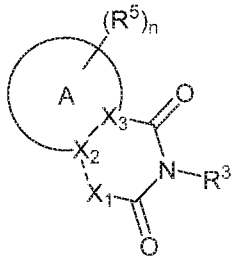
p is 0, 1 or 2;

y is 0, 1 or 2;

m is 0, 1, 2, 3 or 4, and

n is 0, 1, 2, 3 or 4.

**Embodiment 3.** The compound of Embodiment 1 or Embodiment 2, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein p is 0 and the compound of Formula (I) has the structure of Formula (IA):




(IA),

where Ring A, $X_1$, $X_2$, $X_3$, $R^3$, $R^5$, n and the dashed line between $X_1$ and $X_2$ are as defined in Embodiment 1.

**Embodiment 4.** The compound of any one of Embodiments 1 to 3, or a pharmaceutically acceptable salt or stereoisomer thereof,

wherein:

the dashed line between $X_1$ and $X_2$ is a single bond or a double bond;

$X_1$ is $NR^1$, N, $C(R^{2a})_2$, $CR^{2a}$, O, $C{=}C(R^{2a})_2$, $CR^{2a}R^{2b}$, a spiro attached 4 to 6 membered heterocycloalkyl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$, O, C(=O), S and $S(=O)_2$, or a spiro attached $C_3$-$C_8$cycloalkyl, and wherein the heterocycloalkyl and $C_3$-$C_8$cycloalkyl are unsubstituted or are substituted with 1 or 2 OH groups;

$X_2$ is N, C or CH;

$X_3$ is N, C or CH;

$R^1$ is H, $C_1$-$C_6$alkyl, $C_3$-$C_8$cycloalkyl, 4 to 7 membered heterocycloalkyl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$, O and S, a $C_1$-$C_6$alkyl substituted with one or more $R^{12}$ or a $C_1$-$C_6$alkenyl substituted with one or more $R^{12}$, and wherein the cycloalkyl and heterocycloalkyl are unsubstituted or the cycloalkyl and heterocycloalkyl are substituted with 1 or 2 substituents independently selected from the group consisting of CN, -C(=O)OH, $NH_2$, OH, $C_1$-$C_6$haloalkyl, $C_1$-$C_6$alkyl or $C_1$-$C_6$alkyl substituted with -C(=O)OH, -OH, CN or $NH_2$;

each $R^{2a}$ is independently selected from the group consisting of H, CN, $NH_2$, $C_1$-$C_6$alkyl and $C_1$-$C_6$alkyl substituted with -C(=O)OH, -OH, CN or $NH_2$;

$R^{2b}$ is H, $C_1$-$C_6$alkyl, $C_3$-$C_8$cycloalkyl or 4 to 7 membered heterocycloalkyl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$, O and S, and wherein the $C_3$-$C_8$cycloalkyl and heterocycloalkyl are unsubstituted or the $C_3$-$C_8$cycloalkyl and heterocycloalkyl are substituted with 1, 2, 3 or 4 substituents independently selected from the group consisting of $C_1$-$C_6$alkyl, OH and -$N(R^7)_2$;

$R^3$ is selected from the group consisting of:

i) a 6 membered heteroaryl with an attachment point at a carbon atom ring member and a N heteroatom as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 6 membered heteroaryl has 0, 1 or 2 additional N heteroatoms as ring members, and wherein the 6 membered heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

ii) a 10 membered bicyclic heteroaryl with an attachment point at a carbon atom ring member and a N heteroatom as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 10 membered bicyclic heteroaryl has 0, 1, 2 or 3 additional N heteroatoms as ring members, and wherein the 10 membered bicyclic heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

iii) a 6 membered heteroaryl wherein 1, 2 or 3 ring members are each independently selected from N, O and S, and wherein the 6 membered heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

iv) a 9 or 10 membered bicyclic heteroaryl wherein 1, 2, 3, 4 or 5 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 9 or 10 membered bicyclic heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

v) a 9 or 10 membered bicyclic heterocyclyl with an attachment point at a carbon atom ring member and a $NR^6$ as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 9 or 10 membered heterocyclyl further has 0, 1, 2, 3, or 4 ring members each independently selected from N, $NR^6$, O and S, and wherein the 9 or 10 membered heterocyclyl is unsubstituted, substituted with 1 or 2 oxo, or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo;

vi) a 9 or 10 membered bicyclic heterocyclyl wherein 1, 2, 3, 4 or 5 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 9 or 10 membered bicyclic heterocyclyl is unsubstituted, substituted with 1 or 2 oxo, or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo;

vii) a 10 membered bicyclic heterocyclyl with an attachment point at a carbon atom ring member and a carbon atom as a ring member which is substituted

with oxo and located at a beta (β) position relative to the attachment point, wherein the 10 membered heterocyclyl further has 1, 2, 3, or 4 ring members each independently selected from N, $NR^6$, O and S, and wherein the 10 membered heterocyclyl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with an oxo;

Ring A is selected from the group consisting of:

i) phenyl;

ii) a 5 or 6 membered heteroaryl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S;

iii) $C_5$-$C_6$cycloalkenyl;

iv) 5 or 6 membered heterocyclyl wherein 1, 2 or 3 ring members are each independently selected from W, Y and Z, wherein W is $X_2$, $NR^6$, O, S, S=O or $S(=O)_2$, $X_2$ is N; Y is $NR^6$, O, S, S=O or $S(=O)_2$ and Z is $NR^6$, O or S, and wherein the 5 or 6 membered heterocyclyl is optionally substituted with oxo;

v) a 9 or 10 membered bicyclic heterocyclyl wherein 1, 2, 3, 4 or 5 ring members are each independently selected from N, $NR^6$, O and S;

vi) a 5 or 6 membered heterocycloalkyl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 5 or 6 membered heterocycloalkyl is optionally substituted with oxo;

and

vii) a 9 or 10 membered bicyclic heteroaryl wherein 1, 2, 3, 4 or 5 ring members are each independently selected from N, O and S;

each $R^4$ is independently selected from the group consisting of -C(=O)N($R^7$)$_2$, -C(=O)OH, -N($R^7$)$_2$, -CN, -OH, -S(=O)$_2$$R^6$, -S(=O)$_2$N($R^7$)$_2$, -C(=O)N$R^7$$R^6$,  , $C_1$-$C_6$alkyl, halo, phenyl, $C_3$-$C_8$cycloalkyl, 4 to 6 membered heterocycloalkyl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S, 5 or 6 membered heteroaryl wherein 1, 2 or 3 ring members are each independently selected from N, O and S, and $C_1$-$C_6$alkyl substituted with $NH_2$, CN or OH, and wherein the phenyl, heterocycloalkyl and heteroaryl are unsubstituted or are substituted with 1 or 2 OH groups;

each $R^5$ is independently selected from the group consisting of -OH, -N$R^7$$R^8$, -NR6C(=O)C2-C6alkenyl, -$SF_5$, -C(=O)N($R^7$)$_2$, $C_1$-$C_6$alkyl, $C_1$-$C_6$haloalkyl, halo, $C_1$-$C_6$haloalkoxy, $C_1$-$C_6$alkoxy, $C_3$-$C_8$cycloalkyl, 4 to 6 membered heterocycloalkyl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S, a 5 or 6 membered heteroaryl wherein 1, 2 or 3 ring members are each independently selected from N, O and S, and $C_1$-$C_6$alkyl substituted with CN, $NH_2$ or

OH, and wherein the cycloalkyl and heterocycloalkyl are unsubstituted or are substituted with 1, 2, 3 or 4 $R^9$;

each $R^6$ is independently selected from the group consisting of H, $C_1$-$C_6$alkyl, -$S(=O)_2N(R^7)_2$, -$C(=O)N(R^7)_2$ and $C_1$-$C_6$alkyl substituted with –OH, -$OR^7$, CN or –C(=O)OH;

each $R^7$ is independently selected from the group consisting of H and $C_1$-$C_6$alkyl;

$R^8$ is H, $C_1$-$C_6$alkyl, $C_3$-$C_8$cycloalkyl or 4 to 6 membered heterocycloalkyl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S, and wherein the cycloalkyl and heterocycloalkyl are unsubstituted or are substituted with 1, 2, 3 or 4 $R^9$;

each $R^9$ is independently selected from the group consisting of halo, $NR^{10}R^{11}$, -C(=O)OH, -$C(=O)N(R^7)_2$ and $C_1$-$C_6$alkyl substituted with -OH or -$N(R^7)_2$;

$R^{10}$ is H or $C_1$-$C_6$alkyl;

$R^{11}$ is H, $C_1$-$C_6$alkyl or -$S(=O)_2C_1$-$C_6$alkyl;

each $R^{12}$ is independently selected from the group consisting of CN, $NH_2$, -OH, -C(=O)OH, -$C(=O)OR^{10}$, -$C(=O)N(R^7)_2$, -$C_1$-$C_6$alkoxy, $C_1$-$C_6$alkyl, halo, $C_1$-$C_6$haloalkyl, $C_3$-$C_8$cycloalkyl, a 5 or a 6 membered heteroaryl wherein 1, 2, 3, or 4 ring members are each independently selected from N, $NR^6$, O and S, and a 3 to 6 membered heterocycloalkyl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$, O and S, and wherein the cycloalkyl, heteroaryl and heterocycloalkyl are unsubstituted or are substituted with 1, 2 or 3 substituents independently selected from the group consisting of CN, -C(=O)OH, $NH_2$, OH, halo and $C_1$-$C_6$alkyl;

$R^{13}$ is H, -$C(=O)N(R^7)_2$, or a 5 or 6 membered heteroaryl wherein 1, 2 3 or 4 ring members are each independently selected from N, $NR^6$, O and S;

$R^{14}$ is selected from the group consisting of

i) a 5 or 6 membered heterocyclyl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 5 or 6 membered heterocyclyl is unsubstituted, or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo;

and

ii) a 5 or a 6 membered heteroaryl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 5 or a 6 membered heteroaryl is unsubstituted, or is substituted with 1, 2, 3 or 4 $R^4$;

p is 0, 1 or 2, and

n is 0, 1, 2, 3 or 4.

**Embodiment 5.** The compound of any one of Embodiments 1 to 4, or a pharmaceutically acceptable salt or stereoisomer thereof,

wherein:

the dashed line between $X_1$ and $X_2$ is a single bond or a double bond;

$X_1$ is $NR^1$, N, $C(R^{2a})_2$, $CR^{2a}$, O, $C=C(R^{2a})_2$, $CR^{2a}R^{2b}$, a spiro attached 4 to 6 membered heterocycloalkyl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$, O, C(=O), S and $S(=O)_2$, or a spiro attached $C_3$-$C_8$cycloalkyl, and wherein the heterocycloalkyl and $C_3$-$C_8$cycloalkyl are unsubstituted or are substituted with 1 or 2 OH groups;

$X_2$ is N, C or CH;

$X_3$ is N, C or CH;

$R^1$ is H, $C_1$-$C_6$alkyl, $C_3$-$C_8$cycloalkyl, 4 to 7 membered heterocycloalkyl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$, O and S, a $C_1$-$C_6$alkyl substituted with one or more $R^{12}$ or a $C_1$-$C_6$alkenyl substituted with one or more $R^{12}$, and wherein the cycloalkyl and heterocycloalkyl are unsubstituted or the cycloalkyl and heterocycloalkyl are substituted with 1 or 2 substituents independently selected from the group consisting of CN, -C(=O)OH, $NH_2$, OH, $C_1$-$C_6$haloalkyl, $C_1$-$C_6$alkyl or $C_1$-$C_6$alkyl substituted with -C(=O)OH, -OH, CN or $NH_2$;

each $R^{2a}$ is independently selected from the group consisting of H, CN, $NH_2$, $C_1$-$C_6$alkyl and $C_1$-$C_6$alkyl substituted with -C(=O)OH, -OH, CN or $NH_2$;

$R^{2b}$ is H, $C_1$-$C_6$alkyl, $C_3$-$C_8$cycloalkyl or 4 to 7 membered heterocycloalkyl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$, O and S, and wherein the $C_3$-$C_8$cycloalkyl and heterocycloalkyl are unsubstituted or the $C_3$-$C_8$cycloalkyl and heterocycloalkyl are substituted with 1, 2, 3 or 4 substituents independently selected from the group consisting of $C_1$-$C_6$alkyl, OH and $-N(R^7)_2$;

$R^3$ is selected from the group consisting of:

i) a 6 membered heteroaryl with an attachment point at a carbon atom ring member and a N heteroatom as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 6 membered heteroaryl has 0, 1 or 2 additional N heteroatoms as ring members, and wherein the 6 membered heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

ii) a 10 membered bicyclic heteroaryl with an attachment point at a carbon atom ring member and a N heteroatom as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 10 membered bicyclic heteroaryl has 0, 1, 2 or 3 additional N heteroatoms as ring members, and wherein the 10 membered bicyclic heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

iii) a 6 membered heteroaryl wherein 1, 2 or 3 ring members are each independently selected from N, O and S, and wherein the 6 membered heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

iv) a 9 or 10 membered bicyclic heteroaryl wherein 1, 2, 3, 4 or 5 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 9 or 10 membered bicyclic heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

v) a 9 or 10 membered bicyclic heterocyclyl with an attachment point at a carbon atom ring member and a $NR^6$ as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 9 or 10 membered heterocyclyl further has 0, 1, 2, 3, or 4 ring members each independently selected from N, $NR^6$, O and S, and wherein the 9 or 10 membered heterocyclyl is unsubstituted, substituted with 1 or 2 oxo, or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo;

vi) a 9 or 10 membered bicyclic heterocyclyl wherein 1, 2, 3, 4 or 5 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 9 or 10 membered bicyclic heterocyclyl is unsubstituted, substituted with 1 or 2 oxo, or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo;

vii) a 10 membered bicyclic heterocyclyl with an attachment point at a carbon atom ring member and a carbon atom as a ring member which is substituted with oxo and located at a beta (β) position relative to the attachment point, wherein the 10 membered heterocyclyl further has 1, 2, 3, or 4 ring members each independently selected from N, $NR^6$, O and S, and wherein the 10 membered heterocyclyl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with an oxo;

Ring A is selected from the group consisting of:

i) phenyl;

ii) a 5 or 6 membered heteroaryl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S;

iii) $C_5$-$C_6$cycloalkenyl;

iv) 5 or 6 membered heterocyclyl wherein 1, 2 or 3 ring members are each independently selected from W, Y and Z, wherein W is $X_2$, $NR^6$, O, S, S=O or $S(=O)_2$, $X_2$ is N; Y is $NR^6$, O, S, S=O or $S(=O)_2$ and Z is $NR^6$, O or S, and wherein the 5 or 6 membered heterocyclyl is optionally substituted with oxo;

v) a 9 or 10 membered bicyclic heterocyclyl wherein 1, 2, 3, 4 or 5 ring members are each independently selected from N, $NR^6$, O and S;

vi) a 5 or 6 membered heterocycloalkyl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 5 or 6 membered heterocycloalkyl is optionally substituted with oxo;

and

vii) a 9 or 10 membered bicyclic heteroaryl wherein 1, 2, 3, 4 or 5 ring members are each independently selected from N, O and S;

each $R^4$ is independently selected from the group consisting of $-C(=O)N(R^7)_2$, -C(=O)OH, $-N(R^7)_2$, -CN, -OH, $-S(=O)_2R^6$, $-S(=O)_2N(R^7)_2$, $-C(=O)NR^7R^6$,  , $C_1$-$C_6$alkyl, halo, phenyl, $C_3$-$C_8$cycloalkyl, 4 to 6 membered heterocycloalkyl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S, 5 or 6 membered heteroaryl wherein 1, 2 or 3 ring members are each independently selected from N, O and S, and $C_1$-$C_6$alkyl substituted with $NH_2$, CN or OH, and wherein the phenyl, heterocycloalkyl and heteroaryl are unsubstituted or are substituted with 1 or 2 OH groups;

each $R^5$ is independently selected from the group consisting of -OH, $-NR^7R^8$, -NR6C(=O)C2-C6alkenyl, $-SF_5$, $-C(=O)N(R^7)_2$, $C_1$-$C_6$alkyl, $C_1$-$C_6$haloalkyl, halo, $C_1$-$C_6$haloalkoxy, $C_1$-$C_6$alkoxy, $C_3$-$C_8$cycloalkyl, 4 to 6 membered heterocycloalkyl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S, a 5 or 6 membered heteroaryl wherein 1, 2 or 3 ring members are each independently selected from N, O and S, and $C_1$-$C_6$alkyl substituted with CN, $NH_2$ or OH, and wherein the cycloalkyl and heterocycloalkyl are unsubstituted or are substituted with 1, 2, 3 or 4 $R^9$;

each $R^6$ is independently selected from the group consisting of H, $C_1$-$C_6$alkyl, $-S(=O)_2N(R^7)_2$, $-C(=O)N(R^7)_2$ and $C_1$-$C_6$alkyl substituted with –OH, $-OR^7$, CN or –C(=O)OH;

each $R^7$ is independently selected from the group consisting of H and $C_1$-$C_6$alkyl;

$R^8$ is H, $C_1$-$C_6$alkyl, $C_3$-$C_8$cycloalkyl or 4 to 6 membered heterocycloalkyl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S, and wherein the cycloalkyl and heterocycloalkyl are unsubstituted or are substituted with 1, 2, 3 or 4 $R^9$;

each $R^9$ is independently selected from the group consisting of halo, $NR^{10}R^{11}$, $-C(=O)OH$, $-C(=O)N(R^7)_2$ and $C_1$-$C_6$alkyl substituted with -OH or $-N(R^7)_2$;

$R^{10}$ is H or $C_1$-$C_6$alkyl;

$R^{11}$ is H, $C_1$-$C_6$alkyl or $-S(=O)_2C_1$-$C_6$alkyl;

each $R^{12}$ is independently selected from the group consisting of CN, $NH_2$, -OH, $-C(=O)OH$, $-C(=O)OR^{10}$, $-C(=O)N(R^7)_2$, $-C_1$-$C_6$alkoxy, $C_1$-$C_6$alkyl, halo, $C_1$-$C_6$haloalkyl, $C_3$-$C_8$cycloalkyl, a 5 or a 6 membered heteroaryl wherein 1, 2, 3, or 4 ring members are each independently selected from N, $NR^6$, O and S, and a 3 to 6 membered heterocycloalkyl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$, O and S, and wherein the cycloalkyl, heteroaryl and heterocycloalkyl

are unsubstituted or are substituted with 1, 2 or 3 substituents independently selected from the group consisting of CN, -C(=O)OH, $NH_2$, OH, halo and $C_1$-$C_6$alkyl; and

n is 0, 1, 2, 3 or 4.

**Embodiment 6.** The compound of any one of Embodiments 1 to 5, or a pharmaceutically acceptable salt or stereoisomer thereof,

wherein:

the dashed line between $X_1$ and $X_2$ is a single bond or a double bond;

$X_1$ is $NR^1$, N, $C(R^{2a})_2$, $CR^{2a}$, O, $C{=}C(R^{2a})_2$, $CR^{2a}R^{2b}$, a spiro attached 4 to 6 membered heterocycloalkyl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$, O, C(=O), S and $S(=O)_2$, or a spiro attached $C_3$-$C_8$cycloalkyl, and wherein the heterocycloalkyl and $C_3$-$C_8$cycloalkyl are unsubstituted or are substituted with 1 or 2 OH groups;

$X_2$ is N, C or CH;

$X_3$ is N, C or CH;

$R^1$ is H, $C_1$-$C_6$alkyl, $C_3$-$C_8$cycloalkyl, 4 to 7 membered heterocycloalkyl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$, O and S, a $C_1$-$C_6$alkyl substituted with one or more $R^{12}$ or a $C_1$-$C_6$alkenyl substituted with one or more $R^{12}$, and wherein the cycloalkyl and heterocycloalkyl are unsubstituted or the cycloalkyl and heterocycloalkyl are substituted with 1 or 2 substituents independently selected from the group consisting of CN, -C(=O)OH, $NH_2$, OH, $C_1$-$C_6$haloalkyl, $C_1$-$C_6$alkyl or $C_1$-$C_6$alkyl substituted with -C(=O)OH, -OH, CN or $NH_2$;

each $R^{2a}$ is independently selected from the group consisting of H, CN, $NH_2$, $C_1$-$C_6$alkyl and $C_1$-$C_6$alkyl substituted with -C(=O)OH, -OH, CN or $NH_2$;

$R^{2b}$ is H, $C_1$-$C_6$alkyl, $C_3$-$C_8$cycloalkyl or 4 to 7 membered heterocycloalkyl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$, O and S, and wherein the $C_3$-$C_8$cycloalkyl and heterocycloalkyl are unsubstituted or the $C_3$-$C_8$cycloalkyl and heterocycloalkyl are substituted with 1, 2, 3 or 4 substituents independently selected from the group consisting of $C_1$-$C_6$alkyl, OH and $-N(R^7)_2$;

$R^3$ is selected from the group consisting of:

i) a 6 membered heteroaryl with an attachment point at a carbon atom ring member and a N heteroatom as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 6 membered heteroaryl has 0, 1 or 2 additional N heteroatoms as ring members, and wherein the 6 membered heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

ii) a 10 membered bicyclic heteroaryl with an attachment point at a carbon atom ring member and a N heteroatom as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 10 membered

bicyclic heteroaryl has 0, 1, 2 or 3 additional N heteroatoms as ring members, and wherein the 10 membered bicyclic heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

iii) a 6 membered heteroaryl wherein 1, 2 or 3 ring members are each independently selected from N, O and S, and wherein the 6 membered heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

iv) a 9 or 10 membered bicyclic heteroaryl wherein 1, 2, 3, 4 or 5 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 9 or 10 membered bicyclic heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

v) a 9 or 10 membered bicyclic heterocyclyl with an attachment point at a carbon atom ring member and a $NR^6$ as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 9 or 10 membered heterocyclyl further has 0, 1, 2, 3, or 4 ring members each independently selected from N, $NR^6$, O and S, and wherein the 9 or 10 membered heterocyclyl is unsubstituted, substituted with 1 or 2 oxo, or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo;

vi) a 9 or 10 membered bicyclic heterocyclyl wherein 1, 2, 3, 4 or 5 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 9 or 10 membered bicyclic heterocyclyl is unsubstituted, substituted with 1 or 2 oxo, or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo;

vii) a 10 membered bicyclic heterocyclyl with an attachment point at a carbon atom ring member and a carbon atom as a ring member which is substituted with oxo and located at a beta (β) position relative to the attachment point, wherein the 10 membered heterocyclyl further has 1, 2, 3, or 4 ring members each independently selected from N, $NR^6$, O and S, and wherein the 10 membered heterocyclyl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with an oxo;

Ring A is selected from the group consisting of:

i) phenyl;

ii) a 5 or 6 membered heteroaryl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S;

iii) $C_5$-$C_6$cycloalkenyl;

iv) 5 or 6 membered heterocyclyl wherein 1, 2 or 3 ring members are each independently selected from W, Y and Z, wherein W is $X_2$, $NR^6$, O, S, S=O or $S(=O)_2$, $X_2$ is N; Y is $NR^6$, O, S, S=O or $S(=O)_2$ and Z is $NR^6$, O or

S, and wherein the 5 or 6 membered heterocyclyl is optionally substituted with oxo;

and

v) a 5 or 6 membered heterocycloalkyl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 5 or 6 membered heterocycloalkyl is optionally substituted with oxo;

each $R^4$ is independently selected from the group consisting of $-C(=O)N(R^7)_2$, -C(=O)OH, $-N(R^7)_2$, -CN, -OH, $-S(=O)_2R^6$, $-S(=O)_2N(R^7)_2$, $-C(=O)NR^7R^6$,  , $C_1$-$C_6$alkyl, halo, phenyl, $C_3$-$C_8$cycloalkyl, 4 to 6 membered heterocycloalkyl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S, 5 or 6 membered heteroaryl wherein 1, 2 or 3 ring members are each independently selected from N, O and S, and $C_1$-$C_6$alkyl substituted with $NH_2$, CN or OH, and wherein the phenyl, heterocycloalkyl and heteroaryl are unsubstituted or are substituted with 1 or 2 OH groups;

each $R^5$ is independently selected from the group consisting of -OH, $-NR^7R^8$, -NR6C(=O)C2-C6alkenyl, $-SF_5$, $-C(=O)N(R^7)_2$, $C_1$-$C_6$alkyl, $C_1$-$C_6$haloalkyl, halo, $C_1$-$C_6$haloalkoxy, $C_1$-$C_6$alkoxy, $C_3$-$C_8$cycloalkyl, 4 to 6 membered heterocycloalkyl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S, a 5 or 6 membered heteroaryl wherein 1, 2 or 3 ring members are each independently selected from N, O and S, and $C_1$-$C_6$alkyl substituted with CN, $NH_2$ or OH, and wherein the cycloalkyl and heterocycloalkyl are unsubstituted or are substituted with 1, 2, 3 or 4 $R^9$;

each $R^6$ is independently selected from the group consisting of H, $C_1$-$C_6$alkyl, $-S(=O)_2N(R^7)_2$, $-C(=O)N(R^7)_2$ and $C_1$-$C_6$alkyl substituted with –OH, $-OR^7$, CN or –C(=O)OH;

each $R^7$ is independently selected from the group consisting of H and $C_1$-$C_6$alkyl;

$R^8$ is H, $C_1$-$C_6$alkyl, $C_3$-$C_8$cycloalkyl or 4 to 6 membered heterocycloalkyl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S, and wherein the cycloalkyl and heterocycloalkyl are unsubstituted or are substituted with 1, 2, 3 or 4 $R^9$;

each $R^9$ is independently selected from the group consisting of halo, $NR^{10}R^{11}$, -C(=O)OH, $-C(=O)N(R^7)_2$ and $C_1$-$C_6$alkyl substituted with -OH or $-N(R^7)_2$;

$R^{10}$ is H or $C_1$-$C_6$alkyl;

$R^{11}$ is H, $C_1$-$C_6$alkyl or $-S(=O)_2C_1$-$C_6$alkyl;

each $R^{12}$ is independently selected from the group consisting of CN, $NH_2$, -OH, -C(=O)OH, $-C(=O)OR^{10}$, $-C(=O)N(R^7)_2$, $-C_1$-$C_6$alkoxy, $C_1$-$C_6$alkyl, halo, $C_1$-$C_6$haloalkyl,

$C_3$-$C_8$cycloalkyl, a 5 or a 6 membered heteroaryl wherein 1, 2, 3, or 4 ring members are each independently selected from N, $NR^6$, O and S, and a 3 to 6 membered heterocycloalkyl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$, O and S, and wherein the cycloalkyl, heteroaryl and heterocycloalkyl are unsubstituted or are substituted with 1, 2 or 3 substituents independently selected from the group consisting of CN, -C(=O)OH, $NH_2$, OH, halo and $C_1$-$C_6$alkyl; and

n is 0, 1, 2, 3 or 4.

**Embodiment 7.** The compound of any one of Embodiments 1 to 6, or a pharmaceutically acceptable salt or stereoisomer thereof,

wherein:

the dashed line between $X_1$ and $X_2$ is a single bond or a double bond;

$X_1$ is $NR^1$, N, $C(R^{2a})_2$, $CR^{2a}$, O, $C=C(R^{2a})_2$, $CR^{2a}R^{2b}$, a spiro attached 4 to 6 membered heterocycloalkyl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$, O, C(=O), S and $S(=O)_2$, or a spiro attached $C_3$-$C_8$cycloalkyl, and wherein the heterocycloalkyl and $C_3$-$C_8$cycloalkyl are unsubstituted or are substituted with 1 or 2 OH groups;

$X_2$ is N, C or CH;

$X_3$ is N, C or CH;

$R^1$ is H, $C_1$-$C_6$alkyl, $C_3$-$C_8$cycloalkyl, 4 to 7 membered heterocycloalkyl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$, O and S, a $C_1$-$C_6$alkyl substituted with one or more $R^{12}$ or a $C_1$-$C_6$alkenyl substituted with one or more $R^{12}$, and wherein the cycloalkyl and heterocycloalkyl are unsubstituted or the cycloalkyl and heterocycloalkyl are substituted with 1 or 2 substituents independently selected from the group consisting of CN, -C(=O)OH, $NH_2$, OH, $C_1$-$C_6$haloalkyl, $C_1$-$C_6$alkyl or $C_1$-$C_6$alkyl substituted with -C(=O)OH, -OH, CN or $NH_2$;

each $R^{2a}$ is independently selected from the group consisting of H, CN, $NH_2$, $C_1$-$C_6$alkyl and $C_1$-$C_6$alkyl substituted with -C(=O)OH, -OH, CN or $NH_2$;

$R^{2b}$ is H, $C_1$-$C_6$alkyl, $C_3$-$C_8$cycloalkyl or 4 to 7 membered heterocycloalkyl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$, O and S, and wherein the $C_3$-$C_8$cycloalkyl and heterocycloalkyl are unsubstituted or the $C_3$-$C_8$cycloalkyl and heterocycloalkyl are substituted with 1, 2, 3 or 4 substituents independently selected from the group consisting of $C_1$-$C_6$alkyl, OH and $-N(R^7)_2$;

$R^3$ is selected from the group consisting of:

i) a 6 membered heteroaryl with an attachment point at a carbon atom ring member and a N heteroatom as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 6 membered heteroaryl

has 0, 1 or 2 additional N heteroatoms as ring members, and wherein the 6 membered heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

ii) a 10 membered bicyclic heteroaryl with an attachment point at a carbon atom ring member and a N heteroatom as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 10 membered bicyclic heteroaryl has 0, 1, 2 or 3 additional N heteroatoms as ring members, and wherein the 10 membered bicyclic heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

iii) a 6 membered heteroaryl wherein 1, 2 or 3 ring members are each independently selected from N, O and S, and wherein the 6 membered heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

iv) a 9 or 10 membered bicyclic heteroaryl wherein 1, 2, 3, 4 or 5 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 9 or 10 membered bicyclic heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

v) a 9 or 10 membered bicyclic heterocyclyl with an attachment point at a carbon atom ring member and a $NR^6$ as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 9 or 10 membered heterocyclyl further has 0, 1, 2, 3, or 4 ring members each independently selected from N, $NR^6$, O and S, and wherein the 9 or 10 membered heterocyclyl is unsubstituted, substituted with 1 or 2 oxo, or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo;

vi) a 9 or 10 membered bicyclic heterocyclyl wherein 1, 2, 3, 4 or 5 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 9 or 10 membered bicyclic heterocyclyl is unsubstituted, substituted with 1 or 2 oxo, or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo;

vii) a 10 membered bicyclic heterocyclyl with an attachment point at a carbon atom ring member and a carbon atom as a ring member which is substituted with oxo and located at a beta (β) position relative to the attachment point, wherein the 10 membered heterocyclyl further has 1, 2, 3, or 4 ring members each independently selected from N, $NR^6$, O and S, and wherein the 10 membered heterocyclyl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with an oxo;

Ring A is selected from the group consisting of:

i) phenyl;

ii) a 5 or 6 membered heteroaryl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S;

and

iii) $C_5$-$C_6$cycloalkenyl;

each $R^4$ is independently selected from the group consisting of -C(=O)N($R^7$)$_2$, -C(=O)OH, -N($R^7$)$_2$, -CN, -OH, -S(=O)$_2R^6$, -S(=O)$_2$N($R^7$)$_2$, -C(=O)N$R^7R^6$,  , $C_1$-$C_6$alkyl, halo, phenyl, $C_3$-$C_8$cycloalkyl, 4 to 6 membered heterocycloalkyl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S, 5 or 6 membered heteroaryl wherein 1, 2 or 3 ring members are each independently selected from N, O and S, and $C_1$-$C_6$alkyl substituted with $NH_2$, CN or OH, and wherein the phenyl, heterocycloalkyl and heteroaryl are unsubstituted or are substituted with 1 or 2 OH groups;

each $R^5$ is independently selected from the group consisting of -OH, -N$R^7R^8$, -NR6C(=O)C2-C6alkenyl, $-SF_5$, -C(=O)N($R^7$)$_2$, $C_1$-$C_6$alkyl, $C_1$-$C_6$haloalkyl, halo, $C_1$-$C_6$haloalkoxy, $C_1$-$C_6$alkoxy, $C_3$-$C_8$cycloalkyl, 4 to 6 membered heterocycloalkyl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S, a 5 or 6 membered heteroaryl wherein 1, 2 or 3 ring members are each independently selected from N, O and S, and $C_1$-$C_6$alkyl substituted with CN, $NH_2$ or OH, and wherein the cycloalkyl and heterocycloalkyl are unsubstituted or are substituted with 1, 2, 3 or 4 $R^9$;

each $R^6$ is independently selected from the group consisting of H, $C_1$-$C_6$alkyl, -S(=O)$_2$N($R^7$)$_2$, -C(=O)N($R^7$)$_2$ and $C_1$-$C_6$alkyl substituted with –OH, -O$R^7$, CN or –C(=O)OH;

each $R^7$ is independently selected from the group consisting of H and $C_1$-$C_6$alkyl;

$R^8$ is H, $C_1$-$C_6$alkyl, $C_3$-$C_8$cycloalkyl or 4 to 6 membered heterocycloalkyl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S, and wherein the cycloalkyl and heterocycloalkyl are unsubstituted or are substituted with 1, 2, 3 or 4 $R^9$;

each $R^9$ is independently selected from the group consisting of halo, N$R^{10}R^{11}$, -C(=O)OH, -C(=O)N($R^7$)$_2$ and $C_1$-$C_6$alkyl substituted with -OH or -N($R^7$)$_2$;

$R^{10}$ is H or $C_1$-$C_6$alkyl;

$R^{11}$ is H, $C_1$-$C_6$alkyl or -S(=O)$_2$$C_1$-$C_6$alkyl;

each $R^{12}$ is independently selected from the group consisting of CN, $NH_2$, -OH, -C(=O)OH, -C(=O)O$R^{10}$, -C(=O)N($R^7$)$_2$, -$C_1$-$C_6$alkoxy, $C_1$-$C_6$alkyl, halo, $C_1$-$C_6$haloalkyl, $C_3$-$C_8$cycloalkyl, a 5 or a 6 membered heteroaryl wherein 1, 2, 3, or 4 ring members are each independently selected from N, $NR^6$, O and S, and a 3 to 6 membered heterocycloalkyl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$, O and S, and wherein the cycloalkyl, heteroaryl and heterocycloalkyl

are unsubstituted or are substituted with 1, 2 or 3 substituents independently selected from the group consisting of CN, -C(=O)OH, $NH_2$, OH, halo and $C_1$-$C_6$alkyl; and

n is 0, 1, 2, 3 or 4.

**Embodiment 8.** The compound of any one of Embodiments 1 to 3, or a pharmaceutically acceptable salt or stereoisomer thereof,

wherein:

the dashed line between $X_1$ and $X_2$ is a single bond or a double bond;

$X_1$ is $NR^1$, N, $C(R^{2a})_2$, $CR^{2a}$, O, $C=C(R^{2a})_2$, $CR^{2a}R^{2b}$, a spiro attached 4 to 6 membered heterocycloalkyl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$, O, C(=O), S and $S(=O)_2$, or a spiro attached $C_3$-$C_8$cycloalkyl, and wherein the heterocycloalkyl and $C_3$-$C_8$cycloalkyl are unsubstituted or are substituted with 1 or 2 OH groups;

$X_2$ is N, C or CH;

$X_3$ is N, C or CH;

$X_4$ is $C(R^{2a})_2$ or $C=C(R^{2a})_2$;

$R^1$ is H, $C_1$-$C_6$alkyl, $C_3$-$C_8$cycloalkyl, 4 to 7 membered heterocycloalkyl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$, O and S, $C_1$-$C_6$alkyl substituted with one or more $R^{12}$ or $C_1$-$C_6$alkenyl substituted with one or more $R^{12}$, and wherein the cycloalkyl and heterocycloalkyl are unsubstituted or the cycloalkyl and heterocycloalkyl are substituted with 1 or 2 substituents independently selected from the group consisting of CN, -C(=O)OH, $NH_2$, OH, $C_1$-$C_6$haloalkyl, $C_1$-$C_6$alkyl or $C_1$-$C_6$alkyl substituted with -C(=O)OH, -OH, CN or $NH_2$;

each $R^{2a}$ is independently selected from the group consisting of H, CN, $NH_2$, $C_1$-$C_6$alkyl and $C_1$-$C_6$alkyl substituted with -C(=O)OH, -OH, CN or $NH_2$;

$R^{2b}$ is H, $C_1$-$C_6$alkyl, $C_3$-$C_8$cycloalkyl or 4 to 7 membered heterocycloalkyl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$, O and S, and wherein the $C_3$-$C_8$cycloalkyl and heterocycloalkyl are unsubstituted or the $C_3$-$C_8$cycloalkyl and heterocycloalkyl are substituted with 1, 2, 3 or 4 substituents independently selected from the group consisting of $C_1$-$C_6$alkyl, OH and $-N(R^7)_2$;

$R^3$ is selected from the group consisting of:

i) $-(CH_2)_{0\text{-}6}CHR^{13}R^{14}$;

ii) benzyl which is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

iii) a 6 membered heteroaryl wherein 1, 2 or 3 ring members are each independently selected from N, O and S, and wherein the 6 membered heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

iv) a 9 or 10 membered bicyclic heteroaryl wherein 1, 2, 3, 4 or 5 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 9 or

10 membered bicyclic heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

v) a 5 or 6 membered heterocycloalkyl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 5 or 6 membered heterocycloalkyl is unsubstituted, substituted with 1 or 2 oxo, or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo;

vi) a 5 or 6 membered heterocyclyl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 5 or 6 membered heterocyclyl is unsubstituted, substituted with 1 or 2 oxo, or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo;

vii) a 9 or 10 membered bicyclic heterocyclyl wherein 1, 2, 3, 4 or 5 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 9 or 10 membered bicyclic heterocyclyl is unsubstituted, substituted with 1 or 2 oxo, or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo;

Ring A is selected from the group consisting of:

i) phenyl;

ii) a 5 or 6 membered heteroaryl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S;

iii) $C_5$-$C_6$cycloalkenyl;

iv) 5 or 6 membered heterocyclyl wherein 1, 2 or 3 ring members are each independently selected from W, Y and Z, wherein W is $X_2$, $NR^6$, O, S, S=O or $S(=O)_2$, $X_2$ is N; Y is $NR^6$, O, S, S=O or $S(=O)_2$ and Z is $NR^6$, O or S, and wherein the 5 or 6 membered heterocyclyl is optionally substituted with oxo;

v) a 9 or 10 membered bicyclic heterocyclyl wherein 1, 2, 3, 4 or 5 ring members are each independently selected from N, $NR^6$, O and S;

vi) a 5 or 6 membered heterocycloalkyl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 5 or 6 membered heterocycloalkyl is optionally substituted with oxo;

and

vii) a 9 or 10 membered bicyclic heteroaryl wherein 1, 2, 3, 4 or 5 ring members are each independently selected from N, O and S;

each $R^4$ is independently selected from the group consisting of $-C(=O)N(R^7)_2$, -C(=O)OH, $-N(R^7)_2$, -CN, -OH, $-S(=O)_2R^6$, $-S(=O)_2N(R^7)_2$,  , $C_1$-$C_6$alkyl, halo, phenyl, $C_3$-$C_8$cycloalkyl, 4 to 6 membered heterocycloalkyl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S, 5 or 6 membered heteroaryl

wherein 1, 2 or 3 ring members are each independently selected from N, O and S, and $C_1$-$C_6$alkyl substituted with $NH_2$, CN or OH, and wherein the phenyl, heterocycloalkyl and heteroaryl are unsubstituted or are substituted with 1 or 2 OH groups;

each $R^5$ is independently selected from the group consisting of -OH, -$NR^7R^8$, -NR6C(=O)C2-C6alkenyl, -$SF_5$, -C(=O)N($R^7$)$_2$, $C_1$-$C_6$alkyl, $C_1$-$C_6$haloalkyl, halo, $C_1$-$C_6$haloalkoxy, $C_1$-$C_6$alkoxy, $C_3$-$C_8$cycloalkyl, 4 to 6 membered heterocycloalkyl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S, a 5 or 6 membered heteroaryl wherein 1, 2 or 3 ring members are each independently selected from N, O and S, and $C_1$-$C_6$alkyl substituted with CN, $NH_2$ or OH, and wherein the cycloalkyl and heterocycloalkyl are unsubstituted or are substituted with 1, 2, 3 or 4 $R^9$;

each $R^6$ is independently selected from the group consisting of H, $C_1$-$C_6$alkyl, -$S(=O)_2N(R^7)_2$, -C(=O)N($R^7$)$_2$ and $C_1$-$C_6$alkyl substituted with –OH, CN or –C(=O)OH;

each $R^7$ is independently selected from the group consisting of H and $C_1$-$C_6$alkyl;

$R^8$ is H, $C_1$-$C_6$alkyl, $C_3$-$C_8$cycloalkyl or 4 to 6 membered heterocycloalkyl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S, and wherein the cycloalkyl and heterocycloalkyl are unsubstituted or are substituted with 1, 2, 3 or 4 $R^9$;

each $R^9$ is independently selected from the group consisting of $NR^{10}R^{11}$, -C(=O)N($R^7$)$_2$ and $C_1$-$C_6$alkyl substituted with -OH or -N($R^7$)$_2$;

$R^{10}$ is H or $C_1$-$C_6$alkyl;

$R^{11}$ is H, $C_1$-$C_6$alkyl or -$S(=O)_2C_1$-$C_6$alkyl;

each $R^{12}$ is independently selected from the group consisting of CN, $NH_2$, -OH, -C(=O)OH, -C(=O)N($R^7$)$_2$, -C(=O)C(=O)OH, $C_1$-$C_6$alkoxy, halo, $C_1$-$C_6$haloalkyl, $C_3$-$C_8$cycloalkyl, a 5 or a 6 membered heteroaryl wherein 1, 2, 3, or 4 ring members are each independently selected from N, $NR^6$, O and S, and a 3 to 6 membered heterocycloalkyl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$, O and S, and wherein the cycloalkyl, heteroaryl and heterocycloalkyl are unsubstituted or are substituted with 1, 2 or 3 substituents independently selected from the group consisting of CN, -C(=O)OH, $NH_2$, OH and $C_1$-$C_6$alkyl;

$R^{13}$ is H, -C(=O)N($R^7$)$_2$, or a 5 or 6 membered heteroaryl wherein 1, 2 3 or 4 ring members are each independently selected from N, $NR^6$, O and S;

$R^{14}$ is selected from the group consisting of

i) a 5 or 6 membered heterocyclyl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 5 or 6 membered heterocyclyl is unsubstituted, or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo;

and

ii) a 5 or a 6 membered heteroaryl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 5 or a 6 membered heteroaryl is unsubstituted, or is substituted with 1, 2, 3 or 4 $R^4$;

p is 0, 1 or 2, and

n is 0, 1, 2, 3 or 4.

**Embodiment 9.** The compound of any one of Embodiment 1 to 8, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

the dashed line between $X_1$ and $X_2$ is a single bond or a double bond;

$X_1$ is $NR^1$, $C(R^{2a})_2$, $CR^{2a}$, O, or $C{=}C(R^{2a})_2$;

$X_2$ is C or CH;

$X_3$ is C or CH;

$R^1$ is H, $C_1$-$C_6$alkyl, $C_3$-$C_8$cycloalkyl, 4 membered heterocycloalkyl wherein 1 ring member selected from N, $NR^6$ and O, a $C_1$-$C_6$alkyl substituted with one or more $R^{12}$ or a $C_1$-$C_6$alkenyl substituted with one or more $R^{12}$, and wherein the cycloalkyl and heterocycloalkyl are unsubstituted or the cycloalkyl and heterocycloalkyl are substituted with 1 substituent selected from the group consisting of CN, -C(=O)OH, $C_1$-$C_6$haloalkyl and $C_1$-$C_6$alkyl substituted with CN;

each $R^{2a}$ is independently selected from the group consisting of H, $NH_2$, $C_1$-$C_6$alkyl and $C_1$-$C_6$alkyl substituted with -C(=O)OH, -OH or CN;

$R^3$ is selected from the group consisting of:

i) a 6 membered heteroaryl with an attachment point at a carbon atom ring member and a N heteroatom as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 6 membered heteroaryl has 0, 1 or 2 additional N heteroatoms as ring members, and wherein the 6 membered heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

ii) a 10 membered bicyclic heteroaryl with an attachment point at a carbon atom ring member and a N heteroatom as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 10 membered bicyclic heteroaryl has 0, 1, 2 or 3 additional N heteroatoms as ring members, and wherein the 10 membered bicyclic heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

iii) a 6 membered heteroaryl wherein 1, 2 or 3 ring members are each independently selected from N, O and S, and wherein the 6 membered heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

iv) a 9 or 10 membered bicyclic heteroaryl wherein 1, 2, 3, 4 or 5 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 9 or

10 membered bicyclic heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

v) a 9 or 10 membered bicyclic heterocyclyl with an attachment point at a carbon atom ring member and a $NR^6$ as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 9 or 10 membered heterocyclyl further has 0, 1, 2, 3, or 4 ring members each independently selected from N, $NR^6$, O and S, and wherein the 9 or 10 membered heterocyclyl is unsubstituted, substituted with 1 or 2 oxo, or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo;

vi) a 9 or 10 membered bicyclic heterocyclyl wherein 1, 2, 3, 4 or 5 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 9 or 10 membered bicyclic heterocyclyl is unsubstituted, substituted with 1 or 2 oxo, or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo;

and

vii) a 10 membered bicyclic heterocyclyl with an attachment point at a carbon atom ring member and a carbon atom as a ring member which is substituted with oxo and located at a beta (β) position relative to the attachment point, wherein the 10 membered heterocyclyl further has 1, 2, 3, or 4 ring members each independently selected from N, $NR^6$, O and S, and wherein the 10 membered heterocyclyl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with an oxo;

Ring A is selected from the group consisting of:

i) phenyl;

ii) a 5 or 6 membered heteroaryl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S;

iii) $C_5$-$C_6$cycloalkenyl;

iv) 5 or 6 membered heterocyclyl wherein 1, 2 or 3 ring members are each independently selected from W, Y and Z, wherein W is $X_2$, $NR^6$, O, S, S=O or $S(=O)_2$, $X_2$ is N; Y is $NR^6$, O, S, S=O or $S(=O)_2$ and Z is $NR^6$, O or S, and wherein the 5 or 6 membered heterocyclyl is optionally substituted with oxo;

and

v) a 5 or 6 membered heterocycloalkyl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 5 or 6 membered heterocycloalkyl is optionally substituted with oxo;

each $R^4$ is independently selected from the group consisting of -C(=O)N($R^7$)$_2$, -C(=O)OH, -N($R^7$)$_2$, -CN, -OH, -C(=O)N$R^7R^6$,  , $C_1$-$C_6$alkyl, halo, 6 membered heterocycloalkyl wherein 1 or 2 ring members are each independently selected from N and $NR^6$, and $C_1$-$C_6$alkyl substituted with $NH_2$, and wherein the heterocycloalkyl is unsubstituted;

each $R^5$ is independently selected from the group consisting of -NR6C(=O)C2-C6alkenyl, -$SF_5$, $C_1$-$C_6$alkyl, $C_1$-$C_6$haloalkyl, halo, $C_1$-$C_6$haloalkoxy, $C_1$-$C_6$alkoxy, $C_3$-$C_8$cycloalkyl, wherein the cycloalkyl is unsubstituted or is substituted with 1 $R^9$;

each $R^6$ is independently selected from the group consisting of H or $C_1$-$C_6$alkyl;

each $R^7$ is independently selected from the group consisting of H and $C_1$-$C_6$alkyl;

each $R^9$ is independently selected from the group consisting of $C_1$-$C_6$alkyl substituted with -OH;

$R^{10}$ is H or $C_1$-$C_6$alkyl;

each $R^{12}$ is independently selected from the group consisting of CN, -OH, -C(=O)OH, -C(=O)N($R^7$)$_2$, $C_1$-$C_6$alkoxy, halo, $C_1$-$C_6$haloalkyl, $C_3$-$C_8$cycloalkyl, a 5 membered heteroaryl wherein 4 ring members are each independently selected from N and $NR^6$, and a 3 membered heterocycloalkyl wherein 1 ring member is selected from N, $NR^6$ and O, and wherein the cycloalkyl, heteroaryl and heterocycloalkyl are unsubstituted or are substituted with 1 substituent from the group consisting of CN and -C(=O)OH;

$R^{13}$ is H;

$R^{14}$ is a 6 membered heterocyclyl wherein 1 ring member is selected from N or $NR^6$, and wherein the 6 membered heterocyclyl is substituted with an oxo;

and

n is 0, 1 or 2.

**Embodiment 10.** The compound of any one of Embodiments 1 to 3, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

the dashed line between $X_1$ and $X_2$ is a single bond or a double bond;

$X_1$ is $NR^1$, C($R^{2a}$)$_2$, C$R^{2a}$, O, or C=C($R^{2a}$)$_2$;

$X_2$ is C or CH;

$X_3$ is N or C;

$X_4$ is C($R^{2a}$)$_2$ or C=C($R^{2a}$)$_2$;

$R^1$ is H, $C_1$-$C_6$alkyl, $C_3$-$C_8$cycloalkyl, 4 membered heterocycloalkyl wherein 1 ring member selected from N, $NR^6$ and O; $C_1$-$C_6$alkyl substituted with one or more $R^{12}$ or $C_1$-$C_6$alkenyl substituted with one or more $R^{12}$, and wherein the cycloalkyl and heterocycloalkyl are unsubstituted or the cycloalkyl and heterocycloalkyl are

substituted with 1 substituent selected from the group consisting of CN, -C(=O)OH, $C_1$-$C_6$haloalkyl and $C_1$-$C_6$alkyl substituted with CN;

each $R^{2a}$ is independently selected from the group consisting of H, $NH_2$, $C_1$-$C_6$alkyl and $C_1$-$C_6$alkyl substituted with -C(=O)OH, -OH or CN;

$R^3$ is selected from the group consisting of:

i) $-CHR^{13}R^{14}$;

ii) benzyl which is unsubstituted or is substituted with 1 $R^4$;

iii) a 6 membered heteroaryl wherein 1 ring member is selected from N, and wherein the 6 membered heteroaryl is unsubstituted or is substituted with 1 or 2 $R^4$;

iv) a 10 membered bicyclic heteroaryl with an attachment point at a carbon atom ring member and a N heteroatom as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 10 membered bicyclic heteroaryl has 0, 1, 2 or 3 additional N heteroatoms as ring members, and wherein the 10 membered bicyclic heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

v) a 9 or 10 membered bicyclic heteroaryl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$ and O, and wherein the 9 or 10 membered bicyclic heteroaryl is unsubstituted or is substituted with 1 or 2 $R^4$;

vi) a 6 membered heterocyclyl wherein 1 ring member is selected from $NR^6$, and wherein the 6 membered heterocyclyl is substituted with an oxo;

and

vii) a 9 or 10 membered bicyclic heterocyclyl wherein 1 ring member is selected from N, $NR^6$ or O, and wherein the 9 or 10 membered bicyclic heterocyclyl is unsubstituted, or is substituted with an oxo;

Ring A is selected from the group consisting of:

i) phenyl;

ii) a 5 or 6 membered heteroaryl wherein 1 ring member is selected from N or S;

iii) $C_5$-$C_6$cycloalkenyl;

iv) and

v) a 9 or 10 membered bicyclic heterocyclyl wherein 1 ring member is selected from N or $NR^6$;

each $R^4$ is independently selected from the group consisting of $-C(=O)N(R^7)_2$, -C(=O)OH, $-N(R^7)_2$, -CN, -OH,  , $C_1$-$C_6$alkyl, halo, 6 membered heterocycloalkyl wherein 1 or 2 ring members are each independently selected from N and $NR^6$, and $C_1$-$C_6$alkyl substituted with $NH_2$, and wherein the heterocycloalkyl is unsubstituted;

each $R^5$ is independently selected from the group consisting of -NR6C(=O)C2-C6alkenyl, $-SF_5$, $C_1$-$C_6$alkyl, $C_1$-$C_6$haloalkyl, halo, $C_1$-$C_6$haloalkoxy, $C_1$-$C_6$alkoxy, $C_3$-$C_8$cycloalkyl, wherein the cycloalkyl is unsubstituted or is substituted with 1 $R^9$;

each $R^6$ is independently selected from the group consisting of H or $C_1$-$C_6$alkyl;

each $R^7$ is independently selected from the group consisting of H and $C_1$-$C_6$alkyl;

each $R^9$ is independently selected from the group consisting of $C_1$-$C_6$alkyl substituted with -OH;

$R^{10}$ is H or $C_1$-$C_6$alkyl;

each $R^{12}$ is independently selected from the group consisting of CN, -OH, -C(=O)OH, -C(=O)N($R^7$)$_2$, $C_1$-$C_6$alkoxy, halo, $C_1$-$C_6$haloalkyl, $C_3$-$C_8$cycloalkyl, a 5 membered heteroaryl wherein 4 ring members are each independently selected from N and $NR^6$, and a 3 membered heterocycloalkyl wherein 1 ring member is selected from N, $NR^6$ and O, and wherein the cycloalkyl, heteroaryl and heterocycloalkyl are unsubstituted or are substituted with 1 substituent from the group consisting of CN and -C(=O)OH;

$R^{13}$ is H;

$R^{14}$ is a 6 membered heterocyclyl wherein 1 ring member is selected from N or $NR^6$, and wherein the 6 membered heterocyclyl is substituted with an oxo;

and

n is 0, 1 or 2.

**Embodiment 11.** The compound of any one of Embodiments 1 to 10, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

the dashed line between $X_1$ and $X_2$ is a single bond;

$X_1$ is $NR^1$, C($R^{2a}$)$_2$ or O;

$X_2$ is C or CH;

$X_3$ is C or CH;

$R^1$ is H, $C_1$-$C_6$alkyl, $C_3$-$C_8$cycloalkyl, a $C_1$-$C_6$alkyl substituted with one or more $R^{12}$, or a $C_1$-$C_6$alkenyl substituted with one or more $R^{12}$, and wherein the cycloalkyl is unsubstituted or the cycloalkyl is substituted with 1 substituent selected from the group consisting of $C_1$-$C_6$alkyl substituted with CN;

each $R^{2a}$ is independently selected from the group consisting of H, and $C_1$-$C_6$alkyl;

$R^3$ is selected from the group consisting of:

i) a 6 membered heteroaryl with an attachment point at a carbon atom ring member and a N heteroatom as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 6 membered heteroaryl has 0, 1 or 2 additional N heteroatoms as ring members, and wherein the 6 membered heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

ii) a 10 membered bicyclic heteroaryl with an attachment point at a carbon atom ring member and a N heteroatom as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 10 membered bicyclic heteroaryl has 0, 1, 2 or 3 additional N heteroatoms as ring members, and wherein the 10 membered bicyclic heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

iii) a 6 membered heteroaryl wherein 1, 2 or 3 ring members are each independently selected from N, O and S, and wherein the 6 membered heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

iv) a 9 or 10 membered bicyclic heteroaryl wherein 1, 2, 3, 4 or 5 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 9 or 10 membered bicyclic heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

v) a 9 or 10 membered bicyclic heterocyclyl with an attachment point at a carbon atom ring member and a $NR^6$ as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 9 or 10 membered heterocyclyl further has 0, 1, 2, 3, or 4 ring members each independently selected from N, $NR^6$, O and S, and wherein the 9 or 10 membered heterocyclyl is unsubstituted, substituted with 1 or 2 oxo, or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo;

vi) a 9 or 10 membered bicyclic heterocyclyl wherein 1, 2, 3, 4 or 5 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 9 or 10 membered bicyclic heterocyclyl is unsubstituted, substituted with 1 or 2 oxo, or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo;

and

vii) a 10 membered bicyclic heterocyclyl with an attachment point at a carbon atom ring member and a carbon atom as a ring member which is substituted with oxo and located at a beta (β) position relative to the attachment point, wherein the 10 membered heterocyclyl further has 1, 2, 3, or 4 ring members each independently selected from N, $NR^6$, O and S, and wherein the 10 membered heterocyclyl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with an oxo;

Ring A is selected from the group consisting of:

i) phenyl;

ii) a 6 membered heteroaryl wherein 1 ring member is selected from N;

and

iii) $C_5$-$C_6$cycloalkenyl;

each $R^4$ is independently selected from the group consisting of $-C(=O)N(R^7)_2$, $-N(R^7)_2$, -CN, $-S(=O)_2R^6$, $-C(=O)NR^7R^6$,  , $C_1$-$C_6$alkyl, and halo;

each $R^5$ is independently selected from the group consisting of $-SF_5$, $C_1$-$C_6$alkyl, $C_1$-$C_6$haloalkyl, halo, $C_1$-$C_6$haloalkoxy, $C_1$-$C_6$alkoxy, $C_3$-$C_8$cycloalkyl, and a $C_1$-$C_6$alkyl substituted with CN or OH, wherein the cycloalkyl is unsubstituted or is substituted with 1 or 2 $R^9$;

each $R^6$ is independently selected from the group consisting of H, $C_1$-$C_6$alkyl or $C_1$-$C_6$alkyl substituted with $-OR^7$;

each $R^7$ is independently selected from the group consisting of H and $C_1$-$C_6$alkyl;

each $R^9$ is independently selected from the group consisting of halo, -C(=O)OH, and $C_1$-$C_6$alkyl substituted with -OH;

$R^{10}$ is H or $C_1$-$C_6$alkyl;

each $R^{12}$ is independently selected from the group consisting of CN, -OH, -C(=O)OH, $-C(=O)OR^{10}$, $-C(=O)N(R^7)_2$, $C_1$-$C_6$alkoxy, $C_1$-$C_6$alkyl, halo, $C_3$-$C_8$cycloalkyl, a 5 membered heteroaryl wherein 4 ring members are each independently selected from N and $NR^6$, and a 3 to 6 membered heterocycloalkyl wherein 1 or 2 ring members are each independently selected from N, $NR^6$ and O, and wherein the cycloalkyl and heterocycloalkyl are unsubstituted or are substituted with 1 or 2 substituents independently selected from the group consisting of CN, halo and -C(=O)OH;

and

n is 1 or 2.

**Embodiment 12.** The compound of any one of Embodiments 1 to 11, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

$X_1$ is $NR^1$;

$R^1$ is H, $C_1$-$C_6$alkyl, $C_3$-$C_8$cycloalkyl, a $C_1$-$C_6$alkyl substituted with one or more $R^{12}$, or a $C_1$-$C_6$alkenyl substituted with one or more $R^{12}$, and wherein the cycloalkyl is unsubstituted or the cycloalkyl is substituted with 1 substituent selected from the group consisting of $C_1$-$C_6$alkyl substituted with CN;

each $R^{2a}$ is independently selected from the group consisting of H, and $C_1$-$C_6$alkyl;

$R^3$ is selected from the group consisting of:

i) a 6 membered heteroaryl with an attachment point at a carbon atom ring member and a N heteroatom as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 6 membered heteroaryl has 0, 1 or 2 additional N heteroatoms as ring members, and wherein the 6 membered heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

ii) a 10 membered bicyclic heteroaryl with an attachment point at a carbon atom ring member and a N heteroatom as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 10 membered bicyclic heteroaryl has 0, 1, 2 or 3 additional N heteroatoms as ring members, and wherein the 10 membered bicyclic heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

iii) a 6 membered heteroaryl wherein 1, 2 or 3 ring members are each independently selected from N, O and S, and wherein the 6 membered heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

iv) a 9 or 10 membered bicyclic heteroaryl wherein 1, 2, 3, 4 or 5 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 9 or 10 membered bicyclic heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

v) a 9 or 10 membered bicyclic heterocyclyl with an attachment point at a carbon atom ring member and a $NR^6$ as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 9 or 10 membered heterocyclyl further has 0, 1, 2, 3, or 4 ring members each independently selected from N, $NR^6$, O and S, and wherein the 9 or 10 membered heterocyclyl is unsubstituted, substituted with 1 or 2 oxo, or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo;

vi) a 9 or 10 membered bicyclic heterocyclyl wherein 1, 2, 3, 4 or 5 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 9 or 10 membered bicyclic heterocyclyl is unsubstituted, substituted with 1 or 2 oxo, or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo;

and

vii) a 10 membered bicyclic heterocyclyl with an attachment point at a carbon atom ring member and a carbon atom as a ring member which is substituted with oxo and located at a beta (β) position relative to the attachment point, wherein the 10 membered heterocyclyl further has 1, 2, 3, or 4 ring members each independently selected from N, $NR^6$, O and S, and wherein the 10 membered heterocyclyl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with an oxo;

Ring A is selected from the group consisting of:

i) phenyl;

ii) a 6 membered heteroaryl wherein 1 ring member is selected from N;

and

iii) $C_5$-$C_6$cycloalkenyl;

each $R^4$ is independently selected from the group consisting of $-C(=O)N(R^7)_2$, $-N(R^7)_2$, -CN, $-S(=O)_2R^6$, $-C(=O)NR^7R^6$,  , $C_1$-$C_6$alkyl, and halo;

each $R^5$ is independently selected from the group consisting of $-SF_5$, $C_1$-$C_6$alkyl, $C_1$-$C_6$haloalkyl, halo, $C_1$-$C_6$haloalkoxy, $C_1$-$C_6$alkoxy, $C_3$-$C_8$cycloalkyl, and a $C_1$-$C_6$alkyl substituted with CN or OH, wherein the cycloalkyl is unsubstituted or is substituted with 1 or 2 $R^9$;

each $R^6$ is independently selected from the group consisting of H, $C_1$-$C_6$alkyl or $C_1$-$C_6$alkyl substituted with $-OR^7$;

each $R^7$ is independently selected from the group consisting of H and $C_1$-$C_6$alkyl;

each $R^9$ is independently selected from the group consisting of halo, -C(=O)OH, and $C_1$-$C_6$alkyl substituted with -OH;

$R^{10}$ is H or $C_1$-$C_6$alkyl;

each $R^{12}$ is independently selected from the group consisting of CN, -OH, -C(=O)OH, $-C(=O)OR^{10}$, $-C(=O)N(R^7)_2$, $C_1$-$C_6$alkoxy, $C_1$-$C_6$alkyl, halo, $C_3$-$C_8$cycloalkyl, a 5 membered heteroaryl wherein 4 ring members are each independently selected from N and $NR^6$, and a 3 to 6 membered heterocycloalkyl wherein 1 or 2 ring members are each independently selected from N, $NR^6$ and O, and wherein the cycloalkyl and heterocycloalkyl are unsubstituted or are substituted with 1 or 2 substituents independently selected from the group consisting of CN, halo and -C(=O)OH;

and

n is 1 or 2.

**Embodiment 13.** The compound of any one of Embodiments 1 to 12, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

$X_1$ is $NR^1$, $C(R^{2a})_2$ or O;

$R^1$ is H, $C_1$-$C_6$alkyl, $C_3$-$C_8$cycloalkyl, a $C_1$-$C_6$alkyl substituted with one or more $R^{12}$, a $C_1$-$C_6$alkenyl substituted with one or more $R^{12}$, or a 4 membered heterocycloalkyl wherein 1 ring member is selected from N, $NR^6$ and O; and wherein the cycloalkyl and heterocycloalkyl are unsubstituted or the cycloalkyl and heterocycloalkyl are substituted with 1 substituent selected from the group consisting of CN, -C(=O)OH, $C_1$-$C_6$haloalkyl and $C_1$-$C_6$alkyl substituted with CN;

each $R^{2a}$ is independently selected from the group consisting of H, $NH_2$, $C_1$-$C_6$alkyl and $C_1$-$C_6$alkyl substituted with -C(=O)OH, -OH or CN;

$R^3$ is selected from the group consisting of:

i) $-CHR^{13}R^{14}$;

ii) benzyl which is unsubstituted or is substituted with 1 $R^4$;

iii) a 6 membered heteroaryl wherein 1 ring member is selected from N, and wherein the 6 membered heteroaryl is unsubstituted or is substituted with 1 or 2 $R^4$;

iv) a 10 membered bicyclic heteroaryl with an attachment point at a carbon atom ring member and a N heteroatom as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 10 membered bicyclic heteroaryl has 0, 1, 2 or 3 additional N heteroatoms as ring members, and wherein the 10 membered bicyclic heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

v) a 9 or 10 membered bicyclic heteroaryl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$ and O, and wherein the 9 or 10 membered bicyclic heteroaryl is unsubstituted or is substituted with 1 or 2 $R^4$;

and

vi) a 9 or 10 membered bicyclic heterocyclyl wherein 1 ring member is selected from N, $NR^6$ or O, and wherein the 9 or 10 membered bicyclic heterocyclyl is unsubstituted, or is substituted with an oxo;

each $R^4$ is independently selected from the group consisting of $-C(=O)N(R^7)_2$, $-N(R^7)_2$, -CN, $-S(=O)_2R^6$, $-C(=O)NR^7R^6$,  , $C_1$-$C_6$alkyl and halo;

each $R^5$ is independently selected from the group consisting of $-SF_5$, $C_1$-$C_6$alkyl, $C_1$-$C_6$haloalkyl, halo, $C_1$-$C_6$haloalkoxy, $C_1$-$C_6$alkoxy, $C_3$-$C_8$cycloalkyl, and a $C_1$-$C_6$alkyl substituted with CN or OH, wherein the cycloalkyl is unsubstituted or is substituted with 1 or 2 $R^9$;

each $R^6$ is independently selected from the group consisting of H, $C_1$-$C_6$alkyl or $C_1$-$C_6$alkyl substituted with $-OR^7$ ;

each $R^7$ is independently selected from the group consisting of H and $C_1$-$C_6$alkyl;

each $R^9$ is independently selected from the group consisting of halo, -C(=O)OH, and $C_1$-$C_6$alkyl substituted with -OH;

$R^{10}$ is H or $C_1$-$C_6$alkyl;

each $R^{12}$ is independently selected from the group consisting of CN, -OH, -C(=O)OH, $-C(=O)OR^{10}$, $-C(=O)N(R^7)_2$, $C_1$-$C_6$alkoxy, $C_1$-$C_6$alkyl, halo, $C_3$-$C_8$cycloalkyl, a 5 membered heteroaryl wherein 4 ring members are each independently selected from N and $NR^6$, and a 3 to 6 membered heterocycloalkyl wherein 1 or 2 ring members are each independently selected from N, $NR^6$, and O, and wherein the cycloalkyl, and heterocycloalkyl are unsubstituted or are substituted with 1 or 2 substituents independently selected from the group consisting of CN, halo and -C(=O)OH;

$R^{13}$ is H;

$R^{14}$ is a 6 membered heterocyclyl wherein 1 ring member is selected from N or $NR^6$, and wherein the 6 membered heterocyclyl is substituted with an oxo;

and

n is 0, 1 or 2.

**Embodiment 14.** The compound of any one of Embodiments 1 to 13, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

$X_1$ is $NR^1$;

$R^1$ is H, $C_1$-$C_6$alkyl, $C_3$-$C_8$cycloalkyl, a $C_1$-$C_6$alkyl substituted with one or more $R^{12}$, a $C_1$-$C_6$alkenyl substituted with one or more $R^{12}$, or a 4 membered heterocycloalkyl wherein 1 ring member is selected from N, $NR^6$ and O; and wherein the cycloalkyl and heterocycloalkyl are unsubstituted or the cycloalkyl and heterocycloalkyl are substituted with 1 substituent selected from the group consisting of CN, -C(=O)OH, $C_1$-$C_6$haloalkyl and $C_1$-$C_6$alkyl substituted with CN;

each $R^{2a}$ is independently selected from the group consisting of H, $NH_2$, $C_1$-$C_6$alkyl and $C_1$-$C_6$alkyl substituted with -C(=O)OH, -OH or CN;

$R^3$ is selected from the group consisting of:

i) $-CHR^{13}R^{14}$;

ii) benzyl which is unsubstituted or is substituted with 1 $R^4$;

iii) a 6 membered heteroaryl wherein 1 ring member is selected from N, and wherein the 6 membered heteroaryl is unsubstituted or is substituted with 1 or 2 $R^4$;

iv) a 10 membered bicyclic heteroaryl with an attachment point at a carbon atom ring member and a N heteroatom as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 10 membered bicyclic heteroaryl has 0, 1, 2 or 3 additional N heteroatoms as ring members, and wherein the 10 membered bicyclic heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

v) a 9 or 10 membered bicyclic heteroaryl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$ and O, and wherein the 9 or 10 membered bicyclic heteroaryl is unsubstituted or is substituted with 1 or 2 $R^4$;

and

vi) a 9 or 10 membered bicyclic heterocyclyl wherein 1 ring member is selected from N, $NR^6$ or O, and wherein the 9 or 10 membered bicyclic heterocyclyl is unsubstituted, or is substituted with an oxo;

each $R^4$ is independently selected from the group consisting of $-C(=O)N(R^7)_2$, $-N(R^7)_2$, CN, $-S(=O)_2R^6$, $-C(=O)NR^7R^6$,  , $C_1$-$C_6$alkyl and halo;

each $R^5$ is independently selected from the group consisting of -$SF_5$, $C_1$-$C_6$alkyl, $C_1$-$C_6$haloalkyl, halo, $C_1$-$C_6$haloalkoxy, $C_1$-$C_6$alkoxy, $C_3$-$C_8$cycloalkyl, and a $C_1$-$C_6$alkyl substituted with CN or OH, wherein the cycloalkyl is unsubstituted or is substituted with 1 or 2 $R^9$;

each $R^6$ is independently selected from the group consisting of H, $C_1$-$C_6$alkyl or $C_1$-$C_6$alkyl substituted with -$OR^7$ ;

each $R^7$ is independently selected from the group consisting of H and $C_1$-$C_6$alkyl;

each $R^9$ is independently selected from the group consisting of halo, -C(=O)OH, and $C_1$-$C_6$alkyl substituted with -OH;

$R^{10}$ is H or $C_1$-$C_6$alkyl;

each $R^{12}$ is independently selected from the group consisting of CN, -OH, -C(=O)OH, -C(=O)$OR^{10}$, -C(=O)N($R^7$)$_2$, $C_1$-$C_6$alkoxy, $C_1$-$C_6$alkyl, halo, $C_3$-$C_8$cycloalkyl, a 5 membered heteroaryl wherein 4 ring members are each independently selected from N and $NR^6$, and a 3 to 6 membered heterocycloalkyl wherein 1 or 2 ring members are each independently selected from N, $NR^6$, and O, and wherein the cycloalkyl, and heterocycloalkyl are unsubstituted or are substituted with 1 or 2 substituents independently selected from the group consisting of CN, halo and -C(=O)OH;

$R^{13}$ is H;

$R^{14}$ is a 6 membered heterocyclyl wherein 1 ring member is selected from N or $NR^6$, and wherein the 6 membered heterocyclyl is substituted with an oxo;

and

n is 0, 1 or 2.

**Embodiment 15.** The compound of any one of Embodiments 1 to 14, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

$X_1$ is $NR^1$;

$R^1$ is H, $C_1$-$C_6$alkyl, $C_3$-$C_8$cycloalkyl, a $C_1$-$C_6$alkyl substituted with one or more $R^{12}$, a $C_1$-$C_6$alkenyl substituted with one or more $R^{12}$, or a 4 membered heterocycloalkyl wherein 1 ring member is selected from N, $NR^6$ and O; and wherein the cycloalkyl and heterocycloalkyl are unsubstituted or the cycloalkyl and heterocycloalkyl are substituted with 1 substituent selected from the group consisting of CN, -C(=O)OH, $C_1$-$C_6$haloalkyl and $C_1$-$C_6$alkyl substituted with CN;

$R^3$ is selected from the group consisting of:

i) a 6 membered heteroaryl wherein 1 ring member is selected from N, and wherein the 6 membered heteroaryl is unsubstituted or is substituted with 1 or 2 $R^4$;

ii) a 10 membered bicyclic heteroaryl with an attachment point at a carbon atom ring member and a N heteroatom as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 10 membered

bicyclic heteroaryl has 0, 1, 2 or 3 additional N heteroatoms as ring members, and wherein the 10 membered bicyclic heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

iii) a 9 or 10 membered bicyclic heteroaryl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$ and O, and wherein the 9 or 10 membered bicyclic heteroaryl is unsubstituted or is substituted with 1 or 2 $R^4$;

and

iv) a 9 or 10 membered bicyclic heterocyclyl wherein 1 ring member is selected from N, $NR^6$ or O, and wherein the 9 or 10 membered bicyclic heterocyclyl is unsubstituted, or is substituted with an oxo;

each $R^4$ is independently selected from the group consisting of $-C(=O)N(R^7)_2$, $-N(R^7)_2$, -CN, $-S(=O)_2R^6$, $-C(=O)NR^7R^6$,  , $C_1$-$C_6$alkyl and halo;

each $R^5$ is independently selected from the group consisting of $-SF_5$, $C_1$-$C_6$alkyl, $C_1$-$C_6$haloalkyl, halo, $C_1$-$C_6$haloalkoxy, $C_1$-$C_6$alkoxy, $C_3$-$C_8$cycloalkyl, and a $C_1$-$C_6$alkyl substituted with CN or OH, wherein the cycloalkyl is unsubstituted or is substituted with 1 or 2 $R^9$;

each $R^6$ is independently selected from the group consisting of H, $C_1$-$C_6$alkyl or $C_1$-$C_6$alkyl substituted with $-OR^7$ ;

each $R^7$ is independently selected from the group consisting of H and $C_1$-$C_6$alkyl;

each $R^9$ is independently selected from the group consisting of halo, -C(=O)OH, and $C_1$-$C_6$alkyl substituted with -OH;

$R^{10}$ is H or $C_1$-$C_6$alkyl;

each $R^{12}$ is independently selected from the group consisting of CN, -OH, -C(=O)OH, $-C(=O)OR^{10}$, $-C(=O)N(R^7)_2$, $C_1$-$C_6$alkoxy, $C_1$-$C_6$alkyl, halo, $C_3$-$C_8$cycloalkyl, a 5 membered heteroaryl wherein 4 ring members are each independently selected from N and $NR^6$, and a 3 to 6 membered heterocycloalkyl wherein 1 or 2 ring members are each independently selected from N, $NR^6$, and O, and wherein the cycloalkyl, and heterocycloalkyl are unsubstituted or are substituted with 1 or 2 substituents independently selected from the group consisting of CN, halo and -C(=O)OH;

and

n is 0, 1 or 2.

**Embodiment 16.** The compound of any one of Embodiments 1 to 15, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

$X_1$ is $NR^1$;

$R^1$ is H or $C_1$-$C_6$alkyl substituted with one or more $R^{12}$;

$R^3$ is selected from the group consisting of:

i) $-CHR^{13}R^{14}$;

ii) benzyl which is unsubstituted or is substituted with 1 $R^4$;

iii) a 6 membered heteroaryl wherein 1 ring member is selected from N, and wherein the 6 membered heteroaryl is unsubstituted or is substituted with 1 or 2 $R^4$;

iv) a 10 membered bicyclic heteroaryl with an attachment point at a carbon atom ring member and a N heteroatom as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 10 membered bicyclic heteroaryl has 0, 1, 2 or 3 additional N heteroatoms as ring members, and wherein the 10 membered bicyclic heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

v) a 9 or 10 membered bicyclic heteroaryl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$ and O, and wherein the 9 or 10 membered bicyclic heteroaryl is unsubstituted or is substituted with 1 or 2 $R^4$;

vi) a 6 membered heterocyclyl wherein 1 ring member is selected from $NR^6$, and wherein the 6 membered heterocyclyl is substituted with an oxo;

and

vii) a 9 or 10 membered bicyclic heterocyclyl wherein 1 ring member is selected from N, $NR^6$ or O, and wherein the 9 or 10 membered bicyclic heterocyclyl is unsubstituted, or is substituted with an oxo;

each $R^4$ is independently selected from the group consisting of $-C(=O)N(R^7)_2$, -C(=O)OH, $-N(R^7)_2$, -CN, -OH,  , $C_1$-$C_6$alkyl, halo, 6 membered heterocycloalkyl wherein 1 or 2 ring members are each independently selected from N and $NR^6$, and $C_1$-$C_6$alkyl substituted with $NH_2$, and wherein the heterocycloalkyl is unsubstituted;

each $R^5$ is independently selected from the group consisting of -NR6C(=O)C2-C6alkenyl, $-SF_5$, $C_1$-$C_6$alkyl, $C_1$-$C_6$haloalkyl, halo, $C_1$-$C_6$haloalkoxy, $C_1$-$C_6$alkoxy, $C_3$-$C_8$cycloalkyl, wherein the cycloalkyl is unsubstituted or is substituted with 1 $R^9$;

each $R^6$ is independently selected from the group consisting of H or $C_1$-$C_6$alkyl;

each $R^7$ is independently selected from the group consisting of H and $C_1$-$C_6$alkyl;

each $R^9$ is independently selected from the group consisting of $C_1$-$C_6$alkyl substituted with -OH;

$R^{10}$ is H or $C_1$-$C_6$alkyl;

each $R^{12}$ is independently selected from the group consisting of CN, -OH, -C(=O)OH, $-C(=O)N(R^7)_2$, $C_1$-$C_6$alkoxy, halo, $C_1$-$C_6$haloalkyl, $C_3$-$C_8$cycloalkyl, a 5 membered heteroaryl wherein 4 ring members are each independently selected from N and $NR^6$, and a 3 membered heterocycloalkyl wherein 1 ring member is selected from N,

$NR^6$ and O, and wherein the cycloalkyl, heteroaryl and heterocycloalkyl are unsubstituted or are substituted with 1 substituent from the group consisting of CN and -C(=O)OH;

$R^{13}$ is H;

$R^{14}$ is a 6 membered heterocycle wherein 1 ring member is selected from N or $NR^6$, and wherein the 6 membered heterocycle is substituted with an oxo; and

n is 0, 1 or 2.

**Embodiment 17.** The compound of any one of Embodiments 1 to 16, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

$R^1$ is H or $C_1$-$C_6$alkyl substituted with one or more $R^{12}$;

$R^3$ is selected from the group consisting of:

i) a 9 or 10 membered bicyclic heteroaryl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$ and O, wherein the 9 or 10 membered bicyclic heteroaryl is unsubstituted or is substituted with 1 or 2 $R^4$; and

ii) a 10 membered bicyclic heteroaryl with an attachment point at a carbon atom ring member and a N heteroatom as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 10 membered bicyclic heteroaryl has 0, 1, 2 or 3 additional N heteroatoms as ring members, and wherein the 10 membered bicyclic heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

each $R^4$ is independently selected from the group consisting of -C(=O)N($R^7$)$_2$, -C(=O)OH, -N($R^7$)$_2$, -CN, -OH,  , $C_1$-$C_6$alkyl, halo, 6 membered heterocycloalkyl wherein 1 or 2 ring members are each independently selected from N and $NR^6$, and $C_1$-$C_6$alkyl substituted with $NH_2$, and wherein the heterocycloalkyl is unsubstituted;

each $R^5$ is independently selected from the group consisting of -NR6C(=O)C2-C6alkenyl, -$SF_5$, $C_1$-$C_6$alkyl, $C_1$-$C_6$haloalkyl, halo, $C_1$-$C_6$haloalkoxy, $C_1$-$C_6$alkoxy, $C_3$-$C_8$cycloalkyl, wherein the cycloalkyl is unsubstituted or is substituted with 1 $R^9$;

each $R^6$ is independently selected from the group consisting of H or $C_1$-$C_6$alkyl;

each $R^7$ is independently selected from the group consisting of H and $C_1$-$C_6$alkyl;

each $R^9$ is independently selected from the group consisting of $C_1$-$C_6$alkyl substituted with -OH;

$R^{10}$ is H or $C_1$-$C_6$alkyl;

and

each $R^{12}$ is independently selected from the group consisting of CN, -OH, -C(=O)OH, -C(=O)N($R^7$)$_2$, $C_1$-$C_6$alkoxy, halo, $C_1$-$C_6$haloalkyl, $C_3$-$C_8$cycloalkyl, a 5 membered

heteroaryl wherein 4 ring members are each independently selected from N and $NR^6$, and a 3 membered heterocycloalkyl wherein 1 ring member is selected from N, $NR^6$ and O, and wherein the cycloalkyl, heteroaryl and heterocycloalkyl are unsubstituted or are substituted with 1 substituent selected from the group consisting of CN and -C(=O)OH.

**Embodiment 18.** The compound of any one of Embodiments 1 to 17, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

$R^1$ is H or $C_1$-$C_6$alkyl substituted with one or more $R^{12}$;

$R^3$ is a 9 or 10 membered bicyclic heteroaryl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$ and O, wherein the 9 or 10 membered bicyclic heteroaryl is unsubstituted or is substituted with 1 or 2 $R^4$;

each $R^4$ is independently selected from the group consisting of -C(=O)N($R^7$)$_2$, -C(=O)OH, -N($R^7$)$_2$, -CN, -OH,  , $C_1$-$C_6$alkyl, halo, 6 membered heterocycloalkyl wherein 1 or 2 ring members are each independently selected from N and $NR^6$, and $C_1$-$C_6$alkyl substituted with $NH_2$, and wherein the heterocycloalkyl is unsubstituted;

each $R^5$ is independently selected from the group consisting of -NR6C(=O)C2-C6alkenyl, -$SF_5$, $C_1$-$C_6$alkyl, $C_1$-$C_6$haloalkyl, halo, $C_1$-$C_6$haloalkoxy, $C_1$-$C_6$alkoxy, $C_3$-$C_8$cycloalkyl, wherein the cycloalkyl is unsubstituted or is substituted with 1 $R^9$;

each $R^6$ is independently selected from the group consisting of H or $C_1$-$C_6$alkyl;

each $R^7$ is independently selected from the group consisting of H and $C_1$-$C_6$alkyl;

each $R^9$ is independently selected from the group consisting of $C_1$-$C_6$alkyl substituted with -OH;

and

$R^{10}$ is H or $C_1$-$C_6$alkyl;

each $R^{12}$ is independently selected from the group consisting of CN, -OH, -C(=O)OH, -C(=O)N($R^7$)$_2$, $C_1$-$C_6$alkoxy, halo, $C_1$-$C_6$haloalkyl, $C_3$-$C_8$cycloalkyl, a 5 membered heteroaryl wherein 4 ring members are each independently selected from N and $NR^6$, and a 3 membered heterocycloalkyl wherein 1 ring member is selected from N, $NR^6$ and O, and wherein the cycloalkyl, heteroaryl and heterocycloalkyl are unsubstituted or are substituted with 1 substituent selected from the group consisting of CN and -C(=O)OH.

**Embodiment 19.** The compound of any one of Embodiments 1 to 18, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

$X_1$ is $NR^1$, $C(R^{2a})_2$ or O;

$R^1$ is H, methyl, ethyl, isopropyl,-$CH_2R^{12}$, -$CH_2CH_2R^{12}$, -$CH_2CR^{12}$=$CH_2$, -$CH_2CHR^{12}CH_3$, -$CH_2CH$=$CHR^{12}$, -$CH_2CH_2CH(CH_3)R^{12}$, -$CH(CH_3)CH_2CH_2R^{12}$, -$CH_2CH_2C(CH_3)_2R^{12}$, a

cyclopropyl which is unsubstituted, or a cyclopropyl which is substituted with -$CH_2CN$;

each $R^{2a}$ is independently selected from the group consisting of H and -$CH_3$;

$R^3$ is selected from the group consisting of:

i) pyridyl substituted with 1 or 2 $R^4$;

ii) isoquinolin-4-yl which is unsubstituted or is substituted with 1 or 2 $R^4$; and

iii) 5,6,7,8-tetrahydroisoquinolin-4-yl which is unsubstituted;

each $R^4$ is independently selected from the group consisting of -$CH_3$, -$C(=O)N(R^7)_2$, -$N(R^7)_2$, F, Br, -CN, -$S(=O)_2R^6$, -$C(=O)NR^7R^6$, and  ,

each $R^5$ is independently selected from the group consisting of F, Br, Cl, -$CF_3$, -$CHF_2$, -$CH_2F$, -$C(CH_3)F_2$, -$CH_3$, isopropyl, -$OCHF_2$, -$OCClF_2$, -$OCF_3$, -$OCH_3$, $SF_5$, -$C(CH_3)_2OH$, -$CH_2CF_3$, -$CH(CH_3)CF_3$, an unsubstituted cyclopropyl, a cyclopropyl substituted with 1 $R^9$, and a cyclobutyl substituted with 1 or 2 $R^9$;

each $R^6$ is independently selected from the group consisting of H, -$CH_3$, and -$CH_2CH_2OR^7$;

each $R^7$ is independently selected from the group consisting of H and -$CH_3$;

each $R^9$ is independently selected from the group consisting of F, -C(=O)OH, and -$CH_2OH$;

$R^{10}$ is H or -$CH_3$;

each $R^{12}$ is independently selected from the group consisting of CN, -$CH_3$, -$OCH_3$, -OH, -F, -$C(=O)OR^{10}$, -C(=O)OH, -$C(=O)N(R^7)_2$, an unsubstituted morpholinyl, an unsubstituted tetrazolyl, an unsubstituted oxiranyl, a piperidinyl which is unsubstituted or substituted with 1 or 2 fluoro, an unsubstituted cyclopropyl or a cyclopropyl substituted with CN or -C(=O)OH;

and

n is 0, 1 or 2.

**Embodiment 20.** The compound of any one of Embodiments 1 to 19, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

$X_1$ is $NR^1$;

$R^1$ is H, methyl, ethyl, isopropyl,-$CH_2R^{12}$, -$CH_2CH_2R^{12}$, -$CH_2CR^{12}=CH_2$, -$CH_2CHR^{12}CH_3$, -$CH_2CH=CHR^{12}$, -$CH_2CH_2CH(CH_3)R^{12}$, -$CH(CH_3)CH_2CH_2R^{12}$, -$CH_2CH_2C(CH_3)_2R^{12}$, a cyclopropyl which is unsubstituted, or a cyclopropyl which is substituted with -$CH_2CN$;

$R^3$ is selected from the group consisting of:

i) pyridyl substituted with 1 or 2 $R^4$;

ii) isoquinolin-4-yl which is unsubstituted or is substituted with 1 or 2 $R^4$;

and

iii) 5,6,7,8-tetrahydroisoquinolin-4-yl which is unsubstituted;

each $R^4$ is independently selected from the group consisting of $-CH_3$, $-C(=O)N(R^7)_2$, $-N(R^7)_2$, F, Br, -CN, $-S(=O)_2R^6$, $-C(=O)NR^7R^6$, and  ,

each $R^5$ is independently selected from the group consisting of F, Br, Cl, $-CF_3$, $-CHF_2$, $-CH_2F$, $-C(CH_3)F_2$, $-CH_3$, isopropyl, $-OCHF_2$, $-OCClF_2$, $-OCF_3$, $-OCH_3$, $SF_5$, $-C(CH_3)_2OH$, $-CH_2CF_3$, $-CH(CH_3)CF_3$, an unsubstituted cyclopropyl, a cyclopropyl substituted with 1 $R^9$, and a cyclobutyl substituted with 1 or 2 $R^9$;

each $R^6$ is independently selected from the group consisting of H, $-CH_3$, and $-CH_2CH_2OR^7$;

each $R^7$ is independently selected from the group consisting of H and $-CH_3$;

each $R^9$ is independently selected from the group consisting of F, -C(=O)OH, and $-CH_2OH$;

$R^{10}$ is H or $-CH_3$;

each $R^{12}$ is independently selected from the group consisting of CN, $-CH_3$, $-OCH_3$, -OH, -F, $-C(=O)OR^{10}$, -C(=O)OH, $-C(=O)N(R^7)_2$, an unsubstituted morpholinyl, an unsubstituted tetrazolyl, an unsubstituted oxiranyl, a piperidinyl which is unsubstituted or substituted with 1 or 2 fluoro, an unsubstituted cyclopropyl or a cyclopropyl substituted with CN or -C(=O)OH;

and

n is 0, 1 or 2.

**Embodiment 21.** The compound of any one of Embodiments 1 to 20, or a pharmaceutically acceptable salt or stereoisomer thereof stereoisomer thereof, wherein,

$X_1$ is $NR^1$;

$R^1$ is H, methyl, ethyl, isopropyl,$-CH_2R^{12}$, $-CH_2CH_2R^{12}$, $-CH_2CR^{12}=CH_2$, $-CH_2CHR^{12}CH_3$, $-CH_2CH=CHR^{12}$, $-CH_2CH_2CH(CH_3)R^{12}$, $-CH(CH_3)CH_2CH_2R^{12}$, $-CH_2CH_2C(CH_3)_2R^{12}$, a cyclopropyl which is unsubstituted, or a cyclopropyl which is substituted with $-CH_2CN$;

$R^3$ is isoquinolin-4-yl which is unsubstituted or is substituted with 1 or 2 $R^4$;

each $R^4$ is independently selected from the group consisting of $-CH_3$, $-C(=O)N(R^7)_2$, - -$N(R^7)_2$, F, Br, -CN, $-S(=O)_2R^6$, $-C(=O)NR^7R^6$, and  ,

each $R^5$ is independently selected from the group consisting of F, Br, Cl, $-CF_3$, $-CHF_2$, $-CH_2F$, $-C(CH_3)F_2$, $-CH_3$, isopropyl, $-OCHF_2$, $-OCClF_2$, $-OCF_3$, $-OCH_3$, $SF_5$, -

$C(CH_3)_2OH$, $-CH_2CF_3$, $-CH(CH_3)CF_3$, an unsubstituted cyclopropyl, a cyclopropyl substituted with 1 $R^9$, and a cyclobutyl substituted with 1 or 2 $R^9$;

each $R^6$ is independently selected from the group consisting of H, $-CH_3$, and $-CH_2CH_2OR^7$;

each $R^7$ is independently selected from the group consisting of H and $-CH_3$;

each $R^9$ is independently selected from the group consisting of F, -C(=O)OH, and $-CH_2OH$;

$R^{10}$ is H or $-CH_3$;

each $R^{12}$ is independently selected from the group consisting of CN, $-CH_3$, $-OCH_3$, -OH, F, $-C(=O)OR^{10}$, -C(=O)OH, $-C(=O)N(R^7)_2$, an unsubstituted morpholinyl, an unsubstituted tetrazolyl, an unsubstituted oxiranyl, a piperidinyl which is unsubstituted or substituted with 1 or 2 fluoro, an unsubstituted cyclopropyl or a cyclopropyl substituted with CN or -C(=O)OH;

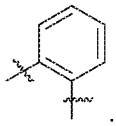
and

n is 0, 1 or 2.

**Embodiment 22.** The compound of any one of Embodiments 1 to 21, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein the dashed line between $X_1$ and $X_2$ is a single bond.

**Embodiment 23.** The compound of any one of Embodiments 1 to 21, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein the dashed line between $X_1$ and $X_2$ is a double bond.

**Embodiment 24.** The compound of any one of Embodiments 1 to 23, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein Ring A is phenyl.

**Embodiment 25.** The compound of any one of Embodiments 1 to 23, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein Ring A is  .

**Embodiment 26.** The compound of any one of Embodiments 1 to 23, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein Ring A is a 5 or 6 membered heteroaryl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S.

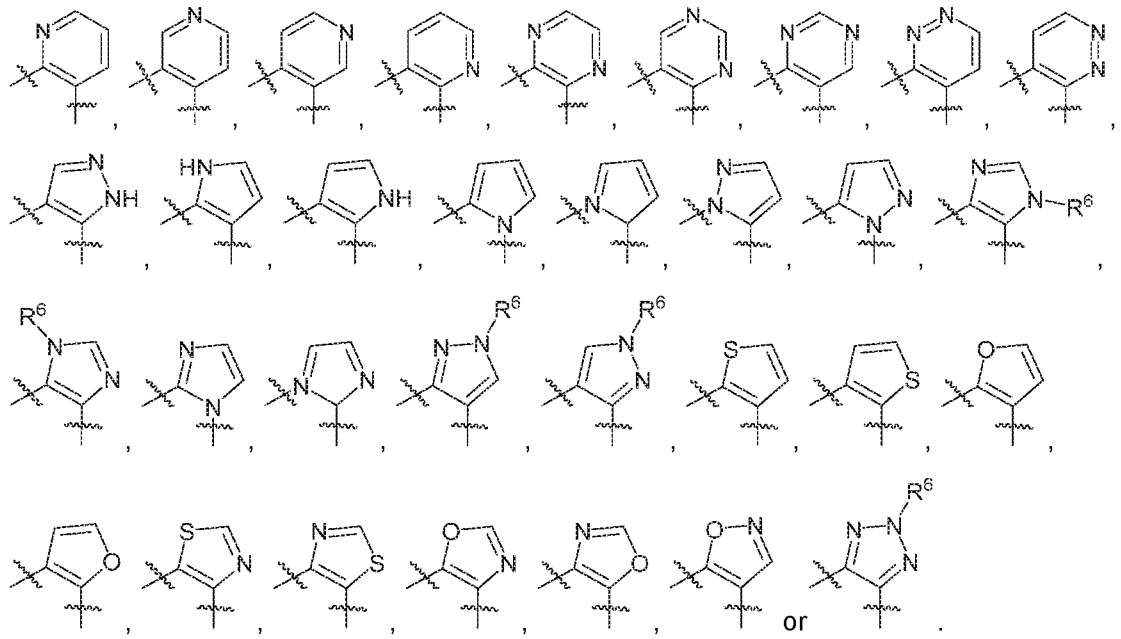
**Embodiment 27.** The compound of any one of Embodiments 1 to 23, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein Ring A is a 5 or 6 membered heteroaryl wherein 1 or 2 ring members are each independently selected from N, $NR^6$, O and S.

**Embodiment 28.** The compound of any one of Embodiments 1 to 23 or a pharmaceutically acceptable salt or stereoisomer thereof, wherein Ring A is a 5 or 6 membered heteroaryl wherein 1 ring member is selected from N, $NR^6$, O and S.

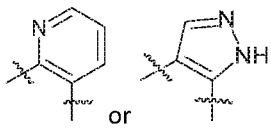
**Embodiment 29.** The compound of any one of Embodiments 1 to 23, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein Ring A is pyridyl,

pyrazinyl, pyrimidinyl, pyridazinyl, pyrazolyl, pyrrolyl, imidazolyl, thienyl, furyl, thiazolyl, oxazolyl, isoxazolyl or triazolyl.

**Embodiment 30.** The compound of any one of Embodiments 1 to 23, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein Ring A is

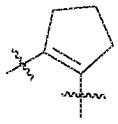


**Embodiment 31.** The compound of any one of Embodiments 1 to 23, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein Ring A is pyridyl or pyrazolyl.

**Embodiment 32.** The compound of any one of Embodiments 1 to 23, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein Ring A is  or .

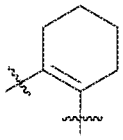
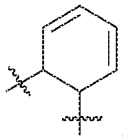
**Embodiment 33.** The compound of any one of Embodiments 1 to 23, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein Ring A is $C_5$cycloalkenyl.

**Embodiment 34.** The compound of any one of Embodiments 1 to 23, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein Ring A is cyclopent-1-enyl or cyclopenta-1,3-dienyl.

**Embodiment 35.** The compound of any one of Embodiments 1 to 23, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein Ring A is  .

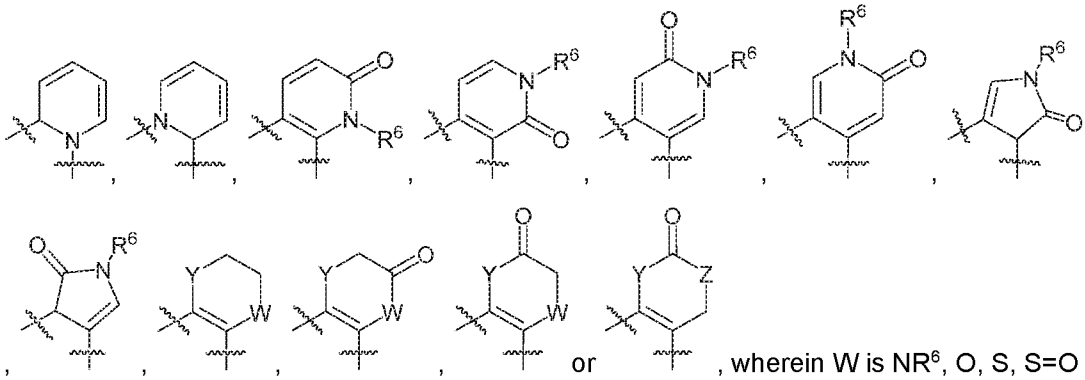
**Embodiment 36.** The compound of any one of Embodiments 1 to 23, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein Ring A is $C_6$cycloalkenyl.

**Embodiment 37.** The compound of any one of Embodiments 1 to 23, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein Ring A is cyclohex-1-enyl or cyclohexa-1,3-dienyl.

**Embodiment 38.** The compound of any one of Embodiments 1 to 23, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein Ring A is  or  .

**Embodiment 39.** The compound of any one of Embodiments 1 to 23, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein Ring A is a 5 or 6 membered heterocyclyl wherein 1, 2 or 3 ring members are each independently selected from W, Y and Z, wherein W is $X_2$, $NR^6$, O, S, S=O or $S(=O)_2$, $X_2$ is N; Y is $NR^6$, O, S, S=O or $S(=O)_2$ and Z is $NR^6$, O or S, and wherein the 5 or 6 membered heterocyclyl is optionally substituted with oxo.

**Embodiment 40.** The compound of any one of Embodiments 1 to 23, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein Ring A is 1,2-dihydropyridinyl, pyridinyl-2(1H)-one, 2,3-dihydro-1H-pyrrolyl or 1,3-dihydro-2H-pyrrolyl-2-one.

**Embodiment 41.** The compound of any one of Embodiments 1 to 23, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein Ring A is  or , wherein W is $NR^6$, O, S, S=O or $S(=O)_2$, Y is $NR^6$, O, S, S=O or $S(=O)_2$ and Z is $NR^6$, O or S.

**Embodiment 42.** The compound of any one of Embodiments 1 to 23, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein Ring A is a 9 or 10 membered bicyclic heterocyclyl wherein 1, 2, 3, 4 or 5 ring members are each independently selected from N, $NR^6$, O and S.

**Embodiment 43.** The compound of any one of Embodiments 1 to 23, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein Ring A is a 9 or 10 membered bicyclic heterocyclyl wherein 1 ring member is selected from N, $NR^6$, O and S.

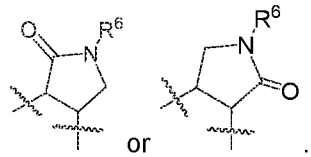
**Embodiment 44.** The compound of any one of Embodiments 1 to 23, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein Ring A is a 9 or 10 membered bicyclic heterocyclyl wherein 1 ring member is selected from $NR^6$.

**Embodiment 45.** The compound of any one of Embodiments 1 to 23, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein Ring A is a 5 or 6 membered heterocycloalkyl wherein 1, 2, 3 or 4 ring members are each independently selected from

N, $NR^6$, O and S, and wherein the 5 or 6 membered heterocycloalkyl is optionally substituted with oxo.

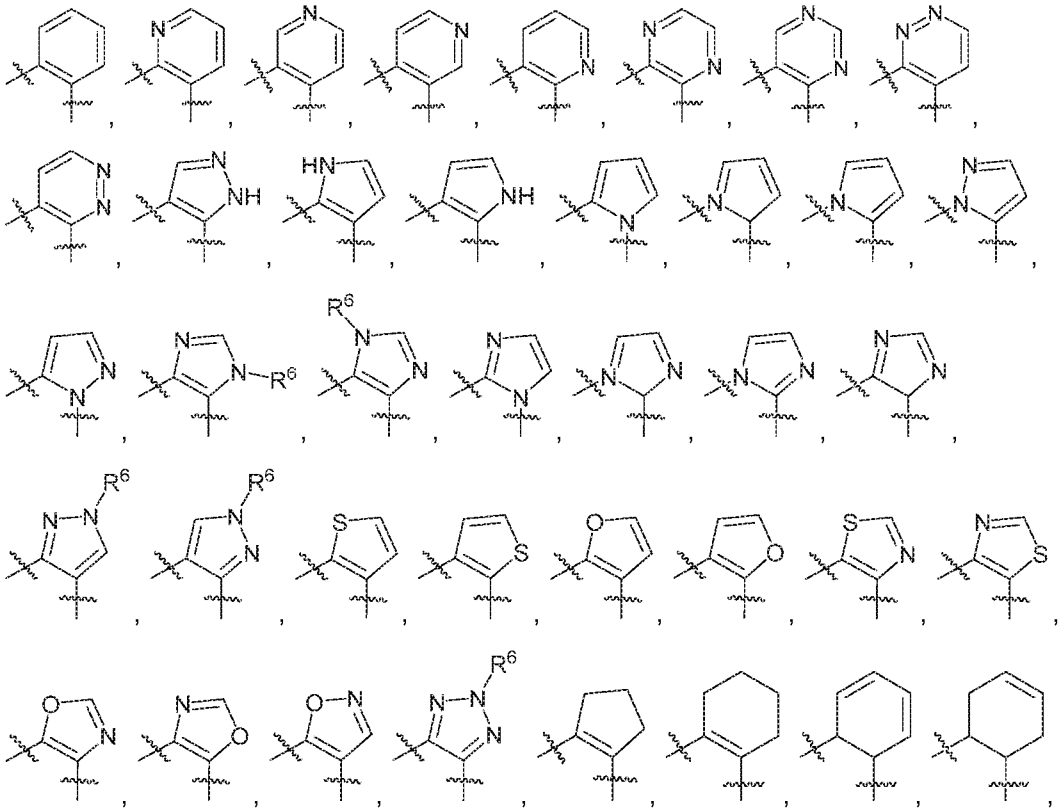
**Embodiment 46.** The compound of any one of Embodiments 1 to 23, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein Ring A is pyrrolidinyl-2-one.

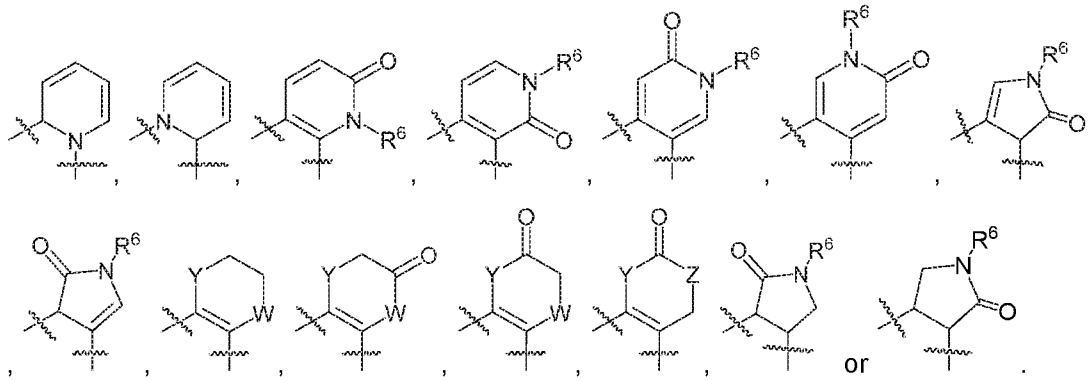
**Embodiment 47.** The compound of any one of Embodiments 1 to 23, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein Ring A is

 or .

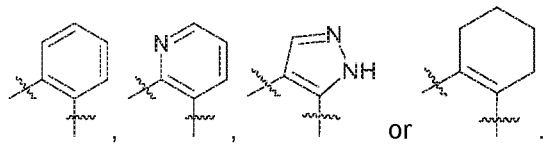
**Embodiment 48.** The compound of any one of Embodiments 1 to 23, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein Ring A is a 9 or 10 membered bicyclic heteroaryl wherein 1, 2, 3, 4 or 5 ring members are each independently selected from N, O and S.

**Embodiment 49.** The compound of any one of Embodiments 1 to 23, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein Ring A is

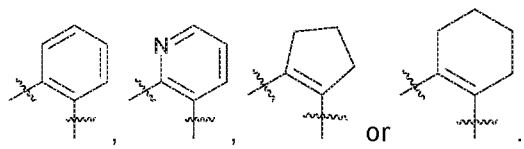




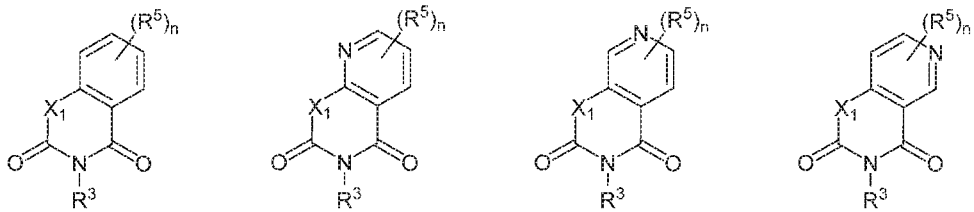
**Embodiment 50.** The compound of any one of Embodiments 1 to 23, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein Ring A is



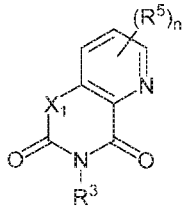
**Embodiment 51.** The compound of any one of Embodiments 1 to 23, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein Ring A is



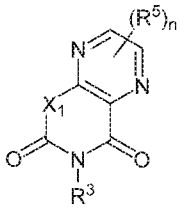
**Embodiment 52.** The compound of any one of Embodiments 1 to 51, or a pharmaceutically acceptable salt or stereoisomer thereof, selected from a compound having the structure of the following sub-formulae (Formula (I-a), Formula (I-b), Formula (I-c), Formula (I-d), Formula (I-e), Formula (I-f), Formula (I-g), Formula (I-h), Formula (I-i), Formula (I-j), Formula (I-k), Formula (I-l), Formula (I-m), Formula (I-n), Formula (I-o), Formula (I-p), Formula (I-q), Formula (I-r), Formula (I-s), Formula (I-t), Formula (I-u), Formula (I-v), Formula (I-w), Formula (I-x), Formula (I-y), Formula (I-z), Formula (I-aa), Formula (I-ab), Formula (I-ac), Formula (I-ad), Formula (I-ae), Formula (I-af), Formula (I-ag), Formula (I-ah), Formula (I-ai), Formula (I-aj), Formula (I-ak), Formula (I-al), Formula (I-am), Formula (I-an), Formula (I-ao), Formula (I-ap), Formula (I-aq), Formula (I-ar), Formula (I-as), Formula (I-at), Formula (I-au), Formula (I-av), Formula (I-aw) and Formula (I-ax):



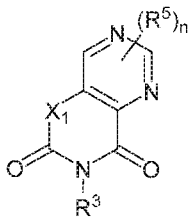
(I-a) (I-b) (I-c) (I-d)



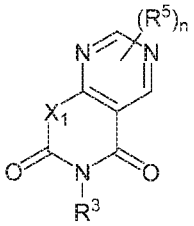
(I-e)



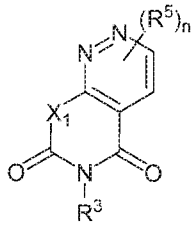
(I-f)



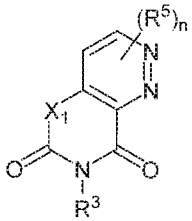
(I-g)



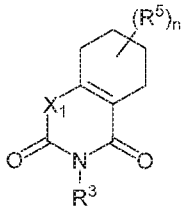
(I-h)



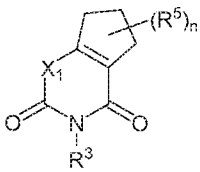
(I-i)



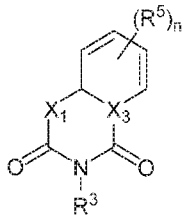
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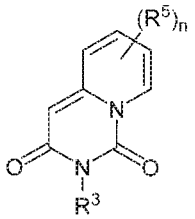
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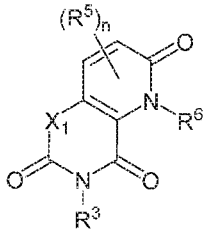
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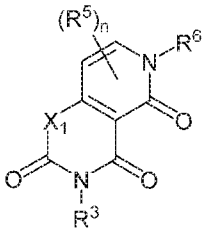
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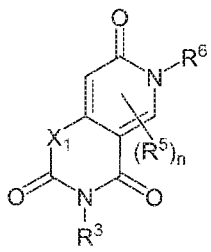
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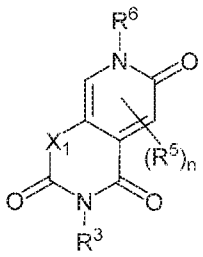
(I-o)



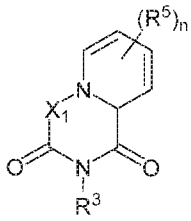
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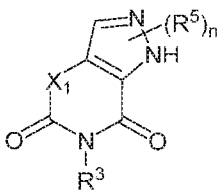
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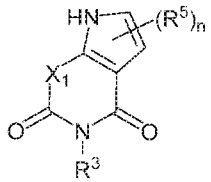
(I-r)



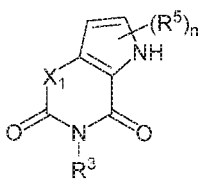
(I-s)



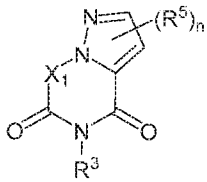
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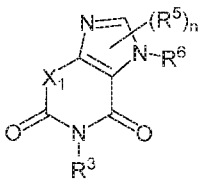
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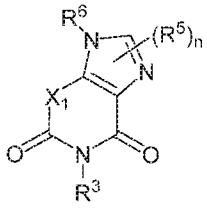
(I-v)



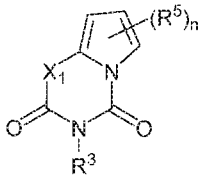
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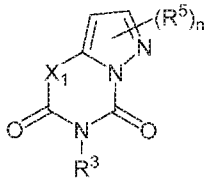
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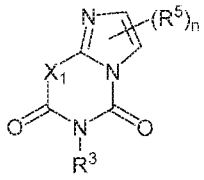
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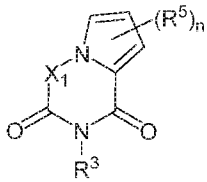
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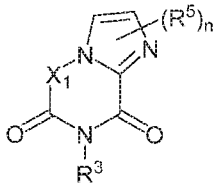
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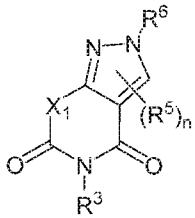
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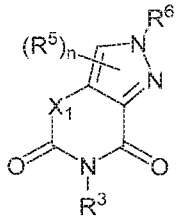
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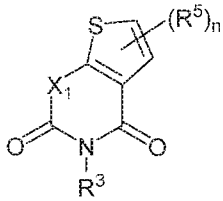
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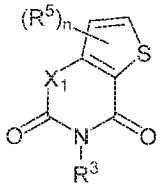
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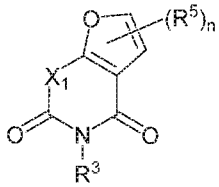
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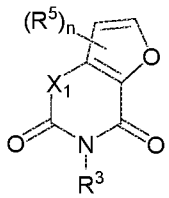
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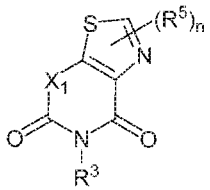
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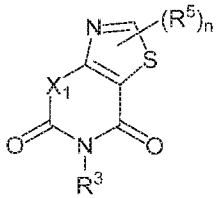
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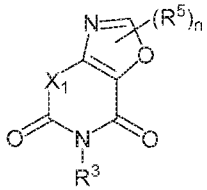
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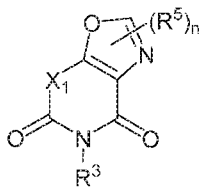
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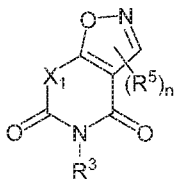
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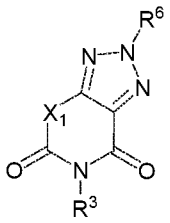
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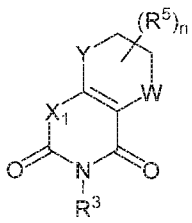
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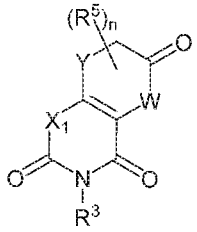
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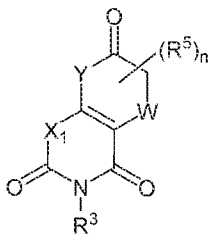
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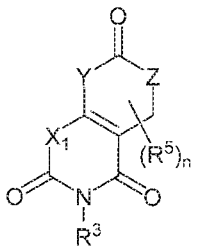
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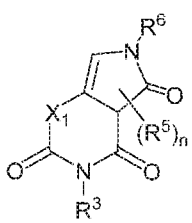
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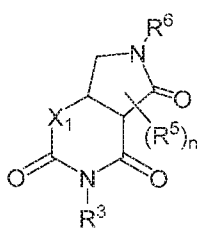
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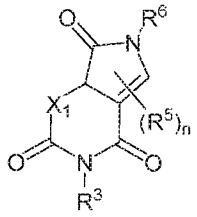
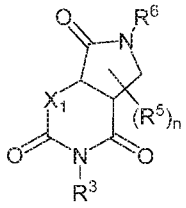
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(I-au)

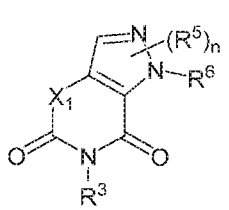
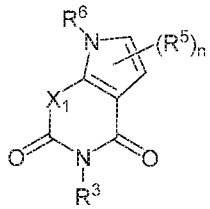
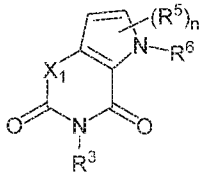


(I-av)


and


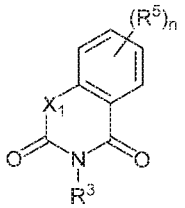
(I-aw) (I-ax).

**Embodiment 53.** The compound of any one of Embodiments 1 to 51, or a pharmaceutically acceptable salt or stereoisomer thereof, selected from a compound having the structure of the following sub-formulae: Formula (I-aaa), Formula (I-aab) and Formula (I-aac)):



and


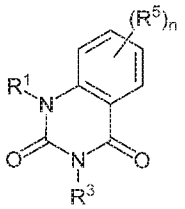
(I-aaa) (I-aab) (I-aac).

**Embodiment 54.** The compound of any one of Embodiments 1 to 52, or a pharmaceutically acceptable salt or stereoisomer thereof, selected from a compound having the structure of Formula (I-a),



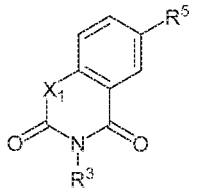
(I-a).

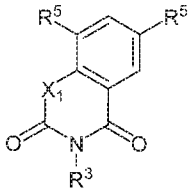
**Embodiment 55.** The compound of any one of Embodiments 1 to 51, or a pharmaceutically acceptable salt or stereoisomer thereof, selected from a compound having the structure of Formula (I-ay),

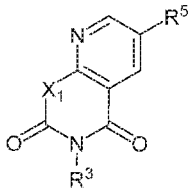


(I-ay).

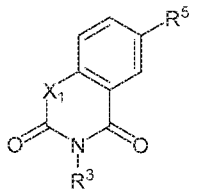
**Embodiment 56.** The compound of any one of Embodiments 1 to 51, or a pharmaceutically acceptable salt or stereoisomer thereof, selected from a compound having the structure of Formula (I-az), Formula (I-ba) or Formula (I-bb), or a pharmaceutically acceptable salt or stereoisomer thereof,

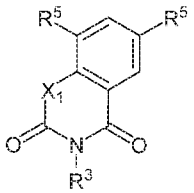

(I-az)

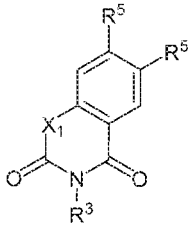

(I-ba)

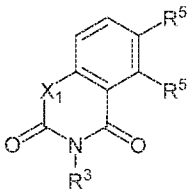

(I-bb).

**Embodiment 57.** The compound of any one of Embodiments 1 to 51, or a pharmaceutically acceptable salt or stereoisomer thereof, selected from a compound having the structure of Formula (I-az), Formula (I-ba), Formula (I-bc) or Formula (I-bd), or a pharmaceutically acceptable salt or stereoisomer thereof,

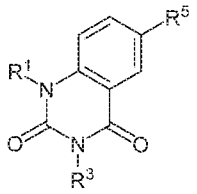

(I-az)

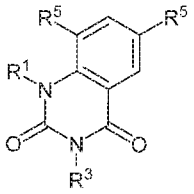

(I-ba)

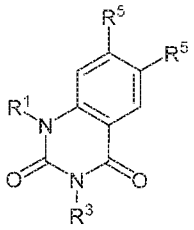

(I-bc)

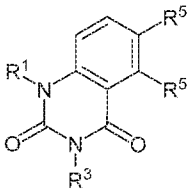

(I-bd).

**Embodiment 58.** The compound of any one of Embodiments 1 to 51, or a pharmaceutically acceptable salt or stereoisomer thereof, selected from a compound having the structure of Formula (I-be), Formula (I-bf), Formula (I-bg) or Formula (I-bh), or a pharmaceutically acceptable salt or stereoisomer thereof,

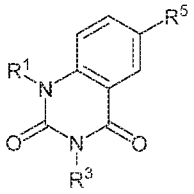

(I-be)


(I-bf)


(I-bg)

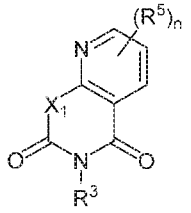

(I-bh).

**Embodiment 59.** The compound of any one of Embodiments 1 to 51, or a pharmaceutically acceptable salt or stereoisomer thereof, selected from a compound having the structure of the Formula (I-be), or a pharmaceutically acceptable salt or stereoisomer thereof,

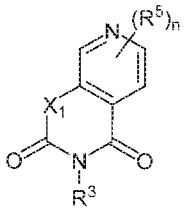

(I-be).

**Embodiment 60.** The compound of any one of Embodiments 1 to 51, or a pharmaceutically acceptable salt or stereoisomer thereof, selected from a compound having the structure of

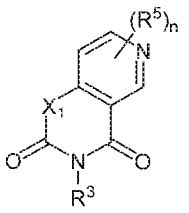
Formula (I-b), Formula (I-c) or Formula (I-e), or a pharmaceutically acceptable salt or stereoisomer thereof,



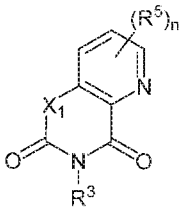
(I-b)



(I-c)

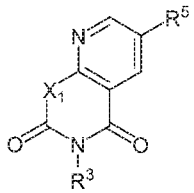


(I-d)

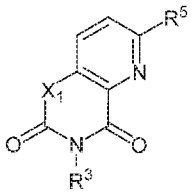


(I-e).

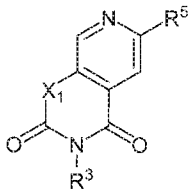
**Embodiment 61.** The compound of any one of Embodiments 1 to 51, or a pharmaceutically acceptable salt or stereoisomer thereof, selected from a compound having the structure of Formula (I-bb), Formula (I-bi) or Formula (I-bj), or a pharmaceutically acceptable salt or stereoisomer thereof,



(I-bb)

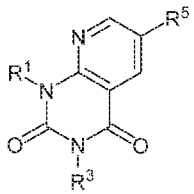


(I-bi)

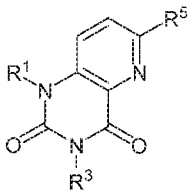


(I-bj).

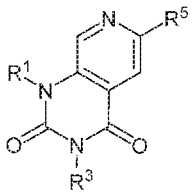
**Embodiment 62.** The compound of any one of Embodiments 1 to 51, or a pharmaceutically acceptable salt or stereoisomer thereof, selected from a compound having the structure of Formula (I-bk), Formula (I-bl) or Formula (I-bm), or a pharmaceutically acceptable salt or stereoisomer thereof,



(I-bk)

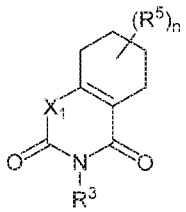


(I-bl)

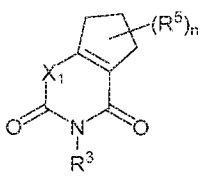


(I-bm).

**Embodiment 63.** The compound of any one of Embodiments 1 to 51, or a pharmaceutically acceptable salt or stereoisomer thereof, selected from a compound having the structure of Formula (I-k) or Formula (I-l), or a pharmaceutically acceptable salt or stereoisomer thereof,

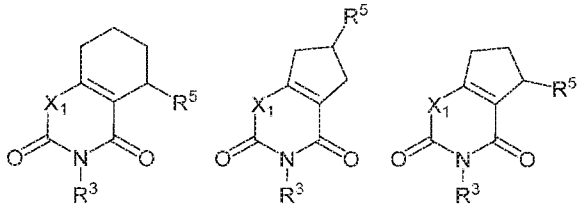


(I-k)



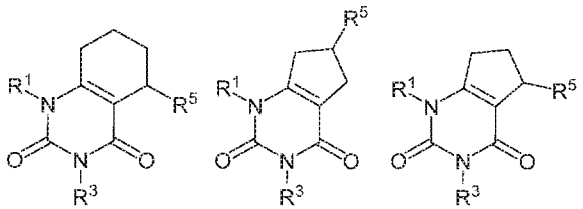
(I-l).

**Embodiment 64.** The compound of any one of Embodiments 1 to 51, or a pharmaceutically acceptable salt or stereoisomer thereof, selected from a compound having the structure of Formula (I-bn), Formula (I-bo) or Formula (I-bp), or a pharmaceutically acceptable salt or stereoisomer thereof,



(I-bn) (I-bo) (I-bp).

**Embodiment 65.** The compound of any one of Embodiments 1 to 51, or a pharmaceutically acceptable salt or stereoisomer thereof, selected from a compound having the structure of Formula (I-bq), Formula (I-br) or Formula (I-bs), or a pharmaceutically acceptable salt or stereoisomer thereof,



(I-bq) (I-br) (I-bs).

**Embodiment 66.** The compound of any one of Embodiment 52 to 65, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

$X_1$ is $NR^1$, N, $C(R^{2a})_2$, $CR^{2a}$, O, $C{=}C(R^{2a})_2$, $CR^{2a}R^{2b}$, a spiro attached 4 to 6 membered heterocycloalkyl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$, O, C(=O), S and $S(=O)_2$, or a spiro attached $C_3$-$C_8$cycloalkyl, and wherein the heterocycloalkyl and $C_3$-$C_8$cycloalkyl are unsubstituted or are substituted with 1 or 2 OH groups;

$R^1$ is H, $C_1$-$C_6$alkyl, $C_3$-$C_8$cycloalkyl, 4 to 7 membered heterocycloalkyl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$, O and S, a $C_1$-$C_6$alkyl substituted with one or more $R^{12}$ or a $C_1$-$C_6$alkenyl substituted with one or more $R^{12}$, and wherein the cycloalkyl and heterocycloalkyl are unsubstituted or the cycloalkyl and heterocycloalkyl are substituted with 1 or 2 substituents independently selected from the group consisting of CN, -C(=O)OH, $NH_2$, OH, $C_1$-$C_6$haloalkyl, $C_1$-$C_6$alkyl or $C_1$-$C_6$alkyl substituted with -C(=O)OH, -OH, CN or $NH_2$;

each $R^{2a}$ is independently selected from the group consisting of H, CN, $NH_2$, $C_1$-$C_6$alkyl and $C_1$-$C_6$alkyl substituted with -C(=O)OH, -OH, CN or $NH_2$;

$R^{2b}$ is H, $C_1$-$C_6$alkyl, $C_3$-$C_8$cycloalkyl or 4 to 7 membered heterocycloalkyl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$, O and S, and

wherein the $C_3$-$C_8$cycloalkyl and heterocycloalkyl are unsubstituted or the $C_3$-$C_8$cycloalkyl and heterocycloalkyl are substituted with 1, 2, 3 or 4 substituents independently selected from the group consisting of $C_1$-$C_6$alkyl, OH and -$N(R^7)_2$;

$R^3$ is selected from the group consisting of:

i) -$(CH_2)_{0-6}CHR^{13}R^{14}$;

ii) benzyl which is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

iii) a 6 membered heteroaryl with an attachment point at a carbon atom ring member and a N heteroatom as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 6 membered heteroaryl has 0, 1 or 2 additional N heteroatoms as ring members, and wherein the 6 membered heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

iv) a 10 membered bicyclic heteroaryl with an attachment point at a carbon atom ring member and a N heteroatom as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 10 membered bicyclic heteroaryl has 0, 1, 2 or 3 additional N heteroatoms as ring members, and wherein the 10 membered bicyclic heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

v) a 10 membered bicyclic heteroaryl with an attachment point at a carbon atom ring member and a N heteroatom as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 10 membered bicyclic heteroaryl further has 0, 1, 2, 3, or 4 ring members each independently selected from N, O and S, and wherein the 10 membered bicyclic heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

vi) a 9 membered bicyclic heteroaryl with an attachment point at a carbon atom ring member and a N heteroatom as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 9 membered bicyclic heteroaryl has 0, 1, 2, 3 or 4 additional N heteroatoms as ring members, and wherein the 9 membered bicyclic heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

vii) a 9 membered bicyclic heteroaryl with an attachment point at a carbon atom ring member and a N heteroatom as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 9 membered bicyclic heteroaryl further has 0, 1, 2, 3, or 4 ring members each independently selected from N, $NR^6$, O and S, and wherein the 9 membered bicyclic heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

viii) a 5 or 6 membered heterocycloalkyl with an attachment point at a carbon atom ring member and a $NR^6$ as a ring member which is located at a beta (β)

position relative to the attachment point, wherein the 5 or 6 membered heterocycloalkyl further has 0, 1, or 2 ring members each independently selected from N, $NR^6$, O and S, and wherein the 5 or 6 membered heterocycloalkyl is unsubstituted, substituted with 1 or 2 oxo, or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo;

ix) a 5 or 6 membered heterocyclyl with an attachment point at a carbon atom ring member and a $NR^6$ as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 5 or 6 membered heterocyclyl further has 0, 1, or 2 ring members each independently selected from N, $NR^6$, O and S, and wherein the 5 or 6 membered heterocyclyl is unsubstituted, substituted with 1 or 2 oxo, or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo;

x) a 9 or 10 membered bicyclic heterocyclyl with an attachment point at a carbon atom ring member and a $NR^6$ as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 9 or 10 membered heterocyclyl further has 0, 1, 2, 3, or 4 ring members each independently selected from N, $NR^6$, O and S, and wherein the 9 or 10 membered heterocyclyl is unsubstituted, substituted with 1 or 2 oxo, or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo;

xi) a 9 or 10 membered bicyclic heterocyclyl with an attachment point at a carbon atom ring member and a O heteroatom as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 9 or 10 membered heterocyclyl further has 0, 1, 2, 3, or 4 ring members each independently selected from N, $NR^6$, O and S, and wherein the 9 or 10 membered heterocyclyl is unsubstituted, substituted with 1 or 2 oxo, or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo;

xii) a 6 membered heteroaryl wherein 1, 2 or 3 ring members are each independently selected from N, O and S, and wherein the 6 membered heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

xiii) a 9 or 10 membered bicyclic heteroaryl wherein 1, 2, 3, 4 or 5 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 9 or 10 membered bicyclic heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

xiv) a 5 or 6 membered heterocycloalkyl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 5 or 6 membered heterocycloalkyl is unsubstituted, substituted with 1 or 2 oxo, or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo;

xv) a 5 or 6 membered heterocyclyl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 5 or 6 membered heterocyclyl is unsubstituted, substituted with 1 or 2 oxo, or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo;

xvi) a 6 membered heterocyclyl with an attachment point at a carbon atom ring member and a carbon atom as a ring member which is substituted with oxo and located at a beta (β) position relative to the attachment point, wherein the 6 membered heterocyclyl further has 1 or 2 ring members each independently selected from N, $NR^6$, O and S, and wherein the 6 membered heterocyclyl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with an oxo;

xvii) a 9 or 10 membered bicyclic heterocyclyl wherein 1, 2, 3, 4 or 5 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 9 or 10 membered bicyclic heterocyclyl is unsubstituted, substituted with 1 or 2 oxo, or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo;

xviii) a 10 membered bicyclic heterocyclyl with an attachment point at a carbon atom ring member and a carbon atom as a ring member which is substituted with oxo and located at a beta (β) position relative to the attachment point, wherein the 10 membered heterocyclyl further has 1, 2, 3, or 4 ring members each independently selected from N, $NR^6$, O and S, and wherein the 10 membered heterocyclyl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with an oxo;

each $R^4$ is independently selected from the group consisting of H, $-C(=O)N(R^7)_2$, $-C(=O)OH$, $-N(R^7)_2$, $-CN$, $-OH$, $-S(=O)_2R^6$, $-S(=O)_2N(R^7)_2$, $-C(=O)NR^7R^6$,  , $C_1$-$C_6$alkyl, halo, phenyl, $C_3$-$C_8$cycloalkyl, 4 to 6 membered heterocycloalkyl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S, 5 or 6 membered heteroaryl wherein 1, 2 or 3 ring members are each independently selected from N, O and S, and $C_1$-$C_6$alkyl substituted with $NH_2$, CN or OH, and wherein the phenyl, heterocycloalkyl and heteroaryl are unsubstituted or are substituted with 1 or 2 OH groups;

each $R^5$ is independently selected from the group consisting of -OH, $-NR^7R^8$, -NR6C(=O)C2-C6alkenyl, $-SF_5$, $-C(=O)N(R^7)_2$, $C_1$-$C_6$alkyl, $C_1$-$C_6$haloalkyl, halo, $C_1$-$C_6$haloalkoxy, $C_1$-$C_6$alkoxy, $C_3$-$C_8$cycloalkyl, 4 to 6 membered heterocycloalkyl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S, a 5 or 6 membered heteroaryl wherein 1, 2 or 3 ring members are each

independently selected from N, O and S, and $C_1$-$C_6$alkyl substituted with CN, $NH_2$ or OH, and wherein the cycloalkyl and heterocycloalkyl are unsubstituted or are substituted with 1, 2, 3 or 4 $R^9$;

each $R^6$ is independently selected from the group consisting of H, $C_1$-$C_6$alkyl, -$S(=O)_2N(R^7)_2$, -$C(=O)N(R^7)_2$ and $C_1$-$C_6$alkyl substituted with –OH, -$OR^7$, CN or –C(=O)OH;

each $R^7$ is independently selected from the group consisting of H and $C_1$-$C_6$alkyl;

$R^8$ is H, $C_1$-$C_6$alkyl, $C_3$-$C_8$cycloalkyl or 4 to 6 membered heterocycloalkyl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S, and wherein the cycloalkyl and heterocycloalkyl are unsubstituted or are substituted with 1, 2, 3 or 4 $R^9$;

each $R^9$ is independently selected from the group consisting of halo, $NR^{10}R^{11}$, -C(=O)OH, -$C(=O)N(R^7)_2$ and $C_1$-$C_6$alkyl substituted with -OH or -$N(R^7)_2$;

$R^{10}$ is H or $C_1$-$C_6$alkyl;

$R^{11}$ is H, $C_1$-$C_6$alkyl or -$S(=O)_2C_1$-$C_6$alkyl;

each $R^{12}$ is independently selected from the group consisting of CN, $NH_2$, -OH, -C(=O)OH, -$C(=O)OR^{10}$, -$C(=O)N(R^7)_2$, $C_1$-$C_6$alkoxy, $C_1$-$C_6$alkyl, halo, $C_1$-$C_6$haloalkyl, $C_3$-$C_8$cycloalkyl, a 5 or a 6 membered heteroaryl wherein 1, 2, 3, or 4 ring members are each independently selected from N, $NR^6$, O and S, and a 3 to 6 membered heterocycloalkyl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$, O and S, and wherein the cycloalkyl, heteroaryl and heterocycloalkyl are unsubstituted or are substituted with 1, 2 or 3 substituents independently selected from the group consisting of CN, -C(=O)OH, $NH_2$, OH, halo and $C_1$-$C_6$alkyl;

$R^{13}$ is H, -$C(=O)N(R^7)_2$, or a 5 or 6 membered heteroaryl wherein 1, 2 3 or 4 ring members are each independently selected from N, $NR^6$, O and S;

$R^{14}$ is selected from the group consisting of

i) a 5 or 6 membered heterocyclyl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 5 or 6 membered heterocyclyl is unsubstituted, substituted with 1 or 2 oxo or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo;

and

ii) a 5 or a 6 membered heteroaryl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 5 or a 6 membered heteroaryl is unsubstituted, or is substituted with 1, 2, 3 or 4 $R^4$;

and

n is 0, 1, 2, 3 or 4.

**Embodiment 67.** The compound of any one of Embodiments 52 to 65, or a pharmaceutically acceptable salt or stereoisomer thereof,

wherein:

$X_1$ is $NR^1$, N, $C(R^{2a})_2$, $CR^{2a}$, O, $C=C(R^{2a})_2$, $CR^{2a}R^{2b}$, a spiro attached 4 to 6 membered heterocycloalkyl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$, O, C(=O), S and $S(=O)_2$, or a spiro attached $C_3$-$C_8$cycloalkyl, and wherein the heterocycloalkyl and $C_3$-$C_8$cycloalkyl are unsubstituted or are substituted with 1 or 2 OH groups;

$R^1$ is H, $C_1$-$C_6$alkyl, $C_3$-$C_8$cycloalkyl, 4 to 7 membered heterocycloalkyl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$, O and S, a $C_1$-$C_6$alkyl substituted with one or more $R^{12}$ or a $C_1$-$C_6$alkenyl substituted with one or more $R^{12}$, and wherein the cycloalkyl and heterocycloalkyl are unsubstituted or the cycloalkyl and heterocycloalkyl are substituted with 1 or 2 substituents independently selected from the group consisting of CN, -C(=O)OH, $NH_2$, OH, $C_1$-$C_6$haloalkyl, $C_1$-$C_6$alkyl or $C_1$-$C_6$alkyl substituted with -C(=O)OH, -OH, CN or $NH_2$;

each $R^{2a}$ is independently selected from the group consisting of H, CN, $NH_2$, $C_1$-$C_6$alkyl and $C_1$-$C_6$alkyl substituted with -C(=O)OH, -OH, CN or $NH_2$;

$R^{2b}$ is H, $C_1$-$C_6$alkyl, $C_3$-$C_8$cycloalkyl or 4 to 7 membered heterocycloalkyl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$, O and S, and wherein the $C_3$-$C_8$cycloalkyl and heterocycloalkyl are unsubstituted or the $C_3$-$C_8$cycloalkyl and heterocycloalkyl are substituted with 1, 2, 3 or 4 substituents independently selected from the group consisting of $C_1$-$C_6$alkyl, OH and $-N(R^7)_2$;

$R^3$ is selected from the group consisting of:

i) a 6 membered heteroaryl with an attachment point at a carbon atom ring member and a N heteroatom as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 6 membered heteroaryl has 0, 1 or 2 additional N heteroatoms as ring members, and wherein the 6 membered heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

ii) a 10 membered bicyclic heteroaryl with an attachment point at a carbon atom ring member and a N heteroatom as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 10 membered bicyclic heteroaryl has 0, 1, 2 or 3 additional N heteroatoms as ring members, and wherein the 10 membered bicyclic heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

iii) a 6 membered heteroaryl wherein 1, 2 or 3 ring members are each independently selected from N, O and S, and wherein the 6 membered heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

iv) a 9 or 10 membered bicyclic heteroaryl wherein 1, 2, 3, 4 or 5 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 9 or 10 membered bicyclic heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

v) a 9 or 10 membered bicyclic heterocyclyl with an attachment point at a carbon atom ring member and a $NR^6$ as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 9 or 10 membered heterocyclyl further has 0, 1, 2, 3, or 4 ring members each independently selected from N, $NR^6$, O and S, and wherein the 9 or 10 membered heterocyclyl is unsubstituted, substituted with 1 or 2 oxo, or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo;

vi) a 9 or 10 membered bicyclic heterocyclyl wherein 1, 2, 3, 4 or 5 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 9 or 10 membered bicyclic heterocyclyl is unsubstituted, substituted with 1 or 2 oxo, or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo;

vii) a 10 membered bicyclic heterocyclyl with an attachment point at a carbon atom ring member and a carbon atom as a ring member which is substituted with oxo and located at a beta (β) position relative to the attachment point, wherein the 10 membered heterocyclyl further has 1, 2, 3, or 4 ring members each independently selected from N, $NR^6$, O and S, and wherein the 10 membered heterocyclyl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with an oxo;

each $R^4$ is independently selected from the group consisting of $-C(=O)N(R^7)_2$, -C(=O)OH, $-N(R^7)_2$, -CN, -OH, $-S(=O)_2R^6$, $-S(=O)_2N(R^7)_2$, $-C(=O)NR^7R^6$,  , $C_1$-$C_6$alkyl, halo, phenyl, $C_3$-$C_8$cycloalkyl, 4 to 6 membered heterocycloalkyl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S, 5 or 6 membered heteroaryl wherein 1, 2 or 3 ring members are each independently selected from N, O and S, and $C_1$-$C_6$alkyl substituted with $NH_2$, CN or OH, and wherein the phenyl, heterocycloalkyl and heteroaryl are unsubstituted or are substituted with 1 or 2 OH groups;

each $R^5$ is independently selected from the group consisting of -OH, $-NR^7R^8$, -NR6C(=O)C2-C6alkenyl, $-SF_5$, $-C(=O)N(R^7)_2$, $C_1$-$C_6$alkyl, $C_1$-$C_6$haloalkyl, halo, $C_1$-$C_6$haloalkoxy, $C_1$-$C_6$alkoxy, $C_3$-$C_8$cycloalkyl, 4 to 6 membered heterocycloalkyl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S, a 5 or 6 membered heteroaryl wherein 1, 2 or 3 ring members are each

independently selected from N, O and S, and $C_1$-$C_6$alkyl substituted with CN, $NH_2$ or OH, and wherein the cycloalkyl and heterocycloalkyl are unsubstituted or are substituted with 1, 2, 3 or 4 $R^9$;

each $R^6$ is independently selected from the group consisting of H, $C_1$-$C_6$alkyl, -$S(=O)_2N(R^7)_2$, -$C(=O)N(R^7)_2$ and $C_1$-$C_6$alkyl substituted with –OH, -$OR^7$, CN or –C(=O)OH;

each $R^7$ is independently selected from the group consisting of H and $C_1$-$C_6$alkyl;

$R^8$ is H, $C_1$-$C_6$alkyl, $C_3$-$C_8$cycloalkyl or 4 to 6 membered heterocycloalkyl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S, and wherein the cycloalkyl and heterocycloalkyl are unsubstituted or are substituted with 1, 2, 3 or 4 $R^9$;

each $R^9$ is independently selected from the group consisting of halo, $NR^{10}R^{11}$, -C(=O)OH, -$C(=O)N(R^7)_2$ and $C_1$-$C_6$alkyl substituted with -OH or -$N(R^7)_2$;

$R^{10}$ is H or $C_1$-$C_6$alkyl;

$R^{11}$ is H, $C_1$-$C_6$alkyl or -$S(=O)_2C_1$-$C_6$alkyl;

each $R^{12}$ is independently selected from the group consisting of CN, $NH_2$, -OH, -C(=O)OH, -$C(=O)OR^{10}$, -$C(=O)N(R^7)_2$, -$C_1$-$C_6$alkoxy, $C_1$-$C_6$alkyl, halo, $C_1$-$C_6$haloalkyl, $C_3$-$C_8$cycloalkyl, a 5 or a 6 membered heteroaryl wherein 1, 2, 3, or 4 ring members are each independently selected from N, $NR^6$, O and S, and a 3 to 6 membered heterocycloalkyl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$, O and S, and wherein the cycloalkyl, heteroaryl and heterocycloalkyl are unsubstituted or are substituted with 1, 2 or 3 substituents independently selected from the group consisting of CN, -C(=O)OH, $NH_2$, OH, halo and $C_1$-$C_6$alkyl;

$R^{13}$ is H, -$C(=O)N(R^7)_2$, or a 5 or 6 membered heteroaryl wherein 1, 2 3 or 4 ring members are each independently selected from N, $NR^6$, O and S;

$R^{14}$ is selected from the group consisting of

i) a 5 or 6 membered heterocyclyl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 5 or 6 membered heterocyclyl is unsubstituted, or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo;

and

ii) a 5 or a 6 membered heteroaryl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 5 or a 6 membered heteroaryl is unsubstituted, or is substituted with 1, 2, 3 or 4 $R^4$;

p is 0, 1 or 2, and

n is 0, 1, 2, 3 or 4.

**Embodiment 68.** The compound of any one of Embodiments 52 to 65, or a pharmaceutically acceptable salt or stereoisomer thereof,

wherein:

$X_1$ is $NR^1$, N, $C(R^{2a})_2$, $CR^{2a}$, O, $C=C(R^{2a})_2$, $CR^{2a}R^{2b}$, a spiro attached 4 to 6 membered heterocycloalkyl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$, O, C(=O), S and $S(=O)_2$, or a spiro attached $C_3$-$C_8$cycloalkyl, and wherein the heterocycloalkyl and $C_3$-$C_8$cycloalkyl are unsubstituted or are substituted with 1 or 2 OH groups;

$R^1$ is H, $C_1$-$C_6$alkyl, $C_3$-$C_8$cycloalkyl, 4 to 7 membered heterocycloalkyl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$, O and S, a $C_1$-$C_6$alkyl substituted with one or more $R^{12}$ or a $C_1$-$C_6$alkenyl substituted with one or more $R^{12}$, and wherein the cycloalkyl and heterocycloalkyl are unsubstituted or the cycloalkyl and heterocycloalkyl are substituted with 1 or 2 substituents independently selected from the group consisting of CN, -C(=O)OH, $NH_2$, OH, $C_1$-$C_6$haloalkyl, $C_1$-$C_6$alkyl or $C_1$-$C_6$alkyl substituted with -C(=O)OH, -OH, CN or $NH_2$;

each $R^{2a}$ is independently selected from the group consisting of H, CN, $NH_2$, $C_1$-$C_6$alkyl and $C_1$-$C_6$alkyl substituted with -C(=O)OH, -OH, CN or $NH_2$;

$R^{2b}$ is H, $C_1$-$C_6$alkyl, $C_3$-$C_8$cycloalkyl or 4 to 7 membered heterocycloalkyl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$, O and S, and wherein the $C_3$-$C_8$cycloalkyl and heterocycloalkyl are unsubstituted or the $C_3$-$C_8$cycloalkyl and heterocycloalkyl are substituted with 1, 2, 3 or 4 substituents independently selected from the group consisting of $C_1$-$C_6$alkyl, OH and $-N(R^7)_2$;

$R^3$ is selected from the group consisting of:

i) a 6 membered heteroaryl with an attachment point at a carbon atom ring member and a N heteroatom as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 6 membered heteroaryl has 0, 1 or 2 additional N heteroatoms as ring members, and wherein the 6 membered heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

ii) a 10 membered bicyclic heteroaryl with an attachment point at a carbon atom ring member and a N heteroatom as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 10 membered bicyclic heteroaryl has 0, 1, 2 or 3 additional N heteroatoms as ring members, and wherein the 10 membered bicyclic heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

iii) a 6 membered heteroaryl wherein 1, 2 or 3 ring members are each independently selected from N, O and S, and wherein the 6 membered heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

iv) a 9 or 10 membered bicyclic heteroaryl wherein 1, 2, 3, 4 or 5 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 9 or

10 membered bicyclic heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

v) a 9 or 10 membered bicyclic heterocyclyl with an attachment point at a carbon atom ring member and a $NR^6$ as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 9 or 10 membered heterocyclyl further has 0, 1, 2, 3, or 4 ring members each independently selected from N, $NR^6$, O and S, and wherein the 9 or 10 membered heterocyclyl is unsubstituted, substituted with 1 or 2 oxo, or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo;

vi) a 9 or 10 membered bicyclic heterocyclyl wherein 1, 2, 3, 4 or 5 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 9 or 10 membered bicyclic heterocyclyl is unsubstituted, substituted with 1 or 2 oxo, or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo;

vii) a 10 membered bicyclic heterocyclyl with an attachment point at a carbon atom ring member and a carbon atom as a ring member which is substituted with oxo and located at a beta (β) position relative to the attachment point, wherein the 10 membered heterocyclyl further has 1, 2, 3, or 4 ring members each independently selected from N, $NR^6$, O and S, and wherein the 10 membered heterocyclyl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with an oxo;

each $R^4$ is independently selected from the group consisting of $-C(=O)N(R^7)_2$, -C(=O)OH, $-N(R^7)_2$, -CN, -OH, $-S(=O)_2R^6$, $-S(=O)_2N(R^7)_2$, $-C(=O)NR^7R^6$,  , $C_1$-$C_6$alkyl, halo, phenyl, $C_3$-$C_8$cycloalkyl, 4 to 6 membered heterocycloalkyl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S, 5 or 6 membered heteroaryl wherein 1, 2 or 3 ring members are each independently selected from N, O and S, and $C_1$-$C_6$alkyl substituted with $NH_2$, CN or OH, and wherein the phenyl, heterocycloalkyl and heteroaryl are unsubstituted or are substituted with 1 or 2 OH groups;

each $R^5$ is independently selected from the group consisting of -OH, $-NR^7R^8$, -NR6C(=O)C2-C6alkenyl, $-SF_5$, $-C(=O)N(R^7)_2$, $C_1$-$C_6$alkyl, $C_1$-$C_6$haloalkyl, halo, $C_1$-$C_6$haloalkoxy, $C_1$-$C_6$alkoxy, $C_3$-$C_8$cycloalkyl, 4 to 6 membered heterocycloalkyl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S, a 5 or 6 membered heteroaryl wherein 1, 2 or 3 ring members are each independently selected from N, O and S, and $C_1$-$C_6$alkyl substituted with CN, $NH_2$ or

OH, and wherein the cycloalkyl and heterocycloalkyl are unsubstituted or are substituted with 1, 2, 3 or 4 $R^9$;

each $R^6$ is independently selected from the group consisting of H, $C_1$-$C_6$alkyl, -$S(=O)_2N(R^7)_2$, -$C(=O)N(R^7)_2$ and $C_1$-$C_6$alkyl substituted with –OH, -$OR^7$, CN or –C(=O)OH;

each $R^7$ is independently selected from the group consisting of H and $C_1$-$C_6$alkyl;

$R^8$ is H, $C_1$-$C_6$alkyl, $C_3$-$C_8$cycloalkyl or 4 to 6 membered heterocycloalkyl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S, and wherein the cycloalkyl and heterocycloalkyl are unsubstituted or are substituted with 1, 2, 3 or 4 $R^9$;

each $R^9$ is independently selected from the group consisting of halo, $NR^{10}R^{11}$, -C(=O)OH, -$C(=O)N(R^7)_2$ and $C_1$-$C_6$alkyl substituted with -OH or -$N(R^7)_2$;

$R^{10}$ is H or $C_1$-$C_6$alkyl;

$R^{11}$ is H, $C_1$-$C_6$alkyl or -$S(=O)_2C_1$-$C_6$alkyl;

each $R^{12}$ is independently selected from the group consisting of CN, $NH_2$, -OH, -C(=O)OH, -$C(=O)OR^{10}$, -$C(=O)N(R^7)_2$, -$C_1$-$C_6$alkoxy, $C_1$-$C_6$alkyl, halo, $C_1$-$C_6$haloalkyl, $C_3$-$C_8$cycloalkyl, a 5 or a 6 membered heteroaryl wherein 1, 2, 3, or 4 ring members are each independently selected from N, $NR^6$, O and S, and a 3 to 6 membered heterocycloalkyl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$, O and S, and wherein the cycloalkyl, heteroaryl and heterocycloalkyl are unsubstituted or are substituted with 1, 2 or 3 substituents independently selected from the group consisting of CN, -C(=O)OH, $NH_2$, OH, halo and $C_1$-$C_6$alkyl;

$R^{13}$ is H, -$C(=O)N(R^7)_2$, or a 5 or 6 membered heteroaryl wherein 1, 2 3 or 4 ring members are each independently selected from N, $NR^6$, O and S;

$R^{14}$ is selected from the group consisting of

i) a 5 or 6 membered heterocyclyl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 5 or 6 membered heterocyclyl is unsubstituted, or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo;

and

ii) a 5 or a 6 membered heteroaryl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 5 or a 6 membered heteroaryl is unsubstituted, or is substituted with 1, 2, 3 or 4 $R^4$;

p is 0, 1 or 2, and

n is 0, 1, 2, 3 or 4.

**Embodiment 69.** The compound of any one of Embodiment 52 to 65, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

$X_1$ is $NR^1$, $C(R^{2a})_2$, $CR^{2a}$, O, or $C=C(R^{2a})_2$;

$R^1$ is H, $C_1$-$C_6$alkyl, $C_3$-$C_8$cycloalkyl, 4 membered heterocycloalkyl wherein 1 ring member selected from N, $NR^6$ and O, a $C_1$-$C_6$alkyl substituted with one or more $R^{12}$ or a $C_1$-$C_6$alkenyl substituted with one or more $R^{12}$, and wherein the cycloalkyl and heterocycloalkyl are unsubstituted or the cycloalkyl and heterocycloalkyl are substituted with 1 substituent selected from the group consisting of CN, -C(=O)OH, $C_1$-$C_6$haloalkyl and $C_1$-$C_6$alkyl substituted with CN;

each $R^{2a}$ is independently selected from the group consisting of H, $NH_2$, $C_1$-$C_6$alkyl and $C_1$-$C_6$alkyl substituted with -C(=O)OH, -OH or CN;

$R^3$ is selected from the group consisting of:

i) a 6 membered heteroaryl with an attachment point at a carbon atom ring member and a N heteroatom as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 6 membered heteroaryl has 0, 1 or 2 additional N heteroatoms as ring members, and wherein the 6 membered heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

ii) a 10 membered bicyclic heteroaryl with an attachment point at a carbon atom ring member and a N heteroatom as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 10 membered bicyclic heteroaryl has 0, 1, 2 or 3 additional N heteroatoms as ring members, and wherein the 10 membered bicyclic heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

iii) a 6 membered heteroaryl wherein 1, 2 or 3 ring members are each independently selected from N, O and S, and wherein the 6 membered heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

iv) a 9 or 10 membered bicyclic heteroaryl wherein 1, 2, 3, 4 or 5 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 9 or 10 membered bicyclic heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

v) a 9 or 10 membered bicyclic heterocyclyl with an attachment point at a carbon atom ring member and a $NR^6$ as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 9 or 10 membered heterocyclyl further has 0, 1, 2, 3, or 4 ring members each independently selected from N, $NR^6$, O and S, and wherein the 9 or 10 membered heterocyclyl is unsubstituted, substituted with 1 or 2 oxo, or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo;

vi) a 9 or 10 membered bicyclic heterocyclyl wherein 1, 2, 3, 4 or 5 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 9 or 10 membered bicyclic heterocyclyl is unsubstituted,

substituted with 1 or 2 oxo, or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo;

and

vii) a 10 membered bicyclic heterocyclyl with an attachment point at a carbon atom ring member and a carbon atom as a ring member which is substituted with oxo and located at a beta (β) position relative to the attachment point, wherein the 10 membered heterocyclyl further has 1, 2, 3, or 4 ring members each independently selected from N, $NR^6$, O and S, and wherein the 10 membered heterocyclyl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with an oxo;

each $R^4$ is independently selected from the group consisting of $-C(=O)N(R^7)_2$, -C(=O)OH, $-N(R^7)_2$, -CN, -OH, $-C(=O)NR^7R^6$,  , $C_1$-$C_6$alkyl, halo, 6 membered heterocycloalkyl wherein 1 or 2 ring members are each independently selected from N and $NR^6$, and $C_1$-$C_6$alkyl substituted with $NH_2$, and wherein the heterocycloalkyl is unsubstituted;

each $R^5$ is independently selected from the group consisting of -NR6C(=O)C2-C6alkenyl, $-SF_5$, $C_1$-$C_6$alkyl, $C_1$-$C_6$haloalkyl, halo, $C_1$-$C_6$haloalkoxy, $C_1$-$C_6$alkoxy, $C_3$-$C_8$cycloalkyl, wherein the cycloalkyl is unsubstituted or is substituted with 1 $R^9$;

each $R^6$ is independently selected from the group consisting of H or $C_1$-$C_6$alkyl;

each $R^7$ is independently selected from the group consisting of H and $C_1$-$C_6$alkyl;

each $R^9$ is independently selected from the group consisting of $C_1$-$C_6$alkyl substituted with -OH;

$R^{10}$ is H or $C_1$-$C_6$alkyl;

each $R^{12}$ is independently selected from the group consisting of CN, -OH, -C(=O)OH, $-C(=O)N(R^7)_2$, $C_1$-$C_6$alkoxy, halo, $C_1$-$C_6$haloalkyl, $C_3$-$C_8$cycloalkyl, a 5 membered heteroaryl wherein 4 ring members are each independently selected from N and $NR^6$, and a 3 membered heterocycloalkyl wherein 1 ring member is selected from N, $NR^6$ and O, and wherein the cycloalkyl, heteroaryl and heterocycloalkyl are unsubstituted or are substituted with 1 substituent from the group consisting of CN and -C(=O)OH;

$R^{13}$ is H;

$R^{14}$ is a 6 membered heterocyclyl wherein 1 ring member is selected from N or $NR^6$, and wherein the 6 membered heterocyclyl is substituted with an oxo;

and

n is 0, 1 or 2.

**Embodiment 70.** The compound of any one of Embodiment 52 to 65, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

$X_1$ is $NR^1$, $C(R^{2a})_2$, $CR^{2a}$, O, or $C=C(R^{2a})_2$;

$R^1$ is H, $C_1$-$C_6$alkyl, $C_3$-$C_8$cycloalkyl, 4 membered heterocycloalkyl wherein 1 ring member selected from N, $NR^6$ and O; $C_1$-$C_6$alkyl substituted with one or more $R^{12}$ or $C_1$-$C_6$alkenyl substituted with one or more $R^{12}$, and wherein the cycloalkyl and heterocycloalkyl are unsubstituted or the cycloalkyl and heterocycloalkyl are substituted with 1 substituent selected from the group consisting of CN, -C(=O)OH, $C_1$-$C_6$haloalkyl and $C_1$-$C_6$alkyl substituted with CN;

each $R^{2a}$ is independently selected from the group consisting of H, $NH_2$, $C_1$-$C_6$alkyl and $C_1$-$C_6$alkyl substituted with -C(=O)OH, -OH or CN;

$R^3$ is selected from the group consisting of:

i) $-CHR^{13}R^{14}$;

ii) benzyl which is unsubstituted or is substituted with 1 $R^4$;

iii) a 6 membered heteroaryl wherein 1 ring member is selected from N, and wherein the 6 membered heteroaryl is unsubstituted or is substituted with 1 or 2 $R^4$;

iv) a 10 membered bicyclic heteroaryl with an attachment point at a carbon atom ring member and a N heteroatom as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 10 membered bicyclic heteroaryl has 0, 1, 2 or 3 additional N heteroatoms as ring members, and wherein the 10 membered bicyclic heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

v) a 9 or 10 membered bicyclic heteroaryl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$ and O, and wherein the 9 or 10 membered bicyclic heteroaryl is unsubstituted or is substituted with 1 or 2 $R^4$;

vi) a 6 membered heterocyclyl wherein 1 ring member is selected from $NR^6$, and wherein the 6 membered heterocyclyl is substituted with an oxo;

and

vii) a 9 or 10 membered bicyclic heterocyclyl wherein 1 ring member is selected from N, $NR^6$ or O, and wherein the 9 or 10 membered bicyclic heterocyclyl is unsubstituted, or is substituted with an oxo;

each $R^4$ is independently selected from the group consisting of $-C(=O)N(R^7)_2$, -C(=O)OH, $-N(R^7)_2$, -CN, -OH,  , $C_1$-$C_6$alkyl, halo, 6 membered heterocycloalkyl wherein 1 or 2 ring members are each independently selected from N and $NR^6$, and $C_1$-$C_6$alkyl substituted with $NH_2$, and wherein the heterocycloalkyl is unsubstituted;

each $R^5$ is independently selected from the group consisting of -NR6C(=O)C2-C6alkenyl, $-SF_5$, $C_1$-$C_6$alkyl, $C_1$-$C_6$haloalkyl, halo, $C_1$-$C_6$haloalkoxy, $C_1$-$C_6$alkoxy, $C_3$-$C_8$cycloalkyl, wherein the cycloalkyl is unsubstituted or is substituted with 1 $R^9$;

each $R^6$ is independently selected from the group consisting of H or $C_1$-$C_6$alkyl;

each $R^7$ is independently selected from the group consisting of H and $C_1$-$C_6$alkyl;

each $R^9$ is independently selected from the group consisting of $C_1$-$C_6$alkyl substituted with -OH;

$R^{10}$ is H or $C_1$-$C_6$alkyl;

each $R^{12}$ is independently selected from the group consisting of CN, -OH, -C(=O)OH, -C(=O)N($R^7$)$_2$, $C_1$-$C_6$alkoxy, halo, $C_1$-$C_6$haloalkyl, $C_3$-$C_8$cycloalkyl, a 5 membered heteroaryl wherein 4 ring members are each independently selected from N and $NR^6$, and a 3 membered heterocycloalkyl wherein 1 ring member is selected from N, $NR^6$ and O, and wherein the cycloalkyl, heteroaryl and heterocycloalkyl are unsubstituted or are substituted with 1 substituent from the group consisting of CN and -C(=O)OH;

$R^{13}$ is H;

$R^{14}$ is a 6 membered heterocyclyl wherein 1 ring member is selected from N or $NR^6$, and wherein the 6 membered heterocyclyl is substituted with an oxo;

and

n is 0, 1 or 2.

**Embodiment 71.** The compound of any one of Embodiment 52 to 65, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

$X_1$ is $NR^1$, C($R^{2a}$)$_2$ or O;

$R^1$ is H, $C_1$-$C_6$alkyl, $C_3$-$C_8$cycloalkyl, a $C_1$-$C_6$alkyl substituted with one or more $R^{12}$, or a $C_1$-$C_6$alkenyl substituted with one or more $R^{12}$, and wherein the cycloalkyl is unsubstituted or the cycloalkyl is substituted with 1 substituent selected from the group consisting of $C_1$-$C_6$alkyl substituted with CN;

each $R^{2a}$ is independently selected from the group consisting of H, and $C_1$-$C_6$alkyl;

$R^3$ is selected from the group consisting of:

i) a 6 membered heteroaryl with an attachment point at a carbon atom ring member and a N heteroatom as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 6 membered heteroaryl has 0, 1 or 2 additional N heteroatoms as ring members, and wherein the 6 membered heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

ii) a 10 membered bicyclic heteroaryl with an attachment point at a carbon atom ring member and a N heteroatom as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 10 membered bicyclic heteroaryl has 0, 1, 2 or 3 additional N heteroatoms as ring members,

and wherein the 10 membered bicyclic heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

iii) a 6 membered heteroaryl wherein 1, 2 or 3 ring members are each independently selected from N, O and S, and wherein the 6 membered heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

iv) a 9 or 10 membered bicyclic heteroaryl wherein 1, 2, 3, 4 or 5 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 9 or 10 membered bicyclic heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

v) a 9 or 10 membered bicyclic heterocyclyl with an attachment point at a carbon atom ring member and a $NR^6$ as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 9 or 10 membered heterocyclyl further has 0, 1, 2, 3, or 4 ring members each independently selected from N, $NR^6$, O and S, and wherein the 9 or 10 membered heterocyclyl is unsubstituted, substituted with 1 or 2 oxo, or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo;

vi) a 9 or 10 membered bicyclic heterocyclyl wherein 1, 2, 3, 4 or 5 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 9 or 10 membered bicyclic heterocyclyl is unsubstituted, substituted with 1 or 2 oxo, or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo;

and

vii) a 10 membered bicyclic heterocyclyl with an attachment point at a carbon atom ring member and a carbon atom as a ring member which is substituted with oxo and located at a beta (β) position relative to the attachment point, wherein the 10 membered heterocyclyl further has 1, 2, 3, or 4 ring members each independently selected from N, $NR^6$, O and S, and wherein the 10 membered heterocyclyl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with an oxo;

each $R^4$ is independently selected from the group consisting of $-C(=O)N(R^7)_2$, $-N(R^7)_2$, -CN, $-S(=O)_2R^6$, $-C(=O)NR^7R^6$,  , $C_1$-$C_6$alkyl, and halo;

each $R^5$ is independently selected from the group consisting of $-SF_5$, $C_1$-$C_6$alkyl, $C_1$-$C_6$haloalkyl, halo, $C_1$-$C_6$haloalkoxy, $C_1$-$C_6$alkoxy, $C_3$-$C_8$cycloalkyl, and a $C_1$-$C_6$alkyl substituted with CN or OH, wherein the cycloalkyl is unsubstituted or is substituted with 1 or 2 $R^9$;

each $R^6$ is independently selected from the group consisting of H, $C_1$-$C_6$alkyl or $C_1$-$C_6$alkyl substituted with -$OR^7$;

each $R^7$ is independently selected from the group consisting of H and $C_1$-$C_6$alkyl;

each $R^9$ is independently selected from the group consisting of halo, -C(=O)OH, and $C_1$-$C_6$alkyl substituted with -OH;

$R^{10}$ is H or $C_1$-$C_6$alkyl;

each $R^{12}$ is independently selected from the group consisting of CN, -OH, -C(=O)OH, -C(=O)$OR^{10}$, -C(=O)N($R^7$)$_2$, $C_1$-$C_6$alkoxy, $C_1$-$C_6$alkyl, halo, $C_3$-$C_8$cycloalkyl, a 5 membered heteroaryl wherein 4 ring members are each independently selected from N and $NR^6$, and a 3 to 6 membered heterocycloalkyl wherein 1 or 2 ring members are each independently selected from N, $NR^6$ and O, and wherein the cycloalkyl and heterocycloalkyl are unsubstituted or are substituted with 1 or 2 substituents independently selected from the group consisting of CN, halo and -C(=O)OH;

and

n is 1 or 2.

**Embodiment 72.** The compound of any one of Embodiment 52 to 65, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

$X_1$ is $NR^1$;

$R^1$ is H, $C_1$-$C_6$alkyl, $C_3$-$C_8$cycloalkyl, a $C_1$-$C_6$alkyl substituted with one or more $R^{12}$, or a $C_1$-$C_6$alkenyl substituted with one or more $R^{12}$, and wherein the cycloalkyl is unsubstituted or the cycloalkyl is substituted with 1 substituent selected from the group consisting of $C_1$-$C_6$alkyl substituted with CN;

$R^3$ is selected from the group consisting of:

i) a 6 membered heteroaryl with an attachment point at a carbon atom ring member and a N heteroatom as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 6 membered heteroaryl has 0, 1 or 2 additional N heteroatoms as ring members, and wherein the 6 membered heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

ii) a 10 membered bicyclic heteroaryl with an attachment point at a carbon atom ring member and a N heteroatom as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 10 membered bicyclic heteroaryl has 0, 1, 2 or 3 additional N heteroatoms as ring members, and wherein the 10 membered bicyclic heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

iii) a 6 membered heteroaryl wherein 1, 2 or 3 ring members are each independently selected from N, O and S, and wherein the 6 membered heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

iv) a 9 or 10 membered bicyclic heteroaryl wherein 1, 2, 3, 4 or 5 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 9 or 10 membered bicyclic heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

v) a 9 or 10 membered bicyclic heterocyclyl with an attachment point at a carbon atom ring member and a $NR^6$ as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 9 or 10 membered heterocyclyl further has 0, 1, 2, 3, or 4 ring members each independently selected from N, $NR^6$, O and S, and wherein the 9 or 10 membered heterocyclyl is unsubstituted, substituted with 1 or 2 oxo, or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo;

vi) a 9 or 10 membered bicyclic heterocyclyl wherein 1, 2, 3, 4 or 5 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 9 or 10 membered bicyclic heterocyclyl is unsubstituted, substituted with 1 or 2 oxo, or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo;

and

vii) a 10 membered bicyclic heterocyclyl with an attachment point at a carbon atom ring member and a carbon atom as a ring member which is substituted with oxo and located at a beta (β) position relative to the attachment point, wherein the 10 membered heterocyclyl further has 1, 2, 3, or 4 ring members each independently selected from N, $NR^6$, O and S, and wherein the 10 membered heterocyclyl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with an oxo;

each $R^4$ is independently selected from the group consisting of $-C(=O)N(R^7)_2$, $-N(R^7)_2$, -CN, $-S(=O)_2R^6$, $-C(=O)NR^7R^6$,  , $C_1$-$C_6$alkyl, and halo;

each $R^5$ is independently selected from the group consisting of $-SF_5$, $C_1$-$C_6$alkyl, $C_1$-$C_6$haloalkyl, halo, $C_1$-$C_6$haloalkoxy, $C_1$-$C_6$alkoxy, $C_3$-$C_8$cycloalkyl, and a $C_1$-$C_6$alkyl substituted with CN or OH, wherein the cycloalkyl is unsubstituted or is substituted with 1 or 2 $R^9$;

each $R^6$ is independently selected from the group consisting of H, $C_1$-$C_6$alkyl or $C_1$-$C_6$alkyl substituted with $-OR^7$;

each $R^7$ is independently selected from the group consisting of H and $C_1$-$C_6$alkyl;

each $R^9$ is independently selected from the group consisting of halo, $-C(=O)OH$, and $C_1$-$C_6$alkyl substituted with -OH;

$R^{10}$ is H or $C_1$-$C_6$alkyl;

each $R^{12}$ is independently selected from the group consisting of CN, -OH, -C(=O)OH, -C(=O)$OR^{10}$, -C(=O)$N(R^7)_2$, $C_1$-$C_6$alkoxy, $C_1$-$C_6$alkyl, halo, $C_3$-$C_8$cycloalkyl, a 5 membered heteroaryl wherein 4 ring members are each independently selected from N and $NR^6$, and a 3 to 6 membered heterocycloalkyl wherein 1 or 2 ring members are each independently selected from N, $NR^6$ and O, and wherein the cycloalkyl and heterocycloalkyl are unsubstituted or are substituted with 1 or 2 substituents independently selected from the group consisting of CN, halo and -C(=O)OH;

and

n is 1 or 2.

**Embodiment 73.** The compound of any one of Embodiment 52 to 65, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

$X_1$ is $NR^1$, $C(R^{2a})_2$ or O;

$R^1$ is H, $C_1$-$C_6$alkyl, $C_3$-$C_8$cycloalkyl, a $C_1$-$C_6$alkyl substituted with one or more $R^{12}$, a $C_1$-$C_6$alkenyl substituted with one or more $R^{12}$, or a 4 membered heterocycloalkyl wherein 1 ring member is selected from N, $NR^6$ and O; and wherein the cycloalkyl and heterocycloalkyl are unsubstituted or the cycloalkyl and heterocycloalkyl are substituted with 1 substituent selected from the group consisting of CN, -C(=O)OH, $C_1$-$C_6$haloalkyl and $C_1$-$C_6$alkyl substituted with CN;

each $R^{2a}$ is independently selected from the group consisting of H, $NH_2$, $C_1$-$C_6$alkyl and $C_1$-$C_6$alkyl substituted with -C(=O)OH, -OH or CN;

$R^3$ is selected from the group consisting of:

i) -$CHR^{13}R^{14}$;

ii) benzyl which is unsubstituted or is substituted with 1 $R^4$;

iii) a 6 membered heteroaryl wherein 1 ring member is selected from N, and wherein the 6 membered heteroaryl is unsubstituted or is substituted with 1 or 2 $R^4$;

iv) a 10 membered bicyclic heteroaryl with an attachment point at a carbon atom ring member and a N heteroatom as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 10 membered bicyclic heteroaryl has 0, 1, 2 or 3 additional N heteroatoms as ring members, and wherein the 10 membered bicyclic heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

v) a 9 or 10 membered bicyclic heteroaryl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$ and O, and wherein the 9 or 10 membered bicyclic heteroaryl is unsubstituted or is substituted with 1 or 2 $R^4$;

and

vi) a 9 or 10 membered bicyclic heterocyclyl wherein 1 ring member is selected from N, $NR^6$ or O, and wherein the 9 or 10 membered bicyclic heterocyclyl is unsubstituted, or is substituted with an oxo;

each $R^4$ is independently selected from the group consisting of $-C(=O)N(R^7)_2$, $-N(R^7)_2$, -CN, $-S(=O)_2R^6$, $-C(=O)NR^7R^6$,  , $C_1$-$C_6$alkyl and halo;

each $R^5$ is independently selected from the group consisting of $-SF_5$, $C_1$-$C_6$alkyl, $C_1$-$C_6$haloalkyl, halo, $C_1$-$C_6$haloalkoxy, $C_1$-$C_6$alkoxy, $C_3$-$C_8$cycloalkyl, and a $C_1$-$C_6$alkyl substituted with CN or OH, wherein the cycloalkyl is unsubstituted or is substituted with 1 or 2 $R^9$;

each $R^6$ is independently selected from the group consisting of H, $C_1$-$C_6$alkyl or $C_1$-$C_6$alkyl substituted with $-OR^7$ ;

each $R^7$ is independently selected from the group consisting of H and $C_1$-$C_6$alkyl;

each $R^9$ is independently selected from the group consisting of halo, -C(=O)OH, and $C_1$-$C_6$alkyl substituted with -OH;

$R^{10}$ is H or $C_1$-$C_6$alkyl;

each $R^{12}$ is independently selected from the group consisting of CN, -OH, -C(=O)OH, $-C(=O)OR^{10}$, $-C(=O)N(R^7)_2$, $C_1$-$C_6$alkoxy, $C_1$-$C_6$alkyl, halo, $C_3$-$C_8$cycloalkyl, a 5 membered heteroaryl wherein 4 ring members are each independently selected from N and $NR^6$, and a 3 to 6 membered heterocycloalkyl wherein 1 or 2 ring members are each independently selected from N, $NR^6$, and O, and wherein the cycloalkyl, and heterocycloalkyl are unsubstituted or are substituted with 1 or 2 substituents independently selected from the group consisting of CN, halo and -C(=O)OH;

$R^{13}$ is H;

$R^{14}$ is a 6 membered heterocyclyl wherein 1 ring member is selected from N or $NR^6$, and wherein the 6 membered heterocyclyl is substituted with an oxo;

and

n is 0, 1 or 2.

**Embodiment 74.** The compound of any one of Embodiment 52 to 65, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

$X_1$ is $NR^1$;

$R^1$ is H, $C_1$-$C_6$alkyl, $C_3$-$C_8$cycloalkyl, a $C_1$-$C_6$alkyl substituted with one or more $R^{12}$, a $C_1$-$C_6$alkenyl substituted with one or more $R^{12}$, or a 4 membered heterocycloalkyl wherein 1 ring member is selected from N, $NR^6$ and O; and wherein the cycloalkyl and heterocycloalkyl are unsubstituted or the cycloalkyl and heterocycloalkyl are substituted with 1 substituent selected from the group consisting of CN, -C(=O)OH, $C_1$-$C_6$haloalkyl and $C_1$-$C_6$alkyl substituted with CN;

$R^3$ is selected from the group consisting of:

i) $-CHR^{13}R^{14}$;

ii) benzyl which is unsubstituted or is substituted with 1 $R^4$;

iii) a 6 membered heteroaryl wherein 1 ring member is selected from N, and wherein the 6 membered heteroaryl is unsubstituted or is substituted with 1 or 2 $R^4$;

iv) a 10 membered bicyclic heteroaryl with an attachment point at a carbon atom ring member and a N heteroatom as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 10 membered bicyclic heteroaryl has 0, 1, 2 or 3 additional N heteroatoms as ring members, and wherein the 10 membered bicyclic heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

v) a 9 or 10 membered bicyclic heteroaryl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$ and O, and wherein the 9 or 10 membered bicyclic heteroaryl is unsubstituted or is substituted with 1 or 2 $R^4$;

and

vi) a 9 or 10 membered bicyclic heterocyclyl wherein 1 ring member is selected from N, $NR^6$ or O, and wherein the 9 or 10 membered bicyclic heterocyclyl is unsubstituted, or is substituted with an oxo;

each $R^4$ is independently selected from the group consisting of $-C(=O)N(R^7)_2$, $-N(R^7)_2$, -CN, $-S(=O)_2R^6$, $-C(=O)NR^7R^6$,  , $C_1$-$C_6$alkyl and halo;

each $R^5$ is independently selected from the group consisting of $-SF_5$, $C_1$-$C_6$alkyl, $C_1$-$C_6$haloalkyl, halo, $C_1$-$C_6$haloalkoxy, $C_1$-$C_6$alkoxy, $C_3$-$C_8$cycloalkyl, and a $C_1$-$C_6$alkyl substituted with CN or OH, wherein the cycloalkyl is unsubstituted or is substituted with 1 or 2 $R^9$;

each $R^6$ is independently selected from the group consisting of H, $C_1$-$C_6$alkyl or $C_1$-$C_6$alkyl substituted with $-OR^7$ ;

each $R^7$ is independently selected from the group consisting of H and $C_1$-$C_6$alkyl;

each $R^9$ is independently selected from the group consisting of halo, -C(=O)OH, and $C_1$-$C_6$alkyl substituted with -OH;

$R^{10}$ is H or $C_1$-$C_6$alkyl;

each $R^{12}$ is independently selected from the group consisting of CN, -OH, -C(=O)OH, $-C(=O)OR^{10}$, $-C(=O)N(R^7)_2$, $C_1$-$C_6$alkoxy, $C_1$-$C_6$alkyl, halo, $C_3$-$C_8$cycloalkyl, a 5 membered heteroaryl wherein 4 ring members are each independently selected from N and $NR^6$, and a 3 to 6 membered heterocycloalkyl wherein 1 or 2 ring members are each independently selected from N, $NR^6$, and O, and wherein the cycloalkyl,

and heterocycloalkyl are unsubstituted or are substituted with 1 or 2 substituents independently selected from the group consisting of CN, halo and -C(=O)OH;

$R^{13}$ is H;

$R^{14}$ is a 6 membered heterocyclyl wherein 1 ring member is selected from N or $NR^6$, and wherein the 6 membered heterocyclyl is substituted with an oxo;

and

n is 0, 1 or 2.

**Embodiment 75.** The compound of any one of Embodiment 52 to 65, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

$X_1$ is $NR^1$;

$R^1$ is H, $C_1$-$C_6$alkyl, $C_3$-$C_8$cycloalkyl, a $C_1$-$C_6$alkyl substituted with one or more $R^{12}$, a $C_1$-$C_6$alkenyl substituted with one or more $R^{12}$, or a 4 membered heterocycloalkyl wherein 1 ring member is selected from N, $NR^6$ and O; and wherein the cycloalkyl and heterocycloalkyl are unsubstituted or the cycloalkyl and heterocycloalkyl are substituted with 1 substituent selected from the group consisting of CN, -C(=O)OH, $C_1$-$C_6$haloalkyl and $C_1$-$C_6$alkyl substituted with CN;

$R^3$ is selected from the group consisting of:

i) a 6 membered heteroaryl wherein 1 ring member is selected from N, and wherein the 6 membered heteroaryl is unsubstituted or is substituted with 1 or 2 $R^4$;

ii) a 10 membered bicyclic heteroaryl with an attachment point at a carbon atom ring member and a N heteroatom as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 10 membered bicyclic heteroaryl has 0, 1, 2 or 3 additional N heteroatoms as ring members, and wherein the 10 membered bicyclic heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

iii) a 9 or 10 membered bicyclic heteroaryl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$ and O, and wherein the 9 or 10 membered bicyclic heteroaryl is unsubstituted or is substituted with 1 or 2 $R^4$;

and

iv) a 9 or 10 membered bicyclic heterocyclyl wherein 1 ring member is selected from N, $NR^6$ or O, and wherein the 9 or 10 membered bicyclic heterocyclyl is unsubstituted, or is substituted with an oxo;

each $R^4$ is independently selected from the group consisting of -C(=O)N($R^7$)$_2$, -N($R^7$)$_2$, -CN, -S(=O)$_2R^6$, -C(=O)N$R^7R^6$,  , $C_1$-$C_6$alkyl and halo;

each $R^5$ is independently selected from the group consisting of -$SF_5$, $C_1$-$C_6$alkyl, $C_1$-$C_6$haloalkyl, halo, $C_1$-$C_6$haloalkoxy, $C_1$-$C_6$alkoxy, $C_3$-$C_8$cycloalkyl, and a $C_1$-$C_6$alkyl substituted with CN or OH, wherein the cycloalkyl is unsubstituted or is substituted with 1 or 2 $R^9$;

each $R^6$ is independently selected from the group consisting of H, $C_1$-$C_6$alkyl or $C_1$-$C_6$alkyl substituted with -$OR^7$ ;

each $R^7$ is independently selected from the group consisting of H and $C_1$-$C_6$alkyl;

each $R^9$ is independently selected from the group consisting of halo, -C(=O)OH, and $C_1$-$C_6$alkyl substituted with -OH;

$R^{10}$ is H or $C_1$-$C_6$alkyl;

each $R^{12}$ is independently selected from the group consisting of CN, -OH, -C(=O)OH, -C(=O)$OR^{10}$, -C(=O)N($R^7$)$_2$, $C_1$-$C_6$alkoxy, $C_1$-$C_6$alkyl, halo, $C_3$-$C_8$cycloalkyl, a 5 membered heteroaryl wherein 4 ring members are each independently selected from N and $NR^6$, and a 3 to 6 membered heterocycloalkyl wherein 1 or 2 ring members are each independently selected from N, $NR^6$, and O, and wherein the cycloalkyl, and heterocycloalkyl are unsubstituted or are substituted with 1 or 2 substituents independently selected from the group consisting of CN, halo and -C(=O)OH;

and

n is 0, 1 or 2.

**Embodiment 76.** The compound of any one of Embodiments 52 to 65, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

$X_1$ is $NR^1$;

$R^1$ is H or $C_1$-$C_6$alkyl substituted with one or more $R^{12}$;

$R^3$ is selected from the group consisting of:

i) -$CHR^{13}R^{14}$;

ii) benzyl which is unsubstituted or is substituted with 1 $R^4$;

iii) a 6 membered heteroaryl wherein 1 ring member is selected from N, and wherein the 6 membered heteroaryl is unsubstituted or is substituted with 1 or 2 $R^4$;

iv) a 10 membered bicyclic heteroaryl with an attachment point at a carbon atom ring member and a N heteroatom as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 10 membered bicyclic heteroaryl has 0, 1, 2 or 3 additional N heteroatoms as ring members, and wherein the 10 membered bicyclic heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

v) a 9 or 10 membered bicyclic heteroaryl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$ and O, and wherein the 9 or 10 membered bicyclic heteroaryl is unsubstituted or is substituted with 1 or 2 $R^4$;

vi) a 6 membered heterocyclyl wherein 1 ring member is selected from $NR^6$, and wherein the 6 membered heterocyclyl is substituted with an oxo;

and

vii) a 9 or 10 membered bicyclic heterocyclyl wherein 1 ring member is selected from N, $NR^6$ or O, and wherein the 9 or 10 membered bicyclic heterocyclyl is unsubstituted, or is substituted with an oxo;

each $R^4$ is independently selected from the group consisting of $-C(=O)N(R^7)_2$, -C(=O)OH, $-N(R^7)_2$, -CN, -OH,  , $C_1$-$C_6$alkyl, halo, 6 membered heterocycloalkyl wherein 1 or 2 ring members are each independently selected from N and $NR^6$, and $C_1$-$C_6$alkyl substituted with $NH_2$, and wherein the heterocycloalkyl is unsubstituted;

each $R^5$ is independently selected from the group consisting of -NR6C(=O)C2-C6alkenyl, $-SF_5$, $C_1$-$C_6$alkyl, $C_1$-$C_6$haloalkyl, halo, $C_1$-$C_6$haloalkoxy, $C_1$-$C_6$alkoxy, $C_3$-$C_8$cycloalkyl, wherein the cycloalkyl is unsubstituted or is substituted with 1 $R^9$;

each $R^6$ is independently selected from the group consisting of H or $C_1$-$C_6$alkyl;

each $R^7$ is independently selected from the group consisting of H and $C_1$-$C_6$alkyl;

each $R^9$ is independently selected from the group consisting of $C_1$-$C_6$alkyl substituted with -OH;

$R^{10}$ is H or $C_1$-$C_6$alkyl;

each $R^{12}$ is independently selected from the group consisting of CN, -OH, -C(=O)OH, $-C(=O)N(R^7)_2$, $C_1$-$C_6$alkoxy, halo, $C_1$-$C_6$haloalkyl, $C_3$-$C_8$cycloalkyl, a 5 membered heteroaryl wherein 4 ring members are each independently selected from N and $NR^6$, and a 3 membered heterocycloalkyl wherein 1 ring member is selected from N, $NR^6$ and O, and wherein the cycloalkyl, heteroaryl and heterocycloalkyl are unsubstituted or are substituted with 1 substituent from the group consisting of CN and -C(=O)OH;

$R^{13}$ is H;

$R^{14}$ is a 6 membered heterocycle wherein 1 ring member is selected from N or $NR^6$, and wherein the 6 membered heterocycle is substituted with an oxo; and

n is 0, 1 or 2.

**Embodiment 77.** The compound of any one of Embodiments 52 to 65, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

$R^1$ is H or $C_1$-$C_6$alkyl substituted with one or more $R^{12}$;

$R^3$ is selected from the group consisting of:

i) a 9 or 10 membered bicyclic heteroaryl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$ and O, wherein the 9 or 10 membered bicyclic heteroaryl is unsubstituted or is substituted with 1 or 2 $R^4$;

and

ii) a 10 membered bicyclic heteroaryl with an attachment point at a carbon atom ring member and a N heteroatom as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 10 membered bicyclic heteroaryl has 0, 1, 2 or 3 additional N heteroatoms as ring members, and wherein the 10 membered bicyclic heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

each $R^4$ is independently selected from the group consisting of -C(=O)N($R^7$)$_2$, -C(=O)OH, -N($R^7$)$_2$, -CN, -OH,  , $C_1$-$C_6$alkyl, halo, 6 membered heterocycloalkyl wherein 1 or 2 ring members are each independently selected from N and $NR^6$, and $C_1$-$C_6$alkyl substituted with $NH_2$, and wherein the heterocycloalkyl is unsubstituted;

each $R^5$ is independently selected from the group consisting of -NR6C(=O)C2-C6alkenyl, -$SF_5$, $C_1$-$C_6$alkyl, $C_1$-$C_6$haloalkyl, halo, $C_1$-$C_6$haloalkoxy, $C_1$-$C_6$alkoxy, $C_3$-$C_8$cycloalkyl, wherein the cycloalkyl is unsubstituted or is substituted with 1 $R^9$;

each $R^6$ is independently selected from the group consisting of H or $C_1$-$C_6$alkyl;

each $R^7$ is independently selected from the group consisting of H and $C_1$-$C_6$alkyl;

each $R^9$ is independently selected from the group consisting of $C_1$-$C_6$alkyl substituted with -OH;

$R^{10}$ is H or $C_1$-$C_6$alkyl;

and

each $R^{12}$ is independently selected from the group consisting of CN, -OH, -C(=O)OH, -C(=O)N($R^7$)$_2$, $C_1$-$C_6$alkoxy, halo, $C_1$-$C_6$haloalkyl, $C_3$-$C_8$cycloalkyl, a 5 membered heteroaryl wherein 4 ring members are each independently selected from N and $NR^6$, and a 3 membered heterocycloalkyl wherein 1 ring member is selected from N, $NR^6$ and O, and wherein the cycloalkyl, heteroaryl and heterocycloalkyl are unsubstituted or are substituted with 1 substituent selected from the group consisting of CN and -C(=O)OH.

**Embodiment 78.** The compound of any one of Embodiments 52 to 65, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

$R^1$ is H or $C_1$-$C_6$alkyl substituted with one or more $R^{12}$;

$R^3$ is a 9 or 10 membered bicyclic heteroaryl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$ and O, wherein the 9 or 10 membered bicyclic heteroaryl is unsubstituted or is substituted with 1 or 2 $R^4$;

each $R^4$ is independently selected from the group consisting of -C(=O)N($R^7$)$_2$, -C(=O)OH, -N($R^7$)$_2$, -CN, -OH,  , $C_1$-$C_6$alkyl, halo, 6 membered heterocycloalkyl

wherein 1 or 2 ring members are each independently selected from N and $NR^6$, and $C_1$-$C_6$alkyl substituted with $NH_2$, and wherein the heterocycloalkyl is unsubstituted;

each $R^5$ is independently selected from the group consisting of -NR6C(=O)C2-C6alkenyl, $-SF_5$, $C_1$-$C_6$alkyl, $C_1$-$C_6$haloalkyl, halo, $C_1$-$C_6$haloalkoxy, $C_1$-$C_6$alkoxy, $C_3$-$C_8$cycloalkyl, wherein the cycloalkyl is unsubstituted or is substituted with 1 $R^9$;

each $R^6$ is independently selected from the group consisting of H or $C_1$-$C_6$alkyl;

each $R^7$ is independently selected from the group consisting of H and $C_1$-$C_6$alkyl;

each $R^9$ is independently selected from the group consisting of $C_1$-$C_6$alkyl substituted with -OH;

$R^{10}$ is H or $C_1$-$C_6$alkyl;

and

each $R^{12}$ is independently selected from the group consisting of CN, -OH, -C(=O)OH, -C(=O)N($R^7$)$_2$, $C_1$-$C_6$alkoxy, halo, $C_1$-$C_6$haloalkyl, $C_3$-$C_8$cycloalkyl, a 5 membered heteroaryl wherein 4 ring members are each independently selected from N and $NR^6$, and a 3 membered heterocycloalkyl wherein 1 ring member is selected from N, $NR^6$ and O, and wherein the cycloalkyl, heteroaryl and heterocycloalkyl are unsubstituted or are substituted with 1 substituent selected from the group consisting of CN and -C(=O)OH.

**Embodiment 79.** The compound of any one of Embodiment 52 to 65, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

$X_1$ is $NR^1$, C($R^{2a}$)$_2$ or O;

$R^1$ is H, methyl, ethyl, isopropyl,-$CH_2R^{12}$, -$CH_2CH_2R^{12}$, -$CH_2CR^{12}$=$CH_2$, -$CH_2CHR^{12}CH_3$, -$CH_2CH$=$CHR^{12}$, -$CH_2CH_2CH(CH_3)R^{12}$, -$CH(CH_3)CH_2CH_2R^{12}$, -$CH_2CH_2C(CH_3)_2R^{12}$, a cyclopropyl which is unsubstituted, or a cyclopropyl which is substituted with -$CH_2CN$;

each $R^{2a}$ is independently selected from the group consisting of H and -$CH_3$;

$R^3$ is selected from the group consisting of:

i) pyridyl substituted with 1 or 2 $R^4$;

ii) isoquinolin-4-yl which is unsubstituted or is substituted with 1 or 2 $R^4$;

and

iii) 5,6,7,8-tetrahydroisoquinolin-4-yl which is unsubstituted;

each $R^4$ is independently selected from the group consisting of -$CH_3$, -C(=O)N($R^7$)$_2$, -N($R^7$)$_2$, F, Br, -CN, -S(=O)$_2R^6$, -C(=O)N$R^7R^6$, and  ,

each $R^5$ is independently selected from the group consisting of F, Br, Cl, -$CF_3$, -$CHF_2$, -$CH_2F$, -C($CH_3$)$F_2$, -$CH_3$, isopropyl, -$OCHF_2$, -$OCClF_2$, -$OCF_3$, -$OCH_3$, $SF_5$, -

$C(CH_3)_2OH$, $-CH_2CF_3$, $-CH(CH_3)CF_3$, an unsubstituted cyclopropyl, a cyclopropyl substituted with 1 $R^9$, and a cyclobutyl substituted with 1 or 2 $R^9$;

each $R^6$ is independently selected from the group consisting of H, $-CH_3$, and $-CH_2CH_2OR^7$;

each $R^7$ is independently selected from the group consisting of H and $-CH_3$;

each $R^9$ is independently selected from the group consisting of F, -C(=O)OH, and $-CH_2OH$;

$R^{10}$ is H or $-CH_3$;

each $R^{12}$ is independently selected from the group consisting of CN, $-CH_3$, $-OCH_3$, -OH, F, $-C(=O)OR^{10}$, -C(=O)OH, $-C(=O)N(R^7)_2$, an unsubstituted morpholinyl, an unsubstituted tetrazolyl, an unsubstituted oxiranyl, a piperidinyl which is unsubstituted or substituted with 1 or 2 fluoro, an unsubstituted cyclopropyl or a cyclopropyl substituted with CN or -C(=O)OH;

and

n is 0, 1 or 2.

**Embodiment 80.** The compound of any one of Embodiment 52 to 65, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

$X_1$ is $NR^1$;

$R^1$ is H, methyl, ethyl, isopropyl,$-CH_2R^{12}$, $-CH_2CH_2R^{12}$, $-CH_2CR^{12}=CH_2$, $-CH_2CHR^{12}CH_3$, $-CH_2CH=CHR^{12}$, $-CH_2CH_2CH(CH_3)R^{12}$, $-CH(CH_3)CH_2CH_2R^{12}$, $-CH_2CH_2C(CH_3)_2R^{12}$, a cyclopropyl which is unsubstituted, or a cyclopropyl which is substituted with $-CH_2CN$;

$R^3$ is selected from the group consisting of:

i) pyridyl substituted with 1 or 2 $R^4$;

ii) isoquinolin-4-yl which is unsubstituted or is substituted with 1 or 2 $R^4$;

and

iii) 5,6,7,8-tetrahydroisoquinolin-4-yl which is unsubstituted;

each $R^4$ is independently selected from the group consisting of $-CH_3$, $-C(=O)N(R^7)_2$, $-N(R^7)_2$, F, Br, -CN, $-S(=O)_2R^6$, $-C(=O)NR^7R^6$, and  ,

each $R^5$ is independently selected from the group consisting of F, Br, Cl, $-CF_3$, $-CHF_2$, $-CH_2F$, $-C(CH_3)F_2$, $-CH_3$, isopropyl, $-OCHF_2$, $-OCClF_2$, $-OCF_3$, $-OCH_3$, $SF_5$, $-C(CH_3)_2OH$, $-CH_2CF_3$, $-CH(CH_3)CF_3$, an unsubstituted cyclopropyl, a cyclopropyl substituted with 1 $R^9$, and a cyclobutyl substituted with 1 or 2 $R^9$;

each $R^6$ is independently selected from the group consisting of H, $-CH_3$, and $-CH_2CH_2OR^7$;

each $R^7$ is independently selected from the group consisting of H and $-CH_3$;

each $R^9$ is independently selected from the group consisting of F, -C(=O)OH, and -$CH_2OH$;

$R^{10}$ is H or -$CH_3$;

each $R^{12}$ is independently selected from the group consisting of CN, -$CH_3$, -$OCH_3$, -OH, -F, -C(=O)$OR^{10}$, -C(=O)OH, -C(=O)$N(R^7)_2$, an unsubstituted morpholinyl, an unsubstituted tetrazolyl, an unsubstituted oxiranyl, a piperidinyl which is unsubstituted or substituted with 1 or 2 fluoro, an unsubstituted cyclopropyl or a cyclopropyl substituted with CN or -C(=O)OH;

and

n is 0, 1 or 2.

**Embodiment 81.** The compound of any one of Embodiments 52 to 65, or a pharmaceutically acceptable salt or stereoisomer thereof stereoisomer thereof, wherein,

$X_1$ is $NR^1$;

$R^1$ is H, methyl, ethyl, isopropyl,-$CH_2R^{12}$, -$CH_2CH_2R^{12}$, -$CH_2CR^{12}=CH_2$, -$CH_2CHR^{12}CH_3$, -$CH_2CH=CHR^{12}$, -$CH_2CH_2CH(CH_3)R^{12}$, -$CH(CH_3)CH_2CH_2R^{12}$, -$CH_2CH_2C(CH_3)_2R^{12}$, a cyclopropyl which is unsubstituted, or a cyclopropyl which is substituted with -$CH_2CN$;

$R^3$ is isoquinolin-4-yl which is unsubstituted or is substituted with 1 or 2 $R^4$;

each $R^4$ is independently selected from the group consisting of -$CH_3$, -C(=O)$N(R^7)_2$, - -$N(R^7)_2$, F, Br, -CN, -S(=O)$_2R^6$, -C(=O)$NR^7R^6$, and  ,

each $R^5$ is independently selected from the group consisting of F, Br, Cl, -$CF_3$, -$CHF_2$, -$CH_2F$, -$C(CH_3)F_2$, -$CH_3$, isopropyl, -$OCHF_2$, -$OCClF_2$, -$OCF_3$, -$OCH_3$, $SF_5$, -$C(CH_3)_2OH$, -$CH_2CF_3$, -$CH(CH_3)CF_3$, an unsubstituted cyclopropyl, a cyclopropyl substituted with 1 $R^9$, and a cyclobutyl substituted with 1 or 2 $R^9$;

each $R^6$ is independently selected from the group consisting of H, -$CH_3$, and -$CH_2CH_2OR^7$;

each $R^7$ is independently selected from the group consisting of H and -$CH_3$;

each $R^9$ is independently selected from the group consisting of F, -C(=O)OH, and -$CH_2OH$;

$R^{10}$ is H or -$CH_3$;

each $R^{12}$ is independently selected from the group consisting of CN, -$CH_3$, -$OCH_3$, -OH, -F, -C(=O)$OR^{10}$, -C(=O)OH, -C(=O)$N(R^7)_2$, an unsubstituted morpholinyl, an unsubstituted tetrazolyl, an unsubstituted oxiranyl, a piperidinyl which is unsubstituted or substituted with 1 or 2 fluoro, an unsubstituted cyclopropyl or a cyclopropyl substituted with CN or -C(=O)OH;

and

n is 0, 1 or 2.

**Embodiment 82.** The compound of any one of Embodiments 1 to 81, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $X_1$ is $NR^1$, N, $C(R^{2a})_2$, $CR^{2a}$, O or $C=C(R^{2a})_2$.

**Embodiment 83.** The compound of any one of Embodiments 1 to 81, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $X_1$ is $NR^1$.

**Embodiment 84.** The compound of any one of Embodiments 1 to 81, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $X_1$ is N.

**Embodiment 85.** The compound of any one of Embodiments 1 to 81, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $X_1$ is $C(R^{2a})_2$.

**Embodiment 86.** The compound of any one of Embodiments 1 to 81, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $X_1$ is $CR^{2a}$.

**Embodiment 87.** The compound of any one of Embodiments 1 to 81, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $X_1$ is O.

**Embodiment 88.** The compound of any one of Embodiments 1 to 81, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $X_1$ is $C=C(R^{2a})_2$.

**Embodiment 89.** The compound of any one of Embodiments 1 to 81, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $X_1$ is $CR^{2a}R^{2b}$.

**Embodiment 90.** The compound of any one of Embodiments 1 to 81, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $X_1$ is a spiro attached 4 to 6 membered heterocycloalkyl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$, O, C(=O), S and $S(=O)_2$, or a spiro attached $C_3$-$C_8$cycloalkyl, and wherein the heterocycloalkyl and $C_3$-$C_8$cycloalkyl are unsubstituted or are substituted with 1 or 2 OH groups.

**Embodiment 91.** The compound of any one of Embodiments 1 to 90, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $X_2$ is N.

**Embodiment 92.** The compound of any one of Embodiments 1 to 90, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $X_2$ is C.

**Embodiment 93.** The compound of any one of Embodiments 1 to 90, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $X_2$ is CH.

**Embodiment 94.** The compound of any one of Embodiments 1 to 93, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $X_3$ is N.

**Embodiment 95.** The compound of any one of Embodiments 1 to 93, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $X_3$ is C.

**Embodiment 96.** The compound of any one of Embodiments 1 to 93, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $X_3$ is CH.

**Embodiment 97.** The compound of any one of Embodiments 1 to 96, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $X_4$ is $C(R^{2a})_2$.

**Embodiment 98.** The compound of any one of Embodiments 1 to 96 or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $X_4$ is $C=C(R^{2a})_2$.

**Embodiment 99.** The compound of any one of Embodiments 1 to 98, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^1$ is H.

**Embodiment 100.** The compound of any one of Embodiments 1 to 98, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^1$ is $C_1$-$C_6$alkyl substituted with one or more $R^{12}$.

**Embodiment 101.** The compound of any one of Embodiments 1 to 98, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^1$ is $–CH_2R^{12}$.

**Embodiment 102.** The compound of any one of Embodiments 1 to 98, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^1$ is $C_1$-$C_6$alkenyl substituted with one or more $R^{12}$.

**Embodiment 103.** The compound of any one of Embodiments 1 to 102, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^{12}$ is CN, $NH_2$, -OH, -C(=O)OH, $-C(=O)N(R^7)_2$, -C(=O)C(=O)OH, $C_1$-$C_6$alkoxy, halo or $C_1$-$C_6$haloalkyl.

**Embodiment 104.** The compound of any one of Embodiments 1 to 103, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^{12}$ is CN.

**Embodiment 105.** The compound of any one of Embodiments 1 to 100, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^{12}$ is $C_1$-$C_6$alkyl substituted with CN.

**Embodiment 106.** The compound of any one of Embodiments 1 to 98, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^1$ is $–CH_2CN$.

**Embodiment 107.** The compound of any one of Embodiments 1 to 98, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^{12}$ is a 3 to 6 membered heterocycloalkyl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$, O and S, and wherein the heterocycloalkyl is unsubstituted or is substituted with 1, 2 or 3 substituents independently selected from the group consisting of CN, -C(=O)OH, $NH_2$, OH and $C_1$-$C_6$alkyl.

**Embodiment 108.** The compound of any one of Embodiments 1 to 101, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^{12}$ is a 3 membered heterocycloalkyl wherein 1 ring member is N, $NR^6$, O and S, and wherein the heterocycloalkyl is unsubstituted.

**Embodiment 109.** The compound of any one of Embodiments 1 to 101, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^{12}$ is oxiranyl.

**Embodiment 110.** The compound of any one of Embodiments 1 to 101, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^{12}$ is $C_3$-$C_8$cycloalkyl,

and wherein the cycloalkyl is unsubstituted or is substituted with 1, 2 or 3 substituents independently selected from the group consisting of CN, -C(=O)OH, $NH_2$, OH and $C_1$-$C_6$alkyl.

**Embodiment 111.** The compound of any one of Embodiments 1 to 101, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^{12}$ is a 5 or a 6 membered heteroaryl wherein 1, 2, 3, or 4 ring members are each independently selected from N, $NR^6$, O and S, and wherein the heteroaryl is unsubstituted or is substituted with 1, 2 or 3 substituents independently selected from the group consisting of CN, -C(=O)OH, $NH_2$, OH and $C_1$-$C_6$alkyl.

**Embodiment 112.** The compound of any one of Embodiments 1 to 101, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein each $R^{12}$ is independently selected from the group consisting of CN, -$CH_3$, -$OCH_3$, -OH, -F, -C(=O)$OR^{10}$, -C(=O)OH, -C(=O)$N(R^7)_2$, an unsubstituted morpholinyl, an unsubstituted tetrazolyl, an unsubstituted oxiranyl, a piperidinyl which is unsubstituted or substituted with 1 or 2 fluoro, an unsubstituted cyclopropyl or a cyclopropyl substituted with CN or -C(=O)OH.

**Embodiment 113.** The compound of any one of Embodiments 1 to 98, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^1$ is $C_1$-$C_6$alkyl.

**Embodiment 114.** The compound of any one of Embodiments 1 to 98, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^1$ is methyl, ethyl, propyl or isopropyl.

**Embodiment 115.** The compound of any one of Embodiments 1 to 98, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^1$ is $C_3$-$C_8$cycloalkyl, and wherein the cycloalkyl is unsubstituted or is substituted with 1 or 2 substituents independently selected from the group consisting of CN, -C(=O)OH, $NH_2$, OH, $C_1$-$C_6$haloalkyl, $C_1$-$C_6$alkyl or $C_1$-$C_6$alkyl substituted with -C(=O)OH, -OH, CN or $NH_2$.

**Embodiment 116.** The compound of any one of Embodiments 1 to 98, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^1$ is a 4 to 7 membered heterocycloalkyl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$, O and S, and wherein the heterocycloalkyl is unsubstituted or is substituted with 1 or 2 substituents independently selected from the group consisting of CN, -C(=O)OH, $NH_2$, OH, $C_1$-$C_6$haloalkyl, $C_1$-$C_6$alkyl or $C_1$-$C_6$alkyl substituted with -C(=O)OH, -OH, CN or $NH_2$.

**Embodiment 117.** The compound of any one of Embodiments 1 to 98, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^1$ is H, methyl, ethyl, isopropyl,-$CH_2R^{12}$, -$CH_2CH_2R^{12}$, -$CH_2CR^{12}$=$CH_2$, -$CH_2CHR^{12}CH_3$, -$CH_2CH$=$CHR^{12}$, -$CH_2CH_2CH(CH_3)R^{12}$, -$CH(CH_3)CH_2CH_2R^{12}$, -$CH_2CH_2C(CH_3)_2R^{12}$, a cyclopropyl which is unsubstituted, or a cyclopropyl which is substituted with -$CH_2CN$.

**Embodiment 118.** The compound of any one of Embodiments 1 to 117, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein each $R^{2a}$ is

independently selected from the group consisting of H, $NH_2$, $C_1$-$C_6$alkyl and $C_1$-$C_6$alkyl substituted with -C(=O)OH, -OH and CN.

**Embodiment 119.** The compound of any one of Embodiments 1 to 117, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein each $R^{2a}$ is independently selected from the group consisting of H, $C_1$-$C_6$alkyl and $C_1$-$C_6$alkyl substituted with CN.

**Embodiment 120.** The compound of any one of Embodiments 1 to 117, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein each $R^{2a}$ is independently selected from the group consisting of H and $C_1$-$C_6$alkyl.

**Embodiment 121.** The compound of any one of Embodiments 1 to 117, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^{2b}$ is H.

**Embodiment 122.** The compound of any one of Embodiments 1 to 117, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^{2b}$ is $C_1$-$C_6$alkyl.

**Embodiment 123.** The compound of any one of Embodiments 1 to 117, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^{2b}$ is $C_3$-$C_8$cycloalkyl, and wherein the $C_3$-$C_8$cycloalkyl is unsubstituted or substituted with 1, 2, 3 or 4 substituents independently selected from the group consisting of $C_1$-$C_6$alkyl, OH and -$N(R^7)_2$.

**Embodiment 124.** The compound of any one of Embodiments 1 to 117, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^{2b}$ is a 4 to 7 membered heterocycloalkyl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$, O and S, and wherein the heterocycloalkyl is unsubstituted or substituted with 1, 2, 3 or 4 substituents independently selected from the group consisting of $C_1$-$C_6$alkyl, OH and -$N(R^7)_2$.

**Embodiment 125.** The compound of any one of Embodiments 1 to 117, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein each $R^{2a}$ is independently selected from the group consisting of H and -$CH_3$.

**Embodiment 126.** The compound of any one of Embodiments 1 to 125, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^3$ is -$(CH_2)_{0\text{-}6}CHR^{13}R^{14}$.

**Embodiment 127.** The compound of any one of Embodiments 1 to 125, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^3$ is -$CHR^{13}R^{14}$.

**Embodiment 128.** The compound of any one of Embodiments 1 to 125, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^3$ is benzyl which is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$.

**Embodiment 129.** The compound of any one of Embodiments 1 to 125, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^3$ is benzyl which is unsubstituted or is substituted with 1 $R^4$.

**Embodiment 130.** The compound of any one of Embodiments 1 to 125, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^3$ is a 6 membered

heteroaryl wherein 1, 2 or 3 ring members are each independently selected from N, O and S, and wherein the 6 membered heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$.

**Embodiment 131.** The compound of any one of Embodiments 1 to 125, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^3$ is a 6 membered heteroaryl wherein 1, ring member is selected from N, and wherein the 6 membered heteroaryl is unsubstituted or is substituted with 1 or 2 $R^4$.

**Embodiment 132.** The compound of any one of Embodiments 1 to 125, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^3$ is pyridyl which is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$.

**Embodiment 133.** The compound of any one of Embodiments 1 to 125, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^3$ is pyrid-3-yl which is unsubstituted or is substituted with 1 or 2 $R^4$.

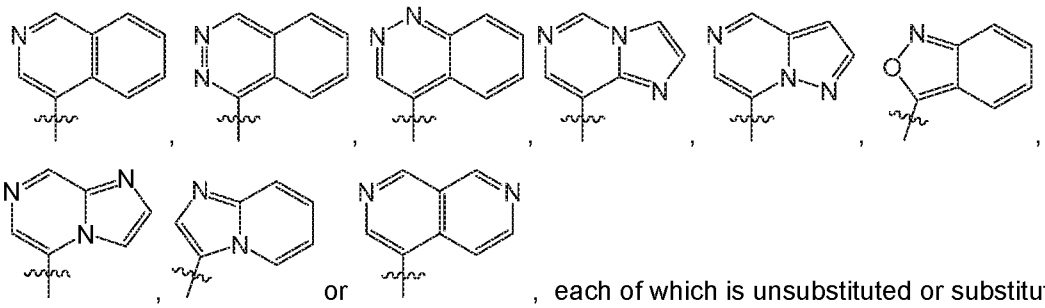
**Embodiment 134.** The compound of any one of Embodiments 1 to 125, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^3$ is a 9 or 10 membered bicyclic heteroaryl wherein 1, 2, 3, 4 or 5 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 9 or 10 membered bicyclic heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$.

**Embodiment 135.** The compound of any one of Embodiments 1 to 125, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^3$ is a 9 or 10 membered bicyclic heteroaryl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$ andO and S, and wherein the 9 or 10 membered bicyclic heteroaryl is unsubstituted or is substituted with 1 or 2 $R^4$.

**Embodiment 136.** The compound of any one of Embodiments 1 to 125, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^3$ is isoquinolinyl, phthalazinyl, cinnolinyl, imidazo[1,2-c]pyrimidinyl, pyrazolo[1,5-a]pyrazinyl, benzo[c]isoxazolyl, imidazo[1,2-a]pyrazinyl, imidazo[1,2-a]pyridinyl or naphthyridinyl, each of which is unsubstituted or substituted with 1, 2, 3 or 4 $R^4$.

**Embodiment 137.** The compound of any one of Embodiments 1 to 125, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^3$ is isoquinolin-4-yl, phthalazin-4-yl, cinnolin-4-yl, imidazo[1,2-c]pyrimidin-8-yl, pyrazolo[1,5-a]pyrazin-7-yl, benzo[c]isoxazol-3-yl, imidazo[1,2-a]pyrazine-5-yl, imidazo[1,2-a]pyridine-3-yl or naphthyridin-4-yl, each of which is unsubstituted or substituted with 1, 2, 3 or 4 $R^4$.

**Embodiment 138.** The compound of any one of Embodiments 1 to 125, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^3$ is



with 1 or 2 $R^4$.

**Embodiment 139.** The compound of any one of Embodiments 1 to 125, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^3$ is isoquinolinyl which is unsubstituted or substituted with 1 or 2 $R^4$.

**Embodiment 140.** The compound of any one of Embodiments 1 to 125, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^3$ is isoquinolin-4-yl which is unsubstituted or substituted with 1 or 2 $R^4$.

**Embodiment 141.** The compound of any one of Embodiments 1 to 125, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^3$ is isoquinolin-4-yl which is unsubstituted.

**Embodiment 142.** The compound of any one of Embodiments 1 to 125, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^3$ is phthalazinyl which is unsubstituted or substituted with 1 or 2 $R^4$.

**Embodiment 143.** The compound of any one of Embodiments 1 to 125, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^3$ is phthalaziny-4-yl which is unsubstituted or substituted with 1 or 2 $R^4$.

**Embodiment 144.** The compound of any one of Embodiments 1 to 125, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^3$ is phthalaziny-4-yl which is unsubstituted.

**Embodiment 145.** The compound of any one of Embodiments 1 to 125, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^3$ is a 5 or 6 membered heterocycloalkyl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 5 or 6 membered heterocycloalkyl is unsubstituted, or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo.

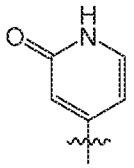
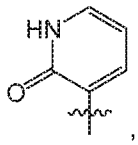
**Embodiment 146.** The compound of any one of Embodiments 1 to 125, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^3$ is a 5 or 6 membered heterocyclyl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 5 or 6 membered heterocyclyl is unsubstituted, or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo.

**Embodiment 147.** The compound of any one of Embodiments 1 to 125, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^3$ is a 6 membered

heterocyclyl wherein 1 ring member is selected from $NR^6$, and wherein the 6 membered heterocyclyl substituted with an oxo.

**Embodiment 148.** The compound of any one of Embodiments 1 to 125, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^3$ is pyridinyl-2(1H)-one which is unsubstituted or substituted with 1, 2, 3 or 4 $R^4$.

**Embodiment 149.** The compound of any one of Embodiments 1 to 125, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^3$ is pyridine-3-yl-2(1H)-one or pyridine-4-yl-2(1H)-one, each of which is unsubstituted or substituted with 1, 2, 3 or 4 $R^4$.

**Embodiment 150.** he compound of any one of Embodiments 1 to 125, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^3$ is  or  , each of which is unsubstituted or substituted with 1 or 2 $R^4$.

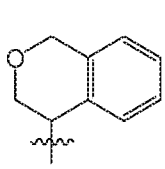
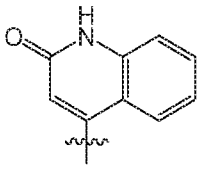
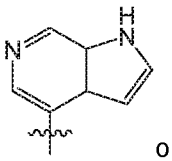
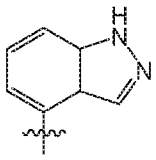
**Embodiment 151.** The compound of any one of Embodiments 1 to 125, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^3$ is a 9 or 10 membered bicyclic heterocyclyl wherein 1, 2, 3, 4 or 5 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 9 or 10 membered bicyclic heterocyclyl is unsubstituted, or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo.

**Embodiment 152.** The compound of any one of Embodiments 1 to 125, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^3$ is a 9 or 10 membered bicyclic heterocyclyl wherein 1 ring member is selected from N, $NR^6$ and O, and wherein the 9 or 10 membered bicyclic heterocyclyl is unsubstituted, or substituted with an oxo.

**Embodiment 153.** The compound of any one of Embodiments 1 to 125, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^3$ is isochromanyl, quinolinyl-2(1H)-one, 3a,7a-dihydro-1H-pyrrolo[2,3-c]pyridinyl or 3a,7a-dihydro-1H-indazolyl, each of which is unsubstituted, or is substituted with 1, 2, 3 or 4 $R^4$.

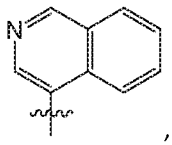
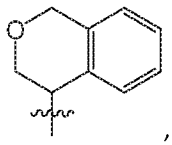
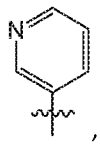
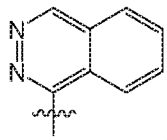
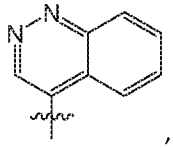
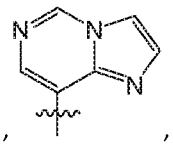
**Embodiment 154.** The compound of any one of Embodiments 1 to 125, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^3$ is isochroman-4-yl, quinolin-4-yl-2(1H)-one, 3a,7a-dihydro-1H-pyrrolo[2,3-c]pyridine-4-yl or 3a,7a-dihydro-1H-indazol-4-yl, each of which is unsubstituted, or is substituted with 1, 2, 3 or 4 $R^4$.

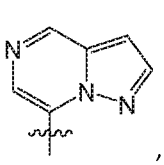
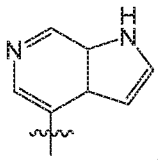
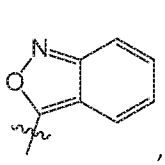
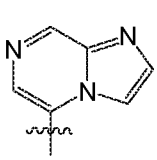
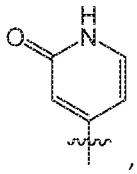
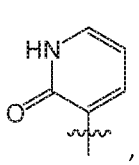
**Embodiment 155.** The compound of any one of Embodiments 1 to 125, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^3$ is

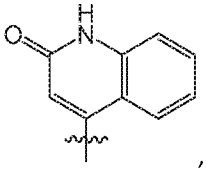
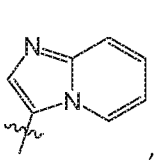
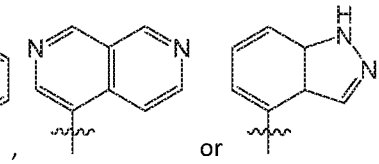
 ,  ,  or  , each of which is unsubstituted or substituted with 1 or 2 $R^4$.

**Embodiment 156.** The compound of any one of Embodiments 1 to 125, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^3$ is isoquinolinyl, isochromanyl, pyridyl, phthalazinyl, cinnolinyl, imidazo[1,2-c]pyrimidinyl, pyrazolo[1,5-a]pyrazinyl, 3a,7a-dihydro-1H-pyrrolo[2,3-c]pyridinyl, benzo[c]isoxazolyl, imidazo[1,2-a]pyrazinyl, pyridinyl-2(1H)-one, quinolinyl-2(1H)-one, imidazo[1,2-a]pyridinyl, naphthyridinyl or 3a,7a-dihydro-1H-indazolyl, each of which is unsubstituted or substituted with 1 or 2 $R^4$.

**Embodiment 157.** The compound of any one of Embodiments 1 to 125, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^3$ is

 ,  ,  ,  ,  ,  ,

 ,  ,  ,  ,  ,  ,

 ,  ,  or , each of which is unsubstituted or substituted with 1 or 2 $R^4$.

**Embodiment 158.** The compound of any one of Embodiments 1 to 125, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^3$ is a 6 membered heteroaryl with an attachment point at a carbon atom ring member and a N heteroatom as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 6 membered heteroaryl has 0, 1 or 2 additional N heteroatoms as ring members, and wherein the 6 membered heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$.

**Embodiment 159.** The compound of any one of Embodiments 1 to 125, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^3$ is a 10 membered bicyclic heteroaryl with an attachment point at a carbon atom ring member and a N heteroatom as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 10 membered bicyclic heteroaryl has 0, 1, 2 or 3 additional N

heteroatoms as ring members, and wherein the 10 membered bicyclic heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$.

**Embodiment 160.** The compound of any one of Embodiments 1 to 125, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^3$ is a 10 membered bicyclic heteroaryl with an attachment point at a carbon atom ring member and a N heteroatom as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 10 membered bicyclic heteroaryl further has 0, 1, 2, 3, or 4 ring members each independently selected from N, O and S, and wherein the 10 membered bicyclic heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$.

**Embodiment 161.** The compound of any one of Embodiments 1 to 125, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^3$ is a 9 membered bicyclic heteroaryl with an attachment point at a carbon atom ring member and a N heteroatom as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 9 membered bicyclic heteroaryl has 0, 1, 2, 3 or 4 additional N heteroatoms as ring members, and wherein the 9 membered bicyclic heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$.

**Embodiment 162.** The compound of any one of Embodiments 1 to 125, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^3$ is a 9 membered bicyclic heteroaryl with an attachment point at a carbon atom ring member and a N heteroatom as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 9 membered bicyclic heteroaryl further has 0, 1, 2, 3, or 4 ring members each independently selected from N, $NR^6$, O and S, and wherein the 9 membered bicyclic heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$.

**Embodiment 163.** The compound of any one of Embodiments 1 to 125, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^3$ is a 5 or 6 membered heterocycloalkyl with an attachment point at a carbon atom ring member and a $NR^6$ as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 5 or 6 membered heterocycloalkyl further has 0, 1, or 2 ring members each independently selected from N, $NR^6$, O and S, and wherein the 5 or 6 membered heterocycloalkyl is unsubstituted, substituted with 1 or 2 oxo, or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo.

**Embodiment 164.** The compound of any one of Embodiments 1 to 125, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^3$ is a 5 or 6 membered heterocyclyl with an attachment point at a carbon atom ring member and a $NR^6$ as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 5 or 6 membered heterocyclyl further has 0, 1, or 2 ring members each independently selected from N, $NR^6$, O and S, and wherein the 5 or 6 membered heterocyclyl is

unsubstituted, substituted with 1 or 2 oxo, or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo.

**Embodiment 165.** The compound of any one of Embodiments 1 to 125, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^3$ is a 9 or 10 membered bicyclic heterocyclyl with an attachment point at a carbon atom ring member and a $NR^6$ as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 9 or 10 membered heterocyclyl further has 0, 1, 2, 3, or 4 ring members each independently selected from N, $NR^6$, O and S, and wherein the 9 or 10 membered heterocyclyl is unsubstituted, substituted with 1 or 2 oxo, or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo.

**Embodiment 166.** The compound of any one of Embodiments 1 to 125, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^3$ is a 9 or 10 membered bicyclic heterocyclyl with an attachment point at a carbon atom ring member and a O heteroatom as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 9 or 10 membered heterocyclyl further has 0, 1, 2, 3, or 4 ring members each independently selected from N, $NR^6$, O and S, and wherein the 9 or 10 membered heterocyclyl is unsubstituted, substituted with 1 or 2 oxo, or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo.

**Embodiment 167.** The compound of any one of Embodiments 1 to 125, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^3$ is a 6 membered heterocyclyl with an attachment point at a carbon atom ring member and a carbon atom as a ring member which is substituted with oxo and located at a beta (β) position relative to the attachment point, wherein the 6 membered heterocyclyl further has 1 or 2 ring members each independently selected from N, $NR^6$, O and S, and wherein the 6 membered heterocyclyl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with an oxo.

**Embodiment 168.** The compound of any one of Embodiments 1 to 125, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^3$ is a 10 membered bicyclic heterocyclyl with an attachment point at a carbon atom ring member and a carbon atom as a ring member which is substituted with oxo and located at a beta (β) position relative to the attachment point, wherein the 10 membered heterocyclyl further has 1, 2, 3, or 4 ring members each independently selected from N, $NR^6$, O and S, and wherein the 10 membered heterocyclyl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with an oxo.

**Embodiment 169.** The compound of any one of Embodiments 1 to 125, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^3$ is selected from the group consisting of:

i) pyridyl substituted with 1 or 2 $R^4$;

ii) isoquinolin-4-yl which is unsubstituted or is substituted with 1 or 2 $R^4$; and

iii) 5,6,7,8-tetrahydroisoquinolin-4-yl which is unsubstituted.

**Embodiment 170.** The compound of any one of Embodiments 1 to 125, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^3$ is isoquinolin-4-yl which is unsubstituted or is substituted with 1 or 2 $R^4$.

**Embodiment 171.** The compound of any one of Embodiments 1 to 170, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein each $R^4$ is independently selected from the group consisting of $-C(=O)N(R^7)_2$, $-C(=O)OH$, $-N(R^7)_2$, $-CN$, $-OH$,  , $C_1$-$C_6$alkyl, halo, and 4 to 6 membered heterocycloalkyl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and $C_1$-$C_6$alkyl substituted with $NH_2$, CN or OH, wherein thr heterocycloalkyl is unsubstituted or are substituted with 1 or 2 OH groups.

**Embodiment 172.** The compound of any one of Embodiments 1 to 170, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein each $R^4$ is independently selected from the group consisting of $-C(=O)N(R^7)_2$, $-C(=O)OH$, $-N(R^7)_2$, $-CN$, $-OH$,  , $C_1$-$C_6$alkyl and halo.

**Embodiment 173.** The compound of any one of Embodiments 1 to 170, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein each $R^4$ is independently selected from $-S(=O)_2R^6$, $-S(=O)_2N(R^7)_2$, phenyl, $C_3$-$C_8$cycloalkyl, 4 to 6 membered heterocycloalkyl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S, and 5 or 6 membered heteroaryl wherein 1, 2 or 3 ring members are each independently selected from N, O and S, wherein the phenyl, heterocycloalkyl and heteroaryl are unsubstituted or are substituted with 1 or 2 OH groups.

**Embodiment 174.** The compound of any one of Embodiments 1 to 170, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein each $R^4$ is independently selected from the group consisting of $-CH_3$, $-C(=O)N(R^7)_2$, $-N(R^7)_2$, F, Br, $-CN$, $-S(=O)_2R^6$, $-C(=O)NR^7R^6$, and  .

**Embodiment 175.** The compound of any one of Embodiments 1 to 174, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein each $R^5$ is independently selected from the group consisting of -NR6C(=O)C2-C6alkenyl, $-SF_5$, $C_1$-$C_6$alkyl, $C_1$-

$C_6$haloalkyl, halo, $C_1$-$C_6$haloalkoxy, $C_1$-$C_6$alkoxy, $C_3$-$C_8$cycloalkyl, wherein the cycloalkyl is unsubstituted or are substituted with 1, 2, 3 or 4 $R^9$.

**Embodiment 176.** The compound of any one of Embodiments 1 to 174, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein each $R^5$ is independently selected from the group consisting of -NR6C(=O)C2-C6alkenyl, -$SF_5$, $C_1$-$C_6$alkyl, $C_1$-$C_6$haloalkyl, halo, $C_1$-$C_6$haloalkoxy, $C_1$-$C_6$alkoxy, $C_3$-$C_8$cycloalkyl, wherein the cycloalkyl is unsubstituted or are substituted with 1 $R^9$.

**Embodiment 177.** The compound of any one of Embodiments 1 to 174, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein each $R^5$ is independently selected from the group consisting of -NR6C(=O)C2-C6alkenyl, -$SF_5$, $C_1$-$C_6$alkyl, $C_1$-$C_6$haloalkyl, halo, $C_1$-$C_6$haloalkoxy, $C_1$-$C_6$alkoxy, $C_3$-$C_8$cycloalkyl, wherein the cycloalkyl is unsubstituted or are substituted with 1 or 2 $R^9$.

**Embodiment 178.** The compound of any one of Embodiments 1 to 174, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein each $R^5$ is independently selected from the group consisting of -OH, -$NR^7R^8$, -C(=O)N($R^7$)$_2$, 4 to 6 membered heterocycloalkyl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S, a 5 or 6 membered heteroaryl wherein 1, 2 or 3 ring members are each independently selected from N, O and S, and $C_1$-$C_6$alkyl substituted with CN, $NH_2$ or OH, and wherein the heterocycloalkyl is unsubstituted or are substituted with 1, 2, 3 or 4 $R^9$.

**Embodiment 179.** The compound of any one of Embodiments 1 to 174, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein each $R^5$ is independently selected from the group consisting of -OH, -$NR^7R^8$, -C(=O)N($R^7$)$_2$, 4 to 6 membered heterocycloalkyl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S, a 5 or 6 membered heteroaryl wherein 1, 2 or 3 ring members are each independently selected from N, O and S, and $C_1$-$C_6$alkyl substituted with CN, $NH_2$ or OH, and wherein the heterocycloalkyl is unsubstituted or are substituted with 1 or 2 $R^9$.

**Embodiment 180.** The compound of any one of Embodiments 1 to 174, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^5$ is $C_1$-$C_6$haloalkyl, halo or $C_1$-$C_6$haloalkoxy.

**Embodiment 181.** The compound of any one of Embodiments 1 to 174, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^5$ is -$CF_3$, F, Cl, -$OCHF_2$ or -$OCF_3$.

**Embodiment 182.** The compound of any one of Embodiments 1 to 174, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein each $R^5$ is independently selected from the group consisting of F, Br, Cl, -$CF_3$, -$CHF_2$, -$CH_2F$, -$C(CH_3)F_2$, -$CH_3$, isopropyl, -$OCHF_2$, -$OCClF_2$, -$OCF_3$, -$OCH_3$, $SF_5$, -$C(CH_3)_2OH$, -$CH_2CF_3$, -$CH(CH_3)CF_3$, an unsubstituted cyclopropyl, a cyclopropyl substituted with 1 $R^9$, and a cyclobutyl substituted with 1 or 2 $R^9$.

**Embodiment 183.** The compound of any one of Embodiments 1 to 181, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein each $R^6$ is independently selected from the group consisting of H and $C_1$-$C_6$alkyl.

**Embodiment 184.** The compound of any one of Embodiments 1 to 181, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein each $R^6$ is independently selected from the group consisting of $-S(=O)_2N(R^7)_2$, $-C(=O)N(R^7)_2$ and $C_1$-$C_6$alkyl substituted with –OH, CN or –C(=O)OH.

**Embodiment 185.** The compound of any one of Embodiments 1 to 181, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein each $R^6$ is independently selected from the group consisting of H, $-CH_3$, and $-CH_2CH_2OR^7$.

**Embodiment 186.** The compound of any one of Embodiments 1 to 185, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein each $R^7$ is H.

**Embodiment 187.** The compound of any one of Embodiments 1 to 185, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein each $R^7$ is $C_1$-$C_6$alkyl.

**Embodiment 188.** The compound of any one of Embodiments 1 to 185, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein each $R^7$ is independently selected from the group consisting of H and $-CH_3$.

**Embodiment 189.** The compound of any one of Embodiments 1 to 188, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^8$ is H.

**Embodiment 190.** The compound of any one of Embodiments 1 to 188, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^8$ is $C_1$-$C_6$alkyl.

**Embodiment 191.** The compound of any one of Embodiments 1 to 188, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^8$ is $C_3$-$C_8$cycloalkyl, wherein the cycloalkyl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^9$.

**Embodiment 192.** The compound of any one of Embodiments 1 to 188, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^8$ is $C_3$-$C_8$cycloalkyl, wherein the cycloalkyl is unsubstituted or is substituted with 1 or 2 $R^9$.

**Embodiment 193.** The compound of any one of Embodiments 1 to 188, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^8$ is a 4 to 6 membered heterocycloalkyl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S, and wherein the heterocycloalkyl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^9$.

**Embodiment 194.** The compound of any one of Embodiments 1 to 188, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^8$ is a 4 to 6 membered heterocycloalkyl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S, and wherein the heterocycloalkyl is unsubstituted or is substituted with 1, or 2 $R^9$.

**Embodiment 195.** The compound of any one of Embodiments 1 to 194, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^9$ is $NR^{10}R^{11}$.

**Embodiment 196.** The compound of any one of Embodiments 1 to 194, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^9$ is $C(=O)N(R^7)_2$.

**Embodiment 197.** The compound of any one of Embodiments 1 to 194, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^9$ is $C_1$-$C_6$alkyl substituted with -OH or $-N(R^7)_2$.

**Embodiment 198.** The compound of any one of Embodiments 1 to 194, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein each $R^9$ is independently selected from the group consisting of F, -C(=O)OH, and $-CH_2OH$.

**Embodiment 199.** The compound of any one of Embodiments 1 to 198, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^{10}$ is H.

**Embodiment 200.** The compound of any one of Embodiments 1 to 198, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^{10}$ is $C_1$-$C_6$alkyl.

**Embodiment 201.** The compound of any one of Embodiments 1 to 198, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^{10}$ is H or $-CH_3$;

**Embodiment 202.** The compound of any one of Embodiments 1 to 201, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^{11}$ is H.

**Embodiment 203.** The compound of any one of Embodiments 1 to 201, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^{11}$ is $C_1$-$C_6$alkyl.

**Embodiment 204.** The compound of any one of Embodiments 1 to 201, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^{11}$ is $-S(=O)_2C_1$-$C_6$alkyl.

**Embodiment 205.** The compound of any one of Embodiments 1 to 204, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^{13}$ is H.

**Embodiment 206.** The compound of any one of Embodiments 1 to 204, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^{13}$ is $-C(=O)N(R^7)_2$.

**Embodiment 207.** The compound of any one of Embodiments 1 to 204, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^{13}$ is a 5 or 6 membered heteroaryl wherein 1, 2 3 or 4 ring members are each independently selected from N, $NR^6$, O and S.

**Embodiment 208.** The compound of any one of Embodiments 1 to 207, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^{14}$ is a 5 or 6 membered heterocyclyl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 5 or 6 membered heterocyclyl is unsubstituted, or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo.

**Embodiment 209.** The compound of any one of Embodiments 1 to 207, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^{14}$ is 6 membered

heterocyclyl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 6 membered heterocyclyl is unsubstituted, or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo.

**Embodiment 210.** The compound of any one of Embodiments 1 to 207 or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^{14}$ is 6 membered heterocyclyl wherein 1 ring member is selected from N, $NR^6$, O and S, and wherein the 6 membered heterocyclyl is substituted with an oxo.

**Embodiment 211.** The compound of any one of Embodiments 1 to 207, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^{14}$ is 6 membered heterocyclyl wherein 1 ring member is selected from $NR^6$, and wherein the 6 membered heterocyclyl is substituted with an oxo.

**Embodiment 212.** The compound of any one of Embodiments 1 to 207, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^{14}$ is a 5 or a 6 membered heteroaryl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 5 or a 6 membered heteroaryl is unsubstituted, or is substituted with 1, 2, 3 or 4 $R^4$.

**Embodiment 213.** The compound of any one of Embodiments 1 to 207, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^{14}$ is a 5 or a 6 membered heteroaryl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 5 or a 6 membered heteroaryl is unsubstituted, or is substituted with 1 or 2 $R^4$.

**Embodiment 214.** The compound of Embodiment 1, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein the compound is selected from:

7-fluoro-3-(isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione;

3-(isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione;

2-(3-(isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2H)-yl)acetonitrile;

3-(isoquinolin-4-yl)-6-(trifluoromethoxy)quinazoline-2,4(1H,3H)-dione;

3-(isoquinolin-4-yl)-6-(trifluoromethyl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione;

3-(8-aminoisoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione;

3-(5,6,7,8-tetrahydroisoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione;

7-(trifluoromethyl)-1H-[2,4'-biisoquinoline]-1,3(4H)-dione;

6-bromo-3-(isoquinolin-4-yl)quinazoline-2,4(1H,3H)-dione;

4,4-dimethyl-7-(trifluoromethyl)-1H-[2,4'-biisoquinoline]-1,3(4H)-dione;

8-fluoro-3-(isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione;

3-(isoquinolin-4-yl)-6-methoxyquinazoline-2,4(1H,3H)-dione;

3-(4-methylpyridin-3-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione;

3-(isoquinolin-4-yl)-6-(trifluoromethyl)-2H-benzo[e][1,3]oxazine-2,4(3H)-dione;

and

5-(2,4-dioxo-6-(trifluoromethyl)-1,4-dihydroquinazolin-3(2H)-yl)nicotinamide.

**Embodiment 215.** The compound of Embodiment 1, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein the compound is selected from:

7-fluoro-3-(isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione;

3-(isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione;

2-(3-(isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2H)-yl)acetonitrile;

3-(isoquinolin-4-yl)-6-(trifluoromethoxy)quinazoline-2,4(1H,3H)-dione;

3-(isoquinolin-4-yl)-6-(trifluoromethyl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione;

3-(8-aminoisoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione;

3-(5,6,7,8-tetrahydroisoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione;

7-(trifluoromethyl)-1H-[2,4'-biisoquinoline]-1,3(4H)-dione;

6-bromo-3-(isoquinolin-4-yl)quinazoline-2,4(1H,3H)-dione;

4,4-dimethyl-7-(trifluoromethyl)-1H-[2,4'-biisoquinoline]-1,3(4H)-dione;

8-fluoro-3-(isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione;

3-(isoquinolin-4-yl)-6-methoxyquinazoline-2,4(1H,3H)-dione;

3-(4-methylpyridin-3-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione;

3-(isoquinolin-4-yl)-6-(trifluoromethyl)-2H-benzo[e][1,3]oxazine-2,4(3H)-dione;

5-(2,4-dioxo-6-(trifluoromethyl)-1,4-dihydroquinazolin-3(2H)-yl)nicotinamide;

3-(3-(isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2H)-yl)propanenitrile;

3-[(3*M*)-3-(Isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2*H*)-yl]propanenitrile;

3-[(3*P*)-3-(Isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2*H*)-yl]propanenitrile;

1-cyclopropyl-3-(isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione;

3-(isoquinolin-4-yl)-6-(pentafluoro-l6-sulfaneyl)quinazoline-2,4(1H,3H)-dione;

3-(isoquinolin-4-yl)-7-methyl-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione;

3-(3-(5-fluoroisoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2H)-yl)propanenitrile;

3-[(3*M*)-3-(5-Fluoroisoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2*H*)-yl]propanenitrile;

3-[(3*P*)-3-(5-Fluoroisoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2*H*)-yl]propanenitrile;

3-(5-fluoroisoquinolin-4-yl)-6-(trifluoromethyl)-5,6,7,8-tetrahydroquinazoline-2,4(1H,3H)-dione;

[(3*M*,6*R*)-3-(5-Fluoroisoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4,5,6,7,8-hexahydroquinazolin-1(2*H*)-yl]acetonitrile;

[(3*M*,*6S*)-3-(5-Fluoroisoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4,5,6,7,8-hexahydroquinazolin-1(2*H*)-yl]acetonitrile;

[(3*P*,6*R*)-3-(5-Fluoroisoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4,5,6,7,8-hexahydroquinazolin-1(2*H*)-yl]acetonitrile;

[(3*P*,*6S*)-3-(5-Fluoroisoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4,5,6,7,8-hexahydroquinazolin-1(2*H*)-yl]acetonitrile;

5-fluoro-3-(isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione;

5-fluoro-3-(isoquinolin-4-yl)-1-methyl-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione;

3-(3-(6-(methylsulfonyl)isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2H)-yl)propanenitrile;

3-[(3*M*)-3-[6-(Methanesulfonyl)isoquinolin-4-yl]-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2*H*)-yl]propanenitrile;

3-[(3*P*)-3-[6-(Methanesulfonyl)isoquinolin-4-yl]-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2*H*)-yl]propanenitrile;

3-(isoquinolin-4-yl)-5-methyl-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione;

3-(isoquinolin-4-yl)-1,5-dimethyl-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione;

3-(isoquinolin-4-yl)-6-(trifluoromethyl)-5,6,7,8-tetrahydroquinazoline-2,4(1H,3H)-dione;

(3*M*,6*R*)-3-(Isoquinolin-4-yl)-6-(trifluoromethyl)-5,6,7,8-tetrahydroquinazoline-2,4(1*H*,3*H*)-dione;

(3*M*,*6S*)-3-(Isoquinolin-4-yl)-6-(trifluoromethyl)-5,6,7,8-tetrahydroquinazoline-2,4(1*H*,3*H*)-dione;

(3*P*,6*R*)-3-(Isoquinolin-4-yl)-6-(trifluoromethyl)-5,6,7,8-tetrahydroquinazoline-2,4(1*H*,3*H*)-dione;

(3*P*,*6S*)-3-(Isoquinolin-4-yl)-6-(trifluoromethyl)-5,6,7,8-tetrahydroquinazoline-2,4(1*H*,3*H*)-dione;

3-[(3*M*,6*R*)-3-(Isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4,5,6,7,8-hexahydroquinazolin-1(2*H*)-yl]propanenitrile;

3-[(3*M*,*6S*)-3-(Isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4,5,6,7,8-hexahydroquinazolin-1(2*H*)-yl]propanenitrile;

3-[(3*P*,6*R*)-3-(Isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4,5,6,7,8-hexahydroquinazolin-1(2*H*)-yl]propanenitrile;

3-[(3*P*,*6S*)-3-(Isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4,5,6,7,8-hexahydroquinazolin-1(2*H*)-yl]propanenitrile;

[(3*M*,6*R*)-3-(Isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4,5,6,7,8-hexahydroquinazolin-1(2*H*)-yl]acetonitrile;

[(3*M*,6*S*)-3-(Isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4,5,6,7,8-hexahydroquinazolin-1(2*H*)-yl]acetonitrile;

[(3*P*,6*R*)-3-(Isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4,5,6,7,8-hexahydroquinazolin-1(2*H*)-yl]acetonitrile;

[(3*P*,6*S*)-3-(Isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4,5,6,7,8-hexahydroquinazolin-1(2*H*)-yl]acetonitrile;

1-{[(3*M*)-3-(5-Fluoroisoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2*H*)-yl]methyl}cyclopropane-1-carbonitrile;

1-{[(3*P*)-3-(5-Fluoroisoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2*H*)-yl]methyl}cyclopropane-1-carbonitrile;

3-(isoquinolin-4-yl)-6-(trifluoromethyl)pyrido[3,2-d]pyrimidine-2,4(1H,3H)-dione;

1-(3-(isoquinolin-4-yl)-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-6-yl)cyclopropane-1-carboxylic acid;

6-(1-(hydroxymethyl)cyclopropyl)-3-(isoquinolin-4-yl)quinazoline-2,4(1H,3H)-dione;

1-isopropyl-3-(isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione;

6-isopropyl-3-(isoquinolin-4-yl)quinazoline-2,4(1H,3H)-dione;

6-isopropyl-3-(isoquinolin-4-yl)-1-methylquinazoline-2,4(1H,3H)-dione;

methyl2-((3-(isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)acrylate;

methyl2-((3-(isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)acrylate;

2-((3-(isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)acrylic acid;

2-((3-(isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)acrylamide;

3-(5-bromoisoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione;

3-(5-methylisoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione;

6-(difluoromethoxy)-3-(isoquinolin-4-yl)quinazoline-2,4(1H,3H)-dione;

1-((3-(isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)cyclopropane-1-carbonitrile;

1-(2-hydroxyethyl)-3-(isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione;

1-(2-fluoroethyl)-3-(isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione;

4-(2,4-dioxo-6-(trifluoromethyl)-1,4-dihydroquinazolin-3(2H)-yl)-N-(2-methoxyethyl)isoquinoline-6-carboxamide;

8-bromo-3-(isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione;

8-(2-hydroxypropan-2-yl)-3-(isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione;

3-(isoquinolin-4-yl)-1-methyl-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione;

4-(2,4-dioxo-6-(trifluoromethyl)-1,4-dihydroquinazolin-3(2H)-yl)isoquinoline-3-carbonitrile;
3-(3-ethynylisoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione;
(3*M*)-3-(3-Ethynylisoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1*H*,3*H*)-dione;
(3*P*)-3-(3-Ethynylisoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1*H*,3*H*)-dione;
3-(isoquinolin-4-yl)-6-(trifluoromethyl)pyrido[3,4-d]pyrimidine-2,4(1H,3H)-dione;
(2*E*)-4-[(3*M*)-3-(Isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2*H*)-yl]but-2-enoic acid;
(2*E*)-4-[(3*P*)-3-(Isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2*H*)-yl]but-2-enoic;
(2*E*)-4-[(3*M*)-3-(Isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2*H*)-yl]but-2-enamide;
(2*E*)-4-[(3*P*)-3-(Isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2*H*)-yl]but-2-enamide;
3-(isoquinolin-4-yl)-1-(2-morpholinoethyl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione;
3-(isoquinolin-4-yl)-8-methyl-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione;
1-(2-(4,4-difluoropiperidin-1-yl)ethyl)-3-(isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione;
1-(2-(3,3-difluoropiperidin-1-yl)ethyl)-3-(isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione;
3-(isoquinolin-4-yl)-1-(2-(piperazin-1-yl)ethyl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione;
3-(isoquinolin-4-yl)-1-(2-methoxyethyl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione;
1-ethyl-3-(isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione;
1-((R)-3-hydroxybutyl)-3-(isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione;
1-((S)-4-hydroxybutan-2-yl)-3-(isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione;
1-((3-(isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)cyclopropane-1-carboxylic acid;
6-(1,1-difluoroethyl)-3-(isoquinolin-4-yl)quinazoline-2,4(1H,3H)-dione;
6-cyclopropyl-3-(isoquinolin-4-yl)quinazoline-2,4(1H,3H)-dione;
1-((1H-tetrazol-5-yl)methyl)-3-(isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione;
3-(1-aminoisoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione;
1-(3-hydroxy-3-methylbutyl)-3-(isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione;
3-(isoquinolin-4-yl)-1-(oxiran-2-ylmethyl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione;
7-chloro-3-(isoquinolin-4-yl)quinazoline-2,4(1H,3H)-dione;
6-chloro-3-(isoquinolin-4-yl)quinazoline-2,4(1H,3H)-dione;

2-(3-(isoquinolin-4-yl)-2,4-dioxo-5-(2,2,2-trifluoroethyl)-2,3,4,5,6,7-hexahydro-1H-cyclopenta[d]pyrimidin-1-yl)acetonitrile;

2-(1-(3-(isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2H)-yl)cyclopropyl)acetonitrile;

{(*1M*)-[(3*M*)-3-(5-Fluoroisoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2*H*)-yl]cyclopropyl}acetonitrile;;

{(*1P*)-[(3*M*)-3-(5-Fluoroisoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2*H*)-yl]cyclopropyl}acetonitrile;

{(*1M or1P*)-[(3*P*)-3-(5-Fluoroisoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2*H*)-yl]cyclopropyl}acetonitrile;;

{(*1P*)-[(3*P*)-3-(5-Fluoroisoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2*H*)-yl]cyclopropyl}acetonitrile;

1-{[(3*M*,6*R*)-3-(5-Fluoroisoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4,5,6,7,8-hexahydroquinazolin-1(2*H*)-yl]methyl}cyclopropane-1-carbonitrile;

1-{[(3*M*,*6S*)-3-(5-Fluoroisoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4,5,6,7,8-hexahydroquinazolin-1(2*H*)-yl]methyl}cyclopropane-1-carbonitrile;

1-{[(3*P*,6*R*)-3-(5-Fluoroisoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4,5,6,7,8-hexahydroquinazolin-1(2*H*)-yl]methyl}cyclopropane-1-carbonitrile;

1-{[(3*P*,*6S*)-3-(5-Fluoroisoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4,5,6,7,8-hexahydroquinazolin-1(2*H*)-yl]methyl}cyclopropane-1-carbonitrile;

(3*M*)-3-(5-Fluoroisoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1*H*,3*H*)-dione;

(3*P*)-3-(5-Fluoroisoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1*H*,3*H*)-dione;

6-cyclopropyl-7-fluoro-3-(isoquinolin-4-yl)quinazoline-2,4(1H,3H)-dione;

6-cyclopropyl-7-fluoro-3-(isoquinolin-4-yl)-1-methylquinazoline-2,4(1H,3H)-dione;

6-(chlorodifluoromethoxy)-3-(isoquinolin-4-yl)quinazoline-2,4(1H,3H)-dione;

2-(3-(isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2H)-yl)acetic acid;

2-(3-(isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2H)-yl)acetamide;

6-(2-hydroxypropan-2-yl)-3-(isoquinolin-4-yl)quinazoline-2,4(1H,3H)-dione;

3-[(3*M*,6*R*)-3-(5-Fluoroisoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4,5,6,7,8-hexahydroquinazolin-1(2*H*)-yl]propanenitrile;

3-[(3*M*,*6S*)-3-(5-Fluoroisoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4,5,6,7,8-hexahydroquinazolin-1(2*H*)-yl]propanenitrile;

3-[(3*P*,6*R*)-3-(5-Fluoroisoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4,5,6,7,8-hexahydroquinazolin-1(2*H*)-yl]propanenitrile;

3-[(3*P*,*6S*)-3-(5-Fluoroisoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4,5,6,7,8-hexahydroquinazolin-1(2*H*)-yl]propanenitrile;

1-{[(3*M*,6*R*)-3-(Isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4,5,6,7,8-hexahydroquinazolin-1(2*H*)-yl]methyl}cyclopropane-1-carbonitrile;

1-{[(3*M*,6*S*)-3-(Isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4,5,6,7,8-hexahydroquinazolin-1(2*H*)-yl]methyl}cyclopropane-1-carbonitrile;

1-{[(3*P*,6*R*)-3-(Isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4,5,6,7,8-hexahydroquinazolin-1(2*H*)-yl]methyl}cyclopropane-1-carbonitrile;

1-{[(3*P*,6S)-3-(Isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4,5,6,7,8-hexahydroquinazolin-1(2*H*)-yl]methyl}cyclopropane-1-carbonitrile;

(2*R*)-3-[(3*M*)-3-(Isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2*H*)-yl]-2-methylpropanoic acid;

(2*S*)-3-[(3*M*)-3-(Isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2*H*)-yl]-2-methylpropanoic acid;

(2*R*)-3-[(3*P*)-3-(Isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2*H*)-yl]-2-methylpropanoic acid;

(2*S*)-3-[(3*P*)-3-(Isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2*H*)-yl]-2-methylpropanoic acid;

6-(difluoromethyl)-3-(isoquinolin-4-yl)quinazoline-2,4(1H,3H)-dione;

6-chloro-8-fluoro-3-(isoquinolin-4-yl)quinazoline-2,4(1H,3H)-dione;

(3*M*)-6-(3,3-Difluorocyclobutyl)-3-(isoquinolin-4-yl)quinazoline-2,4(1*H*,3*H*)-dione;

(3*P*)-6-(3,3-Difluorocyclobutyl)-3-(isoquinolin-4-yl)quinazoline-2,4(1*H*,3*H*)-dione;

(3*M*)-3-(Isoquinolin-4-yl)-6-(2,2,2-trifluoroethyl)quinazoline-2,4(1*H*,3*H*)-dione;

(3*P*)-3-(Isoquinolin-4-yl)-6-(2,2,2-trifluoroethyl)quinazoline-2,4(1*H*,3*H*)-dione;

(3*M*)-3-(Isoquinolin-4-yl)-6-[(2*R**)-1,1,1-trifluoropropan-2-yl]quinazoline-2,4(1*H*,3*H*)-dione;

(3*P*)-3-(Isoquinolin-4-yl)-6-[(2S*)-1,1,1-trifluoropropan-2-yl]quinazoline-2,4(1*H*,3*H*)-dione;

2-(3-(5-fluoroisoquinolin-4-yl)-2,4-dioxo-6-(2,2,2-trifluoroethyl)-2,3,4,5,6,7-hexahydro-1H-cyclopenta[d]pyrimidin-1-yl)acetonitrile;

[(3*M*,6*R*)-3-(5-Fluoro-1,8a-dihydroisoquinolin-4-yl)-2,4-dioxo-6-(2,2,2-trifluoroethyl)-2,3,4,5,6,7-hexahydro-1*H*-cyclopenta[*d*]pyrimidin-1-yl]acetonitrile;

[(3*M*,6*S*)-3-(5-Fluoro-1,8a-dihydroisoquinolin-4-yl)-2,4-dioxo-6-(2,2,2-trifluoroethyl)-2,3,4,5,6,7-hexahydro-1*H*-cyclopenta[*d*]pyrimidin-1-yl]acetonitrile;

[(3*P*,6*R*)-3-(5-Fluoro-1,8a-dihydroisoquinolin-4-yl)-2,4-dioxo-6-(2,2,2-trifluoroethyl)-2,3,4,5,6,7-hexahydro-1*H*-cyclopenta[*d*]pyrimidin-1-yl]acetonitrile;

[(3*P*,*6S*)-3-(5-Fluoro-1,8a-dihydroisoquinolin-4-yl)-2,4-dioxo-6-(2,2,2-trifluoroethyl)-2,3,4,5,6,7-hexahydro-1*H*-cyclopenta[*d*]pyrimidin-1-yl]acetonitrile;

2-(3-(5-fluoroisoquinolin-4-yl)-2,4-dioxo-5-(2,2,2-trifluoroethyl)-2,3,4,5,6,7-hexahydro-1H-cyclopenta[d]pyrimidin-1-yl)acetonitrile;

[(3*M*,5*R*)-3-(5-Fluoroisoquinolin-4-yl)-2,4-dioxo-5-(2,2,2-trifluoroethyl)-2,3,4,5,6,7-hexahydro-1*H*-cyclopenta[*d*]pyrimidin-1-yl]acetonitrile;

[(3*M*,5*S*)-3-(5-Fluoroisoquinolin-4-yl)-2,4-dioxo-5-(2,2,2-trifluoroethyl)-2,3,4,5,6,7-hexahydro-1*H*-cyclopenta[*d*]pyrimidin-1-yl]acetonitrile;

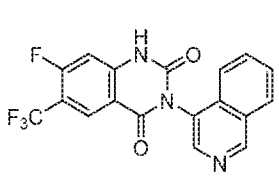
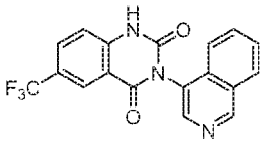
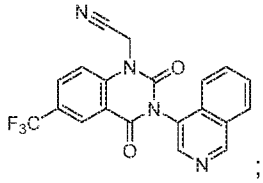
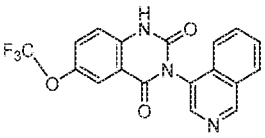
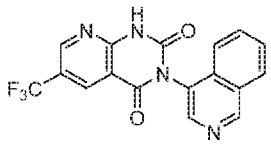
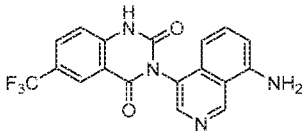
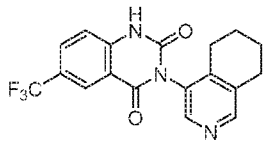
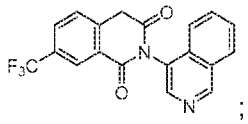
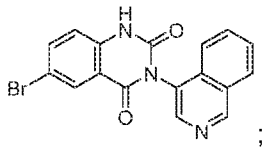
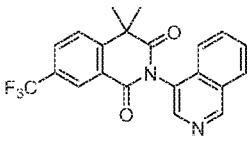
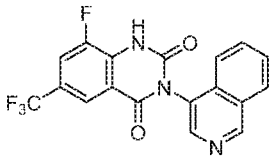
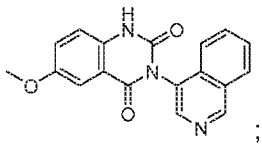
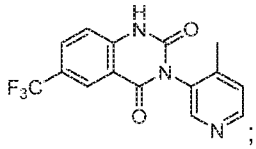
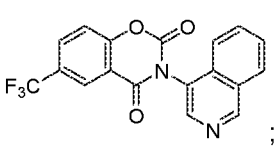
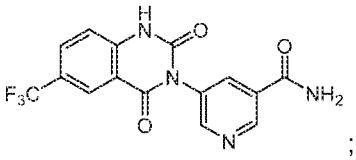
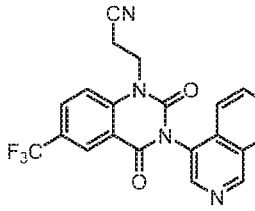
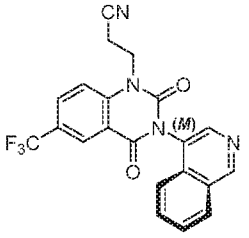
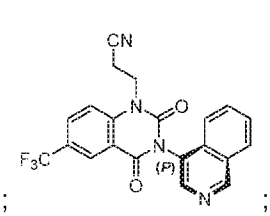
[(3*P*,5*R*)-3-(5-Fluoroisoquinolin-4-yl)-2,4-dioxo-5-(2,2,2-trifluoroethyl)-2,3,4,5,6,7-hexahydro-1*H*-cyclopenta[*d*]pyrimidin-1-yl]acetonitrile;

[(3*P*,5*S*)-3-(5-Fluoroisoquinolin-4-yl)-2,4-dioxo-5-(2,2,2-trifluoroethyl)-2,3,4,5,6,7-hexahydro-1*H*-cyclopenta[*d*]pyrimidin-1-yl]acetonitrile;

2-(3-(5-fluoroisoquinolin-4-yl)-6-(fluoromethyl)-2,4-dioxo-2,3,4,5,6,7-hexahydro-1H-cyclopenta[d]pyrimidin-1-yl)acetonitrile, and

2-(3-(5-fluoroisoquinolin-4-yl)-5-(fluoromethyl)-2,4-dioxo-2,3,4,5,6,7-hexahydro-1H-cyclopenta[d]pyrimidin-1-yl)acetonitrile.

**Embodiment 216.** The compound of Embodiment 1, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein the compound is selected from:

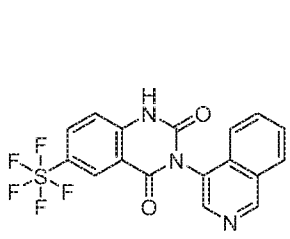
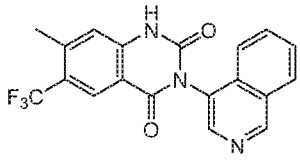
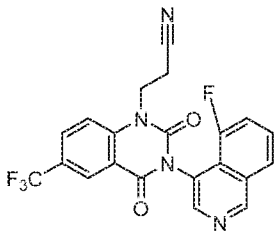
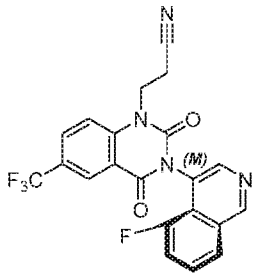
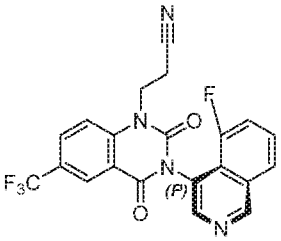
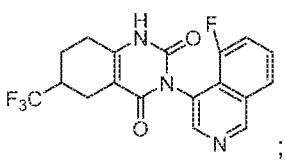
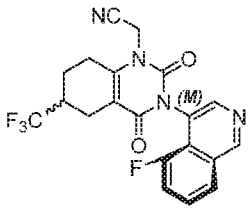
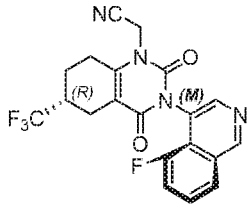
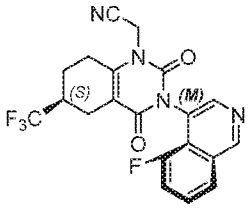
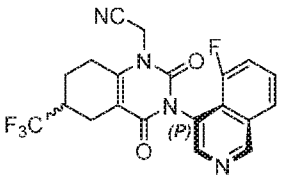
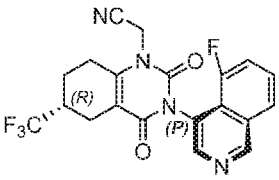
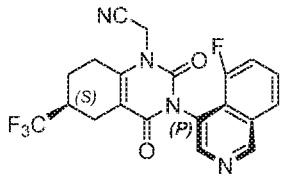
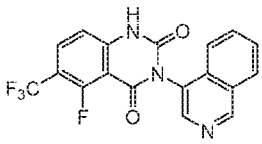
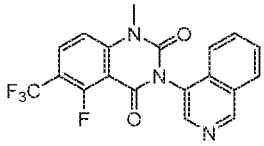
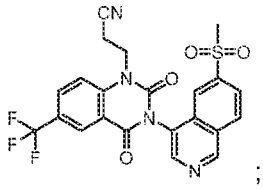
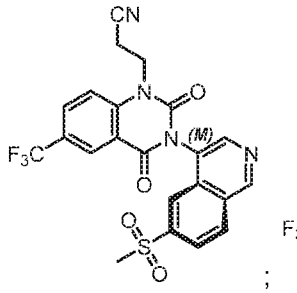
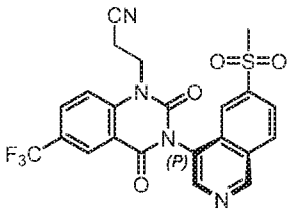
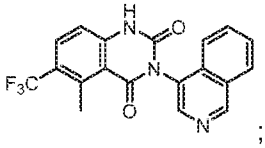
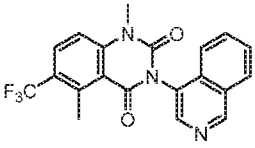
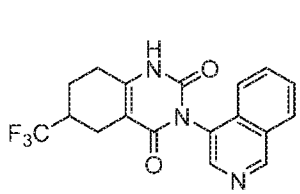
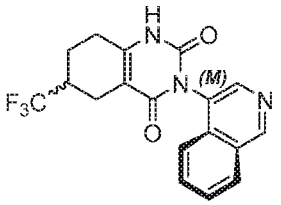
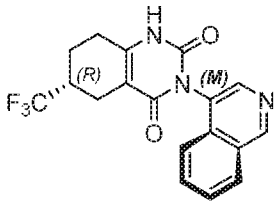
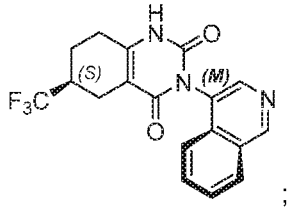
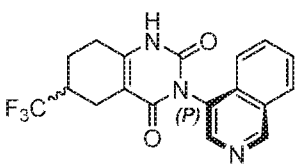
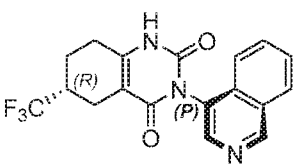

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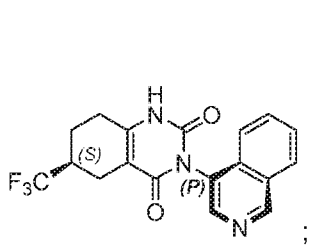
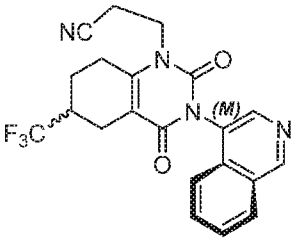
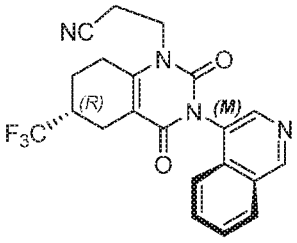
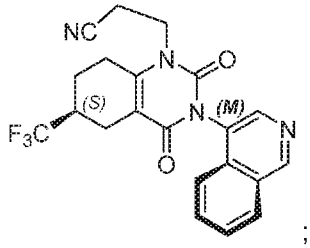
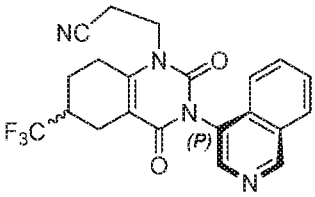
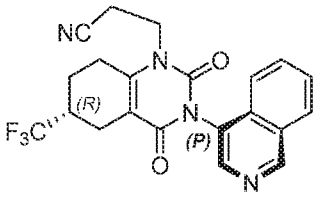
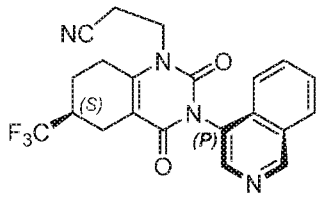
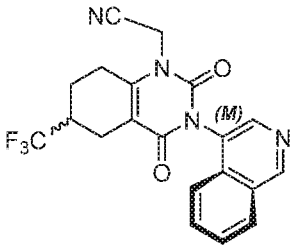
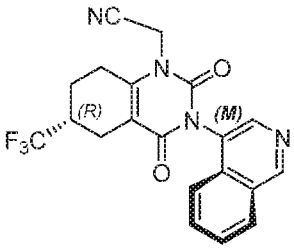
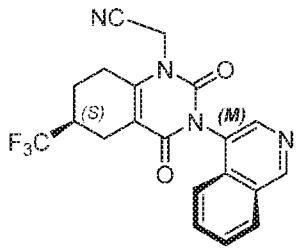
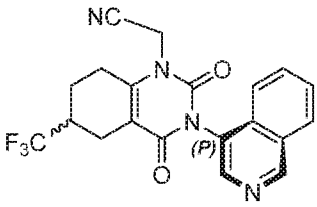
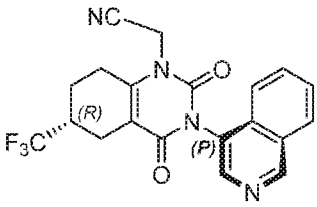
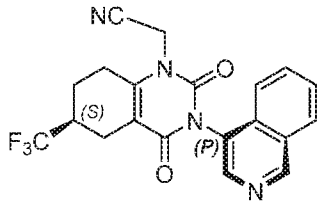
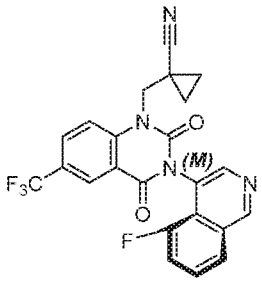
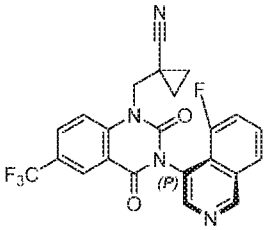
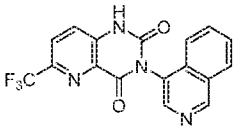
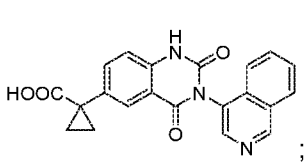
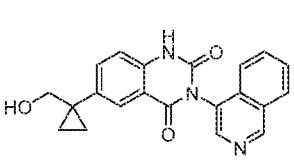
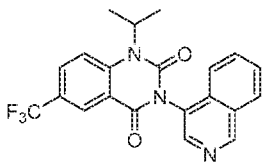
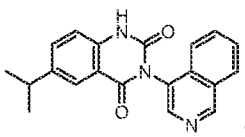
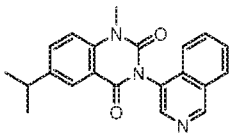
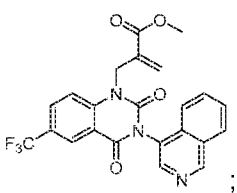
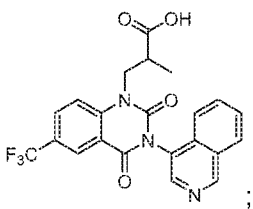
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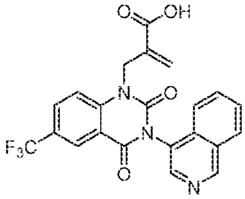
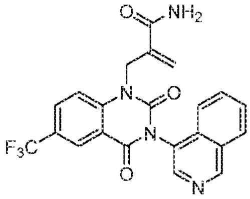
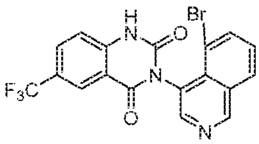
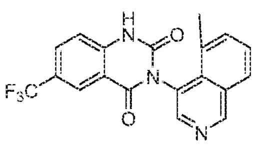
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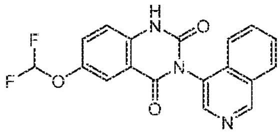
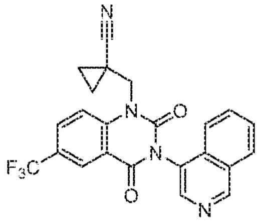
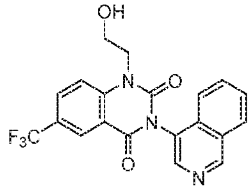
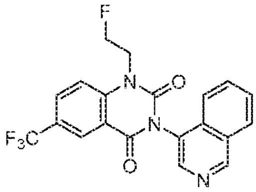
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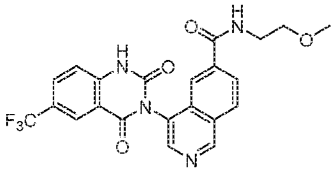
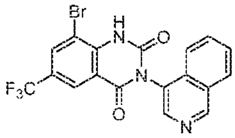
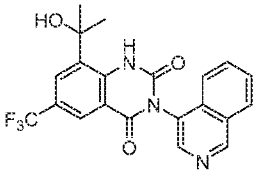
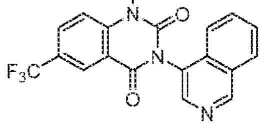

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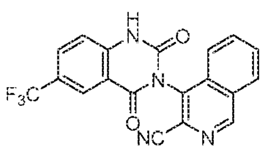
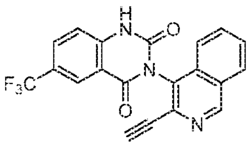
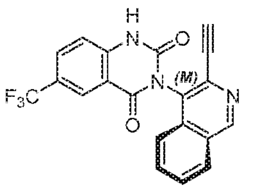
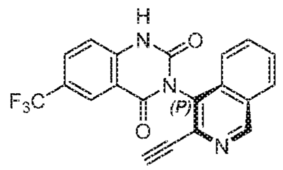

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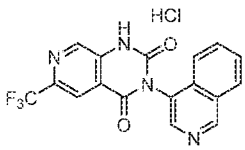
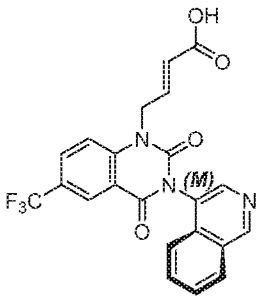
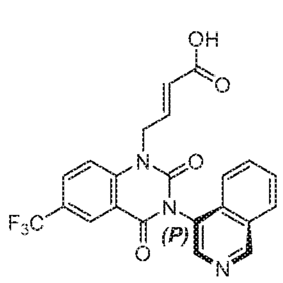
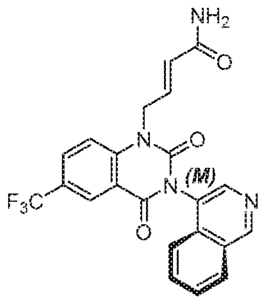
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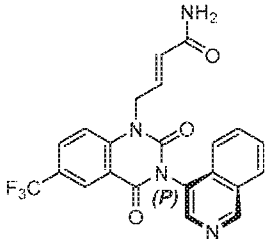
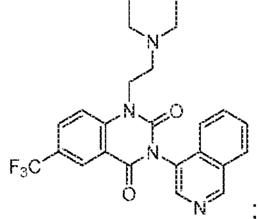
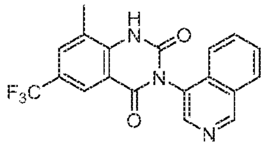
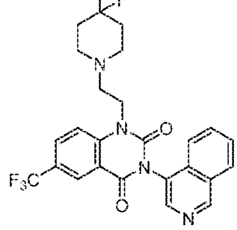
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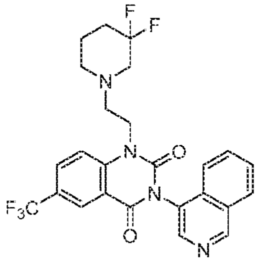
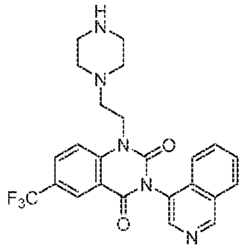
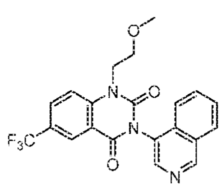
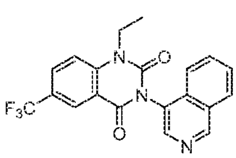
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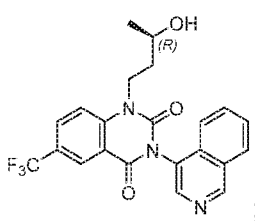
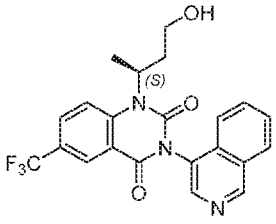
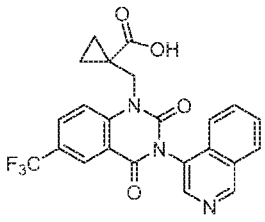
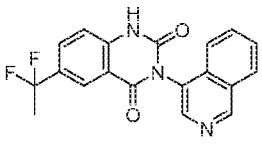
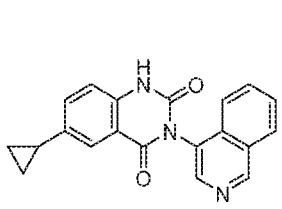
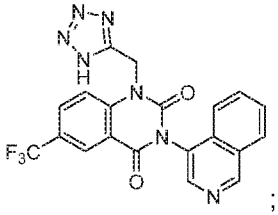
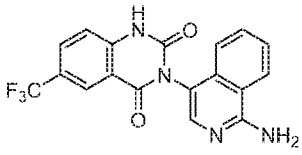
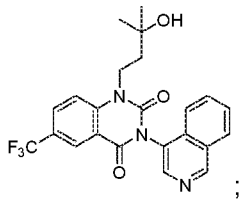
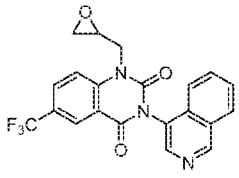
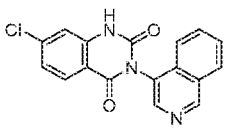
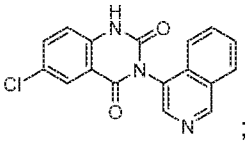
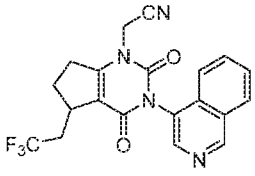
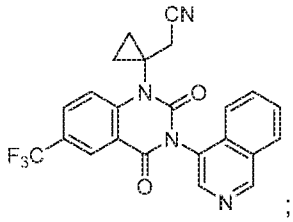
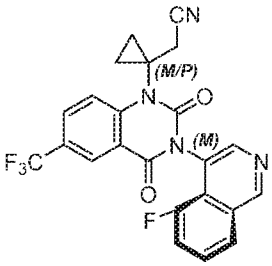
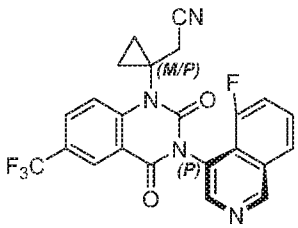
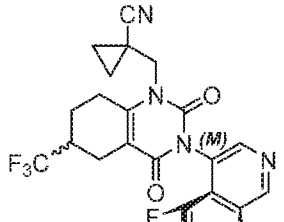
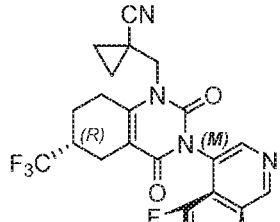
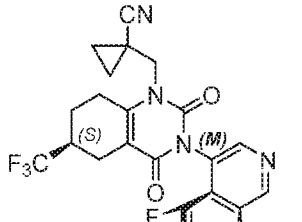
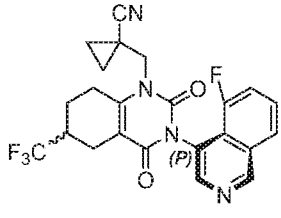
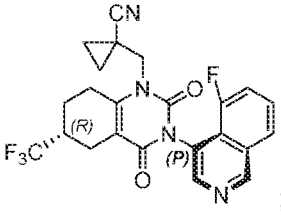
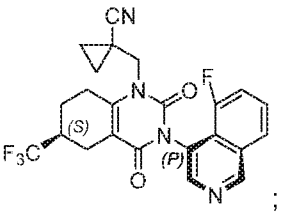
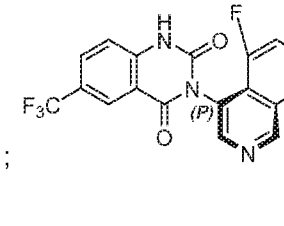
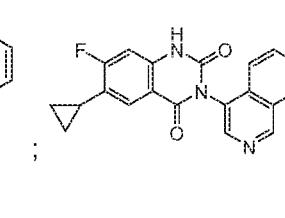
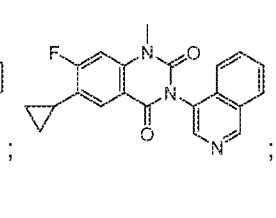
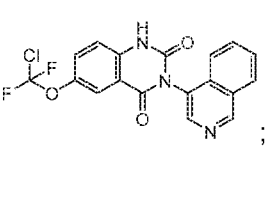
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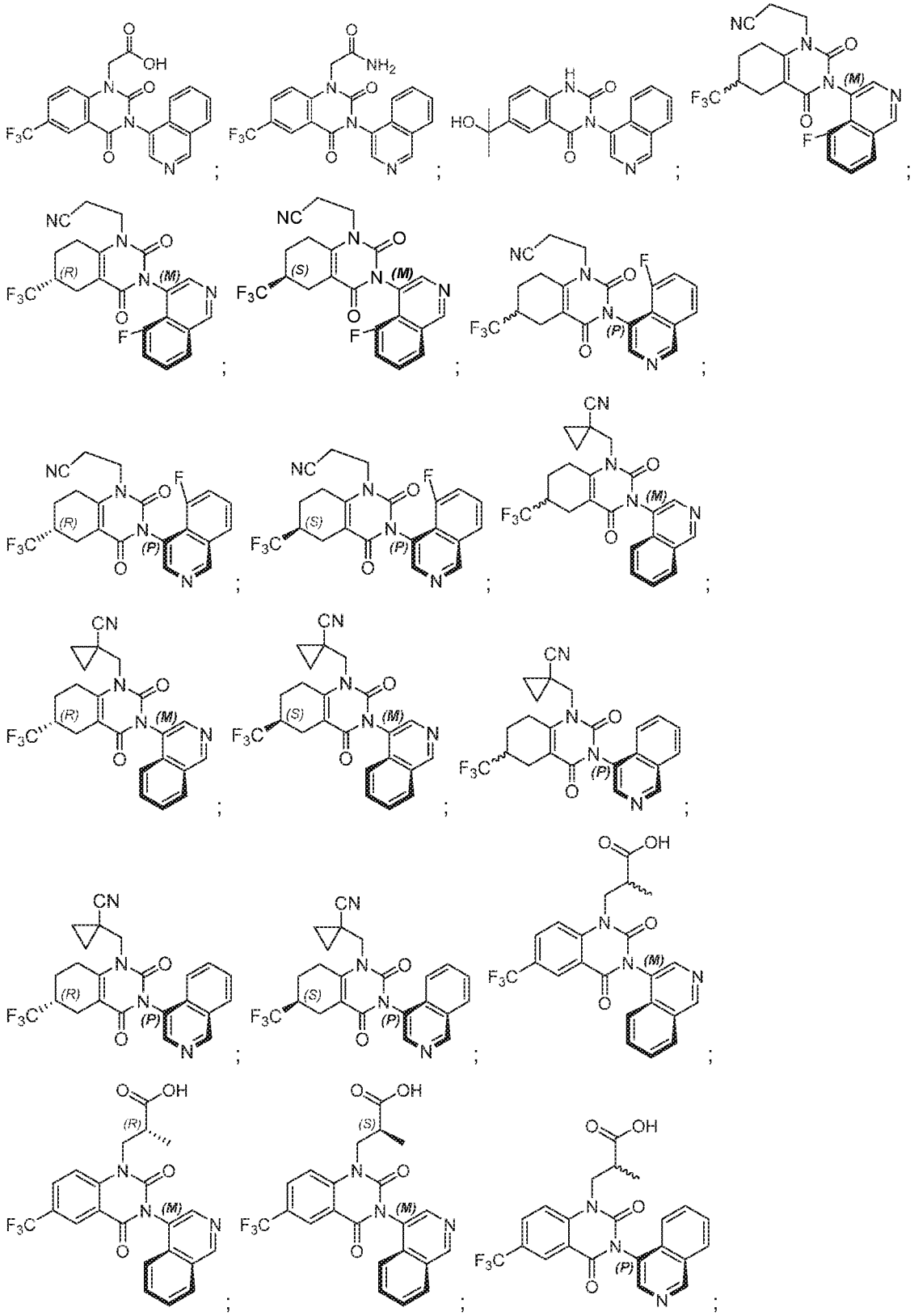

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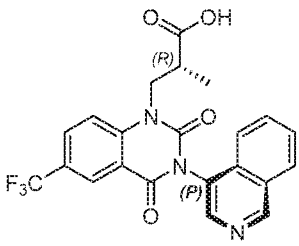
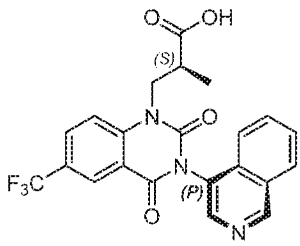
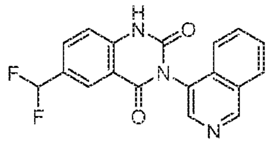
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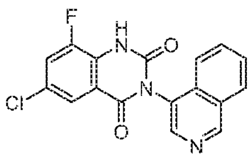
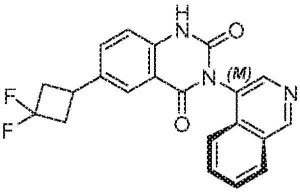
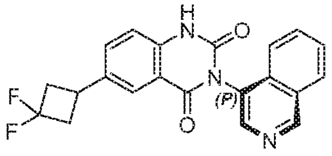
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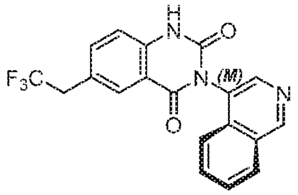
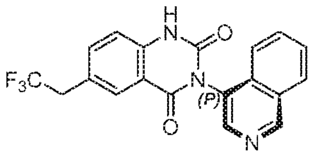
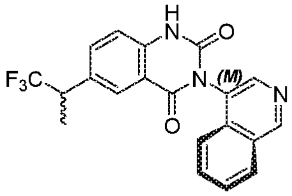
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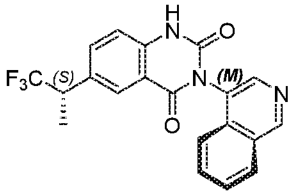
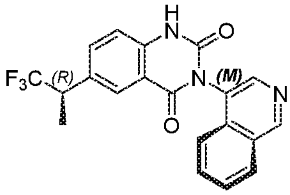
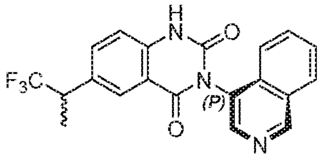
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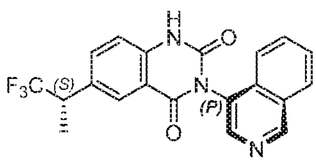
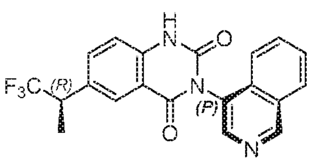
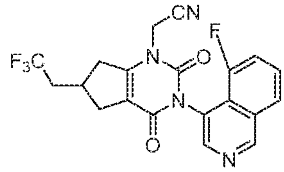


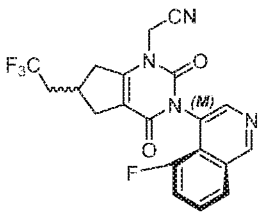
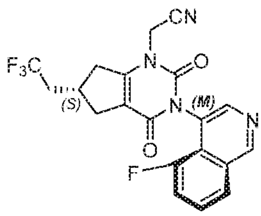
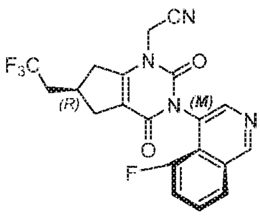
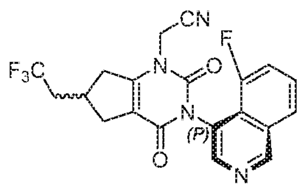
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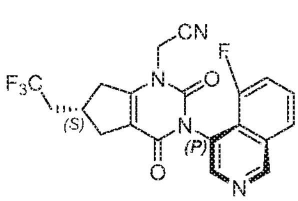
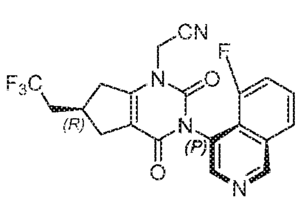
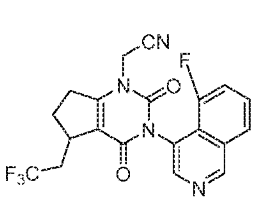
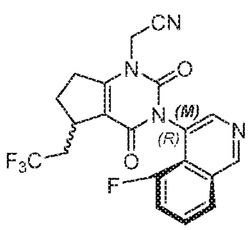
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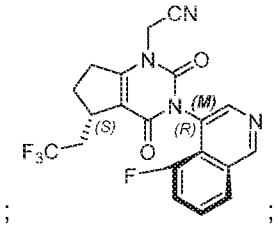
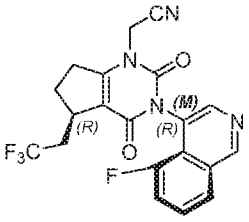
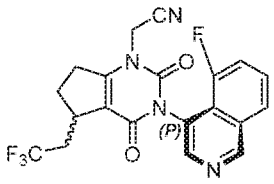
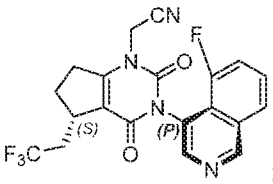
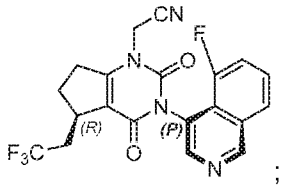
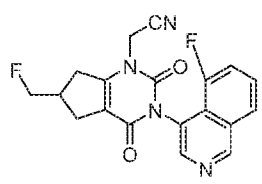
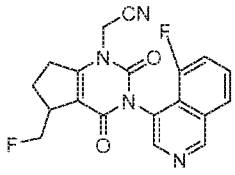
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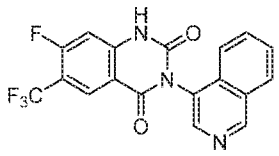
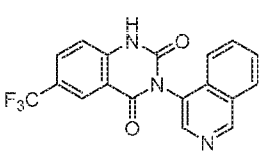
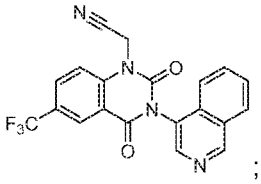
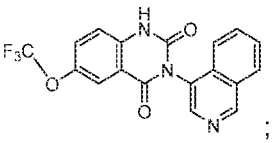
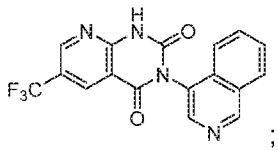
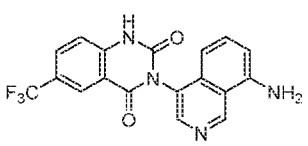
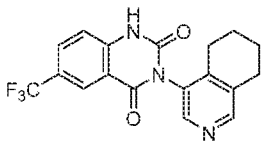
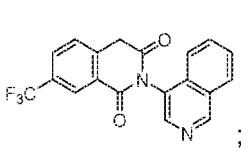
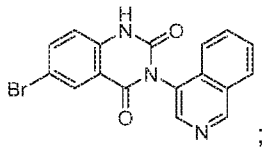
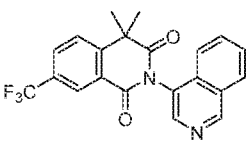
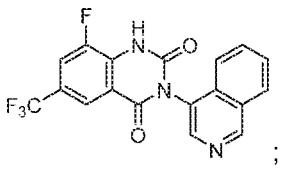
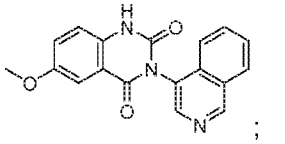
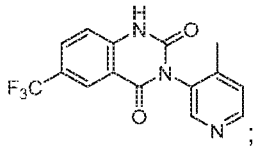
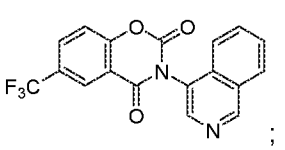
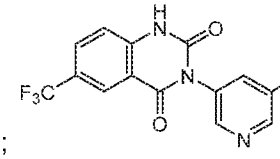
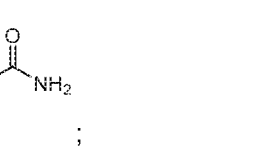
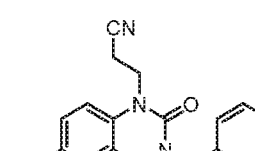
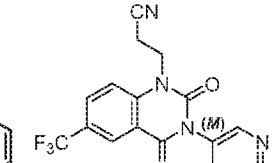
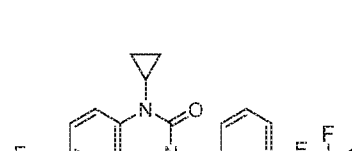
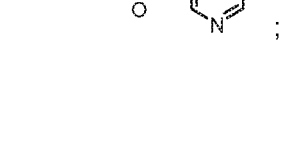
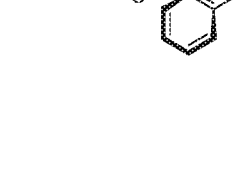
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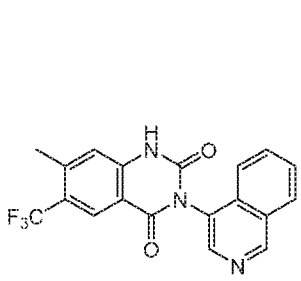
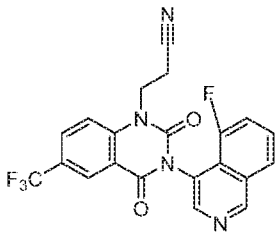
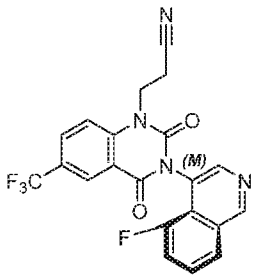
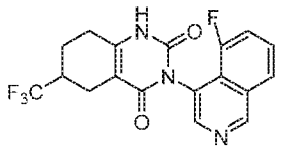
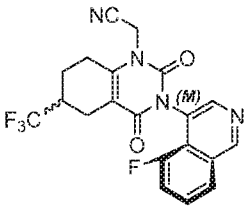
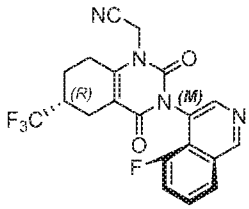
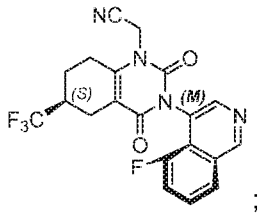
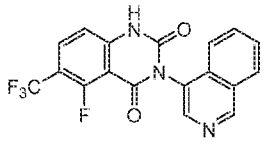
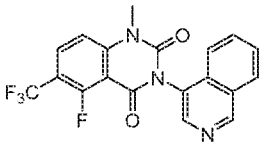
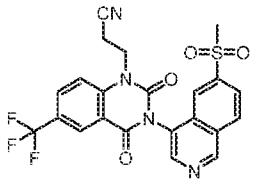
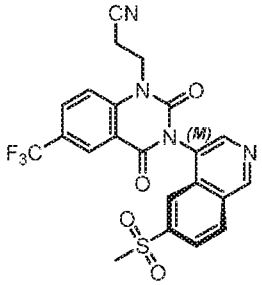
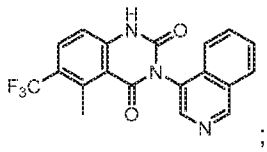
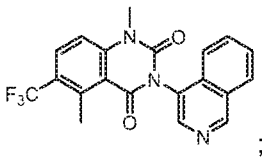
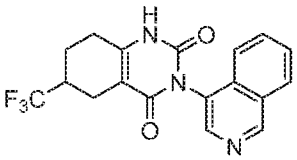
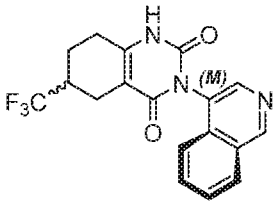
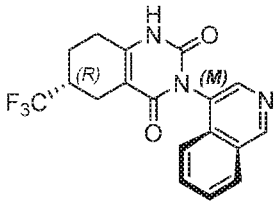
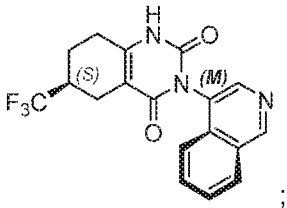
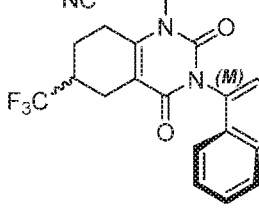
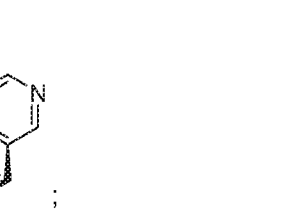
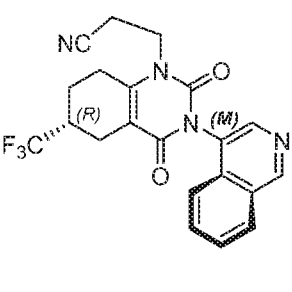
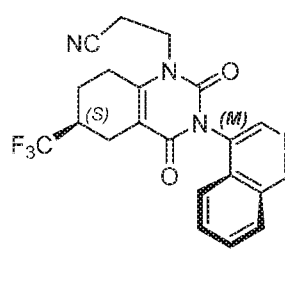
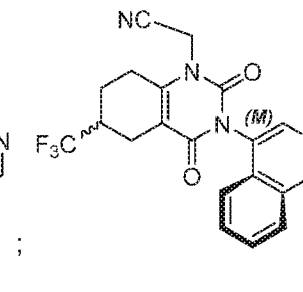

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**Embodiment 217.** The compound of Embodiment 1, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein the compound is selected from:


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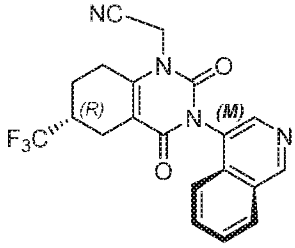
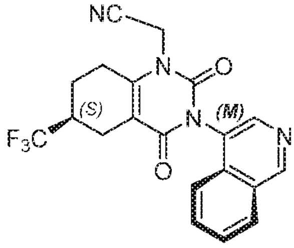
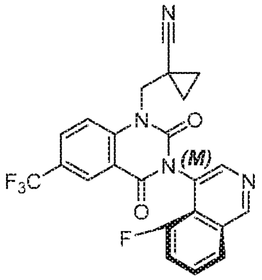
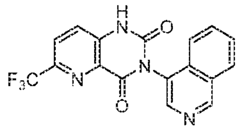
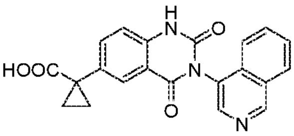
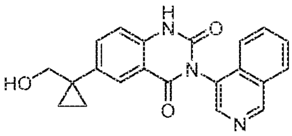
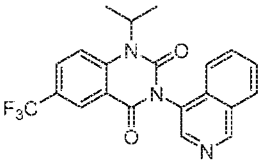
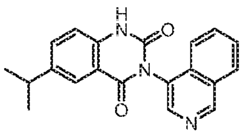
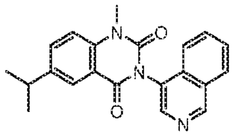
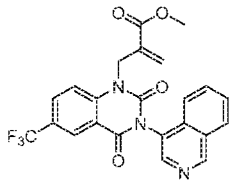
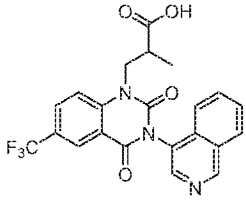
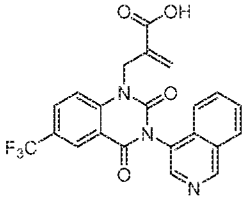
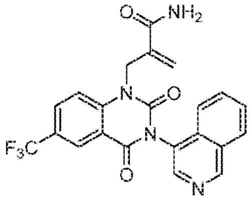
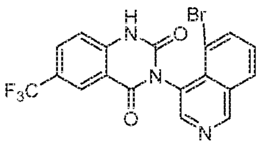
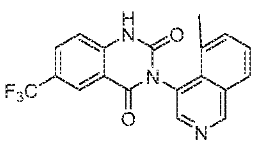
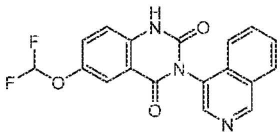
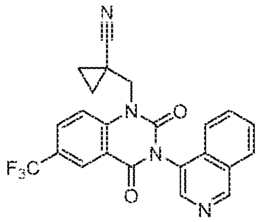
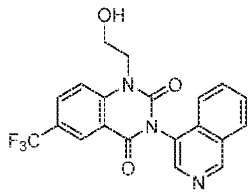
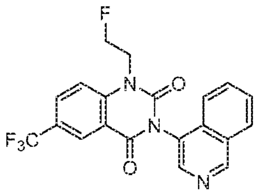
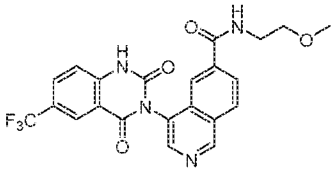
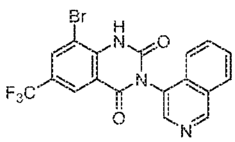
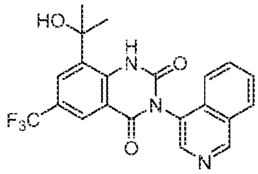
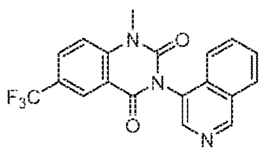
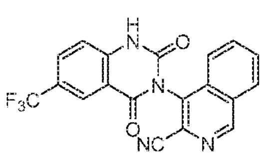
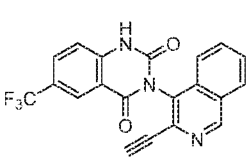
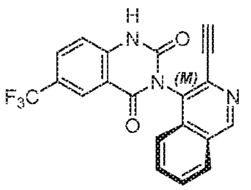
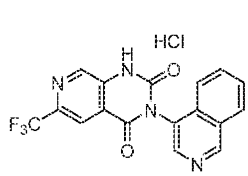
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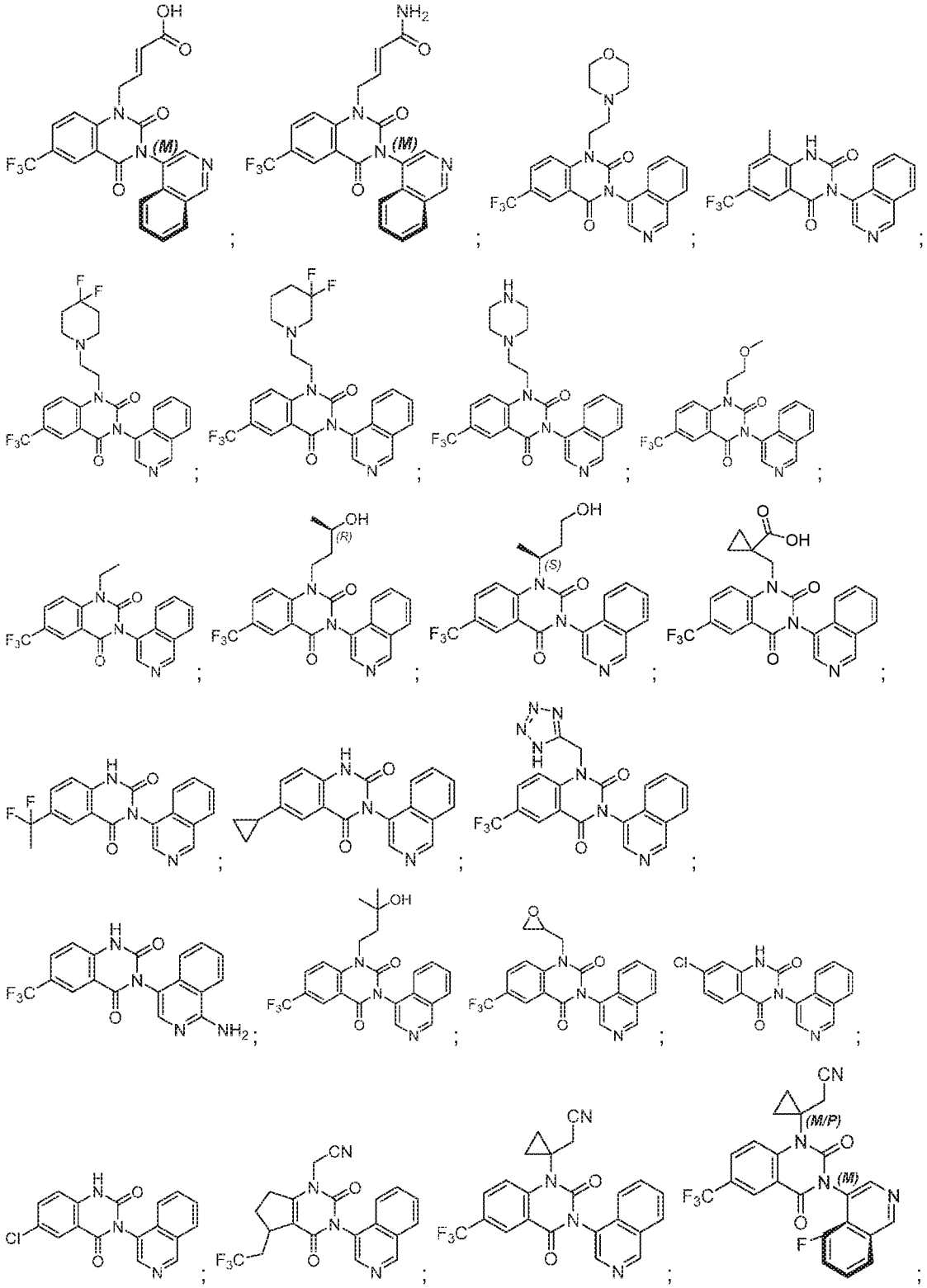

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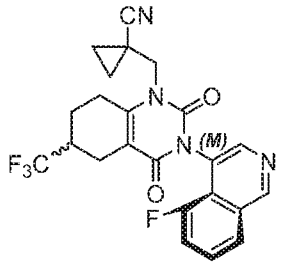
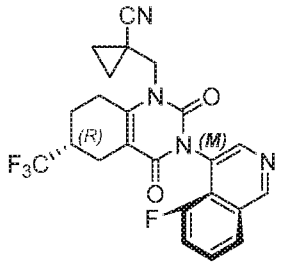
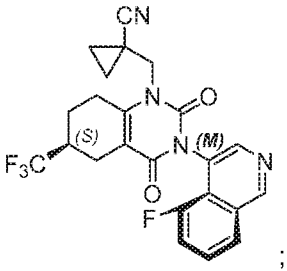
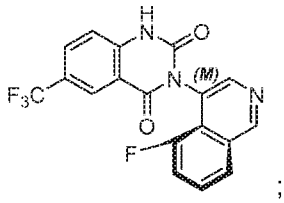
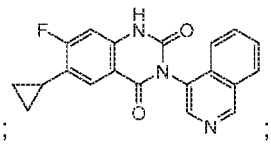
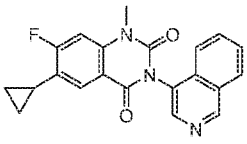
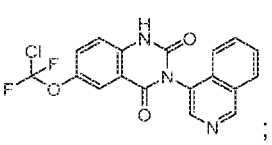
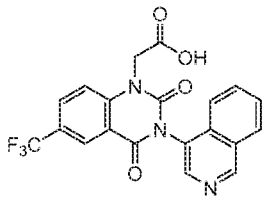
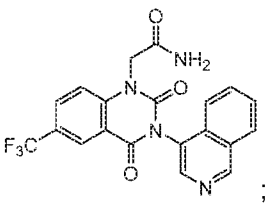
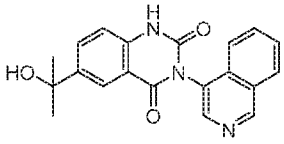
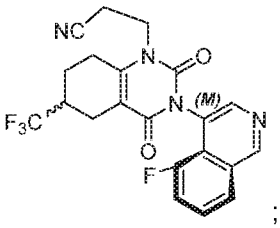
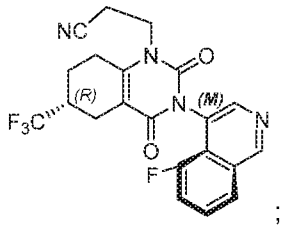
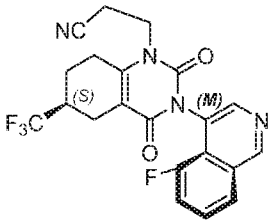
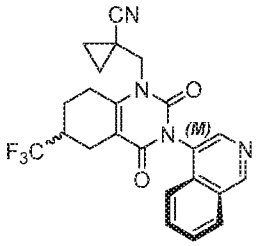
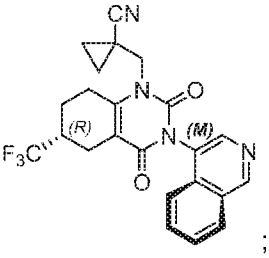
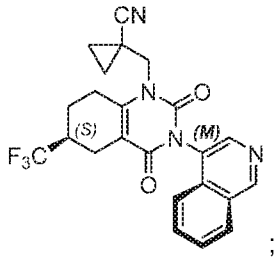
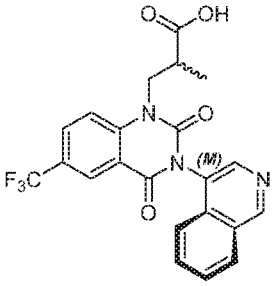
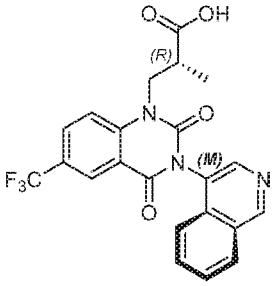
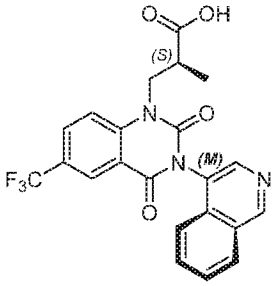
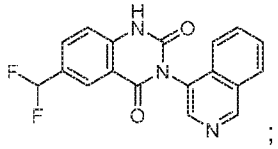
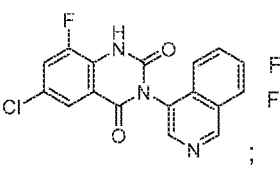
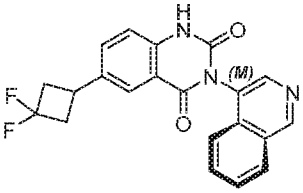
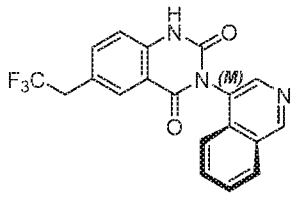
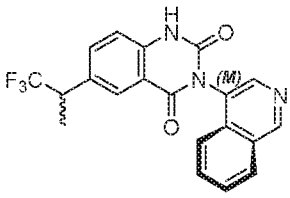
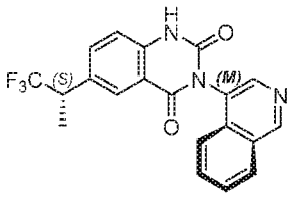
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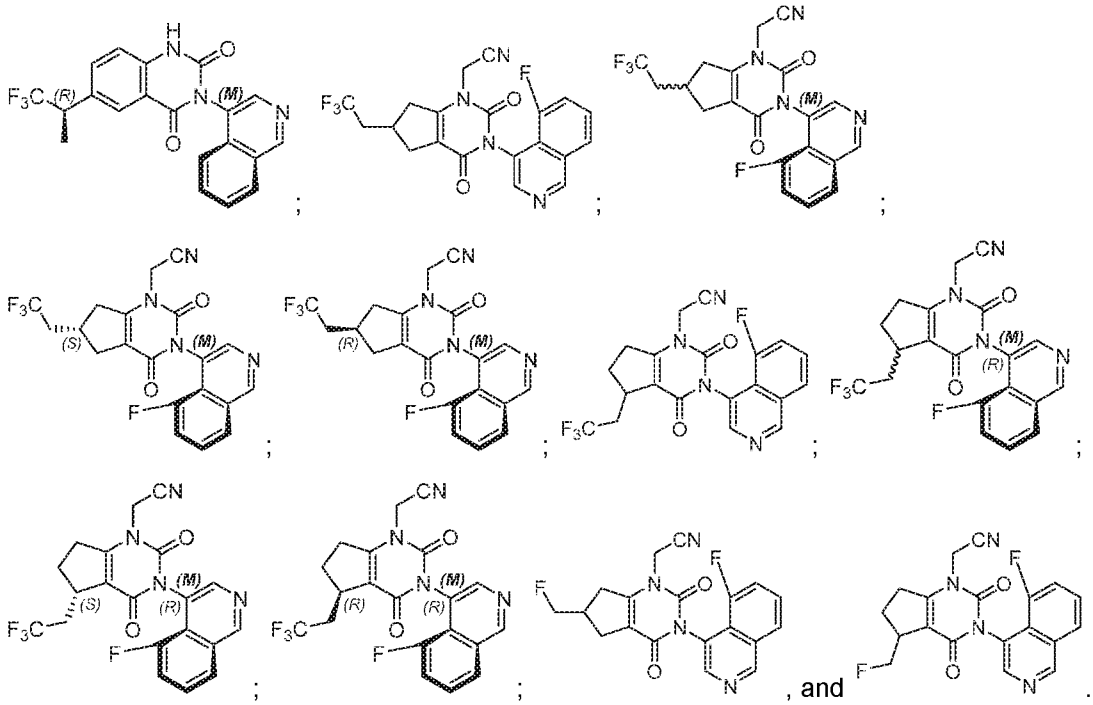
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Depending on the choice of the starting materials and procedures, the compounds can be present in the form of one of the possible isomers or as mixtures thereof, for example as pure optical isomers, or as isomer mixtures, such as racemates and diastereoisomer mixtures, depending on the number of asymmetric carbon atoms. The present invention is meant to include all such possible isomers, including racemic mixtures, diasteriomeric mixtures and optically pure forms. Optically active (*R*)- and (*S*)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. If the compound contains a double bond, the substituent may be *E* or *Z* configuration. If the compound contains a disubstituted cycloalkyl, the cycloalkyl substituent may have a cis- or trans-configuration. All tautomeric forms are also intended to be included.

As used herein, the terms “salt” or “salts” refers to an acid addition or base addition salt of a compound of the invention. “Salts” include in particular “pharmaceutical acceptable salts”. The terms “pharmaceutically acceptable salt” or “pharmaceutically acceptable salts”, as used herein, refers to a salt or salts that retain the biological effectiveness and properties of the compounds of this invention and, which typically are not biologically or otherwise undesirable. In many cases, the compounds of the present invention are capable of forming acid and/or base salts by virtue of the presence of amino and/or carboxyl groups or groups similar thereto.

Pharmaceutically acceptable acid addition salts can be formed with inorganic acids and organic acids. The organic acid or inorganic acids used to form pharmaceutically acceptable acid addition salts of compounds of the present invention include, but are not limited to, acetic acid, adipic acid, ascorbic acid, aspartic acid, benzoic acid, benzenesulfonic acid, carbonic acid,

camphor sulfonic acid, capric acid, chlorotheophyllinate, citric acid, ethanedisulfonic acid, fumaric acid, D-glycero-D-gulo-Heptonicacid, galactaric aid, galactaric acid/mucic acid, gluceptic acid, glucoheptonoic acid, gluconic acid, glucuronic acid, glutamatic acid, glutaric acid, glycolic acid, hippuric acid, hydrobromic acid, hydrochloric acid, hydroiodic acid, isethionic acid, lactic acid, lactobionic acid, lauryl sulfuric acid, malic acid, maleic acid, malonic acid, mandelic acid, mesylic acid, methanesulfonic acid, mucic acid, naphthoic acid, 1-hydroxy-2-naphthoic acid, naphthalenesulfonic acid, 2-naphthalenesulfonic acid, nicotinic acid, nitric acid, octadecanoic acid, oleaic acid, oxalic acid, palmitic acid, pamoic acid, phosphoric acid, polygalacturonic acid, propionic acid, sebacic acid, stearic acid, succinic acid, sulfosalicylic acid, sulfuric acid, tartaric acid, p-toluenesulfonic acid, trifluoroacetic acid and triphenylacetic acid.

Salt forms of the compounds of the present invention can be converted into the free compounds by treatment with a suitable basic agent.

Pharmaceutically acceptable acid addition salts of compounds of the present invention include, but are not limited to, a acetate, adipate, ascorbate, aspartate, benzoate, besylatye, benzenesulfonate, bicarbonate/carbonate, bisulfate/sulfate, bromide/hydrobromide, camphor sulfonate, camsylate, caprate, chloride/hydrochloride, chlorotheophyllinate, citrate, edisylate, ethanedisulfonate, fumarate, gluceptate, glucoheptonate, gluconate, glucuronate, glutamate, glutarate, glycolate, hippurate, hydroiodide/iodide, isethionate, lactate, lactobionate, laurylsulphate, malate, maleate, malonate, mandelate, mesylate, methanesulfonate, methylsulfate, mucate, naphthoate, napsylate, 2-napsylate, naphthalenesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, octadecanoate, oleate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, polygalacturonate, propionate, sebacate, stearate, succinate, sulfosalicylate, sulfate, tartrate, tosylate, p-toluenesulfonate, trifluoroacetate, trifenatate, triphenylacetete and xinafoate salt forms.

Pharmaceutically acceptable base addition salts can be formed with inorganic and organic bases. Organic bases used to form pharmaceutically acceptable base addition salts of compounds of the present invention include, but are not limited to, primary, secondary, and *tert*iary amines, substituted amines including naturally occurring substituted amines, cyclic amines, basic ion exchange resins, and the like. Certain organic amines include isopropylamine, benzathine, cholinate, diethanolamine, diethylamine, lysine, meglumine, piperazine and tromethamine. Inorganic bases used to form pharmaceutically acceptable base addition salts of compounds of the present invention include, but are not limited to, sodium hydroxide, potassium hydroxide, ammonium hydroxide, ammonium salts and metals from columns I to XII of the periodic table. Pharmaceutically acceptable base addition salts of compounds of the present invention include, but are not limited to, sodium, potassium, ammonium, calcium, magnesium, iron, silver, zinc, and copper salts; particularly suitable salts include ammonium, potassium, sodium, calcium and magnesium salts.

The pharmaceutically acceptable salts of the present invention can be synthesized from a

basic or acidic moiety, by conventional chemical methods. Generally, such salts can be prepared by reacting free acid forms of these compounds with a stoichiometric amount of the appropriate base (such as Na, Ca, Mg, or K hydroxide, carbonate, bicarbonate or the like), or by reacting free base forms of these compounds with a stoichiometric amount of the appropriate acid. Such reactions are typically carried out in water or in an organic solvent, or in a mixture of the two. Generally, use of non-aqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile is desirable, where practicable.

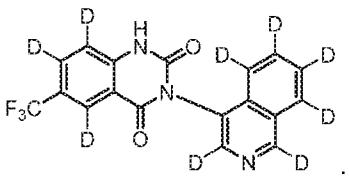
Any formula given herein is also intended to represent unlabeled forms as well as isotopically labeled forms of the compounds. Isotopically labeled compounds have structures depicted by the formulae given herein except that one or more atoms are replaced by an atom having a selected atomic mass or mass number. Isotopes that can be incorporated into compounds of the present invention include, for example, isotopes of hydrogen.

Further, incorporation of certain isotopes, particularly deuterium (i.e., $^{2}H$ or D) may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements or an improvement in therapeutic index or tolerability. It is understood that deuterium in this context is regarded as a substituent of a compound of the present invention. The concentration of deuterium, may be defined by the isotopic enrichment factor. The term "isotopic enrichment factor" as used herein means the ratio between the isotopic abundance and the natural abundance of a specified isotope. If a substituent in a compound of this invention is denoted as being deuterium, such compound has an isotopic enrichment factor for each designated deuterium atom of at least 3500 (52.5% deuterium incorporation at each designated deuterium atom), at least 4000 (60% deuterium incorporation), at least 4500 (67.5% deuterium incorporation), at least 5000 (75% deuterium incorporation), at least 5500 (82.5% deuterium incorporation), at least 6000 (90% deuterium incorporation), at least 6333.3 (95% deuterium incorporation), at least 6466.7 (97% deuterium incorporation), at least 6600 (99% deuterium incorporation), or at least 6633.3 (99.5% deuterium incorporation). It should be understood that the term “isotopic enrichment factor” can be applied to any isotope in the same manner as described for deuterium.

Other examples of isotopes that can be incorporated into compounds of the present invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, and chlorine, such as $^{3}H$, $^{11}C$, $^{13}C$, $^{14}C$, $^{15}N$, $^{18}F$ $^{31}P$, $^{32}P$, $^{35}S$, $^{36}Cl$, $^{123}I$, $^{124}I$, $^{125}I$ respectively. Accordingly it should be understood that the invention includes compounds that incorporate one or more of any of the aforementioned isotopes, including for example, radioactive isotopes, such as $^{3}H$ and $^{14}C$, or those into which non-radioactive isotopes, such as $^{2}H$ and $^{13}C$ are present. Such isotopically labelled compounds are useful in metabolic studies (with $^{14}C$), reaction kinetic studies (with, for example $^{2}H$ or $^{3}H$), detection or imaging techniques, such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT) including drug or substrate tissue distribution assays, or in radioactive treatment of patients. In particular, an $^{18}F$

or labeled compound may be particularly desirable for PET or SPECT studies. Isotopically-labeled compounds of the present invention can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples and Preparations using an appropriate isotopically-labeled reagents in place of the non-labeled reagent previously employed.).

By way of example, compounds of the present invention can exist in a deuterated form as shown below:



Any asymmetric atom (e.g., carbon or the like) of the compound(s) of the present invention can be present in racemic or enantiomerically enriched, for example the (*R*)-, (*S*)- or (*R,S*)-configuration. In certain embodiments, each asymmetric atom has at least 50 % enantiomeric excess, at least 60 % enantiomeric excess, at least 70 % enantiomeric excess, at least 80 % enantiomeric excess, at least 90 % enantiomeric excess, at least 95 % enantiomeric excess, or at least 99 % enantiomeric excess in the (*R*)- or (*S*)- configuration. Substituents at atoms with unsaturated double bonds may, if possible, be present in *cis*- (*Z*)- or *trans*- (*E*)- form.

Accordingly, as used herein a compound of the present invention can be in the form of one of the possible isomers, rotamers, atropisomers, tautomers or mixtures thereof, for example, as substantially pure geometric (*cis* or *trans*) isomers, diastereomers, optical isomers (antipodes), racemates or mixtures thereof.

Any resulting mixtures of isomers can be separated on the basis of the physicochemical differences of the constituents, into the pure or substantially pure geometric or optical isomers, diastereomers, racemates, for example, by chromatography and/or fractional crystallization. Any resulting racemates of final products or intermediates can be resolved into the optical antipodes by known methods, *e.g.*, by separation of the diastereomeric salts thereof, obtained with an optically active acid or base, and liberating the optically active acidic or basic compound. In particular, a basic moiety may thus be employed to resolve the compounds of the present invention into their optical antipodes, *e.g.*, by fractional crystallization of a salt formed with an optically active acid, *e.g.*, tartaric acid, dibenzoyl tartaric acid, diacetyl tartaric acid, di-*O,O'-p*-toluoyl tartaric acid, mandelic acid, malic acid or camphor-10-sulfonic acid. Racemic products can also be resolved by chiral chromatography, *e.g.*, high pressure liquid chromatography (HPLC) using a chiral adsorbent.

Processes for Making Compounds of Invention

General procedures for preparing compounds of the present invention are described herein.

In the reactions described, reactive functional groups, for example hydroxy, amino, imino or carboxy groups, where these are desired in the final product, may be protected to avoid their unwanted participation in the reactions. Within the scope of this text, only a readily removable group that is not a constituent of the particular desired end product of the compounds of the present invention is designated a "protecting group", unless the context indicates otherwise. The protection of functional groups by such protecting groups, the protecting groups themselves, and their cleavage reactions are described for example in standard reference works, such as J. F. W. McOmie, "Protective Groups in Organic Chemistry", Plenum Press, London and New York 1973, in T. W. Greene and P. G. M. Wuts, "Protective Groups in Organic Synthesis", Third edition, Wiley, New York 1999.

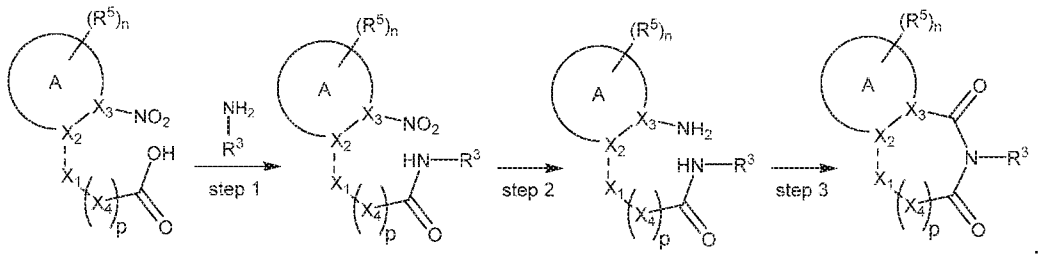
All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g. "such as") provided herein is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention otherwise claimed.

Methods of synthesizing compounds of the invention

Compounds of the present invention were made by processes described herein and as illustrated in the Examples. The combination of various building blocks and intermediates described herein can be applied to yield compounds of the invention. In the schemes below Ring A, $X_1$, $X_2$, X, X, $R^1$, $R^3$, $R^5$, n and p are as defined herein.

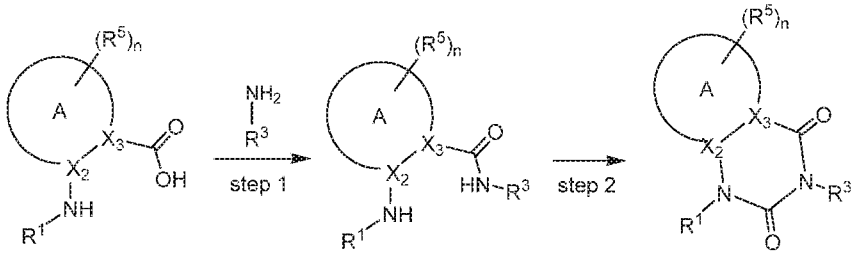
A non-limiting example of a synthetic scheme used to make certain compounds of the present invention is illustrated below in Scheme 1.

Scheme 1.



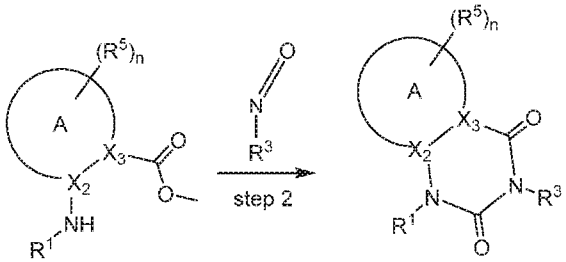

Scheme 2-6 illustrate synthetic schemes used to make compounds of the present invention, with further guidance found in the examples section. Note that in Schemes 2-6, when $R^1$ is H then subsequent N alkylation can occur after ring formation using known methods to obtain $R^1$ groups which are not H.

Scheme 2.



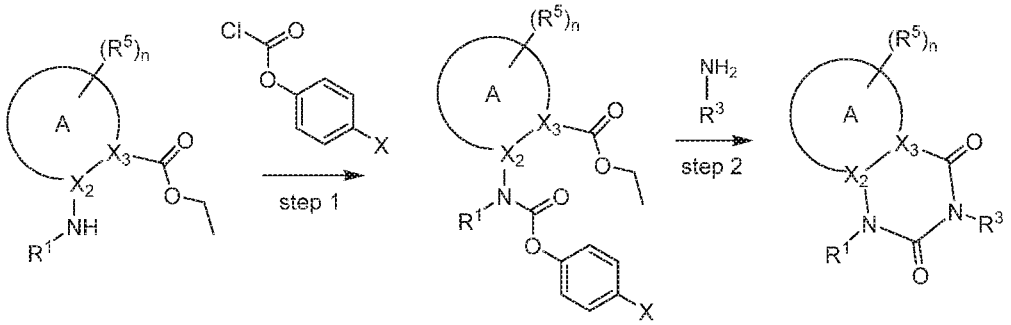

In scheme 2, starting from an amino-acid, e.g. substituted anthranilic acids, amide bond formation with a commercially available amine, e.g. isoquilonine-4-amine, mediated by a coupling agent, e.g. HATU gives an amide. The amide undergoes cyclization in the presence of a carbonyl donor such as triphosgene, CDI or a mixture of CDI and CDT.

Scheme 3.



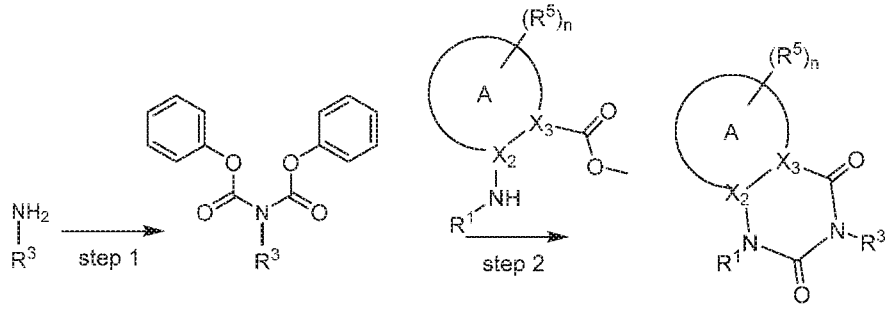

In scheme 3, the product is obtained by addition of an amino-ester to an isocyanate in the presence of a base, e.g. pyridine. The isocyanate is commercially available or can be prepared from the corresponding amine and triphosgene.

Scheme 4.

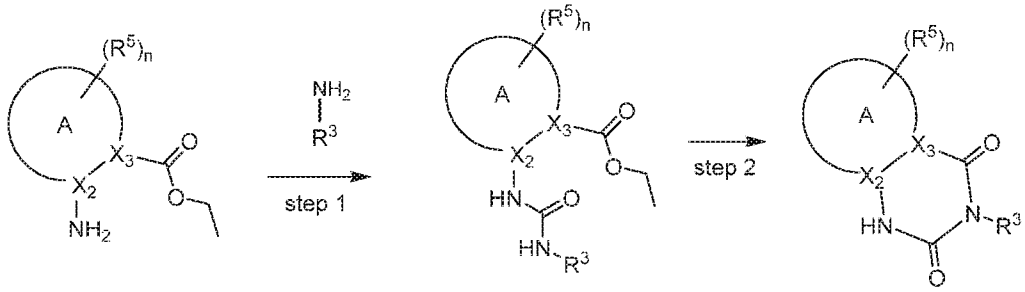



In scheme 4, an amino-ester, e.g. an ethyl ester of substituted anthranilic acid is reacted with a chloroformate, e.g. phenylchloroformate or p-nitrophenylchloroformate in the presence of a base. e.g. pyridine, to give a carbamate. The product is then obtained by addition of an amine, e.g. isoquinoline-4-amine, in the presence of a base, e.g. DBU.

Scheme 5.



Scheme 6.



In Scheme 6, a urea is formed by first reacting an amino-ester with triphosgene and a base, e.g. triethylamine, to form the corresponding isocyanate, which is trapped by amine to form a urea. Treating the urea with a base, such as potassium carbonate, gives the product.

Administration and Pharmaceutical Compositions

For the therapeutic uses of compounds of the present invention, such compounds are administered either alone or as part of a pharmaceutical composition. Accordingly, in another aspect of the present invention provides a pharmaceutical composition, which comprises a compound of the present invention, or pharmaceutically acceptable salt or stereoisomer thereof, and one or more pharmaceutically acceptable carriers. In a further embodiment, the composition comprises at least two pharmaceutically acceptable carriers, such as those described herein. The pharmaceutical composition can be formulated for particular routes of administration such as oral administration, parenteral administration (e.g. by injection, infusion, transdermal or topical administration), and rectal administration. Topical administration may also pertain to inhalation or intranasal application. In certain embodiments, the pharmaceutical composition comprising a compound of the present invention can be formulated for intramuscularly, intravenously, subcutaneously, orally, pulmonary, intrathecally, topically or intranasally administration.

The pharmaceutical compositions of the present invention can be made up in a solid form (including without limitation capsules, tablets, pills, granules, powders or suppositories), or in a liquid form (including without limitation solutions, suspensions or emulsions). Tablets may be either film coated or enteric coated according to methods known in the art.

Typically, the pharmaceutical compositions are tablets or gelatin capsules comprising the active ingredient together with

a) diluents, *e.g.*, lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycine;

b) lubricants, *e.g.*, silica, talcum, stearic acid, its magnesium or calcium salt and/or polyethyleneglycol; for tablets also

c) binders, *e.g.*, magnesium aluminum silicate, starch paste, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose and/or polyvinylpyrrolidone; if desired

d) disintegrants, *e.g.*, starches, agar, alginic acid or its sodium salt, or effervescent mixtures; and/or

e) absorbents, colorants, flavors and sweeteners.

Suitable compositions for oral administration include a compound of the present invention in the form of tablets, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use are prepared according to any method known in the art for the manufacture of pharmaceutical compositions and such compositions can contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets may contain the active ingredient in admixture with nontoxic pharmaceutically acceptable carriers/excipients which are suitable for the manufacture of tablets. These carriers/excipients are, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example, starch, gelatin or acacia; and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets are uncoated or coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate can be employed. Formulations for oral use can be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example, peanut oil, liquid paraffin or olive oil.

The parenteral compositions (e.g, intravenous (IV) formulation) are aqueous isotonic solutions or suspensions. The parenteral compositions may be sterilized and/or contain adjuvants, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure and/or buffers. In addition, they may also contain other therapeutically valuable substances. The compositions are generally prepared according to conventional mixing, granulating or coating methods, respectively, and contain about 0.1-75%, or contain about 1-50%, of the active ingredient.

The compound of the present invention or pharmaceutical composition thereof for use in a

subject (e.g., human) is typically administered orally or parenterally at a therapeutic dose of less than or equal to about 100 mg/kg. When administered intravenously via infusion, the dosage may depend upon the infusion rate at which an iv formulation is administered. In general, the therapeutically effective dosage of a compound, the pharmaceutical composition, or the combinations thereof, is dependent on the species of the subject, the body weight, age and individual condition, the disorder or disease or the severity thereof being treated.

The above-cited dosage properties are demonstrable *in vitro* and *in vivo* tests using advantageously mammals, *e.g.*, mice, rats, dogs, monkeys or isolated organs, tissues and preparations thereof. The compounds of the present invention can be applied *in vitro* in the form of solutions, *e.g.*, aqueous solutions, and *in vivo* either enterally, parenterally, advantageously intravenously, *e.g.*, as a suspension or in aqueous solution.

Certain aspects and examples of the pharmaceutical compositions of the present invention are provided in the following listing of enumerated embodiments. It will be recognized that features specified in each embodiment may be combined with other specified features to provide further embodiments of the present invention.

**Embodiment 218.** A pharmaceutical composition comprising a compound of Formula (I) or any one of Embodiments 1 to 217, or a pharmaceutically acceptable salt or stereoisomer thereof, and one or more pharmaceutically acceptable carriers.

**Embodiment 219.** A pharmaceutical composition comprising a compound of Embodiment 218, or a pharmaceutically acceptable salt or stereoisomer thereof, and one or more pharmaceutically acceptable carriers.

**Embodiment 220.** The pharmaceutical composition of Embodiment 218 or Embodiment 219 comprising one or more additional therapeutic agents.

Pharmacology and Utility

The compounds of the invention, in free form or in pharmaceutically acceptable salt form, exhibit valuable pharmacological properties, e.g. inhibition of SARS-CoV-2 main protease ($M^{pro}$), as indicated by the *in vitro* tests provided herein, and are therefore indicated for therapy or for use as research chemicals, e.g. as tool compounds. Accordingly, the compounds of the invention may generally be useful in the treatment, management and/or prevention of a coronaviral-related disease.

Certain aspects and examples of the use of compounds of the present invention and pharmaceutical compositions of the present invention are provided in the following listing of enumerated embodiments. It will be recognized that features specified in each embodiment may be combined with other specified features to provide further embodiments of the present invention.

**Embodiment 221.** A method for treating a disease or disorder associated with the activity of SARS-CoV-2 main protease ($M^{pro}$), wherein the method comprises administering to a

subject in need of such treatment a therapeutically effective amount of a compound of any one of Embodiments 1 to 217, or a pharmaceutically acceptable salt.

**Embodiment 222.** A method for treating a disease or disorder associated with the activity of SARS-CoV-2 main protease ($M^{pro}$), wherein the method comprises administering to a subject in need of such treatment a compound of any one of Embodiments 1 to 217, or a pharmaceutically acceptable salt.

**Embodiment 223.** Use of a compound of any one of Embodiments 1 to 217, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a disease or disorder associated with the activity of SARS-CoV-2 main protease ($M^{pro}$).

**Embodiment 224.** Use of a compound of any one of Embodiments 1 to 217, or a pharmaceutically acceptable salt thereof, in the treatment of a disease or disorder associated with the activity of SARS-CoV-2 main protease ($M^{pro}$).

**Embodiment 225.** A compound of any one of Embodiments 1 to 217, or a pharmaceutically acceptable salt thereof, for use in the treatment of a disease or disorder associated with the activity of SARS-CoV-2 main protease ($M^{pro}$).

**Embodiment 226.** A method for treating, managing and/or preventing a coronaviral-related disease in a subject in need thereof, wherein the method comprises administering to the subject a therapeutically effective amount of a compound of any one of Embodiments 1 to 217, or a pharmaceutically acceptable salt thereof.

**Embodiment 227.** A method for treating, managing and/or preventing a coronaviral-related disease in a subject in need thereof, wherein the method comprises administering to the subject a compound of any one of Embodiments 1 to 217, or a pharmaceutically acceptable salt thereof.

**Embodiment 228.** Use of a compound of any one of Embodiments 1 to 217, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment, management and/or prevention of a coronaviral-related disease.

**Embodiment 229.** Use of a compound of any one of Embodiments 1 to 217, or a pharmaceutically acceptable salt thereof, in the treatment, management and/or prevention of a coronaviral-related disease.

**Embodiment 230.** A compound of any one of Embodiments 1 to 217, or a pharmaceutically acceptable salt thereof, for use in the treatment, management and/or prevention of a coronaviral-related disease.

**Embodiment 231.** A method for treating a coronaviral-related disease in a subject in need thereof, wherein the method comprises administering to the subject a therapeutically effective amount of a compound of any one of Embodiments 1 to 217, or a pharmaceutically acceptable salt thereof.

**Embodiment 232.** A method for treating a coronaviral-related disease in a subject in need thereof, wherein the method comprises administering to the subject a compound of any one of Embodiments 1 to 217, or a pharmaceutically acceptable salt thereof.

**Embodiment 233.** Use of a compound of any one of Embodiments 1 to 217, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment a coronaviral-related disease.

**Embodiment 234.** Use of a compound of any one of Embodiments 1 to 217, or a pharmaceutically acceptable salt thereof, in the treatment of a coronaviral-related disease.

**Embodiment 235.** A compound of any one of Embodiments 1 to 217, or a pharmaceutically acceptable salt thereof, for use in the treatmen of a coronaviral-related disease.

**Embodiment 236.** A method for treating, managing and/or preventing COVID-19 disease in a subject in need thereof, wherein the method comprises administering to the subject a therapeutically effective amount of a compound of any one of Embodiments 1 to 217, or a pharmaceutically acceptable salt thereof.

**Embodiment 237.** A method for treating, managing and/or preventing COVID-19 disease in a subject in need thereof, wherein the method comprises administering to the subject a compound of any one of Embodiments 1 to 217, or a pharmaceutically acceptable salt thereof.

**Embodiment 238.** Use of a compound of any one of Embodiments 1 to 217, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment, management and/or prevention of COVID-19 disease.

**Embodiment 239.** Use of a compound of any one of Embodiments 1 to 217, or a pharmaceutically acceptable salt thereof, in the treatment, management and/or prevention of COVID-19 disease.

**Embodiment 240.** A compound of any one of Embodiments 1 to 217, or a pharmaceutically acceptable salt thereof, for use in the treatment, management and/or prevention of COVID-19 disease.

**Embodiment 241.** A method for treating COVID-19 disease in a subject in need thereof, wherein the method comprises administering to the subject a therapeutically effective amount of a compound of any one of Embodiments 1 to 217, or a pharmaceutically acceptable salt thereof.

**Embodiment 242.** A method for treating COVID-19 disease in a subject in need thereof, wherein the method comprises administering to the subject a compound of any one of Embodiments 1 to 217, or a pharmaceutically acceptable salt thereof.

**Embodiment 243.** Use of a compound of any one of Embodiments 1 to 217, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of COVID-19 disease.

**Embodiment 244.** Use of a compound of any one of Embodiments 1 to 217, or a pharmaceutically acceptable salt thereof, in the treatment of COVID-19 disease.

**Embodiment 245.** A compound of any one of Embodiments 1 to 217, or a pharmaceutically acceptable salt thereof, for use in the treatment of COVID-19 disease.

**Embodiment 246.** The method of any one of Embodiments 221, 222, 226, 227, 231, 232, 236, 237, 241 and 242, wherein the coronaviral-related disease is COVID-19.

**Embodiment 247.** The use of a compound of any one of Embodiments 223, 224, 228, 229, 233, 234, 238, 239, 243 and 244, wherein the coronaviral-related disease is COVID-19.

**Embodiment 248.** The compound for the use in treatment of any one of Embodiments 225, 230, 235, 240 and 245, wherein the coronaviral-related disease is COVID-19.

**Embodiment 249.** A method for inhibiting the activity of SARS-CoV-2 main protease ($M^{pro}$), wherein the method comprises administering to a subject in need of such treatment a therapeutically effective amount of a compound of any one of Embodiments 1 to 217, or a pharmaceutically acceptable salt.

**Embodiment 250.** A method for inhibiting the activity of SARS-CoV-2 main protease ($M^{pro}$), wherein the method comprises administering to a subject in need of such treatment a compound of any one of Embodiments 1 to 217, or a pharmaceutically acceptable salt.

**Embodiment 251.** Use of a compound of any one of Embodiments 1 to 217, or a pharmaceutically acceptable salt thereof, in the inhibition of the activity of SARS-CoV-2 main protease ($M^{pro}$).

**Embodiment 252.** A compound of any one of Embodiments 1 to 217, or a pharmaceutically acceptable salt thereof, for use in the inhibition of the activity of SARS-CoV-2 main protease ($M^{pro}$).

Combination Therapy

In certain instances, it may be advantageous to administer a compound of the present invention in combination with one or more additional therapeutic agents. A therapeutic agent is, for example, a chemical compound, peptide, antibody, antibody fragment or nucleic acid, which is therapeutically active or enhances the therapeutic activity when administered to a patient in combination with a compound of the present invention.

Compounds of the invention may be administered as the sole active ingredient or together with other active agents useful against a coronaviral-related disease. Accordingly, another aspect of the invention are combination for use in the treatment, prevention and/or management of a coronaviral related disease, wherein a compound of the invention is used in combination with one or more other active agents. In certain embodiments the active agent(s) is selected from a neutralizing antibody and an antiviral agent. In ceratin embodiments the active agent(s) is selected froma neutralizing antibody, an antiviral agent and other agents selected from alvelestat, Lenzilumab, Octagam, Remestemcel-L, RPH-104 + olokizumab, Bucillamine,

CD24FC (MK-7110), Tradipitant, Ifenprodil, Tocilizumab, Leronlimab, Fenretinide, ATYR-1923, CYTO-205, APN-01, and Ampion. In certain embodiments, the neutralizing antibody is selected from Bamlanivimab, bamlanivimab + etesevimab, bamlanivimab + VIR-7831, REGN-COV2, VIR-7831, AZD7442, Regdanvimab/CT-P59, ABP-300, , COVI-AM/STI-2020, VIR-7832, SAB-185, JS016/etesevimab, C-135LS/C-144LS, BRII-196, BRII-198, SCTA-01, MW-33, DXP593, HFB-30132A, ADG20, COVI-GUARD (STI-1499) and convalescent plasma, and the antiviral agents is selected from remdesivir, Avigan/favipiravir, EIDD-2801/molnupiravir, AT-527, PF-00835231, PF-07321332, Ensovibep/DARPins, galidesivir, lopinavir-ritonavir, Virazole (ribavirin), levovir, elsulfavirine, thimerosal, UNI91103, silmitasertib/CX-4945, RBT-9, AT-301, Traneurocin/Neurosivir, Opaganib, ABX-464, SNG001, alisporivir, nafamostat mesylate, Vidofludimus/IMU-838, Emvododstat/PTC299, Brequinar, ATR-002, maraviroc.

In certain embodiments a compound of the invention is used in combination with remdesivir (also known as 2-ethylbutyl ((((2R,3S,4R,5R)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)-L-alaninate) for the treatment, prevention and/or management of a coronaviral related disease.

In certain embodiments a compound of the invention is used in combination with an antibody for the treatment, prevention and/or management of a coronaviral related disease, wherein the antibody selected from ABBV 47D11, ABP-300, ADG20, Bamlanivimab + VIR-7831, Bamlanivimab+etesevimab, BRII196 + BRII198, C-135LS/C-144LS, Convalescent Plasma, COR-101, CT-P63, DXP593, Etesevimab (JS016), Evusheld/AZD-7442, HFB-30132A, IBIO123, IN-006, JMB2002, LY-CoV1404, Ly-CovMab, MAD0004J08, MW-33, REGEN-COV/Ronapreve, Regkirona/Regdanvimab, SAB-185, SCTA-01, STI-2099/COVIDROPS, TY027, VIR-7832 (GSK4182136), Xevudy/Sotrovimab and XVR011.

In certain embodiments a compound of the invention is used in combination with an antiviral agent for the treatment, prevention and/or management of a coronaviral related disease, wherein the antiviral agent selected from ABX-464, alisporivir, alvelestat, ANA-001, Apabetalone, Arakoda (Tafenoquine), ASC-09 + ritonavir, ASC11, AT-100, AT-301, AT-527 (Bemnifosubuvir), AT-H201, ATR-002, boceprivir, brequinar, Bucillamine, Camostat (DWJ1248), Camostat mesylate, Carrimycin, DC-402234 (FB2001), Ebeselen (SPI-1005), EDP-235, Elsulfavirine, Ensitrelvir/S-217622, Ensovibep, Favipiravir, FP-025, Galidesivir, Gamunex-C, Lagevrio/Molnupiravir, LAU-7b, Levovir, lopinavir-ritonavir, maraviroc, Masitinib, nafamostat mesylate, Narsoplimab, Neumifil, Neurosivir, Opaganib, Paxlovid/PF-07321332, PBI-0451, Pentarlandir, PF-07304814, PJS-539, Plitidepsin, Proxalutamide, PTC299 (emvododstat), RBT-9, RESP301, ribavirin, ritonavir, Silmitasertib, SLV213, SNG001, Thimerosal, Tollovir, Trabedersen (OT-101), Traneurocin, UNI91103, Upamostat, Veklury, Vidofludimus and Virazole (ribavirin).

In certain embodiments a compound of the invention is used in combination with other active agents for the treatment, prevention and/or management of a coronaviral related disease,

wherein active agents is selected from Actemra/RoActemra, Ampion, APN-01 (alunacedase alfa), ATR-002, ATYR-1923, CYTO-205, Fenretinide (LAU-7b), Lenzilumab, Leronlimab, Octagam, Olumiant +/- Veklury , Remestemcel-L, RPH-104 + olokizumab, sarilumab , tocilizumab and Tradipitant.

**EXAMPLES**

The compounds of the present invention can be produced as shown in the following examples. The following examples are intended to illustrate the invention and are not to be construed as being limitations thereon. Temperatures are given in degrees Celsius. If not mentioned otherwise, all evaporations are performed under reduced pressure, typically between about 15 mm Hg and 100 mm Hg (= 20-133 mbar). The structure of final products, intermediates and starting materials is confirmed by standard analytical methods, *e.g.*, microanalysis and spectroscopic characteristics, *e.g.*, MS, IR, NMR. Abbreviations used are those conventional in the art or are listed below.

All starting materials, building blocks, reagents, acids, bases, dehydrating agents, solvents, and catalysts utilized to synthesize the compounds of the present invention are either commercially available or can be produced by organic synthesis methods known to one of ordinary skill in the art or can be produced by organic synthesis methods as described herein.

For illustrative purposes, the general reaction schemes depicted herein provide potential routes for synthesizing the compounds of the present invention as well as key intermediates. For a more detailed description of the individual reaction steps, see the Examples section below. Although specific starting materials and reagents are depicted in the schemes and discussed below, other starting materials and reagents can be easily substituted to provide a variety of derivatives and/or reaction conditions. In addition, many of the compounds prepared by the methods described below can be further modified in light of this disclosure using conventional chemistry well known to those skilled in the art.

***Abbreviations:***

| | |
|---|---|
| ACN | acetonitrile |
| abs | absolute |
| AcOH | acetic acid |
| aq. | aqueous |
| br. s | broad singlet |
| BuLi | *n*-Butyl lithium |
| CDI | Carbonyldiimidazole |
| CDT | Carbonylditriazole |
| $Cs_2CO_3$ | cesium carbonate |
| CO | carbon monoxide |

| | |
|---|---|
| CuBr | copper(I) bromide |
| d | doublet |
| DCE | dichloroethane |
| DMAc | N,N-dimethylacetamide |
| DMAP | dimethylaminopyridine |
| DMBNH | 2 2,4-dimethoxybenzylamine |
| DMF | dimethylformamide |
| DMSO | dimethylsulfoxide |
| $Et_3N$ | triethylamine |
| EtOAc | ethyl acetate |
| EtOH | ethanol |
| FA | formic acid |
| h | hour(s) |
| HATU | O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluroniumhexafluorophosphonate |
| HCl | hydrochloric acid |
| HPLC | High Performance Liquid Chromatography |
| IPAm | Isopropylamine |
| L | liter(s) |
| LCMS | Liquid Chromatography/Mass Spectrometry |
| LiOH | lithium hydroxide |
| M | molar (mol/L) |
| Me | methyl |
| MeI | methyl iodide |
| MeOH | methanol |
| min | minute(s) |
| mL | milliliter |
| mm | millimeter |
| MHz | megaHertz |
| MS | Mass Spectrometry |
| µm | micrometer |
| NaCl | sodium chloride |
| $NaHCO_3$ | sodium bicarbonate |
| NaOH | sodium hydroxide |
| $Na_2SO_4$ | sodium sulfate |
| $NH_4Cl$ | ammonium chloride |
| NMI | N-methylimidazole |
| NMM | 4-methylmorpholine |

| | |
|---|---|
| NMR | Nuclear Magnetic Resonance |
| Pd/C | palladium on charcoal |
| Prep | Preparative |
| q | Quartet |
| rt | room temperature |
| $t_R$ | retention time |
| s | singlet |
| sat. | saturated |
| t | triplet |
| TBDPSCl | tert-butylchlorodiphenylsilane |
| TCFH | N, N, N', N'-tetramethylchloroformamidinium hexafluorophosphate |
| TEA | triethylamine |
| TFA | trifluoroacetic acid |
| THF | tetrahydrofuran |
| $TMSCF_3$ | trifluoromethyltrimethylsilane |

***Analytical Methods***

LCMS conditions:

**LCMS Method 1**: Instrument: Agilent 1200 & 6110, ESI; Column: Kinetex C18 50mmx2.1mm, 5 µm; Gradient: mobile phase A: 0.04% trifluoroacetic acid in water, B: 0.02% trifluoroacetic acid in acetonitrile; 5%B for 0.4 min, 5-95% B over 2.6 min, 95% B for 1.0 min, 95-5%B over 0.01 min; Flow rate: 1.0 mL/min; UV detection 215 nm and 254 nm; Mass detection MS range 100-1000 Da (ESI); Column temperature: 40 °C.

**LCMS Method 2**: Instrument: Agilent 1260 & 6120, ESI; Column: Xbridge Shield RP18 50mmx2.1mm, 5 µm; Gradient: mobile phase A: 10 mM $NH_4HCO_3$ in water, B: acetonitrile; 15%B for 0.4 min, 15-90% B over 3 min, 90-100% B over 0.45 min, 100-15%B over 0.01 min; Flow rate: 0.8 mL/min; UV detection 215 nm and 254 nm; Mass detection MS range 100-1000 Da (ESI); Column temperature: 40 °C

**LCMS Method 3**: Instrument: Agilent 1260 & 6120, ESI; Column: Luna LC-C18 50mmx2mm, 5 µm; Gradient: mobile phase A: 0.05% trifluoroacetic acid in water, B: 0.05% trifluoroacetic acid in acetonitrile; 10%B for 0.4 min, 10-100% B over 3.0 min, 100% B for 0.45 min, 100-10%B over 0.01 min; Flow rate: 0.8 mL/min; UV detection 215 nm and 254 nm; Mass detection MS range 100-1000 Da (ESI); Column temperature: 40 °C.

**LCMS Method 4**: Instrument: Agilent 1260 & 6120, ESI; Column: Luna LC-C18 50mmx2mm, 5 µm; Gradient: mobile phase A: 0.05% trifluoroacetic acid in water, B: 0.05% trifluoroacetic acid in acetonitrile; 1%B for 0.4 min, 1-90% B over 3.0 min, 90-100% B over 0.45 min, 100-1%B over

0.01 min; Flow rate: 0.8 mL/min; UV detection 215 nm and 254 nm; Mass detection MS range 100-1000 Da (ESI); Column temperature: 40 °C.

**LCMS Method 5**: Instrument: Agilent 1260 & 6125B, ESI; Column: Agilent Poroshell SB-C18 30mmx3.0mm, 2.7 µm; Gradient: mobile phase A: 0.04% trifluoroacetic acid in water, B: 0.02% trifluoroacetic acid in acetonitrile; 5-95% B over 0.8 min, 95% B for 0.41 min, 95-5%B over 0.01 min; Flow rate: 2.0 mL/min; UV detection 220 nm; Mass detection MS range 100-1000 Da (ESI); Column temperature: 40 °C.

**LCMS Method 6**: Instrument: Agilent 1260 & 6125B, ESI; Column: Agilent Poroshell SB-C18 30mmx3.0mm, 2.7 µm; Gradient: mobile phase A: 0.04% trifluoroacetic acid in water, B: 0.02% trifluoroacetic acid in acetonitrile; 5-95% B over 3 min, 95% B for 0.5 min, 95-5%B over 0.01 min; Flow rate: 1.5 mL/min; UV detection 220 nm; Mass detection MS range 100-1000 Da (ESI); Column temperature: 40 °C.

**LCMS Method 7**: Instrument: Agilent 1200 & G6120B, ESI; Column: Kinetex EVO C18 100A 30mm×2.1mm, 5 µm; Gradient: mobile phase A: 0.04% trifluoroacetic acid in water, B: 0.02% trifluoroacetic acid in acetonitrile; 5-95% B over 0.69 min, 95% B for 0.45 min, 95-5%B over 0.01 min; Flow rate: 1.5 mL/min; UV detection 220 and 254 nm; Mass detection MS range 100-1000 Da (ESI); Column temperature: 40 °C.

**LCMS Method 8**: Instrument: Agilent 1260 & 6125B, ESI; Column: Kinetex EVO C18 30mm×2.1mm, 5 µm; Gradient: mobile phase A: 0.04% trifluoroacetic acid in water, B: 0.02% trifluoroacetic acid in acetonitrile; 5-95% B over 0.8 min, 95% B for 0.4 min, 95-5%B over 0.01 min; Flow rate: 2.0 mL/min; UV detection 220 nm; Mass detection MS range 100-1000 Da (ESI); Column temperature: 40 °C.

**LCMS Method 9**: Instrument: Agilent 1200 & 6110, ESI; Column: Kinetex EVO C18 30mm×2.1mm, 5 µm; Gradient: mobile phase A: 0.04% trifluoroacetic acid in water, B: 0.02% trifluoroacetic acid in acetonitrile; 5-95% B over 1.0 min, 95-100%B over 0.8 min, 100-5% over 0.01 min; Flow rate: 1.0 mL/min; UV detection 220 and 254 nm; Mass detection MS range 100-1000 Da (ESI); Column temperature: 40 °C.

**LCMS Method 10**: Instrument: Shimadzu LC-20AD&MS 2020, ESI; Column: Kinetex EVO C18 30mm×2.1mm, 5 µm; Gradient: mobile phase A: 0.04% trifluoroacetic acid in water, B: 0.02% trifluoroacetic acid in acetonitrile; 5-95% B over 0.69 min, 95%B for 0.46 min, 95-5% over 0.34 min; Flow rate: 1.5 mL/min; UV detection 220 and 254 nm; Mass detection MS range 100-1000 Da (ESI); Column temperature: 40 °C.

**LCMS Method 11**: Instrument: Shimadzu LC-20AD&MS 2020, ESI; Column: Halo C18 30mmx3.0mm, 2.7 µm; Gradient: mobile phase A: 0.04% trifluoroacetic acid in water, B: 0.02% trifluoroacetic acid in acetonitrile; 5% B over 0.01 min., 5-95% B over 0.69 min, 95%B for 0.46

min, 95-5% over 0.34 min; Flow rate: 1.5 mL/min; UV detection 220 and 254 nm; Mass detection MS range 100-1000 Da (ESI); Column temperature: 40 °C.

**LCMS Method 12**: Instrument: Shimadzu LC-20AB&MS 2010, ESI; Column: Xbridge C18 50mmx2.1mm, 5 µm; Gradient: mobile phase A: 10 mM $NH_4HCO_3$ in water, B: acetonitrile; 5%B for 0.01 min., 5-95% B over 0.69 min, 95%B for 0.46 min, 95-5% over 0.34 min; Flow rate: 1.5 mL/min; UV detection 220 and 254 nm; Mass detection MS range 100-1000 Da (ESI); Column temperature: 40 °C.

**LCMS Method 13**: Instrument: Agilent 1260 & 6120, ESI; Column: Luna LC-C18 50mmx2mm, 5 µm; Gradient: mobile phase A: 0.04% trifluoroacetic acid in water, B: 0.02% trifluoroacetic acid in acetonitrile; 5%B for 0.4 min, 5-95% B over 2.6 min, 95% B over 1.0 min, 95-5% B over 0.01 min., 5% B over 0.49 min.; Flow rate: 1.0 mL/min; UV detection 215 nm and 254 nm; Mass detection MS range 100-1000 Da (ESI); Column temperature: 40 °C.

**LCMS Method 14**: Instrument: Shimadzu LC-20AD&MS 2020, ESI; Column: InfinityLab Poroshell SB-C18 30mmx3.0mm 2.7 µm; Gradient: mobile phase A: 0.04% trifluoroacetic acid in water, B: 0.02% trifluoroacetic acid in acetonitrile; 5-95% B over 0.89 min, 95%B for 0.26 min, 95-5% over 0.44 min; Flow rate: 1.5 mL/min; UV detection 220 and 254 nm; Mass detection MS range 100-1000 Da (ESI); Column temperature: 40 °C.

**LCMS Method 15**: Instrument: Shimadzu LC-20ADXR&MS 2020, ESI; Column: Shim-pack Velox SP-C18 30mmx2.1mm 2.7 µm; Gradient: mobile phase A: 0.04% trifluoroacetic acid in water, B: 0.02% trifluoroacetic acid in acetonitrile; 5%B for 0.01 min., 5-95% B over 0.69 min, 95%B for 0.46 min, 95-5% over 0.34 min; Flow rate: 1.5 mL/min; UV detection 220 and 254 nm; Mass detection MS range 100-1000 Da (ESI); Column temperature: 40 °C.

**LCMS Method 16**: Instrument: Agilent 1260 & 6120, ESI; Column: Kinetex LC-C18 50mmx2.1mm, 5 µm; Gradient: mobile phase A: 0.04% trifluoroacetic acid in water, B: 0.02% trifluoroacetic acid in acetonitrile; 5%B for 0.4 min, 5-95% B over 3.0 min, 95% B over 1.0 min, 95-5% B over 0.5 min; Flow rate: 1.0 mL/min; UV detection 215 nm and 254 nm; Mass detection MS range 100-1000 Da (ESI); Column temperature: 40 °C.

**LCMS Method 17**: Instrument: Agilent 1200 & 6120, ESI; Column: XBridge C18 50mmx2.1mm, 5 µm; Gradient: mobile phase A: 10 mM $NH_4HCO_3$ in water, B: acetonitrile; 5-95% B over 3.4 min, 95% B for 0.45 min, 95-5%B over 0.01 min, 5% B for 0.64 min; Flow rate: 0.8 mL/min; UV detection 215 nm and 254 nm; Mass detection MS range 100-1000 Da (ESI); Column temperature: 40 °C.

**LCMS Method 18**: Instrument: Shimadzu LC-20AB&MS 2010, ESI; Column: Xbridge C18 50mmx2.1mm, 5 µm; Gradient: mobile phase A: 10 mM $NH_4HCO_3$ in water, B: acetonitrile; 5%B for 0.01 min., 5-95% B over 2.99 min, 95%B for 0.50 min, 95-5% over 0.01 min; 5%B for 0.79

min., Flow rate: 1.0 mL/min; UV detection 220 and 254 nm; Mass detection MS range 100-1000 Da (ESI); Column temperature: 40 °C.

**LCMS Method 19**: Instrument: Agilent 1200 & 6130, MSD; Column: XBridge C18 50mmx2.1mm, 5 µm; Gradient: mobile phase A: 10 mM $NH_4HCO_3$ in water, B: acetonitrile; 5% B for 0.4 min., 5-95% B over 3.0 min, 95% B for 0.45 min, 95-5%B over 0.01 min, 5% B for 0.64 min; Flow rate: 0.8 mL/min; UV detection 215 nm and 254 nm; Mass detection MS range 100-1000 Da (ESI); Column temperature: 40 °C.

**LCMS Method 20**: Instrument: Shimadzu LC-20AB&MS 2010, ESI; Column: Kinetex C18 50mmx2.1mm, 5 µm; Gradient: mobile phase A: 10 mM $NH_4HCO_3$ in water, B: acetonitrile; 5%B for 0.01 min., 5-95% B over 0.69 min, 95%B for 0.46 min, 95-5% over 0.34 min; Flow rate: 1.5 mL/min; UV detection 220 and 254 nm; Mass detection MS range 100-1000 Da (ESI); Column temperature: 40 °C.

**LCMS Method 21**: Instrument: Shimadzu LC-20AD&MS 2020, ESI; Column: Kinetex EVO C18 30mm×2.1mm, 5 µm; Gradient: mobile phase A: 0.04% trifluoroacetic acid in water, B: 0.02% trifluoroacetic acid in acetonitrile; 5%B over 0.0.01 min., 5-95% B over 0.69 min, 95%B for 0.50 min, 95-5% over 0.01 min; 5%B for 0.29 min Flow rate: 1.5 mL/min; UV detection 220 and 254 nm; Mass detection MS range 100-1000 Da (ESI); Column temperature: 40 °C.

**LCMS Method 22**: Instrument: Shimadzu LC-20AD&MS 2020, ESI; Column: Xbridge C18 50mmx2.1mm, 5 µm; Gradient: mobile phase A: 10 mM $NH_4HCO_3$ in water, B: acetonitrile; 10%B for 0.01 min., 10-80% B over 3.49 min, 80%B for 0.30 min, 80-10%B over 0.01 min; 10%B for 0.49 min.; Flow rate: 0.8 mL/min; UV detection 220 and 254 nm; Mass detection MS range 100-1000 Da (ESI); Column temperature: 40 °C.

**LCMS Method 23**: Instrument: Shimadzu LC-20AD&MS 2020, ESI; Column: Xbridge Shield RPC18 50mmx2.1, 5 µm; Gradient: mobile phase A: 10 mM $NH_4HCO_3$ in water, B: acetonitrile; 5%B for 0.01 min., 5-95% B over 0.99 min, 95-100%B over 0.80 min, 100-5%B% over 0.0.01 min; 5%B for 0.39 min.; Flow rate: 1.0 mL/min (0.01-1.8 min) and 1.2 mL/min (1.81-2.20 min); Diode array detection; Mass detection MS range 100-1000 Da (ESI); Column temperature : 40 °C.

**LCMS Method 24**: Instrument: Agilent 1200 & 1956A, ESI; Column: Xbridge Shield RPC18 50mmx2.1, 5 µm; Gradient: mobile phase A: 10 mM $NH_4HCO_3$ in water, B: acetonitrile; 10-80% B over 2.00 min, 80%B for 0.48 min, 80-10%B over 0.02 min; 10%B for 1.50 min.; Flow rate: 1.0 mL/min (0.00-2.48min) and 1.2 mL/min (2.50-3.00min); Diode array detection; Mass detection MS range 100-1000 Da (ESI); Column temperature: 40 °C.

**LCMS Method 25**: Instrument: Agilent 1200 & 6120, ESI; Column: Kinetex C18 30mmx2.1mm, 5 µm; Gradient: mobile phase A: 0.04% trifluoroacetic acid in water, B: 0.02% trifluoroacetic

acid in acetonitrile; 5-95%B over 1.00 min, 95-100% B over 0.8 min, 100-5% B over 0.01 min, 5% B for 0.19 min; Flow rate: 1.0 mL/min(0-1.80min) and 1.2ml/min (1.81-2.00); Diode array detection; Mass detection MS range 100-1000 Da (ESI); Column temperature: 40 °C.

**LCMS Method 26**: Instrument: Shimadzu LC-20AD&MS 2020, ESI; Column: Kinetix EVO C18 30mmx2.1mm, 5µm; Gradient: mobile phase A: 0.04% trifluoroacetic acid in water, B: 0.02% trifluoroacetic acid in acetonitrile; 5% B over 0.01 min., 5-95% B over 2.99 min, 95%B for 0.50 min, 95-5% over 0.50 min, 5% B for 0.30 min; Flow rate: 1.0 mL/min; Diode array detection; Mass detection MS range 100-1000 Da (ESI); Column temperature: 40 °C.

**LCMS Method 27**: Instrument: Shimadzu LC-20AB MSD: LCMS-2010, ESI; Column: Shim-pack Scepter C18 33mmx3.0mm 3 µm; Gradient: mobile phase A: 10mM $NH_4HCO$ in water, B: ACN; 0-60%B over 3.5 min., 60% B for 0.30 min, 60-0%B over 0.01 min, 0%B for 0.49 min; Flow rate: 0.8 mL/min 0.01 to 3.8 min., and 1.0 mL/min 3.81 to 4.3 min; UV detection 220 and 254 nm; Mass detection MS range 100-1000 Da (ESI); Column temperature: 40 °C.

**LCMS Method 28**: Instrument: Agilent 1200, MSD 6150; Column: Kinetex EVO C18 30mm×2.1mm, 5 µm; Gradient: mobile phase A: 0.04% trifluoroacetic acid in water, B: 0.02% trifluoroacetic acid in acetonitrile; 5% B for 0.01 min., 5-95% B over 3.49 min, 95% B for 0.30 min, 95-5%B over 0.01 min., 5% B for 0.49 min.; Flow rate: 1.0 mL/min; UV detection 220 and 254 nm; Mass detection MS range 100-1000 Da (ESI); Column temperature: 40 °C.

**LCMS Method 29**: Instrument: Waters Acquity SQD; Column: Kinetex by Phenomenex, 2.6 µm, 2.1 x 50 mm; Gradient: mobile phase A: 0.1% trifluoroacetic acid in water, B: 0.12% trifluoroacetic acid in acetonitrile; 2-88% (or 0-45%, or 65-95%) solvent B over a 1.29 min or 9.79 min period (1.5 min or 10 min run time, respectively); flow rate 1.2 mL/min; UV detection 220 and 254 nm; Mass detection MS range 150-850 Da (ESI); Column temperature: 50 °C.

**LCMS Method 30**: Instrument: Waters Acquity-QDA#CA; Column: UPLC BEH C18, 1.7 µm, 2.1 x 50 mm pH 2.6; Gradient: mobile phase A- 0.1% formic acid in water, B- 0.1% formic acid in acetonitrile; 2-98 % B over 4.40 min, 98% B for 0.35 min, 98-2% over 0.15 min; Flow rate: 1.0 mL/min; UV detection 210-400 nm; Mass detection MS range 120-1250 Da (ESI); Column temperature: 50 °C.

The structures of all final products, intermediates and starting materials are confirmed by standard analytical spectroscopic characteristics, e.g. MS, IR, NMR.

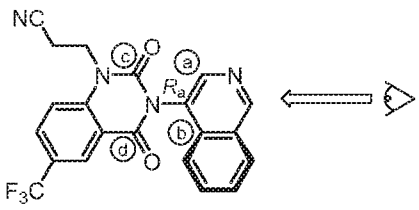
The absolute stereochemistry of representative examples of the preferred (most active) atropisomers has been determined by analysis of X-ray crystal structures of complexes in which the respective compounds are bound to the $M^{pro}$ protein. In all other cases where X-ray structures are not available, the stereochemistry has been assigned by analogy, assuming that, for each pair, the atropoisomer exhibiting the highest activity in the Rapid-Fire MS Biochemical

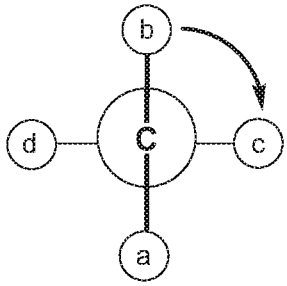
Assay (i.e. lowest $IC_{50}$ value) has the same configuration as observed by X-ray crystallography for the representative examples mentioned above.

Designation of axial chirality: Cahn–Ingold–Prelog rule

The absolute stereochemistry can be assigned according to the Cahn–Ingold–Prelog rule using $R_a/S_a$ nomenclature defined by CIP Priority for tetrahedral stereocenters. Here the chiral axis is viewed end-on and the two "near" and two "far" substituents on the axial unit are ranked, with the additional rule that the two near substituents have higher priority than the far ones. Axial R ($R_a$) is assigned when going fom priority 2 to 3 is clockwise, while axial S ($S_a$) is assigned when going fom priority 2 to 3 is counterclockwise. These assignments are depicted below for Example 16a and Example 16b.

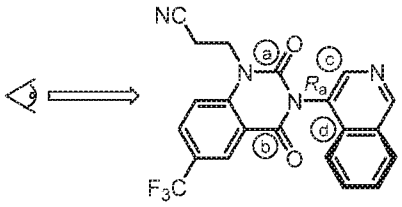
Example 16a axial chirality analysis using Cahn–Ingold–Prelog rules for two separate views is shown below with (a) being priority 1, (b) being priority 2, (c) being priority 3 and (d) being priority 4. Example 16a is assigned axial R ($R_a$) configuration and is the most active atropisomer wherein the phenyl ring of the isoquinoline is pointing upwards. The corresponding compound name for Example 16a using Cahn–Ingold–Prelog rules is also shown. Example 16b is shown for comparison and is assigned axial S ($S_a$) configuration where the phenyl ring of the isoquinoline is pointing downwards. Such atropisomers are the more active atropisomer(s). The corresponding compound name for Example 16b using Cahn–Ingold–Prelog rules is also shown.

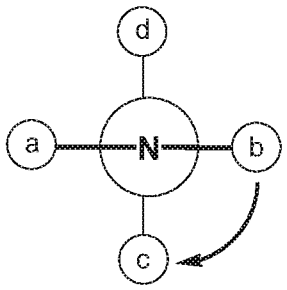



**Example 16a**:
3-[(3$R_a$)-3-(Isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2*H*)-yl]propanenitrile

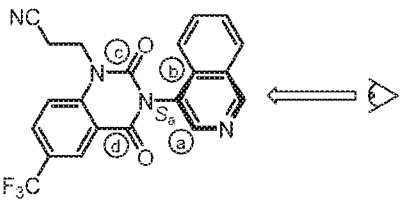
clockwise
*R* axial chirality: $R_a$

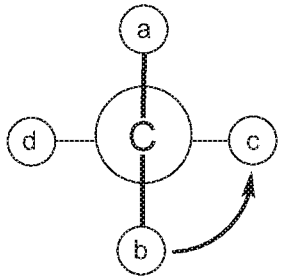



**Example 16a**:
3-[(3$R_a$)-3-(Isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2*H*)-yl]propanenitrile

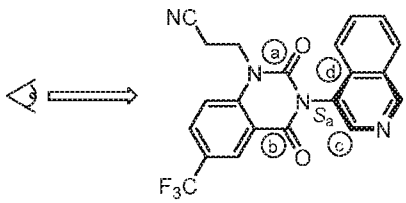
clockwise
*R* axial chirality: $R_a$

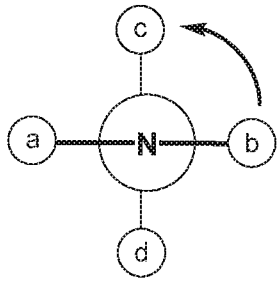




**Example 16b**:
3-[(3*S*$_a$)-3-(Isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2*H*)-yl]propanenitrile

counterclockwise
*S* axial chirality: *S*$_a$





**Example 16b**:
3-[(3*S*$_a$)-3-(Isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2*H*)-yl]propanenitrile

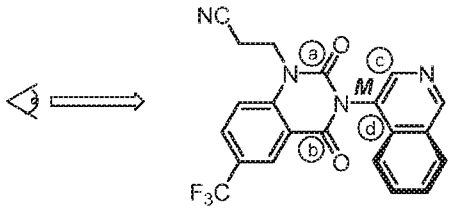
counterclockwise
*S* axial chirality: *S*$_a$

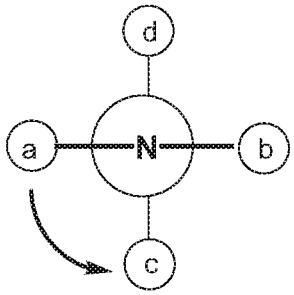
Designation of axial chirality: Prelog and Helmchen

The absolute stereochemistry can also be assigned according to the "helicity" rule of Prelog and Helmchen (*Angew. Chem. Int. Ed.*, 21, 567-583, 1982). Helicity is the chiral sense of a stereogenic axis. Along the axis, the ligands attached to the atoms at either end are arranged in pairs. Proceeding from the ligand to the atom at the near end having priority in that pair to the ligand to the atom at the far end having priority in that pair, chirality is described by the stereodescriptor "*M*" (for "minus") if the path is counterclockwise; the stereodescriptor is "*P*" (for "plus") if the path is clockwise. The stereodescriptors "*M*" and "*P*" are used in preferred IUPAC names (PINs, constructed according to current IUPAC nomenclature) of atropisomers.

Example 16a axial chirality analysis using Prelog and Helmchen rules below where the priority ligand at the near end of the chirality axis (N-3 of the dioxoquinazolinyl) is indicated by "a"; the priority ligand at the far end is indicated by "c". The sense of the path from "a" to "c" defines the helicity, *M* or *P*, of the chirality axis.

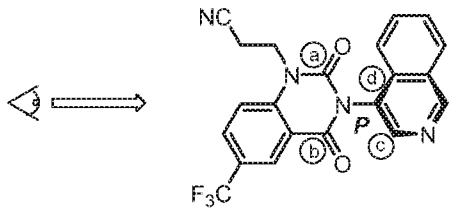
In Example 16a chirality axis is described by the stereodescriptor *M* and is the most active atropisomer where the phenyl ring of the isoquinoline is pointing upwards. The corresponding compound name for Example 16a using Prelog and Helmchen rules is also shown. The structure of Example **16b** (the less active atropisomer), whose chirality axis is described by the stereodescriptor *P*, is shown for comparison where the phenyl ring of the isoquinoline is pointing downwards. The corresponding compound name for Example 16b using Prelog and Helmchen rules is also shown.

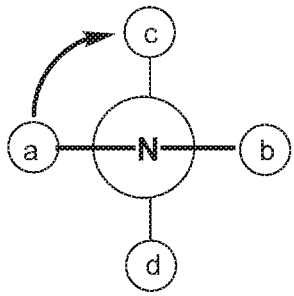




**Example 16a**:
3-[(3*M*)-3-(Isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2*H*)-yl]propanenitrile

Counterclockwise => *M*inus
*M* axial chirality





**Example 16b**:
3-[(3*P*)-3-(Isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2*H*)-yl]propanenitrile

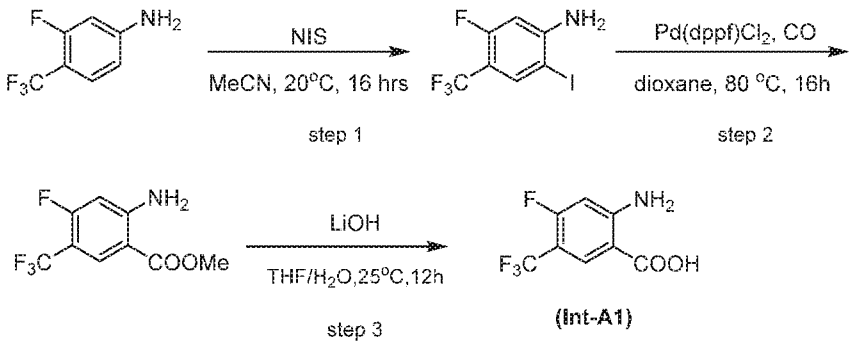
Clockwise => Plus
*P* axial chirality

Note: The atropisomers described in the Example section below are named according the Prelog and Helmchen stereodescriptor. All other compounds, including racemates are named using ChemDraw 19.1. In addition, the stereochemistry assigned to atropisomers in the Examples is by analogy to Example 16, wherein the chirality of the more active atropisomer(s) is assigned as ***(M)*** and subsequently the chirality of the less active atropisomer(s) is assigned as ***(P)***.

***Synthesis of Intermediates***

**Type A Intermediates**

Synthesis of 2-amino-4-fluoro-5-(trifluoromethyl)benzoic acid **(Int-A1)**

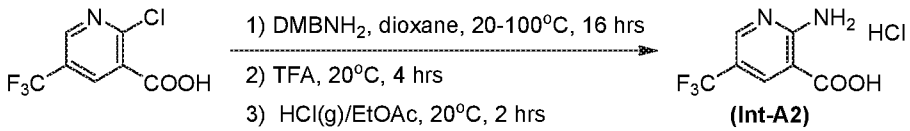


Step 1: To a mixture of 3-fluoro-4-(trifluoromethyl)aniline (2 g, 11.17 mmol, 1.0 eq.) and in AcOH (8 mL) was added N-iodosuccinimide (NIS) (2.5 g, 11.17 mmol, 1.0 eq.) at 20°C under $N_2$. After addition, the reaction mixture was stirred at 20°C for 16 hrs. The mixture was diluted with saturated $Na_2S_2O_3$ aqueous (50 mL) and extracted with EtOAc (50 mL x 2). The combined organic layers were washed with saturated sodium bicarbonate solution (100 mL), dried over $Na_2SO_4$, filtered and concentrated to give 5-fluoro-2-iodo-4-(trifluoromethyl)aniline. **LCMS (Method 5):** $t_R$ = 0.838 min, $[M+1]^+$ 305.9.

Step 2: A mixture of 5-fluoro-2-iodo-4-(trifluoromethyl)aniline (1.75 g, crude, 5.73 mmol, 1.0 eq.), $Pd(dppf)Cl_2$ (418 mg, 0.57 mmol, 0.1 eq. ) in MeOH (20 mL) was degassed and purged with CO (50 psi) for 3 times, and then the mixture was stirred at 80°C for 16 hrs under CO atmosphere. The mixture was filtered and concentrated. The crude product was purified by silica gel chromatography ($SiO_2$, Petroleum ether/EtOAc=10/1 to 3/1) to give methyl 2-amino-4-fluoro-5-(trifluoromethyl)benzoate. **LCMS (Method 5):** $t_R$ = 1.012 min, $[M+1]^+$ 238.0. **$^1$H NMR:** (400MHz, CHLOROFORM-d) δ = 8.14 (d, J=8.3 Hz, 1H), 6.41 (d, J=12.3 Hz, 1H), 6.23 (br s, 2H), 3.90 (s, 3H).

Step 3: To a solution of methyl 2-amino-4-fluoro-5-(trifluoromethyl)benzoate (550 mg, crude, 2.32 mmol, 1.0 eq.) in THF/$H_2O$ (7/3, 10 mL) was added LiOH.$H_2O$ (292 mg, 6.96 mmol, 3.0 eq.) at 25°C under $N_2$. After addition, the mixture reaction was stirred at 25°C for 12 hrs. The mixture was diluted with water (10 mL), the pH adjusted to pH 4-5 with 0.5 N HCl, and extracted with EtOAc (30 mL x 3). The combined organic layers were dried over $Na_2SO_4$, filtered and concentrated to give 2-amino-4-fluoro-5-(trifluoromethyl)benzoic acid **(Int-A1)**. **LCMS (Method 5):** $t_R$ = 0.888 min, $[M+1]^+$ 224.0.

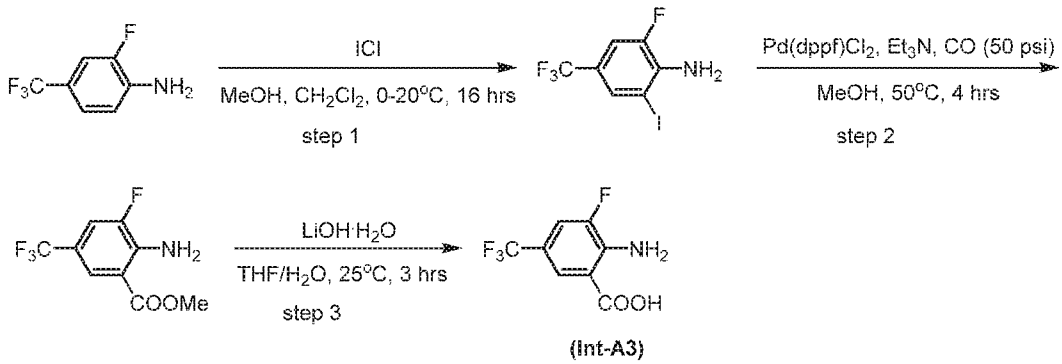
Synthesis of 2-amino-5-(trifluoromethyl)nicotinic acid hydrochloride **(Int-A2)**




**(Int-A2)**

To a solution of 2-chloro-5-(trifluoromethyl)nicotinic acid (3.3 g, 14.63 mmol, 1.0 eq.) in dioxane (5 mL) was added $DMBNH_2$ (4.9 g, 29.26 mmol, 2.0 eq.) at 20°C, and the mixture then stirred at 100°C for 16 hrs. The mixture was filtered and the filter cake triturated with EtOH (20 mL) to give a solid. TFA (15 mL) was added to a round-bottom flask containing the solid and the mixture was stirred at 20°C for 4 hrs. The mixture was concentrated to give a residue which was triturated with HCl(g)/EtOAc (20 mL) at 20°C for 2 hrs to obtain 2-amino-5-(trifluoromethyl)nicotinic acid hydrochloride **(Int-A2)**. **$^1$H NMR:** (400MHz, DMSO-$d_6$) δ = 13.64 (br s, 1H), 8.84 (m, 1H), 8.58 (d, *J*=2.0 Hz, 1H), 8.23 (d, *J*=2.4 Hz, 1H), 8.10 (br s, 2H).

Synthesis of 2-amino-3-fluoro-5-(trifluoromethyl)benzoic acid **(Int-A3)**



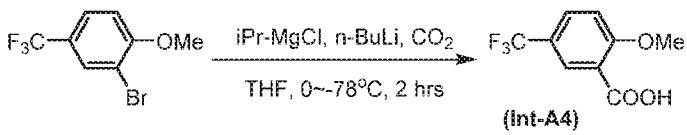

(Int-A3)

Step 1: A solution of iodine monochloride (ICl) (5.4 g, 25.12 mmol, 1.5 eq.) in MeOH (15 mL) was added dropwise to a solution of 2-fluoro-4-(trifluoromethyl)aniline (3.0 g, 16.75 mmol, 1.0 eq.) in $CH_2Cl_2$ (15 mL) at 0°C and the mixture was stirred at 20°C for 16 hrs. The reaction mixture was quenched with water (50 mL) and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine (100 mL), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give a residue which was purified by silica gel chromatography ($SiO_2$, petroleum ether/EtOAc = 100/0 to 70/30) to give 2-fluoro-6-iodo-4-(trifluoromethyl)aniline. **$^1$H NMR:** (400MHz, CHLOROFORM-d) δ = 7.68 (s, 1H), 7.24 (dd, *J*=1.6, 10.7 Hz, 1H), 4.49 (br s, 2H).

Step 2: $Pd(dppf)Cl_2$ (500 mg, cat.) was added to a solution of 2-fluoro-6-iodo-4-(trifluoromethyl)aniline (4.58 g, 15.00 mmol, 1.0 eq) and $Et_3N$ (4.56 g, 3.00 mmol, 3.0 eq) in MeOH (100 mL) and the mixture was stirred at 50°C under CO (50 Psi) for 4 hrs. The reaction mixture was concentrated to give crude product which was purified by silica gel chromatography ($SiO_2$, petroleum ether/EtOAc = 10/1 to 5/1) to obtain methyl 2-amino-3-fluoro-5-(trifluoromethyl)benzoate. **LCMS (Method 5):** $t_R$ = 0.839 min, $[M+1]^+$ 238.2. **$^1$H NMR:** (400MHz, CHLOROFORM-d) δ = 7.95 (s, 1H), 7.32 (dd, *J*=1.9, 11.1 Hz, 1H), 6.18 (br s, 2H), 3.92 (s, 3H).

Step 3: A solution of methyl 2-amino-3-fluoro-5-(trifluoromethyl)benzoate (1.0 g, 4.22mmol, 1 eq.) and $LiOH·H_2O$ (346 mg, 8.43 mmol, 2.0 eq) in THF (9 mL), MeOH (6 mL) and $H_2O$ (3 mL) was stirred at 25°C for 3 hrs. The reaction mixture was poured into water and the pH adjusted pH to 3 with 1M aq.HCl. The mixture was filtered and the filter cake triturated with ether/EtOAc (10/1, 10 mL) to give 2-amino-3-fluoro-5-(trifluoromethyl)benzoic acid **(Int-A3)**. **LCMS (method 7):** $t_R$ = 0.613 min, $[M+1]^+$ 224.0.

Synthesis of 2-methoxy-5-(trifluoromethyl)benzoic acid **(Int-A4)**

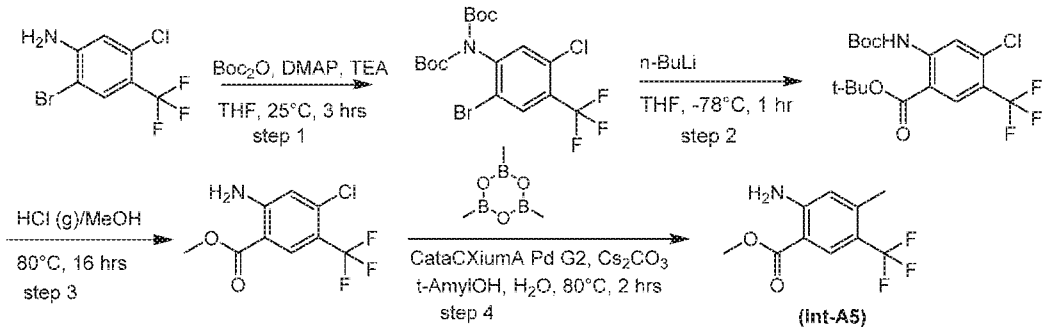



(Int-A4)

n-BuLi (4.1 g, 2.5M, 15 mmol, 1.5 eq.) was added dropwise to iPr-MgCl (3.9 g, 2M, 7.87 mmol, 0.8 eq.) at 0°C under $N_2$, and the mixture was stirred at 0~-10°C for 10 min. THF (30 mL) was

and then was added the mixture stirred at 0°C for 10 min. 2-bromo-1-methoxy-4-(trifluoromethyl)benzene (2.54 g, 9.84 mmol, 1.0 eq.) in THF (20 mL) was added dropwise at 0°C and the mixture was stirred at 0~-78°C for 1.5 hrs. $CO_2$ was then added to the solution. The mixture was poured into $NH_4Cl$ (aq), extracted with EtOAc, dried, filtered and concentrated to give crude product which was suspended in Petroleum ether/ EtOAc (10/1, 10 mL) and stirred for 30 min. The suspension was filtered, the filter cake was dried to give 2-methoxy-5-(trifluoromethyl)benzoic acid **(Int-A4)**. **$^1$H NMR:** (400 MHz, CHLOROFORM-d) δ = 10.87 - 10.26 (m, 1H), 8.47 (d, *J* = 2.1 Hz, 1H), 7.84 (dd, *J* = 2.1, 8.8 Hz, 1H), 7.18 (d, *J* = 8.9 Hz, 1H), 4.15 (s, 3H).

Synthesis of methyl 2-amino-4-methyl-5-(trifluoromethyl)benzoate **(Int-A5)**



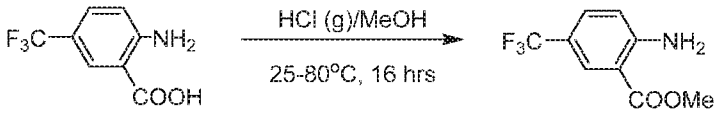

Step 1: A solution of 2-bromo-5-chloro-4-(trifluoromethyl)aniline (5.0 g, 18.22 mmol, 1.0 eq.), $Boc_2O$ (9.9 g, 45.54 mmol, 2.5 eq.), DMAP (1.1 g, 9.11 mmol, 0.5 eq.) and TEA (9.2 g, 91.09 mmol, 5.0 eq.) in THF (50 mL) was stirred at 25°C for 3 hrs. The reaction mixture was quenched with $H_2O$ (100 mL). The reaction mixture was extracted with ethyl acetate (100 mL x 3). The combined organic layers were washed with brine (300 mL x 3), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give a residue. The residue was purified by MPLC (petroleum ether/EtOAc = 1/0 ~ 3/1) to give tert-butyl (2-bromo-5-chloro-4-(trifluoromethyl)phenyl)(tert-butoxycarbonyl)carbamate. **LCMS (Method 13):** $t_R$ = 1.052 min. **$^1$H NMR:** (400MHz, CHLOROFORM-*d*) δ = 7.92 (s, 1H), 7.40 (s, 1H), 1.43 (s, 18H)

Step 2: To a solution of tert-butyl (2-bromo-5-chloro-4-(trifluoromethyl)phenyl)(tert-butoxycarbonyl)carbamate (5.0 g, 10.53 mmol, 1.0 eq.) in THF (80 mL) was added n-BuLi (5 mL, 12.64 mmol, 1.2 eq.) at -78°C. The mixture was stirred at -78°C for 1 hrs. The reaction mixture was quenched with $H_2O$ (120 mL). The reaction mixture was extracted with ethyl acetate (100 mL x 3). The combined organic layers were washed with brine (300 mL x 3), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give a residue. The residue was purified MPLC (petroleum ether/EtOAc = 1/0 ~ 3/1) to give tert-butyl 2-((tert-butoxycarbonyl)amino)-4-chloro-5-(trifluoromethyl)benzoate. **$^1$H NMR:** (400MHz, CHLOROFORM-*d*) δ = 10.57 (s, 1H), 8.73 (s, 1H), 8.23 (s, 1H), 1.62 (s, 9H), 1.55 (s, 9H).

Step 3: A solution of tert-butyl 2-((tert-butoxycarbonyl)amino)-4-chloro-5-(trifluoromethyl)benzoate (2.0 g, 2.31 mmol, 0.6 eq.) in HCl (g)/MeOH (6 M, 20 mL) was stirred at 80°C for 16 hrs. TLC (petroleum ether/EtOAc = 3/1) showed the starting material was consumed completely and the desired product was as major spot. The mixture was concentrated under reduced pressure to afford the crude product. The residue was purified by MPLC (petroleum ether/EtOAc = 1/0 ~ 3/1) to give methyl 2-amino-4-chloro-5-(trifluoromethyl)benzoate. **LCMS (Method 7):** $t_R$ =0.848 min, $[M+1]^+$ 254.1.

Step 4: To a solution of methyl 2-amino-4-chloro-5-(trifluoromethyl)benzoate (400 mg, 1.56 mmol, 1.0 eq.), 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane (990 mg, 7.89 mmol, 5.0 eq.) and $Cs_2CO_3$ (1.0 g, 3.16 mmol, 2.0 eq.) in t-AmylOH (3 mL) was added CataCXiumA Pd G2 (104 mg, 0.16 mmol, 0.1 eq.) and $H_2O$ (0.5 mL) at $N_2$. The mixture was stirred at 80°C for 2 hrs. The reaction mixture was quenched with $H_2O$ (15 mL). The reaction mixture was extracted with ethyl acetate (15 mL x 3). The combined organic layers were washed with brine (30 mL x 3), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (petroleum ether/EtOAc = 3/1) to give methyl 2-amino-4-methyl-5-(trifluoromethyl)benzoate **(Int-A5)**. **LCMS (Method 7):** $t_R$ = 0.838 min, $[M+1]^+$ 234.1.

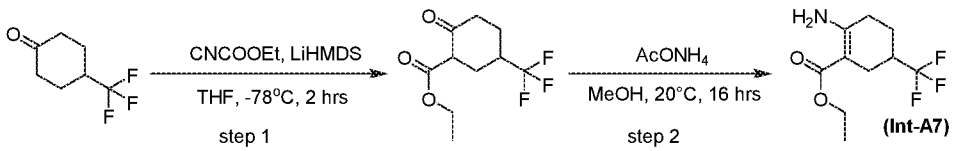
Synthesis of methyl 2-amino-5-(trifluoromethyl)benzoate **(Int-A6)**




(Int-AA1) (Int-A6)

To a solution of 2-amino-5-(trifluoromethyl)benzoic acid **(Int-AA1)** (10 g, 58.50 mmol, 1.0 eq.) was added HCl/MeOH (300 mL, 4 M) at 25°C under $N_2$. The mixture was stirred at 80°C for 16 hrs. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography ($SiO_2$, petroleum ether/ethyl acetate = 10/1 to 1/1) to give methyl 2-amino-5-(trifluoromethyl)benzoate **(Int-A6)**. **$^1$H NMR:** (400MHz, CHLOROFORM-*d*) δ = 8.11 (s, 1H), 7.43 (br d, *J*=8.8 Hz, 1H), 6.69 (d, *J*=8.8 Hz, 1H), 3.88 (s, *J*=1.0 Hz, 3H).

Synthesis of ethyl 2-amino-5-(trifluoromethyl)cyclohex-1-ene-1-carboxylate **(Int-A7)**

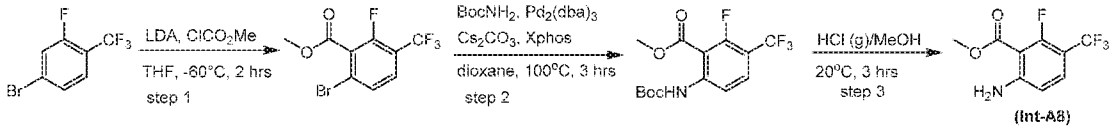



Step 1: To solution of 4-(trifluoromethyl)cyclohexan-1-one (3.0 g, 18.06 mmol, 1.0 eq) in THF (30 mL) was added the solution of LiHMDS (3.6 g, 21.51 mmol, 1.2 eq) in THF (21.5 mL) at -78°C, then the CNCOOEt (2.0 g, 20.18 mmol 1.1 eq) in THF(20 mL) was added and the solution was stirred at -78°C for 2 hrs. The solution was quenched with $H_2O$ (30 mL), extracted with

EtOAc (3x50 mL). The combined organic phase was dried over $Na_2SO_4$, filtrated and concentrated to give crude product which was purified with MPLC (petroleum ether: EtOAc=30/1~2/1) to give ethyl 2-oxo-5-(trifluoromethyl)cyclohexane-1-carboxylate. **$^1$H NMR:** (400MHz, CHLOROFORM-d) δ = 12.27 (s, 1H), 4.24 (q, *J*=7.2 Hz, 2H), 2.67 - 2.55 (m, 1H), 2.47 - 2.37 (m, 2H), 2.33 - 2.20 (m, 2H), 2.12 - 2.06 (m, 1H), 1.72 - 1.58 (m, 1H), 1.35 - 1.30 (m, 3H).

Step 2: A mixture of ethyl 2-oxo-5-(trifluoromethyl)cyclohexane-1-carboxylate (2.6 g, 10.92 mmol, 1.0 eq.) and $AcONH_4$ (841 mg, 10.92 mmol, 1.0 eq.) in MeOH (30 mL) was stirred at 20°C for 16 hrs. The solution was concentrated to remove the MeOH, diluted with $H_2O$ (30 mL), extracted with $CH_2Cl_2$ (3x50 mL). The combined organic phase were dried over $Na_2SO_4$, filtrated and concentrated to give ethyl 2-amino-5-(trifluoromethyl)cyclohex-1-ene-1-carboxylate **(Int-A7)**. **LCMS (Method 7):** $t_R$ = 2.459, $[M+1]^+$ 238.0

Synthesis of methyl 6-amino-2-fluoro-3-(trifluoromethyl)benzoate **(Int-A8)**



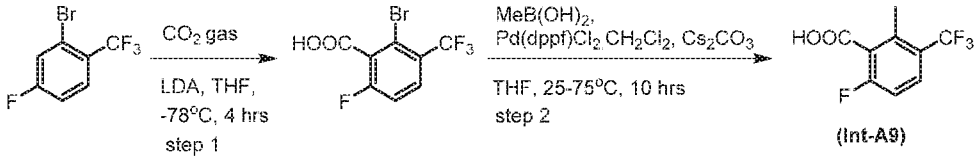

Step 1: To a solution of 4-bromo-2-fluoro-1-(trifluoromethyl)benzene (1.0 g, 4.12 mmol, 1.0 eq.) in THF (20 mL) was added LDA (529 mg, 4.94 mmol, 1.2 eq.2.47 mL) at -60°C. The mixture was stirred at -60°C for 0.5 hr. To the mixture was added $ClCO_2Me$ (583 mg, 6.17 mmol, 1.5 eq.). The mixture was stirred at -60°C for 1.5 hrs. The solution was quenched with sat.$NH_4Cl$ solution (50 mL) and extracted with EtOAc (50 mL x 3). The combined organic phases were dried over $Na_2SO_4$ anhydrous, filtered and evaporated to obtain crude product which was purified by column ($SiO_2$, petroleum ether/EtOAc = 30/1 to 10/1) to give methyl 6-bromo-2-fluoro-3-(trifluoromethyl)benzoate. **$^1$H NMR:** (400 MHz, METHANOL-$d_4$) δ = 7.79 - 7.64 (m, 2H), 3.99 (s, 3H).

Step 2: To a solution of methyl 6-bromo-2-fluoro-3-(trifluoromethyl)benzoate (600 mg, 2.01 mmol, 1.0 eq.), $BocNH_2$ (350 mg, 3.02 mmol, 1.5 eq.) and $Cs_2CO_3$ (1620 mg, 5.02 mmol, 2.5 eq.) in dioxane (20 mL) was added $Pd_2(dba)_3$ (114 mg, 0.20 mmol, 0.1 eq.) and Xphos (190 mg, 0.40 mmol, 0.2 eq.). The mixture was stirred at 100°C for 3 hrs. The reaction mixture was quenched with $H_2O$ (50 mL). The reaction mixture was extracted with ethyl acetate (50 mL x 3). The combined organic layers were washed with brine (100 mL x 3), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography ($SiO_2$, petroleum ether/ethyl acetate = 1/0 to 0/1) to afford methyl 6-((tert-butoxycarbonyl)amino)-2-fluoro-3-(trifluoromethyl)benzoate.

Step 3: A solution of methyl 6-((tert-butoxycarbonyl)amino)-2-fluoro-3-(trifluoromethyl)benzoate (400 mg, 1.18 mmol, 1.0 eq.) in HCl (g)/MeOH (4M, 10 mL) was stirred at 20°C for 3 hrs. The

mixture was concentrated under reduced pressure to afford c methyl 6-amino-2-fluoro-3-(trifluoromethyl)benzoate **(Int-A8)**. **LCMS (Method 7):** $t_R$ = 0.685 min, $[M+1]^+$ 238.0.

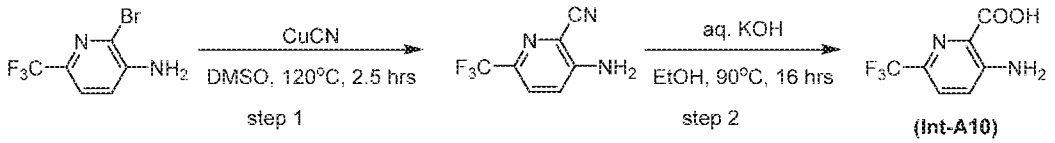
Synthesis of 6-fluoro-2-methyl-3-(trifluoromethyl)benzoic acid **(Int-A9)**




Step 1: To a mixture of 2-bromo-4-fluoro-1-(trifluoromethyl)benzene (7.0 g, 28.81 mmol, 1.0 eq.) in THF (100 mL) was added LDA (17 mL, 34.56 mmol, 1.2 eq.) at -78°C under $N_2$ and the mixture was stirred at -78°C for 30 minutes. $CO_2$ (gas) was bubbled into the reaction for 1 hr and the mixture was stirred at -78°C for 2.5 hrs. The reaction mixture was quenched with sat $NH_4HCl$ (500 mL) at 0°C and extracted with EtOAc (300 mL x 2). The combined organic layers were washed with brine (300 mL), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography ($SiO_2$, petroleum ether/ethyl acetate = 3/1 to 0/1) to give 2-bromo-6-fluoro-3-(trifluoromethyl)benzoic acid. **$^1$H NMR:** (400 MHz, DMSO-$d_6$) δ = 8.01 (dd, *J* = 5.8, 8.8 Hz, 1H), 7.62 (t, *J* = 8.6 Hz, 1H)

Step 2: To a mixture of 2-bromo-6-fluoro-3-(trifluoromethyl)benzoic acid (10.0 g, 34.87 mmol, 1.0 eq.) in THF (300 mL) was added $MeB(OH)_2$ (6.3 g, 104.53mmol, 3.0 eq.), $Cs_2CO_3$ (34.0 g, 104.53 mmol, 3.0 eq.) and $Pd(dppf)Cl_2.CH_2Cl_2$ (2.8 g, 3.49 mmol, 0.1 eq.) at 25°C under $N_2$. The reaction was stirred at 75°C for 10 hrs. The reaction mixture was quenched with $H_2O$ (500 mL) and extracted with EtOAc (300 mL x 2). The combined organic layers were washed with brine (200 mL), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography ($SiO_2$, petroleum ether/ethyl acetate = 3/1 to 0/1) to give crude product. The crude product was purified by prep-HPLC (column: Phenomenex luna C18 250mmx50mm, 10 µm; liquid phase: [A:$H_2O$ (0.09% TFA); B:ACN] B%: 35%-55%, 20 min]) to give 6-fluoro-2-methyl-3-(trifluoromethyl)benzoic acid **(Int-A9)**. **$^1$H NMR:** (400 MHz, DMSO-$d_6$) δ = 14.09 (br s, 1H), 7.84 (dd, *J* = 5.5, 8.8 Hz, 1H), 7.37 (t, *J* = 8.8 Hz, 1H), 2.42 (s, 3H).

Synthesis of 3-amino-6-(trifluoromethyl)picolinic acid **(Int-A10)**

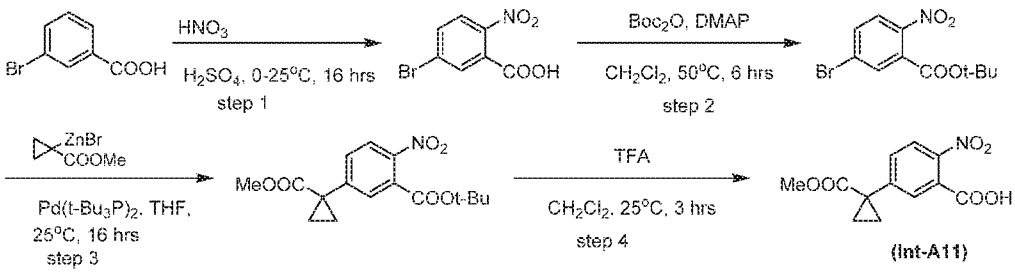



Step 1: A mixture of 2-bromo-6-(trifluoromethyl)pyridin-3-amine (3.0 g, 12.45 mmol, 1.0 eq.) and CuCN (3.0 g, 33.61 mmol, 2.7 eq.) in DMSO (30 mL) was stirred at 120°C for 2.5 hrs. The

reaction mixture was poured into water (100 mL), filtered through a pad of Celite and the filter cake was rinsed with EtOAc (10 mL). The filtrate was extracted with EtOAc (50 mL x 3) and the combined organic phases were concentrated. The crude product was purified by silica gel column chromatography (petroleum ether/EtOAc = 100/0 to 72/28) to give 3-amino-6-(trifluoromethyl)picolinonitrile. **$^1$H NMR:** (400MHz, DMSO-$d_6$) δ = 7.75 (d, *J*=8.9 Hz, 1H), 7.36 (d, *J*=8.9 Hz, 1H), 7.03 (br s, 2H).

Step 2: A mixture of 3-amino-6-(trifluoromethyl)picolinonitrile (1.5 g, 8.02 mmol, 1.0 eq.) and aq. KOH (2 M, 15 mL) in EtOH (7.5 mL) was stirred at 90°C for 16 hrs. The reaction mixture was concentrated to give a crude solution. The solution was adjusted to pH = 3 with 3 N HCl. The resulting precipitate was collected by filtration and dried in vacuum to obtain 3-amino-6-(trifluoromethyl)picolinic acid **(Int-A10)**. **$^1$H NMR:** (400MHz, DMSO-$d_6$) δ = 12.84 (br s, 1H), 7.67 (d, *J*=8.8 Hz, 1H), 7.36 (d, *J*=8.8 Hz, 1H), 7.26 (br s, 2H).

Synthesis of 5-(1-(methoxycarbonyl)cyclopropyl)-2-nitrobenzoic acid **(Int-A11)**




Step 1: To a mixture of 3-bromobenzoic acid (20.0 g, 50.00 mmol, 1.0 eq.) in $H_2SO_4$ (64 mL) was added $HNO_3$ (6.0 mL, 130.00 mmol, 1.3 eq.) dropwise at 0°C. The mixture was stirred at 25°C for 3 hrs. The mixture was quenched with ice water (300 mL) and the precipitate was collected by filtration, washed with water (300 mL) and dried to give 5-bromo-2-nitrobenzoic acid. **HNMR:** (400 MHz, DMSO-$d_6$) δ = 14.20 (br s, 1 H), 8.05 (d, *J*=1.83 Hz, 1 H), 8.00 (d, *J*=1.96 Hz, 1 H), 7.99 (s, 1 H).

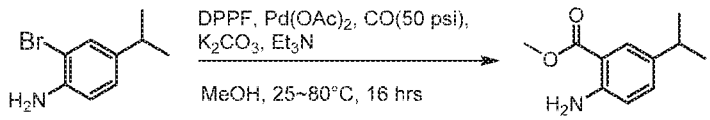
Step 2: To a solution of 5-bromo-2-nitrobenzoic acid (10.4 g, 42.45 mmol, 1.0 eq.) in $CH_2Cl_2$ (63 mL) was added DMAP (518 mg, 4.24 mmol, 0.1 eq.) and $Boc_2O$ (18.4 g, 84.90 mmol, 2.0 eq.) and the mixture was stirred at 50°C for 6 hrs. The mixture was poured into water (150 mL) and then extracted with EtOAc (50 mL x 3). The combined organic phases were washed with brine (200 mL), dried over $Na_2SO_4$, filtered and concentrated to give a crude product. The crude product was triturated with MTBE/Petroleum ether (1/10, 100 mL) at 25°C for 30 min to obtain tert-butyl 5-bromo-2-nitrobenzoate. **HNMR:** 400 MHz, DMSO-$d_6$) δ = 8.04 (d, *J*=1.10 Hz, 1 H), 8.01 (d, *J*=0.86 Hz, 2 H), 1.52 (s, 9 H).

Step 3: The solution of tert-butyl 5-bromo-2-nitrobenzoate (2.7 g, 8.94 mmol, 1.0 eq.) in THF (27 mL) was added Pd(t-$Bu_3P)_2$ (457 mg, 0.90 mmol, 0.1 eq.) and (1-(methoxycarbonyl)cyclopropyl)zinc(II) bromide (45 mL, 44.86 mmol, 5.0 eq.) at 25°C under $N_2$.

The mixture was stirred at 25°C under $N_2$ for 16 hrs. The mixture was filtered and the filtrate was concentrated to give a crude product which was purified by MPLC (Petroleum ether/EtOAc = 100% ~ 93%) to give tert-butyl 5-(1-(methoxycarbonyl)cyclopropyl)-2-nitrobenzoate. **HNMR:** (400MHz, CHLOROFORM-d) δ = 7.81 (d, *J*=8.4 Hz, 1H), 7.66 (d, *J*=2.0 Hz, 1H), 7.56 (dd, *J*=2.0, 8.4 Hz, 1H), 3.69 - 3.63 (m, 3H), 1.74 - 1.69 (m, 2H), 1.58 (s, 10H), 1.28 - 1.22 (m, 2H).

Step 4: To a mixture of tert-butyl 5-(1-(methoxycarbonyl)cyclopropyl)-2-nitrobenzoate (1.0 g, 3.12 mmol, 1.0 eq.) in $CH_2Cl_2$ (10 mL) was added TFA (2 mL) and the mixture was stirred at 25°C for 3 hrs. The reaction mixture was dried under nitrogen gas to give 5-(1-(methoxycarbonyl)cyclopropyl)-2-nitrobenzoic acid **(Int-A11)**. **HNMR:** (400 MHz, CHLOROFORM-*d*) δ = 7.83 - 7.87 (m, 2 H), 7.64 - 7.68 (m, 1 H), 3.68 (s, 3 H), 1.73 - 1.78 (m, 2 H), 1.25 - 1.30 (m, 2 H).

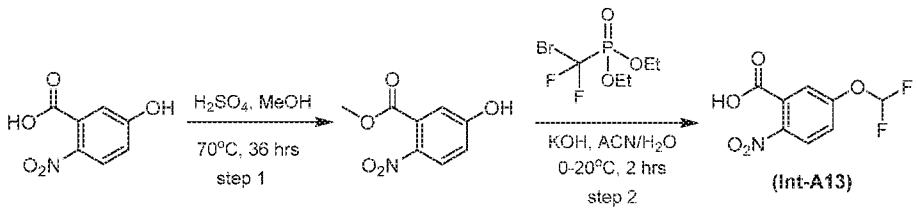
Synthesis of methyl 2-amino-5-isopropylbenzoate **(Int-A12)**




(Int-A12)

To a solution of 2-bromo-4-isopropylaniline (7.0 g, 32.71 mmol, 1.0 eq.) in MeOH (70 mL) was added $K_2CO_3$ (13.5 g, 98.13 mmol, 3.0 eq.), $Et_3N$ (3.3 g, 32.71 mmol, 1.0 eq.), DPPF (1.8 g, 3.27 mmol, 0.1 eq.) and $Pd(OAc)_2$ (732 mg, 3.27 mmol, 0.1 eq.) at 25°C. The reaction was stirred for 16 hrs at 80°C under CO (50 psi). The reaction was filtered and concentrated in vacuum to give crude product which was purified by silica gel column chromatography (petroleum ether/EtOAc = 10-15%) to give 2-amino-5-isopropylbenzoate **(Int-A12)**. **$^1$H NMR:** (400 MHz, CHLOROFORM-*d*) δ ppm 7.71 (d, *J*=2.20 Hz, 1 H) 7.19 (dd, *J*=8.44, 2.20 Hz, 1 H) 6.68 (d, *J*=8.44 Hz, 1 H) 5.82 (br s, 2 H) 3.89 (s, 3 H) 2.82 (dt, *J*=13.81, 6.91 Hz, 1 H) 1.22 (d, *J*=6.97 Hz, 6 H).

Synthesis of 5-(difluoromethoxy)-2-nitrobenzoic acid **(Int-A13)**

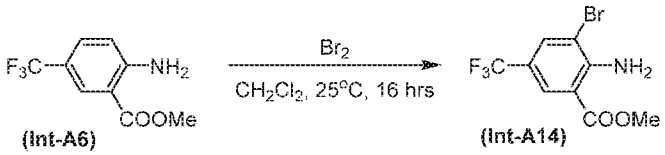



(Int-A13)

Step 1: To the solution of 5-hydroxy-2-nitrobenzoic acid (5.0 g, 27.30 mmol, 1.0 eq) in MeOH (20 mL) was added $H_2SO_4$ (8.0 g, 81.90 mmol, 3.0 eq). The mixture was stirred at 70°C for 36 hrs. The mixture was concentrated under reduced pressure to give crude product which was purified by column (petroleum ether/EtOAc = 10/1) to give methyl 5-hydroxy-2-nitrobenzoate (which was used directly in the next step).

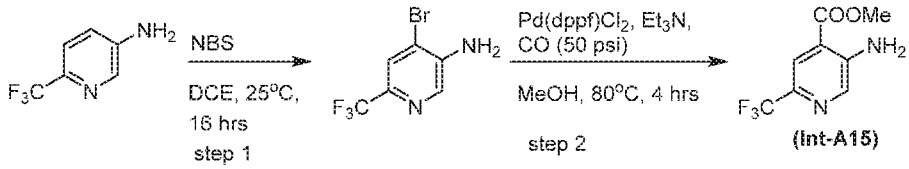
Step 2: To the solution of methyl 5-hydroxy-2-nitrobenzoate (2.0 g, 10.15 mmol, 1.0 eq) in MeCN (20 mL) and $H_2O$ (20 mL) was added KOH (11.4 g, 203.0 mmol, 20.0 eq) at 0°C. The mixture was stirred for 30 mins. To the mixture was added diethyl (bromodifluoromethyl)phosphonate (4.8 g, 20.30 mmol, 2.0 eq) and the mixture was stirred at 20°C for 1.5 hrs. The reaction mixture was neutralized with 3 M HCl aqueous solution (100 mL) until pH = 3～4. The reaction mixture was extracted with ethyl acetate (100 mL x 3). The combined organic layers were dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give 5-(difluoromethoxy)-2-nitrobenzoic acid **(Int-A13)**. **LCMS (Method 12):** $t_R$ = 0.383 min, [M-1] 232.0.

Synthesis of methyl 2-amino-3-bromo-5-(trifluoromethyl)benzoate **(Int-A14)**




To a solution of methyl 2-amino-5-(trifluoromethyl)benzoate **(Int-A6)** (6.0 g, 27.32 mmol, 1.0 eq.) in $CH_2Cl_2$ (80 mL) was added $Br_2$ (21.8 g, 136.60 mmol, 5.0 eq.) at 25°C under $N_2$. The mixture was stirred at 25°C for 16 hrs. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography ($SiO_2$, petroleum ether/ethyl acetate = 10/1 to 3/1) to give methyl 2-amino-3-bromo-5-(trifluoromethyl)benzoate **(Int-A14)**. **$^1$H NMR:** (400MHz, CHLOROFORM-*d*) δ = 8.14 (d, *J*=1.1 Hz, 1H), 7.80 (d, *J*=2.0 Hz, 1H), 3.93 (s, 3H).

Synthesis of methyl 5-amino-2-(trifluoromethyl)isonicotinate **(Int-A15)**

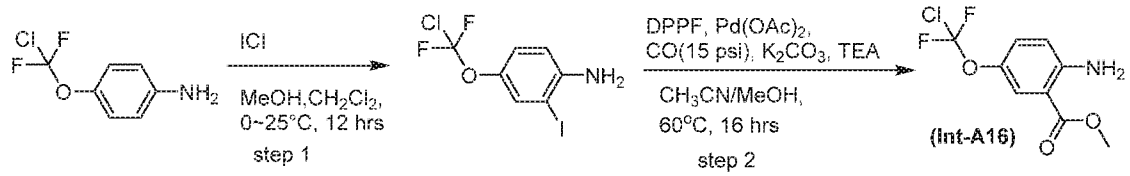



Step 1: To a solution of 6-(trifluoromethyl)pyridin-3-amine (3.0 g, 18.51 mmol, 1.0 eq.) in DCE (30 mL) was added NBS (3.3 g, 18.51 mmol, 1.0 eq.) at 25°C under $N_2$. The reaction mixture was stirred at 25°C for 16 hrs. The reaction mixture was concentrated to give crude product which was purified by column on silica gel (petroleum ether /EtOAc = 10:1, 5:1) to give 4-bromo-6-(trifluoromethyl)pyridin-3-amine. **LCMS (Method 7):** $t_R$ = 0.886 min, $[M+1]^+$ 240.9.

Step 2: To a solution of 4-bromo-6-(trifluoromethyl)pyridin-3-amine (1.5 g, crude, 6.22 mmol, 1.0 eq.) in MeOH (20 mL) was added $Pd(dppf)Cl_2$ (455 mg, 0.62 mmol, 0.1 eq.) and $Et_3N$ (2.52 g, 24.89 mmol, 4.0 eq.) under $N_2$. The reaction mixture was stirred at 80°C for 4 hrs under CO (50 psi). The reaction was complete detected by TLC (petroleum ether /EtOAc = 1/1). The reaction

mixture was filtered and the filtrate was concentrated directly to give a crude product. The mixture was purified by column on silica gel (petroleum ether /EtOAc =10% to 25%) to give methyl 5-amino-2-(trifluoromethyl)isonicotinate **(Int-A15)**. **LCMS (Method 7):** $t_R$ = 0.611 min, $[M+1]^+$ 221.0. **$^1$H NMR:** (400MHz, CHLOROFORM-d) δ = 7.57 (d, *J*=8.8 Hz, 1H), 7.15 (d, *J*=8.8 Hz, 1H), 6.10 (br s, 2H), 3.99 (s, 3H).

Synthesis of methyl 2-amino-5-(chlorodifluoromethoxy)benzoate **(Int-A16)**

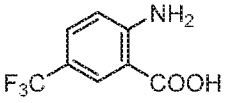


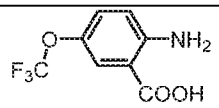
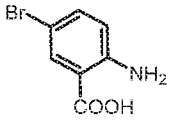
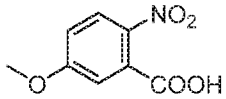
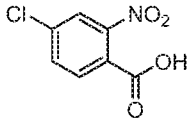
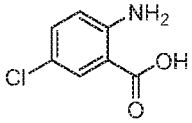
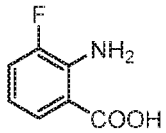
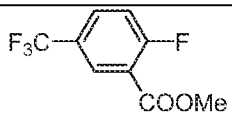

Step 1: To a solution of 4-(chlorodifluoromethoxy)aniline (1.5 g, 7.77 mmol, 1.0 eq.) in MeOH (20 mL) was added the solution of Iodine monochloride (ICl) (1.3 g, 8.16 mmol, 1.05 eq.) in $CH_2Cl_2$ (20 mL) dropwise at 0°C under nitrogen. The resulting mixture was stirred at 25°C for 16 hrs. The reaction was concentrated in vacuum and slowly quenched with water (20 mL) and extracted with $CH_2Cl_2$ (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried ($Na_2SO_4$), filtered and concentrated to give crude product which was purified by column on silica-gel (petroleum ether/EtOAc = 10-20%) to give 4-(chlorodifluoromethoxy)-2-iodoaniline. **$^1$H NMR:** (400 MHz, CHLOROFORM-*d*) δ ppm 7.53 (d, *J*=2.50 Hz, 1 H) 7.04 - 7.09 (m, 1 H) 6.73 (d, *J*=8.76 Hz, 1 H) 3.99 - 4.36 (br, 2 H).

Step 2: To a solution of 4-(chlorodifluoromethoxy)-2-iodoaniline (1.0 g, 3.13 mmol, 1.0 eq.) in $CH_3CN$ (20 mL) and MeOH (10 mL) was added $K_2CO_3$ (1.3 g, 9.40 mmol, 3.0 eq.), TEA (317 mg, 3.13 mmol, 1.0 eq.), DPPF (174 mg, 0.31 mmol, 0.1 eq.) and $Pd(OAc)_2$ (70 mg, 0.31 mmol, 0.1 eq.) at 25°C under nitrogen. The reaction was stirred for 16 hrs at 60°C under CO (15 psi). The reaction was filtered and concentrated in vacuum to give a crude product. The crude product was purified by column (silica-gel, petroleum ether /EtOAc = 10-15%) to give methyl 2-amino-5-(chlorodifluoromethoxy)benzoate **(Int-A16)**. **$^1$H NMR:** (400 MHz, CHLOROFORM-*d*) δ ppm 7.74 (d, *J*=2.88 Hz, 1 H) 7.18 (ddd, *J*=9.01, 1.88, 1.00 Hz, 1 H) 6.68 (d, *J*=9.01 Hz, 1 H) 5.83 (br s, 2 H) 3.90 (s, 3 H).

Table 1 lists Type A intermediates which were purchased.

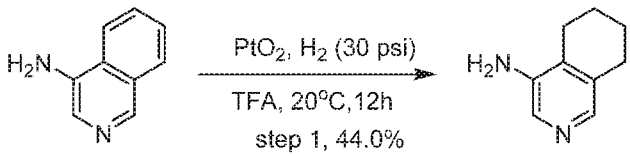
**Table 1**

| Intermediate | Structure | Name | CAS No. |
|---|---|---|---|
| Int-AA1 |  | 2-amino-5-(trifluoromethyl)benzoic acid | 83265-53-6 |

| Intermediate | Structure | Name | CAS No. |
|---|---|---|---|
| Int-AA2 |  | 2-amino-5-(trifluoromethoxy)benzoic acid | 83265-56-9 |
| Int-AA3 |  | 2-amino-5-bromobenzoic acid | 5794-88-7 |
| Int-AA4 |  | 5-methoxy-2-nitrobenzoic acid | 1882-69-5 |
| Int-AA5 |  | 4-chloro-2-nitrobenzoic acid | 6280-88-2 |
| Int-AA6 |  | 2-amino-5-chlorobenzoic acid | 635-21-2 |
| Int-AA7 |  | 2-amino-3-fluorobenzoic acid | 825-22-9 |
| Int-AA8 |  | methyl 2-fluoro-5-(trifluoromethyl)benzoate | 556112-92-6 |

**Type B Intermediates**

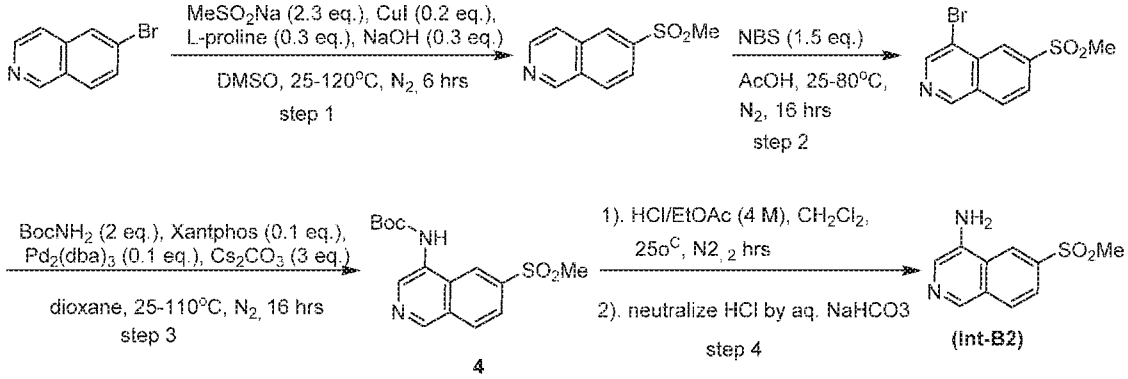
Synthesis of 5,6,7,8-tetrahydroisoquinolin-4-amine **(Int-B1)**




**(Int-B1)**

To a mixture of isoquinolin-4-amine (2 g, 13.87 mmol, 13.5 eq.) in TFA (40 mL) was added $PtO_2$ (233 mg, 0.26 mmol, 1.0 eq.). The mixture was stirred at 20°C under $H_2$ (30 Psi) for 12 hrs. The mixture was concentrated to remove the TFA and the pH was adjusted to 11 with 5N NaOH and extracted with EtOAc (100 mL). The organic phase was concentrated and purified by silica gel chromatography ($SiO_2$, MeOH/EtOAc = 0 - 20%) to give 5,6,7,8-tetrahydroisoquinolin-4-amine **(Int-B1)**. **$^1$H NMR:** (400MHz, DMSO-$d_6$) δ = 7.70 (s, 1H), 7.51 (s, 1H), 4.90 (s, 2H), 2.58 (t, *J*=6.1 Hz, 2H), 2.38 - 2.28 (m, 2H), 1.80 - 1.70 (m, 2H), 1.69 - 1.62 (m, 2H).

Synthesis of 6-(methylsulfonyl)isoquinolin-4-amine **(Int-B2)**




Step 1: To a solution of 6-bromoisoquinoline (38.0 g, 182.65 mmol, 1.0 eq.) in DMSO (400 mL) was added $MeSO_2Na$ (43.0 g, 420.09 mmol, 2.3 eq.), CuI (7.0 g, 36.53 mmol, 0.2 eq.), L-proline (6.3 g, 54.79 mmol, 0.3 eq.) and NaOH (2.2 g, 54.79 mmol, 0.3 eq.) at 25°C. The mixture was stirred at 120°C for 6 hrs. The mixture was quenched with water (500 mL) and extracted with EtOAc (400 mL x 2). The organic layers were washed with brine (400 mL x 2), dried over $Na_2SO_4$, filtered and concentrated to give crude product. The crude was purified by MPLC (Petroleum ether/Ethyl acetate = 100/1~1/1, $R_f$ = 0.20) to give 6-(methylsulfonyl)isoquinoline.

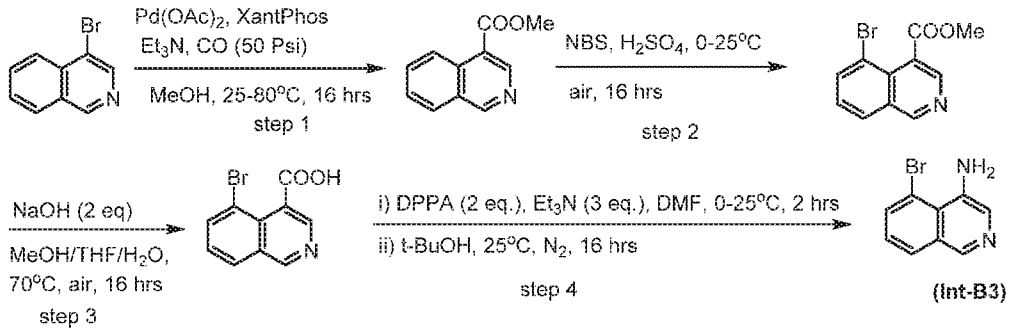
Step 2: To a suspension of 6-(methylsulfonyl)isoquinoline (34.0 g, 164.05 mmol, 1.0 eq.) in AcOH (400 mL) was added NBS (44.0 g, 246.08 mmol, 1.5 eq.) at 25°C and the reaction mixture was then heated to 80°C and stirred at 80°C for 16 hrs. The mixture was diluted with iced water (500 mL), adjusted to pH = 7 with saturated $NaHCO_3$ aqueous at 0°C and extracted with EtOAc (400 mL x 2). The combined organic layers were washed with brine (400 mL x 2), dried over $Na_2SO_4$, filtered and concentrated to give crude product. The crude product was purified by MPLC (Petroleum ether/Ethyl acetate = 100/1~3/1, $R_f$ = 0.60) to give 4-bromo-6-(methylsulfonyl)isoquinoline. **$^1$H NMR:** (400 MHz, DMSO-$d_6$) δ = 9.48 - 9.51 (m, 1 H), 8.93 (s, 1 H), 8.58 (s, 1 H), 8.50 (d, *J*=8.56 Hz, 1 H), 8.27 (dd, *J*=8.62, 1.65 Hz, 1 H), 3.41 (s, 3 H)

Step 3: To a solution of 4-bromo-6-(methylsulfonyl)isoquinoline (29.0 g, 101.07 mmol, 1.0 eq.) and $BocNH_2$ (24.0 g, 202.13 mmol, 2.0 eq.) in dioxane (350 mL) was added $Pd_2(dba)_3$ (4.1 g, 5.05 mmol, 0.05 eq.), Xantphos (6.0 g, 10.11 mmol, 0.1 eq.) and $Cs_2CO_3$ (100.0 g, 303.20 mmol, 3.0 eq.) at 25°C under $N_2$ and the mixture was then heated to 110°C and stirred at 110°C under $N_2$ for 16 hrs. The reaction was quenched with $H_2O$ (350 mL) and extracted with EtOAc (200 mL × 2). The combined organic layers were washed with brine (400 mL × 2), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give a crude product. The crude product was purified by MPLC (Petroleum ether/Ethyl acetate = 100/1 to 0/1) to obtain tert-butyl (6-(methylsulfonyl)isoquinolin-4-yl)carbamate.

Step 4: To the solution of tert-butyl (6-(methylsulfonyl)isoquinolin-4-yl)carbamate (34.0 g, 105.47 mmol, 1.0 eq.) in $CH_2Cl_2$ (400 mL) was added HCl/EtOAc (400 mL, 4 M). Then the reaction mixture was stirred at 25°C under $N_2$ for 2 hrs. LCMS (C-09508-107-1B) showed the starting

material was consumed completely, a main peak with desired MS was detected. The reaction mixture was concentrated under reduced pressure to give a crude product. The crude product was dissolved in $CH_2Cl_2$ (300 mL) and basified with basic resin to pH = 7 – 8. The mixture was filtered and the filter cake was washed with $CH_2Cl_2$ (100 mL x 4). The combined filtrate was dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give 6-(methylsulfonyl)isoquinolin-4-amine **(Int-B2)**. **LCMS (Method 12):** $t_R$ = 0.435 min, $[M+1]^+$ 223.0. **$^1$H NMR:** (400 MHz, CHLOROFORM-*d*) δ = 8.82 - 8.84 (m, 1 H), 8.53 (s, 1 H), 8.20 (s, 1 H), 8.12 (d, *J*=8.56 Hz, 1 H), 8.01 (dd, *J*=8.56, 1.59 Hz, 1 H), 4.31 - 4.47 (s, 2 H), 3.16 (s, 3 H).

Synthesis of 5-bromoisoquinolin-4-amine **(Int-B3)**



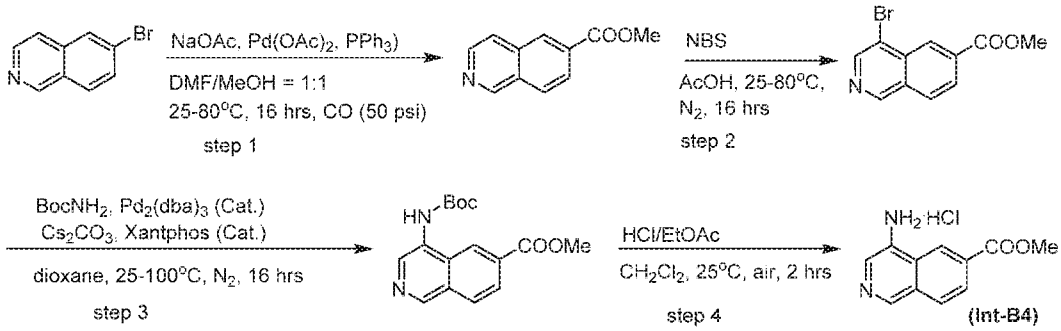

Step 1: To a mixture of 4-bromoisoquinoline (40.0 g, 192.26 mmol, 1.0 eq.) in MeOH (1.0 L) was added $Pd(OAc)_2$ (4.0 g, 17.82 mmol, 0.1 eq.), Xantphos (12.0 g, 20.74 mmol, 0.1 eq.) and $Et_3N$ (58.3 g, 576.78 mmol, 3.0 eq.) at 25°C. The mixture was stirred at 80°C for 16 hrs under CO (50 psi). The reaction was concentrated to give crude product which was purified by silica gel column to give methyl isoquinoline-4-carboxylate. **LCMS (Method 10):** $t_R$ = 0.617 min, $[M+1]^+$ 188.2.

Step 2: NBS (17.0 g, 96.16 mmol, 0.9 eq.) in $H_2SO_4$ (500 mL) was added dropwise to a solution of methyl isoquinoline-4-carboxylate (20.0 g, 106.84 mmol, 1.0 eq.) in $H_2SO_4$ (500 mL) at 0°C over 3 hrs under air. The mixture was then stirred at 25°C for 16 hrs. The reaction mixture was adjusted to pH=7 with NaOH aq. and then extracted with EtOAc (500 mL x 3). The combined organic phases were dried over $Na_2SO_4$ and concentrated to give crude product which was purified by silica gel column (petroleum ether/EtOAc =3/1) to give methyl 5-bromoisoquinoline-4-carboxylate. **LCMS (Method 10):** $t_R$ = 0.640 min, $[M+1]^+$ 266.1.

Step 3: To a mixture of methyl 5-bromoisoquinoline-4-carboxylate (10.0 g, 37.74 mmol, 1.0 eq.) in MeOH/THF/$H_2O$ = 2/3/1 (300 mL) was added NaOH (7.5 g, 188.70 mmol, 5.0 eq.) at 25°C. The mixture was stirred at 70°C for 16 hrs. The mixture was concentrated to give crude product which was purified by RP-MPLC (HCOOH) to give 5-bromoisoquinoline-4-carboxylic acid. **LCMS (Method 10):** $t_R$ = 0.400 min, $[M+1]^+$ 252.0.

Step 4: To a solution of 5-bromoisoquinoline-4-carboxylic acid (1.0 g, 3.98 mmol, 1.0 eq.) and $Et_3N$ (1.2 g, 11.94 mmol, 3.0 eq.) in DMF (15 mL) was added DPPA (2.2 g, 7.97 mmol, 2.0 eq.) at 0°C. The mixture was stirred at 25°C for 2 hrs. t-BuOH (5 mL) was dropwise added to the mixture at 25°C. The mixture was stirred at 25°C for 16 hrs. The reaction was poured into water (30 mL) and extracted with EtOAc (20 mL x 2). The combined organic phases were dried over $Na_2SO_4$, filtered and concentrated to give a crude product. The crude product was purified by RP-HPLC (MeCN-$H_2O$) to give 5-bromoisoquinolin-4-amine **(Int-B3)**. **LCMS (Method 10):** $t_R$ = 0.446 min, $[M+1]^+$ 223.0.

Synthesis of methyl 4-aminoisoquinoline-6-carboxylate hydrochloride **(Int-B4)**




Step 1: To a mixture of 6-bromoisoquinoline (35.0 g, 168.23 mmol, 1.0 eq.) and NaOAc (18.0 g, 218.69 mmol, 1.3 eq.) in DMF/MeOH (1.5 L) was added $PPh_3$ (7.6 g, 33.65 mmol, 0.1 eq.) and $Pd(OAc)_2$ (8.8 g, 33.65 mmol, 0.1 eq.) at 25°C under $N_2$. The reaction mixture was stirred at 80°C under CO (50 Psi) for 16 hrs. The mixture was filtered and the filtrate was concentrated and water (1.0 L) was added. The mixture was extracted with EtOAc (300 mL x 3). The combined organic layers were washed with brine (1.0 L), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give crude product which was purified by silica gel column (petroleum ether/EtOAc =1/0 to 0/1) to give methyl isoquinoline-6-carboxylate.

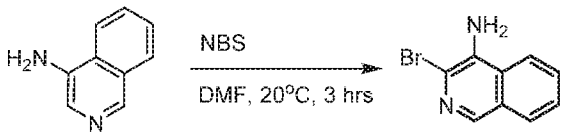
Step 2: To a mixture of methyl isoquinoline-6-carboxylate (10.0 g, 53.42 mmol, 1.0 eq.) in AcOH (200 mL) was added NBS (12.4 g, 69.45 mmol, 1.3 eq.) at 25°C under $N_2$. The reaction mixture was stirred at 80°C for 16 hrs. The mixture was concentrated, added to water (500 mL) and extracted with EtOAc (200 mL x 3). The combined organic layers were washed with brine (500 mL), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give crude product which was purified by silica gel column (petroleum ether/EtOAc =1/0 to 0/1) to give methyl 4-bromoisoquinoline-6-carboxylate. **LCMS (Method 15):** $t_R$ = 0.826 min, $[M+1]^+$ 266.0.

Step 3: To a mixture of methyl 4-bromoisoquinoline-6-carboxylate (25.0 g, 93.95 mmol, 1.0 eq.) and $BocNH_2$ (14.3 g, 122.14 mmol, 1.3 eq.) in dioxane (1.5 L) was added $Cs_2CO_3$ (60.0 g, 187.90 mmol, 2.0 eq.), $Pd_2(dba)_3$ (2.5 g, cat.) and Xantphos (2.5 g, cat.) at 25°C under $N_2$. The reaction mixture was stirred at 100°C for 16 hrs. The mixture was concentrated, added to water (500 mL) and extracted with EtOAc (200 mL x 3). The combined organic layers were washed

with brine (500 mL), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give crude product which was purified by silica gel column (petroleum ether/EtOAc = 1/0 to 0/1) to give methyl 4-((tert-butoxycarbonyl)amino)isoquinoline-6-carboxylate. **$^1$H NMR:** (400 MHz, CHLOROFORM-d) δ = 9.11 (s, 1 H), 9.03 (br s, 1 H), 8.67 (s, 1 H), 8.19 (dd, J=8.50, 1.25 Hz, 1 H), 8.05 (d, J=8.50 Hz, 1 H), 7.00 (br s, 1 H), 4.02 (s, 3 H), 1.58 (s, 9 H).

Step 4: To a mixture of methyl 4-((tert-butoxycarbonyl)amino)isoquinoline-6-carboxylate (25.0 g, 82.75 mmol, 1.0 eq.) in $CH_2Cl_2$ (300 mL) was added HCl/EtOAc (300 mL, 4 N) at 25°C. The reaction mixture was stirred at 25°C for 2 hrs. The mixture was concentrated to give methyl 4-aminoisoquinoline-6-carboxylate hydrochloride. **LCMS (Method 12):** $t_R$ = 0.578 min, $[M+1]^+$ 203.1.

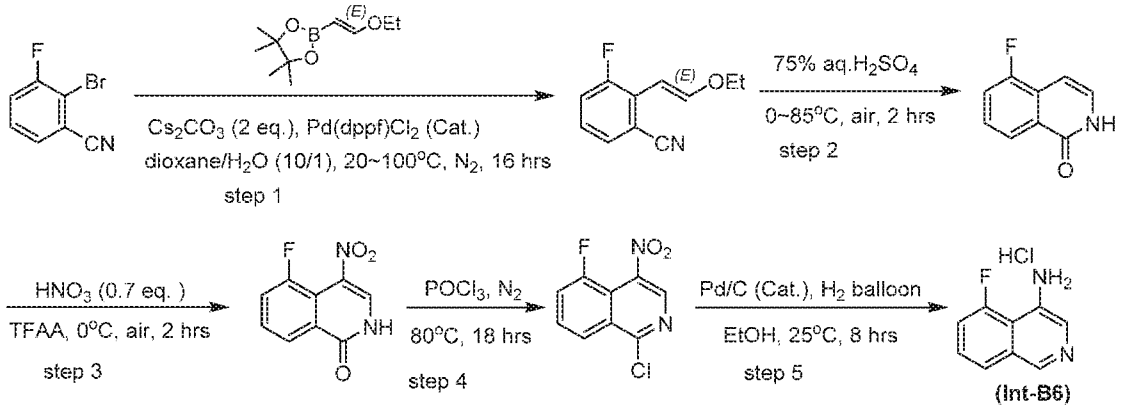
Synthesis of 3-bromoisoquinolin-4-amine **(Int-B5)**




**(Int-B5)**

To a solution of isoquinolin-4-amine (5 g, 34.70 mmol, 1.0 eq.) in DMF (50 mL) was added NBS (6.7 g, 38.20 mmol, 1.1 eq.) at 20°C. The mixture was stirred at 20°C for 3 hrs. The reaction was poured into $H_2O$ (100 mL) and extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine (50 mL x 2), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column (EtOAc /Petroleum ether =70%~100%) to give 3-bromoisoquinolin-4-amine **(Int-B5)**. **$^1$H NMR:** (400 MHz, CHLOROFORM-*d*) δ = 8.52 (s, 1H), 7.93 (d, *J* = 8.3 Hz, 1H), 7.83 - 7.78 (m, 1H), 7.71 (t, *J* = 7.7 Hz, 1H), 7.65 - 7.59 (m, 1H), 5.02 - 4.20 (m, 2H).

Synthesis of 5-fluoroisoquinolin-4-amine **(Int-B6)**




**(Int-B6)**

Step 1: To a mixture of 2-bromo-3-fluorobenzonitrile (25.0 g, 125.67 mmol, 1.0 eq.) in dioxane (300 mL) and $H_2O$ (30 mL) was added $Cs_2CO_3$ (82.0 g, 251.33 mmol, 2.0 eq.), $Pd(dppf)Cl_2$ (4.5

g, 6.28 mmol, 0.05 eq.) and (E)-2-(2-ethoxyvinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (25.0 g, 125.67 mmol, 1.0 eq.) at 20°C. The reaction mixture was heated at 100°C for 16 hrs. The mixture was quenched with $H_2O$ (1.2 L), extracted with ethyl acetate (500 mL x 2). The combined organic layers were washed with brine (800 mL), dried over $Na_2SO_4$, filtered and concentrated to give crude product. The crude product was purified by column (EtOAc/Petroleum ether = 0%~10%) to give (E)-2-(2-ethoxyvinyl)-3-fluorobenzonitrile. **$^1$H NMR:** (400 MHz, CHLOROFORM-d) δ = 7.50 (d, *J* = 13.0 Hz, 1H), 7.40 (d, *J* = 7.6 Hz, 1H), 7.25 - 7.21 (m, 1H), 7.13 (dt, *J* = 5.0, 7.9 Hz, 1H), 6.00 (d, *J* = 12.8 Hz, 1H), 4.01 (q, *J* = 7.0 Hz, 2H), 1.39 (t, *J* = 7.0 Hz, 3H).

Step 2: To $H_2SO_4$ (75%, 400 mL) was added (E)-2-(2-ethoxyvinyl)-3-fluorobenzonitrile (33.8 g, 176.52 mmol, 1.0 eq.) at 0°C. The reaction was stirred at 85°C for 2 hrs. The mixture was poured into ice water (1.2 L) with stirring, then filtered and the filter cake was dried to give a crude product. The crude product was suspended in water (800 mL) and stirred for 0.5 hrs, then the suspension was filtered and filter cake was dried to give 5-fluoroisoquinolin-1(2H)-one. **$^1$H NMR:** (400 MHz, DMSO-$d_6$) δ = 11.45 (s, 1H), 8.01 (d, *J* = 7.9 Hz, 1H), 7.59 - 7.45 (m, 2H), 7.34 - 7.19 (m, 1H), 6.58 (d, *J* = 7.3 Hz, 1H).

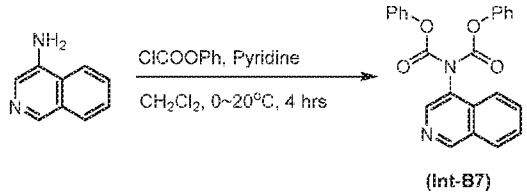
Step 3: $HNO_3$ (9.2 g, 98.68 mmol, 0.7 eq.) was slowly dropwise added to a solution of 5-fluoroisoquinolin-1(2H)-one (23.0 g, 140.97 mmol, 1.0 eq.), in TFAA (250 mL) at 0°C. The mixture was stirred at 0°C for 2 hrs. The mixture was poured into ice water (800 mL), extracted with EtOAc (500 mL x 2). The combined organic layers were washed with brine (600 mL), dried over $Na_2SO_4$, filtered and concentrated to give crude product. The crude product was purified by column (THF/Petroleum ether = 40%~60%) to give a crude product. The crude product was suspended in MTBE/petroleum ether/EtOAc (1/3/1, 300 mL) and stirred for 0.5 hrs, the suspension was filtered and the filter cake was dried to give 5-fluoro-4-nitroisoquinolin-1(2H)-one. **LCMS (Method 14):** $t_R$ = 0.642 min, $[M+1]^+$ 209.1.

Step 4: A solution of 5-fluoro-4-nitroisoquinolin-1(2H)-one (5.0 g, 24.03 mmol, 1.0 eq.) in $POCl_3$ (60 mL) was stirred at 80°C for 18 hrs. The reaction was concentrated in vacuum to remove $POCl_3$ to give a residue. The residue was suspended in toluene (100 mL) and concentrated, repeated for three times to give crude product. The crude product was suspended in hexane (100 mL) and ultrasonicated for 5 min. The supernatant was poured off and the residue was dried in vacuum to give 1-chloro-5-fluoro-4-nitroisoquinoline which used for next step directly.

Step 5: To a solution of 1-chloro-5-fluoro-4-nitroisoquinoline (6.0 g, 26.43 mmol, 1.0 eq.) in EtOH (200 mL) was added Pd/C (5.0 g, Cat.) at 25°C and the mixture was stirred at 25°C for 2 hrs under $H_2$ (15 Psi). The reaction was filtered, the filter cake was washed by EtOH (500 mL x 3), the combined filtrate was concentrated to give a crude product. The crude was suspended in EtOAc/EtOH (200 mL/20 mL) and stirred for 20 mins, the suspension was filtered and the filter

cake was dried to give 5-fluoroisoquinolin-4-amine hydrochloride **(Int-B6)**. **LCMS (Method 15):** $t_R$ = 0.402 min, $[M+1]^+$ 163.1.

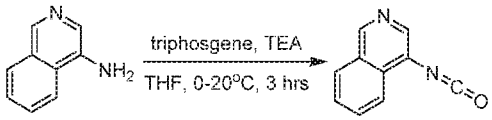
Synthesis of phenyl isoquinolin-4-yl(phenoxycarbonyl)carbamate **(Int-B7)**




(Int-B7)

To a solution of isoquinolin-4-amine (3.0 g, 20.82 mmol, 1.0 eq.) and Pyridine (4.9 g, 62.46 mmol, 3.0 eq.) in $CH_2Cl_2$ (30 mL) was added ClCOOPh (13.0 g, 83.29 mmol, 4.0 eq.) at 0°C. Then the mixture was stirred 20°C for 4 hrs. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was triturated with EtOAc (15 mL). The resulting solid was filtered, rinsed with EtOAc and collected to give phenyl isoquinolin-4-yl(phenoxycarbonyl)carbamate **(Int-B7)**. **LCMS (Method 12) :** $t_R$ = 0.748 min. $[M+1]^+$ 385.11.

Synthesis of 4-isocyanatoisoquinoline **(Int-B8)**

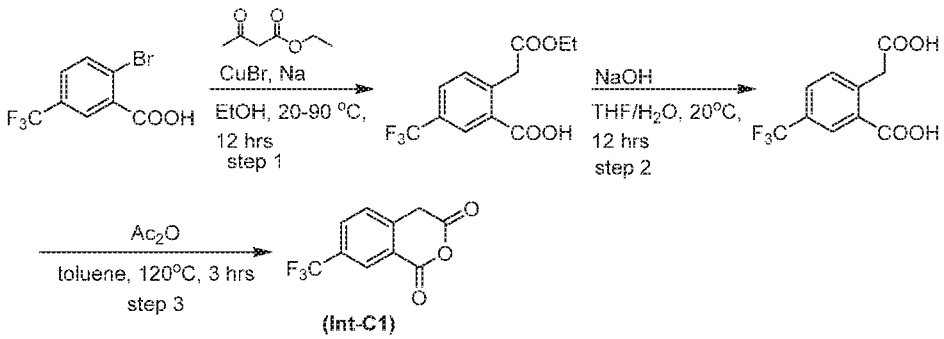



(Int-B8)

To a mixture of isoquinolin-4-amine (800 mg, 7.02 mmol, 1.0 eq.) and TEA (1.8 g, 17.54 mmol, 2.5 eq.) in THF (6 mL) was added dropwise triphosgene (1.0 g, 3.51 mmol, 0.5 eq.) in THF (3 mL) at 0°C and the mixture was stirred at 20°C for 3 hrs under $N_2$. The mixture was quenched with MeOH and concentrated to give 4-isocyanatoisoquinoline **(Int-B8)** which was used directly.

**Type C Intermediates**

Synthesis of 7-(trifluoromethyl)isochromane-1,3-dione **(Int-C1)**




(Int-C1)

Step 1: Na (1.4 g, 60 mmol, 3.0 eq.) was dissolved in EtOH (150 ml) at 20°C under $N_2$ and the mixture was stirred for 30 min. To this solution was added ethyl 3-oxobutanoate (5.5mL, 40 mmol, 2.0 eq), CuBr (2.8 g, 20mmol, 1.0 eq) and 2-bromo-5-(trifluoromethyl)benzoic acid (5g,

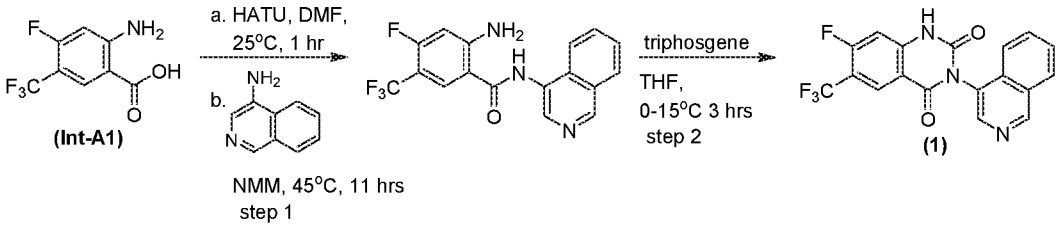
20 mmol, 1.0 eq) at 20°C, and the mixture stirred at 90°C for 12 hrs. The mixture was concentrated, quenched with1N HCl (200 mL) and extracted with EtOAc (300 mL). The organic phase was washed with brine, dried over $Na_2SO_4$ and concentrated. The mixture was purified by preparative silica gel chromatography ($SiO_2$, petroleum ether/EtOAc = 0-100%) to obtain 2-(2-ethoxy-2-oxoethyl)-5-(trifluoromethyl)benzoic acid. **LCMS (Method 12):** $t_R$ = 0.504, [M-1] 274.9. **$^1$H NMR:** (400MHz, DMSO-$d_6$) δ = 13.45 (br s, 1H), 8.26 - 8.08 (m, 1H), 8.02 - 7.83 (m, 1H), 7.63 (d, *J*=8.0 Hz, 1H), 4.13 - 4.09 (m, 2H), 4.06 (q, *J*=7.1 Hz, 2H), 1.17 (t, *J*=7.1 Hz, 3H).

Step 2: A solution of 2-(2-ethoxy-2-oxoethyl)-5-(trifluoromethyl)benzoic acid (3.8 g, 13.80 mmol, 1.0 eq.) in THF/ NaOH (6N) (v/v = 5/3, 40 mL) was stirred at 20°C under $N_2$ for 12 hrs. The pH of the mixture was adjusted to pH=1 with HCl (1N) and extracted with EtOAc (100 mL). The organic phase was washed with brine, dried over $Na_2SO_4$ and concentrated to give 2-(carboxymethyl)-5-(trifluoromethyl)benzoic acid. **$^1$H NMR:** (400MHz, DMSO-$d_6$) δ = 12.85 (br s, 2H), 8.14 (s, 1H), 7.89 (br d, *J*=7.8 Hz, 1H), 7.61 (br d, *J*=7.9 Hz, 1H), 4.05 (s, 2H).

Step 3: A mixture of 2-(carboxymethyl)-5-(trifluoromethyl)benzoic acid (3.7 g, 14.92 mmol, 1.0 eq.) and $Ac_2O$ (4.6 g, 44.76 mmol, 3.0 eq) in toluene (50 ml) was stirred at 120°C under $N_2$ for 3 hrs. The mixture was evaporated and the residue purified by silica gel chromatography ($SiO_2$, EtOAc: petroleum ether = 0-90%) to give 7-(trifluoromethyl)isochromane-1,3-dione **(Int-C1)**. **LCMS (Method 8):** $t_R$ = 0.895, $[M+1]^+$ 231.0. **$^1$H NMR:** (400MHz, DMSO-$d_6$) δ = 8.26 (s, 1H), 8.15 - 8.06 (m, 1H), 7.70 (br d, *J*=8.1 Hz, 1H), 4.37 (s, 2H).

***Synthesis of Example Compounds***

**Example 1:** Synthesis of 7-fluoro-3-(isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(1)**

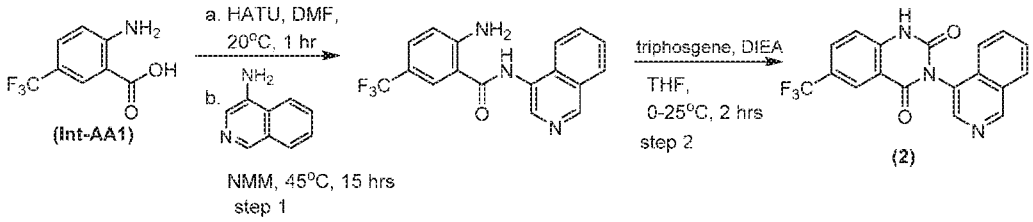



Step 1: HATU (920 mg, 2.42 mmol, 1.2 eq.) was added to a solution of 2-amino-4-fluoro-5-(trifluoromethyl)benzoic acid **(Int-A1)** (450 mg, 2.02 mmol, 1.0 eq.) in DMF (5 mL) at 25°C and the reaction mixture stirred at 25°C for 1 hr. Isoquinolin-4-amine (319 mg, 2.22 mmol, 1.1 eq.) and NMM (611 mg, 6.06 mmol, 3.0 eq.) were added and the reaction mixture stirred at 45°C for 11 hrs. The mixture was diluted with water (20 mL) and extracted with EtOAc (20 mL x 2). The combined organic layers were dried over $Na_2SO_4$, filtered and concentrated to give crude product which was purified by silica gel chromatography ($SiO_2$, Petroleum ether/EtOAc = 10/1 to 3/1) to 2-amino-4-fluoro-N-(isoquinolin-4-yl)-5-(trifluoromethyl)benzamide. **LCMS (Method 5):** $t_R$ = 0.833 min, $[M+1]^+$ 350.0. **$^1$H NMR:** (400MHz, DMSO-d6) δ = 10.49 (s, 1 H) 9.25 (s, 1 H) 8.54

(s, 1 H) 8.29 (d, J=8.0 Hz, 1 H) 8.19 (d, J=8.0 Hz, 1 H) 7.97 (d, J=8.0 Hz, 1 H) 7.82 (t, J=8.0 Hz, 1 H) 7.73 (t, J=8.0 Hz, 1 H) 7.37 (br s, 2 H) 6.73 (d, J=13.8 Hz, 1 H).

Step 2: Triphosgene (200 mg, 0.68 mmol, 1.2 eqv) was added to a mixture of 2-amino-4-fluoro-N-(isoquinolin-4-yl)-5-(trifluoromethyl)benzamide (200 mg, 0.56 mmol, 1.0 eqv) in THF (5 mL) at 0°C. After addition, the reaction mixture was stirred at 15°C for 3 hrs. The mixture was diluted with saturated $NaHCO_3$ aqueous (20 mL) and extracted with EtOAc (20 mL x 2). The combined organic layers were dried over $Na_2SO_4$, filtered and concentrated to give crude product which was purified by prep-HPLC (column: Phenomenex Gemini-NX C18 75mmx30mm, 3μm; liquid phase: [A:10mM $NH_4HCO_3$ in $H_2O$; B:ACN] B%: 35%-55%, 8min]) to give 7-fluoro-3-(isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(1)**. **LCMS (Method 3):** $t_R$ = 2.482min, $[M+1]^+$ 376.1. **$^1$H NMR:** (400MHz, DMSO-d6) 12.26 (s, 1H), 9.44 (s, 1H), 8.56 (s, 1H), 8.27 (d, J=7.6 Hz, 1H), 8.22 (d, J=7.6 Hz, 1H), 7.95 (d, J=7.6 Hz, 1H), 7.95 - 7.76 (m, 2H), 7.27 (d, J=11.4 Hz, 1H).

**Example 2a:** Synthesis of 3-(isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(2)**

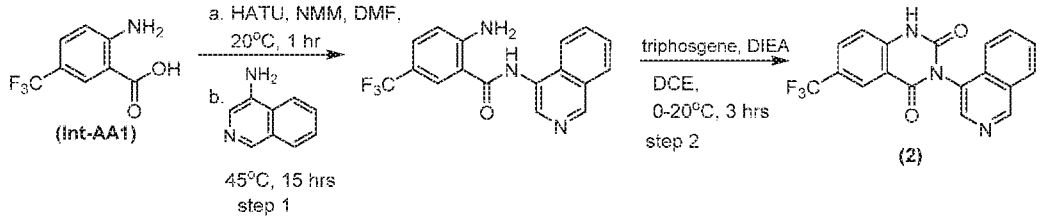



Step 1: HATU (1.11 g, 2.93 mmol, 1.2 eq.) and NMM (740.4 mg, 7.32 mmol, 3.0 eq.) were added to a solution of 2-amino-5-(trifluoromethyl)benzoic acid **(Int-AA1)** (500 mg, 2.44 mmol, 1.0 eq.) in DMF (5 mL) and the mixture was stirred at 20°C for 1 hr. Isoquinolin-4-amine (387 mg, 2.68 mmol, 1.1 eq.) was then added and the mixture was stirred at 45°C for 15 hrs. The mixture was then poured into water (15 mL) and extracted with EtOAc (10 mL x 3). The combined organic phases were washed with brine, dried over $Na_2SO_4$, filtered and concentrated to give crude product. The crude product was purified by silica gel chromatography ($SiO_2$, petroleum ether /EtOAc = 1/0 to 1/1) to give 2-amino-N-(isoquinolin-4-yl)-5-(trifluoromethyl)benzamide. **LCMS (Method 5):** $t_R$ = 0.808 min, $[M+1]^+$ 332.0. **$^1$H NMR:** (400MHz, DMSO-d6) δ = 10.50 (s, 1H), 9.25 (s, 1H), 8.55 (s, 1H), 8.25 (s, 1H), 8.19 (d, J=8.1 Hz, 1H), 7.96 (d, J=8.4 Hz, 1H), 7.86 - 7.78 (m, 1H), 7.77 - 7.69 (m, 1H), 7.53 (dd, J=1.8, 8.8 Hz, 1H), 7.11 (br s, 2H), 6.93 (d, J=8.8 Hz, 1H).

Step 2: DIEA (467 mg, 3.6 mmol, 2 eq.) and triphosgene (804 mg, 2.71 mmol, 1.5 eq.) were added at 0°C to a solution of 2-amino-N-(isoquinolin-4-yl)-5-(trifluoromethyl)benzamide (600 mg, 1.81 mmol, 1.0 eq.) in THF (20 mL) and the mixture was stirred at 25°C for 2 hrs. The reaction was quenched by careful addition of aq. $NaHCO_3$ solution (100 mL) and then extracted with

EtOAc (60 mL x 2), washed with brine (60 mL), dried over $Na_2SO_4$, filtered, and concentrated to give crude product. The crude product was purified by prep-HPLC ($NH_4HCO_3$) to give 3-(isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(2)**. **LCMS (Method 1):** $t_R$ = 2.193 min, $[M+1]^+$ 358.0. **$^1$H NMR:** (400MHz, DMSO-d6) δ = 9.43 (s, 1H), 8.56 (s, 1H), 8.31 - 8.24 (m, 1H), 8.18 (s, 1H), 8.09 (dd, J=2.0, 8.7 Hz, 1H), 7.99 - 7.89 (m, 1H), 7.82 - 7.71 (m, 2H), 7.47 (d, J=8.7 Hz, 1H).

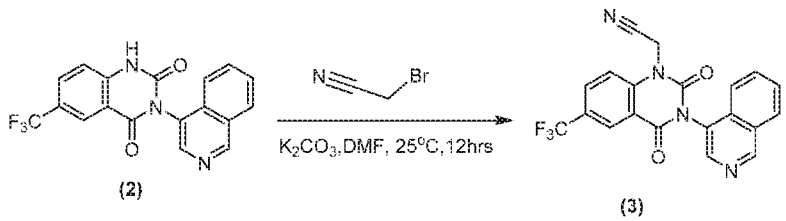
**Example 2b:** Alternative synthesis of 3-(isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(2)**




Step 1: HATU (1.11 g, 2.93 mmol, 1.2 eq.) and NMM (740.4 mg, 7.32 mmol, 3.0 eq.) were added to a solution of 2-amino-5-(trifluoromethyl)benzoic acid **(Int-AA1)** (500 mg, 2.44 mmol, 1.0 eq.) in DMF (5 mL) and the mixture was stirred at 20°C for 1 hr. Isoquinolin-4-amine (387 mg, 2.68 mmol, 1.1 eq.) was then added and the mixture was stirred at 45°C for 15 hrs. The mixture was then poured into water (15 mL) and extracted with EtOAc (10 mL x 3). The combined organic phases were washed with brine, dried over $Na_2SO_4$, filtered and concentrated to give crude product. The crude product was purified by silica gel chromatography ($SiO_2$, petroleum ether /EtOAc = 1/0 to 1/1) to give 2-amino-N-(isoquinolin-4-yl)-5-(trifluoromethyl)benzamide. **LCMS (Method 1):** $t_R$ = 0.808 min, $[M+1]^+$ 332.0. **$^1$H NMR:** (400MHz, DMSO-d6) δ = 10.50 (s, 1H), 9.25 (s, 1H), 8.55 (s, 1H), 8.25 (s, 1H), 8.19 (d, J=8.1 Hz, 1H), 7.96 (d, J=8.4 Hz, 1H), 7.86 - 7.78 (m, 1H), 7.77 - 7.69 (m, 1H), 7.53 (dd, J=1.8, 8.8 Hz, 1H), 7.11 (br s, 2H), 6.93 (d, J=8.8 Hz, 1H).

Step 2: DIEA (468 mg, 3.60 mmol, 2.0 eq.) and triphosgene (801 mg, 2.70 mmol, 1.5 eq.) were added at 0°C to a solution of 2-amino-N-(isoquinolin-4-yl)-5-(trifluoromethyl)benzamide (600 mg, 1.80 mmol, 1.0 eq.) in DCE (10 mL) and the mixture stirred at 20°C for 3 hrs. The mixture was diluted with $H_2O$ (10 mL) and extracted with EtOAc (15 mL x 3). The combined organic layers were dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give crude product which was purified by silica gel chromatography ($SiO_2$, $CH_2Cl_2$/MeOH=100/1 to 5/1) to give 3-(isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(2)**. **LCMS (Method 1):** $t_R$ = 0.769 min, $[M+1]^+$ 358.1. **$^1$H NMR:** (DMSO-d6, 400 MHz) δ = 12.2-12.2 (m, 1H), 9.5-9.6 (m, 1H), 8.6-8.7 (m, 1H), 8.3-8.4 (m, 1H), 8.2-8.2 (m, 1H), 8.1-8.1 (m, 1H), 8.0-8.1 (m, 1H), 7.83 (br d, 2H, *J*=1.7 Hz), 7.50 (d, 1H, *J*=8.6 Hz).

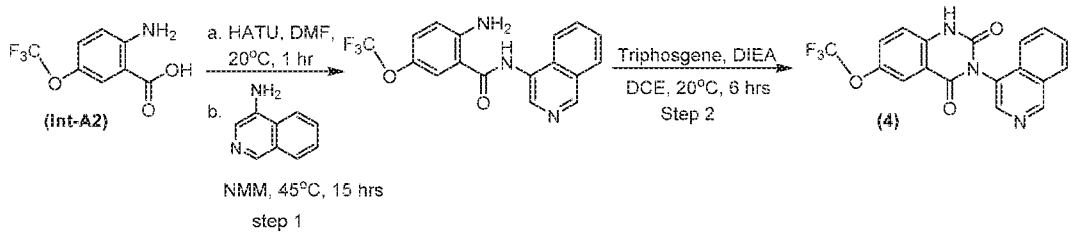
**Example 3:** Synthesis of 2-(3-(isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2H)-yl)acetonitrile **(3)**




(2) (3)

$K_2CO_3$ (116 mg, 0.84 mmol, 3.0 eq.) and 2-bromoacetonitrile (40 mg, 0.34 mmol, 1.2 eq.) were added to a solution of 3-(isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(2)** (100 mg, 0.28 mmol, 1.0 eq.) in DMF (2 mL) and the mixture stirred at 20°C for 12 hrs. The crude product was directly purified by prep-HPLC ($NH_4HCO_3$) to give 2-(3-(isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2H)-yl)acetonitrile **(3)**. **LCMS (Method 2):** $t_R$ = 2.693 min, $[M+1]^+$ 397.1. **$^1$H NMR:** (METHANOL-d4, 400 MHz) δ = 9.40 (s, 1H), 8.53 (s, 2H), 8.50 (s, 1H), 8.28 (d, *J*=8.0 Hz, 1H), 8.22 (d, *J*=8.0 Hz, 1H), 7.88 (t, *J*=8.0 Hz, 1H), 7.84 (t, *J*=8.0 Hz, 1H), 7.78 (t, *J*=8.0 Hz, 1H), 5.42 (d, 1H, *J*=18.0 Hz), 5.34 (d, 1H, *J*=18.0 Hz).

**Example 4:** Synthesis of 3-(isoquinolin-4-yl)-6-(trifluoromethoxy)quinazoline-2,4(1H,3H)-dione **(4)**



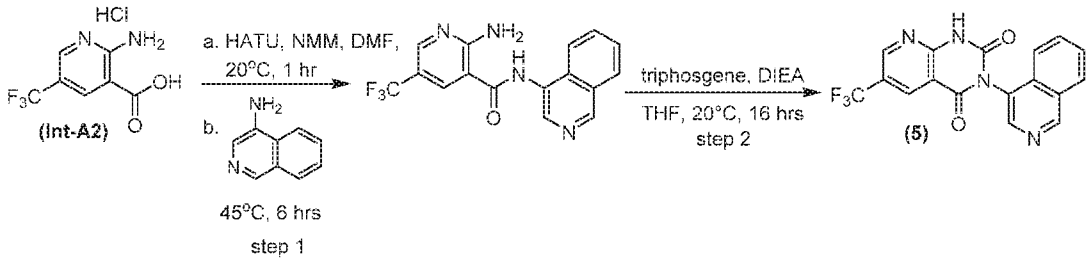

(Int-A2) (4)

Step 1: HATU (1.0 g, 2.71 mmol, 1.2 eq.) was added to a solution of 2-amino-5-(trifluoromethoxy)benzoic acid **(Int-AA2)** (500 mg, 2.26 mmol, 1.0 eq.) in DMF (5 mL) at 20°C and the mixture was stirred at 20°C for 1 hr. Isoquinolin-4-amine (359 mg, 2.49 mmol, 1.1 eq.) and NMM (686 mg, 6.78 mmol, 3.0 eq.) were added and the mixture stirred at 45°C for 15 hrs. The mixture was poured into water (10 mL) and extracted with EtOAc (5 mL x 3). The combined organic phases were washed with brine (10 mL), dried over $Na_2SO_4$, filtered and concentrated. The crude product was purified by silica gel chromatography ($SiO_2$, petroleum ether/EtOAc = 100:0 to 45:55) to obtain 2-amino-N-(isoquinolin-4-yl)-5-(trifluoromethoxy)benzamide. **LCMS: (Method 8):** $t_R$ = 0.816 min, $[M+1]^+$ 348.0. **$^1$H NMR:** (400 MHz, CHLOROFORM-*d*) δ ppm 9.19 (s, 1 H) 8.83 (s, 1 H) 8.1 (br s, 1 H) 8.05 (d, *J*=8.13 Hz, 1 H) 7.91 (dd, *J*=8.5, 0.6 Hz, 1 H) 7.76 - 7.82 (m, 1 H) 7.65 - 7.71 (m, 1 H) 7.56 (d, *J*=2.5 Hz, 1 H) 7.19 - 7.24 (m, 1 H) 6.77 (d, *J*=9.0 Hz, 1 H) 5.66 (br s, 2 H).

Step 2: To a solution of 2-amino-N-(isoquinolin-4-yl)-5-(trifluoromethoxy)benzamide (210 mg, 0.60 mmol, 1.0 eq.) in DCE (1 mL) was added a solution of triphosgene (179 mg, 0.60 mmol,

1.0 eq.) in DCE (1 mL) and DIEA (156 mg, 1.21 mmol, 2.0 eq.) at 20°C, and the mixture was then stirred at 20°C for 6 hrs. The reaction mixture was concentrated to give crude product which was then purified by prep-HPLC (column: Phenomenex Luna C18 75mmx30mm, 3µm; liquid phase: [A:$H_2O$(0.1%FA); B:ACN]B%: 20%-50%,20min] to obtain 3-(isoquinolin-4-yl)-6-(trifluoromethoxy)quinazoline-2,4(1H,3H)-dione **(4)**. **LCMS (Method 3):** $t_R$ = 2.522 min, $[M+1]^+$ 274.0. **$^1$H NMR:** (400 MHz, DMSO-$d_6$) δ ppm 11.95 (s, 1 H) 9.44 (s, 1 H) 8.57 (s, 1 H) 8.25 - 8.31 (m, 1 H) 7.94 (br d, *J*=7.4 Hz, 1 H) 7.80 - 7.85 (m, 2 H) 7.75 - 7.79 (m, 2 H) 7.42 (d, *J*=8.7 Hz, 1 H).

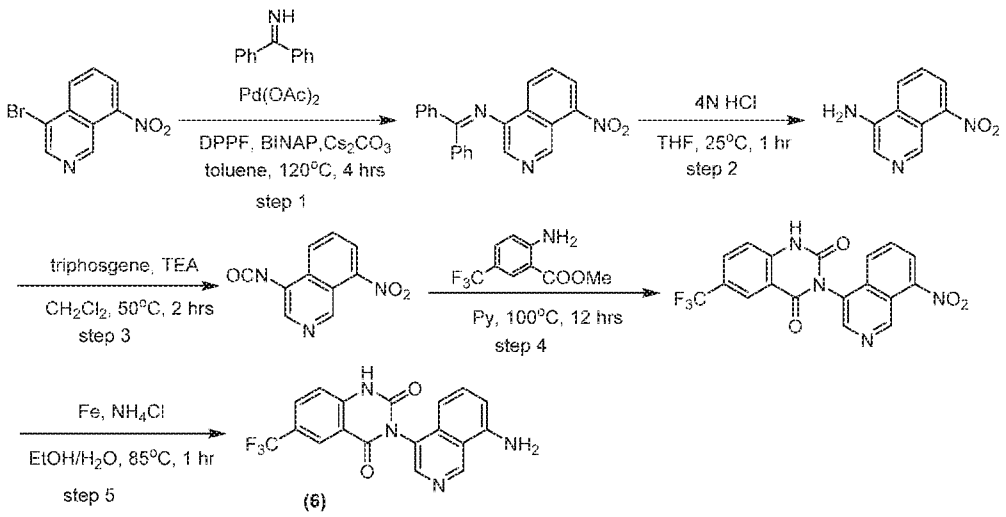
**Example 5:** Synthesis of 3-(isoquinolin-4-yl)-6-(trifluoromethyl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione **(5)**




Step 1: HATU (3.8g, 9.89 mmol, 1.2 eq.) and NMM (2.5 g, 24.73 mmol, 3.0 eq.) at 20°C were added to a solution of 2-amino-5-(trifluoromethyl)nicotinic acid hydrochloride **(Int-A2)** (2.0 g, 8.24 mmol, 1.0 eq.) in DMF (20 mL) and the mixture stirred at 20°C for 1 hr. Isoquinolin-4-amine (1.3 g, 9.07 mmol, 1.1 eq.) was then added and the mixture was stirred at 45°C for 6 hrs. The reaction mixture was concentrated to give crude product which was purified by prep-HPLC (column: Phenomenex luna C18 (250mmx70mm,15µm); liquid phase: [A:$H_2O$(0.1%FA); B:ACN]B%: 8%-35%,20min]) to obtain 2-amino-N-(isoquinolin-4-yl)-5-(trifluoromethyl)nicotinamide. **LCMS (Method 5):** $t_R$ = 0.740 min, $[M+1]^+$ 333.0. **$^1$H NMR:** (400MHz, DMSO-$d_6$) δ = 10.70 (s, 1H), 9.30 (s, 1H), 8.64 - 8.59 (m, 2H), 8.52 (d, *J*=1.4 Hz, 1H), 8.23 (d, *J*=8.1 Hz, 1H), 8.04 (d, *J*=8.4 Hz, 1H), 7.88 - 7.84 (m, 1H), 7.80 - 7.71 (m, 3H).

Step 2: DIEA (163 mg, 1.26 mmol, 3.0 eq.) and triphosgene (63 mg, 0.21 mmol, 0.5 eq.) were added to a solution of 2-amino-N-(isoquinolin-4-yl)-5-(trifluoromethyl)nicotinamide (140 mg, 0.42 mmol, 1.0 eq.) in THF (1.5 mL) at 20°C and the mixture stirred at 20°C for 16 hrs. The reaction mixture was concentrated to give crude product which was then purified by Prep-HPLC (column: Phenomenex Luna C18 150mmx30mm, 5µm; liquid phase: [A:FA/$H_2O$=0.1% v/v; B:ACN]B%: 20%-50%,9min]) to obtain 3-(isoquinolin-4-yl)-6-(trifluoromethyl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione **(5)**. **LCMS (Method 6):** $t_R$ = 2.059 min, $[M+1]^+$ 359.0. **$^1$H NMR:** (400MHz, DMSO-$d_6$) δ = 12.71 (br s, 1H), 9.44 (s, 1H), 9.11 (s, 1H), 8.60 - 8.51 (m, 2H), 8.28 (dd, *J*=2.1, 6.7 Hz, 1H), 8.03 (br d, *J*=7.6 Hz, 1H), 7.81 - 7.74 (m, 2H).

**Example 6:** Synthesis of 3-(8-aminoisoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(6)**




Step 1: 4-bromo-8-nitroisoquinoline (1.1 g, 1.38 mmol, 0.5 eq.), $Pd(OAc)_2$ (40 mg, 0.18 mmol, 0.06 eq.), BINAP (300 mg, 0.48 mmol, 0.17 eq.) and DPPF (300 mg, 0.54 mmol, 0.2 eq.) were added to a solution of diphenylmethanimine (500 mg, 2.76 mmol, 1.0 eq.) in TEA (0.5 mL, 2.99 mmol, 1.1 eq) at 20°C, and the mixture was then concentrated at 30°C for 15 min. $Cs_2CO_3$ (978 mg, 0.33 mmol, 0.1 eq.) and the mixture were added to toluene (25 mL) at 20°C and stirred at 120°C for 4 hrs. The mixture was poured into water (25 mL) and extracted with EtOAc (25 mL x 3). The combined organic phases were washed with brine, dried over $Na_2SO_4$, filtered and concentrated to give crude N-(8-nitroisoquinolin-4-yl)-1,1-diphenylmethanimine. **LCMS (Method 7):** $t_R$ = 0.729 min, $[M+1]^+$ 354.1.

Step 2: 4N HCl (10 mL) was added to a mixture of N-(8-nitroisoquinolin-4-yl)-1,1-diphenylmethanimine (2.0 g, 2.00 mmol, 1.0 eq.) in THF (20 ml) at 25°C and the mixture stirred at 25°C for 1 hr. The mixture was poured into $NaHCO_3$ aq. (100 mL) and then extracted with EtOAc (50 mL x 3). The combined organic phases were washed with brine, dried over $Na_2SO_4$, filtered and concentrated to give crude product. The crude product was purified by silica gel chromatography ($SiO_2$, petroleum ether/EtOAc = 1/0 to 0/1) to give 8-nitroisoquinolin-4-amine. **LCMS (Method 8):** $t_R$ = 0.350 min, $[M+1]^+$ 190.1.

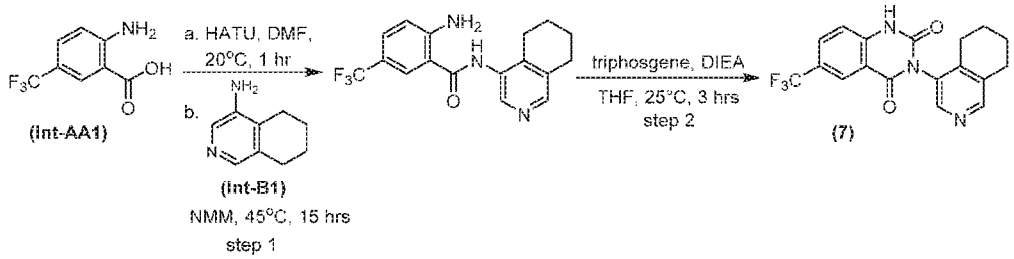
Step 3: TEA (65 mg, 0.65 mmol, 2.5 eq.) and triphosgene (40 mg, 0.13 mmol, 0.5 eq.) were added to a mixture of 8-nitroisoquinolin-4-amine (50 mg, 0.26 mmol, 1.0 eq.) in $CH_2Cl_2$ (5 mL) at 20°C and the mixture was stirred at 50°C for 2 hrs. The reaction was concentrated to give crude 4-isocyanato-8-nitroisoquinoline which was used directly in the next step.

Step 4: Methyl 2-amino-5-(trifluoromethyl)benzoate **(Int-A6)** (101 mg, 0.46 mmol, 2.0 eq.) was added to a solution of 4-isocyanato-8-nitroisoquinoline (50 mg, 0.23 mmol, 1.0 eq.) in pyridine (3 mL) at 20°C. The mixture was stirred at 100°C for 12 hrs. The mixture was poured into water (15

mL) and extracted with EtOAc (10 mL x 3). The combined organic phase was washed with brine, dried over $Na_2SO_4$, filtered and concentrated to give crude product. The crude product was purified by prep-HPLC (neutral, MeCN-$H_2O$) to give 3-(8-nitroisoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione. **LCMS (Method 8):** $t_R$ = 0.921 min, $[M+1]^+$ 402.9.

Step 5: $NH_4Cl$ (35 mg, 0.63 mmol, 5 eq.) and Fe powder (35 mg, 0.63 mmol, 5 eq.) were added to a solution of 3-(8-nitroisoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione (50 mg, 0.13 mmol, 1.0 eq.) in EtOH (5 mL) and $H_2O$ (5 mL) at 20°C, and the mixture stirred at 85°C for 1 hr. The mixture was filtered and the filtrate was concentrated to give crude product. The crude product was purified by prep-HPLC (neutral, MeCN-$H_2O$) to give 3-(8-aminoisoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(6)**. **LCMS (Method 1):** $t_R$ = 1.921 min, $[M+1]^+$ 373.0. **$^1$H NMR:** (400MHz, DMSO-$d_6$) δ = 12.02 (br s, 1H), 9.54 (s, 1H), 8.37 (s, 1H), 8.16 (s, 1H), 8.07 (dd, *J*=1.8, 8.6 Hz, 1H), 7.45 (d, *J*=8.6 Hz, 1H), 7.38 (t, *J*=7.9 Hz, 1H), 6.84 (d, *J*=8.2 Hz, 1H), 6.77 (d, *J*=7.5 Hz, 1H), 6.42 (s, 2H).

**Example 7:** Synthesis of 3-(5,6,7,8-tetrahydroisoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(7)**

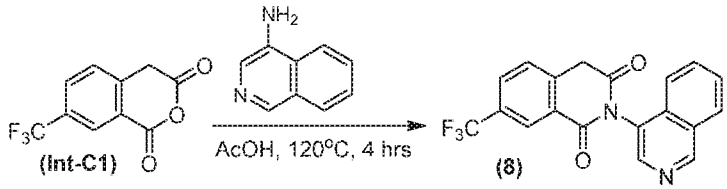



Step 1: HATU (1.1 g, 2.93 mmol, 1.2 eq.) was added to a solution of 2-amino-5-(trifluoromethyl)benzoic acid **(Int-AA1)** (500 mg, 2.44 mmol, 1.0 eq.) in DMF (5 mL) and the mixture stirred at 20°C for 1 hr. 5,6,7,8-tetrahydroisoquinolin-4-amine **(Int-B1)** (397 mg, 2.44 mmol, 1.1 eq.) and NMM (740 mg, 7.32 mmol, 3.0 eq.) were added and the mixture stirred at 45°C for 15 hrs. The mixture was poured into water and extracted with EtOAc (20mL x 2). The combined organic phases were washed with brine, dried over $Na_2SO_4$, filtered, concentrated to obtain crude product which was purified by silica gel chromatography ($SiO_2$, EtOAc/petroleum ether = 0-100%) to give 2-amino-N-(5,6,7,8-tetrahydroisoquinolin-4-yl)-5-(trifluoromethyl)benzamide. **LCMS (Method 7):** $t_R$ = 0.541, $[M+1]^+$ 336.1.

Step 2: DIEA (617 mg, 4.78mmol, 2.0 eq.) and a solution of triphosgene (1.1g, 3.59 mmol, 1.5 eq.) in THF (4 mL) were added to a mixture of 2-amino-N-(5,6,7,8-tetrahydroisoquinolin-4-yl)-5-(trifluoromethyl)benzamide (800 mg, 2.39 mmol, 1.0 eq.) in THF (8 mL) and the mixture stirred at 25°C for 3 hrs. The mixture was quenched with $NaHCO_3$ aq. (30 mL) and extracted with EtOAc (30 mL x 2). The combined organic phases were washed with brine (30 mL), dried over $Na_2SO_4$, filtered, evaporated to obtain crude product which was purified by preparative HPLC

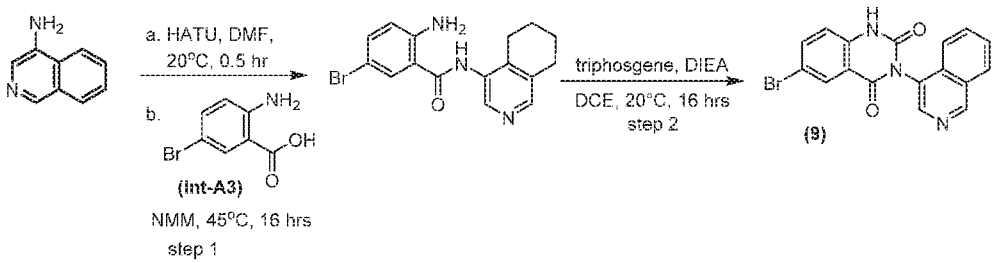
(column: Phenomenex luna C18 80mmx40mm, 3µm; liquid phase: [A:$H_2O$=(0.04%HCl); B:ACN]B%: 25%-40%,20min]) to give 3-(5,6,7,8-tetrahydroisoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(7)**. **LCMS (Method 1):** $t_R$ = 2.036, $[M+1]^+$ 362.1. **$^1$H NMR:** (400MHz, DMSO-$d_6$) δ = 12.18 (s, 1H), 8.55 (s, 1H), 8.50 (s, 1H), 8.18 (s, 1H), 8.10 (dd, *J*=2.0, 8.6 Hz, 1H), 7.47 (d, *J*=8.6 Hz, 1H), 2.88 (br t, *J*=5.9 Hz, 2H), 2.56 (br d, *J*=3.8 Hz, 2H), 1.81 - 1.66 (m, 4H).

**Example 8:** Synthesis of 7-(trifluoromethyl)-1H-[2,4'-biisoquinoline]-1,3(4H)-dione **(8)**




A mixture of 7-(trifluoromethyl)isochromane-1,3-dione **(Int-C1)** (1.4 g, 6.08 mmol, 1.0 eq.) and isoquinolin-4-amine (877 mg, 6.08 mmol, 1.0 eq.) in AcOH (36 mL) was stirred at 120°C under $N_2$ for 4 hrs. The mixture was evaporated and the residue purified by silica gel chromatography ($SiO_2$, EtOAc: petroleum ether = 0-80%) to obtain 7-(trifluoromethyl)-1H-[2,4'-biisoquinoline]-1,3(4H)-dione **(8)**. **LCMS (Method 1):** $t_R$ = 2.319, $[M+1]^+$ 357.0. **$^1$H NMR:** (400MHz, DMSO-$d_6$) δ = 9.43 (s, 1H), 8.48 (s, 1H), 8.31 - 8.23 (m, 2H), 8.14 (dd, *J*=1.6, 8.1 Hz, 1H), 8.04 - 7.97 (m, 1H), 7.85 - 7.68 (m, 3H), 4.66 - 4.38 (m, 2H).

**Example 9:** Synthesis of 6-bromo-3-(isoquinolin-4-yl)quinazoline-2,4(1H,3H)-dione **(9)**

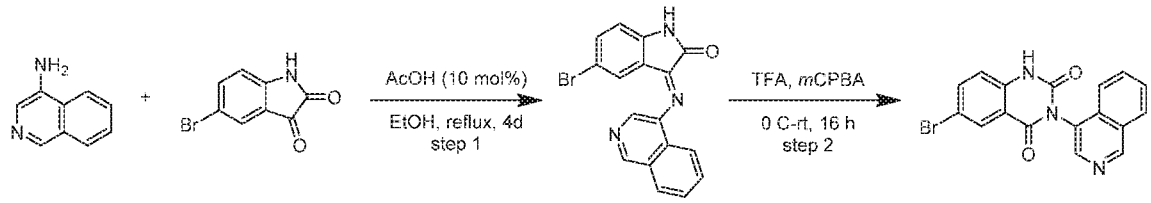



Step 1: A mixture of isoquinolin-4-amine (3.0 g, 13.80 mmol, 1.0 eq.), HATU (6.3 g, 16.56 mmol, 1.2 eq.) in DMF (20 mL) was stirred at 20°C for 0.5 hr. 2-amino-5-bromobenzoic acid **(Int-AA3)** (2.2 g, 15.18 mmol, 1.1 eq.) and NMM (4.2 g, 41.40 mmol, 3.0 eq.) were then added and the mixture was stirred at 45°C for 16 hrs. The reaction mixture was quenched with water (50 mL) and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (50 mL), dried over $Na_2SO_4$, filtered and concentrated to give a residue which was purified by silica gel chromatography ($SiO_2$, Petroleum ether/ EtOAc =1/1) to give 2-amino-5-bromo-N-(isoquinolin-4-yl)benzamide. **LCMS (Method 7):** $t_R$ = 0.516 min, $[M+1]^+$ 342.0. **$^1$H NMR:** (400MHz, DMSO-$d_6$) δ = 11.96 (br s, 1H), 10.40 (br s, 1H), 9.27 (br s, 1H), 8.56 (br s, 1H), 8.21

(br d, *J*=8.0 Hz, 1H), 8.05 (br s, 1H), 7.98 (br d, *J*=7.5 Hz, 1H), 7.90 - 7.68 (m, 2H), 7.39 (br d, *J*=9.5 Hz, 1H), 6.77 (br d, *J*=8.4 Hz, 1H), 5.76 (br d, *J*=1.4 Hz, 2H).

Step 2: A solution of Triphosgene (564 mg, 1.90 mmol, 1.0 eq.) in DCE (3.5 mL) and DIEA (491 mg, 3.80 mmol, 2.0 eq.) were added to a solution of 2-amino-5-bromo-N-(isoquinolin-4-yl)benzamide (650 mg, 1.90 mmol, 1.0 eq.) in DCE (3.5 mL) at 20°C and the mixture stirred at 20°C for 16 hrs. The reaction mixture was concentrated to give a residue. which was purified by Prep-HPLC column: Phenomenex luna C18 (250mmx70mm,15µm); liquid phase: [A:$H_2O$(0.1%FA); B:ACN]B%: 16%-46%,20min] to give 6-bromo-3-(isoquinolin-4-yl)quinazoline-2,4(1H,3H)-dione **(9)**. **LCMS (Method 3):** $t_R$ = 2.290 min, $[M+1]^+$ 368.0. **$^1$H NMR:** (400MHz, DMSO-$d_6$) δ = 11.89 (s, 1H), 9.43 (s, 1H), 8.55 (s, 1H), 8.30 - 8.24 (m, 1H), 8.03 (d, *J*=2.3 Hz, 1H), 7.93 (dd, *J*=2.3, 8.7 Hz, 1H), 7.91 - 7.86 (m, 1H), 7.80 - 7.73 (m, 2H), 7.27 (d, *J*=8.8 Hz, 1H).

**Example 9:** Alternative synthesis of 6-bromo-3-(isoquinolin-4-yl)quinazoline-2,4(1H,3H)-dione **(9)**

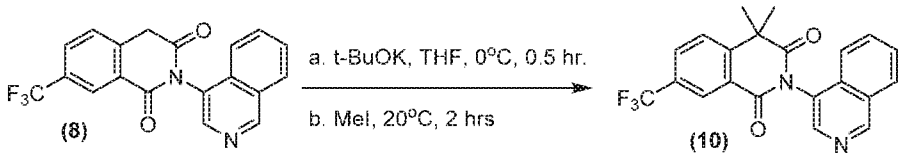



Step 1: To an oven-dried flask was added isoquinolin-4-amine **(Int-B1)** (6.03 g, 1.05 eq., 41.8 mmol), and 5-bromoindoline-2,3-dione (9.00 g, 1 eq., 39.8 mmol). EtOH (500 mL) was added, followed by acetic acid (239 mg, 228 µL, 0.1 Eq, 3.98 mmol). A reflux condensor was attached and the reaction was heated at 90 °C for 4 days. After 4 days, the reaction was concentrated *in vacuo* and then azeotroped with PhMe. The resulting solid was suspended in EtOAc, filtered and dried to give (E)-5-bromo-3-(isoquinolin-4-ylimino)indolin-2-one which was used without further purification **LCMS (Method 29):** $t_R$ = 0.69 min, $[M+1]^+$ 354.2.

Step 2: To a 20 mL vial was added (*E*)-5-bromo-3-(isoquinolin-4-ylimino)indolin-2-one (3.52 g, 1 Eq, 10.00 mmol), DCM (200.00 mL) and TFA (2.280 g, 1.54 mL, 2.0 eq., 20.0 mmol) forming a suspension which was cooled to 0 °C . *m*CPBA (4.60 g, 75% wt, 2.0 eq., 20.00 mmol) was added as a single portion and the reaction was warmed to rt and stirred overnight. The organic phase was wshed with 200 mL $H_2O$. DCM was removed in vacuo and the slurry was filtered and the filtered solid was washed with $H_2O$. The solid was then slurried in MeOH, filtered and dried to give *rac*-6-bromo-3-(isoquinolin-4-yl)quinazoline-2,4(1H,3H)-dione **(9)**.

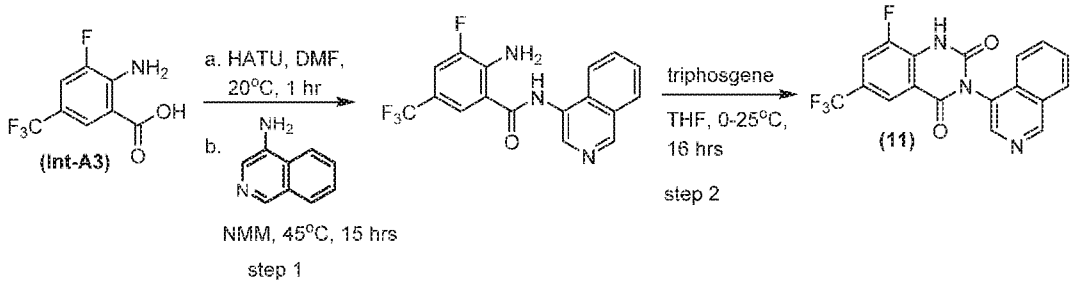
**LCMS (Method 29):** $t_R$ = 0.67 min, $[M+1]^+$ 370.2; **1H NMR** (500 MHz, DMSO) δ 11.90 (s, 1H), 9.42 (d, J = 0.9 Hz, 1H), 8.54 (s, 1H), 8.29 – 8.25 (m, 1H), 8.02 (d, J = 2.4 Hz, 1H), 7.92 (dd, J = 8.7, 2.4 Hz, 1H), 7.89 – 7.86 (m, 1H), 7.81 – 7.71 (m, 2H), 7.26 (d, J = 8.7 Hz, 1H).

**Example 10:** Synthesis of 4,4-dimethyl-7-(trifluoromethyl)-1H-[2,4'-biisoquinoline]-1,3(4H)-dione **(10)**




t-BuOK (1.1 mL, 1.12 mmol, 1 M in THF, 2.0 *eq.*) was added to a solution of 7-(trifluoromethyl)-1H-[2,4'-biisoquinoline]-1,3(4H)-dione **(8)** (200 mg, 0.56 mmol, 1.0 *eq.*) in THF (5 mL) at 0°C and the mixture stirred at 0°C for 0.5 hrs. Methyliodide (398 mg, 2.80 mmol, 5.0 *eq.*) was then added dropwise at 0°C and the mixture stirred at 20°C for 2 hrs. The reaction was quenched with $NH_4Cl$ (10 mL) and extracted with EtOAc (8 mL × 2). The combined organic layers were washed with brine (20 mL × 2), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give crude product which was purified by preparative HPLC (column: Phenomenex Luna C18 75mmx30mm, 3μm; liquid phase: [A:FA/$H_2O$=0.1% v/v; B:ACN] B%: 25%-65%, 8min]) to give 4,4-dimethyl-7-(trifluoromethyl)-1H-[2,4'-biisoquinoline]-1,3(4H)-dione **(10)**. **LCMS (Method 1):** $t_R$ = 2.531 min, $[M+1]^+$ 385.1. **$^1$H NMR:** (400 MHz, DMSO-$d_6$) δ = 9.43 (s, 1H), 8.53 (s, 1H), 8.34 (s, 1H), 8.29 - 8.26 (m, 1H), 8.21 - 8.17 (m, 1H), 8.15 - 8.08 (m, 1H), 7.89 (d, *J* = 7.6 Hz, 1H), 7.82 - 7.72 (m, 2H), 1.80 (s, 3H), 1.77 (s, 3H).

**Example 11:** Synthesis of 8-fluoro-3-(isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(11)**

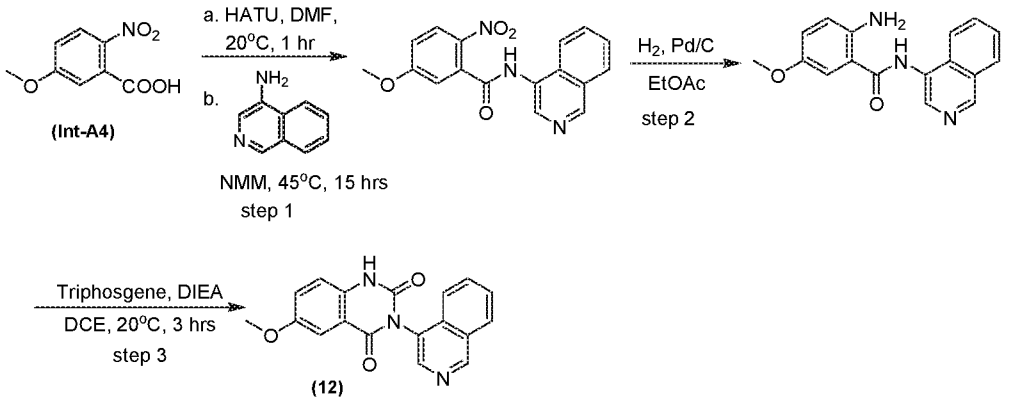



Step 1: A mixture of 2-amino-3-fluoro-5-(trifluoromethyl)benzoic acid **(Int-A3)** (790 mg, 3.54 mmol, 1.0 eq.), HATU (1.03 g, 4.25 mmol, 1.2 eq.) in DMF (10 mL) was stirred at 20°C for 1 hr. Isoquinolin-4-amine (533 mg, 3.89 mmol, 1.1 mmol) and NMM (563 mg, 10.62 mmol, 3.0 eq.) were then added at 20°C and the mixture was stirred at 45°C for 15 hrs. The reaction mixture was quenched with water (20 mL) and extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (50 mL), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give a residue which was purified by silica gel chromatography ($SiO_2$, Petroleum ether/Ethyl acetate=50/1 to 0/1) to obtain 2-amino-3-fluoro-N-(isoquinolin-4-yl)-5-(trifluoromethyl)benzamide. **LCMS (Method 7):** $t_R$ = 0.556 min, $[M+1]^+$ 350.3. **$^1$H NMR:** (400MHz, DMSO-d6) δ = 10.63 (s, 1H), 9.27 (s, 1H), 8.56 (s, 1H), 8.22 - 8.17 (m, 2H), 7.97 (d,

J=8.3 Hz, 1H), 7.87 - 7.80 (m, 1H), 7.78 - 7.71 (m, 1H), 7.66 (dd, J=1.6, 11.5 Hz, 1H), 7.08 (s, 2H).

Step 2: A solution of triphosgene (382 mg, 1.29 mmol, 1.5 eq.) in THF (2.0 mL) was added dropwise to a solution of 2-amino-3-fluoro-N-(isoquinolin-4-yl)-5-(trifluoromethyl)benzamide (300 mg, 0.86 mmol, 1.0 eq.) and DIEA (220 mg, 1.70 mmol, 2.0 eq.) in THF (8.0 mL) at 0°C under $N_2$. The mixture was stirred at 25°C for 16 hrs. The reaction mixture was quenched with $NaHCO_3$ (20 mL) and extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (20 mL x 2), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give crude product which was purified by prep-HPLC (column: Phenomenex Luna C18 200mmx40mm, 10μm; liquid phase: [A:$H_2O$ (0.1%FA); B:ACN] B%: 10%-50%, 20min) to give 8-fluoro-3-(isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(11)**. **LCMS (Method 1):** $t_R$ = 0.576 min, $[M+1]^+$ 376.2. **$^1$H NMR:** (400MHz, DMSO-d6) δ = 12.34 (br s, 1H), 9.44 (s, 1H), 8.56 (s, 1H), 8.28 (br d, *J*=7.1 Hz, 1H), 8.18 (br d, *J*=10.5 Hz, 1H), 8.06 - 7.96 (m, 2H), 7.76-7.80(m, 2H).

**Example 12:** Synthesis of 3-(isoquinolin-4-yl)-6-methoxyquinazoline-2,4(1H,3H)-dione **(12)**



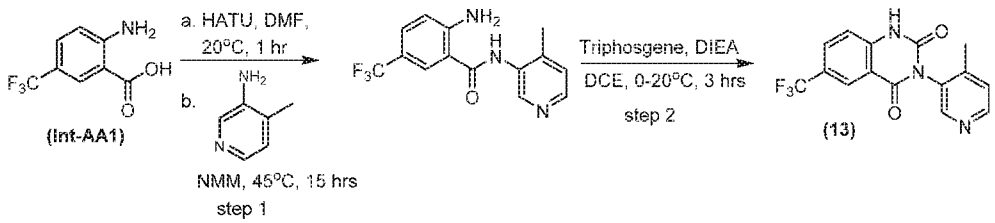

Step 1: HATU (4.6 g, 12.17 mmol, 1.2 eq.) was added to a mixture of 5-methoxy-2-nitrobenzoic acid **(Int-AA4)** (2.0 g, 10.15 mmol, 1.0 eq.) in DMF (20 mL) and the mixture stirred at 20°C for 1 hr. Isoquinolin-4-amine (1.6 mg, 11.16 mmol, 1.1 eq.) and NMM (4.6 g, 15.83 mmol, 3.0 eq.) were added and the mixture then stirred at 45°C for 15 hrs. The mixture was poured into water (40 mL), filtered and the filtered solids were washed to give crude product. The crude product was suspended in EtOH (20 mL) and stirred for 30 min. The suspension was filtered and the the filtered solids were washed to give N-(isoquinolin-4-yl)-5-methoxy-2-nitrobenzamide. **LCMS (Method 8):** $t_R$ = 0.460 min, $[M+1]^+$ 324.1. **$^1$H NMR:** (400MHz, DMSO-$d_6$) δ = 10.73 (s, 1H), 9.24 (s, 1H), 8.80 (s, 1H), 8.26 (d, *J*=9.2 Hz, 1H), 8.19 (dd, *J*=3.3, 8.3 Hz, 2H), 7.90 - 7.71 (m, 2H), 7.44 (d, *J*=2.8 Hz, 1H), 7.28 (dd, *J*=2.8, 9.2 Hz, 1H), 3.99 (s, 3H).

Step 2: A mixture of N-(isoquinolin-4-yl)-5-methoxy-2-nitrobenzamide (1.0 g, 3.09 mmol, 1.0 eq.) and Pd/C (500 mg, 10%) in EtOAc (50 mL) was purged with $H_2$ (3x) and then stirred at 30°C for

5 hrs under $H_2$ (50 psi). The mixture was filtered and the filtrate was concentrated to give 2-amino-N-(isoquinolin-4-yl)-5-methoxybenzamide. **LCMS (Method 9):** $t_R$ = 0.779 min, $[M+1]^+$ 294.2. **$^1$H NMR:** (400MHz, DMSO-$d_6$) δ = 10.29 (br s, 1H), 9.24 (s, 1H), 8.57 (s, 1H), 8.19 (d, *J*=8.2 Hz, 1H), 7.97 (d, *J*=8.4 Hz, 1H), 7.82 (t, *J*=7.3 Hz, 1H), 7.76 - 7.69 (m, 1H), 7.46 (d, *J*=2.8 Hz, 1H), 6.97 (dd, *J*=2.8, 8.9 Hz, 1H), 6.77 (d, *J*=8.9 Hz, 1H), 6.10 - 5.99 (m, 2H), 3.77 (s, 3H).

Step 3: DIEA (106 mg, 0.82 mmol, 2.0 eq.) and triphosgene (181 mg, 0.61 mmol, 1.5 eq.) were added to a solution of 2-amino-N-(isoquinolin-4-yl)-5-methoxybenzamide (120 mg, 0.41 mmol, 1.0 eq.) in DCE (2 mL) and the mixture was stirred at 20°C for 3 hrs. The mixture was concentrated to give crude product which was purified by prep-HPLC (column: Phenomenex Gemini-NX C18 75mmx30mm, 3µm; liquid phase: [A:10mM $NH_4HCO_3$ in $H_2O$; B:ACN]; B%: 20%-40%, 8min]) to give 3-(isoquinolin-4-yl)-6-methoxyquinazoline-2,4(1H,3H)-dione **(12)**. **LCMS (Method 1):** $t_R$ = 1.820 min, $[M+1]^+$ 320.1. **$^1$H NMR:** (400 MHz, DMSO-d6) δ = 11.69 - 11.60 (m, 1H), 9.42 (s, 1H), 8.56 - 8.52 (m, 1H), 8.30 - 8.24 (m, 1H), 7.81 - 7.72 (m, 3H), 7.44 - 7.37 (m, 2H), 7.27 (d, J = 8.7 Hz, 1H), 3.81 (s, 3H).

**Example 13:** Synthesis of 3-(4-methylpyridin-3-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(13)**

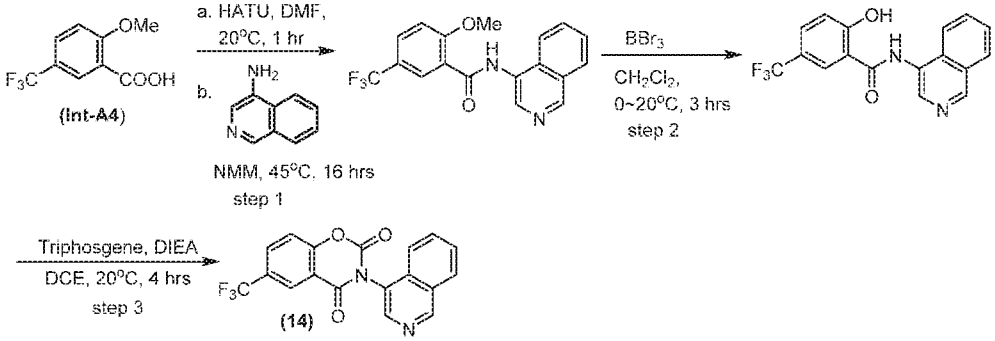



Step 1: HATU (1.1 g, 2.93 mmol, 1.2 eq.) was added to a solution of 2-amino-5-(trifluoromethyl)benzoic acid **(Int-AA1)** (500 mg, 2.44 mmol, 1.0 eq.) in DMF (8 mL) and the mixture was stirred at 20°C for 1 hr. 4-methylpyridin-3-amine (CAS No. 3430-27-1) (527 mg, 4.78 mmol, 2.0 eq.) and NMM (740 mg, 7.32 mmol, 3.0 eq.) were then added and the mixture stirred at 45°C for 15 hrs. The mixture was poured into water (15 mL) and extracted with EtOAc (20 mL x 3). The combined organic phases were washed with brine, dried over $Na_2SO_4$, filtered and concentrated to give crude product which was purified by prep-HPLC (column: Kromasil C18 (250mmx50mm, 10µm); liquid phase: [A:$H_2O$ (10mM $NH_4HCO_3$); B:ACN] B%: 20%-60%, 20 min]) to give 2-amino-N-(4-methylpyridin-3-yl)-5-(trifluoromethyl)benzamide. **LCMS (Method 10):** $t_R$ = 0.451 min, $[M+1]^+$ 296.0.

Step 2: DIEA (174 mg, 1.35 mmol, 2.0 eq.) and triphosgene (302 mg, 1.02 mmol, 1.5 eq.) were added to a solution of 2-amino-N-(4-methylpyridin-3-yl)-5-(trifluoromethyl)benzamide (200 mg, 0.67 mmol, 1.0 eq.) in DCE (3 mL) at 0°C and the mixture stirred at 20°C for 3 hrs. The reaction mixture was dried under nitrogen gas to give crude product which was purified by prep-HPLC (column: Phenomenex Gemini-NX C18 75mmx30mm, 3µm; liquid phase: [A:10mM $NH_4HCO_3$ in

$H_2O$; B:ACN] B%: 20%-40%, 8 min]) to give 3-(4-methylpyridin-3-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(13)**. **LCMS (Method 2):** $t_R$ = 2.288 min, $[M+1]^+$ 322.0. **$^1$H NMR:** (400MHz, DMSO-d6) δ = 8.46 (d, J=5.0 Hz, 1H), 8.38 (s, 1H), 8.12 (s, 1H), 7.95 (dd, J=1.9, 8.6 Hz, 1H), 7.41 (d, J=5.0 Hz, 1H), 7.34 (d, J=8.6 Hz, 1H), 5.78 (br s, 1H), 2.10 (s, 3H).

**Example 14:** Synthesis of 3-(isoquinolin-4-yl)-6-(trifluoromethyl)-2H-benzo[e][1,3]oxazine-2,4(3H)-dione **(14)**



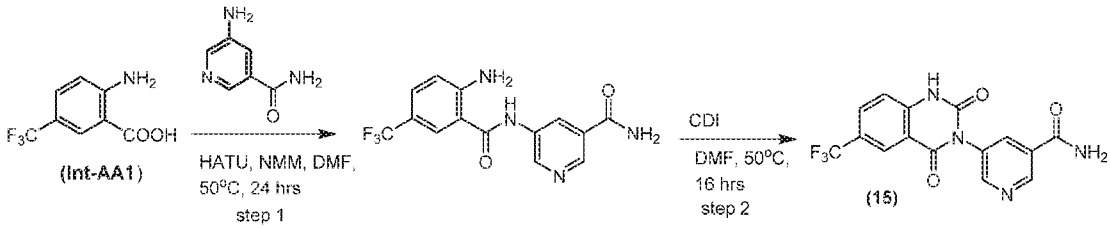

Step 1: HATU (1.8 g, 4.80 mmol, 1.2 eq.) and DMF (10 mL) were added to a solution of 2-methoxy-5-(trifluoromethyl)benzoic acid **(Int-A4)** (880 mg, 4.00 mmol, 1.0 eq.) at 20°C and the mixture was stirred at 20°C for 1 hr. Isoquinolin-4-amine (692 mg, 4.80 mmol, 1.2 eq.) and NMM (1.2 g, 12.00 mmol, 3.0 eq.) were added and the mixture was stirred at 45°C for 16 hrs under $N_2$. The mixture was poured into $H_2O$ (30 mL) and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (50 mL x 2), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give a residue. The residue was suspended in Petroleum ether/ EtOAc (5/1, 10 mL) and stirred for 30 min. The suspension was filtered, the filter cake was dried to give N-(isoquinolin-4-yl)-2-methoxy-5-(trifluoromethyl)benzamide. **LCMS (Method 10):** $t_R$ = 0.690 min, $[M+1]^+$ 346.9. **$^1$H NMR:** (400 MHz, CHLOROFORM-d) δ = 10.08 (br s, 1H), 9.27 (s, 1H), 9.17 (br s, 1H), 8.67 (d, *J* = 2.0 Hz, 1H), 8.06 (d, *J* = 8.3 Hz, 1H), 7.92 (d, *J* = 8.5 Hz, 1H), 7.86 - 7.77 (m, 2H), 7.73 - 7.65 (m, 1H), 7.23 (d, *J* = 8.8 Hz, 1H), 4.25 (s, 3H).

Step 2: $BBr_3$ (751 mg, 3.03 mmol, 1.5 eq.) was added to a solution of N-(isoquinolin-4-yl)-2-methoxy-5-(trifluoromethyl)benzamide (700 mg, 2.02 mmol, 1.0 eq.) in $CH_2Cl_2$ (7 mL) at 0°C and the mixture stirred at 20°C for 3 hrs. The mixture was poured into water (50 mL) and extracted with EtOAc (50 mL x 3). The combined organic phase was dried over $Na_2SO_4$, filtered and concentrated to give crude product which was purified by silica gel chromatography ($SiO_2$, EtOAc /Petroleum ether = 50%~80%) to give 2-hydroxy-N-(isoquinolin-4-yl)-5-(trifluoromethyl)benzamide. **LCMS (Method 5):** $t_R$ = 0.807 min, $[M+1]^+$ 333.0. **$^1$H NMR:** (400 MHz, DMSO-$d_6$) δ = 11.15 (s, 1H), 9.57 (s, 1H), 9.16 (s, 1H), 8.46 (d, *J* = 8.3 Hz, 1H), 8.32 (d, *J*

= 2.1 Hz, 1H), 8.26 (d, *J* = 8.5 Hz, 1H), 8.15 (dt, *J* = 1.1, 7.7 Hz, 1H), 7.98 (t, *J* = 7.3 Hz, 1H), 7.86 (dd, *J* = 2.1, 8.8 Hz, 1H), 7.28 (d, *J* = 8.8 Hz, 1H).

Step 3: Triphosgene (353 mg, 1.20 mmol, 1.0 eq.) was added to a solution of 2-hydroxy-N-(isoquinolin-4-yl)-5-(trifluoromethyl)benzamide (400 mg, 1.20 mmol, 1.0 eq.) and DIEA (310 mg, 2.40 mmol, 2.0 eq.) in $CH_2Cl_2$ (5mL) at 20°C and the mixture was stirred at 20°C for 4 hrs. The mixture was poured into water (20 mL) and extracted with EtOAc (25 mL x 3). The combined organic layers were washed with brine (20 mL x 2), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 75mmx30mm, 3μm; liquid phase: [A:FA/$H_2O$=0.1% v/v; B:ACN] B%: 20%-60%, 8min]) to give 3-(isoquinolin-4-yl)-6-(trifluoromethyl)-2H-benzo[e][1,3]oxazine-2,4(3H)-dione **(14)**. **LCMS (Method 1):** $t_R$ = 2.455 min, $[M+1]^+$ 359.0. **$^1$H NMR:** (400 MHz, CHLOROFORM-d) δ = 9.44 (s, 1H), 8.58 (s, 1H), 8.48 (d, *J* = 1.7 Hz, 1H), 8.18 (d, *J* = 8.2 Hz, 1H), 8.09 (dd, *J* = 1.9, 8.7 Hz, 1H), 7.84 - 7.70 (m, 2H), 7.59-7.65 (m, 2H).

**Example 15:** Synthesis of 5-(2,4-dioxo-6-(trifluoromethyl)-1,4-dihydroquinazolin-3(2H)-yl)nicotinamide **(15)**

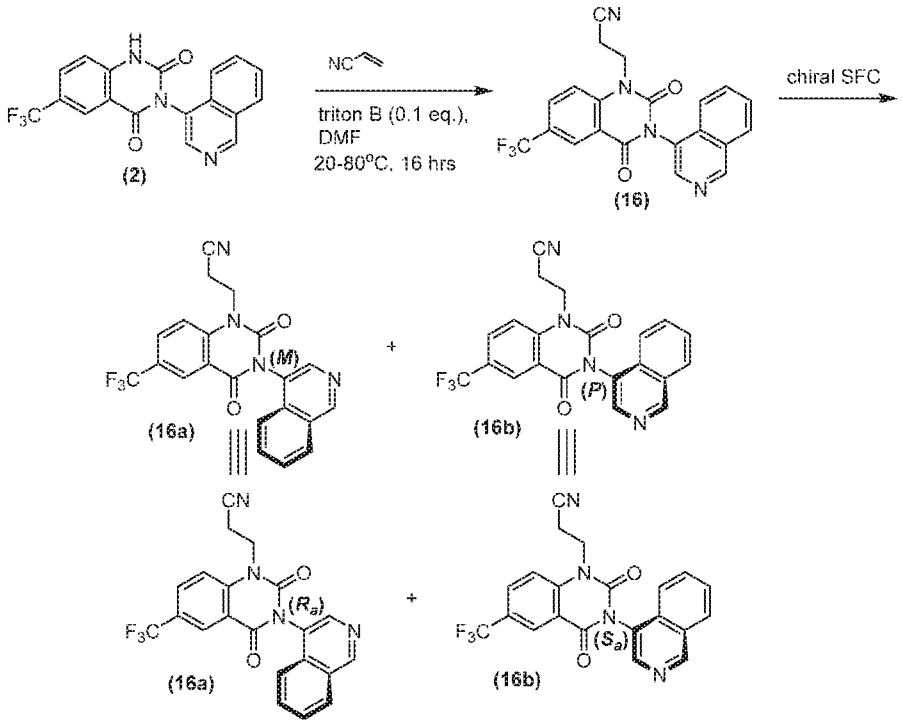



Step 1: 2-amino-5-(trifluoromethyl)benzoic acid **(Int-AA1)** (2.0 g, 9.75 mmol, 1.0 eq.), 5-aminonicotinamide (CAS No. 60524-14-3) (1.5 g, 10.72 mmol, 1.1 eq.), HATU (5.6 g, 14.63 mmol, 1.5 eq.) and NMM (1.5 g, 14.63 mmoL, 1.5 eq.) in DMF (20 mL) were stirred at 50°C for 24 hrs. The solution was poured into water (60 mL) and extracted with EtOAc (20 mL x 3). The combined organic layers were washed with water (30 mL), brine (30 mL), dried over $Na_2SO_4$, filtered and concentrated to give crude product which was purified by silica gel chromatography ($SiO_2$, $CH_2Cl_2$/MeOH = 100/1, 50/1 to 10/1) to obtain 5-(2-amino-5-(trifluoromethyl)benzamido)nicotinamide. **LCMS (Method 1):** $t_R$ = 0.585 min, $[M+1]^+$ 325.1. **$^1$H NMR:** (400 MHz, DMSO-$d_6$) δ = 10.51 (br s, 1H), 9.00 (d, *J*=2.5 Hz, 1H), 8.79 (d, *J*=1.8 Hz, 1H), 8.54 (t, *J*=2.2 Hz, 1H), 8.17 (br s, 1H), 8.05 (s, 1H), 7.61 (br s, 1H), 7.51 (dd, *J*=8.7, 1.8 Hz, 1H), 7.08 (s, 2H), 6.92 (d, *J*=8.7 Hz, 1H).

Step 2: 5-(2-amino-5-(trifluoromethyl)benzamido)nicotinamide (300 mg, 0.93 mmol, 1.0 eq.) and CDI (150 mg, 0.93 mmol, 1.0 eq.) in DMF (6 mL)were stirred at 50°C for 16 hrs. The mixture was directly purified by prep HPLC (column: Phenomenex Luna C18 75mmx30mm, 3μm; mobile phase: [water(0.2%FA)-ACN];B%: 20%-40%,8min ) to obtain 5-(2,4-dioxo-6-(trifluoromethyl)-1,4-dihydroquinazolin-3(2H)-yl)nicotinamide **(15)**. **LCMS (Method 1):** $t_R$ = 1.949

min, $[M+1]^+$ 351.1. **$^1$H NMR:** (400 MHz, DMSO-$d_6$) δ = 12.09 (s, 1H), 9.09 (d, *J*=1.9 Hz, 1H), 8.71 (d, *J*=2.2 Hz, 1H), 8.25 (t, *J*=2.0 Hz, 2H), 8.18 (s, 1H), 8.08 (dd, *J*=8.6, 1.9 Hz, 1H), 7.71 (s, 1H), 7.44 (d, *J*=8.6 Hz, 1H).

**Example 16:** Synthesis of 3-(3-(isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2H)-yl)propanenitrile **(16)**, 3-[(3*M*)-3-(Isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2*H*)-yl]propanenitrile **(16a)** and 3-[(3*P*)-3-(Isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2*H*)-yl]propanenitrile **(16b)**




To a solution of 3-(isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(2)** (400 mg, 1.12 mmol, 1.0 eq.) in DMF (5 mL) was added triton B (18 mg, 0.11 mmol, 0.1 eq.) and acrylonitrile (1.2 g, 47.03 mmol, 20.0 eq.) in turn at 20°C. The mixture was stirred at 80°C for 16 hrs under $N_2$. The reaction mixture was filtered and the filtrate purified by prep-HPLC (column: Phenomenex luna C18 (250mmx70mm, 15μm); liquid phase: [A:$H_2O$ (0.1% HCOOH); B:ACN] B%: 30%-60%, 20 min]) to give racemate 3-(3-(isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2H)-yl)propanenitrile **(16)**. **LCMS (Method 10):** $t_R$ = 0.693 min, $[M+1]^+$ 411.2.

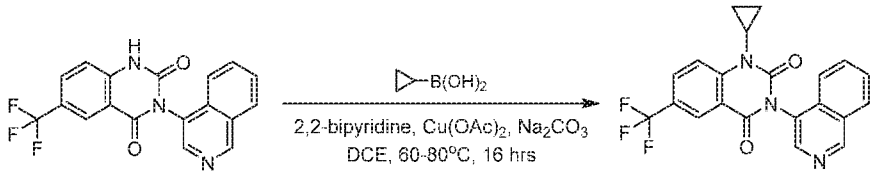
The racemate **(16)** was separated by SFC (column: DAICEL CHIRALCEL OD (250mmx30mm, 10μm); liquid phase: [0.1%$NH_3H_2O$ MeOH B%: 50%, 7 min]) to give 2 peaks. $t_{R1}$ = 1.300 min and $t_{R2}$ = 1.413 min

**Peak 1:** 3-[(3*M*)-3-(Isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2*H*)-yl]propanenitrile **(16a)**; alternatively 3-[(3$R_a$)-3-(Isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2*H*)-yl]propanenitrile **(16a)**

The absolute configuration (*M*) (alternatively ($R_a$)) was confirmed by the X-ray crystal structure of compound (16a) bound to the $M^{pro}$ protein. **LCMS (Method 13):** $t_R$ = 2.322 min, $[M+1]^+$ 411.0. **SFC:** (column: Chiralcel OD-3 (50mmx4.6mm, 3µm); mobile phase: [0.1% $NH_3H_2O$ EtOH]; B%: 5% for 0.2 min, 5-50% for 1.0 min., 50% for 1.0 min., 50-5% for0.4 min., 5% for 0.4 min), $t_R$ = 1.311 min, 98.92%. **$^1$H NMR:** (400 MHz, DMSO-$d_6$) δ = 9.45 (s, 1H), 8.56 (s, 1H), 8.32 (d, *J* = 1.3 Hz, 1H), 8.30 - 8.26 (m, 1H), 8.23 (dd, *J* = 2.0, 8.9 Hz, 1H), 8.03 (d, *J* = 8.9 Hz, 1H), 8.00 - 7.95 (m, 1H), 7.80 - 7.74 (m, 2H), 4.63 - 4.42 (m, 2H), 2.99 (t, *J* = 6.7 Hz, 2H).

**Peak 2:** 3-[(3*P*)-3-(Isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2*H*)-yl]propanenitrile **(16b)**; alternatively 3-[(3$S_a$)-3-(Isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2*H*)-yl]propanenitrile **(16b): LCMS (Method 13):** $t_R$ = 1.772 min, $[M+1]^+$ (411.0). **SFC:** (column: Chiralcel OD-3 (50mmx4.6mm, 3µm); mobile phase: [0.1% $NH_3H_2O$ EtOH]; B%: 5% for 0.2 min, 5-50% for 1.0 min., 50% for 1.0 min., 50-5% for0.4 min., 5% for 0.4 min), $t_R$ = 1.428 min, 99.20%. **$^1$H NMR:** (400 MHz, DMSO-$d_6$) δ = 9.48 (s, 1H), 8.58 (s, 1H), 8.34 (d, *J* = 1.7 Hz, 1H), 8.32 - 8.28 (m, 1H), 8.25 (dd, *J* = 2.1, 9.0 Hz, 1H), 8.05 (d, *J* = 8.9 Hz, 1H), 8.02 - 7.97 (m, 1H), 7.84 - 7.75 (m, 2H), 4.65 - 4.46 (m, 2H), 3.01 (t, *J* = 6.8 Hz, 2H).

**Example 17:** Synthesis of 1-cyclopropyl-3-(isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(16)**

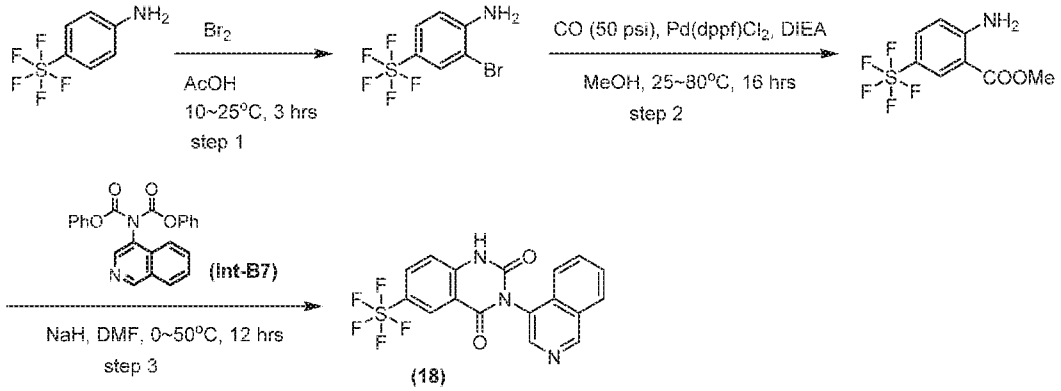



(2) (17)

To a solution of 2,2-bipyridine (109 mg, 0.70 mmol, 1.0 eq.) in DCE (2 mL) was added $Cu(OAc)_2$ (140 mg, 0.70 mmol, 1.0 eq.) and the mixture was stirred at 60°C. To the mixture was added 3-(isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(2)** (250 mg, 0.70 mmol, 1.0 eq.), cyclopropylboronic acid (120 mg, 1.40 mmol, 2.0 eq.) and $Na_2CO_3$ (148 mg, 1.40 mmol, 2.0 eq.). The mixture was stirred at 80°C for 16 hrs under $O_2$. The mixture was quenched with $H_2O$ (10 mL), extracted with EtOAc (10 mL x 2). The organic phase was washed with brine (30 mL), dried over $Na_2SO_4$, filtered and evaporated to give crude product. The crude product was purified by prep-HPLC (column: Kromasil C18 (250mmx50mm, 10µm); liquid phase: [A:$H_2O$ (10 mM $NH_4HCO_3$); B:ACN] B%: 40% - 70%, 20 min]) to give 1-cyclopropyl-3-(isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(17)**. **LCMS (Method 2):** $t_R$ = 2.227 min, $[M+1]^+$ 398.0. **$^1$H NMR:** (400MHz, CHLOROFORM-*d*) δ = 9.44 (br s, 1H), 8.53 (s, 2H), 8.16 (d, *J*=8.2

Hz, 1H), 8.04 - 8.00 (m, 1H), 7.96 - 7.93 (m, 1H), 7.80 - 7.70 (m, 2H), 7.59 (d, *J*=8.2 Hz, 1H), 3.03 (tt, *J*=3.6, 7.0 Hz, 1H), 1.42 - 1.37 (m, 2H), 1.11 - 0.97 (m, 2H)

**Example 18:** Synthesis of 3-(isoquinolin-4-yl)-6-(pentafluoro-λ$^6$-sulfaneyl)quinazoline-2,4(1H,3H)-dione **(18)**



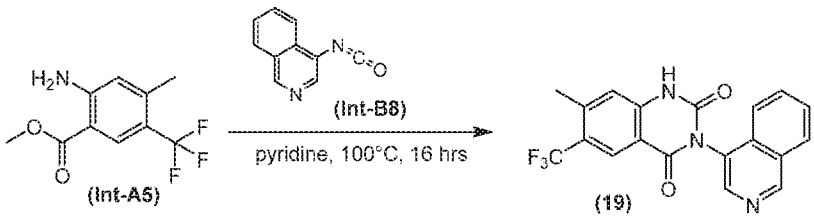

Step 1: To a mixture of 4-(pentafluoro-λ$^6$-sulfaneyl)aniline (2.0 g, 9.13 mmol, 1.0 eq.) in AcOH (60 mL) was added a solution of $Br_2$ (1.6 g, 10.04 mmol, 1.1 eq.) in AcOH (20 mL) at 10°C. The mixture was stirred at 25°C for 3 hrs. The reaction was quenched with $H_2O$ (140 mL) and extracted with EtOAc (80 mL × 2). The combined organic layers were washed with saturated aqueous $Na_2CO_3$ (150 mL), brine (100 mL × 2), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give crude product. The crude product was purified by flash silica gel chromatography (40 g, Eluent of 0~20% Ethyl acetate/Petroleum ether, 80 mL/min) to give 2-bromo-4-(pentafluoro-λ$^6$-sulfaneyl)aniline. **$^1$H NMR:** (400 MHz, CHLOROFORM-*d*) δ = 7.82 (d, *J* = 2.5 Hz, 1H), 7.50 (dd, *J* = 2.4, 8.9 Hz, 1H), 6.72 (d, *J* = 8.9 Hz, 1H), 4.46 (br s, 2H).

Step 2: To a mixture of 2-bromo-4-(pentafluoro-λ$^6$-sulfaneyl)aniline (1.9 g, 6.37 mmol, 1.0 eq.) in MeOH (60 mL) was added $Pd(dppf)Cl_2$ (470 mg, 0.64 mmol, 0.1 eq.) and DIEA (1.6 g, 12.74 mmol, 2.0 eq.) at 25°C. The mixture was stirred at 80°C for 16 hrs under CO (50 psi). The mixture was filtered and the filtrate was concentrated to give crude product. The crude product was purified by flash silica gel chromatography (20 g, Eluent of 0~30% Ethyl acetate/Petroleum ether, 80 mL/min) to give methyl 2-amino-5-(pentafluoro-λ$^6$-sulfaneyl)benzoate. **LCMS (Method 5):** $t_R$ = 1.016 min, $[M+1]^+$ 278.0. **$^1$H NMR:** (400 MHz, CHLOROFORM-*d*) δ = 8.28 (d, *J* = 2.8 Hz, 1H), 7.60 (dd, *J* = 2.6, 9.1 Hz, 1H), 6.64 (d, *J* = 9.1 Hz, 1H), 3.92 (s, 3H).

Step 3: To a mixture of NaH (222 mg, 60%, 5.56 mmol, 1.1 eq.) in DMF (16 mL) was added a solution of methyl 2-amino-5-(pentafluoro-λ$^6$-sulfaneyl)benzoate (1.4 g, 5.05 mmol, 1.0 eq.) in DMF (4 mL) at 0°C under $N_2$. The mixture was stirred at 0°C for 0.5 hrs under $N_2$. Phenyl isoquinolin-4-yl(phenoxycarbonyl)carbamate **(Int-B7)** (1.9 g, 5.05 mmol, 1.0 eq.) in DMF (4 mL) was then added to the mixture at 0°C and the mixture was stirred at 50°C for 12 hrs under $N_2$. The reaction was quenched with saturated aqueous $NH_4Cl$ (100 mL) and extracted with EtOAc

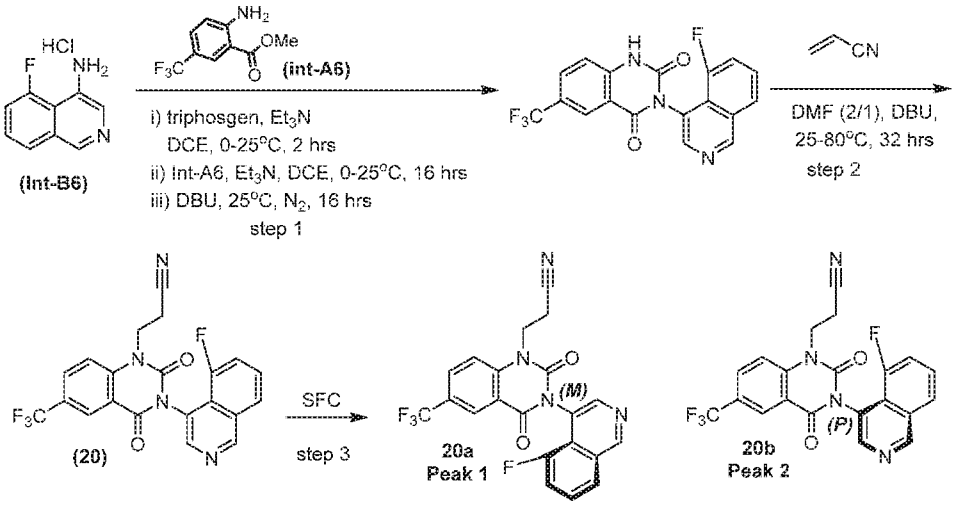
(30 mL × 2). The combined organic layers were washed with brine (120 mL × 2), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give crude product. The crude product was purified by prep-HPLC (column: Phenomenex luna C18 (250mmx70mm, 15μm); liquid phase: [A:$H_2O$ (0.1% HCOOH); B:ACN] B%: 40%-60%, 20 min]) to give 3-(isoquinolin-4-yl)-6-(pentafluoro-$\lambda^6$-sulfaneyl)quinazoline-2,4(1H,3H)-dione **(18)**. **LCMS (Method 13):** $t_R$ = 2.361 min, $[M+1]^+$ 415.9. **$^1$H NMR:** (400 MHz, DMSO-$d_6$) δ = 12.21 (s, 1H), 9.44 (s, 1H), 8.56 (s, 1H), 8.32 - 8.24 (m, 3H), 8.02 - 7.95 (m, 1H), 7.82 - 7.71 (m, 2H), 7.46 (br d, *J* = 9.7 Hz, 1H).

**Example 19:** Synthesis of 3-(isoquinolin-4-yl)-7-methyl-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(19)**




A mixture of 4-isocyanatoisoquinoline **(Int-B8)** (569 mg, 3.34 mmol, 3.0 eq.) and methyl 2-amino-4-methyl-5-(trifluoromethyl)benzoate **(Int-A5)** (260 mg, 1.11 mmol, 1.0 eq.) in pyridine (3 mL) was stirred at 100°C for 16 hrs. The reaction mixture was quenched with $H_2O$ (20 mL). The reaction mixture was extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with brine (20 mL x 3), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex luna C18 80mmx40mm, 3μm; liquid phase: [A:$H_2O$= (0.04%HCl); B:ACN] B%: 35%-55%,20min]) to give 3-(isoquinolin-4-yl)-7-methyl-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(19)**. **HPLC:** $t_R$ = 2.412 min. **LCMS (Method 13):** $t_R$ = 2.265 min, $[M+1]^+$ 372.0. **$^1$H NMR:** (400MHz, DMSO-$d_6$) δ = 12.20 (s, 1H), 9.70 (s, 1H), 8.74 (s, 1H), 8.44 (d, *J*=8.1 Hz, 1H), 8.14 (s, 1H), 8.10 (d, *J*=8.3 Hz, 1H), 7.96 (t, *J*=7.5 Hz, 1H), 7.93 - 7.87 (m, 1H), 7.34 (s, 1H), 2.57 (s, 3H)

**Example 20:** Synthesis of 3-(3-(5-fluoroisoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2H)-yl)propanenitrile **(20)**;
3-[(3*M*)-3-(5-Fluoroisoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2*H*)-yl]propanenitrile **(20a)**, and
3-[(3*P*)-3-(5-Fluoroisoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2*H*)-yl]propanenitrile **(20b)**




Step 1: To a mixture of 5-fluoroisoquinolin-4-amine hydrochloride **(Int-B6)** (9.1 g, 41.47 mmol, 1.0 eq.) and $Et_3N$ (12.2 g, 120.96 mmol, 3.5 eq.) in DCE (80 mL) was added a mixture of triphosgen (10.2 g, 34.56 mmol, 1.0 eq.) in DCE (20 mL) at 0°C. The mixture was stirred at 25°C for 2 hrs. Then a mixture of methyl 2-amino-5-(trifluoromethyl)benzoate **(int-A6)** (5.6 g, 34.56 mmol, 0.9 eq.) and $Et_3N$ (12.2 g, 120.96 mmol, 3.5 eq.) in DCE (20 mL) was added to the mixture at 0°C. The mixture was stirred at 25°C for 16 hrs. DBU (10.5 g, 69.12 mmol, 2.0 eq.) was added to the mixture at 25°C. The mixture was stirred at 25°C for 16 hrs. The reaction was quenched with $H_2O$ (150 mL) and extracted with DCM (100 mL × 2). The combined organic layers were dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give crude product. The crude product was purified by MPLC (petroleum ether/THF = 20/1 to 1/1) to give product 3-(5-fluoroisoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione. **$^1$H NMR:** (400 MHz, DMSO-$d_6$) δ = 12.45 - 12.02 (m, 1H), 9.53 (d, *J* = 2.4 Hz, 1H), 8.62 (s, 1H), 8.21 (s, 1H), 8.17 (d, *J* = 8.0 Hz, 1H), 8.12 (dd, *J* = 1.9, 8.7 Hz, 1H), 7.77 (t, *J* = 5.0, 8.0 Hz, 1H), 7.63 (dd, *J* = 7.7, 12.9 Hz, 1H), 7.50 (d, *J* = 8.6 Hz, 1H).

Step 2: To a solution of 3-(5-fluoroisoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione (500 mg, 1.33 mmol, 1.0 eq.) in DMF (2 mL) was added DBU (400 mg, 2.66 mmol, 2.0 eq.) and acrylonitrile (8 mL) at 25°C. The mixture was stirred at 80°C for 32 hrs. The mixture was poured into water (80 mL) and extracted with EtOAc (50 mL x 2). The combined organic layers were washed with brine (50 mL), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give crude product. The crude product was purified by MPLC (petroleum ether/THF = 20/1 to 1/2) to give 3-(3-(5-fluoroisoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2H)-yl)propanenitrile **(20)** as a racemate. **LCMS (Method 10):** $t_R$ = 1.714 min. $[M+1]^+$ 429.1.

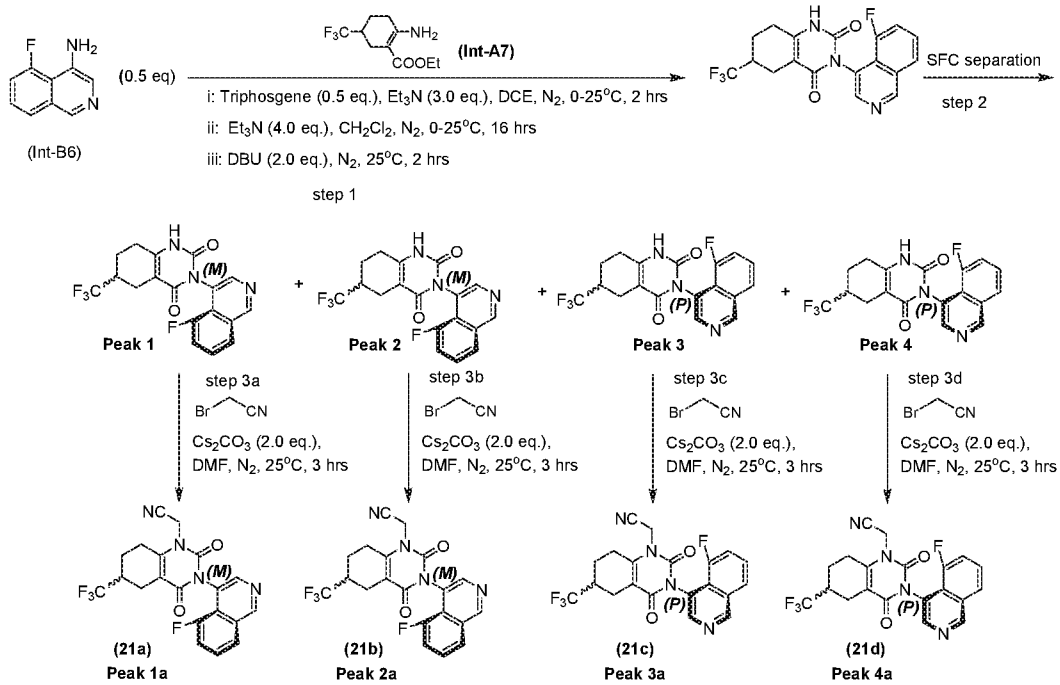
Step 3: The racemate **(20)** was separated by SFC (DAICEL CHIRALPAK AD (250mmx50mm,10um); liquid phase: 0.1%$NH_3H_2O$ EtOH]B%: 10%-70%,8min]) to give 2 peaks: peak 1 and peak 2. **SFC:** peak 1: $t_R$ = 1.196 min.; peak 2: $t_R$ = 1.468 min. Stereochemistry

assigned by analogy to Example 16, wherein the chirality of the more active atropisomer(s) is assigned as ***(M)*** and subsequently the chirality of the more active atropisomer(s) is assigned as ***(P)***.

**Peak 1: 3-[(3*M*)-3-(5-Fluoroisoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2*H*)-yl]propanenitrile (20a): LCMS (Method 13):** $t_R$ = 2.434 min, $[M+1]^+$ 429.1. **SFC:** $t_R$ = 1.188 min, ee = 100%. **$^1$H NMR:** (400 MHz, CHLOROFORM-*d*) δ = 9.41 (d, *J*=1.6 Hz, 1 H) 8.59 (s, 1 H) 8.50 (s, 1 H) 8.04 (d, *J*=8.6 Hz, 1 H) 7.95 (d, *J*=8.2 Hz, 1 H) 7.63 (td, *J*=7.8, 4.9 Hz, 1 H) 7.54 (br d, *J*=8.8 Hz, 1 H) 7.37 (dd, *J*=12.5, 7.9 Hz, 1 H) 4.42 - 4.70 (m, 2 H) 2.93 (t, *J*=6.9 Hz, 2 H).

**Peak 2: 3-[(3*P*)-3-(5-Fluoroisoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2*H*)-yl]propanenitrile (20b):LCMS (Method 16):** $t_R$ = 2.375 mins, $[M+1]^+$ 429.1. **SFC:** $t_R$ = 1.453 min, ee = 97.6%. **$^1$H NMR:** (400 MHz, DMSO-$d_6$) δ = 9.55 (d, *J* = 2.4 Hz, 1H), 8.60 (s, 1H), 8.34 (s, 1H), 8.25 (dd, *J* = 2.2, 8.9 Hz, 1H), 8.19 (d, *J* = 8.3 Hz, 1H), 8.06 (d, *J* = 8.9 Hz, 1H), 7.82 - 7.73 (m, 1H), 7.64 (dd, *J* = 7.8, 12.8 Hz, 1H), 4.68 - 4.46 (m, 2H), 3.00 (t, *J* = 6.6 Hz, 2H).

**Example 21:** Synthesis of [(3*M*,6*R or 6S*)-3-(5-Fluoroisoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4,5,6,7,8-hexahydroquinazolin-1(2*H*)-yl]acetonitrile **(21a)**; [(3*M*,6*R or 6S*)-3-(5-Fluoroisoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4,5,6,7,8-hexahydroquinazolin-1(2*H*)-yl]acetonitrile **(21b)**; [(3*P*,6*R or 6S*)-3-(5-Fluoroisoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4,5,6,7,8-hexahydroquinazolin-1(2*H*)-yl]acetonitrile **(21c)**, and [(3*P*,6*R or 6S*)-3-(5-Fluoroisoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4,5,6,7,8-hexahydroquinazolin-1(2*H*)-yl]acetonitrile **(21d)**




Step 1: To a mixture of ethyl 2-amino-5-(trifluoromethyl)cyclohex-1-ene-1-carboxylate **(Int-A7)** (4.8 g, 20.14 mmol, 1.0 eq.) and $Et_3N$ (6.2 g, 60.42 mmol, 3.0 eq.) in DCE (200 mL) was added dropwise a solution of triphosgene (3.0 g, 10.07 mmol, 0.5 eq.) in DCE (20 mL) at 0°C. The mixture was stirred at 0°C under nitrogen for 2 hrs. Then a suspension of 5-fluoroisoquinolin-4-amine **(Int-B6)** (2.0 g, 10.07 mmol, 0.5 eq.) and $Et_3N$ (8.1 g, 80.56 mmol, 4.0 eq.) in DCE (60 mL) was added dropwise to the mixture at 0°C. The mixture was stirred at 25°C under nitrogen for 16 hrs. Then, DBU (6.2 g, 40.28 mmol, 2.0 eq.) was added to the mixture at 25°C. The mixture was stirred at 25°C under nitrogen for 2 hrs. The reaction was quenched with $H_2O$ (1000 mL). The reaction mixture was extracted with $CH_2Cl_2$ (300 mL × 3). The combined organic layers were washed with brine (300 mL), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give crude product. The crude was purified by flash silica gel chromatography (220 g SepaFlash® Silica Flash Column, Eluent of 70~100% Ethyl acetate/Petroleum ether gradient at 200 mL/min) to give racemic 3-(5-fluoroisoquinolin-4-yl)-6-(trifluoromethyl)-5,6,7,8-tetrahydroquinazoline-2,4(1H,3H)-dione. **LCMS (Method 12):** $t_R$ = 0.659 min, $[M+1]^+$ 380.1.

Step 2: Racemic 3-(5-fluoroisoquinolin-4-yl)-6-(trifluoromethyl)-5,6,7,8-tetrahydroquinazoline-2,4(1H,3H)-dione (890 mg, 2.35 mmol) was separated by chiral SFC (column: REGIS(S, S) WHELK-O1 (250mmx25mm, 10um); mobile phase: [0.1% $NH_3H_2O$ EtOH]; B%: 60%-60%, 8.5min) to obtain four peaks. **SFC:** $t_{R1}$ = 2.976 min., $t_{R2}$ = 3.239 min., $t_{R3}$ = 3.682 min., and $t_{R4}$ = 3.859 min.

**Peak 1: LCMS Method 12):** $t_R$ = 0.674 min, $[M+1]^+$ 380.2. **SFC:** (column: DAICEL CHIRALPAK AD (150mmx4.6 mm, 3µm); mobile phase: A: $CO_2$, B: EtOH(0.1% IPAm); 10%B for 0.5 min., 10-50%B, over 3.0 min., 50%B for 1.0 min. $t_R$ = 3.008 min, ee% = 100%.

**Peak 2: LCMS (Method 12):** $t_R$ = 0.663 min, $[M+1]^+$ 380.2. **SFC:** (column: DAICEL CHIRALPAK AD (150mmx4.6 mm, 3µm); mobile phase: A: $CO_2$, B: EtOH(0.1% IPAm); 10%B for 0.5 min., 10-50%B, over 3.0 min., 50%B for 1.0 min. $t_R$ = 3.264 min, ee% = 100%

**Peak 3: LCMS (Method 12):** $t_R$ = 0.669 min, $[M+1]^+$ 380.2. **SFC:** (column: DAICEL CHIRALPAK AD (150mmx4.6 mm, 3µm); mobile phase: A: $CO_2$, B: EtOH(0.1% IPAm); 10%B for 0.5 min., 10-50%B, over 3.0 min., 50%B for 1.0 min. $t_R$ = 3.695 min, ee% = 100%

**Peak 4: LCMS (Method 12):** $t_R$ = 0.672 min, $[M+1]^+$ 380.1. **SFC:** (column: DAICEL CHIRALPAK AD (150mmx4.6 mm, 3µm); mobile phase: A: $CO_2$, B: EtOH(0.1% IPAm); 10%B for 0.5 min., 10-50%B, over 3.0 min., 50%B for 1.0 min. $t_R$ = 3.862 min, ee% = 93.5%

Step 3a: To a solution of the compound from Peak 1 (70 mg, 0.18 mmol, 1.0 eq.) in DMF (1 mL) was added compound 2-bromoacetonitrile (33 mg, 0.28 mmol, 1.5 eq..) and $Cs_2CO_3$ (121 mg, 0.37 mmol, 2.0 eq..) at 25°C. The reaction was stirred at 25°C under $N_2$ for 3 hrs. The reaction was quenched with $H_2O$ (5 mL) and extracted with EtOAc (2 mL × 3). The combined organic layers were washed with brine (5 mL), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give crude product. The product was purified by prep-HPLC (Waters Xbridge Prep OBD C18 150mmx40mm, 10µm; liquid phase: [A:$H_2O$ (10mM $NH_4HCO_3$); B:ACN] B%: 25%-60%, 20min]) to obtain [(3*M*,6*R or 6S*)-3-(5-Fluoroisoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4,5,6,7,8-hexahydroquinazolin-1(2*H*)-yl]acetonitrile **(21a)-Peak 1a**. **LCMS (Method 17):** $t_R$ = 2.700 min, $[M+1]^+$ 419.1. **$^1$H NMR:** (400 MHz, CHLOROFORM-d) δ = 9.37 (d, *J* = 2.4 Hz, 1H), 8.42 (s, 1H), 7.92 (d, *J* = 7.8 Hz, 1H), 7.62 (dt, *J* = 4.8, 8.0 Hz, 1H), 7.42 - 7.34 (m, 1H), 4.92 (s, 2H), 3.04 - 2.80 (m, 3H), 2.56 - 2.36 (m, 3H), 2.02 - 1.88 (m, 1H)
**SFC:** (column: Lux Cellulose (50mmx4.6mm, 3µm); mobile phase: [0.1% $NH_3H_2O$ EtOH]; B%: 5% for 0.2 min, 5-50% for 1.0 min., 50% for 1.0 min., 50-5% for 0.4 min., 5% for 0.4 min), $t_R$ = 1.453 min, ee% = 98.0%.

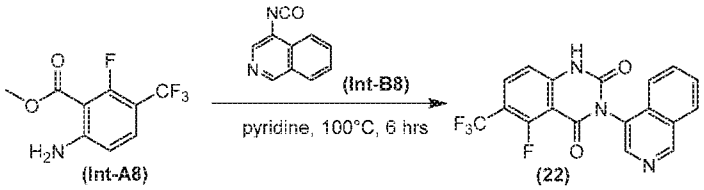
Step 3b: To a solution of the compound from Peak 2 (65 mg, 0.17 mmol, 1.0 eq.) in DMF (1 mL) was added 2-bromoacetonitrile (31 mg, 0.26 mmol, 1.5 eq.) and $Cs_2CO_3$ (112 mg, 0.34 mmol, 2.0 eq.) at 25°C. The reaction was stirred at 25°C under $N_2$ for 3 hrs. The reaction was quenched with $H_2O$ (5 mL) and extracted with EtOAc (2 mL × 3). The combined organic layers were washed with brine (5 mL), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give crude product. The product was purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150mmx40mm, 10µm; liquid phase: [A:$H_2O$ (10mM $NH_4HCO_3$); B:ACN] B%: 25%-60%, 20min]) to obtain [(3*M*,6*R or 6S*)-3-(5-Fluoroisoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4,5,6,7,8-hexahydroquinazolin-1(2*H*)-yl]acetonitrile **(21b)-Peak 2a**. **LCMS**

**(Method 17):** $t_R$ = 2.681 min, $[M+1]^+$ 419.1. **$^1$H NMR:** (400 MHz, CHLOROFORM-d) δ = 9.37 (d, *J* = 2.4 Hz, 1H), 8.43 (s, 1H), 7.92 (d, *J* = 8.3 Hz, 1H), 7.62 (dt, *J* = 4.8, 8.0 Hz, 1H), 7.37 (dd, *J* = 7.8, 12.4 Hz, 1H), 4.91 (s, 2H), 3.03 - 2.81 (m, 3H), 2.56 - 2.43 (m, 2H), 2.43 - 2.34 (m, 1H), 1.99 - 1.83 (m, 1H). **SFC:** (column: Lux Cellulose (50mmx4.6mm, 3μm; mobile phase: [0.1% $NH_3H_2O$ EtOH]; B%: 5% for 0.2 min, 5-50% for 1.0 min., 50% for 1.0 min., 50-5% for 0.4 min., 5% for 0.4 min), $t_R$ = 1.343 min, ee% = 97.9%.

Step 3c: To a solution of the compound from Peak 3 (65 mg, 0.17 mmol, 1.0 eq.) in DMF (1 mL) was added 2-bromoacetonitrile (31 mg, 0.26 mmol, 1.5 eq.) and $Cs_2CO_3$ (112 mg, 0.34 mmol, 2.0 eq.) at 25°C. The reaction was stirred at 25°C under $N_2$ for 3 hrs. The reaction was quenched with $H_2O$ (5 mL) and extracted with EtOAc (2 mL × 3). The combined organic layers were washed with brine (5 mL), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give crude product. The product was purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150mmx40mm, 10μm; liquid phase: [A:$H_2O$ (10mM $NH_4HCO_3$); B:ACN] B%: 25%-60%, 20min]) to obtain [(3*P*,6*R or 6S*)-3-(5-Fluoroisoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4,5,6,7,8-hexahydroquinazolin-1(2*H*)-yl]acetonitrile **(21c)-Peak 3a**. **LCMS (Method 17):** $t_R$ = 2.681 min, $[M+1]^+$ 419.1. **$^1$H NMR:** (400 MHz, CHLOROFORM-d) δ = 9.37 (d, *J* = 2.5 Hz, 1H), 8.43 (s, 1H), 7.92 (d, *J* = 7.6 Hz, 1H), 7.62 (dt, *J* = 4.9, 8.0 Hz, 1H), 7.41 - 7.34 (m, 1H), 4.91 (s, 2H), 3.04 - 2.82 (m, 3H), 2.57 - 2.44 (m, 2H), 2.43 - 2.35 (m, 1H), 1.98 - 1.84 (m, 1H). **SFC:** (column: Lux Cellulose (50mmx4.6mm, 3μm); mobile phase: [0.1% $NH_3H_2O$ EtOH]; B%: 5% for 0.2 min, 5-50% for 1.0 min., 50% for 1.0 min., 50-5% for 0.4 min., 5% for 0.4 min), $t_R$ = 1.588 min, ee% = 99.5%.

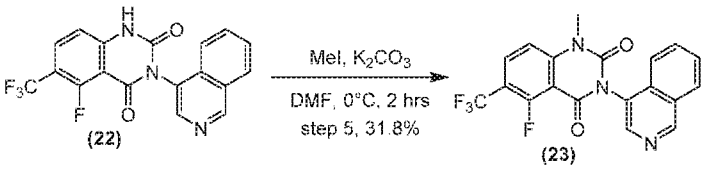
Step 3d: To a solution of the compound from Peak 4 (50 mg, 0.13 mmol, 1.0 eq.) in DMF (1 mL) was added 2-bromoacetonitrile (24 mg, 0.20 mmol, 1.5 eq.) and $Cs_2CO_3$ (86 mg, 0.26 mmol, 2.0 eq.) at 25°C. The reaction was stirred at 25°C under $N_2$ for 3 hrs. The reaction was quenched with $H_2O$ (5 mL) and extracted with EtOAc (2 mL × 3). The combined organic layers were washed with brine (5 mL), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give crude product. The product was purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150mmx40mm, 10μm; liquid phase: [A:$H_2O$ (10mM $NH_4HCO_3$); B:ACN] B%: 25%-60%, 20min]) to obtain [(3*P*,6*R or 6S*)-3-(5-Fluoroisoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4,5,6,7,8-hexahydroquinazolin-1(2*H*)-yl]acetonitrile **(21d)-Peak 4a**. **LCMS (Method 17):** $t_R$ = 2.695 min, $[M+1]^+$ 419.1. **$^1$H NMR:** (400 MHz, CHLOROFORM-d) δ = 9.37 (d, *J* = 2.4 Hz, 1H), 8.42 (s, 1H), 7.92 (d, *J* = 8.3 Hz, 1H), 7.62 (dt, *J* = 4.8, 8.0 Hz, 1H), 7.38 (dd, *J* = 7.8, 12.5 Hz, 1H), 4.92 (s, 2H), 3.04 - 2.80 (m, 3H), 2.55 - 2.35 (m, 3H), 2.01 - 1.89 (m, 1H). **SFC:** (column: Lux Cellulose (50mmx4.6mm, 3μm); mobile phase: [0.1% $NH_3H_2O$ EtOH]; B%: 5% for 0.2 min, 5-50% for 1.0 min., 50% for 1.0 min., 50-5% for 0.4 min., 5% for 0.4 min), $t_R$ = 1.629 min, ee% = 99.7%.

**Example 22:** Synthesis of 5-fluoro-3-(isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(21)**




To a solution of methyl 6-amino-2-fluoro-3-(trifluoromethyl)benzoate **(Int-A8)** (220 mg, 0.93 mmol, 1.0 eq.) in pyridine (10 mL) was added 4-isocyanatoisoquinoline **(Int-B8)** (173 mg, 1.02 mmol, 1.5 eq.). The mixture was stirred at 100°C for 6 hrs. The mixture was concentrated under reduced pressure to give crude product. The crude was purified by prep-HPLC (column: Phenomenex luna C18 80mm x40mm, 3μm; liquid phase: [A:$H_2O$=(0.04%HCl); B:ACN]B%: 27%-53%,20min]) to give 5-fluoro-3-(isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(22)**. **LCMS (Method 13):** $t_R$ = 2.183 min, $[M+1]^+$ 375.9. **$^1$H NMR:** (400 MHz, METHANOL-$d_4$) δ = 9.90 (s, 1H), 8.83 (s, 1H), 8.62 (d, *J* = 8.3 Hz, 1H), 8.31 - 8.27 (m, 1H), 8.26 - 8.18 (m, 1H), 8.15 - 8.07 (m, 1H), 8.03 (m, J = 7.3, 8.7 Hz, 1H), 7.25 (d, J = 8.6 Hz, 1H).

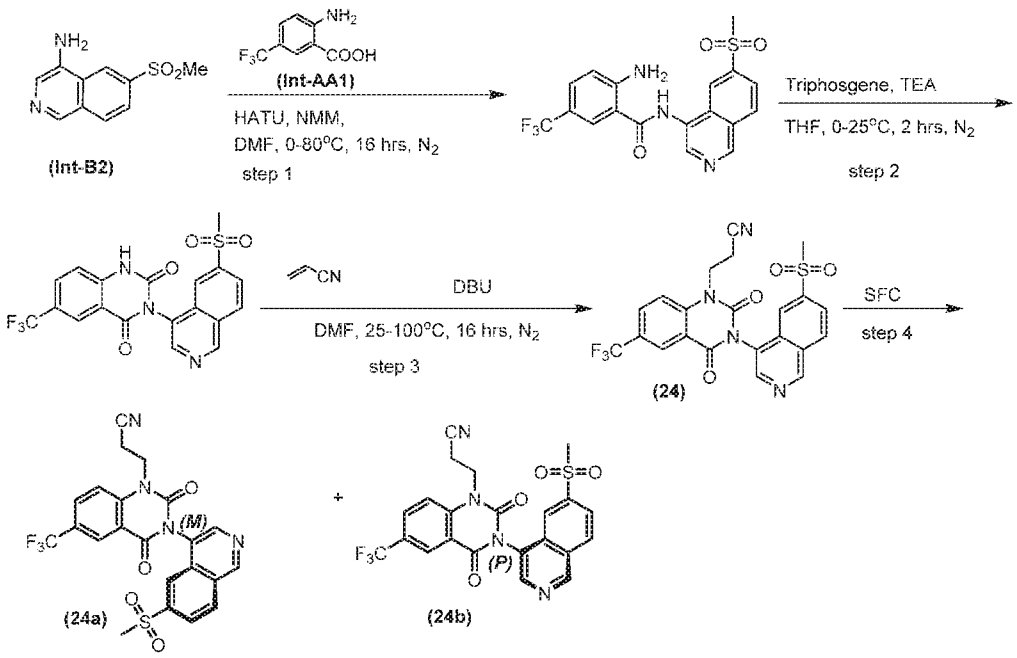
**Example 23:** Synthesis of 5-fluoro-3-(isoquinolin-4-yl)-1-methyl-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(23)**




To a solution of 5-fluoro-3-(isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(22)** (40 mg, 0.10 mmol, 1.0 eq.) and $K_2CO_3$ (41 mg, 0.30 mmol, 3.0 eq.) in DMF (2 mL) was added MeI (21 mg, 0.15 mmol, 1.5 eq.). The mixture was stirred at 0°C for 2 hrs. The reaction mixture was filtered. The filtrate was purified by prep-HPLC (column: Phenomenex luna C18 80mmx40mm, 3μm; liquid phase: [A:$H_2O$ = (0.04%HCl); B:ACN] B%: 27%-53%, 20min]) to give 5-fluoro-3-(isoquinolin-4-yl)-1-methyl-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(23)**. **LCMS (Method 13):** $t_R$ = 2.279 min, $[M+1]^+$ 390.0. **$^1$H NMR:** 400 MHz, METHANOL-$d_4$) δ = 9.98 (s, 1H), 8.86 (s, 1H), 8.67 (d, *J* = 8.4 Hz, 1H), 8.38 - 8.31 (m, 1H), 8.29 - 8.23 (m, 1H), 8.18 - 8.10 (m, 2H), 7.58 (d, J = 9.0 Hz, 1H), 3.72 (s, 3H).

**Example 24:** Synthesis of 3-(3-(isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2H)-yl)propanenitrile **(24),**
3-[(3*M*)-3-[6-(Methanesulfonyl)isoquinolin-4-yl]-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2*H*)-yl]propanenitrile **(24a)** and

3-[(3*P*)-3-[6-(Methanesulfonyl)isoquinolin-4-yl]-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2*H*)-yl]propanenitrile **(24b)**




Step 1: The solution of 2-amino-5-(trifluoromethyl)benzoic acid **(Int-AA1)** (1.9 g, 9.00 mmol, 1.0 eq.) and HATU (4.2 g, 10.80 mmol, 1.2 eq.) in DMF (20 mL) were stirred at 0°C for 1 hr. Then the reaction mixture was warmed up to 25°C. Then to the reaction mixture was 6-(methylsulfonyl)isoquinolin-4-amine (**Int-B2)** (2.0 g, 9.00 mmol, 1.0 eq.) and NMM (1.8 g, 18.00 mmol, 2.0 eq.) at 25°C. The reaction mixture was heated up to 80°C and stirred at 80°C for 16 hrs. The reaction mixture was quenched with water (50 mL) and extracted with EtOAc (20 mL x 2). The combined organic layers were washed with brine (50 mL x 2), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give a crude product. The crude product was purified by MPLC (Petroleum ether/EtOAc = 1/0 ~ 0/1) to give 2-amino-N-(6-(methylsulfonyl)isoquinolin-4-yl)-5-(trifluoromethyl)benzamide. **LCMS (Method 12):** $t_R$ = 0.622 min., $[M+1]^+$ 410.0.

Step 2: To a mixture of 2-amino-N-(6-(methylsulfonyl)isoquinolin-4-yl)-5-(trifluoromethyl)benzamide (500 mg, 1.22 mmol, 1.0 eq.) and TEA (865 mg, 8.55 mmol, 7.0 eq.) in THF (3 mL) was added a solution of triphosgene (360 mg, 1.22 mmol, 1.0 eq.) in THF (2 mL) dropwise at 0°C under $N_2$. The mixture was then warmed up to 25°C and stirred at 25°C under $N_2$ for 2 hrs. The reaction mixture was quenched with water (10 mL) and extracted with EtOAc (10 mL x 2). The combined organic layers were washed with brine (10 mL x 2), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give a crude product. The crude product was purified by MPLC (Petroleum ether/EtOAc = 100/0 to 0/100, $R_{fp1}$ = 0.38) to give 3-(6-(methylsulfonyl)isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione. **LCMS (Method 5):** $t_R$ = 0.842 min, $[M+1]^+$ 436.0. **$^1$H NMR:** (400 MHz, DMSO-$d_6$) δ = 12.10 - 12.27 (m,

1 H), 9.59 - 9.71 (m, 1 H), 8.77 (s, 1 H), 8.62 (s, 1 H), 8.57 (d, *J*=8.68 Hz, 1 H), 8.19 - 8.22 (m, 2 H), 8.13 (dd, *J*=8.68, 1.96 Hz, 1 H), 7.51 (d, *J*=8.56 Hz, 1 H), 3.34 (s, 3 H).

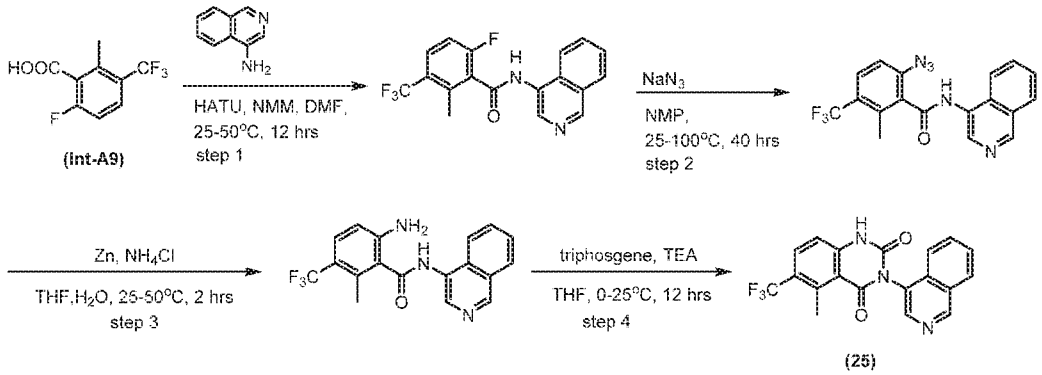
Step 3: To the solution of -(6-(methylsulfonyl)isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione (150 mg, 0.34 mmol, 1.0 eq.) and DBU (105 mg, 0.68 mmol, 2.0 eq.) in DMF (1 mL) was added acrylonitrile (180 mg, 3.40 mmol, 10.0 eq.) at 25°C. The mixture was heated to 100°C and stirred at 100°C for 16 hrs under $N_2$. The reaction mixture was poured into water (10 mL) and extracted with EtOAc (10 mL x 2). The combined organic layers were washed with brine (10 mL x 2), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give a crude product. The crude product was purified by prep-HPLC (column: Waters Xbridge BEH C18 100mmx30mm, 10μm; liquid phase: [A:10mM $NH_4HCO_3$ in $H_2O$; B:ACN] B%: 25% - 55%,10 min]) to give racemic 3-(3-(6-(methylsulfonyl)isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2H)-yl)propanenitrile **(24)**. **LCMS (Method 18):** $t_R$ = 1.637 min, $[M+1]^+$ 488.9. **$^1$H NMR:** (400 MHz, DMSO-$d_6$) δ = 9.65 (s, 1 H), 8.74 - 8.78 (m, 1 H), 8.63 - 8.67 (m, 1 H), 8.58 (d, *J*=8.7 Hz, 1 H), 8.32 - 8.35 (m, 1 H), 8.23 - 8.27 (m, 1 H), 8.20 - 8.23 (m, 1 H), 8.05 (d, *J*=8.92 Hz, 1 H), 4.48 - 4.59 (m, 2 H), 3.33 (br s, 3 H), 2.98 (t, *J*=6.8 Hz, 2 H).

Step 4: Racemic 3-(3-(6-(methylsulfonyl)isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2H)-yl)propanenitrile **(24)** (60 mg, 0.12 mmol, 1.0 eq.) was separated by prep-SFC (column: DAICEL CHIRALCEL OJ (250mmx30mm,10um); liquid phase: [A:IPA; B:ACN] B%: 15%, 12 min]) to give two peaks. (peak 1 and peak 2). Stereochemistry assigned by analogy to Example 16, wherein the chirality of the more active atropisomer(s) is assigned as ***(M)*** and subsequently the chirality of the more active atropisomer(s) is assigned as ***(P)***.
**Peak 1:** 3-[(3*M*)-3-[6-(Methanesulfonyl)isoquinolin-4-yl]-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2*H*)-yl]propanenitrile **(24a)** .**LCMS (Method 17):** $t_R$ = 2.627 min, $[M+1]^+$ 489.1. **SFC:** (column: Chiralcel OD-3 (50mmx4.6mm, 3μm); mobile phase: [0.1% $NH_3H_2O$ EtOH]; B%: 5% for 0.2 min, 5-50% for 1.0 min., 50% for 1.0 min., 50-5% for 0.4 min., 5% for 0.4 min), $t_R$ = 1.425 min, ee% = 100.0%. **$^1$H NMR:** (400 MHz, CHLOROFORM-*d*) δ = 9.63 (br s, 1H), 8.75 (br s, 1H), 8.59 (s, 1 H), 8.37 (d, *J*=8.8 Hz, 1 H), 8.23 (s, 1 H), 8.15 (br d, *J*=9.2 Hz, 1 H), 8.08 - 8.12 (m, 1 H), 7.53 - 7.57 (m, 1 H), 4.61 - 4.68 (m, 1 H), 4.49 - 4.59 (m, 1 H), 3.11 (s, 3 H), 2.90 - 3.03 (m, 2 H).

**Peak 2:** 3-[(3*P*)-3-[6-(Methanesulfonyl)isoquinolin-4-yl]-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2*H*)-yl]propanenitrile **(24b)**. **LCMS (Method 17):** $t_R$ = 2.624 min, $[M+1]^+$ 489.1. **SFC:** column: Chiralcel OD-3 (50mmx4.6mm, 3μm); mobile phase: [0.1% $NH_3H_2O$ EtOH]; B%: 5% for 0.2 min, 5-50% for 1.0 min., 50% for 1.0 min., 50-5% for 0.4 min., 5% for 0.4 min), $t_R$ = 1.714 min, ee% = 98.7%. **$^1$H NMR:** (400 MHz, CHLOROFORM-*d*) δ = 9.63 (br s, 1H), 8.75 (br s, 1H), 8.59 (s, 1 H), 8.37 (d, *J*=8.6 Hz, 1 H), 8.23 (s, 1 H), 8.14 (dd, *J*=8.7, 1.55 Hz, 1

H), 8.09 (dd, *J*=8.9, 1.79 Hz, 1 H), 7.55 (d, *J*=8.8 Hz, 1 H), 4.50 - 4.68 (m, 2 H), 3.10 (s, 3 H), 2.88 - 3.04 (m, 2 H).

**Example 25:** Synthesis of 3-(isoquinolin-4-yl)-5-methyl-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(25)**




Step 1: To a solution of 6-fluoro-2-methyl-3-(trifluoromethyl)benzoic acid **(Int-A9)** (1.1 g, 4.95 mmol, 1.0 eq.) in DMF (20 mL) was added HATU (2.8 g, 7.43 mmol, 1.5 eq.), isoquinolin-4-amine (785 mg, 5.45 mmol, 1.1 eq.) and NMM (1.5 g, 14.85 mmol, 3.0 eq.) at 25°C. The mixture was stirred at 50°C for 12 hrs. The reaction was quenched with $H_2O$ (80 mL) and extracted with EtOAc (30 mL × 2). The combined organic layers were washed with brine (120 mL × 2), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give crude product. The crude product was purified by flash silica gel chromatography (40 g, Eluent of 0~50% Ethyl acetate/Petroleum ether, 80 mL/min) to give 6-fluoro-N-(isoquinolin-4-yl)-2-methyl-3-(trifluoromethyl)benzamide. **$^1$H NMR:** (400 MHz, DMSO-$d_6$) δ = 10.96 (s, 1H), 8.80 (s, 1H), 8.22 (d, *J* = 8.2 Hz, 1H), 8.11 (d, *J* = 8.4 Hz, 1H), 7.95 (s, 1H), 7.93 - 7.87 (m, 2H), 7.79 - 7.74 (m, 1H), 7.49 (t, *J* = 8.7 Hz, 1H), 2.57 (s, 3H).

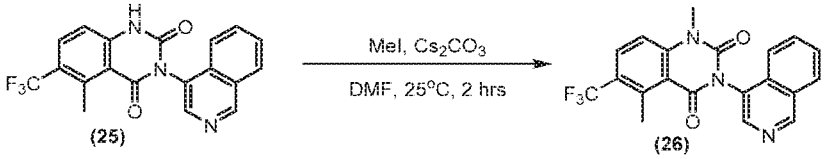
Step 2: To a solution of 6-fluoro-N-(isoquinolin-4-yl)-2-methyl-3-(trifluoromethyl)benzamide (1.1g, 3.16 mmol, 1.0 eq.) in NMP (11 mL) was added $NaN_3$ (350 mg, 5.38 mmol, 1.7 eq.) at 25°C. The mixture was stirred at 100°C for 24 hrs. To the mixture was added $NaN_3$ (225 mg, 3.46 mmol, 1.1 eq.) at 25°C and the mixture was stirred at 100°C for 16 hrs. The reaction was quenched with $H_2O$ (100 mL) and extracted with EtOAc (40 mL × 2). The combined organic layers were washed with brine (120 mL × 2), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give 6-azido-N-(isoquinolin-4-yl)-2-methyl-3-(trifluoromethyl)benzamide. **$^1$H NMR:** (400 MHz, DMSO-$d_6$) δ = 10.74 (s, 1H), 9.25 (s, 1H), 8.80 (s, 1H), 8.21 (dd, *J* = 6.0, 7.7 Hz, 2H), 7.92 - 7.85 (m, 2H), 7.75 (t, *J* = 7.6 Hz, 1H), 7.54 (d, *J* = 8.6 Hz, 1H), 2.45 (s, 3H)

Step 3: To a mixture of 6-azido-N-(isoquinolin-4-yl)-2-methyl-3-(trifluoromethyl)benzamide (900 mg, 2.42 mmol, 1.0 eq.) in THF (12 mL) and $H_2O$ (4 mL) was added $NH_4Cl$ (778 mg, 14.54 mmol, 6.0 eq.) and Zn (475 mg, 7.27 mmol, 3.0 eq.) at 25°C. The mixture was stirred at 50°C for 2 hrs. The mixture was filtered and the filtrate was quenched with $H_2O$ (40 mL) and extracted

with EtOAc (20 mL × 2). The combined organic layers were washed with brine (50 mL × 2), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give crude product. The crude product was purified by flash silica gel chromatography (20 g, Eluent of 0~45% Ethyl acetate/Petroleum ether, 60 mL/min) to give 6-amino-N-(isoquinolin-4-yl)-2-methyl-3-(trifluoromethyl)benzamide. **$^1$H NMR:** (400 MHz, CHLOROFORM-d) δ = 9.17 (s, 1H), 9.09 (s, 1H), 8.07 (br d, *J* = 8.2 Hz, 1H), 8.03 (br s, 1H), 7.96 (br d, *J* = 8.3 Hz, 1H), 7.81 (br t, *J* = 7.6 Hz, 1H), 7.70 (br t, *J* = 7.6 Hz, 1H), 7.47 (br d, *J* = 8.4 Hz, 1H), 6.65 (br d, *J* = 8.4 Hz, 1H), 2.63 (s, 3H).

Step 4: To a mixture of 6-amino-N-(isoquinolin-4-yl)-2-methyl-3-(trifluoromethyl)benzamide (350 mg, 1.01 mmol, 1.0 eq.) and TEA (410 mg, 4.04 mmol, 4.0 eq.) in THF (6 mL) was added a solution of triphosgene (300 mg, 1.01 mmol, 1.0 eq.) in THF (4 mL) at 0°C. The mixture was stirred at 25°C for 12 hrs. The reaction was quenched with $H_2O$ (30 mL) and extracted with EtOAc (20 mL × 2). The combined organic layers were washed with brine (50 mL × 2), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give crude product. The crude product was purified by prep-HPLC (column: Phenomenex Luna C18 200mmx40mm, 10μm; liquid phase: [A:$H_2O$ (0.1% HCOOH); B:ACN] B%: 20%-60%, 20 min]) to give 3-(isoquinolin-4-yl)-5-methyl-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(25): LCMS (Method 3)**: $t_R$ = 2.509 min, $[M+1]^+$ 372.0. **$^1$H NMR:** (400 MHz, DMSO-$d_6$) δ = 11.97 (s, 1H), 9.42 (s, 1H), 8.54 (s, 1H), 8.26 (dd, *J* = 2.0, 6.8 Hz, 1H), 8.01 (d, *J* = 8.8 Hz, 1H), 7.93 (d, *J* = 7.9 Hz, 1H), 7.82 - 7.72 (m, 2H), 7.31 (d, *J* = 8.8 Hz, 1H), 2.75 (s, 3H).

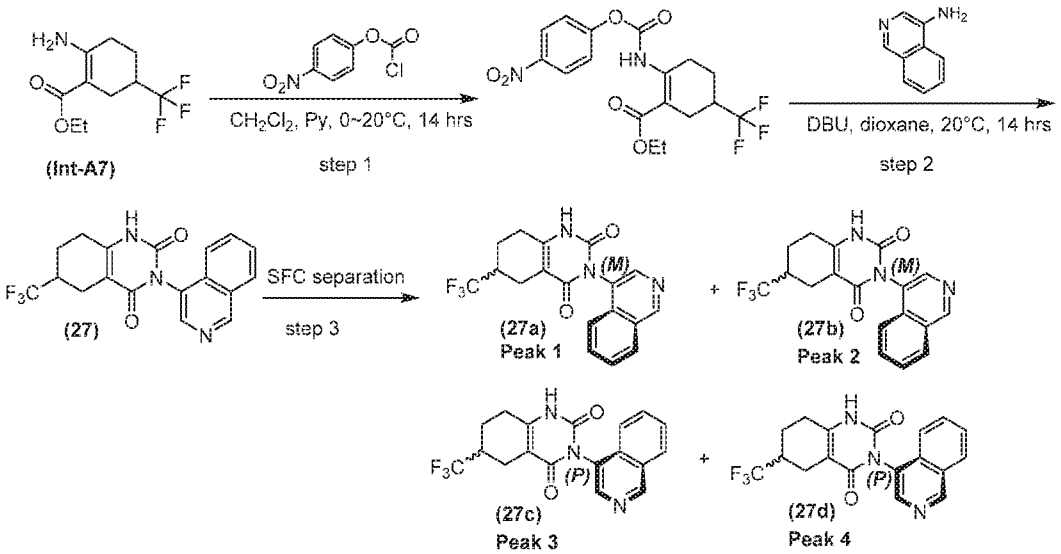
**Example 26:** Synthesis of 3-(isoquinolin-4-yl)-1,5-dimethyl-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(26)**




To a solution of 3-(isoquinolin-4-yl)-5-methyl-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(25)** (20 mg, 0.05 mmol, 1.0 eq.) in DMF (1 mL) was added $Cs_2CO_3$ (35 mg, 0.10 mmol, 2.0 eq.) and MeI (8 mg, 0.06 mmol, 1.1 eq.) at 25°C. The mixture was stirred at 25°C for 2 hrs. The reaction was quenched with $H_2O$ (8 mL) and extracted with EtOAc (4 mL × 2). The combined organic layers were washed with brine (10 mL × 2), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give crude product. The crude product was purified by prep-HPLC (column: Phenomenex Luna C18 150x30mm, 5μm; liquid phase: [A:HCOOH/$H_2O$=0.1% v/v; B:ACN] B%: 33%-63%, 8 min]) to give 3-(isoquinolin-4-yl)-1,5-dimethyl-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(26)**. **LCMS (Method 3):** $t_R$ = 2.402 min, $[M+1]^+$ 386.0. **$^1$H NMR:** (400 MHz, DMSO-$d_6$) δ = 9.43 (s, 1H), 8.52 (s, 1H), 8.27 (br d, *J* =

8.7 Hz, 1H), 8.11 (d, *J* = 9.0 Hz, 1H), 7.94 (br d, *J* = 7.2 Hz, 1H), 7.80 - 7.72 (m, 2H), 7.61 (d, *J* = 9.0 Hz, 1H), 3.59 (s, 3H), 2.77 (s, 3H).

**Example 27:** Synthesis of 3-(isoquinolin-4-yl)-6-(trifluoromethyl)-5,6,7,8-tetrahydroquinazoline-2,4(1H,3H)-dione **(27)**;
(3*M*,6*R or 6S*)-3-(Isoquinolin-4-yl)-6-(trifluoromethyl)-5,6,7,8-tetrahydroquinazoline-2,4(1*H*,3*H*)-dione **(27a)**;
(3*M*,6*R or 6S*)-3-(Isoquinolin-4-yl)-6-(trifluoromethyl)-5,6,7,8-tetrahydroquinazoline-2,4(1*H*,3*H*)-dione **(27b)**;
(3*P*,6*R or 6S*)-3-(Isoquinolin-4-yl)-6-(trifluoromethyl)-5,6,7,8-tetrahydroquinazoline-2,4(1*H*,3*H*)-dione **(27c)**, and
(3*P*,6*R or 6S*)-3-(Isoquinolin-4-yl)-6-(trifluoromethyl)-5,6,7,8-tetrahydroquinazoline-2,4(1*H*,3*H*)-dione **(27d)**




Step 1: To a mixture of ethyl 2-amino-5-(trifluoromethyl)cyclohex-1-ene-1-carboxylate **(Int-A7)** (1.2 g, 5.06 mmol, 1.0 eq.) in $CH_2Cl_2$ (24 mL) was added the pyridine (480 mg, 6.07 mmol, 1.2 eq) and the solution was cooled to 0°C. 4-nitrophenyl carbonochloridate (1.12 g, 5.56 mmol, 1.1 eq) was added and the solution was stirred at 20°C for 14 hrs. The solution was concentrated to remove the $CH_2Cl_2$ and pyridine to give crude ethyl 2-(((4-nitrophenoxy)carbonyl)amino)-5-(trifluoromethyl)cyclohex-1-ene-1-carboxylate which would be used in the next step without purification.

Step 2: To a solution of ethyl 2-(((4-nitrophenoxy)carbonyl)amino)-5-(trifluoromethyl)cyclohex-1-ene-1-carboxylate (2.0 g, 4.97 mmol, 1.0 eq) in dioxane (40 mL) was added isoquinolin-4-amine (788 mg, 5.47 mmol, 1.1 eq) and DBU (1.5 g, 9.94 mmol, 2.0 eq) at 20°C. The reaction mixture was stirred at 20°C for 14 hrs. The solution was diluted with $H_2O$ (40 mL) and extracted with EtOAc (3x50 mL). The combined organic phase was dried over $Na_2SO_4$, filtrated and

concentrated to give crude product. The crude product was purified by prep-HPLC (Column: Waters Xbridge Prep OBD C18 150mmx40mm, 10μm; liquid phase: [A:$H_2O$(10mM $NH_4HCO_3$); B:ACN]B%: 20%-40%,20min]) to give racemic 3-(isoquinolin-4-yl)-6-(trifluoromethyl)-5,6,7,8-tetrahydroquinazoline-2,4(1H,3H)-dione.

Step 3: Racemic 3-(isoquinolin-4-yl)-6-(trifluoromethyl)-5,6,7,8-tetrahydroquinazoline-2,4(1H,3H)-dione was separated by SFC, (Instrument: Waters SFC80Q preparative SFC ; Column: DAICEL CHIRALPAK AD(250mmx30mm,10um); Mobile phase: A:$CO_2$ and B:MeOH(0.1%$NH_3H_2O$); Gradient: B%=33% isocratic elution mode; Flow rate: 60g/min; Wavelength:220nm; Column temperature: 40 °C System back pressure: 100 bar.) to give four peaks. **SFC:** $t_{R1}$ = 3.264 min., $t_{R2}$ = 3.539 min., $t_{R3}$ = 3.861 min. and $t_{R4}$ = 4.056 min.

**Peak 1:** (3*M*,6*R or 6S*)-3-(Isoquinolin-4-yl)-6-(trifluoromethyl)-5,6,7,8-tetrahydroquinazoline-2,4(1*H*,3*H*)-dione **(27a)**. **LCMS (Method 17)**: $t_R$ = 2.478 min, $[M+1]^+$ 362.1. **$^1$H NMR:** (400 MHz, METHANOL-d4) δ = 9.35 (s, 1H), 8.39 (s, 1H), 8.25 (d, *J* = 8.2 Hz, 1H), 7.87 - 7.81 (m, 1H), 7.79 - 7.69 (m, 2H), 2.87 - 2.52 (m, 4H), 2.43 - 2.18 (m, 2H), 1.92 - 1.74 (m, 1H). **SFC:** (column: Chiralcel AD-3 (150mmx4.6mm, 3μm); mobile phase: A: $CO_2$; B:[0.1% $NH_3H_2O$ EtOH]; B%: 10% for 0.5 min, 10-50% for 3.0 min., 50% for 1.0 min., 50-10% for 0.5 min., 2.5mL/min., $t_R$ = 3.264 min, ee% = 100.0%. Stereochemistry assigned by analogy to Example 16, wherein the chirality of the more active atropisomer(s) is assigned as ***(M)*** and subsequently the chirality of the less active atropisomer(s) is assigned as ***(P)***.

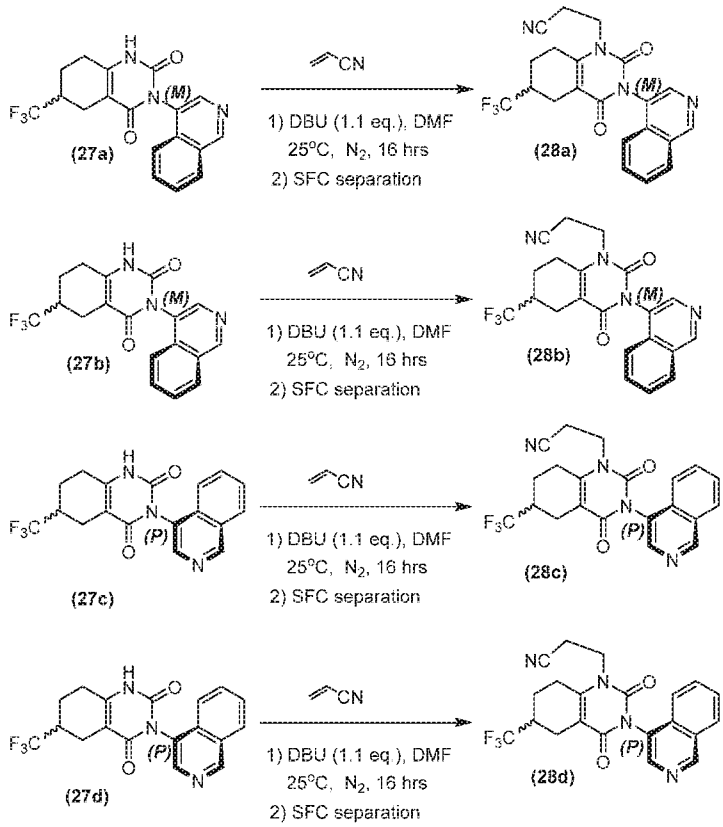
**Peak 2:** (3*M*,6*R or 6S*)-3-(Isoquinolin-4-yl)-6-(trifluoromethyl)-5,6,7,8-tetrahydroquinazoline-2,4(1*H*,3*H*)-dione **(27b)**. **LCMS (Method 17)**: $t_R$ = 2.452 min, $[M+1]^+$ 362.1. **$^1$H NMR:** (400 MHz, METHANOL-d4) δ = 9.35 (s, 1H), 8.40 (s, 1H), 8.25 (d, *J* = 8.1 Hz, 1H), 7.86 - 7.80 (m, 1H), 7.79 - 7.69 (m, 2H), 2.88 - 2.55 (m, 4H), 2.44 - 2.18 (m, 2H), 1.81 (dq, *J* = 6.3, 12.2 Hz, 1H). **SFC:** (column: Chiralcel AD-3 (15 mmx4.6mm, 3μm); mobile phase: A: $CO_2$; B:[0.1% $NH_3H_2O$ EtOH]; B%: 10% for 0.5 min, 10-50% for 3.0 min., 50% for 1.0 min., 50-10% for 0.5 min., 2.5mL/min., $t_R$ = 3.539 min, ee% = 99.3%.

**Peak 3:** (3*P*,6*R or 6S*)-3-(Isoquinolin-4-yl)-6-(trifluoromethyl)-5,6,7,8-tetrahydroquinazoline-2,4(1*H*,3*H*)-dione **(27c)**. **LCMS (Method 17)**: $t_R$ = 2.451 min, $[M+1]^+$ 362.1. **$^1$H NMR:** (400 MHz, METHANOL-d4) δ = 9.35 (s, 1H), 8.40 (s, 1H), 8.25 (d, *J* = 8.1 Hz, 1H), 7.87 - 7.80 (m, 1H), 7.79 - 7.68 (m, 2H), 2.85 - 2.54 (m, 4H), 2.41 - 2.18 (m, 2H), 1.81 (dq, *J* = 6.2, 12.2 Hz, 1H). **SFC:** (column: Chiralcel AD-3 (150mmx4.6mm, 3μm); mobile phase: A: $CO_2$; B:[0.1% $NH_3H_2O$ EtOH]; B%: 10% for 0.5 min, 10-50% for 3.0 min., 50% for 1.0 min., 50-10% for 0.5 min., 2.5mL/min., $t_R$ = 3.861 min, ee% = 95.8%.

**Peak 4:** (3*P*,6*R or 6S*)-3-(Isoquinolin-4-yl)-6-(trifluoromethyl)-5,6,7,8-tetrahydroquinazoline-2,4(1*H*,3*H*)-dione **(27d)**. **LCMS (Method 17)**: $t_R$ = 2.477 min, $[M+1]^+$ 362.1. **$^1$H NMR:** (400 MHz, METHANOL-d4) δ = 9.35 (s, 1H), 8.38 (s, 1H), 8.24 (d, *J* = 8.2 Hz, 1H), 7.87 - 7.80 (m, 1H),

7.79 - 7.68 (m, 2H), 2.86 - 2.54 (m, 4H), 2.39 - 2.19 (m, 2H), 1.90 - 1.74 (m, 1H). **SFC:** (column: Chiralcel AD-3 (150mmx4.6mm, 3μm); mobile phase: A: $CO_2$; B:[0.1% $NH_3H_2O$ EtOH]; B%: 10% for 0.5 min, 10-50% for 3.0 min., 50% for 1.0 min., 50-10% for 0.5 min., 2.5mL/min., $t_R$ = 4.056 min, ee% = 98.8%

**Example 28:** Synthesis of 3-[(3*M*,6*R or 6S*)-3-(Isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4,5,6,7,8-hexahydroquinazolin-1(2*H*)-yl]propanenitrile **(28a)**;
3-[(3*M*,6*R or 6S*)-3-(Isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4,5,6,7,8-hexahydroquinazolin-1(2*H*)-yl]propanenitrile **(28b)**;
3-[(3*P*,6*R or 6S*)-3-(Isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4,5,6,7,8-hexahydroquinazolin-1(2*H*)-yl]propanenitrile **(28c)**, and
3-[(3*P*,6*R or 6S*)-3-(Isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4,5,6,7,8-hexahydroquinazolin-1(2*H*)-yl]propanenitrile **(28d)**




3-[(3*M*,6*R or 6S*)-3-(Isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4,5,6,7,8-hexahydroquinazolin-1(2*H*)-yl]propanenitrile **(28a)**

Step 1: To a solution of (3*M*,6*R or 6S*)-3-(Isoquinolin-4-yl)-6-(trifluoromethyl)-5,6,7,8-tetrahydroquinazoline-2,4(1*H*,3*H*)-dione **(27a)** (150 mg, 0.42 mmol, 1.0 eq.) in DMF (0.8 mL) was added DBU (70 mg, 0.46 mmol, 1.1 eq.) at 25°C. Then acrylonitrile (0.8 mL) was added to the mixture at 25°C and the mixture was stirred at 25°C for 16 hrs under $N_2$. The reaction mixture was quenched with $H_2O$ (10 mL) and acidified pH to 7~8 by aq. HCl solution (1 M). The

mixture was extracted with EtOAc (4 mL × 2). The combined organic layers were washed with brine (12 mL), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give crude product. The crude product was purified by prep-HPLC (column: Waters Xbridge BEH C18 100mmx30mm, 10μm; liquid phase: [A:10 mM $NH_4HCO_3$ in $H_2O$; B:ACN] B%: 20%-50%, 10 min]) to give 3-[(3*M*,6*R or 6S*)-3-(Isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4,5,6,7,8-hexahydroquinazolin-1(2*H*)-yl]propanenitrile **(28a)**. **LCMS (Method 17):** $t_R$ = 2.566 min, $[M+1]^+$ 415.2. **$^1$H NMR: (**400 MHz, CHLOROFORM-d) δ = 9.36 (s, 1H), 8.45 (s, 1H), 8.10 (d, *J* = 8.1 Hz, 1H), 7.78 - 7.73 (m, 1H), 7.71 - 7.65 (m, 1H), 7.56 (d, *J* = 8.3 Hz, 1H), 4.31 - 4.06 (m, 2H), 3.05 - 2.78 (m, 5H), 2.54 - 2.34 (m, 3H), 1.97 - 1.85 (m, 1H). **SFC:** column: Chiralpak (50mmx4.6mm, 3μm); mobile phase: A: $CO_2$; B:[0.1% $NH_3H_2O$ EtOH]; B%: 5% for 0.2 min, 5-50% for 1.0 min., 50% for 1.0 min., 50-5% for 0.4 min., 5% for 0.4 min., 3.4mL/min., $t_R$ = 1.430 min, ee% = 88.4%.

Step 2: 3-[(3*M*,6*R or 6S*)-3-(Isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4,5,6,7,8-hexahydroquinazolin-1(2*H*)-yl]propanenitrile **(28a)** (42.2 mg) was further purified by prep-SFC (column: DAICEL CHIRALPAK IG (250mmx30mm, 10μm); mobile phase: 0.1% $NH_3H_2O$ EtOH; B% 50%-50%, 15 min]). **LCMS (Method 17):** $t_R$ = 2.608 min, $[M+1]^+$ 415.2. **$^1$H NMR:** (400 MHz, CHLOROFORM-d) δ = 9.36 (s, 1H), 8.45 (s, 1H), 8.11 (d, *J* = 8.1 Hz, 1H), 7.79 - 7.74 (m, 1H), 7.71 - 7.66 (m, 1H), 7.56 (d, *J* = 8.1 Hz, 1H), 4.30 - 4.12 (m, 2H), 3.07 - 2.78 (m, 5H), 2.55 - 2.34 (m, 3H), 1.99 - 1.84 (m, 1H). **SFC:** (column: Chiralpak IG-3 (50mmx4.6mm, 3μm); mobile phase: A: $CO_2$; B: EtOH[0.1% IPAm]; B%: 5% for 0.2 min, 5-50% for 1.0 min., 50% for 1.0 min., 50-5% for 0.4 min., 5% for 0.4 min., 3.4mL/min., $t_R$ = 1.426 min, ee% = 99.8%.

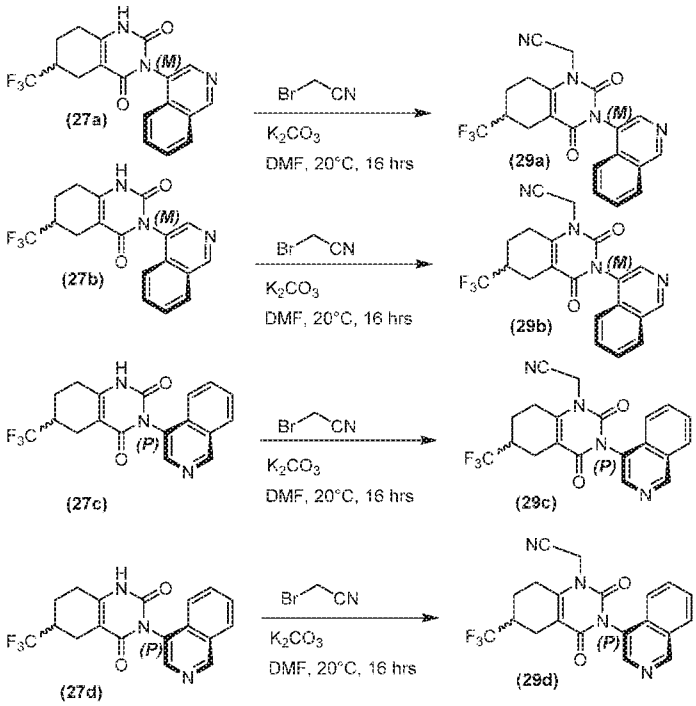
3-[(3*M*,6*R or 6S*)-3-(Isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4,5,6,7,8-hexahydroquinazolin-1(2*H*)-yl]propanenitrile **(28b)** was obtained using the method described above for the synthesis of compound **(28a)**, except (3*M*,6*R or 6S*)-3-(Isoquinolin-4-yl)-6-(trifluoromethyl)-5,6,7,8-tetrahydroquinazoline-2,4(1*H*,3*H*)-dione **(27b)** was used in place of (3*M*,6*R or 6S*)-3-(Isoquinolin-4-yl)-6-(trifluoromethyl)-5,6,7,8-tetrahydroquinazoline-2,4(1*H*,3*H*)-dione **(27a)**. **LCMS (Method 17):** $t_R$ = 2.588 min, $[M+1]^+$ 415.1. **$^1$H NMR:** (400 MHz, CHLOROFORM-d) δ = 9.36 (s, 1H), 8.46 (s, 1H), 8.11 (d, *J* = 8.3 Hz, 1H), 7.78 - 7.72 (m, 1H), 7.71 - 7.65 (m, 1H), 7.54 (d, *J* = 8.4 Hz, 1H), 4.26 - 4.14 (m, 2H), 3.05 - 2.81 (m, 5H), 2.55 - 2.34 (m, 3H), 1.96 - 1.83 (m, 1H). **SFC:** (column: Chiralpak AD-3 (50mmx4.6mm, 3μm); mobile phase: A: $CO_2$; B:IPA[0.1% IPAm]; B%: 5% for 0.2 min, 5-50% for 1.0 min., 50% for 1.0 min., 50-5% for 0.4 min., 5% for 0.4 min., 3.4mL/min., $t_R$ = 1.335 min, ee% = 99.8%.

3-[(3*P*,6*R or 6S*)-3-(Isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4,5,6,7,8-hexahydroquinazolin-1(2*H*)-yl]propanenitrile **(28c)** was obtained using the method described above for the synthesis of compound **(28a)**, except (3*P*,6*R or 6S*)-3-(Isoquinolin-4-yl)-6-(trifluoromethyl)-5,6,7,8-tetrahydroquinazoline-2,4(1*H*,3*H*)-dione **(27c)** was used in place of

(3*M*,6*R or 6S*)-3-(Isoquinolin-4-yl)-6-(trifluoromethyl)-5,6,7,8-tetrahydroquinazoline-2,4(1*H*,3*H*)-dione **(27a)**. **LCMS (Method 17):** $t_R$ = 2.599 min, $[M+1]^+$ 415.2. **$^1$H NMR:** (400 MHz, CHLOROFORM-d) δ = 9.36 (s, 1H), 8.46 (s, 1H), 8.11 (d, *J* = 8.0 Hz, 1H), 7.77 - 7.72 (m, 1H), 7.71 - 7.65 (m, 1H), 7.54 (d, *J* = 8.4 Hz, 1H), 4.27 - 4.13 (m, 2H), 3.03 - 2.80 (m, 5H), 2.53 - 2.33 (m, 3H), 1.94 - 1.83 (m, 1H). **SFC:** (column: Chiralcel OD-3 (50mmx4.6mm, 3µm); mobile phase: A: $CO_2$; B: MeOH[0.1% IPAm]; B%: 5% for 0.2 min, 5-50% for 1.0 min., 50% for 1.0 min., 50-5% for 0.4 min., 5% for 0.4 min., 3.4mL/min., $t_R$ = 1.286 min, ee% =100%.

3-[(3*M*,6*P or 6S*)-3-(Isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4,5,6,7,8-hexahydroquinazolin-1(2*H*)-yl]propanenitrile **(28d)** was obtained using the method described above for the synthesis of compound **(28a)**, except (3*P*,6*R or 6S*)-3-(Isoquinolin-4-yl)-6-(trifluoromethyl)-5,6,7,8-tetrahydroquinazoline-2,4(1*H*,3*H*)-dione **(27d)** was used in place of (3*M*,6*R or 6S*)-3-(Isoquinolin-4-yl)-6-(trifluoromethyl)-5,6,7,8-tetrahydroquinazoline-2,4(1*H*,3*H*)-dione **(27a)**. **LCMS (Method 17):** $t_R$ = 2.606 min, $[M+1]^+$ 415.1. **$^1$H NMR:** (400 MHz, CHLOROFORM-d) δ = 9.36 (br s, 1H), 8.46 (br s, 1H), 8.11 (d, *J* = 8.1 Hz, 1H), 7.78 - 7.73 (m, 1H), 7.71 - 7.65 (m, 1H), 7.56 (d, *J* = 8.4 Hz, 1H), 4.30 - 4.10 (m, 2H), 3.07 - 2.77 (m, 5H), 2.56 - 2.32 (m, 3H), 1.98 - 1.84 (m, 1H). **SFC:** (column: Chiralpak AD-3 (50mmx4.6mm, 3µm); mobile phase: A: $CO_2$; B:EtOH[0.1% IPAm]; B%: 5% for 0.2 min, 5-50% for 1.0 min., 50% for 1.0 min., 50-5% for 0.4 min., 5% for 0.4 min., 3.4mL/min., $t_R$ = 2.032 min, ee% =99.7%.

**Example 29:** Synthesis of [(3*M*,6*R or 6S*)-3-(Isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4,5,6,7,8-hexahydroquinazolin-1(2*H*)-yl]acetonitrile **(29a)**;
[(3*M*,6*R or 6S*)-3-(Isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4,5,6,7,8-hexahydroquinazolin-1(2*H*)-yl]acetonitrile **(29b)**;
[(3*P*,6*R or 6S*)-3-(Isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4,5,6,7,8-hexahydroquinazolin-1(2*H*)-yl]acetonitrile **(29c)**, and
[(3*P*,6*R or 6S*)-3-(Isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4,5,6,7,8-hexahydroquinazolin-1(2*H*)-yl]acetonitrile **(29d)**




[(3*M*,6*R or 6S*)-3-(Isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4,5,6,7,8-hexahydroquinazolin-1(2*H*)-yl]acetonitrile **(29a)**

To a solution of (3*M*,6*R or 6S*)-3-(Isoquinolin-4-yl)-6-(trifluoromethyl)-5,6,7,8-tetrahydroquinazoline-2,4(1*H*,3*H*)-dione **(27a)** (50 mg, 0.14 mmol, 1.0 eq) in DMF (1 mL) was added $K_2CO_3$ (38 mg, 0.28 mmol, 2.0 eq), 2-bromoacetonitrile (25 mg, 0.21 mmol, 1.5 eq) and the solution was stirred at 20°C for 16 hrs. The solution was purified with prep-HPLC (column: Waters Xbridge BEH C18 100mmx30mm, 10μm; liquid phase: [A:10mM $NH_4HCO_3$ in $H_2O$; B:ACN]B%: 20%-55%, 8min]) to give 2-((R or S)-3-((R)-isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4,5,6,7,8-hexahydroquinazolin-1(2H)-yl)acetonitrile **(29a)**. **LCMS (Method 17):** $t_R$ = 2.670 min, $[M+1]^+$ 401.1. **H NMR**: (400 MHz, METHANOL-d4) δ = 9.37 (d, *J* = 0.7 Hz, 1H), 8.42 (s, 1H), 8.25 (d, *J* = 8.1 Hz, 1H), 7.88 - 7.81 (m, 1H), 7.80 - 7.72 (m, 2H), 5.06 (s, 2H), 3.12 - 3.02 (m, 1H), 3.01 - 2.80 (m, 2H), 2.70 - 2.54 (m, 1H), 2.45 - 2.31 (m, 2H), 1.95 - 1.81 (m, 1H). **SFC:** (column: Chiralpak OD-3 (50mmx4.6mm, 3μm); mobile phase: A: $CO_2$; B:MeOH[0.1% IPAm]; B%: 5% for 0.2 min, 5-50% for 1.0 min., 50% for 1.0 min., 50-5% for 0.4 min., 5% for 0.4 min., 3.4mL/min., $t_R$ = 1.194 min, ee% = 100.0%.

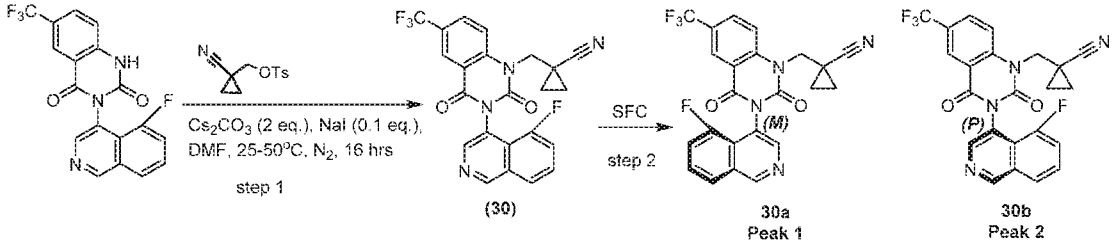
[(3*M*,6*R or 6S*)-3-(Isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4,5,6,7,8-hexahydroquinazolin-1(2*H*)-yl]acetonitrile **(29b)** was obtained using the method described above for the synthesis of compound **(29a)**, except (3*M*,6*R or 6S*)-3-(Isoquinolin-4-yl)-6-(trifluoromethyl)-5,6,7,8-tetrahydroquinazoline-2,4(1*H*,3*H*)-dione **(27b)** was used in place of (3*M*,6*R or 6S*)-3-(Isoquinolin-4-yl)-6-(trifluoromethyl)-5,6,7,8-tetrahydroquinazoline-2,4(1*H*,3*H*)-dione **(27a)**. **LCMS (Method 17):** $t_R$ = 2.646 min, $[M+1]^+$ 401.0. **$^1$H NMR:** (400 MHz,

METHANOL-d4) δ = 9.36 (s, 1H), 8.44 (s, 1H), 8.25 (d, J = 8.1 Hz, 1H), 7.86 - 7.80 (m, 1H), 7.79 - 7.72 (m, 2H), 5.13 - 4.97 (m, 2H), 3.11 - 3.00 (m, 1H), 3.00 - 2.79 (m, 2H), 2.72 - 2.55 (m, 1H), 2.45 - 2.31 (m, 2H), 1.86 (tdd, J = 6.1, 12.2, 18.0 Hz, 1H). **SFC:** (column: Chiralpak AD-3 (50mmx4.6mm, 3µm); mobile phase: A: $CO_2$; B:IPA[0.1% IPAm]; B%: 5% for 0.2 min, 5-50% for 1.0 min., 50% for 1.0 min., 50-5% for 0.4 min., 5% for 0.4 min., 3.4mL/min., $t_R$ = 1.157 min, ee% = 99.5%.

[(3*P*,6*R or 6S*)-3-(Isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4,5,6,7,8-hexahydroquinazolin-1(2*H*)-yl]acetonitrile **(29c)** was obtained using the method described above for the synthesis of compound **(29a)**, except (3*P*,6*R or 6S*)-3-(Isoquinolin-4-yl)-6-(trifluoromethyl)-5,6,7,8-tetrahydroquinazoline-2,4(1*H*,3*H*)-dione **(27c)** was used in place of (3*M*,6*R or 6S*)-3-(Isoquinolin-4-yl)-6-(trifluoromethyl)-5,6,7,8-tetrahydroquinazoline-2,4(1*H*,3*H*)-dione **(27a)**. **LCMS (Method 17):** $t_R$ = 2.634 min, $[M+1]^+$ 401.1. **$^1$H NMR:** (400 MHz, METHANOL-d4) δ = 9.36 (d, *J* = 0.7 Hz, 1H), 8.42 (s, 1H), 8.25 (d, *J* = 8.3 Hz, 1H), 7.88 - 7.80 (m, 1H), 7.80 - 7.73 (m, 2H), 5.05 (s, 2H), 3.12 - 3.02 (m, 1H), 3.01 - 2.79 (m, 2H), 2.69 - 2.51 (m, 1H), 2.46 - 2.30 (m, 2H), 1.95 - 1.81 (m, 1H). **SFC:** (column: Chiralpak AD-3 (50mmx4.6mm, 3µm); mobile phase: A: $CO_2$; B:MeOH[0.1% IPAm]; B%: 5% for 0.2 min, 5-50% for 1.0 min., 50% for 1.0 min., 50-5% for 0.4 min., 5% for 0.4 min., 3.4mL/min., $t_R$ = 1.264 min, ee% =97.3%.

[(3*P*,6*R or 6S*)-3-(Isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4,5,6,7,8-hexahydroquinazolin-1(2*H*)-yl]acetonitrile **(29d)** was obtained using the method described above for the synthesis of compound **(29a)**, except (3*P*,6*R or 6S*)-3-(Isoquinolin-4-yl)-6-(trifluoromethyl)-5,6,7,8-tetrahydroquinazoline-2,4(1*H*,3*H*)-dione **(27d)** was used in place of (3*M*,6*R or 6S*)-3-(Isoquinolin-4-yl)-6-(trifluoromethyl)-5,6,7,8-tetrahydroquinazoline-2,4(1*H*,3*H*)-dione **(27a)**. **LCMS (Method 17):** $t_R$ = 2.661 min, $[M+1]^+$ 401.1. **$^1$H NMR:** (400 MHz, METHANOL-d4) δ = 9.36 (s, 1H), 8.44 (s, 1H), 8.25 (d, J = 8.1 Hz, 1H), 7.86 - 7.80 (m, 1H), 7.80 - 7.72 (m, 2H), 5.14 - 4.98 (m, 2H), 3.11 - 3.01 (m, 1H), 3.00 - 2.80 (m, 2H), 2.73 - 2.53 (m, 1H), 2.45 - 2.31 (m, 2H), 1.86 (dq, J = 5.7, 12.1 Hz, 1H). **SFC:** (column: Chiralcel AD-3 (50mmx4.6mm, 3µm); mobile phase: A: $CO_2$; B: MeOH[0.1% IPAm]; B%: 5% for 0.2 min, 5-50% for 1.0 min., 50% for 1.0 min., 50-5% for 0.4 min., 5% for 0.4 min., 3.4mL/min., $t_R$ = 1.396 min, ee% =99.0%.

**Example 30:** Synthesis of 1-{[(3*M*)-3-(5-Fluoroisoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2*H*)-yl]methyl}cyclopropane-1-carbonitrile **(30a)** and 1-{[(3*P*)-3-(5-Fluoroisoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2*H*)-yl]methyl}cyclopropane-1-carbonitrile **(30b)**




Step 1: To a solution of 3-(5-fluoroisoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione (300 mg, 0.66 mmol, 1.0 eq.) in DMF (6 mL) was added (1-cyanocyclopropyl)methyl 4-methylbenzenesulfonate (200 mg, 0.80 mmol, 1.2 eq.), $Cs_2CO_3$ (430 mg, 1.32 mmol, 2.0 eq.), NaI (10 mg, 0.07 mmol, 0.1 eq.) at 25°C and the mixture stirred at 50°C for 16 hrs. The mixture was quenched with $H_2O$ (30 mL) at 0°C. Ethyl acetate (10 mL) was added to the mixture. The layers were separated, and the aqueous phase was extracted with EtOAc (20 mL x 3). The combined organic phases were washed with brine (20 mL), dried over anhydrous $Na_2SO_4$, filtered and concentrated in vacuum to give a crude product. The crude product was purified by prep-HPLC (column: C18 (250mmx50mm, 10μm); liquid phase: [A:$H_2O$(10mM $NH_4HCO_3$); B:ACN]B%: 10%-35%,20min])) to give 1-((3-(5-fluoroisoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)cyclopropane-1-carbonitrile **(30)** as a racemate. **LCMS (Method 18):** $t_R$ = 1.903 min. $[M+1]^+$ 455.3.

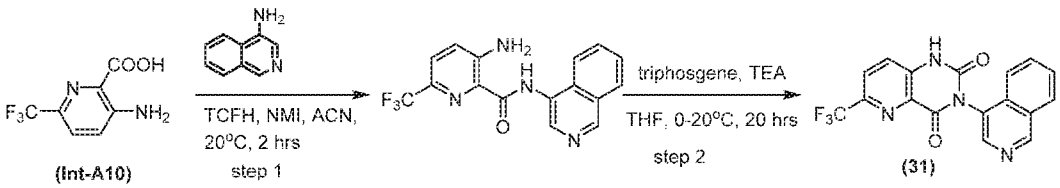
Step 2: The racemate **(30)** was separated by SFC (DAICEL CHIRALPAK AD (250mmx50mm,10um); liquid phase: 0.1%$NH_3H_2O$ EtOH]B%: 10%-50%,10min]) to give 2 peaks: peak 1 and peak 2. **SFC:** peak 1: $t_R$ = 1.144 min.; peak 2: $t_R$ = 1.314 min. Stereochemistry assigned by analogy to Example 16, wherein the chirality of the more active atropisomer(s) is assigned as ***(M)*** and subsequently the chirality of the more active atropisomer(s) is assigned as ***(P)***.

**Peak 1: (1-{[(3*M*)-3-(5-Fluoroisoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2*H*)-yl]methyl}cyclopropane-1-carbonitrile (30a): LCMS (Method 13):** $t_R$ = 2.545 min, $[M+1]^+$ 455.3. **$^1$H NMR:** (400 MHz, CHLOROFORM-d) δ = 9.41 (s, 1H), 8.59 (d, *J* = 1.8 Hz, 1H), 8.50 (s, 1H), 8.07 (dd, *J* = 2.0, 8.8 Hz, 1H), 7.99 - 7.91 (m, 1H), 7.79 (d, *J* = 8.9 Hz, 1H), 7.61-7.66 (m, 1H), 7.35-7.40 (m, 1H), 4.55 - 4.36 (m, 2H), 1.44 - 1.28 (m, 4H). **SFC:** (column: Chiralpak AD-3 (50mmx4.6mm, 3μm); mobile phase: A: $CO_2$; B:EtOH[0.1% IPAm]; B%: 5% for 0.2 min, 5-50% for 1.0 min., 50% for 1.0 min., 50-5% for 0.4 min., 5% for 0.4 min., 3.4mL/min., $t_R$ = 1.140 min, ee = 99.7%.

**Peak 2: 1-{[(3*P*)-3-(5-Fluoroisoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2*H*)-yl]methyl}cyclopropane-1-carbonitrile (30b):LCMS (Method 13):** $t_R$ = 2.542 mins, $[M+1]^+$ 455.3. **$^1$H NMR:** (400 MHz, CHLOROFORM-d) δ = 9.41 (s, 1H), 8.59 (s, 1H), 8.50 (s, 1H), 8.07 (d, *J* = 8.9 Hz, 1H), 7.95 (d, *J* = 8.2 Hz, 1H), 7.79 (d, *J* = 8.9 Hz, 1H), 7.70 - 7.59 (m, 1H), 7.38 (dd, *J* = 7.9, 12.5 Hz, 1H), 4.73 - 4.12 (m, 2H), 1.43 - 1.20 (m, 4H). **SFC:** (column: Chiralpak AD-3 (50mmx4.6mm, 3μm); mobile phase: A: $CO_2$; B:EtOH[0.1%

IPAm]; B%: 5% for 0.2 min, 5-50% for 1.0 min., 50% for 1.0 min., 50-5% for 0.4 min., 5% for 0.4 min., 3.4mL/min., $t_R$ = 1.312 min, ee = 98.6%.

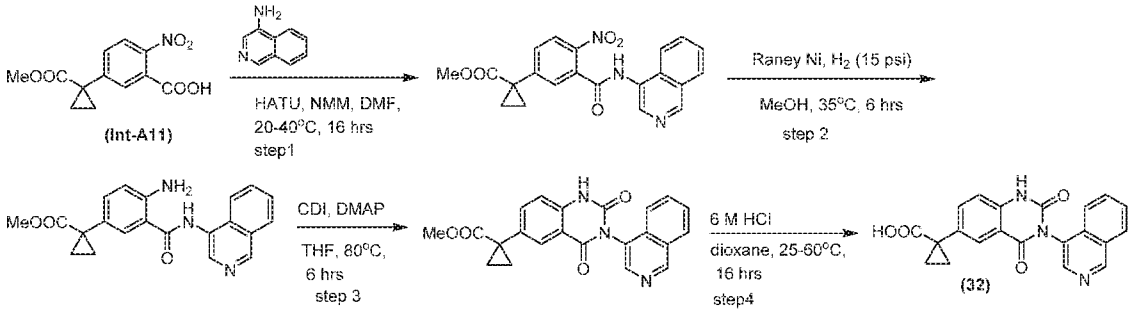
**Example 31:** Synthesis of 3-(isoquinolin-4-yl)-6-(trifluoromethyl)pyrido[3,2-d]pyrimidine-2,4(1H,3H)-dione **(31)**




Step 1: To a mixture of 3-amino-6-(trifluoromethyl)picolinic acid **(Int-A10)** (1.0 g, crude, 4.85 mmol, 1.0 eq.), isoquinolin-4-amine (699 mg, 4.85 mmol, 1.0 eq.), NMI (1.2 g, 14.55 mmol, 3.0 eq.) in ACN (10 mL) was added TCFH (1.6 g, 5.82 mmol, 1.2 eq.) in portions at 20°C. The mixture was stirred at 20°C for 2 hrs. The reaction mixture was poured into water (20 mL), extracted with EtOAc (10 mL x 3), the combined organic phases were washed by brine (20 mL), dried over $Na_2SO_4$, filtered and concentrated to give a crude product. The crude product was purified by silica gel column chromatography (petroleum ether/EtOAc = 100/0 to 70/30) togive 3-amino-N-(isoquinolin-4-yl)-6-(trifluoromethyl)picolinamide. **$^1$H NMR:** (400MHz, DMSO-$d_6$) δ = 10.55 (s, 1H), 9.24 (s, 1H), 8.82 (s, 1H), 8.20 (d, *J*=8.2 Hz, 1H), 7.93 - 7.89 (m, 1H), 7.89 - 7.84 (m, 1H), 7.78 (d, *J*=8.8 Hz, 1H), 7.74 (ddd, *J*=1.2, 6.8, 8.0 Hz, 1H), 7.47 (br s, 2H), 7.43 (s, 1H).

Step 2: To a solution of 3-amino-N-(isoquinolin-4-yl)-6-(trifluoromethyl)picolinamide (100 mg, 0.30 mmol, 1.0 eq.) and TEA (183 mg, 1.81 mmol, 6.0 eq.) in THF (1 mL) was added a solution of triphosgene (179 mg, 0.60 mmol, 2.0 eq.) in THF (0.5 mL) dropwise at 0°C. The mixture was stirred at 20°C for 20 hrs under $N_2$. The mixture was concentrated to give a crude product which was purified by prep-HPLC (column: Waters Xbridge BEH C18 250mmx50mm, 10μm; liquid phase: [A:$H_2O$(10mM $NH_4HCO_3$); B:ACN]B%: 5%-45%,20min]) to give 3-(isoquinolin-4-yl)-6-(trifluoromethyl)pyrido[3,2-d]pyrimidine-2,4(1H,3H)-dione **(31)**. **LCMS (Method 13):** $t_R$ = 1.90 mins, $[M+1]^+$ 359.0. **$^1$H NMR:** (400MHz, DMSO-$d_6$) δ = 12.18 (br s, 1H), 9.44 (s, 1H), 8.56 (s, 1H), 8.28 (br d, *J*=8.6 Hz, 1H), 8.21 (d, *J*=8.7 Hz, 1H), 8.07 (d, *J*=7.8 Hz, 1H), 7.90 (d, *J*=8.6 Hz, 1H), 7.82 - 7.74 (m, 2H).

**Example 32:** Synthesis of 1-(3-(isoquinolin-4-yl)-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-6-yl)cyclopropane-1-carboxylic acid **(32)**



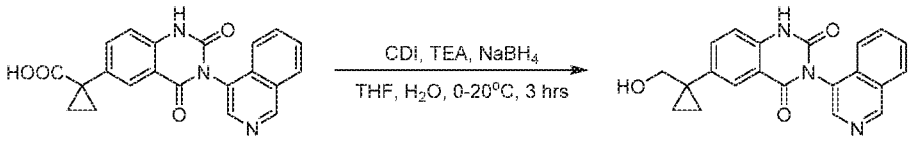

Step 1: To a solution of 5-(1-(methoxycarbonyl)cyclopropyl)-2-nitrobenzoic acid **(Int-A11)** (850 mg, 3.21 mmol, 1.0 eq.) in DMF (8.5 mL) was added HATU (1.5 g, 3.85 mmol, 1.2 eq.). The mixture was stirred at 25°C for 1 hr. Then to the mixture was added isoquinolin-4-amine (508 mg, 3.53 mmol, 1.1 eq.) and NMM (972 mg, 9.62 mmol, 3.0 eq.). The mixture was stirred at 45°C for 15 hrs. The mixture was quenched with $H_2O$ (30 mL), extracted with EtOAc (30 mL x 2). The combined organic phase was washed with brine (60 mL), dried, fitered and evaporated to give crude product which was purified by silca gel column chromatography (petroleum ether / EtOAc = 100%~29%) to give methyl 1-(3-(isoquinolin-4-ylcarbamoyl)-4-nitrophenyl)cyclopropane-1-carboxylate. **$^1$H NMR:** (400 MHz, METHANOL-$d_4$) δ = 9.15 (s, 1 H), 8.76 (s, 1 H), 8.11 - 8.21 (m, 3 H), 7.96 (s, 1 H), 7.81 - 7.91 (m, 2 H), 7.70 - 7.75 (m, 2 H), 3.66 (s, 3 H), 1.68 - 1.74 (m, 2 H), 1.35 - 1.41 (m, 2 H).

Step 2: To a mixture of Raney Ni (1.0 g) in EtOH (10 mL) was added methyl 1-(3-(isoquinolin-4-ylcarbamoyl)-4-nitrophenyl)cyclopropane-1-carboxylate (926 g, 2.37 mmol, 1.0 *eq*). The suspension was degassed under vacuum and purged with $H_2$ several times, and the mixture was stirred under $H_2$ (15 psi) at 35°C for 16 hrs. The mixture was filtered though a pad, the filtrate was concentrated to give methyl 1-(4-amino-3-(isoquinolin-4-ylcarbamoyl)phenyl)cyclopropane-1-carboxylate. **$^1$H NMR:** (400 MHz, CHLOROFORM-*d*) δ = 9.14 (s, 1 H), 8.75 (s, 1 H), 8.45 (s, 1 H), 8.01 (d, *J*=8.19 Hz, 1 H), 7.92 (d, *J*=8.19 Hz, 1 H), 7.75 (td, *J*=7.67, 1.16 Hz, 1 H), 7.62 - 7.69 (m, 2 H), 7.30 (dd, *J*=8.44, 2.08 Hz, 1 H), 6.71 (d, *J*=8.44 Hz, 1 H), 5.61 (br s, 2 H), 3.64 (s, 3 H), 1.58 - 1.63 (m, 2 H), 1.17 - 1.22 (m, 2 H).

Step 3: To a solution of methyl 1-(4-amino-3-(isoquinolin-4-ylcarbamoyl)phenyl)cyclopropane-1-carboxylate (679 mg, 1.88 mmol, 1.0 eq.) in THF (7 mL) was added DMAP (23 mg, 0.20 mmol, 0.1 eq.) and CDI (610 mg, 3.76 mmol, 2.0 eq.). The mixture was stirred at 80°C for 6 hrs. The mixture was quenched with $H_2O$ (10 mL), extracted with $CH_2Cl_2$ (30 mL x 2). The combined organic phase was washed with brine (30 mL), dried, fitered, and evaporated to give methyl 1-(3-(isoquinolin-4-yl)-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-6-yl)cyclopropane-1-carboxylate. **$^1$H NMR:** (400 MHz, CHLOROFORM-*d*) δ = 9.39 (s, 1 H), 8.54 (s, 1 H), 8.07 - 8.13 (m, 2 H), 7.64 - 7.71 (m, 3 H), 7.61 (dd, *J*=8.44, 1.96 Hz, 1 H), 7.10 (s, 1 H), 6.99 (d, *J*=8.31 Hz, 1 H), 3.64 (s, 3 H), 1.65 - 1.70 (m, 2 H), 1.20 - 1.24 (m, 2 H).

Step 4: To a solution of methyl 1-(3-(isoquinolin-4-yl)-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-6-yl)cyclopropane-1-carboxylate (150 mg, 0.39 mmol, 1.0 eq.) in dioxane (1 mL) was added 6 M HCl (1 mL) at 25°C and then the mixture was stirred at 60°C for 16 hrs. The reaction mixture was dried under nitrogen gas to give crude product which was was purified by prep-HPLC (column: Phenomenex C18 80mmx40mm, 3µm; liquid phase: [A:$H_2O$ (10mM $NH_4HCO_3$); B:ACN] B%: 15%-45%, 20min]) to give 1-(3-(isoquinolin-4-yl)-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-6-yl)cyclopropane-1-carboxylic acid **(32)**. **LCMS (Method 11):** $t_R$ = 1.988 mins, $[M+1]^+$ 374.0. **$^1$H NMR:** (400MHz, DMSO-$d_6$) δ = 9.42 (s, 1H), 8.54 (s, 1H), 8.30 - 8.24 (m, 1H), 7.86 - 7.79 (m, 2H), 7.79 - 7.70 (m, 3H), 7.24 (d, *J*=8.3 Hz, 1H), 1.46 (br s, 2H), 1.13 (br s, 2H).

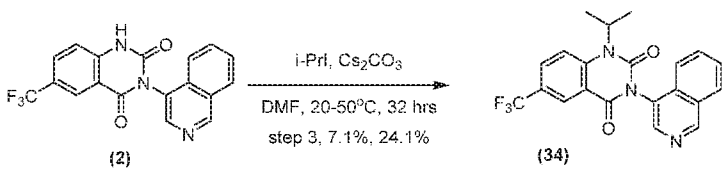
**Example 33:** Synthesis of 6-(1-(hydroxymethyl)cyclopropyl)-3-(isoquinolin-4-yl)quinazoline-2,4(1H,3H)-dione **(33)**




(32) (33)

To a solution of 1-(3-(isoquinolin-4-yl)-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-6-yl)cyclopropane-1-carboxylic acid **(32)** (153 mg, 0.41 mmol, 1.0 eq.) in THF (2 mL) was added TEA (62 mg, 0.61 mmol, 1.5 eq.) and CDI (100 mg, 0.61 mmol, 1.5 eq.) at 20°C. The mixture was stirred at 20°C for 2 hrs. $NaBH_4$ (16 mg, 0.41 mmol, 1.0 eq.) was then added to the mixture at 0°C, and the mixture was stirred at 20°C for 1 hr. The reaction mixture was dried under nitrogen gas to give crude product which was purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150mmx40mm, 10µm; liquid phase: [A:$H_2O$ (10mM $NH_4HCO_3$); B:ACN] B%: 1%-30%, 20 min]) to give 6-(1-(hydroxymethyl)cyclopropyl)-3-(isoquinolin-4-yl)quinazoline-2,4(1H,3H)-dione **(33)**. **LCMS (Method 13):** $t_R$ = 1.810 mins, $[M+1]^+$ 360.0. **$^1$H NMR:** (400MHz, CHLOROFORM-*d*) δ = 10.17 (br s, 1H), 9.31 (s, 1H), 8.15 - 8.03 (m, 3H), 7.73 - 7.53 (m, 4H), 6.89 (d, *J*=8.4 Hz, 1H), 3.76 - 3.63 (m, 2H), 0.94 - 0.79 (m, 4H).

**Example 34:** Synthesis of 1-isopropyl-3-(isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(34)**

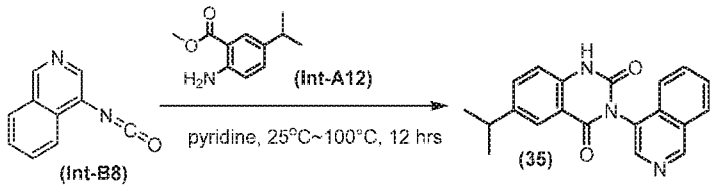



(2) (34)

To a solution of 3-(isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(2)** (200 mg, 0.56 mmol, 1.0 eq.) in DMF (2 mL) was added $Cs_2CO_3$ (364 mg, 1.12 mmol, 2.0 eq.) and 2-iodopropane (190 mg, 1.12 mmol, 2.0 eq.) at 20°C. The mixture was stirred at 50°C for 32 hrs.

The mixture was poured into water (5 mL) and extracted with EtOAc (5 mL x 3). The combined organic phases were washed with brine (5 mL), dried over $Na_2SO_4$, filtered and concentrated to give crude product which was purified by prep-HPLC (prep-HPLC (column: Waters Xbridge BEH C18 100x25mmx5μm; liquid phase: [A:10mM $NH_4HCO_3$ in $H_2O$; B:ACN] B%: 35%-70%, 10 min]) to give 1-isopropyl-3-(isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(34)**. **LCMS (Method 13):** $t_R$ = 2.508 mins, $[M+1]^+$ 400.0. **$^1$H NMR:** (400 MHz, DMSO-$d_6$) δ = 9.43 (s, 1H), 8.56 (s, 1H), 8.32 - 8.25 (m, 2H), 8.15 (dd, *J* = 2.2, 8.9 Hz, 1H), 8.00 (d, *J* = 9.1 Hz, 1H), 7.94 (br d, *J* = 7.4 Hz, 1H), 7.81 - 7.73 (m, 2H), 5.23 - 5.03 (m, 1H), 1.56 (dd, *J* = 4.8, 6.7 Hz, 6H).

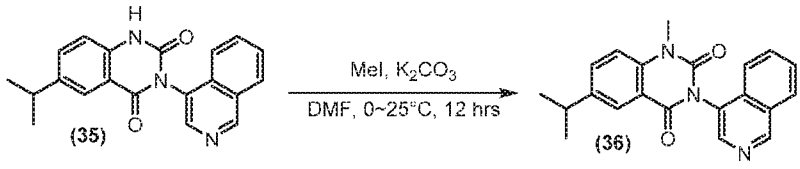
**Example 35:** Synthesis of 6-isopropyl-3-(isoquinolin-4-yl)quinazoline-2,4(1H,3H)-dione **(35)**




To a mixture of methyl 2-amino-5-isopropylbenzoate **(Int-A12)** (1.0 g, 5.18 mmol, 1.0 eq.) in pyridine (10 mL) was added 4-isocyanatoisoquinoline **(Int-B8)** (900 mg, 5.18 mmol, 1.0 eq.) at 25°C and the mixture was stirred at 100°C for 12 hrs under $N_2$. The mixture was quenched with $H_2O$ (10 mL), extracted with EtOAc (10 mL x 3). The combined organic phase was washed with brine (10 mL), dried over $Na_2SO_4$, filtered and concentrated to give crude product which was purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150mmx40mm,10μm; liquid phase: [A:$H_2O$(10mM $NH_4HCO_3$); B:ACN]B%: 25%-55%,20min]) to give 6-isopropyl-3-(isoquinolin-4-yl)quinazoline-2,4(1H,3H)-dione **(35)**. **LCMS (Method 13):** $t_R$ = 2.388 mins, $[M+1]^+$ 332.1.

**$^1$H NMR:** (400 MHz, DMSO-$d_6$) δ ppm 11.67 (s, 1 H) 9.42 (s, 1 H) 8.53 (s, 1 H) 8.25 - 8.28 (m, 1 H) 7.78 - 7.83 (m, 2 H) 7.72 - 7.78 (m, 2 H) 7.69 (dd, *J*=8.44, 2.1 Hz, 1 H) 7.26 (d, *J*=8.5 Hz, 1 H) 2.93 - 3.05 (m, 1 H) 1.23 (d, *J*=6.9 Hz, 6 H).

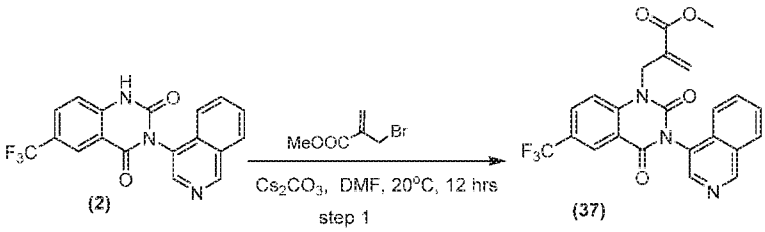
**Example 36:** Synthesis of 6-isopropyl-3-(isoquinolin-4-yl)-1-methylquinazoline-2,4(1H,3H)-dione **(36)**




To the mixture of 6-isopropyl-3-(isoquinolin-4-yl)quinazoline-2,4(1H,3H)-dione **(35)** (160 mg, 0.48 mmol, 1.0 eq.) in DMF (3 mL) were added $K_2CO_3$ (133 mg, 0.96 mmol, 2.0 eq.) and MeI (68 mg, 0.48 mmol, 1.0 eq.) at 0°C and the mixture was stirred at 20°C for 12 hrs. The mixture was quenched with $H_2O$ (5 mL) and extracted with EtOAc (5 mL x 3). The combined organic

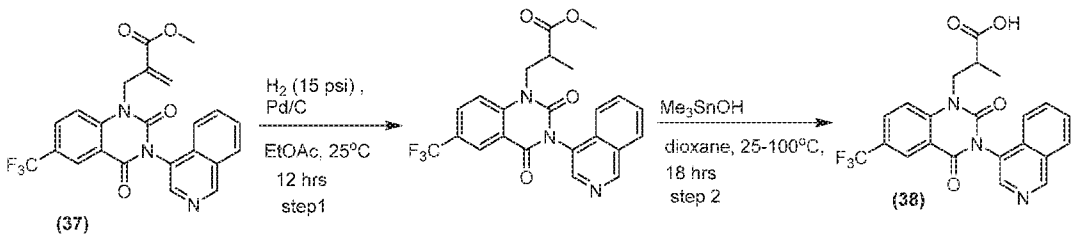
phase was washed with brine (3 mL), dried over $Na_2SO_4$, filtered and concentrated to give the crude product. The crude product was purified by silica gel column chromatography (petroleum ether/EtOAc = 20-25%, Petroleum ether/Ethyl acetate = 0/1, $R_f$ = 0.50) to give 6-isopropyl-3-(isoquinolin-4-yl)-1-methylquinazoline-2,4(1H,3H)-dione **(36)**. **LCMS (Method 13):** $t_R$ = 2.115 mins, $[M+1]^+$ 346.1. **$^1$H NMR:** (400 MHz, DMSO-$d_6$) δ ppm 9.43 (s, 1 H) 8.52 (s, 1 H) 8.24 - 8.30 (m, 1 H) 7.92 (d, *J*=1.7 Hz, 1 H) 7.81 - 7.86 (m, 1 H) 7.73 - 7.81 (m, 3 H) 7.54 (d, *J*=8.6 Hz, 1 H) 3.57 (s, 3 H) 3.05 (dt, *J*=13.7, 6.8 Hz, 1 H) 1.25 (d, *J*=6.88 Hz, 6 H).

**Example 37:** Synthesis of methyl 2-((3-(isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)acrylate **(37)**




To a solution of 3-(isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(2)** (105 mg, 0.30 mmol, 1.0 eq.) in DMF (3 mL) was added $Cs_2CO_3$ (196 mg, 0.60 mmol, 2.0 eq.) and methyl 2-(bromomethyl)acrylate (54 mg, 0.30 mmol, 1.0 eq.) at 20°C. The mixture was stirred at 20°C for 12 hrs. The reaction was quenched with $H_2O$ (10 mL) and extracted with EtOAc (6 mL × 2). The combined organic layers were washed with brine (15 mL × 2), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give crude product which was purified by flash silica gel chromatography (4 g, Eluent of 0~50% Ethyl acetate/Petroleum ether, 50 mL/min) to give methyl 2-((3-(isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)acrylate **(37)**. **LCMS (Method 13):** $t_R$ = 2.756 mins, $[M+1]^+$ 456.1. **$^1$H NMR:** (400 MHz, DMSO-$d_6$) δ = 9.44 (s, 1H), 8.60 (s, 1H), 8.32 (s, 1H), 8.30 - 8.25 (dd, *J* = 1.6, 7.2 Hz, 1H), 8.14 (dd, *J* = 1.8, 8.9 Hz, 1H), 8.04 (d, *J* = 7.9 Hz, 1H), 7.82 - 7.73 (m, 2H), 7.62 (d, *J* = 8.9 Hz, 1H), 6.23 (s, 1H), 5.89 (s, 1H), 5.06 - 4.93 (m, 2H), 3.78 (s, 3H).

**Example 38:** Synthesis of 3-(3-(isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2H)-yl)-2-methylpropanoic acid **(38)**

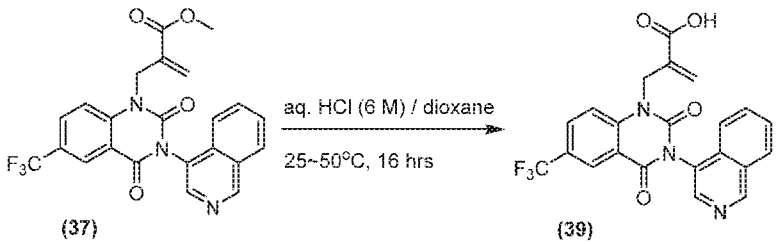



Step 1: To a mixture of methyl 2-((3-(isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)acrylate **(37)** (150 mg, 0.33 mmol, 1.0 eq.) in EtOAc (6 mL)

was added Pd/C (50 mg, 10%) at 25°C. The mixture was stirred at 25°C for 12 hrs under $H_2$ (15 psi) for 12 hrs. The mixture was filtered and the filtrate was concentrated to give a crude product which was purified by flash silica gel chromatography (4 g, Eluent of 0~40% Ethyl acetate/Petroleum ether, 50 mL/min) to give methyl 3-(3-(isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2H)-yl)-2-methylpropanoate. **$^1$H NMR:** (400 MHz, CHLOROFORM-d) δ = 9.39 (s, 1H), 8.58 (d, *J* = 1.8 Hz, 1H), 8.51 (s, 1H), 8.13 (br d, *J* = 8.0 Hz, 1H), 8.01 (br d, *J* = 8.8 Hz, 1H), 7.77 - 7.66 (m, 2H), 7.60 (dd, 1H), 7.53 (d, *J* = 8.9 Hz, 1H), 4.61 - 4.42 (m, 1H), 4.39 - 4.22 (m, 1H), 3.66 - 3.58 (br d, 3H), 3.14 - 3.02 (m, 1H), 1.33 (dd, *J* = 7.2, 8.9 Hz, 3H).

Step 2: To a mixture methyl 3-(3-(isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2H)-yl)-2-methylpropanoate (120 mg, 0.26 mmol, 1.0 eq.) in dioxane (2 mL) was added trimethylstannanol (95 mg, 0.52 mmol, 2.0 eq.) at 25°C. The mixture was stirred at 100°C for 18 hrs. The mixture was filtered and the filtrate was concentrated to give a crude product which was purified by prep-HPLC (column: Phenomenex Luna C18 75mmx30mm, 3μm; liquid phase: [A:FA/$H_2O$=0.1% v/v; B:ACN] B%: 20%-50%, 8 min]) to give 3-(3-(isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2H)-yl)-2-methylpropanoic acid **(38)**. **LCMS (Method 13):** $t_R$ = 1.510 mins, $[M+1]^+$ 444.1. **$^1$H NMR:** (400 MHz, CHLOROFORM-d) δ = 9.38 - 9.23 (br d, 1H), 8.55 (dd, *J* = 1.3, 7.3 Hz, 1H), 8.48 (s, 1H), 8.14 - 7.89 (m, 2H), 7.81 - 7.63 (m, 2H), 7.63 - 7.46 (m, 2H), 4.82 - 4.58 (m, 1H), 4.32 - 4.06 (m, 1H), 3.15 - 2.97 (m, 1H), 1.35 (dd, *J* = 1.6, 6.9 Hz, 3H). **$^1$H NMR:** (400 MHz, DMSO-$d_6$) δ = 9.42 (d, *J* = 1.8 Hz, 1H), 8.53 (d, *J* = 4.4 Hz, 1H), 8.34 (d, *J* = 1.7 Hz, 1H), 8.28 - 8.24 (m, 1H), 8.16 (dd, *J* = 2.1, 9.0 Hz, 1H), 7.87 (dd, *J* = 2.0, 8.9 Hz, 1H), 7.84 - 7.79 (m, 1H), 7.79 - 7.72 (m, 2H), 4.52 - 4.41 (m, 1H), 4.39 - 4.28 (m, 1H), 2.98 (br d, *J* = 7.3 Hz, 1H), 1.21 (dd, *J* = 7.0, 9.8 Hz, 3H).

**Example 39:** Synthesis of 2-((3-(isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)acrylic acid **(39)**

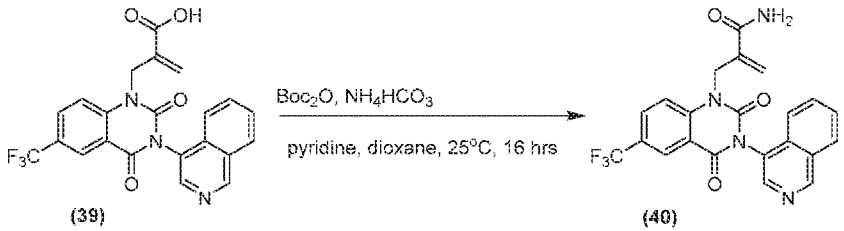



(37) (39)

To a mixture of methyl 2-((3-(isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)acrylate **(37)** (150 mg, 0.33 mmol, 1.0 eq.) in dioxane (2 mL) was added aq. HCl (2 mL, 6 M) at 25°C. The mixture was stirred at 50°C for 16 hrs. The mixture was concentrated to give crude product which was purified by prep-HPLC (column: Phenomenex Luna C18 150mmx30mm, 5μm; liquid phase: [A:HCOOH/$H_2O$=0.1% v/v; B:ACN] B%: 10%-60%, 8 min]) to give 2-((3-(isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-

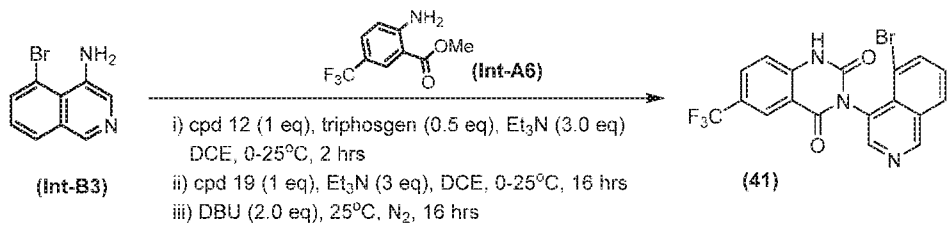
dihydroquinazolin-1(2H)-yl)methyl)acrylic acid **(39)**. **LCMS (Method 13):** $t_R$ = 2.527 mins, $[M+1]^+$ 442.1. **$^1$H NMR:** (400 MHz, DMSO-$d_6$) δ = 9.44 (s, 1H), 8.60 (s, 1H), 8.32 (s, 1H), 8.28 (br d, *J* = 7.3 Hz, 1H), 8.16 (br d, *J* = 8.9 Hz, 1H), 8.03 (br d, *J* = 8.3 Hz, 1H), 7.82 - 7.71 (m, 2H), 7.57 (d, *J* = 8.9 Hz, 1H), 6.17 (s, 1H), 5.79 (s, 1H), 4.97 (br s, 2H).

**Example 40:** Synthesis of 2-((3-(isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)acrylamide **(40)**




To a solution of 2-((3-(isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)acrylic acid **(39)** (150 mg, 0.34 mmol, 1.0 eq.) in dioxane (3 mL) was added pyridine (0.3 mL) and $Boc_2O$ (1.2 g, 5.44 mmol, 16.0 eq.) at 25°C. The mixture was stirred at 25°C for 0.5 hrs. Then $NH_4HCO_3$ (430 mg, 5.44 mmol, 16.0 eq.) was added to the mixture at 25°C. The mixture was stirred at 25°C for 15.5 hrs. The reaction was quenched with $H_2O$ (10 mL) and extracted with EtOAc (6 mL × 2). The combined organic layers were washed with brine (20 mL × 2), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give crude product. The crude product was purified by prep-HPLC (column: Waters Xbridge BEH C18 100mmx30mm, 10μm; liquid phase: [A:10mM $NH_4HCO_3$ in $H_2O$; B:ACN] B%: 20%-55%, 8 min]) to give 2-((3-(isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)acrylamide **(40)**. **LCMS (Method 13):** $t_R$ = 2.358 mins, $[M+1]^+$ 441.1. **$^1$H NMR:** (400 MHz, DMSO-$d_6$) δ = 9.45 (s, 1H), 8.61 (s, 1H), 8.31 (s, 1H), 8.28 (dd, J = 2.0, 6.9 Hz, 1H), 8.18 (dd, J = 1.9, 8.9 Hz, 1H), 8.03 (d, J = 7.6 Hz, 1H), 7.82 - 7.73 (m, 3H), 7.50 (d, J = 8.9 Hz, 1H), 7.33 (br s, 1H), 5.91 (s, 1H), 5.56 (s, 1H), 4.97 (s, 2H).

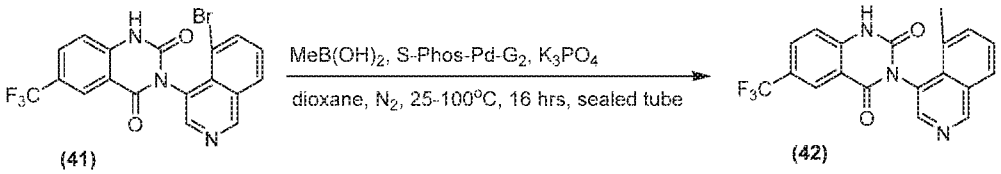
**Example 41:** Synthesis of 3-(5-bromoisoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(41)**




To a mixture of 5-bromoisoquinolin-4-amine **(Int-B3)** (500 mg, 2.30 mmol, 1.0 eq.) and $Et_3N$ (700 mg, 6.90 mmol, 3.0 eq.) in DCE (5 mL) was added a mixture of triphosgene (360 mg, 1.15 mmol, 0.5 eq.) in DCE (3 mL) at 0°C. The mixture was stirred at 0°C for 2 hrs. Then a mixture of methyl 2-amino-5-(trifluoromethyl)benzoate **(Int-A6)** (460 mg, 2.10 mmol, 0.9 eq.) and $Et_3N$

(700 mg, 6.90 mmol, 3.0 eq.) in DCE (2 mL) was added to the mixture at 0°C. The mixture was stirred at 25°C for 16 hrs. DBU (700 mg, 4.60 mmol, 2.0 eq.) was added to the mixture at 25°C and the mixture was stirred at 25°C for 16 hrs. The reaction was quenched with $H_2O$ (30 mL) and extracted with DCM (20 mL × 2). The combined organic layers were washed with brine (40 mL), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give crude product. The crude product was purified by prep-HPLC (column: 3_Phenomenex Luna C18 75mmx30mm, 3μm; liquid phase: [A:HCOOH/$H_2O$=0.1% v/v; B:ACN]B%: 20%-50%, 8min]) to give 3-(5-bromoisoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(41)**. **LCMS (Method 13):** $t_R$ = 2.408 min, $[M+1]^+$ 435.9. **$^1$H NMR:** (400 MHz, DMSO-$d_6$) δ = 12.31 - 12.14 (m, 1H), 9.54 (s, 1H), 8.63 (s, 1H), 8.37 (d, *J* = 7.5 Hz, 1H), 8.20 (s, 1H), 8.15 (dd, *J* = 0.9, 7.6 Hz, 1H), 8.11 (dd, *J* = 2.2, 8.6 Hz, 1H), 7.67 (t, *J* = 7.8 Hz, 1H), 7.49 (d, *J* = 8.6 Hz, 1H).

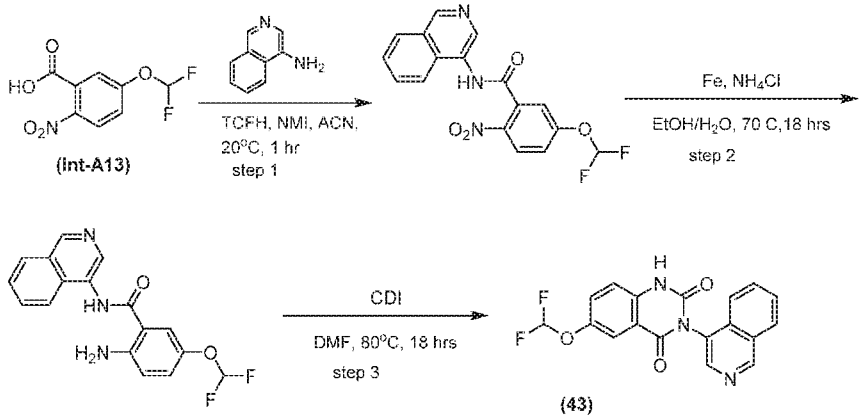
**Example 42:** Synthesis of 3-(5-methylisoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(42)**




(41) (42)

To a solution of 3-(5-bromoisoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(41)** (50 mg, 0.11 mmol, 1.0 eq.) in dioxane (2 mL) was added $MeB(OH)_2$ (35 mg, 0.55 mmol, 5.0 eq.), $K_3PO_4$ (47 mg, 0.22 mmol, 2.0 eq.) and S-Phos-Pd-$G_2$ (10 mg, 0.01 mmol, 0.1 eq.) at 25°C under $N_2$. The mixture was stirred at 100°C for 16 hrs. The reaction was poured into water (10 mL) and extracted with EtOAc (10 mL x 2). The combined organic phases were dried over $Na_2SO_4$, filtered and concentrated to give a crude product which was purified by prep-HPLC (column: 3_Phenomenex Luna C18 75mmx30mm, 3μm; liquid phase: [A:HCOOH/$H_2O$=0.1% v/v; B:ACN]B%: 40%-80%, 10min]) to give 3-(5-methylisoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(42)**. **LCMS (Method 13):** $t_R$ = 2.272 min, $[M+1]^+$ 372.1. **$^1$H NMR: (**400 MHz, DMSO-$d_6$) δ = 12.38 - 12.11 (m, 1H), 9.40 (s, 1H), 8.50 (s, 1H), 8.22 (d, *J* = 1.2 Hz, 1H), 8.18 - 8.07 (m, 2H), 7.68 - 7.59 (m, 2H), 7.49 (d, *J* = 8.6 Hz, 1H), 2.37 (s, 3H).

**Example 43:** Synthesis of 6-(difluoromethoxy)-3-(isoquinolin-4-yl)quinazoline-2,4(1H,3H)-dione **(43)**

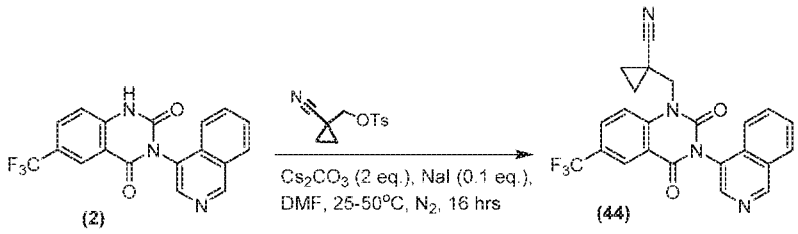



Step 1: A mixture of 5-(difluoromethoxy)-2-nitrobenzoic acid **(Int-A13)** (800 mg, 3.43 mmol, 1.0 eq), isoquinolin-4-amine (495 mg, 3.43 mmol, 1.0 eq), TCFH (962 mg, 3.43 mmol, 1.0 eq) and NMI (985 mg, 12.01 mmol, 3.5 eq) in $CH_3CN$ (8 mL) was stirred at 20°C for 1 hr. The reaction mixture was quenched with $H_2O$ (30 mL) and extracted with ethyl acetate (30 mL x 3). The combined organic layers were dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column (petroleum ether/EtOAc = 10/1) to give 5-(difluoromethoxy)-N-(isoquinolin-4-yl)-2-nitrobenzamide. **LCMS (Method 10):** $t_R$ = 0.614 min, $[M+1]^+$ 360.0.

Step 2: To the solution of 5-(difluoromethoxy)-N-(isoquinolin-4-yl)-2-nitrobenzamide (370 mg, 1.03 mmol, 1.0 eq) in EtOH (4 mL) and $H_2O$ (1 mL) was added Fe (288 mg, 5.15 mmol, 5.0 eq) and $NH_4Cl$ (275 mg, 5.15 mmol, 5.0 eq). The mixture was stirred at 70°C for 18 hrs. The reaction mixture was filtered and concentrated under reduced pressure to give 2-amino-5-(difluoromethoxy)-N-(isoquinolin-4-yl)benzamide which was used directly in the next step. **LCMS (Method 10):** $t_R$ = 0.589 min, $[M+1]^+$ 330.0.

Step 3: A solution of 2-amino-5-(difluoromethoxy)-N-(isoquinolin-4-yl)benzamide (370 mg, 1.12 mmol, 1.0 eq) and CDI (546 mg, 3.37 mmol, 3.0 eq) in DMF (4 mL) was stirred at 80°C for 18 hrs. The mixture was filtered and purified by prep-HPLC (column: Phenomenex Luna C18 75mmx30mm, 3μm; liquid phase: [A:FA/$H_2O$=0.1% v/v; B:ACN] B%: 15%-45%, 8min]) to give 6-(difluoromethoxy)-3-(isoquinolin-4-yl)quinazoline-2,4(1H,3H)-dione **(43)**. **LCMS (Method 13):** $t_R$ = 2.027 min, $[M+1]^+$ 356.1. **$^1$H NMR:** (400 MHz, DMSO-$d_6$) δ = 11.86 (s, 1 H), 9.45 (s, 1 H), 8.57 (s, 1 H), 8.31 - 8.25 (m, 1 H), 7.92 - 7.85 (m, 1 H), 7.82 - 7.73 (m, 2 H), 7.70 (d, *J* = 2.8 Hz, 1 H), 7.64 (dd, *J* = 8.8, 2.8 Hz, 1 H), 7.50 - 7.10 (m, 2 H).

**Example 44:** Synthesis of 1-((3-(isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)cyclopropane-1-carbonitrile **(44)**

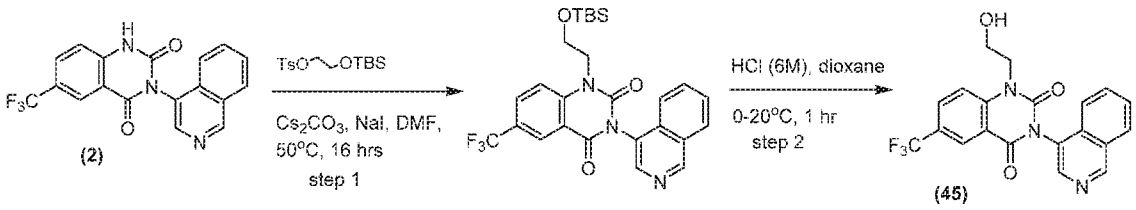



(2) (44)

To a solution of 3-(isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(2)** (200 mg, 0.56 mmol, 1.0 eq.) in DMF (4 mL) was added $Cs_2CO_3$ (364 mg, 1.12 mmol, 2.0 eq.), (1-cyanocyclopropyl)methyl 4-methylbenzenesulfonate (212 mg, 0.84 mmol, 1.5 eq.) and NaI (84 mg, 0.56 mmol, 1.0 eq.) at 25°C and the mixture stirred at 50°C for 16 hrs. The mixture was quenched with $H_2O$ (20 mL) and extracted with EtOAc (10 mL × 3). The combined organic layers were washed with brine (20 mL), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 200x40mm, 10μm; liquid phase: [A:$H_2O$ (0.1%FA); B:ACN] B%: 25%-65%, 20 min]) to give 1-((3-(isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)cyclopropane-1-carbonitrile **(44)**. **LCMS (Method 13):** $t_R$ = 2.688 min. $[M+1]^+$ 437.1. **$^1$H NMR:** (400 MHz, $CD_3OD$) δ (ppm) = 9.39 (s, 1H), 8.52 (s, 1H), 8.49 (d, *J* = 1.8 Hz, 1H), 8.27 (d, *J* = 8.0 Hz, 1H), 8.16 (dd, *J* = 2.1, 9.0 Hz, 1H), 8.04 (d, *J* = 9.0 Hz, 1H), 7.83 (dd, *J* = 1.4, 4.4 Hz, 2H), 7.78 (br dd, *J* = 2.4, 8.0 Hz, 1H), 4.60 (d, *J* = 15.6 Hz, 1H), 4.46 (d, *J* = 15.6 Hz, 1H), 1.44 - 1.33 (m, 4H).

Note: (1-cyanocyclopropyl)methyl 4-methylbenzenesulfonate was obtained using the following procedure: To a solution of 1-(hydroxymethyl)cyclopropane-1-carbonitrile (700 mg, 7.21 mmol, 1.0 eq.) in $CH_2Cl_2$ (4 mL) was added $Et_3N$ (1.3 g, 9.01 mmol, 1.3 eq.) at 25°C. A solution of TsCl (1.6 g, 8.65 mmol, 1.2 eq.) in $CH_2Cl_2$ (2 mL) was added dropwise at 0°C and the reaction was stirred at 25°C for 16 hrs. The reaction was quenched with $H_2O$ (20 mL) and extracted with $CH_2Cl_2$ (10 mL × 3). The combined organic layers were washed with brine (30 mL), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (20 g, Eluent of 15~25% Ethyl acetate/Petroleum ether, 60 mL/min) to give (1-cyanocyclopropyl)methyl 4-methylbenzenesulfonate. **$^1$H NMR:** (400 MHz, CHLOROFORM-d) δ = 7.83 (d, *J* = 8.3 Hz, 2H), 7.39 (d, *J* = 8.2 Hz, 2H), 4.00 (s, 2H), 2.47 (s, 3H), 1.38 (dd, *J* = 8 Hz, J = 6 Hz, 2H), 1.07 (dd, *J* = 8 Hz, J = 6 Hz, 2H).

**Example 45:** Synthesis of 1-(2-hydroxyethyl)-3-(isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(45)**



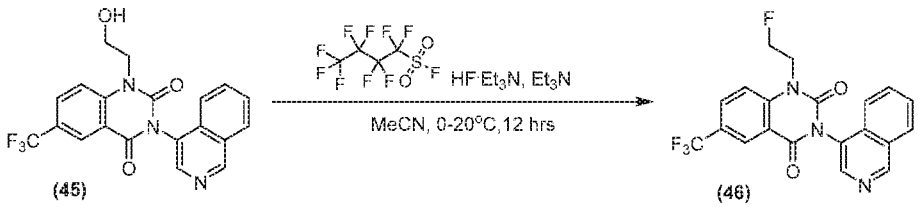

Step 1: A mixture of 3-(isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(2)** (500 mg, 1.51 mmol, 1.0 eq.), 2-((tert-butyldimethylsilyl)oxy)ethyl 4-methylbenzenesulfonate (540 mg, 1.51 mmol, 1.0 eq.), $Cs_2CO_3$ (985 mg, 3.02 mmol, 2.0 eq.) and NaI (230 mg, 1.51 mmol, 1.0 eq.) in DMF (5 mL) was stirred at 50°C for 16 hrs. The reaction mixture was quenched with water (20 mL) and extracted with EtOAc (20 mL x 2). The combined organic layers were washed by brine (20 mL x 2), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give crude product which was purified by column (Petroleum ether/EtOAc = 3/2 to 1/1) to give 1-(2-((tert-butyldimethylsilyl)oxy)ethyl)-3-(isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione. **LCMS (Method 18):** $t_R$ = 0.949 min. $[M+1]^+$ 516.6. **$^1$H NMR:** (400MHz, CHLOROFORM-d) δ = 9.39 (s, 1H), 8.54 (d, *J*=1.5 Hz, 1H), 8.51 (s, 1H), 8.15 - 8.12 (m, 1H), 7.95 (dd, *J*=2.1, 8.9 Hz, 1H), 7.80 - 7.66 (m, 3H), 7.58 (d, *J*=8.3 Hz, 1H), 4.39 (dt, *J*=2.8, 5.2 Hz, 2H), 4.04 (t, *J*=5.3 Hz, 2H), 0.80 (s, 9H), 0.00 (s, 6H).

Step 2: To a solution of 1-(2-((tert-butyldimethylsilyl)oxy)ethyl)-3-(isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione (520 mg, 0.19 mmol, 1.0 eq.) in dioxane (5 mL) was added 6 M HCl (5 mL) dropwise at 0°C and the mixture then stirred at 20°C for 1 hr. The reaction mixture was quenched with water (10 mL) and extracted with MTBE (10 mL). The aqueous phase pH was adjusted to 8 by addition of solid $Na_2CO_3$ and then extracted with $CH_2Cl_2$/i-PrOH (3/1, 10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give 1-(2-hydroxyethyl)-3-(isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(45)**. **LCMS (Method 13):** $t_R$ = 2.162 min. $[M+1]^+$ 402.1. **$^1$H NMR:** (400MHz, DMSO-$d_6$) δ = 9.45 (s, 1H), 8.55 (s, 1H), 8.31 - 8.25 (m, 2H), 8.19 (dd, *J*=2.0, 8.9 Hz, 1H), 7.98 - 7.91 (m, 2H), 7.82 - 7.72 (m, 2H), 4.99 (t, *J*=6.1 Hz, 1H), 4.29 (t, *J*=5.7 Hz, 2H), 3.74 (q, *J*=5.9 Hz, 2H).

Note: 2-((tert-butyldimethylsilyl)oxy)ethyl 4-methylbenzenesulfonate was obtained using the following procedure: To a solution of 2-((tert-butyldimethylsilyl)oxy)ethan-1-ol (2.0 g, 22.34 mmol, 1.0 eq.) and $Et_3N$ (2.3 g, 22.68 mmol, 2.0 eq.) in $CH_2Cl_2$ (10 mL) was added a solution of TsCl (2.5 g, 12.47 mmol, 1.1 eq.) in $CH_2Cl_2$ (10 mL) at 20°C and the mixture was stirred at 20°C for 5 hrs. The reaction mixture was quenched with water (20 mL) and extracted with $CH_2Cl_2$ (20 mL x 3). The combined organic layers were washed with brine (50 mL), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give crude product. The crude product was purified by column (Petroleum ether/EtOAc = 97/3 to 93/7) to give 2-((tert-butyldimethylsilyl)oxy)ethyl 4-methylbenzenesulfonate. **$^1$H NMR:** (400MHz, CHLOROFORM-*d*)

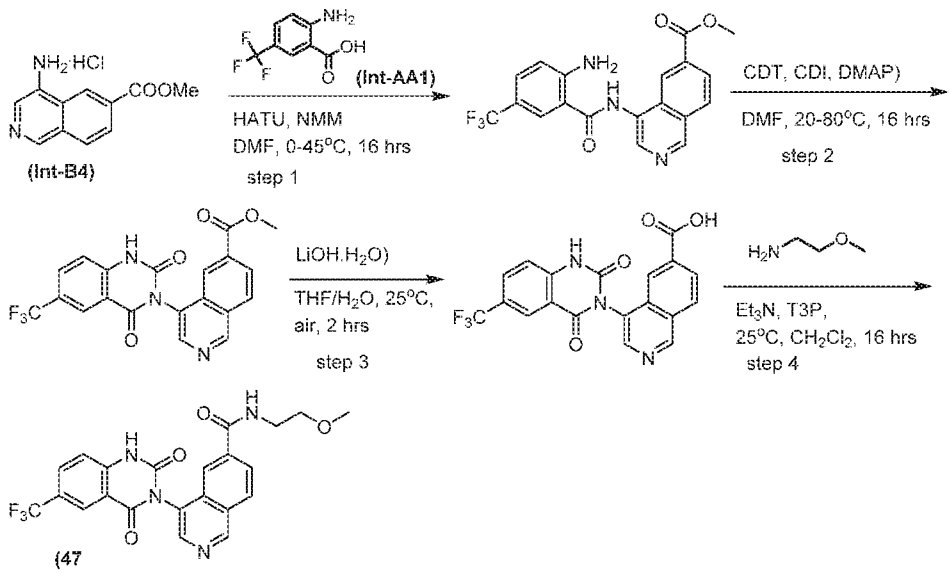
δ = 7.80 (d, *J*=8.3 Hz, 2H), 7.34 (d, *J*=8.3 Hz, 2H), 4.07 (t, *J*=5.1 Hz, 2H), 3.80 (t, *J*=5.0 Hz, 2H), 2.45 (s, 3H), 0.85 (s, 9H), 0.09-0.05 (m, 6H).

**Example 46:** Synthesis of 1-(2-fluoroethyl)-3-(isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(46)**




To a mixture of 1-(2-hydroxyethyl)-3-(isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(45)** (300 mg, 0.73 mmol, 1.0 eq.) in MeCN (5 mL) was added $Et_3N$ (660 mg, 6.57 mmol, 9.0 eq.) and 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonyl fluoride (660 mg, 2.19 mmol, 3.0 eq.) followed by the addition of HF·$Et_3N$ (335 mg, 2.19 mmol, 3.0 eq.) at 0°C under $N_2$ . The mixture was stirred at 20°C for 12 hrs. The reaction mixture was quenched with water (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic layers were washed by brine (20 mL), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give crude product. The crude product was purified by prep-HPLC (column: Phenomenex luna C18 80mmx40mm; 3μm; liquid phase: [A:$H_2O$= (0.04% HCl); B:ACN] B%: 43%-60%, 20 min]) to give 1-(2-fluoroethyl)-3-(isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(46)**. **LCMS (Method 13):** $t_R$ = 2.366 min. $[M+1]^+$ 404.1. **$^1$H NMR:** (400MHz, CHLOROFORM-*d*) δ = 9.69 (br s, 1H), 8.76 (br s, 1H), 8.52 (s, 1H), 8.46 (br d, *J*=7.2 Hz, 1H), 8.14 - 8.06 (m, 1H), 8.05 - 7.95 (m, 2H), 7.85 (br d, *J*=8.2 Hz, 1H), 7.66 (br d, *J*=8.8 Hz, 1H), 4.93 (br s, 1H), 4.81 (br s, 1H), 4.70 - 4.45 (m, 2H).

**Example 47:** Synthesis of 4-(2,4-dioxo-6-(trifluoromethyl)-1,4-dihydroquinazolin-3(2H)-yl)-N-(2-methoxyethyl)isoquinoline-6-carboxamide **(47)**



Step 1: To a mixture of methyl 4-aminoisoquinoline-6-carboxylate hydrochloride **(Int-B4)** (2.8 g, 13.58 mmol, 1.2 eq.) in DMF (30 mL) was added HATU (6.5 g, 16.97 mmol, 1.5 eq.) at 45°C. The reaction mixture was stirred at 45°C for 2 hrs. To the mixture was added 2-amino-5-(trifluoromethyl)benzoic acid **(Int-AA1)** (2.7 g, 11.31 mmol, 1.0 eq.) and NMM (3.4 g, 33.93 mmol, 3.0 eq.) at 80°C. The reaction mixture was stirred at 80°C for 14 hrs. The reaction mixture was poured into water (30 mL) and extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (50 mL), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give crude product. The crude product was purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150mmx40mm, 10μm; liquid phase: [A:$H_2O$ (10 mM $NH_4HCO_3$); B:ACN] B%: 35%-65%, 10 min]) to give methyl 4-(2-amino-5-(trifluoromethyl)benzamido)isoquinoline-6-carboxylate. **LCMS (Method 18):** $t_R$ = 1.823 min. $[M+1]^+$ 390.1.

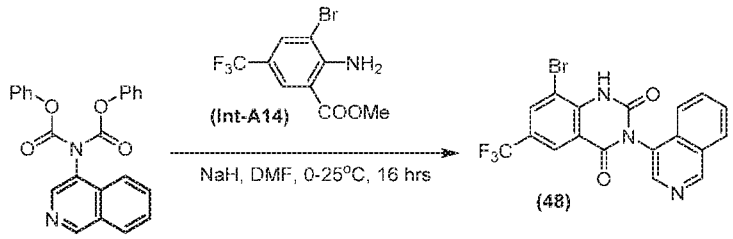
Step 2: To a mixture of methyl 4-(2-amino-5-(trifluoromethyl)benzamido)isoquinoline-6-carboxylate (400 mg, 1.03 mmol, 1.0 eq.) in DMF (5 mL) was added CDI (334 mg, 2.06 mmol, 2.0 eq.), CDT (338 mg, 2.06 mmol, 2.0 eq.) and DMAP (26 mg, 0.21 mmol, 0.2 eq.) at 20°C. The reaction mixture was stirred at 80°C for 16 hrs. The reaction was poured into water (50 mL) and extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (50 mL), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give crude product. The crude product was triturated with water to give methyl 4-(2,4-dioxo-6-(trifluoromethyl)-1,4-dihydroquinazolin-3(2H)-yl)isoquinoline-6-carboxylate. **LCMS (Method 12):** $t_R$ = 0.705 min. $[M+1]^+$ 416.1.

Step 3: To a mixture of methyl 4-(2,4-dioxo-6-(trifluoromethyl)-1,4-dihydroquinazolin-3(2H)-yl)isoquinoline-6-carboxylate (550 mg, 1.33 mmol, 1.0 eq.) in THF/$H_2O$ (5 mL, V/V = 1/1) was added $LiOH.H_2O$ (64 mg, 2.66 mmol, 2.0 eq.) at 25°C. The reaction mixture was stirred at 25°C for 2 hrs. The reaction was poured into HCl aq. (4 N, 20 mL) and filtered. The filter cake was collected to give 4-(2,4-dioxo-6-(trifluoromethyl)-1,4-dihydroquinazolin-3(2H)-yl)isoquinoline-6-carboxylic acid. **LCMS (Method 12):** $t_R$ = 0.536 min. $[M+1]^+$ 402.1.

Step 4: To a mixture of 4-(2,4-dioxo-6-(trifluoromethyl)-1,4-dihydroquinazolin-3(2H)-yl)isoquinoline-6-carboxylic acid, (200 mg, 0.50 mmol, 1.0 eq.), 2-methoxyethan-1-amine (45 mg, 0.60 mmol, 1.2 eq.) and $Et_3N$ (253 mg, 2.50 mmol, 5.0 eq.) in $CH_2Cl_2$ (5 mL) was added T3P (477 mg, 0.75 mmol, 1.5 eq.) at 25°C. The reaction mixture was stirred at 25°C for 16 hrs. The reaction mixture was concentrated to give crude product which was purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150mmx40mm, 10μm; liquid phase: [A:$H_2O$ (10 mM $NH_4HCO_3$); B:ACN] B%: 35%-65%, 20 min]) to give 4-(2,4-dioxo-6-(trifluoromethyl)-1,4-dihydroquinazolin-3(2H)-yl)-N-(2-methoxyethyl)isoquinoline-6-carboxamide **(47)**. **LCMS (Method 17):** $t_R$ = 2.471 min. $[M+1]^+$ 459.1. **$^1$H NMR:** (400 MHz, DMSO-$d_6$) δ = 12.20 (br s, 1 H),

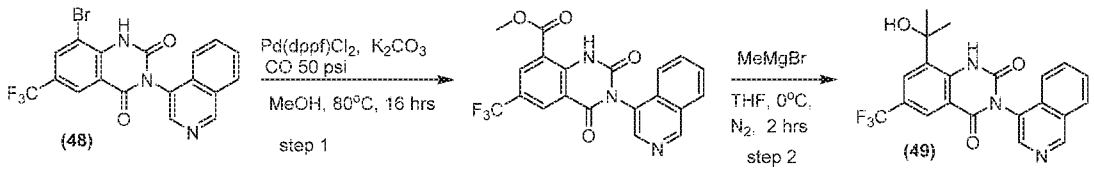
9.51 (s, 1 H), 8.87 (br s, 1 H), 8.66 (s, 1 H), 8.34 - 8.39 (m, 1 H), 8.30 (s, 1 H), 8.22 (s, 1 H), 8.11 - 8.20 (m, 2 H), 7.52 (d, *J*=8.6 Hz, 1 H), 3.42 - 3.44 (m, 4 H), 3.22 (s, 3 H).

**Example 48:** Synthesis of 8-bromo-3-(isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(48)**




To a solution of methyl 2-amino-3-bromo-5-(trifluoromethyl)benzoate **(Int-A14)** (217 mg, 0.73mmol, 1.4 eq.) in DMF (2 mL) was added NaH (19 mg, 0.78 mmol, 1.5 eq.) at 0°C and the mixture was stirred at 0°C for 1 hr. Then phenyl isoquinolin-4-yl(phenoxycarbonyl)carbamate **(Int-B7)** (200 mg, 0.52 mmol, 1.0 eq.) was added to the above mixture at 0°C and the mixture was stirred 25°C for 15 hrs. The mixture was diluted with iced water (10 mL), adjusted to pH = 7 with saturated $NaHCO_3$ aqueous at 0°C. Then the aqueous phase was extracted with EtOAc (20 mL x 2). The combined organic layers were washed with brine (50 mL), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give crude product. The crude product was purified by prep-HPLC (column: Phenomenex luna C18 100mmx40mm, 3μm; liquid phase: [A:TFA/$H_2O$=0.075% v/v; B:ACN] B%: 30%-60%, 8 min]) to give 8-bromo-3-(isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(48)**. **LCMS (Method 3):** $t_R$ = 2.597 min. $[M+1]^+$ 436.18. **$^1$H NMR:** (400MHz, DMSO-$d_6$) δ = 11.42 (s, 1H), 9.46 (s, 1H), 8.59 (s, 1H), 8.46 (s, 1H), 8.31 - 8.27 (dd, 1H), 8.20 (s, 1H), 8.06 (br d, *J*=7.6 Hz, 1H), 7.82 - 7.75 (m, 2H).

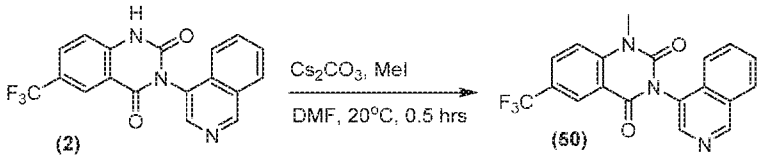
**Example 49:** Synthesis of 8-(2-hydroxypropan-2-yl)-3-(isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(49)**




Step 1: To a mixture of 8-bromo-3-(isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(48)** (200 mg, 0.46 mmol, 1.0 eq.) in MeOH (10 mL) was added $K_2CO_3$ (159 mg, 1.15 mmol, 2.5 eq.) and $Pd(dppf)Cl_2$ (37 mg, 0.05 mmol, 0.1 eq.) at 20°C under CO (50 psi). The reaction was stirred at 80°C for 16 hrs CO (50 psi). The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography ($SiO_2$, petroleum ether/ethyl acetate = 10/1 to 0/1) to give methyl 3-(isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-1,2,3,4-tetrahydroquinazoline-8-carboxylate.

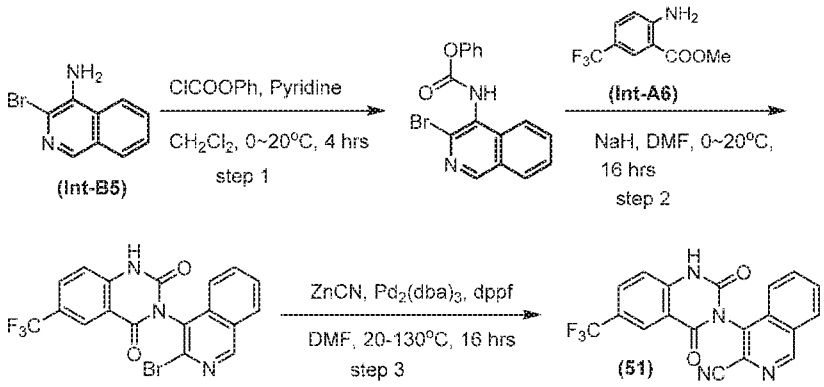
Step 2: To a mixture of methyl 3-(isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-1,2,3,4-tetrahydroquinazoline-8-carboxylate (50 mg, 0.12 mmol, 1.0 eq.) in THF (2 mL) was added MeMgBr (0.2 mL, 0.60 mmol, 5.0 eq.) at 0°C under $N_2$. The reaction was stirred at 0°C for 2 hrs. The reaction mixture was quenched with $NH_4Cl$ (5 mL), extracted with $CH_2Cl_2$ (10 mL x 2). The combined organic layers were washed with brine (10 mL), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge BEH C18 100x25mmx5µm; liquid phase: water ($NH_4HCO_3$)-ACN] B%: 30%-60%, 10 min]) to give 8-(2-hydroxypropan-2-yl)-3-(isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(49)**. **LCMS (Method 19):** $t_R$ = 2.599 min. $[M+1]^+$ 415.9. **$^1$H NMR:** (400MHz, CHLOROFORM-*d*) δ = 10.92 (s, 1H), 9.38 (s, 1H), 8.51 (s, 1H), 8.42 (s, 1H), 8.13 (d, *J*=8.0 Hz, 1H), 7.75 (d, *J*=1.8 Hz, 1H), 7.73 - 7.70 (m, 1H), 7.69 - 7.57 (m, 2H), 3.25 (br s, 1H), 1.83 (d, *J*=4.1 Hz, 6H).

**Example 50:** Synthesis of 3-(isoquinolin-4-yl)-1-methyl-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(50)**




To a solution of 3-(isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(2)** (200 mg, 0.56 mmol, 1.0 eq) in DMF (5 mL) was added $Cs_2CO_3$ (365 mg, 1.12 mmol, 2.0 eq) and MeI (80 mg, 0.56 mmol, 1.0 eq.) at 20°C. The reaction mixture was stirred for 0.5 hrs at 20°C. The reaction was poured into water (20 mL) and extracted with EtOAc (20 mL x 2). The organic phases were washed with brine (20 mL), dried over $Na_2SO_4$, filtered and concentrated to give crude product. The crude was purified by prep-HPLC (column: Phenomenex Gemini-NX C18 75mmx30mm, 3µm; liquid phase: [A:10mM $NH_4HCO_3$ in $H_2O$; B:ACN] B%: 40%-60%, 8min]) to give3-(isoquinolin-4-yl)-1-methyl-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(50)**. **LCMS (Method 1):** $t_R$ = 2.268 min. $[M+1]^+$ 372.1. **$^1$H NMR:** (400MHz, CHLOROFORM-d) δ 9.40 (s, 1H), 8.57 (d, *J*=1.6 Hz, 1H), 8.52 (s, 1H), 8.14 (d, *J*=7.6 Hz, 1H), 8.03 (dd, *J*=2.1, 8.7 Hz, 1H), 7.77 - 7.66 (m, 2H), 7.60 (d, *J*=8.2 Hz, 1H), 7.48 (d, *J*=8.8 Hz, 1H), 3.75 (s, 3H).

**Example 51:** Synthesis of 4-(2,4-dioxo-6-(trifluoromethyl)-1,4-dihydroquinazolin-3(2H)-yl)isoquinoline-3-carbonitrile **(51)**



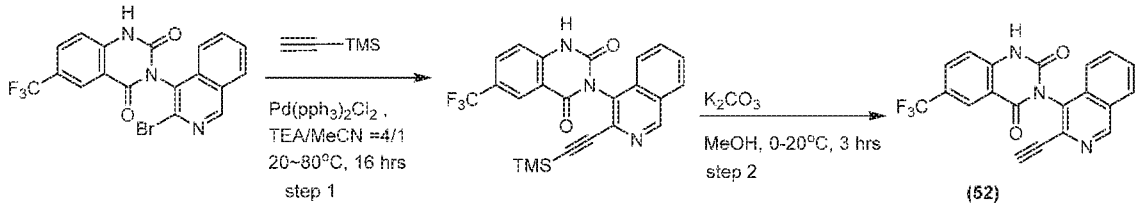

Step 1: To a mixture of 3-bromoisoquinolin-4-amine **(Int-B5)** (3.5 g, 15.76 mmol, 1.0 eq.) and pyridine (5 g, 63.07 mmol, 4.0 eq.) in $CH_2Cl_2$ (40 mL) was added ClCOOPh (6.1 g, 39.40 mmol, 2.5 eq.) at 0°C. The mixture was stirred at 20°C for 4 hrs. The reaction solution was poured into water (80 mL) and extracted with $CH_2Cl_2$ (50 mL x 3), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column (EtOAc/Petroleum ether = 35%~50%) to give phenyl (3-bromoisoquinolin-4-yl)carbamate. **LCMS (Method 5):** $t_R$ = 0.748 min. $[M+1]^+$ 463.0. **$^1$H NMR:** (400 MHz, CHLOROFORM-*d*) δ = 9.14 (s, 1H), 8.12 (d, *J* = 8.5 Hz, 2H), 7.95 (dt, *J* = 1.1, 7.7 Hz, 1H), 7.77 (dt, *J* = 0.8, 7.7 Hz, 1H), 7.38 - 7.31 (m, 4H), 7.26 - 7.19 (m, 2H), 7.12 - 7.05 (m, 4H).

Step 2: To a solution of methyl 2-amino-5-(trifluoromethyl)benzoate **(Int-A6)** (1.7 g, 7.80 mmol, 1.5 eq.) in DMF (30 mL) was added NaH (292 mg, 7.30 mmol, 1.4 eq.) at 0°C under $N_2$. The mixture was stirred at 0°C for 30 mins. Phenyl (3-bromoisoquinolin-4-yl)carbamate (2.4 g, 5.20 mmol, 1.0 eq.) in DMF (20 mL) was added dropwise at 0°C under $N_2$. The mixture was stirred at 20°C for 15.5 hrs. The reaction mixture was poured into water (60 mL) and extracted with EtOAc (50 mL x 3). The combined organic layers were washed by brine (50 mL x 2), dried over Na2SO4, filtered and concentrated under reduced pressure to give the residue. The residue was purified by column (EtOAc/Petroleum ether = 40%~ 60%) to give 3-(3-bromoisoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione. **LCMS (Method 12):** $t_R$ = 0.674 min. [M-1] 433.8).

Step 3: To a solution of 3-(3-bromoisoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione (300 mg, 0.69 mmol, 1.0 eq.) and $ZnCN_2$ (143 mg, 1.38 mmol, 2.0 eq.) in DMF (5 mL) was added $Pd_2(dba)_3$ (30mg) and DPPF (45 mg) at 20°C. The mixture was stirred at 130°C for 16 hrs under $N_2$. The reaction solution was poured into $H_2O$ (10 mL) and extracted with EtOAc (15 mL x 3). The combined organic layers were washed with brine (10 mL x 2), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give a residue. The residue was purified by TLC (EtOAc/Petroleum ether =60%~100%) to give crude product which was purified by prep-HPLC ($NH_4HCO_3$) to give 4-(2,4-dioxo-6-(trifluoromethyl)-1,4-dihydroquinazolin-3(2H)-yl)isoquinoline-3-carbonitrile **(51)**. **LCMS (Method 1):** $t_R$ = 2.488 min. $[M+1]^+$ 383.0. **$^1$H NMR:**

(400 MHz, DMSO-$d_6$) δ = 12.50 (br s, 1H), 9.63 (s, 1H), 8.46 (d, *J* = 7.3 Hz, 1H), 8.33 (d, *J* = 7.9 Hz, 1H), 8.25 (s, 1H), 8.18 (br d, *J* = 8.5 Hz, 1H), 8.06 - 7.95 (m, 2H), 7.55 (d, *J* = 8.4 Hz, 1H).

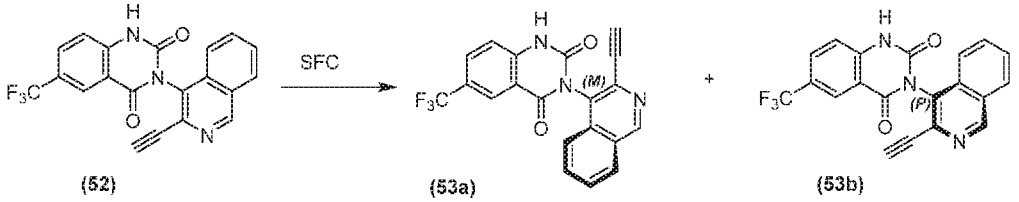
**Example 52:** Synthesis of 3-(3-ethynylisoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(52)**




Step 1: To the solution of 3-(3-bromoisoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione (400 mg, 0.92 mmol, 1.0 eq.) in TEA/MeCN (4/1mL) was added ethynyltrimethylsilane (451 mg, 4.60 mmol, 5.0 eq.) and $Pd(pph_3)_2Cl_2$ (40 mg) at 20°C. The mixture was stirred at 80°C for 16 hrs. The reaction solution was poured into water (20 mL) and extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (10 mL x 2), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column (Petroleum ether/EtOAc = 70%~100%) to give 6-(trifluoromethyl)-3-(3-((trimethylsilyl)ethynyl)isoquinolin-4-yl)quinazoline-2,4(1H,3H)-dione. **LCMS: (Method 20):** $t_R$ = 0.837 min. [M-1] 452.2.

Step 2: To a solution of 6-(trifluoromethyl)-3-(3-((trimethylsilyl)ethynyl)isoquinolin-4-yl)quinazoline-2,4(1H,3H)-dione (300 mg, 0.66 mmol, 1.0 eq.) in MeOH (6 mL) was added $K_2CO_3$ (183 mg, 1.32 mmol, 2.0 eq.) at 0°C. The mixture was stirred at 20°C for 2 hrs. The reaction solution was poured into $H_2O$ (10 mL) and extracted with EtOAc (20 mL x 3), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give the residue. The residue was purified by prep-HPLC ($NH_4CO_3$) to give 3-(3-ethynylisoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(52)**. **LCMS (Method 1):** $t_R$ = 2.424 min. $[M+1]^+$ 382.0. **$^1$H NMR:** (400 MHz, CHLOROFORM-d) δ = 9.48 - 9.42 (m, 1H), 9.39 (s, 1H), 8.49 (s, 1H), 8.18 - 8.11 (m, 1H), 7.88 (dd, J = 1.8, 8.6 Hz, 1H), 7.82 - 7.71 (m, 2H), 7.66 (d, J = 8.2 Hz, 1H), 7.18 (d, J = 8.6 Hz, 1H), 3.27 (s, 1H).

**Example 53:** Synthesis of (3*M*)-3-(3-Ethynylisoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1*H*,3*H*)-dione **(53a)**
(3*P*)-3-(3-Ethynylisoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1*H*,3*H*)-dione **(53b)**



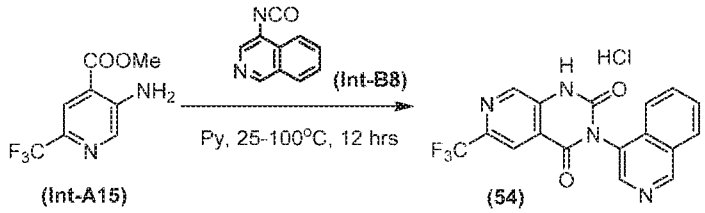

Racemate 3-(3-ethynylisoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(52)** was separated by chiral SFC (Chiralpak IG-3 (100mmx3mm,3um); 5-55% IPA w/ 0.1% $NH_3/CO_2$ 2.5mL/min 1800 psi) to obtain two peaks: peak 1: $t_R$ = 1.44 min.; peak 2: $t_R$ = 1.54 min.

Stereochemistry assigned by analogy to Example 16, wherein the chirality of the more active atropisomer(s) is assigned as ***(M)*** and subsequently the chirality of the more active atropisomer(s) is assigned as ***(P)***.

**Peak 1:** (3*M*)-3-(3-Ethynylisoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1*H*,3*H*)-dione **(53a): LCMS (Method 30):** $t_R$ = 2.424 min, $[M+1]^+$ 382.1. **$^1$H NMR:** (400MHz, DMSO-$d_6$) δ = 12.29 (s (br), 1H), 9.46 (d, *J*=0.9 Hz,1H), 8.37 - 8.28 (m, 1H), 8.27 - 8.22 (m, 1H), 8.19 - 8.06 (m, 2H), 7.91 - 7.79 (m, 2H), 7.54 (d, *J*=8.6 Hz, 1H), 4.45 (s, 1H).

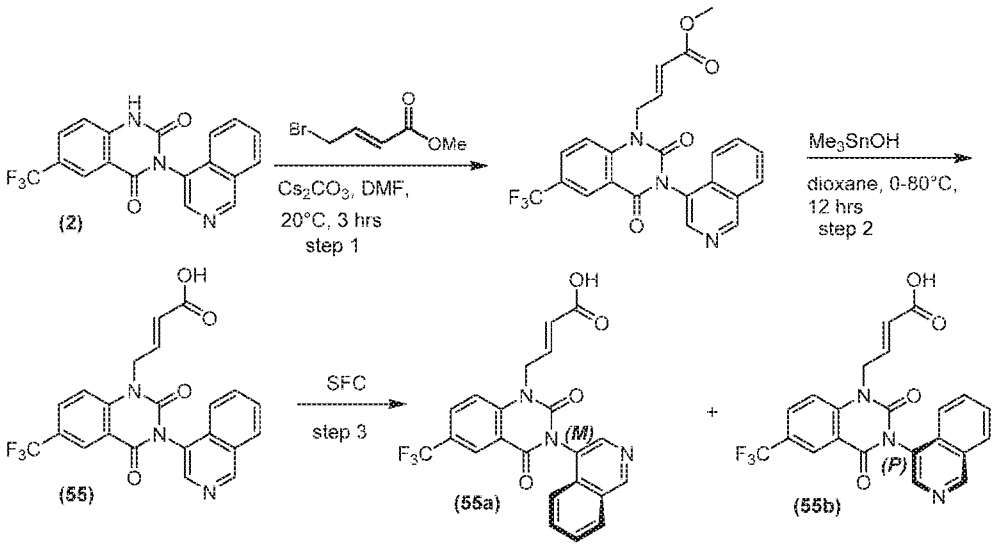
**Peak 2:** (3*P*)-3-(3-Ethynylisoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1*H*,3*H*)-dione **(53a): LCMS (Method 30):** $t_R$ = 2.423 min, $[M+1]^+$ 382.1. **$^1$H NMR:** (400MHz, DMSO-$d_6$) δ = 12.31 (s (br), 1H), 9.48 (d, *J*=0.8 Hz,1H), 8.39 - 8.30 (m, 1H), 8.26 (d, *J*=2.2 Hz,1H), 8.21 - 8.09 (m, 2H), 7.92 – 7.81 (m, 2H), 7.55 (d, *J*=8.6 Hz, 1H), 4.47 (s, 1H).

**Example 54:** Synthesis of 3-(isoquinolin-4-yl)-6-(trifluoromethyl)pyrido[3,4-d]pyrimidine-2,4(1H,3H)-dione **(54)**




A solution of methyl 5-amino-2-(trifluoromethyl)isonicotinate **(Int-A15)** (500 mg, 2.27 mmol, 1.0 eq.) in pyridine (5 mL) was added to 4-isocyanatoisoquinoline **(Int-B8)** (600 mg crude, 2.27 mmol, 1.0 eq.) at 25°C and the mixture was stirred for 12 hrs at 100°C under $N_2$. The reaction mixture was concentrated to give a residue. The residue was diluted with $H_2O$ (20 mL) and extracted with EtOAc (5 mL x 3). The combined organic layers were dried over $Na_2SO_4$, filtered and concentrated to give a crude product. The crude product was purified by prep-HLC (HCl) to obtained 3-(isoquinolin-4-yl)-6-(trifluoromethyl)pyrido[3,4-d]pyrimidine-2,4(1H,3H)-dione **(54)**. **LCMS (Method 1):** $t_R$ = 2.134 min. $[M+1]^+$ 359.1. **$^1$H NMR:** (400MHz, DMSO-d6) δ = 12.26 (s, 1H), 9.60 (s, 1H), 8.65 (s, 1H), 8.38 (d, *J*=7.9 Hz, 1H), 8.26 - 8.15 (m, 2H), 8.01 - 7.78 (m, 3H).

**Example 55:** Synthesis of (2*E*)-4-[(3*M*)-3-(Isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2*H*)-yl]but-2-enoic acid **(55a)**
(2*E*)-4-[(3*P*)-3-(Isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2*H*)-yl]but-2-enoic acid **(55b)**




Step 1: To a solution of 3-(isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(2)** (500 mg, 1.40 mmol, 1.0 eq.) in DMF (5 mL) was added $Cs_2CO_3$ (912 mg, 2.80 mmol, 2.0 eq.) and methyl (E)-4-bromobut-2-enoate (376 mg, 2.10 mmol, 1.5 eq.) at 20°C under nitrogen. The reaction was stirred at 20°C for 3 hrs. The reaction was slowly quenched with water (20 mL) and extracted with EtOAc (10 × 3 mL). The combined organic layers were washed with brine (10 mL), dried over $Na_2SO_4$, filtered and concentrated in vacuum to give a crude product. The crude product was purified by column on silica-gel (petroleum ether /EtOAc = 10 - 40%) to give methyl (E)-4-(3-(isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2H)-yl)but-2-enoate. **$^1$H NMR:** (400 MHz, CHLOROFORM-*d*) δ = 9.42 (s, 1 H), 8.59 (d, *J*=1.38 Hz, 1 H), 8.54 (s, 1 H), 8.17 (d, *J*=7.88 Hz, 1 H), 8.00 (dd, *J*=8.88, 1.88 Hz, 1 H), 7.76 - 7.82 (m, 1 H), 7.70 - 7.75 (m, 1 H), 7.60 (d, *J*=7.88 Hz, 1 H), 7.33 (d, *J*=8.88 Hz, 1 H), 7.06 (dt, *J*=15.82, 4.85 Hz, 1 H), 5.96 - 6.06 (m, 1 H), 5.02 - 5.07 (m, 2 H), 3.76 (s, 3 H).

Step 2: To a solution of methyl (E)-4-(3-(isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2H)-yl)but-2-enoate (450 mg, 0.99 mmol, 1.0 eq.) in dioxane (6 mL) was added $Me_3SnOH$ (358 mg, 1.98 mmol, 2.0 eq.) at 0°C under nitrogen. The reaction was stirred for 12 hrs at 80°C. The reaction was slowly quenched with water (10 mL), adjusted to pH ~5 with 1N HCl and extracted with EtOAc (10 × 3 mL). The combined organic layers were dried over $Na_2SO_4$, filtered and concentrated in vacuum to give a crude product. The crude product was purified by prep-HPLC (column: Waters Xbridge BEH C18 100mmx30mm, 10μm; liquid phase: [A:10mM $NH_4HCO_3$ in $H_2O$; B:ACN]B%: 10%-40%, 8 min]) to give racemic (E)-4-(3-

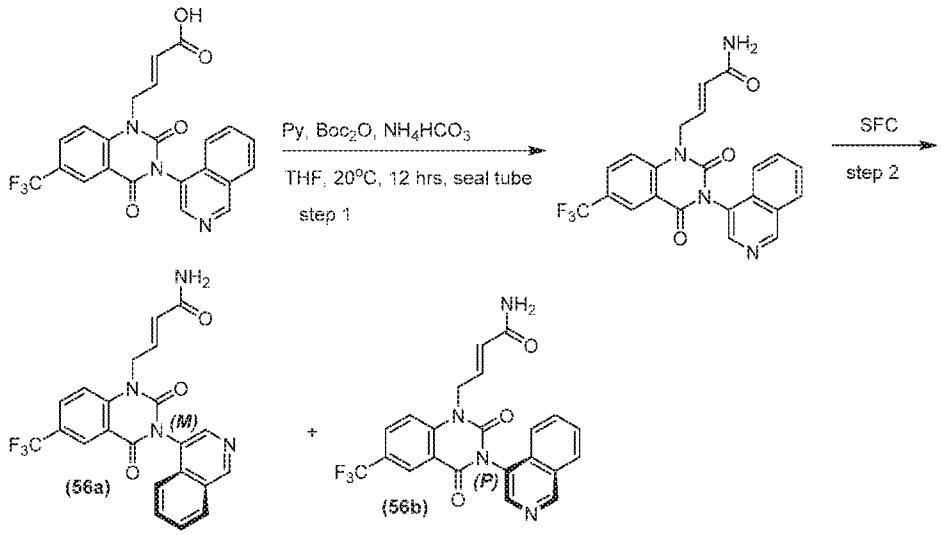
(isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2H)-yl)but-2-enoic acid. **LCMS (Method 12):** $t_R$ = 0.532 min, [M-1] 440.0.

Step 3: Racemic (E)-4-(3-(isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2H)-yl)but-2-enoic acid was separated by SFC, (Preparative SFC ; Column: DAICEL CHIRALPAK AD(250mmx30mm,10um); Mobile phase: A:$CO_2$ and B:IPA(0.1%$NH_3H_2O$); Gradient: B%=43% isocratic elution mode; 10 min.; Wavelength:220nm; Column temperature: 40 °C System back pressure: 100 bar.) to give four peaks. **SFC:** $t_{R1}$ = 1.280 min., $t_{R2}$ = 1.320 min., $t_{R3}$ = 1.488-1.527 min. and $t_{R4}$ = 2.207 min.

**Peak 2:** (2*E*)-4-[(3*M*)-3-(Isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2*H*)-yl]but-2-enoic acid **(55a)**. **LCMS (Method 13)**: $t_R$ = 2.268 min, $[M+1]^+$ 441.9. **SFC:** (column:
Chiralcel AD-3 (50mmx4.6mm, 3µm); mobile phase: A: $CO_2$; B: IPA[0.1% IPAm]; B%: 5% for 0.2 min, 5-50% for 1.0 min., 50% for 1.0 min., 50-5% for 0.4 min., 5% for 0.4 min., 3.4mL/min., $t_R$ = 1.320 min, 100%. **$^1$H NMR:** (400 MHz, DMSO-$d_6$) δ = 9.44 (s, 1 H), 8.61 (s, 1 H), 8.31 (s, 1 H), 8.25 - 8.29 (m, 1 H), 8.18 (br d, *J*=8.94 Hz, 1 H), 8.07 (br d, *J*=7.63 Hz, 1 H), 7.73 - 7.82 (m, 2 H), 7.64 (d, *J*=8.82 Hz, 1 H), 6.94 (dt, *J*=15.88, 3.92 Hz, 1 H), 6.12 (d, *J*=15.97 Hz, 1 H), 4.88 - 5.10 (m, 2 H).

**Peak 4:** (2*E*)-4-[(3*P*)-3-(Isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2*H*)-yl]but-2-enoic acid **(55b)**. **LCMS (Method 13)**: $t_R$ = 2.267 min, $[M+1]^+$ 441.9. **SFC:** (column:
Chiralcel AD-3 (50mmx4.6mm, 3µm); mobile phase: A: $CO_2$; B: IPA[0.1% IPAm]; B%: 5% for 0.2 min, 5-50% for 1.0 min., 50% for 1.0 min., 50-5% for 0.4 min., 5% for 0.4 min., 3.4mL/min., $t_R$ = 2.204 min, 99.2%. **$^1$H NMR:** (400 MHz, DMSO-$d_6$) δ = 9.44 (s, 1 H), 8.61 (s, 1 H), 8.31 (s, 1 H), 8.24 - 8.29 (m, 1 H), 8.18 (br d, *J*=8.82 Hz, 1 H), 8.07 (br d, *J*=7.63 Hz, 1 H), 7.72 - 7.81 (m, 2 H), 7.64 (d, *J*=8.82 Hz, 1 H), 6.93 (dt, *J*=15.88, 3.86 Hz, 1 H), 6.12 (br d, *J*=15.85 Hz, 1 H), 4.90 - 5.10 (m, 2 H).

**Example 56:** Synthesis of (2*E*)-4-[(3*M*)-3-(Isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2*H*)-yl]but-2-enamide **(56a)**
(2*E*)-4-[(3*P*)-3-(Isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2*H*)-yl]but-2-enamide **(56b)**



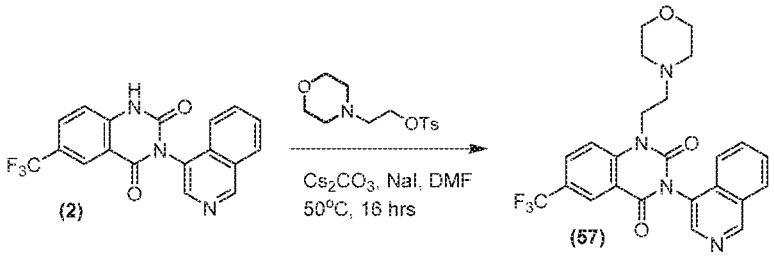

Step 1: To a solution of racemic (E)-4-(3-(isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2H)-yl)but-2-enoic acid (350 mg, 0.79 mmol, 1.0 eq.) in THF (4 mL) was added $Boc_2O$ (346 mg, 1.58 mmol, 2.0 eq.), $NH_4HCO_3$ (125 mg, 1.58 mmol, 2.0 eq.) and pyridine (125 mg, 1.58 mmol, 2.0 eq.) at 20°C under nitrogen. The reaction was stirred for 12 hrs at 20°C. The reaction was slowly quenched with water (10 mL) and extracted with EtOAc (10 x 3 mL). The combined organic layers were washed with brine (10 mL), dried over $Na_2SO_4$, filtered and concentrated in vacuum to give crude product which was purified by prep-HPLC (column: Waters Xbridge BEH C18 100mmx30mm, 10μm; liquid phase: [A:10mM $NH_4HCO_3$ in $H_2O$; B:ACN]B%: 20%-50%, 8 min]) to give racemic (E)-4-(3-(isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2H)-yl)but-2-enamide.

Step 2: Racemic (E)-4-(3-(isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2H)-yl)but-2-enamide separated by SFC, (Preparative SFC ; Column: DAICEL CHIRALPAK AD(250mmx30mm,10um); Mobile phase: A:$CO_2$ and B:IPA(0.1%$NH_3H_2O$); Gradient: B%=43% isocratic elution mode; 20 min.; Wavelength:220nm; Column temperature: 40 °C System back pressure: 100 bar.) to give four peaks. **SFC:** $t_{R1}$ = 1.378 min., $t_{R2}$ = 1.489 min., $t_{R3}$ = 1.769 min. and $t_{R4}$ = 2.073 min.

**Peak 2:** (2*E*)-4-[(3*M*)-3-(Isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2*H*)-yl]but-2-enamide **(56a)**. **LCMS (Method 13)**: $t_R$ = 2.110 min, $[M+1]^+$ 440.9. **SFC:** (column: Chiralcel AD-3 (50mmx4.6mm, 3μm; mobile phase: A: $CO_2$; B: EtOH[0.1% IPAm]; B%: 5% for 0.2 min, 5-50% for 1.0 min., 50% for 1.0 min., 50-5% for 0.4 min., 5% for 0.4 min., 3.4mL/min., $t_R$ = 1.464 min, 99.0%. **$^1$H NMR:** (400 MHz, DMSO-$d_6$) δ = 9.42 - 9.48 (m, 1 H), 8.58 (s, 1 H), 8.33 (d, *J*=1.71 Hz, 1 H), 8.29 (dd, *J*=6.54, 2.75 Hz, 1 H), 8.21 (dd, *J*=8.86, 2.14 Hz, 1 H), 7.95 - 8.01 (m, 1 H), 7.71 - 7.84 (m, 2 H), 7.69 (d, *J*=8.80 Hz, 1 H), 7.34 (br s, 1 H), 7.06 (br s, 1 H), 6.75 (dt, *J*=15.68, 4.26 Hz, 1 H), 6.06 (d, *J*=15.77 Hz, 1 H), 5.00 (br d, *J*=3.91 Hz, 2 H).

**Peak 4:** (2*E*)-4-[(3*P*)-3-(Isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2*H*)-yl]but-2-enamide **(56b)**. **LCMS (Method 13)**: $t_R$ = 2.10 min, $[M+1]^+$ 441.9. **SFC:** (column: Chiralcel AD-3 (50mmx4.6mm, 3µm; mobile phase: A: $CO_2$; B: EtOH[0.1% IPAm]; B%: 5% for 0.2 min, 5-50% for 1.0 min., 50% for 1.0 min., 50-5% for 0.4 min., 5% for 0.4 min., 3.4mL/min., $t_R$ = 2.174 min, 96.8%. **$^1$H NMR:** (400 MHz, DMSO-$d_6$) δ = 9.44 (s, 1 H), 8.61 (s, 1 H), 8.31 (s, 1 H), 8.24 - 8.29 (m, 1 H), 8.18 (br d, *J*=8.82 Hz, 1 H), 8.07 (br d, *J*=7.63 Hz, 1 H), 7.72 - 7.81 (m, 2 H), 7.64 (d, *J*=8.82 Hz, 1 H), 6.93 (dt, *J*=15.88, 3.86 Hz, 1 H), 6.12 (br d, *J*=15.85 Hz, 1 H), 4.90 - 5.10 (m, 2 H).

**Example 57:** Synthesis of 3-(isoquinolin-4-yl)-1-(2-morpholinoethyl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(57)**

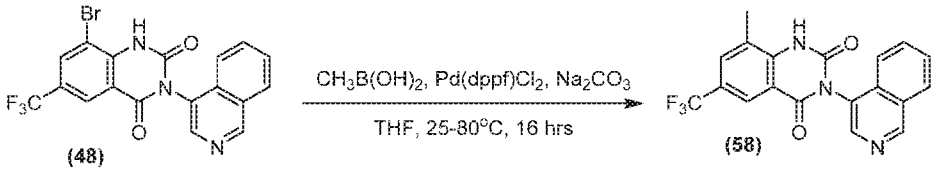



A mixture of 3-(isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(2)** (480 mg, 1.68 mmol, 2.0 eq.), 2-morpholinoethyl 4-methylbenzenesulfonate (300 mg, 0.84 mmol, 1.0 eq.), $Cs_2CO_3$ (547 mg, 1.68 mmol, 2.0 eq.) and NaI (30 mg) in DMF (5 mL) was stirred at 50°C for 16 hrs. The reaction mixture was quenched into water (40 mL) and extracted with EtOAc (40 mL x 2). The combined organic layers were dried over $Na_2SO_4$, filtered and concentrated in vacuum to give crude product. The crude product was purified by prep-HPLC (column: Waters Xbridge BEH C18 100mmx30mm, 10µm; liquid phase: [A:10mM $NH_4HCO_3$ in $H_2O$; B:ACN] B%: 30%-50%, 8min]) to give3-(isoquinolin-4-yl)-1-(2-morpholinoethyl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(57)**. **LCMS (Method 13)**: $t_R$ = 1.867 min, $[M+1]^+$ 471.3. **$^1$H NMR:** (400MHz, METHANOL-$d_4$) δ = 7.84 (br s, 1H), 6.96 (br s, 1H), 6.92 (d, *J*=1.6 Hz, 1H), 6.72 (d, *J*=8.0 Hz, 1H), 6.58 (dd, *J*=2.0, 8.9 Hz, 1H), 6.34 - 6.20 (m, 4H), 2.98 (td, *J*=7.1, 14.6 Hz, 1H), 2.91 - 2.80 (m, 1H), 2.16 - 2.03 (m, 4H), 1.24 (tq, *J*=6.6, 13.2 Hz, 2H), 1.12 - 0.94 (m, 4H).

Note: 2-morpholinoethyl 4-methylbenzenesulfonate was obtained using the following procedure: To a solution of 2-morpholinoethan-1-ol (2.0 g, 15.24 mmol, 1.0 eq.), $Et_3N$ (3.1 g, 62.24 mmol, 2.0 eq.) in $CH_2Cl_2$ (20 mL) was added TsCl (2.9 g, 15.24 mmol, 1.0 eq.) at 20°C, the mixture was stirred at 20°C for 5 hrs. The reaction mixture was quenched with water (20 mL) and extracted with $CH_2Cl_2$ (20 mL x 3). The combined organic layers were washed with brine (50 mL), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give crude product. The crude product was purified by column (Petroleum ether/EtOAc = 90/10 to 85/15) to

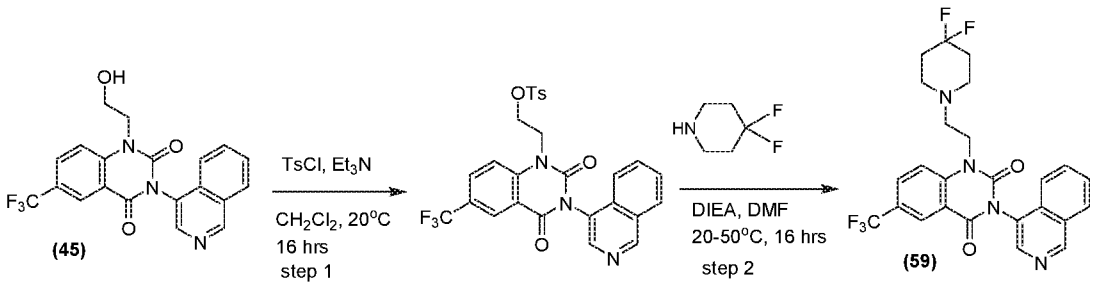
give 2-morpholinoethyl 4-methylbenzenesulfonate. **LCMS (Method 12)**: $t_R$ = 0.684 min, $[M+1]^+$ 286.3.

**Example 58:** Synthesis of 3-(isoquinolin-4-yl)-8-methyl-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(58)**




Step 1: To a solution of 8-bromo-3-(isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(48)** (200 mg, 0.46 mmol, 1.0 eq.) in THF (5 mL) was added methylboronic acid (120 mg, 1.83 mmol, 4.0 eq.), $Pd(dppf)Cl_2$ (40 mg, 0.05 mmol, 0.1 eq.) and $Na_2CO_3$ (100 mg, 0.92 mmol, 2.0 eq.) at 25°C and the mixture was stirred 80°C for 16 hrs. The reaction mixture was quenched with saturated aqueous $NH_4Cl$ (5 mL) and extracted with ethyl acetate (10 mL x 2). The combined organic layers were washed with brine (20 mL), dried over $Na_2SO_4$, filtered and concentrated to give crude product. The crude product was purified by prep-HPLC (column: Phenomenex luna C18 100mmx40mm, 5µm; liquid phase: [A:TFA/$H_2O$ = 0.075% v/v; B:ACN] B%: 1%-45%, 8 min]) to give 3-(isoquinolin-4-yl)-8-methyl-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(58)**. **LCMS (Method 13)**: $t_R$ = 2.308 min, $[M+1]^+$ 372.3. **$^1$H NMR:** (400MHz, DMSO-$d_6$) δ = 11.39 (s, 1H), 9.45 (s, 1H), 8.58 (s, 1H), 8.32 - 8.25 (m, 1H), 8.07 (s, 1H), 7.98 (s, 1H), 7.95 - 7.90 (m, 1H), 7.82 - 7.72 (m, 2H), 2.53 (s, 3H).

**Example 59:** Synthesis of 1-(2-(4,4-difluoropiperidin-1-yl)ethyl)-3-(isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(59)**

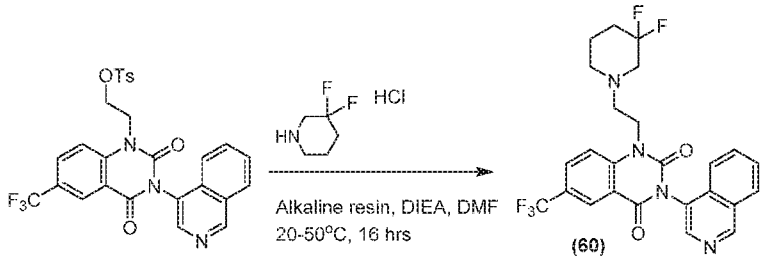



Step 1: To a mixture of 1-(2-hydroxyethyl)-3-(isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(45)** (400mg, 1.00 mmol, 1.0 eq.) and $Et_3N$ (202 mg, 2.00 mmol, 2.0 eq.) in $CH_2Cl_2$ (5 mL) was added TsCl (210 mg, 1.10 mmol, 1.1 eq.) at 20°C, the mixture was stirred at 20°C for 16 hrs. The reaction mixture was quenched into water (20 mL) and extracted with $CH_2Cl_2$ (20 mL x 3). The combined organic layers were washed by brine (50 mL), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give the crude product. The crude product was purified by column (Petroleum ether/THF=2/1 to 1/1) to give 2-(3-(isoquinolin-4-yl)-

2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2H)-yl)ethyl 4-methylbenzenesulfonate. **$^1$H NMR:** (400MHz, DMSO-$d_6$) δ = 9.48 - 9.44 (m, 1H), 8.51 (s, 1H), 8.31 - 8.28 (m, 1H), 8.27 - 8.23 (m, 1H), 8.15 (dd, *J*=2.1, 8.9 Hz, 1H), 7.86 - 7.83 (m, 1H), 7.83 - 7.80 (m, 1H), 7.80 - 7.76 (m, 2H), 7.63 (d, *J*=8.3 Hz, 2H), 7.30 (d, *J*=8.0 Hz, 2H), 4.56 - 4.51 (m, 2H), 4.44 - 4.39 (m, 2H), 2.32 (s, 3H).

Step 2: To a mixture of 2-(3-(isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2H)-yl)ethyl 4-methylbenzenesulfonate (300 mg, 0.54 mmol, 1.0 eq.) in DMF (3 mL) was added 4,4-difluoropiperidine (131 mg, 1.08 mmol, 2.0 eq.) and DIEA (210 mg, 1.62 mmol, 3.0 eq.) at 20°C and the mixture was stirred at 50°C for 16 hrs. The reaction mixture was quenched with water (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic layers were concentrated under reduced pressure to give crude product which was purified by prep-HPLC (column: Phenomenex Luna 80mmx30mm, 3μm; liquid phase: [A:HCl/$H_2O$= 0.04% v/v; B:ACN] B%: 35%-55%, 8 min]) to give1-(2-(4,4-difluoropiperidin-1-yl)ethyl)-3-(isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(59)**. **LCMS (Method 13)**: $t_R$ = 2.006 min, $[M+1]^+$ 504.3. **$^1$H NMR:** (400MHz, METHANOL-$d_4$) δ = 9.39 (s, 1H), 8.48 (d, *J*=12.4 Hz, 2H), 8.28 (d, *J*=7.6 Hz, 1H), 8.16 - 8.11 (m, 1H), 7.86 - 7.74 (m, 4H), 4.62 - 4.52 (m, 1H), 4.37 (td, *J*=5.7, 15.0 Hz, 1H), 2.98 - 2.85 (m, 1H), 2.84 - 2.77 (m, 1H), 2.76 - 2.55 (m, 4H), 1.98 - 1.82 (m, 4H).

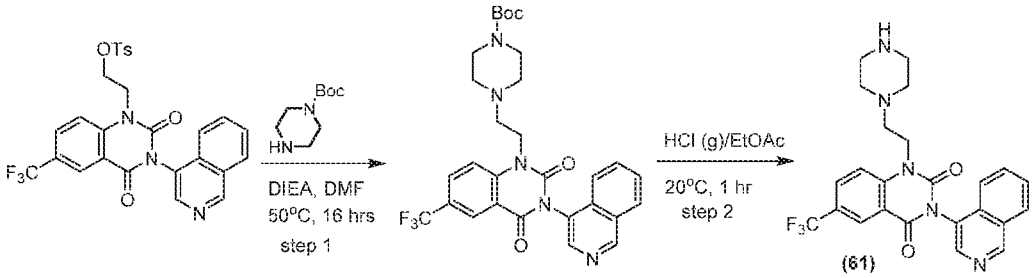
**Example 60:** Synthesis of 1-(2-(3,3-difluoropiperidin-1-yl)ethyl)-3-(isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(60)**




To a mixture of 3,3-difluoropiperidine hydrochloride (282 mg, 1.80 mmol, 5.0 eq.) in DMF (4 mL) was added alkaline resin to adjust pH to 8, the mixture was stirred 1 hr at 20°C and filtered. To the filtrate was added 2-(3-(isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2H)-yl)ethyl 4-methylbenzenesulfonate (200 mg, 0.36 mmol, 1.0 eq.) and DIEA (93 mg, 0.72 mmol, 2.0 eq.), the mixture was stirred at 50°C for 15 hrs. The reaction mixture was quenched with water (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic layers were concentrated under reduced pressure to give crude product which was purified by prep-HPLC (column: Phenomenex luna C18 80mmx40mm, 3μm; liquid phase: [A:$H_2O$= (0.04%HCl); B:ACN] B%: 40%-55%, 20 min]) to give 1-(2-(3,3-difluoropiperidin-1-yl)ethyl)-3-(isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(60)**. **LCMS (Method 13)**: $t_R$ = 2.148 min,

$[M+1]^+$ 505.1. **$^1$H NMR:** (400MHz, DEUTERIUM OXIDE) δ = 9.79 (s, 1H), 8.67 (s, 1H), 8.60 - 8.56 (m, 2H), 8.27 (br d, *J*=8.8 Hz, 1H), 8.21 - 8.14 (m, 1H), 8.07 (br dd, *J*=3.6, 7.8 Hz, 2H), 7.75 (d, *J*=9.0 Hz, 1H), 4.89 - 4.78 (m, 2H), 3.78 (br t, *J*=5.9 Hz, 4H), 3.45 (br s, 2H), 2.27 - 2.12 (m, 2H), 2.10 - 2.00 (m, 2H).

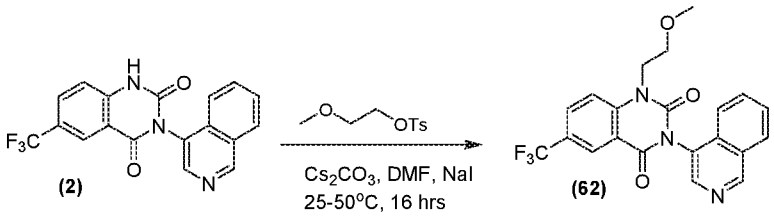
**Example 61:** Synthesis of 3-(isoquinolin-4-yl)-1-(2-(piperazin-1-yl)ethyl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(61)**




Step 1: A mixture of 2-(3-(isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2H)-yl)ethyl 4-methylbenzenesulfonate (300 mg, 0.54 mmol, 1.0 eq.), tert-butyl piperazine-1-carboxylate (150 mg, 0.81 mmol, 1.5 eq.) and DIEA (135 mg, 1.08 mmol, 2.0 eq.) in DMF (5 mL) was stirred at 50°C for 16 hrs. The reaction mixture was quenched with water (5 mL) and extracted with EtOAc (5 mL x 3). The combined organic layers were washed by brine (20 mL), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give crude product which was purified by column (Petroleum ether/THF=2/1 to 1/2) to give tert-butyl 4-(2-(3-(isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2H)-yl)ethyl)piperazine-1-carboxylate. **LCMS (Method 12):** $t_R$ = 0.801 min, $[M+1]^+$ 570.4.

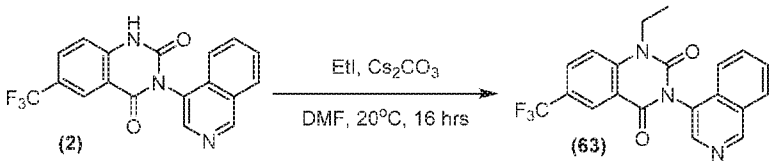
Step 2: A mixture of tert-butyl 4-(2-(3-(isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2H)-yl)ethyl)piperazine-1-carboxylate (160 mg, 0.28 mmol, 1.0 eq.) in HCl (g)/EtOAc (5 mL) was stirred at 20°C for 1 hr. The reaction mixture was poured into water (5 mL) and the precipitate filtered. The filter cake was dried under vacuum to give crude product which was purified by prep-HPLC (column: Phenomenex Luna 80mmx30mm, 3μm; liquid phase: [A:HCl/$H_2O$= 0.04% v/v; B:ACN] B%: 10%-40%, 8 min]) to give 3-(isoquinolin-4-yl)-1-(2-(piperazin-1-yl)ethyl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(61)**. **LCMS (Method 13):** $t_R$ = 1.876 min, $[M+1]^+$ 470.3. **$^1$H NMR:** (400MHz, METHANOL-$d_4$) δ = 9.91 (s, 1H), 9.03 (br s, 1H), 8.63 (d, *J*=8.2 Hz, 1H), 8.49 (s, 1H), 8.38 (br d, *J*=7.7 Hz, 1H), 8.28 - 8.17 (m, 2H), 8.14 - 8.05 (m, 1H), 7.88 (d, *J*=8.8 Hz, 1H), 4.73 (br s, 1H), 3.86 - 3.64 (m, 3H), 3.47 (br s, 2H), 2.19 (br d, *J*=10.4 Hz, 4H).

**Example 62:** Synthesis of 3-(isoquinolin-4-yl)-1-(2-methoxyethyl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(62)**



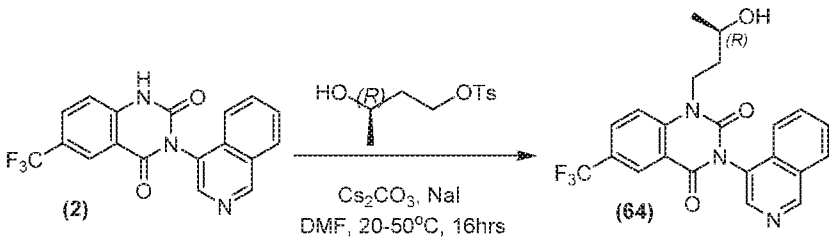

To a mixture of 3-(isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(2)** (200 mg, 0.56 mmol, 1.0 eq.) in DMF (4 mL) was added $Cs_2CO_3$ (365 mg, 1.12 mmol, 2.0 eq.), 2-methoxyethyl 4-methylbenzenesulfonate (114 mg, 0.84 mmol, 1.5 eq.) and NaI (84 mg, 0.56 mmol, 1.0 eq.) at 25°C and the reaction mixture was stirred at 50°C for 16 hrs. The reaction was quenched with $H_2O$ (20 mL) and extracted with EtOAc (10 mL × 3). The combined organic layers were washed with brine (30 mL × 2), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 150x30mm, 5μm; liquid phase: [A:FA/$H_2O$ = 0.1% v/v; B:ACN] B%: 30%-70%, 8 min]) to give 3-(isoquinolin-4-yl)-1-(2-methoxyethyl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(62)**. **LCMS (Method 3):** $t_R$ = 2.620 min, $[M+1]^+$ 416.1. **$^1$H NMR:** (400 MHz, METHANOL-d4) δ = 9.38 (s, 1H), 8.51 (s, 1H), 8.44 (s, 1H), 8.26 (d, *J* = 7.9 Hz, 1H), 8.09 (dd, *J* = 1.5, 9.0 Hz, 1H), 7.90 (d, *J* = 9.0 Hz, 1H), 7.83 - 7.79 (d, *J* = 9.2, 2H), 7.79 - 7.73 (m, 1H), 4.48 (q, *J* = 5.3 Hz, 2H), 3.82 - 3.74 (m, 2H), 3.37 (s, 3H).

**Example 63:** Synthesis of 1-ethyl-3-(isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(63)**




To a solution of 3-(isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(2)** (200 mg, 0.56 mmol, 1.0 eq.) in DMF (2 mL) was added $Cs_2CO_3$ (364 mg, 1.12 mmol, 2.0 eq.) and iodoethane (113 mg, 0.72 mmol, 1.3 eq.) at 20°C and the mixture was stirred at 20°C for 16 hrs. The mixture was poured into $H_2O$ (5 mL) and extracted with EtOAc (5 mL x 3). The combined organic phases were washed with brine (5 mL), dried over $Na_2SO_4$, filtered and concentrated to give crude product which was purified by prep-HPLC ($NH_4HCO_3$) to give 1-ethyl-3-(isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(63)**. **LCMS (Method 13):** $t_R$ = 2.402 min, $[M+1]^+$ 386.0. **$^1$H NMR:** (400 MHz, DMSO-$d_6$) δ = 9.44 (s, 1H), 8.57 (s, 1H), 8.32 - 8.25 (m, 2H), 8.20 (dd, *J* = 2.1, 8.9 Hz, 1H), 7.99 - 7.93 (m, 1H), 7.87 (d, *J* = 8.8 Hz, 1H), 7.81 - 7.72 (m, 2H), 4.32 - 4.15 (m, 2H), 1.29 (t, *J* = 7.0 Hz, 3H).

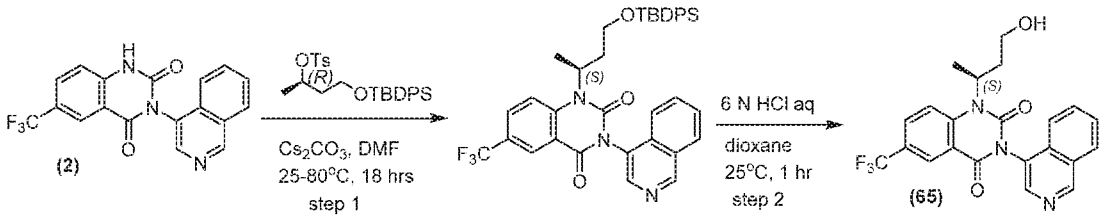
**Example 64:** Synthesis of 1-((R)-3-hydroxybutyl)-3-(isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(64)**




To a solution of 3-(isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(2)** (300 mg, 0.84 mmol, 1.0 eq.) in DMF (5 mL) was added (R)-3-hydroxybutyl 4-methylbenzenesulfonate (151 mg, 1.01 mmol, 1.2 eq.), $Cs_2CO_3$ (550 mg, 1.66 mol, 2.0 eq.) and NaI (126 mg, 1.66 mmol, 2.0 eq.) at 25°C and the mixture was stirred at 50°C for 16 hrs. The mixture was quenched with $H_2O$ (10 mL) at 0°C and ethyl acetate (10 mL) was added. The layers were separated and the aqueous phase was extracted with EtOAc (20 mL x 3). The combined organic phases were washed with brine (20 mL), dried over anhydrous $Na_2SO_4$, filtered and concentrated in vacuum to give crude product which was purified by prep-HPLC (column: Phenomenex C18 75mmx30mm, 3μm; liquid phase: [A - $H_2O$ (10 mM $NH_4HCO_3$); B - ACN] B%: 15% - 45%, 20 min]) to give 1-((R)-3-hydroxybutyl)-3-(isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(64)**. **LCMS (Method 3):** $t_R$ = 2.912 min, $[M+1]^+$ 430.0. **$^1$H NMR:** (400 MHz, DMSO-$d_6$) δ = 9.40 (s, 1 H), 8.58 (s, 1 H), 8.51 (d, J=4.8 Hz, 1 H), 8.15 (d, J=8.17 Hz, 1 H), 8.03 (dd, J=8.9, 2.0 Hz, 1 H), 7.68 - 7.79 (m, 2 H), 7.53 - 7.66 (m, 2 H), 4.57 (dt, J=14.9, 7.5 Hz, 1 H), 4.20 - 4.30 (m, 1 H), 3.87-3.94 (m, 1 H), 2.36-2.65 (m, 1 H), 1.96 - 2.10 (m, 1 H), 1.79 - 1.90 (m, 1 H), 1.27 (d, J=5.7 Hz, 3 H).

Note: (R)-3-hydroxybutyl 4-methylbenzenesulfonate was obtained using the following procedure: A mixture of (R)-butane-1,3-diol (CAS No. 6290-03-5) (1.0 g, 11.10 mmol, 1.0 eq.) and TsOH (2.2 g, 11.65 mmol, 1.1 eq.) in pyridine (10 mL) was stirred at 50°C for 16 hrs. The reaction was quenched with saturated aqueous $NH_4Cl$ (80 mL) and extracted with EtOAc (30 mL × 2). The combined organic layers were washed with brine (80 mL × 2), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give crude product. The crude product was purified by MPLC (12 g, Eluent Ethyl acetate/Petroleum ether = 25 - 40%, 50 mL/min) to give (R)-3-hydroxybutyl 4-methylbenzenesulfonate. **$^1$H NMR:** (400 MHz, DMSO-$d_6$) δ = 7.85 - 7.73 (m, 2H), 7.41 - 7.32 (m, 2H), 4.25 (ddd, *J* = 5.1, 8.7, 9.9 Hz, 1H), 4.17 - 4.08 (m, 1H), 4.00 - 3.89 (m, 1H), 2.46 (s, 3H), 1.94 - 1.78 (m, 1H), 1.75 - 1.66 (m, 1H), 1.58 (br d, *J* = 4.4 Hz, 1H), 1.28 - 1.17 (m, 3H).

**Example 65:** Synthesis of 1-((S)-4-hydroxybutan-2-yl)-3-(isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(65)**




Step 1: To a solution of 3-(isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(2)** (140 mg, 0.39 mmol, 1.0 eq.) in DMF (3 mL) was added $Cs_2CO_3$ (383 mg, 1.18 mmol, 3.0 eq.) at 25°C. A solution of (R)-4-((tert-butyldiphenylsilyl)oxy)butan-2-yl 4-methylbenzenesulfonate (515mg, 1.57 mmol, 4.0 eq.) in DMF (2 mL) was added at 80°C over two hours and the mixture was then stirred at 80°C for 16 hrs under $N_2$. The reaction was quenched with $H_2O$ (30 mL) and extracted with EtOAc (20 mL × 3). The combined organic layers were washed with brine (50 mL), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna 80mmx30mm, 3μm; liquid phase: [A:HCl/$H_2O$ = 0.04% v/v; B:ACN] B%: 30%-45%, 6 min]) to give 1-((S)-4-((tert-butyldiphenylsilyl)oxy)butan-2-yl)-3-(isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione. **LCMS (Method 12):** $t_R$ = 1.007 min, $[M+1]^+$ 668.3.

Step 2: To a solution of 1-((S)-4-((tert-butyldiphenylsilyl)oxy)butan-2-yl)-3-(isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione (230 mg, 0.34 mmol, 1.0 eq.) in dioxane (2 mL) was added HCl (2 mL, 6M) at 25°C. The reaction was stirred at 25°C for 1 hr under $N_2$. The reaction was concentrated to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna 80mmx30mm, 3μm; liquid phase: [A:HCl/$H_2O$ = 0.04% v/v; B:ACN] B%: 25%-40%, 8 min]) to give 1-((S)-4-hydroxybutan-2-yl)-3-(isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(65)**. **LCMS (Method 3):** $t_R$ = 2.471 min, $[M+1]^+$ 430.1. **$^1$H NMR:** (400 MHz, $CD_3OD$) δ = 9.90 (s, 1H), 8.83 (d, *J* = 5.3 Hz, 1H), 8.62 (d, *J* = 8.3 Hz, 1H), 8.46 (s, 1H), 8.24 - 8.17 (m, 2H), 8.16 - 8.07 (m, 2H), 8.03 (br d, *J* = 9.2 Hz, 1H), 5.21 - 4.94 (m, 1H), 3.67 (t, *J* = 5.7 Hz, 2H), 2.62 - 2.41 (m, 1H), 2.08 (br dd, *J* = 1.4, 2.5 Hz, 1H), 1.66 (br d, *J* = 5.9 Hz, 3H).

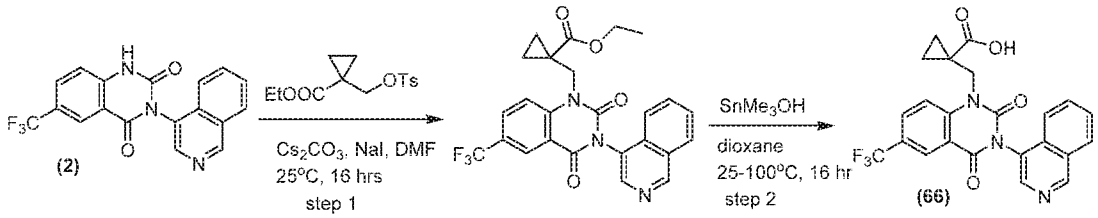
Note: (R)-4-((tert-butyldiphenylsilyl)oxy)butan-2-yl 4-methylbenzenesulfonate was obtained using the following procedure:

Step 1: A mixture of (R)-butane-1,3-diol (CAS No. 6290-03-5) (2.0 g, 22.19 mmol, 1.0 eq.) in $CH_2Cl_2$ (20 mL) was added Imidizole (3.0 g, 44.38 mmol, 2.0 eq.) at 25°C. A solution of TBDPSCl (5.5 g, 19.97 mmol, 0.9 eq.) in $CH_2Cl_2$ (10 mL) was added into the reaction at 0°C. The mixture was stirred at 25°C for 16 hrs under $N_2$. The reaction was quenched with $H_2O$ (100 mL) and extracted with $CH_2Cl_2$ (30 mL × 3). The combined organic layers were washed with brine (100 mL), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (40 g, Eluent of 10~13%

Ethyl acetate/Petroleum ether, 80 mL/min) to give (R)-4-((tert-butyldiphenylsilyl)oxy)butan-2-ol. **$^1$H NMR:** (400 MHz, $CDCl_3$) δ = 7.69 (d, *J* = 7.0 Hz, 4H), 7.47 - 7.38 (m, 6H), 4.12 - 4.08 (m, 1H), 3.91 - 3.83 (m, 2H), 1.81 - 1.70 (m, 1H), 1.68 - 1.59 (m, 1H), 1.22 (d, *J* = 6.2 Hz, 3H), 1.07 - 1.06 (s, 9H).

Step 2: To a solution of (R)-4-((tert-butyldiphenylsilyl)oxy)butan-2-ol (2.0 g, 6.09 mmol, 1.0 eq.) in $CH_2Cl_2$ (20 mL) was added $Et_3N$ (1.2 g, 12.18 mmol, 2.0 eq.) and DMAP (75 mg, 0.61 mmol, 0.1 eq.) at 25°C. A solution of TsCl (1.5 g, 7.92 mmol, 1.3 eq.) in $CH_2Cl_2$ (5 mL) was added into the reaction at 0°C. The mixture was stirred at 25°C for 16 hrs under $N_2$. The reaction was quenched with $H_2O$ (100 mL) and extracted with $CH_2Cl_2$ (50 mL × 3). The combined organic layers were washed with brine (100 mL), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (40 g, Eluent of 16~20% Ethyl acetate/Petroleum ether, 60 mL/min) to give (R)-4-((tert-butyldiphenylsilyl)oxy)butan-2-yl 4-methylbenzenesulfonate. **$^1$H NMR:** (400 MHz, $CDCl_3$) δ = 7.76 (d, *J* = 8.3 Hz, 2H), 7.59 (d, *J* = 1.4 Hz, 2H), 7.57 (d, *J* = 1.5 Hz, 2H), 7.47 - 7.42 (m, 2H), 7.40 - 7.35 (m, 4H), 7.25 (d, *J* = 8.0 Hz, 2H), 4.85 (d, *J* = 6.4 Hz, 1H), 3.56 (t, *J* = 6.1 Hz, 2H), 2.40 (s, 3H), 1.93 - 1.82 (m, 1H), 1.74 - 1.62 (m, 1H), 1.32 (d, *J* = 6.3 Hz, 3H), 1.01 (s, 9H).

**Example 66:** Synthesis of 1-((3-(isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)cyclopropane-1-carboxylic acid **(66)**

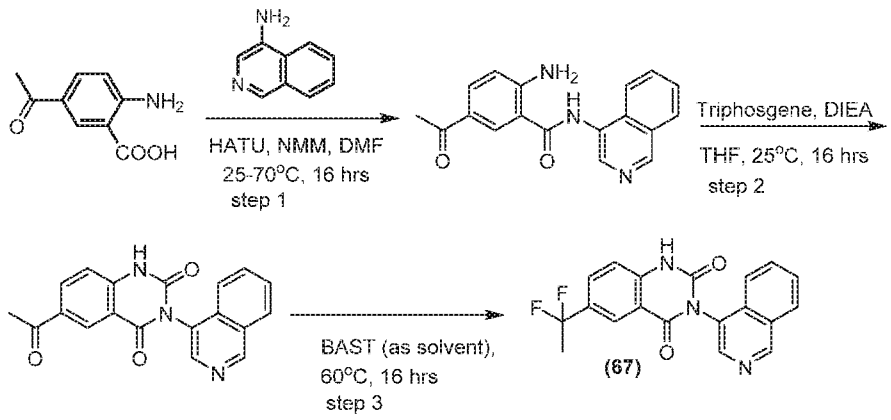



Step 1: To a solution of 3-(isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(2)** (300 mg, 0.84 mmol, 1.0 eq.) in DMF (4 mL) was added $Cs_2CO_3$ (546 mg, 1.68 mmol, 2.0 eq.), ethyl 1-((tosyloxy)methyl)cyclopropane-1-carboxylate (375 mg, 1.26 mmol, 1.5 eq.) and NaI (126 mg, 0.84 mmol, 1.0 eq.) at 25°C. The reaction was stirred at 25°C for 16 hrs. The reaction was quenched with $H_2O$ (20 mL) and extracted with EtOAc (10 mL × 3). The combined organic layers were washed with brine (20 mL), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give crude product which was purified by flash silica gel chromatography (4 g, Eluent of 35~45% Ethyl acetate/Petroleum ether, 50 mL/min) to give ethyl 1-((3-(isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)cyclopropane-1-carboxylate. **$^1$H NMR:** (400 MHz, $CDCl_3$) δ (ppm) = 9.40 (s, 1H), 8.55 (d, *J* = 1.7 Hz, 1H), 8.50 (s, 1H), 8.16 (d, *J* = 7.8 Hz, 1H), 8.01 (br d, *J* = 2.2 Hz, 1H), 7.84 (d, *J* = 8.9 Hz, 1H), 7.80 - 7.69 (m, 2H), 7.55 (d, *J* = 8.3 Hz, 1H), 4.86 (d, *J* = 15.6 Hz, 1H), 4.81 (d, *J* = 15.6 Hz, 1H) , 4.20 (q, *J* = 7.1 Hz, 2H), 1.38-1.40 (m, 2H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.02-1.05 (m, 2H).

Step 2: To a solution of thyl 1-((3-(isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)cyclopropane-1-carboxylate (360 mg, 0.74 mmol, 1.0 eq.) in dioxane (5 mL) was added $SnMe_3OH$ (270 mg, 1.49 mmol, 2.0 eq.) at 25°C. The mixture was stirred at 100°C for 16 hrs under $N_2$. The mixture was concentrated to give a residue. The residue was dissolved in DMF (3 mL) and filtered off. The filtrate was purified by prep-HPLC (column: Phenomenex Luna C18 200mmx40mm, 10μm; liquid phase: [A:$H_2O$ (0.1% FA); B:ACN] B%: 50%-90%, 20 min]) to give 1-((3-(isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2H)-yl)methyl)cyclopropane-1-carboxylic acid **(66)**. **LCMS (Method 3):** $t_R$ = 2.565 min, $[M+1]^+$ 456.0. **$^1$H NMR:** (400 MHz, $CD_3OD$) δ (ppm) = 9.39 (s, 1H), 8.50 (s, 1H), 8.45 (d, *J* = 1.6 Hz, 1H), 8.27 (d, *J* = 8.0 Hz, 1H), 8.13 (dd, *J* = 2.1, 8.9 Hz, 1H), 7.93 (d, *J* = 9.0 Hz, 1H), 7.85 - 7.76 (m, 3H), 4.83 (s, 2H), 1.34 - 1.30 (m, 2H), 1.06 - 1.01 (m, 2H).

Note: Ethyl 1-((tosyloxy)methyl)cyclopropane-1-carboxylate was obtained using the following procedure: To a solution of ethyl 1-(hydroxymethyl)cyclopropane-1-carboxylate (400 mg, 2.77 mmol, 1.0 eq.) in $CH_2Cl_2$ (4 mL) was added $Et_3N$ (561 mg, 5.55 mmol, 2.0 eq.) and DMAP (34 mg, 0.28 mmol, 0.1 eq.) at 25°C. A solution of TsCl (635 mg, 3.33 mmol, 1.2 eq.) in $CH_2Cl_2$ (2 mL) was added dropwise at 0°C and the reaction was stirred at 25°C for 16 hrs. The reaction was quenched with $H_2O$ (20 mL) and extracted with $CH_2Cl_2$ (10 mL × 3). The combined organic layers were washed with brine (30 mL), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give crude product which was purified by flash silica gel chromatography (12 g, Eluent of 15~20% Ethyl acetate/Petroleum ether, 50 mL/min) to give Ethyl 1-((tosyloxy)methyl)cyclopropane-1-carboxylate. **$^1$H NMR:** (400 MHz, CHLOROFORM-d) δ = 7.82 (d, *J* = 8.3 Hz, 2H), 7.36 (d, *J* = 8.1 Hz, 2H), 4.17 (s, 2H), 4.08 (q, *J* = 7.1 Hz, 2H), 2.46 (s, 3H), 1.38 - 1.32 (dd, *J* = 7.2, 4.4 Hz, 2H), 1.18 (t, *J* = 7.2 Hz, 3H), 0.99 - 0.90 (dd, *J* = 7.2, 4.4 Hz, 2H).

**Example 67:** Synthesis of 6-(1,1-difluoroethyl)-3-(isoquinolin-4-yl)quinazoline-2,4(1H,3H)-dione **(67)**

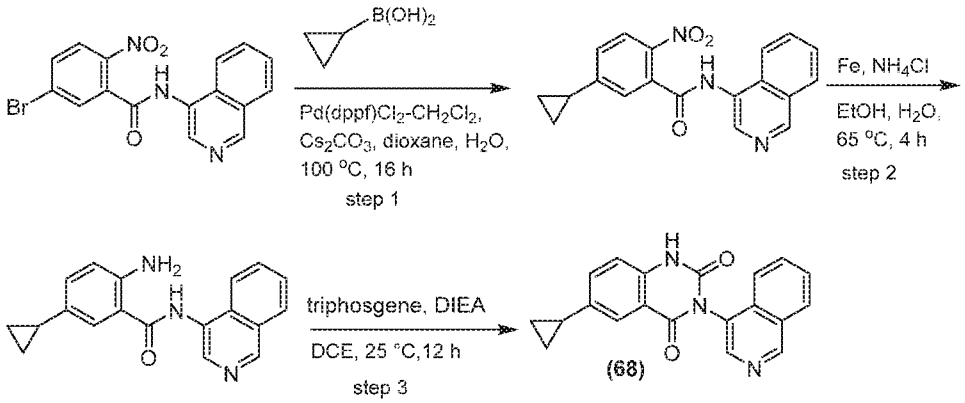


Step 1: To a solution of 5-acetyl-2-aminobenzoic acid (CAS No. 53589-27-8) (2.4 g, 13.41 mmol, 1.0 eq.) in DMF (23 mL) was added HATU (6.1 g, 16.09 mmol, 1.2 eq.) and the mixture was stirred at 25°C for 1 hr. Isoquinolin-4-amine (2.1 g, 14.75 mmol, 1.1 eq.) and NMM (4.1 g, 40.22 mmol, 3.0 eq.) were added and the mixture was stirred at 70°C for 15 hrs. The mixture was quenched with $H_2O$ (30 mL), extracted with EtOAc (30 mL x 2). The combined organic phase was washed with brine (60 mL), dried over $Na_2SO_4$, filtered and evaporated to give crude product which was purified by prep-HPLC (column: Welch Xtimate C18 250mmx70mm, 10μm; liquid phase: [A:$H_2O$ (0.1%FA); B:ACN] B%: 5%-30%, 20 min]) to give 5-acetyl-2-amino-N-(isoquinolin-4-yl)benzamide. **LCMS (Method 18):** $t_R$ = 1.288 min, $[M+1]^+$ 305.9.

Step 2: To a mixture of 5-acetyl-2-amino-N-(isoquinolin-4-yl)benzamide (375 mg, 1.23 mmol, 1.0 eq.) in THF (4 mL) was added DIEA (952 mg, 7.38 mmol, 6.0 eq.) and triphosgene (365 mg, 1.23 mmol, 1.0 eq.). The mixture was stirred at 25°C for 16 hrs. The mixture was quenched with saturated $NaHCO_3$ aqueous (15 mL), extracted with EtOAc (15 mL x 2). The combined organic phases were washed with brine (30 mL), dried over $Na_2SO_4$, filtered and evaporated to give crude product which was purified by column chromatography ($SiO_2$, Petroleum ether / EtOAc = 100% ~ 0%) to give 6-acetyl-3-(isoquinolin-4-yl)quinazoline-2,4(1H,3H)-dione. **LCMS (Method 21):** $t_R$ = 0.571 min, $[M+1]^+$ 332.2.

Step 3: A solution of 6-acetyl-3-(isoquinolin-4-yl)quinazoline-2,4(1H,3H)-dione (106 mg, 0.35 mmol, 1.0 eq.) in BAST (2 mL) was stirred at 60°C for 16 hrs. The reaction was quenched with saturated $NaHCO_3$ aqueous (20 mL) and extracted with EtOAc (15 mL x 2). The combined organic phases were washed with brine (30 mL), dried over $Na_2SO_4$, filtered and evaporated to give crude product which was purified by prep-HPLC (column: Waters Xbridge BEH C18 100mmx30mm, 10μm; liquid phase: [A:10 mM $NH_4HCO_3$ in $H_2O$; B:ACN] B%: 20%-50%, 10 min]) to give 6-(1,1-difluoroethyl)-3-(isoquinolin-4-yl)quinazoline-2,4(1H,3H)-dione **(67)**. **LCMS (Method 21):** $t_R$ = 2.328 min, $[M+1]^+$ 354.0. **$^1$H NMR:** (400 MHz, DMSO-$d_6$) δ = 11.98 (s, 1H), 9.45 (s, 1H), 8.58 (s, 1H), 8.31 - 8.28 (m, 1H), 8.10 (s, 1H), 7.97 (dd, *J*=2.1, 8.6 Hz, 1H), 7.94 - 7.88 (m, 1H), 7.82 - 7.75 (m, 2H), 7.43 (d, *J*=8.4 Hz, 1H), 2.04 (t, *J*=18.8 Hz, 3H).

**Example 68:** Synthesis of 6-cyclopropyl-3-(isoquinolin-4-yl)quinazoline-2,4(1H,3H)-dione **(68)**



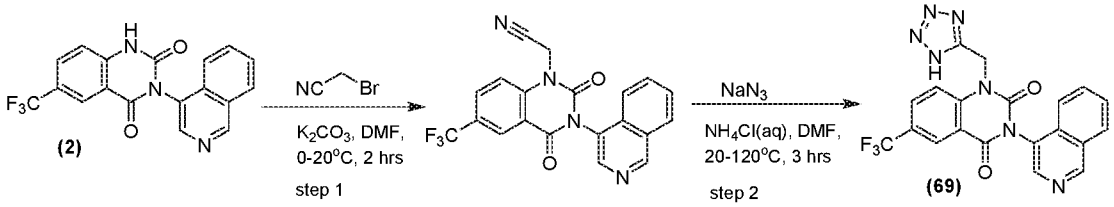

Step 1: To a mixture of 5-bromo-N-(isoquinolin-4-yl)-2-nitrobenzamide (1.4 g, 3.76 mmol, 3.0 eq.), cyclopropylboronic acid (387 mg, 4.51 mmol, 1.2 eq.) and $Cs_2CO_3$ (3.1 g, 9.40 mmol, 2.5 eq) in 1, 4-dioxane (8 mL) and $H_2O$ (2 mL) was added Pd(dppf)$Cl_2$-$CH_2Cl_2$ (307 mg, 376 µmol. 0.1 eq) under $N_2$. The homogeneous reaction mixture was heated to 100°C for 16 h. The solution was poured into water (30 mL) and extracted with EtOAc (20 mLx3). The combined organic phase was washed with water (30 mL), brine (30 mL), dried over $Na_2SO_4$, filtered and concentrated to give crude product which was purified by pre-TLC (petroleum ether : EtOAc = 0:1) to give 5-cyclopropyl-N-(isoquinolin-4-yl)-2-nitrobenzamide. **LCMS (Method 12):** $t_R$ = 0.765 min, $[M+1]^+$ 334.2.

Step 2: To a mixture of 5-cyclopropyl-N-(isoquinolin-4-yl)-2-nitrobenzamide (400 mg, 1.20 mmol, 1 *eq*) in $H_2O$ (1 mL) and EtOH (5 mL) was added $NH_4Cl$ (321 mg, 6.00 mmol, 5.0 *eq*) at 25°C. The mixture was heated to 65°C, Fe powder (201 mg, 3.60 mmol, 3.0 *eq*) was added and the mixture stirred at 65°C for 4 hours. The mixture was poured into water (30 mL) and extracted with EtOAc (10 mL x 3). The combined organic phases were washed with brine, dried over $Na_2SO_4$, filtered and concentrated to give crude product which was triturated with MTBE at 25°C for 5 min to give 2-amino-5-cyclopropyl-N-(isoquinolin-4-yl)benzamide. **LCMS (Method 12):** $t_R$ = 0.797 min, $[M+1]^+$ 304.2.

Step 3: To a mixture of 2-amino-5-cyclopropyl-N-(isoquinolin-4-yl)benzamide (200 mg, 0.06 mmol, 1.0 eq) in 1,2-dichloroethane (2 mL) was added triphosgene (65 mg, 0.02 mmol, 0.3 eq) and DIEA (85 mg, 0.06 mmol, 3.0 eq) at 25°C and the mixture at 25°C for 12 hours. The reaction mixture was diluted with sat. $NaHCO_3$ (10 mL) and extracted with $CH_2Cl_2$ (5 mL x 3). The combined organic layers were dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give the crude product. The crude product was purified by prep-HPLC (column: Waters Xbridge BEH C18 100mmx30mm, 10µm; liquid phase: [A:10mM $NH_4HCO_3$ in $H_2O$; B:ACN] B%: 30%-60%,10min]) to give 6-cyclopropyl-3-(isoquinolin-4-yl)quinazoline-2,4(1H,3H)-dione **(68)**. **LCMS (Method 22):** $t_R$ = 2.077 min, $[M+1]^+$ 330.2. **$^1$H NMR:** (400 MHz, DMSO-$d_6$) δ = 9.41 (s, 1H), 8.52 (s, 1H), 8.30 - 8.22 (m, 1H), 7.84 - 7.71 (m, 3H), 7.34 (s, 1H), 7.52 - 7.44

(m, 1H), 7.25 - 7.16 (m, 1H), 6.06 (s, 1H), 2.12 - 1.97 (m, 2H), 1.04 - 0.92 (m, 2H), 0.75 - 0.63 (m, 2H) .

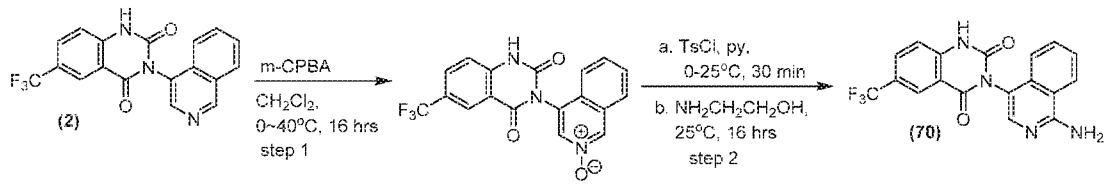
**Example 69:** Synthesis of 1-((1H-tetrazol-5-yl)methyl)-3-(isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(69)**




Step 1: A mixture of 3-(isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(2)** (150 mg, 0.42 mmol, 1.0 eq.) and $K_2CO_3$ (116 mg, 0.84 mmol, 2.0 eq.) in DMF (2 mL) was cooled to 0°C, then 2-bromoacetonitrile (76 mg, 0.63 mmol, 1.5 eq) was added and the reaction mixture was stirred at 20°C for 2 hrs. The solution was diluted with $H_2O$ (10 mL) and extracted with EtOAc (3x15 mL). The combined organic phase were dried over $Na_2SO_4$, filtrated and concentrated to give crude product which was purified with prep-TLC (petroleum ether: EtOAc=0:1) to give 2-(3-(isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2H)-yl)acetonitrile. **LCMS (Method 7):** $t_R$ = 0.724 min, $[M+1]^+$ 397.2.

Step 2: To a mixture of 2-(3-(isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2H)-yl)acetonitrile (130 mg, 0.33 mmol, 1.0 eq.) and $NaN_3$ (21 mg, 0.33 mmol, 1.0 eq.) in DMF (1 mL) was added $NH_4Cl$ (1 mL) at 20°C. The result mixture was stirred at 120°C for 3 hrs. The solution was diluted with $H_2O$ (10 mL) and extracted with EtOAc (3x20 mL). The combined organic phase were washed with brine, dried over $Na_2SO_4$, filtrated and concentrated to give crude product. The aqueous phase was quenched with the solvent of NaClO (pH>12). The crude product was purified with prep-HPLC (column: Waters Xbridge BEH C18 100mmx30mm, 10μm; liquid phase: [A:10mM $NH_4HCO_3$ in $H_2O$; B:ACN]B%: 10%-60%,8min]) to give 1-((1H-tetrazol-5-yl)methyl)-3-(isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(69)**. **LCMS (Method 17):** $t_R$ = 2.285 min, $[M+1]^+$ 440.1. **$^1$H NMR:** (400 MHz, DMSO-d6) δ = 9.46 (s, 1H), 8.58 (s, 1H), 8.35 - 8.26 (m, 2H), 8.24 - 8.17 (m, 1H), 7.97 - 7.85 (m, 2H), 7.84 - 7.72 (m, 2H), 7.28 - 6.85 (m, 1H), 5.80 - 5.58 (m, 2H).

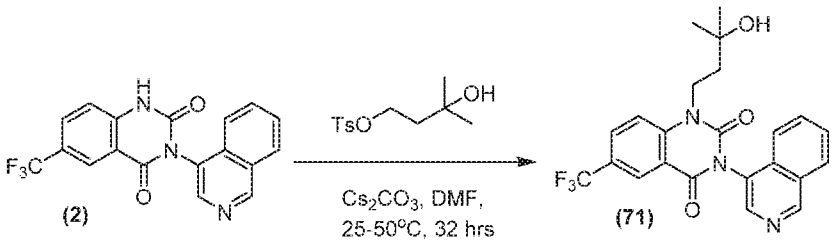
**Example 70:** Synthesis of 3-(1-aminoisoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(70)**



Step 1: A mixture of 3-(isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(2)** (200 mg, 0.56 mmol, 1.0 eq.) in $CH_2Cl_2$ (5 mL) was added m-CPBA (228 mg 1.12 mmol, 2.0 eq.) at 0°C. The mixture was stirred at 40°C for 16 hrs. The precipitated solid was filtered and triturated with petroleum ether/EtOAc (1/10, 10 mL), filtered. The filter cake was dried under vacuum to give 4-(2,4-dioxo-6-(trifluoromethyl)-1,4-dihydroquinazolin-3(2H)-yl)isoquinoline 2-oxide. **LCMS (Method 12):** $t_R$ = 0.637 min, $[M+1]^+$ 374.29.

Step 2: To a mixture of 4-(2,4-dioxo-6-(trifluoromethyl)-1,4-dihydroquinazolin-3(2H)-yl)isoquinoline 2-oxide (160 mg, 0.43 mmol, 1.0 eq.) in pyridine (5 mL) was added TsCl (171 mg, 0.52 mmol, 1.2 eq.) at 0°C and stirred at 25°C for 30 min. $NH_2CH_2CH_2OH$ (657 mg, 10.75 mmol, 25.0 eq.) was added to the mixture at 25°C and the mixture stirred at 25°C for 16 hrs. The crude product was purified by prep-HPLC (column: Waters Xbridge BEH C18 100mmx30mm, 10μm; liquid phase: [A:10 mM $NH_4HCO_3$ in $H_2O$; B:ACN] B%: 25%-50%, 10 min]) to give 3-(1-aminoisoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(70)**. **LCMS (Method 3):** $t_R$ = 2.164 min, $[M+1]^+$ 373.3. **$^1$H NMR:** (400MHz, DMSO-$d_6$) δ = 11.97 (s, 1H), 8.27 (d, *J*=8.3 Hz, 1H), 8.17 (s, 1H), 8.07 (dd, *J*=1.9, 8.6 Hz, 1H), 7.78 (s, 1H), 7.62 - 7.48 (m, 3H), 7.45 (d, *J*=8.6 Hz, 1H), 7.12 (br s, 2H).

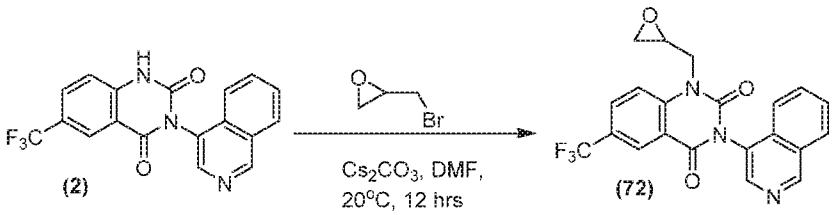
**Example 71:** Synthesis of 1-(3-hydroxy-3-methylbutyl)-3-(isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(71)**




To a solution of 3-(isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(2)** (200 mg, 0.55 mmol, 1.0 eq.) in DMF (5 mL) was added 3-hydroxy-3-methylbutyl 4-methylbenzenesulfonate (723 mg, 2.79 mmol, 5.0 eq.) and $Cs_2CO_3$ (358 mg, 1.10 mmol, 2.0 eq.) and NaI (24 mg, 0.16 mmol, 0.3 eq.) at 25°C under $N_2$. The reaction mixture was stirred at 45°C for 32 hrs. The reaction solution was filtered and concentrated to give crude product which was purified by prep-HPLC (prep-HPLC (column: Waters Xbridge BEH C18 100mmx30mm, 10μm; liquid phase: [A:10mM $NH_4HCO_3$ in $H_2O$; B:ACN] B%: 40%-70%, 8 min]) to give 1-(3-hydroxy-3-methylbutyl)-3-(isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(71)**. **LCMS (Method 13):** $t_R$ = 2.335 min, $[M+1]^+$ 444.0. **$^1$H NMR:** (400 MHz, DMSO-$d_6$) δ = 9.44 (s, 1H), 8.56 (s, 1H), 8.37 - 8.19 (m, 3H), 8.00 - 7.92 (m, 1H), 7.84 - 7.69 (m, 3H), 4.60 (s, 1H), 4.26 (br dd, *J*=5.8, 10.6 Hz, 2H), 1.80 (br dd, *J*=4.8, 9.6 Hz, 2H), 1.20 (s, 6H).

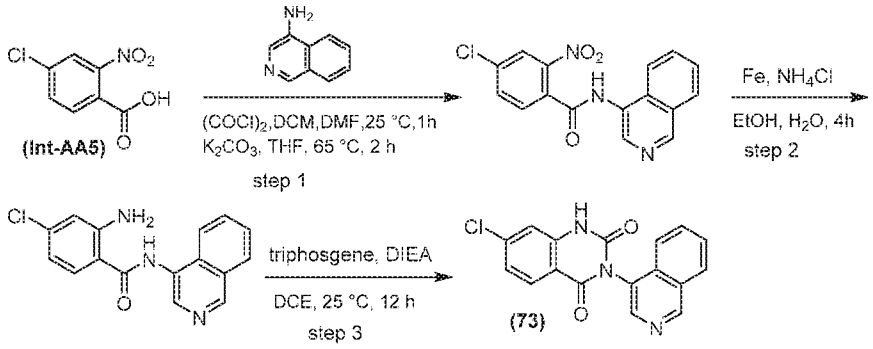
Note: 3-hydroxy-3-methylbutyl 4-methylbenzenesulfonate was obtained using the following procedure: To a mixture of 3-methylbutane-1,3-diol (2.0 g, 19.20 mmol, 1.0 eq.) in Pyridine (20 mL) was added 4-methylbenzenesulfonyl chloride (3.6 g, 19.20 mmol, 1.0 eq.) at 0°C under $N_2$. The reaction mixture was stirred at 25°C for 16 hrs. The mixture was diluted with saturated $NH_4Cl$ aqueous (30 mL) and extracted with $CH_2Cl_2$ (20 mL x 2). The combined organic layers were washed with brine (20 mL), dried over $Na_2SO_4$, filtered and concentrated to give crude product. The crude product was purified by column (Petroleum ether/EtOAc = 10/1 to 3/1) to give 3-hydroxy-3-methylbutyl 4-methylbenzenesulfonate. **$^1$H NMR:** (400MHz, CHLOROFORM-d) δ = 7.77 (d, *J*=8.4 Hz, 2H), 7.33 (d, *J*=8.0 Hz, 2H), 4.19 (t, *J*=6.9 Hz, 2H), 2.02 (s, 3H), 1.84 (t, *J*=6.9 Hz, 2H), 1.19 (s, 6H).

**Example 72:** Synthesis of 3-(isoquinolin-4-yl)-1-(oxiran-2-ylmethyl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(72)**




To a solution of 3-(isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(2)** (200 mg, 0.56 mmol, 1.0 eq) in DMF (5 mL) was added $Cs_2CO_3$ (365 mg, 1.12 mmol, 2.0 eq) and 2-(bromomethyl)oxirane (77 mg, 0.56 mmol, 1.0 eq.) at 20°C. The reaction mixture was stirred for 12 hrs at 20°C. The reaction was poured into water (20 mL) and extracted with EtOAc (20 mL x 2). The organic phases were washed with brine (20 mL), dried over $Na_2SO_4$, filtered and concentrated to give crude product. The crude was purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150mmx40mm, 10μm; liquid phase: [A:$H_2O$ (10mM $NH_4HCO_3$); B:ACN] B%: 30%-60%, 20min]) to give 3-(isoquinolin-4-yl)-1-(oxiran-2-ylmethyl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(72)**. **LCMS (Method 1):** $t_R$ = 2.311 min, $[M+1]^+$ 414.0. **$^1$H NMR:** (400MHz, DMSO-$d_6$) δ 9.44 (s, 1H), 8.60 (s, 1H), 8.31 - 8.25 (m, 2H), 8.21 (br d, *J*=8.9 Hz, 1H), 8.05 - 7.97 (m, 1H), 7.90 (d, *J*=8.9 Hz, 1H), 7.82 - 7.72 (m, 2H), 4.67 (ddd, *J*=2.8, 5.0, 15.7 Hz, 1H), 4.36 - 4.15 (m, 1H), 3.38 - 3.34 (m, 1H), 2.89 - 2.77 (m, 2H).

**Example 73:** Synthesis of 7-chloro-3-(isoquinolin-4-yl)quinazoline-2,4(1H,3H)-dione **(73)**



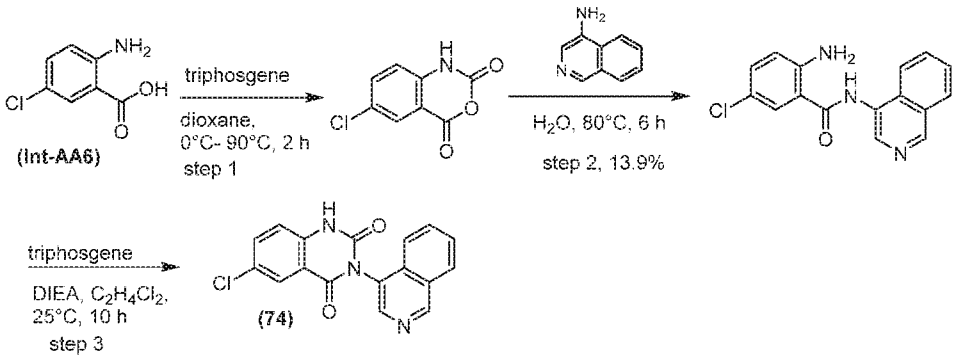

Step 1: To a mixture of 4-chloro-2-nitrobenzoic acid **(Int-AA5)** (2.00 g, 9.92 mmol, 1.3 eq) and $(COCl)_2$ (1.64 g, 12.90 mmol, 1.13 mL, 1.7 eq) in $CH_2Cl_2$ (12 mL) was added DMF (0.1 mL) at 0 °C under $N_2$. The mixture was stirred at 20°C for 1 h. The reaction mixture was concentrated to get crude product which was dissolved with THF (12 mL), $K_2CO_3$ (1.15 g, 8.33 mmol, 1.2eq), DMAP (896 mg, 694.11µmol, 0.1eq) and then isoquinolin-4-amine (1.00 g, 6.94 mmol, 1eq) was added. The mixture was stirred at 65°C for 2 hrs. The mixture was cooled to 25 °C, poured into ice-water (20 mL) and stirred for 3 min. The aqueous phase was extracted with ethyl acetate (20 mL x 3). The combined organic phases were washed with brine (20 mLx3), dried with anhydrous $Na_2SO_4$, filtered and concentrated in vacuum to give crude product. The crude product was triturated with MTBE at 25°C for 5 min to give 4-chloro-N-(isoquinolin-4-yl)-2-nitrobenzamide. **LCMS (Method 23):** $t_R$ = 0.771 min, $[M+1]^+$ 328.1.

Step 2: To a mixture of 4-chloro-N-(isoquinolin-4-yl)-2-nitrobenzamide (1 g, 3.05 mmol, 1 eq) in $H_2O$ (2 mL) and EtOH (10 mL) was added $NH_4Cl$ (816 mg, 15.26 mmol, 5 eq) in one portion at 25°C. The mixture was heated to 65°C and Fe powder (511 mg, 9.15 mmol, 3 eq) was added. Then the mixture was stirred at 65°C for 4 hours. The mixture was poured into water (30 mL) and extracted with EtOAc (10 mL x 3). The combined organic phases were washed with brine, dried over $Na_2SO_4$, filtered and concentrated to give crude product. The crude product was triturated with MTBE at 25°C for 5 min to give 2-amino-4-chloro-N-(isoquinolin-4-yl)benzamide. **LCMS (Method 24):** $t_R$ = 2.184 min, $[M+1]^+$ 298.0.

Step 3: To a mixture of 2-amino-4-chloro-N-(isoquinolin-4-yl)benzamide (300 mg, 1.01 mmol, 1 eq) in DCE was added triphosgene (89 mg, 302 µmol, 0.3 eq) and DIEA (143 mg, 1.11 mmol, 1.1 eq) in one portion at 25°C. Then the mixture was stirred at 25°C for 12 hours. The reaction mixture was diluted with sat.aq.$NaHCO_3$ (10 mL) and extracted with $CH_2Cl_2$ (5 mL x 3). The combined organic layers were dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give crude product which was purified by prep-HPLC (column: Phenomenex Luna C18 200mmx40mm, 10µm; liquid phase: [A:$H_2O$(0.1%FA); B:ACN]B%: 15%-55%,20min]) to give 7-chloro-3-(isoquinolin-4-yl)quinazoline-2,4(1H,3H)-dione **(73)**. **LCMS (Method 1):** $t_R$ =1.979 min, $[M+1]^+$ 324.0. **$^1$H NMR:** (400MHz, DMSO-d6) δ = 11.87 (br s, 1H), 9.43 (s, 1H),

8.55 (s, 1H), 8.26 (d, *J*=4.8 Hz, 1H), 7.97 (d, *J*=9.0 Hz, 1H), 7.86 (d, *J*=4.2 Hz, 1H), 7.81 - 7.72 (m, 2H), 7.35 - 7.30 (m, 2H).

**Example 74:** Synthesis of 6-chloro-3-(isoquinolin-4-yl)quinazoline-2,4(1H,3H)-dione **(74)**

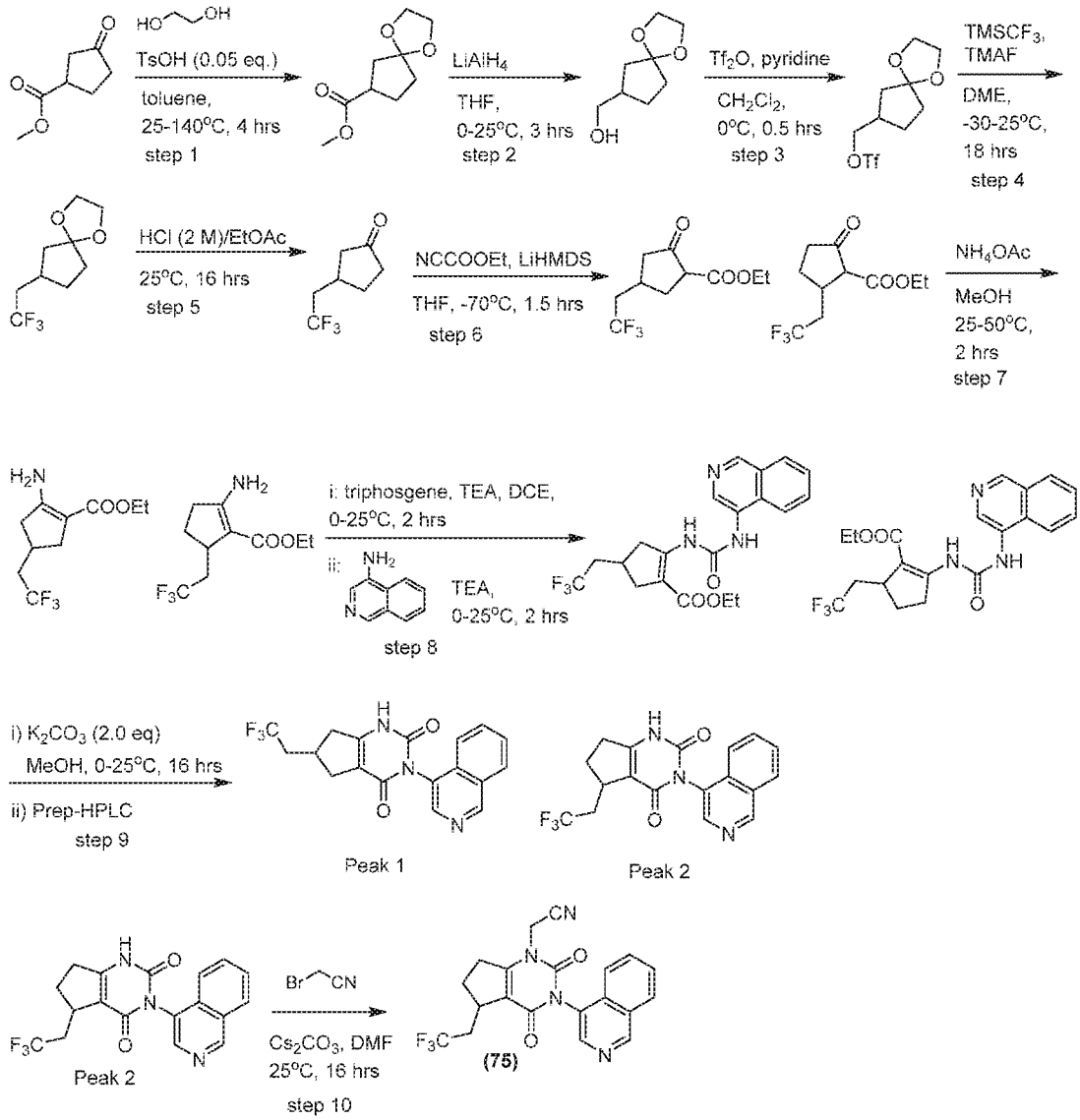



Step 1: To a mixture of triphosgene (576 mg, 0.02 mmol, 3.0 eq.) was added to a suspension of 2-amino-5-chlorobenzoic acid **(Int-AA6)** (1 g, 0.06 mmol, 3.0 eq.) in 1,4- dioxane (10 mL) at 0°C. The homogeneous reaction mixture was heated to 90°C for 2 hrs. The reaction mixture was cooled and filtered to give 6-chloro-2H-benzo[d][1,3]oxazine-2,4(1H)-dione. **$^1$H NMR:** (400MHz, DMSO-$d_6$) δ = 7.87 (d, *J*=2.4 Hz, 1H), 7.78 (dd, *J*=2.5, 8.7 Hz, 1H), 7.16 (d, *J*=8.6 Hz, 1H).

Step 2: A mixture of 6-chloro-2H-benzo[d][1,3]oxazine-2,4(1H)-dione (1.0 g, 5.06 mmol, 1.0 eq.) and isoquinolin-4-amine (700 mg, 5.06 mmol, 1.0 eq.) in $H_2O$ (20 mL) was stirred at 80°C for 6 hrs. The solution was poured into water (30 mL) and extracted with EtOAc (40 mL x 2). The organic phase was washed with water (30 mL), brine (30 mL), dried over $Na_2SO_4$, filtered and concentrated to give crude product which was triturated with ACN to give 2-amino-5-chloro-N-(isoquinolin-4-yl)benzamide. **LCMS (Method 25):** $t_R$ =0.903 min, $[M+1]^+$ 298.1.

Step 3: A mixture of 2-amino-5-chloro-N-(isoquinolin-4-yl)benzamide (100 mg, 0.33mmol, 3.0 eq.), triphosgene (34 mg, 0.11 mmol, 1.0 eq.) and DIEA (15 mg, 0.11 mmoL, 1.0 eq) in $CH_2Cl_2$ (5 mL) was stirred at 25°C for 10 hrs. The solution was poured into water (40 mL) and extracted with EtOAc (40 mL x 2). The organic phase was washed with water (40 mL), brine (40 mL), dried over $Na_2SO_4$, filtered and concentrated to give crude product. The crude product was purified by preparative HPLC (column: Phenomenex Gemini-NX 80mmx40mm, 3μm; liquid phase: [A:$H_2O$ (10mM $NH_4HCO_3$); B:ACN] B%: 20%-40%, 20min]) to give 6-chloro-3-(isoquinolin-4-yl)quinazoline-2,4(1H,3H)-dione **(74)**. **LCMS (Method 3):** $t_R$ =2.301 min, $[M+1]^+$ 324.1. **$^1$H NMR:** (400MHz, DMSO-$d_6$) δ = 11.83 (br s, 1H), 9.44 (s, 1H), 8.56 (s, 1H), 8.36 - 8.21 (m, 1H), 8.01 - 7.63 (m, 5H), 7.34 (d, *J*=8.8 Hz, 1H).

**Example 75:** Synthesis of 2-(3-(isoquinolin-4-yl)-2,4-dioxo-5-(2,2,2-trifluoroethyl)-2,3,4,5,6,7-hexahydro-1H-cyclopenta[d]pyrimidin-1-yl)acetonitrile **(75)**




Step 1: To a stirred solution of methyl 3-oxocyclopentane-1-carboxylate (5.0 g, 35.17 mmol, 1.0 eq.) in toluene (50 mL) was added ethane-1,2-diol (4.4 g, 70.35 mmol, 2.0 eq.) and TsOH (0.3 g, 1.76 mmol, 0.05 eq.) at 25°C. The mixture was stirred at 140°C for 4 hrs (water removal by Dean–Stark). The reaction mixture was evaporated under reduced pressure to give a residue. The residue was taken up in EtOAc (100 mL), washed with aqueous $NaHCO_3$ (10%, 25 mL), brine (25 mL) and dried over $Na_2SO_4$. After filtering, the solvents were removed under reduced pressure to yield crude product which was purified by flash silica gel chromatography (40 g, Eluent of 0~20% Ethyl acetate/Petroleum ether, 100 mL/min) to give methyl 1,4-dioxaspiro[4.4]nonane-7-carboxylate. **$^1$H NMR:** (400 MHz, CHLOROFORM-d) δ = 3.94 - 3.89 (m, 4H), 3.69 (s, 3H), 2.97 - 2.86 (m, 1H), 2.10 (d, *J* = 9.0 Hz, 2H), 2.07 - 1.85 (m, 4H), 1.85 - 1.78 (m, 1H).

Step 2: $LiAlH_4$ (0.9 g, 22.56 mmol, 1.2 eq.) was added dropwise to a stirred solution of methyl 1,4-dioxaspiro[4.4]nonane-7-carboxylate (3.5 g, 18.80 mmol, 1.0 eq.) in THF (50 mL) at 0°C

under a $N_2$ atmosphere and the mixture stirred at 25°C for 3 hrs. The reaction mixture was cooled to 0°C, quenched with $H_2O$ (2 mL), aqueous NaOH (10%, 10 mL) and stirred at 25°C for 10 mins. The inorganics were filtered through Celite and washed with EtOAc (2 x 10 mL). The filtrate was washed with water (10 mL), brine (10 mL), dried over $Na_2SO_4$, filtered and the solvents were removed under reduced pressure to give (1,4-dioxaspiro[4.4]nonan-7-yl)methanol which was used directly in the next step without purification. **$^1$H NMR:** (400 MHz, CHLOROFORM-d) δ = 3.97 - 3.87 (m, 4H), 3.59 (br d, *J* = 3.6 Hz, 2H), 2.38 - 2.22 (m, 1H), 2.06 - 2.00 (m, 1H), 1.95 - 1.77 (m, 3H), 1.63 - 1.59 (m, 1H), 1.53 - 1.44 (m, 1H).

Step 3: Under $N_2$ flow and at 0°C, $Tf_2O$ (3.2 g, 11.38 mmol, 1.2 eq.) was added to a solution of (1,4-dioxaspiro[4.4]nonan-7-yl)methanol (1.5 g, 9.48 mmol, 1.0 eq.) and pyridine (1.5 g, 18.96 mmol, 1.2 eq.) in $CH_2Cl_2$ (30 mL). The reaction mixture was stirred for 0.5 hrs at 0°C. The mixture was quenched with water (30 mL). The aqueous layer was separated from the organic and extracted with $CH_2Cl_2$ (5 mL x 2). The combined organic solutions were washed with HCl (0.5 M, 15 mL), dried ($Na_2SO_4$), filtered, and concentrated by $N_2$ flow to give (1,4-dioxaspiro[4.4]nonan-7-yl)methyl trifluoromethanesulfonate which was unstable and used immediately in the next step.

Step 4: At -30°C, TMAF (1.1 g, 11.38 mmol, 1.2 eq.) was added to a solution of (1,4-dioxaspiro[4.4]nonan-7-yl)methyl trifluoromethanesulfonate (1.5 g, 9.48 mmol, 1.0 eq.) and $TMSCF_3$ (4.0 g, 28.45 mmol, 3.0 eq.) in DME (50 mL). The reaction mixture was stirred for 0.5 hrs at -30°C and then at 0°C for 1.5 hrs. The mixture was then stirred for 16 hrs at 25°C. The mixture was quenched with water (100 mL). The aqueous layer was separated from the organic phase and extracted with EtOAc (50 mL x 3). The combined organic solutions were washed with brine (100 mL), dried ($Na_2SO_4$), filtered, and concentrated under reduced pressure to give crude product. The crude product was purified by MPLC (petroleum ether/EtOAc =0 ~ 1/5) to give 7-(2,2,2-trifluoroethyl)-1,4-dioxaspiro[4.4]nonane. **$^1$H NMR:** (400 MHz, CHLOROFORM-d) δ = 3.99 - 3.84 (m, 4H), 2.35 - 2.26 (m, 1H), 2.24 - 2.08 (m, 3H), 2.04 - 1.92 (m, 2H), 1.88 - 1.78 (m, 1H), 1.55 (br dd, *J* = 10.1, 13.4 Hz, 1H), 1.49 - 1.36 (m, 1H). **$^{19}$F NMR:** (377 MHz, CHLOROFORM-d) δ = -63.64 - 66.34 (m, 1F).

Step 5: At 25°C, HCl (0.5 mL, 2 M) was added to a solution of 7-(2,2,2-trifluoroethyl)-1,4-dioxaspiro[4.4]nonane (100 mg, 0.47 mmol, 1.0 eq.) in EtOAc (1.5 mL). The reaction mixture was stirred at 25°C for 16 hrs. The mixture was quenched with $NaHCO_3$ (10 mL). The aqueous layer was separated from the organic phase and extracted with EtOAc (2 mL x 3). The combined organic solutions were dried ($Na_2SO_4$), filtered, and concentrated under reduced pressure to give 3-(2,2,2-trifluoroethyl)cyclopentan-1-one. **$^1$H NMR:** (400 MHz, CHLOROFORM-d) δ = 2.79 - 2.42 (m, 2H), 2.42 - 2.08 (m, 4H), 2.00 - 1.80 (m, 1H), 1.73 - 1.55 (m, 1H), 1.49 - 1.32 (m, 1H). **$^{19}$F NMR:** $^{19}$F NMR (376 MHz, CHLOROFORM-d) δ = -64.71 (s, 1F).

Step 6: To a solution of 3-(2,2,2-trifluoroethyl)cyclopentan-1-one (150 mg, 0.90 mmol, 1.0 eq.) in THF (2 mL) was added LiHMDS (1.08 mL, 1.08 mmol, 1.2 eq.) at -70°C under $N_2$. The mixture was stirred at -70°C for 0.5 hrs under $N_2$. NCCOOEt (99 mg, 0.99 mmol, 1.1 eq.) was added to at -70°C under $N_2$ and the mixture stirred at -70°C for 1 hr under $N_2$. The reaction was quenched with saturated aqueous $NH_4Cl$ (10 mL) and extracted with EtOAc (10 mL x 2). The combined organic layers were washed with brine (10 mL), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give crude product. The crude product was purified by MPLC (petroleum ether / EtOAc = 1/0 to 5/1) to give a mixture of ethyl 2-oxo-4-(2,2,2-trifluoroethyl)cyclopentane-1-carboxylate and ethyl 2-oxo-5-(2,2,2-trifluoroethyl)cyclopentane-1-carboxylate. **$^1$H NMR:** (400 MHz, CHLOROFORM-d) δ = 4.24 (m, 2H), 2.99 - 2.88 (m, 1H), 2.67 - 2.01 (m, 6H), 1.73 - 1.57 (m, 1H), 1.39 - 1.23 (m, 3H).

Step 7: To a solution of the mixture of ethyl 2-oxo-4-(2,2,2-trifluoroethyl)cyclopentane-1-carboxylate and ethyl 2-oxo-5-(2,2,2-trifluoroethyl)cyclopentane-1-carboxylate (100 mg, 0.42 mmol, 1.0 eq.) in MeOH (2 mL) was added $NH_4OAc$ (324 mg, 4.20 mmol, 10.0 eq.) at 25°C and the mixture stirred at 50°C for 2 hrs. The mixture was concentrated to give a residue which was suspended in saturated $NaHCO_3$ solution (10 mL) and extracted with EtOAc (5 mL × 3). The combined organic layers were washed with brine (5 mL), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give crude product. The crude product was purified by MPLC (petroleum ether / EtOAc = 1/0 to 5/1) to give a mixture of ethyl 2-amino-4-(2,2,2-trifluoroethyl)cyclopent-1-ene-1-carboxylate and ethyl 2-amino-5-(2,2,2-trifluoroethyl)cyclopent-1-ene-1-carboxylate. **$^1$H NMR:** (400 MHz, CHLOROFORM-d) δ = 4.26 - 4.08 (m, 2H), 3.27 - 3.14 (m, 1H), 2.81 (dd, *J* = 8.1, 13.6 Hz, 1H), 2.75 - 2.50 (m, 2H), 2.47 - 2.03 (m, 3H), 1.98 - 1.85 (m, 1H), 1.83 - 1.70 (m, 1H), 1.34 - 1.21 (m, 3H). **$^{19}$F NMR:** (376 MHz, CHLOROFORM-d) δ = -64.15 (s, 1F), -64.97 (s, 1F).

Step 8: To a mixture of ethyl 2-amino-4-(2,2,2-trifluoroethyl)cyclopent-1-ene-1-carboxylate and ethyl 2-amino-5-(2,2,2-trifluoroethyl)cyclopent-1-ene-1-carboxylate (50 mg, 0.21 mmol, 1.0 eq.) and TEA (64 mg, 0.63 mmol, 3.0 eq.) in DCE (0.5 mL) was added drop-wise a solution of triphosgene (31 mg, 0.11 mmol, 0.5 eq.) in DCE (0.5 mL) at 0°C. The mixture was stirred at 25°C for 2 hrs. Then a suspension of isoquinolin-4-amine (30 mg, 0.21 mmol, 1.0 eq.) and TEA (64 mg, 0.63 mmol, 3.0 eq.) in DCE (0.5 mL) was added drop-wise to the mixture at 0°C. The mixture was stirred at 25°C for 2 hrs. The reaction was quenched with $H_2O$ (5 mL) and separated. The aqueous layer was extracted with $CH_2Cl_2$ (5 mL × 2). The combined organic layers were washed with brine (5 mL), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give a mixture of ethyl 2-(3-(isoquinolin-4-yl)ureido)-4-(2,2,2-trifluoroethyl)cyclopent-1-ene-1-carboxylate and ethyl 2-(3-(isoquinolin-4-yl)ureido)-5-(2,2,2-trifluoroethyl)cyclopent-1-ene-1-carboxylate which was used in the next step directly without purification. **LCMS (Method 12):** $t_R$ = 0.768 min, $[M+1]^+$ 408.1.

Step 9: To a mixture of ethyl 2-(3-(isoquinolin-4-yl)ureido)-4-(2,2,2-trifluoroethyl)cyclopent-1-ene-1-carboxylate and ethyl 2-(3-(isoquinolin-4-yl)ureido)-5-(2,2,2-trifluoroethyl)cyclopent-1-ene-1-carboxylate (100 mg, crude) in MeOH (2 mL) was added $K_2CO_3$ (100 mg, 0.49 mmol, 2.0 eq.) at 0°C. The mixture was stirred at 25°C for 16 hrs. The reaction mixture was filtered and the filtrate was purified by prep-HPLC ($NH_4HCO_3$) to give two peaks: **HPLC:** Instrument: Agilent 1200 LC-20AB&MS 2010, ESI; Column: Xbridge C18 50mmx2.1mm, 5 µm; Gradient: mobile phase A: 15 mM $NH_4HCO_3$ in water, B: acetonitrile; Gradient was 0-60% B over 4.50 min., 60% B for 0.80 min., 60-0% B over 0.01 min., 0%B for 0.69 min. Flow rate: 0.8 mL/min (0.00-5.31min) and 1.2 mL/min (5.31-5.32 min). Diode array detection. Mass detection MS range 100-1000 Da (ESI); Column temperature : 40 °C. **Peak 1:** 3-(isoquinolin-4-yl)-6-(2,2,2-trifluoroethyl)-1,5,6,7-tetrahydro-2H-cyclopenta[d]pyrimidine-2,4(3H)-dione ($t_R$ = 3.116 min.) and **Peak 2:** 3-(isoquinolin-4-yl)-5-(2,2,2-trifluoroethyl)-1,5,6,7-tetrahydro-2H-cyclopenta[d]pyrimidine-2,4(3H)-dione ($t_R$ = 3.333 min.).

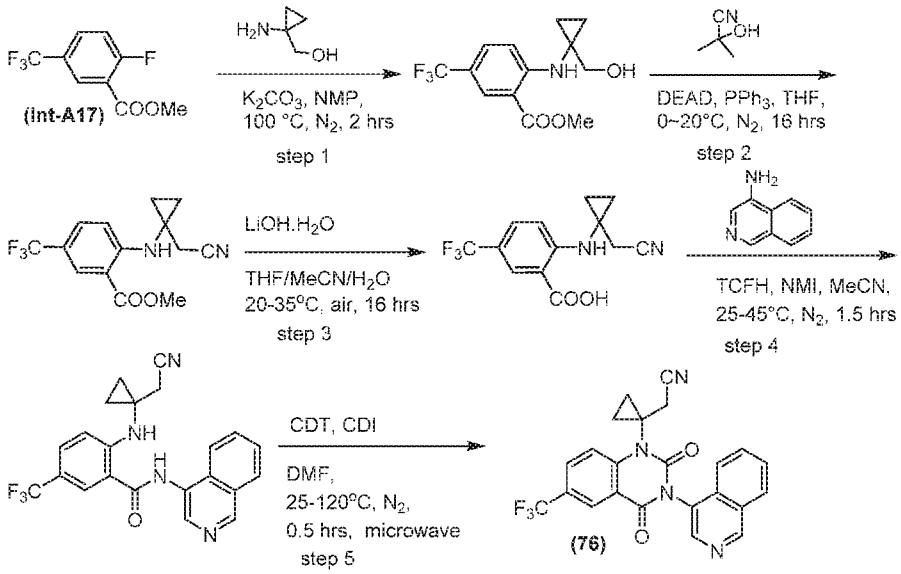
**Peak 1:** 3-(isoquinolin-4-yl)-6-(2,2,2-trifluoroethyl)-1,5,6,7-tetrahydro-2H-cyclopenta[d]pyrimidine-2,4(3H)-dione. **$^1$H NMR:** (400 MHz, METHANOL-$d_4$) δ = 9.33 (s, 1H), 8.37 (s, 1H), 8.23 (d, *J* = 8.3 Hz, 1H), 7.86 - 7.80 (m, 1H), 7.75 (dt, *J* = 0.9, 7.5 Hz, 1H), 7.71 (d, *J* = 8.3 Hz, 1H), 3.09 (dd, *J* = 8.2, 17.1 Hz, 1H), 3.04 - 2.86 (m, 2H), 2.84 - 2.73 (m, 1H), 2.52 (dq, *J* = 7.0, 11.2 Hz, 3H).

**Peak 2:** 3-(isoquinolin-4-yl)-5-(2,2,2-trifluoroethyl)-1,5,6,7-tetrahydro-2H-cyclopenta[d]pyrimidine-2,4(3H)-dione**. $^1$H NMR:** (400 MHz, METHANOL-$d_4$) δ = 9.34 (s, 1H), 8.38 (d, *J* = 3.0 Hz, 1H), 8.24 (d, *J* = 8.1 Hz, 1H), 7.89 - 7.81 (m, 1H), 7.80 - 7.74 (m, 1H), 7.74 - 7.68 (m, 1H), 3.50 - 3.42 (m, 1H), 3.11 - 2.80 (m, 3H), 2.59 - 2.43 (m, 1H), 2.35 - 2.15 (m, 1H), 2.13 - 1.97 (m, 1H).

Step 10: To a mixture of 3-(isoquinolin-4-yl)-5-(2,2,2-trifluoroethyl)-1,5,6,7-tetrahydro-2H-cyclopenta[d]pyrimidine-2,4(3H)-dione (30 mg, 0.08 mmmol, 1.0 eq.) and $Cs_2CO_3$ (54 mg, 0.16 mmmol, 2.0 eq.) in DMF (1 mL) was added 2-bromoacetonitrile (15 mg, 0.12 mmmol, 1.5 eq.). The reaction mixture was stirred at 25°C for 16 hrs. The mixture was filtered and the filtrate was purified by prep-HPLC ($NH_4HCO_3$) to give 2-(3-(isoquinolin-4-yl)-2,4-dioxo-5-(2,2,2-trifluoroethyl)-2,3,4,5,6,7-hexahydro-1H-cyclopenta[d]pyrimidin-1-yl)acetonitrile **(75)**.

**LCMS (Method 17):** $t_R$ = 2.702 min, $[M+1]^+$ 401.2. **$^1$H NMR:** (400 MHz, ACETONITRILE-$d_3$) δ = 9.35 (s, 1H), 8.40 (s, 1H), 8.19 (d, *J* = 8.0 Hz, 1H), 7.84 - 7.77 (m, 1H), 7.76 - 7.67 (m, 2H), 4.89 - 4.64 (m, 2H), 3.54 - 3.41 (m, 1H), 3.19 - 3.08 (m, 1H), 3.08 - 3.01 (m, 1H), 3.01 - 2.89 (m, 1H), 2.58 - 2.44 (m, 1H), 2.24 (tt, *J* = 10.9, 15.5 Hz, 1H), 2.09 - 2.01 (m, 1H).

**Example 76:** Synthesis of 2-(1-(3-(isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2H)-yl)cyclopropyl)acetonitrile **(76)**




Step 1: To a solution of methyl 2-fluoro-5-(trifluoromethyl)benzoate **(Int-AA8)** (1.0 g, 4.50 mmol, 1.0 eq.), (1-aminocyclopropyl)methanol (508 mg, 5.86 mmol, 1.5 eq.) in NMP (10 mL) was added $K_2CO_3$ (1.2 g, 0.90 mmol, 2.0 eq.). The mixture was stirred at 100 °C for 2 hrs under $N_2$. The reaction mixture was diluted with $H_2O$ (20 mL) and extracted with ethyl acetate (15 mL × 3). The ethyl acetate layers were combined, washed with brine (20 mL), dried over $Na_2SO_4$, filtered and concentrated to give a residue. The residue was purified by column (Petroleum ether/Ethyl acetate = 1/0 to 0/1) to give methyl 2-((1-(hydroxymethyl)cyclopropyl)amino)-5-(trifluoromethyl)benzoate. **$^1$H NMR:** (400 MHz, CHLOROFORM-d) δ = 8.17 (d, *J*=1.5 Hz, 1 H), 7.55 (dd, *J*=8.9, 2.2 Hz, 1 H), 7.17 (d, *J*=8.9 Hz, 1 H), 3.89 (s, 3 H), 3.69 (s, 2 H), 0.95 - 0.99 (m, 2 H), 0.89 - 0.93 (m, 2 H).

Step 2: To a solution of $PPh_3$ (400 mg, 1.66 mmol, 2.0 eq.) in THF (5 mL) was added DEAD (264 mg, 1.66 mmol, 2.0 eq.) at 0°C under $N_2$. The reaction was stirred at 0°C for 1 hr. To the mixture was added methyl 2-((1-(hydroxymethyl)cyclopropyl)amino)-5-(trifluoromethyl)benzoate (240 mg, 0.83 mmol, 1.0 eq.) and 2-hydroxy-2-methylpropanenitrile (120 mg, 1.41 mmol, 1.7 eq.) at 0°C. The mixture was stirred at 20°C for 15 hrs. The reaction mixture was quenched with $H_2O$ (10 mL), and then extracted with ethyl acetate (15 mL x 3). The combined organic layers were washed with brine (20 mL), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column ($SiO_2$, Petroleum ether/EtOAc = 3/1) to give methyl 2-((1-(cyanomethyl)cyclopropyl)amino)-5-(trifluoromethyl)benzoate. **$^1$H NMR:** (400 MHz, CHLOROFORM-*d*) δ = 8.55 (s, 1 H), 8.21 (d, *J*=1.50 Hz, 1 H), 7.61 (dd, *J*=8.88, 2.25 Hz, 1 H), 7.06 (d, *J*=8.88 Hz, 1 H), 3.90 (s, 3 H), 2.79 (s, 2 H), 1.10 - 1.15 (m, 2 H), 1.05 - 1.09 (m, 2 H).

Step 3: To a solution of methyl 2-((1-(cyanomethyl)cyclopropyl)amino)-5-(trifluoromethyl)benzoate (100 mg, 0.34 mmol, 1.0 eq.) in THF (0.4 mL) and MeCN (0.4 mL)

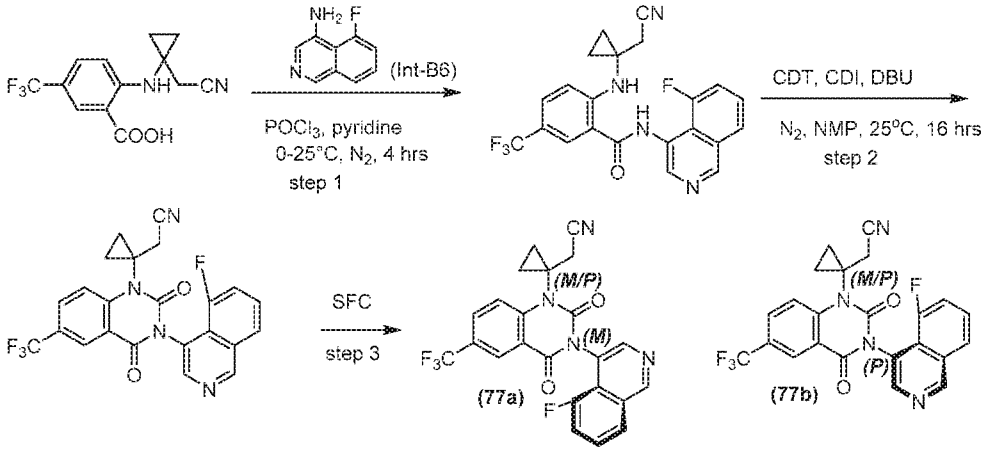
was added LiOH (16 mg, 0.68 mmol, 2.0 eq.) in $H_2O$ (0.4 mL) at 20°C. The reaction was stirred at 35°C for 16 hrs. The mixture was diluted with ice water (2 mL), adjusted to pH = 5 with 3 M HCl at 0°C and extracted with EtOAc (10 mL x 2). The combined organic layers were washed with brine (10 mL), dried over $Na_2SO_4$, filtered and concentrated to give 2-((1-(cyanomethyl)cyclopropyl)amino)-5-(trifluoromethyl)benzoic acid. **LCMS (Method 7):** $t_R$ = 0.775 min, $[M+1]^+$ 285.1.

Step 4: The solution of 2-((1-(cyanomethyl)cyclopropyl)amino)-5-(trifluoromethyl)benzoic acid (210 mg, 0.74 mmol, 1.0 eq.) and isoquinolin-4-amine (127mg, 0.88 mmol, 1.2 eq.) in MeCN (5 mL) was added TCFH (250 mg, 0.88 mmol, 1.2 eq.) and NMI (240 mg, 2.22 mmol, 3.0 eq.) at 25°C under $N_2$. The solution was stirred at 45°C for 1.5 hrs. The reaction was quenched with $H_2O$ (10 mL) and extracted with EtOAc (20 mL × 2). The combined organic layers were washed with brine (10 mL × 2), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give crude product. The crude product was purified by column (12 g, Eluent of 0~60% EtOAc/Petroleum ether, 50 mL/min) to give 2-((1-(cyanomethyl)cyclopropyl)amino)-N-(isoquinolin-4-yl)-5-(trifluoromethyl)benzamide. **$^1$H NMR:** (400 MHz, METHANOL-$d_4$) δ = 9.21 (s, 1 H), 8.55 (s, 1 H), 8.29 (d, *J*=1.1 Hz, 1 H), 8.20 (d, *J*=8.1 Hz, 1 H), 7.99 - 8.04 (m, 1 H), 7.86 (ddd, *J*=8.4, 7.0, 1.2 Hz, 1 H), 7.68 - 7.79 (m, 2 H), 7.31 (d, *J*=8.9 Hz, 1 H), 2.92 (s, 2 H), 1.05 - 1.11 (m, 2 H), 0.98 - 1.04 (m, 2 H).

Step 5: To a solution of 2-((1-(cyanomethyl)cyclopropyl)amino)-N-(isoquinolin-4-yl)-5-(trifluoromethyl)benzamide (100 mg, 0.50 mmol, 1.0 eq.) in DMF (2 mL) was added CDI (80 mg, 1.01 mmol, 2.0 eq.) and CDT (80 mg, 1.01 mmol, 2.0 eq.). The mixture was stirred at 120°C for 0.5 hr. The reaction mixture was concentrated to dryness to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150mmx40mm, 10μm; liquid phase: [A - $H_2O$ (10 mM $NH_4HCO_3$); B - ACN] B%: 10% - 40%, 20 min]) to give 2-(1-(3-(isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2H)-yl)cyclopropyl)acetonitrile as a mixture of four atropisomers **(76)**. **LCMS (Method 13):** $t_R$ = 2.409 min, $[M+1]^+$ 437.0. **$^1$H NMR:** (400 MHz, DMSO-$d_6$) δ = 9.44 (s, 1 H), 8.54 (d, *J*=13.1 Hz, 1 H), 8.26 - 8.32 (m, 2 H), 8.23 (br d, *J*=8.9 Hz, 1 H), 7.96 - 8.10 (m, 2 H), 7.72 - 7.83 (m, 2 H), 3.04 - 3.24 (m, 2 H), 1.49 - 1.62 (m, 1 H), 1.18 - 1.42 (m, 3 H). SFC: (column: Lux Cellulose (50mmx4.6mm, 3μm); mobile phase: A: $CO_2$, B: EtOH (0.1% IPAm); B%: 5% for 0.2 min, 5-50% for 1.0 min., 50% for 1.0 min., 50-5% for 0.4 min., 5% for 0.4 min.), $t_{R1}$ = 1.173 min, $t_{R2}$ = 1.233 min, $t_{R3}$ = 1.404 min, $t_{R4}$ = 1.535 min.

**Example 77:** Synthesis of {(1*M* or 1*P*)-[(3*M*)-3-(5-Fluoroisoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2*H*)-yl]cyclopropyl}acetonitrile **(77a)** and

{(1*M* or 1*P*)-[(3*P*)-3-(5-Fluoroisoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2*H*)-yl]cyclopropyl}acetonitrile **(77b)**




Step 1: To a solution of 2-((1-(cyanomethyl)cyclopropyl)amino)-5-(trifluoromethyl)benzoic acid (500 mg, 1.76 mmol, 1.0 eq.) and 5-fluoroisoquinolin-4-amine **(Int-B6)** (285 mg, 1.76 mmol, 1.0 eq.) in pyridine (20 mL) was added $POCl_3$ (650 mg, 3.52 mmol, 2.0 eq.) at 0°C. The reaction was stirred at 25°C for 4 hrs under $N_2$. The reaction mixture was quenched with $H_2O$ (100 mL) and extracted with $CH_2Cl_2$ (100 mL x 3). The combined organic layers were concentrated under reduced pressure to give crude product which was purified by column (Petroleum ether/EtOAc= 2/1 to 1/2) to give 2-((1-(cyanomethyl)cyclopropyl)amino)-N-(5-fluoroisoquinolin-4-yl)-5-(trifluoromethyl)benzamide. **LCMS (Method 5):** $t_R$ = 0.955 min, $[M+1]^+$ 429.1.

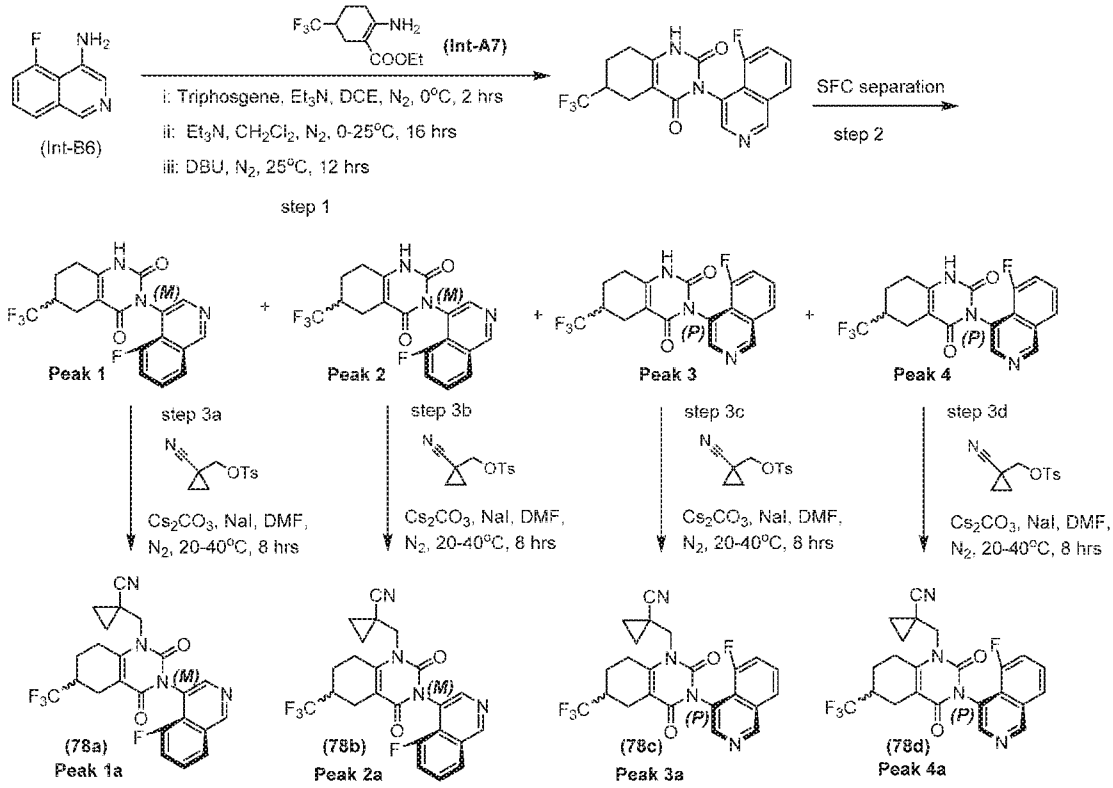
Step 2: To a solution of 2-((1-(cyanomethyl)cyclopropyl)amino)-N-(5-fluoroisoquinolin-4-yl)-5-(trifluoromethyl)benzamide (150 mg, 0.35 mmol, 1.0 eq.), CDI (142 mg, 0.88 mmol, 2.5 eq.) and CDT (144 mg, 0.88 mmol, 2.5 eq.) in NMP (10 mL) was added DBU (160 mg, 1.05 mmol, 3.0 eq.) at 25°C. The mixture was stirred at 25°C for 16 hrs under $N_2$. The reaction mixture was quenched with ice water (50 mL) and extracted with $CH_2Cl_2$ (30 mL x 2). The combined organic layers were concentrated under reduced pressure to give crude product which was purified by prep-HPLC (column: Phenomenex Luna 80mmx30mm, 3μm; liquid phase: [A:TFA/$H_2O$ = 0.075% v/v; B:ACN] B%: 30%-55%, 8 min]) to give the racemate 2-(1-(3-(5-fluoroisoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2H)-yl)cyclopropyl)acetonitrile. **LCMS (Method 26):** $t_R$ =1.843 min, $[M+1]^+$ 455.2.

Step 3: The racemate 2-(1-(3-(5-fluoroisoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2H)-yl)cyclopropyl)acetonitrile was separated by chiral SFC (Column: DAICEL CHIRALCEL OX (250 mm x 30 mm, 10 um); Mobile phase: A for $CO_2$ and B for EtOH (0.1% $NH_3H_2O$); Gradient: B% = 35% isocratic elution mode; Flow rate: 65 g/min; Wavelength:220 nm; Column temperature: 40 degrees centigrade; System back pressure: 100 bar.) to obtain four peaks. **SFC:** $t_{R1}$ = 2.899 min. (41%), $t_{R2}$ = 3.140 min. (59%), $t_{R3}$ = 3.458 min. (40%), and $t_{R4}$ = 3.740 min (59%).

**Peak 1 and Peak 2 were combined to give a mixture of atropisomers.** {(1*M* or 1*P*)-[(3*M*)-3-(5-Fluoroisoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2*H*)-yl]cyclopropyl}acetonitrile: **LCMS**: $R_{t1}$ = 2.582 min, M+1 (455.0), 44.4%, $R_{t2}$ = 2.637 min, M+1 (455.0), 55.2%. **$^1$H NMR** (400 MHz, METHANOL-$d_4$) δ = 9.45 (d, *J* = 2.3 Hz, 1H), 8.51 (d, *J* = 10.1 Hz, 1H), 8.44 (s, 1H), 8.19 - 8.3.40 (d, *J* = 17.5 Hz, 0.5H, one atropisomer), 3.39 (d, *J* = 17.5 Hz, 0.5H, other atropisomer), 3.12 (d, *J* = 17.5 Hz, 0.5H, one atropisomer), 3.09 (d, *J* = 17.5 Hz, 0.5H, other atropisomer), 1.72 - 1.59 (m, 1H), 1.50 - 1.44 (m, 1H), 1.43 - 1.37 (m, 1H), 1.35 - 1.24 (m, 1H).**SFC**: (column: Chiralpak OD-3 (150mmx4.6mm, 3µm); mobile phase: A: $CO_2$; B:IPA[0.1% IPAm]; B%: 10% for 0.5 min., 10-50% over 3.0 min., 50% for 1.0 min., 50-10% over 0.5 min., 3.4 mL/min.) $R_{t1}$ = 2.899 min, 41.0%, $R_{t2}$ = 3.140 min, 59.0%

**Peak 3 and peak 4 were combined to give a mixture of atropisomers.** {(1*M* or 1*P*)-[(3*P*)-3-(5-Fluoroisoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2*H*)-yl]cyclopropyl}acetonitrile**. LCMS**: $R_{t1}$ = 2.580 min, M+1 (455.1), 44.4%, $R_{t2}$ = 2.638 min, M+1 (455.0), 55.2%. **$^1$H NMR**: (400 MHz, METHANOL-$d_4$) δ = 9.45 (d, *J* = 2.3 Hz, 1H), 8.51 (d, *J* = 10.1 Hz, 1H), 8.44 (s, 1H), 8.19 - 8.09 (m, 3H), 7.76 (tdd, *J* = 2.3, 8.0, 10.5 Hz, 1H), 7.58 - 7.51 (m, 1H), 3.40 (d, *J* = 17.5 Hz, 0.5H, one atropisomer), 3.39 (d, *J* = 17.5 Hz, 0.5H, other atropisomer), 3.12 (d, *J* = 17.5 Hz, 0.5H, one atropisomer), 3.09 (d, *J* = 17.5 Hz, 0.5H, other atropisomer), 1.72 - 1.59 (m, 1H), 1.50 - 1.44 (m, 1H), 1.43 - 1.37 (m, 1H), 1.35 - 1.24 (m, 1H). **SFC**: (column: Chiralpak OD-3 (150mmx4.6mm, 3µm); mobile phase: A: $CO_2$; B:IPA[0.1% IPAm]; B%: 10% for 0.5 min., 10-50% over 3.0 min., 50% for 1.0 min., 50-10% over 0.5 min., 3.4 mL/min.) $R_{t1}$ = 3.458 min, 40.3%, $R_{t2}$ = 3.740 min, 59.0%

**Example 78:** Synthesis of 1-{[(3*M*,6*R or 6S*)-3-(5-Fluoroisoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4,5,6,7,8-hexahydroquinazolin-1(2*H*)-yl]methyl}cyclopropane-1-carbonitrile **(78a)**;
1-{[(3*M*,6*R or 6S*)-3-(5-Fluoroisoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4,5,6,7,8-hexahydroquinazolin-1(2*H*)-yl]methyl}cyclopropane-1-carbonitrile **(78b)**;
1-{[(3*P*,6*R or 6S*)-3-(5-Fluoroisoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4,5,6,7,8-hexahydroquinazolin-1(2*H*)-yl]methyl}cyclopropane-1-carbonitrile **(78c)**, and
1-{[(3*P*,6*R or 6S*)-3-(5-Fluoroisoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4,5,6,7,8-hexahydroquinazolin-1(2*H*)-yl]methyl}cyclopropane-1-carbonitrile **(78d)**




Step 1: To a mixture of ethyl 2-amino-5-(trifluoromethyl)cyclohex-1-ene-1-carboxylate **(Int-A7)** (3.6 g, 15.10 mmol, 1.0 eq.) and $Et_3N$ (4.6 g, 45.30 mmol, 3.0 eq.) in DCE (150 mL) was added dropwise a solution of triphosgene (2.2 g, 7.55 mmol, 0.5 eq.) in DCE (15 mL) at 0°C. The mixture was stirred at 0°C for 2 hrs. Then a suspension of 5-fluoroisoquinolin-4-amine **(Int-B6)** (1.5 g, 7.55 mmol, 0.5 eq.) and $Et_3N$ (6.1 g, 60.40 mmol, 4.0 eq.) in DCE (45 mL) was added dropwise to the mixture at 0°C. The mixture was stirred at 25°C for 16 hrs. Then, DBU (4.6 g, 30.20 mmol, 2.0 eq.) was added to the mixture at 25°C. The mixture was stirred at 25°C for 12 hrs. The reaction was quenched with $H_2O$ (600 mL). The reaction mixture was extracted with $CH_2Cl_2$ (300 mL x 3). The combined organic layers were washed with brine (300 mL), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give crude product. The crude was purified by flash silica gel chromatography (120 g SepaFlash® Silica Flash Column, Eluent of 70~100% Ethyl acetate/Petroleum ether gradient at 150 mL/min) to give racemic 3-(5-fluoroisoquinolin-4-yl)-6-(trifluoromethyl)-5,6,7,8-tetrahydroquinazoline-2,4(1H,3H)-dione. **LCMS (Method 12):** $t_R$ = 0.661 min, $[M+1]^+$ 380.1.

Step 2: Racemic 3-(5-fluoroisoquinolin-4-yl)-6-(trifluoromethyl)-5,6,7,8-tetrahydroquinazoline-2,4(1H,3H)-dione (5.5 g, 14.50 mmol) was separated by chiral SFC (DAICEL CHIRALPAK AD (250mmx50mm, 10 μm); mobile phase: [0.1% $NH_3H_2O$ EtOH]; B%: 30%-30%, 8 min) to obtain four peaks. **SFC:** $t_{R1}$ = 2.976 min., $t_{R2}$ = 3.239 min., $t_{R3}$ = 3.682 min., and $t_{R4}$ = 3.859 min.

**Peak 1: LCMS Method 12):** $t_R$ = 0.664 min, $[M+1]^+$ 380.1. **SFC:** (column: DAICEL CHIRALPAK AD (150mmx4.6mm, 3µm); mobile phase: A: $CO_2$, B: EtOH(0.1% IPAm); 10%B for 0.5 min., 10-50%B, over 3.0 min., 50%B for 1.0 min. $t_R$ = 3.017 min, ee% = 100%.

**Peak 2: LCMS (Method 12):** $t_R$ = 0.657 min, $[M+1]^+$ 380.1. **SFC:** (column: DAICEL CHIRALPAK AD (150mmx4.6mm, 3µm); mobile phase: A: $CO_2$, B: EtOH(0.1% IPAm); 10%B for 0.5 min., 10-50%B, over 3.0 min., 50%B for 1.0 min. $t_R$ = 3.284min, ee% = 98.8%

**Peak 3: LCMS (Method 12):** $t_R$ = 0.662 min, $[M+1]^+$ 380.2. **SFC:** (column: DAICEL CHIRALPAK AD (150mmx4.6mm, 3µm); mobile phase: A: $CO_2$, B: EtOH(0.1% IPAm); 10%B for 0.5 min., 10-50%B, over 3.0 min., 50%B for 1.0 min. $t_R$ = 3.729 min, ee% = 99.2%

**Peak 4: LCMS (Method 12):** $t_R$ = 0.656 min, $[M+1]^+$ 380.1. **SFC:** (column: DAICEL CHIRALPAK AD (150mmx4.6mm, 3µm); mobile phase: A: $CO_2$, B: EtOH(0.1% IPAm); 10%B for 0.5 min., 10-50%B, over 3.0 min., 50%B for 1.0 min. $t_R$ = 3.890 min, ee% = 96.7%

Step 3a: To a solution of the compound from Peak 1 (127 mg, 0.33 mmol, 1.0 eq.) in DMF (8 mL) was added $Cs_2CO_3$ (109 mg, 0.33 mmol, 1.0 eq.), NaI (5 mg, 0.03 mmol, 0.1 eq.) and (1-cyanocyclopropyl)methyl 4-methylbenzenesulfonate (127 mg, 0.50 mmol, 1.5 eq.) at 20°C. The reaction was stirred at 40°C under $N_2$ for 8 hrs. The reaction mixture was quenched with saturated aqueous HCl (0.5 M, 80 mL) and extracted with ethyl acetate (30 mL x 3). The combined organic layers were washed with brine (30 mL), dried over $Na_2SO_4$, filtered and concentrated to give crude product. The crude was purified by prep-HPLC (column: Waters Xbridge BEH C18 100mmx30mm, 10µm; liquid phase: [A:10 mM $NH_4HCO_3$ in $H_2O$; B:ACN] B%: 35%-55%, 8 min]) to obtain 1-{[(3*M*,6*R or 6S*)-3-(5-Fluoroisoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4,5,6,7,8-hexahydroquinazolin-1(2*H*)-yl]methyl}cyclopropane-1-carbonitrile **(78a)-Peak 1a**. **LCMS (Method 17):** $t_R$ = 2.775 min, $[M+1]^+$ 459.2. **$^1$H NMR:** (400 MHz, CHLOROFORM-d) δ = 9.36 (s, 1H), 8.43 (s, 1H), 7.91 (d, *J* = 8.3 Hz, 1H), 7.61 (dt, *J* = 4.8, 8.0 Hz, 1H), 7.38 (dd, *J* = 7.8, 12.4 Hz, 1H), 4.13 (d, *J* = 15.2 Hz, 1H), 4.09 (d, *J* = 15.2 Hz, 1H), 3.13-3.17 (m, 1H), 2.98 - 2.86 (m, 2H), 2.56 - 2.41 (m, 2H), 2.41 - 2.32 (m, 1H), 1.99 - 1.87 (m, 1H), 1.39 - 1.35 (m, 2H), 1.34 - 1.26 (m, 2H).

**SFC:** (column: Lux Cellulose (50mmx4.6mm, 3µm); mobile phase: A: $CO_2$, B: EtOH (0.1% IPAm); B%: 5% for 0.2 min, 5-50% for 1.0 min., 50% for 1.0 min., 50-5% for 0.4 min., 5% for 0.4 min., $t_R$ = 2.131 min, ee% = 100.0%.

Step 3b: To a solution of the compound from Peak 2 (150 mg, 0.40 mmol, 1.0 eq.) in DMF (8 mL) was added $Cs_2CO_3$ (130 mg, 0.40 mmol, 1.0 eq.), NaI (6 mg, 0.04 mmol, 0.1 eq.) and (1-cyanocyclopropyl)methyl 4-methylbenzenesulfonate (127 mg, 0.50 mmol, 1.5 eq.) at 20°C. The reaction was stirred at 40°C under $N_2$ for 7 hrs. The reaction mixture was quenched with saturated aqueous HCl (0.5 M, 80 mL), extracted with ethyl acetate (30 mL x 3). The combined organic layers were washed with brine (30 mL), dried over $Na_2SO_4$, filtered and concentrated to

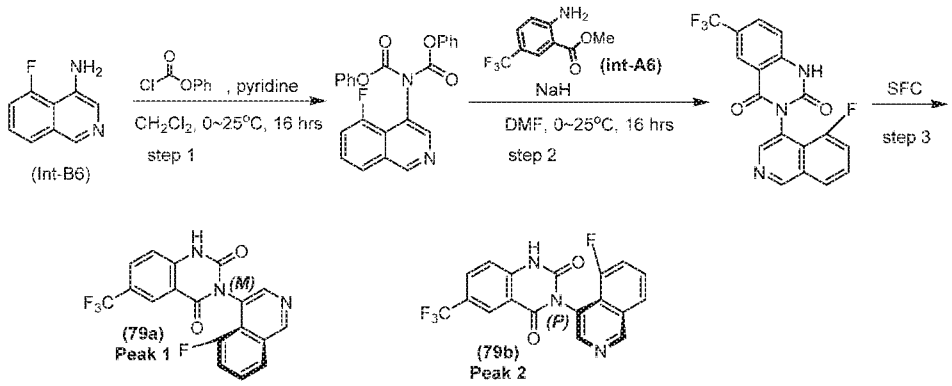
give crude product. The crude was purified by prep-HPLC (column: Waters Xbridge BEH C18 100mmx30mm, 10µm; liquid phase: [A:10 mM $NH_4HCO_3$ in $H_2O$; B:ACN] B%: 35%-55%, 8 min]) to obtain 1-{[(3*M*,6*R or 6S*)-3-(5-Fluoroisoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4,5,6,7,8-hexahydroquinazolin-1(2*H*)-yl]methyl}cyclopropane-1-carbonitrile **(78b)-Peak 2a**. **LCMS (Method 17):** $t_R$ = 2.774 min, $[M+1]^+$ 459.2. **$^1$H NMR:** (400 MHz, CHLOROFORM-d) δ = 9.36 (d, *J* = 2.5 Hz, 1H), 8.44 (s, 1H), 7.91 (d, *J* = 8.1 Hz, 1H), 7.60 (dt, *J* = 4.9, 8.0 Hz, 1H), 7.37 (dd, *J* = 7.5, 12.3 Hz, 1H), 4.13 (d, *J* = 15.2 Hz, 1H), 4.08 (d, *J* = 15.2 Hz, 1H), 3.12 - 3.05 (m, 1H), 3.03 - 2.93 (m, 2H), 2.46-2.50 (m, 2H), 2.42 - 2.34 (m, 1H), 1.95 - 1.83 (m, 1H), 1.40 - 1.35 (m, 2H), 1.35 - 1.29 (m, 2H). **SFC:** (column: Lux Cellulose (50mmx4.6mm, 3µm); mobile phase: A: $CO_2$, B: MeOH (0.1% IPAm); B%: 5% for 0.2 min, 5-50% for 1.0 min., 50% for 1.0 min., 50-5% for 0.4 min., 5% for 0.4 min., $t_R$ = 1.608 min, ee% = 100.0%.

Step 3c: To a solution of the compound from Peak 3 (150 mg, 0.40 mmol, 1.0 eq.) in DMF (8 mL) was added $Cs_2CO_3$ (130 mg, 0.40 mmol, 1.0 eq.), NaI (6 mg, 0.04 mmol, 0.1 eq.) and (1-cyanocyclopropyl)methyl 4-methylbenzenesulfonate (150 mg, 0.60 mmol, 1.5 eq.) at 20°C. The reaction was stirred at 40°C under $N_2$ for 7 hrs. The mixture was quenched with saturated aqueous HCl (0.5 M, 80 mL), extracted with ethyl acetate (30 mL x 3). The combined organic layers were washed with brine (30 mL), dried over $Na_2SO_4$, filtered and concentrated to give crude product. The crude was purified by prep-HPLC (column: Waters Xbridge BEH C18 100mmx30mm, 10µm; liquid phase: [A:10 mM $NH_4HCO_3$ in $H_2O$; B:ACN] B%: 35%-55%, 8 min]) to obtain 1-{[(3*P*,6*R or 6S*)-3-(5-Fluoroisoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4,5,6,7,8-hexahydroquinazolin-1(2*H*)-yl]methyl}cyclopropane-1-carbonitrile **(78c)-Peak 3a**. **LCMS (Method 17):** $t_R$ = 2.571 min, $[M+1]^+$ 459.1. **$^1$H NMR:** (400 MHz, CHLOROFORM-d) δ = 9.35 (d, *J* = 2.4 Hz, 1H), 8.44 (s, 1H), 7.91 (d, *J* = 8.1 Hz, 1H), 7.60 (dt, *J* = 4.8, 8.0 Hz, 1H), 7.43 - 7.33 (m, 1H), 4.12 (d, *J* = 15.2 Hz, 1H), 4.08 (d, *J* = 15.2 Hz, 1H), 3.14 - 3.04 (m, 1H), 3.03 - 2.92 (m, 2H), 2.55 - 2.42 (m, 2H), 2.41 - 2.33 (m, 1H), 1.95 - 1.81 (m, 1H), 1.40 - 1.34 (m, 2H), 1.34 - 1.27 (m, 2H). **SFC:** (column: Lux Cellulose (50mmx4.6mm, 3µm); mobile phase: A: $CO_2$, B: MeOH (0.1% IPAm); B%: 5% for 0.2 min, 5-50% for 1.0 min., 50% for 1.0 min., 50-5% for 0.4 min., 5% for 0.4 min., $t_R$ = 2.201 min, ee% = 99.4%.

Step 3d: To a solution of the compound from Peak 4 150 mg, 0.40 mmol, 1.0 eq.) in DMF (8 mL) was added $Cs_2CO_3$ (130 mg, 0.40 mmol, 1.0 eq.), NaI (6 mg, 0.04 mmol, 0.1 eq.) and (1-cyanocyclopropyl)methyl 4-methylbenzenesulfonate (150 mg, 0.60 mmol, 1.5 eq.) at 20°C. The reaction was stirred at 40°C under $N_2$ for 7 hrs. The mixture was quenched with saturated aqueous HCl (0.5 M, 80 mL), extracted with ethyl acetate (30 mL x 3). The combined organic layers were washed with brine (30 mL), dried over $Na_2SO_4$, filtered and concentrated to give crude product. The crude was purified by prep-HPLC (column: Waters Xbridge BEH C18 100mmx30mm, 10µm; liquid phase: [A:10 mM $NH_4HCO_3$ in $H_2O$; B:ACN] B%: 35%-55%, 8 min])

to obtain 1-{[(3*P*,6*R or 6S*)-3-(5-Fluoroisoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4,5,6,7,8-hexahydroquinazolin-1(2*H*)-yl]methyl}cyclopropane-1-carbonitrile **(78d)-Peak 4a**. **LCMS (Method 17):** $t_R$ = 2.776 min, $[M+1]^+$ 459.1. **$^1$H NMR:** (400 MHz, CHLOROFORM-d) δ = 9.36 (d, *J* = 2.4 Hz, 1H), 8.43 (s, 1H), 7.95 - 7.88 (m, 1H), 7.61 (dt, *J* = 4.8, 8.0 Hz, 1H), 7.38 (ddd, *J* = 0.9, 7.8, 12.4 Hz, 1H), 4.14 (d, *J* = 15.2 Hz, 1H), 4.09 (d, *J* = 15.2 Hz, 1H), 3.13-3.17 (m, 1H), 3.00 - 2.84 (m, 2H), 2.57 - 2.41 (m, 2H), 2.41 - 2.33 (m, 1H), 2.01 (s, 1H), 1.99 - 1.87 (m, 1H), 1.40 - 1.34 (m, 2H), 1.34 - 1.25 (m, 2H). **SFC:** (column: Lux Cellulose (50mmx4.6mm, 3μm); mobile phase: A: $CO_2$, B: MeOH (0.1% IPAm); B%: 5% for 0.2 min, 5-50% for 1.0 min., 50% for 1.0 min., 50-5% for 0.4 min., 5% for 0.4 min., $t_R$ = 2.156 min, ee% = 99.1%.

**Example 79:** Synthesis of (3*M*)-3-(5-Fluoroisoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1*H*,3*H*)-dione **(79a)** and (3*P*)-3-(5-Fluoroisoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1*H*,3*H*)-dione **(79b)**




Step 1: To a solution of 5-fluoroisoquinolin-4-amine **(Int-B6)** (400 mg, 2.47 mmol, 1.0 eq.) and pyridine (598 mg, 7.41 mmol, 3.0 eq.) in $CH_2Cl_2$ (10 mL) was added dropwise phenyl carbonochloridate (966 mg, 6.17 mmmol, 2.5 eq.) at 0°C under $N_2$. The reaction was stirred at 25°C for 16 hrs. The mixture was poured into ice water (40 mL) and extracted with $CH_2Cl_2$ (20 mL x 3). The organic layers were concentrated to give a residue. The residue was purified by column (petroleum ether/THF = 1/1) and triturated by MTBE (5 mL) to give phenyl (5-fluoroisoquinolin-4-yl)(phenoxycarbonyl)carbamate. **$^1$H NMR:** (400MHz, CHLOROFORM-*d*) δ = 9.35 (d, *J*=2.1 Hz, 1H), 8.69 (s, 1H), 7.93 (d, *J*=8.1 Hz, 1H), 7.67 (dt, *J*=4.9, 7.9 Hz, 1H), 7.56 (dd, *J*=7.7, 12.3 Hz, 1H), 7.38 - 7.32 (m, 4H), 7.26 - 7.19 (m, 2H), 7.09-7.11 (m, 4H).

Step 2: To a mixture of NaH (74 mg, 1.86 mmol, 1.5 eq.) in DMF (5 mL) was added dropwise a solution of methyl 2-amino-5-(trifluoromethyl)benzoate **(int-A6)** (544 mg, 2.48 mmol, 2.5 eq.) in DMF (2 mL) at 0°C under $N_2$. The mixture was stirred at 25°C for 1 hr. Then a solution of phenyl (5-fluoroisoquinolin-4-yl)(phenoxycarbonyl)carbamate (400 mg, 0.10 mmol, 1.0 eq.) in DMF (5 mL) was added dropwise to the system at 0°C under $N_2$. The reaction was stirred at 25°C under $N_2$ for 15 hrs. The reaction mixture was diluted with aq. $NH_4Cl$ (60 mL) and extracted with

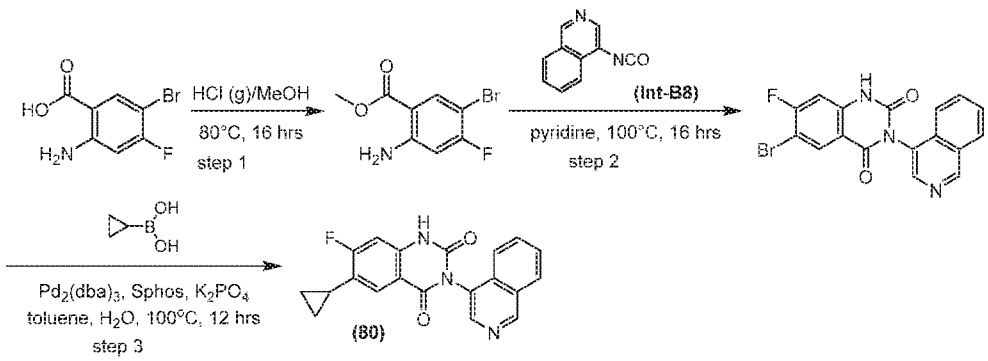
EtOAc (30 mL x 3). The organic layers were washed with brine (50 mL), dried over $Na_2SO_4$ and concentrated to give a residue. The residue was purified by prep-HPLC (column: Phenomenex luna C18 250mmx50mm, 10μm; liquid phase: [A:$H_2O$(10mM $NH_4HCO_3$); B:ACN]B%: 20%-50%,20min]) to give racemic 3-(5-fluoroisoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione. **LCMS (Method 6):** $t_R$ = 1.750 min, $[M+1]^+$ 376.0.

Step 3: Racemic 3-(5-fluoroisoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione was separated by chiral SFC (column: DAICEL CHIRALPAK AD (250mmx30mm,10μm); IPA (0.1%$NH_3{\cdot}H_2O$); 27%, 10 min) to give (3*M*)-3-(5-Fluoroisoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1*H*,3*H*)-dione **(79a)** (peak 1) and (3*P*)-3-(5-Fluoroisoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1*H*,3*H*)-dione **(79b)** (peak 2). Stereochemistry assigned by analogy to Example 16, wherein the chirality of the more active atropisomer(s) is assigned as ***(M)*** and subsequently the chirality of the more active atropisomer(s) is assigned as ***(P)***.

**Peak 1: (3*M*)-3-(5-Fluoroisoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1*H*,3*H*)-dione (79a): LCMS (Method 13):** $t_R$ = 2.391 min, $[M+1]^+$ 376.0. **SFC:** (column: DAICEL CHIRALPAK AD (150mmx4.6mm, 3μm); mobile phase: A: $CO_2$, B: IPA(0.1% IPAm); 10%B for 0.5 min., 10-50%B, over 3.0 min., 50%B for 1.0 min. $t_R$ = 2.997 min, ee = 100%. **$^1$H NMR:** (400MHz, DMSO-$d_6$) δ = 12.21 (br s, 1H), 9.53 (d, *J*=2.4 Hz, 1H), 8.61 (s, 1H), 8.21 (d, *J*=1.3 Hz, 1H), 8.18 (d, *J*=7.6 Hz, 1H), 8.13 (dd, *J*=2.1, 8.7 Hz, 1H), 7.77 (dt, *J*=4.9, 8.0 Hz, 1H), 7.64 (dd, *J*=7.5, 13.2 Hz, 1H), 7.50 (d, *J*=8.6 Hz, 1H).

**Peak 2: (3*P*)-3-(5-Fluoroisoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1*H*,3*H*)-dione (79b):LCMS (Method 13):** $t_R$ = 2.390 mins, $[M+1]^+$ 376.0. **SFC:** (column: DAICEL CHIRALPAK AD (150mmx4.6mm, 3μm); mobile phase: A: $CO_2$, B: IPA(0.1% IPAm); 10%B for 0.5 min., 10-50%B, over 3.0 min., 50%B for 1.0 min.$t_R$ = 3.315 min, ee = 97.5%. **$^1$H NMR:** (400MHz, DMSO-$d_6$) δ = 12.22 (br s, 1H), 9.53 (d, *J*=2.4 Hz, 1H), 8.61 (s, 1H), 8.21 (s, 1H), 8.18 (d, *J*=8.2 Hz, 1H), 8.13 (dd, *J*=2.2, 8.7 Hz, 1H), 7.77 (dt, *J*=4.8, 8.0 Hz, 1H), 7.64 (dd, *J*=7.8, 13.0 Hz, 1H), 7.50 (d, *J*=8.7 Hz, 1H).

**Example 80:** Synthesis of 6-cyclopropyl-7-fluoro-3-(isoquinolin-4-yl)quinazoline-2,4(1H,3H)-dione **(80)**

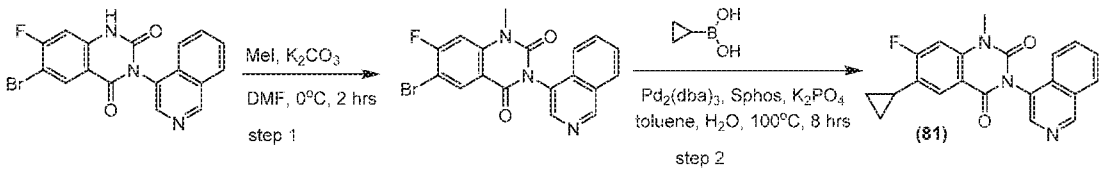


Step 1: A mixture of 2-amino-5-bromo-4-fluorobenzoic acid (3.0 g, 4.27 mmol, 1.0 eq.) in HCl (g)/MeOH (100 mL) was stirred at 80°C for 16 hrs. The mixture was concentrated under reduced pressure to give methyl 2-amino-5-bromo-4-fluorobenzoate. **LCMS (Method 10):** $t_R$ = 0.693 min, $[M+1]^+$ 249.0.

Step 2: A mixture of methyl 2-amino-5-bromo-4-fluorobenzoate (2.0 g, 8.06 mmol, 1.0 eq.) and 4-isocyanatoisoquinoline **(Int-B8)** (1.37g, 8.06 mmol, 1.0 eq.) in pyridine (20 mL) was stirred at 100°C for 16 hrs. The reaction mixture was quenched with $H_2O$ (20 mL) and extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with brine (20 mL x 3), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give 6-bromo-7-fluoro-3-(isoquinolin-4-yl)quinazoline-2,4(1H,3H)-dione. **LCMS (Method 10):** $t_R$ = 0.608 min, $[M+1]^+$ 388.0.

Step 3: To a mixture of 6-bromo-7-fluoro-3-(isoquinolin-4-yl)quinazoline-2,4(1H,3H)-dione (400 mg, 0.36 mmol, 1.0 eq.), cyclopropylboronic acid(48 mg, 1.55 mmol, 1.5 eq.) and $K_2PO_4$ (158 mg, 0.04 mmol, 0.1 eq.) in toluene (5 mL) and $H_2O$ (0.5 mL) was added Sphos (16 mg, 0.04 mmol, 0.1 eq.) and $Pd_2(dba)_3$ (37 mg, 0.04 mmol, 0.1 eq.) under $N_2$. The mixture was stirred at 100°C for 12 hrs. The reaction mixture was quenched with $H_2O$ (50 mL) and extracted with ethyl acetate (50 mL x 3). The combined organic layers were washed with brine (100 mL x 3), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give crude product which was purified by preparative prep-HPLC (column: Waters Xbridge BEH C18 250mmx50mm, 10μm; liquid phase: [A:$H_2O$(10mM $NH_4HCO_3$); B:ACN]B%: 30%-50%,20min] to to give 6-cyclopropyl-7-fluoro-3-(isoquinolin-4-yl)quinazoline-2,4(1H,3H)-dione **(80)**. **LCMS (Method 13):** $t_R$ = 2.145 min, $[M+1]^+$ 348.1. **$^1$H NMR:** (400 MHz, DMSO-$d_6$) δ = 11.75 (s, 1H), 9.42 (s, 1H), 8.52 (s, 1H), 8.29 - 8.23 (m, 1H), 7.83 - 7.70 (m, 3H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.02 (d, *J* = 10.9 Hz, 1H), 2.10 - 2.02 (m, 1H), 1.03 - 0.96 (m, 2H), 0.77 - 0.68 (m, 2H).

**Example 81:** Synthesis of 6-cyclopropyl-7-fluoro-3-(isoquinolin-4-yl)-1-methylquinazoline-2,4(1H,3H)-dione **(81)**

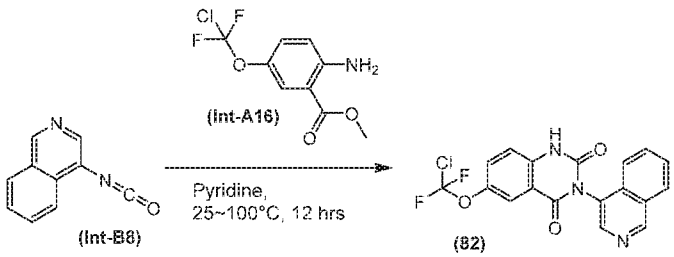



Step 1: To a mixture of 6-bromo-7-fluoro-3-(isoquinolin-4-yl)quinazoline-2,4(1H,3H)-dione (140 mg, 0.36 mmol, 1.0 eq.) and $K_2CO_3$ (150 mg, 1.09 mmol, 3.0 eq.) in DMF (2 mL) was added MeI (77 mg, 0.54 mmol, 1.5 eq.). The mixture was stirred at 0°C for 2 hrs. The reaction mixture was quenched with $H_2O$ (20 mL) and extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with brine (20 mL x 3), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give a residue. The residue was purified by preparative TLC (petroleum

ether/EtOAc = 1:0 ~ 0:1) to give 6-bromo-7-fluoro-3-(isoquinolin-4-yl)-1-methylquinazoline-2,4(1H,3H)-dione. **LCMS (Method 10):** $t_R$ = 0.603 min, $[M+1]^+$ 402.0.

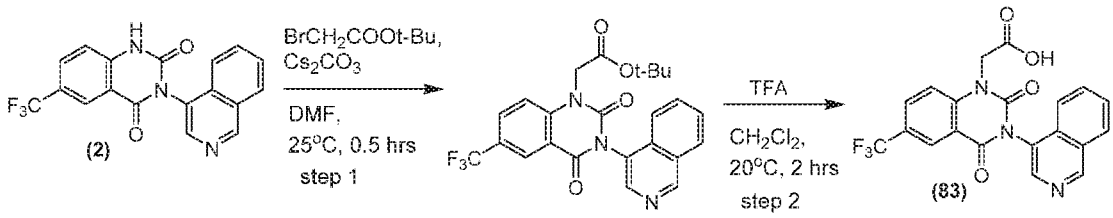
Step 2: To a mixture of 6-bromo-7-fluoro-3-(isoquinolin-4-yl)-1-methylquinazoline-2,4(1H,3H)-dione (120 mg, 0.30 mmol, 1.0 eq.), cyclopropylboronic acid (39 mg, 0.45 mmol, 1.5 eq.) and $K_2PO_4$ (65 mg, 0.03 mmol, 2.5 eq.) in toluene (2 mL) and $H_2O$ (0.2 mL) was added sphos (13 mg, 0.03 mmol, 0.1 eq.) and $Pd_2(dba)_3$ (28 mg, 0.03 mmol, 0.1 eq.). The mixture was stirred at 100°C for 8 hrs. The reaction mixture was quenched with $H_2O$ (20 mL) and extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with brine (20 mL x 3), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give a residue. The residue was purified by preparative prep-HPLC (column: Waters Xbridge BEH C18 100mmx30mm, 10μm; liquid phase: [A:FA/$H_2O$=0.1% v/v; B:ACN]B%: 30%-60%,10min]) to give 6-cyclopropyl-7-fluoro-3-(isoquinolin-4-yl)-1-methylquinazoline-2,4(1H,3H)-dione **(81)**. **LCMS (Method 17):** $t_R$ = 2.853 min, $[M+1]^+$ 348.1. **$^1$H NMR:** (400 MHz, DMSO-$d_6$) δ = 9.42 (s, 1H), 8.51 (s, 1H), 8.29 - 8.23 (m, 1H), 7.86 - 7.79 (m, 1H), 7.79 - 7.70 (m, 2H), 7.65 (d, *J* = 8.3 Hz, 1H), 7.50 (d, *J* = 12.1 Hz, 1H), 3.54 (s, 3H), 2.15 - 2.04 (m, 1H), 1.06 - 0.98 (m, 2H), 0.79 - 0.71 (m, 2H).

**Example 82:** Synthesis of 6-(chlorodifluoromethoxy)-3-(isoquinolin-4-yl)quinazoline-2,4(1H,3H)-dione **(82)**




To a mixture of 4-isocyanatoisoquinoline **(Int-B8)** (516 mg, 2.05 mmol, 1.0 eq.) in pyridine (4 mL) was added methyl 2-amino-5-(chlorodifluoromethoxy)benzoate **(Int-A16)** (350 mg, 2.05 mmol, 1.0 eq.) at 25°C and the mixture was stirred at 100°C for 12 hrs under $N_2$. The mixture was quenched with $H_2O$ (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic phase was washed with brine (10 mL), dried over $Na_2SO_4$, filtered and concentrated to give crude product which was purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150mmx40mm, 10μm; liquid phase: [A:$H_2O$ (10mM $NH_4HCO_3$); B:ACN] B%: 30%-60%, 20min]) to give 6-(chlorodifluoromethoxy)-3-(isoquinolin-4-yl)quinazoline-2,4(1H,3H)-dione **(82)**. **LCMS (Method 3):** $t_R$ = 2.494 min, $[M+1]^+$ 390.0. **$^1$H NMR:** (400 MHz, DMSO-$d_6$) δ ppm 11.93 (br s, 1 H) 9.42 (s, 1 H) 8.55 (s, 1 H) 8.25 - 8.28 (m, 1 H) 7.91 (br d, *J*=7.2 Hz, 1 H) 7.81 (s, 1 H) 7.72 - 7.79 (m, 3 H) 7.41 (d, *J*=8.9 Hz, 1 H).

**Example 83:** Synthesis of 2-(3-(isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2H)-yl)acetic acid **(83)**



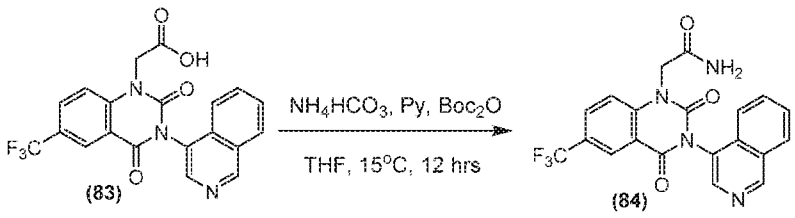

Step 1: To a mixture of 3-(isoquinolin-4-yl)-6-(trifluoromethyl)quinazoline-2,4(1H,3H)-dione **(2)** (200 mg, 0.56 mmol, 1.0 eq) in DMF (5 mL) was added $Cs_2CO_3$ (365 mg, 1.12 mmol, 2.0 eq) and $BrCH_2COOt$-Bu (109 mg, 0.56 mmol, 1.0 eq.) at 25°C. The reaction mixture was stirred for 0.5 hrs at 25°C. The reaction was poured into water (20 mL) and extracted with EtOAc (20 mL x 2). The combined organic phase was washed with brine (20 mL), dried over $Na_2SO_4$, filtered and concentrated to give tert-butyl 2-(3-(isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2H)-yl)acetate. **LCMS (Method 5):** $t_R$ = 1.011 min, $[M+1]^+$ 472.0.

**$^1$H NMR:** (400MHz, CHLOROFORM-d) δ 9.38 (s, 1H), 8.58 (d, *J*=1.6 Hz, 1H), 8.53 (s, 1H), 8.11 (d, *J*=7.5 Hz, 1H), 8.00 - 7.98 (m, 1H), 7.76 - 7.57 (m, 3H), 7.22 (d, *J*=8.9 Hz, 1H), 5.00 (d, *J*=17.8 Hz, 1H), 4.80 (d, *J*=17.8 Hz, 1H), 1.49 (s, 9H).

Step 2: To a solution of tert-butyl 2-(3-(isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2H)-yl)acetate (600 mg, 1.27 mmol, 1.0 eq) in $CH_2Cl_2$ (6 mL) was added TFA (12 mL) at 20°C. The reaction mixture was stirred for 2 hrs at 20°C. The reaction was poured into water (20 mL) and adjust to pH = 4~5 with 1 N HCl, and extracted with EtOAc (20 mL x 2). The combined organic phase was washed with brine (20 mL), dried over $Na_2SO_4$, filtered and concentrated to give crude product. The crude product was purified by prep-HPLC (column: Phenomenex Gemini-NX 80mmx40mm, 3μm; liquid phase: [A:$H_2O$ (10mM $NH_4HCO_3$); B:ACN] B%: 10%-40%, 20min]) to give 2-(3-(isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2H)-yl)acetic acid **(83)**. **LCMS (Method 1):** $t_R$ = 2.139 min, $[M+1]^+$ 416.2.

**$^1$H NMR:** (400MHz, DMSO-$d_6$) δ = 9.45 (s, 1H), 8.55 (s, 1H), 8.31 - 8.26 (m, 2H), 8.17 (dd, *J*=2.0, 8.9 Hz, 1H), 7.82 - 7.72 (m, 3H), 7.66 (d, *J*=8.9 Hz, 1H), 4.85 - 4.63 (m, 2H).

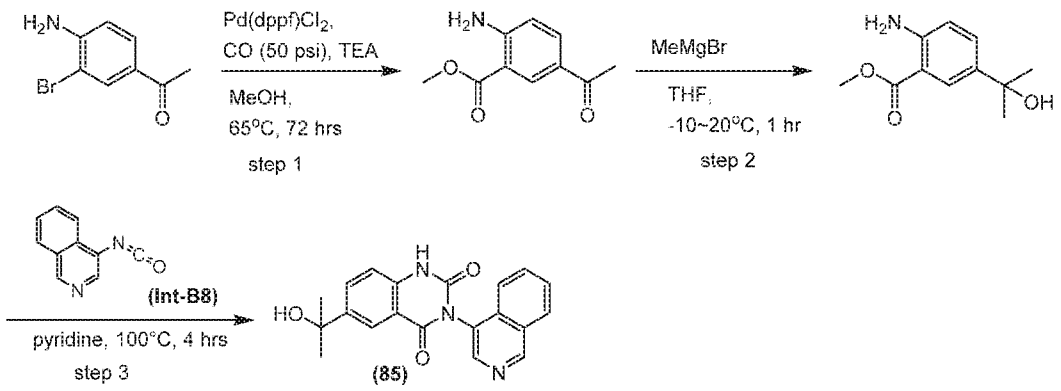
**Example 84:** Synthesis of 2-(3-(isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2H)-yl)acetamide **(84)**




To the mixture of 2-(3-(isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2H)-yl)acetic acid **(83)** (84 mg, 0.20 mmol, 1.0 eq.) in THF (2 mL) was added $Boc_2O$ (86 mg, 0.40 mmol, 2.0 eq.) and $NH_4HCO_3$ (32 mg, 0.40 mmol, 2.0 eq.) and Py (32 mg, 0.40 mmol, 2.0

eq.) at 15°C. The mixture was stirred at 15°C for 12 hrs. The mixture was poured into water (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic phases were washed with brine, dried over $Na_2SO_4$, filtered and concentrated to give crude product. The crude product was purified prep-HPLC (column: Waters Xbridge BEH C18 100mm x30mm, 10μm; liquid phase: [A:10mM $NH_4HCO_3$ in $H_2O$; B:ACN] B%: 20%-50%, 8min]) to give 2-(3-(isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2H)-yl)acetamide **(84)**. **LCMS (Method 1):** $t_R$ = 2.038 min, $[M+1]^+$ 415.1. **$^1$H NMR:** (400MHz, DMSO-d6) δ 9.46 (s, 1H), 8.55 (s, 1H), 8.34 - 8.27 (m, 2H), 8.22 (dd, *J*=2.1, 8.8 Hz), 7.94 (d, *J*=8.0 Hz, 1H), 7.83 - 7.73 (m, 3H), 7.61 (d, *J*=8.8 Hz, 1H), 7.43 (s, 1H), 4.92 - 4.70 (m, 2H).

**Example 85:** Synthesis of 6-(2-hydroxypropan-2-yl)-3-(isoquinolin-4-yl)quinazoline-2,4(1H,3H)-dione **(85)**

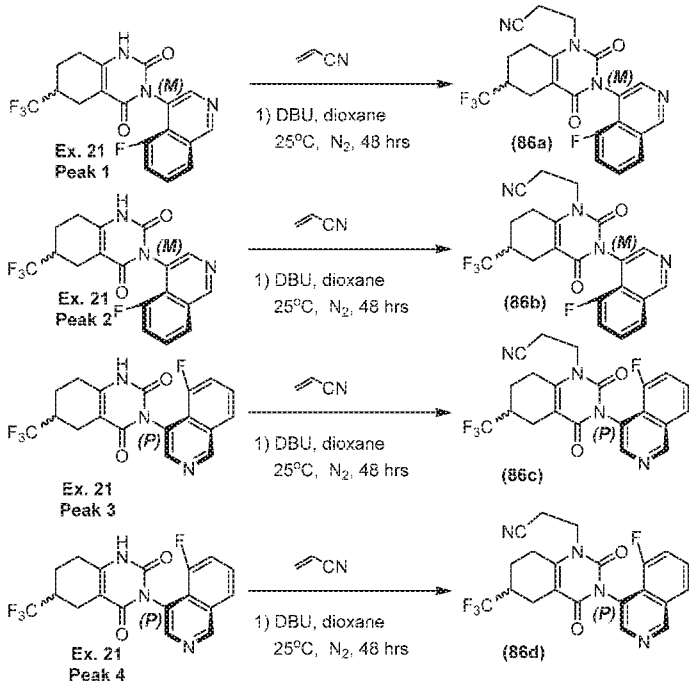



Step 1: A solution of 1-(4-amino-3-bromophenyl)ethan-1-one (5 g, 23.4 mmol, 1.0 eq), $Pd(dppf)Cl_2$ (1.71 g, 2.37 mmol, 0.1 eq) and TEA (23.6 g, 234 mmol, 10 eq) in MeOH (150 mL) was degassed and purged with CO (50 psi) three times. The mixture was stirred at 65°C for 72 hrs under CO atmosphere. The reaction mixture was filtered and concentrated under reduced pressure to give crude product which was purified by prep-HPLC (column: Phenomenex C18 250mmx100mm 10μm; liquid phase: [A:$H_2O$ (10mM $NH_4HCO_3$); B:ACN] B%: 20%-45%, 20 min]) to give methyl 5-acetyl-2-aminobenzoate. **LCMS (Method 22):** $t_R$ = 1.611 min, $[M+1]^+$ 194.1.

Step 2: To a solution of methyl 5-acetyl-2-aminobenzoate (500 mg, 2.50 mmol, 1.0 eq) in THF (18 mL) was added MeMgBr (122 mg, 5.20 mmol, 2.0 eq) at -10°C. The mixture was stirred at -10°C for 0.5 hr and 20°C for 0.5 hr. To the mixture was added additional MeMgBr (60 mg, 2.50 mmol, 1.0 eq). The mixture was stirred at 20°C for 1 hr. The reaction mixture was quenched with $H_2O$ (100 mL) and extracted with ethyl acetate (80 mL x 3). The combined organic layers were washed with brine (20 mL x 3), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (petroleum ether/EtOAc = 1/1) to give methyl 2-amino-5-(2-hydroxypropan-2-yl)benzoate. **LCMS (Method 10):** $t_R$ = 0.571 min, $[M+1]^+$ 194.1.

Step 3: To a mixture of methyl 2-amino-5-(2-hydroxypropan-2-yl)benzoate (190 mg, 0.91 mmol, 1.0 eq.) in pyridine (3 mL) was added 4-isocyanatoisoquinoline **(Int-B8)** (154 mg, 0.91 mmol, 1.0 eq.). The reaction mixture was stirred at 100°C for 4 hrs. The reaction mixture was concentrated under reduced pressure to give crude product which was purified by prep-HPLC (column: Waters Xbridge BEH C18 100mmx30mm, 10μm; liquid phase: [A:10mM $NH_4HCO_3$ in $H_2O$; B:ACN] B%: 15%-35%, 8min]) to give 6-(2-hydroxypropan-2-yl)-3-(isoquinolin-4-yl)quinazoline-2,4(1H,3H)-dione **(85)**. **LCMS (Method 13):** $t_R$ = 1.695 min, $[M+1]^+$ 348.1. **$^1$H NMR:** (400 MHz, DMSO-$d_6$) δ = 11.69 (s, 1H), 9.42 (s, 1H), 8.54 (s, 1H), 8.31 - 8.24 (m, 1H), 8.06 (d, *J* = 2.0 Hz, 1H), 7.85 (dd, *J* = 2.2, 8.6 Hz, 1H), 7.83 - 7.78 (m, 1H), 7.78 - 7.73 (m, 2H), 7.26 (d, *J* = 8.6 Hz, 1H), 5.22 (s, 1H), 1.45 (s, 6H).

**Example 86:** Synthesis of 3-[(3*M*,6*R or 6S*)-3-(5-Fluoroisoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4,5,6,7,8-hexahydroquinazolin-1(2*H*)-yl]propanenitrile **(86a)**;
3-[(3*M*,6*R or 6S*)-3-(5-Fluoroisoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4,5,6,7,8-hexahydroquinazolin-1(2*H*)-yl]propanenitrile **(86b)**;
3-[(3*P*,6*R or 6S*)-3-(5-Fluoroisoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4,5,6,7,8-hexahydroquinazolin-1(2*H*)-yl]propanenitrile **(86c)**, and
3-[(3*P*,6*R or 6S*)-3-(5-Fluoroisoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4,5,6,7,8-hexahydroquinazolin-1(2*H*)-yl]propanenitrile **(86d)**




To a solution of (3*M*,6*R or 6S*)-3-(5-fluoroisoquinolin-4-yl)-6-(trifluoromethyl)-5,6,7,8-tetrahydroquinazoline-2,4(1*H*,3*H*)-dione (Compound from Peak 1 of Example 21) (200 mg, 0.60 mmol, 1.0 eq.), acrylonitrile (4 mL) and dioxane (4 mL) was added DBU (80 mg, 0.60 mmol, 1.1 eq.) at 25°C. Then the mixture was stirred at 25°C for 48 hrs under $N_2$. The reaction mixture was

quenched with $H_2O$ (20 mL) and extracted with EtOAc (10 mL × 3). The combined organic layers were washed with brine (30 mL), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give crude product. The crude product was purified by prep-HPLC (column: Waters XBridge BEH C18 100x30mmx10um; mobile phase: [water ($NH_4HCO_3$)-ACN]; B%: 25%-55%, 8min) to give 3-[(3*M*,6*R or 6S*)-3-(5-Fluoroisoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4,5,6,7,8-hexahydroquinazolin-1(2*H*)-yl]propanenitrile **(86a)**. **LCMS (Method 13):** $t_R$ = 2.318 $[M+1]^+$ 433.1. **$^1$H NMR: (**400 MHz, CHLOROFORM-d) δ = 9.36 (d, J = 2.4 Hz, 1H), 8.42 (s, 1H), 7.91 (d, J = 8.1 Hz, 1H), 7.61 (dt, J = 4.9, 8.0 Hz, 1H), 7.38 (dd, J = 7.8, 12.5 Hz, 1H), 4.31 - 4.23 (m, 1H), 4.18 - 4.09 (m, 1H), 3.08 - 2.74 (m, 5H), 2.55 - 2.32 (m, 3H), 1.98 - 1.85 (m, 1H). **SFC:** column: Chiralcel AD-3 (50mmx4.6mm, 3μm); mobile phase: A: $CO_2$; B: IPA[0.1% IPAm]; B%: 5% for 0.2 min, 5-50% for 1.0 min., 50% for 1.0 min., 50-5% for 0.4 min., 5% for 0.4 min., 3.4mL/min., $t_R$ = 1.181 min., ee% =98.5%.

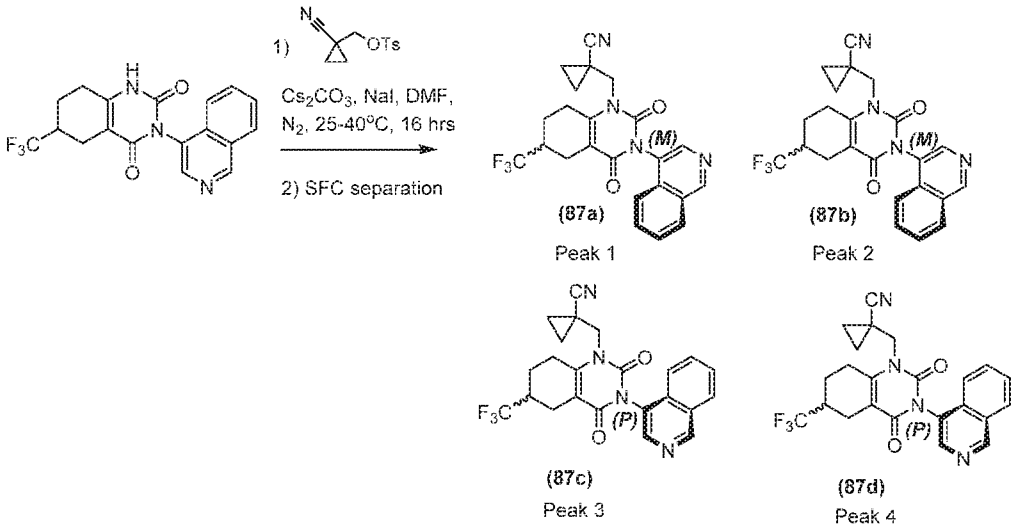
3-[(3*M*,6*R or 6S*)-3-(5-Fluoroisoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4,5,6,7,8-hexahydroquinazolin-1(2*H*)-yl]propanenitrile **(86b)** was obtained using the method described above for the synthesis of compound **(86a)**, except the Compound from Peak 2 of Example 21 was used in place of the Compound from Peak 1 of Example 21. **LCMS (Method 13):** $t_R$ = 2.274 min, $[M+1]^+$ 433.1. **$^1$H NMR:** (400 MHz, CHLOROFORM-d) δ = 9.36 (d, J = 2.4 Hz, 1H), 8.43 (s, 1H), 7.92 (d, J = 8.0 Hz, 1H), 7.65 - 7.51 (m, 1H), 7.42 - 7.33 (m, 1H), 4.35 - 4.04 (m, 2H), 3.04 - 2.79 (m, 5H), 2.55 - 2.42 (m, 2H), 2.41 - 2.31 (m, 1H), 1.94 - 1.81 (m, 1H). **SFC:** column: Chiralcel AD-3 (50mmx4.6mm, 3μm); mobile phase: A: $CO_2$; B: IPA[0.1% IPAm]; B%: 5% for 0.2 min, 5-50% for 1.0 min., 50% for 1.0 min., 50-5% for 0.4 min., 5% for 0.4 min., 3.4mL/min., $t_R$ = 1.268 min., ee% =99.1%.

3-[(3*P*,6*R or 6S*)-3-(5-Fluoroisoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4,5,6,7,8-hexahydroquinazolin-1(2*H*)-yl]propanenitrile **(86c)** was obtained using the method described above for the synthesis of compound **(86a)**, except the Compound from Peak 3 of Example 21 was used in place of the Compound from Peak 1 of Example 21. **LCMS (Method 13):** $t_R$ = 2.283 min, $[M+1]^+$ 433.1. **$^1$H NMR:** (400 MHz, CHLOROFORM-d) δ = 9.36 (d, J = 2.3 Hz, 1H), 8.43 (s, 1H), 7.91 (d, J = 8.1 Hz, 1H), 7.61 (dt, J = 4.8, 8.0 Hz, 1H), 7.37 (dd, J = 7.8, 12.5 Hz, 1H), 4.20 (q, J = 6.5 Hz, 2H), 2.97 - 2.85 (m, 5H), 2.52 - 2.42 (m, 2H), 2.40 - 2.32 (m, 1H), 1.87 (dq, J = 6.1, 11.7 Hz, 1H). **SFC:** (column: Chiralcel AD-3 (50mmx4.6mm, 3μm); mobile phase: A: $CO_2$; B: IPA[0.1% IPAm]; B%: 5% for 0.2 min, 5-50% for 1.0 min., 50% for 1.0 min., 50-5% for 0.4 min., 5% for 0.4 min., 3.4mL/min., $t_R$ = 1.337 min., ee% =100%.

3-[(3*P*,6*R or 6S*)-3-(5-Fluoroisoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4,5,6,7,8-hexahydroquinazolin-1(2*H*)-yl]propanenitrile **(86d)** was obtained using the method described above for the synthesis of compound **(86a)**, except the Compound from Peak 4 of Example 21

was used in place of the Compound from Peak 1 of Example 21. **LCMS (Method 13):** $t_R$ = 2.315 min, $[M+1]^+$ 433.0. **$^1$H NMR:** (400 MHz, CHLOROFORM-d) δ = 9.36 (d, J = 2.4 Hz, 1H), 8.42 (s, 1H), 7.91 (d, J = 8.3 Hz, 1H), 7.61 (dt, J = 4.8, 8.0 Hz, 1H), 7.38 (ddd, J = 0.8, 7.8, 12.5 Hz, 1H), 4.31 - 4.22 (m, 1H), 4.17 - 4.09 (m, 1H), 3.06 - 2.77 (m, 5H), 2.55 - 2.32 (m, 3H), 1.97 - 1.84 (m, 1H). **SFC:** (column: Chiralcel OJ-3 (50mmx4.6mm, 3μm); mobile phase: A: $CO_2$; B:IPA[0.1% IPAm]; B%: 5% for 0.2 min, 5-50% for 1.0 min., 50% for 1.0 min., 50-5% for 0.4 min., 5% for 0.4 min., 3.4mL/min., $t_R$ = 1.218 min, ee% =95.5%.

**Example 87:** Synthesis of 1-{[(3*M*,6*R or 6S*)-3-(Isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4,5,6,7,8-hexahydroquinazolin-1(2*H*)-yl]methyl}cyclopropane-1-carbonitrile **(87a)**;
1-{[(3*M*,6*R or 6S*)-3-(Isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4,5,6,7,8-hexahydroquinazolin-1(2*H*)-yl]methyl}cyclopropane-1-carbonitrile **(87b)**;
1-{[(3*P*,6*R or 6S*)-3-(Isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4,5,6,7,8-hexahydroquinazolin-1(2*H*)-yl]methyl}cyclopropane-1-carbonitrile **(87c)**, and
1-{[(3*P*,6*R or 6S*)-3-(Isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4,5,6,7,8-hexahydroquinazolin-1(2*H*)-yl]methyl}cyclopropane-1-carbonitrile **(87d)**




Step 1: To a solution of 3-(isoquinolin-4-yl)-6-(trifluoromethyl)-5,6,7,8-tetrahydroquinazoline-2,4(1H,3H)-dione (see Example 27) (100 mg, 276.76 umol, 1.0 eq.) in DMF (1 mL) was added (1-cyanocyclopropyl)methyl 4-methylbenzenesulfonate (84 mg, 332.11 umol, 1.2 eq.), $Cs_2CO_3$ (180 mg, 556.52 umol, 2.0 eq.), NaI (4 mg, 27.67 umol, 0.1 eq.) and 4Å MS (50 mg) at 25°C under $N_2$. The mixture was stirred at 40°C for 16 hrs. The mixture was quenched by $H_2O$ (10 mL) at 0°C. Ethyl acetate (10 mL) was added to the mixture and the layers were separated. The aqueous phase was then extracted with EtOAc (20 mL x 3). The combined organic phases were washed with brine (20 mL), dried over anhydrous $Na_2SO_4$, filtered and concentrated in vacuum to give crude product which was purified by prep-HPLC (column: Phenomenex Luna C18

75mmx 30 mm, 3 µm; liquid phase: [A - FA/$H_2O$ = 0.1% v/v; B - ACN] B%: 40% - 70%, 8 min]) to give racemic 1-((3-(isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4,5,6,7,8-hexahydroquinazolin-1(2H)-yl)methyl)cyclopropane-1-carbonitrile. **LCMS (Method 15):** $t_R$ = 0.719 min, $[M+1]^+$ 430.3.

Step 2: Racemic 1-((3-(isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4,5,6,7,8-hexahydroquinazolin-1(2H)-yl)methyl)cyclopropane-1-carbonitrile was purified by SFC (column: DAICEL CHIRALPAK AD 250mmx30mm, 10um; liquid phase: [A - 0.1% $NH_3H_2O$ ETOH v/v; B – $CO_2$] B%: 15% - 40%]) to give four peaks. **SFC:** $t_{R1}$ = 3.230 min., $t_{R2}$ = 3.428 min., $t_{R3}$ = 3.682 min., and $t_{R4}$ = 3.819 min.

**Peak 1:** 1-{[(3*M*,6*R or 6S*)-3-(Isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4,5,6,7,8-hexahydroquinazolin-1(2*H*)-yl]methyl}cyclopropane-1-carbonitrile **(87a): LCMS (Method 13):** $t_R$ = 2.258 min, $[M+1]^+$ 441.1. **SFC:** column: DAICEL CHIRALPAK AD-3 (150mmx4.6mm, 3µm); mobile phase: A: $CO_2$, B: EtOH(0.1% IPAm); 10%B for 0.5 min., 10-50%B, over 3.0 min., 50%B for 1.0 min. $t_R$ = 3.172 min, ee% = 100%. **$^1$H NMR:** (400 MHz, CHLOROFORM-d) δ = 9.35 (s, 1H), 8.46 (s, 1H), 8.10 (d, *J* = 8.1 Hz, 1H), 7.78 - 7.73 (m, 1H), 7.70 - 7.65 (m, 1H), 7.58 (d, *J* = 8.9 Hz, 1H), 4.09 (s, 2H), 3.24 - 3.12 (m, 1H), 3.01 - 2.92 (m, 2H), 2.57 - 2.49 (m, 1H), 2.49 - 2.36 (m, 2H), 2.03 - 1.88 (m, 1H), 1.43 - 1.36 (m, 2H), 1.34 - 1.29 (m, 2H).

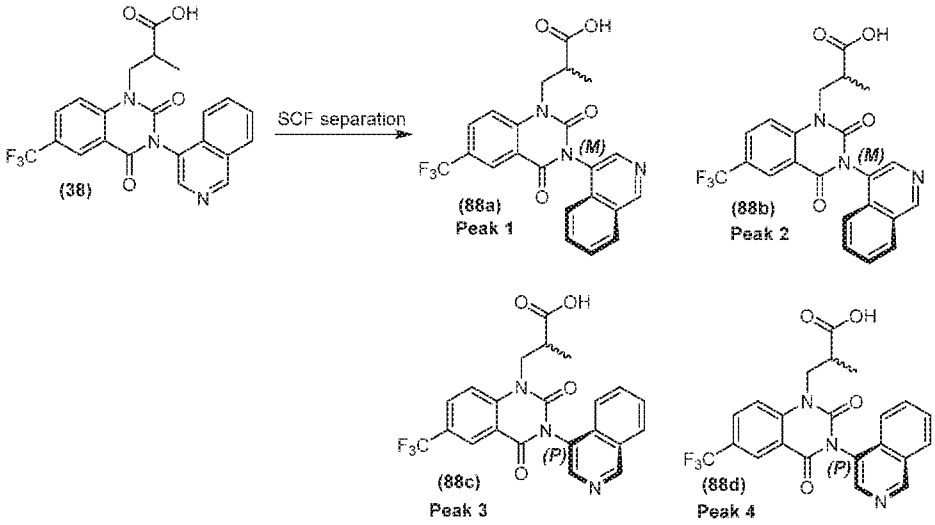
**Peak 2:** 1-{[(3*M*,6*R or 6S*)-3-(Isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4,5,6,7,8-hexahydroquinazolin-1(2*H*)-yl]methyl}cyclopropane-1-carbonitrile **(87b): LCMS (Method 13):** $t_R$ = 2.239 min, $[M+1]^+$ 441.0. **SFC:** column: DAICEL CHIRALPAK AD (150mmx4.6mm, 3µm); mobile phase: A: $CO_2$, B: EtOH(0.1% IPAm); 10%B for 0.5 min., 10-50%B, over 3.0 min., 50%B for 1.0 min. $t_R$ = 3.372 min, ee% = 94.6%. **$^1$H NMR:** (400 MHz, CHLOROFORM-d) δ = 9.36 (s, 1H), 8.47 (s, 1H), 8.10 (d, *J* = 8.1 Hz, 1H), 7.77 - 7.72 (m, 1H), 7.70 - 7.64 (m, 1H), 7.56 (d, *J* = 8.5 Hz, 1H), 4.14 - 4.04 (m, 2H), 3.19 - 3.07 (m, 1H), 3.04 - 2.93 (m, 2H), 2.56 - 2.45 (m, 2H), 2.42 - 2.34 (m, 1H), 1.97 - 1.85 (m, 1H), 1.41 - 1.28 (m, 2H), 1.42 (s, 1H), 1.43 - 1.28 (m, 1H).

**Peak 3:** 1-{[(3*P*,6*R or 6S*)-3-(Isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4,5,6,7,8-hexahydroquinazolin-1(2*H*)-yl]methyl}cyclopropane-1-carbonitrile **(87c): LCMS (Method 13):** $t_R$ = 2.239 min, $[M+1]^+$ 441.0. **SFC:** column: DAICEL CHIRALPAK AD (150mmx4.6mm, 3µm); mobile phase: A: $CO_2$, B: EtOH(0.1% IPAm); 10%B for 0.5 min., 10-50%B, over 3.0 min., 50%B for 1.0 min. $t_R$ = 3.578 min, ee% = 99.4%. **$^1$H NMR:** (400 MHz, CHLOROFORM-d) δ = 9.36 (s, 1H), 8.47 (s, 1H), 8.10 (d, *J* = 8.1 Hz, 1H), 7.78 - 7.71 (m, 1H), 7.70 - 7.64 (m, 1H), 7.56 (d, *J* = 8.4 Hz, 1H), 4.15 - 4.04 (m, 2H), 3.17 - 3.07 (m, 1H), 3.03 - 2.92 (m, 2H), 2.56 - 2.45 (m, 2H), 2.41 - 2.34 (m, 1H), 1.98 - 1.85 (m, 1H), 1.41 - 1.28 (m, 4H).

**Peak 4:** 1-{[(3*P*,6*R or 6S*)-3-(Isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4,5,6,7,8-hexahydroquinazolin-1(2*H*)-yl]methyl}cyclopropane-1-carbonitrile **(87d): LCMS (Method 13):** $t_R$ = 2.255 min, $[M+1]^+$ 441.0. **SFC:** column: DAICEL CHIRALPAK AD (150mmx4.6mm, 3µm); mobile phase: A: $CO_2$, B: EtOH(0.1% IPAm); 10%B for 0.5 min., 10-50%B, over 3.0 min., 50%B

for 1.0 min. $t_R$ = 3.765 min, ee% = 98.2%. **$^1$H NMR:** (400 MHz, CHLOROFORM-d) δ = 9.35 (s, 1H), 8.46 (s, 1H), 8.10 (d, *J* = 8.1 Hz, 1H), 7.78 - 7.73 (m, 1H), 7.70 - 7.65 (m, 1H), 7.58 (d, *J* = 8.3 Hz, 1H), 4.09 (s, 2H), 3.22 - 3.11 (m, 1H), 3.02 - 2.90 (m, 2H), 2.57 - 2.49 (m, 1H), 2.48 - 2.35 (m, 2H), 2.00 - 1.88 (m, 1H), 1.43 - 1.35 (m, 2H), 1.34 - 1.27 (m, 2H).

**Example 88:** Synthesis of (2*R or 2S*)-3-[(3*M*)-3-(Isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2*H*)-yl]-2-methylpropanoic acid **(88a)**;
(2*R or 2S*)-3-[(3*M*)-3-(Isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2*H*)-yl]-2-methylpropanoic acid **(88b)**;
(2*R or 2S*)-3-[(3*P*)-3-(Isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2*H*)-yl]-2-methylpropanoic acid **(88c)**, and
(2*R or 2S*)-3-[(3*P*)-3-(Isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2*H*)-yl]-2-methylpropanoic acid **(88d)**




3-(3-(isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2H)-yl)-2-methylpropanoic acid **(38)** (670 mg, 1.51 mmol, 1.0 eq.) was separated by chiral SFC (column: DAICEL CHIRALPAK AD (250 mmx30 mm, 10 µm; mobile phase: 0.1% $NH_3H_2O$ IPA; B% 10%-50%, 22 min]) to give four peaks. **SFC:** $t_{R1}$ = 1.187 min., $t_{R2}$ = 1.354 min., $t_{R3}$ = 1.637 min., and $t_{R4}$ = 1.745 min.

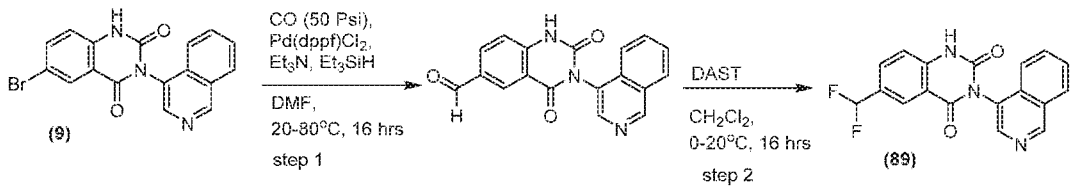
**Peak 1:** (2*R or 2S*)-3-[(3*M*)-3-(Isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2*H*)-yl]-2-methylpropanoic acid **(88a): LCMS (Method 13):** $t_R$ = 2.236 min, $[M+1]^+$ 444.0. **SFC:** column: DAICEL CHIRALPAK AD-3 (50mmx4.6mm, 3µm); mobile phase: A: $CO_2$, B: IPA(0.1% IPAm); 5%B for 0.2 min., 5-50%B, over 1.0 min., 50%B for 1.0 min., 50-5%B, over 0.4 min., 5%B for 0.4 min. $t_R$ = 1.185 min, ee% = 94.6%. **$^1$H NMR:** (400 MHz, DMSO-$d_6$) δ = 9.45 (s, 1H), 8.57 (s, 1H), 8.31 (d, *J* = 1.7 Hz, 1H), 8.30 - 8.26 (m, 1H), 8.20 (dd, *J* = 2.1, 8.9 Hz, 1H), 7.92 - 7.84 (m, 2H), 7.80 - 7.75 (m, 2H), 4.44 - 4.38 (m, 1H), 4.35 - 4.28 (m, 1H), 2.91 (q, *J* = 7.3 Hz, 1H), 1.18 (d, *J* = 7.0 Hz, 3H).

**Peak 2:** (2*R or 2S*)-3-[(3*M*)-3-(Isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2*H*)-yl]-2-methylpropanoic acid **(88b): LCMS (Method 13):** $t_R$ = 2.236 min, $[M+1]^+$ 444.0. **SFC:** column: DAICEL CHIRALPAK AD-3 (50mmx4.6mm, 3µm); mobile phase: A: $CO_2$, B: IPA(0.1% IPAm); 5%B for 0.2 min., 5-50%B, over 1.0 min., 50%B for 1.0 min., 50-5%B, over 0.4 min., 5%B for 0.4 min. $t_R$ = 1.365 min, ee% = 96.3%. **$^1$H NMR:** (400 MHz, DMSO-$d_6$) δ = 9.45 (s, 1H), 8.57 (s, 1H), 8.31 (d, *J* = 1.7 Hz, 1H), 8.30 - 8.26 (m, 1H), 8.20 (dd, *J* = 2.1, 8.9 Hz, 1H), 7.92 - 7.85 (m, 2H), 7.81 - 7.75 (m, 2H), 4.44 - 4.38 (m, 1H), 4.35 - 4.28 (m, 1H), 2.94 - 2.87 (m, 1H), 1.18 (d, *J* = 7.0 Hz, 3H).

**Peak 3:** (2*R or 2S*)-3-[(3*P*)-3-(Isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2*H*)-yl]-2-methylpropanoic acid **(88c): LCMS (Method 13):** $t_R$ = 2.255 min, $[M+1]^+$ 444.0. **SFC:** column: DAICEL CHIRALPAK AD-3 (50mmx4.6mm, 3µm); mobile phase: A: $CO_2$, B: IPA(0.1% IPAm); 5%B for 0.2 min., 5-50%B, over 1.0 min., 50%B for 1.0 min., 50-5%B, over 0.4 min., 5%B for 0.4 min. $t_R$ = 1.657 min, ee% = 95.3%. **$^1$H NMR:** (400 MHz, DMSO-$d_6$) δ = 9.45 (s, 1H), 8.53 (s, 1H), 8.31 (d, *J* = 1.8 Hz, 1H), 8.30 - 8.27 (m, 1H), 8.20 (dd, *J* = 2.1, 8.9 Hz, 1H), 7.95 - 7.88 (m, 2H), 7.81 - 7.74 (m, 2H), 4.44 - 4.31 (m, 2H), 2.94 - 2.87 (m, 1H), 1.15 (d, *J* = 7.0 Hz, 3H).

**Peak 4:** (2*R or 2S*)-3-[(3*P*)-3-(Isoquinolin-4-yl)-2,4-dioxo-6-(trifluoromethyl)-3,4-dihydroquinazolin-1(2*H*)-yl]-2-methylpropanoic acid **(88d): LCMS (Method 13):** $t_R$ = 2.256 min, $[M+1]^+$ 444.0. **SFC:** column: DAICEL CHIRALPAK AD-3 (50mmx4.6mm, 3µm); mobile phase: A: $CO_2$, B: IPA(0.1% IPAm); 5%B for 0.2 min., 5-50%B, over 1.0 min., 50%B for 1.0 min., 50-5%B, over 0.4 min., 5%B for 0.4 min. $t_R$ = 1.768 min, ee% = 95.0%. **$^1$H NMR:** (400 MHz, DMSO-$d_6$) δ = 9.45 (s, 1H), 8.53 (s, 1H), 8.32 - 8.26 (m, 2H), 8.20 (dd, *J* = 1.9, 8.9 Hz, 1H), 7.96 - 7.89 (m, 2H), 7.81 - 7.73 (m, 2H), 4.45 - 4.29 (m, 2H), 2.94 - 2.87 (m, 1H), 1.15 (d, *J* = 7.0 Hz, 3H).

**Example 89:** Synthesis of 6-(difluoromethyl)-3-(isoquinolin-4-yl)quinazoline-2,4(1H,3H)-dione **(89)**

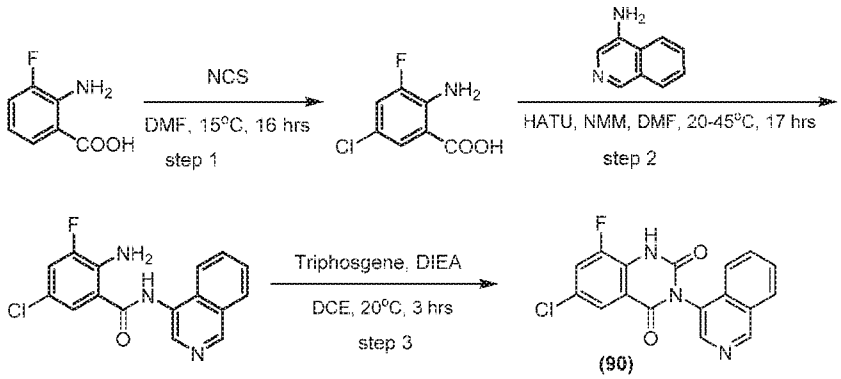



Step 1: To a mixture of 6-bromo-3-(isoquinolin-4-yl)quinazoline-2,4(1H,3H)-dione **(9)** (620 mg, 1.68 mmol, 1.0 eq.), $Pd(dppf)Cl_2$ (50 mg) and $Et_3N$ (390 mg, 3.86 mmol, 2.0 eq.) in DMF (20 mL) was added $Et_3SiH$ (2.0 g, 16.80 mmol, 10.0 eq.) at 20°C. The mixture was stirred at 80°C under CO (50 psi) for 16 hrs. The reaction mixture was quenched with water (20 mL), extracted with $CH_2Cl_2$/i-PrOH (3/1, 10 mL x 3), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give crude product. The crude product was purified by column (Petroleum

ether/THF = 2/1 to 1/1) to give 3-(isoquinolin-4-yl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carbaldehyde. **LCMS (Method 5):** $t_R$ = 0.460 min, $[M+1]^+$ 318.1.

Step 2: To a solution of 3-(isoquinolin-4-yl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carbaldehyde (300 mg, 0.94 mmol, 1.0 eq.) in $CH_2Cl_2$ (5 mL) was added DAST (456 mg, 2.82 mmol, 3.0 eq.) at 0°C under $N_2$, the mixture was stirred at 20°C for 16 hrs. The reaction mixture was quenched with 10% $NaHCO_3$ aqueous (10 mL) and extracted with $CH_2Cl_2$/i-PrOH (3/1, 10 mL x 3). The combined organic layers were dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give crude product. The crude was purified by prep-HPLC (column: Phenomene x Luna C18 200mmx40mm, 10um; liquid phase: [A-$H_2O$ (0.1% FA); B-ACN] B%: 25%- 65%, 20 min]) to give 6-(difluoromethyl)-3-(isoquinolin-4-yl)quinazoline-2,4(1H,3H)-dione **(89)**. **LCMS (Method 13):** $t_R$ = 1.955 min, $[M+1]^+$ 340.1. **$^1$H NMR:** (400MHz, DMSO-$d_6$) δ = 12.00 (s, 1H), 9.44 (s, 1H), 8.58 (s, 1H), 8.30 - 8.26 (m, 1H), 8.17 (s, 1H), 7.97 (br d, *J*=8.6 Hz, 1H), 7.92 (br d, *J*=6.9 Hz, 1H), 7.81 - 7.73 (m, 2H), 7.44 (d, *J*=8.5 Hz, 1H), 7.16 (s, 1H).

**Example 90:** Synthesis of 6-chloro-8-fluoro-3-(isoquinolin-4-yl)quinazoline-2,4(1H,3H)-dione **(90)**



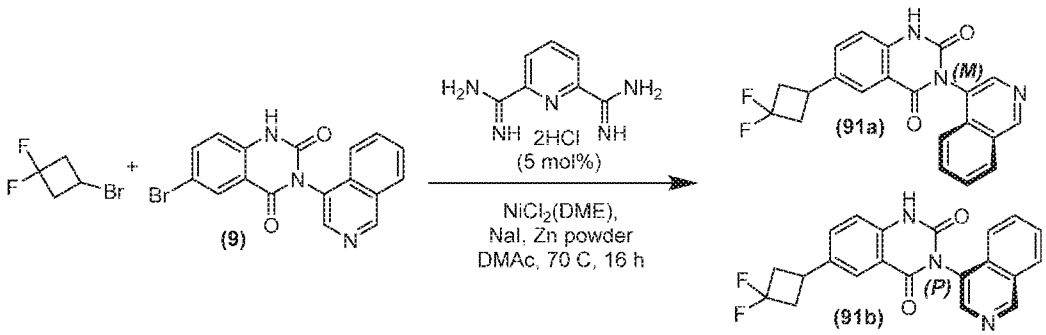

Step 1: To a mixture of 2-amino-3-fluorobenzoic acid **(Int-AA7)** (4.0 g, 25.78 mmol, 1.0 eq.) in DMF (100 mL) was added NCS (4.5 g, 33.52 mmol, 1.3 eq.) at 20°C dropwise. Then the mixture was stirred at 20°C for 16 hrs. The mixture was poured into water (80 mL) and extracted with MTBE (20 mL x 3). The combined organic phase was dried over $Na_2SO_4$, filtered and concentrated. The crude product was suspended in petroleum ether/EtOAc = 5:1 (30 mL) and stirred for 1 hr. The suspension was filtered and the filter cake was dried to give 2-amino-5-chloro-3-fluorobenzoic acid. **$^1$H NMR:** (400MHz, DMSO-$d_6$) δ = 7.51 (dd, *J*=1.6, 2.4 Hz, 1H), 7.44 (dd, *J*=2.5, 11.2 Hz, 1H).

Step 2: To a solution of 2-amino-5-chloro-3-fluorobenzoic acid (1.0 g, 5.28 mmol, 1.0 eq.) in DMF (10 mL) was added HATU (2.4 g, 6.33 mmol, 1.2 eq.) at 20°C and the mixture was stirred at 20°C for 1 hr. NMM (1.6 g, 15.83 mmol, 3.0 eq.) and isoquinolin-4-amine (837 mg, 5.80 mmol, 1.1 eq.) were added at 45°C and the mixture stirred at 45°C for 16 hrs. The mixture was poured into water (20 mL) and extracted with EtOAc (10 mL x 3). The combined organic layers

were dried over $Na_2SO_4$, filtered and concentrated to give a crude product which was purified by MPLC with (petroleum ether/EtOAc = 5:1 to 3:1 to 1:1) to give 2-amino-5-chloro-3-fluoro-N-(isoquinolin-4-yl)benzamide. **$^1$H NMR:** (400MHz, CHLOROFORM-d) δ = 9.17 (s, 1H), 8.74 (s, 1H), 8.45 (br s, 1H), 8.03 (d, *J*=8.3 Hz, 1H), 7.89 (d, *J*=8.4 Hz, 1H), 7.76 (br t, *J*=7.3 Hz, 1H), 7.69 - 7.62 (m, 1H), 7.54 (s, 1H), 7.17 (dd, *J*=2.0, 10.5 Hz, 1H), 5.70 (br s, 2H).

Step 3: A solution of triphosgene (310 mg, 1.05 mmol, 1.0 eq.) in DCE (2 mL) was added dropwise at 0°C to a mixture of 2-amino-5-chloro-3-fluoro-N-(isoquinolin-4-yl)benzamide (300 mg, 0.95 mmol, 1.0 eq.) and DIEA (420 mg, 3.33 mmol, 3.5 eq.) in DCE (4 mL). The mixture was stirred at 20°C for 16 hrs. The mixture was concentrated to give a crude product which was purified by prep-HPLC (HCOOH) to give 6-chloro-8-fluoro-3-(isoquinolin-4-yl)quinazoline-2,4(1H,3H)-dione **(90)**. **1H NMR:** (400MHz, DMSO-d6) δ = 12.08 (s, 1H), 9.43 (s, 1H), 8.56 (s, 1H), 8.31 - 8.23 (m, 1H), 8.00 - 7.91 (m, 2H), 7.82 - 7.72 (m, 3H).

**Example 91:** Synthesis of (3*M*)-6-(3,3-Difluorocyclobutyl)-3-(isoquinolin-4-yl)quinazoline-2,4(1*H*,3*H*)-dione **(91a)**
(3*P*)-6-(3,3-Difluorocyclobutyl)-3-(isoquinolin-4-yl)quinazoline-2,4(1*H*,3*H*)-dione **(91b)**




To an oven-dried 1 mL microwave vial was added 6-bromo-3-(isoquinolin-4-yl)quinazoline-2,4(1H,3H)-dione **(9)** (147.3 mg, 1 eq., 0.400 mmol), $NiCl_2$(DME) complex (4.394 mg, 0.05 eq., 20 µmol), pyridine-2,6-bis(carboximidamide) dihydrochloride (4.722 mg, 0.05 Eq., 20.00 µmol) (Prepared according to *Chem. Commun.*, **2014**, *50*, 7269-7272), activated zinc (65.4 mg, 2.5 Eq., 1.00 mmol), and sodium iodide (15.0 mg, 0.25 Eq., 100 µmol). The reaction was sealed with a septa-top cap and purged with vac/$N_2$ x3 via needle. DMAc (1.0 mL) was added, followed by 3-bromo-1,1-difluorocyclobutane (88.9 mg, 1.3 Eq., 520 µmol) and the reaction was heated to 70 °C and stirred at 70 °C overnight. The reaction was quenched by pouring into an ice-cold solution of 1 M $KHSO_4$ and stirred for 10 mins, precipitating a solid which was filtered and then dissolved in EtOH/DCM and filtered a second time. The eluent was concentrated *in vacuo* and purified by preparative HPLC (column: waters SunFire, C18, 21x50mm, 3µm; liquid phase: [A: water+0.1%TFA; B: ACN+0.1%TFA] B%: 10%-50%, 4min). The racemic material was then separated using chiral SFC separation (column: CHIRALCEL® OD, 21x250 mm, 25% MeOH in

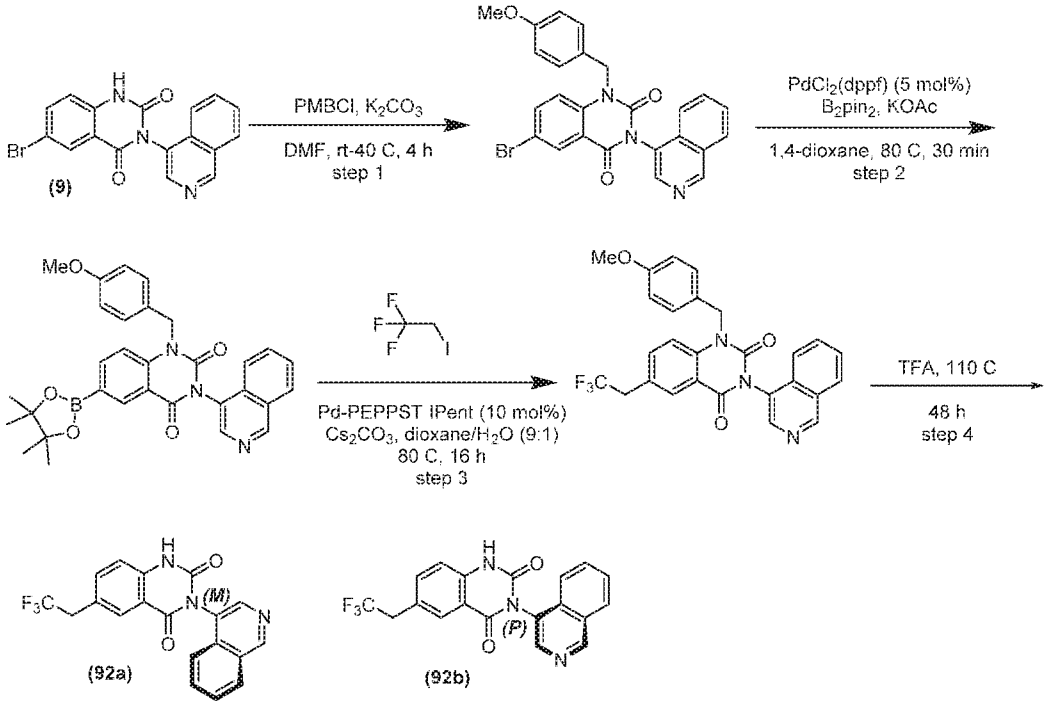
$sCO_2$, 100 mL/min, 276 bar) to give twp peaks. The respective the fractions were concentrated *in vacuo* without heating to avoid interconversion of atropisomers. The residue was suspended in sat. $NaHCO_3$ (aq), and extracted into EtOAc x 3. The combined organics were dried over $Na_2SO_4$, filtered and concentrated *in vacuo* without heating. The residue was dissolved in MeCN/$H_2O$ (1:1) and lyophilized.

Peak 1: (3*M*)-6-(3,3-Difluorocyclobutyl)-3-(isoquinolin-4-yl)quinazoline-2,4(1*H*,3*H*)-dione **(91a)**

Peak 2: (3*P*)-6-(3,3-Difluorocyclobutyl)-3-(isoquinolin-4-yl)quinazoline-2,4(1*H*,3*H*)-dione **(91b)**

**LCMS (Method 29):** $t_R$ = 0.72 min, M+1]$^+$ 380.4; **Chiral SFC** (column: CHIRALCEL® OD, 4.6x1000 mm, 5 µm, 25% MeOH in $sCO_2$, 5 mL/min), peak 1 $t_{R1}$ = 1.59 min. 99.8%; peak 2 $t_{R2}$ = 3.29 min. 100%; **$^1$H NMR** (500 MHz, DMSO) δ 9.41 (s, 1H), 8.51 (s, 1H), 8.29 – 8.23 (m, 1H), 7.84 (d, J = 2.1 Hz, 1H), 7.79 – 7.72 (m, 3H), 7.70 (dd, J = 8.4, 2.1 Hz, 1H), 7.27 (d, J = 8.5 Hz, 1H), 3.57 – 3.46 (m, 2H), 3.10 – 2.98 (m, 2H), 2.77 – 2.62 (m, 2H); **$^{19}$F NMR** (470 MHz, DMSO) δ -80.67 (d, J = 189.9 Hz), -96.82 (d, J = 190.4 Hz).

**Example 92:** Synthesis of (3*M*)-3-(Isoquinolin-4-yl)-6-(2,2,2-trifluoroethyl)quinazoline-2,4(1*H*,3*H*)-dione **(92a)** and (3*P*)-3-(Isoquinolin-4-yl)-6-(2,2,2-trifluoroethyl)quinazoline-2,4(1*H*,3*H*)-dione **(92b)**




Step 1: To a 8 mL vial was added *rac*-6-bromo-3-(isoquinolin-4-yl)quinazoline-2,4(1H,3H)-dione **(9)** (184 mg, 1 eq., 0.500 mmol) and potassium carbonate (138 mg, 2.0 eq., 1.00 mmol). The vial was sealed and purged with vac/$N_2$ x3 via needle. DMF (2.00 mL) was added, followed by 4-methoxybenzyl chloride (90.1 mg, 78.3 µL, 1.15 eq., 575 µmol). The reaction was stirred at rt. For 1.5 hrs. The reaction was warmed to 40 °C and stirred for 4 h at 40 °C. The reaction was

poured into an ice cold solution of 1M $KHSO_4$ and stirred for 5 mins, precipitating a suspension which was filtered, washed with $H_2O$ and dried. The solid was dissolved in 1:1 EtOH/DCM and concentrated to give *rac*-6-bromo-3-(isoquinolin-4-yl)-1-(4-methoxybenzyl)quinazoline-2,4(1H,3H)-dione which was used without further purification. **LCMS (Method 29):** $t_R$ = 0.93 min, $[M+1]^+$ 490.3.

Step 2: To an oven-dried 8 mL vial was added *rac*-6-bromo-3-(isoquinolin-4-yl)-1-(4-methoxybenzyl)quinazoline-2,4(1H,3H)-dione (100.00 mg, 1 Eq., 204 µmol), $PdCl_2$(dppf) (7.5 mg, 0.05 eq., 10 µmol) and bis(pinacolato)diboron (62.4 mg, 1.2 eq., 246 µmol), followed by potassium acetate (80.4 mg, 4 eq., 819 µmol). The vial was sealed with a septa-top cap and purged with vac/$N_2$ x3 via needle. 1,4-Dioxane (1.0 mL) was added and the reaction was heated to 80 °C for 30 mins. The reaction was cooled to rt, quenched with 1:1 $H_2O$/brine and extracted into EtOAc x 4. The combined organics were dried over $Na_2SO_4$, filtered and concentrated in vacuo. Purification by ISCO (0-100% EtOAc/Hept) gave *rac*-3-(isoquinolin-4-yl)-1-(4-methoxybenzyl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinazoline-2,4(1H,3H)-dione. **LCMS (Method 29):** $t_R$ = 1.06 min, $[M+1]^+$ 536.6.

Step 3: To a 4 mL vial was added *rac*-3-(isoquinolin-4-yl)-1-(4-methoxybenzyl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinazoline-2,4(1H,3H)-dione (100.00 mg, 1 eq., 187 µmol), $Cs_2CO_3$ (182.6 mg, 3 eq., 560.2 µmol) and Pd-PEPPSI IPent catalyst (14.8 mg, 0.1 eq., 19 µmol). The vial was sealed, purged with vac/$N_2$ x3 via needle. 1,4-Dioxane (1.62 mL) and water (0.180 mL) were added, followed by 2,2,2-trifluoroiodoethane (196 mg, 92 µL, 5 eq., 934 µmol). The reaction was then heated to 80 °C and stirred overnight. The reaction was quenched with AcOH, filtered through a plug of $SiO_2$ with EtOAc and concentrated *in vacuo*. Purification by ISCO (0-100% EtOAc/Hept) gave *rac*-3-(isoquinolin-4-yl)-1-(4-methoxybenzyl)-6-(2,2,2-trifluoroethyl)quinazoline-2,4(1H,3H)-dione which was used without further purification. **LCMS (Method 29):** $t_R$ = 1.06 min, $[M+1]^+$ 536.6.

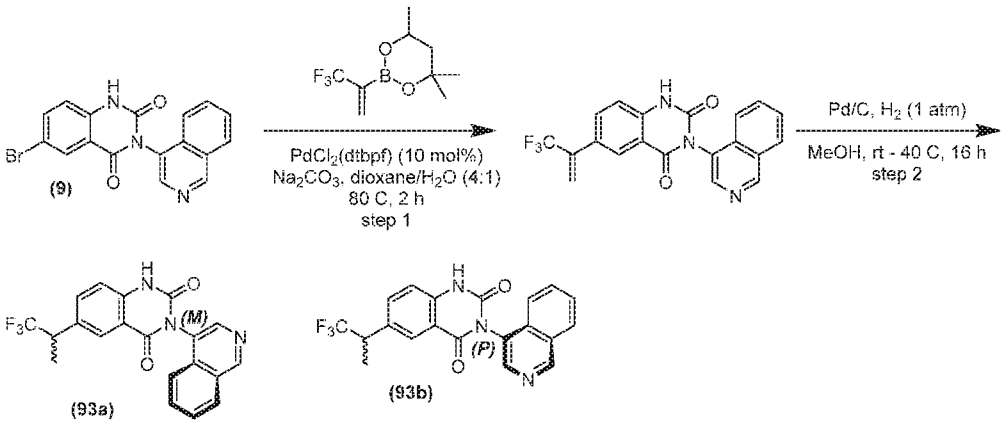
Step 4: To a 2-5 mL MW vial was added *rac*-3-(isoquinolin-4-yl)-1-(4-methoxybenzyl)-6-(2,2,2-trifluoroethyl)quinazoline-2,4(1H,3H)-dione (155 mg, 80% wt, 1 eq., 252 µmol) and TFA (0.5 mL). The reaction was sealed and heated to 110 °C for 48 hr. The reaction was concentrated *in vacuo* and purified by preparative HPLC (column: waters SunFire, C18, 21x50mm, 3µm; liquid phase: [A: Water+0.1%TFA; B: ACN+0.1%TFA] B%: 10%-50%, 4min) . The racemic material was then separated using chiral SFC separation (column: CHIRALCEL® OD, 21x250 mm, 20% MeOH in $sCO_2$, 90 mL/min, 236 bar) followed by lyophilization to give two peaks:

Peak 1: (3*M*)-3-(Isoquinolin-4-yl)-6-(2,2,2-trifluoroethyl)quinazoline-2,4(1*H*,3*H*)-dione **(92a)** and Peak 2: (3*P*)-3-(Isoquinolin-4-yl)-6-(2,2,2-trifluoroethyl)quinazoline-2,4(1*H*,3*H*)-dione **(92b)**.

**LCMS (Method 29):** $t_R$ = 0.49 min, $[M+1]^+$ 372.3; **Chiral SFC** (column: CHIRALCEL® OD, 4.6x1000 mm, 5 µm, 20% MeOH in $sCO_2$, 5 mL/min), peak 1 $t_{R1}$ = 1.80 min. 99.7%; peak 2 $t_{R2}$ =

2.56 min. 100%; **$^1$H NMR** (500 MHz, DMSO) δ 11.81 (s, 1H), 9.42 (s, 1H), 8.55 (s, 1H), 8.29 – 8.23 (m, 1H), 7.99 (s, 1H), 7.89 – 7.85 (m, 1H), 7.79 – 7.71 (m, 3H), 7.32 (d, J = 8.4 Hz, 1H), 3.78 (q, J = 11.4 Hz, 2H). **$^{19}$F NMR** (470 MHz, DMSO) δ -64.7.

**Example 93:** Synthesis of (3*M*)-3-(Isoquinolin-4-yl)-6-[(2*R** or 2S*)-1,1,1-trifluoropropan-2-yl]quinazoline-2,4(1*H*,3*H*)-dione **(93a)** and
and (3*P*)-3-(Isoquinolin-4-yl)-6-[(2*R** or 2S*)-1,1,1-trifluoropropan-2-yl]quinazoline-2,4(1*H*,3*H*)-dione **(93b)**



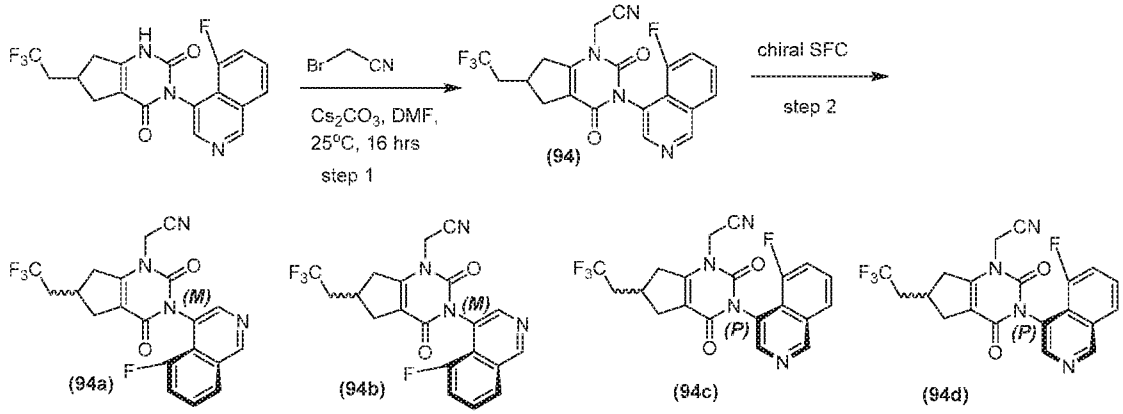

Step 1: To a 20 mL vial was added *rac*-6-bromo-3-(isoquinolin-4-yl)quinazoline-2,4(1H,3H)-dione **(9)** (368.2 mg, 1 Eq, 1.000 mmol), $PdCl_2$(dtbpf) (65.18 mg, 0.1 Eq, 100.0 µmol), sodium carbonate (318.0 mg, 3 Eq, 3.00 mmol) and 4,4,6-trimethyl-2-(3,3,3-trifluoroprop-1-en-2-yl)-1,3,2-dioxaborinane (333.0 mg, 1.50 Eq, 1.50 mmol). The vial was sealed, purged with vac/$N_2$ x 3 and 1,4-dioxane (4.0 mL) and water (1.0 mL) were added forming a slurry which was heated to 80 °C for 2 hrs (the reaction slowly becomes homogenous over 5 mins). The reaction was cooled to rt and poured into an ice cold solution of 1M $KHSO_4$ precipitating the product which was filtered, washed with $H_2O$ and then dried. The crude solid was recrystallised from MeOH to give 3-(isoquinolin-4-yl)-6-(3,3,3-trifluoroprop-1-en-2-yl)quinazoline-2,4(1H,3H)-dione. **LCMS (Method 29):** $t_R$ = 0.77 min, $[M+1]^+$ 384.3.

Step 2: To a 20 mL vial was added *rac*-3-(isoquinolin-4-yl)-6-(3,3,3-trifluoroprop-1-en-2-yl)quinazoline-2,4(1H,3H)-dione (130.0 mg, 1 Eq, 339 µmol) and Pd/C (40.0 mg, 10% wt, 0.111 eq., 38 µmol). The vial was sealed with a septa-top cap and purged with vac/$N_2$ x3 via needle. The vial was then placed under a balloon of $H_2$, MeOH (6 mL) and the reaction was stirred at rt for 2 h. The reaction was heated to 40 °C and stirred overnight, after which the reaction was filtered through celite with MeOH and concentrated *in vacuo*. The crude material was purified by preparative HPLC (column: waters SunFire, C18, 21x50mm, 3µm; liquid phase: [A: Water+0.1%TFA; B: ACN+0.1%TFA] B%: 10%-50%, 4min) to give a mixture of 4 diastereomers in a single peak. Chiral SFC (column: CHIRALCEL® OD, 21x250 mm, 20% MeOH in $sCO_2$, 90 mL/min, 236 bar) was able to separate the pairs of atropisomers: Peak 1 containing (3*M*)-3-

(Isoquinolin-4-yl)-6-[(2*R** or 2S*)-1,1,1-trifluoropropan-2-yl]quinazoline-2,4(1*H*,3*H*)-dione **(93a)** and peak 2 containing (3*P*)-3-(Isoquinolin-4-yl)-6-[(2*R** or 2S*)-1,1,1-trifluoropropan-2-yl]quinazoline-2,4(1*H*,3*H*)-dione **(93b)**. The respective residues was taken up in 1:1:2 MeCN/dioxane/$H_2O$ and lyophilized to give a mixture of 3-((R)-isoquinolin-4-yl)-6-((S)-1,1,1-trifluoropropan-2-yl)quinazoline-2,4(1H,3H)-dione/3-((R)-isoquinolin-4-yl)-6-(( R)-1,1,1-trifluoropropan-2-yl)quinazoline-2,4(1H,3H)-dione **(93a)** and a mixture of 3-((S)-isoquinolin-4-yl)-6-((R)-1,1,1-trifluoropropan-2-yl)quinazoline-2,4(1H,3H)-dione/3-((S)-isoquinolin-4-yl)-6-((S)-1,1,1-trifluoropropan-2-yl)quinazoline-2,4(1H,3H)-dione **(93b)**. A sample of the first peak was taken up in DMSO and heated to 100 C overnight. LCMS shows no degradation of the material. the solution was concentrated in vacuo and chrial analysis which showed the material to be a 1:1 mixture of peak 1 and peak 2 indicating that the separated peaks were atropisomers.

**Chiral SFC** (column: CHIRALCEL® OD, 4.6x1000 mm, 5 µm, 20% MeOH in $sCO_2$, 5 mL/min), peak 1 $t_R$ = 1.56 min. 100%, peak 2 $t_R$ = 2.38 min. 100%; **LCMS (Method 29):** $t_R$ = 0.76 min, $[M+1]^+$ 386.4; **$^1$H NMR** (500 MHz, DMSO) δ 11.82 (s, 1H), 9.49 (s, 1H), 8.60 (s, 1H), 8.31 (dd, J = 7.6, 1.8 Hz, 1H), 7.98 (d, J = 2.0 Hz, 1H), 7.92 (dd, J = 8.3, 3.8 Hz, 1H), 7.79 (ddt, J = 8.3, 6.9, 4.2 Hz, 3H), 7.34 (d, J = 8.5 Hz, 1H), 4.07 – 3.92 (m, 1H), 1.47 (d, J = 7.2 Hz, 3H). **$^{19}$F NMR** (470 MHz, DMSO) δ -70.31 (d, J = 7.1 Hz).

**Example 94:** Synthesis of 2-(3-(5-fluoroisoquinolin-4-yl)-2,4-dioxo-6-(2,2,2-trifluoroethyl)-2,3,4,5,6,7-hexahydro-1H-cyclopenta[d]pyrimidin-1-yl)acetonitrile **(94)**;
[(3*M*,6*R or 6S*)-3-(5-Fluoro-1,8a-dihydroisoquinolin-4-yl)-2,4-dioxo-6-(2,2,2-trifluoroethyl)-2,3,4,5,6,7-hexahydro-1*H*-cyclopenta[*d*]pyrimidin-1-yl]acetonitrile **(94a)**;
[(3*M*,6*R or 6S*)-3-(5-Fluoro-1,8a-dihydroisoquinolin-4-yl)-2,4-dioxo-6-(2,2,2-trifluoroethyl)-2,3,4,5,6,7-hexahydro-1*H*-cyclopenta[*d*]pyrimidin-1-yl]acetonitrile **(94b)**;
[(3*P*,6*R or 6S*)-3-(5-Fluoro-1,8a-dihydroisoquinolin-4-yl)-2,4-dioxo-6-(2,2,2-trifluoroethyl)-2,3,4,5,6,7-hexahydro-1*H*-cyclopenta[*d*]pyrimidin-1-yl]acetonitrile **(94c)**, and
[(3*P*,6*R or 6S*)-3-(5-Fluoro-1,8a-dihydroisoquinolin-4-yl)-2,4-dioxo-6-(2,2,2-trifluoroethyl)-2,3,4,5,6,7-hexahydro-1*H*-cyclopenta[*d*]pyrimidin-1-yl]acetonitrile **(94d)**




Step 1: To a mixture of 3-(5-fluoroisoquinolin-4-yl)-6-(2,2,2-trifluoroethyl)-1,5,6,7-tetrahydro-2H-cyclopenta[d]pyrimidine-2,4(3H)-dione (300 mg, 0.79 mmol, 1.0 eq.) and $Cs_2CO_3$ (515 mg, 1.58 mmol, 2.0 eq.) in DMF (5 mL) was added 2-bromoacetonitrile (142 mg, 1.19 mmmol, 1.5 eq.) and the reaction mixture was stirred at 25°C for 16 hrs. The mixture was filtered and the filtrate was purified by prep-HPLC ($NH_4HCO_3$) to give racemic 2-(3-(5-fluoroisoquinolin-4-yl)-2,4-dioxo-6-(2,2,2-trifluoroethyl)-2,3,4,5,6,7-hexahydro-1H-cyclopenta[d]pyrimidin-1-yl)acetonitrile **(94)**.

Step 2: Racemic 2-(3-(5-fluoroisoquinolin-4-yl)-2,4-dioxo-6-(2,2,2-trifluoroethyl)-2,3,4,5,6,7-hexahydro-1H-cyclopenta[d]pyrimidin-1-yl)acetonitrile **(94)** was separated by SFC (column: Lux cellulose-2 (100mmx4.6mm, 3µm); mobile phase A: $CO_2$; mobile phase B: EtOH(0.1% IPAm); B%: 10% for 0.2 min, 10-50% for 2.2 min., 50% for 1.0 min., 50-10% for 0.6 min.) to give four peaks: $t_{R1}$ = 2.240 min.; $t_{R2}$ = 2.508 min.; $t_{R3}$ = 2.653 min. and $t_{R4}$ = 3.153 min.

**Peak 1:** [(3*M*,6*R or 6S*)-3-(5-Fluoro-1,8a-dihydroisoquinolin-4-yl)-2,4-dioxo-6-(2,2,2-trifluoroethyl)-2,3,4,5,6,7-hexahydro-1*H*-cyclopenta[*d*]pyrimidin-1-yl]acetonitrile **(94a)**. **LCMS (Method 17):** $t_R$ = 2.673 min, $[M+1]^+$ 419.1. **SFC:** column: Lux cellulose-2 (100mmx4.6mm, 3µm); mobile phase A: $CO_2$; mobile phase B: EtOH(0.1% IPAm); B%: 10% for 0.2 min, 10-50% for 2.2 min., 50% for 1.0 min., 50-10% for 0.6 min.; $t_R$ = 2.181 min., ee% = 100%.; **$^1$H NMR:** (400 MHz, CHLOROFORM-d) δ = 9.36 (br s, 1H), 8.42 (s, 1H), 7.91 (d, J = 8.3 Hz, 1H), 7.68 - 7.51 (m, 1H), 7.37 (dd, J = 7.8, 12.3 Hz, 1H), 4.90 - 4.68 (m, 2H), 3.34 (br dd, J = 8.0, 16.5 Hz, 1H), 3.18 (br dd, J = 8.7, 15.3 Hz, 1H), 3.10 - 2.90 (m, 2H), 2.61 (br dd, J = 7.2, 15.3 Hz, 1H), 2.54 - 2.32 (m, 2H).

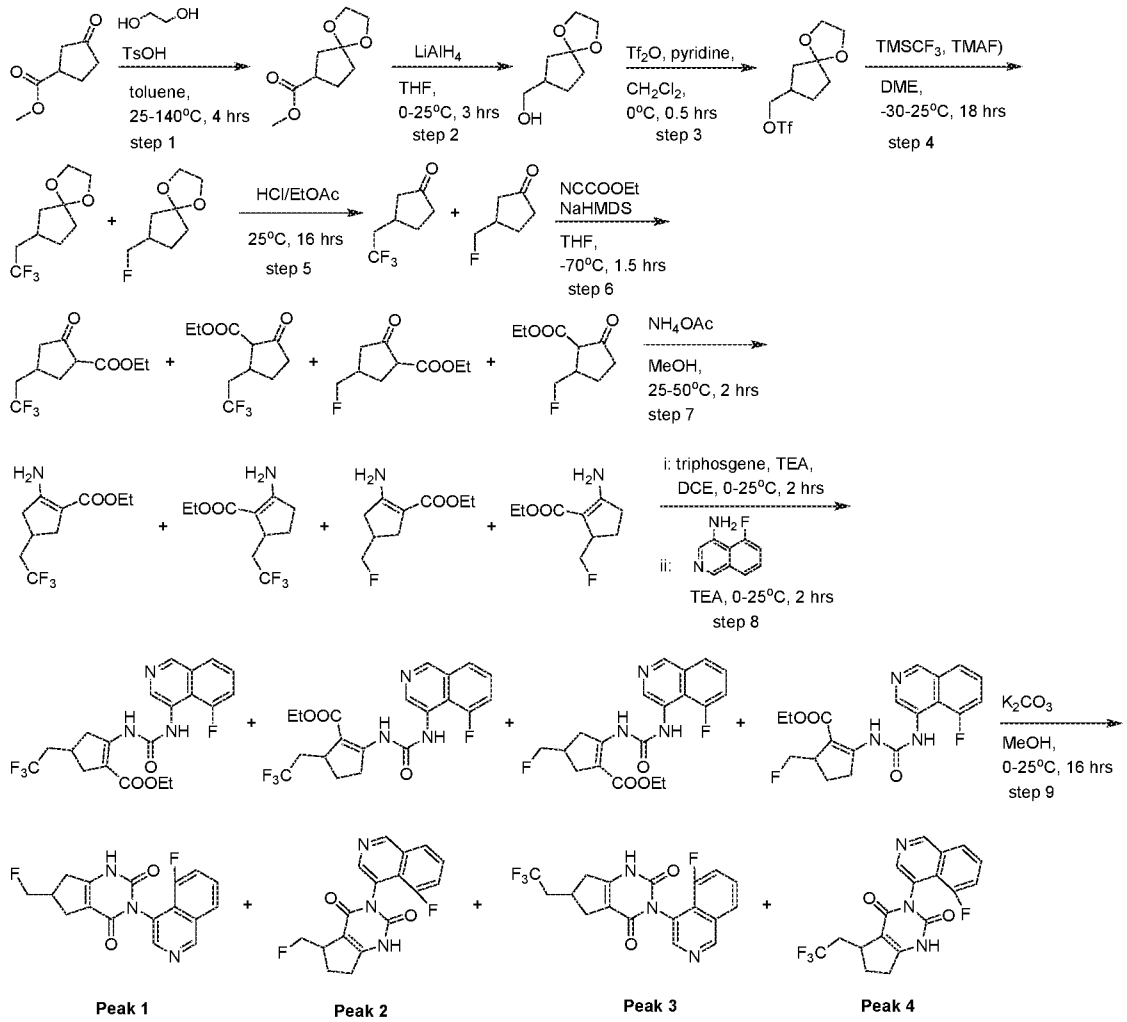
**Peak 2:** [(3*M*,6*R or 6S*)-3-(5-Fluoro-1,8a-dihydroisoquinolin-4-yl)-2,4-dioxo-6-(2,2,2-trifluoroethyl)-2,3,4,5,6,7-hexahydro-1*H*-cyclopenta[*d*]pyrimidin-1-yl]acetonitrile **(94b)**. **LCMS (Method 17):** $t_R$ = 2.635 min, $[M+1]^+$ 419.1. **SFC:** column: Lux cellulose-2 (100mmx4.6mm, 3µm); mobile phase A: $CO_2$; mobile phase B: EtOH(0.1% IPAm); B%: 10% for 0.2 min, 10-50% for 2.2 min., 50% for 1.0 min., 50-10% for 0.6 min.; $t_R$ = 2.435 min., ee% = 97.0%.; **$^1$H NMR:** (400 MHz, CHLOROFORM-d) δ = 9.36 (d, J = 1.8 Hz, 1H), 8.42 (s, 1H), 7.91 (d, J = 8.3 Hz, 1H), 7.61 (dt, J = 4.8, 8.0 Hz, 1H), 7.37 (dd, J = 7.8, 12.4 Hz, 1H), 4.79 (d, J = 1.6 Hz, 2H), 3.43

- 3.25 (m, 1H), 3.24 - 3.10 (m, 1H), 3.08 - 2.91 (m, 2H), 2.64 (br dd, J = 6.6, 14.3 Hz, 1H), 2.57 - 2.34 (m, 2H).

**Peak 3:** [(3*P*,6*R or 6S*)-3-(5-Fluoro-1,8a-dihydroisoquinolin-4-yl)-2,4-dioxo-6-(2,2,2-trifluoroethyl)-2,3,4,5,6,7-hexahydro-1*H*-cyclopenta[*d*]pyrimidin-1-yl]acetonitrile **(94c)**. **LCMS (Method 17):** $t_R$ = 2.640 min, $[M+1]^+$ 419.1. **SFC:** column: Lux cellulose-2 (100mmx4.6mm, 3µm); mobile phase A: $CO_2$; mobile phase B: EtOH(0.1% IPAm); B%: 10% for 0.2 min, 10-50% for 2.2 min., 50% for 1.0 min., 50-10% for 0.6 min.; $t_R$ = 2.579 min., ee% = 99.5%; **$^1$H NMR:** (400 MHz, CHLOROFORM-d) δ = 9.39 (br s, 1H), 8.43 (br s, 1H), 7.94 (d, J = 8.1 Hz, 1H), 7.63 (dt, J = 4.8, 8.0 Hz, 1H), 7.40 (dd, J = 7.8, 12.4 Hz, 1H), 4.93 - 4.70 (m, 2H), 3.41 - 3.25 (m, 1H), 3.16 (br dd, J = 9.8, 15.3 Hz, 1H), 3.09 - 2.91 (m, 2H), 2.73 - 2.57 (m, 1H), 2.57 - 2.35 (m, 2H).

**Peak 4:** [(3*P*,6*R or 6S*)-3-(5-Fluoro-1,8a-dihydroisoquinolin-4-yl)-2,4-dioxo-6-(2,2,2-trifluoroethyl)-2,3,4,5,6,7-hexahydro-1*H*-cyclopenta[*d*]pyrimidin-1-yl]acetonitrile **(94d)**. **LCMS (Method 17):** $t_R$ = 2.670 min, $[M+1]^+$ 419.1. **SFC:** column: Lux cellulose-2 (100mmx4.6mm, 3µm); mobile phase A: $CO_2$; mobile phase B: EtOH(0.1% IPAm); B%: 10% for 0.2 min, 10-50% for 2.2 min., 50% for 1.0 min., 50-10% for 0.6 min.; $t_R$ = 3.057 min.,ee% = 100%; **$^1$H NMR:** (400 MHz, CHLOROFORM-d) δ = 9.36 (br s, 1H), 8.42 (s, 1H), 7.91 (d, J = 8.3 Hz, 1H), 7.61 (dt, J = 5.0, 7.9 Hz, 1H), 7.37 (br dd, J = 7.8, 12.3 Hz, 1H), 4.90 - 4.68 (m, 2H), 3.34 (br dd, J = 7.9, 16.3 Hz, 1H), 3.18 (br dd, J = 8.3, 15.3 Hz, 1H), 3.11 - 2.90 (m, 2H), 2.61 (br dd, J = 7.3, 15.4 Hz, 1H), 2.54 - 2.34 (m, 2H).

Note: 3-(5-fluoroisoquinolin-4-yl)-6-(2,2,2-trifluoroethyl)-1,5,6,7-tetrahydro-2H-cyclopenta[d]pyrimidine-2,4(3H)-dione was obtained using the following procedure.




Step 1: Ethane-1,2-diol (17.5 g, 281.39 mmol, 2.0 eq.) and TsOH (1.3 g, 7.03 mmol, 0.05 eq.) were added to a stirred solution of methyl 3-oxocyclopentane-1-carboxylate (20.0 g, 140.69 mmol, 1.0 eq.) in toluene (200 mL) at 25°C. The mixture was stirred at 140°C for 4 hrs (water removal by Dean–Stark). Solvent was removed under reduced pressure to give a residue. The residue was taken up in EtOAc (1000 mL), washed with aqueous $NaHCO_3$ (10%, 250 mL), brine (250 mL) and dried over $Na_2SO_4$. After filtering, the solvents were removed under reduced pressure to yield crude product which was purified by flash silica gel chromatography (330 g, Eluent of 0~20% EtOAc/Petroleum ether, 300 mL/min) to give methyl 1,4-dioxaspiro[4.4]nonane-7-carboxylate. **$^1$H NMR:** (400 MHz, CHLOROFORM-d) δ = 3.94 - 3.89 (m, 4H), 3.69 (s, 3H), 2.97 - 2.86 (m, 1H), 2.10 (d, *J* = 9.0 Hz, 2H), 2.07 - 1.85 (m, 4H), 1.85 - 1.78 (m, 1H).

Step 2: $LiAlH_4$ (4.9 g, 128.89 mmol, 1.2 eq.) was added dropwise to a stirred solution of methyl 1,4-dioxaspiro[4.4]nonane-7-carboxylate (20.0 g, 107.41 mmol, 1.0 eq.) in THF (80 mL) at 0 °C under at $N_2$ atmosphere and the mixture stirred at 25 °C for 3 hrs. The reaction mixture was cooled to 0°C, quenched with $H_2O$ (4.9 mL), aqueous NaOH (10%, 4.9 mL), $H_2O$ (14.7 mL),

$Na_2SO_4$ (49.0 g) and stirred at 25 °C for 10 mins. The inorganics were filtered through Celite and washed with EtOAc (2 × 40 mL). The filtrate was washed with water (40 mL), brine (40 mL), dried over $Na_2SO_4$, filtered and the solvents were removed under reduced pressure to yield crude (1,4-dioxaspiro[4.4]nonan-7-yl)methanol which was used directly without purification. **$^1$H NMR:** (400 MHz, CHLOROFORM-d) δ = 3.93 - 3.77 (m, 4H), 3.47 (br d, *J* = 6.0 Hz, 2H), 2.27 - 2.13 (m, 1H), 1.93 (dd, *J* = 8.5, 13.6 Hz, 1H), 1.86 - 1.68 (m, 3H), 1.51 (dd, *J* = 8.2, 13.6 Hz, 1H), 1.45 - 1.32 (m, 1H).

Step 3: Under $N_2$ flow and at 0°C, $Tf_2O$ (3.2 g, 11.38 mmol, 1.2 eq.) was added to a solution of (1,4-dioxaspiro[4.4]nonan-7-yl)methanol (1.5 g, 9.48 mmol, 1.0 eq.) and pyridine (1.5 g, 18.96 mmol, 2.0 eq.) in $CH_2Cl_2$ (15 mL). The reaction mixture was stirred for 0.5 hrs at 0°C. The mixture was quenched with water (30 mL). The aqueous layer was separated from the organic and extracted with $CH_2Cl_2$ (5 mL x 2). The combined organic layers were washed with HCl (0.5 M, 15 mL), dried ($Na_2SO_4$), filtered, and concentrated by $N_2$ flow to give (1,4-dioxaspiro[4.4]nonan-7-yl)methyl trifluoromethanesulfonate which was used immediately in the next step.

Step 4: At -30°C, TMAF (1.1 g, 11.38 mmol, 1.2 eq.) was added to a solution of (1,4-dioxaspiro[4.4]nonan-7-yl)methyl trifluoromethanesulfonate (1.5 g, 9.48 mmol, 1.0 eq.) and $TMSCF_3$ (4.0 g, 28.45 mmol, 3.0 eq.) in DME (50 mL). The reaction mixture was stirred for 0.5 hrs at -30°C and then at 0°C for 1.5 hrs. The mixture was further stirred for 16 hrs at 25°C. The mixture was quenched with water (1 L). The aqueous layer was separated from the organic and extracted with EtOAc (200 mL x 3). The combined organic layers were washed with brine (500 mL), dried ($Na_2SO_4$), filtered, and concentrated under reduced pressure to give crude product which was purified by MPLC (petroleum ether / EtOAc =0 ~ 1/5) to give a mixture of 7-(2,2,2-trifluoroethyl)-1,4-dioxaspiro[4.4]nonane and 7-(fluoromethyl)-1,4-dioxaspiro[4.4]nonane.**$^1$H NMR:** (400 MHz, CHLOROFORM-d) δ = 3.97 - 3.83 (m, 4H), 2.37 - 2.23 (m, 1H), 2.22 - 2.07 (m, 2H), 2.01 - 1.76 (m, 4H), 1.66 - 1.35 (m, 3H). **$^{19}$F NMR:** (376 MHz, CHLOROFORM-d) δ = -64.84 (s, 1F).

Step 5: At 25°C, HCl (15 mL, 2 M) was added to a solution of a mixture of compound 7-(2,2,2-trifluoroethyl)-1,4-dioxaspiro[4.4]nonane and 7-(fluoromethyl)-1,4-dioxaspiro[4.4]nonane (5.0 g, 23.79 mmol, 1.0 eq.) in EtOAc (45 mL). The reaction mixture was stirred at 25°C for 16 hrs. The reaction was quenched with saturated aqueous $NaHCO_3$ (500 mL) and the aqueous layer was separated from the organic and extracted with EtOAc (50 mL x 3). The combined organic layers were dried ($Na_2SO_4$), filtered, and concentrated under reduced pressure to give a mixture of 3-(2,2,2-trifluoroethyl)cyclopentan-1-one and 3-(fluoromethyl)cyclopentan-1-one which was used for next step directly without purification. **$^1$H NMR:** (400 MHz, CHLOROFORM-d) δ = 2.58 - 2.48 (m, 1H), 2.40 - 2.18 (m, 4H), 1.97 - 1.76 (m, 1H), 1.70 - 1.55 (m, 1H). **$^{19}$F NMR:** (376 MHz, CHLOROFORM-d) δ = -64.68 (br t, J = 11.0 Hz, 1F).

Step 6: To a solution containing a mixture of 3-(2,2,2-trifluoroethyl)cyclopentan-1-one and 3-(fluoromethyl)cyclopentan-1-one (5.0 g, 30.00 mmol, 1.0 eq.) in THF (100 mL) was added NaHMDS (36 mL, 36.00 mmol, 1.2 eq.) at -70°C under $N_2$. The mixture was stirred at -70°C for 0.5 hrs under $N_2$. NCCOOEt (3.3 g, 33.00 mmol, 1.1 eq.) was added to the mixture at -70°C under $N_2$. The mixture was stirred at -70°C for 1 hr under $N_2$. The reaction was quenched with saturated aqueous $NH_4Cl$ (800 mL) and extracted with EtOAc (300 mL × 2). The combined organic layers were washed with brine (300 mL), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give a mixture of ethyl 2-oxo-4-(2,2,2-trifluoroethyl)cyclopentane-1-carboxylate, ethyl 2-oxo-5-(2,2,2-trifluoroethyl)cyclopentane-1-carboxylate, ethyl 4-(fluoromethyl)-2-oxocyclopentane-1-carboxylate and ethyl 2-(fluoromethyl)-5-oxocyclopentane-1-carboxylate which was used directly in the next step.

Step 7: To a solution containing a mixture of ethyl 2-oxo-4-(2,2,2-trifluoroethyl)cyclopentane-1-carboxylate, ethyl 2-oxo-5-(2,2,2-trifluoroethyl)cyclopentane-1-carboxylate, ethyl 4-(fluoromethyl)-2-oxocyclopentane-1-carboxylate and ethyl 2-(fluoromethyl)-5-oxocyclopentane-1-carboxylate (5.0 g, crude) in MeOH (200 mL) was added $NH_4OAc$ (16 g, 16.20 mmol, 10.0 eq.) at 25°C. The mixture was stirred at 50°C for 2 hrs. The mixture was concentrated to give a residue which was suspended in saturated $NaHCO_3$ solution (500 mL) and extracted with EtOAc (200 mL × 3). The combined organic layers were washed with brine (200 mL), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give crude product. The crude product was purified by MPLC (petroleum ether / EtOAc = 1/0 to 5/1) to give a mixture of ethyl 2-amino-4-(2,2,2-trifluoroethyl)cyclopent-1-ene-1-carboxylate, ethyl 2-amino-5-(2,2,2-trifluoroethyl)cyclopent-1-ene-1-carboxylate, ethyl 2-amino-4-(fluoromethyl)cyclopent-1-ene-1-carboxylate and ethyl 2-amino-5-(fluoromethyl)cyclopent-1-ene-1-carboxylate. **$^1$H NMR:** (400 MHz, CHLOROFORM-d) δ = 4.25 - 4.11 (m, 2H), 3.27 - 3.16 (m, 1H), 2.81 (dd, *J* = 8.0, 13.9 Hz, 1H), 2.74 - 2.50 (m, 2H), 2.47 - 1.86 (m, 3H), 1.83 - 1.71 (m, 1H), 1.29 (dt, *J* = 3.7, 7.1 Hz, 3H). **$^{19}$F NMR:** (376 MHz, CHLOROFORM-d) δ = -64.15 (s, 1F), -64.97 (s, 1F)
**LCMS (Method 7):** $t_R$ = 0.549 min, $[M+1]^+$ 188.3; $t_R$ = 0.646 min, $[M+1]^+$ 238.2.

Step 8: To a mixture of ethyl 2-amino-4-(2,2,2-trifluoroethyl)cyclopent-1-ene-1-carboxylate, ethyl 2-amino-5-(2,2,2-trifluoroethyl)cyclopent-1-ene-1-carboxylate, ethyl 2-amino-4-(fluoromethyl)cyclopent-1-ene-1-carboxylate and ethyl 2-amino-5-(fluoromethyl)cyclopent-1-ene-1-carboxylate (1.0 g, 4.22 mmol, 1.0 eq.) and TEA (1.28 g, 12.65 mmol, 3.0 eq.) in DCE (20 mL) was added drop wise a solution of triphosgene (0.63 g, 2.11 mmol, 0.5 eq.) in DCE (10 mL) at 0°C. The mixture was stirred at 0°C for 2 hrs. The reaction mixture was quenched with MeOH and a suspension of 5-fluoroisoquinolin-4-amine (0.84 g, 4.22 mmol, 1.0 eq.) and TEA (2.13 g, 21.08 mmol, 5.0 eq.) in DCE (10 mL) was added dropwise to the mixture at 0°C. The mixture was stirred at 25°C for 2 hrs. The reaction was quenched with $H_2O$ (100 mL) and separated. The aqueous layer was extracted with $CH_2Cl_2$ (50 mL × 2). The combined organic layers were

washed with brine (50 mL), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give a mixture of ethyl 2-(3-(5-fluoroisoquinolin-4-yl)ureido)-4-(2,2,2-trifluoroethyl)cyclopent-1-ene-1-carboxylate, ethyl 2-(3-(5-fluoroisoquinolin-4-yl)ureido)-5-(2,2,2-trifluoroethyl)cyclopent-1-ene-1-carboxylate, ethyl 2-(3-(5-fluoroisoquinolin-4-yl)ureido)-4-(fluoromethyl)cyclopent-1-ene-1-carboxylate, and ethyl 2-(3-(5-fluoroisoquinolin-4-yl)ureido)-5-(fluoromethyl)cyclopent-1-ene-1-carboxylate which was used directly in the next step without purification.

Step 9: To a mixture of of ethyl 2-(3-(5-fluoroisoquinolin-4-yl)ureido)-4-(2,2,2-trifluoroethyl)cyclopent-1-ene-1-carboxylate, ethyl 2-(3-(5-fluoroisoquinolin-4-yl)ureido)-5-(2,2,2-trifluoroethyl)cyclopent-1-ene-1-carboxylate, ethyl 2-(3-(5-fluoroisoquinolin-4-yl)ureido)-4-(fluoromethyl)cyclopent-1-ene-1-carboxylate, and ethyl 2-(3-(5-fluoroisoquinolin-4-yl)ureido)-5-(fluoromethyl)cyclopent-1-ene-1-carboxylate (2.5 g, crude) in MeOH (40 mL) was added $K_2CO_3$ (2.0 g). The mixture was stirred at 25°C for 16 hrs. The reaction mixture was filtered, and the filtrate purified by prep-HPLC ($NH_4HCO_3$) to give crude product. The crude product was purified twice by prep-HPLC (column: C18 (250x50mm x10 μm); liquid phase: [A-$H_2O$ (10mM $NH_4HCO_3$); B-ACN] B%: 10%-50%, 20min]) to give four compounds. **LCMS (Method 27):** $t_{R1}$ = 2.185 min, $[M+1]^+$ 329.9; $t_{R2}$ = 2.287 min, $[M+1]^+$ 329.9, $t_{R3}$ = 2.802 min, $[M+1]^+$ 379.9; $t_{R4}$ = 2.987 min, $[M+1]^+$ 379.9.

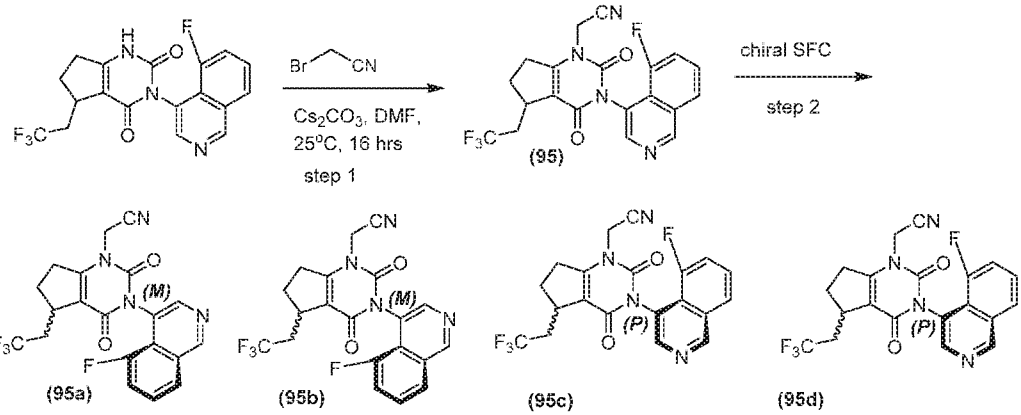
Peak 1: 3-(5-fluoroisoquinolin-4-yl)-6-(fluoromethyl)-1,5,6,7-tetrahydro-2H-cyclopenta[d]pyrimidine-2,4(3H)-dione: $t_R$ = 2.185 min, $[M+1]^+$ 379.9. **$^1$H NMR:** (400 MHz, METHANOL-d4) δ = 9.39 (d, *J* = 1.1 Hz, 1H), 8.45 - 8.32 (m, 1H), 8.09 (d, *J* = 8.3 Hz, 1H), 7.73 (dt, *J* = 4.8, 8.0 Hz, 1H), 7.53 (dd, *J* = 7.9, 12.6 Hz, 1H), 4.58 - 4.48 (m, 1H), 4.46 - 4.34 (m, 1H), 3.12 - 3.01 (m, 1H), 2.92 - 2.74 (m, 3H), 2.53 (br dd, J = 4.6, 15.5 Hz, 1H).

Peak 2: 3-(5-fluoroisoquinolin-4-yl)-5-(fluoromethyl)-1,5,6,7-tetrahydro-2H-cyclopenta[d]pyrimidine-2,4(3H)-dione: $t_R$ = 2.287 min, $[M+1]^+$ 379.9. **$^1$H NMR** (400 MHz, METHANOL-d4) δ = 9.39 (d, *J* = 1.8 Hz, 1H), 8.42 - 8.33 (m, 1H), 8.09 (d, *J* = 8.3 Hz, 1H), 7.73 (dt, *J* = 4.8, 8.0 Hz, 1H), 7.52 (dd, *J* = 7.8, 12.6 Hz, 1H), 4.71 - 4.64 (m, 1H), 4.64 - 4.57 (m, 1H), 4.57 - 4.52 (m, 1H), 4.52 - 4.45 (m, 1H), 3.51 - 3.35 (m, 1H), 3.04 - 2.90 (m, 1H), 2.90 - 2.77 (m, 1H), 2.48 - 2.33 (m, 1H), 2.18 (tdd, *J* = 4.5, 9.0, 13.4 Hz, 1H).

Peak 3: 3-(5-fluoroisoquinolin-4-yl)-6-(2,2,2-trifluoroethyl)-1,5,6,7-tetrahydro-2H-cyclopenta[d]pyrimidine-2,4(3H)-dione: $t_R$ = 2.802 min, $[M+1]^+$ 329.9. **$^1$H NMR:** (400 MHz, METHANOL-d4) δ = 9.39 (d, *J* = 2.4 Hz, 1H), 8.37 (s, 1H), 8.09 (d, *J* = 8.3 Hz, 1H), 7.72 (dt, *J* = 4.8, 8.0 Hz, 1H), 7.57 - 7.48 (m, 1H), 3.09 (td, *J* = 8.8, 17.1 Hz, 1H), 3.02 - 2.87 (m, 2H), 2.86 - 2.73 (m, 1H), 2.60 - 2.44 (m, 3H).

Peak 4: 3-(5-fluoroisoquinolin-4-yl)-5-(2,2,2-trifluoroethyl)-1,5,6,7-tetrahydro-2H-cyclopenta[d]pyrimidine-2,4(3H)-dione: $t_R$ = 2.987 min, $[M+1]^+$ 329.9. **$^1$H NMR:** (400 MHz, METHANOL-d4) δ = 9.39 (d, *J* = 2.1 Hz, 1H), 8.38 (d, *J* = 2.8 Hz, 1H), 8.09 (d, *J* = 8.3 Hz, 1H), 7.73 (dt, *J* = 4.8, 8.1 Hz, 1H), 7.59 - 7.47 (m, 1H), 3.44 (br dd, *J* = 2.2, 3.2 Hz, 1H), 3.07 - 2.80 (m, 3H), 2.56 - 2.41 (m, 1H), 2.30 - 2.14 (m, 1H), 2.12 - 1.98 (m, 1H).

**Example 95:** Synthesis of 2-(3-(5-fluoroisoquinolin-4-yl)-2,4-dioxo-5-(2,2,2-trifluoroethyl)-2,3,4,5,6,7-hexahydro-1H-cyclopenta[d]pyrimidin-1-yl)acetonitrile **(95)**; [(3*M*,5*R or 5S*)-3-(5-Fluoroisoquinolin-4-yl)-2,4-dioxo-5-(2,2,2-trifluoroethyl)-2,3,4,5,6,7-hexahydro-1*H*-cyclopenta[*d*]pyrimidin-1-yl]acetonitrile **(95a)**; [(3*M*,5*R or 5S*)-3-(5-Fluoroisoquinolin-4-yl)-2,4-dioxo-5-(2,2,2-trifluoroethyl)-2,3,4,5,6,7-hexahydro-1*H*-cyclopenta[*d*]pyrimidin-1-yl]acetonitrile **(95b)**; [(3*P*,5*R or 5S*)-3-(5-Fluoroisoquinolin-4-yl)-2,4-dioxo-5-(2,2,2-trifluoroethyl)-2,3,4,5,6,7-hexahydro-1*H*-cyclopenta[*d*]pyrimidin-1-yl]acetonitrile **(95c)**, and [(3*P*,5*R or 5S*)-3-(5-Fluoroisoquinolin-4-yl)-2,4-dioxo-5-(2,2,2-trifluoroethyl)-2,3,4,5,6,7-hexahydro-1*H*-cyclopenta[*d*]pyrimidin-1-yl]acetonitrile **(95d)**




Step 1: To a mixture of 3-(5-fluoroisoquinolin-4-yl)-5-(2,2,2-trifluoroethyl)-1,5,6,7-tetrahydro-2H-cyclopenta[d]pyrimidine-2,4(3H)-dione (see Example 94) (380 mg, 1.05 mmol, 1.0 eq.) and $Cs_2CO_3$ (685 mg, 2.10 mmol, 2.0 eq.) in DMF (6 mL) was added 2-bromoacetonitrile (189 mg, 1.58 mmol, 1.5 eq.) and the reaction mixture was stirred at 25°C for 16 hrs. The mixture was filtered and the filtrate was purified by prep-HPLC ($NH_4HCO_3$) to give racemic 2-(3-(5-fluoroisoquinolin-4-yl)-2,4-dioxo-5-(2,2,2-trifluoroethyl)-2,3,4,5,6,7-hexahydro-1H-cyclopenta[d]pyrimidin-1-yl)acetonitrile **(95)**.

Step 2: Racemic 2-(3-(5-fluoroisoquinolin-4-yl)-2,4-dioxo-5-(2,2,2-trifluoroethyl)-2,3,4,5,6,7-hexahydro-1H-cyclopenta[d]pyrimidin-1-yl)acetonitrile **(95)** was separated by SFC (column: Lux cellulose-2 (100mmx4.6mm, 3μm); mobile phase A: $CO_2$; mobile phase B: EtOH(0.1% IPAm);

B%: 10% for 0.2 min, 10-50% for 2.2 min., 50% for 1.0 min., 50-10% for 0.6 min.) to give four peaks: $t_{R1}$ = 1.727 min.; $t_{R2}$ = 2.076 min.; $t_{R3}$ = 2.261 min. and $t_{R4}$ = 2.995 min.

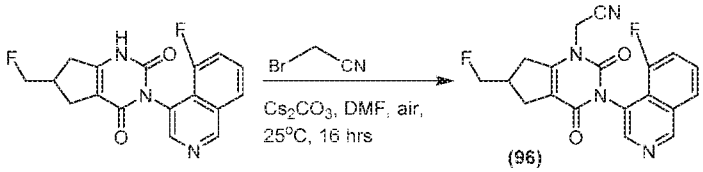
**Peak 1:** [(3*M*,5*R or 5S*)-3-(5-Fluoroisoquinolin-4-yl)-2,4-dioxo-5-(2,2,2-trifluoroethyl)-2,3,4,5,6,7-hexahydro-1*H*-cyclopenta[*d*]pyrimidin-1-yl]acetonitrile **(95a)**. **LCMS (Method 1):** $t_R$ = 2.414 min, $[M+1]^+$ 419.1. **SFC:** column: Lux cellulose-2 (100mmx4.6mm, 3µm); mobile phase A: $CO_2$; mobile phase B: EtOH(0.1% IPAm); B%: 10% for 0.2 min, 10-50% for 2.2 min., 50% for 1.0 min., 50-10% for 0.6 min.; $t_R$ = 1.674 min., ee% = 100%; **$^1$H NMR:** (400 MHz, CHLOROFORM-d) δ = 9.41 (br s, 1H), 8.45 (s, 1H), 7.96 (d, *J* = 8.3 Hz, 1H), 7.66 (dt, *J* = 4.8, 7.9 Hz, 1H), 7.43 (dd, *J* = 7.8, 12.3 Hz, 1H), 4.81 (s, 2H), 3.59 (br d, *J* = 8.0 Hz, 1H), 3.28 - 3.01 (m, 3H), 2.72 - 2.52 (m, 1H), 2.26 - 2.02 (m, 2H).

**Peak 2:** [(3*M*,5*R or 5S*)-3-(5-Fluoroisoquinolin-4-yl)-2,4-dioxo-5-(2,2,2-trifluoroethyl)-2,3,4,5,6,7-hexahydro-1*H*-cyclopenta[*d*]pyrimidin-1-yl]acetonitrile **(95b)**. **LCMS (Method 1):** $t_R$ = 2.413 min, $[M+1]^+$ 419.1. **SFC:** column: Lux cellulose-2 (100mmx4.6mm, 3µm); mobile phase A: $CO_2$; mobile phase B: EtOH(0.1% IPAm); B%: 10% for 0.2 min, 10-50% for 2.2 min., 50% for 1.0 min., 50-10% for 0.6 min.; $t_R$ = 2.037 min., ee% = 100%; **$^1$H NMR:** (400 MHz, CHLOROFORM-d) δ = 9.47 (br s, 1H), 8.50 (br s, 1H), 8.02 (br d, *J* = 8.1 Hz, 1H), 7.69 (dt, *J* = 4.8, 7.8 Hz, 1H), 7.47 (dd, *J* = 7.8, 12.2 Hz, 1H), 5.01 - 4.71 (m, 2H), 3.58 (br d, *J* = 6.0 Hz, 1H), 3.28 - 3.00 (m, 3H), 2.61 (br dd, *J* = 5.8, 12.9 Hz, 1H), 2.30 - 2.01 (m, 2H).

**Peak 3:** [(3*P*,5*R or 5S*)-3-(5-Fluoroisoquinolin-4-yl)-2,4-dioxo-5-(2,2,2-trifluoroethyl)-2,3,4,5,6,7-hexahydro-1*H*-cyclopenta[*d*]pyrimidin-1-yl]acetonitrile **(95c)**. **LCMS (Method 1):** $t_R$ = 2.405 min, $[M+1]^+$ 419.1. **SFC:** column: Lux cellulose-2 (100mmx4.6mm, 3µm); mobile phase A: $CO_2$; mobile phase B: EtOH(0.1% IPAm); B%: 10% for 0.2 min, 10-50% for 2.2 min., 50% for 1.0 min., 50-10% for 0.6 min.; $t_R$ = 2.194 min., ee% = 97.1%; **$^1$H NMR:** (400 MHz, CHLOROFORM-d) δ = 9.39 (br s, 1H), 8.45 (br s, 1H), 7.92 (d, *J* = 8.0 Hz, 1H), 7.63 (dt, *J* = 4.8, 8.0 Hz, 1H), 7.40 (dd, *J* = 7.8, 12.4 Hz, 1H), 4.81 (s, 2H), 3.58 (br d, *J* = 7.8 Hz, 1H), 3.25 - 3.00 (m, 3H), 2.68 - 2.53 (m, 1H), 2.25 - 2.07 (m, 2H).

**Peak 4:** [(3*P*,5*R or 5S*)-3-(5-Fluoroisoquinolin-4-yl)-2,4-dioxo-5-(2,2,2-trifluoroethyl)-2,3,4,5,6,7-hexahydro-1*H*-cyclopenta[*d*]pyrimidin-1-yl]acetonitrile **(95d)**. **LCMS (Method 1):** $t_R$ = 2.402 min, $[M+1]^+$ 419.1. **SFC:** column: Lux cellulose-2 (100mmx4.6mm, 3µm); mobile phase A: $CO_2$; mobile phase B: EtOH(0.1% IPAm); B%: 10% for 0.2 min, 10-50% for 2.2 min., 50% for 1.0 min., 50-10% for 0.6 min.; $t_R$ = 2.931 min., ee% = 100%; **$^1$H NMR:** (400 MHz, CHLOROFORM-d) δ = 9.39 (br s, 1H), 8.45 (br s, 1H), 7.92 (d, *J* = 8.0 Hz, 1H), 7.63 (dt, *J* = 4.8, 8.0 Hz, 1H), 7.40 (dd, *J* = 7.8, 12.4 Hz, 1H), 4.81 (s, 2H), 3.58 (br d, *J* = 7.8 Hz, 1H), 3.25 - 3.00 (m, 3H), 2.68 - 2.53 (m, 1H), 2.25 - 2.07 (m, 2H).

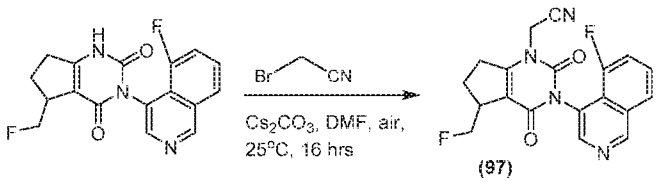
**Example 96:** Synthesis of 2-(3-(5-fluoroisoquinolin-4-yl)-6-(fluoromethyl)-2,4-dioxo-2,3,4,5,6,7-hexahydro-1H-cyclopenta[d]pyrimidin-1-yl)acetonitrile **(96)**




(96)

To the mixture of 3-(5-fluoroisoquinolin-4-yl)-6-(fluoromethyl)-1,5,6,7-tetrahydro-2H-cyclopenta[d]pyrimidine-2,4(3H)-dione (see Example 95) (50 mg, 0.15 mmol, 1.0 eq.) and $Cs_2CO_3$ (99 mg, 0.30 mmol, 2.0 eq.) in DMF (1 mL) was added 2-bromoacetonitrile (27 mg, 0.22 mmol, 1.5 eq.). The reaction mixture was stirred at 25°C for 16 hrs. The mixture was filtered. The filtrate was purified by prep-HPLC (HCOOH) to give 2-(3-(5-fluoroisoquinolin-4-yl)-6-(fluoromethyl)-2,4-dioxo-2,3,4,5,6,7-hexahydro-1H-cyclopenta[d]pyrimidin-1-yl)acetonitrile **(96)**. **LCMS (Method 13):** $t_R$ = 2.051 min, $[M+1]^+$ 369.0; **$^1$H NMR:** (400 MHz, CHLOROFORM-d) δ = 9.37 (d, *J* = 2.4 Hz, 1H), 8.44 (d, *J* = 1.8 Hz, 1H), 7.92 (d, *J* = 8.3 Hz, 1H), 7.62 (dt, *J* = 4.8, 8.0 Hz, 1H), 7.38 (dd, *J* = 7.8, 12.4 Hz, 1H), 4.94 - 4.83 (m, 1H), 4.79 - 4.70 (m, 1H), 4.68 - 4.60 (m, 1H), 4.58 - 4.48 (m, 1H), 4.46 - 4.38 (m, 1H), 3.40 - 3.25 (m, 1H), 3.18 - 2.97 (m, 3H), 2.69 (br dd, *J* = 3.3, 12.3 Hz, 1H).

**Example 97:** Synthesis of 2-(3-(5-fluoroisoquinolin-4-yl)-5-(fluoromethyl)-2,4-dioxo-2,3,4,5,6,7-hexahydro-1H-cyclopenta[d]pyrimidin-1-yl)acetonitrile **(97)**




(97)

To a mixture of 3-(5-fluoroisoquinolin-4-yl)-5-(fluoromethyl)-1,5,6,7-tetrahydro-2H-cyclopenta[d]pyrimidine-2,4(3H)-dione (see Example 95) (250 mg, 0.76 mmol, 1.0 eq.) and $Cs_2CO_3$ (494 mg, 1.52 mmol, 2.0 eq.) in DMF (5 mL) was added 2-bromoacetonitrile (136 mg, 1.14 mmol, 1.5 eq.). The reaction mixture was stirred at 25 °C for 16 hrs. The mixture was filtered and the filtrate purified by prep-HPLC ($NH_4HCO_3$) to give 2-(3-(5-fluoroisoquinolin-4-yl)-5-(fluoromethyl)-2,4-dioxo-2,3,4,5,6,7-hexahydro-1H-cyclopenta[d]pyrimidin-1-yl)acetonitrile **(97)**. **LCMS (Method 28):** $t_R$ = 1.171 min, $[M+1]^+$ 369.1; **$^1$H NMR:** (400 MHz, CHLOROFORM-d) δ = 9.38 (s, 1H), 8.46 (d, J = 10.4 Hz, 1H), 7.92 (br d, J = 8.3 Hz, 1H), 7.62 (dt, J = 4.8, 8.0 Hz, 1H), 7.39 (br dd, J = 7.8, 12.2 Hz, 1H), 4.97 - 4.85 (m, 1H), 4.84 - 4.69 (m, 2H), 4.68 - 4.56 (m, 1H), 3.68 - 3.48 (m, 1H), 3.28 - 3.15 (m, 1H), 3.14 - 3.02 (m, 1H), 2.59 - 2.44 (m, 1H), 2.39 - 2.24 (m, 1H).

**Biological Assays:**

Production of SARS-CoV-2 Main Protease expression plasmid

The coding sequence for SARS-CoV-2 main protease was codon-optimized for *E. coli* and synthesized by Integrated DNA Technologies. The sequence was amplified by PCR and cloned into the pGEX6P-1 vector, downstream of GST and an HRV 3C protease cleavage site, using the Gibson Assembly Master Mix kit (New England BioLabs, Inc). To ensure authentic termini, the amino acids AVLQ were added to the N-terminus of the main protease by addition of their coding sequence to the 5′ end of the gene product. This sequence reconstitutes the NSP4/5 cleavage site, resulting in auto-cleavage by the main protease protein product. Similarly, we added a gly-pro-$(his)_6$ tag to the C-terminus (the GP completes a non-consensus 3C cleavage site along with the C-terminus of the main protease which allows for cleavage of the poly-histidine tag after purification by HRV-3C protease, resulting in an authentic C-terminus). The expressed protein sequence (SEQ ID NO:1) is shown below (autocleavage site indicated with underline with a slash where the cleavage takes place; Mpro sequence in bold):

MSPILGYWKIKGLVQPTRLLLEYLEEKYEEHLYERDEGDKWRNKKFELGLEFPNLPYYIDGDVK
LTQSMAIIRYIADKHNMLGGCPKERAEISMLEGAVLDIRYGVSRIAYSKDFETLKVDFLSKLPEML
KMFEDRLCHKTYLNGDHVTHPDFMLYDALDVVLYMDPMCLDAFPKLVCFKKRIEAIPQIDKYLK
SSKYIAWPLQGWQATFGGGDHPPKSDLEVLFQGPLGSAVLQ/**SGFRKMAFPSGKVEGCMVQ**
**VTCGTTTLNGLWLDDVVYCPRHVICTSEDMLNPNYEDLLIRKSNHNFLVQAGNVQLRVIGHSM**
**QNCVLKLKVDTANPKTPKYKFVRIQPGQTFSVLACYNGSPSGVYQCAMRPNFTIKGSFLNGS**
**CGSVGFNIDYDCVSFCYMHHMELPTGVHAGTDLEGNFYGPFVDRQTAQAAGTDTTITVNVLA**
**WLYAAVINGDRWFLNRFTTTLNDFNLVAMKYNYEPLTQDHVDILGPLSAQTGIAVLDMCASL**
**KELLQNGMNGRTILGSALLEDEFTPFDVVRQCSGVTFQ**GPHHHHHH*

Production of SARS-CoV-2 Main Protease protein

Hi Control BL21(DE3) cells (Lucigen Corporation) were transformed with the expression plasmid via heat shock at 42 °C followed by recovery in LB media at 37 °C for one hour. Transformed cells were selected via growth on LB agar plates containing 100 µg/mL carbenicillin. We used Hi Control cells as we observed expression of the main protease was toxic in other standard *E. coli* cell lines. A single colony was used to start an overnight culture in LB + carbenicillin media. This culture was used to inoculate 1 L cultures in Terrific Broth, supplemented with 50 mM sodium phosphate pH 7.0 and 100 µg/mL carbenicillin. These cultures grew in Fernbach flasks at 37 °C while shaking at 225 rpm, until the OD600 reached approximately 2.0, at which point the temperature was reduced to 20 °C and 0.5 mM IPTG (final) was added to each culture. The cells were allowed to grow overnight.

The next day, the cultures were centrifuged at 6,000 x *g* for 20 minutes at 4 °C, and the resulting cell pellets were resuspended in IMAC_A buffer (50 mM Tris pH 8.0, 400 mM NaCl, 1 mM Tris(2-carboxyethyl)phosphine (TCEP)). Cells were lysed with two to three passes through

a cell homogenizer (Microfluidics model M-110P) at 18,000 psi. The lysate was clarified with centrifugation at 42,000 x *g* for 30 minutes and the cleared lysate was loaded onto 3 x 5 mL HiTrap Ni-NTA silica gel chromatographys (GE) pre-equilibrated with IMAC_A buffer, using an AKTA Pure FPLC. After loading, the silica gel chromatographys were washed with IMAC_A buffer until the A280 levels reached a sustained baseline. The protein was then eluted with a linear gradient with IMAC_B buffer (50 mM Tris pH 8.0, 400 mM NaCl, 500 mM imidazole, 1 mM TCEP) across 25 silica gel chromatography volumes, while 2 mL fractions were collected automatically. Peak fractions were analyzed by SDS-PAGE and those containing SARS-CoV-2 main protease were pooled. Importantly, auto-cleavage of the N-terminal GST tag was observed, and the eluted protein had a mass consistent with SARS-CoV-2 main protease along with the C-terminal GP-6xHis tag, as determined by ESI-LC/MS.

Pooled fractions were treated with HRV 3C protease (also known as “PreScission” protease) while dialyzing against IMAC_A buffer at room temperature (2 x 2 L dialyses for 1 hour each). Room temperature dialysis was important as we observed a tendency for the main protease protein to precipitate with prolonged exposure to 4 °C temperatures. Cleavage of the C-terminal GP-6xHis tag was confirmed after 2 hours by electrospray ionization-liquid chromatography/mass spectrometry (ESI-LC/MS). The dialyzed and cleaved protein was then re-run through a 5 mL HiTrap Ni-NTA silica gel chromatography pre-equilibrated with IMAC_A buffer. The main protease eluted in the flow-through as expected.

The protein was then concentrated to approximately 5 mL and loaded onto a Superdex 75 16/60 silica gel chromatography pre-equilibrated with SEC Buffer (25 mM HEPES pH 7.5, 150 mM NaCl, 1 mM TCEP). The protein was run through the silica gel chromatography at 1 mL/min and eluted as one peak well in the included volume (at ~75 mL). Fractions from this peak were analyzed by SDS-PAGE and pure fractions were pooled and concentrated to 10 mg/mL, aliquotted, and stored at -80 °C.

<u>Rapid-Fire MS Biochemical Assay measuring $M^{pro}$ activity (12.5nM Mpro)</u>

Assay buffer preparation: 50 mM HEPES pH 7.3, 150 mM NaCl, 1 mM EDTA, 0.01% pluronic f-127(Catalog # 59005, Biotium) was prepared using UltraPure Distilled Water (Catalog # 10977015, Thermo Scientific). The $M^{pro}$ enzyme stock consisted of a 25nM solution of $M^{pro}$ made in buffer. The substrate solution stock consisted of a 10 µM solution of $M^{pro}$ peptide (AVLSGFRKK (SEQ ID NO:2); Purchased from Vivitide) made in buffer. The quench solution consisted of a 200 nM solution of 2% acetic acid spiked with 200 nM of the internal standard peptide ($^{13}$C AVLQ; Purchased from Vivitide).

The Rapidfire Mass Spectrometry setup consisted of a Rapidfire autosampler platform (Agilent) coupled with a Sciex 6500 QQQ Mass Spectrometer (Sciex). A C18 Rapidfire cartridge type C (Catalog # G9205A) was used in the analysis, the load solvent consisted of 0.1% formic acid flowed at 1.5 mL/min and the elute solvent consisted of 75% acetonitrile, 5% isopropal alcohol,

20% ultrapure distilled water with 0.1% formic acid. MS transitions were created for the substrate peptide AVLQSGFRKK (SEQ ID NO:3) (378.6 Da – 482.6 Da), product peptide AVLQ (430.3 Da- 260.4Da) and the internal standard peptide $^{13}$C AVLQ (434.3 Da- 288.3 Da)
Compound plates were prepared in 384 Echo plate (cat# LPL0200, Labcyte) and the starting concentration of compound was 10 mM, then 1 to 3 serial dilution in 100% DMSO, 8 µl/ well).
To generate assay ready plates, 50 nl compounds were transferred to a 384-well clear assay plate using an Echo® 555 Liquid Handler (Labcyte). 5 µL of M$^{pro}$ enzyme solution was dispensed in each well throughout entire plate (Col 1-24) using buffer distributor (Multidrop ComB1 from Thermo Scientific) with 5 µL of assay buffer only dispensed to no enzyme control in Col 24. Enzyme allowed to preincubate with compounds for 15 minutes at room temperature (25°C) prior to starting reaction by addition of 5 µL of substrate peptide solution to all wells in the plate (Col 1-24). The plates were incubated for 30 minutes at room temperature with a final volume of 10 µl/ well buffer, such that the compound concentration was 200-fold of final concentration. Final assay concentrations were 12.5 nM M$^{pro}$ and 5 µM substrate peptide. After incubation, reaction was quenched by adding 40 µL of quench solution and plates were analyzed by the Rapidfire/Sciex MS platform.
Mass spectral data was analyzed as ratiometric measurements between the integrated areas of the peak for the product peptide and the labeled internal standard peptide for each sample (Multiquant, Sciex). Percent activity measurements were calculated comparing each ratio of product/Internal standard from compound treatments to the ratios calculated for the DMSO only wells with and without enzyme (Neutral and active controls respectively). M$^{pro}$ Inhibitor qualified absolute $IC_{50}$ values (concentration of inhibitor that inhibits M$^{pro}$ activity at least 50%), were determined with 8 inhibitor concentrations measured in duplicate for each inhibitor. The qualified absolute $IC_{50}$ was calculated by non-linear regression analysis to sigmoidal-logistic curves by HELIOS (PROD 2) system.

<u>Rapid-Fire MS Biochemical Assay measuring M$^{pro}$ activity (5nM Mpro)</u>

Assay buffer preparation: 50 mM HEPES pH 7.3, 150 mM NaCl, 1 mM EDTA, 0.01% pluronic f-127(Catalog # 59005, Biotium) was prepared using UltraPure Distilled Water (Catalog # 10977015, Thermo Scientific). The Mpro enzyme stock consisted of a 10 nM solution of Mpro made in buffer. The substrate solution stock consisted of a 10 µM solution of Mpro peptide (AVLSGFRKK (SEQ ID NO:2); Purchased from Vivitide) made in buffer. The quench solution consisted of a 2% acetic acid solution spiked with 200 nM of the internal standard peptide (13C AVLQ; Purchased from Vivitide).
The Rapidfire Mass Spectrometry setup consisted of a Rapidfire autosampler platform (Agilent) coupled with a Sciex 6500 QQQ Mass Spectrometer (Sciex). A C18 Rapidfire cartridge type C (Catalog # G9205A) was used in the analysis, the load solvent consisted of 0.1% formic acid flowed at 1.5 mL/min and the elute solvent consisted of 75% acetonitrile, 5% isopropal alcohol,

20% ultrapure distilled water with 0.1% formic acid. MS transitions were created for the substrate peptide AVLQSGFRKK (SEQ ID NO:3) (378.6 Da – 482.6 Da), product peptide AVLQ (430.3 Da- 260.4Da) and the internal standard peptide 13C AVLQ (434.3 Da- 288.3 Da) Compound plates were prepared in 384 Echo plate (cat# LPL0200, Labcyte) and the starting concentration of compound was 10 mM, then 1 to 3 serial dilution in 100% DMSO, 8 µl/ well). To generate assay ready plates, 10 nl of compound were transferred to a 384-well clear assay plate using an Echo® 555 Liquid Handler (Labcyte). 5 µL of Mpro enzyme solution was dispensed in each well throughout entire plate (Col 1-24) using buffer distributor (Multidrop Combi from Thermo Scientific) with 5 µL of assay buffer only dispensed to no enzyme control in Col 24. Enzyme allowed to preincubate with compounds for 15 minutes at room temperature (25□C) prior to starting reaction by addition of 5 µL of substrate peptide solution to all wells in the plate (Col 1-24). The plates were incubated for 120 minutes at room temperature with a final volume of 10 µl/ well buffer, such that the compound concentration was diluted 1000-fold to final concentration. Final assay concentrations were 5 nM Mpro and 5 µM substrate peptide. After incubation, reaction was quenched by adding 40 µL of quench solution and plates were analyzed by the Rapidfire/Sciex MS platform.

Mass spectral data was analyzed as ratiometric measurements between the integrated areas of the peak for the product peptide and the labeled internal standard peptide for each sample (Multiquant, Sciex). Percent activity measurements were calculated comparing each ratio of product/Internal standard from compound treatments to the ratios calculated for the DMSO only wells with and without enzyme (Neutral and active controls respectively). $M^{pro}$ Inhibitor qualified absolute $IC_{50}$ values (concentration of inhibitor that inhibits $M^{pro}$ activity at least 50%), were determined with 8 inhibitor concentrations measured in duplicate for each inhibitor. The qualified absolute $IC_{50}$ was calculated by non-linear regression analysis to sigmoidal-logistic curves by HELIOS (PROD 2) system.

**Biological Data:**

Table 2 lists the corresponding $IC_{50}$ (µM) values obtained using the Rapid-Fire MS Biochemical Assay measuring $M^{pro}$ activity (12.5nM Mpro) described above.

Table 2

| Compound Number | $IC_{50}$ |
|---|---|
| 1 | 0.030 |
| 2 | 0.031 |
| 3 | 0.016 |
| 4 | 0.068 |
| 5 | 0.42 |
| 6 | 0.23 |

| Compound Number | $IC_{50}$ |
|---|---|
| 7 | 0.18 |
| 8 | 0.15 |
| 9 | 0.13 |
| 10 | 0.69 |
| 11 | 0.39 |
| 12 | 1.3 |
| 13 | 2.5 |
| 14 | 5.9 |
| 15 | 2.1 |

Table 3 lists the corresponding $IC_{50}$ (μM) values obtained using the Rapid-Fire MS Biochemical Assay measuring $M^{pro}$ activity (5nM Mpro) described above.

Table 3

| Compound Number | Rapid-Fire Assay $IC_{50}$ | Compound Number | Rapid-Fire Assay $IC_{50}$ (μM) |
|---|---|---|---|
| 1 | B | 53a | A |
| 2 | B | 53b | D |
| 3 | A | 54 | B |
| 4 | B | 55a | D |
| 5 | B | 55b | D |
| 6 | B | 56a | C |
| 7 | B | 56b | D |
| 8 | C | 57 | D |
| 9 | B | 58 | C |
| 10 | B | 59 | D |
| 11 | C | 60 | D |
| 12 | C | 61 | D |
| 13 | D | 62 | C |
| 14 | D | 63 | D |
| 15 | D | 64 | C |
| 16 | A | 65 | C |
| 16a | A | 66 | D |
| 16b | D | 67 | B |
| 17 | C | 68 | B |

| Compound Number | Rapid-Fire Assay $IC_{50}$ | Compound Number | Rapid-Fire Assay $IC_{50}$ (μM) |
|---|---|---|---|
| 18 | B | 69 | D |
| 19 | C | 70 | D |
| 20 | nd | 71 | D |
| 20a | A | 72 | B |
| 20b | D | 73 | D |
| 21 | nd | 74 | D |
| 21a | A | 75 | A |
| 21b | A | 76 | A |
| 21c | D | 77a | B |
| 21d | D | 77b | D |
| 22 | B | 78a | A |
| 23 | C | 78b | A |
| 24 | nd | 78c | D |
| 24a | A | 78d | C |
| 24b | D | 79a | B |
| 25 | C | 79b | D |
| 26 | D | 80 | B |
| 27 | nd | 81 | C |
| 27a | B | 82 | B |
| 27b | B | 83 | D |
| 27c | D | 84 | B |
| 27d | D | 85 | D |
| 28a | A | 86a | B |
| 28b | A | 86b | A |
| 28c | C | 86c | D |
| 28d | D | 86d | D |
| 29a | A | 87a | A |
| 29b | A | 87b | A |
| 29c | C | 87c | C |
| 29d | C | 87d | C |
| 30a | B | 88a | C |
| 30b | D | 88b | C |
| 31 | C | 88c | D |
| 32 | D | 88d | D |

| Compound Number | Rapid-Fire Assay $IC_{50}$ | Compound Number | Rapid-Fire Assay $IC_{50}$ (μM) |
|---|---|---|---|
| 33 | B | 89 | B |
| 34 | C | 90 | D |
| 35 | B | 91a | B |
| 36 | B | 91b | D |
| 37 | A | 92a | B |
| 38 | D | 92b | D |
| 39 | D | 93a | A |
| 40 | A | 93b | D |
| 41 | B | 94 | nd |
| 42 | B | 94a | A |
| 43 | C | 94b | A |
| 44 | A | 94c | D |
| 45 | C | 94d | D |
| 46 | B | 95 | nd |
| 47 | C | 95a | A |
| 48 | D | 95b | A |
| 49 | D | 95c | D |
| 50 | C | 95d | D |
| 51 | D | 96 | C |
| 52 | A | 97 | C |

Note: A refers to $IC_{50}$ values < 20 nM;

B refers to $IC_{50}$ values from 20 nM to 200 nM;

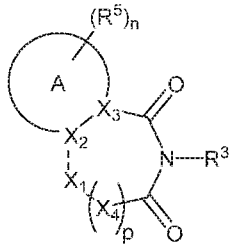
C refers to $IC_{50}$ values from > 200 nM to 1000 nM; and

D refers to $IC_{50}$ values >1000 nM

nd refers to not determined

**CLAIMS**

1. A compound of Formula (I) or a pharmaceutically acceptable salt or stereoisomer thereof,



(I)

wherein:

the dashed line between $X_1$ and $X_2$ is a single bond or a double bond;

$X_1$ is $NR^1$, N, $C(R^{2a})_2$, $CR^{2a}$, O, $C=C(R^{2a})_2$, $CR^{2a}R^{2b}$, a spiro attached 4 to 6 membered heterocycloalkyl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$, O, C(=O), S and $S(=O)_2$, or a spiro attached $C_3$-$C_8$cycloalkyl, and wherein the heterocycloalkyl and $C_3$-$C_8$cycloalkyl are unsubstituted or are substituted with 1 or 2 OH groups;

$X_2$ is N, C or CH;

$X_3$ is N, C or CH;

$X_4$ is $C(R^{2a})_2$ or $C=C(R^{2a})_2$;

$R^1$ is H, $C_1$-$C_6$alkyl, $C_3$-$C_8$cycloalkyl, 4 to 7 membered heterocycloalkyl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$, O and S, a $C_1$-$C_6$alkyl substituted with one or more $R^{12}$ or a $C_1$-$C_6$alkenyl substituted with one or more $R^{12}$, and wherein the cycloalkyl and heterocycloalkyl are unsubstituted or the cycloalkyl and heterocycloalkyl are substituted with 1 or 2 substituents independently selected from the group consisting of CN, -C(=O)OH, $NH_2$, OH, $C_1$-$C_6$haloalkyl, $C_1$-$C_6$alkyl or $C_1$-$C_6$alkyl substituted with -C(=O)OH, -OH, CN or $NH_2$;

each $R^{2a}$ is independently selected from the group consisting of H, CN, $NH_2$, $C_1$-$C_6$alkyl and $C_1$-$C_6$alkyl substituted with -C(=O)OH, -OH, CN or $NH_2$;

$R^{2b}$ is H, $C_1$-$C_6$alkyl, $C_3$-$C_8$cycloalkyl or 4 to 7 membered heterocycloalkyl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$, O and S, and wherein the $C_3$-$C_8$cycloalkyl and heterocycloalkyl are unsubstituted or the $C_3$-$C_8$cycloalkyl and heterocycloalkyl are substituted with 1, 2, 3 or 4 substituents independently selected from the group consisting of $C_1$-$C_6$alkyl, OH and $-N(R^7)_2$;

$R^3$ is selected from the group consisting of:

i) $-(CH_2)_{0\text{-}6}CHR^{13}R^{14}$;

ii) benzyl which is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

iii) a 6 membered heteroaryl with an attachment point at a carbon atom ring member and a N heteroatom as a ring member which is located at a beta

(β) position relative to the attachment point, wherein the 6 membered heteroaryl has 0, 1 or 2 additional N heteroatoms as ring members, and wherein the 6 membered heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

iv) a 10 membered bicyclic heteroaryl with an attachment point at a carbon atom ring member and a N heteroatom as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 10 membered bicyclic heteroaryl has 0, 1, 2 or 3 additional N heteroatoms as ring members, and wherein the 10 membered bicyclic heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

v) a 10 membered bicyclic heteroaryl with an attachment point at a carbon atom ring member and a N heteroatom as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 10 membered bicyclic heteroaryl further has 0, 1, 2, 3, or 4 ring members each independently selected from N, O and S, and wherein the 10 membered bicyclic heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

vi) a 9 membered bicyclic heteroaryl with an attachment point at a carbon atom ring member and a N heteroatom as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 9 membered bicyclic heteroaryl has 0, 1, 2, 3 or 4 additional N heteroatoms as ring members, and wherein the 9 membered bicyclic heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

vii) a 9 membered bicyclic heteroaryl with an attachment point at a carbon atom ring member and a N heteroatom as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 9 membered bicyclic heteroaryl further has 0, 1, 2, 3, or 4 ring members each independently selected from N, $NR^6$, O and S, and wherein the 9 membered bicyclic heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

viii) a 5 or 6 membered heterocycloalkyl with an attachment point at a carbon atom ring member and a $NR^6$ as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 5 or 6 membered heterocycloalkyl further has 0, 1, or 2 ring members each independently selected from N, $NR^6$, O and S, and wherein the 5 or 6 membered heterocycloalkyl is unsubstituted, substituted with 1 or 2 oxo, or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo;

ix) a 5 or 6 membered heterocyclyl with an attachment point at a carbon atom ring member and a $NR^6$ as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 5 or 6 membered heterocyclyl further has 0, 1, or 2 ring members each independently selected from N, $NR^6$, O and S, and wherein the 5 or 6 membered heterocyclyl is unsubstituted, substituted with 1 or 2 oxo, or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo;

x) a 9 or 10 membered bicyclic heterocyclyl with an attachment point at a carbon atom ring member and a $NR^6$ as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 9 or 10 membered heterocyclyl further has 0, 1, 2, 3, or 4 ring members each independently selected from N, $NR^6$, O and S, and wherein the 9 or 10 membered heterocyclyl is unsubstituted, substituted with 1 or 2 oxo, or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo;

xi) a 9 or 10 membered bicyclic heterocyclyl with an attachment point at a carbon atom ring member and a O heteroatom as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 9 or 10 membered heterocyclyl further has 0, 1, 2, 3, or 4 ring members each independently selected from N, $NR^6$, O and S, and wherein the 9 or 10 membered heterocyclyl is unsubstituted, substituted with 1 or 2 oxo, or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo;

xii) a 6 membered heteroaryl wherein 1, 2 or 3 ring members are each independently selected from N, O and S, and wherein the 6 membered heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

xiii) a 9 or 10 membered bicyclic heteroaryl wherein 1, 2, 3, 4 or 5 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 9 or 10 membered bicyclic heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

xiv) a 5 or 6 membered heterocycloalkyl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 5 or 6 membered heterocycloalkyl is unsubstituted, substituted with 1 or 2 oxo, or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo;

xv) a 5 or 6 membered heterocyclyl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 5 or 6 membered heterocyclyl is unsubstituted, substituted with 1 or 2 oxo, or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo;

xvi) a 6 membered heterocyclyl with an attachment point at a carbon atom ring member and a carbon atom as a ring member which is substituted with

oxo and located at a beta (β) position relative to the attachment point, wherein the 6 membered heterocyclyl further has 1 or 2 ring members each independently selected from N, $NR^6$, O and S, and wherein the 6 membered heterocyclyl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with an oxo;

xvii) a 9 or 10 membered bicyclic heterocyclyl wherein 1, 2, 3, 4 or 5 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 9 or 10 membered bicyclic heterocyclyl is unsubstituted, substituted with 1 or 2 oxo, or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo;

and

xviii) a 10 membered bicyclic heterocyclyl with an attachment point at a carbon atom ring member and a carbon atom as a ring member which is substituted with oxo and located at a beta (β) position relative to the attachment point, wherein the 10 membered heterocyclyl further has 1, 2, 3, or 4 ring members each independently selected from N, $NR^6$, O and S, and wherein the 10 membered heterocyclyl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with an oxo;

Ring A is selected from the group consisting of:

i) phenyl;

ii) a 5 or 6 membered heteroaryl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S;

iii) $C_5$-$C_6$cycloalkenyl;

iv) 5 or 6 membered heterocyclyl wherein 1, 2 or 3 ring members are each independently selected from W, Y and Z, wherein W is $X_2$, $NR^6$, O, S, S=O or $S(=O)_2$, $X_2$ is N; Y is $NR^6$, O, S, S=O or $S(=O)_2$ and Z is $NR^6$, O or S, and wherein the 5 or 6 membered heterocyclyl is optionally substituted with oxo;

v) a 9 or 10 membered bicyclic heterocyclyl wherein 1, 2, 3, 4 or 5 ring members are each independently selected from N, $NR^6$, O and S;

vi) a 5 or 6 membered heterocycloalkyl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S and wherein the 5 or 6 membered heterocycloalkyl is optionally substituted with oxo;

and

vii) a 9 or 10 membered bicyclic heteroaryl wherein 1, 2, 3, 4 or 5 ring members are each independently selected from N, O and S;

each $R^4$ is independently selected from the group consisting of H, -C(=O)N($R^7$)$_2$, -C(=O)OH, -N($R^7$)$_2$, -CN, -OH, -S(=O)$_2$$R^6$, -S(=O)$_2$N($R^7$)$_2$, -C(=O)N$R^7$$R^6$,  , $C_1$-$C_6$alkyl, halo, phenyl, $C_3$-$C_8$cycloalkyl, 4 to 6 membered heterocycloalkyl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S, 5 or 6 membered heteroaryl wherein 1, 2 or 3 ring members are each independently selected from N, O and S, and $C_1$-$C_6$alkyl substituted with $NH_2$, CN or OH, and wherein the phenyl, heterocycloalkyl and heteroaryl are unsubstituted or are substituted with 1 or 2 OH groups;

each $R^5$ is independently selected from the group consisting of -OH, -N$R^7$$R^8$, -NR6C(=O)C2-C6alkenyl, -$SF_5$, -C(=O)N($R^7$)$_2$, $C_1$-$C_6$alkyl, $C_1$-$C_6$haloalkyl, halo, $C_1$-$C_6$haloalkoxy, $C_1$-$C_6$alkoxy, $C_3$-$C_8$cycloalkyl, 4 to 6 membered heterocycloalkyl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S, a 5 or 6 membered heteroaryl wherein 1, 2 or 3 ring members are each independently selected from N, O and S, and a $C_1$-$C_6$alkyl substituted with CN, $NH_2$ or OH, and wherein the cycloalkyl and heterocycloalkyl are unsubstituted or are substituted with 1, 2, 3 or 4 $R^9$;

each $R^6$ is independently selected from the group consisting of H, $C_1$-$C_6$alkyl, -S(=O)$_2$N($R^7$)$_2$, -C(=O)N($R^7$)$_2$ and $C_1$-$C_6$alkyl substituted with –OH, -O$R^7$, CN or –C(=O)OH;

each $R^7$ is independently selected from the group consisting of H and $C_1$-$C_6$alkyl;

$R^8$ is H, $C_1$-$C_6$alkyl, $C_3$-$C_8$cycloalkyl or 4 to 6 membered heterocycloalkyl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S, and wherein the cycloalkyl and heterocycloalkyl are unsubstituted or are substituted with 1, 2, 3 or 4 $R^9$;

each $R^9$ is independently selected from the group consisting of halo, N$R^{10}$$R^{11}$, -C(=O)OH, -C(=O)N($R^7$)$_2$ and $C_1$-$C_6$alkyl substituted with -OH or -N($R^7$)$_2$;

$R^{10}$ is H or $C_1$-$C_6$alkyl;

$R^{11}$ is H, $C_1$-$C_6$alkyl or -S(=O)$_2$$C_1$-$C_6$alkyl;

each $R^{12}$ is independently selected from the group consisting of CN, $NH_2$, -OH, -C(=O)OH, -C(=O)O$R^{10}$, -C(=O)N($R^7$)$_2$, -$C_1$-$C_6$alkoxy, $C_1$-$C_6$alkyl, halo, $C_1$-$C_6$haloalkyl, $C_3$-$C_8$cycloalkyl, a 5 or a 6 membered heteroaryl wherein 1, 2, 3, or 4 ring members are each independently selected from N, $NR^6$, O and S, and a 3 to 6 membered heterocycloalkyl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$, O and S, and wherein the cycloalkyl, heteroaryl and heterocycloalkyl are unsubstituted or are substituted with 1, 2 or 3

substituents independently selected from the group consisting of CN, -C(=O)OH, $NH_2$, OH, halo and $C_1$-$C_6$alkyl;

$R^{13}$ is H, -C(=O)N($R^7$)$_2$, or a 5 or 6 membered heteroaryl wherein 1, 2 3 or 4 ring members are each independently selected from N, $NR^6$, O and S;

$R^{14}$ is selected from the group consisting of

i) a 5 or 6 membered heterocyclyl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 5 or 6 membered heterocyclyl is unsubstituted, substituted with 1 or 2 oxo or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo;

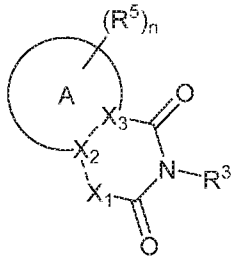
and

ii) a 5 or a 6 membered heteroaryl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 5 or a 6 membered heteroaryl is unsubstituted, or is substituted with 1, 2, 3 or 4 $R^4$;

p is 0, 1 or 2, and

n is 0, 1, 2, 3 or 4.

2. The compound of claim 1, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein p is 0 and the compound of Formula (I) has the structure of Formula (IA):



(IA),

where Ring A, $X_1$, $X_2$, $X_3$, $R^3$, $R^5$, n and the dashed line between $X_1$ and $X_2$ are as defined in Claim 1.

3. The compound of claim 1 or claim 2, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

the dashed line between $X_1$ and $X_2$ is a single bond or a double bond;

$X_1$ is $NR^1$, N, C($R^{2a}$)$_2$, C$R^{2a}$, O, C=C($R^{2a}$)$_2$, C$R^{2a}R^{2b}$, a spiro attached 4 to 6 membered heterocycloalkyl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$, O, C(=O), S and S(=O)$_2$, or a spiro attached $C_3$-$C_8$cycloalkyl, and wherein the heterocycloalkyl and $C_3$-$C_8$cycloalkyl are unsubstituted or are substituted with 1 or 2 OH groups;

$X_2$ is N, C or CH;

$X_3$ is N, C or CH;

$R^1$ is H, $C_1$-$C_6$alkyl, $C_3$-$C_8$cycloalkyl, 4 to 7 membered heterocycloalkyl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$, O and S, a $C_1$-$C_6$alkyl substituted with one or more $R^{12}$ or a $C_1$-$C_6$alkenyl substituted with one or more $R^{12}$, and wherein the cycloalkyl and heterocycloalkyl are unsubstituted or the cycloalkyl and heterocycloalkyl are substituted with 1 or 2 substituents independently selected from the group consisting of CN, -C(=O)OH, $NH_2$, OH, $C_1$-$C_6$haloalkyl, $C_1$-$C_6$alkyl or $C_1$-$C_6$alkyl substituted with -C(=O)OH, -OH, CN or $NH_2$;

each $R^{2a}$ is independently selected from the group consisting of H, CN, $NH_2$, $C_1$-$C_6$alkyl and $C_1$-$C_6$alkyl substituted with -C(=O)OH, -OH, CN or $NH_2$;

$R^{2b}$ is H, $C_1$-$C_6$alkyl, $C_3$-$C_8$cycloalkyl or 4 to 7 membered heterocycloalkyl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$, O and S, and wherein the $C_3$-$C_8$cycloalkyl and heterocycloalkyl are unsubstituted or the $C_3$-$C_8$cycloalkyl and heterocycloalkyl are substituted with 1, 2, 3 or 4 substituents independently selected from the group consisting of $C_1$-$C_6$alkyl, OH and -$N(R^7)_2$;

$R^3$ is selected from the group consisting of:

i) a 6 membered heteroaryl with an attachment point at a carbon atom ring member and a N heteroatom as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 6 membered heteroaryl has 0, 1 or 2 additional N heteroatoms as ring members, and wherein the 6 membered heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

ii) a 10 membered bicyclic heteroaryl with an attachment point at a carbon atom ring member and a N heteroatom as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 10 membered bicyclic heteroaryl has 0, 1, 2 or 3 additional N heteroatoms as ring members, and wherein the 10 membered bicyclic heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

iii) a 6 membered heteroaryl wherein 1, 2 or 3 ring members are each independently selected from N, O and S, and wherein the 6 membered heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

iv) a 9 or 10 membered bicyclic heteroaryl wherein 1, 2, 3, 4 or 5 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 9 or 10 membered bicyclic heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

v) a 9 or 10 membered bicyclic heterocyclyl with an attachment point at a carbon atom ring member and a $NR^6$ as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 9 or 10

membered heterocyclyl further has 0, 1, 2, 3, or 4 ring members each independently selected from N, $NR^6$, O and S, and wherein the 9 or 10 membered heterocyclyl is unsubstituted, substituted with 1 or 2 oxo, or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo;

vi) a 9 or 10 membered bicyclic heterocyclyl wherein 1, 2, 3, 4 or 5 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 9 or 10 membered bicyclic heterocyclyl is unsubstituted, substituted with 1 or 2 oxo, or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo;

and

vii) a 10 membered bicyclic heterocyclyl with an attachment point at a carbon atom ring member and a carbon atom as a ring member which is substituted with oxo and located at a beta (β) position relative to the attachment point, wherein the 10 membered heterocyclyl further has 1, 2, 3, or 4 ring members each independently selected from N, $NR^6$, O and S, and wherein the 10 membered heterocyclyl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with an oxo;

Ring A is selected from the group consisting of:

i) phenyl;

ii) a 5 or 6 membered heteroaryl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S;

iii) $C_5$-$C_6$cycloalkenyl;

iv) 5 or 6 membered heterocyclyl wherein 1, 2 or 3 ring members are each independently selected from W, Y and Z, wherein W is $X_2$, $NR^6$, O, S, S=O or $S(=O)_2$, $X_2$ is N; Y is $NR^6$, O, S, S=O or $S(=O)_2$ and Z is $NR^6$, O or S, and wherein the 5 or 6 membered heterocyclyl is optionally substituted with oxo;

v) a 9 or 10 membered bicyclic heterocyclyl wherein 1, 2, 3, 4 or 5 ring members are each independently selected from N, $NR^6$, O and S;

vi) a 5 or 6 membered heterocycloalkyl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 5 or 6 membered heterocycloalkyl is optionally substituted with oxo;

and

vii) a 9 or 10 membered bicyclic heteroaryl wherein 1, 2, 3, 4 or 5 ring members are each independently selected from N, O and S;

each $R^4$ is independently selected from the group consisting of -C(=O)N($R^7$)$_2$, -C(=O)OH, -N($R^7$)$_2$, -CN, -OH, -S(=O)$_2$$R^6$, -S(=O)$_2$N($R^7$)$_2$, -C(=O)N$R^7$$R^6$,  , $C_1$-$C_6$alkyl, halo, phenyl, $C_3$-$C_8$cycloalkyl, 4 to 6 membered heterocycloalkyl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S, 5 or 6 membered heteroaryl wherein 1, 2 or 3 ring members are each independently selected from N, O and S, and $C_1$-$C_6$alkyl substituted with $NH_2$, CN or OH, and wherein the phenyl, heterocycloalkyl and heteroaryl are unsubstituted or are substituted with 1 or 2 OH groups;

each $R^5$ is independently selected from the group consisting of -OH, -N$R^7$$R^8$, -NR6C(=O)C2-C6alkenyl, $-SF_5$, -C(=O)N($R^7$)$_2$, $C_1$-$C_6$alkyl, $C_1$-$C_6$haloalkyl, halo, $C_1$-$C_6$haloalkoxy, $C_1$-$C_6$alkoxy, $C_3$-$C_8$cycloalkyl, 4 to 6 membered heterocycloalkyl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S, a 5 or 6 membered heteroaryl wherein 1, 2 or 3 ring members are each independently selected from N, O and S, and $C_1$-$C_6$alkyl substituted with CN, $NH_2$ or OH, and wherein the cycloalkyl and heterocycloalkyl are unsubstituted or are substituted with 1, 2, 3 or 4 $R^9$;

each $R^6$ is independently selected from the group consisting of H, $C_1$-$C_6$alkyl, -S(=O)$_2$N($R^7$)$_2$, -C(=O)N($R^7$)$_2$ and $C_1$-$C_6$alkyl substituted with –OH, -O$R^7$, CN or –C(=O)OH;

each $R^7$ is independently selected from the group consisting of H and $C_1$-$C_6$alkyl;

$R^8$ is H, $C_1$-$C_6$alkyl, $C_3$-$C_8$cycloalkyl or 4 to 6 membered heterocycloalkyl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S, and wherein the cycloalkyl and heterocycloalkyl are unsubstituted or are substituted with 1, 2, 3 or 4 $R^9$;

each $R^9$ is independently selected from the group consisting of halo, N$R^{10}$$R^{11}$, -C(=O)OH, -C(=O)N($R^7$)$_2$ and $C_1$-$C_6$alkyl substituted with -OH or -N($R^7$)$_2$;

$R^{10}$ is H or $C_1$-$C_6$alkyl;

$R^{11}$ is H, $C_1$-$C_6$alkyl or -S(=O)$_2$$C_1$-$C_6$alkyl;

each $R^{12}$ is independently selected from the group consisting of CN, $NH_2$, -OH, -C(=O)OH, -C(=O)O$R^{10}$, -C(=O)N($R^7$)$_2$, -$C_1$-$C_6$alkoxy, $C_1$-$C_6$alkyl, halo, $C_1$-$C_6$haloalkyl, $C_3$-$C_8$cycloalkyl, a 5 or a 6 membered heteroaryl wherein 1, 2, 3, or 4 ring members are each independently selected from N, $NR^6$, O and S, and a 3 to 6 membered heterocycloalkyl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$, O and S, and wherein the cycloalkyl, heteroaryl and heterocycloalkyl are unsubstituted or are substituted with 1, 2 or 3

substituents independently selected from the group consisting of CN, -C(=O)OH, $NH_2$, OH, halo and $C_1$-$C_6$alkyl;

and

n is 0, 1, 2, 3 or 4.

4. The compound of any one of claim 1 to 3, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

the dashed line between $X_1$ and $X_2$ is a single bond or a double bond;

$X_1$ is $NR^1$, N, $C(R^{2a})_2$, $CR^{2a}$, O, $C{=}C(R^{2a})_2$, $CR^{2a}R^{2b}$, a spiro attached 4 to 6 membered heterocycloalkyl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$, O, C(=O), S and $S(=O)_2$, or a spiro attached $C_3$-$C_8$cycloalkyl, and wherein the heterocycloalkyl and $C_3$-$C_8$cycloalkyl are unsubstituted or are substituted with 1 or 2 OH groups;

$X_2$ is N, C or CH;

$X_3$ is N, C or CH;

$R^1$ is H, $C_1$-$C_6$alkyl, $C_3$-$C_8$cycloalkyl, 4 to 7 membered heterocycloalkyl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$, O and S, a $C_1$-$C_6$alkyl substituted with one or more $R^{12}$ or a $C_1$-$C_6$alkenyl substituted with one or more $R^{12}$, and wherein the cycloalkyl and heterocycloalkyl are unsubstituted or the cycloalkyl and heterocycloalkyl are substituted with 1 or 2 substituents independently selected from the group consisting of CN, -C(=O)OH, $NH_2$, OH, $C_1$-$C_6$haloalkyl, $C_1$-$C_6$alkyl or $C_1$-$C_6$alkyl substituted with -C(=O)OH, -OH, CN or $NH_2$;

each $R^{2a}$ is independently selected from the group consisting of H, CN, $NH_2$, $C_1$-$C_6$alkyl and $C_1$-$C_6$alkyl substituted with -C(=O)OH, -OH, CN or $NH_2$;

$R^{2b}$ is H, $C_1$-$C_6$alkyl, $C_3$-$C_8$cycloalkyl or 4 to 7 membered heterocycloalkyl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$, O and S, and wherein the $C_3$-$C_8$cycloalkyl and heterocycloalkyl are unsubstituted or the $C_3$-$C_8$cycloalkyl and heterocycloalkyl are substituted with 1, 2, 3 or 4 substituents independently selected from the group consisting of $C_1$-$C_6$alkyl, OH and $-N(R^7)_2$;

$R^3$ is selected from the group consisting of:

i) a 6 membered heteroaryl with an attachment point at a carbon atom ring member and a N heteroatom as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 6 membered heteroaryl has 0, 1 or 2 additional N heteroatoms as ring members, and wherein the 6 membered heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

ii) a 10 membered bicyclic heteroaryl with an attachment point at a carbon atom ring member and a N heteroatom as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 10 membered

bicyclic heteroaryl has 0, 1, 2 or 3 additional N heteroatoms as ring members, and wherein the 10 membered bicyclic heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

iii) a 6 membered heteroaryl wherein 1, 2 or 3 ring members are each independently selected from N, O and S, and wherein the 6 membered heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

iv) a 9 or 10 membered bicyclic heteroaryl wherein 1, 2, 3, 4 or 5 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 9 or 10 membered bicyclic heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

v) a 9 or 10 membered bicyclic heterocyclyl with an attachment point at a carbon atom ring member and a $NR^6$ as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 9 or 10 membered heterocyclyl further has 0, 1, 2, 3, or 4 ring members each independently selected from N, $NR^6$, O and S, and wherein the 9 or 10 membered heterocyclyl is unsubstituted, substituted with 1 or 2 oxo, or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo;

vi) a 9 or 10 membered bicyclic heterocyclyl wherein 1, 2, 3, 4 or 5 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 9 or 10 membered bicyclic heterocyclyl is unsubstituted, substituted with 1 or 2 oxo, or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo;

vii) a 10 membered bicyclic heterocyclyl with an attachment point at a carbon atom ring member and a carbon atom as a ring member which is substituted with oxo and located at a beta (β) position relative to the attachment point, wherein the 10 membered heterocyclyl further has 1, 2, 3, or 4 ring members each independently selected from N, $NR^6$, O and S, and wherein the 10 membered heterocyclyl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with an oxo;

Ring A is selected from the group consisting of:

i) phenyl;

ii) a 5 or 6 membered heteroaryl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S;

iii) $C_5$-$C_6$cycloalkenyl;

iv) 5 or 6 membered heterocyclyl wherein 1, 2 or 3 ring members are each independently selected from W, Y and Z, wherein W is $X_2$, $NR^6$, O, S, S=O or $S(=O)_2$, $X_2$ is N; Y is $NR^6$, O, S, S=O or $S(=O)_2$ and Z is $NR^6$, O or

S, and wherein the 5 or 6 membered heterocyclyl is optionally substituted with oxo

and

v) a 5 or 6 membered heterocycloalkyl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 5 or 6 membered heterocycloalkyl is optionally substituted with oxo;

each $R^4$ is independently selected from the group consisting of $-C(=O)N(R^7)_2$, $-C(=O)OH$, $-N(R^7)_2$, $-CN$, $-OH$, $-S(=O)_2R^6$, $-S(=O)_2N(R^7)_2$, $-C(=O)NR^7R^6$,  , $C_1$-$C_6$alkyl, halo, phenyl, $C_3$-$C_8$cycloalkyl, 4 to 6 membered heterocycloalkyl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S, 5 or 6 membered heteroaryl wherein 1, 2 or 3 ring members are each independently selected from N, O and S, and $C_1$-$C_6$alkyl substituted with $NH_2$, CN or OH, and wherein the phenyl, heterocycloalkyl and heteroaryl are unsubstituted or are substituted with 1 or 2 OH groups;

each $R^5$ is independently selected from the group consisting of -OH, $-NR^7R^8$, -NR6C(=O)C2-C6alkenyl, $-SF_5$, $-C(=O)N(R^7)_2$, $C_1$-$C_6$alkyl, $C_1$-$C_6$haloalkyl, halo, $C_1$-$C_6$haloalkoxy, $C_1$-$C_6$alkoxy, $C_3$-$C_8$cycloalkyl, 4 to 6 membered heterocycloalkyl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S, a 5 or 6 membered heteroaryl wherein 1, 2 or 3 ring members are each independently selected from N, O and S, and $C_1$-$C_6$alkyl substituted with CN, $NH_2$ or OH, and wherein the cycloalkyl and heterocycloalkyl are unsubstituted or are substituted with 1, 2, 3 or 4 $R^9$;

each $R^6$ is independently selected from the group consisting of H, $C_1$-$C_6$alkyl, $-S(=O)_2N(R^7)_2$, $-C(=O)N(R^7)_2$ and $C_1$-$C_6$alkyl substituted with –OH, $-OR^7$, CN or –C(=O)OH;

each $R^7$ is independently selected from the group consisting of H and $C_1$-$C_6$alkyl;

$R^8$ is H, $C_1$-$C_6$alkyl, $C_3$-$C_8$cycloalkyl or 4 to 6 membered heterocycloalkyl wherein 1, 2, 3 or 4 ring members are each independently selected from N, $NR^6$, O and S, and wherein the cycloalkyl and heterocycloalkyl are unsubstituted or are substituted with 1, 2, 3 or 4 $R^9$;

each $R^9$ is independently selected from the group consisting of halo, $NR^{10}R^{11}$, $-C(=O)OH$, $-C(=O)N(R^7)_2$ and $C_1$-$C_6$alkyl substituted with -OH or $-N(R^7)_2$;

$R^{10}$ is H or $C_1$-$C_6$alkyl;

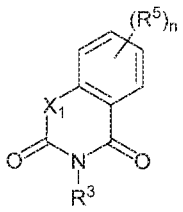
$R^{11}$ is H, $C_1$-$C_6$alkyl or $-S(=O)_2C_1$-$C_6$alkyl;

each $R^{12}$ is independently selected from the group consisting of CN, $NH_2$, -OH, $-C(=O)OH$, $-C(=O)OR^{10}$, $-C(=O)N(R^7)_2$, $-C_1$-$C_6$alkoxy, $C_1$-$C_6$alkyl, halo, $C_1$-$C_6$haloalkyl,

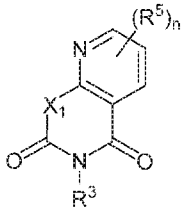
$C_3$-$C_8$cycloalkyl, a 5 or a 6 membered heteroaryl wherein 1, 2, 3, or 4 ring members are each independently selected from N, $NR^6$, O and S, and a 3 to 6 membered heterocycloalkyl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$, O and S, and wherein the cycloalkyl, heteroaryl and heterocycloalkyl are unsubstituted or are substituted with 1, 2 or 3 substituents independently selected from the group consisting of CN, -C(=O)OH, $NH_2$, OH, halo and $C_1$-$C_6$alkyl; and

n is 0, 1, 2, 3 or 4.

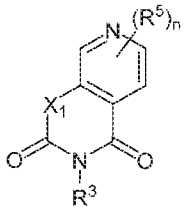
5. The compound of any one of claim 1 to 4, or a pharmaceutically acceptable salt or stereoisomer thereof, having a structure selected from the following:



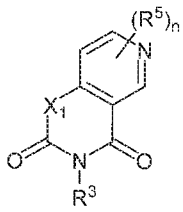
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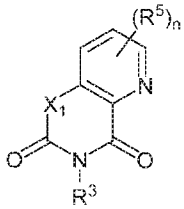
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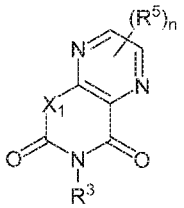
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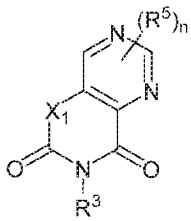
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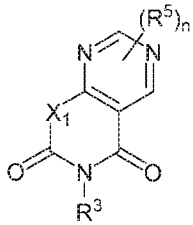
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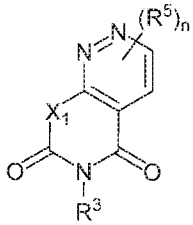
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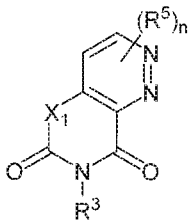
(I-g)



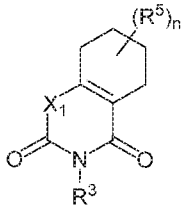
(I-h)



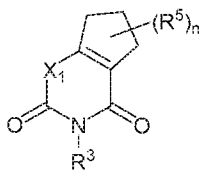
(I-i)



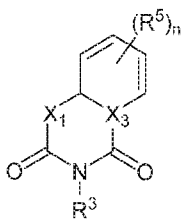
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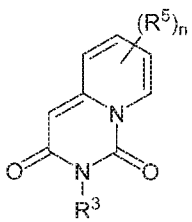
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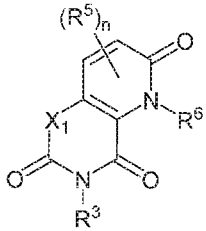
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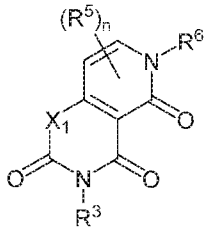
(I-m)



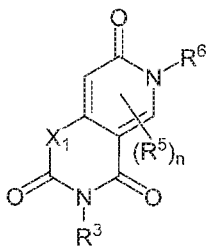
(I-n)



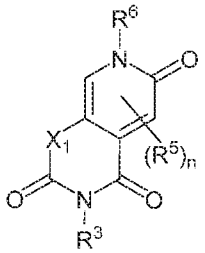
(I-o)



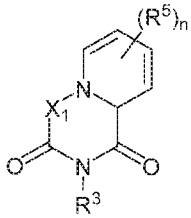
(I-p)



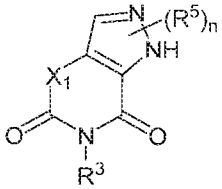
(I-q)



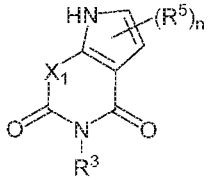
(I-r)



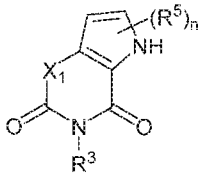
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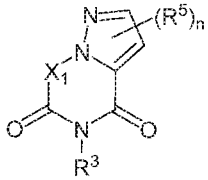
(I-t)



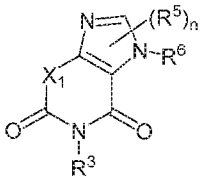
(I-u)



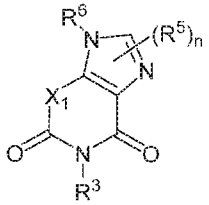
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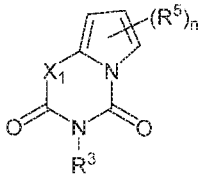
(I-w)



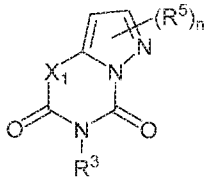
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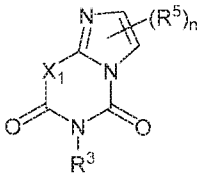
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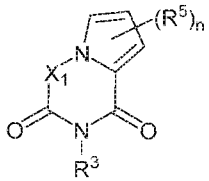
(I-z)



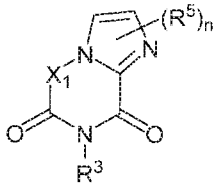
(I-aa)



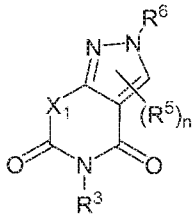
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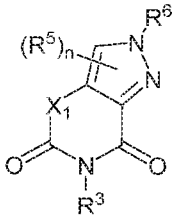
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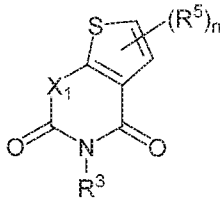
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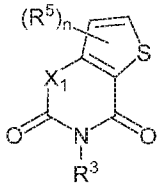
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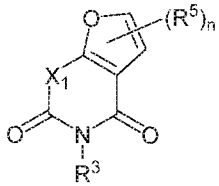
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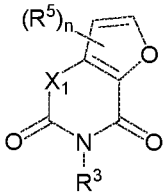
(I-ag)



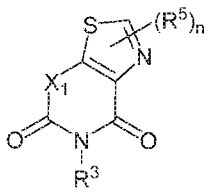
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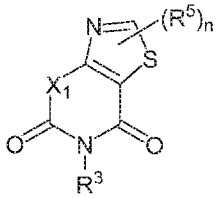
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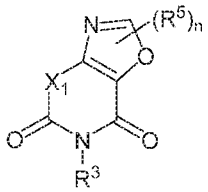
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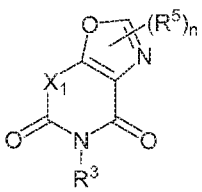
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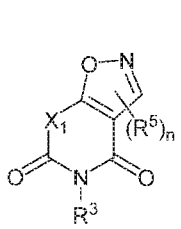
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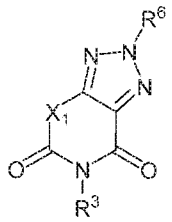
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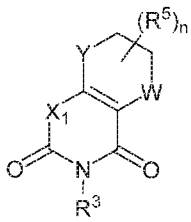
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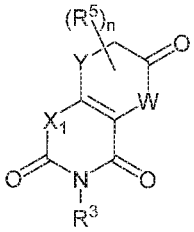
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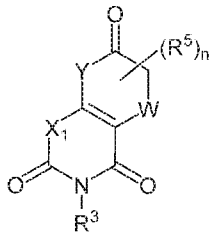
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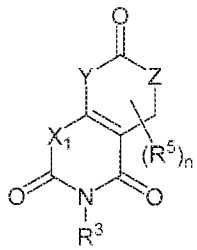
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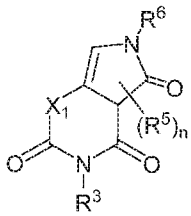
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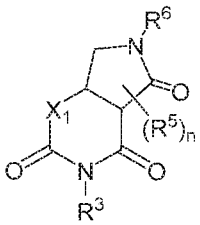
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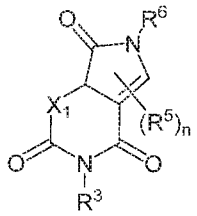
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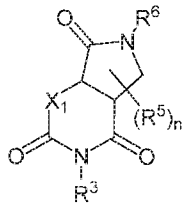
(I-au)



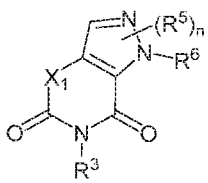
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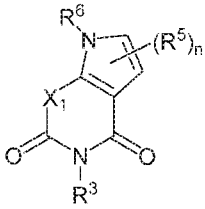
(I-aw)



(I-ax)

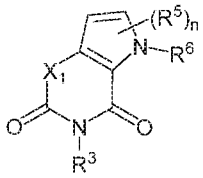


(I-aaa)



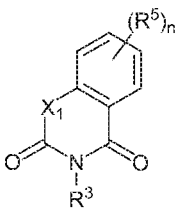
(I-aab)

and

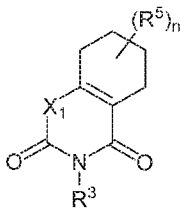


(I-aac).

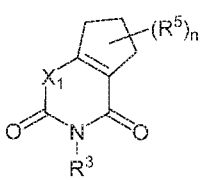
6. The compound of any one of claims 1 to 5 having the structure of Formula (I-a), Formula (I-k), Formula (I-l), Formula (I-b), Formula (I-c), Formula (I-d) or Formula (I-e), or a pharmaceutically acceptable salt or stereoisomer thereof,



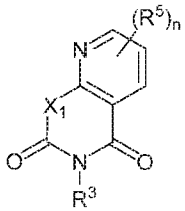
(I-a)



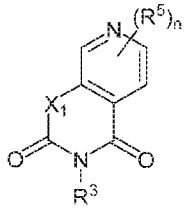
(I-k)

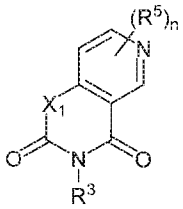


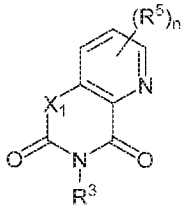
(I-l)



(I-b)


(I-c)


(I-d)


(I-e).

7. The compound of any one of claims 1 to 6 wherein,

$X_1$ is $NR^1$;

$R^1$ is H, $C_1$-$C_6$alkyl, $C_3$-$C_8$cycloalkyl, a $C_1$-$C_6$alkyl substituted with one or more $R^{12}$, or a $C_1$-$C_6$alkenyl substituted with one or more $R^{12}$, and wherein the cycloalkyl is unsubstituted or the cycloalkyl is substituted with 1 substituent selected from the group consisting of $C_1$-$C_6$alkyl substituted with CN;

$R^3$ is selected from the group consisting of:

i) a 6 membered heteroaryl with an attachment point at a carbon atom ring member and a N heteroatom as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 6 membered heteroaryl has 0, 1 or 2 additional N heteroatoms as ring members, and wherein the 6 membered heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

ii) a 10 membered bicyclic heteroaryl with an attachment point at a carbon atom ring member and a N heteroatom as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 10 membered bicyclic heteroaryl has 0, 1, 2 or 3 additional N heteroatoms as ring members, and wherein the 10 membered bicyclic heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

iii) a 6 membered heteroaryl wherein 1, 2 or 3 ring members are each independently selected from N, O and S, and wherein the 6 membered heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

iv) a 9 or 10 membered bicyclic heteroaryl wherein 1, 2, 3, 4 or 5 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 9 or 10 membered bicyclic heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

v) a 9 or 10 membered bicyclic heterocyclyl with an attachment point at a carbon atom ring member and a $NR^6$ as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 9 or 10 membered heterocyclyl further has 0, 1, 2, 3, or 4 ring members each independently selected from N, $NR^6$, O and S, and wherein the 9 or 10

membered heterocyclyl is unsubstituted, substituted with 1 or 2 oxo, or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo;

vi) a 9 or 10 membered bicyclic heterocyclyl wherein 1, 2, 3, 4 or 5 ring members are each independently selected from N, $NR^6$, O and S, and wherein the 9 or 10 membered bicyclic heterocyclyl is unsubstituted, substituted with 1 or 2 oxo, or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with 1 or 2 oxo;

and

vii) a 10 membered bicyclic heterocyclyl with an attachment point at a carbon atom ring member and a carbon atom as a ring member which is substituted with oxo and located at a beta (β) position relative to the attachment point, wherein the 10 membered heterocyclyl further has 1, 2, 3, or 4 ring members each independently selected from N, $NR^6$, O and S, and wherein the 10 membered heterocyclyl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$ and optionally substituted with an oxo;

each $R^4$ is independently selected from the group consisting of $-C(=O)N(R^7)_2$, $-N(R^7)_2$, -CN, $-S(=O)_2R^6$, $-C(=O)NR^7R^6$,  , $C_1$-$C_6$alkyl, and halo;

each $R^5$ is independently selected from the group consisting of $-SF_5$, $C_1$-$C_6$alkyl, $C_1$-$C_6$haloalkyl, halo, $C_1$-$C_6$haloalkoxy, $C_1$-$C_6$alkoxy, $C_3$-$C_8$cycloalkyl, and a $C_1$-$C_6$alkyl substituted with CN or OH, wherein the cycloalkyl is unsubstituted or is substituted with 1 or 2 $R^9$;

each $R^6$ is independently selected from the group consisting of H, $C_1$-$C_6$alkyl or $C_1$-$C_6$alkyl substituted with $-OR^7$;

each $R^7$ is independently selected from the group consisting of H and $C_1$-$C_6$alkyl;

each $R^9$ is independently selected from the group consisting of halo, -C(=O)OH, and $C_1$-$C_6$alkyl substituted with -OH;

$R^{10}$ is H or $C_1$-$C_6$alkyl;

each $R^{12}$ is independently selected from the group consisting of CN, -OH, -C(=O)OH, $-C(=O)OR^{10}$, $-C(=O)N(R^7)_2$, $C_1$-$C_6$alkoxy, $C_1$-$C_6$alkyl, halo, $C_3$-$C_8$cycloalkyl, a 5 membered heteroaryl wherein 4 ring members are each independently selected from N and $NR^6$, and a 3 to 6 membered heterocycloalkyl wherein 1 or 2 ring members are each independently selected from N, $NR^6$ and O, and wherein the cycloalkyl and heterocycloalkyl are unsubstituted or are substituted with 1 or 2 substituents independently selected from the group consisting of CN, halo and -C(=O)OH;

and

n is 1 or 2.

8. The compound of any one of claims 1 to 7 wherein, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

$X_1$ is $NR^1$;

$R^1$ is H, $C_1$-$C_6$alkyl, $C_3$-$C_8$cycloalkyl, a $C_1$-$C_6$alkyl substituted with one or more $R^{12}$, a $C_1$-$C_6$alkenyl substituted with one or more $R^{12}$, or a 4 membered heterocycloalkyl wherein 1 ring member is selected from N, $NR^6$ and O; and wherein the cycloalkyl and heterocycloalkyl are unsubstituted or the cycloalkyl and heterocycloalkyl are substituted with 1 substituent selected from the group consisting of CN, -C(=O)OH, $C_1$-$C_6$haloalkyl and $C_1$-$C_6$alkyl substituted with CN;

$R^3$ is selected from the group consisting of:

i) a 6 membered heteroaryl wherein 1 ring member is selected from N, and wherein the 6 membered heteroaryl is unsubstituted or is substituted with 1 or 2 $R^4$;

ii) a 10 membered bicyclic heteroaryl with an attachment point at a carbon atom ring member and a N heteroatom as a ring member which is located at a beta (β) position relative to the attachment point, wherein the 10 membered bicyclic heteroaryl has 0, 1, 2 or 3 additional N heteroatoms as ring members, and wherein the 10 membered bicyclic heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 $R^4$;

iii) a 9 or 10 membered bicyclic heteroaryl wherein 1, 2 or 3 ring members are each independently selected from N, $NR^6$ and O, and wherein the 9 or 10 membered bicyclic heteroaryl is unsubstituted or is substituted with 1 or 2 $R^4$; and

iv) a 9 or 10 membered bicyclic heterocyclyl wherein 1 ring member is selected from N, $NR^6$ or O, and wherein the 9 or 10 membered bicyclic heterocyclyl is unsubstituted, or is substituted with an oxo;

each $R^4$ is independently selected from the group consisting of -C(=O)N($R^7$)$_2$, -N($R^7$)$_2$, -CN, -S(=O)$_2$$R^6$, -C(=O)N$R^7$$R^6$,  , $C_1$-$C_6$alkyl and halo;

each $R^5$ is independently selected from the group consisting of -$SF_5$, $C_1$-$C_6$alkyl, $C_1$-$C_6$haloalkyl, halo, $C_1$-$C_6$haloalkoxy, $C_1$-$C_6$alkoxy, $C_3$-$C_8$cycloalkyl, and a $C_1$-$C_6$alkyl substituted with CN or OH, wherein the cycloalkyl is unsubstituted or is substituted with 1 or 2 $R^9$;

each $R^6$ is independently selected from the group consisting of H, $C_1$-$C_6$alkyl or $C_1$-$C_6$alkyl substituted with -$OR^7$ ;

each $R^7$ is independently selected from the group consisting of H and $C_1$-$C_6$alkyl;

each $R^9$ is independently selected from the group consisting of halo, -C(=O)OH, and $C_1$-$C_6$alkyl substituted with -OH;

$R^{10}$ is H or $C_1$-$C_6$alkyl;

each $R^{12}$ is independently selected from the group consisting of CN, -OH, -C(=O)OH, -C(=O)$OR^{10}$, -C(=O)$N(R^7)_2$, $C_1$-$C_6$alkoxy, $C_1$-$C_6$alkyl, halo, $C_3$-$C_8$cycloalkyl, a 5 membered heteroaryl wherein 4 ring members are each independently selected from N and $NR^6$, and a 3 to 6 membered heterocycloalkyl wherein 1 or 2 ring members are each independently selected from N, $NR^6$, and O, and wherein the cycloalkyl, and heterocycloalkyl are unsubstituted or are substituted with 1 or 2 substituents independently selected from the group consisting of CN, halo and -C(=O)OH;

and

n is 0, 1 or 2.

9. The compound of any one of claims 1 to 8, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein,

$X_1$ is $NR^1$;

$R^1$ is H, methyl, ethyl, isopropyl,-$CH_2R^{12}$, -$CH_2CH_2R^{12}$, -$CH_2CR^{12}$=$CH_2$, -$CH_2CHR^{12}CH_3$, -$CH_2CH$=$CHR^{12}$, -$CH_2CH_2CH(CH_3)R^{12}$, -$CH(CH_3)CH_2CH_2R^{12}$, -$CH_2CH_2C(CH_3)_2R^{12}$, a cyclopropyl which is unsubstituted, or a cyclopropyl which is substituted with -$CH_2CN$;

$R^3$ is selected from the group consisting of:

i) pyridyl substituted with 1 or 2 $R^4$;

ii) isoquinolin-4-yl which is unsubstituted or is substituted with 1 or 2 $R^4$;

and

iii) 5,6,7,8-tetrahydroisoquinolin-4-yl which is unsubstituted;

each $R^4$ is independently selected from the group consisting of -$CH_3$, -C(=O)$N(R^7)_2$, - -$N(R^7)_2$, F, Br, -CN, -S(=O)$_2R^6$, -C(=O)$NR^7R^6$, and  ,

each $R^5$ is independently selected from the group consisting of F, Br, Cl, -$CF_3$, -$CHF_2$, -$CH_2F$, -$C(CH_3)F_2$, -$CH_3$, isopropyl, -$OCHF_2$, -$OCClF_2$, -$OCF_3$, -$OCH_3$, $SF_5$, -$C(CH_3)_2OH$, -$CH_2CF_3$, -$CH(CH_3)CF_3$, an unsubstituted cyclopropyl, a cyclopropyl substituted with 1 $R^9$, and a cyclobutyl substituted with 1 or 2 $R^9$;

each $R^6$ is independently selected from the group consisting of H, -$CH_3$, and -$CH_2CH_2OR^7$;

each $R^7$ is independently selected from the group consisting of H and -$CH_3$;

each $R^9$ is independently selected from the group consisting of F, -C(=O)OH, and -$CH_2OH$;

$R^{10}$ is H or $-CH_3$;

each $R^{12}$ is independently selected from the group consisting of CN, $-CH_3$, $-OCH_3$, -OH, -F, $-C(=O)OR^{10}$, -C(=O)OH, $-C(=O)N(R^7)_2$, an unsubstituted morpholinyl, an unsubstituted tetrazolyl, an unsubstituted oxiranyl, a piperidinyl which is unsubstituted or substituted with 1 or 2 fluoro, an unsubstituted cyclopropyl or a cyclopropyl substituted with CN or -C(=O)OH;

and

n is 0, 1 or 2.

10. The compound of any one of claims 1 to 9, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein,

$X_1$ is $NR^1$;

$R^1$ is H, methyl, ethyl, isopropyl,$-CH_2R^{12}$, $-CH_2CH_2R^{12}$, $-CH_2CR^{12}=CH_2$, $-CH_2CHR^{12}CH_3$, $-CH_2CH=CHR^{12}$, $-CH_2CH_2CH(CH_3)R^{12}$, $-CH(CH_3)CH_2CH_2R^{12}$, $-CH_2CH_2C(CH_3)_2R^{12}$, a cyclopropyl which is unsubstituted, or a cyclopropyl which is substituted with $-CH_2CN$;

$R^3$ is isoquinolin-4-yl which is unsubstituted or is substituted with 1 or 2 $R^4$;

each $R^4$ is independently selected from the group consisting of $-CH_3$, $-C(=O)N(R^7)_2$, - -$N(R^7)_2$, F, Br, -CN, $-S(=O)_2R^6$, $-C(=O)NR^7R^6$, and  ,

each $R^5$ is independently selected from the group consisting of F, Br, Cl, $-CF_3$, $-CHF_2$, $-CH_2F$, $-C(CH_3)F_2$, $-CH_3$, isopropyl, $-OCHF_2$, $-OCClF_2$, $-OCF_3$, $-OCH_3$, $SF_5$, $-C(CH_3)_2OH$, $-CH_2CF_3$, $-CH(CH_3)CF_3$, an unsubstituted cyclopropyl, a cyclopropyl substituted with 1 $R^9$, and a cyclobutyl substituted with 1 or 2 $R^9$;

each $R^6$ is independently selected from the group consisting of H, $-CH_3$, and $-CH_2CH_2OR^7$;

each $R^7$ is independently selected from the group consisting of H and $-CH_3$;

each $R^9$ is independently selected from the group consisting of F, -C(=O)OH, and $-CH_2OH$;

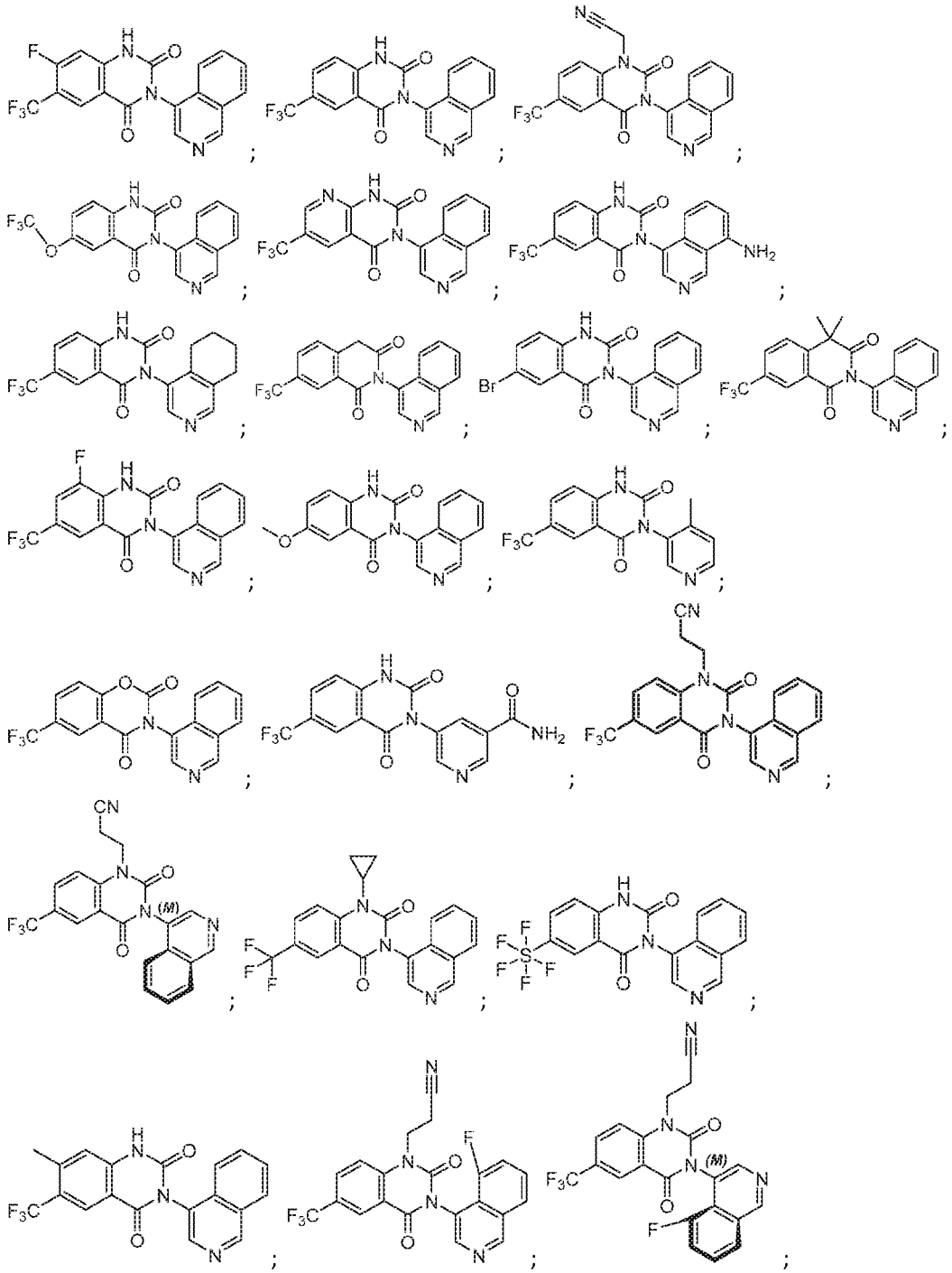
$R^{10}$ is H or $-CH_3$;

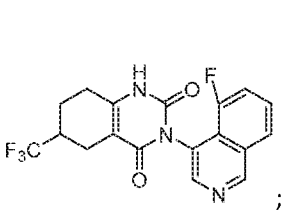
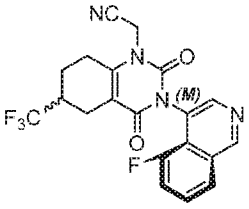
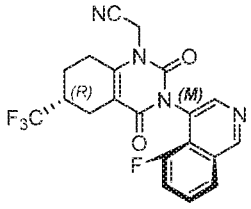
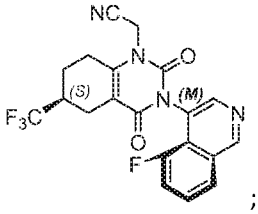
each $R^{12}$ is independently selected from the group consisting of CN, $-CH_3$, $-OCH_3$, -OH, -F, $-C(=O)OR^{10}$, -C(=O)OH, $-C(=O)N(R^7)_2$, an unsubstituted morpholinyl, an unsubstituted tetrazolyl, an unsubstituted oxiranyl, a piperidinyl which is unsubstituted or substituted with 1 or 2 fluoro, an unsubstituted cyclopropyl or a cyclopropyl substituted with CN or -C(=O)OH;

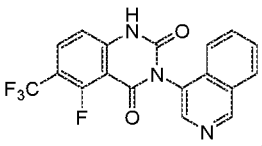
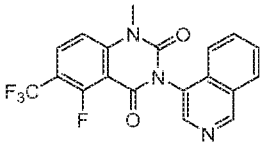
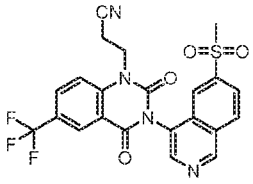
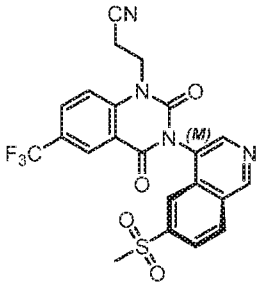
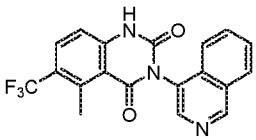
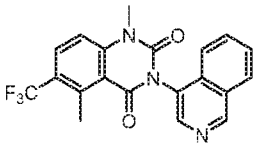
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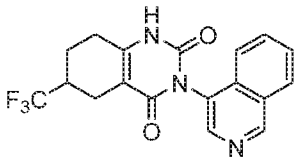
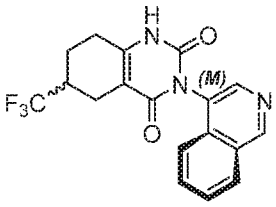
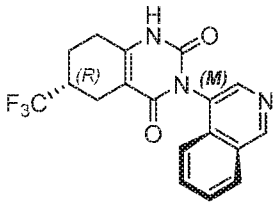
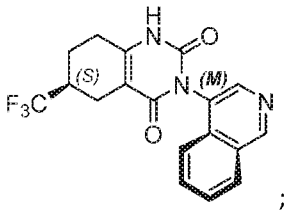
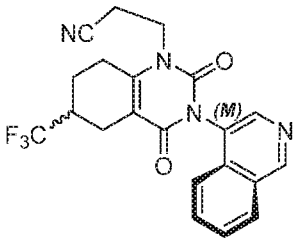
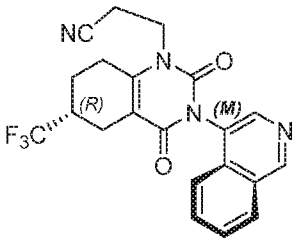
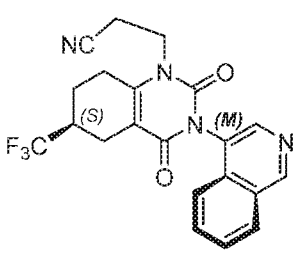
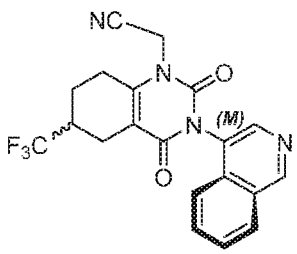
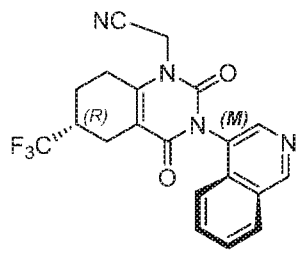
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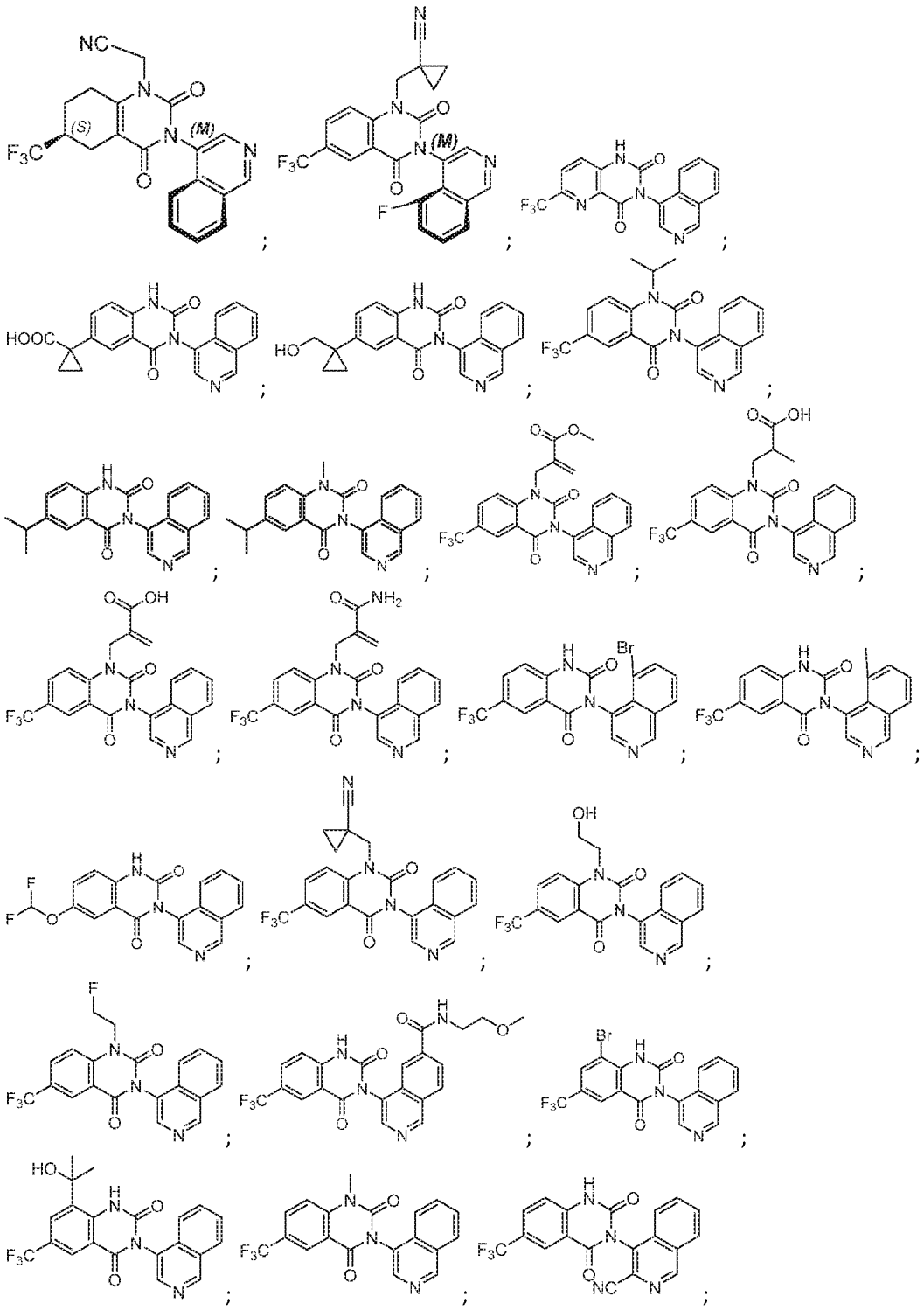
11. The compound of claim 1, or a pharmaceutically acceptable salt or stereoisomer thereof, selected from:

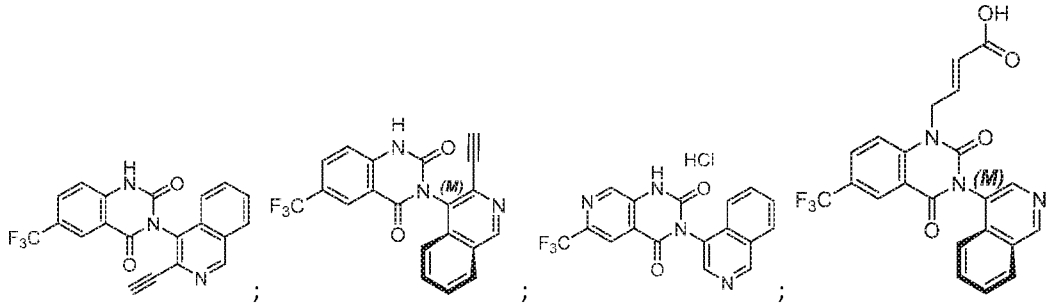


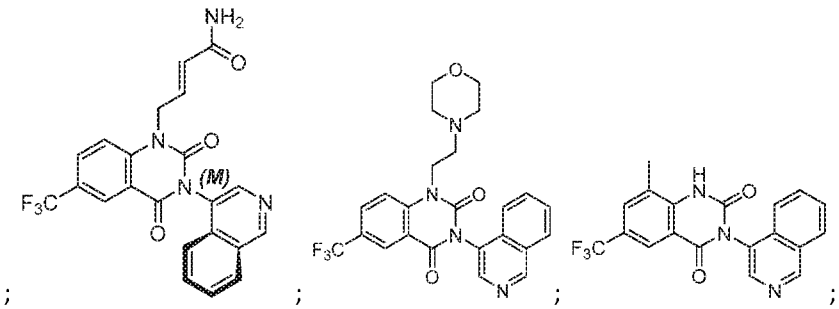

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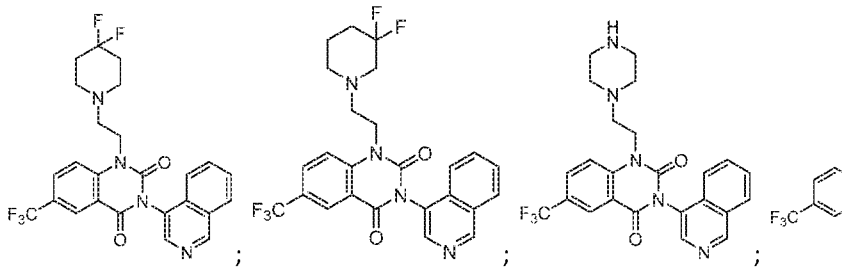
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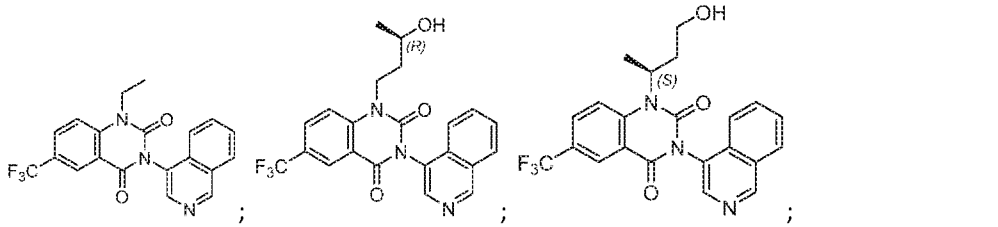
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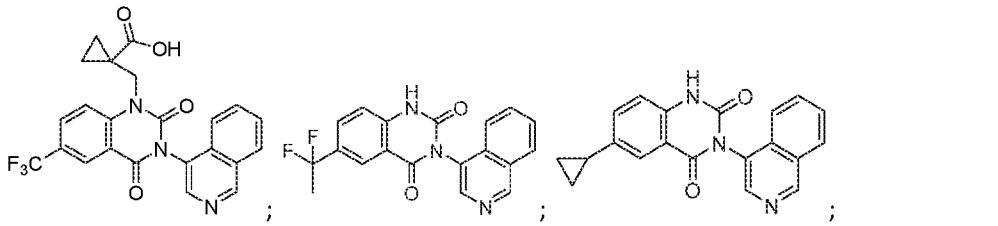


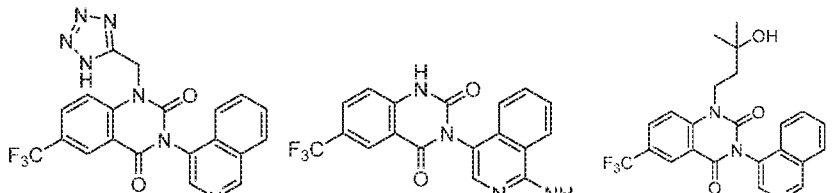

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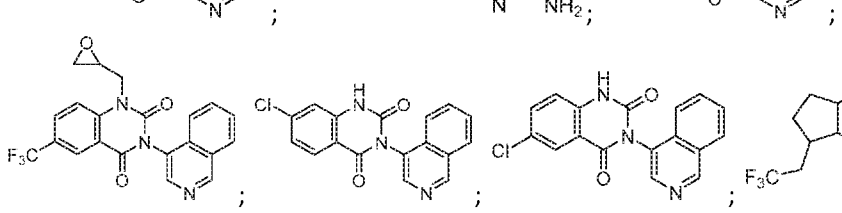

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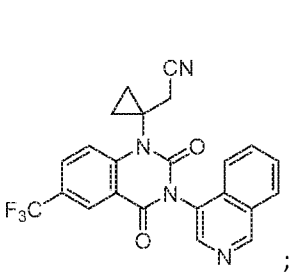
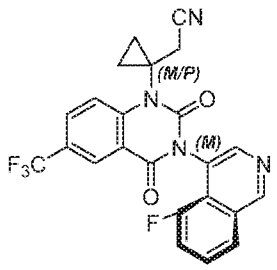
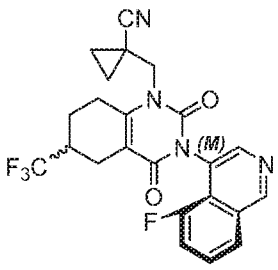
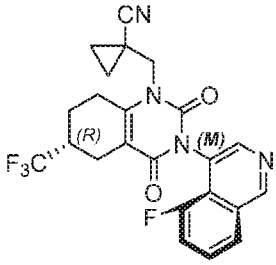
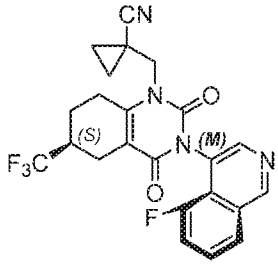
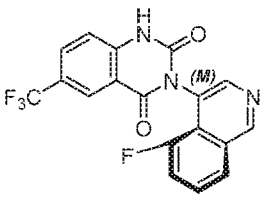
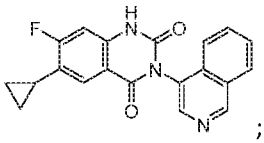
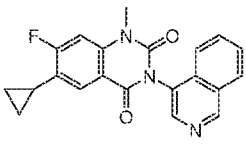
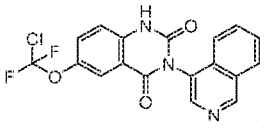
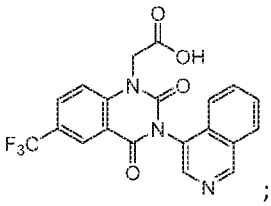
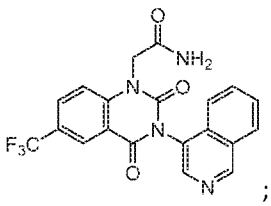
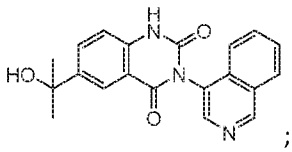
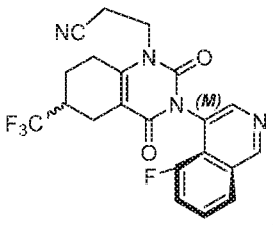
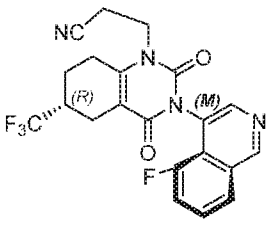
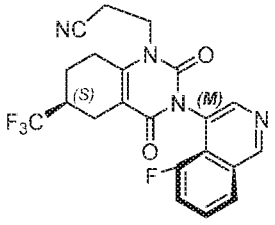
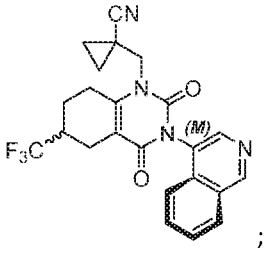
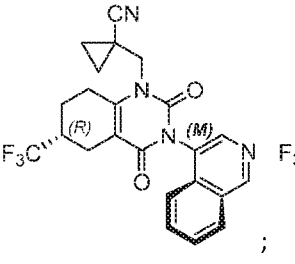
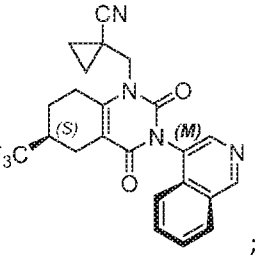
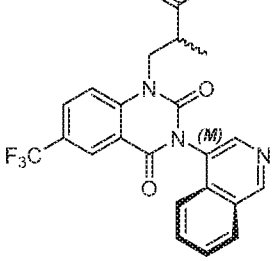
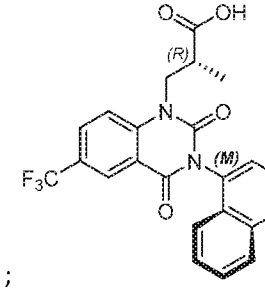
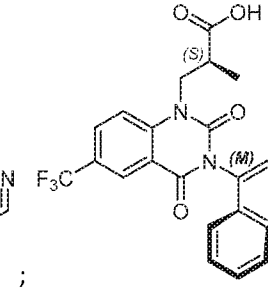

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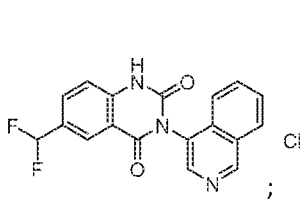
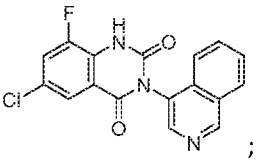
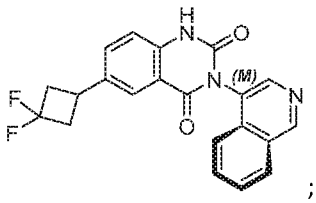
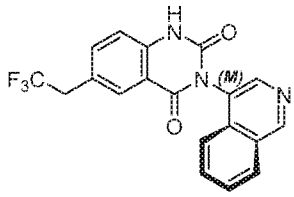
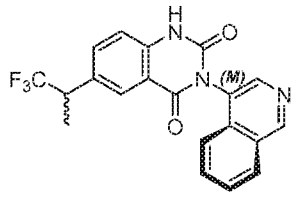
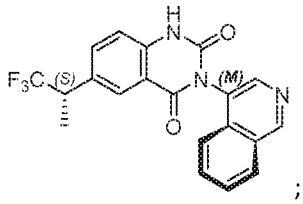
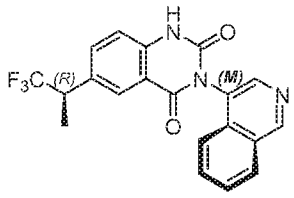
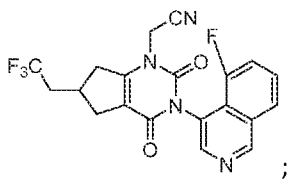
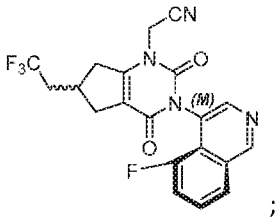
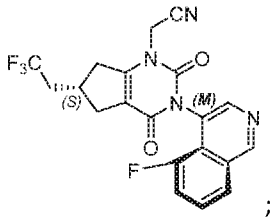
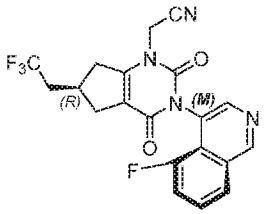
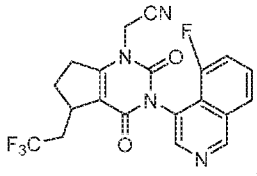
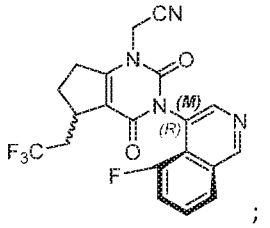
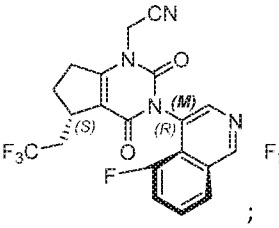
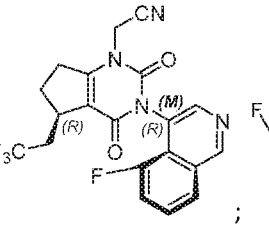

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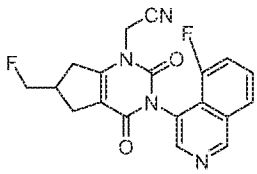
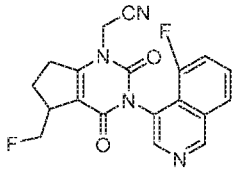
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and .

13. A pharmaceutical composition comprising a compound of any one of claims 1 to 11, or a pharmaceutically acceptable salt or stereoisomer thereof, and one or more pharmaceutically acceptable carriers.

14. The pharmaceutical composition of claim 12 comprising one or more additional therapeutic agents.

15. A method for treating, managing and/or preventing a coronaviral-related disease in a subject in need thereof, wherein the method comprises administering to the subject a therapeutically effective amount of a compound of any one of claims 1 to 11, or a pharmaceutically acceptable salt thereof.

16. Use of a compound of any one of claims 1 to 11, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment, management and/or prevention of a coronaviral-related disease.
17. Use of a compound of any one of claims 1 to 11, or a pharmaceutically acceptable salt thereof, in the treatment, management and/or prevention of a coronaviral-related disease.
18. A compound of any one of claims 1 to 11, or a pharmaceutically acceptable salt thereof, for use in the treatment, management and/or prevention of a coronaviral-related disease.
19. The method of claim 14, the use of claim 15 or claim 16, and the compound for the use in claim 16, wherein the coronaviral-related disease is COVID-19.
20. A compound of any one of claims 1 to 11, or a pharmaceutically acceptable salt thereof, for use in medicine.

# INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2022/053794

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/04 C07D413/04 C07D471/04 A61K31/517 A61P31/14
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61P A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | RAVI OWK ET AL: "Copper-Catalyzed Domino C-C Bond Cleavage of 2,3-Unsubstituted Indoles/Indolines and Oxindoles via Oxidation and Directed Insertion of 2-Aminopyridines: Direct Access to Quinazolinediones", ADVANCED SYNTHESIS AND CATALYSIS, [Online] vol. 360, no. 16, 17 August 2018 (2018-08-17), pages 3009-3014, XP055947173, ISSN: 1615-4150, DOI: 10.1002/adsc.201800536 Retrieved from the Internet: URL:https://api.wiley.com/onlinelibrary/tdm/v1/articles/10.1002%2Fadsc.201800536> tables 2-4 ----- -/-- | 1-9 |

[x] Further documents are listed in the continuation of Box C.

[x] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance;; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance;; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 29 July 2022 | 10/08/2022 |

| Name and mailing address of the ISA/ | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040,<br>Fax: (+31-70) 340-3016 | Grégoire, Ariane |

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB2022/053794

**Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)**

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:

   a. [X] forming part of the international application as filed:

      [X] in the form of an Annex C/ST.25 text file.

      [ ] on paper or in the form of an image file.

   b. [ ] furnished together with the international application under PCT Rule 13ter.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. [ ] furnished subsequent to the international filing date for the purposes of international search only:

      [ ] in the form of an Annex C/ST.25 text file (Rule 13ter.1(a)).

      [ ] on paper or in the form of an image file (Rule 13ter.1(b) and Administrative Instructions, Section 713).

2. [ ] In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

# INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2022/053794

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | BUCKMAN B O ET AL: "Solid-Phase Synthesis of 1,3-Dialkyl Quinazoline-2,4-Diones", TETRAHEDRON LETTERS, ELSEVIER, AMSTERDAM , NL, [Online] vol. 37, no. 26, 24 June 1996 (1996-06-24) , pages 4439-4442, XP004029035, ISSN: 0040-4039, DOI: 10.1016/0040-4039(96)00878-7 table 1; compound 9o | 1-9 |
| X | EP 3 064 491 A1 (EA PHARMA CO LTD [JP]) 7 September 2016 (2016-09-07) pages 27, 35, paragraphs 0101, 0145 | 1-9 |
| X | ENCISO EDUARDO ET AL: "Synthesis of new quinazolin-2,4-diones as anti-Leishmania mexicanaagents", MOLECULAR DIVERSITY, SPRINGER INTERNATIONAL PUBLISHING, CHAM, [Online] vol. 20, no. 4, 16 August 2016 (2016-08-16), pages 821-828, XP036072058, ISSN: 1381-1991, DOI: 10.1007/S11030-016-9693-8 [retrieved on 2016-08-16] compound 6b | 1-9,13, 20 |
| X | H. GREIG NIGEL ET AL: "A Simple One-Pot Synthesis of Benzoxazine-2,4-diones and Benzothiazine-2,4-diones", HETEROCYCLES, [Online] vol. 59, no. 1, 1 January 2003 (2003-01-01), page 115, XP055946887, JP ISSN: 0385-5414, DOI: 10.3987/COM-02-S2 Retrieved from the Internet: URL:http://dx.doi.org/10.3987/COM-02-S2> compounds 4d-4f | 1-5 |
| X | WO 2020/063982 A1 (SHANDONG CYNDA CHEMICAL CO LTD [CN]) 2 April 2020 (2020-04-02) Intermediate compounds 1-5 to 1-7; page 20 | 1-8 |
| X | WO 2020/225330 A1 (UNIV HAMBURG [DE]; AIX MARSEILLE UNIV [FR]) 12 November 2020 (2020-11-12) scheme 12 page 47; page 30, line 12 - line 15; claim 3; example 23 | 1,2,5,6, 13-20 |

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# INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2022/053794

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | KUINDERSMA M. ET AL: "Ketanserin as potential additive drug to improve V/Q mismatch in COVID-19?", CRITICAL CARE, vol. 24, no. 1, 1 December 2020 (2020-12-01), XP055947238, DOI: 10.1186/s13054-020-03257-y Retrieved from the Internet: URL:https://ccforum.biomedcentral.com/track/pdf/10.1186/s13054-020-03257-y.pdf> the whole document<br>----- | 1,2,5,6, 13-20 |

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2022/053794

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
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| | | CA 2928619 A1 | 07-05-2015 |
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| | | WO 2020225330 A1 | 12-11-2020 |