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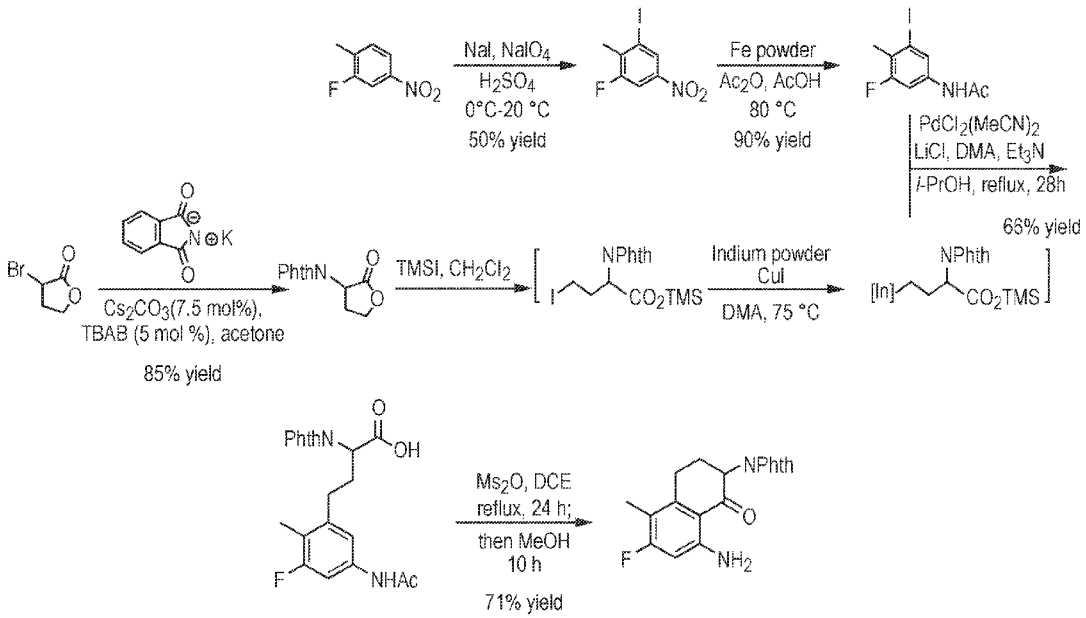

FIG. 1

(57) Abstract: Intermediates useful in the preparation of exatecan mesylate and related compounds. Further provided are methods for preparing these compounds. Also provided is an improved, scalable synthesis of exatecan mesylate using the provided intermediates. The synthesis of exatecan mesylate utilizes a convergent approach, involving fewer steps and utilizing fewer reagents and increasing efficiency.

[Continued on next page]

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INTERMEDIATES FOR SYNTHESIZING EXATECAN MESYLATE

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] The present application claims the benefit of priority of U.S. provisional patent application no. 63/516,024, filed July 27, 2023, the content of which is incorporated by reference herein in its entirety.

BACKGROUND

[0002] Exatecan mesylate is a highly sought-after payload for use in antibody-drug conjugates (ADCs). Enhertu is a commercial ADC therapy utilizing deruxtecan, which is synthesized from exatecan mesylate. Additionally, there are currently several experimental ADCs utilizing exatecan-based payloads.

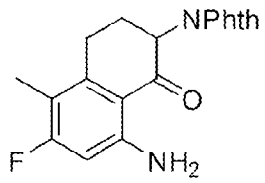
[0003] The commercial supply of exatecan is tightly controlled with high cost of entry and a challenging synthetic route for production. Current state of the art processes for synthesizing exatecan mesylate rely on a linear assembly of a bicyclic core and subsequent late-stage low yielding amination. Such processes are described in published patent applications, such as US20200384121 and WO2022000868.

[0004] A need exists for new synthetic methods that can overcome the significant supply issues limiting the investigation and commercialization of exatecan payload-based ADCs. Such a route should provide improved yield, be scalable for manufacture, and avoid the need for chromatographic purification.

SUMMARY

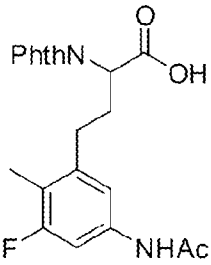
[0005] Provided are new intermediates useful in the synthesis of exatecan mesylate and related syntheses.

[0006] A first intermediate provided is the compound of formula I:

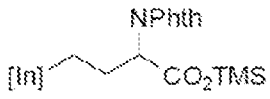


I.

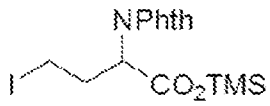
[0007] Additional intermediates provided include those of formulae II, III and IV:



II

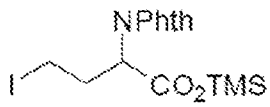


III



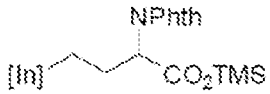
IV.

[0008] Further provided are methods of preparing a compound of formula I, the method including the steps of providing N-(3-fluoro-5-iodo-4-methylphenyl)acetamide, and separately (a) reacting 3-bromo-2-oxotetrahydrofuran with potassium phthalimide to provide 2-(2-oxotetrahydrofuran-3-yl)isoindoline-1,3-dione; (b) reacting 2-(2-oxotetrahydrofuran-3-yl)isoindoline-1,3-dione with trimethylsilyl iodide (TMSI) to form the corresponding carboxylic acid (IV)



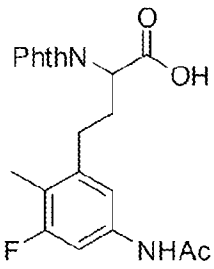
IV

(c) reacting the carboxylic acid of (c) with Indium powder and copper(I) iodide to form indium intermediate (III)



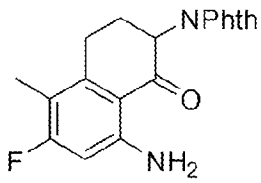
III

(d) reacting the indium intermediate (III) with the N-(3-fluoro-5-iodo-4-methylphenyl)acetamide to form intermediate (II)



II

(e) performing a ring closing to yield the compound of formula (I)



I.

BRIEF DESCRIPTION OF THE DRAWINGS

[0009] The drawings are provided to illustrate one or more versions of the present invention and are not to be construed as limiting the scope of the claims.

[0010] FIG. 1 shows the preparation of the intermediate provided herein.

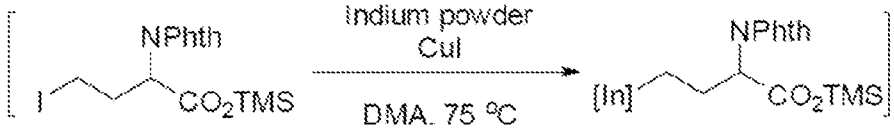
[0011] FIG. 2 shows the synthesis of exatecan mesylate from the provided intermediate.

DETAILED DESCRIPTION

[0012] Provided herein are new intermediates useful in the preparation of exatecan mesylate and methods of synthesizing these intermediates, thus providing a new, efficient route to synthesize exatecan mesylate and other exatecan-based payloads.

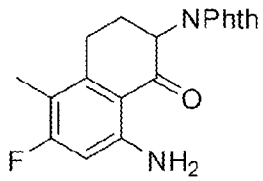
[0013] The improved synthesis is shown in FIG. 1. Utilization of the bromo-lactone arm of the synthesis provides a key improvement over state-of-the-art methods. By incorporating the amine, protected as the phthalimide into the palladium couple partner, a shorter longest linear route is achieved compared with conventional synthetic routes. Additionally, the route provided herein, as shown in the examples, does not utilize or need column chromatography. Furthermore, this route is scalable for manufacture.

[0014] As shown in FIG. 1, a significant improvement in the synthesis is achieved by utilizing an indium-based palladium cross-coupling reaction:



in the preparation of the cyclized intermediate.

[0015] Additionally, the cyclized intermediate protected as the phthalimide, Compound I



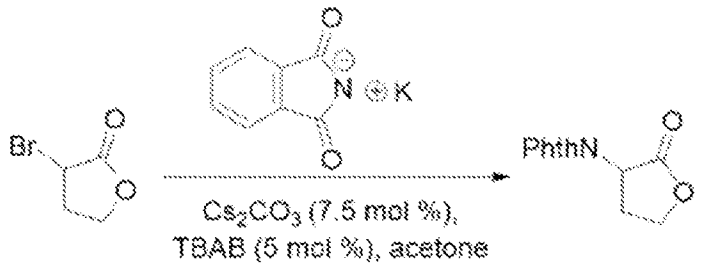
I

provides significant advantages in streamlining the synthesis of exatecan mesylate. Moreover, this route allows an alternative, scalable, route to exatecan mesylate, providing significant advantage by reducing the longest linear route of the synthesis, which in turn decreases raw material input quantity. By utilizing a more convergent approach, individual reaction sizes are lower and syntheses are more efficient.

[0016] Preparation of Intermediates

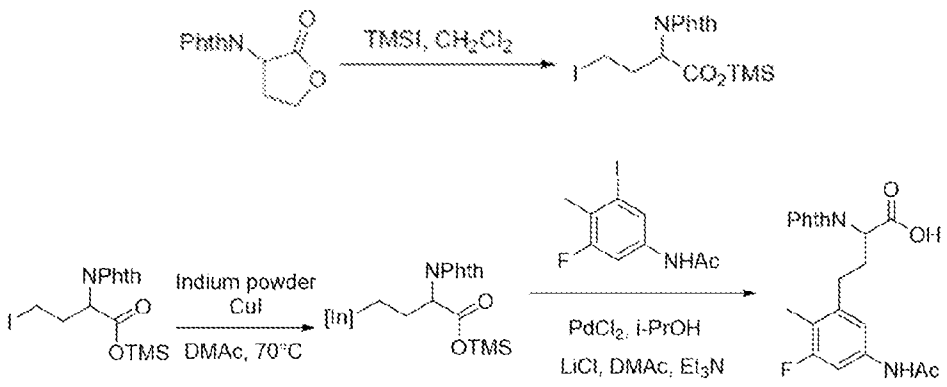
[0017] N-(3-fluoro-5-iodo-4-methylphenyl)acetamide is prepared according to the route described below, or may be obtained through commercial sources.

[0018] Preparation of 2-(2-oxotetrahydrofuran-3-yl)isoindoline-1,3-dione



[0019] 3-Bromo-2-oxotetrahydrofuran is reacted with potassium phthalimide in acetone in the presence of catalyst, preferably tetrabutylammonium bromide (TBAB) and base, preferably cesium carbonate, to form 2-(2-oxotetrahydrofuran-3-yl)isoindoline-1,3-dione.

[0020] Preparation of 4-(5-acetamido-3-fluoro-2-methylphenyl)-2-(1,3-dioxoisoindolin-2-yl)butanoic acid, compound (II), through compounds (III) and (IV)

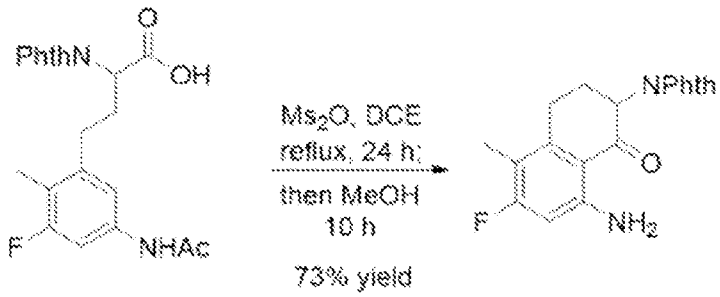


(IV) (III) (II)

[0021] In a first reactor, 2-(2-oxotetrahydrofuran-3-yl)isoindoline-1,3-dione is reacted with excess trimethylsilyl iodide in methylene chloride to yield the corresponding terminally iodinated carboxylic acid. The resulting carboxylic acid is isolated, then subsequently, copper(I) iodide and indium powder are sequentially added. The resulting suspension is purged with nitrogen and N,N-dimethylacetamide (DMAc) is added. The mixture is heated, the reaction allowed proceed, then cooled to form the indium-containing intermediate. Fluoro-5-iodo-4-methylphenyl)acetamide and dry lithium chloride are added to a second reactor, then the organics from the first reactor are filtered into the

second reactor. Palladium(II) chloride is added, the reaction mixture is heated to 110 °C and stirred vigorously for a time sufficient for the reaction to complete. The mixture is then cooled to 80 °C, the volatiles removed, then cooled to 40 °C. Methyl ethyl ketone is charged, and the suspension stirred, then is filtered. The filtrate is heated to 60 °C and concentrated to remove the methyl ethyl ketone. The resulting solution is cooled to 15 °C and a solution of phosphoric acid is water is added slowly with stirring. The mixture is cooled to 5 °C and the product is allowed to precipitate and is filtered, washed and concentrated. The product further is further purified in nitromethane and MTBE, then dried.

[0022] Ring Closure and aniline deprotection to form compound (I)



(I)

[0023] 4-(5-acetamido-3-fluoro-2-methylphenyl)-2-(1,3-dioxoisoindolin-2-yl)butanoic acid and methanesulfonic anhydride are combined and the reaction is heated to reflux and stirred until complete. The reaction is cooled to 15 °C, methanol is added and the mixture stirred for 10 h. The mixture is then concentrated, cooled to 5 °C and water is slowly added, with the temperature not exceeding 30 °C. The product is subsequently washed, filtered and dried to provide 2-(8-amino-6-fluoro-5-methyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)isoindoline-1,3-dione.

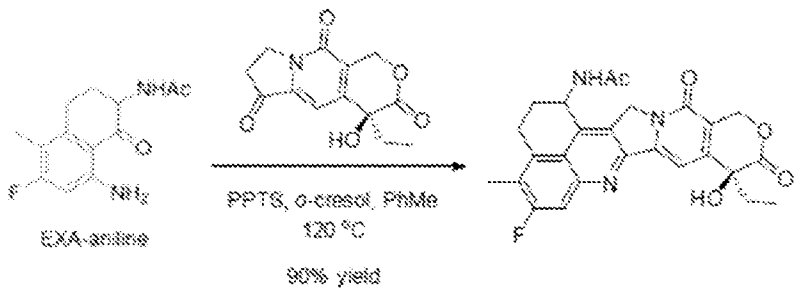
[0024] Preparation of EXA-aniline

[0025] A reactor is sequentially charged with 2-(8-amino-6-fluoro-5-methyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)isoindoline-1,3-dione aqueous HCl and

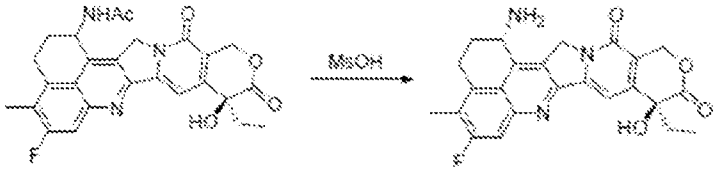
acetic acid, then purged with nitrogen and heated to reflux. The reaction is allowed to proceed to completion, then cooled, allowing the phthalic acid by-product to form a white precipitate. The reaction is filtered, concentrated and dried. To the resulting residue was charged to solvent, (preferably THF, EtOAc or acetone) isopropanol and base (preferably, aq. $KHCO_3$ or aq. K_2CO_3), with stirring. The reaction is cooled to 5 °C with nitrogen sparging, and acetic anhydride is carefully added with stirring; the reaction is stirred for an additional 30 min. Methanol is charged, and the reactor stirred an additional 15 minutes, then the volatiles removed. Water is added, the mixture is heat to 40 °C and vigorously stirred for 15 minutes. The aqueous layer is filtered off, then the solids are washed with water and aqueous ethanol and dried. Acetone was added and the resulting suspension heated to 50 °C and stirred for 3 h then cooled. The crystals are filtered again and dried to provide EXA-analine.

[0026] Preparation of exatecan mesylate using EXA-analine.

[0027] In a first step, EXA-aniline is condensed with (4S)-4-Ethyl-7,8-dihydro-4-hydroxy-1*H*-pyrano[3,4-*f*]indolizine-3,6,10(4*H*)-trione (EXA-trione).



This condensation step is carried out in toluene containing o-cresol, in the presence of an acid catalyst, preferably pyridinium p-toluenesulfonate (PPTS). The acid catalyst may be used in an amount sufficient for the reaction to proceed, preferably 0.03 to 0.3 equivalents based on EXA-aniline. The reaction is carried out at a temperature in the range from 90 to 130 °C, for a time sufficient for the reaction to complete, typically 16 hours or longer.

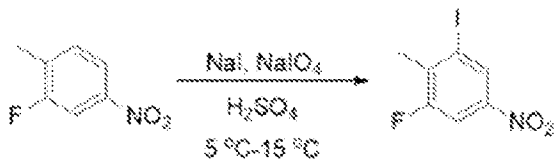


The resulting compound is deprotected using methanesulfonic acid (MsOH) to yield exatecan mesylate.

EXAMPLES

[0028] The following examples are illustrative in nature and are not meant to limit the scope of the invention as defined by the claims.

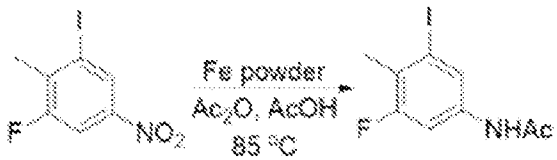
[0029] Example 1. Preparation of 1-fluoro-3-iodo-2-methyl-5-nitrobenzene.



[0030] In air, sulfuric acid (8 vol) was charged to a stirring reactor. The reactor was cooled to 5 °C, and sodium iodide (0.96 equiv.) was added in one portion, after which a slight exotherm occurred. The reactor was cooled back down to 5 °C, and sodium periodate (0.32 equiv.) was charged in one portion. The resulting dark brown liquid was stirred at 5 °C for an additional 30 min. 2-Fluoro-1-methyl-4-nitrobenzene (100.0 g, 1 equiv.) was charged in a single portion, and the reactor temperature was raised to 15 °C. The viscous mixture was vigorously stirred for 22 h, after which less than 5% of the starting material remained. The reaction was poured slowly into 0 °C stirring ice (1200 g) over 1 h. The quenched reaction was then allowed to warm to 15 °C with continued stirring. The reaction was vacuum filtered to produce a reddish solid, which was subsequently washed twice with water (2 x 8 vol). Toluene (12 vol) was charged, followed by aqueous sodium sulfite (0.8 M, 8 vol). The biphasic suspension was heated to 40 °C with vigorous stirring for 30 min.

Stirring was ceased and the suspension was allowed to separate over 10 min at 40 °C. The aqueous layer was removed, and additional toluene (4 vol) was added to the aqueous layer. The biphasic mixture was stirred an additional 5 min at 40 °C then allowed to separate, and the depleted aqueous layer was again removed and discarded. The combined organic layers were sequentially washed with aqueous sodium carbonate (ReagentPlus® grade from MilliporeSigma, St. Louis, MO, 0.75 M, 3 vol) and aqueous sodium chloride (2.0 M, 3 vol). The resulting pale-yellow mixture was filtered through a pad of celite, washing with minimal toluene (2 vol). The filtrate was concentrated in vacuo to deliver a yellow residue. The residue was crystallized from boiling MeCN/water (5 vol/2 vol based on crude mass) according to the following procedure: the stirred suspension was heated to a boil, aged 30 min, and cooled back down to 5 °C with very gentle stirring (~10 rpm) over 5 hours to precipitate pale yellow crystals. The mother liquor was filtered away, and the crystals were washed twice with 50% MeCN in Water (2 x 4 vol) and concentrated in vacuo to deliver pale yellow crystals (92.5 g, 50% yield).

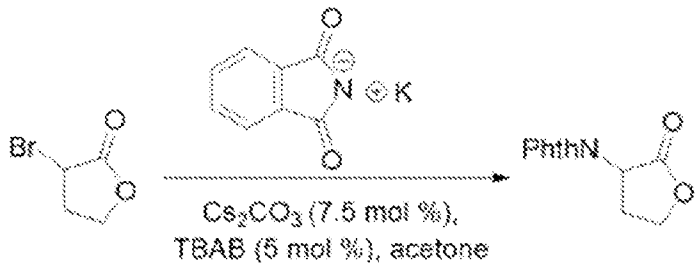
[0031] Example 2. Preparation of *N*-(3-fluoro-5-iodo-4-methylphenyl)acetamide.



[0032] To a stirring reactor under N_2 were sequentially charged iron powder (4.4 Eq) in one portion and acetic acid (6 vol) in one portion. The reactor was heated to 85 °C, and a pre-made solution of 1-fluoro-3-iodo-2-methyl-5-nitrobenzene (56.2 g, 1 Eq) in toluene (8 vol) was slowly added dropwise with vigorous stirring, ensuring the temperature did not exceed 100 °C. After complete addition, the reaction was cooled to 50 °C, and acetic anhydride (1.77 equiv.) was added over 10 min. The reaction was vigorously stirred an additional 30 min, after which the solvent was evaporated off (75 mBar, 50 °C). The resulting solids were azeotropically dried twice with additional toluene (2 x 6 vol). The reactor temperature was set to 30 °C, and acetone

(5 vol) was charged. The mixture was stirred vigorously for 10 min, and the product containing organics were filtered off into stirring aqueous sodium carbonate (Reagent Plus® grade from MilliporeSigma, St. Louis, MO, 2.0 M, 4 vol). The reactor vessel was washed with acetone four more times (4 x 2 vol) following the same procedure. The resulting filtrate suspension was stirred for 10 min and allowed to settle for 30 min, during which a biphasic mixture formed. The dark-colored aqueous (bottom) layer was discarded, and the pale-yellow organic layer was treated with activated charcoal (10 g). The suspension was vigorously stirred for 15 min. then filtered through a pad of celite. The celite pad was washed with minimal acetone (3 vol), and the collected organic filtrate was concentrated down to 8 vol in vacuo. Water (8 vol) was charged with stirring, and the remaining acetone was evaporated off. Methanol (2 vol) was charged with stirring, and the suspension was vacuum filtered. The resulting white solid was washed twice with 25% MeOH in water. The white solid was thoroughly dried in vacuo to deliver the product as a chalky white solid (53.0 g, 90% yield).

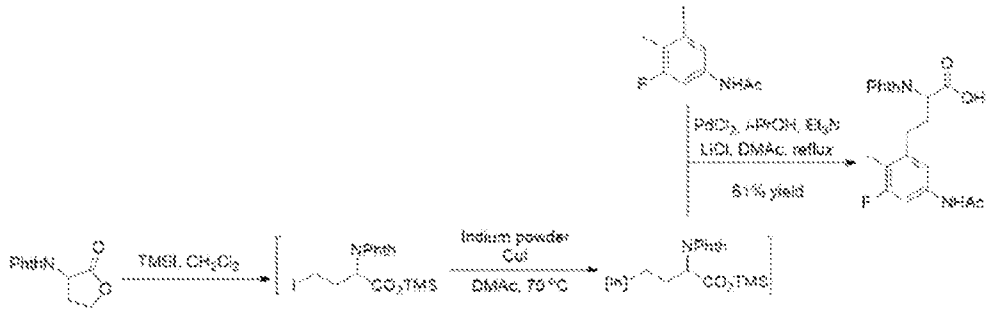
[0033] Example 3. Preparation of 2-(2-oxotetrahydrofuran-3-yl)isoindoline-1,3-dione



[0034] To reactor were sequentially charged tetrabutylammonium bromide (0.05 equiv.), cesium carbonate (0.075 equiv.) and 1H-Isoindole-1,3(2H)-dione, potassium salt (100.0 g, 1 equiv.) The reactor was purged with nitrogen, and acetone (7 vol) was added in one portion. Stirring was commenced, and the temperature was lowered to 10 °C. 3-Bromotetrahydrofuran-2-one (1.3 equiv.) was then added dropwise such that the internal temperature did not exceed 15 °C (~1 drop/sec). Upon complete addition, the reaction was stirred at 15 °C for 2 h, and then at 20 °C for 10 h.

Following this, the temperature was lowered to 5 °C, and water (7 vol) was added at a rate such that the temperature did not exceed 20 °C. After stirring for an additional 15 min, the acetone was removed in vacuo at 20 °C. Methanol (2 vol) was added, and the mixture was stirred vigorously for an additional 5 min. The mixture was vacuum filtered, and the solid was rinsed three more times with a solution of 2/1 H_2O/MeOH (3 x 6 vol). The filtrate was thoroughly dried in vacuo with heat (50 °C) over several days to deliver a chalky white solid (98.0 g, 79% yield).

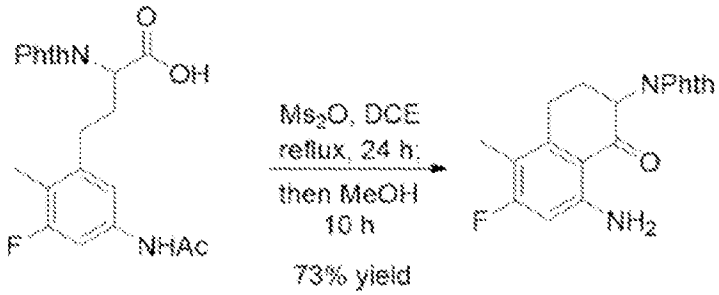
[0035] Example 4. Preparation of 4-(5-acetamido-3-fluoro-2-methylphenyl)-2-(1,3-dioxoisoindolin-2-yl)butanoic acid



[0036] To a stirring reactor were sequentially charged 2-(2-oxotetrahydrofuran-3-yl)isoindoline-1,3-dione (13.41 g, 1.7 Eq, 58.00 mmol), dichloromethane (38.83 g, 29.42 mL, 13.4 Eq, 457.2 mmol), and iodotrimethylsilane (14.68 g, 9.985 mL, 2.15 Eq, 73.36 mmol) in single portions. The reaction was allowed to stir at ambient temperature for 16 h, after which it was concentrated in vacuo at 40 °C to deliver a viscous brown residue. To the residue were sequentially charged copper(I) iodide (11.70 g, 1.8 Eq, 61.42 mmol) and indium powder (13.32 g, 1.824 mL, 3.4 Eq, 116.0 mmol) in single portions. The suspension was purged with N_2, and N,N-dimethylacetamide (25.18 g, 26.8 mL, 8.47 Eq, 289.0 mmol) was added. The mixture was heated to 70 °C and stirred for 20 h, after which it was cooled down to 20 °C. Meanwhile, to a second reactor were added N-(3-fluoro-5-iodo-4-methylphenyl)acetamide (10.00 g, 1 Eq, 34.12 mmol) and dry lithium chloride (5.785 g, 4.0 eq., 136.5 mmol) in single portions. The product-containing organics from the first reactor were filtered into reactor 2. Reactor 1

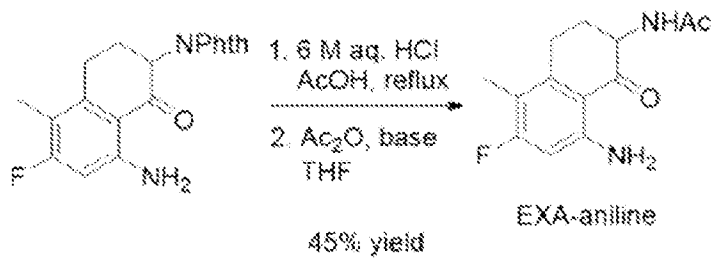
was rinsed with additional N,N-dimethylacetamide (25.18 g, 26.8 mL, 8.47 eq, 289.0 mmol) and the rinse was used to wash the filtrate into reactor 2. Palladium(II) chloride (605 mg, 0.1 equiv.) was charged in one portion, after which the reaction turned black. The reaction was heated to 110 °C (approximate reflux) and vigorously stirred for 26 h, after which it was cooled to 80 °C. The volatiles were removed in vacuo, and the mixture was cooled down to 40 °C. fluoro-5-iodo-4-methylphenyl)acetamide (100 mL) was charged, and the suspension was stirred for 5 min. The reaction was filtered through a pad of celite, washing with minimal methyl ethyl ketone (20 mL). The filtrate was heated to 60 °C and again concentrated in vacuo to remove methyl ethyl ketone. The resulting red solution was cooled to 15 °C, and a solution of phosphoric acid (5.0 g, 85% wt., 1.5 Eq) in water (125 mL) was added dropwise with stirring over 30 min. The mixture was cooled to 5 °C, and the dark-colored product was allowed to oil/precipitate out at the bottom of the vessel with gentle stirring over 2 h. The light-colored, opaque supernatant was removed with a filter stick, and the dark oil residue was washed several more times with water (3 x 100 mL) in a similar manner. The resulting brown residue was thoroughly concentrated in vacuo, azeotropically drying with toluene as needed. Nitromethane (~15 vol based on theoretical yield) was charged with gentle stirring, during which a fine, white precipitate crashed out. The mixture was heated to 45 °C and aged with vigorous stirring for 3 h, after which it was cooled to 10 °C with gentle stirring for an additional hour. The suspension was filtered, and the collected solid was sequentially washed with cold nitromethane (2 x 2 vol) and MTBE (2 x 2 vol). The solids were dried in vacuo to deliver the cross-coupled product as an off-white powder (8.3 g, 61% yield.)

[0037] Example 5. Preparation of 2-(8-amino-6-fluoro-5-methyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)isoindoline-1,3-dione



[0038] To a reactor were sequentially charged 4-(5-acetamido-3-fluoro-2-methylphenyl)-2-(1,3-dioxoisoindolin-2-yl)butanoic acid (3.0 g), methanesulfonic anhydride (4.5 eq) and 1,2-dichloroethane (10 vol). The reaction was heated to reflux and stirred until full conversion was observed (~24 h). The reaction was cooled to 15 °C, and methanol (10 vol) was charged in one portion. The mixture was stirred for 10 h, after which it was concentrated to 5 vol. Additional methanol (15 Vol) was charged with stirring, and the suspension was again concentrated to 5 vol. A final charge of methanol (15 vol) and concentration to 5 vol was performed. Following this, the suspension was cooled to 5 °C, and water (15 vol) was slowly added over 20 min, ensuring the temperature did not exceed 30 °C. After stirring an additional 5 min, the resulting solid was filtered off and sequentially washed twice with water (2 x 8 vol) and twice with methanol (2 x 8 vol). Upon drying, the resulting solid was aged in boiling ethanol (8 vol) with stirring for 15 min. After cooling down to 15 °C, the suspension was filtered and dried to deliver the product as off-white crystals (1.85 g, 73% yield).

[0039] Example 6. Preparation of *N*-(8-Amino-6-fluoro-1,2,3,4-tetrahydro-5-methyl-1-oxo-2-naphthalenyl)acetamide (EXA-aniline)



[0040] To a reactor were sequentially charged 2-(8-amino-6-fluoro-5-methyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)isoindoline-1,3-dione (1 eq), aqueous HCl (6 M, 12 vol), and acetic acid (6 vol). The reaction was purged with nitrogen and then heated to reflux until full conversion was observed (~24 h). The reaction was cooled 15 °C, and it was gently stirred for an additional 6 h, during which a white precipitate formed (phthalic acid by-product). The reaction was filtered without washing, and the filtrate was concentrated in vacuo. The residue was azeotropically dried with isopropanol (2 x 4 vol) to deliver a residue which was satisfactorily pure for the next step.

[0041] To the resulting residue were sequentially charged solvent (THF or EtOAC or acetone; 5-8 vol), isopropanol (0.3 equiv.) and base (aq. $KHCO_3$ or aq. K_2CO_3; ~3.5 equiv.) with stirring. The reaction was cooled to 5 °C with N_2 sparging for 30 min, and acetic anhydride (~1.2 equiv.) was added over 30 min. The reaction was stirred for an additional 30 min.

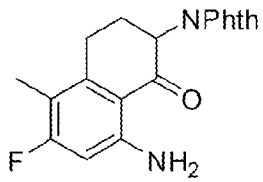
[0042] Methanol (5 vol) was charged, and the reactor was stirred 15 min. The volatiles were removed in vacuo, and to the resulting residue was charged water (10 vol). The mixture was heated to 40 °C with vigorous stirring for 15 min. The aqueous layer was filtered off, and the solids were sequentially washed twice more with water (2 x 5 vol) and cold 60% aqueous ethanol (10 vol). The solids were dried in vacuo to deliver darkly colored crystals. Acetone (10 vol) was added to the crystals, and the resulting suspension was heated to 50 °C with stirring for 3 h. Upon cooling to ambient temperature, the crystals were again filtered and washed with additional acetone (5 vol). The crystals were dried in vacuo to deliver EXA-Aniline as off-white crystals.

[0043] EXA-aniline can then be converted to exatecan mesylate using the procedure described above.

CLAIMS

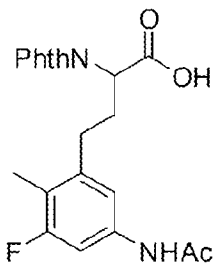
What is claimed is:

1. A compound of formula I



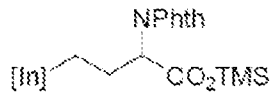
I.

2. A compound of formula II



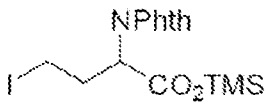
II.

3. A compound of formula III



III.

4. A compound of formula IV



IV.

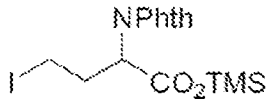
5. A method for preparing a compound of formula I, the method comprising the steps

providing N-(3-fluoro-5-iodo-4-methylphenyl)acetamide,

separately

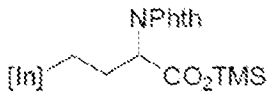
a. reacting 3-bromo-2-oxotetrahydrofuran with potassium phthalimide to provide 2-(2-oxotetrahydrofuran-3-yl)isoindoline-1,3-dione

b. reacting 2-(2-oxotetrahydrofuran-3-yl)isoindoline-1,3-dione with trimethylsilyl iodide (TMSI) to form the corresponding carboxylic acid (IV)



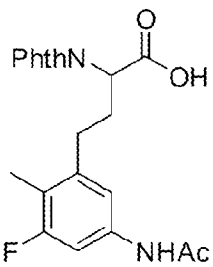
IV

c. reacting the carboxylic acid of (c) with Indium powder and copper(I) iodide to form indium intermediate (III)



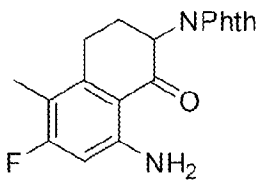
III

d. reacting the indium intermediate (III) with the N-(3-fluoro-5-iodo-4-methylphenyl)acetamide to form intermediate (II)



II

e. performing a ring closing to yield the compound of formula (I)



I.

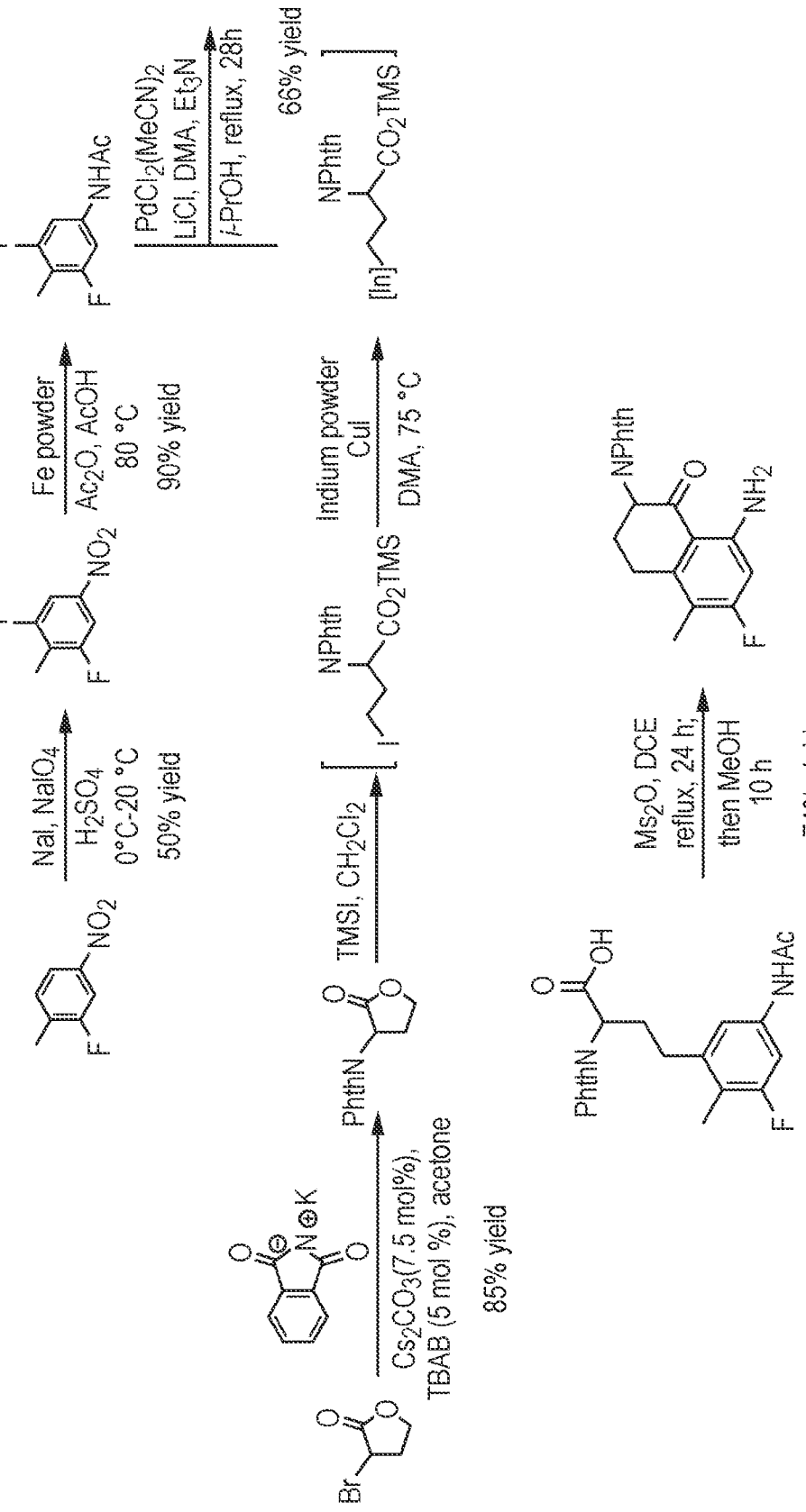

NaI, NaIO4
H2SO4
0°C-20 °C
50% yield
Fe powder
Ac2O, AcOH
80 °C
90% yield
PdCl2(MeCN)2
LiCl, DMA, Et3N
i-PrOH, reflux, 28h
66% yield
TMSI, CH2Cl2
Indium powder
CuI
DMA, 75 °C
Cs2CO3(7.5 mol%),
TBAB (5 mol %), acetone
85% yield
Ms2O, DCE
reflux, 24 h;
then MeOH
10 h
71% yield

FIG. 1

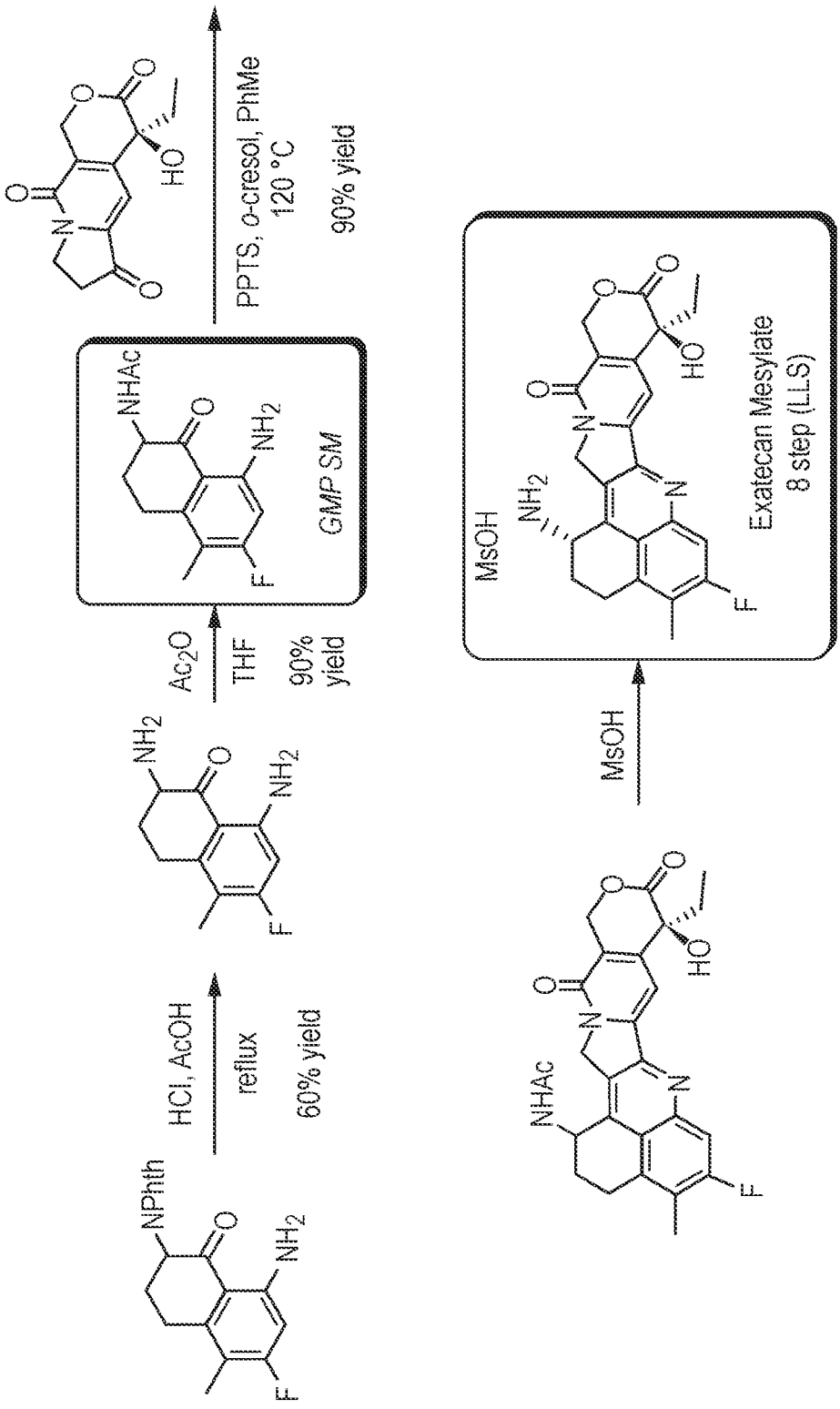

NPhth
NH2
F
HCl, AcOH
reflux
60% yield
NH2
NH2
F
Ac2O
THF
90% yield
NHAc
NH2
F
GMP SM
PPTS, o-cresol, PhMe
120 °C
90% yield
HO
MsOH
NHAc
F
MsOH
NH2
F
HO
Exatecan Mesylate
8 step (LLS)

FIG. 2

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2024/039606

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D209/48 C07D471/14 C07F5/00 C07F7/08 A61P35/00
A61K31/435
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 C07F A61P A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, 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	WO 2023/072143 A1 (SHANGHAI BEST LINK BIOSCIENCE LLC [CN]) 4 May 2023 (2023-05-04) page 2, compound 7, page 8, compound, 1st row, 1st on left side;; claims 1-24	1-5
A	WO 2023/025138 A1 (HANGZHOU ZHONGMEIHUADONG PHARMACEUTICAL CO LTD [CN]) 2 March 2023 (2023-03-02) page 6, reaction scheme; page 21, compound B;; claims 1-24	1-5
A	EP 3 909 961 A1 (CJ CHEILJEDANG CORP [KR]) 17 November 2021 (2021-11-17) paragraph [0125]	3,4

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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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

"Y" document of particular relevance;; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 October 2024	14/11/2024

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Kleidernigg, Oliver

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
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