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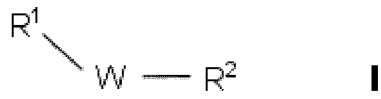
(54) Title: SUBSTITUTED BI-AND TRICYCLIC HSET INHIBITORS

(57) Abstract: The invention relates to substituted bi- and tricycles of the general formula (I),and the use of the compounds of the present invention as inhibitorsof HSET for the treatment and/or prevention of hyperproliferative diseases and disorders in mammals, especially humans, and pharmaceutical compositions containing such compound.

Substituted bi-and tricyclic HSET Inhibitors

The invention relates to substituted bi- and tricycles of the general formula I,



I

and the use of the compounds of the present invention for the treatment and/or prevention of hyperproliferative diseases and disorders such as cancer in mammals, especially humans, and pharmaceutical compositions containing such compounds.

Background of the invention

DNA replication, followed by equal chromosome segregation, ensures the accurate transmission of the genetic information to daughter cells (Hall et al., 2003; Nigg, 2002; Zyss and Gergely, 2009). In most normal and malignant cells, centrosomes act as the dominant sites for spindle pole formation (Meunier and Vernos, 2012). Centrosome duplication is also tightly controlled and occurs simultaneously with DNA replication, thereby ensuring the generation of two functional centrosomes that form the poles of the mitotic spindle (Sharp et al., 2000). In the assembly of a functional mitotic spindle, microtubule (MT) motor proteins play a central role (Cai et al., 2010; Ganem and Compton, 2004). One such protein, HSET (encoded by KIFC1 in humans and Kifc5a in mice), a minus-end MT motor, is of interest in cancer due to its impact on cell division (Cai et al., 2010; Goshima et al., 2005).

In recent years, the importance of centrosomes, and in particular HSET, for bipolar spindle formation has attracted much attention, although the precise role of HSET in this process remains a topic for debate (Mahoney et al., 2006; Tillement et al., 2009). Recent reports have linked centrosome amplification and high HSET expression to chromosome missegregation and aneuploidy, which are hallmarks of human cancer (Marx et al., 2009). Centrosome amplification disrupts asymmetric

cell division in neuroblastoma cells and causes tumorigenesis in a fly model (Basto et al., 2008), and supernumerary centrosomes are also found in most solid tumor types, forming markers for aggressiveness in breast, brain, prostate, cervix, kidney, and bladder cancers (Chan, 2011). Hence, it is increasingly apparent that supernumerary centrosomes are not only indicative of malignancy but may also drive malignant transformation (Ogden et al., 2013). However, not all cells with centrosome amplification undergo multipolar mitosis, and a key mechanism by which cells with extra centrosomes achieve a pseudo-bipolar spindle is centrosome clustering (Basto et al., 2008; Ganem et al., 2009).

Although centrosome clustering prevents multipolar mitosis and cell death, it prolongs mitosis and increases the frequency of chromosome missegregation as a result of merotelic kinetochore attachments (Ganem et al., 2009; Kwon et al., 2008; Yang et al., 2008). Based on previous studies, centrosome clustering may prove to be the Achilles heel of cancer cells with supernumerary centrosomes (Basto et al., 2008), and a growing body of evidence suggests that inhibition of centrosome clustering could provide a new therapeutic strategy for tumors with a high incidence of centrosome amplification (Jordan and Wilson, 2004; Ogden et al., 2012).

A key protein that is known to be crucial for centrosome clustering is HSET (Ncd in flies). HSET is required by tumour cells to cluster supernumerary centrosomes (Basto et al., 2008; Kwon et al., 2008). HSET is a member of the Kinesin 14 family of MT motor proteins, which are force-generating enzymes that facilitate movement along MTs within the cell (Mountain et al., 1999) and which transport organelles, protein complexes and mRNAs along microtubules in an ATP-dependent fashion. HSET is a minus-end directed motor kinesin, that cross-links and slides microtubules exerting inward forces (Walczak et al., 1997; Cai et al., 2009; Rath et al., 2012). Although the precise role of HSET in cell division is not clear, previous evidence suggests that it is essential for the survival of cancer, but not normal, cells (Ganem et al., 2009; Kwon et al., 2008). High HSET expression levels are strongly correlated with metastasis of non-small cell lung cancer to the brain, pointing to an association between HSET, centrosome amplification, and tumorigenesis (Cai et al., 2010; Gordon et al., 2001; Grinberg-Rashi et al., 2009). Knockdown of HSET in normal retinal pigment epithelial 1 (RPE-1) cells or the breast cancer cell line MCF-7 (which does not have a high incidence of centrosome amplification) does not inhibit

bipolar spindle formation, and cells undergo normal division (Kleylein-Sohn et al., 2012; Kwon et al., 2008). In contrast, knockdown of HSET in the supernumerary centrosome-containing breast cancer and neuroblastoma cell lines MDA-MB-231 and N1E-115, respectively, prevents centrosome clustering and induces cell death by multipolar anaphases (Kwon et al., 2008). Hence, the above findings point to HSET as a target of interest in cancer treatment (Basto et al., 2008; Kraljevic Pavelic et al., 2011; Krämer et al., 2011; Kwon et al., 2008).

A number of studies have shown that HSET depletion increases cell death and the frequency of multipolarity in cells with supernumerary centrosomes, but not in cells with a normal number of centrosomes. For example, HSET depletion induces spindle multi-polarity and selectively sensitizes centrosome amplified ER- breast cancer cell lines, including triple negative breast cancer (TNBC), to cell death (Patel et al., 2018). Depletion of HSET was identified as inducing selective cytotoxicity in centrosome amplified cancer cells (Drosopoulos et al., 2014). In addition, HSET overexpression has been correlated with poor prognosis and resistance to docetaxel in breast cancer (De et al., 2009; Li et al., 2015), is observed in ovarian adenocarcinoma patients (Pawar et al., 2014) and in numerous other cancer types (Pannu et al., 2015). Furthermore, in non-small cell lung carcinoma (NSCLC) HSET expression was found to be highly predictive of the presence of brain metastasis in both early and advanced disease (Grinberg-Rashi et al., 2009).

A wide range of tumours, including centrosome amplified tumours, are treated by cytotoxic microtubule-targeted drugs (e.g. taxol, eribulin). Although inducing temporary remission, these drugs typically show severe side effects and the emergence of drug resistance leading to early relapse. More recently, agents targeting kinesin motor proteins, e.g. Eg5 inhibitors, have been explored to treat a variety of human tumours, which induce mono-polar spindles (the opposite phenotype to HSET inhibition), and target all rapidly dividing cells, including bone marrow cells. Consequently, they share dose-limiting toxicities with other antimitotic therapies. In contrast, an HSET inhibitor is anticipated to show reduced toxicity by selectively killing cells with centrosome amplification whereas cells with the normal number of centrosomes will remain unaffected (Ganem et al., 2009; Patel et al., 2015). These data together provide support for developing agents that selectively inhibit HSET to target centrosome-amplified tumours (Myers and Collins, 2016).

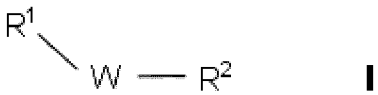
Examples of small molecule HSET inhibitors have been described in the literature. AZ82 is an ADP/ATP competitive inhibitor shown to be selective against a panel of nine other kinesins including Eg5 (Wu et al., 2013). AZ82 inhibited microtubule-stimulated HSET ATPase activity (IC_{50} = 0.3 µM) in a biochemical assay and induced multipolar spindle formation and mitotic catastrophe in cells with amplified centrosomes. CW069 was an inhibitor of HSET (IC_{50} = 75 µM) in biochemical assays (Watts et al., 2013). SR31527, also showed biochemical inhibition of HSET (IC_{50} = 6.6 µM) (Zhang et al., 2016). More information can be found in WO09155025 and WO15085088.

Thus, there remains a need for therapies for the treatment and prevention of hyperproliferative diseases and disorders such as cancer. Therefore, the aim was to find HSET inhibitors that serve as potential therapeutics for the treatment of cancer diseases.

Summary of the invention

Surprisingly, it has been found that the compounds according to the invention are highly selective and effective inhibitors of HSET and thus the compounds of the present invention can be used for the treament of hyperproliferative diseases and disorders such as cancer.

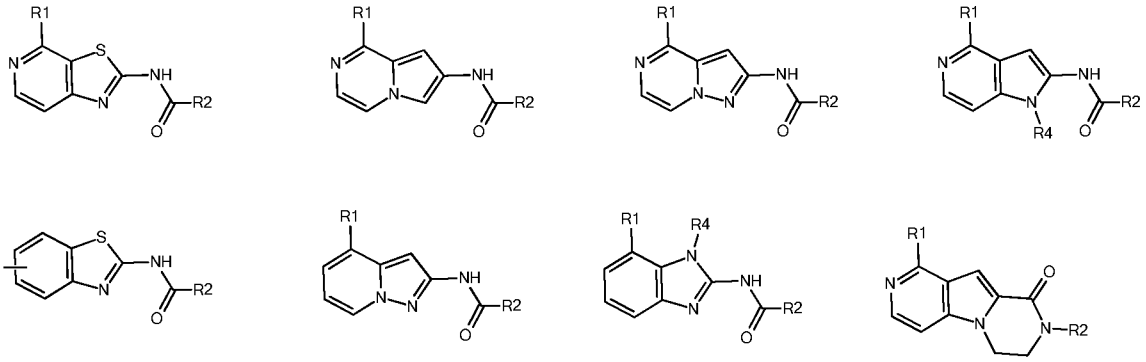
The invention relates to the compounds of the general formula I,



I

wherein

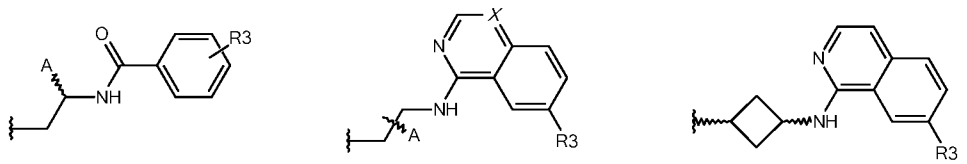
W denotes



wherein 1-4 H-atoms may be replaced by D

R^1 denotes Hal, A or OA,

R^2 denotes



X denotes CH or N,

A denotes H, F, OH, NH_2, or unbranched or branched alkyl or cycloalkyl with 1-12 C-atoms, which may be substituted by R^4 and wherein two adjacent CH- and/or CH_2-groups may form a double or triple bond and wherein one or two non-adjacent CH- and/or CH_2-groups may be replaced by N-, O- and/or S-atoms and wherein 1-7 H-atoms may be replaced by D, F or Cl,

R^3 denotes H or A,

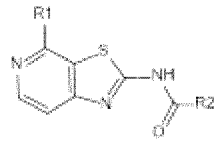
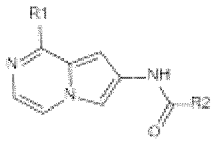
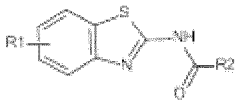
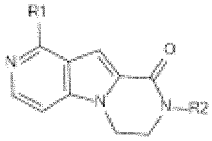
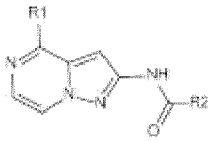
R^4 denotes H or unbranched or branched alkyl with 1-4 C-atoms,

Hal denotes F, Cl, Br or I

and physiologically acceptable salts, derivatives, solvates, prodrugs and stereoisomers thereof, including mixtures thereof in all ratios.

A preferred embodiment of the present invention are compounds according to formula I, wherein

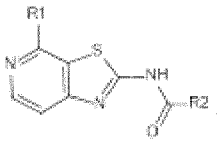
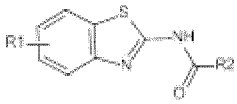
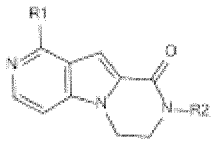
W denotes

and R^1, R^2, R^3, R^4, X and A have the meanings as disclosed above, and physiologically acceptable salts, derivatives, solvates, prodrugs and stereoisomers thereof, including mixtures thereof in all ratios.

A preferred embodiment of the present invention are compounds according to formula I, wherein

W denotes

and R^1, R^2, R^3, R^4, X and A have the meanings as disclosed above, and physiologically acceptable salts, derivatives, solvates, prodrugs and stereoisomers thereof, including mixtures thereof in all ratios.

A preferred embodiment of the present invention are compounds according to formula I, wherein

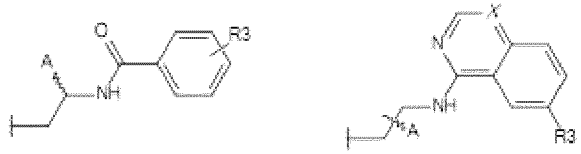
R^1 denotes OA

and W, R^2, R^3, R^4, X and A have the meanings as disclosed above, and physiologically acceptable salts, derivatives, solvates, prodrugs and stereoisomers thereof, including mixtures thereof in all ratios.

A preferred embodiment of the present invention are compounds according to formula I, wherein

R^1 denotes OA, wherein A denotes an unbranched or branched alkyl wherein 1-3 H-atoms may be replaced by D, F or Cl
and W, R^2, R^3, R^4, X and A have the meanings as disclosed above, and physiologically acceptable salts, derivatives, solvates, prodrugs and stereoisomers thereof, including mixtures thereof in all ratios.

A preferred embodiment of the present invention are compounds according to formula I, wherein
R^2 denotes



and W, R^1, R^3, R^4, X and A have the meanings as disclosed above, and physiologically acceptable salts, derivatives, solvates, prodrugs and stereoisomers thereof, including mixtures thereof in all ratios.

A preferred embodiment of the present invention are compounds according to formula I, wherein
R^3 denotes 5-methyloxadiazol or 2-methyltretrazol
and W, R^1, R^2, R^4, X and A have the meanings as disclosed above, and physiologically acceptable salts, derivatives, solvates, prodrugs and stereoisomers thereof, including mixtures thereof in all ratios.

A preferred embodiment of the present invention are compounds according to formula I, wherein
R^3 denotes 5-methyloxadiazol
and W, R^1, R^2, R^4, X and A have the meanings as disclosed above, and physiologically acceptable salts, derivatives, solvates, prodrugs and stereoisomers thereof, including mixtures thereof in all ratios.

A preferred embodiment of the present invention are compounds according to formula I, wherein R^4 denotes methyl

and W, R^1, R^2, R^3, X and A have the meanings as disclosed above, and physiologically acceptable salts, derivatives, solvates, prodrugs and stereoisomers thereof, including mixtures thereof in all ratios.

The invention preferably relates to a compound selected from the group consisting of:

1	N-{4-ethoxy-[1,3]thiazolo[5,4-c]pyridin-2-yl}-3-{[3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]formamido}propanamide
2	3-{[3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]formamido}-N-[4-(propan-2-yloxy)-[1,3]thiazolo[5,4-c]pyridin-2-yl]propanamide
3	N-{4-cyclobutoxy-[1,3]thiazolo[5,4-c]pyridin-2-yl}-3-{[3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]formamido}propanamide
4	N-[4-(butan-2-yloxy)-[1,3]thiazolo[5,4-c]pyridin-2-yl]-3-{[3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]formamido}propanamide
5	N-[4-(2,2-difluoroethoxy)-[1,3]thiazolo[5,4-c]pyridin-2-yl]-3-{[3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]formamido}propanamide
6	3-{[3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]formamido}-N-[4-(2,2,2-trifluoroethoxy)-[1,3]thiazolo[5,4-c]pyridin-2-yl]propanamide
7	N-[4-(3,3-difluorocyclobutoxy)-[1,3]thiazolo[5,4-c]pyridin-2-yl]-3-{[3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]formamido}propanamide
8	3-{[3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]formamido}-N-{4-[(1,1,1-trifluoropropan-2-yl)oxy]-[1,3]thiazolo[5,4-c]pyridin-2-yl}propanamide
9	N-{4-ethoxy-[1,3]thiazolo[5,4-c]pyridin-2-yl}-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}propanamide
10	3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}-N-{4-propoxy-[1,3]thiazolo[5,4-c]pyridin-2-yl}propanamide
11	3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}-N-[4-(propan-2-yloxy)-[1,3]thiazolo[5,4-c]pyridin-2-yl]propanamide
12	N-[4-(butan-2-yloxy)-[1,3]thiazolo[5,4-c]pyridin-2-yl]-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}propanamide
13	N-{4-cyclobutoxy-[1,3]thiazolo[5,4-c]pyridin-2-yl}-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}propanamide

14	N-[4-(3,3-difluorocyclobutoxy)-[1,3]thiazolo[5,4-c]pyridin-2-yl]-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}propanamide
15	N-[4-(3-fluoropropoxy)-[1,3]thiazolo[5,4-c]pyridin-2-yl]-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}propanamide
16	N-[4-(2,2-difluoropropoxy)-[1,3]thiazolo[5,4-c]pyridin-2-yl]-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}propanamide
17	N-[4-(2,2-difluoroethoxy)-[1,3]thiazolo[5,4-c]pyridin-2-yl]-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}propanamide
18	3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}-N-[4-(2,2,2-trifluoroethoxy)-[1,3]thiazolo[5,4-c]pyridin-2-yl]propanamide
19	3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}-N-{4-[(1,1,1-trifluoropropan-2-yl)oxy]-[1,3]thiazolo[5,4-c]pyridin-2-yl}propanamide
20	(1s,3s)-N-{4-methoxy-[1,3]thiazolo[5,4-c]pyridin-2-yl}-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}cyclobutane-1-carboxamide
21	(1s,3s)-N-{4-ethoxy-[1,3]thiazolo[5,4-c]pyridin-2-yl}-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}cyclobutane-1-carboxamide
22	(1s,3s)-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}-N-{4-propoxy-[1,3]thiazolo[5,4-c]pyridin-2-yl}cyclobutane-1-carboxamide
23	N-{1-ethoxypyrrolo[1,2-a]pyrazin-7-yl}-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}propanamide
24	3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}-N-{1-propoxypyrrolo[1,2-a]pyrazin-7-yl}propanamide
25	11-(2-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}ethyl)-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02.7]trideca-2(7),3,5,8-tetraen-10-one
26	3-(2-methyl-2H-1,2,3,4-tetrazol-5-yl)-N-{2-[10-oxo-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02.7]trideca-2,4,6,8-tetraen-11-yl]ethyl}benzamide

27	3-(2-methyl-2H-1,2,3,4-tetrazol-5-yl)-N-{2-[10-oxo-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02.7]trideca-2(7),3,5,8-tetraen-11-yl](1,1,2,2-2H4)ethyl}benzamide
28	3-(5-methyl-1,2,4-oxadiazol-3-yl)-N-{2-[10-oxo-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02.7]trideca-2(7),3,5,8-tetraen-11-yl](1,1,2,2-2H4)ethyl}benzamide
29	11-(2-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}(1,1,2,2-2H4)ethyl)-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02.7]trideca-2(7),3,5,8-tetraen-10-one
30	3-(5-methyl-2H-1,2,3,4-tetrazol-2-yl)-N-{2-[10-oxo-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02.7]trideca-2,4,6,8-tetraen-11-yl]ethyl}benzamide
31	11-(2-{[7-(2-methyl-2H-1,2,3,4-tetrazol-5-yl)isoquinolin-1-yl]amino}ethyl)-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02.7]trideca-2,4,6,8-tetraen-10-one
32	11-(2-{[7-(5-methyl-2H-1,2,3,4-tetrazol-2-yl)isoquinolin-1-yl]amino}ethyl)-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02.7]trideca-2,4,6,8-tetraen-10-one
33	11-(2-{[6-(5-methyl-1,2,4-oxadiazol-3-yl)quinazolin-4-yl]amino}ethyl)-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02.7]trideca-2,4,6,8-tetraen-10-one
34	3-fluoro-5-(2-methyl-2H-1,2,3,4-tetrazol-5-yl)-N-{2-[10-oxo-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02.7]trideca-2,4,6,8-tetraen-11-yl]ethyl}benzamide
35	3-(2-methyl-2H-1,2,3,4-tetrazol-5-yl)-N-{2-[10-oxo-6-(2,2,2-trifluoroethoxy)(12,12,13,13-2H4)-1,5,11-triazatricyclo[7.4.0.02.7]trideca-2(7),3,5,8-tetraen-11-yl]ethyl}benzamide
36	11-(2-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}ethyl)-6-(2,2,2-trifluoroethoxy)(12,12,13,13-2H4)-1,5,11-triazatricyclo[7.4.0.02.7]trideca-2(7),3,5,8-tetraen-10-one
37	11-(2-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}ethyl)-6-propoxy-1,5,11-triazatricyclo[7.4.0.02.7]trideca-2(7),3,5,8-tetraen-10-one

38	3-(2-methyl-2H-1,2,3,4-tetrazol-5-yl)-N-(2-{10-oxo-6-propoxy-1,5,11-triazatricyclo[7.4.0.02.7]trideca-2,4,6,8-tetraen-11-yl}ethyl)benzamide
39	1-(Dodec-11-yn-1-yloxy)-8-(2-((7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl)amino)ethyl)-7,8-dihydropyrido[3',4':4,5]pyrrolo[1,2-a]pyrazin-9(6H)-one
40	N-(2-{6-chloro-10-oxo-1,5,11-triazatricyclo[7.4.0.0^{2,7}]trideca-2,4,6,8-tetraen-11-yl}ethyl)-3-(5-methyl-1,2,4-oxadiazol-3-yl)benzamide
41	N-{2-[6-(3-fluoropropoxy)-10-oxo-1,5,11-triazatricyclo[7.4.0.0^{2,7}]trideca-2,4,6,8-tetraen-11-yl]ethyl}-3-(5-methyl-1,2,4-oxadiazol-3-yl)benzamide
42	N-{2-[6-(2,2-difluoroethoxy)-10-oxo-1,5,11-triazatricyclo[7.4.0.0^{2,7}]trideca-2,4,6,8-tetraen-11-yl]ethyl}-3-(5-methyl-1,2,4-oxadiazol-3-yl)benzamide
43	3-(5-methyl-1,2,4-oxadiazol-3-yl)-N-{2-[10-oxo-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.0^{2,7}]trideca-2,4,6,8-tetraen-11-yl]ethyl}benzamide
44	6-(3-fluoropropoxy)-11-(2-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}ethyl)-1,5,11-triazatricyclo[7.4.0.02.7]trideca-2(7),3,5,8-tetraen-10-one
45	3-(2-methyl-2H-1,2,3,4-tetrazol-5-yl)-N-(2-{10-oxo-6-[(1,1,2,2,3,3,3-2H7)propoxy]-1,5,11-triazatricyclo[7.4.0.02.7]trideca-2,4,6,8-tetraen-11-yl}ethyl)benzamide
46	3-(2-methyl-2H-1,2,3,4-tetrazol-5-yl)-N-(2-{10-oxo-6-[2,2,2-trifluoro(1,1-2H2)ethoxy]-1,5,11-triazatricyclo[7.4.0.02.7]trideca-2,4,6,8-tetraen-11-yl}ethyl)benzamide
47	N-(2-(1-(dodec-11-yn-1-yloxy)-9-oxo-6,7-dihydropyrido[3',4':4,5]pyrrolo[1,2-a]pyrazin-8(9H)-yl)ethyl)-3-(2-methyl-2H-tetrazol-5-yl)benzamide
48	11-(3-amino-2-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}propyl)-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[[7.4.0.02.7]trideca-2,4,6,8-tetraen-10-one

49	(S)-3-(2-Methyl-2H-tetrazol-5-yl)-N-(6-(methylamino)-1-(9-oxo-1-(2,2,2-trifluoroethoxy)-6,7-dihydropyrido[3',4':4,5]pyrrolo[1,2-a]pyrazin-8(9H)-yl)hexan-2-yl)benzamide
50	3-(2-methyl-2H-1,2,3,4-tetrazol-5-yl)-N-[6-(methylamino)-1-[10-oxo-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02.7]trideca-2(7),3,5,8-tetraen-11-yl]hexan-2-yl]benzamide
51	N-{6-[methyl(prop-2-yn-1-yl)amino]-1-[10-oxo-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02.7]trideca-2,4,6,8-tetraen-11-yl]hexan-2-yl}-3-(2-methyl-2H-1,2,3,4-tetrazol-5-yl)benzamide
52	11-[(2S)-6-[methyl(prop-2-yn-1-yl)amino]-2-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}hexyl]-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7[7.4.0.02.7]trideca-2,4,6,8-tetraen-10-one
53	N-{(S)-4-Methylamino-1-[(7-propoxy-benzothiazol-2-ylcarbamoyl)-methyl]-butyl}-3-(5-methyl-[1,2,4]oxadiazol-3-yl)-benzamide
54	(3S)-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}-6-(methylamino)-N-(7-propoxy-1,3-benzothiazol-2-yl)hexanamide
55	(3S)-N-(4-fluoro-7-propoxy-1,3-benzothiazol-2-yl)-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}-6-(methylamino)hexanamide
56	N-[4-fluoro-7-(3-fluoropropoxy)-1,3-benzothiazol-2-yl]-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}propanamide
57	N-[4-fluoro-7-(2-fluoroethoxy)-1,3-benzothiazol-2-yl]-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}propanamide
58	3-[7-(5-Methyl-[1,2,4]oxadiazol-3-yl)-isoquinolin-1-ylamino]-N-(7-propoxy-benzothiazol-2-yl)-propionamide
59	3-[7-(5-Methyl-[1,2,4]oxadiazol-3-yl)-isoquinolin-1-ylamino]-cyclobutanecarboxylic acid (7-propoxy-benzothiazol-2-yl)-amide
60	3-[7-(5-Methyl-[1,2,4]oxadiazol-3-yl)-isoquinolin-1-ylamino]-cyclobutanecarboxylic acid (7-methoxy-4-methyl-benzothiazol-2-yl)-amide

61	3-[7-(5-Methyl-[1,2,4]oxadiazol-3-yl)-isoquinolin-1-ylamino]-cyclobutanecarboxylic acid (7-methoxy-benzothiazol-2-yl)-amide
62	N-(4-fluoro-7-propoxy-1,3-benzothiazol-2-yl)-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}propanamide
63	N-(4-chloro-7-propoxy-1,3-benzothiazol-2-yl)-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}propanamide
64	3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}-N-{4-propoxypyrazolo[1,5-a]pyridin-2-yl}propanamide
65	3-[7-(5-Methyl-[1,2,4]oxadiazol-3-yl)-isoquinolin-1-ylamino]-N-(4-propoxy-pyrazolo[1,5-a]pyrazin-2-yl)-propionamide
66	N-{4-ethoxypyrazolo[1,5-a]pyrazin-2-yl}-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}propanamide
67	N-[4-(3-fluoropropoxy)pyrazolo[1,5-a]pyrazin-2-yl]-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}propanamide
68	N-[4-(2-fluoroethoxy)pyrazolo[1,5-a]pyrazin-2-yl]-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}propanamide
69	3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}-N-[4-(oxetan-3-yloxy)pyrazolo[1,5-a]pyrazin-2-yl]propanamide
70	N-{4-cyclopropoxypyrazolo[1,5-a]pyrazin-2-yl}-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}propanamide
71	3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}-N-{1-methyl-4-propoxy-1H-pyrrolo[3,2-c]pyridin-2-yl}propanamide
72	3-[7-(5-Methyl-[1,2,4]oxadiazol-3-yl)-isoquinolin-1-ylamino]-cyclobutanecarboxylic acid (4-methoxy-pyrazolo[1,5-a]pyridin-2-yl)-amide
73	3-[7-(5-Methyl-[1,2,4]oxadiazol-3-yl)-isoquinolin-1-ylamino]-N-(4-methyl-7-propoxy-benzothiazol-2-yl)-propionamide
74	3-(5-Methyl-[1,2,4]oxadiazol-3-yl)-N-[2-(4-methyl-7-propoxy-benzothiazol-2-ylcarbamoyl)-ethyl]-benzamide
75	3-(2-Methyl-2H-tetrazol-5-yl)-N-[2-(7-propoxy-benzothiazol-2-ylcarbamoyl)-ethyl]-benzamide
76	3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}-N-[7-propoxy-4-(trifluoromethyl)-1,3-benzothiazol-2-yl]propanamide

77	(2R)-2-amino-N-(4-fluoro-7-propoxy-1,3-benzothiazol-2-yl)-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}propanamide
78	(S)-2-Hydroxy-3-[7-(5-methyl-[1,2,4]oxadiazol-3-yl)-isoquinolin-1-ylamino]-N-(7-propoxy-benzothiazol-2-yl)-propionamide
79	N-(7-ethoxy-1,3-benzothiazol-2-yl)-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}propanamide
80	(2S)-N-(7-ethoxy-1,3-benzothiazol-2-yl)-2-hydroxy-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}propanamide
81	3-(5-Methyl-[1,2,4]oxadiazol-3-yl)-N-[2-(7-propoxy-benzothiazol-2-ylcarbamoyl)-ethyl]-benzamide
82	(2R)-N-(7-ethoxy-1,3-benzothiazol-2-yl)-2-hydroxy-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}propanamide
83	3-(5-methyl-1,2,4-oxadiazol-3-yl)-N-(2-{10-oxo-6-propoxy-1,5,11-triazatricyclo[7.4.0.02.7]trideca-2,4,6,8-tetraen-11-yl}ethyl)benzamide
84	2,2-difluoro-N-(4-fluoro-7-propoxy-1,3-benzothiazol-2-yl)-3-{[3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]formamido}propanamide
85	3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}-N-(1-methyl-7-propoxy-1H-1,3-benzodiazol-2-yl)propanamide
86	3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}-N-(7-propoxy-1H-1,3-benzodiazol-2-yl)propanamide
87	8-(2-((7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl)amino)ethyl-1,1,2,2-d4)-1-(2,2,2-trifluoroethoxy-1,1-d2)-7,8-dihydropyrido[3',4':4,5]pyrrolo[1,2-a]pyrazin-9(6H)-one-6,6,7,7-d4
88	3-(2-methyl-2H-tetrazol-5-yl)-N-(2-(9-oxo-1-(2,2,2-trifluoroethoxy-1,1-d2)-6,7-dihydropyrido[3',4':4,5]pyrrolo[1,2-a]pyrazin-8(9H)-yl-6,6,7,7-d4)ethyl-1,1,2,2-d4)benzamide

and physiologically acceptable salts, derivatives, solvates, prodrugs and stereoisomers thereof, including mixtures thereof in all ratios.

Furthermore, the abbreviations below have the following meanings:

Boc ter-butoxycarbonyl

CBZ benzyloxycarbonyl

DNP 2,4-dinitrophenyl

FMOC	9-fluorenylmethoxycarbonyl
imi-DNP	2,4-dinitrophenyl in the 1-position of the imidazole ring
OMe	methyl ester
POA	phenoxyacetyl
DCCI	dicyclohexylcarbodiimide
HOBt	1-hydroxybenzotriazole

The invention further relates to a pharmaceutical preparation comprising one or more compounds according to the present invention and/or one of its physiologically acceptable salts, derivatives, solvates, prodrugs and stereoisomers, including mixtures thereof in all ratios.

The invention also relates to a pharmaceutical preparation according to the invention of this type, comprising further excipients and/or adjuvants.

In addition, the invention relates to an above pharmaceutical preparation according to the invention, comprising at least one further medicament active compound.

Pharmaceutically or physiologically acceptable derivatives are taken to mean, for example, salts of the compounds of the present invention, and also so-called pro-drug compounds. Prodrug compounds are taken to mean derivatives of the compounds of the present invention which have been modified by means of, for example, alkyl or acyl groups (see also amino- and hydroxyl-protecting groups below), sugars or oligopeptides and which are rapidly cleaved or liberated in the organism to form the effective molecules. These also include biodegradable polymer derivatives of the compound of the present invention, as described, for example, in Int. J. Pharm. 115 (1995), 61-67.

The compound of the present invention can be used in its final non-salt form. On the other hand, the present invention also encompasses the use of the compound of the present invention in the form of its pharmaceutically acceptable salts, which can be derived from various organic and inorganic bases by procedures known in the art. Pharmaceutically acceptable salt forms of the compound of the present invention are for the most part prepared by conventional methods. If the compound of the present invention contains a carboxyl group, one of its suitable salts can be formed

by reacting the compound of the present invention ith a suitable base to give the corresponding base-addition salt. Such bases are, for example, alkali metal hydroxides, including potassium hydroxide, sodium hydroxide and lithium hydroxide; alkaline-earth metal hydroxides, such as barium hydroxide and calcium hydroxide; alkali metal alkoxides, for example potassium ethoxide and sodium propoxide; and various organic bases, such as piperidine, diethanolamine and N-methylglutamine. The aluminium salts of the compound of the present invetion are likewise included.

Furthermore, the base salts of the compounds of the present invention include aluminium, ammonium, calcium, copper, iron(III), iron(II), lithium, magnesium, manganese(III), manganese(II), potassium, sodium and zinc salts, but this is not intended to represent a restriction.

Of the above-mentioned salts, preference is given to ammonium; the alkali metal salts sodium and potassium, and the alkaline-earth metal salts calcium and magnesium. Salts of the compounds of the present invention which are derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary and tertiary amines, substituted amines, also including naturally occurring substituted amines, cyclic amines, and basic ion exchanger resins, for example arginine, betaine, caffeine, chloroprocaine, choline, N,N'-dibenzylethylenediamine (benzathine), dicyclohexylamine, diethanolamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lidocaine, lysine, meglumine, N-methyl-D-glucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethanolamine, triethylamine, trimethylamine, tripropylamine and tris-(hydroxymethyl)methylamine (tromethamine), but this is not intended to represent a restriction.

As mentioned, the pharmaceutically acceptable base-addition salts of the compound of the present invention are formed with metals or amines, such as alkali metals and alkaline-earth metals or organic amines. Preferred metals are sodium, potassium, magnesium and calcium. Preferred organic amines are N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, N-methyl-D-glucamine and procaine.

The base-addition salts of the compounds of the present invention are prepared by bringing the free acid form into contact with a sufficient amount of the desired base, causing the formation of the salt in a conventional manner. The free acid can be regenerated by bringing the salt form into contact with an acid and isolating the free acid in a conventional manner. The free acid forms differ in a certain respect from the corresponding salt forms thereof with respect to certain physical properties, such as solubility in polar solvents; for the purposes of the invention, however, the salts otherwise correspond to the respective free acid forms thereof.

In view of that stated above, it can be seen that the term “pharmaceutically acceptable salt” in the present connection is taken to mean an active compound which comprises the compound of the present invention in the form of one of its salts, in particular if this salt form imparts improved pharmacokinetic properties on the active compound compared with the free form of the active compound or any other salt form of the active compound used earlier. The pharmaceutically acceptable salt form of the active compound can also provide this active compound for the first time with a desired pharmacokinetic property which it did not have earlier and can even have a positive influence on the pharmacodynamics of this active compound with respect to its therapeutic efficacy in the body.

Solvates of the compound of the present invention are taken to mean adductions of inert solvent molecules of the compound of the present invention which form owing to their mutual attractive force. Solvates are, for example, hydrates, such as monohydrates or dihydrates, or alcoholates, i.e. addition compounds with alcohols, such as, for example, with methanol or ethanol.

All physiologically acceptable salts, derivatives, solvates and stereoisomers of these compounds, including mixtures thereof in all ratios, are also in accordance with the invention.

Compounds of the present invention may contain one or more centres of chirality, so that all stereoisomers, enantiomers, diastereomers, etc., of the compounds of the present inventionare also claimed in the present invention.

The invention also relates to the optically active forms (stereoisomers), the enantiomers, the racemates, the diastereomers and hydrates and solvates of these compounds.

Compounds of the present invention according to the invention may be chiral owing to their molecular structure and may accordingly occur in various enantiomeric forms. They may therefore be in racemic or optically active form. Since the pharmaceutical efficacy of the racemates or stereoisomers of the compounds according to the invention may differ, it may be desirable to use the enantiomers. In these cases, the end product, but also even the intermediates, may be separated into enantiomeric compounds by chemical or physical measures known to the person skilled in the art or already employed as such in the synthesis.

Pharmaceutically or physiologically acceptable derivatives are taken to mean, for example, salts of the compounds according to the invention and also so-called prodrug compounds. Prodrug compounds are taken to mean compounds of the present invention which have been modified with, for example, alkyl or acyl groups (see also amino- and hydroxyl-protecting groups below), sugars or oligopeptides and which are rapidly cleaved or liberated in the organism to form the effective compounds according to the invention. These also include biodegradable polymer derivatives of the compounds according to the invention, as described, for example, in Int. J. Pharm. 115 (1995), 61-67.

Suitable acid-addition salts are inorganic or organic salts of all physiologically or pharmacologically acceptable acids, for example halides, in particular hydrochlorides or hydrobromides, lactates, sulfates, citrates, tartrates, maleates, fumarates, oxalates, acetates, phosphates, methylsulfonates or p-toluenesulfonates.

Very particular preference is given to the hydrochlorides, the trifluoroacetates or the bistrifluoroacetates of the compounds according to the invention.

Solvates of the compounds of the present invention are taken to mean adductions of inert solvent molecules onto the compounds of the present invention which form owing to their mutual attractive force. Solvates are, for example, hydrates, such as

monohydrates or dihydrates, or alcoholates, i.e. addition compounds with alcohols, such as, for example, with methanol or ethanol.

It is furthermore intended that a compound of the present invention includes isotope-labelled forms thereof. An isotope-labelled form of a compound of the present inventionis identical to this compound apart from the fact that one or more atoms of the compound have been replaced by an atom or atoms having an atomic mass or mass number which differs from the atomic mass or mass number of the atom which usually occurs naturally. Examples of isotopes which are readily commercially available, and which can be incorporated into a compound of the present invention by well-known methods include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, fluorine and chlorine, for example ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F and ^{36}Cl, respectively. A compound of the present invention, a prodrug thereof or a pharmaceutically acceptable salt of either which contains one or more of the above-mentioned isotopes and/or other isotopes of other atoms is intended to be part of the present invention. An isotope-labelled compound of the present invention can be used in a number of beneficial ways. For example, an isotope-labelled compound of the present invention into which, for example, a radioisotope, such as ^{3}H or ^{14}C, has been incorporated is suitable for medicament and/or substrate tissue distribution assays. These radioisotopes, i.e. tritium (^{3}H) and carbon-14 (^{14}C), are particularly preferred owing to their simple preparation and excellent detectability. Incorporation of heavier isotopes, for example deuterium (^{2}H), into a compound of the present invention has therapeutic advantages owing to the higher metabolic stability of this isotope-labelled compound. Higher metabolic stability translates directly into an increased in-vivo half-life or lower dosages, which under most circumstances would represent a preferred embodiment of the present invention. An isotope-labelled compound of the present invention can usually be prepared by carrying out the procedures disclosed in the synthesis schemes and the related description, in the example part and in the preparation part in the present text, replacing a non-isotope-labelled reactant with a readily available isotope-labelled reactant.

In order to manipulate the oxidative metabolism of the compound by way of the primary kinetic isotope effect, deuterium (^{2}H) can also be incorporated into a compound of the present invention. The primary kinetic isotope effect is a change in the

rate of a chemical reaction that results from exchange of isotopic nuclei, which in turn is caused by the change in ground state energies necessary for covalent bond formation after this isotopic exhange. Exchange of a heavier isotope usually results in a lowering of the ground state energy for a chemical bond and thus causes a reduction in the rate in rate-limiting bond breakage. If the bond breakage occurs in or in the vicinity of a saddle-point region along the coordinate of a multi-product reaction, the product distribution ratios can be altered substantially. For explanation: if deuterium is bonded to a carbon atom in a non-exchangeable position, rate differences of k_M/k_D = 2-7 are typical. If this rate difference is successfully applied to a compound of the present invention that is susceptible to oxidation, the profile of this compound in vivo can thereby be drastically modified and result in improved pharmacokinetic propeties.

When discovering and developing therapeutic agents, the person skilled in the art attempts to optimise pharmacokinetic parameters while retaining desirable in-vitro properties. It is reasonable to assume that many compounds with poor pharmacokinetic profiles are susceptible to oxidative metabolism. In-vitro liver microsomal assays currently available provide valuable information on the course of oxidative metabolism of this type, which in turn permits the rational design of deuterated compounds of the present invention with improved stability through resistance to such oxidative metabolism. Significant improvements in the pharmacokinetic profiles of the compounds of the present invention are thereby obtained and can be expressed quantitatively in terms of increases in the in-vivo half-life (T1/2), concentration at maximum therapeutic effect (C_{max}), area under the dose response curve (AUC), and F; and in terms of reduced clearance, dose and costs of materials.

The following is intended to illustrate the above: a compound of the present invention which has multiple potential sites of attack for oxidative metabolism, for example benzylic hydrogen atoms and hydrogen atoms bonded to a nitrogen atom, is prepared as a series of analogues in which various combinations of hydrogen atoms are replaced by deuterium atoms, so that some, most or all of these hydrogen atoms have been replaced by deuterium atoms. Half-life determinations enable favourable and accurate determination of the extent to which the improvement in resistance to oxidative metabolism has improved. In this way, it is determined that

the half-life of the parent compound can be extended by up to 100% as the result of deuterium-hydrogen exchange of this type.

The replacement of hydrogen by deuterium in a compound of the present inventioncan also be used to achieve a favourable modification of the metabolite spectrum of the starting compound in order to diminish or eliminate undesired toxic metabolites. For example, if a toxic metabolite arises through oxidative carbon-hydrogen (C-H) bond cleavage, it can reasonably be assumed that the deuterated analogue will greatly diminish or eliminate production of the undesired metabolite, even if the particular oxidation is not a rate-determining step. Further information on the state of the art with respect to deuterium-hydrogen exchange is given, for example in Hanzlik et al., J. Org. Chem. 55, 3992-3997, 1990, Reider et al., J. Org. Chem. 52, 3326-3334, 1987, Foster, Adv. Drug Res. 14, 1-40, 1985, Gillette et al., Biochemistry 33(10), 2927-2937, 1994, and Jarman et al., Carcinogenesis 16(4), 683-688, 1993.

The invention also relates to mixtures of the compounds of the present invention according to the invention, for example mixtures of two diastereomers, for example in the ratio 1:1, 1:2, 1:3, 1:4, 1:5, 1:10, 1:100 or 1:1000. These are particularly preferably mixtures of two stereoisomeric compounds. However, preference is also given to mixtures of two or more compounds of the present invention.

In addition, the invention relates to a process for the preparation of the compounds of the present invention, characterized in that

a) the base of a compound of the present invention is converted into one of its salts by treatment with an acid, or

b) an acid of a compound of the present invention is converted into one of its salts by treatment with a base.

It is also possible to carry out the reactions stepwise in each case and to modify the sequence of the linking reactions of the building blocks with adaptation of the protecting-group concept.

The starting materials or starting compounds are generally known. If they are novel, they can be prepared by methods known per se.

If desired, the starting materials can also be formed in situ by not isolating them from the reaction mixture, but instead immediately converting them further into the compounds of the present invention.

The compounds of the present invention are preferably obtained by liberating them from their functional derivatives by solvolysis, in particular by hydrolysis, or by hydrogenolysis. Preferred starting materials for the solvolysis or hydrogenolysis are those which contain correspondingly protected amino, carboxyl and/or hydroxyl groups instead of one or more free amino, carboxyl and/or hydroxyl groups, preferably those which carry an amino-protecting group instead of an H atom which is connected to an N atom. Preference is furthermore given to starting materials which carry a hydroxyl-protecting group instead of the H atom of a hydroxyl group. Preference is also given to starting materials which carry a protected carboxyl group instead of a free carboxyl group. It is also possible for a plurality of identical or different protected amino, carboxyl and/or hydroxyl groups to be present in the molecule of the starting material. If the protecting groups present are different from one another, they can in many cases be cleaved off selectively.

The term “amino-protecting group” is generally known and relates to groups which are suitable for protecting (blocking) an amino group against chemical reactions, but which can easily be removed after the desired chemical reaction has been carried out elsewhere in the molecule. Typical of such groups are, in particular, unsubstituted or substituted acyl groups, furthermore unsubstituted or substituted aryl (for example 2,4-dinitophenyl) or aralkyl groups (for example benzyl, 4-nitrobenzyl, triphenylmethyl). Since the amino-protecting groups are removed after the desired reaction or reaction sequence, their type and size are, in addition, not crucial, but preference is given to those having 1-20, in particular 1-8, C atoms. The term “acyl group” is to be understood in the broadest sense in connection with the present process. It encompasses acyl groups derived from aliphatic, araliphatic, aromatic or heterocyclic carboxylic acids or sulfonic acids and, in particular, alkoxy-carbonyl, aryloxycarbonyl and especially aralkoxycarbonyl groups. Examples of such acyl groups are alkanoyl, such as acteyl, propionyl, buturyl, aralkanoyl, such as phenylacetyl, aroyl, such as benzoyl or toluyl, aryoxyaklkanoyl, such as phenoxyacetyl, alkyoxycarbonyyl, such as methoxycarbonyl, ethoxycarbonyl, 2,2,2-

trichloroethoxycarbonyl, BOC, 2-iodoethoxycaronyl, aralkoxycarbonyl, such as CBZ, 4-methoxybenzyloxycarbonyl or FMOC. Preferred acyl groups are CBZ, FMOC, benzyl and acetyl.

The term “acid-protecting group” or “carboxyl-protecting group” is likewise generally known and relates to groups which are suitable for protecting a −COOH group against chemical reactions, but which can easily be removed after the desired chemical reaction has been carried out elsewhere in the molecule. The use of esters instead of the free acids, for example of substituted and unsubstituted alkyl esters (such as methyl, ethyl, tert-butyl and substituted derivatives thereof), of substituted and unsubstituted benzyl esters or silyl esters, is typical. The type and size of the acid-protecting groups is not crucial, but preference is given to those having 1-20, in particular 1-10, C atoms.

The term “hydroxyl-protecting group” is likewise generally known and relates to groups which are suitable for protecting a hydroxyl group against chemical reactions, but which can easily be removed after the desired chemical reaction has been carried out elsewhere in the molecule. Typical of such groups are the above-mentioned unsubstituted or substituted aryl, aralkyl or acyl groups, furthermore also alkyl groups. Their type and size of the hydroxyl-protecting groups is not crucial, but preference is given to those having 1-20, in particular 1-10, C atoms. Examples of hyrdoxyl-protecting groups are, inter alia, benzyl, p-nitrobenzoyl, p-toluenesulfonyl and acetyl, where benzyl and acetyl are preferred.

Further typical examples of amino-, acid- and hydroxyl-protecting groups are found, for example, in “Greene’s Protective Groups in Organic Synthesis”, fourth edition, Wiley-Interscience, 2007.

The functional derivatives of the compounds of the present invention to be used as starting materials can be prepared by known methods of amino-acid and peptide synthesis, as described, for example, in the said standard works and patent applications.

The compounds of the present invention are liberated from their functional derivatives, depending on the protecting group used, for example, with the aid of strong

acids, advantageously using trifluoroacetic acid or perchloric acid, but also using other strong inorganic acids, such as hydrochloric acid or sulfuric acid, strong organic acids, such as trichloroacetic acid, or sulfonic acids, such as benzoyl- or p-toluenesulfonic acid. The presence of an additional inert solvent and/or a catalyst is possible but is not always necessary.

Depending on the respective synthetic route, the starting materials can optionally be reacted in the presence of an inert solvent.

Suitable inert solvents are, for example, heptane, hexane, petroleum ether, DMSO, benzene, toluene, xylene, trichloroethylene-, 1,2-dichloroethane, carbon tetrachloride, chloroform or dichloromethane; alcohols, such as methanol, ethanol, isopropanol, n-propanol, n-butanol or tert-butanol; ethers, such as diethyl ether, diisopropyl ether (preferably for substitution on the indole nitrogen), tetrahydrofuran (THF) or dioxane; glycol ethers, such as ethylene glycol monomethyl or monoethyl ether, ethylene glycol dimethyl ether (diglyme); ketones, such as acetone or butanone; amides, such as acetamide, dimethylacetamide, N-methylpyrrolidone (NMP) or dimethylformamide (DMF); nitriles, such as acetonitrile; esters, such as ethyl acetate, carboxylic acids or acid anhydrides, such as, for example, such as acetic acid or acetic anhydride, nitro compounds, such as nitromethane or nitro-benzene, optionally also mixtures of the said solvents with one another or mixtures with water.

The amount of solvent is not crucial; 10 g to 500 g of solvent can preferably be added per g of the compound of the present invention to be reacted.

It may be advantageous to add an acid-binding agent, for example an alkali metal or alkaline-earth metal hydroxide, carbonate or bicarbonate or other alkali or alkaline-earth metal salts of weak acids, preferably a potassium, sodium or calcium salt, or to add an organic base, such as, for example, triethylamine, dimethylamine, pyridine or quinoline, or an excess of the amine component.

The resultant compounds according to the invention can be separated from the corresponding solution in which they are prepared (for example by centrifugation and washing) and can be stored in another composition after separation, or they can

remain directly in the preparation solution. The resultant compounds according to the invention can also be taken up in desired solvents for the particular use.

The reaction duration depends on the reaction conditions selected. In general, the reaction duration is 0.5 hour to 10 days, preferably 1 to 24 hours. On use of a microwave, the reaction time can be reduced to values of 1 to 60 minutes.

The compounds of the present invention and also the starting materials for their preparation are, in addition, prepared by known methods, as described in the literature (for example in standard works, such as Houben-Weyl, Methoden der organischen Chemie [Methods of Organic Chemistry], Georg-Thieme-Verlag, Stuttgart), for example under reaction conditions which are known and suitable for the said reactions. Use can also be made here of variants known per se, which are not described here in greater detail.

Conventional work-up steps, such as, for example, addition of water to the reaction mixture and extraction, enable the compounds to be obtained after removal of the solvent. It may be advantageous, for further purification of the product, to follow this with a distillation or crystallisation or to carry out a chromatographic purification.

An acid of the present invention can be converted into the associated addition salt using a base, for example by reaction of equivalent amounts of the acid and base in an inert solvent, such as ethanol, and inclusive evaporation. Suitable bases for this reaction are, in particular, those which give physiologically acceptable salts. Thus, the acid of the present inventioncan be converted into the corresponding metal salt, in particular alkali or alkaline-earth metal salt, using a base (for example sodium hydroxide, potassium hydroxide, sodium carbonate or potassium carbonate) or into the corresponding ammonium salt. Organic bases which give physiologically acceptable salts, such as, for example, ethanolamine, are also suitable for this reaction.

On the other hand, a base of the present invention can be converted into the associated acid-addition salt using an acid, for example by reaction of equivalent amounts of the base and acid in an inert solvent, such as ethanol, with subsequent evaporation. Suitable acids for this reaction are, in particular, those which give

physiologically acceptable salts. Thus, it is possible to use inorganic acids, for example sulfuric acid, nitric acid, hydrohalic acids, such as hydrochloric acid or hydrobromic acid, phosphoric acids, such as orthophosphoric acid, sulfamic acid, furthermore organic acids, in particular aliphatic, alicyclic, araliphatic, aromatic or heterocyclic, mono- or polybasic carboxylic, sulfonic or sulfuric acids, for example formic acid, acetic acid, propionic acid, pivalic acid, diethylacetic acid, malonic acid, succinic acid, pimelic acid, fumaric acid, maleic acid, lactic acid, tartaric acid, malic acid, citric acid, gluconic acid, ascorbic acid, nicotinic acid, isonicotinic acid, methane- or ethanesulfonic acid, ethanedisulfonic acid, 2-hydroxysulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, naphthalenemom- and disulfonic acids or laurylsulfuric acid. Salts with physiologically unacceptable acids, for example picrates, can be used for the isolation and/or purfication of the compounds of the present invention.

It has been found that the compounds of the present invention are well tolerated and have valuable pharmacological properties.

The invention therefore furthermore relates to the use of compounds according to the invention for the preparation of a medicament for the treatment and/or prophylaxis of diseases which are caused, promoted and/or propagated by HSET.

The invention thus also relates, in particular, to a medicament comprising at least one compound according to the invention and/or one of its physiologically acceptable salts, derivatives, solvates, prodrugs and stereoisomers, including mixtures thereof in all ratios, for use in the treatment and/or prophylaxis of physiological and/or pathophysiological states.

Particular preference is given to physiological and/or pathophysiological states which are connected to HSET.

Physiological and/or pathophysiological states are taken to mean physiological and/or pathophysiological states which are medically relevant, such as, for example, diseases or illnesses and medical disorders, complaints, symptoms or complications and the like, in particular diseases.

The invention furthermore relates to a medicament comprising at least one compound according to the invention and/or one of its physiologically acceptable salts, derivatives, solvates, prodrugs and stereoisomers, including mixtures thereof in all ratios, for use in the treatment and/or prophylaxis of physiological and/or pathophysiological states selected from the group consisting of hyperproliferative diseases and disorders.

The invention further relates to a medicament comprising at least one compound according to the invention and/or one of its physiologically acceptable salts, derivatives, solvates, prodrugs and stereoisomers, including mixtures thereof in all ratios, for use in the treatment and/or prophylaxis of physiological and/or pathophysiological states selected from the group consisting of hyperproliferative and infectious diseases and disorders, wherein the hyperproliferative disease or disorder is cancer.

The invention thus particularly preferably relates to a medicament comprising at least one compound according to the invention and/or one of its physiologically acceptable salts, derivatives, solvates, prodrugs and stereoisomers, including mixtures thereof in all ratios, wherein the cancer is selected from the group consisting of from the group consisting of acute lymphocytic leukemia, acute granulocytic leukemia, adrenal cortex cancer, bladder cancer, brain cancer, breast cancer, cervical hyperplasia, cervical cancer, chorio cancer, chronic granulocytic leukemia, chronic lymphocytic leukemia, colon cancer, endometrial ccancer, esophageal cancer, essential thrombocytosis, genitourinary carcinoma, glioma, glioblastoma, hairy cell leukemia, head and neck carcinoma, Hodgkin's disease, Kaposi's sarcoma, lung carcinoma, lymphoma, malignant carcinoid carcinoma, malignant hypercalcemia, malignant melanoma, malignant pancreatic insulinoma, medullary thyroid carcinoma, melanoma, multiple myeloma, mycosis fungoides, myeloid and lymphocytic leukemia, neuroblastoma, non-Hodgkin's lymphoma, non-small cell lung cancer, osteogenic sarcoma, ovarian carcinoma, pancreatic carcinoma, polycythemia vera, primary brain carcinoma, primary macroglobulinemia, prostatic cancer, renal cell cancer, rhabdomyosarcoma, skin cancer, small-cell lung cancer, soft-tissue sarcoma, squamous cell cancer, stomach cancer, testicular cancer, thyroid cancer and Wilms' tumor.

The invention further preferably relates to a medicament comprising at least one compound according to the invention and/or one of its physiologically acceptable salts, derivatives, solvates, prodrugs and stereoisomers, including mixtures thereof in all ratios, for use in the treatment and/or prophylaxis of physiological and/or pathophysiological states selected from the group consisting of hyperproliferative and infectious diseases and disorders, wherein the hyperproliferative disease or disorder is selected from the group consisting of age-related macular degeneration, Crohn's disease, cirrhosis, chronic inflammatory-related disorders, proliferative diabetic retinopathy, proliferative vitreoretinopathy, retinopathy of prematurity, granulomatosis, immune hyperproliferation associated with organ or tissue transplantation and an immunoproliferative disease or disorder selected from the group comnsisting of inflammatory bowel disease, psoriasis, rheumatoid arthritis, systemic lupus erythematosus (SLE), vascular hyperproliferation secondary to retinal hypoxia and vasculitis.

It is intended that the medicaments disclosed above include a corresponding use of the compounds according to the invention for the preparation of a medicament for the treatment and/or prophylaxis of the above physiological and/or pathophysiological states.

It is additionally intended that the medicaments disclosed above include a corresponding method for the treatment and/or prophylaxis of the above physiological and/or pathophysiological states in which at least one compound according to the invention is administered to a patient in need of such a treatment.

The compounds according to the invention preferably exhibit an advantageous biological activity which can easily be demonstrated in enzyme assays and animal experiments, as described in the examples. In such enzyme-based assays, the compounds according to the invention preferably exhibit and cause an inhibiting effect, which is usually documented by IC_{50} values in a suitable range, preferably in the micromolar range and more preferably in the nanomolar range.

The compounds according to the invention can be administered to humans or animals, in particular mammals, such as apes, dogs, cats, rats or mice, and can be used in the therapeutic treatment of the human or animal body and in the combating

of the above-mentioned diseases. They can furthermore be used as diagnostic agents or as reagents.

Furthermore, compounds according to the invention can be used for the isolation and investigation of the activity or expression of HSET. In addition, they are particularly suitable for use in diagnostic methods for diseases in connection with disturbed HSET activity. The invention therefore furthermore relates to the use of the compounds according to the invention for the isolation and investigation of the activity or expression of HSET or as binders and inhibitors of HSET.

For diagnostic purposes, the compounds according to the invention can, for example, be radioactively labelled. Examples of radioactive labels are ^{3}H, ^{14}C, ^{231}I and ^{125}I. A preferred labelling method is the iodogen method (Fraker et al., 1978). In addition, the compounds according to the invention can be labelled by enzymes, fluorophores and chemophores. Examples of enzymes are alkaline phosphatase, β-galactosidase and glucose oxidase, an example of a fluorophore is fluorescein, an example of a chemophore is luminol, and automated detection systems, for example for fluorescent colorations, are described, for example, in US 4,125,828 and US 4,207,554.

The present invention further relates to pharmaceutical compositions containing the compounds of the present invention and their use for the treatment and/or prophylaxis of diseases and disorders where the partial or total inactivation of HSET could be beneficial.

The compounds of the present invention can be used for the preparation of pharmaceutical preparations, in particular by non-chemical methods. In this case, they are brought into a suitable dosage form together with at least one solid, liquid and/or semi-liquid excipient or adjuvant and optionally in combination with one or more further active compound(s).

The invention therefore furthermore relates to pharmaceutical preparations comprising at least one compound of the present invention and/or physiologically acceptable salts, derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios. In particular, the invention also relates to pharmaceutical

preparations which comprise further excipients and/or adjuvants, and also to pharmaceutical preparations which comprise at least one further medicament active compound.

In particular, the invention also relates to a process for the preparation of a pharmaceutical preparation, characterised in that a compound of the present inventionand/or one of its physiologically acceptable salts, derivatives, solvates and stereoisomers, including mixtures thereof in all ratios, is brought into a suitable dosage form together with a solid, liquid or semi-liquid excipient or adjuvant and optionally with a further medicament active compound.

The pharmaceutical preparations according to the invention can be used as medicaments in human or veterinary medicine. The patient or host can belong to any mammal species, for example a primate species, particularly humans; rodents, including mice, rats and hamsters; rabbits; horses, cattle, dogs, cats, etc. Animal models are of interest for experimental investigations, where they provide a model for the treatment of a human disease.

Suitable carrier substances are organic or inorganic substances which are suitable for enteral (for example oral), parenteral or topical administration and do not react with the novel compounds, for example water, vegetable oils (such as sunflower oil or cod-liver oil), benzyl alcohols, polyethylene glycols, gelatine, carbohydrates, such as lactose or starch, magnesium stearate, talc, lanolin or vaseline. Owing to his expert knowledge, the person skilled in the art is familiar which adjuvants are suitable for the desired medicament formulation. Besides solvents, for example water, physiological saline solution or alcohols, such as, for example, ethanol, propanol or glycerol, sugar solutions, such as glucose or mannitol solutions, or a mixture of the said solvents, gel formers, tablet assistants and other active-ingredient carriers, it is also possible to use, for example, lubricants, stabilisers and/or wetting agents, emulsifiers, salts for influencing the osmotic pressure, anti-oxidants, dispersants, antifoams, buffer substances, flavours and/or aromas or flavour correctants, preservatives, solubilisers or dyes. If desired, preparations or medicaments according to the invention may comprise one or more further active compounds, for example one or more vitamins.

If desired, preparations or medicaments according to the invention may comprise one or more further active compounds and/or one or more action enhancers (adjuvants).

The terms “pharmaceutical formulation” and “pharmaceutical preparation” are used as synonyms for the purposes of the present invention.

As used here, “pharmaceutically tolerated” relates to medicaments, precipitation reagents, excipients, adjuvants, stabilisers, solvents and other agents which facilitate the administration of the pharmaceutical preparations obtained therefrom to a mammal without undesired physiological side effects, such as, for example, nausea, dizziness, digestion problems or the like.

In pharmaceutical preparations for parenteral administration, there is a requirement for isotonicity, euhydration and tolerability and safety of the formulation (low toxicity), of the adjuvants employed and of the primary packaging. Surprisingly, the compounds according to the invention preferably have the advantage that direct use is possible and further purification steps for the removal of toxicologically unacceptable agents, such as, for example, high concentrations of organic solvents or other toxicologically unacceptable adjuvants, are thus unnecessary before use of the compounds according to the invention in pharmaceutical formulations.

The invention particularly preferably also relates to pharmaceutical preparations comprising at least one compound according to the invention in precipitated non-crystalline, precipitated crystalline or in dissolved or suspended form, and optionally excipients and/or adjuvants and/or further pharmaceutical active compounds.

The compounds according to the invention preferably enable the preparation of highly concentrated formulations without unfavourable, undesired aggregation of the compounds according to the invention occurring. Thus, ready-to-use solutions having a high active-ingredient content can be prepared with the aid of compounds according to the invention with aqueous solvents or in aqueous media.

The compounds and/or physiologically acceptable salts and solvates thereof can also be lyophilised and the resultant lyophilisates used, for example, for the preparation of injection preparations.

Aqueous preparations can be prepared by dissolving or suspending compounds according to the invention in an aqueous solution and optionally adding adjuvants. To this end, defined volumes of stock solutions comprising the said further adjuvants in defined concentration are advantageously added to a solution or suspension having a defined concentration of compounds according to the invention, and the mixture is optionally diluted with water to the pre-calculated concentration. Alternatively, the adjuvants can be added in solid form. The amounts of stock solutions and/or water which are necessary in each case can subsequently be added to the aqueous solution or suspension obtained. Compounds according to the invention can also advantageously be dissolved or suspended directly in a solution comprising all further adjuvants.

The solutions or suspensions comprising compounds according to the invention and having a pH of 4 to 10, preferably having a pH of 5 to 9, and an osmolality of 250 to 350 mosmol/kg can advantageously be prepared. The pharmaceutical preparation can thus be administered directly substantially without pain intravenously, intra-arterially, intraarticularly, subcutaneously or percutaneously. In addition, the preparation may also be added to infusion solutions, such as, for example, glucose solution, isotonic saline solution or Ringer‘s solution, which may also contain further active compounds, thus also enabling relatively large amounts of active compound to be administered.

Pharmaceutical preparations according to the invention may also comprise mixtures of a plurality of compounds according to the invention.

The preparations according to the invention are physiologically well tolerated, easy to prepare, can be dispensed precisely and are preferably stable with respect to assay, decomposition products and aggregates throughout storage and transport and during multiple freezing and thawing processes. They can preferably be stored in a stable manner over a period of at least three months to two years at refrigerator

temperature (2-8°C) and at rt (23-27 °C) and 60% relative atmospheric humidity (R.H.).

For example, the compounds according to the invention can be stored in a stable manner by drying and when necessary converted into a ready-to-use pharmaceutical preparation by dissolution or suspension. Possible drying methods are, for example, without being restricted to these examples, nitrogen-gas drying, vacuum-oven drying, lyophilisation, washing with organic solvents and subsequent air drying, liquid-bed drying, fluidised-bed drying, spray drying, roller drying, layer drying, air drying at rt and further methods.

The term “effective amount” denotes the amount of a medicament or of a pharmaceutical active compound which causes in a tissue, system, animal or human a biological or medical response which is sought or desired, for example, by a researcher or physician.

In addition, the term “therapeutically effective amount” denotes an amount which, compared with a corresponding subject who has not received this amount, has the following consequence: improved treatment, healing, prevention or elimination of a disease, syndrome, disease state, complaint, disorder or prevention of side effects or also a reduction in the progress of a disease, complaint or disorder. The term “therapeutically effective amount” also encompasses the amounts which are effective for increasing normal physiological function.

On use of preparations or medicaments according to the invention, the compounds according to the invention and/or physiologically acceptable salts and solvates thereof are generally used analogously to known, commercially available preparations or preparations, preferably in dosages of between 0.1 and 500 mg, in particular 5 and 300 mg, per use unit. The daily dose is preferably between 0.001 and 250 mg/kg, in particular 0.01 and 100 mg/kg, of body weight. The preparation can be administered one or more times per day, for example two, three or four times per day. However, the individual dose for a patient depends on a large number of individual factors, such as, for example, on the efficacy of the particular compound used, on the age, body weight, general state of health, sex, nutrition, on the time

and method of administration, on the excretion rate, on the combination with other medicaments and on the severity and duration of the particular disease.

A measure of the uptake of a medicament active compound in an organism is its bioavailability. If the medicament active compound is delivered to the organism intravenously in the form of an injection solution, its absolute bioavailability, i.e. the proportion of the pharmaceutical which reaches the systemic blood, i.e. the major circulation, in unchanged form, is 100%. In the case of oral administration of a therapeutic active compound, the active compound is generally in the form of a solid in the formulation and must therefore first be dissolved in order that it is able to overcome the entry barriers, for example the gastrointestinal tract, the oral mucous membrane, nasal membranes or the skin, in particular the stratum corneum, or can be absorbed by the body. Data on the pharmacokinetics, i.e. on the bioavailability, can be obtained analogously to the method of J. Shaffer et al., J. Pharm. Sciences, 88 (1999), 313-318.

Furthermore, medicaments of this type can be prepared by means of one of the processes generally known in the pharmaceutical art.

Medicaments can be adapted for administration via any desired suitable route, for example by the oral (including buccal or sublingual), rectal, pulmonary, nasal, topical (including buccal, sublingual or transdermal), vaginal or parenteral (including subcutaneous, intramuscular, intravenous, intradermal and in particular intra-articular) routes. Medicaments of this type can be prepared by means of all processes known in the pharmaceutical art by, for example, combining the active compound with the excipient(s) or adjuvant(s).

Parenteral administration is preferably suitable for administration of the medicaments according to the invention. In the case of parenteral administration, intra-articular administration is particularly preferred.

The compounds according to the invention are also suitable for the preparation of medicaments to be administered parenterally having slow, sustained and/or controlled release of active compound. They are thus also suitable for the

preparation of delayed-release formulations, which are advantageous for the patient since administration is only necessary at relatively large time intervals.

The medicaments adapted to parenteral administration include aqueous and non-aqueous sterile injection solutions comprising antioxidants, buffers, bacteriostatics and solutes, by means of which the formulation is rendered isotonic with the blood or synovial fluid of the recipient to be treated; as well as aqueous and non-aqueous sterile suspensions, which can comprise suspension media and thickeners. The formulations can be delivered in sigle-dose or multi-dose containers, for example sealed ampoules and vials, and stored in the freeze-dried (lyophilised) state, so that only the addition of the sterile carrier liquid, for example water for injection purposes, immediately before use is necessary. Injection solutions and suspensions prepared in accordance with the formulation can be prepared from sterile powders, granules and tablets.

The compounds according to the invention can also be administered in the form of liposome delivery systems, such as, for example, small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from various phospholipids, such as, for example, cholesterol, stearylamine or phosphatidylcholines.

The compounds according to the invention can also be coupled to soluble polymers as targeted medicament excipients. Such polymers can encompass polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamidophenol, polyhydroxyethylaspartamidophenol or polyethylene oxide polylysine, substituted by palmitoyl radicals. The compounds according to the invention can furthermore be coupled to a class of biodegradable polymers which are suitable for achieving slow release of a medicament, for example polylactic acid, poly-epsilon-caprolactone, polyhydroxybutyric acid, polyorthoesters, polyacetals, polydihydroxypyrans, poly-cyanoacrylates, polylactic-co-glycolic acid, polymers, such as conjugates between dextran and methacrylates, polyphosphoesters, various polysaccharides and poly-amines and poly-ε-caprolactone, albumin, chitosan, collagen or modified gelatine and crosslinked or amphipathic block copolymers of hydrogels.

Suitable for enteral administration (oral or rectal) are, in particular, tablets, dragees, capsules, syrups, juices, drops or suppositories, and suitable for topical use are ointments, creams, pastes, lotions, gels, sprays, foams, aerosols, solutions (for example solutions in alcohols, such as ethanol or isopropanol, acetonitrile, DMF, dimethylacetamide, 1,2-propanediol or mixtures thereof with one another and/or with water) or powders. Also, particularly suitable for topical uses are liposomal preparations.

In the case of formulation to give an ointment, the active compound can be employed either with a paraffinic or a water-miscible cream base. Alternatively, the active compound can be formulated to a cream with an oil-in-water cream base or a water-in-oil base.

Medicaments adapted to transdermal administration can be delivered as independent plasters for extended, close contact with the epidermis of the recipient. Thus, for example, the active compound can be supplied from the plaster by means of iontophoresis, as described in general terms in Pharmaceutical Research, 3 (6), 318 (1986).

It goes without saying that, besides the constituents particularly mentioned above, the medicaments according to the invention may also comprise other agents usual in the art with respect to the particular type of pharmaceutical formulation.

The invention also relates to a set (kit) consisting of separate packs of
a) an effective amount of a compound of the present invention and/or physiologically acceptable salts, derivatives, solvates, prodrugs and stereoisomers thereof, including mixtures thereof in all ratios, and
b) an effective amount of a further medicament active compound.

The set comprises suitable containers, such as boxes or cartons, individual bottles, bags or ampoules. The set may, for example, comprise separate ampoules each containing an effective amount of a compound of the present inventionand/or pharmaceutically acceptable salts, derivatives, solvates, prodrugs and stereoisomers thereof, including mixtures thereof in all ratios, and an effective amount of a further medicament active compound in dissolved or lyophilised form.

Furthermore, the medicaments according to the invention can be used in order to provide additive or synergistic effects in certain known therapies and/or can be used in order to restore the efficacy of certain existing therapies.

Besides the compounds according to the invention, the pharmaceutical preparations according to the invention may also comprise further medicament active compounds, for example for use in the treatment of cancer, other anti-tumor medicaments. For the treatment of the other diseases mentioned, the pharmaceutical preparations according to the invention may also, besides the compounds according to the invention, comprise further medicament active compounds which are known to the person skilled in the art in the treatment thereof.

In one principal embodiment, methods are provided for enhancing an immune response in a host in need thereof. The immune response can be enhanced by reducing T cell tolerance, including by increasing IFN-γ release, by decreasing regulatory T cell production or activation, or by increasing antigen-specific memory T cell production in a host. In one embodiment, the method comprises administering a compound of the present invention to a host in combination or alternation with an antibody. In particular subembodiments, the antibody is a therapeutic antibody. In one particular embodiment, a method of enhancing efficacy of passive antibody therapy is provided comprising administering a compound of the present invention in combination or alternation with one or more passive antibodies. This method can enhance the efficacy of antibody therapy for treatment of abnormal cell proliferative disorders such as cancer or can enhance the efficacy of therapy in the treatment or prevention of infectious diseases. The compound of the present invention can be administered in combination or alternation with antibodies such as rituximab, herceptin or erbitux, for example.

In another principal embodiment, a method of treating or preventing abnormal cell proliferation is provided comprising administering a compound of the present invention to a host in need thereof substantially in the absence of another anti-cancer agent.

In another principal embodiment, a method of treating or preventing abnormal cell proliferation in a host in need thereof is provided, comprising administering a first compound of the present invention substantially in combination with a first anti-cancer agent to the host and subsequently administering a second compound of the present invention receptor antagonist. In one subembodiment, the second antagonist is administered substantially in the absence of another anti-cancer agent. In another principal embodiment, a method of treating or preventing abnormal cell proliferation in a host in need thereof is provided, comprising administering a compound of the present invention substantially in combination with a first anti-cancer agent to the host and subsequently administering a second anti-cancer agent in the absence of the antagonist.

Thus, the cancer treatment disclosed here can be carried out as therapy with a compound of the present invention or in combination with an operation, irradiation or chemotherapy. Chemotherapy of this type can include the use of one or more active compounds of the following categories of antitumour active compounds:
(i) antiproliferative/antineoplastic/DNA-damaging active compounds and combinations thereof, as used in medical oncology, such as alkylating active compounds (for example cis-platin, parboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan and nitrosoureas); antimetabolites (for example antifolates such as fluoropyrimidines such as 5-fluorouracil and tegafur, raltitrexed, methotrexate, cytosine arabinoside, hydroxyurea and gemcitabine); antitumour antibiotics (for example anthracyclines, such as adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin and mithramycin); antimitotic active compounds (for example vinca alkaloids, such as vincristine, vinblastine, vindesine and vinorelbine, and taxoids, such as taxol and taxotere); topoisomerase inhibitors (for example epipodophyllotoxins, such as etoposide and teniposide, amsacrine, topotecan, irinotecan and camptothecin) and cell-differentiating active compounds (for example all-trans-retinoic acid, 13-cis-retinoic acid and fenretinide);
(ii) cytostatic active compounds, such as anti-oestrogens (for example tamoxifen, toremifene, raloxifene, droloxifene and iodoxyfene), oestrogen receptor regulators (for example fulvestrant), anti-androgens (for example bicalutamide, flutamide, nilutamide and cyproterone acetate), LHRH antagonists or LHRH agonists (for example goserelin, leuprorelin and buserelin), progesterones (for example

megestrol acetate), aromatase inhibitors (for example anastrozole, letrozole, vorazole and exemestane) and inhibitors of 5α-reductase, such as finasteride;

(iii) active compounds which inhibit cancer invasion including for example metallo-proteinase inhibitors, like marimastat, and inhibitors of urokinase plasminogen activator receptor function;

(iv) inhibitors of growth factor function, for example growth factor antibodies, growth factor receptor antibodies, for example the anti-erbb2 antibody trastuzumab [Herceptin™] and the anti-erbbl antibody cetuximab [C225]), farnesyl transferase inhibitors, tyrosine kinase inhibitors and serine/threonine kinase inhibitors, for example inhibitors of the epidermal growth factor family (for example EGFR family tyrosine kinase inhibitors, such as N-(3-chloro-4-fluorophenyl)-7-methoxy-6- (3-morpholinopropoxy) quinazolin-4-amine (gefitinib, AZD1839), N-(3-ethynylphenyl)-6,7-bis (2-methoxyethoxy)quinazolin-4-amine (erlotinib, OSI-774) and 6-acrylamido-N-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)quinazolin-4-amine (CI 1033), for example inhibitors of the platelet-derived growth factor family and, for example, inhibitors of the hepatocyte growth factor family;

(v) anti-angiogenic active compounds, such as bevacizumab, angiostatin, endostatin, linomide, batimastat, captopril, cartilage derived inhibitor, genistein, interleukin 12, lavendustin, medroxypregesterone acetate, recombinant human platelet factor 4, tecogalan, thrombospondin, TNP-470, anti-VEGF monoclonal antibody, soluble VEGF-receptor chimaeric protein, anti-VEGF receptor antibodies, anti-PDGF receptors, inhibitors of integrins, tyrosine kinase inhibitors, serine/threonine kinase inhibitors, antisense oligonucleotides, antisense oligodexoynucleotides, siRNAs, anti-VEGF aptamers, pigment epithelium derived factor and compounds which have been published in the international patent applications WO 97/22596, WO 97/30035, WO 97/32856 and WO 98/13354);

(vi) vessel-destroying agents, such as combretastatin A4 and compounds which have been published in the international patent applications WO 99/02166, WO 00/40529, WO 00/41669, WO 01/92224, WO 02/04434 and WO 02/08213;

(vii) antisense therapies, for example those directed to the targets mentioned above, such as ISIS 2503, an anti-Ras antisense;

(viii) gene therapy approaches, including, for example, approaches for replacement of abnormal, modified genes, such as abnormal p53 or abnormal BRCA1 or BRCA2, GDEPT approaches (gene-directed enzyme pro-drug therapy), such as those which use cytosine deaminase, thymidine kinase or a bacterial nitroreductase enzyme,

and approaches which increase the tolerance of a patient to chemotherapy or radiotherapy, such as multi-drug resistance therapy; and

(ix) immunotherapy approaches, including, for example, ex-vivo and in-vivo approaches for increasing the immunogenicity of tumour cells of a patient, such as transfection with cytokines, such as interleukin 2, interleukin 4 or granulocyte macrophage colony stimulating factor, approaches for decreasing T-cell anergy, approaches using transfected immune cells, such as cytokine-transfected dendritic cells, approaches for use of cytokine-transfected tumour cells and approaches for use of anti-idiotypic antibodies

(x) chemotherapeutic agents including foor example abarelix, aldesleukin, alemtuzumab, alitretinoin, allopurinol, altretamine, amifostine, anastrozole, arsenic trioxide, asparaginase, BCG live, bevaceizumab, bexarotene, bleomycin, bortezomib, busulfan, calusterone, camptothecin, capecitabine, carboplatin, carmustine, celecoxib, cetuximab, chlorambucil, cinacalcet, cisplatin, cladribine, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, darbepoetin alfa, daunorubicin, denileukin diftitox, dexrazoxane, docetaxel, doxorubicin, dromostanolone, epirubicin, epoetin alfa, estramustine, etoposide, exemestane, filgrastim, floxuridine, fludarabine, fluorouracil, fulvestrant and gemcitabine.

The medicaments from table 1 can preferably, but not exclusively, be combined with the compounds of the present invention.

Table 1		
Alkylating active compounds	Cyclophosphamide Busulfan Ifosfamide Melphalan Hexamethylmelamine Thiotepa chloroambucil Dacarbazine Carmustine	Lomustine Procarbazine Altretamine Estramustine phosphate Mechloroethamine Streptozocin Temozolomide Semustine
Platinum active	Cisplatin	Carboplatin

compounds	Oxaliplatin Spiroplatin Carboxyphthalatoplatinum Tetraplatin Ormiplatin Iproplatin	ZD-0473 (AnorMED) Lobaplatin (Aetema) Satraplatin (Johnson Matthey) BBR-3464 (Hoffrnann-La Roche) SM-11355 (Sumitomo) AP-5280 (Access)
Antimetabolites	Azacytidine Gemcitabine Capecitabine 5-Fluorouracil Floxuridine 2-Chlorodesoxyadenosine 6-Mercaptopurine 6-Thioguanine Cytarabine 2-Fluorodesoxycytidine Methotrexate Idatrexate	Tomudex Trimetrexate Deoxycoformycin Fludarabine Pentostatin Raltitrexed Hydroxyurea Decitabine (SuperGen) Clofarabine (Bioenvision) Irofulven (MGI Pharrna) DMDC (Hoffmann-La Roche) Ethynylcytidine (Taiho)
Topoisomerase inhibitors	Amsacrine Epirubicin Etoposide Teniposide or mitoxantrone Irinotecan (CPT-11) 7-ethyl-10-hydroxycamptothecin Topotecan Dexrazoxanet (TopoTarget) Pixantrone (Novuspharrna) Rebeccamycin analogue (Exelixis)	Rubitecan (SuperGen) Exatecan mesylate (Daiichi) Quinamed (ChemGenex) Gimatecan (Sigma- Tau) Diflomotecan (Beaufour-Ipsen) TAS-103 (Taiho) Elsamitrucin (Spectrum) J-107088 (Merck & Co) BNP-1350 (BioNumerik) CKD-602 (Chong Kun Dang) KW-2170 (Kyowa Hakko)

	BBR-3576 (Novuspharrna)	
Antitumour antibiotics	Dactinomycin (Actinomycin D) Doxorubicin (Adriamycin) Deoxyrubicin Valrubicin Daunorubicin (Daunomycin) Epirubicin Therarubicin Idarubicin Rubidazon Plicamycinp Porfiromycin Cyanomorpholinodoxorubicin Mitoxantron (Novantron)	Amonafide Azonafide Anthrapyrazole Oxantrazole Losoxantrone Bleomycin sulfate (Blenoxan) Bleomycinic acid Bleomycin A Bleomycin B Mitomycin C MEN-10755 (Menarini) GPX-100 (Gem Pharmaceuticals)
Antimitotic active compounds	Paclitaxel Docetaxel Colchicine Vinblastine Vincristine Vinorelbine Vindesine Dolastatin 10 (NCI) Rhizoxin (Fujisawa) Mivobulin (Warner-Lambert) Cemadotin (BASF) RPR 109881A (Aventis) TXD 258 (Aventis) Epothilone B (Novartis) T 900607 (Tularik) T 138067 (Tularik) Cryptophycin 52 (Eli Lilly)	SB 408075 (GlaxoSmithKline) E7010 (Abbott) PG-TXL (Cell Therapeutics) IDN 5109 (Bayer) A 105972 (Abbott) A 204197 (Abbott) LU 223651 (BASF) D 24851 (ASTA Medica) ER-86526 (Eisai) Combretastatin A4 (BMS) Isohomohalichondrin-B (PharmaMar) ZD 6126 (AstraZeneca) PEG-Paclitaxel (Enzon) AZ10992 (Asahi) !DN-5109 (Indena)

	Vinflunine (Fabre) Auristatin PE (Teikoku Hormone) BMS 247550 (BMS) BMS 184476 (BMS) BMS 188797 (BMS) Taxoprexin (Protarga)	AVLB (Prescient NeuroPharma) Azaepothilon B (BMS) BNP- 7787 (BioNumerik) CA-4-prodrug (OXiGENE) Dolastatin-10 (NrH) CA-4 (OXiGENE)
Aromatase inhibitors	Aminoglutethimide Letrozole Anastrazole Formestan	Exemestan Atamestan (BioMedicines) YM-511 (Yamanouchi)
Thymidylate Synthase inhibitors	Pemetrexed (Eli Lilly) ZD-9331 (BTG)	Nolatrexed (Eximias) CoFactor™ (BioKeys)
DNA antagonists	Trabectedin (PharmaMar) Glufosfamide (Baxter International) Albumin + 32P (isotope solutions) Thymectacin (NewBiotics) Edotreotid (Novartis)	Mafosfamide (Baxter International) Apaziquone (Spectrum Pharmaceuticals) O6-benzylguanine (Paligent)
Farnesyl transferase inhibitors	Arglabin (NuOncology Labs) Lonafarnib (Schering-Plough) BAY-43-9006 (Bayer)	Tipifarnib (Johnson & Johnson) Perillyl alcohol (DOR BioPharma)
Pump inhibitors	CBT-1 (CBA Pharma) Tariquidar (Xenova) MS-209 (Schering AG)	Zosuquidar trihydrochloride (Eli Lilly) Biricodar dicitrate (Vertex)

Histone acetyl trans-ferase inhibitors	Tacedinaline (Pfizer) SAHA (Aton Pharma) MS-275 (Schering AG)	Pivaloyloxymethyl butyrate (Titan) Depsipeptide (Fujisawa)
Metalloproteinase inhibitors Ribonucleoside reductase inhibitors	Neovastat (Aeterna Laboratories) Marimastat (British Biotech) Gallium maltolate (Titan) Triapin (Vion)	CMT -3 (CollaGenex) BMS-275291 (Celltech) Tezacitabine (Aventis) Didox (Molecules for Health)
TNF-alpha agonists / antagonists	Virulizin (Lorus Therapeutics) CDC-394 (Celgene)	Revimid (Celgene)
Endothelin-A re-ceptor antagonists	Atrasentan (Abbot) ZD-4054 (AstraZeneca)	YM-598 (Yamanouchi)
Retinoic acid receptor agonists	Fenretinide (Johnson & Johnson) LGD-1550 (ligand)	Alitretinoin (Ligand)
Immunomodulators	Interferon Oncophage (Antigenics) GMK (Progenics) Adenocarcinoma vaccine (Biomira) CTP-37 (AVI BioPharma) JRX-2 (Immuno-Rx) PEP-005 (Peplin Biotech) Synchrovax vaccines (CTL Immuno) Melanoma vaccines (CTL Immuno) p21-RAS vaccine (GemVax)	Dexosome therapy (Anosys) Pentrix (Australian Cancer Technology) JSF-154 (Tragen) Cancer vaccine (Intercell) Norelin (Biostar) BLP-25 (Biomira) MGV (Progenics) !3-Alethin (Dovetail) CLL-Thera (Vasogen)

Hormonal and antihormonal active compounds	Oestrogens Conjugated oestrogens Ethynyloestradiol Chlorotrianisene Idenestrol Hydroxyprogesterone caproate Medroxyprogesterone Testosterone Testosterone propionate Fluoxymesterone Methyltestosterone Diethylstilbestrol Megestrol Tamoxifen Toremofin Dexamethasone	Prednisone Methylprednisolone Prednisolone Aminoglutethimide Leuprolide Goserelin Leuporelin Bicalutamide Flutamide Octreotide Nilutamide Mitotan P-04 (Novogen) 2-Methoxyoestradiol (En_-treMed) Arzoxifen (Eli Lilly)
Photodynamic active compounds	Talaporfin (Light Sciences) Theralux (Theratechnologies) Motexafin-Gadolinium (Pharmacyclics)	Pd bacteriopheophorbide (Yeda) Lutetium texaphyrin (Pharmacyclics) Hypericin

Tyrosine kinase inhibitors	Imatinib (Novartis) Leflunomide(Sugen/Pharmacia ZDI839 (AstraZeneca) Erlotinib (Oncogene Science) Canertjnib (Pfizer) Squalamine (Genaera) SU5416 (Pharmacia) SU6668 (Pharmacia) ZD4190 (AstraZeneca) ZD6474 (AstraZeneca) Vatalanib (Novartis) PKI166 (Novartis) GW2016 (GlaxoSmithKline) EKB-509 (Wyeth) EKB-569 (Wyeth)	Kahalide F (PharmaMar) CEP- 701 (Cephalon) CEP-751 (Cephalon) MLN518 (Millenium) PKC412 (Novartis) Phenoxodiol O Trastuzumab (Genentech) C225 (ImClone) rhu-Mab (Genentech) MDX-H210 (Medarex) 2C4 (Genentech) MDX-447 (Medarex) ABX-EGF (Abgenix) IMC-1C11 (ImClone)
Various other active compounds	SR-27897 (CCK-A inhibitor, Sanofi-Synthelabo) Tocladesine (cyclic AMP agonist, Ribapharm) Alvocidib (CDK inhibitor, Aventis) CV-247 (COX-2 inhibitor, Ivy Medical) P54 (COX-2 inhibitor, Phytopharm) CapCell™ (CYP450 stimulant, Bavarian Nordic) GCS-IOO (gal3 antagonist, GlycoGenesys) G17DT immunogen (gastrin inhibitor, Aphton) Efaproxiral (oxygenator, Allos Therapeutics) PI-88 (heparanase inhibitor, Progen)	BCX-1777 (PNP inhibitor, BioCryst) Ranpirnase (ribonuclease stimulant, Alfacell) Galarubicin (RNA synthesis inhibitor, Dong-A) Tirapazamine (reducing agent, SRI International) N-Acetylcysteine (reducing agent, Zambon) R-Flurbiprofen (NF-kappaB inhibitor, Encore) 3CPA (NF-kappaB inhibitor, Active Biotech) Seocalcitol (vitamin D receptor agonist, Leo) 131-I-TM-601 (DNA antagonist, TransMolecular) Eflornithin (ODC inhibitor,

	Tesmilifen (histamine antagonist, YM BioSciences) Histamine (histamine H2 receptor agonist, Maxim) Tiazofurin (IMPDH inhibitor, Ribapharm) Cilengitide (integrin antagonist, Merck KGaA) SR-31747 (IL-1 antagonist, Sanofi-Synthelabo) CCI-779 (mTOR kinase inhibitor, Wyeth) Exisulind (PDE-V inhibitor, Cell Pathways) CP-461 (PDE-V inhibitor, Cell Pathways) AG-2037 (GART inhibitor, Pfizer) WX-UK1 (plasminogen activator inhibitor, Wilex) PBI-1402 (PMN stimulant, ProMetic LifeSciences) Bortezomib (proteasome inhibitor, Millennium) SRL-172 (T-cell stimulant, SR Pharma) TLK-286 (glutathione-S transferase inhibitor, Telik) PT-100 (growth factor agonist, Point Therapeutics) Midostaurin (PKC inhibitor, Novartis) Bryostatin-1 (PKC stimulant, GPC Biotech)	ILEX Oncology) Minodronic acid (osteoclast inhibitor, Yamanouchi) Indisulam (p53 stimulant, Eisai) Aplidin (PPT inhibitor, PharmaMar) Rituximab (CD20 antibody, Genentech) Gemtuzumab (CD33 antibody, Wyeth Ayerst) PG2 (haematopoiesis promoter, Pharmagenesis) Immunol™ (triclosan mouthwash, Endo) Triacetyluridine (uridine prodrug, Wellstat) SN-4071 (sarcoma agent, Signature BioScience) TransMID-107™ (immunotoxin, KS Biomedix) PCK-3145 (apoptosis promoter, Procyon) Doranidazole (apoptosis promoter, Pola) CHS-828 (cytotoxic agent, Leo) trans-Retinoic acid (differentiator, NIH) MX6 (apoptosis promoter, MAXIA) Apomine (apoptosis promoter, ILEX Oncology) Urocidin (apoptosis

	CDA-II (apoptosis promoter, Everlife) SDX-101 (apoptosis promoter, Salmedix) Ceflatonin (apoptosis promoter, ChemGenex)	promoter, Bioniche) Ro-31-7453 (apoptosis promoter, La Roche) Brostallicin (apoptosis promoter, Pharmacia)

Even without further embodiments, it is assumed that a person skilled in the art will be able to use the above description in the broadest scope. The preferred embodiments should therefore merely be regarded as descriptive disclosure which is absolutely not limiting in any way.

The following examples are thus intended to explain the invention without limiting it. Unless indicated otherwise, per cent data denote per cent by weight. All temperatures are indicated in degrees Celsius. “Conventional work-up”: water is added if necessary, the pH is adjusted, if necessary, to values between 2 and 10, depending on the constitution of the end product, the mixture is extracted with ethyl acetate or dichloromethane, the phases are separated, the organic phase is dried over sodium sulfate or magnesium sulfate, filtered and evaporated, and the product is purified by chromatography on silica gel and/or by crystallisation.
Rf values on silica gel; mass spectrometry: EI (electron impact ionisation): M^+, FAB (fast atom bombardment): $(M+H)^+$, THF (tetrahydrofuran), NMP (N-methlpyrrolidone), DMSO (dimethyl sulfoxide), EtOAc (ethyl acetate), MeOH (methanol), EtOH (ethanol), TLC (thin-layer chromatography)

List of Abbreviations

AUC	Area under the plasma drug concentration-time curve
C_{max}	Maximum plasma concentration
CL	Clearance
CV	Coefficient of variation
CYP	Cytochrome P450
DMSO	Dimethyl sulfoxide
F	Bioavailability
f_a	Fraction absorbed
iv	Intravenous

LC-MS/MS	Liquid chromatography tandem mass spectrometry
LLOQ	Lower limit of quantification
NC	Not calculated
ND	Not determined
PEG	Polyethylene glycol
Pgp	Permeability glycoprotein
PK	Pharmacokinetic(s)
po	Per os (oral)
rt	Room temperature
$t_{1/2}$	Half-life
t_{max}	Time at which maximum plasma concentration of drug is reached
UPLC	Ultra performance liquid chromatography
V_{ss}	Volume of distribution (at steady state)
v/v	Volume to volume

Preparation of the compounds of the present invention and analytical methods

The invention especially relates to the compounds of the following examples and physiologically acceptable salts, derivatives, solvates, prodrugs and stereoisomers thereof, including mixtures thereof in all ratios.

All solvents used were commercially available and used without further purification. Reactions were typically run using anhydrous solvents under an inert atmosphere of nitrogen or argon. Flash column chromatography was carried out using Silica gel 60 (0.035-0.070 mm particle size). Flash column chromatography was also carried out using a Biotage purification system using SNAP KP-Sil cartridges or on reverse-phase mode using SNAP Ultra C18 cartridges. Microwave-assisted reactions were carried out using a Biotage Initiator microwave system.

^{1}H NMR spectra were recorded on Bruker DPX-300, DRX-400, Avance II-400, Avance III HD-400, Avance II+-500, Avance III-500, Avance Neo 600 or on a Avance III-700 spectrometer, using residual signal of deuterated solvent as internal

reference. Chemical shifts (δ) are reported in ppm relative to tetramethylsilane (TMS), referenced to the internal deuterated solvent. ^{1}H NMR data are reported as follows: chemical shift (multiplicity, coupling constants, and number of hydrogens). Multiplicity is abbreviated as follows: s (singlet), d (doublet), t (triplet), q (quartet), sext (sextet), hept (heptet), m (multiplet), br (broad).

HPLC/MS spectra of the products were recorded on an Agilent 1100 HPLC system (1100 high pressure gradient pump, 1100 diode array detector, wavelength: 220 nm) interfaced to an Agilent 1100 mass spectrometer detector (positive mode). LC-MS analyses were performed on a SHIMADZU LC-MS machine consisting of an UFLC 20-AD system and LCMS 2020 MS detector.

Details of the applied conditions for HPLC/MS spectra recorded on a Shimadzu LCMS-2020 system or an Agilent 1100 system:

(A): column: Kinetex EVO C18, 4.6x50 mm, 5.0 µm; mobile phase A: water with 0.05% FA, mobile phase B: ACN with 0.04% FA and 1% water; gradient: 1% B to 99% B till min 0.8, 99% B to 1% B till min 1.1, stop after 1.50; flow: 3.3 mL/min.

(B): column: Chromolith HR RP-18e, 4.6x50 mm; mobile phase A: water with 0.05% FA, mobile phase B: ACN with 0.04% FA + 1% water; gradient: 0% B to 100% B till min 2.0, hold till min 2.5, 100% B to 0% B till min 2.51, stop after 2.95; flow: 3.3 mL/min.

(C) column: Sunfire C18, 3.0x100 mm, 5 µm; mobile phase A: water with 0.05% FA, mobile phase B: ACN with 0.04% FA and 1% water; gradient: 1% B to 99% B in 2.0 min, hold till min 2.7, 99% B to 1% B till min 2.71, stop after 3.5; flow: 1.4 mL/min.

(D): column: Chromolith HR C18, 4.6x50 mm; mobile phase A: water with 0.1% TFA, mobile phase B: ACN with 0.1% TFA; gradient: 1% B to 99% B till min 2.0, hold till min 2.5, 99% B to 1% B till min 2.51, stop after 2.95; flow: 3.3 mL/min.

(E): column: Kinetex EVO C18, 2.1x30 mm, 5.0 µm; mobile phase A: 0.0375% TFA in water (v/v), mobile phase B: 0.01875% TFA in Acetonitrile (v/v); gradient: 5% B to 95% B in 0.8 min, 95% B till min 1.2, 5% B til stop after 1.55 min; flow: 1.5 mL/min.

(F): column: Kinetex EVO C18, 2.1x30 mm, 5.0 µm; mobile phase A: 0.0375% TFA in water (v/v), mobile phase B: 0.01875% TFA in Acetonitrile (v/v); gradient: 0% B to 60% B in 0.8 min, 60% B till min 1.2, 0% B til stop after 1.55 min; flow: 1.5 mL/min.

(G): column: Kinetex EVO C18, 2.1x30 mm, 5.0 µm; mobile phase A: 0.025% $NH_3 \cdot H_2O$ in water (v/v), mobile phase B: Acetonitrile; gradient: 5% B to 95% B in 0.8 min, 95% B till min 1.2, 5% B til stop after 1.55 min; flow: 1.5 mL/min.

Details of the applied conditions for HPLC/MS spectra on an Agilent 1200 series HPLC and diode array detector coupled to a 6210 time of flight mass spectrometer with dual multimode APCI/ESI source.

(P): Analytical separation was carried out at 40°C on a Merck Chromolith Flash column (RP-18e, 25 x 2 mm) using a flow rate of 1.5 mL/min in a 2 minute gradient elution with detection at 254 nm. The mobile phase was a mixture of methanol (solvent A) and water (solvent B), both containing formic acid at 0.1%. Gradient elution was as follows: 5:95 (A/B) to 100:0 (A/B) over 1.25 min, 100:0 (A/B) for 0.5 min, and then reversion back to 5:95 (A/B) over 0.05 min, finally 5:95 (A/B) for 0.2 min.

(Q) Analytical separation was carried out at 30°C on a Merck Chromolith Flash column (RP-18e, 25 x 2 mm) using a flow rate of 0.75 mL/min in a 4 minute gradient elution with detection at 254 nm. The mobile phase was a mixture of methanol (solvent A) and water (solvent B), both containing formic acid at 0.1%. Gradient elution was as follows: 5:95 (A/B) to 100:0 (A/B) over 2.5 min, 100:0 (A/B) for 1 min, and then reversion back to 5:95 (A/B) over 0.1 min, finally 5:95 (A/B) for 0.4 min.

Details of the applied conditions for HPLC/MS spectra on a Waters Acquity UPLC and diode array detector coupled to a Waters G2 QToF mass spectrometer fitted with a multimode ESI/APCI source.

(R) Analytical separation was carried out at 30°C on a Phenomenex Kinetex C18 column (30 x 2.1 mm, 2.6u, 100A) using a flow rate of 0.5 mL/min in a 2 minute gradient elution with detection at 254 nm. The mobile phase was a mixture of

methanol (solvent A) and water (solvent B), both containing formic acid at 0.1%. Gradient elution was as follows: 10:90 (A/B) to 90:10 (A/B) over 1.25 min, 90:10 (A/B) for 0.5 min, and then reversion back to 10:90 (A/B) over 0.15 min, finally 10:90 (A/B) for 0.1 min.

(S) Analytical separation was carried out at 30°C on a Phenomenex Kinetex C18 column (30 x 2.1 mm, 2.6u, 100A) using a flow rate of 0.3 mL/min in a 4 minute gradient elution with detection at 254 nm. The mobile phase was a mixture of methanol (solvent A) and water (solvent B), both containing formic acid at 0.1%. Gradient elution was as follows: 10:90 (A/B) to 90:10 (A/B) over 3 min, 90:10 (A/B) for 0.5 min, and then reversion back to 10:90 (A/B) over 0.3 min, finally 10:90 (A/B) for 0.2 min.

(T) Analytical separation was carried out at 30°C on an Agilent Poroshell C18 column (30 x 2.1 mm, 2.6u, 100A) using a flow rate of 0.5 mL/min in a 2 minute gradient elution with detection at 254 nm. The mobile phase was a mixture of methanol (solvent A) and water (solvent B), both containing formic acid at 0.1%. Gradient elution was as follows: 10:90 (A/B) to 90:10 (A/B) over 1.25 min, 90:10 (A/B) for 0.5 min, and then reversion back to 10:90 (A/B) over 0.15 min, finally 10:90 (A/B) for 0.1 min.

(U) Analytical separation was carried out at 30°C on an Agilent Poroshell C18 column (30 x 2.1 mm, 2.6u, 100A) using a flow rate of 0.3 mL/min in a 4 minute gradient elution with detection at 254 nm. The mobile phase was a mixture of methanol (solvent A) and water (solvent B), both containing formic acid at 0.1%. Gradient elution was as follows: 10:90 (A/B) to 90:10 (A/B) over 3 min, 90:10 (A/B) for 0.5 min, and then reversion back to 10:90 (A/B) over 0.3 min, finally 10:90 (A/B) for 0.2 min.

Details of the applied conditions for HPLC/MS spectra on an Agilent 1260 Infinity II series UPLC and diode array detector coupled to a 6530 Quadrupole time of flight mass spectrometer with Agilent Jet Stream ESI source.

(V) Analytical separation was carried out at 40°C on an Agilent Poroshell C18 column (30 x 2.1 mm, 2.6u, 100A) using a flow rate of 0.6 mL/min in a 2 minute

gradient elution with detection at 254, 280 and 214 nm. The mobile phase was a mixture of methanol (solvent A) and water (solvent B), both containing formic acid at 0.1%. Gradient elution was as follows: 10:90 (A/B) to 90:10 (A/B) over 1.25 min, 90:10 (A/B) for 0.5 min, and then reversion back to 10:90 (A/B) over 0.15 min, finally 10:90 (A/B) for 0.1 min.

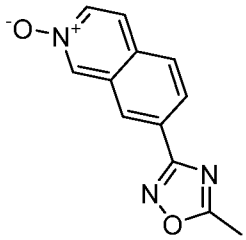
(X) Analytical separation was carried out at 40°C on an Agilent Poroshell C18 column (30 x 2.1 mm, 2.6u, 100A) using a flow rate of 0.4 mL/min in a 4 minute gradient elution with detection at 254, 280 and 214 nm. The mobile phase was a mixture of methanol (solvent A) and water (solvent B), both containing formic acid at 0.1%. Gradient elution was as follows: 10:90 (A/B) to 90:10 (A/B) over 2.5 min, 90:10 (A/B) for 1 min, and then reversion back to 10:90 (A/B) over 0.3 min, finally 10:90 (A/B) for 0.2 min.

(Y) Analytical separation was carried out at 40°C on a Phenomenex Kinetex C18 column (30 x 2.1 mm, 2.6u, 100A) using a flow rate of 0.6 mL/min in a 2 minute gradient elution with detection at 254, 280 and 214 nm. The mobile phase was a mixture of methanol (solvent A) and water (solvent B), both containing formic acid at 0.1%. Gradient elution was as follows: 10:90 (A/B) to 90:10 (A/B) over 1.25 min, 90:10 (A/B) for 0.5 min, and then reversion back to 10:90 (A/B) over 0.15 min, finally 10:90 (A/B) for 0.1 min.

(Z) Analytical separation was carried out at 40°C on a Phenomenex Kinetex C18 column (30 x 2.1 mm, 2.6u, 100A) using a flow rate of 0.4 mL/min in a 4 minute gradient elution with detection at 254, 280 and 214 nm. The mobile phase was a mixture of methanol (solvent A) and water (solvent B), both containing formic acid at 0.1%. Gradient elution was as follows: 10:90 (A/B) to 90:10 (A/B) over 2.5 min, 90:10 (A/B) for 1 min, and then reversion back to 10:90 (A/B) over 0.3 min, finally 10:90 (A/B) for 0.2 min.

Synthesis of intermediates:

A1: 5-Methyl-3-(2-oxidoisoquinolin-2-ium-7-yl)-1,2,4-oxadiazole

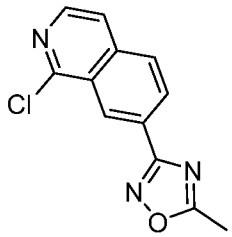


A1.1: Isoquinoline-7-carbonitrile (4.00 g, 25.9 mmol), triethylamine (7.23 mL, 51.9 mmol) and [bmim]OAc (26 mL) were mixed and heated to 80 °C. Hydroxylamine hydrochloride (3.61 g, 51.9 mmol) was added. The reaction mixture was continued to stir at 80 °C for 1.5 h. The reaction mixture was cooled to room temperature and mixed thoroughly with EtOAc (250 mL). The emulsion was then mixed with water (750 mL). The layers were separated and the aqueous layer was further extracted with EtOAc (5 x 100 mL). The combined organic layer was washed with sat. NaCl (3 x 100 mL), dried over anhydr. $MgSO_4$, filtered and concentrated under reduced pressure to yield 3.70 g (76%) of N'-hydroxyisoquinoline-7-carboxamidine as an off-white solid. HPLC/MS m/z: 188.0829 [M+H]+, Rt (S): 0.37 min.

A1.2: Four individual 20 mL microwave vials were each charged with a quarter of the following: N'-hydroxyisoquinoline-7-carboxamidine (3.67 g, 19.6 mmol) was mixed with acetonitrile (40 mL) and acetic anhydride (2.2 mL, 23.5 mmol) under an argon atmosphere. Each portion of the reaction mixture was heated at 180 °C under microwave irradiation for 10 min. The combined reaction mixture was evaporated onto silica gel and purified by flash chromatography (20–80% EtOAc in cyclohexane) to yield 3.59 g (87%) of 3-(7-isoquinolyl)-5-methyl-1,2,4-oxadiazole as an off-white solid. HPLC/MS m/z: 212.1 [M+H]+, Rt (R): 0.88 min.

A1.3: 3-(7-isoquinolyl)-5-methyl-1,2,4-oxadiazole (3.59 g, 17.0 mmol) was suspended in anhydr. chloroform (57 mL) under an argon atmosphere and cooled in an ice bath. 3-Chloroperoxybenzoic acid (4.57 g, 20.4 mmol) was added. The stirred reaction mixture was allowed to warm to ambient temperature and continued to stir overnight. Potassium carbonate (9.40 g, 68.0 mmol) was added. The mixture was stirred at room temperature for 4 h before filtering through a pad of anhydr. $MgSO_4$. The filtrate was concentrated under reduced pressure to yield 5-methyl-3-(2-oxidoisoquinolin-2-ium-7-yl)-1,2,4-oxadiazole (3.12 g, 81%) as an off-white powder. HPLC/MS m/z: 228.0713 [M+H]+, Rt (X): 1.73 min.

A2: 3-(1-Chloro-7-isoquinolyl)-5-methyl-1,2,4-oxadiazole



A2.1: Nitrogen gas was bubbled through a mixture of 7-bromoisoquinolin-1-ol (0.500 g, 2.23 mmol) and zinc cyanide (0.341 g, 2.90 mmol) in DMF (12.4 mL) for 15 min. Palladium tetrakis(triphenylphosphine) (0.155 g, 0.13 mmol) was added and the mixture heated at 100 °C in a sealed vial for 16 h. The reaction mixture was diluted with brine (100 mL) and extracted with ethyl acetate (100 mL). The organic layer was washed with brine (2 x 50 mL). Aqueous layers containing some precipitated product were re-extracted with dichloromethane (2 x 50 mL). Combined organic layers were dried over anhydrous sodium sulfate, filtered, preabsorbed onto silica and purified by column chromatography (Eluent: methanol/dichloromethane= 0 to 10% gradient) to afford 0.314 g (83%) of 1-hydroxyisoquinoline-7-carbonitrile. HPLC/MS m/z: 171.05 [M+H]+, Rt (R): 0.84 min. ^{1}H NMR (500 MHz, DMSO-d6) δ 11.64 (s, 1H), 8.53-8.47 (m, 1H), 8.03 (dd, J = 8.3, 1.8 Hz, 1H), 7.84 (d, J = 8.3 Hz, 1H), 7.38 (d, J = 7.1 Hz, 1H), 6.65 (d, J = 7.2 Hz, 1H).

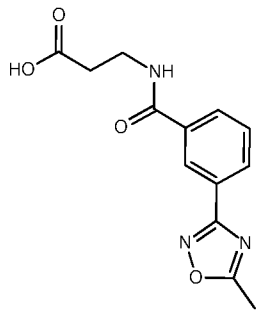
A2.2: 1-hydroxyisoquinoline-7-carbonitrile (0.215 g, 1.26 mmol) and hydroxylamine hydrochloride (0.176 g, 2.52 mmol) in 1-Butyl-3-methylimidazolium acetate (1.3 mL) were heated at 80 °C for 30 min. Water (50 mL) was added and the resulting precipitate filtered, washed with water (50 mL) and dried to afford 0.235 g (92%) of N',1-dihydroxyisoquinoline-7-carboxamidine. HPLC/MS m/z: 204.07 [M+H]+, Rt (R): 0.36 min.

A2.3: N',1-Dihydroxyisoquinoline-7-carboxamidine (0.235 g, 1.16 mmol) and acetic anhydride (0.13 mL, 1.39 mmol) in acetonitrile (4.6 mL) were heated at 180 °C for 10 min by microwave irradiation. Water (25 mL) was added, and the resulting precipitate filtered, washed with water (25 mL), diethyl ether (2 x 10 mL) and dried to

afford 0.180 g (68%) of 7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-ol. HPLC/MS m/z: 228.08 [M+H]+, Rt (R): 1.07 min.

A2.4: 7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-ol (50 mg, 0.22 mmol) in phosphorus oxychloride (2 mL) was heated at 100 °C for 1 h. The mixture was concentrated to afford 0.054 g (100%) of 3-(1-chloro-7-isoquinolyl)-5-methyl-1,2,4-oxadiazole. HPLC/MS m/z: 246/248 Cl split [M+H]+, Rt (R): 1.32 min.

B1: 3-{[3-(5-Methyl-1,2,4-oxadiazol-3-yl)phenyl]formamido}propanoic acid

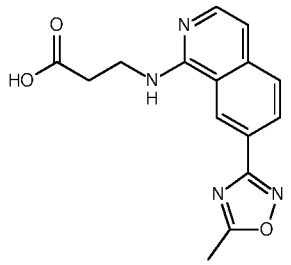


B1.1: 3-(5-Methyl-1,2,4-oxadiazol-3-yl)benzoic acid (147.0 mg, 0.720 mmol) and methyl 3-aminopropanoate dihydrochloride (126.7 mg, 0.720 mmol) were dissolved in DMF (2.3 mL). HATU (260.1 mg, 0.684 mmol) and N-Ethyldiisopropylamine (489,7 µl, 2.880 mmol) were added and the clear yellow solution was stirred for 1 h at room temperature. The reaction was concentrated *in vacuo*, and the residue was purified by RP-flash chromatography. The fractions were combined, diluted with saturated aqueous $NaHCO_3$-solution and extracted with dichloromethane. The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo* to give 206 mg (99%) of methyl 3-{[3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]formamido}propanoate as a colorless solid. HPLC/MS m/z: 289.9 $[M+H]^+$, Rt (A): 0.83 min.

B1.2: Methyl 3-{[3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]formamido}propanoate (413.0 mg, 1.428 mmol) was dissolved in THF (18.0 mL) and water (9.0 mL). While stirring lithium hydroxide (85.5 mg, 3.569 mmol) was added and the reaction mixture was stirred at room temperature overnight. The reaction mixture was diluted

with water, acidified to pH 3-4 0.1 N HCl solution, and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by RP-flash chromatography to afford 390 mg (99%) of 3-{[3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]formamido}propanoic acid as a colorless solid. HPLC/MS m/z: 275.9 $[M+H]^+$, Rt (A): 0.77 min.

B2: 3-{[7-(5-Methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}propanoic acid

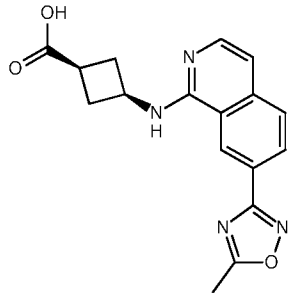


B2.1: 1-Chloro-7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinoline [Intermediate A2] (243.0 mg, 0.989 mmol) and tert-butyl 3-aminopropanoate (861.8 mg, 5.935 mmol) were dissolved in NMP (17.0 mL) in a microwave vessel. N-Ethyldiisopropylamine (420.5 µl, 2.473 mmol) was added and the mixture was stirred at 150 °C for 20 h. The reaction mixture was cooled to room temperature, diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by RP-flash chromatography, the product fractions were combined, diluted with saturated aqueous $NaHCO_3$-solution and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo* to give 192 mg (55%) of tert-butyl 3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}propanoate as an orange solid. HPLC/MS m/z: 354.9 $[M+H]^+$, Rt (A): 0.74 min.

B2.2.: To a solution of tert-butyl 3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}propanoate (192.0 mg, 0.542 mmol) in dichloromethane (3.0 mL) trifluoroacetic acid (788.5 µl, 10.235 mmol) was added and the yellow solution was stirred at room temperature overnight. The reaction mixture was concentrated under

vacuum and the residue (165 mg) was in the next step without further purification. HPLC/MS m/z: 289.9 $[M+H]^+$, Rt (A): 0.65 min.

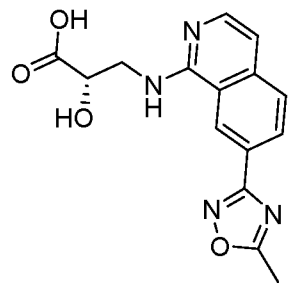
B3: (1S,3S)-3-{[7-(5-Methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}cyclobutane-1-carboxylic acid



B3.1: 7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-2-ium-2-olate [Intermediate A1](500.0 mg, 2.201 mmol) and cis-methyl 3-aminocyclobutanecarboxylate hydrochloride (355.3 mg, 2.751 mmol) were dissolved in dry dichloromethane (11.0 mL) under argon atmosphere. N-Ethyldiisopropylamine (1.78 mL, 10.452 mmol) and PyBroP (1.33 g, 2.853 mmol) were added, and the reaction mixture was stirred at room temperature for 3 d. The reaction mixture was concentrated under reduced pressure and the crude product was purified by flash-chromatography to yield 392 mg (56%) of methyl (1s,3s)-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}cyclobutane-1-carboxylate as a colorless solid. HPLC/MS m/z: 339.1 $[M+H]^+$, Rt (D): 1.22 min.

B3.2: Intermediate B3.1 (417.0 mg, 1.232 mmol) was dissolved in methanol (4.0 mL), THF (9.0 mL) and water (6 mL) at room temperature. Lithium hydroxide (59 mg, 2.465 mmol) was added, and the reaction mixture was stirred for 1h. The reaction mixture was concentrated *in vacuo* and the residue was purified by RP flash-chromatography to afford 355 mg (89%) of (1s,3s)-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}cyclobutane-1-carboxylic acid as a colorless solid. HPLC/MS m/z: 325.1 $[M+H]^+$, Rt (D): 1.12 min.

B4: (2S)-2-Hydroxy-3-[[7-(5-methyl-1,2,4-oxadiazol-3-yl)-1-isoquinolyl]amino]propanoic acid

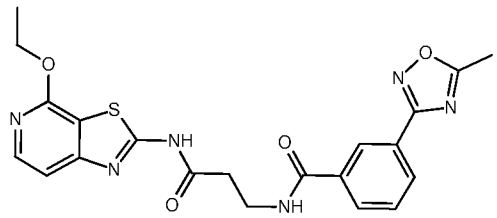


B4.1: To a solution of methyl (2S)-3-amino-2-hydroxy-propanoate hydrochloride (342.36 mg, 2.2005 mmol) in dry DCM, DIPEA (1.30 mL, 7.4817 mmol) was added then 5-methyl-3-(2-oxidoisoquinolin-2-ium-7-yl)-1,2,4-oxadiazole [Intermediate A1] (1.76 mL, 1.7604 mmol), followed by Bromotri(pyrrolidino)phosphonium hexafluorophosphate (1066.87 mg, 2.2885 mmol) The mixture was stirred for 42 hrs. The mixture was diluted in water and extracted with DCM (2x 70 mL). The organic phase has been dried on Na_2SO_4. Purification by NP silica column chromatography (Eluent: 25-100% EtOAc in cyclohexane) afforded methyl (2S)-2-hydroxy-3-[[7-(5-methyl-1,2,4-oxadiazol-3-yl)-1-isoquinolyl]amino]propanoate (230mg). HPLC/MS m/z: 329.126 [M+H]+, Rt (T): 0.79 min.

B4.2: methyl (2S)-2-hydroxy-3-[[7-(5-methyl-1,2,4-oxadiazol-3-yl)-1-isoquinolyl]amino]propanoate (215.00 mg, 0.6548 mmol) was dissolved in a 3:1 mixture of MeOH and H_2O (1.06 mL). Lithium hydroxide monohydrate (56.28 mg, 1.3097 mmol) was added. The solution was stirred for before diluting with water (2 mL) and acidifying with 1M HCl (pH = 1). The product precipitated out to give (2S)-2-hydroxy-3-[[7-(5-methyl-1,2,4-oxadiazol-3-yl)-1-isoquinolyl]amino]propanoic acid (100 mg, 49%, 0.3182 mmol). HPLC/MS m/z: 315.111 [M+H]+, Rt (T): 0.80 min.

Examples

Example 1: N-{4-ethoxy-[1,3]thiazolo[5,4-c]pyridin-2-yl}-3-{[3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]formamido}propanamide



Example 1.1: 4-Amino-2-chloropyridine (1.96 g, 15.246 mmol) and sodium hydroxide (3.17 g, 79.279 mmol) were dissolved in dry ethanol (15.0 mL) in a microwave tube. The reaction mixture was heated to 150 °C in a microwave reactor for 7 h. The reaction mixture was cooled to room temperature, diluted with water (40 mL) and extracted with ethyl acetate. The combined organic layers were washed with brine, dried with sodium sulfate, filtered and concentrated. The residue was purified by flash-chromatography to yield 1.76 g (84%) of 2-ethoxypyridin-4-amine as a colorless solid. HPLC/MS m/z: 139.1 $[M+H]^+$, Rt (B): 0.74 min.

Example 1.2: A solution of 2-ethoxypyridin-4-amine (548.0 mg, 3.966 mmol) in dichloromethane (12.7 mL) was cooled to 0 °C. NBS (777.0 g, 4.366 mmol) was added at this temperature and after 5 min the reaction mixture was allowed to warm up to room temperature and was stirred for 45 min. The reaction was quenched with water (50 mL) and extracted with dichloromethane. The combined organic layers were washed with brine, dried with sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash-chromatography to give 789 mg (92%) of 3-bromo-2-ethoxypyridin-4-amine as a pale-brown oil. HPLC/MS m/z: 216.9/218.9 $[M+H]^+$, Rt (B): 1.09 min.

Example 1.3: A solution of 3-bromo-2-ethoxypyridin-4-amine (789.0 mg, 3.635 mmol) and benzoyl isothiocyanate (1.78 g, 10.907 mmol) in acetone (4.0 mL) was stirred at room temperature overnight. A yellow precipitate formed, which was filtered by suction, washed with heptane and dried to yield 1.23 g (89%) of 1-benzoyl-3-(3-bromo-2-ethoxypyridin-4-yl)thiourea as a yellow solid. HPLC/MS m/z: 379.7/381.7 $[M+H]^+$, Rt (B): 1.09 min.

Example 1.4: Intermediate 1.3 (1.23 g, 3.235 mmol) was dissolved in methanol (5.0 mL). Sodium hydroxide (360.0 mg, 9.001 mmol) was dissolved in water (1.5 mL) and added to the reaction mixture. The reaction mixture was refluxed for 2 h, cooled

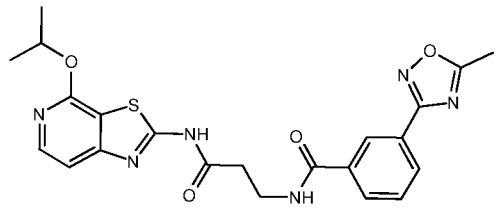
down to room temperature and treated with aqueous saturated NH_4Cl solution until a precipitate was formed. The precipitate was filtered off by suction, washed with water and dichloromethane and dried to afford 870 mg (97%) of (3-bromo-2-ethoxypyridin-4-yl)thiourea as a colorless solid. HPLC/MS m/z: 275.8/277.8 $[M+H]^+$, Rt (B): 1.27 min.

Example 1.5: Intermediate 1.4 (2.42 g, 8.763 mmol), DL-proline (302.9 mg, 2.631 mmol), cesium carbonate (5.71 g, 17.526 mmol) and copper(I) iodide (501.1 mg, 2.631 mmol) were suspended in dry DMSO (7.5 mL). The reaction mixture was heated under an argon atmosphere to 70 °C and stirred overnight, cooled to room temperature, and stirred for 2 d. The reaction mixture was filtered, and the filtrate was evaporated to dryness. The crude product was purified by RP flash-chromatography to yield 688 mg (33%) of 4-ethoxy-[1,3]thiazolo[5,4-c]pyridin-2-ammonium formate as a pale-green solid. HPLC/MS m/z: 195.9 $[M+H]^+$, Rt (B): 1.13 min.

Example 1.6: Intermediate B1 (36.6 mg, 0.144 mmol) was dissolved in DMF (1.1 mL). 1-Methylimidazole (68.5 mg, 0.834 mmol), intermediate 1.5 (43.4 mg, 0.180 mmol) and Chloro-N,N,N′,N′-tetramethylformamidinium hexafluorophosphate (68.0 mg, 0.230 mmol) were added and the reaction was stirred at room temperature for 1 h, heated to 60 °C and stirred for 5 h. The reaction mixture was cooled down to room temperature and diluted with water (5 mL). A precipitate was formed, which was filtered with suction, thoroughly rinsed with water and dried. The crude product was purified by flash-chromatography to afford 38 mg 58%) of N-{4-ethoxy-[1,3]thiazolo[5,4-c]pyridin-2-yl}-3-{[3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]formamido}propanamide as a colorless solid. HPLC/MS m/z: 452.8 $[M+H]^+$, Rt (C): 2.31 min. ^1H NMR (700 MHz, DMSO-d_6): δ 12.74 (s, 1H), 8.89 (t, *J* = 5.6 Hz, 1H), 8.47-8.46 (m, 1H), 8.14-8.12 (m, 1H), 8.09 (d, *J* = 5.7 Hz, 1H), 8.05-8.03 (m, 1H), 7.66 (t, *J* = 7.7 Hz, 1H), 7.33 (d, *J* = 5.6 Hz, 1H), 4.49 (q, *J* = 7.0 Hz, 2H), 3.64 (q, *J* = 6.6 Hz, 2H), 2.86 (t, *J* = 6.8 Hz, 2H), 2.68 (s, 3H), 1.38 (t, *J* = 7.0 Hz, 3H).

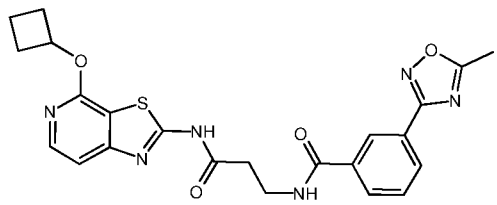
The following examples were prepared in an analogous manner.

Example 2: 3-{[3-(5-Methyl-1,2,4-oxadiazol-3-yl)phenyl]formamido}-N-[4-(propan-2-yloxy)-[1,3]thiazolo[5,4-c]pyridin-2-yl]propenamide



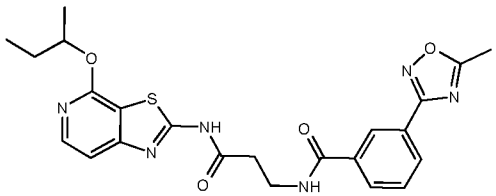
29 mg colorless solid. HPLC/MS m/z: 466.8 $[M+H]^+$, Rt (C): 2.40 min. ^{1}H NMR (700 MHz, DMSO-d_6): δ 12.76-12.74 (m, 1H), 8.91 (t, *J* = 5.5 Hz, 1H), 8.47-8.46 (m, 1H), 8.14-8.12 (m, 1H), 8.08 (d, *J* = 5.6 Hz, 1H), 8.06-8.03 (m, 1H), 7.66 (t, *J* = 7.7 Hz, 1H), 7.31 (d, *J* = 5.7 Hz, 1H), 5.46-5.40 (m, 1H), 3.64 (q, *J* = 6.9 Hz, 2H), 2.87 (t, *J* = 6.9 Hz, 2H), 2.68 (s, 3H), 1.36 (d, *J* = 6.2 Hz, 6H).

Example 3: N-{4-cyclobutoxy-[1,3]thiazolo[5,4-c]pyridin-2-yl}-3-{[3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]formamido}propenamide



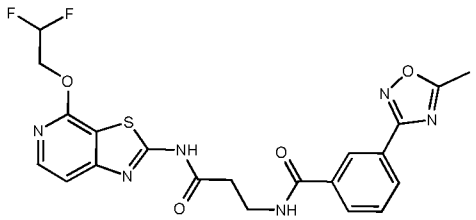
17 mg colorless solid. HPLC/MS m/z: 478.8 $[M+H]^+$, Rt (A): 0.96 min. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.83-12.60 (m, 1H), 8.88 (t, *J* = 5.4 Hz, 1H), 8.48-8.46 (m, 1H), 8.15-8.10 (m, 1H), 8.07-8.02 (m, 1H), 7.99 (d, *J* = 5.7 Hz, 1H), 7.66 (t, *J* = 7.8 Hz, 1H), 7.23 (d, *J* = 5.7 Hz, 1H), 5.32 (quint, *J* = 7.5 Hz, 1H), 3.63 (q, *J* = 6.5 Hz, 2H), 2.79 (t, *J* = 6.9 Hz, 2H), 2.68 (s, 3H), 2.48-2.39 (m, 2H), 2.18-2.07 (m, 2H), 1.86-1.75 (m, 1H), 1.73-1.59 (m, 1H).

Example 4: N-[4-(butan-2-yloxy)-[1,3]thiazolo[5,4-c]pyridin-2-yl]-3-{[3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]formamido}propenamide



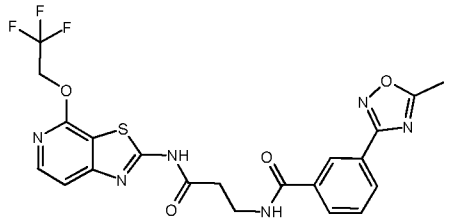
56 mg colorless solid. HPLC/MS m/z: 480.8 $[M+H]^+$, Rt (C): 2.50 min. ^{1}H NMR (700 MHz, DMSO-d_6): δ 12.73 (s, 1H), 8.88 (t, *J* = 5.5 Hz, 1H), 8.47-8.46 (m, 1H), 8.14-8.12 (m, 1H), 8.08 (d, *J* = 5.7 Hz, 1H), 8.04-8.02 (m, 1H), 7.66 (t, *J* = 7.8 Hz, 1H), 7.31 (d, *J* = 5.6 Hz, 1H), 5.30-5.25 (m, 1H), 3.66-3.62 (m, 2H), 2.86 (t, *J* = 6.8 Hz, 2H), 2.68 (s, 3H), 1.77-1.65 (m, 2H), 1.33 (d, *J* = 6.2 Hz, 3H), 0.93 (t, *J* = 7.4 Hz, 3H).

Example 5: N-[4-(2,2-difluoroethoxy)-[1,3]thiazolo[5,4-c]pyridin-2-yl]-3-{[3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]formamido}propenamide



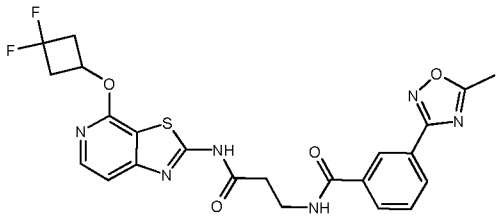
34 mg colorless solid. HPLC/MS m/z: 488.8 $[M+H]^+$, Rt (C): 2.33 min. ^{1}H NMR (700 MHz, DMSO-d_6): δ 12.82 (s, 1H), 8.90 (t, *J* = 5.5 Hz, 1H), 8.48-8.46 (m, 1H), 8.14-8.12 (m, 1H), 8.13 (d, *J* = 5.7 Hz, 1H), 8.05-8.02 (m, 1H), 7.66 (t, *J* = 7.8 Hz, 1H), 7.43 (d, *J* = 5.6 Hz, 1H), 6.55-6.38 (m, 1H), 4.77 (td, *J* = 15.0, 3.6 Hz, 2H), 3.64 (q, *J* = 6.7 Hz, 2H), 2.88 (t, *J* = 6.8 Hz, 2H), 2.68 (s, 3H).

Example 6: 3-{[3-(5-Methyl-1,2,4-oxadiazol-3-yl)phenyl]formamido}-N-[4-(2,2,2-trifluoroethoxy)-[1,3]thiazolo[5,4-c]pyridin-2-yl]propenamide



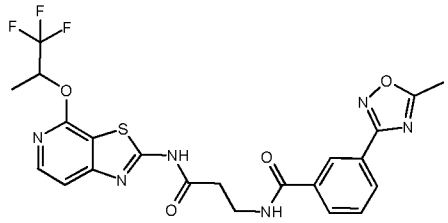
14 mg colorless solid. HPLC/MS m/z: 506.7 $[M+H]^+$, Rt (A): 0.95 min. ^{1}H NMR (700 MHz, DMSO-d_6): δ 12.87 (s, 1H), 8.89 (t, *J* = 5.5 Hz, 1H), 8.47-8.46 (m, 1H), 8.14 (d, *J* = 5.7 Hz, 1H), 8.14-8.12 (m, 1H), 8.04-8.02 (m, 1H), 7.66 (t, *J* = 7.7 Hz, 1H), 7.47 (d, *J* = 5.7 Hz, 1H), 5.20 (q, *J* = 9.0 Hz, 2H), 3.66-3.62 (m, 2H), 2.88 (t, *J* = 6.8 Hz, 2H), 2.68 (s, 3H).

Example 7: N-[4-(3,3-difluorocyclobutoxy)-[1,3]thiazolo[5,4-c]pyridin-2-yl]-3-{[3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]formamido}propenamide



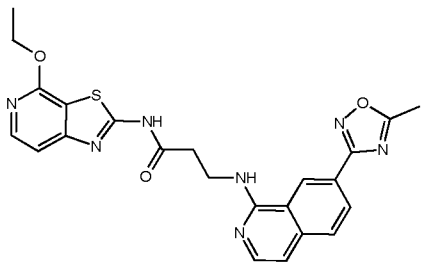
31.5 mg colorless solid. HPLC/MS m/z: 514.7 $[M+H]^+$, Rt (C): 2.43 min. ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.78 (s, 1H), 8.88 (t, *J* = 5.5 Hz, 1H), 8.46 (t, *J* = 1.8 Hz, 1H), 8.14-8.11 (m, 1H), 8.10 (d, *J* = 5.7 Hz, 1H), 8.05-8.02 (m, 1H), 7.66 (t, *J* = 7.8 Hz, 1H), 7.39 (d, *J* = 5.7 Hz, 1H), 5.35-5.27 (m, 1H), 3.64 (q, *J* = 6.4 Hz, 2H), 3.24-3.15 (m, 2H), 2.87 (t, *J* = 6.8 Hz, 2H), 2.87-2.77 (m, 2H), 2.68 (s, 3H).

Example 8: 3-{[3-(5-Methyl-1,2,4-oxadiazol-3-yl)phenyl]formamido}-N-{4-[(1,1,1-trifluoropropan-2-yl)oxy]-[1,3]thiazolo[5,4-c]pyridin-2-yl}propenamide



36 mg colorless solid. HPLC/MS m/z: 520.7 $[M+H]^+$, Rt (C): 2.52 min. ^1H NMR (700 MHz, DMSO-d_6): δ 12.88-12.81 (m, 1H), 8.89 (t, *J* = 5.6 Hz, 1H), 8.47-8.45 (m, 1H), 8.14-8.13 (m, 1H), 8.13-8.11 (m, 1H), 8.05-8.02 (m, 1H), 7.66 (t, *J* = 7.8 Hz, 1H), 7.44 (d, *J* = 5.7 Hz, 1H), 6.09-6.02 (m, 1H), 3.64 (q, *J* = 6.5 Hz, 2H), 2.86 (t, *J* = 6.8 Hz, 2H), 2.68 (s, 3H), 1.53 (d, *J* = 6.5 Hz, 3H).

Example 9: N-{4-ethoxy-[1,3]thiazolo[5,4-c]pyridin-2-yl}-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}propenamide

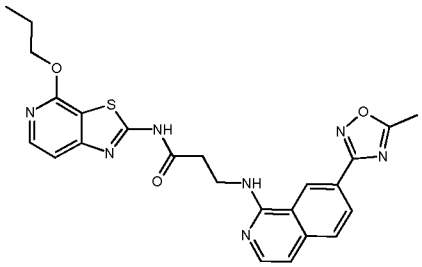


Intermediate B2 (170.0 mg, 0.570 mmol) was dissolved in dry DMF (4.4 mL) and treated with intermediate 1.5 (206.3 mg, 0.855 mmol) and triethylamine (576.7 mg, 5.699 mmol). T3P was added (50 wt% in ethyl acetate; 847.4 µl, 1.425 mmol) and the reaction mixture was heated to 60 °C under nitrogen atmosphere and stirred for 1 d. The reaction mixture was cooled to room temperature, diluted with water and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried with sodium sulfate, filtered, and concentrated. The crude product was triturated with DMSO and filtered by suction. From the filtrate further product was isolated by RP flash-chromatography to give 139 mg (51%) of the title compound as a pale-yellow solid. HPLC/MS m/z: 475.8 $[M+H]^+$, Rt (C): 1.84 min. ^1H NMR (700 MHz, DMSO-d_6): δ 12.79-12.75 (m, 1H), 8.89-8.88 (m, 1H), 8.15 (dd, *J* = 8.5, 1.6 Hz, 1H), 8.08 (d, *J* = 5.7 Hz, 1H), 8.06 (t, *J* = 5.4 Hz, 1H), 7.97 (d, *J* = 5.7 Hz, 1H), 7.86 (d, *J* = 8.4 Hz, 1H), 7.33 (d, *J* = 5.7 Hz, 1H), 6.98 (d, *J* = 5.7 Hz, 1H), 4.49 (q, *J*

= 7.1 Hz, 2H), 3.85 (q, *J* = 6.4 Hz, 2H), 2.97 (t, *J* = 6.8 Hz, 2H), 2.69 (s, 3H), 1.38 (t, *J* = 7.0 Hz, 3H).

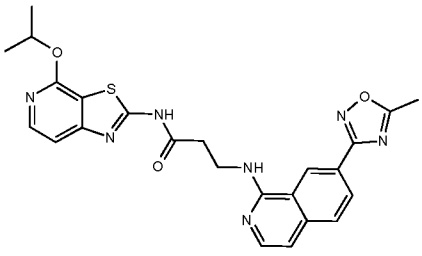
The following examples were prepared in an analogous manner.

Example 10: 3-{[7-(5-Methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}-N-{4-propoxy-[1,3]thiazolo[5,4-c]pyridin-2-yl}propenamide



15 mg colorless solid. HPLC/MS m/z: 490.1 $[M+H]^+$, Rt (D): 1.47 min. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.91-8.85 (m, 1H), 8.14 (dd, *J* = 8.5, 1.5 Hz, 1H), 8.06-7.95 (m, 3H), 7.84 (d, *J* = 8.5 Hz, 1H), 7.22 (d, *J* = 5.7 Hz, 1H), 7.00-6.92 (m, 1H), 4.38 (t, *J* = 6.6 Hz, 2H), 3.84 (q, *J* = 6.5 Hz, 2H), 2.90 (t, *J* = 6.9 Hz, 2H), 2.69 (s, 3H), 1.84-1.70 (m, 2H), 0.99 (t, *J* = 7.4 Hz, 3H).

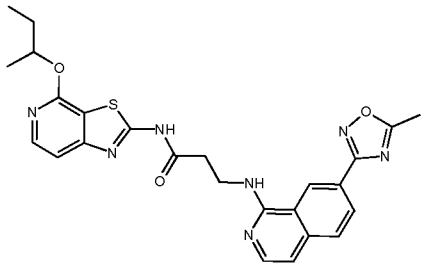
Example 11: 3-{[7-(5-Methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}-N-[4-(propan-2-yloxy)-[1,3]thiazolo[5,4-c]pyridin-2-yl]propanamide



19 mg colorless solid. HPLC/MS m/z: 489.8 $[M+H]^+$, Rt (C): 1.90 min. ^{1}H NMR (700 MHz, DMSO-d_6): δ 12.78-12.72 (m, 1H), 8.90-8.88 (m, 1H), 8.15 (dd, *J* = 8.4, 1.5 Hz, 1H), 8.07 (d, *J* = 5.7 Hz, 1H), 8.05 (t, *J* = 5.4 Hz, 1H), 7.97 (d, *J* = 5.6 Hz, 1H), 7.86 (d, *J* = 8.5 Hz, 1H), 7.29 (d, *J* = 5.6 Hz, 1H), 6.97 (d, *J* = 5.7 Hz, 1H), 5.46-5.40

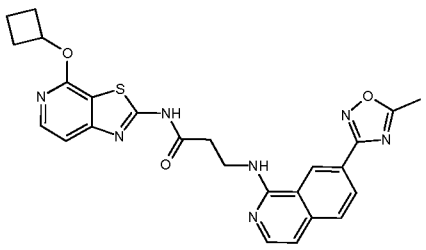
(m, 1H), 3.85 (td, *J* = 6.9, 5.4 Hz, 2H), 2.96 (t, *J* = 6.9 Hz, 2H), 2.69 (s, 3H), 1.36 (d, *J* = 6.2 Hz, 6H).

Example 12: N-[4-(butan-2-yloxy)-[1,3]thiazolo[5,4-c]pyridin-2-yl]-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}propanamide



112 mg colorless foam. HPLC/MS m/z: 503.8 $[M+H]^+$, Rt (C): 1.96 min. ^{1}H NMR (700 MHz, DMSO-d_6): δ 12.76 (s, 1H), 8.89-8.88 (m, 1H), 8.15 (dd, *J* = 8.4, 1.5 Hz, 1H), 8.08 (d, *J* = 5.6 Hz, 1H), 8.05 (t, *J* = 5.5 Hz, 1H), 7.97 (d, *J* = 5.7 Hz, 1H), 7.86 (d, *J* = 8.5 Hz, 1H), 7.30 (d, *J* = 5.6 Hz, 1H), 6.98 (d, *J* = 5.7 Hz, 1H), 5.30-5.25 (m, 1H), 3.85 (q, *J* = 6.6 Hz, 2H), 2.97 (t, *J* = 6.8 Hz, 2H), 2.69 (s, 3H), 1.77-1.71 (m, 1H), 1.71-1.65 (m, 1H), 1.34 (d, *J* = 6.2 Hz, 3H), 0.93 (t, *J* = 7.4 Hz, 3H).

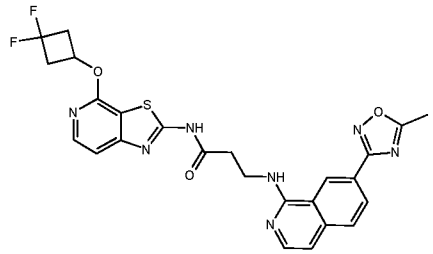
Example 13: N-{4-cyclobutoxy-[1,3]thiazolo[5,4-c]pyridin-2-yl}-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}propanamide



33 mg colorless solid. HPLC/MS m/z: 501.8 $[M+H]^+$, Rt (A): 0.79 min. ^{1}H NMR (700 MHz, DMSO-d_6): δ 12.77 (s, 1H), 8.90-8.88 (m, 1H), 8.15 (dd, *J* = 8.5, 1.5 Hz, 1H), 8.06 (d, *J* = 5.7 Hz, 1H), 8.08-8.04 (m, 1H), 7.97 (d, *J* = 5.7 Hz, 1H), 7.86 (d, *J* = 8.4 Hz, 1H), 7.32 (d, *J* = 5.7 Hz, 1H), 6.98 (d, *J* = 5.7 Hz, 1H), 5.36-5.31 (m, 1H), 3.85

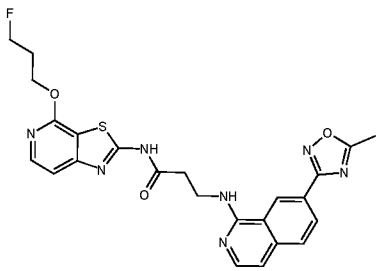
(q, *J* = 6.5 Hz, 2H), 2.97 (t, *J* = 6.8 Hz, 2H), 2.69 (s, 3H), 2.47-2.42 (m, 2H), 2.17-2.10 (m, 2H), 1.84-1.78 (m, 1H), 1.71-1.63 (m, 1H).

Example 14: N-[4-(3,3-difluorocyclobutoxy)-[1,3]thiazolo[5,4-c]pyridin-2-yl]-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}propanamide



23 mg colorless solid. HPLC/MS m/z: 537.8 $[M+H]^+$, Rt (C): 1.95 min. ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.82 (s, 1H), 8.89 (s, 1H), 8.15 (dd, *J* = 8.4, 1.6 Hz, 1H), 8.10 (d, *J* = 5.7 Hz, 1H), 8.05 (t, *J* = 5.5 Hz, 1H), 7.97 (d, *J* = 5.7 Hz, 1H), 7.85 (d, *J* = 8.5 Hz, 1H), 7.38 (d, *J* = 5.7 Hz, 1H), 6.97 (d, *J* = 5.8 Hz, 1H), 5.35-5.27 (m, 1H), 3.85 (q, *J* = 6.4 Hz, 2H), 3.25-3.15 (m, 2H), 2.98 (t, *J* = 6.7 Hz, 2H), 2.89-2.77 (m, 2H), 2.69 (s, 3H).

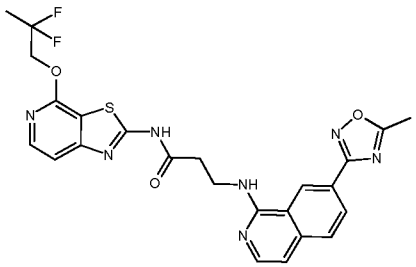
Example 15: N-[4-(3-fluoropropoxy)-[1,3]thiazolo[5,4-c]pyridin-2-yl]-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}propanamide



13 mg colorless solid. HPLC/MS m/z: 507.8 $[M+H]^+$, Rt (A): 0.76 min. ^{1}H NMR (700 MHz, DMSO-d_6): δ 12.81-12.77 (m, 1H), 8.90-8.88 (m, 1H), 8.15 (dd, *J* = 8.4, 1.5 Hz, 1H), 8.09 (d, *J* = 5.7 Hz, 1H), 8.05 (t, *J* = 5.5 Hz, 1H), 7.97 (d, *J* = 5.7 Hz, 1H), 7.86 (d, *J* = 8.4 Hz, 1H), 7.34 (d, *J* = 5.7 Hz, 1H), 6.97 (d, *J* = 5.5 Hz, 1H), 4.66 (t, *J* = 5.8 Hz, 1H), 4.59 (t, *J* = 5.8 Hz, 1H), 4.55 (t, *J* = 6.4 Hz, 2H), 3.85 (q, *J* = 6.6 Hz,

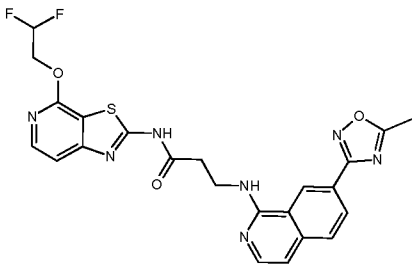
2H), 2.97 (t, *J* = 6.8 Hz, 2H), 2.69 (s, 3H), 2.19 (quint, *J* = 6.2 Hz, 1H), 2.15 (quint, *J* = 6.1 Hz, 1H).

Example 16: N-[4-(2,2-difluoropropoxy)-[1,3]thiazolo[5,4-c]pyridin-2-yl]-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}propanamide



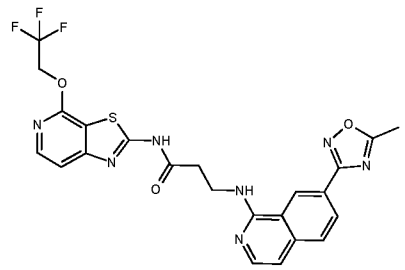
6 mg brown solid. HPLC/MS m/z: 525.9 $[M+H]^+$, Rt (A): 0.78 min. ^{1}H NMR (700 MHz, DMSO-d_6): δ 12.87-12.84 (m, 1H), 8.89-8.88 (m, 1H), 8.15 (dd, *J* = 8.5, 1.6 Hz, 1H), 8.12 (d, *J* = 5.6 Hz, 1H), 8.05 (t, *J* = 5.5 Hz, 1H), 7.97 (d, *J* = 5.7 Hz, 1H), 7.86 (d, *J* = 8.5 Hz, 1H), 7.42 (d, *J* = 5.6 Hz, 1H), 6.97 (d, *J* = 5.9 Hz, 1H), 4.76 (t, *J* = 13.1 Hz, 2H), 3.85 (q, *J* = 6.5 Hz, 2H), 2.98 (t, *J* = 6.8 Hz, 2H), 2.69 (s, 3H), 1.76 (t, *J* = 19.1 Hz, 3H).

Example 17: N-[4-(2,2-difluoroethoxy)-[1,3]thiazolo[5,4-c]pyridin-2-yl]-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}propanamide



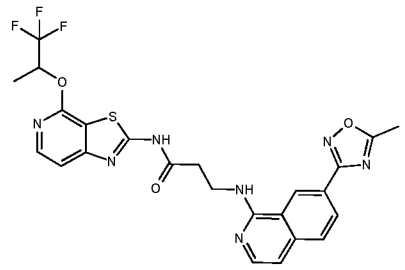
46 mg colorless solid. HPLC/MS m/z: 511.7 $[M+H]^+$, Rt (A): 0.77 min. ^{1}H NMR (700 MHz, DMSO-d_6): δ 12.88 (s, 1H), 8.97-8.92 (m, 1H), 8.52-8.02 (m, 1H), 8.20 (s, 1H), 8.12 (d, *J* = 5.7 Hz, 1H), 7.94 (d, *J* = 5.8 Hz, 1H), 7.93-7.88 (m, 1H), 7.43 (d, *J* = 5.7 Hz, 1H), 7.08-7.00 (m, 1H), 6.56-6.38 (m, 1H), 4.77 (td, *J* = 14.9, 3.5 Hz, 2H), 3.87 (q, *J* = 6.4 Hz, 2H), 3.01 (t, *J* = 6.7 Hz, 2H), 2.69 (s, 3H).

Example 18: 3-{[7-(5-Methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}-N-[4-(2,2,2-trifluoroethoxy)-[1,3]thiazolo[5,4-c]pyridin-2-yl]propanamide



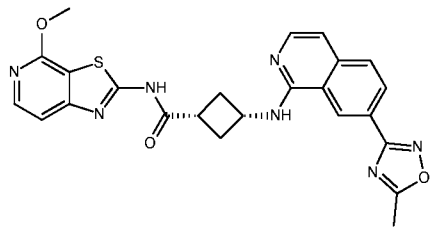
15 mg pale-yellow solid. HPLC/MS m/z: 529.7 $[M+H]^+$, Rt (A): 0.80 min. ^{1}H NMR (700 MHz, DMSO-d_6): δ 12.90 (s, 1H), 8.90-8.88 (m, 1H), 8.17-8.15 (m, 1H), 8.14 (d, *J* = 5.7 Hz, 1H), 8.10-8.03 (m, 1H), 7.97 (d, *J* = 5.8 Hz, 1H), 7.86 (d, *J* = 8.5 Hz, 1H), 7.47 (d, *J* = 5.6 Hz, 1H), 6.98 (d, *J* = 5.6 Hz, 1H), 5.20 (q, *J* = 9.0 Hz, 2H), 3.86 (q, *J* = 6.4 Hz, 2H), 2.99 (t, *J* = 6.7 Hz, 2H), 2.69 (s, 3H).

Example 19: 3-{[7-(5-Methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}-N-{4-[(1,1,1-trifluoropropan-2-yl)oxy]-[1,3]thiazolo[5,4-c]pyridin-2-yl}propanamide



34 mg colorless solid. HPLC/MS m/z: 543.7 $[M+H]^+$, Rt (A): 0.81 min. ^{1}H NMR (700 MHz, DMSO-d_6): δ 12.88 (s, 1H), 8.89-8.87 (m, 1H), 8.15 (dd, *J* = 8.4, 1.5 Hz, 1H), 8.14 (d, *J* = 5.7 Hz, 1H), 8.05 (t, *J* = 5.4 Hz, 1H), 7.97 (d, *J* = 5.7 Hz, 1H), 7.86 (d, *J* = 8.4 Hz, 1H), 7.46 (d, *J* = 5.7 Hz, 1H), 6.97 (d, *J* = 5.6 Hz, 1H), 6.10-6.03 (m, 1H), 3.85 (q, *J* = 6.5 Hz, 2H), 2.98 (t, *J* = 6.8 Hz, 2H), 2.69 (s, 3H), 1.54 (d, *J* = 6.5 Hz, 3H).

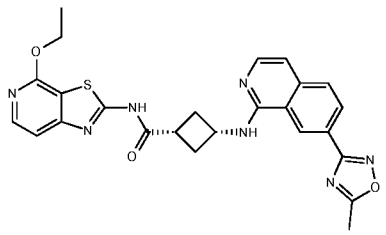
Example 20: (1s,3s)-N-{4-methoxy-[1,3]thiazolo[5,4-c]pyridin-2-yl}-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}cyclobutane-1-carboxamide



Intermediate B3 (25.0 mg, 0.077 mmol) was dissolved in dry DMF (1.0 mL) and treated with HATU (64.5 mg, 0.170 mmol) and N-Ethyldiisopropylamine (59.8 mg, 0.463 mmol). 4-Methoxy-[1,3]thiazolo[5,4-c]pyridin-2-amine (14.6 mg, 0.077 mmol) was added, and the reaction mixture was stirred at room temperature for 2 d. The reaction mixture was diluted with water and extracted with dichloromethane. The combined organic phases were washed with water and brine, dried with sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by preparative HPLC to yield 10 mg (27%) of the title compound as a colorless solid. HPLC/MS m/z: 488.2 $[M+H]^+$, Rt (D): 1.39 min. ^{1}H NMR (700 MHz, Methanol-d_4): δ 9.34-9.31 (m, 1H), 8.55-8.52 (m, 1H), 8.09 (d, *J* = 5.8 Hz, 1H), 8.05 (d, *J* = 8.4 Hz, 1H), 7.72 (d, *J* = 6.8 Hz, 1H), 7.34 (d, *J* = 5.8 Hz, 1H), 7.30 (d, *J* = 6.8 Hz, 1H), 4.56-4.51 (m, 1H), 4.11 (s, 3H), 3.39-3.34 (m, 1H), 3.01-2.96 (m, 2H), 2.81-2.75 (m, 2H), 2.74 (s, 3H).

The following examples were prepared in an analogous manner.

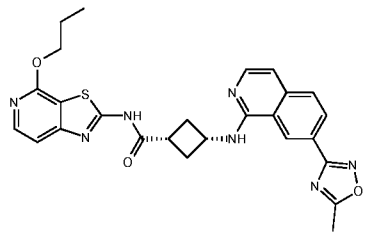
Example 21: (1s,3s)-N-{4-ethoxy-[1,3]thiazolo[5,4-c]pyridin-2-yl}-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}cyclobutane-1-carboxamide



29 mg brown oil. HPLC/MS m/z: 502.2 $[M+H]^+$, Rt (C): 2.00 min. ^{1}H NMR (700 MHz, DMSO-d_6): δ 12.70 (s, 1H), 9.04 (s, 1H), 8.16 (d, *J* = 8.4 Hz, 1H), 8.22-8.06 (m, 1H),

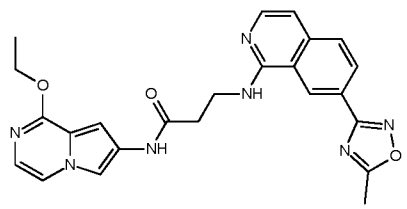
8.10 (d, *J* = 5.7 Hz, 1H), 7.96 (d, *J* = 5.8 Hz, 1H), 7.86 (d, *J* = 8.5 Hz, 1H), 7.35 (d, *J* = 5.6 Hz, 1H), 7.02-6.97 (m, 1H), 4.77-4.69 (m, 1H), 4.51 (q, *J* = 7.0 Hz, 2H), 3.22-3.16 (m, 1H), 2.71 (s, 3H), 2.68-2.62 (m, 2H), 2.51-2.45 (m, 2H), 1.39 (t, *J* = 7.1 Hz, 3H).

Example 22: (1s,3s)-3-{[7-(5-Methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}-N-{4-propoxy-[1,3]thiazolo[5,4-c]pyridin-2-yl}cyclobutane-1-carboxamide



12 mg brown oil. HPLC/MS m/z: 516.2 $[M+H]^+$, Rt (D): 1.52 min. ^{1}H NMR (700 MHz, DMSO-d_6): δ 12.76-12.64 (m, 1H), 9.03-9.01 (m, 1H), 8.16-8.14 (m, 1H), 8.12 (d, *J* = 7.2 Hz, 1H), 8.10 (d, *J* = 5.8 Hz, 1H), 7.97 (d, *J* = 5.7 Hz, 1H), 7.85 (d, *J* = 8.5 Hz, 1H), 7.35 (d, *J* = 5.7 Hz, 1H), 6.98 (d, *J* = 5.7 Hz, 1H), 4.77-4.70 (m, 1H), 4.41 (t, *J* = 6.6 Hz, 2H), 3.22-3.16 (m, 1H), 2.71 (s, 3H), 2.67-2.62 (m, 2H), 2.50-2.45 (m, 2H), 1.83-1.77 (m, 2H), 1.00 (t, *J* = 7.4 Hz, 3H).

Example 23: N-{1-ethoxypyrrolo[1,2-a]pyrazin-7-yl}-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}propanamide



Example 23.1: 1-Chloro-7-nitropyrrolo[1,2-a]pyrazine (190.0 mg, 0.962 mmol) was dissolved in ethanol (3 mL) and dichloromethane (3 mL), potassium hydroxide (200.0 mg, 3.565 mmol) was added and the mixture was heated to 50 °C and stirred for 1.5 h. The dark brown solution was diluted with water and extracted with

ethyl acetate. The combined organic layers were washed with brine, dried with sodium sulfate, filtered, and evaporated to dryness to afford 172.5 mg (87%) of 1-ethoxy-7-nitropyrrolo[1,2-a]pyrazine as a red-brown solid. HPLC/MS m/z: 208.1 $[M+H]^+$, Rt (D): 1.54 min.

Example 23.2: 1-Ethoxy-7-nitropyrrolo[1,2-a]pyrazine (172.5 mg, 0.833 mmol), zinc dust (272.3 mg, 4.164 mmol) and ammonium acetate (770.4 mg, 9.994 mmol) were suspended in ethanol (5.0 mL), and the mixture was heated to 80 °C and stirred for 2 min. The reaction mixture was cooled to room temperature, filtered and the filter cake was washed with ethyl acetate. The filtrate was diluted with ethyl acetate and extracted with water and 2N NaOH. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried with sodium sulfate, filtered, and evaporated to dryness to give 145 mg (98%) of 1-ethoxypyrrolo[1,2-a]pyrazin-7-amine as s brown gum. HPLC/MS m/z: 178.1 $[M+H]^+$, Rt (D): 0.82 min.

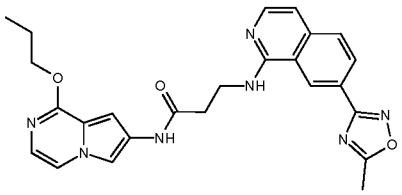
Example 23.3: 3-{[(tert-Butoxy)carbonyl]amino}propanoic acid (63.4 mg, 0.335 mmol), 1-ethoxypyrrolo[1,2-a]pyrazin-7-amine (57.7 mg, 0.305 mmol) and HATU (140.5 mg, 0.366 mmol) were suspended in DMF (2.0 mL). N-Ethyldiisopropylamine (104.7 µl, 0.610 mmol) was added and the clear brown solution was stirred at room temperature for 1 h. The reaction mixture was diluted with 30 ml water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried with sodium sulfate, filtered, and evaporated to dryness. The crude product was purified by flash-chromatography to yield 76.5 mg (72%) of tert-butyl N-[2-({1-ethoxypyrrolo[1,2-a]pyrazin-7-yl}carbamoyl)ethyl]carbamate as an off-white solid. HPLC/MS m/z: 349.2 $[M+H]^+$, Rt (D): 1.28 min.

Example 23.4: Intermediate 23.3 (76.5 mg, 0.220 mmol) was dissolved in 1,4-dioxane (1.0 mL) and treated with a HCl solution in 1,4-dioxane (4 M, 1.5 mL). The mixture was stirred at room temperature overnight. The reaction mixture was evaporated to dryness and the residue was used in the next step without further purification. Yield: 70.5 mg (100%) of 3-amino-N-{1-ethoxypyrrolo[1,2-a]pyrazin-7-yl}propanamide dihydrochloride as a pale-orange solid. HPLC/MS m/z: 249.1 $[M+H]^+$, Rt (D): 0.86 min.

Example 23.5: The amide coupling reaction was performed as described for intermediate B3.1. Yield: 11 mg (13%) of N-{1-ethoxypyrrolo[1,2-a]pyrazin-7-yl}-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquin¬olin-1-yl]amino}propanamide as a colorless solid. HPLC/MS m/z: 458.1 $[M+H]^+$, Rt (D): 1.26 min. ^1H NMR (700 MHz,

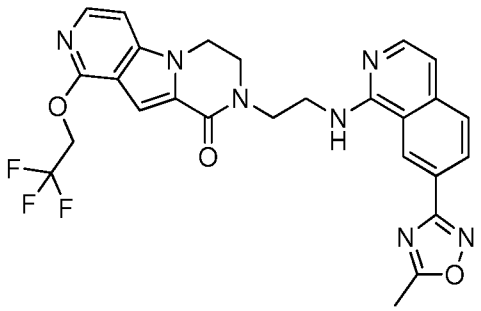
DMSO-d_6): δ 10.30-10.27 (m, 1H), 8.94-8.89 (m, 1H), 8.19-8.14 (m, 1H), 8.09-7.95 (m, 2H), 7.99 (d, *J* = 1.6 Hz, 1H), 7.90 (dd, *J* = 4.7, 0.8 Hz, 1H), 7.89-7.85 (m, 1H), 7.03 (d, *J* = 4.7 Hz, 1H), 7.02-6.97 (m, 1H), 6.56-6.55 (m, 1H), 4.41 (q, *J* = 7.1 Hz, 2H), 3.81 (q, *J* = 6.6 Hz, 2H), 2.77 (t, *J* = 7.0 Hz, 2H), 2.70 (s, 3H), 1.35 (t, *J* = 7.0 Hz, 3H).

Example 24: 3-{[7-(5-Methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}-N-{1-propoxypyrrolo[1,2-a]pyrazin-7-yl}propanamide



Preparation as described for example 23. Yield: 16 mg pale-yellow solid. HPLC/MS m/z: 472.1 $[M+H]^+$, Rt (D): 1.33 min. ^{1}H NMR (700 MHz, DMSO-d_6): δ 10.26 (s, 1H), 8.90-8.88 (m, 1H), 8.16-8.14 (m, 1H), 8.03-7.99 (m, 1H), 8.00 (d, *J* = 5.7 Hz, 1H), 7.98 (d, *J* = 1.5 Hz, 1H), 7.90 (dd, *J* = 4.7, 0.9 Hz, 1H), 7.85 (d, *J* = 8.6 Hz, 1H), 7.03 (d, *J* = 4.8 Hz, 1H), 6.97 (d, *J* = 5.7 Hz, 1H), 6.58-6.57 (m, 1H), 4.32 (t, *J* = 6.6 Hz, 2H), 3.83-3.79 (m, 2H), 2.75 (t, *J* = 7.0 Hz, 2H), 2.69 (s, 3H), 1.79-1.73 (m, 2H), 0.98 (t, *J* = 7.4 Hz, 3H).

Example 25: 11-[2-[[7-(5-Methyl-1,2,4-oxadiazol-3-yl)-1-isoquinolyl]amino]ethyl]-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2,4,6,8-tetraen-10-one



Example 25.1: A suspension of methyl 4-chloro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate (600.00 mg, 2.8487 mmol), 2,2,2-trifluoroethanol (0.37 mL, 4.9853 mmol), cesium carbonate (1600.00 mg, 4.9107 mmol), tBuBrettPhos Pd G3 (97.36 mg, 0.1139 mmol), tBuBrettPhos (110.46 mg, 0.2279 mmol) and 4Å MS (1600 mg) in toluene (4.00 mL, 0.3600 M) and THF (4.00 mL, 0.3600 M) was heated at 80 °C for 22 h in a sealed vial. The reaction mixture was filtered and washed with EtOAc (100 mL). Purification by NP silica column chromatography (Eluent: 20-80% EtOAc in cyclohexane) afforded methyl 4-(2,2,2-trifluoroethoxy)-1H-pyrrolo[3,2-c]pyridine-2-carboxylate (658.4 mg, 79%, 2.2571 mmol) as a cream coloured solid. HPLC/MS m/z 275.0579 $[M+H]^+$, Rt (Y): 1.48 min. ^{1}H NMR (600 MHz, Chloroform-d): δ 9.14 (s, 1H), 7.90 (d, *J* = 6.0 Hz, 1H), 7.38-7.33 (m, 1H), 7.04 (dd, *J* = 5.9, 1.0 Hz, 1H), 4.92 (q, *J* = 8.5 Hz, 2H), 3.96 (s, 3H).

Example 25.2: A solution of methyl 4-(2,2,2-trifluoroethoxy)-1H-pyrrolo[3,2-c]pyridine-2-carboxylate (600.00 mg, 2.0569 mmol), tert-butyl-N-hydroxyethyl carbamate (0.57 mL, 3.7024 mmol), and triphenylphosphine (809.25 mg, 3.0853 mmol) in THF (5.14 mL, 0.4000 M) was cooled to 0 °C. Diisopropyl azodicarboxylate, (0.65 mL, 3.291 mmol) was added dropwise over 20 min, and the resulting mixture was warmed to RT and stirred for 18 h. The crude was evaporated and subjected to NP silica column chromatography (0-60% EtOAc:cyclohexane) to afford methyl 1-[2-(tert-butoxycarbonylamino)ethyl]-4-(2,2,2-trifluoroethoxy)pyrrolo[3,2-c]pyridine-2-carboxylate (867.2 mg, 101%, 2.0777 mmol) as a colorless solid. HPLC/MS m/z 418.1587 $[M+H]^+$, Rt (R): 1.49 min. ^{1}H NMR (600 MHz, Chloroform-d): δ 7.87 (d, *J* = 6.1 Hz, 1H), 7.47 (d, *J* = 0.9 Hz, 1H), 7.09 (d, *J* = 6.1 Hz, 1H), 4.91 (q, *J* = 8.6 Hz, 2H), 4.64 (dt, *J* = 19.4, 6.1 Hz, 3H), 3.91 (s, 3H), 3.52 (q, *J* = 6.0 Hz, 2H), 1.39 (s, 9H). ^{13}C NMR (151 MHz, Chloroform-d): δ 162.09, 157.04, 156.10, 145.63, 140.51, 127.04, 124.81, 122.97, 110.88, 109.90, 102.59, 79.80, 62.52, 62.29, 62.05, 61.81, 52.07, 44.99, 41.37, 28.46.

Example 25.3: Methyl 1-[2-(tert-butoxycarbonylamino)ethyl]-4-(2,2,2-trifluoroethoxy)pyrrolo[3,2-c]pyridine-2-carboxylate (867.20 mg, 2.0777 mmol) was mixed with 4N HCl in dioxane (20.78 mL, 83.109 mmol) and 1,4-dioxane (20.78 mL, 0.1000 M) at RT under argon and stirred for 2 h. Volatiles were removed under reduced pressure. Crude solid was washed with chloroform to give methyl 1-(2-aminoethyl)-4-(2,2,2-trifluoroethoxy)pyrrolo[3,2-c]pyridine-2-carboxylate hydrochloride (724.2 mg, 99%, 2.0474 mmol) as a pale yellow solid. HPLC/MS m/z 318.1071 $[M+H-HCl]^+$, Rt (Y): 1.13 min. ^{1}H NMR (600 MHz, DMSO-d_6): δ 8.40 (d, *J*

= 5.9 Hz, 2H), 7.97 (d, *J* = 6.1 Hz, 1H), 7.68 (dd, *J* = 6.2, 0.9 Hz, 1H), 7.31 (d, *J* = 0.9 Hz, 1H), 5.17 (q, *J* = 9.1 Hz, 2H), 4.81 (t, *J* = 6.8 Hz, 2H), 3.88 (s, 3H), 3.18 (sext, *J* = 6.1 Hz, 2H). ^{13}C NMR (151 MHz, DMSO-d_6): δ 160.92, 155.97, 144.96, 140.29, 127.48, 126.85, 125.01, 123.17, 121.33, 109.93, 108.19, 103.21, 61.43, 61.20, 60.97, 60.74, 52.18, 52.10, 42.60, 38.87.

Example 25.4: The crude methyl 1-(2-aminoethyl)-4-(2,2,2-trifluoroethoxy)pyrrolo[3,2-c]pyridine-2-carboxylate hydrochloride was dissolved in EtOH (9.33 mL, 0.2100 M) and triethylamine (1.39 mL, 9.8948 mmol) and the mixture was stirred for overnight at 80 °C. The crude mixture was evaporated under reduced pressure, redissolved in DCM and water was added. The water was extracted several times with DCM and the combined organic layer washed dried over $MgSO_4$ and evaporated under reduced pressure to afford 6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2,4,6,8-tetraen-10-one (566.4 mg, 100%, 1.9858 mmol) as a white solid. Used in next step without further purification. HPLC/MS m/z 286.0760 $[M+H]^+$, Rt (Y): 1.27 min. ^{1}H NMR (600 MHz, DMSO-d_6): δ 8.28 (t, *J* = 2.8 Hz, 1H), 7.90 (d, *J* = 6.0 Hz, 1H), 7.33 (dd, *J* = 6.0, 0.9 Hz, 1H), 7.00 (d, *J* = 0.9 Hz, 1H), 5.16 (q, *J* = 9.1 Hz, 2H), 4.34-4.29 (m, 2H), 3.67-3.61 (m, 2H). ^{13}C NMR (151 MHz, DMSO-d_6): δ 159.43, 155.70, 141.63, 138.92, 130.05, 125.07, 123.23, 110.51, 103.03, 101.45, 61.22, 60.99, 60.76, 60.53, 40.78, 39.44.

Example 25.5: 6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2,4,6,8-tetraen-10-one (600.00 mg, 2.1036 mmol) was dissolved in DMF (30.05 mL, 0.0700 M). The obtained solution was cooled down to 0 °C in an ice bath followed by the addition of NaH (168.29 mg, 4.2073 mmol). The reaction mixture was left stirring at 0 °C for 30 min. *N*-Boc-2-chloroethylamine (467.50 mg, 2.5244 mmol) dissolved in DMF (2.5 mL) was added dropwise to the reaction mixture and allowed to warm to RT. The reaction mixture was left stirring at RT for 2 d. 0.6 equiv. of the *N*-Boc-2-chloroethylamine reagent was added to the reaction cooled to 0 °C, followed by the addition of another 1 equiv. of NaH and the reaction was left to stir overnight at RT. Water was added and the reaction was extracted with EtOAc (3x), and the combined organic layer was washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure. The crude was subjected to NP chromatography (0-100% EtOAc:cyclohexane) to afford tert-butyl N-[2-[10-oxo-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2,4,6,8-tetraen-11-yl]ethyl]carbamate (694.7 mg, 77%, 1.6216 mmol). HPLC/MS m/z 429.1699 $[M+H]^+$,

Rt (Y): 1.48 min. ^{1}H NMR (600 MHz, Chloroform-d): δ 7.88 (d, *J* = 6.0 Hz, 1H), 7.39-7.36 (m, 1H), 6.90 (dd, *J* = 6.0, 0.9 Hz, 1H), 4.92 (q, *J* = 8.5 Hz, 2H), 4.30-4.25 (m, 2H), 3.89-3.84 (m, 2H), 3.73 (t, *J* = 6.1 Hz, 2H), 3.43 (q, *J* = 6.1 Hz, 2H), 1.35 (s, 9H).

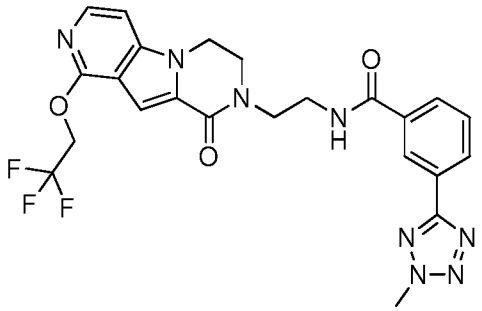
Example 25.6: tert-butyl *N*-[2-[10-oxo-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2,4,6,8-tetraen-11-yl]ethyl]carbamate (52.00 mg, 0.1214 mmol) was mixed with 4N HCl in 1,4-dioxane (5.60 mL, 22.408 mmol) and 1,4-dioxane (5.60 mL, 0.1000 M) at RT under argon and stirred for 2 h. Volatiles were removed under reduced pressure to give 11-(2-aminoethyl)-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2,4,6,8-tetraen-10-one;hydrochloride (199.4 mg). The solid salt was redissolved in MeOH and passed through an SCX-II column, releasing with 2N NH_3 in methanol to afford 11-(2-aminoethyl)-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2,4,6,8-tetraen-10-one (180 mg, 98%, 0.5483 mmol) as a white solid. HPLC/MS m/z 329.1221 [M+H]+, Rt (R): 0.84 min.

Example 25.7: DIPEA (0.28 mL, 1.5992 mmol) was added dropwise to a suspension of 11-(2-aminoethyl)-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2,4,6,8-tetraen-10-one (140.00 mg, 0.4265 mmol), 5-methyl-3-(2-oxidoisoquinolin-2-ium-7-yl)-1,2,4-oxadiazole (116.28 mg, 0.5117 mmol) and PyBrop (238.56 mg, 0.5117 mmol) in DCM (3.55 mL, 0.1200 M). The tube was sealed, and this was heated to 60 °C for 1 h in the microwave. The reaction was evaporated in vacuo and subjected to RP column chromatography (10-80% MeOH:water + 0.1% formic acid) afforded partially pure product. The pure fractions were run through a SCX-II column, released using 2N NH_3 in methanol and evaporated. A second subsequent RP column yielded 11-[2-[[7-(5-methyl-1,2,4-oxadiazol-3-yl)-1-isoquinolyl]amino]ethyl]-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2,4,6,8-tetraen-10-one (61.4 mg, 27%, 0.1142 mmol) as a cream-coloured powder. HPLC/MS m/z 538.1807 $[M+H]^+$, Rt (Z): 2.33 min. ^{1}H NMR (600 MHz, DMSO-d_6): δ 8.89-8.86 (m, 1H), 8.15 (dd, *J* = 8.5, 1.5 Hz, 1H), 8.07 (t, *J* = 5.5 Hz, 1H), 7.97 (d, *J* = 5.7 Hz, 1H), 7.88 (d, *J* = 6.0 Hz, 1H), 7.85 (d, *J* = 8.5 Hz, 1H), 7.29 (dd, *J* = 6.0, 0.9 Hz, 1H), 7.00 (d, *J* = 0.9 Hz, 1H), 6.96 (dd, *J* = 5.8, 0.8 Hz, 1H), 5.15 (q, *J* = 9.1 Hz, 2H), 4.37-4.32 (m, 2H), 3.88-3.82 (m, 4H), 3.79 (q, *J* = 5.8 Hz, 2H), 2.67 (s, 3H). ^{13}C NMR (151 MHz, DMSO-d6): δ 177.47, 167.60, 158.33, 155.73, 155.65, 143.49, 141.36, 138.90, 138.42, 130.03, 127.68, 127.34,

123.33, 122.70, 117.56, 110.71, 109.32, 102.89, 101.56, 60.79, 46.59, 45.57, 40.58, 39.14, 12.03.

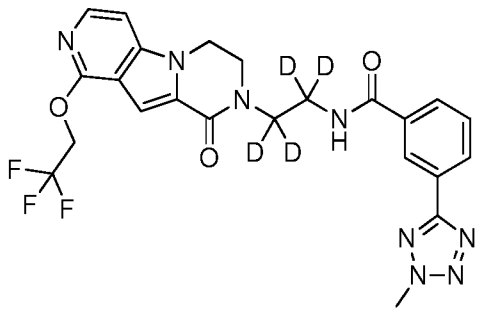
The intermediates for the following examples were prepared in an analogous manner.

Example 26: 3-(2-Methyltetrazol-5-yl)-N-[2-[10-oxo-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2,4,6,8-tetraen-11-yl]ethyl]benzamide



Example 26.1: DIPEA (0.03 mL, 0.1462 mmol) was added to a mixture of 3-(2-Methyl-2H-tetrazol-5-yl)-benzoic acid (8.58 mg, 0.0420 mmol), HATU (27.80 mg, 0.0731 mmol) and 11-(2-aminoethyl)-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2,4,6,8-tetraen-10-one [Example 25.6] (12.00 mg, 0.0366 mmol) in DCM (0.37 mL, 0.1000 M). This was stirred for 2 h before sat. aq. $NaHCO_3$ was added. This was extracted with DCM, filtered over $MgSO_4$ and evaporated. The compound was subjected to RP column chromatography (10-80% MeOH:water + 0.1% formic acid) to afford 3-(2-methyltetrazol-5-yl)-N-[2-[10-oxo-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2,4,6,8-tetraen-11-yl]ethyl]benzamide (11.9 mg, 63%, 0.0231 mmol) as a white solid. HPLC/MS m/z 515.1753 $[M+H]^+$, Rt (Z): 2.54 min. ^1H NMR (600 MHz, DMSO-d_6): δ 8.87 (t, *J* = 5.8 Hz, 1H), 8.50 (t, *J* = 1.8 Hz, 1H), 8.18 (dt, *J* = 7.7, 1.4 Hz, 1H), 7.95 (dt, *J* = 7.8, 1.5 Hz, 1H), 7.90 (d, *J* = 6.0 Hz, 1H), 7.65 (t, *J* = 7.7 Hz, 1H), 7.32 (dd, *J* = 6.0, 0.9 Hz, 1H), 7.01 (d, *J* = 0.9 Hz, 1H), 5.15 (q, *J* = 9.2 Hz, 2H), 4.44 (s, 3H), 4.40 (dd, *J* = 6.9, 4.7 Hz, 2H), 3.93-3.88 (m, 2H), 3.74 (t, *J* = 6.0 Hz, 2H), 3.58 (q, *J* = 5.9 Hz, 2H). ^{13}C NMR (151 MHz, DMSO-d_6): δ 166.30, 164.14, 158.90, 156.12, 141.84, 139.41, 135.93, 130.35, 129.89, 129.55, 129.25, 127.54, 125.54, 123.68, 111.17, 103.37, 102.14, 61.48, 61.26, 61.03, 46.58, 46.20, 41.10, 40.17, 37.90.

Example 27: 3-(2-Methyltetrazol-5-yl)-N-[1,1,2,2-tetradeuterio-2-[10-oxo-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2(7),3,5,8-tetraen-11-yl]ethyl]benzamide



Example 27.1: To a stirred suspension of 6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2(7),3,5,8-tetraen-10-one (700.00 mg, 2.4542 mmol) in DMF (35.06 mL, 0.0700 M), NaH (60% dispersion in mineral oil) (215.97 mg, 5.3993 mmol) was added in portions at RT and then stirred for 30 min at 60 °C. The reaction was cooled to RT and to this solution 1,2-dibromoethane-d_4 (1.06 mL, 12.271 mmol) was added and stirred at RT overnight. The reaction mixture was poured into water, and the precipitated product was collected by filtration to give 11-(2-bromo-1,1,2,2-tetradeuterio-ethyl)-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2(7),3,5,8-tetraen-10-one (249.8 mg, 26%, 0.6305 mmol) as a white solid. HPLC/MS m/z 396.0402 [M+H, ^{79}Br]$^+$, Rt (Y): 1.42 min. ^{1}H NMR (600 MHz, Chloroform-d): δ 7.90 (d, *J* = 6.0 Hz, 1H), 7.41 (d, *J* = 0.9 Hz, 1H), 6.93 (dd, *J* = 6.0, 0.9 Hz, 1H), 4.92 (q, *J* = 8.6 Hz, 2H), 4.36-4.30 (m, 2H), 4.01-3.95 (m, 2H). Then, water and ethyl acetate were added. The organic layer was separated and dried over anhydrous $MgSO_4$. After filtration, solvent was removed under reduced pressure to give 11-(1,1,2,2-tetradeuterio-2-hydroxy-ethyl)-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2(7),3,5,8-tetraen-10-one (398.8 mg, 49%, 1.1965 mmol) as a pure white solid. HPLC/MS m/z 334.1234 [M+H]+, Rt (Y): 1.22 min. ^{1}H NMR (600 MHz, Chloroform-d): δ 7.85 (dd, *J* = 10.3, 6.0 Hz, 1H), 7.31 (d, *J* = 0.9 Hz, 1H), 6.88 (ddd, *J* = 17.1, 6.0, 0.9 Hz, 1H), 4.88 (dq, *J* = 23.7, 8.5 Hz, 2H), 4.29-4.23 (m, 2H), 3.96-3.90 (m, 2H).

Example 27.2: To a stirred solution of sodium azide (43.32 mg, 0.6663 mmol) in DMF (4.04 mL, 0.1500 M) was added 11-(2-bromo-1,1,2,2-tetradeuterio-ethyl)-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2(7),3,5,8-tetraen-10-

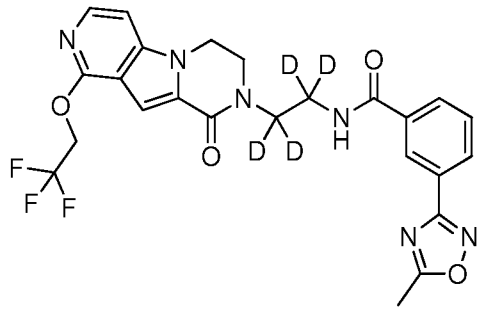
one (240.00 mg, 0.6058 mmol). The reaction mixture was stirred at 80 °C overnight. Then the reaction mixture was cooled to RT and diluted with water (5 mL). The mixture was extracted with ethyl acetate (3×5 mL) and washed by brine, dried over $MgSO_4$ and concentrated in vacuo to give 11-(2-azido-1,1,2,2-tetradeuterio-ethyl)-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2(7),3,5,8-tetraen-10-one (158.4 mg, 73%, 0.4421 mmol) as a yellow solid. It was used directly without further purification. Rt (Y): 1.40 min

Example 27.3: To a solution of 11-(2-azido-1,1,2,2-tetradeuterio-ethyl)-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2(7),3,5,8-tetraen-10-one (200.00 mg, 0.5582 mmol) in THF (5.14 mL, 0.0800 M) was added Triphenylphosphine (439.21 mg, 1.6745 mmol). The mixture was stirred at RT for 48 h, then H_2O (1.84 mL, 0.0800 M) was added, and the reaction was heated to 60 °C and allowed to stir for 4 h. The solvent was removed by reduced pressure, and the resulting residue was purified by a very short silica gel column (eluting with 1:10 to 1:5 methanol-DCM) to afford 11-(2-amino-1,1,2,2-tetradeuterio-ethyl)-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2(7),3,5,8-tetraen-10-one (93.1 mg, 50%, 0.2802 mmol) as a white solid. HPLC/MS m/z 333.1480 $[M+H]^+$, Rt (R): 0.83 min. ^1H NMR (600 MHz, DMSO-d_6): δ 7.90 (d, *J* = 6.0 Hz, 1H), 7.33 (dd, *J* = 6.0, 0.9 Hz, 1H), 6.99 (d, *J* = 0.9 Hz, 1H), 5.16 (q, *J* = 9.1 Hz, 2H), 4.41-4.37 (m, 2H), 3.87-3.81 (m, 2H).

Example 27.4: DIPEA (0.08 mL, 0.4606 mmol) was added to a mixture of 3-(2-Methyl-2H-tetrazol-5-yl)-benzoic acid (31.80 mg, 0.1557 mmol), HATU (102.98 mg, 0.2708 mmol) and 11-(2-amino-1,1,2,2-tetradeuterio-ethyl)-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2(7),3,5,8-tetraen-10-one (45.00 mg, 0.1354 mmol) in DCM (1.35 mL, 0.1000 M). This was stirred for 2 h before sat. aq. $NaHCO_3$ was added. This was extracted with DCM, filtered over $MgSO_4$ and evaporated. Silica gel chromatography with DCM and MeOH as eluents (100:0 to 96:4) afforded a slightly impure product by NMR. The compound was subjected to RP column chromatography (10-80% MeOH:water + 0.1% formic acid) and the fractions were run through an SCX-II column releasing with 2N NH_3 in methanol to afford 3-(2-methyltetrazol-5-yl)-N-[1,1,2,2-tetradeuterio-2-[10-oxo-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2(7),3,5,8-tetraen-11-yl]ethyl]benzamide (28.7 mg, 41%, 0.0554 mmol) as a fine white solid after evaporation. HPLC/MS m/z 519.1961 $[M+H]^+$, Rt (Z): 2.50 min. ^1H NMR (600 MHz, DMSO-d_6): δ 8.84 (s, 1H), 8.50 (t, *J* = 1.8 Hz, 1H), 8.18 (dt, *J* = 7.8, 1.4 Hz, 1H), 7.97-7.92 (m, 1H), 7.89 (d, *J* =

6.0 Hz, 1H), 7.65 (t, *J* = 7.8 Hz, 1H), 7.31 (dd, *J* = 6.0, 0.9 Hz, 1H), 7.00 (d, *J* = 0.9 Hz, 1H), 5.15 (q, *J* = 9.1 Hz, 2H), 4.43 (s, 3H), 4.41-4.37 (m, 2H), 3.92-3.87 (m, 2H). ^{13}C NMR (151 MHz, DMSO-d_6): δ 204.66, 166.30, 164.14, 158.89, 156.12, 141.84, 139.40, 135.94, 130.36, 129.88, 129.55, 129.24, 127.54, 127.37, 125.54, 123.68, 111.17, 103.37, 102.12, 61.71, 61.49, 61.26, 61.03, 46.51, 41.09, 40.17.

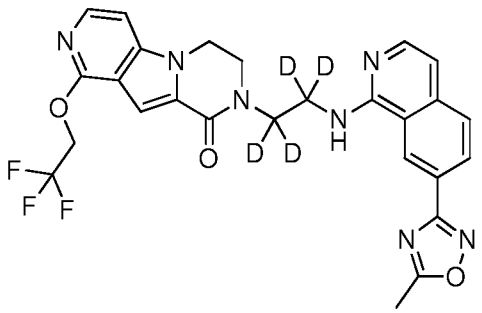
Example 28: 3-(5-Methyl-1,2,4-oxadiazol-3-yl)-N-[1,1,2,2-tetradeuterio-2-[10-oxo-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2(7),3,5,8-tetraen-11-yl]ethyl]benzamide



DIPEA (0.09 mL, 0.5417 mmol) was added to a mixture of 3-(5-Methyl-1,2,4-oxadiazol-3-yl)benzoic acid (31.80 mg, 0.1557 mmol), HATU (102.98 mg, 0.2708 mmol) and 11-(2-amino-1,1,2,2-tetradeuterio-ethyl)-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2(7),3,5,8-tetraen-10-one (45.00 mg, 0.1354 mmol) in DCM (1.35 mL, 0.1000 M). This was stirred for 2 h before sat. aq. $NaHCO_3$ was added. This was extracted with DCM, filtered over $MgSO_4$ and evaporated. Silica gel chromatography with DCM and MeOH as eluents (100:0 to 96:4) afforded a slightly impure product by NMR. The compound was subjected to RP column chromatography (10-80% MeOH:water + 0.1% formic acid) and clean fractions were collected and evaporated to give 3-(5-methyl-1,2,4-oxadiazol-3-yl)-N-[1,1,2,2-tetradeuterio-2-[10-oxo-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2(7),3,5,8-tetraen-11-yl]ethyl]benzamide (19.5 mg, 28%, 0.0376 mmol) as a fine white solid. HPLC/MS m/z 519.1847 $[M+H]^+$, Rt (Z): 2.60 min. ^{1}H NMR (600 MHz, DMSO-d_6): δ 8.84 (s, 1H), 8.43 (t, *J* = 1.7 Hz, 1H), 8.11 (dt, *J* = 7.7, 1.3 Hz, 1H), 7.99 (ddd, *J* = 7.8, 1.8, 1.2 Hz, 1H), 7.89 (d, *J* = 6.0 Hz, 1H), 7.64 (t, *J* = 7.7 Hz, 1H), 7.31 (dd, *J* = 6.0, 0.9 Hz, 1H), 7.00 (d, *J* = 0.9 Hz, 1H), 5.15 (q, *J* = 9.1 Hz, 2H), 4.42-4.37 (m, 2H), 3.91-3.86 (m, 2H), 2.67 (s, 3H). ^{13}C NMR (151 MHz, DMSO-d_6): δ 178.14, 167.72, 166.18, 158.90, 156.13, 141.84,

139.40, 135.92, 130.49, 130.36, 129.86, 126.92, 126.21, 125.53, 123.68, 121.84, 111.17, 103.37, 102.14, 61.72, 61.49, 61.26, 61.03, 46.49, 41.09, 12.48.

Example 29: 11-[1,1,2,2-Tetradeuterio-2-[[7-(5-methyl-1,2,4-oxadiazol-3-yl)-1-isoquinolyl]amino]ethyl]-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2(7),3,5,8-tetraen-10-one



Example 29.1: To a dry 250 mL round-bottom flask equipped with a stirbar under N_2 were added *p*-toluene-sulfonyl-chloride (188.76 mg, 0.9901 mmol), 4-dimethylaminopyridine (11.00 mg, 0.0900 mmol), triethylamine (0.25 mL, 1.8002 mmol), and DCM (3.00 mL, 0.1500 M). The resulting mixture was cooled to 0 °C, and a solution of 11-(1,1,2,2-tetradeuterio-2-hydroxy-ethyl)-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2(7),3,5,8-tetraen-10-one (300.00 mg, 0.9001 mmol) in DCM (3.00 mL, 0.1500 M) was added dropwise. The mixture was warmed to RT and was allowed to stir overnight. The solution was then washed with sat. aq. $NaHCO_3$ (120 mL) and H_2O (120 mL). The combined aqueous layers were extracted with DCM (120 mL) and the combined organic layers were dried over Na_2SO_4, decanted, and concentrated in vacuo. The residue was purified by flash column chromatography (0-80% EtOAc:cyclohexane) to 11-(2-chloro-1,1,2,2-tetradeuterio-ethyl)-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2(7),3,5,8-tetraen-10-one (208.2 mg, 66%, 0.5919 mmol) as white solid. HPLC/MS m/z 352.0974 [M+H, $^{35}Cl]^+$, Rt (R): 1.27 min. ^1H NMR (600 MHz, Chloroform-d*):* δ 7.91 (d, *J* = 6.0 Hz, 1H), 7.41 (d, *J* = 0.9 Hz, 1H), 6.93 (dd, *J* = 6.0, 0.9 Hz, 1H), 4.92 (q, *J* = 8.5 Hz, 2H), 4.34-4.29 (m, 2H), 4.01-3.96 (m, 2H).

Example 29.2: To a stirred solution of sodium azide (39.64 mg, 0.6098 mmol) in DMF (3.70 mL, 0.1500 M) was added 11-(2-chloro-1,1,2,2-tetradeuterio-ethyl)-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2(7),3,5,8-tetraen-10-

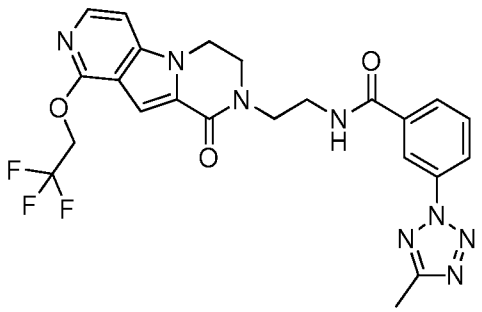
one (195.00 mg, 0.5544 mmol). The reaction mixture was stirred at 80 °C overnight. Then the reaction mixture was cooled to RT and diluted with water (5 mL). The mixture was extracted with ethyl acetate (3×5 mL) and washed by brine, dried over $MgSO_4$ and concentrated in vacuo to give 11-(2-azido-1,1,2,2-tetradeuterio-ethyl)-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2(7),3,5,8-tetraen-10-one (153.2 mg, 77%, 0.4276 mmol) as a yellow solid. It was used directly without further purification. HPLC/MS m/z 359.1377 $[M+H]^+$, Rt (R): 1.25 min.

Example 29.3: To a solution of 11-(2-azido-1,1,2,2-tetradeuterio-ethyl)-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2(7),3,5,8-tetraen-10-one (150.00 mg, 0.4186 mmol) in THF (5.14 mL, 0.0600 M) was added PPh_3 (329.41 mg, 1.2559 mmol). The mixture was stirred at RT for 48 h, then H_2O (1.84 mL, 0.0600 M) was added, and the reaction was heated to 60 °C and allowed to stir for 4 h. The solvent was removed by reduced pressure, and the resulting residue was purified by a very short silica gel column (eluting with 1:10 to 1: 5 methanol-DCM) to afford 11-(2-amino-1,1,2,2-tetradeuterio-ethyl)-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2(7),3,5,8-tetraen-10-one (73.9 mg, 53%, 0.2224 mmol) as a white solid. HPLC/MS m/z 333.1467 $[M+H]^+$, Rt (R): 0.84 min.

Example 29.4: DIPEA (0.14 mL, 0.7899 mmol) was added dropwise to a suspension of 11-(2-amino-1,1,2,2-tetradeuterio-ethyl)-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2(7),3,5,8-tetraen-10-one (70.00 mg, 0.2106 mmol), 5-methyl-3-(2-oxidoisoquinolin-2-ium-7-yl)-1,2,4-oxadiazole (57.44 mg, 0.2528 mmol) and PyBrop (117.84 mg, 0.2528 mmol) in DCM (1.76 mL, 0.1200 M). The tube was sealed, and this was heated to 60 °C for 1 h in the microwave. Water was added and this was extracted with DCM. The organic layers were dried over $MgSO_4$ and evaporated *in vacuo*. NP silica column chromatography (0-7% MeOH in DCM) afforded an almost pure product. A second NP column (0-4% MeOH in DCM) gave pure 11-[1,1,2,2-tetradeuterio-2-[[7-(5-methyl-1,2,4-oxadiazol-3-yl)-1-isoquinolyl]amino]ethyl]-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2(7),3,5,8-tetraen-10-one (63.6 mg, 56%, 0.1174 mmol) as a cream-coloured solid. HPLC/MS m/z 542.2065 $[M+H]^+$, Rt (Z): 2.32 min. ^1H NMR (600 MHz, DMSO-d_6): δ 8.89-8.85 (m, 1H), 8.15 (dd, *J* = 8.5, 1.5 Hz, 1H), 8.05 (s, 1H), 7.97 (d, *J* = 5.7 Hz, 1H), 7.88 (d, *J* = 6.0 Hz, 1H), 7.85 (d, *J* = 8.5 Hz, 1H), 7.29 (dd, *J* = 6.1, 0.9 Hz, 1H), 7.00 (d, *J* = 0.9 Hz, 1H), 6.96 (dd, *J* = 5.9, 0.8 Hz, 1H), 5.15 (q, *J* = 9.1 Hz, 2H), 4.37-4.32 (m, 2H), 3.88-3.83 (m, 2H), 2.67 (s, 3H). ^{13}C NMR (151 MHz, DMSO-d_6): δ 177.46, 167.61, 158.33, 155.76, 155.65, 143.50,

141.36, 138.90, 138.42, 130.04, 127.67, 127.33, 126.91, 125.07, 123.33, 123.22, 122.71, 121.40, 117.56, 110.71, 109.30, 102.89, 101.55, 61.25, 61.02, 60.79, 60.56, 46.51, 40.58, 12.03.

Example 30: 3-(5-Methyltetrazol-2-yl)-N-[2-[10-oxo-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2,4,6,8-tetraen-11-yl]ethyl]benzamide



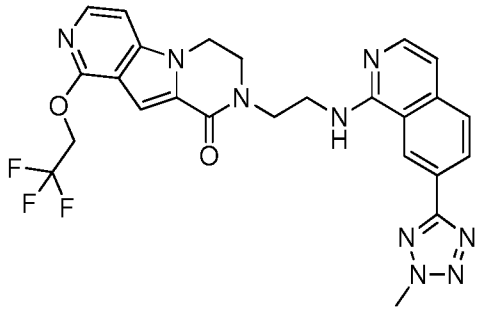
Example 30.1: Ethyl 3-amino benzoate (0.81 mL, 5 mmol) was dissolved in a mixture of water (1.00 mL) and 50% aqueous hydrofluroboric acid (1.90 mL, 30.293 mmol). Sodium nitrite (689.90 mg, 10 mmol) was dissolved in water (1.00 mL) and added dropwise. The reaction was stirred at 0 °C for 30 min, the formation of a pale pink solid was observed. The reaction was filtered and the solid was washed with Et_2O. The solid was transferred into a flask and dried *in vacuo* for 30 min to give 3-ethoxycarbonylbenzenediazonium; tetrafluoroboron (1.10 g, 83%, 4.167 mmol) as a pale pink powder. Rt (T): 1.36 min

Example 30.2: To a solution of acetamidine hydrochloride (0.39 g, 4.167 mmol) and K_2CO_3 (2.88 g, 20.835 mmol) in DMSO (20.25 mL) was added 3-ethoxycarbonylbenzenediazonium; tetrafluoroboron (1.10 g, 4.167 mmol) in portions. After stirring for 1.5 h at RT, KI (1.04 g, 6.2505 mmol) and iodine (1.27 g, 5.0004 mmol) were added, stirred at RT for 1.5 h. A solution of brine and $Na_2S_2O_3$ were added to the mixture. The product was extrated with EtOAc, the organic layer was dried over $MgSO_4$, and concentrated *in vacuo*. The crude was purificed by NP silica column chromatography (elutant: 5-30% EtOAc in cyclohexane) to give ethyl 3-(5-methyltetrazol-2-yl)benzoate (582 mg, 60%, 2.506 mmol) as yellow powder. HPLC/MS m/z 233.0991 $[M+H]^+$, Rt (T): 1.36 min. ^1H NMR (500 MHz, DMSO-d_6): δ 8.55-8.52 (m, 1H), 8.36 (ddd, J = 8.2, 2.3, 1.0 Hz, 1H), 8.14 (dt, J = 7.9, 1.2 Hz, 1H), 7.82 (t, J = 8.0 Hz, 1H), 4.39 (q, J = 7.1 Hz, 2H), 2.61 (s, 3H), 1.36 (t, J = 7.1 Hz, 3H).

Example 30.3: ethyl 3-(5-methyltetrazol-2-yl)benzoate (150.00 mg, 0.6459 mmol) was dissolved in THF (3.23 mL) and H2O (1.00 mL, 0.1500 M). LiOH (77.34 mg, 3.2294 mmol) was added, and the mixture was stirred at 50 °C for 2 h. The mixture was cooled to RT, concentrated, and diluted with 1 mL of water. The pH was adjusted to pH ~3 and the product was extracted with EtOAc (60 mL). After phase separation the organic layer was dried over $MgSO_4$, filtered, and evaporated to dryness give 3-(5-methyltetrazol-2-yl)benzoic acid (142 mg, 108%, 0.6954 mmol) as a yellow powder. The product was taken through to the next step without further purification. HPLC/MS m/z 205.0723 $[M+H]^+$, Rt (R): 1.09 min.

Example 30.4: DIPEA (0.08 mL, 0.4606 mmol) was added to a mixture of 3-(5-methyltetrazol-2-yl)benzoic acid (27.04 mg, 0.1324 mmol), HATU (87.56 mg, 0.2303 mmol) and 11-(2-aminoethyl)-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2,4,6,8-tetraen-10-one hydrochloride (42.00 mg, 0.1151 mmol) in DCM (1.15 mL, 0.1000 M). This was stirred for 2 h before sat. aq. $NaHCO_3$ was added. This was extracted with DCM, filtered over $MgSO_4$ and evaporated. Silica gel chromatography with DCM and MeOH as eluents (100:0 to 96:4) afforded a slightly impure product by NMR. The compound was subjected to RP column chromatography (10-80% MeOH:water + 0.1% formic acid) and the fractions were passed through an SCX-II column releasing with 2N NH_3 in methanol to afford 3-(5-methyltetrazol-2-yl)-N-[2-[10-oxo-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2,4,6,8-tetraen-11-yl]ethyl]benzamide (34.3 mg, 56%, 0.0650 mmol) as a fine white solid after evaporation. HPLC/MS m/z 515.1768 $[M+H]^+$, Rt (S): 2.84 min. ^1H NMR (600 MHz, DMSO-d_6): δ 8.94 (t, *J* = 5.8 Hz, 1H), 8.47 (t, *J* = 2.0 Hz, 1H), 8.20 (ddd, *J* = 8.1, 2.2, 1.0 Hz, 1H), 7.98 (dt, *J* = 7.9, 1.3 Hz, 1H), 7.89 (d, *J* = 6.0 Hz, 1H), 7.74 (t, *J* = 7.9 Hz, 1H), 7.31 (dd, *J* = 6.0, 0.9 Hz, 1H), 6.99 (d, *J* = 0.9 Hz, 1H), 5.14 (q, *J* = 9.1 Hz, 2H), 4.42-4.37 (m, 2H), 3.92-3.87 (m, 2H), 3.76-3.71 (m, 2H), 3.59 (q, *J* = 5.9 Hz, 2H), 2.59 (s, 3H). ^{13}C NMR (151 MHz, DMSO-d_6): δ 165.57, 163.69, 158.93, 156.12, 141.85, 139.41, 136.77, 136.62, 130.81, 130.33, 128.85, 127.36, 125.52, 123.68, 122.52, 118.77, 111.17, 103.37, 102.14, 61.72, 61.49, 61.26, 61.03, 46.54, 46.15, 41.09, 37.95, 10.99.

Example 31: 11-[2-[[7-(2-Methyltetrazol-5-yl)-1-isoquinolyl]amino]ethyl]-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2,4,6,8-tetraen-10-one



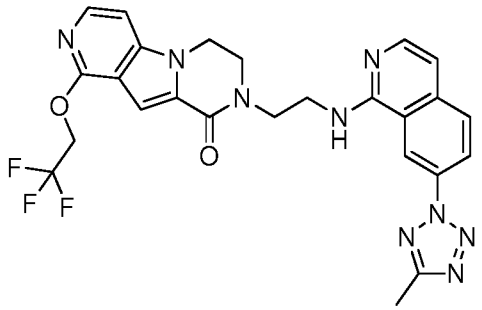
Example 31.1: To a stirred solution of a 5-bromo-2-methyl-1H-tetrazole (75.00 mg, 0.4602 mmol), Isoquinoline-7-boronic acid (103.48 mg, 0.5982 mmol), sodium carbonate (73.16 mg, 0.6903 mmol) in a mixture of DME (1.84 mL, 0.2000 M)/water (0.46 mL, 0.2000 M) 4:1 was added $Pd(PPh_3)_4$ (53.18 mg, 0.0460 mmol) under an argon atmosphere. The solution was stirred at 90 °C for 18 h and then treated with water. In a standard work-up, the mixture was extracted with DCM and the organic layer was dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material was purified by NP column chromatography (20-100% EtOAc:cyclohexane) to give 7-(2-methyltetrazol-5-yl)isoquinoline (72.74 mg, 75%, 0.3444 mmol) as a pale yellow solid. HPLC/MS m/z 212.0929 $[M+H]^+$, Rt (Y): 0.81 min. ^1H NMR (600 MHz, Chloroform-d): δ 9.37 (t, *J* = 0.9 Hz, 1H), 8.82-8.78 (m, 1H), 8.60 (d, *J* = 5.7 Hz, 1H), 8.44 (dd, *J* = 8.6, 1.6 Hz, 1H), 7.96 (d, *J* = 8.6 Hz, 1H), 7.70 (d, *J* = 5.7 Hz, 1H), 4.46 (s, 3H).

Example 31.2: 7-(2-Methyltetrazol-5-yl)isoquinoline (70.00 mg, 0.3314 mmol) was dissolved in chloroform (2.53 mL, 0.1300 M) and cooled in an ice bath. 3-Chloroperoxybenzoic acid (98.04 mg, 0.3977 mmol) was added. The reaction was stirred at r.t. overnight. K_2CO_3 (183.22 mg, 1.3256 mmol) was added. This was stirred for 4 h at RT before filtering through a pad of anhydr. $MgSO_4$. The filtrate was concentrated *in vacuo* to yield 7-(2-methyltetrazol-5-yl)-2-oxido-isoquinolin-2-ium (78.5 mg, 104%, 0.3455 mmol) as an off-white powder. Significant triphenylphosphine oxide impurities from ligand. Carried on to the next reaction. HPLC/MS m/z 228.0809 $[M+H]^+$, Rt (Y): 0.92 min. ^1H NMR (600 MHz, Chloroform-d): δ 8.88 (t, *J* = 1.3 Hz, 1H), 8.56-8.53 (m, 1H), 8.34 (dd, *J* = 8.5, 1.5 Hz, 1H), 8.20 (dd, *J* = 7.1, 1.8 Hz, 1H), 7.92 (d, *J* = 8.5 Hz, 1H), 7.72 (d, *J* = 7.1 Hz, 1H), 4.46 (s, 3H).

Example 31.3: 7-(2-Methyltetrazol-5-yl)-2-oxido-isoquinolin-2-ium (58.14 mg, 0.2559 mmol), PyBrop (119.28 mg, 0.2559 mmol) and DIPEA (0.14 mL, 0.7996 mmol) in

DCM (1.08 mL, 0.1200 M) were stirred under a nitrogen atmosphere for 30 min at 40 °C in a microwave vial. 11-(2-aminoethyl)-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2,4,6,8-tetraen-10-one (70.00 mg, 0.2132 mmol) was then added in DCM (0.70 mL, 0.1200 M) and the reaction was heated at 60 °C by microwave irradiation for 1 h. Water was added, and this was extracted with DCM. The organic layer was dried over $MgSO_4$ and evaporated *in vacuo*. Normal-phase chromatography (0-5% MeOH in DCM) followed by two further RP columns were used to purify the product (10-80% MeOH:water + 0.1% formic acid), and the fractions were passed through an SCX-II column releasing with 2N NH_3 in methanol to afford 11-[2-[[7-(2-methyltetrazol-5-yl)-1-isoquinolyl]amino]ethyl]-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2,4,6,8-tetraen-10-one (6.5 mg, 5%, 0.0114 mmol) as a white solid. HPLC/MS m/z 538.1939 $[M+H]^+$, Rt (Z): 2.25 min. ^1H NMR (600 MHz, DMSO-d_6): δ 8.95 (s, 1H), 8.24 (d, *J* = 8.4 Hz, 1H), 8.08 (s, 1H), 7.95 (d, *J* = 5.7 Hz, 1H), 7.88 (dd, *J* = 7.2, 3.2 Hz, 2H), 7.29 (dd, *J* = 6.0, 0.9 Hz, 1H), 6.99 (d, *J* = 13.7 Hz, 2H), 5.15 (q, *J* = 9.1 Hz, 2H), 4.44 (s, 3H), 4.38-4.29 (m, 2H), 3.89-3.77 (m, 6H). ^{13}C NMR (151 MHz, DMSO-d_6): δ 164.13, 158.35, 155.65, 141.37, 138.91, 137.82, 130.02, 127.76, 125.07, 124.13, 123.23, 121.48, 117.81, 110.71, 109.40, 102.90, 101.57, 61.26, 61.03, 60.80, 60.57, 46.59, 45.56, 40.60, 40.06, 39.68.

Example 32: 11-[2-[[7-(5-Methyltetrazol-2-yl)-1-isoquinolyl]amino]ethyl]-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2,4,6,8-tetraen-10-one



Example 32.1: 7-Aminoisoquinoline (1000.00 mg, 6.9363 mmol) was dissolved in a mixture of 50% aqueous hydrofluroboric acid (3.47 mL, 27.647 mmol) and EtOH (2.08 mL, 3.33 M). The reaction mixture was cooled to 0 °C and tert-butyl nitrite (1.65 mL, 13.873 mmol) was added dropwise. Stirred for 1 h at RT, diethyl ether (10

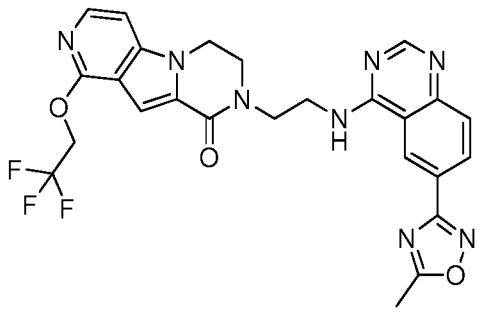
mL) was added to precipitate the diazonium compound that was filtered off and washed with diethyl ether (3x5 mL). The desired compound isoquinoline-7-diazonium; tetrafluoroboron (1.41 g, 84%, 5.7982 mmol) was dried *in vacuo* to give a dark red powder. Rt (Y): 0.15 min. ^{1}H NMR (600 MHz, DMSO-d_6): δ 9.78-9.73 (m, 2H), 8.97 (d, *J* = 5.7 Hz, 1H), 8.64 (dd, *J* = 9.1, 2.1 Hz, 1H), 8.50 (d, *J* = 9.0 Hz, 1H), 8.19 (d, *J* = 5.8 Hz, 1H). ^{13}C NMR (151 MHz, DMSO-d_6): δ 154.52, 149.72, 139.29, 138.64, 130.36, 127.53, 125.83, 121.10, 114.12.

Example 32.2: To a solution of acetamidine hydrochloride (544.74 mg, 5.762 mmol) and potassium carbonate (3.98 g, 28.81 mmol) in DMSO (28.00 mL, 0.2100 M) was added isoquinoline-7-diazonium; tetrafluoroboron (1.40 g, 5.762 mmol) in portions. After stirring for 1.5 h at RT LC/MS showed complete addition of the acetamidine moiety, KI (1434.75 mg, 8.643 mmol) and iodine (1754.95 mg, 6.9144 mmol) were added, stirred at RT for 1.5 h. A solution of brine and $Na_2S_2O_3$ were added to the mixture. The product was extracted with EtOAc (7x100 mL), the organic layer was dried over $MgSO_4$, and concentrated *in vacuo*. The crude was purified by NP column chromatography (Eluent: 0-70% EtOAc in cyclohexane) to give 7-(5-methyltetrazol-2-yl)isoquinoline (169.1 mg, 14%, 0.8006 mmol) as an orange powder. Rt (Y): 1.02 min. ^{1}H NMR (600 MHz, Chloroform-d*):* δ 9.40 (d, *J* = 1.0 Hz, 1H), 8.70 (d, *J* = 2.2 Hz, 1H), 8.64 (d, *J* = 5.7 Hz, 1H), 8.49 (dd, *J* = 8.9, 2.2 Hz, 1H), 8.03 (d, *J* = 8.9 Hz, 1H), 7.74 (dt, *J* = 5.7, 1.0 Hz, 1H), 2.69 (s, 3H). ^{13}C NMR (151 MHz, Chloroform-d): δ 163.81, 153.19, 144.54, 135.75, 135.22, 128.91, 128.47, 122.36, 120.47, 117.71, 11.19.

Example 32.3: 7-(5-Methyltetrazol-2-yl)isoquinoline (155.00 mg, 0.7338 mmol) was dissolved in $CHCl_3$ (2.45 mL, 0.3000 M) and cooled in an ice bath. 3-Chloroperoxybenzoic acid (0.22 g, 0.8806 mmol) was added. The reaction was stirred at RT for 2 h. K_2CO_3 (0.41 g, 2.9353 mmol) was added, stirred for 0.5 h before filtering. The filtrate was concentrated in vacuo to give a yellow/orange powder. The powder was redissolved in $CHCl_3$, washed with a saturated solution of $NaHCO_3$, dried over $MgSO_4$ and concentrated *in vacuo* to give 7-(5-methyltetrazol-2-yl)-2-oxido-isoquinolin-2-ium (163.6 mg, 98%, 0.7200 mmol) as a yellow powder. Rt (Y): 0.97 min. ^{1}H NMR (600 MHz, Chloroform-d*):* δ 8.86 (dd, *J* = 1.6, 0.8 Hz, 1H), 8.44 (d, *J* = 2.1 Hz, 1H), 8.37 (dd, *J* = 8.8, 2.1 Hz, 1H), 8.20 (dd, *J* = 7.1, 1.7 Hz, 1H), 7.98 (d, *J* = 8.9 Hz, 1H), 7.75 (d, *J* = 7.1 Hz, 1H), 2.68 (s, 3H). ^{13}C NMR (151 MHz, Chloroform-d): δ 164.03, 138.30, 137.07, 136.50, 130.06, 129.02, 128.41, 124.35, 120.63, 114.63, 11.16.

Example 32.4: 7-(5-Methyltetrazol-2-yl)-2-oxido-isoquinolin-2-ium (83.06 mg, 0.3655 mmol), PyBrop (170.40 mg, 0.3655 mmol) and DIPEA (0.20 mL, 1.1423 mmol) in DCM (1.54 mL, 0.1200 M) were stirred under a nitrogen atmosphere for 30 min at 40 °C in a microwave vial. 11-(2-Aminoethyl)-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2,4,6,8-tetraen-10-one (100.00 mg, 0.3046 mmol) was then added in DCM (1.00 mL, 0.1200 M) and the reaction was heated at 60 °C by microwave irradiation for 1 h. The reaction was evaporated *in vacuo* and subjected to RP column chromatography (10-80% MeOH:water + 0.1% formic acid). The pure fractions were run through a SCX-II column, released using 2N NH_3 in methanol solution and evaporated, affording 11-[2-[[7-(5-methyltetrazol-2-yl)-1-isoquinolyl]amino]ethyl]-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2,4,6,8-tetraen-10-one (40 mg, 24%, 0.0744 mmol) as a white powder. HPLC/MS m/z 538.1883 $[M+H]^+$, Rt (Z): 2.37 min. ^{1}H NMR (600 MHz, DMSO-d_6): δ 8.94 (d, *J* = 2.1 Hz, 1H), 8.28 (dd, *J* = 8.8, 2.1 Hz, 1H), 8.08 (t, *J* = 5.4 Hz, 1H), 8.01-7.95 (m, 2H), 7.88 (d, *J* = 6.0 Hz, 1H), 7.28 (dd, *J* = 6.0, 0.9 Hz, 1H), 7.04-6.98 (m, 2H), 5.15 (q, *J* = 9.1 Hz, 2H), 4.37-4.32 (m, 2H), 3.89-3.77 (m, 6H), 2.60 (s, 3H). ^{13}C NMR (151 MHz, DMSO-d_6): δ 163.13, 158.35, 155.68, 155.65, 143.19, 141.36, 138.92, 137.17, 133.35, 130.00, 128.91, 125.07, 123.22, 121.49, 117.50, 114.12, 110.71, 109.17, 102.89, 101.58, 61.26, 61.03, 60.79, 60.57, 46.59, 45.57, 40.59, 39.14, 10.58.

Example 33: 11-[2-[[6-(5-Methyl-1,2,4-oxadiazol-3-yl)quinazolin-4-yl]amino]ethyl]-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2,4,6,8-tetraen-10-one



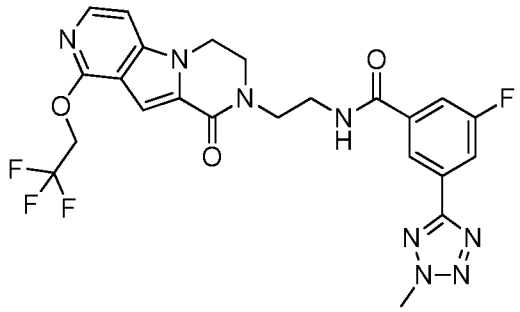
Example 33.1: 4-Hydroxyquinazoline-6-carbonitrile (500 mg, 2.92 mmol) and triethylamine (0.41 mL, 2.92 mmol) were heated at 80 °C in [bmim]OAc (2.9 mL). Hydroxylamine hydrochloride (406 mg, 5.84 mmol) was added, after which some

foaming was observed. The reaction mixture was continued to stir at 80 °C for 30 min. The reaction mixture was cooled down to room temperature and water was added (50 mL). The precipitate was filtered off, washed with water (50 mL) and dried under reduced pressure to yield 536 mg (90%) of *N*,4-dihydroxyquinazoline-6-carboxamidine. HPLC/MS m/z: 205.1 $[M+H]^+$, Rt (U): 0.46 min.

Example 33.2: A suspension of *N*,4-dihydroxyquinazoline-6-carboxamidine (480 mg, 2.35 mmol) and acetic anhydride (0.27 mL, 2.82 mmol) in anhydrous ACN (4.70 mL) under an argon atmosphere was heated under microwave irradiation at 180 °C for 10 min. The reaction mixture was cooled to room temperature and cold water was added (50 mL). The precipitate was filtered off, washed with water (50 mL) and diethyl ether (10 mL), and dried under reduced pressure to yield 293 mg (55%) of 6-(5-methyl-1,2,4-oxadiazol-3-yl)quinazolin-4-ol. HPLC/MS m/z: 229.0727 $[M+H]^+$, Rt (U): 1.93 min.

Example 33.3: 6-(5-Methyl-1,2,4-oxadiazol-3-yl)quinazolin-4-ol (60.00 mg, 0.2629 mmol), 11-(2-aminoethyl)-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2,4,6,8-tetraen-10-one (94.94 mg, 0.2892 mmol) and DIPEA (0.14 mL, 0.7887 mmol) were dissolved in DMF (2.63 mL, 0.1000 M) at RT under argon. PyBOP (191.55 mg, 0.3681 mmol) was added, and the reaction was stirred for 3 h. The reaction mixture was mixed with water (30 mL) and extracted with EtOAc (3 x 10 mL). The combined organic phase was washed with sat. NaCl (3x10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was first purified by NP flash chromatography (0-5% MeOH in DCM) to give a semi pure product. The fractions were combined, evaporated and subjected to RP column chromatography (0-80% MeOH:water with 0.1% formic acid) to afford 11-[2-[[6-(5-methyl-1,2,4-oxadiazol-3-yl)quinazolin-4-yl]amino]ethyl]-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2,4,6,8-tetraen-10-one (57 mg, 40%, 0.1041 mmol) as an off-white solid. HPLC/MS m/z 539.1768 $[M+H]^+$, Rt (Z): 2.26 min. ^1H NMR (600 MHz, DMSO-d_6): δ 8.94-8.89 (m, 2H), 8.53 (s, 1H), 8.29 (dd, *J* = 8.7, 1.8 Hz, 1H), 7.89 (d, *J* = 6.0 Hz, 1H), 7.81 (d, *J* = 8.7 Hz, 1H), 7.30 (dd, *J* = 6.0, 0.9 Hz, 1H), 6.98 (d, *J* = 0.9 Hz, 1H), 5.15 (q, *J* = 9.1 Hz, 2H), 4.38-4.33 (m, 2H), 3.90-3.86 (m, 2H), 3.86 (s, 4H), 2.67 (s, 3H). ^{13}C NMR (151 MHz, DMSO-d_6): δ 177.67, 167.22, 159.77, 158.40, 156.39, 155.65, 150.87, 141.37, 138.94, 130.27, 129.90, 128.70, 123.39, 122.44, 115.10, 110.70, 102.91, 101.64, 61.24, 61.02, 60.77, 60.56, 46.46, 45.29, 40.60, 38.75, 12.03.

Example 34: 3-Fluoro-5-(2-methyltetrazol-5-yl)-N-[2-[10-oxo-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2,4,6,8-tetraen-11-yl]ethyl]benzamide

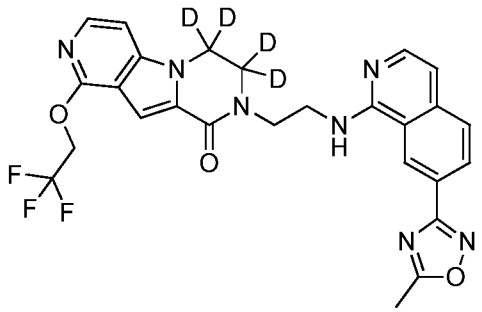


Example 34.1: To a stirred solution of 5-bromo-2-methyl-1H-tetrazole (70.00 mg, 0.4295 mmol), Na_2CO_3 (68.28 mg, 0.6443 mmol), $Pd(PPh_3)_4$ (49.63 mg, 0.0430 mmol) in a mixture of DME/water (4:1, conc. 0.2000 M) at 60 °C was added (3-fluoro-5-methoxycarbonyl-phenyl)boronic acid (110.53 mg, 0.5584 mmol) in DME (0.36 mL, 0.2000 M) under an argon atmosphere and the reaction was heated to 90 °C for 18 h and then treated with water. In a standard work-up, the mixture was extracted with DCM and the organic layer was dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material was purified by flash column chromatography (0-80% EtOAc:cyclohexane) to give methyl 3-fluoro-5-(2-methyltetrazol-5-yl)benzoate (43.6 mg, 43%, 0.1846 mmol) as a pale yellow solid. HPLC/MS m/z 237.0783 $[M+H]^+$, Rt (Y): 1.41 min. ^1H NMR (600 MHz, DMSO-d_6): δ 8.44 (t, *J* = 1.5 Hz, 1H), 8.10 (ddd, *J* = 9.0, 2.6, 1.5 Hz, 1H), 7.87 (ddd, *J* = 9.0, 2.6, 1.5 Hz, 1H), 4.47 (s, 3H), 3.93 (s, 3H).

Example 34.2: Methyl 3-fluoro-5-(2-methyltetrazol-5-yl)benzoate (40.00 mg, 0.1693 mmol), THF (0.68 mL, 0.1000 M), MeOH (0.34 mL, 0.1000 M) and H_2O (0.68 mL, 0.1000 M) were mixed at ambient temperature. Lithium hydroxide monohydrate (35.53 mg, 0.8467 mmol) was added, and the reaction mixture was stirred for 1 h. The reaction was quenched with 2N HCl and DCM was added. The water layer was extracted with DCM (3 x 20 mL), dried over $MgSO_4$ and evaporated under reduced pressure to afford 3-fluoro-5-(2-methyltetrazol-5-yl)benzoic acid (34 mg, 90%, 0.1530 mmol) as an off-white, crystalline solid. Used in the next step without further purification. HPLC/MS m/z 223.0627 $[M+H]^+$, Rt (Y): 1.25 min.

Example 34.3: DIPEA (0.10 mL, 0.5483 mmol) was added to a mixture of 3-fluoro-5-(2-methyltetrazol-5-yl)benzoic acid (33.50 mg, 0.1508 mmol), HATU (104.24 mg, 0.2741 mmol) and 11-(2-aminoethyl)-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2,4,6,8-tetraen-10-one (45.00 mg, 0.1371 mmol) in DCM (1.22 mL, 0.1100 M) and stirred at RT overnight before sat. aq. $NaHCO_3$ was added. This was extracted with DCM, filtered over $MgSO_4$ and evaporated. The compound was subjected to RP column chromatography (10-80% MeOH:water) to afford 3-fluoro-5-(2-methyltetrazol-5-yl)-N-[2-[10-oxo-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2,4,6,8-tetraen-11-yl]ethyl]benzamide (35.4 mg, 49%, 0.0665 mmol) as a white solid. HPLC/MS m/z 533.1660 $[M+H]^+$, Rt (Z): 2.64 min. ^1H NMR (600 MHz, DMSO-d_6): δ 8.95 (t, *J* = 5.9 Hz, 1H), 8.35 (t, *J* = 1.5 Hz, 1H), 7.95 (ddd, *J* = 9.0, 2.6, 1.4 Hz, 1H), 7.89 (d, *J* = 6.0 Hz, 1H), 7.76 (ddd, *J* = 9.4, 2.6, 1.5 Hz, 1H), 7.32 (dd, *J* = 6.0, 0.9 Hz, 1H), 7.00 (d, *J* = 0.9 Hz, 1H), 5.15 (q, *J* = 9.1 Hz, 2H), 4.44 (s, 3H), 4.42-4.37 (m, 2H), 3.92-3.87 (m, 2H), 3.76-3.71 (m, 2H), 3.58 (q, *J* = 5.9 Hz, 2H). ^{13}C NMR (151 MHz, DMSO-d_6): δ 164.52, 164.51, 163.02, 162.73, 162.71, 161.39, 158.46, 155.65, 141.38, 138.94, 137.99, 137.94, 129.86, 129.22, 129.17, 125.05, 123.21, 121.24, 121.22, 116.08, 115.93, 115.56, 115.40, 110.70, 102.91, 101.66, 61.24, 61.01, 60.78, 60.55, 46.08, 45.65, 40.62, 37.50.

Example 35: 12,12,13,13-Tetradeuterio-11-[2-[[7-(5-methyl-1,2,4-oxadiazol-3-yl)-1-isoquinolyl]amino]ethyl]-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2(7),3,5,8-tetraen-10-one



Example 35.1: A solution of methyl 4-(2,2,2-trifluoroethoxy)-1H-pyrrolo[3,2-c]pyridine-2-carboxylate (750.00 mg, 2.7352 mmol), 2-bromo-1,1,2,2-tetradeuterio-ethanol (0.35 mL, 4.9234 mmol), and PPh_3 (1076.14 mg, 4.1028 mmol) in THF (6.84 mL, 0.4000 M) was cooled to 0 °C. Diisopropyl azodicarboxylate (0.86 mL, 4.3764 mmol) was added dropwise over 20 min, and the resulting mixture was warmed to

RT and stirred for 18 h. The crude was evaporated and subjected to NP chromatography (0-60% EtOAc:cyclohexane) and the fractions containing were combined and evaporated under reduced pressure to afford methyl 1-(2-bromo-1,1,2,2-tetradeuterio-ethyl)-4-(2,2,2-trifluoroethoxy)pyrrolo[3,2-c]pyridine-2-carboxylate (591 mg, 56%, 1.5344 mmol) as a white solid. HPLC/MS m/z 385.0285 [M+H, $^{79}Br]^+$, 387.0261 [M+H, $^{81}Br]^+$, Rt (Y): 1.66 min. ^1H NMR (600 MHz, Chloroform-d*):* δ 7.93 (d, *J* = 6.1 Hz, 1H), 7.49 (t, *J* = 0.8 Hz, 1H), 7.07 (dt, *J* = 6.1, 0.8 Hz, 1H), 4.91 (q, *J* = 8.5 Hz, 2H), 3.93 (s, 3H). ^{13}C NMR (151 MHz, Chloroform-d): δ 161.89, 157.14, 145.18, 140.77, 126.91, 124.78, 122.94, 111.02, 110.27, 102.43, 62.60, 62.36, 62.13, 61.88, 52.19.

Example 35.2: To a stirred solution of sodium azide (107.68 mg, 1.6564 mmol) in DMF (11.58 mL, 0.1300 M) was added methyl 1-(2-bromo-1,1,2,2-tetradeuterio-ethyl)-4-(2,2,2-trifluoroethoxy)pyrrolo[3,2-c]pyridine-2-carboxylate (580.00 mg, 1.5058 mmol). The reaction mixture was stirred at 80 °C overnight. Then the reaction mixture was cooled to RT and diluted with water (5 mL). The mixture was extracted with ethyl acetate (3×5 mL) and washed by brine, dried over $MgSO_4$ and concentrated *in vacuo* to give methyl 1-(2-azido-1,1,2,2-tetradeuterio-ethyl)-4-(2,2,2-trifluoroethoxy)pyrrolo[3,2-c]pyridine-2-carboxylate (506.4 mg, 97%, 1.4581 mmol) as a yellow solid. It was used directly without further purification. HPLC/MS m/z 348.1229 $[M+H]^+$, Rt (R): 1.44 min.

Example 35.3: To a solution of methyl 1-(2-azido-1,1,2,2-tetradeuterio-ethyl)-4-(2,2,2-trifluoroethoxy)pyrrolo[3,2-c]pyridine-2-carboxylate (480.00 mg, 1.3821 mmol) in THF (17.28 mL, 0.0600 M) was added PPh_3 (1087.56 mg, 4.1464 mmol). The mixture was stirred at RT for 16 h, then water (5.76 mL, 0.0600 M) was added, and the reaction was heated to 40 °C and allowed to stir for 4 h. The solvent was removed by reduced pressure, and the resulting residue was purified by RP column chromatography (0-5% Methanol in DCM) to afford 12,12,13,13-tetradeuterio-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2,4,6,8-tetraen-10-one (401 mg, 100%, 1.3863 mmol) as a white solid. HPLC/MS m/z 290.0985 $[M+H]^+$, Rt (Y): 1.26 min. ^1H NMR (600 MHz, DMSO-d_6): δ 8.26 (s, 1H), 7.90 (d, *J* = 6.0 Hz, 1H), 7.33 (dd, *J* = 6.0, 0.9 Hz, 1H), 7.00 (d, *J* = 0.9 Hz, 1H), 5.16 (q, *J* = 9.1 Hz, 2H).

Example 35.4: 12,12,13,13-tetradeuterio-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2,4,6,8-tetraen-10-one (380.00 mg, 1.3137 mmol) was dissolved in DMF (18.77 mL, 0.0700 M). The obtained solution was cooled down 0 °C in an ice bath followed by the addition of NaH (115.61 mg, 2.8902 mmol).

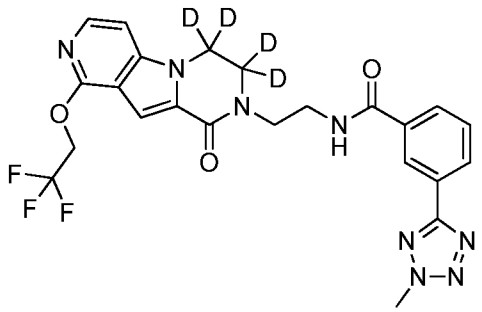
The reaction mixture was left stirring at 0 °C for 30 min. *N*-Boc-2-chloroethylamine (291.96 mg, 1.5765 mmol) dissolved in DMF (2.5 mL) was added dropwise to the reaction mixture and allowed to warm to RT. The reaction mixture was left stirring at RT for 5 d. Water was added and the reaction was extracted with EtOAc (3x10 mL), and the combined organic layers were washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure. The crude was subjected to NP chromatography (0-100% EtOAc:cyclohexane) to afford tert-butyl N-[2-[12,12,13,13-tetradeuterio-10-oxo-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2,4,6,8-tetraen-11-yl]ethyl]carbamate (247 mg, 26%, 0.3427 mmol). The product had a purity of 60% and was used directly without further purification. HPLC/MS m/z 433.1871 $[M+H]^+$, Rt (Y): 1.49 min.

Example 35.5: tert-Butyl N-[2-[12,12,13,13-tetradeuterio-10-oxo-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2,4,6,8-tetraen-11-yl]ethyl]carbamate (240.00 mg, 0.3330 mmol) was mixed with 4N HCl in 1,4-dioxane (3.33 mL, 13.32 mmol) and 1,4-dioxane (3.33 mL, 0.1000 M) at RT under argon and stirred for 2 h. Volatiles were removed under reduced pressure to give 11-(2-aminoethyl)-12,12,13,13-tetradeuterio-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2,4,6,8-tetraen-10-one hyrochloride (93.5 mg, 84%, 0.2814 mmol) as a white solid. The crude product was subjected to RP column chromatography (10-80% MeOH:water with 0.1% formic acid). The pure fractions were run through an SCX-II column, releasing with 2N NH_3 in methanol, to afford 11-(2-aminoethyl)-12,12,13,13-tetradeuterio-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2,4,6,8-tetraen-10-one (93.5 mg, 84%, 0.2814 mmol) as a white solid. HPLC/MS m/z 333.1381 $[M+H]^+$, Rt (Y): 0.96 min. ^1H NMR (600 MHz, DMSO-d_6): δ 7.90 (d, *J* = 6.0 Hz, 1H), 7.33 (dd, *J* = 6.0, 0.9 Hz, 1H), 6.99 (d, *J* = 0.9 Hz, 1H), 5.16 (q, *J* = 9.1 Hz, 2H), 3.49 (t, *J* = 6.5 Hz, 2H), 2.76 (t, *J* = 6.5 Hz, 2H). ^{13}C NMR (151 MHz, DMSO-d_6): δ 158.25, 155.63, 141.39, 138.82, 130.06, 125.07, 123.23, 110.72, 102.91, 101.42, 61.22, 60.99, 60.77, 60.53, 49.25, 39.70.

Example 35.6: DIPEA (0.13 mL, 0.7335 mmol) was added dropwise to a suspension of 11-(2-aminoethyl)-12,12,13,13-tetradeuterio-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2,4,6,8-tetraen-10-one (65.00 mg, 0.1956 mmol), 5-methyl-3-(2-oxidoisoquinolin-2-ium-7-yl)-1,2,4-oxadiazole (53.33 mg, 0.2347 mmol) and PyBrop (109.42 mg, 0.2347 mmol) in DCM (1.63 mL, 0.1200 M). The tube was sealed, and this was heated to 60 °C for 1 h in the microwave. The reaction was evaporated *in vacuo* and subjected to RP column chromatography (10-80%

MeOH:water + 0.1% formic acid). The pure fractions were run through a SCX-II column, released using 2N NH_3 in methanol solution and evaporated, affording 12,12,13,13-tetradeuterio-11-[2-[[7-(5-methyl-1,2,4-oxadiazol-3-yl)-1-isoquinolyl]amino]ethyl]-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2(7),3,5,8-tetraen-10-one (39 mg, 37%, 0.0720 mmol) as a cream-coloured powder. HPLC/MS m/z 542.2072 $[M+H]^+$, Rt (Z): 2.32 min. ^1H NMR (600 MHz, DMSO-d_6): δ 8.89-8.86 (m, 1H), 8.15 (dd, *J* = 8.4, 1.5 Hz, 1H), 8.07 (t, *J* = 5.5 Hz, 1H), 7.97 (d, *J* = 5.7 Hz, 1H), 7.88 (d, *J* = 6.0 Hz, 1H), 7.85 (d, *J* = 8.5 Hz, 1H), 7.29 (dd, *J* = 6.0, 0.9 Hz, 1H), 7.00 (d, *J* = 0.9 Hz, 1H), 6.96 (dd, *J* = 5.9, 0.8 Hz, 1H), 5.15 (q, *J* = 9.1 Hz, 2H), 3.84 (t, *J* = 5.7 Hz, 2H), 3.81-3.76 (m, 2H), 2.67 (s, 3H). ^{13}C NMR (151 MHz, DMSO-d_6): δ 177.47, 167.60, 158.33, 155.73, 155.65, 143.49, 141.37, 138.89, 138.42, 130.03, 127.68, 127.34, 123.33, 122.70, 117.56, 110.72, 109.32, 102.90, 101.54, 61.02, 60.79, 45.51, 39.15, 12.03.

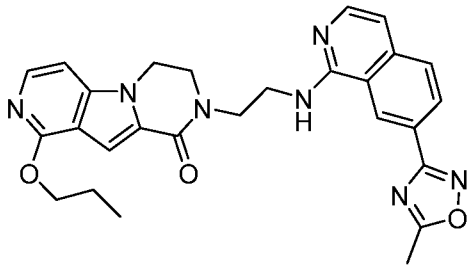
Example 36: 3-(2-Methyltetrazol-5-yl)-N-[2-[12,12,13,13-tetradeuterio-10-oxo-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2(7),3,5,8-tetraen-11-yl]ethyl]benzamide



DIPEA (0.05 mL, 0.2648 mmol) was added to a mixture of 3-(2-methyl-2H-tetrazol-5-yl)-benzoic acid (15.55 mg, 0.0761 mmol), HATU (50.34 mg, 0.1324 mmol) and 11-(2-aminoethyl)-12,12,13,13-tetradeuterio-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2,4,6,8-tetraen-10-one (22.00 mg, 0.0662 mmol) in DCM (0.66 mL, 0.1000 M). This was stirred for 2 h before sat. aq. $NaHCO_3$ was added. This was extracted with DCM, filtered over $MgSO_4$ and evaporated. The compound was subjected to RP column chromatography (10-80% MeOH:water + 0.1% formic acid). The pure fractions were run through a SCX-II column, released using 2N NH_3 in methanol solution and evaporated, affording 3-(2-methyltetrazol-5-yl)-N-[2-[12,12,13,13-tetradeuterio-10-oxo-6-(2,2,2-trifluoroethoxy)-1,5,11-

triazatricyclo[7.4.0.02,7]trideca-2(7),3,5,8-tetraen-11-yl]ethyl]benzamide (26 mg, 76%, 0.0501 mmol) as a white solid. HPLC/MS m/z 519.2021 $[M+H]^+$, Rt (Z): 2.52 min. ^1H NMR (600 MHz, DMSO-d_6): δ 8.86 (t, *J* = 5.9 Hz, 1H), 8.50 (t, *J* = 1.7 Hz, 1H), 8.18 (dt, *J* = 7.8, 1.4 Hz, 1H), 7.95 (dt, *J* = 7.9, 1.4 Hz, 1H), 7.89 (d, *J* = 6.0 Hz, 1H), 7.65 (t, *J* = 7.8 Hz, 1H), 7.31 (dd, *J* = 6.0, 0.9 Hz, 1H), 7.00 (d, *J* = 0.9 Hz, 1H), 5.15 (q, *J* = 9.1 Hz, 2H), 4.43 (s, 3H), 3.73 (t, *J* = 6.0 Hz, 2H), 3.58 (q, *J* = 6.0 Hz, 2H). ^{13}C NMR (151 MHz, DMSO-d_6): δ 165.82, 163.66, 158.42, 155.65, 141.39, 138.92, 135.47, 129.89, 129.41, 129.08, 128.77, 127.07, 125.07, 110.71, 102.91, 101.64, 61.01, 60.76, 45.67, 40.06, 37.43.

Example 37: 8-(2-((7-(5-Methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl)amino)ethyl)-1-propoxy-7,8-dihydropyrido[3',4':4,5]pyrrolo[1,2-a]pyrazin-9(6H)-one



Example 37.1: A mixture of methyl 4-chloro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate (553 mg, 2.63 mmol, 1.0 eq.), propan-1-ol (28 µL, 3.68 mmol, 1.4 eq.), Cs_2CO_3 (1.20 g, 3.68 mmol, 1.4 eq.), tBuBrettPhos Pd G3 (90 mg, 0.11 mmol, 4 mol%), tBuBrettPhos (102 mg, 0.21 mmol, 8 mol%) and 4Å molecular sieves (1.0 g) in THF (6.56 mL, 0.4 M) was heated at 80 °C overnight in a sealed vial. Silica was added and the solvent was evaporated. Normal-phase column chromatography (0-80% EtOAc in cyclohexane) afforded pure methyl 4-propoxy-1H-pyrrolo[3,2-c]pyridine-2-carboxylate (442 mg, 72% yield) as a yellowish powder. HPLC/MS m/z: 235.1 $[M+H]^+$, Rt (Y): 1.188 min.

Example 37.2: Aqueous NaOH (3N, 11.8 mL) was added to a solution of methyl 4-propoxy-1H-pyrrolo[3,2-c]pyridine-2-carboxylate (554.00 mg, 2.37 mmol, 1.0 eq.) in EtOH (11.8 mL) and this was heated to 45 °C for 45 min before the solvent was evaporated and the crude solid triturated with Et_2O. The solid was filtered, washed with further Et_2O and dried under vacuum to afford a mixture of NaOH and sodium

4-propoxy-1H-pyrrolo[3,2-c]pyridine-2-carboxylate as a yellow solid which was engaged into the next step without further purification (crude mass 950 mg). HPLC/MS m/z: 221.1 $[M+H]^+$, Rt (Y): 0.815 min.

Example 37.3: A mixture of sodium 4-propoxy-1H-pyrrolo[3,2-c]pyridine-2-carboxylate (22 mg, 89 µmol, 1.0 eq) and HATU (41 mg, 107 µmol, 1.2 eq.) in DCM/DMF (2:1, 300 µL) was stirred for 15 min before a solution of tert-butyl N-{2-[(2-hydroxyethyl)amino]ethyl}carbamate (19 mg, 90 µmol, 1.05 eq.) in DCM (200 µL) was added. After 5 min, the reaction was quenched with sat. aq. $NaHCO_3$ and extracted with DCM, dried over $MgSO_4$, then evaporated under vacuum. The crude was precipitated with water and the aqueous phase was discarded. The product was used in the next step without purification (26.3 mg, 73% crude yield). Rf (EtOAc:DCM, 9:1) = 0.34; HPLC/MS m/z: 407.2 $[M+H]^+$, Rt (Y): 1.154 min.

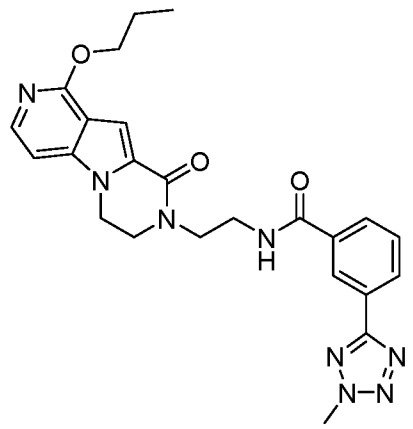
Example 37.4: A solution of tert-butyl N-[2-[2-hydroxyethyl-(4-propoxy-1H-pyrrolo[3,2-c]pyridine-2-carbonyl)amino]ethyl]carbamate (221.30 mg, 0.5444 mmol) and triphenylphosphine (428.39 mg, 1.6333 mmol) in THF (5.44 mL, 0.1000 M) was cooled to 0 °C. DIAD (321.58 µL, 1.6333 mmol) was added dropwise over 30 min and the resulting mixture was warmed to RT, stirred for 2 h. After the solvent was removed under reduced pressure, the residue was diluted with EtOAc and extracted with aq. HCl (1M)(x 4). The combined aqueous extracts were basified to pH 8-9 with 10% aq. Na_2CO_3, and the resulting mixture was extracted with EtOAc, then sequentially filtered over pads of $MgSO_4$ and silica to afford tert-butyl (2-(9-oxo-1-propoxy-6,7-dihydropyrido[3',4':4,5]pyrrolo[1,2-a]pyrazin-8(9H)-yl)ethyl)carbamate as a clear oil. HPLC/MS m/z: 398.2 $[M+H]^+$, Rt (Y): 1.319 min.

Example 37.5: Aqueous HCl (1M) (1.63 mL, 1.63 mmol, 3.0 eq.) was added to the crude solid and this was stirred for 10 min until all the material had dissolved, then evaporated to dryness. The solid was triturated with DCM and the solvent filtered off, washed with further DCM to afford pure 2-(10-oxo-6-propoxy-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2(7),3,5,8-tetraen-11-yl)ethylammonium chloride (90.4 mg, 51% yield over 2 steps) as a white solid. HPLC/MS m/z: 289.2 $[M+H]^+$, Rt (Y): 0.547 min.

Example 37.6: DIPEA (67.03 µL, 0.3848 mmol) was added to a mixture of 5-methyl-3-(2-oxidoisoquinolin-2-ium-7-yl)-1,2,4-oxadiazole (27.98 mg, 0.1231 mmol), 2-(10-oxo-6-propoxy-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2(7),3,5,8-tetraen-11-yl)ethylammonium chloride (25.00 mg, 0.0770 mmol) and PyBroP (43.06 mg, 0.0924 mmol) in DCM (0.51 mL, 0.1500 M) and this was heated via microwave irradiation

(60 °C; 1 h). The solvent was evaporated and the residue subjected to AccQ Prep reverse-phase HPLC (20-30% MeCN in H_2O), then normal-phase preparative TLC (5% MeOH in DCM) to afford 11-[2-[[7-(5-methyl-1,2,4-oxadiazol-3-yl)-1-isoquinolyl]amino]ethyl]-6-propoxy-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2(7),3,5,8-tetraen-10-one (6.6 mg, 17%, 0.0127 mmol). HPLC/MS m/z: 498.2 $[M+H]^+$, Rt (Y): 1.221 min; ^1H NMR (500 MHz, Methanol-d_4/Chloroform-d; 2:1): δ 8.73 (dt, *J* = 1.5, 0.8 Hz, 1H), 8.17 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.89 (d, *J* = 5.9 Hz, 1H), 7.78 (d, *J* = 6.1 Hz, 1H), 7.73 (d, *J* = 8.5 Hz, 1H), 7.31 (d, *J* = 1.1 Hz, 1H), 6.93 (ddd, *J* = 6.1, 2.2, 0.9 Hz, 2H), 4.34 (t, *J* = 6.6 Hz, 2H), 4.30-4.24 (m, 2H), 3.99 (dd, *J* = 6.6, 5.2 Hz, 2H), 3.96-3.91 (m, 2H), 3.88 (dd, *J* = 6.6, 5.2 Hz, 2H), 2.67 (s, 3H), 1.85 (dtd, *J* = 14.0, 7.4, 6.5 Hz, 2H), 1.05 (t, *J* = 7.4 Hz, 3H).

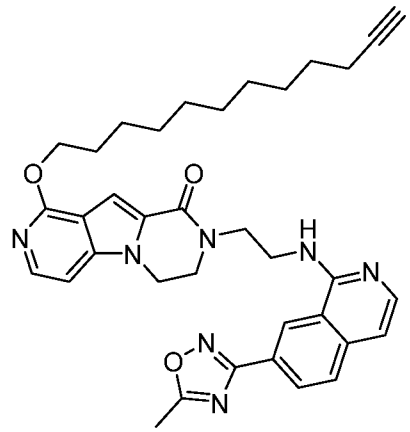
Example 38: 3-(2-Methyl-2H-tetrazol-5-yl)-N-(2-(9-oxo-1-propoxy-6,7-dihydropyrido[3',4':4,5]pyrrolo[1,2-a]pyrazin-8(9H)-yl)ethyl)benzamide



Obtained from 2-(10-oxo-6-propoxy-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2(7),3,5,8-tetraen-11-yl)ethylammonium chloride [Example 37.5] and 3-(2-methyl-2H-tetrazol-5-yl)-benzoic acid using the procedure from Example 54.3 at 60 °C to afford 3-(2-methyltetrazol-5-yl)-N-[2-(10-oxo-6-propoxy-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2,4,6,8-tetraen-11-yl)ethyl]benzamide (7.1 mg, 0.0149 mmol) as a white solid. HPLC/MS m/z: 475.221 $[M+H]^+$, Rt (Z): 2.18 min. ^1H NMR (600 MHz, DMSO-d_6): δ 8.86 (t, *J* = 5.8 Hz, 1H), 8.50 (t, *J* = 1.8 Hz, 1H), 8.18 (dt, *J* = 7.7, 1.4 Hz, 1H), 7.95 (dt, *J* = 7.9, 1.5 Hz, 1H), 7.84 (d, *J* = 6.0 Hz, 1H), 7.65 (t, *J* = 7.7 Hz, 1H), 7.15 (dd, *J* = 6.0, 0.9 Hz, 1H), 6.97 (d, *J* = 0.8 Hz, 1H), 4.43 (s,

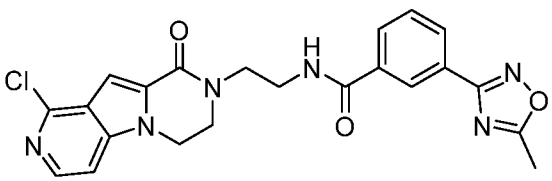
3H), 4.38-4.32 (m, 4H), 3.90-3.85 (m, 2H), 3.72 (t, *J* = 6.0 Hz, 2H), 3.60-3.54 (m, 2H), 1.81-1.72 (m, 2H), 0.98 (t, *J* = 7.4 Hz, 3H).

Example 39: 1-(Dodec-11-yn-1-yloxy)-8-(2-((7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl)amino)ethyl)-7,8-dihydropyrido[3',4':4,5]pyrrolo[1,2-a]pyrazin-9(6H)-one



Was synthesized in an analogous manner as Example 37 with dodec-11-yn-1-ol as the starting alcohol. Preparative TLC (5% MeOH in DCM) (46.8 mg, 31 % yield). Light orange powder. HPLC/MS m/z: 620.3 $[M+H]^+$, Rt (Y): 1.624 min; ^{1}H NMR (600 MHz, Methanol-d_4/Chloroform-d, 1:1): δ 8.71 (dt, *J* = 1.5, 0.8 Hz, 1H), 8.16 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.90 (d, *J* = 5.9 Hz, 1H), 7.78 (d, *J* = 6.1 Hz, 1H), 7.72 (d, *J* = 8.5 Hz, 1H), 7.35 (d, *J* = 0.9 Hz, 1H), 6.92 (dd, *J* = 6.0, 0.9 Hz, 1H), 6.90 (dd, *J* = 6.1, 0.9 Hz, 1H), 4.38 (t, *J* = 6.6 Hz, 2H), 4.30-4.24 (m, 2H), 4.00 (dd, *J* = 6.6, 5.3 Hz, 2H), 3.97-3.92 (m, 2H), 3.88 (dd, *J* = 6.6, 5.3 Hz, 2H), 2.68 (s, 3H), 2.14 (td, *J* = 7.1, 2.7 Hz, 2H), 2.03 (t, *J* = 2.6 Hz, 1H), 1.83 (quint, *J* = 6.8 Hz, 2H), 1.51-1.45 (m, 2 x 2 H), 1.37 (m, 2 x 2 H), 1.33-1.26 (m, 3 x 2 H).

Example 40: N-(2-(1-chloro-9-oxo-6,7-dihydropyrido[3',4':4,5]pyrrolo[1,2-a]pyrazin-8(9H)-yl)ethyl)-3-(5-methyl-1,2,4-oxadiazol-3-yl)benzamide



Example 40.1: Aqueous NaOH (3 N, 21 mL) was added to a solution of methyl 4-chloro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate (1.0 g, 4.75 mmol, 1.0 eq.) in EtOH (21 mL) and this was heated to 45 °C for 1 h before the solvent was evaporated and the crude solid triturated with Et_2O. The solid was filtered and washed with further Et_2O, then dried *in vacuo* to afford a mixture of NaOH and sodium 4-chloro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate as a yellow solid which was engaged into the next step without further purification (crude mass 1.2 g, quant.). HPLC/MS m/z: 197.0 $[M+H]^+$, Rt (Y): 0.947 min.

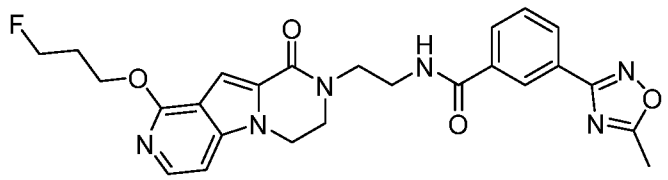
Example 40.2: DMF (9.72 mL) was added dropwise to a mixture of sodium 4-chloro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate (1.71 g, 7.8 mmol, 1.0 eq.) and HATU (3.99 g, 10.5 mmol, 1.34 eq.) in DCM (19.6 mL) and this was stirred for 30 min before a solution of tert-butyl N-{2-[(2-hydroxyethyl)amino]ethyl}carbamate (1.95 g, 9.53 mmol, 1.22 eq.) in DCM (19.6 mL) was added. This was stirred for 4 h before water was added and the solvents were evaporated to dryness. Reverse phase chromatography (0-100% MeOH in H_2O) to remove major impurities afforded crude product (crude mass 2.535 g) which was taken to the next step. HPLC/MS m/z: 383.1 $[M+H]^+$, Rt (R): 1.083 min.

Example 40.3: DIAD (3.91 mL, 19.868 mmol) was added over 40 min to a solution of tert-butyl N-[2-[(4-chloro-1H-pyrrolo[3,2-c]pyridine-2-carbonyl)-(2-hydroxyethyl)amino]ethyl]carbamate (2.54 g, 6.6226 mmol) and PPh_3 (5.21 g, 19.868 mmol) in THF (65.30 mL, 0.1000 M) at 0 °C. After 1 h, the resulting mixture was brought back to RT and stirred for an additional 3 h. After the solvent was removed under reduced pressure, the residue was diluted with EtOAc and 10% aq. Na_2CO_3, extracted with EtOAc and filtered over $MgSO_4$ to afford crude tert-butyl 2-(6-chloro-10-oxo-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2(7),3,5,8-tetraen-11-yl)ethylammonium chloride (1.2 g, 60%, 3.9682 mmol) as a yellow solid. HPLC/MS m/z: 365.1 $[M+H]^+$, Rt (Y): 1.307 min.

Example 40.4: The crude was diluted in DCM (30 mL), and TFA (30 mL) was added at 0 °C at which point the solution became red. This was stirred for 30 min at RT before the solvent was evaporated and taken back in aq. HCl (3 N). After concentration, the residue was washed several times with DCM, then reverse phase chromatography (5-25% MeOH in H_2O) afforded 2-(6-chloro-10-oxo-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2(7),3,5,8-tetraen-11-yl)ethylammonium chloride (1.2 g, 60%, 3.9682 mmol). HPLC/MS m/z: no ionisation, Rt (Y): 0.522 min.

Example 40.5: DIPEA (0.35 mL, 1.9922 mmol) was added to a mixture of 3-(5-methyl-1,2,4-oxadiazol-3-yl)benzoic acid (116.95 mg, 0.5728 mmol), HATU (378.75 mg, 0.9961 mmol) and 2-(6-chloro-10-oxo-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2,4,6,8-tetraen-11-yl)ethylammonium chloride (150.00 mg, 0.4981 mmol) in DCM (3.32 mL, 0.1500 M). This was stirred for 2 h before sat. aq. $NaHCO_3$ was added. This was extracted with DCM, filtered over $MgSO_4$ and evaporated. Slow silica gel chromatography with DCM and MeOH as eluents (100:0 to 96:4) afforded N-[2-(6-chloro-10-oxo-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2,4,6,8-tetraen-11-yl)ethyl]-3-(5-methyl-1,2,4-oxadiazol-3-yl)benzamide (119.5 mg, 53%, 0.2650 mmol). HPLC/MS m/z: 473.1 $[M+Na]^+$, Rt (Y): 1.305 min; ^1H NMR (600 MHz, Methanol-d_4): δ 8.39 (t, *J* = 1.8 Hz, 1H), 8.11 (dt, *J* = 7.8, 1.4 Hz, 1H), 8.02 (d, *J* = 6.0 Hz, 1H), 7.90 (dt, *J* = 7.8, 1.4 Hz, 1H), 7.55 (t, *J* = 7.8 Hz, 1H), 7.43 (dd, *J* = 5.9, 0.9 Hz, 1H), 7.15 (d, *J* = 0.9 Hz, 1H), 4.41 (dd, *J* = 6.9, 4.9 Hz, 2H), 4.03-3.98 (m, 2H), 3.88 (dd, *J* = 6.7, 5.0 Hz, 2H), 3.75 (dd, *J* = 6.7, 5.0 Hz, 2H), 2.61 (s, 3H).

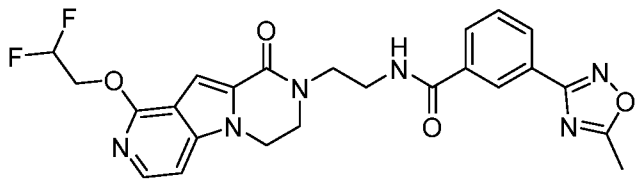
Example 41: N-(2-(1-(3-fluoropropoxy)-9-oxo-6,7-dihydropyrido[3',4':4,5]pyrrolo[1,2-a]pyrazin-8(9H)-yl)ethyl)-3-(5-methyl-1,2,4-oxadiazol-3-yl)benzamide



Obtained from 3-fluoropropan-1-ol and N-[2-(6-chloro-10-oxo-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2,4,6,8-tetraen-11-yl)ethyl]-3-(5-methyl-1,2,4-oxadiazol-3-yl)benzamide, using Example 37.1 conditions. Normal-phase silica gel chromatography with DCM and MeOH as eluents (slow gradient elution 100:0 to 96:4) afforded N-[2-[6-(3-fluoropropoxy)-10-oxo-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2,4,6,8-tetraen-11-yl]ethyl]-3-(5-methyl-1,2,4-oxadiazol-3-yl)benzamide (5.42 mg, 12%, 0.0110 mmol) as a white solid. HPLC/MS m/z: 493.2 $[M+H]^+$, Rt (Y): 1.31 min; ^1H NMR (600 MHz, Methanol-d_4): δ 8.43 (t, *J* = 1.7 Hz, 1H), 8.14 (dt, *J* = 7.8, 1.4 Hz, 1H), 7.91 (dt, *J* = 7.9, 1.5 Hz, 1H), 7.81 (d, *J* = 6.1 Hz, 1H), 7.57 (t, *J* = 7.8 Hz, 1H), 7.17 (d, *J* = 0.8 Hz, 1H), 7.04 (dd, *J* = 6.1, 0.9 Hz, 1H), 4.67 (t, *J* = 5.9 Hz, 1H), 4.59 (t, *J* = 5.9 Hz, 1H), 4.51 (t, *J* = 6.3 Hz, 2H),

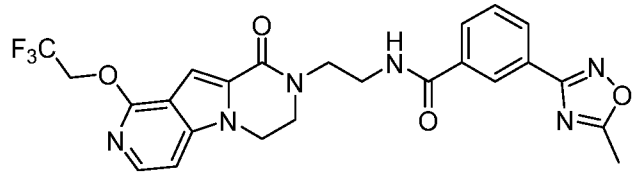
4.38-4.33 (m, 2H), 4.03-3.93 (m, 2H), 3.87 (dd, *J* = 6.7, 5.0 Hz, 2H), 3.73 (dd, *J* = 6.6, 5.1 Hz, 2H), 2.63 (s, 3H), 2.22 (quint, *J* = 6.1 Hz, 1H), 2.18 (quint, *J* = 6.1 Hz, 1H).

Example 42: N-(2-(1-(2,2-difluoroethoxy)-9-oxo-6,7-dihydropyrido[3',4':4,5]pyrrolo[1,2-a]pyrazin-8(9H)-yl)ethyl)-3-(5-methyl-1,2,4-oxadiazol-3-yl)benzamide



Obtained from 2,2-difluoroethanol and N-[2-(6-chloro-10-oxo-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2,4,6,8-tetraen-11-yl)ethyl]-3-(5-methyl-1,2,4-oxadiazol-3-yl)benzamide, using Example 37.1 conditions.
Preparative TLC with DCM and MeOH as eluents (94:6). (11.4 mg, 20% yield).
HPLC/MS m/z: 497.2 $[M+H]^+$, Rt (Z): 2.44 min; ^1H NMR (600 MHz, Methanol-d_4/Chloroform-d, 1:1): δ 8.43 (t, *J* = 1.7 Hz, 1H), 8.13 (dt, *J* = 7.8, 1.4 Hz, 1H), 7.90 (dt, *J* = 7.9, 1.4 Hz, 1H), 7.83 (d, *J* = 6.1 Hz, 1H), 7.55 (t, *J* = 7.8 Hz, 1H), 7.27 (d, *J* = 0.9 Hz, 1H), 7.00 (dd, *J* = 6.1, 0.9 Hz, 1H), 6.32-6.05 (m, 1H), 4.61 (td, *J* = 13.6, 4.2 Hz, 2H), 4.35-4.30 (m, 2H), 3.97-3.92 (m, 2H), 3.85 (dd, *J* = 6.7, 5.4 Hz, 2H), 3.72 (dd, *J* = 6.7, 5.4 Hz, 2H), 2.65 (s, 3H).

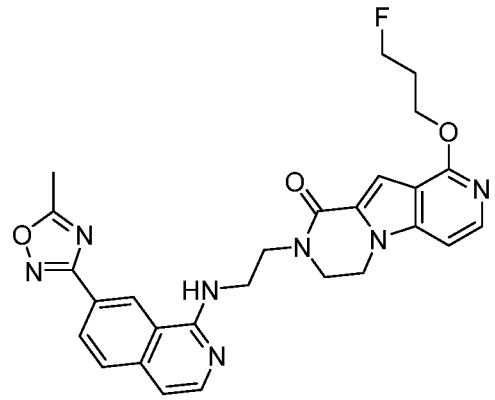
Example 43: 3-(5-Methyl-1,2,4-oxadiazol-3-yl)-N-(2-(9-oxo-1-(2,2,2-trifluoroethoxy)-6,7-dihydropyrido[3',4':4,5]pyrrolo[1,2-a]pyrazin-8(9H)-yl)ethyl)benzamide



A mixture of Cs_2CO_3 (98.3 mg, 0.3 mmol, 2.7 eq.), N-[2-(6-chloro-10-oxo-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2,4,6,8-tetraen-11-yl)ethyl]-3-(5-methyl-1,2,4-

oxadiazol-3-yl)benzamide (51 mg, 0.11 mmol, 1.0 eq.), BrettPhos (10 mg, 18.6 µmol, 16 mol%), crotyl(2-dicyclohexylphosphino-2′,4′,6′-triisopropyl-3,6-dimethoxy-1,1′-biphenyl)palladium(II) triflate (10 mg, 11.8 µmol, 10 mol%), molecular sieves 4Å (130.00 mg) and 2,2,2 trifluoroethanol (16.4 µL, 0.23 mmol, 2.0 eq.) in THF (283 µL, 0.4 M) was heated to 0 °C overnight. Water was added and the mixture was filtered over cotton and evaporated. Normal-phase silica gel chromatography with DCM and MeOH as eluents (slow gradient elution 100:0 to 98:2) afforded 3-(5-methyl-1,2,4-oxadiazol-3-yl)-N-[2-[10-oxo-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2,4,6,8-tetraen-11-yl]ethyl]benzamide (7.99 mg, 14%, yield) as a white solid. HPLC/MS m/z: 515.2 $[M+H]^+$, Rt (Z): 2.60 min; ^{1}H NMR (600 MHz, Methanol-d_4): δ 8.45 (t, *J* = 1.8 Hz, 1H), 8.16 (dt, *J* = 7.8, 1.4 Hz, 1H), 7.94-7.89 (m, 1H), 7.87 (d, *J* = 6.1 Hz, 1H), 7.59 (t, *J* = 7.8 Hz, 1H), 7.21 (d, *J* = 0.8 Hz, 1H), 7.15 (dd, *J* = 6.0, 0.9 Hz, 1H), 4.98 (q, *J* = 8.8 Hz, 2H), 4.40 (t, *J* = 5.9 Hz, 2H), 4.02-3.95 (m, 2H), 3.89 (dd, *J* = 6.6, 5.1 Hz, 2H), 3.74 (dd, *J* = 6.6, 5.1 Hz, 2H), 2.64 (s, 3H).

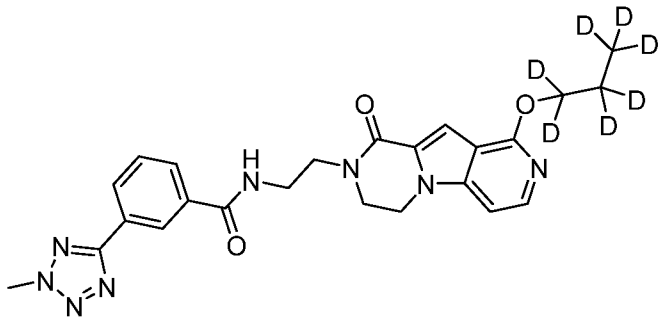
Example 44: 1-(3-Fluoropropoxy)-8-(2-((7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl)amino)ethyl)-7,8-dihydropyrido[3',4':4,5]pyrrolo[1,2-a]pyrazin-9(6H)-one



Obtained from 1-chloro-8-(2-((7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl)amino)ethyl)-7,8-dihydropyrido[3',4':4,5]pyrrolo[1,2-a]pyrazin-9(6H)-one and 3-fluoropropan-1-ol, using Example 37.1 conditions.
Preparative TLC (5% MeOH in DCM) (4.6 mg, 9% yield). HPLC/MS m/z: 516.2 $[M+H]^+$, Rt (Y): 1.18 min; ^{1}H NMR (600 MHz, Methanol-d_4): δ 8.75-8.67 (m, 1H), 8.11 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.89 (d, *J* = 5.8 Hz, 1H), 7.75 (d, *J* = 6.1 Hz, 1H), 7.70

(d, *J* = 8.5 Hz, 1H), 7.14 (d, *J* = 0.9 Hz, 1H), 6.97 (dd, *J* = 6.2, 0.9 Hz, 1H), 6.91 (dd, *J* = 6.0, 0.9 Hz, 1H), 4.67 (t, *J* = 5.9 Hz, 1H), 4.59 (t, *J* = 5.8 Hz, 1H), 4.49 (t, *J* = 6.3 Hz, 2H), 4.29-4.25 (m, 2H), 3.96 (dd, *J* = 6.6, 4.9 Hz, 2H), 3.95-3.92 (m, 2H), 3.89 (dd, *J* = 6.6, 5.0 Hz, 2H), 2.59 (s, 3H), 2.25-2.15 (m, 2H).

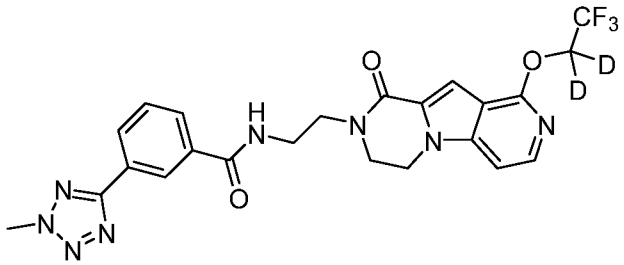
Example 45: 3-(2-Methyl-2H-tetrazol-5-yl)-N-(2-(9-oxo-1-(propoxy-d7)-6,7-dihydropyrido[3',4':4,5]pyrrolo[1,2-a]pyrazin-8(9H)-yl)ethyl)benzamide



Example 45.1: N-(2-(1-chloro-9-oxo-6,7-dihydropyrido[3',4':4,5]pyrrolo[1,2-a]pyrazin-8(9H)-yl)ethyl)-3-(2-methyl-2H-tetrazol-5-yl)benzamide was obtained from 2-(6-chloro-10-oxo-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2,4,6,8-tetraen-11-yl)ethylammonium chloride and 3-(2-Methyl-2H-tetrazol-5-yl)-benzoic acid, using Example 40.5 conditions. Purification by column chromatography (Eluent: 0-4% MeOH in DCM) afforded N-(2-(1-chloro-9-oxo-6,7-dihydropyrido[3',4':4,5]pyrrolo[1,2-a]pyrazin-8(9H)-yl)ethyl)-3-(2-methyl-2H-tetrazol-5-yl)benzamide (288.9 mg, 87% yield). HPLC/MS m/z: 451.1 $[M+H]^+$, Rt (R): 1.097 min.

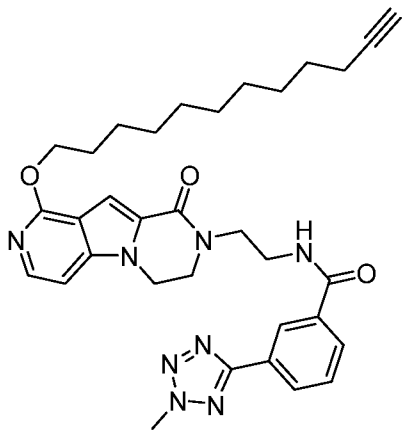
Example 45.2 1-Propanol-1,1,2,2,3,3,3-d_7 and N-[2-(6-chloro-10-oxo-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2,4,6,8-tetraen-11-yl)ethyl]-3-(2-methyltetrazol-5-yl)benzamide, using Example 37.1 conditions. Purified by preparative TLC (6% MeOH in DCM) to afford 3-(2-methyl-2H-tetrazol-5-yl)-N-(2-(9-oxo-1-(propoxy-d7)-6,7-dihydropyrido[3',4':4,5]pyrrolo[1,2-a]pyrazin-8(9H)-yl)ethyl)benzamide as a white powder (5.0 mg, 9% yield). HPLC/MS m/z: 482.3 $[M+H]^+$, Rt (R): 1.09 min; ^{1}H NMR (600 MHz, Methanol-d_4/Chloroform-d, 1:1): δ 8.51 (d, *J* = 1.8 Hz, 1H), 8.23 (dt, *J* = 7.8, 1.4 Hz, 1H), 7.89 (dt, *J* = 7.9, 1.5 Hz, 1H), 7.82 (d, *J* = 6.1 Hz, 1H), 7.58 (t, *J* = 7.8 Hz, 1H), 7.31-7.28 (m, 1H), 6.98-6.93 (m, 1H), 4.43 (s, 3H), 4.34 (dd, *J* = 6.9, 4.8 Hz, 2H), 4.00-3.95 (m, 2H), 3.88 (t, *J* = 6.0 Hz, 2H), 3.74 (t, *J* = 6.0 Hz, 2H).

Example 46: 3-(2-Methyl-2H-tetrazol-5-yl)-N-(2-(9-oxo-1-(2,2,2-trifluoroethoxy-1,1-d2)-6,7-dihydropyrido[3',4':4,5]pyrrolo[1,2-a]pyrazin-8(9H)-yl)ethyl)benzamide



Obtained from 2,2,2-trifluoroethanol-1,1-d2 (45.00 µL, 0.6085 mmol) and N-[2-(6-chloro-10-oxo-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2,4,6,8-tetraen-11-yl)ethyl]-3-(2-methyltetrazol-5-yl)benzamide, using Example 37.1 conditions.
Silica gel chromatography (0-2% MeOH in DCM) (15.99 mg, 31% yield). White powder. HPLC/MS m/z: 517.2 $[M+H]^+$, Rt (R): 1.270 min; ^{1}H NMR (600 MHz, Methanol-d_4/Chloroform-d, 1:1): δ 8.50 (s, 1H), 8.23 (d, *J* = 7.7 Hz, 1H), 7.89 (d, *J* = 7.8 Hz, 1H), 7.86 (d, *J* = 6.0 Hz, 1H), 7.57 (d, *J* = 15.8 Hz, 1H), 7.31 (d, *J* = 2.0 Hz, 1H), 7.05 (d, *J* = 6.0 Hz, 1H), 4.42 (d, *J* = 2.0 Hz, 3H), 4.36 (t, *J* = 5.9 Hz, 2H), 3.98 (t, *J* = 5.9 Hz, 2H), 3.89 (t, *J* = 6.1 Hz, 2H), 3.75 (t, *J* = 6.1 Hz, 2H).

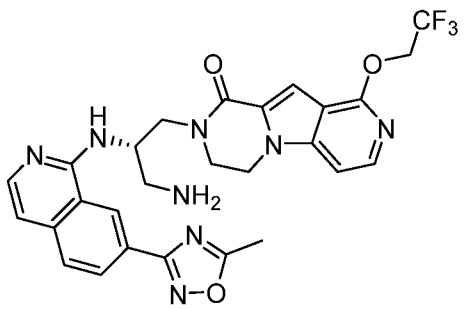
Example 47: N-(2-(1-(dodec-11-yn-1-yloxy)-9-oxo-6,7-dihydropyrido[3',4':4,5]pyrrolo[1,2-a]pyrazin-8(9H)-yl)ethyl)-3-(2-methyl-2H-tetrazol-5-yl)benzamide



Obtained from 3-(2-methyl-2H-tetrazol-5-yl)-benzoic acid and 11-(2-aminoethyl)-6-dodec-11-ynoxy-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2,4,6,8-tetraen-10-one, using Example 40.5 conditions.

Silica gel chromatography (0-3.25% MeOH in DCM), followed by preparative TLC (10% MeOH in DCM), then trituration with EtOAc. (72.1 mg, 50% yield). White solid. HPLC/MS m/z: 597.3 $[M+H]^+$, Rt (R): 1.56 min; ^1H NMR (600 MHz, Methanol-d_4/Chloroform-d, 1:1): δ 8.51 (t, *J* = 1.7 Hz, 1H), 8.22 (dt, *J* = 7.8, 1.4 Hz, 1H), 7.89 (dt, *J* = 7.9, 1.4 Hz, 1H), 7.81 (d, *J* = 6.1 Hz, 1H), 7.60-7.54 (m, 1H), 7.28 (d, *J* = 0.9 Hz, 1H), 6.94 (dd, *J* = 6.2, 0.9 Hz, 1H), 4.42 (s, 3H), 4.38 (t, *J* = 6.6 Hz, 2H), 4.35-4.31 (m, 2H), 4.00-3.94 (m, 2H), 3.88 (dd, *J* = 6.7, 5.4 Hz, 2H), 3.74 (dd, *J* = 6.7, 5.3 Hz, 2H), 2.14 (td, *J* = 7.1, 2.7 Hz, 2H), 2.03 (t, *J* = 2.7 Hz, 1H), 1.82 (quint, *J* = 6.8 Hz, 2H), 1.52-1.44 (m, 2 x 2 H), 1.40-1.34 (m, 2 x 2 H), 1.33-1.26 (m, *J* = 5.5, 4.7 Hz, 3 x 2 H).

Example 48: (S)-8-(3-Amino-2-((7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl)amino)propyl)-1-(2,2,2-trifluoroethoxy)-7,8-dihydropyrido[3',4':4,5]pyrrolo[1,2-a]pyrazin-9(6H)-one



Example 48.1: DIPEA (1029.54 µL, 5.9109 mmol) was added to a mixture of Boc-N3-Cbz-L-2,3-diaminopropionic acid (1.00 g, 2.9554 mmol) and HATU (1573.24 mg, 4.1376 mmol) in DCM (14.78 mL). This was heated to 70 °C for 15 min or until the mixture became a clear yellow solution. A solution of ethanolamine (231.89 µL, 3.8421 mmol) in DCM (14.78 mL) was added dropwise at RT, at which point a precipitate formed, and this was stirred at this temperature for 2 h. The mixture was washed with H_2O, aq. HCl (1N), extracted with DCM. The solvent was dried over $MgSO_4$ and evaporated. Normal-phase column chromatography (0-5% MeOH in DCM) afforded tert-butyl N-[(1S)-1-(benzyloxycarbonylaminomethyl)-2-(2-

hydroxyethylamino)-2-oxo-ethyl]carbamate (1.0 g, 89% yield). HPLC/MS m/z: 382.2 $[M+H]^+$, Rt (R): 1.127 min.

Example 48.2: $BF_3.OEt_2$ (7.4 µL, 60.3 µmol, 1.0 eq.) was added dropwise to a solution of tert-butyl N-[(1S)-1-(benzyloxycarbonylaminomethyl)-2-(2-hydroxyethylamino)-2-oxo-ethyl]carbamate (23 mg, 60.3 µmol) in THF (600 µL) at 0 °C, followed immediately with BH_3·THF (1M in THF) (362 µL, 0.36 mmol, 6.0 eq.) dropwise. The ice bath was removed, and the solution was stirred at RT for 2 h. The solution was quenched with addition of MeOH and the solvents were evaporated. Normal-phase column chromatography (0-20% MeOH in DCM) afforded tert-butyl N-[(1R)-1-(benzyloxycarbonylaminomethyl)-2-(2-hydroxyethylamino)ethyl]carbamate (16.7 mg, 75% yield). HPLC/MS m/z: 368.2 $[M+H]^+$, Rt (R): 0.93 min.

Example 48.3: A 15 min pre-stirred yellow solution of sodium 4-(2,2,2-trifluoroethoxy)-1H-pyrrolo[3,2-c]pyridine-2-carboxylate (208.00 mg, 0.7372 mmol) and HATU (392.43 mg, 1.0321 mmol) in DMF (3.69 mL) was added dropwise to a solution of tert-butyl N-[(1R)-1-(benzyloxycarbonylaminomethyl)-2-(2-hydroxyethylamino)ethyl]carbamate (325.05 mg, 0.8846 mmol) and DIPEA (256.81 µL, 1.4744 mmol) in DMF (3.69 mL). After 15 min, water was added, and the solvent evaporated. The residue was washed with water, extracted with DCM. The organic phase was dried over $MgSO_4$ and evaporated. Normal-phase chromatography (20-90% EtOAc in DCM) afforded tert-butyl N-[(1S)-1-(benzyloxycarbonylaminomethyl)-2-[2-hydroxyethyl-[4-(2,2,2-trifluoroethoxy)-1H-pyrrolo[3,2-c]pyridine-2-carbonyl]amino]ethyl]carbamate (334 mg, 74% yield) as a pale oil. HPLC/MS m/z: 610.2 $[M+H]^+$, Rt (Y): 1.59 min.

Example 48.4: DIAD (298.74 µL, 1.5172 mmol) was added dropwise to a solution of tert-butyl N-[(1S)-1-(benzyloxycarbonylaminomethyl)-2-[2-hydroxyethyl-[4-(2,2,2-trifluoroethoxy)-1H-pyrrolo[3,2-c]pyridine-2-carbonyl]amino]ethyl]carbamate (308.30 mg, 0.5057 mmol) and PPh_3 (397.96 mg, 1.5172 mmol) in THF (5.06 mL, 0.1000 M) at 0 °C. After 1 h, the ice bath was removed and stirred overnight. The reaction was quenched with water, the mixture was extracted with DCM and the organic phase was dried over $MgSO_4$, evaporated *in vacuo*. Normal-phase chromatography (0-100% EtOAc in DCM) afforded a mixture of $Ph_3P=O$ and tert-butyl N-[(1S)-1-(benzyloxycarbonylaminomethyl)-2-[10-oxo-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2,4,6,8-tetraen-11-yl]ethyl]carbamate. Engaged in the next step without further purification. HPLC/MS m/z: 592.2 $[M+H]^+$, Rt (Y): 1.608 min.

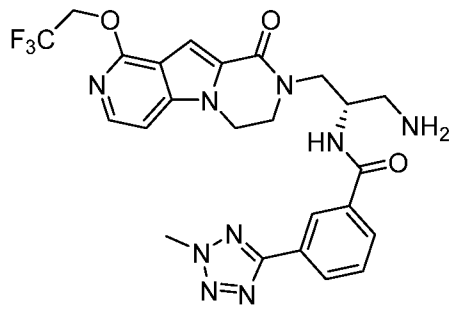
Example 48.5: tert-Butyl N-[(1S)-1-(benzyloxycarbonylaminomethyl)-2-[10-oxo-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2,4,6,8-tetraen-11-yl]ethyl]carbamate (300.00 mg, 0.5071 mmol) was stirred in DCM/TFA (1:1) (20.00 mL) for 30 min then evaporated. Elution through a SCX-2 column with MeOH to remove impurities, then NH_4 in MeOH (2M) afforded benzyl N-[(2S)-2-amino-3-[10-oxo-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2,4,6,8-tetraen-11-yl]propyl]carbamate (229.1 mg, 92% yield over 2 steps). HPLC/MS m/z: 492.2 $[M+H]^+$, Rt (Y): 1.253 min.

Example 48.6: DIPEA (304.48 µL, 1.7481 mmol) was added dropwise to a suspension of benzyl N-[(2S)-2-amino-3-[10-oxo-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2,4,6,8-tetraen-11-yl]propyl]carbamate (229.10 mg, 0.4662 mmol), 5-methyl-3-(2-oxidoisoquinolin-2-ium-7-yl)-1,2,4-oxadiazole (127.11 mg, 0.5594 mmol) and PyBrop (260.78 mg, 0.5594 mmol) in DCM (4.66 mL, 0.1000 M). The tube was sealed, and this was heated to 60 °C for 1 h. Water was added, and this was extracted with DCM. The organic layer was dried over $MgSO_4$ and evaporated *in vacuo*. Normal-phase chromatography (1-1.5% MeOH in DCM) (140.2 mg, 43% yield). Orange oil. HPLC/MS m/z: 701.2509 $[M+H]^+$, Rt (R): 1.32 min.

Example 48.7: To a solution of Pd(OAc)2 (5.6 mg, 24.9 µL mmol, 23 mol%) in DCM (543 µL) were added successively Et_3N (13 µL, 95.3 µmol, 0.9 eq.) and Et_3SiH (38 µL, 0.24 mmol, 2.2 eq.) at RT. The dark mixture was stirred 5 min before a solution of benzyl N-[(2S)-2-[[7-(5-methyl-1,2,4-oxadiazol-3-yl)-1-isoquinolyl]amino]-3-[10-oxo-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2,4,6,8-tetraen-11-yl]propyl]carbamate (76 mg, 0.11 mmol, 1.0 eq.) in DCM (543 µL) was added. The vial was sealed and stirred for 18 h. The black precipitate was washed with an aq. sat. $NaHCO_3$ solution, extracted with DCM (3 x 2 mL), passed through a SCX-2 column, eluting with MeOH, then NH_3 (2M in MeOH) to obtain the crude amine. Normal phase silica gel chromatography (0-20% NH_3 (2M in MeOH) in DCM) afforded 11-[(2S)-3-amino-2-[[7-(5-methyl-1,2,4-oxadiazol-3-yl)-1-isoquinolyl]amino]propyl]-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2,4,6,8-tetraen-10-one (13.84 mg, 22% yield). HPLC/MS m/z: 567.2 $[M+H]^+$, Rt (R): 1.153 min; ^1H NMR (600 MHz, Methanol-d_4/Chloroform-d, 1:1): δ 8.87-8.77 (m, 1H), 8.19 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.89 (d, *J* = 5.8 Hz, 1H), 7.84 (d, *J* = 6.0 Hz, 1H), 7.73 (d, *J* = 8.5 Hz, 1H), 7.31 (d, *J* = 0.9 Hz, 1H), 7.02 (dd, *J* = 6.0, 0.9 Hz, 1H), 6.93 (dd, *J* = 5.9, 0.9 Hz, 1H), 4.88 (qt, *J* = 8.8, 4.4 Hz, 2H), 4.72-4.67 (m, 1H), 4.30-4.24 (m, 2H), 3.99 (dq, *J* = 7.6, 5.0 Hz,

1H+2H), 3.92 (dd, *J* = 14.0, 6.2 Hz, 1H), 3.04 (dd, *J* = 13.4, 5.9 Hz, 1H), 2.99 (dd, *J* = 13.4, 5.1 Hz, 1H), 2.73 (s, 3H).

Example 49: (S)-N-(1-amino-3-(9-oxo-1-(2,2,2-trifluoroethoxy)-6,7-dihydropyrido[3',4':4,5]pyrrolo[1,2-a]pyrazin-8(9H)-yl)propan-2-yl)-3-(2-methyl-2H-tetrazol-5-yl)benzamide

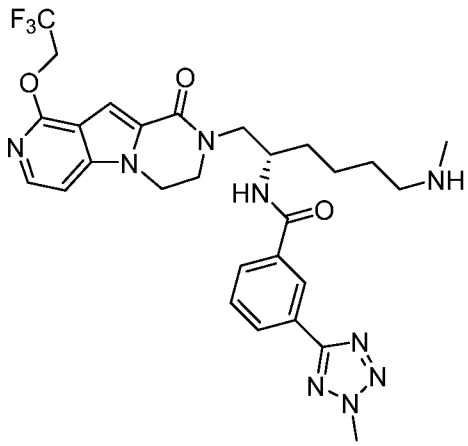


Example 49.1: DIPEA (142 µL, 0.8 mmol, 4.0 eq.) was added to a mixture of 3-(2-Methyl-2H-tetrazol-5-yl)-benzoic acid (48 mg, 0.23 mmol, 1.15 eq.) and HATU (154.7 mg, 0.41 mmol, 2.0 eq.) in DCM (1.0 mL) and this was stirred at 40 ºC for 30 min before a solution of benzyl N-[(2S)-2-amino-3-[10-oxo-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2(7),3,5,8-tetraen-11-yl]propyl]carbamate (100 mg, 0.2 mmol, 1.0 eq.) in DCM (1.0 mL) was added at RT. The mixture was stirred for 4 h then washed with water, extracted with DCM, filtered over $MgSO_4$ and evaporated. Silica gel chromatography (70-100% EtOAc in cyclohexane) afforded benzyl N-[(2S)-2-[[3-(2-methyltetrazol-5-yl)benzoyl]amino]-3-[10-oxo-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2(7),3,5,8-tetraen-11-yl]propyl]carbamate (96.9 mg, 70% yield). HPLC/MS m/z: 678.2 $[M+H]^+$, Rt (Y): 1.57 min.

Example 49.2: Et_3SiH (50 µL, 0.3 mmol, 5.7 eq.) was added to a mixture of benzyl N-[(2S)-2-[[3-(2-methyltetrazol-5-yl)benzoyl]amino]-3-[10-oxo-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2(7),3,5,8-tetraen-11-yl]propyl]carbamate (37 mg, 55.2 µmol, 1.0 eq.) and Pd/C (35 mg, 100% wt/wt) in EtOH (552 µL, 0.1 M) at RT. The mixture was passed through a SCX-2 column, eluting successively with MeOH and DCM, then 10% NH_3 (2N in MeOH) in DCM to collect the expected free amine. Further purification was performed with preparative TLC (10% NH_3 (2M in MeOH) in DCM). HPLC/MS m/z: 544.2 $[M+H]^+$, Rt (Y): 1.21 min; ^1H NMR (600 MHz, Methanol-d_4/Chloroform-d, 1:1): δ 8.53 (t, *J* = 1.8 Hz, 1H),

8.24 (dt, *J* = 7.8, 1.4 Hz, 1H), 7.92 (ddd, *J* = 7.8, 1.9, 1.2 Hz, 1H), 7.86 (d, *J* = 6.1 Hz, 1H), 7.58 (t, *J* = 7.8 Hz, 1H), 7.32 (d, *J* = 0.9 Hz, 1H), 7.06 (dd, *J* = 6.1, 0.9 Hz, 1H), 4.93-4.84 (m, 2H), 4.58-4.53 (m, 1H), 4.44 (s, 3H), 4.39-4.32 (m, 2H), 4.06-3.99 (m, 1H+1H), 3.96 (ddd, *J* = 12.9, 6.7, 4.7 Hz, 1H), 3.71 (dd, *J* = 14.1, 5.5 Hz, 1H), 3.04 (d, *J* = 1.5 Hz, 1H), 3.03 (d, *J* = 3.3 Hz, 1H).

Example 50*:* (S)-3-(2-Methyl-2H-tetrazol-5-yl)-N-(6-(methylamino)-1-(9-oxo-1-(2,2,2-trifluoroethoxy)-6,7-dihydropyrido[3',4':4,5]pyrrolo[1,2-a]pyrazin-8(9H)-yl)hexan-2-yl)benzamide



Example 50.1: DIPEA (721.88 µL, 4.1445 mmol) was added to a mixture of Fmoc-Lys(Me,Boc)-OH (1.00 g, 2.0722 mmol) and HATU (1.03 g, 2.7037 mmol) in DCM (10.36 mL, 0.1000 M). This was heated to 50 °C for 15 min until the mixture became a clear yellow solution. A solution of ethanolamine (162.64 uL, 2.6939 mmol) in DCM (10.36 mL) was added dropwise at RT, at which point a precipitate formed, and this was stirred at this temperature for 2 h. The mixture was washed with aq. HCl (1M) and the solvent evaporated. Normal-phase chromatography (0-7% MeOH in DCM) afforded tert-butyl N-[(5S)-5-(9H-fluoren-9-ylmethoxycarbonylamino)-6-(2-hydroxyethylamino)-6-oxo-hexyl]-N-methyl-carbamate (5.45 g, quant.) as a white solid. HPLC/MS m/z: 526.3 $[M+H]^+$, Rt (R): 1.477 min.

Example 50.2: $BF_3{\cdot}OEt_2$ (1.28 mL, 10.361 mmol) was added dropwise to a solution of tert-butyl N-[(5S)-5-(9H-fluoren-9-ylmethoxycarbonylamino)-6-(2-hydroxyethylamino)-6-oxo-hexyl]-N-methyl-carbamate (5.45 g, 10.361 mmol) in THF (103.61 mL) at 0 °C, followed immediately with $BH_3{\cdot}THF$ (1M in THF) (62.16 mL, 62.164 mmol) dropwise. The ice bath was removed, and the solution was stirred at

RT overnight. The solution was quenched with addition of MeOH at 0 °C and the solvents were evaporated. Normal-phase chromatography (0-20% MeOH in DCM) afforded tert-butyl N-[(5S)-5-(9H-fluoren-9-ylmethoxycarbonylamino)-6-(2-hydroxyethylamino)hexyl]-N-methyl-carbamate (3.43 g, 65% yield). HPLC/MS m/z: 512.3 $[M+H]^+$, Rt (Y): 1.401 min.

Example 50.3: A 15 min pre-stirred yellow solution of sodium 4-(2,2,2-trifluoroethoxy)-1H-pyrrolo[3,2-c]pyridine-2-carboxylate (1.00 g, 3.5442 mmol) and HATU (4.04 g, 10.633 mmol) in DMF (17.72 mL) was added dropwise to a solution of tert-butyl N-[(5S)-5-(9H-fluoren-9-ylmethoxycarbonylamino)-6-(2-hydroxyethylamino)hexyl]-N-methyl-carbamate (1.81 g, 3.5442 mmol) and DIPEA (1.85 mL, 10.633 mmol) in DMF (17.72 mL). After 1 min, water was added, and the solvent evaporated. The residue was washed with water, extracted with DCM. The organic phase was dried over $MgSO_4$ and evaporated. Normal-phase chromatography (0-5% MeOH in DCM), then reverse phase chromatography (20-100% MeOH in H_2O) afforded tert-butyl N-[(5S)-5-(9H-fluoren-9-ylmethoxycarbonylamino)-6-[2-hydroxyethyl-[4-(2,2,2-trifluoroethoxy)-1H-pyrrolo[3,2-c]pyridine-2-carbonyl]amino]hexyl]-N-methyl-carbamate (1.37 g, 51% yield). R_f (DCM:EtOAc, 1:1) = 0.13; HPLC/MS m/z: 754.3 $[M+H]^+$, Rt (R): 1.59 min.

Example 50.4: A solution of PPh_3 (1.56 g, 6.0 mmol, 3.0 eq.) in THF (9.9 mL) was added to a solution of tert-butyl N-[(5S)-5-(9H-fluoren-9-ylmethoxycarbonylamino)-6-[2-hydroxyethyl-[4-(2,2,2-trifluoroethoxy)-1H-pyrrolo[3,2-c]pyridine-2-carbonyl]amino]hexyl]-N-methyl-carbamate (1.50 g, 2.0 mmol, 1.0 eq.) in THF (9.9 mL) at -40 °C to prevent Fmoc removal. DIAD (1.2 mL, 6.0 mmol, 3.0 eq.) was added dropwise immediately after, allowing the yellow colour to fade between each addition. After 30 seconds of vigorous stirring at -40 °C, the reaction was quenched with water. The mixture was extracted with DCM and the organic phase was dried over $MgSO_4$, evaporated *in vacuo*. Normal-phase chromatography (0-70% EtOAc in DCM) afforded a mixture of triphenylphosphine oxide and tert-butyl N-[(5S)-5-(9H-fluoren-9-ylmethoxycarbonylamino)-6-[10-oxo-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2,4,6,8-tetraen-11-yl]hexyl]-N-methyl-carbamate which was taken to the next step without further purification. HPLC/MS m/z: 736.3 $[M+H]^+$, Rt (Y): 1.862 min.

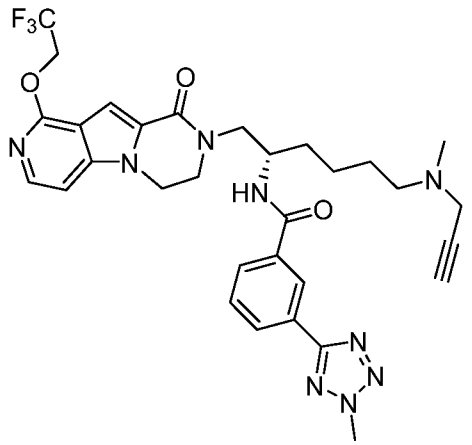
Example 50.5: Piperidine (392 µL, 3.97 mmol, 2.0 eq.) was added to a solution of tert-butyl N-[(5S)-5-(9H-fluoren-9-ylmethoxycarbonylamino)-6-[10-oxo-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2,4,6,8-tetraen-11-yl]hexyl]-N-

methyl-carbamate (1.46 g, 2.0 mmol, 1.0 eq.) in DMF (19.9 mL, 0.1 M). After 30 min, water was added, and the solvents were evaporated. Normal-phase chromatography (0-15% MeOH in DCM) afforded tert-butyl N-[(5S)-5-amino-6-[10-oxo-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2,4,6,8-tetraen-11-yl]hexyl]-N-methyl-carbamate (824 mg, 81% yield over 2 steps). HPLC/MS m/z: 514.3 $[M+H]^+$, Rt (R): 1.17.

Example 50.6: DIPEA (60.64 µL, 0.3482 mmol) was added to a mixture of 3-(2-Methyl-2H-tetrazol-5-yl)-benzoic acid (20.44 mg, 0.1001 mmol), HATU (66.19 mg, 0.1741 mmol) and tert-butyl N-[(5S)-5-amino-6-[10-oxo-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2(7),3,5,8-tetraen-11-yl]hexyl]-N-methyl-carbamate (44.70 mg, 0.0870 mmol) in DCM (870.41 uL, 0.1000 M). This was stirred for 2 h before the solution was washed with water once, then extracted with DCM, filtered over $MgSO_4$ and evaporated. Silica gel chromatography (70-100% EtOAc in cyclohexane) (51.4 mg, 84%, 0.0735 mmol). The product was taken to the next step without further purification. HPLC/MS m/z: 700.3 $[M+H]^+$, Rt (R): 1.47 min.

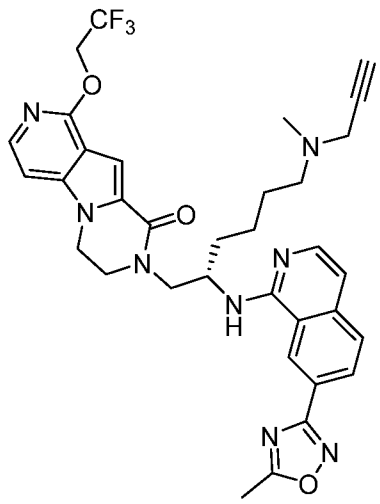
Example 50.7: tert-Butyl N-methyl-N-[(5S)-5-[[3-(2-methyltetrazol-5-yl)benzoyl]amino]-6-[10-oxo-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2(7),3,5,8-tetraen-11-yl]hexyl]carbamate (46.50 mg, 0.0665 mmol) was stirred in DCM/TFA (1:1) (664.55 µL) for 30 min. The solvents were evaporated, taken back in aq. HCl (3 N) and evaporated (x2). The solid was washed with DCM, taken back in MeOH and filtered through an SCX-2 column, eluting with MeOH. The free amine was recovered by washing the column with NH_3 in MeOH (2M). N-[(1S)-5-(methylamino)-1-[[10-oxo-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2(7),3,5,8-tetraen-11-yl]methyl]pentyl]-3-(2-methyltetrazol-5-yl)benzamide (40 mg, quant. over 2 steps). HPLC/MS m/z: 600.3 $[M+H]^+$, Rt (Y): 1.248 min; ^1H NMR (600 MHz, Methanol-d_4): δ 8.46 (dt, *J* = 1.8, 1.0 Hz, 1H), 8.20 (dt, *J* = 7.8, 1.5 Hz, 1H), 7.87 (ddd, *J* = 7.8, 1.9, 1.2 Hz, 1H), 7.84 (d, *J* = 6.1 Hz, 1H), 7.57 (t, *J* = 7.8 Hz, 1H), 7.17 (d, *J* = 0.9 Hz, 1H), 7.11 (dd, *J* = 6.1, 0.9 Hz, 1H), 5.03-4.89 (m, 2H), 4.58 (dtd, *J* = 11.1, 7.1, 4.2 Hz, 1H), 4.41 (s, 3H), 4.41-4.29 (m, 2H), 4.10-4.01 (m, 1H+1H), 3.94 (ddd, *J* = 12.9, 6.9, 4.5 Hz, 1H), 3.60 (dd, *J* = 13.9, 4.2 Hz, 1H), 2.93 (ddd, *J* = 8.6, 6.5, 3.5 Hz, 2H), 2.64 (s, 3H), 1.79 (quint, J = 7.6 Hz, 2H), 1.84-1.75 (m, 1H), 1.75-1.67 (m, 1H), 1.67-1.49 (m, 2H).

Example 51*:* (S)-N-(6-(methyl(prop-2-yn-1-yl)amino)-1-(9-oxo-1-(2,2,2-trifluoroethoxy)-6,7-dihydropyrido[3',4':4,5]pyrrolo[1,2-a]pyrazin-8(9H)-yl)hexan-2-yl)-3-(2-methyl-2H-tetrazol-5-yl)benzamide



A solution of propargyl bromide (80 % in toluene) (26 µL, 0.27 mmol, 1.05 eq.) was added to a mixture of N-[(1S)-5-(methylamino)-1-[[10-oxo-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2,4,6,8-tetraen-11-yl]methyl]pentyl]-3-(2-methyltetrazol-5-yl)benzamide (154 mg, 0.26 mmol, 1.0 eq.) and Cs_2CO_3 (336.8 mg, 1.03 mmol, 4.0 eq.) in DMF (1.3 mL, 0.2 M) at 0 °C and this was stirred at RT for 18 h. Water was added and the solvents were evaporated. Silica gel chromatography (0-6% MeOH in DCM) afforded N-[(1S)-5-[methyl(prop-2-ynyl)amino]-1-[[10-oxo-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2,4,6,8-tetraen-11-yl]methyl]pentyl]-3-(2-methyltetrazol-5-yl)benzamide (100.4 mg, 61% yield) as a white powder. HPLC/MS m/z: 638.3 $[M+H]^+$, Rt (Y): 1.10 min; ^1H NMR (600 MHz, Methanol-d_4): δ 8.44 (t, *J* = 1.8 Hz, 1H), 8.20 (dq, *J* = 7.9, 1.5 Hz, 1H), 7.85 (m, 1H + 1H), 7.57 (td, *J* = 7.8, 1.3 Hz, 1H), 7.18 (t, *J* = 1.1 Hz, 1H), 7.12 (d, *J* = 6.1 Hz, 1H), 5.06-4.89 (m, 2H), 4.61-4.52 (m, 1H), 4.42 (d, *J* = 1.1 Hz, 3H), 4.40-4.31 (m, 2H), 4.12 (dd, *J* = 13.8, 10.1 Hz, 1H), 4.07 (ddd, *J* = 12.4, 7.4, 4.6 Hz, 1H), 3.93 (ddd, *J* = 13.0, 6.9, 4.5 Hz, 1H), 3.50 (dd, *J* = 13.9, 4.2 Hz, 1H), 3.35 (d, *J* = 2.5 Hz, 2H), 2.64 (t, *J* = 2.4 Hz, 1H), 2.50 (td, *J* = 6.4, 3.5 Hz, 2H), 2.32 (s, 3H), 1.75 (q, *J* = 7.4 Hz, 2H), 1.63 (tdd, *J* = 11.8, 6.5, 3.8 Hz, 1H), 1.59-1.45 (m, 2H + 1H).

Example 52*:* (S)-8-(6-(Methyl(prop-2-yn-1-yl)amino)-2-((7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl)amino)hexyl)-1-(2,2,2-trifluoroethoxy)-7,8-dihydropyrido[3',4':4,5]pyrrolo[1,2-a]pyrazin-9(6H)-one



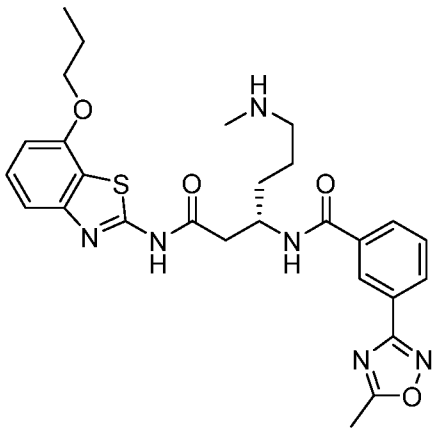
Example 52.1: DIPEA (0.13 mL, 0.7302 mmol) was added dropwise to a suspension of tert-butyl N-[(5S)-5-amino-6-[10-oxo-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2(7),3,5,8-tetraen-11-yl]hexyl]-N-methyl-carbamate (100.00 mg, 0.1947 mmol), 5-methyl-3-(2-oxidoisoquinolin-2-ium-7-yl)-1,2,4-oxadiazole (53.09 mg, 0.2337 mmol) and PyBrop (108.93 mg, 0.2337 mmol) in DCM (1.62 mL, 0.1200 M). The tube was sealed and this was heated to 60 °C for 1 h in the microwave. Water was added and this was extracted with DCM. The organic layer was dried over $MgSO_4$ and evaporated *in vacuo*. Normal-phase chromatography (50-100% EtOAc in cyclohexane) (140 mg, 99% yield). HPLC/MS m/z: 723.3 $[M+H]^+$, Rt (R): 1.36 min.

Example 52.2: tert-Butyl N-methyl-N-[(5S)-5-[[7-(5-methyl-1,2,4-oxadiazol-3-yl)-1-isoquinolyl]amino]-6-[10-oxo-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2(7),3,5,8-tetraen-11-yl]hexyl]carbamate (112.00 mg, 0.1550 mmol) was stirred in DCM/TFA (1:1) (1.55 mL) for 30 min. The solvents were evaporated, taken back in MeOH and filtered through an SCX-2 column, washing with MeOH. The free amine was recovered by washing the column with NH_3 in MeOH (2M). (76.9 mg, 80% yield). HPLC/MS m/z: 300.6 $[M+2H]^+$, Rt (Y): 1.248 min.

Example 52.3: A solution of propargyl bromide (80 % in toluene) (12 µL, 0.13 mmol, 1.05 eq.) was added to a mixture of 11-[(2S)-6-(methylamino)-2-[[7-(5-methyl-1,2,4-oxadiazol-3-yl)-1-isoquinolyl]amino]hexyl]-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2(7),3,5,8-tetraen-10-one (76.9 mg, 0.12 mmol, 1.0 eq.) and Cs_2CO_3 (162 mg, 0.49 mmol, 4.0 eq.) in DMF (0.62 mL, 0.2 M) at 0 °C and this was stirred at RT for 18 h. Water was added and the solvents were evaporated.

Preparative TLC (5% MeOH in DCM) afforded 11-[(2S)-2-[[7-(5-methyl-1,2,4-oxadiazol-3-yl)-1-isoquinolyl]amino]-6-[methyl(prop-2-ynyl)amino]hexyl]-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2(7),3,5,8-tetraen-10-one (38.8 mg, 48% yield) as a white powder. Rf (DCM:MeOH, 95:5) = 0.46; HPLC/MS m/z: 661.3 $[M+H]^+$, Rt (Z): 2.21 min (broad); ^1H NMR (500 MHz, Methanol-d_4): δ 8.83 (quint, *J* = 0.8 Hz, 1H), 8.10 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.81 (d, *J* = 5.9 Hz, 1H), 7.79 (d, *J* = 6.0 Hz, 1H), 7.66 (d, *J* = 8.5 Hz, 1H), 7.09 (d, *J* = 0.9 Hz, 1H), 7.01 (dd, *J* = 6.0, 0.9 Hz, 1H), 6.81 (dd, *J* = 5.9, 0.9 Hz, 1H), 5.00-4.86 (m, 2H+1H), 4.19 (ddd, *J* = 11.7, 6.9, 4.6 Hz, 1H), 4.13 (ddd, *J* = 12.3, 7.4, 4.5 Hz, 1H), 4.04-3.86 (m, 2H + 1H), 3.79 (dd, *J* = 13.8, 4.9 Hz, 1H), 3.28 (d, *J* = 2.5 Hz, 2H), 2.66 (s, 3H), 2.57 (t, *J* = 2.4 Hz, 1H), 2.46-2.41 (m, 2H), 2.25 (s, 3H), 1.91-1.76 (m, 2H), 1.64-1.47 (m, 2H + 2H).

Example 53: N-[(1S)-4-(methylamino)-1-[2-oxo-2-[(7-propoxy-1,3-benzothiazol-2-yl)amino]ethyl]butyl]-3-(5-methyl-1,2,4-oxadiazol-3-yl)benzamide



Example 53.1: To a solution of tert-butyl (3S)-3-amino-6-[tert-butoxycarbonyl(methyl)amino]hexanoate (500.00 mg, 1.5801 mmol) and 3-(5-Methyl-1,2,4-oxadiazol-3-yl)benzoic acid (354.88 mg, 1.7381 mmol) in dry DMF (7.70 mL) were added T3P in DMF (3.72 mL, 3.1602 mmol) and triethylamine (0.67 mL, 4.7402 mmol). The reaction mixture was stirred at room temperature for 2 h 15 min. The mixture was diluted with EtOAc (50 mL) and washed with water (75 mL). After phase separation, the organic layer was washed with aqueous saturated $NaHCO_3$ (50 mL) and aqueous saturated NH_4Cl (75 mL) before drying over Na_2SO_4 and concentration *in vacuo* to give tert-butyl (3S)-6-[tert-

butoxycarbonyl(methyl)amino]-3-[[3-(5-methyl-1,2,4-oxadiazol-3-yl)benzoyl]amino]hexanoate (710 mg, 89%) as a pale-yellow oil. HPLC/MS m/z: 503.3 $[M+H]^+$, Rt (R): 1.47 min.

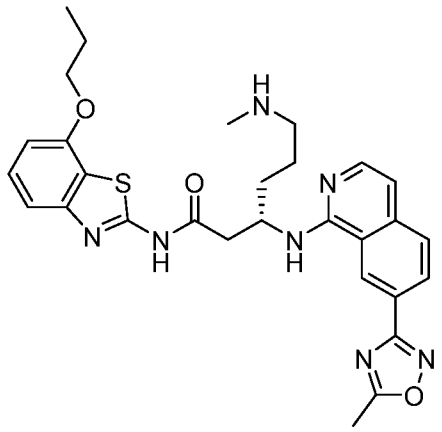
Example 53.2: To a solution of tert-butyl (3S)-6-[tert-butoxycarbonyl(methyl)amino]-3-[[3-(5-methyl-1,2,4-oxadiazol-3-yl)benzoyl]amino]hexanoate (710.00 mg, 1.4127 mmol) in THF (14.13 mL) were added potassium hydroxide (792.64 mg, 14.127 mmol) and water (0.5 mL, enough to dissolve the KOH) and 8 drops of MeOH. The mixture was stirred at 50 °C for 2 h. The mixture was allowed to cool and the volatiles were removed under reduced pressure. Water (20 mL) was added, and this was acidified to pH 3 with aqueous 2M HCl solution. This was extracted x 2 with EtOAc and the combined organics were dried over Na_2SO_4 before concentration under reduced pressure to give a pale-yellow foam/solid, 381 mg. Purification by reverse phase flash chromatography (Eluent: 0-80% MeOH/H_2O + 0.1% formic acid) afforded rac-(3S)-6-[tert-butoxycarbonyl(methyl)amino]-3-[[3-(5-methyl-1,2,4-oxadiazol-3-yl)benzoyl]amino]hexanoic acid as a clear oil, 196 mg (31%). HPLC/MS m/z: 347.1 $[M-BOC+H]^+$, Rt (R): 1.29 min.

Example 53.3: To a mixture of rac-(3S)-6-[tert-butoxycarbonyl(methyl)amino]-3-[[3-(5-methyl-1,2,4-oxadiazol-3-yl)benzoyl]amino]hexanoic acid (20.00 mg, 0.0448 mmol), 7-propoxy-1,3-benzothiazol-2-amine [Example 75.3] (12.13 mg, 0.0582 mmol), 1-hydroxybenzotriazole (12.10 mg, 0.0896 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (17.17 mg, 0.0896 mmol) under N_2 was added dry DMF (0.22 mL). This mixture was stirred at 60 °C for 23 h. The mixture was concentrated under reduced pressure. Purification by reverse phase flash chromatography (Eluent: 10-80% MeOH/H_2O + 0.1% formic acid) afforded tert-butyl N-methyl-N-[(4S)-4-[[3-(5-methyl-1,2,4-oxadiazol-3-yl)benzoyl]amino]-6-oxo-6-[(7-propoxy-1,3-benzothiazol-2-yl)amino]hexyl]carbamate as an off-white solid, 9 mg (32%). HPLC/MS m/z: 537.2 $[M-BOC+H]^+$, Rt (S): 2.54 min.

Example 53.4: To a flask charged with tert-butyl N-methyl-N-[(4S)-4-[[3-(5-methyl-1,2,4-oxadiazol-3-yl)benzoyl]amino]-6-oxo-6-[(7-propoxy-1,3-benzothiazol-2-yl)amino]hexyl]carbamate (9.00 mg, 0.0141 mmol) was added 4M HCl in dioxane (1.00 mL, 4 mmol). This solution was stirred at RT for 2 h. The mixture was concentrated under reduced pressure to give a pale-yellow solid. The crude was dissolved in MeOH and purified using a 1 g SCX-2 column, first flushing through with MeOH and then eluting with 2N NH_3 in MeOH solution. The basic eluents were

concentrated under reduced pressure to give N-[(1S)-4-(methylamino)-1-[2-oxo-2-[(7-propoxy-1,3-benzothiazol-2-yl)amino]ethyl]butyl]-3-(5-methyl-1,2,4-oxadiazol-3-yl)benzamide as a pale-orange solid, 5.4 mg (69%). HPLC/MS m/z: 537.3 $[M+H]^+$, Rt (Z): 2.45 min. ^{1}H NMR (600 MHz, Chloroform-d*):* δ 8.49 (t, *J* = 1.8 Hz, 1H), 8.16 (dt, *J* = 7.8, 1.4 Hz, 1H), 8.02 (dt, *J* = 7.9, 1.4 Hz, 1H), 7.54 (t, *J* = 7.8 Hz, 1H), 7.38 (dd, *J* = 8.1, 0.8 Hz, 1H), 7.31 (t, *J* = 8.0 Hz, 1H), 6.72 (dd, *J* = 8.0, 0.8 Hz, 1H), 4.43 (s, 1H), 4.08 (t, *J* = 6.4 Hz, 2H), 2.99 (dd, *J* = 14.7, 4.7 Hz, 1H), 2.80 (dd, *J* = 14.7, 6.2 Hz, 3H), 2.72-2.67 (m, 3H), 2.65 (s, 3H), 2.40 (s, 3H), 1.98-1.80 (m, 4H), 1.72 (qquint, *J* = 13.6, 6.5 Hz, 2H), 1.07 (t, *J* = 7.4 Hz, 3H).

Example 54: (3S)-6-(Methylamino)-3-[[7-(5-methyl-1,2,4-oxadiazol-3-yl)-1-isoquinolyl]amino]-N-(7-propoxy-1,3-benzothiazol-2-yl)hexanamide



Example 54.1: To a solution of tert-butyl 3-amino-6-[tert-butoxycarbonyl(methyl)amino]hexanoate (522.25 mg, 1.6504 mmol) in dry DCM (8.63 mL) were added 5-methyl-3-(2-oxidoisoquinolin-2-ium-7-yl)-1,2,4-oxadiazole (300 mg, 1.32 mmol), PyBroP (0.75 g, 1.6108 mmol) and DIPEA (0.86 mL, 4.9511 mmol). This mixture was stirred at room temperature under N_2 for 16 h. Additional PyBroP (300mg, 0.644 mmol) was added and this was stirred under N_2 for further 18 h. The mixture was concentrated under reduced pressure and purified by silica column chromatography (Eluent: 20-50%% EtOAc in cyclohexane) to afford tert-butyl (3S)-6-[tert-butoxycarbonyl(methyl)amino]-3-[[7-(5-methyl-1,2,4-oxadiazol-3-yl)-1-isoquinolyl]amino]hexanoate as a green gum, 522 mg (75%). HPLC m/z: 526.3 $[M+H]^+$, Rt (R): 1.24 min.

Example 54.2: To a solution of tert-butyl (3S)-6-[tert-butoxycarbonyl(methyl)amino]-3-[[7-(5-methyl-1,2,4-oxadiazol-3-yl)-1-isoquinolyl]amino]hexanoate (522.00 mg, 0.9931 mmol) in THF (9.93 mL) were added potassium hydroxide (557.21 mg, 9.9308 mmol) and water (0.5 mL enough to dissolve the KOH) followed by 8 drops of MeOH. The mixture was allowed to stir for 18 h at 50 °C. Additional potassium hydroxide (557.21 mg, 9.9308 mmol) was added and stirring was continued at 50 °C for 13 d. Addition of extra MeOH (1 mL) and water (1 mL) was required to complete conversion. The mixture was allowed to cool, and the volatiles removed under reduced pressure. Water (20 mL) was added, and this was acidified to pH3 with aq. 2M HCl solution. Extraction with EtOAc (3x) was carried out and the combined organics were dried over Na_2SO_4. These were then concentrated under reduced pressure to give a pale yellow solid. Purification by reverse phase flash chromatography (Eluent: 10-100% MeOH/H_2O + 0.1% formic acid) afforded (3S)-6-[tert-butoxycarbonyl(methyl)amino]-3-[[7-(5-methyl-1,2,4-oxadiazol-3-yl)-1-isoquinolyl]amino]hexanoic acid as a pale yellow glassy solid, 177 mg (38%). HPLC m/z: 470.2 $[M+H]^+$, Rt (R): 1.12 min.

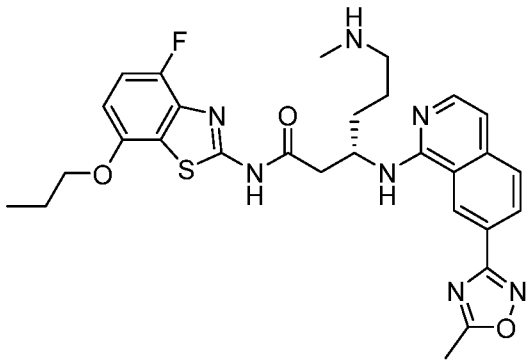
Example 54.3: To a mixture of (3S)-6-[tert-butoxycarbonyl(methyl)amino]-3-[[7-(5-methyl-1,2,4-oxadiazol-3-yl)-1-isoquinolyl]amino]hexanoic acid (30.00 mg, 0.0639 mmol) and 7-propoxy-1,3-benzothiazol-2-amine [Example 75.3] (13.31 mg, 0.0639 mmol) in DMF (0.32 mL) under N_2 were added triethylamine (0.03 mL, 0.1917 mmol) and then 1-propanephosphonic anhydride (50% in DMF) (0.08 mL, 0.1278 mmol). This mixture was stirred at 70 °C under N_2 for 5 d followed by an additional 3 d at 60 °C. Purification by reverse phase flash chromatography (Eluent: 20-80% MeOH/H_2O + 0.1% formic acid) afforded tert-butyl N-methyl-N-[(4S)-4-[[7-(5-methyl-1,2,4-oxadiazol-3-yl)-1-isoquinolyl]amino]-6-oxo-6-[(7-propoxy-1,3-benzothiazol-2-yl)amino]hexyl]carbamate as a pale yellow solid, 31 mg (73%). HPLC/MS m/z: 452.2 $[M+H]^+$, Rt (R): 1.40 min.

Example 54.4: To a flask charged with tert-butyl N-methyl-N-[(4S)-4-[[7-(5-methyl-1,2,4-oxadiazol-3-yl)-1-isoquinolyl]amino]-6-oxo-6-[(7-propoxy-1,3-benzothiazol-2-yl)amino]hexyl]carbamate (34.00 mg, 0.0515 mmol) was added 4M HCl in dioxane (1.03 mL, 4.1225 mmol). This solution was stirred at RT for 20 min. The mixture was concentrated under reduced pressure before purification using preparative HPLC to give (3S)-6-(methylamino)-3-[[7-(5-methyl-1,2,4-oxadiazol-3-yl)-1-isoquinolyl]amino]-N-(7-propoxy-1,3-benzothiazol-2-yl)hexanamide as an off-white amorphous solid, 10.5 mg (36%). HPLC/MS m/z: 560.2 $[M+H]^+$, Rt (S): 2.28 min. ^1H NMR (600 MHz,

Methanol-d_4): δ 8.90 (s, 1H), 8.19 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.96 (d, *J* = 5.9 Hz, 1H), 7.79 (d, *J* = 8.5 Hz, 1H), 7.37-7.30 (m, 2H), 6.97 (d, *J* = 5.9 Hz, 1H), 6.83 (dd, *J* = 7.4, 1.3 Hz, 1H), 4.82 (d, *J* = 8.7 Hz, 1H), 4.12 (t, *J* = 6.4 Hz, 2H), 3.03 (dd, *J* = 14.7, 5.9 Hz, 1H), 2.85 (dd, *J* = 14.7, 6.8 Hz, 1H), 2.81-2.65 (m, 5H), 2.44 (s, 3H), 2.01-1.69 (m, 6H), 1.09 (t, *J* = 7.4 Hz, 3H).

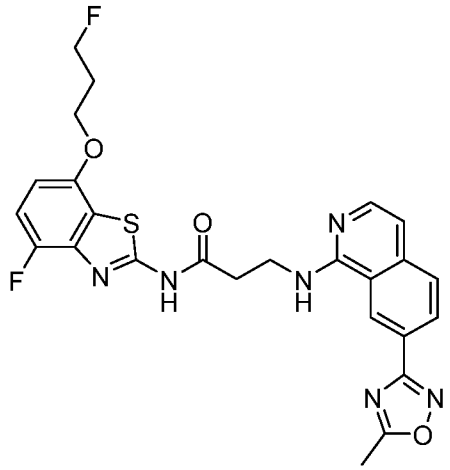
The following examples were synthesised by an analogous procedure.

Example 55: (S)-N-(4-fluoro-7-propoxybenzo[d]thiazol-2-yl)-3-((7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl)amino)-6-(methylamino)hexanamide



Obtained from 4-fluoro-7-propoxy-1,3-benzothiazol-2-amine [Example 77.2] and (3S)-6-[tert-butoxycarbonyl(methyl)amino]-3-[[7-(5-methyl-1,2,4-oxadiazol-3-yl)-1-isoquinolyl]amino]hexanoic acid [Example 54.2] to afford (S)-N-(4-fluoro-7-propoxybenzo[d]thiazol-2-yl)-3-((7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl)amino)-6-(methylamino)hexanamide dichloride (430 mg, 95%, 0.6603 mmol) as a white solid. HPLC/MS m/z: 578.234 $[M+H]^+$, Rt (AE): 2.33 min. ^{1}H NMR (600 MHz, DMSO-d_6): δ 13.52 (br s, 1H), 12.88 (s, 1H), 9.57 (br s, 1H), 9.31 (s, 1H), 8.78-8.63 (m, 2H), 8.46 (d, *J* = 8.5 Hz, 1H), 8.13 (d, *J* = 8.4 Hz, 1H), 7.84 (d, *J* = 6.8 Hz, 1H), 7.36 (d, *J* = 6.7 Hz, 1H), 7.22-7.17 (m, 1H), 6.85-6.82 (m, 1H), 4.89-4.84 (m, 1H), 4.06 (td, *J* = 6.4, 1.1 Hz, 2H), 3.18 (dd, *J* = 16.8, 7.8 Hz, 1H), 3.11 (dd, *J* = 16.8, 4.6 Hz, 1H), 2.99-2.87 (m, 2H), 2.71 (s, 3H), 2.51 (d, *J* = 5.4 Hz, 3H), 1.93-1.83 (m, 2H), 1.79-1.69 (m, 4H), 0.97 (t, *J* = 7.4 Hz, 3H).

Example 56: N-[4-fluoro-7-(3-fluoropropoxy)-1,3-benzothiazol-2-yl]-3-[[7-(5-methyl-1,2,4-oxadiazol-3-yl)-1-isoquinolyl]amino]propanamide

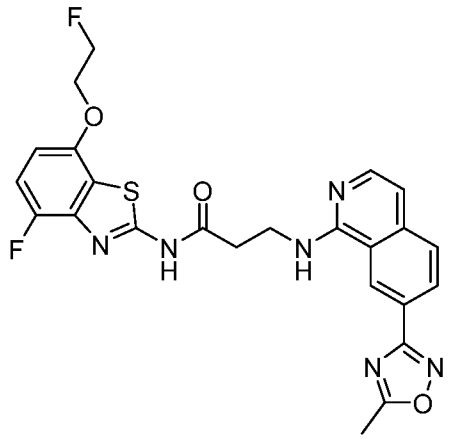


Example 56.1: To a solution of 2-amino-4-fluoro-1,3-benzothiazol-7-ol (80.00 mg, 0.4343 mmol) in DMF (4.01 mL, 0.1100 M) stirring at RT under N_2 was added potassium carbonate (120.06 mg, 0.8687 mmol). This was stirred for 30 min before the addition of 1-iodo-3-fluoropropane (0.04 mL, 0.4343 mmol). This was then stirred under N_2 for 7 h. The mixture was diluted with water (2 mL), acidified to pH6 with 2N HCl solution and then MeOH (20 mL) was added. This was loaded onto a 5 g SCX-2 column, washed with MeOH and then eluted with 2N NH_3 in MeOH solution. The basic flush was concentrated under reduced pressure to give 4-fluoro-7-(3-fluoropropoxy)-1,3-benzothiazol-2-amine as a dark grey solid, 70 mg (66%). HPLC/MS m/z: 245.1 $[M+H]^+$, Rt (R): 1.11 min.

Example 56.2: To a mixture of 3-[[7-(5-methyl-1,2,4-oxadiazol-3-yl)-1-isoquinolyl]amino]propanoic acid B2 (25.00 mg, 0.0838 mmol) and 4-fluoro-7-(3-fluoropropoxy)-1,3-benzothiazol-2-amine (20.47 mg, 0.0838 mmol) in DMF (0.84 mL) was added triethylamine (0.04 mL, 0.2514 mmol) and then 1-propanephosphonic anhydride (50% in DMF) (0.10 mL, 0.1676 mmol). This mixture was stirred at 70 °C under N_2 for 3 d. A further 2 eq. of 1-propanephosphonic anhydride (50% in DMF) (0.10 mL, 0.1676 mmol) was added and this was stirred at 70 °C under N_2 for 18 h. A further 2 eq. of 1-propanephosphonic anhydride (50% in DMF) (0.10 mL, 0.1676 mmol) was added and the mixture was stirred at 70 °C under N_2 for 4 h. The crude was purified by prep-HPLC to give N-[4-fluoro-7-(3-fluoropropoxy)-1,3-benzothiazol-2-yl]-3-[[7-(5-methyl-1,2,4-oxadiazol-3-yl)-1-isoquinolyl]amino]propanamide as a white solid, 8.5 mg (19%). HPLC/MS m/z: 525.2 $[M+H]^+$, Rt (Z): 2.41 min. ^1H NMR (500 MHz, DMSO-d_6): δ 12.74 (s, 1H), 8.91-

8.87 (m, 1H), 8.15 (dd, *J* = 8.5, 1.6 Hz, 1H), 8.04 (t, *J* = 5.5 Hz, 1H), 7.97 (d, *J* = 5.8 Hz, 1H), 7.85 (d, *J* = 8.5 Hz, 1H), 7.21 (dd, *J* = 10.5, 8.8 Hz, 1H), 7.00-6.95 (m, 1H), 6.89 (dd, *J* = 8.8, 3.1 Hz, 1H), 4.68 (t, *J* = 5.9 Hz, 1H), 4.59 (t, *J* = 5.8 Hz, 1H), 4.24 (t, *J* = 6.2 Hz, 2H), 3.84 (q, *J* = 6.5 Hz, 2H), 2.94 (t, *J* = 6.8 Hz, 2H), 2.69 (s, 3H), 2.16 (dquint, *J* = 25.9, 6.0 Hz, 2H).

Example 57: N-[4-fluoro-7-(3-fluoroethoxy)-1,3-benzothiazol-2-yl]-3-[[7-(5-methyl-1,2,4-oxadiazol-3-yl)-1-isoquinolyl]amino]propanamide



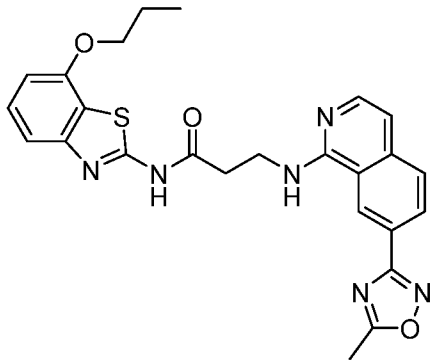
Example 57.1: To a solution of 2-amino-4-fluoro-1,3-benzothiazol-7-ol (80.00 mg, 0.4343 mmol) in DMF (4.01 mL, 0.1100 M) stirring at RT under N_2 was added potassium carbonate (120.06 mg, 0.8687 mmol). This was stirred for 30 min before the addition of 1-iodo-3-fluoroethane (0.05 mL, 0.4343 mmol). This was then stirred under N_2 for 25 h. The mixture was diluted with water (2 mL), acidified to pH6 with 2N HCl in water solution and then MeOH (20 mL) was added. This was loaded onto a 5 g SCX-2 column, washed with MeOH and then eluted with 2N NH_3 in MeOH solution. The basic flush was concentrated under reduced pressure to give 4-fluoro-7-(2-fluoroethoxy)-1,3-benzothiazol-2-amine as a dark grey solid, 93 mg (93%). HPLC/MS m/z: 231.0 $[M+H]^+$, Rt (R): 0.96 min.

Example 57.2: To a mixture of 3-[[7-(5-methyl-1,2,4-oxadiazol-3-yl)-1-isoquinolyl]amino]propanoic acid B2 (35.00 mg, 0.1173 mmol), and 4-fluoro-7-(2-fluoroethoxy)-1,3-benzothiazol-2-amine (32.42 mg, 0.1408 mmol) in DMF (0.50 mL) was added 1-propanephosphonic anhydride (0.06 mL, 0.2347 mmol). This mixture was stirred at 70 °C under N_2 for 3 d. Extra 1-propanephosphonic anhydride (50% in DMF) (0.06 mL, 0.2347 mmol) was added and this was stirred at 70 °C under N_2 for

3 d. Purification by NP silica column chromatography (Eluent: 0-10% MeOH/DCM) followed by purification by reverse phase flash chromatography (Eluent: 20-100% MeOH/H_2O) afforded N-[4-fluoro-7-(3-fluoroethoxy)-1,3-benzothiazol-2-yl]-3-[[7-(5-methyl-1,2,4-oxadiazol-3-yl)-1-isoquinolyl]amino]propanamide as a white solid, 22 mg (36%). HPLC/MS m/z: 511.2 $[M+H]^+$, Rt (Z): 2.25 min. ^1H NMR (600 MHz, DMSO-d_6): δ 12.74 (s, 1H), 8.89 (d, *J* = 1.6 Hz, 1H), 8.15 (dd, *J* = 8.5, 1.5 Hz, 1H), 8.05 (t, *J* = 5.4 Hz, 1H), 7.97 (d, *J* = 5.7 Hz, 1H), 7.85 (d, *J* = 8.5 Hz, 1H), 7.23 (dd, *J* = 10.5, 8.8 Hz, 1H), 6.97 (d, *J* = 5.7 Hz, 1H), 6.90 (dd, *J* = 8.8, 3.0 Hz, 1H), 4.86-4.81 (m, 1H), 4.78-4.73 (m, 1H), 4.46-4.42 (m, 1H), 4.41-4.37 (m, 1H), 3.84 (q, *J* = 6.6 Hz, 2H), 2.95 (t, *J* = 6.8 Hz, 2H), 2.69 (s, 3H).

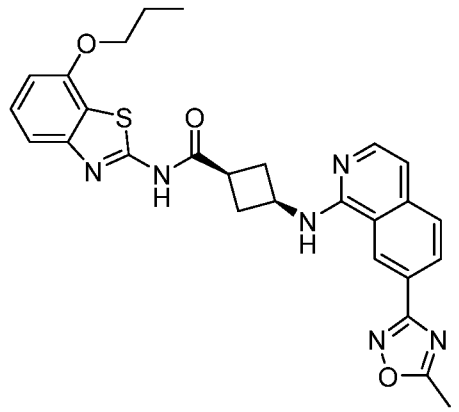
The following example followed an analogous procedure:

Example 58: 3-((7-(5-Methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl)amino)-N-(7-propoxybenzo[d]thiazol-2-yl)propanamide



Obtained using 7-propoxy-1,3-benzothiazol-2-amine [Example 73.1] and 3-[[7-(5-methyl-1,2,4-oxadiazol-3-yl)-1-isoquinolyl]amino]propanoic acid B2. White powder (37 mg, 0.0757 mmol). HPLC/MS m/z: 489.158 $[M+H]^+$, Rt (Z): 2.50 min. ^1H NMR (600 MHz, DMSO-d_6): δ 12.42 (s, 1H), 8.91-8.87 (m, 1H), 8.15 (dd, *J* = 8.5, 1.6 Hz, 1H), 8.04 (t, *J* = 5.4 Hz, 1H), 7.98 (d, *J* = 5.7 Hz, 1H), 7.85 (d, *J* = 8.5 Hz, 1H), 7.39-7.30 (m, 2H), 6.97 (dd, *J* = 5.9, 0.8 Hz, 1H), 6.89 (dd, *J* = 7.7, 1.2 Hz, 1H), 4.12 (t, *J* = 6.4 Hz, 2H), 3.84 (q, *J* = 6.6 Hz, 2H), 2.93 (t, *J* = 6.8 Hz, 2H), 2.69 (s, 3H), 1.86-1.75 (m, 2H), 1.02 (t, *J* = 7.4 Hz, 3H).

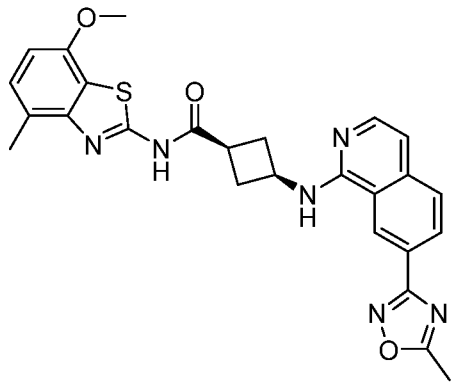
Example 59: (1s,3s)-3-((7-(5-Methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl)amino)-N-(7-propoxybenzo[d]thiazol-2-yl)cyclobutane-1-carboxamide



3-[[7-(5-Methyl-1,2,4-oxadiazol-3-yl)-1-isoquinolyl]amino]cyclobutanecarboxylic acid B3 (46.72 mg, 0.1440 mmol) and BTFFH (91.09 mg, 0.2881 mmol) were mixed in DCM (0.53 mL, 0.1800 M) at RT under argon. DIPEA (0.11 mL, 0.6242 mmol) was added, and the reaction mixture was stirred for 30 min. 7-Propoxy-1,3-benzothiazol-2-amine [Example 73.1] (0.07 mL, 0.0960 mmol) was added followed by DMF (0.010 mL). The vial was capped and the reaction was heated to 80 °C in a microwave for 1 h. Purification by reverse phase flash chromatography (Eluent: 20-70% MeOH/H_2O + 0.1% formic acid) followed by ion exchange SCX-2 chromatography eluting with 2M NH_3 in MeOH afforeded 3-[[7-(5-methyl-1,2,4-oxadiazol-3-yl)-1-isoquinolyl]amino]-N-(7-propoxy-1,3-benzothiazol-2-yl)cyclobutanecarboxamide (15 mg, 29%, 0.0277 mmol) as a colorless oil. HPLC/MS m/z: 515.185 $[M+H]^+$, Rt (S): 2.74 min. ^1H NMR (600 MHz, DMSO-d_6): δ 12.36 (s, 1H), 9.02 (s, 1H), 8.15 (dd, *J* = 8.5, 1.4 Hz, 1H), 8.11 (d, *J* = 6.8 Hz, 1H), 7.96 (d, *J* = 5.7 Hz, 1H), 7.84 (d, *J* = 8.5 Hz, 1H), 7.42-7.32 (m, 2H), 6.97 (d, *J* = 5.7 Hz, 1H), 6.90 (dd, *J* = 7.5, 1.1 Hz, 1H), 4.76-4.66 (m, 1H), 4.13 (t, *J* = 6.4 Hz, 2H), 3.19-3.07 (m, 1H), 2.71 (s, 3H), 2.63 (qd, *J* = 7.9, 2.5 Hz, 2H), 2.49-2.41 (m, 2H), 1.80 (sext, *J* = 7.2 Hz, 2H), 1.02 (t, *J* = 7.4 Hz, 3H).

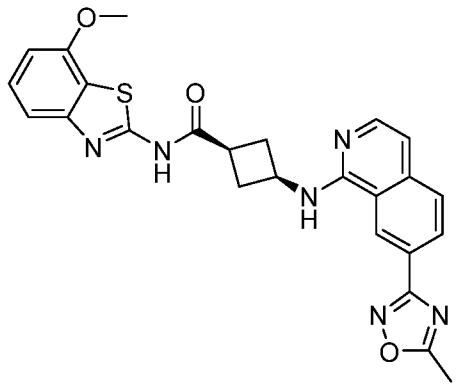
The following examples followed an analogous procedure:

Example 60: (1s,3s)-N-(7-methoxy-4-methylbenzo[d]thiazol-2-yl)-3-((7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl)amino)cyclobutane-1-carboxamide



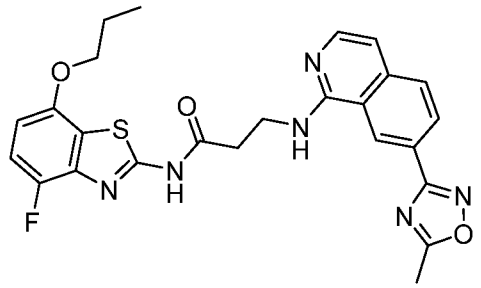
White powder, 10 mg, 0.0190 mmol. HPLC/MS m/z: 501.168 $[M+H]^+$, Rt (S): 2.34 min. ^{1}H NMR (600 MHz, DMSO-d_6): δ 12.46 (s, 1H), 9.04-9.02 (m, 1H), 8.15 (dd, *J* = 8.5, 1.6 Hz, 1H), 8.12 (d, *J* = 7.2 Hz, 1H), 7.97 (d, *J* = 5.7 Hz, 1H), 7.85 (d, *J* = 8.5 Hz, 1H), 7.20 (dd, *J* = 8.0, 1.1 Hz, 1H), 6.98 (dd, *J* = 5.9, 0.8 Hz, 1H), 6.82 (d, *J* = 8.1 Hz, 1H), 4.73 (ddt, *J* = 16.7, 9.3, 7.3 Hz, 1H), 3.92 (s, 3H), 3.23-3.08 (m, 1H), 2.72 (s, 3H), 2.66-2.59 (m, 2H), 2.50 (d, *J* = 1.7 Hz, 3H), 2.47 (dt, *J* = 11.6, 9.5 Hz, 2H).

Example 61: (1s,3s)-N-(7-methoxybenzo[d]thiazol-2-yl)-3-((7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl)amino)cyclobutane-1-carboxamide



Off-white solid, 32 mg, 0.0645 mmol. HPLC/MS m/z: 487.154 $[M+H]^+$, Rt (X): 2.68 min. ^{1}H NMR (600 MHz, DMSO-d_6): δ 2.47 (td, *J* = 2.5, 9.5 Hz, 2H), 2.63 (qd, *J* = 2.6, 7.8 Hz, 2H), 2.72 (s, 3H), 3.16 (tt, *J* = 7.8, 9.7 Hz, 1H), 3.95 (s, 3H), 4.74 (ddt, *J* = 7.4, 9.1, 16.7 Hz, 1H), 6.92 (dd, *J* = 1.1, 7.8 Hz, 1H), 6.98 (d, *J* = 5.7 Hz, 1H), 7.35-7.43 (m, 2H), 7.85 (d, *J* = 8.5 Hz, 1H), 7.97 (d, *J* = 5.7 Hz, 1H), 8.12 (d, *J* = 7.2 Hz, 1H), 8.14-8.17 (m, 1H), 9.03 (d, *J* = 1.6 Hz, 1H), 12.38 (s, 1H).

Example 62: N-(4-fluoro-7-propoxybenzo[d]thiazol-2-yl)-3-((7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl)amino)propanamide

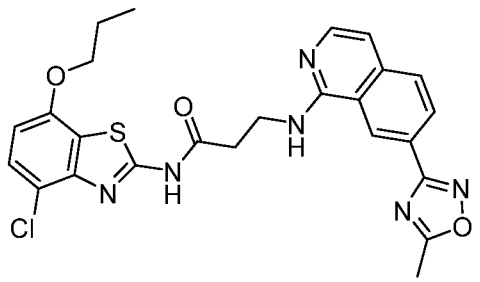


Example 62.1: A mixture of 2-amino-4-fluorobenzo[*d*]thiazol-7-ol (200 mg, 1.09 mmol, 1.00 *eq*), potassium carbonate (599 mg, 4.33 mmol, 3.99 *eq*) and 1-iodopropane (222 mg, 1.30 mmol, 1.20 *eq*) in acetonitrile (2.00 mL) was stirred at 50 °C for 12 h. After the reaction was completed, the mixture was filtered. The filtrate was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 10/1 to 2/1) to afford 4-fluoro-7-propoxybenzo[*d*]thiazol-2-amine (160 mg, 707 umol, 65% yield) as a white solid. ^{1}H NMR (400 MHz, Chloroform-d): δ = 6.96 (dd, *J* = 8.8, 10.4 Hz, 1H), 6.51 (dd, *J* = 3.2, 8.8 Hz, 1H), 5.86 (br s, 2H), 4.03 (t, *J* = 6.4 Hz, 2H), 1.84 (sext, *J* = 7.0 Hz, 2H), 1.06 (t, *J* = 7.2 Hz, 3H).

Example 62.2: A mixture of 3-((7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl)amino)propanoic acid (60.0 mg, 201 umol, 1.00 eq), 4-fluoro-7-propoxybenzo[d]thiazol-2-amine (50.0 mg, 221 umol, 1.10 eq), propylphosphonicanhydride (256 mg, 402 umol, 239 uL, 50% purity in dimethyl formamide, 2.00 eq) in dimethyl formamide (0.500 mL) was stirred at 50 °C for 2 h. After the reaction was completed, the mixture was poured into saturated aqueous sodium bicarbonate solution (10 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were concentrated to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Synergi C18 150*25mm* 10um; mobile phase: [water(0.225%FA)-ACN];B%: 20%-50%,10 min) and lyophilized to afford N-(4-fluoro-7-propoxybenzo[d]thiazol-2-yl)-3-((7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1- yl)amino)propanamide (25.37 mg, 45.4 umol, 22% yield, 99% purity) as a white solid. HPLC/MS m/z: 507.1 $[M+H]^+$, Rt (E): 0.87 min. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.72 (br s, 1H), 8.89 (s, 1H), 8.16 (d, *J* = 1.6 Hz, 1H), 8.14 (s, 1H), 8.07-8.01 (m, 1H), 7.97 (d, *J* = 6.0 Hz, 1H), 7.85 (d, *J* = 8.4 Hz, 1H), 7.20 (dd, *J*

= 8.8, 10.8 Hz, 1H), 6.97 (d, *J* = 5.6 Hz, 1H), 6.85 (dd, *J* = 3.2, 8.8 Hz, 1H), 4.10 (t, *J* = 6.4 Hz, 2H), 3.87-3.80 (m, 2H), 2.94 (br t, *J* = 6.8 Hz, 2H), 2.69 (s, 3H), 1.83-1.72 (m, 2H), 1.01 (t, *J* = 7.2 Hz, 3H).

Example 63: N-(4-chloro-7-propoxybenzo[d]thiazol-2-yl)-3-((7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl)amino)propanamide



Example 63.1: To a solution of potassium thiocyanate (1.36 g, 14.0 mmol, 1.10 *eq*) in acetone (20 mL) was added a solution of acetyl chloride (1.10 g, 14.0 mmol, 0.996 mL, 1.10 *eq*) in acetone (10 mL) at 20 °C. The mixture was stirred at 50 °C for 0.2 h. Then to the mixture was added a solution of 2-chloro-5-methoxyaniline (2.00 g, 12.7 mmol, 1.00 *eq*) in acetone (20 mL). The resulting mixture was stirred at 50 °C for 0.5 h. Then the mixture was poured into water (200 mL) and filtered. The filter cake was dried under reduce pressure to give a residue. The residue was diluted with methanol (10 mL) and to the mixture was added potassium carbonate (3.51 g, 25.4 mmol, 2.00 *eq*). The mixture was stirred at 25 °C for 12 h. The mixture was poured into water (200 mL) and filtered. The filter cake was dried under reduce pressure to afford 1-(2-chloro-5-methoxyphenyl)thiourea (2.00 g, 9.23 mmol, 72% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.27 (s, 1H), 7.37 (d, *J* = 9.0 Hz, 1H), 7.35 (d, *J* = 3.0 Hz, 1H), 6.82 (dd, *J* = 3.0, 9.0 Hz, 1H), 3.74 (s, 3H).

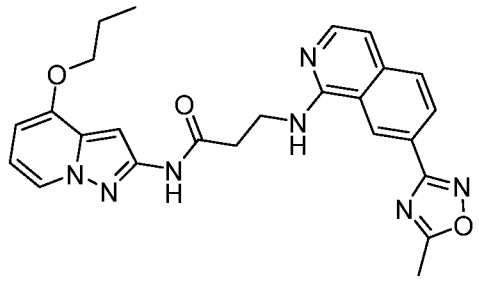
Example 63.2: To a solution of 1-(2-chloro-5-methoxyphenyl)thiourea (1.50 g, 6.92 mmol, 1.00 *eq*) in acetic acid (15 mL) was added bromine (608 mg, 3.81 mmol, 196 uL, 0.55 *eq*) at 0 °C. The mixture was stirred at 20 °C for 2 h. The mixture was filtered, and the filter cake was dried under reduced pressure to afford 4-chloro-7-methoxybenzo[*d*]thiazol-2-amine (1.50 g, crude) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.86 (br s, 2H), 7.25 (d, *J* = 8.7 Hz, 1H), 6.68 (d, *J* = 8.8 Hz, 1H), 3.86 (s, 3H).

Example 63.3: To a solution of 4-chloro-7-methoxybenzo[*d*]thiazol-2-amine (1.70 g, 7.92 mmol, 1.00 *eq*) in dichloromethane (10 mL) was added boron tribromide (9.92 g, 39.6 mmol, 3.82 mL, 5.00 *eq*) at 0 °C. The mixture was stirred at 30 °C for 12 h. Then the mixture was poured into methanol (50 mL) at 0 °C carefully. The mixture was concentrated under reduced pressure to give a residue. The residue was purified by reversed phase column chromatography (C18, 40 g; condition: water/acetonitrile = 1/0 to 0/1, 0.1% formic acid) to afford 2-amino-4-chlorobenzo[*d*]thiazol-7-ol (1.10 g, 5.48 mmol, 69% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.30 (br s, 1H), 7.94 (br s, 2H), 7.11 (d, J = 8.5 Hz, 1H), 6.51 (d, J = 8.5 Hz, 1H).

Example 63.4: To a solution of 2-amino-4-chlorobenzo[*d*]thiazol-7-ol (0.400 g, 1.99 mmol, 1.00 *eq*) in dimethyl formamide (5 mL) were added potassium carbonate (551 mg, 3.99 mmol, 2.00 *eq*) and 1-iodopropane (407 mg, 2.39 mmol, 234 uL, 1.20 *eq*). The mixture was stirred at 30 °C for 12 h. Then the mixture was filtered. The filtrate was purified by reversed phase column chromatography (C18, 120 g; condition: water/acetonitrile = 1/0 to 0/1, 0.1% formic acid) to afford 4-chloro-7-propoxybenzo[*d*]thiazol-2-amine (0.24 g, 989 umol, 49% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.82 (s, 2H), 7.21 (d, J = 8.6 Hz, 1H), 6.67 (d, J = 8.6 Hz, 1H), 4.04 (t, J = 6.5 Hz, 2H), 1.80-1.65 (m, 2H), 0.97 (t, J = 7.4 Hz, 3H).

Example 63.5: To a solution of 4-chloro-7-propoxybenzo[d]thiazol-2-amine (100 mg, 412 umol, 1.00 *eq*) and 3-((7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl)amino)propanoic acid B2 (123 mg, 0.412 mmol, 1.00 *eq*) in dimethyl formamide (3 mL) were added 1-methylimidazole (67.7 mg, 0.824 mmol, 65.7 uL, 2.00 *eq*) and N,N,N,N-tetramethylchloroformamidinium hexafluorophosphate (347 mg, 1.24 mmol, 3.00 *eq*). The mixture was stirred at 30 °C for 4 h. Then the mixture was filtered. The filtrate was purified by prep-HPLC (column: Waters Xbridge 150*25mm* 5um; mobile phase: [water(10mM NH_4HCO_3)-ACN];B%: 58%-88%, 9min) and lyophilized to afford *N*-(4-chloro-7-propoxybenzo[*d*]thiazol-2-yl)-3-((7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl)amino)propanamide (24 mg, 45.43 umol, 11% yield, 99% purity) as a white solid. HPLC/MS m/z: 523.1 $[M+H]^+$, Rt (E): 0.87 min. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.84 (br s, 1H), 8.89 (s, 1H), 8.15 (br d, J = 8.5 Hz, 1H), 8.03 (br t, J = 5.0 Hz, 1H), 7.98 (d, J = 5.8 Hz, 1H), 7.85 (d, J = 8.4 Hz, 1H), 7.43 (br d, J = 8.5 Hz, 1H), 6.97 (br d, J = 5.6 Hz, 1H), 6.90 (br d, J = 8.5 Hz, 1H), 4.12 (br t, J = 6.2 Hz, 2H), 3.90-3.76 (m, 2H), 2.93 (br t, J = 6.5 Hz, 2H), 2.72-2.65 (m, 3H), 1.79 (qd, J = 6.8, 13.8 Hz, 2H), 1.01 (t, J = 7.3 Hz, 3H).

Example 64: 3-((7-(5-Methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl)amino)-N-(4-propoxypyrazolo[1,5-a]pyridin-2-yl)propanamide



Example 64.1: To a solution of 2-bromopyridin-3-ol (12.0 g, 69.0 mmol, 1.00 *eq*) in DMF (90 mL) was added potassium carbonate (11.4 g, 82.8 mmol, 1.20 *eq*). The mixture was stirred at 90 °C for 1 h. To the mixture was added 1-iodopropane (21.1 g, 124 mmol, 1.80 *eq*). The mixture was stirred at 90 °C for 3 h. The mixture was diluted with saturated ammonium chloride aqueous solution (100 mL) and extracted with ethyl acetate (3 × 80 mL). The combined organic layers were washed with brine (3 × 50 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford 2-bromo-3-propoxypyridine (14.0 g, 64.8 mmol, 93% yield) as brown oil. ^{1}H NMR (400 MHz, Chloroform-d): δ 7.95 (dd, J = 1.5, 4.6 Hz, 1H), 7.50 (dd, J = 1.4, 8.2 Hz, 1H), 7.39 (dd, J = 4.6, 8.2 Hz, 1H), 4.06 (t, J = 6.4 Hz, 2H), 1.86-1.64 (m, 2H), 1.01 (t, J = 7.4 Hz, 3H).

Example 64.2: To a solution of acetonitrile (3.06 g, 74.5 mmol, 2.80 *eq*) in tetrahydrofuran (100 mL) was added *n*-butyllithium (2.5 M in hexane, 74.5 mmol, 29.8 mL, 2.80 *eq*) dropwise at -78 °C. The mixture was stirred at -78°C for 0.2 h. To the mixture was added a solution of 2-bromo-3-propoxy-pyridine (5.75 g, 26.6 mmol, 1.00 *eq*) in tetrahydrofuran (10 mL). The mixture was stirred at -78 °C for 1 h, warmed to 0 °C and stirred at 0 °C for 3 h. The mixture was diluted with saturated ammonium chloride aqueous solution (20 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine (3 × 50 mL), dried over anhydrous sodium sulfate, filtered and 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 afford 2-(3-propoxypyridin-2-yl)acetonitrile (5.00 g, crude) as yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.10

(dd, *J* = 1.3, 4.6 Hz, 1H), 7.47 (dd, *J* = 1.3, 8.4 Hz, 1H), 7.36 (dd, *J* = 4.7, 8.3 Hz, 1H), 4.06 (s, 2H), 4.03-4.01 (m, 2H), 1.77 (s, 2H), 1.17 (t, *J* = 7.1 Hz, 3H).

Example 64.3: To a solution of ethyl (1*E*)-*N*-(2,4,6-trimethylphenyl)sulfonyloxyethanimidate (10.0 g, 35.0 mmol, 1.00 *eq*) in dioxane (20 mL) was added perchloric acid (9.32 g, 64.9 mmol, 5.61 mL, 70% purity, 1.85 *eq*) at 0 °C. Then the mixture was stirred at 0 °C for 0.5 h. The solution was diluted with ice-water (30 mL) and filtered. The filter cake was extracted with dichloromethane (50 mL). The combined organic layers were dried over anhydrous sodium sulfate and filtered to afford a solution of *O*-(mesitylsulfonyl)hydroxylamine (6.50 g) in dichloromethane (0.6 M, 50 mL) as a colorless solution. It was used directly for the next step.

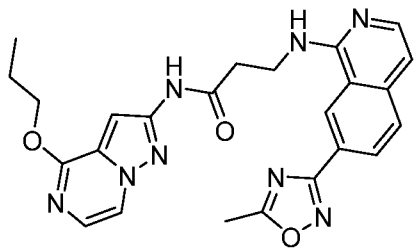
Example 64.4: To a solution of amino 2,4,6-trimethylbenzenesulfonate (0.600 M, 15.3 mmol, 25.5 mL, 1.35 *eq*) in dichloromethane (15 mL) was added 2-(3-propoxypyridin-2-yl)acetonitrile (2.00 g, 11.4 mmol, 1.00 *eq*). The mixture was stirred at 20 °C for 2 h. The mixture was concentrated under reduced pressure to afford 1-amino-2-(cyanomethyl)-3-propoxypyridin-1-ium 2,4,6-trimethylbenzenesulfonate (5.00 g, crude) as brown oil. It was used for next step directly.

Example 64.5: To a solution of 1-amino-2-(cyanomethyl)-3-propoxypyridin-1-ium 2,4,6-trimethylbenzenesulfonate in methanol (60 mL) was added potassium carbonate (2.82 g, 20.4 mmol, 2.00 *eq*). The mixture was stirred at 20 °C for 12 h. The mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 5/1 to 1/1), reversed phase column chromatography (C18, 40 g; condition: water/acetonitrile = 1/0 to 0/1, 0.1% formic acid) and concentrated under reduced pressure to afford 4-propoxypyrazolo[1,5-*a*]pyridin-2-amine (0.130 g, crude) as yellow oil. ^{1}H NMR (400 MHz, Chloroform-d): δ 7.81 (d, *J* = 6.8 Hz, 1H), 6.45-6.39 (m, 1H), 6.29 (d, *J* = 7.5 Hz, 1H), 5.86 (s, 1H), 4.01-3.98 (m, 2H), 1.88-1.84 (m, 2H), 1.07-1.04 (m, 3H).

Example 64.6: To a solution of 3-((7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl)amino)propanoic acid B2 (46.8 mg, 0.157 mmol, 1.00 *eq*), 4-propoxypyrazolo[1,5-*a*]pyridin-2-amine (30.0 mg, 0.157 mmol, 1.00 *eq*) and 1-methylimidazole (51.5 mg, 0.628 mmol, 50.0 uL, 4.00 *eq*) in DMF (1 mL) was added *N*,*N*,*N*,*N*-tetramethylchloroformamidinium hexafluorophosphate (132 mg, 0.471 mmol, 3.00 *eq*). The mixture was stirred at 20 °C for 12 h. Three batches of reaction mixture

were combined and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (ethyl acetate/methanol = 20/1), prep-HPLC (column: Shim-pack C18 150*25*10um; mobile phase: [water(0.225%FA)-ACN]; B%: 21%-51%,10 min) and lyophilized to afford 3-((7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl)amino)-*N*- (4-propoxypyrazolo[1,5-*a*]pyridin-2-yl)propanamide (9.78 mg, 18.52 umol, 3.93% yield, 98% purity, formate) as a white solid. HPLC/MS m/z: 472.2 $[M+H]^+$, Rt (E): 0.83 min. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.91 (br s, 1H), 9.11 (br s, 1H), 8.35 (br s, 1H), 8.13 (s, 1H), 8.10 (d, J = 6.9 Hz, 1H), 8.03 (br s, 1H), 7.86 (br s, 1H), 7.20 (br s, 1H), 6.85 (s, 1H), 6.74-6.67 (m, 1H), 6.61 (d, J = 7.6 Hz, 1H), 4.07 (t, J = 6.4 Hz, 2H), 3.85 (br d, J = 5.6 Hz, 2H), 2.89 (br s, 2H), 2.70 (s, 3H), 1.84-1.76 (m, 2H), 1.01 (t, J = 7.4 Hz, 3H).

Example 65: 3-((7-(5-Methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl)amino)-N-(4-propoxypyrazolo[1,5-a]pyrazin-2-yl)propanamide



Example 65.1: To a solution of 3-nitro-1*H*-pyrazole-5-carboxylic acid (6.00 38.2 mmol, 1.00 *eq*) in acetonitrile (60 mL) was added 1,1-carbonyldiimidazole (7.43 g, 45.8 mmol, 1.20 *eq*). The mixture was stirred at 60 °C for 3 h. To the mixture was added 2,2-dimethoxyethanamine (4.02 g, 38.2 mmol, 1.00 *eq*) and the mixture was stirred at 60 °C for 12 h. The mixture was concentrated to give a residue. The residue was dissolved in ethyl acetate (60 mL) and washed with aqueous hydrochloric acid solution (1 M, 3 × 20 mL). The organic layer was separated, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford *N*-(2,2-dimethoxyethyl)-3-nitro-1*H*-pyrazole-5-carboxamide (6.00 g, 24.6 mmol, 64% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 14.82 (br s, 1H), 8.90 (br t, J = 5.6 Hz, 1H), 7.67 (s, 1H), 4.49 (t, J = 5.4 Hz, 1H), 3.42-3.38 (m, 2H), 3.31 (s, 6H).

Example 65.2: A solution of *N*-(2,2-dimethoxyethyl)-3-nitro-1*H*-pyrazole-5-carboxamide (6.00 g, 24.57 mmol, 1.00 *eq*) in hydrochloric acid (5.00 M, 20 mL) was

stirred at 20 °C for 12 h. The mixture was filtered. The filter cake was concentrated under reduced pressure to afford 7-hydroxy-2-nitro-6,7-dihydropyrazolo[1,5-*a*]pyrazin-4(5*H*)-one (5.00 g, crude) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.57 (br d, J = 3.6 Hz, 1H), 7.85 (br d, J = 5.9 Hz, 1H), 7.43 (s, 1H), 5.89 (br s, 1H), 3.87 (dd, J = 2.9, 13.9 Hz, 1H), 3.67-3.42 (m, 1H).

Example 65.3: To a solution of 7-hydroxy-2-nitro-6,7-dihydropyrazolo[1,5-*a*]pyrazin-4(5*H*)-one (2.00 g, 10.1 mmol, 1.00 *eq*) in toluene (50 mL) were added thionyl chloride (2.40 g, 20.2 mmol, 2.00 *eq*) and dimethyl formamide (73.8 mg, 1.01 mmol, 0.10 *eq*). The mixture was stirred at 125 °C for 12 h. After cooling to room temperature, the mixture was filtered. The filter cake was triturated with acetonitrile (5 mL) and dimethyl formamide (1.5 mL) to afford 2-nitropyrazolo[1,5-*a*]pyrazin-4-ol (1.60 g, crude) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.75 (br d, J = 1.2 Hz, 1H), 7.81 (s, 1H), 7.73 (d, J = 0.7 Hz, 1H), 7.22 (t, J = 5.9 Hz, 1H).

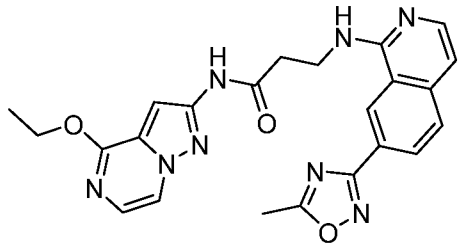
Example 65.4: To a solution of 2-nitropyrazolo[1,5-*a*]pyrazin-4-ol (0.800 g, 4.44 mmol, 1.00 *eq*) in phosphoryl trichloride (6 mL) was added dimethyl formamide (16.2 mg, 0.05 *eq*). The mixture was stirred at 100 °C for 12 h. The mixture was poured into water (20 mL) and the pH was adjusted to pH8 with sodium carbonate. The mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine (3 × 20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford 4-chloro-2-nitropyrazolo[1,5-*a*]pyrazine (0.600 g, crude) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.03 (dd, J = 0.9, 4.8 Hz, 1H), 8.10 (d, J = 4.9 Hz, 1H), 7.92 (d, J = 0.9 Hz, 1H).

Example 65.5: To a solution of propan-1-ol (363 mg, 6.04 mmol, 2.00 *eq*) in tetrahydrofuran (20 mL) was added sodium hydride (266 mg, 6.65 mmol, 60% purity, 2.20 *eq*) at 0 °C. The mixture was stirred at 20 °C for 0.5 h. To the mixture was added 4-chloro-2-nitropyrazolo[1,5-*a*]pyrazine (0.600 g, 3.02 mmol, 1.00 *eq*). The mixture was stirred at 20 °C for 2 h. The mixture was diluted with saturated ammonium chloride aqueous solution (20 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine (3 × 20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford 2-nitro-4-propoxypyrazolo[1,5-*a*]pyrazine (0.6 g, 2.70 mmol, 89% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.54 (dd, J = 0.8, 4.8 Hz, 1H), 7.75 (d, J = 4.9 Hz, 1H), 7.68 (d, J = 0.7 Hz, 1H), 4.46 (t, J = 6.6 Hz, 2H), 1.86-1.79 (m, 2H), 1.03-0.98 (m, 3H).

Example 65.6: To a solution of 2-nitro-4-propoxypyrazolo[1,5-*a*]pyrazine (300 mg, 1.35 mmol, 1.00 *eq*) in methanol (8 mL) and water (8 mL) were added iron powder (377 mg, 6.75 mmol, 5.00 *eq*) and ammonium chloride (361 mg, 6.75 mmol, 5.00 *eq*). The mixture was stirred at 80 °C for 3 h. The mixture was filtered. The filtrate was concentrated under reduced pressure to give a residue. The residue was purified by reversed phase column chromatography (C18, 40 g; condition: water/acetonitrile = 1/0 to 0/1, 0.1% hydrochloric acid) and concentrated under reduced pressure to afford 4-propoxypyrazolo[1,5-*a*]pyrazin-2-amine (200 mg, 1.04 mmol, 77% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.01 (d, J = 4.6 Hz, 1H), 7.15 (d, J = 4.6 Hz, 1H), 5.89 (s, 1H), 4.33 (t, J = 6.7 Hz, 2H), 1.84-1.68 (m, 2H), 0.98 (t, J = 7.4 Hz, 3H).

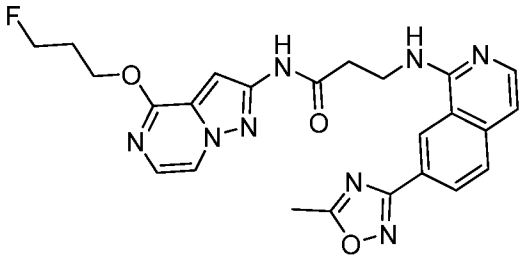
Example 65.7: To a solution of 3-((7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl)amino)propanoic acid B2 (15.5 mg, 52.0 umol, 1.00 *eq*), 4-propoxypyrazolo[1,5-*a*]pyrazin-2-amine (10 mg, 52.02 umol, 1.00 *eq*) and 1-methylimidazole (12.8 mg, 156 umol, 3.00 *eq*) in DMF (1 mL) was added *N*-(chloro(dimethylamino)methylene)-N-methylmethanaminium hexafluorophosphate(V) (29.2 mg, 104.05 umol, 2.00 *eq*). The mixture was stirred at 20 °C for 12 h. Four batches of reaction mixture were combined and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (ethyl acetate/methanol = 20/1), prep-HPLC (column: Shim-pack C18 150*25*10um; mobile phase: [water(0.225%FA)-ACN]; B%: 19%-52%,11 min) and lyophilized to afford 3-((7-(5-methyl-1,2,4- oxadiazol-3-yl)isoquinolin-1-yl)amino)-*N*-(4-propoxypyrazolo[1,5-*a*]pyrazin-2-yl)propanamide (9.47 mg, 19.0 umol, 9% yield, 95% purity) as a white solid. HPLC/MS m/z: 473.1 $[M+H]^+$, Rt (E): 0.82 min. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.17 (s, 1H), 9.23 (br s, 1H), 8.55-8.39 (m, 1H), 8.21 (d, J = 4.9 Hz, 1H), 8.13 (br d, J = 8.4 Hz, 1H), 7.80 (br d, J = 7.0 Hz, 1H), 7.37 (d, J = 4.8 Hz, 1H), 7.33 (br d, J = 7.1 Hz, 1H), 7.01 (s, 1H), 4.39 (t, J = 6.6 Hz, 2H), 3.89 (q, J = 6.0 Hz, 2H), 2.96 (br t, J = 6.2 Hz, 2H), 2.71 (s, 3H), 1.84-1.75 (m, 2H), 0.99 (t, J = 7.4 Hz, 3H).

Example 66: N-(4-ethoxypyrazolo[1,5-a]pyrazin-2-yl)-3-((7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl)amino)propanamide



4-Ethoxypyrazolo[1,5-*a*]pyrazin-2-amine (0.16 g, 898 µmol) was prepared by an analogous procedure to Example 65 using ethanol. To a solution of 4-ethoxypyrazolo[1,5-*a*]pyrazin-2-amine (70.0 mg, 393 umol, 1.00 *eq*) and 3-((7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl)amino)propanoic acid (105 mg, 354 umol, 0.900 *eq*) in dimethyl formamide (5.00 mL) was added propylphosphonicanhydride (500 mg, 786 umol, 467 uL, 50% in dimethyl formamide, 2.00 *eq*). The mixture was stirred at 30 °C for 12 h. The mixture was diluted with saturated sodium bicarbonate aqueous solution (10 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine (3 × 20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC(column: Phenomenex Synergi C18 150*25mm* 10um; mobile phase: [water(0.225%FA)-ACN]; B%: 13%-43%,10 min) and lyophilized to afford *N*-(4-ethoxypyrazolo[1,5-*a*]pyrazin-2-yl)-3-((7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl)amino)propanamide (66.32 mg, 143 umol, 36% yield, 99% purity) as a white solid. HPLC/MS m/z: 459.2 $[M+H]^+$, Rt (E): 0.77 min. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.03 (s, 1H), 8.89 (s, 1H), 8.21 (d, J = 4.6 Hz, 1H), 8.17-8.11 (m, 1H), 7.99 (d, J = 5.8 Hz, 2H), 7.85 (d, J = 8.5 Hz, 1H), 7.36 (d, J = 4.8 Hz, 1H), 7.03 (s, 1H), 6.97 (d, J = 5.8 Hz, 1H), 4.48 (q, J = 7.1 Hz, 2H), 3.84-3.75 (m, 2H), 2.83 (br t, J = 6.8 Hz, 2H), 2.69 (s, 3H), 1.40 (t, J = 7.0 Hz, 3H).

Example 67: N-(4-(3-fluoropropoxy)pyrazolo[1,5-a]pyrazin-2-yl)-3-((7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl)amino)propanamide



Example 67.1: A mixture of 4-chloro-2-nitro-pyrazolo[1,5-*a*]pyrazine [Example 65] (300 mg, 1.51 mmol, 1.00 *eq*), cesium carbonate (985 mg, 3.02 mmol, 2.00 *eq*) and 3-fluoropropan-1-ol (142 mg, 1.81 mmol, 1.20 *eq*) in acetonitrile (6.00 mL) was stirred at 50 °C for 2 h. After the reaction was completed, the mixture was filtered and the filtrate was concentrated to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 6/1 to 2/1) to afford 4-(3-fluoropropoxy)-2-nitropyrazolo[1,5-*a*]pyrazine (180 mg, 749 umol, 49% yield) as a yellow solid. ^{1}H NMR (400 MHz, Chloroform-d): δ 8.06 (dd, J = 0.8, 4.8 Hz, 1H), 7.63 (d, J = 5.2 Hz, 1H), 7.41 (d, J = 0.8 Hz, 1H), 4.74 (t, J = 5.6 Hz, 1H), 4.70 (t, J = 6.4 Hz, 2H), 4.62 (t, J = 5.6 Hz, 1H), 2.36-2.21 (m, 2H).

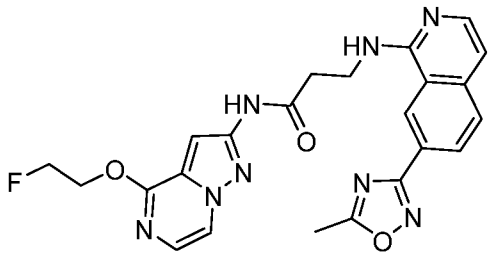
Example 67.2: A mixture of 4-(3-fluoropropoxy)-2-nitro-pyrazolo[1,5-*a*]pyrazine (170 mg, 708 umol, 1.00 eq) and palladium on activated carbon (17.0 mg, 10% purity, wet) in ethyl acetate (10.0 mL) was stirred at 25 °C for 2 h under hydrogen atmosphere (15 Psi). After the reaction was completed, the mixture was filtered and filtrate was concentrated to afford 4-(3-fluoropropoxy)pyrazolo[1,5-*a*]pyrazin-2-amine (140 mg, 666 umol, 94% yield) as yellow oil. ^{1}H NMR (400 MHz, Chloroform-d): δ 7.76 (d, J = 4.8 Hz, 1H), 7.18 (d, J = 4.4 Hz, 1H), 5.98 (s, 1H), 4.71 (t, J = 5.6 Hz, 1H), 4.62-4.57 (m, 3H), 2.31-2.17 (m, 2H).

Example 67.3: A mixture of 3-((7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl)amino)propanoic acid B2 (50.0 mg, 167 umol, 1.00 eq), propylphosphonicanhydride (213 mg, 335 umol, 50% in DMF, 2.00 eq) and 4-(3-fluoropropoxy)pyrazolo[1,5-*a*]pyrazin-2-amine (38.8 mg, 184 umol, 1.10 eq) in DMF (0.500 mL) was stirred at 40 °C for 2 h. After the reaction was completed, the mixture was poured into saturated sodium bicarbonate aqueous solution (6 mL) and extracted with ethylacetate (3 × 4 mL). The combined organic layers were concentrated to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge 150*25mm* 5um; mobile phase: [water(10mM NH_4HCO_3)-ACN]; B%: 42%-72%,10 min) and lyophilized to afford *N*-(4-(3-fluoropropoxy)pyrazolo[1,5-

a]pyrazin-2-yl)-3-((7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl)amino)-propanamide (42.53 mg, 85.8 umol, 51% yield, 99% purity) as a yellow solid. HPLC/MS m/z: 494.4 $[M+H]^+$, Rt (G): 0.90 min. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.04 (s, 1H), 8.89 (s, 1H), 8.23 (dd, J = 0.8, 4.8 Hz, 1H), 8.14 (dd, J = 1.6, 8.4 Hz, 1H), 8.04-7.96 (m, 2H), 7.85 (d, J = 8.4 Hz, 1H), 7.37 (d, J = 4.8 Hz, 1H), 7.06 (s, 1H), 6.97 (d, J = 5.6 Hz, 1H), 4.69 (t, J = 6.0 Hz, 1H), 4.57 (t, J = 6.0 Hz, 1H), 4.54 (t, J = 6.0 Hz, 2H), 3.84-3.77 (m, 2H), 2.83 (t, J = 6.8 Hz, 2H), 2.69 (s, 3H), 2.22 (quin, J = 6.0 Hz, 1H), 2.16 (quin, J = 6.0 Hz, 1H).

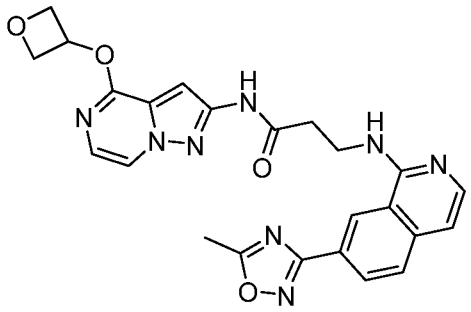
The following examples were prepared by an analogous procedure.

Example 68: N-(4-(2-fluoroethoxy)pyrazolo[1,5-a]pyrazin-2-yl)-3-((7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl)amino)propanamide



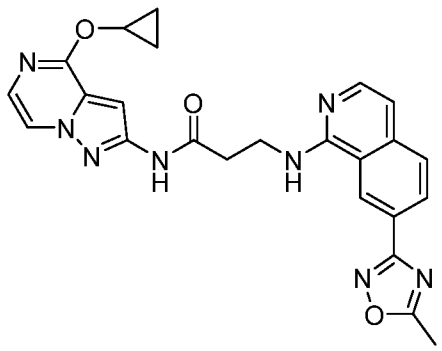
White solid, 41.12 mg, 77.1 umol, 98% purity, formate salt.
HPLC/MS m/z: 477.2 $[M+H]^+$, Rt (E): 0.80 min. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.06 (s, 1H), 8.89 (s, 1H), 8.26 (d, J = 4.8 Hz, 1H), 8.17 (s, 1H), 8.14 (dd, J = 1.2, 8.4 Hz, 1H), 8.04-7.92 (m, 2H), 7.85 (d, J = 8.4 Hz, 1H), 7.38 (d, J = 4.8 Hz, 1H), 7.07 (s, 1H), 6.97 (d, J = 6.0 Hz, 1H), 4.92-4.85 (m, 1H), 4.81-4.70 (m, 2H), 4.68-4.63 (m, 1H), 3.84-3.77 (m, 2H), 2.83 (br t, J = 6.8 Hz, 2H), 2.69 (s, 3H).

Example 69: 3-((7-(5-Methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl)amino)-N-(4-(oxetan-3-yloxy)pyrazolo[1,5-a]pyrazin-2-yl)propanamide



White solid, 3.29 mg, 6.70 umol, 99% purity. HPLC/MS m/z: 487.4 $[M+H]^+$, Rt (G): 0.86 min. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.07 (s, 1H), 8.90 (br s, 1H), 8.30-8.24 (m, 1H), 8.19-8.10 (m, 1H), 8.04-7.95 (m, 2H), 7.92-7.81 (m, 1H), 7.33 (d, J = 4.8 Hz, 1H), 7.12 (s, 1H), 7.04-6.91 (m, 1H), 5.78-5.68 (m, 1H), 4.97-4.91 (m, 2H), 4.70-4.65 (m, 2H), 3.85-3.79 (m, 2H), 2.87-2.82 (m, 2H), 2.70 (s, 3H).

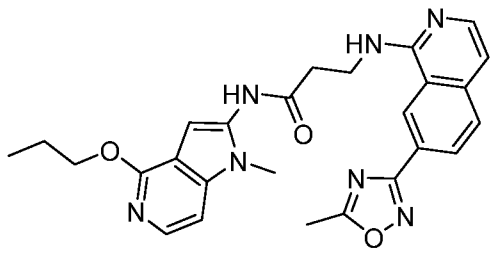
Example 70: N-(4-cyclopropoxypyrazolo[1,5-a]pyrazin-2-yl)-3-((7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl)amino)propanamide



4-(Cyclopropoxy)pyrazolo[1,5-a]pyrazin-2-amine (20.00 mg, 0.1052 mmol), 3-[[7-(5-methyl-1,2,4-oxadiazol-3-yl)-1-isoquinolyl]amino]propanoic acid B2 (34.50 mg, 0.1157 mmol), EDC (40.32 mg, 0.2103 mmol), HOBt (32.21 mg, 0.2103 mmol) and DIPEA (0.04 mL, 0.2103 mmol) were mixed in anhydrous DMF (0.53 mL, 0.2000 M) under argon at ambient temperature. The reaction mixture was heated to 70 °C for 24 h. The crude reaction mixture was directly purified by prep-HPLC (AccqPrep, focused gradient, 34-44% MeOH in water, pH3) to give N-[4-(cyclopropoxy)pyrazolo[1,5-a]pyrazin-2-yl]-3-[[7-(5-methyl-1,2,4-oxadiazol-3-yl)-1-isoquinolyl]amino]propanamide (5.3 mg, 10%, 0.0109 mmol) as an off-white solid. HPLC/MS m/z: 471.189 $[M+H]^+$, Rt (Z): 2.19 min. ^{1}H NMR (600 MHz, DMSO-d_6): δ

11.04 (s, 1H), 8.88 (d, *J* = 1.6 Hz, 1H), 8.26 (dd, *J* = 4.7, 1.0 Hz, 1H), 8.14 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.96-8.01 (m, 2H), 7.85 (d, *J* = 8.5 Hz, 1H), 7.41 (d, *J* = 4.7 Hz, 1H), 6.98 (s, 1H), 6.96 (d, *J* = 5.7 Hz, 1H), 4.45 (tt, *J* = 6.2, 3.3 Hz, 1H), 3.77-3.83 (m, 2H), 2.82 (t, *J* = 7.0 Hz, 2H), 2.69 (s, 3H), 0.78-0.86 (m, 4H).

Example 71: 3-((7-(5-Methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl)amino)-N-(1-methyl-4-propoxy-1H-pyrrolo[3,2-c]pyridin-2-yl)propanamide



Example 71.1: To a mixture of methyl 4-chloro-1*H*-pyrrolo[3,2-*c*]pyridine-2-carboxylate (900 mg, 4.27 mmol, 1.00 eq) and cesium carbonate (2.78 g, 8.55 mmol, 2.00 eq) in *N*,*N*-dimethylacetamide (9.00 mL) was added iodomethane (728 mg, 5.13 mmol, 1.20 *eq*). The mixture was stirred at 25 °C for 2 h. After the reaction was completed, the mixture was quenched with saturated ammonium chloride aqueous solution (30 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were concentrated to give a residue. The residue was triturated with methyl tert-butyl ether (20 mL) for 10 min. The suspension was filtered, and filter cake was dried to afford methyl 4-chloro-1-methyl-1*H*-pyrrolo[3,2-*c*]pyridine-2-carboxylate (930 mg, 4.14 mmol, 96% yield) as a yellow solid. ^{1}H NMR (400 MHz, Chloroform-d): δ 8.18 (d, *J* = 6.0 Hz, 1H), 7.41 (s, 1H), 7.24 (d, *J* = 6.0 Hz, 1H), 4.09 (s, 3H), 3.96 (s, 3H).

Example 71.2: To a suspension of methyl 4-chloro-1-methyl-1*H*-pyrrolo[3,2-*c*]pyridine-2-carboxylate (700 mg, 3.12 mmol, 1.00 *eq*) in acetic acid (7.00 mL) was added ammonium acetate (480 mg, 6.23 mmol, 2.00 *eq*). The mixture was stirred at 120 °C for 12 h. After the reaction was completed, the mixture was concentrated to give a residue. The residue was triturated with water (5 mL) at 25 °C for 0.5 h. The suspension was filtered, and filter cake was dried to afford methyl 4-hydroxy-1-methyl-1*H*-pyrrolo[3,2-*c*]pyridine-2-carboxylate (600 mg, 2.91 mmol, 93% yield) as a brown solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.02 (br s, 1H), 7.24 (s, 1H), 7.22-7.17 (m, 1H), 6.58 (d, *J* = 7.2 Hz, 1H), 3.93 (s, 3H), 3.81 (s, 3H).

Example 71.3: A mixture of methyl 4-hydroxy-1-methyl-1*H*-pyrrolo[3,2-*c*]pyridine-2-carboxylate (700 mg, 3.39 mmol, 1.00 *eq*), silver carbonate (1.87 g, 6.79 mmol, 2.00 *eq*) and 1-iodopropane (866 mg, 5.09 mmol, 1.50 *eq*) in chloroform (7.00 mL) was stirred at 65 °C for 1 h. After the reaction was completed, the mixture was filtered and filtrate was concentrated to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 15/1 to 4/1) to afford methyl 1-methyl- 4-propoxy-1*H*-pyrrolo[3,2-*c*]pyridine-2-carboxylate (500 mg, 2.01 mmol, 59% yield) as a white solid. ^{1}H NMR (400 MHz, Chloroform-d): δ 7.92 (d, J = 6.4 Hz, 1H), 7.42 (s, 1H), 6.89 (d, J = 6.0 Hz, 1H), 4.42 (t, J = 6.8 Hz, 2H), 4.04 (s, 3H), 3.92 (s, 3H), 1.88 (sext, J = 7.2 Hz, 2H), 1.08 (t, J = 7.6 Hz, 3H).

Example 71.4: A mixture of methyl 1-methyl- 4-propoxy-1*H*-pyrrolo[3,2-*c*]pyridine-2-carboxylate (480 mg, 1.93 mmol, 1.00 *eq*) and lithium hydroxide monohydrate (163 mg, 3.87 mmol, 2.00 *eq*) in a mixture solvent of tetrahydrofuran (200 uL) and water (200 uL) was stirred at 30 °C for 12 h. The mixture was concentrated to remove tetrahydrofuran and diluted with water (10 mL). The pH of the aqueous phase was adjusted to around 4 by adding hydrochloric acid (1 M). A white solid was precipitated and filtered. The filter cake was dried to afford 1-methyl-4-propoxy-1*H*-pyrrolo[3,2-*c*] pyridine-2-carboxylic acid (400 mg, 1.71 mmol, 88% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.31 (s, 1H), 7.87 (d, J = 6.0 Hz, 1H), 7.29-7.14 (m, 2H), 4.38 (br t, J = 6.8 Hz, 2H), 4.00 (s, 3H), 1.84-1.71 (m, 2H), 1.00 (t, J = 7.2 Hz, 3H).

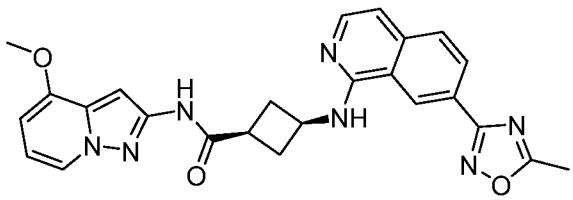
Example 71.5: A mixture of 1-methyl-4-propoxy-1*H*-pyrrolo[3,2-*c*]pyridine-2-carboxylic acid (200 mg, 854 umol, 1.00 *eq*), diphenylphosphoryl azide (352 mg, 1.28 mmol, 1.50 *eq*) and triethylamine (259 mg, 2.56 mmol, 3.00 *eq*) in tert-butanol (2.00 mL) was stirred at 100 °C for 12 h. The mixture was concentrated to give a residue and purified by flash silica gel chromatography (Eluent: 0-45% ethyl acetate/petroleum ether, gradient 25 mL/min) to afford *tert*-butyl (1-methyl-4-propoxy-1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)carbamate (140 mg, 458 umol, 53% yield) as colorless oil. ^{1}H NMR (400 MHz, Chloroform-d): δ 7.83 (d, J = 6.0 Hz, 1H), 6.81 (d, J = 6.0 Hz, 1H), 6.47 (s, 1H), 6.33-6.17 (m, 1H), 4.39 (t, J = 6.8 Hz, 2H), 3.61 (s, 3H), 1.85 (sext, J = 7.2 Hz, 2H), 1.52 (s, 9H), 1.06 (t, J = 7.2 Hz, 3H).

Example 71.6: A mixture of *tert*-butyl (1-methyl-4-propoxy-1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)carbamate (140 mg, 458 umol, 1.00 *eq*) in hydrochloric acid/ethyl acetate (4 M, 500 uL) was stirred at 25 °C for 1 h. The mixture was concentrated to afford 1-

methyl-4-propoxy-pyrrolo[3,2-*c*]pyridin-2-amine (110 mg, crude, hydrochloride) as a white solid. HPLC/MS m/z: 206.2 $[M+H]^+$, Rt (F): 0.75 min.

Example 71.7: A mixture of 3-((7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl)amino)propanoic acid B2 (85.0 mg, 285 umol, 1.00 *eq*), 1-methyl-4-propoxy-pyrrolo[3,2-*c*]pyridin-2-amine (58.5 mg, 285 umol, 1.00 *eq*) and propylphosphonic anhydride (181 mg, 285 umol, 169 uL, 50% in DMF, 1.00 *eq*) in DMF (2.00 mL) was stirred at 30 °C for 2 h. After the reaction was completed, the mixture was poured into saturated aqueous sodium bicarbonate solution (7 mL) and extracted with ethyl acetate (3 × 4 mL). The combined organic layers were concentrated to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Gemini-NX C18 75*30mm*3um; mobile phase: [water(10mM NH_4HCO_3) -ACN]; B%: 32%-62%, 8 min) and lyophilized to afford 3-((7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl)amino)-*N*-(1-methyl-4-propoxy-1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)propanamide (18.75 mg, 38.2 umol, 13% yield, 99% purity) as a pink solid. HPLC/MS m/z: 486.2 $[M+H]^+$, Rt (E): 0.74 min. ^1H NMR (400 MHz, DMSO-d_6): δ 10.01 (s, 1H), 8.92 (s, 1H), 8.16 (dd, J = 1.2, 8.4 Hz, 1H), 8.07-7.97 (m, 2H), 7.86 (d, J = 8.4 Hz, 1H), 7.69 (d, J = 6.0 Hz, 1H), 7.03 (d, J = 5.6 Hz, 1H), 6.98 (d, J = 5.6 Hz, 1H), 6.38 (s, 1H), 4.31 (t, J = 6.8 Hz, 2H), 3.87-3.79 (m, 2H), 3.55 (s, 3H), 2.84 (br t, J = 6.8 Hz, 2H), 2.70 (s, 3H), 1.75 (sext, J = 7.2 Hz, 2H), 0.98 (t, J = 7.2 Hz, 3H).

Example 72: (*cis*)-*N*-(4-methoxypyrazolo[1,5-*a*]pyridin-2-yl)-3-((7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl)amino)cyclobutanecarboxamide



Example 72.1: To a solution of acetonitrile (769 mg, 18.7 mmol, 4.40 eq) in tetrahydrofuran (10 mL) was added *n*-butyllithium (2.50 M, 6.81 mL, 17.0 mmol, 4.00 eq) dropwise at -78 °C. The mixture was stirred at -78°C for 0.2 h. To the mixture was added a solution of 2-bromo-3-methoxy-pyridine (0.800 g, 4.25 mmol, 1.00 eq) in tetrahydrofuran (3 mL). The mixture was stirred at -78 °C for 1 h. Then the mixture was warmed to 0 °C and stirred at 0 °C for 3 h. The mixture was diluted with saturated aqueous ammonium chloride solution (20 mL) and extracted with ethyl

acetate (3 × 20 mL). The combined organic layers were washed with brine (3 × 20 mL), dried over anhydrous sodium sulfate, filtered, and 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) and prep-HPLC (column: Phenomenex Gemini-NX C18 75*30mm*3um; mobile phase: [water(10mM NH_4HCO_3)-ACN]; B%: 6%-36%, 8 min) to afford 2-(3-methoxypyridin-2-yl)acetonitrile (0.300 g, 2.02 mmol, 47% yield) as a yellow solid. ^{1}H NMR (400 MHz, Chloroform-d): δ 8.19 (dd, J = 1.3, 4.7 Hz, 1H), 7.30-7.27 (m, 1H), 7.23-7.18 (m, 1H), 3.92 (s, 2H), 3.91 (s, 3H).

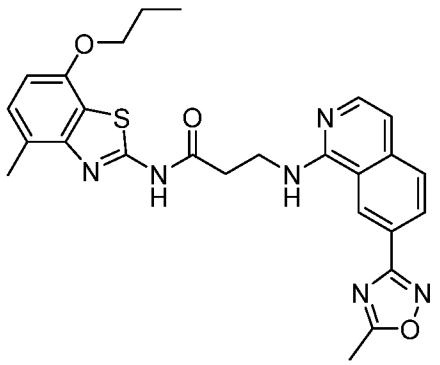
Example 72.2: To a solution of *O*-(mesitylsulfonyl)hydroxylamine [Example 64.3] (0.140 M, 14.5 mL, 2.03 mmol, 1.20 *eq*) in dichloromethane (15 mL) was added 2-(3-methoxy-2-pyridyl)acetonitrile (0.250 g, 1.69 mmol, 1.00 *eq*). The mixture was stirred at 20 °C for 12 h. The mixture was concentrated to afford 1-amino-2-(cyanomethyl)-3-methoxypyridin-1-ium 2,4,6-trimethylbenzenesulfonate (0.600 g, crude) as a brown oil. It was used for next step directly. HPLC/MS m/z: 164.0 $[M+H]^+$, Rt (G): 0.67 min.

Example 72.3: To a solution of 1-amino-2-(cyanomethyl)-3-methoxypyridin-1-ium 2,4,6-trimethylbenzenesulfonate (0.600 g, 1.65 mmol, 1.00 *eq*) in methanol (10 mL) was added potassium carbonate (570 mg, 4.13 mmol, 2.50 *eq*). The mixture was stirred at 20 °C for 12 h. The mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 5/1 to 1/1) to afford 4-methoxypyrazolo[1,5-*a*]pyridin-2-amine (75.0 mg, 460 umol, 28% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.89-7.87 (m, 1H), 6.47-6.42 (m, 2H), 5.62 (d, J = 0.6 Hz, 1H), 5.17 (s, 2H), 3.85 (s, 3H).

Example 72.4: To a solution of (*cis*)-3-((7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl)amino)cyclobutanecarboxylic acid B3 (139 mg, 429 umol, 1.00 *eq*), *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N'*,*N'*-tetramethyluronium hexafluorophosphate and diisopropylethylamine (166 mg, 1.29 mmol, 3.00 *eq*) in dimethyl formamide (2 mL) was added 4-methoxypyrazolo[1,5-*a*]pyridin-2-amine (70.0 mg, 429 umol, 1.00 *eq*). The mixture was stirred at 20 °C for 12 h. The mixture was filtered. The filtrate was purified by prep-HPLC (column: Unisil 3-100 C18 Ultra 150*50mm*3 um; mobile phase: [water(0.225% formic acid)-ACN]; B%: 25%-45%, 10 min), prep-HPLC (column: Phenomenex Gemini-NX C18 75*30mm*3um; mobile phase: [water(10 mM NH_4HCO_3)-ACN]; B%: 30%-60%, 8 min) and lyophilized to afford (*cis*)-*N*-(4-

methoxypyrazolo[1,5-*a*]pyridin-2-yl)-3-((7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl)amino)cyclobutanecarboxamide (29.0 mg, 61.2 umol, 14% yield, 99% purity) as a pink solid. HPLC/MS m/z: 470.3 $[M+H]^+$, Rt (G): 1.00 min. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.72 (s, 1H), 9.04 (s, 1H), 8.19-8.06 (m, 3H), 7.96 (d, J = 5.8 Hz, 1H), 7.83 (d, J = 8.5 Hz, 1H), 6.96 (d, J = 5.8 Hz, 1H), 6.89 (s, 1H), 6.77-6.70 (m, 1H), 6.62 (d, J = 7.8 Hz, 1H), 4.75-4.58 (m, 1H), 3.92 (s, 3H), 3.12-2.98 (m, 1H), 2.71 (s, 3H), 2.60-2.53 (m, 2H), 2.48-2.36 (m, 2H).

Example 73: 3-((7-(5-Methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl)amino)-N-(4-methyl-7-propoxybenzo[d]thiazol-2-yl)propanamide

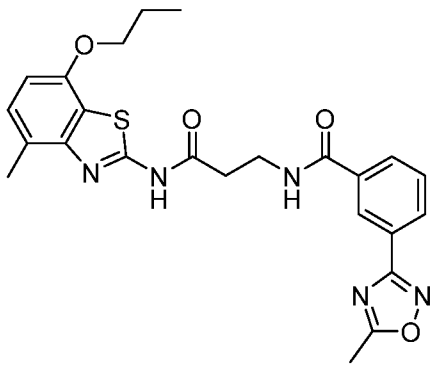


Example 73.1: 2-Amino-4-methyl-1,3-benzothiazol-7-ol (100.00 mg, 0.5548 mmol) and K_2CO_3 (153.36 mg, 1.1097 mmol) were mixed in anhydrous DMF (0.55 mL, 1 M) at RT under argon. 1-Iodopropane (0.05 mL, 0.5548 mmol) was added, and the reaction mixture was stirred for 24 h. The reaction mixture was mixed with water (2 mL), acidified with 1M HCl to pH 6 and diluted with MeOH (20 mL), filtered through a 2 g SCX2 column. The product was released with 2M ammonia in MeOH to give 4-methyl-7-propoxy-1,3-benzothiazol-2-amine (110 mg, 89%, 0.4948 mmol) as an off-white solid, which was used for the next step without further purification. HPLC/MS m/z: 223.091 $[M+H]^+$, Rt (Z): 2.12 min. ^{1}H NMR (600 MHz, DMSO-d_6): δ 7.45 (s, 2H), 6.95 (d, J = 8.1 Hz, 1H), 6.55 (d, J = 8.1 Hz, 1H), 4.00 (t, J = 6.5 Hz, 2H), 2.33 (s, 3H), 1.68-1.76 (m, 2H), 0.97 (t, J = 7.4 Hz, 3H).

Example 73.2: 4-Methyl-7-propoxy-1,3-benzothiazol-2-amine (39.13 mg, 0.1760 mmol) and 3-[[7-(5-methyl-1,2,4-oxadiazol-3-yl)-1-isoquinolyl]amino]propanoic acid B2 (50.00 mg, 0.1676 mmol) were mixed in anhydrous DMF (0.34 mL, 0.5000 M) under argon at ambient temperature. 1-Propanephosphonic anhydride (50% in

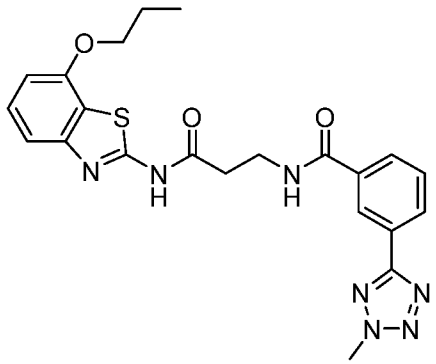
DMF) (0.20 mL, 0.3352 mmol) was added, and the reaction mixture was stirred for 18 h. Purification by prep-HPLC afforded 3-[[7-(5-methyl-1,2,4-oxadiazol-3-yl)-1-isoquinolyl]amino]-N-(4-methyl-7-propoxy-1,3-benzothiazol-2-yl)propanamide (45 mg, 53%, 0.0890 mmol) as an off-white solid. HPLC/MS m/z: 503.187[M+H]$^+$, Rt (Z): 2.68 min. ^{1}H NMR (600 MHz, DMSO-d_6): δ 12.47 (br s, 1H), 8.87-8.91 (m, 1H), 8.15 (dd, *J* = 8.5, 1.5 Hz, 1H), 8.03 (t, *J* = 5.4 Hz, 1H), 7.98 (d, *J* = 5.7 Hz, 1H), 7.85 (d, *J* = 8.5 Hz, 1H), 7.16 (dd, *J* = 8.0, 1.0 Hz, 1H), 6.97 (dd, *J* = 5.9, 0.8 Hz, 1H), 6.79 (d, *J* = 8.1 Hz, 1H), 4.08 (t, *J* = 6.4 Hz, 2H), 3.81-3.87 (m, 2H), 2.92 (t, *J* = 6.8 Hz, 2H), 2.69 (s, 3H), 2.47 (s, 3H), 1.74-1.81 (m, 2H), 1.01 (t, *J* = 7.4 Hz, 3H).

Example 74: 3-(5-Methyl-1,2,4-oxadiazol-3-yl)-N-(3-((4-methyl-7-propoxybenzo[d]thiazol-2-yl)amino)-3-oxopropyl)benzamide



Prepared in an analogous procedure to Example 73Example 74 using B1. Off-white solid, 2.2 mg, 0.0045 mmol. HPLC/MS m/z: 480.170 [M+H]$^+$, Rt (Z): 3.01 min. ^{1}H NMR (600 MHz, Chloroform-d): δ 9.45 (s, 1H), 8.41-8.44 (m, 1H), 8.15-8.20 (m, 1H), 7.96 (ddd, *J* = 7.8, 1.8, 1.2 Hz, 1H), 7.55 (t, *J* = 7.8 Hz, 1H), 7.13 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.06 (t, *J* = 6.2 Hz, 1H), 6.67 (d, *J* = 8.0 Hz, 1H), 4.07 (t, *J* = 6.4 Hz, 2H), 3.90 (q, *J* = 5.9 Hz, 2H), 2.90 (t, *J* = 5.7 Hz, 2H), 2.65 (s, 3H), 2.52 (s, 3H), 1.81-1.89 (m, 2H), 1.07 (t, *J* = 7.4 Hz, 3H).

Example 75: 3-(2-Methyl-2H-tetrazol-5-yl)-N-(3-oxo-3-((7-propoxybenzo[d]thiazol-2-yl)amino)propyl)benzamide



Example 75.1: To methyl 3-aminopropanoate hydrochloride (100.00 mg, 0.7164 mmol), 3-(2-methyl-2H-tetrazol-5-yl)-benzoic acid (146.29 mg, 0.7164 mmol) in DMF (4.21 mL) was added DIPEA (0.50 mL, 2.8657 mmol) followed by HATU (252.83 mg, 1.0747 mmol). The obtained yellow solution was stirred for 18 h. The reaction mixture was diluted with EtOAc (150 mL) and washed with water (120 mL). The water was extracted with fresh EtOAc (100 mL). The organics were combined and washed with aq. sat. bicarb. (150 mL), and brine (200 mL) before drying over $MgSO_4$. After filtering and concentrating *in vacuo* methyl 3-[[3-(2-methyltetrazol-5-yl)benzoyl]amino]propanoate (170 mg, 82%, 0.5876 mmol) was obtained as a light-yellow film that was used without further purification. HPLC/MS m/z: 290.13 $[M+H]^+$, Rt (P): 1.15 min.

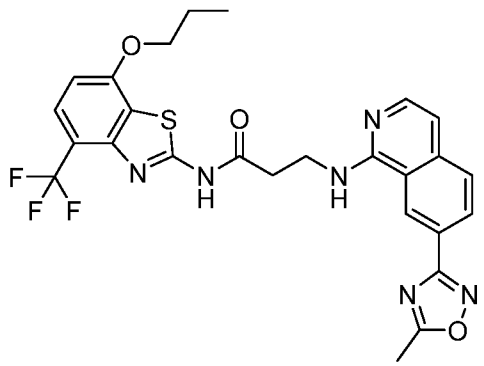
Example 75.2: To methyl 3-[[3-(2-methyltetrazol-5-yl)benzoyl]amino]propanoate (170.00 mg, 0.5876 mmol) in THF (2.90 mL) was added water (2.90 mL) followed by lithium hydroxide monohydrate (98.63 mg, 2.3506 mmol). After stirring for 45 min water (25 mL) was added and the THF removed *in vacuo*. The solution was acidified to pH 3 with 1M citric acid solution and extracted with EtOAc (2 x 60 mL). The organics were combined, washed with brine (60 mL) and dried over $MgSO_4$ to afford 3-[[3-(2-methyltetrazol-5-yl)benzoyl]amino]propanoic acid (137 mg, 85%, 0.4977 mmol) as a white solid. HPLC/MS m/z: 276.12 $[M+H]^+$, Rt (P): 1.03 min.

Example 75.3: 2-Amino-1,3-benzothiazol-7-ol (79.00 mg, 0.4753 mmol) and K_2CO_3 (78.83 mg, 0.5704 mmol) were dissolved in dry DMF (3.17 mL), the mixture was stirred during 30 min at RT. At 0 °C 1-iodopropane (0.05 mL, 0.4753 mmol) was then added. The mixture was stirred during 1 h 30 min at 0 °C. The ice bath was then removed, and the reaction mixture stirred for 2 d. Additional K_2CO_3 (24 mg) was added and stirred during 20 min. At 0 °C 1-iodopropane (14 mL) was added. The mixture was stirred during 1 h at 0 °C then 30 min at RT. Some drops of

water were added to the reaction mixture. Purification by reverse phase flash chromatography (Eluent: 10-80% MeOH/H_2O + 0.1% formic acid) followed by ion exchange SCX-2 chromatography eluting with 2M NH_3 in MeOH afforded 7-propoxy-1,3-benzothiazol-2-amine (75.9 mg, 77%, 0.3644 mmol) as a white amorphous solid. HPLC/MS m/z: 209.072 $[M+H]^+$, Rt (R): 1.02 min.

Example 75.4: To a mixture of 7-propoxy-1,3-benzothiazol-2-amine (15.13 mg, 0.0727 mmol), 3-[[3-(2-methyltetrazol-5-yl)benzoyl]amino]propanoic acid (20.00 mg, 0.0727 mmol), HOBt (22.25 mg, 0.1453 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (27.86 mg, 0.1453 mmol) was added under argon atmosphere DMF (0.36 mL).The resulting solution was stirred at 70 °C overnight. The reaction mixture was cooled to ambient temperature, diluted with DMSO and directly purified by prep-HPLC (AccqPrep, focused gradient, ACN in water, pH3) to give 3-(2-methyltetrazol-5-yl)-N-[3-oxo-3-[(7-propoxy-1,3-benzothiazol-2-yl)amino]propyl]benzamide (24 mg, 71%, 0.0512 mmol) as an off-white solid. HPLC/MS m/z: 466.166 $[M+H]^+$, Rt (Z): 2.81 min. ^1H NMR (600 MHz, DMSO-d_6): δ 12.41 (s, 1H), 8.88 (t, *J* = 5.5 Hz, 1H), 8.52-8.56 (m, 1H), 8.16-8.21 (m, 1H), 7.97-8.02 (m, 1H), 7.66 (t, *J* = 7.8 Hz, 1H), 7.32-7.38 (m, 2H), 6.89 (dd, *J* = 7.6, 1.2 Hz, 1H), 4.44 (s, 3H), 4.12 (t, *J* = 6.4 Hz, 2H), 3.60-3.66 (m, 2H), 2.83 (t, *J* = 6.8 Hz, 2H), 1.75-1.83 (m, 2H), 1.02 (t, J = 7.4 Hz, 3H).

Example 76: 3-((7-(5-Methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl)amino)-N-(7-propoxy-4-(trifluoromethyl)benzo[d]thiazol-2-yl)propanamide



Example 76.1: 3-Nitro-4-(trifluoromethyl)phenol (410.00 mg, 1.9796 mmol), potassium carbonate (300.96 mg, 2.1776 mmol) and 1-iodopropane (0.21 mL, 2.1776 mmol) were mixed in anhydrous acetone (3.96 mL, 0.5000 M) in a

microwave vial under argon. The reaction mixture was heated at 100 °C for 2 h under microwave irradiation. Purified by NP flash chromatography (Eluent: 0-10% EtOAc in cyclohexane) to give 2-nitro-4-propoxy-1-(trifluoromethyl)benzene (463 mg, 94%, 1.858 mmol) as an off-white, crystalline solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.92 (d, *J* = 8.9 Hz, 1H), 7.71 (d, *J* = 2.6 Hz, 1H), 7.41 (ddd, *J* = 8.9, 2.6, 0.9 Hz, 1H), 4.11 (t, *J* = 6.5 Hz, 2H), 1.71-1.81 (m, 2H), 0.98 (t, *J* = 7.4 Hz, 3H).

Example 76.2: 2-Nitro-4-propoxy-1-(trifluoromethyl)benzene (455.00 mg, 1.8259 mmol) and zinc (596.89 mg, 9.1296 mmol) were mixed under argon at 0 °C. Acetic acid (5.00 mL, 0.3700 M) was added and the reaction mixture was stirred at ambient temperature for 3 h. The reaction mixture was diluted with EtOAc (10 mL) directly loaded onto silica gel. The crude was directly purified by NP chromatography (0-20% EtOAc in cyclohexane) to give 5-propoxy-2-(trifluoromethyl)aniline (272 mg, 68%, 1.2409 mmol) as a clear oil. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.20 (d, *J* = 8.8 Hz, 1H), 6.36 (d, *J* = 2.4 Hz, 1H), 6.19 (dd, *J* = 8.6, 2.4 Hz, 1H), 5.48 (s, 2H), 3.87 (t, *J* = 6.6 Hz, 2H), 1.66-1.75 (m, 2H), 0.95 (t, *J* = 7.4 Hz, 3H).

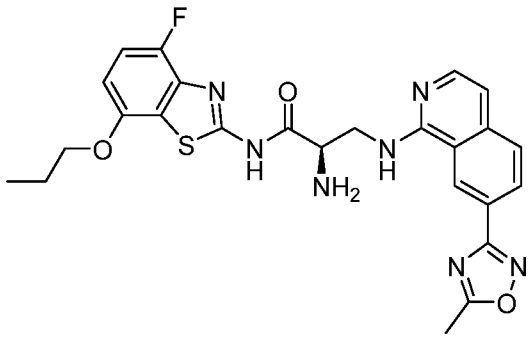
Example 76.3: To a suspension of potassium thiocyanate (129.23 mg, 1.3298 mmol) in acetone (2.00 mL) was added dropwise at ambient temperature a solution of acetyl chloride (0.09 mL, 1.3298 mmol) in acetone (2.00 mL). The mixture was stirred for 15 min at 50 °C. Then, a solution of 5-propoxy-2-(trifluoromethyl)aniline (265.00 mg, 1.2089 mmol) in acetone (2.00 mL) was added and the reaction mixture was continued to stir for 15 min at 50 °C. The reaction mixture was continued to stir for another 15 min before being removed from the heating. Water (50 mL) was added, and the precipitated intermediate was filtered off, washed with water and dried under reduced pressure. The solid was dissolved in MeOH (4.00 mL) at ambient temperature. Potassium carbonate (339.04 mg, 2.4179 mmol) was added, and the reaction mixture was stirred at ambient temperature for 1 h. Water (50 mL) was added. The precipitated product was filtered off, washed with water and dried under reduced pressure to give [5-propoxy-2-(trifluoromethyl)phenyl]thiourea (228 mg, 68%, 0.8193 mmol) as an off-white solid, which was used in the next reaction without further purification. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.18 (s, 1H), 7.86 (br s, 1H), 7.59 (d, *J* = 8.8 Hz, 1H), 7.28 (br s, 1H), 7.07 (d, *J* = 2.5 Hz, 1H), 6.97 (dd, *J* = 8.6, 2.6 Hz, 1H), 3.99 (t, *J* = 6.5 Hz, 2H), 1.69-1.80 (m, 2H), 0.97 (t, *J* = 7.4 Hz, 3H).

Example 76.4: To a solution of [5-propoxy-2-(trifluoromethyl)phenyl]thiourea (220.00 mg, 0.7905 mmol) in AcOH (3.95 mL) kept at ambient temperature under argon was added a solution of bromine (0.04 mL, 0.7905 mmol) in AcOH (3.95 mL) over 15

min. The reaction mixture was continued to stir for 1 h. The reaction mixture was concentrated under reduced pressure. The crude was dissolved in MeOH filtered through an SCX2 ion exchange column. The product was released with 2M ammonia in MeOH to give 7-propoxy-4-(trifluoromethyl)-1,3-benzothiazol-2-amine (185 mg, 85%, 0.6696 mmol) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.98 (s, 2H), 7.48 (d, *J* = 8.7 Hz, 1H), 6.77 (d, *J* = 8.5 Hz, 1H), 4.13 (t, *J* = 6.5 Hz, 2H), 1.71-1.81 (m, 2H), 0.98 (t, *J* = 7.4 Hz, 3H).

Example 76.5: 7-Propoxy-4-(trifluoromethyl)-1,3-benzothiazol-2-amine B2 (27.79 mg, 0.1006 mmol) and 3-[[7-(5-methyl-1,2,4-oxadiazol-3-yl)-1-isoquinolyl]amino]propanoic acid (30.00 mg, 0.1006 mmol) were mixed in anhydrous DMF (0.20 mL, 0.5000 M) under argon at ambient temperature. 1-Propanephosphonic anhydride (50% in DMF) (0.12 mL, 0.2011 mmol) and TEA (0.04 mL, 0.3017 mmol) were added successively, and the reaction mixture was stirred for 30 min. The reaction mixture was heated to 60 °C for 1 h then at 80 °C for 1 h. 2 x 1-Propanephosphonic anhydride (50% in DMF) (0.12 mL, 0.2011 mmol) were added, and the reaction was continued to stir at 80 °C for 1 h. The reaction mixture was cooled to ambient temperature, quenched with a few drops of water, diluted with DMSO and directly purified by prep HPLC (AccqPrep, focused gradient, 35.2-45.2% ACN in water, pH3). Fractions containing product were filtered through a 2 g SCX2 ion exchange column. The product was released with 2M ammonia in MeOH to give 3-((7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl)amino)-N-(7-propoxy-4-(trifluoromethyl)benzo[d]thiazol-2-yl)propanamide (6.8 mg, 12%, 0.0121 mmol) as an off-white solid. HPLC/MS m/z: 557.158 $[M+H]^+$, Rt (Z): 2.76 min. ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.90 (s, 1H), 8.89 (s, 1H), 8.16 (d, *J* = 8.4 Hz, 1H), 8.04 (br s, 1H), 7.97 (d, *J* = 5.8 Hz, 1H), 7.86 (d, *J* = 8.5 Hz, 1H), 7.73 (d, *J* = 8.5 Hz, 1H), 7.03 (d, *J* = 8.5 Hz, 1H), 6.98 (d, *J* = 5.8 Hz, 1H), 4.22 (t, *J* = 6.5 Hz, 2H), 3.81-3.89 (m, 2H), 2.96 (t, *J* = 6.8 Hz, 2H), 2.68 (s, 3H), 1.78-1.86 (m, 2H), 1.02 (t, *J* = 7.4 Hz, 3H).

Example 77: (R)-2-Amino-N-(4-fluoro-7-propoxybenzo[d]thiazol-2-yl)-3-((7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl)amino)propanamide



Example 77.1: To a solution of 4-fluoro-7-methoxy-1,3-benzothiazol-2-amine (1.00 g, 5.0449 mmol) in DCM (9.01 mL) at 0 °C was added dropwise a solution of BBr_3 in DCM (1M) (9.23 mL, 9.2322 mmol) and the mixture was allowed to reach RT and stirred overnight. MeOH was then added at 0 °C and this was stirred for an additional 10 min after which the solvent was evaporated *in vacuo*. The cycle dissolution/evaporation with MeOH was repeated two additional times to afford 2-amino-4-fluoro-1,3-benzothiazol-7-ol (929 mg, 100%, 5.0437 mmol) as a dark powder. The product was taken to the next step without further purification. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.00 (dd, *J* = 10.7, 8.8 Hz, 1H), 6.53 (dd, *J* = 8.8, 3.3 Hz, 1H).

Example 77.2: To a mixture of 2-amino-4-fluoro-1,3-benzothiazol-7-ol (838.00 mg, 4.5496 mmol) and cesium carbonate (2.98 g, 9.0993 mmol) in MeCN (11.00 mL, 0.3800 M) were successively added DMF (1.00 mL) and 1-bromopropane (454.59 uL, 5.0046 mmol). This was stirred at 65 °C for 2 h. The solvent was evaporated, the residue taken back in EtOAc and water, extracted with EtOAc, dried over $MgSO_4$ and evaporated. Purification by NP silica column chromatography (0-40% EtOAc in cyclohexane) afforded pure 4-fluoro-7-propoxy-1,3-benzothiazol-2-amine (503.8 mg, 49%, 2.2265 mmol). HPLC/MS m/z: 227.065 $[M+H]^+$, Rt (R): 1.25 min.

Example 77.3: Ethyl (2R)-3-amino-2-(benzyloxycarbonylamino)propanoate (367mg, 1.38 mmol), 5-methyl-3-(2-oxidoisoquinolin-2-ium-7-yl)-1,2,4-oxadiazole (345mg, 1.52 mmol), PyBroP (707 mg, 1.52 mmol), DIPEA (0.90 ml) and anhydrous DCM (2.8 mL, 0.50 M) in a microwave vial at RT under argon. The reaction mixture was heated at 60 °C by microwave irradiation for 1 h. Volatiles were removed, and the crude was purified by RP flash chromatography (30-60% MeOH in water). Fractions containing product were filtered through a 1 g SCX-2 ion exchange column. The product was released by 2 M ammonia in MeOH to give ethyl (2R)-2-(benzyloxycarbonylamino)-3-[[7-(5-methyl-1,2,4-oxadiazol-3-yl)-1-

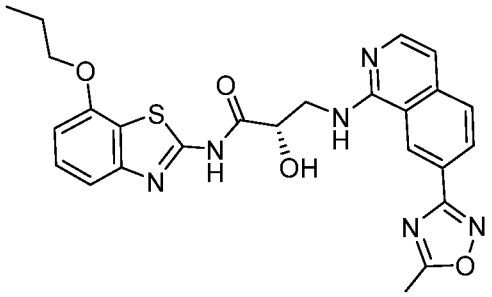
isoquinolyl]amino]propanoate (409 mg, 62%, 0.8601 mmol) as an off-white solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.84 (d, *J* = 1.7 Hz, 1H), 8.17 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.96 (d, *J* = 5.7 Hz, 1H), 7.92-7.83 (m, 3H), 7.35-7.24 (m, 5H), 7.01 (d, *J* = 5.7 Hz, 1H), 5.02 (s, 2H), 4.48 (q, *J* = 6.7 Hz, 1H), 4.01 (q, *J* = 7.1 Hz, 2H), 3.88 (t, *J* = 6.1 Hz, 2H), 2.70 (s, 3H), 1.04 (t, *J* = 7.1 Hz, 3H).

Example 77.4: Ethyl (2R)-2-(benzyloxycarbonylamino)-3-[[7-(5-methyl-1,2,4-oxadiazol-3-yl)-1-isoquinolyl]amino]propanoate (200.00 mg, 0.4206 mmol) was dissolved in THF (2.10 mL) at ambient temperature. EtOH (0.42 mL) and aqueous 2M NaOH (0.42 mL, 0.8412 mmol) were added and the reaction mixture was stirred at ambient temperature for 1 h. The reaction mixture was neutralized with aq. 2M HCl and concentrated under reduced pressure. The crude was directly purified by RP flash column chromatography (20-80% MeOH in water) to give (2R)-2-(benzyloxycarbonylamino)-3-[[7-(5-methyl-1,2,4-oxadiazol-3-yl)-1-isoquinolyl]amino]-propanoic acid (94 mg, 50%, 0.2101 mmol) as an off-white powder. ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.71 (s, 1H), 8.85 (d, *J* = 1.6 Hz, 1H), 8.17 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.97 (d, *J* = 5.7 Hz, 1H), 7.91 (t, *J* = 5.9 Hz, 1H), 7.88 (d, *J* = 8.5 Hz, 1H), 7.74 (d, *J* = 7.5 Hz, 1H), 7.40-7.17 (m, 5H), 7.01 (d, *J* = 5.7 Hz, 1H), 5.01 (s, 2H), 4.45 (td, *J* = 7.7, 5.1 Hz, 1H), 3.92 (dt, *J* = 13.5, 5.2 Hz, 1H), 3.79 (ddd, *J* = 13.6, 7.9, 5.9 Hz, 1H), 2.70 (s, 3H).

Example 77.5: (2R)-2-(Benzyloxycarbonylamino)-3-[[7-(5-methyl-1,2,4-oxadiazol-3-yl)-1-isoquinolyl]amino]propanoic acid (50.00 mg, 0.1117 mmol), 4-fluoro-7-propoxy-1,3-benzothiazol-2-amine (25.28 mg, 0.1117 mmol) and TEA (0.05 mL, 0.3352 mmol) were mixed in anhydrous DMF (0.22 mL, 0.5000 M) at ambient temperature under argon. 50% T3P in DMF (0.13 mL, 0.2235 mmol) was added and the reaction mixture was heated at 70 °C (in a preheated heating block) for 2.5 h. The reaction mixture was cooled to room temperature, quenched with water. Purification by NP column chromatography (Eluent: 0-100% EtOAc in cyclohexane) afforded benzyl N-[(1R)-2-[(4-fluoro-7-propoxy-1,3-benzothiazol-2-yl)amino]-1-[[[7-(5-methyl-1,2,4-oxadiazol-3-yl)-1-isoquinolyl]amino]methyl]-2-oxo-ethyl]carbamate (55 mg, 75%, 0.0839 mmol) as an off-white solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.95 (s, 1H), 8.83 (s, 1H), 8.19-8.14 (m, 1H), 7.98 (d, *J* = 6.7 Hz, 2H), 7.85 (d, *J* = 8.6 Hz, 1H), 7.79 (d, *J* = 5.7 Hz, 1H), 7.42-7.25 (m, 5H), 7.21 (dd, *J* = 10.5, 8.7 Hz, 1H), 6.94 (d, *J* = 5.9 Hz, 1H), 6.85 (dd, *J* = 8.9, 3.1 Hz, 1H), 5.07 (d, *J* = 12.5 Hz, 1H), 5.02 (d, *J* = 12.6 Hz, 1H), 4.65-4.58 (m, 1H), 4.19-4.11 (m, 1H), 4.09 (t, J = 6.4 Hz, 2H), 3.91-3.83 (m, 1H), 2.67 (s, 3H), 1.80-1.71 (m, 2H), 0.99 (t, *J* = 7.4 Hz, 3H).

Example 77.6: Benzyl N-[(1R)-2-[(4-fluoro-7-propoxy-1,3-benzothiazol-2-yl)amino]-1-[[[7-(5-methyl-1,2,4-oxadiazol-3-yl)-1-isoquinolyl]amino]methyl]-2-oxo-ethyl]carbamate (50.00 mg, 0.0763 mmol) was suspended in acetic acid (1.80 mL, 0.0400 M) at room temperature under an argon atmosphere. HBr in AcOH (33% w/w, 0.93 mL, 5.3378 mmol) was added and the reaction mixture was stirred for 1 h. The reaction mixture was cooled in an ice bath and neutralized with 3M NaOH. The precipitate was filtered off, washed with water, dissolved in DMSO/MeOH and purified by prep-HPLC (AccqPrep, focused gradient, 72.3-82.3% MeOH in water [+ 0.1% NH3]) to give (2R)-2-amino-N-(4-fluoro-7-propoxy-1,3-benzothiazol-2-yl)-3-[[7-(5-methyl-1,2,4-oxadiazol-3-yl)-1-isoquinolyl]amino]propanamide (7.6 mg, 18%, 0.0138 mmol) as a white solid. HPLC/MS m/z: 522.172 $[M+H]^+$, Rt (Z): 2.57 min. ^1H NMR (600 MHz, DMSO-d_6): δ 8.89 (d, *J* = 1.6 Hz, 1H), 8.15 (dd, *J* = 8.4, 1.5 Hz, 1H), 7.98 (br s, 1H), 7.91 (d, *J* = 5.7 Hz, 1H), 7.85 (d, *J* = 8.5 Hz, 1H), 7.12 (dd, *J* = 10.5, 8.7 Hz, 1H), 6.97 (d, *J* = 5.8 Hz, 1H), 6.77 (dd, *J* = 8.8, 3.0 Hz, 1H), 6.27 (br s, 3H), 4.08 (t, *J* = 6.4 Hz, 2H), 3.98 (t, *J* = 6.3 Hz, 1H), 3.96-3.90 (m, 1H), 3.78-3.72 (m, 1H), 2.68 (s, 3H), 1.81-1.72 (m, 2H), 1.00 (t, *J* = 7.4 Hz, 3H).

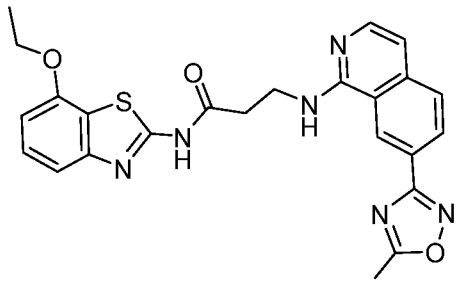
Example 78: (S)-2-Hydroxy-3-((7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl)amino)-N-(7-propoxybenzo[d]thiazol-2-yl)propenamide



To a mixture of (2S)-2-hydroxy-3-[[7-(5-methyl-1,2,4-oxadiazol-3-yl)-1-isoquinolyl]amino]propanoic acid B4 (15.0 mg, 0.048 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (18.3 mg, 0.096 mmol), 7-propoxy-1,3-benzothiazol-2-amine (Example 75.3) (11.9 mg, 0.057 mmol) in anhydrous DMF (0.3 mL) was added under nitrogen atmosphere 1-hydroxybenzotriazole (12.9 mg, 0.096 mmol). The resulting solution was stirred at 45 °C overnight. Purification by reverse phase flash chromatography (Eluent: 20-80% MeOH/H_2O + 0.1% formic acid) followed by ion exchange SCX-2

chromatography eluting with 2M NH_3 in MeOH afforded (2S)-2-hydroxy-3-[[7-(5-methyl-1,2,4-oxadiazol-3-yl)-1-isoquinolyl]amino]-N-(7-propoxy-1,3-benzothiazol-2-yl)propanamide (10 mg, 42%, 0.02 mmol) as a beige amorphous powder. HPLC/MS m/z: 505.2 $[M+H]^+$, Rt (U): 2.65 min. ^1H NMR (600 MHz, DMSO-d_6): δ 8.97-8.86 (m, 1H), 8.17 (dd, *J* = 8.5, 1.5 Hz, 1H), 8.10 (t, *J* = 5.6 Hz, 1H), 7.93 (d, *J* = 5.8 Hz, 1H), 7.87 (d, *J* = 8.5 Hz, 1H), 7.42-7.27 (m, 2H), 7.00 (dd, *J* = 5.9, 0.8 Hz, 1H), 6.91 (dd, *J* = 7.8, 1.1 Hz, 1H), 6.48 (s, 1H), 4.63 (t, *J* = 5.6 Hz, 1H), 4.13 (t, *J* = 6.4 Hz, 2H), 3.99-3.69 (m, 2H), 2.69 (s, 3H), 1.80 (dt, *J* = 7.4, 6.4 Hz, 2H), 1.02 (t, *J* = 7.4 Hz, 3H).

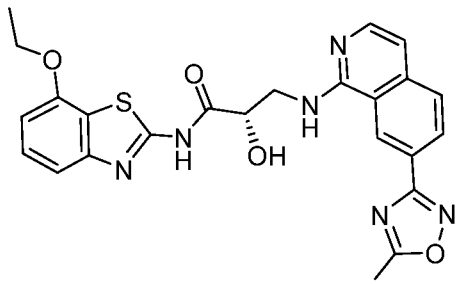
Example 79: N-(7-ethoxybenzo[d]thiazol-2-yl)-3-((7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl)amino)propenamide



Example 79.1: 2-Amino-1,3-benzothiazol-7-ol (94.0 mg, 0.56 mmol) and K_2CO_3 (93.8 mg, 0.68 mmol) were dissolved in dry DMF (3.8 mL) and the obtained mixture was stirred at room temperature for 40 min. Iodoethane (51 uL, 0.56 mmol) was then added at 0 °C. The mixture was stirred during 1 h at 0 °C. The ice bath was then removed, and the reaction mixture stirred at room temperature for 3 d. Water (~1 mL) was then added to the reaction mixture. The crude solution was purified by reverse phase column chromatography eluting with 10-80% MeOH in water (+0.1% formic acid in both). Pure fractions were combined and concentrated, followed by purification using a SCX-II ion exchange cartridge (2 g, 15 mL) and eluting with MeOH and 2M NH_3 in MeOH. Basic fractions were combined and concentrated *in vacuo* to give 7-ethoxy-1,3-benzothiazol-2-amine (74.3 mg, 68%, 0.38 mmol) as a white amorphous solid. HPLC/MS m/z: 195.1 $[M+H]^+$, Rt (T): 0.86 min. ^1H NMR (600 MHz, DMSO-d_6): δ 7.42 (s, 2H), 7.14 (t, *J* = 8.0 Hz, 1H), 6.96 (dd, *J* = 8.0, 0.8 Hz, 1H), 6.65 (dd, *J* = 8.2, 0.8 Hz, 1H), 4.14 (q, *J* = 7.0 Hz, 2H), 1.34 (t, *J* = 7.0 Hz, 3H).

Example 79.2: To a mixture of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride [B2] (32.1 mg, 0.17 mmol), 7-ethoxy-1,3-benzothiazol-2-amine (19.5 mg, 0.10 mmol) in DMF (0.52 mL) was added 1-hydroxybenzotriazole (22.6 mg, 0.17 mmol) under N_2. The resulting solution was stirred at 60 °C overnight. The reaction crude purified by reverse phase column chromatography eluting with 20-100% MeOH in water (+0.1% formic acid in both). Fractions with pure compound were combined and evaporated to dryness and further purified by SCX-II ion exchange cartridge (2 g, 15 mL) using MeOH and 2M NH_3 in MeOH as eluents. Basic fractions were combined and evaporated to dryness to give N-(7-ethoxy-1,3-benzothiazol-2-yl)-3-[[7-(5-methyl-1,2,4-oxadiazol-3-yl)-1-isoquinolyl]amino]propanamide (22.1 mg, 56%, 0.05 mmol) as a beige amorphous powder. HPLC/MS m/z: 475.2 $[M+H]^+$, Rt (U): 2.54 min. ^1H NMR (600 MHz, DMSO-d_6): δ 12.05 (s, 1H), 8.90 (d, *J* = 1.6 Hz, 1H), 8.16 (dd, *J* = 8.4, 1.5 Hz, 1H), 8.05 (t, *J* = 5.4 Hz, 1H), 7.99 (d, *J* = 5.7 Hz, 1H), 7.86 (d, *J* = 8.5 Hz, 1H), 7.49-7.24 (m, 2H), 6.98 (d, *J* = 5.7 Hz, 1H), 6.89 (dd, *J* = 7.7, 1.1 Hz, 1H), 4.22 (q, *J* = 7.0 Hz, 2H), 3.85 (q, *J* = 6.6 Hz, 2H), 2.94 (t, *J* = 6.8 Hz, 2H), 2.70 (s, 3H), 1.40 (t, *J* = 7.0 Hz, 3H).

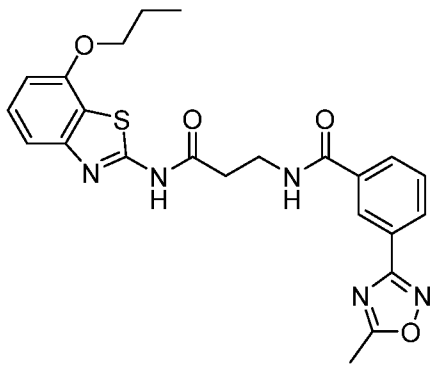
Example 80: (S)-N-(7-ethoxybenzo[d]thiazol-2-yl)-2-hydroxy-3-((7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl)amino)propenamide



To a mixture of (2S)-2-hydroxy-3-[[7-(5-methyl-1,2,4-oxadiazol-3-yl)-1-isoquinolyl]amino]propanoic acid [B4] (25.0 mg, 0.08 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (30.5 mg, 0.16 mmol), 7-ethoxy-1,3-benzothiazol-2-amine [Example 79.1] (18.5 mg, 0.096 mmol) in anhydrous DMF (0.50 mL) was added under nitrogen atmosphere 1-hydroxybenzotriazole (21.5 mg, 0.16 mmol). The resulting solution was stirred at 60 °C overnight. The crude was purified by reverse phase column chromatography (Eluent: 20-100% MeOH in water (+0.1% formic acid in both)). Fractions of the pure

product were combined and evaporated to dryness and further purified by SCX-II ion exchange cartridge (2 g, 15 mL) using MeOH and 2M NH_3 in MeOH as eluents. Basic fractions were combined and evaporated to dryness to give the required product, but this was not pure (8.5 mg, 88%). The impure product was further purified by preparative TLC (500 microns) using 5% MeOH in DCM as eluent to give (2S)-N-(7-ethoxy-1,3-benzothiazol-2-yl)-2-hydroxy-3-[[7-(5-methyl-1,2,4-oxadiazol-3-yl)-1-isoquinolyl]amino]propanamide (4 mg, 10%, 0.0082 mmol) as a white amorphous powder. HPLC/MS m/z: 491.1 $[M+H]^+$, Rt (U): 1.18 min. ^1H NMR (600 MHz, DMSO-d_6): δ 12.11 (s, 1H), 8.91 (d, *J* = 1.7 Hz, 1H), 8.16 (dd, *J* = 8.5, 1.5 Hz, 1H), 8.09 (t, *J* = 5.6 Hz, 1H), 7.93 (d, *J* = 5.7 Hz, 1H), 7.86 (d, *J* = 8.5 Hz, 1H), 7.44-7.29 (m, 2H), 7.04-6.96 (m, 1H), 6.89 (dd, *J* = 7.8, 1.0 Hz, 1H), 6.46 (s, 1H), 4.61 (t, *J* = 5.6 Hz, 1H), 4.21 (q, *J* = 6.9 Hz, 2H), 3.86 (ddt, *J* = 49.6, 13.5, 5.6 Hz, 2H), 2.68 (s, 3H), 1.39 (t, *J* = 7.0 Hz, 3H).

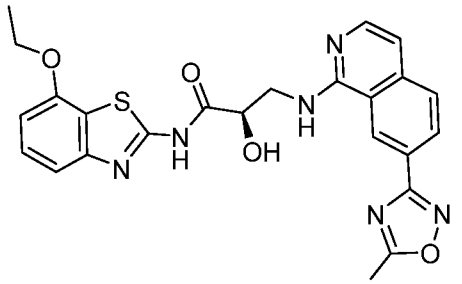
Example 81: 3-(5-Methyl-1,2,4-oxadiazol-3-yl)-N-[3-oxo-3-[(7-propoxy-1,3-benzothiazol-2-yl)amino]propyl]benzamide



To a mixture of 2-amino-1,3-benzothiazol-7-ol (9.8 mg, 0.047 mmol), B1 (10.0 mg, 0.036 mmol), HOBt (9.8 mg, 0.073 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (13.9 mg, 0.073 mmol) was added under nitrogen atmosphere DMF (0.18 mL). The resulting solution was stirred at 60 °C for 19 h. The crude was purified by reverse phase column chromatography, eluting with 20-100% MeOH in water (+0.1% formic acid in both) to give the desired compound (11 mg, 65%, 0.024 mmol) as a white amorphous solid. HPLC/MS m/z: 466.2 $[M+H]^+$, Rt (T): 1.46 min. ^1H NMR (600 MHz, DMSO-d_6): δ 12.41 (s, 1H), 8.88 (t, *J* = 5.5 Hz, 1H), 8.47 (t, *J* = 1.8 Hz, 1H), 8.13 (dt, *J* = 7.7, 1.4 Hz, 1H), 8.04 (dt, *J* = 7.8, 1.5 Hz,

1H), 7.65 (t, *J* = 7.8 Hz, 1H), 7.45-7.22 (m, 2H), 6.89 (dd, *J* = 7.7, 1.2 Hz, 1H), 4.12 (t, *J* = 6.4 Hz, 2H), 3.63 (q, *J* = 6.7 Hz, 2H), 2.83 (t, *J* = 6.8 Hz, 2H), 2.68 (s, 3H), 1.79 (sext, *J* = 7.0 Hz, 2H), 1.02 (t, *J* = 7.4 Hz, 3H).

Example 82: (R)-N-(7-ethoxybenzo[d]thiazol-2-yl)-2-hydroxy-3-((7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl)amino)propenamide



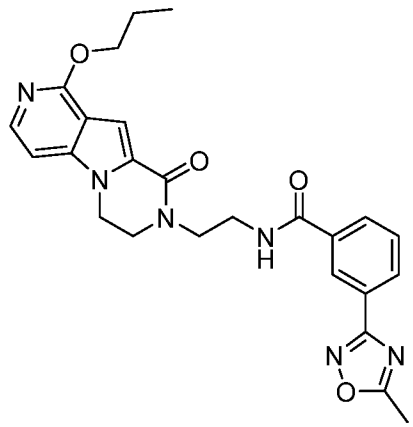
Example 82.1: A1 (200.0 mg, 0.88 mmol) and methyl (2R)-3-amino-2-hydroxy-propanoate hydrochloride (150.6 mg, 0.99 mmol) were dissolved/suspended in anhydrous DCM (2.93 mL) in a microwave vial. DIPEA (0.77 mL, 4.40 mmol) was added followed by PyBroP (533.4 mg, 1.14 mmol) and the mixture stirred at room temperature for 4 d. The volatiles were evaporated, and crude purified by RP column chromatography (Eluent: 0-70% MeOH in water (+0.1% formic acid modifier in both)) to afford the required product methyl (2R)-2-hydroxy-3-[[7-(5-methyl-1,2,4-oxadiazol-3-yl)-1-isoquinolyl]amino]propanoate (107.5 mg, 37%, 0.33 mmol) as a clear oil. HPLC/MS m/z: 329.1 $[M+H]^+$, Rt (Y): 0.87 min. ^{1}H NMR (500 MHz, Methanol-d_4): δ 8.98 (dd, *J* = 1.6, 0.8 Hz, 1H), 8.38 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.94 (d, *J* = 8.4 Hz, 1H), 7.80 (d, *J* = 6.4 Hz, 1H), 7.16 (dd, *J* = 6.4, 0.9 Hz, 1H), 4.61 (dd, *J* = 6.3, 3.9 Hz, 1H), 4.11-3.89 (m, 2H), 3.80 (s, 3H), 2.72 (s, 3H).

Example 82.2: Methyl (2R)-2-hydroxy-3-[[7-(5-methyl-1,2,4-oxadiazol-3-yl)-1-isoquinolyl]amino]propanoate (107.5 mg, 0.33 mmol) was dissolved in anhydrous THF (0.82 mL) and water (0.82 mL). To this was added lithium hydroxide monohydrate (30.2 mg, 0.72 mmol) and the obtained mixture was stirred at RT for 21 h. The volatiles were removed *in vacuo* and the crude dissolved in DMSO (2 mL) and purified by reverse phase column chromatography (Eluent: 5-80% MeOH in water (+0.1% formic acid modifier in both)) to give (2R)-2-hydroxy-3-[[7-(5-methyl-1,2,4-oxadiazol-3-yl)-1-isoquinolyl]amino]propanoic acid (68.8 mg, 67%, 0.22 mmol) as a white solid as the formate salt. HPLC/MS m/z: 315.1 $[M+H]^+$, Rt (Y): 0.88 min.

^{1}H NMR (500 MHz, DMSO-d_6): δ 8.94-8.89 (m, 1H), 8.16 (dd, *J* = 8.5, 1.5 Hz, 1H), 8.14 (s, 1H), 8.00 (d, *J* = 5.6 Hz, 1H), 7.95 (d, *J* = 5.8 Hz, 1H), 7.87 (d, *J* = 8.6 Hz, 1H), 6.99 (dd, *J* = 5.9, 0.8 Hz, 1H), 4.38 (dd, *J* = 7.1, 4.6 Hz, 1H), 3.81 (dt, *J* = 13.6, 4.4 Hz, 1H), 3.71-3.60 (m, 1H), 2.71 (s, 3H).

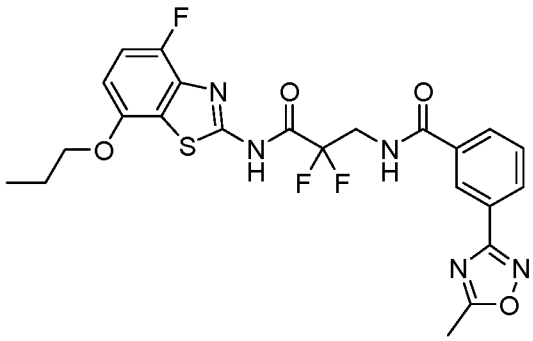
Example 82.3: To a mixture of (2R)-2-hydroxy-3-[[7-(5-methyl-1,2,4-oxadiazol-3-yl)-1-isoquinolyl]amino]propanoic acid (30.0 mg, 0.096 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (30.5 mg, 0.16 mmol), 7-ethoxy-1,3-benzothiazol-2-amine [Example 79.1] (22.2 mg, 0.11 mmol) in anhydrous DMF (0.60 mL) was added under nitrogen atmosphere 1-hydroxybenzotriazole (25.8 mg, 0.19 mmol). The resulting solution was stirred at 60 °C overnight. The crude was purified by reverse phase column chromatography (Eluent: 20-100% MeOH in water (+0.1% formic acid modifier in both)). Fractions of pure product were combined and evaporated to dryness (23.3 mg) and further purified by SCX-II ion exchange cartridge (2 g, 15 mL) using MeOH and 2M NH_3 in MeOH as eluents. Further purified by preparative TLC (500 microns) using 5% MeOH in DCM as eluent to give (2R)-N-(7-ethoxy-1,3-benzothiazol-2-yl)-2-hydroxy-3-[[7-(5-methyl-1,2,4-oxadiazol-3-yl)-1-isoquinolyl]amino]propanamide (5 mg, 11%, 0.0102 mmol) as a white amorphous powder. HPLC/MS m/z: 491.1 $[M+H]^+$, Rt (Y): 1.32 min. ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.13 (s, 1H), 8.92 (s, 1H), 8.17 (d, *J* = 8.5 Hz, 1H), 8.12 (d, *J* = 12.7 Hz, 1H), 7.92 (d, *J* = 5.8 Hz, 1H), 7.87 (d, *J* = 8.5 Hz, 1H), 7.43-7.27 (m, 2H), 7.00 (d, *J* = 5.8 Hz, 1H), 6.90 (dd, *J* = 7.8, 1.2 Hz, 1H), 6.50 (d, *J* = 16.2 Hz, 1H), 4.62 (t, *J* = 5.6 Hz, 1H), 4.22 (q, *J* = 7.0 Hz, 2H), 3.95-3.80 (m, 2H), 2.68 (s, 3H), 1.39 (t, *J* = 7.0 Hz, 3H).

Example 83: 3-(5-Methyl-1,2,4-oxadiazol-3-yl)-N-(2-(9-oxo-1-propoxy-6,7-dihydropyrido[3',4':4,5]pyrrolo[1,2-a]pyrazin-8(9H)-yl)ethyl)benzamide



3-(5-Methyl-1,2,4-oxadiazol-3-yl)benzoic acid (20.7 mg, 0.10 mmol) and 2-(10-oxo-6-propoxy-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2(7),3,5,8-tetraen-11-yl)ethylammonium chloride [Example 37.5] (30.00 mg, 0.0924 mmol) were dissolved in dry DMF (0.46 mL). Triethylamine (40 uL, 0.28 mmol) and T3P (0.11 mL, 0.18 mmol) were then added. After 4 h, more T3P (109 uL) and TEA (39 uL) were added to the reaction mixture. This was left stirring at RT for 2 d. The crude was purified by reverse phase column chromatography (Eluent: 20-90% MeOH in water (+0.1% formic acid in both)). Fractions with pure product were combined and concentrated, followed by purification via an SCX-II ion exchange cartridge (2 g, 15 mL). Basic fractions were combined and evaporated to dryness to give 3-(5-methyl-1,2,4-oxadiazol-3-yl)-N-[2-(10-oxo-6-propoxy-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2,4,6,8-tetraen-11-yl)ethyl]benzamide (10 mg, 23%, 0.02 mmol) as a clear film. HPLC/MS m/z: 475.2 $[M+H]^+$, Rt (Y): 1.33 min. ^{1}H NMR (600 MHz, DMSO-d_6): δ 8.86 (t, *J* = 5.9 Hz, 1H), 8.43 (t, *J* = 1.8 Hz, 1H), 8.11 (dt, *J* = 7.7, 1.4 Hz, 1H), 7.99 (dt, *J* = 7.8, 1.5 Hz, 1H), 7.84 (d, *J* = 6.0 Hz, 1H), 7.64 (t, *J* = 7.8 Hz, 1H), 7.15 (dd, *J* = 6.1, 0.9 Hz, 1H), 6.97 (d, *J* = 0.9 Hz, 1H), 4.35 (td, *J* = 6.5, 2.9 Hz, 4H), 3.94-3.79 (m, 2H), 3.72 (t, *J* = 6.0 Hz, 2H), 3.56 (q, *J* = 5.9 Hz, 2H), 2.67 (s, 3H), 1.77 (sext, *J* = 7.2 Hz, 2H), 0.98 (t, *J* = 7.4 Hz, 3H).

Example 84: N-(2,2-difluoro-3-((4-fluoro-7-propoxybenzo[d]thiazol-2-yl)amino)-3-oxopropyl)-3-(5-methyl-1,2,4-oxadiazol-3-yl)benzamide



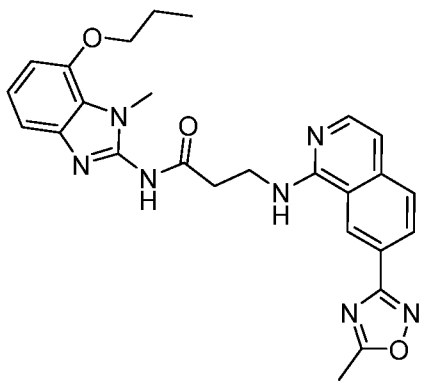
Example 84.1: DIPEA (0.70 mL, 4.00 mmol) was added to a solution of ethyl 2,2-difluoro-3-aminopropanoate hydrochloride (200.0 mg, 1.00 mmol), 3-(5-methyl-1,2,4-oxadiazol-3-yl)benzoic acid (204.6 mg, 1.00 mmol) and HATU (571.7 mg, 1.50 mmol) in DMF (6.68 mL). The yellow reaction mixture was stirred at room temperature for 2 d. The reaction mixture was then diluted with EtOAc (50 mL) and washed with water (100 mL). The organic layer was washed with aqueous saturated bicarbonate solution (70 mL), and brine (70 mL) before drying over magnesium sulfate. The organic layer was then filtered and evaporated to dryness. The obtained crude was purified by NP flash silica column chromatography using a gradient of 0-10% MeOH in DCM as eluent to give ethyl 2,2-difluoro-3-[[3-(5-methyl-1,2,4-oxadiazol-3-yl)benzoyl]amino]propanoate (305 mg, 79%, 0.79 mmol) as a pink oil. HPLC/MS m/z: 362.1 $[M+Na]^+$, Rt (Y): 1.30 min. ^1H NMR (600 MHz, Chloroform-d): δ 8.43 (t, *J* = 1.8 Hz, 1H), 8.26 (dt, *J* = 7.8, 1.4 Hz, 1H), 8.00 (ddd, *J* = 7.8, 1.9, 1.2 Hz, 1H), 7.66-7.57 (m, 1H), 6.53 (d, *J* = 6.6 Hz, 1H), 4.38 (q, *J* = 7.2 Hz, 2H), 4.17 (td, *J* = 13.6, 6.3 Hz, 2H), 2.70 (s, 3H), 1.37 (t, *J* = 7.2 Hz, 3H).

Example 84.2: Lithium hydroxide (47.4 mg, 1.98 mmol) was added to a solution of ethyl 2,2-difluoro-3-[[3-(5-methyl-1,2,4-oxadiazol-3-yl)benzoyl]amino]propanoate (305.0 mg, 0.90 mmol) in THF (2.25 mL) and water (2.25 mL). The reaction mixture was left stirring at room temperature for 2 h 20 min. The reaction mixture was concentrated and the aqueous was acidified with a 1M aqueous solution of citric acid to pH 3 and extracted with EtOAc (60 mL). After phase separation the organic layer was washed with brine (30 mL), dried over magnesium sulfate, filtered, and evaporated to dryness to give 2,2-difluoro-3-[[3-(5-methyl-1,2,4-oxadiazol-3-yl)benzoyl]amino]propanoic acid (183 mg, 65%, 0.59 mmol) as a off white solid that was used in the next step with no further purification. HPLC/MS m/z: 312.1 $[M+H]^+$, Rt (T): 0.87 min. ^1H NMR (600 MHz, Methanol-d_4): δ 8.53 (t, *J* = 1.6 Hz, 1H), 8.24

(dt, *J* = 7.8, 1.4 Hz, 1H), 8.00 (ddd, *J* = 7.8, 1.9, 1.2 Hz, 1H), 7.65 (td, *J* = 7.8, 0.6 Hz, 1H), 4.26-3.83 (m, 2H), 2.69 (s, 3H).

Example 84.3: 2,2-Difluoro-3-[[3-(5-methyl-1,2,4-oxadiazol-3-yl)benzoyl]amino]propanoic acid (34.3 mg, 0.11 mmol), 4-fluoro-7-propoxy-1,3-benzothiazol-2-amine [Example 77.2] (24.9 mg, 0.11 mmol) and TEA (50 uL, 0.33 mmol) were mixed in anhydrous DMF (0.22 mL) at room temperature. 50% T3P in DMF (0.17 mL, 0.29 mmol) was added and the reaction mixture was heated at 70 °C for 3 h, the reaction was cooled down to room temperature, quenched with water (0.2 mL), diluted with DMSO (0.5 mL) and loaded directly onto a Biotage C18 SNAP Ultra column and purified by reverse phase. Fractions with pure compound were combined and further purified by a SCX-II column (2 g, 15 mL) using MeOH and 2M ammonia solution in MeOH as eluents to give the required product (14.7 mg, 26%, 0.028 mmol) as an off-white solid. HPLC/MS m/z: 520.1 $[M+H]^+$, Rt (T): 1.47 min. ^1H NMR (600 MHz, DMSO-d_6): δ 13.75 (s, 1H), 9.22 (t, *J* = 6.2 Hz, 1H), 8.43 (t, *J* = 1.8 Hz, 1H), 8.20-8.09 (m, 1H), 8.01 (dt, *J* = 7.8, 1.5 Hz, 1H), 7.66 (t, *J* = 7.8 Hz, 1H), 7.27 (dd, *J* = 10.4, 8.7 Hz, 1H), 6.93 (dd, *J* = 8.8, 3.0 Hz, 1H), 4.23-4.06 (m, 4H), 2.67 (s, 3H), 1.78 (sext, *J* = 7.0 Hz, 2H), 1.00 (t, *J* = 7.4 Hz, 3H).

Example 85: 3-((7-(5-Methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl)amino)-N-(1-methyl-7-propoxy-1H-benzo[d]imidazol-2-yl)propenamide

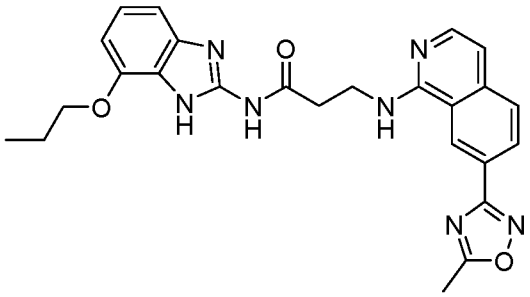


Example 85.1: 7-Propoxy-1H-benzimidazol-2-amine [Example 86] (83.0 mg, 0.43 mmol), potassium hydroxide (43.8 mg, 0.78 mmol) and iodomethane (28 uL, 0.45 mmol) were stirred in ethanol (5.4 mL) at RT for 2 d. Potassium hydroxide (61 mg) and iodomethane (20 uL) were added to the reaction mixture and this was stirred overnight. The volatiles were evaporated, and the crude dissolved in ethyl acetate

(30 mL) and this was washed with an aqueous saturated solution of sodium bicarbonate solution (30 mL), water (30 mL) and brine (30 mL). The organic layer was then dried over $MgSO_4$, filtered, and evaporated to dryness. The obtained crude (58 mg) was purified by normal phase silica column chromatography (Eluent: 0-20% gradient of MeOH in DCM) affording the desired regioisomer 1-methyl-7-propoxy-1H-benzo[d]imidazol-2-amine (9.2 mg). Fractions with mixture of regioisomers were combined and were further purified by preparative TLC (500 microns) using 10% MeOH in DCM as eluent to give and extra 4.6 mg of pure desired product. Pure product obtained from column chromatography and preparative TLC was combined to afford 1-methyl-7-propoxy-benzimidazol-2-amine (13.8 mg, 15.5%, 0.067 mmol). HPLC/MS m/z: 206.1 $[M+H]^+$, Rt (Y): 1.01 min. ^1H NMR (600 MHz, Methanol-d_4): δ 6.94 (t, *J* = 8.0 Hz, 1H), 6.86 (dd, *J* = 8.0, 0.9 Hz, 1H), 6.59 (dd, *J* = 8.1, 0.9 Hz, 1H), 4.05 (t, *J* = 6.3 Hz, 2H), 3.81 (s, 3H), 1.88 (dtd, *J* = 13.9, 7.5, 6.4 Hz, 2H), 1.11 (t, *J* = 7.5 Hz, 3H).

Example 85.2: To a 5 mL microwave vial was added B2 (10.00 mg, 0.033 mmol), 1-methyl-7-propoxy-benzimidazol-2-amine (13.8 mg, 0.067 mmol), PyBrop (37.5 mg, 0.080 mmol) followed by anhydrous DMF (0.2 mL) and DIPEA (21 uL, 0.12 mmol). The resulting solution was stirred at RT for 2 d. The reaction was diluted with DMSO (0.3 mL) and purified by reverse phase column chromatography (Eluent: 20-100% MeOH in water (+0.1% formic acid modifier in both)). Fractions of pure compound were combined and evaporated to dryness and further purified by a SCX-II ion exchange column (2 g, 15 mL) using MeOH and 2M NH_3 solution in MeOH as eluents. Basic fractions were combined and concentrated under reduced pressure to yield 3-((7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl)amino)-N-(1-methyl-7-propoxy-1H-benzo[d]imidazol-2-yl)propenamide (5 mg, 31%, 0.01 mmol) as a light pink solid. HPLC/MS m/z: 486.2 $[M+H]^+$, Rt (T): 1.11 min. ^1H NMR (600 MHz, DMSO-d_6): δ 10.54 (s, 1H), 8.96-8.83 (m, 1H), 8.21-8.12 (m, 1H), 8.09-7.94 (m, 2H), 7.85 (d, *J* = 8.4 Hz, 1H), 7.16-6.98 (m, 2H), 6.96 (t, *J* = 5.7 Hz, 1H), 6.75 (dd, *J* = 11.6, 7.7 Hz, 1H), 4.05 (t, *J* = 6.1 Hz, 2H), 3.87-3.79 (m, 2H), 3.74 (brs, 3H), 2.89-2.84 (m, 2H), 2.69 (t, *J* = 5.8 Hz, 3H), 1.79 (q, *J* = 6.9 Hz, 2H), 1.02 (q, *J* = 7.6 Hz, 3H) [Note: Tautomeric forms present].

Example 86: 3-((7-(5-Methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl)amino)-N-(7-propoxy-1H-benzo[d]imidazol-2-yl)propenamide



Example 86.1: 1-Iodopropane (0.35 mL, 3.57 mmol) was added to a mixture of 2-amino-3-nitrophenol (500.0 mg, 3.24 mmol) and K_2CO_3 (672.6 mg, 4.87 mmol) in anhydrous DMF (32.4 mL). Reaction stirred for 22 h 30 min at RT. The crude was partioned between EtOAc (50 mL) and aqueous saturated solution of sodium bicarbonate (50 mL). After phase separation, the aqueous layer was further extracted with EtOAc (50 mL). The combined organic layers were washed with water (80 mL), aqueous saturated solution of sodium bicarbonate (80 mL), brine (50 mL), dried over $MgSO_4$, filtered, and evaporated to dryness. The crude was purified by SCX-II ion exchange column using MeOH and a 2M NH_3 solution in MeOH as eluents. After solvent evaporation, the obtained crude (0.99 g) was purified by NP silica column chromatography (Eluent: 0-10% EtOAc in cyclohexane) to give 2-nitro-6-propoxy-aniline (576 mg, 90%, 2.94 mmol) as a bright orange solid. HPLC/MS m/z: 197.1 $[M+H]^+$, Rt (Y): 1.44 min. ^1H NMR (500 MHz, Chloroform-d): δ 7.74 (dd, *J* = 8.8, 1.3 Hz, 1H), 6.89 (dd, *J* = 7.7, 1.2 Hz, 1H), 6.61 (dd, *J* = 8.9, 7.7 Hz, 1H), 6.45 (s, 2H), 4.02 (t, *J* = 6.5 Hz, 2H), 1.90 (dtd, *J* = 13.8, 7.4, 6.5 Hz, 2H), 1.09 (t, *J* = 7.4 Hz, 3H).

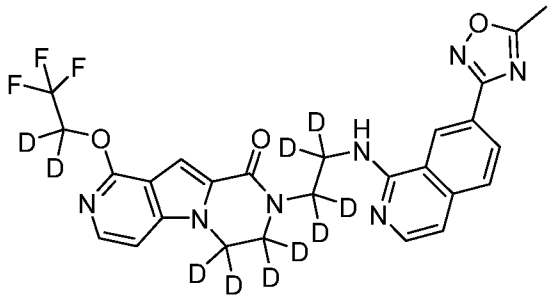
Example 86.2: 2-Nitro-6-propoxy-aniline (280.0 mg, 1.43 mmol) and tin(II) chloride (1367.4 mg, 7.14 mmol) were taken into EtOH (14.0 mL) in a 20 mL microwave vial. The reaction mixture was heated for 10 min at 140 °C in the microwave. Extra of tin(II) chloride (317 mg) was added and after re-sealing the microwave vial, the reaction mixture was further heated for 5 min at 135 °C. After cooling down, the reaction mixture was poured into an aqueous saturated solution of sodium bicarbonate (75 mL). The bicarbonate phase was extracted with EtOAc (2x 60 mL). The combined organic layers were washed with aqueous saturated solution of sodium bicarbonate (75 mL), water (10 mL) and brine (50 mL). The organic layer was then dried, filtered, and evaporated to dryness to afford 3-propoxybenzene-1,2-diamine (209.5 mg, 88%, 1.26 mmol) as a yellow solid). HPLC/MS m/z: 167.1 $[M+H]^+$, Rt (Y): 0.76 min. ^1H NMR (500 MHz, Chloroform-d): δ 6.66 (t, *J* = 8.0 Hz,

1H), 6.41 (td, *J* = 8.2, 1.2 Hz, 2H), 3.97 (t, *J* = 6.5 Hz, 2H), 3.40 (brs, 4H), 1.85 (dtd, *J* = 13.9, 7.4, 6.5 Hz, 2H), 1.07 (t, *J* = 7.4 Hz, 3H).

Example 86.3: Bromine cyanide 5M in MeCN (0.19 mL, 0.97 mmol) was added to a mixture of 3-propoxybenzene-1,2-diamine (135.0 mg, 0.81 mmol) in MeCN (3.9 mL) and water (0.99 mL). The reaction mixture was stirred at RT overnight. The volatiles were evaporated to dryness and the obtained crude was purified by normal phase silica column chromatography (eluent: 2-15% gradient of MeOH in DCM) to afford the 7-propoxy-1H-benzimidazol-2-amine (65 mg, 42%, 0,34 mmol). HPLC/MS m/z: 192.1 $[M+H]^+$, Rt (Y): 0.99 min. ^{1}H NMR (500 MHz, Chloroform-d): δ 7.10-6.80 (m, 2H), 6.63 (dd, *J* = 7.6, 1.3 Hz, 1H), 4.61 (brs, 6H), 4.09 (t, *J* = 6.7 Hz, 2H), 1.83 (sext, *J* = 7.2 Hz, 2H), 1.01 (t, *J* = 7.4 Hz, 3H) [Note: tautomers present].

Example 86.4: B2 (31.2 mg, 0.1 mmol) and 7-propoxy-1H-benzimidazol-2-amine (20 mg, 0.1 mmol) were dissolved in anhydrous DMF (0.52 mL), followed by the addition of triethylamine (59 uL, 0.42 mmol). The reaction mixture was placed in a preheated heating block at 70 °C, 50% T3P in DMF (0.18 mL, 0.31 mmol) was added dropwise over 5 min. The reaction mixture was left stirring at 70 °C for 18 h. More T3P (92 uL) and TEA (28 uL) were added to the reaction mixture, and this was stirred further at 70 °C for 18 h. The reaction was quenched with water (0.3 mL) and stirred for 5 min before diluting with DMSO (0.4 mL) and purified by reverse phase column chromatography (Eluent: 20-100% MeOH in water (+0.1% formic acid in both)). Pure compound fractions were combined and concentrated, followed by purification via a SCX-II ion exchange cartridge (2 g, 15 mL). Basic fraction was evaporated to dryness to give the required product as a light yellow amorphous solid. [96% pure by LC-MS]. The compound formed crystals in deuterated MeOH solution over 2 d, so the mother liquid was pipetted out and the crystals were washed with MeOH to give pure 3-[[7-(5-methyl-1,2,4-oxadiazol-3-yl)-1-isoquinolyl]amino]-N-(7-propoxy-1H-benzimidazol-2-yl)propanamide (4 mg, 8%, 0.0085 mmol) as a light yellow solid. HPLC/MS m/z: 472.2 $[M+H]^+$, Rt (Y): 1.29 min. ^{1}H NMR (500 MHz, Methanol-d_4): 8.82 (s, 1H), 8.21 (d, *J* = 8.5 Hz, 1H), 7.95 (d, *J* = 5.9 Hz, 1H), 7.80 (d, *J* = 8.4 Hz, 1H), 7.07 (s, 1H), 6.99 (d, *J* = 5.9 Hz, 1H), 6.72 (dd, *J* = 6.1, 2.7 Hz, 1H), 4.11 (t, *J* = 6.6 Hz, 2H), 3.98 (t, *J* = 6.6 Hz, 2H), 2.96 (t, *J* = 6.6 Hz, 2H), 2.66 (s, 3H), 1.88 (q, *J* = 7.2 Hz, 2H), 1.15-1.04 (m, 3H) [Note: 1 aromatic proton not observed].

Example 87: 8-(2-((7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl)amino)ethyl-1,1,2,2-d4)-1-(2,2,2-trifluoroethoxy-1,1-d2)-7,8-dihydropyrido[3',4':4,5]pyrrolo[1,2-a]pyrazin-9(6H)-one-6,6,7,7-d4



Example 87.1: A solution of NaOH (1.04 g, 26.0 mmol, 1.0 eq.) in H_2O (21.1 mL) was added to a solution of glycine-2,2-d2 (2.0 g, 26.0 mmol, 1.0 eq.) in Water (21.1 mL). Then, a solution of Boc_2O (7.04 g, 31.3 mmol, 1.2 eq.) in Dioxane (44.3 mL) was added dropwise and the resulting reaction mixture was stirred at r.t. overnight. After evaporation, the residue was re-dissolved in water and extracted with diethyl. The ether fraction as washed with water and the aqueous fractions were combined, acidified with 1M HCl and extracted with EtOAc. The combined EtOAc fraction was dried over anhydrous $MgSO_4$, and then concentrated under diminished pressure. Crude 2-(tert-butoxycarbonylamino)-2,2-dideuterio-acetic acid (4.43 g, crude yield 96%) was isolated as a colourless oil. Rf (iPrOH: AcOH: H_2O = 3:1:1) = 0.86; ^1H NMR (500 MHz, $CDCl_3$) δ 5.03 (s, 1H), 1.47 (s, 9H).

Example 87.2: 1,1'-Carbonyldiimidazole (5.37 g, 33.1 mmol, 1.3 eq.) was added to a solution of 2-(tert-butoxycarbonylamino)-2,2-dideuterio-acetic acid (4.42 g, 24.9 mmol, 1 eq.) in THF (83.1 mL, 0.2 M) at RT. After 15 min, the solution was cooled to 0°C and a solution of $NaBD_4$ (1.06 g, 25.4 mmol) in H_2O (41.6 mL, 0.2 M) was added. After 1 h, HCl (1M) was added and the mixture was extracted with EtOAc. The combined organics were dried over $MgSO_4$ and concentrated under vacuum. Purification by NP column chromatography (0%-20%-50% EtOAc in cHex) gave tert-butyl N-(1,1,2,2-tetradeuterio-2-hydroxy-ethyl)carbamate (3.19 g, 77%) as a colourless oil. Rf ($CHCl_3$:MeOH = 9:1) = 0.54. ^1H NMR (500 MHz, CDCl3) δ 4.92 (s, 1H), 1.46 (s, 9H).

Example 87.3: A suspension of Methyl 4-chloro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate (1.21 g, 5.73 mmol, 1 eq.), 2,2,2-Trifluoroethanol-1,1-d2 (683 uL, 9.18 mmol, 1.6 eq.), 4Å Molecular sieves (3.49 g), tBuBrettPhos Pd G3 (215 mg, 0.252

mmol, 4 mol%), tBuBrettPhos (125 mg, 0.250 mmol, 4 m l%) and Cs_2CO_3 (3.49 g, 10.7 mmol, 1.9 eq.) in a mixture of toluene (8.19 mL, 0.35 M) and THF (8.19 mL, 0.35 M) was heated at 80 °C for 24 h in a sealed vial under argon atmosphere. The mixture was filtered over a pad of silica gel, eluting with MeOH and the solvents were evaporated. The residue was purified using NP column chromatography (Eluent: 0%-42% EtOAc in cHex) and concentrated under vacuum. Purified methyl 4-(1,1-dideuterio-2,2,2-trifluoro-ethoxy)-1H-pyrrolo[3,2-c]pyridine-2-carboxylate (1.18 g, 75%) was isolated as a white crystalline solid. Rf (cHex:EtOAc = 7:3) = 0.50. HPLC/MS m/z: 277.1 $[M+H]^+$, Rt (Y): 1.43 min. ^1H NMR (600 MHz, DMSO) δ 12.55 (s, 1H), 7.87 (d, *J* = 5.9 Hz, 1H), 7.17 – 7.13 (m, 2H), 3.89 (s, 3H).

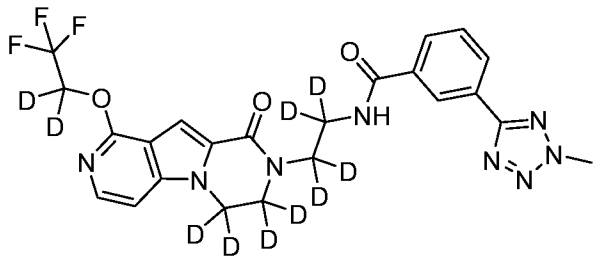
Example 87.4: DIAD (2.3 mL, 11.6 mmol, 3.2 eq.) was added over 50 min to a solution of tert-butyl N-(1,1,2,2-tetradeuterio-2-hydroxy-ethyl)carbamate (2.16 g, 13.1 mmol, 3.6 eq.), PPh_3 (2.86 g, 10.9 mmol, 3.0 eq.) and methyl 4-(1,1-dideuterio-2,2,2-trifluoro-ethoxy)-1H-pyrrolo[3,2-c]pyridine-2-carboxylate (1.0 g, 3.63 mmol, 1.0 eq.) in THF (9.1 mL, 0.4 M) at 0 °C. After 1h, the ice bath was removed and the reaction mixture was stirred overnight at r.t. Then, the reaction was quenched with water, extracted with DCM and the organic phase was dried over $MgSO_4$, evaporated in vacuo. The crude mixture was dissolved in DCM/TFA (1:1) (40 mL, 0.09 M) and stirred at RT for 30 min. The solvents were evaporated and the crude mixture was passed through an SCX-2 column eluting with DCM then MeOH and then NH_3 (2 M in MeOH) to recover 12,12,13,13-tetradeuterio-6-(1,1-dideuterio-2,2,2-trifluoro-ethoxy)-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2(7),3,5,8-tetraen-10-one (1.19 g, 112%) as a white powder. Rf (EtOAc) = 0.57; HPLC/MS m/z: 292.1 $[M+H]^+$, Rt (T): 1.10 min. ^1H NMR (500 MHz, DMSO) δ 8.25 (s, 1H), 7.90 (d, *J* = 6.0 Hz, 1H), 7.33 (d, *J* = 6.0 Hz, 1H), 7.00 (d, *J* = 0.9 Hz, 1H).

Example 87.5: A solution of TsCl (2.08 g, 10.9 mmol, 2 eq.) in DCM (18.2 mL) was slowly added to a solution of tert-butyl N-(1,1,2,2-tetradeuterio-2-hydroxy-ethyl)carbamate (0.90 g, 5.45 mmol, 1 eq.), DMAP (50.6 mg, 0.414 mmol, 8 mol%) and Et_3N (2.3 mL, 16.3 mmol, 3 eq.) in DCM (36.3 mL, 0.1 M) at 0°C. The resulting solution was stirred at 0°C for 30 min and then at RT for 3h. After concentrating in vacuo, purification by normal phase flash chromatography (Eluent: 10%-40% EtOAc in cHex) gave [2-(tert-butoxycarbonylamino)-1,1,2,2-tetradeuterio-ethyl] 4-methylbenzenesulfonate (1.56 g, 90%) as a white solid. Rf (cHex:EtOAc = 7:3) = 0.44. ^1H NMR (500 MHz, CDCl3) δ 7.80 (d, 2H), 7.36 (d, 2H), 4.83 (s, 1H), 2.46 (s, 3H), 1.42 (s, 9H).

Example 87.6: A solution of [2-(tert-butoxycarbonylamino)-1,1,2,2-tetradeuterio-ethyl] 4-methylbenzene sulfonate (1.35 g, 4.22 mmol, 1.2 eq.) in DMSO (8.7 mL) was added to 12,12,13,13-tetradeuterio-6-(1,1-dideuterio-2,2,2-trifluoro-ethoxy)-1,5,11-triazatricyclo [7.4.0.02,7]trideca-2(7),3,5,8-tetraen-10-one (0.99 g, 3.39 mmol, 1 eq.), KOH (0.40 g, 7.11 mmol, 2.1 eq.), K_2CO_3 (1.40 g, 10.2 mmol, 3 eq.), and TBAB (0.44 g, 1.35 mmol, 0.4 eq.) in DMSO (17.37 mL, 0.13 M). The mixture was stirred at RT for 10 min, at 40°C for 4 h and then overnight at 55°C. The reaction was quenched using HCl (3M). The solvents were evaporated and the crude was dissolved in TFA/DCM (1:1, 20 mL) with stirring for 30 min. After evaporation, the crude was submitted to SCX-2 column, eluting successively with DCM, MeOH then NH_3 (2N in MeOH) to give 11-(2-amino-1,1,2,2-tetradeuterio-ethyl)-12,12,13,13-tetradeuterio-6-(1,1-dideuterio-2,2,2-trifluoro-ethoxy)-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2(7),3,5,8-tetraen-10-one. HPLC/MS m/z: 339.2 $[M+H]^+$, Rt (U): 0.85 min.

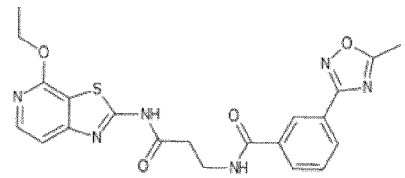
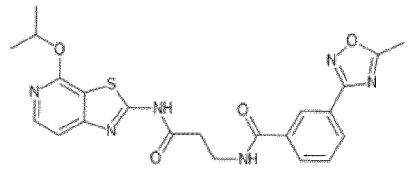
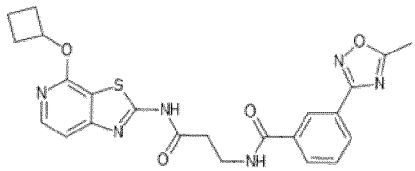
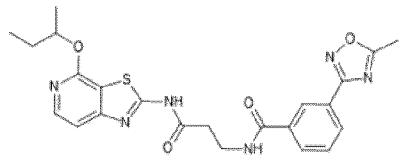
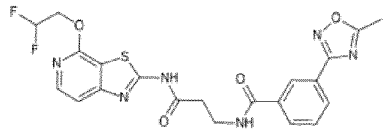
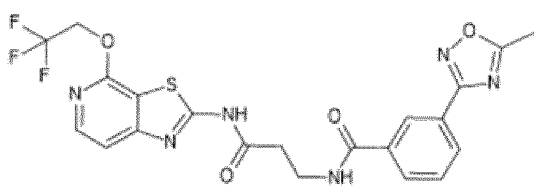
Example 87.7: DIPEA (96.52 uL, 0.5542 mmol) was added dropwise to a suspension of 11-(2-amino-1,1,2,2-tetradeuterio-ethyl)-12,12,13,13-tetradeuterio-6-(1,1-dideuterio-2,2,2-trifluoro-ethoxy)-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2(7),3,5,8-tetraen-10-one (50.00 mg, 0.1478 mmol), **A1** (40.29 mg, 0.1773 mmol) and PyBroP (82.67 mg, 0.1773 mmol) in DCM (1.48 mL, 0.1 M). The tube was sealed and this was heated to 60 °C for 1h. Water was added and this was extracted with DCM. The organic layer was dried over $MgSO_4$ and evaporated in vacuo. Purification by semi prep HPLC (Eluent: 55-65% MeCN in pH10 0.1% [NH_3 in H_2O]) afforded 12,12,13,13-tetradeuterio-6-(1,1-dideuterio-2,2,2-trifluoro-ethoxy)-11-[1,1,2,2-tetradeuterio-2-[[7-(5-methyl-1,2,4-oxadiazol-3-yl)-1-isoquinolyl]amino]ethyl]-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2(7),3,5,8-tetraen-10-one (20.16 mg, 25%, 0.0368 mmol) as a yellow oil. ^{1}H NMR (600 MHz, DMSO) δ 8.88 (dd, *J* = 1.8, 0.9 Hz, 1H), 8.15 (dd, *J* = 8.5, 1.6 Hz, 1H), 8.06 (s, 1H), 7.98 (d, *J* = 5.7 Hz, 1H), 7.89 (d, *J* = 6.0 Hz, 1H), 7.85 (d, *J* = 8.5 Hz, 1H), 7.29 (dd, *J* = 6.0, 0.9 Hz, 1H), 7.01 (d, *J* = 0.9 Hz, 1H), 6.96 (d, *J* = 5.8 Hz, 1H), 2.68 (s, 3H); HPLC/MS m/z: 548.2 [M+H]+, Rt (U): 2.45 min

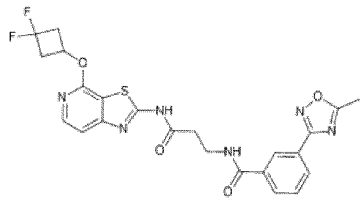
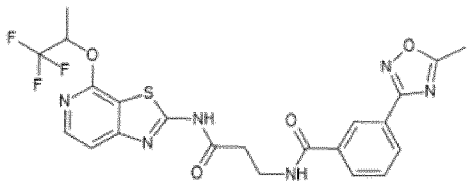
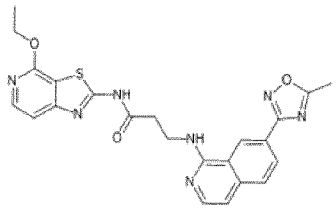
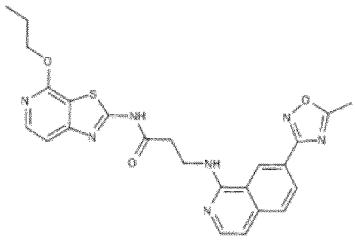
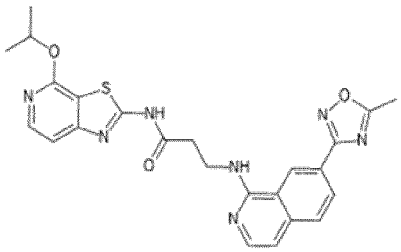
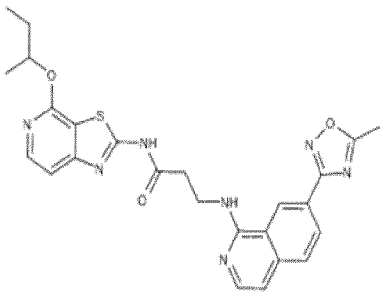
Example 88: 3-(2-methyl-2H-tetrazol-5-yl)-N-(2-(9-oxo-1-(2,2,2-trifluoroethoxy-1,1-d2)-6,7-dihydropyrido[3',4':4,5]pyrrolo[1,2-a]pyrazin-8(9H)-yl-6,6,7,7-d4)ethyl-1,1,2,2-d4)benzamide

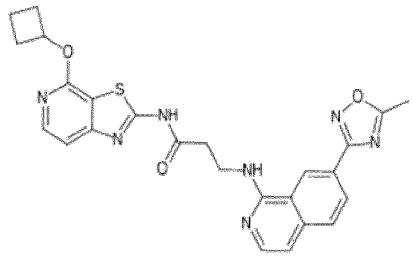
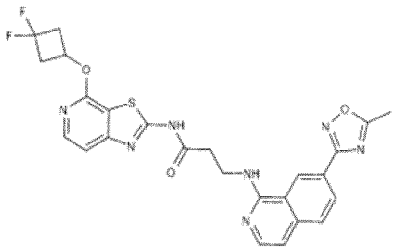
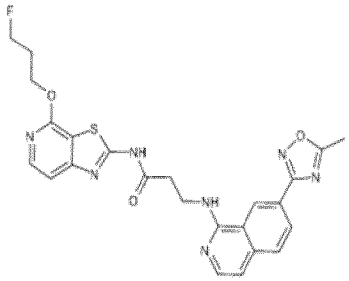
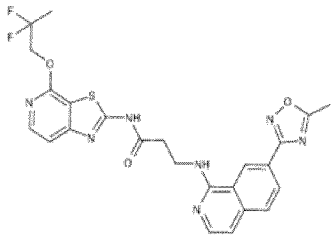
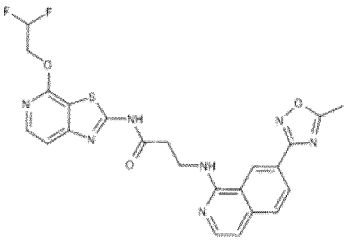
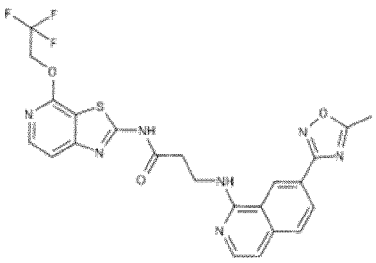


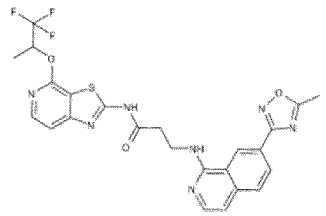
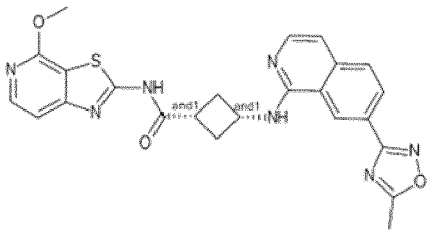
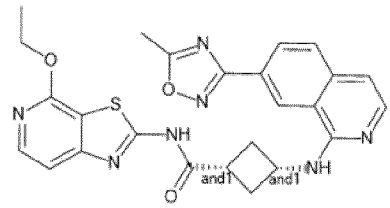
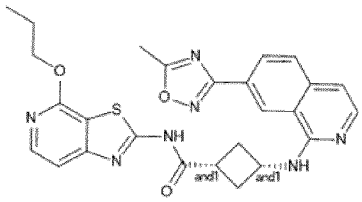
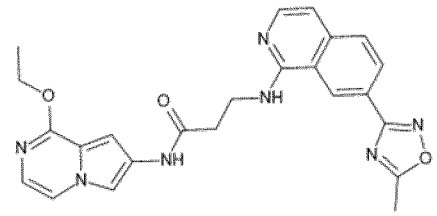
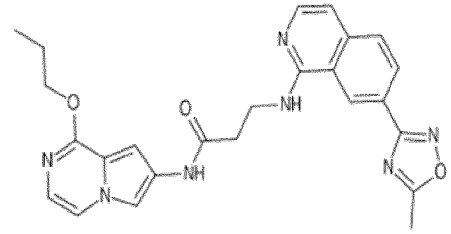
DIPEA (164.73 uL, 0.9458 mmol) was added to a mixture of 11-(2-amino-1,1,2,2-tetradeuterio-ethyl)-12,12,13,13-tetradeuterio-6-(1,1-dideuterio-2,2,2-trifluoro-ethoxy)-1,5,11-triazatricyclo[7.4.0.02,7]trideca-2(7),3,5,8-tetraen-10-one [See Example 87.6] (80.00 mg, 0.2364 mmol), 3-(2-Methyl-2H-tetrazol-5-yl)-benzoic acid (55.52 mg, 0.2719 mmol) and HATU (179.80 mg, 0.4729 mmol) in DCM (1.97 mL, 0.12 M) . This was stirred for 1h at 50 °C before the mixture was washed with water once then extracted with DCM, filtered over MgSO4 and evaporated. Purification by flash column chromatography (Eluent: 0-3.25% MeOH in DCM), followed by a prep TLC (10% MeOH in DCM), then trituration with EtOAc afforded 3-(2-methyl-2H-tetrazol-5-yl)-N-(2-(9-oxo-1-(2,2,2-trifluoroethoxy-1,1-d2)-6,7-dihydropyrido[3',4':4,5]pyrrolo[1,2-a]pyrazin-8(9H)-yl-6,6,7,7-d4)ethyl-1,1,2,2-d4)benzamide (27.4 mg, 22%, 0.0522 mmol) as a white solid. HPLC/MS m/z: 525.2 [M+H]+, Rt (U): 2.65 min.

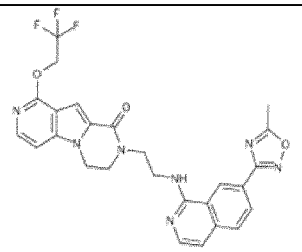
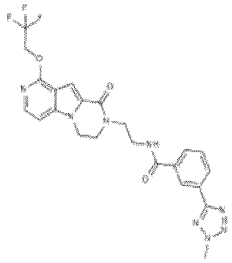
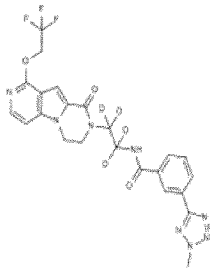
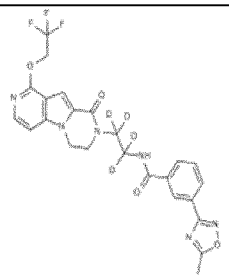
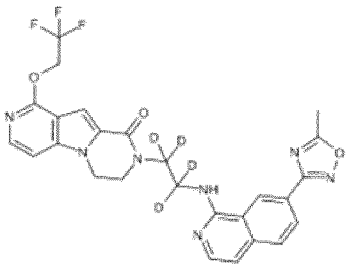
Example 89: Compound structures an IUPAC names

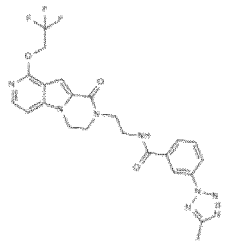
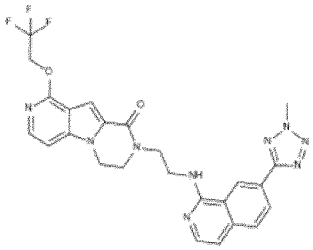
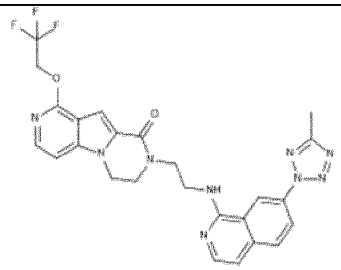
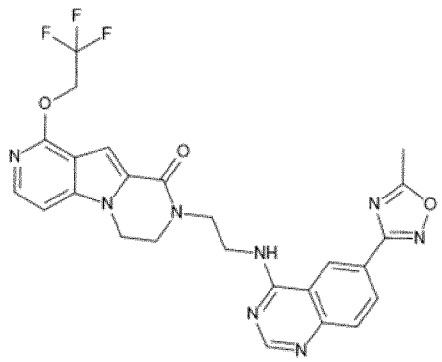
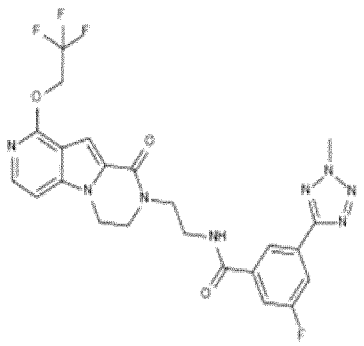
No	Structure	IUPAC names
1		N-{4-ethoxy-[1,3]thiazolo[5,4-c]pyridin-2-yl}-3-{[3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]formamido}propanamide
2		3-{[3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]formamido}-N-[4-(propan-2-yloxy)-[1,3]thiazolo[5,4-c]pyridin-2-yl]propanamide
3		N-{4-cyclobutoxy-[1,3]thiazolo[5,4-c]pyridin-2-yl}-3-{[3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]formamido}propanamide
4		N-[4-(butan-2-yloxy)-[1,3]thiazolo[5,4-c]pyridin-2-yl]-3-{[3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]formamido}propanamide
5		N-[4-(2,2-difluoroethoxy)-[1,3]thiazolo[5,4-c]pyridin-2-yl]-3-{[3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]formamido}propanamide
6		3-{[3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]formamido}-N-[4-(2,2,2-trifluoroethoxy)-[1,3]thiazolo[5,4-c]pyridin-2-yl]propanamide

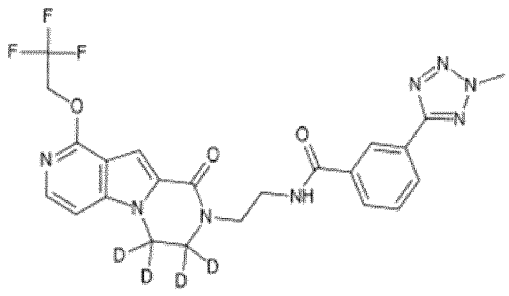
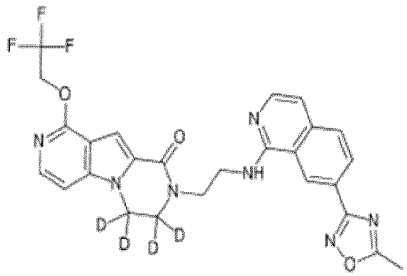
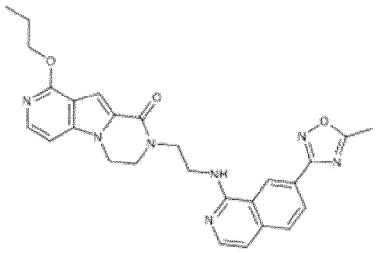
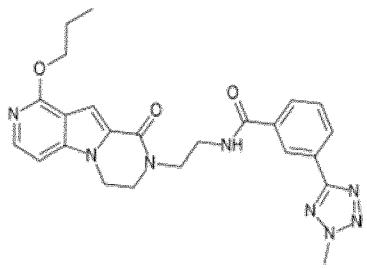
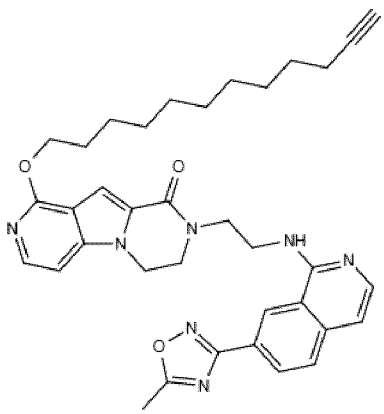
7		N-[4-(3,3-difluorocyclobutoxy)-[1,3]thiazolo[5,4-c]pyridin-2-yl]-3-{[3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]formamido}propanamide
8		3-{[3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]formamido}-N-{4-[(1,1,1-trifluoropropan-2-yl)oxy]-[1,3]thiazolo[5,4-c]pyridin-2-yl}propanamide
9		N-{4-ethoxy-[1,3]thiazolo[5,4-c]pyridin-2-yl}-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}propanamide
10		3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}-N-{4-propoxy-[1,3]thiazolo[5,4-c]pyridin-2-yl}propanamide
11		3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}-N-[4-(propan-2-yloxy)-[1,3]thiazolo[5,4-c]pyridin-2-yl]propanamide
12		N-[4-(butan-2-yloxy)-[1,3]thiazolo[5,4-c]pyridin-2-yl]-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}propanamide

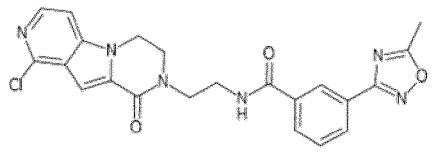
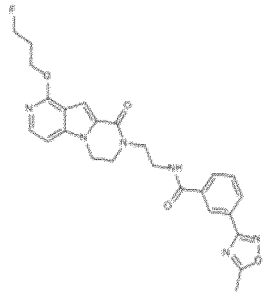
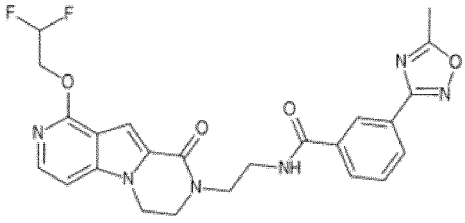
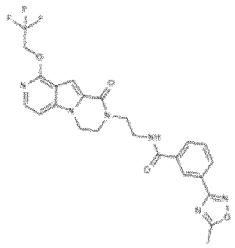
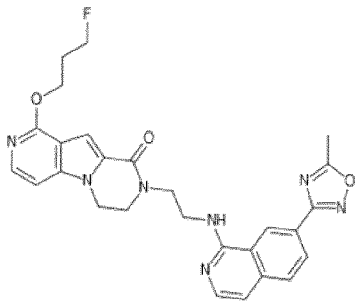
13		N-{4-cyclobutoxy-[1,3]thiazolo[5,4-c]pyridin-2-yl}-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}propanamide
14		N-[4-(3,3-difluorocyclobutoxy)-[1,3]thiazolo[5,4-c]pyridin-2-yl]-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}propanamide
15		N-[4-(3-fluoropropoxy)-[1,3]thiazolo[5,4-c]pyridin-2-yl]-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}propanamide
16		N-[4-(2,2-difluoropropoxy)-[1,3]thiazolo[5,4-c]pyridin-2-yl]-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}propanamide
17		N-[4-(2,2-difluoroethoxy)-[1,3]thiazolo[5,4-c]pyridin-2-yl]-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}propanamide
18		3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}-N-[4-(2,2,2-trifluoroethoxy)-[1,3]thiazolo[5,4-c]pyridin-2-yl]propanamide

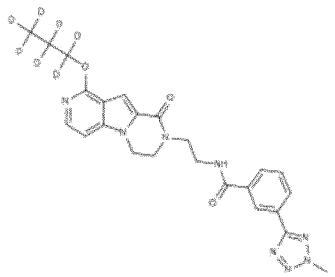
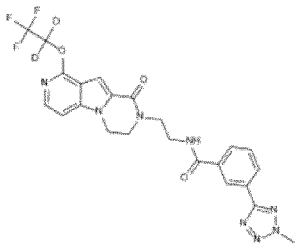
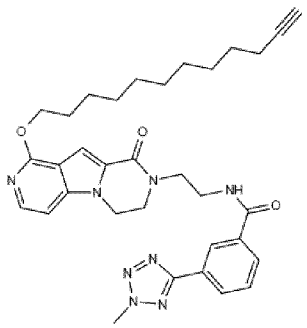
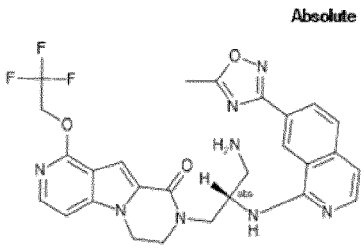
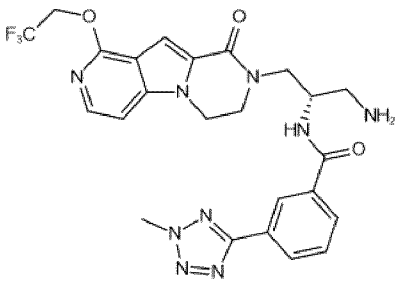
19		3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}-N-{4-[(1,1,1-trifluoropropan-2-yl)oxy]-[1,3]thiazolo[5,4-c]pyridin-2-yl}propanamide
20		(1s,3s)-N-{4-methoxy-[1,3]thiazolo[5,4-c]pyridin-2-yl}-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}cyclobutane-1-carboxamide
21		(1s,3s)-N-{4-ethoxy-[1,3]thiazolo[5,4-c]pyridin-2-yl}-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}cyclobutane-1-carboxamide
22		(1s,3s)-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}-N-{4-propoxy-[1,3]thiazolo[5,4-c]pyridin-2-yl}cyclobutane-1-carboxamide
23		N-{1-ethoxypyrrolo[1,2-a]pyrazin-7-yl}-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}propanamide
24		3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}-N-{1-propoxypyrrolo[1,2-a]pyrazin-7-yl}propanamide

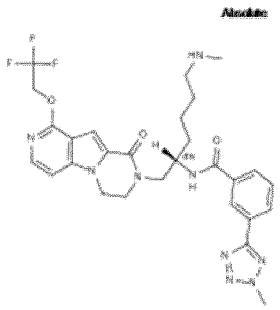
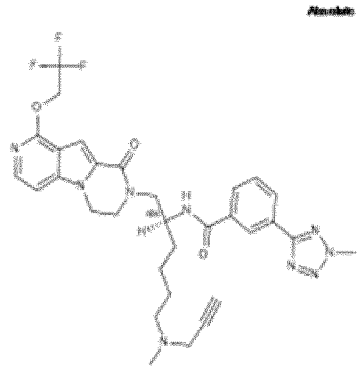
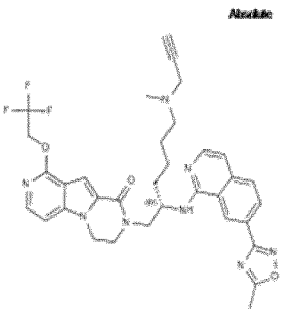
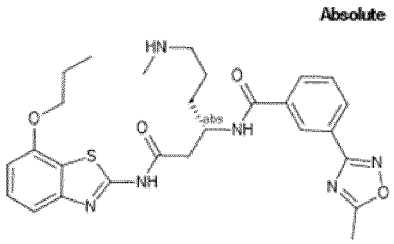
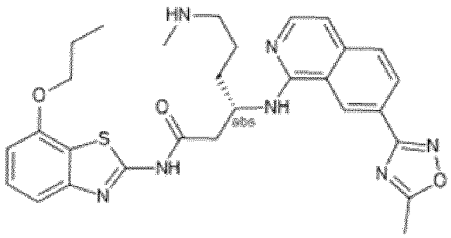
25		11-(2-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}ethyl)-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02.7]trideca-2(7),3,5,8-tetraen-10-one
26		3-(2-methyl-2H-1,2,3,4-tetrazol-5-yl)-N-{2-[10-oxo-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02.7]trideca-2,4,6,8-tetraen-11-yl]ethyl}benzamide
27		3-(2-methyl-2H-1,2,3,4-tetrazol-5-yl)-N-{2-[10-oxo-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02.7]trideca-2(7),3,5,8-tetraen-11-yl](1,1,2,2-2H4)ethyl}benzamide
28		3-(5-methyl-1,2,4-oxadiazol-3-yl)-N-{2-[10-oxo-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[[7.4.0.02.7]trideca-2(7),3,5,8-tetraen-11-yl](1,1,2,2-2H4)ethyl}benzamide
29		11-(2-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}(1,1,2,2-2H4)ethyl)-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02.7]trideca-2(7),3,5,8-tetraen-10-one

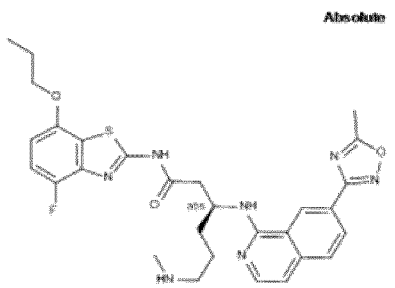
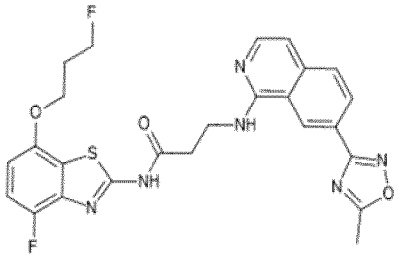
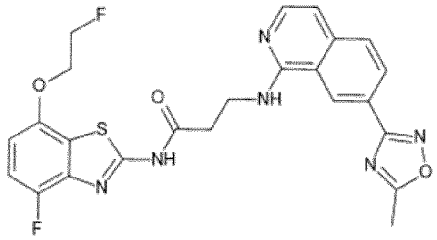
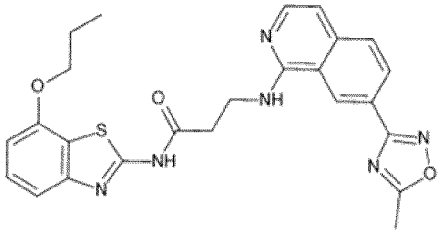
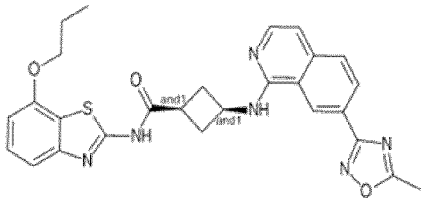
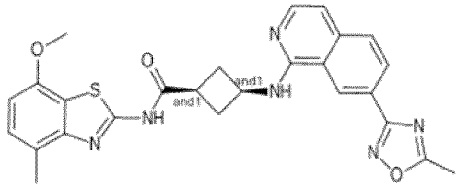
30		3-(5-methyl-2H-1,2,3,4-tetrazol-2-yl)-N-{2-[10-oxo-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02.7]trideca-2,4,6,8-tetraen-11-yl]ethyl}benzamide
31		11-(2-{[7-(2-methyl-2H-1,2,3,4-tetrazol-5-yl)isoquinolin-1-yl]amino}ethyl)-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02.7]trideca-2,4,6,8-tetraen-10-one
32		11-(2-{[7-(5-methyl-2H-1,2,3,4-tetrazol-2-yl)isoquinolin-1-yl]amino}ethyl)-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02.7]trideca-2,4,6,8-tetraen-10-one
33		11-(2-{[6-(5-methyl-1,2,4-oxadiazol-3-yl)quinazolin-4-yl]amino}ethyl)-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02.7]trideca-2,4,6,8-tetraen-10-one
34		3-fluoro-5-(2-methyl-2H-1,2,3,4-tetrazol-5-yl)-N-{2-[10-oxo-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02.7]trideca-2,4,6,8-tetraen-11-yl]ethyl}benzamide

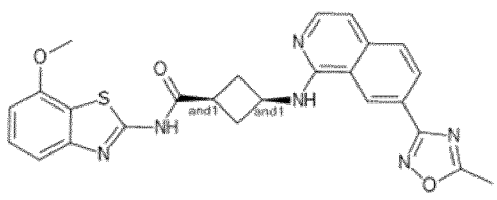
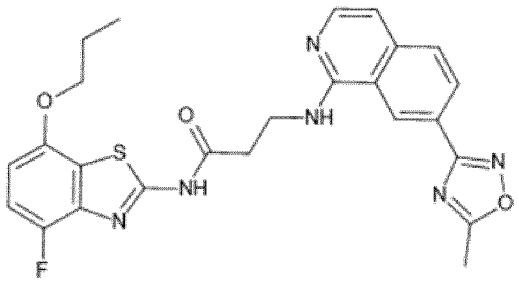
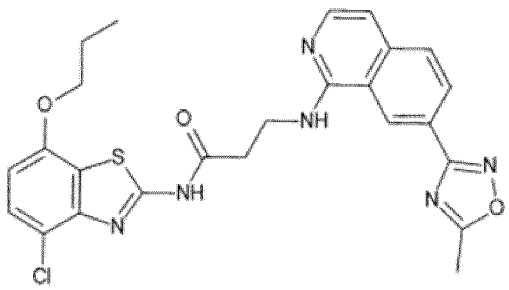
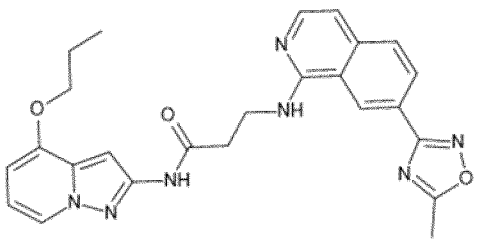
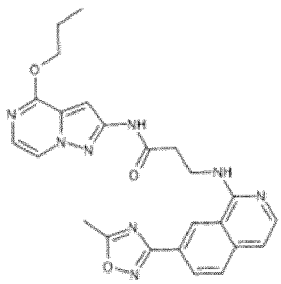
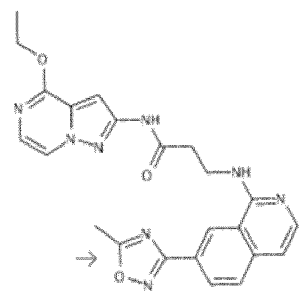
35		3-(2-methyl-2H-1,2,3,4-tetrazol-5-yl)-N-{2-[10-oxo-6-(2,2,2-trifluoroethoxy)(12,12,13,13-2H4)-1,5,11-triazatricyclo[7.4.0.02.7]trideca-2(7),3,5,8-tetraen-11-yl]ethyl}benzamide
36		11-(2-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}ethyl)-6-(2,2,2-trifluoroethoxy)(12,12,13,13-2H4)-1,5,11-triazatricyclo[7.4.0.02.7]trideca-2(7),3,5,8-tetraen-10-one
37		11-(2-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}ethyl)-6-propoxy-1,5,11-triazatricyclo[7.4.0.02.7]trideca-2(7),3,5,8-tetraen-10-one
38		3-(2-methyl-2H-1,2,3,4-tetrazol-5-yl)-N-(2-{10-oxo-6-propoxy-1,5,11-triazatricyclo[7.4.0.02.7]trideca-2,4,6,8-tetraen-11-yl}ethyl)benzamide
39		1-(Dodec-11-yn-1-yloxy)-8-(2-((7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl)amino)ethyl)-7,8-dihydropyrido[3',4':4,5]pyrrolo[1,2-a]pyrazin-9(6H)-one

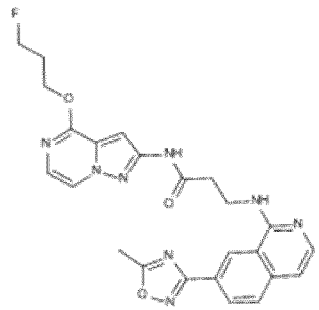
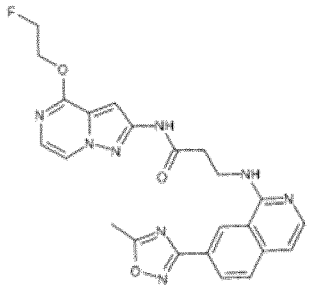
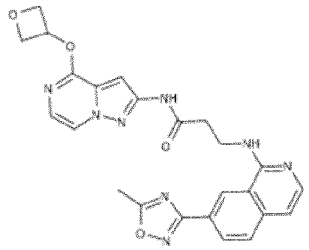
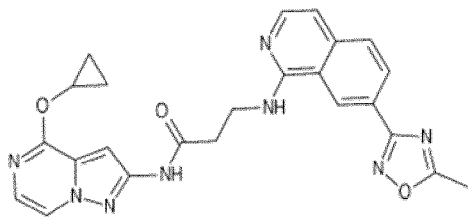
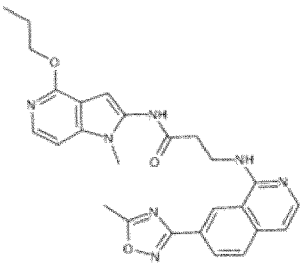
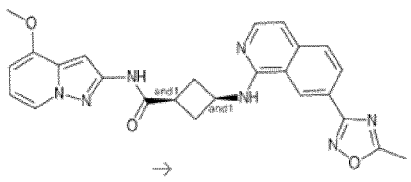
40		N-(2-{6-chloro-10-oxo-1,5,11-triazatricyclo[7.4.0.02.7]trideca-2,4,6,8-tetraen-11-yl}ethyl)-3-(5-methyl-1,2,4-oxadiazol-3-yl)benzamide
41		N-{2-[6-(3-fluoropropoxy)-10-oxo-1,5,11-triazatricyclo[7.4.0.02.7]trideca-2,4,6,8-tetraen-11-yl]ethyl}-3-(5-methyl-1,2,4-oxadiazol-3-yl)benzamide
42		N-{2-[6-(2,2-difluoroethoxy)-10-oxo-1,5,11-triazatricyclo[7.4.0.02.7]trideca-2,4,6,8-tetraen-11-yl]ethyl}-3-(5-methyl-1,2,4-oxadiazol-3-yl)benzamide
43		3-(5-methyl-1,2,4-oxadiazol-3-yl)-N-{2-[10-oxo-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02.7]trideca-2,4,6,8-tetraen-11-yl]ethyl}benzamide
44		6-(3-fluoropropoxy)-11-(2-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}ethyl)-1,5,11-triazatricyclo[7.4.0.02.7]trideca-2(7),3,5,8-tetraen-10-one

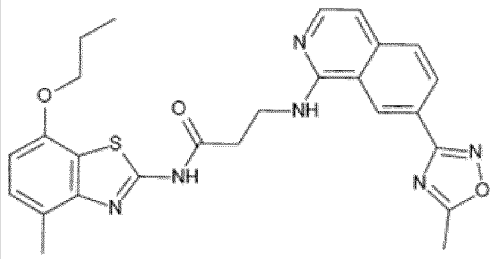
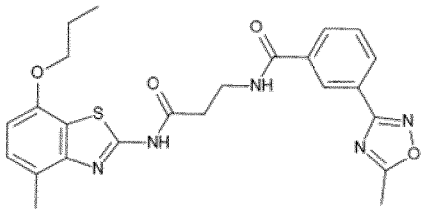
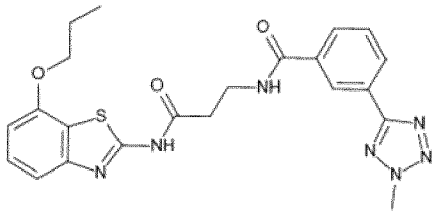
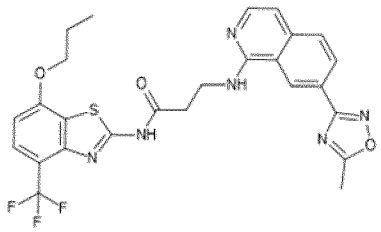
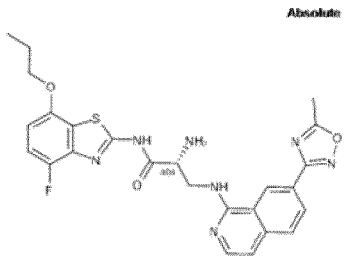
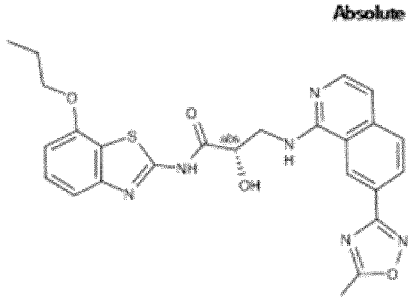
45		3-(2-methyl-2H-1,2,3,4-tetrazol-5-yl)-N-(2-{10-oxo-6-[(1,1,2,2,3,3,3-2H7)propoxy]-1,5,11-triazatricyclo[7.4.0.02.7]trideca-2,4,6,8-tetraen-11-yl}ethyl)benzamide
46		3-(2-methyl-2H-1,2,3,4-tetrazol-5-yl)-N-(2-{10-oxo-6-[2,2,2-trifluoro(1,1-2H2)ethoxy]-1,5,11-triazatricyclo[7.4.0.02.7]trideca-2,4,6,8-tetraen-11-yl}ethyl)benzamide
47		N-(2-(1-(dodec-11-yn-1-yloxy)-9-oxo-6,7-dihydropyrido[3',4':4,5]pyrrolo[1,2-a]pyrazin-8(9H)-yl)ethyl)-3-(2-methyl-2H-tetrazol-5-yl)benzamide
48	Absolute 	11-(3-amino-2-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}propyl)-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02.7]trideca-2,4,6,8-tetraen-10-one
49		(S)-3-(2-Methyl-2H-tetrazol-5-yl)-N-(6-(methylamino)-1-(9-oxo-1-(2,2,2-trifluoroethoxy)-6,7-dihydropyrido[3',4':4,5]pyrrolo[1,2-a]pyrazin-8(9H)-yl)hexan-2-yl)benzamide

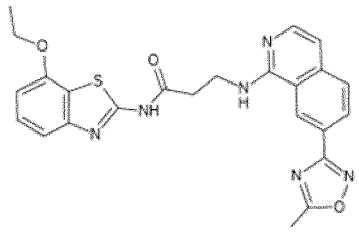
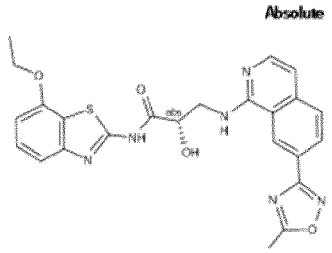
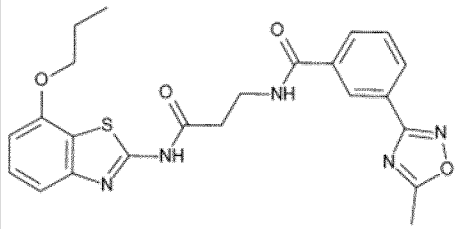
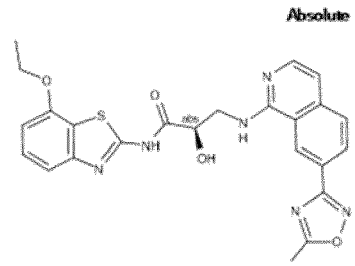
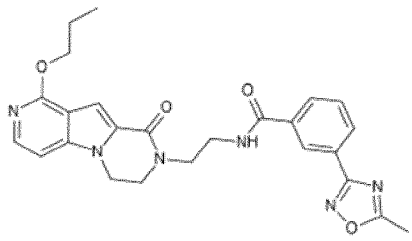
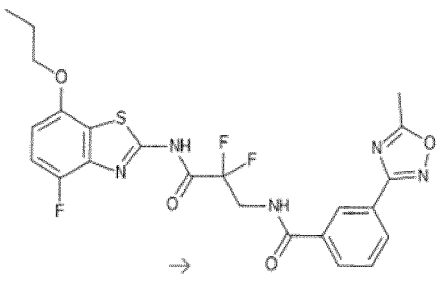
50		3-(2-methyl-2H-1,2,3,4-tetrazol-5-yl)-N-[6-(methylamino)-1-[10-oxo-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02.7]trideca-2(7),3,5,8-tetraen-11-yl]hexan-2-yl]benzamide
51		N-{6-[methyl(prop-2-yn-1-yl)amino]-1-[10-oxo-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02.7]trideca-2,4,6,8-tetraen-11-yl]hexan-2-yl}-3-(2-methyl-2H-1,2,3,4-tetrazol-5-yl)benzamide
52		11-[(2S)-6-[methyl(prop-2-yn-1-yl)amino]-2-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}hexyl]-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02.7]trideca-2,4,6,8-tetraen-10-one
53		N-{(S)-4-Methylamino-1-[(7-propoxy-benzothiazol-2-ylcarbamoyl)-methyl]-butyl}-3-(5-methyl-[1,2,4]oxadiazol-3-yl)-benzamide
54		(3S)-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}-6-(methylamino)-N-(7-propoxy-1,3-benzothiazol-2-yl)hexanamide

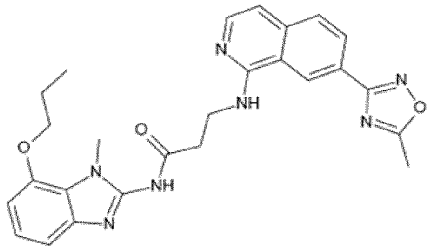
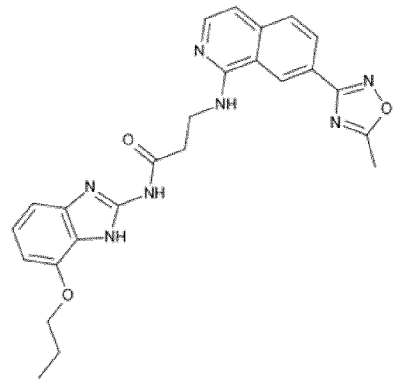
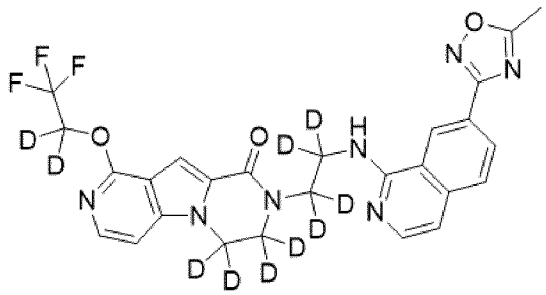
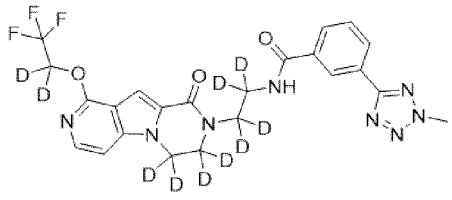
55		(3S)-N-(4-fluoro-7-propoxy-1,3-benzothiazol-2-yl)-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}-6-(methylamino)hexanamide
56		N-[4-fluoro-7-(3-fluoropropoxy)-1,3-benzothiazol-2-yl]-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}propanamide
57		N-[4-fluoro-7-(2-fluoroethoxy)-1,3-benzothiazol-2-yl]-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}propanamide
58		3-[7-(5-Methyl-[1,2,4]oxadiazol-3-yl)-isoquinolin-1-ylamino]-N-(7-propoxy-benzothiazol-2-yl)-propionamide
59		3-[7-(5-Methyl-[1,2,4]oxadiazol-3-yl)-isoquinolin-1-ylamino]-cyclobutanecarboxylic acid (7-propoxy-benzothiazol-2-yl)-amide
60		3-[7-(5-Methyl-[1,2,4]oxadiazol-3-yl)-isoquinolin-1-ylamino]-cyclobutanecarboxylic acid (7-methoxy-4-methyl-benzothiazol-2-yl)-amide

61		3-[7-(5-Methyl-[1,2,4]oxadiazol-3-yl)-isoquinolin-1-ylamino]-cyclobutanecarboxylic acid (7-methoxy-benzothiazol-2-yl)-amide
62		N-(4-fluoro-7-propoxy-1,3-benzothiazol-2-yl)-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}propanamide
63		N-(4-chloro-7-propoxy-1,3-benzothiazol-2-yl)-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}propanamide
64		3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}-N-{4-propoxypyrazolo[1,5-a]pyridin-2-yl}propanamide
65		3-[7-(5-Methyl-[1,2,4]oxadiazol-3-yl)-isoquinolin-1-ylamino]-N-(4-propoxy-pyrazolo[1,5-a]pyrazin-2-yl)-propionamide
66		N-{4-ethoxypyrazolo[1,5-a]pyrazin-2-yl}-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}propanamide

67		N-[4-(3-fluoropropoxy)pyrazolo[1,5-a]pyrazin-2-yl]-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}propanamide
68		N-[4-(2-fluoroethoxy)pyrazolo[1,5-a]pyrazin-2-yl]-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}propanamide
69		3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}-N-[4-(oxetan-3-yloxy)pyrazolo[1,5-a]pyrazin-2-yl]propanamide
70		N-{4-cyclopropoxypyrazolo[1,5-a]pyrazin-2-yl}-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}propanamide
71		3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}-N-{1-methyl-4-propoxy-1H-pyrrolo[3,2-c]pyridin-2-yl}propanamide
72		3-[7-(5-Methyl-[1,2,4]oxadiazol-3-yl)-isoquinolin-1-ylamino]-cyclobutanecarboxylic acid (4-methoxy-pyrazolo[1,5-a]pyridin-2-yl)-amide

73		3-[7-(5-Methyl-[1,2,4]oxadiazol-3-yl)-isoquinolin-1-ylamino]-N-(4-methyl-7-propoxy-benzothiazol-2-yl)-propionamide
74		3-(5-Methyl-[1,2,4]oxadiazol-3-yl)-N-[2-(4-methyl-7-propoxy-benzothiazol-2-ylcarbamoyl)-ethyl]-benzamide
75		3-(2-Methyl-2H-tetrazol-5-yl)-N-[2-(7-propoxy-benzothiazol-2-ylcarbamoyl)-ethyl]-benzamide
76		3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}-N-[7-propoxy-4-(trifluoromethyl)-1,3-benzothiazol-2-yl]propanamide
77		(2R)-2-amino-N-(4-fluoro-7-propoxy-1,3-benzothiazol-2-yl)-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}propanamide
78		(S)-2-Hydroxy-3-[7-(5-methyl-[1,2,4]oxadiazol-3-yl)-isoquinolin-1-ylamino]-N-(7-propoxy-benzothiazol-2-yl)-propionamide

79		N-(7-ethoxy-1,3-benzothiazol-2-yl)-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}propanamide
80		(2S)-N-(7-ethoxy-1,3-benzothiazol-2-yl)-2-hydroxy-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}propanamide
81		3-(5-Methyl-[1,2,4]oxadiazol-3-yl)-N-[2-(7-propoxy-benzothiazol-2-ylcarbamoyl)-ethyl]-benzamide
82		(2R)-N-(7-ethoxy-1,3-benzothiazol-2-yl)-2-hydroxy-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}propanamide
83		3-(5-methyl-1,2,4-oxadiazol-3-yl)-N-(2-{10-oxo-6-propoxy-1,5,11-triazatricyclo[7.4.0.02.7]trideca-2,4,6,8-tetraen-11-yl}ethyl)benzamide
84		2,2-difluoro-N-(4-fluoro-7-propoxy-1,3-benzothiazol-2-yl)-3-{[3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]formamido}propanamide

85		3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}-N-(1-methyl-7-propoxy-1H-1,3-benzodiazol-2-yl)propanamide
86		3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}-N-(7-propoxy-1H-1,3-benzodiazol-2-yl)propanamide
87		8-(2-((7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl)amino)ethyl-1,1,2,2-d4)-1-(2,2,2-trifluoroethoxy-1,1-d2)-7,8-dihydropyrido[3',4':4,5]pyrrolo[1,2-a]pyrazin-9(6H)-one-6,6,7,7-d4
88		3-(2-methyl-2H-tetrazol-5-yl)-N-(2-(9-oxo-1-(2,2,2-trifluoroethoxy-1,1-d2)-6,7-dihydropyrido[3',4':4,5]pyrrolo[1,2-a]pyrazin-8(9H)-yl-6,6,7,7-d4)ethyl-1,1,2,2-d4)benzamide

Example 90: Testing compounds of the present invention for inhibitory activities against HSET - HSET ADP-Glo Assay S – 3 µM ATP

Reagents: (+4 °C Storage)

– Paclitaxel Prod.No.TXD.01 2 mM in DMSO (from Universal Biologicals Cambridge).
– Tubulin Protein (Pre-formed Microtubules): Bovine Brain Prod.No.MT001-XL Lot.025 10 mg/mL (from Universal Biologicals Cambridge).

Reagents: (-80 °C Storage)
– MT001-XL - Tubulin Protein (Pre-formed Microtubules): Bovine Brain - reconstituted in buffer – 15 mM PIPES pH7, 1 mM MgCl2, 20 µM paclitaxel (aliquots at 10 mg/mL) from Universal Biologicals Cambridge.
– HSET full length protein - Current batch is FL HSET Prep1 (SEQ-000096_002-01_01)
– Buffer is 20 mM Hepes pH 7.5, 200 mM NaCl, 2 mM TCEP, 5% glycerol (5 µL aliquots at 10.2 µM)

Reagents: (-20°C Storage)
– ADP-Glo Kinase Assay kit (Promega Prod.No.V9102) 10,000 assay points
– ADP-Glo reagent (50 mL), Kinase Detection Reagent (100 mL), and Ultrapure ATP (10 mM) aliquoted

Buffer Stocks (filtered and stored at rt for up to 1 month)
– HEPES acid, 4-(2-Hydroxyethyl)piperazine-1-ethanesulfonic acid MW:238, 238.3 mg/mL = 1M
– 7149 mg/30 mL = 1M (pH to 6.8 with 5 M NaOH)
– PIPES, 1,4-Piperazinediethanesulfonic acid MW: 302.4, 30.24 mg/mL = 100 mM; 907.2 mg/30 mL = 100 mM (pH to 7 with 5 M NaOH, white cloudy suspension until the pH changes)
– EGTA, Ethylene glycol-bis(2-aminoethylether)-N,N,N′,N′-tetraacetic acid MW: 380.35, 38.035 mg/mL = 100 mM
– 1901.75 mg/50 mL = 100 mM (pH to ~7 with 5 M NaOH) - takes a long time to get into solution and for pH to stabilize
– Triton-X-100, MW: 625, 62.5 mg/mL = 100 mM (6.25% w/v) (viscous, pipette Triton X-100 with a Gilson using a trimmed pipette tip)

ECHO Protocol

– Create an ECHO intermediate plate by adding 24.5 µL DMSO to columns 1 & 2, and 40 µL DMSO to columns 23 & 24 of an ECHO 384PP plate
– Add 100 nL of compound/DMSO per well in 384-well Proxi-Plate Plus (white) – Perkin Elmer Cat# 6008289 using ECHO dose response protocol 100 nL normal to proxi_8pt_200 uM.

Assay buffer (Keep on ice): HEPES pH 6.8, $MgCl_2$, EGTA, Triton X-100, DTT, HPLC H_2O

Microtubule Working Solution (3.2):
– 1 ml PM buffer: PIPES pH 7.0, $MgCl_2$, HPLC H_2O, Paclitaxel, mix well, store at rt
– Then add 26.4 µL of 10 mg/ml microtubules to724 µL of the above PM buffer to make 750 µL of microtubule working solution @ 350 µg/mL microtubules (store at rt)

Stock HSET enzyme solution (3.1) - keep on ice
– Add 1.33 µL 10.2 µM HSET Prep1 (SEQ-000096_002-01_01) to 1358 µL assay buffer to make a 10 nM stock for a 5 nM final assay concentration (1/1020 dilution).

HSET/Microtubule working solution (3.3)
– Mix solutions 3.1 and 3.2 in the ratio of 2.5:1 (1214.3 µL 3.1 + 485.7 µL 3.2) keep at rt for 15 min
– 3.2 is diluted 3.5-fold, 3.1 is diluted 1.4-fold

BLANK solution is 357 µL 2XAB + 143 µL microtubule working solution 3.2.
(Same proportions as HSET/Microtubule working solution (3.3))

ATP Working solution is 1 µL 10 mM UltraPure ATP (Promega kit) + 999 µL ddH_2O gives 10 µM ATP for a 3 µM final assay concentration, stored on ice.

Assay procedure in PROXIPLATE 384 PLUS WHITE (Perkin Elmer) plates
(Remove 2.4 mL ADP Glo and 4.5 mL Kinase detection reagent from freezer to warm up to rt)
- Add 3.5 µL BLANK solution to assay plate (column 12)
- Add 3.5 µL HSET/Microtubule solution (3.3) (columns 1-11 & 13-24)
- Centrifuge at 1000 rpm for 1 min

- (pre-incubate enzyme and compound for 10 min)

Add 1.5 µL of 10 µM ATP to start reaction gives a final [HSET] of 5 nM, [ATP] of 3 µM and [microtubule] of 70 µg/mL, centrifuge at 1000 rpm for 1 min and incubated at rt for 80 min.

After the 80-minute incubation, stop reaction by adding 5 µL ADP-Glo reagent to all wells. Centrifuge for 1 min at 1000 rpm, leave for 40 min at rt.
In the dark/away from direct light, add 10 µL Kinase Detection Reagent (KDR) to all wells, Seal plate with a Topseal (Perkin Elmer Cat# 6050185) and centrifuge as above, leave for 40 min at rt covered in foil.

Read luminescence on New Envision using Protocol: US luminescence 384.

Results:

Compound Example No.	**COMBINED HSET ADP GLO IC_{50} (µM)**
1	0,13
2	0,074
3	0,06
4	0,14
5	0,064
6	0,01
7	0,067
8	0,034
9	0,012
10	0,008
11	0,008
12	0,008
13	0,016
14	0,016
15	0,003
16	0,002

17	0,006
18	0,003
19	0,007
20	6,5
21	0,33
22	0,23
23	0,96
24	0,24
25	0,002
26	0,002
27	0,002
28	0,003
29	0,001
30	0,005
31	0,001
32	0,002
33	0,001
34	0,002
35	<0.001
36	<0.001
37	0,003
38	0,008
39	0,009
40	1,346
41	0,016
42	0,017
43	0,004
44	0,002
45	0,007
46	0,001
47	0,001
48	0,043
49	0,654
50	1,214

51	0,503
52	0,036
53	0,014
54	0,008
55	0,006
56	0,008
57	0,012
58	0,005
59	0,193
60	0,33
61	0,358
62	0,008
63	0,014
64	0,015
65	0,024
66	0,094
67	0,045
68	0,203
69	0,835
70	0,104
71	1,079
72	1,216
73	0,008
74	0,048
75	0,017
76	0,105
77	0,048
78	0,002
79	0,007
80	0,011
81	0,027
82	0,006
83	0,011
84	0,022

85	0,169
86	0,027
87	0,001
88	0,003

Example 91: Injection vials

A solution of 100 g of a compound of the present invention and 5 g of disodium hydrogenphosphate in 3 L of bidistilled water is adjusted to pH 6.5 using 2 N hydrochloric acid, filtered under sterile conditions, transferred into injection vials, lyophilised under sterile conditions and sealed under sterile conditions. Each injection vial contains 5 mg of a compound of the present invention.

Example 92: Solution

A solution is prepared from 1 g of a compound of the present invention, 9.38 g of NaH_2PO_4. 2 H_2O, 28.48 g of Na_2HPO_4. 12 H_2O and 0.1 g of benzalkonium chloride in 940 mL of bidistilled water. The pH is adjusted to 6.8, and the solution is made up to 1 L and sterilised by irradiation.

Example 93: Ampoules

A solution of 1 kg of a compound of the present invention in 60 L of bidistilled water is filtered under sterile conditions, transferred into ampoules, lyophilised under sterile conditions and sealed under sterile conditions. Each ampoule contains 10 mg of a compound of the present invention.

References

Basto, R., Brunk, K., Vinadogrova, T., Peel, N., Franz, A., Khodjakov, A., and Raff, J.W. (2008). Centrosome amplification can initiate tumorigenesis in flies. Cell 133, 1032–1042.

Bender, A., Young, D.W., Jenkins, J.L., Serrano, M., Mikhailov, D., Clemons, P.A., and Davies, J.W. (2007). Chemogenomic data analysis: prediction of small-molecule targets and the advent of biological fingerprint. Comb. Chem. High Throughput Screen. 10, 719–731.

Bickerton, G.R., Paolini, G.V., Besnard, J., Muresan, S., and Hopkins, A.L. (2012). Quantifying the chemical beauty of drugs. Nat. Chem. 4, 90–98.

Boveri, T. (2008). Concerning the origin of malignant tumours by Theodor Boveri. Translated and annotated by Henry Harris. J. Cell Sci. 121(Suppl 1), 1–84.

Cai, S., Weaver, L.N., Ems-McClung, S.C., and Walczak, C.E. (2010). Proper organization of microtubule minus ends is needed for midzone stability and cytokinesis. Curr. Biol. 20, 880–885.

Cai, S., Weaver, L.N., Ems-McClung, S.C., Walczak, C.E. (2009) Kinesin-14 family proteins HSET/XCTK2 control spindle length by cross-linking and sliding microtubules. Molecular Biology of the Cell 20(5), pp. 1348-1359

Chan, J.Y. (2011). A clinical overview of centrosome amplification in human cancers. Int. J. Biol. Sci. 7, 1122–1144.

De, S., Cipriano, R., Jackson, M.W., Stark, G.R.(2009) Overexpression of kinesins mediates docetaxel resistance in breast cancer cells. Cancer Research 69(20), pp. 8035-8042

Drosopoulos K., Tang C., Chao W. C., Linardopoulos S. (2014) APC/C is an essential regulator of centrosome clustering. Nat Commun. 2014, 5: 3686

Ganem, N.J., and Compton, D.A. (2004). The Kinl kinesin Kif2a is required for bipolar spindle assembly through a functional relationship with MCAK. J. Cell Biol. 166, 473–478.

Ganem, N.J., Godinho, S.A., and Pellman, D. (2009). A mechanism linking extra centrosomes to chromosomal instability. Nature 460, 278–282.

Gatlin, J.C., and Bloom, K. (2010). Microtubule motors in eukaryotic spindle assembly and maintenance. Semin. Cell Dev. Biol. 21, 248–254.

Gaulton, A., Bellis, L.J., Bento, A.P., Chambers, J., Davies, M., Hersey, A., Light, Y., McGlinchey, S., Michalovich, D., Al-Lazikani, B., and Overington, J.P. (2012). ChEMBL: a large-scale bioactivity database for drug discovery. Nucleic Acids Res. 40(Database issue), D1100–D1107.

Gordon, M.B., Howard, L., and Compton, D.A. (2001). Chromosome movement in mitosis requires microtubule anchorage at spindle poles. J. Cell Biol. 152, 425–434.

Goshima, G., Nédélec, F., and Vale, R.D. (2005). Mechanisms for focusing mitotic spindle poles by minus end-directed motor proteins. J. Cell Biol. 171, 229–240.

Grinberg-Rashi, H., Ofek, E., Perelman, M., Skarda, J., Yaron, P., Hajdúch, M., Jacob-Hirsch, J., Amariglio, N., Krupsky, M., Simansky, D.A., et al. (2009). The expression of three genes in primary non-small cell lung cancer is associated with metastatic spread to the brain. Clin. Cancer Res. 15, 1755–1761.

Hall, I.M., Noma, K., and Grewal, S.I. (2003). RNA interference machinery regulates chromosome dynamics during mitosis and meiosis in fission yeast. Proc. Natl. Acad. Sci. USA 100, 193–198.

Holdgate, G.A., and Ward, W.H.J. (2005). Measurements of binding thermodynamics in drug discovery. Drug Discov. Today 10, 1543–1550.

Huszar, D., Theoclitou, M.E., Skolnik, J., and Herbst, R. (2009). Kinesin motor proteins as targets for cancer therapy. Cancer Metastasis Rev. 28, 197–208.

Jordan, M.A., and Wilson, L. (2004). Microtubules as a target for anticancer drugs. Nat. Rev. Cancer 4, 253–265.

Klabunde, T. (2007). Chemogenomic approaches to drug discovery: similar receptors bind similar ligands. Br. J. Pharmacol. 152, 5–7.

Kleylein-Sohn, J., Pöllinger, B., Ohmer, M., Hofmann, F., Nigg, E.A., Hemmings, B.A., and Wartmann, M. (2012). Acentrosomal spindle organization renders cancer cells dependent on the kinesin HSET. J. Cell Sci. 125, 5391–5402.

Kraljevic Pavelic, S., Sedic, M., Bosnjak, H., Spaventi, S., and Pavelic, K. (2011) Metastasis: new perspectives on an old problem. Mol. Cancer 10, 22.

Krämer, A., Maier, B., and Bartek, J. (2011). Centrosome clustering and chromosomal (in)stability: a matter of life and death. Mol. Oncol. 5, 324–335.

Kwon, M., Godinho, S.A., Chandhok, N.S., Ganem, N.J., Azioune, A., Thery, M., and Pellman, D. (2008). Mechanisms to suppress multipolar divisions in cancer cells with extra centrosomes. Genes Dev. 22, 2189–2203.

Li, Y., Lu, W., Chen, D., Boohaker, R. J., Zhai, L., Padmalayam, I., Wennerberg, K., Xu, B., Zhang, W. 2015) KIFC1 is a novel potential therapeutic target for breast cancer. Cancer Biology and Therapy 16(9), pp. 1316-1322

Lipinski, C.A., Lombardo, F., Dominy, B.W., and Feeney, P.J. (2001). Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Adv. Drug Deliv. Rev. 46, 3–26.

Luo, L., Carson, J.D., Dhanak, D., Jackson, J.R., Huang, P.S., Lee, Y., Sakowicz, R., and Copeland, R.A. (2004). Mechanism of inhibition of human KSP by monastrol: insights from kinetic analysis and the effect of ionic strength on KSP inhibition. Biochemistry 43, 15258–15266.

Mahoney, N.M., Goshima, G., Douglass, A.D., and Vale, R.D. (2006). Making microtubules and mitotic spindles in cells without functional centrosomes. Curr. Biol. 16, 564–569.

Marx, A., Hoenger, A., and Mandelkow, E. (2009). Structures of kinesin motor proteins. Cell Motil. Cytoskeleton 66, 958–966.

Mayer, T.U., Kapoor, T.M., Haggarty, S.J., King, R.W., Schreiber, S.L., and Mitchison, T.J. (1999). Small molecule inhibitor of mitotic spindle bipolarity identified in a phenotype-based screen. Science 286, 971–974.

Meunier, S., and Vernos, I. (2012). Microtubule assembly during mitosis - from distinct origins to distinct functions? J. Cell Sci. 125, 2805–2814.

Mountain, V., Simerly, C., Howard, L., Ando, A., Schatten, G., and Compton, D.A. (1999). The kinesin-related protein, HSET, opposes the activity of Eg5 and cross-links microtubules in the mammalian mitotic spindle. J. Cell Biol. 147, 351–366.

Myers and Collins, 2016: Myers S., Collins I. (2016). Recent findings and future directions for interpolar mitotic kinesin inhibitors in cancer therapy. Future Med Chem. 8: 463-89

Neres, J., Wilson, D.J., Celia, L., Beck, B.J., and Aldrich, C.C. (2008). Aryl acid adenylating enzymes involved in siderophore biosynthesis: fluorescence polarization assay, ligand specificity, and discovery of non-nucleoside inhibitors via high-throughput screening. Biochemistry 47, 11735–11749.

Niesen, F.H., Berglund, H., and Vedadi, M. (2007). The use of differential scanning fluorimetry to detect ligand interactions that promote protein stability. Nat. Protoc. 2, 2212–2221.

Nigg, E.A. (2002). Centrosome aberrations: cause or consequence of cancer progression? Nat. Rev. Cancer 2, 815–825.

Ogden, A., Rida, P.C., and Aneja, R. (2012). Let's huddle to prevent a muddle: centrosome declustering as an attractive anticancer strategy. Cell Death Differ. 19, 1255–1267.

Ogden, A., Rida, P.C., and Aneja, R. (2013). Heading off with the herd: how cancer cells might maneuver supernumerary centrosomes for directional migration. Cancer Metastasis Rev. 32, 269–287.

Rath, O., Kozielski, F. (2012) Kinesins and cancer. Nature Reviews Cancer 12(8), pp. 527-539

Pannu, V., Rida, P.C.G., Ogden, A., Turaga, R. C., Donthamsetty, S, Bowen N. J., Rudd K, Gupta M. V., Reid M. D., Cantuaria G., Walczak, C.E., Aneja, R. (2015) HSET overexpression fuels tumor progression via centrosome clustering-independent mechanisms in breast cancer patients. Oncotarget. 6: 6076-6091

Patel N. E., Weekes D., Drosopoulos K., Gazinska P., Noel E., Rashid M., Mirza H., Quist J., Braso-Maristany F., Mathew S., Ferro R., Mendes Pereira A., Prince C., Noor F., Francesch-Domenech E., Marlow R., de Rinaldis E., Grigoriadis A., Linardopoulos S., Marra P., Tutt A. N. J. (2018). Integrated genomics and functional validation identifys malignant cell specific dependencies in triple negative breast cancer. Nat. Commun. 9: 1044

Pawar, S., Donthamsetty, S., Pannu, V., Rida, P., Ogden, A., Bowen, N., Osan, R., Cantuaria, G., Aneja, R. (2014) KIFCI, a novel putative prognostic biomarker for ovarian adenocarcinomas: Delineating protein interaction networks and signaling circuitries. Journal of Ovarian Research 7(1),53

Sharp, D.J., Rogers, G.C., and Scholey, J.M. (2000). Microtubule motors in mitosis. Nature 407, 41–47.

Tillement, V., Remy, M.H., Raynaud-Messina, B., Mazzolini, L., Haren, L., and Merdes, A. (2009). Spindle assembly defects leading to the formation of a monopolar mitotic apparatus. Biol. Cell 101, 1–11.

Vichai, V., and Kirtikara, K. (2006). Sulforhodamine B colorimetric assay for cytotoxicity screening. Nat. Protoc. 1, 1112–1116.

Walczak, C.E., Verma, S., Mitchison, T.J. (1997) XCTK2: A kinesin-related protein that promotes mitotic spindle assembly in Xenopus laevis egg extracts. Journal of Cell Biology 136(4), pp. 859-870

Watts C. A., Richards F. M., Bender A., Bond P. J., Korb O., Kern O., Riddick M., Owen P., Myers R. M., Raff J., Gergely F., Jodrell D. I. (2013) Design, synthesis, and biological evaluation of an allosteric inhibitor of HSET that targets cancer cells with supernumerary centrosomes. Chemistry & Biology 20: 1399-1410

Wu J., Mikule K., Wang W., Su N., Petteruti P., Gharahdaghi F., Code E., Zhu X., Jacques K., Lai Z., Yang B., Lamb M.L. (2013) Discovery and mechanistic study of a small molecule inhibitor for motor protein KIFC1. ACS Chem Biol. 8: 2201-2208
Zhang et al., 2016: Zhang W., Zhai L., Wang Y., Boohaker R. J., Lu W., Gupta V. V., Padmalayam I., Bostwick R. J., White E. L., Ross L. J., Maddry J., Ananthan S. Discovery of a novel inhibitor of kinesin-like protein KIFC1. Biochem J. 473: 1027-1035

Yang, Z., Loncarek, J., Khodjakov, A., and Rieder, C.L. (2008). Extra centrosomes and/or chromosomes prolong mitosis in human cells. Nat. Cell Biol. 10, 748–751.

Zyss, D., and Gergely, F. (2009). Centrosome function in cancer: guilty or innocent? Trends Cell Biol. 19, 334–346.

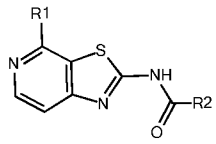
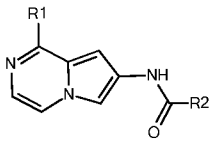
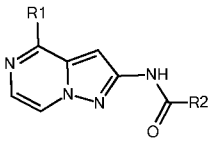
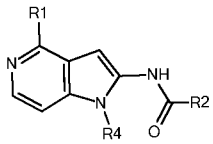
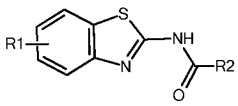
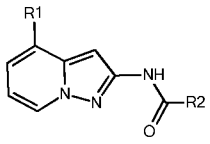
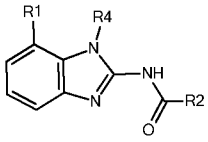
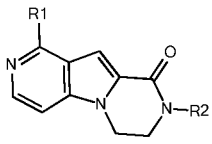
Claims

1. Compound of the formula I,

I

wherein

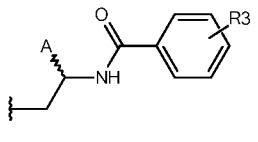
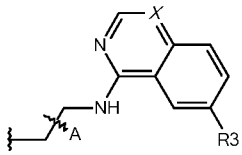
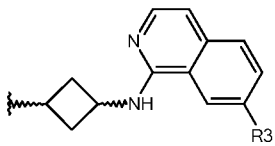
W denotes

wherein 1-4 H-atoms may be replaced by D

R^1 denotes Hal, A or OA,

R^2 denotes

X denotes CH or N,

A denotes H, F, OH, NH_2, or unbranched or branched alkyl or cycloalkyl with 1-12 C-atoms, which may be substituted by R^4 and wherein two adjacent CH- and/or CH_2-groups may form a double or triple bond and wherein one or two non-adjacent CH- and/or CH_2-groups may be replaced by N-, O- and/or S-atoms and wherein 1-7 H-atoms may be replaced by D, F or Cl,

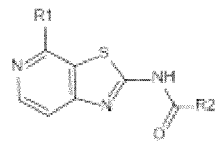
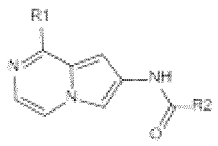
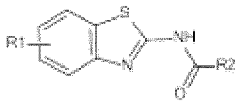
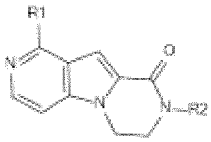
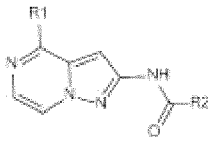
R^3 denotes H or A,

R^4 denotes H or unbranched or branched alkyl with 1-4 C-atoms,

Hal denotes F, Cl, Br or I

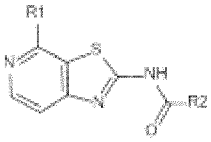
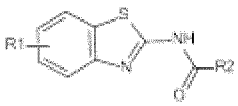
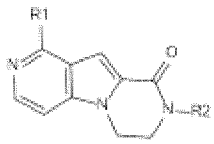
and physiologically acceptable salts, derivatives, solvates, prodrugs and stereoisomers thereof, including mixtures thereof in all ratios.

2. Compound according to claim 1, W denotes

and R^1, R^2, R^3, R^4, X and A have the meanings as in Claim 1, and physiologically acceptable salts, derivatives, solvates, prodrugs and stereoisomers thereof, including mixtures thereof in all ratios.

2. Compound according to claim 1 or 2, wherein
W denotes

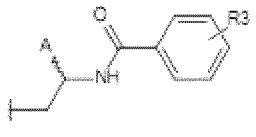




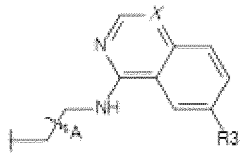
and R^1, R^2, R^3, R^4, X and A have the meanings as in Claim 1, and physiologically acceptable salts, derivatives, solvates, prodrugs and stereoisomers thereof, including mixtures thereof in all ratios.

3. Compound according to one or more of the preceding claims, wherein
R^1 denotes OA
and W, R^2, R^3, R^4, X and A have the meanings as in Claim 1, and physiologically acceptable salts, derivatives, solvates, prodrugs and stereoisomers thereof, including mixtures thereof in all ratios.

4. Compound according to one or more of the preceding claims, wherein R^1 denotes OA, wherein denotes A an unbranched or branched alkyl wherein 1-3 H-atoms may be replaced by D, F or Cl
and W, R^2, R^3, R^4, X and A have the meanings as in Claim 1, and physiologically acceptable salts, derivatives, solvates, prodrugs and stereoisomers thereof, including mixtures thereof in all ratios.

5. Compound according to one or more of the preceding claims, wherein R^2 denotes





and W, R^1, R^3, R^4, X and A have the meanings as in Claim 1, and physiologically acceptable salts, derivatives, solvates, prodrugs and stereoisomers thereof, including mixtures thereof in all ratios.

6. Compound according to one or more of the preceding claims, wherein R^3 denotes 5-methyloxadiazol or 2-methyltretrazol
and W, R^1, R^2, R^4, X and A have the meanings as in Claim 1, and physiologically acceptable salts, derivatives, solvates, prodrugs and stereoisomers thereof, including mixtures thereof in all ratios.

7. Compound according to one or more of the preceding claims, wherein R^3 denotes 5-methyloxadiazol
and W, R^1, R^2, R^4, X and A have the meanings as in Claim 1, and physiologically acceptable salts, derivatives, solvates, prodrugs and stereoisomers thereof, including mixtures thereof in all ratios.

8. Compound according to one or more of the preceding claims, wherein R^4 denotes methyl
and W, R^1, R^2, R^3, X and A have the meanings as in Claim 1, and physiologically acceptable salts, derivatives, solvates, prodrugs and stereoisomers thereof, including mixtures thereof in all ratios.

9. Compound selected from the group consisting of:

1	N-{4-ethoxy-[1,3]thiazolo[5,4-c]pyridin-2-yl}-3-{[3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]formamido}propanamide
2	3-{[3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]formamido}-N-[4-(propan-2-yloxy)-[1,3]thiazolo[5,4-c]pyridin-2-yl]propanamide
3	N-{4-cyclobutoxy-[1,3]thiazolo[5,4-c]pyridin-2-yl}-3-{[3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]formamido}propanamide
4	N-[4-(butan-2-yloxy)-[1,3]thiazolo[5,4-c]pyridin-2-yl]-3-{[3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]formamido}propanamide
5	N-[4-(2,2-difluoroethoxy)-[1,3]thiazolo[5,4-c]pyridin-2-yl]-3-{[3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]formamido}propanamide
6	3-{[3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]formamido}-N-[4-(2,2,2-trifluoroethoxy)-[1,3]thiazolo[5,4-c]pyridin-2-yl]propanamide
7	N-[4-(3,3-difluorocyclobutoxy)-[1,3]thiazolo[5,4-c]pyridin-2-yl]-3-{[3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]formamido}propanamide
8	3-{[3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]formamido}-N-{4-[(1,1,1-trifluoropropan-2-yl)oxy]-[1,3]thiazolo[5,4-c]pyridin-2-yl}propanamide
9	N-{4-ethoxy-[1,3]thiazolo[5,4-c]pyridin-2-yl}-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}propanamide
10	3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}-N-{4-propoxy-[1,3]thiazolo[5,4-c]pyridin-2-yl}propanamide
11	3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}-N-[4-(propan-2-yloxy)-[1,3]thiazolo[5,4-c]pyridin-2-yl]propanamide
12	N-[4-(butan-2-yloxy)-[1,3]thiazolo[5,4-c]pyridin-2-yl]-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}propanamide
13	N-{4-cyclobutoxy-[1,3]thiazolo[5,4-c]pyridin-2-yl}-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}propanamide
14	N-[4-(3,3-difluorocyclobutoxy)-[1,3]thiazolo[5,4-c]pyridin-2-yl]-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}propanamide

15	N-[4-(3-fluoropropoxy)-[1,3]thiazolo[5,4-c]pyridin-2-yl]-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}propanamide
16	N-[4-(2,2-difluoropropoxy)-[1,3]thiazolo[5,4-c]pyridin-2-yl]-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}propanamide
17	N-[4-(2,2-difluoroethoxy)-[1,3]thiazolo[5,4-c]pyridin-2-yl]-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}propanamide
18	3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}-N-[4-(2,2,2-trifluoroethoxy)-[1,3]thiazolo[5,4-c]pyridin-2-yl]propanamide
19	3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}-N-{4-[(1,1,1-trifluoropropan-2-yl)oxy]-[1,3]thiazolo[5,4-c]pyridin-2-yl}propanamide
20	(1s,3s)-N-{4-methoxy-[1,3]thiazolo[5,4-c]pyridin-2-yl}-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}cyclobutane-1-carboxamide
21	(1s,3s)-N-{4-ethoxy-[1,3]thiazolo[5,4-c]pyridin-2-yl}-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}cyclobutane-1-carboxamide
22	(1s,3s)-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}-N-{4-propoxy-[1,3]thiazolo[5,4-c]pyridin-2-yl}cyclobutane-1-carboxamide
23	N-{1-ethoxypyrrolo[1,2-a]pyrazin-7-yl}-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}propanamide
24	3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}-N-{1-propoxypyrrolo[1,2-a]pyrazin-7-yl}propanamide
25	11-(2-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}ethyl)-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02.7]trideca-2(7),3,5,8-tetraen-10-one
26	3-(2-methyl-2H-1,2,3,4-tetrazol-5-yl)-N-{2-[10-oxo-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02.7]trideca-2,4,6,8-tetraen-11-yl]ethyl}benzamide
27	3-(2-methyl-2H-1,2,3,4-tetrazol-5-yl)-N-{2-[10-oxo-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02.7]trideca-2(7),3,5,8-tetraen-11-yl](1,1,2,2-2H4)ethyl}benzamide

28	3-(5-methyl-1,2,4-oxadiazol-3-yl)-N-{2-[10-oxo-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02.7]trideca-2(7),3,5,8-tetraen-11-yl](1,1,2,2-2H4)ethyl}benzamide
29	11-(2-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}(1,1,2,2-2H4)ethyl)-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02.7]trideca-2(7),3,5,8-tetraen-10-one
30	3-(5-methyl-2H-1,2,3,4-tetrazol-2-yl)-N-{2-[10-oxo-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02.7]trideca-2,4,6,8-tetraen-11-yl]ethyl}benzamide
31	11-(2-{[7-(2-methyl-2H-1,2,3,4-tetrazol-5-yl)isoquinolin-1-yl]amino}ethyl)-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02.7]trideca-2,4,6,8-tetraen-10-one
32	11-(2-{[7-(5-methyl-2H-1,2,3,4-tetrazol-2-yl)isoquinolin-1-yl]amino}ethyl)-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02.7]trideca-2,4,6,8-tetraen-10-one
33	11-(2-{[6-(5-methyl-1,2,4-oxadiazol-3-yl)quinazolin-4-yl]amino}ethyl)-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02.7]trideca-2,4,6,8-tetraen-10-one
34	3-fluoro-5-(2-methyl-2H-1,2,3,4-tetrazol-5-yl)-N-{2-[10-oxo-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02.7]trideca-2,4,6,8-tetraen-11-yl]ethyl}benzamide
35	3-(2-methyl-2H-1,2,3,4-tetrazol-5-yl)-N-{2-[10-oxo-6-(2,2,2-trifluoroethoxy)(12,12,13,13-2H4)-1,5,11-triazatricyclo[7.4.0.02.7]trideca-2(7),3,5,8-tetraen-11-yl]ethyl}benzamide
36	11-(2-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}ethyl)-6-(2,2,2-trifluoroethoxy)(12,12,13,13-2H4)-1,5,11-triazatricyclo[7.4.0.02.7]trideca-2(7),3,5,8-tetraen-10-one
37	11-(2-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}ethyl)-6-propoxy-1,5,11-triazatricyclo[7.4.0.02.7]trideca-2(7),3,5,8-tetraen-10-one
38	3-(2-methyl-2H-1,2,3,4-tetrazol-5-yl)-N-(2-{10-oxo-6-propoxy-1,5,11-triazatricyclo[7.4.0.02.7]trideca-2,4,6,8-tetraen-11-yl}ethyl)benzamide

39	1-(Dodec-11-yn-1-yloxy)-8-(2-((7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl)amino)ethyl)-7,8-dihydropyrido[3',4':4,5]pyrrolo[1,2-a]pyrazin-9(6H)-one
40	N-(2-{6-chloro-10-oxo-1,5,11-triazatricyclo[7.4.0.0^{2,7}]trideca-2,4,6,8-tetraen-11-yl}ethyl)-3-(5-methyl-1,2,4-oxadiazol-3-yl)benzamide
41	N-{2-[6-(3-fluoropropoxy)-10-oxo-1,5,11-triazatricyclo[7.4.0.0^{2,7}]trideca-2,4,6,8-tetraen-11-yl]ethyl}-3-(5-methyl-1,2,4-oxadiazol-3-yl)benzamide
42	N-{2-[6-(2,2-difluoroethoxy)-10-oxo-1,5,11-triazatricyclo[7.4.0.0^{2,7}]trideca-2,4,6,8-tetraen-11-yl]ethyl}-3-(5-methyl-1,2,4-oxadiazol-3-yl)benzamide
43	3-(5-methyl-1,2,4-oxadiazol-3-yl)-N-{2-[10-oxo-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.0^{2,7}]trideca-2,4,6,8-tetraen-11-yl]ethyl}benzamide
44	6-(3-fluoropropoxy)-11-(2-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}ethyl)-1,5,11-triazatricyclo[7.4.0.02.7]trideca-2(7),3,5,8-tetraen-10-one
45	3-(2-methyl-2H-1,2,3,4-tetrazol-5-yl)-N-(2-{10-oxo-6-[(1,1,2,2,3,3,3-2H7)propoxy]-1,5,11-triazatricyclo[7.4.0.02.7]trideca-2,4,6,8-tetraen-11-yl}ethyl)benzamide
46	3-(2-methyl-2H-1,2,3,4-tetrazol-5-yl)-N-(2-{10-oxo-6-[2,2,2-trifluoro(1,1-2H2)ethoxy]-1,5,11-triazatricyclo[7.4.0.02.7]trideca-2,4,6,8-tetraen-11-yl}ethyl)benzamide
47	N-(2-(1-(dodec-11-yn-1-yloxy)-9-oxo-6,7-dihydropyrido[3',4':4,5]pyrrolo[1,2-a]pyrazin-8(9H)-yl)ethyl)-3-(2-methyl-2H-tetrazol-5-yl)benzamide
48	11-(3-amino-2-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}propyl)-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[[7.4.0.02.7]trideca-2,4,6,8-tetraen-10-one
49	(S)-3-(2-Methyl-2H-tetrazol-5-yl)-N-(6-(methylamino)-1-(9-oxo-1-(2,2,2-trifluoroethoxy)-6,7-dihydropyrido[3',4':4,5]pyrrolo[1,2-a]pyrazin-8(9H)-yl)hexan-2-yl)benzamide

50	3-(2-methyl-2H-1,2,3,4-tetrazol-5-yl)-N-[6-(methylamino)-1-[10-oxo-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02.7]trideca-2(7),3,5,8-tetraen-11-yl]hexan-2-yl]benzamide
51	N-{6-[methyl(prop-2-yn-1-yl)amino]-1-[10-oxo-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7.4.0.02.7]trideca-2,4,6,8-tetraen-11-yl]hexan-2-yl}-3-(2-methyl-2H-1,2,3,4-tetrazol-5-yl)benzamide
52	11-[(2S)-6-[methyl(prop-2-yn-1-yl)amino]-2-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}hexyl]-6-(2,2,2-trifluoroethoxy)-1,5,11-triazatricyclo[7[7.4.0.02.7]trideca-2,4,6,8-tetraen-10-one
53	N-{(S)-4-Methylamino-1-[(7-propoxy-benzothiazol-2-ylcarbamoyl)-methyl]-butyl}-3-(5-methyl-[1,2,4]oxadiazol-3-yl)-benzamide
54	(3S)-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}-6-(methylamino)-N-(7-propoxy-1,3-benzothiazol-2-yl)hexanamide
55	(3S)-N-(4-fluoro-7-propoxy-1,3-benzothiazol-2-yl)-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}-6-(methylamino)hexanamide
56	N-[4-fluoro-7-(3-fluoropropoxy)-1,3-benzothiazol-2-yl]-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}propanamide
57	N-[4-fluoro-7-(2-fluoroethoxy)-1,3-benzothiazol-2-yl]-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}propanamide
58	3-[7-(5-Methyl-[1,2,4]oxadiazol-3-yl)-isoquinolin-1-ylamino]-N-(7-propoxy-benzothiazol-2-yl)-propionamide
59	3-[7-(5-Methyl-[1,2,4]oxadiazol-3-yl)-isoquinolin-1-ylamino]-cyclobutanecarboxylic acid (7-propoxy-benzothiazol-2-yl)-amide
60	3-[7-(5-Methyl-[1,2,4]oxadiazol-3-yl)-isoquinolin-1-ylamino]-cyclobutanecarboxylic acid (7-methoxy-4-methyl-benzothiazol-2-yl)-amide
61	3-[7-(5-Methyl-[1,2,4]oxadiazol-3-yl)-isoquinolin-1-ylamino]-cyclobutanecarboxylic acid (7-methoxy-benzothiazol-2-yl)-amide
62	N-(4-fluoro-7-propoxy-1,3-benzothiazol-2-yl)-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}propanamide

63	N-(4-chloro-7-propoxy-1,3-benzothiazol-2-yl)-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}propanamide
64	3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}-N-{4-propoxypyrazolo[1,5-a]pyridin-2-yl}propanamide
65	3-[7-(5-Methyl-[1,2,4]oxadiazol-3-yl)-isoquinolin-1-ylamino]-N-(4-propoxy-pyrazolo[1,5-a]pyrazin-2-yl)-propionamide
66	N-{4-ethoxypyrazolo[1,5-a]pyrazin-2-yl}-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}propanamide
67	N-[4-(3-fluoropropoxy)pyrazolo[1,5-a]pyrazin-2-yl]-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}propanamide
68	N-[4-(2-fluoroethoxy)pyrazolo[1,5-a]pyrazin-2-yl]-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}propanamide
69	3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}-N-[4-(oxetan-3-yloxy)pyrazolo[1,5-a]pyrazin-2-yl]propanamide
70	N-{4-cyclopropoxypyrazolo[1,5-a]pyrazin-2-yl}-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}propanamide
71	3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}-N-{1-methyl-4-propoxy-1H-pyrrolo[3,2-c]pyridin-2-yl}propanamide
72	3-[7-(5-Methyl-[1,2,4]oxadiazol-3-yl)-isoquinolin-1-ylamino]-cyclobutanecarboxylic acid (4-methoxy-pyrazolo[1,5-a]pyridin-2-yl)-amide
73	3-[7-(5-Methyl-[1,2,4]oxadiazol-3-yl)-isoquinolin-1-ylamino]-N-(4-methyl-7-propoxy-benzothiazol-2-yl)-propionamide
74	3-(5-Methyl-[1,2,4]oxadiazol-3-yl)-N-[2-(4-methyl-7-propoxy-benzothiazol-2-ylcarbamoyl)-ethyl]-benzamide
75	3-(2-Methyl-2H-tetrazol-5-yl)-N-[2-(7-propoxy-benzothiazol-2-ylcarbamoyl)-ethyl]-benzamide
76	3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}-N-[7-propoxy-4-(trifluoromethyl)-1,3-benzothiazol-2-yl]propanamide
77	(2R)-2-amino-N-(4-fluoro-7-propoxy-1,3-benzothiazol-2-yl)-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}propanamide
78	(S)-2-Hydroxy-3-[7-(5-methyl-[1,2,4]oxadiazol-3-yl)-isoquinolin-1-ylamino]-N-(7-propoxy-benzothiazol-2-yl)-propionamide

79	N-(7-ethoxy-1,3-benzothiazol-2-yl)-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}propanamide
80	(2S)-N-(7-ethoxy-1,3-benzothiazol-2-yl)-2-hydroxy-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}propanamide
81	3-(5-Methyl-[1,2,4]oxadiazol-3-yl)-N-[2-(7-propoxy-benzothiazol-2-ylcarbamoyl)-ethyl]-benzamide
82	(2R)-N-(7-ethoxy-1,3-benzothiazol-2-yl)-2-hydroxy-3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}propanamide
83	3-(5-methyl-1,2,4-oxadiazol-3-yl)-N-(2-{10-oxo-6-propoxy-1,5,11-triazatricyclo[7.4.0.02.7]trideca-2,4,6,8-tetraen-11-yl}ethyl)benzamide
84	2,2-difluoro-N-(4-fluoro-7-propoxy-1,3-benzothiazol-2-yl)-3-{[3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]formamido}propanamide
85	3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}-N-(1-methyl-7-propoxy-1H-1,3-benzodiazol-2-yl)propanamide
86	3-{[7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl]amino}-N-(7-propoxy-1H-1,3-benzodiazol-2-yl)propanamide
87	8-(2-((7-(5-methyl-1,2,4-oxadiazol-3-yl)isoquinolin-1-yl)amino)ethyl-1,1,2,2-d4)-1-(2,2,2-trifluoroethoxy-1,1-d2)-7,8-dihydropyrido[3',4':4,5]pyrrolo[1,2-a]pyrazin-9(6H)-one-6,6,7,7-d4
88	3-(2-methyl-2H-tetrazol-5-yl)-N-(2-(9-oxo-1-(2,2,2-trifluoroethoxy-1,1-d2)-6,7-dihydropyrido[3',4':4,5]pyrrolo[1,2-a]pyrazin-8(9H)-yl-6,6,7,7-d4)ethyl-1,1,2,2-d4)benzamide

and physiologically acceptable salts, derivatives, solvates, prodrugs and stereoisomers thereof, including mixtures thereof in all ratios.

10. Pharmaceutical preparation comprising at least one compound according to one or more of claims 1 to 9 and/or physiologically acceptable salts, derivatives, solvates, prodrugs and stereoisomers thereof, including mixtures thereof in all ratios.

11. Pharmaceutical preparation according to claim 10 comprising further excipients and/or adjuvants.

12. Pharmaceutical preparation comprising at least one compound according to one or more of claims 1 to 11 and/or physiologically acceptable salts, derivatives, solvates, prodrugs and stereoisomers thereof, including mixtures thereof in all ratios, and at least one further medicament active compound.

13. Process for the preparation of a pharmaceutical preparation, characterised in that a compound according to one or more of claims 1 to 9 and/or one of its physiologically acceptable salts, derivatives, solvates, prodrugs and stereoisomers, including mixtures thereof in all ratios, is brought into a suitable dosage form together with a solid, liquid or semi-liquid excipient or adjuvant.

14. Medicament comprising at least one compound according to one or more of claims 1 to 9 and/or one of its physiologically acceptable salts, derivatives, solvates, prodrugs and stereoisomers, including mixtures thereof in all ratios, for use in the treatment and/or prophylaxis of physiological and/or patho-physiological states.

15. Medicament comprising at least one compound according to one or more of claims 1 to 9 and/or one of its physiologically acceptable salts, derivatives, solvates, prodrugs and stereoisomers, including mixtures thereof in all ratios, for use in the treatment and/or prophylaxis of physiological and/or patho-physiological states, selected from the group consisting of hyperproliferative diseases and disorders.

16. Medicament for use according to claim 15, wherein the hyperproliferative disease or disorder is cancer.

17. Medicament for use according to claim 16, wherein the cancer is selected from the group consisting of acute lymphocytic leukemia, acute granulocytic leukemia, adrenal cortex cancer, bladder cancer, brain cancer, breast cancer, cervical hyperplasia, cervical cancer, chorio cancer, chronic granulocytic leukemia, chronic lymphocytic leukemia, colon cancer, endometrial ccancer, esophageal cancer, essential thrombocytosis, genitourinary carcinoma, glioma, glioblastoma, hairy cell leukemia, head and neck carcinoma, Hodgkin's disease, Kaposi's sarcoma, lung carcinoma, lymphoma, malignant

carcinoid carcinoma, malignant hypercalcemia, malignant melanoma, malignant pancreatic insulinoma, medullary thyroid carcinoma, melanoma, multiple myeloma, mycosis fungoides, myeloid and lymphocytic leukemia, neuroblastoma, non-Hodgkin's lymphoma, non-small cell lung cancer, osteogenic sarcoma, ovarian carcinoma, pancreatic carcinoma, polycythemia vera, primary brain carcinoma, primary macroglobulinemia, prostatic cancer, renal cell cancer, rhabdomyosarcoma, skin cancer, small-cell lung cancer, soft-tissue sarcoma, squamous cell cancer, stomach cancer, testicular cancer, thyroid cancer and Wilms' tumor.

18. Set (kit) consisting of separate packs of

a) an effective amount of a compound according to one or more of claims 1 to 9 and/or physiologically acceptable salts, derivatives, solvates, prodrugs and stereoisomers thereof, including mixtures thereof in all ratios, and

b) an effective amount of a further medicament active compound.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2023/080663

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D417/10 C07D417/14 C07D471/04 C07D487/04 C07D487/14
C07D513/04 A61K31/437 A61P35/00
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

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.
A	US 2006/084687 A1 (BOYCE RUSTUM S [SG] ET AL) 20 April 2006 (2006-04-20) paragraph [0007]; compound 38	1-18
A	US 2007/135435 A1 (QIAN XIANGPING [US] ET AL) 14 June 2007 (2007-06-14) paragraph [0462]	1-18
A	WO 2005/070930 A2 (CHIRON CORP [US]; WANG WEIBO [US] ET AL.) 4 August 2005 (2005-08-04) page 1; compound 104	1-18
A	WO 2006/060737 A2 (TAKEDA SAN DIEGO INC [US]; BRESSI JEROME C [US] ET AL.) 8 June 2006 (2006-06-08) page 1 page 133; example 19	1-18

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[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
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"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
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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 January 2024	30/01/2024

Name and mailing address of the ISA/	Authorized officer
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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE PubChem [Online] 13 November 2007 (2007-11-13), Pubchem: "N-[3-(1H-benzimidazol-2-ylamino)-3-oxopropyl]-2-methoxybenzamide", XP093120796, retrieved from NCBI Database accession no. 17409968 abstract ----- DATABASE PubChem [Online] 30 July 2006 (2006-07-30), Pubchem: "N-[3-(1H-benzimidazol-2-ylamino)-3-oxopropyl]-4-tert-butylbenzamide", XP093120803, retrieved from NCBI Database accession no. 8832915 abstract ----- DATABASE PubChem [Online] 28 May 2009 (2009-05-28), Pubchem: "N-[3-oxo-3-[(1-propylbenzimidazol-2-yl)amino]propyl]benzamide", XP093120806, retrieved from NCBI Database accession no. 26186777 abstract ----- DATABASE PubChem [Online] 18 October 2012 (2012-10-18), Pubchem: "N-[3-(1H-benzimidazol-2-ylamino)-3-oxopropyl]-4-fluorobenzamide", XP093120808, retrieved from NCBI Database accession no. 60564482 abstract ----- DATABASE PubChem [Online] 25 May 2018 (2018-05-25), Pubchem: "N-[4-oxo-4-[(1-propylbenzimidazol-2-yl)amino]butan-2-yl]benzamide", XP093120809, retrieved from NCBI Database accession no. 133894627 abstract ----- -/--	1 1 1 1 1

1

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE PubChem [Online] 30 July 2006 (2006-07-30), Pubchem: "N-[3-[(6-ethoxy-1,3-benzothiazol-2-yl)amino]-3-oxopropyl]benzamide", XP093120887, retrieved from NCBI Database accession no. 8883008 abstract ----- DATABASE PubChem [Online] 13 November 2007 (2007-11-13), Pubchem: "N-[3-[(6-methoxy-1,3-benzothiazol-2-yl)amino]-3-oxopropyl]benzamide", XP093120888, retrieved from NCBI Database accession no. 17154528 abstract ----- DATABASE PubChem [Online] 13 November 2007 (2007-11-13), Pubchem: "N-[3-[(6-methoxy-1,3-benzothiazol-2-yl)amino]-3-oxopropyl]-3-methylbenzamide", XP093120896, retrieved from NCBI Database accession no. 17191471 abstract ----- DATABASE PubChem [Online] 13 November 2007 (2007-11-13), Pubchem: "N-[3-[(6-ethoxy-1,3-benzothiazol-2-yl)amino]-3-oxopropyl]-3-methylbenzamide", XP093120897, retrieved from NCBI Database accession no. 17191524 abstract ----- DATABASE PubChem [Online] 13 November 2007 (2007-11-13), Pubchem: "3-methoxy-N-[3-[(6-methoxy-1,3-benzothiazol-2-yl)amino]-3-oxopropyl]benzamide", XP093120898, retrieved from NCBI Database accession no. 17226185 abstract -----	1 1 1 1 1

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2023/080663

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2006084687 A1	20-04-2006	AU 2005301133 A1	11-05-2006
		BR PI0517314 A	07-10-2008
		CA 2584979 A1	11-05-2006
		CN 101233115 A	30-07-2008
		EP 1807399 A2	18-07-2007
		EP 2275412 A1	19-01-2011
		JP 2008517057 A	22-05-2008
		KR 20070072598 A	04-07-2007
		RU 2007118523 A	27-11-2008
		US 2006084687 A1	20-04-2006
		US 2008317744 A1	25-12-2008
		WO 2006049835 A2	11-05-2006
US 2007135435 A1	14-06-2007	EP 1942888 A2	16-07-2008
		JP 2009514866 A	09-04-2009
		US 2007135435 A1	14-06-2007
		WO 2007056078 A2	18-05-2007
WO 2005070930 A2	04-08-2005	AU 2005206570 A1	04-08-2005
		BR PI0506977 A	03-07-2007
		CA 2554150 A1	04-08-2005
		CN 1910183 A	07-02-2007
		EP 1706404 A2	04-10-2006
		JP 2007518822 A	12-07-2007
		MX PA06008211 A	31-08-2006
		US 2005215580 A1	29-09-2005
		WO 2005070930 A2	04-08-2005
WO 2006060737 A2	08-06-2006	US 2010093767 A1	15-04-2010
		WO 2006060737 A2	08-06-2006