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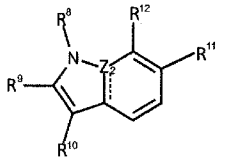
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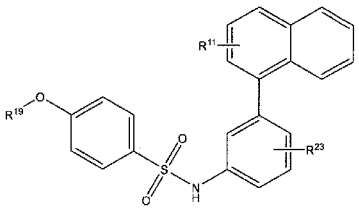
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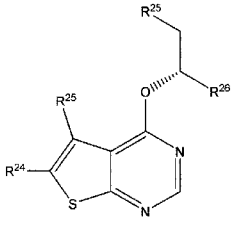
(54) **Title:** TARGETED PROTEIN DEGRADATION USING BIFUNCTIONAL COMPOUNDS THAT BIND UBIQUITIN LIGASE AND TARGET MCL-1 PROTEIN



(A)



(B)



(C)

(57) **Abstract:** A compound of formula (I) [MCL-1 ligand moiety] - [linker] - [ligase ligand moiety] (I) or a salt, solvate, hydrate, isomer or prodrug thereof, wherein [MCL-1 ligand moiety] is a compound of Formula (A), Formula (B) or Formula (C) and its use in the treatment of cancer.

[Continued on next page]

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TARGETED PROTEIN DEGRADATION USING BIFUNCTIONAL COMPOUNDS THAT BIND UBIQUITIN LIGASE AND TARGET MCL-1 PROTEIN

FIELD OF THE INVENTION

The present invention relates to bifunctional compounds which can bind to a ubiquitin ligase and also to a target protein, such that the target protein is placed in proximity to the ubiquitin ligase in order to induce its degradation.

BACKGROUND

The Ubiquitin-Proteasome System (UPS) is responsible for the maintenance of healthy and well-balanced proteome. In the process of ubiquitination, ubiquitin units are covalently attached to the protein, forming a polyubiquitin chain, which marks the protein for degradation via the proteasome. Ubiquitination is central to the regulation of nearly all cellular processes and is also tightly regulated itself. Ubiquitin ligases facilitate ubiquitination of different proteins *in vivo* and contribute to precise regulation of the system. Upon recognition, the ubiquitin ligases mediate the attachment of ubiquitin moieties to the target protein, which label it for degradation by the proteasome.

The idea of selective target protein degradation (TPD) by modulation of UPS was first described in 1999 (US2002173049 A1 (PROTEINIX INC) 21 November 2002). One approach to TPD is by the use of bifunctional molecules that bind the ubiquitin ligase and the target protein simultaneously, allowing for efficient ubiquitin transfer to the latter. This concept was first described by Sakamoto KM et al. (Proc Natl Acad Sci U S A. 2001 Jul 17;98(15):8554-9) and more recently reviewed by Burslem GM and Crews CM (Cell. 2020 Apr 2;181(1):102-114).

Oncogenic stress, such as DNA damage, may result in programmed cell death, the cellular response meant to prevent the oncogenic transformation. This mechanism depends on an interplay between pro-apoptotic and anti-apoptotic Bcl-2 proteins, and the balance of these proteins is essential for the proper functioning of the cell.

BCL-2, BCL-xL and MCL-1are BH3-domain-containing anti-apoptotic proteins. These proteins bind to effector Bcl-2 proteins Bak and Bax (via their BH3 domains), preventing their pro-apoptotic activity. Inhibition of BH3 domain – BH3 pocket binding interface is a well-known approach to cancer therapy (Leber B, Kale J, Andrews DW. Cancer Discov. 2018 Dec;8(12):1511-1514).

High expression of induced myeloid leukaemia cell differentiation protein (MCL-1) is observed in many human cancers and is associated with resistance to cytotoxic drugs. Research shows that inhibition of MCL-1protein in some malignancies leads to the release of pro-apoptotic proteins and induction of apoptosis. Therefore, targeting MCL-1 can be applied as a therapeutic strategy in these types of cancer which are MCL-1dependent, such as multiple myeloma, acute myeloid leukaemia, chronic myeloid leukaemia, B-cell acute lymphoblastic leukaemia, hepatocellular carcinoma and non-small cell lung cancers. This concept was confirmed *in vitro* and *in vivo* (Tron AE et al. Nat Commun. 2018 Dec 17;9(1):5341). Also, treatment with Bcl-2 inhibitors and MEK inhibitors often elicits MCL-1 dependence and subsequent inactivation of MCL-1 results in synthetic lethality (Leber B, Kale J, Andrews DW. Cancer Discov. 2018 Dec;8(12):1511-1514). As demonstrated by Montero, J. et al. (Nat. Commun. 10, 5157 (2019)) and Sale, M. J. et al. (Nat. Commun. 10, 5167 (2019)), MCL-1 is a driver of adaptive survival in tumor cells treated with oncogene targeted therapies, therefore MCL-1 targeting drugs are likely to overcome cancer resistance to these therapeutics.

In parallel to the efforts focused on inhibition of MCL-1, targeted degradation appears as an attractive therapeutic alternative. Both Papatizamas et al. (J. Med. Chem. 2019, 62, 11, 5522–5540) and Wang Z et al. (J. Med. Chem. 2019, 62, 17, 8152–8163) have demonstrated degradation of the MCL-1protein. However, the potency of reported compounds in terms of cellular degradation and the ability to induce apoptosis remains suboptimal. Therefore, alternative chemotypes with improved potency are needed to develop therapeutically applicable MCL-1degraders.

One of the challenges in the development of MCL-1 targeted therapeutics is related to safety, as MCL-1 has been shown to be essential for cardiac homeostasis in adult murine models, and the absence of MCL-1 led to loss of cardiomyocytes. Clinical trials involving MCL-1 inhibitors are currently on clinical hold to evaluate a safety signal for cardiac toxicity (Wei AH et al. Blood Rev. 2020 Nov;44:100672).

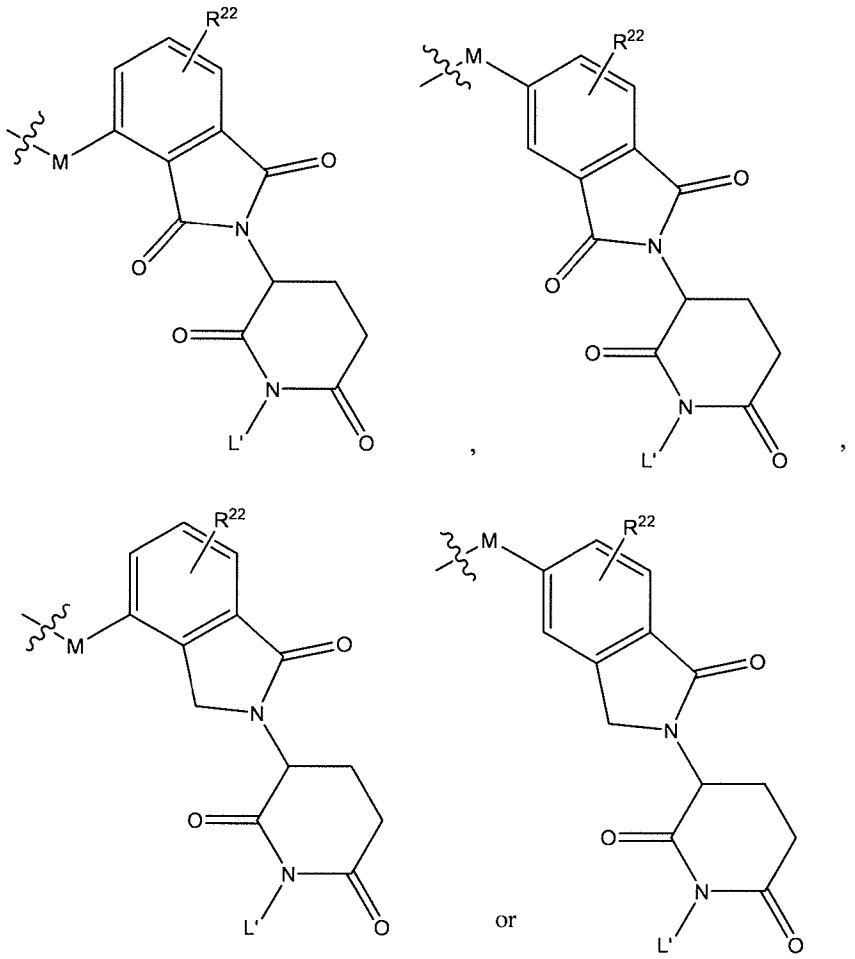
SUMMARY OF INVENTION

In accordance with a first aspect of the invention, there is provided a compound of formula (I)

[MCL-1 ligand moiety] – linker – [ligase ligand moiety] (I)

or a salt, solvate, hydrate, isomer or prodrug thereof,

wherein **[ligase ligand moiety]** is:



wherein

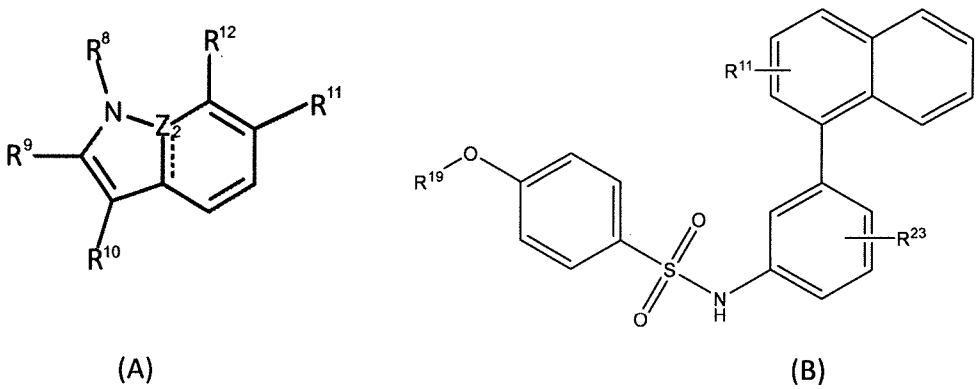
M is O or NH, or is absent;

 indicates attachment to **R^{18}** of the linker;

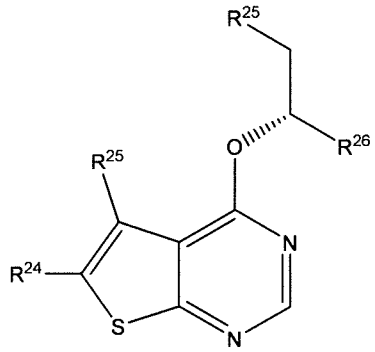
R^{22} is hydrogen, halogen or an amino group; and

L' is hydrogen, alkyl, benzyl, acetyl or pivaloyl;

[MCL-1 ligand moiety] is a compound of Formula (A), Formula (B) or Formula (C)



(A) (B)



(C)

wherein

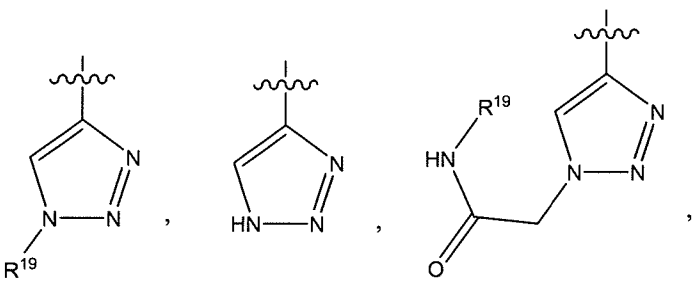
 is a single bond or a double bond;

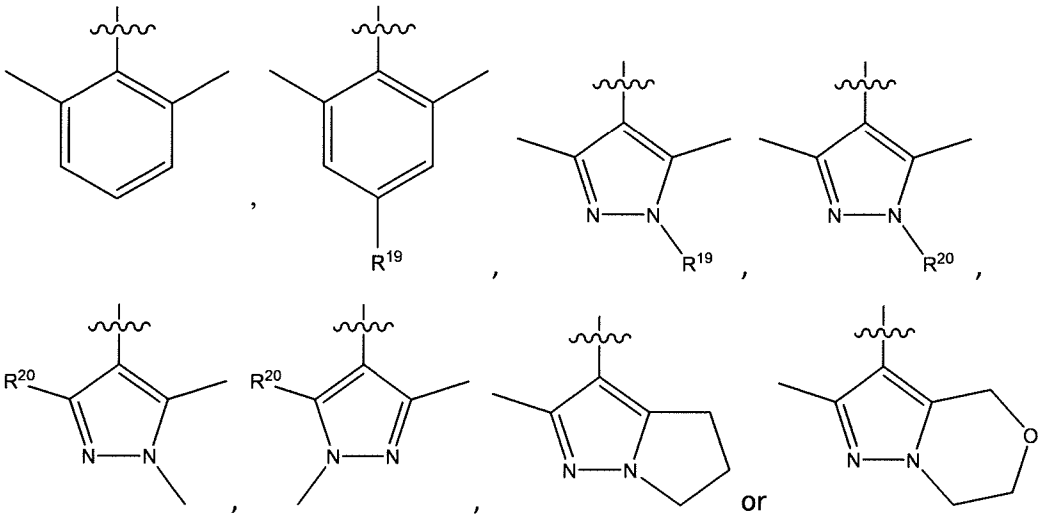
$\mathbf{R^8}$ is H, $\mathbf{R^{19}}$, or C_1-C_6 alkyl optionally substituted with morpholine;

$\mathbf{R^9}$ is -C(O)OH, -C(O)OC_1-C_6alkyl; -C(O)NH_2; -C(O)O$\mathbf{R^{19}}$ or -C(O)NH$\mathbf{R^{19}}$,

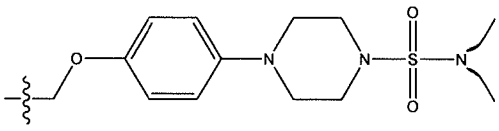
$\mathbf{R^{10}}$ is -$C_{2\text{-}5}$alkyl-O-R^{13}, wherein R^{13} is phenyl, naphthyl or tetraline, wherein the phenyl, naphthyl or tetraline is optionally substituted with at least one substituent selected from halogen, C_1-C_6 alkyl and -O(C_1-C_6 alkyl); or wherein the naphthyl is optionally substituted with -O- or -S-,

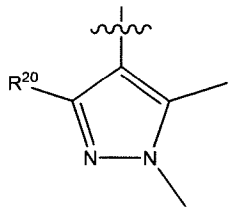
$\mathbf{R^{11}}$ is H, halogen or C_1-C_6 alkyl,

$\mathbf{R^{12}}$ is H, 

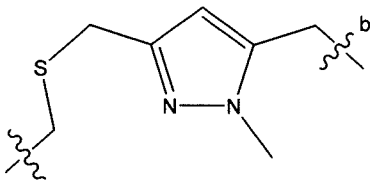


or

wherein R^{20} is Me, -CH_2-O-bromobenzaldehyde, or  ; or when



R^{12} is and R^{10} is -O-naphthyl substituted with -O- or -S-, then R^{20} is



, wherein  indicates attachment to -O- or -S- of R^{10};

and wherein

R^{19} is a bond connected to R^{14} of the linker;

R^{23} is -C(O)OH or -C(O)OC_1-C_6alkyl;

Z_2 is N or C, wherein when Z_2 is N, then  is a single bond; and when Z_2 is C, then  is a double bond,

R^{24} is furan optionally substituted with at least one halogen,

each R^{25} is independently phenyl substituted with -OR^{28} and optionally further substituted with at least one substituent selected from halogen and C_1-C_6 alkyl;

R^{26} is -C(O)OR^{19} or -C(O)NHR^{19}; and

each R^{28} is independently -C_{1-3}alkyl-(N-alkyl piperazine) or -C_{1-3}alkyl-(N-haloalkylpyrazole)

and wherein each of Formula (A), Formula (B) and Formula (C) contains a single R^{19};

and wherein **[linker]** has the following formula

R^{14}-R^{15}-R^{16}-R^{17}-R^{18}

wherein

R^{14} is -C_{1-6} alkyl, -C_{2-6} alkenyl, -C_{2-6} alkynyl, -C(O)-, -SO_2- or is absent

R^{15} is cycloalkyl, heterocycloalkyl, aryl, heteroaryl, -C_{1-6} alkyl-NH-, -cycloalkyl-NH- or is absent

R^{16} is -C_{1-6} alkyl, -C(O)-, -C(O)-NH-, -C(O)O-, -CH_2-C(O)-, -CH_2-C(O)-NH-, -CH_2-C(O)O- or is absent

R^{17} is -$CH_2(C_2H_4\text{-}O)_y$, $(C_2H_4\text{-}O)_x$, $(C_3H_6\text{-}O)_x$, or is absent

x is 1-10

y is 2-10

R^{18} is -C_{1-6} alkyl, heterocycloalkyl, or is absent

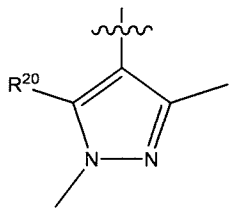
wherein at least one of R^{14}-R^{18} is present

with the proviso that:

when

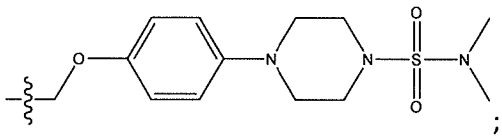
R^{10} is -C_3H_6-O-naphthyl,

R^{12} is



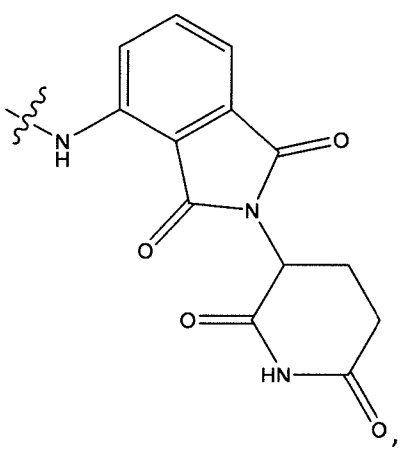
, and

R^{20} is

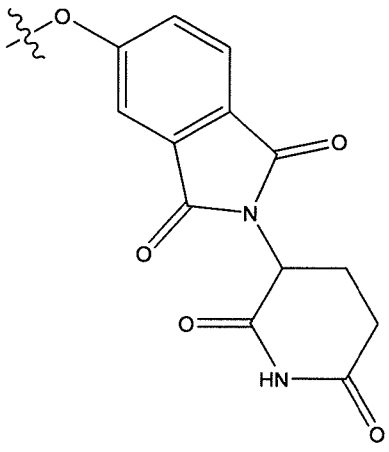


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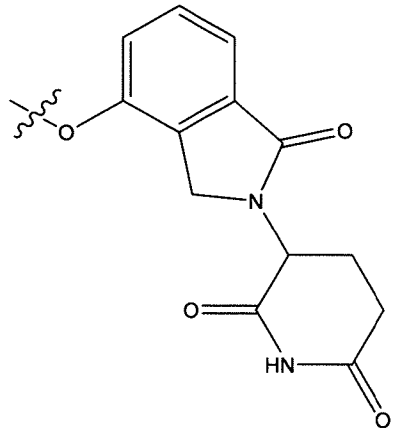
then **R^9** is -C(O)OH, -C(O)OC_1-C_6alkyl or -C(O)NH_2, and **[ligase ligand moiety]** is



,



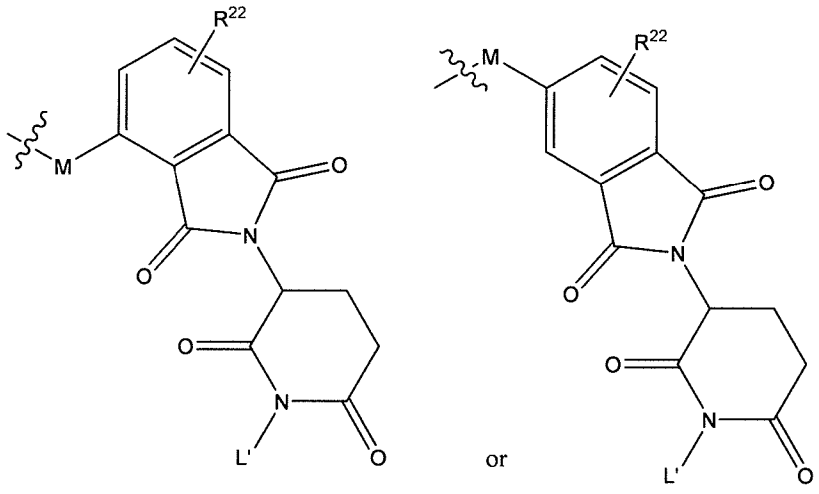
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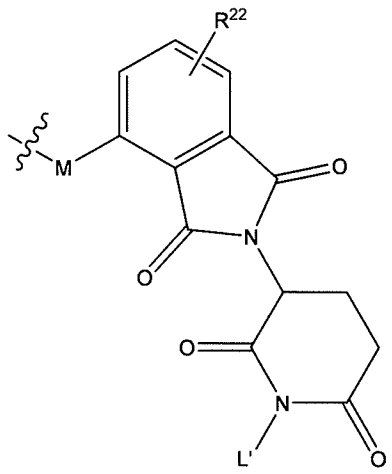
In some embodiments, R^{22} is hydrogen or an amino group. In some embodiments, R^{22} is hydrogen.

In some embodiments, **L'** is hydrogen or methyl. In some embodiments, **L'** is hydrogen.

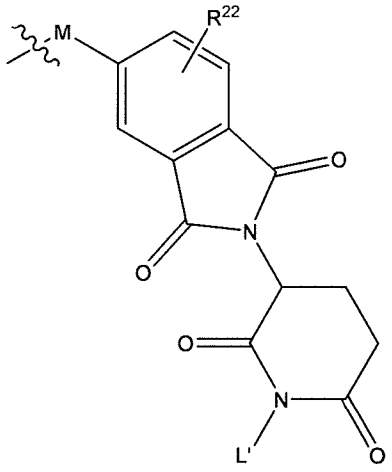
In some embodiments, **[ligase ligand moiety]** is:



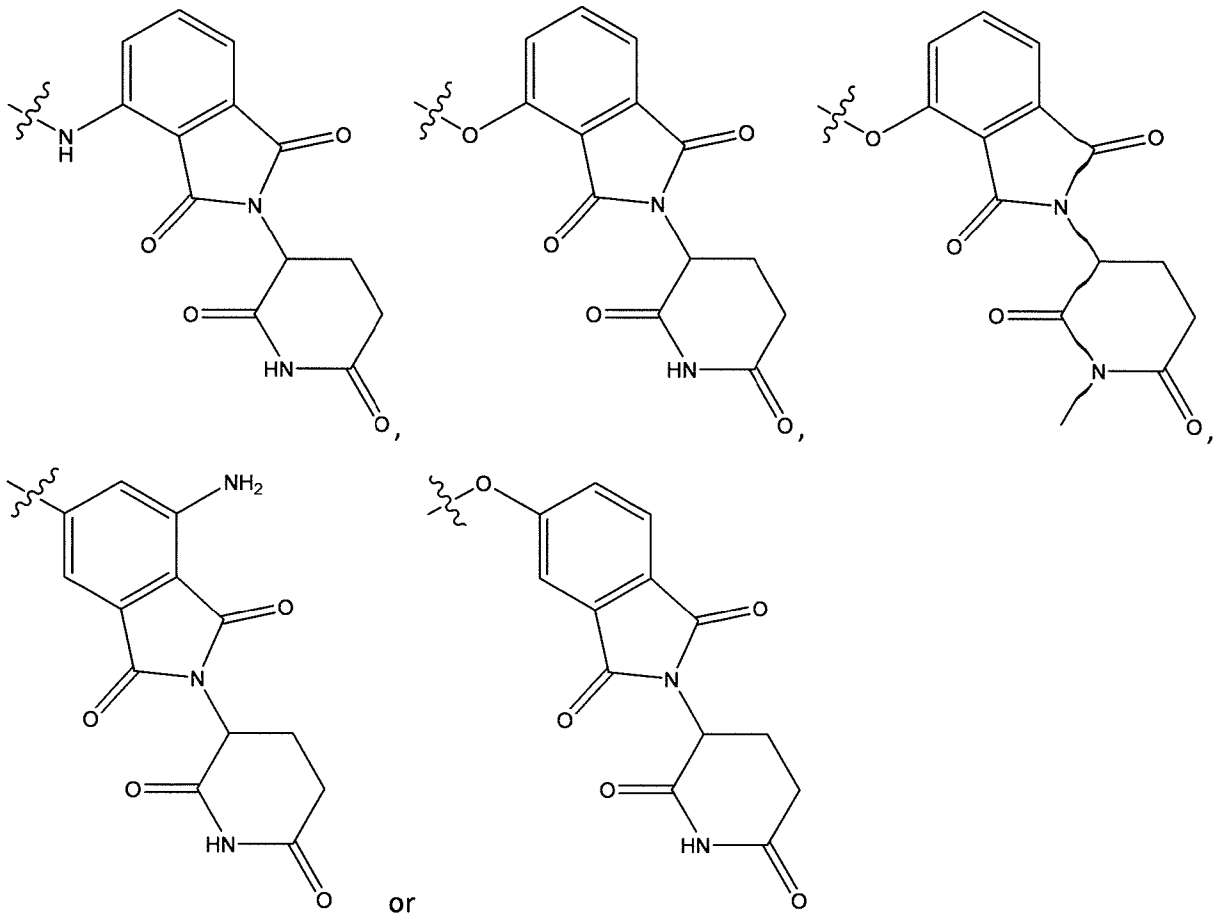
In some embodiments, **[ligase ligand moiety]** is:



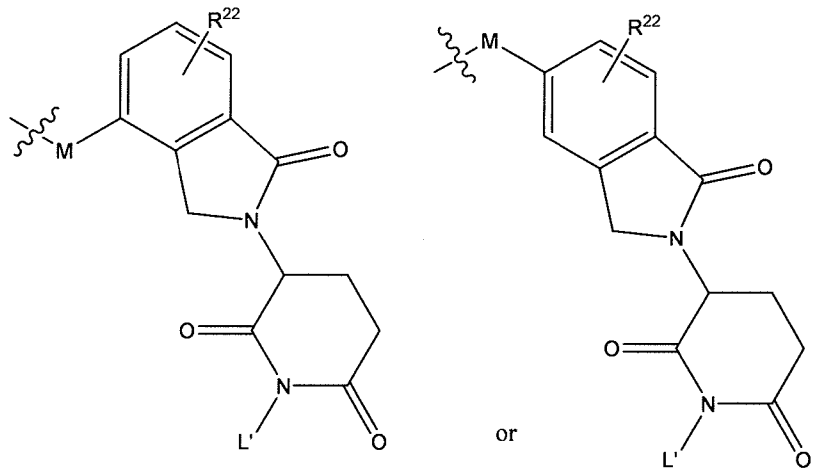
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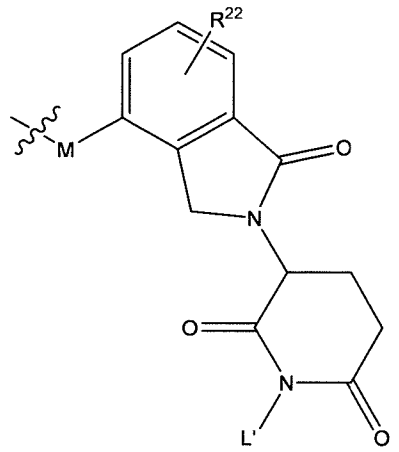
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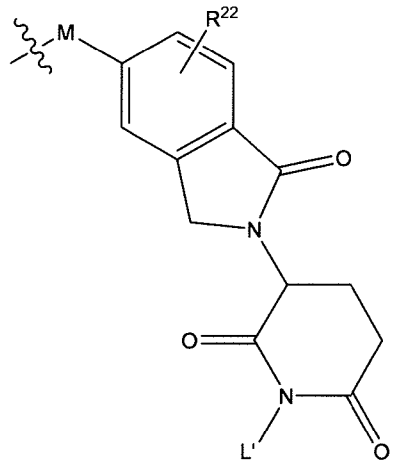
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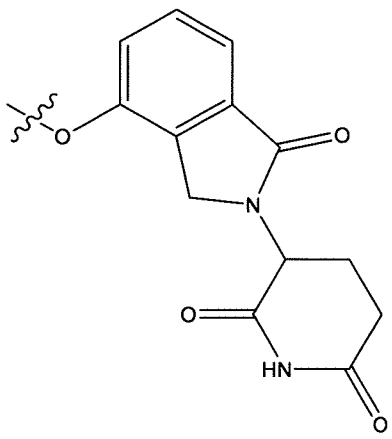
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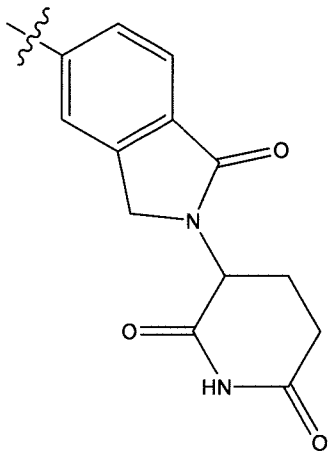
In some embodiments, **[ligase ligand moiety]** is:



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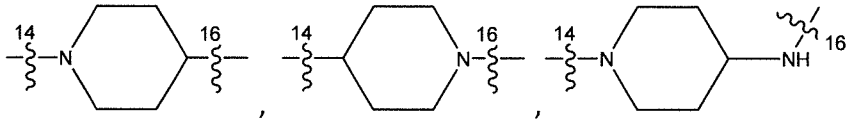
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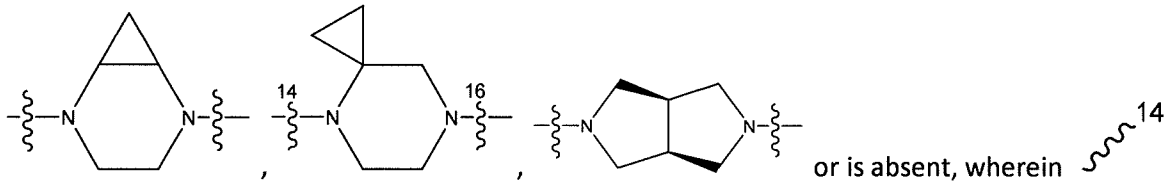


In some embodiments,

R^{14} is -C_{1-6} alkyl, -SO_2- or is absent

R15 is piperazine, bridged piperazine, piperazine N-oxide, piperazine cation, -C_{1-6} al kyl-NH-,





or is absent, wherein indicates attachment to **R14** and  indicates attachment to **R16**,

R16 is -C_{1-6} alkyl, -C(O)-, -C(O)-NH-, -CH_2-C(O)-NH- or is absent

R17 is -$CH_2(C_2H_4\text{-}O)_y$, $(C_2H_4\text{-}O)_x$, $(C_3H_6\text{-}O)_x$, or is absent

x is 1-6

y is 2-6

R18 is -C_{1-6} alkyl, piperazine, or is absent

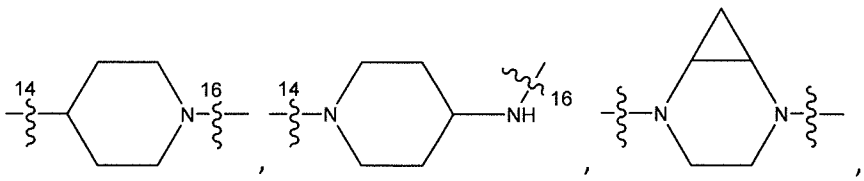
wherein at least one of R^{14}-R^{18} is present.

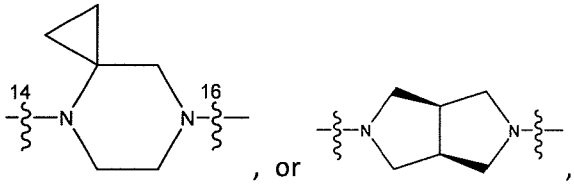
In some embodiments, **R18** is -C_{1-6} alkyl or is absent.

In some embodiments, when **R14** is -SO_2-, at least two of **R15**-**R18** are present, and at least one of **R15**-**R18** is not C_{1-6} alkyl.

In some embodiments, **R14** is -SO_2-; **R15** is -C_{1-6} alkyl-NH-; **R16** is -C(O)-; **R17** is -$CH_2(C_2H_4\text{-}O)_y$, $(C_2H_4\text{-}O)_x$ or is absent; and **R18** is -C_{2-4} alkyl. In some such embodiments, **R15** is -C_2alkyl-NH-; x is 1 or 2; and y is 1.

In some embodiments, when **R15** is piperazine, bridged piperazine, piperazine N-oxide, piperazine cation, -C_{1-6} alkyl-NH-,



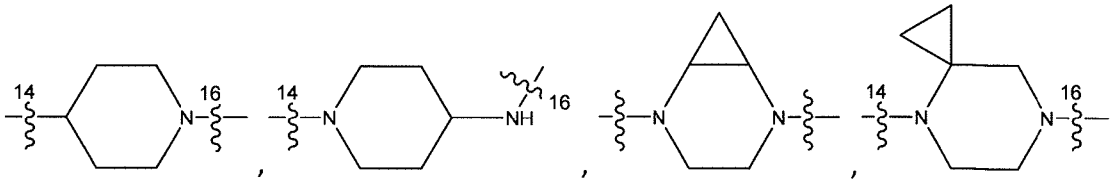


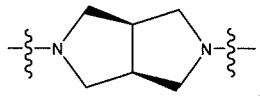
, then **R14** is -C_{1-6} alkyl.

In some embodiments,

R^{14} is -C_{1-6} alkyl,

R^{15} is piperazine, bridged piperazine, piperazine N-oxide,



or 

,

R^{16} is -C(O)-, -CH_2-C(O)-NH-, or is absent

R^{17} is -$CH_2(C_2H_4\text{-}O)_y$, $(C_2H_4\text{-}O)_x$, $(C_3H_6\text{-}O)_x$, or is absent, and

R^{18} is -C_{1-6} alkyl.

wherein when R^{16} and R^{17} are absent, R^{18} is -C_{3-6} alkyl.

In some such embodiments, R^{14} is -C_2 alkyl; x is 1, 2 or 6; and y is 2.

In some embodiments, R^{14} is absent, R^{15} is absent, R^{16} is -C(O)-NH- or is absent; R^{17} is -$CH_2(C_2H_4\text{-}O)_y$, $(C_2H_4\text{-}O)_x$, $(C_3H_6\text{-}O)_x$, or is absent; and R^{18} is -C_{1-6} alkyl.

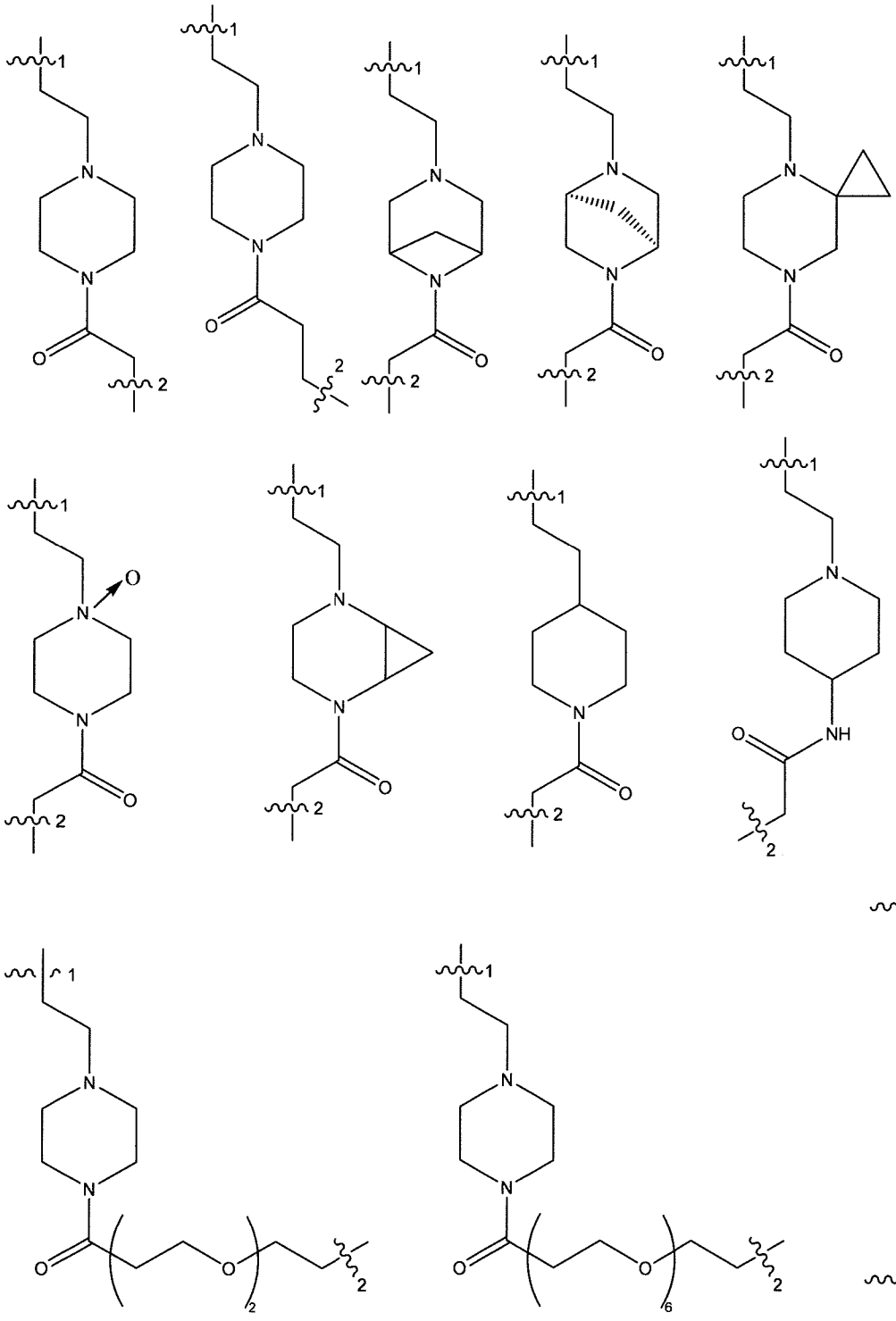
In some embodiments, at least one of R^{14}-R^{18} is not -C_{1-6} alkyl.

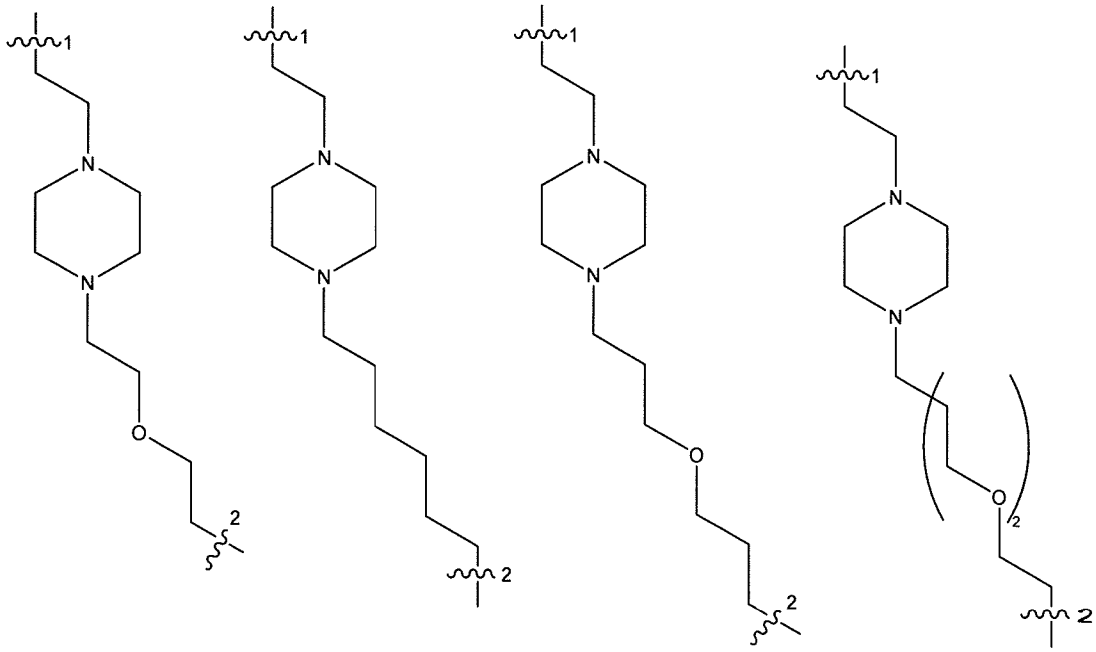
In some embodiments, x is 1, 2 or 3; y is 2; and R^{18} is -C_{2-6} alkyl.

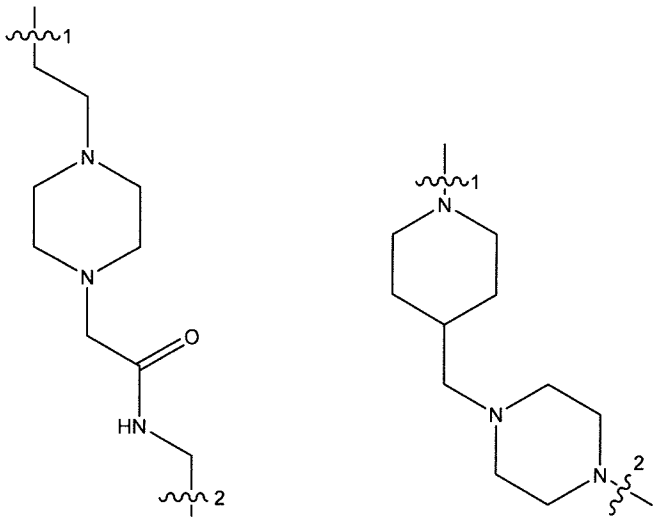
In some embodiments, when R^{15} is -C_{1-6} alkyl-NH-, at least one of R^{16}-R^{18} is present.

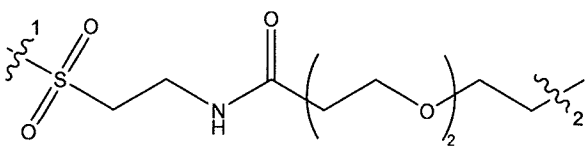
In some embodiments, when R^{17} is -$CH_2(C_2H_4\text{-}O)_y$, $(C_2H_4\text{-}O)_x$ or $(C_3H_6\text{-}O)_x$, at least one of R^{14}-R^{16} and R^{18} is present, wherein at least one of R^{14} and R^{18} is not -C_{1-6} alkyl.

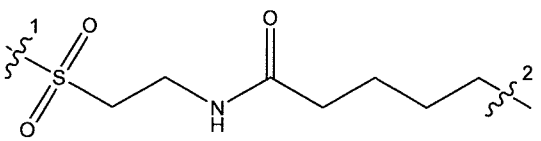
In some embodiments, **[linker]** is selected from

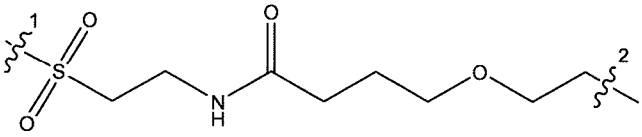


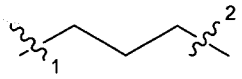


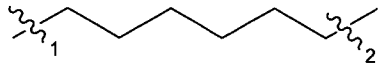


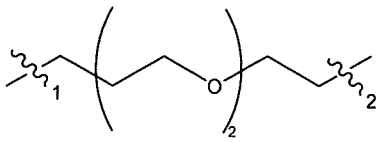


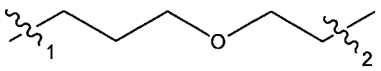


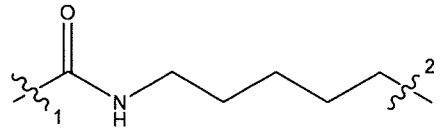


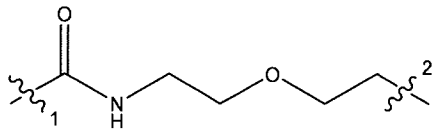


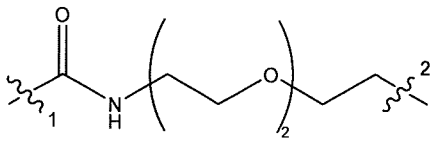




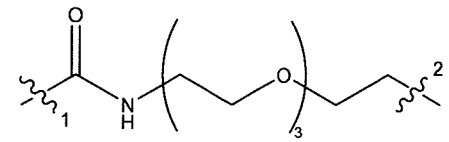








and



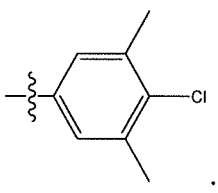
wherein



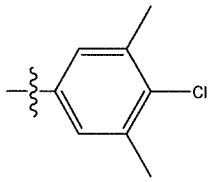
indicates attachment to **[MCL-1 ligand moiety]** and



indicates attachment to **[ligase ligand moiety].**

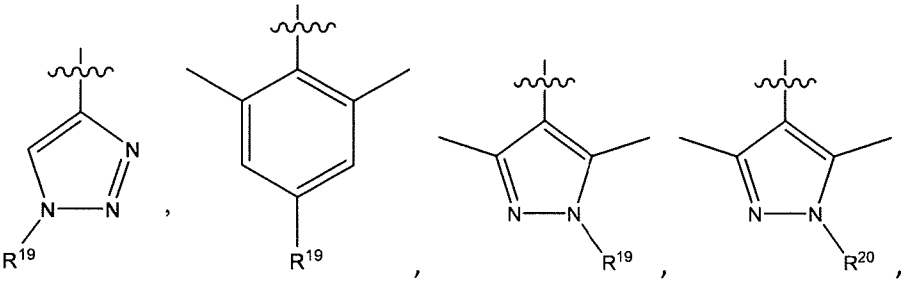
In some embodiments, when $\mathbf{R^8}$ is H, $\mathbf{R^{13}}$ is  .

In some embodiments, $\mathbf{R^8}$ is H, $\mathbf{R^{19}}$, methyl, or -CH_2CH_2-morpholine; $\mathbf{R^9}$ is -C(O)OH or -C(O)NH$\mathbf{R^{19}}$;

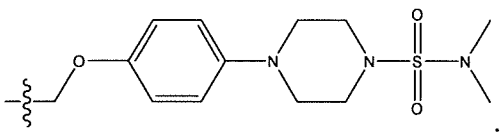


R^{10} is $-C_3H_6O-R^{13}$, wherein R^{13} is , tetraline, or naphthyl optionally substituted with fluorine;

R^{11} is H, Cl, F or methyl, and

R^{12} is 

, or , wherein R^{20} is Me, $-CH_2$-O-bromobenzaldehyde, or

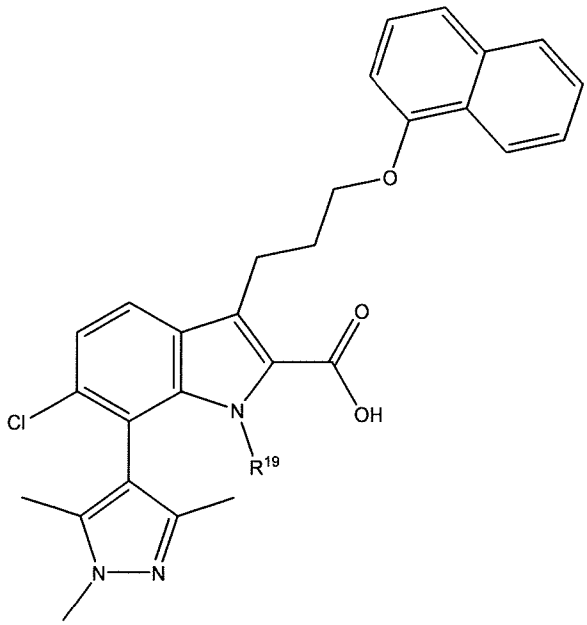


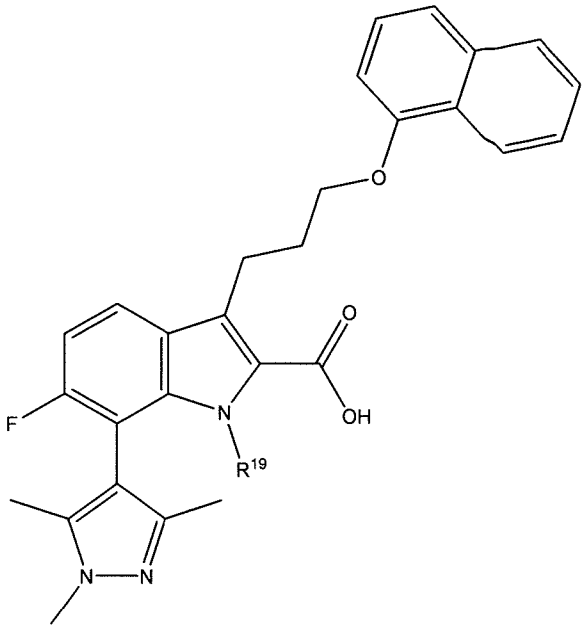
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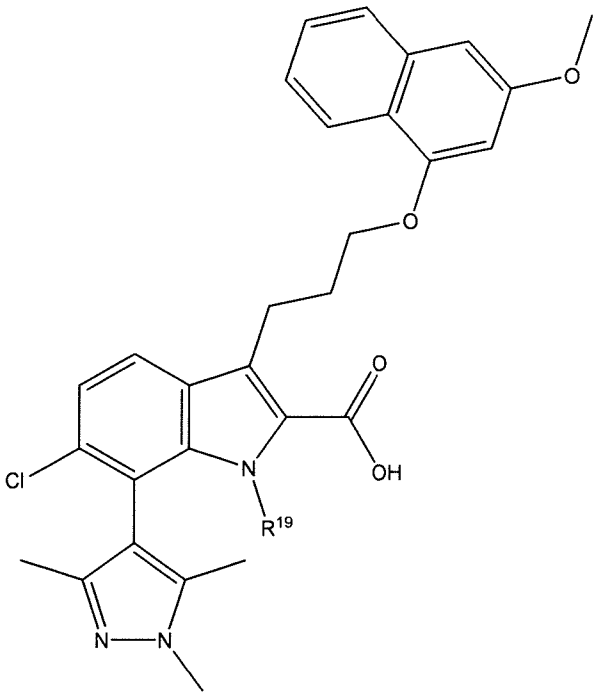
In some embodiments, Z_2 is N and is a single bond. In other embodiments, Z_2 is C and is a double bond.

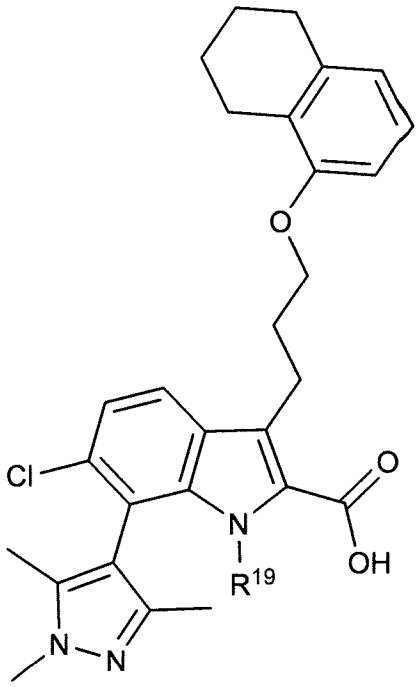
In some embodiments, R^{11} is hydrogen. In other embodiments, R^{11} is halogen or C_1-C_6 alkyl. In some embodiments, R^{11} is halogen.

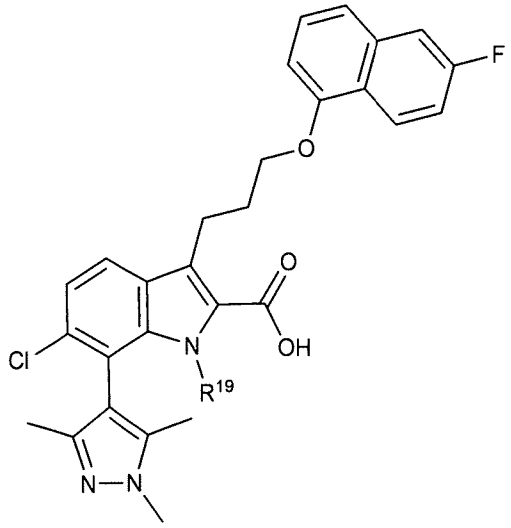
In some embodiments, **[MCL-1 ligand moiety]** is selected from:

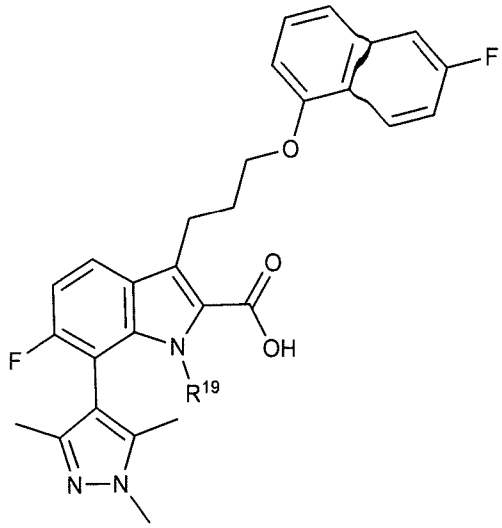


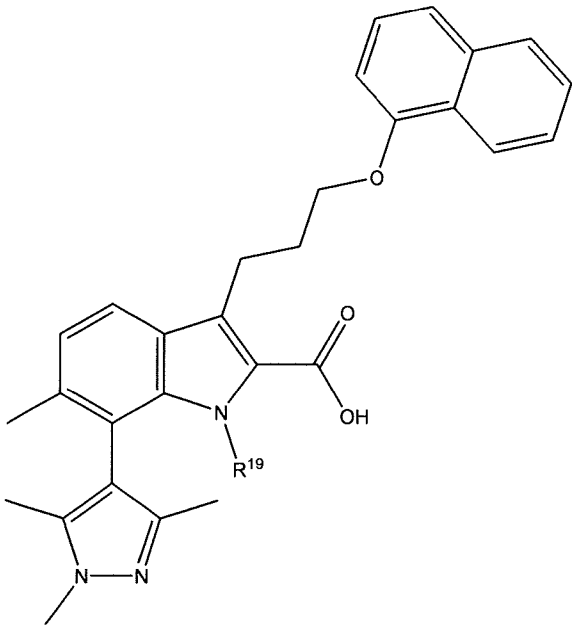


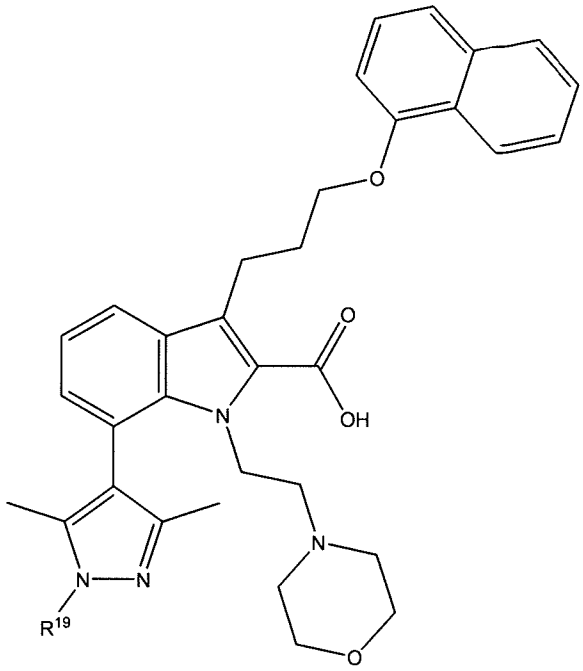


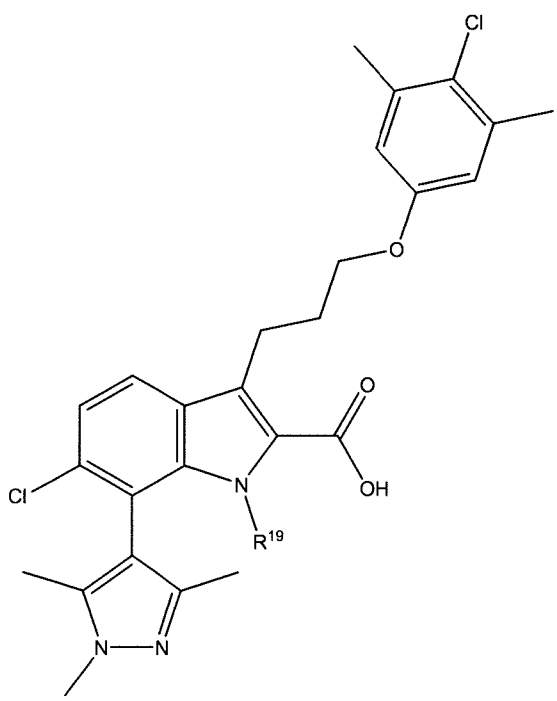


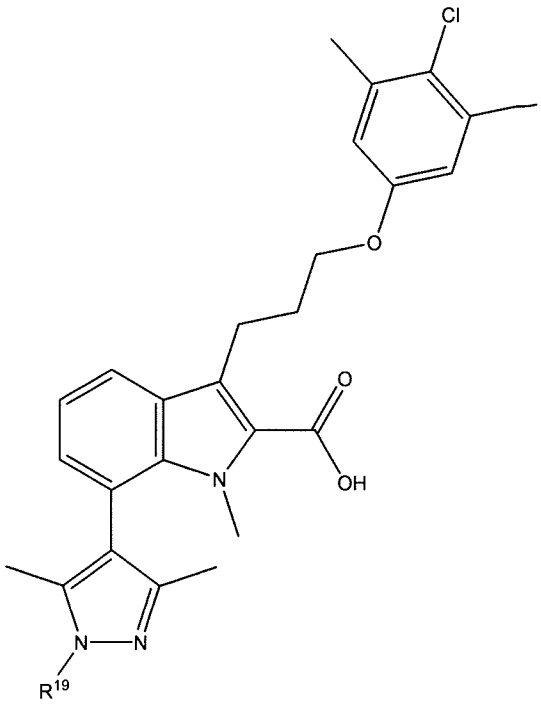


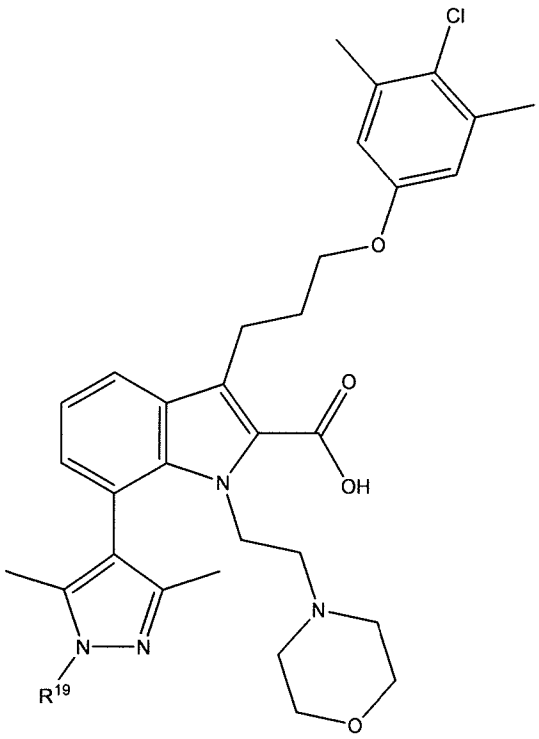


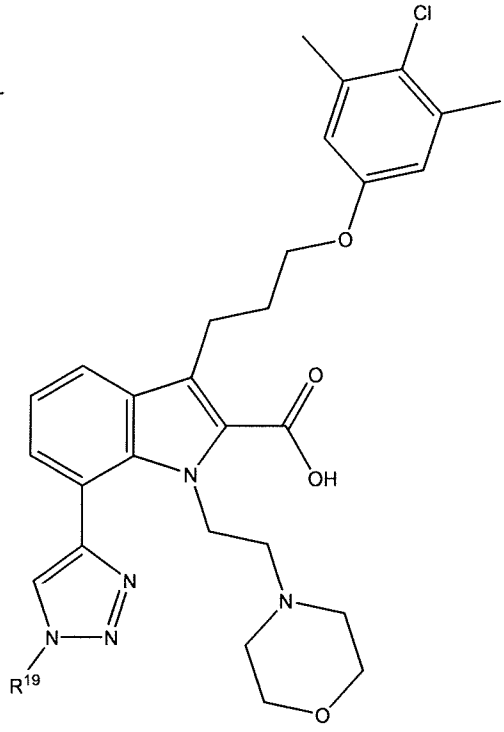


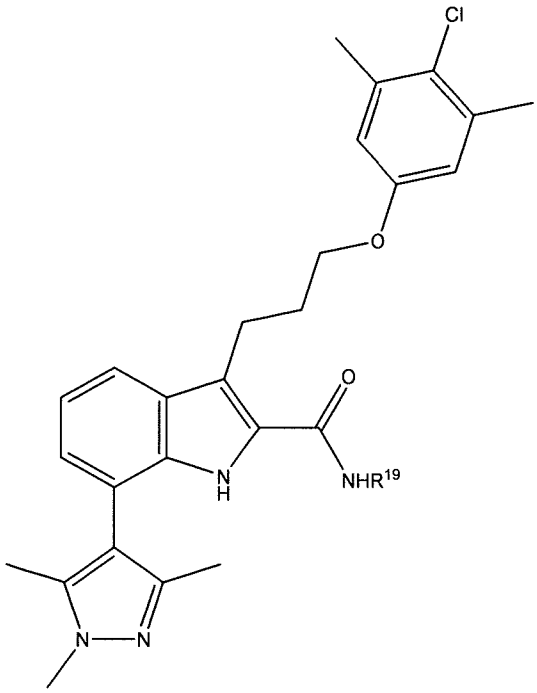


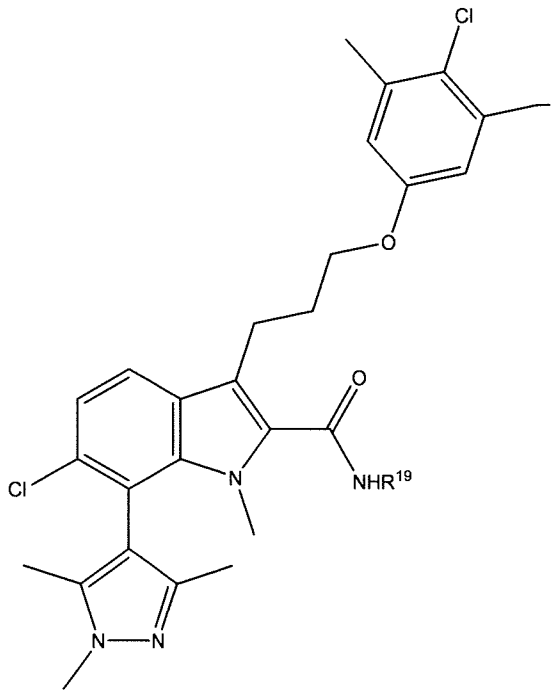


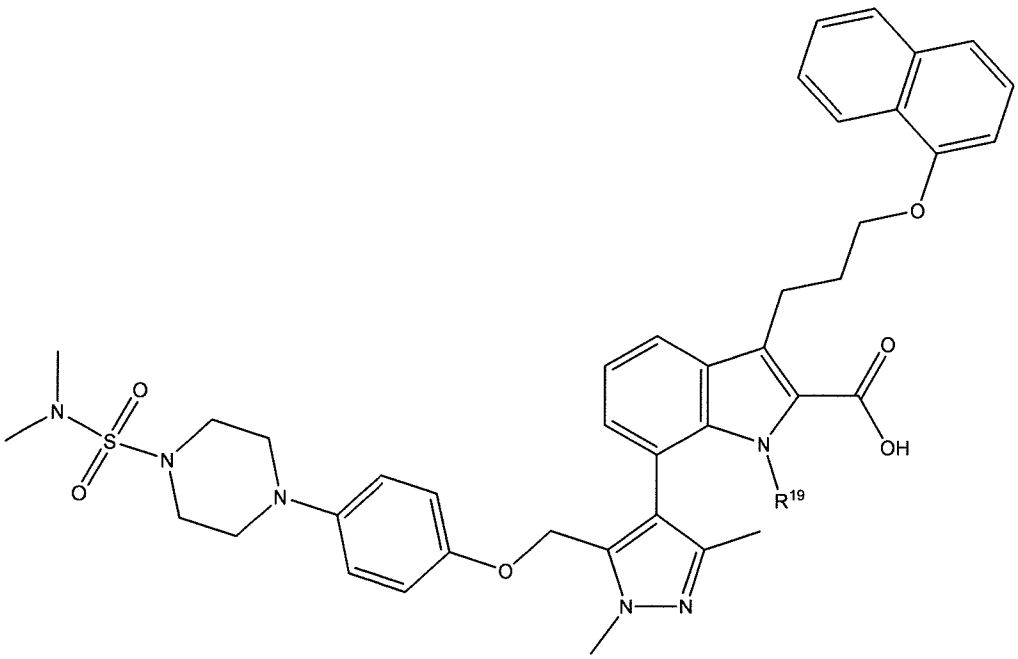


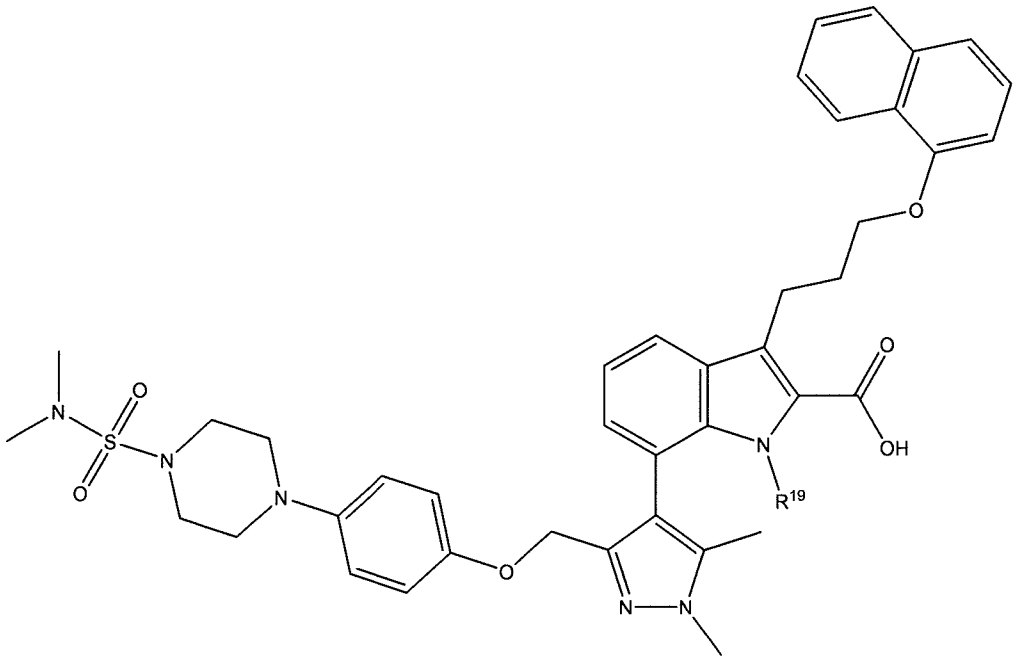


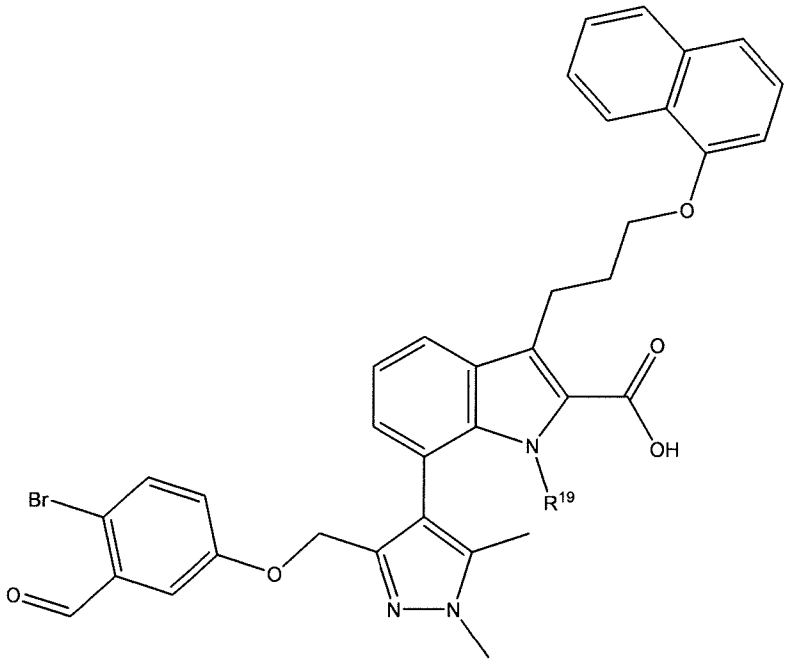


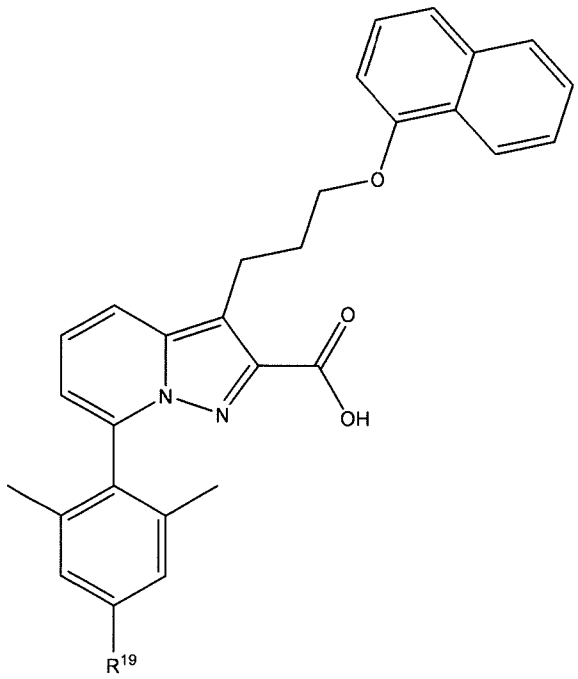


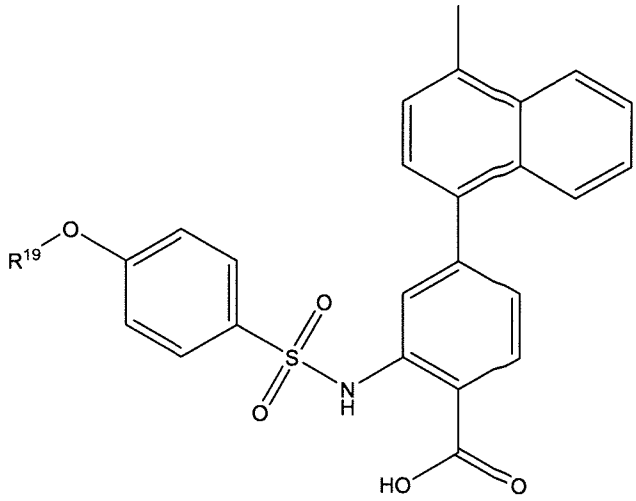


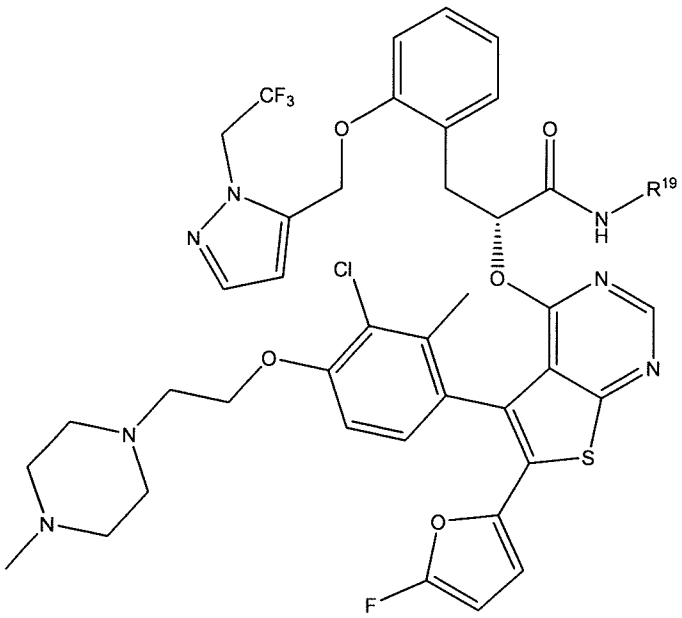




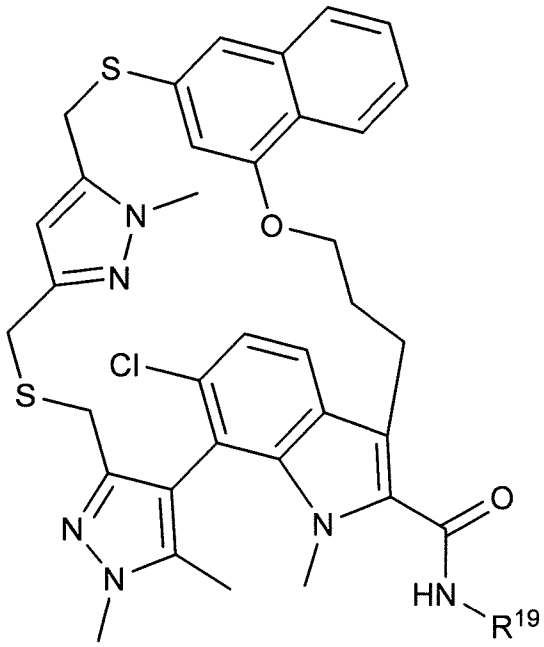




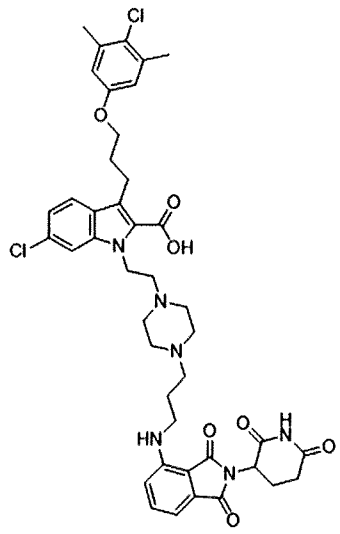
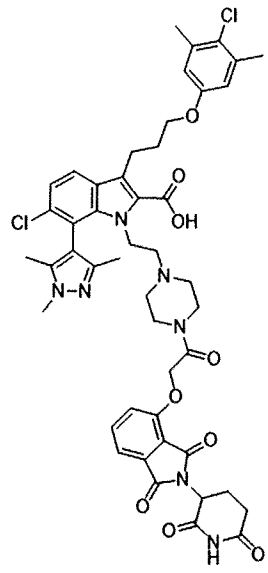
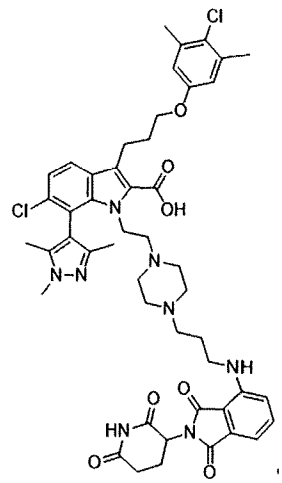


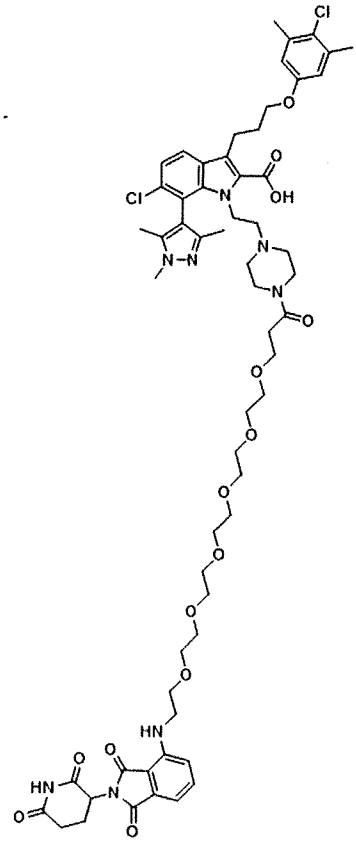
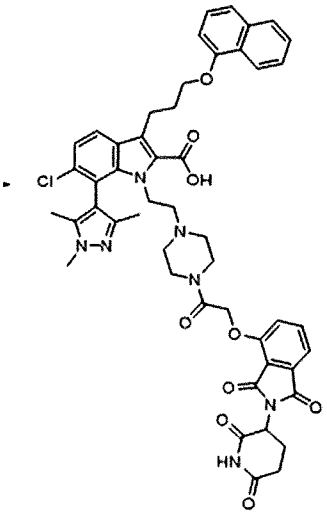
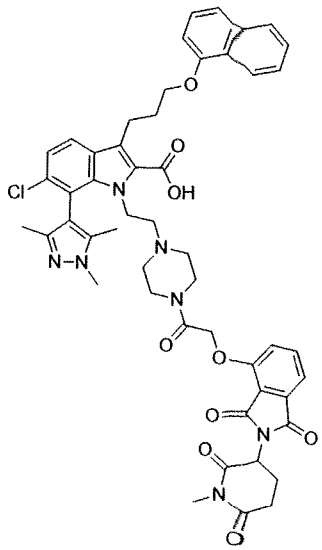
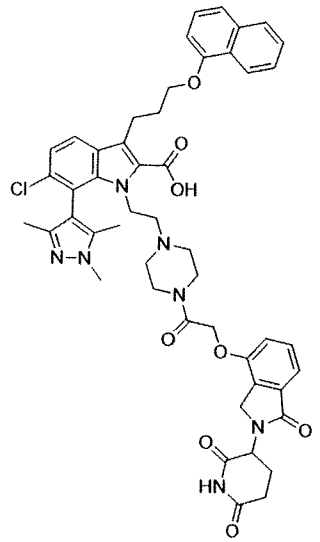
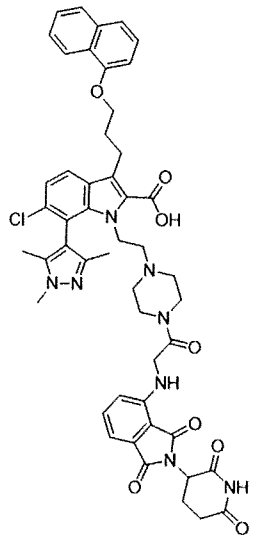
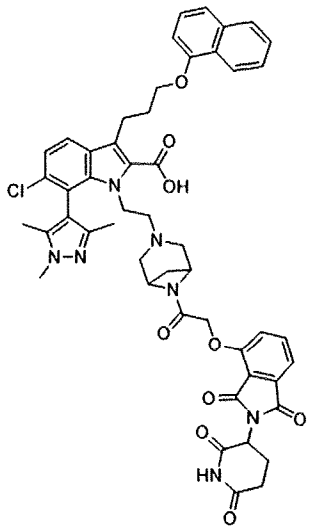


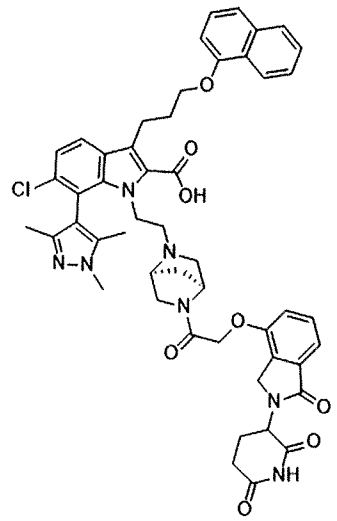
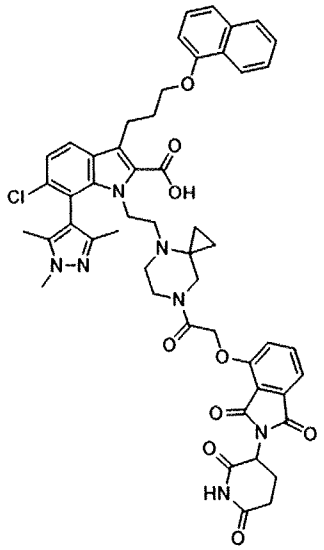
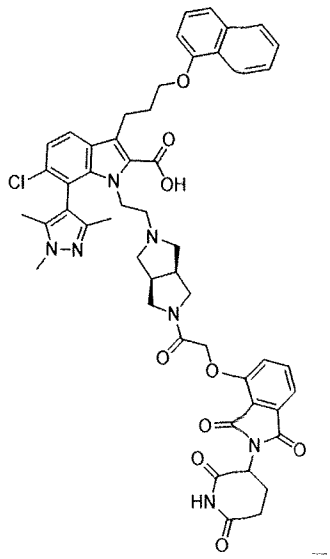
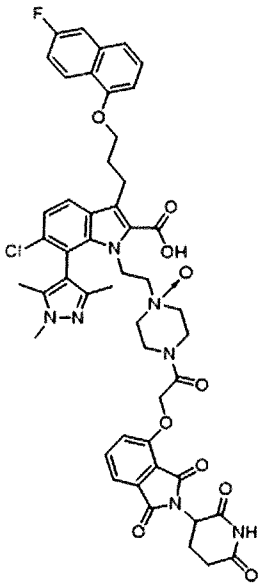
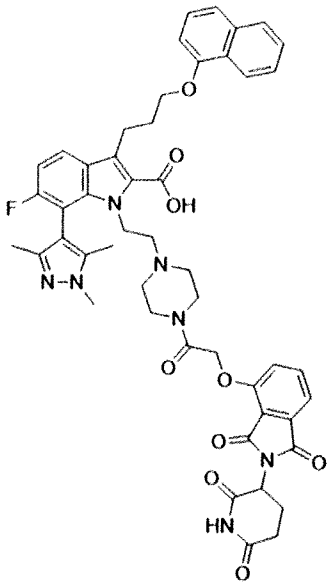
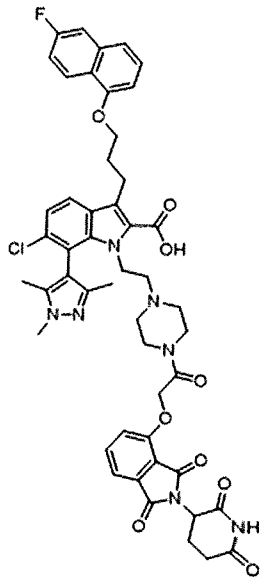
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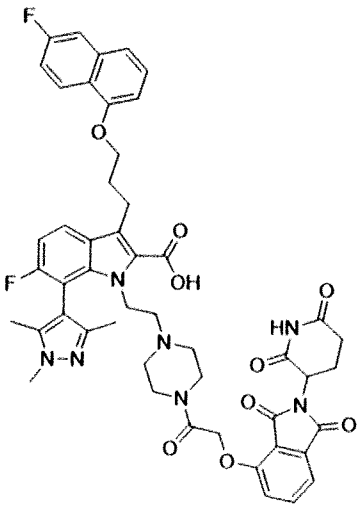
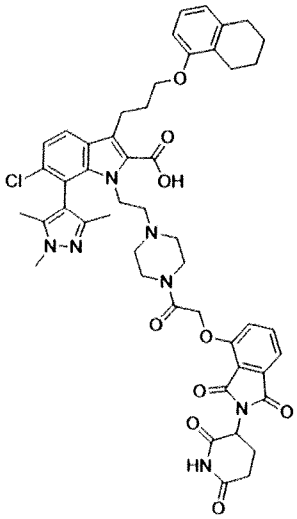
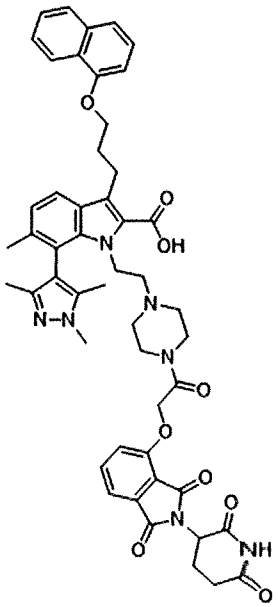
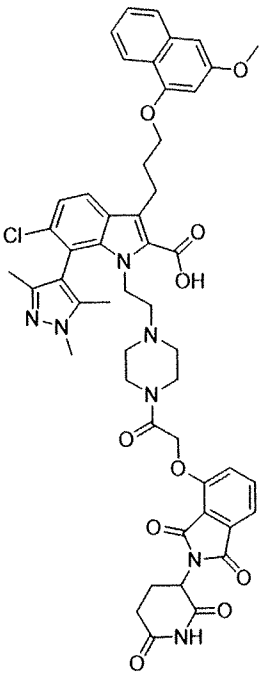
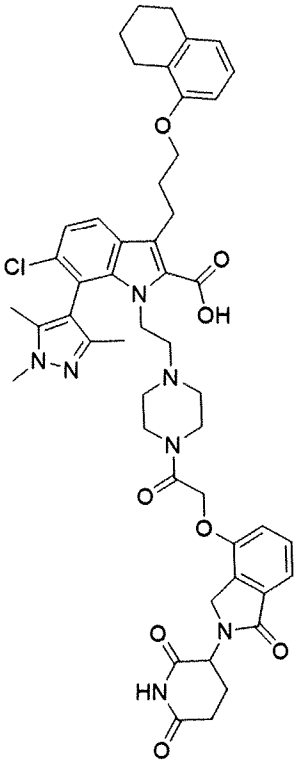
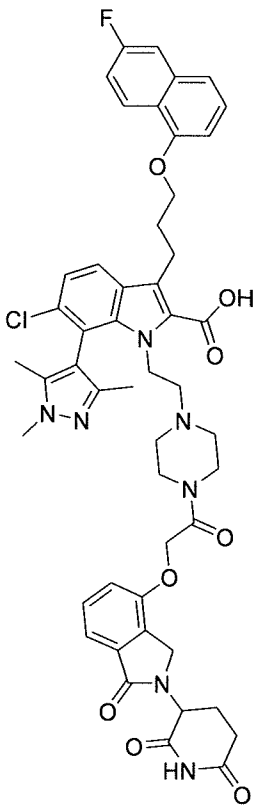


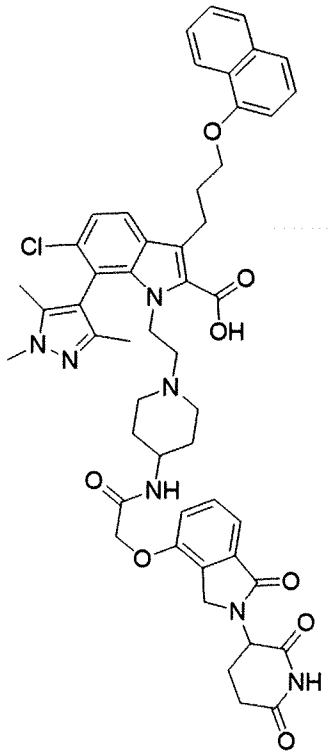
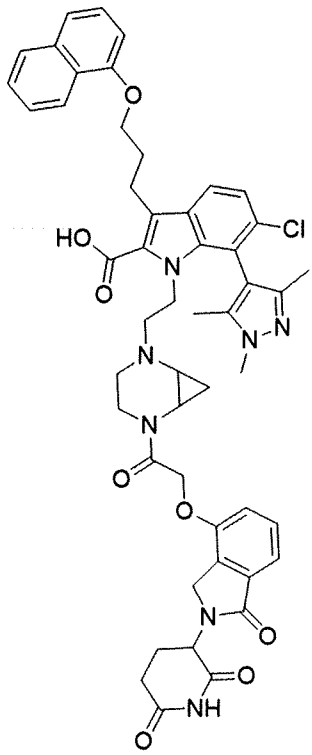
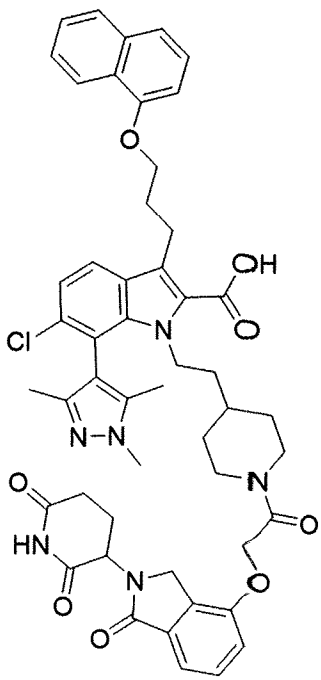
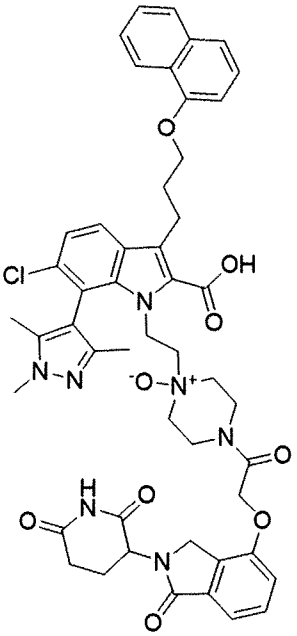
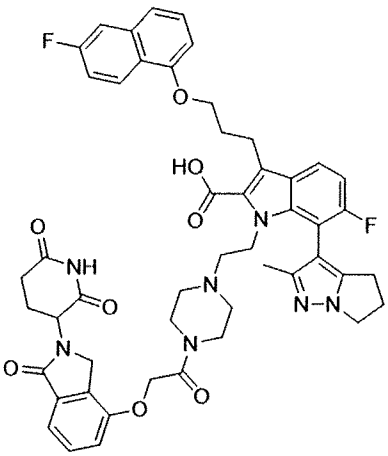
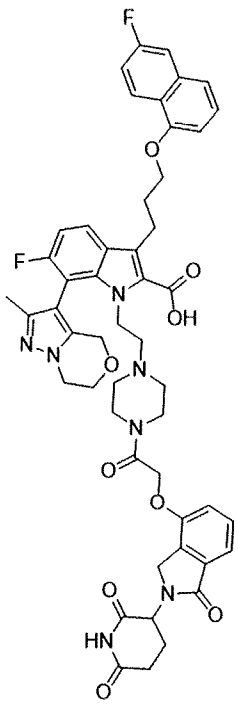
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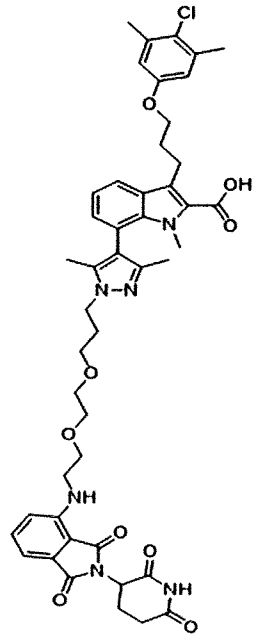
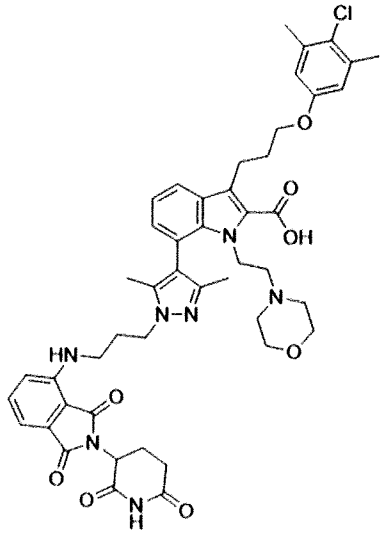
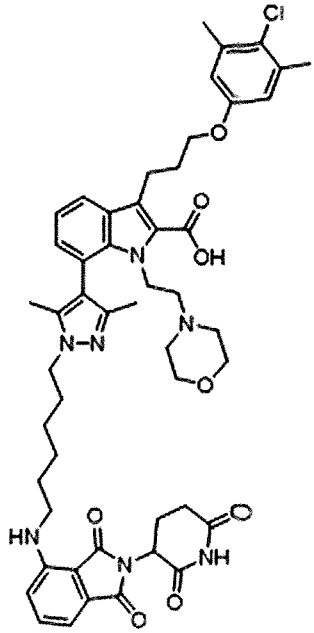
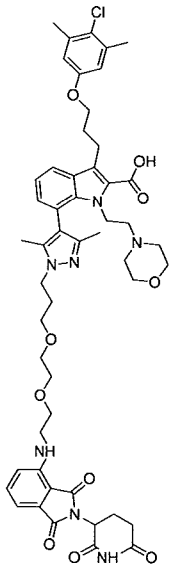
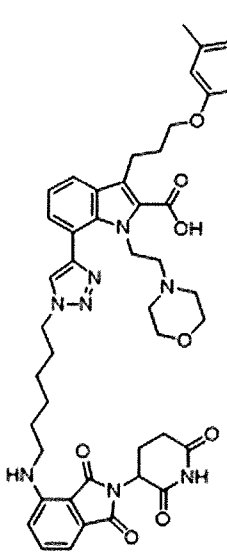
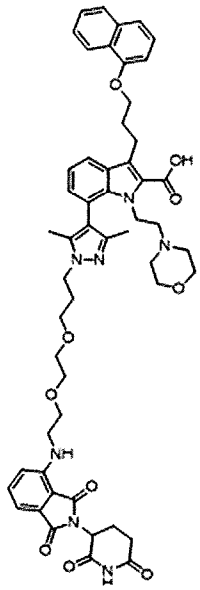
		
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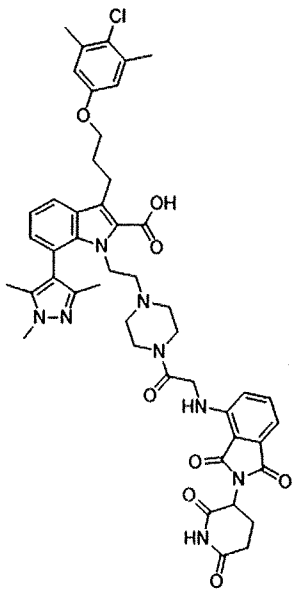
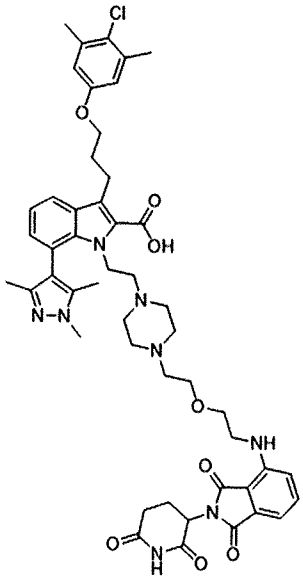
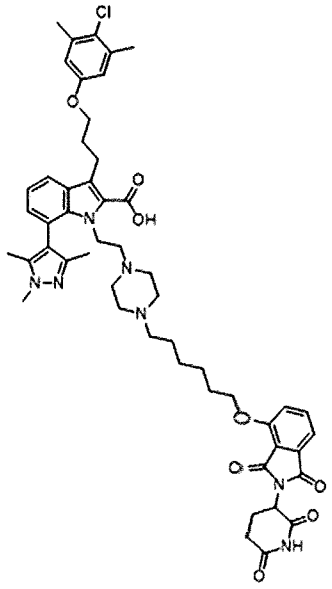
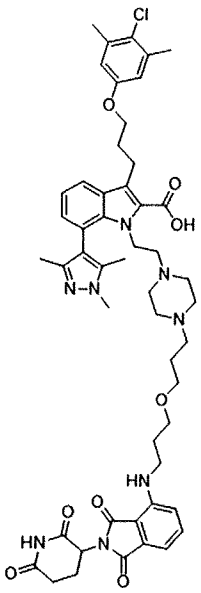
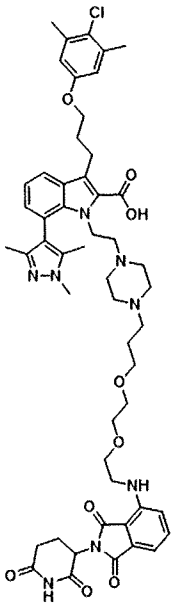
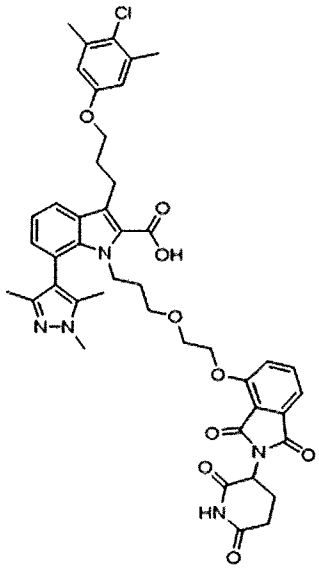
		
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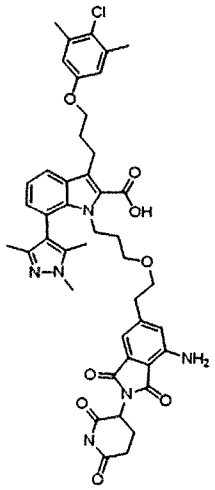
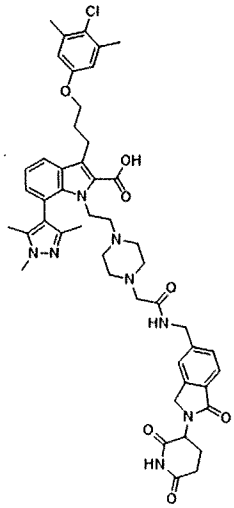
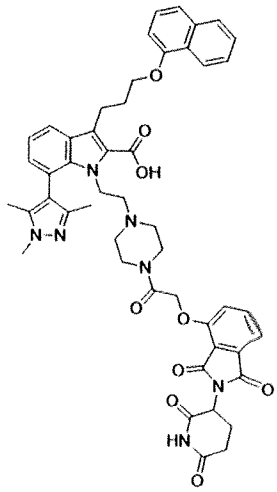
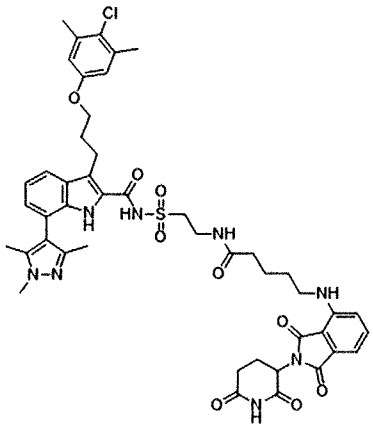
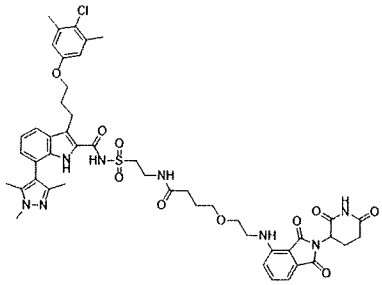
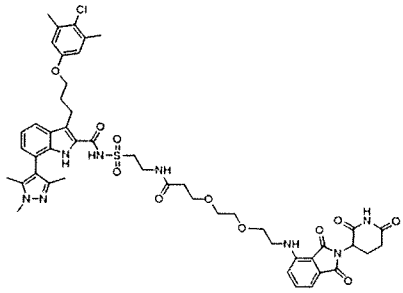
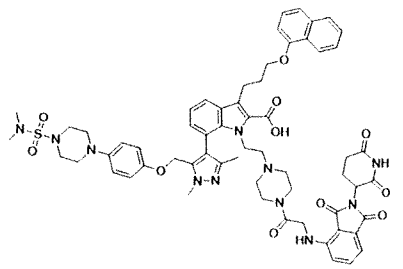
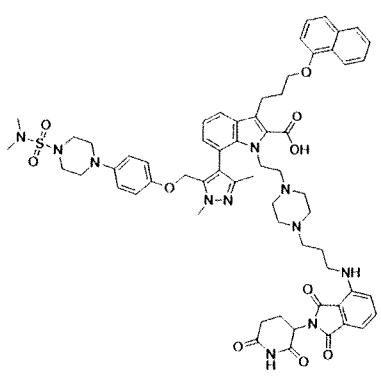
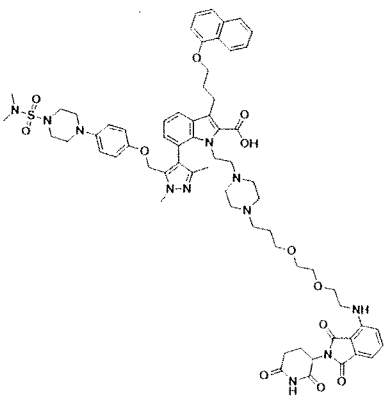
		
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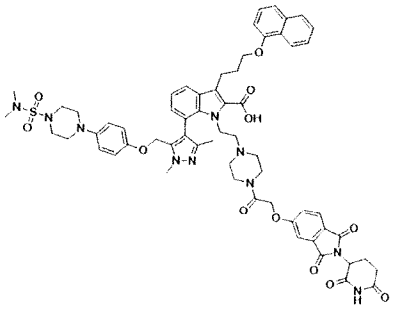
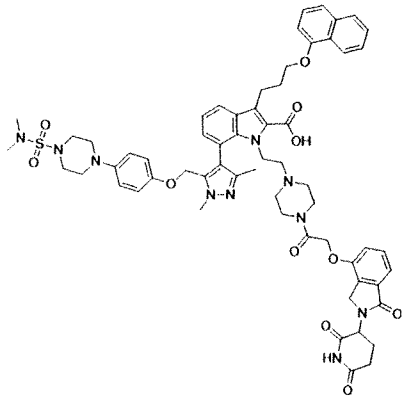
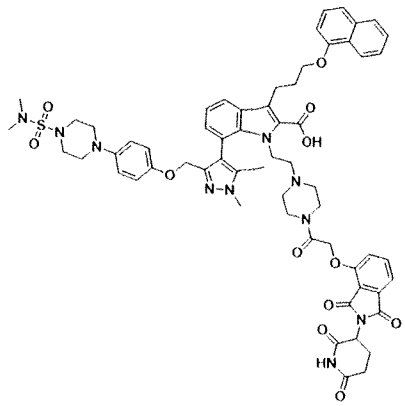
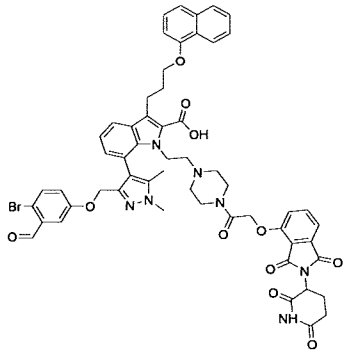
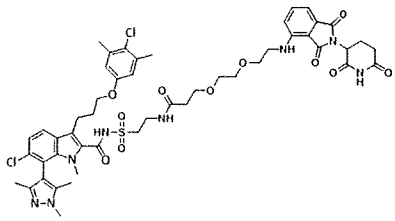
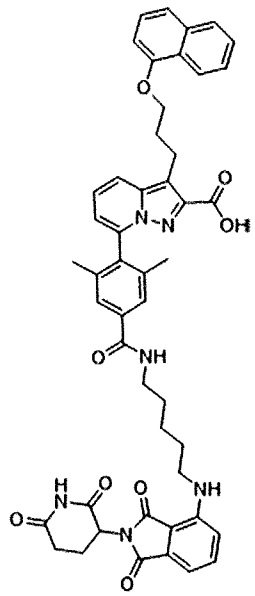
		
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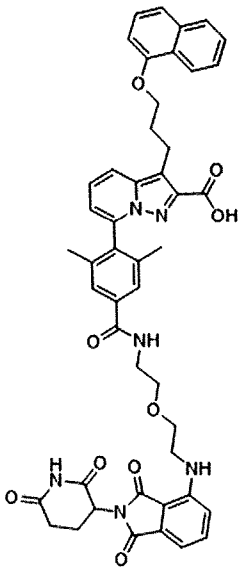
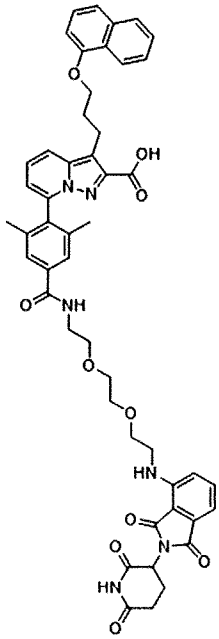
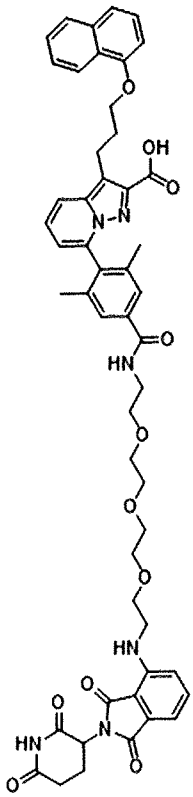
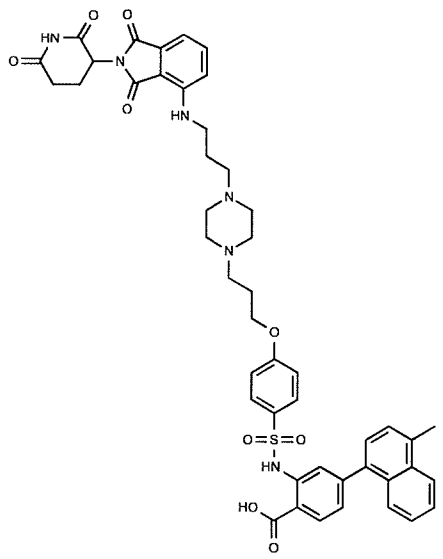
		
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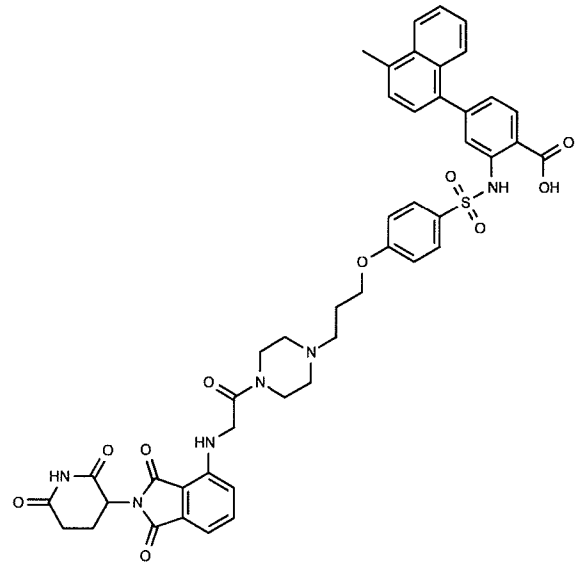
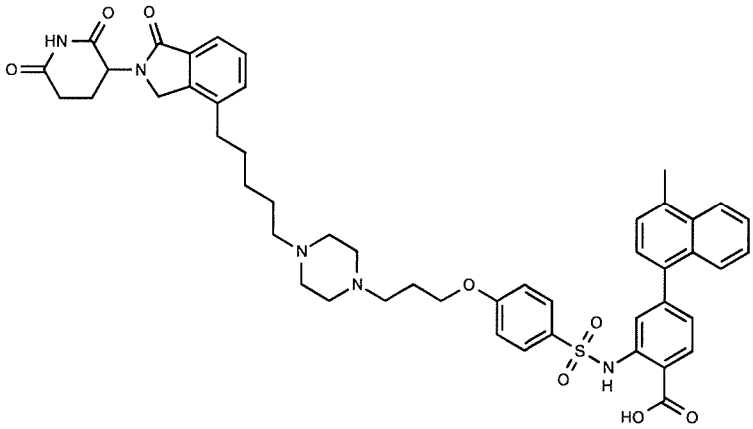
		
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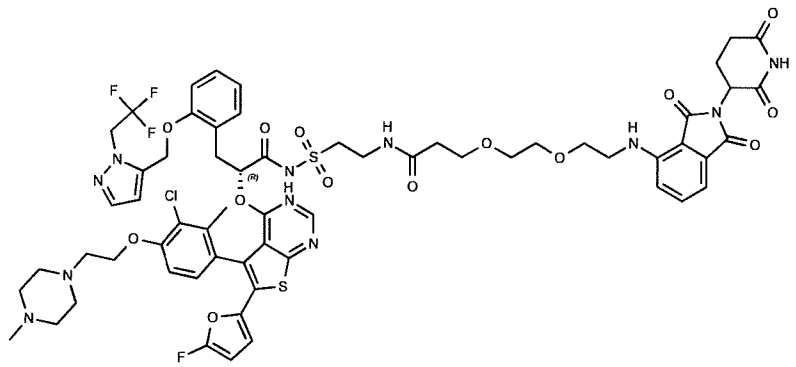
		
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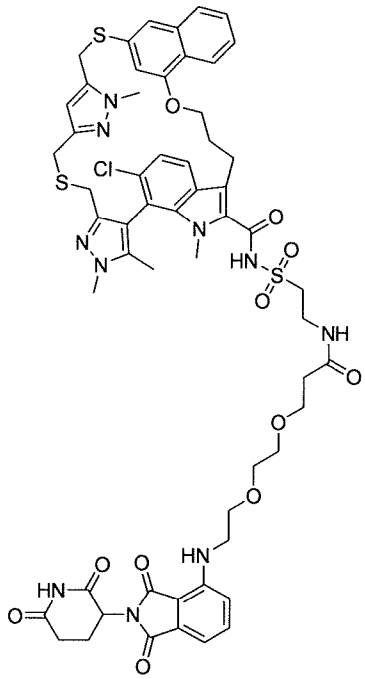
		
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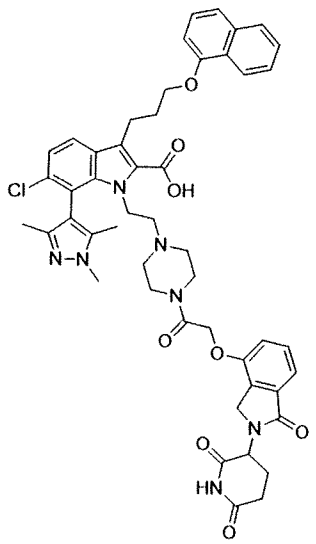
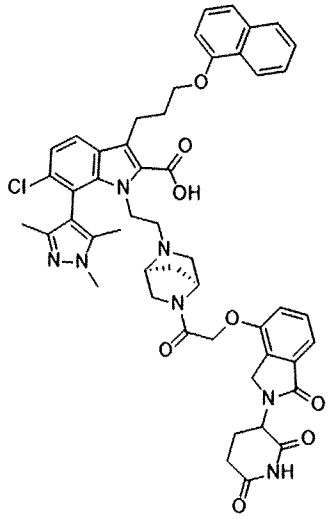
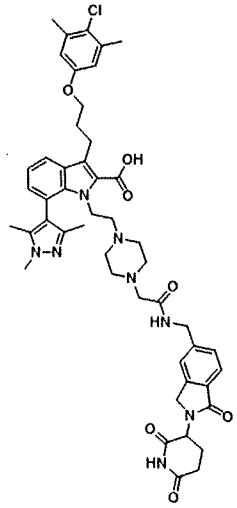
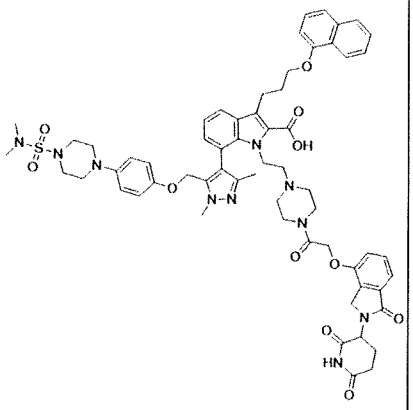
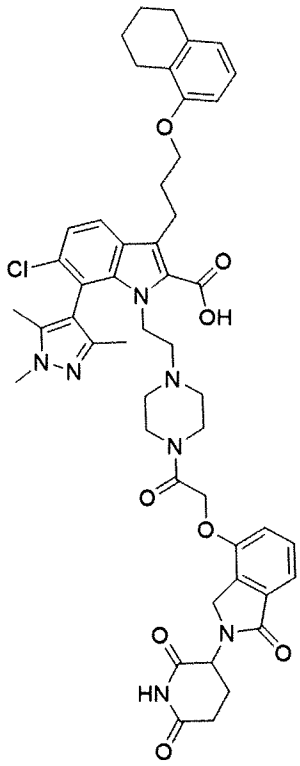
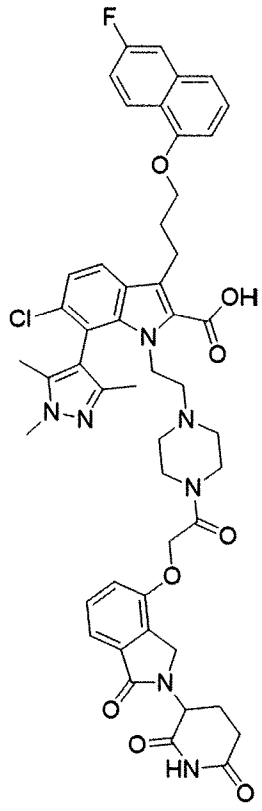


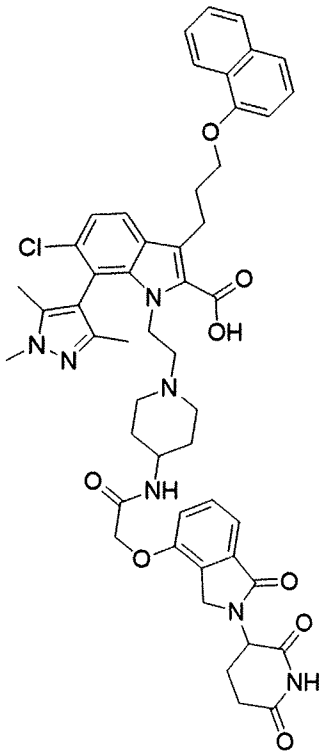
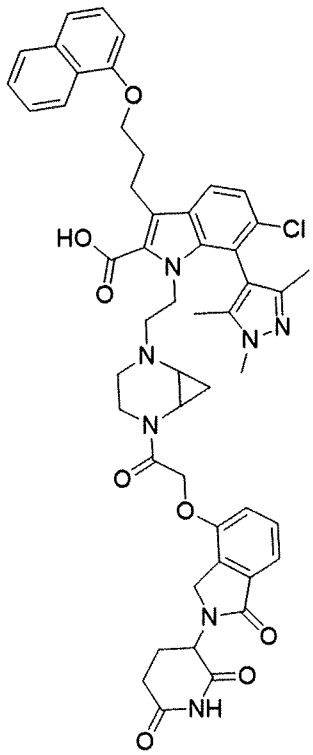
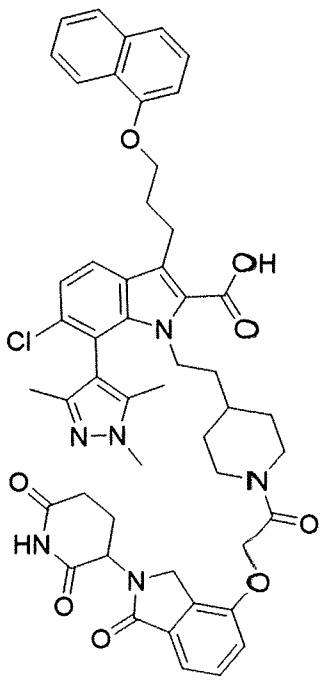
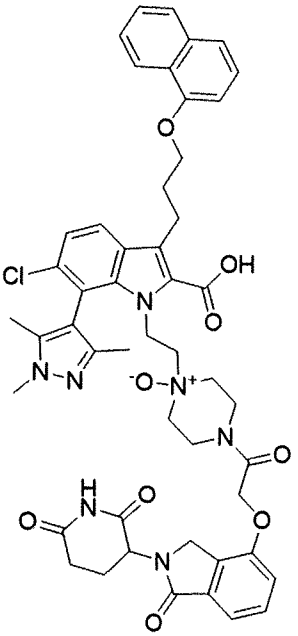
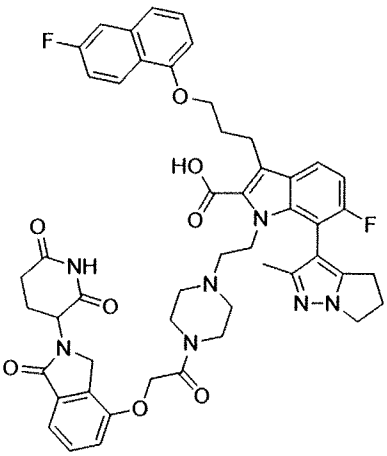
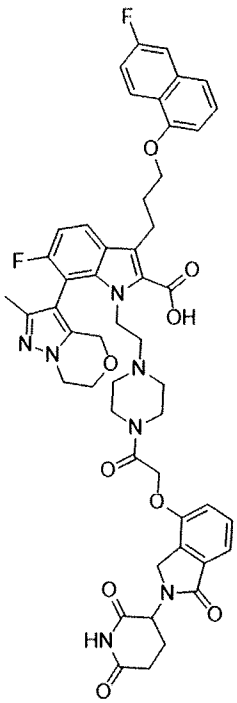
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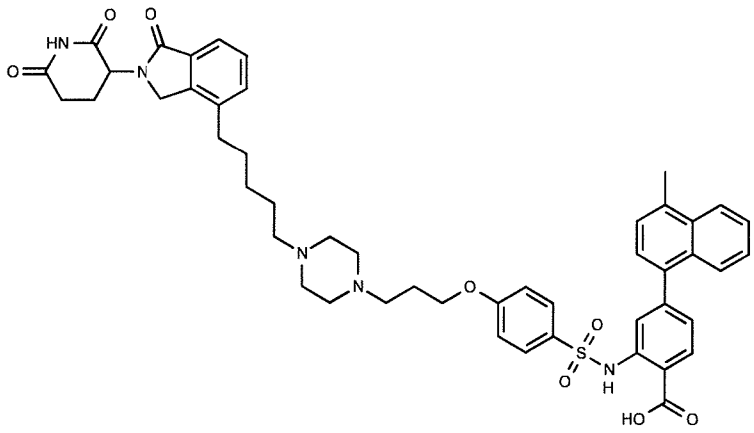


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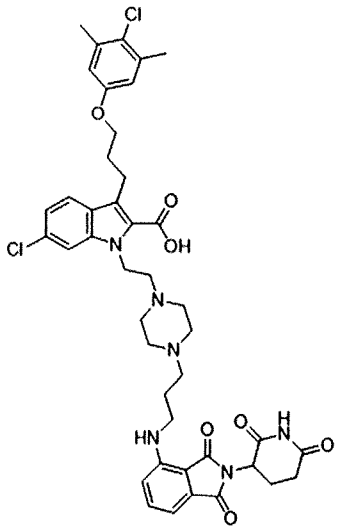
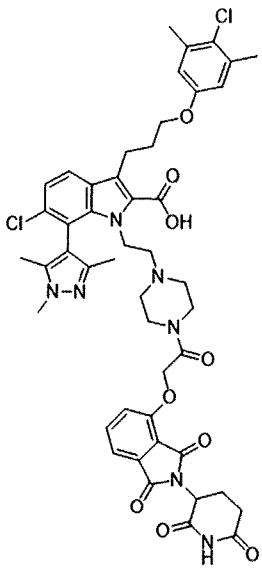
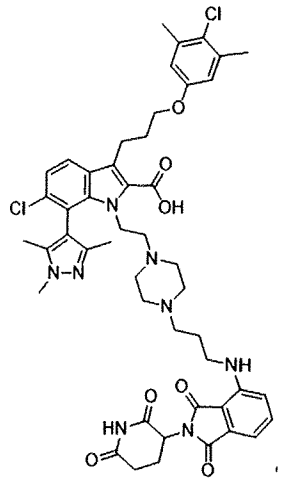
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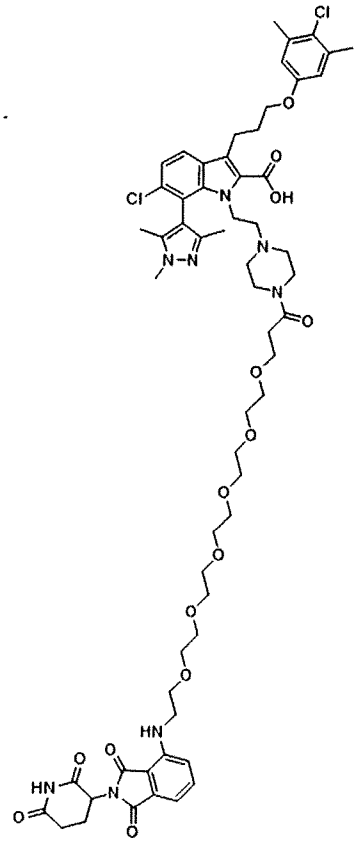
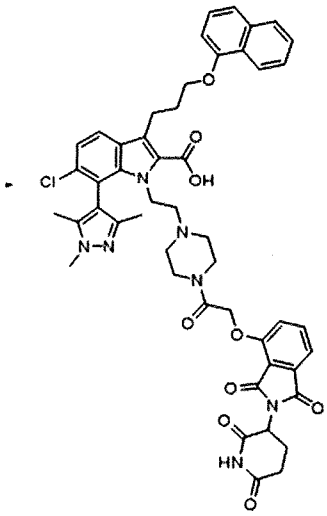
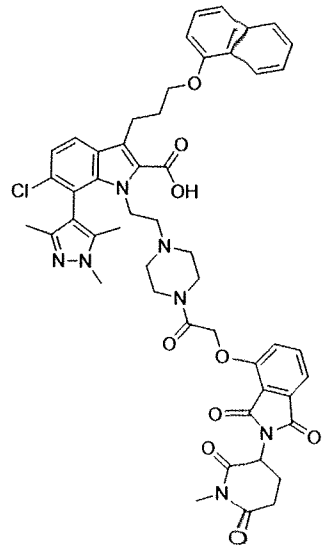
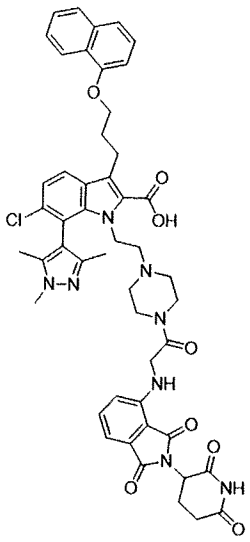
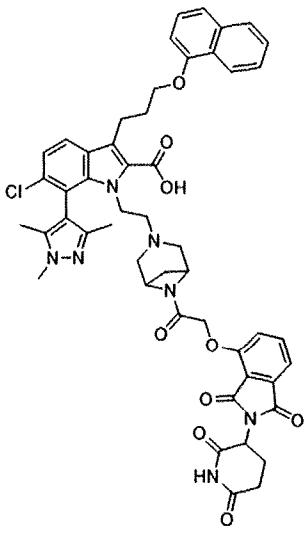
		
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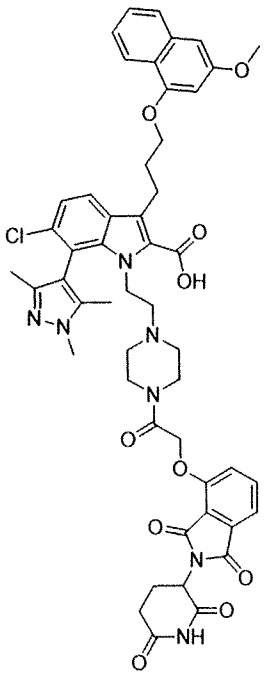
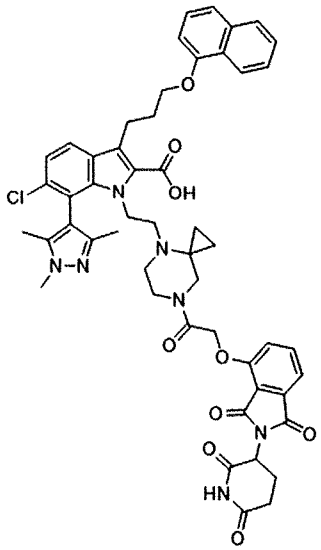
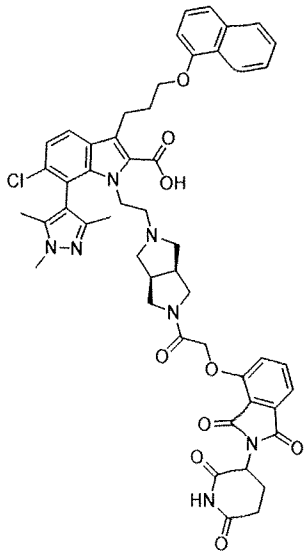
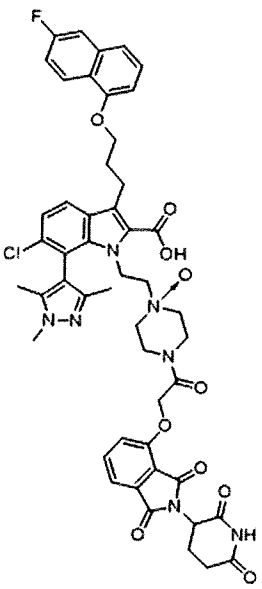
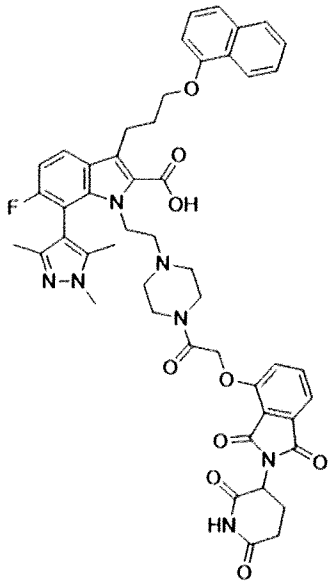
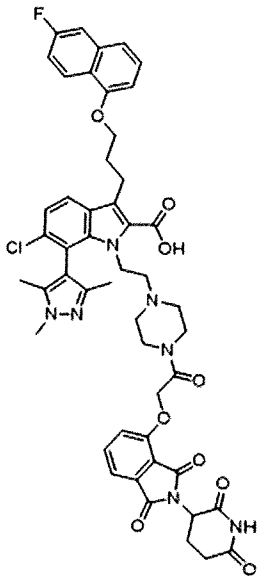
		
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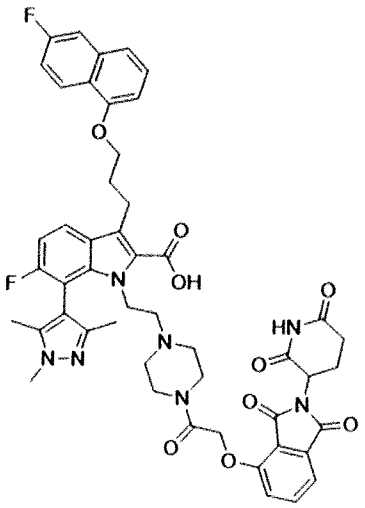
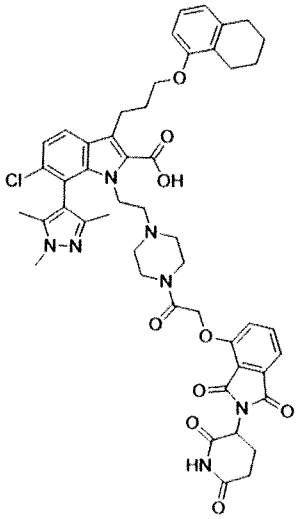
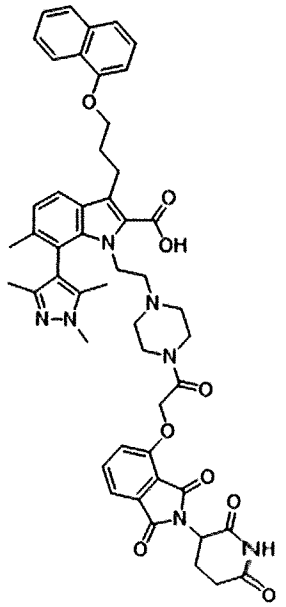
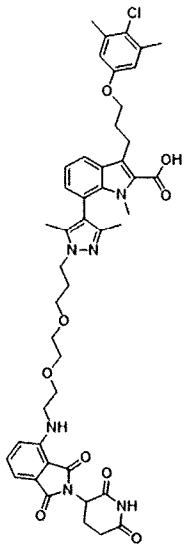
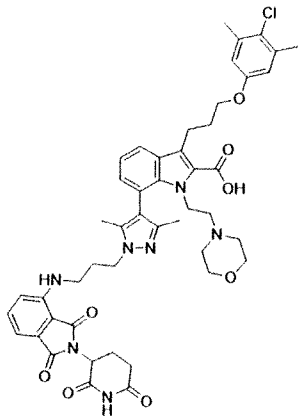
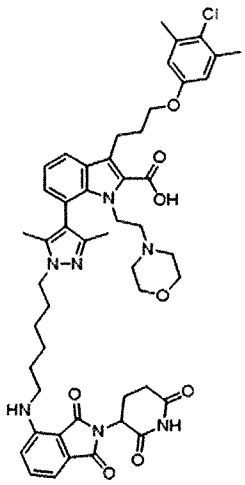

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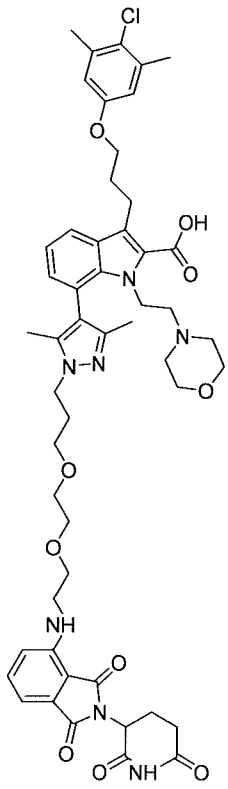
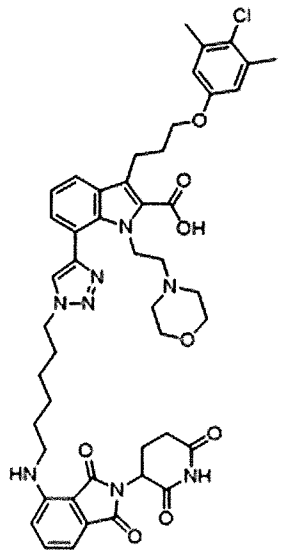
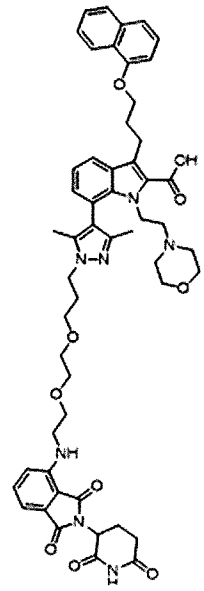
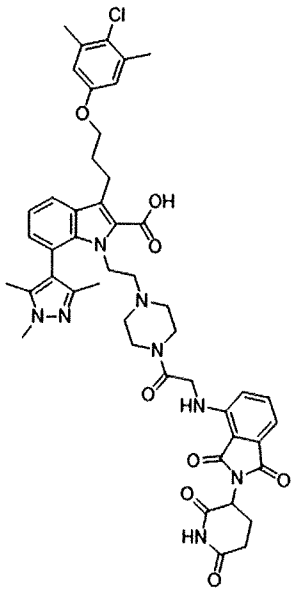
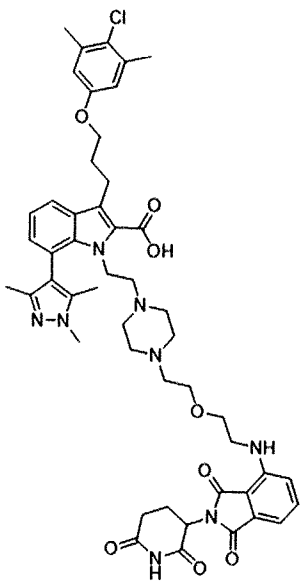
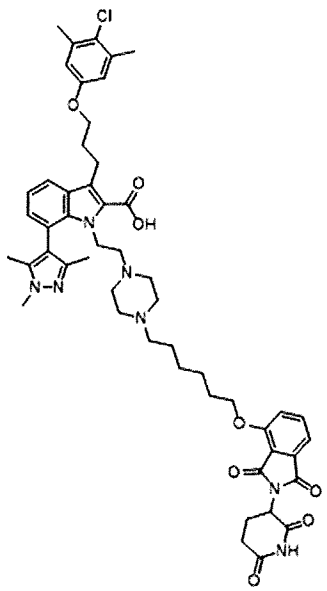
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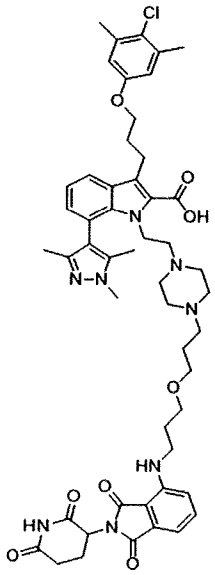
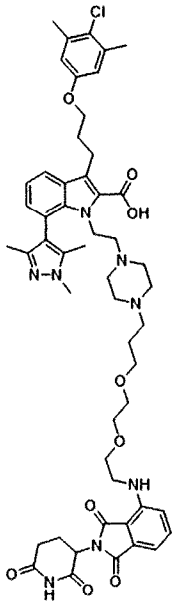
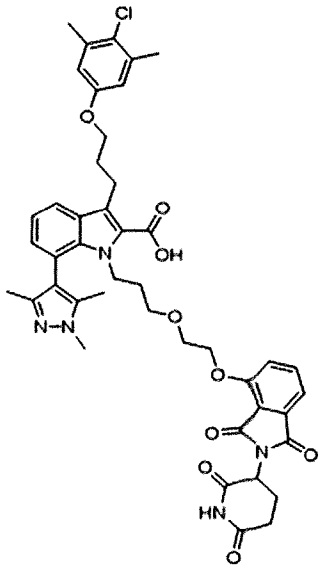
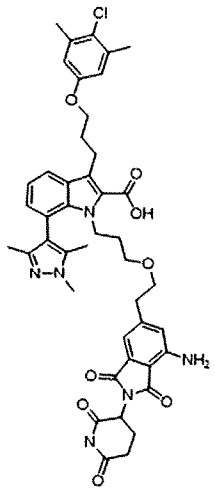
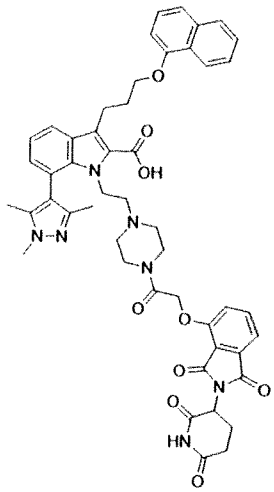
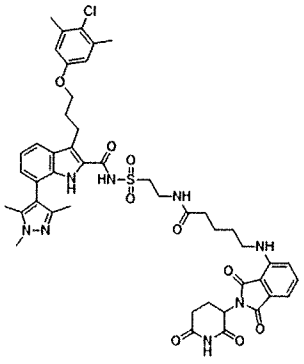
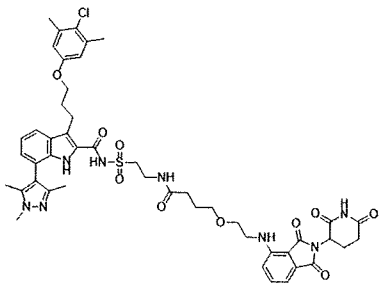
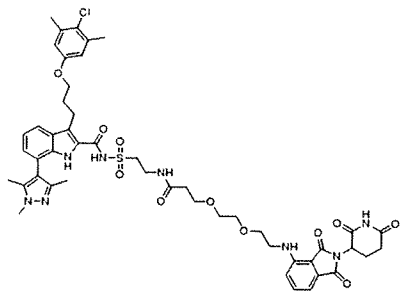
		
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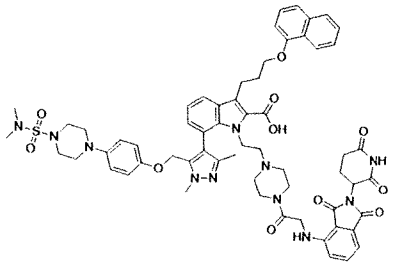
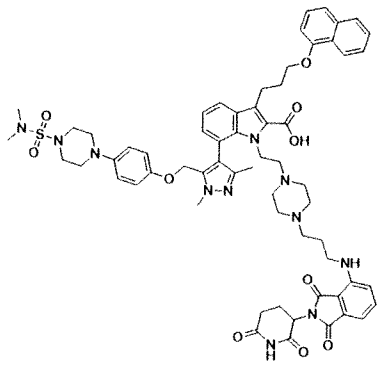
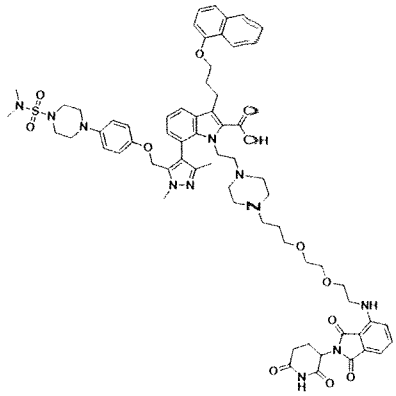
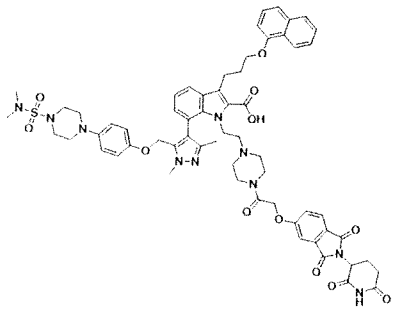
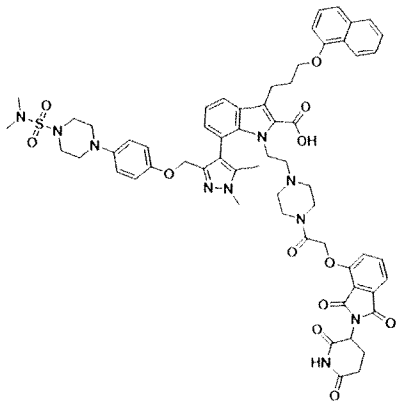
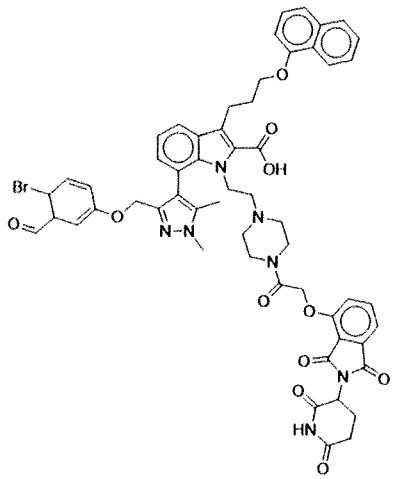
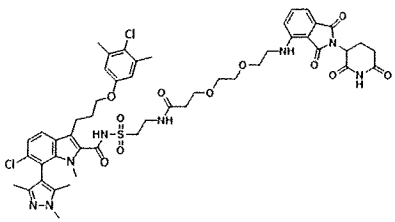
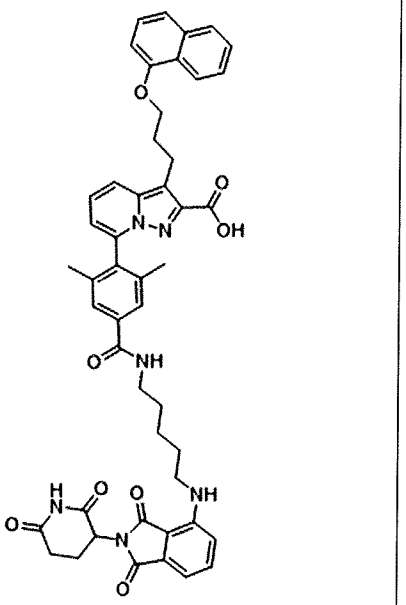
		
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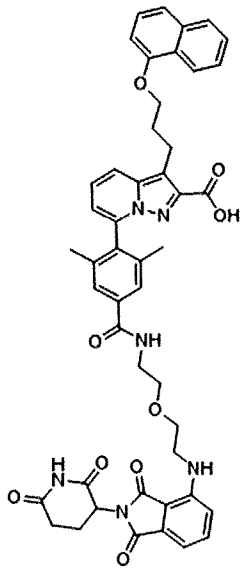
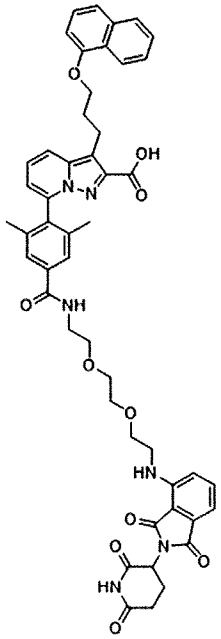
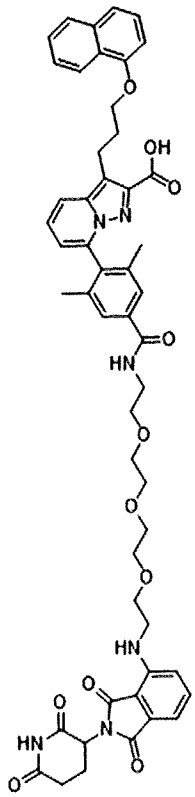
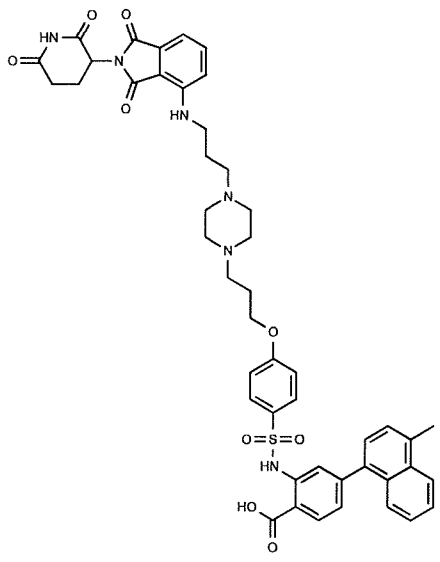
		
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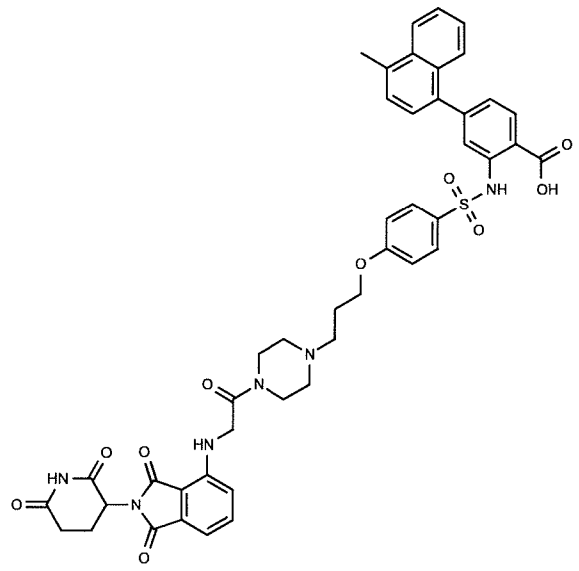
		
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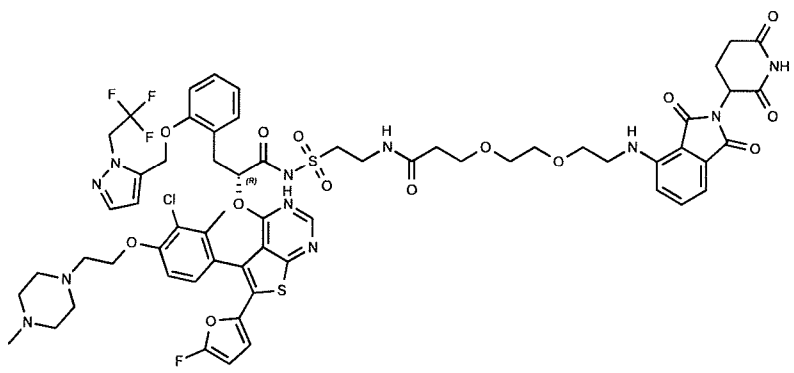
		
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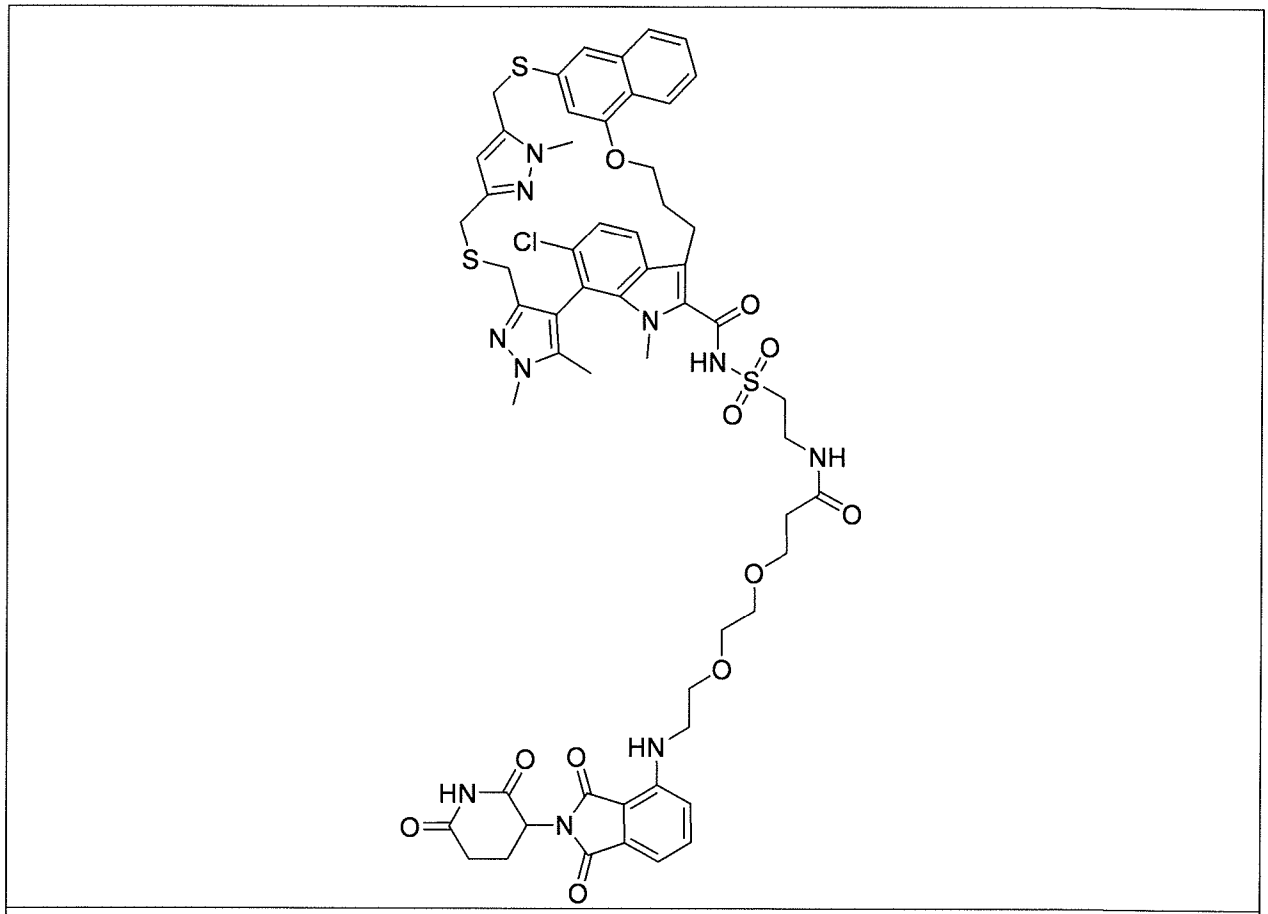
		
254	255	256
		
257		



258



260



261

In some embodiments, each alkyl, alkenyl, alkynyl, aryl, heteroaryl and benzyl is unsubstituted.

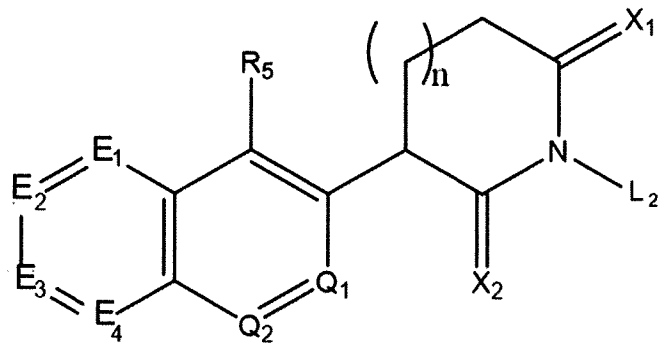
In accordance with a second aspect of the invention, there is provided a compound of formula (I)

[MCL-1 ligand moiety] – [linker] – [ligase ligand moiety] (I)

or a salt, solvate, hydrate, isomer or prodrug thereof,

wherein **[ligase ligand moiety]** is:

(a) Formula (IV)



(IV)

wherein:

each of X_1 and X_2 is independently O or S;

each of Q_1 and Q_2 is independently N or CR^5, wherein at least one of Q_1 and Q_2 is N;

each of E_1, E_2, E_3 and E_4 is independently N or CR';

n is 0, 1 or 2;

L_2 is hydrogen, alkyl, alkenyl, aryl, heteroaryl, benzyl, haloalkyl, haloalkenyl, -C(O)R''', -C(O)OR''', -C(O)NH_2, -C(O)NHR''', -C(O)NR'''_2, -OR''', -NR'''_2, or -$S(O)_2$R''';

each R^5 is independently hydrogen, halogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, benzyl, haloalkyl, haloalkenyl, -NH_2, -NHR''', -NR''_2, -NR'''C(O)R''', -NR'''C(O)OR''', -NO_2, -CN, -C(O)R''', -C(O)OR''', -C(O)NH_2, -C(O)NHR''', -C(O)NR'''_2, -OR''', -OC(O)R''', -OC(O)OR''', -OC(O)NH_2, -OC(O)NHR''', -OC(O)NR'''_2, -SR''', -$S(O)_2$R''', -$S(O)_2$OR''', -$S(O)_2NH_2$, -$S(O)_2$NHR''', -$S(O)_2NR'''_2$; -O-**R^{21}**, -NH-**R^{21}**, -C(O)-NH-**R^{21}**, or -CH_2-NH-C(O)-**R^{21}**;

each R' is independently hydrogen, halogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, benzyl, haloalkyl, haloalkenyl, -NH_2, -NHR''', -NR'''_2, -NR'''C(O)R''', -NR'''C(O)OR''', -NO_2, -CN, -C(O)R''', -C(O)OR''', -C(O)NH_2, -C(O)NHR''', -C(O)NR'''_2, -OR''', -OC(O)R''', -OC(O)OR''', -OC(O)NH_2, -OC(O)NHR''', -OC(O)NR'''_2, -SR''', -$S(O)_2$R''', -$S(O)_2$OR''', $S(O)_2NH_2$, -$S(O)_2$NHR''', -$S(O)_2NR'''_2$, -O-**R^{21}**, -NH-**R^{21}**, -C(O)-NH-**R^{21}**, or -CH_2-NH-C(O)-**R^{21}**;

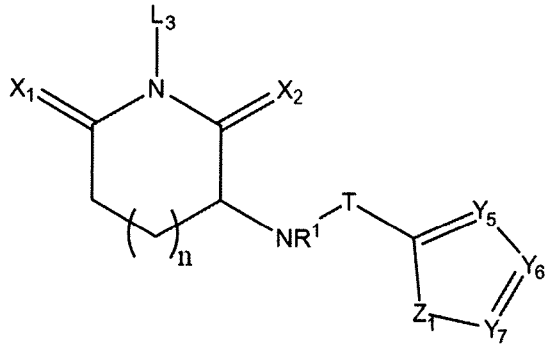
and

each R''' is independently hydrogen, alkyl, alkenyl, aryl, heteroaryl, or benzyl;

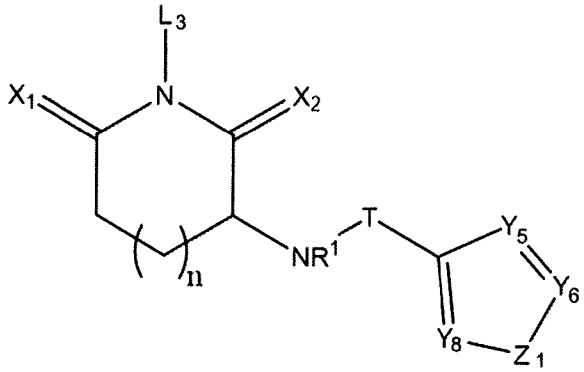
wherein **R^{21}** is a bond connected to **R^{18}** of the linker, and wherein Formula (IV) contains a single **R^{21}**;

or

(b) Formula (Va) or (Vb):



(Va)



(Vb)

or a pharmaceutically acceptable salt or tautomer thereof,

wherein

each of X_1 and X_2 is independently O or S;

Z_1 is O, S or NR^6;

T is is C=O or SO_2;

R^1 is hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, aryl, heteroaryl, or benzyl;

each of Y_5, Y_6, Y_7, and Y_8 is independently N or CR^7,

wherein at least one of Y_5, Y_6 and Y_7 in Formula (Va) is CR^7, and at least one of Y_5, Y_5 and Y_8 in Formula (Vb) is CR^7;

n is 0, 1 or 2;

L_3 is hydrogen, alkyl, alkenyl, aryl, heteroaryl, benzyl, haloalkyl, haloalkenyl, -C(O)R'''', -CH_2C(O)OR'''', -C(O)OR'''', -C(O)NH_2, -C(O)NHR'''', -C(O)NR''''_2, -OR'''', -NR''''_2, or -$S(O)_2$R'''';

each R^7 is independently hydrogen, halogen, alkyl, cycloalkyl, heterocycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, heteroaryl, benzyl, haloalkyl, haloalkenyl, -NH_2, -NHR'''', -NR''''_2, -$CH_2NR''''_2$, -NR''''C(O)R'''', -NR''''C(O)$CH_2NR''''_2$, -NR''''C(O)CH_2-heterocycloalkyl, -NR''''C(O)CH(OH)R'''', -CH_2NR''''C(O)OR'''', -NR''''C(O)OR'''', -NR''''SO_2R'''', -NO_2, -CN,

-C(O)R'''', -C(O)OR'''', -C(O)NH_2, -C(O)NHR'''', -C(O)NR''''_2, -OR'''', -OC(O)R'''', -OC(O)OR'''', -OC(O)NH_2, -OC(O)NHR'''', -OC(O)NR''''_2, --NHC(S)NHR'''', SR'''', or -$S(O)_2$R'''',-$S(O)_2$OR'''', -$S(O)_2NH_2$, -$S(O)_2$NHR'''', -$S(O)_2NR''''_2$, -O-**R^{21}**, -NH-**R^{21}**, -C(O)-NH-**R^{21}**, or -CH_2-NH-C(O)-**R^{21}**;

each R'''' is independently hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, aryl, heteroaryl, or benzyl;

R^6 is hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, heteroaryl, benzyl, haloalkyl, haloalkenyl, -NH_2, -NHR'''', -NR''''_2, -NR''''C(O)R'''', -N[C(O)R''''$]_2$, -NR''''C(O)OR'''', -NO_2, -CN, -C(O)R'''', -C(O)OR'''', -C(O)NH_2, -C(O)NHR'''', -C(O)NR''''_2, -OR'''', -OC(O)R'''', -OC(O)OR'''', -OC(O)NH_2, -OC(O)NHR'''', -OC(O)NR''''_2, -SR'''', or -$S(O)_2$R'''',-$S(O)_2$OR'''', -$S(O)_2NH_2$, -$S(O)_2$NHR'''', -$S(O)_2NR''''_2$, -**R^{21}**, -C(O)-NH-**R^{21}**, or -CH_2-NH-C(O)-**R^{21}**;

wherein **R^{21}** is a bond connected to **R^{18}** of the linker, and wherein formula (Va) and formula (Vb) each contain a single **R^{21}**;

wherein when Z_1 is O, then Y_6 is CR^7 and

wherein when the compound is of Formula (Va), then

(i) when each of Y_5, Y_6 and Y_7 is CR^7, then at least one of R^7 is not H;

(ii) when Z_1 is NR^6, then Y_6 and Y_7 are CR^7;

(iii) when Z_1 is S, then Y_5 is not C-OMe and Y_6 is not C-OMe;

(iv) when Z_1 is S and Y_5 is C-NHCOMe, then Y_7 is not C-CH_2NR''''C(O)OR'''';

(v) when Z_1 is S and Y_5 is N, then Y_6 is not C-H, C-aryl or C-C(O)OR''''; and

(vi) when Z_1 is S and Y_6 is N, then Y_7 is C-NH_2, C-NHR'''', C-NR''''_2, C-NR''''C(O)OR'''', C-CH_2NR''''C(O)OR'''', C-haloalkyl, C-^{t}Butyl, C-OR'''', C-COOR'''' or C-SR''''; wherein when Y_7 is C-NH_2, C-NHR'''' or C-NR''''_2, then Y_5 is C-H;

and when the compound is of Formula (Vb), then:

(vii) when each of Y_5, Y_6 and Y_8 is CR^7, then at least one of R^7 is not H;

(viii) when Z_1 is S, then Y_5 is not C-COOH or C-NHC(O)Me, and Y_8 is not C-Br;

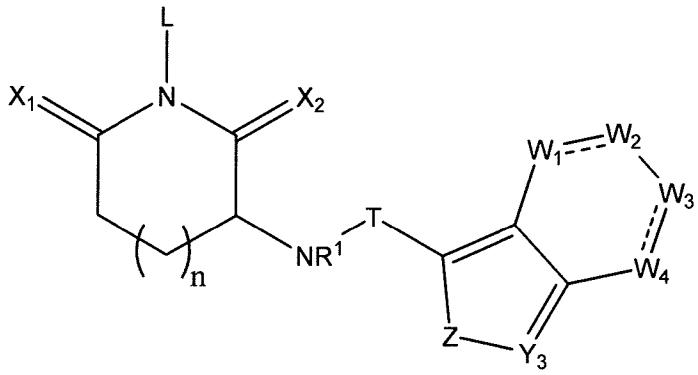
(ix) when Z_1 is S and Y_6 is C-Br, then Y_8 is C-OR''''

(x) when Z_1 is S, Y_5 is N and Y_6 is C-H or C-NH_2, then Y_8 is not C-H

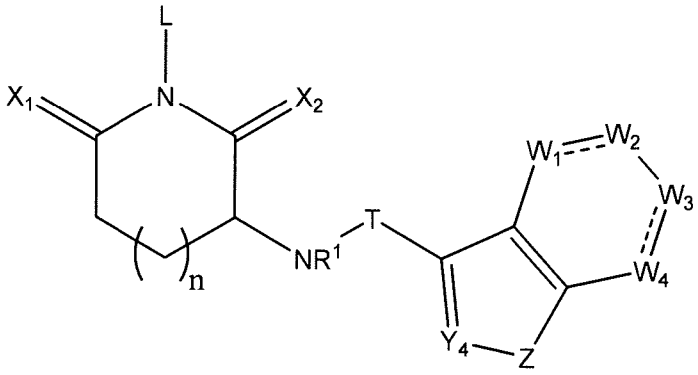
(xi) when Z_1 is S and Y_5 is N, then Y_6 is not C- halogen, C-alkyl, C-cycloalkyl, C-aryl, C-heteroaryl, C-CH_2NH_2, C-COOalkyl, or C-NHC(O)alkyl; (xii) when Z_1 is NR^6, then Y_5, Y_6 and Y_8 are CR^7.

or

(c) Formula (IIa) or (IIb):



(IIa)



(IIb)

wherein

each of X_1 and X_2 is independently O or S;

Z is O, S or NR^2;

T is C=O or SO_2;

Y_3 is N or CR;

Y_4 is N or CR;

 indicates a single or double bond, wherein

when each  is a double bond, each of W_1, W_2, W_3 and W_4 is independently N or CR^a, wherein at least one of W_1, W_2, W_3 and W_4 is N, and

when each  is a single bond, W_1, W_2, W_3 and W_4 are each CR^a_2 and Y_4 is CR;

n is 0, 1 or 2;

L is hydrogen, alkyl, alkenyl, aryl, heteroaryl, benzyl, haloalkyl, haloalkenyl, $-C(O)R^h$, $-C(O)OR^h$, $-C(O)NH_2$, $-C(O)NHR^h$, $-C(O)NR^h_2$, $-OR^h$, $-NR^h_2$, or $-S(O)_2R^h$;

each R is independently hydrogen, halogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, heteroaryl, benzyl, haloalkyl, haloalkenyl, $-NH_2$, $-NHR^h$, $-NR^h_2$, $-NR^hC(O)R^h$, $-NR^hC(O)CH_2R^h$, $-NR^hC(O)CH(OH)R^h$, $-NR^hC(O)OR^h$, $-NR^hSO_2R^h$, $-NO_2$, -CN, $-C(O)R^h$, $-C(O)OR^h$, $-C(O)NH_2$, $-C(O)NHR^h$, -

$C(O)NR^h_2$, $-OR^h$, $-OC(O)R^h$, $-OC(O)OR^h$, $-OC(O)NH_2$, $-OC(O)NHR^h$, $-OC(O)NR^h_2$, $-SR^h$, or $-S(O)_2R^h$, $-S(O)_2OR^h$, $-S(O)_2NH_2$, $-S(O)_2NHR^h$, or $-S(O)_2NR^h_2$;

each R^a is independently hydrogen, halogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, heteroaryl, benzyl, haloalkyl, haloalkenyl, $-NH_2$, $-NHR^h$, $-NR^h_2$, $-NR^hC(O)R^h$, $-NR^hC(O)CH(OH)R^h$, $-NR^hC(O)OR^h$, $-NR^hSO_2R^h$, $-NO_2$, $-CN$, $-C(O)R^h$, $-C(O)OR^h$, $-C(O)NH_2$, $-C(O)NHR^h$, $-C(O)NR^h_2$, $-OR^h$, $-OC(O)R^h$, $-OC(O)OR^h$, $-OC(O)NH_2$, $-OC(O)NHR^h$, $-OC(O)NR^h_2$, $-SR^h$, $-S(O)_2R^h$, $-S(O)_2OR^h$, $-S(O)_2NH_2$, $-S(O)_2NHR^h$, $-S(O)_2NR^h_2$, $-O-\mathbf{R^{21}}$, $-NH-\mathbf{R^{21}}$, $-C(O)-NH-\mathbf{R^{21}}$, or $-CH_2-NH-C(O)-\mathbf{R^{21}}$;

each R^h is independently hydrogen, alkyl, cycloalkyl, heterocycloalkyl, alkenyl, cycloalkenyl, aryl, heteroaryl, or benzyl;

R^2 is hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, heteroaryl, benzyl, haloalkyl, haloalkenyl, $-NH_2$, $-NHR^h$, $-NR^h_2$, $-NR^hC(O)R^h$, $-N[C(O)R^h]_2$, $-NR^hC(O)OR^h$, $-NO_2$, $-CN$, $-C(O)R^h$, $-C(O)OR^h$, $-C(O)NH_2$, $-C(O)NHR^h$, $-C(O)NR^h_2$, $-OR^h$, $-OC(O)R^h$, $-OC(O)OR^h$, $-OC(O)NH_2$, $-OC(O)NHR^h$, $-OC(O)NR^h_2$, $-SR^h$, $-S(O)_2R^h$, $-S(O)_2OR^h$, $-S(O)_2NH_2$, $-S(O)_2NHR^h$, or $-S(O)_2NR^h_2$; and

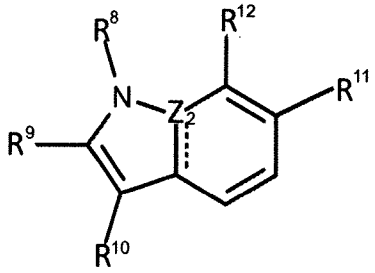
R^1 is hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, aryl, heteroaryl, or benzyl;

$\mathbf{R^{21}}$ is a bond connected to $\mathbf{R^{18}}$ of the linker, and wherein formula (IIa) and formula (IIb) each contain a single $\mathbf{R^{21}}$;

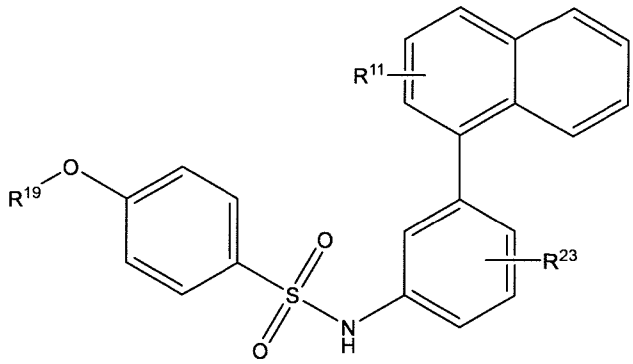
wherein when each  is a double bond, Z is NR^2, R^2 is hydrogen, and each R^a is hydrogen, then W_4 is CR^a;

wherein

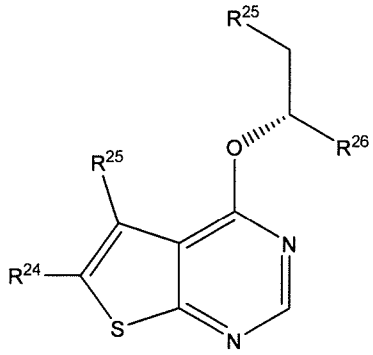
[MCL-1 ligand moiety] is a compound of Formula (A), Formula (B) or Formula (C)



(A)



(B)



(C)

wherein

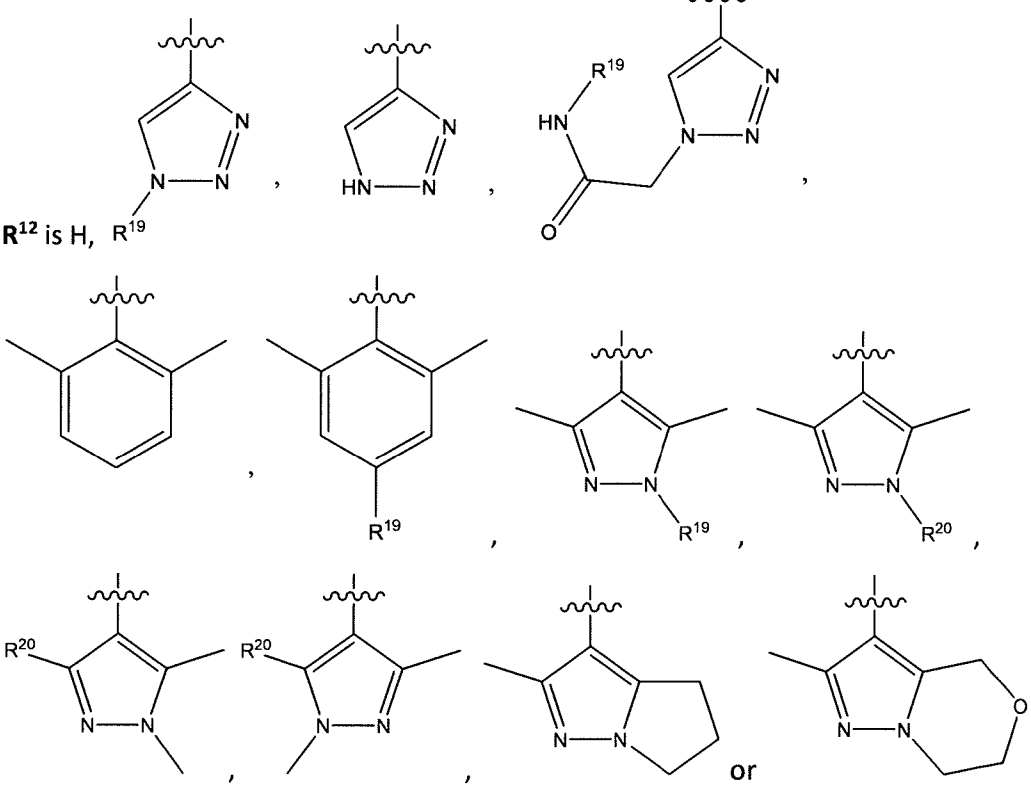
 is a single bond or a double bond;

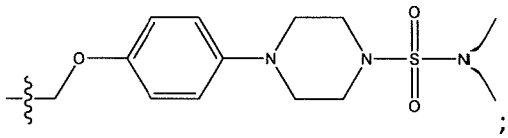
$\mathbf{R^8}$ is H, $\mathbf{R^{19}}$, or C_1-C_6 alkyl optionally substituted with morpholine;

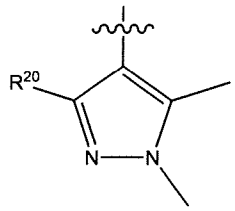
$\mathbf{R^9}$ is -C(O)OH, -C(O)OC_1-C_6alkyl, -C(O)NH_2, -C(O)O$\mathbf{R^{19}}$ or -C(O)NH$\mathbf{R^{19}}$,

$\mathbf{R^{10}}$ is -$C_{2\text{-}5}$alkyl-O-R^{13}, wherein R^{13} is phenyl, naphthyl or tetraline, wherein the phenyl, naphthyl or tetraline is optionally substituted with at least one substituent selected from halogen, C_1-C_6 alkyl and -O(C_1-C_6 alkyl); or wherein the naphthyl is optionally substituted with -O- or -S-,

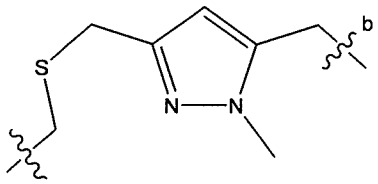
$\mathbf{R^{11}}$ is H, halogen or C_1-C_6 alkyl,

$\mathbf{R^{12}}$ is H, 

wherein R^{20} is Me, -CH_2-O-bromobenzaldehyde, or  ; or when



R^{12} is and R^{10} is -O-naphthyl substituted with -O- or -S-, then R^{20} is



, wherein  indicates attachment to -O- or -S- of R^{10};

and wherein

R^{19} is a bond connected to R^{14} of the linker;

R^{23} is -C(O)OH or -C(O)OC_1-C_6alkyl;

Z_2 is N or C, wherein when Z_2 is N, then  is a single bond; and when Z_2 is C, then  is a double bond,

R^{24} is furan optionally substituted with at least one halogen,

each R^{25} is independently phenyl substituted with -OR^{28} and optionally further substituted with at least one substituent selected from halogen and C_1-C_6 alkyl;

R^{26} is -C(O)OR^{19} or -C(O)NHR^{19}; and

each R^{28} is independently -C_{1-3}alkyl-(N-alkyl piperazine) or -C_{1-3}alkyl-(N-haloalkylpyrazole)

and wherein each of Formula (A), Formula (B) and Formula (C) contains a single R^{19};

and wherein **[linker]** has the following formula

R^{14}-R^{15}-R^{16}-R^{17}-R^{18}

wherein

R^{14} is -C_{1-6} alkyl, -C_{2-6} alkenyl, -C_{2-6} alkynyl, -C(O)-, -SO_2- or is absent

R^{15} is cycloalkyl, heterocycloalkyl, aryl, heteroaryl, -C_{1-6} alkyl-NH-, -cycloalkyl-NH- or is absent

R^{16} is -C_{1-6} alkyl, -C(O)-, -C(O)-NH-, -C(O)O-, -CH_2-C(O)-, -CH_2-C(O)-NH-, -CH_2-C(O)O- or is absent

R^{17} is -$CH_2(C_2H_4\text{-}O)_y$, $(C_2H_4\text{-}O)_x$, $(C_3H_6\text{-}O)_x$, or is absent

x is 1-10

y is 2-10

R^{18} is -C_{1-6} alkyl, heterocycloalkyl, or is absent

wherein at least one of R^{14}-R^{18} is present.

In some embodiments, each alkyl, alkenyl, alkynyl, aryl, heteroaryl and benzyl group is unsubstituted.

In some embodiments, each R is independently hydrogen, halogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, heteroaryl, benzyl, haloalkyl, haloalkenyl, -NH_2, -NHR'''', -NR''''$_2$, -NR''''C(O)R'''', -NR''''C(O)CH(OH)R'''', -NR''''C(O)OR'''', -NR''''SO_2R'''', -NO_2, -CN,-C(O)R'''', -C(O)OR'''', -C(O)NH_2, -C(O)NHR'''', -C(O)NR''''$_2$, -OR'''', -OC(O)R'''', -OC(O)OR'''', -OC(O)NH_2, -OC(O)NHR'''', -OC(O)NR''''$_2$, -SR'''', or -S(O)$_2$R'''', -S(O)$_2$OR'''', -S(O)$_2$$NH_2$, -S(O)$_2$NHR'''', or -S(O)$_2NR''''_2$, -O-**$R^{21}$**, -NH-**$R^{21}$**, -C(O)-NH-**$R^{21}$**, or -$CH_2$-NH-C(O)-**$R^{21}$**.

In some embodiments, R^1 is hydrogen.

In some embodiments, R^6 is hydrogen.

In some embodiments, when Z_1 is S in Formula (Vb), then Y_5 is not C- NHC(O)R'''' or -C(O)OR''''.

In some embodiments, Z_1 is NR^6.

In some embodiments, **[ligase ligand moiety]** is of Formula (Va) and Y_5, Y_6 and Y_7 are each CR^7. In some such embodiments, Y_5 is -C-NHC(O)R'''', Y_6 is CH, and Y_7 is CH or CCl. In some such embodiments, L_3 is hydrogen; Z_1 is S; R^1 is hydrogen; T is C=O; and Y_7 is CH.

In some embodiments, the compound is of Formula (Vb) and Y_5, Y_6 and Y_8 are each CR^7. In some such embodiments: L_3 is hydrogen; Z_1 is S; R^1 is H; T is C=O; Y_5 is CH, C-OR'''', CCl, C-CN, or C-NHC(O)R''''; Y_6 is CH, CCl, C-alkyl, C-cycloalkyl, or C-haloalkyl; and Y_8 is CH, C-OR'''', C-NHC(O)R'''', C-NHC(O)OR'''', C-NHR'''', C-NH_2, or C-$NHSO_2$R''''; wherein, when Y_5 is CCl, then Y_6 is CH, C-alkyl, C-cycloalkyl, or C-haloalkyl. In some such embodiments, each R'''' is independently alkyl, cycloalkyl, aryl or benzyl. In some embodiments, Y_5 is CH; Y_6 is CH or CCl; and Y_8 is C-OR'''' or C-NH_2. In some su h embodiments, Y_8 is C-OMe or C-NH_2.

In some embodiments, Z is NR^2. In other embodiments, Z is S.

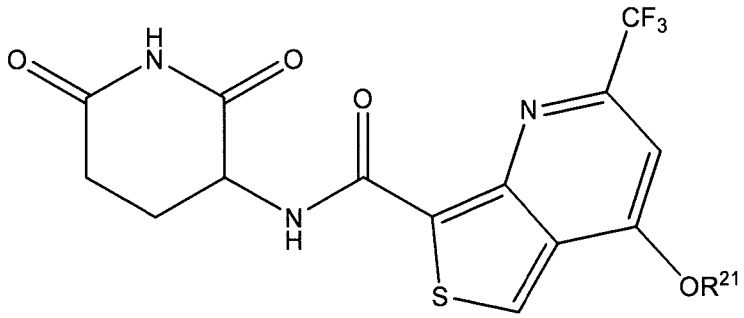
In some embodiments, each  is a double bond.

In some embodiments, L is hydrogen.

In some embodiments, one of W_1, W_2, W_3 and W_4 is N, and the remaining three of W_1, W_2, W_3 and W_4 are each CR^a. In some such embodiments, W_4 is CR^a. In other embodiments, two of W_1, W_2, W_3 and W_4 is N, and the remaining two of W_1, W_2, W_3 and W_4 are each CR^a. In other embodiments, one of W_1, W_2, W_3 and W_4 is CR^a, and the remaining three of W_1, W_2, W_3 and W_4 are each N.

In some embodiments, each R is independently hydrogen, halogen or $-NR^hC(O)R^h$.

In some embodiments, **[ligase ligand moiety]** is:



In some embodiments, E_1, E_2, E_3 and E_4 are each CR'.

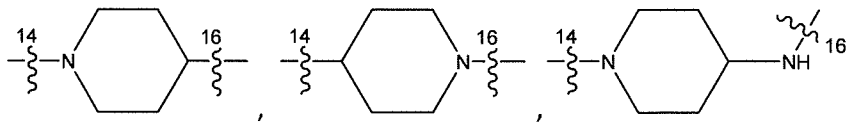
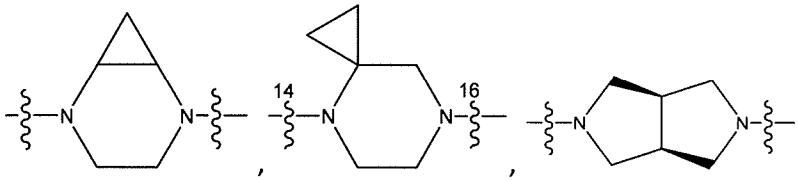
In some embodiments, one of E_1, E_2, E_3 and E_4 is N and the remaining three of E_1, E_2, E_3 and E_4 are each CR'.

In some embodiments, Q_1 is CR^5. In other embodiments, Q_2 is CR^5

In some embodiments,

R^{14} is $-C_{1-6}$ alkyl, $-SO_2-$ or is absent

R^{15} is piperazine, bridged piperazine, piperazine N-oxide, piperazine cation, $-C_{1-6}$ alkyl-NH-,



or is absent,, wherein  indicates attachment to **R**^{14} and  indicates attachment to **R**^{16},

R^{16} is -C_{1-6} alkyl, -C(O)-, -C(O)-NH-, -CH_2-C(O)-NH- or is absent

R^{17} is -$CH_2(C_2H_4\text{-}O)_y$, $(C_2H_4\text{-}O)_x$, $(C_3H_6\text{-}O)_x$, or is absent

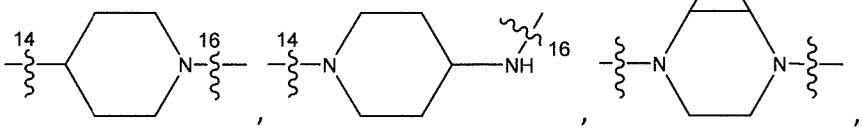
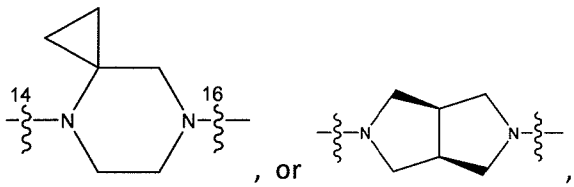
x is 1-6

y is 2-6

R^{18} is -C_{1-6} alkyl, piperazine, or is absent

wherein at least one of R^{14}-R^{18} is present.

In some embodiments, **R**^{18} is -C_{1-6} alkyl or is absent.

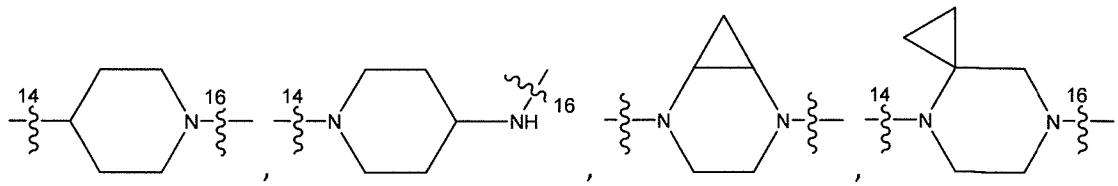
In some embodiments, when **R**^{15} is piperazine, bridged piperazine, piperazine N-oxide, piperazine cation, -C_{1-6} alkyl-NH-, 

, or ,

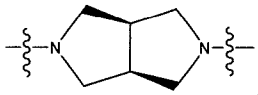
then **R**^{14} is -C_{1-6} alkyl.

In some embodiments,

R^{14} is -C_{1-6} alkyl,

R^{15} is piperazine, bridged piperazine, piperazine N-oxide,



or  ,

R^{16} is -C(O)-, $-CH_2$-C(O)-NH-, or is absent

R^{17} is $-CH_2(C_2H_4-O)_y$, $(C_2H_4-O)_x$, $(C_3H_6-O)_x$, or is absent

R^{18} is $-C_{1-6}$ alkyl,

wherein when R^{16} and R^{17} are absent, R^{18} is $-C_{3-6}$ alkyl. In some such embodiments, R^{14} is $-C_2$ alkyl; x is 1, 2 or 6; and y is 2. In some such embodiments, R^{15} is piperazine, R^{16} is -C(O)-, and R^{17} is absent. In some such embodiments, R^{14} is $-C_2$ alkyl, and R^{18} is $-C_{1-2}$ alkyl.

In some embodiments, when R^{14} is $-SO_2-$, at least two of R^{15}-R^{18} are present, and at least one of R^{15}-R^{18} is not C_{1-6} alkyl.

In some embodiments, R^{14} is $-SO_2-$; R^{15} is $-C_{1-6}$ alkyl-NH-; R^{16} is -C(O)-; R^{17} is $-CH_2(C_2H_4-O)_y$, $(C_2H_4-O)_x$ or is absent; and R^{18} is $-C_{2-4}$ alkyl. In some such embodiments, R^{15} is $-C_2$alkyl-NH-, x is 1 or 2, y is 1 and R^{18} is $-C_{2-4}$ alkyl.

In some embodiments, R^{14} is absent; R^{15} is absent; R^{16} is -C(O)-NH-, or is absent; R^{17} is $-CH_2(C_2H_4-O)_y$, $(C_2H_4-O)_x$, $(C_3H_6-O)_x$, or is absent; a ndR^{18} is $-C_{1-6}$ alkyl.

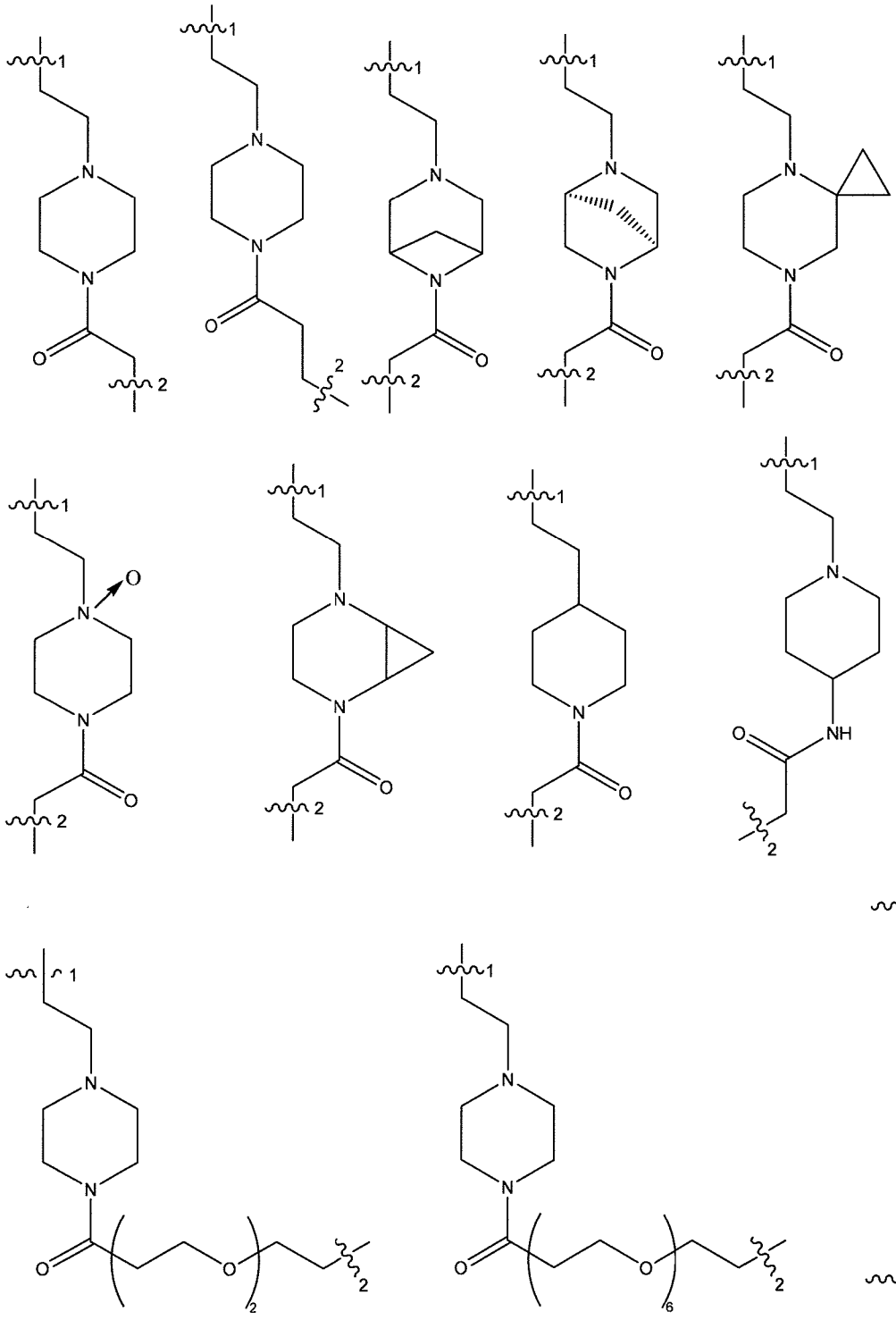
In some embodiments, at least one of R^{14}-R^{18} is not $-C_{1-6}$ alkyl.

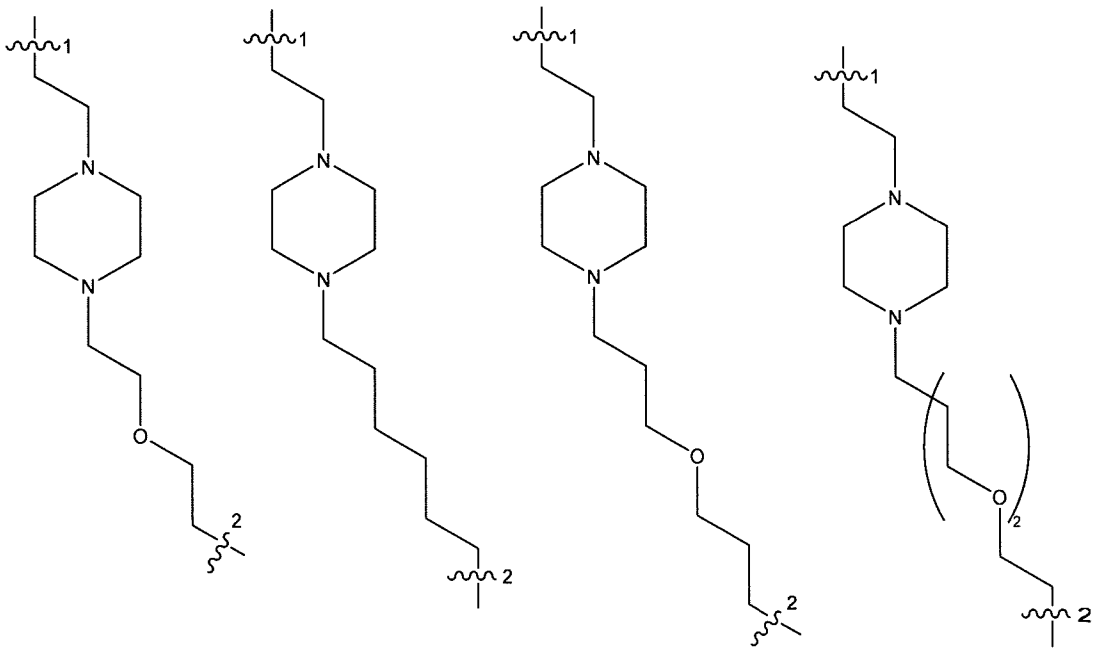
In some embodiments, x is 1, 2 or 3; y is 2 and R^{18} is $-C_{2-6}$ alkyl.

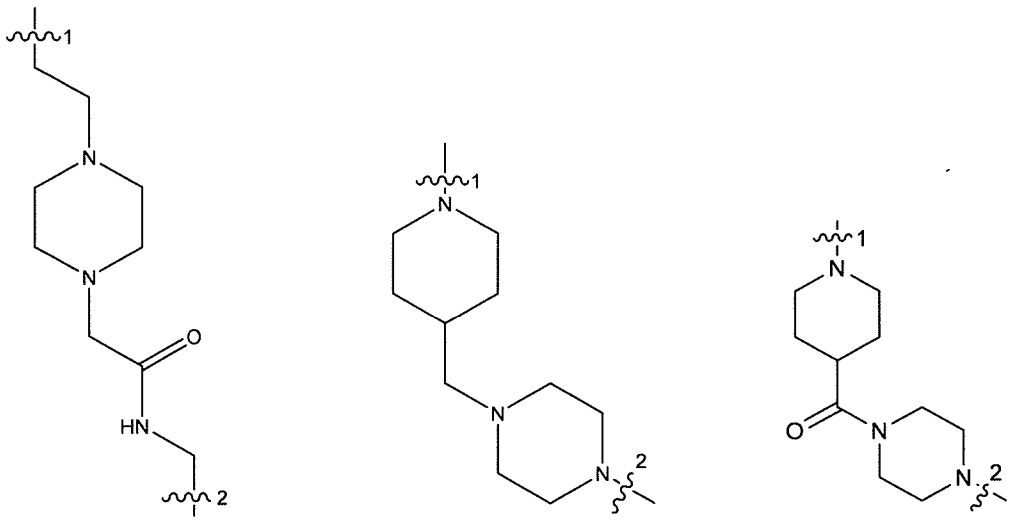
In some embodiments, when R^{15} is $-C_{1-6}$ alkyl-NH-, at least one of R^{16}-R^{18} is present.

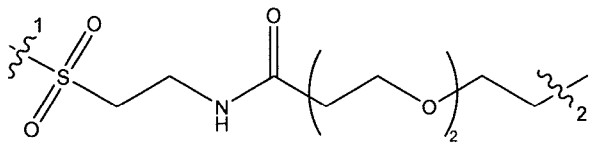
In some embodiments, when R^{17} is $-CH_2(C_2H_4-O)_y$, $(C_2H_4-O)_x$ or $(C_3H_6-O)_x$, at least one of R^{14}-R^{16} and R^{18} is present, wherein at least one of R^{14} and R^{18} is not $-C_{1-6}$ alkyl.

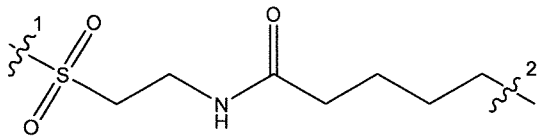
In some embodiments, **[linker]** is selected from

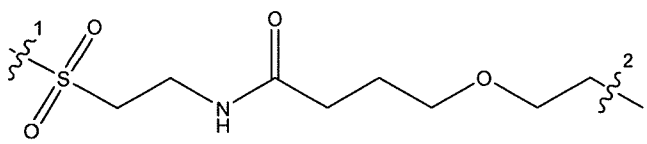


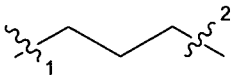


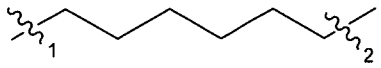


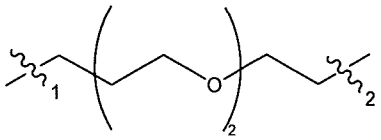


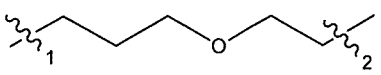


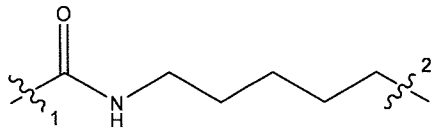


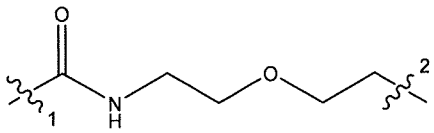


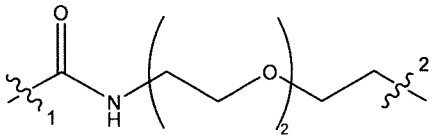




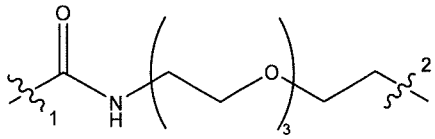








and

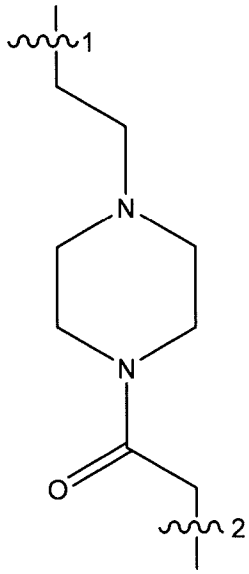


wherein

 indicates attachment to **[MCL-1 ligand moiety]** and

 indicates attachment to **[ligase ligand moiety].**

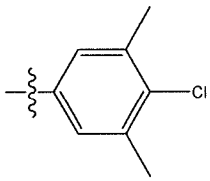
In some embodiments, **[linker]** is



wherein

1 indicates attachment to **[MCL-1 ligand moiety]** and

2 indicates attachment to **[ligase ligand moiety].**

In some embodiments, when $\mathbf{R^8}$ is H, $\mathbf{R^{13}}$ is 

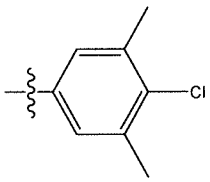
.

In some embodiments,

$\mathbf{R^8}$ is H, $\mathbf{R^{19}}$, methyl, or -CH_2CH_2-morpholine;

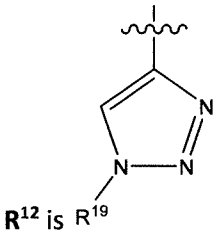
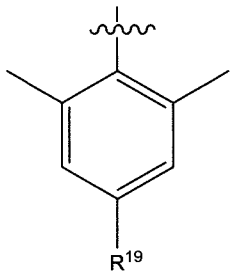
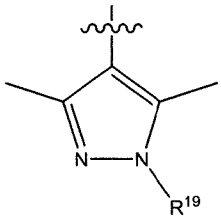
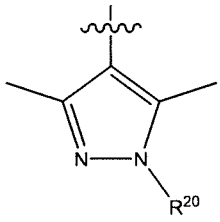
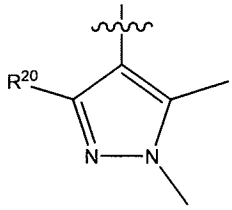
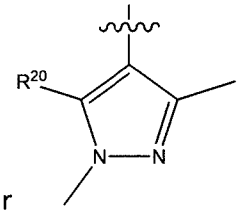
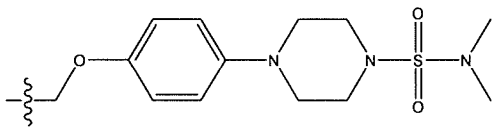
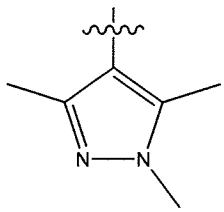
$\mathbf{R^9}$ is -C(O)OH or -C(O)NH$\mathbf{R^{19}}$,

$\mathbf{R^{10}}$ is -C_3H_6O-R^{13},

wherein $\mathbf{R^{13}}$ is 

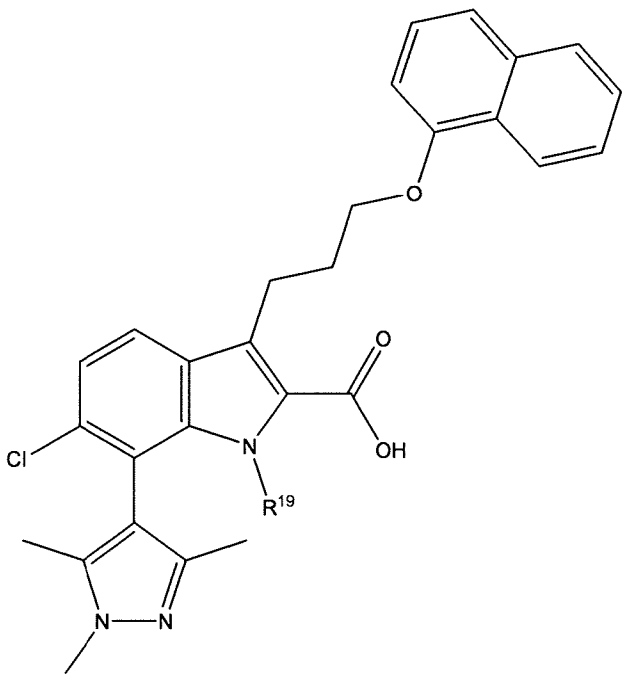
, tetraline, or naphthyl optionally substituted with fluorine;

$\mathbf{R^{11}}$ is H, Cl, F or methyl,

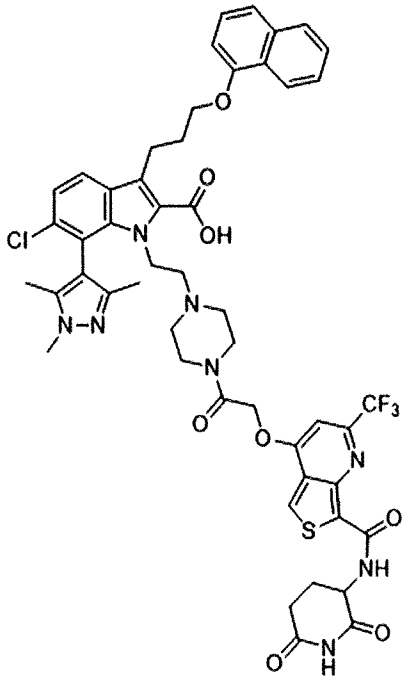
R^{12} is  ,  ,  ,  ,  , or  , wherein **R^{20}** is Me, -CH_2-O-bromobenzaldehyde, or  . In some such embodiments, **R^8** is **R^{19}** or methyl; **R^{10}** is -C_3H_6O-R^{13}, wherein **R^{13}** is naphthyl optionally substituted with fluorine; **R^{11}** is Cl or F, and **R^{12}** is  .

In some embodiments, **Z_2** is C and  is a double bond.

In some embodiments, **[MCL-1 ligand moiety]** is

 .

In some embodiments, the compound is:



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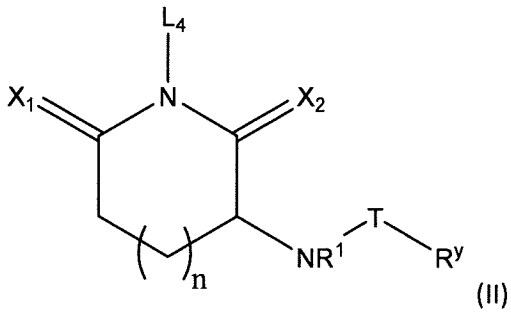
In accordance with a third aspect of the invention, there is provided a compound of formula (I)

[MCL-1 ligand moiety] – [linker] – [ligase ligand moiety] (I)

or a salt, solvate, hydrate, isomer or prodrug thereof,

wherein **[ligase ligand moiety]** is:

(a) Formula (II):



(II)

wherein:

each of X_1 and X_2 is independently O or S;

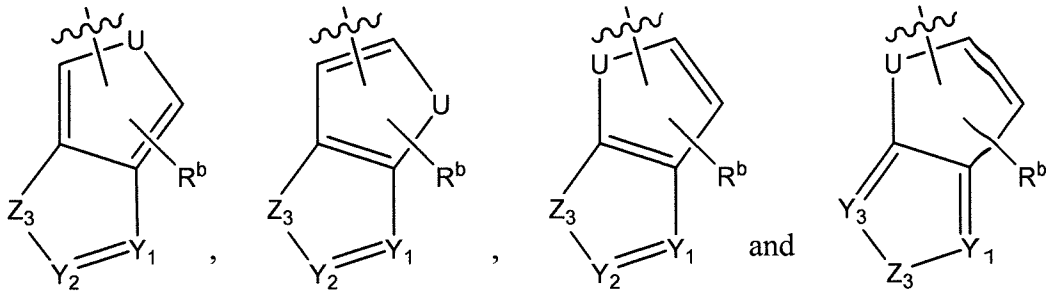
T is C=O or SO_2;

R^1 is hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, aryl, heteroaryl, or benzyl;

n is 0, 1 or 2;

L_4 is hydrogen, alkyl, alkenyl, aryl, heteroaryl, benzyl, haloalkyl, haloalkenyl, -C(O)H, -C(O)R'',-C(O)OH, -C(O)OR'', -C(O)NH_2, -C(O)NHR'', -C(O)NR''_2, -OH, -OR'', -NH_2, -NHR'', -NR''_2, -S(O)$_2$H or -$S(O)_2R''$;

R^y is selected from



wherein ~ indicates attachment to T,

Z_3 is O, S or NR^3;

U is O, S, NR^b or CR^b_2;

each of Y_1, Y_2 and Y_3 is independently N or CR^d;

each R^d is independently hydrogen, halogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, heteroaryl, benzyl, haloalkyl, haloalkenyl, -NH_2, -NHR'', -NR''_2, -NHC(O)R'', -NR''C(O)R'', NHC(O)CH(OH)R'', -NR''C(O)CH(OH)R'', -NHC(O)OR'', -NR''C(O)OR'', -$NHSO_2R''$, -$NR''SO_2R''$, -NO_2, -CN, -C(O)H, C(O)R'', -C(O)OH, -C(O)OR'', -C(O)NH_2, -C(O)NHR'', -C(O)NR''_2,-OH, -OR'', -OC(O)H, -OC(O)R'', -OC(O)OH,-OC(O)OR'', -OC(O)NH_2, -OC(O)NHR'', -OC(O)NR''_2, -SH, -SR'', -S(O)$_2$H, -S(O)$_2$R'', -S(O)$_2$OH, -S(O)$_2$OR'', -S(O)$_2$$NH_2$, -S(O)$_2$NHR'', -S(O)$_2$$NR''_2$, -O-**R^{21}**, -NH-**R^{21}**, -C(O)-NH-**R^{21}**, or -CH_2-NH-C(O)-**R^{21}**;

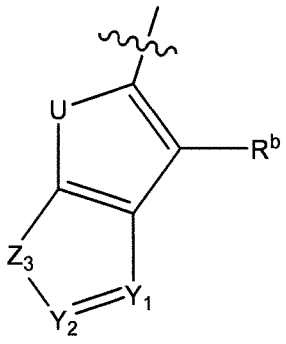
each R^b is independently hydrogen, halogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, heteroaryl, benzyl, haloalkyl, haloalkenyl, -NH_2, -NHR'', -NR''_2, -NHC(O)R'', -NR''C(O)R'', NHC(O)CH(OH)R'', -NR''C(O)CH(OH)R'', -NHC(O)OR'', -NR''C(O)OR'', -$NHSO_2R''$, -$NR''SO_2R''$, -NO_2, -CN, -C(O)H, C(O)R'', -C(O)OH, -C(O)OR'', -C(O)NH_2, -C(O)NHR'', -C(O)NR''_2,-OH, -OR'', -OC(O)H, -OC(O)R'', -OC(O)OH,-OC(O)OR'', -OC(O)NH_2, -OC(O)NHR'', -OC(O)NR''_2, -SH, -SR'', -S(O)$_2$H, -S(O)$_2$R'', -S(O)$_2$OH, -S(O)$_2$OR'', -S(O)$_2$$NH_2$, -S(O)$_2$NHR'', or -S(O)$_2$$NR''_2$;

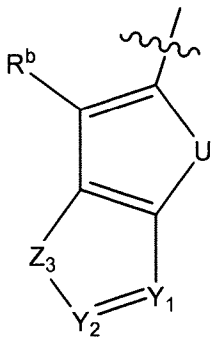
each R^3 is independently hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, heteroaryl, benzyl, haloalkyl, haloalkenyl, -NH_2, -NHR'', -NR''_2, -NHC(O)R'', -NR''C(O)R'', NHC(O)CH(OH)R'', -NR''C(O)CH(OH)R'', -NHC(O)OR'', -NR''C(O)OR'', -$NHSO_2R''$, -$NR''SO_2R''$, -NO_2, -CN, -C(O)H, C(O)R'', -C(O)OH, -C(O)OR'', -C(O)NH_2, -C(O)NHR'', -C(O)NR''_2,-OH, -OR'', -OC(O)H, -OC(O)R'', -OC(O)OH,-OC(O)OR'', -OC(O)NH_2, -OC(O)NHR'', -OC(O)NR''_2, -SH, -SR'', -S(O)$_2$H, -S(O)$_2$R'', -S(O)$_2$OH, -S(O)$_2$OR'', -S(O)$_2$$NH_2$, -S(O)$_2$NHR'', -S(O)$_2$$NR''_2$, -**R^{21}**, -C(O)-NH-**R^{21}**, or -CH_2-NH-C(O)-**R^{21}**;

each R'' is independently alkyl, cycloalkyl, alkenyl, cycloalkenyl, aryl, heteroaryl, or benzyl;

R^{21} is a bond connected to R^{18} of the linker, wherein Formula (II) contains a single R^{21};

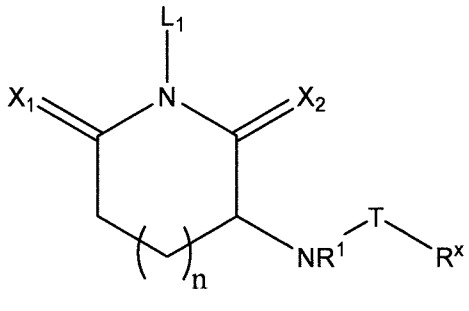
wherein,

(i) when R^y is  then Y_2 is CR^d; and

(ii) when R^y is  , then R^b in CR^b_2 is not hydrogen

or

(b) Formula (III):



(III)

wherein:

each of X_1 and X_2 is independently O or S;

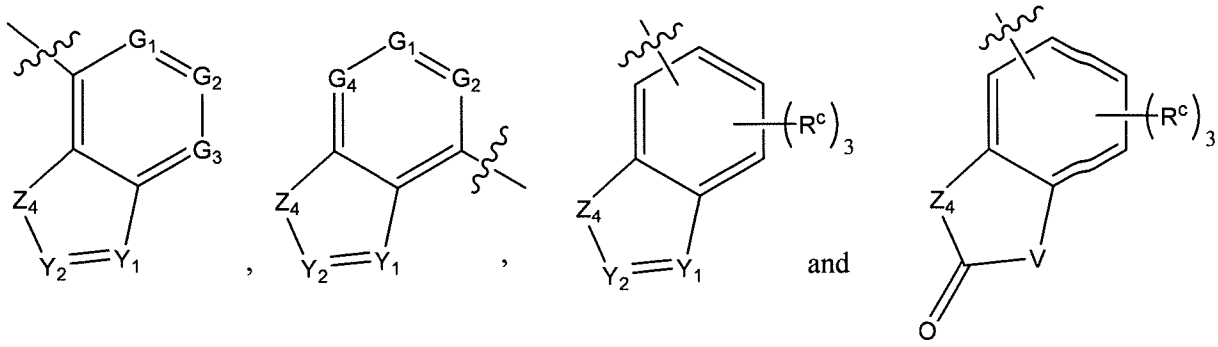
T is C=O or SO_2;

R^1 is hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, aryl, heteroaryl, or benzyl;

n is 0, 1 or 2;

L_1 is hydrogen, alkenyl, aryl, heteroaryl, benzyl, haloalkyl, haloalkenyl, -C(O)H, -C(O)R'', -C(O)OH, -C(O)OR'', $-CH_2C(O)OR''$, $-C(O)NH_2$, -C(O)NHR'', $-C(O)NR''_2$, -OH, -OR'', $-NH_2$, -NHR'', $-NR''_2$, $-S(O)_2H$ or $-S(O)_2R''$;

R^x is selected from



wherein ~ indicates attachment to T,

Z_4 is O, S or NR^4;

V is CR^f_2, NR^4 or S;

each of G_1, G_2, G_3 and G_4 is independently N or CR^c,

each of Y_1 and Y_2 is independently N or CR^f,

each R^f is independently hydrogen, halogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, fused aryl-cycloalkyl, fused aryl-heterocycloalkyl, heteroaryl, heteroaryl substituted with at least one aryl group, benzyl, haloalkyl, haloalkenyl, $-NH_2$, -NHR'', $-NR''_2$, -NHC(O)R'', -NR''C(O)R'', NHC(O)CH(OH)R'', -NR''C(O)CH(OH)R'', -NHC(O)OR'', -NR''C(O)OR'', $-NHSO_2R''$, $-NR''SO_2R''$, $-NO_2$, -CN, -C(O)H, C(O)R'', -C(O)OH, -C(O)OR'', $-C(O)NH_2$, -C(O)NHR'', $-C(O)NR''_2$,-OH, -OR'', -OC(O)H, -OC(O)R'', -OC(O)OH,-OC(O)OR'', $-OC(O)NH_2$, -OC(O)NHR'', $-OC(O)NR''_2$, -SH, -SR'', $-S(O)_2H$, $-S(O)_2R''$, $-S(O)_2OH$, $-S(O)_2OR''$, $-S(O)_2NH_2$, -S(O)2NHR'', $-S(O)_2NR''_2$, - $\mathbf{R^{21}}$,-O-$\mathbf{R^{21}}$, -NH-$\mathbf{R^{21}}$, -C(O)-NH-$\mathbf{R^{21}}$, or $-CH_2$-NH-C(O)-$\mathbf{R^{21}}$; or when Y_1 and Y_2 are CR^f then each R^f, together with the carbon atom to which it is attached, forms a 5- or 6- membered ring;

each R^c is independently hydrogen, halogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, aryl substituted with at least one –OR'', heteroaryl, benzyl, haloalkyl, haloalkenyl, $-NH_2$, -NHR'', $-NR''_2$, $-CH_2NH_2$, -NHC(O)R'', -NR''C(O)R'', NHC(O)CH(OH)R'', -NR''C(O)CH(OH)R'', -NHC(O)OR'', -NR''C(O)OR'', $-NHSO_2R''$, $-NR''SO_2R''$, $-NO_2$, -CN, -C(O)H, C(O)R'', -C(O)OR'', $-C(O)NH_2$, -C(O)NHR'', $-C(O)NR''_2$,-OH, -OR'', -OC(O)H, -OC(O)R'', -OC(O)OH,-OC(O)OR'', $-OC(O)NH_2$, -OC(O)NHR'', $-OC(O)NR''_2$, -SH, -SR'', $-S(O)_2H$, $-S(O)_2R''$, $-S(O)_2OH$, $-S(O)_2OR''$, $-S(O)_2NH_2$, -S(O)2NHR'', $-S(O)_2NR''_2$, -O-$\mathbf{R^{21}}$, -NH-$\mathbf{R^{21}}$, -C(O)-NH-$\mathbf{R^{21}}$, or $-CH_2$-NH-C(O)-$\mathbf{R^{21}}$;

each R^4 is independently hydrogen, halogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, heteroaryl, benzyl, haloalkyl, haloalkenyl, -C(O)H, C(O)R'', -C(O)OH, -C(O)OR'', $-C(O)NH_2$, -C(O)NHR'', $-C(O)NR''_2$, -OH, -OR'', $-NH_2$, -NHR'', $-NR''_2$, $-S(O)_2H$, $-S(O)_2R''$, - $\mathbf{R^{21}}$, -C(O)-NH-$\mathbf{R^{21}}$, or $-CH_2$-NH-C(O)-$\mathbf{R^{21}}$; and

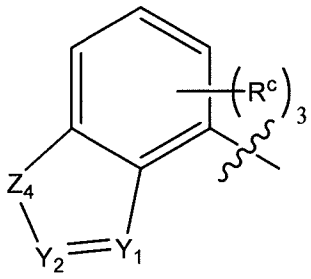
each R'' is independently alkyl, cycloalkyl, alkenyl, cycloalkenyl, aryl, heteroaryl, or benzyl;

$\mathbf{R^{21}}$ is a bond connected to $\mathbf{R^{18}}$ of the linker, wherein Formula (III) contains a single $\mathbf{R^{21}}$;

wherein, when n = 2, each R^c is hydrogen, and each of G_1, G_2, G_3 and G_4 is CR^c, then $C=X_1$ may be replaced by CH;

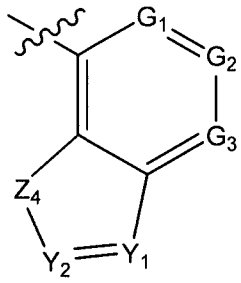
and wherein:

(i) when R^x is

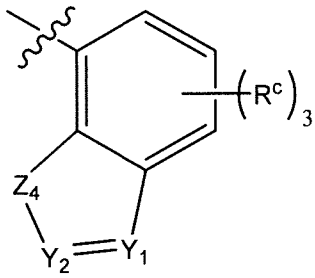


and Z_4 is NH, then L_1 is hydrogen, $-CH_2C(O)OR''$, or -OR'';

(ii) when R^x is

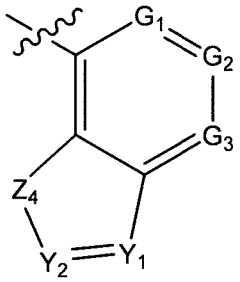


or



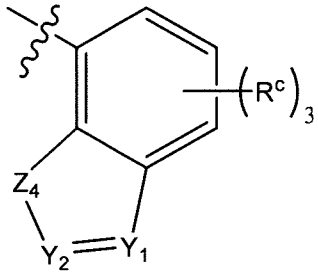
, Z_4 is NR^4, Y_1 is CR^f, and Y_2 is N, then R^4 is not alkyl and at least one of R^2 and R is not H;

(iii) when R^x is



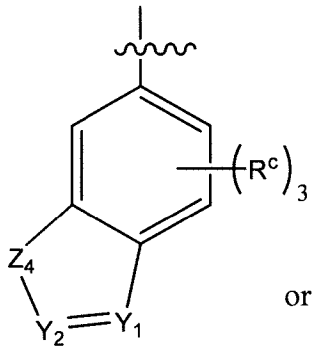
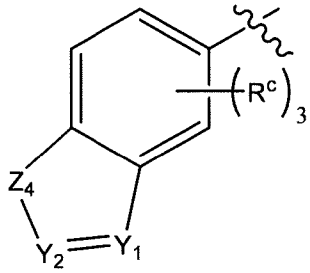
, Z_4 is NR^4, and Y_1 and Y_2 are CR^f, then at least one of G_1, G_2 and G_3 is N;

(iv) when Z_4 is NR^4, and Y_1 and Y_2 are CR^f, then R^x is not



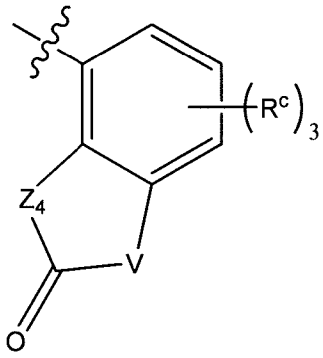
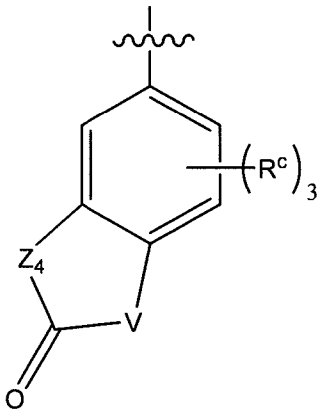
;

(v) when R^x is

, Z_4 is NR^4, and Y_1 or Y_2 is N, then R^4 is not alkyl;

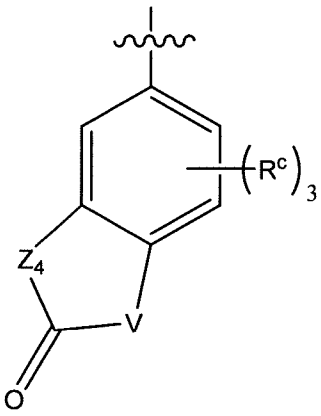
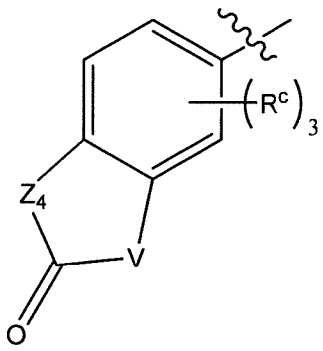
(vi) when R^x is

, then n = 1 or 2;

and

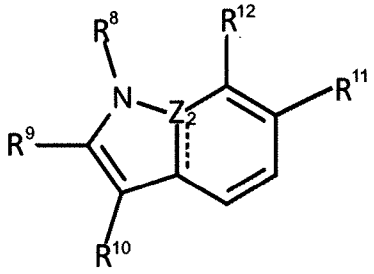
(vii) when R^x is

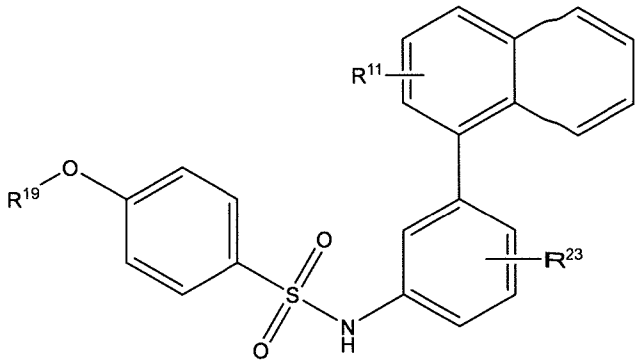
, then Z_4 = O or S

wherein

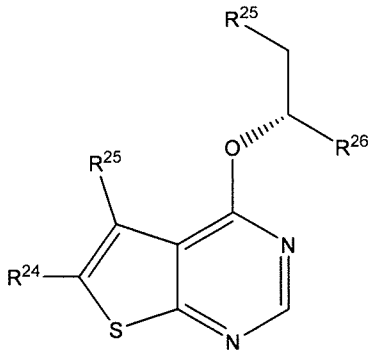
[MCL-1 ligand moiety] is a compound of Formula (A), Formula (B) or Formula (C)



(A)



(B)



(C)

wherein

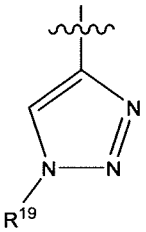
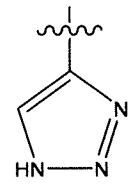
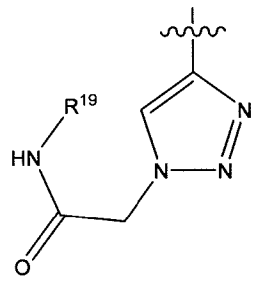
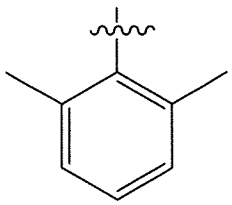
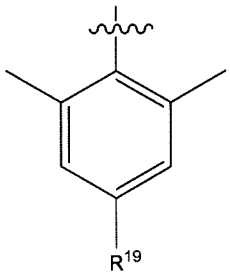
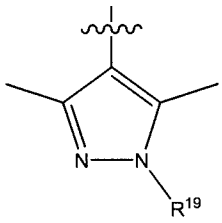
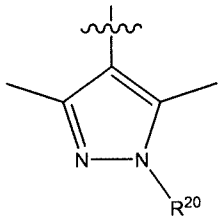
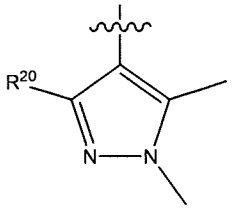
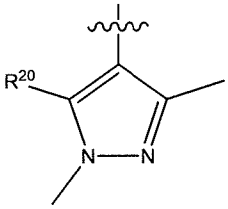
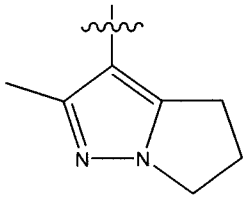
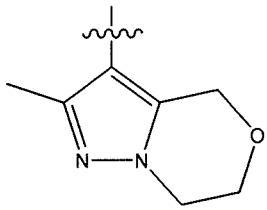
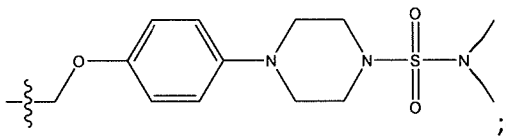
 is a single bond or a double bond;

R^{8} is H, **R**^{19}, or C_1-C_6 alkyl optionally substituted with morpholine;

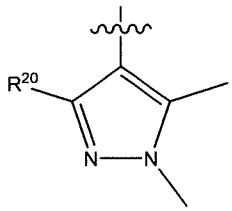
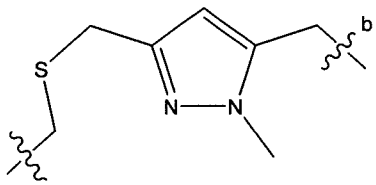
R^{9} is -C(O)OH, -C(O)OC_1-C_6alkyl; -C(O)NH_2; -C(O)O**R**^{19} or -C(O)NH**R**^{19},

R^{10} is -C_{2-5}alkyl-O-R^{13}, wherein R^{13} is phenyl, naphthyl or tetraline, wherein the phenyl, naphthyl or tetraline is optionally substituted with at least one substituent selected from halogen, C_1-C_6 alkyl and -O(C_1-C_6 alkyl); or wherein the naphthyl is optionally substituted with -O- or -S-,

R^{11} is H, halogen or C_1-C_6 alkyl,

R12 is H,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , or  ;

wherein **R20** is Me, -CH_2-O-bromobenzaldehyde, or ;or when

R12 is  and **R10** is -O-naphthyl substituted with -O- or -S-, then **R20** is  , wherein  indicates attachment to -O- or -S- of **R10**;

and wherein

R19 is a bond connected to **R14** of the linker;

R23 is -C(O)OH or -C(O)OC_1-C_6alkyl;

Z2 is N or C, wherein when **Z2** is N, then  is a single bond; and when **Z2** is C, then  is a double bond,

R24 is furan optionally substituted with at least one halogen,

each R^{25} is independently phenyl substituted with -OR^{28} and optionally further substituted with at least one substituent selected from halogen and C_1-C_6 alkyl;

R^{26} is -C(O)OR^{19} or -C(O)NHR^{19}; and

each R^{28} is independently -C_{1-3}alkyl-(N-alkyl piperazine) or -C_{1-3}alkyl-(N-haloalkylpyrazole)

and wherein each of Formula (A), Formula (B) and Formula (C) contains a single R^{19};

and wherein **[linker]** has the following formula

R^{14}-R^{15}-R^{16}-R^{17}-R^{18}

wherein

R^{14} is -C_{1-6} alkyl, -C_{2-6} alkenyl, -C_{2-6} alkynyl, -C(O)-, -SO_2- or is absent

R^{15} is cycloalkyl, heterocycloalkyl, aryl, heteroaryl, -C_{1-6} alkyl-NH-, -cycloalkyl-NH- or is absent

R^{16} is -C_{1-6} alkyl, -C(O)-, -C(O)-NH-, -C(O)O-, -CH_2-C(O)-, -CH_2-C(O)-NH-, -CH_2-C(O)O- or is absent

R^{17} is -$CH_2(C_2H_4\text{-}O)_y$, $(C_2H_4\text{-}O)_x$, $(C_3H_6\text{-}O)_x$, or is absent

x is 1-10

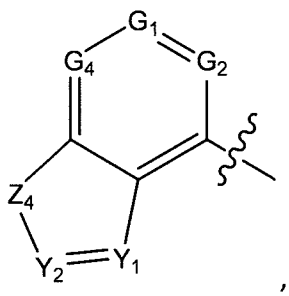
y is 2-10

R^{18} is -C_{1-6} alkyl, heterocycloalkyl, or is absent

wherein at least one of R^{14}-R^{18} is present

In some embodiments, each alkyl, alkenyl, alkynyl, aryl, heteroaryl and benzyl is unsubstituted.

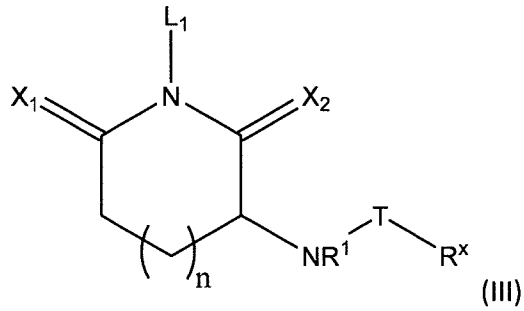
In some embodiments, in Formula (III): each of X_1 and X_2 is O; T is C=O; R^1 is hydrogen, L_1 is hydrogen, R^x is



,

Z_4 is NR^4; each of G_1, G_2 and G_4 is CR^c, Y_1 is N, and Y_2 is CR^f, wherein R^f is not hydrogen.

In some embodiments, **[ligase ligand moiety]** is Formula (III):



(III)

In some embodiments, one of R^c is -O-$\mathbf{R^{21}}$, -NH-$\mathbf{R^{21}}$, -C(O)-NH-$\mathbf{R^{21}}$, or -CH_2-NH-C(O)-$\mathbf{R^{21}}$.

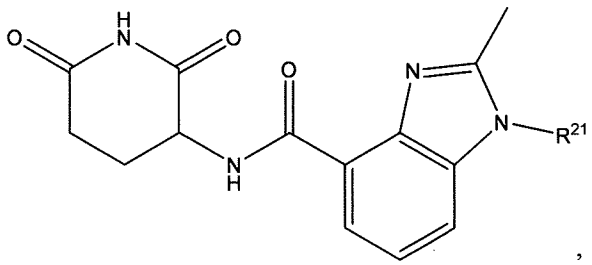
In some embodiments, G_1 is C-O-$\mathbf{R^{21}}$, C-NH-$\mathbf{R^{21}}$, C-C(O)-NH-$\mathbf{R^{21}}$, or C-CH_2-NH-C(O)-$\mathbf{R^{21}}$. In other embodiments, G_2 is C-O-$\mathbf{R^{21}}$, C-NH-$\mathbf{R^{21}}$, C-C(O)-NH-$\mathbf{R^{21}}$, or C-CH_2-NH-C(O)-$\mathbf{R^{21}}$.

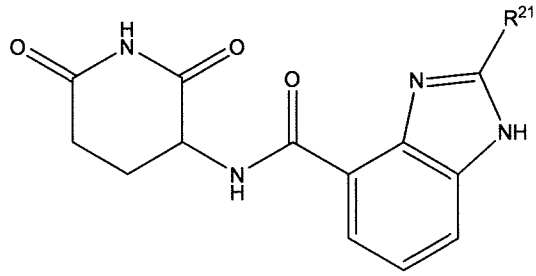
In some embodiments, R^4 is $\mathbf{R^{21}}$, -C(O)-NH-$\mathbf{R^{21}}$, or -CH_2-NH-C(O)-$\mathbf{R^{21}}$.

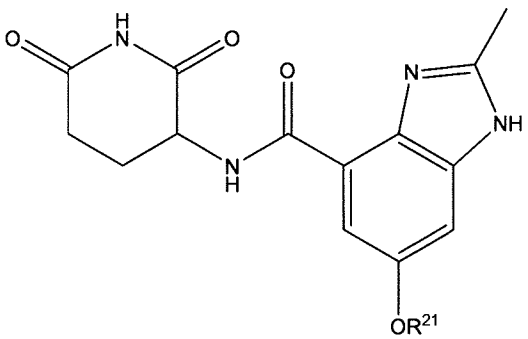
In some embodiments, one of R^f is - $\mathbf{R^{21}}$, -O-$\mathbf{R^{21}}$, -NH-$\mathbf{R^{21}}$, -C(O)-NH-$\mathbf{R^{21}}$, or -CH_2-NH-C(O)-$\mathbf{R^{21}}$.

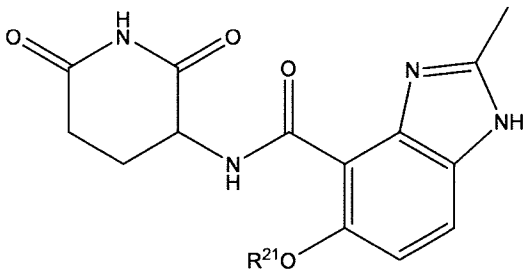
In some embodiments, Y_2 is C-$\mathbf{R^{21}}$, CO-$\mathbf{R^{21}}$, C-NH-$\mathbf{R^{21}}$, C-C(O)-NH-$\mathbf{R^{21}}$, or C-CH_2-NH-C(O)-$\mathbf{R^{21}}$.

In some embodiments, **[ligase ligand moiety]** is selected from

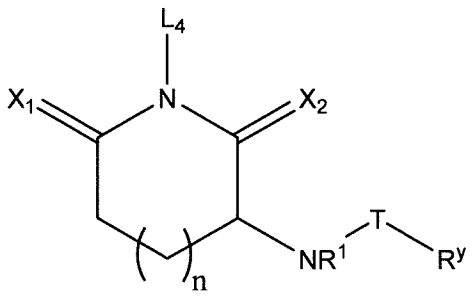

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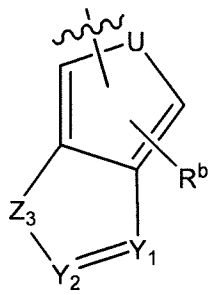
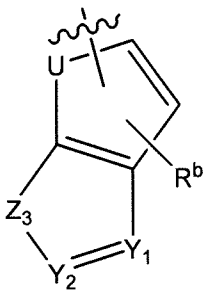
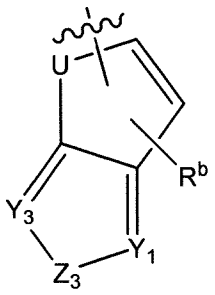
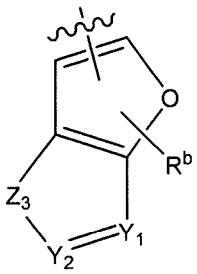
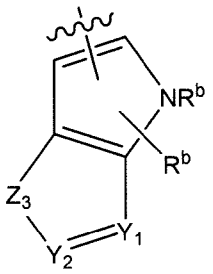
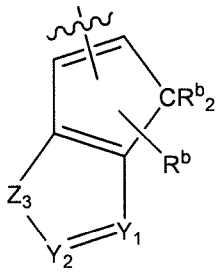
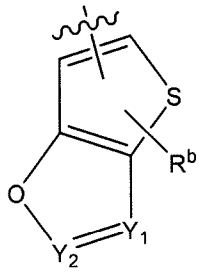
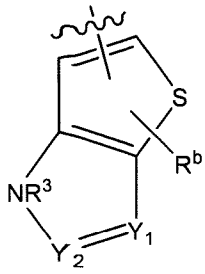

and


.

In some embodiments, **[ligase ligand moiety]** is of Formula (II):


(II)

In some embodiments, R^y is selected from








and


In some embodiments, Z_3 is S or NR^3; U is O or S; andeach of Y_1, Y_2 and Y_3 is independently N or CR^d.

In some embodiments, R^b is hydrogen or alkyl.

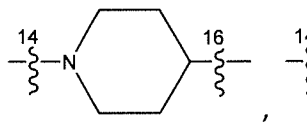
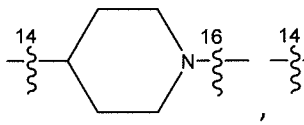
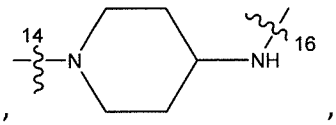
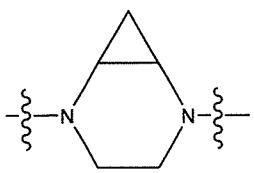
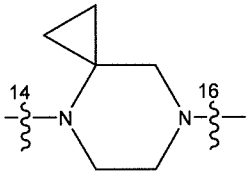
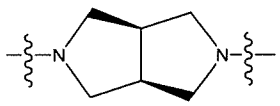
In some embodiments, R^3 is hydrogen, alkyl, cycloalkyl, -**R**^{21}, -C(O)-NH-**R**^{21}, or -CH_2-NH-C(O)-**R**^{21}.

In some embodiments, each R^d is independently hydrogen, alkyl, -O-**R**^{21}, -NH-**R**^{21}, -C(O)-NH-**R**^{21}, or -CH_2-NH-C(O)-**R**^{21}.

In some embodiments,

R^{14} is -C_{1-6} alkyl, -SO_2- or is absent

R^{15} is piperazine, bridged piperazine, piperazine N-oxide, piperazine cation, -C_{1-6} alkyl-NH-,







or is absent, wherein  indicates attachment to **R**^{14} and  indicates attachment to **R**^{16},

R^{16} is -C_{1-6} alkyl, -C(O)-, -C(O)-NH-, -CH_2-C(O)-NH- or is absent

R^{17} is -$CH_2(C_2H_4\text{-}O)_y$, $(C_2H_4\text{-}O)_x$, $(C_3H_6\text{-}O)_x$, or is absent

x is 1-6

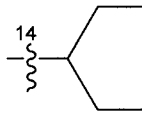
y is 2-6

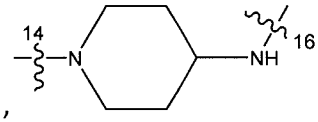
R^{18} is -C_{1-6} alkyl, piperazine, or is absent

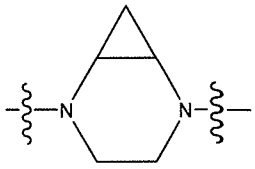
wherein at least one of R^{14}-R^{18} is present.

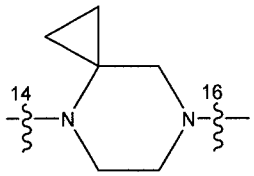
In some embodiments, R^{18} is -C_{1-6} alkyl or is absent.

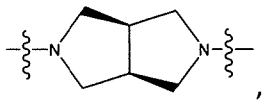
In some embodiments, when R^{15} is piperazine, bridged piperazine, piperazine N-oxide, piperazine cation, -C_{1-6} alkyl-NH-,



,


,


,


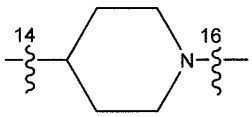
, or


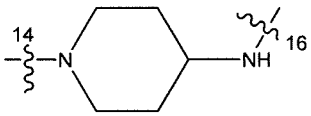
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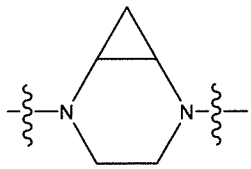
then R^{14} is -C_{1-6} alkyl.

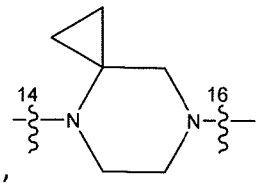
In some embodiments, R^{14} is -C_{1-6} alkyl,

R^{15} is piperazine, bridged piperazine, piperazine N-oxide,

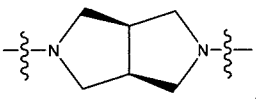


,


,


,


,

or


,

R^{16} is -C(O)-, -CH_2-C(O)-NH-, or is absent

R^{17} is -$CH_2(C_2H_4\text{-}O)_y$, $(C_2H_4\text{-}O)_x$, $(C_3H_6\text{-}O)_x$, or is absent

R^{18} is -C_{1-6} alkyl.

wherein when R^{16} and R^{17} are absent, R^{18} is -C_{3-6} alkyl. In some such embodiments, R^{14} is -C_2 alkyl; x is 1, 2 or 6; and y is 2. In other such embodiments, R^{15} is piperazine, R^{16} is -C(O)-, and R^{17} is – absent. In some such embodiments, R^{14} is -C_2 alkyl, and R^{18} is -C_{1-2} alkyl.

In some embodiments, when R^{14} is $-SO_2-$, at least two of R^{15}-R^{18} are present, and at least one of R^{15}-R^{18} is not C_{1-6} alkyl.

In some embodiments, R^{14} is $-SO_2-$; R^{15} is $-C_{1-6}$ alkyl-NH-; R^{16} is -C(O)-; R^{17} is $-CH_2(C_2H_4-O)_y$, $(C_2H_4-O)_x$ or is absent; and R^{18} is $-C_{2-4}$ alkyl. In some such embodiments, R^{15} is $-C_2$alkyl-NH-; x is 1 or 2; y is 1; and R^{18} is $-C_{2-4}$ alkyl

In some embodiments, R^{14} is absent; R^{15} is absent; R^{16} is -C(O)-NH-, or is absent; R^{17} is $-CH_2(C_2H_4-O)_y$, $(C_2H_4-O)_x$, $(C_3H_6-O)_x$, or is absent; and R^{18} is $-C_{1-6}$ alkyl.

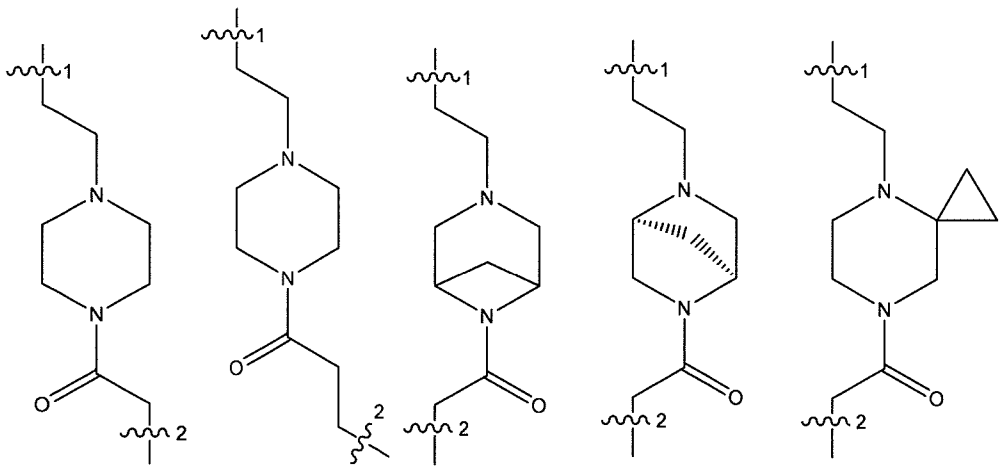
In some embodiments, at least one of R^{14}-R^{18} is not $-C_{1-6}$ alkyl.

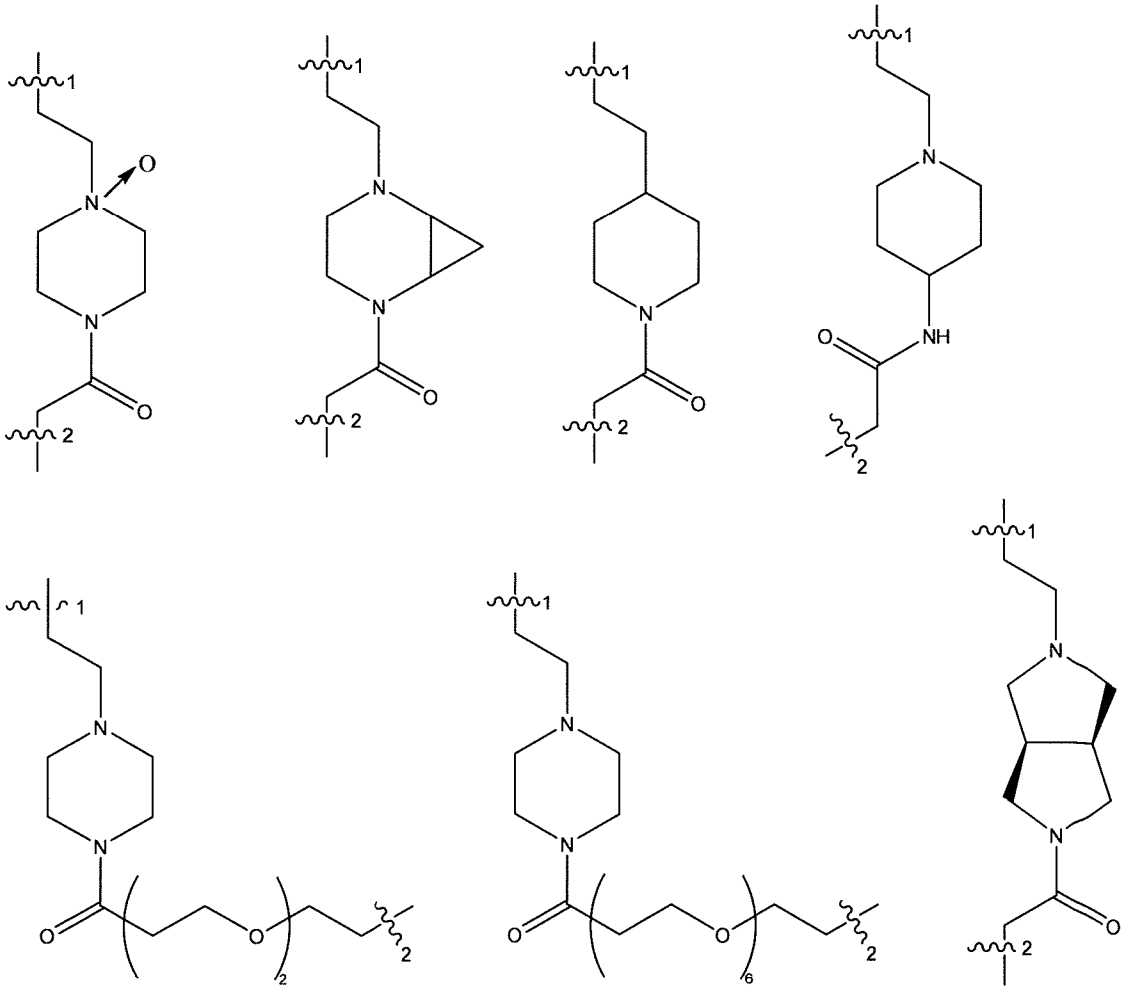
In some embodiments, x is 1, 2 or 3; y is 2; and R^{18} is $-C_{2-6}$ alkyl.

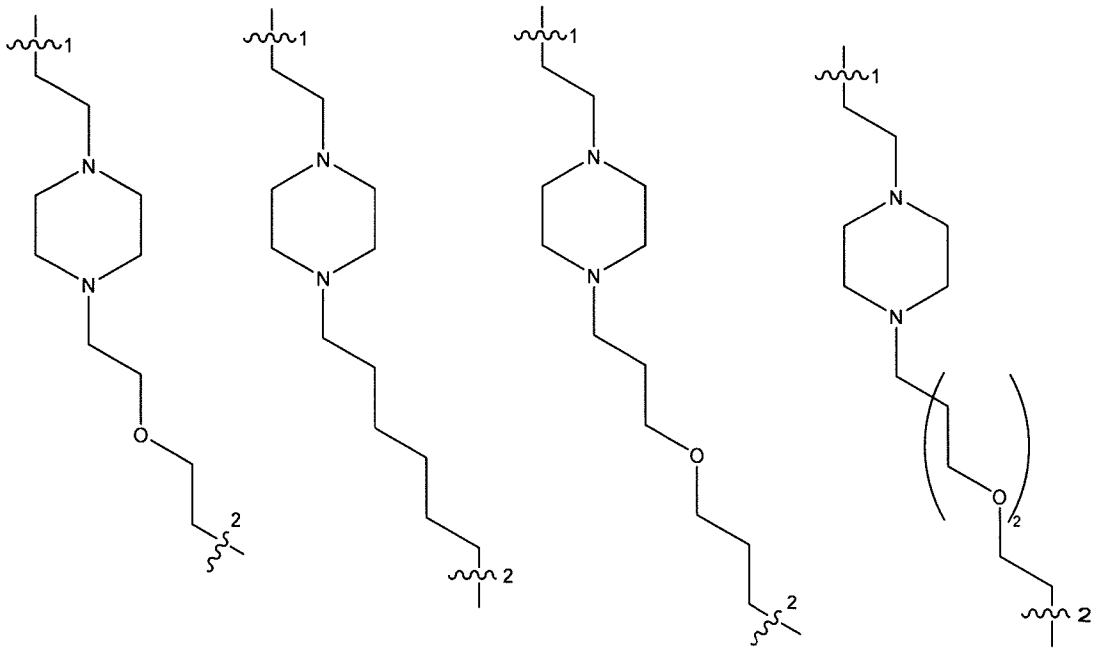
In some embodiments, R^{15} is $-C_{1-6}$ alkyl-NH-, at least one of R^{16}-R^{18} is present.

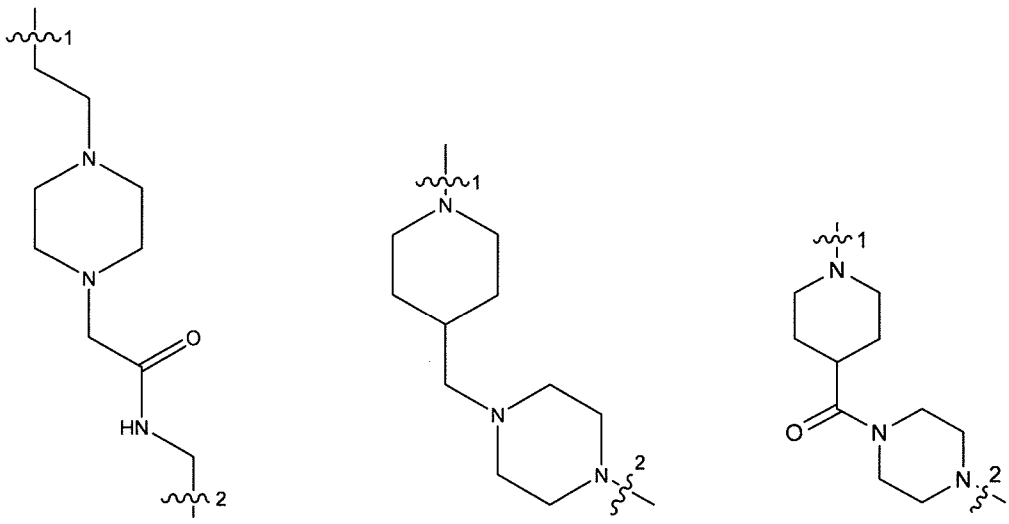
In some embodiments, when R^{17} is $-CH_2(C_2H_4-O)_y$, $(C_2H_4-O)_x$ or $(C_3H_6-O)_x$, at least one of R^{14}-R^{16} and R^{18} is present, wherein at least one of R^{14} and R^{18} is not $-C_{1-6}$ alkyl.

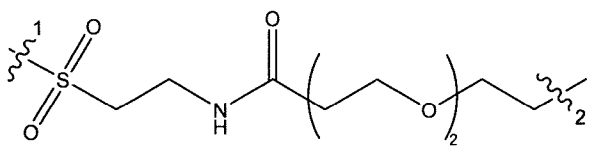
In some embodiments, **[linker]** is selected from

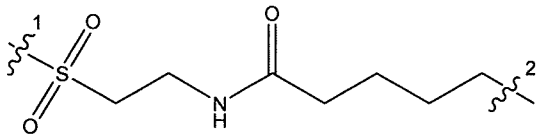


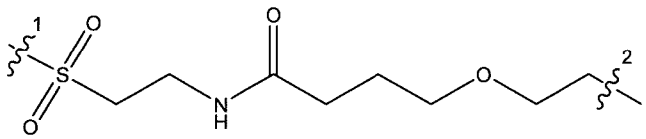


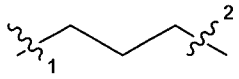


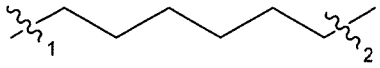


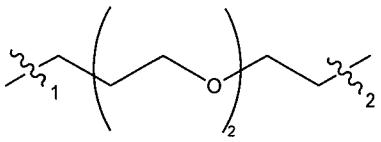


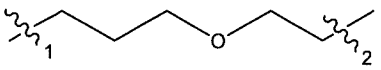


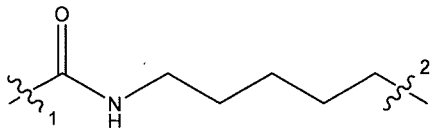


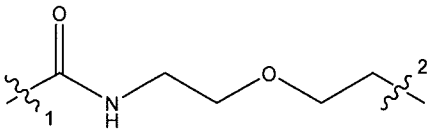


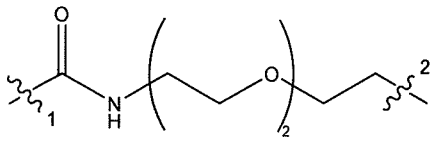




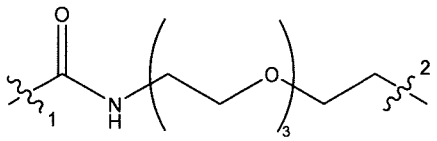








and

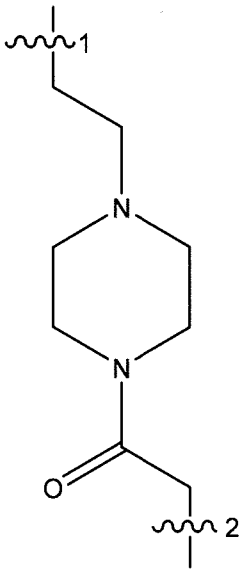


wherein

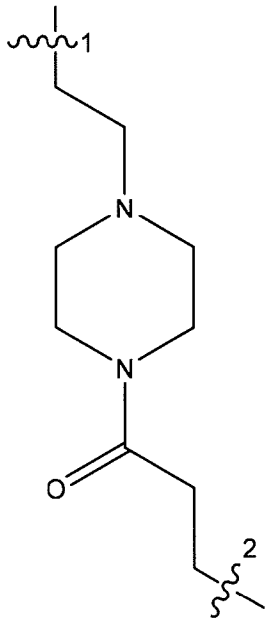
 indicates attachment to **[MCL-1 ligand moiety]** and

 indicates attachment to **[ligase ligand moiety].**

122. The compound of any one of claims 89-121, wherein **[linker]** is selected from



and



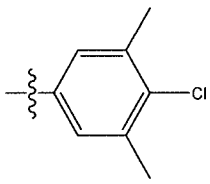
wherein



indicates attachment to **[MCL-1 ligand moiety]** and



indicates attachment to **[ligase ligand moiety].**

In some embodiments, when R^8 is H, R^{13} is 

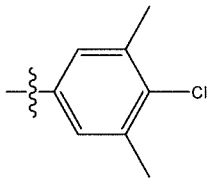
.

In some embodiments,

R^8 is H, R^{19}, methyl, or -CH_2CH_2-morpholine;

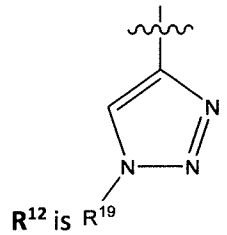
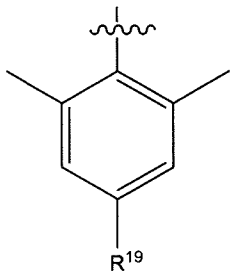
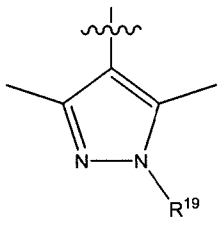
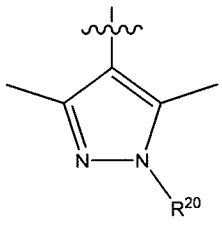
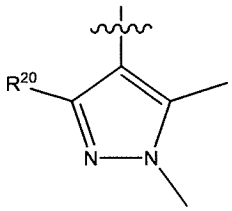
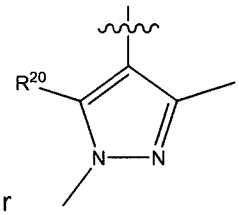
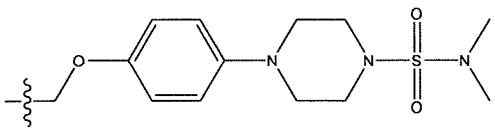
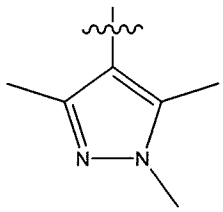
R^9 is -C(O)OH or -C(O)NHR^{19},

R^{10} is -C_3H_6O-R^{13},

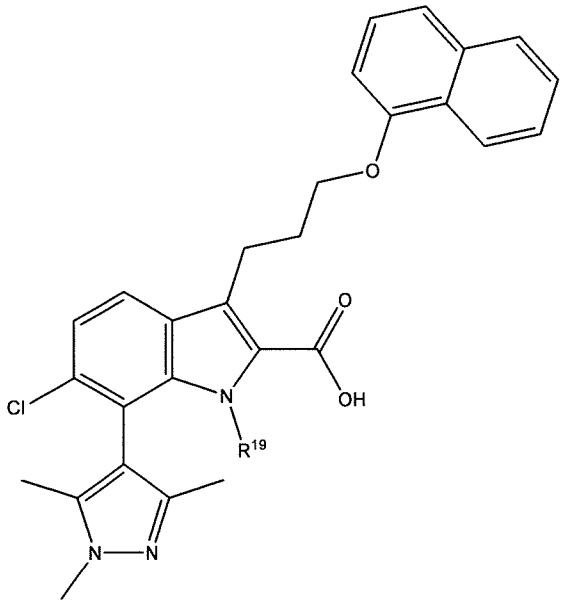
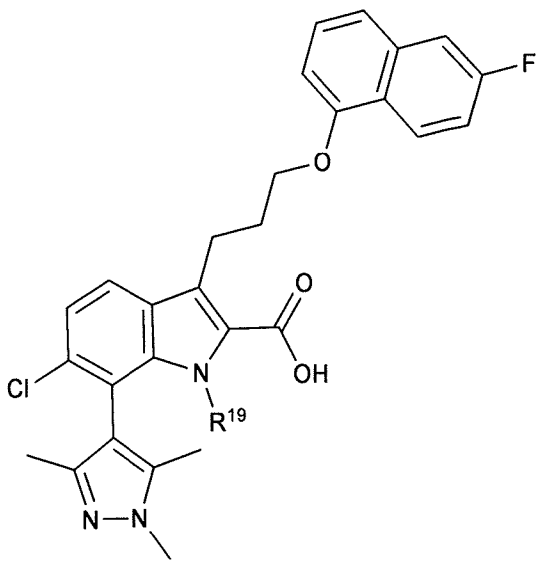
wherein R^{13} is 

, tetraline or naphthyl optionally substituted with fluorine;

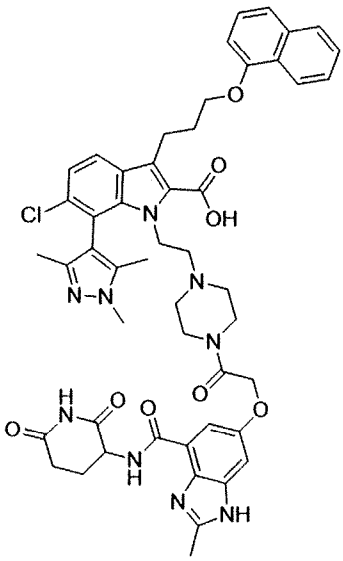
R^{11} is H, Cl, F or methyl,

R^{12} is  ,  ,  ,  ,  , or  , wherein **R^{20}** is Me, -CH_2-O-bromobenzaldehyde, or  . In some such embodiments, **R^8** is **R^{19}** or methyl; **R^{10}** is -C_3H_6O-R^{13}, wherein **R^{13}** is naphthyl optionally substituted with fluorine; **R^{11}** is Cl or F, and **R^{12}** is  .

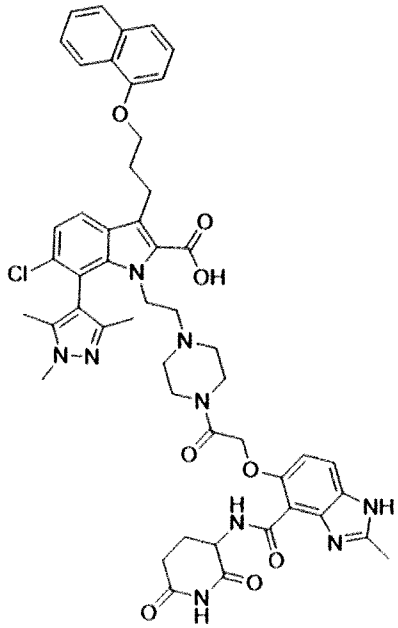
In some embodiments, **Z_2** is C and  is a double bond.

In some embodiments, **[MCL-1 ligand moiety]** is  or  .

In some embodiments, the compound is selected from:

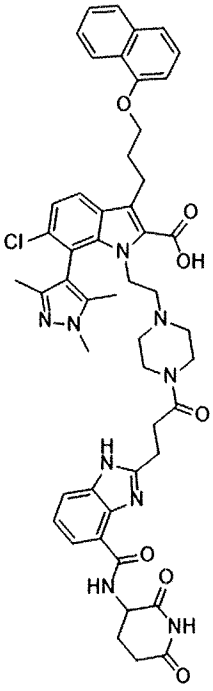


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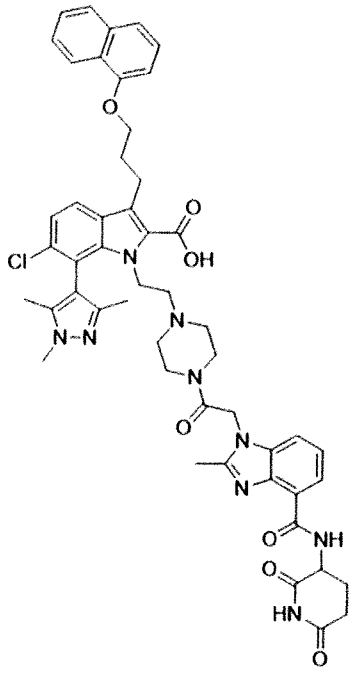


,

263 264

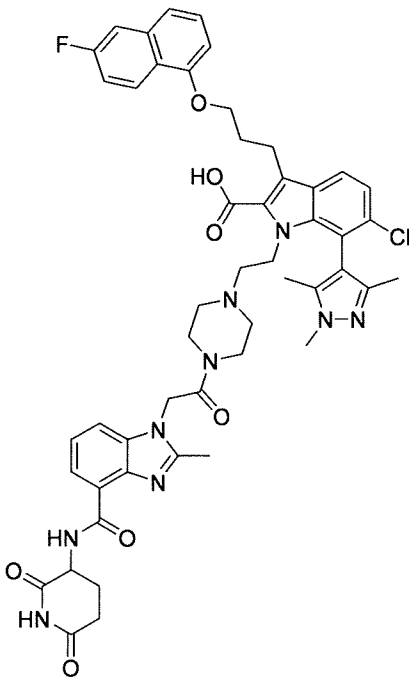


,



and

265 266



268.

In some embodiments of any of the above aspects, T is C=O. In other embodiments, T is SO_2.

In some embodiments of any of the above aspects, X_1 and X_2 are O. In other embodiments, X_1 is O and X_2 is S. In other embodiments, X_1 is S and X_2 is O. In other embodiments, X_1 and X_2 are S.

In some embodiments of any of the above aspects, n is 0. In other embodiments, n is 1 or 2. In some embodiments, n is 1. In other embodiments, n is 2.

In some embodiments of any of the above aspects, **[MCL-1 ligand moiety]** is a compound of Formula (A), and $\mathbf{R^{10}}$ is $-C_{2\text{-}5}$alkyl-O-R^{13},

In some embodiments of any of the above aspects, $\mathbf{R^{10}}$ is $-C_3H_6$-O-R^{13},
In accordance with a fourth aspect of the invention, there is provided a pharmaceutical composition comprising a compound according to any of the above aspects of the present invention.

The invention also provides a compound or composition according to any of the above aspects of the present invention, for use in medicine.

The invention also provides a compound or composition according to any of the above aspects of the present invention, for use in the treatment of cancer. In some embodiments the cancer is selected

from breast cancer, triple negative breast cancer, colorectal cancer, pancreatic cancer, skin cancer, melanoma, ovarian cancer, kidney cancer, lung cancer, small-cell lung cancer, non-small-cell lung cancer, lymphoma, non-Hodgkin's lymphoma, multiple myeloma, cervical cancer, leukaemia, chronic lymphocytic leukaemia (CLL), acute myeloid leukaemia (AML), chronic myelogenous leukemia (CML), acute lymphoblastic leukaemia (ALL), bladder cancer, and prostate cancer. In some embodiments, the cancer is multiple myeloma or acute myeloid leukaemia.

The present invention also provides a method of treating cancer in a subject in need thereof, the method comprising administering to the subject an effective amount of a compound or composition according to any of the above aspects of the present invention. In some embodiments, the cancer is selected from breast cancer, triple negative breast cancer, colorectal cancer, pancreatic cancer, skin cancer, melanoma, ovarian cancer, kidney cancer, lung cancer, small-cell lung cancer, non-small-cell lung cancer, lymphoma, non-Hodgkin's lymphoma, multiple myeloma, cervical cancer, leukaemia, chronic lymphocytic leukaemia (CLL), acute myeloid leukaemia (AML), chronic myelogenous leukemia (CML), acute lymphoblastic leukaemia (ALL), bladder cancer, and prostate cancer. In some embodiments, the cancer is multiple myeloma or acute myeloid leukaemia. In some embodiments, the administration does not result in cytotoxicity in cardiomyocytes in the subject. In some embodiments, the method further comprises administering at least one additional active agent to the subject. In some embodiments, the at least one additional active agent is an anti-cancer agent selected from eribulin; fulvestrant; midostaurin; an immune checkpoint inhibitor selected from anti-pd-1 antibody, anti-pd-l1 antibody, and anti pd-1/pd-l1 interaction inhibitor; nivolumab; pembrolizumab; atezolizumab; pidilizumab; carfilzomib; venetoclax; cytarabine; anthracyclines; a taxane compound; and hypomethylating agents.

The invention also provides a compound or composition according to any of the above aspects of the present invention, for use in reversing resistance to chemotherapy or targeted cancer therapies.

The invention also provides a method of reversing resistance to chemotherapy or targeted cancer therapies in a subject in need thereof, the method comprising administering to the subject an effective amount of a compound or composition of the present invention.

The invention also provides a combined preparation of a compound of the present invention and at least one additional active agent, for simultaneous, separate or sequential use in therapy. In some

embodiments, the at least one additional active agent is an anti-cancer agent selected from eribulin; fulvestrant; midostaurin; an immune checkpoint inhibitor selected from anti-pd-1 antibody, anti-pd-l1 antibody, and anti pd-1/pd-l1 interaction inhibitor; nivolumab; pembrolizumab; atezolizumab; pidilizumab; carfilzomib; venetoclax; cytarabine; anthracyclines; a taxane compound; and hypomethylating agents. In some embodiments, the therapy is the treatment of cancer.

The invention also provides a compound of formula (X):

[MCL-1 inhibitor] – L – [cereblon binding moiety] (X)

wherein L is a bond or a linker compound. In some embodiments, the cereblon binding moiety is a **[ligase ligand moiety]** of the present invention. In some embodiments, the MCL-1 inhibitor is an **[MCL-1 binding moiety]** of the present invention. In some embodiments, the cereblon binding moiety is coupled to the MCL-1 inhibitor by a linker compound, wherein the linker compound is covalently attached to the cereblon binding moiety and the MCL-1 inhibitor. In some embodiments, the linker compound is a **[linker]** of the present invention

The invention also provides a method of reducing the cardiac cytotoxicity of an MCL-1 inhibitor, comprising coupling a cereblon binding moiety to the MCL-1 inhibitor. In some embodiments, the cereblon binding moiety is a **[ligase ligand moiety]** of the present invention. In some embodiments, the MCL-1 inhibitor is an **[MCL-1 binding moiety]** of the present invention. In some embodiments, the cereblon binding moiety is coupled to the MCL-1 inhibitor by a linker compound, wherein the linker compound is covalently attached to the cereblon binding moiety and the MCL-1 inhibitor. In some embodiments, the linker compound is a **[linker]** of the present invention.

As used herein the term "alkyl" is intended to include both unsubstituted alkyl groups, and alkyl groups which are substituted by one or more additional groups. In some embodiments, the alkyl group is an unsubstituted alkyl group. In some embodiments, the alkyl group is substituted by one or more groups selected from -OH, $-OR^W$, $-NH_2$, $-NHR^W$, $-NR^W_2$, $-SO_2R^W$, $-C(O)R^W$, -CN, and $-NO_2$, wherein each R^W is unsubstituted and is independently alkyl, cycloalkyl, alkenyl, cycloalkenyl, aryl, heteroaryl, or benzyl. In some embodiments, the alkyl group is a C_1-C_{12} alkyl, a C_1-C_{10} alkyl, a C_1-C_8 alkyl, a C_1-C_6 alkyl, or a C_1-C_4 alkyl group. In some embodiments the alkyl group is a linear alkyl group. In some embodiments the alkyl group is an unsubstituted linear alkyl group. In some embodiments the alkyl group is a linear alkyl group which is substituted by one or more groups selected from -OH, $-OR^W$, $-NH_2$, $-NHR^W$, $-NR^W_2$, $-SO_2R^W$, $-C(O)R^W$, -CN, and $-NO_2$, wherein each R^W is unsubstituted and is independently alkyl, cycloalkyl,

alkenyl, cycloalkenyl, aryl, heteroaryl, or benzyl. In some embodiments the alkyl group is a branched alkyl group. In some embodiments the alkyl group is an unsubstituted branched alkyl group. In some embodiments the alkyl group is a branched alkyl group which is substituted by one or more groups selected from -OH, $-OR^W$, $-NH_2$, $-NHR^W$, $-NR^W_2$, $-SO_2R^W$, $-C(O)R^W$, -CN, and $-NO_2$, wherein each R^W is unsubstituted and is independently alkyl, cycloalkyl, alkenyl, cycloalkenyl, aryl, heteroaryl, or benzyl.

As used herein the term "alkenyl" is intended to include both unsubstituted alkenyl groups, and alkenyl groups which are substituted by one or more additional groups. In some embodiments, the alkenyl group is an unsubstituted alkenyl group. In some embodiments, the alkenyl group is substituted by one or more groups selected from -OH, $-OR^W$, $-NH_2$, $-NHR^W$, $-NR^W_2$, $-SO_2R^W$, $-C(O)R^W$, -CN, and $-NO_2$, wherein each R^W is unsubstituted and is independently alkyl, cycloalkyl, alkenyl, cycloalkenyl, aryl, heteroaryl, or benzyl. In some embodiments, the alkenyl group is a C_2-C_{12} alkenyl, a C_2-C_{10} alkenyl, a C_2-C_8 alkenyl, a C_2-C_6 alkenyl, or a C_2-C_4 alkenyl group. In some embodiments the alkenyl group is a linear alkenyl group. In some embodiments the alkenyl group is an unsubstituted linear alkenyl group. In some embodiments the alkenyl group is a linear alkenyl group which is substituted by one or more groups selected from -OH, $-OR^W$, $-NH_2$, $-NHR^W$, $-NR^W_2$, $-SO_2R^W$, $-C(O)R^W$, -CN, and $-NO_2$, wherein each R^W is unsubstituted and is independently alkyl, cycloalkyl, alkenyl, cycloalkenyl, aryl, heteroaryl, or benzyl. In some embodiments the alkenyl group is a branched alkenyl group. In some embodiments the alkenyl group is an unsubstituted branched alkenyl group. In some embodiments the alkenyl group is a branched alkenyl group which is substituted by one or more groups selected from -OH, $-OR^W$, $-NH_2$, $-NHR^W$, $-NR^W_2$, $-SO_2R^W$, $-C(O)R^W$, -CN, and $-NO_2$, wherein each R^W is unsubstituted and is independently alkyl, cycloalkyl, alkenyl, cycloalkenyl, aryl, heteroaryl, or benzyl.

As used herein the term "alkynyl" is intended to include both unsubstituted alkynyl groups, and alkynyl groups which are substituted by one or more additional groups. In some embodiments, the alkynyl group is an unsubstituted alkynyl group. In some embodiments, the alkynyl group is substituted by one or more groups selected from -OH, $-OR^W$, $-NH_2$, $-NHR^W$, $-NR^W_2$, $-SO_2R^W$, $-C(O)R^W$, -CN, and $-NO_2$, wherein each R^W is unsubstituted and is independently alkyl, cycloalkyl, alkenyl, cycloalkenyl, aryl, heteroaryl, or benzyl. In some embodiments, the alkynyl group is a C_2-C_{12} alkynyl, a C_2-C_{10} alkynyl, a C_2-C_8 alkynyl, a C_2-C_6 alkynyl, or a C_2-C_4 alkynyl group. In some embodiments the alkynyl group is a linear alkynyl group. In some embodiments the alkynyl group is an unsubstituted linear alkynyl group. In some embodiments the alkynyl group is a linear alkynyl group which is substituted by one or more groups selected from -OH, $-OR^W$, $-NH_2$, $-NHR^W$, $-NR^W_2$, $-SO_2R^W$, $-C(O)R^W$, -CN, and $-NO_2$, wherein each R^W is unsubstituted and is independently alkyl, cycloalkyl, alkenyl, cycloalkenyl, aryl, heteroaryl, or benzyl. In some embodiments the alkynyl group is a branched alkynyl group. In some embodiments

the alkynyl group is an unsubstituted branched alkynyl group. In some embodiments the alkynyl group is a branched alkynyl group which is substituted by one or more groups selected from -OH, $-OR^W$, $-NH_2$, $-NHR^W$, $-NR^W_2$, $-SO_2R^W$, $-C(O)R^W$, -CN, and $-NO_2$, wherein each R^W is unsubstituted and is independently alkyl, cycloalkyl, alkenyl, cycloalkenyl, aryl, heteroaryl, or benzyl.

As used herein the term "aryl" is intended to include both unsubstituted aryl groups, and aryl groups which are substituted by one or more additional groups. In some embodiments, the aryl group is an unsubstituted aryl group. In some embodiments, the aryl group is substituted by one or more groups selected from -OH, $-OR^W$, $-NH_2$, $-NHR^W$, $-NR^W_2$, $-SO_2R^W$, $-C(O)R^W$, -CN, and $-NO_2$, wherein each R^W is unsubstituted and is independently alkyl, cycloalkyl, alkenyl, cycloalkenyl, aryl, heteroaryl, or benzyl. In some embodiments, the aryl group is a C_6-C_{10} aryl, a C_6-C_8 aryl, or a C_6 aryl.

As used herein the term "heteroaryl" is intended to include both unsubstituted heteroaryl groups, and heteroaryl groups which are substituted by one or more additional groups. In some embodiments, the heteroaryl group is an unsubstituted heteroaryl group. In some embodiments, the heteroaryl group is substituted by one or more groups selected from -OH, $-OR^W$, $-NH_2$, $-NHR^W$, $-NR^W_2$, $-SO_2R^W$, $-C(O)R^W$, -CN, and $-NO_2$, wherein each R^W is unsubstituted and is independently alkyl, cycloalkyl, alkenyl, cycloalkenyl, aryl, heteroaryl, or benzyl. In some embodiments, the heteroaryl group is a C_6-C_{10} heteroaryl, a C_6-C_9 heteroaryl, a C_6-C_8 heteroaryl, or a C_6 heteroaryl.

As used herein the term "benzyl" is intended to include both unsubstituted benzyl groups, and benzyl groups which are substituted by one or more additional groups. In some embodiments, the benzyl group is an unsubstituted benzyl group. In some embodiments, the benzyl group is substituted by one or more groups selected from -OH, $-OR^W$, $-NH_2$, $-NHR^W$, $-NR^W_2$, $-SO_2R^W$, $-C(O)R^W$, -CN, and $-NO_2$, wherein each R^W is unsubstituted and is independently alkyl, cycloalkyl, alkenyl, cycloalkenyl, aryl, heteroaryl, or benzyl.

In some embodiments of any of the above aspects of the invention, all alkyl, alkenyl, alkynyl, aryl, heteroaryl and benzyl groups in the compounds are unsubstituted..

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 is a schematic illustration of the general principle for targeted protein degradation upon treatment with a bifunctional compound. Bifunctional compounds of the present invention comprise an E3 ligase binding moiety (LBM) on the one end and an MCL-1 binding moiety on the other end (MBM).

Figure 2 is an assay showing the dose-dependent effect of various compounds of the invention on the level of MCL-1 protein in the OPM-2 cell line after 6h treatment (2A) and 24h treatment (2B)

Figure 3 is an assay showing the dose-dependent effect of compounds of the invention and reference compounds on the level of MCL-1 protein in the OPM-2 (Fig. 3A) and MV-4-11 (Fig. 3B) cell line after 3h, 6h, and 24h treatment, as indicated

Figure 4 is an assay showing the dose-dependent effect of compound 204 of the invention on the viability of OPM-2, MV-4-11 and ARH-77 cells

Figure 5 is an assay showing the effect of compound of the invention and the reference compound on caspase 3/7 activity in iPSC-derived cardiomyocytes (iPSC-CMs) (NB 100 μM Concentration point for AZD-5991 is not displayed because of the excessive cell death)

Figure 6 is an assay showing the dose-dependent effect of compounds of the invention on the population of late apoptotic/cell death (Annexin +/PI +) cells after 24 hours of treatment.

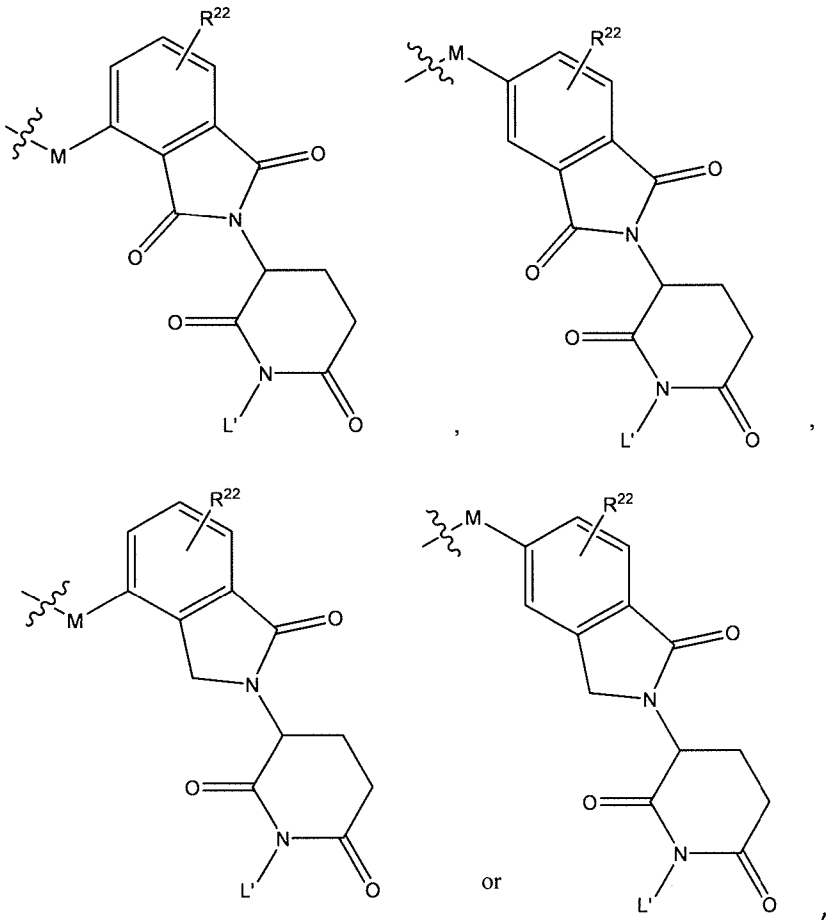
DETAILED DESCRIPTION OF THE INVENTION

As discussed above, the present invention provides a compound of formula (I)

[MCL-1 ligand moiety] – linker – [ligase ligand moiety] (I)

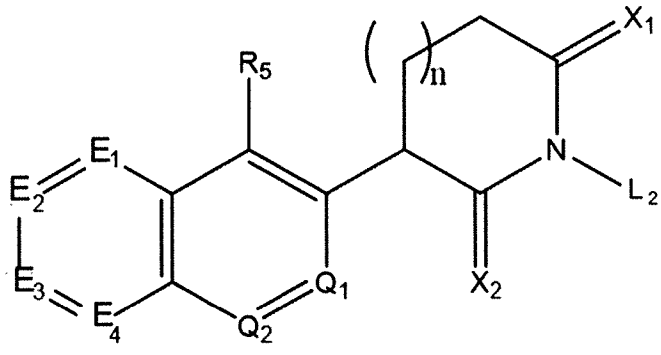
or a salt, solvate, hydrate, isomer or prodrug thereof,

wherein **[ligase ligand moiety]** is:



or

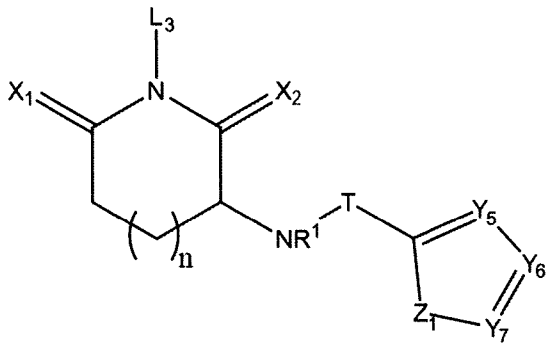
Formula (IV)



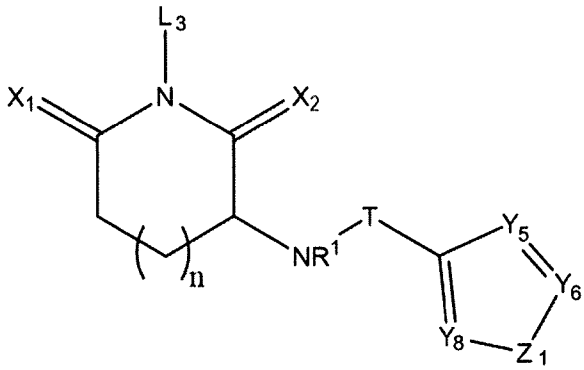
(IV)

or

Formula (Va) or (Vb):



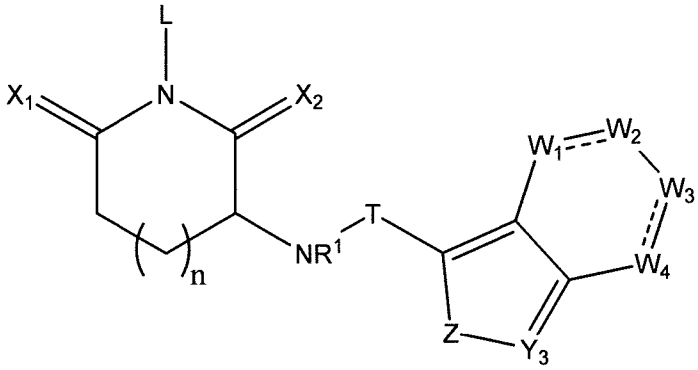
(Va)



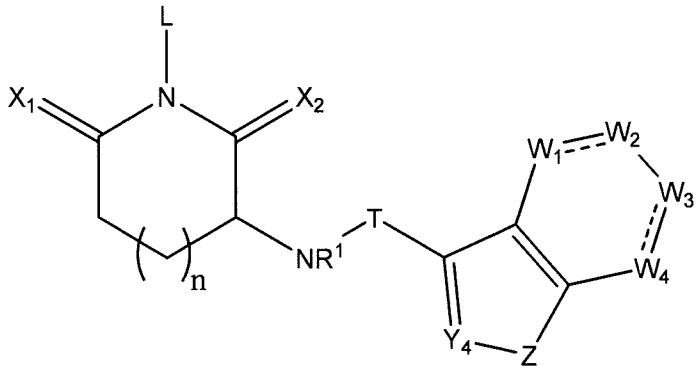
(Vb)

or

Formula (IIa) or (IIb):



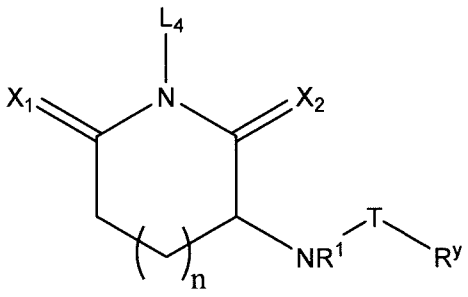
(IIa)



(IIb)

or

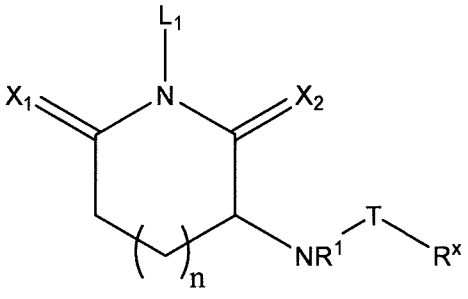
Formula (II):



(II)

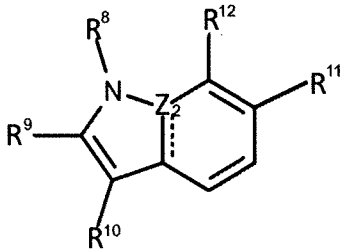
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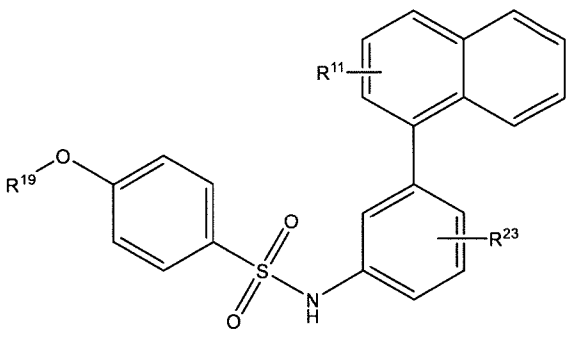
Formula (III):



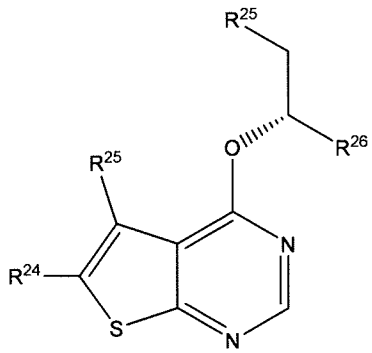
(III)

wherein **[MCL-1 ligand moiety]** is a compound of Formula (A), Formula (B) or Formula (C)





(A) (B)



(C)

and wherein **[linker]** has the following formula

R^{14}-R^{15}-R^{16}-R^{17}-R^{18}

wherein

R^{14} is -C_{1-6} alkyl, -C_{2-6} alkenyl, -C_{2-6} alkynyl, -C(O)-, -SO_2- or is absent

R^{15} is cycloalkyl, heterocycloalkyl, aryl, heteroaryl, -C_{1-6} alkyl-NH-, -cycloalkyl-NH- or is absent

R^{16} is -C_{1-6} alkyl, -C(O)-, -C(O)-NH-, -C(O)O-, -CH_2-C(O)-, -CH_2-C(O)-NH-, -CH_2-C(O)O- or is absent

R^{17} is -$CH_2(C_2H_4\text{-}O)_y$, $(C_2H_4\text{-}O)_x$, $(C_3H_6\text{-}O)_x$, or is absent

x is 1-10

y is 2-10

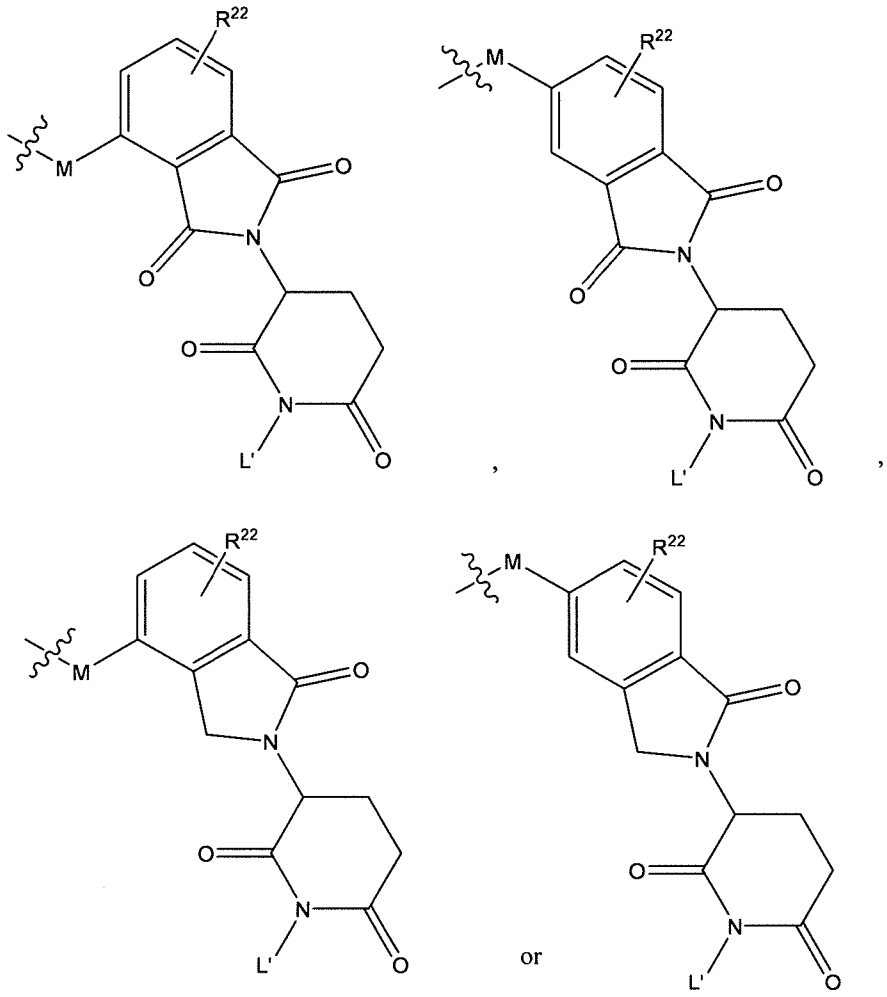
R^{18} is -C_{1-6} alkyl, heterocycloalkyl, or is absent

wherein at least one of R^{14}-R^{18} is present

LIGASE LIGAND MOIETIES

Ligase ligand moieties with thalidomide-type structure

In one aspect, the ligase ligand moiety is:



wherein

M is O or NH, or is absent;

 indicates attachment to **R^{18}** of the linker;

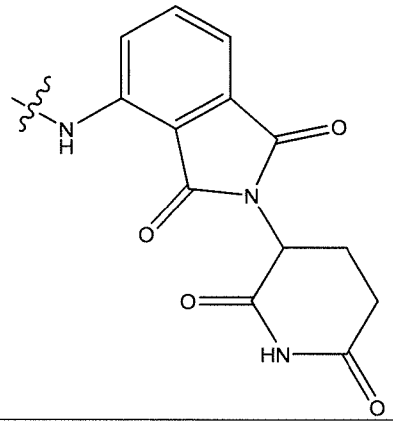
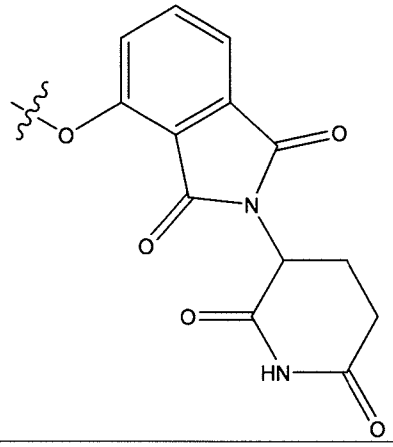
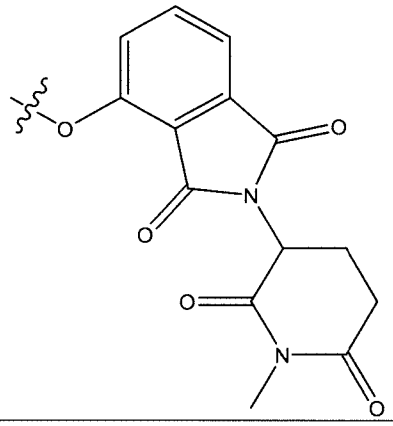
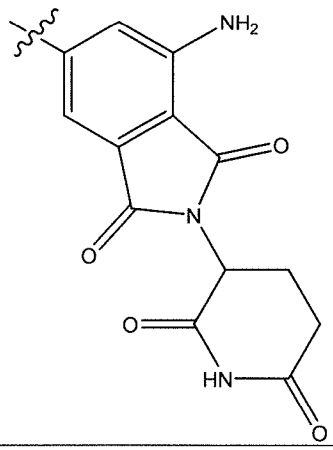
R^{22} is hydrogen, halogen or an amino group; and

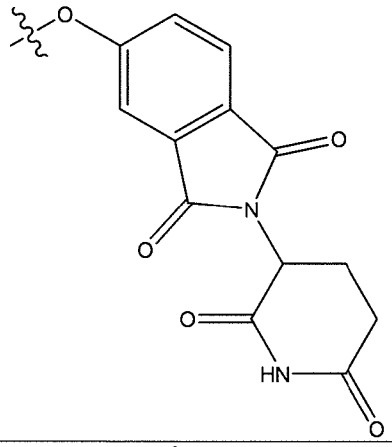
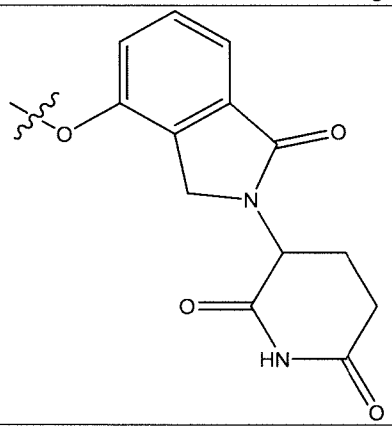
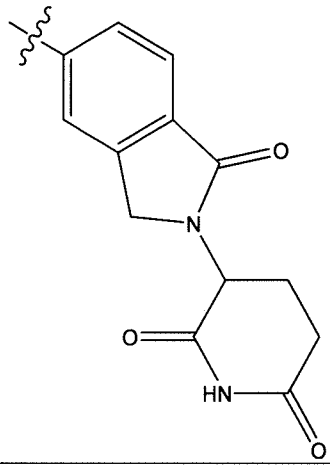
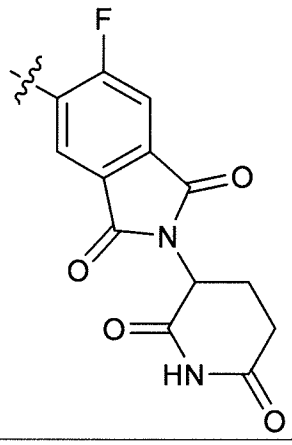
L' is hydrogen, alkyl, benzyl, acetyl or pivaloyl.

Examples of the above ligase ligand moieties are shown in Table 1 below:

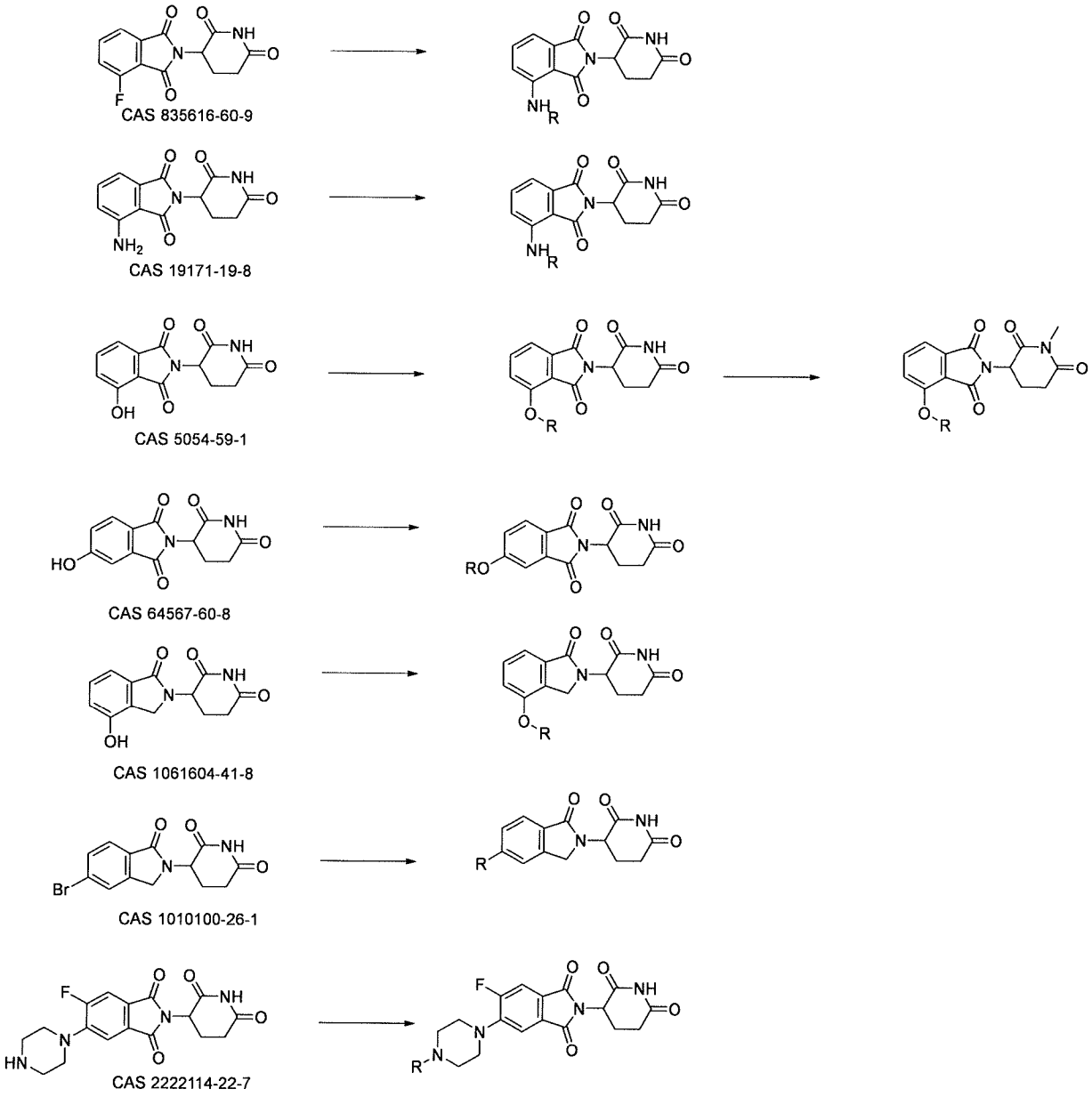
Table 1:

Compound number	Structure

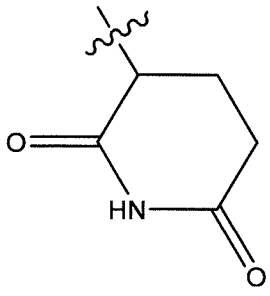
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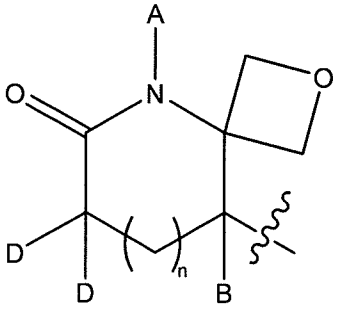
Compounds 108-110 and 112-115 are commercially available in the forms shown below. The synthesis of compound 111 is disclosed in the Examples section, below.

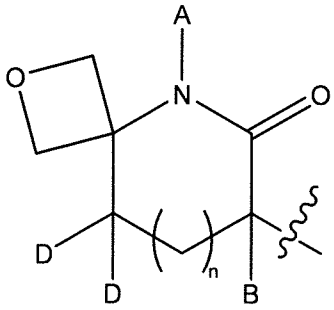


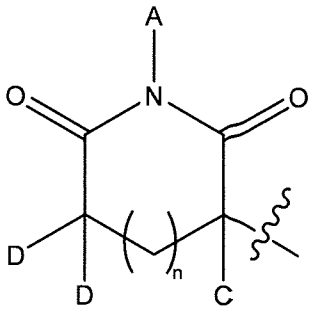
In some embodiments of the above ligase ligands, the



moiety may be replaced with one of the following moieties:







wherein

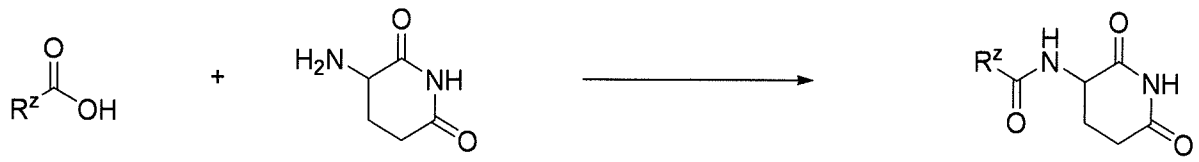
A is , hydrogen, alkyl, alkenyl, benzyl, aryl, heteroaryl, haloalkyl, haloalkenyl, $-CH_2OC(O)^tBu$, $-CH_2C(O)OR^{27}$, $-C(O)R^{27}$, $-C(O)OR^{27}$, $-C(O)NH_2$, $-C(O)NHR^{27}$, $-C(O)NR^{27}_2$, $-OR^{27}$, $-NR^{27}_2$, $-S(O)_2R^{27}$ or $P(O)(OR^{27})(OR^{27})$, wherein each R^{27} is independently hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, aryl, heteroaryl, or benzyl,

B is hydrogen, deuterium or alkyl,

C is hydrogen, deuterium or alkyl.

Ligase ligand moieties of Formula (II) and Formula (III)

The synthesis of the ligase ligand moieties of Formula (II) and Formula (III) (as defined above) can be summarized as follows:



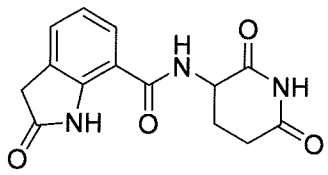
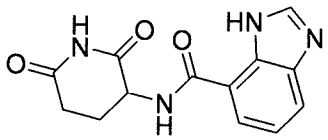
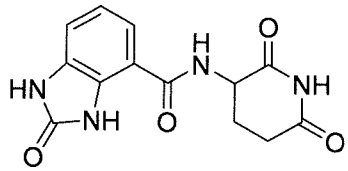
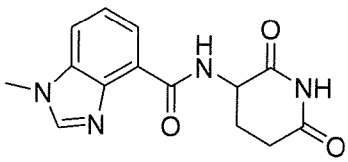
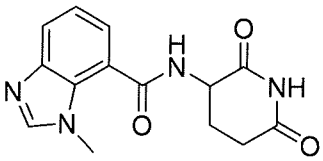
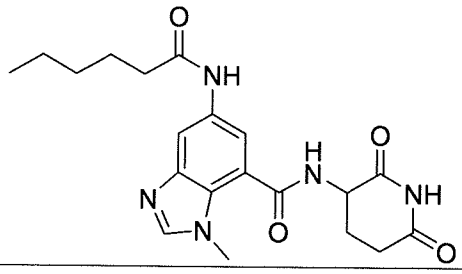
Reaction Scheme 1

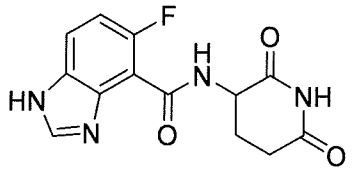
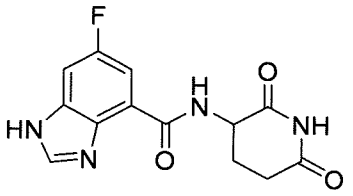
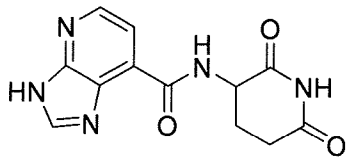
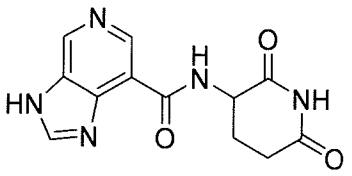
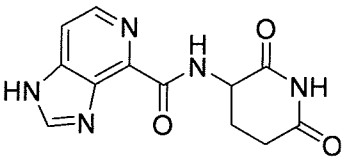
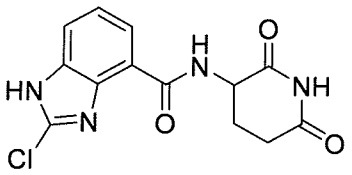
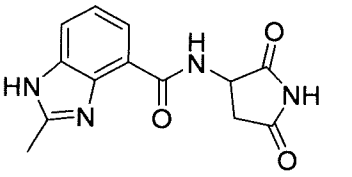
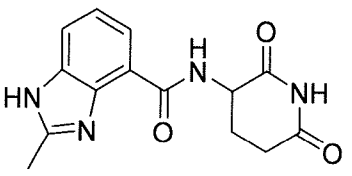
(R^z is R^x or R^y)

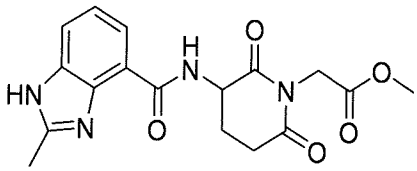
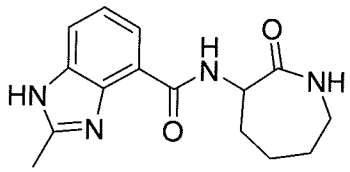
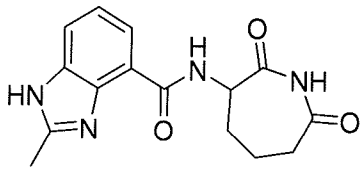
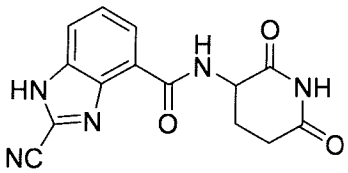
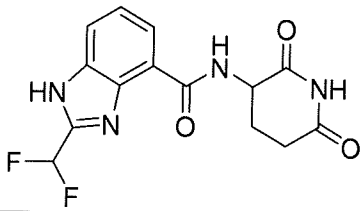
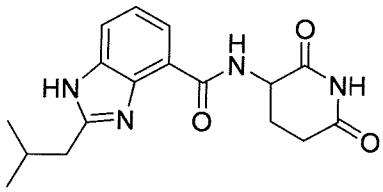
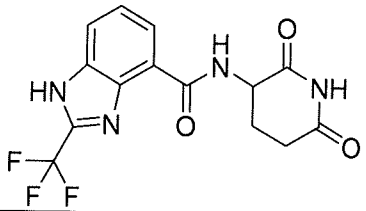
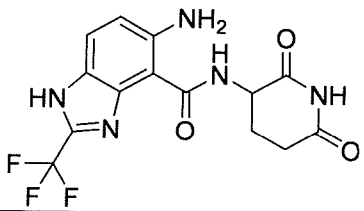
Example ligase ligand moieties of Formula (II) and Formula (III) are shown in Table 2 below. Compounds 4-6, 29, 39-41, 50-54, 58 and 62 could be modified to allow attachment to the [linker]

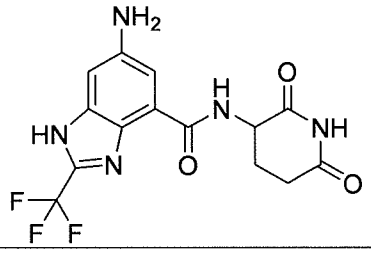
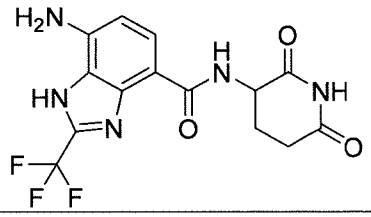
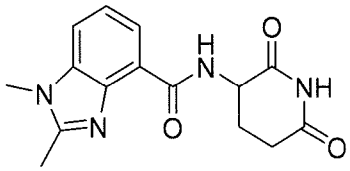
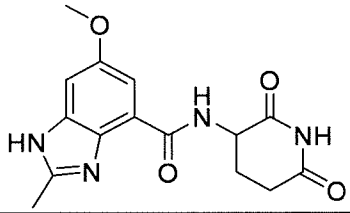
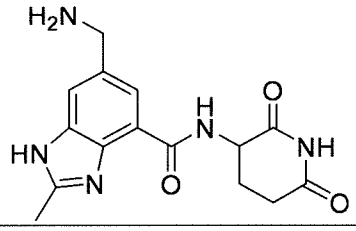
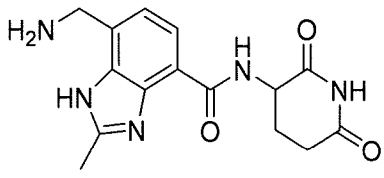
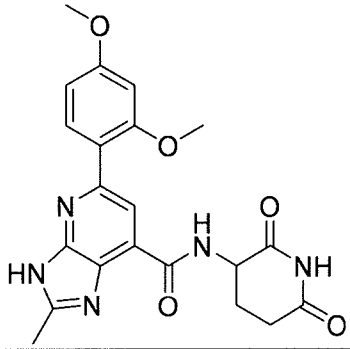
(for example, by bromination of the aromatic ring followed by attachment - by palladium coupling – of either the [linker] itself, or of a functional group to which the [linker] could be attached).

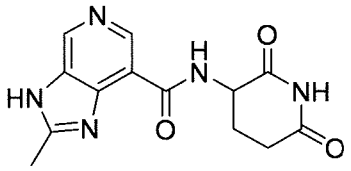
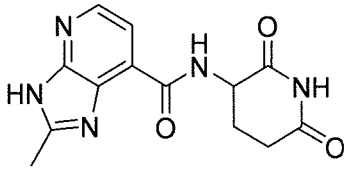
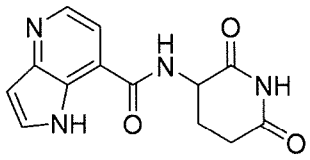
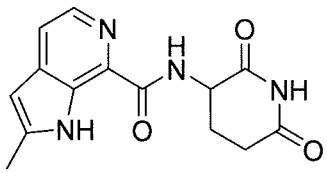
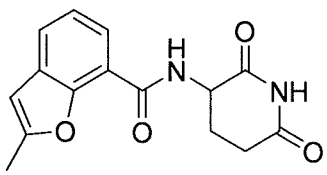
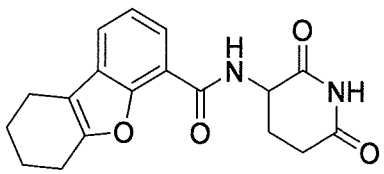
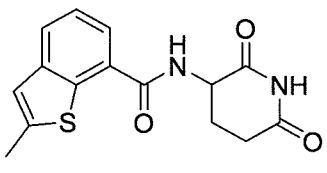
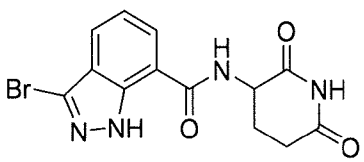
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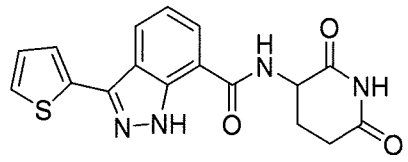
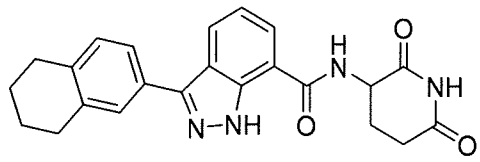
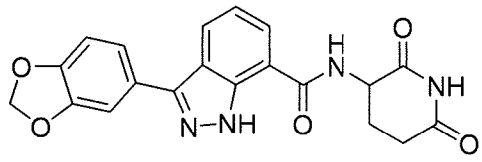
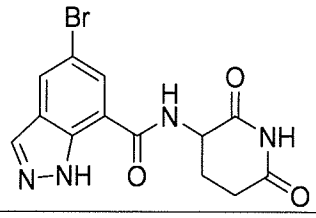
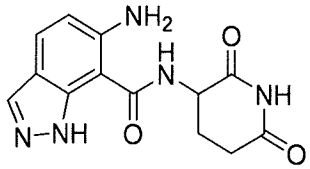
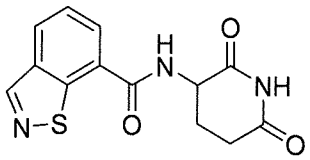
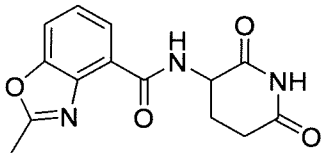
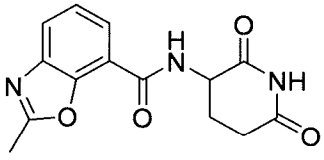
Compound number	Structure
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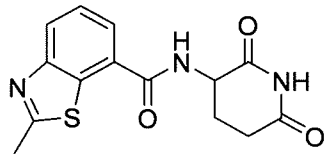
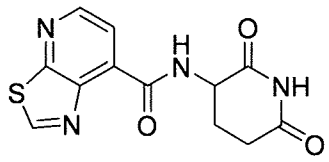
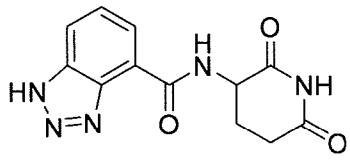
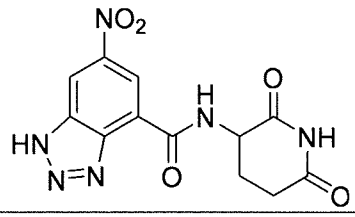
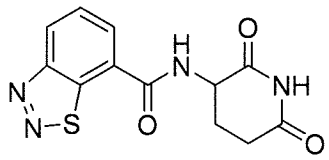
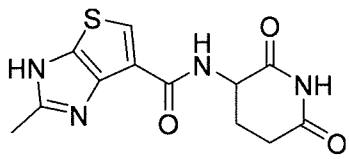
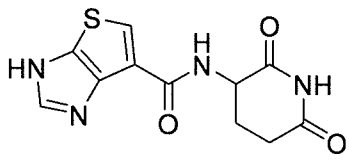
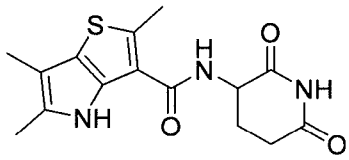
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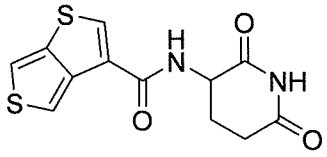
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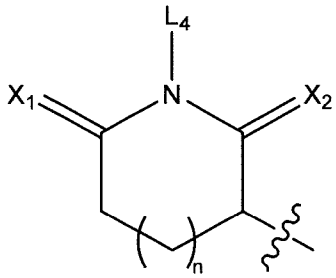
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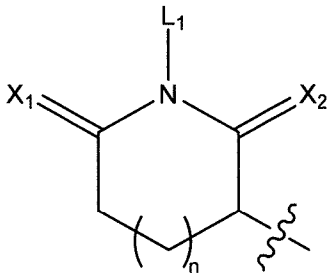
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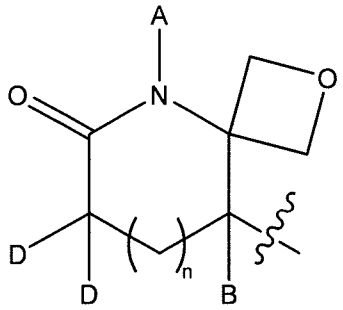
In some embodiments of Formula (II) and Formula (III), the

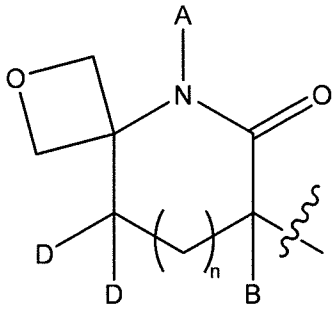


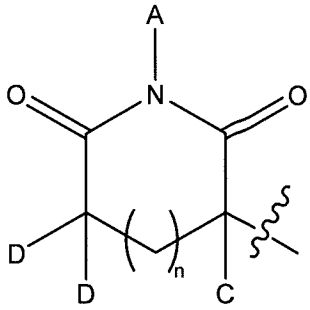
and



moieties may be replaced with one of the following moieties:







wherein

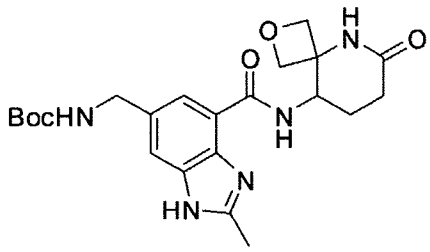
A is , hydrogen, alkyl, alkenyl, benzyl, aryl, heteroaryl, haloalkyl, haloalkenyl, $-CH_2OC(O)^tBu$, $-CH_2C(O)OR^{27}$, $-C(O)R^{27}$, $-C(O)OR^{27}$, $-C(O)NH_2$, $-C(O)NHR^{27}$, $-C(O)NR^{27}_2$, $-OR^{27}$, $-NR^{27}_2$, $-S(O)_2R^{27}$ or $P(O)(OR^{27})(OR^{27})$, wherein each R^{27} is independently hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, aryl, heteroaryl, or benzyl,

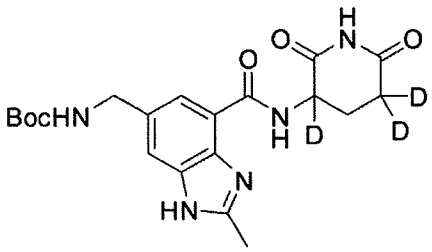
B is hydrogen, deuterium or alkyl,

C is hydrogen, deuterium or alkyl,

each D is independently deuterium or hydrogen,

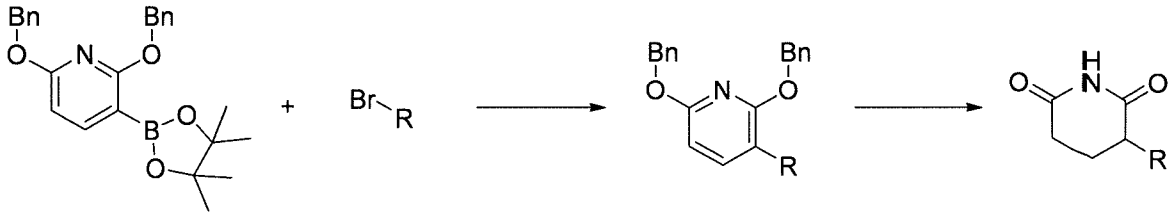
as shown, for example, in the compounds below:





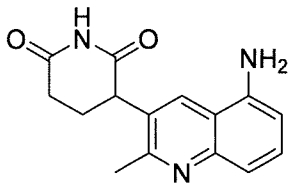
Ligase ligand moieties of Formula (IV)

The synthesis of the ligase ligand moieties of Formula (IV) (as defined above) can be summarized as follows:



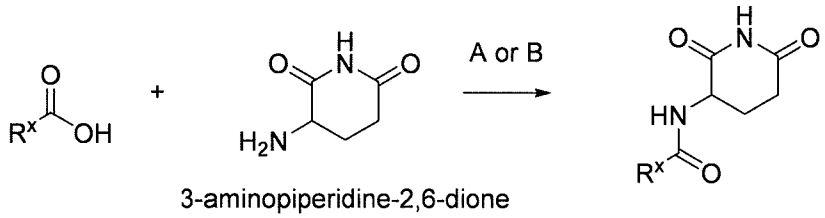
Example ligase ligand moieties of Formula (IV) are shown in Table 3 below. Compound 65 could be modified to allow attachment to the [linker] (e.g. by nucleophilic aromatic substitution; or by exchange of fluorine for bromine followed by attachment - by palladium coupling – of either the [linker] itself, or of a functional group to which the [linker] could be attached).

Table 3:

Compound number	Structure
63	
64	
65	

Ligase ligand moieties of Formula (Va) and Formula (Vb), and Formula (IIa) and Formula (IIb)

The synthesis of the ligase ligand moieties of Formulae (Va), (Vb), (IIa) and (IIb) (as defined above) can be summarized in the following general procedure (carried out under Synthetic Conditions D, E, F or G, as set out below:



Reaction Scheme 2: General procedure

Synthetic Conditions D

An appropriate acid (R^xCOOH in the above reaction scheme) (1.1 eq), DMAP (0.04 eq), and EDC (1.2 eq) were added to a solution of 3-aminopiperidine-2,6-dione (1 eq) and *N*-hydroxybenzotriazole (1.2 eq) in DMF (0.5 M). The reaction mixture was stirred overnight at room temperature (20-25°C). Water (2 x DMF volume) was added and the obtained solution was extracted with dichloromethane (3 × DMF volume). The combined organic layers were washed with water, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by preparative HPLC or by column chromatography.

Synthetic Conditions E

An appropriate acid R^xCOOH in the above reaction scheme) (1 eq) and EDC (1.2 eq) were added to a solution of 3-aminopiperidine-2,6-dione (hydrochloride salt, 1.1 eq), triethylamine (1.2 eq) and *N*-hydroxybenzotriazole (1.2 eq) in DMA (0.5 M). The reaction mixture was stirred overnight at rt. Water (2 x DMA volume) was added and obtained mixture was extracted with dichloromethane (3 × DMA volume). The combined organic layers were washed with water, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was isolated by preparative HPLC or by column chromatography.

Synthetic Conditions F

To a solution of appropriate acid (R^xCOOH in the above reaction scheme) (1 eq) and HATU (1.5 eq) in dry DMF were added 3-aminopiperidine-2,6-dione (hydrochloride salt, 1.2 eq) and DIPEA (3 eq). The reaction mixture was stirred overnight at rt. The crude product was purified by preparative HPLC or/and by preparative TLC.

Synthetic Conditions G

To a solution of appropriate acid (R^xCOOH in the above reaction scheme) (1 eq) 3-aminopiperidine-2,6-dione (hydrochloride salt, 1.2 eq) and DMAP (0.1 eq.) in an inert atmosphere in dry DMF were added DIPEA (2.2 eq.) and HATU (1.5 eq) in dry DMF. The reaction mixture was stirred overnight at rt. The crude product was purified by preparative HPLC or/and by preparative TLC.

Example method 1: formation of chlorinated R^x group of R^xCOOH (or its ester R^xCOOR^y)

NCS (1.1 eq) was added to a solution of an appropriate starting material (1 eq) in DMF (0.5 M) and the reaction mixture was stirred for 2 h at room temperature (20-25°C). The reaction mixture was poured into water (2 x DMF volume) and occurred precipitate was filtered. The solids were washed with water and dried in vacuum to give the acid, ROOH.

Example method 2: synthesis of R^xCOOH from corresponding ester R^xCOOR^y)

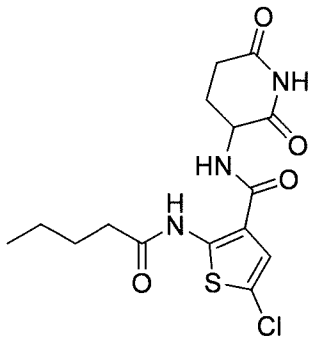
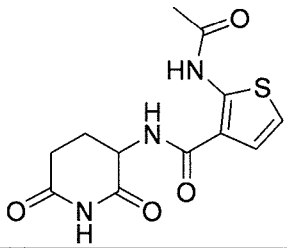
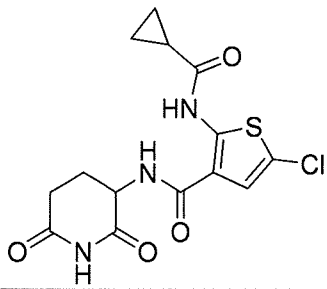
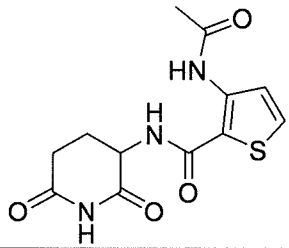
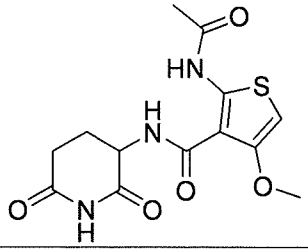
LiOH (1.1 eq) was added to a solution of an appropriate ester (1 eq) in THF:water mixture (3:1 or 5:1, 85 mM) and the resulting mixture was stirred overnight at room temperature (20-25°C). The mixture was concentrated under reduced pressure, diluted with water, and acidified with concentrated HCl to pH=2-3. The precipitate was filtered, washed with water, and dried in vacuum to give the target carboxylic acid.

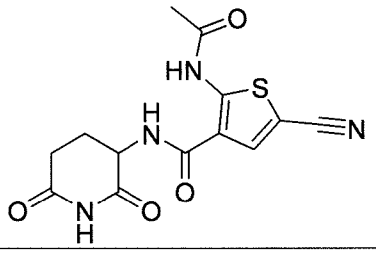
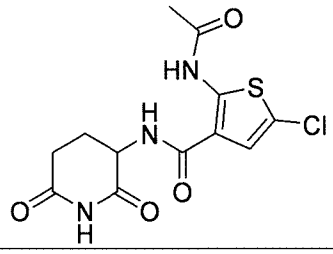
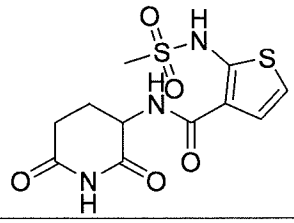
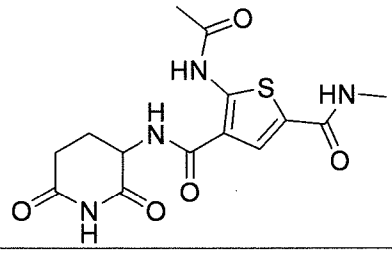
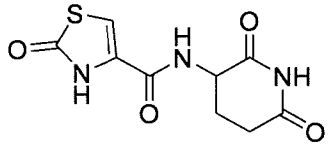
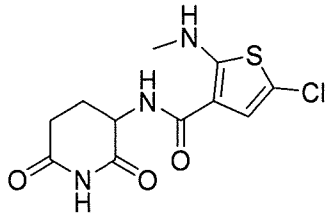
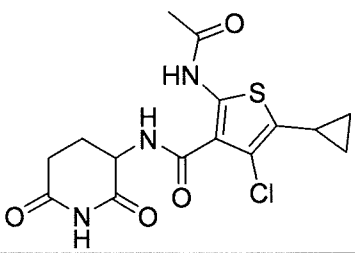
Example method 3: formation of acetylated R^x group of R^xCOOR^y

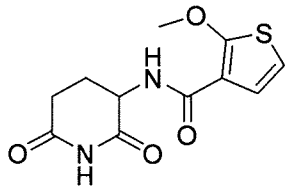
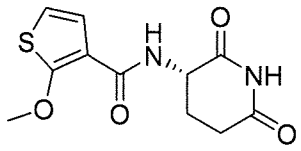
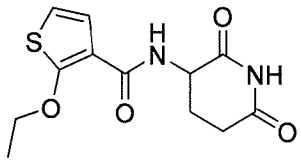
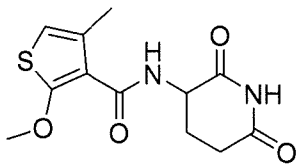
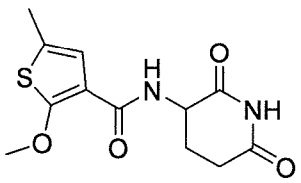
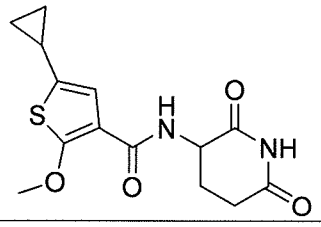
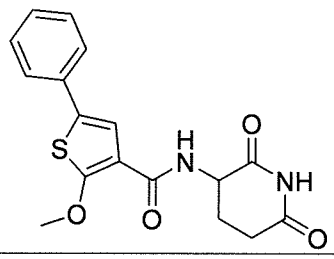
A mixture of an appropriate amine (1 eq.), Ac_2O (3 eq.), and DMAP (0.2 eq.) in dioxane (0.2 M) was heated to 80°C for 2 h. Upon completion, the mixture was cooled down to room temperature (20-25°C) and concentrated under reduced pressure. The residue was diluted with water (1 x dioxane volume) and extracted with EtOAc (3 x dioxane volume). The organic layers were washed with water, brine, dried over Na_2SO_4, and evaporated to dryness to afford an acylated product typically used without further purification.

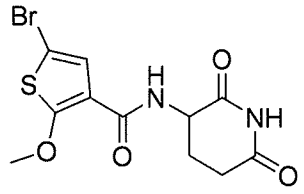
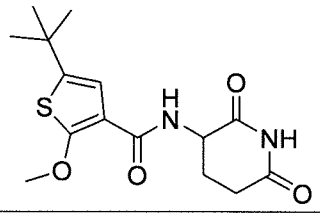
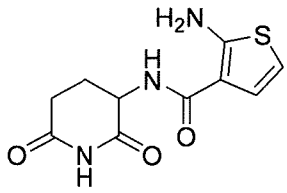
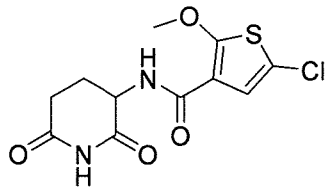
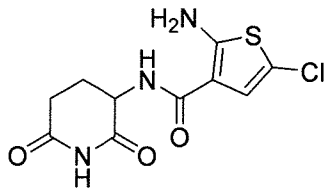
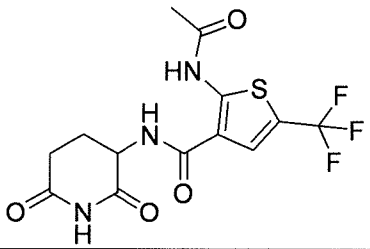
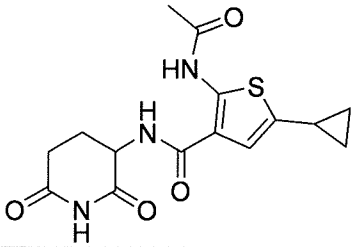
Example ligase ligand moieties of Formula (Va) and Formula (Vb) are shown in Table 4 below. Compounds 66-74, 77-86, 88, 90-92, 96, 97 and 100 could be modified to allow attachment to the [linker] (e.g. by C-H bond activation).

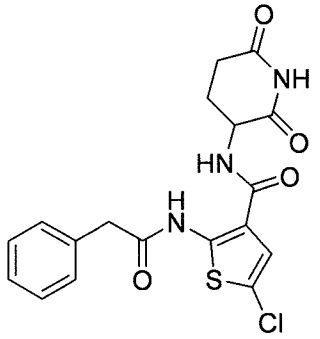
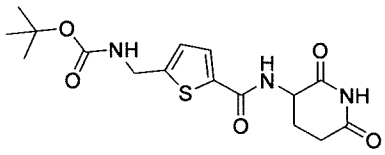
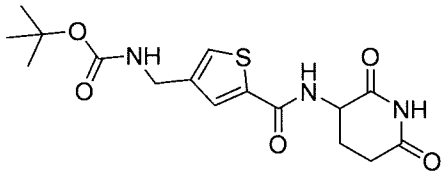
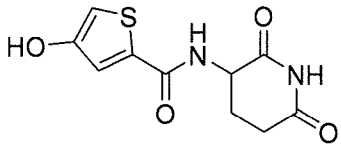
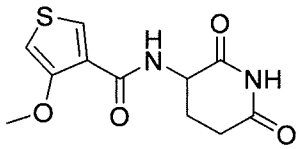
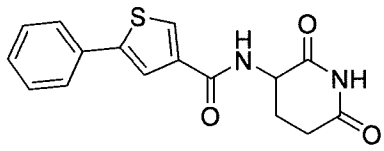
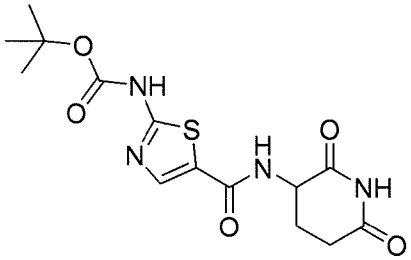
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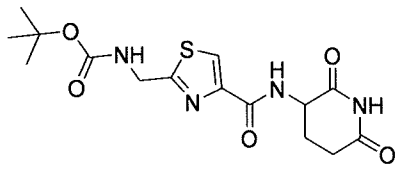
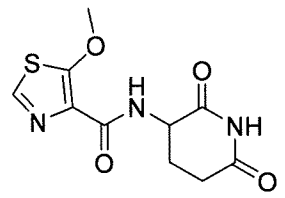
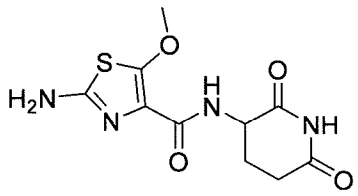
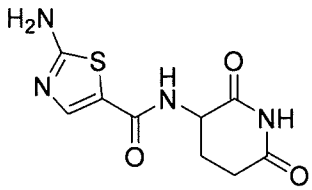
Compound number	Structure
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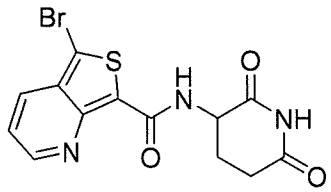
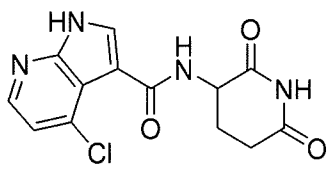
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89	
90	
91	

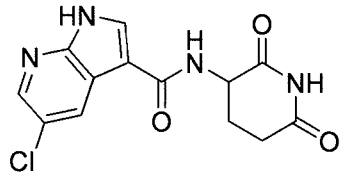
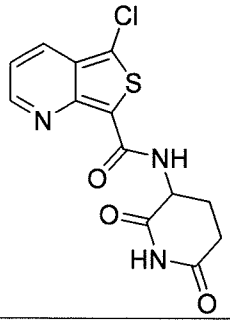
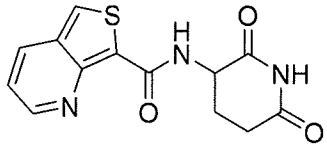
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101	
102	

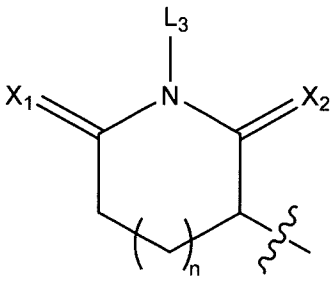
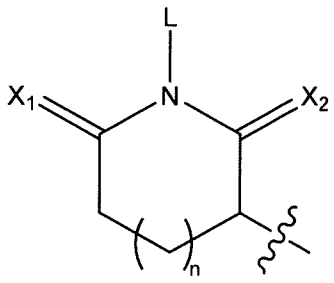
Example ligase ligand moieties of Formula (IIa) and Formula (IIb) are shown in Table 5 below. Compounds 103, 106 and 107 could be modified to allow attachment to the [linker] (e.g. by C-H bond activation).

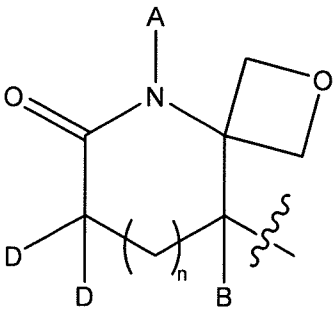
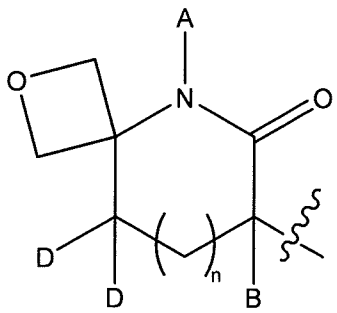
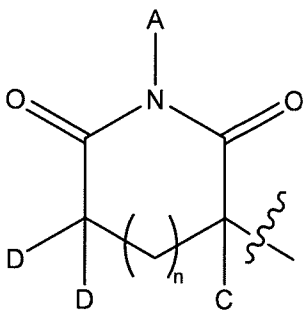
Table 5:

Compound number	**Structure**
103	
104	

105	
106	
107	

In some embodiments of Formulas (Va), (Vb), (IIa) and (IIb) the

 and  moieties may be replaced with one of the following moieties:

wherein

A is , hydrogen, alkyl, alkenyl, benzyl, aryl, heteroaryl, haloalkyl, haloalkenyl, $-CH_2OC(O)^tBu$, $-CH_2C(O)OR^{27}$, $-C(O)R^{27}$, $-C(O)OR^{27}$, $-C(O)NH_2$, $-C(O)NHR^{27}$, $-C(O)NR^{27}_2$, $-OR^{27}$, $-NR^{27}_2$, $-S(O)_2R^{27}$ or

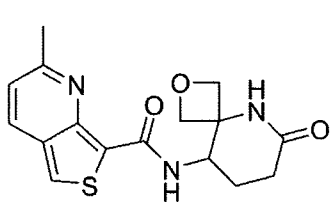
$P(O)(OR^{27})(OR^{27})$, wherein each R^{27} is independently hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, aryl, heteroaryl, or benzyl,

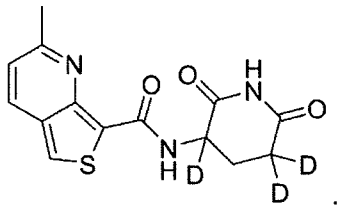
B is hydrogen, deuterium or alkyl,

C is hydrogen, deuterium or alkyl,

each D is independently deuterium or hydrogen,

as shown, for example, in the compounds below:





LINKERS

In the compounds of the present invention, the **[linker]** has the formula $\mathbf{R^{14}\text{-}R^{15}\text{-}R^{16}\text{-}R^{17}\text{-}R^{18}}$ wherein

$\mathbf{R^{14}}$ is $-C_{1\text{-}6}$ alkyl, $-C_{2\text{-}6}$ alkenyl, $-C_{2\text{-}6}$ alkynyl, -C(O)-, $-SO_2-$ or is absent

$\mathbf{R^{15}}$ is cycloalkyl, heterocycloalkyl, aryl, heteroaryl, $-C_{1\text{-}6}$ alkyl-NH-, -cycloalkyl-NH- or is absent

$\mathbf{R^{16}}$ is $-C_{1\text{-}6}$ alkyl, -C(O)-, -C(O)-NH-, -C(O)O-, $-CH_2$-C(O)-, $-CH_2$-C(O)-NH-, $-CH_2$-C(O)O- or is absent

$\mathbf{R^{17}}$ is $-CH_2(C_2H_4\text{-}O)_y$, $(C_2H_4\text{-}O)_x$, $(C_3H_6\text{-}O)_x$, or is absent

x is 1-10

y is 2-10

$\mathbf{R^{18}}$ is $-C_{1\text{-}6}$ alkyl, heterocycloalkyl, or is absent

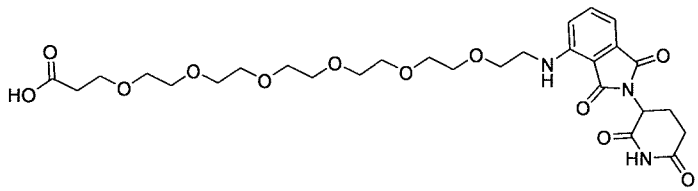
wherein at least one of R^{14}-R^{18} is present.

Linkers as used in the compounds of the present invention may be synthesized according to standard methods.

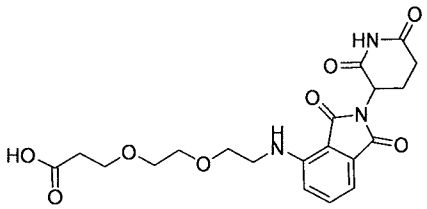
Most of the alkyl and polyethylene glycol (PEG) linkers were commercially available, or prepared due to procedures described in literature.

Examples of commercially available linkers include:

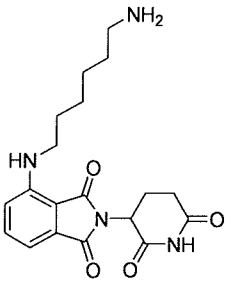
(2225148-49-0 Sigma Aldrich)



(2140807-17-4 Sigma Aldrich)

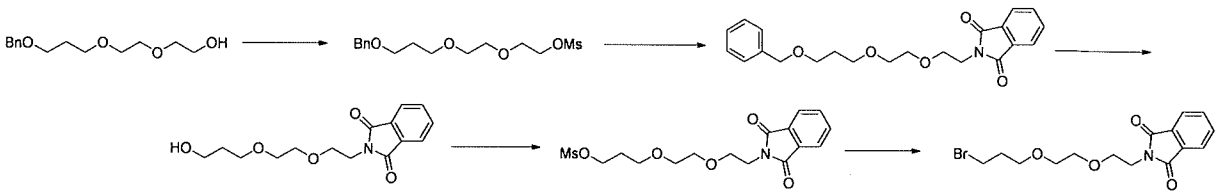


(2375194-37-7 Sigma Aldrich)

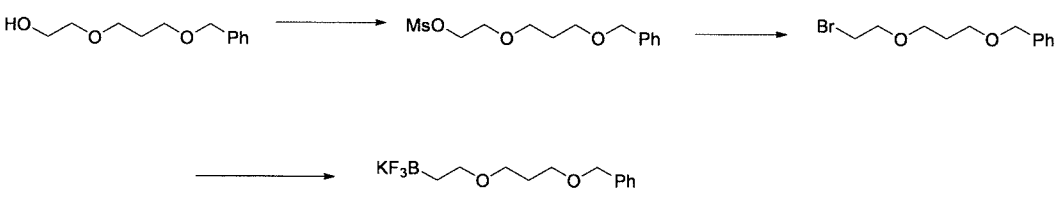


Synthesis of linkers which are not commercially available are described in the examples, e.g.:

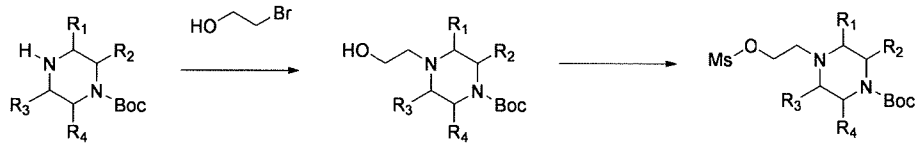
In the synthesis of 227:



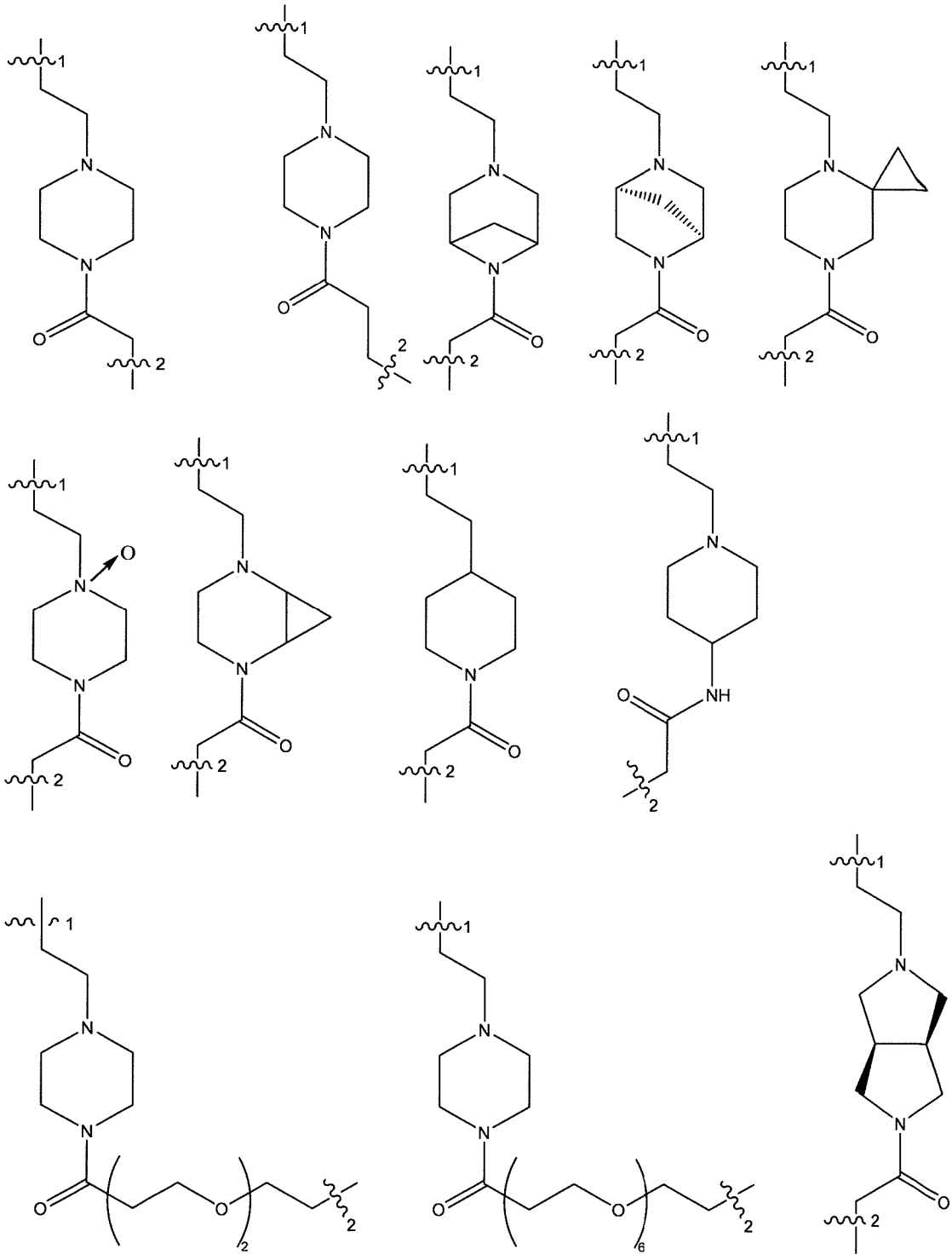
In the synthesis of 239:

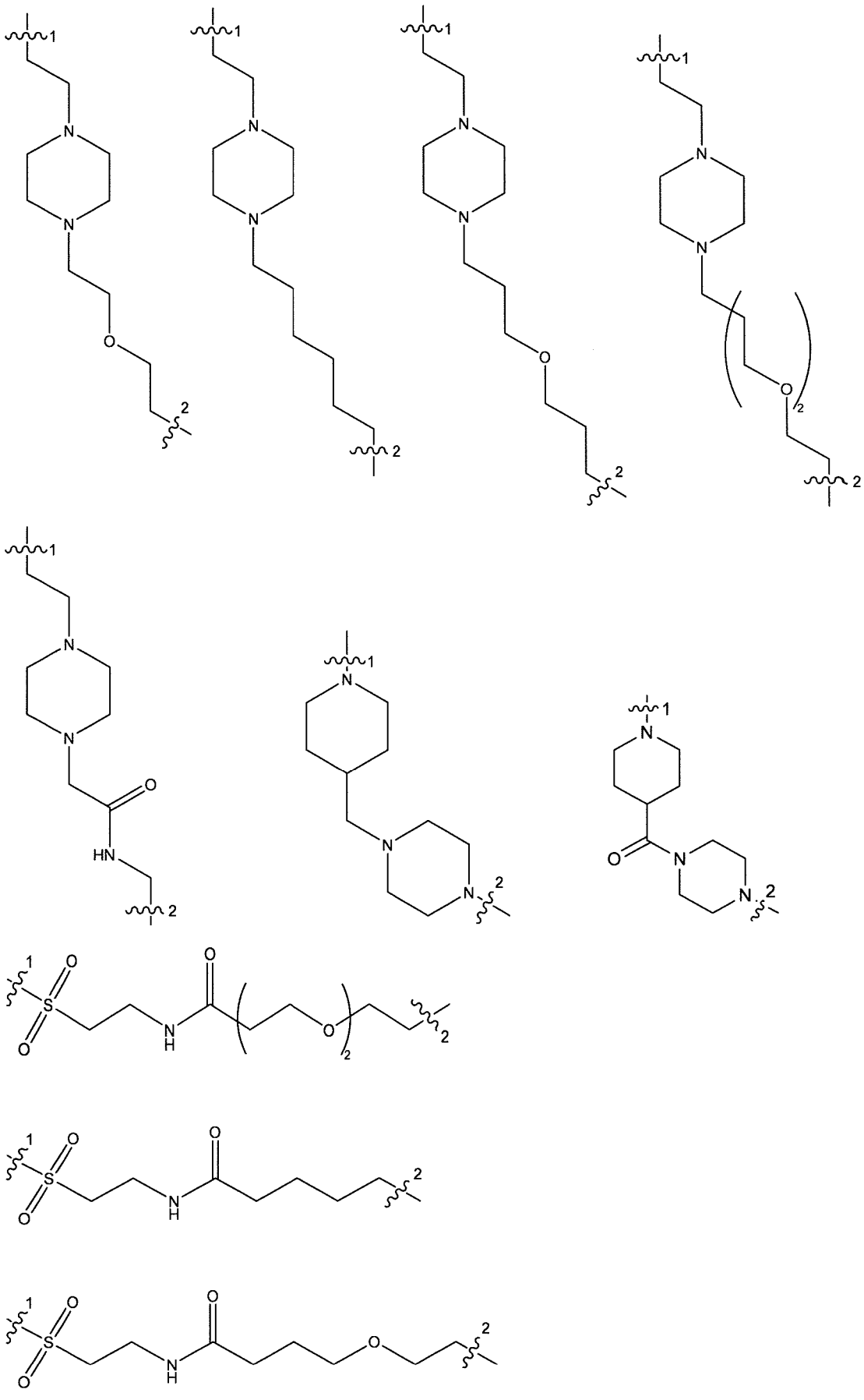


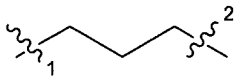
Linkers containing modifications of piperazine were prepared according to the following scheme:

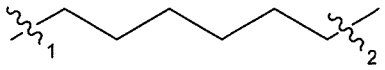


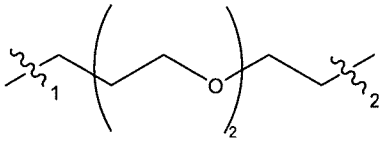
Examples of linkers which can be used in the compounds of the present invention include:

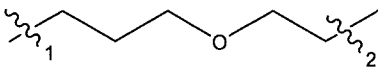


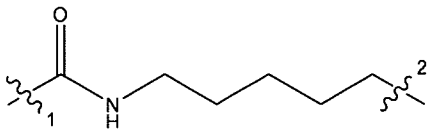


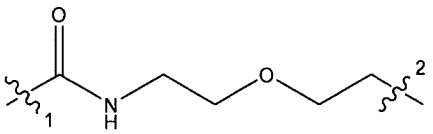


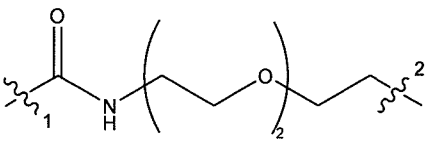




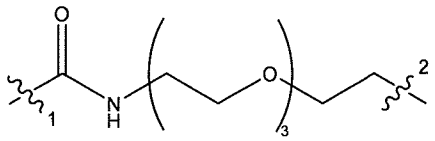








and



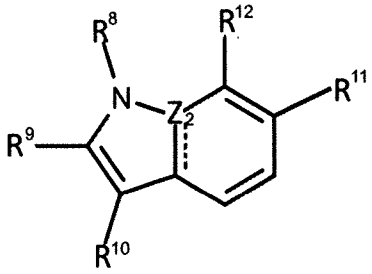
wherein


indicates attachment to **[MCL-1 ligand moiety]** and

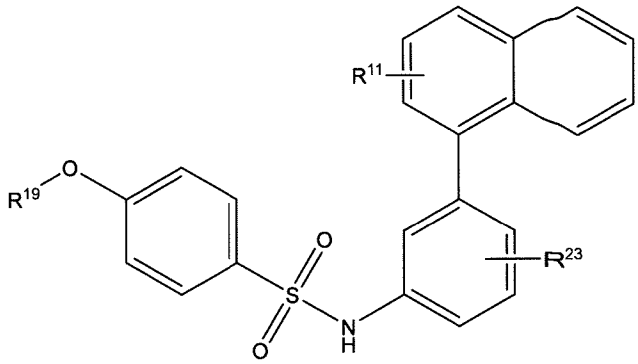

indicates attachment to **[ligase ligand moiety].**

MCL-1 LIGAND MOIETIES

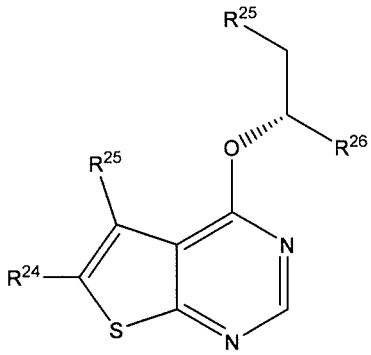
In the compounds of the present invention, the **[MCL-1 ligand moiety]** is a compound of Formula (A), Formula (B) or Formula (C)



(A)



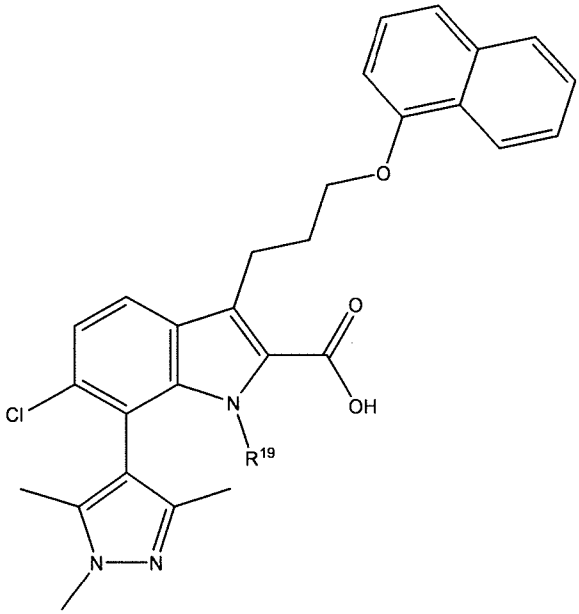
(B)

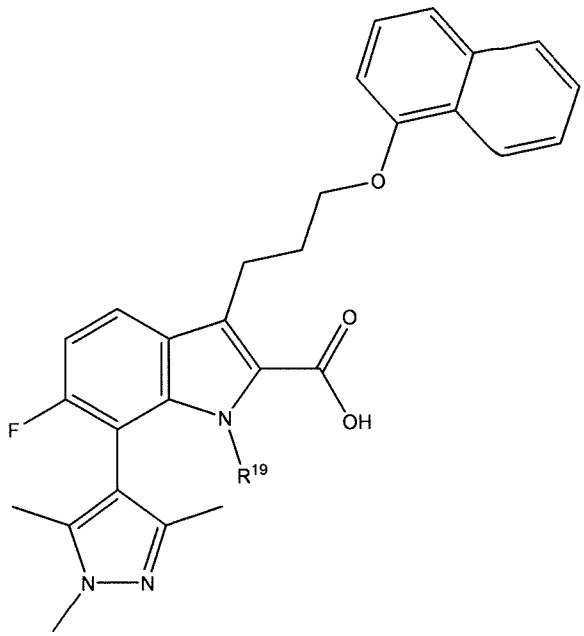


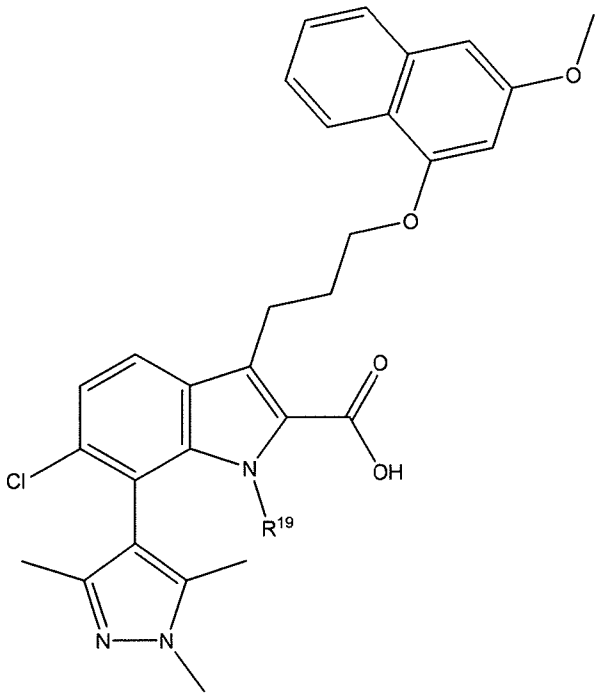
(C)

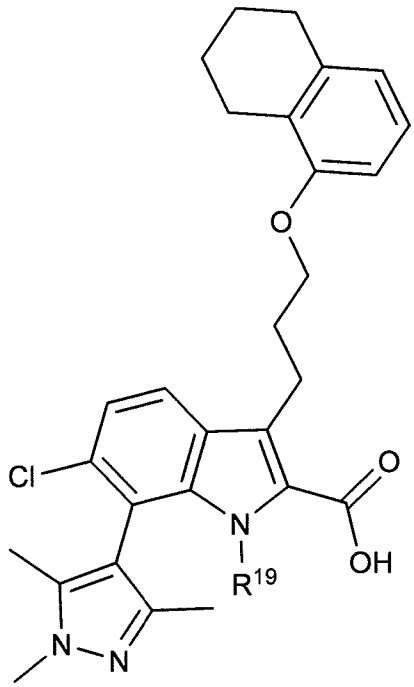
as described above.

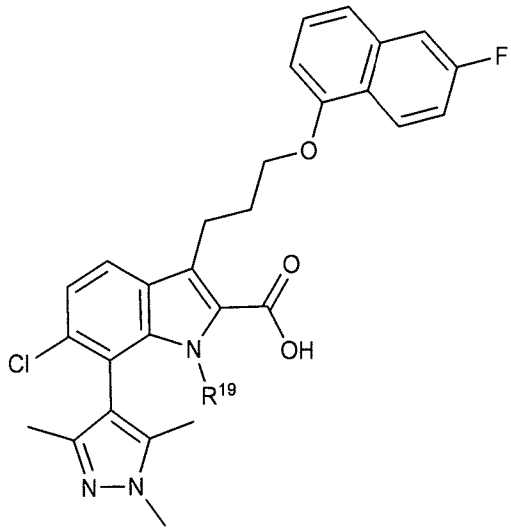
Examples of MCL-1 ligand moieties which may be used in the compounds of the present invention include:

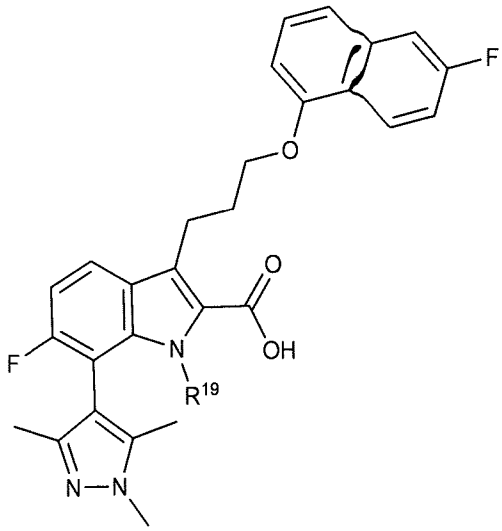

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OH
N
R19
N
N

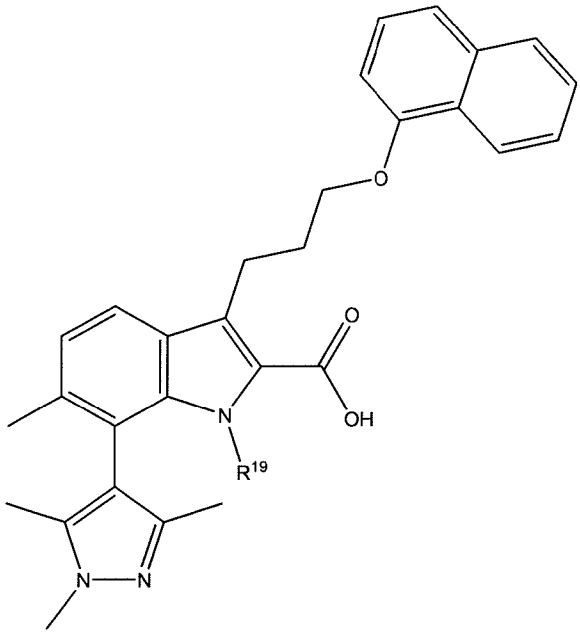

F
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O
OH
N
R19
N
N

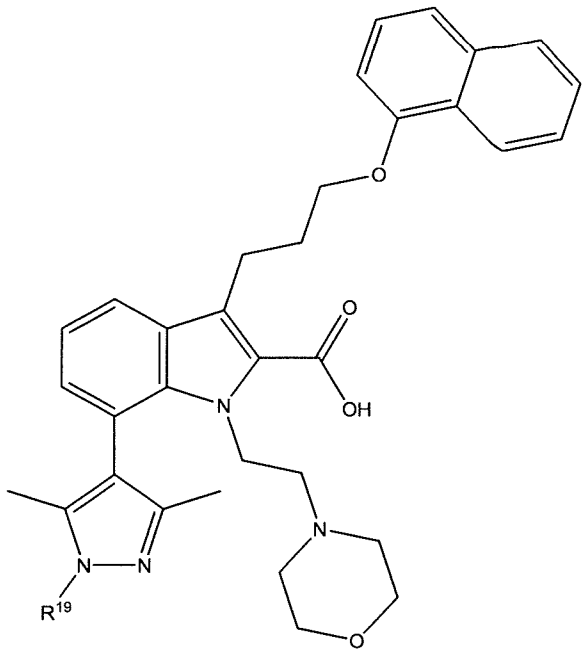

Cl
O
O
O
OH
N
R19
N
N

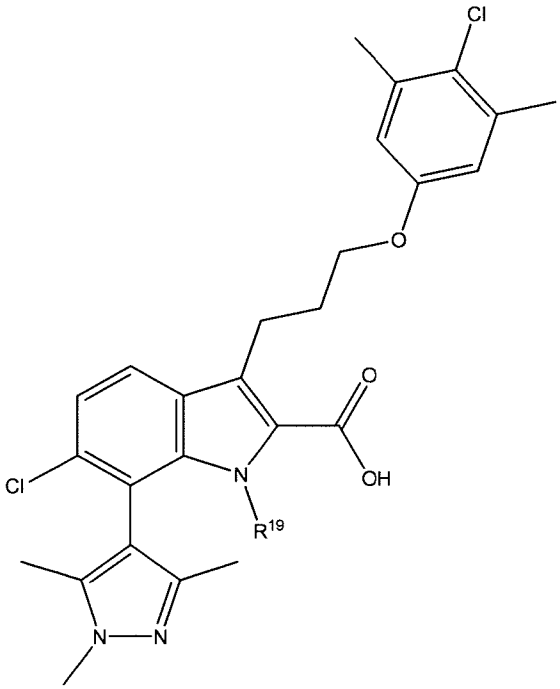

Cl
O
O
OH
N
R19
N
N

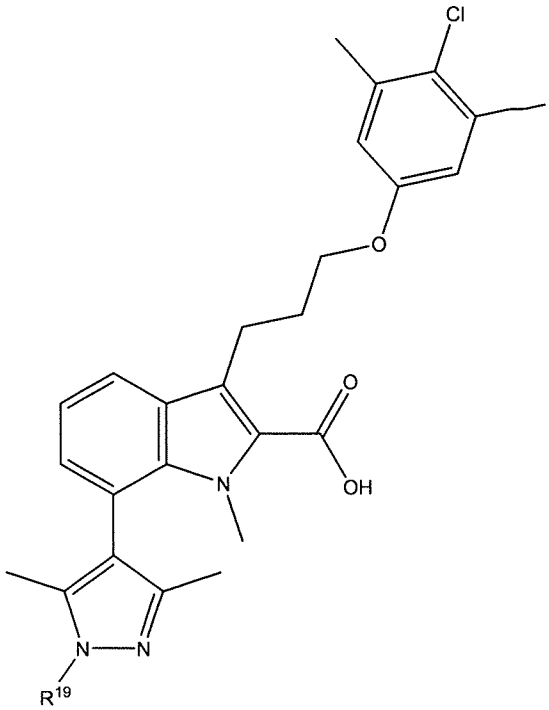

F
O
O
OH
Cl
N
R19
N
N

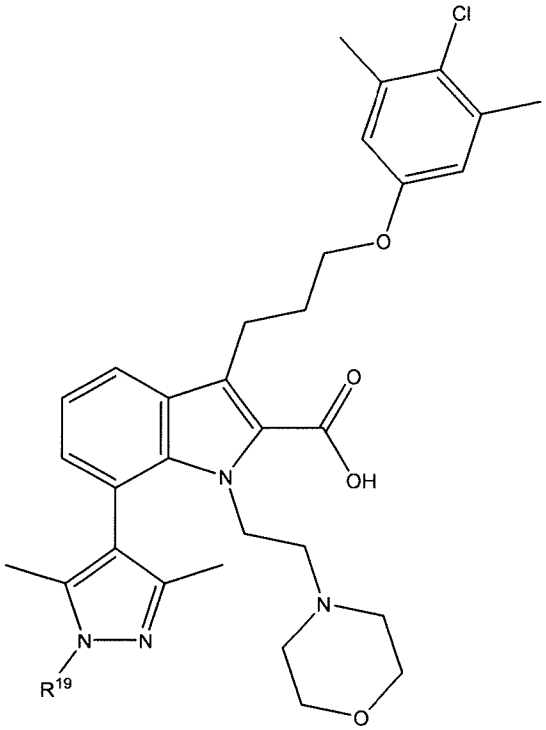

F
O
O
OH
F
N
R19
N
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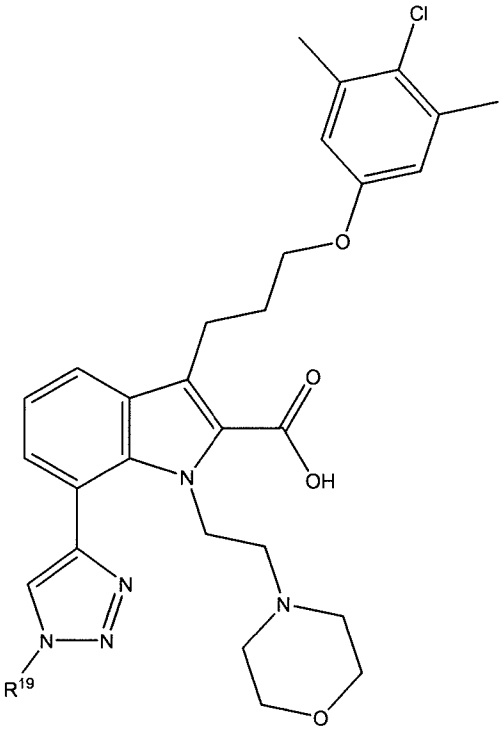

O
O
OH
N
R19
N
N

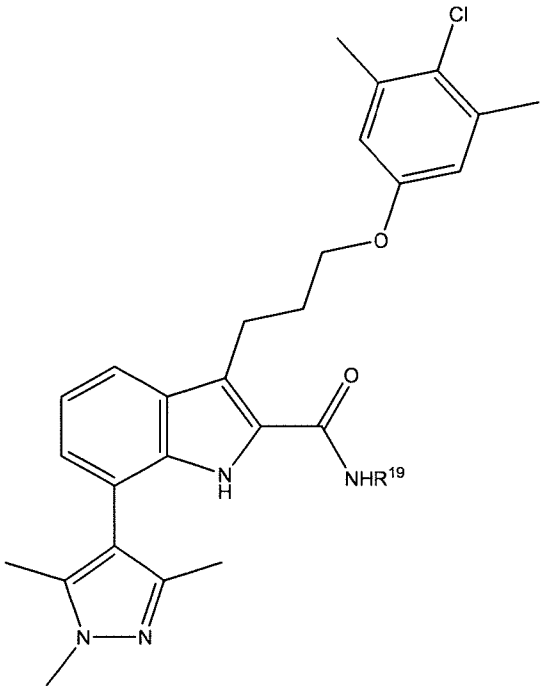

O
O
OH
N
N
N
R19
N
O

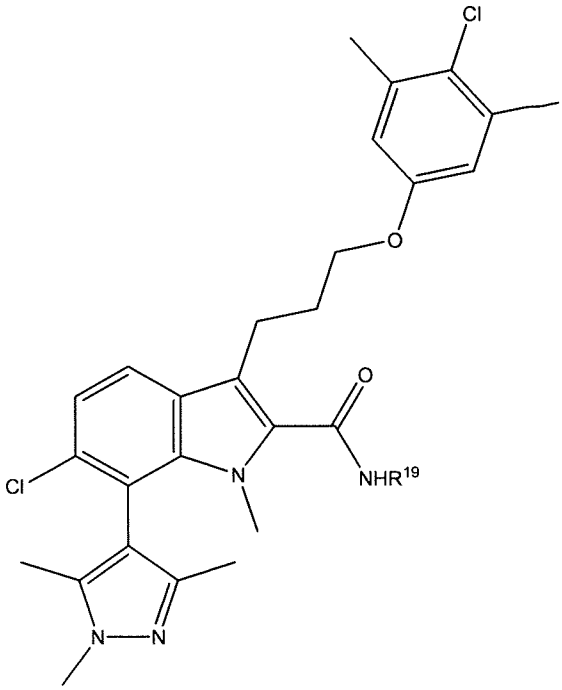


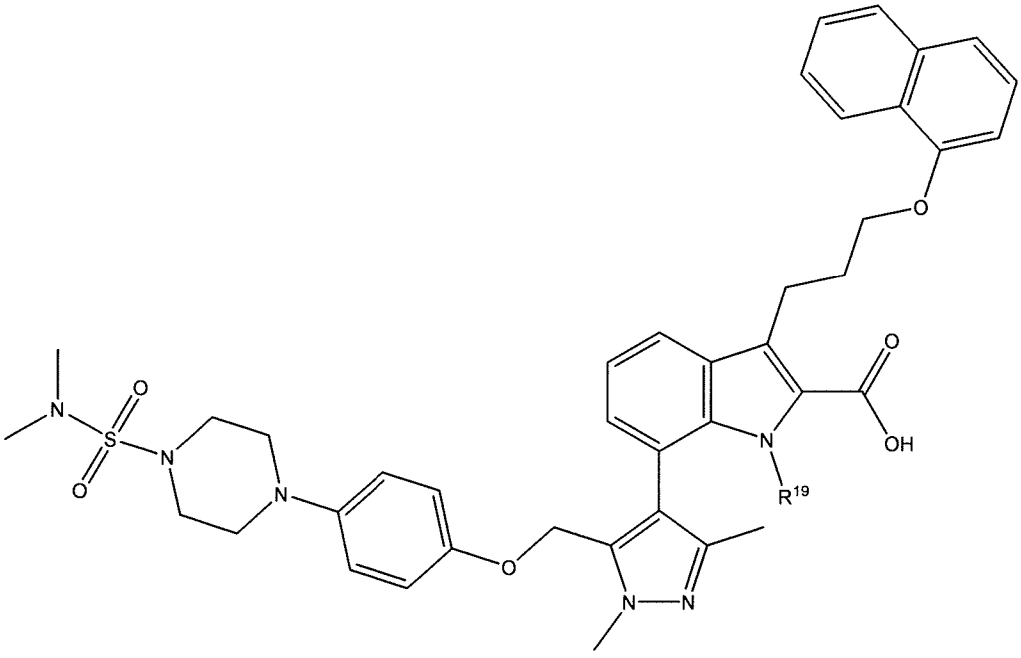


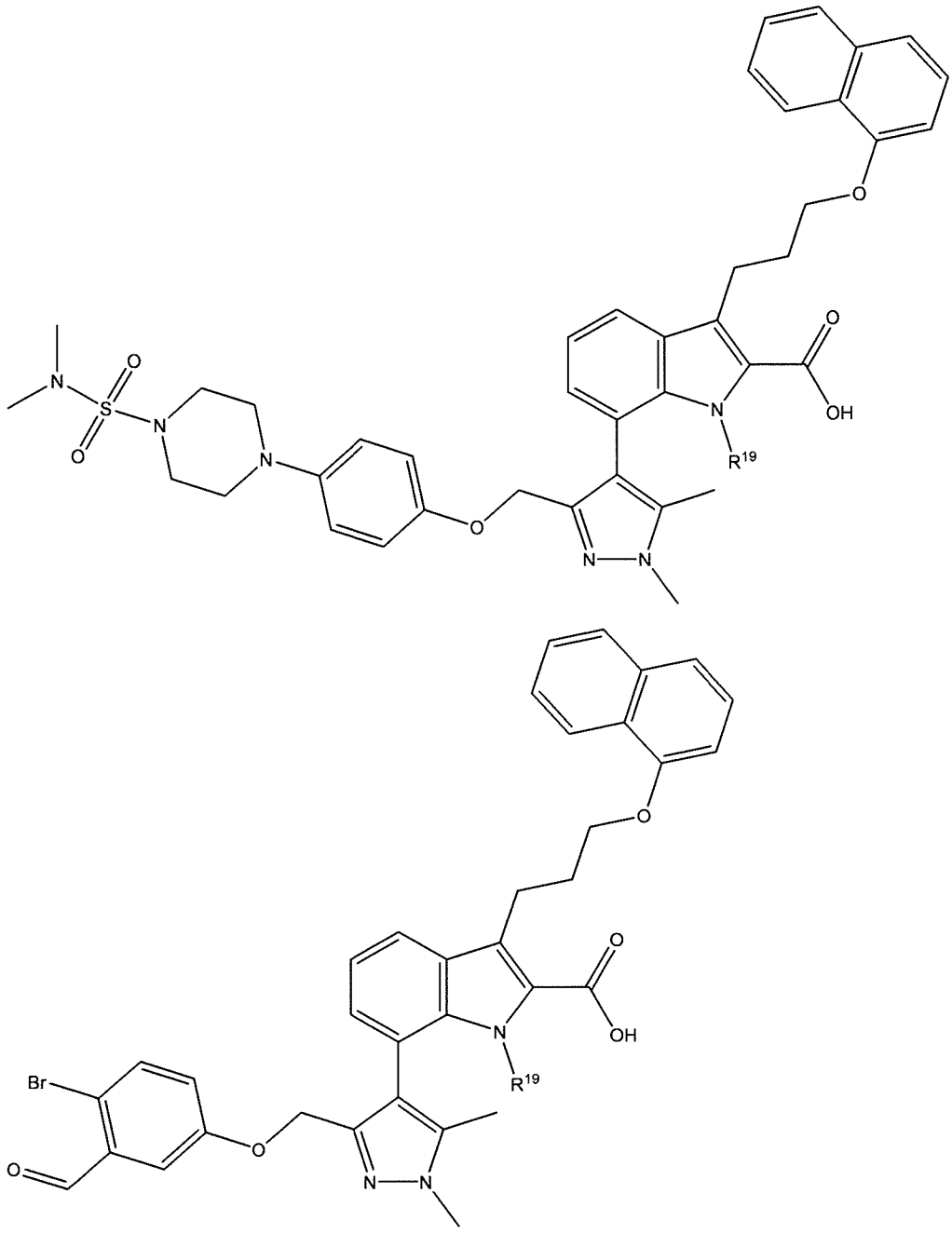


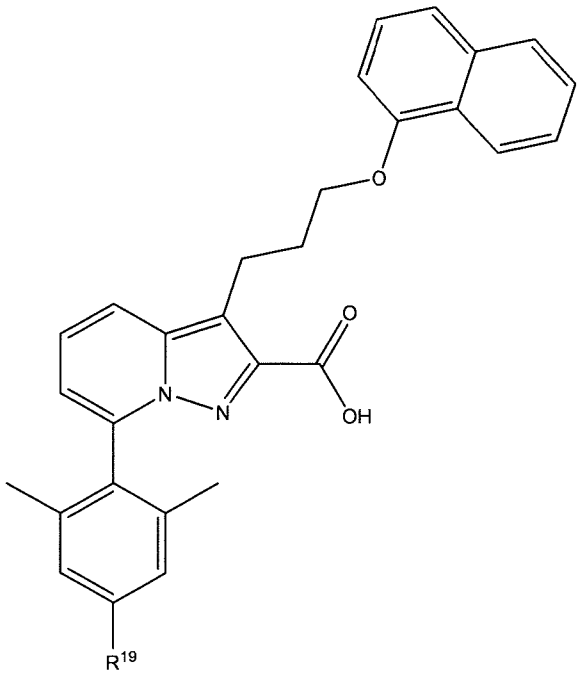


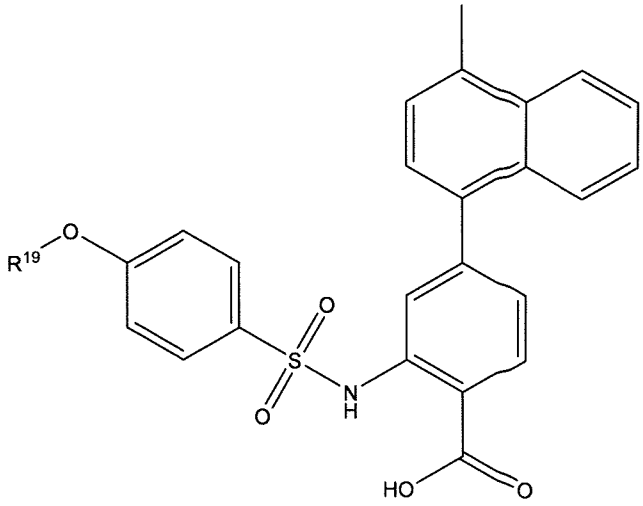


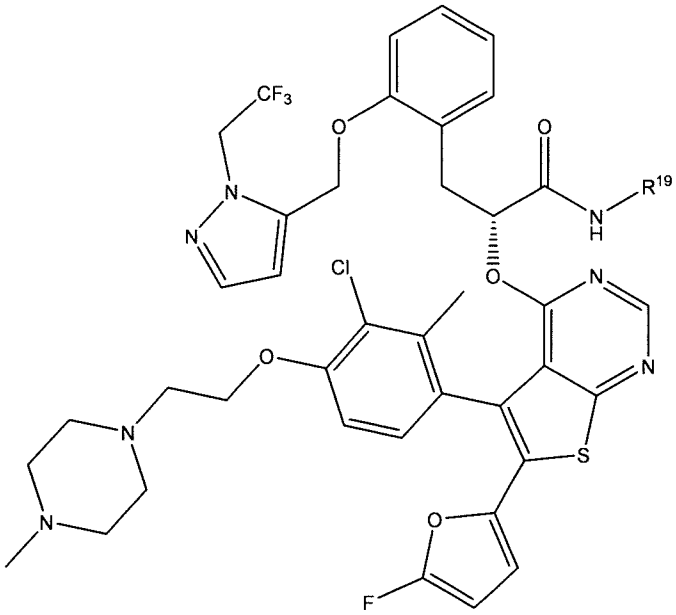




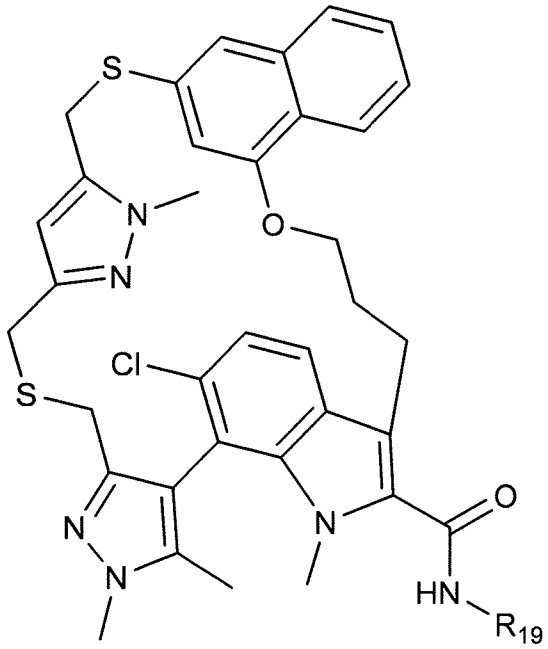








and

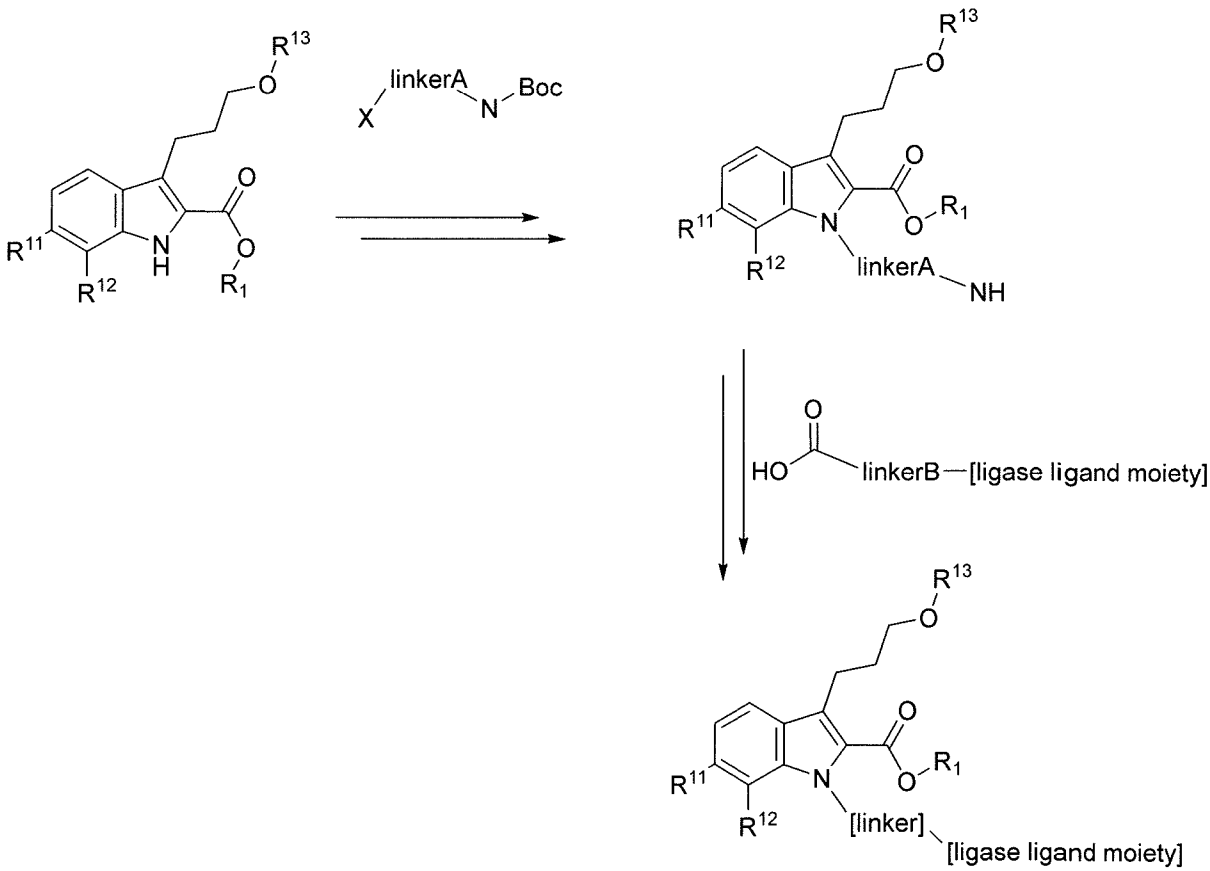

S
N
N
O
Cl
S
N
N
N
O
HN
R19

EXAMPLES

There are a number of ways in which the bifunctional compounds **[MCL-1 ligand moiety]-[linker]-[ligase ligand moiety]** of the present application may be synthesized:

1. [Mcl-1 ligand moiety] is coupled with linkerA, followed by coupling with [ligase ligand moiety]-linkerB

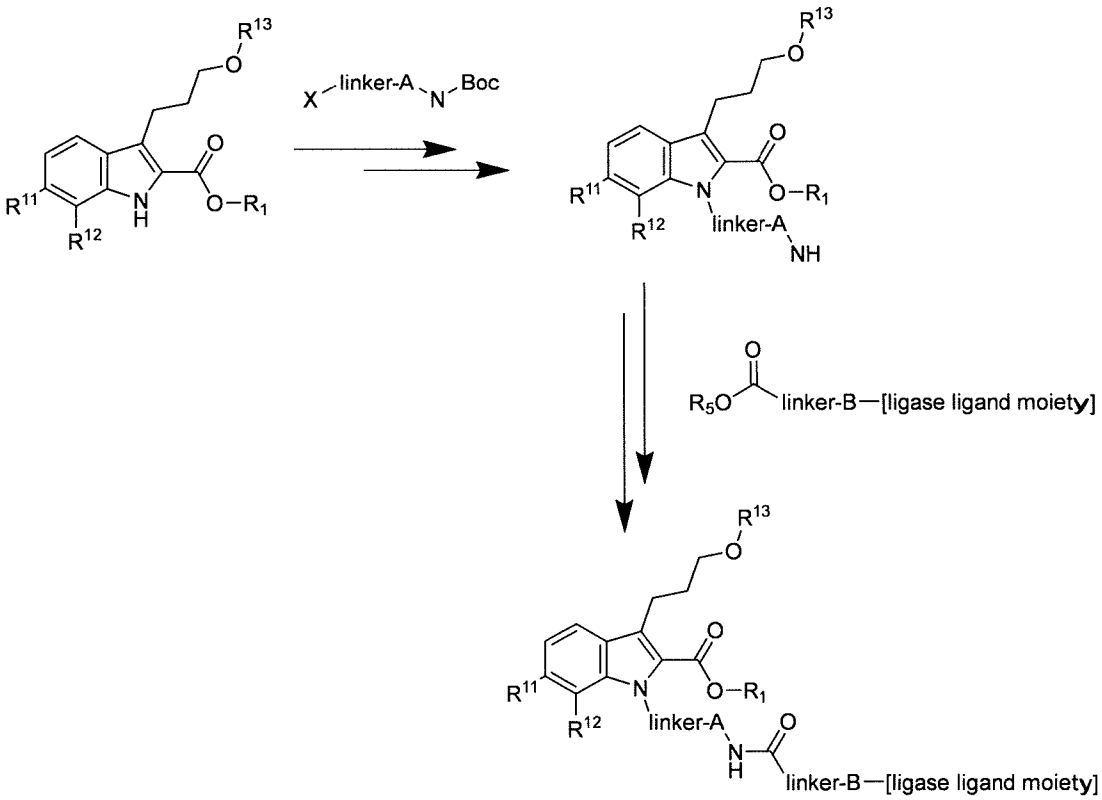
[Mcl-1 ligand moiety]-linkerA + **[ligase ligand moiety]**-linkerB



wherein R_1 is -H, -C_1-C_6alkyl, or -NH_2; X is halogen or OMs, OTs; linkerA-N-Boc corresponds to linkerA terminating with a Boc-protected primary or secondary amine; linkerA-NH corresponds to linkerA terminating with a primary or secondary amine; and R^{11}-R^{13} and [linker] are as defined herein; wherein [linker] is formed in the above synthesis by the reaction of -linkerA-NHR^w with -linkerB-COOH.

Examples of this method are set out below:

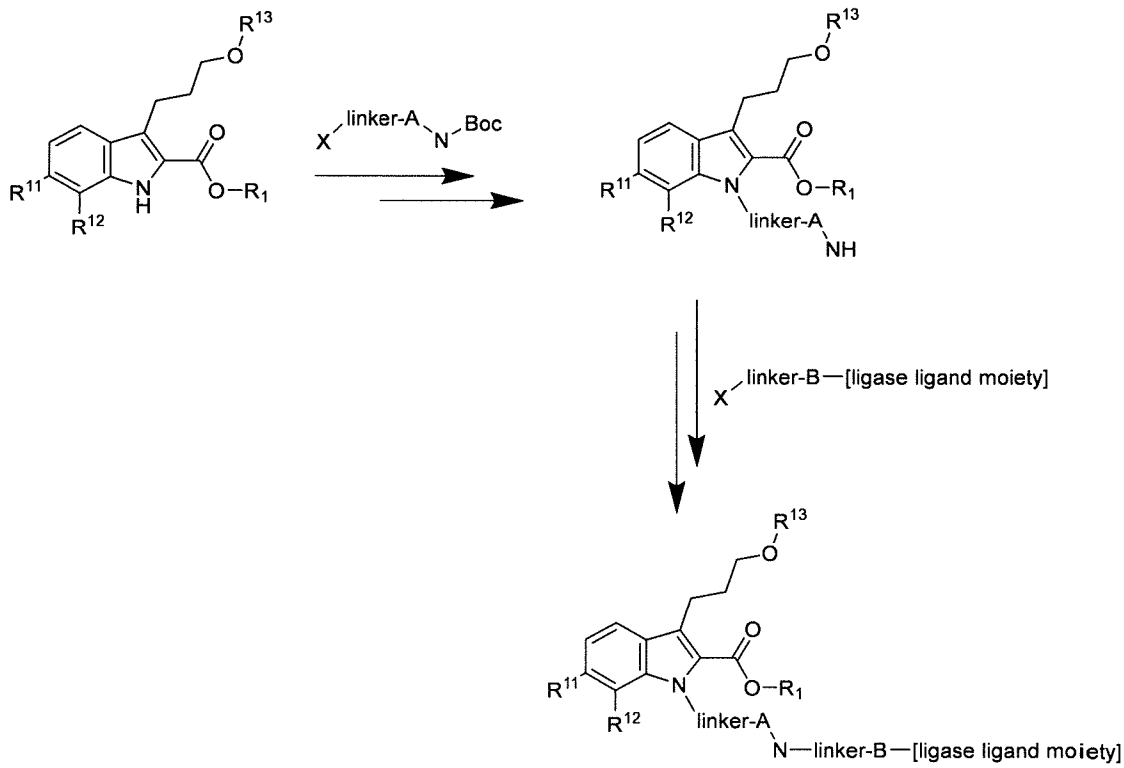
*(a) attachment of linker via R^8 of **[MCL-1 ligand moiety]**, and coupling of linkerA and linkerB via an amide bond:*



wherein R_1 is -H, -C_1-C_6alkyl, or -NH_2; X is halogen or OMs, OTs; linkerA-N-Boc corresponds to linkerA terminating with a Boc-protected primary or secondary amine; linkerA-NH corresponds to linkerA terminating with a primary or secondary amine; R_5 is succinimidyl or pentafluorophenyl; and R^{11}-R^{13} are as defined herein; and wherein linkerA-NHC(O)-linkerB corresponds to **[linker]**.

This method was used for the synthesis of 201, 203, 204, 205, 206, 207, 211, 208, 210, 209, 214, 216, 213, 215, 217, 233, 241, 245, 248, 249 and 251, below.

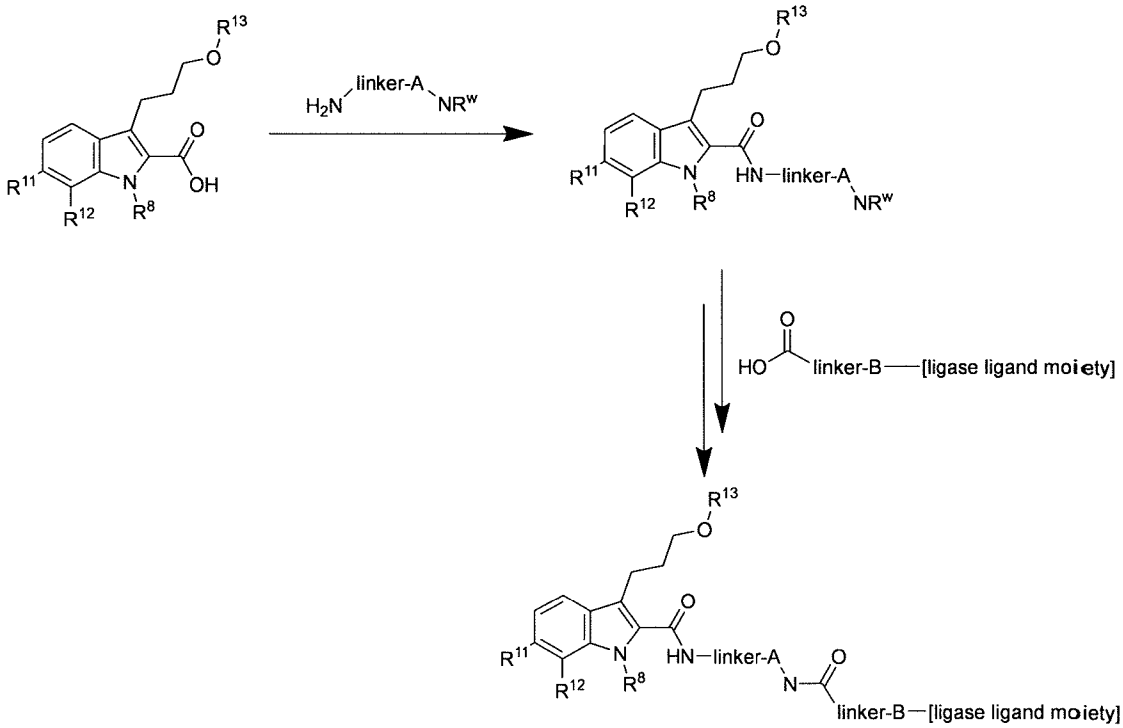
*(b) attachment of linker via R^8 of **[MCL-1 ligand moiety]**, and coupling of linkerA and linkerB by alkylation or reductive amination*



wherein R_1 is -H, -C_1-C_6alkyl, or -NH_2; X is halogen or OMs, OTs; linkerA-N-Boc corresponds to linkerA terminating with a Boc-protected primary or secondary amine; linkerA-NH corresponds to linkerA terminating with a primary or secondary amine; and R^{11}-R^{13} are as defined herein; and wherein linkerA-N-linkerB corresponds to **[linker]**.

This method was used for the synthesis of 202, 233, 234, 235, 236, 237, 240 and 246, below.

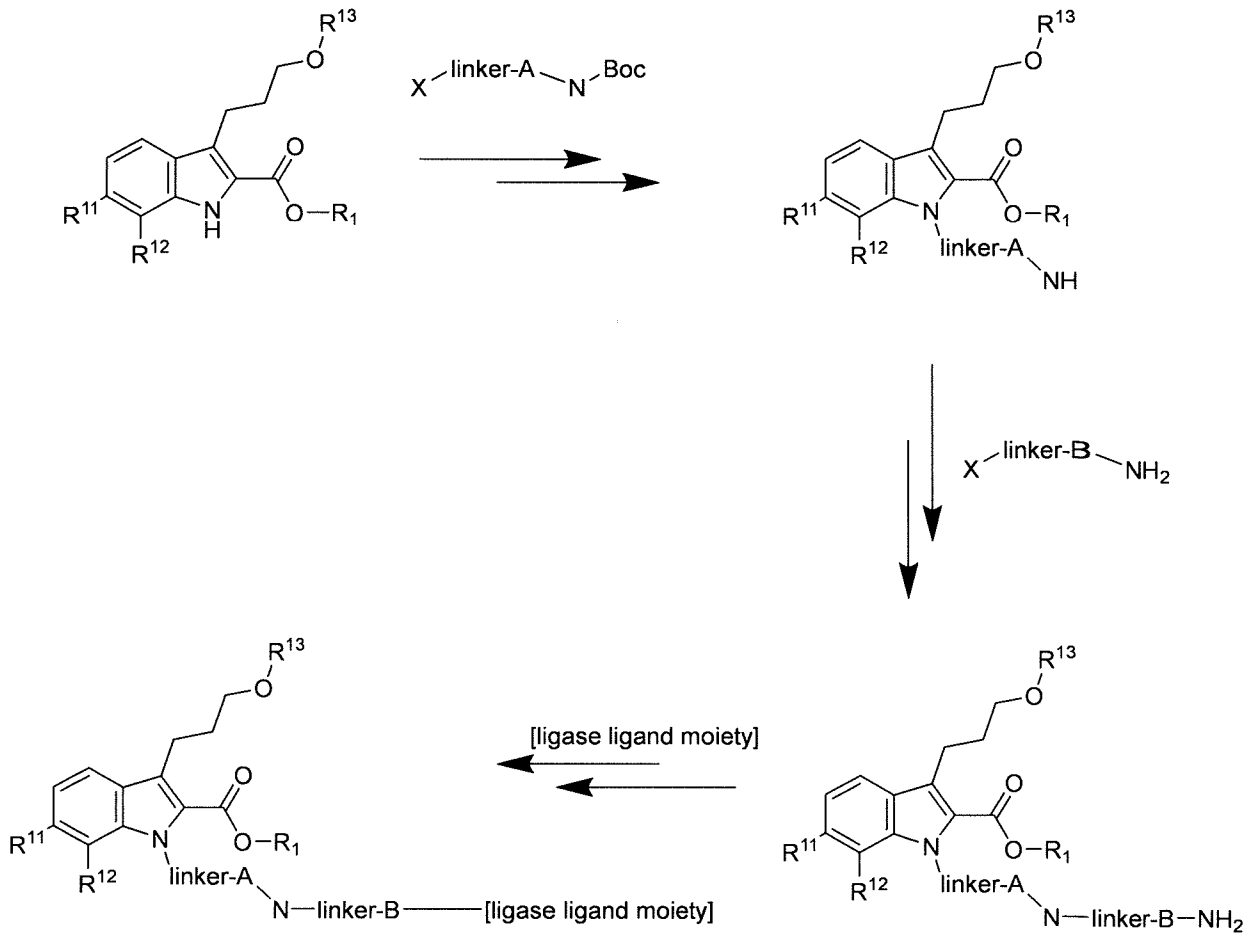
(c) *attachment of linker via R^9 of **[MCL-1 ligand moiety]**, and coupling of linkerA and linkerB via an amide bond:*



wherein linkerA-N-R^w corresponds to linkerA terminating with an R^w-protected primary or secondary amine; R^8 and R^{11}-R^{13} are as defined herein; and wherein linkerA-NC(O)-linkerB corresponds to **[linker]**.

This method was used for the synthesis of 242, 243 and 244, below.

2. <u>[Mcl-1 ligand moiety] is coupled with linkerA, followed by coupling with linker B, followed coupling with [ligase ligand moiety]</u>

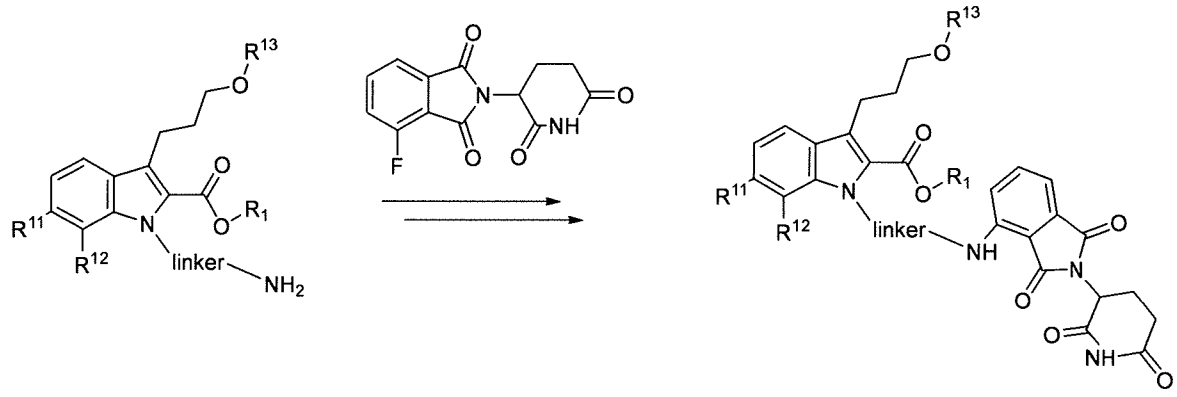


wherein R_1 is -H, -C_1-C_6alkyl, or -NH_2; X is halogen or OMs, OTs; linkerA-N-Boc corresponds to linkerA terminating with a Boc-protected primary or secondary amine; linkerA-NH corresponds to linkerA terminating with a primary or secondary amine; and R^{11}-R^{13} are as defined herein; and wherein linkerA-N-linkerB corresponds to **[linker]**.

This method was used for the synthesis of 200 and 247, below.

3. [Mcl-1 ligand moiety]-[linker] is coupled with [ligase ligand moiety]

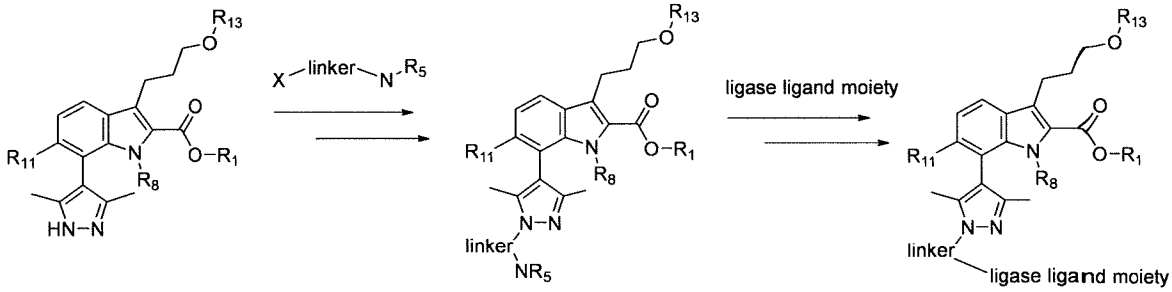
[Mcl-1 ligand moiety]-[linker] + [ligase ligand moiety]



wherein R_1 is -H, -C_1-C_6alkyl, or -NH_2; and R^{11}-R^{13} are as defined herein.

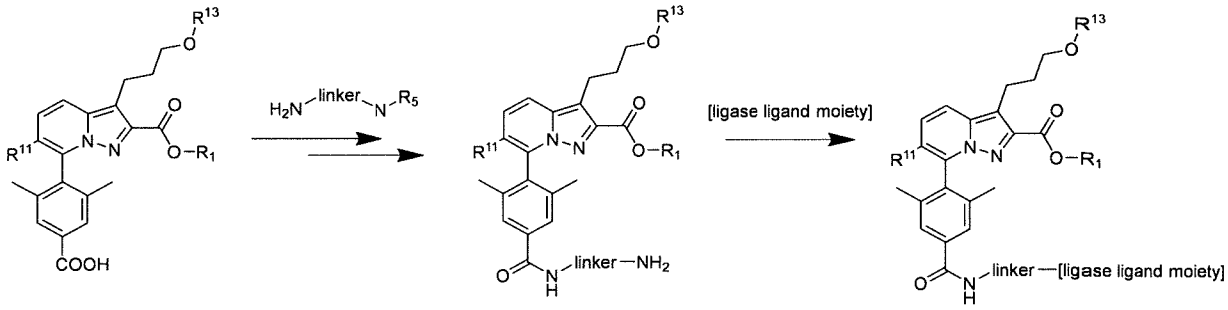
Examples of this method are set out below:

(i) (as used for the synthesis of 227, 228, 229, 230 and 232):



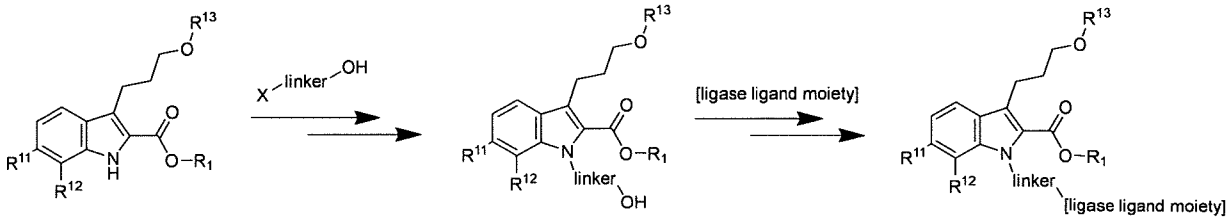
wherein R_1 is -H, -C_1-C_6alkyl, or -NH_2; R^8, R^{11} and R^{13} are as defined herein; and wherein linker-N-R_5 corresponds to [linker] terminating with an R_5-protected primary or secondary amine.

(ii) (as used for the synthesis of 253, 254, 255 and 256)



wherein R_1 is -H, -C_1-C_6alkyl, or -NH_2; R^{11} and R^{13} are as defined herein; and wherein linker-N-R_5 corresponds to [linker] terminating with an R_5-protected primary or secondary amine.

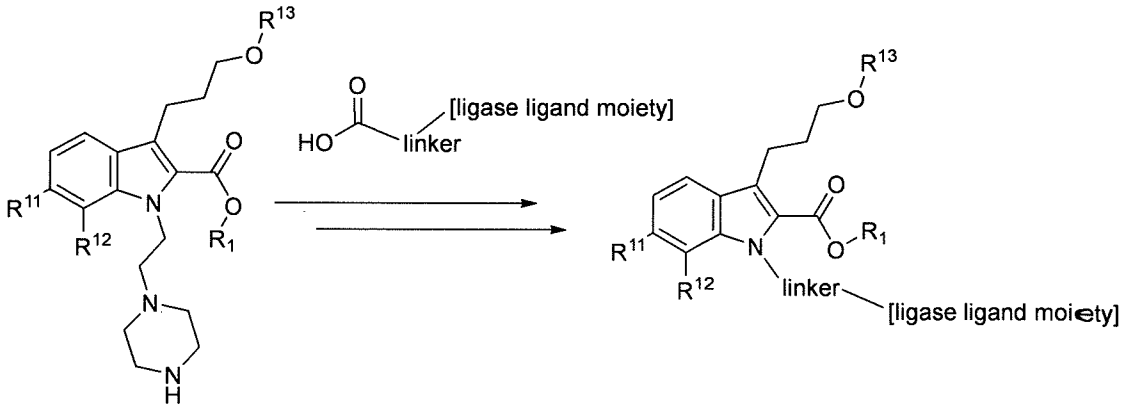
(iii) (as used for the synthesis of 238)



wherein R_1 is -H, -C_1-C_6alkyl, or -NH_2; and R^{11}-R^{13} are as defined herein.

4. [Mcl-1 ligand moiety] is coupled with [linker]-[ligase ligand moiety]

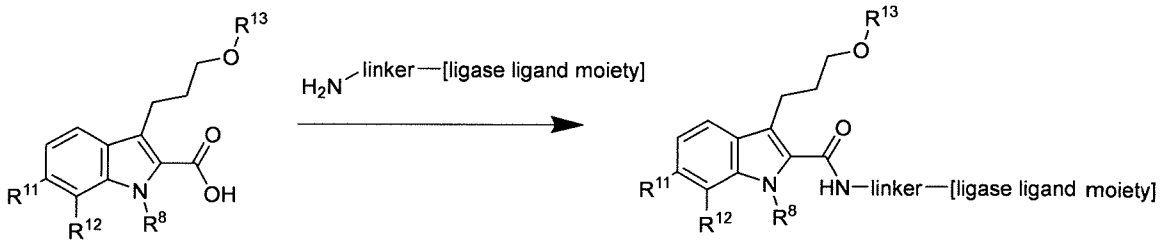
[Mcl-1 ligand moiety] + [linker]-[ligase ligand moiety]



wherein R_1 is -H, -C_1-C_6alkyl, or -NH_2; and R^{11}-R^{13} are as defined herein.

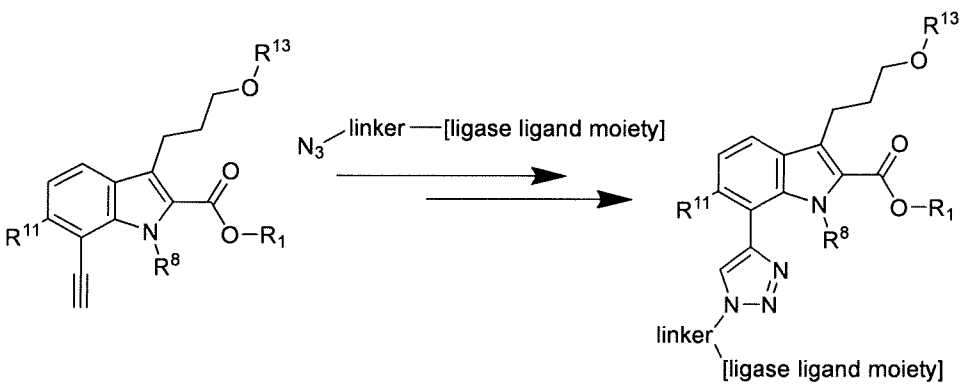
Examples of this method are set out below:

(i) (as used for the synthesis of 252)



wherein R^8, R^{11} and R^{13} are as defined herein.

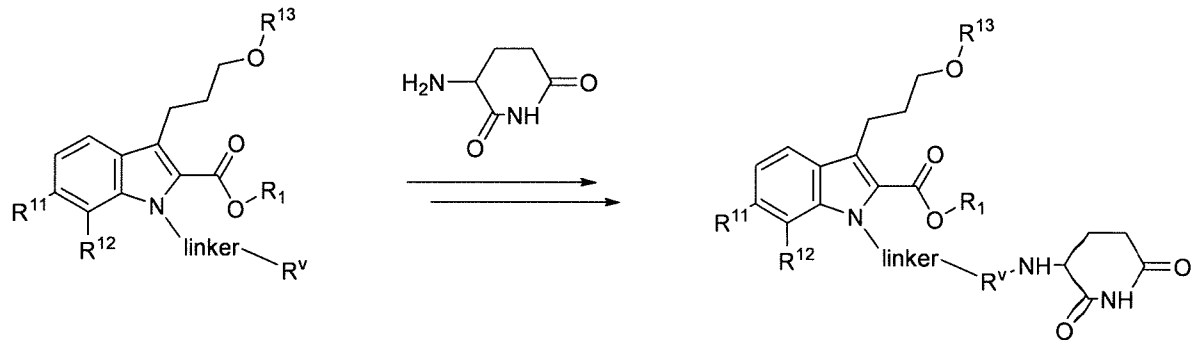
(ii) (as used for the synthesis of 231)



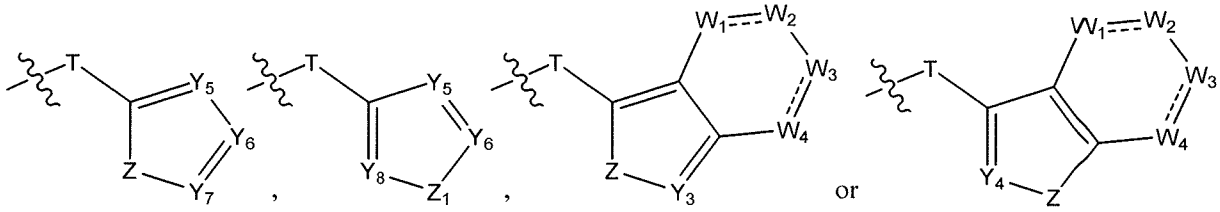
wherein R_1 is -H, -C_1-C_6alkyl, or -NH_2; and R^8, R^{11} and R^{13} are as defined herein.

5. [Mcl-1 ligand moiety]-[linker]-R^v is coupled with 3-aminopiperidine-2,6-dione

[Mcl-1 ligand moiety]-[linker]-R^v + 3-Aminopiperidine-2,6-dione

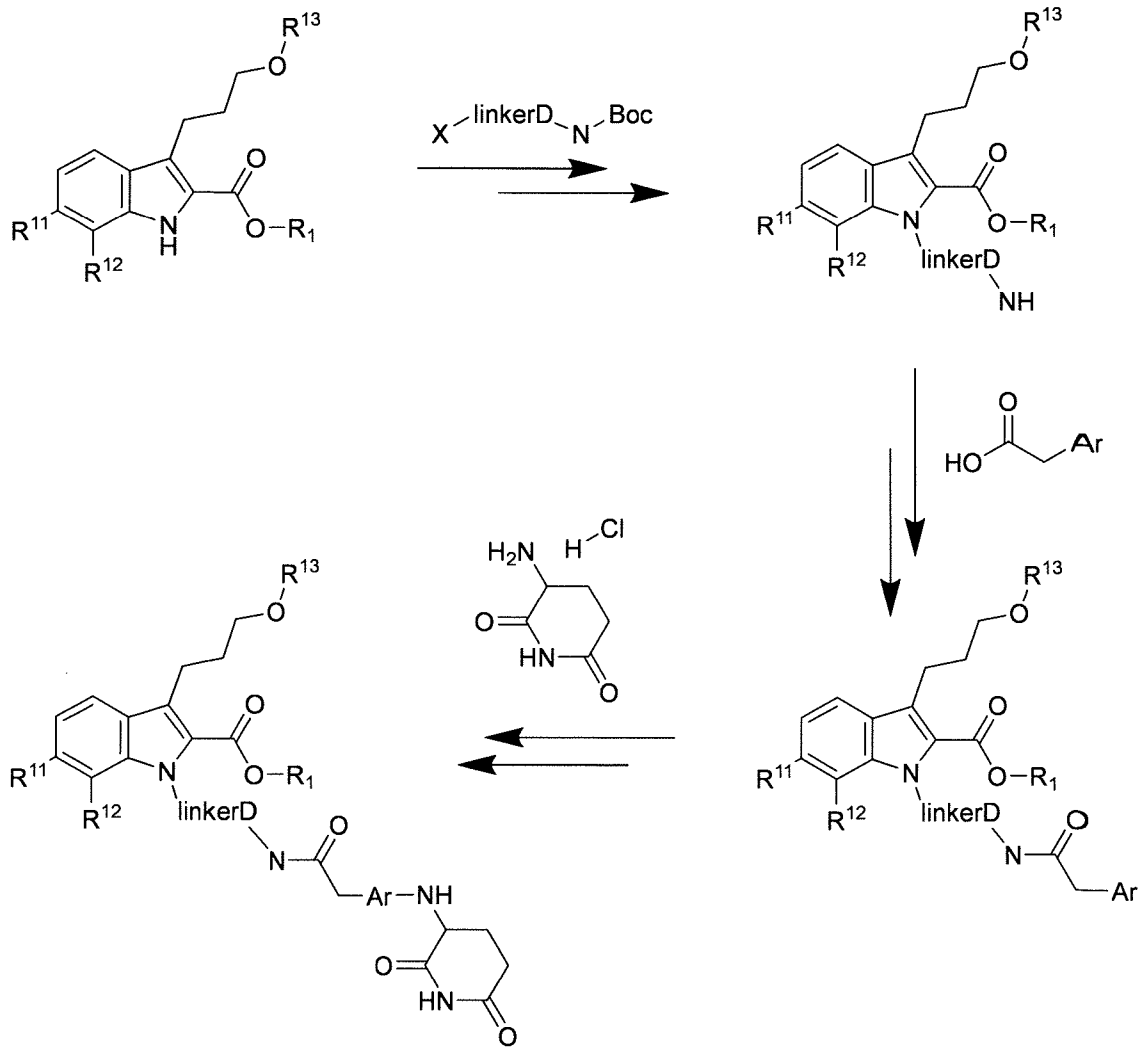


wherein R_1 is -H, -C_1-C_6alkyl, or -NH_2; R^{11}-R^{13} are as defined herein; and R^v is -T-R^x, -T-R^y,

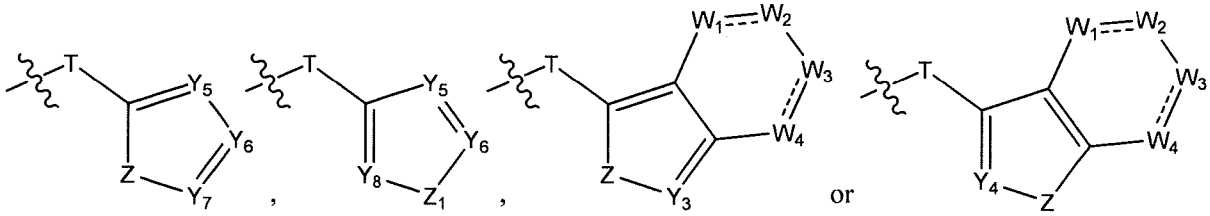


Examples of this method are set out below:

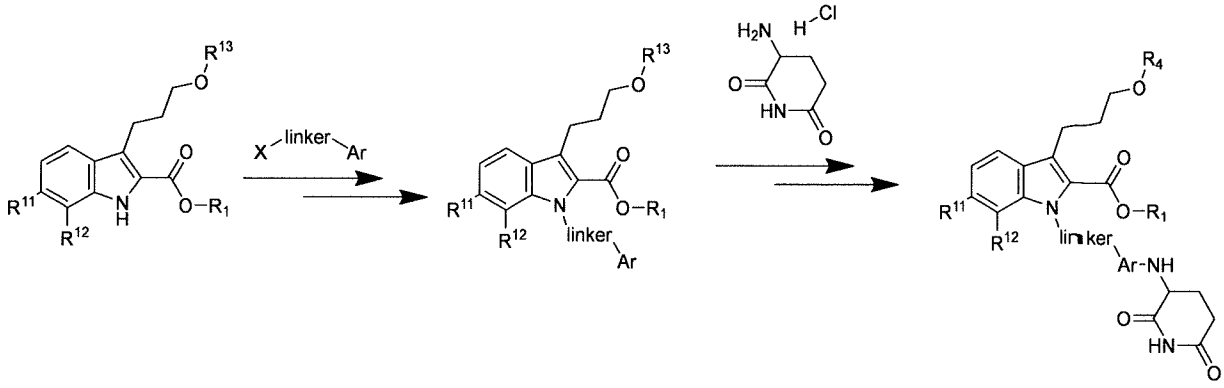
(i) (as used for the synthesis of 263, 264, 265, 266 and 267)



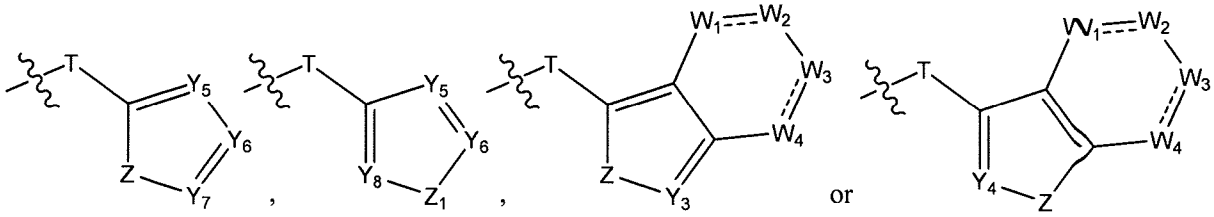
wherein R_1 is -H, -C_1-C_6alkyl, or -NH_2; R^{11}-R^{13} are as defined herein; linker-N-Boc corresponds to [linker] terminating with a Boc-protected primary or secondary amine; linkerD-NC(O)CH_2- corresponds to [linker] as defined herein; and Ar is -T-R^x, -T-R^y,



(ii) (as used for the synthesis of 239)

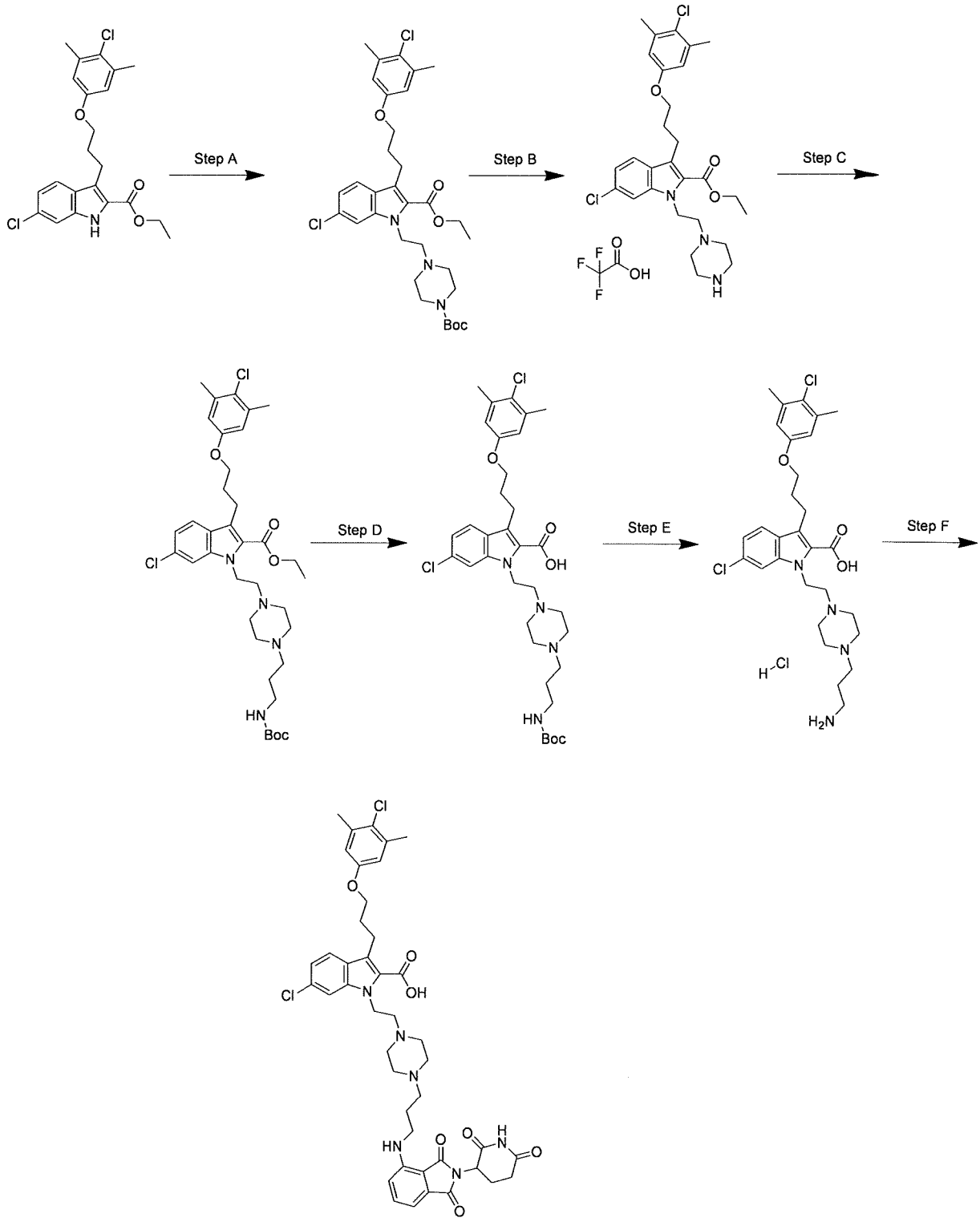


wherein R_1 is -H, -C_1-C_6alkyl, or -NH_2; R^{11}-R^{13} are as defined herein; and Ar is -T-R^x, -T-R^y,

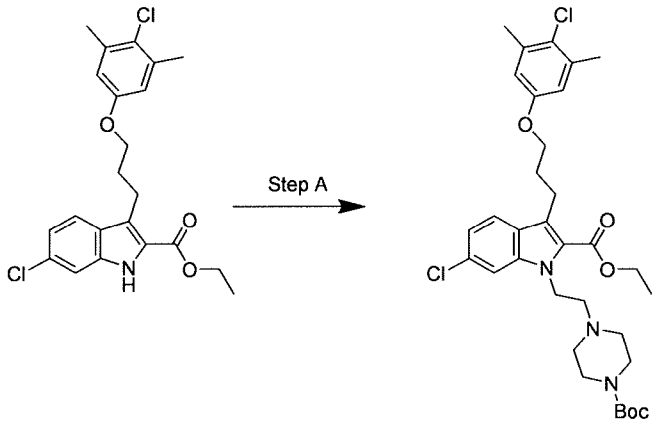


The bifunctional compounds of the present invention were prepared as follows:

Example 1: 6-Chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-(2-(4-(3-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)propyl)piperazin-1-yl)ethyl)-1*H*-indole-2-carboxylic acid (200)



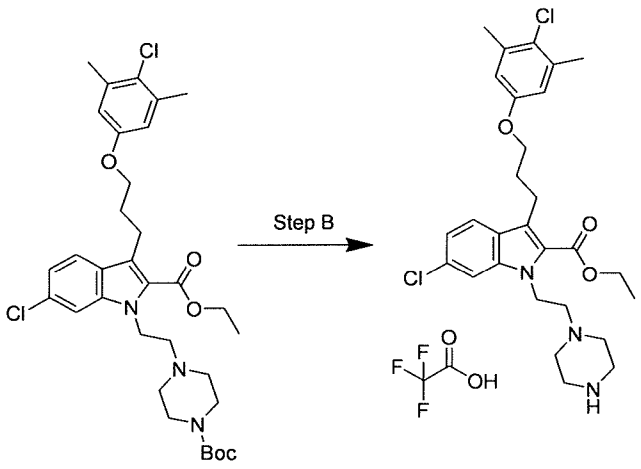
Step A



To a mixture of ethyl 6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carboxylate (0.30 g, 0.71 mmol) and K_2CO_3 (0.30 g, 2.14 mmol) in DMF (3.78 mL) was added *tert*-butyl 4-(2-bromoethyl)piperazine-1-carboxylate (0.27 g, 0.93 mmol). Mixture was sealed, and heated in 80°C for overnight. Solvents were removed under reduced pressure, and crude mixture was treated with EtOAc and brine. The organic layer was separated, dried, and evaporated. Mixture was purified using flash chromatography (SiO_2, 20% EtOAc in hexane) to get ethyl 1-(2-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)ethyl)-6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carboxylate (319 mg, 0.504 mmol, 71%) as colorless oil.

LCMS (ESI+): m/z 632.5 $[M+H]^+$

Step B

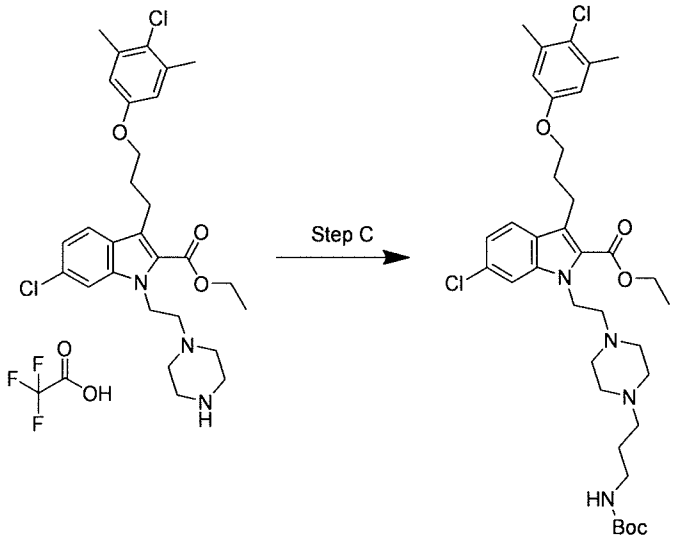


To a solution of ethyl 1-(2-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)ethyl)-6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carboxylate (0.32 g, 0.50 mmol), in DCM (6.30 mL) was added TFA (1.14 mL, 14.94 mmol) and reaction mixture was stirred in RT for overnight. Solvents were removed under reduced pressure to get ethyl 6-chloro-3-[3-(4-chloro-3,5-

dimethylphenoxy)propyl]-1-[2-(piperazin-1-yl)ethyl]-1*H*-indole-2-carboxylate trifluoroacetate (322 mg, 0.498 mmol, 100%) as a product.

LCMS (ESI+): m/z 532.4 $[M+H]^+$

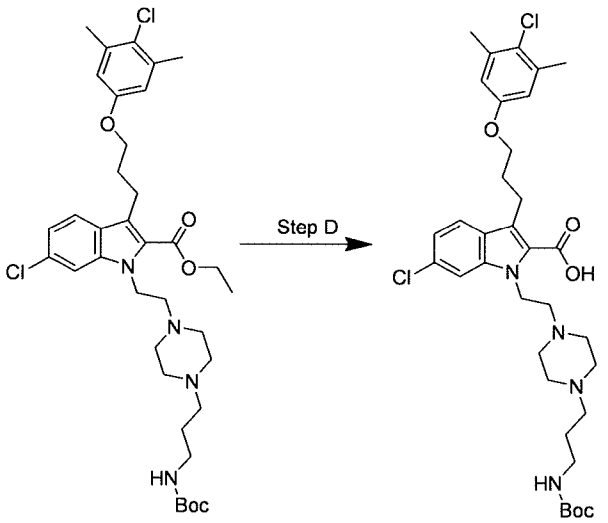
Step C



Ethyl 6-chloro-3-[3-(4-chloro-3,5-dimethylphenoxy)propyl]-1-[2-(piperazin-1-yl)ethyl]-1*H*-indole-2-carboxylate trifluoroacetate (0.06 g, 0.09 mmol) was mixed with K_2CO_3 (0.06 g, 0.45 mmol, 5.00 Eq), in MeCN (0.62 mL) and 1-Boc-3-chloropropylamine (0.02 g, 0.09 mmol) was added. Mixture was stirred in 80°C for over weekend. After this time to mixture were added EtOAc and brine, and mixture extracted with EtOAc. The crude mixture was purified using flash chromatography (SiO_2, 10% MeOH in DCM). Ethyl 1-(2-(4-(3-((*tert*-butoxycarbonyl)amino)propyl)piperazin-1-yl)ethyl)-6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carboxylate (16.00 mg, 0.023 mmol, 27%) was obtained as colorless oil.

LCMS (ESI+): m/z 689.6 $[M+H]^+$

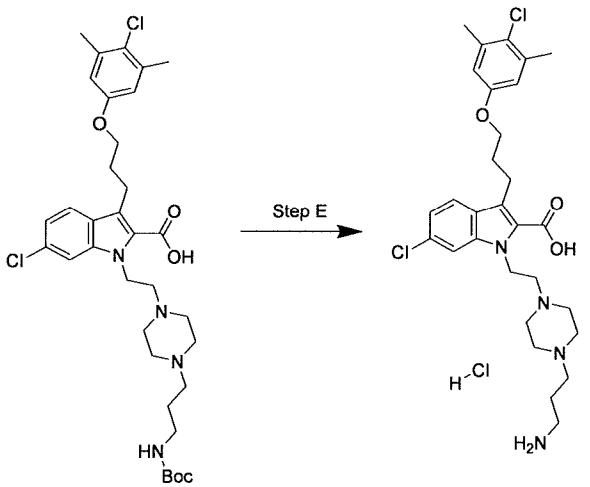
Step D



To solution of ethyl 1-(2-(4-(3-((*tert*-butoxycarbonyl)amino)propyl)piperazin-1-yl)ethyl)-6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carboxylate (16 mg, 0.02 mmol) in mixture of MeOH:H_2O (1:1, 0.09 mL) was added 5% solution of LiOH in water (33 µL, 0.07 mmol). Mixture was stirred at 50°C for 18 hours. Methanol was removed under reduced pressure, 1M HCl was added. Mixture was extracted 3x with DCM. Organic phases dried over Na_2SO_4 and concentrated in vacuum to give 1-(2-(4-(3-((*tert*-butoxycarbonyl)amino)propyl)piperazin-1-yl)ethyl)-6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carboxylic acid (10.00 mg, 0.015 mmol, 65%).

LCMS (ESI+): m/z 661.5 $[M+H]^+$

Step E

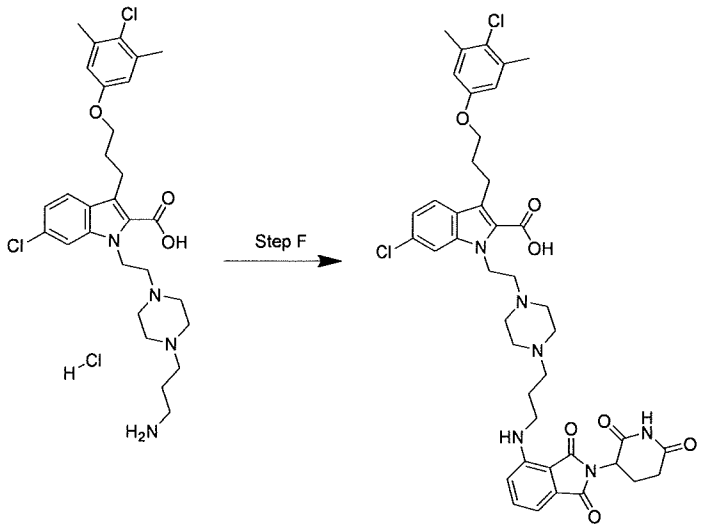


1-(2-(4-(3-((*tert*-butoxycarbonyl)amino)propyl)piperazin-1-yl)ethyl)-6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carboxylic acid (0.01 g, 0.02 mmol) was dissolved in THF (0.08 mL) and 4M HCl in dioxane (0.02 g, 0.06 mmol) was added. Mixture was stirred for overnight

in RT. Solvents were removed under reduced pressure, and crude co-evaporated three times with Et_2O. 8.50 mg of crude material with 1-{2-[4-(3-aminopropyl)piperazin-1-yl]ethyl}-6-chloro-3-[3-(4-chloro-3,5-dimethylphenoxy)propyl]-1*H*-indole-2-carboxylic acid hydrochloride was used without further purification to the next step.

LCMS (ESI-): m/z 559.5 $[M-H]^-$

Step F

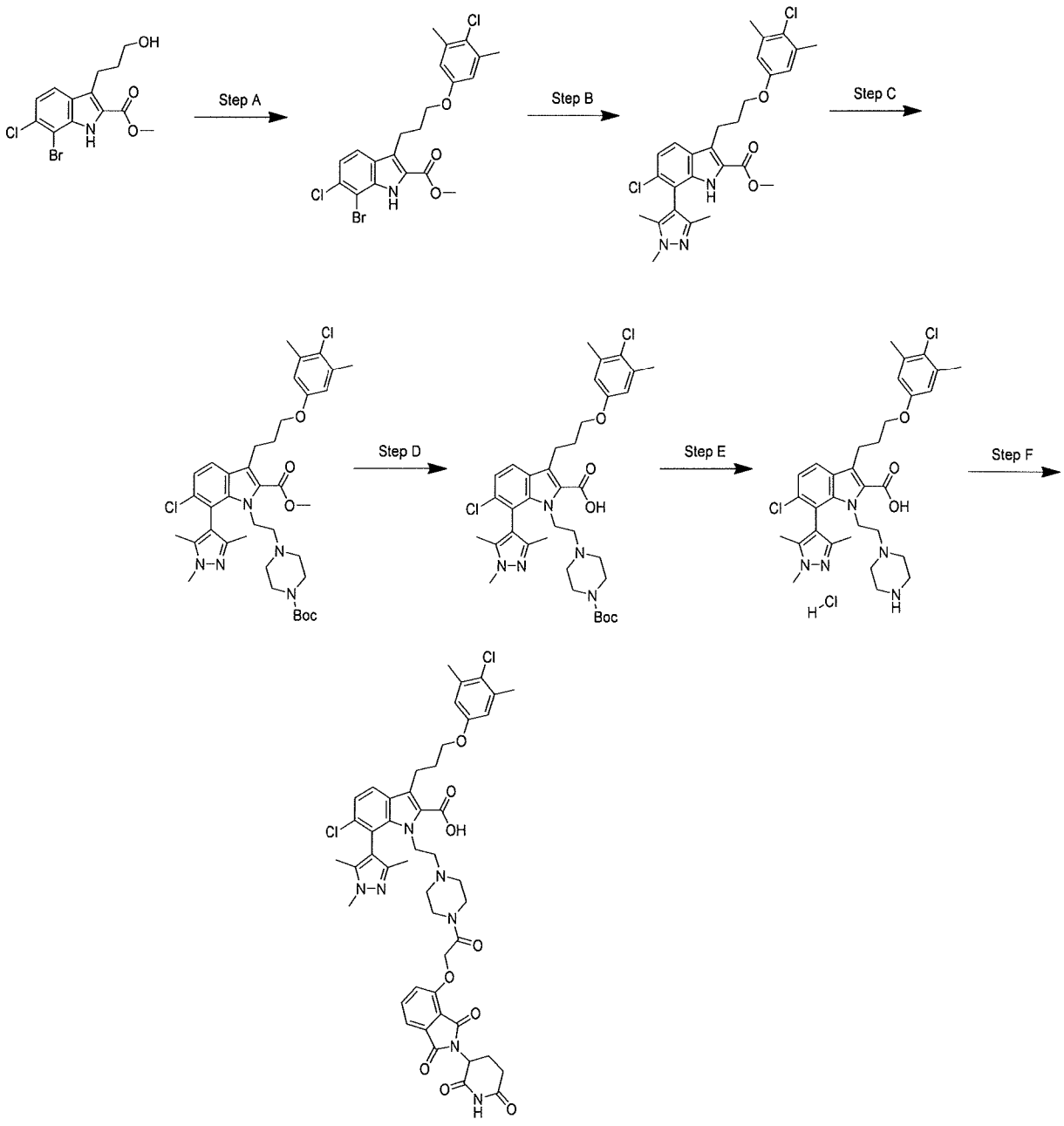


To a solution of 1-{2-[4-(3-aminopropyl)piperazin-1-yl]ethyl}-6-chloro-3-[3-(4-chloro-3,5-dimethylphenoxy)propyl]-1*H*-indole-2-carboxylic acid hydrochloride (0.01 g, 0.02 mmol) and 2-(2,6-dioxopiperidin-3-yl)-4-fluoroisoindoline-1,3-dione (0.04 g, 0.15 mmol) in DMSO (0.21 mL) was added DIPEA (0.01 mL, 0.05 mmol). The reaction mixture was heated at 90°C for 20 h. Crude was purified by flash chromatography (SiO_2, 5% MeOH in DCM) and then re-purified via preparative TLC (5% MeOH in DCM). 6-Chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-(2-(4-(3-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)propyl)piperazin-1-yl)ethyl)-1*H*-indole-2-carboxylic acid (2.20 mg, 0.003 mmol, 20% over two steps) was isolated as yellow solid.

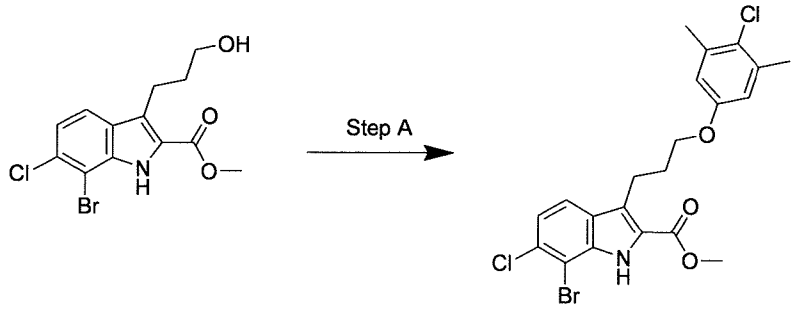
LCMS (ESI+): m/z 817.6 $[M+H]^+$

^1H NMR (500 MHz, DMSO) δ 13.41 (s, 1H), 11.08 (s, 1H), 7.71 (s, 1H), 7.67 (d, *J* = 8.5 Hz, 1H), 7.58 (t, 1H), 7.12 (d, *J* = 8.6 Hz, 1H), 7.07 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.03 (d, *J* = 7.0 Hz, 1H), 6.77 (s, 1H), 6.71 (s, 2H), 5.05 (dd, *J* = 12.7, 5.4 Hz, 1H), 4.61 (s, 2H), 3.90 (t, *J* = 6.4 Hz, 2H), 3.64 – 3.57 (m, 1H), 3.51 (s, 1H), 3.34 (q, *J* = 6.4 Hz, 2H), 3.16 – 3.09 (m, 3H), 2.95 – 2.81 (m, 1H), 2.61 – 2.49 (m, 3H), 2.26 (s, 6H), 2.05 – 1.64 (m, 6H), 1.52 – 1.22 (m, 7H).

Example 2: 6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-(2-(4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)acetyl)piperazin-1-yl)ethyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (201)

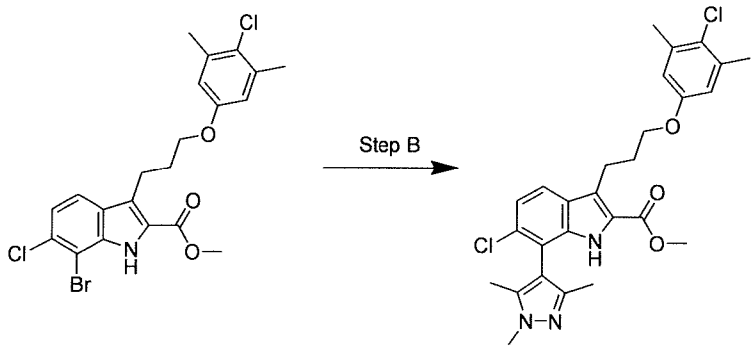


Step A



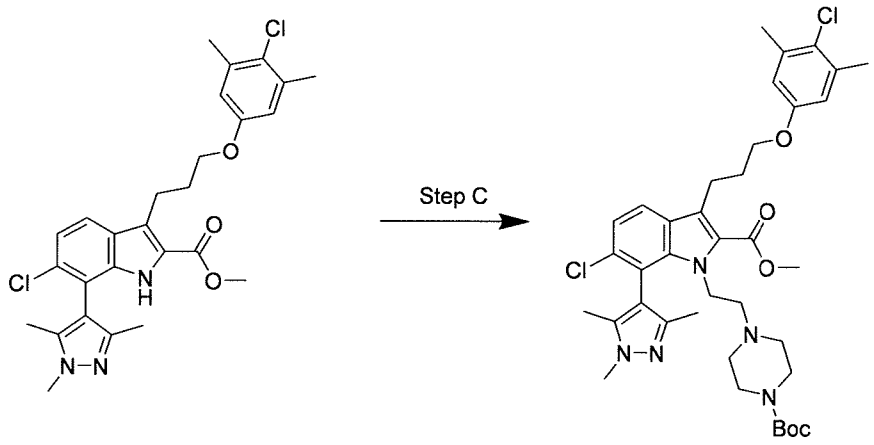
To a stirred solution of methyl 7-bromo-6-chloro-3-(3-hydroxypropyl)-1*H*-indole-2-carboxylate (20 g, 57.7 mmol), 4-chloro-3,5-dimethylphenol (10.84 g, 69.2 mmol), PPh_3 (18.2 g, 69.4 mmol) in THF (470 mL) was added in portions (*E*)-*N*-{[(*tert*-butoxy)carbonyl]imino}(*tert*-butoxy)formamide (16 g, 69.5 mmol). The reaction mixture was stirred at room temperature overnight. Then the solvent was removed under reduced pressure and the residue was purified by flash chromatography to afford methyl 7-bromo-6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carboxylate (13.8 g, 28.4 mmol, 49%).

Step B



To a stirred solution of methyl 7-bromo-6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1H-indole-2-carboxylate (13.8 g, 28.4 mmol) and 1,3,5-trimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (7.4 g, 31.4 mmol) in dioxane (200 mL) was added aqueous solution of K_2CO_3 (5.5 g, 40 mmol in 30 mL water). The reaction mixture was degassed and $Pd(PPh_3)_4$ (2 g, 1.7 mmol) was added under argon atmosphere. The reaction mixture was heated at 80°C for 24 h. New portion of 1,3,5-trimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (7.4 g, 31.4 mmol), K_2CO_3 (5.5 g, 40 mmol) and $Pd(PPh_3)_4$ (4 g, 3.4 mmol) were added and the reaction was continued for 2 days. Then the solid was filtered, washed with EtOAc, and the filtrate was concentrated. The residue was dissolved in CH_2Cl_2, washed with water and purified by flash chromatography to afford methyl 6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (2.20 g, 4.28 mmol, 15%).

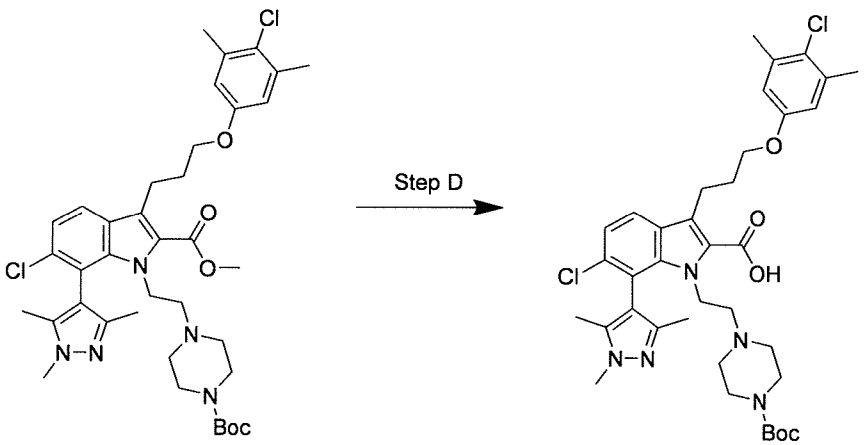
Step C



Methyl 6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (200.0 mg, 0.389 mmol) was dissolved in DMF (3.9 mL) and Cs_2CO_3 was added followed by *tert*-butyl 4-(2chloroethyl)piperazine-1-carboxylate (97.7 mg, 0.393 mmol). Mixture was heated in 80°C for overnight. Solvent was evaporated, EtOAc and brine were added, and mixture was extracted with EtOAc. Combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuum to give methyl 1-(2-{4-[(*tert*-butoxy)carbonyl]piperazin-1-yl}ethyl)-6-chloro-3-[3-(4-chloro-3,5-dimethylphenoxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate) (273.0 mg, 0.376 mmol, 96.6%) as white foam.

LCMS (ESI+): m/z 726.2 $[M+H]^+$

Step D

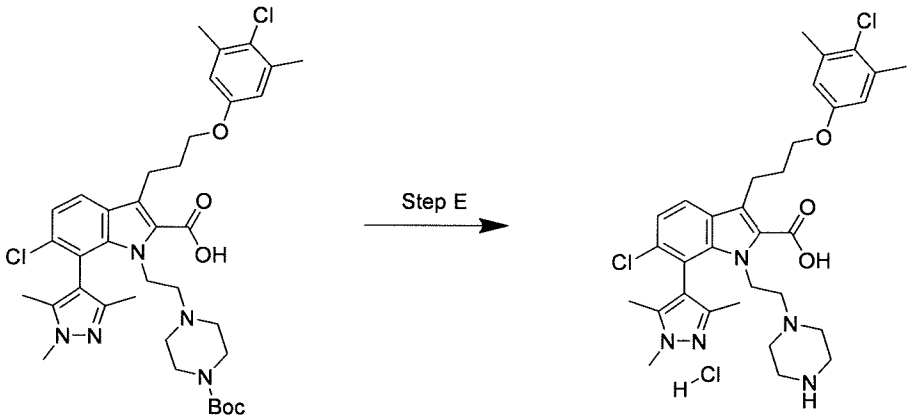


Methyl 1-(2-{4-[(*tert*-butoxy)carbonyl]piperazin-1-yl}ethyl)-6-chloro-3-[3-(4-chloro-3,5-dimethylphenoxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (270.0 mg, 0.372 mmol) was dissolved in EtOH (1.9mL) and water (1.9mL) and 1M LiOH (1.5 mL, 1.486 mmol) was added. The reaction was allowed to stir overnight. THF (1.9mL) was added and reaction

was heated for overnight in 50°C. The reaction was diluted with water and washed with EtOAc. The water layer was then acidified with 1N HCl to pH 2. The resulting suspension was extracted with DCM. The organic layer was washed with saturated sodium chloride, dried over $MgSO_4$, filtered, and concentrated. Pure 1-(2-{4-[(*tert*-butoxy)carbonyl]piperazin-1-yl}ethyl)-6-chloro-3-[3-(4-chloro-3,5-dimethylphenoxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (258.0 mg, 0.344 mmol, 92.6%) was obtained as a white solid.

LCMS (ESI^+): m/z 712.3 $[M+H]^+$

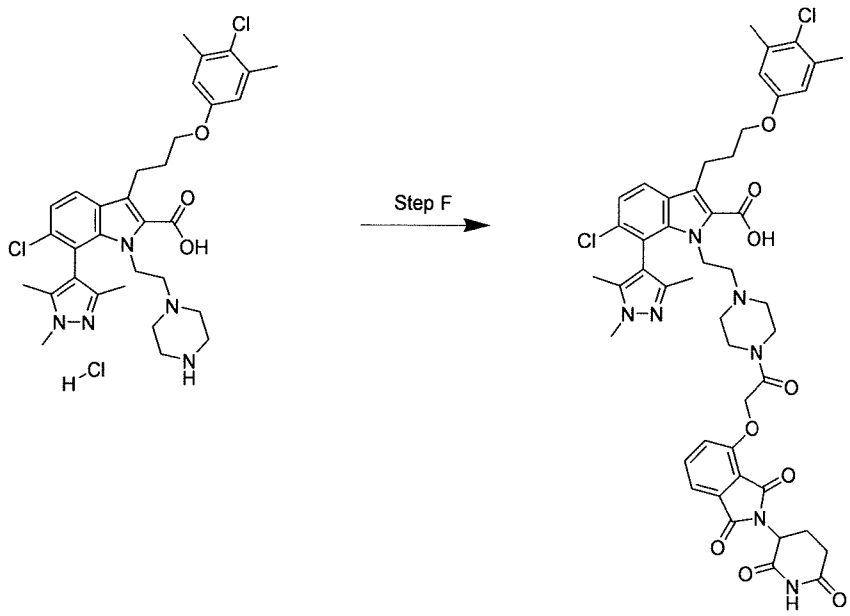
Step E



1-(2-{4-[(T*ert*-butoxy)carbonyl]piperazin-1-yl}ethyl)-6-chloro-3-[3-(4-chloro-3,5-dimethylphenoxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (258.0 mg, 0.362 mmol) was dissolved in THF (3.6 mL) and 4M HCl in dioxane (0.271 mL, 1.086 mmol) was added. Mixture was stirred in room temperature. After 2 days solvents were removed and residue was coevaporated with Et_2O. 6-Chloro-3-[3-(4-chloro-3,5-dimethylphenoxy)propyl]-1-[2-(piperazin-1-yl)ethyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid hydrochloride (215.0 mg, 0.331 mmol, 91.5%) was obtained as white solid.

LCMS (ESI^+): m/z 611.4 $[M+H]^+$

Step F

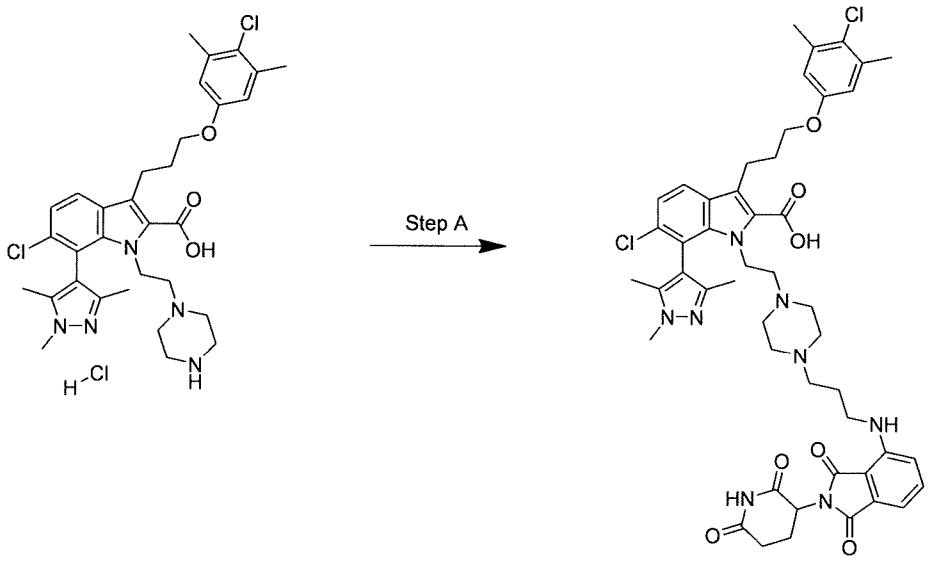


A solution of 2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)acetic acid (25 mg, 0.075 mmol) and CDI (12.2 mg, 0.075 mmol) in DCM (0.6 mL) was stirred for 1 h in 50°C. After this time 6-chloro-3-[3-(4-chloro-3,5-dimethylphenoxy)propyl]-1-[2-(piperazin-1-yl)ethyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid hydrochloride (38.8 mg, 0.060 mmol), was added and the mixture was allowed to stir under nitrogen for 16 h in room temperature. The reaction mixture diluted with EtOAc, washed successively with cold water (3 times) and brine. Organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. Crude was purified using preparative HPLC (H_2O:MeCN + 0.1% FA) to get 6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-(2-(4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)acetyl)piperazin-1-yl)ethyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (7.0 mg, 0.008 mmol, 13%) as white solid.

LCMS (ESI+): m/z 926.9 $[M+H]^+$

^{1}H NMR (500 MHz, DMSO) δ 13.32 (s, 1H), 11.09 (s, 1H), 7.76 (dd, *J* = 8.6, 7.3 Hz, 1H), 7.68 (d, *J* = 8.6 Hz, 1H), 7.44 (d, *J* = 7.2 Hz, 1H), 7.29 (d, *J* = 8.6 Hz, 1H), 7.24 (d, *J* = 8.5 Hz, 1H), 6.73 (s, 2H), 5.19 – 5.00 (m, 3H), 4.35 – 4.22 (m, 1H), 4.22 – 4.09 (m, 1H), 3.98 (t, *J* = 6.4 Hz, 2H), 3.75 (s, 3H), 3.12 (t, *J* = 7.4 Hz, 2H), 2.88 (ddd, *J* = 16.8, 13.8, 5.5 Hz, 1H), 2.61 – 2.52 (m, 3H), 2.26 (s, 7H), 2.18 – 1.92 (m, 14H), 1.88 (s, 3H).

Example 3: 6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-(2-(4-(3-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)propyl)piperazin-1-yl)ethyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (202)



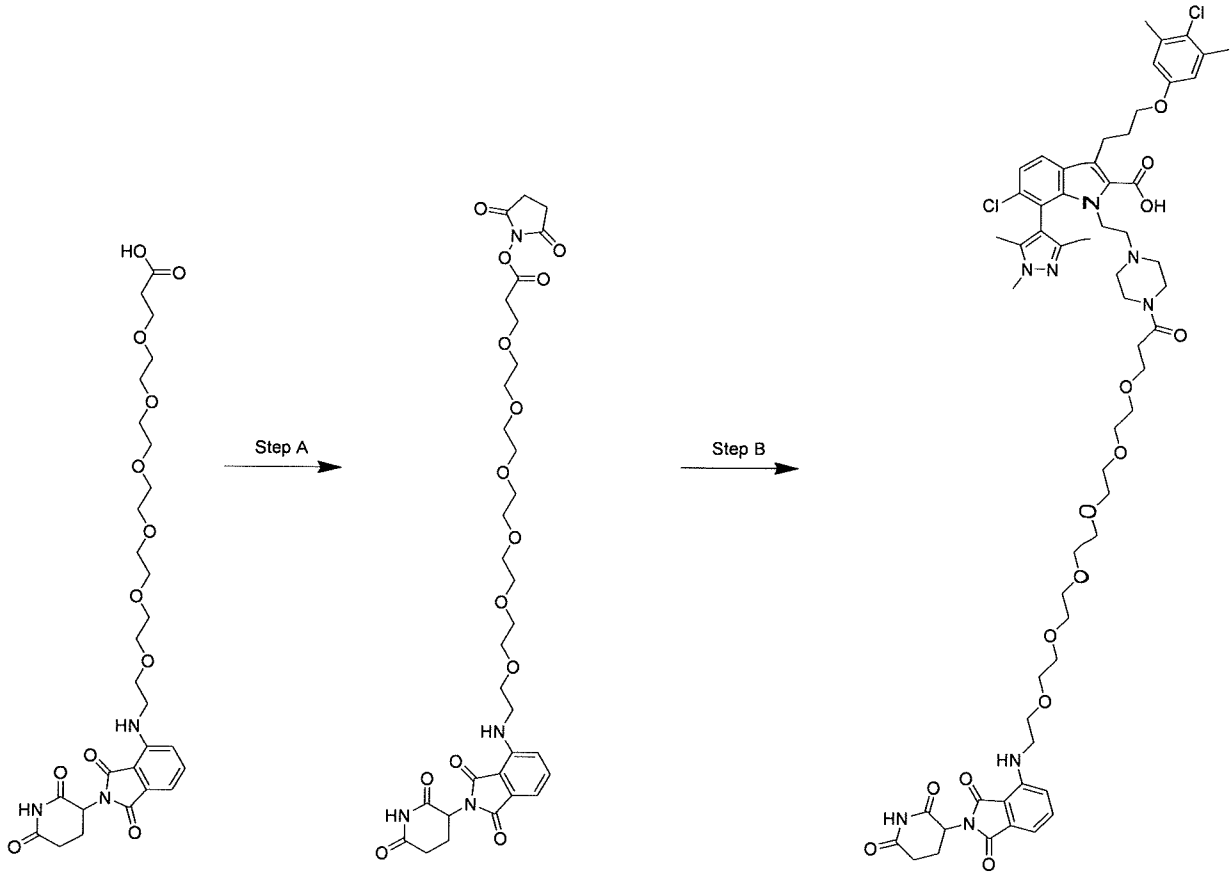
Step A

3-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)propyl methanesulfonate (0.205 g, 0.50 mmol), 6-chloro-3-[3-(4-chloro-3,5-dimethylphenoxy)propyl]-1-[2-(piperazin-1-yl)ethyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid hydrochloride (0.241 g, 0.37 mmol) and DIPEA (0.301 g, 2.5 mmol) were dissolved in DMSO (10 mL) and stirred for 2 days at 90°C. Then the reaction mixture was purified by preparative HPLC to afford 6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-(2-(4-(3-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)propyl)piperazin-1-yl)ethyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (43 mg, 0.046 mmol, 13%) as a yellow solid.

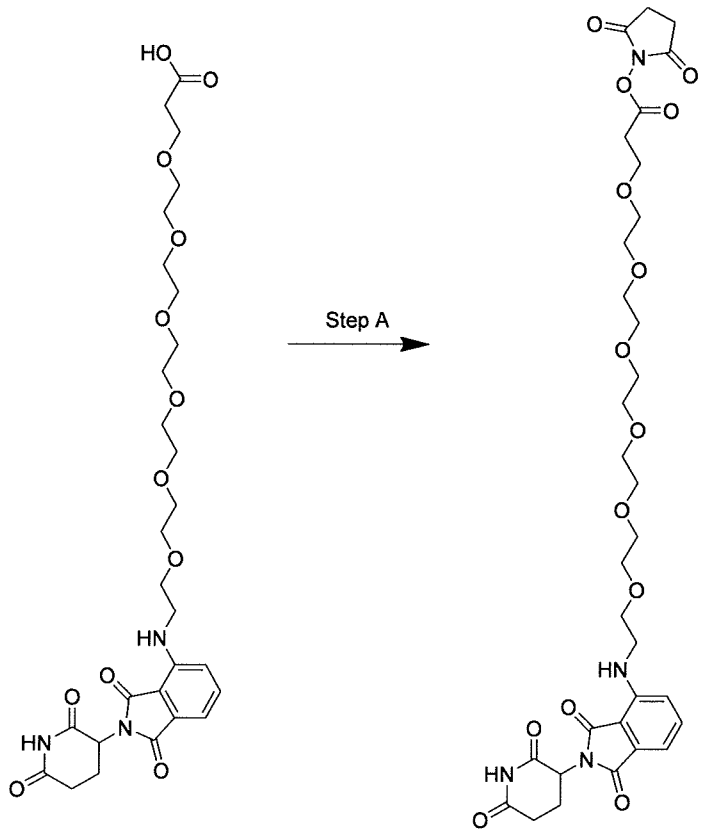
LCMS (ESI+): m/z 925.5 $[M+H]^+$

^{1}H NMR (400 MHz, CD_3OD) δ 8.40 (s, 1H), 7.75 – 7.69 (m, 1H), 7.52 – 7.45 (m, 1H), 7.30 – 7.25 (m, 1H), 7.01 (dd, *J* = 7.7, 4.9 Hz, 2H), 6.60 (s, 2H), 4.97 – 4.91 (m, 1H), 4.46 (t, *J* = 5.9 Hz, 2H), 4.31 – 4.22 (m, 2H), 3.92 (t, *J* = 5.8 Hz, 2H), 3.83 (s, 3H), 3.55 – 3.43 (m, 2H), 3.27 – 3.20 (m, 2H), 3.06 (t, *J* = 5.0 Hz, 4H), 2.85 – 2.63 (m, 2H), 2.57 – 2.46 (m, 1H), 2.41 – 2.33 (m, 4H), 2.25 (s, 6H), 2.20 (t, *J* = 7.0 Hz, 2H), 2.17 – 2.12 (m, 2H), 2.10 – 2.05 (m, 5H), 2.02 – 1.90 (m, 4H).

Example 4: 6-chloro-3-[3-(4-chloro-3,5-dimethylphenoxy)propyl]-1-{2-[4-(1-{[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl]amino}-3,6,9,12,15,18-hexaoxahenicosanoyl)piperazin-1-yl]ethyl}-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1H-indole-2-carboxylic acid (203)



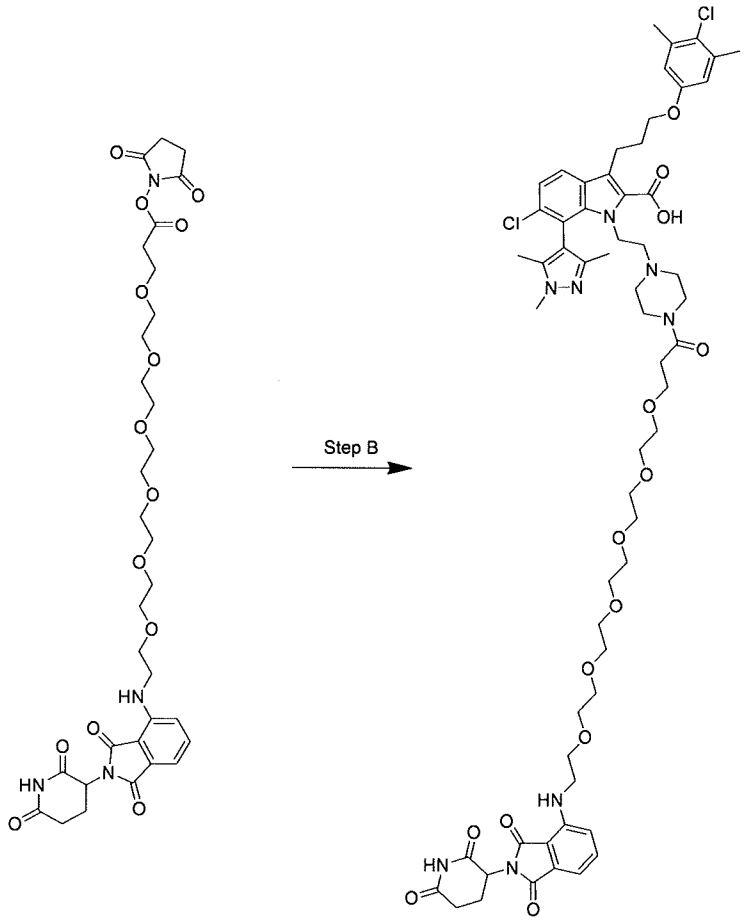
Step A



N-hydroxysuccinimide (11.3 mg, 0.098 mmol) was added into a mixture of 1-{[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl]amino}-3,6,9,12,15,18-hexaoxahenicosan-21-oic acid (50.0 mg, 0.082 mmol) and DCM (1.6 mL) and the reaction mixture was kept cold at 0°C, DCC (20.3 mg, 0.098 mmol) in 0.5 mL DCM was added slowly and the mixture was stirred at room temperature for 4 hours under argon atmosphere. Solvent was removed under reduced pressure. Desired product was purified using flash chromatography (SiO_2, 10% MeOH in DCM). 2,5-dioxopyrrolidin-1-yl 1-{[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl]amino}-3,6,9,12,15,18-hexaoxahenicosan-21-oate (39.0 mg, 0.051 mmol, 61.9%) was obtained as yellow oil.

LCMS (ESI+): m/z 707.4 $[M+H]^+$

Step B



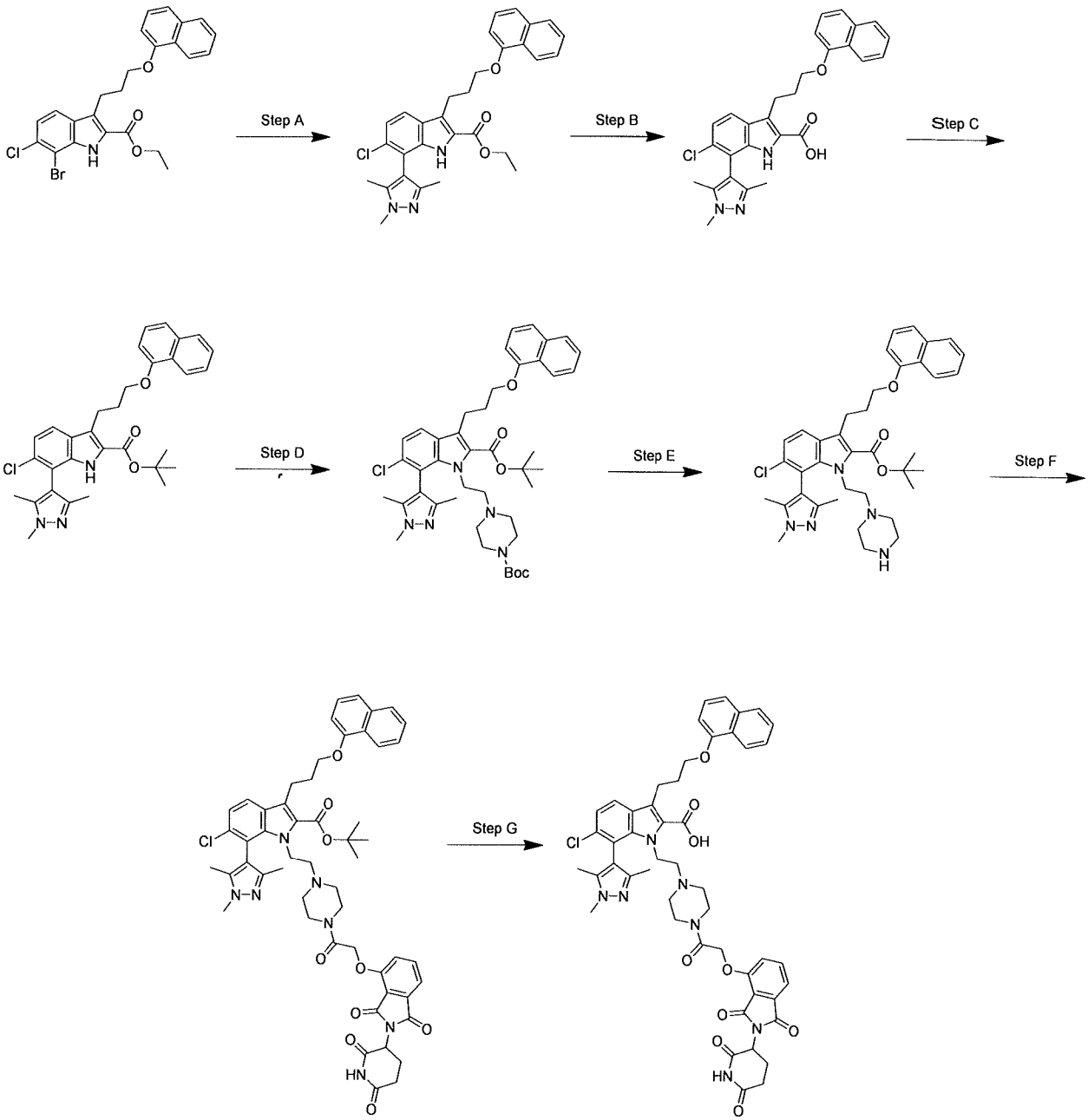
To a stirred solution of 6-chloro-3-[3-(4-chloro-3,5-dimethylphenoxy)propyl]-1-[2-(piperazin-1-yl)ethyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid hydrochloride (32.1 mg, 0.050 mmol) in DMF (0.495 mL) was added DIPEA (0.035 mL, 0.198 mmol). After stirring for 5 min, the 2,5-dioxopyrrolidin-1-yl 1-{[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl]amino}-3,6,9,12,15,18-hexaoxahenicosan-21-oate (35.0 mg, 0.050 mmol) was added and stirred for 16 h at 25°C. Solvents were removed under reduced pressure. Desired product was purified using flash chromatography (SiO_2, 10% MeOH in DCM) and preparative HPLC (H_2O:MeCN + 0.1% FA). 6-Chloro-3-[3-(4-chloro-3,5-dimethylphenoxy)propyl]-1-{2-[4-(1-{[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl]amino}-3,6,9,12,15,18-hexaoxahenicosanoyl)piperazin-1-yl]ethyl}-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (16.0 mg, 0.013 mmol, 27%) was obtained as yellow solid.

LCMS (ESI+): m/z 603.14 $[M+2H]^{2+}$

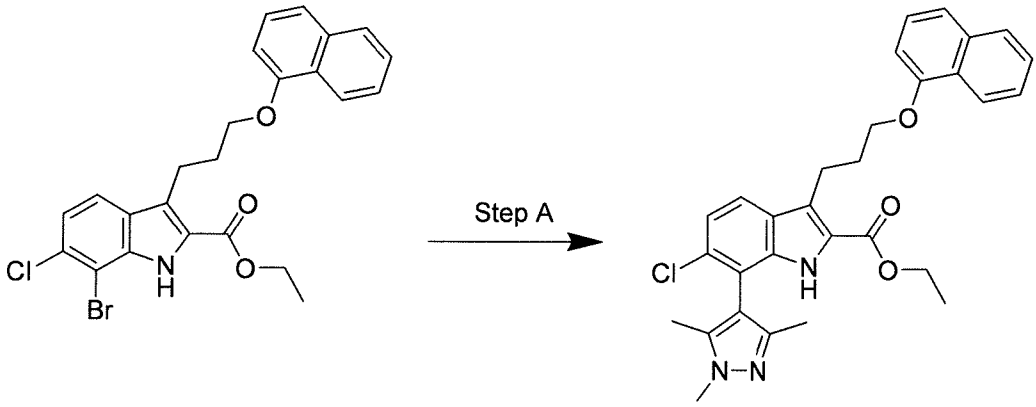
1H NMR (500 MHz, DMSO) δ 7.66 (d, *J* = 8.6 Hz, 1H), 7.55 (dd, *J* = 8.6, 7.1 Hz, 1H), 7.22 (d, *J* = 8.5 Hz, 1H), 7.09 (d, *J* = 8.6 Hz, 1H), 7.01 (d, *J* = 7.0 Hz, 1H), 6.64 (s, 2H), 5.00 (dd, *J* = 12.9, 5.5 Hz, 1H), 4.25 – 4.15 (m, 1H), 4.15 – 4.04 (m, 1H), 3.93 (t, *J* = 6.5 Hz, 2H), 3.58 (t, *J* = 5.4 Hz, 2H), 3.57 – 3.49 (m, 5H), 3.51 – 3.38 (m, 20H), 3.33 – 3.21 (m, 4H), 3.08 (t, *J* = 7.3 Hz, 2H), 2.83 (ddd, *J* = 17.2, 13.9,

5.4 Hz, 1H), 2.58 (ddd, *J* = 17.2, 4.4, 2.5 Hz, 1H), 2.56 – 2.50 (m, 2H), 2.49 – 2.40 (m, 4H), 2.21 (s, 6H), 2.10 – 1.93 (m, 12H), 1.84 (s, 3H).

Example 5: 6-chloro-1-(2-(4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)acetyl)piperazin-1-yl)ethyl)-3-(3-(naphthalen-1-yloxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (204)



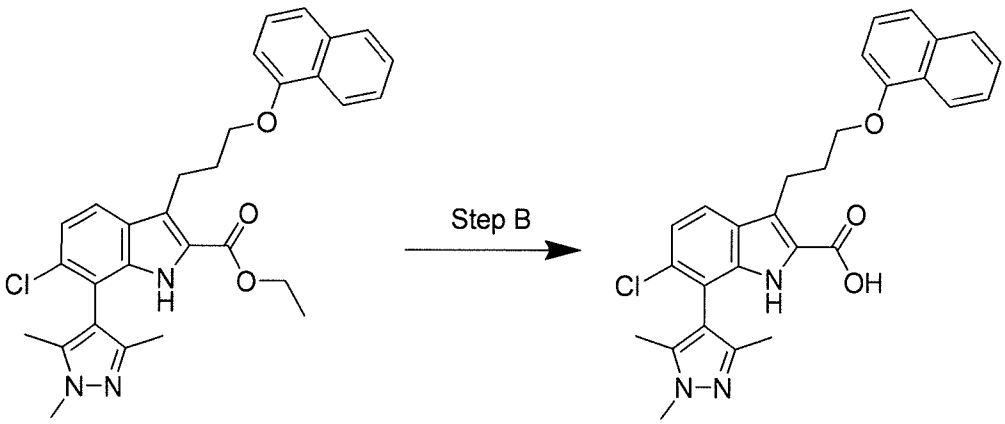
Step A



To a stirred solution of ethyl 7-bromo-6-chloro-3-(3-(naphthalen-1-yloxy)propyl)-1*H*-indole-2-carboxylate (6 g, 12.3 mmol) in dioxane (150 mL) and water (30 mL) were added 1,3,5-trimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (8.8 g, 37.3 mmol) and K_2CO_3 (4.5 g, 32.6 mmol). The mixture was deoxygenated with argon and to it was added Pd(dppf)Cl_2 (1 g, 1.37 mmol) under argon atmosphere. Then the reaction mixture was heated under reflux for 16 h. After complete consumption of the starting material (monitored by TLC and LCMS) the reaction mixture was filtered through celite pad and the solvents were evaporated under reduced pressure to get the crude material. It was then diluted with EtOAc, washed successively with water and brine, the organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to get the crude compound, which was then purified by flash chromatography (SiO_2, 3% MeOH in DCM) to get ethyl 6-chloro-3-(3-(naphthalen-1-yloxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (4.2 g, 8.13 mmol, 66%) as brown sticky solid.

LCMS (ESI$^+$): m/z 516.5 $[M+H]^+$

Step B

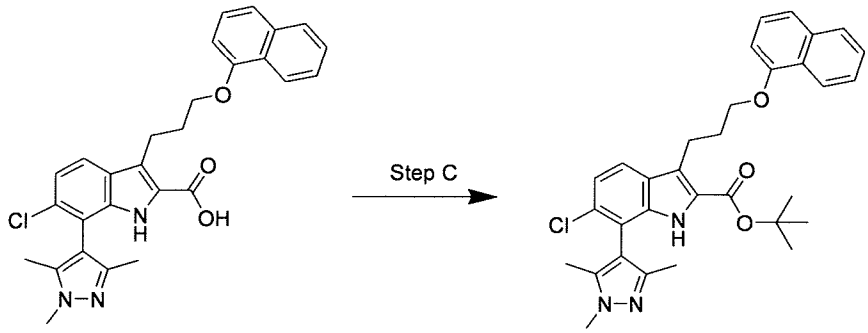


Ethyl 6-chloro-3-(3-(naphthalen-1-yloxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (4.2 g, 8.13 mmol) was dissolved in EtOH (100 mL) and a solution of NaOH (1.2 g,

30.0 mmol) in water (20 mL) was added to it. The mixture was heated under reflux for 3 h. The reaction mixture was cooled down to room temperature, solvents were evaporated under reduced pressure to get the crude reaction mixture. It was then diluted with water and washed with EtOAc. Aqueous layer was carefully acidified using 1 (N) HCl to pH=3, extracted with DCM (3×50 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to afford 6-chloro-3-(3-(naphthalen-1-yloxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (2.3 g, 4.71 mmol, 58%) as brown gummy solid.

LCMS (ESI^+): m/z 488.4 $[M+H]^+$

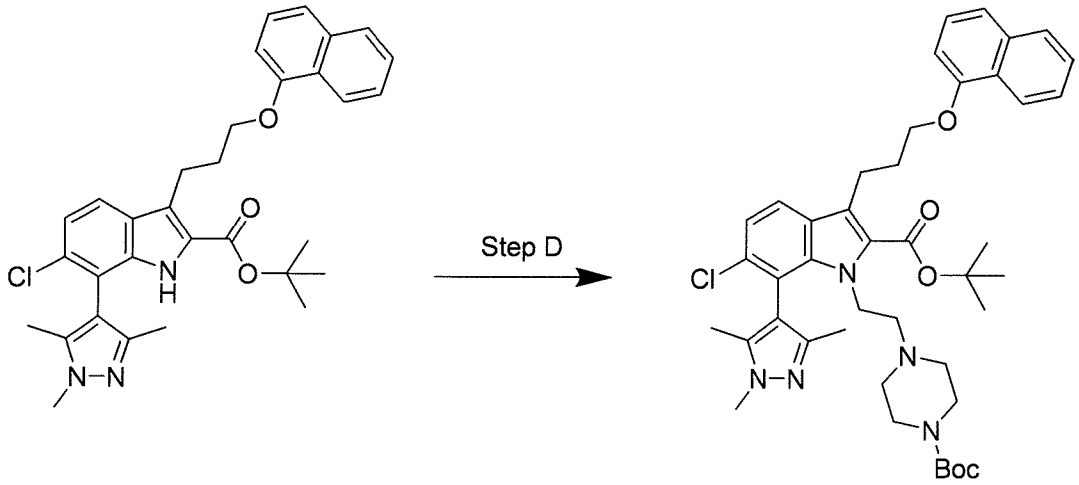
Step C



6-Chloro-3-(3-(naphthalen-1-yloxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (2.3 g, 4.71 mmol) was suspended in toluene (50 mL) and the mixture was heated to reflux under nitrogen. *N*,*N*-dimethylformamide di-*tert*-butyl acetal (5.6 mL, 23.4 mmol) was added drop wise to the refluxing mixture. Refluxing was continued for an additional 12 h under nitrogen. After 16 h another 3.4 mL (14.2 mmol) of *N*,*N*-dimethylformamide di-*tert*-butyl acetal was added to it and the reaction was continued for another 12 h. Reaction mixture was then diluted with EtOAc, washed successively with $NaHCO_3$ (sat), water and brine, organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to get the crude compound, which was then purified by flash chromatography (SiO_2, 50% EtOAc in DCM) to get *tert*-butyl 6-chloro-3-(3-(naphthalen-1-yloxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (2.1 g, 3.86 mmol, 82%) as yellow sticky solid.

LCMS (ESI^+): m/z 544.5 $[M+H]^+$

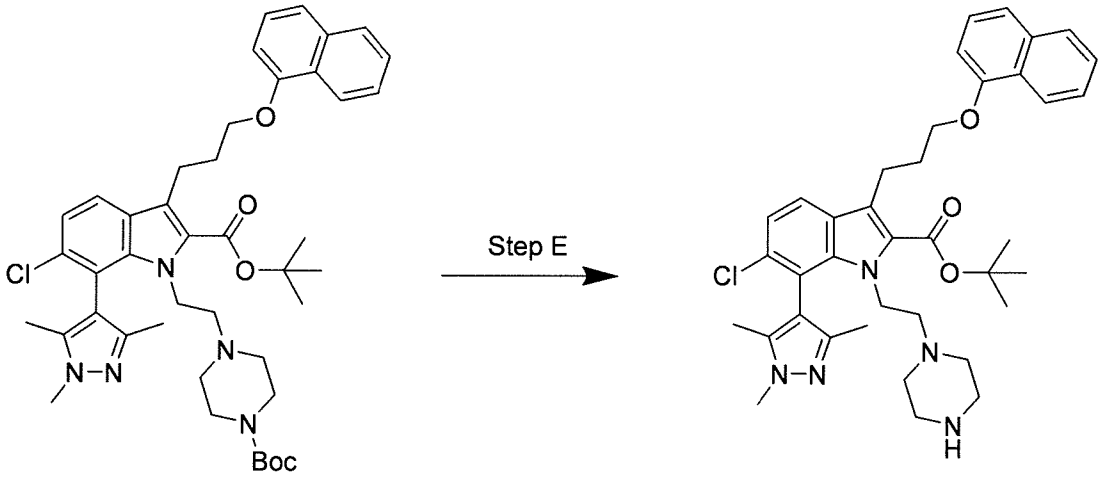
Step D



To a well stirred solution of *tert*-butyl 6-chloro-3-(3-(naphthalen-1-yloxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (2.1 g, 3.86 mmol) in DMF (20 mL) was added *tert*-butyl 4-(2-chloroethyl)piperazine-1-carboxylate (1.9 g, 7.6 mmol) followed by Cs_2CO_3 (6.3 g, 19.3 mmol) in DMF and the mixture was allowed to stir at 90°C for 16 h under nitrogen. The reaction mixture was diluted with EtOAc, washed successively with water and brine, the organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to get the crude compound, which was then purified by flash chromatography (SiO_2, 70% EtOAc in hexane) to get *tert*-butyl 1-(2-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)ethyl)-6-chloro-3-(3-(naphthalen-1-yloxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (2 g, 2.64 mmol, 68%) as off light yellow solid.

LCMS (ESI^+): m/z 756.2 $[M+H]^+$

Step E



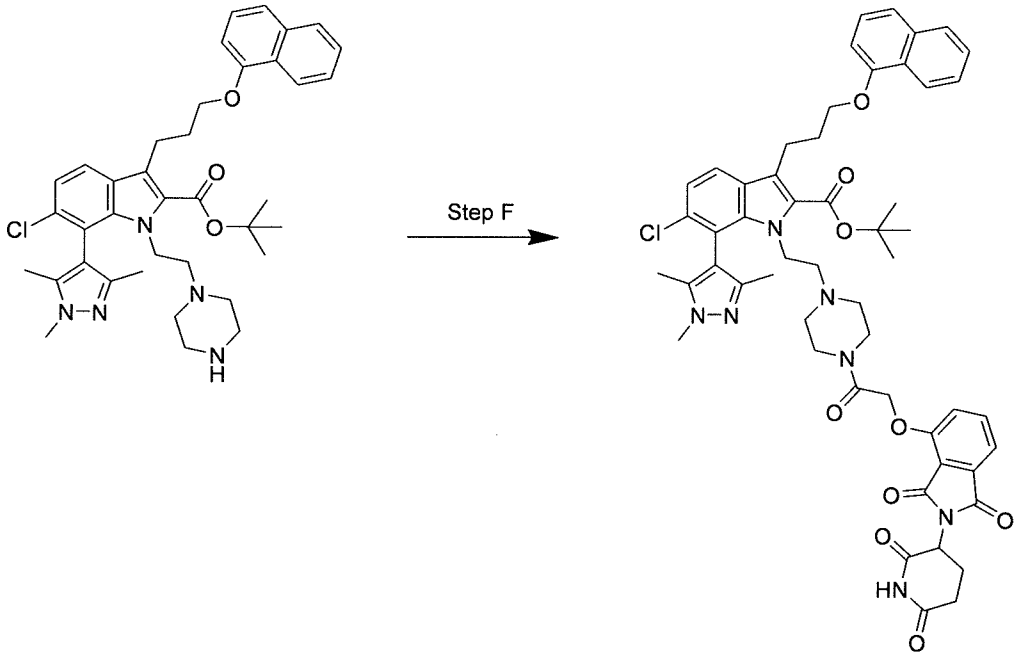
To a stirred solution of *tert*-butyl 1-(2-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)ethyl)-6-chloro-3-(3-(naphthalen-1-yloxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (1.7 g,

2.24 mmol) in dioxane (20 mL) was added 20 mL of 4M HCl in dioxane at 0°C under nitrogen and the reaction mixture was allowed to stir at room temperature for 1h. After consuming of starting material (monitored by TLC and LCMS) the reaction mixture was quenched by drop wise addition of aq 1N NaOH at 0°C and adjusted the pH to 7, then it was extracted with DCM (3×150 mL), dried over Na_2SO_4, filtered, and concentrated in vacuum to afford the crude material which was further purified by triturating by Et_2O and pentane to afford *tert*-butyl 6-chloro-3-[3-(naphthalen-1-yloxy)propyl]-1-[2-(piperazin-1-yl)ethyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate

(1 g, 1.52 mmol, 68%) as off white solid.

LCMS (ESI^+): m/z 656.4 $[M+H]^+$

Step F

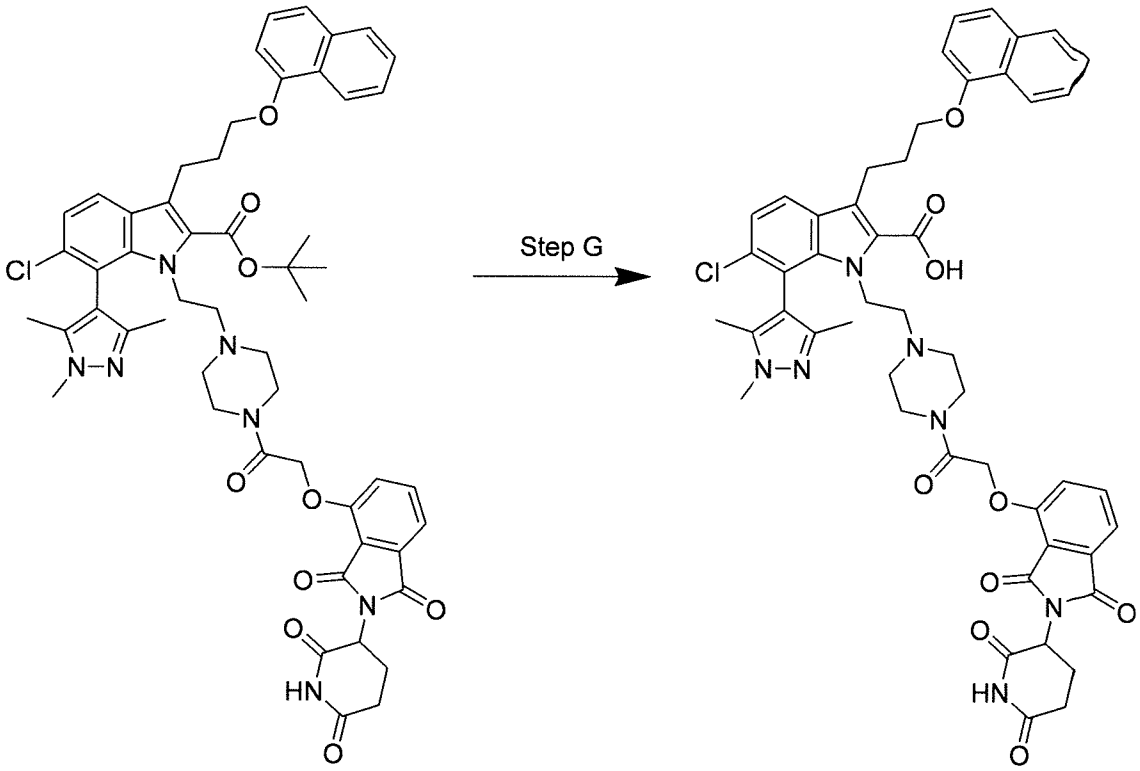


To a well stirred solution of 2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)acetic acid (30.4 mg, 0.091 mmol) and *tert*-butyl 6-chloro-3-[3-(naphthalen-1-yloxy)propyl]-1-[2-(piperazin-1-yl)ethyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (50.0 mg, 0.072 mmol) in DMF (0.762 mL) was added DIPEA (0.040 mL, 0.229 mmol) and HATU (34.8 mg, 0.091 mmol) and the mixture was allowed to stir under nitrogen for 16 h. After complete consumption of the starting material (monitored by TLC and LCMS), then the reaction mixture diluted with EtOAc, washed successively with cold water and brine. Organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. Crude material was purified using flash chromatography (SiO_2, 10% MeOH in DCM) to afford *tert*-butyl 6-chloro-1-(2-(4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-

dioxoisoindolin-4-yl)oxy)acetyl)piperazin-1-yl)ethyl)-3-(3-(naphthalen-1-yloxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (65 mg, 0.067 mmol, 88%) as white solid.

LCMS (ESI$^+$): m/z 970.4 $[M+H]^+$

Step G



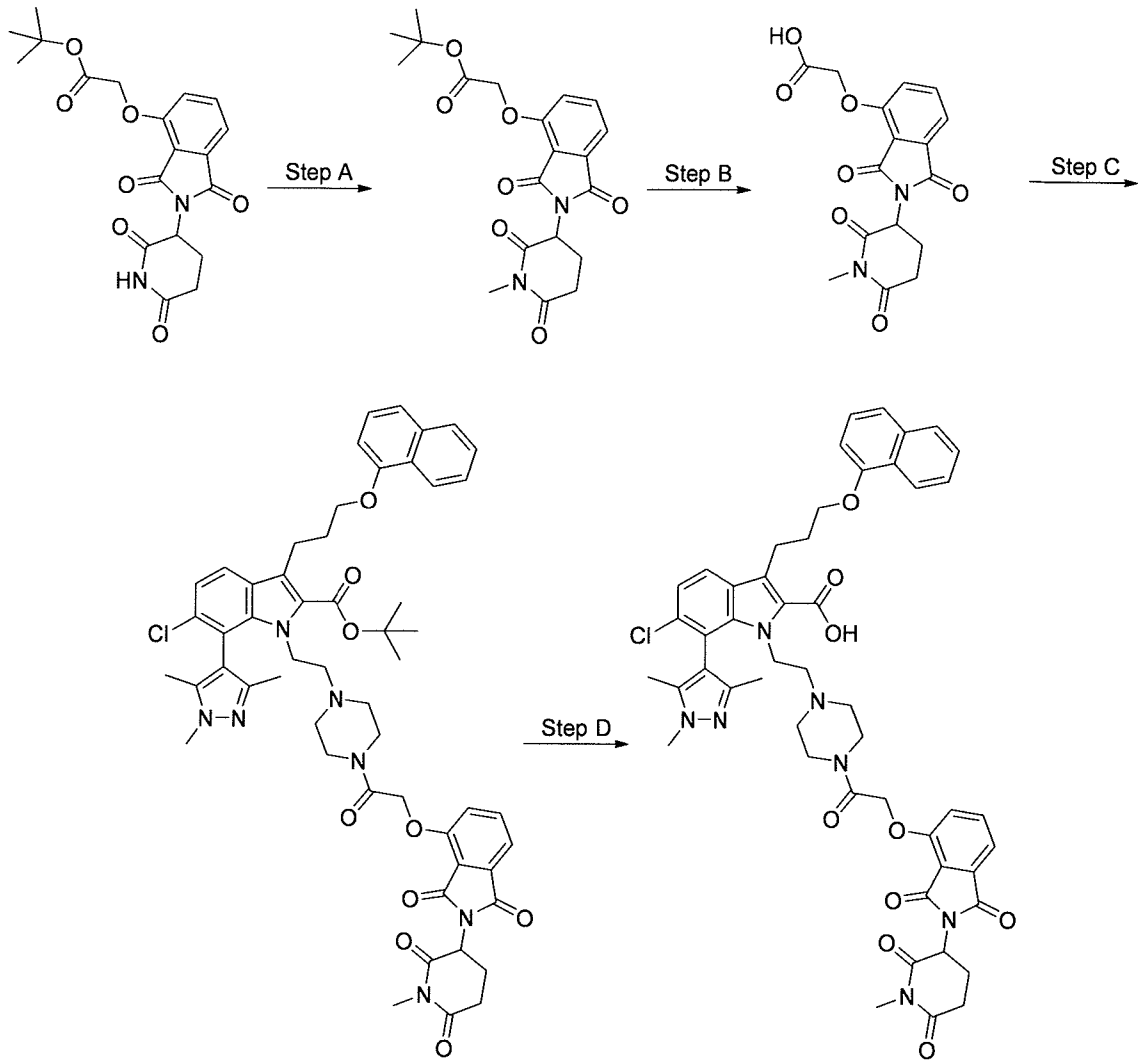
Tert-butyl 6-chloro-1-(2-(4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)acetyl)piperazin-1-yl)ethyl)-3-(3-(naphthalen-1-yloxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (110.0 mg, 0.11 mmol) was placed in a capped vial, dissolved in DCM and then TFA (0.087 mL, 1.133 mmol) was added. Reaction was stirred overnight at room temperature. Solvents were removed under reduced pressure and crude was purified using preparative HPLC (H_2O:MeCN + 0.1% FA) to afford 6-chloro-1-{2-[4-(2-{[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl]oxy}acetyl)piperazin-1-yl]ethyl}-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (50.0 mg, 0.055 mmol, 49%) as white solid.

LCMS (ESI$^+$): m/z 914.4 $[M+H]^+$

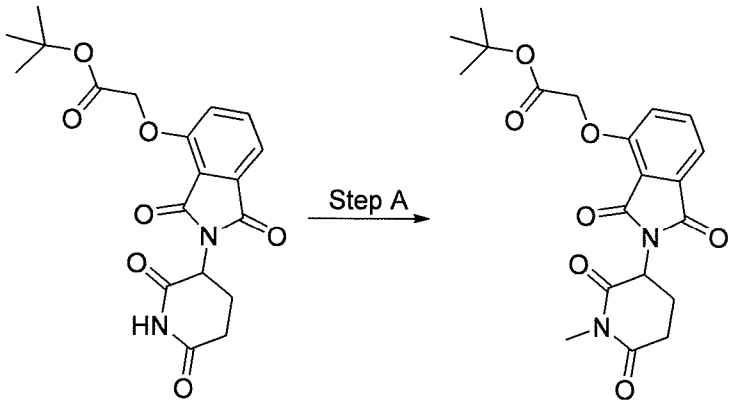
^{1}H NMR (500 MHz, DMSO) δ 13.43 (s, 1H), 11.11 (s, 1H), 8.26 – 8.19 (m, 1H), 7.91 – 7.85 (m, 1H), 7.81 – 7.73 (m, 2H), 7.57 – 7.49 (m, 2H), 7.46 (dd, *J* =7.7, 6.1 Hz, 2H), 7.40 (t, *J* = 7.9 Hz, 1H), 7.31 (d, *J* =

8.6 Hz, 1H), 7.24 (d, *J* = 8.5 Hz, 1H), 6.92 (dd, *J* = 7.7, 1.0 Hz, 1H), 5.19 – 5.06 (m, 3H), 4.36 – 4.27 (m,1H), 4.27 – 4.14 (m, 3H), 3.78 (s, 3H), 3.31 – 3.27 (m, 2H), 2.91 (ddd, *J* = 16.8, 13.8, 5.4 Hz, 1H), 2.65 – 2.53 (m, 2H), 2.24 (p, *J* = 6.5 Hz, 2H), 2.19 – 1.99 (m, 10H), 1.90 (s, 3H). 4 protons in aliphatic area overlaps with water.

Example 6: 6-chloro-1-(2-(4-(2-((2-(1-methyl-2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)acetyl)piperazin-1-yl)ethyl)-3-(3-(naphthalen-1-yloxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (205)

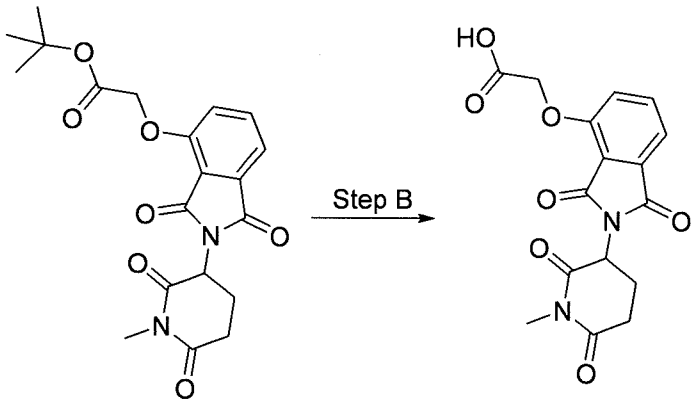


Step A



Tert-butyl 2-{[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl]oxy}acetate (50.0 mg, 0.129 mmol) was dissolved in acetone (1.3 mL). Potassium carbonate (53.4 mg, 0.386 mmol) was added and the reaction mixture was cooled down to 0°C. Next, iodomethane was (0.012 mL, 0.193 mmol) was slowly added and the reaction mixture was stirred at room temperature for 16 h. Water was added to the mixture and reaction product was extracted with DCM. Solvents were removed under reduced pressure and reaction product *tert*-butyl 2-((2-(1-methyl-2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)acetate (22.0 mg, 0.055 mmol, 43%) was used to the next step.

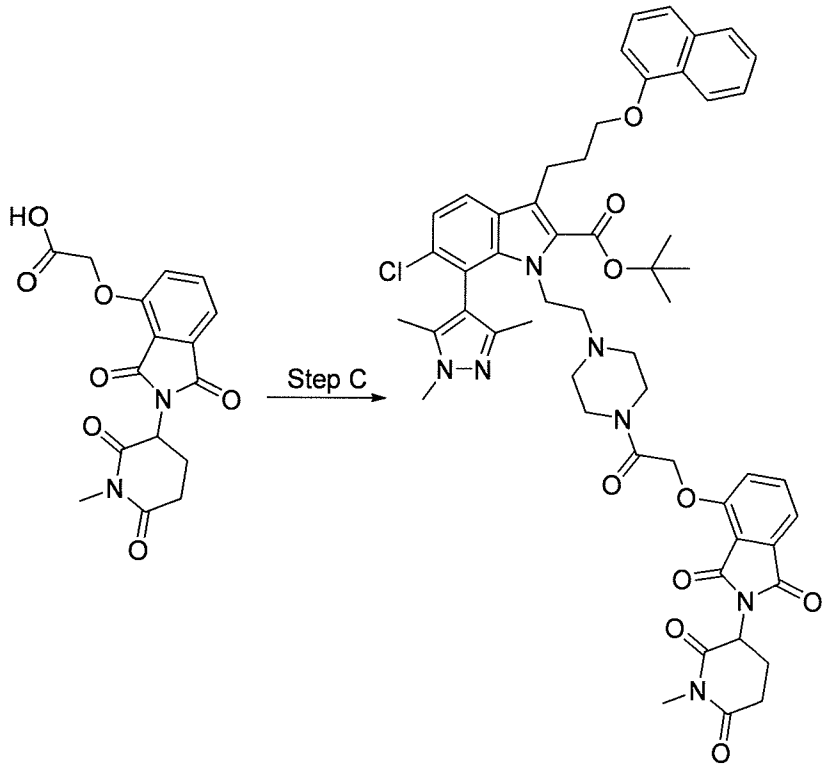
Step B



Tert-butyl 2-{[2-(1-methyl-2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl]oxy}acetate (21.0 mg, 0.052 mmol) was dissolved in DCM (0.522 mL), and trifluoroacetic acid (0.080 mL, 1.044 mmol) was added. The mixture was stirred for 4h. Reaction mixture was separated between water and DCM. Organic phase was collected, solvent evaporated and the resulting product_(2-{[2-(1-methyl-2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl]oxy}acetic acid (13.3 mg, 0.038 mmol, 74%) was obtained as white solid and subjected to the subsequent step.

LCMS (ESI+): m/z 347.2 $[M+H]^+$

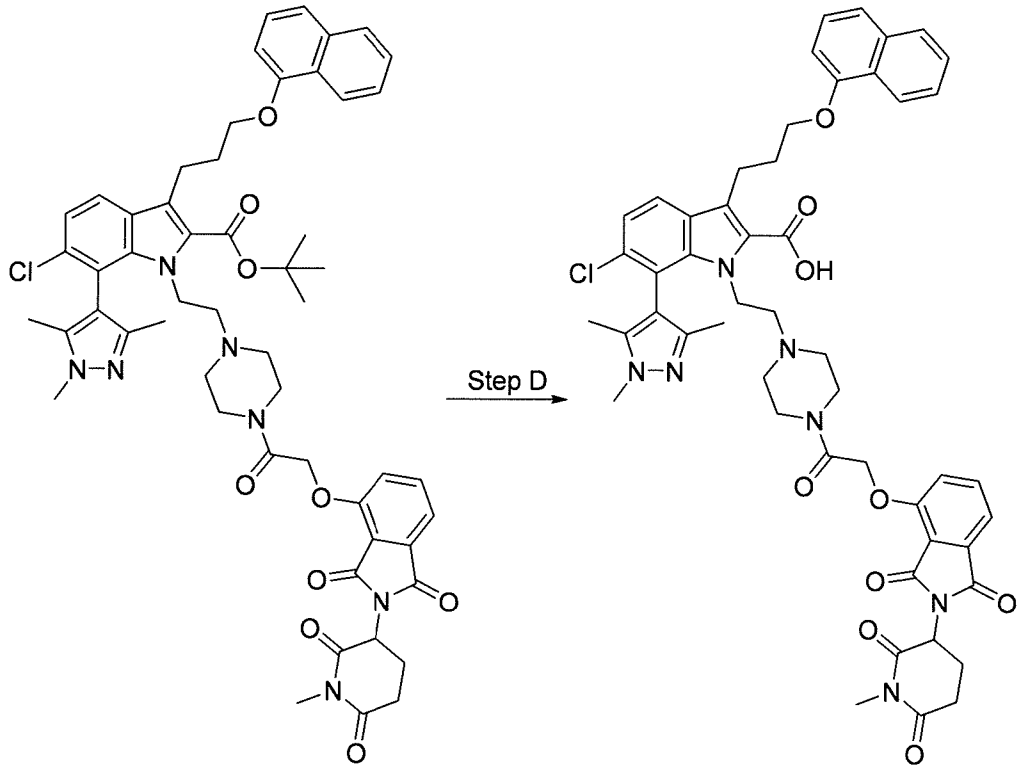
Step C



2-{[2-(1-methyl-2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl]oxy}acetic acid (13.3 mg, 0.038 mmol) was dissolved in DMF (1.3 mL). DIPEA (0.020 mL, 0.115 mmol) followed by HATU (17.5 mg, 0.046 mmol) were added and the reaction stirred for 15 min in room temperature. Next, *tert*-butyl 6-chloro-3-(3-(naphthalen-1-yloxy)propyl)-1-(2-(piperazin-1-yl)ethyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (30.2 mg, 0.046 mmol) was added and the reaction stirred for 2 h. After that time DMF was removed, the resulting solid dissolved in EtOAc and washed 3x with water. Organic layer was collected, dried over Na_2SO_4, filtered and concentrated in vacuum. Solvents were evaporated and reaction product dried under reduced pressure to give 32.0 mg of crude *tert*-butyl 6-chloro-1-(2-(4-(2-((2-(1-methyl-2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)acetyl)piperazin-1-yl)ethyl)-3-(3-(naphthalen-1-yloxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate that was used in the next step without further purification.

LCMS (ESI+): m/z 984.8 $[M+H]^+$

Step D

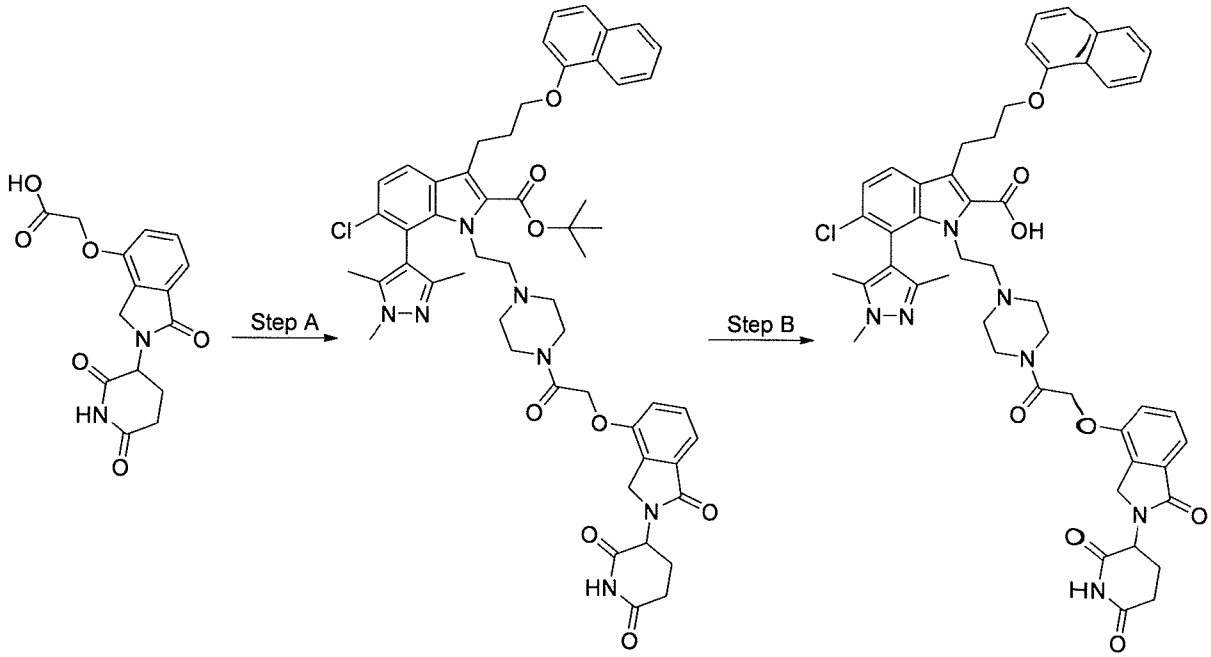


Tert-butyl 6-chloro-1-(2-(4-(2-((2-(1-methyl-2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)acetyl)piperazin-1-yl)ethyl)-3-(3-(naphthalen-1-yloxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (32.0 mg, crude) was dissolved in dry DCM (0.25 mL) under an inert gas atmosphere. TFA (0.25 mL, 3.250 mmol) was added and the reaction was stirred in room temperature. After 18 h full conversion of the starting material was observed. DCM and TFA acid were evaporated under reduced pressure and the resulting solid dissolved in DMSO and purified by preparative HPLC (H_2O:MeCN + 0.1% FA) to give a corresponding 6-chloro-1-(2-(4-(2-((2-(1-methyl-2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)acetyl)piperazin-1-yl)ethyl)-3-(3-(naphthalen-1-yloxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (18.0 mg, 0.019 mmol, 50% over two steps) as white solid.

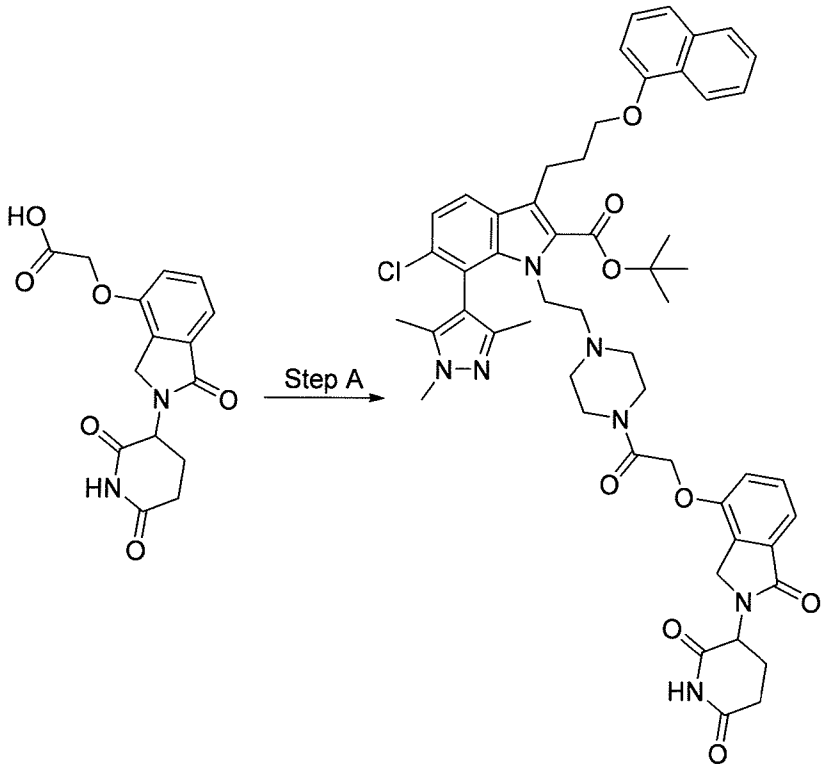
LCMS (ESI+): m/z 928.8 $[M+H]^+$

^{1}H NMR (500 MHz, DMSO) δ 13.42 (s, 1H), 8.28 – 8.19 (m, 1H), 7.94 – 7.84 (m, 1H), 7.83 – 7.73 (m, 2H), 7.62 – 7.50 (m, 2H), 7.50 – 7.44 (m, 2H), 7.41 (t, *J* = 7.9 Hz, 1H), 7.33 (d, *J* = 8.4 Hz, 1H), 7.26 (d, *J* = 8.5 Hz, 1H), 6.93 (d, *J* = 7.5 Hz, 1H), 5.25 – 5.06 (m, 3H), 4.47 – 4.11 (m, 4H), 3.78 (s, 3H), 3.47 – 3.35 (m, 6H), 3.02 (s, 3H), 2.99 – 2.87 (m, 1H), 2.82 – 2.74 (m, 1H), 2.62 – 2.53 (m, 1H), 2.30 – 1.97 (m, 12H), 1.91 (s, 3H).

Example 7: 6-chloro-1-(2-(4-(2-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)oxy)acetyl)piperazin-1-yl)ethyl)-3-(3-(naphthalen-1-yloxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (206)



Step A

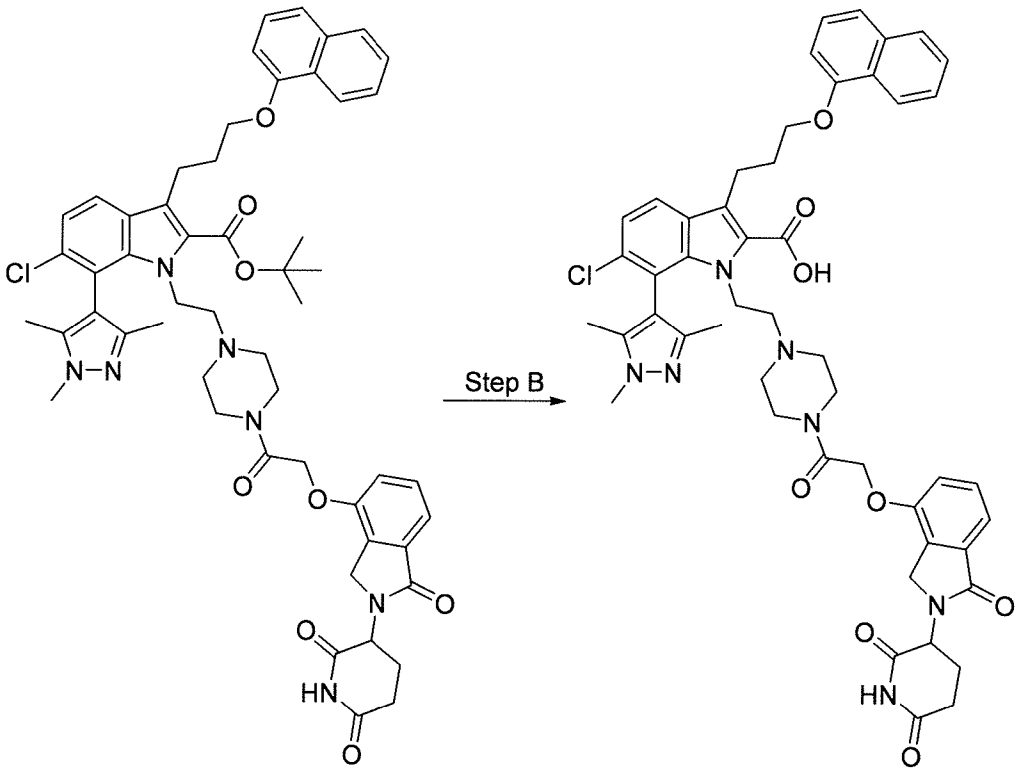


2-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)oxy)acetic acid (15.0 mg, 0.047 mmol) was dissolved in dry DMF (0.943 mL) under inert gas atmosphere. DIPEA (0.025 mL, 0.141

mmol) followed by HATU (26.9 mg, 0.071 mmol) were added and the reaction mixture stirred for 15 min in room temperature. *Tert*-butyl 6-chloro-3-(3-(naphthalen-1-yloxy)propyl)-1-(2-(piperazin-1-yl)ethyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (30.9 mg, 0.047 mmol) was added and the solution stirred for additional 2 h. DMF was removed under reduced pressure, crude product dissolved in EtOAc and washed 3x with water. Organic layer was collected and dried over Na_2SO_4. Solvent was evaporated to get crude (45 mg) *tert*-butyl 6-chloro-1-(2-(4-(2-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)oxy)acetyl)piperazin-1-yl)ethyl)-3-(3-(naphthalen-1-yloxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate as dark solid.

LCMS (ESI+): 956.8 m/z $[M+H]^+$

Step B



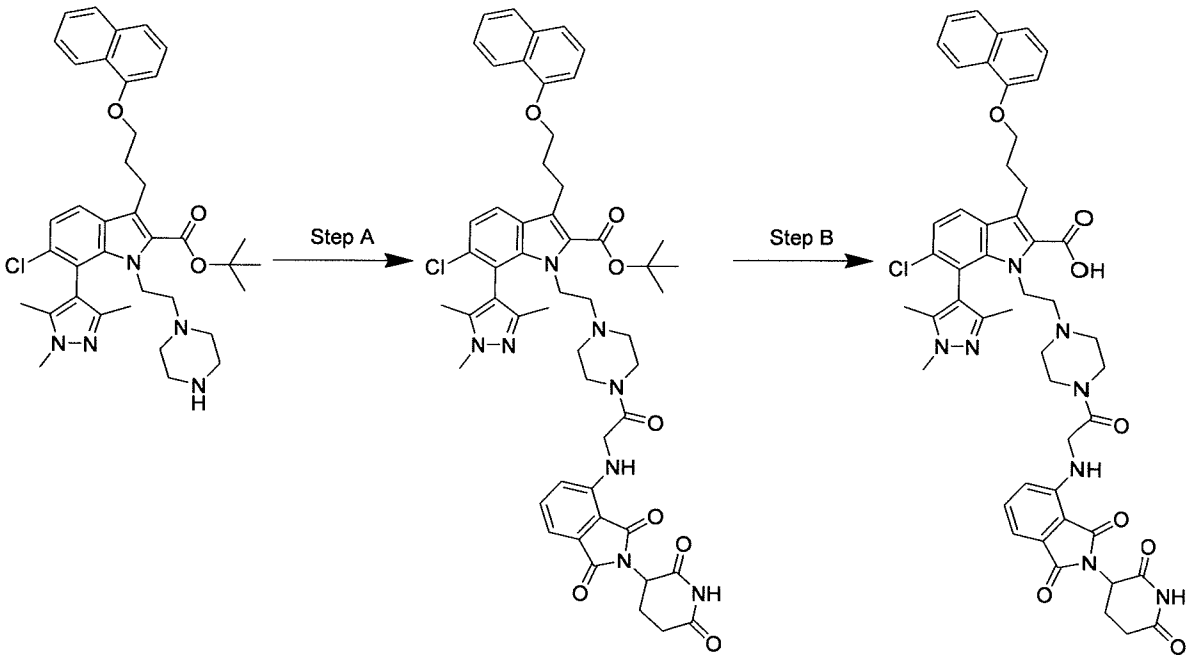
Tert-butyl 6-chloro-1-(2-(4-(2-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)oxy)acetyl)piperazin-1-yl)ethyl)-3-(3-(naphthalen-1-yloxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (45.0 mg, crude) was dissolved in dry DCM (0.1 mL). TFA was added (0.100 mL, 1.303 mmol) and the reaction was stirred at room temperature for 16 h. DCM and TFA acid were evaporated under reduced pressure and the resulting solid dissolved in DMSO and was purified by preparative HPLC (H_2O:MeCN + 0.1% FA) to give 6-chloro-1-(2-(4-(2-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)oxy)acetyl)piperazin-1-yl)ethyl)-3-(3-(naphthalen-1-

yloxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (16.8 mg, 0.019 mmol, 38% yield over two steps) as white powder.

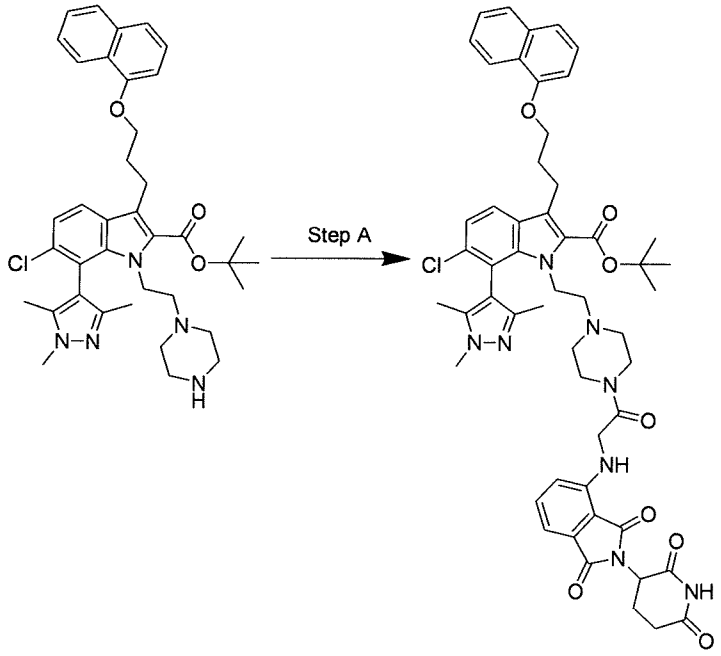
LCMS (ESI+): m/z 899.9 $[M+H]^+$

^{1}H NMR (500 MHz, DMSO) δ 13.42 (s, 1H), 10.98 (s, 1H), 8.22 (d, *J* = 9.0 Hz, 1H), 7.90 – 7.84 (m, 1H), 7.76 (d, *J* = 8.2 Hz, 1H), 7.53 (dq, *J* = 6.8, 5.4 Hz, 2H), 7.46 (t, *J* = 8.0 Hz, 2H), 7.40 (t, *J* = 7.9 Hz, 1H), 7.33 (d, *J* = 7.4 Hz, 1H), 7.24 (d, *J* = 8.4 Hz, 1H), 7.13 (d, *J* = 8.2 Hz, 1H), 6.92 (d, *J* = 7.5 Hz, 1H), 5.12 (dd, *J* = 13.3, 5.1 Hz, 1H), 4.96 (s, 2H), 4.42 – 4.14 (m, 6H), 3.77 (d, *J* = 1.7 Hz, 3H), 3.41 – 3.34 (m, 6H), 3.01 – 2.85 (m, 1H), 2.63 – 2.57 (m, 2H), 2.29 – 2.18 (m, 2H), 2.15 – 1.99 (m, 10H), 1.89 (s, 3H).

Example 8: 6-chloro-1-{2-[4-(2-{[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl]amino}acetyl)piperazin-1-yl]ethyl}-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid) (207)



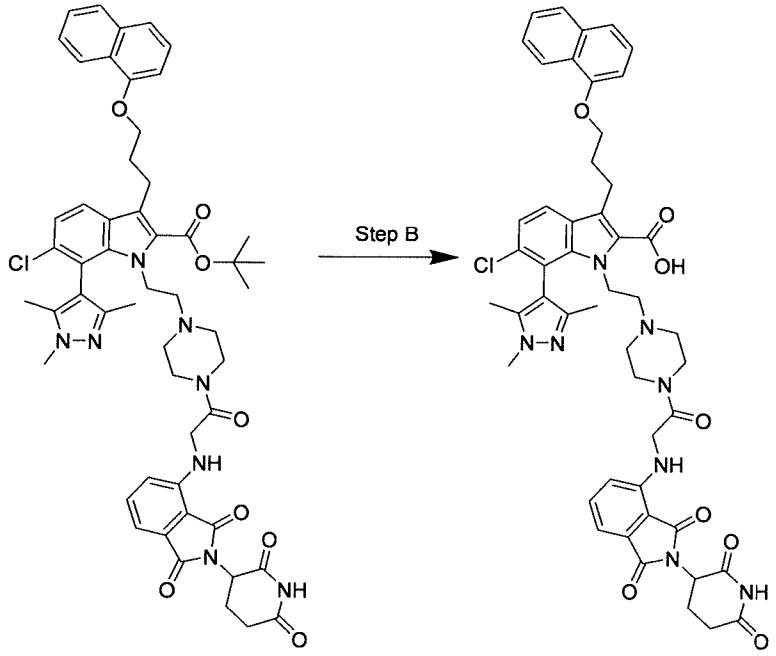
Step A



To a well stirred solution of 2-{[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*–isoindol-4-yl]amino}acetic acid (30.3 mg, 0.091 mmol) and *tert*-butyl 6-chloro-3-(3-(naphthalen-1-yloxy)propyl)-1-(2-(piperazin-1-yl)ethyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (50.0 mg, 0.076 mmol) in DMF (0.762 mL) was added DIPEA (0.040 mL, 0.229 mmol) and HATU (43.5 mg, 0.114 mmol) and the mixture was allowed to stir under nitrogen for 2h at room temperature. The reaction mixture diluted with EtOAc, washed successively with cold water and brine. Organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. The crude *tert*-butyl 6-chloro-1-{2-[4-(2-{[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl]amino}acetyl)piperazin-1-yl]ethyl}-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (68.7 mg) was obtained as yellow gum, which was used for the next step without further purification.

LCMS (ESI+): m/z 969.3 $[M+H]^+$

Step B



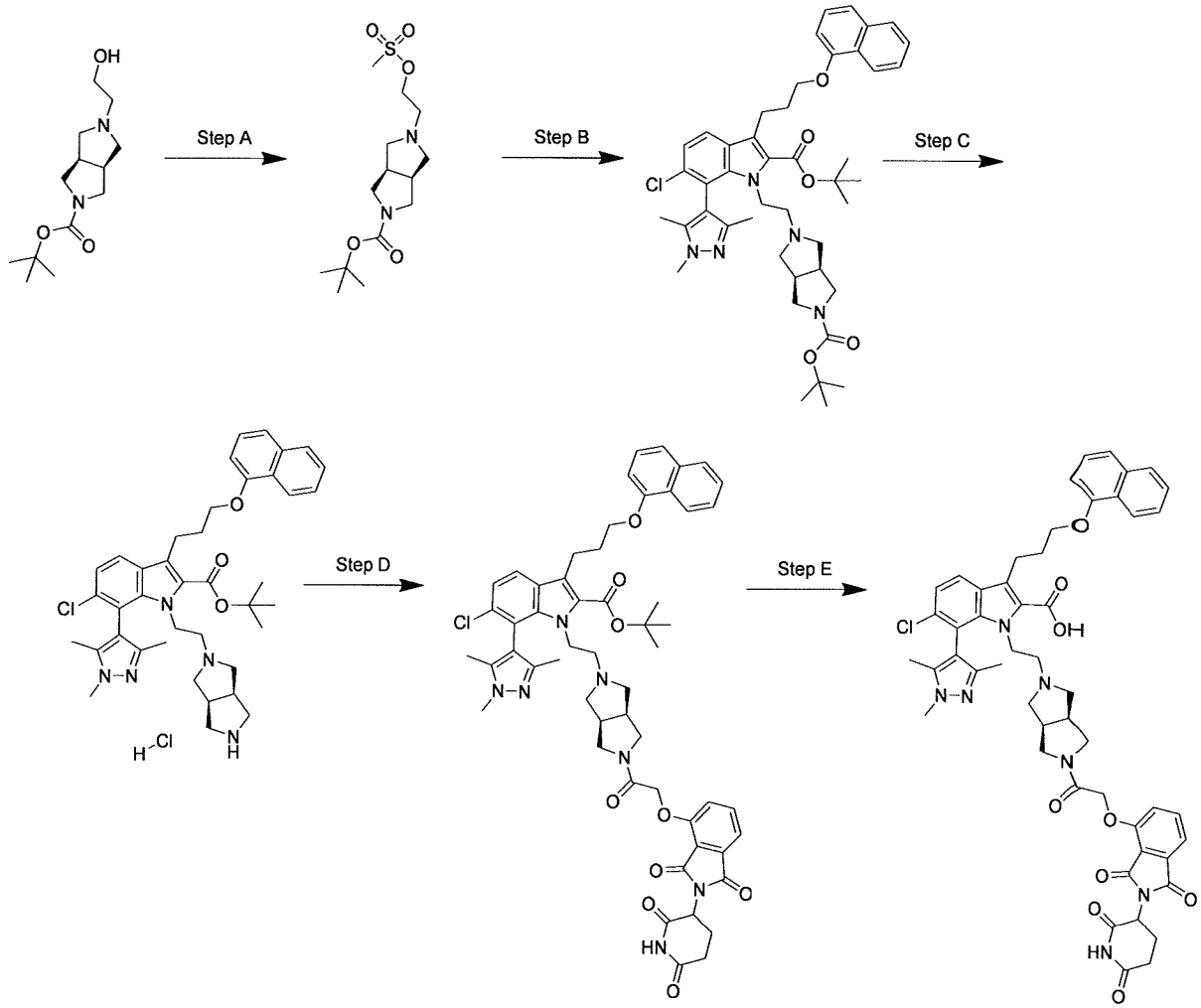
Tert-butyl 6-chloro-1-{2-[4-(2-{[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl]amino}acetyl)piperazin-1-yl]ethyl}-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (68.7 mg, crude) was dissolved in DCM (0.15mL) and then TFA (0.054 mL, 0.708 mmol) was added. Reaction was stirred overnight at room temperature. Solvents were removed under reduced pressure, and crude was purified using preparative HPLC (H_2O:MeCN + 0.1% FA) to afford 6-chloro-1-{2-[4-(2-{[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl]amino}acetyl)piperazin-1-yl]ethyl}-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (21.8 mg, 0.024 mmol, 32% over two steps) as yellow solid.

LCMS (ESI+): m/z 913.2 $[M+H]^+$

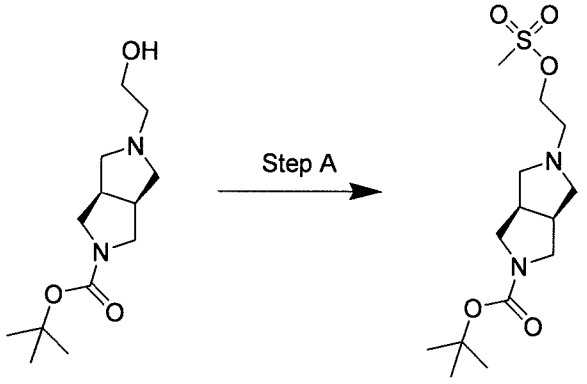
^{1}H NMR (500 MHz, DMSO) δ 13.40 (s, 1H), 11.10 (s, 1H), 8.25 – 8.19 (m, 1H), 7.90 – 7.84 (m, 1H), 7.77 (d, *J* = 8.6 Hz, 1H), 7.66 – 7.56 (m, 2H), 7.56 – 7.50 (m, 2H), 7.47 (d, *J* = 8.3 Hz, 1H), 7.40 (t, *J* = 7.9 Hz, 1H), 7.25 (d, *J* = 8.5 Hz, 1H), 7.10 – 7.08 (m, 1H), 7.07 – 7.04 (m, 1H), 6.92 (dd, *J* = 7.7, 1.0 Hz, 1H), 5.08 (dd, *J* = 12.8, 5.4 Hz, 1H), 4.35 – 4.27 (m, 1H), 4.27 – 4.15 (m, 3H), 4.12 (d, *J* = 4.6 Hz, 2H), 3.79 (s, 3H), 3.48 – 3.40 (m, 2H), 3.40 – 3.35 (m, 2H), 3.30 – 3.25 (m, 2H), 2.90 (ddd, *J* = 16.9, 13.8, 5.4 Hz, 1H), 2.64 – 2.55 (m, 2H), 2.28 – 2.20 (m, 2H), 2.16 – 2.08 (m, 5H), 2.08 – 2.00 (m, 5H), 1.90 (s, 3H).

Example 9: 6-chloro-1-(2-((3*aR*,6*aS*)-5-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)acetyl)hexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl)ethyl)-3-(3-(naphthalen-1-yloxy)propyl)-

7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (211)



Step A

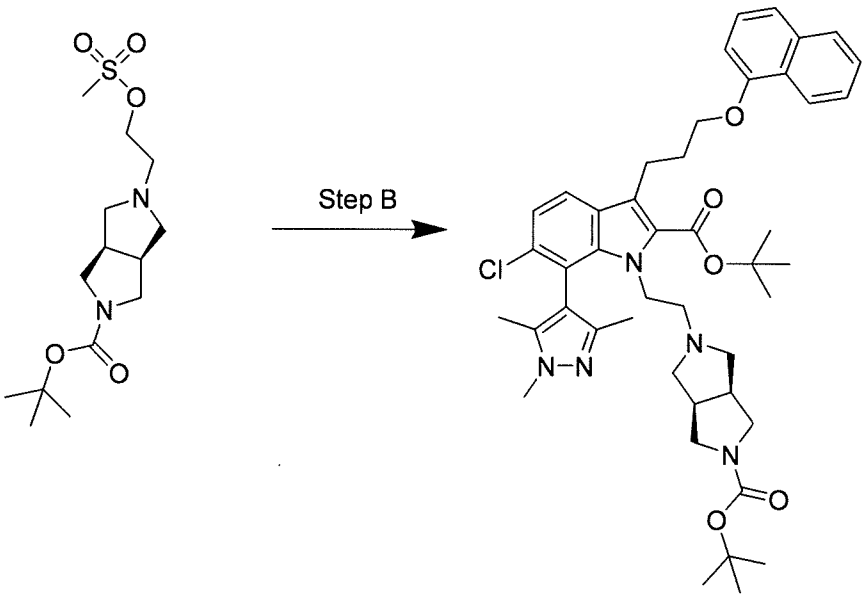


Tert-butyl 5-(2-hydroxyethyl)-octahydropyrrolo[3,4-*c*]pyrrole-2-carboxylate (485.0 mg, 1.892 mmol) was dissolved in DCM (5.0 mL), Et_3N (0.395 mL, 2.838 mmol) and DMAP (23.1 mg, 0.189 mmol) were added and reaction mixture cooled to 0°C. Then MsCl (0.176 mL, 2.270 mmol) was added dropwise and reaction mixture was let to stir at RT for 4 h and next 36 h in a fridge (at 4°C). The crude was extracted with brine, dried over Na_2SO_4, filtered and concentrated in vacuo.

The product, *tert*-butyl 5-[2-(methanesulfonyloxy)ethyl]-octahydropyrrolo[3,4-*c*]pyrrole-2-carboxylate (520.8 mg, 1.557 mmol, 82.3%) was an orange oil.

LCMS (ESI$^+$): m/z 334.8 $[M+H]^+$

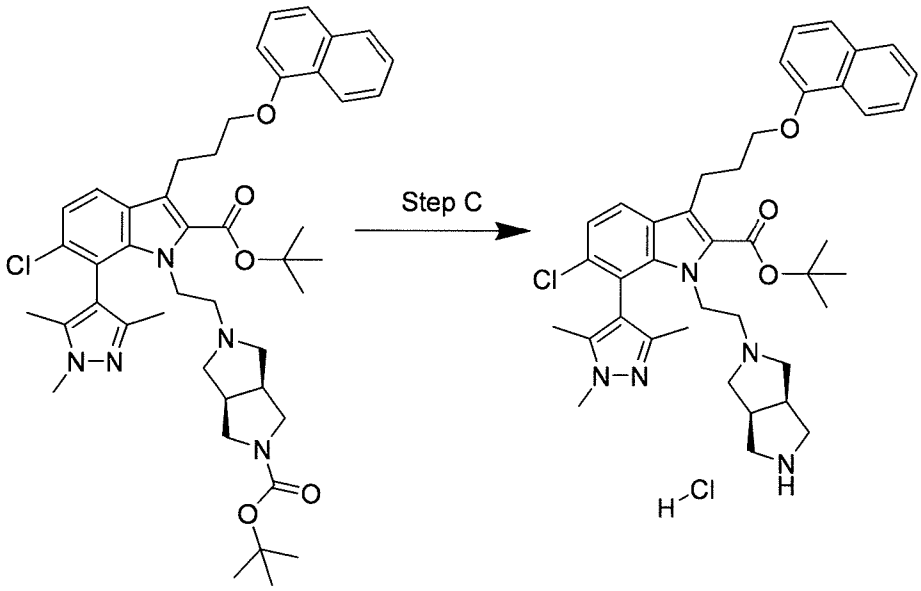
Step B



Tert-butyl 6-chloro-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (50.0 mg, 0.092 mmol), *tert*-butyl 5-[2-(methanesulfonyloxy)ethyl]-octahydropyrrolo[3,4-*c*]pyrrole-2-carboxylate (36.9 mg, 0.110 mmol) and Cs_2CO_3 (89.8 mg, 0.276 mmol) were dissolved in dry DMF (2.0 mL) and stirred at 60°C for overnight. After complete consumption of the starting material solvent was evaporated under reduced pressure, the residues were dissolved in DCM and washed with H_2O and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated in vacuum. Product *tert*-butyl 1-(2-{5-[(*tert*-butoxy)carbonyl]-octahydropyrrolo[3,4-*c*]pyrrol-2-yl}ethyl)-6-chloro-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (71.7 mg, 0.092 mmol) was used to next step without further purification.

LCMS (ESI$^+$): m/z 782.0 $[M+H]^+$

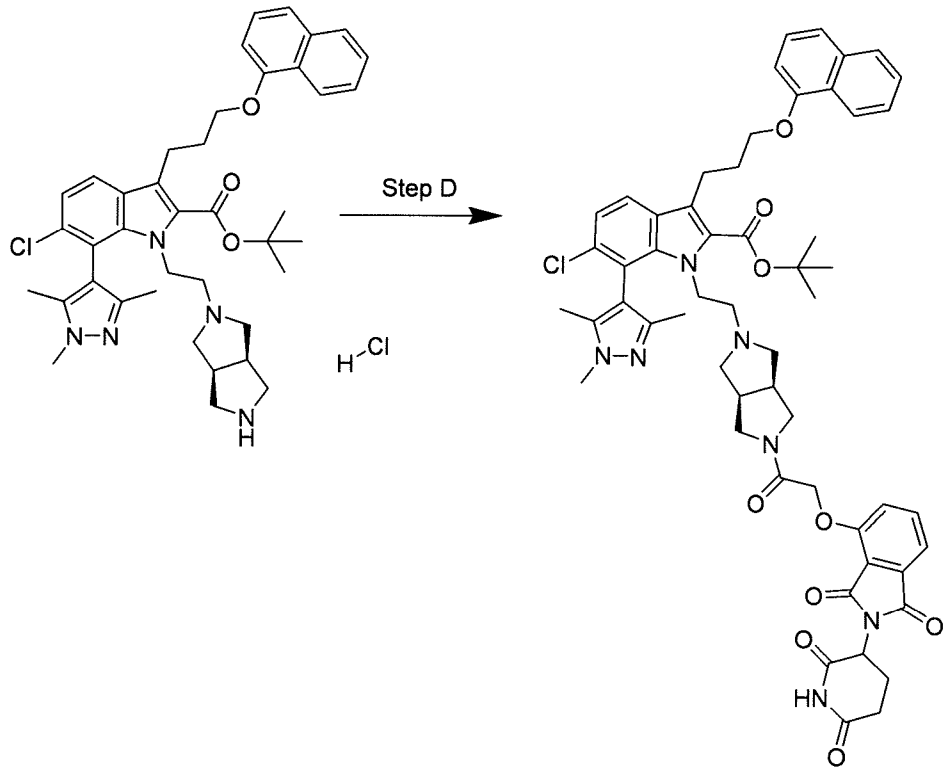
Step C



To a solution of *tert*-butyl 1-(2-{5-[(*tert*-butoxy)carbonyl]-octahydropyrrolo[3,4-*c*]pyrrol-2-yl}ethyl)-6-chloro-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (71.7 mg, 0.092 mmol) in THF (3.5 mL) at 0°C was added 4M HCl in dioxane (0.573 mL, 2.291 mmol). The mixture was stirred for next 24 h at RT. LCMS analysis after 24 h confirmed a presence of starting material, therefore next portion of 4M HCl in dioxane was added and a reaction was stirred next 18 h at RT. After complete consumption of the substrate the crude was concentrated under vacuum and a product *tert*-butyl 6-chloro-3-[3-(naphthalen-1-yloxy)propyl]-1-(2-{octahydropyrrolo[3,4-*c*]pyrrol-2-yl}ethyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate hydrochloride (77.0 mg) was used to next step without further purification.

LCMS (ESI+): m/z 682.0 $[M+H]^+$

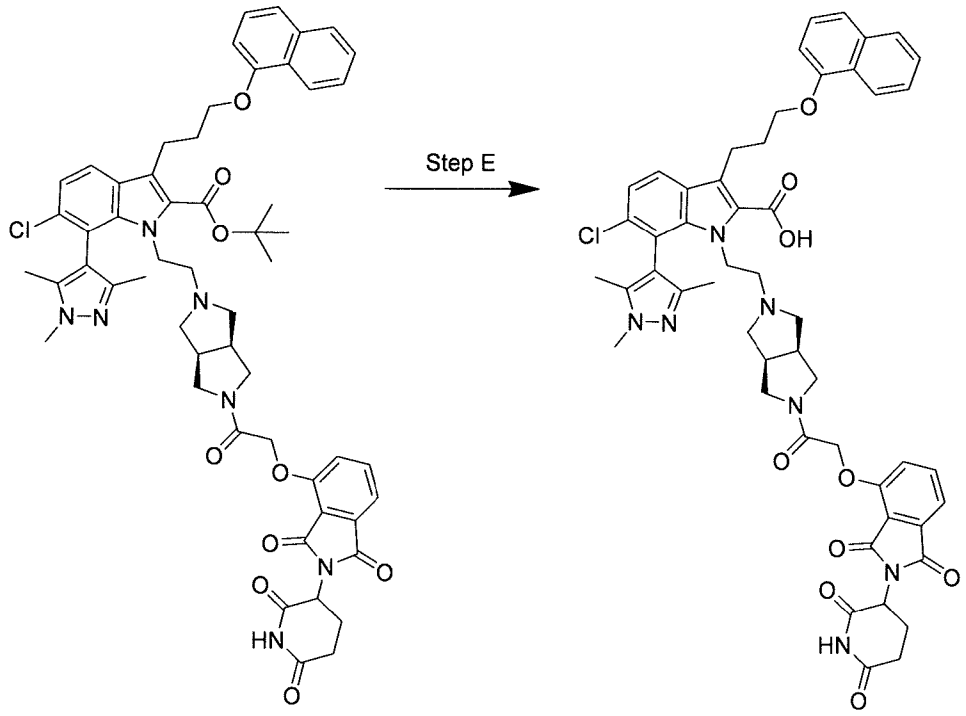
Step D



To a well stirred solution of *tert*-butyl 6-chloro-3-[3-(naphthalen-1-yloxy)propyl]-1-(2-{octahydropyrrolo[3,4-*c*]pyrrol-2-yl}ethyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate hydrochloride (50.0 mg, crude) and 2-{[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl]oxy}acetic acid (27.7 mg, 0.083 mmol) in DMF (2.0 mL) were added DIPEA (0.095 mL, 0.545 mmol) and HATU (52.9 mg, 0.139 mmol) and the mixture was allowed to stir under argon for 2 h at RT. After complete consumption of the starting material (monitored by LCMS) reaction mixture was diluted with DCM, washed successively with water and brine. Organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. Product *tert*-butyl 1-{2-[(3*aR*,6*aS*)-5-(2-{[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl]oxy}acetyl)-octahydropyrrolo[3,4-c]pyrrol-2-yl]ethyl}-6-chloro-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (87.2 mg, crude) was obtained as brown oil, which was used for the next step without further purification.

LCMS (ESI+): m/z 995.7 $[M+H]^+$

Step E

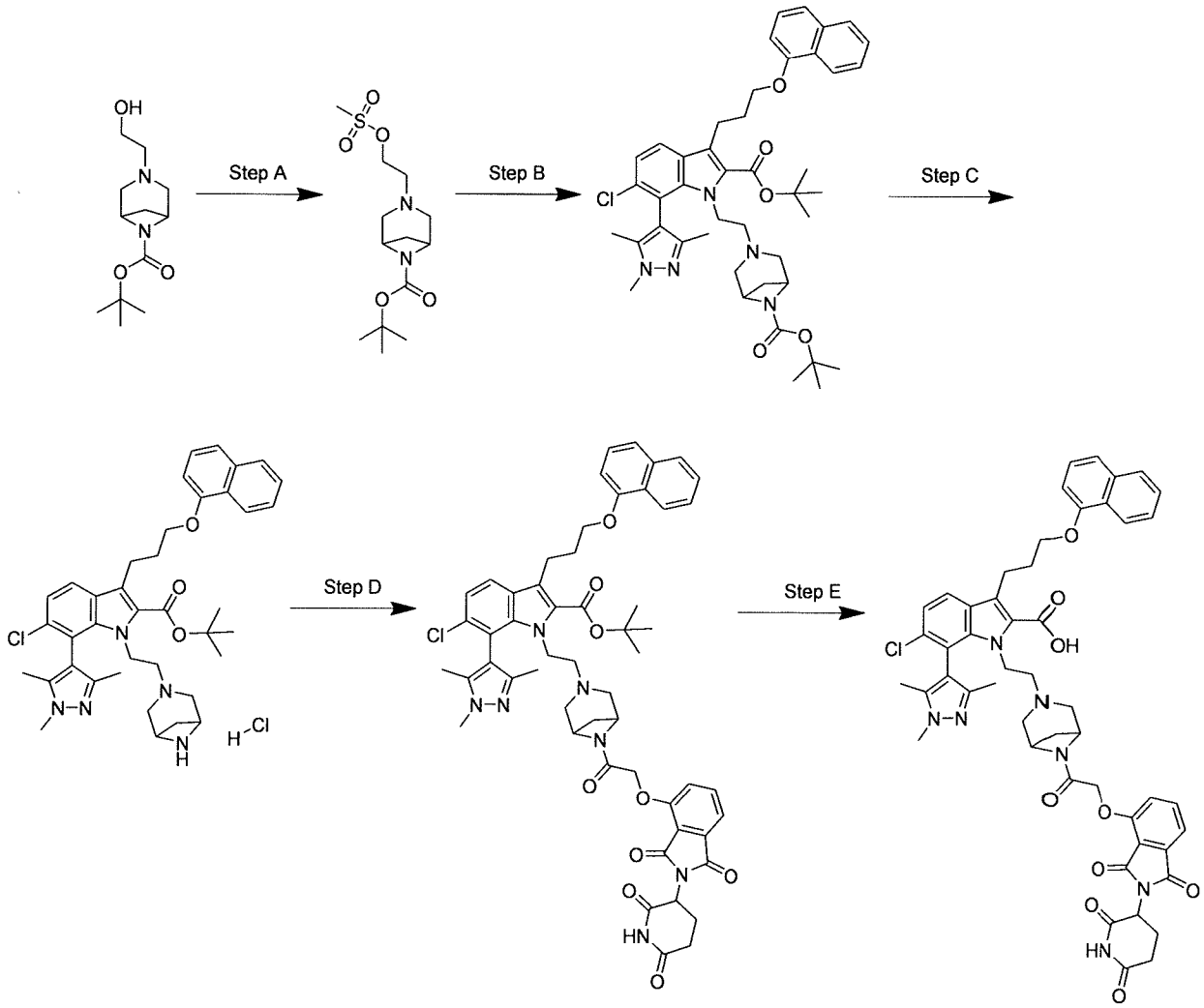


To a solution of *tert*-butyl 1-{2-[(3*aR*,6*aS*)-5-(2-{[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl]oxy}acetyl)-octahydropyrrolo[3,4-*c*]pyrrol-2-yl]ethyl}-6-chloro-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (87.2 mg crude) in DCM (1.0 mL) was added TFA (1.0 mL, 13.059 mmol). The mixture was stirred for 18 h at RT. After complete consumption of the starting material (monitored by LCMS), the crude was concentrated under vacuum. The residues were dissolved in DMSO and purified by preparative HPLC (H_2O:MeCN + 0.1% FA). The isolated product 1-{2-[(3*aR*,6*aS*)-5-(2-{[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl]oxy}acetyl)-octahydropyrrolo[3,4-*c*]pyrrol-2-yl]ethyl}-6-chloro-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (10.3 mg, 0.011 mmol, 12.0% over four steps) was a white solid.

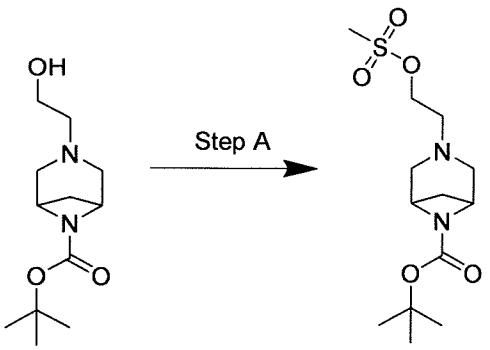
LCMS (ESI+): m/z 939.8 $[M+H]^+$

^{1}H NMR (500 MHz, DMSO) δ 13.67 (s, 1H), 11.09 (s, 1H), 8.18 (d, *J* = 8.1 Hz, 1H), 7.88 – 7.82 (m, 1H), 7.79 – 7.73 (m, 1H), 7.69 (d, *J* = 8.6 Hz, 1H), 7.54 – 7.45 (m, 2H), 7.45 – 7.35 (m, 4H), 7.19 (d, *J* = 8.4 Hz, 1H), 6.87 (d, *J* = 7.6 Hz, 1H), 5.09 (dd, *J* = 12.8, 5.4 Hz, 1H), 5.04 (d, *J* = 5.8 Hz, 2H), 4.35 – 4.23 (m, 1H), 4.23 – 4.11 (m, 3H), 3.74 (d, *J* = 2.6 Hz, 3H), 3.67 (q, *J* = 9.0 Hz, 1H), 3.57 – 3.48 (m, 1H), 3.27 – 3.20 (m, 1H), 3.19 – 3.10 (m, 1H), 2.89 (ddd, *J* = 17.5, 13.6, 5.4 Hz, 1H), 2.84 – 2.76 (m, 1H), 2.71 – 2.52 (m, 4H), 2.35 – 2.10 (m, 8H), 2.09 – 1.94 (m, 5H), 1.88 (d, *J* = 4.5 Hz, 3H).

Example 10: 6-chloro-1-(2-(6-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)acetyl)-3,6-diazabicyclo[3.1.1]heptan-3-yl)ethyl)-3-(3-(naphthalen-1-yloxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (208)



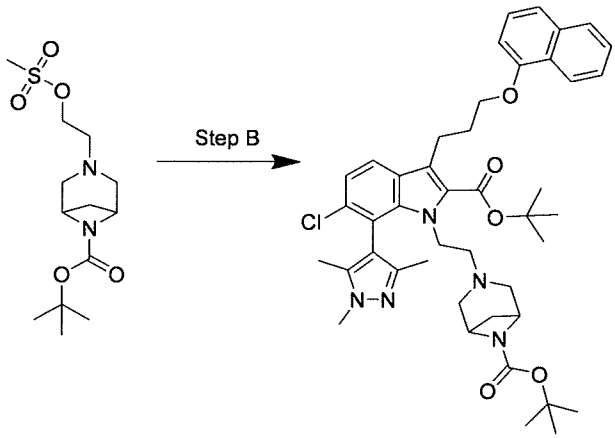
Step A



Tert-butyl 3-(2-hydroxyethyl)-3,6-diazabicyclo[3.1.1]heptane-6-carboxylate (132.0 mg, 0.545 mmol) was dissolved in DCM (5.4 mL), Et_3N (0.114 mL, 0.817 mmol) and DMAP (6.7 mg, 0.054 mmol) were added and reaction mixture cooled to -15°C. Then MsCl (0.051 mL, 0.654 mmol)

was added dropwise and reaction mixture was let to stir at RT and monitored by TLC (5% MeOH in DCM). Completion of the reaction and formation of one spot was observed after 2 hours. The reaction mixture was diluted in EtOAc and washed with brine. The organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo to get 35.0 mg of crude *tert*-butyl 3-[2-(methanesulfonyloxy)ethyl]-3,6-diazabicyclo[3.1.1]heptane-6-carboxylate, which was used directly in the next step without further purification.

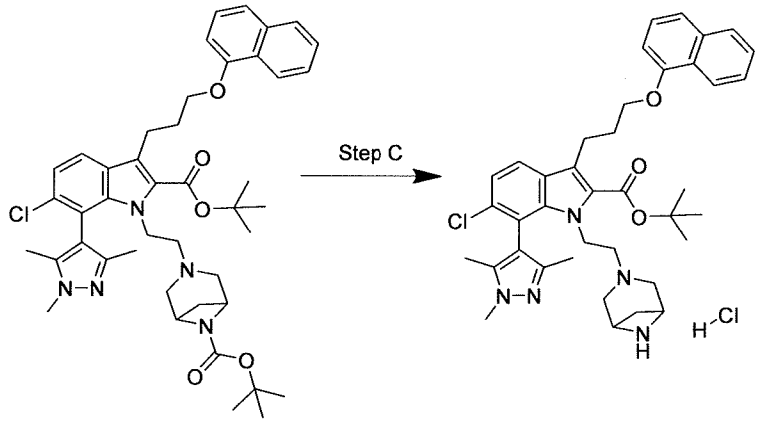
Step B



Tert-butyl 6-chloro-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (50.0 mg, 0.092 mmol), *tert*-butyl 3-[2-(methanesulfonyloxy)ethyl]-3,6-diazabicyclo[3.1.1]heptane-6-carboxylate (35.0 mg) and Cs_2CO_3 (89.8 mg, 0.276 mmol) were placed in a vial, dissolved in dry DMF (1.8 mL) and stirred at 60°C for overnight. Another portion of *tert*-butyl 3-[2-(methanesulfonyloxy)ethyl]-3,6-diazabicyclo[3.1.1]heptane-6-carboxylate (30.0 mg, 0.093 mmol) was added and reaction mixture was stirred for additional 18 hours at 60°C. The reaction mixture was diluted in EtOAc and washed with brine. The organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo to get 64.0 mg of crude *tert*-butyl 1-(2-{6-[(*tert*-butoxy)carbonyl]-3,6-diazabicyclo[3.1.1]heptan-3-yl}ethyl)-6-chloro-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate, which was used directly to the next step.

LCMS (ESI^+): m/z 768.3 $[M+H]^+$

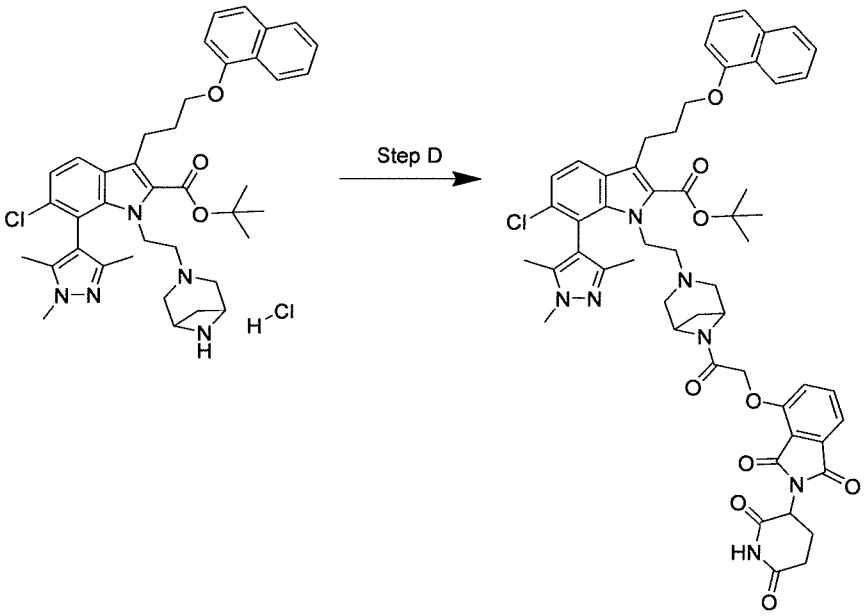
Step C



Tert-butyl 1-(2-{6-[(*tert*-butoxy)carbonyl]-3,6-diazabicyclo[3.1.1]heptan-3-yl}ethyl)-6-chloro-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (64.0 mg) was dissolved in THF (1.7 mL) and reaction mixture was cooled to 0°C. 4M HCl in dioxane (0.521 mL, 2.082 mmol) was then added dropwise and reaction was let to warm up to RT and stirred overnight. After complete consumption of the substrate (monitored by LCMS), solvent was evaporated and crude of *tert*-butyl 6-chloro-1-(2-{3,6-diazabicyclo[3.1.1]heptan-3-yl}ethyl)-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate hydrochloride was used directly to the next step.

LCMS (ESI$^+$): m/z 668.3 $[M+H]^+$

Step D

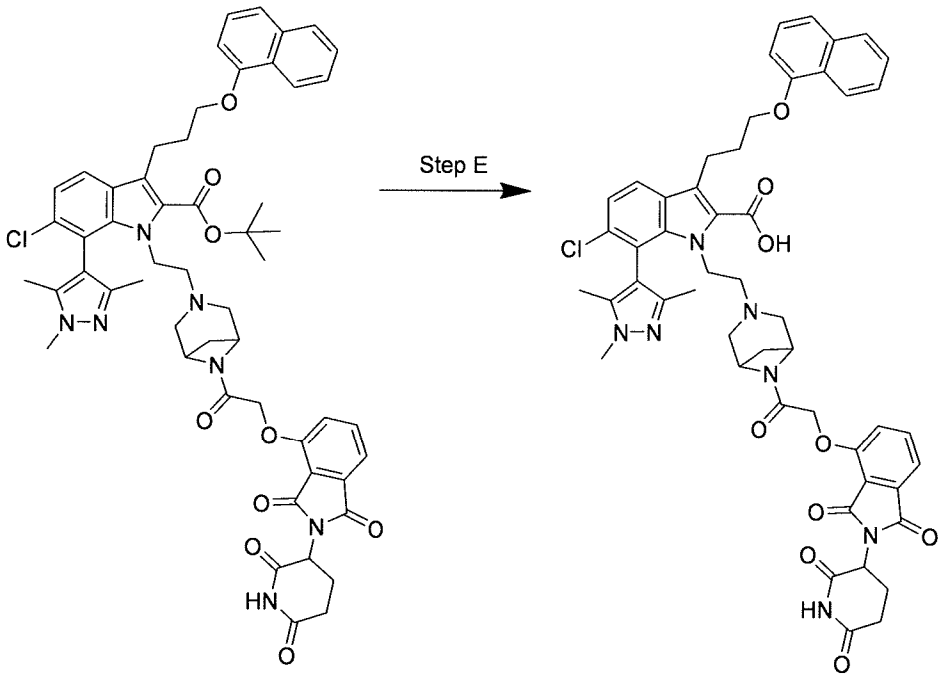


Tert-butyl 6-chloro-1-(2-{3,6-diazabicyclo[3.1.1]heptan-3-yl}ethyl)-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate hydrochloride (10.0 mg, 0.014 mmol), 2-{[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-

yl]oxy}acetic acid (5.7 mg, 0.017 mmol) and HATU (8.1 mg, 0.021 mmol) were placed in a vial, dissolved in dry DMF (0.167 mL) and then DIPEA (0.010 mL, 0.057 mmol) was added. Reaction was stirred at RT overnight. After complete consumption of the substrate (monitored by LCMS), solvent was evaporated and 56.0 mg crude mixture of *tert*-butyl 6-chloro-1-{2-[6-(2-{[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl]oxy}acetyl)-3,6-diazabicyclo[3.1.1]heptan-3-yl]ethyl}-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1H-indole-2-carboxylate was used directly to the next step.

LCMS (ESI$^+$): m/z 982.3 $[M+H]^+$

Step E

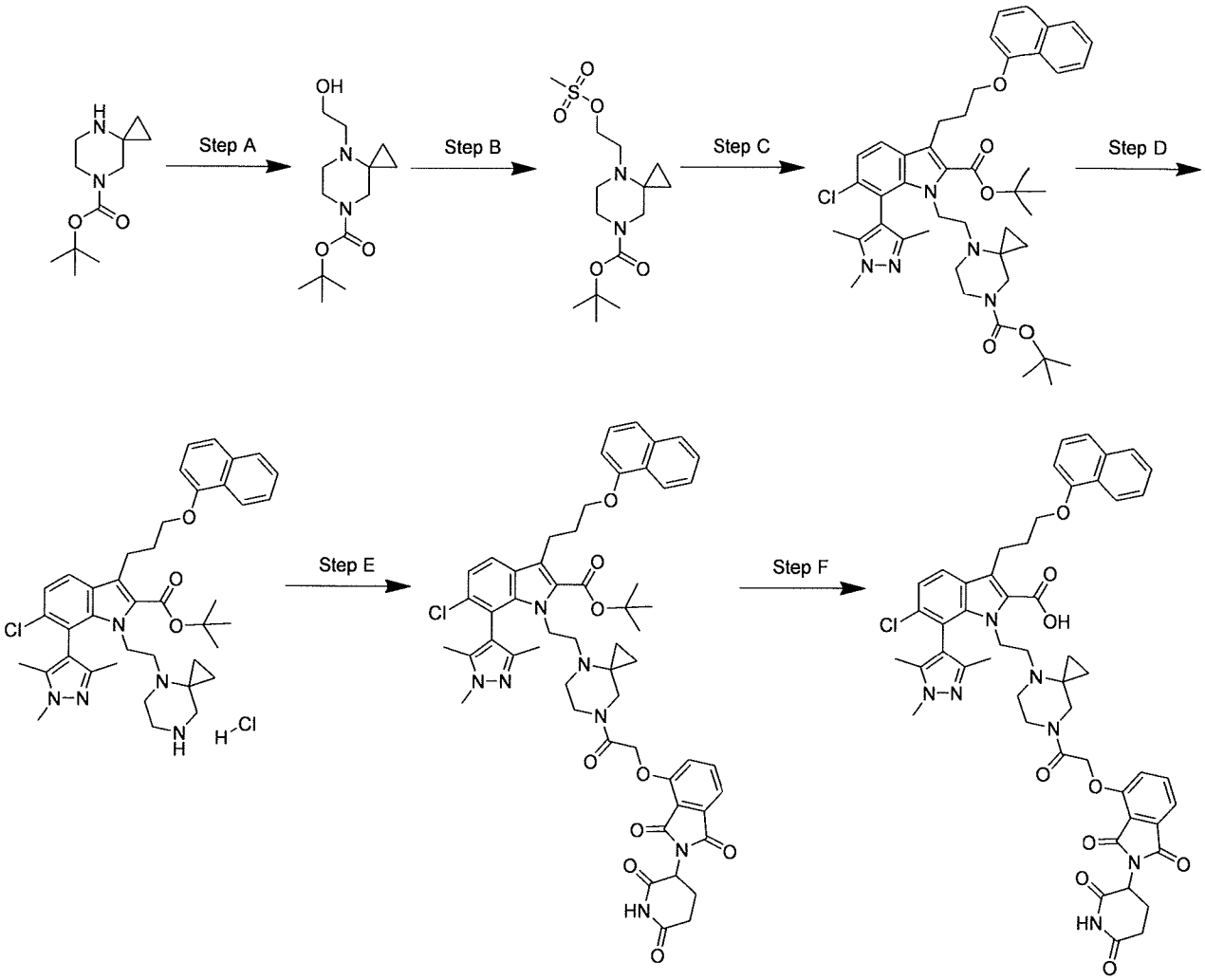


56 mg crude mixture of *tert*-butyl 6-chloro-1-{2-[6-(2-{[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl]oxy}acetyl)-3,6-diazabicyclo[3.1.1]heptan-3-yl]ethyl}-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate was dissolved in DCM (1.1 mL), TFA (0.109 mL, 1.425 mmol) was added and reaction was stirred at RT overnight. Another portion of TFA was added (0.500 mL, 6.537 mmol) and reaction was stirred at RT overnight. Solvent was evaporated and crude mixture purified by preparative TLC (20% MeOH in DCM) and repurified by preparative HPLC (H_2O:MeCN + 0.1% FA) to get 6-chloro-1-{2-[6-(2-{[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl]oxy}acetyl)-3,6-diazabicyclo[3.1.1]heptan-3-yl]ethyl}-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (2.6 mg, 0.003 mmol, 21% over two steps) as a white solid.

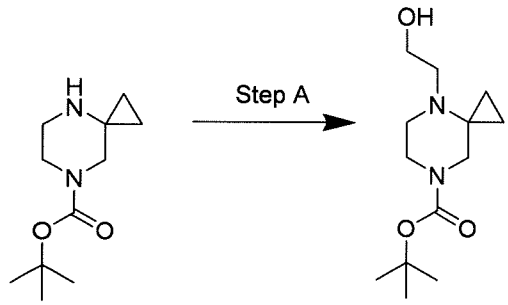
LCMS (ESI+): m/z 926.0 $[M+H]^+$

^{1}H NMR (500 MHz, DMSO) δ 10.77 (s, 1H), 8.24 – 8.18 (m, 1H), 7.90 – 7.82 (m, 1H), 7.82 – 7.77 (m, 1H), 7.72 (d, *J* = 8.6 Hz, 1H), 7.53 – 7.46 (m, 3H), 7.43 (t, *J* = 9.2 Hz, 2H), 7.38 (t, *J* = 7.8 Hz, 1H), 7.21 (d, *J* = 8.6 Hz, 1H), 6.90 (d, *J* = 7.7 Hz, 1H), 5.05 (dd, *J* = 12.5, 5.5 Hz, 1H), 4.80 (s, 2H), 4.32 – 4.22 (m, 4H), 3.73 (s, 3H), 3.30 (t, *J* = 7.6 Hz, 2H), 2.93 – 2.89 (m, 2H), 2.90 – 2.82 (m, 1H), 2.82 – 2.75 (m, 3H), 2.62 – 2.57 (m, 3H), 2.44 – 2.39 (m, 2H), 2.30 – 2.19 (m, 2H), 2.13 – 1.95 (m, 6H), 1.88 (s, 3H).

Example 11: 6-chloro-1-(2-(7-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)acetyl)-4,7-diazaspiro[2.5]octan-4-yl)ethyl)-3-(3-(naphthalen-1-yloxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (210)

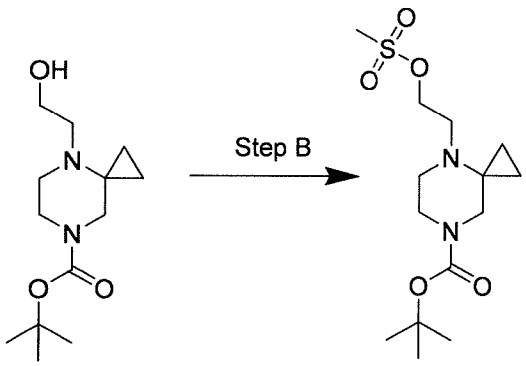


Step A



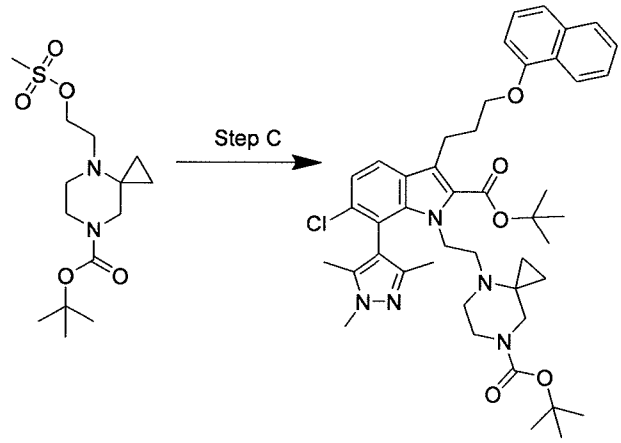
Tert-butyl 4,7-diazaspiro[2.5]octane-7-carboxylate (100.0 mg, 0.471 mmol) and K_2CO_3 (195.3 mg, 1.413 mmol) were placed in a flask, dissolved in dry DMF (5.5 mL) and then 2-bromoethanol (0.167 mL, 2.355 mmol) was added. Reaction was stirred at 80°C and monitored by TLC (10% MeOH/DCM, Rf=0.6). After 18 hours full conversion was observed and formation of one spot (presumably product). The reaction mixture was diluted in EtOAc and washed with brine. The organic layer was dried over magnesium sulfate, filtered and concentrated to dryness. *Tert*-butyl 4-(2-hydroxyethyl)-4,7-diazaspiro[2.5]octane-7-carboxylate (115 mg, crude) was used directly in the next step without further purification.

Step B



Tert-butyl 4-(2-hydroxyethyl)-4,7-diazaspiro[2.5]octane-7-carboxylate (115.0 mg, crude) was dissolved in DCM (4.5 mL), Et_3N (0.094 mL, 0.673 mmol) and DMAP (5.5 mg, 0.045 mmol) were added and reaction mixture cooled to -15°C. Then MsCl (0.042 mL, 0.538 mmol) was added dropwise and reaction mixture was let to stir at RT. After 30 minutes reaction mixture was diluted in EtOAc and washed with brine. The organic layer was dried over magnesium sulfate, filtered and concentrated to dryness. *Tert*-butyl 4-(2-((methylsulfonyl)oxy)ethyl)-4,7-diazaspiro[2.5]octane-7-carboxylate (143.8 mg, crude) was used directly in the next step without further purification.

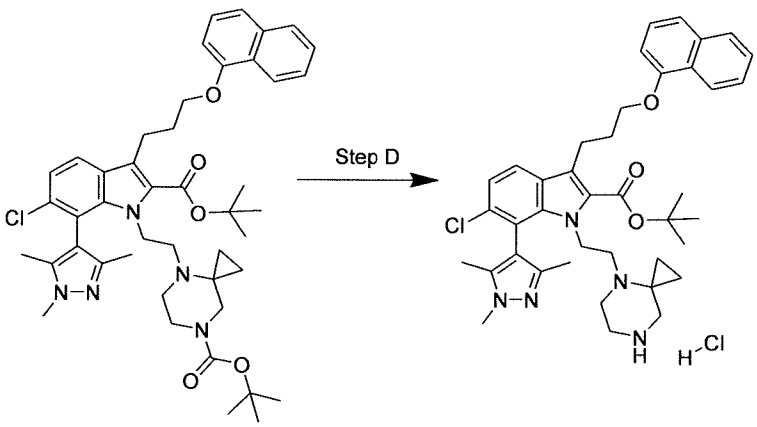
Step C



Tert-butyl 6-chloro-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (195.0 mg, 0.358 mmol), *tert*-butyl 4-[2-(methanesulfonyloxy)ethyl]-4,7-diazaspiro[2.5]octane-7-carboxylate (143.8 mg, crude) and Cs_2CO_3 (350.3 mg, 1.075 mmol) were placed in a vial, dissolved in dry DMF (7.2 mL) and stirred at 60°C overnight. The reaction mixture was diluted with EtOAc and washed with brine. The organic layer was dried over magnesium sulfate, filtered and concentrated to dryness. The crude mixture of *tert*-butyl 1-(2-(7-(*tert*-butoxycarbonyl)-4,7-diazaspiro[2.5]octan-4-yl)ethyl)-6-chloro-3-(3-(naphthalen-1-yloxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (276.0 mg, crude) was used directly in the next step.

LCMS (ESI^+): m/z 782.2 $[M+H]^+$

Step D

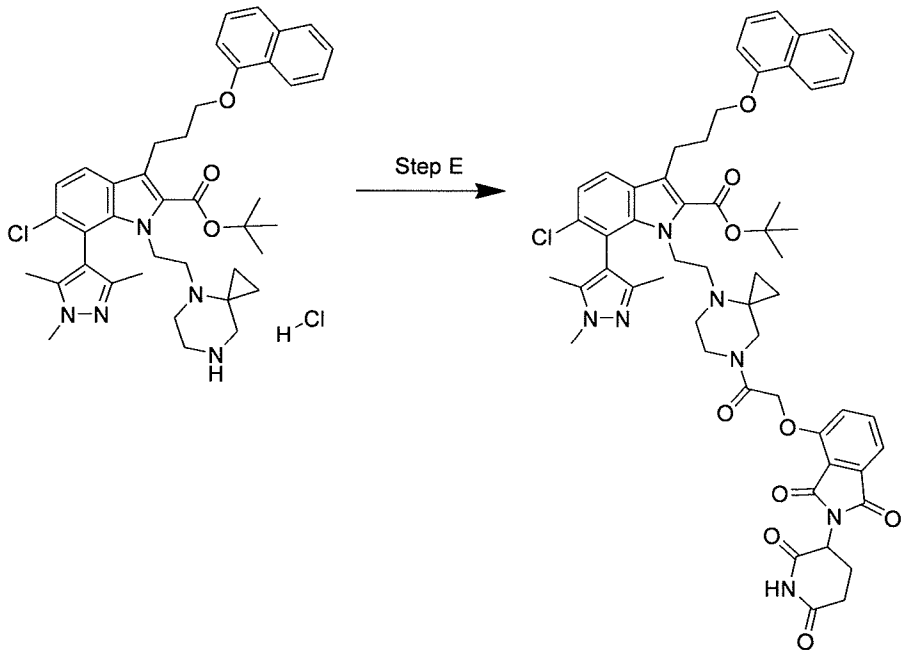


Tert-butyl 1-(2-{7-[(*tert*-butoxy)carbonyl]-4,7-diazaspiro[2.5]octan-4-yl}ethyl)-6-chloro-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (276.0 mg, crude) was dissolved in THF (3.6 mL), cooled to -15°C and then 4 M HCl in dioxane (1.1 mL, 4.498 mmol) was added dropwise. Reaction was let to stir at RT overnight. Solvent was evaporated, and crude mixture of *tert*-butyl 6-chloro-1-(2-{4,7-diazaspiro[2.5]octan-4-yl}ethyl)-3-

[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate hydrochloride (290.0 mg, crude) was used directly in the next step.

LCMS (ESI$^+$): m/z 682.3 $[M+H]^+$

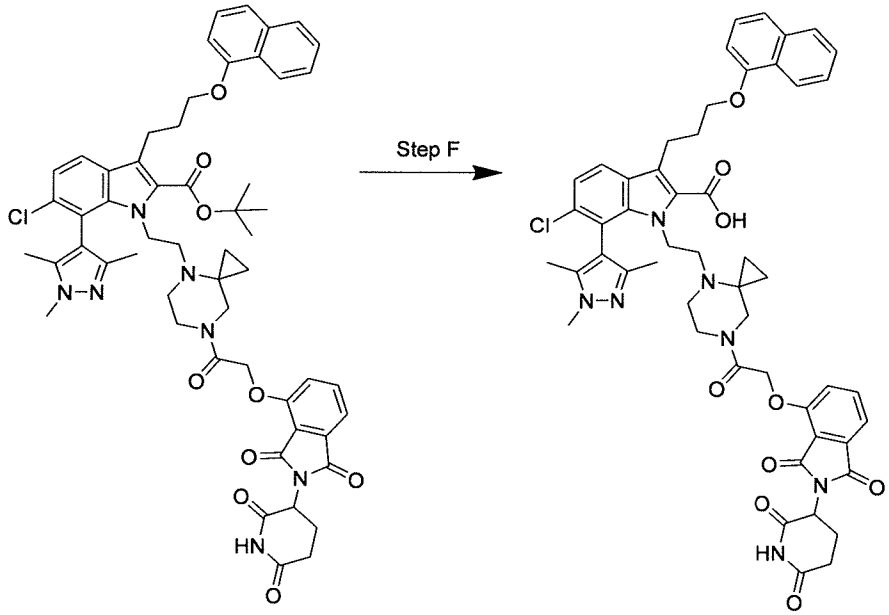
Step E



Tert-butyl 6-chloro-1-(2-{4,7-diazaspiro[2.5]octan-4-yl}ethyl)-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate hydrochloride (290.0 mg, crude), 2-{[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl]oxy}acetic acid (40.2 mg, 0.121 mmol) and HATU (52.2 mg, 0.137 mmol) were placed in a vial, dissolved in dry DMF (0.949 mL) and then DIPEA (0.084 mL, 0.484 mmol) was added. Reaction was stirred at RT overnight. The reaction mixture was diluted in EtOAc and washed with $NaHCO_3$. The organic layer was dried $MgSO_4$, filtered and concentrated to dryness. The crude mixture of *tert*-butyl 6-chloro-1-(2-(7-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)acetyl)-4,7-diazaspiro[2.5]octan-4-yl)ethyl)-3-(3-(naphthalen-1-yloxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (330.0 mg, crude) was used directly in the next step.

LCMS (ESI$^+$): m/z 995.9 $[M+H]^+$

Step F

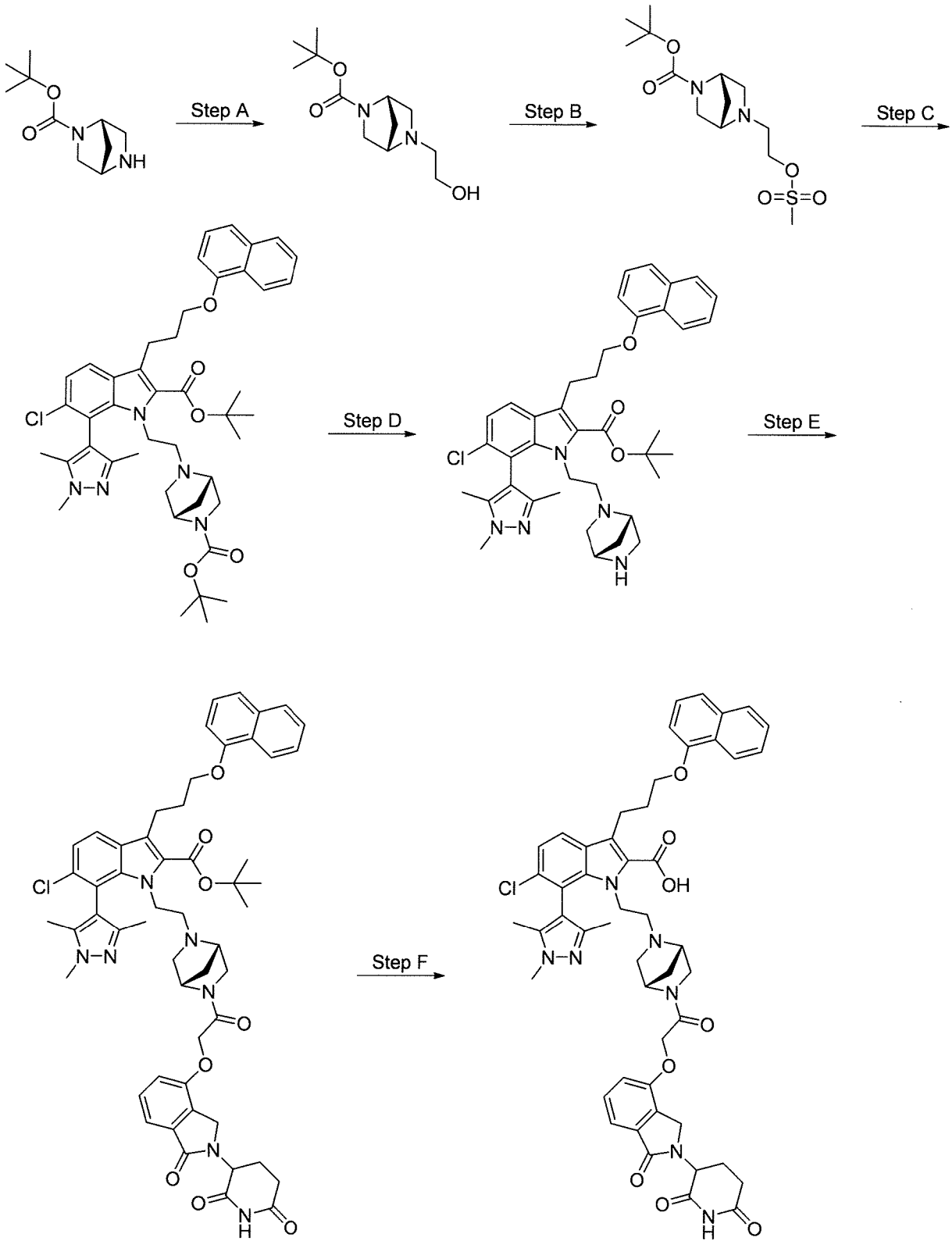


A crude *tert*-butyl 6-chloro-1-{2-[7-(2-{[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl]oxy}acetyl)-4,7-diazaspiro[2.5]octan-4-yl]ethyl}-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (330.0 mg, crude) was dissolved in DCM (1.0 mL), TFA (1.0 mL, 13.246 mmol) was added and reaction was stirred at RT overnight.. Solvent was evaporated and crude mixture was purified by preparative HPLC (H_2O:MeCN + 0.1% FA) to get a pure product 6-chloro-1-{2-[7-(2-{[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl]oxy}acetyl)-4,7-diazaspiro[2.5]octan-4-yl]ethyl}-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (6.1 mg, 0.006 mmol, 9.8%) as a beige solid.

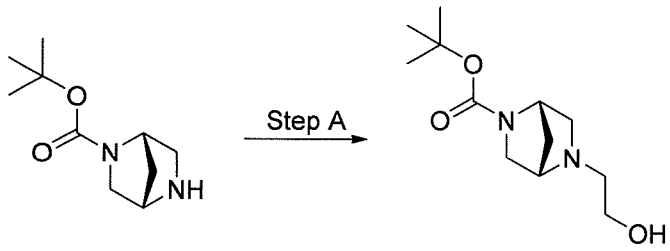
LCMS (ESI+): m/z 939.8 $[M+H]^+$

^{1}H NMR (500 MHz, DMSO) δ 10.76 (s, 1H), 8.25 – 8.21 (m, 1H), 7.87 – 7.82 (m, 1H), 7.77 – 7.69 (m, 2H), 7.54 – 7.47 (m, 2H), 7.46 – 7.42 (m, 2H), 7.41 – 7.37 (m, 1H), 7.32 (d, *J* = 8.5 Hz, 1H), 7.21 (d, 1H), 6.92 (d, *J* = 7.6 Hz, 1H), 5.10 – 4.92 (m, 3H), 4.25 (t, *J* = 6.3 Hz, 2H), 4.18 – 4.05 (m, 2H), 3.77 (s, 3H), 3.43 – 3.32 (m, 2H), 3.27 (t, *J* = 7.5 Hz, 2H), 3.11 (s, 2H), 2.89 – 2.82 (m, 2H), 2.66 – 2.56 (m, 5H), 2.46 – 2.42 (m, 3H), 2.29 – 2.20 (m, 2H), 2.12 – 1.99 (m, 5H), 1.91 (s, 3H).

Example 12: 6-chloro-1-{2-[(1*S*,4*S*)-5-(2-{[2-(2,6-dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1*H*-isoindol-4-yl]oxy}acetyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl]ethyl}-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (209)



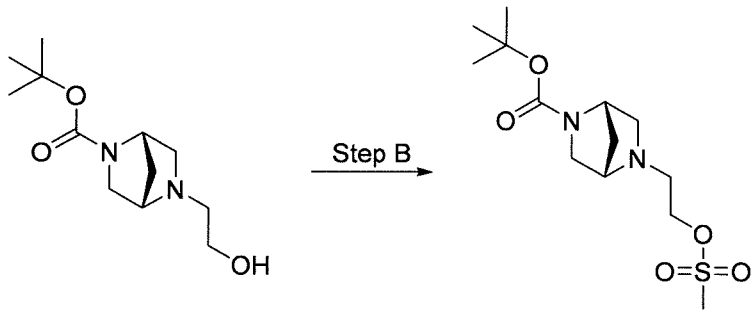
Step A



To a solution of *tert*-butyl (1*S*,4*S*)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (0.500 g, 2.522 mmol) in DMF (4.3 mL) under argon was added K_2CO_3 (1.046 g, 7.566 mmol). The mixture was stirred for 2 h at 80°C. After complete consumption of the starting material (monitored by TLC, 10% MeOH in DCM, visualization in ninhydrin), the reaction mixture was cooled down to room temperature and solvents were evaporated under reduced pressure. The resulting residue was dissolved EtOAc and washed with water and brine. Organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo to get crude *tert*-butyl (1*S*,4*S*)-5-(2-hydroxyethyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (463.5 mg of crude) as pale yellow oil that was used in the next step without further purification.

LCMS (ESI+): 243.2 m/z $[M+H]^+$

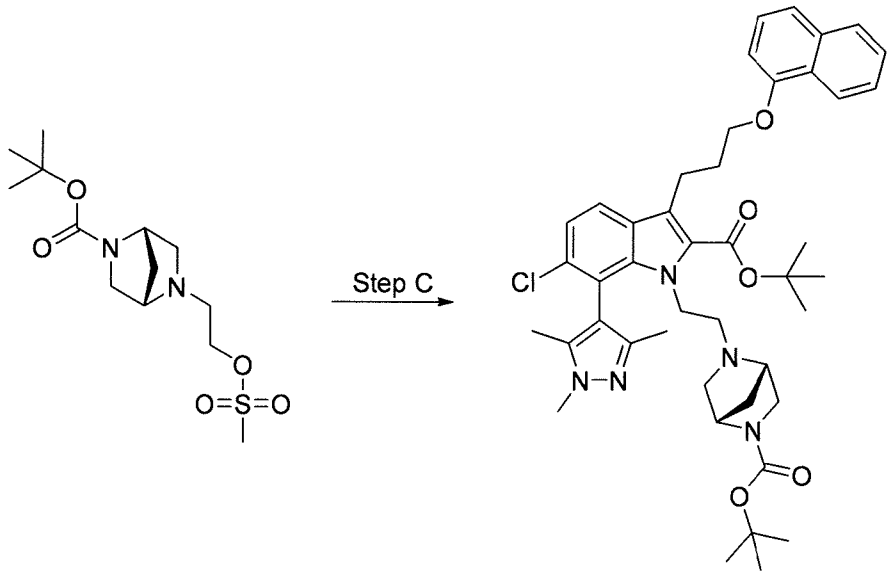
Step B



Tert-butyl (1*S*,4*S*)-5-(2-hydroxyethyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (463.5 mg, crude) was dissolved in DCM (19.1 mL) and Et_3N (0.399 mL, 2.869 mmol), followed by DMAP (23.4 mg, 0.191 mmol) were added. Reaction mixture was cooled down to 0°C and MsCl (0.178 mL, 2.295 mmol) was added drop-wise. The mixture was allowed to slowly reach RT and stirred for 16 h. After complete consumption of the starting material (monitored with TLC, 20% MeOH in DCM), reaction mixture was diluted with DCM (25 mL) and washed with brine and water. Organic phase was combined, dried over Na_2SO_4, filtered and concentrated in vacuo to give crude (380.5 mg) *tert*-butyl (1*S*,4*S*)-5-[2-(methanesulfonyloxy)ethyl]-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate as yellow oil that was used in the next step without further purification.

LCMS (ESI+): 321.1 m/z $[M+H]^+$

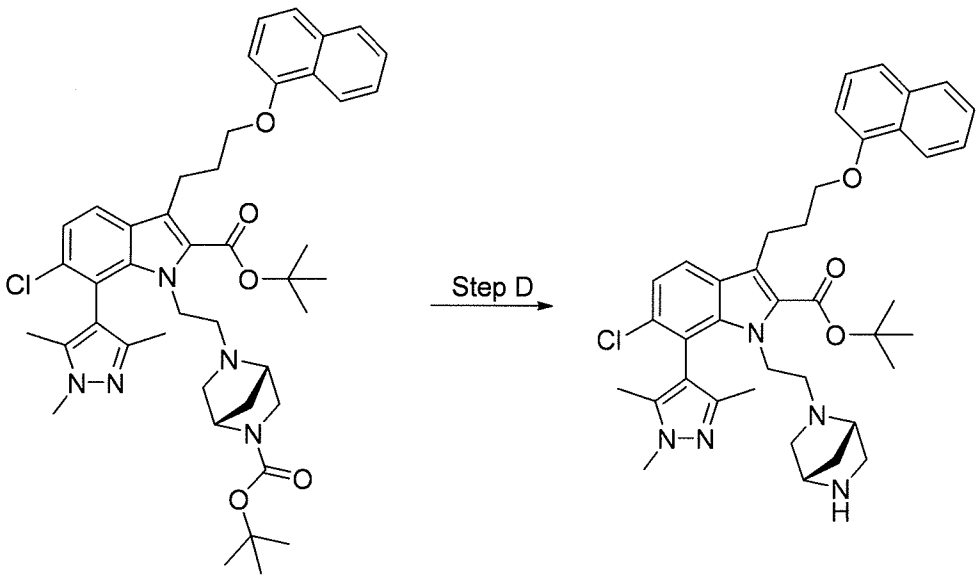
Step C



Tert-butyl 6-chloro-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (50.0 mg, 0.092 mol) was dissolved in dry DMF (2.0 mL). Cs_2CO_3 (89.8 mg, 0276 mmol) along with *tert*-butyl (1*S*,4*S*)-5-[2-(methanesulfonyloxy)ethyl]-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (35.3 mg, crude) were added and the reaction was stirred in RT for 18 h. After complete consumption of the starting material (monitored by TLC, (5% MeOH in DCM), and LCMS), the solvent was evaporated under reduced pressure. The resulting residue was dissolved in DCM and washed with water and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to give 84.5 mg crude *tert*-butyl 1-(2-{5-[(tert-butoxy)carbonyl]-2,5-diazabicyclo[2.2.1]heptan-2-yl}ethyl)-6-chloro-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate as yellow oil that was used in next step without further purification.

LCMS (ESI+): 768.3 m/z $[M+H]^+$

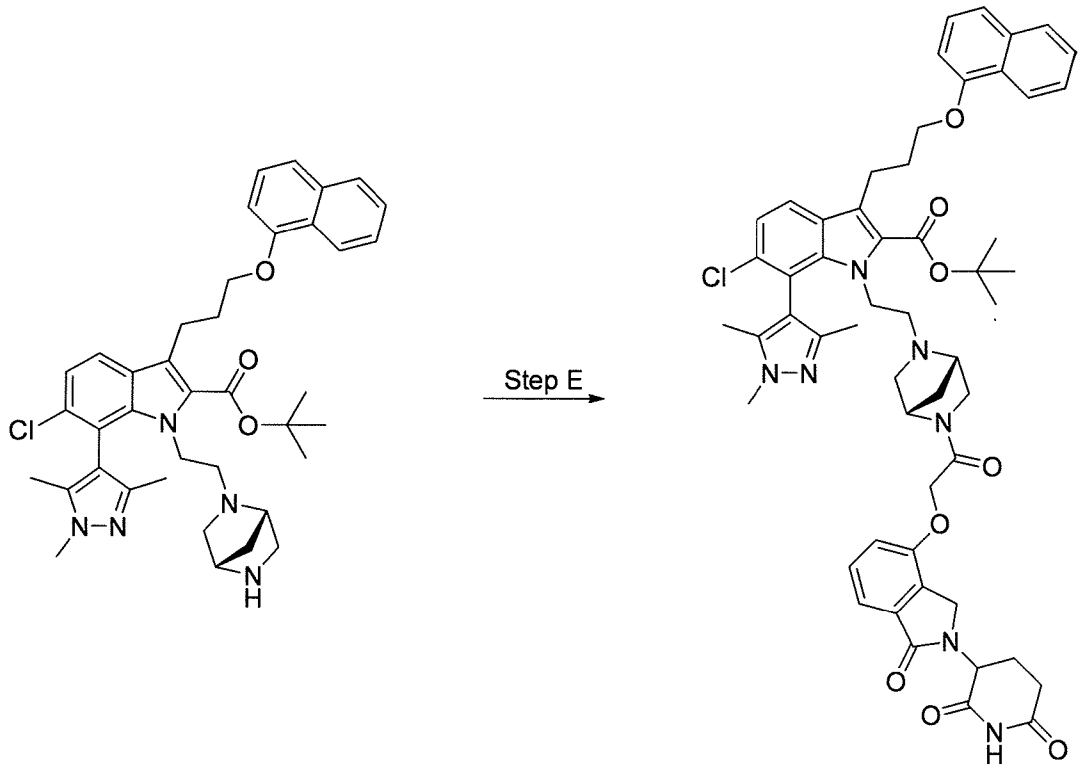
Step D



Tert-butyl 1-(2-{5-[(tert-butoxy)carbonyl]-2,5-diazabicyclo[2.2.1]heptan-2-yl}ethyl)-6-chloro-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (84.5 mg, crude) was dissolved in THF (2.2 mL) under argon atmosphere and cooled down to 0°C. To it, 4M HCl in dioxane (1.4 mL, 5.495 mmol) was added and the reaction (monitored with LCMS) was allowed to reach room temperature (over 4 h). After 16 h of mixing, LCMS analysis indicated full consumption of the starting material. The solution was again cooled down to 0°C and cool aqueous solution of 1M NaOH was added to pH = 7. The solution was diluted in DCM and washed with brine and water. Organic layer was dried over Na_2SO_4, filtered, concentrated and dried under reduced pressure to give 82.0 mg crude *tert*-butyl 6-chloro-1-(2-{2,5-diazabicyclo[2.2.1]heptan-2-yl}ethyl)-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate that was used in the next step without further purification.

LCMS (ESI+): 668.3 m/z $[M+H]^+$

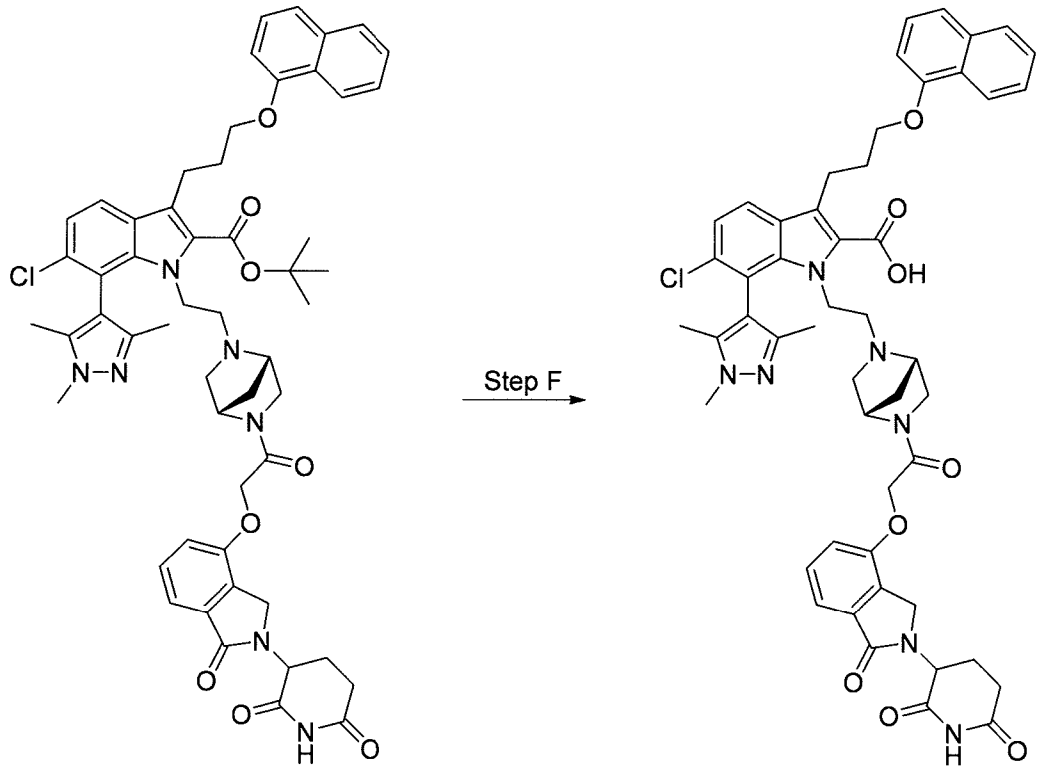
Step E



2-{[2-(2,6-Dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1*H*-isoindol-4-yl]oxy}acetic acid (20.0 mg, 0.063 mmol) was dissolved in DMF (1.3 mL) under argon atmosphere and DIPEA (0.033 mL, 0.189 mmol) and HATU (35.8 mg, 0.094 mmol) were added. Reaction was stirred in room temperature for 15 min and *tert*-butyl 6-chloro-1-(2-{2,5-diazabicyclo[2.2.1]heptan-2-yl}ethyl)-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (42.0 mg, crude) was added. Reaction was continued in room temperature for 1h. After consumption of the starting material (monitored with LCMS) solvent was evaporated, resulting residue dissolved in DCM and washed with aqueous $NaHCO_3$ (saturated), brine and water. Organic layer was collected, dried over Na_2SO_4, filtered, concentrated and dried under reduced pressure to give crude *tert*-butyl 6-chloro-1-{2-[5-(2-{[2-(2,6-dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1*H*-isoindol-4-yl]oxy}acetyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl]ethyl}-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (60.0 mg, crude) as yellow oil, that was used in the next step without further purification.

LCMS (ESI+): 968.3 m/z $[M+H]^+$

Step F



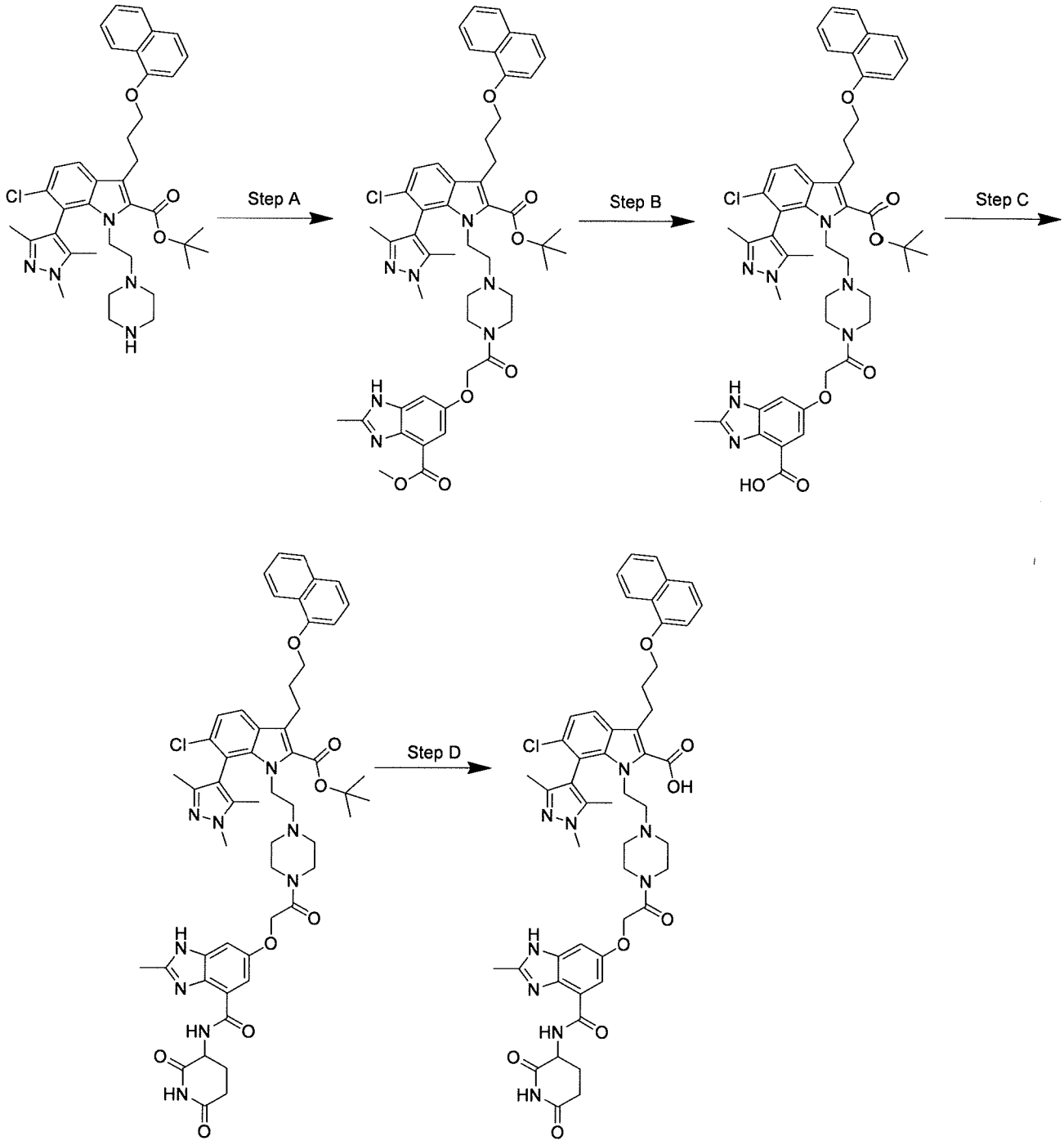
Tert-butyl 6-chloro-1-{2-[5-(2-{[2-(2,6-dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1*H*-isoindol-4-yl]oxy}acetyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl]ethyl}-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (60.0 mg, crude) was dissolved in dry DCM (0.4 mL) under argon atmosphere and TFA (0.4 ml, 595.6 mg, 5.224 mmol) was added. Reaction (monitored with LCMS) was stirred in room temperature for 16 h. After full conversion of the starting material, solvent along with TFA was evaporated under reduced pressure, resulting residue dissolved in DMSO and passed through a syringe filter. The filtrate was purified with reverse phase preparative HPLC (H_2O:MeCN +0.1% FA) to give the corresponding 6-chloro-1-{2-[(1*S*,4*S*)-5-(2-{[2-(2,6-dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1*H*-isoindol-4-yl]oxy}acetyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl]ethyl}-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (2.2 mg, 0.002 mmol, 3% over two steps) as white solid.

LCMS (ESI+): 912.1 m/z $[M+H]^+$

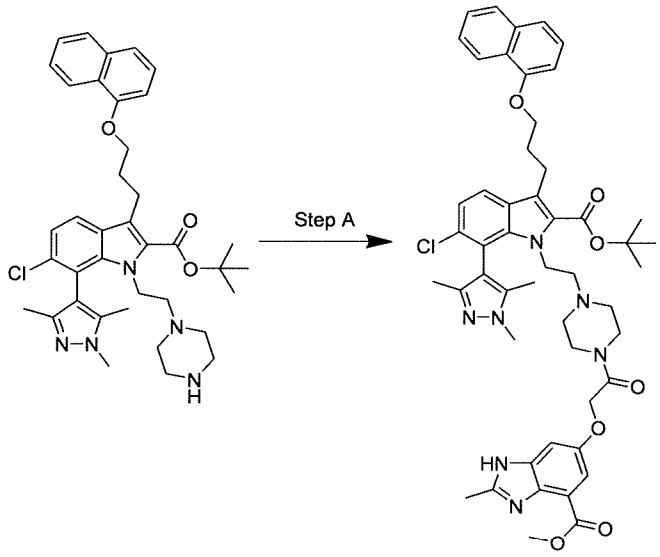
^{1}H NMR (500 MHz, DMSO) δ 10.65 (s, 1H), 8.22 (d, *J* = 7.5 Hz, 1H), 7.86 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.70 (d, *J* = 8.4 Hz, 1H), 7.56 – 7.42 (m, 4H), 7.39 (t, J = 7.9 Hz, 1H), 7.34 (d, J = 7.6 Hz, 1H), 7.21 (d, J = 8.4 Hz, 1H), 7.15 (bs, 1H), 6.91 (d, J = 7.6 Hz, 1H), 5.06 (dd, J = 12.9, 5.3 Hz, 1H), 4.96 – 4.65 (m, 2H), 4.51 – 4.31 (m, 3H), 4.26 (t, J = 6.3 Hz, 2H), 4.24 – 4.07 (m, 2H), 3.82 – 3.70 (m, 3H), 3.46 – 3.36 (m, 1H), 3.28 (t, 2H), 3.22-3.14 (m, 2H), 2.93 – 2.86 (m, 2H), 2.63 – 2.59 (m, 2H), 2.47 – 2.45

(m, 1H), 2.37 – 2.30 (m, 2H), 2.25 (p, J = 6.7 Hz, 2H), 2.11 – 1.97 (m, 4H), 1.90 (d, J = 5.5 Hz, 3H), 1.70 – 1.49 (m, 2H).

Example 13: 6-chloro-1-(2-{4-[2-({4-[(2,6-dioxopiperidin-3-yl)carbamoyl]-2-methyl-1*H*-1,3-benzodiazol-6-yl}oxy)acetyl]piperazin-1-yl}ethyl)-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (263)



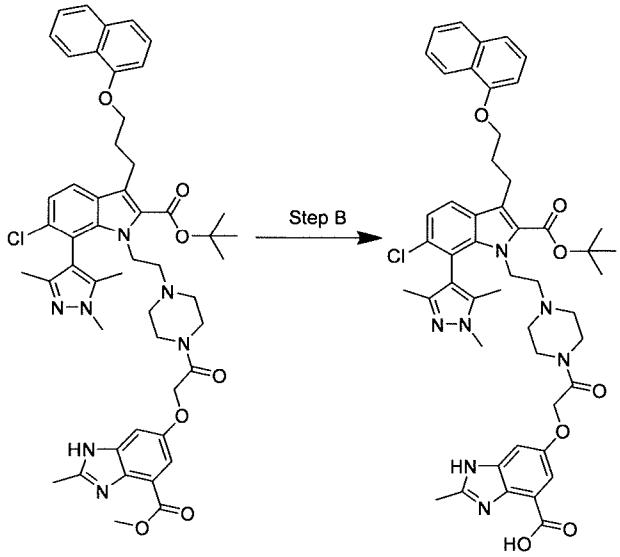
Step A



To a well stirred solution of 2-((4-(methoxycarbonyl)-2-methyl-1*H*-benzo[*d*]imidazol-6-yl)oxy)acetic acid (24.2 mg, 0.091 mmol) and *tert*-butyl 6-chloro-3-(3-(naphthalen-1-yloxy)propyl)-1-(2-(piperazin-1-yl)ethyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (50.0 mg, 0.076 mmol) in DMF (0.762 mL) was added DIPEA (0.040 mL, 0.229 mmol) and HATU (34.8 mg, 0.091 mmol) and the mixture was allowed to stir under nitrogen for 16 h. After complete consumption of the starting material solvents were removed under reduced pressure and the reaction mixture diluted with DCM washed successively with cold water (3 times) and brine. Organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to afford methyl 6-{2-[4-(2-{2-[(*tert*-butoxy)carbonyl]-6-chloro-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indol-1-yl}ethyl)piperazin-1-yl]-2-oxoethoxy}-2-methyl-1*H*-1,3-benzodiazole-4-carboxylate (40.0 mg crude) as brown solid which was used for next step without further purification.

LCMS (ESI+): m/z 902.5 $[M+H]^+$

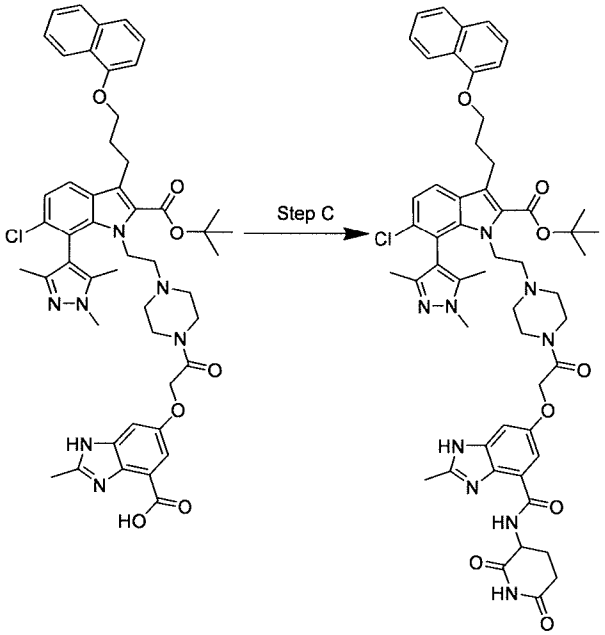
Step B



Methyl 6-{2-[4-(2-{2-[(*tert*-butoxy)carbonyl]-6-chloro-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indol-1-yl}ethyl)piperazin-1-yl]-2-oxoethoxy}-2-methyl-1*H*-1,3-benzodiazole-4-carboxylate (40.0 mg crude) was dissolved in MeOH (4.4 mL) and few drops of DCM were added for solubility. 1M LiOH (222 µL, 0.222 mmol) was added, and mixture was stirred in RT for overnight. To mixture water and 1M HCl were added till pH ~3 and mixture was extracted with DCM. 6-{2-[4-(2-{2-[(*tert*-butoxy)carbonyl]-6-chloro-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indol-1-yl}ethyl)piperazin-1-yl]-2-oxoethoxy}-2-methyl-1*H*-1,3-benzodiazole-4-carboxylic acid (25.0 mg of crude) was obtained as brow gum, which was used for next step without further purification.

LCMS (ESI+): m/z 887.5 $[M+H]^+$

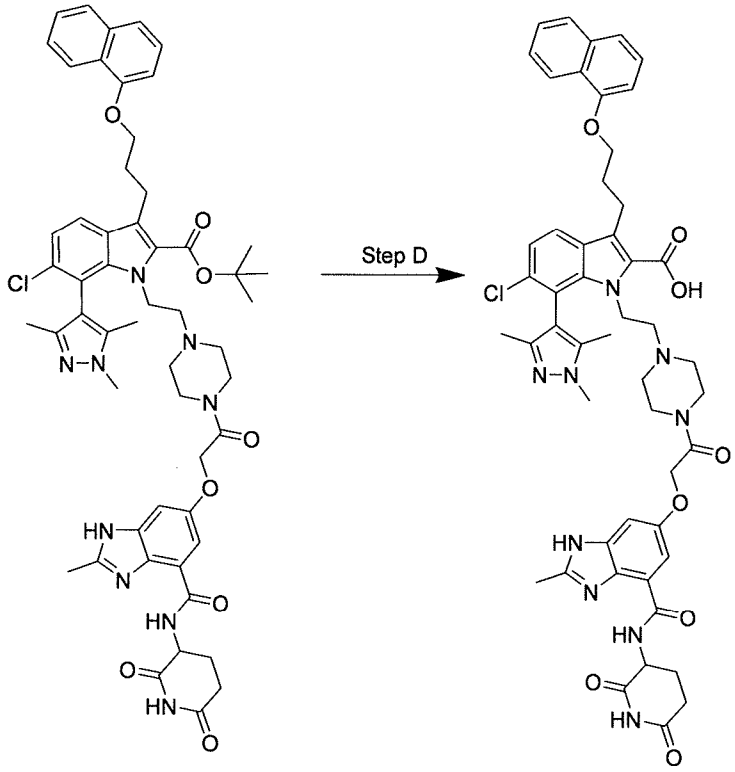
Step C



To a well stirred solution of 3-aminopiperidine-2,6-dione (3.7 mg, 0.023 mmol) and 6-{2-[4-(2-{2-[(*tert*-butoxy)carbonyl]-6-chloro-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indol-1-yl}ethyl)piperazin-1-yl]-2-oxoethoxy}-2-methyl-1*H*-1,3-benzodiazole-4-carboxylic acid (10.0 mg, crude) in DMF (0.113 mL) was added DIPEA (0.006 mL, 0.034 mmol) and HATU (4.3 mg, 0.011 mmol) and the mixture was allowed to stir under nitrogen for 16 h. After complete consumption of the starting material the reaction mixture diluted with DCM, washed successively with brine. Organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. Mixture was purified using flash chromatography (SiO_2, 7% MeOH in DCM) to afford *tert*-butyl 6-chloro-1-(2-{4-[2-({4-[(2,6-dioxopiperidin-3-yl)carbamoyl]-2-methyl-1*H*-1,3-benzodiazol-6-yl}oxy)acetyl]piperazin-1-yl}ethyl)-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (11.5 mg, 0.010 mmol, 57% over two steps) as brown semisolid.

LCMS (ESI+): m/z 998.4 $[M+H]^+$

Step D

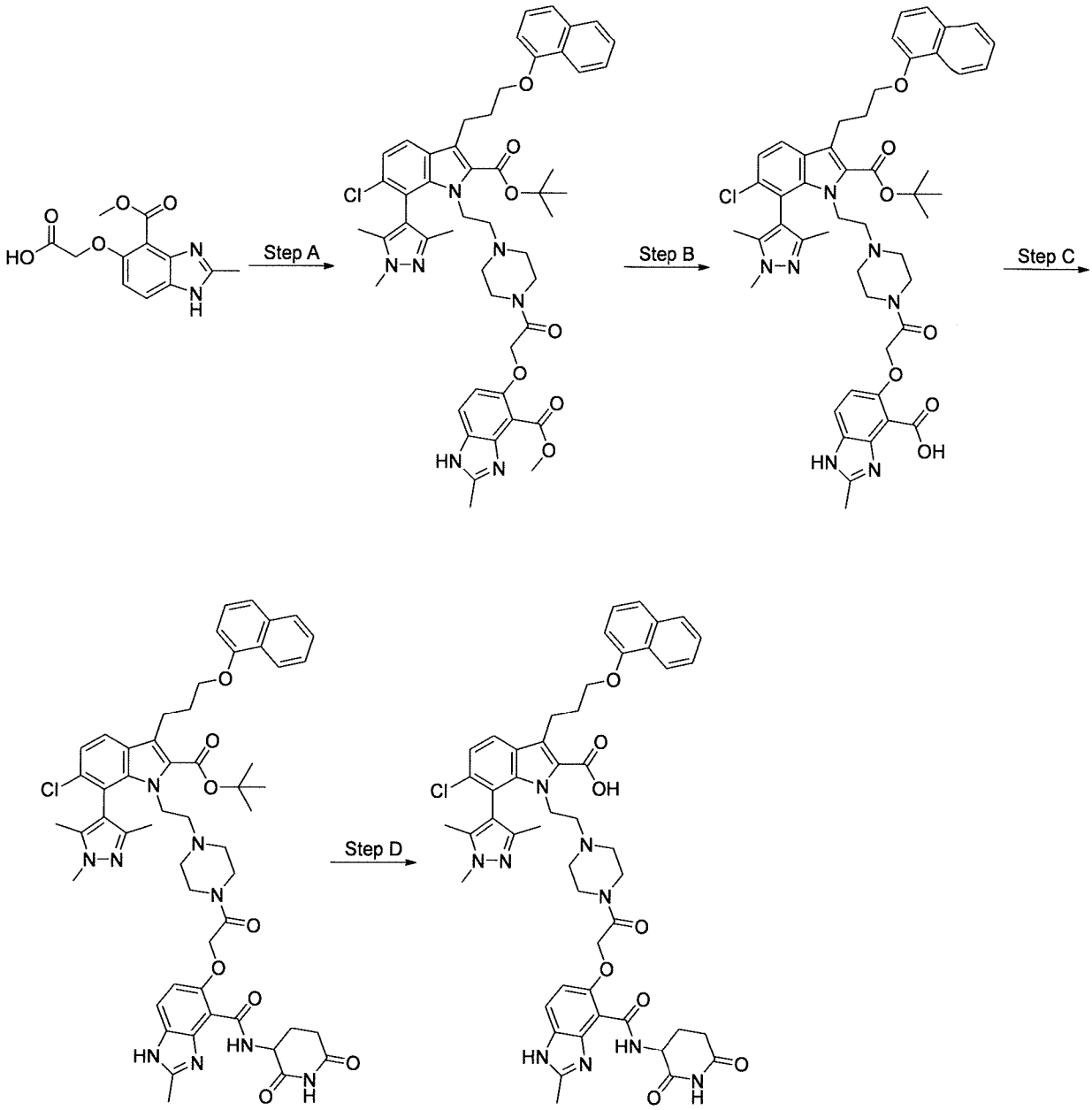


Tert-butyl 6-chloro-1-(2-{4-[2-({4-[(2,6-dioxopiperidin-3-yl)carbamoyl]-2-methyl-1*H*-1,3-benzodiazol-6-yl}oxy)acetyl]piperazin-1-yl}ethyl)-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (11.0 mg, 0.011 mmol) was dissolved in DCM (0.110 mL), and TFA (0.017 mL, 0.220 mmol) was added. Mixture was stirred for 4 h, then solvents were removed under reduced pressure, and crude was purified using preparative HPLC (H_2O:MeCN + 0.1% FA) to get 6-chloro-1-(2-{4-[2-({4-[(2,6-dioxopiperidin-3-yl)carbamoyl]-2-methyl-1*H*-1,3-benzodiazol-6-yl}oxy)acetyl]piperazin-1-yl}ethyl)-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (1.7 mg, 0.002 mmol, 16.4%) as white solid.

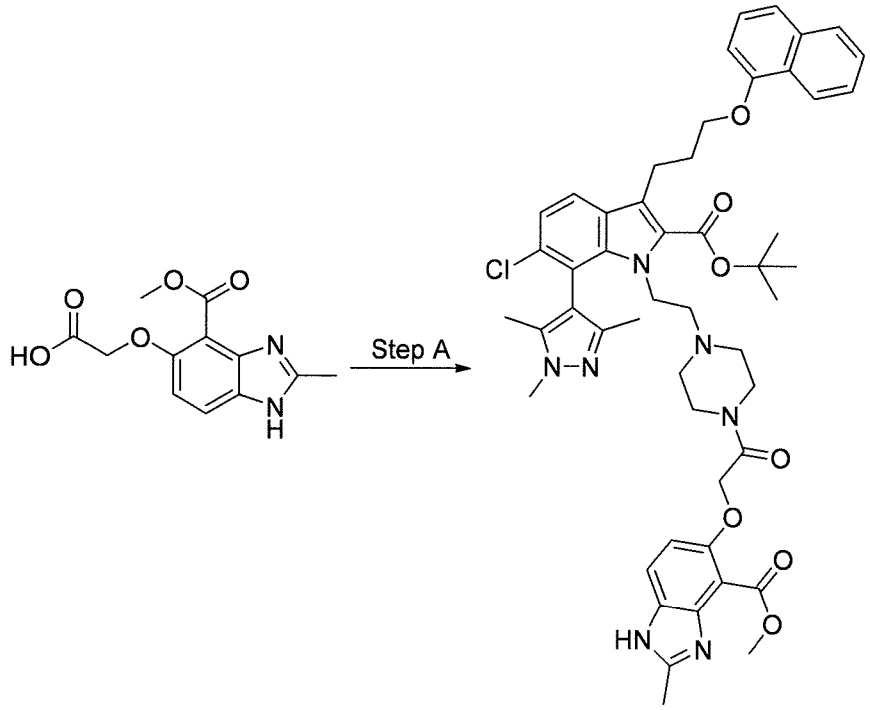
LCMS (ESI+): m/z 942.9 $[M+H]^+$

^{1}H NMR (500 MHz, DMSO) δ 12.79 – 12.70 (m, 1H), 12.55 (s, 1H), 10.92 (s, 1H), 10.26 (d, *J* = 7.3 Hz, 1H), 8.26 – 8.19 (m, 1H), 7.92 – 7.84 (m, 1H), 7.77 (d, *J* = 8.6 Hz, 1H), 7.57 – 7.48 (m, 2H), 7.46 (d, *J* = 8.3 Hz, 1H), 7.40 (t, *J* = 7.9 Hz, 2H), 7.24 (d, *J* = 8.5 Hz, 1H), 7.17 (s, 1H), 6.97 – 6.88 (m, 1H), 4.91 – 4.79 (m, 3H), 4.36 – 4.26 (m, 1H), 4.26 – 4.13 (m, 3H), 3.76 (s, 3H), 3.47 – 3.35 (m, 5H), 3.30 – 3.26 (m, 3H), 2.90 – 2.76 (m, 1H), 2.62 – 2.55 (m, 2H), 2.28 – 2.19 (m, 3H), 2.19 – 1.97 (m, 10H), 1.89 (s, 3H).

Example 14: 6-chloro-1-(2-(4-(2-((4-((2,6-dioxopiperidin-3-yl)carbamoyl)-2-methyl-1*H*-benzo[*d*]imidazol-5-yl)oxy)acetyl)piperazin-1-yl)ethyl)-3-(3-(naphthalen-1-yloxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (264)



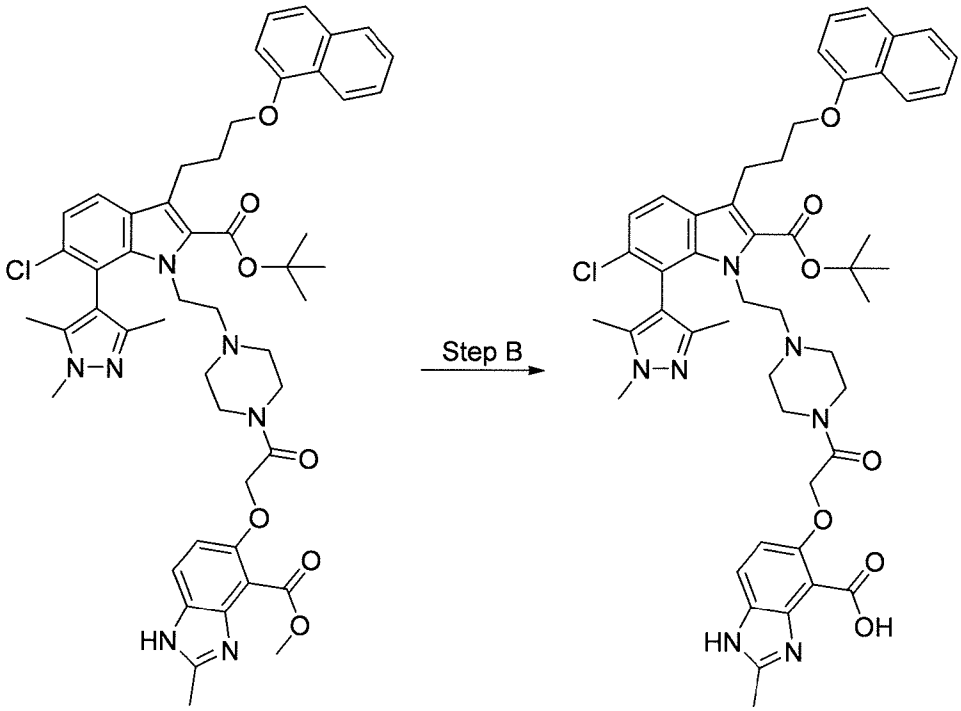
Step A



2-((4-(methoxycarbonyl)-2-methyl-1*H*-benzo[*d*]imidazol-5-yl)oxy)acetic acid (15.0 mg, 0.057 mmol) was dissolved in dry DMF (1.1 mL) under argon atmosphere. DIPEA (0.030 mL, 0.170 mmol), followed by HATU (32.4 mg, 0.085 mmol) were added and the solution was stirred for 15 min in room temperature. To the mixture was added *tert*-butyl 6-chloro-3-(3-(naphthalen-1-yloxy)propyl)-1-(2-(piperazin-1-yl)ethyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (37.3 mg, 0.057 mmol) and the reaction was stirred in room temperature. Reaction progress was monitored with LCMS. After 90 min starting material was still present (monitored by LCMS) in the reaction mixture. Additional portion of 2-{[4-(methoxycarbonyl)-2-methyl-1*H*-1,3-benzodiazol-5-yl]oxy}acetic acid (1.5 mg, 0.006 mmol) and HATU (3.2 mg, 0.008 mmol) were added and the reaction was continued in room temperature. After next 60 min DMF was evaporated, resulting residue dissolved in EtOAc (30 ml) and washed with brine (2x20 ml) and water (20 ml). Organic layer was dried over Na_2SO_4, filtered and dried under reduced pressure to give 50 mg crude methyl 5-{2-[4-(2-{2-[(*tert*-butoxy)carbonyl]-6-chloro-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indol-1-yl}ethyl)piperazin-1-yl]-2-oxoethoxy}-2-methyl-1*H*-1,3-benzodiazole-4-carboxylate as dark yellow sticky solid that was used in the next step without further purification.

LCMS (ESI+): m/z 902.8 $[M+H]^+$

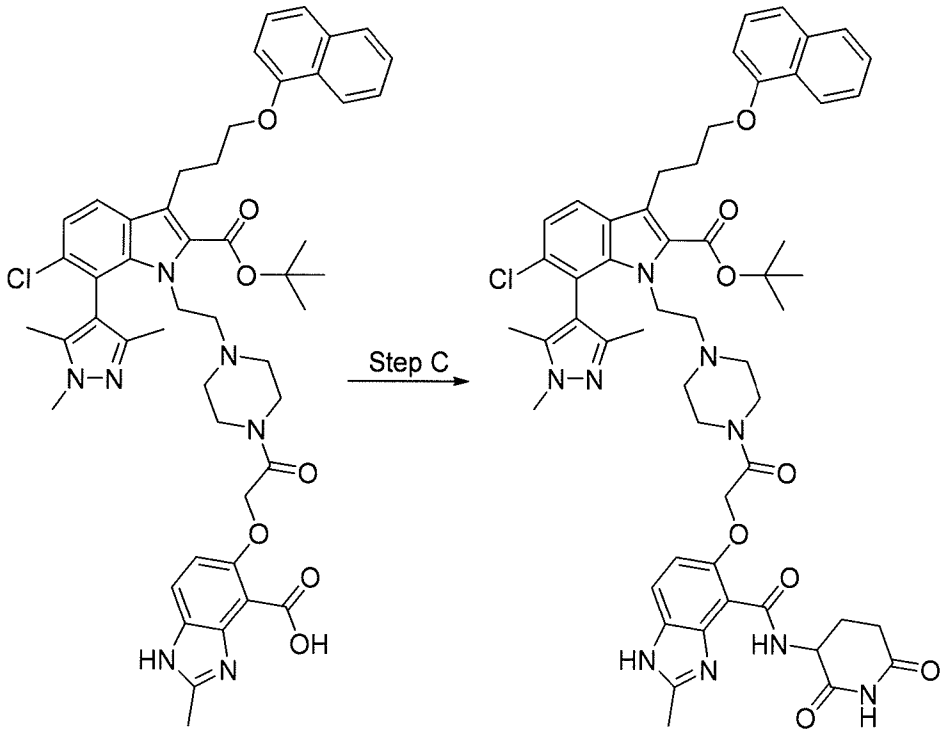
Step B



To a solution of methyl 5-{2-[4-(2-{2-[(*tert*-butoxy)carbonyl]-6-chloro-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indol-1-yl}ethyl)piperazin-1-yl]-2-oxoethoxy}-2-methyl-1*H*-1,3-benzodiazole-4-carboxylate (50 mg, crude) in MeCN (3.0 mL), was added LiBr (192.4 mg, 2.216 mmol) in water (0.2 ml), followed by Et_3N (0.046 mL, 0.332 mmol) and the reaction was stirred for 36 h at 60°C. After that time, the addition of LiBr (192.4 mg, 2.216 mmol) and Et_3N (0.046 mL, 0.332 mmol) was repeated and the reaction stirred for the next 36 h at 60°C. After that time LCMS indicated full conversion. Solvents along with Et_3N were evaporated under reduced pressure, crude product dissolved in EtOAc and washed with water. EtOAc was evaporated and reaction product dried under vacuo to give 44.5 mg crude *tert*-butyl 6-chloro-1-(2-{4-[2-({4-[(2,6-dioxopiperidin-3-yl)carbamoyl]-2-methyl-1*H*-1,3-benzodiazol-5-yl}oxy)acetyl]piperazin-1-yl}ethyl)-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate as brown solid that was used in the next step without further purification.

LCMS (ESI+): m/z 888.3 $[M+H]^+$

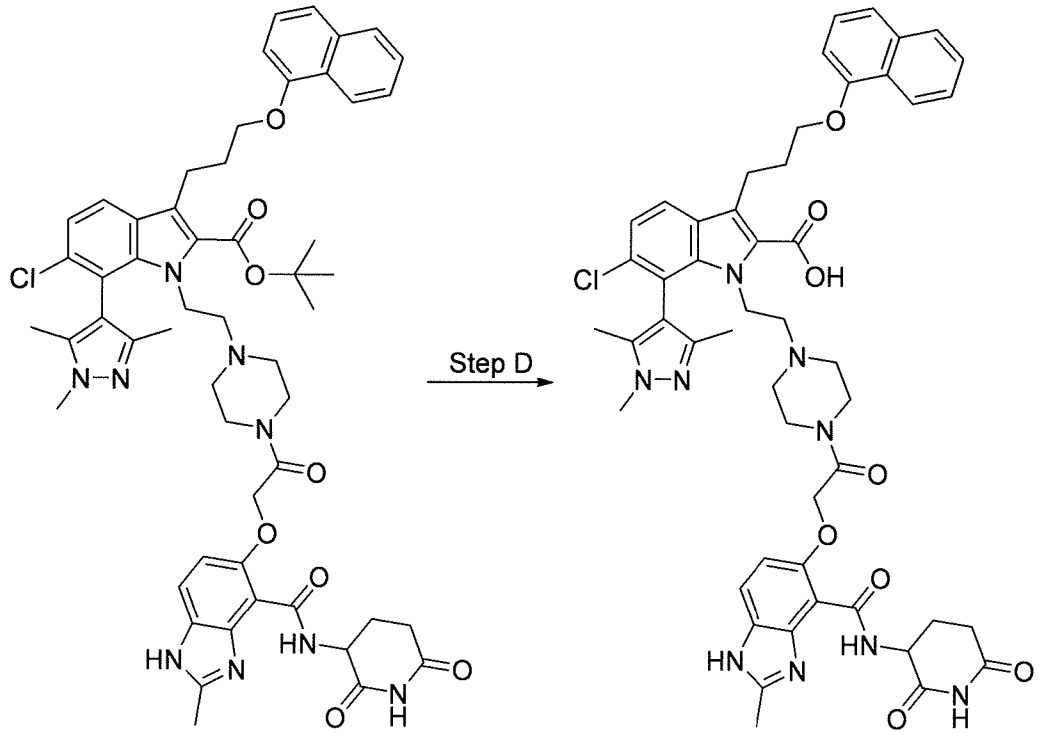
Step C



To a solution of crude 5-(2-(4-(2-(2-(*tert*-butoxycarbonyl)-6-chloro-3-(3-(naphthalen-1-yloxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indol-1-yl)ethyl)piperazin-1-yl)-2-oxoethoxy)-2-methyl-1*H*-1,3-benzodiazole-4-carboxylic acid (44.5 mg) in dry DMF (1.0 mL), was added DIPEA (0.026 mL, 0.150 mmol), followed by HATU (28.6 mg, 0.075 mmol) and solution was stirred at room temperature. After 15 min 3-aminopiperidine-2,6-dione hydrochloride (12.4 mg, 0.075 mmol) was added and the reaction was stirred for 4 h at room temperature. DMF was evaporated, residues were dissolved in EtOAc and washed 3x with water. Solvents were removed under reduced pressure and reaction product dried overnight under reduced pressure to give crude (45.1 mg) *tert*-butyl 6-chloro-1-(2-{4-[2-({4-[(2,6-dioxopiperidin-3-yl)carbamoyl]-2-methyl-1*H*-1,3-benzodiazol-5-yl}oxy)acetyl]piperazin-1-yl}ethyl)-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate as yellow oil, which was used to the next step without further purification.

LCMS (ESI+): m/z 998.1 $[M+H]^+$

Step D

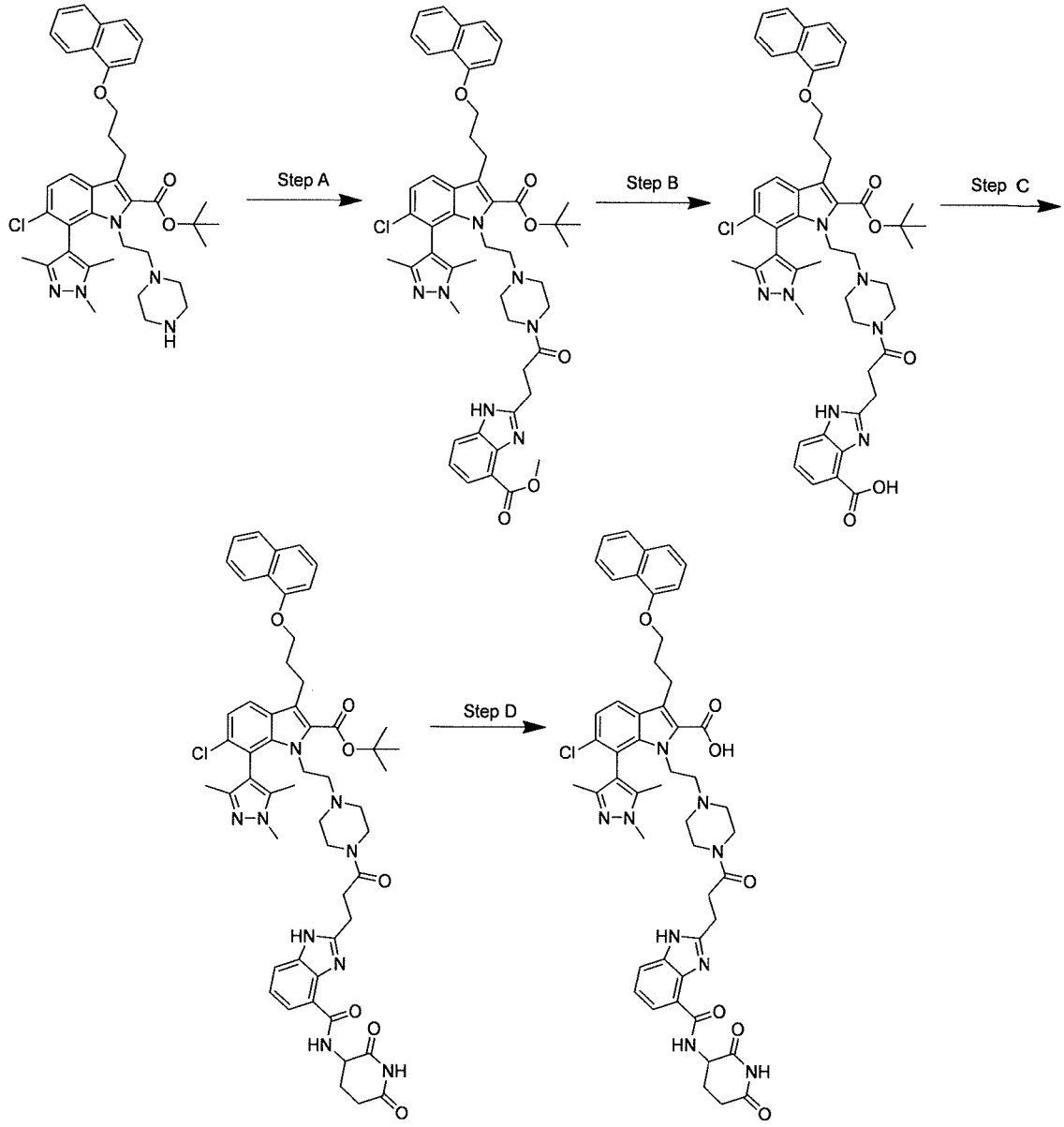


The crude *tert*-butyl 6-chloro-1-(2-{4-[2-({4-[(2,6-dioxopiperidin-3-yl)carbamoyl]-2-methyl-1*H*-1,3-benzodiazol-5-yl}oxy)acetyl]piperazin-1-yl}ethyl)-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (45.1 mg) was dissolved in dry DCM (0.350 mL) under argon atmosphere and TFA (0.346 mL, 4.515 mmol) was added. Reaction mixture was stirred at room temperature for 48 h. Reaction mixture was concentrated and dried under reduced pressure and the resulting solid dissolved in DMSO and purified twice by preparative HPLC (H_2O:MeCN + 0.1% FA) to give 6-chloro-1-(2-(4-(2-((4-((2,6-dioxopiperidin-3-yl)carbamoyl)-2-methyl-1*H*-benzo[*d*]imidazol-5-yl)oxy)acetyl)piperazin-1-yl)ethyl)-3-(3-(naphthalen-1-yloxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (2.7 mg, 0.003 mmol, 5% yield over four steps) as white solid.

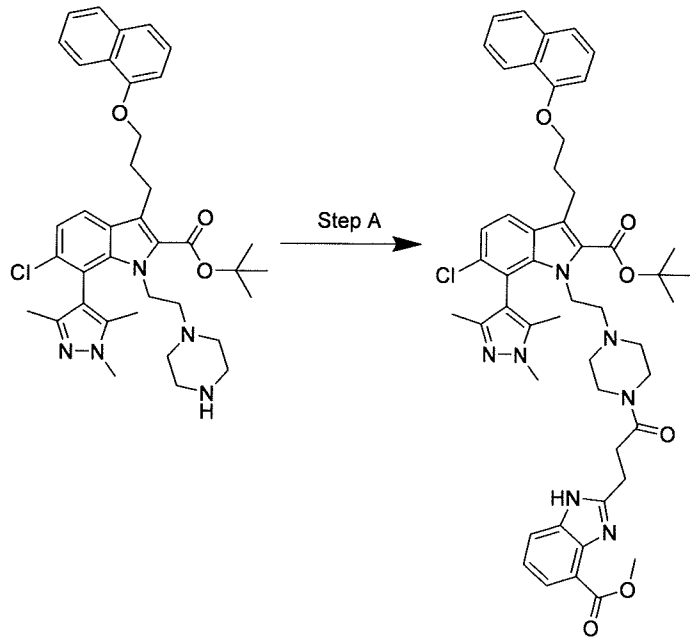
LCMS (ESI+): m/z 942.5 $[M+H]^+$

^{1}H NMR (500 MHz, DMSO) δ 13.42 (s, 1H), 12.11 (s, 1H), 10.85 (d, *J* = 5.2 Hz, 1H), 10.04 (d, *J* = 8.1 Hz, 1H), 8.26 – 8.18 (m, 1H), 7.90 – 7.83 (m, 1H), 7.79 – 7.73 (m, 1H), 7.64 (d, *J* = 8.7 Hz, 1H), 7.56 – 7.49 (m, 2H), 7.46 (d, *J* = 8.2 Hz, 1H), 7.40 (t, *J* = 7.9 Hz, 1H), 7.28 – 7.20 (m, 1H), 7.02 (d, *J* = 8.8 Hz, 1H), 6.92 (d, *J* = 7.4 Hz, 1H), 5.02 (s, 2H), 4.79 (ddd, *J* = 12.0, 8.1, 5.5 Hz, 1H), 4.34 – 4.16 (m, 4H), 3.78 (s, 3H), 3.41 – 3.35 (m, 5H), 3.30 (s, 3H), 2.88 – 2.80 (m, 1H), 2.61 – 2.59 (m, 2H), 2.29 – 2.17 (m, 3H), 2.16 – 2.11 (m, 3H), 2.09 – 1.98 (m, 7H), 1.90 (s, 3H).

Example 15: 6-chloro-1-{2-[4-(3-{4-[(2,6-dioxopiperidin-3-yl)carbamoyl]-1*H*-1,3-benzodiazol-2-yl}propanoyl)piperazin-1-yl]ethyl}-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (265)



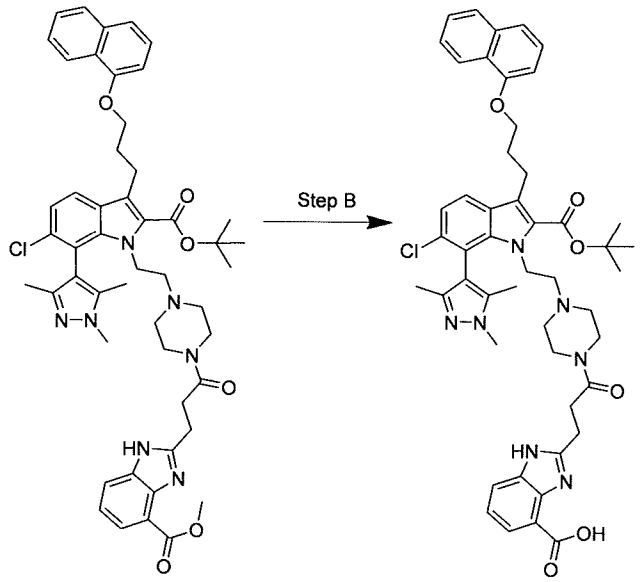
Step A



To a well stirred solution of 3-(7-(methoxycarbonyl)-1*H*-benzo[*d*]imidazol-2-yl)propanoic acid (21.2 mg, 0.084 mmol) and *tert*-butyl 6-chloro-3-(3-(naphthalen-1-yloxy)propyl)-1-(2-(piperazin-1-yl)ethyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (50.0 mg, 0.076 mmol) in DMF (0.762 mL) was added DIPEA (0.040 mL, 0.229 mmol) and HATU (34.8 mg, 0.091 mmol) and the mixture was allowed to stir under nitrogen for 16 h. After complete consumption of the starting material, solvents were removed under reduced pressure and the reaction mixture diluted with DCM washed successively with $NaHCO_3$ (sat.) and brine. Organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to afford methyl 2-{3-[4-(2-{2-[(*tert*-butoxy)carbonyl]-6-chloro-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indol-1-yl}ethyl)piperazin-1-yl]-3-oxopropyl}-1*H*-1,3-benzodiazole-4-carboxylate (55 mg, crude) as brown semi solid which was used for next step without further purification.

LCMS (ESI+): m/z 886.1 $[M+H]^+$

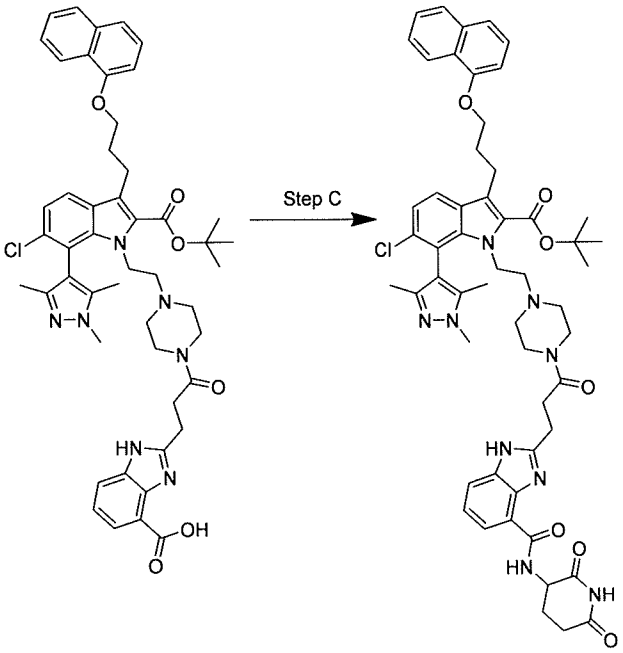
Step B



Methyl 2-{3-[4-(2-{2-[(*tert*-butoxy)carbonyl]-6-chloro-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indol-1-yl}ethyl)piperazin-1-yl]-3-oxopropyl}-1*H*-1,3-benzodiazole-4-carboxylate (55.0 mg) was dissolved in THF (0.472 mL) and H_2O (0.472 mL). LiOH (0.236 mL, 0.236 mmol) was added, and mixture was stirred in room temperature for 4 days. In the meantime precipitate was observed, and THF was added for solubility. After reaction was finished THF was removed under reduced pressure and to mixture water and 1M HCl were added till pH ~3 and mixture was extracted with DCM. 2-{3-[4-(2-{2-[(*tert*-butoxy)carbonyl]-6-chloro-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indol-1-yl}ethyl)piperazin-1-yl]-3-oxopropyl}-1*H*-1,3-benzodiazole-4-carboxylic acid (23.0 mg, crude) was obtained as brown gum, which was used for next step without further purification.

LCMS (ESI+): m/z 872.0 $[M+H]^+$

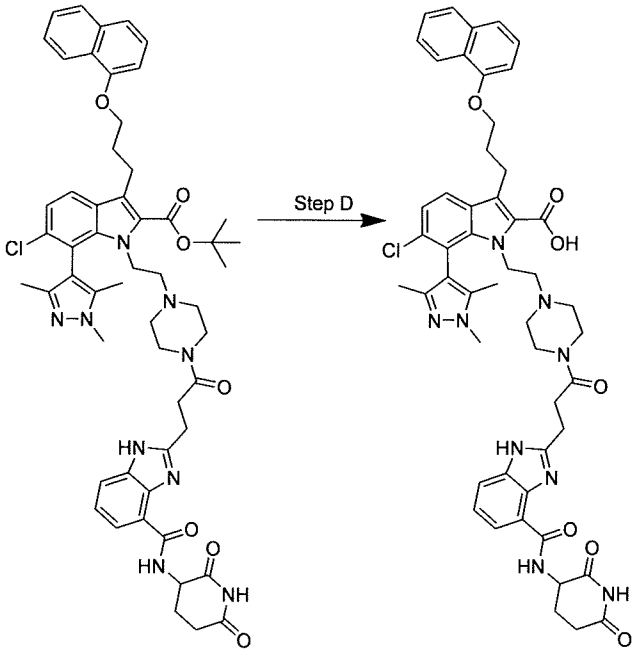
Step C



To a well stirred solution of 3-aminopiperidine-2,6-dione hydrochloride (7.8 mg, 0.047 mmol) and 2-{3-[4-(2-{2-[(*tert*-butoxy)carbonyl]-6-chloro-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indol-1-yl}ethyl)piperazin-1-yl]-3-oxopropyl}-1*H*-1,3-benzodiazole-4-carboxylic acid (23.0 mg) in DMF (0.237 mL) was added DIPEA (0.012 mL, 0.071 mmol) and HATU (10.8 mg, 0.028 mmol) and the mixture was allowed to stir under nitrogen for 16 h at room temperature. After complete consumption of the starting material solvents were removed under reduced pressure and the reaction mixture diluted with DCM washed successively with cold water (3 times) and brine. Organic layer was dried over Na_2SO_4, filtered and evaporated under reduced pressure. Crude of *tert*-butyl 6-chloro-1-{2-[4-(3-{4-[(2,6-dioxopiperidin-3-yl)carbamoyl]-1*H*-1,3-benzodiazol-2-yl}propanoyl)piperazin-1-yl]ethyl}-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (15.0 mg, crude) as brownish solid was used for next step without further purification.

LCMS (ESI+): m/z 981.6 $[M+H]^+$

Step D

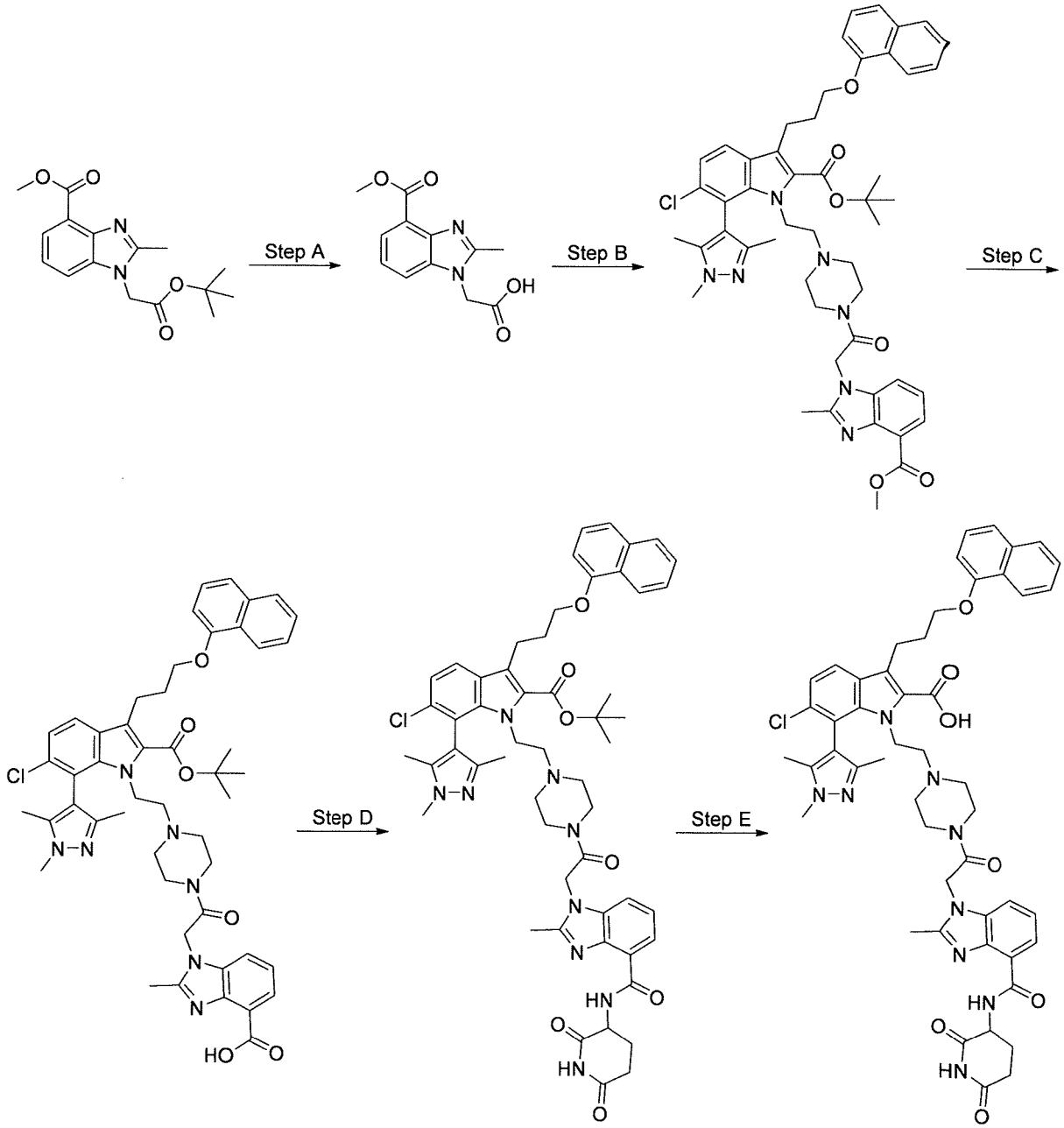


Tert-butyl 6-chloro-1-{2-[4-(3-{4-[(2,6-dioxopiperidin-3-yl)carbamoyl]-1*H*-1,3-benzodiazol-2-yl}propanoyl)piperazin-1-yl]ethyl}-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (15.0 mg, crude) was dissolved in DCM (0.104 mL) and TFA (0.013 mL, 0.175 mmol) was added. Mixture was stirred for 7 days at room temperature. During this time additional amounts of TFA (1 mL) was added. After full conversion was reached solvents were removed under reduced pressure, and purified using preparative HPLC (H_2O:MeCN + 0.1% FA). 6-chloro-1-{2-[4-(3-{4-[(2,6-dioxopiperidin-3-yl)carbamoyl]-1*H*-1,3-benzodiazol-2-yl}propanoyl)piperazin-1-yl]ethyl}-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (1.6 mg, 0.002 mmol, 3% over four steps) was obtained as white solid.

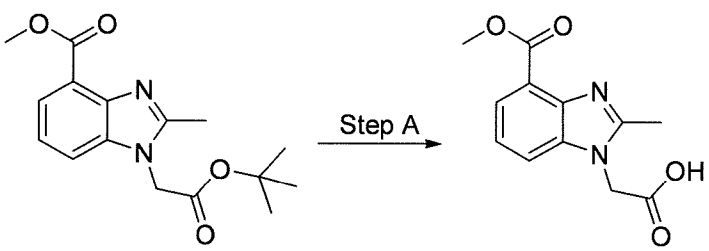
LCMS (ESI+): m/z 925.6 $[M+H]^+$

^{1}H NMR (500 MHz, DMSO) δ 12.70 (s, 1H), 10.51 (t, *J* = 6.3 Hz, 1H), 8.24 – 8.16 (m, 1H), 7.87 – 7.82 (m, 1H), 7.80 (dd, *J* = 7.6, 1.1 Hz, 1H), 7.76 – 7.67 (m, 1H), 7.67 – 7.58 (m, 1H), 7.54 – 7.46 (m, 2H), 7.46 – 7.40 (m, 1H), 7.37 (t, *J* = 7.9 Hz, 1H), 7.27 (t, *J* = 7.7 Hz, 1H), 7.22 – 7.14 (m, 1H), 6.89 (d, *J* = 7.5 Hz, 1H), 4.88 – 4.77 (m, 1H), 4.35 – 4.23 (m, 1H), 4.23 – 4.17 (m, 3H), 3.73 (d, *J* = 5.0 Hz, 3H), 3.46 – 3.36 (m, 6H), 3.09 (t, *J* = 7.2 Hz, 2H), 3.02 – 2.89 (m, 1H), 2.86 – 2.76 (m, 1H), 2.60 – 2.52 (m, 2H), 2.23 – 2.17 (m, 2H), 2.14 – 2.05 (m, 3H), 2.05 – 1.97 (m, 8H), 1.87 (d, *J* = 3.7 Hz, 3H).

Example 16: 6-chloro-1-{2-[4-(2-{4-[(2,6-dioxopiperidin-3-yl)carbamoyl]-2-methyl-1*H*-1,3-benzodiazol-1-yl}acetyl)piperazin-1-yl]ethyl}-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (266)



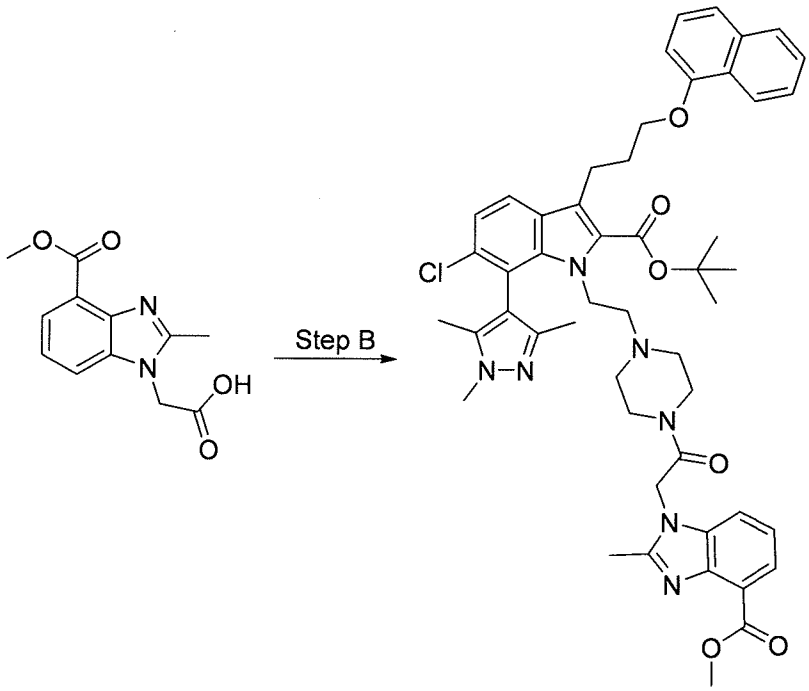
Step A



Methyl 1-(2-(*tert*-butoxy)-2-oxoethyl)-2-methyl-1*H*-benzo[*d*]imidazole-4-carboxylate (30.4 mg, 0.100 mmol) was dissolved in TFA (3.0 ml) and mixed 16 h at room temperature. Solvent was evaporated under reduced pressure to obtain 24 mg crude of 2-(4-(methoxycarbonyl)-2-methyl-1*H*-benzo[*d*]imidazol-1-yl)acetic acid as a brown oil that was used directly in the next step.

LCMS (ESI+): m/z 249.3 $[M+H]^+$

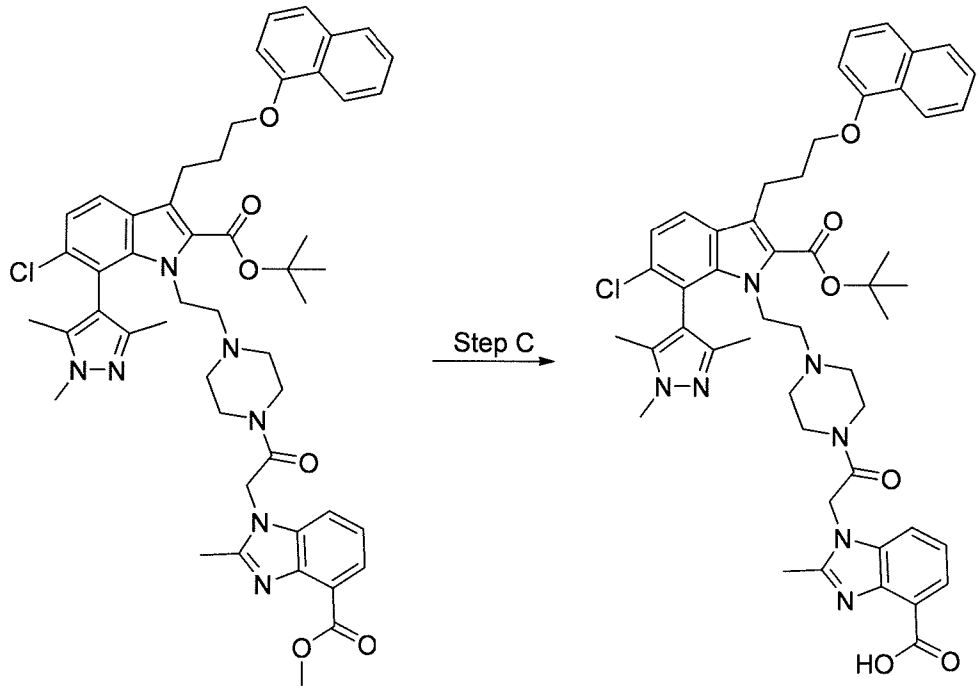
Step B



To a well stirred solution of crude 2-(4-(methoxycarbonyl)-2-methyl-1*H*-benzo[*d*]imidazol-1-yl)acetic acid (12.0 mg) and *tert*-butyl 6-chloro-3-(3-(naphthalen-1-yloxy)propyl)-1-(2-(piperazin-1-yl)ethyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (31.1 mg, 0.047 mmol) in DMF (0.474 ml) was added DIPEA (0.023 ml, 0.129 mmol) and HATU (19.8 mg, 0.052 mmol). The mixture was allowed to stir under nitrogen for 16 h at room temperature. After complete consumption of the starting material, the reaction mixture was diluted with EtOAc, washed successively with cold water (3 times) and brine. Organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to afford 41.0 mg of crude methyl 1-(2-(4-(2-(2-(*tert*-butoxycarbonyl)-6-chloro-3-(3-(naphthalen-1-yloxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indol-1-yl)ethyl)piperazin-1-yl)-2-oxoethyl)-2-methyl-1*H*-benzo[*d*]imidazole-4-carboxylate as brown solid which was used for next step without further purification.

LCMS (ESI+): m/z 886.8 $[M+H]^+$

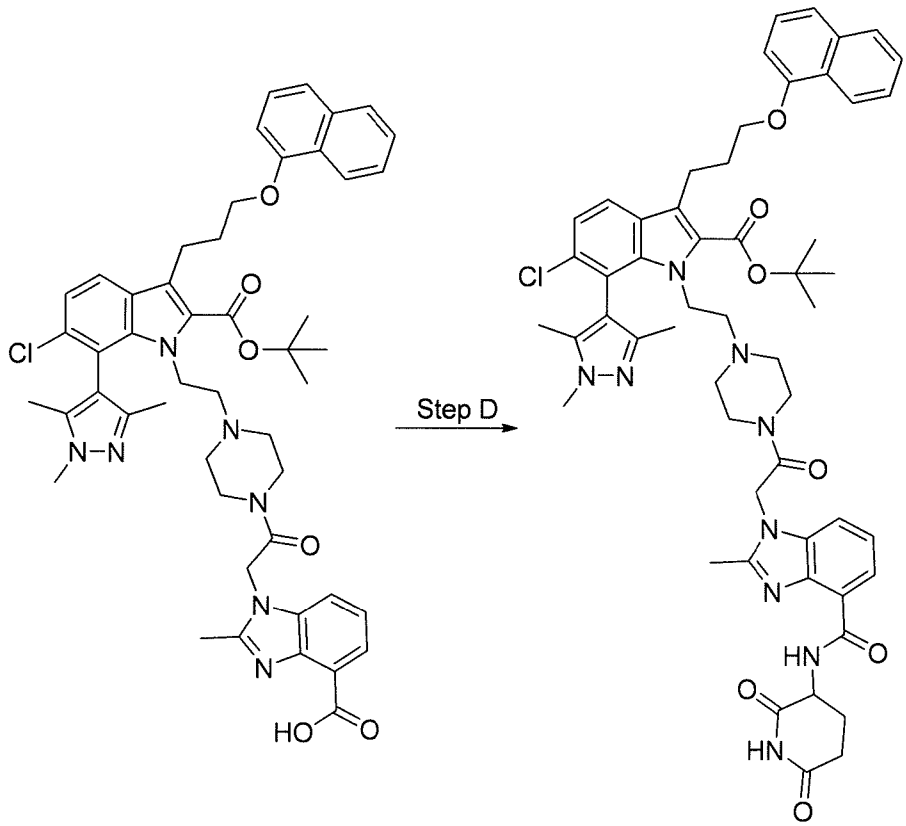
Step C



Methyl 1-(2-(4-(2-(2-(*tert*-butoxycarbonyl)-6-chloro-3-(3-(naphthalen-1-yloxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indol-1-yl)ethyl)piperazin-1-yl)-2-oxoethyl)-2-methyl-1*H*-benzo[*d*]imidazole-4-carboxylate (41.0 mg, crude) was dissolved in MeOH (4.6 ml) and a few drops of DCM were added for solubility. Water (4.6 ml) was added followed by aqueous solution of 1M LiOH (0.231 mL, 0.231 mmol) and the mixture was stirred in room temperature for 16 h. To mixture water and 1M HCl were added till pH = 3 and the mixture was extracted with DCM to afford 40 mg of crude 1-(2-(4-(2-(2-(*tert*-butoxycarbonyl)-6-chloro-3-(3-(naphthalen-1-yloxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indol-1-yl)ethyl)piperazin-1-yl)-2-oxoethyl)-2-methyl-1*H*-benzo[*d*]imidazole-4-carboxylic acid as a brow gum, which was used for next step without further purification.

LCMS (ESI+): m/z 872.1 $[M+H]^+$

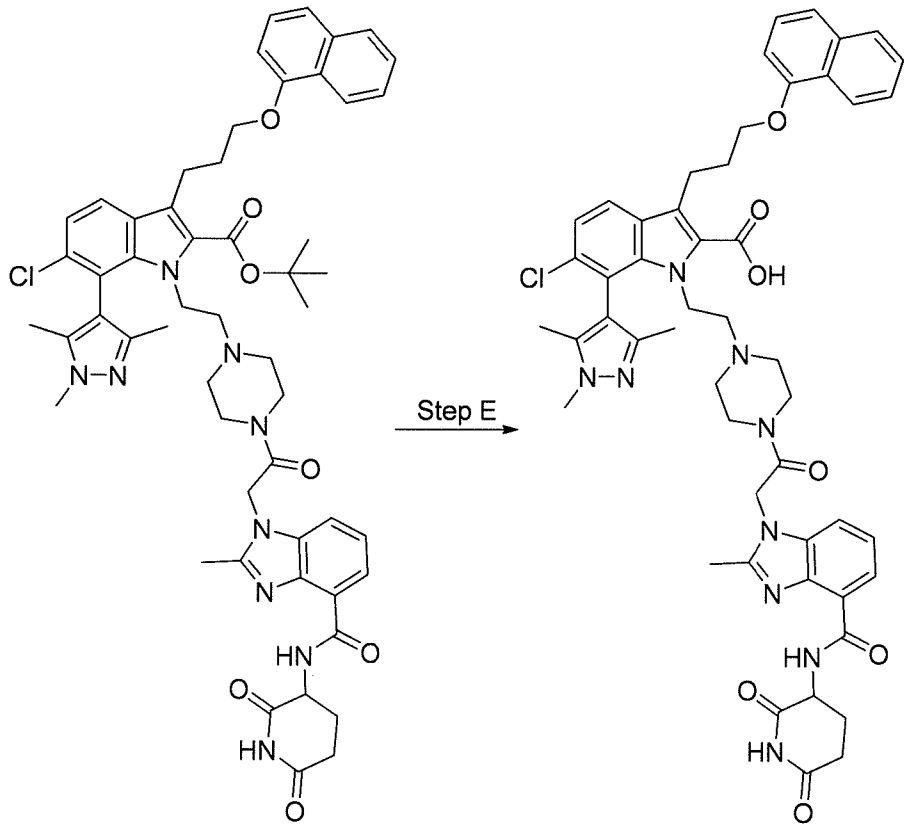
Step D



To a well stirred solution of 3-aminopiperidine-2,6-dione hydrochloride (15.1 mg, 0.092 mmol) and 1-(2-(4-(2-(2-(*tert*-butoxycarbonyl)-6-chloro-3-(3-(naphthalen-1-yloxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indol-1-yl)ethyl)piperazin-1-yl)-2-oxoethyl)-2-methyl-1*H*-benzo[*d*]imidazole-4-carboxylic acid (40.0 mg, crude) in DMF (0.458 ml) was added DIPEA (0.024 mL, 0.138 mmol) and HATU (20.9 mg, 0.055 mmol). The mixture was allowed to stir under nitrogen for 16 h. After complete consumption of the starting material, the reaction mixture was diluted with EtOAc, washed successively with cold water (3 times) and brine. Organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to afford 45 mg of crude *tert*-butyl 6-chloro-1-{2-[4-(2-{4-[(2,6-dioxopiperidin-3-yl)carbamoyl]-2-methyl-1*H*-1,3-benzodiazol-1-yl}acetyl)piperazin-1-yl]ethyl}-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate as a brown solid which was used for next step without further purification.

LCMS (ESI+): m/z 982.0 $[M+H]^+$

Step E

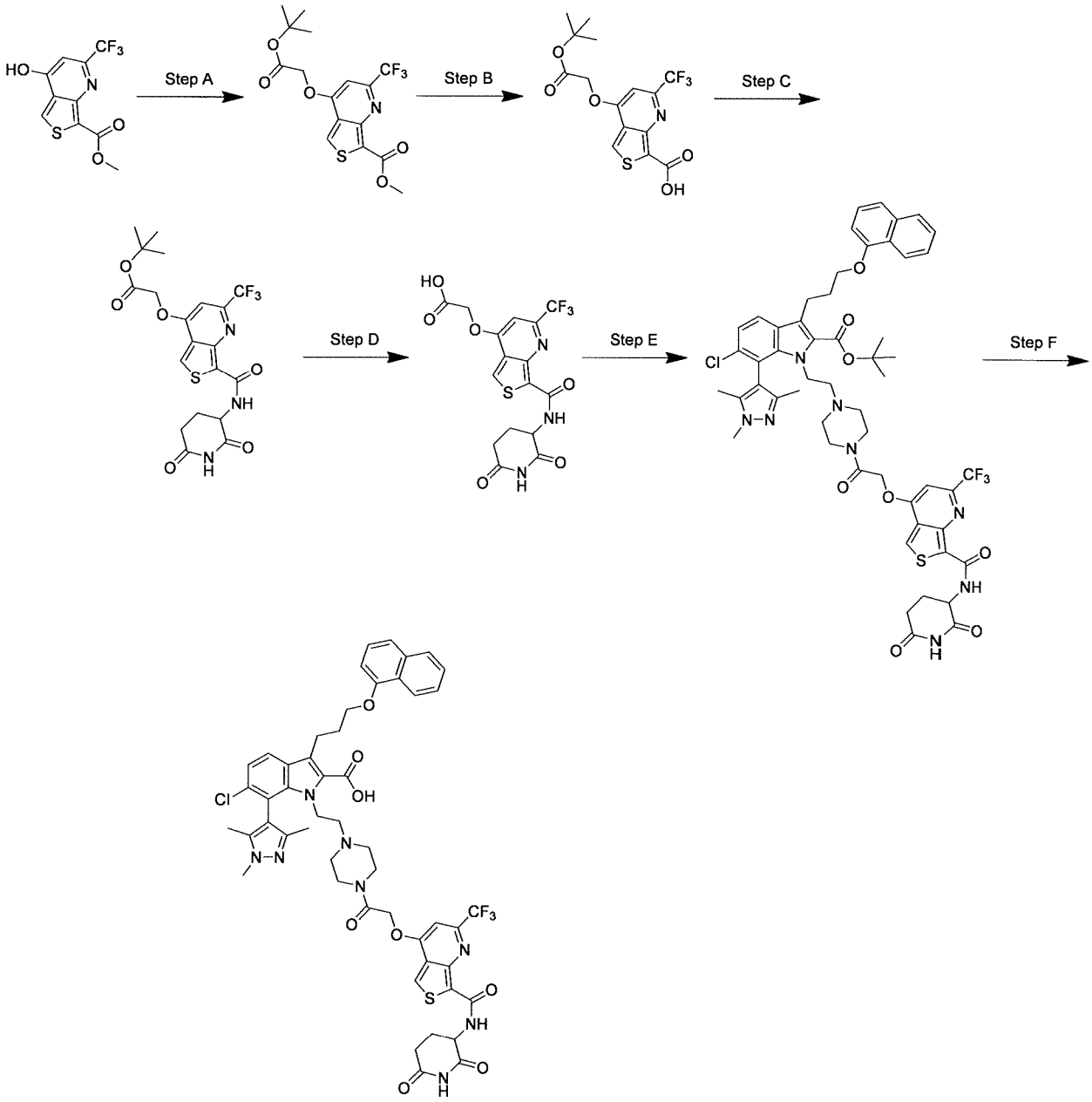


Tert-butyl 6-chloro-1-{2-[4-(2-{4-[(2,6-dioxopiperidin-3-yl)carbamoyl]-2-methyl-1*H*-1,3-benzodiazol-1-yl}acetyl)piperazin-1-yl]ethyl}-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (45 mg, crude) was suspended in dry DCM (0.342 mL) under argon atmosphere and TFA (0.336 mL, 4.386 mmol) was added. Reaction was stirred in a sealed vial in room temperature. After 16 h full substrate conversion was observed. DCM along with TFA were evaporated under reduced pressure. Crude product was dissolved in DMSO and purified by preparative HPLC (H_2O:MeCN + 0.1% FA) to give a corresponding 6-chloro-1-{2-[4-(2-{4-[(2,6-dioxopiperidin-3-yl)carbamoyl]-2-methyl-1*H*-1,3-benzodiazol-1-yl}acetyl)piperazin-1-yl]ethyl}-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (7.0 mg, 0.008 mmol, 17% yield over four steps) as white powder.

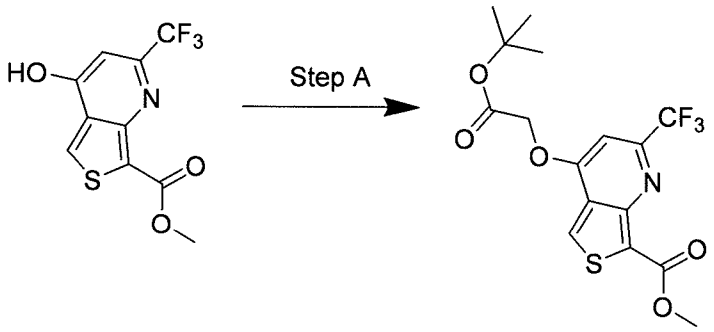
LCMS (ESI+): m/z 925.8 $[M+H]^+$

^{1}H NMR (500 MHz, DMSO) δ 13.43 (s, 1H), 10.93 (s, 1H), 10.25 (d, J = 7.4 Hz, 1H), 8.24 (dd, J = 7.9, 1.8 Hz, 1H), 7.92 – 7.83 (m, 2H), 7.77 (d, J = 8.6 Hz, 1H), 7.66 (dd, J = 8.1, 1.1 Hz, 1H), 7.57 – 7.50 (m, 2H), 7.48 (d, J = 8.2 Hz, 1H), 7.41 (t, J = 7.9 Hz, 1H), 7.31 (t, J = 7.8 Hz, 1H), 7.25 (d, J = 8.5 Hz, 1H), 6.93 (d, J = 7.6 Hz, 1H), 5.30 (s, 2H), 4.90 (ddd, J = 12.6, 7.3, 5.3 Hz, 1H), 4.42 – 4.28 (m, 1H), 4.28 – 4.16 (m, 3H), 3.79 (s, 3H), 3.55 – 3.46 (m, 2H), 3.42 – 3.36 (m, 3H), 2.84 (ddd, J = 17.4, 13.5, 5.6 Hz, 1H), 2.62 – 2.59 (m, 1H), 2.57 – 2.55 (m, 1H), 2.49 (s, 3H), 2.32 – 2.21 (m, 5H), 2.21 – 2.06 (m, 5H), 2.04 (s, 3H), 1.91 (s, 3H).

Example 17: 6-chloro-1-(2-{4-[2-({7-[(2,6-dioxopiperidin-3-yl)carbamoyl]-2-(trifluoromethyl)thieno[3,4-*b*]pyridin-4-yl}oxy)acetyl]piperazin-1-yl}ethyl)-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (267)



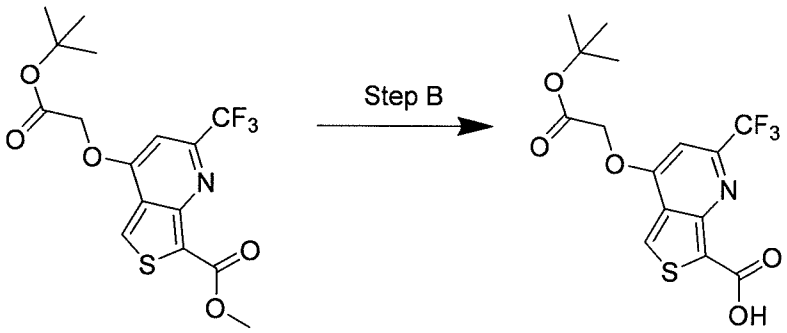
Step A



Methyl 4-hydroxy-2-(trifluoromethyl)thieno[3,4,*b*]pyridine-7-carboxylate (200.0 mg, 0.721 mmol) was dissolved in dry DMF (2.0 mL). To the mixture was added *tert*-butyl bromoacetate (0.160 mL, 1.082 mmol) and K_2CO_3 (199.4 mg, 1.443 mmol). The reaction was stirred for 24 h at RT. The solvent was evaporated and the crude was dissolved in EtOAc and purified by flash chromatography (SiO_2, isohaxane:EtOAc, 0-50%). Isolated fraction was concentrated *in vacuo*. The product, methyl 4-[2-(*tert*-butoxy)-2-oxoethoxy]-2-(trifluoromethyl)thieno[3,4-*b*]pyridine-7-carboxylate (247.0 mg, 0.631 mmol, 87.5%) was a light yellow solid.

LCMS (ESI^+): m/z 392.0 $[M+H]^+$

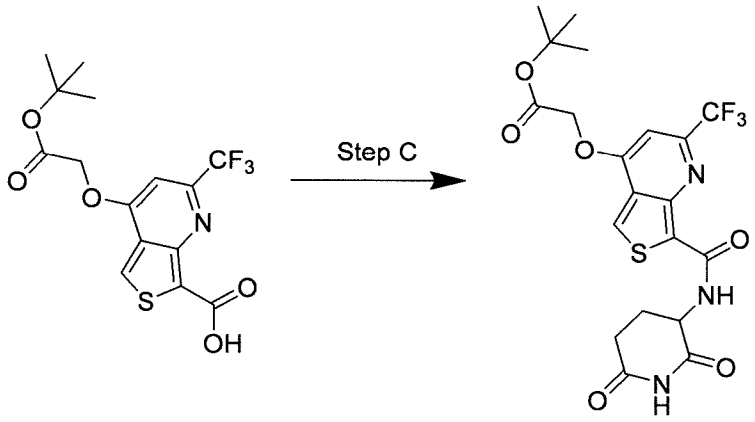
Step B



To a solution of methyl 4-[2-(*tert*-butoxy)-2-oxoethoxy]-2-(trifluoromethyl)thieno[3,4-b]pyridine-7-carboxylate (247.0 mg, 0.631 mmol) in a mixture of acetonitrile (15.0 mL) and water (1.5 mL) was added LiBr (548.1 mg, 6.311 mmol) and Et_3N (0.494 mL, 3.552 mmol). The mixture was stirred at 60°C for 2 days and 24 h at RT. The crude was concentrated in vacuo. Residues was dissolved in EtOAc and was extracted with water and brine. Organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. The product, 4-[2-(*tert*-butoxy)-2-oxoethoxy]-2-(trifluoromethyl)thieno[3,4-*b*]pyridine-7-carboxylic acid (233.9 mg, crude) was a yellow solid and was used without further purification to next step.

LCMS (ESI^+): m/z 378.0 $[M+H]^+$

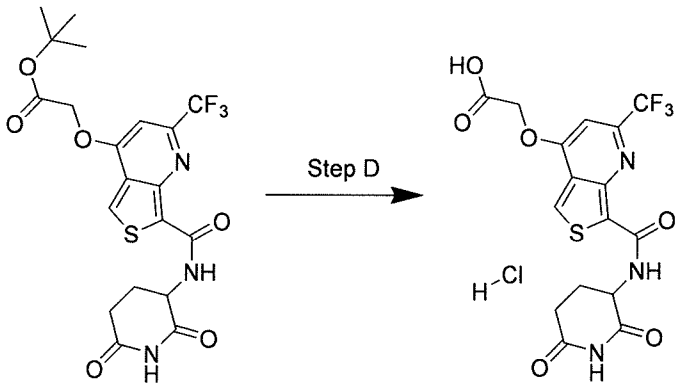
Step C



4-[2-(*Tert*-butoxy)-2-oxoethoxy]-2-(trifluoromethyl)thieno[3,4-*b*]pyridine-7-carboxylic acid (55.0 mg, crude) and 3-aminopiperidine-2,6-dione hydrochloride (28.8 mg, 0.175 mmol) was dissolved in DMF (1.5 mL). To the mixture were added DIPEA (0.076 mL, 0.437 mmol) and HATU (83.1 mg, 0.219 mmol). The reaction was stirred at RT for 18h. The solvent was evaporated. The residues was dissolved in EtOAc, washed two times with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The mixture was purified by flash chromatography (SiO_2, DCM:MeOH, 0-20%) to give *tert*-butyl 2-({7-[(2,6-dioxopiperidin-3-yl)carbamoyl]-2-(trifluoromethyl)thieno[3,4-*b*]pyridin-4-yl}oxy)acetate (66.0 mg, crude) as a yellow solid.

LCMS (ESI^+): m/z 487.9 $[M+H]^+$

Step D

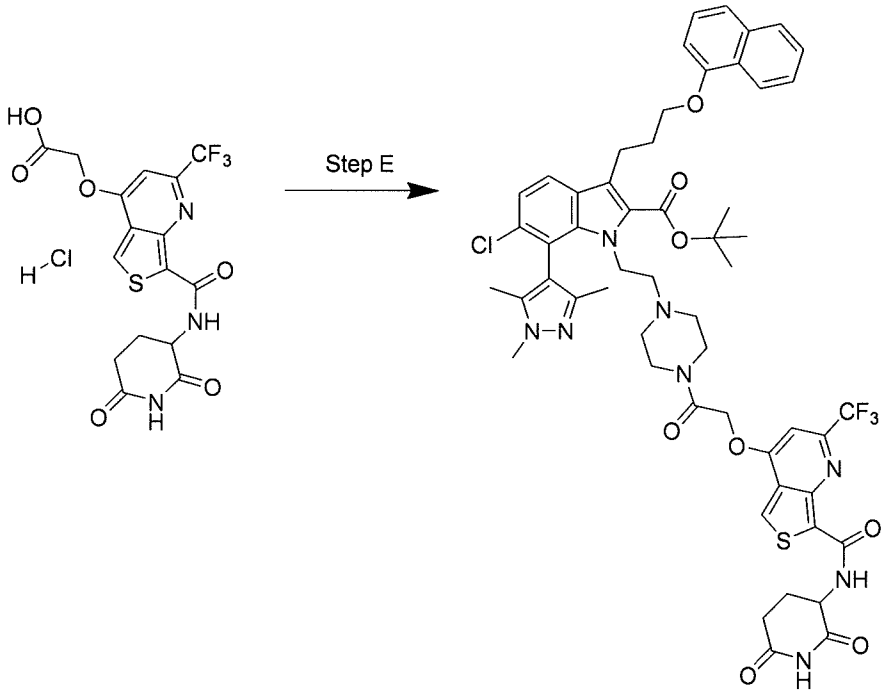


To the mixture of *tert*-butyl 2-({7-[(2,6-dioxopiperidin-3-yl)carbamoyl]-2-(trifluoromethyl)thieno[3,4-*b*]pyridin-4-yl}oxy)acetate (66.0 mg, crude) in DCM (1 mL) was added TFA (1 mL). The mixture was stirred for 17 h at RT. The solvent was evaporated and to the crude was added HCl and mixture was concentrated in vacuo. The product, 2-({7-[(2,6-dioxopiperidin-3-

yl)carbamoyl]-2-(trifluoromethyl)thieno[3,4-*b*]pyridin-4-yl}oxy)acetic acid hydrochloride (54.0 mg, crude) as yellow solid was used to next step without further purification.

LCMS (ESI$^+$): m/z 431.8 $[M+H]^+$

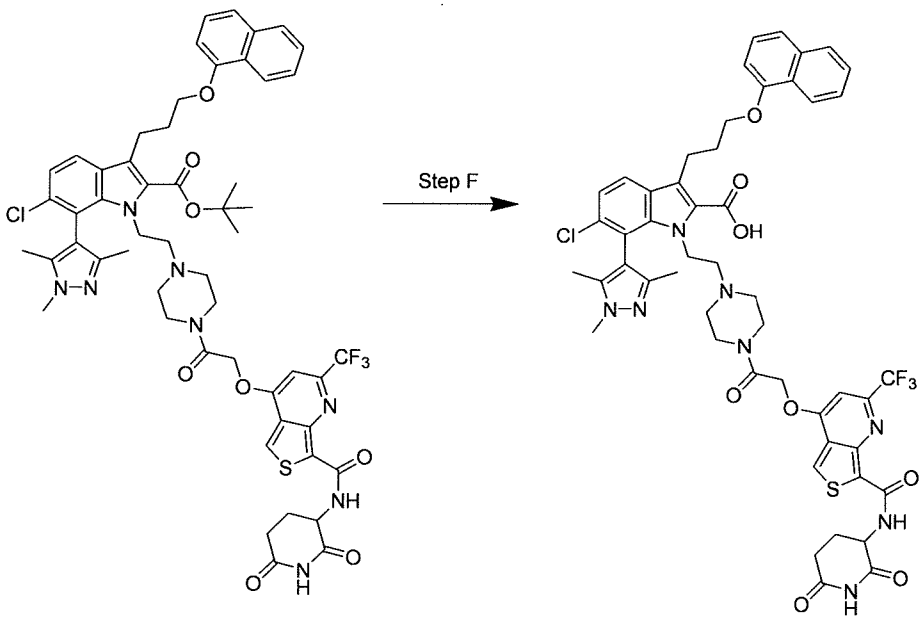
Step E



To a solution of 2-({7-[(2,6-dioxopiperidin-3-yl)carbamoyl]-2-(trifluoromethyl)thieno[3,4-*b*]pyridin-4-yl}oxy)acetic acid hydrochloride (30.0 mg, crude) and *tert*-butyl 6-chloro-3-[3-(naphthalen-1-yloxy)propyl]-1-[2-(piperazin-1-yl)ethyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (41.5 mg, 0.063 mmol) in dry DMF (2.0 mL) was added DIPEA (0.055 mL, 0.316 mmol) and HATU (48.1 mg, 0.126 mmol). The mixture was stirred for 2 h at RT. Then, the crude was concentrated in vacuo. The residues were dissolved in DCM and washed with H_2O and brine. The organic layers was dried over Na_2SO_4, filtered and evaporated under reduced pressure. *Tert*-butyl 6-chloro-1-(2-{4-[2-({7-[(2,6-dioxopiperidin-3-yl)carbamoyl]-2-(trifluoromethyl)thieno[3,4-*b*]pyridin-4-yl}oxy)acetyl]piperazin-1-yl}ethyl)-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (35.0 mg, crude) was used to next step without further purification.

LCMS (ESI$^+$): m/z 1068.9 $[M+H]^+$

Step F

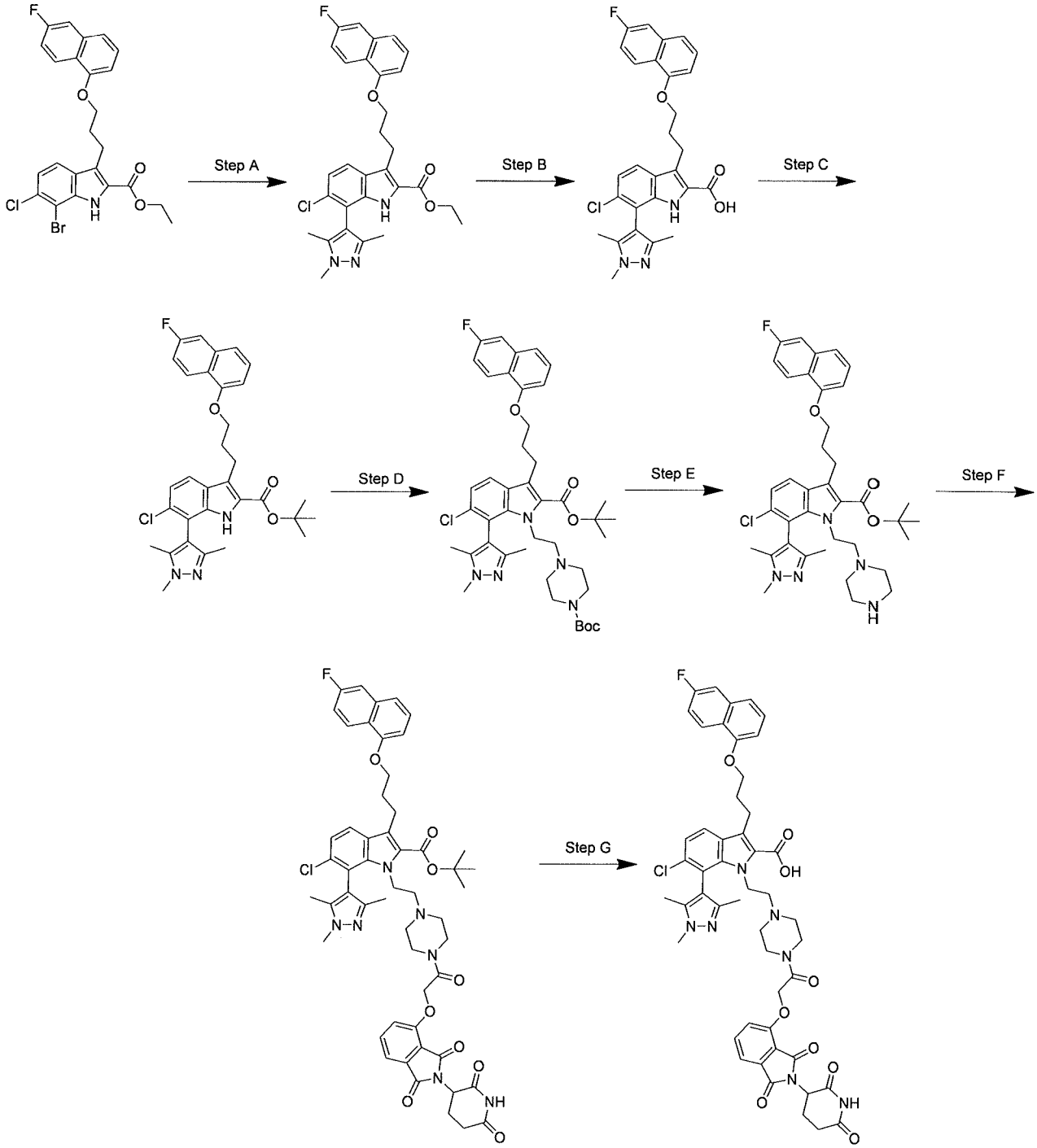


To a solution of *tert*-butyl 6-chloro-1-(2-{4-[2-({7-[(2,6-dioxopiperidin-3-yl)carbamoyl]-2-(trifluoromethyl)thieno[3,4-*b*]pyridin-4-yl}oxy)acetyl]piperazin-1-yl}ethyl)-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (35.0 mg, crude) in DCM (1.0 mL) was added TFA (1.0 mL, 13.059 mmol). The reaction was stirred for 17 h at RT. The crude was concentrated in vacuo, dissolved in DMSO and purified by preparative HPLC (H_2O:MeCN + 0.1% FA) to give 6-chloro-1-(2-{4-[2-({7-[(2,6-dioxopiperidin-3-yl)carbamoyl]-2-(trifluoromethyl)thieno[3,4-*b*]pyridin-4-yl}oxy)acetyl]piperazin-1-yl}ethyl)-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (10.6 mg, 0.010 mmol, 32.0%) as a light yellow solid.

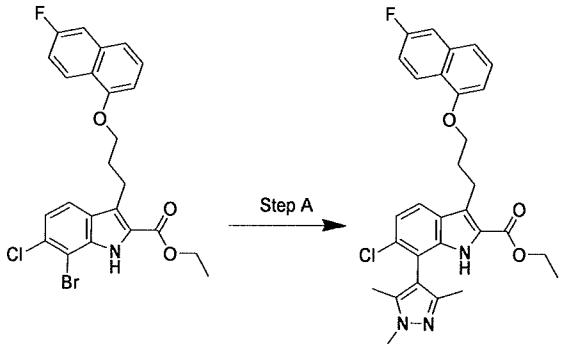
LCMS (ESI^+): m/z 1012.69 $[M+H]^+$

^1H NMR (500 MHz, DMSO) δ 13.38 (s, 1H), 10.99 (s, 1H), 9.43 (d, *J* = 6.5 Hz, 1H), 8.71 (s, 1H), 8.24 – 8.17 (m, 1H), 7.85 (dd, *J* = 7.3, 2.0 Hz, 1H), 7.75 (d, *J* = 8.6 Hz, 1H), 7.50 (dtd, *J* = 8.0, 6.8, 5.2 Hz, 2H), 7.45 (d, *J* = 8.3 Hz, 1H), 7.38 (t, *J* = 7.9 Hz, 1H), 7.22 (d, *J* = 8.6 Hz, 1H), 7.05 (s, 1H), 6.93 – 6.88 (m, 1H), 5.30 (s, 2H), 4.87 (ddd, *J* = 12.2, 6.6, 5.2 Hz, 1H), 4.35 – 4.26 (m, 1H), 4.22 (t, *J* = 6.1 Hz, 3H), 3.76 (s, 3H), 3.37 (d, *J* = 12.9 Hz, 2H), 3.27 (d, *J* = 10.3 Hz, 2H), 2.87 – 2.77 (m, 1H), 2.52-2.62 (m, 3H), 2.25 – 2.18 (m, 2H), 2.18 – 2.00 (m, 11H), 1.88 (s, 3H).

Example 18: 6-chloro-1-{2-[4-(2-{[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl]oxy}acetyl)piperazin-1-yl]ethyl}-3-{3-[(6-fluoronaphthalen-1-yl)oxy]propyl}-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (214)



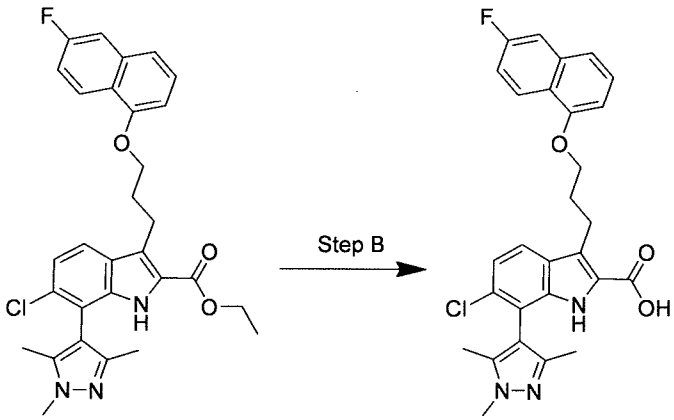
Step A



To a stirred solution of ethyl 7-bromo-6-chloro-3-(3-((6-fluoronaphthalen-1-yl)oxy)propyl)-1*H*-indole-2-carboxylate (1.7g, 3.368 mmol) in dioxane (20 mL) and water (5 mL) were added 1,3,5-trimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (2.386 g, 10.103 mmol) and K_2CO_3 (1.859 g, 13.471 mmol). The mixture was deoxygenated with argon and to it was added $Pd(dppf)Cl_2$ (0.369 g, 0.505 mmol) under argon atmosphere. Then the reaction mixture was heated under reflux for 16 h. After complete consumption of the starting material (monitored by TLC and LCMS) the reaction mixture was filtered through celite pad and the solvents were evaporated under reduced pressure get the crude material. It was then diluted with EtOAc, washed successively with water and brine, the organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to get the crude compound, which was then purified by column chromatography (SiO_2, 50% EtOAc in hexane) to get ethyl 6-chloro-3-(3-((6-fluoronaphthalen-1-yl)oxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (1.2 g, 2.247 mmol, 66.72%) as brown solid.

LCMS (ESI+): m/z 534.2 $[M+H]^+$

Step B

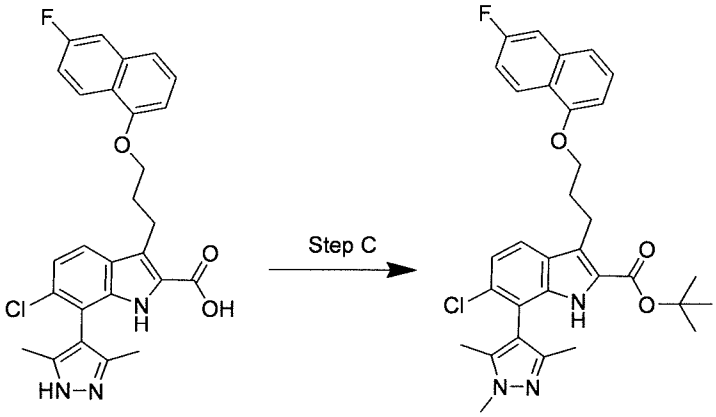


Ethyl 6-chloro-3-(3-((6-fluoronaphthalen-1-yl)oxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (1.2 g, 2.251 mmol) was dissolved in EtOH (20 mL) and solution of NaOH

(0.315 g, 7.88 mmol) in water (10 mL) was added to it. The mixture was heated under reflux for 16 h. After complete consumption of the starting material (monitored by TLC and LCMS) the reaction mixture was cooled down to room temperature, solvents were evaporated under reduced pressure to get the crude reaction mixture. It was then diluted with water, washed with EtOAc. Aqueous layer was carefully acidified using 1M HCl to pH=3 and extracted with EtOAc (x3). The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo to afford 6-chloro-3-(3-((6-fluoronaphthalen-1-yl)oxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (0.9 g, crude) as brown liquid which was used for the next step without further purification.

LCMS (ESI+): m/z 506.3 $[M+H]^+$

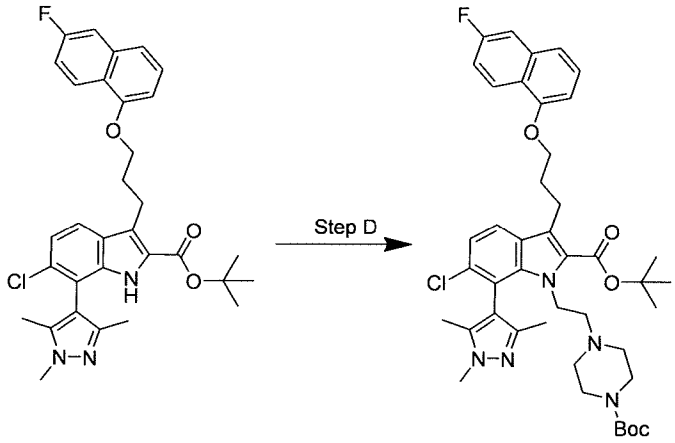
Step C



6-chloro-3-(3-((6-fluoronaphthalen-1-yl)oxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (1.2 g, 2.376 mmol) was suspended in toluene (20 mL) and the mixture was heated to reflux under nitrogen. *N*,*N*-dimethylformamide di-*tert*-butyl acetal (4.547 mL, 19.01 mmol) was added drop-wise to the refluxing mixture. The mixture was heated under reflux for 16 h under nitrogen. After complete consumption of the starting material (monitored by TLC and LCMS) the reaction mixture was then diluted with EtOAc, washed successively with sodium bicarbonate (aqueous, saturated), water and brine. Organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to get the crude compound, which was then purified by column chromatography (SiO_2, 70% EtOAc in hexane) to get *tert*-butyl 6-chloro-3-(3-((6-fluoronaphthalen-1-yl)oxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (0.772 g, 1.373 mmol, 61% over two steps) as brownish liquid.

LCMS (ESI+): m/z 561.9 $[M+H]^+$

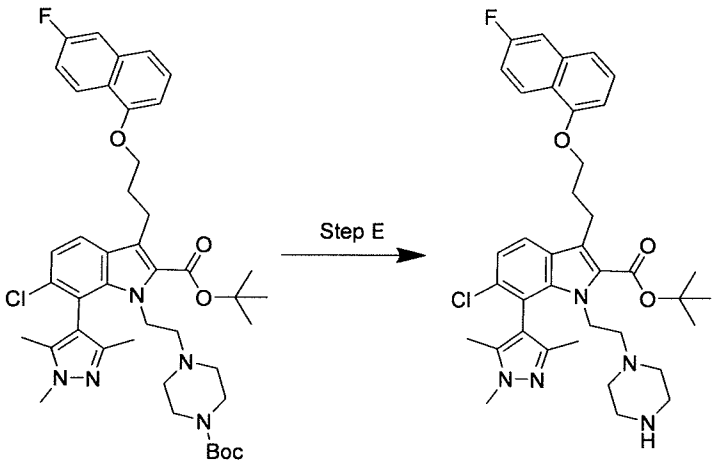
Step D



To solution of *tert*-butyl 6-chloro-3-(3-((6-fluoronaphthalen-1-yl)oxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (0.555 g, 0.989 mmol) in DMF (10 mL) was added *tert*-butyl 4-(2-chloroethyl)piperazine-1-carboxylate (0.492 g, 1.979 mmol) followed by cesium carbonate (1.607 g, 4.947 mmol) in DMF (5 mL) and the mixture was allowed to stir at 90°C for 16 h under nitrogen. After complete consumption of the starting material (monitored by TLC and LCMS) the reaction mixture was diluted with EtOAc, washed successively with water and brine. The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to get the crude compound, which was then purified by column chromatography (SiO_2, 30% EtOAc in hexane) to get *tert*-butyl 1-(2-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)ethyl)-6-chloro-3-(3-((6-fluoronaphthalen-1-yl)oxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (0.5 g, 0.645 mmol, 65.27%) as off white solid.

LCMS (ESI+): m/z 774.6 $[M+H]^+$

Step E

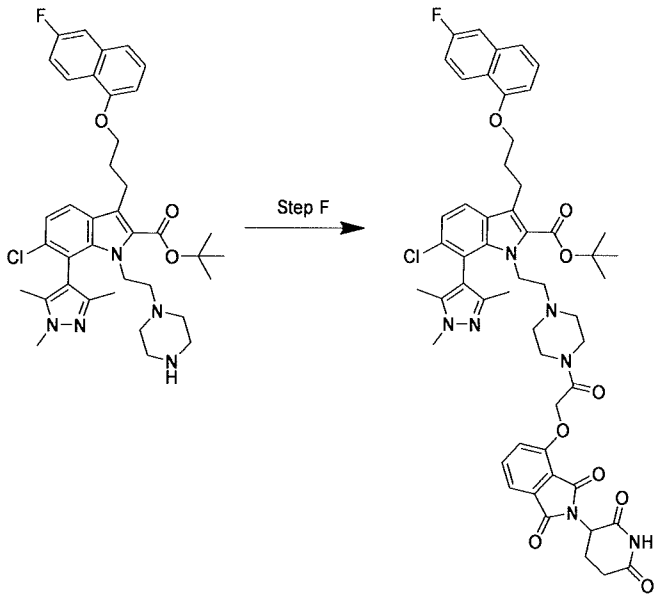


tert-butyl 1-(2-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)ethyl)-6-chloro-3-(3-((6-fluoronaphthalen-1-yl)oxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (0.3 g, 0.388 mmol)

dissolved in 20 mL of 4M HCl in dioxan at 0°C and the mixture was stirred for 2 h under nitrogen at the same temperature. After complete consumption of the starting material (monitored by TLC and LCMS) the reaction mixture was poured in to cold 1M NaOH solution and extracted several times with DCM. The combined organics were dried over Na_2SO_4 and concentrated in vacuo to get the crude compound which was then purified by column chromatography (amine SiO_2, 10% MeOH in DCM) to get *tert*-butyl 6-chloro-3-(3-((6-fluoronaphthalen-1-yl)oxy)propyl)-1-(2-(piperazin-1-yl)ethyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (0.165 g, 0.244 mmol, 62.98%) as off white solid.

LCMS (ESI+): m/z 674.4 $[M+H]^+$

Step F

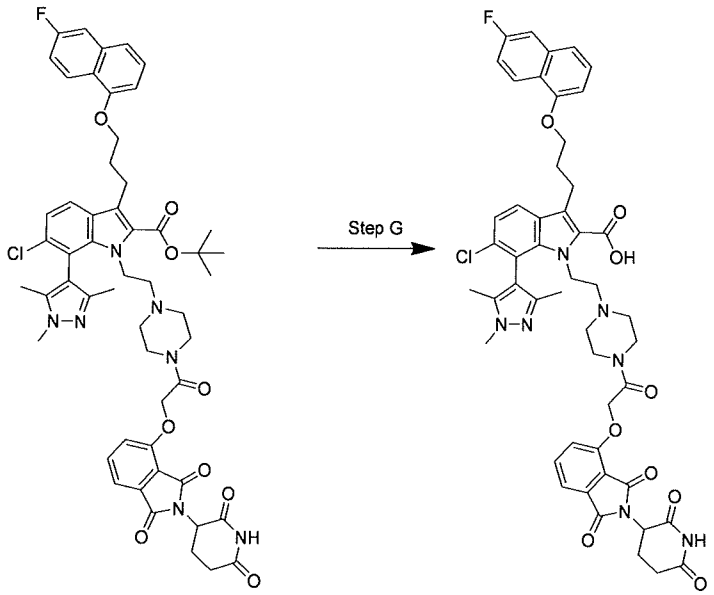


To a well stirred solution of 2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)acetic acid (18.9 mg, 0.057 mmol) and *tert*-butyl 6-chloro-3-(3-((6-fluoronaphthalen-1-yl)oxy)propyl)-1-(2-(piperazin-1-yl)ethyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate) (32.0 mg, 0.047 mmol) in DMF (0.475 mL) was added DIPEA (0.025 mL, 0.142 mmol) and HATU (21.7 mg, 0.057 mmol) and the mixture was allowed to stir under nitrogen for 2 h. After complete consumption of the starting material (monitored by TLC and LCMS), the reaction mixture diluted with EtOAc, washed successively with cold water (3 times) and brine. Organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. *Tert*-butyl 6-chloro-1-{2-[4-(2-{[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl]oxy}acetyl)piperazin-1-yl]ethyl}-3-{3-[(6-fluoronaphthalen-1-yl)oxy]propyl}-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-

carboxylate (39.0 mg, crude) was obtained as brown gum, which was used for the next step without further purification.

LCMS (ESI+): m/z 988.2 $[M+H]^+$

Step G

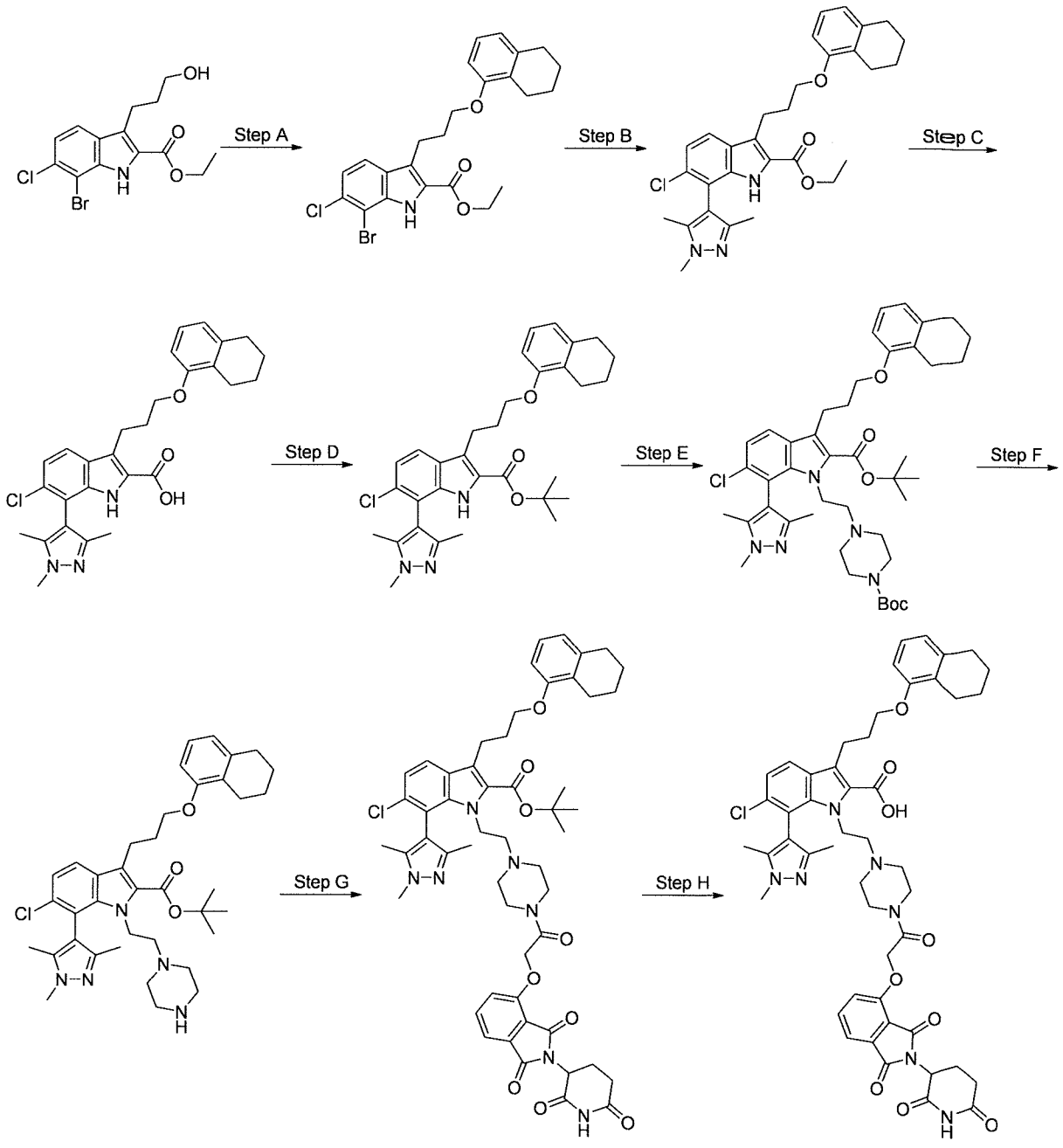


Crude mixture of *tert*-butyl 6-chloro-1-{2-[4-(2-{[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl]oxy}acetyl)piperazin-1-yl]ethyl}-3-{3-[(6-fluoronaphthalen-1-yl)oxy]propyl}-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (39.0 mg) was placed in a capped vial, dissolved in DCM (0.28 mL) and then TFA (0.030 mL) was added. Reaction was stirred overnight at RT. Solvents were removed under reduced pressure, and crude was purified using preparative HPLC (H_2O:MeCN + 0.1% FA) followed by preparative TLC to afford 6-chloro-1-{2-[4-(2-{[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl]oxy}acetyl)piperazin-1-yl]ethyl}-3-{3-[(6-fluoronaphthalen-1-yl)oxy]propyl}-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (11.8 mg, 0.013 mmol, 28% over two steps).

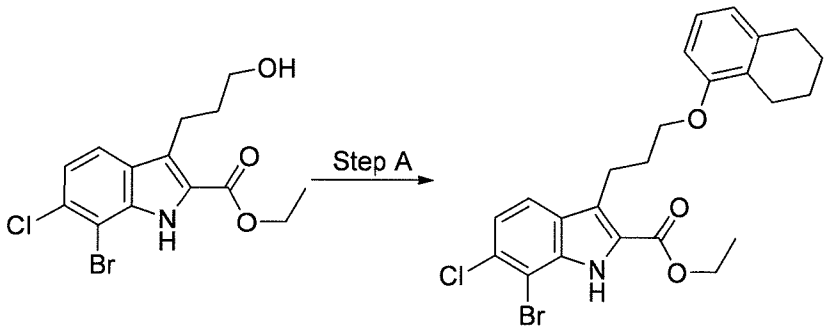
LCMS (ESI+): m/z 932.12 $[M+H]^+$

^{1}H NMR (500 MHz, DMSO) δ 13.46 (bs, 1H), 11.11 (s, 1H), 8.26 (dd, *J* = 9.2, 5.9 Hz, 1H), 7.77 (dd, *J* = 8.6, 7.2 Hz, 1H), 7.72 (d, *J* = 8.5 Hz, 1H), 7.67 (dd, *J* = 10.4, 2.6 Hz, 1H), 7.45 (q, *J* = 3.1, 2.3 Hz, 3H), 7.38 (td, *J* = 8.9, 2.7 Hz, 1H), 7.31 (d, *J* = 8.6 Hz, 1H), 7.22 (d, *J* = 8.5 Hz, 1H), 6.90 (dd, *J* = 5.6, 3.1 Hz, 1H), 5.16 – 5.08 (m, 3H), 4.38 – 4.28 (m, 1H), 4.26 – 4.14 (m, 3H), 3.77 (s, 3H), 3.31 – 3.21 (m, 4H), 2.97 – 2.84 (m, 1H), 2.64 – 2.54 (m, 2H), 2.27 – 2.19 (m, 2H), 2.18 – 2.00 (m, 12H), 1.89 (s, 3H).

Example 20: 6-chloro-1-{2-[4-(2-{[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1 *H*-isoindol-4-yl]oxy}acetyl)piperazin-1-yl]ethyl}-3-[3-(5,6,7,8-tetrahydronaphthalen-1-yloxy)pro pyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (216)

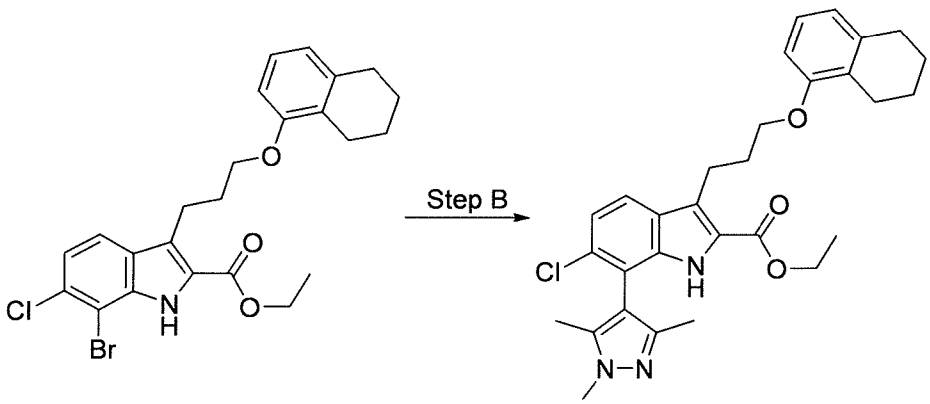


Step A



To a well stirred solution of ethyl 7-bromo-6-chloro-3-(3-hydroxypropyl)-1*H*-indole-2-carboxylate (5 g, 13.9 mmol) in toluene (65 mL) were added PPh_3 (4.7 g, 18.1 mmol), 5,6,7,8-tetahydronaphthalen-1-ol (4.1 g, 27.7 mmol) and DBAD (6.4 g, 27.9 mmol) consecutively and the reaction mixture was allowed to stir at 130°C for 16 h under nitrogen. After complete consumption of the starting material, the solvent of reaction mixture was then evaporated under reduced pressure to get the crude compound, which was then purified by flash chromatography (SiO_2, 5% EtOAC in hexane) to get 5 g (10.2 mmol, 73%) of ethyl 7-bromo-6-chloro-3-(3-((5,6,7,8-tetrahydronaphthalen-1-yl)oxy)propyl)-1*H*-indole-2-carboxylate as white solid.

Step B

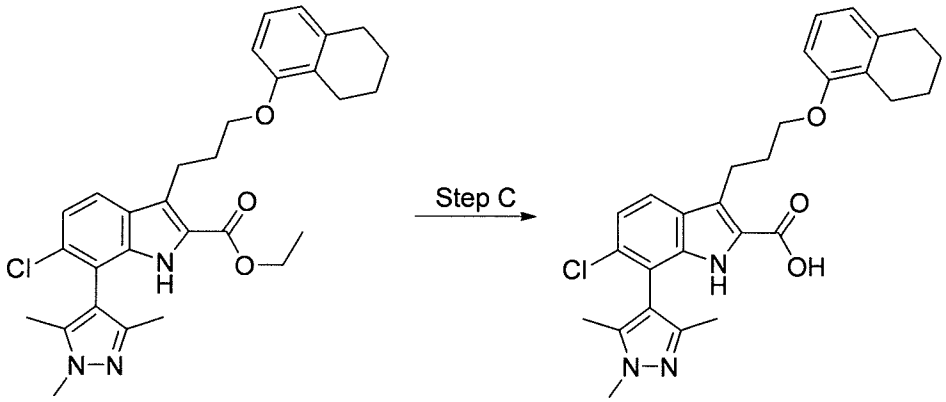


To a stirred solution of ethyl 7-bromo-6-chloro-3-(3-((5,6,7,8-tetrahydronaphthalen-1-yl)oxy)propyl)-1*H*-indole-2-carboxylate (5.0 g, 10.2 mmol) in dioxane (50 ml) and water (10 ml) were added 1,3,5-trimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (7.2 g, 30.7 mmol) and K_2CO_3 (5.6 g, 40.9 mmol). The mixture was deoxygenated with argon and to it was added $Pd(dppf)Cl_2$ (1.12 g, 1.5 mmol) under argon atmosphere. Then the reaction mixture was heated under reflux for 16 h. After complete consumption of the starting material, the reaction mixture was filtered through celite pad and the solvents were evaporated under reduced pressure get the crude material. It was then diluted with EtOAc, washed successively with water

and brine, the organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to get the crude compound, which was then purified by flash chromatography (SiO_2, 50% EtOAc in hexane) to get 4 g (7.7 mmol, 75%) of ethyl 6-chloro-3-(3-((5,6,7,8-tetrahydronaphthalen-1-yl)oxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate as brown solid.

LCMS (ESI+): m/z 520.2 $[M+H]^+$

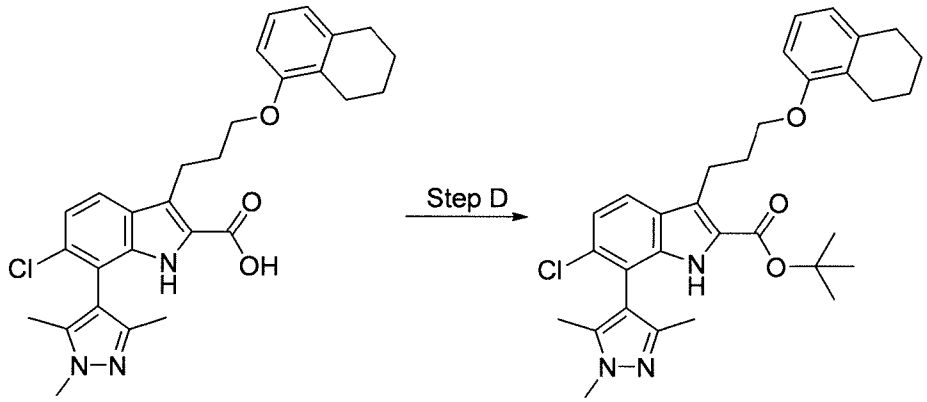
Step C



Ethyl 6-chloro-3-(3-((5,6,7,8-tetrahydronaphthalen-1-yl)oxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (4.0 g, 7.7 mmol) was dissolved in EtOH (50 mL) and a solution of NaOH (1.5 g, 38.5 mmol) in water (40 mL) was added to it. The mixture was heated under reflux for 16 h. After complete consumption of the starting material, the reaction mixture was cooled down to room temperature, solvents were evaporated under reduced pressure to get the crude reaction mixture. It was then diluted with water, washed with EtOAc. Aqueous layer was carefully acidified using 1M HCl to pH=3, extracted with EtOAc, the organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo to afford 3.3 g (6.7 mmol, 87%) of 6-chloro-3-(3-((5,6,7,8-tetrahydronaphthalen-1-yl)oxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid as off white solid.

LCMS (ESI+): m/z 492.1 $[M+H]^+$

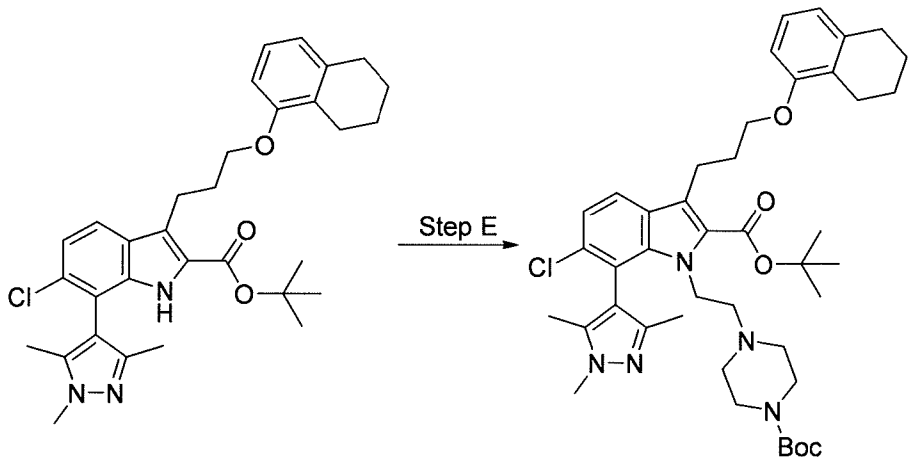
Step D



6-chloro-7-(3,5-dimethyl-1*H*-pyrazol-4-yl)-3-(3-((5,6,7,8-tetrahydronaphthalen-1-yl)oxy)propyl)-1*H*-indole-2-carboxylic acid (3.3 g, 6.9 mmol) was suspended in toluene (50 ml) and the mixture was heated to reflux under nitrogen. *N*,*N*-dimethylformamide di-*tert*-butyl acetal (12 ml, 53.7 mmol) was added drop wise to the refluxing mixture. The mixture was heated under reflux for 16 h under nitrogen. After complete consumption of the starting material, the reaction mixture was then diluted with EtOAc, washed successively with aqueous $NaHCO_3$ (sat.), water and brine, organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to get the crude compound, which was then purified by flash chromatography (SiO_2, 70% EtOAc in hexane) to get 3.3 g (6.0 mmol, 87%) of *tert*-butyl 6-chloro-3-(3-((5,6,7,8-tetrahydronaphthalen-1-yl)oxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate as brown solid.

LCMS (ESI+): m/z 548.4 $[M+H]^+$

Step E

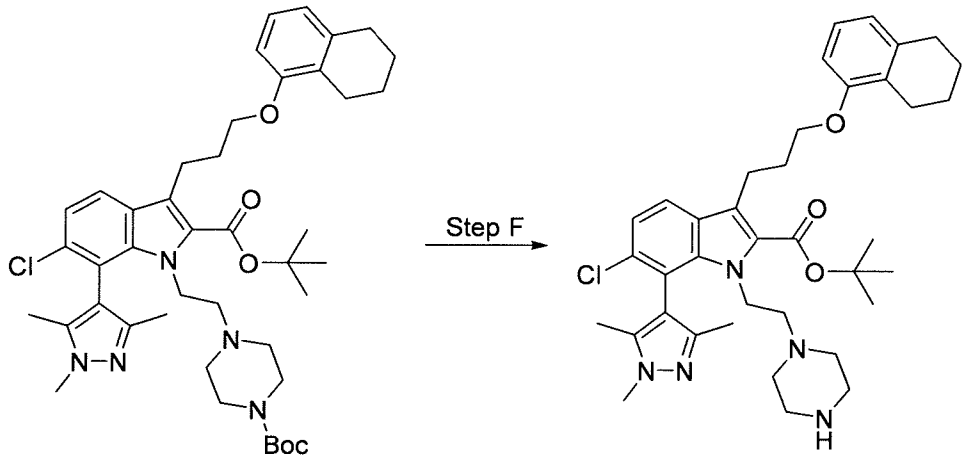


To a well stirred solution of *tert*-butyl 6-chloro-3-(3-((5,6,7,8-tetrahydronaphthalen-1-yl)oxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (3.3 g, 6.0 mmol) in DMF (30 mL) was added *tert*-butyl 4-(2-chloroethyl)piperazine-1-carboxylate (3.0 g, 12.1 mmol) followed by Cs_2CO_3 (9.8 g, 30.2 mmol) in DMF (10 mL) and the mixture was allowed to stir at

90°C for 16 h under nitrogen. After complete consumption of the starting material, the reaction mixture was diluted with EtOAc, washed successively with water and brine. The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to get the crude compound, which was then purified by flash chromatography (SiO_2, 30% EtOAc in hexane) to get 3.0 g (3.95 mmol, 66%) of *tert*-butyl 1-(2-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)ethyl)-6-chloro-3-(3-((5,6,7,8-tetrahydronaphthalen-1-yl)oxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate as off white solid.

LCMS (ESI+): m/z 761.1 $[M+H]^+$

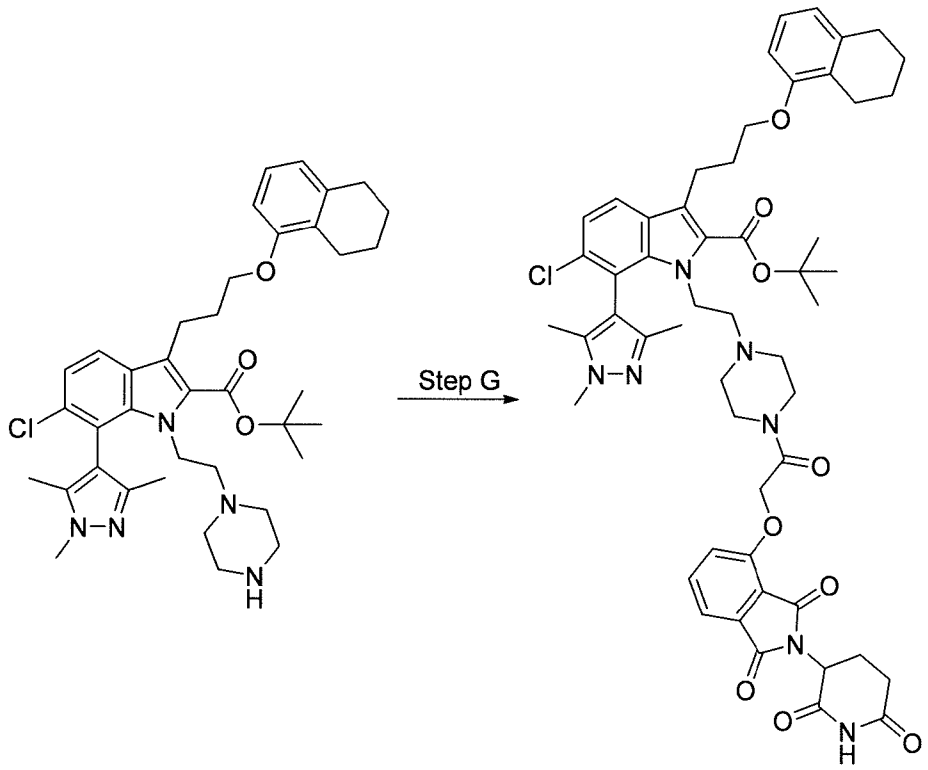
Step F



Tert-butyl 1-(2-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)ethyl)-6-chloro-3-(3-((5,6,7,8-tetrahydronaphthalen-1-yl)oxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (3.0 g, 3.95 mmol) was dissolved in 50 mL of 4M HCl in dioxane at 0°C and the mixture stirred for 2 h under nitrogen at same temperature. The reaction mixture was poured in to cold 1M NaOH solution and extracted several times with DCM. The combined organics were dried over Na_2SO_4 and concentrated in vacuo to get the crude compound which was then purified by flash chromatography (amine SiO_2, 10% MeOH in DCM) to get 1.54 g (2.33 mmol, 60%) of *tert*-butyl 6-chloro-1-(2-(piperazin-1-yl)ethyl)-3-(3-((5,6,7,8-tetrahydronaphthalen-1-yl)oxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate as white solid.

LCMS (ESI+): m/z 660.5 $[M+H]^+$

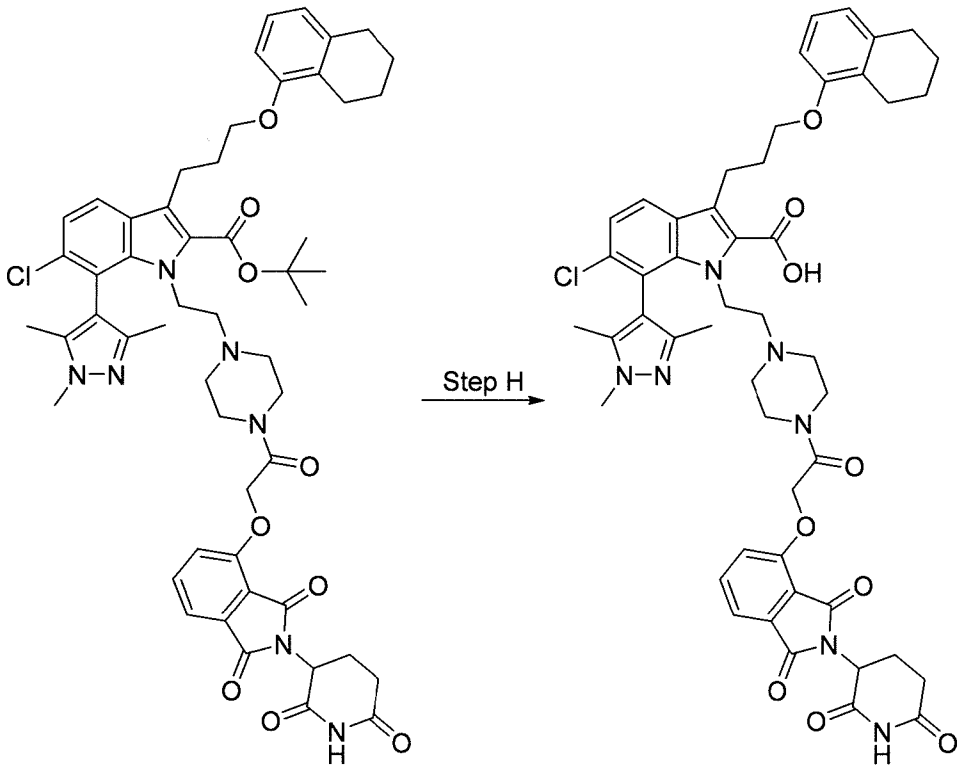
Step G



2-{[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl]oxy}acetic acid (27.7 mg, 0.083 mmol) was dissolved in DMF (1.5 ml) under argon atmosphere. To it, CDI (18.4 mg, 0.114 mmol) was added and the reaction was stirred for 1 h in 60°C. Reaction mixture was then allowed to cool down to RT and a solution of *tert*-butyl 6-chloro-1-[2-(piperazin-1-yl)ethyl]-3-[3-(5,6,7,8-tetrahydronaphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (50.0 mg, 0.076 mmol) and DIPEA (0.040 mL, 0.227 mmol) was added in 1 ml of DMF. The reaction was stirred in RT for 72 h. After the reaction was completed (monitored with LCMS), DMF was evaporated, residue dissolved in DCM and washed with brine and water. Organic layer was dried over anhydrous Na_2SO_4, filtered, concentrated and dried under reduced pressure to give crude *tert*-butyl 6-chloro-1-{2-[4-(2-{[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl]oxy}acetyl)piperazin-1-yl]ethyl}-3-[3-(5,6,7,8-tetrahydronaphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (49.9 mg, crude) as yellow oil that was used in the next step without further purification.

LCMS (ESI+): m/z 973.9 $[M+H]^+$

Step H

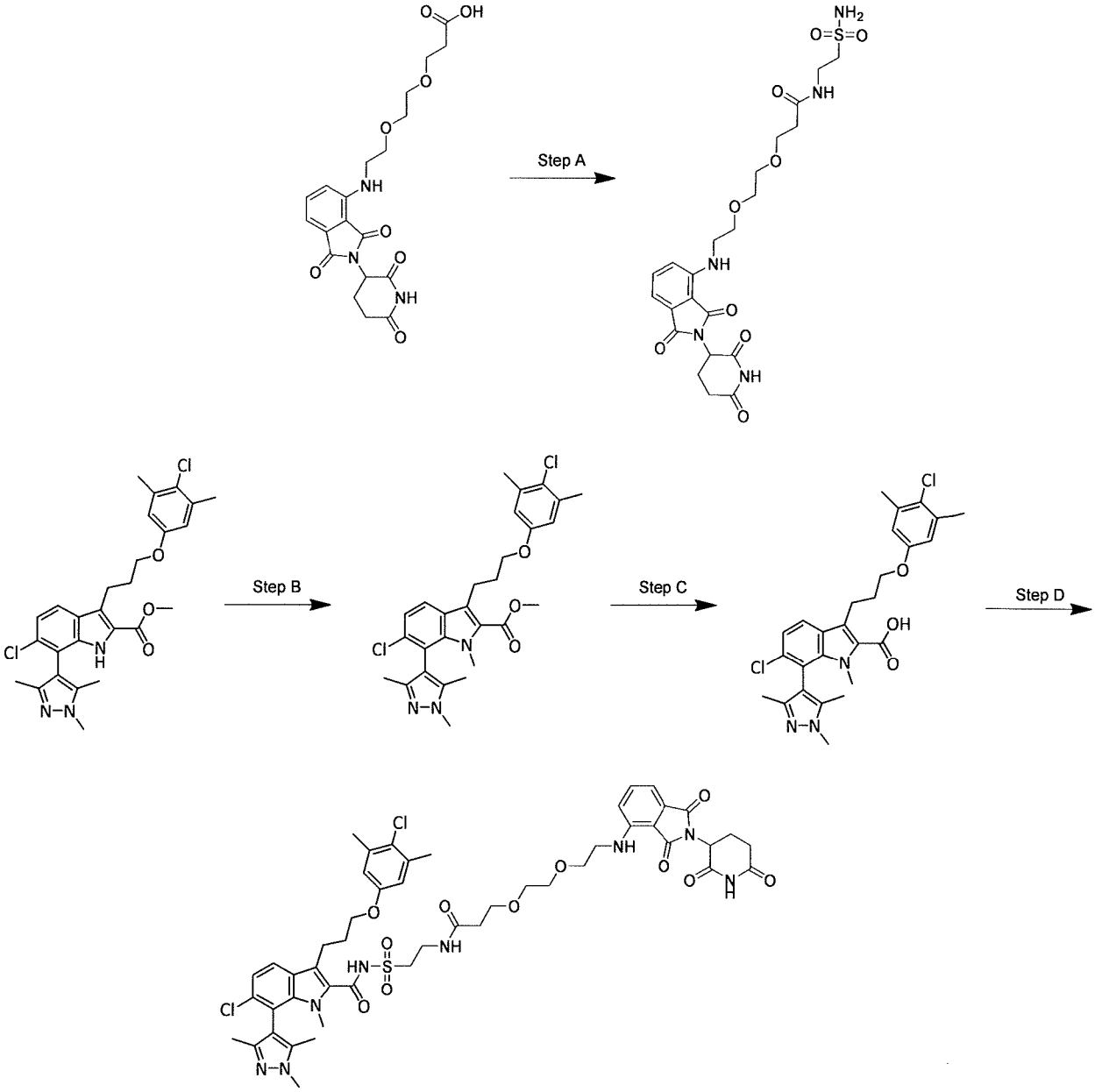


Tert-butyl 6-chloro-1-{2-[4-(2-{[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl]oxy}acetyl)piperazin-1-yl]ethyl}-3-[3-(5,6,7,8-tetrahydronaphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (49.9 mg, crude) was dissolved in dry DCM (0.3 mL) under argon atmosphere and TFA (0.3 mL, 3.918 mmol) was added. Reaction was stirred for 16 h at room temperature under argon. After complete consumption of the starting material, solvent along with TFA were evaporated under reduced pressure and the resulting residue was dissolved in DMSO and purified by preparative HPLC (H_2O:MeCN + 0.1% FA) to give the corresponding 6-chloro-1-{2-[4-(2-{[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl]oxy}acetyl)piperazin-1-yl]ethyl}-3-[3-(5,6,7,8-tetrahydronaphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (32.4 mg, 0.035 mmol, 46% over two steps) as white powder.

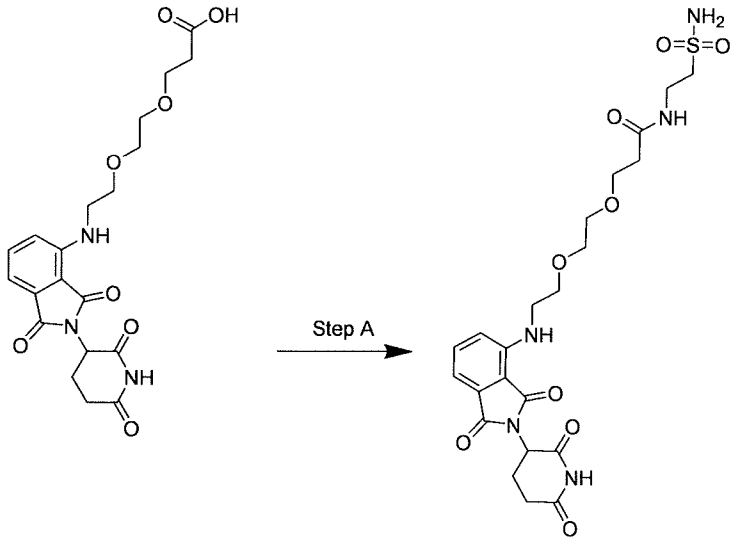
LCMS (ESI+): m/z 918.1 $[M+H]^+$

^{1}H NMR (500 MHz, DMSO) δ 13.36 (s, 1H), 11.09 (s, 1H), 7.76 (dd, *J* = 8.6, 7.3 Hz, 1H), 7.68 (d, *J* = 8.5 Hz, 1H), 7.44 (d, *J* = 7.2 Hz, 1H), 7.27 (dd, *J* = 23.3, 8.6 Hz, 2H), 6.99 (t, *J* = 7.8 Hz, 1H), 6.63 (t, *J* = 7.2 Hz, 2H), 5.25 – 4.96 (m, 3H), 4.37 – 4.23 (m, 1H), 4.23 – 4.12 (m, 1H), 3.98 (t, *J* = 6.2 Hz, 2H), 3.75 (s, 3H), 3.56 – 3.41 (m, 1H), 3.41 – 3.34 (m, 2H), 3.24 – 3.13 (m, 3H), 2.88 (ddd, *J* = 16.9, 13.8, 5.5 Hz, 1H), 2.68 (t, *J* = 6.1 Hz, 2H), 2.63 – 2.55 (m, 3H), 2.54 – 2.52 (m, 1H), 2.22 – 2.03 (m, 8H), 2.02 (s, 3H), 2.01 – 1.95 (m, 1H), 1.88 (s, 3H), 1.77 – 1.63 (m, 4H).

Example 21: 6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-*N*-((2-(3-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)propanamido)ethyl)sulfonyl)-1-methyl-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxamide (252)



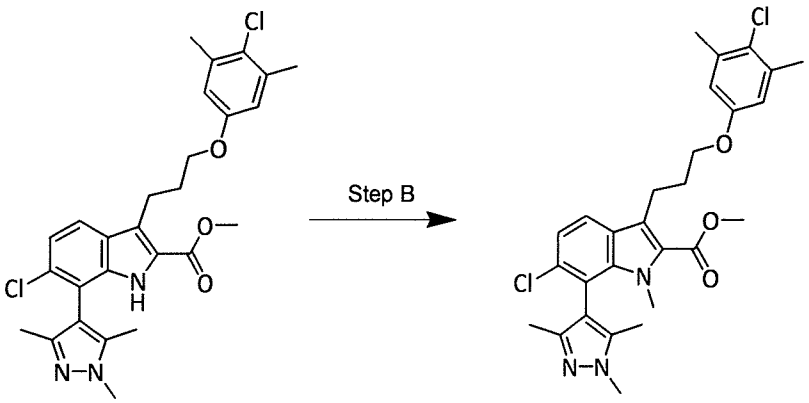
Step A



3-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)propanoic acid (195.0 mg, 0.450 mmol) and HATU (205.3 mg, 0.540 mmol) were flashed with argon and dissolved in dry DMF (2.2 mL). DIPEA (0.235 mL, 1.350 mmol) was then added and the mixture stirred for 1 h in RT. After this time, 2-aminoethane-1-sulfonamide hydrochloride (72.3 mg, 0.450 mmol) was added and the reaction was stirred at RT for 1 hour. Solvents were removed under reduced pressure, aqueous NH_4Cl (saturated) and crude product was extracted with DCM. Desired product was purified using flash chromatography (SiO_2, DCM:MeOH, 0-10%) to get 3-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)-*N*-(2-sulfamoylethyl)propanamide (135.0 mg, 0.250 mmol, 55.6%) as yellow oil.

LCMS (ESI+): m/z 540.4 $[M+H]^+$

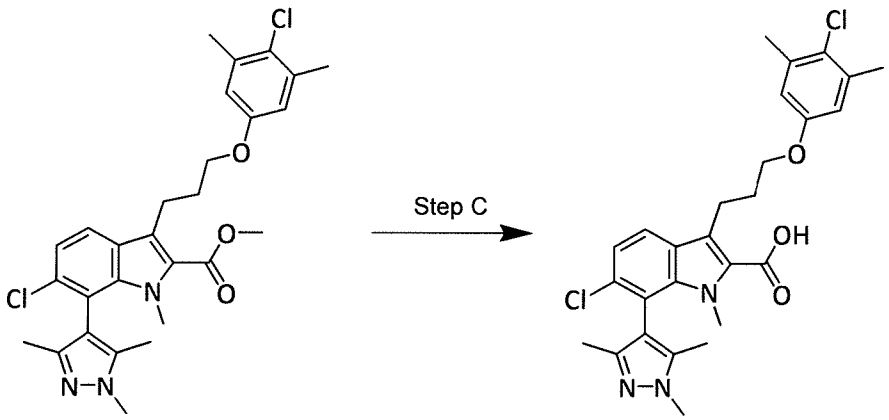
Step B



Iodomethane (0.133 mL, 2.138 mmol) was added to a stirred mixture of methyl 6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (1.000 g, 1.944 mmol) in DMF (6.0 mL), followed by K_2CO_3 (0.672 g, 4.860 mmol). The resulting mixture was stirred at room temperature for 24 hours. After the reaction was completed solvents were evaporated and the resulting residue was partitioned between EtOAc and H_2O. The organic layer was further washed with brine, dried over Na_2SO_4, filtered and evaporated. The methyl 6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-methyl-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (0.975 g, 1.845 mmol, 95%) was obtained as an orangish solid.

LCMS (ESI+): m/z 528.2 $[M+H]^+$

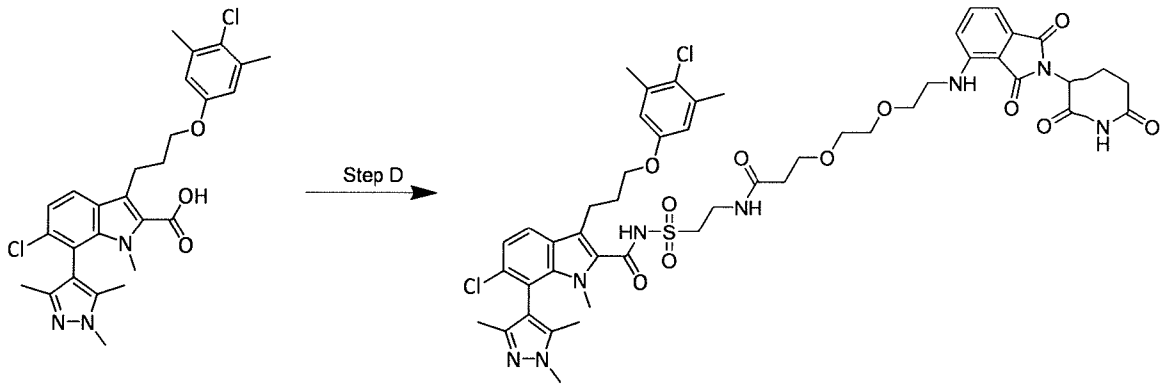
Step C



NaOH (5.4 mL, 5.450 mmol) was added to a stirred mixture of methyl 6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-methyl-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (0.720 g, 1.362 mmol) in MeOH (6.0 mL). The resulting mixture was stirred at room temperature for 20 hours and 4 h in 45°C. After the reaction was completed (monitored by LCMS), solvents were evaporated and the resulting residue was dissolved in DCM and H_2O. 1M HCl was added to achieve pH = ~3 of aqueous layer. The organic layer was further washed with brine, dried over Na_2SO_4, filtered and evaporated. The final product 6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-methyl-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (0.500 g, crude) was obtained as a white powder.

LCMS (ESI-): m/z 512.4 $[M-H]^-$

Step D

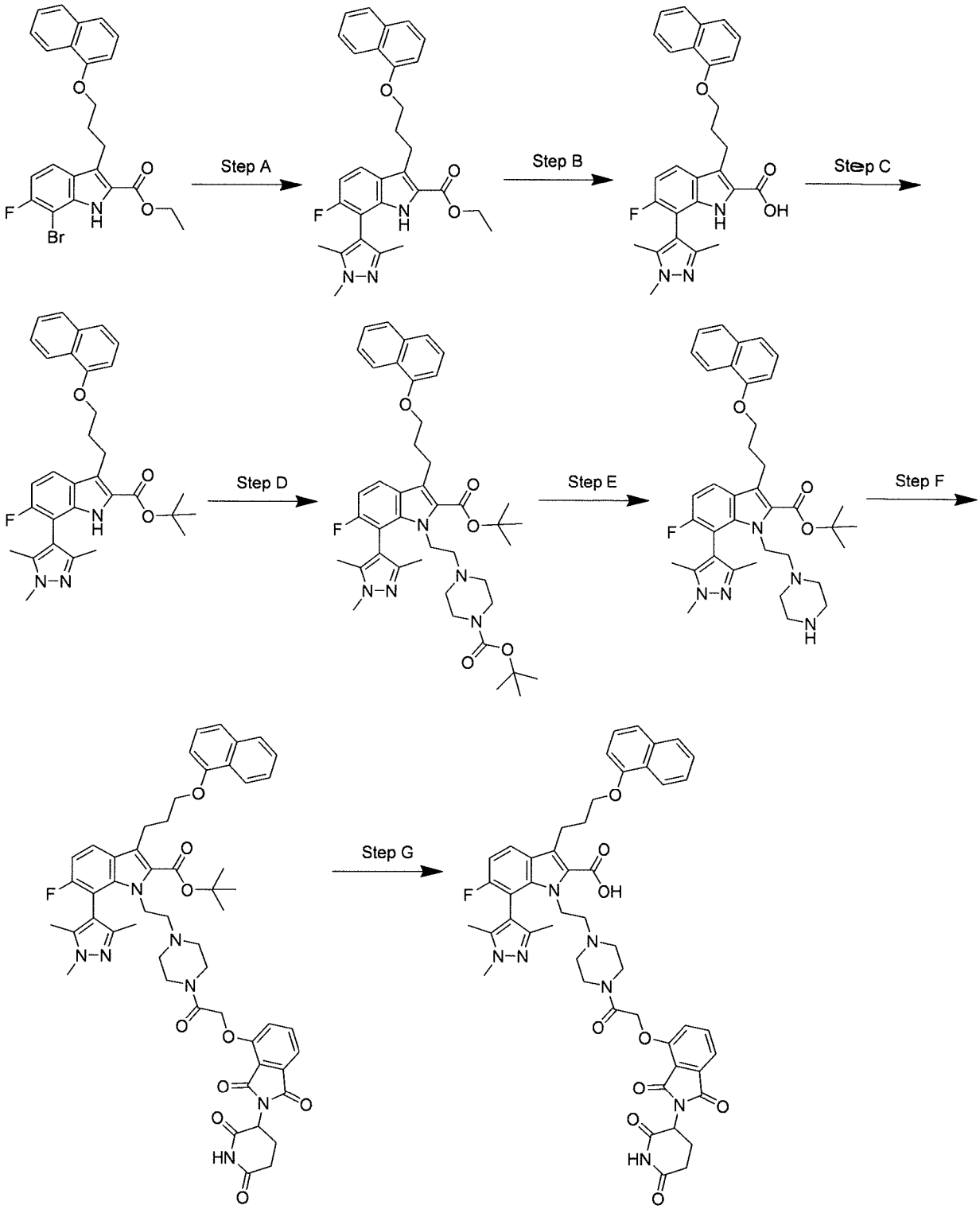


To a stirred solution of 3-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)-*N*-(2-sulfamoylethyl)propanamide (20.0 mg, crude) in DCM (0.371 mL) were added EDC (7.1 mg, 0.037 mmol), DMAP (13.6 mg, 0.111 mmol), Et_3N (0.015 mL, 0.111 mmol) and 6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-methyl-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (18.1 mg, 0.035 mmol). The reaction mixture was stirred for 15 h at ambient temperature and then reaction was continued in 60°C overnight. After this time solvents were removed under reduces pressure. The residue was dissolved in 1:1 mixture of DMSO:MeOH and filtered. The filtrate was purified by preparative HPLC (H_2O:MeCN + 0.1% FA) to give a corresponding 6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-*N*-((2-(3-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)propanamido)ethyl)sulfonyl)-1-methyl-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxamide (1.0 mg, 0.001 mmol, 2.6%) as a yellow solid.

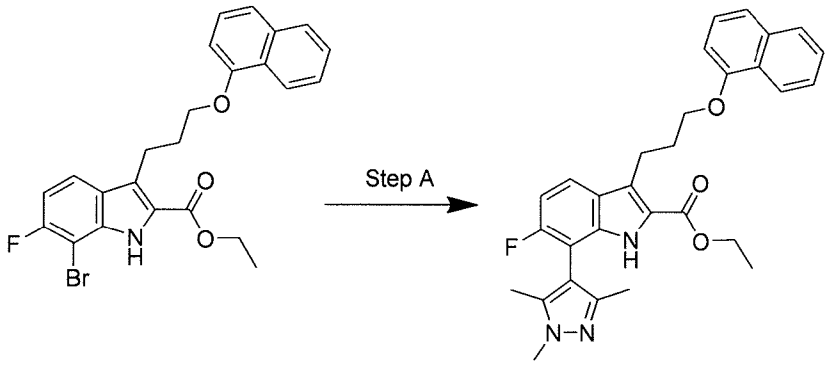
LCMS (ESI+): m/z 1034.9 $[M+H]^+$

^1H NMR (500 MHz, DMSO) δ 12.28 (s, 1H), 11.07 (s, 1H), 8.09 (s, 1H), 7.67 (s, 1H), 7.56 (dd, *J* = 8.6, 7.1 Hz, 1H), 7.24 (s, 1H), 7.12 (d, *J* = 8.6 Hz, 1H), 7.02 (d, *J* = 7.0 Hz, 1H), 6.75 (s, 2H), 6.58 (t, *J* = 5.8 Hz, 1H), 5.04 (dd, *J* = 12.7, 5.4 Hz, 1H), 3.94 (t, *J* = 6.5 Hz, 2H), 3.75 (s, 3H), 3.72 – 3.54 (m, 6H), 3.54 – 3.48 (m, 3H), 3.48 – 3.42 (m, 6H), 3.03 (t, *J* = 7.5 Hz, 2H), 2.87 (ddd, *J* = 16.7, 13.7, 5.4 Hz, 1H), 2.60 – 2.54 (m, 4H), 2.30 – 2.24 (m, 8H), 2.05 – 1.96 (m, 6H), 1.88 (s, 3H).

Example 22: 1-{2-[4-(2-{[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl]oxy}acetyl)piperazin-1-yl]ethyl}-6-fluoro-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (213)



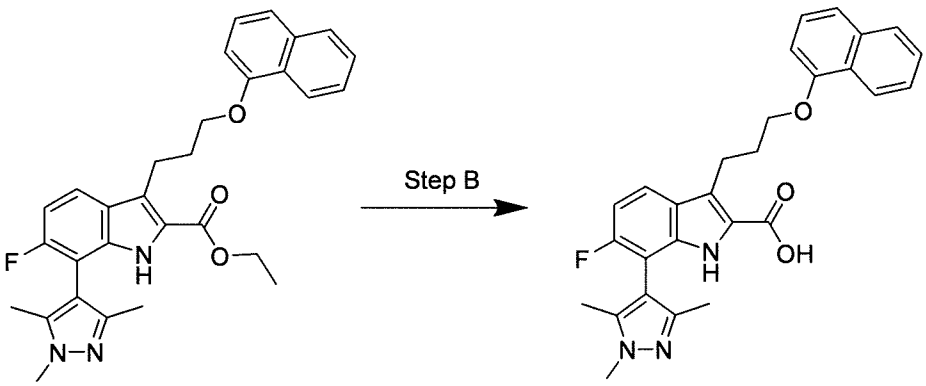
Step A



To a stirred solution of ethyl 7-bromo-6-fluoro-3-(3-(naphthalen-1-yloxy)propyl)-1*H*-indole-2-carboxylate (2.689 g, 5.717 mmol) in dioxane (25 mL) and water (5 mL) were added 1,3,5-trimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (4.062 g, 17.2 mmol) and K_2CO_3 (3.165 g, 22.9 mmol) successively at RT. The mixture was deoxygenated with argon and to it was added $Pd(dppf)Cl_2$ (0.629 g, 0.86 mmol) under argon atmosphere. Then the reaction mixture was heated under reflux for 16 h. After complete consumption of the starting material the reaction mixture was filtered over celite and the filtrate was evaporated under reduced pressure to get the crude material. It was then diluted with EtOAc, washed successively with water and brine, the organic layer was dried over sodium sulphate and evaporated under reduced pressure to get the crude compound, which was purified by column chromatography (SiO_2, 50% EtOAc in hexane) to get ethyl 6-fluoro-3-(3-(naphthalen-1-yloxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (2.125 g, 4.254 mmol, 74.4%) as brown solid.

LCMS (ESI+): m/z 500.0 $[M+H]^+$

Step B

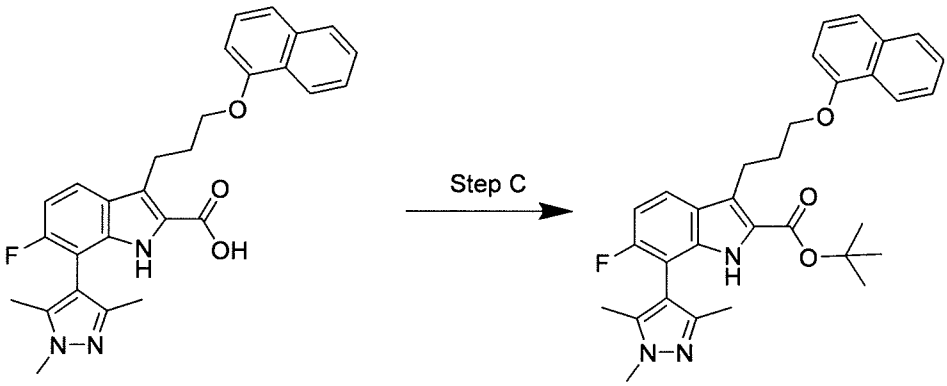


Ethyl 6-fluoro-3-(3-(naphthalen-1-yloxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (2.65 g, 5.30 mmol) was dissolved in EtOH (20 mL) and solution of NaOH (0.743 g, 18.58 mmol) in water (10 mL) was added to it. The mixture was heated under reflux for 16 h. After complete consumption of the starting material the reaction mixture was cooled down to room

temperature, solvents were evaporated under reduced pressure to get the crude reaction mixture. It was then diluted with water, washed with EtOAc. Aqueous layer was carefully acidified using 1 (N) HCl to maintain pH=3, extracted with EtOAc, dried over Na_2SO_4, filtered, and concentrated under vacuum to afford 6-fluoro-3-(3-(naphthalen-1-yloxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (2.3 g, crude) as dark brown gummy solid.

LCMS (ESI+): m/z 471.9 $[M+H]^+$

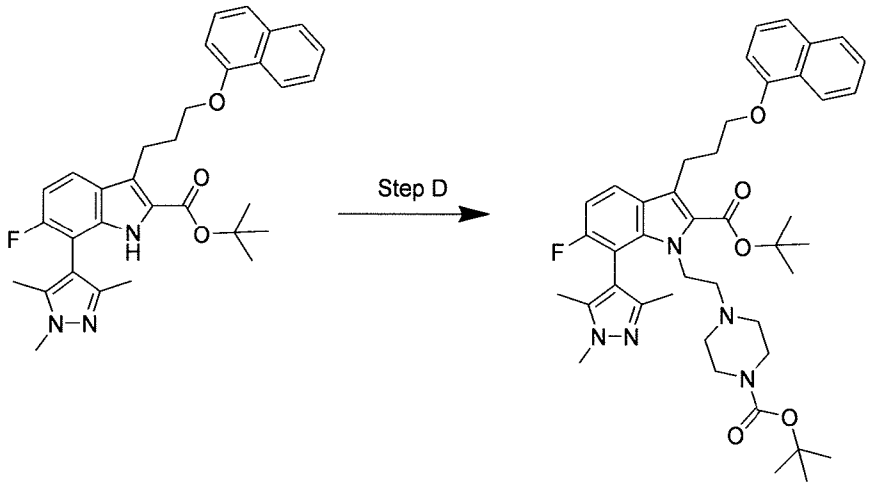
Step C



6-fluoro-3-(3-(naphthalen-1-yloxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (1.428 g, crude) was suspended in toluene (20 mL) and the mixture was heated to reflux under nitrogen. *N*,*N*-dimethylformamide di-*tert*-butyl acetal (5.8 ml, 24.25 mmol) was added drop wise to the refluxing mixture. The mixture was heated under reflux for 16 h under nitrogen. After complete consumption of the starting material reaction mixture was diluted with EtOAc, washed successively with $NaHCO_3$ (sat), water and brine, organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to get the crude compound, which was then purified by column chromatography (SiO_2, 70% EtOAc in hexane) to get *tert*-butyl 6-fluoro-3-(3-(naphthalen-1-yloxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (1.4 g, 2.65 mmol, 87.5%) as brown solid.

LCMS (ESI+): m/z 528.35 $[M+H]^+$

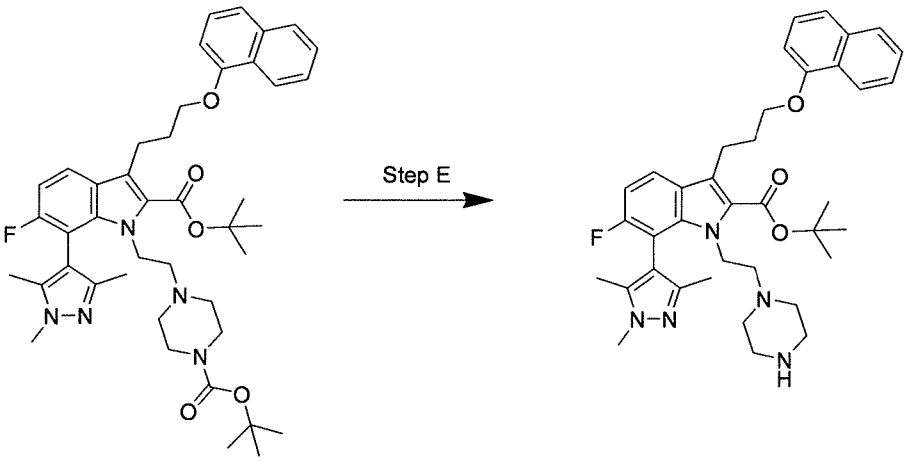
Step D



To a well stirred solution of *tert*-butyl 6-fluoro-3-(3-(naphthalen-1-yloxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (1.86 g, 3.525 mmol) in DMF (20 mL) was added *tert*-butyl 4-(2-chloroethyl)piperazine-1-carboxylate (1.756 g, 7.059 mmol) followed by Cs_2CO_3 (5.735 g, 17.602 mmol) at RT under nitrogen. The reaction mixture was allowed to stir at 90°C for 16 h under nitrogen. After complete consumption of the starting material the reaction mixture was diluted with EtOAc, washed successively with water and brine, the organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to get the crude compound, which was then purified by column chromatography (SiO_2, 30% EtOAc in hexane) to get *tert*-butyl 1-(2-(4-(tert-butoxycarbonyl)piperazin-1-yl)ethyl)-6-fluoro-3-(3-(naphthalen-1-yloxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate(1.8 g, 2.434 mmol, 69.0%) as off white solid.

LCMS (ESI+): m/z 739.9 $[M+H]^+$

Step E

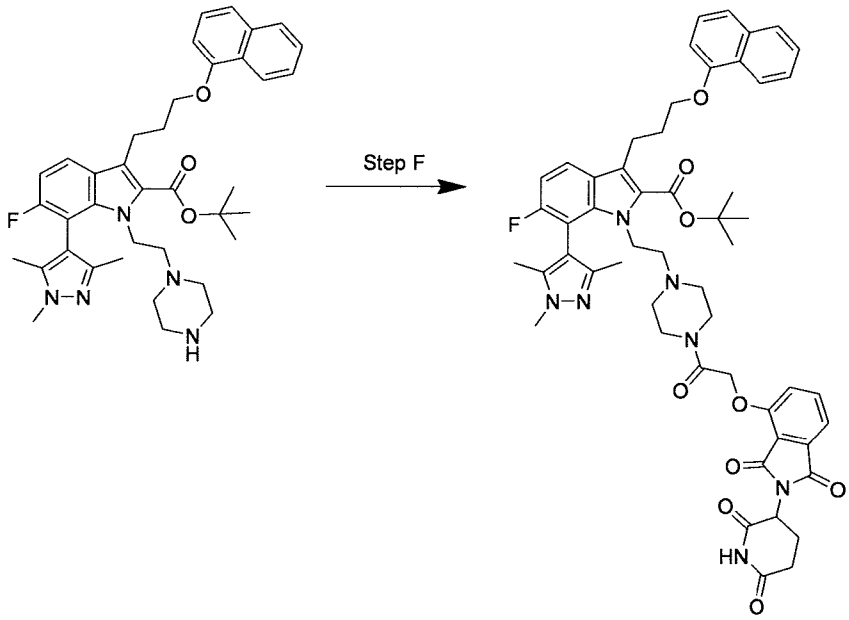


Tert-butyl 1-(2-(4-(tert-butoxycarbonyl)piperazin-1-yl)ethyl)-6-fluoro-3-(3-(naphthalen-1-yloxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (1.6 g, 2.164 mmol)

was dissolved in 4 (M) HCl in dioxane (20 mL) at 0°C and the mixture was stirred for 2 h under nitrogen at same temperature. Where upon LCMS indicated the reaction was completed, to the mixture was added drop wise cold 1M NaOH solution at 0°C to maintain the pH~5 to 6. The aqueous layer was extracted 2-3 times with DCM. The combined organics were dried over Na_2SO_4 and concentrated in vacuo to get the crude compound which was triturated with Et_2O to get *tert*-butyl 6-fluoro-3-(3-(naphthalen-1-yloxy)propyl)-1-(2-(piperazin-1-yl)ethyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (1.03 g, 1.61 mmol, 74.4%) as white solid.

LCMS (ESI+): m/z 640.47 $[M+H]^+$

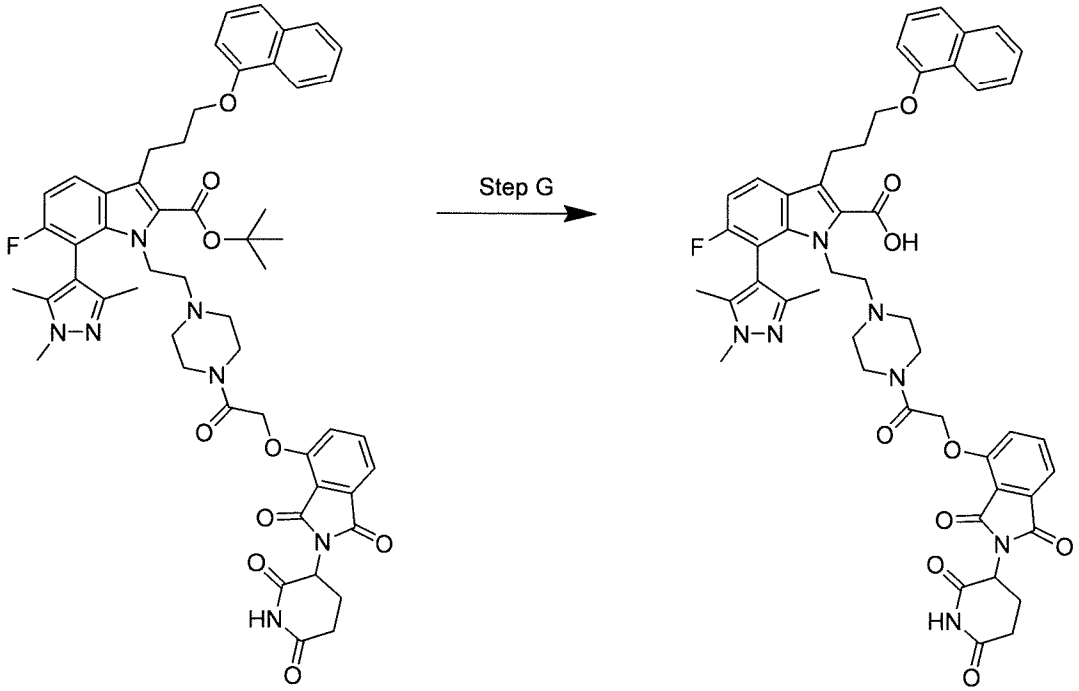
Step F



To a solution of 2-{[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl]oxy}acetic acid (51.9 mg, 0.156 mmol) and *tert*-butyl 6-fluoro-3-[3-(naphthalen-1-yloxy)propyl]-1-[2-(piperazin-1-yl)ethyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (50.0 mg, 0.078 mmol) in dry DMF (1.0 mL) was added DIPEA (0.041 mL, 0.234 mmol) and HATU (35.7 mg, 0.094 mmol). The mixture was stirred for 36 h at RT. After complete consumption of the starting material the solvent was evaporated and residues were dissolved in EtOAc. Organic phase was extracted with $NaHCO_3$ sat. and brine. Then, organic layer was dried over Na_2SO_4, filtered and concentrated under vacuum to get 30.0 mg crude of *tert*-butyl 1-{2-[4-(2-{[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl]oxy}acetyl)piperazin-1-yl]ethyl}-6-fluoro-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate was used to next step without further purification.

LCMS (ESI+): m/z 954.23 $[M+H]^+$

Step G



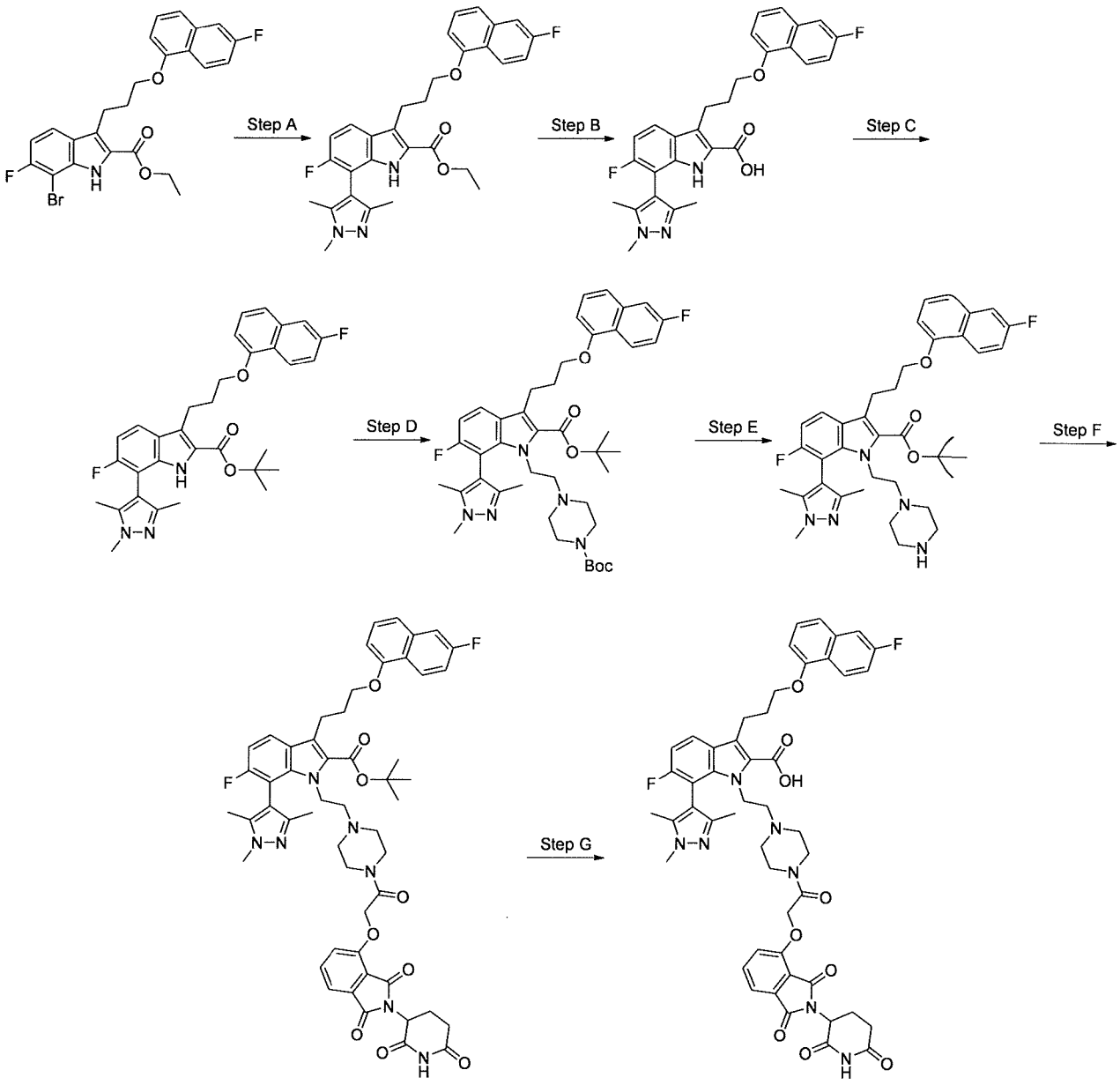
To a solution of *tert*-butyl 1-{2-[4-(2-{[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl]oxy}acetyl)piperazin-1-yl]ethyl}-6-fluoro-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (30.0 mg, crude) in DCM (1.0 mL) was added TFA (1.0 mL, 13.059 mmol). The reaction was stirred for 18h at RT. The crude was concentrated in vacuo, dissolved in DMSO and purified by preparative HPLC (H_2O:MeCN + 0.1% FA) to give a final product 1-{2-[4-(2-{[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl]oxy}acetyl)piperazin-1-yl]ethyl}-6-fluoro-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (3.2 mg, 0.004 mmol, 2.6% over two steps) as a white solid.

LCMS (ESI+): m/z 898.29 $[M+H]^+$

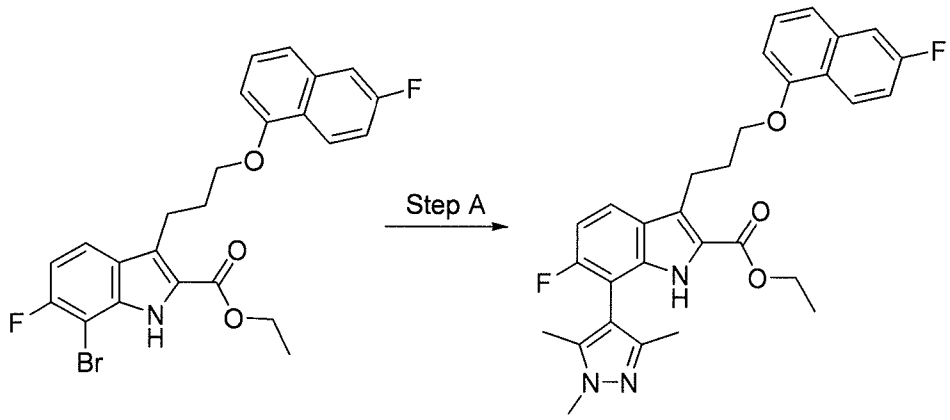
^{1}H NMR (500 MHz, DMSO) δ 13.32 (s, 1H), 11.09 (s, 1H), 8.21 (dd, *J* = 7.7, 1.9 Hz, 1H), 7.89 – 7.84 (m, 1H), 7.82 – 7.73 (m, 2H), 7.55 – 7.48 (m, 2H), 7.45 (dd, *J* = 7.7, 4.7 Hz, 2H), 7.43 – 7.37 (m, 1H), 7.31 (d, *J* = 8.5 Hz, 1H), 7.08 – 6.99 (m, 1H), 6.94 – 6.88 (m, 1H), 5.17 – 5.05 (m, 3H), 4.40 (s, 1H), 4.33 (s, 1H), 4.22 (t, *J* = 6.2 Hz, 2H), 3.76 (s, 3H), 3.30 (t, *J* = 7.6 Hz, 4H), 2.88 (ddd, *J* = 16.9, 14.5, 5.3 Hz, 1H), 2.62 – 2.52 (m, 2H), 2.28 – 2.16 (m, 4H), 2.08 – 2.00 (m, 6H), 1.93 (s, 3H).

4 protons in aliphatic area overlaps with water.

Example 23: 1-{2-[4-(2-{[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*–isoindol-4-yl]oxy}acetyl)piperazin-1-yl]ethyl}-6-fluoro-3-{3-[(6-fluoronaphthalen-1-yl)oxy]propyl}-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (215)



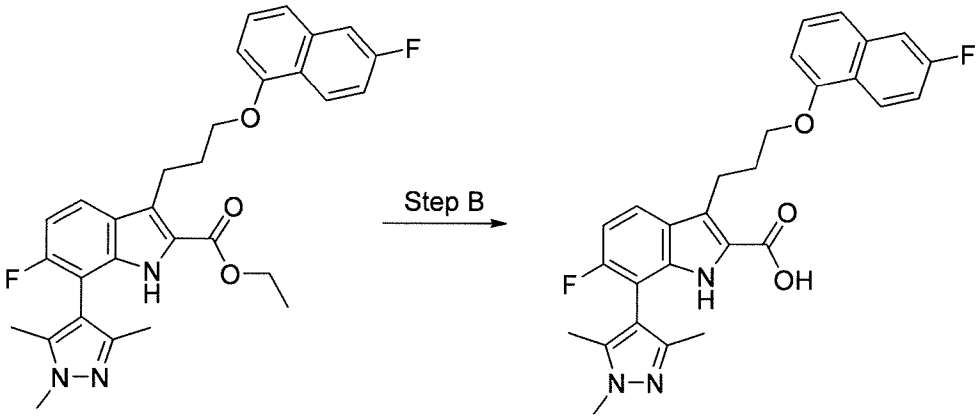
Step A



To a stirred solution of ethyl 7-bromo-6-fluoro-3-(3-((6-fluoronaphthalen-1-yl)oxy)propyl)-1*H*-indole-2-carboxylate (2.38 g, 4.87 mmol) in dioxane (25 mL) and water (5 mL), were added 1,3,5-trimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (3.46 g, 14.6 mmol) and K_2CO_3 (2.7 g, 19.5 mmol) at room temperature in an inert atmosphere. To the mixture was added $Pd(dppf)Cl_2$ (0.54 g, 0.73 mmol). Then, the reaction mixture was heated under reflux for 16 h. After complete consumption of the starting material, the reaction mixture was filtered through celite pad and the filtrate was evaporated under reduced pressure to get the residue. It was then diluted with EtOAc and washed successively with water and brine solution. The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to get the crude compound, which was then triturated with Et_2O to get 2.2 g (crude) of ethyl 6-fluoro-3-(3-((6-fluoronaphthalen-1-yl)oxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate as a brown solid which was directly used in the next step without further purification.

LCMS (ESI+): m/z 518.3 $[M+H]^+$

Step B

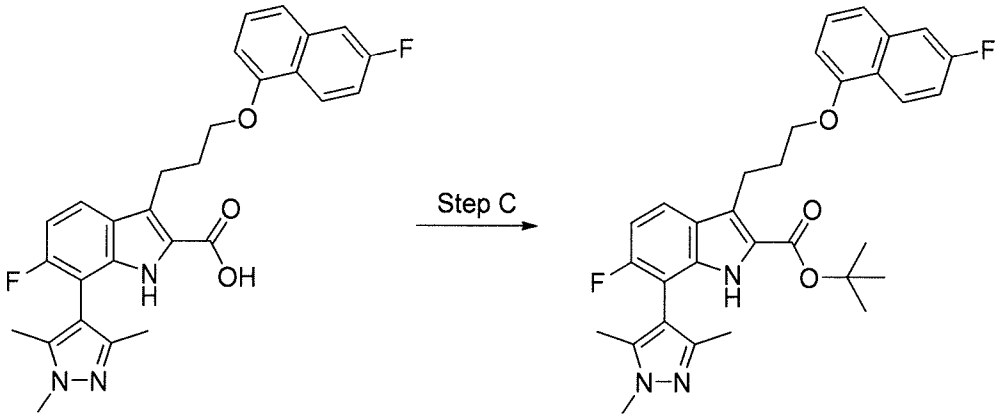


The crude (3.8 g) of ethyl 6-fluoro-3-(3-((6-fluoronaphthalen-1-yl)oxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate was dissolved in EtOH (40 mL) and solution of NaOH

(1.03 g, 25.7 mmol) in water (20 mL) was added to it. The mixture was heated under reflux for 16 h. After complete consumption of the starting material, the reaction mixture was cooled down to room temperature and solvents were evaporated under reduced pressure. It was then diluted with water and washed with EtOAc. Aqueous layer was carefully acidified using 1M HCl to pH = 3, extracted with EtOAc, dried over Na_2SO_4, filtered, and concentrated in vacuo to afford 3.2 g crude of 6-fluoro-3-(3-((6-fluoronaphthalen-1-yl)oxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid as dark brown gummy solid which was directly used for next step.

LCMS (ESI+): m/z 490.0 $[M+H]^+$

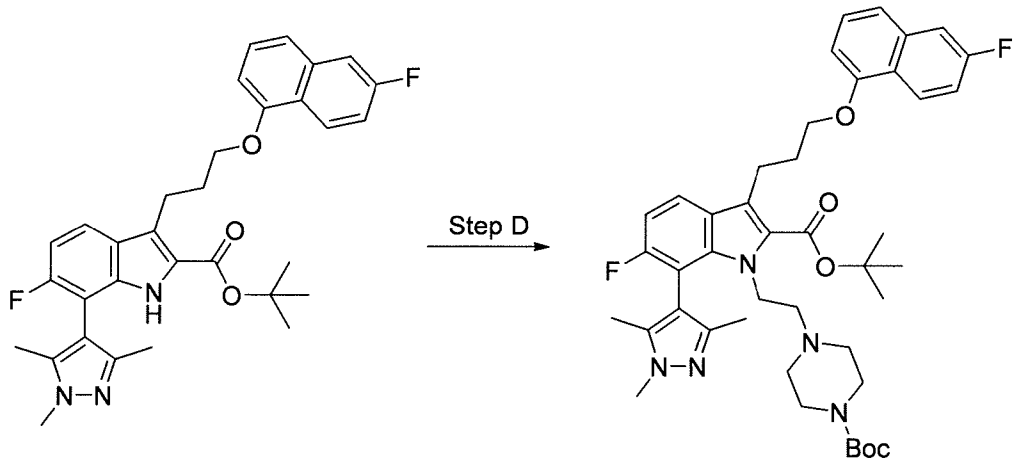
Step C



6-fluoro-3-(3-((6-fluoronaphthalen-1-yl)oxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (1.48 g of crude) was suspended in toluene (20 mL) and the mixture was heated to reflux under nitrogen. *N*,*N*-dimethylformamide di-*tert*-butyl acetal (5.82 ml, 24.3 mmol) was added drop wise to the refluxing mixture. The mixture was heated under reflux for 16 h under nitrogen. After complete consumption of the starting material, reaction mixture was then diluted with EtOAc, washed successively with $NaHCO_3$ (sat.), water and brine. Organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to get the crude compound, which was then purified by flash chromatography (SiO_2, 70% EtOAc in hexane) to get *tert*-butyl 6-fluoro-3-(3-((6-fluoronaphthalen-1-yl)oxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (1.42g, 2.60 mmol, 53% over three steps) as brown solid.

LCMS (ESI+): m/z 546.5 $[M+H]^+$

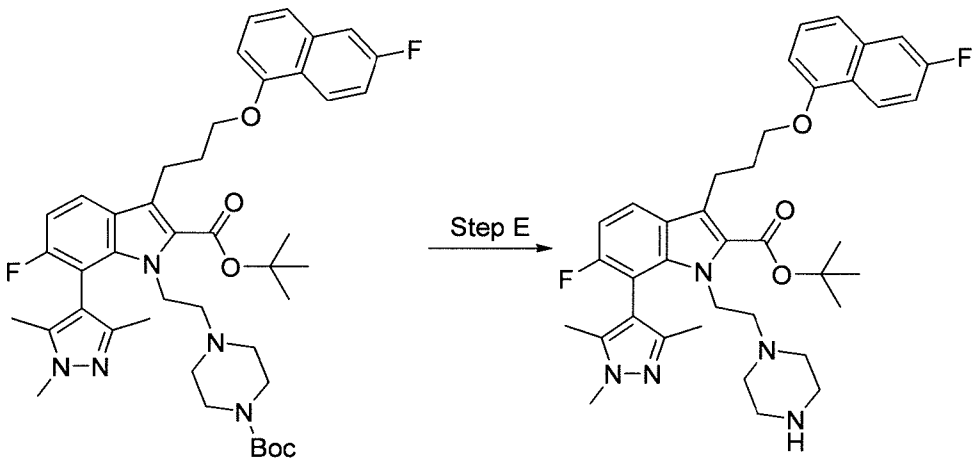
Step D



To a well stirred solution of *tert*-butyl 6-fluoro-3-(3-((6-fluoronaphthalen-1-yl)oxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (1.0 g, 1.8 mmol) in DMF (10 mL) was added *tert*-butyl 4-(2-chloroethyl)piperazine-1-carboxylate (0.91 g, 3.7 mmol) followed by Cs_2CO_3 (2.98 g, 9.2 mmol) at room temperature under nitrogen. The resulting mixture was allowed to stir at 90°C for 16 h under nitrogen. After complete consumption of the starting material, the reaction mixture was diluted with EtOAc and washed successively with water and brine. The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to get the crude compound, which was then purified by flash chromatography (SiO_2, 30% EtOAc in hexane) to get *tert*-butyl 1-(2-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)ethyl)-6-fluoro-3-(3-((6-fluoronaphthalen-1-yl)oxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (900 mg, 1.18 mmol, 65%) as off white solid.

LCMS (ESI+): m/z 757.8 $[M+H]^+$

Step E

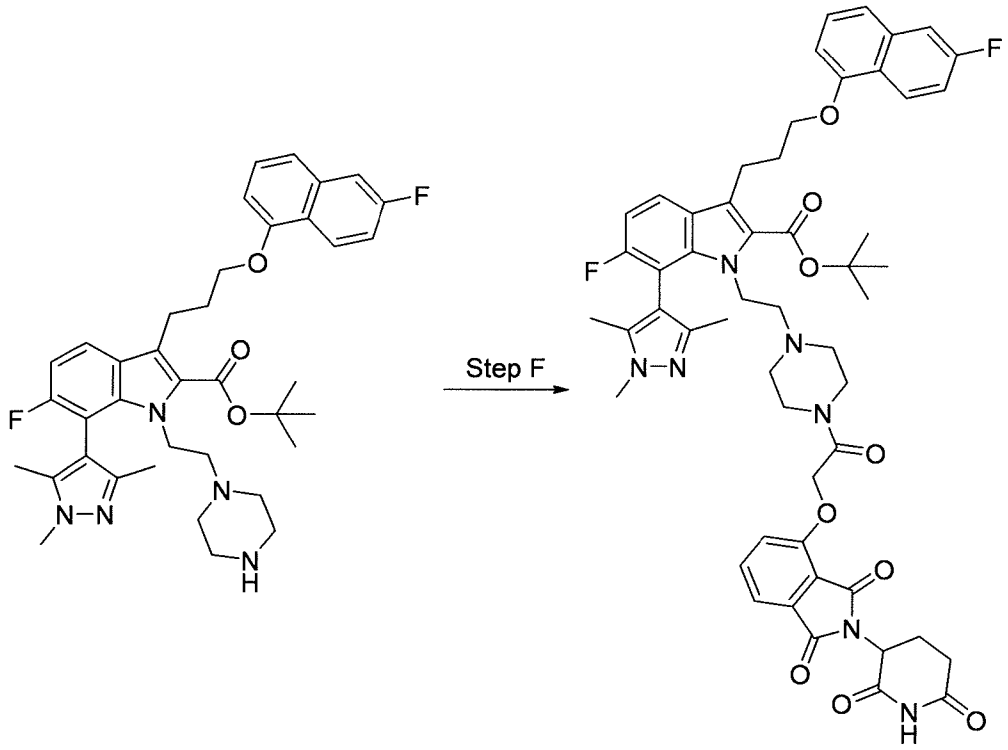


Tert-butyl 1-(2-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)ethyl)-6-fluoro-3-(3-((6-fluoronaphthalen-1-yl)oxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (0.9 g, 1.2 mmol)

dissolved in 4M HCl in dioxane (20 mL) at 0°C and the mixture stirred for 2 h under nitrogen at the same temperature. Cold 1M NaOH was added drop-wise to the reaction mixture at 0°C until pH = 5-6 was reached. The aqueous layer was extracted 2-3 times with DCM, the combined organics were dried over Na_2SO_4 and concentrated in vacuum to get the crude compound. Reaction product was purified by preparative HPLC (10mM ammonium acetate in H_2O:MeCN) to get of *tert*-butyl 6-fluoro-3-(3-((6-fluoronaphthalen-1-yl)oxy)propyl)-1-(2-(piperazin-1-yl)ethyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (225 mg, 0.34 mmol, 28 %) as off white solid.

LCMS (ESI+): m/z 658.5 $[M+H]^+$

Step F

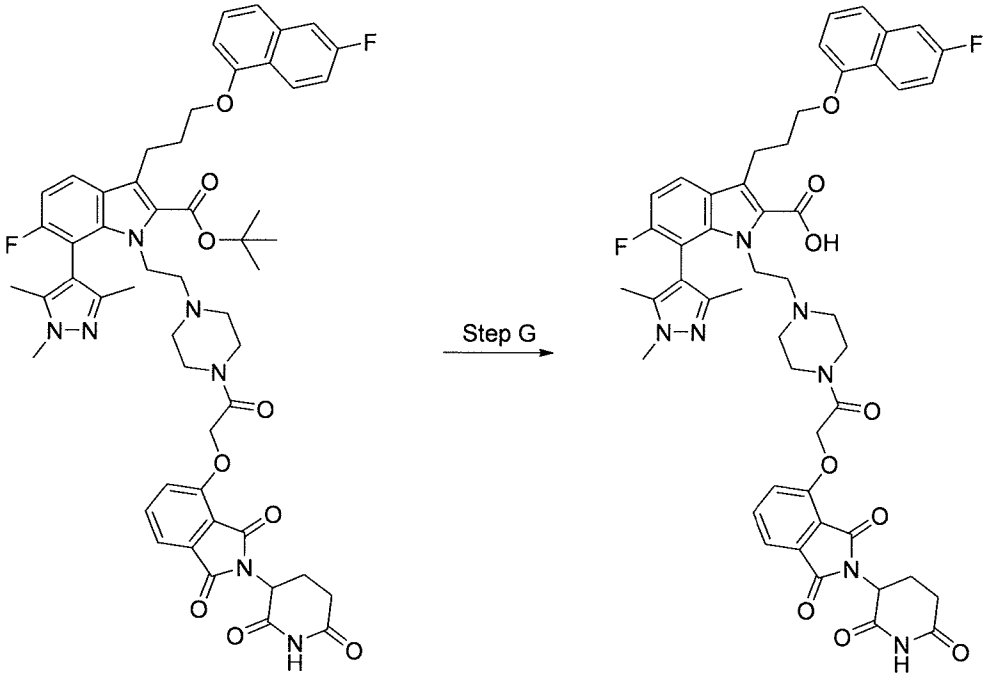


2-{[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl]oxy}acetic acid (16.7 mg, 0.050 mmol) was dissolved in dry DMF (0.91 ml) under argon atmosphere and DIPEA (0.024 mL, 0.137 mmol,), followed by HATU (26.0 mg, 0.068 mmol) were added. After 15 min of mixing at room temperature *tert*-butyl 6-fluoro-3-{3-[(6-fluoronaphthalen-1-yl)oxy]propyl}-1-[2-(piperazin-1-yl)ethyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (30.0 mg, 0.046 mmol) was added. Reaction was continued for 16 h at room temperature. Solvents were evaporated, resulting material dissolved in DCM (30 ml) and successfully washed with brine and water. Organic layer was dried over anhydrous Na_2SO_4, filtered, concentrated and dried under reduced pressure. Resulting product, *tert*-butyl 1-(2-(4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-

yl)oxy)acetyl)piperazin-1-yl)ethyl)-6-fluoro-3-(3-((6-fluoronaphthalen-1-yl)oxy)propyl)–7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (44 mg, crude) was used in the next step without further purification.

LCMS (ESI+): m/z 972.2 $[M+H]^+$

Step G

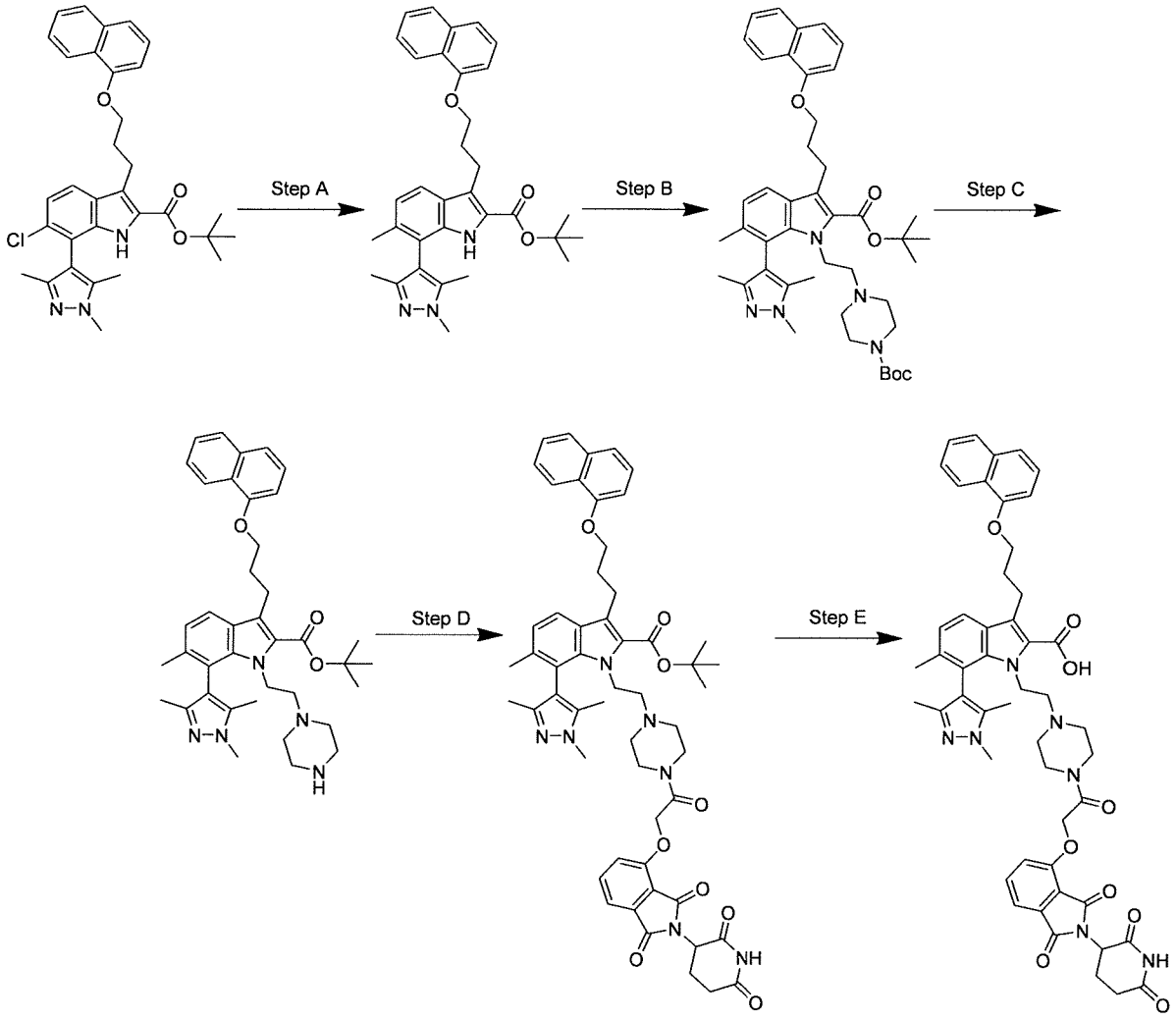


Tert-butyl 1-{2-[4-(2-{[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl]oxy}acetyl)piperazin-1-yl]ethyl}-6-fluoro-3-{3-[(6-fluoronaphthalen-1-yl)oxy]propyl}-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (44.0 mg, crude) was dissolved in dry DCM (0.35 mL) and TFA (0.347 mL, 4.526 mmol) was added. Reaction was stirred for 13 h at room temperature. After full consumption of the starting material was confirmed with LCMS, the solution was concentrated and resulting material dried under reduced pressure. Crude product was purified twice with preparative TLC (20% MeOH in DCM and 10% to 20% MeOH in DCM). Reaction product was washed from silica gel with eluent solution, filtered and dried under reduced pressure to give 1-{2-[4-(2-{[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl]oxy}acetyl)piperazin-1-yl]ethyl}-6-fluoro-3-{3-[(6-fluoronaphthalen-1-yl)oxy]propyl}-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (3.1 mg, 0.003 mmol, 6% yield over two steps) as off white solid.

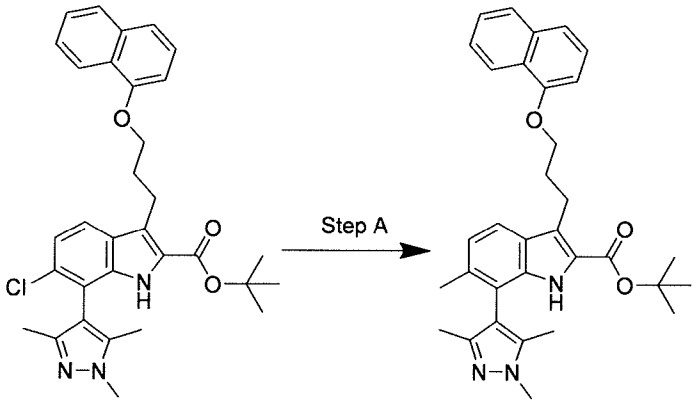
LCMS (ESI+): m/z 916.0 $[M+H]^+$

^{1}H NMR (500 MHz, DMSO) δ 13.26 (bs, 1H), 11.11 (s, 1H), 8.27 (dd, *J* = 9.3, 5.9 Hz, 1H), 7.77 (dd, *J* = 8.6, 7.2 Hz, 2H), 7.67 (dd, *J* = 10.4, 2.6 Hz, 1H), 7.46 (dd, *J* = 5.3, 2.0 Hz, 3H), 7.39 (td, *J* = 8.9, 2.6 Hz, 1H), 7.31 (d, *J* = 8.6 Hz, 1H), 7.09 – 6.98 (m, 1H), 6.90 (dd, *J* = 5.4, 3.3 Hz, 1H), 5.20 — 5.06 (m, 3H), 4.47 – 4.32 (m, 1H), 4.41 – 4.18 (m, 3H), 3.77 (s, 3H), 3.54 – 3.43 (m, 1H), 3.41 (s, 1H), 3.28-3.26 (m, 2H), 2.90 (ddd, *J* = 16.9, 13.7, 5.4 Hz, 1H), 2.65 – 2.60 (m, 1H), 2.60 – 2.57 (m, 1H), 2.57 – 2.55 (m, 1H), 2.28 – 2.18 (m, 2H), 2.18 – 1.96 (m, 11H), 1.93 (s, 3H).

Example 24: 1-(2-(4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)acetyl)piperazin-1-yl)ethyl)-6-methyl-3-(3-(naphthalen-1-yloxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (217)



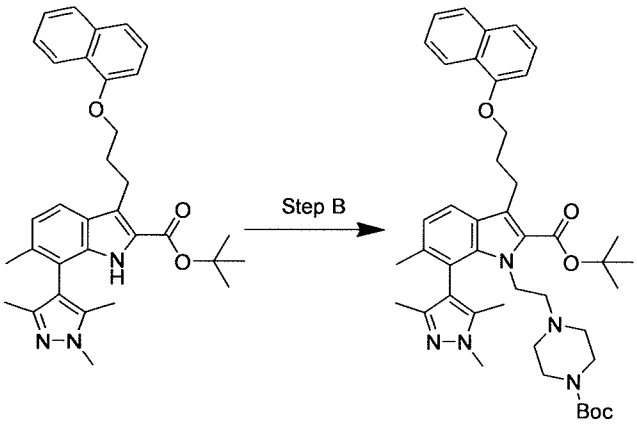
Step A



To a stirred solution of *tert*-butyl 6-chloro-3-(3-(naphthalen-1-yloxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (2 g, 3.683 mmol) in dioxane (20 mL) were added methyl boronic acid (761 mg, 12.891 mmol) and potassium phosphate (2.343 g, 11.05 mmol), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (SPhos, 453 mg, 1.105 mmol). The mixture was deoxygenated with argon and to it was added $Pd(OAc)_2$ (0.124 g, 0.552 mmol) under argon atmosphere. Then the reaction mixture was heated under reflux for 16 h. After complete consumption of the starting material (monitored by TLC and LCMS) the reaction mixture was filtered through celite pad and the solvents were evaporated under reduced pressure. It was then diluted with EtOAc and washed successively with water and brine. The organic layer was dried over sodium sulphate and concentrated under reduced pressure to get the crude compound, which was then purified by column chromatography (SiO_2, 30% EtOAc in DCM) to get *tert*-butyl 6-methyl-3-(3-(naphthalen-1-yloxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (1.6 g, 3.05 mmol, 82.8%) as brown solid.

LCMS (ESI+): m/z 523.7 $[M+H]^+$

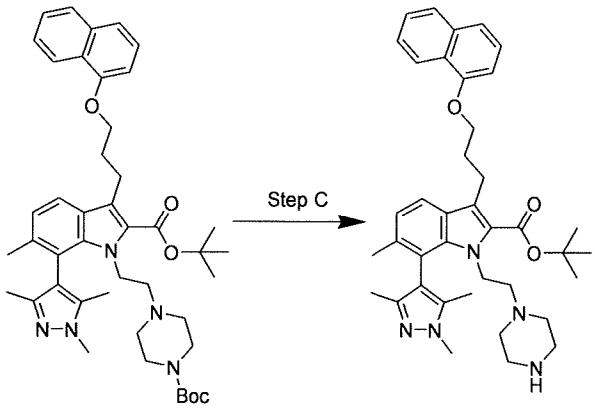
Step B



To a well stirred solution of *tert*-butyl 6-methyl-3-(3-(naphthalen-1-yloxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (1.6 g, 3.05 mmol) in DMF (15 mL) was added *tert*-butyl 4-(2-chloroethyl)piperazine-1-carboxylate (1.5 g, 6.119 mmol) followed by cesium carbonate (4.9 g, 15.296 mmol) in DMF and the mixture was allowed to stir at 90°C for 16 h under nitrogen. After complete consumption of the starting material (monitored by TLC and LCMS) the reaction mixture was diluted with EtOAc, washed successively with water and brine, the organic layer was dried over sodium sulphate and evaporated under reduced pressure to get the crude compound, which was then purified by column chromatography (SiO_2, 30% EtOAc in DCM) to get *tert*-butyl 1-(2-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)ethyl)-6-methyl-3-(3-(naphthalen-1-yloxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (1.2 g, 1.63 mmol, 53.4%) as white solid.

LCMS (ESI+): m/z 737.4 $[M+H]^+$

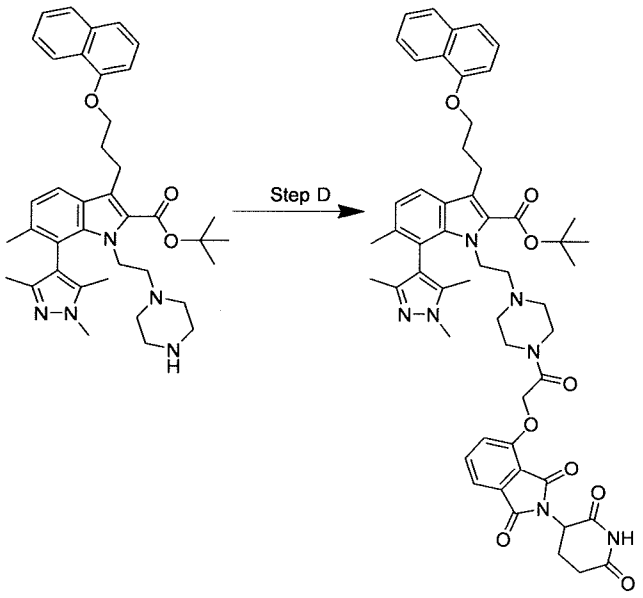
Step C



Tert-butyl 1-(2-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)ethyl)-6-methyl-3-(3-(naphthalen-1-yloxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (800 mg, 1.088 mmol) was dissolved in DCM (30 mL) and 4M HCl in dioxane (20 mL) was added drop-wise at 0°C. The mixture was stirred for 2 h under nitrogen at that temperature. Upon indication by LCMS full conversion of the starting material, the reaction mixture was quenched by drop wise addition of cold 1M NaOH solution at 0°C to reach the pH~7 to 8. The aqueous layer was extracted 2-3 times with DCM. The combined organics were dried over Na_2SO_4 and concentrated under vacuum to get the crude compound which was then purified by column chromatography (amine SiO_2, 70% EtOAc in DCM) to get *tert*-butyl 6-methyl-3-(3-(naphthalen-1-yloxy)propyl)-1-(2-(piperazin-1-yl)ethyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (440 mg, 0.692 mmol, 63.58%) as white solid.

LCMS (ESI+): m/z 636.5 $[M+H]^+$

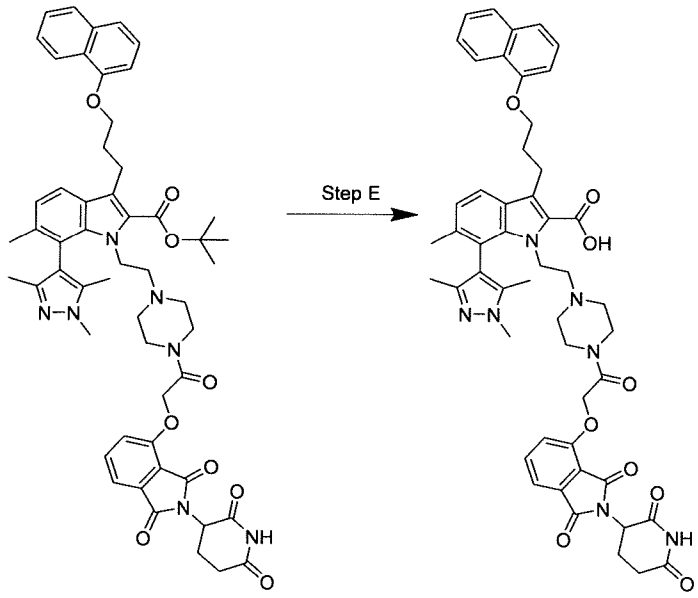
Step D



To a well stirred solution of 2-{[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl]oxy}acetic acid (30.4 mg, 0.091 mmol) and *tert*-butyl 6-methyl-3-(3-(naphthalen-1-yloxy)propyl)-1-(2-(piperazin-1-yl)ethyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1H-indole-2-carboxylate (48.4 mg, 0.076 mmol) in DMF (0.762 mL) was added DIPEA (0.040 mL, 0.229 mmol) and HATU (43.5 mg, 0.114 mmol) and the mixture was allowed to stir under nitrogen for 2 h. After complete consumption of the starting material (monitored by TLC and LCMS), the reaction mixture was diluted with EtOAc and washed successively with cold water and brine. Organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. Crude mixture was purified by flash chromatography (SiO_2 DCM:MeOH, 0 – 10% MeOH) to give *tert*-butyl 1-(2-(4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)acetyl)piperazin-1-yl)ethyl)-6-methyl-3-(3-(naphthalen-1-yloxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (39.0 mg, 0.036 mmol, 47.8%) as yellow gum.

LCMS (ESI+): m/z 950.4 $[M+H]^+$

Step E

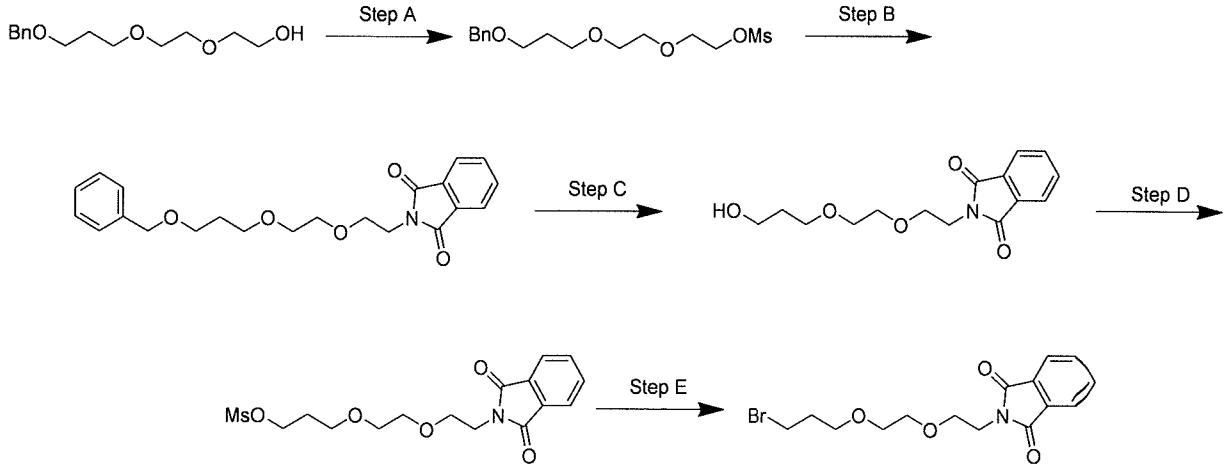


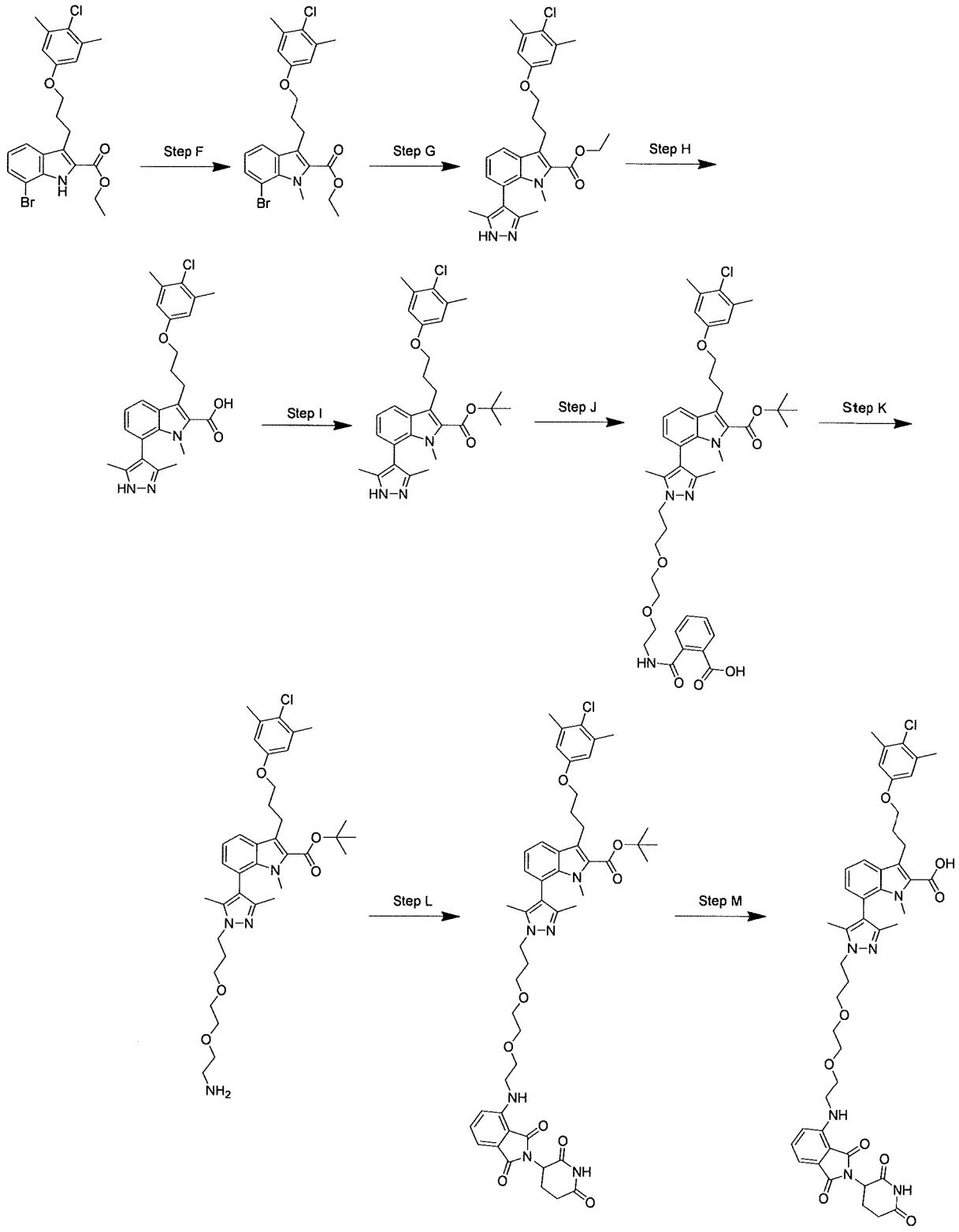
Tert-butyl 1-(2-(4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)acetyl)piperazin-1-yl)ethyl)-6-methyl-3-(3-(naphthalen-1-yloxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (39.0 mg, 0.041 mmol) was placed in a capped vial, dissolved in DCM and then TFA (0.629 mL, 8.210 mmol) was added. Reaction was stirred overnight at RT. Solvents were removed under reduced pressure, and crude product was purified using preparative HPLC (H_2O:MeCN + 0.1% FA) to afford 1-(2-(4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)acetyl)piperazin-1-yl)ethyl)-6-methyl-3-(3-(naphthalen-1-yloxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (16.6 mg, 0.019 mmol, 45.2%) as yellow solid.

LCMS (ESI+): m/z 894.2 $[M+H]^+$

^{1}H NMR (500 MHz, DMSO) δ 13.14 (s, 1H), 11.09 (s, 1H), 8.28 – 8.21 (m, 1H), 7.89 – 7.82 (m, 1H), 7.75 (dd, *J* = 8.6, 7.2 Hz, 1H), 7.61 (d, *J* = 8.1 Hz, 1H), 7.56 – 7.48 (m, 2H), 7.45 (t, 2H), 7.39 (t, *J* = 7.9 Hz, 1H), 7.29 (d, *J* = 8.6 Hz, 1H), 7.02 (d, *J* = 8.2 Hz, 1H), 6.94 – 6.86 (m, 1H), 5.15 – 5.05 (m, 3H), 4.29 (dt, *J* = 13.8, 7.0 Hz, 1H), 4.21 (t, *J* = 6.2 Hz, 2H), 4.18 – 4.10 (m, 1H), 3.75 (s, 3H), 3.36 – 3.33 (m, 3H), 3.28 – 3.24 (m, 3H), 2.88 (ddd, *J* = 16.8, 13.8, 5.4 Hz, 1H), 2.62 – 2.52 (m, 2H), 2.21 (p, *J* = 6.4 Hz, 2H), 2.16 – 2.02 (m, 7H), 2.01 (s, 3H), 1.98 (s, 3H), 1.85 (s, 3H).

Example 25: 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1-(3-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)propyl)-3,5-dimethyl-1*H*-pyrazol-4-yl)-1-methyl-1*H*-indole-2-carboxylic acid (227)




Step F
Step G
Step H
Step I
Step J
Step K
Step L
Step M

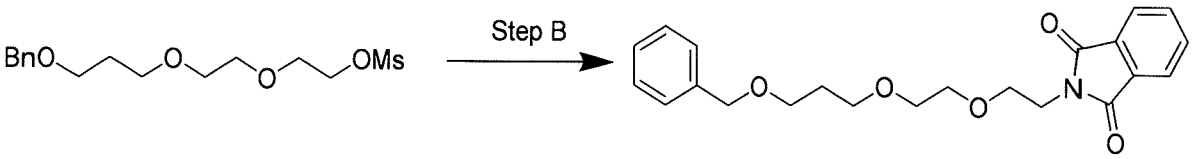
Step A



To a stirred solution of 2-(2-(3-(benzyloxy)propoxy)ethoxy)ethan-1-ol (5.8 g, 22.8 mmol) in DCM (100 mL) was added MsCl (10 mL, 68.4 mmol), followed by triethyl amine (6.4 mL, 45.6 mmol) at 0°C under nitrogen and the reaction mixture was allowed to stir at room temperature for 2 h. After complete consumption of the starting material the reaction mixture was diluted with EtOAc, washed successively with water and brine, the organic layer was dried over sodium sulphate and evaporated under reduced pressure to get the crude compound, which was then purified by column chromatography (SiO_2, 50% EtOAc in hexane) to get 2-(2-(3-(benzyloxy)propoxy)ethoxy)ethyl methanesulfonate (6.7 g, 20.2 mmol, 88%) as colorless liquid.

LCMS (ESI+): m/z 333.0 $[M+H]^+$

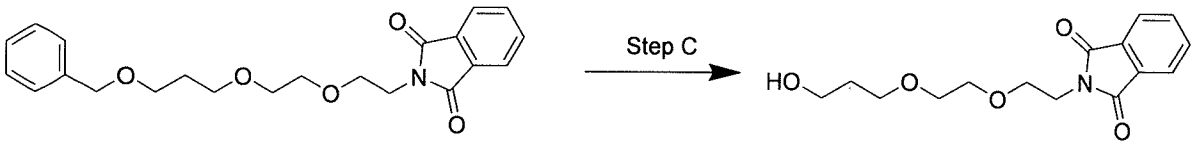
Step B



To a stirred solution of 2-(2-(3-(benzyloxy)propoxy)ethoxy)ethyl methanesulfonate (6.2 g, 18.6 mmol) in DMF (60 mL) was added lithium bromide (4.8 g, 56 mmol) and the reaction mixture was allowed to stir at 100°C under nitrogen for 4 h. After complete consumption of the starting material reaction mixture was cooled to room temperature, to it was added potassium phthalimide (6.9 g, 37.3 mmol) and reaction mixture was stirred for another 16 h at 100°C under nitrogen. After complete consumption of the starting material the reaction mixture was diluted with EtOAc and washed successively with water and brine. The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to get the crude compound, which was then purified by column chromatography (SiO_2, 30% EtOAc in hexane) to get 2-(2-(2-(3-(benzyloxy)propoxy)ethoxy)ethyl)isoindoline-1,3-dione (3.2 g, 8.35 mmol, 45%) as yellow dense liquid.

LCMS (ESI+): m/z 384.2 $[M+H]^+$

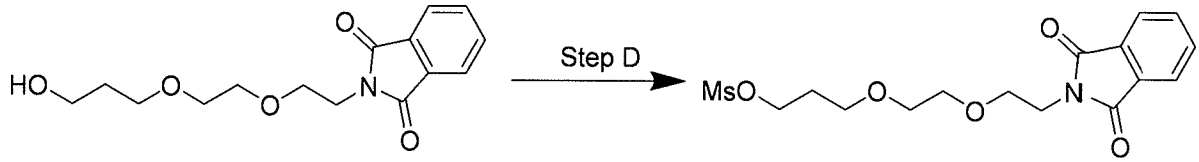
Step C



To a stirred solution of 2-(2-(2-(3-(benzyloxy)propoxy)ethoxy)ethyl)isoindoline-1,3-dione (3.5 g, 9.13 mmol) in DCM (50ml) was added boron trichloride (1M solution in DCM, 28 mL, 28 mmol) drop wise at -78°C under nitrogen. The reaction mixture was allowed to stir at same temp for 1h. After complete consumption of the starting material the reaction mixture was poured into ice, extracted with EtOAc and washed successively with water and brin. The organic layer was dried over sodium sulphate and evaporated under reduced pressure to get the crude compound, which was then purified by column chromatography (SiO_2, 80% EtOAc in DCM) to get 2-(2-(2-(3-hydroxypropoxy)ethoxy)ethyl)isoindoline-1,3-dione (2.1 g, 7.16 mmol, 78%) as colorless dense liquid.

LCMS (ESI+): m/z 293.8 $[M+H]^+$

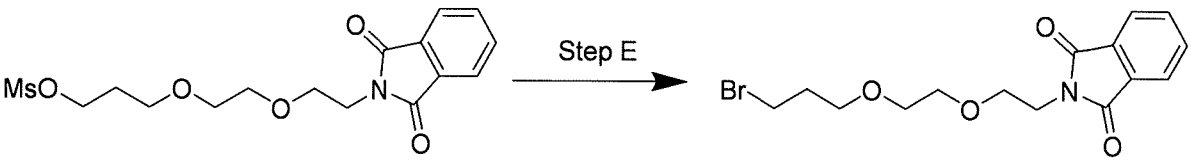
Step D



To a stirred solution of 2-(2-(2-(3-hydroxypropoxy)ethoxy)ethyl)isoindoline-1,3-dione (2.5 g, 8.5 mmol) in DCM (60 mL) was added mesyl chloride (2.5 mL, 17.06 mmol) followed by Et_3N (3.5 mL, 25.6 mmol) at 0°C under nitrogen and the reaction mixture was allowed to stir at room temperature for 2 h. After complete consumption of the starting material the reaction mixture was diluted with EtOAc and washed successively with water and brine. The organic layer was dried over sodium sulphate and evaporated under reduced pressure to get the crude compound, which was then purified by column chromatography (SiO_2, 40% EtOAc in hexane) to get 3-(2-(2-(1,3-dioxoisoindolin-2-yl)ethoxy)ethoxy)propyl methanesulfonate (3 g, 8.08 mmol, 95%) as colorless liquid.

LCMS (ESI+): m/z 372.2 $[M+H]^+$

Step E

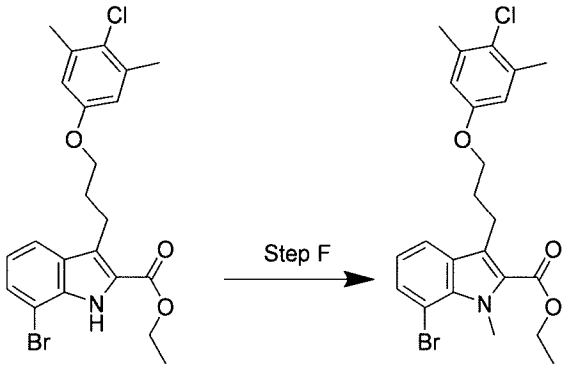


To a stirred solution of 3-(2-(2-(1,3-dioxoisoindolin-2-yl)ethoxy)ethoxy)propyl methanesulfonate (3 g, 8.08 mmol) in DMF (40 mL) was added lithium bromide (3.5 g, 40.43 mmol) and the reaction mixture was allowed to stir at room temperature for 16 h under nitrogen. After complete consumption of the starting material (monitored by TLC and LCMS) the reaction mixture was diluted with EtOAc, and washed successively with water and brine. The organic layer was dried

over Na_2SO_4 and evaporated under reduced pressure to get the crude compound, which was then purified by column chromatography (SiO_2, 30% EtOAc in hexane) to get 2-(2-(2-(3-bromopropoxy)ethoxy)ethyl)isoindoline-1,3-dione (2.5 g, 7.02 mmol, 87%) as colorless dense liquid.

LCMS (ESI+): m/z 356.2 $[M+H]^+$

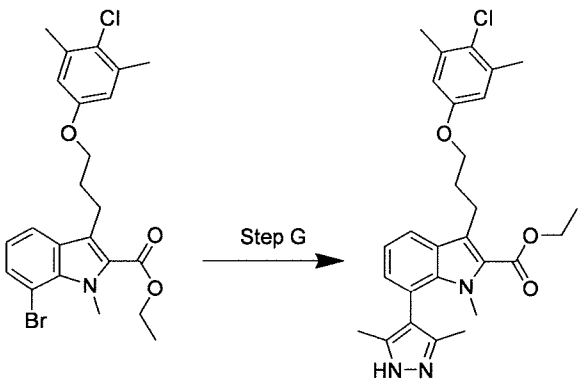
Step F



To a well stirred solution of ethyl 7-bromo-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carboxylate (10 g, 21.55 mmol) in DMF (100 mL) was added potassium carbonate (11.9 g, 86.2 mmol) followed by methyl iodide (2.8 mL, 43.1 mmol) and the mixture was allowed to stir at 90°C for 16 h under nitrogen. After complete consumption of the starting material the reaction mixture was diluted with EtOAc, washed successively with water and brine, the organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to get the crude compound, which was then purified by column chromatography (SiO_2, EtOAc:hexane, 10-20%) to get ethyl 7-bromo-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-methyl-1*H*-indole-2-carboxylate (10 g, 21 mmol, 97%) as off white solid.

LCMS (ESI+): m/z 477.7$[M+H]^+$

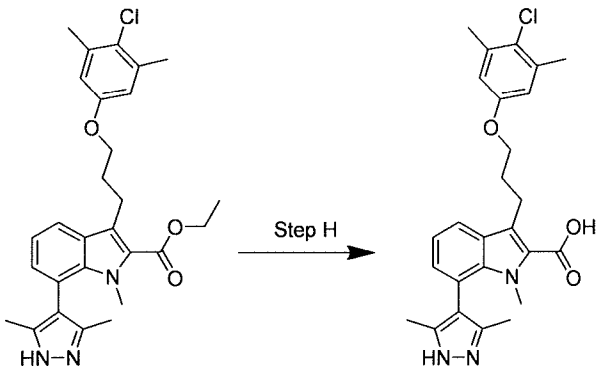
Step G



To a stirred solution of ethyl 7-bromo-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-methyl-1*H*-indole-2-carboxylate (5 g, 10.46 mmol) in dioxane (150 mL) and water (30 mL) were added 3,5-dimethyl-1-(tetrahydro-2*H*-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) -1*H*-pyrazole (7 g, 31.4 mmol) and K_2CO_3 (5.8 g, 41.84 mmol). The mixture was deoxygenated with argon and to it was added $Pd(dppf)Cl_2$ (1.14 g, 1.57 mmol) under argon atmosphere. Then the reaction mixture was heated under reflux for 16 h. After complete consumption of the starting material the reaction mixture was filtered through celite pad and the solvents were evaporated under reduced pressure get the crude material. It was then diluted with EtOAc, washed successively with water and brine, the organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to get the crude compound, which was then purified by column chromatography (SiO_2, 5% MeOH in DCM) to get ethyl 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(3,5-dimethyl-1*H*-pyrazol-4-yl)-1-methyl-1*H*-indole-2-carboxylate (3 g, 6.05 mmol, 58%) as brown gummy solid.

LCMS (ESI+): m/z 494.2 $[M+H]^+$

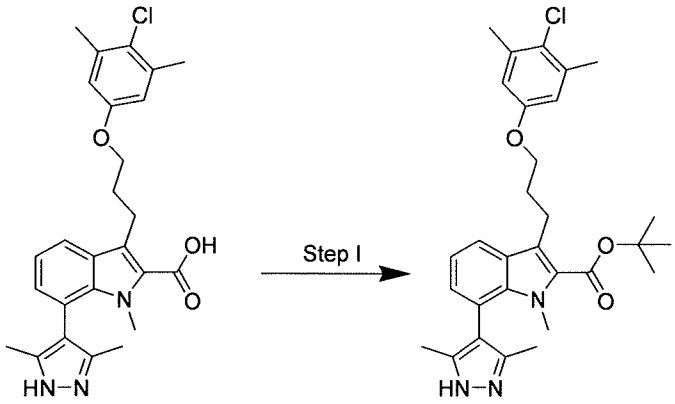
Step H



3-(3-(4-Chloro-3,5-dimethylphenoxy)propyl)-7-(3,5-dimethyl-1*H*-pyrazol-4-yl)-1-methyl-1*H*-indole-2-carboxylate (2 g, 4.06 mmol) was dissolved in EtOH (40 mL) and a solution of NaOH (0.57 g, 14.2 mmol) in water (8 mL) was added to it. The mixture was heated under reflux for 3 h. After complete consumption of the starting material the reaction mixture was cooled down to room temperature, solvents were evaporated under reduced pressure to get the crude reaction mixture. It was then diluted with water, washed with EtOAc. Aqueous layer was carefully acidified using 1M HCl to pH = 3, extracted with DCM, dried over Na_2SO_4, filtered, and concentrated in vacuo to afford 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(3,5-dimethyl-1*H*-pyrazol-4-yl)-1-methyl-1*H*-indole-2-carboxylic acid (2 g, crude) as dark brown gummy solid.

LCMS (ESI+): m/z 466.5 $[M+H]^+$

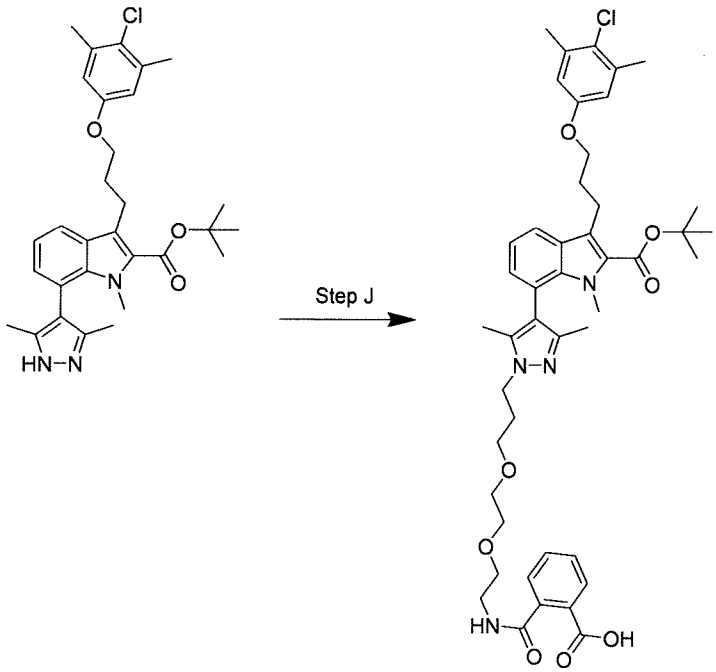
Step I



3-(3-(4-Chloro-3,5-dimethylphenoxy)propyl)-7-(3,5-dimethyl-1*H*-pyrazol-4-yl)-1-methyl-1*H*-indole-2-carboxylic acid (2 g, crude) was suspended in toluene (20 mL) and the mixture was heated to reflux under nitrogen. *N*,*N*-dimethylformamide di-*tert*-butyl acetal (3.5 mL, 17.2 mmol) was added drop wise to the refluxing mixture. Refluxing was continued for an additional 16 h under nitrogen. After 16 h another 1.7 mL (8.6 mmol) of *N*,*N*-dimethylformamide di-*tert*-butyl acetal was added to it and the reaction was continued for another 24 h. Reaction mixture was then diluted with EtOAc, washed successively with $NaHCO_3$ (saturated), water and brine. Organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to get the crude compound, which was then purified by column chromatography (SiO_2, 2% MeOH in DCM) to get *tert*-butyl 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(3,5-dimethyl-1*H*-pyrazol-4-yl)-1-methyl-1*H*-indole-2-carboxylate (1.4 g, 2.68 mmol, 62%) as brown solid.

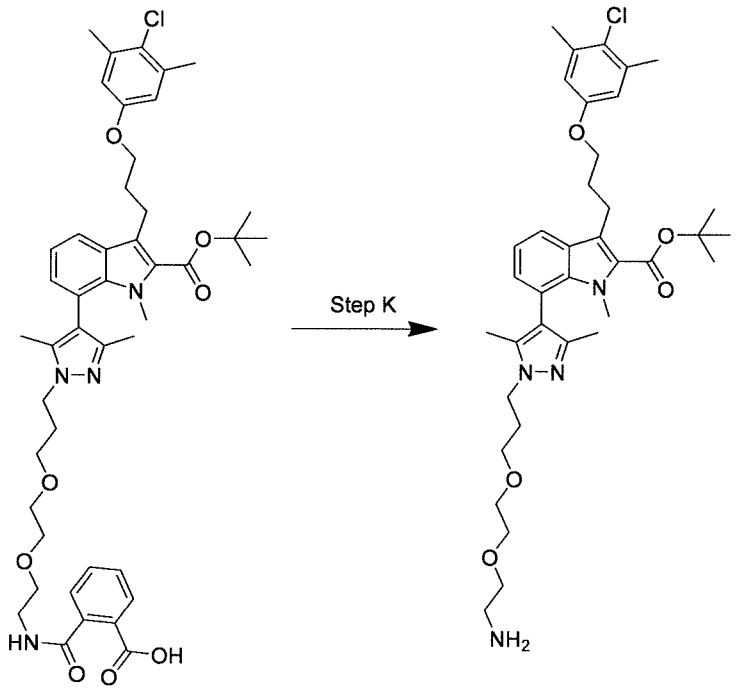
LCMS (ESI+): m/z 522.2 $[M+H]^+$

Step J



To a stirred solution of *tert*-butyl 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(3,5-dimethyl-1*H*-pyrazol-4-yl)-1-methyl-1*H*-indole-2-carboxylate (600 mg, 1.15 mmol) in DMF (15 mL) at 0°C was added sodium hydride (55.3 mg, 2.3 mmol) portion-wise under nitrogen and the reaction mixture was allowed to stir at the same temperature for 1 h, after that to the reaction mixture was added 2-(2-(2-(3-bromopropoxy)ethoxy)ethyl)isoindoline-1,3-dione (1.3 g, 3.45 mmol) dissolved in DMF (5 mL) at 0°C and the reaction mixture was allowed to stir at room temperature for 16 h under nitrogen. After complete consumption of the starting material (monitored by TLC and LCMS) the reaction mixture was again cooled to 0°C and quenched the excess of NaH with ammonium chloride solution. The volatiles were evaporated under reduced pressure to get the crude 2-((2-(2-(3-(4-(2-(*tert*-butoxycarbonyl)-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-methyl-1*H*-indol-7-yl)-3,5-dimethyl-1*H*-pyrazol-1-yl)propoxy)ethoxy)ethyl)carbamoyl)benzoic acid which was used for the next step without further purification.

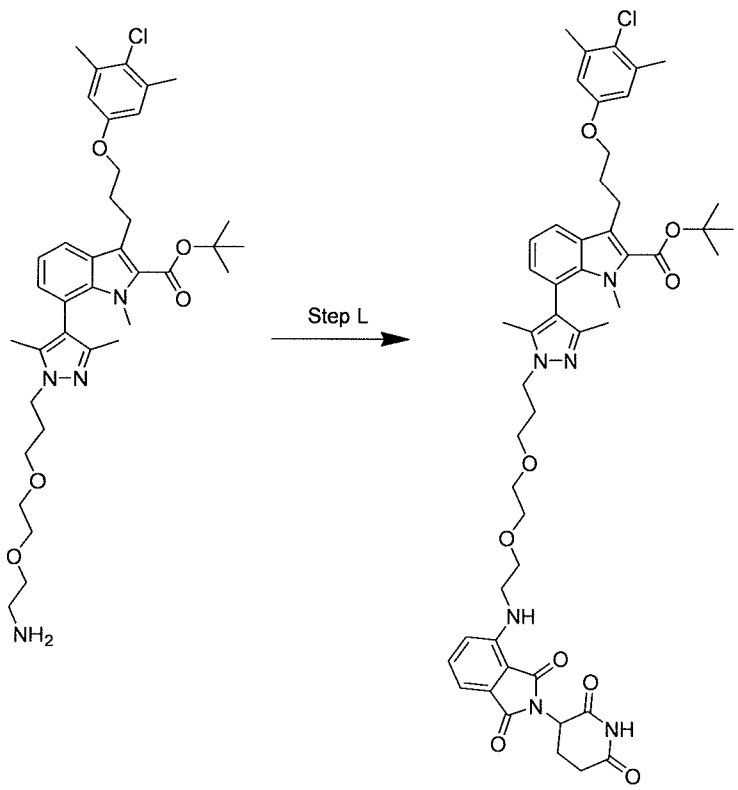
Step K



A mixture of 2-((2-(2-(3-(4-(2-(*tert*-butoxycarbonyl)-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-methyl-1*H*-indol-7-yl)-3,5-dimethyl-1*H*-pyrazol-1-yl)propoxy)ethoxy)ethyl)carbamoyl)benzoic acid and hydrazine hydrate (1.63 mL, 33 mmol) in 30 mL of dry *tert*-butanol was refluxed for 16 h at 140°C under nitrogen. Then it was allowed to cool down to room temperature. Volatiles were evaporated under reduced pressure, the resulting residue was dissolved in DCM and washed successively with water and brine. The organic layer was dried over $MgSO_4$, filtered and evaporated under reduced pressure to get the crude compound which was purified by column chromatography (amine SiO_2, 2% MeOH in DCM) *tert*-butyl 7-(1-(3-(2-(2-aminoethoxy)ethoxy)propyl)-3,5-dimethyl-1*H*-pyrazol-4-yl)-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-methyl-1*H*-indole-2-carboxylate (150 mg, 0.224 mmol, 19% over 2 steps) as brown liquid.

LCMS (ESI+): m/z 667.5 $[M+H]^+$

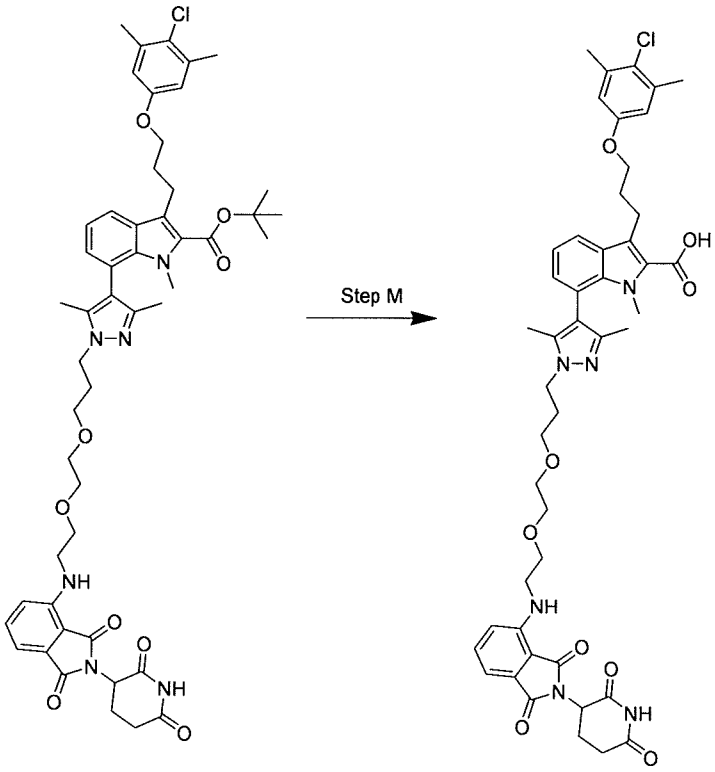
Step L



To a well stirred solution of *tert*-butyl 7-(1-(3-(2-(2-aminoethoxy)ethoxy)propyl)-3,5-dimethyl-1*H*-pyrazol-4-yl)-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-methyl-1*H*-indole-2-carboxylate (650 mg, 0.975 mmol) in DMSO (15 mL) was added 2-(2,6-dioxopiperidin-3-yl)-4-fluoroisoindoline-1,3-dione (403 mg, 1.46 mmol), followed by DIPEA (339 µL, 1.95 mmol) and the reaction mixture was allowed to stir in 90°C for 2 h under nitrogen. After complete consumption of the starting material the reaction mixture was diluted with EtOAc and washed successively with water and brine. The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to get the crude compound, which was then purified by column chromatography (SiO_2, 80% EtOAc in DCM) to get *tert*-butyl 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1-(3-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)propyl)-3,5-dimethyl-1*H*-pyrazol-4-yl)-1-methyl-1*H*-indole-2-carboxylate (230 mg, 0.25 mmol, 25%) as yellow solid.

LCMS (ESI+): m/z 923.9 $[M+H]^+$

Step M

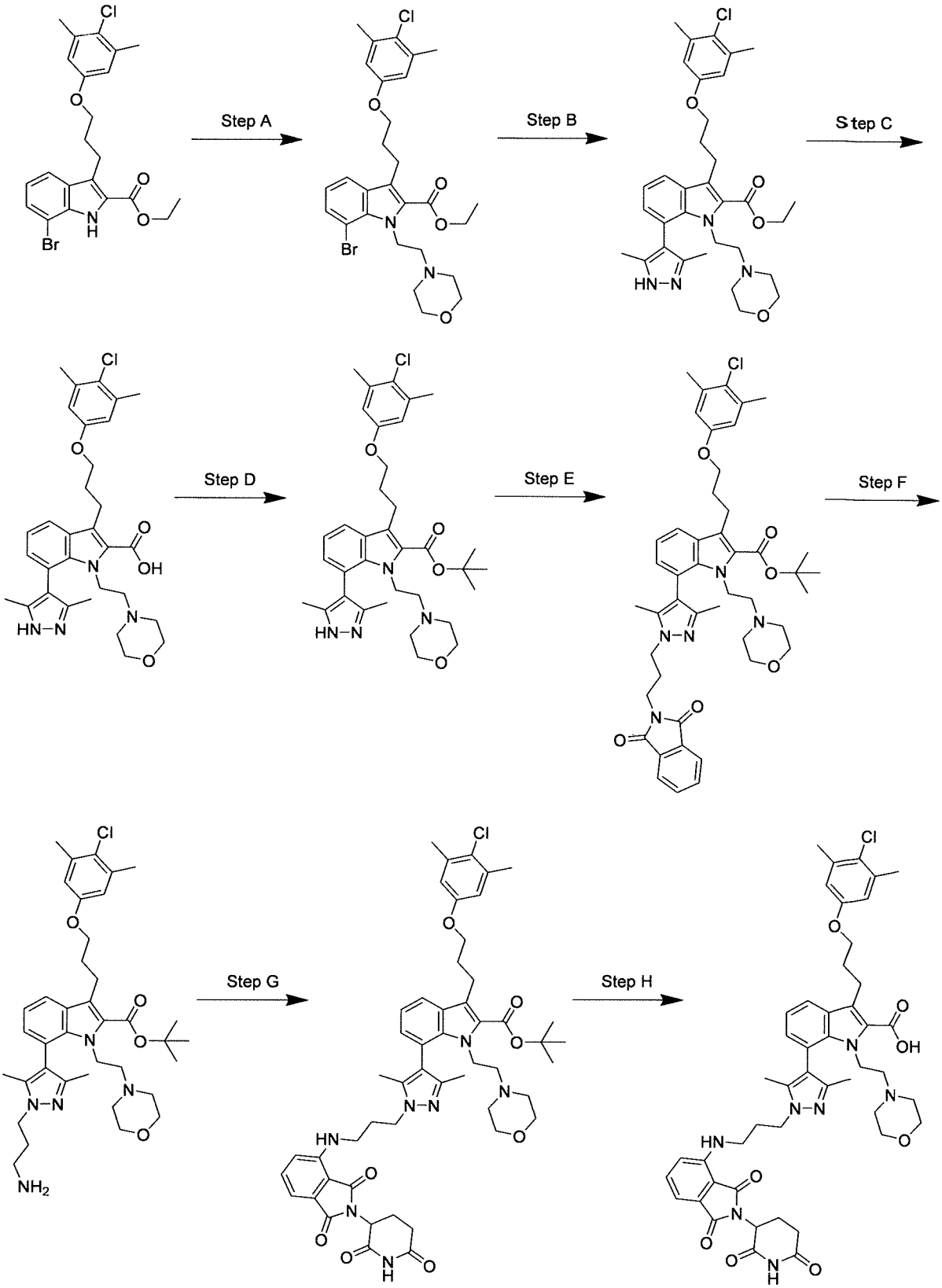


To a well stirred solution of *tert*-butyl 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1-(3-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)propyl)-3,5-dimethyl-1*H*-pyrazol-4-yl)-1-methyl-1*H*-indole-2-carboxylate (120 mg, 0.13 mmol) in dioxane (3 mL) was added 5 mL of 4M HCl in dioxane and the reaction mixture was allowed to stir at room temperature for 28 h. After complete consumption of the starting material the reaction mixture was evaporated under reduced pressure to get the crude compound, which was then purified by preparative HPLC (H_2O:MeCN + 0.1% HCl) to get 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1-(3-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)propyl)-3,5-dimethyl-1*H*-pyrazol-4-yl)-1-methyl-1*H*-indole-2-carboxylic acid (18 mg, 0.02 mmol, 15%) as yellow solid.

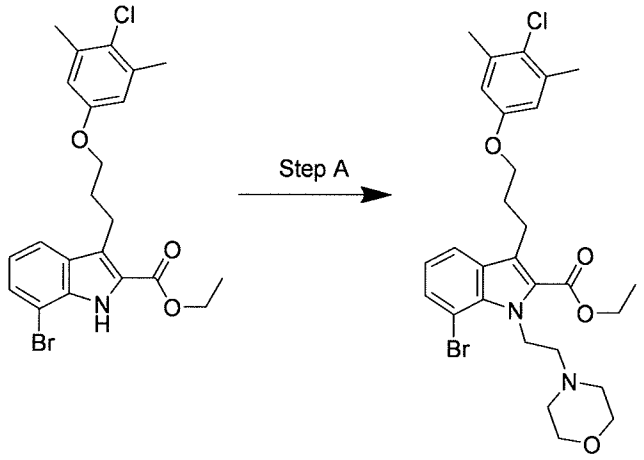
LCMS (ESI+): m/z 867.6 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO) δ 11.10 (s, 1H), 7.67 (d, *J* = 8.1 Hz, 1H), 7.56 (t, *J* = 7.8 Hz, 1H), 7.12 (dd, *J* = 15.5, 8.0 Hz, 2H), 7.03 (d, *J* = 7.0 Hz, 1H), 6.98 (d, *J* = 6.9 Hz, 1H), 6.78 (s, 2H), 6.67 – 6.55 (m, 1H), 5.06 (dd, J = 12.9, 5.2 Hz, 1H), 4.08 (t, *J* = 5.6 Hz, 2H), 4.00 (t, *J* = 6.2 Hz, 2H), 3.71 – 3.64 (m, 4H), 3.53 – 3.45 (m, 7H), 3.42 – 3.30 (m, 2H), 3.18 (t, *J* = 7.2 Hz, 2H), 2.88 (ddd, *J* = 18.1, 14.3, 3.7 Hz, 1H), 2.62 – 2.55 (m, 2H), 2.29 (s, 6H), 2.11 – 1.97 (m, 8H), 1.96 (s, 3H).

Example 26: 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1-(3-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)propyl)-3,5-dimethyl-1*H*-pyrazol-4-yl)-1-(2-morpholinoethyl)-1*H*-indole-2-carboxylic acid (228)



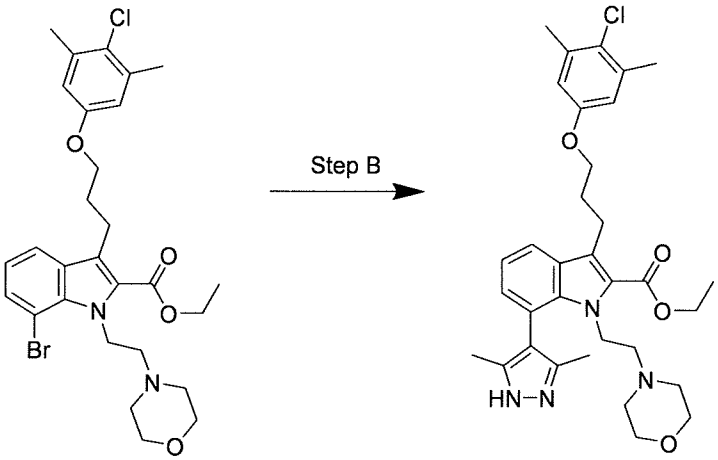
Step A



To a well stirred solution of ethyl 7-bromo-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carboxylate (5 g, 10.78 mmol) in DMF (50 mL) was added 4-(2-bromoethyl)morpholine (6 g, 30.92 mmol) followed by Cs_2CO_3 (17.5 g, 53.71 mmol) in DMF and the mixture was allowed to stir at 90°C for 16 h under nitrogen. After complete consumption of the starting material the reaction mixture was diluted with EtOAc, washed successively with water and brine, the organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to get the crude compound, which was then purified by column chromatography (SiO_2, 30% EtOAc in hexane) to get of ethyl 7-bromo-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-(2-morpholinoethyl)-1*H*-indole-2-carboxylate (4.8 g, 8.32 mmol, 77%) as off white solid.

LCMS (ESI+): m/z 577.0 $[M+H]^+$

Step B

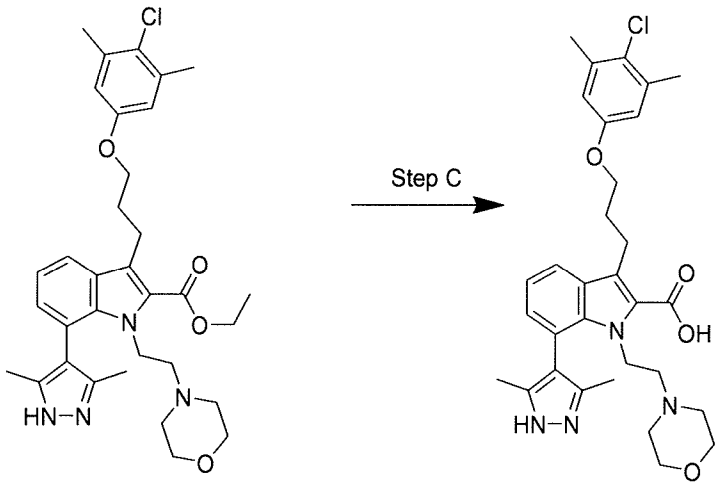


To a stirred solution of ethyl 7-bromo-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-(2-morpholinoethyl)-1*H*-indole-2-carboxylate (4.8 g, 8.32 mmol) in dioxane (150 mL) and water

(30 mL) were added 3,5-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (5.54 g, 24.9 mmol) and K_2CO_3 (4.5 g, 32.5 mmol). The mixture was deoxygenated with argon and to it was added $Pd(dppf)Cl_2$ (1 g, 1.37 mmol) under argon atmosphere. Then the reaction mixture was heated under reflux for 16 h. After complete consumption of the starting material the reaction mixture was filtered through celite pad and the solvents were evaporated under reduced pressure to get the crude material. It was then diluted with EtOAc, washed successively with water and brine, the organic layer was dried over sodium sulphate and evaporated under reduced pressure to get the crude compound, which was then purified by column chromatography (SiO_2, 5% MeOH in DCM) to get ethyl 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(3,5-dimethyl-1*H*-pyrazol-4-yl)-1-(2-morpholinoethyl)-1*H*-indole-2-carboxylate (2.5 g, 4.21 mmol, 50%) as brown solid.

LCMS (ESI+): m/z 593.8 $[M+H]^+$

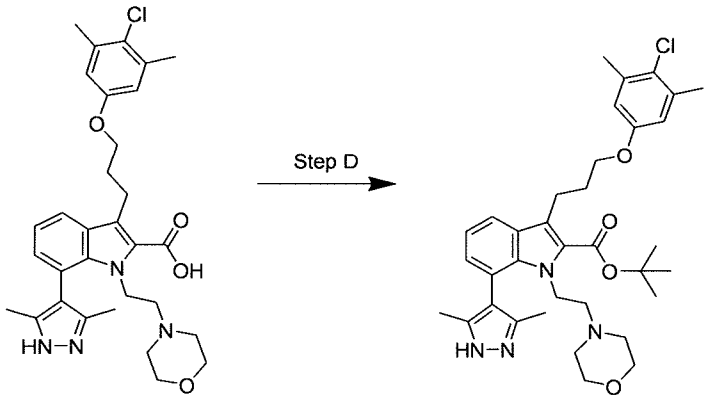
Step C



Ethyl 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(3,5-dimethyl-1*H*-pyrazol-4-yl)-1-(2-morpholinoethyl)-1*H*-indole-2-carboxylate (1.8 g, 3.0 mmol) was dissolved in EtOH (40 mL) and a solution of NaOH (0.43 g, 10.7 mmol) in water (20 mL) was added to it. The mixture was heated under reflux for 3 h. After complete consumption of the starting material the reaction mixture was cooled down to room temperature, solvents were evaporated under reduced pressure to get the crude reaction mixture. It was then diluted with water, washed with EtOAc. Aqueous layer was carefully acidified using 1 (N) HCl to pH=3, extracted with DCM, dried over Na_2SO_4, filtered, and concentrated in vacuo to afford of 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(3,5-dimethyl-1*H*-pyrazol-4-yl)-1-(2-morpholinoethyl)-1*H*-indole-2-carboxylic acid (1.5 g, 2.65 mmol, 88%) as dark brown gummy solid.

LCMS (ESI+): m/z 565.2 $[M+H]^+$

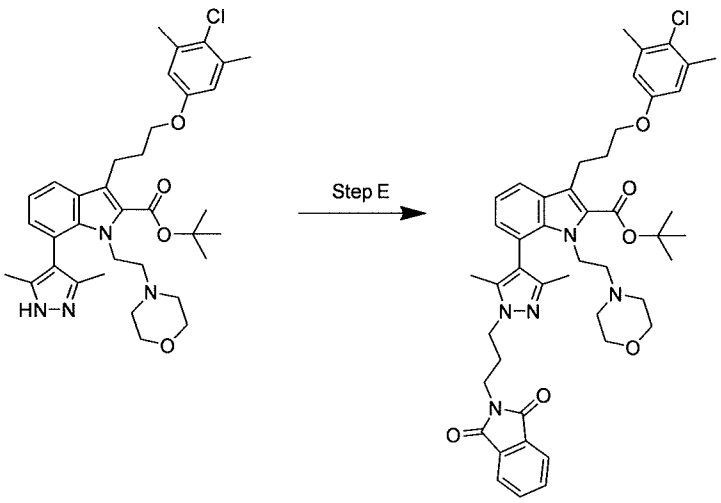
Step D



3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(3,5-dimethyl-1*H*-pyrazol-4-yl)-1-(2-morpholinoethyl)-1*H*-indole-2-carboxylic acid (1.5 g, 2.65 mmol) was suspended in toluene (50 mL) and the mixture was heated to reflux under nitrogen. *N*,*N*-dimethylformamide di-*tert*-butyl acetal (0.848 g, 4.2 mmol) was added drop wise to the refluxing mixture. Refluxing was continued for an additional 16 h under nitrogen. After this time another 0.5 mL (2.1 mmol) of *N*,*N*-dimethylformamide di-*tert*-butyl acetal was added to it and the reaction was continued for another 24 h. Reaction mixture was then diluted with EtOAc, washed successively with sodium bicarbonate (saturated), water and brine, organic layer was dried over sodium sulphate and evaporated under reduced pressure to get the crude compound, which was then purified by column chromatography (SiO_2, 6% MeOH in DCM) to get *tert*-butyl 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(3,5-dimethyl-1*H*-pyrazol-4-yl)-1-(2-morpholinoethyl)-1*H*-indole-2-carboxylate (800 mg, 1.29 mmol, 49%) as brown solid.

LCMS (ESI+): m/z 621.7 $[M+H]^+$

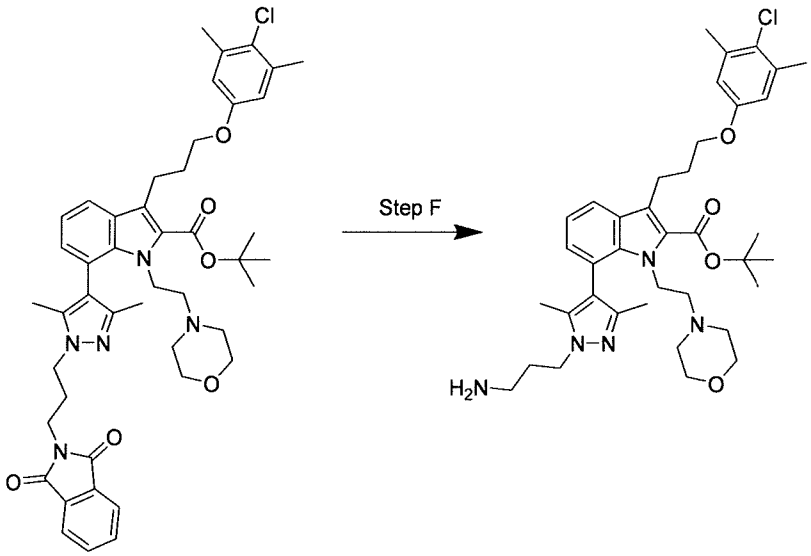
Step E



To a stirred solution of *tert*-butyl 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(3,5-dimethyl-1*H*-pyrazol-4-yl)-1-(2-morpholinoethyl)-1*H*-indole-2-carboxylate (200 mg, 0.32 mmol) in DMF (1.5 mL) in a pressure tube was added *N*-(3-bromopropyl)phthalimide (173 mg, 0.64 mmol) followed by cesium carbonate (524 mg, 1.6 mmol) and the reaction mixture was allowed to stir at 100°C for 16 h. After complete consumption of the starting material the reaction mixture was diluted with EtOAc, washed successively with water and brine, the organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to get the crude compound, which was then purified by column chromatography (SiO_2, 80% EtOAc in DCM) to get *tert*-butyl 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1-(3-(1,3-dioxoisoindolin-2-yl)propyl)-3,5-dimethyl-1*H*-pyrazol-4-yl)-1-(2-morpholinoethyl)-1*H*-indole-2-carboxylate (180 mg, 0.22 mmol, 69%) as gummy solid.

LCMS (ESI+): m/z 808.9 $[M+H]^+$

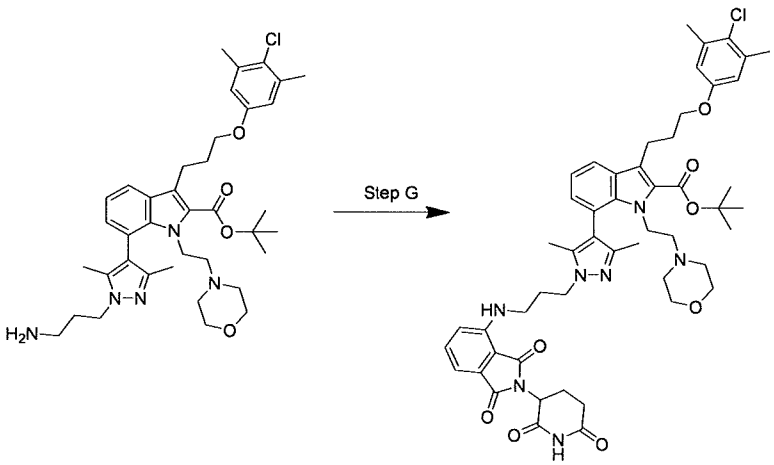
Step F



Tert-butyl 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1-(3-(1,3-dioxoisoindolin-2-yl)propyl)-3,5-dimethyl-1*H*-pyrazol-4-yl)-1-(2-morpholinoethyl)-1*H*-indole-2-carboxylate (270 mg, 0.33 mmol) and hydrazine hydrate (0.3 mL, 6.7 mmol) in 3 mL of dry *tert*-butanol was refluxed for 2 h at 140°C under nitrogen. Then it was allowed to cool down to room temperature, volatiles were removed under reduced pressure, the residue was dissolved in DCM, washed successively with water and brine. The organic layer was dried over $MgSO_4$, filtered, and evaporated under reduced pressure to get the crude compound which was purified by column chromatography (amine SiO_2, 2% MeOH in DCM) to get *tert*-butyl 7-(1-(3-aminopropyl)-3,5-dimethyl-1*H*-pyrazol-4-yl)-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-(2-morpholinoethyl)-1*H*-indole-2-carboxylate (160 mg, 0.23 mmol, 70%) as brown liquid.

LCMS (ESI+): m/z 678.8 $[M+H]^+$

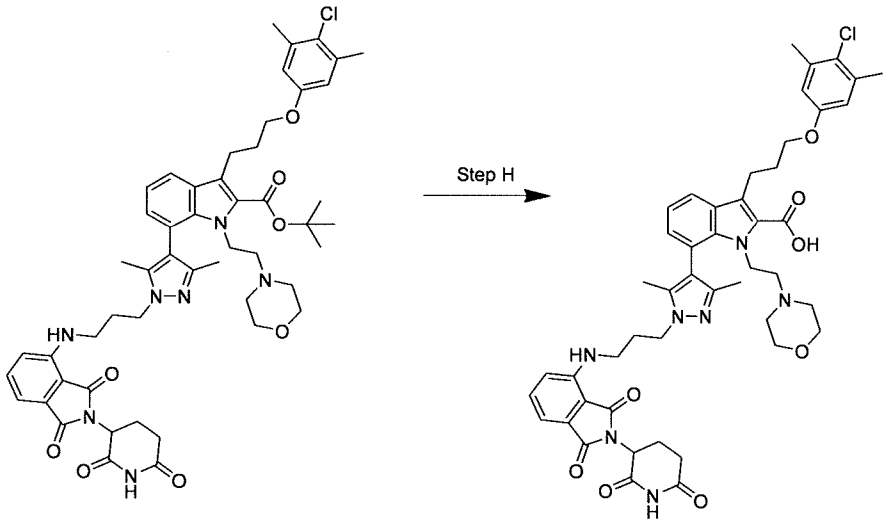
Step G



To a well stirred solution of *tert*-butyl 7-(1-(3-aminopropyl)-3,5-dimethyl-1*H*-pyrazol-4-yl)-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-(2-morpholinoethyl)-1*H*-indole-2-carboxylate (170 mg, 0.25 mmol) in DMSO (1 mL) was added 2-(2,6-dioxopiperidin-3-yl)-4-fluoroisoindoline-1,3-dione (104 mg, 0.37 mmol), followed by DIPEA (87 µL, 0.5 mmol) and the reaction mixture was allowed to stir 90°C for 16 h under nitrogen. After complete consumption of the starting material (monitored by TLC and LCMS) the reaction mixture was diluted with EtOAc, washed successively with water and brine solution, the organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to get the crude compound, which was then purified by column chromatography (amine SiO_2, 80% EtOAc in DCM) to get *tert*-butyl 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1-(3-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)propyl)-3,5-dimethyl-1*H*-pyrazol-4-yl)-1-(2-morpholinoethyl)-1*H*-indole-2-carboxylate (180 mg, 0.19 mmol, 76%) as yellow solid.

LCMS (ESI+): m/z 935.1 $[M+H]^+$

Step H



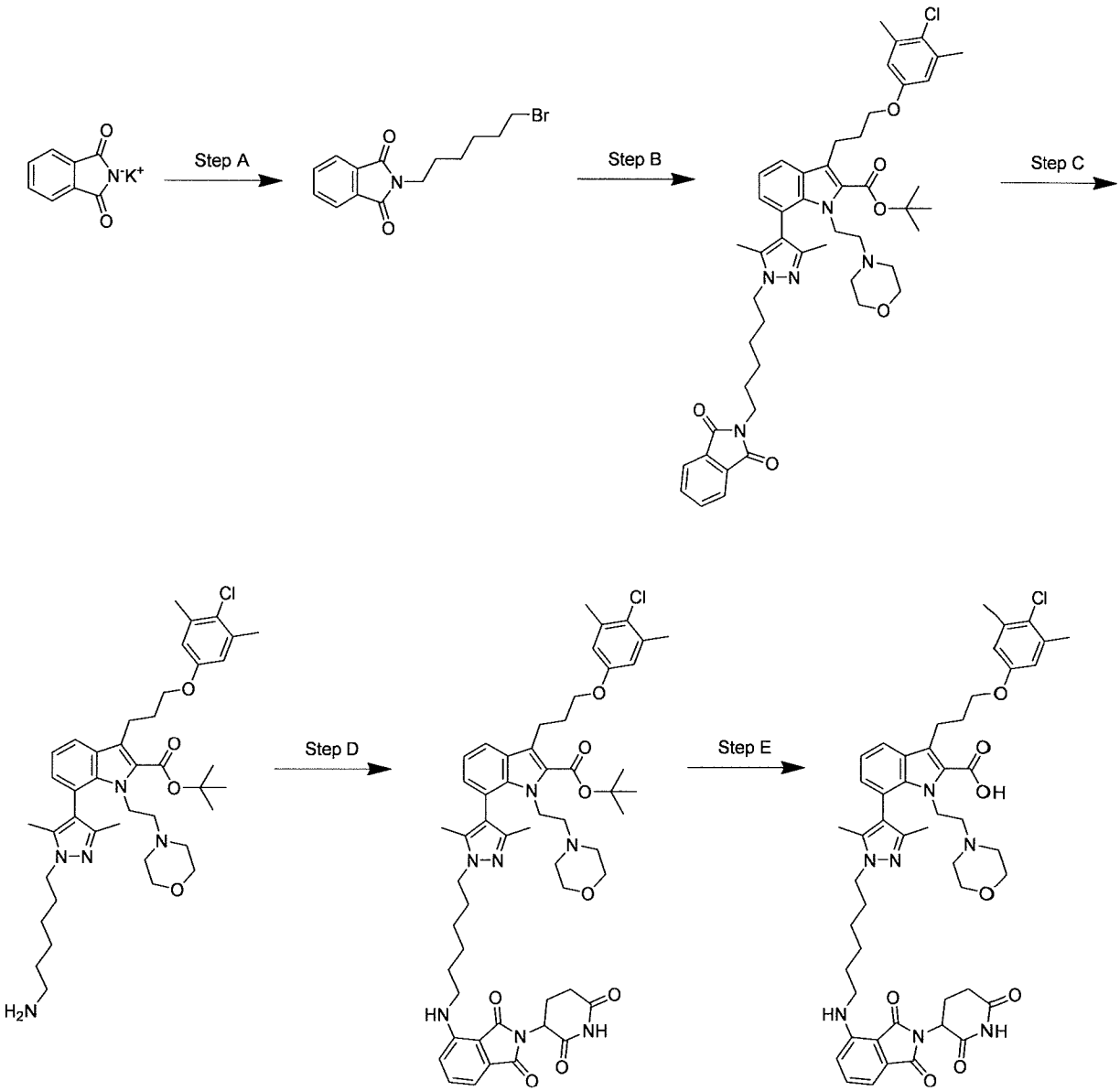
To a well stirred solution of *tert*-butyl 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1-(3-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)propyl)-3,5-dimethyl-1*H*-pyrazol-4-yl)-1-(2-morpholinoethyl)-1*H*-indole-2-carboxylate (180 mg, 0.19 mmol) in dioxane (5 mL) was added 5 mL of 4M HCl in dioxane and the reaction mixture was allowed to stir at room temperature for 28 h. After complete consumption of the starting material the reaction mixture was evaporated under reduced pressure to get the crude compound, which was then purified by preparative HPLC (10 mM ammonium acetate in H_2O and MeCN) to get 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1-(3-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)propyl)-3,5-dimethyl-1*H*-pyrazol-4-yl)-1-(2-morpholinoethyl)-1*H*-indole-2-carboxylic acid (45 mg, 0.05 mmol, 26%) as yellow solid.

LCMS (ESI+): m/z 878.4 $[M+H]^+$

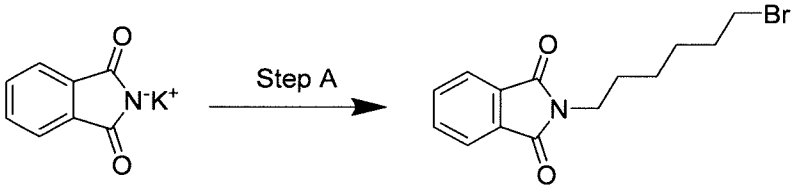
^{1}H NMR (400 MHz, DMSO) δ 11.08 (s, 1H), 7.67 – 7.57 (m, 2H), 7.14 (d, *J* = 8.6 Hz, 1H), 7.09 (t, *J* = 7.5 Hz, 1H), 7.05 (d, *J* = 7.1 Hz, 1H), 6.92 (d, *J* = 7.0 Hz, 1H), 6.75 – 6.69 (m, 3H), 5.06 (dd, *J* = 12.9, 5.4 Hz, 1H), 4.39 – 4.20 (m, 2H), 4.12 (t, *J* = 6.8 Hz, 2H), 3.98 (t, *J* = 6.4 Hz, 2H), 3.45 – 3.37 (m, 3H), 3.14 (t, *J* = 7.5 Hz, 2H), 2.95 – 2.83 (m, 1H), 2.63 – 2.53 (m, 2H), 2.25 (s, 6H), 2.14 – 1.89 (m, 18H).

3 protons in aliphatic area overlaps with water

Example 27: 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1-(6-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)hexyl)-3,5-dimethyl-1*H*-pyrazol-4-yl)-1-(2-morpholinoethyl)-1*H*-indole-2-carboxylic acid (229)



Step A

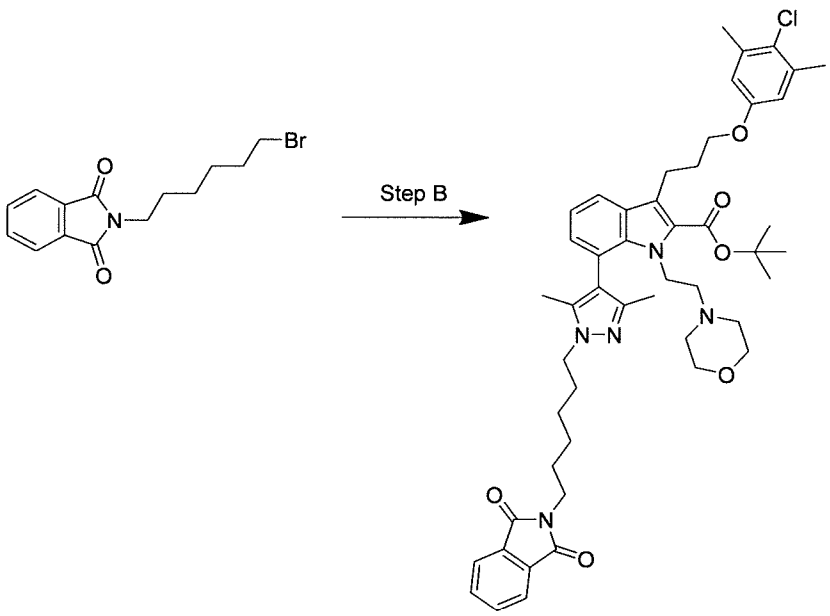


Potassium phthalimide (5 g, 27 mmol) was added in 4 parts to a solution of 1,6-dibromohexane (8.282 mL, 54 mmol) dissolved in boiling acetone (300 mL) and the reaction mixture was allowed to stir at 60°C for 24 h under nitrogen. After complete consumption of the starting material the

solution was cooled to room temperature. The white solid obtained was removed by filtration and the filtrate was concentrated under reduced pressure to get the crude compound, which was then purified by column chromatography (SiO_2, 10% EtOAc in DCM) to get (8 g, 25.8 mmol, 95%) of 2-(6-bromohexyl)isoindoline-1,3-dione as white solid.

LCMS (ESI+): m/z 310.2 $[M+H]^+$

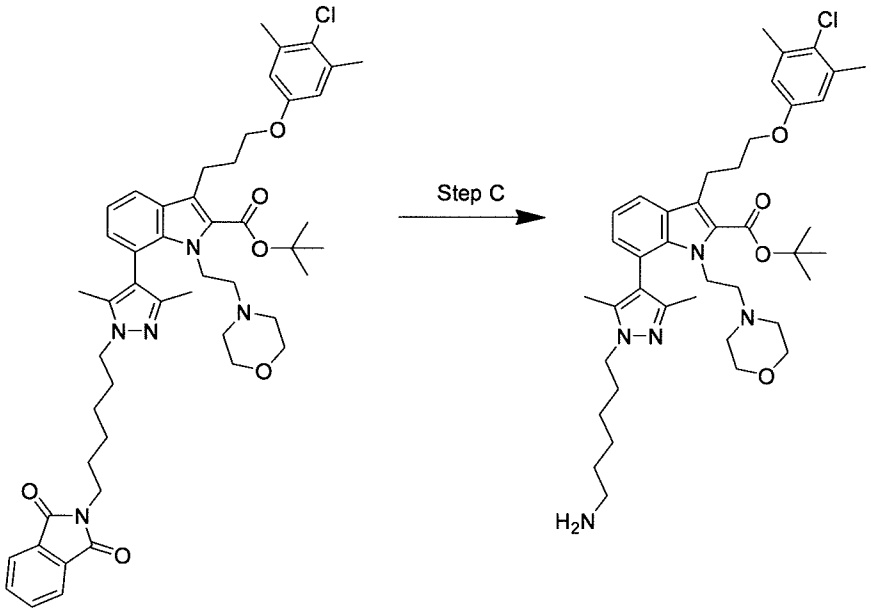
Step B



To a stirred solution of *tert*-butyl 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(3,5-dimethyl-1*H*-pyrazol-4-yl)-1-(2-morpholinoethyl)-1*H*-indole-2-carboxylate (650 mg, 1.05 mmol) in DMF (8 mL) in a pressure tube was added 2-(6-bromohexyl)isoindoline-1,3-dione (650 mg, 2.1 mmol) followed by cesium carbonate (1 g, 3.15 mmol) and the reaction mixture was allowed to stir at 100°C for 16 h. After complete consumption of the starting material the reaction mixture was diluted with EtOAc, washed successively with water and brine, the organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to get the crude compound, which was then purified by column chromatography (SiO_2, 80% EtOAc in DCM) to get *tert*-butyl 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1-(6-(1,3-dioxoisoindolin-2-yl)hexyl)-3,5-dimethyl-1*H*-pyrazol-4-yl)-1-(2-morpholinoethyl)-1*H*-indole-2-carboxylate (650 mg, crude) as gummy solid.

LCMS (ESI+): m/z 851.0 $[M+H]^+$

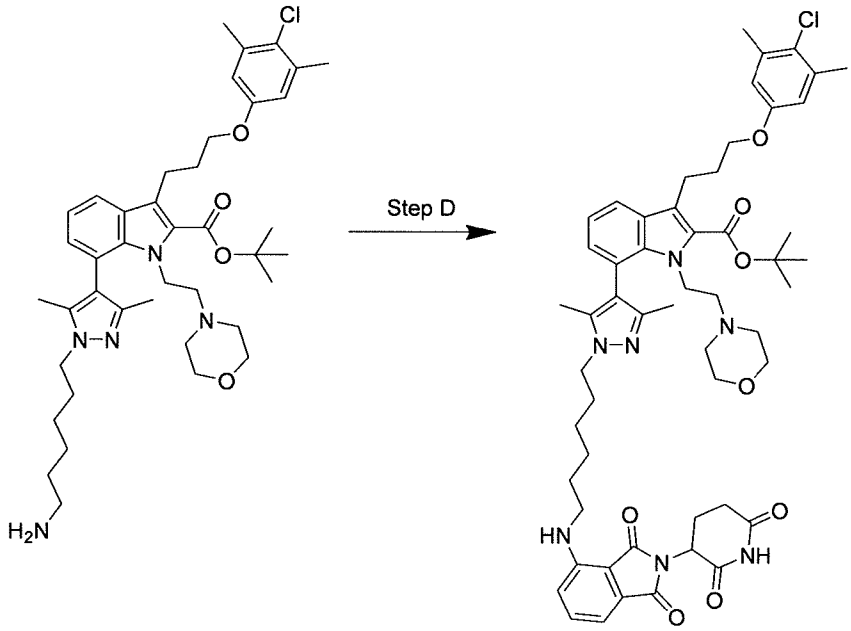
Step C



A mixture of *tert*-butyl 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1-(6-(1,3-dioxoisoindolin-2-yl)hexyl)-3,5-dimethyl-1*H*-pyrazol-4-yl)-1-(2-morpholinoethyl)-1*H*-indole-2-carboxylate (500 mg, crude) and hydrazine hydrate (0.3 mL, 6.7 mmol) in 6 mL of dry *tert*-butanol was refluxed for 2 h at 140°C under nitrogen. Then it was allowed to cool down to room temperature. Volatiles were evaporated under reduced pressure. The residue was then dissolved in DCM, washed successively with water and brine, the organic layer was dried over $MgSO_4$, filtered, and evaporated under reduced pressure to get the crude compound which was purified by column chromatography (amine SiO_2, 2% MeOH in DCM) to get *tert*-butyl 7-(1-(6-aminohexyl)-3,5-dimethyl-1*H*-pyrazol-4-yl)-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-(2-morpholinoethyl)-1*H*-indole-2-carboxylate (300 mg, 0.42 mmol, 70%) as brown liquid.

LCMS (ESI+): m/z 720.9 $[M+H]^+$

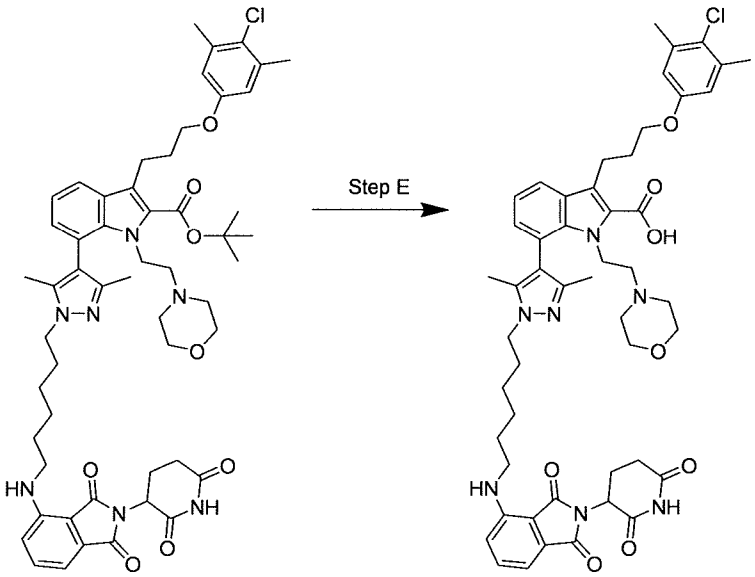
Step D



To a well stirred solution of *tert*-butyl 7-(1-(6-aminohexyl)-3,5-dimethyl-1*H*-pyrazol-4-yl)-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-(2-morpholinoethyl)-1*H*-indole-2-carboxylate (300 mg, 0.38 mmol) in DMSO (3 mL) was added 2-(2,6-dioxopiperidin-3-yl)-4-fluoroisoindoline-1,3-dione (158 mg, 0.57 mmol), followed by DIPEA (133 µL, 0.76 mmol) and the reaction mixture was allowed to stir 90°C for 16 h under nitrogen. After complete consumption of the starting material the reaction mixture was diluted with EtOAc, washed successively with water and brine solution, the organic layer was dried over sodium sulphate and evaporated under reduced pressure to get the crude compound, which was then purified by column chromatography (amine SiO_2, 80% MeOH in DCM) to get *tert*-butyl 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1-(6-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)hexyl)-3,5-dimethyl-1*H*-pyrazol-4-yl)-1-(2-morpholinoethyl)-1*H*-indole-2-carboxylate (220 mg, 0.22 mmol, 59%) as yellow solid.

LCMS (ESI+): m/z 977.1 $[M+H]^+$

Step E

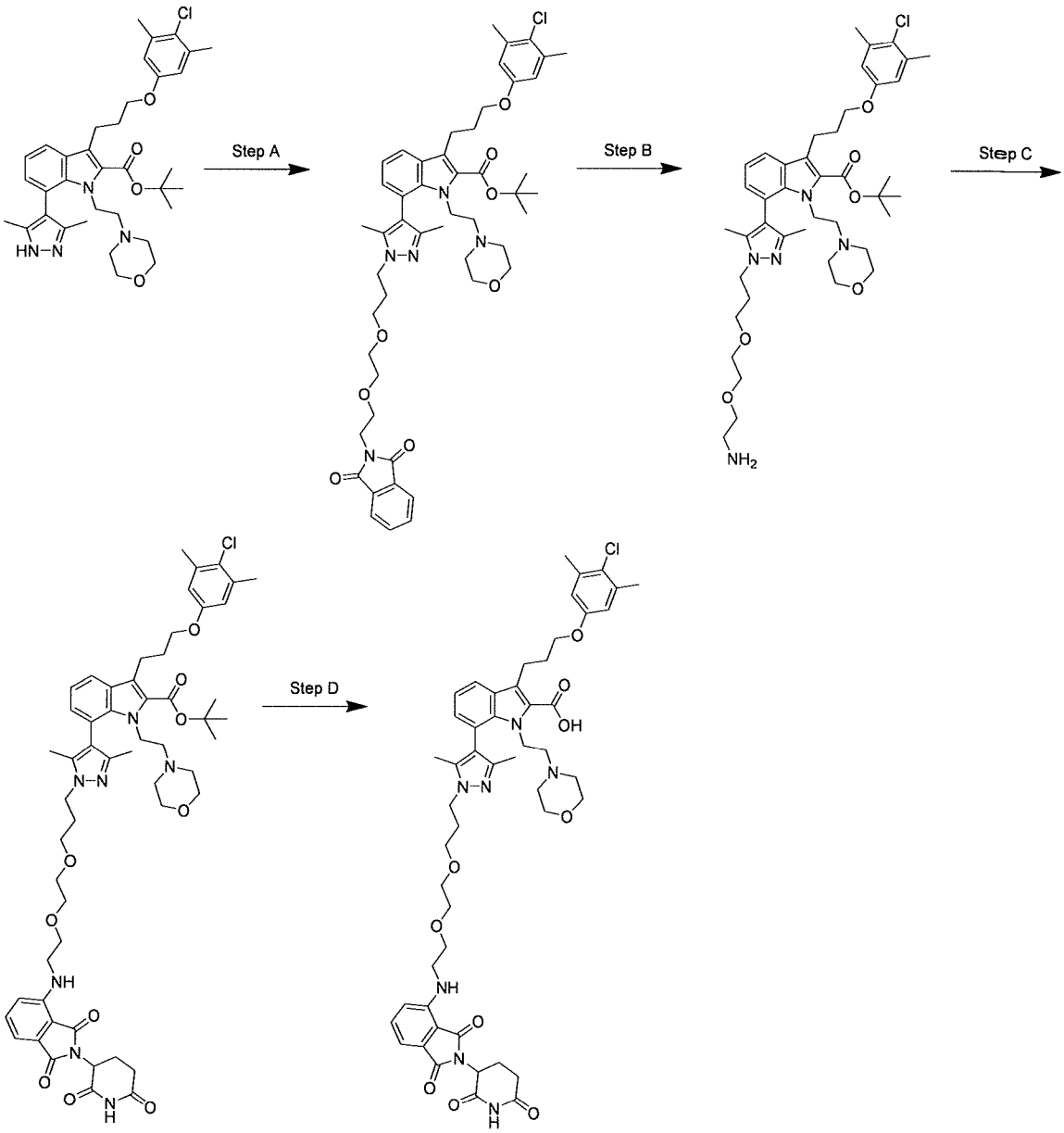


To a well stirred solution of *tert*-butyl 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1-(6-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)hexyl)-3,5-dimethyl-1*H*-pyrazol-4-yl)-1-(2-morpholinoethyl)-1*H*-indole-2-carboxylate (220 mg, 0.23 mmol) in dioxane (5 mL) was added 5 mL of 4M HCl in dioxane and the reaction mixture was allowed to stir at room temperature for 28 h. After complete consumption of the starting material the reaction mixture was evaporated under reduced pressure to get the crude compound, which was then purified by preparative HPLC (10mM ammonium acetate in H_2O and MeCN) to get 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1-(6-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)hexyl)-3,5-dimethyl-1*H*-pyrazol-4-yl)-1-(2-morpholinoethyl)-1*H*-indole-2-carboxylic acid (70 mg, 0.08 mmol, 34%) as yellow solid.

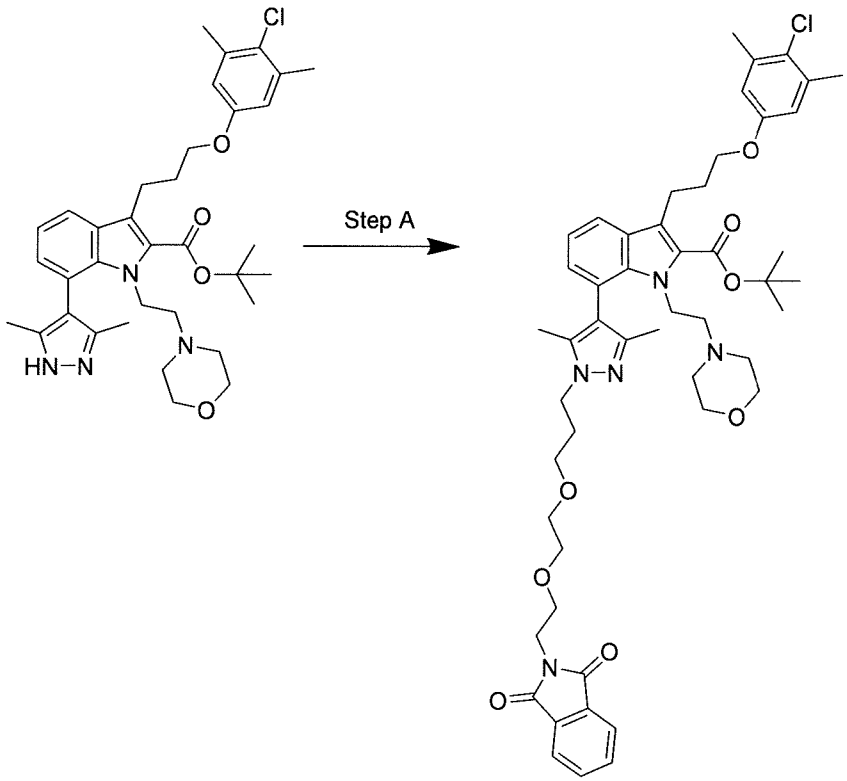
LCMS (ESI+): m/z 920.4 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO) δ 13.29 (s, 1H), 11.08 (s, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.58 (t, *J* = 7.8 Hz, 1H), 7.09 (t, *J* = 7.4 Hz, 2H), 7.02 (d, *J* = 7.0 Hz, 1H), 6.92 (d, *J* = 7.0 Hz, 1H), 6.73 (s, 2H), 6.56 (t, *J* = 6.1 Hz, 1H), 5.04 (dd, *J* = 12.8, 5.3 Hz, 1H), 4.41 – 4.22 (m, 2H), 3.99 (dt, *J* = 12.3, 6.8 Hz, 4H), 3.37 (t, *J* = 4.6 Hz, 4H), 3.29 (s, 2H), 3.14 (t, *J* = 7.5 Hz, 2H), 2.88 (td, *J* = 17.4, 15.4, 5.2 Hz, 1H), 2.63 – 2.53 (m, 2H), 2.25 (s, 6H), 2.08 – 1.89 (m, 15H), 1.76 (t, *J* = 7.2 Hz, 2H), 1.66 – 1.54 (m, 2H), 1.47 – 1.28 (m, 4H).

Example 28: 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1-(3-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-inden-4-yl)amino)ethoxy)ethoxy)propyl)-3,5-dimethyl-1*H*-pyrazol-4-yl)-1-(2-morpholinoethyl)-1*H*-indole-2-carboxylic acid (230)

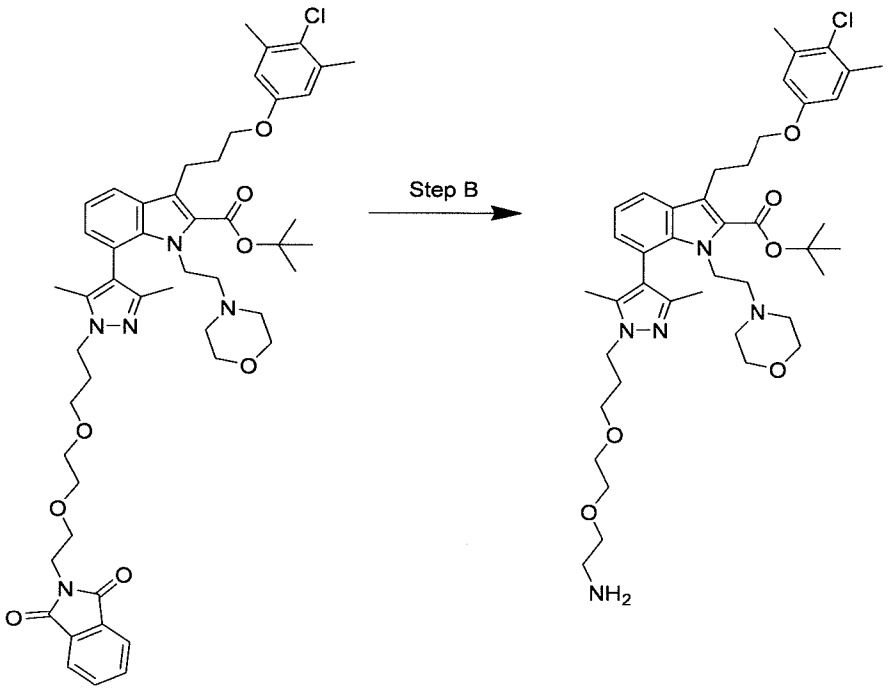


Step A



To a stirred solution of *tert*-butyl 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(3,5-dimethyl-1*H*-pyrazol-4-yl)-1-(2-morpholinoethyl)-1*H*-indole-2-carboxylate (600 mg, 1.15 mmol) in dry DMF (5 mL) was added NaH (56 mg, 2.3 mmol) portion wise at 0°C under nitrogen. The reaction mixture was allowed to at the same temperature for 1 h. After that to it was added 2-(2-(2-(3-bromopropoxy)ethoxy)ethyl)isoindoline-1,3-dione (1.2 g, 3.45 mmol) at 0°C and reaction mixture was allowed to stir at room temperature for 16 h. After complete consumption of the starting material (monitored by TLC and LCMS) the excess NaH was quenched using ice, the volatiles were evaporated under reduced pressure to get the crude compound, which was then purified by column chromatography (SiO_2, 2% MeOH in DCM) to get *tert*-butyl 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1-(3-(2-(2-(1,3-dioxoisoindolin-2-yl)ethoxy)ethoxy)propyl)-3,5-dimethyl-1*H*-pyrazol-4-yl)-1-(2-morpholinoethyl)-1*H*-indole-2-carboxylate (400 mg , 0.44 mmol, 39%) as gummy solid.

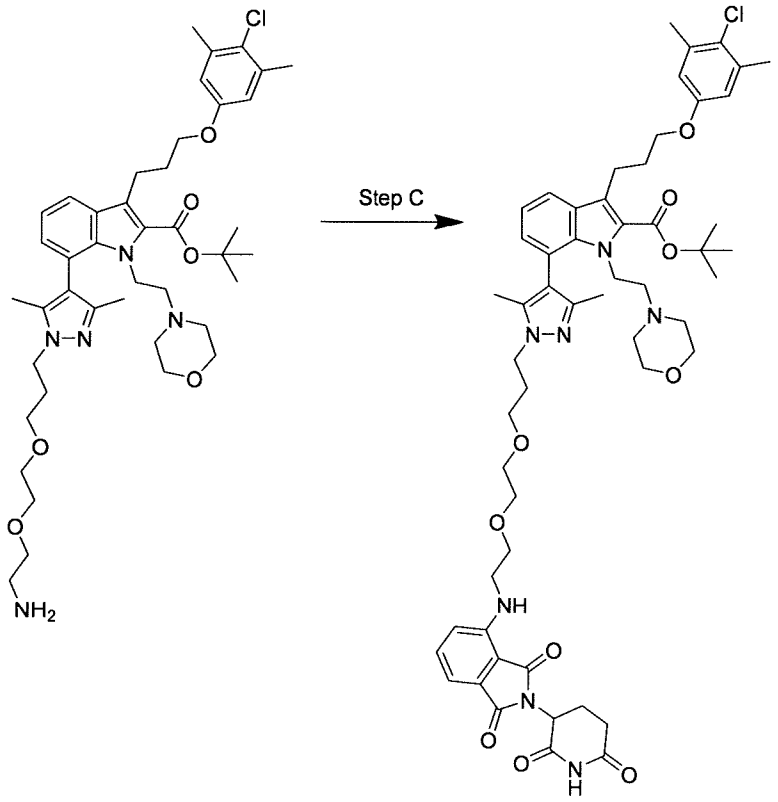
Step B



A mixture of *tert*-butyl 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1-(3-(2-(2-(1,3-dioxoisoindolin-2-yl)ethoxy)ethoxy)propyl)-3,5-dimethyl-1*H*-pyrazol-4-yl)-1-(2-morpholinoethyl)-1*H*-indole-2-carboxylate (400 mg, 0.44 mmol) and hydrazine hydrate (0.43 mL, 8.75 mmol) in 10 mL of dry *tert*-butanol was refluxed for 16 h at 100°C under nitrogen. Then it was allowed to cool down to room temperature, volatiles were removed under reduced pressure, the residue was dissolved in DCM, washed successively with water and brine. The organic layer was dried over $MgSO_4$, filtered, and evaporated under reduced pressure to get 350 mg of crude compound (*tert*-butyl 7-(1-(3-(2-(2-aminoethoxy)ethoxy)propyl)-3,5-dimethyl-1*H*-pyrazol-4-yl)-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-(2-morpholinoethyl)-1*H*-indole-2-carboxylate) which was used for the next step without further purification.

LCMS (ESI+): m/z 767.0 $[M+H]^+$

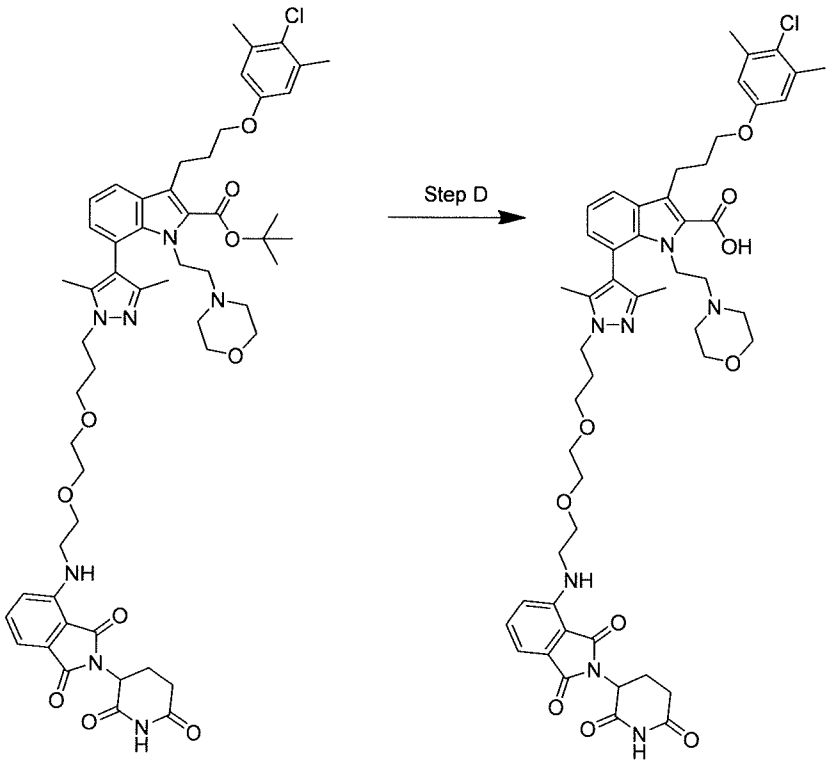
Step C



To a well stirred solution of *tert*-butyl 7-(1-(3-(2-(2-aminoethoxy)ethoxy)propyl)-3,5-dimethyl-1*H*-pyrazol-4-yl)-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-(2-morpholinoethyl)-1*H*-indole-2-carboxylate (350 mg) in DMSO (15 mL) was added 2-(2,6-dioxopiperidin-3-yl)-4-fluoroisoindoline-1,3-dione (190 mg, 0.69 mmol), followed by DIPEA (160 µL, 0.9 mmol) and the reaction mixture was allowed to stir 90°C for 16 h under nitrogen. After complete consumption of the starting material the reaction mixture was diluted with EtOAc, washed successively with water and brine solution, the organic layer was dried over sodium sulphate and evaporated under reduced pressure to get the crude compound, which was then purified by column chromatography (amine SiO_2, 80% EtOAc in DCM) to get of *tert*-butyl 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1-(3-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-inden-4-yl)amino)ethoxy)ethoxy)propyl)-3,5-dimethyl-1*H*-pyrazol-4-yl)-1-(2-morpholinoethyl)-1*H*-indole-2-carboxylate (150 mg, 0.15 mmol, 32%) as yellow solid.

LCMS (ESI+): m/z 1023.2 $[M+H]^+$

Step D

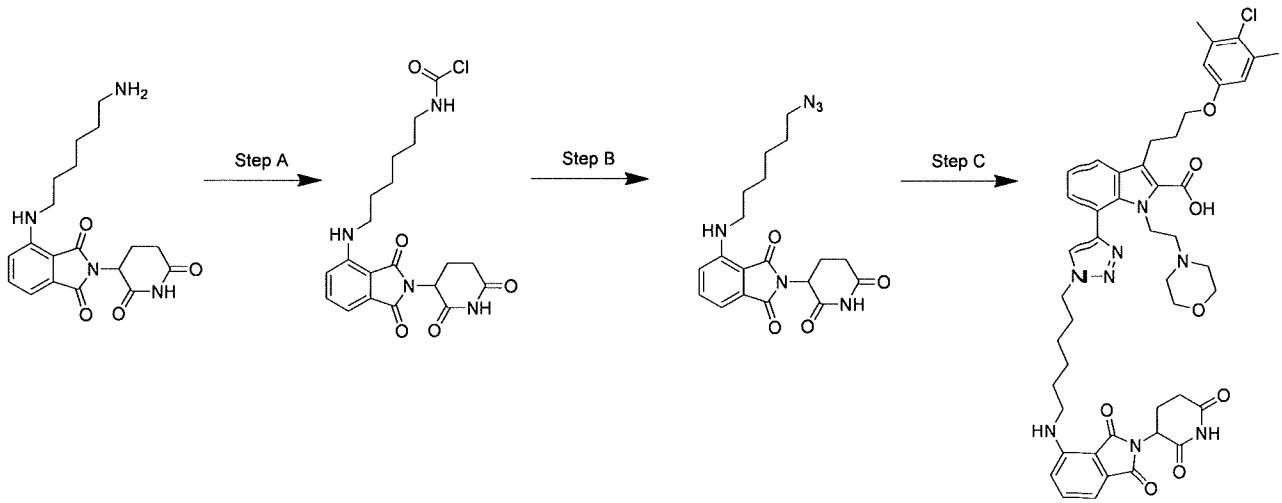


To a well stirred solution of *tert*-butyl 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1-(3-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-inden-4-yl)amino)ethoxy)ethoxy)propyl)-3,5-dimethyl-1*H*-pyrazol-4-yl)-1-(2-morpholinoethyl)-1*H*-indole-2-carboxylate (150 mg, 0.19 mmol) in dioxane (5 mL) was added 5 mL of 4M HCl in dioxane and the reaction mixture was allowed to stir at room temperature for 28 h. After complete consumption of the starting material the reaction mixture was evaporated under reduced pressure to get the crude compound, which was then divided into two parts. Half of material was purified by reverse phase prep-HPLC (10mM ammonium acetate in water and acetonitrile) to get of 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1-(3-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-inden-4-yl)amino)ethoxy)ethoxy)propyl)-3,5-dimethyl-1*H*-pyrazol-4-yl)-1-(2-morpholinoethyl)-1*H*-indole-2-carboxylic acid as free base (9 mg, 0.009 mmol, 4.7%).

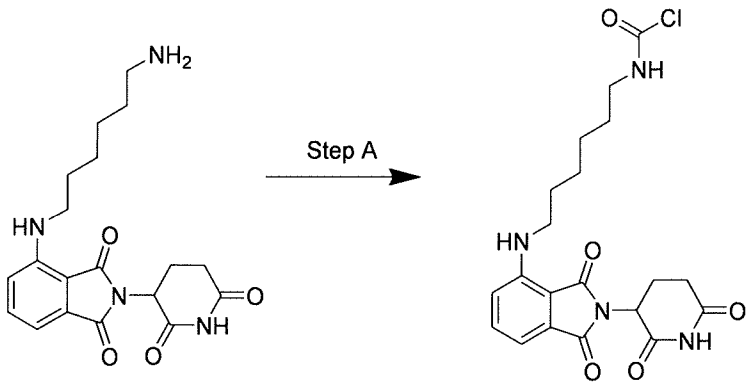
LCMS (ESI+): m/z 966.3 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO) δ 11.10 (s, 1H), 7.73 (d, *J* = 8.0 Hz, 1H), 7.56 (t, *J* = 7.8 Hz, 1H), 7.14 (t, *J* = 7.9 Hz, 2H), 7.05 – 6.98 (m, 2H), 6.76 (s, 2H), 6.61 (t, *J* = 5.7 Hz, 1H), 5.04 (dd, *J* = 12.8, 5.3 Hz, 1H), 4.57 (s, 2H), 4.14 – 3.94 (m, 4H), 3.93 – 3.68 (m, 1H), 3.60 (ddd, *J* = 24.0, 14.7, 5.1 Hz, 8H), 3.45 (dt, *J* = 10.3, 7.9 Hz, 6H), 3.19 (t, *J* = 7.2 Hz, 2H), 2.93 – 2.81 (m, 1H), 2.57 (dd, *J* = 18.3, 2.6 Hz, 2H), 2.30 – 2.19 (m, 7H), 2.12 – 1.85 (m, 12H), 1.76 – 1.52 (m, 1H), 1.17 – 1.06 (m, 2H).

Example 29: 3-[3-(4-chloro-3,5-dimethylphenoxy)propyl]-7-(1-{[(6-{[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl]amino}hexyl)carbamoyl]methyl}-1*H*-1,2,3-triazol-4-yl)-1-[2-(morpholin-4-yl)ethyl]-1*H*-indole-2-carboxylic acid (231)



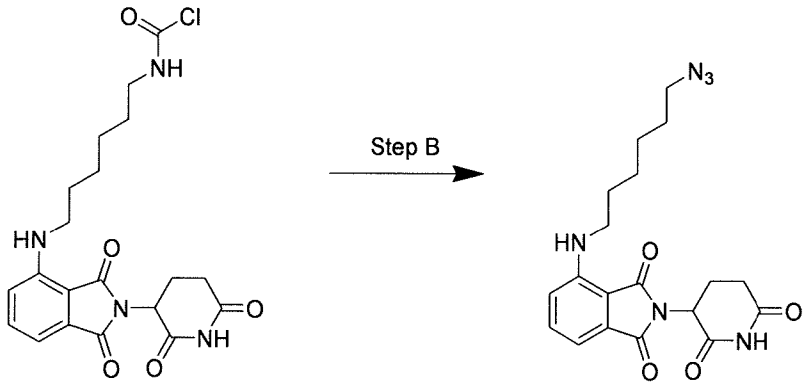
Step A



DIPEA (0.213 mL, 1.223 mmol) was added to a stirred solution of 4-[(6-aminohexyl)amino]-2-(2,6-dioxopiperidin-3-yl)-2,3-dihydro-1*H*-isoindole-1,3-dione hydrochloride (100.0 mg, 0.245 mmol) in DMF (5.0 mL). Subsequently, the mixture was purging by argon for 10 min and chloroacetyl chloride (0.021 mL, 0.269 mmol) was added. The resulting mixture was stirring at RT for 24 h. After the reaction was completed (monitored by LCMS), the solvent was evaporated and the crude material was purified by flash chromatography (SiO_2, 20% acetone in DCM). The final product 2-chloro-*N*-(6-{[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl]amino}hexyl)acetamide (65.7 mg, 0.146 mmol, 59%) was a yellow oil.

LCMS (ESI+): m/z 449.2 $[M+H]^+$

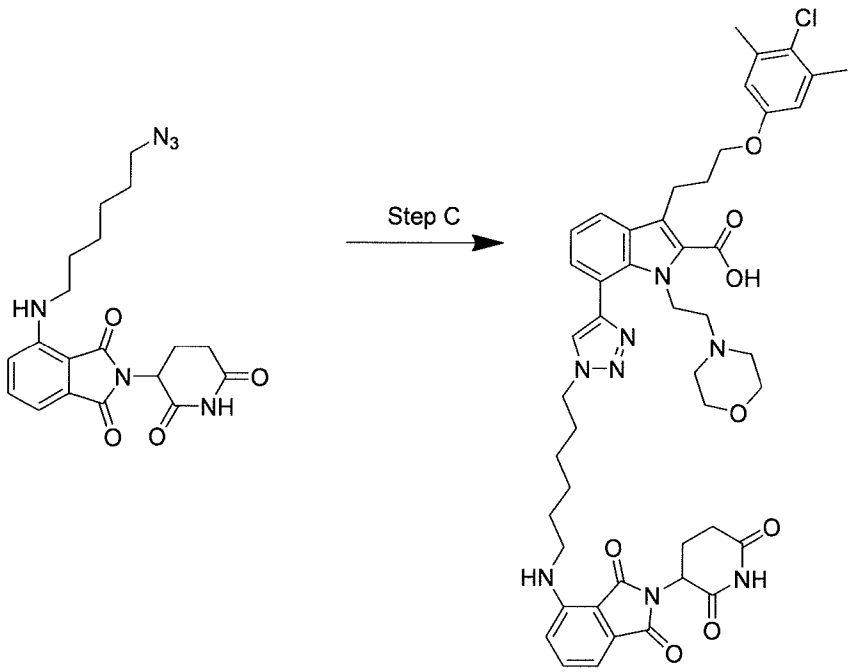
Step B



2-Chloro-*N*-(6-{[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl]amino}hexyl)acetamide (64.0 mg, 0.143 mmol) and NaN_3 (64.9 mg, 0.998 mmol) were dissolved in DMF (2.0 mL). The reaction mixture was stirring in room temperature for 24 h. After this time to the reaction mixture was added H_2O (2 mL) and stirred 15 min. DMF and H_2O was evaporated and the resultant residue was partitioned between DCM and H_2O. The organic layer was further washed with brine, dried over Na_2SO_4, filtered and evaporated. The final product 2-azido-*N*-(6-{[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl]amino}hexyl)acetamide (45.0 mg, 0.099 mmol, 69%) was a yellow solid.

LCMS (ESI+): m/z 455.9 $[M+H]^+$

Step C



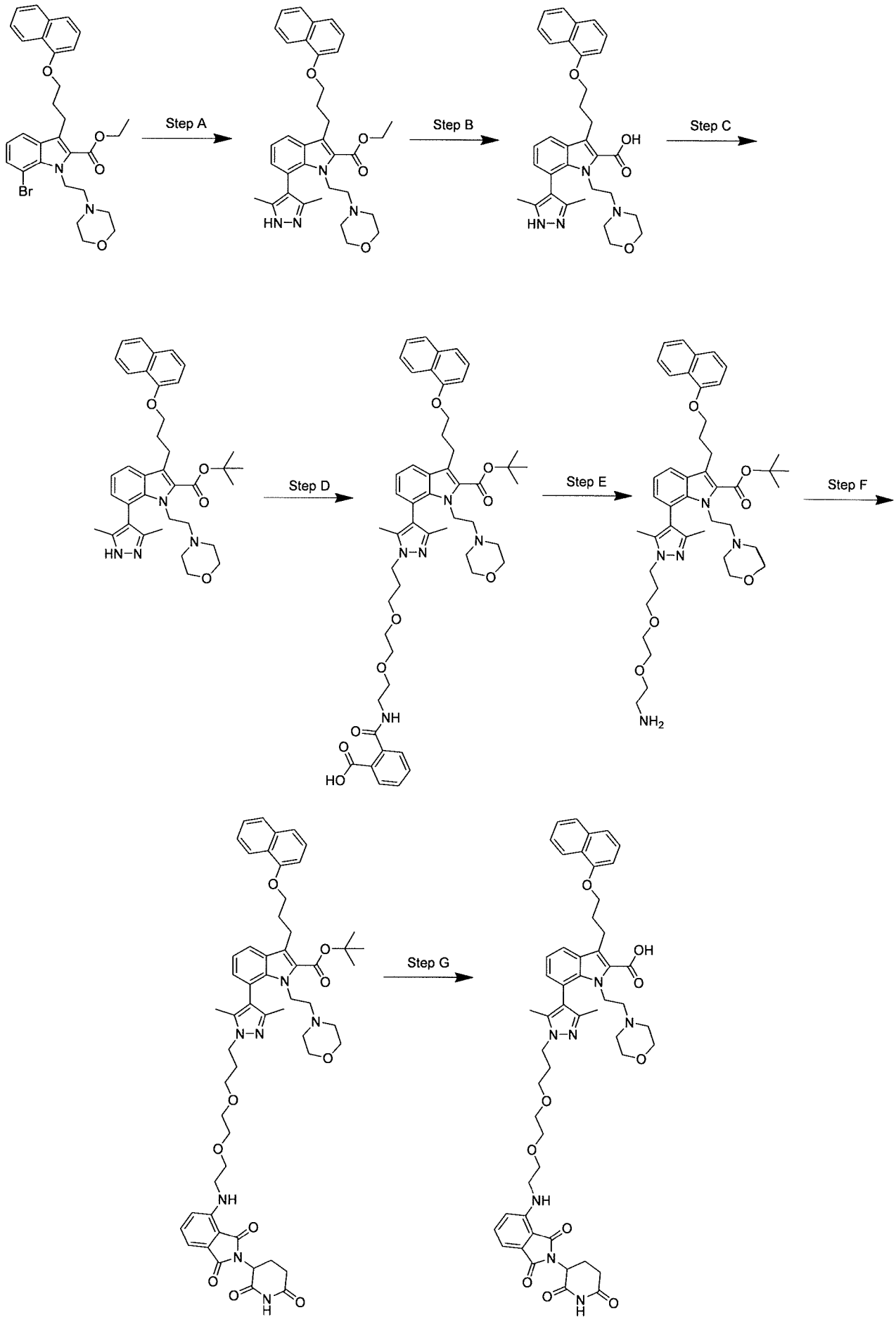
To a solution of 2-azido-*N*-(6-{[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl]amino}hexyl)acetamide (10.1 mg, 0.022 mmol) and 3-[3-(4-chloro-3,5-

dimethylphenoxy)propyl]-7-ethynyl-1-[2-(morpholin-4-yl)ethyl]-1*H*-indole-2-carboxylic acid (10.0 mg, 0.020 mmol) in mixture of H_2O (0.500 mL), EtOH (0.500 mL) and DCM (0.500 mL) was added L-ascorbic acid (3.6 mg, 0.020 mmol) and $CuSO_4 \times 5H_2O$ (2.5 mg, 0.010 mmol). Reaction was stirred at RT and continued for 4 days. Therefore, the solvents were evaporated. Resultant residue was dissolved in DMSO, filtrated and purified by preparative HPLC (H_2O:MeCN + 0.1% FA). The final product 3-[3-(4-chloro-3,5-dimethylphenoxy)propyl]-7-(1-{[(6-{[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl]amino}hexyl)carbamoyl]methyl}-1*H*-1,2,3-triazol-4-yl)-1-[2-(morpholin-4-yl)ethyl]-1*H*-indole-2-carboxylic acid (13.4 mg, 0.014 mmol, 69%) was a yellow solid.

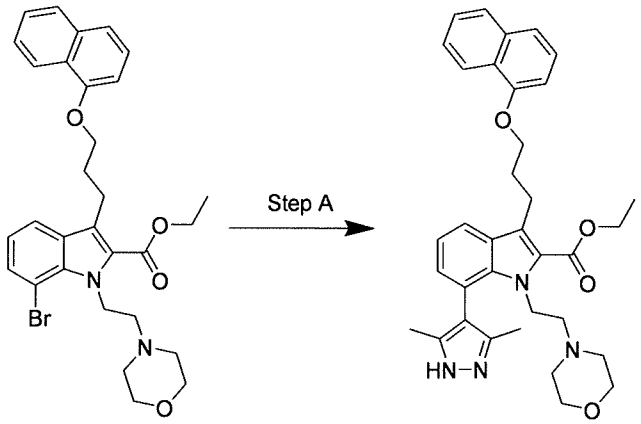
LCMS (ESI+): m/z 950.8 $[M+H]^+$

^1H NMR (500 MHz, DMSO) δ 13.44 (s, 1H), 11.08 (s, 1H), 8.35 (t, *J* = 5.4 Hz, 1H), 8.32 (s, 1H), 7.74 (s, 1H), 7.57 (t, *J* = 7.8 Hz, 1H), 7.14 – 7.07 (m, 3H), 7.01 (d, *J* = 7.0 Hz, 1H), 6.74 (s, 2H), 6.54 (t, *J* = 5.7 Hz, 1H), 5.16 (s, 2H), 5.04 (dd, *J* = 12.7, 5.4 Hz, 1H), 4.40 (t, *J* = 5.6 Hz, 2H), 3.95 (t, *J* = 6.3 Hz, 2H), 3.40 – 3.37 (m, 4H), 3.18 – 3.11 (m, 4H), 2.92 – 2.83 (m, 1H), 2.62 – 2.53 (m, 2H), 2.26 (s, 6H), 2.07 – 1.99 (m, 9H), 1.62 – 1.55 (m, 2H), 1.51 – 1.44 (m, 2H), 1.36 (d, *J* = 5.0 Hz, 4H), 1.24 (s, 2H).

Example 30: 7-(1-(3-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)propyl)-3,5-dimethyl-1*H*-pyrazol-4-yl)-1-(2-morpholinoethyl)-3-(3-(naphthalen-1-yloxy)propyl)-1*H*-indole-2-carboxylic acid (232)


Step A
Step B
Step C
Step D
Step E
Step F
Step G

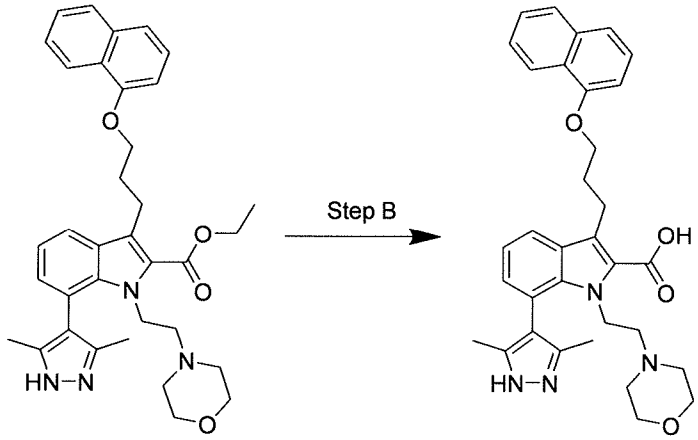
Step A



To a stirred solution of ethyl 7-bromo-1-(2-morpholinoethyl)-3-(3-(naphthalen-1-yloxy)propyl)-1*H*-indole-2-carboxylate (10 g, 17.68 mmol) in dioxane (150 mL) and water (30 mL) were added 3,5-dimethyl-1-(tetrahydro-2*H*-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (12 g, 53.05 mmol) and K_2CO_3 (9.7 g, 70.7 mmol). The mixture was deoxygenated with argon and to it was added Pd(dppf)Cl_2 (1.9 g, 2.65 mmol) under argon atmosphere. The reaction mixture was heated under reflux for 16 h. After complete consumption of the starting material the reaction mixture was filtered through celite pad and the solvents were evaporated under reduced pressure get the crude material. It was then diluted with EtOAc and washed successively with water and brine The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to get the crude compound, which was then purified by column chromatography (SiO_2, 5% MeOH in DCM) to get ethyl 7-(3,5-dimethyl-1*H*-pyrazol-4-yl)-1-(2-morpholinoethyl)-3-(3-(naphthalen-1-yloxy)propyl)-1*H*-indole-2-carboxylate (6 g, 10.34 mmol, 58.5%) as brown solid.

LCMS (ESI+): m/z 581.0 $[M+H]^+$

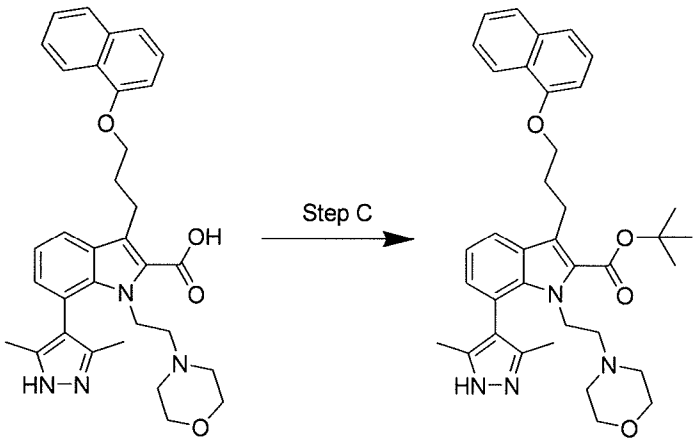
Step B



Ethyl 7-(3,5-dimethyl-1*H*-pyrazol-4-yl)-1-(2-morpholinoethyl)-3-(3-(naphthalen-1-yloxy)propyl)-1*H*-indole-2-carboxylate (5 g, 8.4 mmol) was dissolved in EtOH (80 mL) and a solution of NaOH (1.2 g, 29.5 mmol) in water (20 mL) was added to it. The mixture was heated under reflux for 3 h. After complete consumption of the starting material the reaction mixture was cooled down to room temperature and solvents were evaporated under reduced pressure. It was then diluted with water, washed with EtOAc. Aqueous layer was carefully acidified using 1M HCl to pH=3, extracted with DCM (3×50 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to afford 7-(3,5-dimethyl-1*H*-pyrazol-4-yl)-1-(2-morpholinoethyl)-3-(3-(naphthalen-1-yloxy)propyl)-1*H*-indole-2-carboxylic acid (3 g, 5.43 mmol, 64%) as dark brown gummy solid.

LCMS (ESI+): m/z 553.2 $[M+H]^+$

Step C

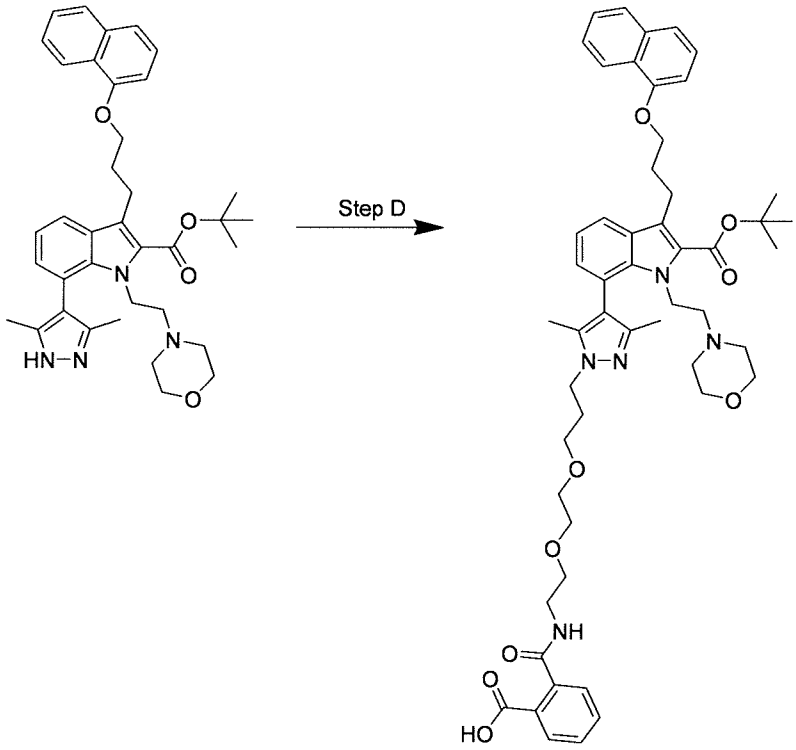


7-(3,5-dimethyl-1*H*-pyrazol-4-yl)-1-(2-morpholinoethyl)-3-(3-(naphthalen-1-yloxy)propyl)-1*H*-indole-2-carboxylic acid (2 g, 3.6 mmol) was suspended in toluene (20 mL) and the mixture was heated to reflux under nitrogen. *N*,*N*-dimethylformamide di-*tert*-butyl acetal (3 mL, 14.5 mmol) was added drop-wise to the refluxing mixture. Refluxing was continued for an

additional 16 h under nitrogen. After that time another 1.5 mL (7.3 mmol) of *N,N*-dimethylformamide di-*tert*-butyl acetal was added to it and the reaction was continued for another 24 h. Reaction mixture was then diluted with EtOAc, washed successively with sodium bicarbonate (saturated aqueous solution), water and brine. Organic layer was dried over sodium sulphate and evaporated under reduced pressure to get the crude compound, which was then purified by column chromatography (SiO_2, 6% MeOH in DCM) to get *tert*-butyl 7-(3,5-dimethyl-1*H*-pyrazol-4-yl)-1-(2-morpholinoethyl)-3-(3-(naphthalen-1-yloxy)propyl)-1*H*-indole-2-carboxylate (1.4 g, 2.3 mmol, 63%) as brown sticky solid.

LCMS (ESI+): m/z 609.0 $[M+H]^+$

Step D

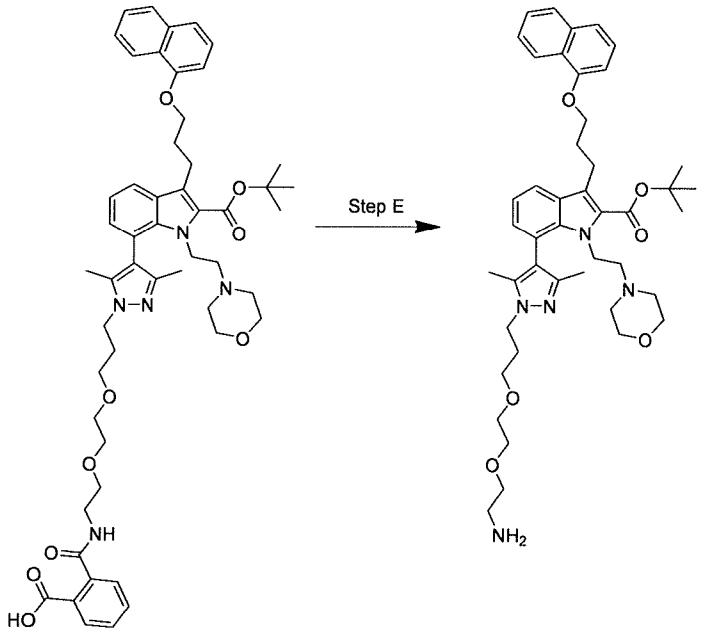


To a solution of *tert*-butyl 7-(3,5-dimethyl-1*H*-pyrazol-4-yl)-1-(2-morpholinoethyl)-3-(3-(naphthalen-1-yloxy)propyl)-1*H*-indole-2-carboxylate (500 mg, 0.82 mmol) in DMF (15 mL) at 0°C was added sodium hydride (197 mg, 8.2 mmol) portion wise under nitrogen and the reaction mixture was allowed to stir at the same temperature for 1 h, after that to the reaction mixture was added 2-(2-(2-(3-bromopropoxy)ethoxy)ethyl)isoindoline-1,3-dione (585 mg, 1.64 mmol) dissolved in DMF (5 mL) at 0°C and the reaction mixture was allowed to stir at room temperature for 16 h under nitrogen. After complete consumption of the starting material the reaction mixture was again cooled to 0°C and the excess of NaH was quenched with ammonium chloride (saturated

aqueous solution). The volatiles were evaporated under reduced pressure to get the crude 2-((2-(2-(3-(4-(2-(*tert*-butoxycarbonyl)-1-(2-morpholinoethyl)-3-(3-(naphthalen-1-yloxy)propyl)-1*H*-indol-7-yl)-3,5-dimethyl-1*H*-pyrazol-1-yl)propoxy)ethoxy)ethyl)carbamoyl)benzoic acid which was used for the next step without further purification.

LCMS (ESI+): m/z 903.1 $[M+H]^+$

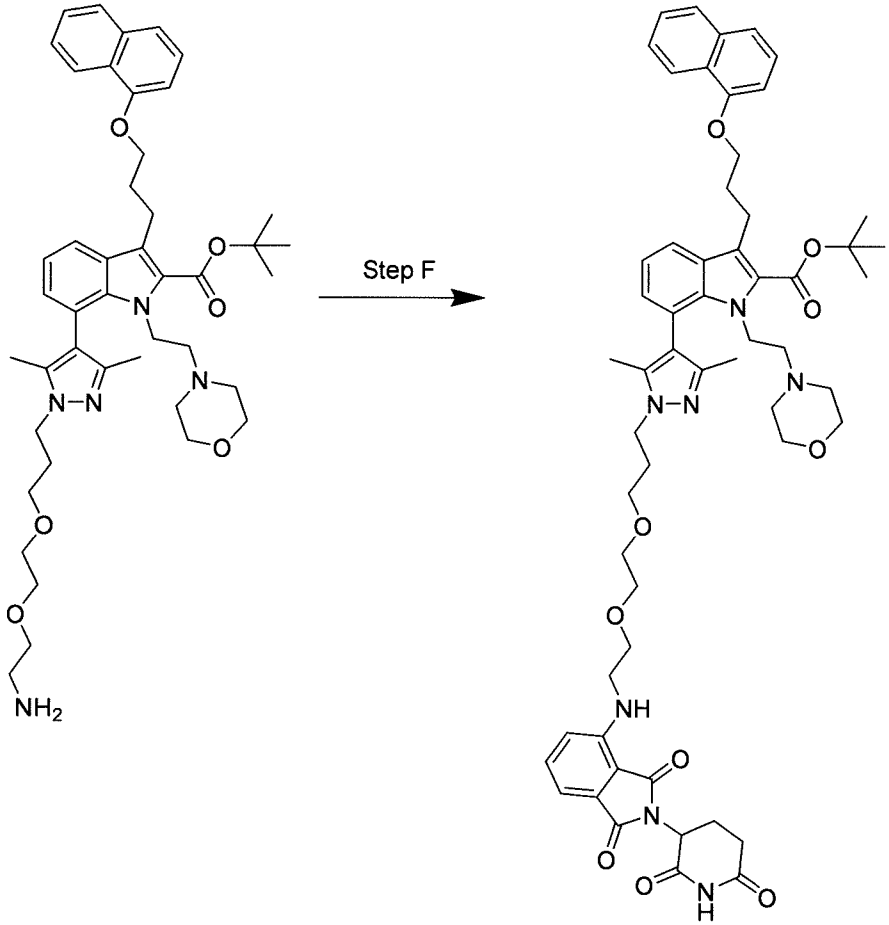
Step E



A mixture of 2-((2-(2-(3-(4-(2-(*tert*-butoxycarbonyl)-1-(2-morpholinoethyl)-3-(3-(naphthalen-1-yloxy)propyl)-1*H*-indol-7-yl)-3,5-dimethyl-1*H*-pyrazol-1-yl)propoxy)ethoxy)ethyl)carbamoyl)benzoic acid (crude product after step D) and hydrazine hydrate (0.326 mL, 6.65 mmol) in 6 mL of dry *tert*-butanol was refluxed for 16 h at 140°C under nitrogen. Then it was allowed to cool down to room temperature and volatiles were evaporated under reduced pressure. The resulting residue was then dissolved in DCM and washed successively with water and brine. The organic layer was dried over magnesium sulfate, filtered and evaporated under reduced pressure to get the crude compound which was purified by column chromatography (amine SiO_2, 2% MeOH in DCM) to get *tert*-butyl 7-(1-(3-(2-(2-aminoethoxy)ethoxy)propyl)-3,5-dimethyl-1*H*-pyrazol-4-yl)-1-(2-morpholinoethyl)-3-(3-(naphthalen-1-yloxy)propyl)-1*H*-indole-2-carboxylate (100 mg, 0.13 mmol, 15% over steps D and E) as brown liquid.

LCMS (ESI+): m/z 754.5 $[M+H]^+$

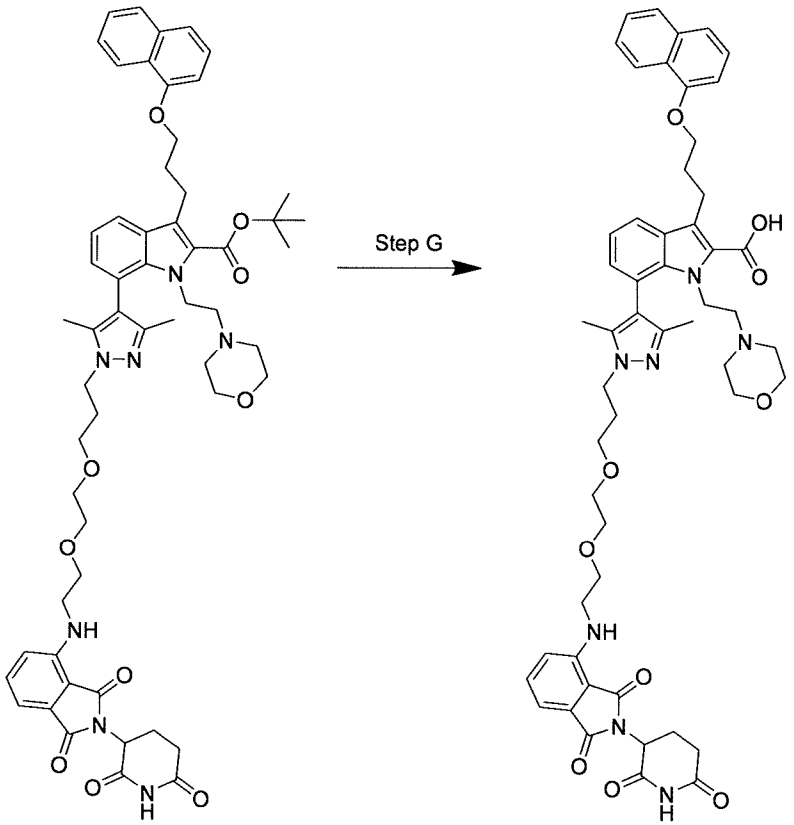
Step F



To a solution of *tert*-butyl 7-(1-(3-(2-(2-aminoethoxy)ethoxy)propyl)-3,5-dimethyl-1*H*-pyrazol-4-yl)-1-(2-morpholinoethyl)-3-(3-(naphthalen-1-yloxy)propyl)-1*H*-indole-2-carboxylate (200 mg, 0.27 mmol) in DMSO (1 mL) was added 2-(2,6-dioxopiperidin-3-yl)-4-fluoroisoindoline-1,3-dione (124 mg, 0.45 mmol), followed by DIPEA (104 µL, 0.6 mmol) and the reaction mixture was allowed to stir in 90°C for 16 h under nitrogen. After complete consumption of the starting material, (monitored by TLC and LCMS), the reaction mixture was diluted with EtOAc, washed successively with water and brine solution, the organic layer was dried over sodium sulphate and evaporated under reduced pressure to get the crude compound, which was then purified by column chromatography (amine SiO_2, 80% EtOAc in DCM) to get *tert*-butyl 7-(1-(3-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)propyl)-3,5-dimethyl-1*H*-pyrazol-4-yl)-1-(2-morpholinoethyl)-3-(3-(naphthalen-1-yloxy)propyl)-1*H*-indole-2-carboxylate (80 mg, 0.08 mmol, 30%) as yellow solid.

LCMS (ESI+): m/z 1010.8 $[M+H]^+$

Step G

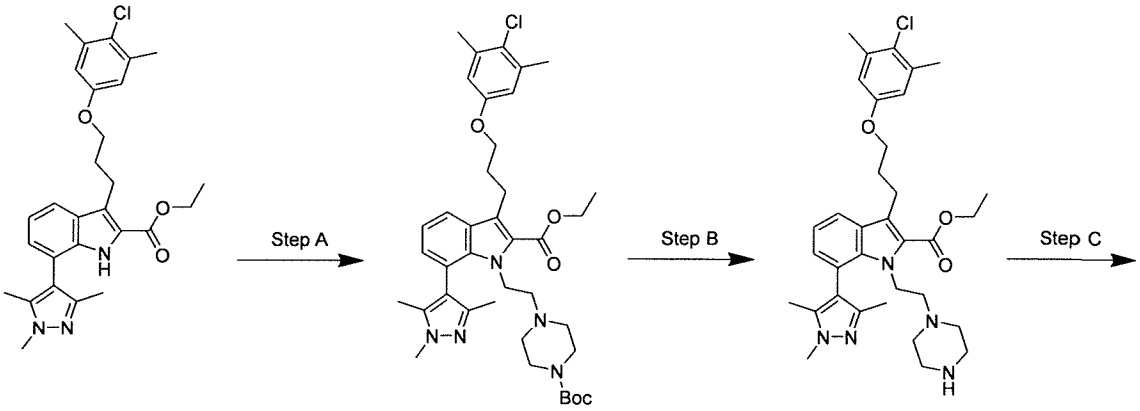


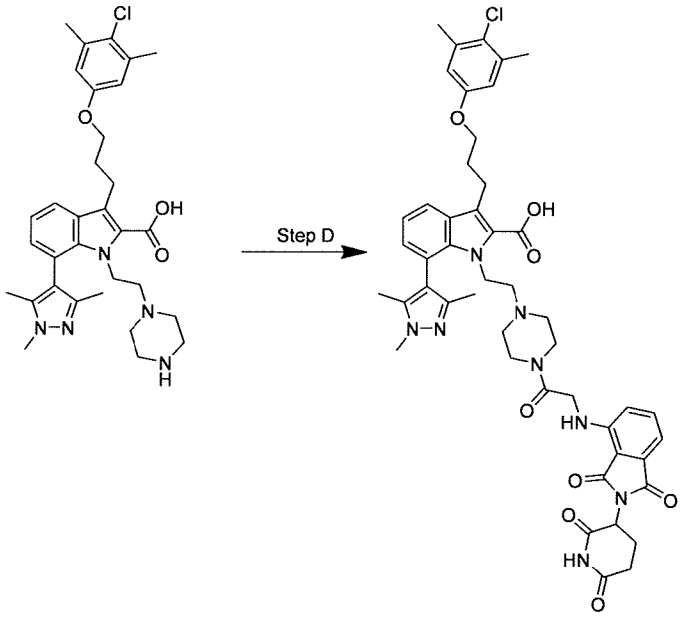
To a well stirred solution of *tert*-butyl 7-(1-(3-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)propyl)-3,5-dimethyl-1*H*-pyrazol-4-yl)-1-(2-morpholinoethyl)-3-(3-(naphthalen-1-yloxy)propyl)-1*H*-indole-2-carboxylate (90 mg, 0.089 mmol) in dioxane (2 mL) was added 4 mL of 4M HCl in dioxane and the reaction mixture was allowed to stir at room temperature for 28 h. After complete consumption of the starting material (monitored by TLC and LCMS) the reaction mixture was evaporated under reduced pressure to get the crude compound, which was then purified by preparative HPLC (H_2O:MeCN + 0.1% HCl) to get 7-(1-(3-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)propyl)-3,5-dimethyl-1*H*-pyrazol-4-yl)-1-(2-morpholinoethyl)-3-(3-(naphthalen-1-yloxy)propyl)-1*H*-indole-2-carboxylic acid (17 mg, 0.018 mmol, 20%) as yellow solid.

LCMS (ESI+): m/z 954.9 $[M+H]^+$

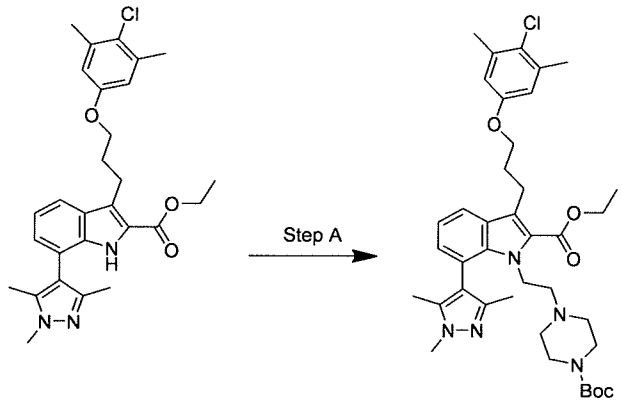
^{1}H NMR (400 MHz, DMSO) δ 10.69 (s, 1H), 8.31 – 8.21 (m, 1H), 7.85 (dd, *J* = 7.0, 2.1 Hz, 1H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.57 (dd, *J* = 8.4, 7.2 Hz, 1H), 7.54 – 7.48 (m, 2H), 7.48 – 7.43 (m, 1H), 7.38 (t, *J* = 7.8 Hz, 1H), 7.16 – 7.10 (m, 2H), 7.04 (d, *J* = 7.1 Hz, 1H), 7.01 – 6.97 (m, 1H), 6.91 (d, *J* = 7.4 Hz, 1H), 5.00 (dd, *J* = 12.2, 5.4 Hz, 1H), 4.57 – 4.44 (m, 2H), 4.28 (t, *J* = 6.3 Hz, 2H), 4.16 – 4.02 (m, 2H), 3.70 (t, *J* = 5.5 Hz, 2H), 3.68 – 3.61 (m, 6H), 3.61 – 3.56 (m, 2H), 3.50 (dd, *J* = 11.4, 5.7 Hz, 4H), 3.38 – 3.32 (m, 3H), 2.91 – 2.80 (m, 1H), 2.70 – 2.53 (m, 8H), 2.29 – 2.24 (m, 2H), 2.08 (s, 3H), 2.07 – 2.01 (m, 3H), 1.99 (s, 3H).

Example 31: 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-(2-(4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)glycyl)piperazin-1-yl)ethyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (233)





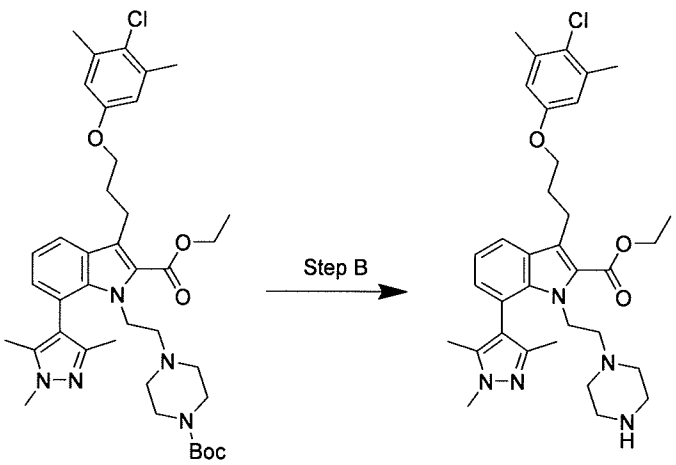
Step A



To a mixture of ethyl 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (300 mg, 0.61 mmol) and K_2CO_3 (252 mg, 1.82 mmol) in DMF (3.00 mL) was added *tert*-butyl 4-(2-bromoethyl)piperazine-1-carboxylate (214 mg, 0.73 mmol). The reaction vessel was sealed, and heated in 80°C for 2 days. After that time solvents were removed under reduced pressure, and the crude mixture was separated between EtOAc and brine. The organic layer was collected, concentrated and dried under reduced pressure. The crude product was purified using column chromatography (SiO_2, 10% Acetone in DCM, then 5% MeOH in DCM) to give ethyl 1-(2-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)ethyl)-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (185.00 mg, 0.262 mmol, 43%) as light brown semisolid.

LCMS (ESI+): m/z 706.7 $[M+H]^+$

Step B

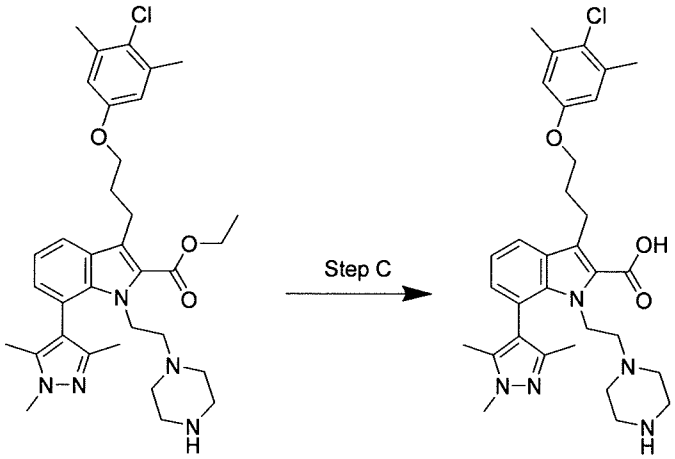


To a solution of ethyl 1-(2-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)ethyl)-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (186 mg,

0.26 mmol) in DCM (3.72 mL) was added trifluoroacetic acid (605 µL, 7.90 mmol) and reaction mixture was stirred in RT overnight. Solvents were removed under reduced pressure, $NaHCO_3$ and DCM were added and crude was extracted with DCM to give ethyl 3-[3-(4-chloro-3,5-dimethylphenoxy)propyl]-1-[2-(piperazin-1-yl)ethyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (140.00 mg, 0.231 mmol, 88%) as light brown semisolid.

LCMS (ESI+): m/z 606.6 $[M+H]^+$

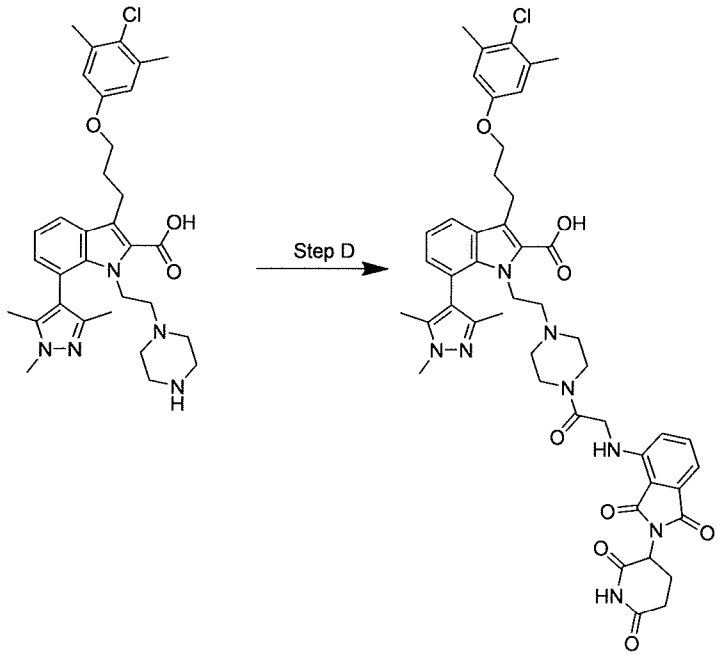
Step C



To a solution of ethyl 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-(2-(piperazin-1-yl)ethyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (0.05 g, 0.08 mmol) in mixture of MeOH:H_2O:THF 1:1:1 (1.20 mL) was added a solution of lithium hydroxide 5% (0.11 mL, 0.23 mmol). The mixture was stirred at 65°C overnight. The reaction was quenched with a solution of NH_4Cl in H_2O, and was stirred at ambient temperature for 1 hour. The mixture was neutralized with dropwise addition of 0.13 M HCl. Solvent was removed in vacuo and the residue was triturated with $CHCl_3$. The inorganic salts were filtered off and the filtrate was concentrated in vacuo to afford 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-(2-(piperazin-1-yl)ethyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (48.00 mg, 0.08 mmol, 100%).

LCMS (ESI+): m/z 578.4 $[M+H]^+$

Step D

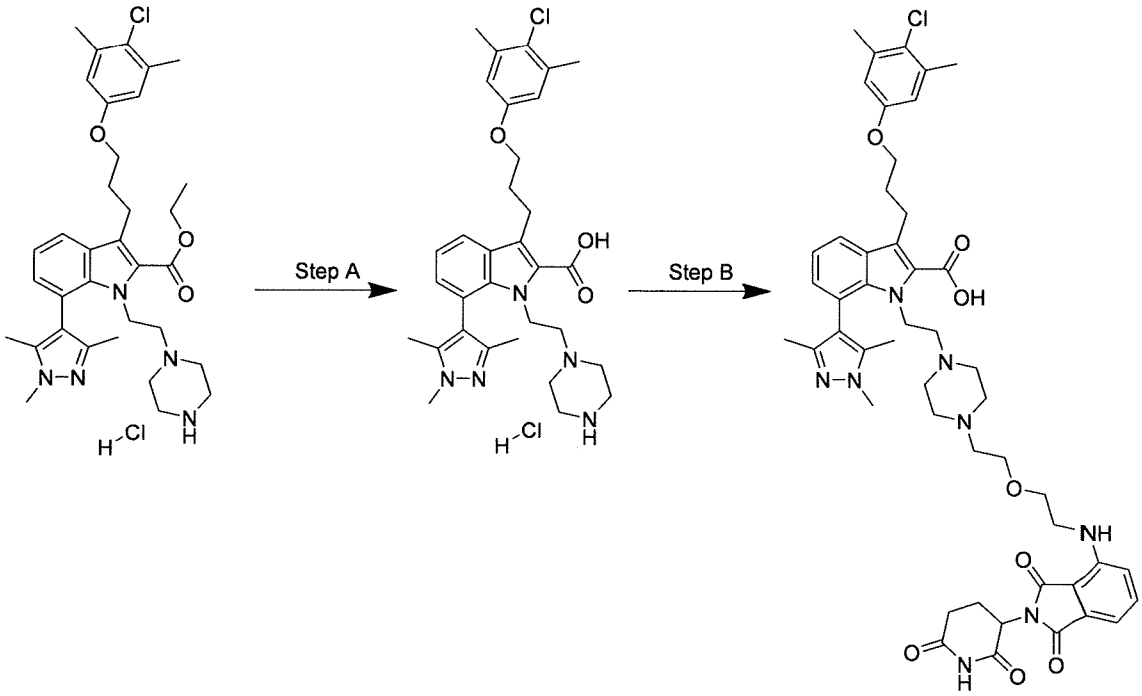


HATU (33 mg, 0.09 mmol) was mixed with 2-{[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl]amino}acetic acid hydrochloride (31 mg, 0.08 mmol) and DIPEA (0.07 mL, 0.42 mmol) in DMF (0.60 mL) for 1 h and then added to the solution of 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-(2-(piperazin-1-yl)ethyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (48 mg, 0.08 mmol) in DMF (0.60 mL) and the mixture was stirred in 70°C overnight. Crude product was purified using flash chromatography (SiO_2, DCM:MeOH, 0-10%) and repurified using preparative TLC (SiO_2, 10% MeOH in DCM). 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-(2-(4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)glycyl)piperazin-1-yl)ethyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (15 mg, 0.017 mmol, 21%) was isolated as yellow solid.

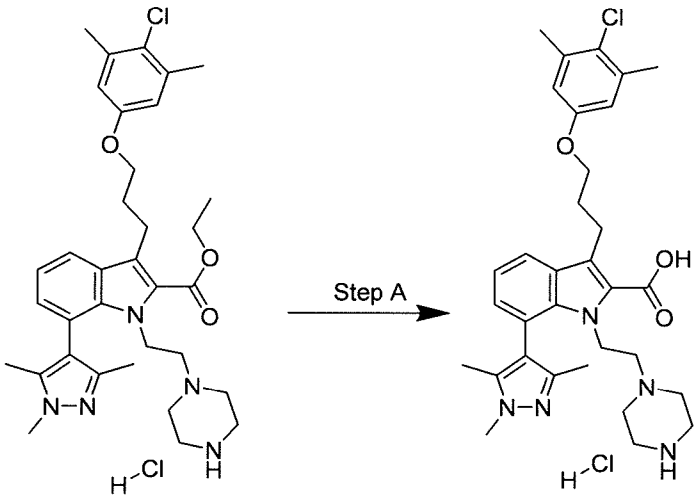
LCMS (ESI+): m/z 891.4 $[M+H]^+$

^1H NMR (500 MHz, DMSO) δ 11.09 (s, 1H), 7.65 (d, *J* = 7.8 Hz, 1H), 7.60 (dd, *J* = 8.4, 7.2 Hz, 1H), 7.13 – 7.02 (m, 4H), 6.92 (d, *J* = 6.7 Hz, 1H), 6.74 (s, 2H), 5.07 (dd, *J* = 12.8, 5.4 Hz, 1H), 4.48 – 4.39 (m, 1H), 4.31 – 4.23 (m, 1H), 4.10 (d, *J* = 3.6 Hz, 2H), 4.00 (t, *J* = 6.5 Hz, 2H), 3.76 (s, 3H), 3.42 – 3.34 (m, 4H), 3.16 (t, *J* = 7.3 Hz, 2H), 2.94 – 2.85 (m, 1H), 2.62 – 2.57 (m, 1H), 2.57 – 2.52 (m, 1H), 2.26 (s, 6H), 2.10 – 1.99 (m, 12H), 1.94 (s, 3H).

Example 32: 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-(2-(4-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethyl)piperazin-1-yl)ethyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (234)



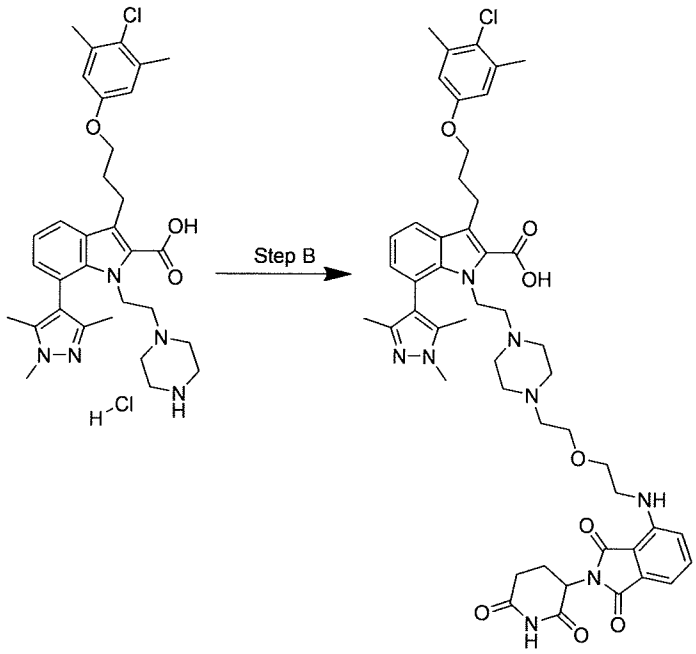
Step A



To the solution of ethyl 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-(2-(piperazin-1-yl)ethyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate hydrochloride (6.2 g, 9.6 mmol) in THF (30 mL) and MeOH (100 mL) was added LiOH (3 g) in water (10 mL). The reaction mixture was heated under reflux for 2 h, cooled to RT and concentrated in vacuo. The residue was dissolved in water (200 mL) and washed with EtOAc (100 mL). Water was acidified to neutral pH and extracted with DCM. The organic layer was dried over Na_2SO_4, filtered and concentrated in

vacuo. The residue was acidified with dioxane saturated with HCl, the solvent was removed under reduced pressure. The residue was recrystallized from EtOAc to give the 3-[3-(4-chloro-3,5-dimethylphenoxy)propyl]-1-[2-(piperazin-1-yl)ethyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid hydrochloride (5.40 g, 8.79 mmol, 91%).

Step B



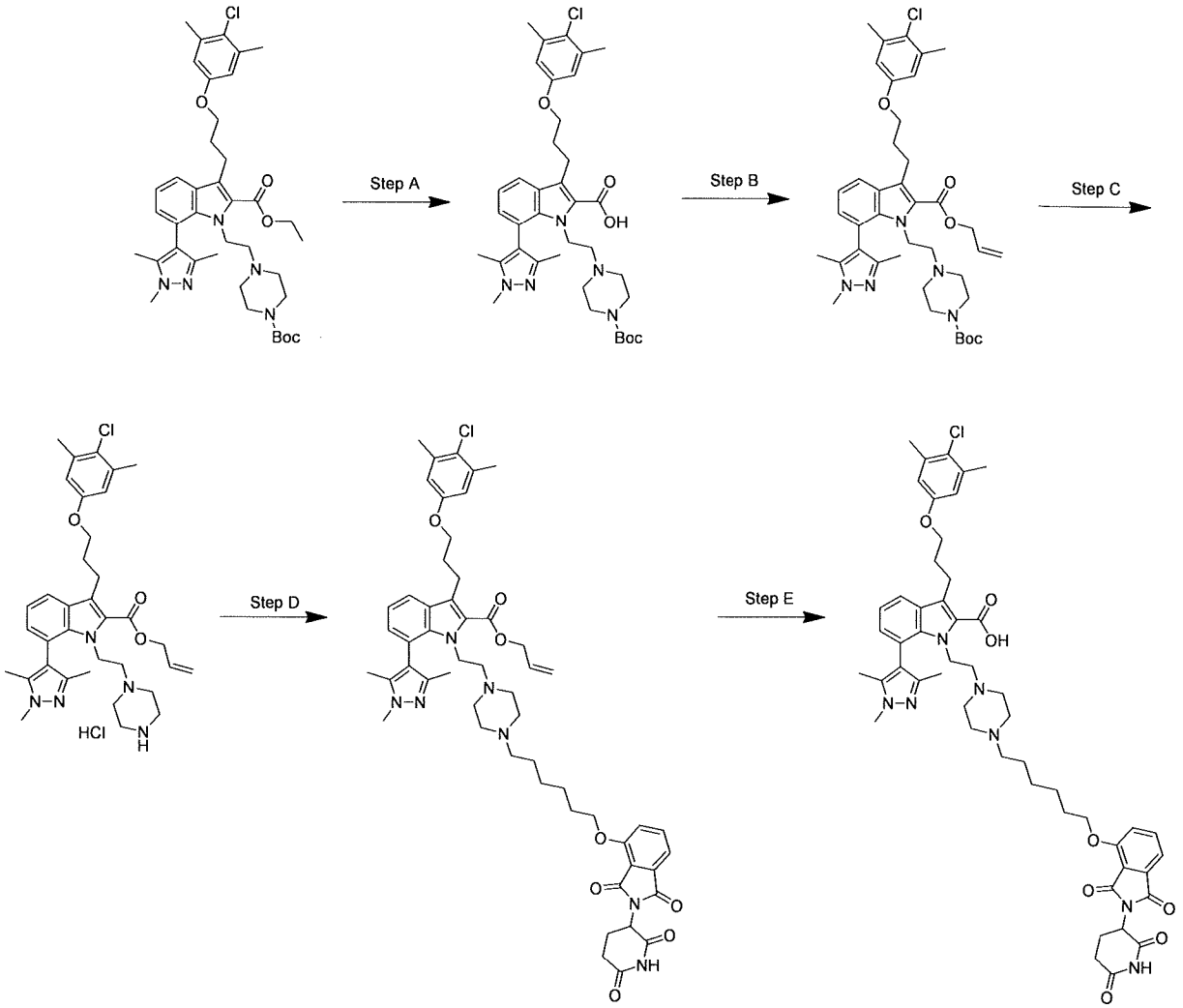
To a solution of 3-[3-(4-chloro-3,5-dimethylphenoxy)propyl]-1-[2-(piperazin-1-yl)ethyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid hydrochloride (1.00 g, 1.63 mmol) in DMSO (10 mL) were added DIPEA (2.05 mL, 11.73 mmol) and 2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethyl methanesulfonate (0.86 g, 1.95 mmol). The reaction mixture was stirred at 80°C (LCMS control). Upon completion, the mixture was poured into water and extracted with $CHCl_3$. The combined organic layers were dried over anhydrous Na_2SO_4. and concentrated under reduced pressure. Crude product was purified by column chromatography on silica gel to afford 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-(2-(4-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethyl)piperazin-1-yl)ethyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (50 mg, 0.054 mmol, 3%) as yellow solid.

LCMS (ESI+): m/z 921.4 $[M+H]^+$

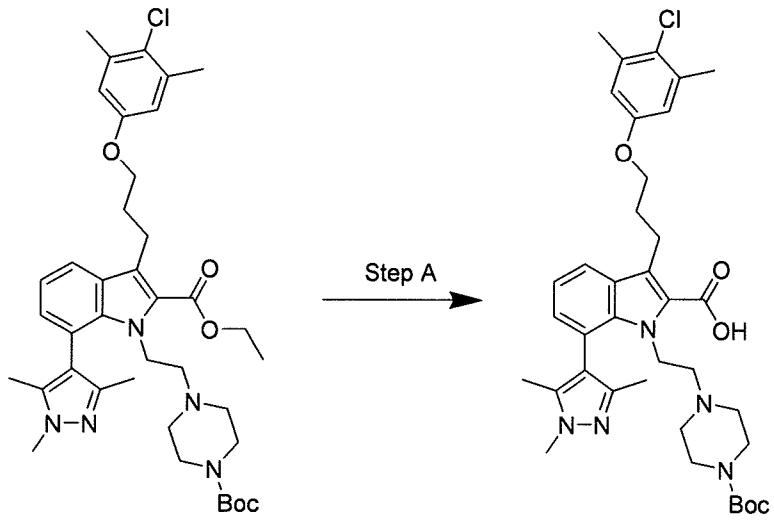
^1H NMR (500 MHz, DMSO) δ 11.09 (s, 1H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.55 (t, *J* = 7.8 Hz, 1H), 7.16 – 7.06 (m, 2H), 7.02 (d, *J* = 7.0 Hz, 1H), 6.89 (d, 1H), 6.72 (s, 2H), 6.57 (t, *J* = 5.9 Hz, 1H), 5.04 (dd, *J* = 12.8, 5.4 Hz, 1H), 4.42 – 4.28 (m, 1H), 4.28 – 4.16 (m, 1H), 3.96 (t, *J* = 6.5 Hz, 2H), 3.71 (s, 3H), 3.55

(t, *J* = 5.4 Hz, 2H), 3.47 (t, *J* = 5.7 Hz, 2H), 3.45 – 3.42 (m, 2H), 3.12 (t, *J* = 7.4 Hz, 2H), 2.92 – 2.80 (m, 1H), 2.60 – 2.54 (m, 2H), 2.42 – 2.27 (m, 5H), 2.25 (s, 7H), 2.15 – 1.95 (m, 12H), 1.91 (s, 3H).

Example 33: 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-(2-(4-(6-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)hexyl)piperazin-1-yl)ethyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (235)



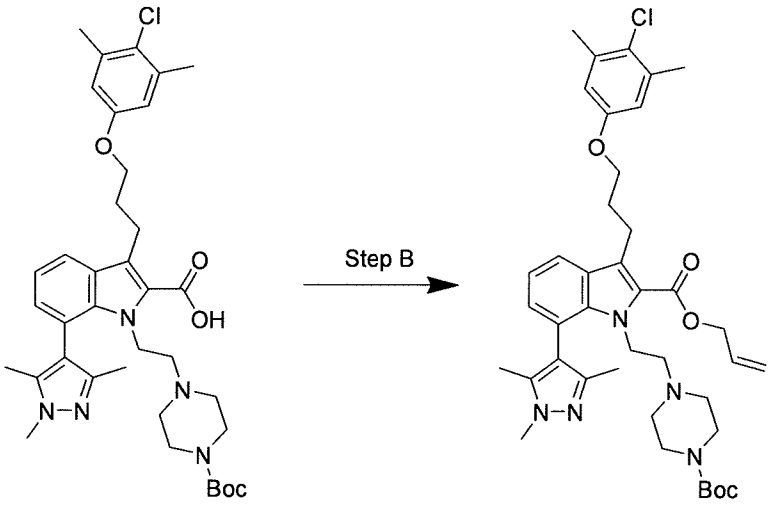
Step A



To solution of ethyl 1-(2-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)ethyl)-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (60 mg, 0.085 mmol) in the mixture of MeOH and H_2O (1:1, 0.42 mL) was added NaOH (27 mg, 0.68 mmol). Mixture was stirred at 50°C for 3 days. Methanol was removed under reduced pressure and 1M HCl was added. Mixture was extracted 3x with DCM. Organic phases were combined, dried over Na_2SO_4, and concentrated. 1-(2-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)ethyl)-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (55.00 mg, crude) was used directly in the next step.

LCMS (ESI+): m/z 678.2 $[M+H]^+$

Step B

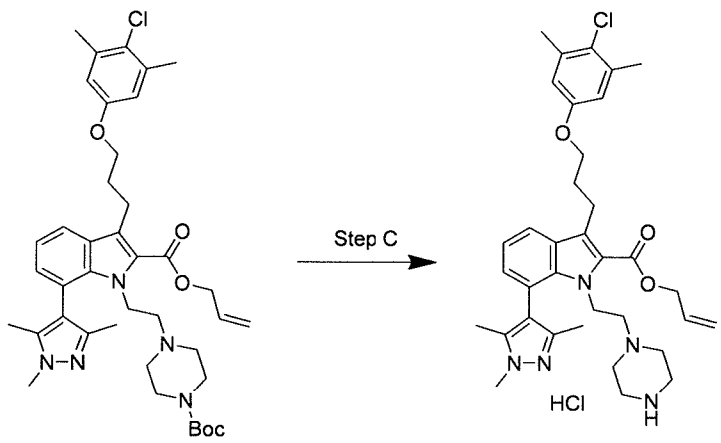


1-(2-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)ethyl)-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (55 mg, crude) was suspended in dry

DMF (0.41 mL) and K_2CO_3 (34 mg, 0.24 mmol) was added. The reaction mixture was stirred at ambient temperature for 5 min, then allyl bromide (13 µL, 0.08 mmol) was added dropwise and the resulting solution was allowed to stir at ambient temperature for 17 h. The reaction mixture was quenched with water and extracted with 3x EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced to give crude allyl 1–(2-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)ethyl)-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (55.00 mg, crude) which was used in next step without further purification.

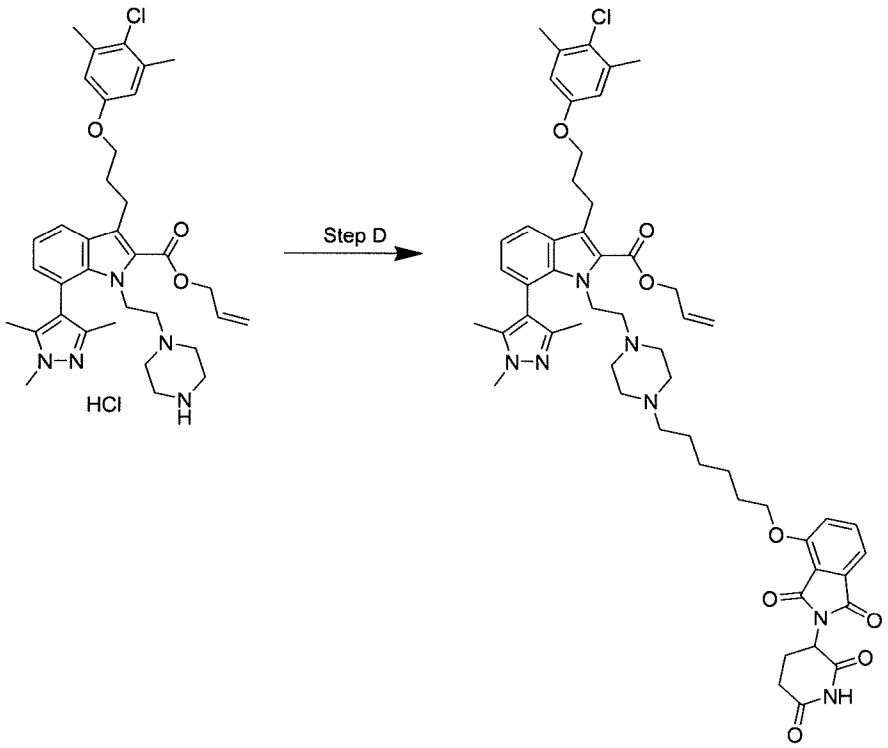
LCMS (ESI+): m/z 718.3 $[M+H]^+$

Step C



Allyl 1-(2-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)ethyl)-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (55 mg, 0.08 mmol) was dissolved in THF (1.23 mL) and 4M HCl in dioxane (287 µL, 1.15 mmol) was added. Mixture was stirred overnight in RT. Solvents were removed under reduced pressure, and crude co-evaporated three times with Et_2O. Allyl 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-(2-(piperazin-1-yl)ethyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate hydrochloride (50 mg, crude) was used directly in the next step.

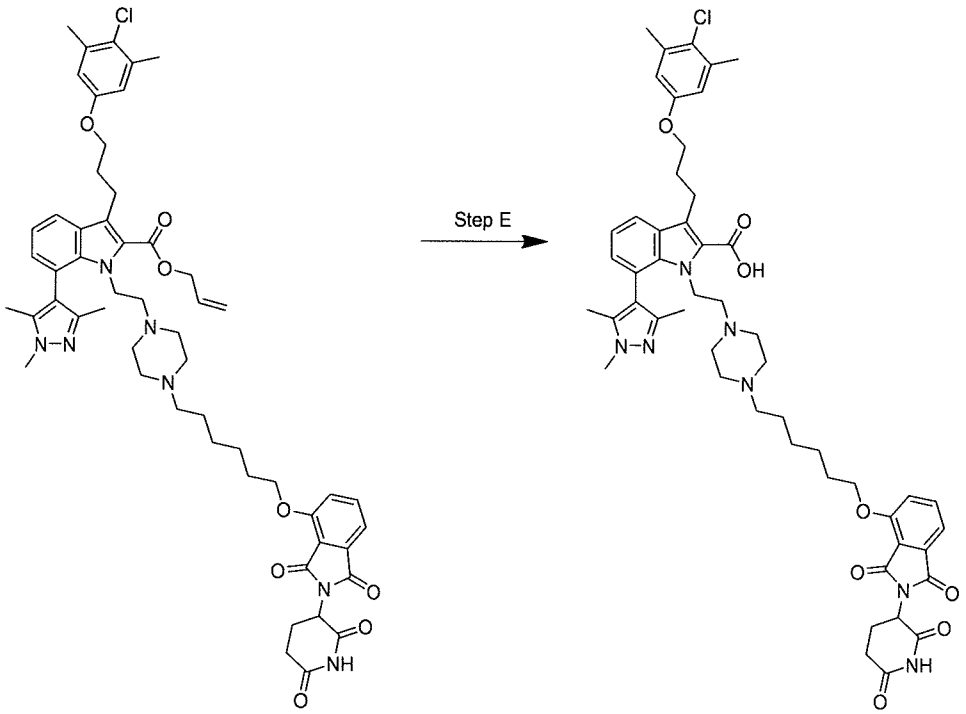
Step D



To a solution of allyl 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-(2-(piperazin-1-yl)ethyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate hydrochloride (59 mg, crude) $KHCO_3$ (36 mg, 0.36 mmol) and KI (15 mg, 0.09 mmol) in DMF (0.64 mL), was added 4-((6-chlorohexyl)oxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (57 mg, 0.14 mmol). The reaction mixture was stirred at 60°C for 2 days. Solvents were removed under reduced pressure, Mixture was suspended in DCM and filtered through Celite. DCM was removed, and solid was washed from Celite using DCM:THF 1:1. Solvents were removed under reduced pressure and allyl 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-(2-(4-(6-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)hexyl)piperazin-1-yl)ethyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (88.00 mg, crude) was used directly in the next step.

LCMS (ESI+): m/z 973.9 $[M+H]^+$

Step E

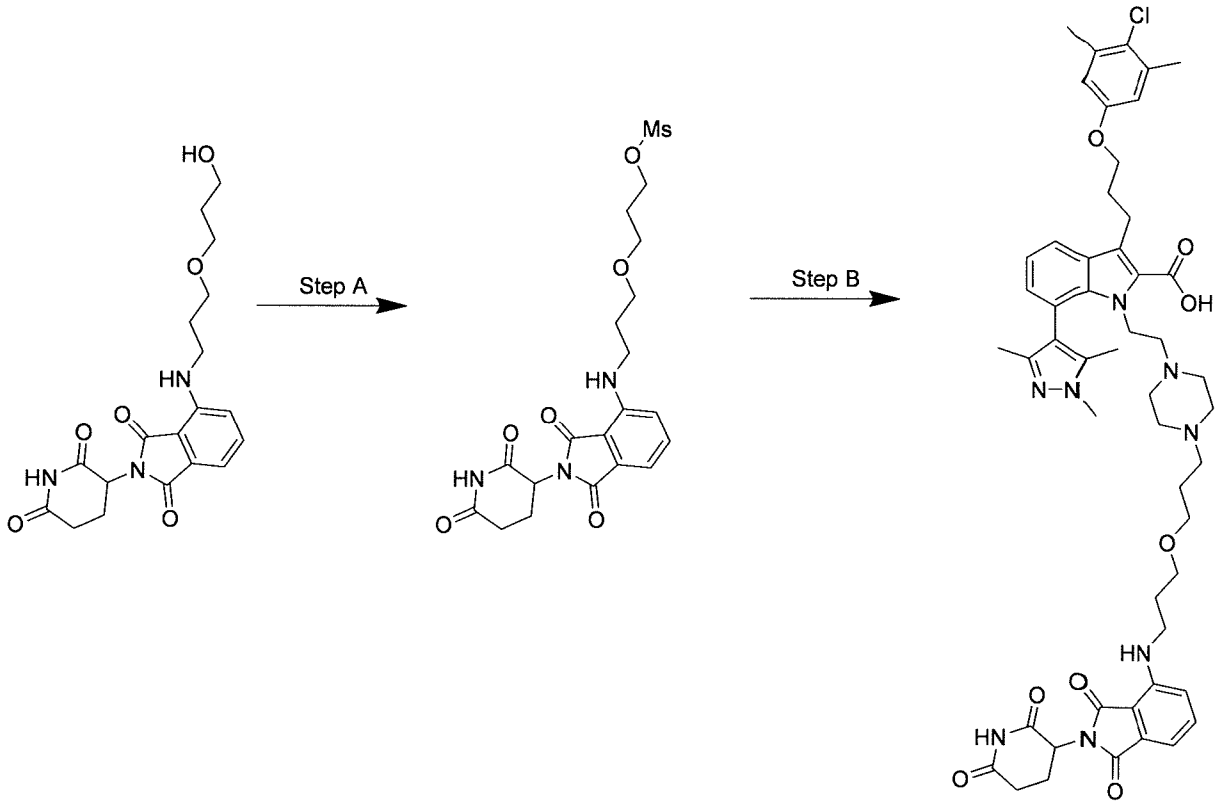


To an ice cooled solution of allyl 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-(2-(4-(6-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)hexyl)piperazin-1-yl)ethyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (88 mg, crude) and tetrakis(triphenylphosphine)palladium(0) (10 mg, 0.01 mmol) in DCM (0.21 mL) was added morpholine (9 µL, 0.11 mmol). Reaction was stirred in RT overnight. Solvents were evaporated and crude product was purified with reverse phase flash chromatography (H_2O:MeCN + 0.1% FA) to give 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-(2-(4-(6-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)hexyl)piperazin-1-yl)ethyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (1.58 mg, 0.002 mmol, 2% yield over five steps) as white solid.

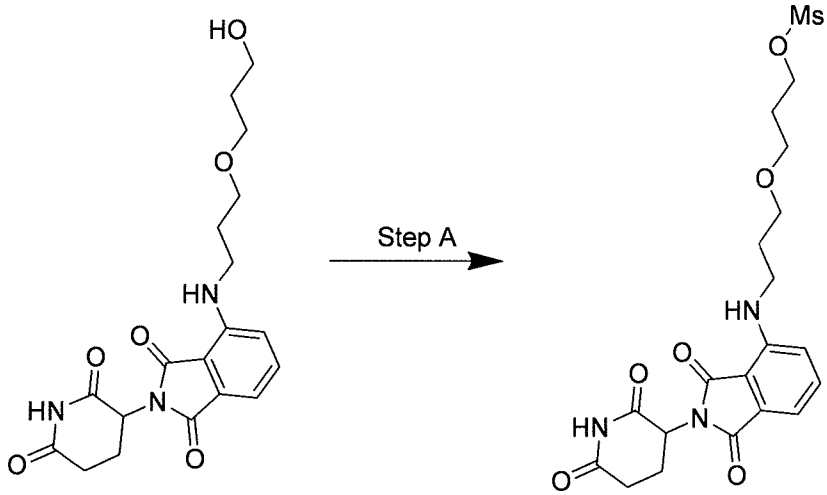
LCMS (ESI+): m/z 934.1 $[M+H]^+$

^{1}H NMR (500 MHz, DMSO) δ 11.09 (s, 1H), 7.79 (dd, *J* = 8.5, 7.3 Hz, 1H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.49 (d, *J* = 8.5 Hz, 1H), 7.43 (d, *J* = 7.2 Hz, 1H), 7.08 (t, *J* = 7.5 Hz, 1H), 6.89 (d, *J* = 7.0 Hz, 1H), 6.72 (s, 2H), 5.07 (dd, *J* = 12.8, 5.5 Hz, 1H), 4.42 – 4.30 (m, 1H), 4.27 – 4.13 (m, 3H), 3.97 (t, *J* = 6.5 Hz, 2H), 3.72 (s, 3H), 3.12 (t, *J* = 7.3 Hz, 2H), 2.88 (ddd, *J* = 17.0, 13.9, 5.5 Hz, 1H), 2.62 – 2.56 (m, 1H), 2.56 – 2.51 (m, 2H), 2.25 (s, 6H), 2.24 – 2.07 (m, 10H), 2.06 (s, 3H), 2.05 – 1.99 (m, 3H), 1.92 (s, 3H), 1.73 (dt, *J* = 14.1, 6.4 Hz, 2H), 1.50 – 1.38 (m, 3H), 1.38 – 1.30 (m, 4H).

Example 34: 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-(2-(4-(3-(3-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)propoxy)propyl)piperazin-1-yl)ethyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (236)



Step A

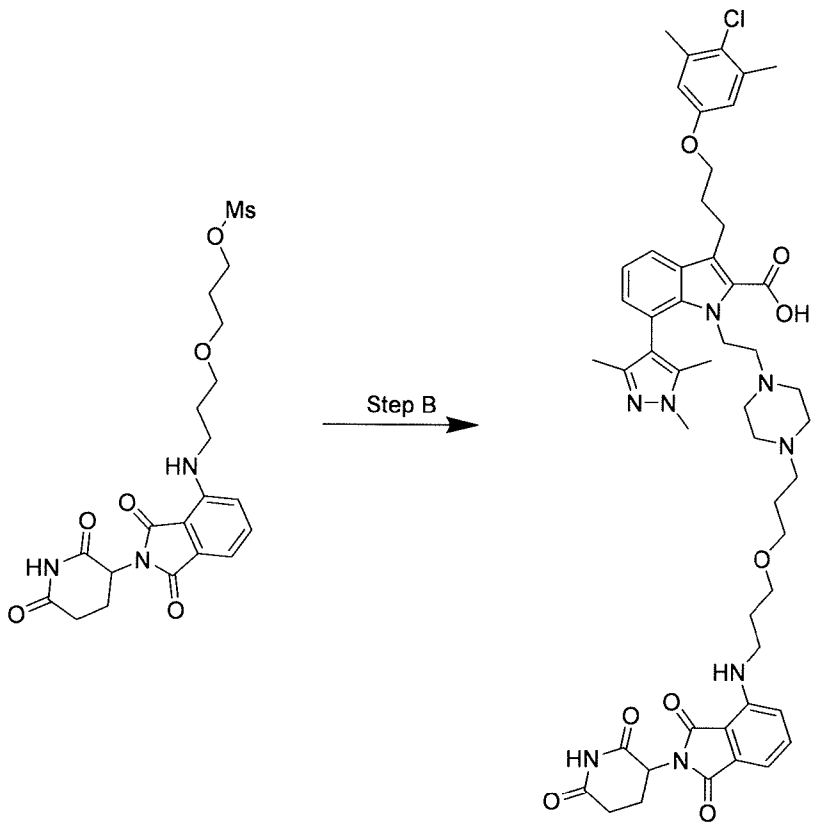


General procedure 1:

Starting material and Et_3N were dissolved in DCM and cooled down to 0°C. A solution of MsCl in DCM was added dropwise in that temperature. The mixture was stirred at RT for 18 h and H_2O was added. The layers were separated and the aqueous layer was extracted with DCM. The

combined organic extracts were washed with H_2O, dried over Na_2SO_4, and concentrated to obtain crude of methanesulfonate, which was used for next step without further purification.

Step B



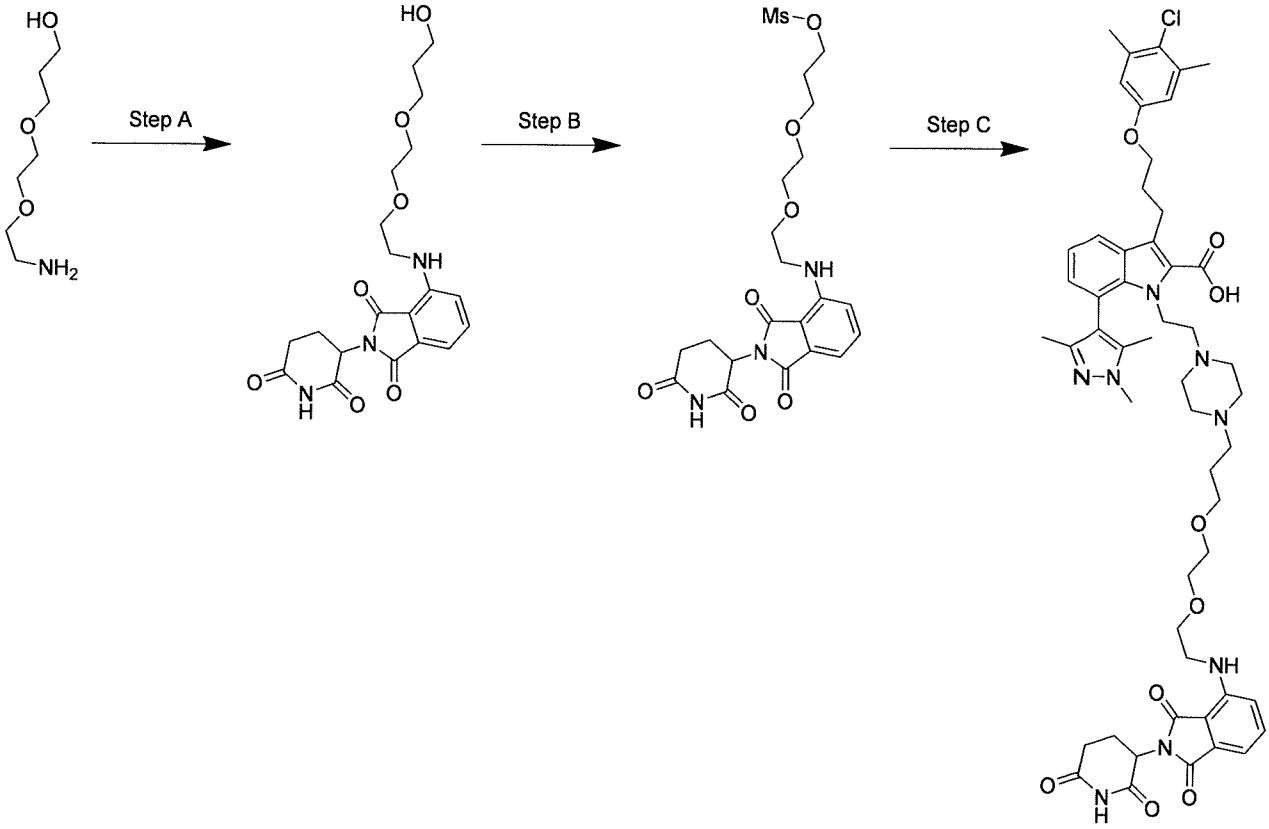
To a solution of 3-[3-(4-chloro-3,5-dimethylphenoxy)propyl]-1-[2-(piperazin-1-yl)ethyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid hydrochloride (1.00 g, 1.63 mmol) in DMSO (10 mL) were added DIPEA (2.05 mL, 11.73 mmol) and 3-(3-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)propoxy)propyl methanesulfonate (0.91 g, 1.95 mmol). The reaction mixture was stirred at 80°C. Upon completion, the mixture was poured into water, extracted with $CHCl_3$, and the combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. Crude product was purified by column chromatography on silica gel to afford 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-(2-(4-(3-(3-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)propoxy)propyl)piperazin-1-yl)ethyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (36 mg, 0.038 mmol, 2% over steps A and B) as yellow solid.

LCMS (ESI+): m/z 949.4 $[M+H]^+$

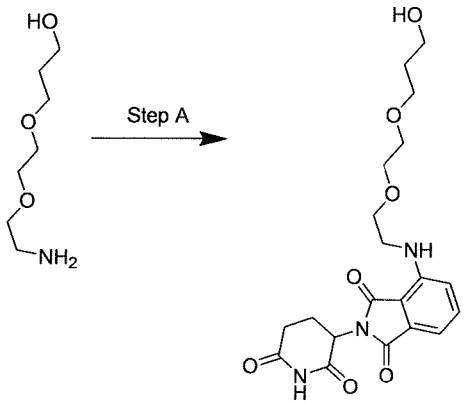
^1H NMR (400 MHz, CD_3OD) δ 7.62 (d, *J* = 7.9 Hz, 1H), 7.50 (t, *J* = 7.7 Hz, 1H), 7.09 (t, *J* = 7.6 Hz, 1H), 7.04 – 6.95 (m, 2H), 6.88 (d, *J* = 7.1 Hz, 1H), 6.63 (s, 2H), 5.05 (dd, *J* = 12.3, 5.2 Hz, 1H), 4.38 (s, 2H),

3.95 (t, *J* = 6.6 Hz, 2H), 3.79 (d, *J* = 3.2 Hz, 3H), 3.54 (t, *J* = 5.7 Hz, 2H), 3.44 (t, *J* = 6.3 Hz, 2H), 3.37 (t, *J* = 6.2 Hz, 2H), 3.20 (t, *J* = 7.3 Hz, 2H), 2.85 – 2.68 (m, 8H), 2.51 (s, 4H), 2.41 (s, 2H), 2.26 (s, 6H), 2.11 (d, *J* = 4.9 Hz, 6H), 2.04 (s, 3H), 1.89 (t, *J* = 6.0 Hz, 3H), 1.85 – 1.76 (m, 2H).

Example 35. 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-(2-(4-(3-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)propyl)piperazin-1-yl)ethyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (237)

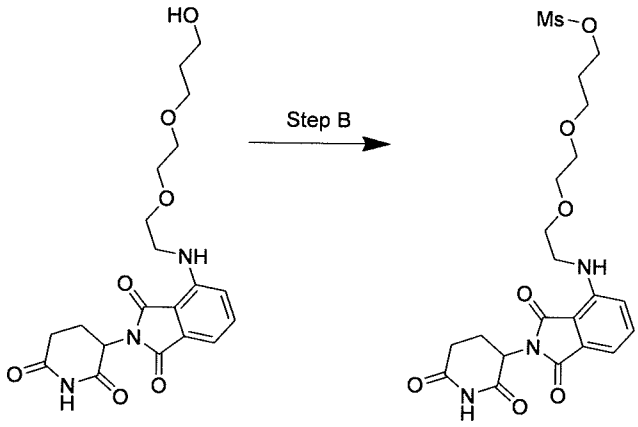


Step A



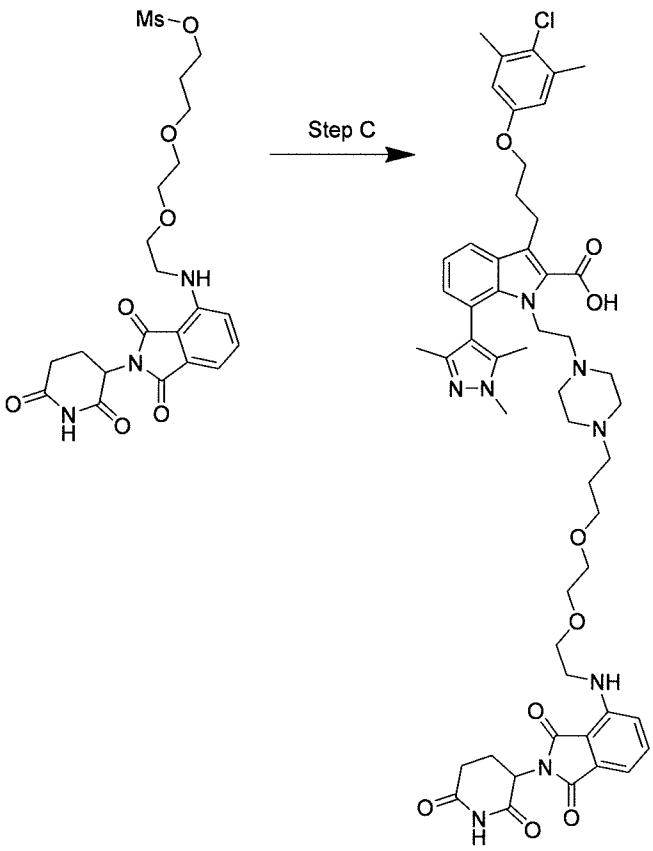
To a stirred solution of 2-(2,6-dioxopiperidin-3-yl)-4-fluoroisoindoline-1,3-dione (38.20 g, 138.31 mmol) in DMF (300 mL) were added DIPEA (48.31 mL, 276.61 mmol) and 3-(2-(2-aminoethoxy)ethoxy)propan-1-ol (22.57 g, 138.31 mmol). The reaction mixture was heated to 100°C overnight, then cooled to room temperature, and taken up in EtOAc (300 mL) and water (300 mL). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel to give 2-(2,6-dioxopiperidin-3-yl)-4-((2-(2-(3-hydroxypropoxy)ethoxy)ethyl)amino)isoindoline-1,3-dione (9.80 g, 23.389 mmol, 17%).

Step B



3-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)propyl methanesulfonate was prepared according to general procedure 1 using 2-(2,6-dioxopiperidin-3-yl)-4-((2-(2-(3-hydroxypropoxy)ethoxy)ethyl)amino)isoindoline-1,3-dione (0.7 g, 1.68 mmol), Et_3N (1 mL, 7 mmol) and MsCl (0.23 g, 2 mmol) to obtain 0.83 g (crude) of title compound.

Step C

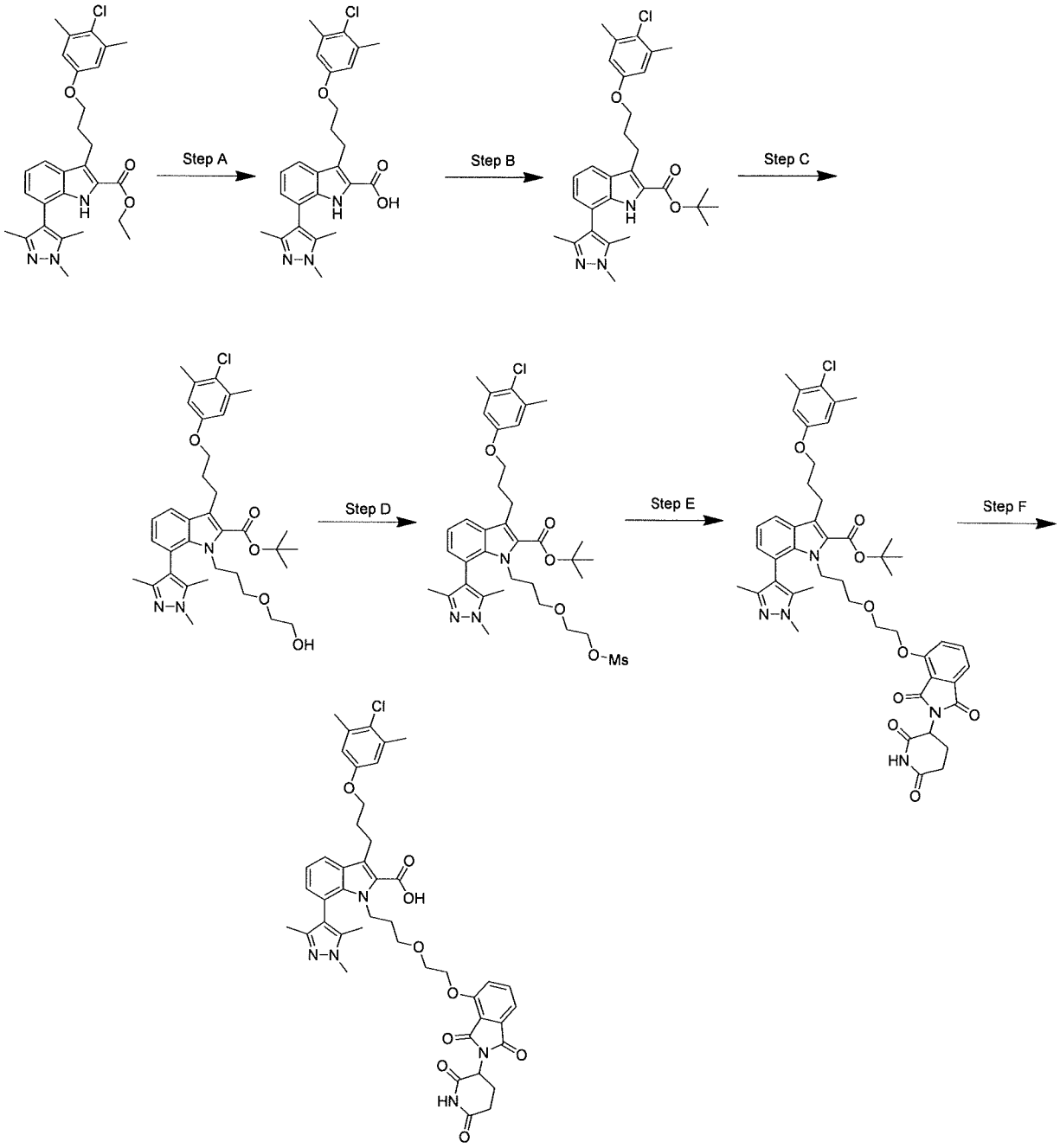


To a solution of 3-[3-(4-chloro-3,5-dimethylphenoxy)propyl]-1-[2-(piperazin-1-yl)ethyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid hydrochloride (0.52 g, crude) in DMSO (5 mL) were added DIPEA (0.75 g, 5.80 mmol) and 3-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)propyl methanesulfonate (0.51 g, 1.03 mmol). The reaction mixture was left stirred at 80°C until accepted conversion of target compound was observed. The reaction mixture was poured in water, extracted with chloroform, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by column chromatography to obtain 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-(2-(4-(3-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)propyl)piperazin-1-yl)ethyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (0.016 g, 0.016 mmol, 1.9%) as yellow solid.

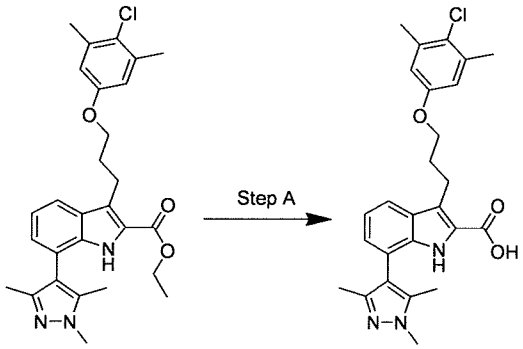
LCMS (ESI+): m/z 978.8 $[M+H]^+$

^1H NMR (400 MHz, $CDCl_3$) δ 7.68 – 7.56 (m, 1H), 7.47 (td, *J* = 7.8, 3.8 Hz, 1H), 7.17 – 7.02 (m, 2H), 6.97 – 6.81 (m, 2H), 6.60 (d, *J* = 3.7 Hz, 2H), 6.57 – 6.47 (m, 1H), 5.16 – 4.82 (m, 1H), 4.80 – 4.17 (m, 2H), 4.05 – 3.88 (m, 2H), 3.77 (d, *J* = 17.4 Hz, 3H), 3.70 (t, *J* = 5.2 Hz, 2H), 3.65 – 3.57 (m, 2H), 3.57 – 3.48 (m, 2H), 3.46 – 3.32 (m, 4H), 3.27 – 3.13 (m, 2H), 2.94 – 2.63 (m, 6H), 2.61 – 2.30 (m, 8H), 2.30 – 2.24 (m, 6H), 2.24 – 1.93 (m, 10H), 1.93 – 1.67 (m, 2H).

Example 36. 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-(3-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)ethoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (238)

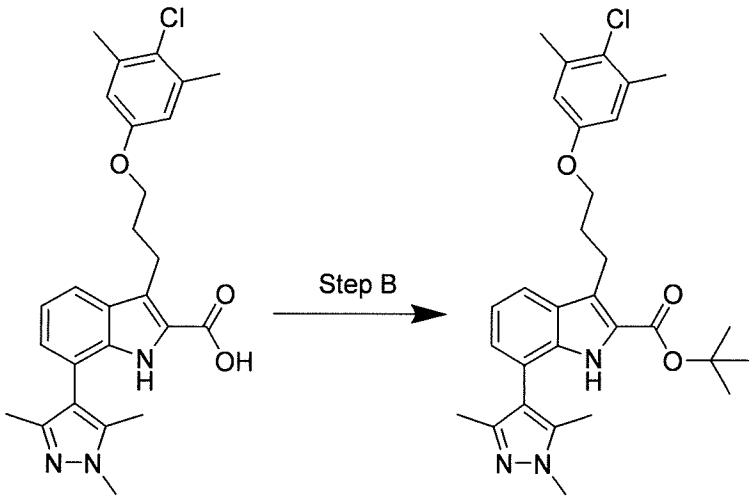


Step A



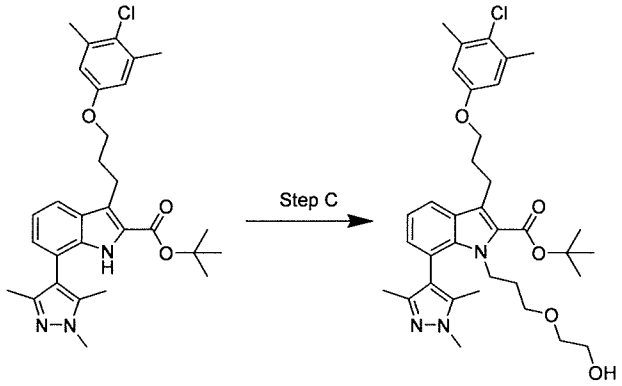
To a solution of compound ethyl 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (7 g, 14.2 mmol) in THF (50 mL) and MeOH (50 mL) was added a solution of NaOH (2.3 g, 57.5 mmol) in water (20 mL). The reaction mixture was heated under reflux for 2 h, cooled to room temperature and concentrated in vacuo. The residue was dissolved in water and washed with EtOAc. The water phase was acidified to neutral pH and extracted with DCM. The organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo to give 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (5.1 g, 11 mmol), which was used to next step without further purification.

Step B



To a solution of 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid from the previous step (5.1 g, 11 mmol) in DCM (100 mL) was added *tert*-butyl 2,2,2-trichloroacetimidate (7.16 g, 33 mmol) at 20°C. The reaction mixture was stirred for 48 h at 20°C. The solution was concentrated in vacuo and the crude residue was purified by flash chromatography to give *tert*-butyl 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (2.2 g, 4.2 mmol, 30% over two steps) as a solid.

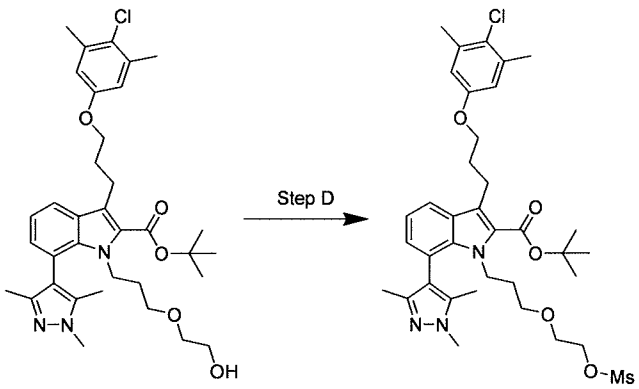
Step C



To a solution of the *tert*-butyl 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (100 mg, 0.192 mmol) in DMF (6 mL), 2-(3-chloropropoxy)ethanol (265 mg, 1.92 mmol), KI (64 mg, 0.38 mmol), and K_2CO_3 (79 mg, 0.57 mmol) were added. Subsequently, the reaction mixture was stirring at 70 °C for 24 h. After the reaction was complete (monitored by TLC), DMF was evaporated and the resultant residue was partitioned between EtOAc and H_2O. The organic layer was further washed with brine, dried over Na_2SO_4, filtered and evaporated. The final product was purified on preparative TLC (hexane:EtOAc:MeOH, 50:47:3) to obtain *tert*-butyl 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-(3-(2-hydroxyethoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (36.00 mg, 0.058 mmol, 30%).

LCMS (ESI+): m/z 624.3 $[M+H]^+$

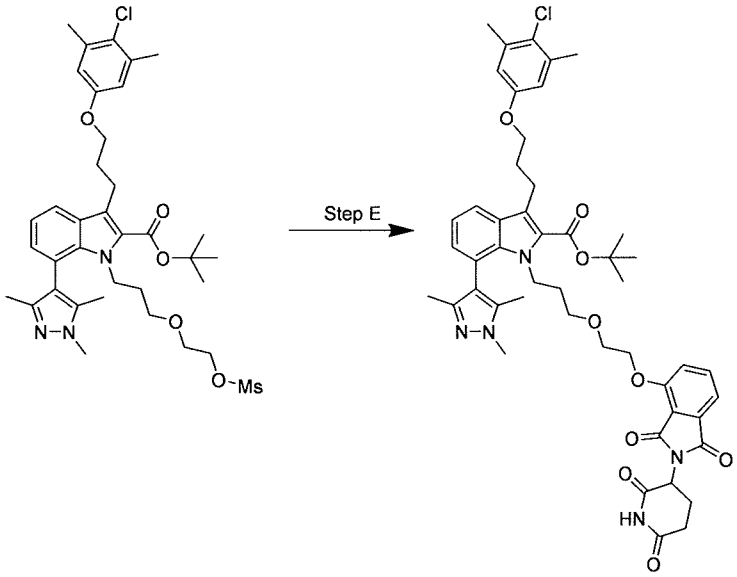
Step D



To a solution of *tert*-butyl 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-(3-(2-hydroxyethoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (30 mg, 0.05 mmol) in dry DCM (6mL) Et_3N (19 mg, 0.19 mmol) was added under argon atmosphere and the mixture was cooled to 0°C. Subsequently, methanesulfonyl chloride (28 mg, 0.24 mmol) was

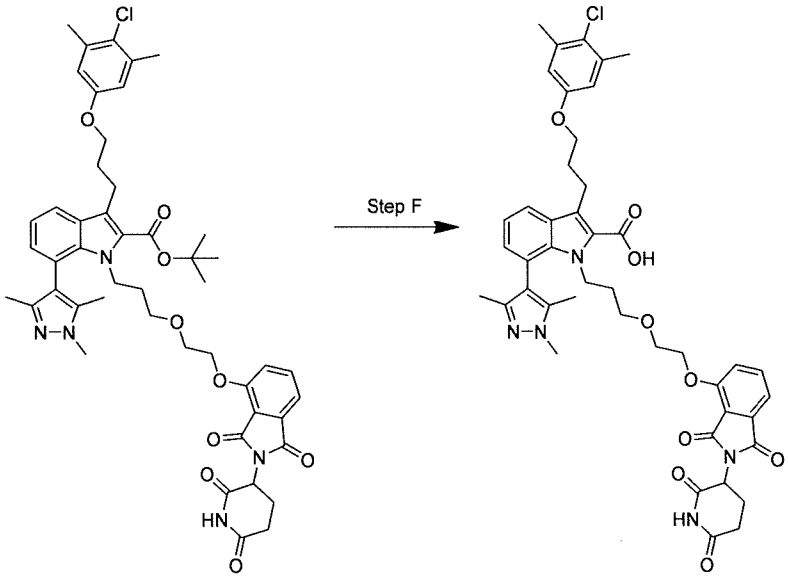
added dropwise at 0°C, followed by stirring of the mixture at room temperature for 24 h. After the reaction was complete (monitored by TLC), MeOH (20 mL) was added to the mixture carefully. The volatiles were then evaporated and the resultant residue was partitioned between EtOAc and H_2O. The organic layer was further washed with brine, dried over Na_2SO_4, filtered and evaporated to give *tert*-butyl 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-(3-(2-((methylsulfonyl)oxy)ethoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (30.00 mg, crude) which was used directly to the next step.

Step E



To a solution of the *tert*-butyl 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-(3-(2-((methylsulfonyl)oxy)ethoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (30 mg, crude) and 2-(2,6-dioxopiperidin-3-yl)-4-hydroxyisoindoline-1,3-dione (15 mg, 0.056 mmol) in DMF (0.95 mL), KI (8 mg, 0.05 mmol) followed by $KHCO_3$ (11 mg, 0.11 mmol). The mixture was stirred in 60°C for 24 h. Additional portion of K_2CO_3 (9 mg, 0.06 mmol) and KI (8 mg, 0.05 mmol) was added after this time. The reaction mixture was stirred in 60 °C for the next 24 h. The crude was purified on preparative TLC (hexane:EtOAc:MeOH, 50:42:8) to obtain *tert*-butyl 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-(3-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)ethoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (3.00 mg, 0.003 mmol, 6% over two steps).

Step F

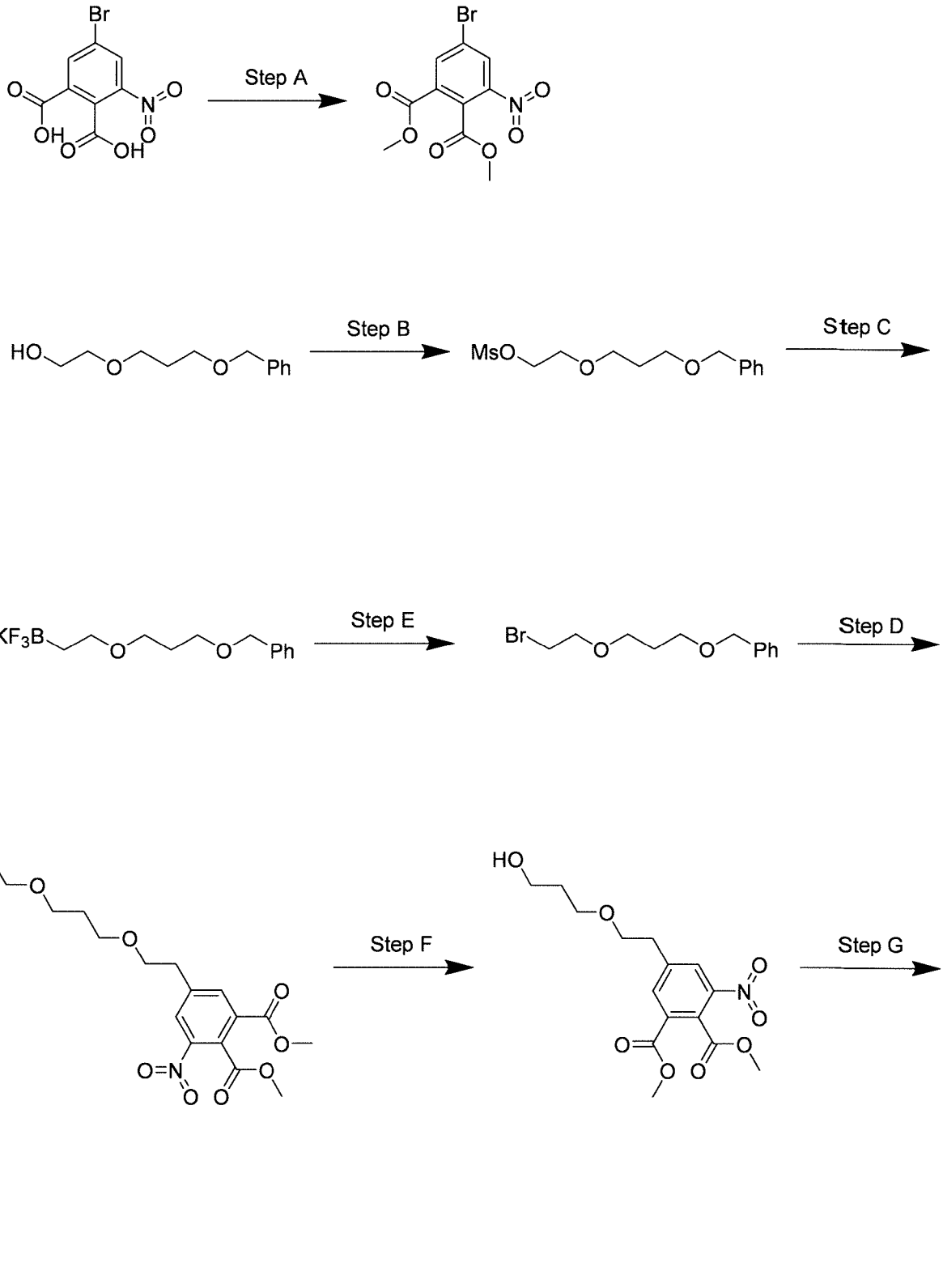


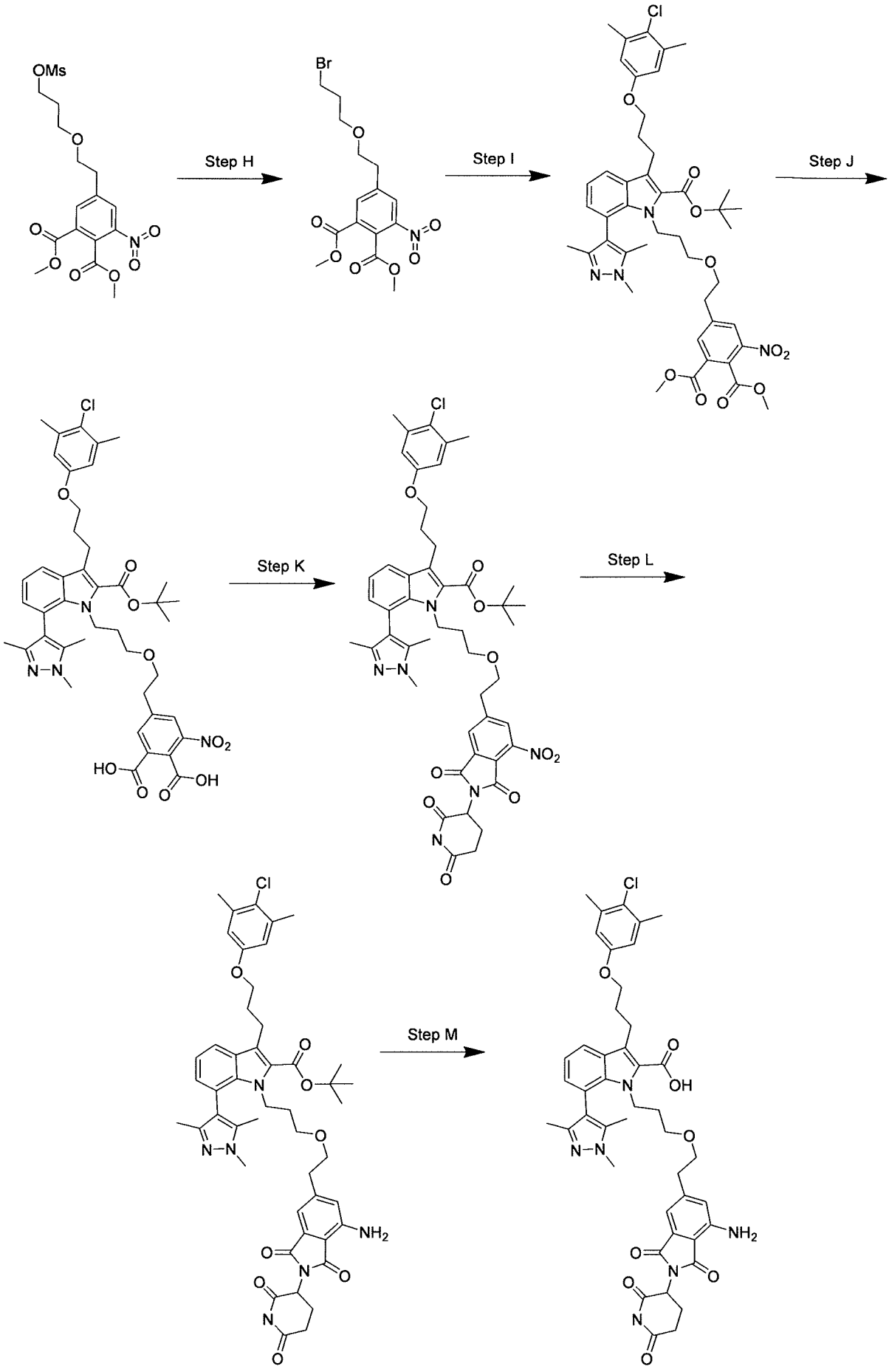
Tert-butyl 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-(3-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)ethoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (3 mg, 0.003 mmol) was dissolved in 4 M HCl in dioxane (17 µL, 0.068 mmol). Subsequently, the mixture was stirring at room temperature for 24 h. After the reaction was completed (monitored by LCMS), solvent was evaporated and the compound was purified twice on preparative TLC (hexane:EtOAc:EtOH 50:43:7). The final product 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-(3-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)ethoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (2.00 mg, 0.002 mmol, 71%) was obtained as white solid.

LCMS (ESI+): m/z 824.2 $[M+H]^+$

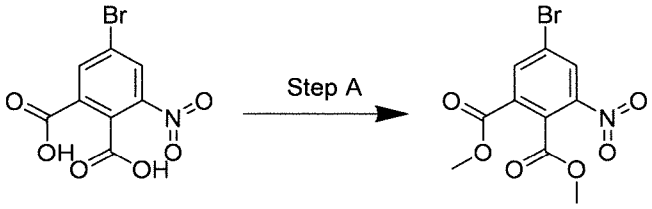
^{1}H NMR (500 MHz, DMSO) δ 11.09 (s, 1H), 7.80 (dd, *J* = 8.6, 7.3 Hz, 1H), 7.51 (d, *J* = 8.5 Hz, 1H), 7.45 (d, *J* = 7.2 Hz, 1H), 7.31 (dt, *J* = 7.3, 1.2 Hz, 1H), 7.08 (t, *J* = 7.5 Hz, 1H), 6.94 (ddd, *J* = 7.7, 4.1, 1.4 Hz, 1H), 6.69 (d, *J* = 3.2 Hz, 2H), 5.11 – 5.03 (m, 1H), 4.36 – 4.22 (m, 2H), 3.92 – 3.75 (m, 2H), 3.71 – 3.65 (m, 3H), 3.65 – 3.59 (m, 2H), 3.27 – 3.20 (m, 1H), 3.15 – 3.03 (m, 2H), 2.87 (ddd, *J* = 17.1, 13.8, 5.4 Hz, 1H), 2.62 – 2.53 (m, 1H), 2.54 – 2.50 (m, 1H), 2.25 (s, 6H), 2.10 – 1.80 (m, 10H), 1.55 – 1.32 (m, 4H).

Example 37. 1-(3-(2-(7-amino-2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)ethoxy)propyl)-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*–pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (239)



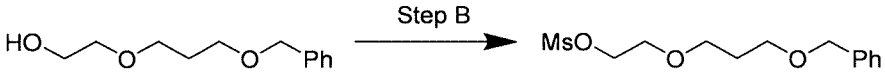

OMs
Step H
Br
Step I
Cl
Step J
NO2
Cl
Step K
HO
OH
Step L
NO2
Cl
Step M
NH2
Cl
OH
NH2

Step A



To a stirred solution of 5-bromo-3-nitrophthalic acid (10 g, 34.5 mmol) in DMF (5 mL) was added sodium bicarbonate (23.2 g, 276 mmol) followed by methyl iodide (12.9 mL, 206.9 mmol) and the reaction mixture was allowed to stir at 100°C for 16 h under nitrogen. The reaction mixture was diluted with EtOAc, washed successively with water and brine, the organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to get the crude compound, which was then purified by flash chromatography (SiO_2, 30% EtOAc in hexane) to get dimethyl 5-bromo-3-nitrophthalate (6 g, 18.9 mmol, 65%) as off white solid.

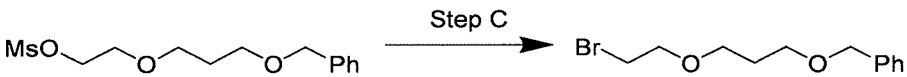
Step B



To a stirred solution of 2-(3-(benzyloxy)propoxy)ethan-1-ol (10 g, 47.6 mmol) in DCM (200 mL) was added MsCl (10 mL, 71.4 mmol) followed by Et_3N (20 mL, 142 mmol) at 0°C under nitrogen and the reaction mixture was allowed to stir at room temperature for 2 h. The reaction mixture was diluted with EtOAc, washed successively with water and brine, the organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to get the crude compound, which was then purified by flash chromatography (SiO_2, 30% EtOAc in hexane) to get 2-(3-(benzyloxy)propoxy)ethyl methanesulfonate (12.3 g, 42.6 mmol, 89%) as colorless oil.

LCMS (ESI+): m/z 289.4 $[M+H]^+$

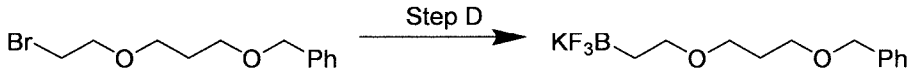
Step C



To a stirred solution of 2-(3-(benzyloxy)propoxy)ethyl methanesulfonate (12.3 g, 42.6 mmol) in DMF (40 mL) was added LiBr (18.45 g, 213 mmol) and the reaction mixture was allowed to stir at 80°C for 2 h under nitrogen. The reaction mixture was diluted with EtOAc, washed successively with water and brine, the organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to get the crude compound, which was then purified by flash chromatography (SiO_2, 20%

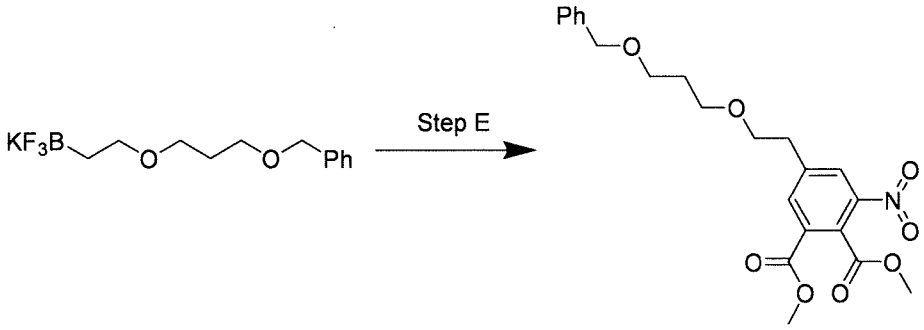
EtOAc in hexane) to get ((3-(2-bromoethoxy)propoxy)methyl)benzene (7.5 g, 27.5 mmol, 64%) as light green dense liquid.

Step D



A solution of ((3-(2-bromoethoxy)propoxy)methyl)benzene (5.5 g, 20.1 mmol) in DMF (70 mL) was added to the mixture of BISPIN (7.6 g, 30.2 mmol), LiOMe (1.53 g, 37.97 mmol), triphenylphosphine polymer-bound (2.1 g, 2.6 mmol) and CuI (0.4 g, 2.01 mmol) in a nitrogen atmosphere and the reaction was stirred at room temperature for 20 h. The reaction mixture was then diluted with DCM and filtered through a pad of Celite and the resulting solution was concentrated, poured into NH_4Cl (sat.), and extracted with Et_2O. The organic layers were washed successively with H_2O and brine. The organic layer was dried over anhydrous Na_2SO_4, and concentrated to get the crude product which was dissolved in THF (100ml), a saturated solution of KHF_2 (8 mL, 4.1 g, 52.5 mmol) was added to it and the reaction mixture stirred for 2 h at RT. The reaction mixture was then concentrated to dryness, and resulting salt was extracted with hot acetone. The organic part was concentrated and precipitation was achieved by drop wise addition of Et_2O at 0°C. The resulting product was collected by filtration and dried to get (2-(3-(benzyloxy)propoxy)ethyl)trifluoro-λ^4-borane as a potassium salt (2.5 g, 8.3 mmol, 41%) as white solid.

Step E

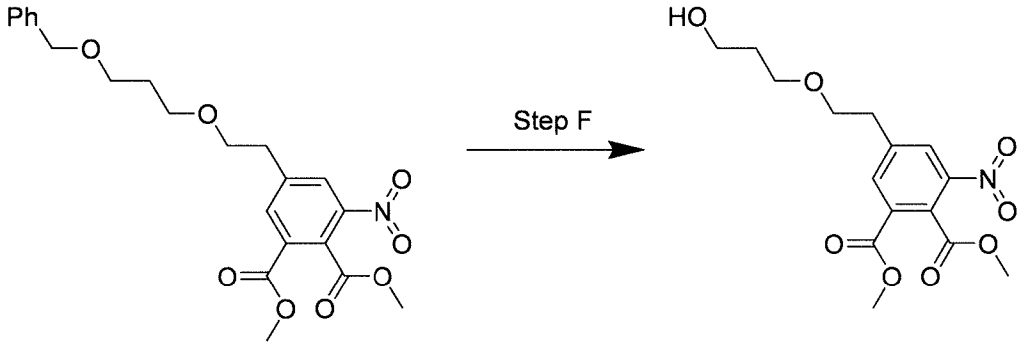


A suspension of (2-(3-(benzyloxy)propoxy)ethyl)trifluoro-λ^4-borane as a potassium salt (600 mg, 2.00 mmol), dimethyl-5-bromo-3-nitrophthalate (1.48 g, 5.66 mmol) and Cs_2CO_3 (1.8 g, 5.66 mmol) in a mixture of toluene-water (4:1) (20 mL) was deoxygenated using argon and to the reaction mixture was added Pd(amphos)Cl_2 (133 mg, 0.19 mmol) and it was allowed to stir at 100°C for 16h. The volatiles were evaporated under reduced pressure to get the crude compound, which was diluted with EtOAc, washed successively with water and brine, the organic layer was

dried over Na_2SO_4 and evaporated under reduced pressure to get the crude compound, which was then purified by flash chromatography (SiO_2, 20% EtOAc in hexane) to get dimethyl 5-(2-(3-(benzyloxy)propoxy)ethyl)-3-nitrophthalate (500 mg, 1.16 mmol, 58%) as gummy solid .

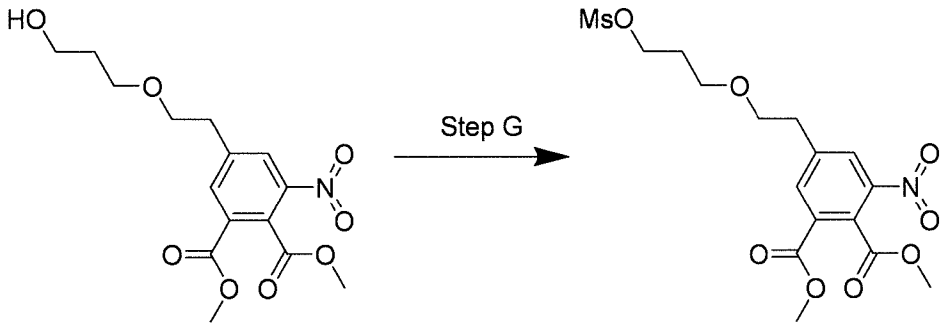
LCMS (ESI+): m/z 432.1 $[M+H]^+$

Step F



To a stirred solution of dimethyl 5-(2-(3-(benzyloxy)propoxy)ethyl)-3-nitrophthalate (5.5 g, 12.7 mmol) in DCM, boron trichloride (1 M solution in DCM) (127 mL, 127 mmol) was added drop wise at -78°C under nitrogen. It was stirred at same temperature for 2h. The reaction mixture was poured into ice and extracted with DCM. The organic layer was washed with water and brine successively. The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure to get 5.0 mg crude of dimethyl 5-(2-(3-hydroxypropoxy)ethyl)-3-nitrophthalate as brown dense liquid which was used for the next step without further purification.

Step G

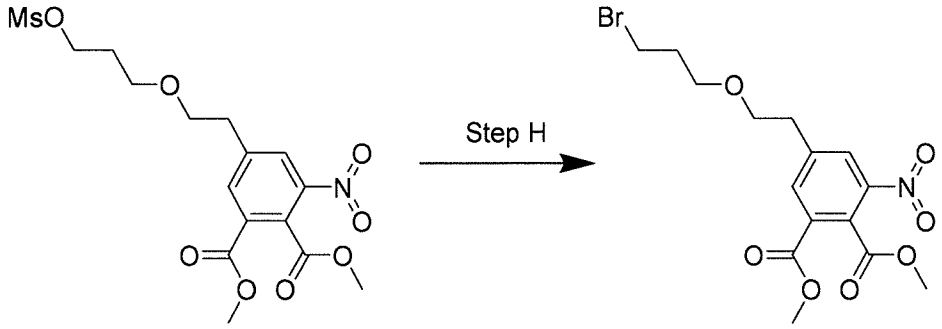


To a stirred solution of dimethyl 5-(2-(3-hydroxypropoxy)ethyl)-3-nitrophthalate (5 g crude) in DCM (80 mL) was added MsCl (3.2 mL, 22 mmol) followed by Et_3N (6 mL, 44 mmol) at 0°C under nitrogen and the reaction mixture was allowed to stir at room temperature for 2 h. The reaction mixture was diluted with EtOAc, washed successively with water and brine, the organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to get the crude compound, which was then purified by flash chromatography (SiO_2, 30% EtOAc in hexane) to get dimethyl 5-(2-(3-

((methylsulfonyl)oxy)propoxy)ethyl)-3-nitrophthalate (3.5 g, 8.3 mmol, 66% over two steps) as colorless liquid.

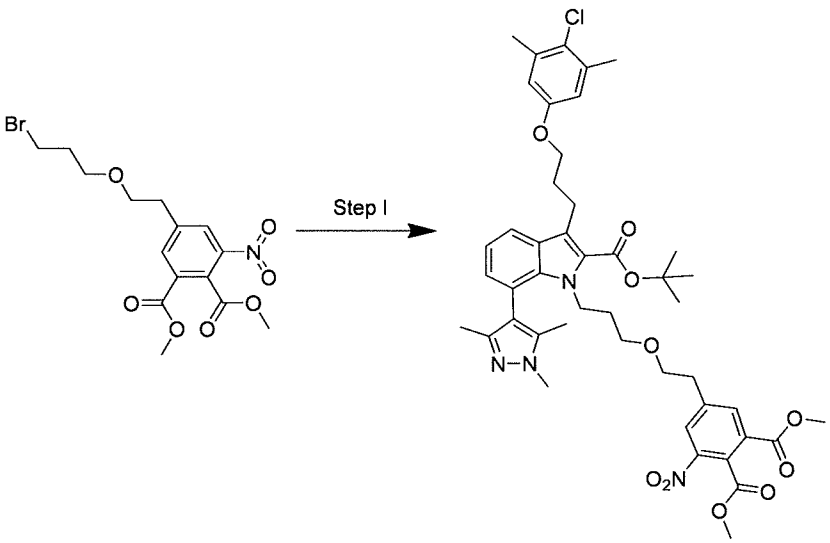
LCMS (ESI+): m/z 420.1 $[M+H]^+$

Step H



To a stirred solution of dimethyl 5-(2-(3-((methylsulfonyl)oxy)propoxy)ethyl)-3-nitrophthalate (3.6 g, 8.6 mmol) in DMF (30 mL) was added LiBr (3.7 g, 43 mmol) and the reaction mixture was allowed to stir at 80°C for 2 h under nitrogen. The reaction mixture was diluted with EtOAc, washed successively with water and brine, the organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to get the crude compound, which was then purified by flash chromatography (SiO_2, 20% EtOAc in hexane) to get dimethyl 5-(2-(3-bromopropoxy)ethyl)-3-nitrophthalate (2.5 g, 6.2 mmol, 72%) as light yellow dense liquid.

Step I

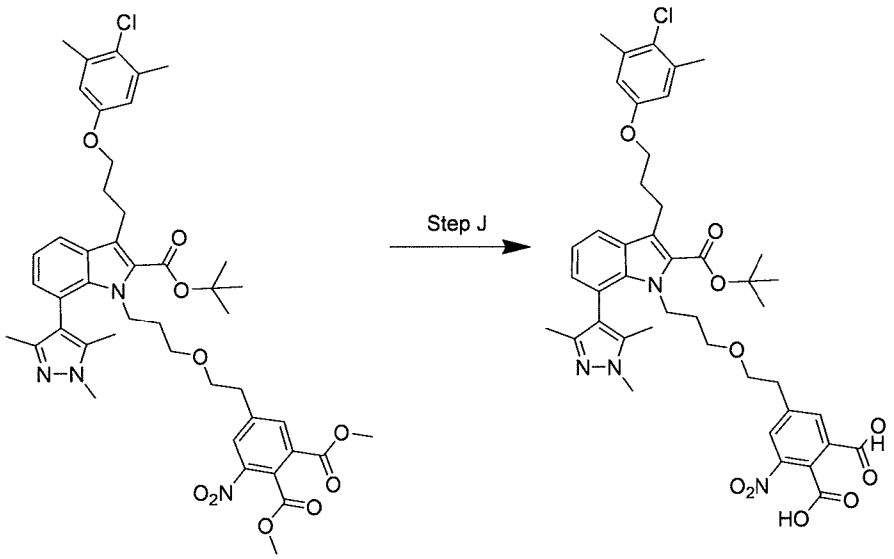


To a stirred solution of *tert*-butyl 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (500 mg, 0.958 mmol) in DMF (5 mL) was added sodium hydride (50 mg, 1.15 mmol) was added portion wise at 0°C under nitrogen. It was stirred

for 30 min at same temperature. A DMF (5 mL) solution of dimethyl 5-(2-(3-bromopropoxy)ethyl)-3-nitrophthalate (967 mg, 2.4 mmol) was added drop wise to the solution and the reaction mixture was allowed to stir for 16 h at room temperature. After complete consumption of the starting material (monitored by TLC and LCMS) the excess sodium hydride was quenched with ice water. It was then extracted EtOAc and washed with cold water (2-3 times) and brine successively. The combined organic layer was evaporated under reduced pressure to get the crude which was then purified by flash chromatography (SiO_2, 50% EtOAc in hexane) to afford dimethyl 5-(2-(3-(2-(*tert*-butoxycarbonyl)-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indol-1-yl)propoxy)ethyl)-3-nitrophthalate (400 mg, 0.47 mmol, 49%) as sticky gum.

LCMS (ESI+): m/z 845.0 $[M+H]^+$

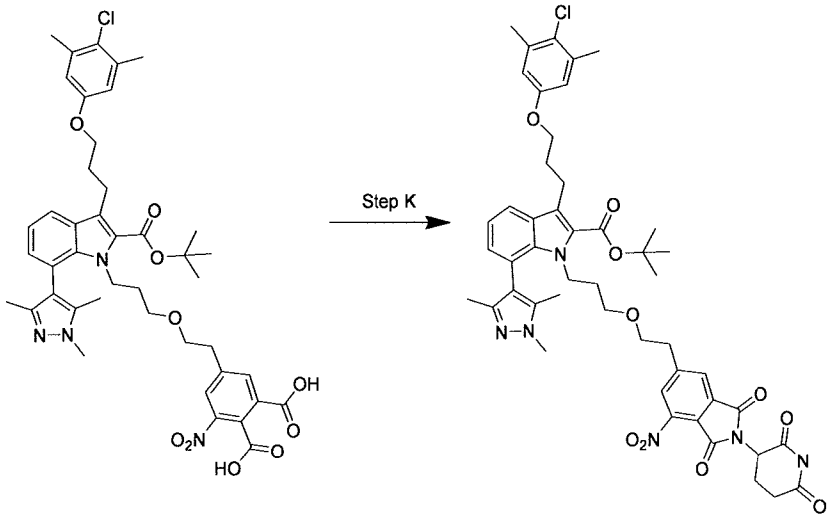
Step J



To a stirred solution of dimethyl 5-(2-(3-(2-(*tert*-butoxycarbonyl)-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indol-1-yl)propoxy)ethyl)-3-nitrophthalate (400 mg, 0.47 mmol) in methanol (5 mL), solid sodium hydroxide (189 mg, 4.7 mmol) was added at 0°C. The reaction mixture was allowed to stir at reflux for 16h. The volatiles were evaporated under reduced pressure to get the crude reaction which was then dissolved in water, washed with Et_2O. The aqueous layer was acidified with 6 N HCl to pH – 1-2. It was extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4 and evaporated under reduced pressure to get 5-(2-(3-(2-(*tert*-butoxycarbonyl)-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indol-1-yl)propoxy)ethyl)-3-nitrophthalic acid (320 mg, 0.39 mmol, 83%) as off white solid.

LCMS (ESI+): m/z 817.5 $[M+H]^+$

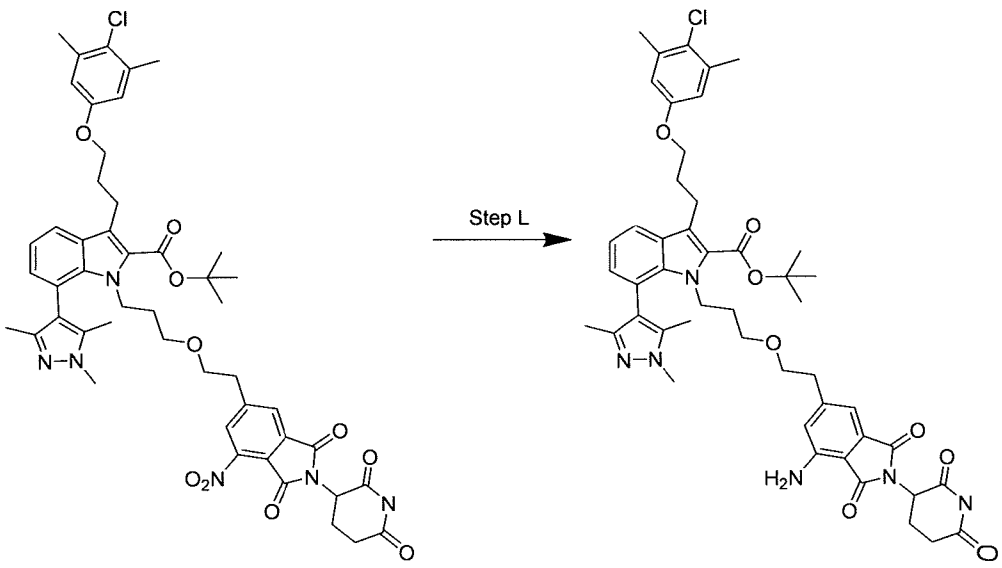
Step K



To a stirred solution of 5-(2-(3-(2-(*tert*-butoxycarbonyl)-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indol-1-yl)propoxy)ethyl)-3-nitrophthalic acid (300 mg, 0.36 mmol) in acetic acid (1 mL) was added 3-aminopiperidine-2,6-dione hydrochloride (120 mg, 0.73 mmol) followed by sodium acetate (150 mg, 1.8 mmol) and the reaction mixture was allowed to stir at 100°C for 16 h under nitrogen. The volatiles were evaporated under reduced pressure to get the crude reaction mass which was then purified by flash chromatography (SiO_2, 30% EtOAc in DCM) to afford *tert*-butyl 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-(3-(2-(2-(2,6-dioxopiperidin-3-yl)-7-nitro-1,3-dioxoisoindolin-5-yl)ethoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (300 mg, 0.33 mmol, 92%) as sticky gum.

LCMS (ESI+): m/z 909.2 $[M+H]^+$

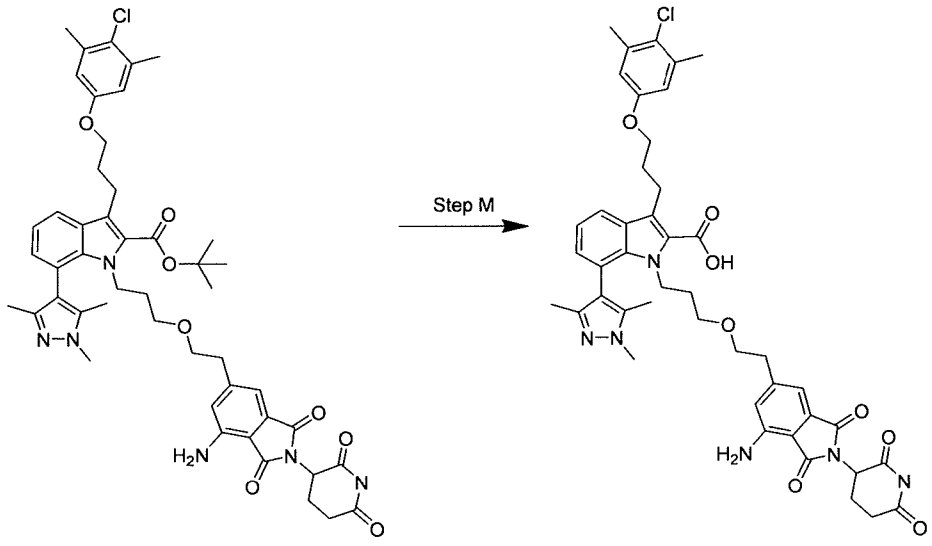
Step L



To a well stirred solution of *tert*-butyl 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-(3-(2-(2-(2,6-dioxopiperidin-3-yl)-7-nitro-1,3-dioxoisoindolin-5-yl)ethoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (400 mg, 0.44 mmol) in acetic acid (2 mL) was added triethyl silane (255 mg, 2.2 mmol) followed by 10% Pd/C (250 mg) and the reaction mixture was allowed to stir at room temperature for 3 h. The reaction mixture was filtered through celite pad. The filtrate was evaporated under reduced pressure to get 300 mg crude *tert*-butyl 1-(3-(2-(7-amino-2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)ethoxy)propyl)-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate which was used for the next step without further purification.

LCMS (ESI+): m/z 879.6 $[M+H]^+$

Step M

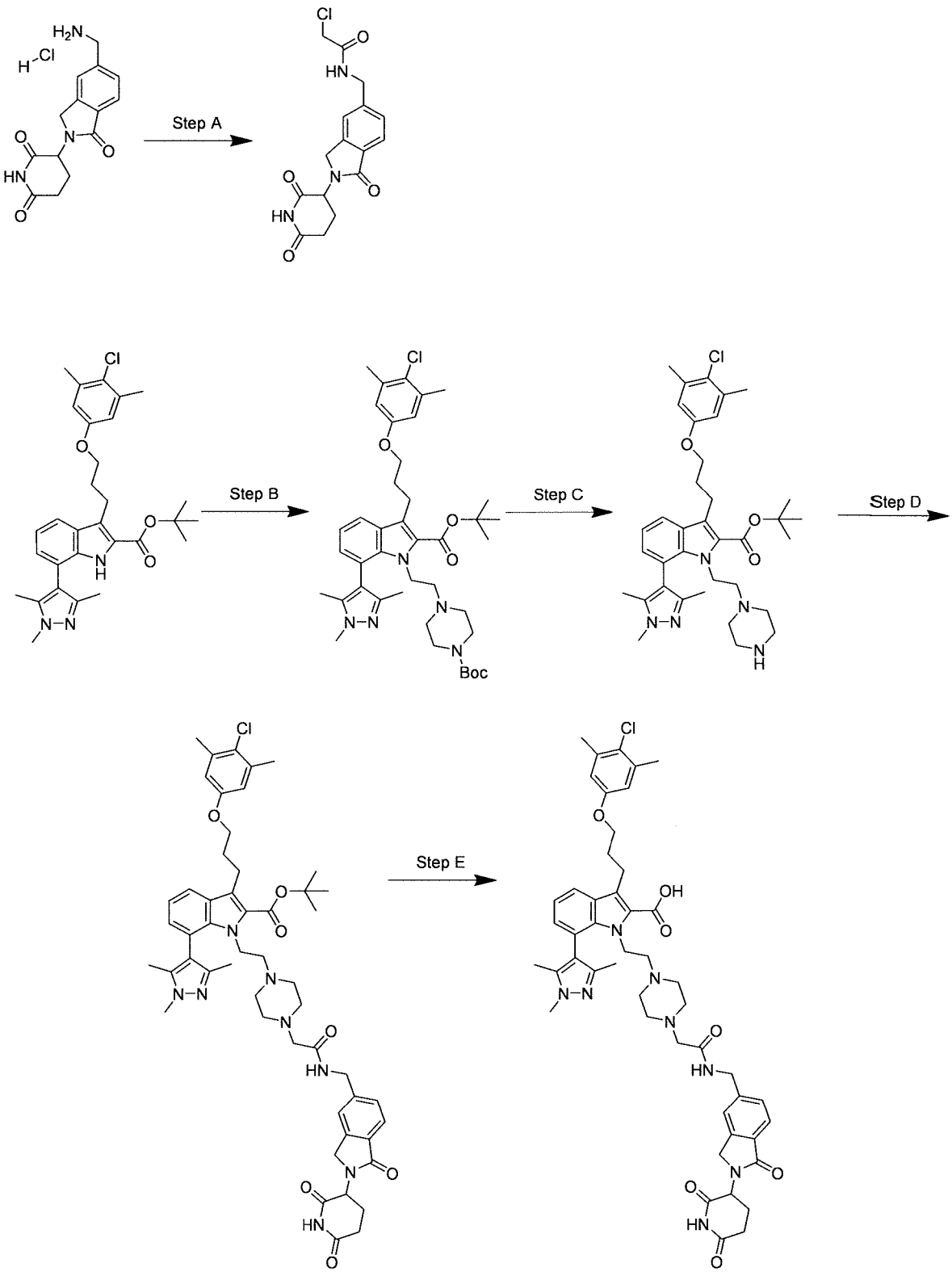


To a well stirred solution of *tert*-butyl 1-(3-(2-(7-amino-2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)ethoxy)propyl)-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (300 mg crude) in dioxane (8 mL) was added 2 mL of 4M HCl in dioxane and the reaction mixture was allowed to stir at room temperature for 28 h. The reaction mixture was evaporated under reduced pressure to get the crude compound, which was then purified by preparative HPLC (H_2O:MeCN + 0.1% FA) to get 1-(3-(2-(7-amino-2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)ethoxy)propyl)-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (20 mg, 0.024 mmol, 6% over two steps) as white solid.

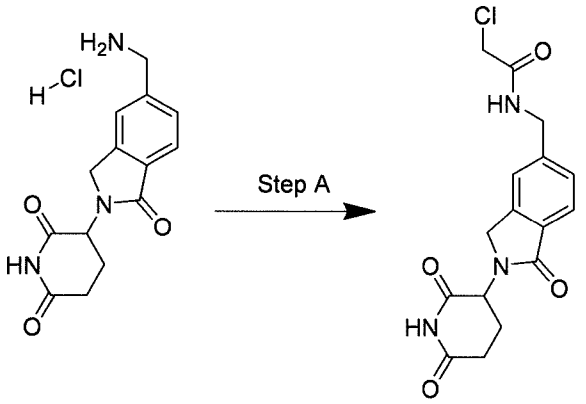
LCMS (ESI+): m/z 823.4 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO) δ 11.04 (s, 1H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.06 (t, *J* = 7.4 Hz, 1H), 6.91 – 6.85 (m, 1H), 6.85 – 6.82 (m, 1H), 6.82 – 6.78 (m, 1H), 6.71 (s, 2H), 6.45 (s, 2H), 4.99 (dd, *J* = 13.0, 5.5 Hz, 1H), 4.33 – 4.19 (m, 1H), 4.16 – 4.04 (m, 1H), 3.95 (t, *J* = 6.2 Hz, 2H), 3.68 (s, 3H), 3.37 – 3.30 (m, 1H), 3.18 – 3.05 (m, 2H), 2.91 – 2.69 (m, 3H), 2.71 – 2.61 (m, 2H), 2.61 – 2.50 (m, 2H), 2.23 (s, 6H), 2.07 – 1.93 (m, 6H), 1.91 (s, 4H), 1.40 – 1.18 (m, 2H).

Example 38. 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-(2-(4-(2-(((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)methyl)amino)-2-oxoethyl)piperazin-1-yl)ethyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (240)



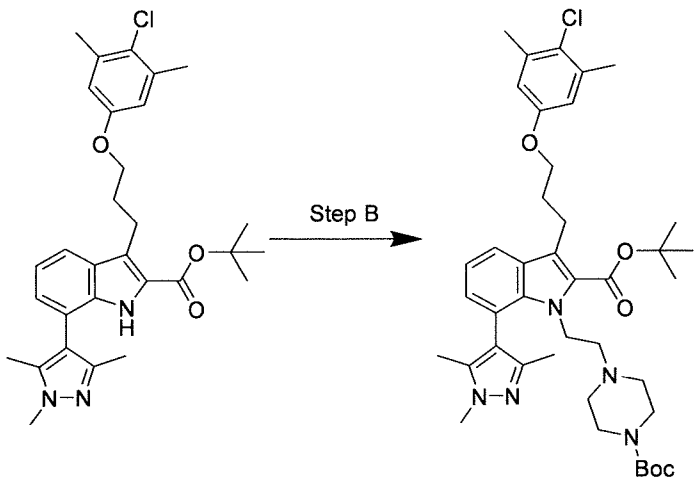
Step A



To the solution of 3-[5-(aminomethyl)-1-oxo-2,3-dihydro-1*H*-isoindol-2-yl]piperidine-2,6-dione hydrochloride (50.0 mg, 0.161 mmol) in DMF (1.5 mL) was added DIPEA (0.042 mL, 0.242 mmol), followed by chloroacetyl chloride (0.014 mL, 0.178 mmol). Mixture was stirred for overnight at RT. DMF was evaporated and the resultant residue was partitioned between EtOAc and H_2O. The organic layer was further washed with brine, dried over Na_2SO_4, filtered and evaporated. 2-Chloro-*N*-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)methyl)acetamide (60.0 mg, 0.161 mmol, 99.8%) was obtained as orangish solid.

LCMS (ESI+): m/z 349.9 $[M+H]^+$

Step B

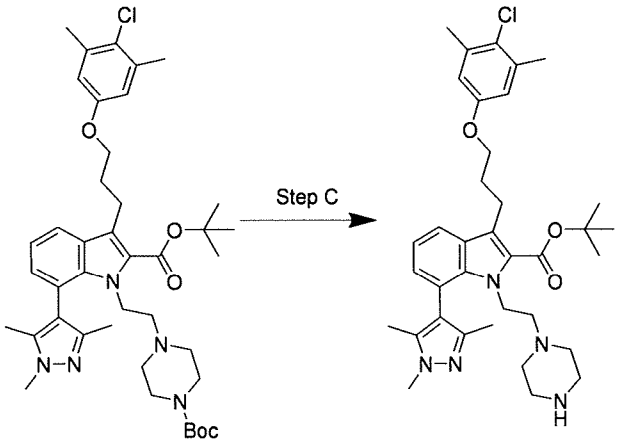


Tert-butyl 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (0.200 g, 0.383 mmol) and *tert*-butyl 4-(2-chloroethyl)piperazine-1-carboxylate (0.095 g, 0.383 mmol) were dissolved in DMF (3.8 mL). Subsequently, KI (0.064 g, 0.383 mmol) and Cs_2CO_3 (0.374 g, 1.149 mmol) were added. The reaction mixture was stirring at 70 °C for 24 h. DMF was evaporated and the resultant residue was partitioned between EtOAc and H_2O. The organic layer was further washed with brine, dried over Na_2SO_4, filtered and

evaporated. *Tert*-butyl 1-(2-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)ethyl)-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (214 mg, crude) was used to the next step without purification.

LCMS (ESI+): m/z 734.2 $[M+H]^+$

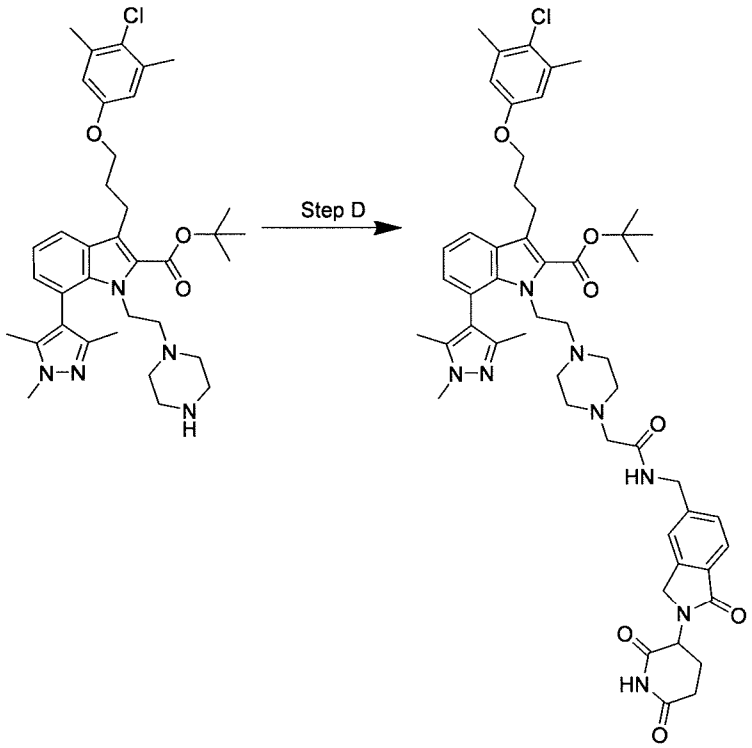
Step C



Tert-butyl 1-(2-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)ethyl)-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (214.0 mg, crude) was dissolved in THF (5.8 mL) and 4M HCl in dioxane (0.506 mL, 14.57 mmol) was added at 0 °C and the mixture stirred for 24 h. The reaction mixture was quenched by cold 0.1M NaOH solution (10 mL) and extracted several times with EtOAc and one time with acetonitrile. The combined organics were dried over Na_2SO_4 and concentrated in vacuo. Desired product was purified using flash chromatography (SiO_2, 20% MeOH in DCM). *Tert*-butyl 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-(2-(piperazin-1-yl)ethyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (139.0 mg, 0.210 mmol, 55% over two steps) was obtained as orange oil.

LCMS (ESI+): m/z 634.3 $[M+H]^+$

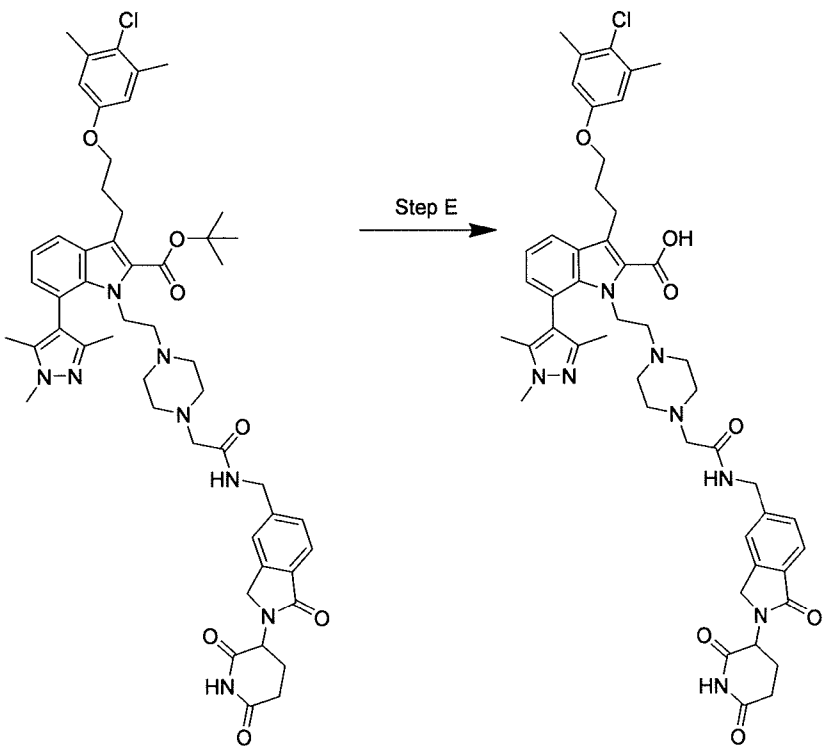
Step D



Tert-butyl 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-(2-(piperazin-1-yl)ethyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (40.0 mg, 0.063 mmol) and 2-chloro-*N*-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)methyl)acetamide (24.3 mg, 0.069 mmol) were dissolved in DMF (1.3 mL). Subsequently, KI (10.5 mg, 0.063 mmol) and DIPEA (0.033 mL, 0.189 mmol) were added and the mixture was stirring in 70 °C for 24 h. DMF was evaporated and the resultant residue was partitioned between EtOAc and H_2O. The organic layer was further washed with brine, dried over Na_2SO_4, filtered and evaporated. Desired product was purified using flash chromatography (SiO_2, 10% MeOH in DCM). *Tert*-butyl 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-(2-(4-(2-(((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)methyl)amino)-2-oxoethyl)piperazin-1-yl)ethyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (39.0 mg, 0.036 mmol, 57%) was obtained as orange oil.

LCMS (ESI+): m/z 948.1 $[M+H]^+$

Step E

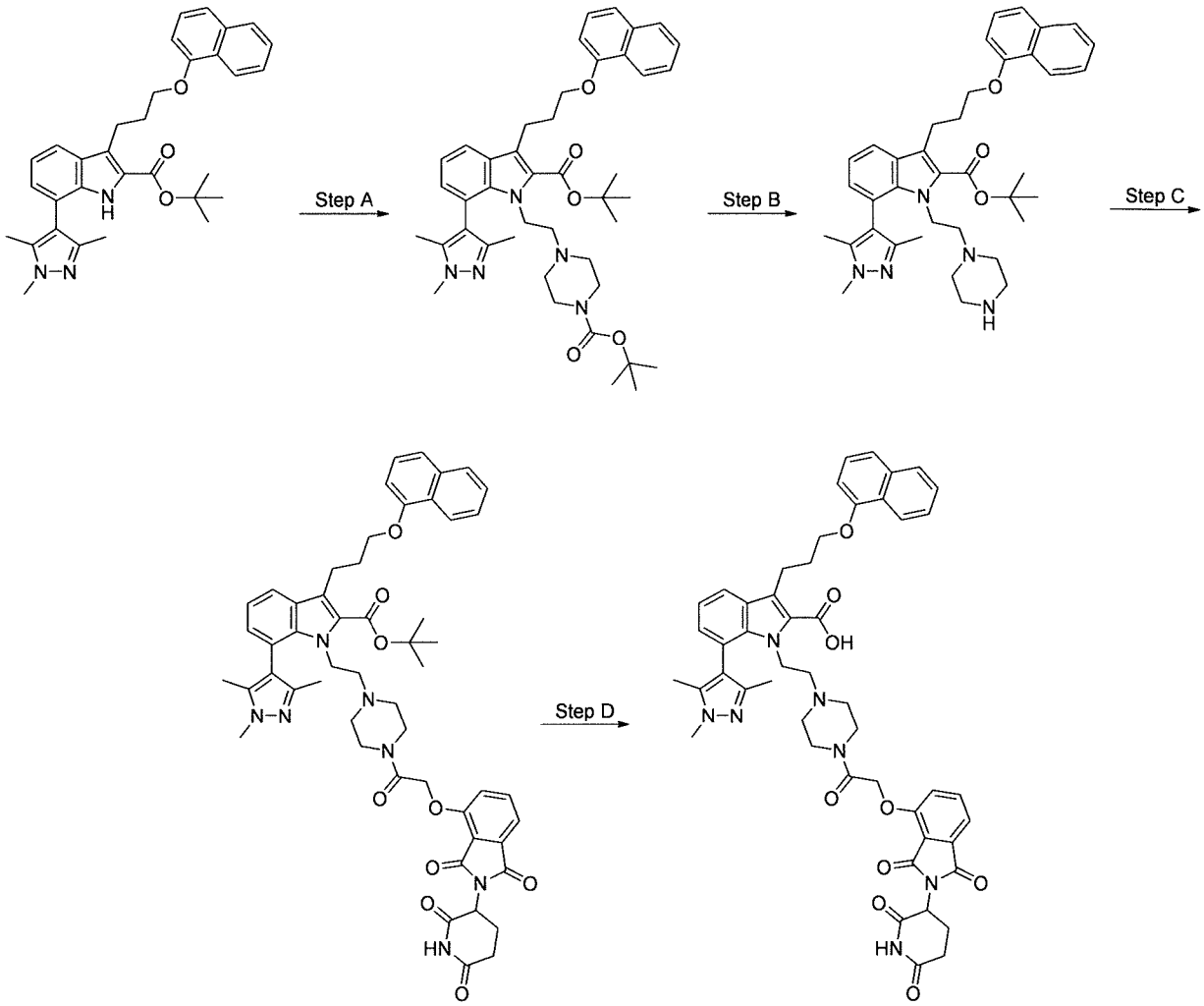


Tert-butyl 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-(2-(4-(2-(((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)methyl)amino)-2-oxoethyl)piperazin-1-yl)ethyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (40.0 mg, 0.042 mmol) was dissolved in 4 M HCl in dioxane (0.073 mL, 2.111 mmol). Subsequently, the mixture was stirring at room temperature for overnight. The solvent was evaporated and the resultant residue was dissolved in DMSO and filtered. The compound was purified by preparative HPLC (H_2O:MeCN + 0.1% FA). 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1-(2-(4-(2-(((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)methyl)amino)-2-oxoethyl)piperazin-1-yl)ethyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (13.0 mg, 0.015 mmol, 36%) was obtained as yellowish solid.

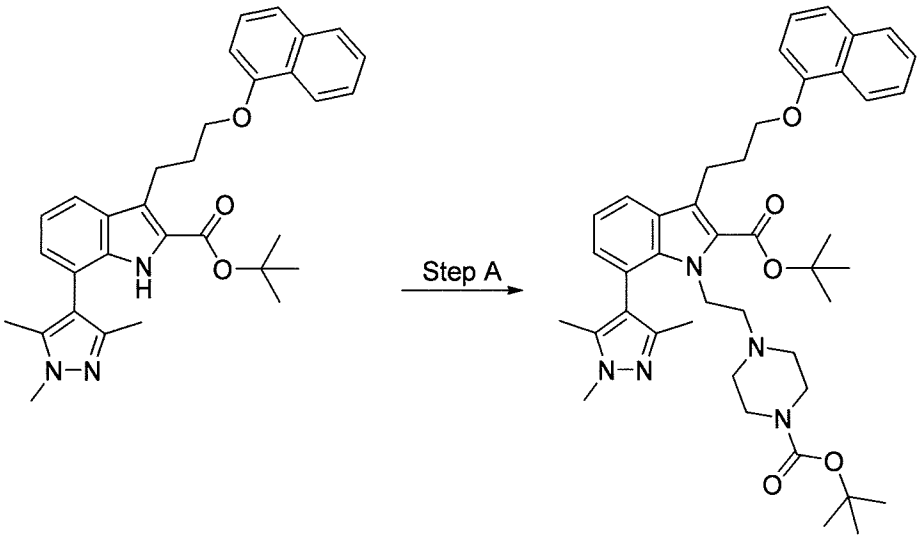
LCMS (ESI+): m/z 891.0 $[M+H]^+$

^{1}H NMR (500 MHz, DMSO) δ 10.97 (s, 1H), 8.28 (s, 1H), 7.70 – 7.61 (m, 2H), 7.44 (s, 1H), 7.38 (d, *J* = 7.8 Hz, 1H), 7.10 (t, *J* = 7.6 Hz, 1H), 6.92 (dd, *J* = 7.0, 1.2 Hz, 1H), 6.73 (s, 2H), 5.10 (dd, *J* = 13.3, 5.1 Hz, 1H), 4.47 – 4.18 (m, 6H), 3.98 (t, *J* = 6.4 Hz, 2H), 3.73 – 3.66 (m, 3H), 3.14 (t, *J* = 7.4 Hz, 2H), 2.96 – 2.85 (m, 2H), 2.62 – 2.57 (m, 1H), 2.53 – 2.51 (m, 1H), 2.44 – 2.27 (m, 5H), 2.26 (s, 6H), 2.13 (s, 5H), 2.06 (s, 3H), 2.06 – 1.96 (m, 4H), 1.92 (s, 3H).

Example 39. 1-(2-(4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)acetyl)piperazin-1-yl)ethyl)-3-(3-(naphthalen-1-yloxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (241)



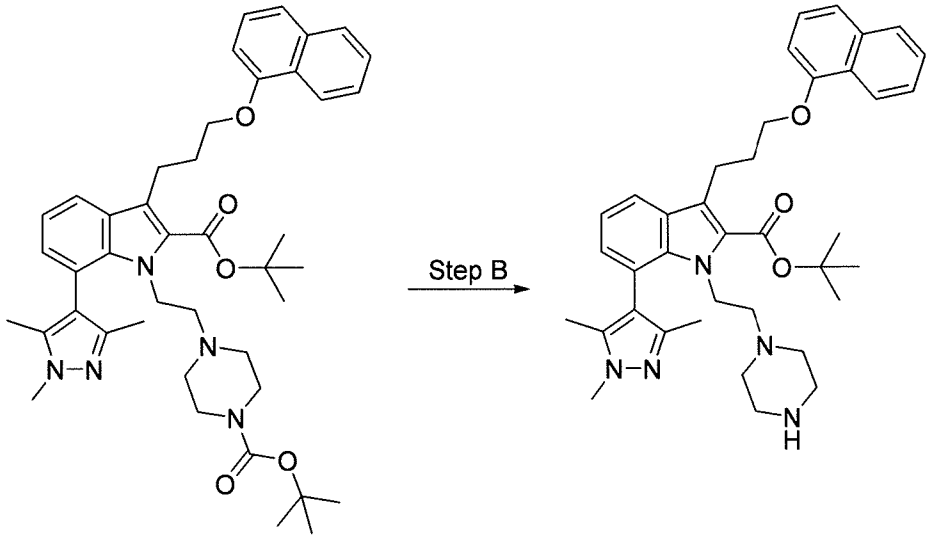
Step A



Tert-butyl 3-(3-(naphthalen-1-yloxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (300.0 mg, 0.589 mmol) was dissolved in dry DMF (5.9 mL). Cs_2CO_3 (958.9 mg, 1.766 mmol), KI (97.7 mg, 0.589 mmol) and *tert*-butyl 4-(2-chloroethyl)piperazine-1-carboxylate (161.0 mg, 0.648 mmol) were added and the reaction was stirred in 70°C. After 20 h, DMF was evaporated, and the residues were dissolved in EtOAc. Organic layer was washed 3x with water and 3x with brine. The organic phase was collected and combined aqueous layer was 2x washed with EtOAc. Merged organic layers were once again washed with water, dried over anhydrous Na_2SO_4, filtered and the solvent was evaporated. The reaction product was dried under reduced pressure, to afford *tert*-butyl 1-(2-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)ethyl)-3-(3-(naphthalen-1-yloxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (404.0 mg, crude) as yellow oil.

LCMS (ESI+): m/z 722.0 $[M+H]^+$

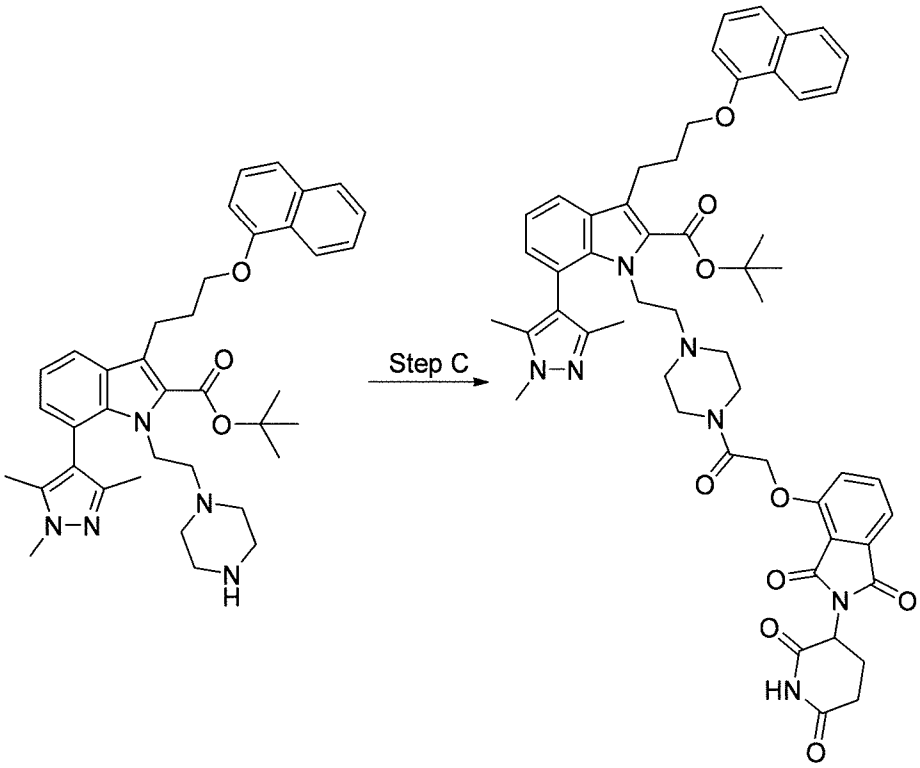
Step B



Tert-butyl 1-(2-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)ethyl)-3-(3-(naphthalen-1-yloxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (404.0 mg, crude) was dissolved in dry THF (11.2 mL) under an inert gas atmosphere, cooled down to 0°C and 4 M solution of HCl in dioxane (7.0 mL, 27.980 mmol) was added. After 9 h full conversion of the starting material was observed. The reaction was quenched by the addition of cold 1 M NaOH aqueous solution to neutral pH. Reaction product was extracted several times with EtOAc. The combined organics were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Desired product was purified using flash chromatography (SiO_2, 20% MeOH in DCM). *Tert*-butyl 3-(3-(naphthalen-1-yloxy)propyl)-1-(2-(piperazin-1-yl)ethyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (293.0 mg, 0.451 mmol, 77% yield) was obtained as orange oil.

LCMS (ESI+): m/z 622.8 $[M+H]^+$

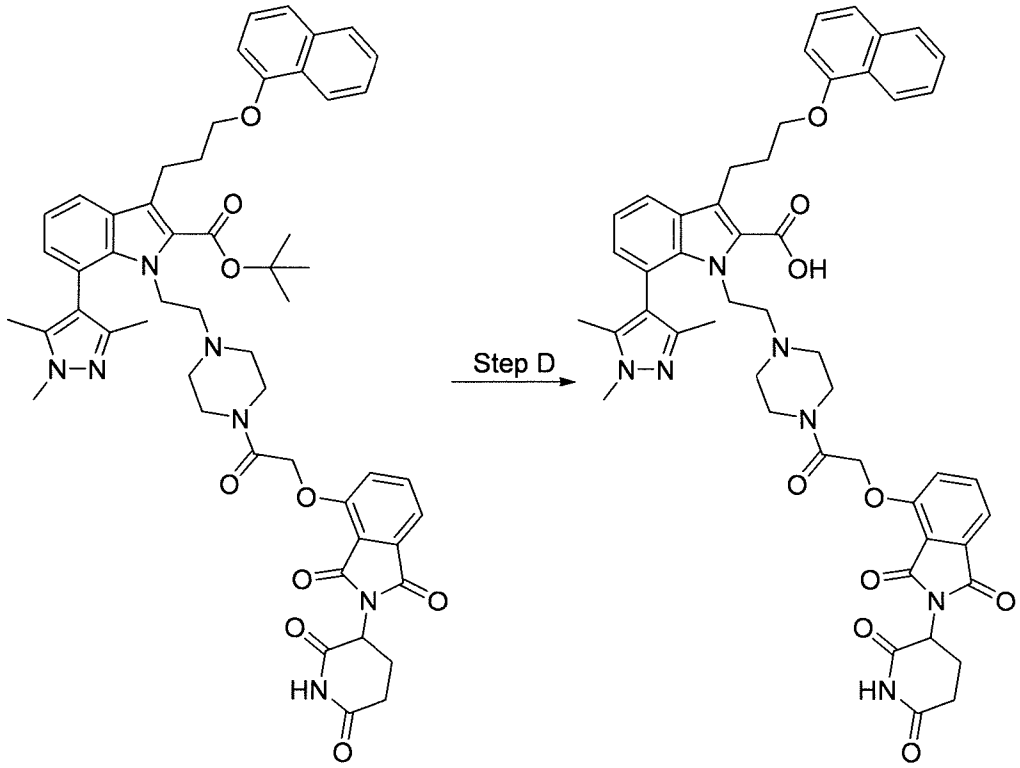
Step C



To a solution of 2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)acetic acid (19.2 mg, 0.058 mmol) in dry DMF (1.9 mL), DIPEA (0.025 mL, 0.145 mmol) and HATU (27.5 mg, 0.072 mmol) were added and the mixture was allowed to stir under argon atmosphere for 15 min. Next, *tert*-butyl 3-(3-(naphthalen-1-yloxy)propyl)-1-(2-(piperazin-1-yl)ethyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (30.0 mg, 0.048 mmol) was added and the solution was stirred for 2h at room temperature. DMF was evaporated, the reaction mixture diluted with EtOAc, washed successively with cold water (3 times) and brine. Organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to afford *tert*-butyl 1-(2-(4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)acetyl)piperazin-1-yl)ethyl)-3-(3-(naphthalen-1-yloxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (36.6 mg, crude) as a black solid which was used in next step without further purification.

LCMS (ESI+): m/z 936.87 $[M+H]^+$

Step D

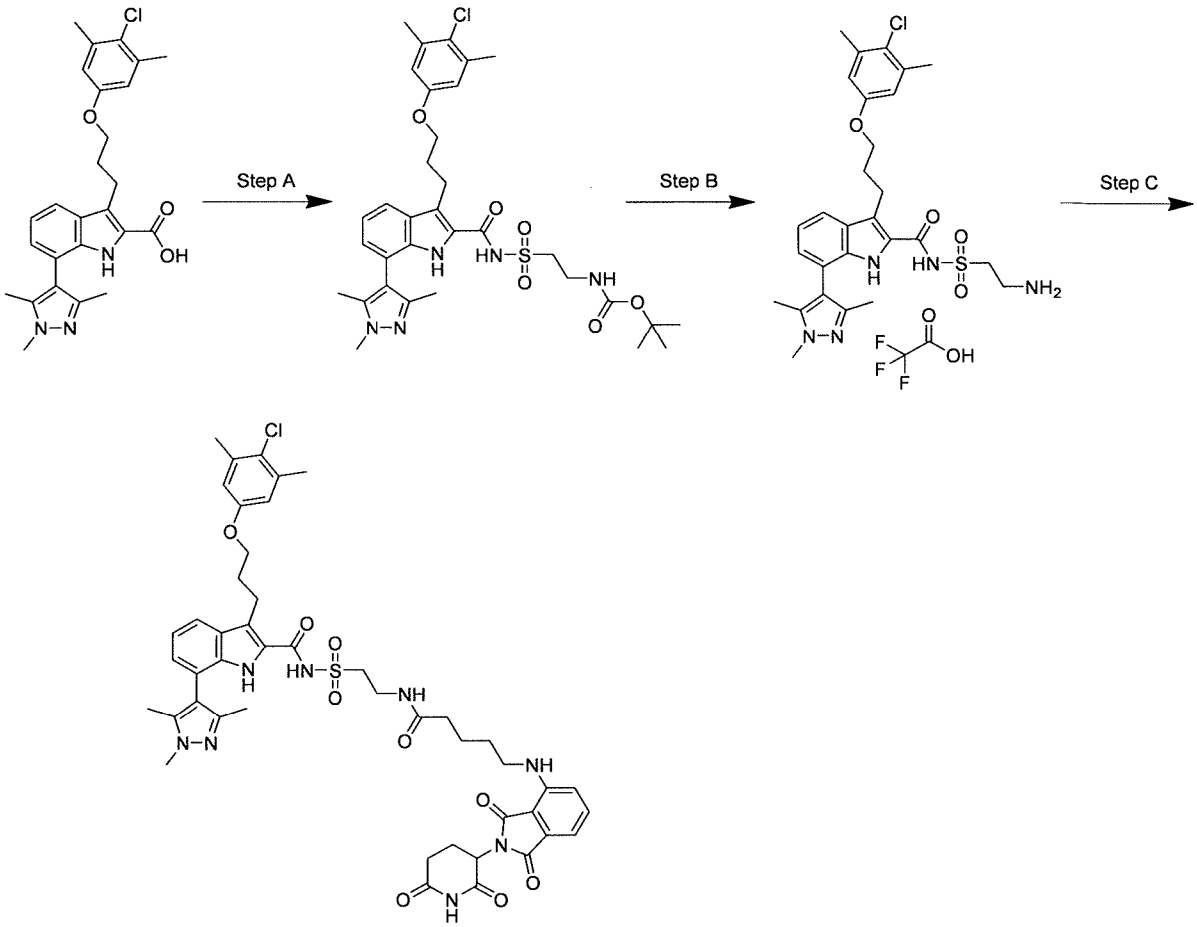


Tert-butyl 1-(2-(4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)acetyl)piperazin-1-yl)ethyl)-3-(3-(naphthalen-1-yloxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (36.6 mg, crude) was dissolved in dry DCM (0.18 mL) under argon atmosphere. TFA (0.18 mL, 0.782 mmol) was added and the reaction was stirred at room temperature in a sealed vial for 18 h. DCM and TFA were evaporated under reduced pressure. The residues were dissolved in DMSO and purified by preparative HPLC (H_2O:MeCN + 0.1% FA) to give a corresponding 1-(2-(4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)acetyl)piperazin-1-yl)ethyl)-3-(3-(naphthalen-1-yloxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (12.7 mg, 0.014 mmol, 29% yield over two steps) as white powder.

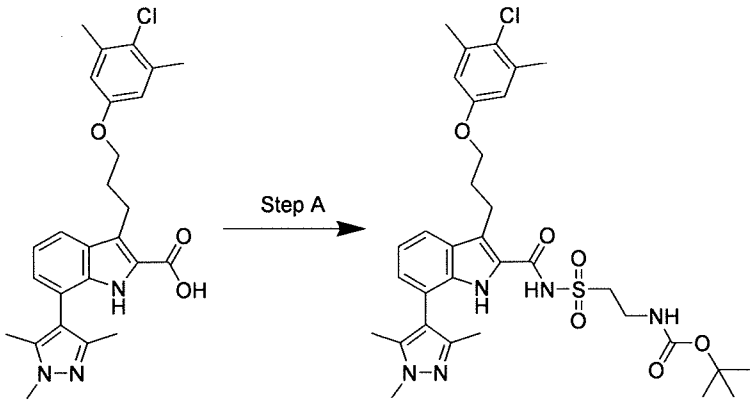
LCMS (ESI+): m/z 881.1 $[M+H]^+$

^{1}H NMR (500 MHz, DMSO) δ 13.27 (s, 1H), 11.11 (s, 1H), 8.30 – 8.22 (m, 1H), 7.92 – 7.86 (m, 1H), 7.83 – 7.69 (m, 2H), 7.57 – 7.50 (m, 2H), 7.47 (t, *J* = 6.8 Hz, 2H), 7.41 (t, *J* = 7.9 Hz, 1H), 7.32 (d, *J* = 7.2 Hz, 1H), 7.15 – 7.09 (m, 1H), 7.00 – 6.95 (m, 1H), 6.93 (d, *J* = 7.5 Hz, 1H), 5.29 – 5.01 (m, 3H), 4.61 – 4.27 (m, 2H), 4.25 (t, *J* = 6.0 Hz, 2H), 3.77 (s, 3H), 3.42 – 3.36 (m, 4H), 3.30-3.27 (m, 2H), 2.96 – 2.84 (m, 1H), 2.64 – 2.57 (m, 2H), 2.56 – 2.54 (m, 1H), 2.25 (d, *J* = 6.8 Hz, 2H), 2.11 (s, 3H), 2.10 – 1.99 (m, 5H), 1.96 (s, 3H), 1.96 – 1.88 (m, 1H).

Example 40. 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-*N*-((2-(5-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)pentanamido)ethyl)sulfonyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxamide (242)



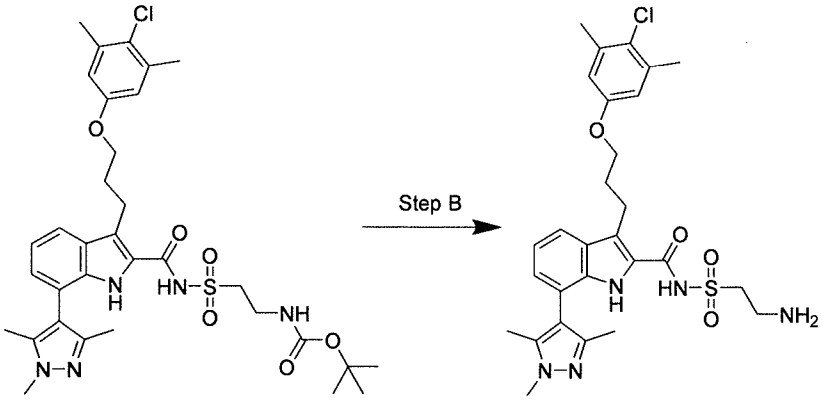
Step A



3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (6.6 g, 14.2 mmol), Et_3N (5 mL, 28.1 mmol), DMAP (0.86 g, 7.1 mmol) and HATU

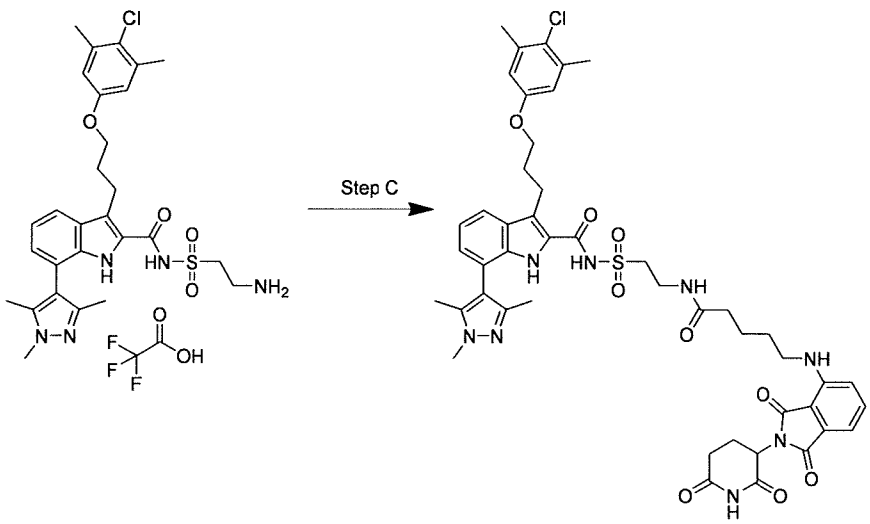
(8.6 g, 22.6 mmol) were dissolved in DMF (100 mL) and reaction mixture was stirred at room temperature for 15 min. Followed by *tert*-butyl (2-sulfamoylethyl)carbamate (4.75 g, 21.2 mmol) was added in one portion and the reaction mixture was stirred at 50°C for 24 h. The mixture was poured into water and the aqueous solution was extracted with DCM. The combined organic extracts were washed with H_2O and dried over Na_2SO_4. The solvent was removed under vacuum and the residue was purified by flash chromatography to afford *tert*-butyl (2-(*N*-(3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carbonyl)sulfamoyl)ethyl)carbamate (3.4 g, 5.06 mmol, 36%).

Step B



Tert-butyl (2-(*N*-(3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carbonyl)sulfamoyl)ethyl)carbamate (3.4 g, 5.06 mmol) was dissolved in DCM (50 mL) and TFA (10 mL) was added dropwise to the mixture. The reaction was stirred at room temperature for 24 h and then evaporated under reduced pressure to give crude *N*-((2-aminoethyl)sulfonyl)-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxamide trifluoroacetate (4.10 g of crude), which was used into the next step without further purification.

Step C

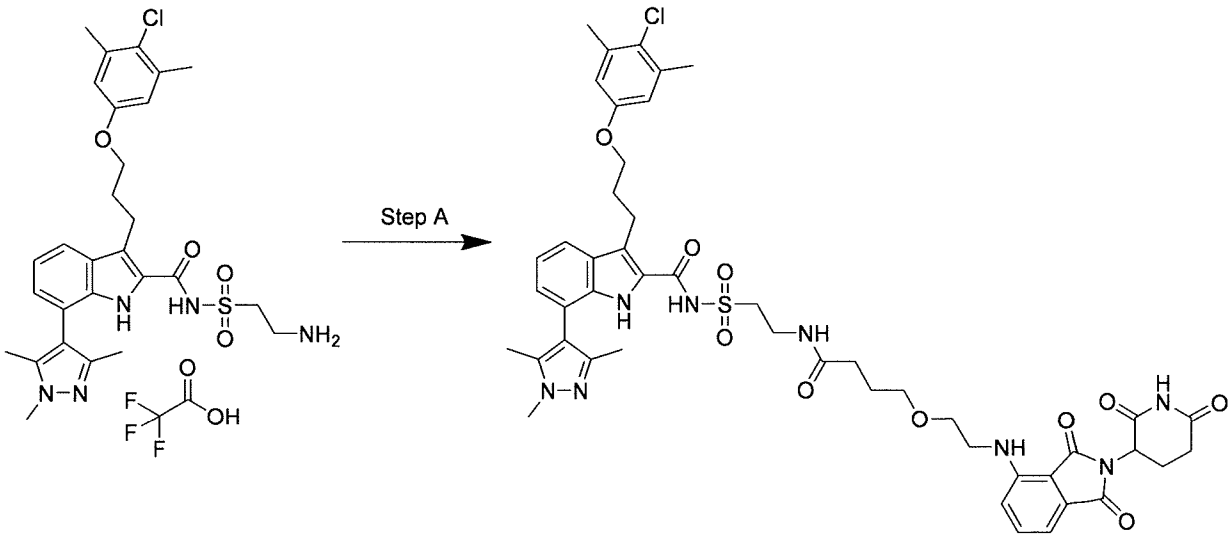


5-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)pentanoic acid (0.45 g, 1.21 mmol), DIPEA (0.61 mL, 3.50 mmol), and HATU (0.50 g, 1.30 mmol) were dissolved in DMF (6 mL) and the reaction mixture were stirred at room temperature for 15 min. Followed by *N*-((2-aminoethyl)sulfonyl)-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxamide trifluoroacetate (0.60 g, 0.87 mmol) in DMF (5 mL) was added in one portion and the reaction mixture were stirred at 50°C for 24 h. The mixture was poured into water and the aqueous solution was extracted with DCM. The combined organic extracts were washed with H_2O and dried over Na_2SO_4. The solvent was removed under vacuum and the residue was purified by preparative HPLC (H_2O:MeCN + 0.1% FA) to afford 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-*N*-((2-(5-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)pentanamido)ethyl)sulfonyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxamide (64 mg, 0.069 mmol, 8% over two steps) as yellow solid.

LCMS (ESI+): m/z 927.7 $[M+H]^+$

^1H NMR (400 MHz, CD_3OD) δ 7.64 – 7.55 (m, 1H), 7.52 – 7.42 (m, 1H), 7.05 (t, *J* = 7.5 Hz, 1H), 7.02 – 6.96 (m, 2H), 6.87 (d, *J* = 8.6 Hz, 1H), 6.71 – 6.60 (m, 2H), 5.04 (dd, *J* = 12.5, 5.4 Hz, 1H), 3.98 (t, *J* = 6.4 Hz, 2H), 3.82 (s, 3H), 3.63 (t, *J* = 6.3 Hz, 2H), 3.46 (t, *J* = 6.3 Hz, 2H), 3.39 – 3.34 (m, 2H), 3.08 (t, *J* = 6.9 Hz, 1H), 2.86 – 2.70 (m, 2H), 2.68 – 2.64 (m, 4H), 2.29 (s, 6H), 2.20 – 2.03 (m, 11H), 1.58 – 1.39 (m, 4H).

Example 41. 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-*N*-((2-(4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)butanamido)ethyl)sulfonyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxamide (243)



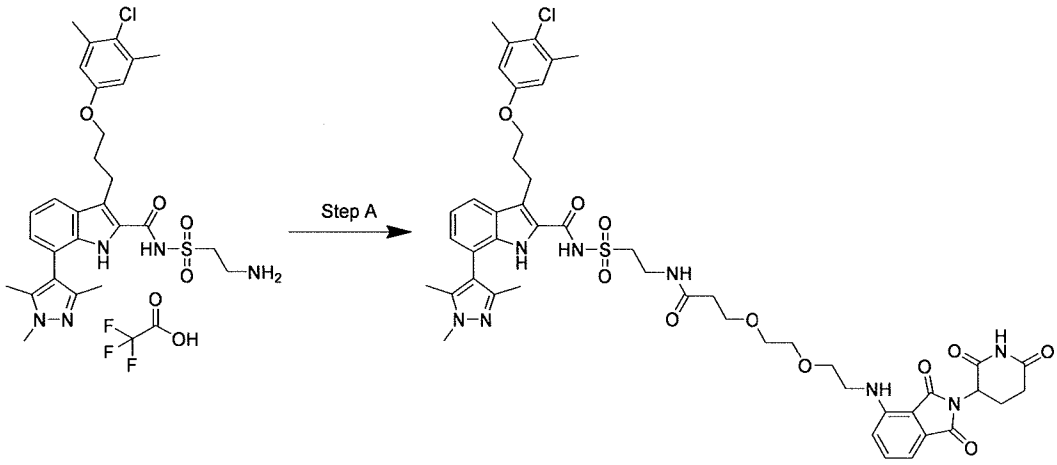
Step A

4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)butanoic acid (0.49 g, 1.21 mmol), DIPEA (0.61 mL, 3.50 mmol) and HATU (0.50 g, 1.30 mmol) were dissolved in DMF (6 mL) and the reaction mixture were stirred at room temperature for 15 min. Followed *N*-((2-aminoethyl)sulfonyl)-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxamide trifluoroacetate (0.60 g, 0.87 mmol) in DMF (5 mL) was added in one portion and the reaction mixture were stirred at 50°C for 24 h. The mixture was poured into water and the aqueous solution was extracted with DCM. The combined organic extracts were washed with H_2O and dried over Na_2SO_4. The solvent was removed under vacuum and the residue was purified by preparative HPLC to afford 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-*N*-((2-(4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)butanamido)ethyl)sulfonyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxamide (0.06 g, 0.063 mmol, 7%) as a yellow solid.

LCMS (ESI+): m/z 957.2 $[M+H]^+$

^1H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.0 Hz, 1H), 7.49 (t, *J* = 7.8 Hz, 1H), 7.20 – 7.03 (m, 3H), 6.94 – 6.80 (m, 2H), 6.66 (s, 2H), 6.56 – 6.47 (m, 1H), 5.06 – 4.93 (m, 1H), 3.96 (t, *J* = 6.0 Hz, 2H), 3.84 – 3.66 (m, 7H), 3.66 – 3.54 (m, 2H), 3.49 – 3.27 (m, 6H), 2.92 – 2.67 (m, 3H), 2.38 – 2.25 (m, 8H), 2.24 – 2.10 (m, 6H), 2.05 (s, 3H), 1.83 (s, 2H).

Example 42. 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-*N*-((2-(3-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)propanamido)ethyl)sulfonyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxamide (244)



Step A

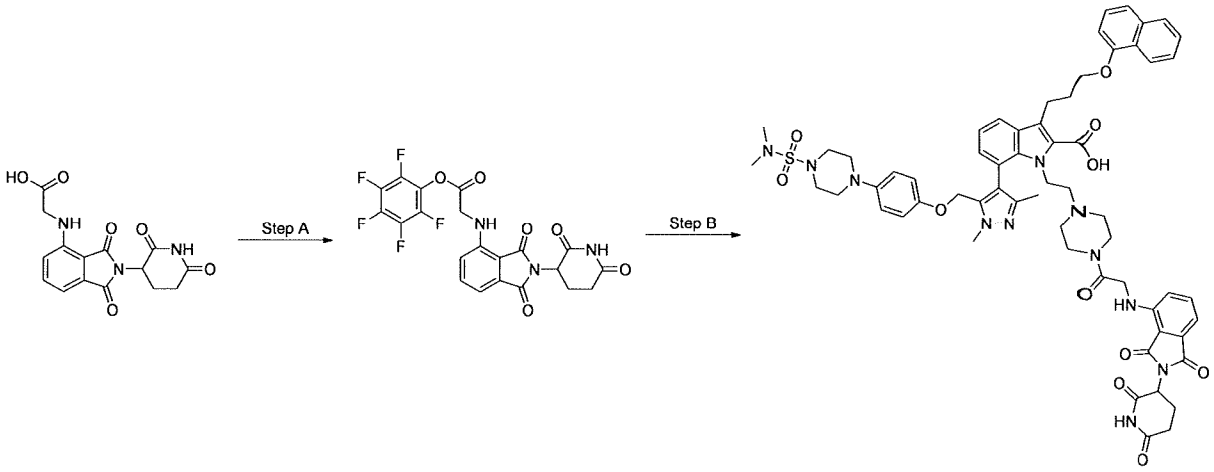
3-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)propanoic acid (0.53 g, 1.22 mmol), DIPEA (0.61 mL, 3.50 mmol), and HATU (0.50 g, 1.30 mmol) were dissolved in DMF (6 mL) and the reaction mixture were stirred at room temperature for 15 min. Followed by *N*-((2-aminoethyl)sulfonyl)-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxamide trifluoroacetate (0.60 g, 0.87 mmol) in DMF (5 mL) was added in one portion and the reaction mixture were stirred at 50°C for 24 h. The mixture was poured into water and the aqueous solution was extracted with DCM. The combined organic extracts were washed with H_2O and dried over Na_2SO_4. The solvent was removed under vacuum and the residue was purified by preparative HPLC (H_2O:MeCN + 0.1% FA) to afford 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-*N*-((2-(3-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)propanamido)ethyl)sulfonyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxamide (92 mg, 0.093 mmol, 11%) as a yellow solid.

LCMS (ESI+): m/z 987.7 $[M+H]^+$

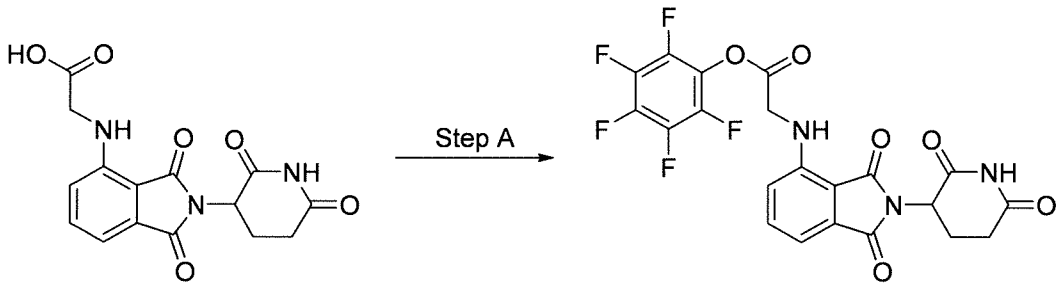
^1H NMR (600 MHz, DMSO) δ 11.70 (s, 1H), 11.09 (s, 1H), 10.78 (s, 1H), 8.10 – 8.00 (m, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.55 (dd, *J* = 8.6, 7.0 Hz, 1H), 7.16 – 7.05 (m, 3H), 7.02 (d, *J* = 7.0 Hz, 1H), 6.76 (s, 2H), 6.57 (t, *J* = 5.8 Hz, 1H), 5.04 (dd, *J* = 12.9, 5.5 Hz, 1H), 3.97 (t, *J* = 6.4 Hz, 2H), 3.77 (s, 3H), 3.71 – 3.62 (m, 2H), 3.56 (t, *J* = 5.5 Hz, 2H), 3.49 – 3.40 (m, 8H), 3.38 – 3.34 (m, 2H), 3.23 (t, *J* = 8.5, 6.5

Hz, 2H), 2.87 (ddd, *J* = 17.0, 13.8, 5.4 Hz, 1H), 2.61 – 2.51 (m, 2H), 2.26 (s, 6H), 2.20 (t, *J* = 6.6 Hz, 2H), 2.09 (s, 3H), 2.06 – 1.98 (m, 6H).

Example 43. 7-(5-((4-(4-(*N*,*N*-dimethylsulfamoyl)piperazin-1-yl)phenoxy)methyl)-1,3-dimethyl-1*H*-pyrazol-4-yl)-1-(2-(4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)glycyl)piperazin-1-yl)ethyl)-3-(3-(naphthalen-1-yloxy)propyl)-1*H*-indole-2-carboxylic acid (245)

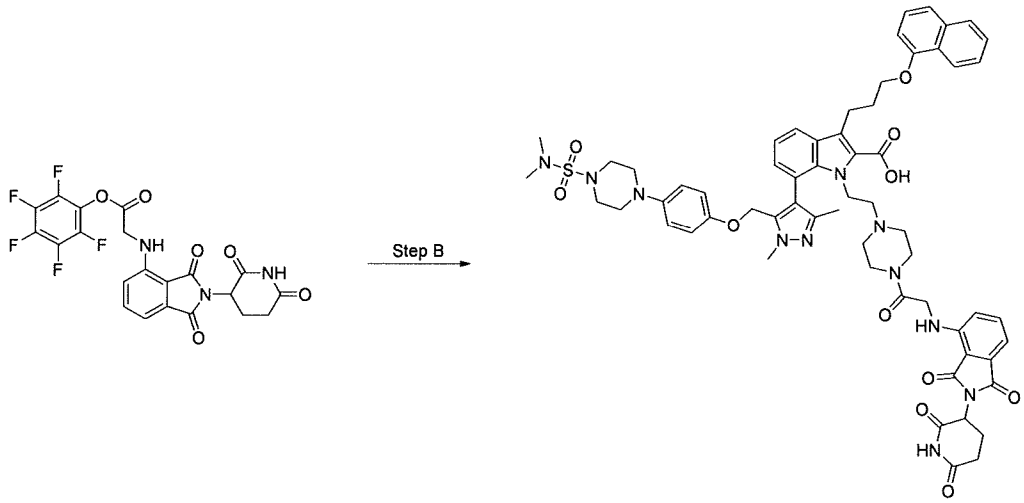


Step A



To a solution of (2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)glycine (200 mg, 0.60 mmol) in DMF (2 ml), DIPEA (1 ml, 6 mmol) was added and the reaction mixture was cooled down to 0°C. Pentafluorophenyl trifluoroacetate (843 mg, 3.0 mmol) was added and the mixture was allowed to stir at ambient temperature for 2 h under nitrogen. After complete consumption of the starting material (monitored by LCMS) the volatiles were evaporated under reduced pressure to obtain 200 mg of crude perfluorophenyl (2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)glycinate as brown sticky solid which was used for the next step without further purification.

Step B

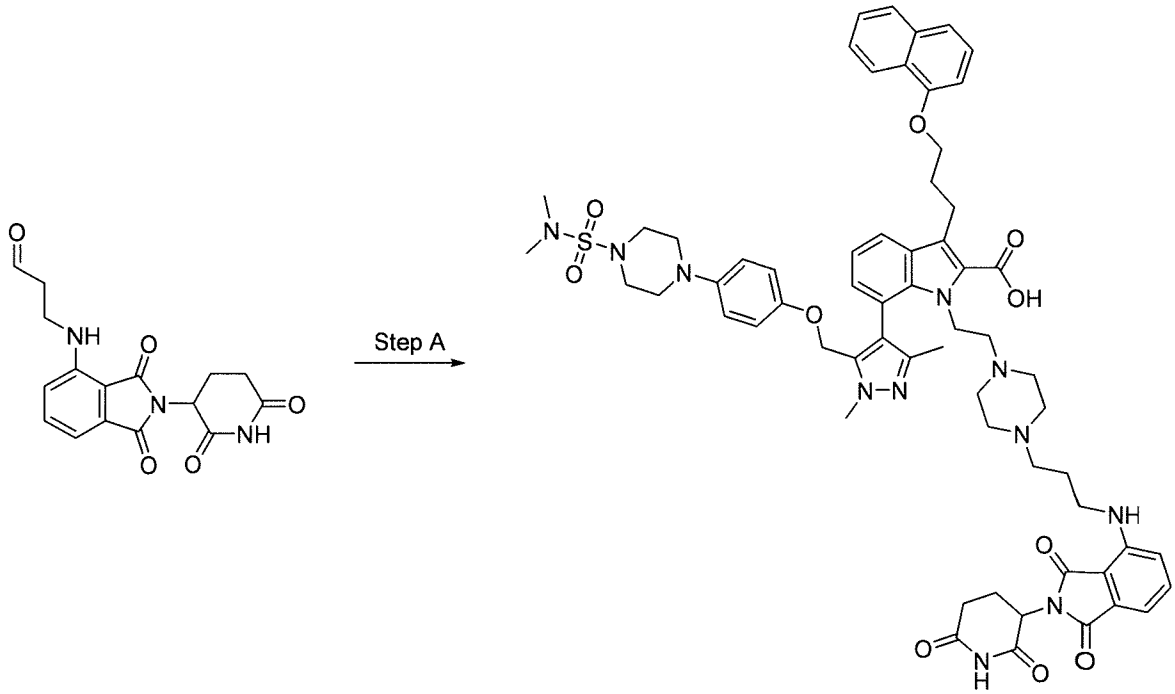


To a solution of 200 mg crude perfluorophenyl (2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)glycinate in DMF (2 mL), DIPEA (85 µL, 0.7 mmol) was added, followed by a solution of 7-(5-((4-(4-(*N*,*N*-dimethylsulfamoyl)piperazin-1-yl)phenoxy)methyl)-1,3-dimethyl-1*H*-pyrazol-4-yl)-3-(3-(naphthalen-1-yloxy)propyl)-1-(2-(piperazin-1-yl)ethyl)-1*H*-indole-2-carboxylic acid (120 mg, 0.14 mmol) in DMF (1 ml) at 0°C under nitrogen. The reaction mixture was allowed to stir at ambient temperature for 16 h. After complete consumption of the starting material (monitored by LCMS), the reaction mixture was concentrated in vacuo and purified by preparative HPLC to get 7-(5-((4-(4-(*N*,*N*-dimethylsulfamoyl)piperazin-1-yl)phenoxy)methyl)-1,3-dimethyl-1*H*-pyrazol-4-yl)-1-(2-(4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)glycyl)piperazin-1-yl)ethyl)-3-(3-(naphthalen-1-yloxy)propyl)-1*H*-indole-2-carboxylic acid (20 mg, 0.017 mmol, 12% over two steps) as white solid.

LCMS (ESI+): m/z 1162.8 $[M+H]^{+\cdot}$

^{1}H NMR (400 MHz, DMSO) δ 13.25 (s, 1H), 11.09 (s, 1H), 8.25 – 8.18 (m, 1H), 7.88 – 7.81 (m, 1H), 7.73 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.63 – 7.54 (m, 1H), 7.54 – 7.46 (m, 2H), 7.44 (d, *J* = 8.2 Hz, 1H), 7.36 (t, *J* = 7.9 Hz, 1H), 7.10 – 7.02 (m, 3H), 6.93 – 6.84 (m, 2H), 6.79 (s, 4H), 5.06 (dd, *J* = 12.9, 5.4 Hz, 1H), 4.93 – 4.78 (m, 2H), 4.66 – 4.48 (m, 1H), 4.20 (t, *J* = 6.2 Hz, 3H), 4.08 (s, 2H), 3.88 (s, 3H), 3.47 – 3.32 (m, 6H), 3.24 – 3.16 (m, 4H), 2.99 – 2.91 (m, 4H), 2.91 – 2.83 (m, 1H), 2.77 (s, 6H), 2.63 – 2.53 (m, 2H), 2.27 – 2.16 (m, 2H), 2.15 – 2.00 (m, 7H), 1.97 (s, 3H).

Example 44. 7-(5-((4-(4-(*N*,*N*-dimethylsulfamoyl)piperazin-1-yl)phenoxy)methyl)-1,3-dimethyl-1*H*-pyrazol-4-yl)-1-(2-(4-(3-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)propyl)piperazin-1-yl)ethyl)-3-(3-(naphthalen-1-yloxy)propyl)-1*H*-indole-2-carboxylic acid (246)



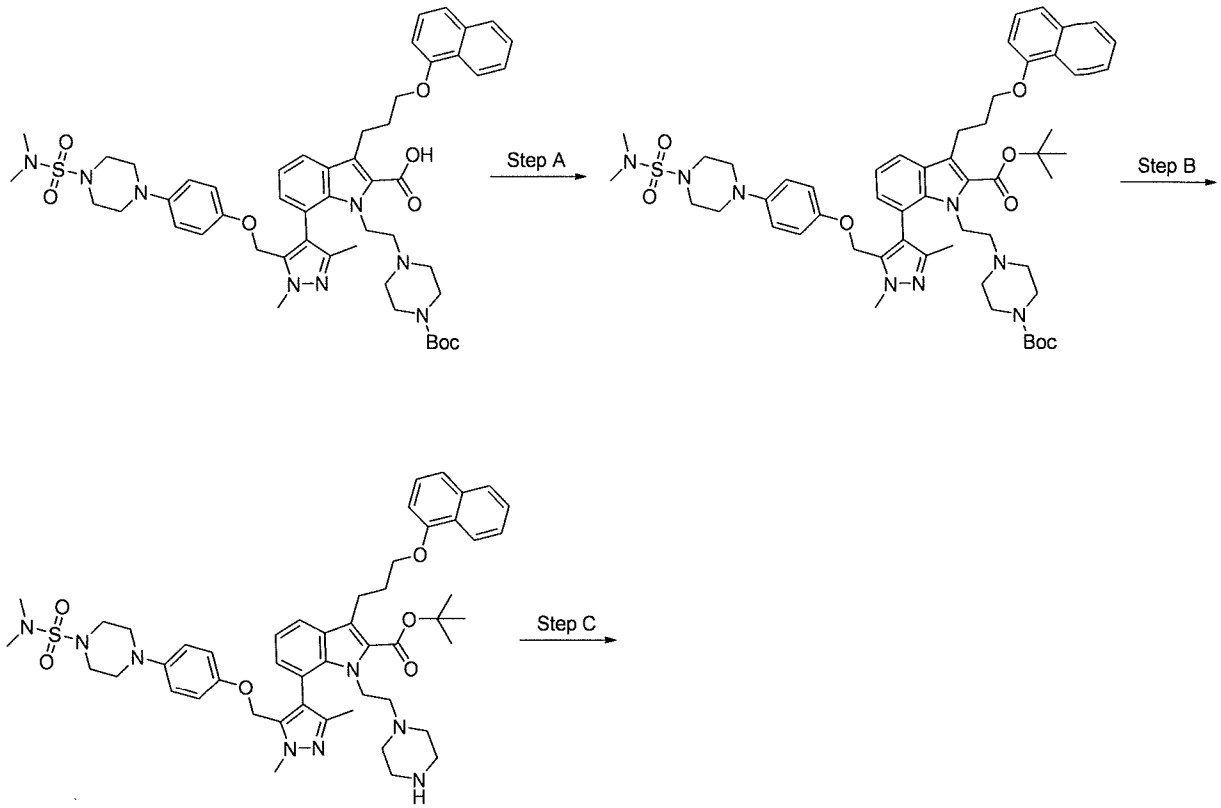
Step A

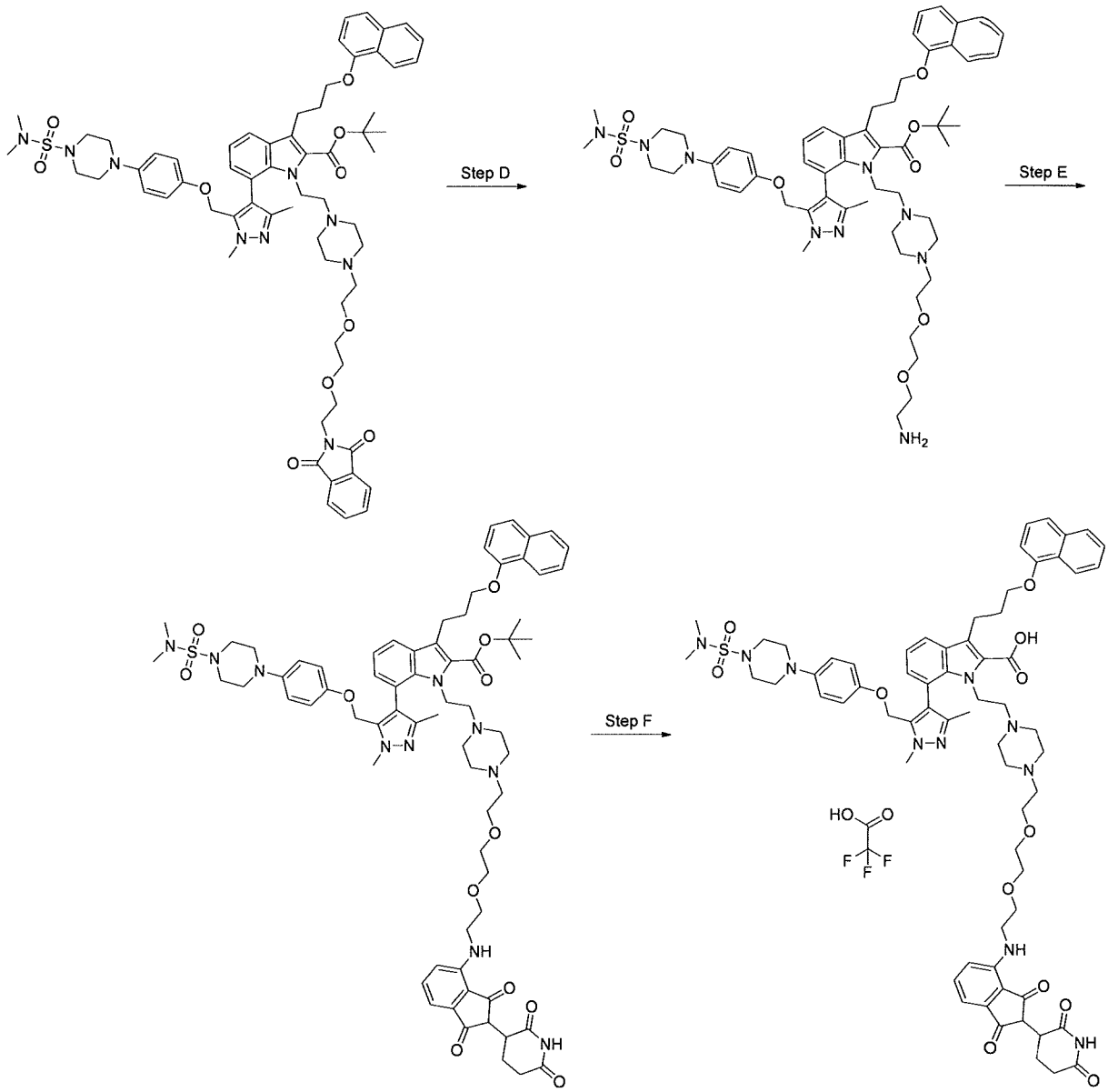
To a solution of 3-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)propanal (40 mg, 0.12 mmol) and 7-(5-((4-(4-(*N*,*N*-dimethylsulfamoyl)piperazin-1-yl)phenoxy)methyl)-1,3-dimethyl-1*H*-pyrazol-4-yl)-3-(3-(naphthalen-1-yloxy)propyl)-1-(2-(piperazin-1-yl)ethyl)-1*H*-indole-2-carboxylic acid hydrochloride (100 mg, 0.11 mmol) in THF (2 ml) was added dibutyl tindichloride (54 mg, 0.18 mmol) followed by DIPEA (0.42 mL, 0.23 mmol), pH of the reaction mixture was adjusted to ~8-9 and the reaction mixture was allowed to stir at ambient temperature for 30 min under nitrogen. Phenyl silane (13 mg, 0.12 mmol) was then added to the reaction mixture and it was allowed to stir at 85°C for 16 h under nitrogen. The volatiles were evaporated under reduced pressure. The reaction mixture was diluted with EtOAc, washed successively with water and brine. The organic layer was evaporated under reduced pressure to afford 30 mg of crude compound which was then purified by preparative HPLC (H_2O:MeCN +0.1% FA) to afford of 7-(5-((4-(4-(*N*,*N*-dimethylsulfamoyl)piperazin-1-yl)phenoxy)methyl)-1,3-dimethyl-1*H*-pyrazol-4-yl)-1-(2-(4-(3-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)propyl)piperazin-1-yl)ethyl)-3-(3-(naphthalen-1-yloxy)propyl)-1*H*-indole-2-carboxylic acid (20 mg, 0.017 mmol, 15%) as yellow solid.

LCMS (ESI+): m/z 1162.7 $[M+H]^+$.

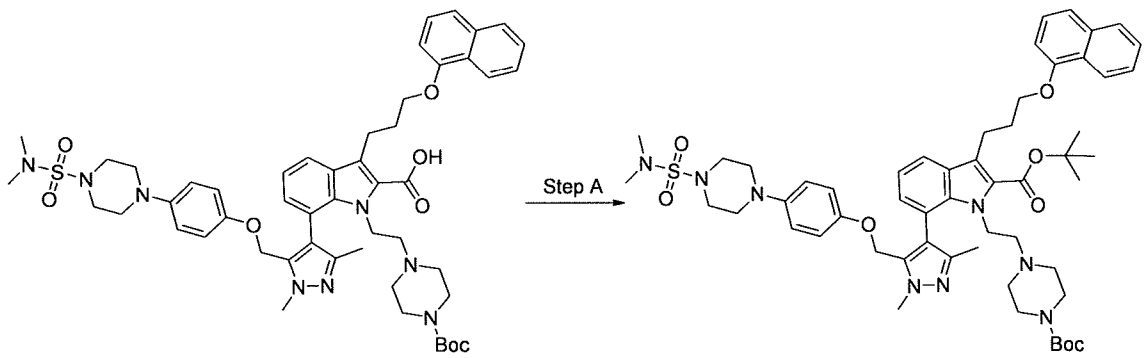
^{1}H NMR (400 MHz, DMSO) δ 11.08 (s, 1H), 8.24 – 8.14 (m, 1H), 7.83 (d, *J* = 7.4 Hz, 1H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.58 – 7.30 (m, 4H), 7.09 – 6.96 (m, 3H), 6.91 – 6.82 (m, 2H), 6.79 (s, 3H), 6.63 (s, 1H), 5.03 (dd, *J* = 12.8, 5.4 Hz, 1H), 4.92 – 4.75 (m, 2H), 4.53 (s, 1H), 4.30 – 4.10 (m, 3H), 3.85 (s, 3H), 3.24 – 3.07 (m, 10H), 3.07 – 2.83 (m, 6H), 2.76 (s, 6H), 2.62 – 2.54 (m, 1H), 2.42 – 2.08 (m, 12H), 2.07 – 1.93 (m, 4H), 1.66 – 1.50 (m, 2H).

Example 45. 7-(5-((4-(4-(*N*,*N*-dimethylsulfamoyl)piperazin-1-yl)phenoxy)methyl)-1,3-dimethyl-1*H*-pyrazol-4-yl)-1-(2-(4-(3-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)propyl)piperazin-1-yl)ethyl)-3-(3-(naphthalen-1-yloxy)propyl)-1*H*-indole-2-carboxylic acid trifluoroacetate (247)





Step A

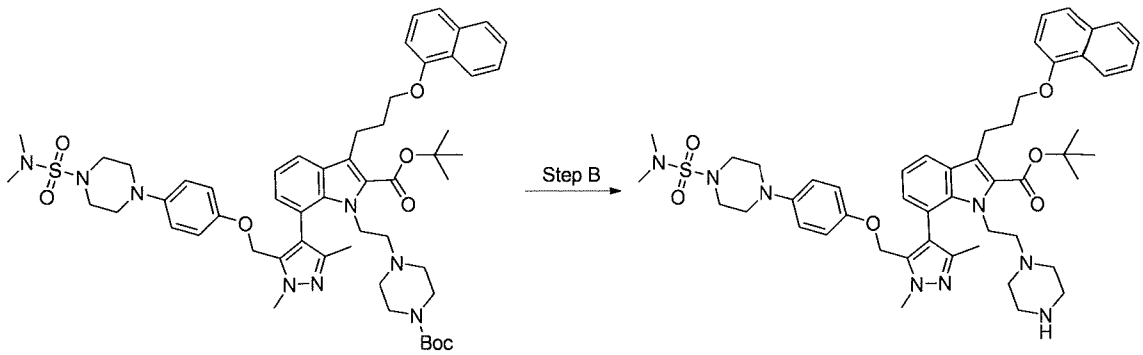


1-(2-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)ethyl)-7-(5-((4-(4-(*N*,*N*-dimethylsulfamoyl)piperazin-1-yl)phenoxy)methyl)-1,3-dimethyl-1*H*-pyrazol-4-yl)-3-(3-(naphthalen-1-yloxy)propyl)-1*H*-indole-2-carboxylic acid (2.0 g, 2.1 mmol) was suspended in toluene (20 ml) and the mixture was heated

to reflux under nitrogen. *N,N*-dimethylformamide di-*tert*-butyl acetal (2.5 ml, 10.5 mmol) was added drop wise to the refluxing mixture. Refluxing was continued for an additional 12 h under nitrogen. After 16 h another 1.3 ml (5.3 mmol) of *N,N*-dimethylformamide di-*tert*-butyl acetal was added to it and the reaction was continued for another 12 h. Reaction mixture was then diluted with EtOAc, washed successively with $NaHCO_3$ (aqueous saturated solution), water and brine. Organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to get the crude compound, which was then purified by flash chromatography (SiO_2, 50% EtOAc in DCM) to obtain of *tert*-butyl 1-(2-(4-(tert-butoxycarbonyl)piperazin-1-yl)ethyl)-7-(5-((4-(4-(*N,N*-dimethylsulfamoyl)piperazin-1-yl)phenoxy)methyl)-1,3-dimethyl-1*H*-pyrazol-4-yl)-3-(3-(naphthalen-1-yloxy)propyl)-1*H*-indole-2-carboxylate (1.6 g, 1.6 mmol, 76%) as yellow sticky solid.

LCMS (ESI+): m/z 1005.6 $[M+H]^+$

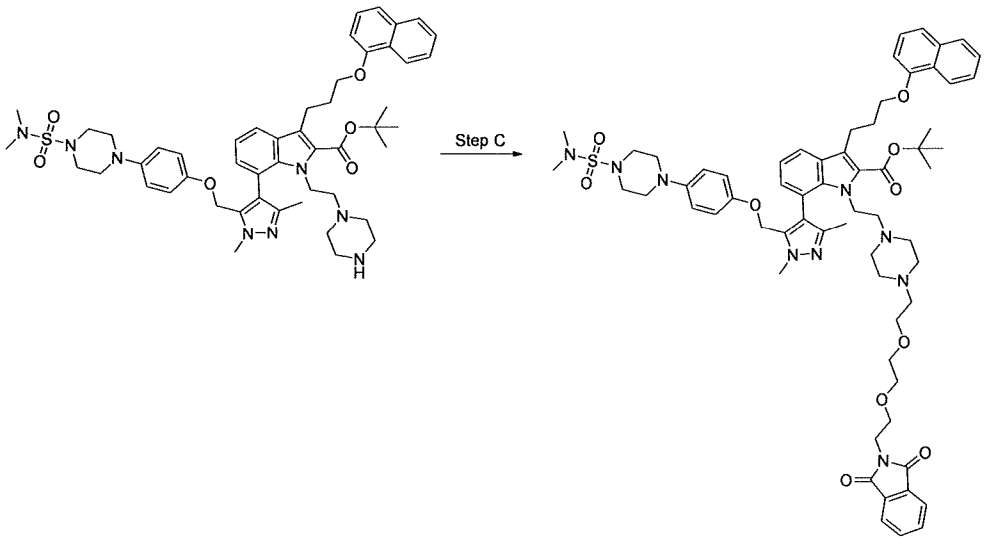
Step B



To a stirred solution of compound *tert*-butyl 1-(2-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)ethyl)-7-(5-((4-(4-(*N,N*-dimethylsulfamoyl)piperazin-1-yl)phenoxy)methyl)-1,3-dimethyl-1*H*-pyrazol-4-yl)-3-(3-(naphthalen-1-yloxy)propyl)-1*H*-indole-2-carboxylate (500 mg, 0.5 mmol) in dioxane (2 mL) was added 4M HCl in dioxane at 0°C under nitrogen atmosphere. The reaction mixture was allowed to stir at room temperature for 1h. The reaction mixture was quenched by slow addition of aqueous 1M NaOH at 0°C adjusting the pH to 7. Reaction product was extracted with 3x DCM, dried over Na_2SO_4, filtered, and concentrated in vacuo to afford the crude material which was further purified by triturating it with ether and pentane to get *tert*-butyl 7-(5-((4-(4-(*N,N*-dimethylsulfamoyl)piperazin-1-yl)phenoxy)methyl)-1,3-dimethyl-1*H*-pyrazol-4-yl)-3-(3-(naphthalen-1-yloxy)propyl)-1-(2-(piperazin-1-yl)ethyl)-1*H*-indole-2-carboxylate (300 mg, 1.52 mmol, 68%) as white solid.

LCMS (ESI+): m/z 905.7 $[M+H]^+$

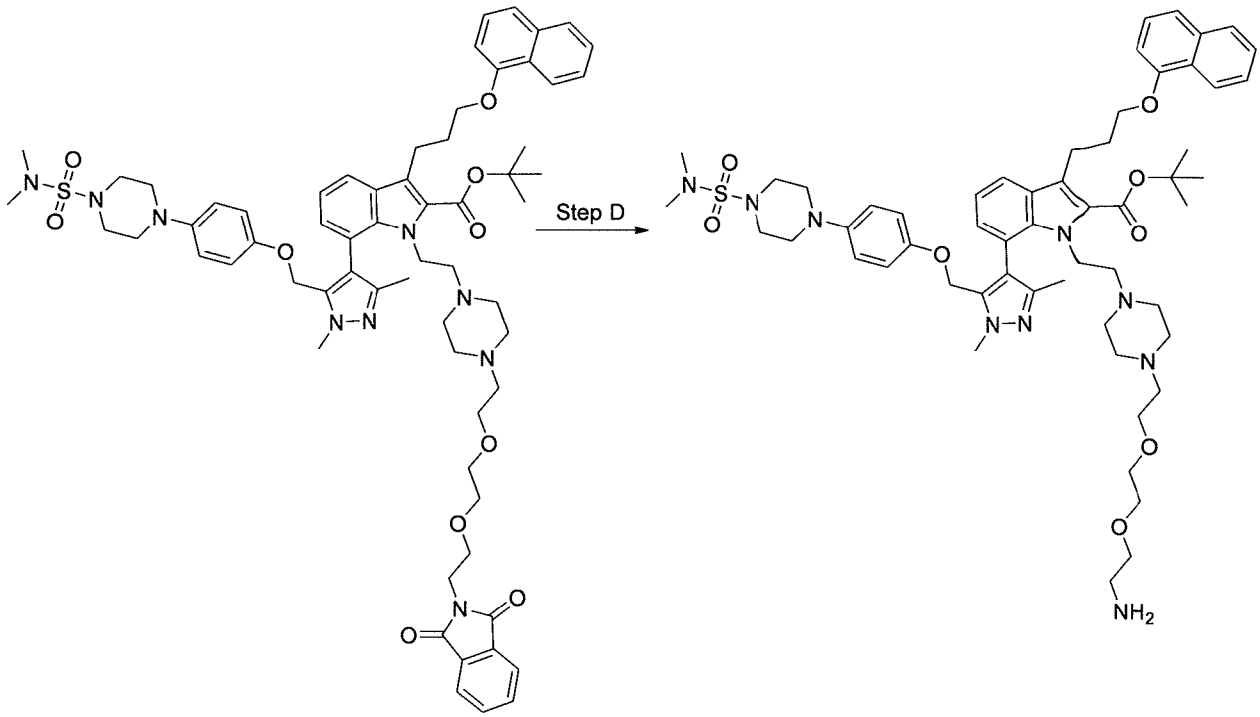
Step C



To a solution of *tert*-butyl 7-(5-((4-(4-(*N*,*N*-dimethylsulfamoyl)piperazin-1-yl)phenoxy)methyl)-1,3-dimethyl-1*H*-pyrazol-4-yl)-3-(3-(naphthalen-1-yloxy)propyl)-1-(2-(piperazin-1-yl)ethyl)-1*H*-indole-2-carboxylate (600 mg, 0.66 mmol), Et_3N (0.465 ml, 3.32 mmol) and KI (198 mg, 1.19 mmol) in DMF (12 ml) 2-(2-(2-(3-bromopropoxy)ethoxy)ethyl)isoindoline-1,3-dione (401.2 mg, 1.13 mmol) was added and the reaction mixture was allowed to stir at 60°C for 16h under nitrogen. The reaction mixture was evaporated under reduced pressure to get the crude compound, which was then purified by flash chromatography (SiO2, 5% MeOH in DCM) to get *tert*-butyl 7-(5-((4-(4-(*N*,*N*-dimethylsulfamoyl)piperazin-1-yl)phenoxy)methyl)-1,3-dimethyl-1*H*-pyrazol-4-yl)-1-(2-(4-(3-(2-(2-(1,3-dioxoisoindolin-2-yl)ethoxy)ethoxy)propyl)piperazin-1-yl)ethyl)-3-(3-(naphthalen-1-yloxy)propyl)-1*H*-indole-2-carboxylate (720 mg, 0.61 mmol, 92%) as yellowish liquid.

LCMS (ESI+): m/z 1181.4 $[M+H]^+$

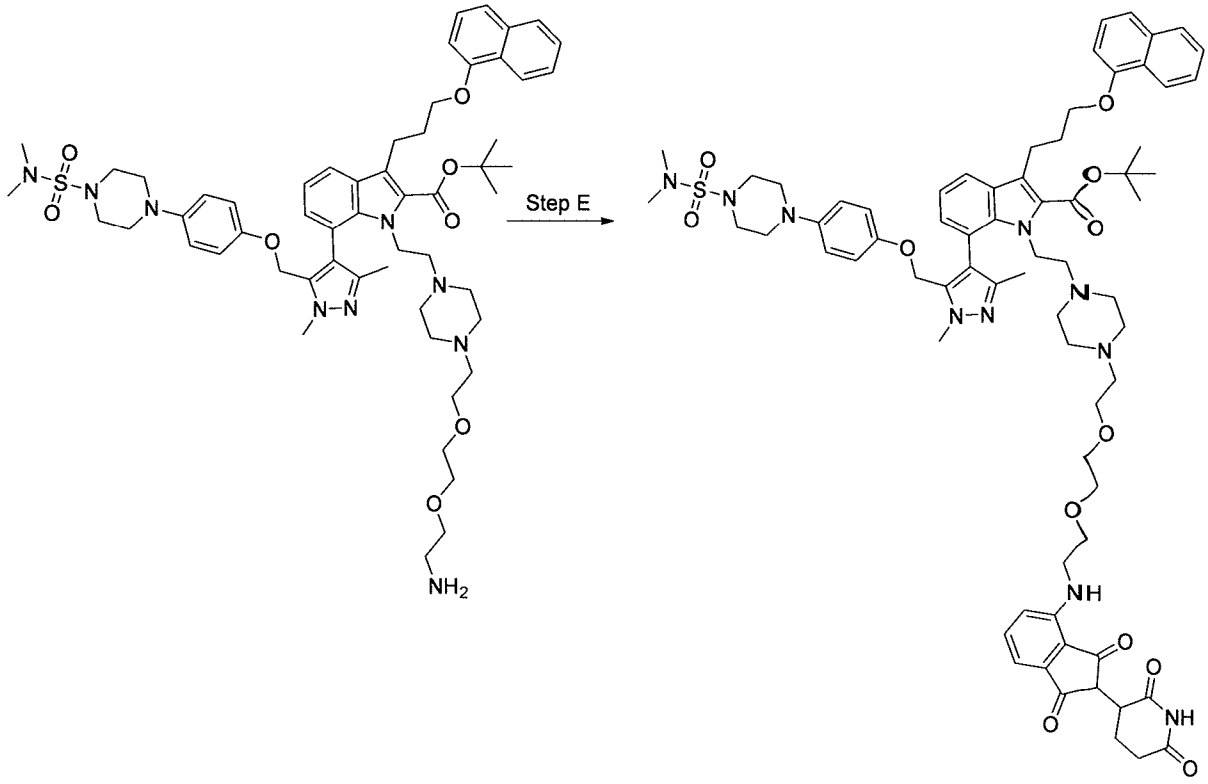
Step D



To a stirred solution of *tert*-butyl 7-(5-((4-(4-(*N*,*N*-dimethylsulfamoyl)piperazin-1-yl)phenoxy)methyl)-1,3-dimethyl-1*H*-pyrazol-4-yl)-1-(2-(4-(3-(2-(2-(1,3-dioxoisoindolin-2-yl)ethoxy)ethoxy)propyl)piperazin-1-yl)ethyl)-3-(3-(naphthalen-1-yloxy)propyl)-1*H*-indole-2-carboxylate (720 mg, 0.610 mmol) in *tert*-butanol (30 mL), hydrazine hydrate (5.0 mL) was added. Reaction mixture was heated to 90°C for 16h in a sealed tube. The reaction mixture was evaporated under reduced pressure in order to obtain the crude compound, which was then purified by preparative HPLC to afford *tert*-butyl 1-(2-(4-(3-(2-(2-aminoethoxy)ethoxy)propyl)piperazin-1-yl)ethyl)-7-(5-((4-(4-(*N*,*N*-dimethylsulfamoyl)piperazin-1-yl)phenoxy)methyl)-1,3-dimethyl-1*H*-pyrazol-4-yl)-3-(3-(naphthalen-1-yloxy)propyl)-1*H*-indole-2-carboxylate (240 mg, 0.23 mmol, 37%) as white solid.

LCMS (ESI+): m/z 1050.9 $[M+H]^+$

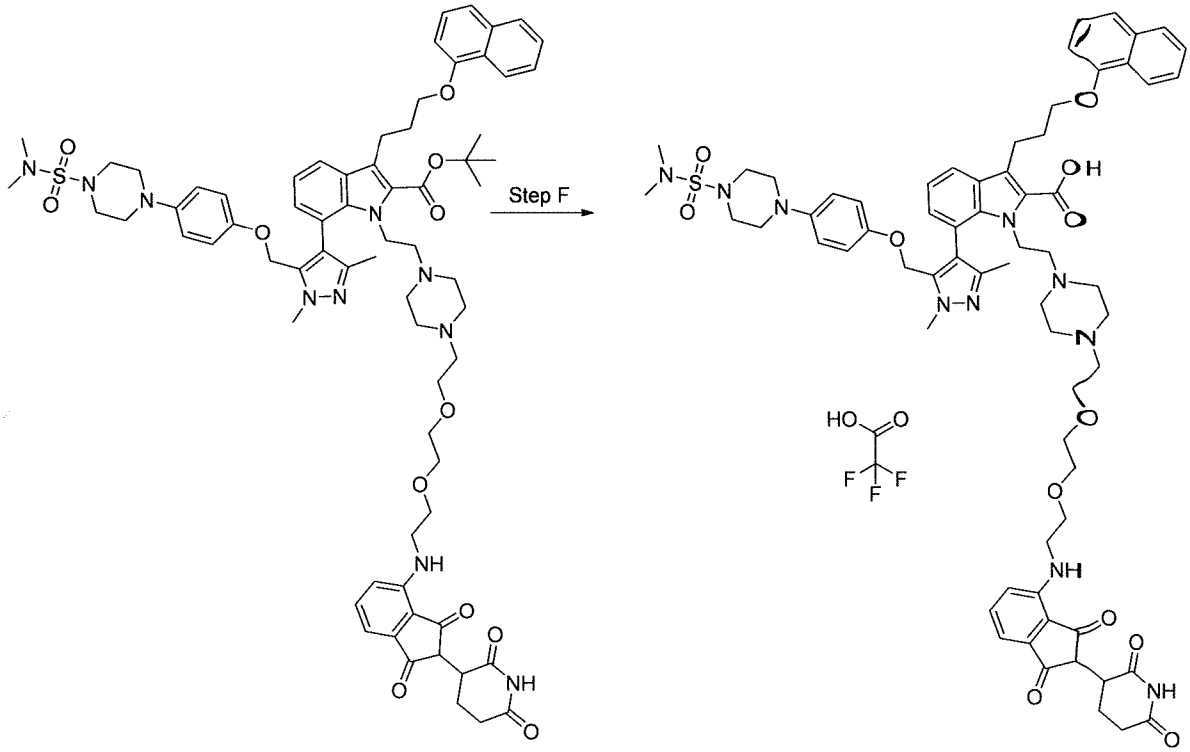
Step E



To a well stirred solution of *tert*-butyl 1-(2-(4-(3-(2-(2-aminoethoxy)ethoxy)propyl)piperazin-1-yl)ethyl)-7-(5-((4-(4-(*N*,*N*-dimethylsulfamoyl)piperazin-1-yl)phenoxy)methyl)-1,3-dimethyl-1*H*-pyrazol-4-yl)-3-(3-(naphthalen-1-yloxy)propyl)-1*H*-indole-2-carboxylate (130 mg, 0.12 mmol) in DMSO (10.0 ml) was added 2-(2,6-dioxopiperidin-3-yl)-4-fluoroisoindoline-1,3-dione (78.6 mg, 0.28 mmol), followed by DIPEA (0.11 mL, 0.62 mmol) and the mixture was allowed to stir at 90°C for 16 h under nitrogen. The reaction mixture was diluted with EtOAc, washed successively with cold water and brine, the organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to get the crude compound, which was then purified by preparative HPLC (H_2O:MeCN + 0.1% FA) to afford *tert*-butyl 7-(5-((4-(4-(*N*,*N*-dimethylsulfamoyl)piperazin-1-yl)phenoxy)methyl)-1,3-dimethyl-1*H*-pyrazol-4-yl)-1-(2-(4-(3-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)propyl)piperazin-1-yl)ethyl)-3-(3-(naphthalen-1-yloxy)propyl)-1*H*-indole-2-carboxylate (49 mg, 0.038 mmol, 31%) as yellow solid.

LCMS (ESI+): m/z 1306.9 $[M+H]^+$

Step F

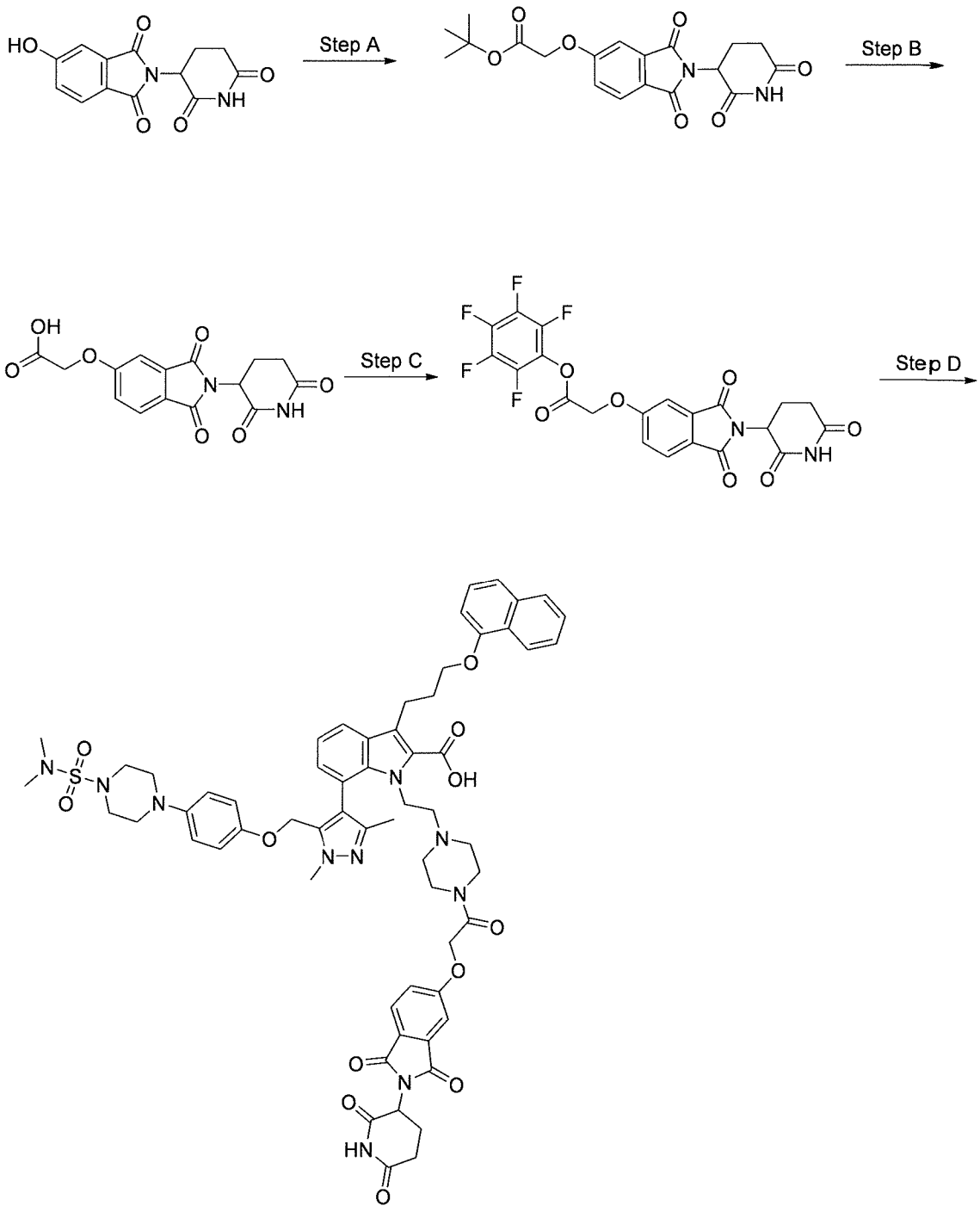


To a well stirred solution of *tert*-butyl 7-(5-((4-(4-(*N*,*N*-dimethylsulfamoyl)piperazin-1-yl)phenoxy)methyl)-1,3-dimethyl-1*H*-pyrazol-4-yl)-1-(2-(4-(3-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)propyl)piperazin-1-yl)ethyl)-3-(3-(naphthalen-1-yloxy)propyl)-1*H*-indole-2-carboxylate (34 mg, 0.026 mmol) in DCM (4 mL) was added TFA (4 mL) and the mixture was allowed to stir at room temperature for 16 h under nitrogen. After complete consumption of the starting material (monitored by LCMS), the volatiles were evaporated under reduced pressure to get the crude compound which was triturated using diethyl ether to afford 7-(5-((4-(4-(*N*,*N*-dimethylsulfamoyl)piperazin-1-yl)phenoxy)methyl)-1,3-dimethyl-1*H*-pyrazol-4-yl)-1-(2-(4-(3-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)propyl)piperazin-1-yl)ethyl)-3-(3-(naphthalen-1-yloxy)propyl)-1*H*-indole-2-carboxylic acid trifluoroacetate (30 mg, 0.024 mmol, 92%) as yellow solid.

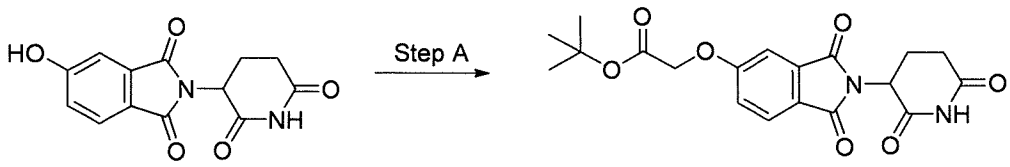
LCMS (ESI+): m/z 1250.7 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO) δ 11.10 (s, 1H), 9.27 (s, 1H), 8.27 – 8.17 (m, 1H), 7.86 (dd, *J* = 6.6, 2.7 Hz, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.58 (dd, *J* = 8.6, 7.1 Hz, 1H), 7.54 – 7.47 (m, 2H), 7.45 (d, *J* = 8.2 Hz, 1H), 7.37 (t, *J* = 7.9 Hz, 1H), 7.13 (d, *J* = 8.5 Hz, 1H), 7.10 – 7.03 (m, 2H), 6.90 (dd, *J* = 13.9, 7.4 Hz, 2H), 6.84 – 6.74 (m, 4H), 6.59 (t, *J* = 5.8 Hz, 1H), 5.05 (dd, *J* = 12.7, 5.4 Hz, 1H), 4.90 – 4.78 (m, 2H), 4.53 (s, 1H), 4.20 (t, *J* = 6.2 Hz, 3H), 3.87 (s, 3H), 3.63 – 3.27 (m, 15H, overlaps with water), 3.24 (dd, *J* = 6.4, 3.5 Hz, 4H), 3.07 – 2.96 (m, 6H), 2.92 – 2.79 (m, 2H), 2.77 (s, 6H), 2.63 – 2.53 (m, 2H), 2.26 – 2.08 (m, 6H), 2.05 – 1.92 (m, 4H), 1.88 – 1.77 (m, 2H).

Example 46. 7-(5-((4-(4-(*N*,*N*-dimethylsulfamoyl)piperazin-1-yl)phenoxy)methyl)-1,3–dimethyl-1*H*-pyrazol-4-yl)-1-(2-(4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)oxy)acetyl)piperazin-1-yl)ethyl)-3-(3-(naphthalen-1-yloxy)propyl)-1*H*-indole-2-carboxylic acid (248)



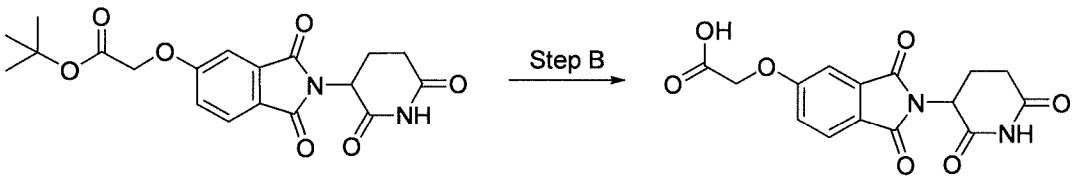
Step A



To a solution of 2-(2,6-dioxopiperidin-3-yl)-5-hydroxyisoindoline-1,3-dione (0.2 g, 0.73 mmol) in DMF (2 ml) was added potassium iodide (60.584 mg, 0.365 mmol) and potassium bicarbonate (145.985 mg, 1.46 mmol) followed by *tert*-butyl bromo acetate (140.0 mg, 0.73 mmol) and the resulting reaction mixture was allowed to stir at 60°C for 16 h under nitrogen. After complete consumption of the starting material the reaction mixture was diluted with ethyl acetate and washed successively with cold water and brine. Organic layer was dried over sodium sulphate and evaporated under reduced pressure to give the crude compound which was then triturated with diethyl ether to afford *tert*-butyl 2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)oxy)acetate (260 mg, 0.670 mmol, 91.72%) as white solid.

LCMS (ESI+): m/z 388.8 $[M+H]^+$

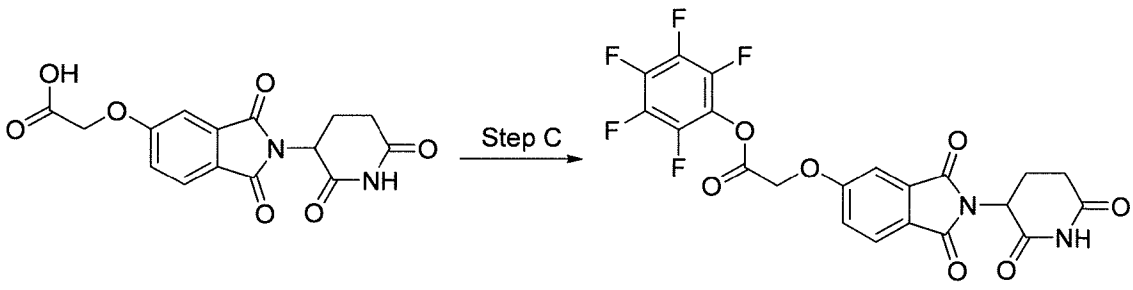
Step B



To a suspension of *tert*-butyl 2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)oxy)acetate (0.1 g, 0.258 mmol) in DCM (3 ml) was added TFA (1 ml) dropwise at 0°C under nitrogen. The mixture was allowed to stir at RT for 16h. After complete consumption of the starting material the volatiles were evaporated under reduced pressure to get the crude compound which was triturated with diethyl ether to afford 2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)oxy)acetic acid (58 mg, 0.174mmol, 67.73%) as off white solid.

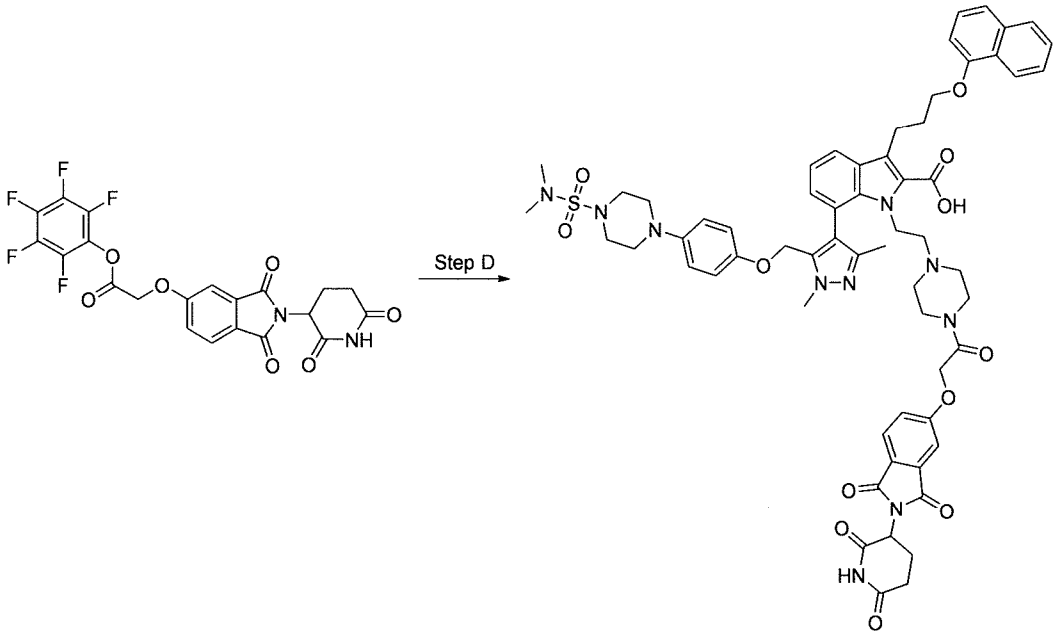
LCMS (ESI-): m/z 330.9 $[M-H]^-$

Step C



To a well stirred solution of 2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)oxy)acetic acid (200 mg, 0.6 mmol) in DMF (2 ml) was added DIPEA (1 ml, 6 mmol) and the reaction mixture was cooled to 0°C. Pentafluorophenyl trifluoroacetate (843 mg, 3 mmol) was added and the mixture was allowed to stir at RT for 2 h under nitrogen. After complete consumption of the starting material (monitored by LCMS) the volatiles were evaporated under reduced pressure to obtain 200 mg of crude perfluorophenyl 2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)oxy)acetate as brown sticky solid which was used for the next step without further purification.

Step D

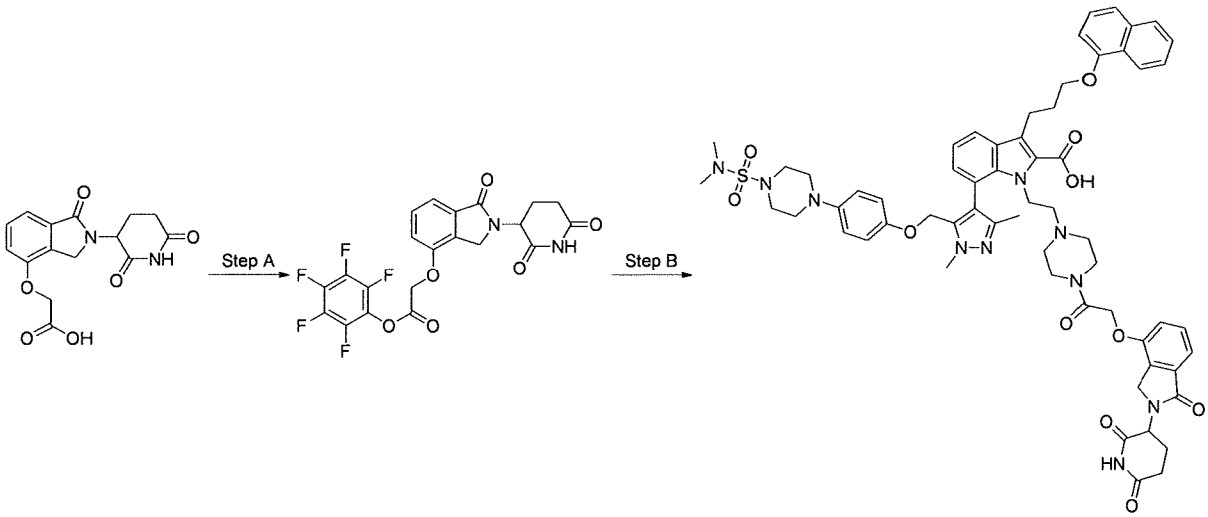


To a solution of perfluorophenyl 2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)oxy)acetate (200 mg, crude) in DMF (2 mL) were added DIPEA (85 µL, 0.7mmol) and a solution of 7-(5-((4-(4-(*N*,*N*-dimethylsulfamoyl)piperazin-1-yl)phenoxy)methyl)-1,3-dimethyl-1*H*-pyrazol-4-yl)-3-(3-(naphthalen-1-yloxy)propyl)-1-(2-(piperazin-1-yl)ethyl)-1*H*-indole-2-carboxylic acid (120 mg, 0.14 mmol) in DMF (1 ml) at 0°C under nitrogen. The reaction mixture was allowed to stir at ambient temperature for 16h. After complete consumption of starting material (monitored by LCMS), the reaction mixture was concentrated in vacuo and purified by reverse phase preparative HPLC (H_2O:MeCN + 0.1% FA) to obtain 7-(5-((4-(4-(*N*,*N*-dimethylsulfamoyl)piperazin-1-yl)phenoxy)methyl)-1,3-dimethyl-1*H*-pyrazol-4-yl)-1-(2-(4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)oxy)acetyl)piperazin-1-yl)ethyl)-3-(3-(naphthalen-1-yloxy)propyl)-1*H*-indole-2-carboxylic acid (40 mg, 0.034 mmol, 24%) as off white solid.

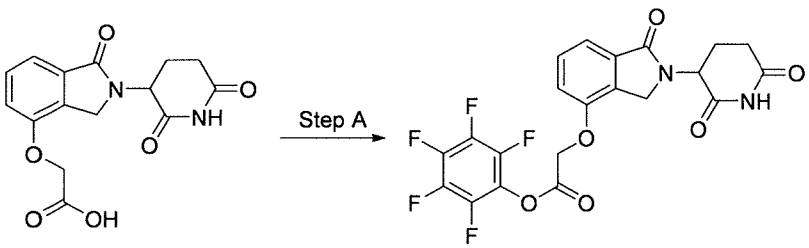
LCMS (ESI+): m/z 1163.7 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO) δ 13.21 (bs, 1H), 11.10 (s, 1H), 8.27 – 8.17 (m, 1H), 7.88 – 7.83 (m, 1H), 7.81 (d, *J* = 8.3 Hz, 1H), 7.73 (d, *J* = 8.0 Hz, 1H), 7.54 – 7.46 (m, 2H), 7.39 (dt, *J* = 18.6, 8.1 Hz, 3H), 7.30 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.06 (t, *J* = 7.6 Hz, 1H), 6.89 (dd, *J* = 13.1, 7.3 Hz, 2H), 6.85 – 6.71 (m, 4H), 5.11 (dd, *J* = 12.8, 5.4 Hz, 1H), 5.01 (s, 2H), 4.86 (q, *J* = 11.9 Hz, 2H), 4.63 – 4.48 (m, 1H), 4.20 (t, *J* = 6.1 Hz, 3H), 3.87 (s, 3H), 3.29 – 3.25 (m, 5H), 3.24 – 3.21 (m, 4H), 3.01 – 2.95 (m, 4H), 2.94 – 2.83 (m, 1H), 2.75 (s, 6H), 2.64 – 2.52 (m, 2H), 2.21 (p, *J* = 7.3, 6.9 Hz, 2H), 2.17 – 1.98 (m, 8H), 1.97 (s, 3H).

Example 47. 7-(5-((4-(4-(*N,N*-dimethylsulfamoyl)piperazin-1-yl)phenoxy)methyl)-1,3-dimethyl-1*H*-pyrazol-4-yl)-1-(2-(4-(2-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)oxy)acetyl)piperazin-1-yl)ethyl)-3-(3-(naphthalen-1-yloxy)propyl)-1*H*-indole-2-carboxylic acid (249)



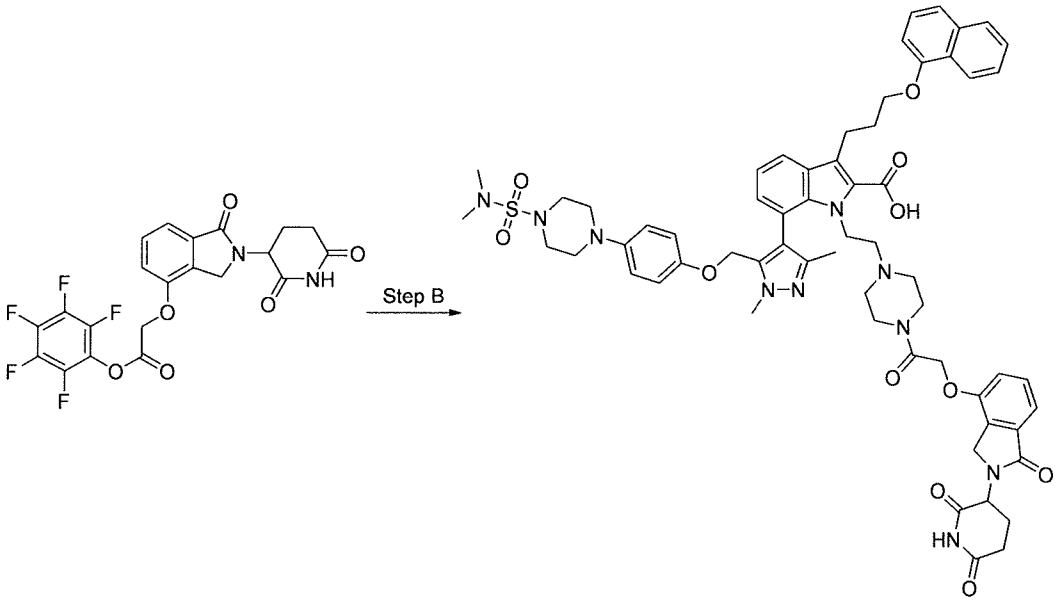
Step A



To a solution of 2-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)oxy)acetic acid (200 mg, 0.63 mmol) in DMF (2 ml) DIPEA (1 ml, 6 mmol) was added. The reaction mixture was cooled to 0°C, to it was added pentafluorophenyl trifluoroacetate (843 mg, 3 mmol) and the mixture was allowed to stir at ambient temperature for 2 h under nitrogen. After complete consumption of

the starting material (monitored by LCMS) the volatiles are evaporated under reduced pressure to get 200 mg of crude perfluorophenyl 2-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin–4-yl)oxy)acetate as brown sticky solid which was used for the next step without further purification.

Step B



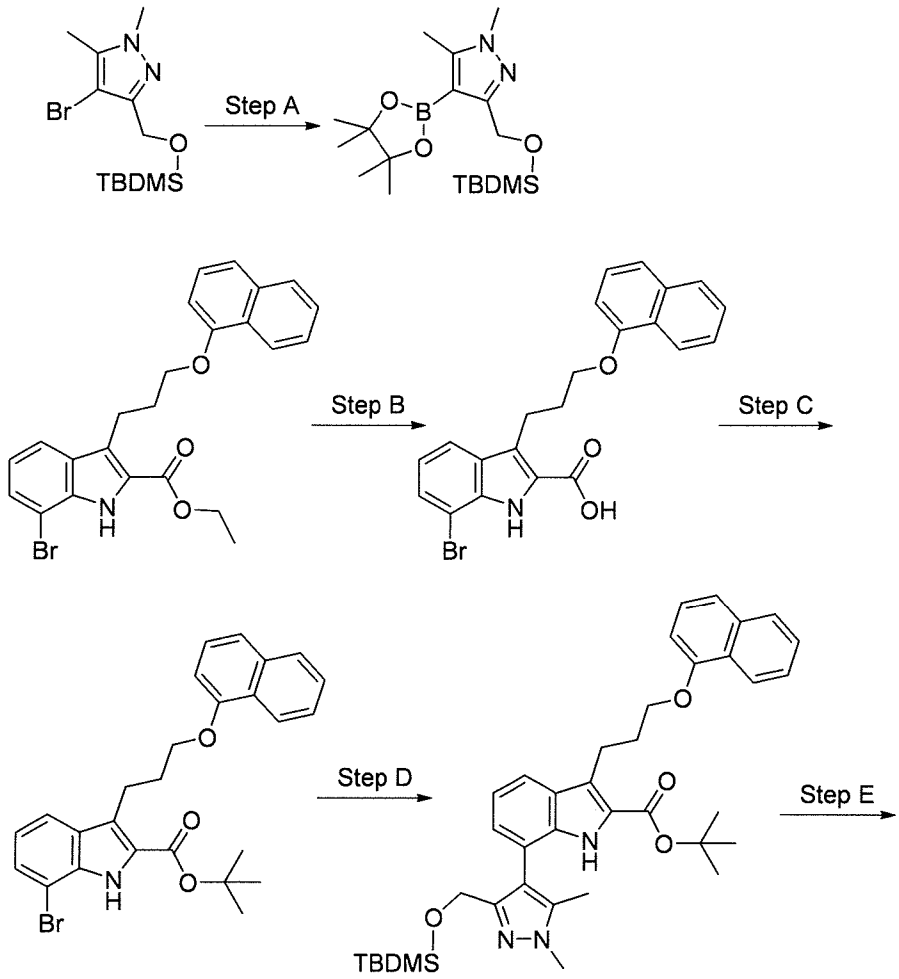
To a solution of perfluorophenyl 2-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)oxy)acetate (200 mg, crude) in DMF (2 ml) were added DIPEA (85 µL, 0.7 mmol) and a solution of 7-(5-((4-(4-(*N,N*-dimethylsulfamoyl)piperazin-1-yl)phenoxy)methyl)-1,3-dimethyl-1*H*-pyrazol-4-yl)-3-(3-(naphthalen-1-yloxy)propyl)-1-(2-(piperazin-1-yl)ethyl)-1*H*-indole-2-carboxylic acid (120 mg, 0.142 mmol) in DMF (1ml) successively at 0°C under nitrogen. The reaction mixture was allowed to stir at ambient temperature for 16h. The reaction mixture was concentrated in vacuo and purified by preparative HPLC (H_2O:MeCN +0.1% FA) to get 7-(5-((4-(4-(*N,N*-dimethylsulfamoyl)piperazin-1-yl)phenoxy)methyl)-1,3-dimethyl-1*H*-pyrazol-4-yl)-1-(2-(4-(2-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)oxy)acetyl)piperazin-1-yl)ethyl)-3-(3-(naphthalen-1-yloxy)propyl)-1*H*-indole-2-carboxylic acid (45mg, 0.039 mmol, 28%) as off white solid.

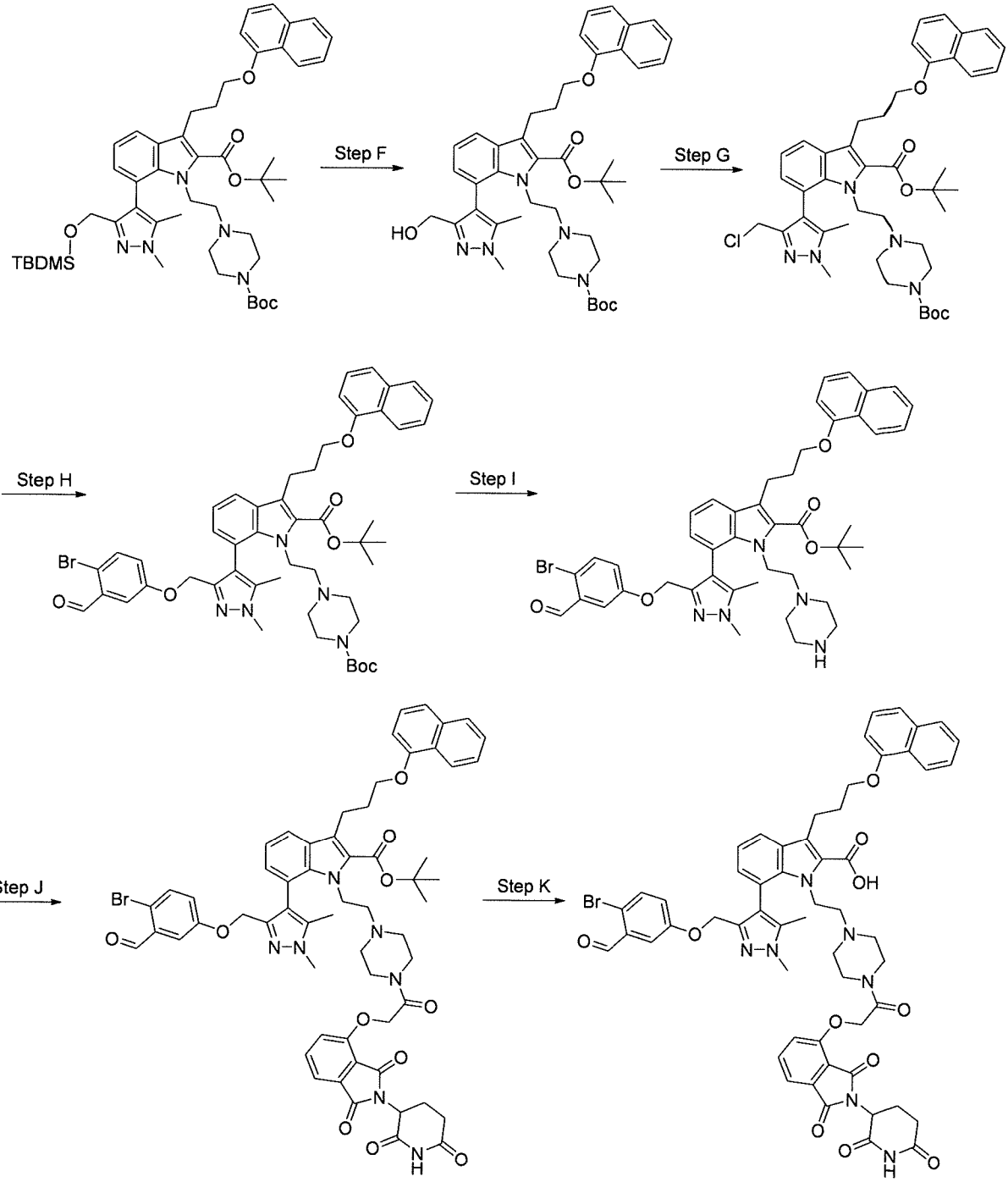
LCMS (ESI+): m/z 1149.7 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO) δ 13.27 (s, 1H), 10.97 (s, 1H), 8.26 – 8.17 (m, 1H), 7.90 – 7.80 (m, 1H), 7.72 (d, *J* = 8.0 Hz, 1H), 7.56 – 7.46 (m, 2H), 7.46 – 7.33 (m, 3H), 7.31 (d, *J* = 7.5 Hz, 1H), 7.14 – 7.01 (m, 2H), 6.96 – 6.85 (m, 2H), 6.85 – 6.75 (m, 4H), 5.10 (dd, *J* = 13.1, 4.9 Hz, 1H), 4.97 – 4.79 (m, 4H), 4.62 – 4.48 (m, 1H), 4.42 – 4.31 (m, 1H), 4.28 – 4.13 (m, 4H), 3.85 (d, *J* = 4.0 Hz, 3H), 3.30 –

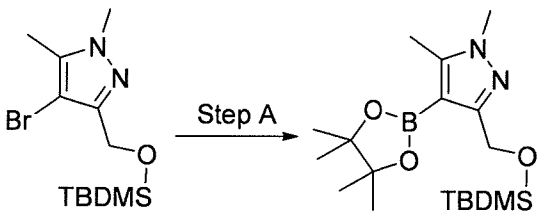
3.29 (m, 8H), 3.24 – 3.20 (m, 4H), 3.02 – 2.93 (m, 5H), 2.93 – 2.84 (m, 1H), 2.62 – 2.52 (m, 2H), 2.45 – 2.36 (m, 1H), 2.36 – 2.30 (m, 1H), 2.26 – 2.15 (m, 2H), 2.15 – 1.97 (m, 8H), 1.96 (s, 3H).

Example 48. 7-(3-((4-Bromo-3-formylphenoxy)methyl)-1,5-dimethyl-1*H*-pyrazol-4-yl)-1-(2-(4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)acetyl)piperazin-1-yl)ethyl)-3-(3-(naphthalen-1-yloxy)propyl)-1*H*-indole-2-carboxylic acid (251)





Step A

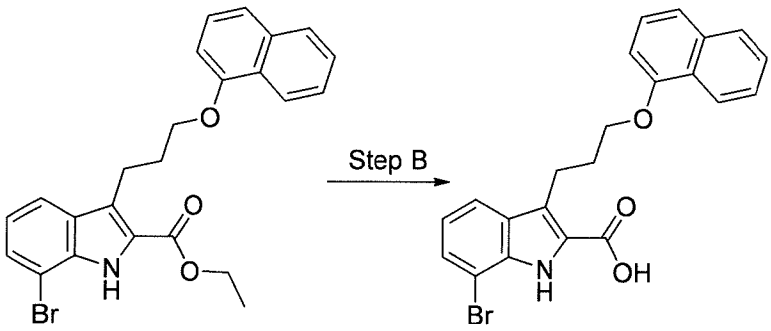


To a well stirred solution of 4-bromo-3-(((*tert*-butyldimethylsilyl)oxy)methyl)-1,5-dimethyl-1*H*-pyrazole (5 g, 15.674 mmol) in THF (120 ml) was added butyllithium (10.7 ml, 17.241 mmol, 1.6 M

in hexane) at -78°C under argon. The mixture was stirred at -78°C for 50 min. 2-Isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.5 ml, 17.241 mmol) was added to the reaction mixture. The dry ice bath was removed. The mixture was slowly warmed to RT and was stirred for 1 h. After complete consumption of the starting material (monitored by TLC and LCMS) the excess butyl lithium was quenched by addition of saturated ammonium chloride. It was then diluted with EtOAc, washed successively with water and brine, dried over Na_2SO4 and evaporated under reduced pressure to afford 5.2 g of 3-(((*tert*-butyldimethylsilyl)oxy)methyl)-1,5-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole as white gummy solid which was used for the next step without further purification.

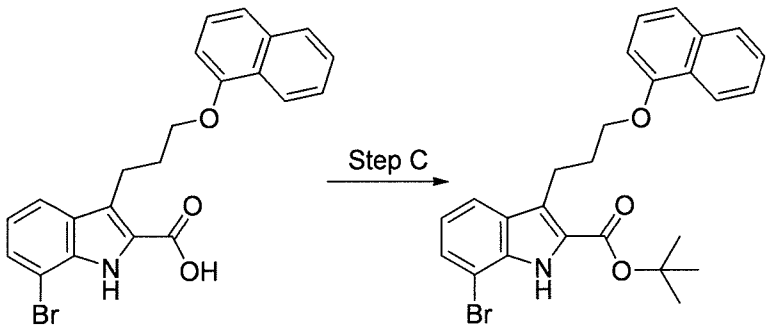
LCMS (ESI+): m/z 366.3 $[M+H]^+$

Step B



Ethyl 7-bromo-3-(3-(naphthalen-1-yloxy)propyl)-1*H*-indole-2-carboxylate (7 g, 15.52 mmol) was dissolved in EtOH (220 mL) and a solution of NaOH (2.5 g, 62.08 mmol) in water (12 mL) was added to it. The mixture was heated under reflux for 16 h. After complete consumption of the starting material (monitored by TLC and LCMS) the reaction mixture was cooled down to room temperature, solvents were evaporated under reduced pressure to get the crude reaction mixture. It was then diluted with water and washed with EtOAc. Aqueous layer was carefully acidified using 1M HCl to pH = 3, extracted with dichloromethane (3×50 ml), dried over Na_2SO_4, filtered, and concentrated in vacuo to afford 7-bromo-3-(3-(naphthalen-1-yloxy)propyl)-1*H*-indole-2-carboxylic acid (5.7 g, 13.47 mmol, 86.56 %) as brown solid.

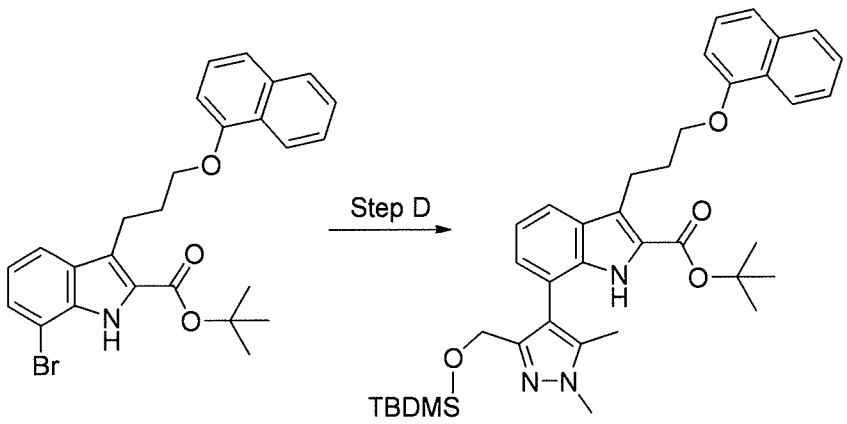
Step C



7-Bromo-3-(3-(naphthalen-1-yloxy)propyl)-1*H*-indole-2-carboxylic acid (3 g, 7.092 mmol) was suspended in toluene (45 mL) and the mixture was heated to reflux under nitrogen. *N,N*-dimethylformamide di-*tert*-butyl acetal (4.3 ml, 21.277 mmol) was added drop wise to the refluxing reaction mixture and the reaction was continued for an additional 16 h under nitrogen. After 16 h another 2.8 mL (14.2 mmol) of *N,N*-dimethylformamide di-*tert*-butyl acetal was added to it and the reaction was continued for another 8 h. Reaction mixture was then diluted with EtOAc, washed successively with sodium bicarbonate (saturated), water and brine. Organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get the crude compound, which was then purified by column chromatography (SiO_2, DCM:MeOH 2%) to get *tert*-butyl 7-bromo-3-(3-(naphthalen-1-yloxy)propyl)-1*H*-indole-2-carboxylate (2 g, 4.17 mmol, 58.7%) as brown solid.

LCMS (ESI-): m/z 480.3 $[M-H]^-$

Step D

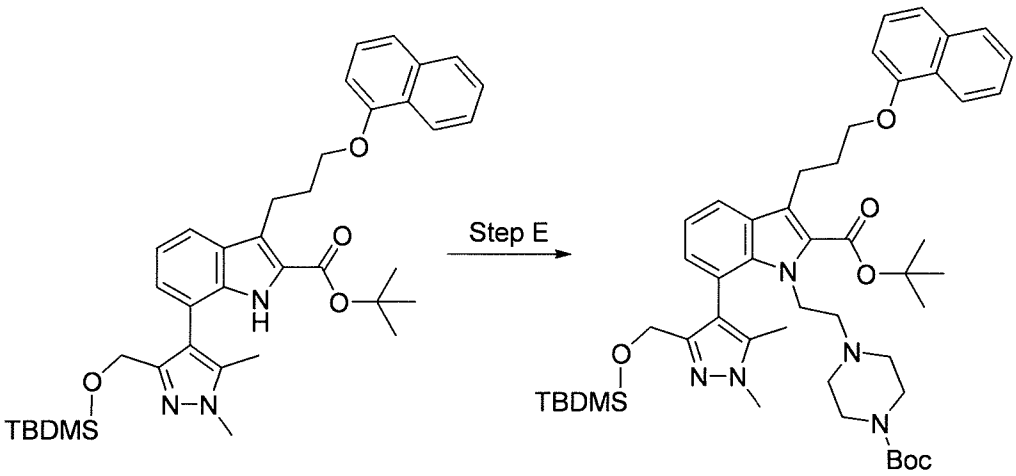


To a solution of *tert*-butyl 7-bromo-3-(3-(naphthalen-1-yloxy)propyl)-1*H*-indole-2-carboxylate (1.8 g, 3.758 mmol) in dioxane (30 ml) and water (6 ml) were added 3-(((*tert*-butyldimethylsilyl)oxy)methyl)-1,5-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (2.75 g, 7.516 mmol) and K_2CO_3 (2 g, 15.031 mmol). The mixture was deoxygenated with argon and to it was added $Pd(dppf)Cl_2$ (412 mg, 0.564 mmol) under argon atmosphere. Then the

reaction mixture was heated under reflux for 16 h. After complete consumption of the starting material (monitored by TLC and LCMS) the reaction mixture was filtered through celite and the solvent was evaporated under reduced pressure get the crude material. It was then diluted with EtOAc, washed successively with water and brine, the organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to get *tert*-butyl 7-(3-(((*tert*-butyldimethylsilyl)oxy)methyl)-1,5-dimethyl-1*H*-pyrazol-4-yl)-3-(3-(naphthalen-1-yloxy)propyl)-1*H*-indole-2-carboxylate (2 g, crude) as brown gummy liquid. The crude product was used for the next step without further purification.

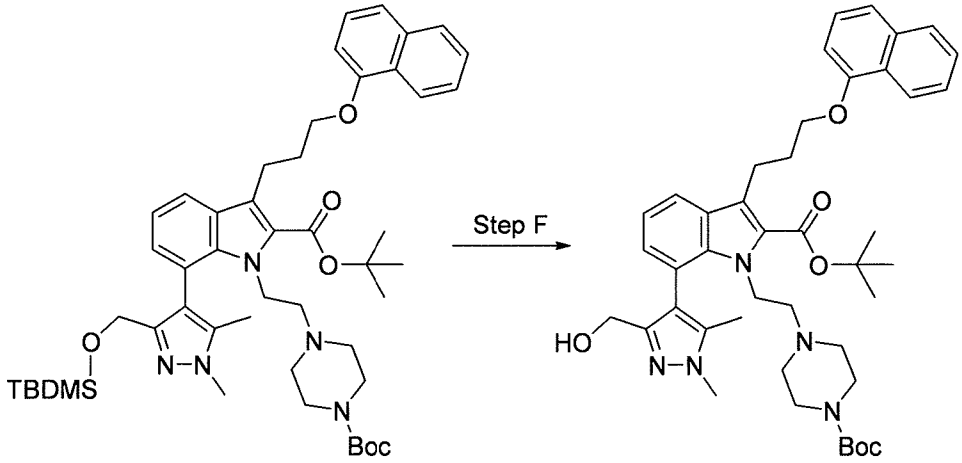
LCMS (ESI+): m/z 640.7 $[M+H]^+$.

Step E



To a solution of *tert*-butyl 7-(3-(((*tert*-butyldimethylsilyl)oxy)methyl)-1,5-dimethyl-1*H*-pyrazol-4-yl)-3-(3-(naphthalen-1-yloxy)propyl)-1*H*-indole-2-carboxylate (2 g, crude) in DMF (20 ml) was added *tert*-butyl 4-(2-chloroethyl)piperazine-1-carboxylate (1.6 g, 6.463 mmol) followed by cesium carbonate (4.2 g, 12.926 mmol) in DMF and the mixture was allowed to stir at 90°C for 16 h under nitrogen. After complete consumption of the starting material (monitored by TLC and LCMS) the reaction mixture was diluted with EtOAc, washed successively with water and brine, the organic layer was dried over sodium sulphate and evaporated under reduced pressure to get the crude compound, which was then purified by column chromatography (SiO_2, 50% EtOAc in DCM) to get *tert*-butyl 1-(2-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)ethyl)-7-(3-(((*tert*-butyldimethylsilyl)oxy)methyl)-1,5-dimethyl-1*H*-pyrazol-4-yl)-3-(3-(naphthalen-1-yloxy)propyl)-1*H*-indole-2-carboxylate (1.4 g, 1.64 mmol, 44% over two steps) as gummy solid.

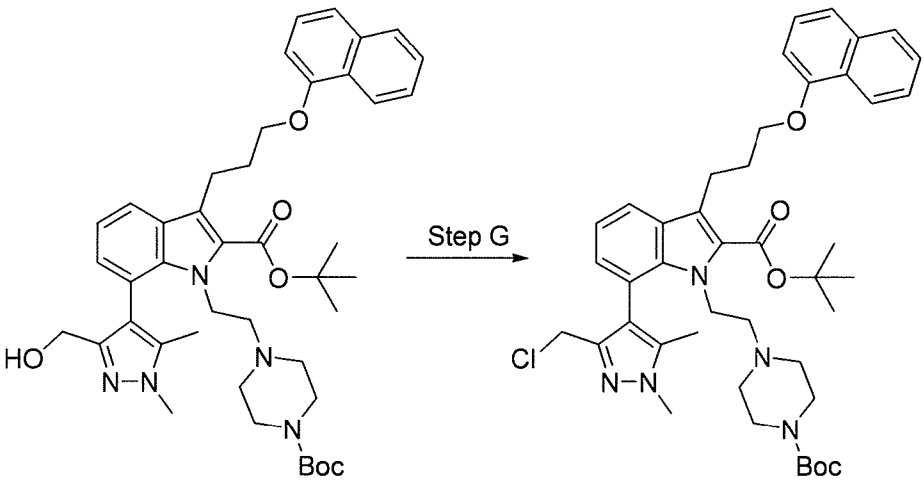
Step F



To a stirred solution of *tert*-butyl 1-(2-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)ethyl)-7-(3-(((*tert*-butyldimethylsilyl)oxy)methyl)-1,5-dimethyl-1*H*-pyrazol-4-yl)-3-(3-(naphthalen-1-yloxy)propyl)-1*H*-indole-2-carboxylate (1.4 g, 1.64 mmol) in THF (20 mL) was added TBAF (8 mL) drop-wise at 0°C under nitrogen and the reaction mixture was allowed to stir at ambient temperature for 2 h. After complete consumption of the starting material (monitored by TLC and LCMS) the excess TBAF of the reaction mixture was quenched by addition of an aqueous solution of $NaHCO_3$. The reaction mixture was then diluted with EtOAc and washed successively with water and brine, the organic layer was dried over sodium sulphate and evaporated under reduced pressure to get the crude compound, which was then purified by column chromatography (SiO_2, 5% MeOH in DCM) to get *tert*-butyl 1-(2-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)ethyl)-7-(3-(hydroxymethyl)-1,5-dimethyl-1*H*-pyrazol-4-yl)-3-(3-(naphthalen-1-yloxy)propyl)-1*H*-indole-2-carboxylate (500 mg, 0.678 mmol, 42%) as gummy solid.

LCMS (ESI+): m/z 738.5 $[M+H]^+$

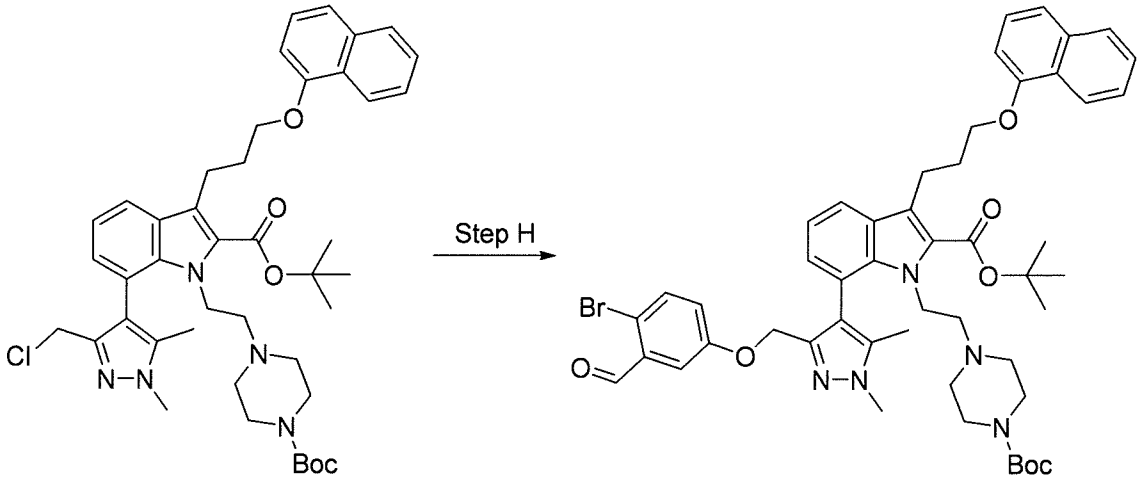
Step G



To a solution of *tert*-butyl 1-(2-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)ethyl)-7-(3-(hydroxymethyl)-1,5-dimethyl-1*H*-pyrazol-4-yl)-3-(3-(naphthalen-1-yloxy)propyl)-1*H*-indole-2-carboxylate (200 mg, 0.271 mmol) in DCM (10 mL) was added thionyl chloride (0.1 mL, 0.543 mmol) drop-wise at 0°C. The reaction mixture was allowed to reach room temperature and was stirred for 1 h. After complete consumption of the starting material (monitored by TLC and LCMS) the reaction mixture was then poured into an ice-cold solution of saturated aqueous $NaHCO_3$ (20 mL) and DCM (20 mL). The phases were separated and the aqueous phase was re-extracted with DCM. The combined organic phases were washed with water (1 x 50 ml), dried over $MgSO_4$ and concentrated under reduced pressure to give 150 mg crude of *tert*-butyl 1-(2-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)ethyl)-7-(3-(chloromethyl)-1,5-dimethyl-1*H*-pyrazol-4-yl)-3-(3-(naphthalen-1-yloxy)propyl)-1*H*-indole-2-carboxylate which was used for the next step without further purification.

LCMS (ESI+): m/z 756.5 $[M+H]^+$

Step H

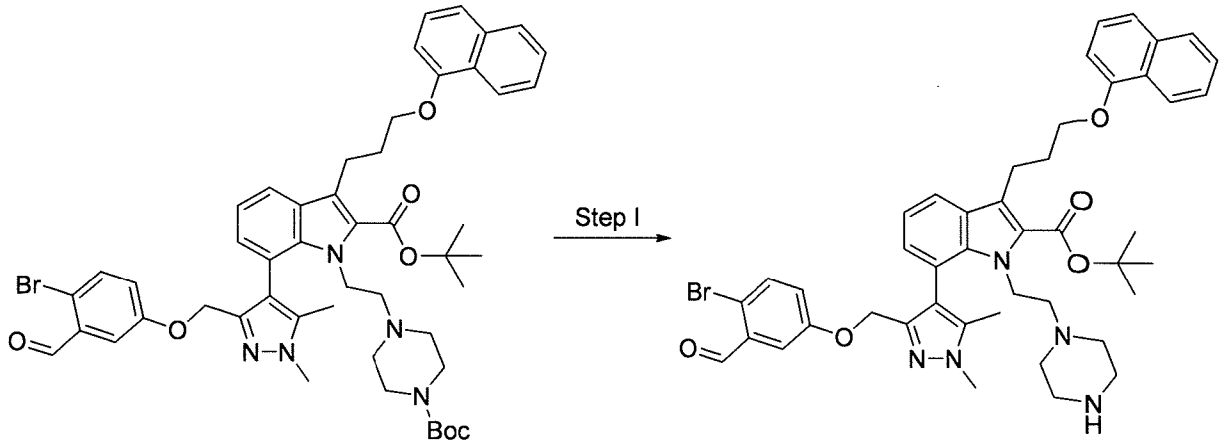


2-Bromo-5-hydroxybenzaldehyde (60 mg, 0.298 mmol) and potassium *tert*-butoxide (0.4 ml, 0.397 mmol) were dissolved in DMF (3 mL), followed by the addition of *tert*-butyl 1-(2-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)ethyl)-7-(3-(chloromethyl)-1,5-dimethyl-1*H*-pyrazol-4-yl)-3-(3-(naphthalen-1-yloxy)propyl)-1*H*-indole-2-carboxylate (150 mg, crude). The resulting mixture was stirred at 60°C for 2 h under nitrogen. After complete consumption of the starting material (monitored by TLC and LCMS) the reaction mixture was then cooled down to room temperature, diluted with ethyl acetate and washed successively with water and brine. The organic layer was dried over sodium sulphate and evaporated under reduced pressure to get the crude compound, which was then purified by preparative HPLC to afford *tert*-butyl 7-(3-((4-bromo-3-

formylphenoxy)methyl)-1,5-dimethyl-1*H*-pyrazol-4-yl)-1-(2-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)ethyl)-3-(3-(naphthalen-1-yloxy)propyl)-1*H*-indole-2-carboxylate (15 mg, 0.016 mmol, 5% over two steps) as off white solid.

LCMS (ESI+): m/z 920.2 $[M+H]^+$

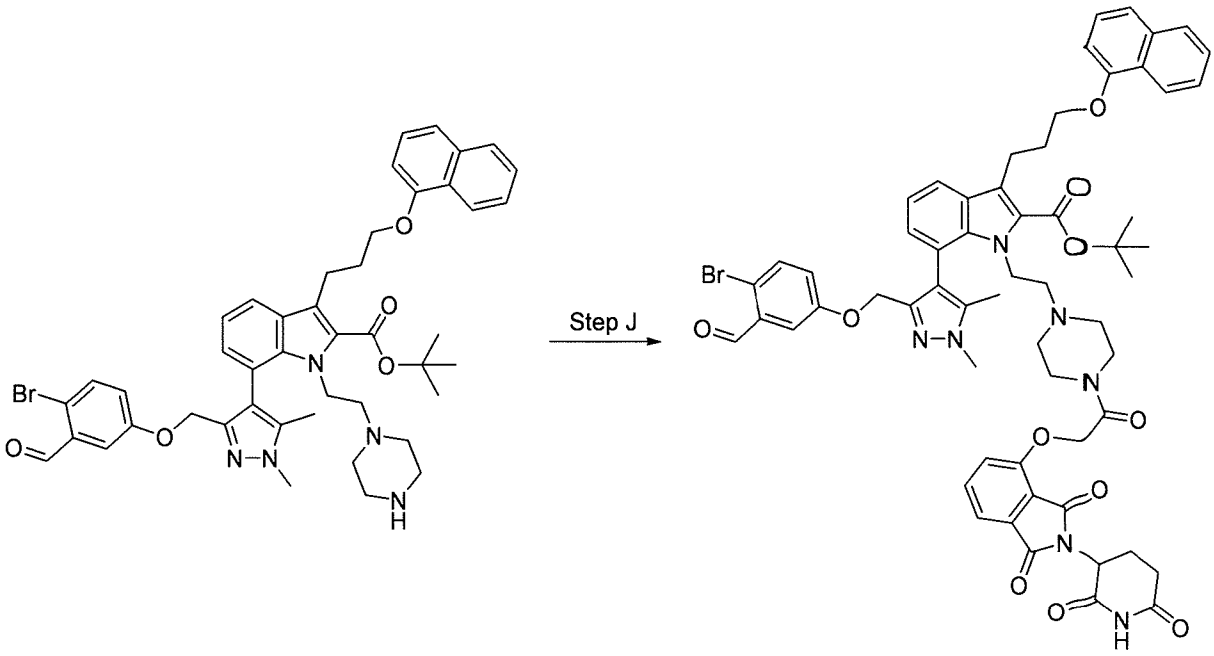
Step I



To a stirred solution of *tert*-butyl 7-(3-((4-bromo-3-formylphenoxy)methyl)-1,5-dimethyl-1*H*-pyrazol-4-yl)-1-(2-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)ethyl)-3-(3-(naphthalen-1-yloxy)propyl)-1*H*-indole-2-carboxylate (200 mg, 0.218 mmol) in DCM (2 mL) was added 2 ml of 4M HCl in dioxan at 0°C under nitrogen and the reaction mixture was allowed to stir at room temperature for 1 h. After consumption of the starting material (monitored by TLC and LCMS) the reaction mixture was quenched by the slow addition of aq. 1M NaOH at 0°C to the pH = 7. Then it was extracted with DCM (3×50 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to afford 180 mg of crude *tert*-butyl 7-(3-((4-bromo-3-formylphenoxy)methyl)-1,5-dimethyl-1*H*-pyrazol-4-yl)-3-(3-(naphthalen-1-yloxy)propyl)-1-(2-(piperazin-1-yl)ethyl)-1*H*-indole-2-carboxylate as brown solid.

LCMS (ESI+): m/z 822.8 $[M+H]^+$

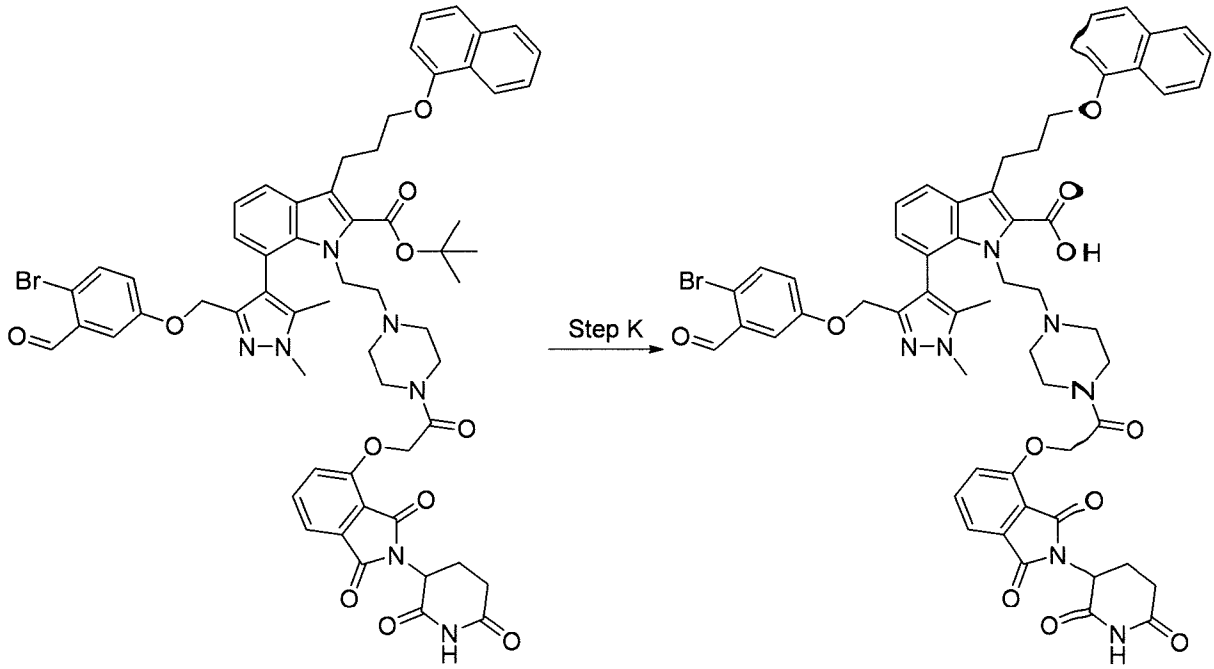
Step J



2-((2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)acetic acid (82 mg, 0.249 mmol) was added to a mixture of *tert*-butyl 7-(3-((4-bromo-3-formylphenoxy)methyl)-1,5-dimethyl-1*H*-pyrazol-4-yl)-3-(3-(naphthalen-1-yloxy)propyl)-1-(2-(piperazin-1-yl)ethyl)-1*H*-indole-2-carboxylate (170 mg, crude) in DMF (3 ml). The mixture was stirred in room temperature under nitrogen atmosphere and to it was added DIPEA (0.2 ml, 0.83mmol), followed by HATU (236 mg, 0.623mmol) and the mixture was stirred for additional 16 h. After complete consumption of the starting material (monitored by TLC and LCMS) the reaction mixture diluted with ethyl acetate, washed successively with cold water (3 times) and brine. Organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to get the 180 mg of crude *tert*-butyl 7-(3-((4-bromo-3-formylphenoxy)methyl)-1,5-dimethyl-1*H*-pyrazol-4-yl)-1-(2-(4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)acetyl)piperazin-1-yl)ethyl)-3-(3-(naphthalen-1-yloxy)propyl)-1*H*-indole-2-carboxylate as black solid which was used for next step without further purification.

LCMS (ESI+): m/z 1135.25 $[M+H]^+$

Step K

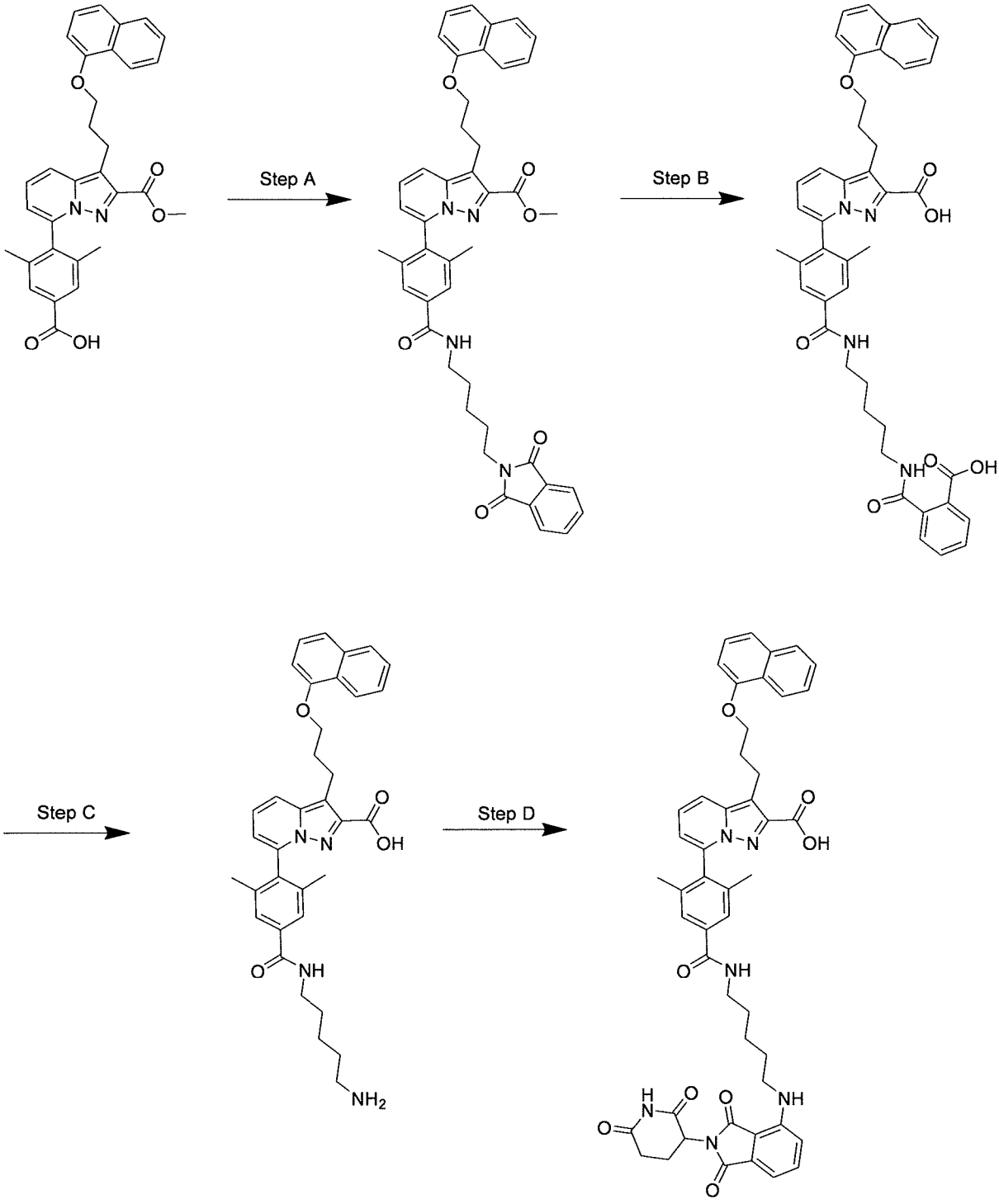


Tert-butyl 7-(3-((4-bromo-3-formylphenoxy)methyl)-1,5-dimethyl-1*H*-pyrazol-4-yl)-1-(2-(4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)acetyl)piperazin-1-yl)ethyl)-3-(3-(naphthalen-1-yloxy)propyl)-1*H*-indole-2-carboxylate (180 mg, crude) was suspended in 1,4-dioxane (1.0 mL) and the reaction mixture was cooled to 0°C then added 2 ml of 4M HCl in dioxane drop wise to the reaction mixture, then the reaction mixture was allowed to stir at ambient temperature for 16 h under nitrogen. After complete consumption of the starting material (monitored by TLC and LCMS) the volatiles were evaporated under reduced pressure to afford the crude reaction mass which was purified by reverse phase preparatory HPLC (H_2O:MeCN + 0.1% FA) to afford 7-(3-((4-bromo-3-formylphenoxy)methyl)-1,5-dimethyl-1*H*-pyrazol-4-yl)-1-(2-(4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)acetyl)piperazin-1-yl)ethyl)-3-(3-(naphthalen-1-yloxy)propyl)-1*H*-indole-2-carboxylic acid (5.5 mg, 0.0051 mmol, 2.3 % over three steps) as white solid.

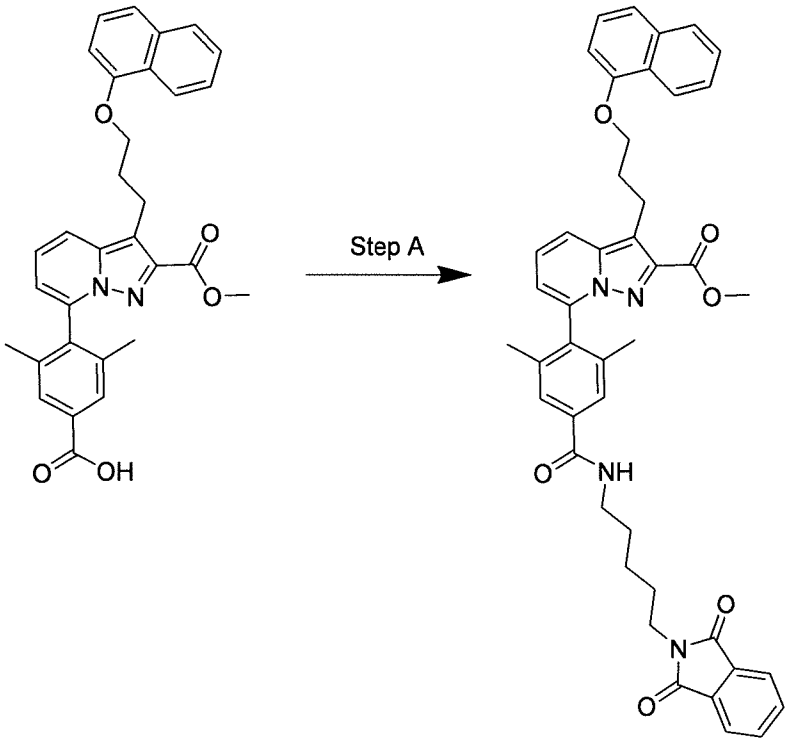
LCMS (ESI+): m/z 1078.7 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO) δ 11.09 (s, 1H), 10.06 (s, 1H), 8.28 – 8.17 (m, 1H), 7.90 – 7.80 (m, 1H), 7.78 – 7.70 (m, 1H), 7.67 (d, *J* = 7.7 Hz, 1H), 7.56 – 7.47 (m, 3H), 7.47 – 7.40 (m, 2H), 7.35 (t, *J* = 7.9 Hz, 1H), 7.28 (d, *J* = 8.6 Hz, 1H), 7.21 (d, *J* = 3.2 Hz, 1H), 7.09 – 6.98 (m, 2H), 6.96 (d, *J* = 6.8 Hz, 1H), 6.89 – 6.80 (m, 1H), 5.15 – 5.04 (m, 3H), 4.98 – 4.84 (m, 2H), 4.43 – 4.25 (m, 2H), 4.24 – 4.10 (m, 2H), 3.83 (s, 3H), 3.29 (s, 6H), 2.95 – 2.80 (m, 1H), 2.61 (s, 2H), 2.24 – 2.15 (m, 2H), 2.10 (s, 6H), 2.05 – 1.96 (m, 4H).

Example 49. 7-(4-((5-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)pentyl)carbamoyl)-2,6-dimethylphenyl)-3-(3-(naphthalen-1-yloxy)propyl)pyrazolo[1,5-*a*]pyridine-2-carboxylic acid (253)



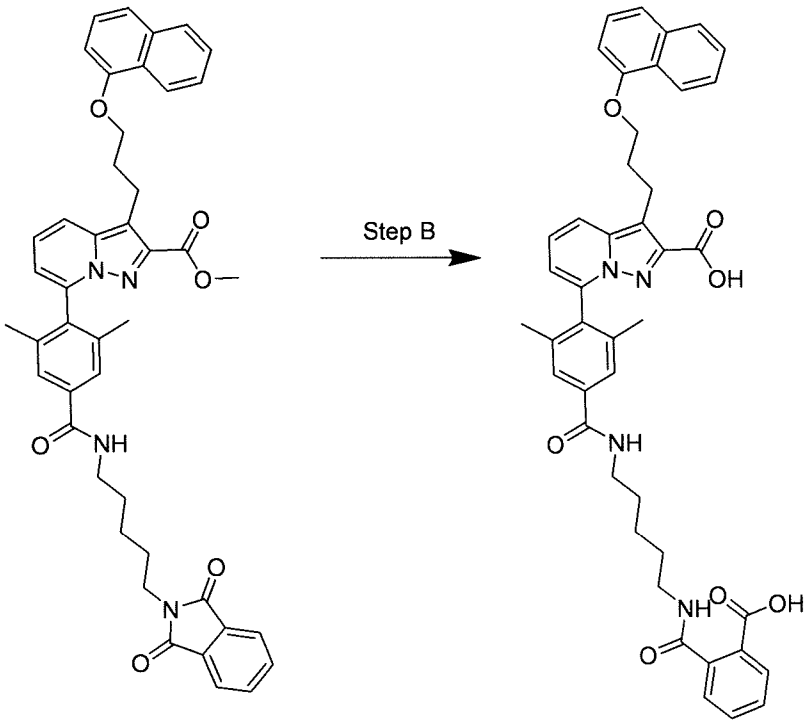
Step A



4-(2-(Methoxycarbonyl)-3-(3-(naphthalen-1-yloxy)propyl)pyrazolo[1,5-*a*]pyridin-7-yl)-3,5-dimethylbenzoic acid (100 mg, 0.20 mmol) was dissolved in anhydrous DMF (1.26 mL). DIPEA (103 µL, 0.59 mmol) and HATU (90 mg, 0.24 mmol) were added under inert atmosphere, and mixture was stirred in RT for 1h. Then 2-(5-(l2-azaneyl)pentyl)isoindoline-1,3-dione (55 mg, 0.24 mmol) was added in solution of DMF (1.26 mL). Vial was sealed, and mixture was stirred at RT for overnight. Solvent was removed under reduced pressure, brine and DCM were added and product was extracted with DCM to give methyl 7-(4-((5-(1,3-dioxoisoindolin-2-yl)pentyl)carbamoyl)-2,6-dimethylphenyl)-3-(3-(naphthalen-1-yloxy)propyl)pyrazolo[1,5-*a*]pyridine-2-carboxylate (142.0 mg of crude) which was used without further purification to the next step.

LCMS (ESI+): m/z 723.2 $[M+H]^+$

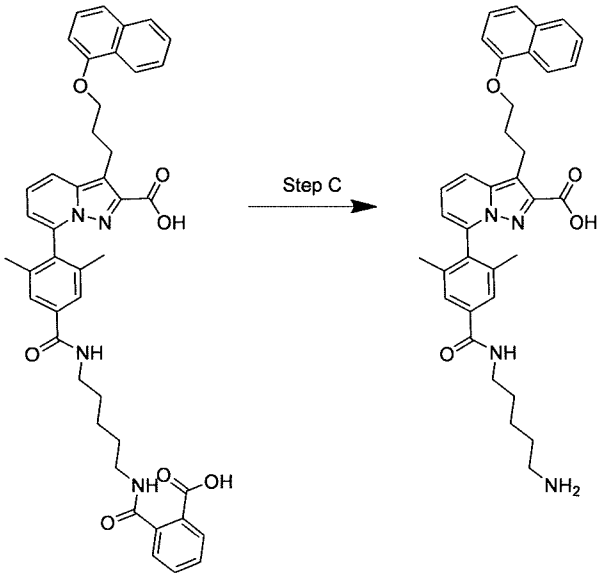
Step B



To solution of methyl 7-(4-((5-(1,3-dioxoisoindolin-2-yl)pentyl)carbamoyl)-2,6-dimethylphenyl)-3-(3-(naphthalen-1-yloxy)propyl)pyrazolo[1,5-*a*]pyridine-2-carboxylate (145 mg of crude) in a mixture MeOH:H_2O:THF 1:1:1 (2.16 mL) was added NaOH dissolved in 0.5 mL of H_2O. Mixture was stirred at 70°C for 18 h. Solvents were removed under reduced pressure, mixture was extracted with DCM, then aqueous phase was acidified until pH = 1 and product was extracted with DCM:MeOH 9:1 to give 7-(4-((5-(2-carboxybenzamido)pentyl)carbamoyl)-2,6-dimethylphenyl)-3-(3-(naphthalen-1-yloxy)propyl)pyrazolo[1,5-*a*]pyridine-2-carboxylic acid (123 mg, 0.174 mmol, 87% over two steps) as orange foam.

LCMS (ESI+): m/z 727.4 $[M+H]^+$

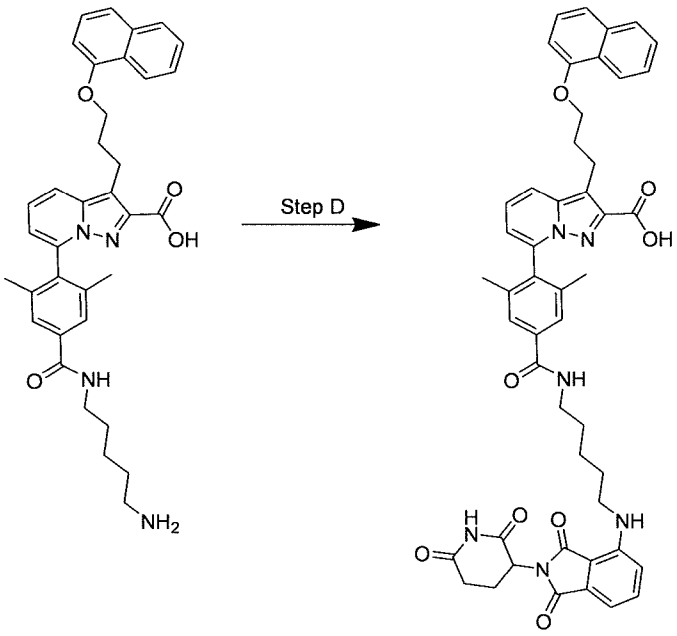
Step C



Hydrazine hydrate 50% (30 µL, 0.47 mmol) was added to solution of 7-(4-((5-(2-carboxybenzamido)pentyl)carbamoyl)-2,6-dimethylphenyl)-3-(3-(naphthalen-1-yloxy)propyl)pyrazolo[1,5-*a*]pyridine-2-carboxylic acid (115 mg, 0.16 mmol) in MeOH (0.63 mL) and mixture was heated in 60°C for 18h. Precipitate was observed which was filtered off. 7-(4-((5-aminopentyl)carbamoyl)-2,6-dimethylphenyl)-3-(3-(naphthalen-1-yloxy)propyl)pyrazolo[1,5-*a*]pyridine-2-carboxylic acid (45.00 mg, 0.078 mmol, 60%) was obtained as white solid.

LCMS (ESI+): m/z 579.3 $[M+H]^+$

Step D

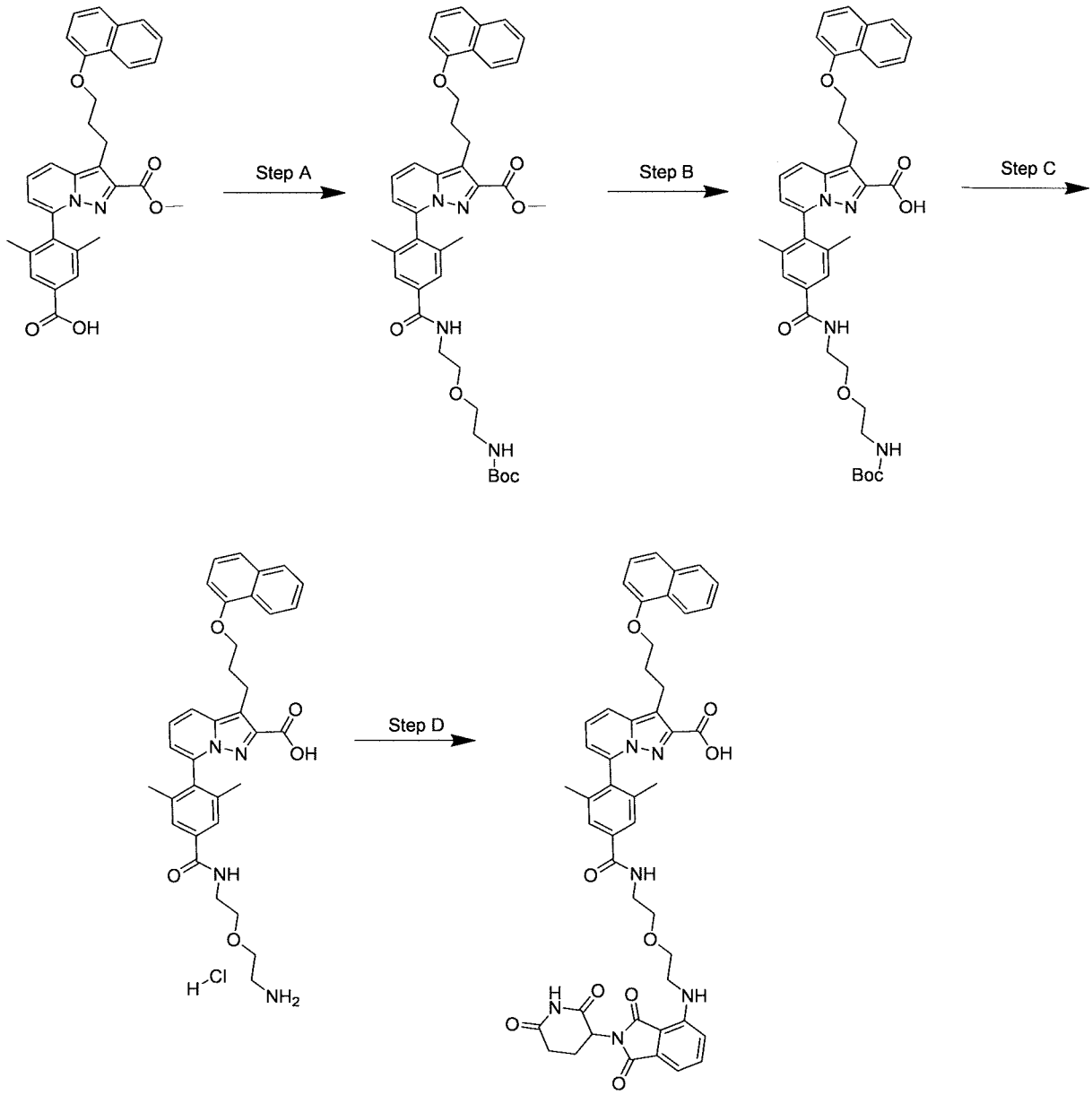


DIPEA (18 µL, 0.10 mmol) was added to a solution of 7-(4-((5-aminopentyl)carbamoyl)-2,6-dimethylphenyl)-3-(3-(naphthalen-1-yloxy)propyl)pyrazolo[1,5-*a*]pyridine-2-carboxylic acid (20 mg, 0.03 mmol) and 2-(2,6-dioxopiperidin-3-yl)-4-fluoroisoindoline-1,3-dione (29 mg, 0.10 mmol) in DMSO (0.24 mL). The reaction mixture was heated at 90°C for 20h. Crude was purified by flash chromatography (SiO_2, 5% MeOH in DCM). 7-(4-((5-((2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)pentyl)carbamoyl)-2,6-dimethylphenyl)-3-(3-(naphthalen-1-yloxy)propyl)pyrazolo[1,5-*a*]pyridine-2-carboxylic acid (7.50 mg, 0.009 mmol, 30%) was isolated as yellow solid.

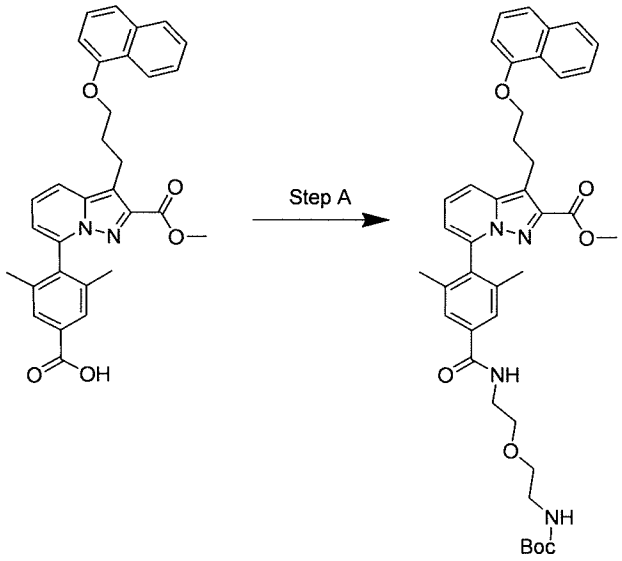
LCMS (ESI+): m/z 835.2 $[M+H]^+$

^{1}H NMR (600 MHz, DMSO) δ 12.99 (s, 1H), 11.08 (s, 1H), 8.48 (t, *J* = 5.7 Hz, 1H), 8.25 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.90 – 7.85 (m, 1H), 7.85 – 7.76 (m, 1H), 7.64 (s, 2H), 7.58 (dd, *J* = 8.5, 7.1 Hz, 1H), 7.56 – 7.48 (m, 2H), 7.45 (d, *J* = 8.3 Hz, 1H), 7.38 (t, *J* = 7.9 Hz, 1H), 7.29 – 7.20 (m, 1H), 7.12 (d, *J* = 8.6 Hz, 1H), 7.02 (d, *J* = 7.0 Hz, 1H), 6.89 (d, *J* = 7.5 Hz, 2H), 6.56 (t, *J* = 5.9 Hz, 1H), 5.04 (dd, *J* = 12.8, 5.5 Hz, 1H), 4.17 (t, *J* = 6.2 Hz, 2H), 3.30 – 3.27 (m, 3H), 2.87 (ddd, *J* = 16.9, 13.8, 5.5 Hz, 1H), 2.60 – 2.57 (m, 1H), 2.59 – 2.54 (m, 1H), 2.54 – 2.50 (m, 1H), 2.47 – 2.41 (m, 1H), 2.26 – 2.19 (m, 2H), 2.05 – 1.99 (m, 1H), 1.94 (s, 7H), 1.66 – 1.57 (m, 4H), 1.42 (t, *J* = 7.6 Hz, 2H).

Example 50. 7-(4-((2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethyl)carbamoyl)-2,6-dimethylphenyl)-3-(3-(naphthalen-1-yloxy)propyl)pyrazolo[1,5-*a*]pyridine-2-carboxylic acid (254)



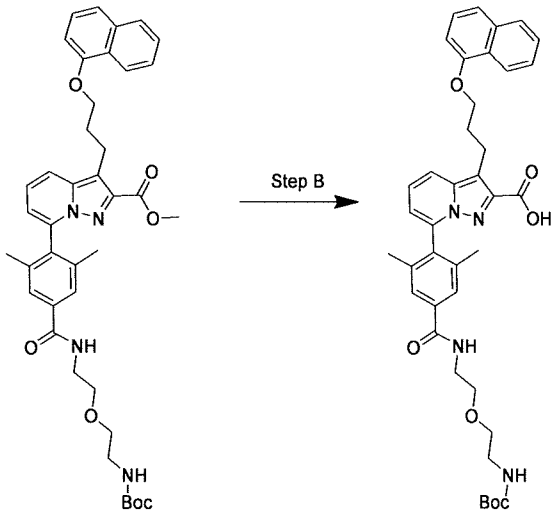
Step A



4-(2-(Methoxycarbonyl)-3-(3-(naphthalen-1-yloxy)propyl)pyrazolo[1,5-*a*]pyridin-7-yl)-3,5-dimethylbenzoic acid (100 mg, 0.20 mmol) and HATU (90 mg, 0.24 mmol) were dissolved in anhydrous DMF (1.5mL) and DIPEA (76 mg, 0.59 mmol) was added. The solution was stirred in an inert atmosphere at RT for 1h. In a separate vial *tert*-butyl (2-(2-aminoethoxy)ethyl)carbamate (48 mg, 0.24 mmol) was dissolved in anhydrous DMF (0.5mL) and added to the main solution. The mixture was stirred at RT overnight. DMF was evaporated and the residue was dissolved in DCM and brine was added followed by extraction by DCM. The solvent was removed on rotavapor and the crude methyl 7-(4-((2-(2-((*tert*-butoxycarbonyl)amino)ethoxy)ethyl)carbamoyl)-2,6-dimethylphenyl)-3-(3-(naphthalen-1-yloxy)propyl)pyrazolo[1,5-*a*]pyridine-2-carboxylate (100.0 mg, crude) was used in the next step.

LCMS (ESI+): m/z 595.5 $[M+H-Boc]^+$

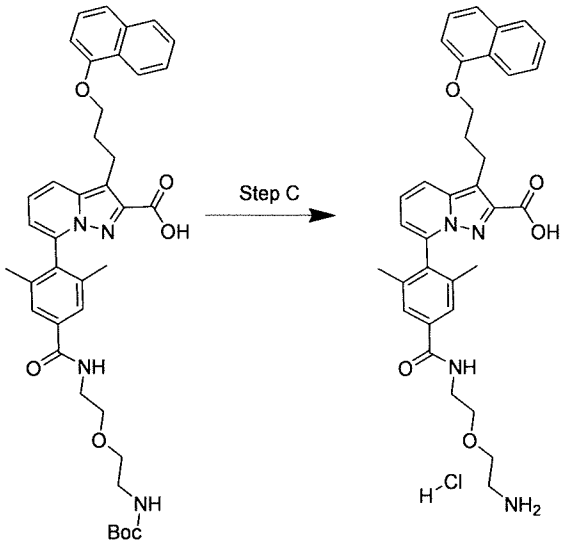
Step B



Methyl 7-(4-((2-(2-((*tert*-butoxycarbonyl)amino)ethoxy)ethyl)carbamoyl)-2,6-dimethylphenyl)-3-(3-(naphthalen-1-yloxy)propyl)pyrazolo[1,5-*a*]pyridine-2-carboxylate (100 mg, crude) was dissolved in THF (6 mL) and the solution of NaOH (90 mg, 2.25 mmol) in 2 mL of water was added. The solution was stirred at 50°C for 18 h. The reaction was cooled to RT, water was added and extracted 4 times by EtOAc. The organic phase was evaporated to dryness and the crude 7-(4-((2-(2-((*tert*-butoxycarbonyl)amino)ethoxy)ethyl)carbamoyl)-2,6-dimethylphenyl)-3-(3-(naphthalen-1-yloxy)propyl)pyrazolo[1,5-*a*]pyridine-2-carboxylic acid (100.0 mg, crude) was used directly for the next step.

LCMS (ESI+): m/z 581.5 $[M+H\text{-}Boc]^+$

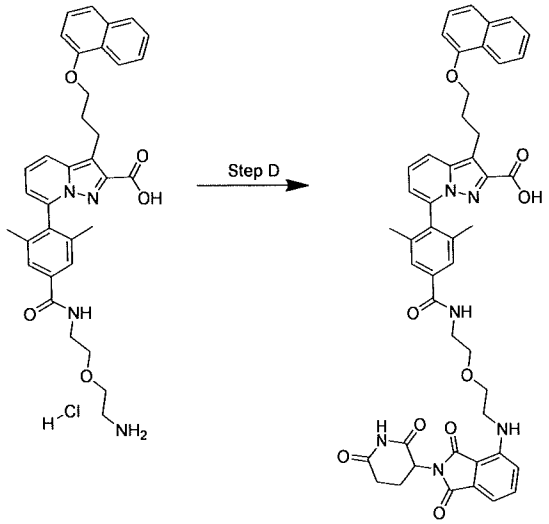
Step C



7-(4-((2-(2-((*tert*-butoxycarbonyl)amino)ethoxy)ethyl)carbamoyl)-2,6-dimethylphenyl)-3-(3-(naphthalen-1-yloxy)propyl)pyrazolo[1,5-*a*]pyridine-2-carboxylic acid (100 mg, crude) was dissolved in dry THF (1.6mL) and 4M HCl in dioxane (0.75 mL) was added. The mixture was stirred overnight at RT. Solvents were evaporated to give 7-(4-((2-(2-aminoethoxy)ethyl)carbamoyl)-2,6-dimethylphenyl)-3-(3-(naphthalen-1-yloxy)propyl)pyrazolo[1,5-*a*]pyridine-2-carboxylic acid hydrochloride (40.0 mg, crude) as yellow sticky gum. The obtained crude was used directly for the next step.

LCMS (ESI+): m/z 581.5 $[M+H]^+$

Step D

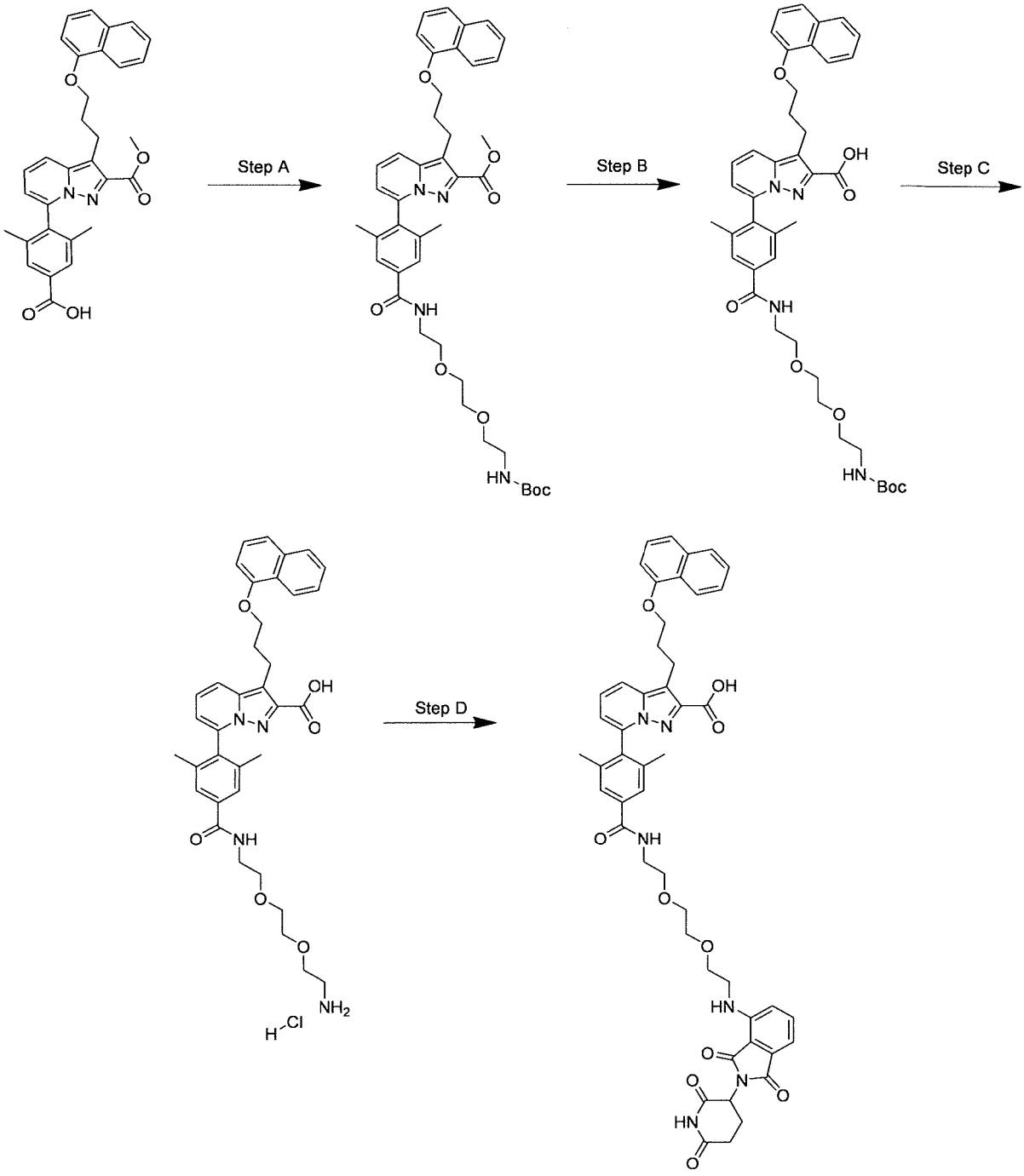


7-(4-((2-(2-aminoethoxy)ethyl)carbamoyl)-2,6-dimethylphenyl)-3-(3-(naphthalen-1-yloxy)propyl)pyrazolo[1,5-*a*]pyridine-2-carboxylic acid hydrochloride (9.0 mg, crude) and 2-(2,6-dioxopiperidin-3-yl)-4-fluoroisoindoline-1,3-dione (41 mg, 0.15 mmol) were dissolved in DMSO (0.21 mL) and DIPEA (6 mg, 0.05 mmol) was added to the mixture. Reaction was stirred in 90°C for 20 h. The solvent was evaporated and the residue was purified by flash chromatography (SiO_2, 5% MeOH in DCM) to obtain 7-(4-((2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethyl)carbamoyl)-2,6-dimethylphenyl)-3-(3-(naphthalen-1-yloxy)propyl)pyrazolo[1,5-*a*]pyridine-2-carboxylic acid (2.10 mg, 0.003 mmol, 6% over 4 steps) as yellow solid.

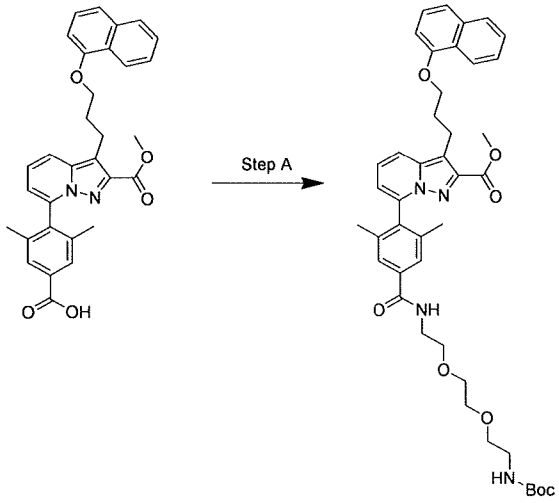
LCMS (ESI+): m/z 837.6 $[M+H]^+$

1H NMR (500 MHz, $CDCl_3$) δ 8.34 – 8.27 (m, 1H), 7.78 – 7.70 (m, 1H), 7.53 – 7.36 (m, 5H), 7.33 (d, *J* = 8.2 Hz, 1H), 7.29 – 7.20 (m, 1H), 7.04 – 6.96 (m, 2H), 6.86 (d, *J* = 8.5 Hz, 1H), 6.67 (d, *J* = 7.6 Hz, 1H), 6.65 – 6.57 (m, 2H), 4.80 – 4.69 (m, 1H), 4.15 – 4.02 (m, 2H), 3.75 – 3.46 (m, 7H), 3.45 – 3.36 (m, 2H), 3.36 – 3.26 (m, 2H), 2.73 – 2.56 (m, 2H), 2.36 – 2.25 (m, 2H), 1.99 – 1.80 (m, 7H).

Example 51. 7-(4-((2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)ethyl)carbamoyl)-2,6-dimethylphenyl)-3-(3-(naphthalen-1-yloxy)propyl)pyrazolo[1,5-*a*]pyridine-2-carboxylic acid (255)


Step A
Step B
Step C
Step D
Boc
HCl

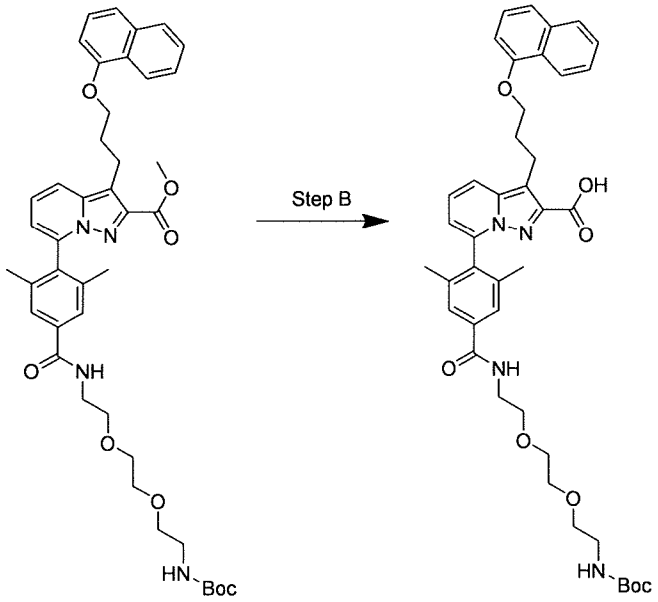
Step A



4-(2-(methoxycarbonyl)-3-(3-(naphthalen-1-yloxy)propyl)pyrazolo[1,5-*a*]pyridin-7-yl)-3,5-dimethylbenzoic acid (100 mg, 0.20 mmol) and HATU (90 mg, 0.24 mmol) was dissolved in anhydrous DMF (1.5 mL) and DIPEA (103 µL, 0.59 mmol) was added to the mixture. The reaction was stirred in an inert atmosphere at RT for 1 h. The solution of *tert*-butyl (2-(2-(2-aminoethoxy)ethoxy)ethyl)carbamate (59 mg, 0.24 mmol) in anhydrous DMF (0.5 mL) was added and the resulting solution was stirred at RT overnight. DMF was evaporated and the residue was taken up in DCM and brine was added followed by extraction by DCM. The solvent was concentrated in vacuo and the crude product of methyl 7-(4-((2,2-dimethyl-4-oxo-3,8,11-trioxa-5-azatridecan-13-yl)carbamoyl)-2,6-dimethylphenyl)-3-(3-(naphthalen-1-yloxy)propyl)pyrazolo[1,5-*a*]pyridine-2-carboxylate (105 mg, crude) was used without purification in the next step.

LCMS (ESI+): m/z 639.6 $[M\text{-}Boc+H]^+$

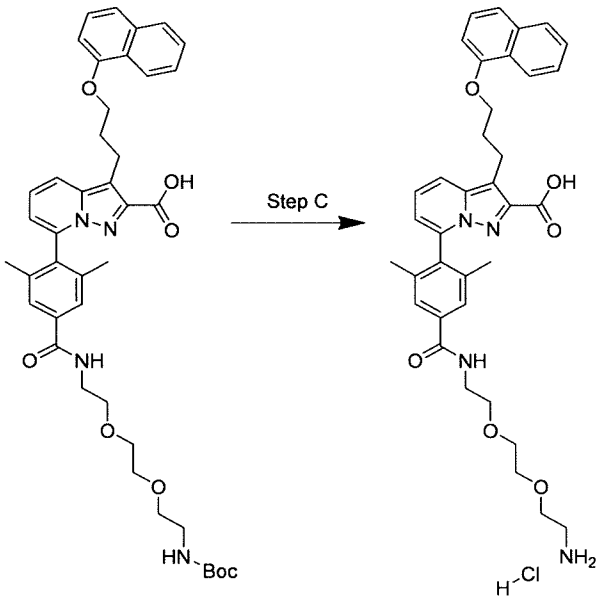
Step B



The residue of methyl 7-(4-((2,2-dimethyl-4-oxo-3,8,11-trioxa-5-azatridecan-13-yl)carbamoyl)-2,6-dimethylphenyl)-3-(3-(naphthalen-1-yloxy)propyl)pyrazolo[1,5-*a*]pyridine-2-carboxylate (105 mg, of crude) was dissolved in THF (6 mL) and the solution of NaOH (90 mg, 2.25 mmol) in 2 mL of H_2O was added. The solution was stirred at 50°C for 18h. The reaction was cooled to RT, water was added and the mixture was extracted with EtOAc. The organic phase was evaporated and to give 143 mg crude of 7-(4-((2,2-dimethyl-4-oxo-3,8,11-trioxa-5-azatridecan-13-yl)carbamoyl)-2,6-dimethylphenyl)-3-(3-(naphthalen-1-yloxy)propyl)pyrazolo[1,5-*a*]pyridine-2-carboxylic acid was used directly for the next step.

LCMS (ESI+): m/z 723.7 $[M-H]^-$

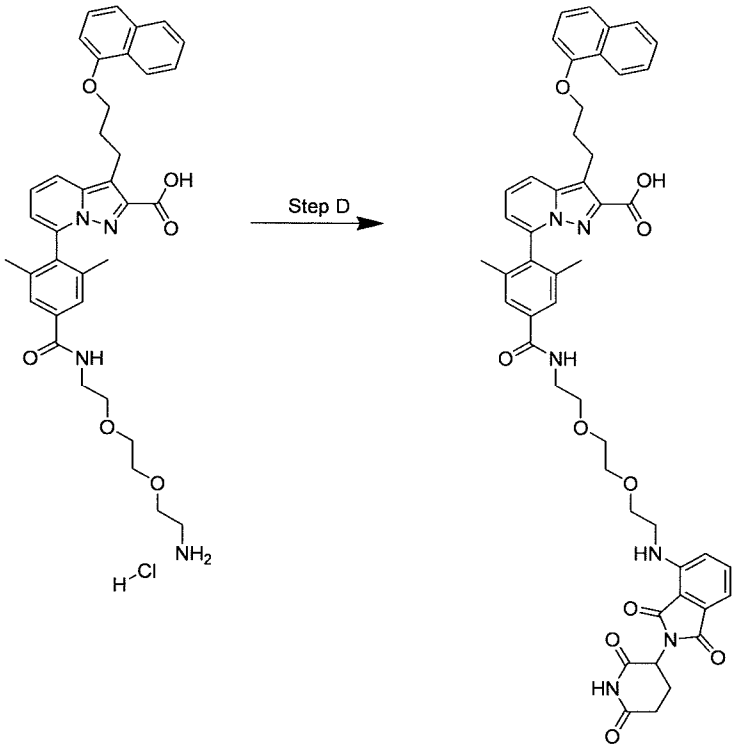
Step C



The residue of 7-(4-((2,2-dimethyl-4-oxo-3,8,11-trioxa-5-azatridecan-13-yl)carbamoyl)-2,6-dimethylphenyl)-3-(3-(naphthalen-1-yloxy)propyl)pyrazolo[1,5-*a*]pyridine-2-carboxylic acid (143 mg, crude) was dissolved in dry THF (2 mL) and 4M HCl in dioxane (344 µL, 1.38 mmol) was added. The resulting solution was mixed overnight at RT. After this time additional portion of 4M HCl in dioxane (885 µL, 3.54 mmol) was added and left stirring overnight. The solvents were evaporated to give 7-(4-((2-(2-(2-aminoethoxy)ethoxy)ethyl)carbamoyl)-2,6-dimethylphenyl)-3-(3-(naphthalen-1-yloxy)propyl)pyrazolo[1,5-*a*]pyridine-2-carboxylic acid hydrochloride (74.0 mg, crude) which was used directly for the next step.

LCMS (ESI+): m/z 625.6 $[M+H]^+$

Step D



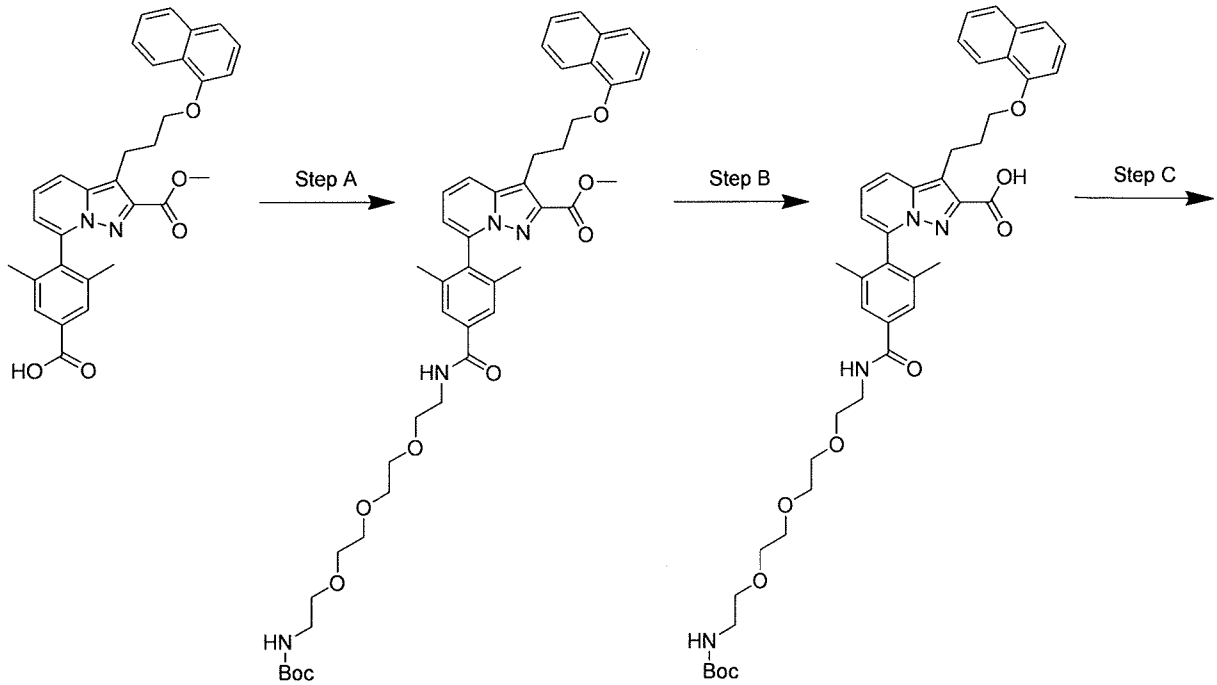
To 7-(4-((2-(2-(2-aminoethoxy)ethoxy)ethyl)carbamoyl)-2,6-dimethylphenyl)-3-(3-(naphthalen-1-yloxy)propyl)pyrazolo[1,5-*a*]pyridine-2-carboxylic acid hydrochloride (74 mg, crude) and 2-(2,6-dioxopiperidin-3-yl)-4-fluoroisoindoline-1,3-dione (266 mg, 0.96 mmol) suspended in DMSO was added DIPEA (55 uL, 0.29 mmol). The mixture was stirred at 90°C for 18 h. Then the reaction was cooled, the solvents were evaporated. The residue was purified using flash chromatography (SiO_2, 5% MeOH in DCM) and by preparative TLC (SiO_2, 5% MeOH in DCM). 7-(4-((2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)ethyl)carbamoyl)-2,6-

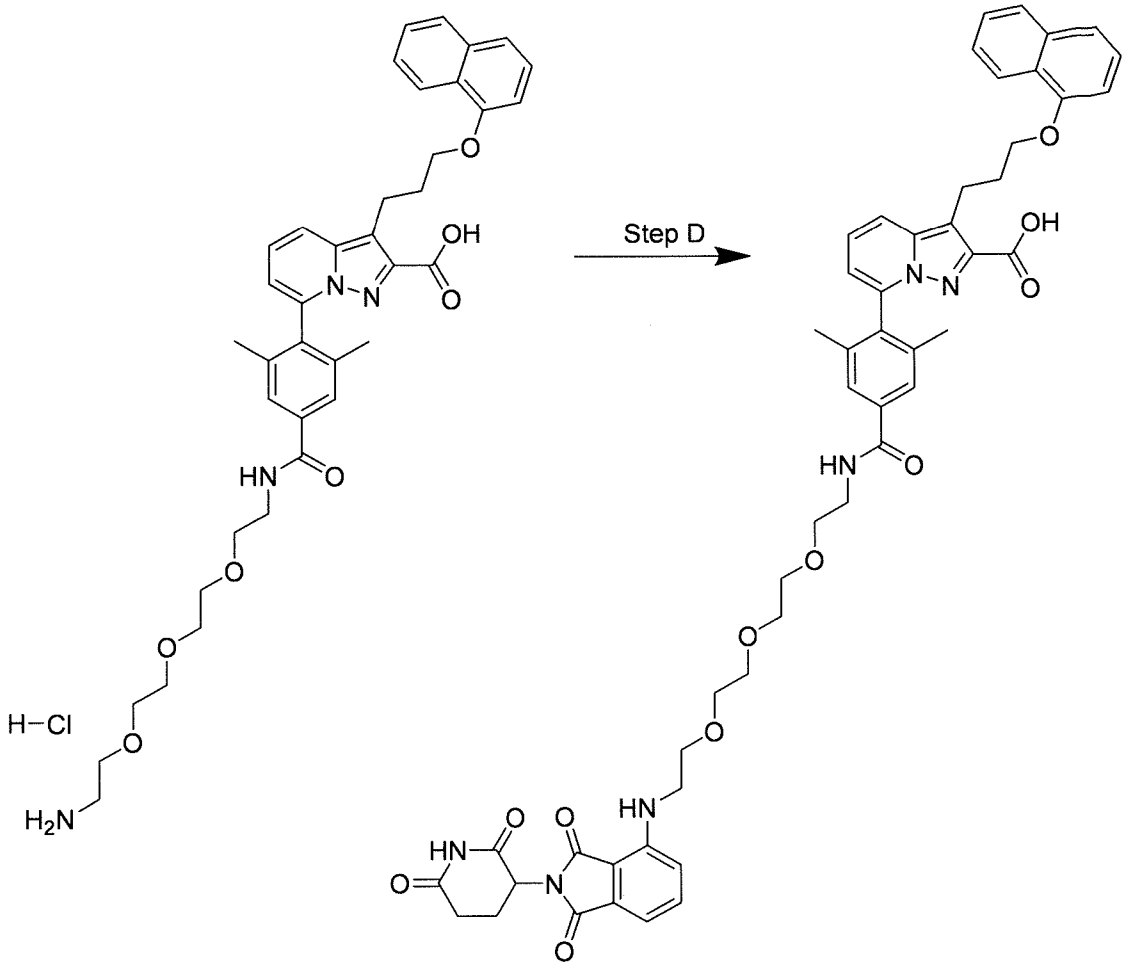
dimethylphenyl)-3-(3-(naphthalen-1-yloxy)propyl)pyrazolo[1,5-*a*]pyridine-2-carboxylic acid (8.50 mg, 0.010 mmol, 10%) was obtained as yellow solid.

LCMS (ESI+): m/z 881.6 $[M+H]^+$

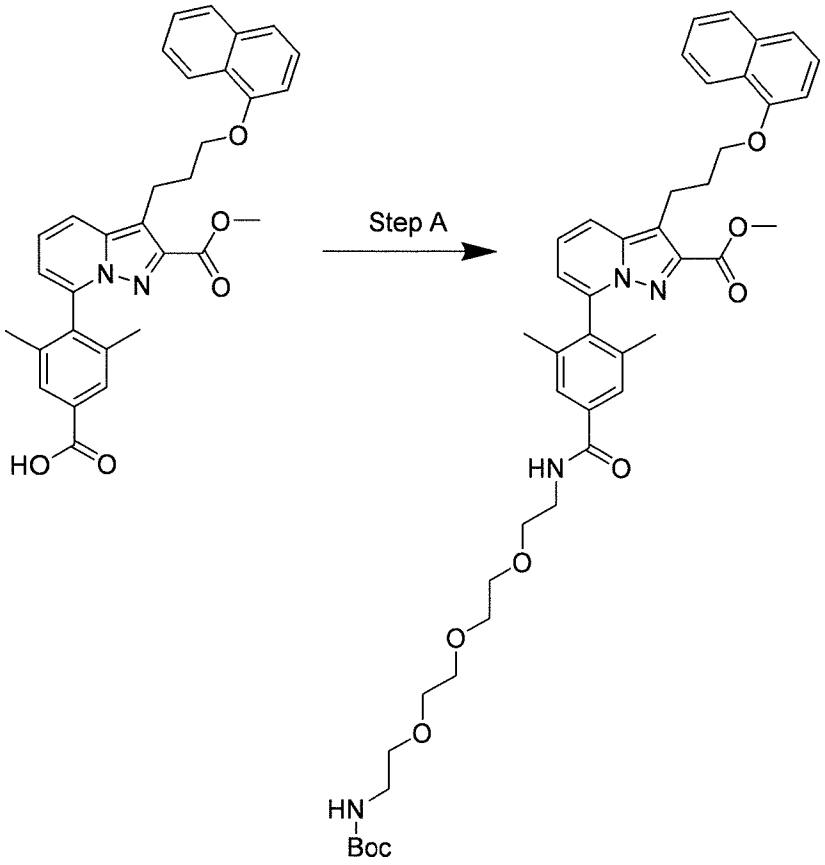
1H NMR (500 MHz, $CDCl_3$) δ 8.34 – 8.28 (m, 1H), 7.77 – 7.70 (m, 1H), 7.59 (s, 1H), 7.53 – 7.46 (m, 2H), 7.46 – 7.36 (m, 3H), 7.33 (d, *J* = 8.3 Hz, 1H), 7.28 – 7.23 (m, 1H), 7.03 – 6.94 (m, 2H), 6.79 (d, *J* = 8.5 Hz, 1H), 6.67 (d, *J* = 7.7 Hz, 1H), 6.65 – 6.56 (m, 1H), 4.72 – 4.63 (m, 1H), 4.15 – 4.04 (m, 2H), 3.74 – 3.49 (m, 11H), 3.41 – 3.36 (m, 2H), 3.33 (t, *J* = 7.2 Hz, 2H), 2.71 – 2.50 (m, 3H), 2.36 – 2.26 (m, 2H), 1.98 – 1.83 (m, 6H).

Example 52. 7-(4-((2-(2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)ethoxy)ethyl)carbamoyl)-2,6-dimethylphenyl)-3-(3-(naphthalen-1-yloxy)propyl)pyrazolo[1,5-*a*]pyridine-2-carboxylic acid (256)




Step D
OH
O
N
N
HN
O
H−Cl
H_2N
HN
O
O
N
O

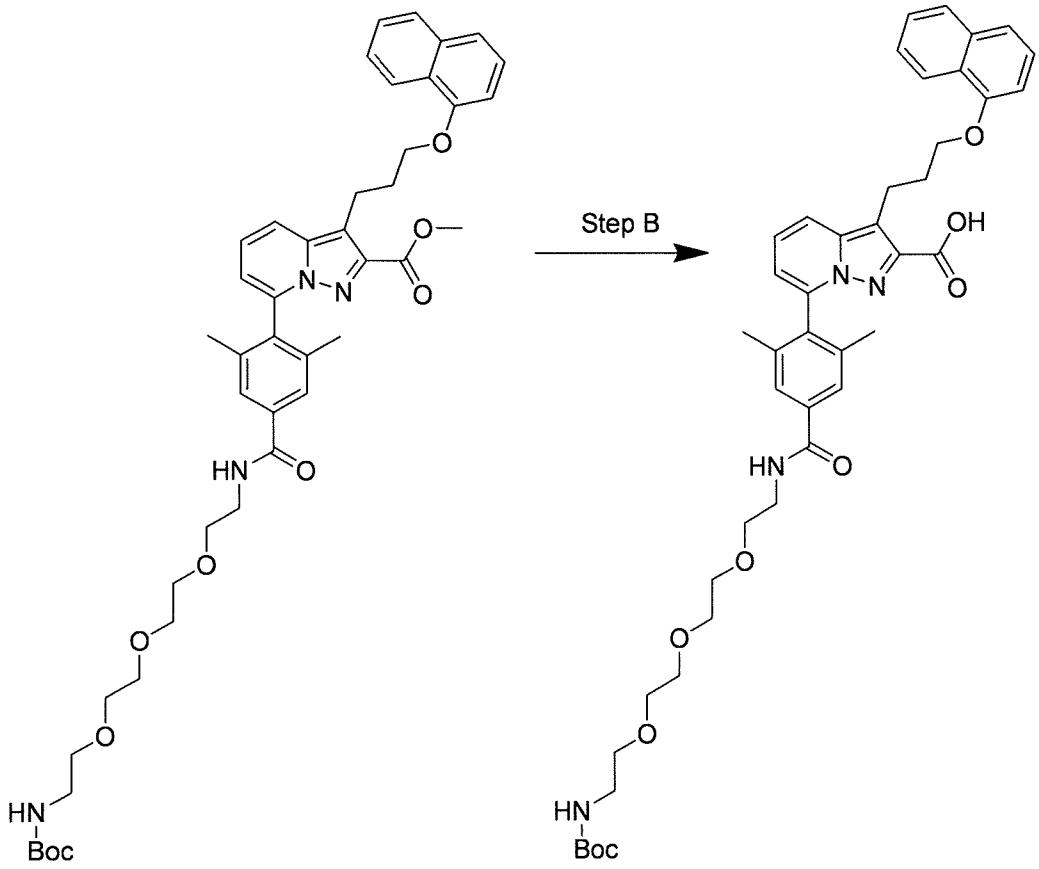
Step A



4-(2-(methoxycarbonyl)-3-(3-(naphthalen-1-yloxy)propyl)pyrazolo[1,5-*a*]pyridin-7-yl)-3,5-dimethylbenzoic acid (100 mg, 0.20 mmol) was dissolved in anhydrous DMF (1.26 mL). DIPEA (103 µL, 0.59 mmol) and HATU (90 mg, 0.24 mmol) were added under an inert atmosphere, and mixture was stirred in RT for 1 h. Then *tert*-butyl *N*-(2-{2-[2-(2-aminoethoxy)ethoxy]ethoxy}ethyl)carbamate (69 mg, 0.24 mmol) was added in solution of DMF (1.26 mL). The mixture was stirred at RT for overnight. Solvent was removed under reduced pressure, brine and DCM were added and product was extracted with DCM to give methyl 7-(4-((2,2-dimethyl-4-oxo-3,8,11,14-tetraoxa-5-azahexadecan-16-yl)carbamoyl)-2,6-dimethylphenyl)-3-(3-(naphthalen-1-yloxy)propyl)pyrazolo[1,5-*a*]pyridine-2-carboxylate (151 mg, crude) which was used without further purification to the next step.

LCMS (ESI+): m/z 683.3 $[M+H\text{-}Boc]^+$

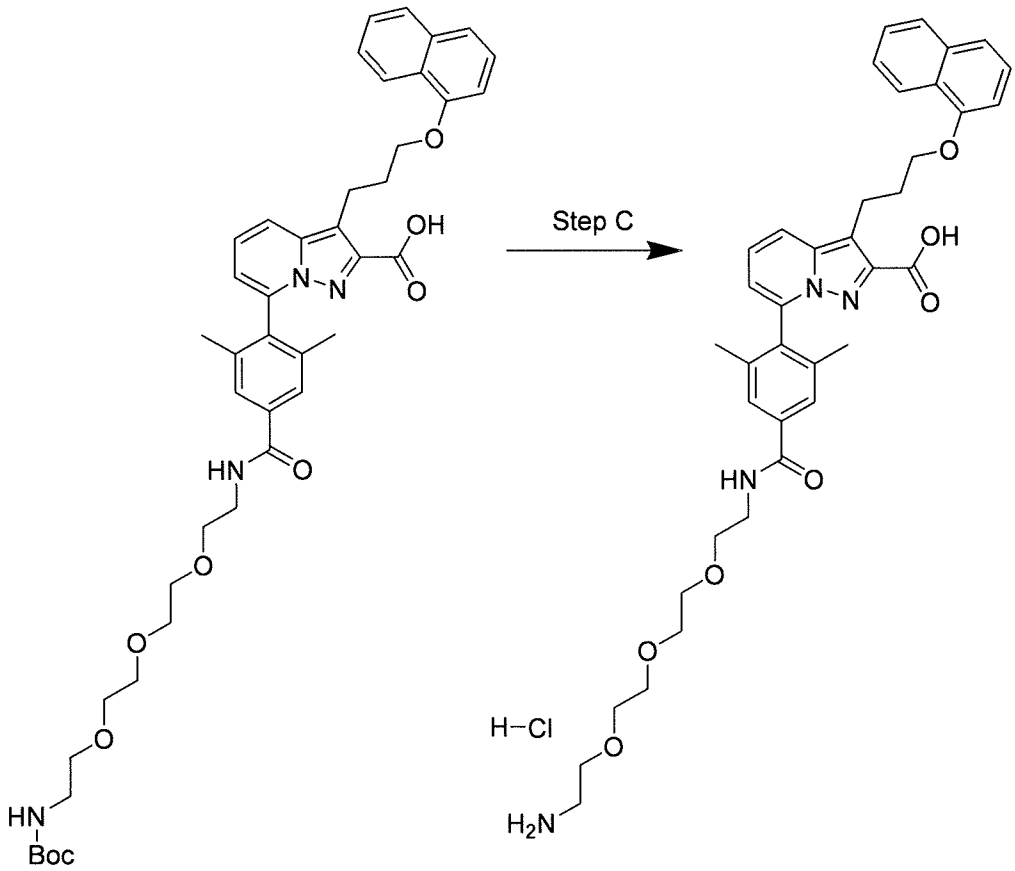
Step B



To solution of methyl 7-(4-((2,2-dimethyl-4-oxo-3,8,11,14-tetraoxa-5-azahexadecan-16-yl)carbamoyl)-2,6-dimethylphenyl)-3-(3-(naphthalen-1-yloxy)propyl)pyrazolo[1,5-*a*]pyridine-2-carboxylate (151 mg, crude) in MeOH and THF (1:1, 2.12 mL) was added NaOH (77 mg, 1.93 mmol) dissolved in 0.5 mL of water. Mixture was stirred at 70°C for 18 . Organic solvents were removed under reduced pressure, and product was extracted from aqueous phase with DCM. 7-(4-((2,2-dimethyl-4-oxo-3,8,11,14-tetraoxa-5-azahexadecan-16-yl)carbamoyl)-2,6-dimethylphenyl)-3-(3-(naphthalen-1-yloxy)propyl)pyrazolo[1,5-*a*]pyridine-2-carboxylic acid (150 mg, crude) was used for next step without further purification.

LCMS (ESI-): m/z 787.7 $[M-H]^-$

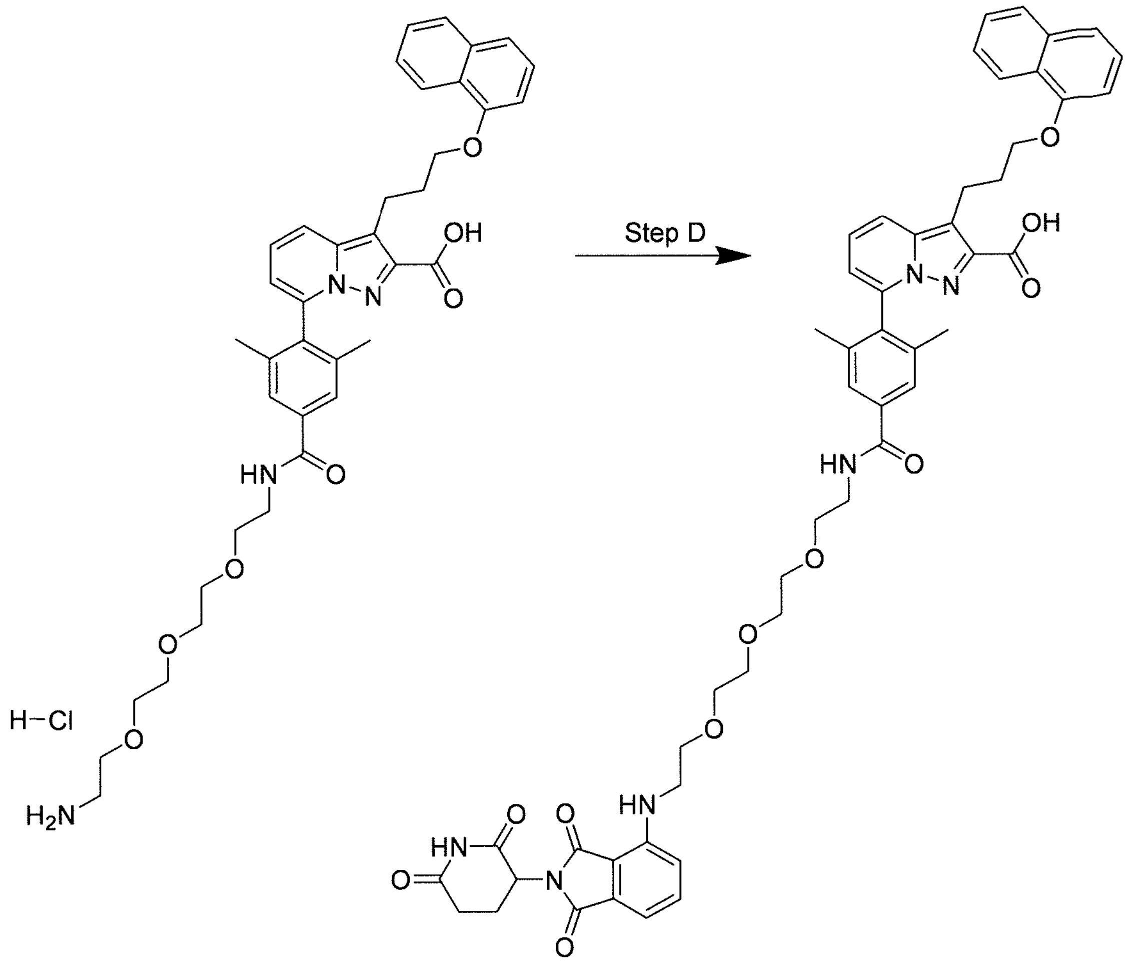
Step C



7-(4-((2,2-dimethyl-4-oxo-3,8,11,14-tetraoxa-5-azahexadecan-16-yl)carbamoyl)-2,6-dimethylphenyl)-3-(3-(naphthalen-1-yloxy)propyl)pyrazolo[1,5-*a*]pyridine-2-carboxylic acid (154 mg, crude) was dissolved in THF (0.98 mL) and 4M HCl in dioxane (197 µL, 0.79 mmol) was added. Mixture was stirred at RT overnight. Solvents were removed under reduced pressure, and crude co-evaporated three times with Et_2O. 7-{4-[(2-{2-[2-(2-aminoethoxy)ethoxy]ethoxy}ethyl)carbamoyl]-2,6-dimethylphenyl}-3-[3-(naphthalen-1-yloxy)propyl]pyrazolo[1,5-*a*]pyridine-2-carboxylic acid hydrochloride (140 mg, crude) was used for next step without further purification.

LCMS (ESI+): m/z 669.4 $[M+H]^+$

Step D



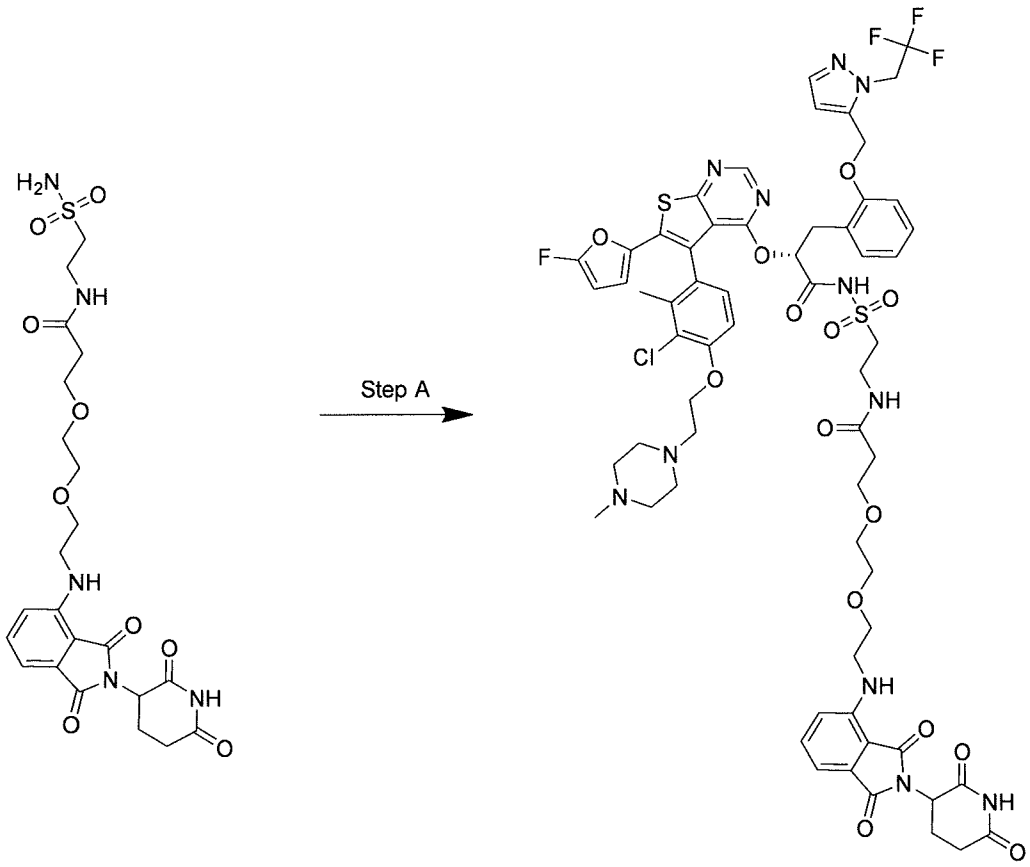
DIPEA (20 µL, 0.11 mmol) was added to a solution of 7-{4-[(2-{2-[2-(2-aminoethoxy)ethoxy]ethoxy}ethyl)carbamoyl]-2,6-dimethylphenyl}-3-[3-(naphthalen-1-yloxy)propyl]pyrazolo[1,5-a]pyridine-2-carboxylic acid hydrochloride (25 mg crude) and 2-(2,6-dioxopiperidin-3-yl)-4-fluoroisoindoline-1,3-dione (31 mg, 0.11 mmol) in DMSO (0.26 mL). The reaction mixture was heated at 90°C for 20 h. Crude was purified by flash chromatography (SiO_2, 5% MeOH in DCM). 7-(4-((2-(2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)ethoxy)ethyl)carbamoyl)-2,6-dimethylphenyl)-3-(3-(naphthalen-1-yloxy)propyl)pyrazolo[1,5-*a*]pyridine-2-carboxylic acid (6.50 mg, 0.007 mmol, 4% over four steps) was isolated as yellow solid.

LCMS (ESI+): m/z 925.9 $[M+H]^+$

^1H NMR (601 MHz, DMSO) δ 12.99 (s, 1H), 11.08 (s, 1H), 8.52 (t, *J* = 5.6 Hz, 1H), 8.27 – 8.22 (m, 1H), 7.89 – 7.83 (m, 1H), 7.78 (d, *J* = 8.5 Hz, 1H), 7.65 (s, 2H), 7.59 – 7.47 (m, 3H), 7.45 (d, *J* = 8.3 Hz, 1H), 7.38 (t, *J* = 7.9 Hz, 1H), 7.26 – 7.20 (m, 1H), 7.13 (d, *J* = 8.6 Hz, 1H), 7.03 (d, *J* = 7.0 Hz, 1H), 6.88 (d, *J* = 7.6 Hz, 1H), 6.87 – 6.80 (m, 1H), 6.60 (t, *J* = 5.8 Hz, 1H), 5.05 (dd, *J* = 12.8, 5.5 Hz, 1H),

4.17 (t, *J* = 6.1 Hz, 2H), 3.61 (t, *J* = 5.6 Hz, 2H), 3.58 – 3.52 (m, 9H), 3.47 – 3.41 (m, 4H), 3.29 – 3.23 (m, 3H), 2.88 (ddd, *J* = 17.0, 13.8, 5.4 Hz, 1H), 2.62 – 2.55 (m, 1H), 2.25 – 2.19 (m, 2H), 2.05 – 1.97 (m, 2H), 1.94 (s, 6H).

Example 53. (2*R*)-2-[(5-{3-chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}-6-(5-fluorofuran-2-yl)thieno[2,3-*d*]pyrimidin-4-yl)oxy]-*N*-(2-{3-[2-(2-{[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl]amino}ethoxy)ethoxy]propanamido}ethanesulfonyl)-3-(2-{[1-(2,2,2-trifluoroethyl)-1*H*-pyrazol-5-yl]methoxy}phenyl)propanamide (260)



Step A

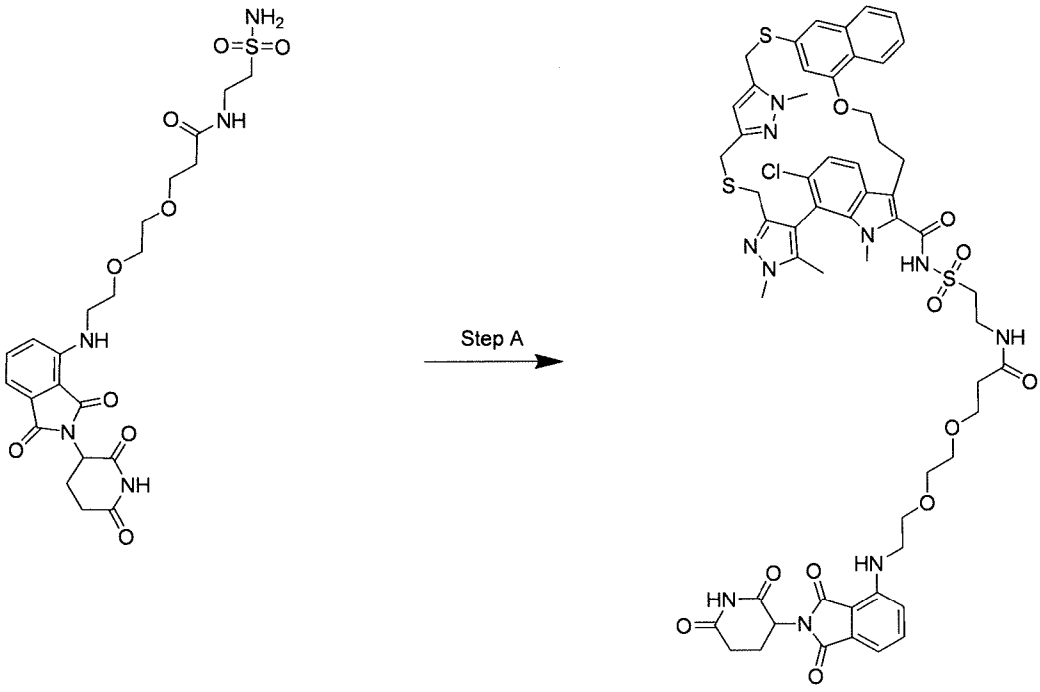
To a stirred solution of (*R*)-2-((5-(3-chloro-2-methyl-4-(2-(4-methylpiperazin-1-yl)ethoxy)phenyl)-6-(5-fluorofuran-2-yl)thieno[2,3-*d*]pyrimidin-4-yl)oxy)-3-(2-((1-(2,2,2-trifluoroethyl)-1*H*-pyrazol-5-yl)methoxy)phenyl)propanoic acid (15.0 mg, 0.018 mmol) in DCM (0.181 mL) were added EDC (4.2 mg, 0.022 mmol), DMAP (4.4 mg, 0.036 mmol), triethylamine (0.013 mL, 0.090 mmol), and 3-[2-(2-{[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl]amino}ethoxy)ethoxy]-*N*-(2-sulfamoylethyl)propanamide (12.7 mg, 0.024 mmol). The reaction mixture was stirred for 15 h at ambient temperature then for overnight in 60°C. Solvents were removed under reduced

pressure. Desired product was purified using flash chromatography (SiO_2, DCM:MeOH, 0 - 10%), then obtained residue was purified using preparative TLC (SiO_2 10% MeOH in DCM). Final purification by reverse phase preparative HPLC (H_2O:MeCN + 0.1% FA) resulted (2*R*)-2-[(5-{3-chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}-6-(5-fluorofuran-2-yl)thieno[2,3-*d*]pyrimidin-4-yl)oxy]-*N*-(2-{3-[2-(2-{[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl]amino}ethoxy)ethoxy]propanamido}ethanesulfonyl)-3-(2-{[1-(2,2,2-trifluoroethyl)-1*H*-pyrazol-5-yl]methoxy}phenyl)propanamide (1.0 mg, 0.001 mmol, 4.1%) as a yellow solid.

LCMS (ESI+): m/z 1349.6 $[M+H]^+$

^1H NMR (500 MHz, DMSO) δ 11.08 (s, 1H), 8.45 (s, 1H), 7.82 – 7.64 (m, 1H), 7.56 – 7.52 (m, 2H), 7.25 – 7.16 (m, 1H), 7.16 – 7.07 (m, 4H), 7.07 – 6.97 (m, 3H), 6.82 (s, 1H), 6.70 (t, J = 7.4 Hz, 1H), 6.60 (t, J = 5.8 Hz, 1H), 5.84 (dd, J = 6.8, 3.7 Hz, 2H), 5.67 (t, J = 3.5 Hz, 1H), 5.35 – 5.14 (m, 7H), 5.06 (dd, J = 12.7, 5.4 Hz, 1H), 4.37 – 4.26 (m, 1H), 4.26 – 4.18 (m, 1H), 3.60 (q, J = 6.6, 6.0 Hz, 6H), 3.57 – 3.53 (m, 3H), 3.53 – 3.48 (m, 3H), 3.46 (q, J = 5.7 Hz, 3H), 3.13 – 3.08 (m, 1H), 2.96 – 2.81 (m, 6H), 2.62 – 2.60 (m, 2H), 2.40 – 2.35 (m, 4H), 2.27 (t, J = 6.5 Hz, 2H), 2.15 – 1.98 (m, 2H).

Example 54. *N*-{2-[({17-chloro-5,13,14,22-tetramethyl-28-oxa-2,9-dithia-5,6,12,13,22-pentaazaheptacyclo[27.7.1.1^{4},^{7}.0^{11},^{15}.0^{16},^{21}.0^{20},^{24}.0^{30},^{35}]octatriaconta-1(37),4(38),6,11,14,16,18,20,23,29,31,33,35-tridecaen-23-yl}formamido)sulfonyl]ethyl}-3-[2-(2-{[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl]amino}ethoxy)ethoxy]propanamide (261)



Step A

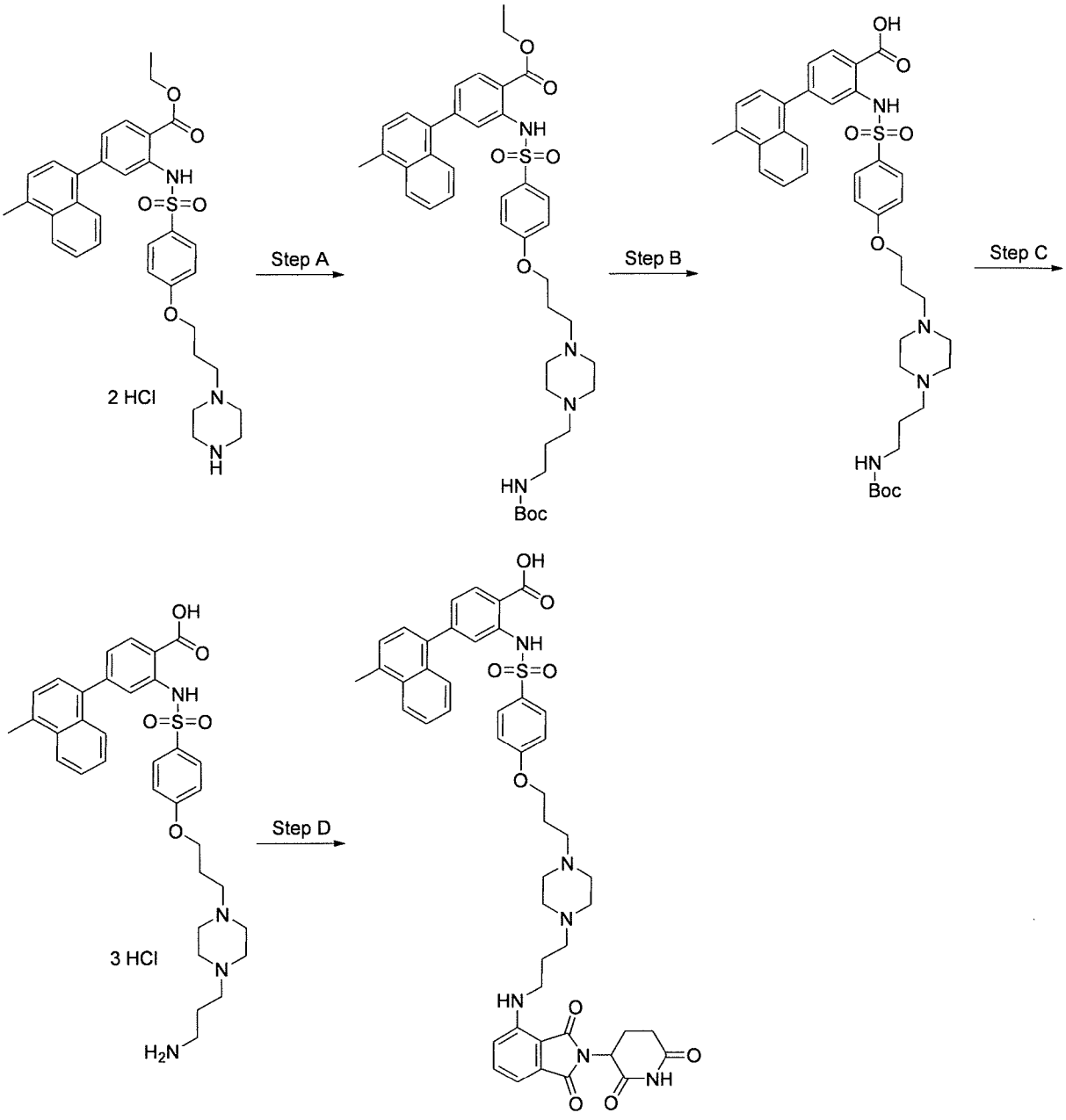
To a stirred solution of 17-chloro-5,13,14,22-tetramethyl-28-oxa-2,9-dithia-5,6,12,13,22-pentaazaheptacyclo[27.7.1.1^{4,7}.0^{11,15}.0^{16,21}.0^{20,24}.0^{30,35}]octatriaconta-1(37),4(38),6,11,14,16,18,20,23,29,31,33,35-tridecaene-23-carboxylic acid (15.0 mg, 0.022 mmol) in DCM (0.223 mL) were added EDC (4.3 mg, 0.022 mmol), DMAP (5.5 mg, 0.045 mmol), triethylamine (0.016 mL, 0.112 mmol) and 3-[2-(2-{[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl]amino}ethoxy)ethoxy]-*N*-(2-sulfamoylethyl)propanamide (15.7 mg, 0.029 mmol) The reaction mixture was stirred for 15 h at ambient temperature then for overnight in 60°C. The crude was concentrated in vacuo and the residue was purified by reverse phase preparative HPLC (H_2O:CH_3CN + 0.1% FA) to give a corresponding *N*-{2-[({17-chloro-5,13,14,22-tetramethyl-28-oxa-2,9-dithia-5,6,12,13,22-pentaazaheptacyclo[27.7.1.1^{4,7}.0^{11,15}.0^{16,21}.0^{20,24}.0^{30,35}]octatriaconta-1(37),4(38),6,11,14,16,18,20,23,29,31,33,35-tridecaen-23-yl}formamido)sulfonyl]ethyl}-3-[2-(2-{[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl]amino}ethoxy)ethoxy]propanamide (4.7 mg, 0.004 mmol, 17.3%) as yellow solid.

LCMS (ESI+): m/z 1193.1 $[M+H]^+$

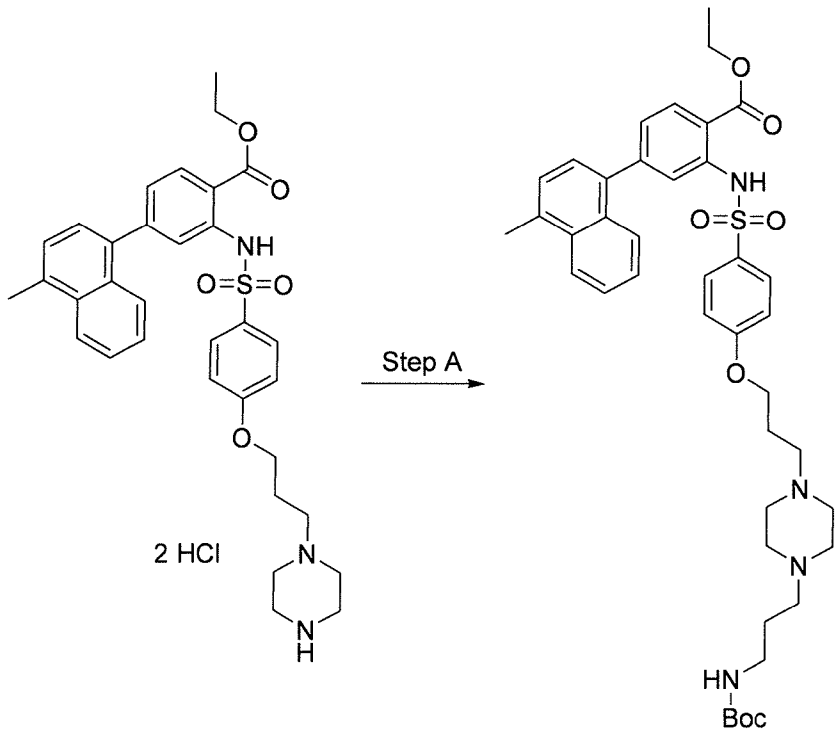
^{1}H NMR (500 MHz, DMSO) δ 12.40 (s, 1H), 11.07 (s, 1H), 8.19 – 7.97 (m, 2H), 7.81 (s, 1H), 7.68 (d, *J* = 8.1 Hz, 1H), 7.56 (dd, *J* = 8.6, 7.1 Hz, 1H), 7.44 (dt, *J* = 19.5, 7.2 Hz, 2H), 7.33 (s, 1H), 7.25 – 7.09 (m, 2H), 7.02 (d, *J* = 7.0 Hz, 1H), 6.73 (s, 1H), 6.59 (t, *J* = 5.8 Hz, 1H), 5.13 – 4.87 (m, 2H), 4.39 (s,

1H), 4.20 (d, *J* = 15.4 Hz, 1H), 3.97 (s, 2H), 3.76 (s, 3H), 3.71 (s, 3H), 3.62 – 3.56 (m, 5H), 3.55 – 3.37 (m, 12H), 3.15 (d, *J* = 13.0 Hz, 2H), 3.10 (s, 1H), 2.97 (d, *J* = 13.7 Hz, 1H), 2.87 (ddd, *J* = 16.7, 13.7, 5.4 Hz, 1H), 2.62 – 2.52 (m, 2H), 2.30 (t, *J* = 6.4 Hz, 4H), 2.06 – 1.96 (m, 5H).

Example 55. 2-((4-(3-(4-(3-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)propyl)piperazin-1-yl)propoxy)phenyl)sulfonamido)-4-(4-methylnaphthalen-1-yl)benzoic acid (257)

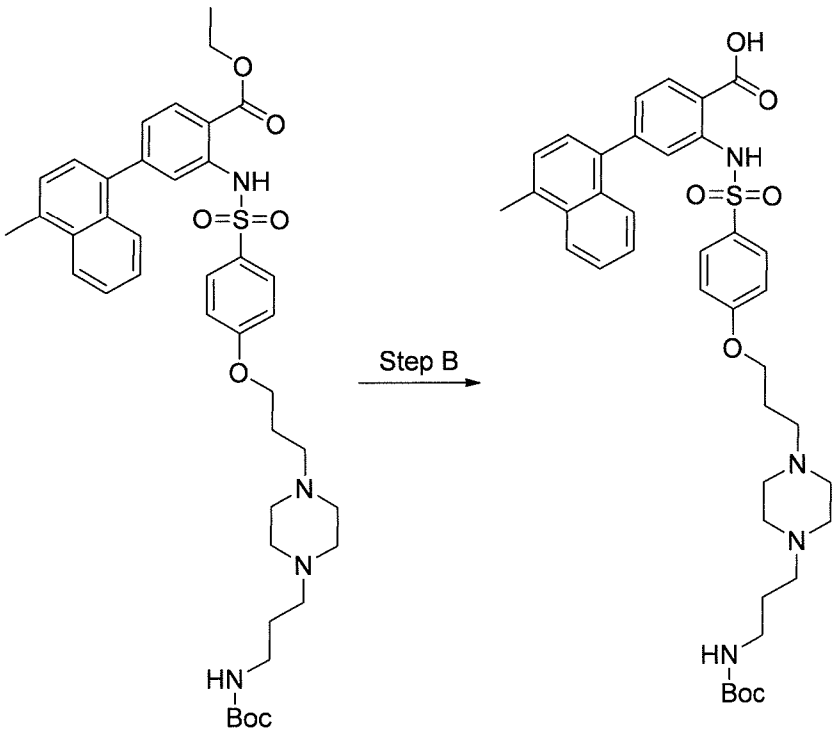


Step A



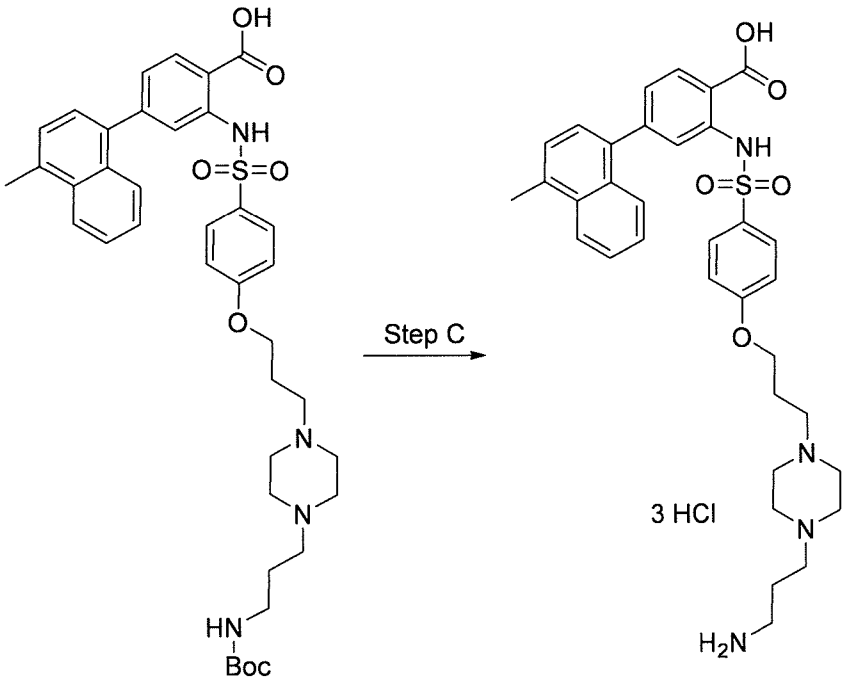
Ethyl 4-(4-methylnaphthalen-1-yl)-2-((4-(3-(piperazin-1-yl)propoxy)phenyl)sulfonamido)benzoate (dihydrochloride salt) (100 mg, 0.151 mmol) and *tert*-butyl (3-oxopropyl)carbamate (59 mg, 0.340 mmol) were dissolved in DCM (1.5 mL). $NaBH(OAc)_3$ (72 mg 0.340 mmol) was added in one portion and the mixture was stirred for 16 h, whereupon LCMS and TLC indicated the reaction was complete. The reaction mixture was diluted with DCM and washed with saturated $NaHCO_3$. The aqueous phase was extracted with DCM, the organic phases were combined and dried over Na_2SO_4. Solvent was evaporated and crude product purified with flash column chromatography (SiO_2, MeOH:DCM, 0-10%) to afford ethyl 2-((4-(3-(4-(3-((*tert*-butoxycarbonyl)amino)propyl)piperazin-1-yl)propoxy)phenyl)sulfonamido)-4-(4-methylnaphthalen-1-yl)benzoate as an opaque oil (103 mg, 91%).

Step B



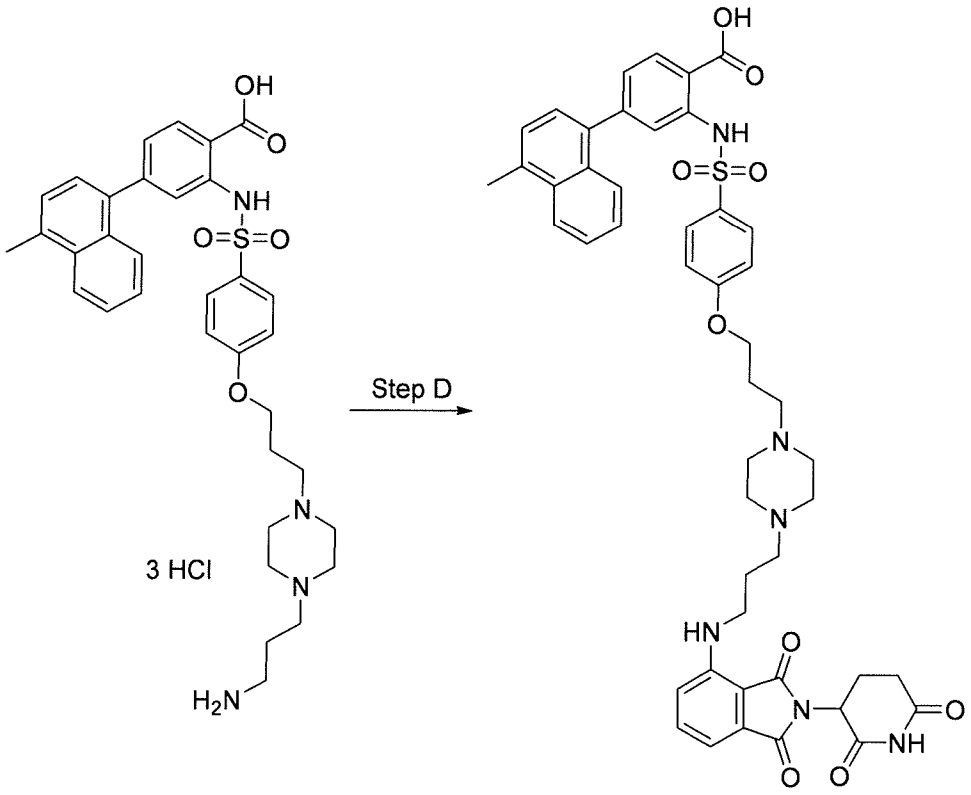
Ethyl 2-((4-(3-(4-(3-((*tert*-butoxycarbonyl)amino)propyl)piperazin-1-yl)propoxy)phenyl)sulfonamido)-4-(4-methylnaphthalen-1-yl)benzoate (90 mg, 0.121 mmol) was dissolved in THF/water (1 mL, 1:1). NaOH (24 mg, 0.604 mmol) was added in one portion and the mixture stirred for 18 h. The reaction mixture was concentrated in vacuo. The resulting solid was dissolved in a small amount of H_2O and the mixture neutralized with 1M HCl solution. The aqueous phase was extracted several times with 10% MeOH in CH_2Cl_2, the organics combined and dried over Na_2SO_4. Crude product was purified with flash column chromatography (SiO_2, MeOH:DCM, 5-50%) to afford 2-((4-(3-(4-(3-((*tert*-butoxycarbonyl)amino)propyl)piperazin-1-yl)propoxy)phenyl)sulfonamido)-4-(4-methylnaphthalen-1-yl)benzoic acid as an off-white solid (42 mg, 0.058, 49%).

Step C



2-((4-(3-(4-(3-((*tert*-butoxycarbonyl)amino)propyl)piperazin-1-yl)propoxy)phenyl)sulfonamido)-4-(4-methylnaphthalen-1-yl)benzoic acid (38 mg, 0.053 mmol) was dissolved in 4M HCl in dioxane (1 mL) at 0°C and the mixture was stirred for 2 h, allowing for slow warming to room temperature, whereupon LCMS indicated the reaction was complete. The reaction mixture was concentrated in vacuo, and triturated with Et_2O to afford 2-((4-(3-(4-(3-aminopropyl)piperazin-1-yl)propoxy)phenyl)sulfonamido)-4-(4-methylnaphthalen-1-yl)benzoic acid trihydrochloride as a beige solid (38 mg, 0.052 mmol, 99%).

Step D

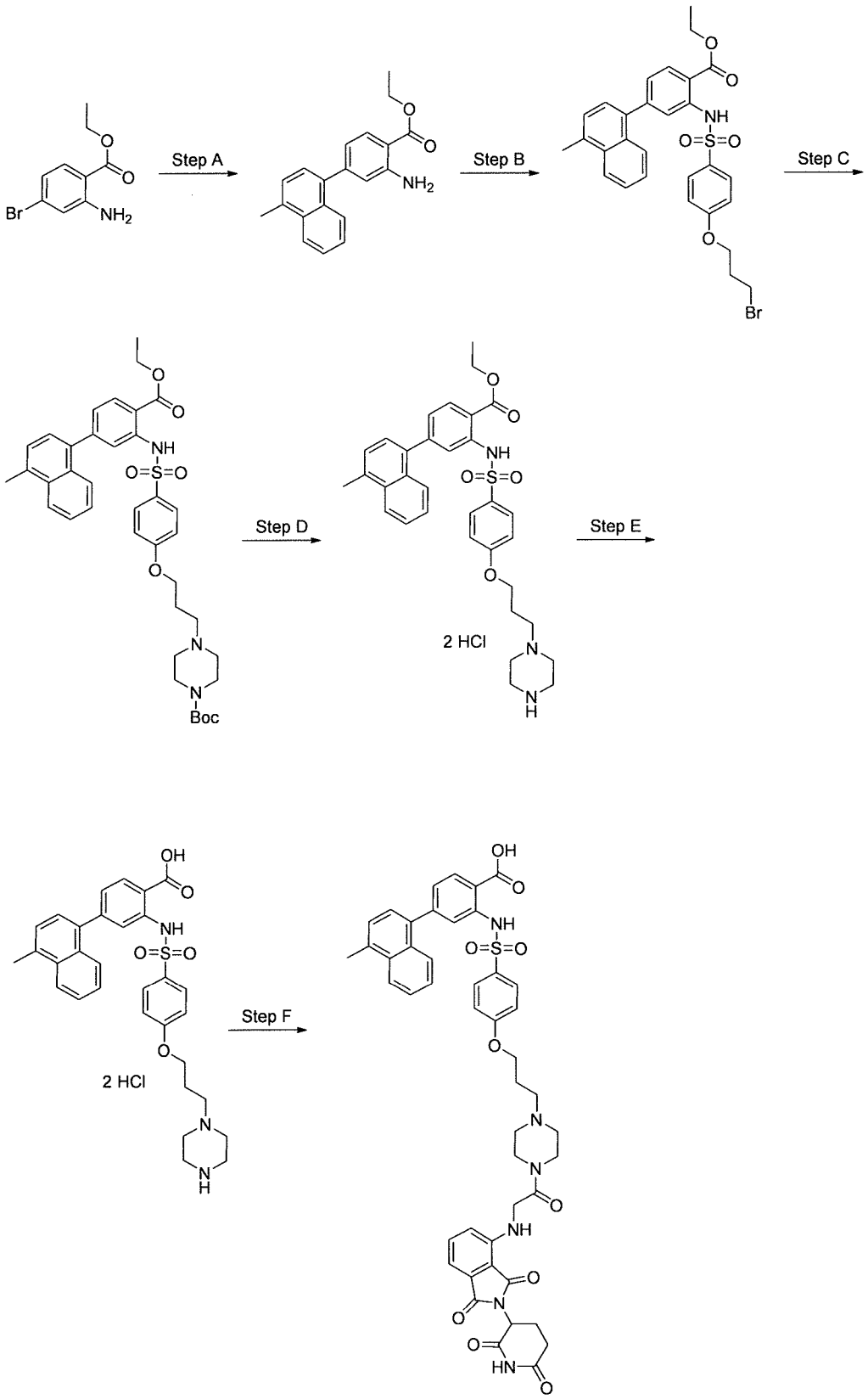


2-((4-(3-(4-(3-aminopropyl)piperazin-1-yl)propoxy)phenyl)sulfonamido)-4-(4-methylnaphthalen-1-yl)benzoic acid trihydrochloride (38 mg, 0.052 mmol) and 2-(2,6-dioxopiperidin-3-yl)-4-fluoroisoindoline-1,3-dione (14.5 mg, 0.052 mmol) were dissolved in DMSO (0.2 mL). DIPEA (36.5 µL, 0.209 mmol) was added and the mixture was stirred for until full conversion (monitored with LCMS) at 90°C under argon. The reaction mixture was concentrated in vacuo and the crude product purified with flash column chromatography to afford 2-((4-(3-(4-(3-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)propyl)piperazin-1-yl)propoxy)phenyl)sulfonamido)-4-(4-methylnaphthalen-1-yl)benzoic acid as a yellow solid (1.98 mg, 0.002 mmol. 4.3% yield).

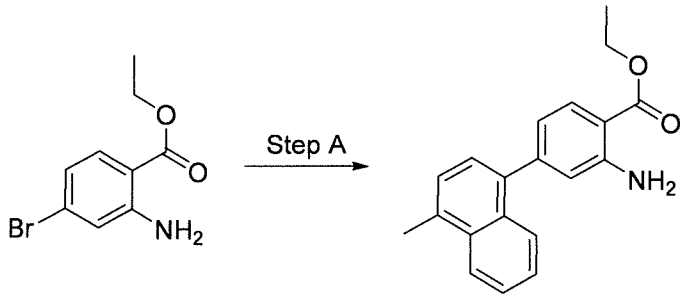
LCMS (ESI+): m/z 873.9 $[M+H]^+$

^{1}H NMR (500 MHz, DMSO) δ 11.10 (s, 1H), 8.10 (dd, *J* = 8.8, 1.3 Hz, 1H), 7.96 (d, *J* = 7.9 Hz, 1H), 7.68 (d, *J* = 9.1 Hz, 2H), 7.64 – 7.54 (m, 3H), 7.52 – 7.39 (m, 3H), 7.24 (d, *J* = 7.1 Hz, 1H), 7.12 (d, *J* = 8.6 Hz, 1H), 7.09 – 7.01 (m, 3H), 6.94 (d, *J* = 7.7 Hz, 1H), 6.89 – 6.80 (m, 1H), 5.05 (dd, *J* = 12.9, 6.2 Hz, 1H), 4.10 (t, *J* = 6.2 Hz, 2H), 3.41 – 3.33 (m, 4H), 3.30 – 3.27 (m, 6H), 2.88 (ddd, *J* = 16.9, 13.8, 5.4 Hz, 1H), 2.70 (s, 3H), 2.63 – 2.58 (m, 1H), 2.58 – 2.54 (m, 1H), 2.54 – 2.51 (m, 2H), 2.49 – 2.41 (m, 2H), 2.11 – 1.92 (m, 3H), 1.83 (bs, 2H).

Example 56. 2-((4-(3-(4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)glycyl)piperazin-1-yl)propoxy)phenyl)sulfonamido)-4-(4-methylnaphthalen-1-yl)benzoic acid (258)

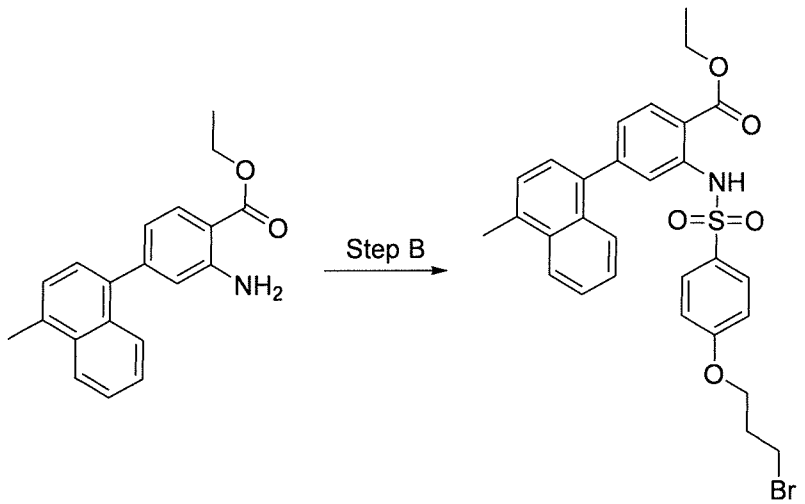


Step A



To a solution of ethyl 2-amino-4-bromobenzoate (14.1 g, 57.8 mmol) in mixture of dioxane and H_2O (4:1) was added (4-methylnaphthalen-1-yl)boronic acid (16.2 g, 87.1 mmol), Na_2CO_3 (18.4 g, 174 mmol), and $Pd(PPh_3)_4$ (2 g, 1.73 mmol) under argon atmosphere. The mixture was heated at 90°C for 24 h. Then it was cooled down to room temperature, poured in H_2O (500 mL), and extracted with EtOAc (3×200 mL). The combined organic phases were washed with H_2O and brine, and dried over anhydrous sodium sulfate. The organic phase was concentrated and purified by column chromatography to give ethyl 2-amino-4-(4-methylnaphthalen-1-yl)benzoate (13.7 g, 44.9 mmol, 78% yield).

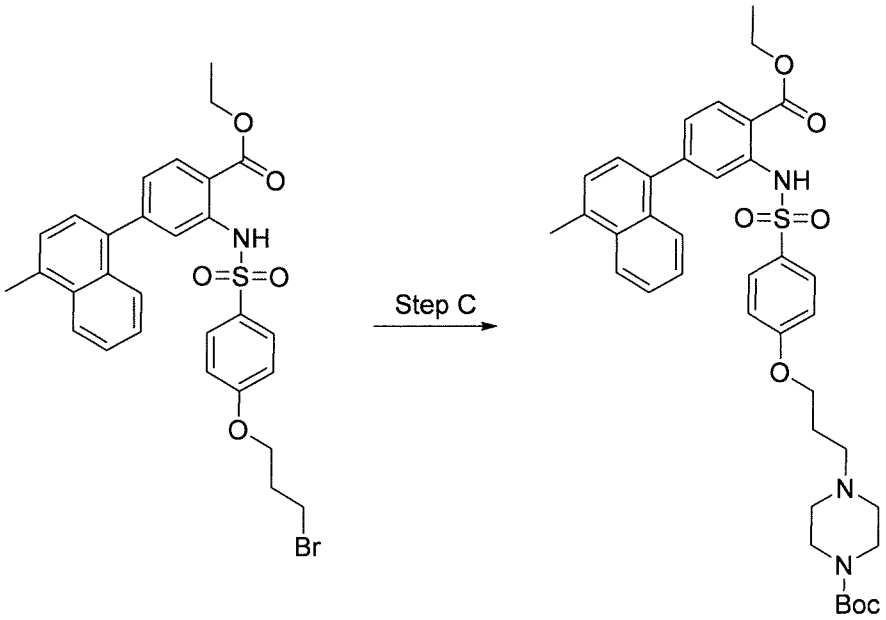
Step B



A solution of 4-(3-bromopropoxy)benzenesulfonyl chloride (16.7 g, 53.3 mmol) in anhydrous THF (50 mL) was slowly added to a solution of ethyl 2-amino-4-(4-methylnaphthalen-1-yl)benzoate (11.2 g, 36.7 mmol) in the mixture of pyridine and THF (1:2, 100 mL) maintaining temperature below -5°C. The mixture was slowly warmed to room temperature and stirred overnight. Then, it was poured in H_2O and extracted with EtOAc (3x). The combined organic layers were washed with 10% HCl, H_2O, aq. solution of $NaHCO_3$, brine and dried over Na_2SO_4. The solution was evaporated

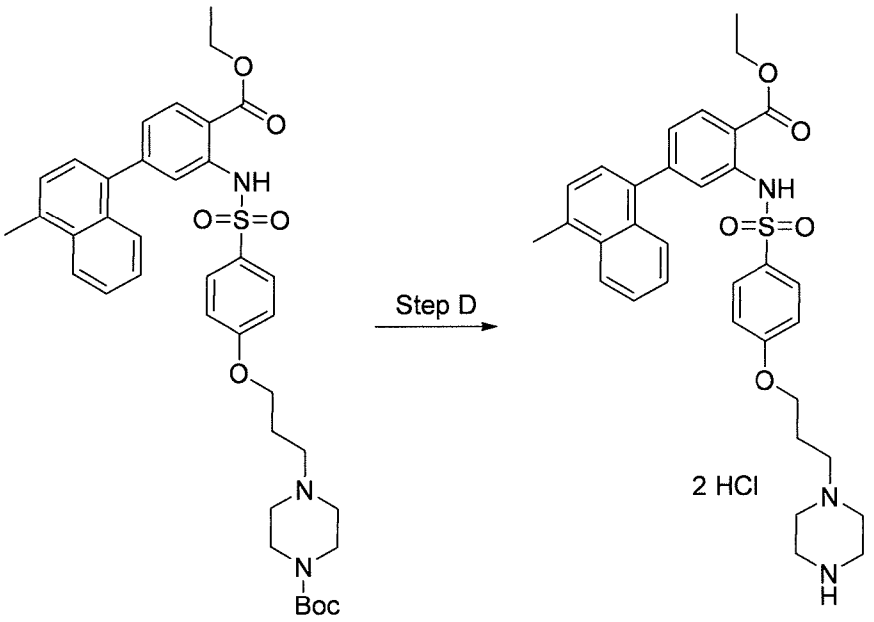
under reduced pressure to give ethyl 2-((4-(3-bromopropoxy)phenyl)sulfonamido)-4-(4-methylnaphthalen-1-yl)benzoate (11.2 g, 19.2 mmol, 57.6% yield).

Step C



A mixture of ethyl 2-((4-(3-bromopropoxy)phenyl)sulfonamido)-4-(4-methylnaphthalen-1-yl)benzoate (11.2 g, 19.2 mmol), *tert*-butyl piperazine-1-carboxylate (10.7 g, 57.4 mmol), and K_2CO_3 (2.8 g, 20.3 mmol) in *N*-methyl pyrrolidone (100 mL) was heated at 100°C overnight. Then, it was cooled down to room temperature, poured into H_2O (200 mL), and extracted with EtOAc (3×). The combined organic layers were washed with H_2O and brine, dried over Na_2SO_4, and evaporated under reduced pressure to give *tert*-butyl 4-(3-(4-(*N*-(2-(ethoxycarbonyl)-5-(4-methylnaphthalen-1-yl)phenyl)sulfamoyl)phenoxy)propyl)piperazine-1-carboxylate (9.8 g, 14.2 mmol, 74% yield).

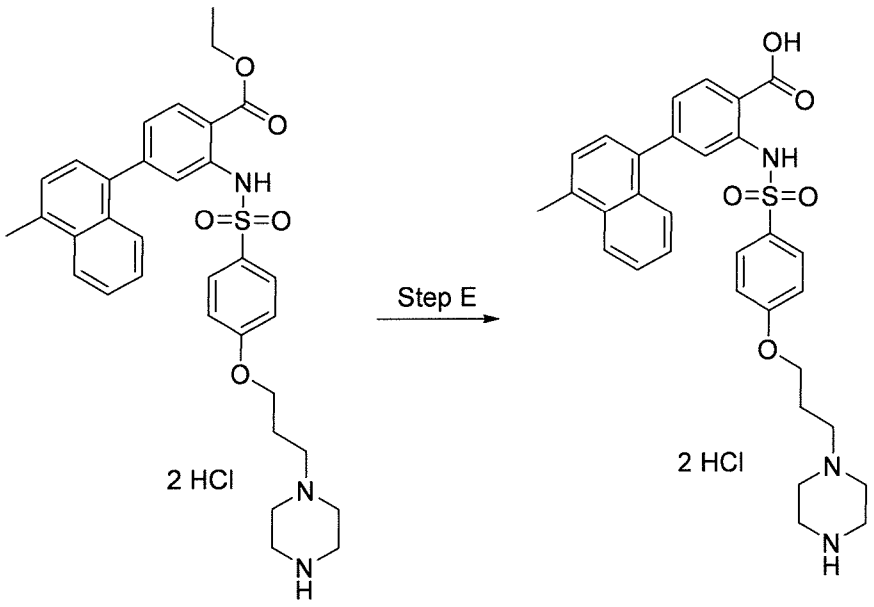
Step D



Dry HCl (gas) was slowly bubbled through a solution of *tert*-butyl 4-(3-(4-(*N*-(2-(ethoxycarbonyl)-5-(4-methylnaphthalen-1-yl)phenyl)sulfamoyl)phenoxy)propyl)piperazine-1-carboxylate (9.8 g, 14.2 mmol) in dry $CHCl_3$ at 0°C. The mixture was then slowly warmed to room temperature and left stirring overnight. The precipitate was filtered, washed with $CHCl_3$ and hexane, and dried under reduced pressure to give ethyl 4-(4-methylnaphthalen-1-yl)-2-((4-(3-(piperazin-1-yl)propoxy)phenyl)sulfonamido)benzoate (5.5 g, 8.24 mmol, 58% yields) as dihydrochloride salt.

LCMS (ESI+): m/z 588.4 $[M+H]^+$

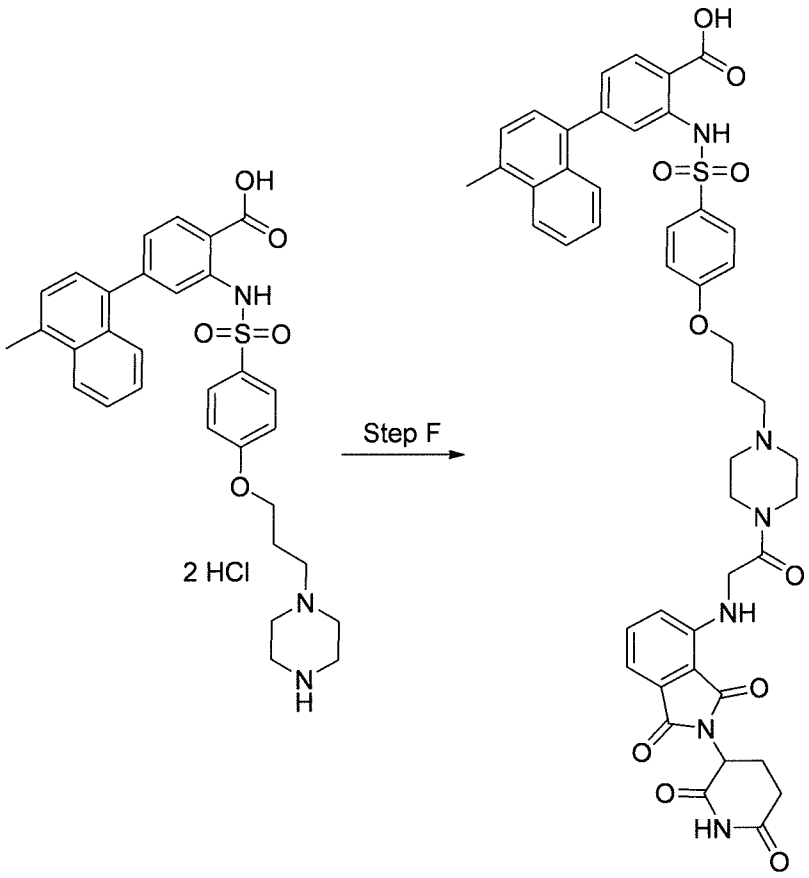
Step E



Ethyl 4-(4-methylnaphthalen-1-yl)-2-((4-(3-(piperazin-1-yl)propoxy)phenyl)sulfonamido)benzoate (dichloride salt) (25.0 mg, 0.0378 mmol) and LiOH (5.1 mg, 0.213 mmol) were dissolved in THF (0.500 mL) and water (0.500 mL) and the mixture was stirred at 60°C for 16 h, whereupon LCMS indicated the reaction was complete. THF was removed under reduced pressure and the aqueous solution washed with DCM (2x). The aqueous phase was neutralized by the addition of aq. 1M HCl and concentrated under reduced pressure to afford 4-(4-methylnaphthalen-1-yl)-2-((4-(3-(piperazin-1-yl)propoxy)phenyl)sulfonamido)benzoic acid (23.8 mg, crude) as dihydrochloride salt as a white solid which was used without further purification.

LCMS (ESI+): m/z 560.9 $[M+H]^+$

Step F



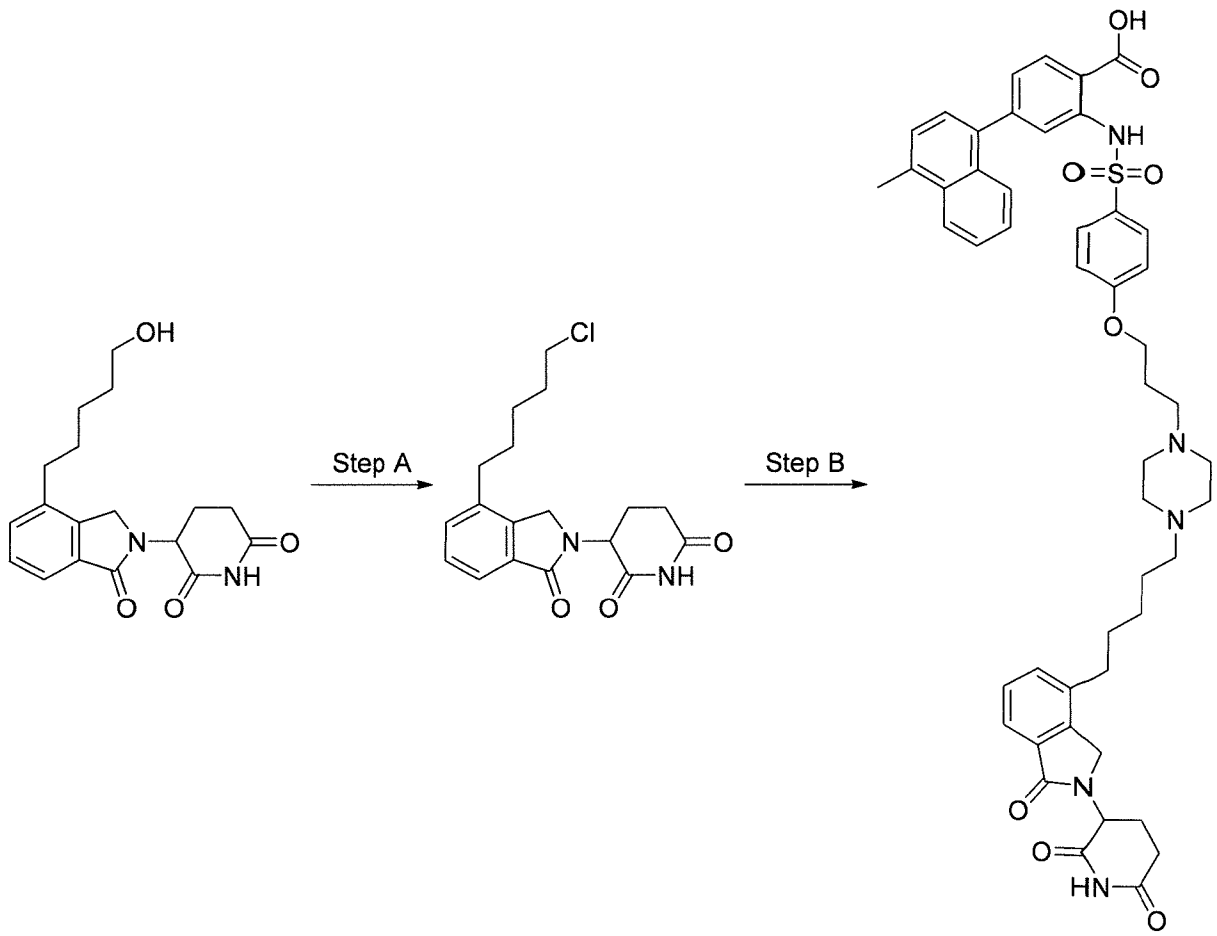
(2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)glycine hydrochloride (17.2 mg, 0.047 mmol) and HATU (19.4 mg, 0.510 mmol) were dissolved in DMF (0.500 mL) and the mixture stirred for 16 h. LCMS (morpholine quench) indicated incomplete consumption of the starting material. Another portion of HATU (19.4 mg, 0.510 mmol) was added and the mixture stirred for 1 h, whereupon LCMS (morpholine quench) indicated the formation of the active ester was complete. 4-(4-Methylnaphthalen-1-yl)-2-((4-(3-(piperazin-1-yl)propoxy)phenyl)sulfonamido)benzoic acid

dihydrochloride salt (23.8 mg of crude) was added and the reaction mixture was stirred for 16 h. The reaction mixture was concentrated in vacuo and purified by flash chromatography (SiO_2, MeOH:DCM, 4-20%) to afford 2-((4-(3-(4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)glycyl)piperazin-1-yl)propoxy)phenyl)sulfonamido)-4-(4-methylnaphthalen-1-yl)benzoic acid (24.0 mg, 0.027 mmol, 73% over 2 steps) as a yellow solid.

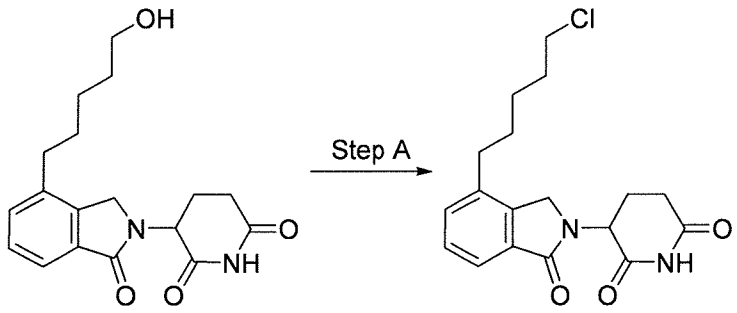
LCMS (ESI+): m/z 874.4 $[M+H]^+$

^1H NMR (500 MHz, DMSO) δ 12.88 (s, 1H), 11.09 (s, 1H), 8.12 (d, *J* = 8.4 Hz, 1H), 8.02 (d, *J* = 8.0 Hz, 1H), 7.73 (d, *J* = 8.8 Hz, 2H), 7.66 – 7.58 (m, 2H), 7.56 (d, *J* = 8.1 Hz, 1H), 7.52 – 7.42 (m, 3H), 7.26 (d, *J* = 7.1 Hz, 1H), 7.16 – 7.06 (m, 5H), 7.03 (t, *J* = 4.4 Hz, 1H), 5.07 (dd, *J* = 12.8, 5.4 Hz, 1H), 4.22 (d, *J* = 4.2 Hz, 2H), 4.13 (t, *J* = 6.0 Hz, 2H), 3.90 – 3.53 (m, 4H), 3.04 – 2.83 (m, 6H), 2.70 (s, 3H), 2.62 – 2.51 (m, 3H), 2.10 – 2.00 (m, 3H).

Example 57. 2-((4-(3-(4-(5-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)pentyl)piperazin-1-yl)propoxy)phenyl)sulfonamido)-4-(4-methylnaphthalen-1-yl)benzoic acid (259)



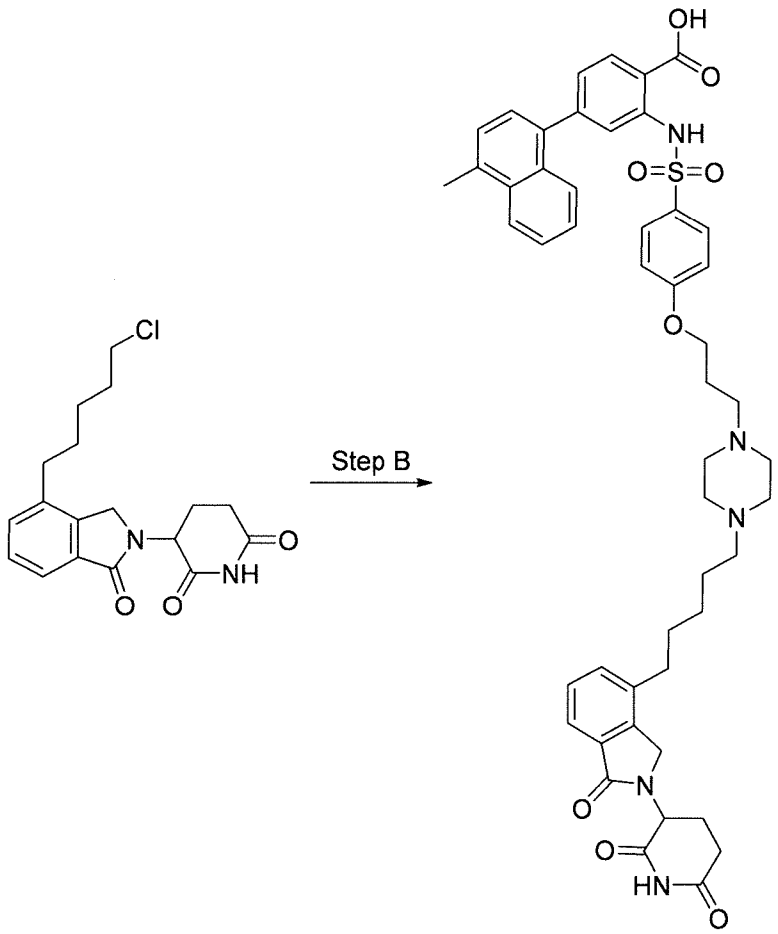
Step A



To a suspension of 3-(4-(5-hydroxypentyl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (1.65 g, 5 mmol) in DCM (60 mL) was added thionyl chloride (0.72 g, 6 mmol). The mixture was heated to 60°C for 18 hours, giving a clear orange liquid. The mixture was cooled and concentrated under argon atmosphere giving a thick solid precipitate which was filtered, washed with ethyl ether and dried in vacuo, to give 3-(4-(5-chloropentyl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione as a beige solid (0.842 g, 2.4 mmol, 48%).

LCMS (ESI+): m/z 349.2 $[M+H]^+$

Step B



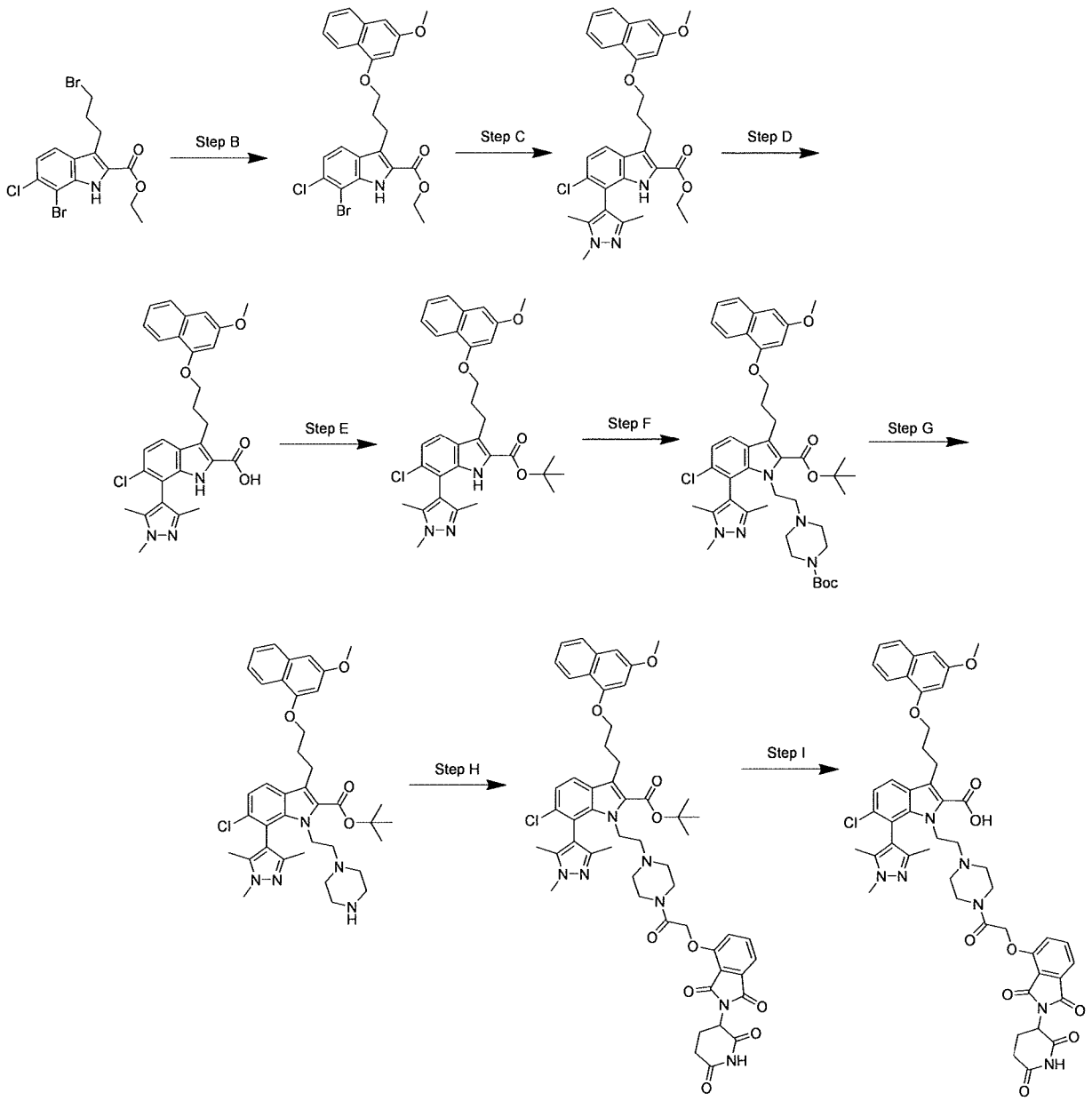
4-(4-methylnaphthalen-1-yl)-2-((4-(3-(piperazin-1-yl)propoxy)phenyl)sulfonamido)benzoic acid dihydrochloride (25.0 mg, 0.045 mmol), 3-(4-(5-chloropentyl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (15.6 mg, 0.045 mmol), KI (7.4 mg, 0.045 mmol) and $KHCO_3$ (17.9 mg, 0.179 mmol) were dissolved in DMF (0.500 mL), the mixture warmed to 60°C and stirred for 2 h. After that time LCMS second portion of 3-(4-(5-chloropentyl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (7.0 mg, 0.020 mmol) was added and the mixture stirred at 60°C for 1.5 h, whereupon LCMS indicated full consumption of the starting material. The reaction mixture was concentrated in vacuo and purified by flash column chromatography (SiO2, MeOH:DCM, 10-30%) to give 2-((4-(3-(4-(5-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)pentyl)piperazin-1-yl)propoxy)phenyl)sulfonamido)-4-(4-methylnaphthalen-1-yl)benzoic acid (23.6 mg, 0.027 mmol, 61%) as a yellow solid.

LCMS (ESI+): m/z 872.9 $[M+H]^+$

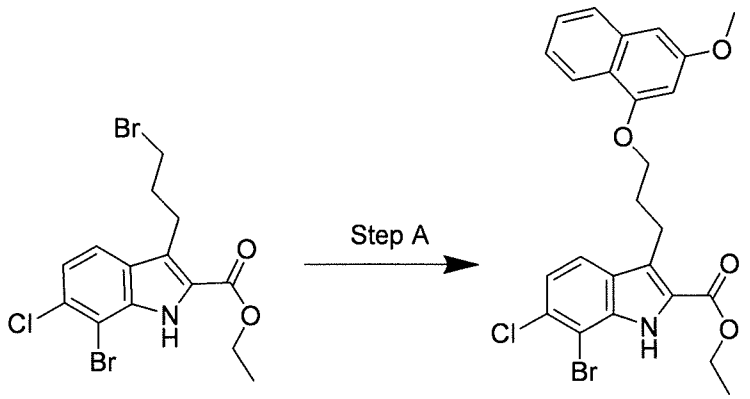
^1H NMR (500 MHz, DMSO) δ 10.99 (s, 1H), 8.11 (d, *J* = 8.5 Hz, 1H), 7.99 (d, *J* = 8.0 Hz, 1H), 7.70 (d, *J* = 8.8 Hz, 2H), 7.66 – 7.52 (m, 3H), 7.52 – 7.38 (m, 5H), 7.25 (d, *J* = 7.1 Hz, 1H), 7.06 (d, *J* = 8.9 Hz,

3H), 5.14 (dd, *J* = 13.3, 5.1 Hz, 1H), 4.46 (d, *J* = 17.1 Hz, 1H), 4.30 (d, *J* = 17.1 Hz, 1H), 4.09 (t, *J* = 6.1 Hz, 2H), 3.48 – 3.31 (m, 6H), 2.98 – 2.87 (m, 1H), 2.70 (s, 3H), 2.68 – 2.57 (m, 3H), 2.54 – 2.51 (m, 1H), 2.47 – 2.33 (m, 2H), 2.06 – 1.98 (m, 1H), 1.98 – 1.86 (m, 2H), 1.71 – 1.53 (m, 4H), 1.37 – 1.24 (m, 6H).

Example 58. 6-chloro-1-(2-(4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)acetyl)piperazin-1-yl)ethyl)-3-(3-((3-methoxynaphthalen-1-yl)oxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (218)

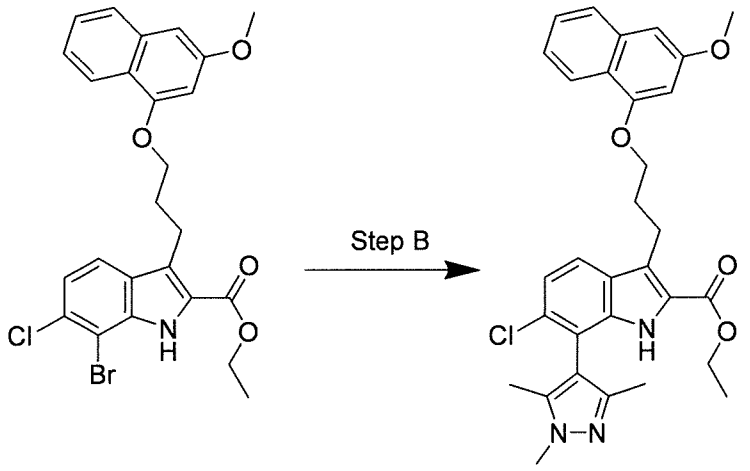


Step A



To a well stirred solution of crude ethyl 7-bromo-3-(3-bromopropyl)-6-chloro-1*H*-indole-2-carboxylate (3 g, 7.09 mmol) in DMF (35 mL) was added 3-methoxynaphthalen-1-ol, (0.987 g, 5.674 mmol), KI (1.2 g, 7.096 mmol), Cs_2CO_3 (6.95 g, 21.27 mmol) successively at RT under nitrogen. The reaction mixture was allowed to stir at 60°C for 16h. After complete consumption of the starting material (monitored by TLC and LCMS) the reaction mixture was diluted with EtOAc and washed successively with water and brine. The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to get the crude compound, which was then purified by triturating with Et_2O to get 2 g (3.875mmol, 45% over two steps) of as off white solid.

Step B

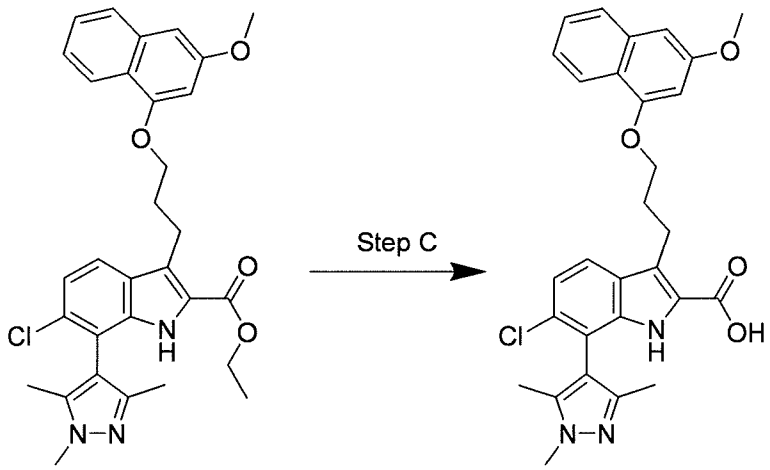


To a stirred solution of ethyl 7-bromo-6-chloro-3-(3-((3-methoxynaphthalen-1-yl)oxy)propyl)-1*H*-indole-2-carboxylate (1.5 g, 2.907 mmol) in dioxane (15 mL) and water (3 mL) were added 1,3,5-trimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (2.058 g, 8.72 mmol) and K_2CO_3 (1.60 g, 11.62 mmol) successively at RT. The mixture was deoxygenated with argon and to

it was added $Pd(dppf)Cl_2$ (0.319 g, 0.436 mmol) under argon atmosphere. Then the reaction mixture was heated under reflux for 16 h. After complete consumption of the starting material (monitored by TLC and LCMS) the reaction mixture was filtered through celite pad and the filtrate was evaporated under reduced pressure get the crude material. It was then diluted with EtOAc and washed successively with water and brine The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to get the crude compound, which was then purified by column chromatography (SiO2, 20% EtOAc in DCM) to get 1.2 g (2.2 mmol, 75%) of ethyl 6-chloro-3-(3-((3-methoxynaphthalen-1-yl)oxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate as brown solid.

LCMS (ESI+): m/z 545.9 $[M+H]^+$

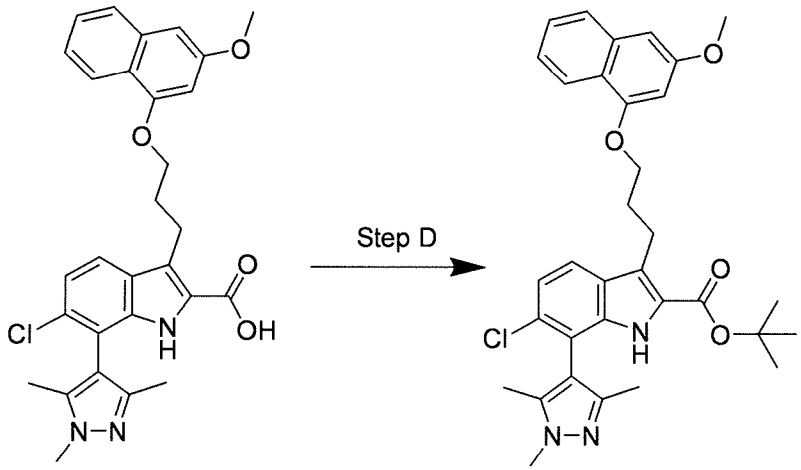
Step C



Ethyl 6-chloro-3-(3-((3-methoxynaphthalen-1-yl)oxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (1.2 g, 2.2 mmol) was dissolved in EtOH (20 mL) and a solution of NaOH (0.35 g, 8.8 mmol) in water (4 mL) was added to it. The mixture was heated under reflux for 16 h. After complete consumption of the starting material (monitored by TLC and LCMS) the reaction mixture was cooled down to room temperature, solvents were evaporated under reduced pressure to get the crude reaction mixture. It was then diluted with water and extracted with EtOAc. Aqueous layer was carefully acidified using 1M HCl to maintain pH=3, extracted with EtOAc (3×50 ml), dried over Na_2SO_4, filtered, and concentrated in vacuum to afford 0.9 g (1.73 mmol, 79%) of 6-chloro-3-(3-((3-methoxynaphthalen-1-yl)oxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid as off white solid

LCMS (ESI+): m/z 518.0 $[M+H]^+$

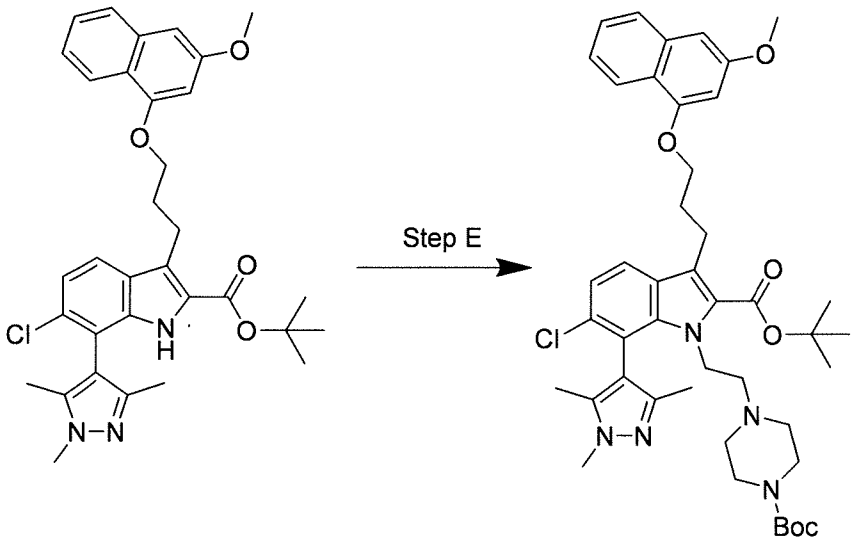
Step D



6-chloro-3-(3-((3-methoxynaphthalen-1-yl)oxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (0.9 g, 1.73 mmol,) was suspended in toluene (9 mL) and the mixture was heated to reflux under nitrogen. *N*,*N*-dimethylformamide di-*tert*-butyl acetal (5 ml, 20.85 mmol) was added dropwise to the refluxing mixture. The mixture was heated under reflux for 16 h under nitrogen. After complete consumption of the starting material (monitored by TLC and LCMS) reaction mixture was then diluted with EtOAc, washed successively with $NaHCO_3$ (sat.), water and brine. Organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to get the crude compound, which was then purified by column chromatography (SiO2, 30% EtOAc in DCM) to get *tert*-butyl 6-chloro-3-(3-((3-methoxynaphthalen-1-yl)oxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (700 mg, 1.22 mmol, 70%) as off white solid.

LCMS (ESI+): m/z 574.4 $[M+H]^+$

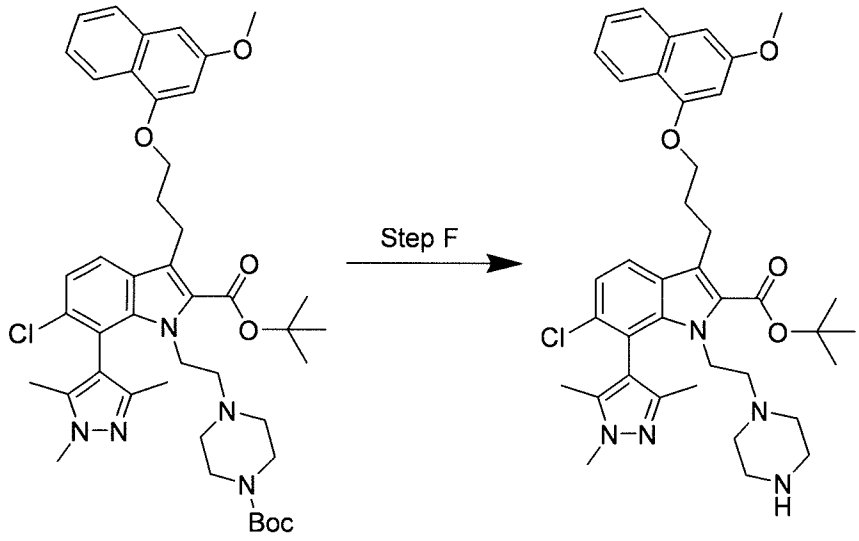
Step E



To a well stirred solution of *tert*-butyl 6-chloro-3-(3-((3-methoxynaphthalen-1-yl)oxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (0.70 g, 1.22 mmol) in DMF (6 mL) was added *tert*-butyl 4-(2-chloroethyl)piperazine-1-carboxylate (0.606 g, 2.44 mmol) followed by Cs_2CO_3 (1.98 g, 6.098 mmol) at RT under nitrogen. The reaction mixture was stirred at 90°C for 16 h under nitrogen. After complete consumption of the starting material (monitored by TLC and LCMS) the reaction mixture was diluted with EtOAc and washed successively with water and brine. The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to get the crude compound, which was then purified by column chromatography (SiO_2, 50% EtOAc in hexane) to get *tert*-butyl 1-(2-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)ethyl)-6-chloro-3-(3-((3-methoxynaphthalen-1-yl)oxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (650 mg, 0.827 mmol, 67.7%) as off white solid.

LCMS (ESI+): m/z 786.4 $[M+H]^+$

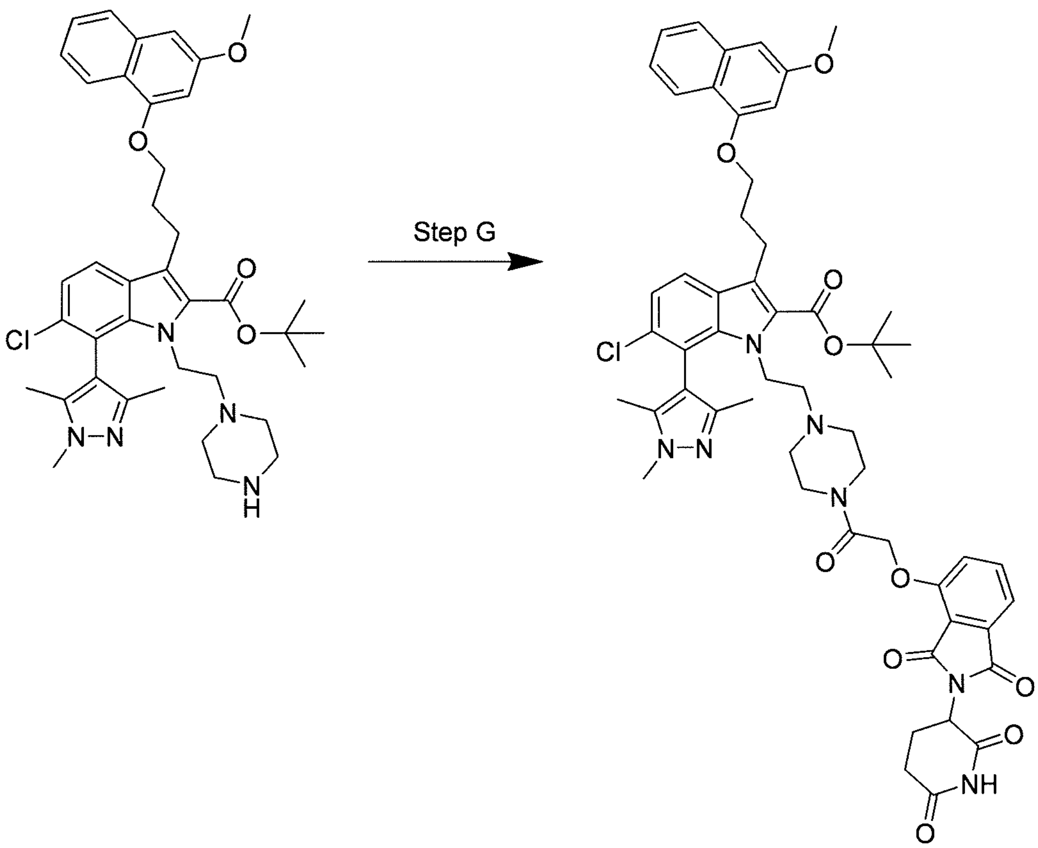
Step F



tert-butyl 1-(2-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)ethyl)-6-chloro-3-(3-((3-methoxynaphthalen-1-yl)oxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (0.65 g, 0.827 mmol) was dissolved in 4M HCl in dioxane (20 mL) at 0 °C and the mixture was stirred for 2 h under nitrogen at same temperature. After complete consumption of the starting material (monitored by LCMS) to the reaction mixture was added drop wise cold 1M NaOH solution at 0°C to maintain the pH~5 to 6. The aqueous layer was extracted 2-3 times with DCM. The combined organics were dried over Na_2SO_4 and concentrated in vacuo to get the crude compound which was purified by column chromatography (amine SiO_2, MeOH:DCM, 5-10%) to get *tert*-butyl 6-chloro-3-(3-((3-methoxynaphthalen-1-yl)oxy)propyl)-1-(2-(piperazin-1-yl)ethyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (360 mg, 0.52 mmol, 63%) as off white solid.

LCMS (ESI+): m/z 686.4 $[M+H]^+$

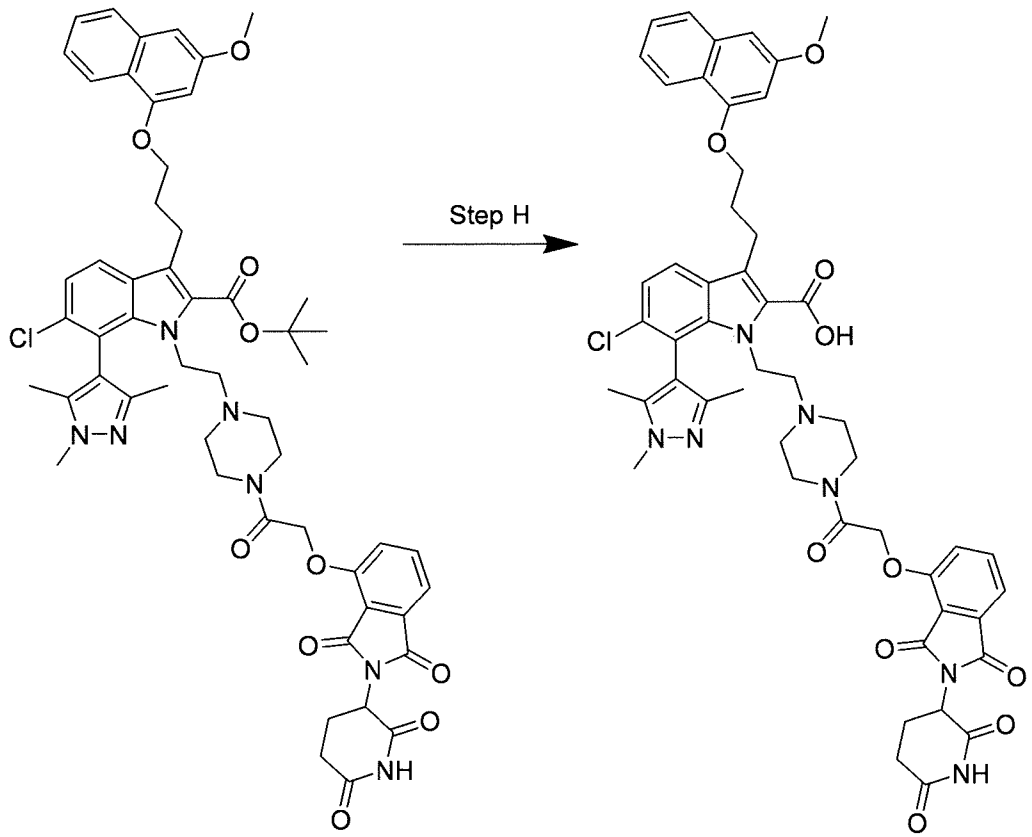
Step G



Tert-butyl 6-chloro-3-{3-[(3-methoxynaphthalen-1-yl)oxy]propyl}-1-[2-(piperazin-1-yl)ethyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (50.0 mg, 0.073 mmol), 2-{[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl]oxy}acetic acid (29.0 mg, 0.087 mmol) and HATU (33.2 mg, 0.087 mmol) were dissolved in dry DMF (2.0 mL) and to the mixture was added DIPEA (0.063 mL, 0.364 mmol). The reaction was stirred at RT for 2 h. The solvent was evaporated, resulting residues were dissolved in DCM and washed with brine. The organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. The crude *tert*-butyl 6-chloro-1-(2-(4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)acetyl)piperazin-1-yl)ethyl)-3-(3-((3-methoxynaphthalen-1-yl)oxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (85.0 mg, crude) was used in the next step without further purification.

LCMS (ESI+): m/z 1000.3 $[M+H]^+$

Step H

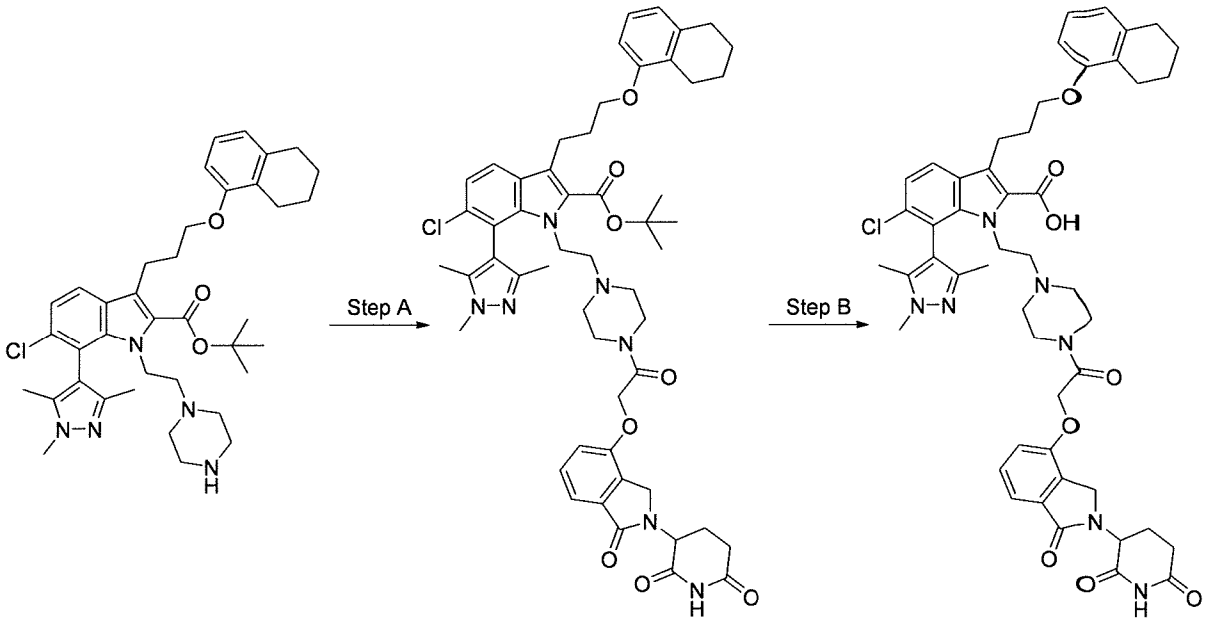


To *tert*-butyl 6-chloro-1-(2-(4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)acetyl)piperazin-1-yl)ethyl)-3-(3-((3-methoxynaphthalen-1-yl)oxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (85.0 mg, crude) a product in DCM (1.0 mL) was added TFA (1.0 mL, 13.059 mmol) and the mixture was stirred for 18 h at RT. After the reaction was completed (monitored by LCMS), the crude mixture was concentrated in vacuo and purified by preparative HPLC (H_2O:MeCN + 0.1% FA). The isolated product, 6-chloro-1-(2-(4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)acetyl)piperazin-1-yl)ethyl)-3-(3-((3-methoxynaphthalen-1-yl)oxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (41.6 mg, 0.044 mmol, 60% over 2 steps) was obtained as light yellow solid.

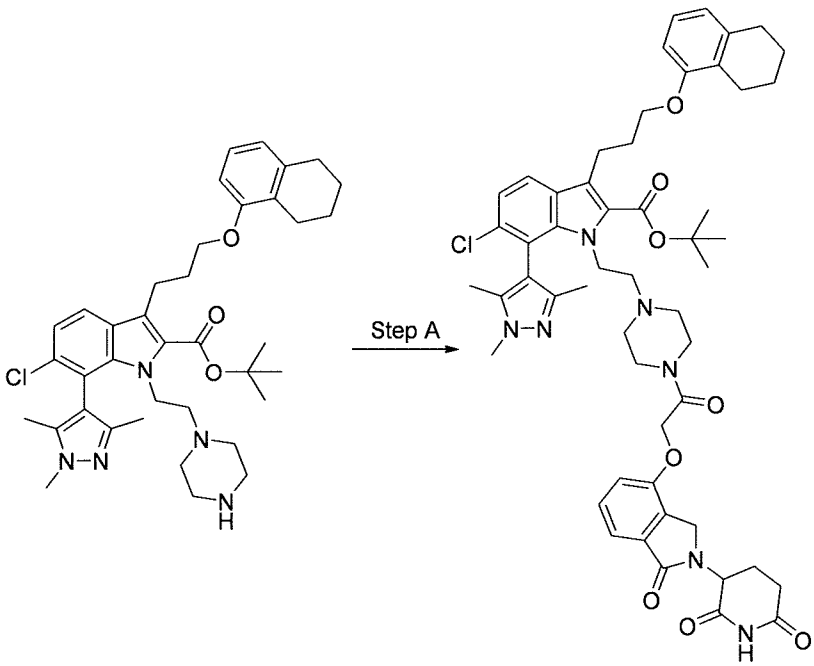
LCMS (ESI+): m/z 944.3 $[M+H]^+$

^{1}H NMR (500 MHz, DMSO) δ 13.07 (bs, *J* = 333.2 Hz, 1H), 11.09 (s, 1H), 8.06 (d, *J* = 8.3 Hz, 1H), 7.78 – 7.72 (m, 3H), 7.49 – 7.42 (m, 2H), 7.33 – 7.26 (m, 2H), 7.22 (d, *J* = 8.5 Hz, 1H), 6.87 (d, *J* = 2.1 Hz, 1H), 6.52 (d, J = 2.2 Hz, 1H), 5.13 – 5.06 (m, 3H), 4.32 – 4.25 (m, 1H), 4.17 (t, *J* = 6.1 Hz, 3H), 3.84 (s, 3H), 3.75 (s, 3H), 3.29 – 3.23 (m, 4H), 2.88 (ddd, *J* = 16.9, 13.7, 5.4 Hz, 1H), 2.62 – 2.52 (m, 2H), 2.48-2.46 (m, 1H), 2.20 (p, *J* = 6.5 Hz, 2H), 2.16 – 1.96 (m, 11H), 1.87 (s, 3H).

Example 59. 6-chloro-1-(2-(4-(2-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)oxy)acetyl)piperazin-1-yl)ethyl)-3-(3-((5,6,7,8-tetrahydronaphthalen-1-yl)oxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (219)



Step A

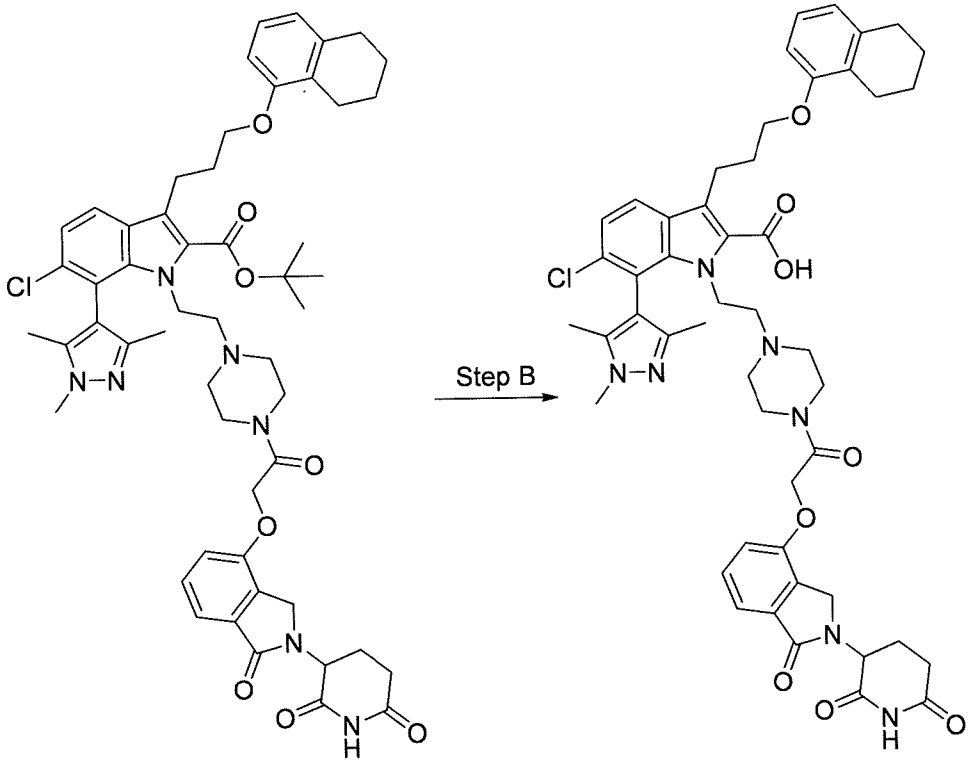


2-{[2-(2,6-dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1*H*-isoindol-4-yl]oxy}acetic acid (26.5 mg, 0.083 mmol) was dissolved in dry DMF (1.5 mL) under argon atmosphere and DIPEA (0.040 mL, 0.227 mmol), followed by *tert*-butyl 6-chloro-1-(2-(piperazin-1-yl)ethyl)-3-(3-((5,6,7,8-

tetrahydronaphthalen-1-yl)oxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (50.0 mg, 0.076 mmol) was added. Reaction mixture was cooled down to 0°C and HATU (34.6 mg, 0.091 mmol) was added as a solution in dry DMF (0.2 mL). The reaction was stirred under argon at RT for 20 min. The solution was diluted with DCM and washed with brine, $NaHCO_3$ (2x), again brine and water. Organic layer was dried over anhydrous $MgSO_4$, filtered, concentrated and dried under reduced pressure to give *tert*-butyl 6-chloro-1-(2-(4-(2-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)oxy)acetyl)piperazin-1-yl)ethyl)-3-(3-((5,6,7,8-tetrahydronaphthalen-1-yl)oxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (70.7 mg, crude) as orange oil. The product was used in the next step without further purification.

LCMS (ESI+): m/z 960.2 $[M+H]^+$

Step B



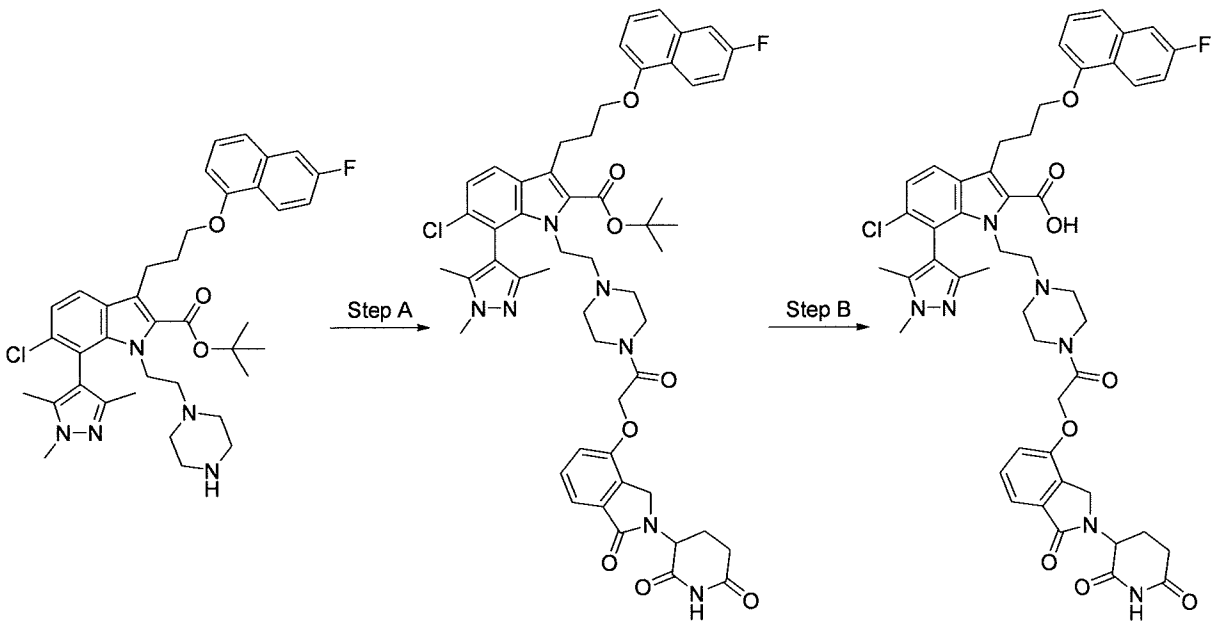
Tert-butyl 6-chloro-1-(2-(4-(2-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)oxy)acetyl)piperazin-1-yl)ethyl)-3-(3-((5,6,7,8-tetrahydronaphthalen-1-yl)oxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (70.7 mg, crude) was dissolved in dry DCM (0.56 mL) under argon atmosphere. TFA (0.56 mL, 7.358 mmol) was added and the reaction was stirred for 18 h at RT. After that time LCMS indicated complete consumption of the starting material. DCM and TFA were evaporated under reduced pressure and the resulting residue dissolved in DMSO (4 mL). The solution was passed through a syringe filter and purified by

preparative HPLC (H_2O:MeCN + 0.1% FA) to give 6-chloro-1-(2-(4-(2-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)oxy)acetyl)piperazin-1-yl)ethyl)-3-(3-((5,6,7,8-tetrahydronaphthalen-1-yl)oxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (16.7 mg, 0.018 mmol, 24% over two steps) as white solid.

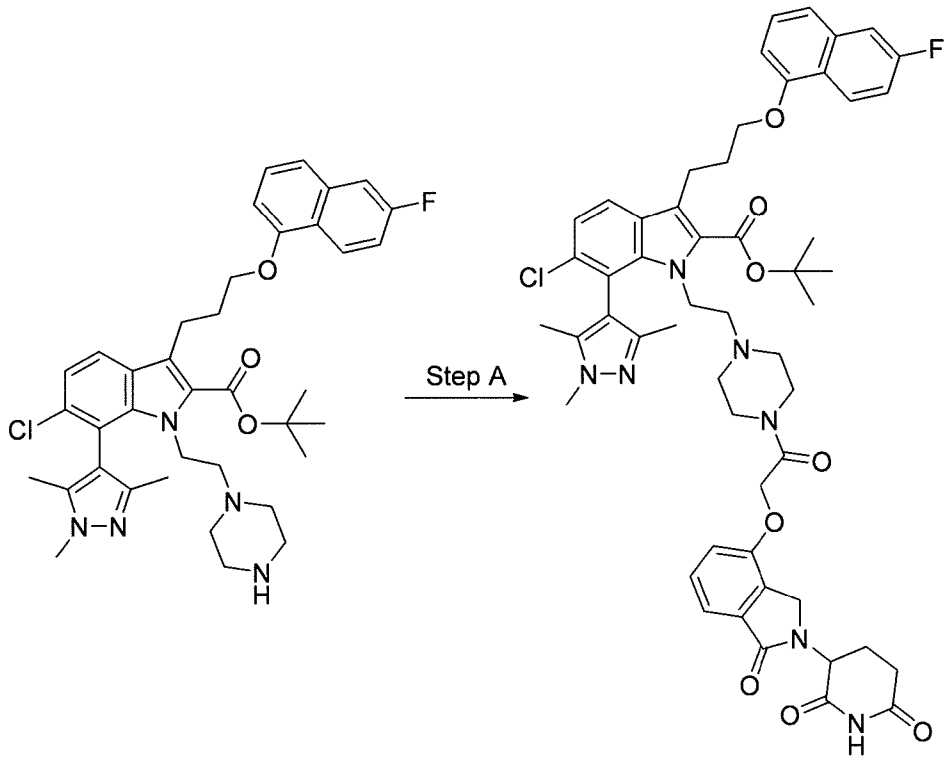
LCMS (ESI+): m/z 903.7 $[M+H]^+$

^1H NMR (500 MHz, DMSO) δ 13.35 (s, 1H), 10.98 (s, 1H), 7.71 (d, *J* = 8.5 Hz, 1H), 7.46 (t, *J* = 7.8 Hz, 1H), 7.33 (d, *J* = 7.5 Hz, 1H), 7.27 (d, *J* = 8.5 Hz, 1H), 7.13 (d, *J* = 8.2 Hz, 1H), 7.00 (t, *J* = 7.9 Hz, 1H), 6.65 (t, *J* = 7.5 Hz, 2H), 5.12 (dd, *J* = 13.3, 5.1 Hz, 1H), 4.97 (s, 2H), 4.40 (d, *J* = 17.3 Hz, 1H), 4.27 (d, *J* = 17.4 Hz, 2H), 4.22 – 4.14 (m, 1H), 4.00 (t, *J* = 6.3 Hz, 2H), 3.77 (d, *J* = 1.8 Hz, 3H), 3.38 – 3.36 (m, 1H), 3.30 – 3.28 (m, 1H), 3.18 (t, *J* = 7.5 Hz, 2H), 2.93 (ddd, *J* = 17.2, 13.5, 5.3 Hz, 1H), 2.69 (t, *J* = 6.1 Hz, 2H), 2.64 – 2.59 (m, 3H), 2.57 – 2.54 (m, 2H), 2.48 – 2.41 (m, 1H), 2.17 – 2.04 (m, 8H), 2.03 (s, 3H), 2.02 – 1.98 (m, 1H), 1.90 (s, 3H), 1.80 – 1.65 (m, 4H).

Example 60. 6-chloro-1-{2-[4-(2-{[2-(2,6-dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1*H*-isoindol-4-yl]oxy}acetyl)piperazin-1-yl]ethyl}-3-{3-[(6-fluoronaphthalen-1-yl)oxy]propyl}-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (220)



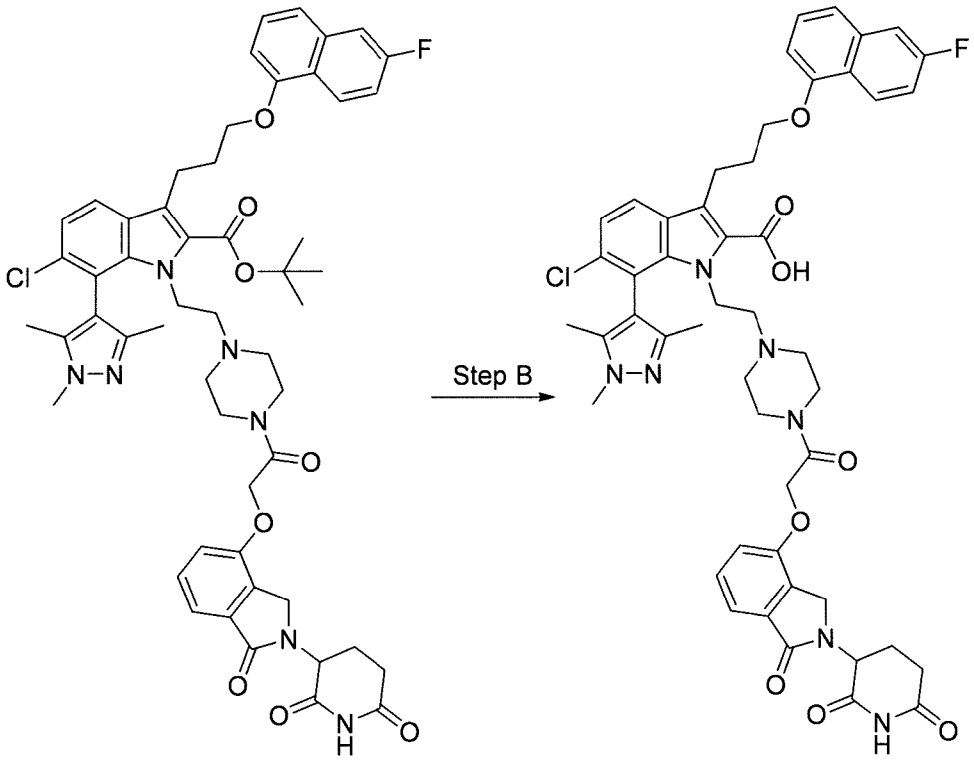
Step A



2-{[2-(2,6-Dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1*H*-isoindol-4-yl]oxy}acetic acid (18.3 mg, 0.058 mmol) was dissolved in dry DMF (1.0 mL) under argon atmosphere and DIPEA (0.025 mL, 0.144 mmol) was added, followed by *tert*-butyl 6-chloro-3-{3-[(6-fluoronaphthalen-1-yl)oxy]propyl}-1-[2-(piperazin-1-yl)ethyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (32.3 mg, 0.048 mmol). The solution was cooled down to 0°C and HATU (21.9 mg, 0.058 mmol) was added dropwise as a solution in 0.2 mL of dry DMF. The reaction was stirred under argon atmosphere, allowing to warm to room temperature. After 15 min full conversion was observed (monitored with LCMS). The solution was diluted with DCM and washed with brine, $NaHCO_3$ (sat.), again brine and water. Organic layer was dried over anhydrous $MgSO_4$, filtered, concentrated and dried under reduced pressure to give *tert*-butyl 6-chloro-1-{2-[4-(2-{[2-(2,6-dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1*H*-isoindol-4-yl]oxy}acetyl)piperazin-1-yl]ethyl}-3-{3-[(6-fluoronaphthalen-1-yl)oxy]propyl}-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (44.7 mg, crude) as orange oil. The product was used in the next step without further purification.

LCMS (ESI+): 974.6 $[M+H]^+$

Step B

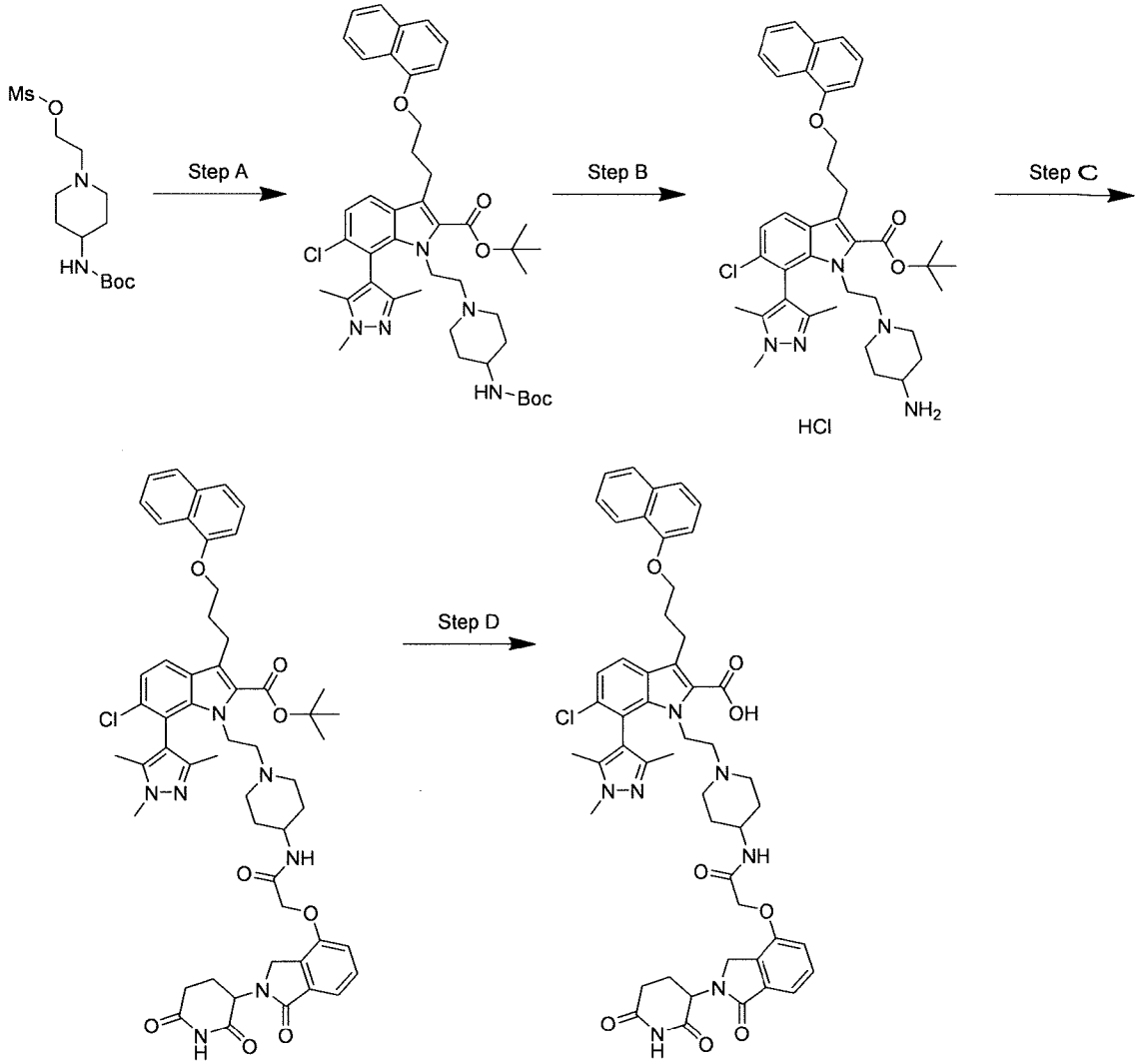


Tert-butyl 6-chloro-1-{2-[4-(2-{[2-(2,6-dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1*H*-isoindol-4-yl]oxy}acetyl)piperazin-1-yl]ethyl}-3-{3-[(6-fluoronaphthalen-1-yl)oxy]propyl}-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (44.7 mg, crude) was dissolved in dry DCM (0.351 mL) under argon atmosphere. TFA (0.351 mL, 4.584 mmol) was added and the reaction was stirred for 18 h at room temperature. DCM and TFA were evaporated under reduced pressure and the resulting residue dissolved in DMSO and purified with preparative HPLC (H_2O:MeCN + 0.1% FA) to give 6-chloro-1-{2-[4-(2-{[2-(2,6-dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1*H*-isoindol-4-yl]oxy}acetyl)piperazin-1-yl]ethyl}-3-{3-[(6-fluoronaphthalen-1-yl)oxy]propyl}-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (12.6 mg, 0.014 mmol, 29% over two steps) as white solid.

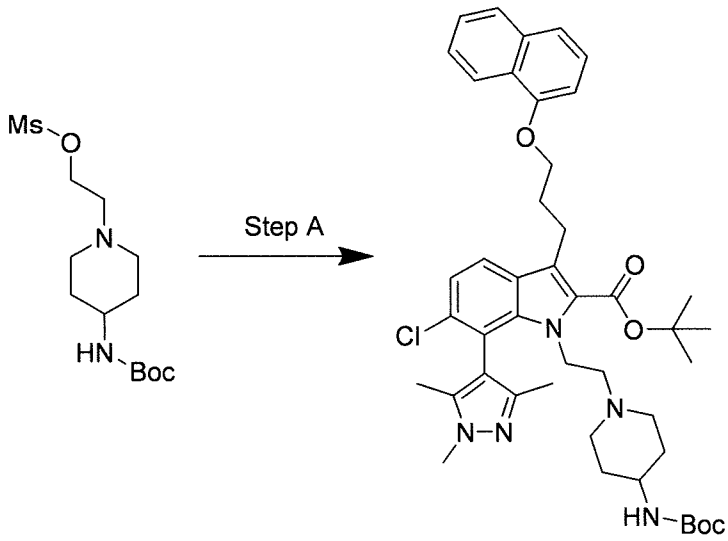
LCMS (ESI+): m/z 917.6 $[M+H]^+$

^{1}H NMR (500 MHz, DMSO) δ 13.44 (s, 1H), 10.98 (s, 1H), 8.26 (dd, *J* = 9.2, 5.8 Hz, 1H), 7.75 (d, *J* = 8.6 Hz, 1H), 7.67 (dd, *J* = 10.4, 2.7 Hz, 1H), 7.50 – 7.42 (m, 3H), 7.38 (td, *J* = 8.9, 2.7 Hz, 1H), 7.33 (d, *J* = 7.4 Hz, 1H), 7.25 (d, *J* = 8.5 Hz, 1H), 7.13 (d, *J* = 8.2 Hz, 1H), 6.90 (dd, *J* = 5.4, 3.3 Hz, 1H), 5.12 (dd, *J* = 13.3, 5.1 Hz, 1H), 4.96 (s, 2H), 4.39 (d, *J* = 17.3 Hz, 1H), 4.35 – 4.14 (m, 5H), 3.77 (d, *J* = 1.9 Hz, 3H), 3.42 – 3.37 (m, 2H), 3.29 – 3.26 (m, 2H), 2.93 (ddd, *J* = 17.2, 13.6, 5.4 Hz, 1H), 2.64 – 2.56 (m, 2H), 2.49 – 2.40 (m, 2H), 2.28 – 2.18 (m, 2H), 2.17 – 2.03 (m, 6H), 2.02 (s, 3H), 2.02 – 1.99 (m, 1H), 1.89 (s, 3H).

Example 61. 6-chloro-1-{2-[4-(2-{[2-(2,6-dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1*H*-isoindol-4-yl]oxy}acetamido)piperidin-1-yl]ethyl}-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (221)



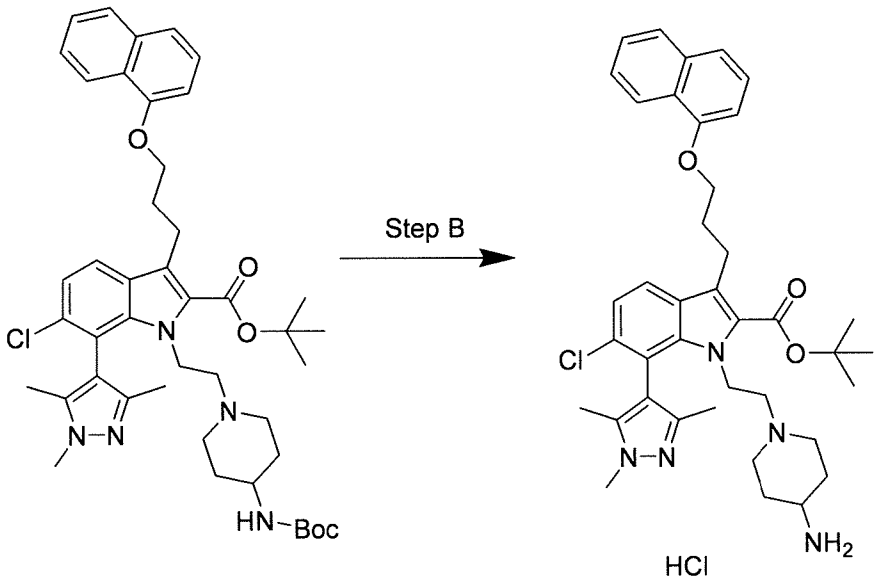
Step A



Tert-butyl *N*-{1-[2-(methanesulfonyloxy)ethyl]piperidin-4-yl}carbamate (40.0 mg, 0.124 mmol), *tert*-butyl 6-chloro-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (45.0 mg, 0.083 mmol) and Cs_2CO_3 (80.8 mg, 0.248 mmol) were placed in a vial, dissolved in dry DMF (2.0 mL) and stirred at RT for 4 days. After complete consumption of the starting material (monitored by LCMS), the solvent was evaporated under reduced pressure. The residues were dissolved in DCM and washed with H_2O and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. The product *tert*-butyl 1-[2-(4-{[(*tert*-butoxy)carbonyl]amino}piperidin-1-yl)ethyl]-6-chloro-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (49.1 mg, crude) was used to next step without further purification.

LCMS (ESI+): m/z 769.9 $[M+H]^+$

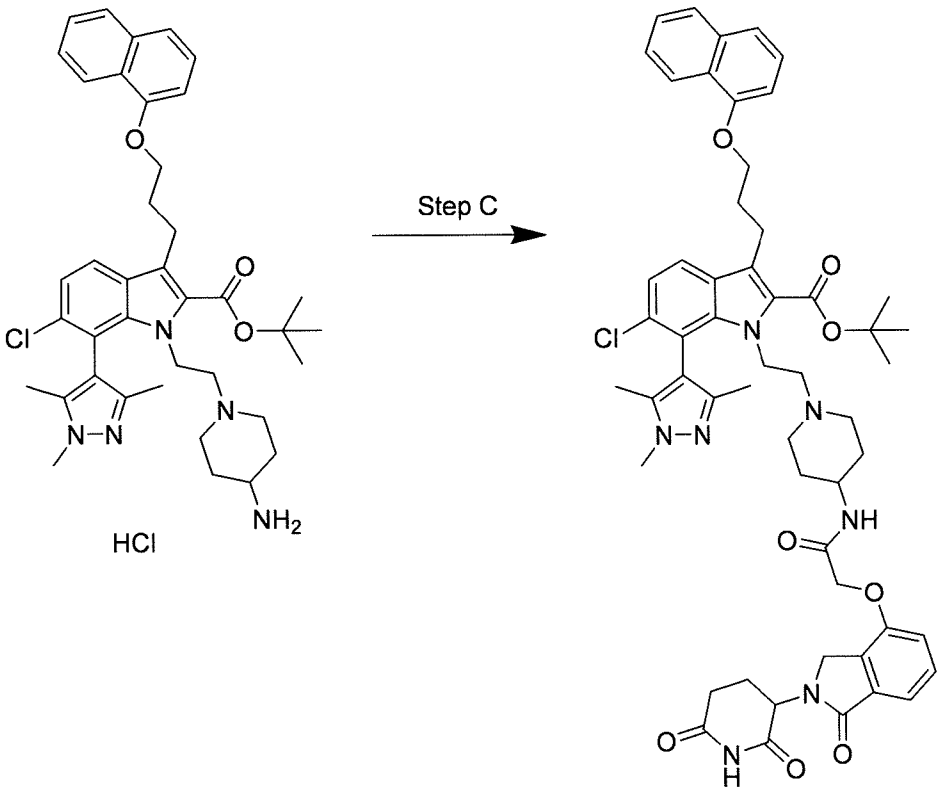
Step B



Tert-butyl 1-[2-(4-{[(*tert*-butoxy)carbonyl]amino}piperidin-1-yl)ethyl]-6-chloro-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (49.1 mg, crude) was dissolved in THF (5.0 mL) and cooled to 0°C. To the mixture was added 4M HCl in dioxane (1.0 mL, 4.000 mmol) and a reaction was stirred at room temperature for 18 h. The crude was concentrated in vacuo, dissolved in water and freeze dried. The product *tert*-butyl 1-[2-(4-aminopiperidin-1-yl)ethyl]-6-chloro-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate hydrochloride (52.3 mg, crude) was a yellowish solid which was used to next step without further purification.

LCMS (ESI+): m/z 669.9 $[M+H]^+$

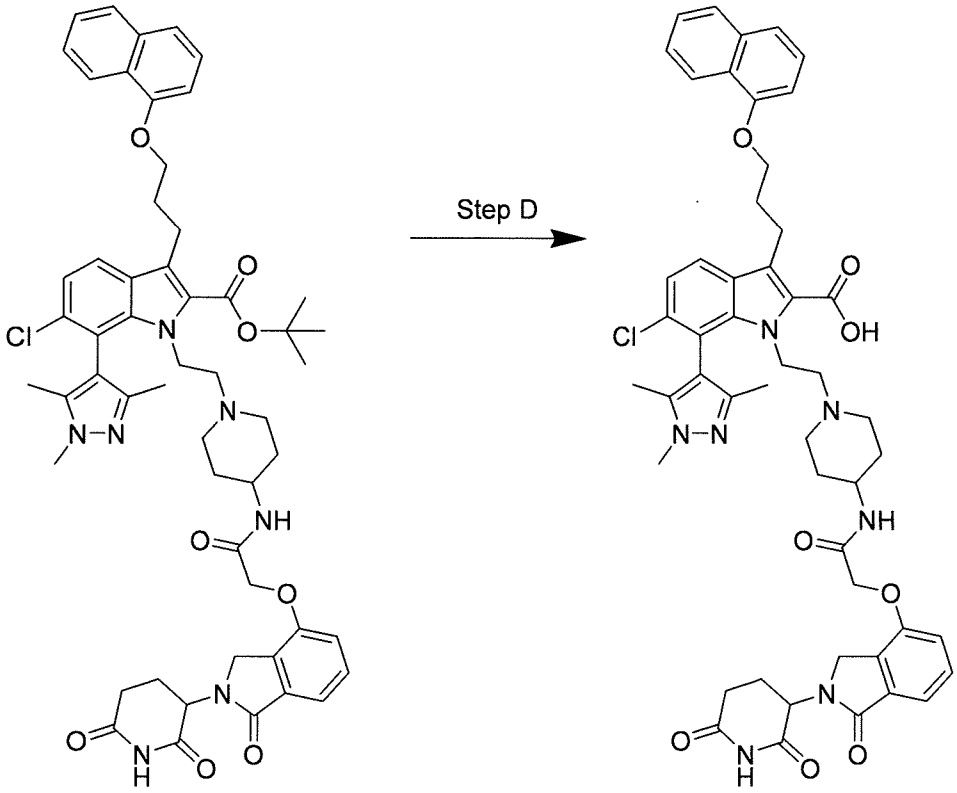
Step C



Tert-butyl 1-[2-(4-aminopiperidin-1-yl)ethyl]-6-chloro-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate hydrochloride (42.2 mg, crude), 2-{[2-(2,6-dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1*H*-isoindol-4-yl]oxy}acetic acid (22.8 mg, 0.072 mmol) and HATU (45.4 mg, 0.119 mmol) were dissolved in dry DMF (2.0 mL) and to the mixture was added DIPEA (0.052 mL, 0.298 mmol). The reaction was stirred at RT for 2 h. The solvent was evaporated. Residues were dissolved in DCM and washed with brine. The organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. The *tert*-butyl 6-chloro-1-{2-[4-(2-{[2-(2,6-dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1*H*-isoindol-4-yl]oxy}acetamido)piperidin-1-yl]ethyl}-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (55 mg, crude) was a brown oil and was used without a further purification to next step.

LCMS (ESI+): m/z 969.7 $[M+H]^+$

Step D



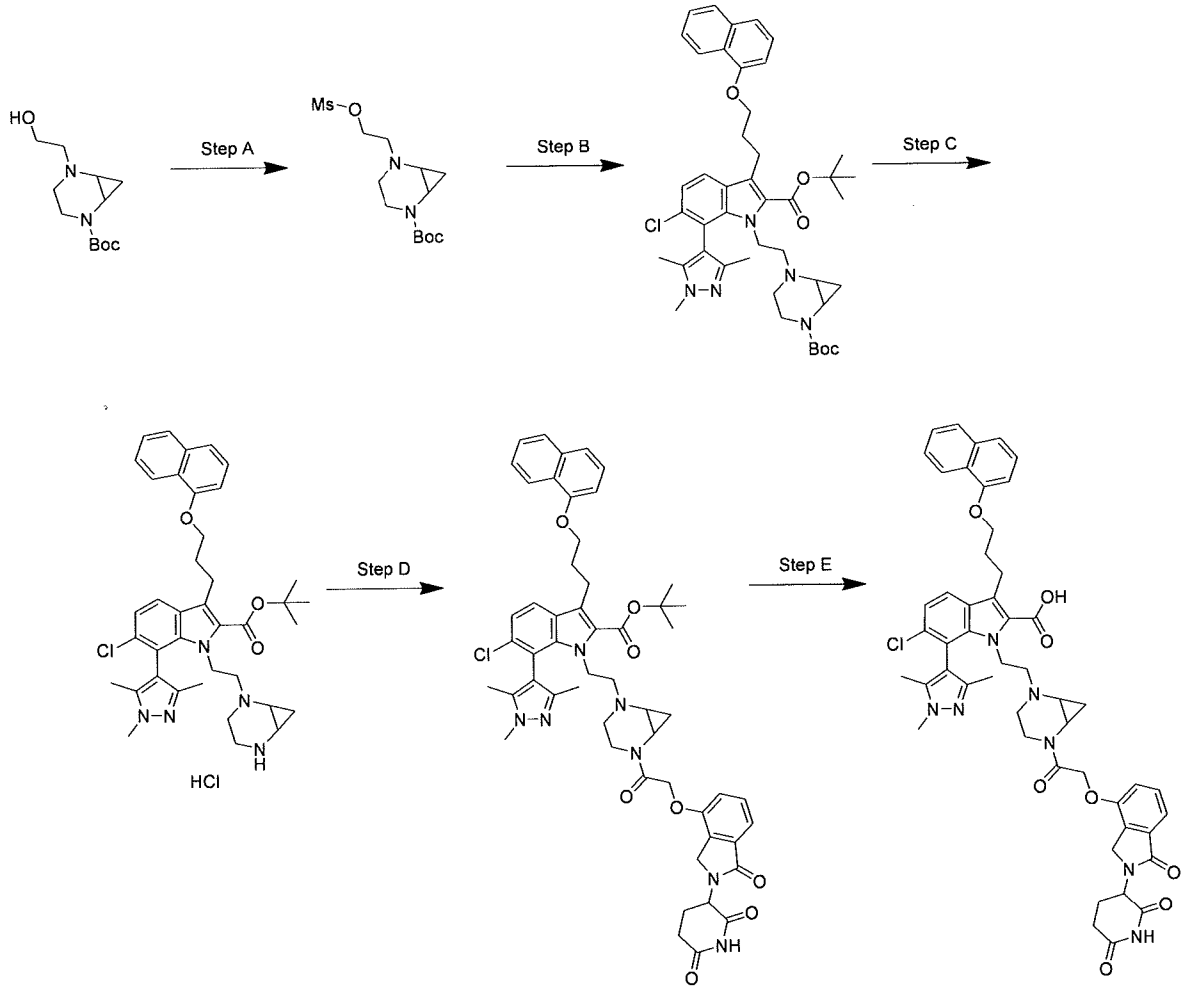
To a solution of *tert*-butyl 6-chloro-1-{2-[4-(2-{[2-(2,6-dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1*H*-isoindol-4-yl]oxy}acetamido)piperidin-1-yl]ethyl}-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (55.0 mg, crude) in DCM (1.0 mL) was added TFA (0.500 mL, 6.529 mmol). The mixture was stirred for 18 h at RT. The crude was concentrated in vacuo, the residues were dissolved in DMSO and purified by preparative HPLC (H_2O:MeCN + 0.1% FA) to give 6-chloro-1-{2-[4-(2-{[2-(2,6-dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1*H*-isoindol-4-yl]oxy}acetamido)piperidin-1-yl]ethyl}-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (8.3 mg, 0.009 mmol, 10% over 4 steps) as a white solid.

LCMS (ESI+): m/z 914.3 $[M+H]^+$

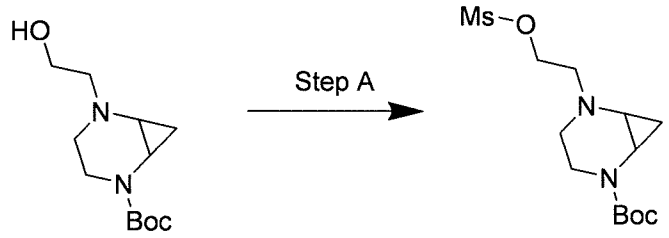
^{1}H NMR (500 MHz, DMSO) δ 11.00 (s, 1H), 8.23 (dd, *J* = 7.3, 2.0 Hz, 1H), 8.07 (d, *J* = 7.8 Hz, 1H), 7.88 (dd, *J* = 7.4, 2.0 Hz, 1H), 7.68 (d, *J* = 8.5 Hz, 1H), 7.57 – 7.50 (m, 2H), 7.46 (dt, *J* = 7.8, 3.7 Hz, 2H), 7.43 – 7.39 (m, 1H), 7.39 – 7.33 (m, 1H), 7.19 (d, *J* = 8.5 Hz, 1H), 7.11 (d, *J* = 8.2 Hz, 1H), 6.92 (d, *J* = 7.5 Hz, 1H), 5.13 (dd, *J* = 13.3, 5.1 Hz, 1H), 4.61 (d, *J* = 3.4 Hz, 2H), 4.44 (d, J = 17.5 Hz, 1H), 4.33 (d, J = 17.4 Hz, 1H), 4.30 – 4.23 (m, 1H), 4.20 (t, *J* = 6.3 Hz, 3H), 3.76 (s, 3H), 3.68 – 3.59 (m, 1H), 3.23 (dd, *J* = 8.6, 6.5 Hz, 2H), 2.97 – 2.86 (m, 1H), 2.65 – 2.56 (m, 1H), 2.49 – 2.37 (m, 2H), 2.34

– 2.25 (m, 4H), 2.21 (p, *J* = 6.6 Hz, 2H), 2.05 – 1.97 (m, 5H), 1.89 (s, 3H), 1.69 – 1.62 (m, 2H), 1.57 – 1.45 (m, 2H).

Example 62. 6-chloro-1-{2-[5-(2-{[2-(2,6-dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1*H*-isoindol-4-yl]oxy}acetyl)-2,5-diazabicyclo[4.1.0]heptan-2-yl]ethyl}-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (222)

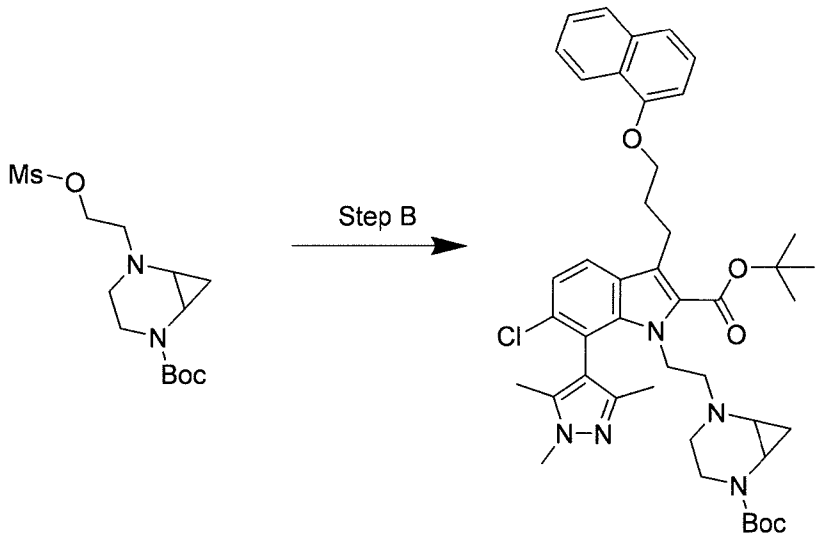


Step A



Tert-butyl 5-(2-hydroxyethyl)-2,5-diazabicyclo[4.1.0]heptane-2-carboxylate (55.7 mg, 0.230 mmol) was dissolved in DCM (3.0 mL), Et_3N (0.048 mL, 0.345 mmol) and DMAP (2.8 mg, 0.023 mmol) were added and reaction mixture was cooled down to 0°C. Then, MsCl (0.021 mL, 0.276 mmol) was added dropwise and reaction mixture was let to stir at RT for 18h. The crude was extracted with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The product *tert*-butyl 5-[2-(methanesulfonyloxy)ethyl]-2,5-diazabicyclo[4.1.0]heptane-2-carboxylate (78.7 mg, crude) was an orange oil and was used in the next step without further purification (TLC, 5% MeOH in DCM, R_f = 0.7).

Step B

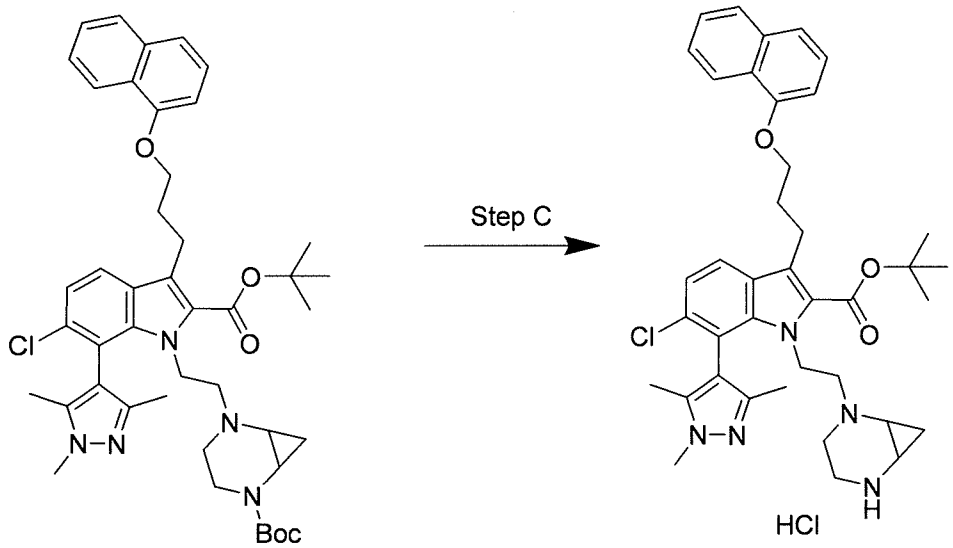


To a solution of *tert*-butyl 5-[2-(methanesulfonyloxy)ethyl]-2,5-diazabicyclo[4.1.0]heptane-2-carboxylate (88.3 mg, 0.276 mmol) and *tert*-butyl 6-chloro-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (50.0 mg, crude) in dry DMF (1.0 mL) was added Cs_2CO_3 (89.8 mg, 0.276 mmol). The mixture was stirred for 6 days at RT. To the mixture was added DCM and washed with brine. The organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. The product *tert*-butyl 1-(2-{5-[(*tert*-butoxy)carbonyl]-2,5-

diazabicyclo[4.1.0]heptan-2-yl}ethyl)-6-chloro-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (88.7 mg, crude) was a light yellow oil, which was used in next step without further purification.

LCMS (ESI+): m/z 768.3 $[M+H]^+$

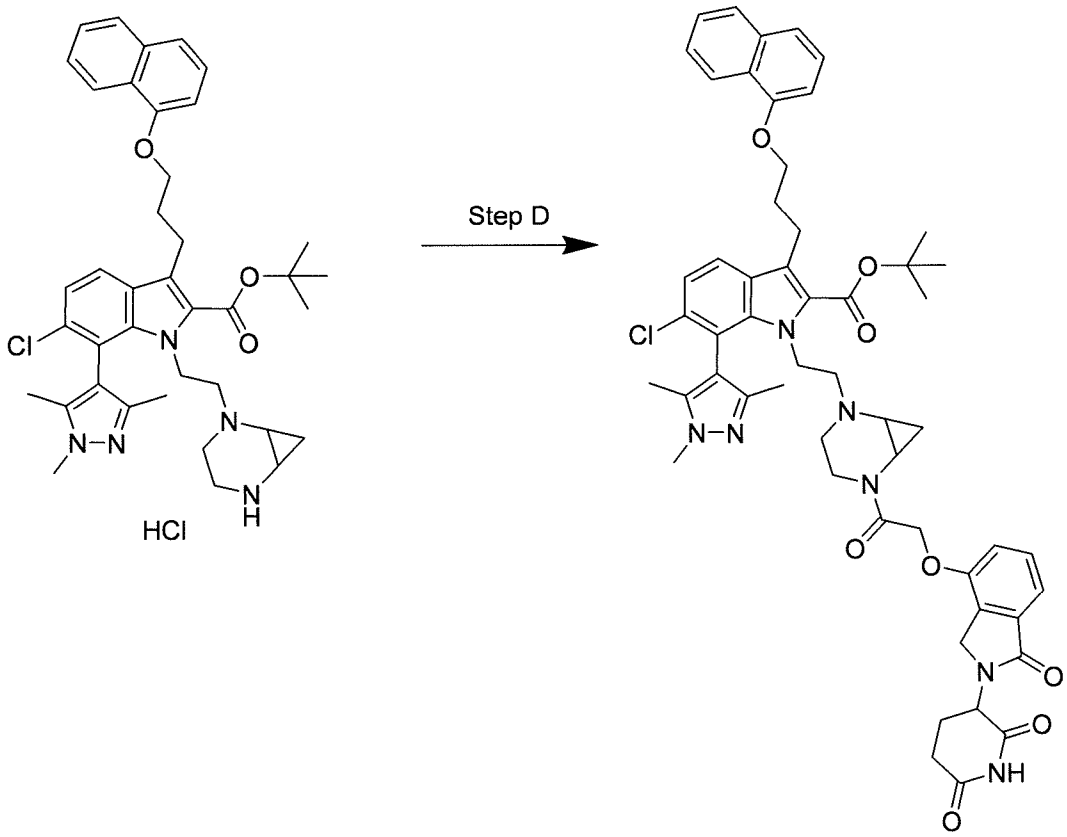
Step C



tert-butyl 1-(2-{5-[(tert-butoxy)carbonyl]-2,5-diazabicyclo[4.1.0]heptan-2-yl}ethyl)-6-chloro-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (102.0 mg, crude) was dissolved in THF (2.0 mL) and cooled to 0°C. To the mixture was added 4M HCl in dioxane (0.184 mL, 5.310 mmol) and a reaction was stirred at room temperature for 18 h. The crude was concentrated in vacuo. The product *tert*-butyl 6-chloro-1-(2-{2,5-diazabicyclo[4.1.0]heptan-2-yl}ethyl)-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate hydrochloride (90.0 mg, crude) was a yellowish solid which was used in next step without further purification.

LCMS (ESI+): m/z 668.3 $[M+H]^+$

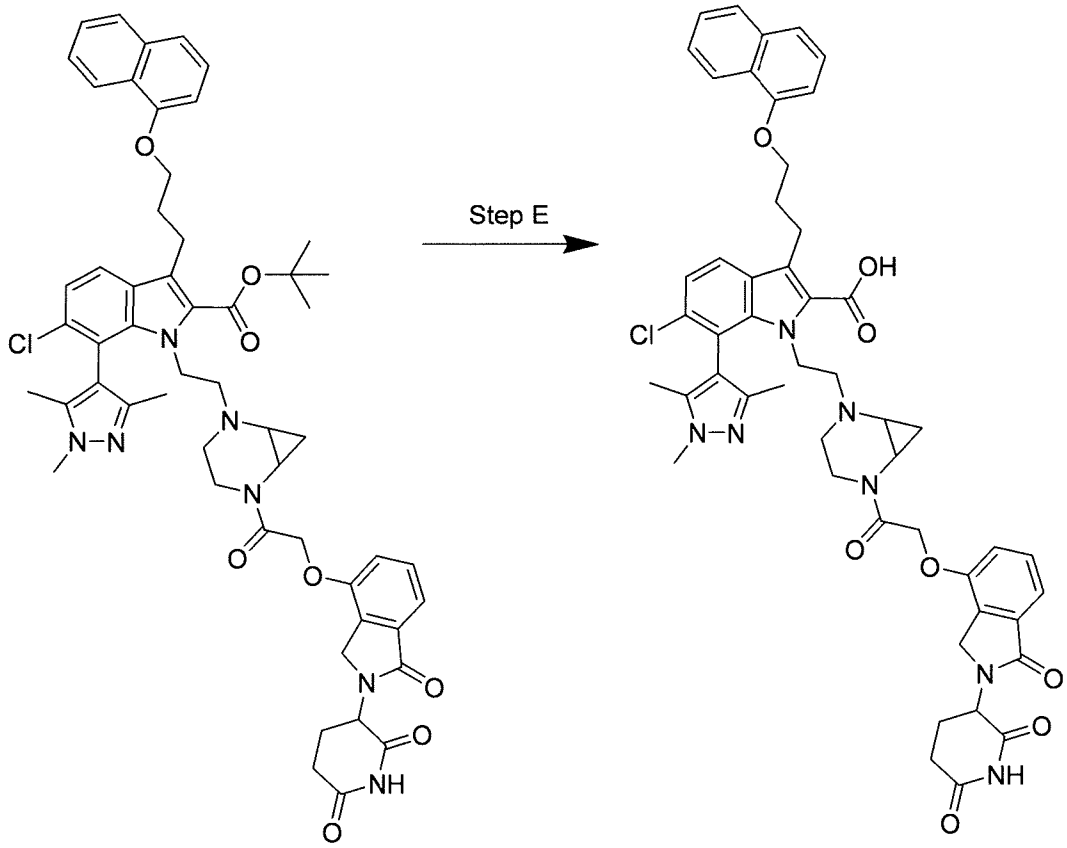
Step D



Tert-butyl 6-chloro-1-(2-{2,5-diazabicyclo[4.1.0]heptan-2-yl}ethyl)-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate hydrochloride (35.0 mg, crude), 2-{[2-(2,6-dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1*H*-isoindol-4-yl]oxy}acetic acid (19.0 mg, 0.060 mmol) and HATU (37.8 mg, 0.099 mmol) was dissolved in dry DMF (2.0 mL) and to the mixture was added DIPEA (0.043 mL, 0.248 mmol). The reaction was stirred at RT for 2h. The solvent was evaporated. Residues were dissolved in DCM and washed with brine. The organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. The product *tert*-butyl 6-chloro-1-{2-[5-(2-{[2-(2,6-dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1*H*-isoindol-4-yl]oxy}acetyl)-2,5-diazabicyclo[4.1.0]heptan-2-yl]ethyl}-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (50.0 mg, crude) was used in next step without further purification.

LCMS (ESI+): m/z 967.9 $[M+H]^+$

Step E



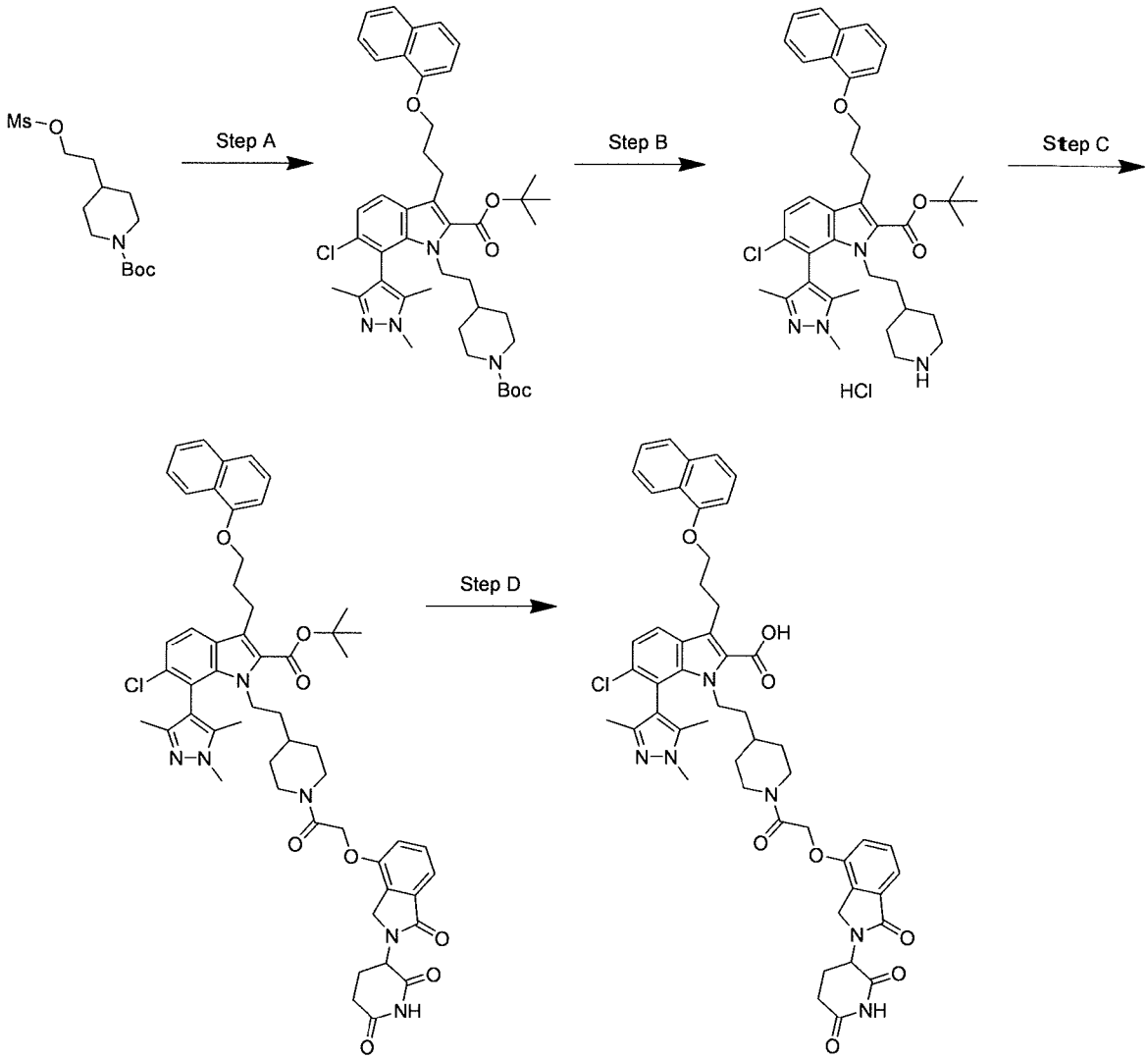
To a solution of *tert*-butyl 6-chloro-1-{2-[5-(2-{[2-(2,6-dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1*H*-isoindol-4-yl]oxy}acetyl)-2,5-diazabicyclo[4.1.0]heptan-2-yl]ethyl}-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (50.0 mg, crude) in DCM (1.0 mL) was added TFA (0.500 mL, 6.529 mmol). The mixture was stirred for 18 h at RT. The crude was concentrated in vacuo and purified by preparative HPLC (H_2O:MeCN + 0.1% FA) to give 6-chloro-1-{2-[5-(2-{[2-(2,6-dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1*H*-isoindol-4-yl]oxy}acetyl)-2,5-diazabicyclo[4.1.0]heptan-2-yl]ethyl}-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (3.9 mg, 0.004 mmol, 8% over 5 steps) as a white solid.

LCMS (ESI+): m/z 912.3 $[M+H]^+$

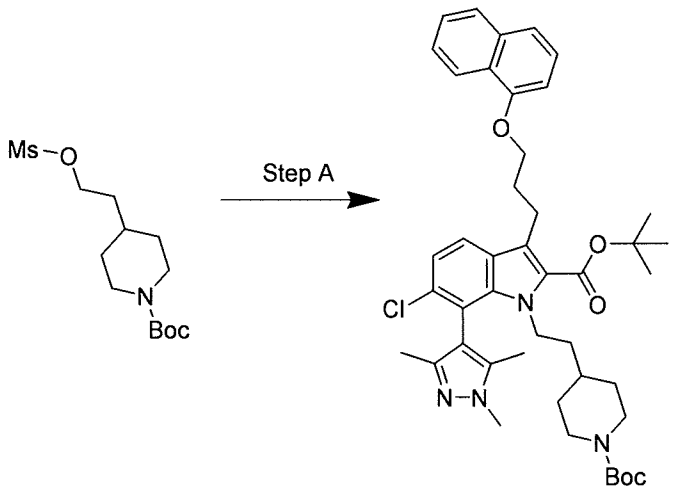
^{1}H NMR (500 MHz, DMSO) δ 13.24 (s, 1H), 10.97 (s, 1H), 8.20 (d, *J* = 7.2 Hz, 1H), 7.86 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.71 (d, *J* = 9.0 Hz, 1H), 7.54 – 7.47 (m, 2H), 7.48 – 7.42 (m, 2H), 7.40 – 7.36 (m, 1H), 7.31 (d, *J* = 7.4 Hz, 1H), 7.20 (d, *J* = 8.4 Hz, 1H), 7.10 (d, *J* = 8.1 Hz, 1H), 6.90 (d, *J* = 7.5 Hz, 1H), 5.19 – 4.93 (m, 3H), 4.45 – 4.15 (m, 7H), 3.75 – 3.67 (m, 4H), 2.96 – 2.84 (m, 2H), 2.77 – 2.65 (m, 1H), 2.62-2.27 (m, 3H), 2.22 (p, *J* = 7.0 Hz, 2H), 2.14 – 2.07 (m, 1H), 2.05 – 1.96 (m, 6H), 1.89 (d, *J* = 8.4 Hz, 3H), 0.62 – 0.50 (m, 2H).

2H in aliphatic area overlaps with water

Example 63. 6-chloro-1-{2-[1-(2-{[2-(2,6-dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1*H*–isoindol-4-yl]oxy}acetyl)piperidin-4-yl]ethyl}-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (223)



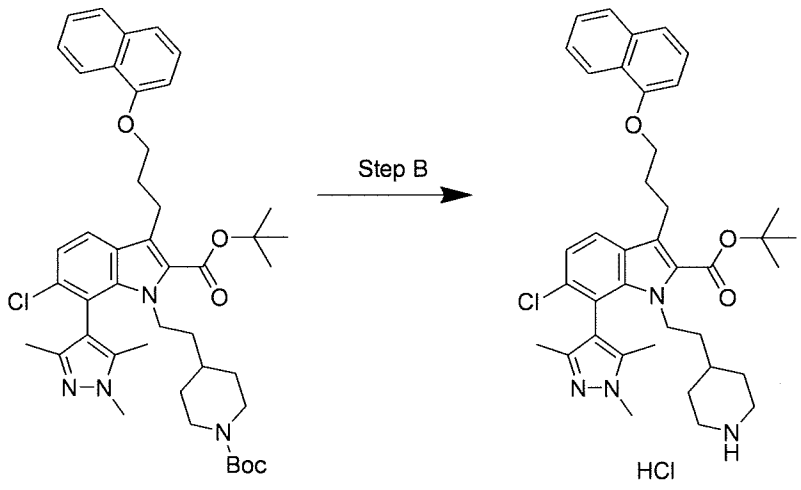
Step A



N-Boc-4-(2-bromo-ethyl)-piperidine (25.8 mg, 0.088 mmol), *tert*-butyl 6-chloro-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (40.0 mg, 0.074 mmol) and Cs_2CO_3 (71.9 mg, 0.221 mmol) were placed in a vial, dissolved in dry DMF (2.0 mL) and stirred at RT for 4 days. After complete consumption of the starting material (monitored by LCMS), the solvent was evaporated under reduced pressure, the residues were dissolved in DCM and washed with H_2O and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. The product *tert*-butyl 1-(2-{1-[(*tert*-butoxy)carbonyl]piperidin-4-yl}ethyl)-6-chloro-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (49.1 mg, crude) was used in the next step without further purification.

LCMS (ESI+): m/z 754.9 $[M+H]^+$

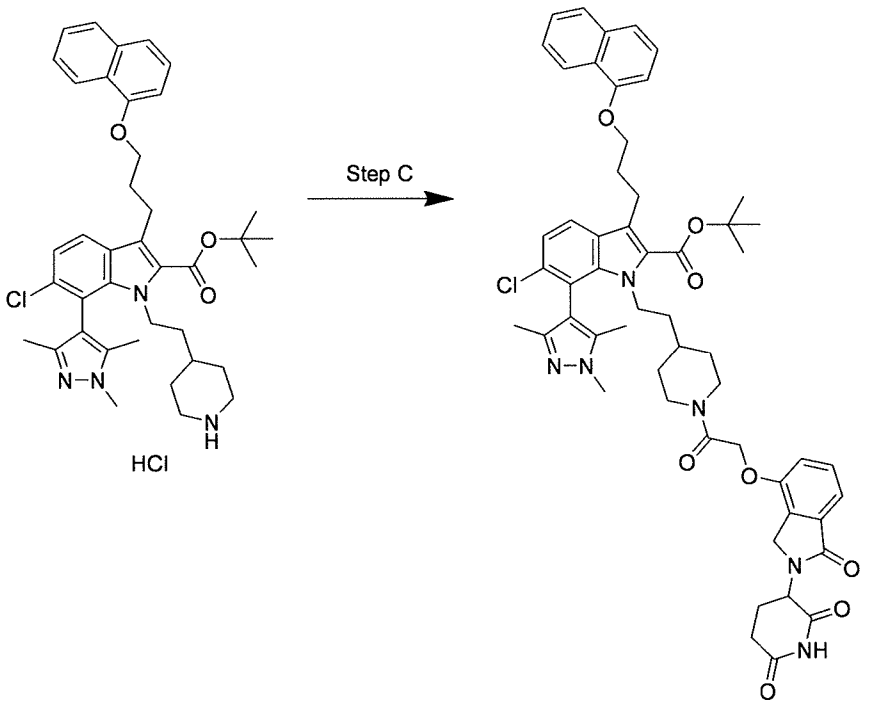
Step B



To a solution of *tert*-butyl 1-(2-{1-[(*tert*-butoxy)carbonyl]piperidin-4-yl}ethyl)-6-chloro-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (49.1 mg, crude) in THF (5.0 mL) at 0°C was added 4M HCl in dioxane (2.0 mL, 8.000 mmol). The mixture was stirred for next 36 h at RT. After complete consumption of the substrate (monitored by LCMS), the crude was concentrated in vacuo and *tert*-butyl 6-chloro-3-[3-(naphthalen-1-yloxy)propyl]-1-[2-(piperidin-4-yl)ethyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate hydrochloride (52.3 mg, crude) was used in the next step without further purification.

LCMS (ESI+): m/z 655.1 $[M+H]^+$

Step C

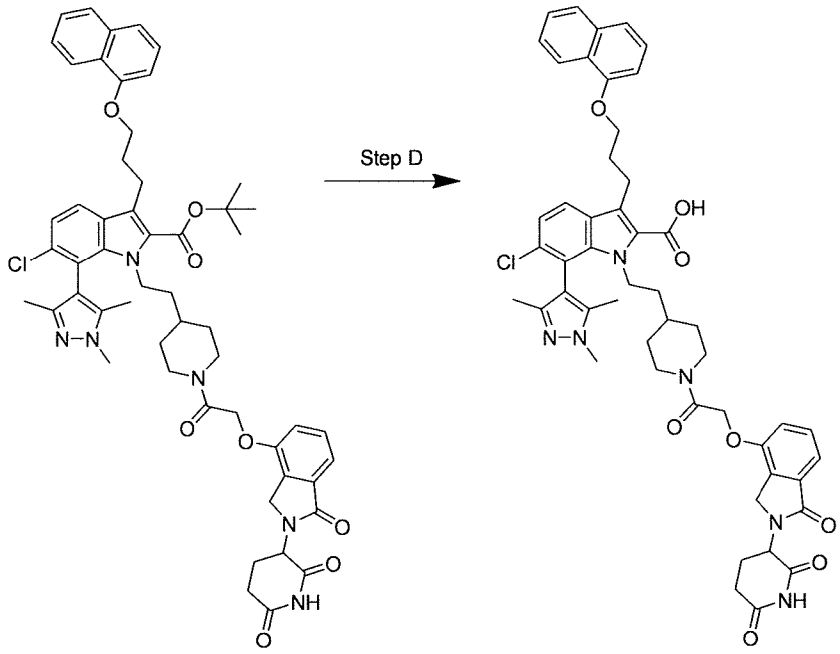


2-{4-[(2,6-Dioxopiperidin-3-yl)carbamoyl]-2-methyl-1*H*-1,3-benzodiazol-1-yl}acetic acid (14.6 mg, 0.046 mmol), *tert*-butyl 6-chloro-3-[3-(naphthalen-1-yloxy)propyl]-1-[2-(piperidin-4-yl)ethyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate hydrochloride (25.0 mg, crude) and HATU (29.0 mg, 0.076 mmol) were dissolved in dry DMF (2.0 mL) and to the mixture was added DIPEA (0.033 mL, 0.191 mmol). The reaction was stirred at RT for 30 min. The solvent was evaporated. Residues were dissolved in DCM and washed with brine. The organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. The product *tert*-butyl 6-chloro-1-{2-[1-(2-{[2-(2,6-dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1*H*-isoindol-4-yl]oxy}acetyl)piperidin-4-yl]ethyl}-3-[3-

(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (44 mg, crude) was used without further purification in the next step.

LCMS (ESI+): m/z 954.7 $[M+H]^+$

Step D



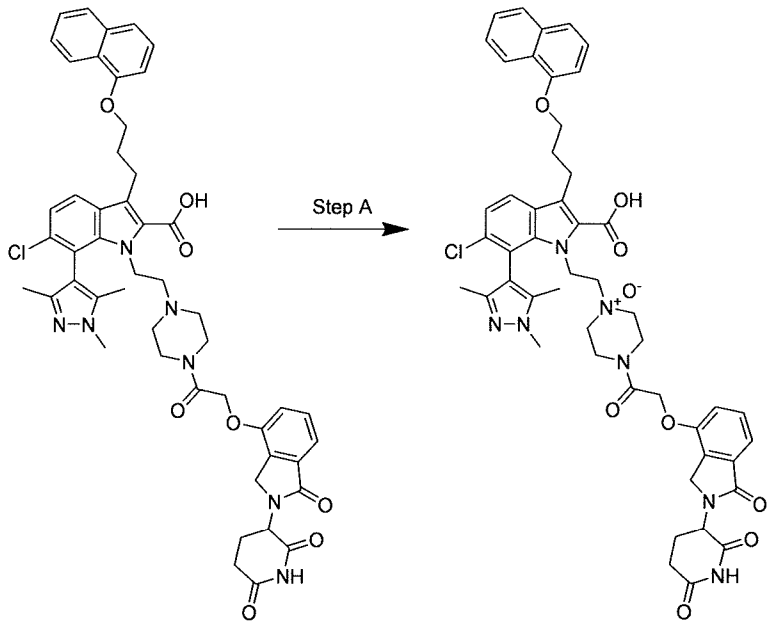
To a solution of *tert*-butyl 6-chloro-1-{2-[1-(2-{[2-(2,6-dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1*H*-isoindol-4-yl]oxy}acetyl)piperidin-4-yl]ethyl}-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (44.0 mg, crude) in DCM (1.0 mL) was added TFA (0.500 mL, 6.529 mmol). The mixture was stirred for 18h at RT. The crude was concentrated in vacuo. The residues were dissolved in DMSO and purified by preparative HPLC (H_2O:MeCN + 0.1% FA) to give 6-chloro-1-{2-[1-(2-{[2-(2,6-dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1*H*-isoindol-4-yl]oxy}acetyl)piperidin-4-yl]ethyl}-3-[3-(naphthalen-1-yloxy)propyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (7.0 mg, 0.008 mmol, 11% over 4 steps) as a white solid.

LCMS (ESI+): m/z 899.4 $[M+H]^+$

^{1}H NMR (500 MHz, DMSO) δ 12.52 (s, 1H), 10.63 (s, 1H), 8.20 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.84 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.70 (d, *J* = 8.5 Hz, 1H), 7.53 – 7.46 (m, 2H), 7.46 – 7.42 (m, 2H), 7.37 (t, *J* = 7.9 Hz, 1H), 7.33 (d, *J* = 7.5 Hz, 1H), 7.18 (dd, *J* = 11.6, 8.3 Hz, 2H), 6.90 (d, *J* = 7.7 Hz, 1H), 5.05 (dd, *J* = 13.0, 5.2 Hz, 1H), 4.90 (s, 2H), 4.45 – 4.38 (m, 1H), 4.38 – 4.31 (m, 1H), 4.24 (t, *J* = 6.3 Hz, 2H), 4.22 – 4.17 (m, 1H), 4.14 – 4.07 (m, 1H), 3.75 (d, *J* = 3.5 Hz, 3H), 3.32 – 3.26 (m, 2H), 2.93 – 2.82 (m, 4H),

2.67 – 2.60 (m, 1H), 2.48 – 2.42 (m, 2H), 2.27 – 2.20 (m, 2H), 2.09 – 2.01 (m, 2H), 2.00 (s, 3H), 1.88 (s, 3H), 1.46 – 1.36 (m, 2H), 1.25 – 1.19 (m, 1H), 1.17 – 1.07 (m, 2H).

Example 64. 1-(2-(2-carboxy-6-chloro-3-(3-(naphthalen-1-yloxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indol-1-yl)ethyl)-4-(2-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)oxy)acetyl)piperazine 1-oxide (224)



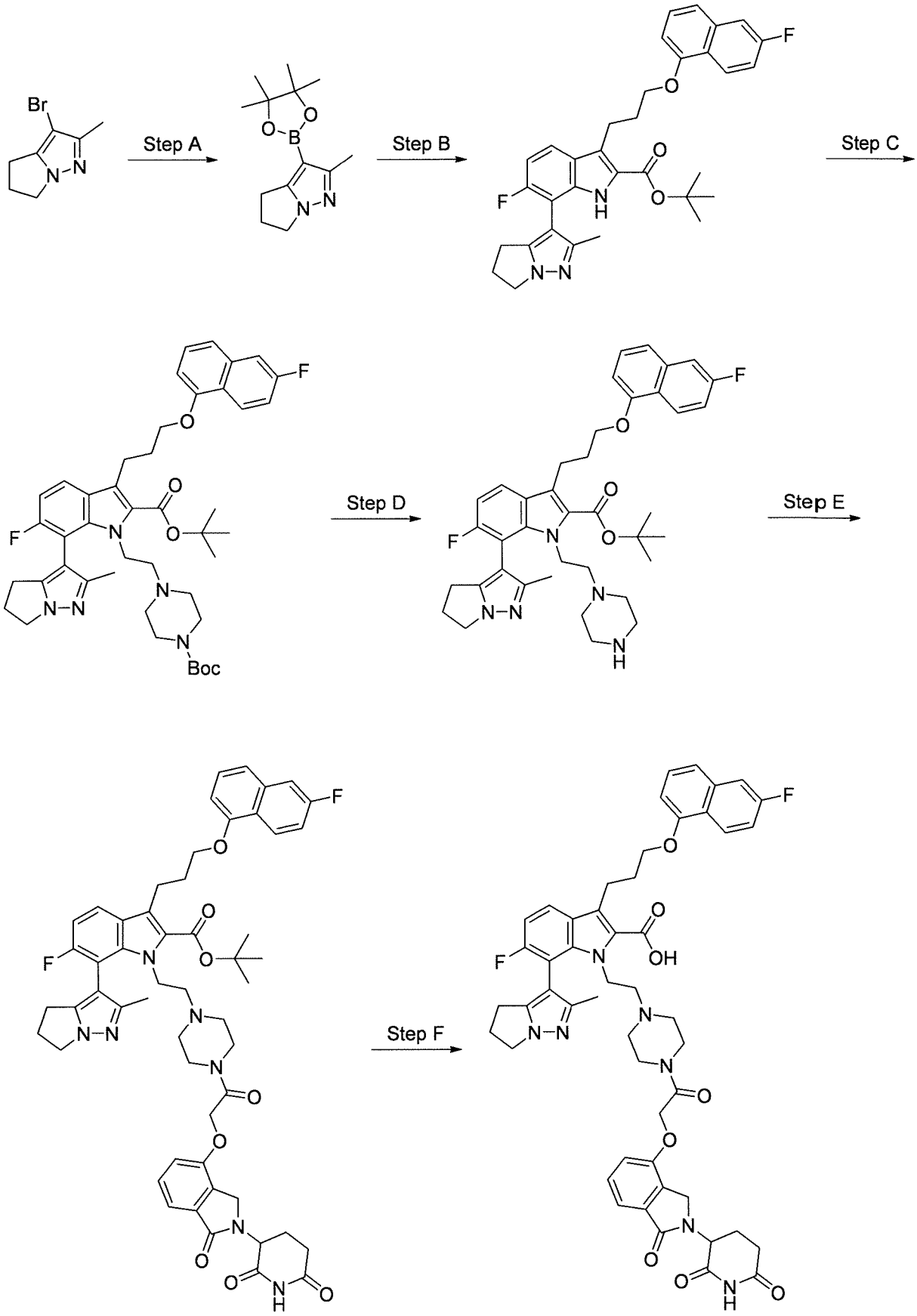
Step A

6-chloro-1-(2-(4-(2-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)oxy)acetyl)piperazin-1-yl)ethyl)-3-(3-(naphthalen-1-yloxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (5.0 mg, 0.006 mmol) was dissolved in ethyl acetate (222 µL) and the mixture was cooled down to 0°C. *m*-CPBA (1.5 mg, 0.006 mmol) was added and after 5 min mixture was filtrated through SiO_2 pad. Reaction product was washed from silica with MeOH and crude product was purified using preparative HPLC (H_2O:MeCN +0.1% FA). 1-(2-(2-carboxy-6-chloro-3-(3-(naphthalen-1-yloxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indol-1-yl)ethyl)-4-(2-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)oxy)acetyl)piperazine 1-oxide (1.3 mg, 0.001 mmol, 24.6%) was isolated as white solid.

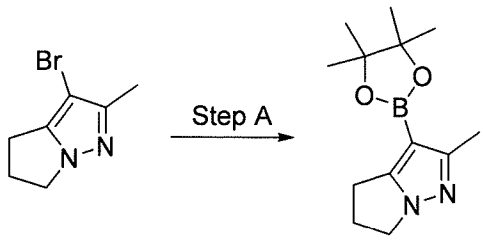
LCMS (ESI+): m/z 916.3 $[M+H]^+$

^{1}H NMR (500 MHz, DMSO) δ 10.98 (s, 1H), 8.25 – 8.15 (m, 2H), 7.90 – 7.81 (m, 1H), 7.55 – 7.47 (m, 2H), 7.47 – 7.40 (m, 2H), 7.40 – 7.28 (m, 2H), 7.21 – 7.06 (m, 2H), 6.95 – 6.85 (m, 1H), 5.11 (dd, *J* = 13.2, 5.1 Hz, 1H), 4.95 (s, 2H), 4.49 – 4.07 (m, 4H), 3.77 – 3.72 (m, 3H), 3.40 – 3.36 (m, 3H), 2.97 – 2.85 (m, 1H), 2.61 – 2.52 (m, 2H), 2.46 – 2.45 (m, 2H), 2.24 – 2.15 (m, 2H), 2.15 – 2.08 (m, 2H), 2.07 – 1.92 (m, 9H), 1.87 (d, *J* = 3.0 Hz, 3H).

Example 65. 1-(2-(4-(2-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)oxy)acetyl)piperazin-1-yl)ethyl)-6-fluoro-3-(3-((6-fluoronaphthalen-1-yl)oxy)propyl)-7-(2-methyl-5,6-dihydro-4*H*-pyrrolo[1,2-*b*]pyrazol-3-yl)-1*H*-indole-2-carboxylic acid (225)



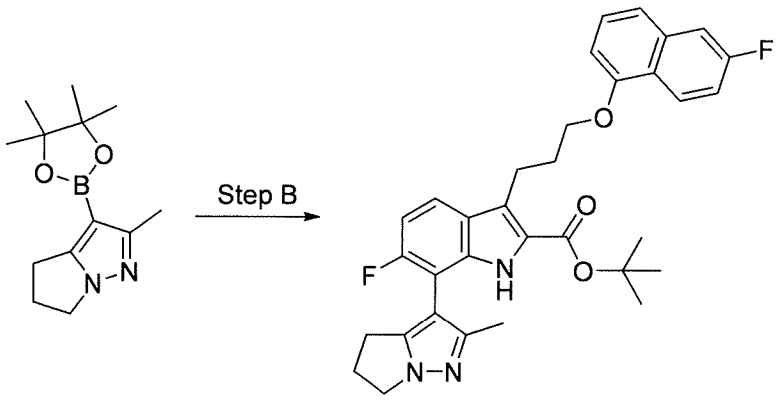
Step A



To a well stirred solution of 3-bromo-2-methyl-5,6-dihydro-4*H*-pyrrolo[1,2-*b*]pyrazole (1.2 g, 6.03 mmol) and 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.4 mL, 18.09 mmol) in THF (25 mL), was added *n*-butyllithium (1.8 M, 8 mL, 14.472 mmol) at -78 °C under argon. The resulting mixture was then allowed to stir at -78 °C for 2h. The mixture was slowly warmed to RT and was stirred for another 30 minutes. After complete consumption of the starting material (monitored by TLC and LCMS) the excess n-butyllithium was quenched by slow addition of saturated ammonium chloride solution. It was then diluted with EtOAc, washed successively with water and brine. The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to get the crude compound, which was then purified by column chromatography (SiO_2, EtOAc:hexane, 30-40%) to get 2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydro-4*H*-pyrrolo[1,2-*b*]pyrazole (650 mg, 2.62 mmol, 44%) as white sticky solid.

LCMS (ESI+): m/z 247.8 $[M+H]^+$

Step B

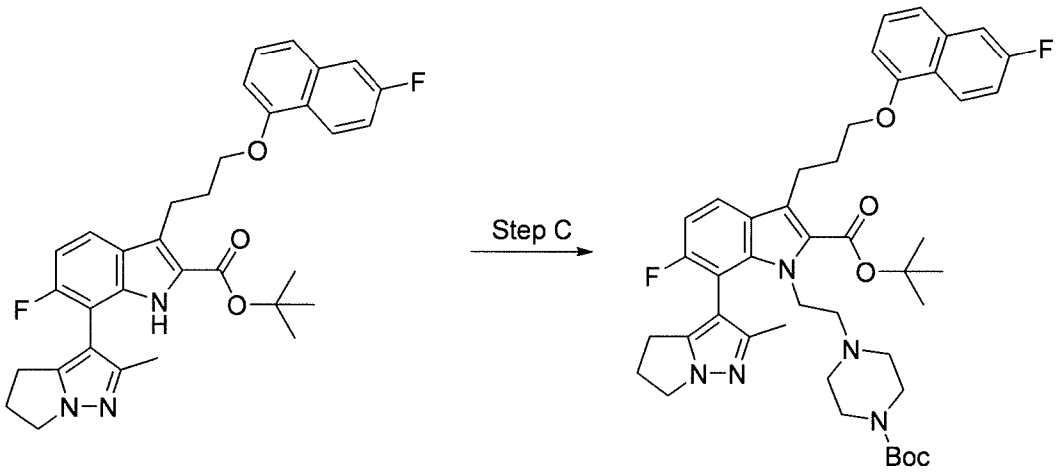


To a stirred solution of *tert*-butyl 7-bromo-6-fluoro-3-(3-((6-fluoronaphthalen-1-yl)oxy)propyl)-1*H*-indole-2-carboxylate (700 mg, 1.357 mmol) in dioxane (12 mL) and water (3 mL) were added 2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydro-4*H*-pyrrolo[1,2-*b*]pyrazole (672 mg, 2.713 mmol) followed by potassium phosphate (862 mg, 4.07 mmol). The mixture was deoxygenated with argon and to it was added [1,1'-Bis(di-*tert*-butylphosphino)ferrocene]dichloro palladium(II) (176 mg, 0.0.271 mmol) under argon atmosphere. Then the reaction mixture was heated under reflux for 16 h. After complete consumption of the starting material (monitored by

TLC and LCMS) the reaction mixture was filtered through celite pad and the filtrate was evaporated under reduced pressure get the crude material. It was then diluted with EtOAc, washed successively with water and brine, the organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to get the crude compound, which was then purified by column chromatography (SiO2, 30% EtOAc in DCM) to get *tert*-butyl 6-fluoro-3-(3-((6-fluoronaphthalen-1-yl)oxy)propyl)-7-(2-methyl-5,6-dihydro-4*H*-pyrrolo[1,2-*b*]pyrazol-3-yl)-1*H*-indole-2-carboxylate (650 mg, 1.166 mmol, 86%) as brown solid.

LCMS (ESI+): m/z 558.0 $[M+H]^+$

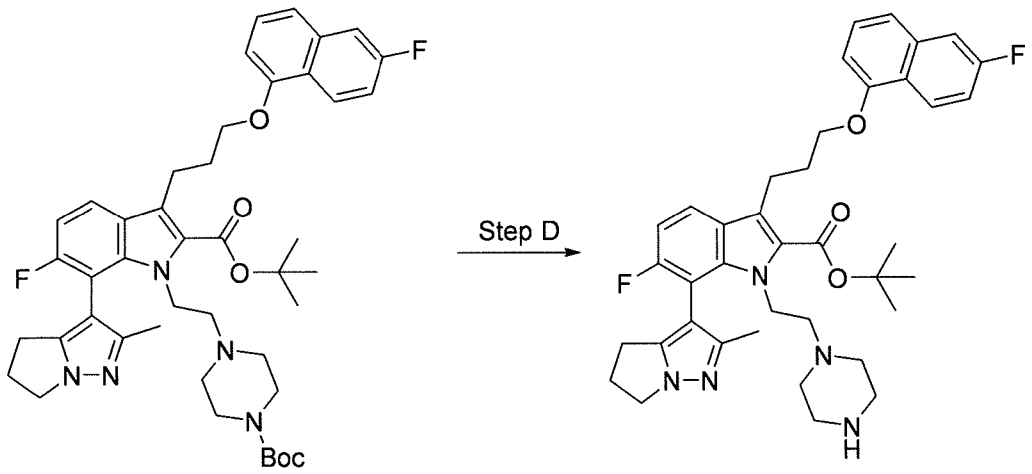
Step C



To a well stirred solution of *tert*-butyl 6-fluoro-3-(3-((6-fluoronaphthalen-1-yl)oxy)propyl)-7-(2-methyl-5,6-dihydro-4*H*-pyrrolo[1,2-*b*]pyrazol-3-yl)-1*H*-indole-2-carboxylate (650 mg, 1.167 mmol) in DMF (8 mL) was added *tert*-butyl 4-(2-chloroethyl)piperazine-1-carboxylate (377 mg, 1.517 mmol), followed by Cs_2CO_3 (568 mg, 1.75 mmol) in DMF and the mixture was allowed to stir at 90°C for 16 h under nitrogen. After complete consumption of the starting material (monitored by TLC and LCMS) the reaction mixture was diluted with EtOAc and washed successively with water and brine. The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to get the crude compound, which was then purified by column chromatography (SiO_2, 40% EtOAc in DCM) to get *tert*-butyl 1-(2-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)ethyl)-6-fluoro-3-(3-((6-fluoronaphthalen-1-yl)oxy)propyl)-7-(2-methyl-5,6-dihydro-4*H*-pyrrolo[1,2-*b*]pyrazol-3-yl)-1*H*-indole-2-carboxylate (635 mg, 0.825 mmol, 71%) as white solid.

LCMS (ESI+): m/z 770.4 $[M+H]^+$

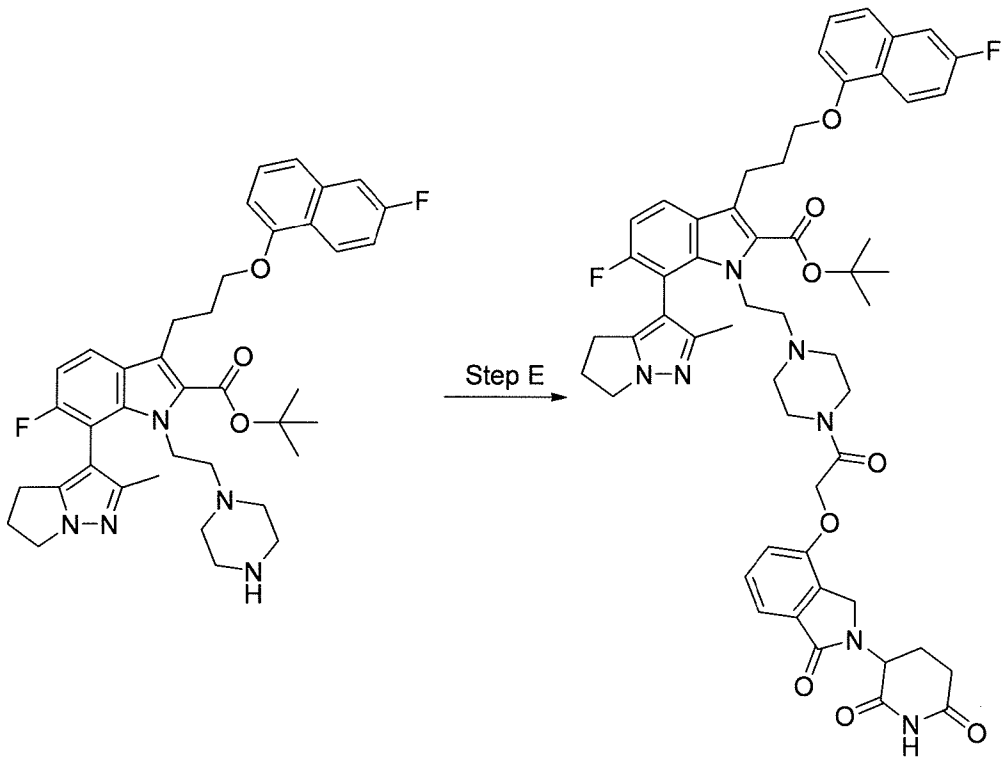
Step D



tert-butyl 1-(2-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)ethyl)-6-fluoro-3-(3-((6-fluoronaphthalen-1-yl)oxy)propyl)-7-(2-methyl-5,6-dihydro-4*H*-pyrrolo[1,2-*b*]pyrazol-3-yl)-1*H*-indole-2-carboxylate (630 mg, 0.819 mmol) was dissolved in dioxane (20 mL). To it was added 4M HCl in dioxane (10 mL) drop wise at 0°C under nitrogen and the mixture was allowed to stir for 2 h at same temperature. Whereupon LCMS indicated the reaction was complete, the reaction mixture was quenched by dropwise addition of cold 1M NaOH solution at 0°C to maintain the pH~7 to 8. The aqueous layer was extracted 2-3 times with DCM. The combined organics were dried over Na_2SO_4 and concentrated in vacuum to get the crude compound which was then purified by column chromatography (amine SiO_2, 70% EtOAc in DCM) to get *tert*-butyl 6-fluoro-3-(3-((6-fluoronaphthalen-1-yl)oxy)propyl)-7-(2-methyl-5,6-dihydro-4*H*-pyrrolo[1,2-*b*]pyrazol-3-yl)-1-(2-(piperazin-1-yl)ethyl)-1*H*-indole-2-carboxylate (343 mg, 0.512 mmol, 62%) as white solid.

LCMS (ESI+): m/z 670.5 $[M+H]^+$

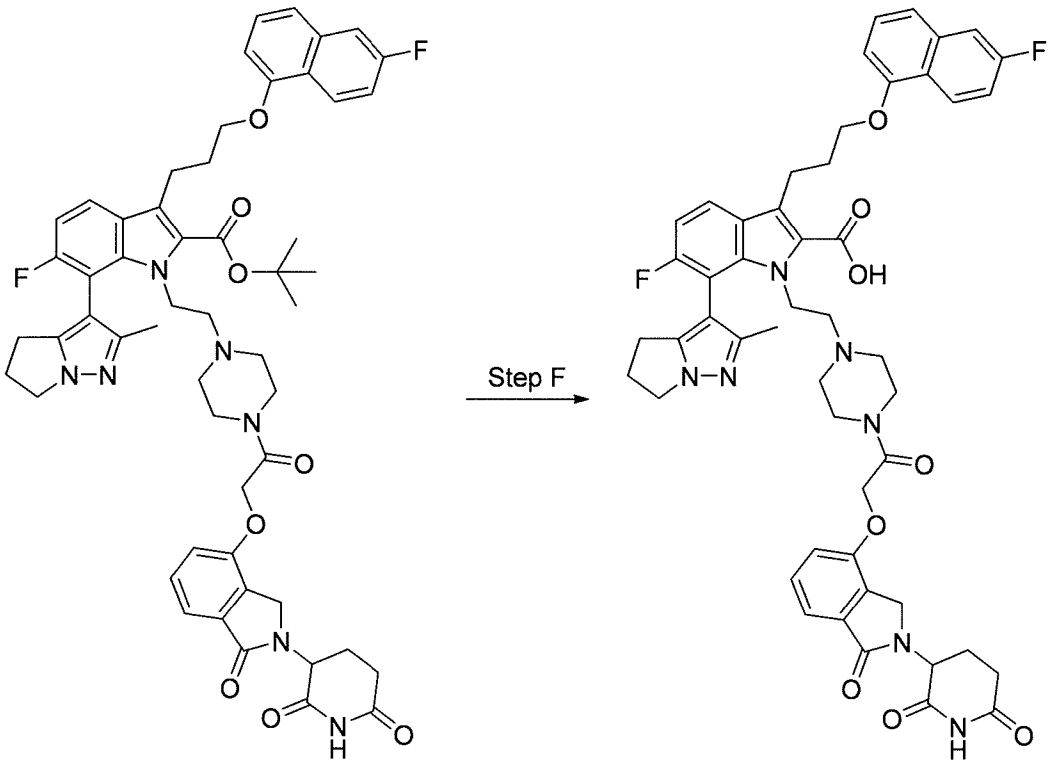
Step E



2-{[2-(2,6-dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1*H*-isoindol-4-yl]oxy}acetic acid (26.1 mg, 0.082 mmol) was dissolved in dry DMF under argon atmosphere and DIPEA (0.039 mL, 0.224 mmol) was added along with, *tert*-butyl 6-fluoro-3-(3-((6-fluoronaphthalen-1-yl)oxy)propyl)-7-(2-methyl-5,6-dihydro-4*H*-pyrrolo[1,2-*b*]pyrazol-3-yl)-1-(2-(piperazin-1-yl)ethyl)-1*H*-indole-2-carboxylate (50.0 mg, 0.075 mmol) as a solution in DMF (1 mL). Reaction mixture was cooled down to 0°C and HATU (31.2 mg, 0.082 mmol) in DMF (1 mL) was added dropwise. The reaction was allowed to slowly warm to room temperature and mixed for 15 min (monitored with LCMS) under argon atmosphere. After complete consumption of the starting material the reaction was quenched with aqueous saturated solution of $NaHCO_3$, diluted with DCM and brine. Organic layer was again washed with aqueous $NaHCO_3$, brine and water, collected and dried over anhydrous $MgSO_4$. The solution was filtrated, concentrated and dried under reduced pressure to give crude *tert*-butyl 1-(2-(4-(2-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)oxy)acetyl)piperazin-1-yl)ethyl)-6-fluoro-3-(3-((6-fluoronaphthalen-1-yl)oxy)propyl)-7-(2-methyl-5,6-dihydro-4*H*-pyrrolo[1,2-*b*]pyrazol-3-yl)-1*H*-indole-2-carboxylate (72.5 mg) as yellow oil which was used in the next step without further purification.

LCMS (ESI+): m/z 969.7 $[M+H]^+$

Step F

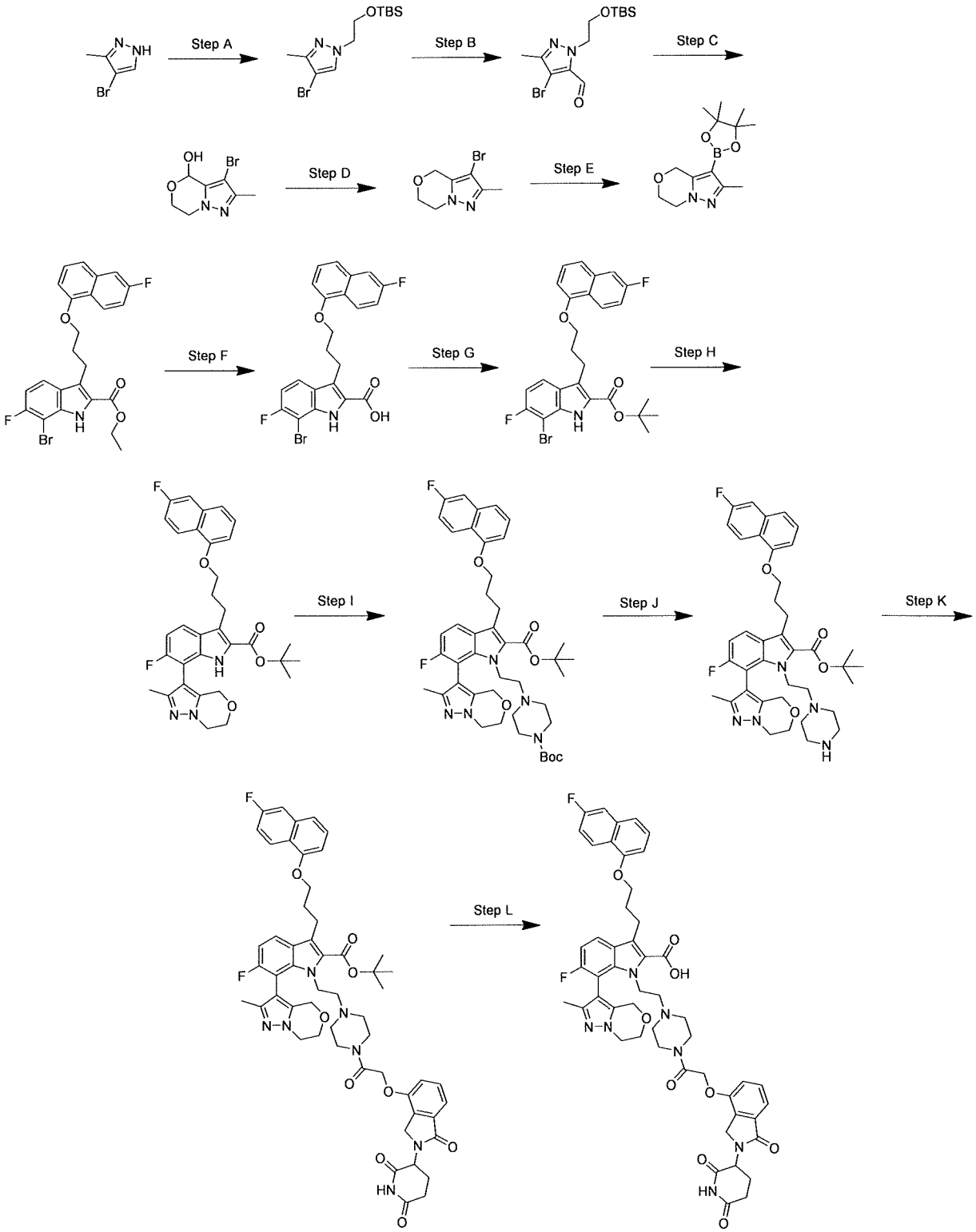


tert-butyl 1-(2-(4-(2-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)oxy)acetyl)piperazin-1-yl)ethyl)-6-fluoro-3-(3-((6-fluoronaphthalen-1-yl)oxy)propyl)-7-(2-methyl-5,6-dihydro-4*H*-pyrrolo[1,2-*b*]pyrazol-3-yl)-1*H*-indole-2-carboxylate (72.0 mg, crude) was dissolved in dry DCM (0.40 mL) under argon atmosphere and TFA (0.40 mL, 5.224 mmol) was added. The reaction (monitored with LCMS) was stirred for 18 h in room temperature under argon. After complete consumption of the starting material, reaction mixture was diluted with DCM and washed with brine and water. Solvent was evaporated under reduced pressure and dissolved in DMSO and purified with preparative HPLC (H_2O:MeCN + 0.1% FA) to give 1-(2-(4-(2-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)oxy)acetyl)piperazin-1-yl)ethyl)-6-fluoro-3-(3-((6-fluoronaphthalen-1-yl)oxy)propyl)-7-(2-methyl-5,6-dihydro-4*H*-pyrrolo[1,2-*b*]pyrazol-3-yl)-1*H*-indole-2-carboxylic acid (36.3 mg, 0.040 mmol, 53% over two steps) as white powder.

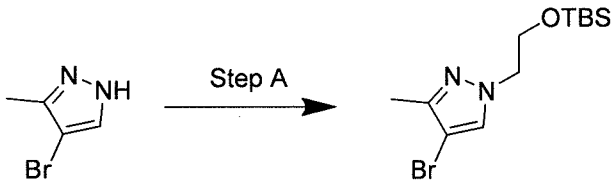
LCMS (ESI+): m/z 914.08 $[M+H]^+$

^{1}H NMR (500 MHz, DMSO, 353K) δ 12.80 (s, 1H), 10.65 (s, 1H), 8.25 (dd, *J* = 9.2, 5.8 Hz, 1H), 7.72 (dd, *J* = 8.7, 5.4 Hz, 1H), 7.60 (dd, *J* = 10.4, 2.6 Hz, 1H), 7.51 – 7.39 (m, 3H), 7.39 – 7.29 (m, 2H), 7.15 (d, *J* = 8.1 Hz, 1H), 7.04 – 6.95 (m, 1H), 6.93 – 6.84 (m, 1H), 5.06 (dd, *J* = 13.0, 5.2 Hz, 1H), 4.89 (s, 2H), 4.47 – 4.30 (m, 4H), 4.27 (t, *J* = 6.3 Hz, 2H), 4.19 – 4.04 (m, 2H), 3.39 – 3.27 (m, 6H), 2.89 (ddd, *J* = 17.2, 13.4, 5.5 Hz, 1H), 2.80 – 2.69 (m, 2H), 2.64 – 2.55 (m, 2H), 2.48 – 2.40 (m, 2H), 2.31 – 2.21 (m, 2H), 2.16 – 2.04 (m, 7H), 2.00 (s, 3H).

Example 66. 1-{2-[4-(2-{[2-(2,6-dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1*H*-isoindol-4-yl]oxy}acetyl)piperazin-1-yl]ethyl}-6-fluoro-3-{3-[(6-fluoronaphthalen-1-yl)oxy]propyl}-7-{2-methyl-4*H*,6*H*,7*H*-pyrazolo[3,2-*c*][1,4]oxazin-3-yl}-1*H*-indole-2-carboxylic acid (226)



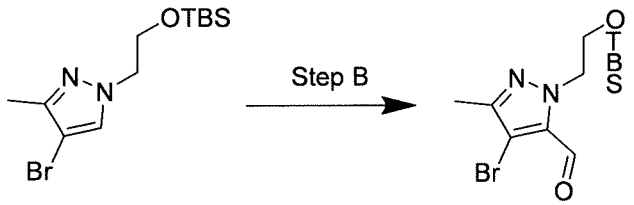
Step A



To a stirred solution of 4-bromo-3-methyl-1*H*-pyrazole (5 g, 31.1 mmol) in acetonitrile (120 mL) was added Cs_2CO_3 (15.2g, 5.10 mmol), followed by a solution of (2-bromoethoxy)-*tert*-butyldimethylsilane (0.562 mL, 3.57 mmol) in acetonitrile (30 mL) drop wise at ambient temperature under nitrogen. The reaction mixture was stirred at RT for 16 h, and then reaction mixture was filtered through Celite bed, washing with Et_2O (50 mL). The filtrate was concentrated and the resultant residue was purified by column chromatography (SiO_2, EtOAc:hexane, 0-10%) to get 4-bromo-1-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-3-methyl-1*H*-pyrazole (6 g, 18.8 mmol, 60.5%) as colorless oil.

LCMS (ESI+): m/z 319.1 $[M+H]^+$

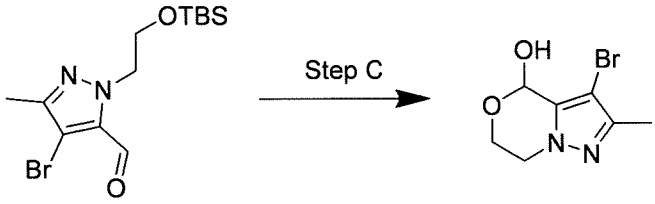
Step B



To a well stirred solution of 2M LDA (18.8 mL, 37.6 mmol) in THF was added a solution of 4-bromo-1-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-3-methyl-1*H*-pyrazole (6 g, 18.8 mmol) in THF (12 mL) drop wise at -78°C under nitrogen. The reaction mixture was allowed to stir at same temperature for 30 min. To the mixture was added a solution of DMF (2.6 ml, 33.85 mmol) in THF (10 ml) drop wise at -78°C and the resulting reaction mixture was stirred for another 1 h at same temperature. After complete consumption of the starting material the excess LDA was quenched by saturated NH_4Cl solution and the reaction mixture was diluted with EtOAc, washed successively with water and brine, the organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to get the crude compound, which was then purified by column chromatography (SiO_2, EtOAc:hexane, 5-10%) to get 4-bromo-1-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-3-methyl-1*H*-pyrazole-5-carbaldehyde (3 g, 8.64 mmol, 46%) as white sticky solid.

LCMS (ESI+): m/z 349.0 $[M+H]^+$

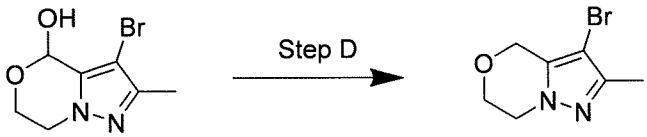
Step C



To a stirred solution of 4-bromo-1-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-3-methyl-1*H*-pyrazole-5-carbaldehyde (3 g, 8.64 mmol) in 2-methyl THF (15 mL) and water (15 mL) was added TFA (30 mL) dropwise at RT under nitrogen. The reaction mixture was allowed to stir at RT for 1 h. After complete consumption of the starting material the volatiles were evaporated under reduced pressure, crude mixture was diluted with EtOAc, washed successively with saturated $NaHCO_3$ solution, water and brine, the organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to get 4 g of crude 3-bromo-2-methyl-6,7-dihydro-4*H*-pyrazolo[5,1-*c*][1,4]oxazin-4-ol as white solid which was then directly used for next step without further purification.

LCMS (ESI+): m/z 234.8 $[M+H]^+$

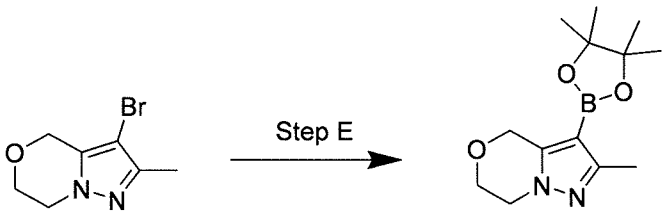
Step D



To a well stirred solution of crude 3-bromo-2-methyl-6,7-dihydro-4*H*-pyrazolo[5,1-*c*][1,4]oxazin-4-ol (3 g, 12.8 mmol) in DCM (50 mL) was added TFA (8.8 mL, 77.2 mmol), and Et_3SiH (4.48 mL, 38.6 mmol) successively at 0°C under nitrogen. The reaction mixture was allowed to stir at 0°C for 1h. After that again TFA (4.4 mL, 38.6 mmol), and Et_3SiH (2.3 mL, 19.4 mmol) were added successively and it was stirred for 16h at RT. After complete consumption of starting material (monitored by TLC and LCMS) the reaction mixture was evaporated under reduced pressure to get the crude, which was diluted with DCM, washed successively with saturated $NaHCO_3$ solution and brine. The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to get the crude compound, which was then purified by column chromatography (SiO2, EtOAc:hexane, 30-40%) to get 3-bromo-2-methyl-

6,7-dihydro-4*H*-pyrazolo[5,1-*c*][1,4]oxazine (800 mg, 3.68 mmol, 42% over two steps) as off white sticky solid.

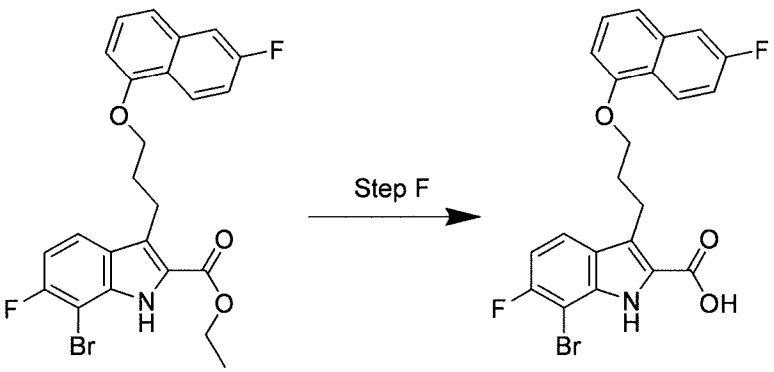
Step E



To a well stirred solution of 3-bromo-2-methyl-6,7-dihydro-4*H*-pyrazolo[5,1-*c*][1,4]oxazine (1.2 g, 5.6 mmol) and 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.2 mL, 16.7 mmol) in THF (120 mL), was added n-butyllithium (1.7 M, 7.9 mL, 13.4 mmol) at -78 °C under argon. The resulting mixture was then allowed to stir at -78 °C for 2h. The mixture was slowly warmed to RT and was stirred for another 30 min. After complete consumption of the starting material (monitored by TLC and LCMS) the excess n-butyllithium was quenched by addition of saturated NH_4Cl and it was diluted with EtOAc, washed successively with water and brine. The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to get the crude compound, which was then purified by column chromatography (SiO2, EtOAc:hexane, 10-20%) to get 2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6,7-dihydro-4*H*-pyrazolo[5,1-*c*][1,4]oxazine (610 mg, 2.31 mmol, 41%) as white sticky solid.

LCMS (ESI+): m/z 265.1 $[M+H]^+$

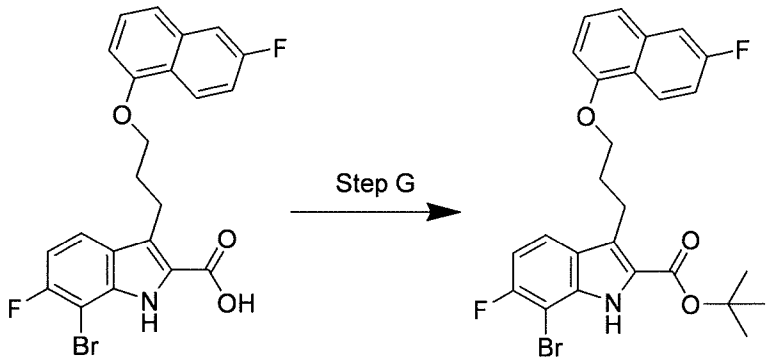
Step F



Ethyl 7-bromo-6-fluoro-3-(3-((6-fluoronaphthalen-1-yl)oxy)propyl)-1*H*-indole-2-carboxylate (3.3 g, 6.8 mmol) was dissolved in EtOH (40 mL) and a solution of NaOH (1.3 g, 33.9 mmol) in water (6 mL) was added to it. The mixture was heated under reflux for 16 h. After complete consumption of the starting material (monitored by TLC and LCMS) the reaction mixture was cooled down to room temperature. The solvents were evaporated under reduced pressure to get the crude reaction mixture. It was then diluted with water, extracted with EtOAc. Aqueous layer was carefully acidified using 1 (N) HCl to pH=3, extracted with DCM (3x), dried over Na_2SO_4, filtered, and concentrated in vacuo to afford 7-bromo-6-fluoro-3-(3-((6-fluoronaphthalen-1-yl)oxy)propyl)-1*H*-indole-2-carboxylic acid (2.8 g, 6.1 mmol, 90%) as brown solid.

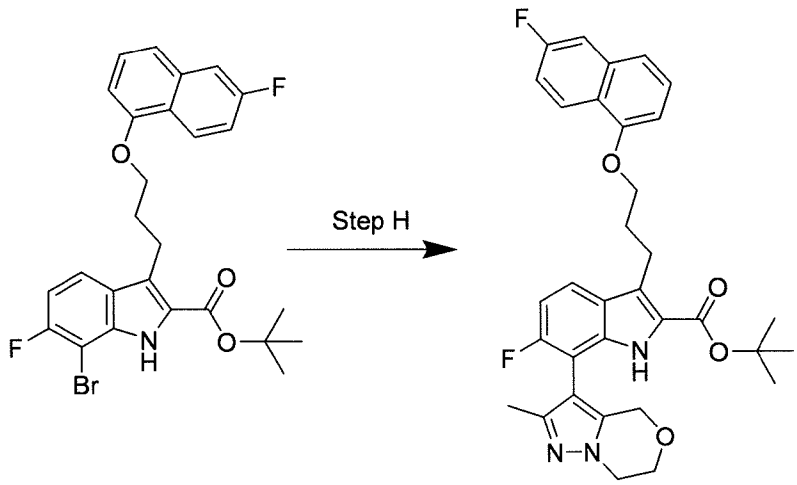
LCMS (ESI+): m/z 458.2 $[M+H]^+$

Step G



7-bromo-6-fluoro-3-(3-((6-fluoronaphthalen-1-yl)oxy)propyl)-1*H*-indole-2-carboxylic acid (2.8 g, 6.1 mmol) was suspended in toluene (40 mL) and the mixture was heated to reflux under nitrogen. *N,N*-dimethylformamide di-*tert*-butyl acetal (9.9 mL, 48.8 mmol) was added drop wise to the refluxing mixture and stirred for an additional 16 h under nitrogen. After 16 h next 4.9 mL (24.4 mmol) of *N,N*-dimethylformamide di-*tert*-butyl acetal was added to it and the reaction was continued for another 8 h. After complete consumption of the stating material (monitored by TLC and LCMS) reaction mixture was diluted with EtOAc, washed successively with $NaHCO_3$ (sat), water and brine. The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to get the crude compound, which was then purified by column chromatography (SiO_2, 10% EtOAc in DCM) to get *tert*-butyl 7-bromo-6-fluoro-3-(3-((6-fluoronaphthalen-1-yl)oxy)propyl)-1*H*-indole-2-carboxylate (2.4 g, 4.65 mmol, 76.19%) as brown gummy solid.

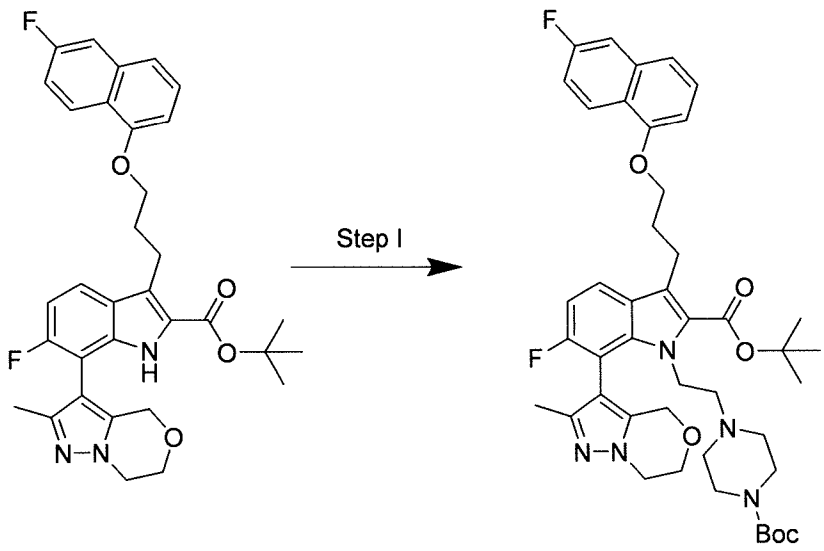
Step H



To a stirred solution of *tert*-butyl 7-bromo-6-fluoro-3-(3-((6-fluoronaphthalen-1-yl)oxy)propyl)-1*H*-indole-2-carboxylate (600 mg, 1.2 mmol) in dioxane (8 mL) and water (2 mL) were added 2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6,7-dihydro-4*H*-pyrazolo[5,1-*c*][1,4]oxazine (613 mg, 2.3 mmol) followed by potassium phosphate (739 mg, 3.5 mmol).The mixture was deoxygenated with argon and to it was added [1,1'-bis(di-*tert*-butylphosphino)ferrocene]dichloropalladium(II) (151 mg, 0.233 mmol) under argon atmosphere. Then the reaction mixture was heated under reflux for 16 h. After complete consumption of the starting material (monitored by TLC and LCMS) the reaction mixture was filtered over Celite pad and the solvents were evaporated under reduced pressure. The residues were diluted with EtOAc, washed successively with water and brine. The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to get the crude compound, which was then purified by column chromatography (SiO_2, 30% EtOAc in DCM) to get *tert*-butyl 6-fluoro-3-(3-((6-fluoronaphthalen-1-yl)oxy)propyl)-7-(2-methyl-6,7-dihydro-4*H*-pyrazolo[5,1-*c*][1,4]oxazin-3-yl)-1*H*-indole-2-carboxylate (550 mg, 0.958 mmol, 82%) as brown solid.

LCMS (ESI+): m/z 574.0 $[M+H]^+$

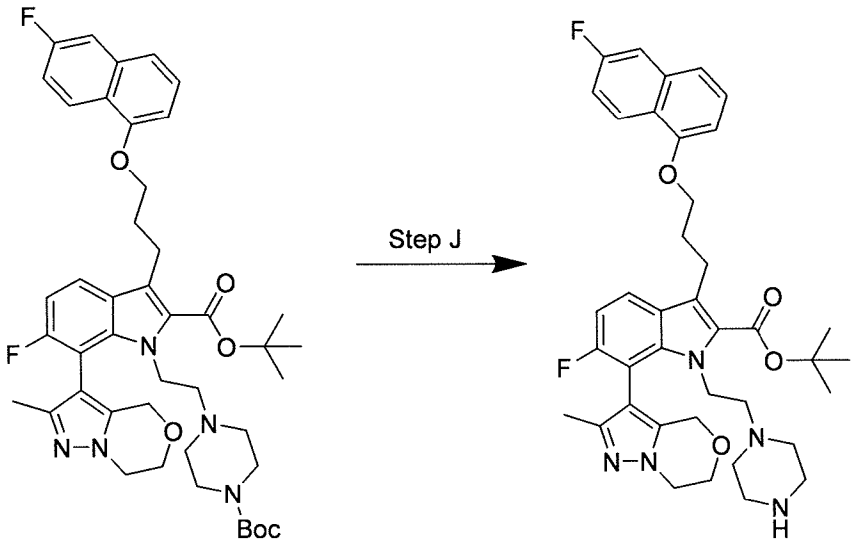
Step I



To a well stirred solution of get *tert*-butyl 6-fluoro-3-(3-((6-fluoronaphthalen-1-yl)oxy)propyl)-7-(2-methyl-6,7-dihydro-4*H*-pyrazolo[5,1-*c*][1,4]oxazin-3-yl)-1*H*-indole-2-carboxylate (550 mg, 0.96 mmol) in DMF (6 mL) was added *tert*-butyl 4-(2-chloroethyl)piperazine-1-carboxylate (309 mg, 1.25 mmol) followed by Cs_2CO_3 (467 mg, 1.4 mmol) in DMF (5 mL) and the mixture was allowed to stir at 90°C for 16 h under nitrogen. After complete consumption of the starting material (monitored by TLC and LCMS) the reaction mixture was diluted with EtOAc, washed successively with water and brine. The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to get the crude compound, which was then purified by column chromatography (SiO_2, 40% EtOAc in DCM) to get *tert*-butyl 1-(2-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)ethyl)-6-fluoro-3-(3-((6-fluoronaphthalen-1-yl)oxy)propyl)-7-(2-methyl-6,7-dihydro-4*H*-pyrazolo[5,1-*c*][1,4]oxazin-3-yl)-1*H*-indole-2-carboxylate (520 mg, 0.662 mmol, 69%) as white solid.

LCMS (ESI+): m/z 786.4 $[M+H]^+$

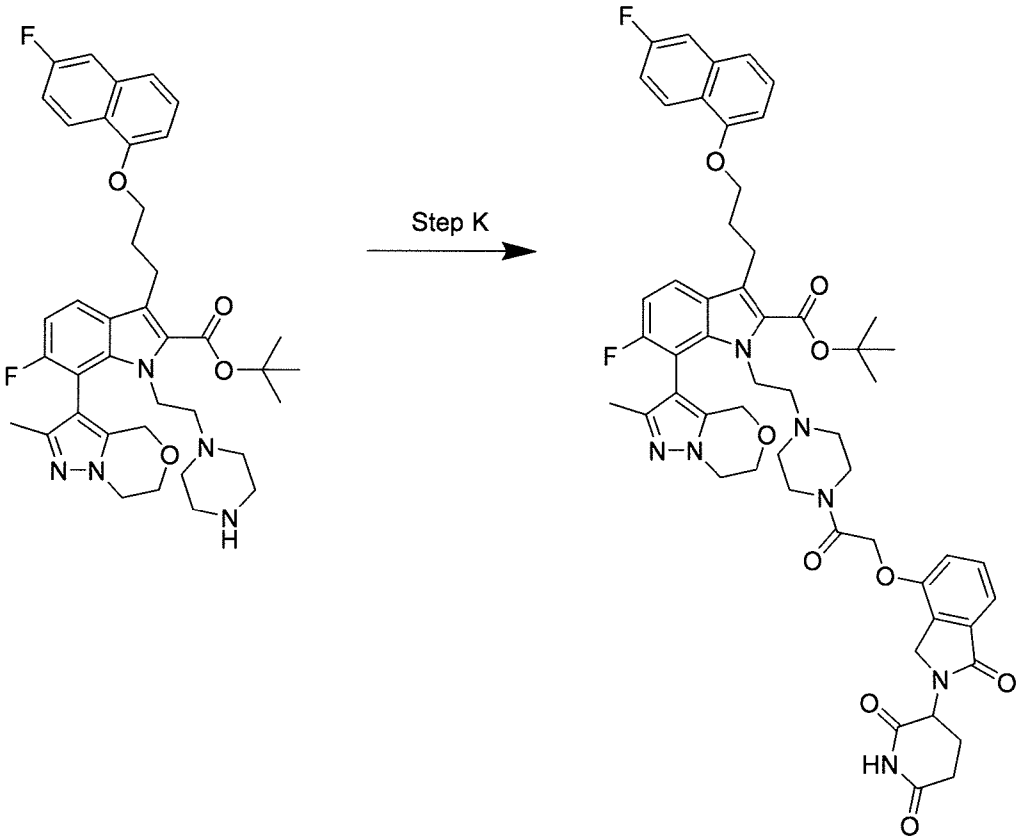
Step J



To a solution of *tert*-butyl 1-(2-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)ethyl)-6-fluoro-3-(3-((6-fluoronaphthalen-1-yl)oxy)propyl)-7-(2-methyl-6,7-dihydro-4*H*-pyrazolo[5,1-*c*][1,4]oxazin-3-yl)-1*H*-indole-2-carboxylate (520 mg, 0.662 mmol) in DCM (20 mL) was added 4 (M) HCl in dioxane (10 mL) drop wise at 0°C and the mixture was allowed to stir for 2 h under nitrogen at same temperature. After complete consumption of the starting material (monitored by TLC and LCMS), the reaction mixture was quenched by drop wise addition of cold 1M NaOH solution at 0°C to maintain the pH~7 to 8. The aqueous layer was extracted with DCM (3x). The combined organics layers were dried over Na_2SO_4 and concentrated in vacuo to get the crude compound which was then purified by column chromatography (amine SiO2, 70% EtOAc in DCM) to get *tert*-butyl 6-fluoro-3-(3-((6-fluoronaphthalen-1-yl)oxy)propyl)-7-(2-methyl-6,7-dihydro-4*H*-pyrazolo[5,1-*c*][1,4]oxazin-3-yl)-1-(2-(piperazin-1-yl)ethyl)-1*H*-indole-2-carboxylate (190 mg, 0.277 mmol, 42.92%) as white solid.

LCMS (ESI+): m/z 686.5 $[M+H]^+$

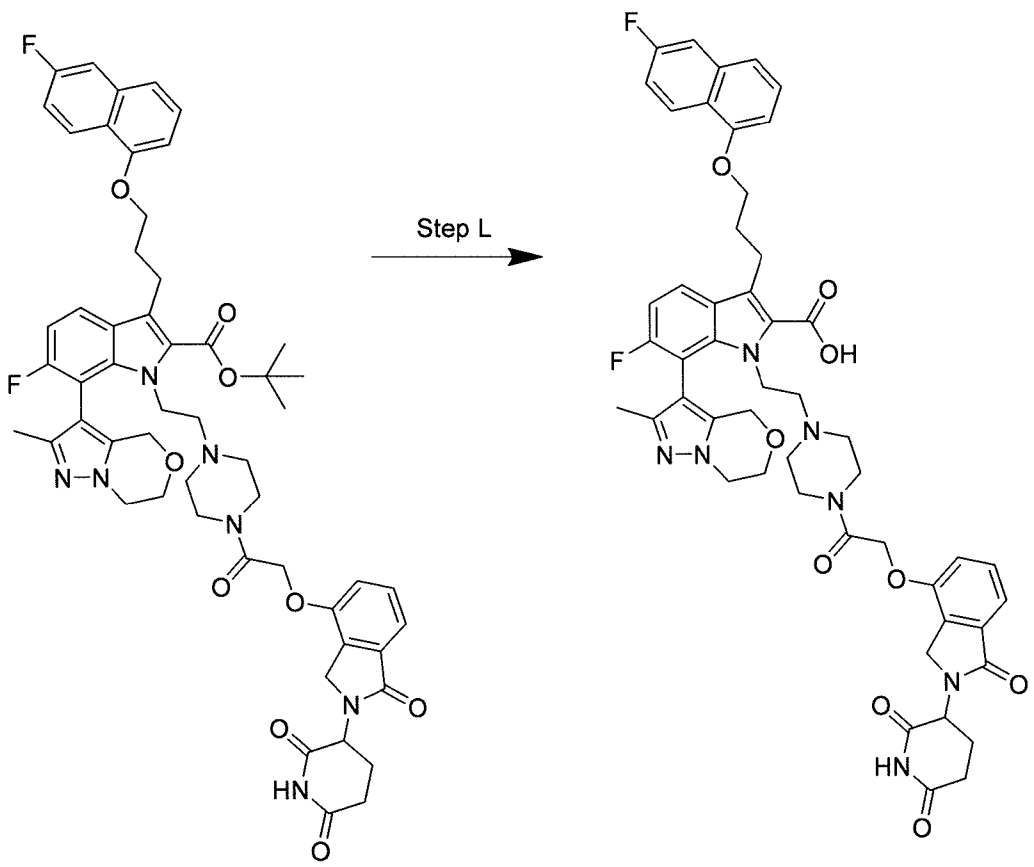
Step K



To a well stirred solution of 2-{[2-(2,6-dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1*H*-isoindol-4-yl]oxy}acetic acid (27.8 mg, 0.087 mmol) and *tert*-butyl 6-fluoro-3-(3-((6-fluoronaphthalen-1-yl)oxy)propyl)-7-(2-methyl-6,7-dihydro-4*H*-pyrazolo[5,1-*c*][1,4]oxazin-3-yl)-1-(2-(piperazin-1-yl)ethyl)-1*H*-indole-2-carboxylate (50.0 mg, 0.073 mmol) in DMF (2.0 mL) was added DIPEA (0.063 mL, 0.365 mmol) and HATU (55.4 mg, 0.146 mmol) and the mixture was allowed to stir under nitrogen for 1 h at RT. After complete consumption of the starting material (monitored by LCMS), then the reaction mixture diluted with DCM and washed twice with brine. Organic layer was dried over $MgSO_4$ and evaporated under reduced pressure. The product *tert*-butyl 1-(2-(4-(2-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)oxy)acetyl)piperazin-1-yl)ethyl)-6-fluoro-3-(3-((6-fluoronaphthalen-1-yl)oxy)propyl)-7-(2-methyl-6,7-dihydro-4*H*-pyrazolo[5,1-*c*][1,4]oxazin-3-yl)-1*H*-indole-2-carboxylate (55.0 mg, crude) was obtained as brown oil, which was used for the next step without further purification.

LCMS (ESI+): m/z 985.6 $[M+H]^+$

Step L



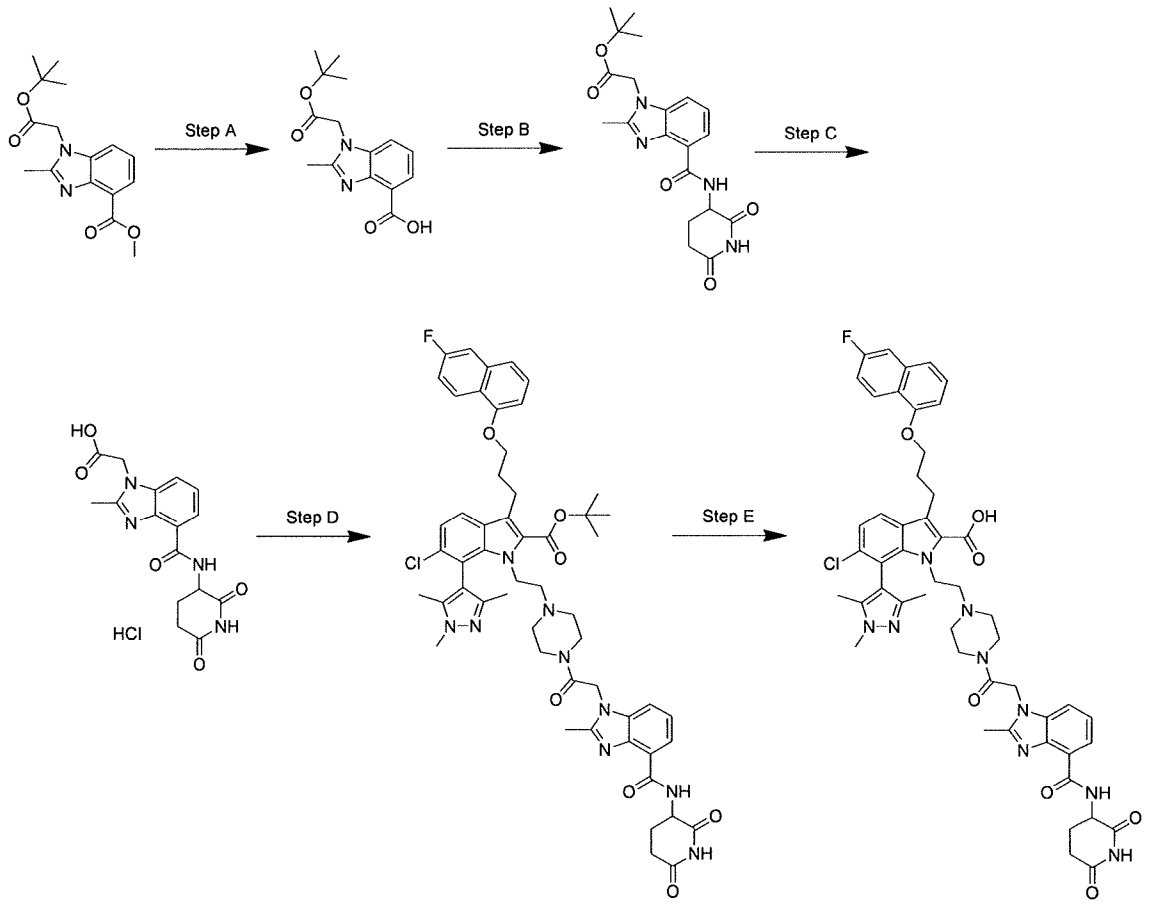
To a 55.0 mg crude *tert*-butyl 1-(2-(4-(2-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)oxy)acetyl)piperazin-1-yl)ethyl)-6-fluoro-3-(3-((6-fluoronaphthalen-1-yl)oxy)propyl)-7-(2-methyl-6,7-dihydro-4*H*-pyrazolo[5,1-*c*][1,4]oxazin-3-yl)-1*H*-indole-2-carboxylate was added dry DCM (0.500 mL) followed by TFA (0.5 mL, 6.529 mmol) and a mixture was stirred for 18 h at RT. After a reaction was completed (monitored by LCMS), solvents were evaporated and residues were dissolved in DMSO and purified by preparative HPLC (H_2O:MeCN + 0.1% FA) to give 1-(2-(4-(2-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)oxy)acetyl)piperazin-1-yl)ethyl)-6-fluoro-3-(3-((6-fluoronaphthalen-1-yl)oxy)propyl)-7-(2-methyl-6,7-dihydro-4*H*-pyrazolo[5,1-*c*][1,4]oxazin-3-yl)-1*H*-indole-2-carboxylic acid (26.2 mg, 0.028 mmol, 50.5%) as a white solid.

LCMS (ESI+): m/z 930.3 $[M+H]^+$

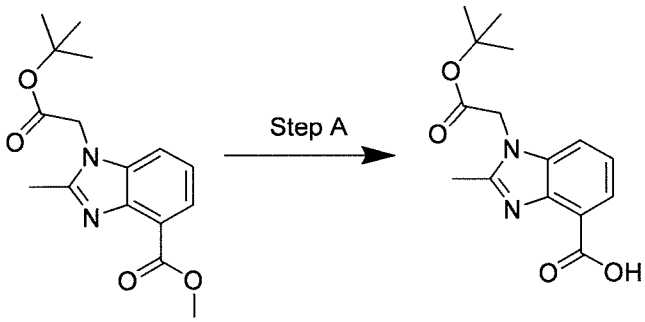
^{1}H NMR (500 MHz, DMSO) δ 13.27 (s, 1H), 10.96 (s, 1H), 8.23 (dd, *J* = 9.2, 5.9 Hz, 1H), 7.76 (dd, *J* = 8.7, 5.4 Hz, 1H), 7.64 (dd, *J* = 10.4, 2.7 Hz, 1H), 7.46 – 7.40 (m, 3H), 7.36 (td, *J* = 8.9, 2.7 Hz, 1H), 7.31 (d, *J* = 7.4 Hz, 1H), 7.10 (d, *J* = 8.2 Hz, 1H), 7.02 (t, *J* = 9.2 Hz, 1H), 6.87 (p, *J* = 4.8 Hz, 1H), 5.10 (dd, *J* = 13.3, 5.1 Hz, 1H), 4.98 – 4.88 (m, 2H), 4.56 (s, 2H), 4.46 – 4.33 (m, 2H), 4.29 – 4.04 (m, 8H), 3.29 – 3.24 (m,

4H), 2.90 (ddd, *J* = 17.3, 13.6, 5.5 Hz, 1H), 2.62 – 2.52 (m, 2H), 2.47 – 2.39 (m, 1H), 2.20 (p, *J* = 6.3 Hz, 2H), 2.13 – 1.93 (m, 11H).

Example 67. 6-chloro-1-{2-[4-(2-{4-[(2,6-dioxopiperidin-3-yl)carbamoyl]-2-methyl-1*H*-1,3-benzodiazol-1-yl}acetyl)piperazin-1-yl]ethyl}-3-{3-[(6-fluoronaphthalen-1-yl)oxy]propyl}-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (268)



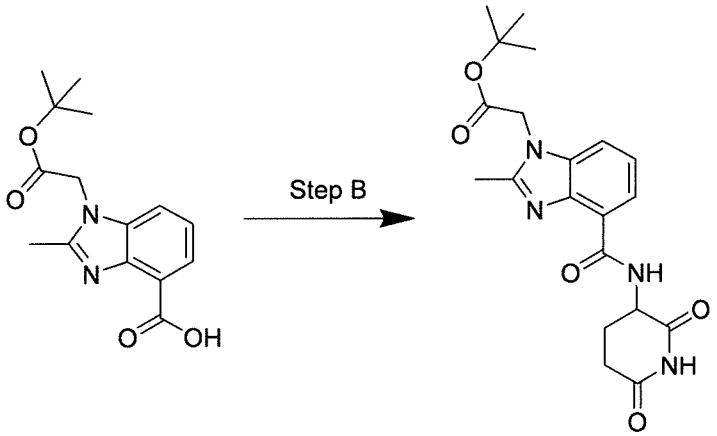
Step A



To a solution of methyl 1-[2-(*tert*-butoxy)-2-oxoethyl]-2-methyl-1*H*-1,3-benzodiazole-4-carboxylate (152.0 mg, 0.499 mmol) in H_2O (0.500 mL) and MeCN (5.0 mL) was added LiBr (867.4 mg, 9.989 mmol) and Et_3N (0.695 mL, 4.994 mmol). The mixture was stirred for 4 days at RT. The crude was concentrated in vacuo and purified by reverse phase flash chromatography (H_2O:MeCN + 0.1% FA) to get 1-[2-(*tert*-butoxy)-2-oxoethyl]-2-methyl-1*H*-1,3-benzodiazole-4-carboxylic acid (75.0 mg, 0.233 mmol, 47%) as a yellow solid.

LCMS (ESI+): m/z 291.0 $[M+H]^+$

Step B

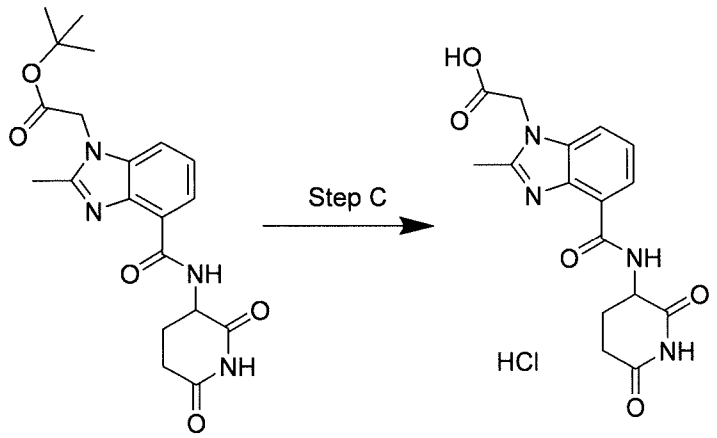


To a solution of 1-[2-(*tert*-butoxy)-2-oxoethyl]-2-methyl-1*H*-1,3-benzodiazole-4-carboxylic acid (100.0 mg, 0.344 mmol) and 3-aminopiperidine-2,6-dione hydrochloride (68.0 mg, 0.413 mmol) in dry DMF (2.0 mL) was added DIPEA (0.300 mL, 1.722 mmol) and HATU (196.5 mg, 0.517 mmol). The mixture was stirred for 18 h at RT. After this time, the crude was concentrated in vacuo and the residues were dissolved in DCM and purified by flash chromatography (SiO_2, MeOH:DCM, 0-50%) to

isolate *tert*-butyl 2-{4-[(2,6-dioxopiperidin-3-yl)carbamoyl]-2-methyl-1*H*-1,3-benzodiazol-1-yl}acetate (74.0 mg, 0.185 mmol, 54%) as a yellow solid.

LCMS (ESI+): m/z 401.1 $[M+H]^+$

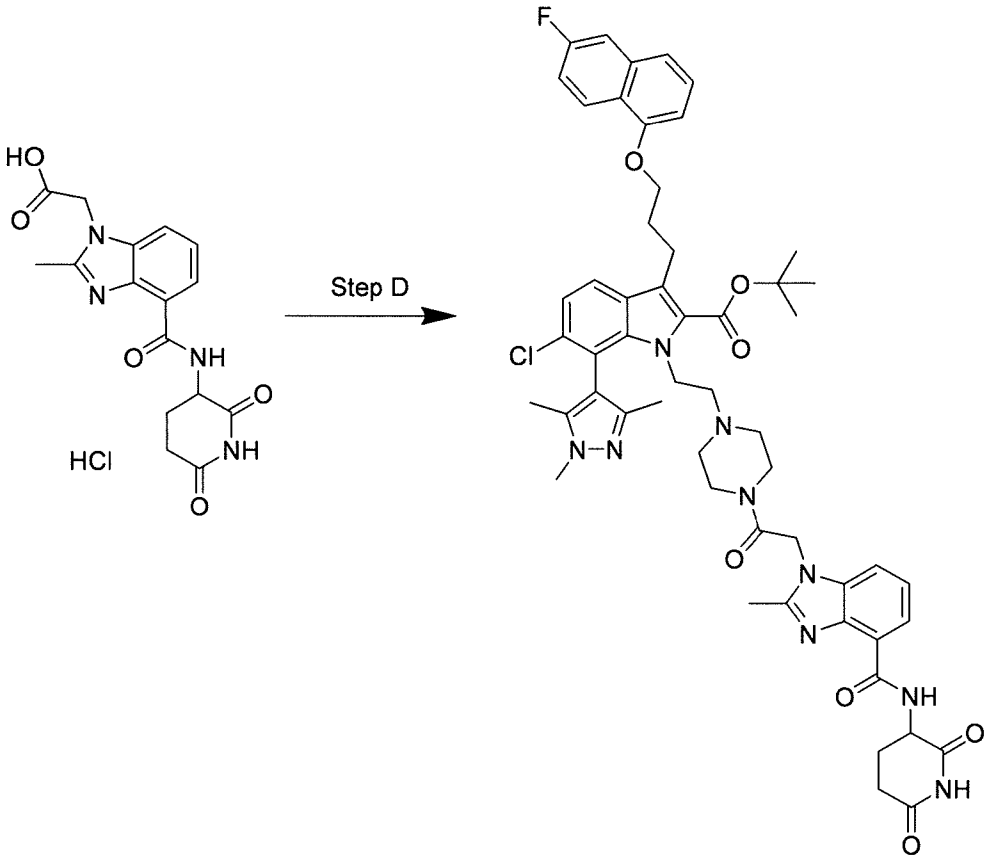
Step C



To a solution of *tert*-butyl 2-{4-[(2,6-dioxopiperidin-3-yl)carbamoyl]-2-methyl-1*H*-1,3-benzodiazol-1-yl}acetate (64.5 mg, 0.161 mmol) in DCM (2.0 mL) was added TFA (1.0 mL, 13.059 mmol). The mixture was stirred for 18 h at RT. The crude was concentrated in vacuo and dissolved in H_2O. To the solution was added 1M HCl in water and it was evaporated. The product, 2-{4-[(2,6-dioxopiperidin-3-yl)carbamoyl]-2-methyl-1H-1,3-benzodiazol-1-yl}acetic acid hydrochloride (58.8 mg, 0.154 mmol, 96%) was isolated as beige solid.

LCMS (ESI+): m/z 344.8 $[M+H]^+$

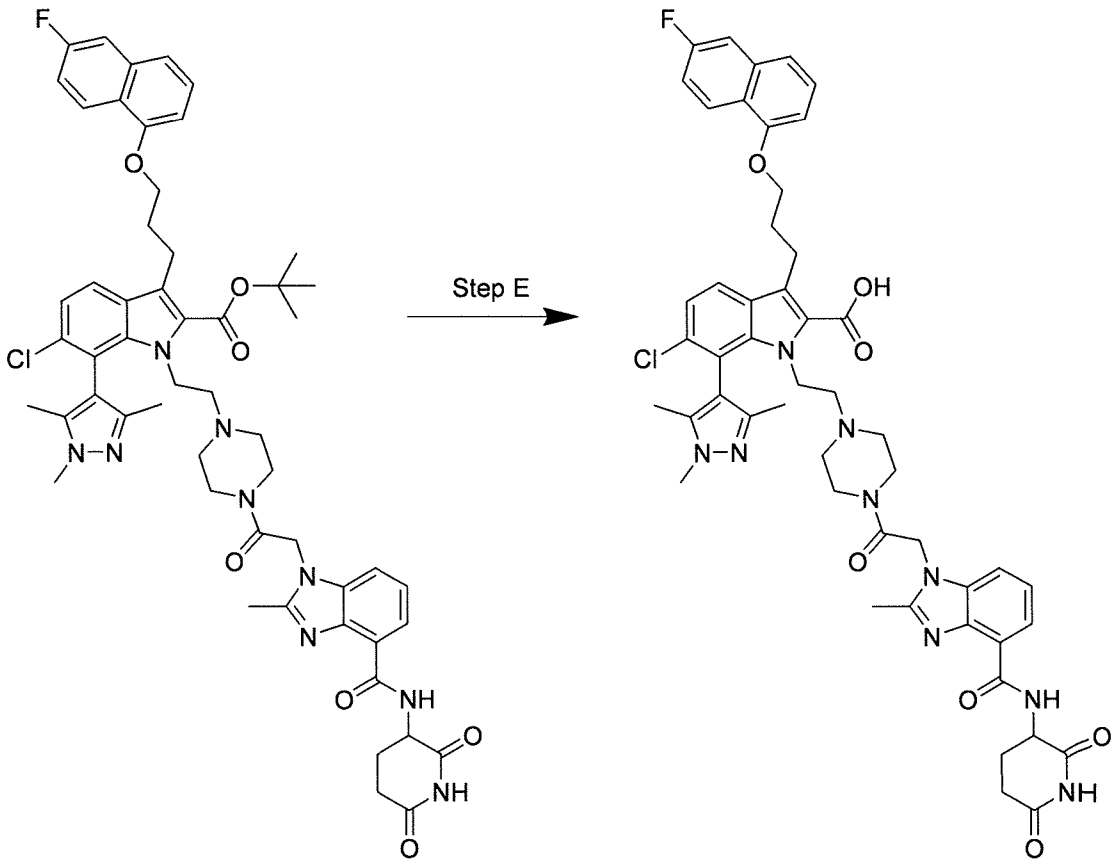
Step D



2-{4-[(2,6-Dioxopiperidin-3-yl)carbamoyl]-2-methyl-1*H*-1,3-benzodiazol-1-yl}acetic acid hydrochloride (37.3 mg, 0.098 mmol), *tert*-butyl 6-chloro-3-{3-[(6-fluoronaphthalen-1-yl)oxy]propyl}-1-[2-(piperazin-1-yl)ethyl]-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (55.0 mg, 0.082 mmol) and HATU (62.0 mg, 0.163 mmol) were dissolved in dry DMF (2.0 mL) and to the mixture was added DIPEA (0.071 mL, 0.408 mmol). The reaction was stirred at RT for 2 h. The solvent was evaporated. Residues were dissolved in DCM and washed with brine. The organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo to get *tert*-butyl 6-chloro-1-{2-[4-(2-{4-[(2,6-dioxopiperidin-3-yl)carbamoyl]-2-methyl-1*H*-1,3-benzodiazol-1-yl}acetyl)piperazin-1-yl]ethyl}-3-{3-[(6-fluoronaphthalen-1-yl)oxy]propyl}-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (102.2 mg, crude) which was used without a further purification to next step.

LCMS (ESI+): m/z 1001.3 $[M+H]^+$

Step E



To a solution of *tert*-butyl 6-chloro-1-{2-[4-(2-{4-[(2,6-dioxopiperidin-3-yl)carbamoyl]-2-methyl-1*H*-1,3-benzodiazol-1-yl}acetyl)piperazin-1-yl]ethyl}-3-{3-[(6-fluoronaphthalen-1-yl)oxy]propyl}-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylate (102.2 mg, crude) in DCM (1.0 mL) was added TFA (0.500 mL, 6.529 mmol). The mixture was stirred for 18 h at RT. The crude was concentrated in vacuo and purified by preparative HPLC (H_2O:MeCN + 0.1% FA) to give 6-chloro-1-{2-[4-(2-{4-[(2,6-dioxopiperidin-3-yl)carbamoyl]-2-methyl-1*H*-1,3-benzodiazol-1-yl}acetyl)piperazin-1-yl]ethyl}-3-{3-[(6-fluoronaphthalen-1-yl)oxy]propyl}-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (32.3 mg, 0.034 mmol, 35%) as a white solid.

LCMS (ESI+): m/z 944.3 $[M+H]^+$

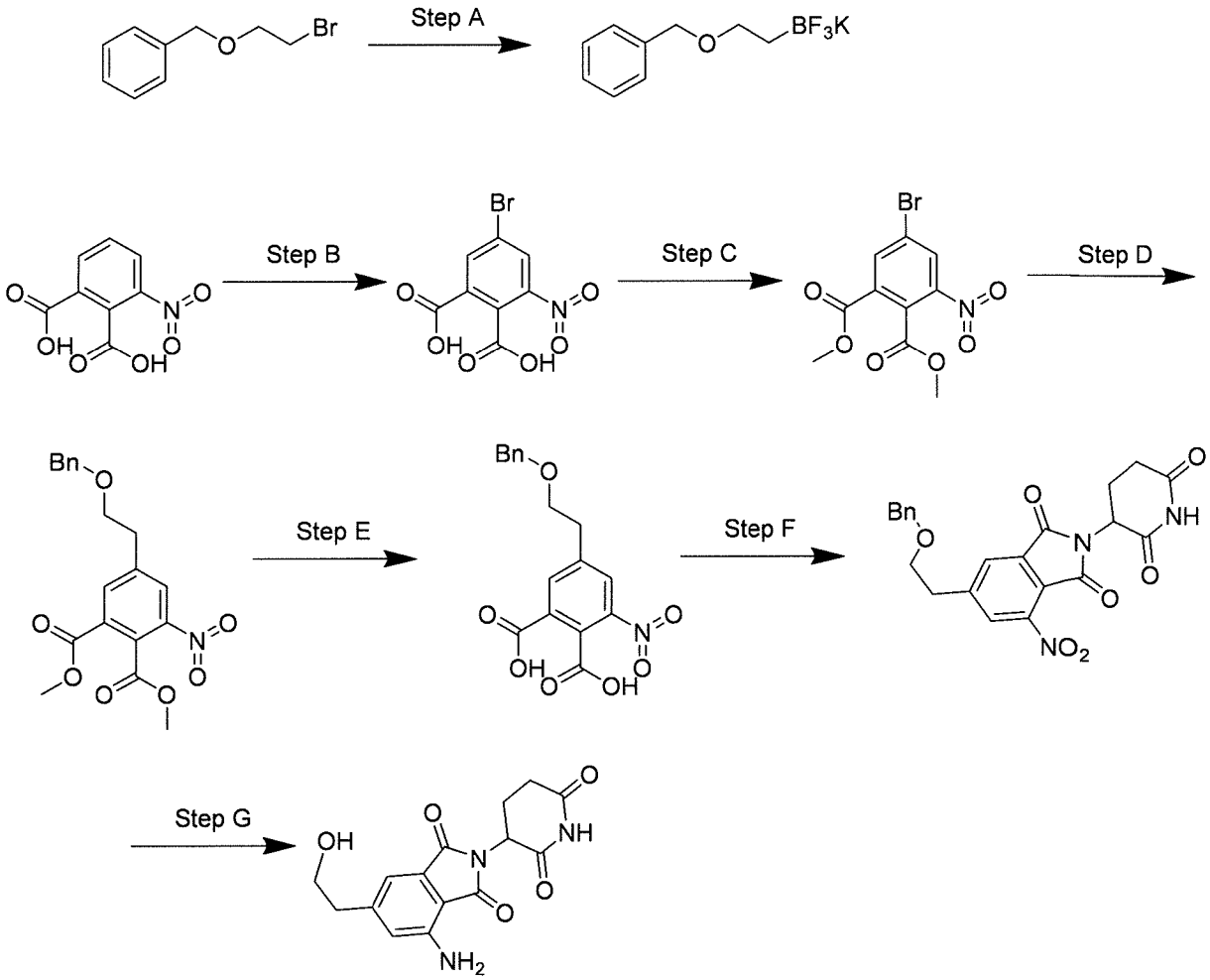
^{1}H NMR (500 MHz, DMSO) δ 13.34 (s, 1H), 10.91 (s, 1H), 10.23 (d, *J* = 7.3 Hz, 1H), 8.25 (dd, *J* = 9.3, 5.9 Hz, 1H), 7.84 (dd, *J* = 7.6, 1.0 Hz, 1H), 7.75 (d, *J* = 8.6 Hz, 1H), 7.68 – 7.62 (m, 2H), 7.46 – 7.42 (m, 2H), 7.37 (td, *J* = 8.9, 2.7 Hz, 1H), 7.29 (t, *J* = 7.8 Hz, 1H), 7.24 (d, *J* = 8.5 Hz, 1H), 6.89 (p, *J* = 4.8 Hz, 1H), 5.29 (s, 2H), 4.88 (ddd, *J* = 12.6, 7.3, 5.3 Hz, 1H), 4.34 – 4.26 (m, 1H), 4.24 – 4.15 (m, 3H), 3.77 (s, 3H),

3.52 – 3.45 (m, 2H), 2.82 (ddd, *J* = 17.4, 13.4, 5.5 Hz, 1H), 2.60 – 2.52 (m, 2H), 2.47 (s, 3H), 2.28 – 2.04 (m, 11H), 2.02 (s, 3H)1.89 (s, 3H).

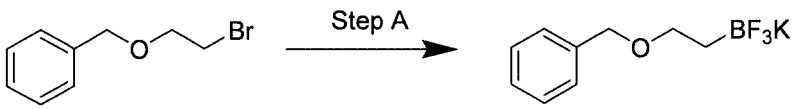
2 protons in aliphatic area overlap with water

SYNTHESIS OF LIGASE LIGAND MOIETIES – COMPOUND 111

Example 68: 4-amino-2-(2,6-dioxopiperidin-3-yl)-6-(2-hydroxyethyl)isoindoline-1,3-dione (Compound 111)

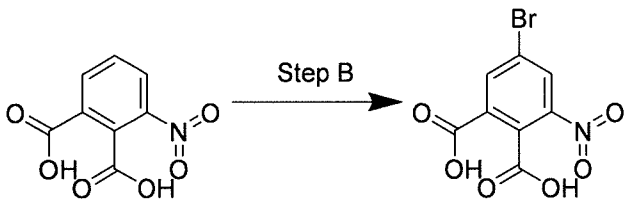


Step A



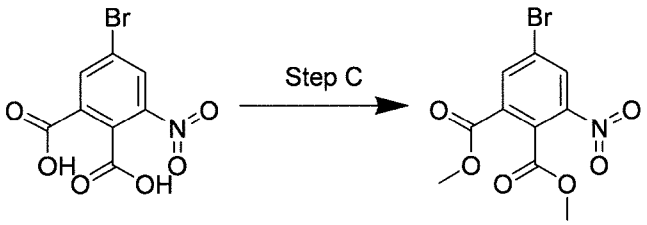
BISPIN (8.855 g, 34.869 mmol), LiOMe (1.766 g, 46.492 mmol), triphenylphosphine polymer-bound (2.3 g, 3.022 mmol) and CuI (0.433 g, 2.325 mmol) were weighed in a round-bottomed flask equipped with a stir bar, under argon atmosphere. The flask was closed with a septum, evacuated, and backfilled with nitrogen. A solution of ((2-bromoethoxy)methyl)benzene (5.0 g, 23.246 mmol) in DMF (116ml) was added with a syringe and the resulting mixture was vigorously stirred at room temperature for 20 h. The reaction mixture was then diluted with dichloromethane and filtered through a Celite pad. The resulting solution was concentrated, poured into sat. aq NH_4Cl, and extracted with Et_2O (2x150ml). The organic layers were washed successively with H_2O (3x100 ml) and brine (100 ml). The organic layer was dried over anhydrous Na_2SO_4, and concentrated to get the crude product which was dissolved in THF (100 ml). A saturated solution of KHF_2 (15 ml, 91.547 mmol) was added to it and the reaction mixture was stirred for 2 h in RT. The reaction mixture was dried, and resulting salt was extracted with hot acetone (2x100 ml). The organic part was concentrated and precipitation was achieved by dropwise addition of diethyl ether at 0°C. The resulting product was collected by filtration and dried to get potassium (2-benzyloxyethyl)trifluoroborate (5 g, 13.6 mmol, 59%) as white solid.

Step B



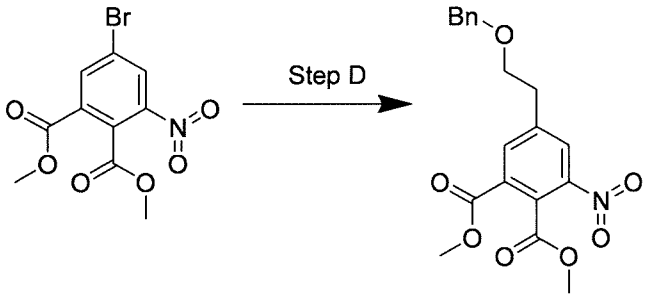
To a well stirred solution of 3-Nitrophthalic acid (15 g, 71 mmol) in concentrated H2SO4 (60 ml) was added 1,3-Dibromo-5,5-dimethylhydantoin (11 g, 38.38 mmol) at 0°C and the reaction mixture was allowed to stir at ambient temperature for 16 h. Reaction mixture was then poured into ice cold water to get the a white precipitate. The precipitate was filtered, the residue was washed with cold water several times then dried under vacuum to get 5-bromo-3-nitrophthalic acid (15 g, 51.7 mmol; 72%) as white solid.

Step C



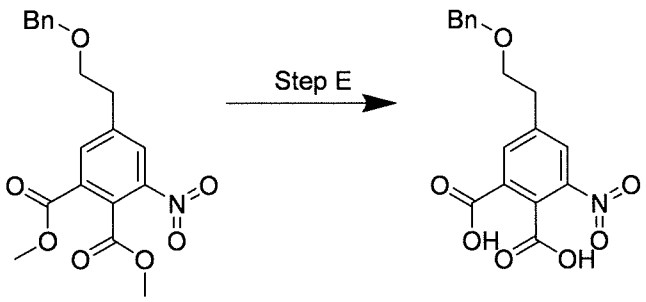
To a solution of 5-bromo-3-nitrophthalic acid (10 g, 34.5 mmol) in DMF (5 ml) was added sodium bicarbonate (23.2 g, 276 mmol) followed by methyl iodide (12.9 ml, 206.9 mmol) and the reaction mixture was allowed to stir at 100°C for 16 h under nitrogen. After complete consumption of the starting material the reaction mixture was diluted with ethyl acetate, washed successively with water and brine, the organic layer was dried over sodium sulphate and evaporated under reduced pressure to get the crude compound, which was then purified by column chromatography (SiO_2, 30% ethyl acetate in hexane) to get dimethyl 5-bromo-3-nitrophthalate (6 g, 21 mmol, 60%) as off white solid.

Step D



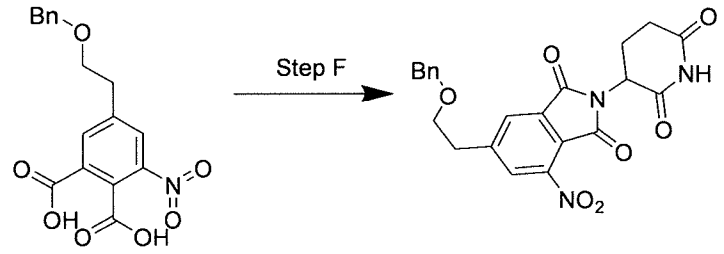
A suspension of dimethyl 5-bromo-3-nitrophthalate (2.0 g, 6.289 mmol), potassium (2-benzyloxyethyl)trifluoroborate (3.805 g, 15.723 mmol) and Cs_2CO_3 (6.148 g, 18.868 mmol) in a toluene:water mixture (4:1, 30 ml) was deoxygenated using argon for 10 min. To the reaction mixture was added $Pd(amphos)_2Cl_2$ (0.891 g, 1.258 mmol) and it was allowed to stir at 100°C for 16 h. After complete consumption of the starting material the volatiles were evaporated under reduced pressure to get the crude compound, which was diluted with ethyl acetate, washed successively with water and brine, the organic layer was dried over sodium sulphate and evaporated under reduced pressure to get the crude compound, which was then purified by column chromatography (SiO_2, 20% ethyl acetate in hexane) to get dimethyl 5-(2-(benzyloxy)ethyl)-3-nitrophthalate (1.6 g, 4.28 mmol, 68%) as gummy solid.

Step E



To a solution of dimethyl 5-(2-(benzyloxy)ethyl)-3-nitrophthalate (1.6 g, 4.285 mmol) in methanol (30 ml) was added NaOH (1.714 g, 42.853 mmol) and the reaction mixture was then refluxed for 4 h. The reaction mixture was cooled to room temperature; volatiles were evaporated under reduced pressure. The residue was dissolved in water (100 ml) and acidified by 2M HCl solution. The aqueous part was extracted by ethyl acetate. Next, the combined organic layer was washed by water and brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to get 5-(2-(benzyloxy)ethyl)-3-nitrophthalic acid (1.4 g, 4.05 mmol, 94.6%) as off white solid.

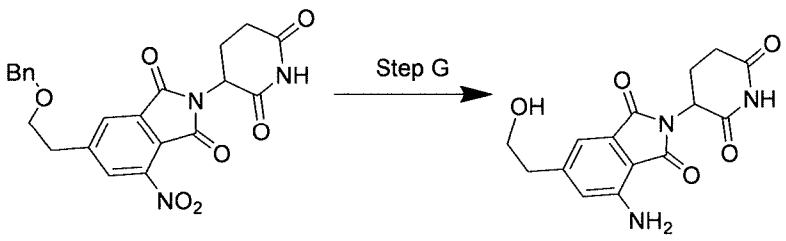
Step F



To a solution of 5-(2-(benzyloxy)ethyl)-3-nitrophthalic acid (1.4 g, 4.06 mmol) in acetic acid (40 ml) and was added 3-aminopiperidine-2,6-dione hydrochloride (670 mg, 4.06 mmol) followed by sodium acetate (1 g, 12.17 mmol) and the reaction mixture was allowed to stir at 120°C for 4 h under nitrogen. After complete consumption of the starting material the reaction mixture was evaporated under reduced pressure get the crude material which was then purified by column chromatography (SiO_2, 10% ethyl acetate in dichloromethane) to get 6-(2-(benzyloxy)ethyl)-2-(2,6-dioxopiperidin-3-yl)-4-nitroisoindoline-1,3-dione (1 g, 2.28 mmol, 56%) as light brown solid.

LCMS (ESI+): m/z 438.3 $[M+H]^+$

Step G



6-(2-(benzyloxy)ethyl)-2-(2,6-dioxopiperidin-3-yl)-4-nitroisoindoline-1,3-dione (500 mg, 1.14 mmol) was dissolved in acetic acid (10 ml). To it was added 10% Pd/C (50 mg), the reaction vessel was then filled with hydrogen (using balloon) and the reaction mixture was allowed to stir at room temperature for 16 h. After complete consumption of the starting material the reaction mixture was filtered through Celite pad and evaporated under reduced pressure to get the crude compound which was purified by column chromatography (SiO_2, 5% methanol in dichloromethane) to get 4-amino-2-(2,6-dioxopiperidin-3-yl)-6-(2-hydroxyethyl)isoindoline-1,3-dione (200 mg, 0.63 mmol, 55%) as yellow solid.

LCMS (ESI+): m/z 318.2 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO) δ 11.07 (s, 1H), 6.90 (s, 1H), 6.84 (s, 1H), 6.42 (s, 2H), 5.02 (dd, *J* = 12.9, 5.4 Hz, 1H), 4.69 (t, *J* = 5.2 Hz, 1H), 3.61 (q, *J* = 6.2 Hz, 2H), 2.94 – 2.80 (m, 1H), 2.72 (t, *J* = 6.6 Hz, 2H), 2.62 – 2.52 (m, 2H), 2.06 – 1.94 (m, 1H).

SYNTHESIS OF LIGASE LIGAND MOIETIES – COMPOUNDS OF FORMULA (II) AND FORMULA (III)



Reaction Scheme 1

(R^z is R^x or R^y)

Synthetic Conditions A

An appropriate acid (R^zCOOH in the above Reaction Scheme 1) (1. eq), DMAP (0.04 eq), and EDC (1.2 eq) were added to a solution of 3-aminopiperidine-2,6-dione (1 eq) and *N*-

hydroxybenzotriazole (1.2 eq) in DMF (0.5 M). The reaction mixture was stirred overnight at room temperature (20-25°C). After removal of the solvent under reduced pressure, the crude product was purified by preparative HPLC, flash column chromatography or preparative TLC.

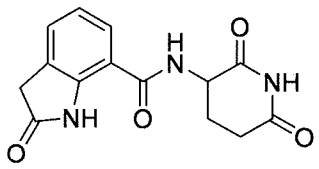
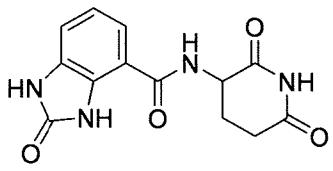
Synthetic Conditions B

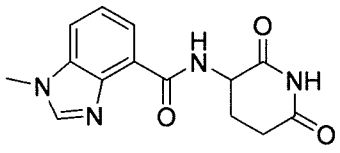
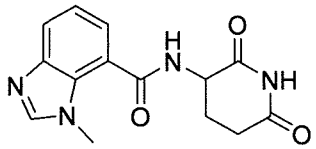
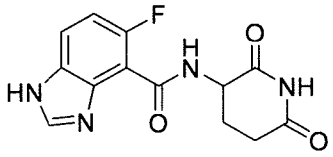
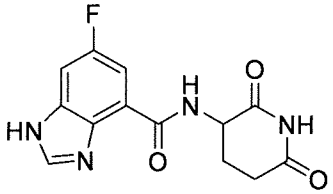
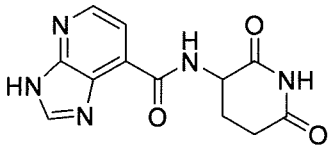
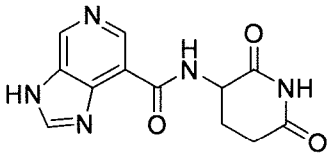
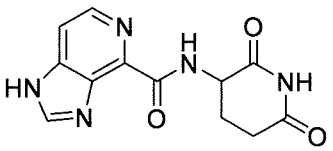
DIPEA (2-3 eq) was added to a solution of an appropriate acid (R^2COOH in the above Reaction Scheme 1), DMAP (0-0.1 eq), HATU (1.0-1.5 eq) and 3-aminopiperidine-2,6-dione hydrochloride (1.2-3.0 eq) in DMF (0.1-0.5 M). The reaction mixture was stirred overnight at room temperature (20-25°C). After removal of the solvent under reduced pressure, the crude product was purified by preparative HPLC, flash column chromatography or preparative TLC.

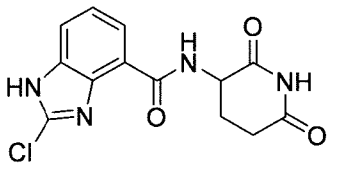
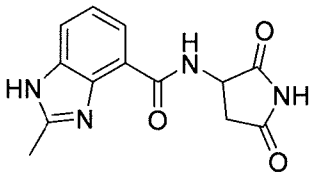
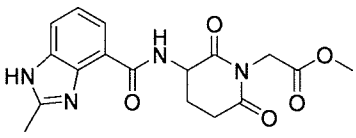
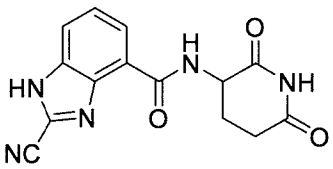
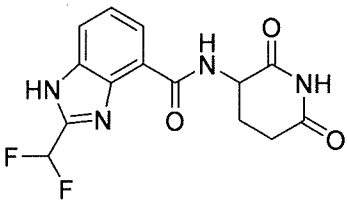
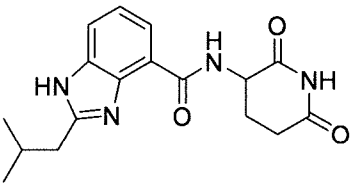
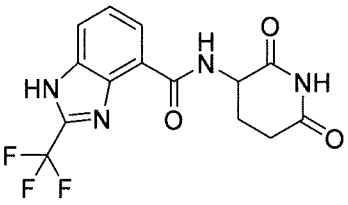
Synthetic Conditions C

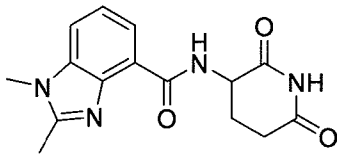
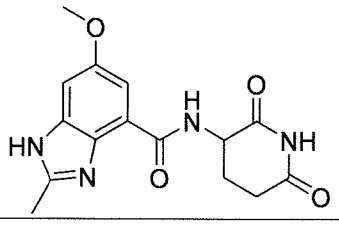
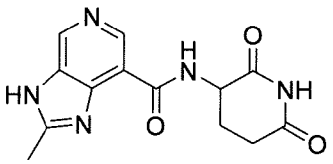
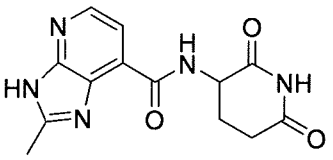
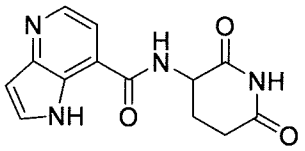
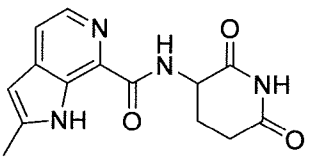
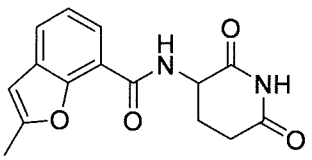
CDI (1.2-2 eq) was added to a solution of an appropriate acid (R^2COOH in the above Reaction Scheme 1) in DMF (0.1-0.5 M) and stirred for 1h at 50 °C. After cooling to room temperature, 3-aminopiperidine-2,6-dione hydrochloride (1.2-1.5 equiv) was added and the reaction mixture was stirred overnight at room temperature (20-25°C). After removal of the solvent under reduced pressure, the crude product was purified by preparative HPLC, flash column chromatography or preparative TLC.

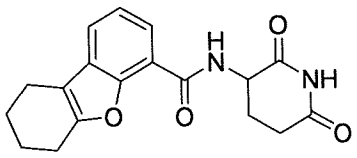
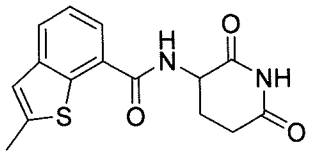
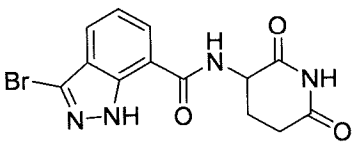
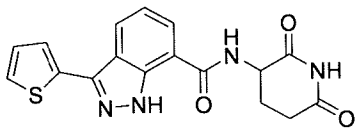
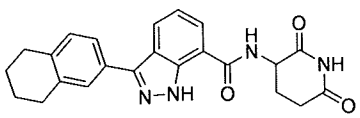
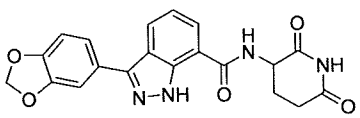
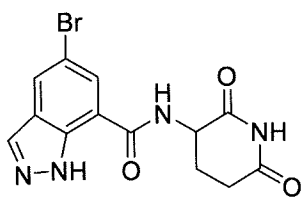
Table 6:

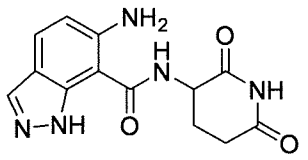
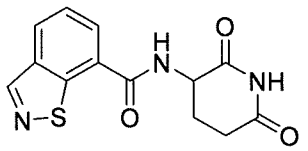
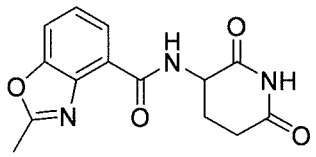
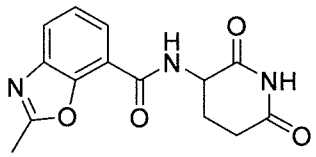
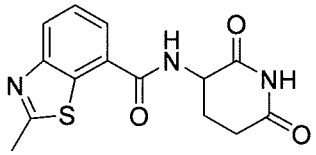
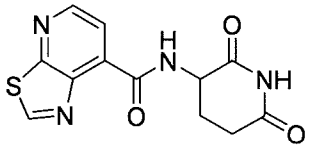
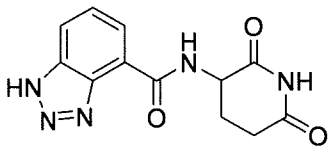
Compound number	Structure	Synthesis method
1		Synthetic Conditions A
3		Synthetic Conditions B

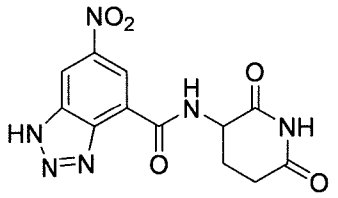
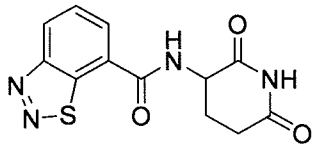
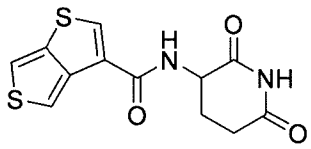
4		Synthetic Conditions B
5		Synthetic Conditions B (also described in detail below)
7		Synthetic Conditions C
8		Synthetic Conditions B
9		Synthetic Conditions C
10		Synthetic Conditions C
11		Synthetic Conditions C

12		Synthetic Conditions B
14		Synthetic Conditions C
17		Synthetic Conditions B
22		Synthetic Conditions B
23		Synthetic Conditions B
24		Synthetic Conditions B
25		Synthetic Conditions B

29		Synthetic Conditions B
30		Synthetic Conditions B
35		Synthetic Conditions B
36		Synthetic Conditions B
37		Synthetic Conditions B
38		Synthetic Conditions B
39		Synthetic Conditions B

40		Synthetic Conditions B
41		Synthetic Conditions B
42		Synthetic Conditions B
43		Synthetic Conditions B
45		Synthetic Conditions B
46		Synthetic Conditions B
47		Synthetic Conditions B

48		Synthetic Conditions B
50		Synthetic Conditions B
51		Synthetic Conditions B
52		Synthetic Conditions B
53		Synthetic Conditions B
54		Synthetic Conditions B
55		Synthetic Conditions C

57		Synthetic Conditions C
58		Synthetic Conditions B
62		Synthetic Conditions B

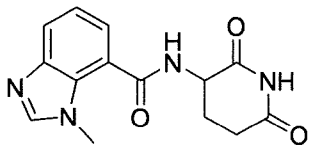
Example 69: Synthesis of N-(2,6-dioxopiperidin-3-yl)-1H-1,3-benzodiazole-7-carboxamide (2)

To a solution of 3-aminopiperidine-2,6-dione (0.96 g, 7.5 mmol) and *N*-hydroxybenzotriazole (1.22 g, 9.0 mmol) in DMF (15 mL) were added 1H-benzo[d]imidazole-7-carboxylic acid (8.25 g, 1.3 mmol), DMAP (37 mg, 0.30 mmol), and EDC (1.40 g, 9.0 mmol). The reaction mixture was stirred overnight at room temperature. Water (30 mL) was added and the obtained solution was extracted with dichloromethane (3×20 mL). The combined organic layers were washed with water, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by preparative HPLC to obtain target compound (0.41 g, 20% yield).

^{1}H NMR: (400MHz, DMSO-d_6) δ 10.49 (s, 1H), 9.67 – 9.52 (m, 1H), 9.45 – 9.28 (m, 1H), 8.12 (d, *J*= 7.4 Hz, 1H) 8.01 (d, *J*= 8.1 Hz, 1H), 7.64 (t, *J*= 8.0 Hz, 1H), 4.90 – 4.78 (m, 1H), 3.85 (brs, 1H), 2.92 – 2.77 (m, 1H), 2.65 – 2.54 (m, 1H), 2.36 – 2.16 (m, 1H), 2.15 – 2.02 (m, 1H)

LCMS (m/z $[M+H]^+$): 273.1

Example 70: Synthesis of *N*-(2,6-dioxopiperidin-3-yl)-1-methyl-1*H*-benzo[d]imidazole-7-carboxamide (5)

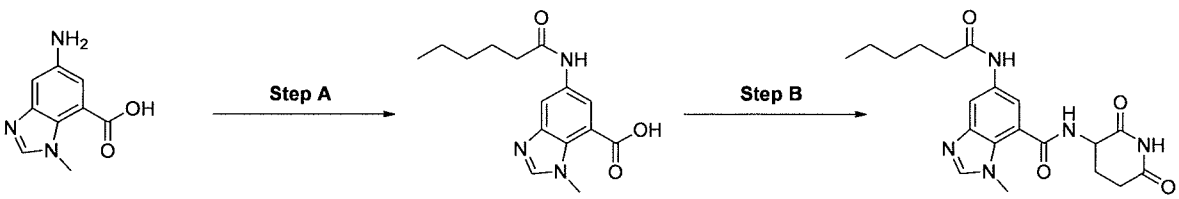


This compound was synthesized using the general procedure shown in Reaction Scheme 1 and Synthetic Conditions B, above (4% yield), and 1-methyl-1*H*-benzo[*d*]imidazole-7-carboxylic acid (20 mg) as a starting material.

^{1}H NMR (500 MHz, DMSO) δ 10.87 (s, 1H), 8.94 (d, *J* = 8.4 Hz, 1H), 8.29 (s, 1H), 7.84 – 7.71 (m, 1H), 7.37 (dt, *J* = 7.4, 3.7 Hz, 1H), 7.28 (dd, *J* = 8.0, 7.5 Hz, 1H), 4.80 (ddd, *J* = 12.5, 8.4, 5.5 Hz, 1H), 3.87 (s, 3H), 2.83 (ddd, *J* = 17.4, 13.1, 5.7 Hz, 1H), 2.56 (ddd, *J* = 9.9, 5.2, 2.5 Hz, 1H), 2.15 (qd, *J* = 12.9, 4.5 Hz, 1H), 2.07 (tdd, *J* = 8.5, 5.6, 2.8 Hz, 1H).

LCMS (m/z [M+H]$^+$): 286.7

Example 71: Synthesis of *N*-(2,6-dioxopiperidin-3-yl)-5-hexanamido-1-methyl-1*H*-benzo[*d*]imidazole-7-carboxamide (6)



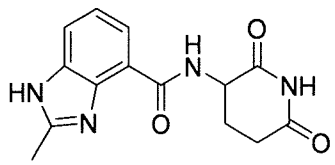
Step A: 5-amino-1-methyl-1*H*-benzo[*d*]imidazole-7-carboxylic acid dihydrochloride (20 mg, 0.076 mmol) and hexanoyl chloride (1.1eq.) were dissolved in 4 mL of dry DCM and cooled in water/ice bath. TEA (4 eq.) was slowly injected into the reaction mixture. The ice bath was removed and the reaction was allowed to warm up to ambient temperature. The reaction was completed in two hours, monitored by LCMS. The solution was diluted with DCM (10mL) and washed with 7mL 3% HCl water soln. The aqueous phase was then evaporated to yield off-white crystals and 5-hexanamido-1-methyl-1*H*-benzo[*d*]imidazole-7-carboxylic acid was used directly in the next step.

Step B: This compound was synthesized using the general procedure shown in Reaction Scheme 1 and Synthetic Conditions B, above (29% yield), and 5-hexanamido-1-methyl-1*H*-benzo[*d*]imidazole-7-carboxylic acid (20 mg) as a starting material.

^{1}H NMR (500 MHz, DMSO) δ 10.87 (s, 1H), 10.00 (s, 1H), 8.97 (t, *J* = 14.9 Hz, 1H), 8.21 (s, 1H), 8.16 (d, *J* = 1.9 Hz, 1H), 7.51 (d, *J* = 1.9 Hz, 1H), 4.79 (ddd, *J* = 12.6, 8.4, 5.4 Hz, 1H), 3.82 (s, 3H), 2.82 (ddd, *J* = 17.4, 13.1, 5.6 Hz, 1H), 2.57 (dt, *J* = 16.6, 3.2 Hz, 1H), 2.31 (t, *J* = 7.4 Hz, 2H), 2.20 – 2.09 (m, 1H), 2.09 – 2.01 (m, 1H), 1.67 – 1.56 (m, 2H), 1.37 – 1.25 (m, 4H), 0.87 (dt, *J* = 7.1, 5.0 Hz, 3H).

LCMS (m/z [M+H]$^+$): 400.2

Example 72: Synthesis of *N*-(2,6-dioxopiperidin-3-yl)-2-methyl-1*H*-benzo[*d*]imidazole-4-carboxamide (15)

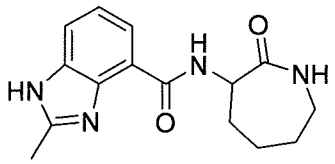


This compound was synthesized using the general procedure shown in Reaction Scheme 1 and Synthetic Conditions B, above (20% yield), and 2-methyl-1*H*-benzo[*d*]imidazole-4-carboxylic acid (20 mg) as a starting material.

^{1}H NMR (500 MHz, DMSO) δ 12.73 (s, 1H), 10.90 (s, 1H), 10.29 (d, *J* = 7.3 Hz, 1H), 7.82 (d, *J* = 7.0 Hz, 1H), 7.63 (s, 1H), 7.32 – 7.23 (m, 1H), 4.87 (ddd, *J* = 12.6, 7.1, 5.4 Hz, 1H), 2.89 – 2.76 (m, 1H), 2.58 (s, 3H), 2.55 (d, *J* = 3.7 Hz, 1H), 2.28 – 2.19 (m, 1H), 2.18 – 2.07 (m, 1H).

LCMS (m/z [M+H]$^+$): 286.5

Example 73: Synthesis of 2-methyl-*N*-(2-oxoazepan-3-yl)-1*H*-1,3-benzodiazole-4-carboxamide (19)



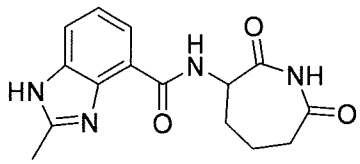
A vial was charged with 2-methyl-1*H*-1,3-benzodiazole-4-carboxylic acid (60.0 mg, 0.341 mmol, 1.000 eq), 3-aminoazepan-2-one hydrochloride (67.3 mg, 0.409 mmol, 1.200 eq), DMAP (4.2 mg, 0.034 mmol, 0.100 eq) and purged with Argon for 15 min. DMF (10 mL) added via syringe followed by DIPEA (0.119 mL, 0.681 mmol, 2.000 eq) and HATU (155.4 mg, 0.409 mmol, 1.200 eq) and the

reaction mixture was stirred overnight. Solvent was evaporated under reduced pressure and the crude compound was purified by preparative TLC to provide 81 mg (82% yield) of the product.

^{1}H NMR (500 MHz, DMSO) δ 12.77 (s, 1H), 10.45 (s, 1H), 7.90 – 7.73 (m, 2H), 7.61 (dd, *J* = 7.8, 0.7 Hz, 1H), 7.23 (t, *J* = 7.8 Hz, 1H), 4.73 (ddd, *J* = 10.9, 6.6, 1.3 Hz, 1H), 3.30 – 3.21 (m, 1H), 3.18 — 3.06 (m, 1H), 2.58 (s, 3H), 2.03 – 1.90 (m, 2H), 1.82 – 1.70 (m, 2H), 1.53 (dd, *J* = 24.4, 11.9 Hz, 1H), 1.34 – 1.21 (m, 1H).

LCMS (m/z [M+H]$^+$): 286.9

Example 74: Synthesis of *N*-(2,7-dioxoazepan-3-yl)-2-methyl-1*H*-benzo[*d*]imidazole-4-carboxamide (20)

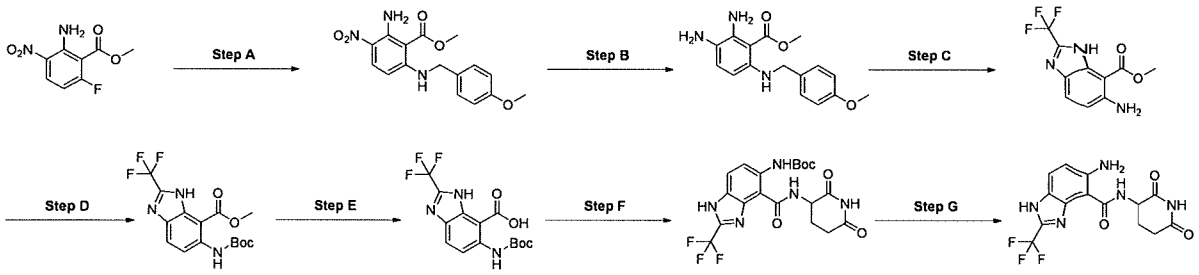


To a solution of 2-methyl-N-(2-oxoazepan-3-yl)-1H-1,3-benzodiazole-4-carboxamide (20.0 mg, 0.070 mmol, 1.000 eq) in MeCN (4.0 mL)/DMSO (0.085 mL)/water (0.010 mL) was added Dess-Martin periodinane (74.1 mg, 0.175 mmol, 2.500 eq). The suspension was heated at 80 °C for 1 h. Solvent was evaporated under reduced pressure and the crude product was purified by preparative TLC and HPLC to provide 16 mg (76%) of the product.

^{1}H NMR (500 MHz, DMSO) δ 12.73 (s, 1H), 10.67 (s, 1H), 10.38 (d, *J* = 6.5 Hz, 1H), 7.81 (dd, *J* = 7.6, 1.0 Hz, 1H), 7.64 (d, *J* = 7.8 Hz, 1H), 7.27 (t, *J* = 7.7 Hz, 1H), 5.19 – 5.06 (m, 1H), 3.08 – 2.95 (m, 1H), 2.65 – 2.61 (m, 1H), 2.60 (s, 3H), 2.35 – 2.22 (m, 1H), 2.08 – 1.94 (m, 1H), 1.89 – 1.69 (m, 2H).

LCMS (m/z [M+H]$^+$): 301.1

Example 75: Synthesis of 6-amino-*N*-(2,6-dioxopiperidin-3-yl)-2-(trifluoromethyl)-1*H*-1,3-benzodiazole-7-carboxamide (26)



Step A: To a stirred solution of methyl 2-amino-6-fluoro-3-nitrobenzoate (2 g, 9.339 mmol) in DMSO (20 mL) was added K_2CO_3 (2.58 g, 18.67 mmol) followed by addition of (4-methoxyphenyl) methanamine (1.59 mL, 12.14 mmol). Then the reaction mixture was stirred at RT for 16 h. After completion of the reaction, quenched with ice water and precipitate was filtered and dried to give methyl 2-amino-6-((4-methoxybenzyl)amino)-3-nitrobenzoate 2.0 g (64% yield).

Step B: To a stirred solution of methyl 2-amino-6-((4-methoxybenzyl)amino)-3-nitrobenzoate (550 mg, 1.66 mmol) in THF (16 ml) was added Zn (1.5 g, 21.6 mmol) followed by addition of NH_4Cl (1.15 g, 21.6 mmol) in water (3 ml) at 0 °C and stirred at RT for 1h. After completion of the reaction, reaction mixture was filtered through celite, washed with ethyl acetate. Organic layer was washed with water, brine, dried over sodium sulphate and concentrated under reduced pressure to give methyl 2,3-diamino-6- ((4-methoxybenzyl)amino)benzoate (250 mg, crude) as brownish solid.

Step C: Methyl 2,3-diamino-6-((4-methoxybenzyl)amino)benzoate (2 g, 6.645 mmol) in TFA (20 mL) was stirred at rt for 16 h . After completion of the reaction, TFA was removed and quenched with aqueous $NaHCO_3$ and extracted with ethyl acetate. Organic layer washed with brine and dried over Na_2SO_4 and concentrated and purified by flash column chromatography to give methyl 6-amino-2-(trifluoromethyl)-1*H*-benzo[*d*]imidazole-7-carboxylate 200 mg (13% yield).

Step D: To a stirred solution of methyl 6-amino-2-(trifluoromethyl)-1*H*-benzo[*d*]imidazole-7-carboxylate (600 mg, 2.317 mmol) in dioxane (5 mL) was added aq NaOH (1N) (15 mL) followed by addition of Boc_2O (3.2 mL , 13.9 mmol) at 0 °C and stirred at RT for 72h. After completion of the reaction quenched with ice water and extracted with ethyl acetate, dried over sodium sulphate and concentrated. The crude product was purified by flash column chromatography to give methyl 6-((*tert*-butoxycarbonyl)amino)-2-(trifluoromethyl)-1*H*-benzo[*d*]imidazole-7-carboxylate 600 mg (72% yield).

Step E: Solution of methyl 6-((*tert*-butoxycarbonyl)amino)-2-(trifluoromethyl)-1*H*-benzo[*d*]imidazole-7-carboxylate in 50% aq NaOH (13 mL) was stirred at 80 °C for 4 h. After completion of reaction, reaction mixture was acidified with 2M HCl and the precipitate was filtered to give 6-((*tert*-butoxycarbonyl)amino)-2-(trifluoromethyl)-1*H*-benzo[*d*]imidazole-7-carboxylic acid 300 mg (52% yield).

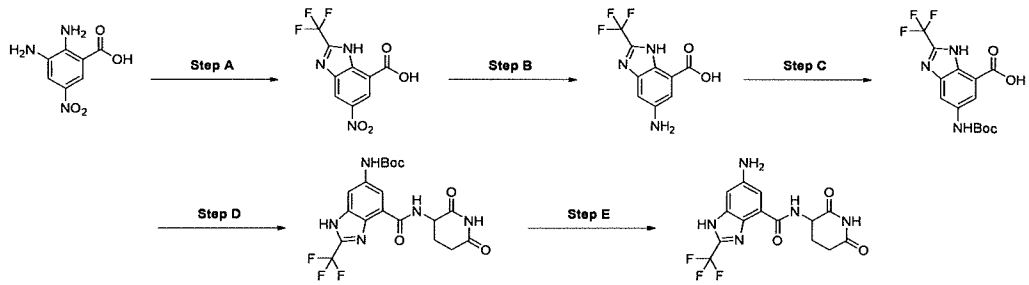
Step F: *tert*-butyl *N*-{7-[(2,6-dioxopiperidin-3-yl)carbamoyl]-2-(trifluoromethyl)-1*H*-1,3-benzodiazol-6-yl}carbamate was synthesized using the general procedure shown in Reaction Scheme 1 and Synthetic Conditions B, above (36% yield) using 5-((*tert*-butoxycarbonyl)amino)-2-(trifluoromethyl)-1*H*-benzo[*d*]imidazole-4-carboxylic acid (30.0 mg) as a starting material.

Step G: *Tert*-butyl (4-((2,6-dioxopiperidin-3-yl)carbamoyl)-2-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-5-yl)carbamate (10.0 mg, 0.022 mmol, 1.000 eq) was dissolved in THF (0.220 mL) and 4M HCl in dioxane (0.038 mL, 1.098 mmol, 50.000 eq) was added. The mixture was stirring in RT for 4 h. Solvent was evaporated under reduced pressure to give 6-amino-*N*-(2,6-dioxopiperidin-3-yl)-2-(trifluoromethyl)-1*H*-1,3-benzodiazole-7-carboxamide hydrochloride 8.0 mg (88.0% yield).

1H NMR (500 MHz, DMSO) δ 14.15 (s, 1H), 10.91 (s, 1H), 10.19 (s, 1H), 7.54 (d, *J* = 9.0 Hz, 1H), 6.94 (d, *J* = 9.0 Hz, 1H), 4.86 – 4.77 (m, 1H), 2.88 – 2.75 (m, 1H), 2.63 – 2.54 (m, 1H), 2.33 – 2.22 (m, 1H), 2.10 (qd, *J* =12.9, 4.4 Hz, 1H).

LCMS (m/z $[M+H]^+$): 356.3

Example 76: Synthesis of 5-amino-*N*-(2,6-dioxopiperidin-3-yl)-2-(trifluoromethyl)-1*H*-benzo[*d*]imidazole-7-carboxamide (27)



Step A: TFA (2 mL) and 4(N) HCl (5 mL) were added to 2,3-diamino-5-nitrobenzoic acid (500 mg , 2.54 mmol). Then the resulting reaction mixture was allowed to reflux for 12 h. After completion of

reaction, the reaction mixture was cooled to 0 °C and then carefully neutralized with 10M NaOH solution. Aqueous part was extracted by DCM (100 mL x 3). Organic layer was washed with brine and dried over Na_2SO_4 and concentrated to get the crude. Finally the crude was triturated with pentane and ether to get crude compound of 5-nitro-2-(trifluoromethyl)-1*H*-benzo[*d*]imidazole-7-carboxylic acid (500 mg) as dark brown solid. Compound was used in next step without further purification

Step B: To a stirred solution of 5-nitro-2-(trifluoromethyl)-1*H*-benzo[*d*]imidazole-7-carboxylic acid (500.0 mg, 1.82 mmol) in MeOH (10 mL) was added 10% Pd/C (193 mg). The reaction mixture was allowed to stir at rt for 4 h under hydrogen atmosphere. After completion of the reaction, the reaction mixture was filtered through celite and concentrated under reduced pressure to get methyl 5-amino-2-(trifluoromethyl)-1*H*-benzo[*d*]imidazole-7-carboxylic acid (500 mg) as crude which was used in next step without further purification.

Step C: To an ice cooled solution of methyl 5-amino-2-(trifluoromethyl)-1*H*-benzo[*d*]imidazole-7-carboxylic acid (1.0 g, 4.1 mmol) in dioxane (5.0 mL) and H_2O (5.0 mL) was added TEA (0.85 mL, 6.1 mmol). The reaction mixture was allowed to stir at ice cool condition for 2-3 min. Boc_2O (1.0 mL, 4.49 mmol) was added and the reaction mixture was stirred at RT for 6h. After completion of reaction, solvent was evaporated and the crude product was purified by preparative HPLC to give 5-((*tert*-butoxycarbonyl)amino)-2-(trifluoromethyl)-1*H*-benzo[*d*]imidazole-7-carboxylic acid (50 mg) as white solid (2.8% yield over 3 steps).

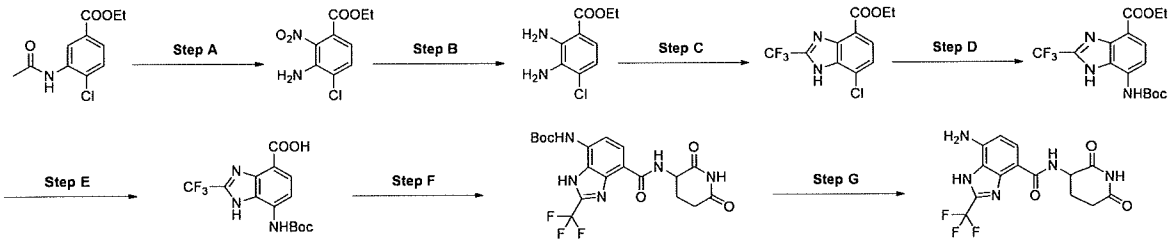
Step D: *Tert*-butyl (7-((2,6-dioxopiperidin-3-yl)carbamoyl)-2-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-5-yl)carbamate was synthesized using the general procedure shown in Reaction Scheme 1 and Synthetic Conditions B, above (37% yield) using 5-((*tert*-butoxycarbonyl)amino)-2-(trifluoromethyl)-1*H*-benzo[*d*]imidazole-7-carboxylic acid (30.0 mg) as a starting material.

Step E: *Tert*-butyl (7-((2,6-dioxopiperidin-3-yl)carbamoyl)-2-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-5-yl)carbamate (10.0 mg, 0.022 mmol, 1.000 eq) was dissolved in THF (0.220 mL) and 4 M HCl in dioxane (0.038 mL, 1.098 mmol, 50.000 eq) was added. The mixture was stirring in RT for 4 h. Solvent was evaporated under reduced pressure to give 5-amino-*N*-(2,6-dioxopiperidin-3-yl)-2-(trifluoromethyl)-1*H*-benzo[*d*]imidazole-7-carboxamide hydrochloride.

^{1}H NMR (500 MHz, DMSO) δ 13.67 (s, 1H), 10.91 (s, 1H), 9.71 (s, 1H), 7.48 – 7.34 (m, 1H), 6.86 (d, *J* = 2.1 Hz, 1H), 5.53 (s, 1H), 4.84 (ddd, *J* = 12.4, 7.0, 5.2 Hz, 2H), 2.80 (ddd, *J* = 17.3, 13.5, 5.5 Hz, 1H), 2.59 – 2.52 (m, 1H), 2.32 – 2.21 (m, 1H), 2.15 – 2.03 (m, 1H).

LCMS (m/z [M+H]$^+$): 355.9

Example 77: Synthesis of 7-amino-*N*-(2,6-dioxopiperidin-3-yl)-2-(trifluoromethyl)-1*H*-benzo[*d*]imidazole-4-carboxamide (28)



Step A: To ethyl 3-acetamido-4-chlorobenzoate (20.0 g, 82.97 mmol) was dropwise added 40.0 mL of 100% HNO_3 at -15 °C and the resultant reaction mixture was stirred and warmed up slowly to 10°C during 2 h and then stirred at RT for 12 h, poured into crashed ice, the solids were filtered, dried under reduced pressure and the mixture of nitro compounds (16 g) was used directly in the next step. To a stirred solution of nitro compounds in 160 mL of ethanol was added 7.5 mL of conc. H_2SO_4. The reaction mixture was refluxed for 16 h, concentrated under reduced pressure and ice-cold water was added. The product was extracted into DCM, the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The crude product was purified by flash column chromatography to give ethyl 3-amino-4-chloro-2-nitrobenzoate (6.3 g, 30%).

Step B: To a stirred solution of ethyl 3-amino-4-chloro-2-nitrobenzoate (6.3 g, 25.753 mmol) in ethanol (60.0 mL) and water (30.0 mL) was added Fe powder (10.78 g) followed by NH_4Cl (1.791 g). The reaction mixture was refluxed for 12 h, concentrated under reduced pressure, diluted with DCM, filtered through celite bed and concentrated under reduced pressure. The crude product was purified by flash column chromatography to give ethyl 2,3-diamino-4-chlorobenzoate (5 g, 90.45%).

Step C: To ethyl 2,3-diamino-4-chlorobenzoate (2.0 g , 9.317 mmol , 1.0 eq) was added 15 ml of TFA and the reaction mixture was refluxed for 12 h and concentrated under reduced pressure. To the

residue was added $NaHCO_3$ solution and the product was extracted with ethyl acetate, washed with brine, dried over Na_2SO_4 and concentrated. The crude product was purified by flash column chromatography to give ethyl 7-chloro-2-(trifluoromethyl)-1*H*-benzo[*d*]imidazole-4-carboxylate (2.4 g, 88% yield).

Step D: A solution of ethyl 7-chloro-2-(trifluoromethyl)-1*H*-benzo[*d*]imidazole-4-carboxylate (1.0 g, 3.417 mmol) in dioxane (12 mL) was degassed under argon atmosphere for 10-15 min. Cs_2CO_3 (2.22 g, 6.834 mmol), NH_2Boc (1.60 g, 13.669 mmol), X-phos (326 mg, 0.683 mmol) and X-phos PdG3 (0.289 g, 0.342 mmol) were added and reaction mixture was stirred at 85°C for 16 h. Reaction mixture was filtered through celite bed, concentrated and purified by flash column chromatography to give ethyl 7-((tert-butoxycarbonyl)amino)-2-(trifluoromethyl)-1*H*-benzo[*d*]imidazole-4-carboxylate (800mg, 62% yield).

Step E: A stirred solution of ethyl 7-((tert-butoxycarbonyl)amino)-2-(trifluoromethyl)-1*H*-benzo[*d*]imidazole-4-carboxylate (500.0 mg, 1.339 mmol) in MeOH (3.0 mL) and THF (3.0mL) was added slowly 50% aqueous NaOH solution (6.0 mL) at ice cool condition. Then the resultant reaction mixture was allowed to stir at rt for 16 h. Reaction mixture was concentrated under reduced pressure and then it was diluted with water and washed with ethyl acetate. After that the aqueous part was gently neutralized with saturated aqueous citric acid solution in ice cool condition and then it was extracted with ethyl acetate. Then the combined organic layer was washed with brine and then dried over Na_2SO_4, filtered and concentrated to get the crude which was triturated with pentane and ether to get 7-((*tert*-butoxycarbonyl)amino)-2-(trifluoromethyl)-1*H*-benzo[*d*]imidazole-4-carboxylic acid (250mg, 54.06% yield) as white solid.

Step F: *Tert*-butyl (4-((2,6-dioxopiperidin-3-yl)carbamoyl)-2-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-7-yl)carbamate was synthesized using the general procedure shown in Reaction Scheme 1 and Synthetic Conditions B, above (80% yield), and 7-((*tert*-butoxycarbonyl)amino)-2-(trifluoromethyl)-1*H*-benzo[*d*]imidazole-4-carboxylic acid (30 mg) as a starting material.

1H NMR (500 MHz, DMSO) δ 14.02 (s, 1H), 10.93 (s, 1H), 9.57 (s, 1H), 8.93 (s, 1H), 7.98 (s, 2H), 4.86 (dt, *J* = 12.3, 5.9 Hz, 1H), 2.88 – 2.79 (m, 1H), 2.57 (s, 1H), 2.29 (d, *J* = 12.4 Hz, 1H), 2.11 (td, *J* = 13.1, 4.5 Hz, 1H), 1.53 (s, 9H).

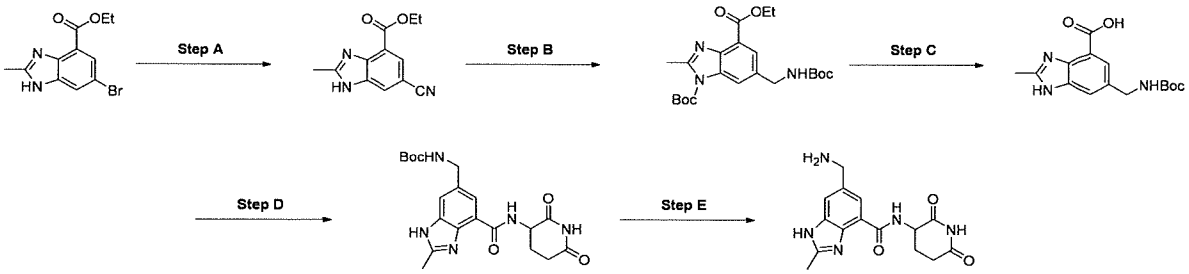
LCMS (m/z $[M+H]^+$): 456.5

Step G: To the mixture of *tert*-butyl (4-((2,6-dioxopiperidin-3-yl)carbamoyl)-2-(trifluorom ethyl)-1H-benzo[d]imidazol-7-yl)carbamate (8 mg, 0.018 mmol) in DCM (0.5 mL) was added TFA (0. 1 mL) and the reaction mixture was stirred at RT for 18h. The mixture was concentrated under reduced pressure and was purified by HPLC to give 7-amino-N-(2,6-dioxopiperidin-3-yl)-2-(trifluoromethyl)-1H-1,3-benzodiazole-4-carboxamide trifluoroacetate (44% yield).

^{1}H NMR (500 MHz, DMSO) δ 10.51 (s, 1H), 7.75 (d, *J* = 8.3 Hz, 1H), 6.58 (s, 1H), 5.97 (d, *J* = 72.1 Hz, 2H), 4.76 (d, *J* = 10.7 Hz, 1H), 2.81 – 2.73 (m, 1H), 2.60 (dd, *J* = 17.5, 3.9 Hz, 1H), 2.12 (d, *J* = 26.4 Hz, 2H).

LCMS (m/z $[M+H]^+$): 356.0

Example 78: Synthesis of 6-(aminomethyl)-*N*-(2,6-dioxopiperidin-3-yl)-2-methyl-1*H*-benzo[*d*]imidazole-4-carboxamide (31)



Step A: To a degassed solution of ethyl 6-bromo-2-methyl-1H-benzo[d]imidazole-4-carboxylate (500mg, 1.76 mmol) in DMF (12 mL) were added $ZN(CN)_2$ (518 mg, 4.41 mmol) and $Pd(PPh_3)_4$ (408 mg, 0.35 mmol) and the reaction mixture was at 120 °C for 16h, quenched with ice water, extracted with ethyl acetate, dried over Na_2SO_4, concentrated under reduced pressure and purified by flash column chromatography to give ethyl 6-cyano-2-methyl-1H-benzo[d]imidazole-4-carboxylate (27% yield).

Step B: To a solution of ethyl 6-cyano-2-methyl-1H-benzo[d]imidazole-4-carboxylate (400 mg, 1.747 mmol) in ethanol (13 ml) were added Raney-nickel and Boc_2O (2.1 ml, 8.734 mmol) and the reaction mixture was stirred under hydrogen (15 psi) for 16h, filtered through celite bed, filtrates were concentrated under reduced pressure and purified by flash column chromatography to give 1-(*tert*-butyl) 4-ethyl 6-(((tert-butoxycarbonyl)amino)methyl)-2-methyl-1H-benzo[d]imidazole-1,4-dicarboxylate (47% yield).

Step C: To a solution of 1-(*tert*-butyl) 4-ethyl 6-(((*tert*-butoxycarbonyl)amino)methyl)-2-methyl-1H-benzo[d]imidazole-1,4-dicarboxylate (430 mg, 0.993 mmol) in THF:MeOH 1:1 (10 mL) was added 50% aqueous NaOH (4 mL) and the reaction mixture was stirred at RT for 16h, neutralized with 1M HCl, and filtered. The solids were dried to give 6-(((tert-butoxycarbonyl)amino)methyl)-2-methyl-1H-benzo[d]imidazole-4-carboxylic acid (62% yield).

Step D: *Tert*-butyl ((4-((2,6-dioxopiperidin-3-yl)carbamoyl)-2-methyl-1*H*-benzo[d]imidazol-6-yl)methyl)carbamate was synthesized using the general procedure shown in Reaction Scheme 1 and Synthetic Conditions B, above (45 % yield), and 6-(((tert-butoxycarbonyl)amino)methyl)-2-methyl-1*H*-benzo[*d*]imidazole-4-carboxylic acid (30 mg) as a starting material.

^{1}H NMR (500 MHz, DMSO) δ 12.64 (s, 1H), 10.89 (s, 1H), 10.24 (d, *J* = 7.3 Hz, 1H), 8.16 (s, 1H), 7.74 (s, 1H), 7.49 (s, 1H), 7.45 (t, *J* = 6.4 Hz, 1H), 4.88 (dt, *J* = 12.6, 6.4 Hz, 1H), 4.24 (d, *J* = 6.2 Hz, 2H), 2.82 (ddd, *J* = 17.3, 13.3, 5.5 Hz, 1H), 2.61 – 2.52 (m, 4H), 2.27 – 2.20 (m, 1H), 2.11 (qd, *J* = 12.9, 4.3 Hz, 1H), 1.40 (s, 9H).

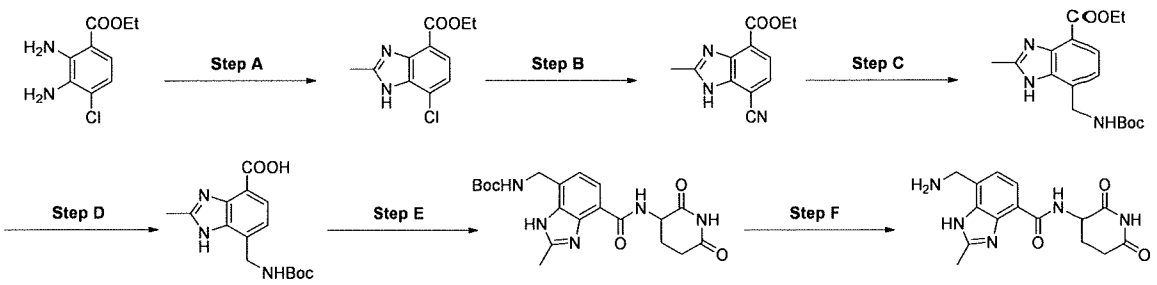
LCMS (m/z [M+H]+): 416.0

Step E: *Tert*-butyl ((4-((2,6-dioxopiperidin-3-yl)carbamoyl)-2-methyl-1*H*-benzo[d]imidazol-6-yl)methyl)carbamate was suspended in DCM (0.5 mL). To the mixture was added TFA (0.1 mL) and stirred for 2 h at RT. The crude was concentrated in vacuo, dissolved in water and freeze-dried to give 6-(aminomethyl)-*N*-(2,6-dioxopiperidin-3-yl)-2-methyl-1*H*-benzo[*d*]imidazole-4-carboxamide.

^{1}H NMR (500 MHz, DMSO) δ 10.93 (s, 1H), 10.12 (s, 1H), 8.14 (s, 3H), 7.97 (d, *J* = 1.6 Hz, 1H), 7.79 (s, 1H), 4.88 (dt, *J* = 13.0, 7.1 Hz, 1H), 4.20 (q, *J* = 5.8 Hz, 2H), 2.84 (ddd, *J* = 17.3, 13.0, 6.0 Hz, 1H), 2.67 – 2.53 (m, 4H), 2.25 – 2.09 (m, 2H).

LCMS (m/z [M+H]$^+$): 315.8

Example 79: Synthesis of 7-(aminomethyl)-*N*-(2,6-dioxopiperidin-3-yl)-2-methyl-1*H*-benzo[*d*]imidazole-4-carboxamide (32)



Step A: To a stirred solution of ethyl 2,3-diamino-4-chlorobenzoate (1.5 g, 6.99 mmol) in toluene (20.0 mL) was added respectively triethyl orthoacetate (5.1 mL, 27.95 mmol) and PTSA (0.337 g, 1.957 mmol) and the reaction mixture was refluxed for 16 h, concentrated under reduced pressure and the crude product was purified by flash column chromatography to give ethyl 7-chloro-2-methyl-1H-benzo[d]imidazole-4-carboxylate 1.2 g (71% yield).

Step B: A solution of ethyl 7-chloro-2-methyl-1H-benzo[d]imidazole-4-carboxylate (400 mg, 1.676 mmol) in DMF (10 mL) was degassed under argon atmosphere for 10-15 minutes. $Zn(CN)_2$ (492 mg, 4.19 mmol), X-phos (159.792 mg, 0.335 mmol) and X-phosPdG3 (0141.86 mg, 0.168 mmol) were added and the reaction mixture was heated to 110°C for 16 h. The mixture was filtered through celite bed, diluted with water, the product was extracted with ethyl acetate, washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography to give ethyl 7-cyano-2-methyl-1H-benzo[d]imidazole-4-carboxylate 251 mg (65% yield).

Step C: The a stirred solution of ethyl 7-cyano-2-methyl-1H-benzo[*d*]imidazole-4-carboxylate (3) (375 mg, 1.636 mmol) in ethanol (10 mL) was added Boc_2O (0.564 mL, 2.454 mmol) and Raney-nickel (200 mg) and reaction mixture was stirred at RT under hydrogen atmosphere for 16 h, filtered through celite bed and concentrated under reduced pressure. The crude product was purified by flash column chromatography to give ethyl 7-(((*tert*-butoxycarbonyl)amino)methyl)-2-methyl-1*H*-benzo[*d*]imidazole-4-carboxylate 230 mg (42% yield).

Step D: To a solution of ethyl 7-(((*tert*-butoxycarbonyl)amino)methyl)-2-methyl-1*H*-benzo[*d*]imidazole-4-carboxylate (200.0 mg, 0.6 mmol) in MeOH (1 mL) and THF (1 mL) was added 50% NaOH solution (2 mL) at 0 °C. The reaction mixture was stirred at RT for 16 h, concentrated under reduced pressure, diluted with water and washed with DCM. The aqueous phase was gently acidified by citric acid solution and the product was extracted with ethyl acetate, washed with

brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was triturated with diethyl ether to give 7-(((tert-butoxycarbonyl)amino)methyl)-2-methyl-1*H*-benzo[*d*]imidazole-4-carboxylic acid 60 mg (32%).

Step E: *Tert*-butyl ((4-((2,6-dioxopiperidin-3-yl)carbamoyl)-2-methyl-1*H*-benzo[*d*]imidazol-7-yl)methyl)carbamate was synthesized using the general procedure shown in Reaction Scheme 1 and Synthetic Conditions B, above (47 % yield), and 7-(((*tert*-butoxycarbonyl)amino)methyl)-2-methyl-1*H*-benzo[*d*]imidazole-4-carboxylic acid (20 mg) as a starting material.

^{1}H NMR (500 MHz, DMSO) δ 12.66 (s, 1H), 10.89 (s, 1H), 10.24 (d, *J* = 7.3 Hz, 1H), 8.15 (s, 1H), 7.79 (d, *J* = 7.8 Hz, 1H), 7.47 (t, *J* = 6.1 Hz, 1H), 7.13 (d, *J* = 7.9 Hz, 1H), 4.86 (ddd, *J* = 12.5, 7.2, 5.2 Hz, 1H), 4.42 (d, *J* = 6.1 Hz, 2H), 2.81 (ddd, *J* = 17.3, 13.5, 5.5 Hz, 1H), 2.61 – 2.51 (m, 4H), 2.26 – 2.20 (m, 1H), 2.16 – 2.07 (m, 1H), 1.40 (s, 9H).

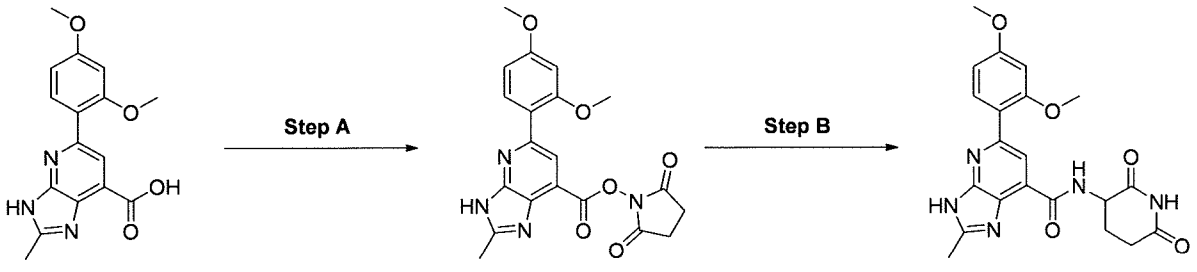
LCMS (m/z [M+H]+): 416.0

Step F: *Tert*-butyl ((4-((2,6-dioxopiperidin-3-yl)carbamoyl)-2-methyl-1*H*-benzo[*d*]imidazol-7-yl)methyl)carbamate was suspended in DCM (0.5 mL). To the mixture was added TFA (0.1 mL) and stirred for 2 h at RT. The crude was concentrated in vacuo, dissolved in water and freeze-dried to give 7-(aminomethyl)-*N*-(2,6-dioxopiperidin-3-yl)-2-methyl-1*H*-benzo[*d*]imidazole-4-carboxamide.

^{1}H NMR (500 MHz, DMSO) δ10.91 (s, 1H), 10.12 (s, 1H), 9.20 (s, 1H), 8.30 (s, 3H), 7.85 (d, *J* = 7.8 Hz, 1H), 7.37 (d, *J* = 7.9 Hz, 1H), 4.82 (d, *J* = 10.7 Hz, 1H), 4.39 (d, *J* = 5.7 Hz, 2H), 2.88 – 2.77 (m, 1H), 2.64 (s, 3H), 2.62 – 2.50 (m, 1H), 2.17 (s, 2H).

LCMS (m/z [M+H]$^+$): 316.1

Example 80: Synthesis of 5-(2,4-dimethoxyphenyl)-*N*-(2,6-dioxopiperidin-3-yl)-2-methyl-3*H*-imidazo[4,5-*b*]pyridine-7-carboxamide (33)



Step A: To a suspension of 5-(2,4-dimethoxyphenyl)-2-methyl-1*H*-imidazo[4,5-*b*]pyridine–7-carboxylic acid (10.0 mg, 31.917 µmol, 1.000 eq) and HOSu (4.4 mg, 38.300 µmol, 1.200 eq) in DCM (1.0 mL) was added a solution of DCC (7.9 mg, 38.300 µmol, 1.200 eq) in DCM (0.500 mL). The reaction mixture was stirred at RT for 18h. The reaction mixture was concentrated under reduced pressure and purified by preparative TLC to give 2,5-dioxopyrrolidin-1-yl 5-(2,4-dimethoxyphenyl)-2-methyl-1*H*-imidazo[4,5-*b*]pyridine-7-carboxylate (71% yield).

Step B: To a solution of 3-aminopiperidine-2,6-dione hydrochloride (8.4 mg, 51.171 µmol, 3.000 eq) and DIPEA (9 µL, 51.171 µmol, 3.000 eq) in DMF (2.0 mL) was added 2,5-dioxopyrrolidin-1-yl 5-(2,4-dimethoxyphenyl)-2-methyl-1*H*-imidazo[4,5-*b*]pyridine-7-carboxylate (7.0 mg, 17.057 µmol, 1.000 eq) in one portion. The reaction mixture was stirred at RT for 18h. The solvent was evaporated under reduced pressure and the residue was purified by preparative TLC to provide 4.1 mg (56%) of product.

^{1}H NMR (500 MHz, DMSO) δ 13.04 (s, 1H), 10.54 (s, 1H), 8.72 (d, *J* = 8.0 Hz, 1H), 7.76 (d, *J* = 8.5 Hz, 1H), 7.65 (s, 1H), 6.73 (d, *J* = 2.4 Hz, 1H), 6.70 (dd, *J* = 8.6, 2.4 Hz, 1H), 4.81 (q, *J* = 8.2 Hz, 1H), 3.87 (s, 3H), 3.87 (s, 3H), 2.81 (dt, *J* = 18.0, 9.5 Hz, 1H), 2.67 – 2.57 (m, 1H), 2.53 (s, 3H), 2.15 (dq, *J* = 9.1, 5.2, 4.1 Hz, 2H).

LCMS (m/z $[M+H]^+$): 423.9

Example 81: Synthesis of *N*-(2,6-dioxopiperidin-3-yl)-2-methyl-1*H*-thieno[2,3-*d*]imidazole-6-carboxamide (59)



Step A: A mixture of methyl 4,5-diaminothiophene-3-carboxylate (400 mg, 2.04 mmol) in dioxane (3 mL), triethyl orthoacetate (3 mL) and PTSA (102 mg, 0.40 mmol) was heated to reflux for 16 h, the reaction mixture was concentrated under reduced pressure and the crude material was purified by flash column chromatography to give methyl 2-methyl-1*H*-thieno[2,3-d]imidazole-6-carboxylate 200 mg (50% yield).

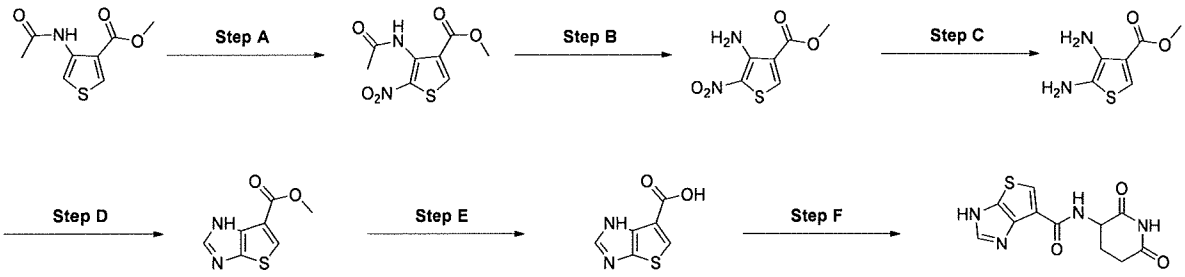
Step B: To a stirred solution of methyl 2-methyl-1H-thieno[2,3-d]imidazole-6-carboxylate (0.13 g, 1.02 mmol) in methanol (0.5 mL) and THF (2 mL) was added NaOH (27 mg, 0.68 mmol) in water (0.5 mL) and the resulting solution was stirred at RT for 16 h. The reaction mixture was diluted with water and washed with ethyl acetate. The aqueous part was acidified with 6N HCl to pH~5 and the resulting precipitate was filtered, washed with water and purified by HPLC to give 2-methyl-1*H*-thieno[2,3-*d*]imidazole-6-carboxylic acid 70 mg (37%).

Step C: *N*-(2,6-dioxopiperidin-3-yl)-2-methyl-1*H*-thieno[2,3-*d*]imidazole-6-carboxamide was synthesized using the general procedure shown in Reaction Scheme 1 and Synthetic Conditions B, above (17% yield), and 2-methyl-3*H*-thieno[2,3-*d*]imidazole-6-carboxylic acid (20 mg) as a starting material.

^{1}H NMR (500 MHz, DMSO): δ 12.53 (s, 1H), 10.87 (s, 1H), 8.70 (d, *J* = 8.0 Hz, 1H), 7.82 (s, 1H), 4.78 – 4.67 (m, 1H), 2.81 (ddd, *J* = 17.4, 13.3, 5.5 Hz, 1H), 2.56 (ddd, *J* = 17.1, 4.1, 2.9 Hz, 1H), 2.43 (s, 3H), 2.16 (qd, *J* = 12.9, 4.5 Hz, 1H), 2.04 – 1.96 (m, 1H).

LCMS (m/z [M+H]+): 293.0

Example 82: Synthesis of *N*-(2,6-dioxopiperidin-3-yl)-1*H*-thieno[2,3-*d*]imidazole-6-carboxamide (60)



Step A: A Solution of methyl 4-acetamidothiophene-3-carboxylate (3 g, 12.3 mmol) in acetic anhydride (40 mL) was cooled at -15 °C. To it a precooled solution (at -15 °C) of concentrated nitric acid (6 mL) in 30 mL acetic anhydride was added drop wise very slowly with stirring. After 30 min the reaction mixture was poured into crushed ice and the resulting light yellow coloured solid was filtered. The solid was thoroughly washed with water and diethyl ether to give 2.4 g (81%) of methyl 4-acetamido-5-nitrothiophene-3-carboxylate.

Step B: To a stirred solution of methyl 4-acetamido-5-nitrothiophene-3-carboxylate (2g, 8.19 mmol) in 4N HCl-dioxane (20 mL), methanol (10 mL) was added and the resulting solution was heated at 100 °C for 16 h. After cooling, dioxane was removed under reduced pressure. The residue was diluted with water and extracted with ethyl acetate. The organic layer was washed with saturated sodium bicarbonate and brine and dried over Na_2SO_4. After concentration under reduced pressure, the crude methyl 4-amino-5-nitrothiophene-3-carboxylate 850 mg (51%) was used in the next step without further purification.

Step C: To a stirred solution of methyl 4-amino-5-nitrothiophene-3-carboxylate (1 g, 4.95 mmol) in a mixture of dioxane-HCl (10 mL) and methanol (10 mL), $SnCl_2$ was added and the resulting solution was stirred at RT for 2h. The reaction mixture was then poured on to a precooled solution of ammonium hydroxide and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, filtered and dried under reduced pressure. The crude methyl 4,5-diamino-thiophene-3-carboxylate 700 mg (82%) was used in the next step without further purification.

Step D: To a stirred solution of methyl 4,5-diaminothiophene-3-carboxylate (650 mg, 3.78 mmol) in a mixture of trimethyl orthoformate (2.5 mL) and toluene (2.5 mL), a catalytic amount of PTSA (189 mg, 0.75 mmol) was added and the resulting solution was heated at 110 °C for 2h. After that the volatiles were removed under reduced pressure, the crude material was purified by flash column chromatography to give 350 mg (50%) of methyl 1*H*-thieno[2,3-*d*]imidazole-6-carboxylate.

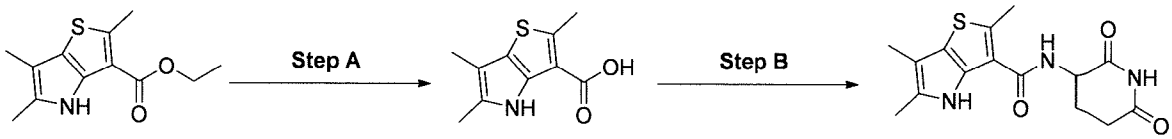
Step E: To a stirred solution of methyl 1*H*-thieno[2,3-*d*]imidazole-6-carboxylate (400 mg, 2.2 mmol mmol) in methanol (3 mL) and THF (3 mL), NaOH (439 mg, 10.9 mmol) dissolved in water (1 mL) was added and the resulting solution was stirred for 16 h. The reaction mixture was diluted with water and washed with ethyl acetate. The aqueous part was acidified with 6N HCl to pH~5 and the resulting brown coloured precipitate was filtered, washed with water and diethyl ether to obtain 1*H*-thieno[2,3-*d*]imidazole-6-carboxylic acid 230 mg (62%).

Step F: *N*-(2,6-dioxopiperidin-3-yl)-1*H*-thieno[2,3-*d*]imidazole-6-carboxamide was synthesized using the general procedure shown in Reaction Scheme 1 and Synthetic Conditions B, above (40% yield), and 1*H*-thieno[2,3-*d*]imidazole-6-carboxylic acid (20 mg) as a starting material.

^{1}H NMR (500 MHz, DMSO) δ 12.79 (s, 1H), 10.88 (s, 1H), 8.74 (d, *J* = 8.2 Hz, 1H), 7.99 (d, *J* = 1.3 Hz, 1H), 7.90 (s, 1H), 4.74 (ddd, *J* = 13.3, 8.1, 5.3 Hz, 1H), 2.81 (ddd, *J* = 17.2, 13.3, 5.5 Hz, 1H), 2.57 (dt, *J* = 18.0, 4.1 Hz, 1H), 2.16 (qd, *J* = 12.9, 4.5 Hz, 1H), 2.01 (dtd, *J* = 13.1, 5.4, 2.8 Hz, 1H).

LCMS (m/z [M+H]$^+$): 279.0

Example 83: Synthesis of *N*-(2,6-dioxopiperidin-3-yl)-2,5,6-trimethyl-4*H*-thieno[3,2-*b*]pyrrole-3-carboxamide (61)



Step A: To a solution of ethyl 2,5,6-trimethyl-4*H*-thieno[3,2-*b*]-pyrrole-3-carboxylate (10.0 mg, 0.042 mmol, 1.000 eq) in a mixture of H_2O (1.0 mL), THF (1.0 mL) and MeOH (1.0 mL) was added 1M LiOH (2.0 mL, 2.000 mmol, 17.702 eq). The reaction was stirred for 24h at rt. After this time, to a mixture was added 1M HCl (2.0 mL, 2.000 mmol, 17.702 eq) to neutralize pH. The crude was concentrated *in vacuo* and used to the next step without further purification.

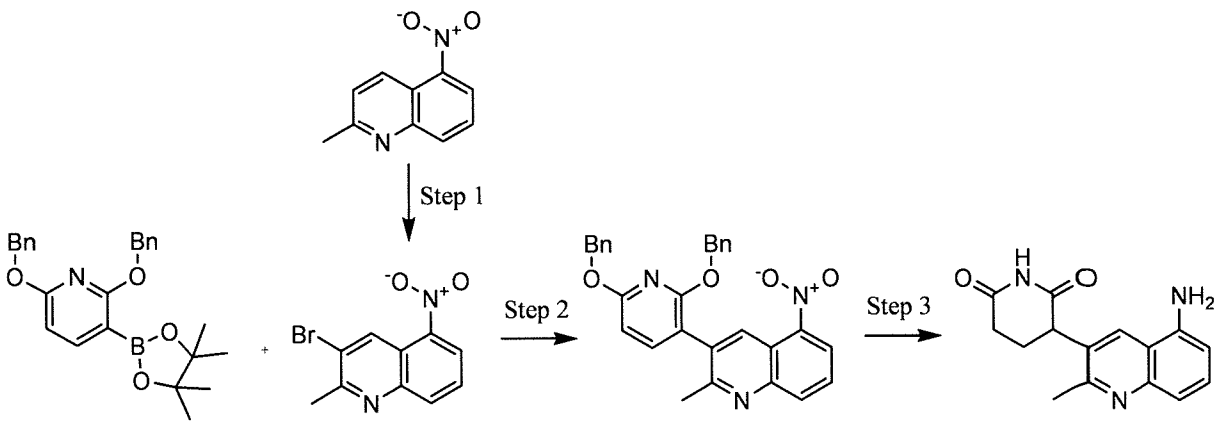
Step B: *N*-(2,6-dioxopiperidin-3-yl)-2,5,6-trimethyl-4*H*-thieno[3,2-*b*]pyrrole-3-carboxamide was synthesized using the general procedure shown in Reaction Scheme 1 and Synthetic Conditions B, above (23% yield), and 2,5,6-trimethyl-4*H*-thieno[3,2-*b*]pyrrole-3-carboxylic acid (8.8 mg) as a starting material.

1H NMR (500 MHz, DMSO) δ 10.87 (s, 1H), 10.45 (s, 1H), 7.94 (d, *J* = 8.2 Hz, 1H), 4.76 (ddd, *J* = 12.3, 8.2, 5.4 Hz, 1H), 2.80 (ddd, *J* = 17.3, 13.4, 5.6 Hz, 1H), 2.63 (s, 3H), 2.59 – 2.52 (m, 1H), 2.22 (s, 3H), 2.16 (qd, *J* = 13.0, 4.5 Hz, 1H), 2.05 (qd, *J* = 4.8, 2.3 Hz, 1H), 2.02 (s, 3H).

LCMS (m/z [M+H]$^+$): 319.8

SYNTHESIS OF LIGASE LIGAND MOIETIES – COMPOUNDS OF FORMULA (IV)

Example 84: Synthesis of 3-(5-amino-2-methylquinolin-3-yl)piperidine-2,6-dione (63)



63

Step 1: Synthesis of 3-bromo-2-methyl-5-nitro-8,8a-dihydroquinoline

2-Methyl-5-nitro-8,8a-dihydroquinoline (19.8 g, 105.3 mmol) was dissolved in dichloromethane (250 mL) and cooled to 5°C in an ice bath. m-CPBA (32.9 g, 133.4 mmol, 70%) was added in portions thereto and the reaction mixture was stirred at room temperature (20-25°C) for 12 hrs. The mixture was washed with 2M NaOH solution (2×150 mL), dried over anhydrous sodium sulfate, and evaporated under vacuum to afford a yellow solid (22 g). The solid was dissolved in $CHCl_3$ (200 mL), the obtained solution was cooled to 5°C in the ice-bath, and phosphoryl bromide (62.6 g, 218.3 mmol) in $CHCl_3$ (300 mL) was added dropwise to the reaction mixture. The mixture was stirred at room temperature (20-25°C) for 12 hrs, poured into ice-water, basified to pH=12 with solid potassium carbonate, and extracted with $CHCl_3$ (3 x 100 mL). The combined extracts were dried over anhydrous sodium sulfate and evaporated under vacuum. The crude product was purified by flash column chromatography (eluent Hexane-MTBE 0-100%) to afford 2.9 g of 3-bromo-2-methyl-5-nitro-8,8a-dihydroquinoline (10% yield) as a brown solid.

Step 2: Synthesis of 3-[2,6-bis(benzyloxy)pyridin-3-yl]-2-methyl-5-nitro-8,8a-dihydroquinoline

2,6-Bis(benzyloxy)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (4.55 g, 10.9 mmol), tripotassium phosphate (4.8 g, 22.6 mmol), and $Pd(dppf)Cl_2$ CH_2Cl_2 (0.86 g, 1 mmol) were added sequentially to a solution of 3-bromo-2-methyl-5-nitro-8,8a-dihydroquinoline (2.9 g, 10.86 mmol) in 1,4-dioxane (50 mL) and water (5 mL). The obtained mixture was stirred at 100°C for 12 hrs under an argon atmosphere. The solvents were removed under vacuum, the residue was diluted with EtOAc (100 mL) and filtered through a pad of silica gel. The filtrate was evaporated under vacuum and recrystallized from

EtOAc to afford 2.05 g 3-[2,6-bis(benzyloxy)pyridin-3-yl]-2-methyl-5-nitro-8,8a-dihydroquinoline (4.3 mmol, 39% yield) as a pale yellow solid.

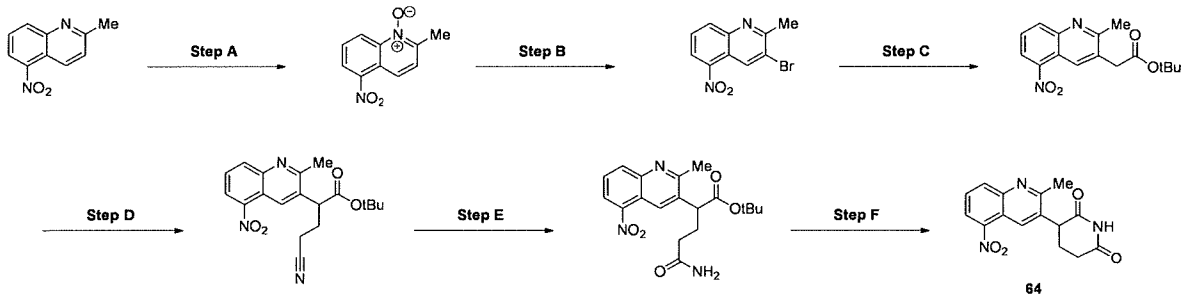
Step 4: Synthesis of 3-(5-amino-2-methylquinolin-3-yl)piperidine-2,6-dione

Pd on activated charcoal (1.2 g) was added to a solution of 3-[2,6-bis(benzyloxy)pyridin-3-yl]-2-methyl-5-nitro-8,8a-dihydroquinoline (2.05 g, 4.29 mmol) in THF/methanol (5:1, 300 mL). The reaction mixture was stirred under H_2 atmosphere for 96 hrs. The catalyst was removed by filtration and the filtrate was evaporated under vacuum. The obtained crude product was purified by HPLC (eluent water-acetonitrile) to afford 0.05 g of the target compound 3-(5-amino-2-methylquinolin-3-yl)piperidine-2,6-dione (4% yield) as a white solid.

^{1}H NMR: (500MHz, DMSO-d_6) δ 10.92 (s, 1H), 8.25 (s, 1H), 7.33 (t, *J*= 7.9 Hz, 1H) 7.07 (d, *J*= 8.2 Hz, 1H), 6.61 (d, *J*= 7.5 Hz, 1H), 5.86 (brs, 2H), 4.25 – 4.17 (m, 1H), 2.89 – 2.79 (m, 1H), 2.69 – 2.61 (m, 1H), 2.59 (s, 3H), 2.46 – 2.36 (m, 1H), 2.15 – 2.08 (m, 1H)

LCMS (m/z $[M+H]^+$): 270.2

Example 85: Synthesis of 3-(2-methyl-5-nitroquinolin-3-yl)piperidine-2,6-dione (64)



Step A: To an ice cold solution of 5-nitro-2-methyl quinoline (2.3 g, 12.22 mmol) in DCM (25 mL) was added *m*-CPBA (2.3 g, 13.67 mmol). The reaction mixture was warmed to RT and stirred for 16 h. The mixture was filtered and filtrates were washed with 1 M KOH solution, dried over Na_2SO_4, and concentrated under reduced pressure to give 2-methyl-5-nitroquinoline 1-oxide (88% yield).

Step B: To an ice cold solution of 2-methyl-5-nitroquinoline 1-oxide (500.0 mg, 2.44 mmol) in DCM (5 mL) was added $POBr_3$ (1.4 g, 4.9 mmol) in DCM (5 mL). The reaction mixture warmed to RT and

stirred for 48 h. Ice water was added, the solution was neutralized with 10% NH_3 solution, extracted with DCM, dried over Na_2SO_4, concentrated under reduced pressure and purified by flash column chromatography to give 2-methyl-3-bromo-5-nitroquinoline (14% yield).

Step C: To a solution of 2-methyl-3-bromo-5-nitroquinoline (600 mg, 2.24 mmol) in dioxane (8 mL) was added KOAc (441 mg, 4.49 mmol) followed by 1-(*tert*-butyldimethylsilyloxy)-1-*tert*-butoxyethylene (2.07 g, 8.98 mmol) and the reaction mixture was degassed for 15 min under N_2. $Pd[P(o\text{-}Tol)_3]_2Cl_2$ (353.2 mg, 0.449 mmol) was added and the reaction mixture was stirred at 130 °C for 48 h, diluted with ethyl acetate, filtered through celite bed, concentrated under reduced pressure and purified by flash column chromatography to give *tert*-butyl 2-(2-methyl-5-nitroquinolin-3-yl)acetate (58% yield).

Step D: To a solution of *tert*-butyl 2-(2-methyl-5-nitroquinolin-3-yl)acetate (200 mg, 0.662 mmol) in DMF (10 mL) were added K_2CO_3 (150.6 mg, 0.662 mmol), benzyltriethylammonium chloride (91.4 mg, 0.662mmol) and acrylonitrile (0.043 mL, 0.662 mmol) and the reaction mixture was stirred at RT for 16h. The reaction mixture was diluted with water, extracted with ethyl acetate, dried over Na_2SO_4, concentrated under reduced pressure and purified by flash column chromatography to give tert-butyl 4-cyano-2-(2-methyl-5-nitroquinolin-3-yl)butanoate (40% yield).

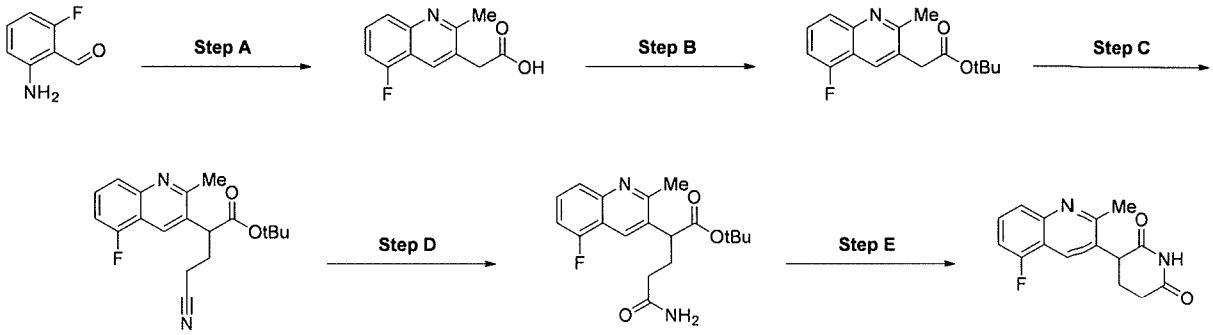
Step E: To an ice cold solution of tert-butyl 4-cyano-2-(2-methyl-5-nitroquinolin-3-yl)butanoate (120.0 mg, 0.338 mmol) in DMSO (5 mL) were added H_2O_2 (0.052 mL,1.688 mmol) and K_2CO_3 (6.533 mg, 0.047 mmol). The reaction mixture warmed to RT and stirred for 16h, diluted with water, extracted with ethyl acetate, dried over Na_2SO_4, concentrated under reduced pressure and purified by SFC to give *tert*-butyl 5-amino-2-(2-methyl-5-nitroquinolin-3-yl)-5-oxopentanoate (51% yield).

Step F: In a vial were placed *tert*-butyl 5-amino-2-(2-methyl-5-nitroquinolin-3-yl)-5-oxopentanoate (5.0 mg, 0.013 mmol, 1.000 eq), p-toluenesulfonic acid (25.5 mg, 0.134 mmol, 10.000 eq) and acetonitrile (0.5 mL) and the reaction mixture was stirred at 80°C for 2h. The mixture was concentrated under reduced pressure and purified by HPLC to give 3-(2-methyl-5-nitroquinolin-3-yl)piperidine-2,6-dione (77% yield).

^1H NMR (500 MHz, DMSO) δ 10.98 (s, 1H), 8.60 (s, 1H), 8.40 – 8.30 (m, 2H), 7.89 (dd, *J* = 8.5, 7.7 Hz, 1H), 4.42 (dd, *J* = 12.5, 4.7 Hz, 1H), 2.82 (ddd, *J* = 17.8, 12.8, 5.3 Hz, 1H), 2.71 (s, 3H), 2.66 – 2.61 (m, 1H), 2.44 (dd, *J* = 12.8, 4.3 Hz, 1H), 2.14 (ddt, *J* = 10.0, 7.8, 3.9 Hz, 1H).

LCMS (m/z $[M+H]^+$): 299.9

Example 86: Synthesis of 3-(5-fluoro-2-methylquinolin-3-yl)piperidine-2,6-dione (65)



Step A: To a solution of 2-amino-6-fluorobenzaldehyde (1.0 g, 7.19 mmol) in MeOH (20 mL) was added 4-oxopentanoic acid (0.739 mL, 7.194 mmol) followed by 2M NaOH (5.0 mL). The reaction mixture was refluxed for 18 h, concentrated under reduced pressure, neutralized with acetic acid, the solids were filtered and washed with ether and pentane to give 2-(5-fluoro-2-methylquinolin-3-yl)acetic acid (38%).

Step B: To a solution of DCC (1.036 g, 5.023 mmol) in DCM (5.0 mL) were added DMAP (446 mg, 3.653 mmol) and 2-(5-fluoro-2-methylquinolin-3-yl)acetic acid (1.0 g, 4.566 mmol). *Tert*-butanol (0.406 mL, 13.7 mmol) was added and the reaction mixture was warmed to RT and stirred for 12 h. The reaction mixture was diluted water, extracted with ethyl acetate, dried over Na_2SO_4, concentrated under reduced pressure and purified by flash column chromatography to give *tert*-butyl 2-(5-fluoro-2-methylquinolin-3-yl)acetate (35% yield).

Step C: To a solution of *tert*-butyl 2-(5-fluoro-2-methylquinolin-3-yl)acetate (500 mg, 1.816 mmol) in DMF (10 mL) were added K_2CO_3 (251 mg, 1.816 mmol), benzyltriethylammonium chloride (413.6 mg, 1.816 mmol) and acrylonitrile (0.119 mL, 1.816 mmol) and the reaction mixture was stirred at RT for 16h. The reaction mixture was diluted with water, extracted with ethyl acetate, dried over Na_2SO_4, concentrated under reduced pressure and purified by flash column chromatography to give *tert*-butyl 4-cyano-2-(5-fluoro-2-methylquinolin-3-yl)butanoate (50% yield).

Step D: To an ice cold solution of *tert*-butyl 4-cyano-2-(5-fluoro-2-methylquinolin-3-yl)butanoate (500 mg, 1.524 mmol) in DMSO (5 mL) were added H_2O_2 (0.238 mL, 7.77 mmol) and K_2CO_3 (29.5 mg,

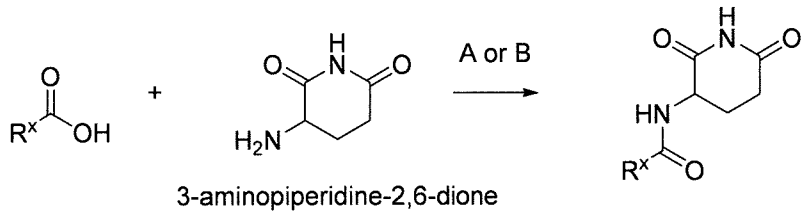
0.14 mmol). The reaction mixture warmed to RT and stirred for 16h, diluted with water, extracted with ethyl acetate, dried over Na_2SO_4, concentrated under reduced pressure and purified by flash column chromatography to give *tert*-butyl 5-amino-2-(5-fluoro-2-methylquinolin-3-yl)-5-oxopentanoate (45% yield).

Step E: In a vial were placed *tert*-butyl 5-amino-2-(5-fluoro-2-methylquinolin-3-yl)-5-oxopentanoate (5.0 mg, 0.014 mmol, 1.000 eq), p-toluenesulfonic acid (27.5 mg, 0.144 mmol, 10.000 eq) and acetonitrile (0.5 mL) and the reaction mixture was stirred at 80°C for 2h. The mixture was concentrated under reduced pressure and purified by HPLC to give 3-(5-fluoro-2-methylquinolin-3-yl)piperidine-2,6-dione (84% yield).

^{1}H NMR (500 MHz, DMSO) δ 10.94 (s, 1H), 8.24 (s, 1H), 7.79 (d, *J* = 8.5 Hz, 1H), 7.70 (td, *J* = 8.2, 6.2 Hz, 1H), 7.37 (dd, *J* = 10.0, 7.6 Hz, 1H), 4.36 (dd, *J* = 12.7, 4.7 Hz, 1H), 2.82 (ddd, *J* = 17.8, 13.2, 5.4 Hz, 1H), 2.68 (s, 3H), 2.61 (dd, *J* = 17.4, 3.5 Hz, 1H), 2.57 – 2.51 (m, 1H), 2.12 (dtd, *J* = 12.8, 5.1, 2.6 Hz, 1H).

LCMS (m/z $[M+H]^+$): 272.9

SYNTHESIS OF LIGASE LIGAND MOIETIES – COMPOUNDS OF FORMULA (Va) AND (Vb)



Reaction Scheme 2: General procedure

Synthetic Conditions D

An appropriate acid (R^xCOOH in the above reaction scheme) (1.1 eq), DMAP (0.04 eq), and EDC (1.2 eq) were added to a solution of 3-aminopiperidine-2,6-dione (1 eq) and *N*-hydroxybenzotriazole (1.2 eq) in DMF (0.5 M). The reaction mixture was stirred overnight at room temperature (20-25°C). Water (2 x DMF volume) was added and the obtained solution was extracted with dichloromethane (3 × DMF volume). The combined organic layers were washed with water, dried over Na_2SO_4, and

concentrated under reduced pressure. The crude product was purified by preparative HPLC or by column chromatography.

Synthetic Conditions E

An appropriate acid R^xCOOH in the above reaction scheme) (1 eq) and EDC (1.2 eq) were added to a solution of 3-aminopiperidine-2,6-dione (hydrochloride salt, 1.1 eq), triethylamine (1.2 eq) and *N*-hydroxybenzotriazole (1.2 eq) in DMA (0.5 M). The reaction mixture was stirred overnight at rt. Water (2 x DMA volume) was added and obtained mixture was extracted with dichloromethane (3 × DMA volume). The combined organic layers were washed with water, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was isolated by preparative HPLC or by column chromatography.

Synthetic Conditions F

To a solution of appropriate acid (R^xCOOH in the above reaction scheme) (1 eq) and HATU (1.5 eq) in dry DMF were added 3-aminopiperidine-2,6-dione (hydrochloride salt, 1.2 eq) and DIPEA (3 eq). The reaction mixture was stirred overnight at rt. The crude product was purified by preparative HPLC or/and by preparative TLC.

Synthetic Conditions G

To a solution of appropriate acid (R^xCOOH in the above reaction scheme) (1 eq) 3-aminopiperidine-2,6-dione (hydrochloride salt, 1.2 eq) and DMAP (0.1 eq.) in an inert atmosphere in dry DMF were added DIPEA (2.2 eq.) and HATU (1.5 eq) in dry DMF. The reaction mixture was stirred overnight at rt. The crude product was purified by preparative HPLC or/and by preparative TLC.

Example method 1: formation of chlorinated R^x group of R^xCOOH (or its ester R^xCOOR')

N-chlorosuccinimide(1.1 eq) was added to a solution of an appropriate starting material (1 eq) in DMF (0.5 M) and the reaction mixture was stirred for 2 h at room temperature (20-25°C). The reaction mixture was poured into water (2 x DMF volume) and occurred precipitate was filtered. The solids were washed with water and dried in vacuum to give the acid, R^xCOOH.

Example method 2: synthesis of R^xCOOH from corresponding ester R^xCOOR')

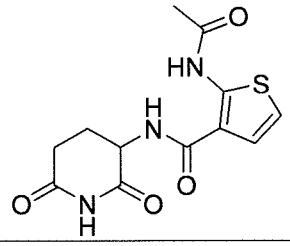
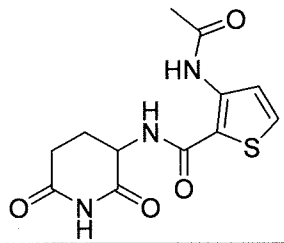
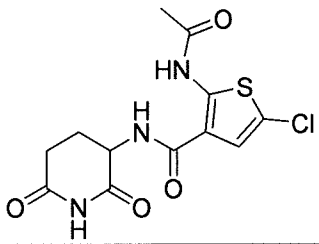
LiOH (1.1 eq) was added to a solution of an appropriate ester (1 eq) in THF:water mixture (3:1 or 5:1, 85 mM) and the resulting mixture was stirred overnight at room temperature (20-25°C). The

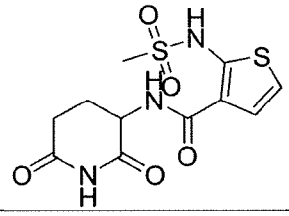
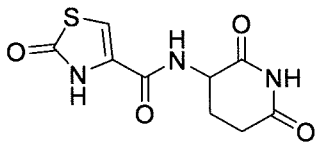
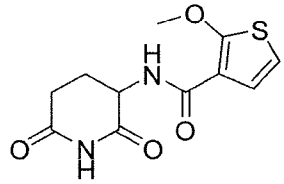
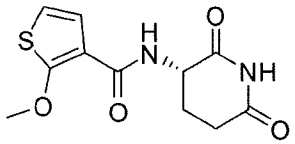
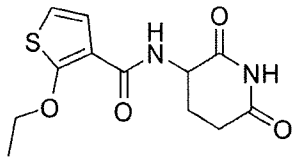
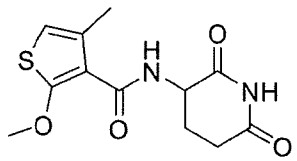
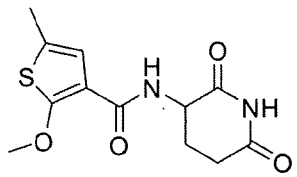
mixture was concentrated under reduced pressure, diluted with water, and acidified with concentrated HCl to pH=2-3. The precipitate was filtered, washed with water, and dried in vacuum to give the target carboxylic acid.

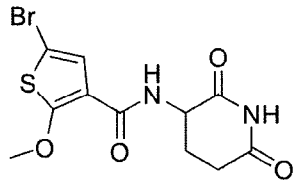
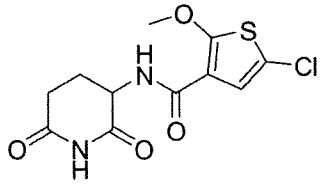
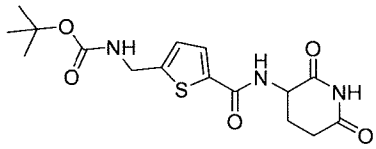
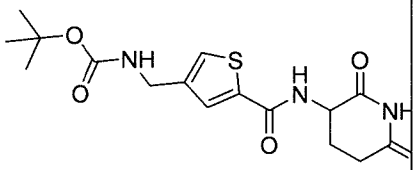
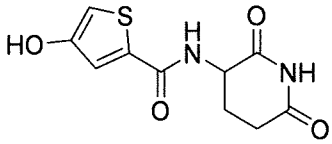
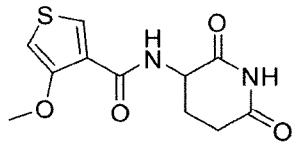
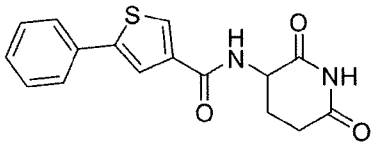
Example method 3: formation of acetylated R^x group of R^xCOOR'

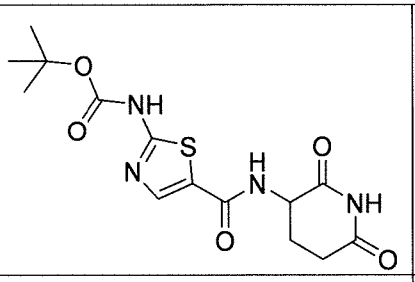
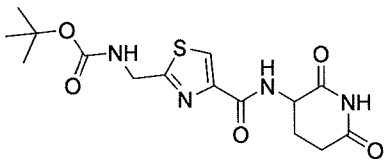
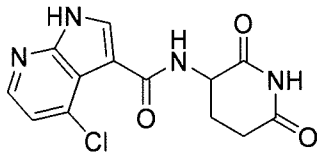
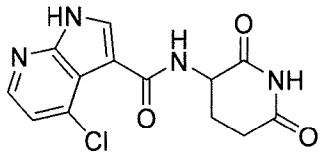
A mixture of an appropriate amine (1 eq.), Ac_2O (3 eq.), and DMAP (0.2 eq.) in dioxane (0.2 M) was heated to 80°C for 2 h. Upon completion, the mixture was cooled down to room temperature (20-25°C) and concentrated under reduced pressure. The residue was diluted with water (1 x dioxane volume) and extracted with EtOAc (3 x dioxane volume). The organic layers were washed with water, brine, dried over Na_2SO_4, and evaporated to dryness to afford an acylated product typically used without further purification.

Table 7:

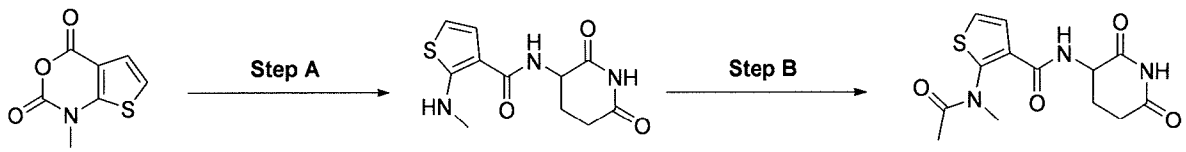
Compound number	Structure	Synthesis method
67		Synthetic Conditions E (2-acetamidothiophene-3-carboxylic acid starting material)
69		Synthetic Conditions E (*N*-(2,6-dioxopiperidin-3-yl)-3-acetamidothiophene-2-carboxamide starting material)
72		Synthetic Conditions E (5-chloro-2-acetamidothiophene-3-carboxylic acid starting material)

73		Synthetic Conditions E (2-(methylsulfonamido)thiophene-3-carboxylic acid starting material)
75		Synthetic Conditions F (2-oxo-2,3-dihydrothiazole-4-carboxylic acid starting material)
78		Synthetic Conditions E (2-methoxythiophene-3-carboxylic acid starting material)
79		Synthetic Conditions G (2-methoxythiophene-3-carboxylic acid (20 mg) and (*S*)-3-aminopiperidine-2,6-dione starting material)
80		Synthetic Conditions G (2-ethoxythiophene-3-carboxylic acid starting material)
81		Synthetic Conditions F (2-methoxy-4-methylthiophene-3-carboxylic acid starting material)
82		Synthetic Conditions F (2-methoxy-5-methylthiophene-3-carboxylic acid a starting material)

85		Synthetic Conditions G (5-bromo-2-methoxythiophene-3-carboxylic acid starting material)
88		Synthetic Conditions D (5-chloro-2-methoxythiophene-3-carboxylic acid starting material)
93		Synthetic Conditions F (5-[(tert-butoxycarbonylamino)methyl]thiophene-2-carboxylic acid starting material
94		Synthetic Conditions F (4-((tert-butoxycarbonyl)aminomethyl)thiophene-2-carboxylic acid starting material
95		Synthetic Conditions G (4-hydroxythiophene-2-carboxylic acid starting material
96		Synthetic Conditions G (4-methoxythiophene-3-carboxylic acid starting material)
97		Synthetic Conditions G (5-phenylthiophene-3-carboxylic acid starting material)

98		Synthetic Conditions F (2-((*tert*-butoxycarbonyl)amino)thiazole-5-carboxylic acid starting material
99		Synthetic Conditions F (2-(((*tert*-butoxycarbonyl)amino)methyl)thiazole-4-carboxylic acid starting material
104		Synthetic Conditions F (4-chloro-1*H*-pyrrolo[2,3-*b*]pyridine-3-carboxylic acid starting material
105		Synthetic Conditions F (5-chloro-1*H*-pyrrolo[2,3-*b*]pyridine-3-carboxylic acid starting material.

Example 87: Synthesis of N-(2,6-dioxopiperidin-3-yl)-2-(N-methylacetamido)thiophene-3-carboxamide (66)



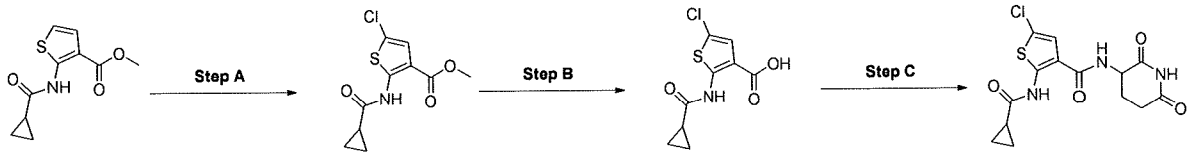
Step A: 3-Aminopiperidine-2,6-dione (3.3 g, 25.8 mmol) and triethylamine (2.45 g, 24.2 mmol) were added to a solution of 1-methyl-1H,2H,4H-thieno[2,3-d][1,3]oxazine-2,4-dione (3.7 g, 20.2 mmol) in ethanol (20 mL). The reaction mixture was refluxed for 16 h and filtered. The precipitate was washed with water to give N-(2,6-dioxopiperidin-3-yl)-2-(methylamino)thiophene-3-carboxamide (19% yield).

Step B: Acetic anhydride (0.265 g, 2.60 mmol) and DMAP (0.026 g, 0.213 mmol) were added to a solution of N-(2,6-dioxopiperidin-3-yl)-2-(methylamino)thiophene-3-carboxamide (0.579 g, 2.17 mmol) and triethylamine (0.263 g, 2.60 mmol) in dioxane (10 mL). The reaction mixture was stirred at 60°C for 16 h, washed with water and extracted with EtOAc (3 x 10 mL), dried over Na_2SO_4, concentrated under reduced pressure and purified by HPLC to give N-(2,6-dioxopiperidin-3-yl)-2-(N-methylacetamido)thiophene-3-carboxamide (11% yield).

^{1}H NMR (500MHz, DMSO) δ 10.86 (s, 1H), 8.53 (d, *J* = 8.0 Hz, 1H), 7.56 (d, *J* = 5.7 Hz, 1H), 7.34 (d, *J* = 5.7 Hz, 1H), 4.72 – 4.62 (m, 1H), 3.09 (s, 3H), 2.83 – 2.71 (m, 1H), 2.58 – 2.53 (m, 1H), 2.19 – 2.02 (m, 1H), 1.99 – 1.90 (m, 1H), 1.81 (s, 3H).

LCMS (m/z $[M+H]^+$): 310.2

Example 88: Synthesis of 5-chloro-2-cyclopropaneamido-N-(2,6-dioxopiperidin-3-yl)thiophene-3-carboxamide (68)



Step A: Methyl 5-chloro-2-cyclopropaneamidothiophene-3-carboxylate was synthesized using Example Method 1, above (80% yield) using methyl 2-cyclopropaneamidothiophene-3-carboxylate as a starting material.

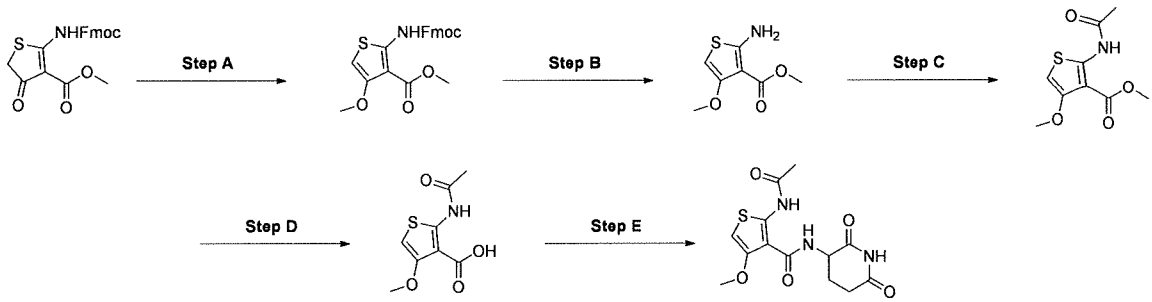
Step B: 5-chloro-2-cyclopropaneamidothiophene-3-carboxylic acid was synthesized using Example Method 2, above (86% yield) using methyl 5-chloro-2-cyclopropaneamidothiophene-3-carboxylate as a starting material.

Step C: 5-chloro-2-cyclopropaneamido-N-(2,6-dioxopiperidin-3-yl)thiophene-3-carboxamide was synthesized using the general procedure shown in Reaction Scheme 1 and Synthetic Conditions E, above (30% yield), using 5-chloro-2-cyclopropaneamidothiophene-3-carboxylic acid as a starting material.

^{1}H NMR (500MHz, DMSO) δ 12.11 (s, 1H), 10.88 (s, 1H), 8.69 – 8.60 (m, 1H), 7.50 (s, 1H), 4.79 – 4.69 (m, 1H), 2.84 – 2.72 (m, 1H), 2.61 – 2.53 (m, 1H), 2.21 – 2.08 (m, 1H), 2.04 – 1.92 (m, 2H), 0.98 – 0.84 (m, 4H).

LCMS (m/z $[M+H]^+$): 356.2

Example 89: Synthesis of N-(2,6-dioxopiperidin-3-yl)-2-acetamido-4-methoxythiophene-3-carboxamide (70)



Step A: H_2SO_4 (1 mL) was added dropwise to a stirred suspension of methyl 2-({[(9H-fluoren-9-yl)methoxy]carbonyl}amino)-4-oxo-4,5-dihydrothiophene-3-carboxylate (9.65 g, 24.4 mmol) in MeOH (200 mL). The reaction mixture was refluxed for 16 h, cooled to RT and filtered to give 2-({[(9H-fluoren-9-yl)methoxy]carbonyl}amino)-4-methoxythiophene-3-carboxylate (63% yield).

Step B: Morpholine (13.5 g, 155 mmol) was added to a solution of methyl 2-({[(9H-fluoren-9-yl)methoxy]carbonyl}amino)-4-methoxythiophene-3-carboxylate (6.3 g, 15.4 mmol) in dichloromethane (100 mL) and the reaction mixture was stirred overnight at room temperature, concentrated under reduced pressure, diluted with MTBE, filtered, and rinsed with small amount of MTBE. The filtrate was evaporated in vacuo to give crude methyl 2-amino-4-methoxythiophene-3-carboxylate, which was used in the next step without further purification.

Step C: methyl 2-acetamido-4-methoxythiophene-3-carboxylate was obtained in 73% yield using Example Method 3, above, with methyl 2-amino-4-methoxythiophene-3-carboxylate as a starting material.

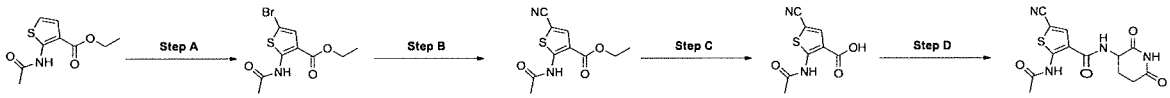
Step D: 2-acetamido-4-methoxythiophene-3-carboxylic acid was obtained in 20% yield using Example Method 2, above, with methyl 2-acetamido-4-methoxythiophene-3-carboxylate as a starting material.

Step E: N-(2,6-dioxopiperidin-3-yl)-2-acetamido-4-methoxythiophene-3-carboxamide was synthesized using the general procedure shown in Reaction Scheme 1 and Synthetic Conditions E, above (47% yield), and 2-acetamido-4-methoxythiophene-3-carboxylic acid as a starting material.

^{1}H NMR (500MHz, DMSO) δ 12.05 (s, 1H), 10.92 (s, 1H), 8.30 (d, *J* = 7.1 Hz, 1H), 6.14 (s, 1H), 4.76 – 4.66 (m, 1H), 3.83 (s, 3H), 2.82 – 2.70 (m, 1H), 2.58 – 2.52 (m, 1H), 2.19 (s, 3H), 2.16 – 2.06 (m, 2H)

LCMS (m/z $[M+H]^+$): 326.2

Example 90: Synthesis of 5-cyano-N-(2,6-dioxopiperidin-3-yl)-2-acetamidothiophene-3-carboxamide (71)



Step A: Ethyl 2-acetamidothiophene-3-carboxylate (11 g, 51.6 mmol) was dissolved in AcOH (110 mL) and solution of bromine (3.2 mL, 61.9 mmol) in AcOH (55 mL) was added dropwise over 15 min at RT. The reaction mixture was stirred at RT for 18h, concentrated under reduced pressure and diluted water. The precipitate was filtered, washed with water and dried to give ethyl 5-bromo-2-acetamidothiophene-3-carboxylate (93% yield).

Step B: $Zn(CN)_2$ (8.45 g, 72 mmol) and $Pd(dppf)Cl_2$·DCM (3.92 g, 4.8 mmol) were added to a solution of ethyl 5-bromo-2-acetamidothiophene-3-carboxylate (14 g, 48 mmol) in DMF (120 mL). Argon was bubbled through the reaction mixture for 10 min, then the reaction mixture was stirred at 150°C for 16 h, cooled to RT, filtered and washed with EtOAc. The organic layer was dried over Na_2SO_4, concentrated under reduced pressure and purified by flash column chromatography to give 5-cyano-2-acetamidothiophene-3-carboxylate (83% yield).

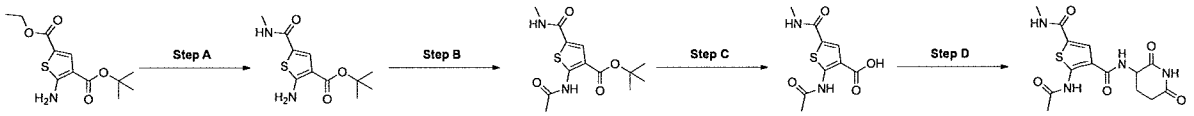
Step C: Ethyl 5-cyano-2-acetamidothiophene-3-carboxylate (9.45 g, 39.7 mmol) was dissolved in EtOH:THF solution (120 mL:360 mL), the solution was cooled to +5°C and lithium hydroxide monohydrate (11.7 g, 278 mmol) in H_2O (120 mL) was added dropwise over 20 min. The reaction mixture was stirred ar RT for 18h, concentrated under reduced pressure and acidified with 15% citric acid. The product was extracted with EtOAc, dried over Na_2SO_4 and evaporated under reduced pressure to give 5-cyano-2-acetamidothiophene-3-carboxylic acid (57% yield).

Step D: 5-cyano-*N*-(2,6-dioxopiperidin-3-yl)-2-acetamidothiophene-3-carboxamide was synthesized using the general procedure shown in Reaction Scheme 1 and Synthetic Conditions D, above (35% yield), and 5-cyano-2-acetamidothiophene-3-carboxylic acid as a starting material.

^{1}H NMR (400MHz, DMSO) δ 12.08 (s, 1H), 10.94 (s, 1H), 8.89 (d, *J* = 7.9 Hz, 1H), 8.27 (s, 1H), 4.82 – 4.65 (m, 1H), 2.87 – 2.72 (m, 1H), 2.62 – 2.53 (m, 1H), 2.30 (s, 3H), 2.24 – 2.08 (m, 1H), 2.06 – 1.93 (m, 1H)

LCMS (m/z $[M+H]^+$): 321.0

Example 91: Synthesis of 5-acetamido-*N*^{4}-(2,6-dioxopiperidin-3-yl)-5-acetamido-*N*^{2}-methylthiophene-2,4-dicarboxamide (74)



Step A: 4-*tert*-butyl 2-ethyl 5-aminothiophene-2,4-dicarboxylate (3.71 g, 13.7 mmol) was added to 20% solution of methylamine in methanol (20 mL) and the reaction mixture was stirred for 5 days at 70°C, concentrated under reduced pressure and triturated with isopropyl alcohol:hexane (1:1). The precipitate was filtered to give *tert*-butyl 2-amino-5-(methylcarbamoyl)thiophene-3-carboxylate (93% yield).

Step B: Triethylamine (3.3 g, 32.6 mmol), DMAP (0.13 g, 1.06 mmol) and acetic acid (1.67 g, 27.8 mmol) were added to a solution of *tert*-butyl 2-amino-5-(methylcarbamoyl)thiophene-3-carboxylate (2.8 g, 10.9 mmol) in dry MeCN (30 mL). The reaction mixture was stirred overnight at 50°C, cooled to room temperature, diluted with water, extracted with DCM, dried over Na_2SO_4 and concentrated under reduced pressure to give *tert*-butyl 2-acetamido-5-(methylcarbamoyl)thiophene-3-carboxylate (95% yield).

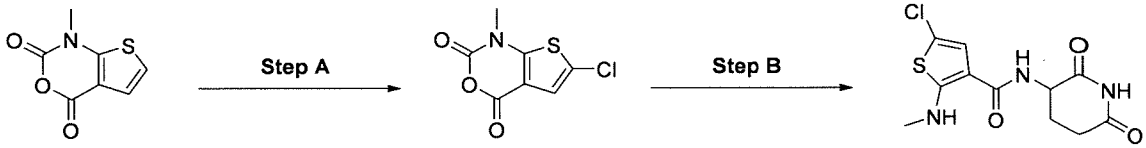
Step C: 10% HCl in dioxane (20 mL) was added to a solution of *tert*-butyl 2-acetamido-5-(methylcarbamoyl)thiophene-3-carboxylate (3.1 g, 10.4 mmol) in DCM (20 mL) and the reaction mixture was stirred for 3 days at RT. The precipitate was filtered, washed with DCM and dried to give 2-acetamido-5-(methylcarbamoyl)thiophene-3-carboxylic acid (60% yield).

Step D: N^4-(2,6-dioxopiperidin-3-yl)-5-acetamido-N^2-methylthiophene-2,4-dicarboxamide was synthesized using the general procedure shown in Reaction Scheme 1 and Synthetic Conditions E, above (44% yield), and 2-acetamido-5-(methylcarbamoyl)thiophene-3-carboxylic acid as a starting material.

^{1}H NMR (400MHz, DMSO) δ 11.84 (s, 1H), 10.92 (s, 1H), 8.78 (d, *J* = 8.1 Hz, 1H), 8.35 – 8.25 (m, 1H), 7.96 (s, 1H), 4.81 – 4.68 (m, 1H), 2.85 – 2.74 (m, 1H), 2.73 (d, *J* = 4.4 Hz, 3H), 2.62 – 2.52 (m, 1H), 2.24 (s, 3H), 2.20 – 2.07 (m, 1H), 2.04 – 1.93 (m, 1H)

LCMS (m/z $[M+H]^+$): 352.9

Example 92: Synthesis of 5-chloro-N-(2,6-dioxopiperidin-3-yl)-2-(methylamino)thiophene-3-carboxamide (76)



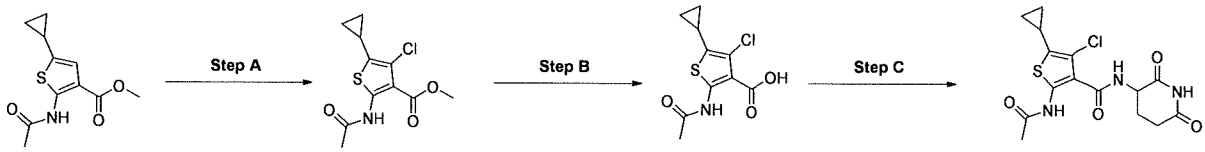
Step A: *N*-chlorosuccinimide (0.884 g, 6.62 mmol) was added to a solution of 1-methyl-1*H*,2*H*,4*H*-thieno[2,3-d][1,3]oxazine-2,4-dione (1 g, 5.46 mmol) in mixture of toluene (4 mL) and acetic acid (4 mL). The reaction mixture was stirred at 70°C for 2h, concentrated under reduced pressure, diluted with water and filtered. The solids were washed with water and dried 6-chloro-1-methyl-1*H*,2*H*,4*H*-thieno[2,3-d][1,3]oxazine-2,4-dione (72% yield).

Step B: 3-Aminopiperidine-2,6-dione hydrochloride (0.655 g, 3.98 mmol) and triethylamine (0.483 g, 4.77 mmol) were added to a solution of 6-chloro-1-methyl-1*H*,2*H*,4*H*-thieno[2,3-d][1,3]oxazine-2,4-dione (0.865 g, 3.97 mmol) in ethanol (20 mL) and the reaction mixture was refluxed for 18h, concentrated under reduced pressure and diluted with water. The precipitate was filtered, washed with water and isopropyl alcohol, and dried to give 5-chloro-N-(2,6-dioxopiperidin-3-yl)-2-(methylamino)thiophene-3-carboxamide (44% yield).

^{1}H NMR (400MHz, DMSO) δ 10.79 (s, 1H), 8.18 – 8.04 (m, 1H), 8.03 – 7.91(m, 1H), 7.26 (s, 1H), 4.68 – 4.52 (m, 1H), 2.85 (s, 3H), 2.79 – 2.67 (m, 1H), 2.60 – 2.53 (m, 1H), 2.16 – 2.01 (m, 1H), 1.99 – 1.85 (m, 1H).

LCMS (m/z $[M+H]^+$): 302.2

Example 93: Synthesis of 4-chloro-5-cyclopropyl-N-(2,6-dioxopiperidin-3-yl)-2-acetamidothiophene-3-carboxamide (77)



Step A: SO_2Cl_2 (0.207 g, 1.53 mmol) was added to a solution of methyl 5-cyclopropyl-2-acetamidothiophene-3-carboxylate (0.306 g, 1.28 mmol) in $CHCl_3$ (15 mL). The reaction mixture was refluxed for 2 h, concentrated under reduced pressure and diluted with water. The product was extracted with EtOAc, dried over Na_2SO_4 and concentrated under reduced pressure to give methyl 4-chloro-5-cyclopropyl-2-acetamidothiophene-3-carboxylate (81% yield).

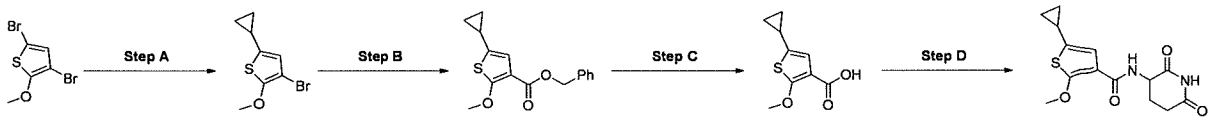
Step B: 4-chloro-5-cyclopropyl-2-acetamidothiophene-3-carboxylic acid was obtained in 78% yield using Example Method 2, above, with methyl 4-chloro-5-cyclopropyl-2-acetamidothiophene-3-carboxylate as a starting material.

Step C: HATU (0.370 g, 0.973 mmol) was added to the solution of 4-chloro-5-cyclopropyl-2-acetamidothiophene-3-carboxylic acid (0.211 g, 0.812 mmol), 3-aminopiperidine-2,6-dione (0.134 g, 1.05 mmol) and *N*-methylmorpholine (0.205 g, 2.03 mmol) in DMF (5 mL) at 0°C. The reaction mixture was stirred overnight at room temperature, diluted with water, extracted with AcOEt, dried over Na_2SO_4, concentrated under reduced pressure and purified by HPLC to give 4-chloro-5-cyclopropyl-N-(2,6-dioxopiperidin-3-yl)-2-acetamidothiophene-3-carboxamide (41% yield).

^1H NMR (400MHz, DMSO) δ 11.07 (s, 1H), 11.04 (s, 1H), 8.54 (d, J = 8.2 Hz, 1H), 4.90 – 4.78 (m, 1H), 2.89 – 2.72 (m, 1H), 2.65 – 2.52 (m, 2H), 2.16 (s, 3H), 2.12 – 1.98 (m, 2H), 1.08 – 0.98 (m, 2H), 0.71 – 0.58 (m, 2H).

LCMS (m/z $[M+H]^+$): 369.8

Example 94: Synthesis of 5-cyclopropyl-*N*-(2,6-dioxopiperidin-3-yl)-2-methoxythiophene-3-carboxamide (83)



Step A: To a stirred solution of 3,5-dibromo-2-methoxythiophene (500.0 mg, 1.845 mmol) in toluene (9 mL) was added cyclopropyl boronic acid (206 mg, 2.399 mmol) and K_3PO_4 (784 mg, 3.69 mmol) in water (3 ml), the reaction mixture was purged with argon for 15 min and then $Pd(PPh_3)_4$ (320 mg, 0.277 mmol) was added. The reaction was stirred at 90 °C for 20h, filtered through celite bed, concentrated under reduced pressure and purified by flash column chromatography to give 3-bromo-5-cyclopropyl-2-methoxythiophene (34% yield).

Step B: To a stirred solution of 3-bromo-5-cyclopropyl-2-methoxythiophene (700 mg, 3 mmol) in THF (20 mL) was added n-BuLi (1.8 M in THF) (3.4 mL, 6.005 mmol) dropwise at -78°C. Reaction mixture was stirred for 1h at -78°C and benzyl chloroformate (0.86 mL, 6 mmol) was added dropwise. The reaction was continued for 1h, quenched with water, extracted with ethyl acetate and concentrated under reduced pressure. The product was purified by flash column chromatography to give benzyl 5-cyclopropyl-2-methoxythiophene-3-carboxylate (23% yield).

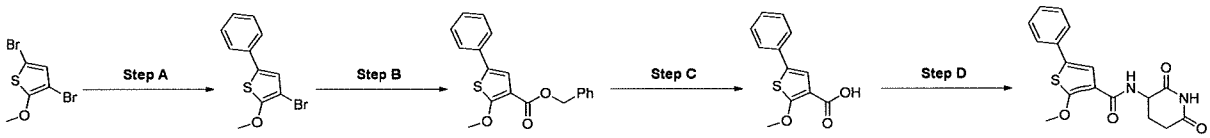
Step C: To a stirred solution of benzyl 5-cyclopropyl-2-methoxythiophene-3-carboxylate (350 mg, 1.215 mmol) in THF (6 mL) and methanol (6 mL) at 5-10 °C was added 50 % aq. NaOH (12 ml). The reaction mixture was stirred at RT for 16h and acidified with 6 M HCl. The solids were filtered, washed with pentane and dried to give 5-cyclopropyl-2-methoxythiophene-3-carboxylic acid (76% yield).

Step D: 5-cyclopropyl-*N*-(2,6-dioxopiperidin-3-yl)-2-methoxythiophene-3-carboxamide was synthesized using the general procedure shown in Reaction Scheme 1 and Synthetic Conditions C, above, (76% yield) using 5-cyclopropyl-2-methoxythiophene-3-carboxylic acid (20 mg) as a starting material.

^{1}H NMR (500 MHz, DMSO) δ 10.85 (s, 1H), 7.74 (d, *J* = 7.5 Hz, 1H), 6.78 (d, *J* = 1.0 Hz, 1H), 4.67 (ddd, *J* = 12.1, 7.5, 5.8 Hz, 1H), 4.00 (s, 3H), 2.77 (ddd, *J* = 17.3, 13.1, 6.1 Hz, 1H), 2.60 – 2.51 (m, 1H), 2.15 – 1.95 (m, 3H), 0.95 – 0.88 (m, 2H), 0.65 – 0.59 (m, 2H).

LCMS (m/z $[M+H]^+$): 309.0

Example 95: Synthesis of *N*-(2,6-dioxopiperidin-3-yl)-2-methoxy-5-phenylthiophene-3-carboxamide (84)



Step A: To 3,5-dibromo-2-methoxythiophene (4.0 g, 14.71 mmol) in dry THF (30 mL) was added 2.5M n-BuLi hexane solution (6.47 mL, 16.2 mmol) at -78 °C under argon atmosphere and the solution was stirred for 1h. Tri-n-butyl borate (8.35 mL, 29.42 mmol) was added to the reaction mixture, the mixture was stirred for 1.5h and warmed to RT. 20% Na_2CO_3 (33.6 mL), iodobenzene (1.65 mL, 14.71 mmol), and $Pd(PPh_3)_4$ (0.85 g, 0.73 mmol) were added and the reaction mixture was refluxed for 16h. The reaction mixture was extracted with ether, dried over $MgSO_4$, concentrated under reduced pressure and purified by flash column chromatography to give 3-bromo-2-methoxy-5-phenylthiophene (50% yield).

Step B: 3-Bromo-2-methoxy-5-phenylthiophene (900 mg, 3.34 mmol) was dissolved in THF (15 mL) and cooled to -78 °C. 1.8M n-BuLi in hexane (3.7 mL, 6.68 mmol) was added dropwise at -78°C. Reaction mixture was stirred for 1h at -78°C and benzyl chloroformate (0.95 mL, 6.68 mmol) was added dropwise. The reaction was continued for 1h, quenched with water, extracted with ethyl acetate and concentrated under reduced pressure. The product was purified by flash column chromatography to give benzyl 2-methoxy-5-phenylthiophene-3-carboxylate (23% yield).

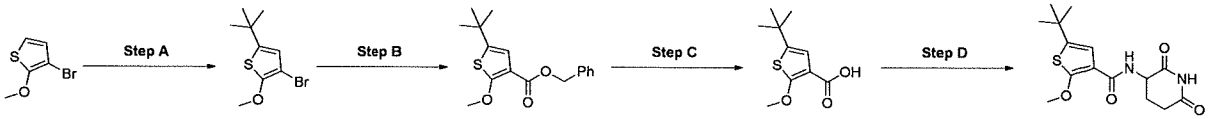
Step C: Benzyl 2-methoxy-5-phenylthiophene-3-carboxylate (230 mg, 0.71 mmol) was dissolved in THF (5 mL). MeOH (5 mL) and 50% NaOH solution (10 mL) were added and the reaction mixture was stirred at RT for 16h and acidified with 6 M HCl. The solids were filtered, washed with pentane and dried to give 2-methoxy-5-phenylthiophene-3-carboxylic acid (130 mg, 78%) as off white solid.

Step D: *N*-(2,6-dioxopiperidin-3-yl)-2-methoxy-5-phenylthiophene-3-carboxamide was synthesized using the general procedure shown in Reaction Scheme 1 and Synthetic Conditions C, above, (71% yield) using 2-methoxy-5-phenylthiophene-3-carboxylic acid (20 mg) as a starting material.

^{1}H NMR (500 MHz, DMSO) δ 10.88 (s, 1H), 7.87 (d, *J* = 7.6 Hz, 1H), 7.63 – 7.57 (m, 2H), 7.51 (s, 1H), 7.48 – 7.38 (m, 2H), 7.33 – 7.27 (m, 1H), 4.73 (ddd, *J* = 12.7, 7.6, 5.6 Hz, 1H), 4.12 (s, 3H), 2.79 (ddd, *J* = 17.3, 13.4, 5.8 Hz, 1H), 2.57 – 2.52 (m, 1H), 2.19 – 2.03 (m, 2H).

LCMS (m/z $[M+H]^+$): 345.2

Example 96: Synthesis of 5-(*tert*-butyl)-N-(2,6-dioxopiperidin-3-yl)-2-methoxythiophene-3-carboxamide (86)



Step A: To stirred solution of $AlCl_3$ (2.1 g, 15.544 mmol) in DCM (20 mL) at -78° C was added *tert*-butyl bromide (1.9 g, 13.472 mmol) in DCM (10 mL) dropwise at -78°C and stirred for 20 min. 3-bromo-2-methoxythiophene (2 g, 10.363 mmol) in DCM (10 mL) was added dropwise stirred for 2h. The reaction mixture was warmed to RT and stirred for another 16 h. The reaction mixture was quenched with water and extracted with DCM, concentrated under reduced pressure and purified by flash column chromatography to give 3-bromo-5-(*tert*-butyl)-2-methoxythiophene (31% yield).

Step B: To a stirred solution of 3-bromo-5-(*tert*-butyl)-2-methoxythiophene (900 mg, 3.614 mmol) in THF (22 mL) was added n-BuLi (1.8 M in THF) (4ml, 7.229 mmol) dropwise at -78°C. Reaction mixture was stirred for 1h at -78°C and benzyl chloroformate (1.03 ml, 7.229 mmol) was added dropwise. The reaction was continued for 1h, quenched with water, extracted with ethyl acetate and concentrated under reduced pressure. The product was purified by flash column chromatography to give benzyl 5-(*tert*-butyl)-2-methoxythiophene-3-carboxylate (220 mg, 20% yield) as light yellow oil.

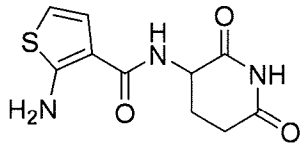
Step C: To a stirred solution of benzyl 5-(*tert*-butyl)-2-methoxythiophene-3-carboxylate (450 mg, 1.47 mmol) in THF (8 mL) and methanol (8mL) at 5 °C was added 50 % aq. NaOH (16 mL). The reaction mixture was stirred at RT for 16h and acidified with 6 M HCl. The solids were filtered, washed with pentane and dried to give 5-(*tert*-butyl)-2-methoxythiophene-3-carboxylic acid (69% yield).

Step D: 5-(*tert*-butyl)-*N*-(2,6-dioxopiperidin-3-yl)-2-methoxythiophene-3-carboxamide was synthesized using the general procedure shown in Reaction Scheme 1 and Synthetic Conditions C, above, (75% yield) using 5-(*tert*-butyl)-2-methoxythiophene-3-carboxylic acid (20 mg) as a starting material.

^{1}H NMR (500 MHz, DMSO) δ 10.85 (s, 1H), 7.75 (d, *J* = 7.5 Hz, 1H), 6.83 (s, 1H), 4.68 (ddd, *J* = 12.2, 7.5, 5.7 Hz, 1H), 4.02 (s, 3H), 2.77 (ddd, *J* = 17.3, 13.3, 6.0 Hz, 1H), 2.57 – 2.52 (m, 1H), 2.17 – 1.99 (m, 2H), 1.31 (s, 9H).

LCMS (m/z [M+H]$^+$): 325.2

Example 97: Synthesis of 2-amino-N-(2,6-dioxopiperidin-3-yl)thiophene-3-carboxamide (87)

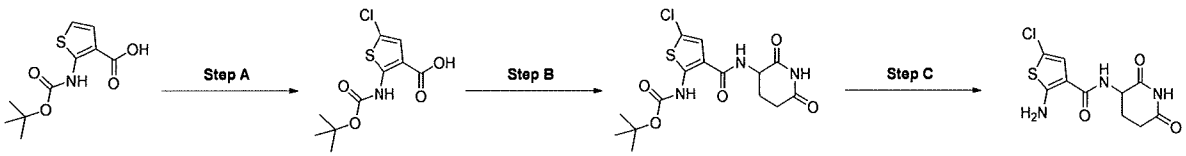


Tert-butyl (3-((2,6-dioxopiperidin-3-yl)carbamoyl)thiophen-2-yl)carbamate (1.0 g, 2.8 mmol) was dissolved in dichloromethane (10 mL) and a 10% solution of HCl in dioxane (3 mL) was added dropwise. The reaction mixture was stirred for 48 h at room temperature. The mixture was concentrated under reduced pressure and purified by preparative HPLC to give 2-amino-N-(2,6-dioxopiperidin-3-yl)thiophene-3-carboxamide (4% yield).

^{1}H NMR (500 MHz, DMSO) δ 10.78 (s, 1H), 7.96 (d, *J* = 8.3 Hz, 1H), 7.22 (s, 2H), 7.07 (d, *J* = 5.8 Hz, 1H), 6.28 (d, *J* = 8.3 Hz, 1H), 4.69 – 4.61 (m, 1H), 2.82 – 2.68 (m, 1H), 2.57 – 2.52 (m, 1H), 2.15 – 2.04 (m, 1H), 1.96 – 1.84 (m, 1H).

LCMS (m/z [M+H]$^+$): 254.0

Example 98: Synthesis of 2-amino-5-chloro-N-(2,6-dioxopiperidin-3-yl)thiophene-3-carboxamide (89)



Step A: *N*-chlorosuccinimide (2.2 g, 16.5 mmol) was added to a solution of 2-((*tert*-butoxycarbonyl)amino)thiophene-3-carboxylic acid (3.3 g, 13.6 mmol) in DMF (20 mL) and the reaction mixture was stirred at RT for 2 h. The mixture was diluted with water and filtered. The

solids were washed with water and dried to give 2-{[(*tert*-butoxy)carbonyl]amino}-5-chlorothiophene-3-carboxylic acid (84% yield).

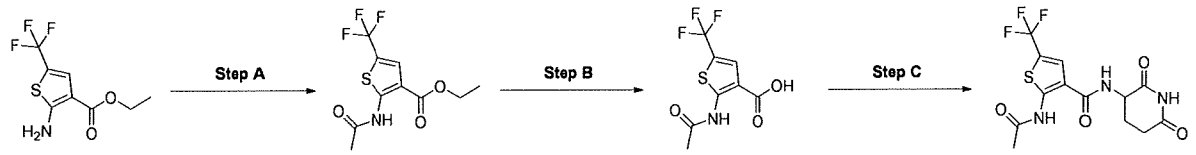
Step B: *Tert*-butyl N-{5-chloro-3-[(2,6-dioxopiperidin-3-yl)carbamoyl]thiophen-2-yl}carbamate was synthesized using the general procedure shown in Reaction Scheme 1 and Synthetic Conditions D, above (81% yield), and 2-{[(*tert*-butoxy)carbonyl]amino}-5-chlorothiophene-3-carboxylic acid as a starting material.

Step C: 10% HCl in dioxane (2 mL) was added dropwise to a solution of the *tert*-butyl *N*-{5-chloro-3-[(2,6-dioxopiperidin-3-yl)carbamoyl]thiophen-2-yl}carbamate (2.0 g, 5.16 mmol) in dichloromethane (15 mL) and the mixture was stirred in ultrasonic bath for 8 h, concentrated under reduced pressure and purified by HPLC to give 2-amino-5-chloro-N-(2,6-dioxopiperidin-3-yl)thiophene-3-carboxamide (15% yield).

^{1}H NMR (400MHz, DMSO) δ 10.81 (s, 1H), 7.97 (d, *J* = 8.3 Hz, 1H), 7.41 (brs, 2H), 7.13 (s, 1H), 4.66 – 4.56 (m, 1H), 2.83 – 2.68 (m, 1H), 2.59 – 2.52 (m, 1H), 2.13 – 1.99 (m, 1H), 1.97 – 1.82 (m, 1H)

LCMS (m/z $[M+H]^+$): 288.1

Example 99: Synthesis of N-(2,6-dioxopiperidin-3-yl)-2-acetamido-5-(trifluoromethyl)thiophene-3-carboxamide (90)



Step A: Triethylamine (0.397 g, 3.92 mmol) and acetic anhydride (0.400 g, 3.92 mmol) were added to a solution of ethyl 2-amino-5-(trifluoromethyl)thiophene-3-carboxylate (0.852 g, 3.56 mmol) in MeCN (15 mL). The reaction mixture was stirred overnight at 50°C, cooled to rt, concentrated under reduced pressure, and extracted with DCM, dried over Na_2SO_4, and concentrated to give ethyl 2-acetamido-5-(trifluoromethyl)thiophene-3-carboxylate (91% yield).

Step B: 10% solution of LiOH (0.081 g, 3.4 mmol) was added to a solution of ethyl 2-acetamido-5-(trifluoromethyl)thiophene-3-carboxylate (0.911 g, 3.24 mmol) in THF (15 mL) and the resulting mixture was stirred for 5 days at RT. The solvents were evaporated under reduced pressure, the

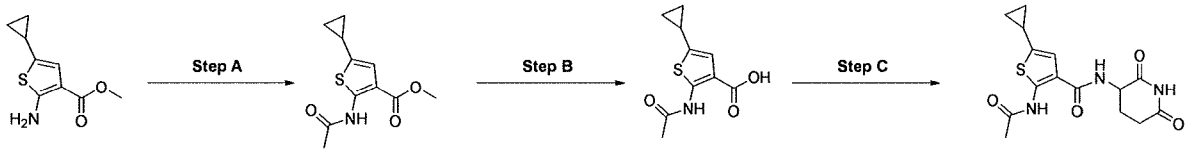
residue was diluted with water and washed with MTBE. The aqueous layer acidified by citric acid and the precipitate was filtered, washed with water, and dried to give 2-acetamido-5-(trifluoromethyl)thiophene-3-carboxylic acid (28% yield).

Step C: *N*-(2,6-dioxopiperidin-3-yl)-2-acetamido-5-(trifluoromethyl)thiophene-3-carboxamide was synthesized using the general procedure shown in Reaction Scheme 1 and Synthetic Conditions D, above (26% yield), and 2-acetamido-5-(trifluoromethyl)thiophene-3-carboxylic acid as a starting material.

^{1}H NMR (400MHz, DMSO) δ 11.98 (s, 1H), 10.93 (s, 1H), 9.00 – 8.81 (m, 1H), 8.13 (s, 1H), 4.87 – 4.62 (m, 1H), 2.98 – 2.65 (m, 2H), 2.28 (s, 3H), 2.20 – 2.08 (m, 1H), 2.07 – 1.88 (m, 1H).

LCMS (m/z $[M+H]^+$): 364.2

Example 100: Synthesis of 5-cyclopropyl-N-(2,6-dioxopiperidin-3-yl)-2-acetamidothiophene-3-carboxamide (91)



Step A: methyl 5-cyclopropyl-2-acetamidothiophene-3-carboxylate was synthesized in 69% yield using Example Method 3, above, using 2-amino-5-cyclopropylthiophene-3-carboxylate as a starting material.

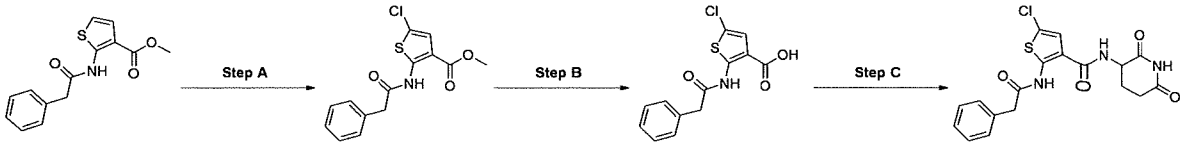
Step B: 5-cyclopropyl-2-acetamidothiophene-3-carboxylic acid was synthesized in 57% yield using Example Method 2, above, and methyl 5-cyclopropyl-2-acetamidothiophene-3-carboxylate as a starting material.

Step C: 5-cyclopropyl-N-(2,6-dioxopiperidin-3-yl)-2-acetamidothiophene-3-carboxamide was synthesized using the general procedure shown in Reaction Scheme 1 and Synthetic Conditions E, above (56% yield), and 5-cyclopropyl-2-acetamidothiophene-3-carboxylic acid as a starting material.

^{1}H NMR (400MHz, DMSO) δ 11.73 (s, 1H), 10.89 (s, 1H), 8.52 (d, J = 8.5 Hz, 1H), 7.09 (s, 1H), 4.76 – 4.64 (m, 1H), 2.85 – 2.71 (m, 1H), 2.62 – 2.53 (m, 1H), 2.22 – 2.04 (m, 4H), 2.04 – 1.89 (m, 2H), 1.00 – 0.87 (m, 2H), 0.68 – 0.57 (m, 2H)

LCMS (m/z $[M+H]^+$): 336.2

Example 101: Synthesis of 5-chloro-N-(2,6-dioxopiperidin-3-yl)-2-(2-phenylacetamido)thiophene-3-carboxamide (92)



Step A: Methyl 5-chloro-2-(2-phenylacetamido)thiophene-3-carboxylate was synthesized using Example Method 1, above (75% yield), using methyl 2-(2-phenylacetamido)thiophene-3-carboxylate as a starting material.

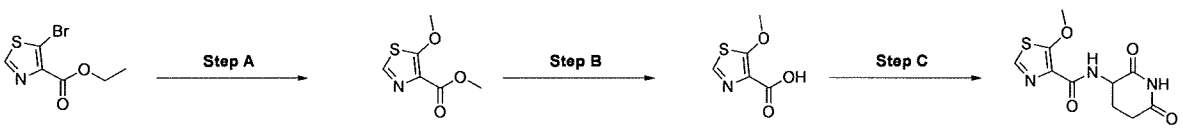
Step B: 5-chloro-2-(2-phenylacetamido)thiophene-3-carboxylic acid was synthesized using Example Method 2, above (82% yield), using methyl 5-chloro-2-(2-phenylacetamido)thiophene-3-carboxylate as a starting material.

Step C: 5-chloro-*N*-(2,6-dioxopiperidin-3-yl)-2-(2-phenylacetamido)thiophene-3-carboxamide was synthesized using the general procedure shown in Reaction Scheme 1 and Synthetic Conditions D, above (15% yield), with 5-chloro-2-(2-phenylacetamido)thiophene-3-carboxylic acid as a starting material.

^{1}H NMR (400MHz, DMSO) δ 11.94 (s, 1H), 10.91 (s, 1H), 8.72 – 8.54 (m, 1H), 7.66 – 7.45 (m, 2H), 7.43 – 7.21 (m, 4H), 4.82 – 4.64 (m, 1H), 3.90 (s, 2H), 2.89 – 2.71 (m, 1H), 2.61 – 2.53 (m, 1H), 2.17 – 2.02 (m, 1H), 2.01 – 1.88 (m, 1H)

LCMS (m/z $[M+H]^+$): 406.2

Example 102: Synthesis of *N*-(2,6-dioxopiperidin-3-yl)-5-methoxythiazole-4-carboxamide (100)



Step A: To a stirred solution of ethyl 5-bromothiazole-4-carboxylate (2.0 g, 8.475 mmol, 1eq) in methanol (24 mL) was added NaOMe (25% in MeOH) (3.8 ml, 16.95mmol, 2eq). The reaction

mixture was refluxed for 2h, cooled to RT and quenched by saturated ammonium chloride solution (10 mL). The mixture was concentrated under reduced pressure and purified by flash column chromatography to give methyl 5-methoxythiazole-4-carboxylate (27% yield).

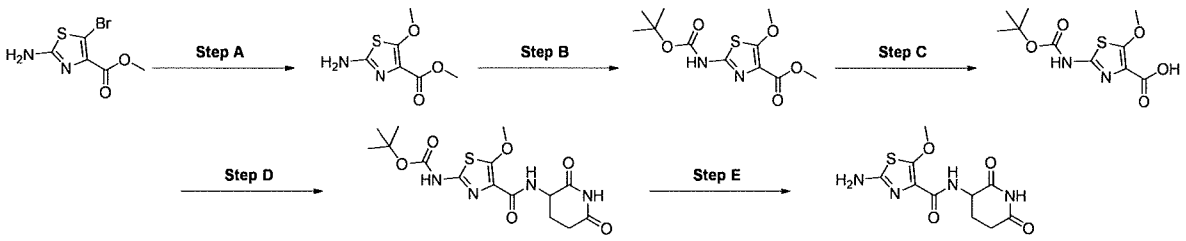
Step B: To a stirring solution of methyl 5-methoxythiazole-4-carboxylate (100 mg, 0.578 mmol, 1eq) in a solution of THF, MeOH, H_2O (4:2:1) (7 mL) was added LiOH, H_2O (73 mg, 1.734 mmol, 3eq). The reaction mixture was stirred at RT for 16h, evaporated, redissolved in water and washed with ethyl acetate. The aqueous layer was acidified by 0.5 M HCl, extracted with 10% MeOH in DCM, dried over Na_2SO_4, concentrated under reduced pressure and purified by flash column chromatography to give 5-methoxythiazole-4-carboxylic acid (32% yield).

Step C: *N*-(2,6-dioxopiperidin-3-yl)-5-methoxythiazole-4-carboxamide was synthesized using the general procedure shown in Reaction Scheme 1 and Synthetic Conditions C, above, (9% yield) using 5-methoxythiazole-4-carboxylic acid (20 mg) as a starting material.

^{1}H NMR (500 MHz, DMSO) δ 10.81 (s, 1H), 8.51 (s, 1H), 8.23 (d, *J* = 8.2 Hz, 1H), 4.67 (ddd, *J* = 12.5, 8.2, 5.3 Hz, 1H), 4.04 (s, 3H), 2.83 – 2.73 (m, 1H), 2.52 (dt, *J* = 3.9, 2.5 Hz, 1H), 2.19 – 2.09 (m, 1H), 1.97 (dtd, *J* = 12.7, 5.5, 2.6 Hz, 1H).

LCMS (m/z $[M+H]^+$): 269.8

Example 103: Synthesis of 2-amino-*N*-(2,6-dioxopiperidin-3-yl)-5-methoxythiazole-4-carboxamide (101)



Step A: To a stirring solution of methyl 2-amino-5-bromothiazole-4-carboxylate (1 g, 4.255 mmol, 1eq) in methanol (30 mL) was added NaOMe (25% in MeOH) (2.3 ml, 10.638 mmol, 2.5 eq). The reaction mixture was refluxed for 1.5 h, cooled to RT and quenched by saturated ammonium chloride solution (10 mL). The mixture was concentrated under reduced pressure and purified by flash column chromatography to give methyl 2-amino-5-methoxythiazole-4-carboxylate (50% yield).

Step B: Methyl 2-amino-5-methoxythiazole-4-carboxylate (400 mg, 2.128 mmol. 1eq.) was dissolved in DCM then were added triethylamine (0.532 mmol, 2eq.) and Boc_2O (0.532 mmol, 2 eq). The reaction mixture was stirred at RT for 18h, diluted with DCM and washed successively with water and brine, dried over Na_2SO_4, concentrated under reduced pressure and purified by flash column chromatography to give methyl 2-((*tert*-butoxycarbonyl)amino)-5-methoxythiazole-4-carboxylate (49% yield).

Step C: To a stirring solution of methyl 2-((*tert*-butoxycarbonyl)amino)-5-methoxythiazole-4-carboxylate (300 mg, 1.042 mmol, 1eq) in THF:MeOH:H_2O 3:2:1 (12 mL) was added LiOH·H_2O (131 mg, 3.125 mmol, 3eq). The reaction mixture was stirred at RT for 16h, evaporated, redissolved in water and washed with ethyl acetate. The aqueous layer was acidified by 0.5 M HCl, extracted with 10% MeOH in DCM, dried over Na_2SO_4, concentrated under reduced pressure and triturated with ether and pentane to give 2-((*tert*-butoxycarbonyl)amino)-5-methoxythiazole-4-carboxylic acid (49% yield).

Step D: *Tert*-butyl (4-((2,6-dioxopiperidin-3-yl)carbamoyl)-5-methoxythiazol-2-yl)carbamate was synthesized using the general procedure shown in Reaction Scheme 1 and Synthetic Conditions F, above (50 % yield), and 2-((*tert*-butoxycarbonyl)amino)-5-methoxythiazole-4-carboxylic acid (20 mg) as a starting material.

Step E: To a solution of *tert*-butyl (4-((2,6-dioxopiperidin-3-yl)carbamoyl)-5-methoxythiazol-2-yl)carbamate (19.6 mg, 0.051 mmol, 1 eq.) in water (3 mL) and dioxane (3 mL) was added 36% HCl (1.5 mL). The reaction was stirred at RT for 3h and concentrated under reduced pressure to give 2-amino-*N*-(2,6-dioxopiperidin-3-yl)-5-methoxythiazole-4-carboxamide hydrochloride (100% yield).

^{1}H NMR (500 MHz, DMSO) δ 10.84 (s, 1H), 7.75 (d, *J* = 7.8 Hz, 1H), 7.41 – 6.65 (m, 2H), 4.63 (ddd, *J* = 12.0, 7.8, 5.8 Hz, 1H), 3.89 (s, 3H), 2.75 (ddd, *J* = 17.3, 13.1, 6.2 Hz, 1H), 2.60 – 2.52 (m, 1H), 2.11 – 1.98 (m, 2H).

LCMS (m/z $[M+H]^+$): 285.0

Example 104: Synthesis of 2-amino-*N*-(2,6-dioxopiperidin-3-yl)thiazole-5-carboxamide (102)



To the suspension of *tert*-butyl (5-((2,6-dioxopiperidin-3-yl)carbamoyl)thiazol-2-yl)carbamate (71, 30 mg, 0.085 mmol, 1 eq) in DCM (1.5 mL) was added TFA (0.2 mL) and mixture was stirred for 18h at RT, concentrated under reduced pressure and purified by HPLC to give 2-amino-*N*-(2,6-dioxopiperidin-3-yl)thiazole-5-carboxamide (yield 37%).

^{1}H NMR (500 MHz, DMSO) δ 10.81 (s, 1H), 8.35 (d, *J* = 8.4 Hz, 1H), 7.64 (s, 1H), 7.49 (s, 2H), 4.64 (ddd, *J* = 12.5, 8.4, 5.4 Hz, 1H), 2.76 (ddd, *J* = 17.4, 13.3, 5.6 Hz, 1H), 2.53 – 2.51 (m, 2H), 2.05 (qd, *J* = 12.8, 4.3 Hz, 1H), 1.93 (dddd, *J* = 10.7, 8.1, 5.3, 2.9 Hz, 1H).

LCMS (m/z [M+H]$^+$): 255.2

SYNTHESIS OF LIGASE LIGAND MOIETIES – COMPOUNDS OF FORMULA (IIa) AND (IIb)

Example 105: Synthesis of 7-bromo-*N*-(2,6-dioxopiperidin-3-yl)thieno[3,4-*b*]pyridine-5-carboxamide (103)

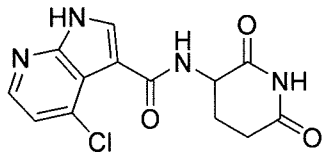


N-bromosuccinimide (96.8 mg, 0.544 mmol, 1.1 eq) was added to a suspension of N-(2,6-dioxopiperidin-3-yl)thieno[3,4-b]pyridine-7-carboxamide (143.0 mg, 0.494 mmol, 1.000 eq,) in DMF (4.9 mL) at ambient temperature. The reaction mixture was heated to 60°C and stirred for 3 h. The obtained crude compound was purified by HPLC to give 5-bromo-*N*-(2,6-dioxopiperidin-3-yl)thieno[3,4-*b*]pyridine-7-carboxamide (15% yield).

^{1}H NMR (500 MHz, DMSO) δ 10.97 (s, 1H), 9.53 (d, *J* = 7.4 Hz, 1H), 8.87 (dd, *J* = 4.0, 1.5 Hz, 1H), 8.11 (dd, *J* = 8.9, 1.5 Hz, 1H), 7.41 (dd, *J* = 8.9, 4.0 Hz, 1H), 4.91 (ddd, *J* = 12.8, 7.3, 5.6 Hz, 1H), 2.84 (ddd, *J* = 17.5, 13.4, 5.7 Hz, 1H), 2.57 (ddd, *J* = 17.4, 4.3, 2.3 Hz, 1H), 2.30 – 2.13 (m, 2H)

LCMS (m/z [M+H]$^+$): 368.37

Example 106: Synthesis of 4-chloro-*N*-(2,6-dioxopiperidin-3-yl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carboxamide (104)

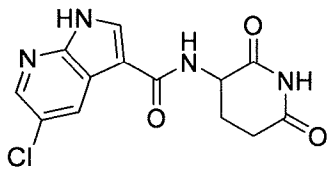


This compound was synthesized using the general procedure shown in Reaction Scheme 1 and Synthetic Conditions C, above, (15% yield) using 4-chloro-1*H*-pyrrolo[2,3-*b*]pyridine-3-carboxylic acid (20 mg) as a starting material.

^{1}H NMR (500 MHz, DMSO) δ 12.40 (s, 1H), 10.82 (s, 1H), 8.38 (d, *J* = 8.3 Hz, 1H), 8.22 (d, *J* = 5.1 Hz, 1H), 7.96 (s, 1H), 7.25 (d, *J* = 5.1 Hz, 1H), 4.79 – 4.72 (m, 1H), 2.79 (ddd, *J* = 17.9, 9.7, 7.0 Hz, 1H), 2.59 – 2.52 (m, 1H), 2.12 – 2.01 (m, 2H).

LCMS (m/z [M+H]$^+$): 306.9

Example 107: Synthesis of 5-chloro-*N*-(2,6-dioxopiperidin-3-yl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carboxamide (105)



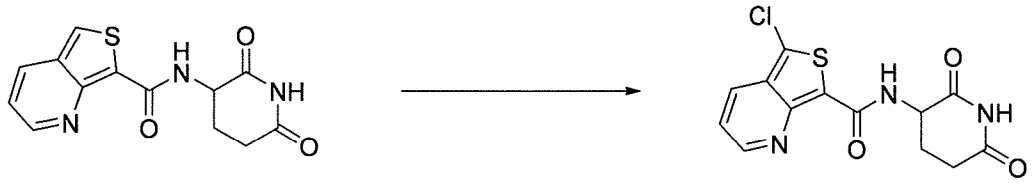
This compound was synthesized using the general procedure shown in Reaction Scheme 1 and Synthetic Conditions C, above, (31% yield) using 5-chloro-1*H*-pyrrolo[2,3-*b*]pyridine-3-carboxylic acid (20 mg) as a starting material.

^{1}H NMR (500 MHz, DMSO) δ 12.40 (s, 1H), 10.85 (s, 1H), 8.44 (d, *J* = 2.5 Hz, 1H), 8.39 (d, *J* = 8.4 Hz, 1H), 8.30 (d, *J* = 2.4 Hz, 1H), 8.27 (d, *J* = 2.9 Hz, 1H), 4.79 (ddd, *J* = 12.2, 8.3, 5.3 Hz, 1H), 2.81 (ddd, *J*

= 17.3, 13.2, 5.5 Hz, 1H), 2.59 – 2.52 (m, 1H), 2.11 (qd, *J* = 12.8, 4.4 Hz, 1H), 2.01 (dtd, *J* = 13.0, 5.4, 2.9 Hz, 1H).

LCMS (m/z $[M+H]^+$): 307.2

Example 108: Synthesis of 5-chloro-*N*-(2,6-dioxopiperidin-3-yl)thieno[3,4-*b*]pyridine-7-carboxamide (106)

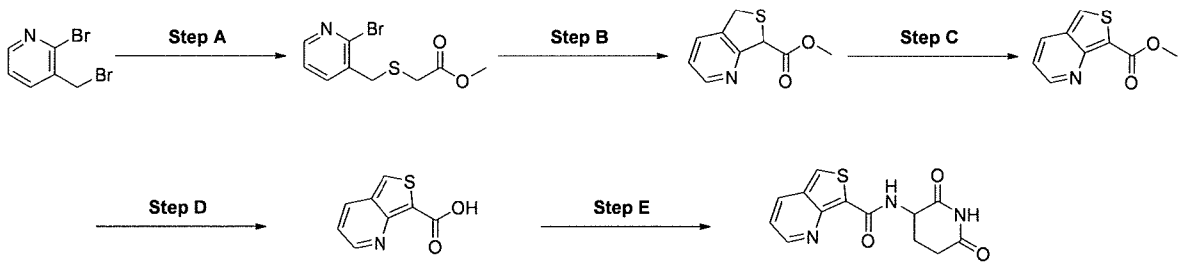


N-chlorosuccinimide (0.059 g, 0.442 mmol, 1.1 eq) was added to a suspension of *N*-(2,6-dioxopiperidin-3-yl)thieno[3,4-*b*]pyridine-7-carboxamide (0.116 g, 0.401 mmol) in DMF (5 mL) at RT. The reaction mixture was heated to 60°C and stirred for 3 h. The obtained crude compound was purified by HPLC to give 5-chloro-*N*-(2,6-dioxopiperidin-3-yl)thieno[3,4-*b*]pyridine-7-carboxamide (43% yield).

^{1}H NMR (400MHz, DMSO) δ 10.97 (s, 1H), 9.51 (d, *J* = 7.4 Hz, 1H), 8.91 – 8.83 (m, 1H), 8.19 (d, *J* = 8.8 Hz, 1H), 7.41 – 7.33 (m, 1H), 4.95 – 4.84 (m, 1H), 2.89 – 2.74 (m, 1H), 2.62 – 2.55 (m, 1H), 2.28 – 2.11 (m, 2H)

LCMS (m/z $[M+H]^+$): 323.8

Example 109: Synthesis of *N*-(2,6-dioxopiperidin-3-yl)thieno[3,4-*b*]pyridine-7-carboxamide (107)



Step A: To an ice-cold solution of 2-bromo-3-(bromomethyl)pyridine 2 (10.5 g, 42.0 mmol) in THF (100 mL) was added methyl thioglycolate (4.089g, 18.124mmol) followed by Et_3N under stirring. The

mixture was warmed to RT and stirred for further 30 min. The reaction mixture was diluted with water and extracted with DCM, dried over Na_2SO_4, concentrated under reduced pressure and purified by flash column chromatography to give methyl 2-{[(2-bromopyridin-3-yl)methyl]sulfanyl}acetate (53% yield).

Step B: A solution of methyl 2-{[(2-bromopyridin-3-yl)methyl]sulfanyl}acetate (4.5 g, 16.295 mmol) in THF (25 mL) was added slowly to a suspension of KH (1.307 g, 32.591 mmol) and stirred for 20 min at room temperature. The reaction mixture was then cooled to -78°C and treated with saturated aqueous NH_4Cl solution, warmed to RT, extracted with DCM, dried over Na_2SO_4, concentrated under reduced pressure and purified by flash column chromatography to give methyl 5*H*,7*H*-thieno[3,4-*b*]pyridine-7-carboxylate (56% yield).

Step C: To the stirred solution of methyl 5*H*,7*H*-thieno[3,4-*b*]pyridine-7-carboxylate (3 g, 15.385 mmol) in $CHCl_3$ (25 mL) was added activated MnO_2 (13.375 g, 153.846 mmol) and the reaction mixture was stirred at RT for 16h, filtered through celite bed, concentrated under reduced pressure and purified by flash column chromatography to give methyl thieno[3,4-*b*]pyridine-7-carboxylate (46% yield).

Step D: To a stirred solution of methyl thieno[3,4-*b*]pyridine-7-carboxylate (1.5 g, 7.772 mmol) in THF:MeOH:H_2O, 4:2:1 (14 mL) was added LiOH·H_2O (1.304g, 31.088 mmol) at 0°C and then ice-bath was removed and the mixture was stirred at RT for 2.5h. Saturated aqueous citric acid solution was added and the product was extracted with 10% MeOH in DCM, dried over Na_2SO_4, concentrated under reduced pressure and purified by HPLC to give thieno[3,4-*b*]pyridine-7-carboxylic acid (72 mg, 5%).

Step E: Synthesis of *N*-(2,6-dioxopiperidin-3-yl)thieno[3,4-*b*]pyridine-7-carboxamide was synthesized using the general procedure shown in Reaction Scheme 1 and Synthetic Conditions C, above (69 % yield), and thieno[3,4-*b*]pyridine-7-carboxylic acid (25.0 mg) as a starting material.

^{1}H NMR (500 MHz, DMSO) δ 10.95 (s, 1H), 9.71 (d, *J* = 7.4 Hz, 1H), 8.83 (dd, *J* = 4.0, 1.6 Hz, 1H), 8.59 (s, 1H), 8.32 (dd, *J* = 8.8, 1.6 Hz, 1H), 7.29 (dd, *J* = 8.7, 4.0 Hz, 1H), 4.92 (ddd, *J* = 12.7, 7.4, 5.4 Hz, 1H), 2.89 – 2.79 (m, 1H), 2.60 – 2.52 (m, 1H), 2.30 – 2.11 (m, 2H).

LCMS (m/z $[M+H]^+$): 290.0

COMPLEX FORMATION AND PROTEIN DEGRADATION EXAMPLES

Example 110: Ternary complex formation assay

The effect of the bifunctional compounds of the invention on the formation of a ternary complex composed of [MCL-1]–[compound of formula (I)]–[CRBN/DDB1] was investigated.

Two types of protein solution were prepared:

- 40 nM biotinylated hMCL-1, 40 µg/ml AlphaScreen Streptavidin-coated Donor Beads in PBS buffer with 0.1% Tween-20 and 1mM DTT,
- 200 nM 6XHis-CRBN/Strep-DDB1, 40 µg/ml AlphaLISA Anti-6xHis Acceptor beads in PBS buffer with 0.1% Tween-20 and 1mM DTT.

The prepared solutions were incubated at room temperature for 45 min and then the solution containing the donor beads was mixed with the solution containing the acceptor beads.

The tested compounds were dispensed onto a white 384-well AlphaPlate 384 SW. DMSO was backfilled to all wells, resulting in a final DMSO content of 2%. Wells containing only DMSO served as background. Next, 10 µl of solution with donor and acceptor beads was added to the wells.

The plate was sealed with transparent film and shaken using a VibroTurbulator for 60 sec at room temperature, level 3. The plate was then spun down shortly (10 s, 1000 rcf, room temperature) and incubated at 25°C for 30 min.

The read-out was performed with PerkinElmer Enspire Multimode Plate Reader (method for AlphaLISA 384-well low volume, Filterset: λexc = 680 nm, λem = 615 nm).

The results were analyzed as follows:

1) an average of luminescence for background signal was calculated and used as a negative control;

2) average of the maximum measured luminescence for 233 was calculated and used as an internal positive control;

3) raw luminescence values were normalized against positive and negative controls;

4) concentration points above the hook point were excluded;

5) EC50 and pEC50 values were determined.

As illustrated in Table 8, the compounds of the present invention have the capability to induce the formation of the [MCL-1]–[compound of formula (I)]–[CRBN/DDB1] complex.

Table 8: Ternary complex assay results for the compounds of the invention

Synonyms	Average pEC50 by molecule
210	>7.0
208	>7.0
216	>7.0
211	>7.0
267	>7.0
217	>7.0
215	>7.0
212	>7.0
213	>7.0
207	>7.0
214	>7.0
266	>7.0
247	>6.0
201	>7.0
206	>7.0
241	>7.0
263	>7.0
249	>7.0
248	>6.0

245	>6.0
204	>7.0
203	>7.0
251	>7.0
250	>7.0
233	>6.0
200	>6.0

Example 111: MCL-1protein degradation, Western blot

The effect of various compounds of the invention and the reference compounds on MCL-1 protein degradation in the OPM-2 cell line was investigated, using the degradation assay protocol below.

OPM-2 cells were maintained in RPMI-1640 medium, supplemented with penicillin/streptomycin and 10% Fetal Bovine Serum (FBS). During the treatment, FBS concentration was reduced to 1%.

Compound stocks were pre-diluted in DMSO and added directly to the cells growth medium (final DMSO concentration: 0.5%).

OPM-2 cells were collected, centrifuged (250 rcf, 5 min), resuspended in a growth medium containing 1% FBS and counted. The cell suspension was then adjusted to $1x10^6$ cell/ml using a growth medium containing 1% FBS. Afterwards, $0.5x10^6$ cells were seeded on 24-well plates in 0.5 mL of medium per well. Immediately after seeding cells, compounds in appropriate concentrations were added to the cell culture medium.

Following the treatment with the compounds, cells were collected from the plates and suspended in a lysis buffer (2% SDS, 50 mM Tris, pH 8.0, 100 U/ml Pierce Universal Nuclease for Cell Lysis, complete EDTA-free Protease Inhibitor Cocktail) and incubated on ice for 45 min. The amount of protein was determined via BCA assay, and the equal quantity of each sample was loaded on the precast gel for the protein separation. Following the electrophoresis and transfer to the membrane, the membrane

was stained with Ponceau (0.1 % (w/v) Ponceau in 5% acetic acid). After total protein detection, the stain was washed out using TBST. After the antibody staining for MCL-1 and α-tubulin, the membranes were washed and signals developed.

Densitometric values for MCL-1were normalized to total protein level (the Ponceau Stainıng). [%] of protein reduction is calculated in comparison to the cells treated with DMSO, which stand for 0%.

The results for the 6h treatment with 100nM compounds are shown in Table 9, using the following labels:

< 30% for 0-29% of MCL-1protein reduction,

≥ 30% for 30-49% of MCL-1protein reduction,

≥ 50% for 50-100% of MCL-1protein reduction.

As illustrated in Table 9, the compounds of the present invention have the capability to induce degradation of MCL-1protein with improved potency as compared to the known compound dMCL1-2.

Example 112: MCL-1protein degradation, Simple Western

The effect of various compounds of the invention and the reference compounds on MCL-1protein degradation in the OPM-2 cell line was investigated, using the degradation assay protocol below.

OPM-2 cells were maintained in RPMI-1640 medium, supplemented with penicillin/streptomycin and 10% Fetal Bovine Serum (FBS). During the treatment, FBS concentration was reduced to 1%.

Compound stocks were pre-diluted in DMSO and added directly to the cells growth medium (final DMSO concentration: 0.5%).

OPM-2 cells were collected, centrifuged (250 rcf, 5 min), resuspended in a growth medium containing 1% FBS and counted. The cell suspension was then adjusted to 1x106 cell/ml using a growth medium containing 1% FBS. Afterwards, 0.5x106 cells were seeded on 24-well plates in 0.5 mL of medium per

well. Immediately after seeding cells, compounds in appropriate concentrations were added to the cell culture medium.

Following the treatment with the compounds, cells were collected from the plates and suspended in a lysis buffer (2% SDS, 50 mM Tris, pH 8.0, 100 U/ml Pierce Universal Nuclease for Cell Lysis, cOmplete EDTA-free Protease Inhibitor Cocktail) and incubated on ice for 45 min.

The following steps, including sample loading, protein separation, immunoprobing or labelling, washes and detection analysis was performed using Jess from ProteinSimple, an automatic system for analyzing protein levels in cell lysates (12-230 kDa Jess or Wes separation module 8×25 capillaries, protein normalization assay, no. SM-PN01-1). The Protein of Interest was detected using MCL-1 (D35A5) Rabbit monoclonal antibody (Cell Signaling, #5453, LOT: 4). Antibody was diluted in a ratio of 1:100 in Antibody diluent.

[%] of protein reduction is calculated in comparison to the cells treated with DMSO, which stand for 0%.

The results for the 6h treatment with 100nM compounds are shown in Table 2, using the following labels:

< 20% for 0-19% of MCL-1protein reduction,

≥ 20% for 20-39% of MCL-1protein reduction,

≥ 40% for 40-100% of MCL-1protein reduction.

As illustrated in Table 9, the compounds of the present invention have the capability to induce degradation of MCL-1protein with improved potency as compared to the known compound dMCL1-2.

Table 9: MCL-1 protein degradation results for the compounds of the invention and the reference compound

Compound	Western blot, % of protein reduction	Simple Western, % of protein reduction
204	≥50%	≥40%
249	-	≥20%
263	≥50%	≥40%
241	≥50%	-
206	≥50%	≥40%
201	≥50%	≥20%
266	-	≥50%
214	≥50%	-
212	≥30%	≥40%
215	≥50%	≥20%
264	-	≥20%
217	-	≥40%
dMCL1-2	<30%	<20%

Example 113: Dose-dependent MCL-1 protein degradation and induction of apoptosis in cancer cells, Western blot

The experiments were performed as described for the "MCL-1 protein degradation, Western blot".

In addition to MCL-1 and α-Tubulin, PARP and cleaved caspase-3 were detected to monitor apoptosis.

Figure 2 presents the results of MCL-1 protein degradation and induction of apoptosis for the cells treated with 204, 212 or 215 at 0.01, 0.1 or 1 μM concentration for 6 hours or 24 hours, as indicated.

All tested compounds decreased MCL-1 protein level in a dose-dependent manner. At 1μM concentration, all compounds degraded over 80% of Mcl1-L protein both at 6h and 24h-time point. All compounds induced apoptosis, observed by the appearance of cleaved caspase 3 and cleaved PARP, at 1uM concentrations within 6 hours of treatment and 100nM and 1uM concentrations within 24 hours of treatment.

Figure 3A presents the results of MCL-1 protein degradation and induction of apoptosis for the cells treated with 204 and control compounds dMCL1-2 (Papatizamas et al., J. Med. Chem. 2019, 62, 11, 5522-5540) at 0.01, 0.03, 0.1, 0.3 or 1 μM concentration for 3 hours, 6 hours or 24 hours, as indicated.

Figure 3B presents the results of MCL-1 protein degradation and induction of apoptosis for the cells treated with 204 and control compounds C3 (Wang Z et al., J. Med. Chem. 2019, 62, 17, 8152-8163) at 0.1, 1 or 10 μM concentration for 24 hours, as indicated.

The results show that the compounds of the invention, as exemplified by 204 are more potent in terms of MCL-1 protein degradation and induction of apoptosis.

As illustrated in Figure 2 and Figure 3, the compounds of the present invention, as exemplified by 204, 212, and 215 have the capability to induce degradation of MCL-1 protein and apoptosis of OPM2 cells with improved potency as compared to the known compound dMCL1-2 and C3.

Example 114: Cell viability assays

The effect of various compounds of the invention on the viability of OPM-2, MV-4-11 and ARH-77 cell lines was investigated, using the CTG protocol described below.

OPM-2 and MV-4-11 cell lines are derived from multiple myeloma and acute myeloid leukaemia, respectively. Both cell lines are described in the literature as MCL-1 dependent lines, as opposed to lymphoblast–like ARH-77 cell line, which is described as independent of MCL-1 (Tron A E et al. Nat Commun. 2018; 9: 5341; Caenepeel S et al. Cancer Discov. 2018 Dec;8(12):1582-1597).

Cells (OPM-2, MV-4-11 or ARH-77) were seeded on 348-well plates in a growth medium with FBS reduced to 1%. Next, compound stocks were pre-diluted in DMSO and added directly to the cells growth medium (final DMSO concentration: 0.5%). Compound concentrations used in this assay: 1/3 dilutions starting at 30 uM (9 to 12 points).

After 24 hours of incubation, cell viability was evaluated using CellTiter-Glo Luminescent Cell Viability Assay (Promega, cat# G7572). Luminescence signal was measured using a CLARIOstar Plus Multi-Mode Microplate Reader (574-590 nm).

Results were normalized to DMSO control. Collected data were analyzed using GraphPad Prism to calculate pIC50 values, which are presented in Table 10. The representative dose-response graphs for 204 are shown in Figure 4.

Table 10: The effect of various compounds of the invention on the viability of OPM-2, MV-4-11 and ARH-77 cell lines

Compound	Average pIC50 by molecule OPM-2	Average pIC50 by molecule MV-2-11	Average pIC50 by molecule ARH-77
204	> 6.0	> 6.0	< 5.0
263	> 6.0	-	< 5.0
206	> 6.0	> 6.0	< 5.0
201	> 6.0	> 6.0	< 5.0
266	> 6.0	> 6.0	< 5.0
214	> 6.0	-	< 5.0
207	> 6.0	> 6.0	< 5.0
215	> 6.0	> 6.0	< 5.0

217	-	> 6.0	-
267	-	> 6.0	< 5.0
216	> 6.0	> 6.0	< 5.0
210	> 6.0	> 6.0	< 5.0
C3		5.0	

As illustrated in Table 10 and Figure 4, the compounds of the present invention, as exemplified by 204, 263, 206, 201, 266, 214, 207, 215, 217, 267, 216, and 210, have the capability to decrease the viability of multiple myeloma and acute myeloid leukaemia cells, thus can be useful in the treatment of cancer. Simultaneously, the compounds of the present invention have no / little impact on the viability of ARH-77, which further supports a specific, MCL-1 dependent activity of said compounds.

Example 115: Assessment of cardiac safety

The effect of various compounds of the invention and a reference compound AZD5991 on cardiac safety was investigated by the evaluation of caspase 3 and 7 activation using Caspase-Glo 3/7 Assay (Promega; G8092) in iCELLTM Cardiomyocytes from FUJIFILM Cellular Dynamics (Catalog number: 11713). In the Caspase-Glo® 3/7 Assay, the luminescence (measured as Relative Luciferase Units, RLU) is proportional to the amount of caspase activity present in each sample.

The assay is initiated by thawing and seeding iCell® Cardiomyocytes as specified in the User Guide. After 48 hours, the cells are washed to remove unattached cells and debris and immediately treated with compounds or DMSO diluted in the maintenance medium (FCDI; cat: M1003). Compound concentrations used in this assay: 7 points 1/3 dilution curve starting at 100 uM. After 24 hours of incubation with compounds, caspase activity is measured by the addition of the Caspase-Glo® 3/7 Reagent followed by the luminescence measurement.

The analysis of the results is performed by calculation of the fold change in caspase 3/7 activity at a given compound concentration. Fold change is calculated with the formula:

FOLD CHANGE = [(RLU Xi)-(RLU BG)]/{Average[(RLU C)-(RLU BG)]}

where:

RLU Xi is the Relative Luciferase Units of sample I;

RLU BG is the Background Relative Luciferase Units;

RLU C is the Relative Luciferase Units of Control (DMSO).

The experiments were performed in technical duplicates. The results are presented in Table 11. A representative dose-response curve is presented in Figure 5.

Table 11: The effect of various compounds of the invention and the reference compound on the caspase 3/7 activity in cardiomyocytes

Compound	Fold change at 1.2 uM
204	≤1.5 ± 0.2
206	≤1.5 ± 0.2
266	≤1.5 ± 0.2
214	≤1.5 ± 0.2
AZD5991	2.9±0.5

As illustrated in Table 11 and Figure 5, the compounds of the present invention, as exemplified by 204, 206, 266, 214 show little to no activity in caspase activity assay in cardiomyocytes, as opposed to the reference compound AZD5991.

Together, the results described in Examples 89, 90, and 91 demonstrate a surprising technical effect of compounds of the present invention which is the ability to induce apoptosis in cancer cells combined with no / little activity in cardiomyocytes.

Example 116: Induction of apoptosis in cancer cells, flow cytometry

The effect of compound 204 of the invention MV-4-11 cells was investigated using the following protocol.

MV-4-11 cells were seeded on 24-well plates (1 ml) in growth medium containing 1% FBS. Immediately after seeding, compounds in appropriate concentrations were added directly to the cell culture medium. After 24 hours incubation, cells were washed twice with cold DPBS and the staining was performed using the FITC Annexin V Apoptosis Detection Kit I (BD Pharmingen; 556547). Samples were then analyzed by flow cytometry (LSR Fortessa X-20; BD Biosciences) within 1 hr. Results were evaluated using FlowJo (V10) software.

Figure 6 presents the induction of apoptosis in MV-4-11 cells treated with 204 at 1, 3, 10, 30, and 100 nM concentration for 24 hours, as indicated.

As illustrated in Figure 6, the compounds of the invention, as exemplified by 204, cause a concentration dependent increase of the population of late apoptotic/cell death (Annexin +/PI +) cells after 24 hours of treatment.

ABBREVIATIONS AND DEFINITIONS

A list of the abbreviations used in the present application is shown in Table 3, below:

Table 10: Abbreviations

Abbreviation	Meaning
CRBN	Cereblon
DDB1	damaged DNA binding protein 1
TFA	trifluoroacetic acid
CDI	carbonyldiimidazole
FA	formic acid
MsCl	methanesulfonyl chloride
DBAD	di-tert-butyl azodicarboxylate
Tris	Tris(hydroxymethyl)aminomethane
DMSO	Dimethylsulfoxide
THF	tetrahydrofuran
DMF	dimethylformamide
DMA	dimethylacetamide
DMAP	4-dimethylaminopyridine
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
HPLC	High performance liquid chromatography
NCS	N-chlorosuccinimide
DIPEA	N,N-diisopropylethylamine
MTBE	Methyl tert-butyl ether
HATU	Hexafluorophosphate Azabenzotriazole Tetramethyl Uronium (1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazol[4,5-b]pyridinium-2-oxide hexafluorophosphate)

m-CPBA	*meta*-chloroperbenzoic acid
Pd(amphos)Cl_2	Bis(di-tert-butyl(4-dimethylaminophenyl)phosphine)dichloropalladium(II)
Pd(dppf)Cl_2 CH_2Cl_2	[1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane
DTT	dithiothreitol
RT	Room temperature

As used herein, the term "room temperature" means a temperature of between 20°C and 25°C.

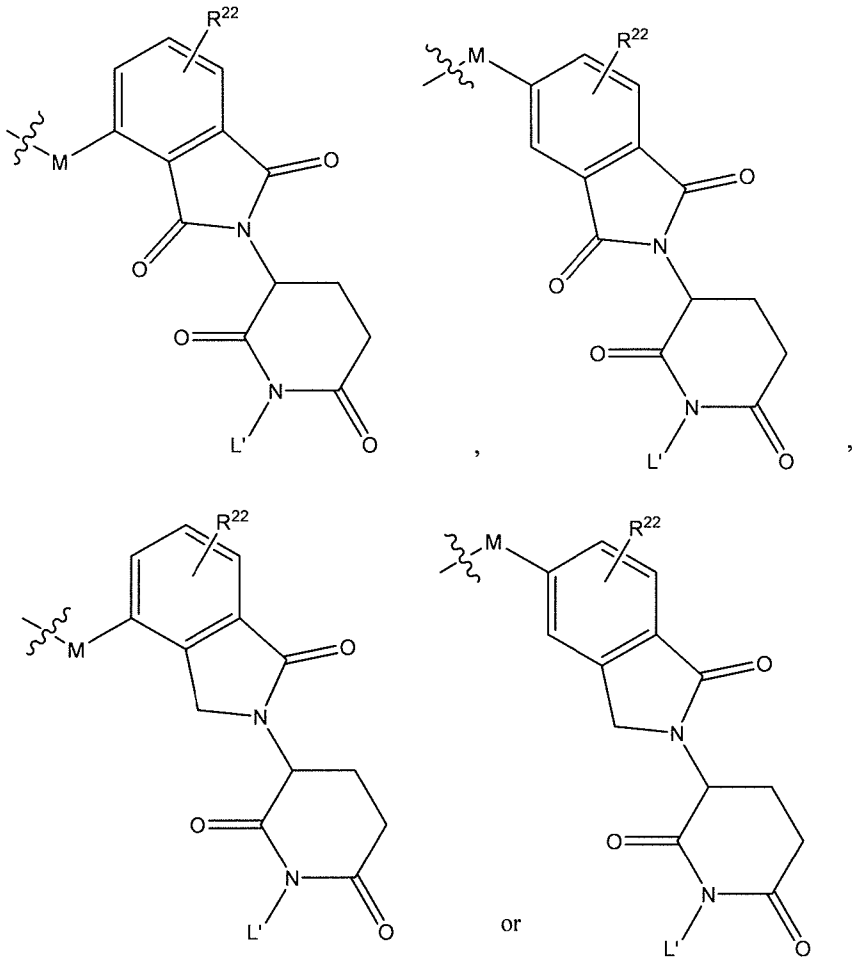
CLAIMS

1. A compound of formula (I)

[MCL-1 ligand moiety] – linker – [ligase ligand moiety] (I)

or a salt, solvate, hydrate, isomer or prodrug thereof,

wherein **[ligase ligand moiety]** is:



wherein

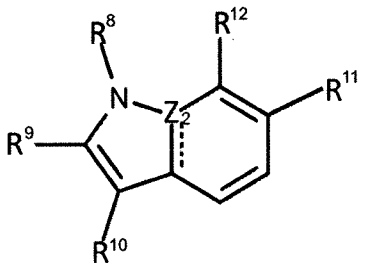
M is O or NH, or is absent;

 indicates attachment to $\mathbf{R^{18}}$ of the linker;

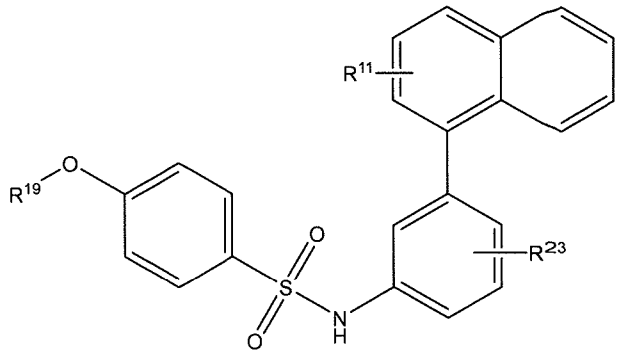
$\mathbf{R^{22}}$ is hydrogen, halogen or an amino group; and

L' is hydrogen, alkyl, benzyl, acetyl or pivaloyl;

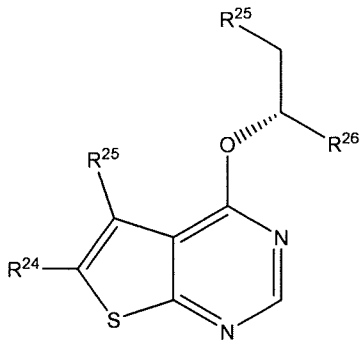
[MCL-1 ligand moiety] is a compound of Formula (A), Formula (B) or Formula (C)



(A)



(B)



(C)

wherein

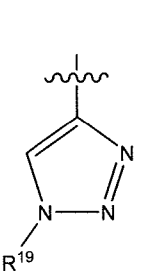
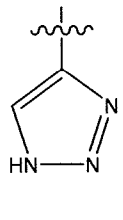
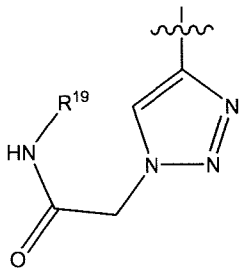
 is a single bond or a double bond;

$\mathbf{R^8}$ is H, $\mathbf{R^{19}}$, or C_1-C_6 alkyl optionally substituted with morpholine;

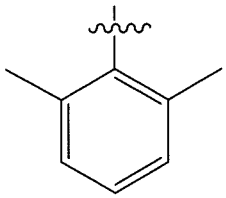
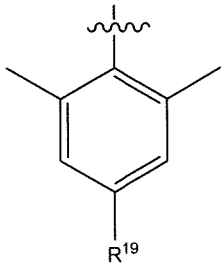
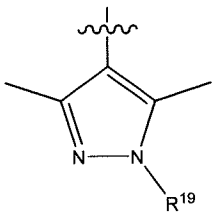
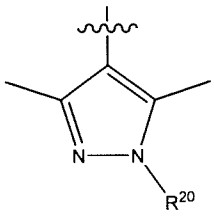
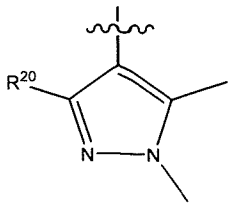
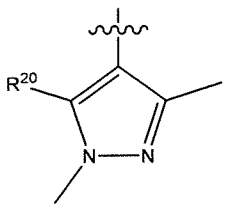
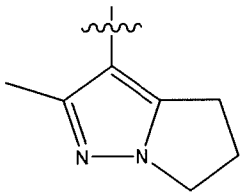
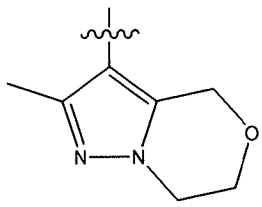
$\mathbf{R^9}$ is -C(O)OH, -C(O)OC_1-C_6alkyl; -C(O)NH_2; -C(O)O$\mathbf{R^{19}}$ or -C(O)NH$\mathbf{R^{19}}$,

$\mathbf{R^{10}}$ is -$C_{2\text{-}5}$alkyl-O-R^{13}, wherein R^{13} is phenyl, naphthyl or tetraline, wherein the phenyl, naphthyl or tetraline is optionally substituted with at least one substituent selected from halogen, C_1-C_6 alkyl and -O(C_1-C_6 alkyl); or wherein the naphthyl is optionally substituted with -O- or -S-,

$\mathbf{R^{11}}$ is H, halogen or C_1-C_6 alkyl,

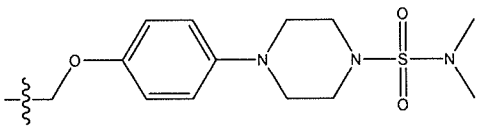




R^{12} is H,

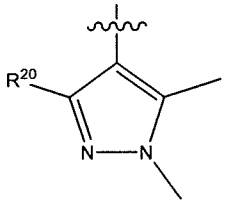









or

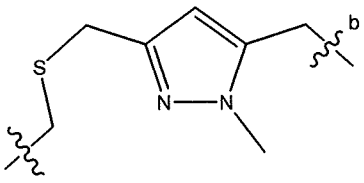
wherein R^{20} is Me, -CH_2-O-bromobenzaldehyde, or



; or when



R^{12} is and R^{10} is -O-naphthyl substituted with -O- or -S-, then R^{20} is



, wherein  indicates attachment to -O- or -S- of R^{10};

and wherein

R^{19} is a bond connected to R^{14} of the linker;

R^{23} is -C(O)OH or -C(O)OC_1-C_6alkyl;

Z_2 is N or C, wherein when Z_2 is N, then ⁄ is a single bond; and when Z_2 is C, then ⁄ is a double bond,

R^{24} is furan optionally substituted with at least one halogen,

each R^{25} is independently phenyl substituted with $-OR^{28}$ and optionally further substituted with at least one substituent selected from halogen and C_1-C_6 alkyl;

R^{26} is $-C(O)OR^{19}$ or $-C(O)NHR^{19}$; and

each R^{28} is independently $-C_{1-3}$alkyl-(N-alkyl piperazine) or $-C_{1-3}$alkyl-(N-haloalkylpyrazole)

and wherein each of Formula (A), Formula (B) and Formula (C) contains a single R^{19};

and wherein **[linker]** has the following formula

R^{14}-R^{15}-R^{16}-R^{17}-R^{18}

wherein

R^{14} is $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, -C(O)-, $-SO_2$- or is absent

R^{15} is cycloalkyl, heterocycloalkyl, aryl, heteroaryl, $-C_{1-6}$ alkyl-NH-, -cycloalkyl-NH- or is absent

R^{16} is $-C_{1-6}$ alkyl, -C(O)-, -C(O)-NH-, -C(O)O-, $-CH_2$-C(O)-, $-CH_2$-C(O)-NH-, $-CH_2$-C(O)O- or is absent

R^{17} is $-CH_2(C_2H_4-O)_y$, $(C_2H_4-O)_x$, $(C_3H_6-O)_x$, or is absent

x is 1-10

y is 2-10

R^{18} is $-C_{1-6}$ alkyl, heterocycloalkyl, or is absent

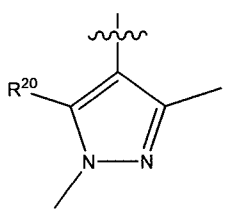
wherein at least one of R^{14}-R^{18} is present

with the proviso that:

when

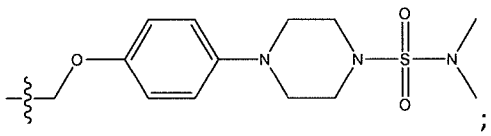
R^{10} is $-C_3H_6$-O-naphthyl,

R^{12} is



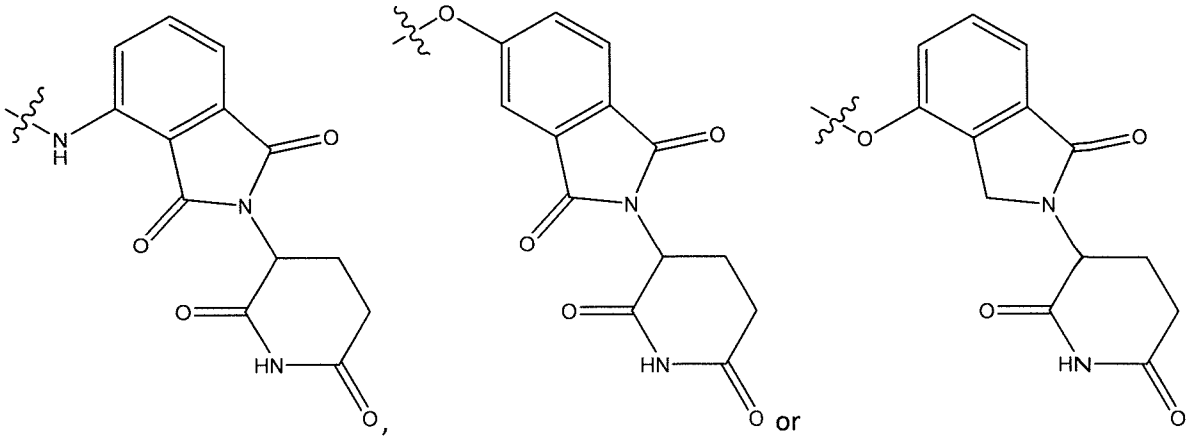
, and

R^{20} is



;

then R^9 is -C(O)OH, -C(O)OC_1-C_6alkyl or -C(O)NH_2, and **[ligase ligand moiety]** is



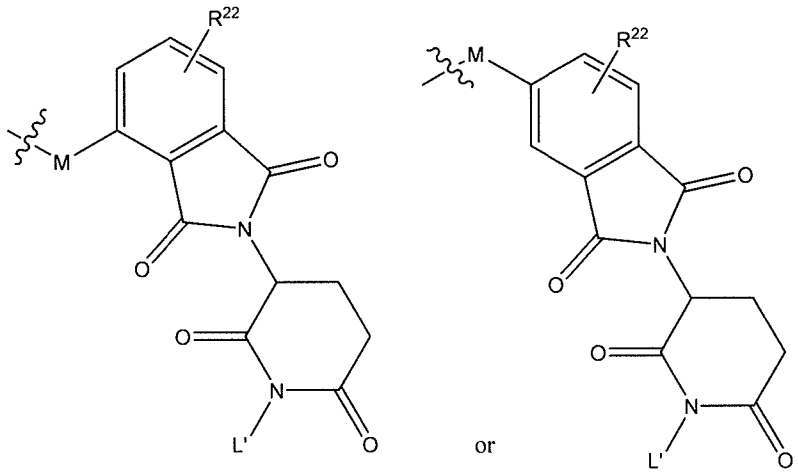
2. The compound of claim 1, wherein R^{22} is hydrogen or an amino group.

3. The compound of claim 2, wherein R^{22} is hydrogen.

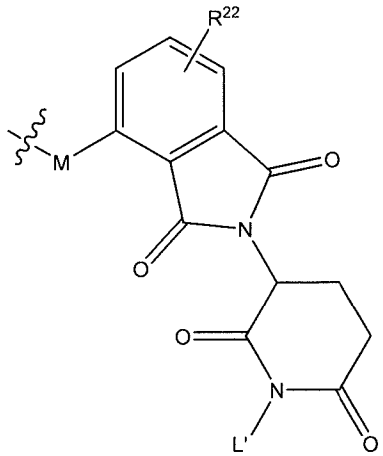
4. The compound of any one of claims 1-3, wherein **L'** is hydrogen or methyl.

5. The compound of claim 4, wherein **L'** is hydrogen.

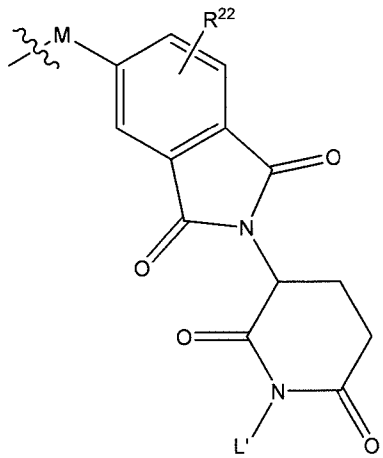
6. The compound of any one of claims 1-5, wherein **[ligase ligand moiety]** is:



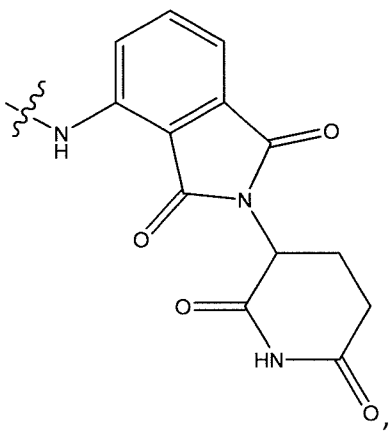
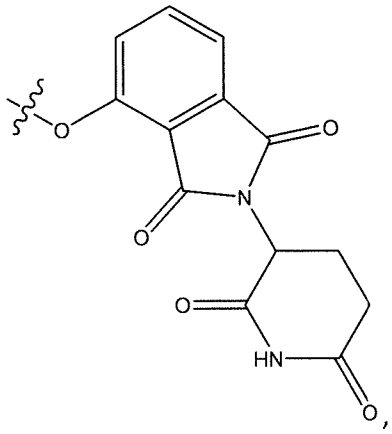
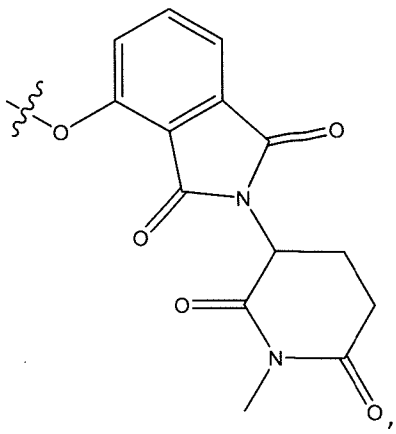
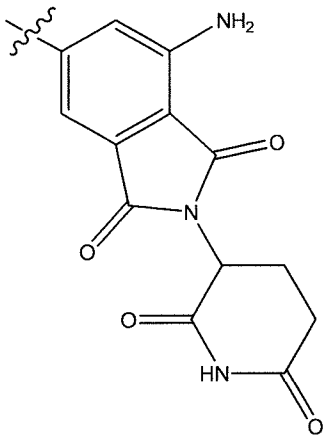
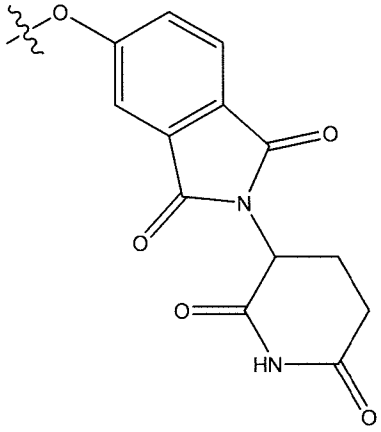
7. The compound of claim 6, wherein **[ligase ligand moiety]** is:



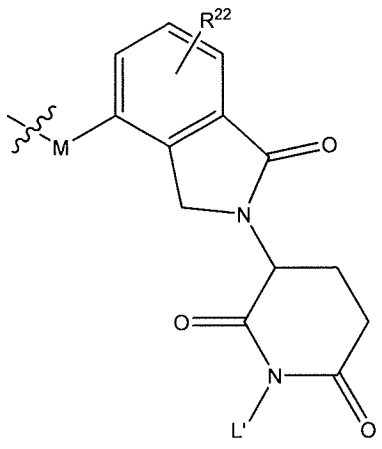
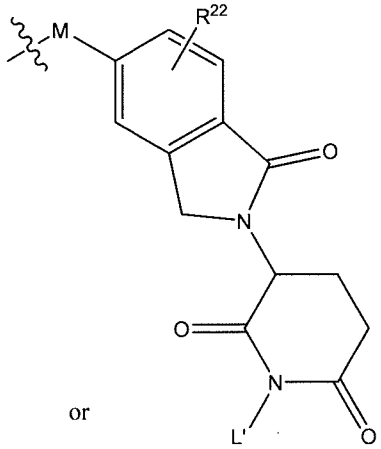
8. The compound of claim 6, wherein **[ligase ligand moiety]** is:



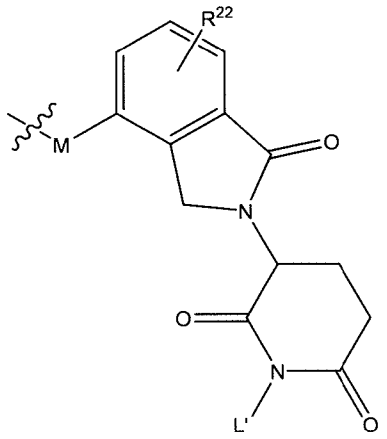
9. The compound of claim 6, wherein **[ligase ligand moiety]** is





or


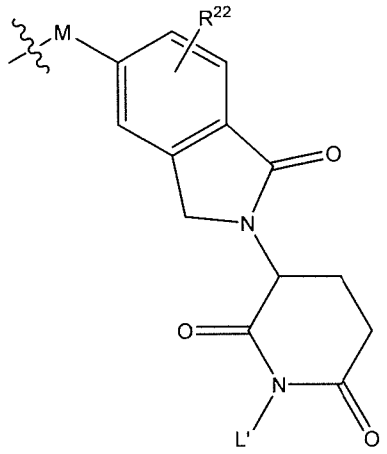
10. The compound of any one of claims 1-5, wherein **[ligase ligand moiety]** is:


or


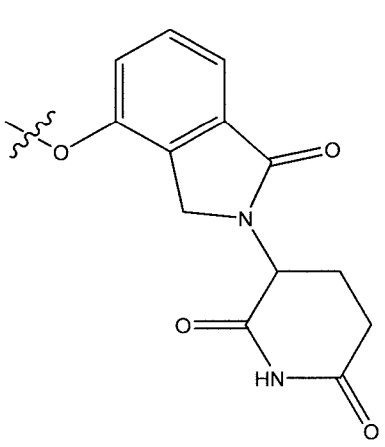
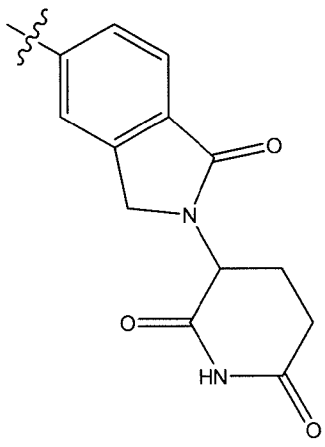
11. The compound of claim 10, wherein **[ligase ligand moiety]** is:



12. The compound of claim 10, wherein **[ligase ligand moiety]** is:



13. The compound of claim 10, wherein **[ligase ligand moiety]** is

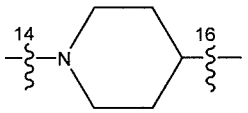
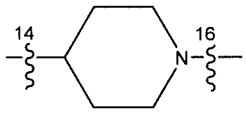
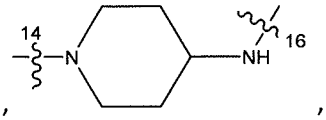
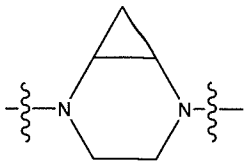
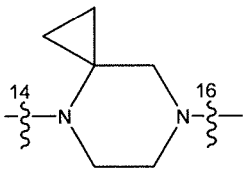
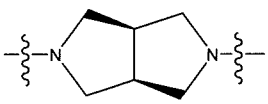



or

14. The compound of any one of claims 1-13, wherein

R^{14} is -C_{1-6} alkyl, -SO_2- or is absent

R^{15} is piperazine, bridged piperazine, piperazine N-oxide, piperazine cation, -C_{1-6} alkyl-NH-,


,

,

,

,

,

or is absent, wherein  indicates attachment to R^{14} and  indicates attachment to R^{16},

R^{16} is -C_{1-6} alkyl, -C(O)-, -C(O)-NH-, -CH_2-C(O)-NH- or is absent

R^{17} is -$CH_2(C_2H_4\text{-}O)_y$, $(C_2H_4\text{-}O)_x$, $(C_3H_6\text{-}O)_x$, or is absent

x is 1-6

y is 2-6

R^{18} is -C_{1-6} alkyl, piperazine, or is absent

wherein at least one of R^{14}-R^{18} is present.

15. The compound of any one of claims 1-14, wherein R^{18} is -C_{1-6} alkyl or is absent.

16. The compound of any one of claims 1-15, wherein when $\mathbf{R^{14}}$ is $-SO_2-$, at least two of $\mathbf{R^{15}}$-$\mathbf{R^{18}}$ are present, and at least one of $\mathbf{R^{15}}$-$\mathbf{R^{18}}$ is not C_{1-6} alkyl.

17. The compound of any one of claims 1-16, wherein

$\mathbf{R^{14}}$ is $-SO_2-$

$\mathbf{R^{15}}$ is $-C_{1-6}$ alkyl-NH-

$\mathbf{R^{16}}$ is -C(O)-

$\mathbf{R^{17}}$ is $-CH_2(C_2H_4-O)_y$, $(C_2H_4-O)_x$ or is absent

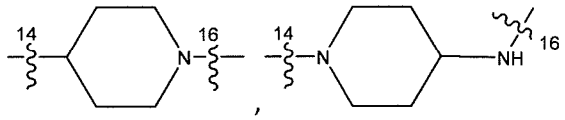
$\mathbf{R^{18}}$ is $-C_{2-4}$ alkyl.

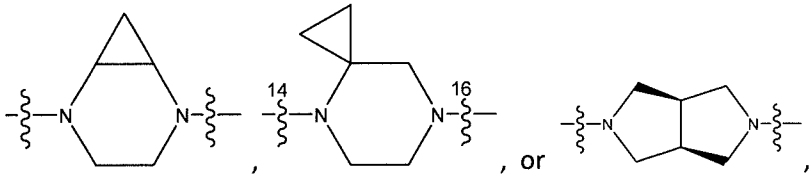
18. The compound of claim 17, wherein

$\mathbf{R^{15}}$ is $-C_2$alkyl-NH-

x is 1 or 2

y is 1.

19. The compound of any one of claims 1-15, wherein when $\mathbf{R^{15}}$ is piperazine, bridged piperazine, piperazine N-oxide, piperazine cation, $-C_{1-6}$ alkyl-NH-, 

, , 

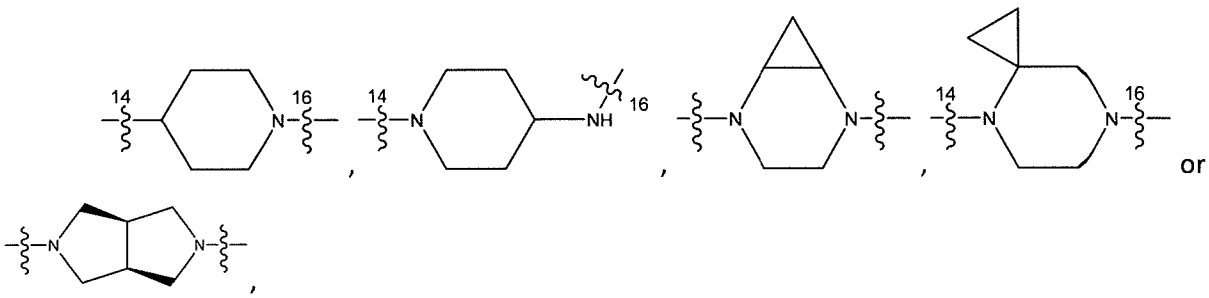
, , or ,

then $\mathbf{R^{14}}$ is $-C_{1-6}$ alkyl.

20. The compound of any one of claims 1-15, wherein

$\mathbf{R^{14}}$ is $-C_{1-6}$ alkyl,

$\mathbf{R^{15}}$ is piperazine, bridged piperazine, piperazine N-oxide,



$\mathbf{R^{16}}$ is -C(O)-, -CH_2-C(O)-NH-, or is absent

$\mathbf{R^{17}}$ is -$CH_2(C_2H_4\text{-}O)_y$, $(C_2H_4\text{-}O)_x$, $(C_3H_6\text{-}O)_x$, or is absent

$\mathbf{R^{18}}$ is -$C_{1\text{-}6}$ alkyl.

wherein when $\mathbf{R^{16}}$ and $\mathbf{R^{17}}$ are absent, $\mathbf{R^{18}}$ is -$C_{3\text{-}6}$ alkyl.

21. The compound of claim 20, wherein

$\mathbf{R^{14}}$ is -C_2 alkyl,

x is 1, 2 or 6

y is 2.

22. The compound of any one of claims 1-15, wherein

$\mathbf{R^{14}}$ is absent

$\mathbf{R^{15}}$ is absent

$\mathbf{R^{16}}$ is -C(O)-NH-, or is absent

$\mathbf{R^{17}}$ is -$CH_2(C_2H_4\text{-}O)_y$, $(C_2H_4\text{-}O)_x$, $(C_3H_6\text{-}O)_x$, or is absent

$\mathbf{R^{18}}$ is -$C_{1\text{-}6}$ alkyl.

23. The compound of any one of claims 1-22, wherein at least one of $\mathbf{R^{14}}$-$\mathbf{R^{18}}$ is not -$C_{1\text{-}6}$ alkyl.

24. The compound of claim 22 or 23, wherein

x is 1, 2 or 3

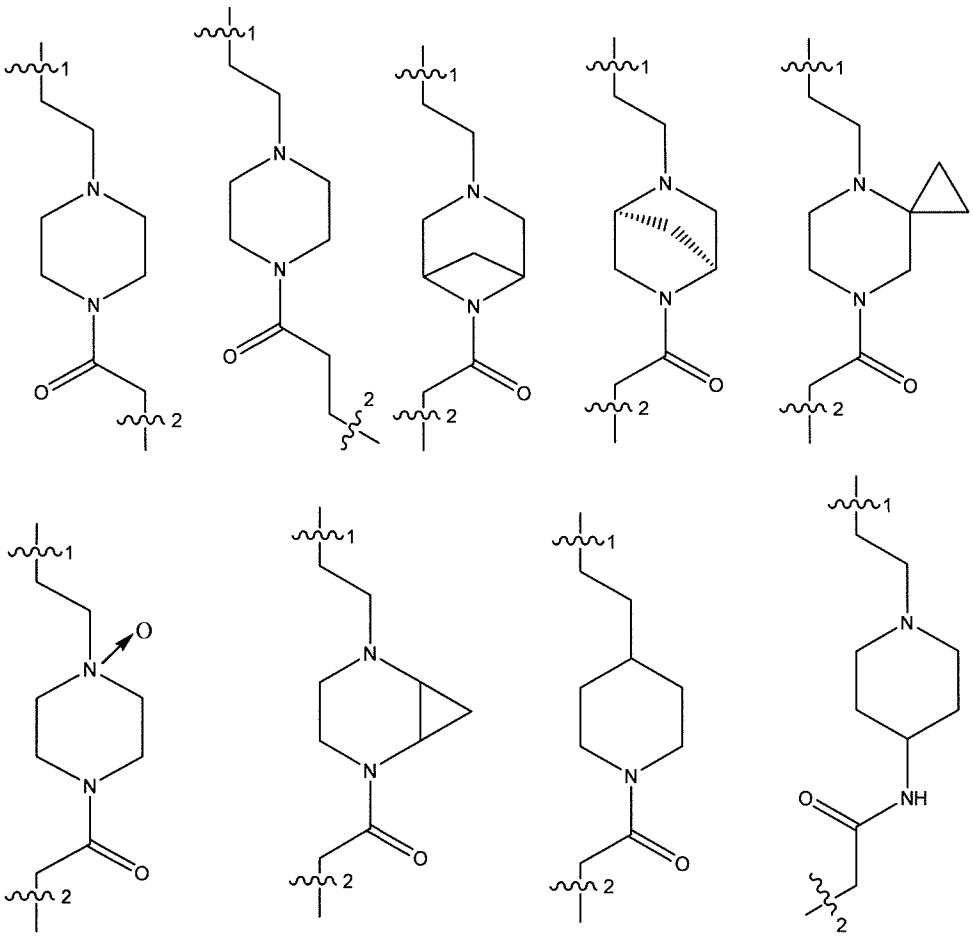
y is 2

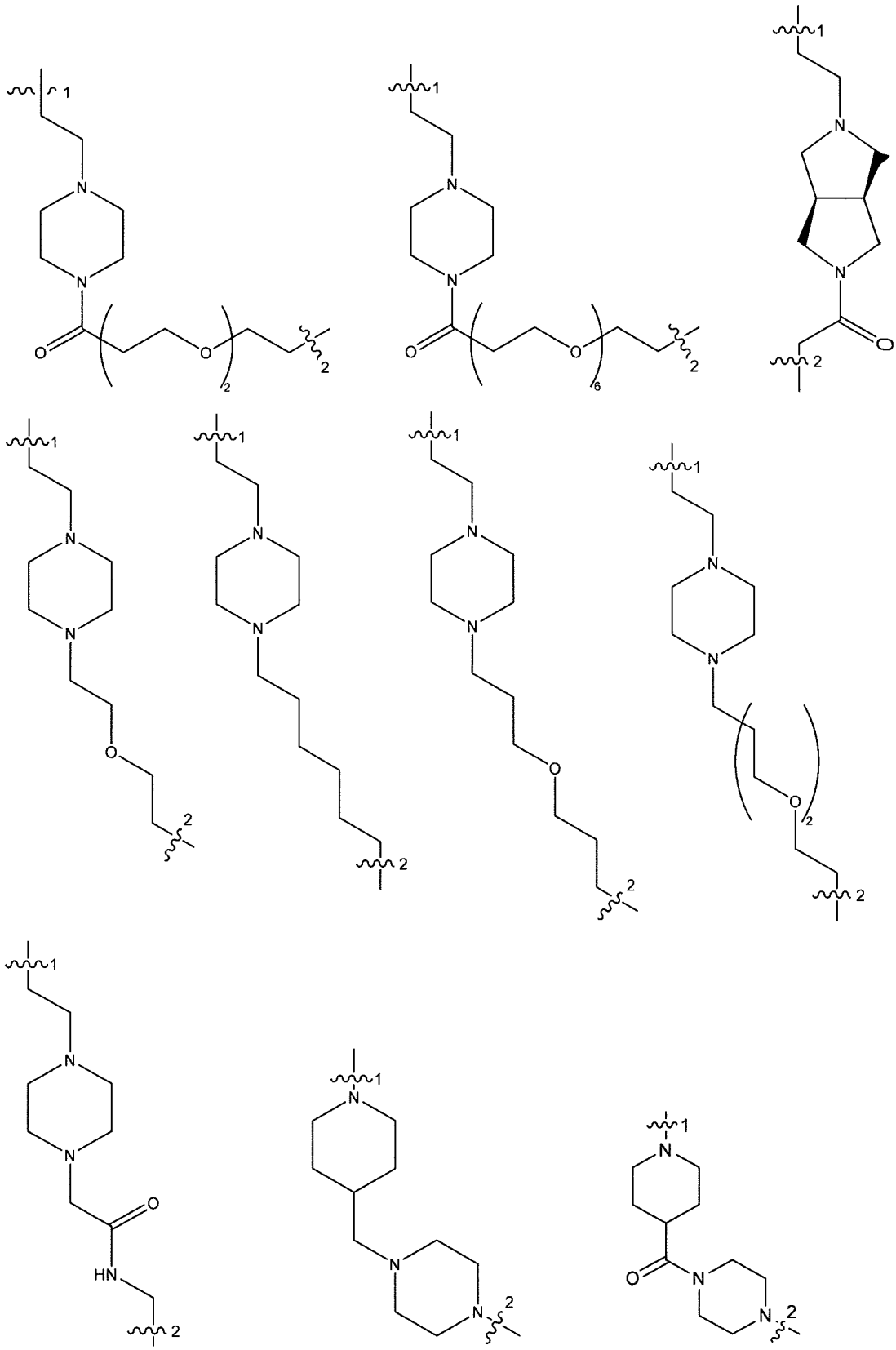
$\mathbf{R^{18}}$ is -$C_{2\text{-}6}$ alkyl.

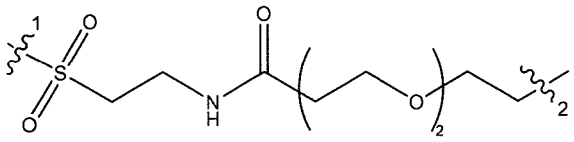
25. The compound of any one of claims 1-24, wherein when $\mathbf{R^{15}}$ is -$C_{1\text{-}6}$ alkyl-NH-, at least one of $\mathbf{R^{16}}$-$\mathbf{R^{18}}$ is present.

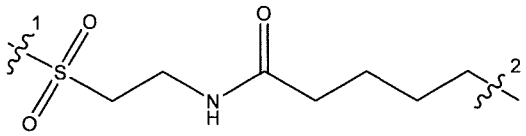
26. The compound of any one of claims 1-24, wherein when R^{17} is $-CH_2(C_2H_4-O)_y$, $(C_2H_4-O)_x$ or $(C_3H_6-O)_x$, at least one of R^{14}-R^{16} and R^{18} is present, wherein at least one of R^{14} and R^{18} is not $-C_{1-6}$ alkyl.

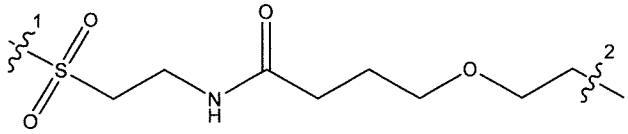
27. The compound of any one of claims 1-26, wherein **[linker]** is selected from

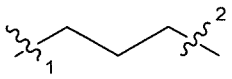


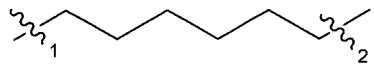


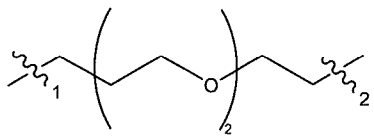


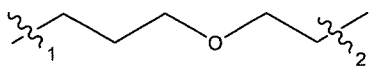


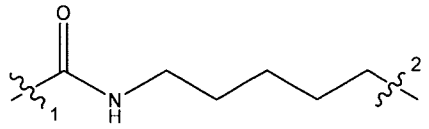


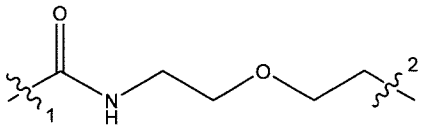


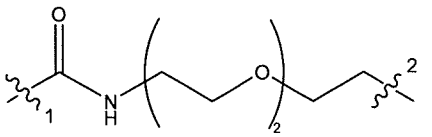




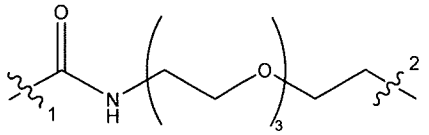








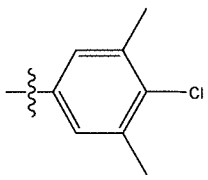
and



wherein

 indicates attachment to **[MCL-1 ligand moiety]** and

 indicates attachment to **[ligase ligand moiety].**

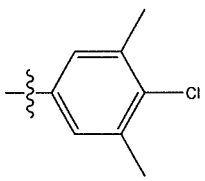
28. The compound of any one of claims 1-27 wherein when R^8 is H, R^{13} is  .

29. The compound of any one of claims 1-28, wherein

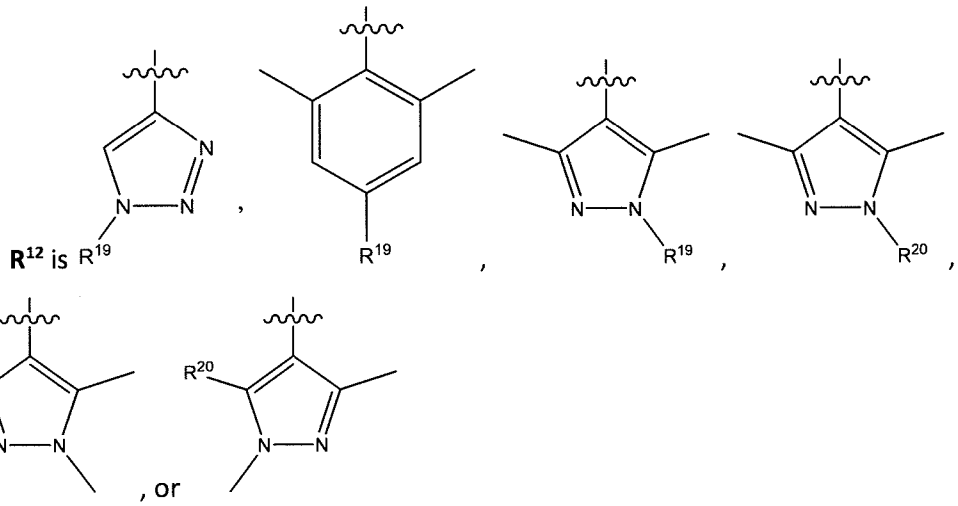
R^8 is H, R^{19}, methyl, or -CH_2CH_2-morpholine;

R^9 is -C(O)OH or -C(O)NHR^{19},

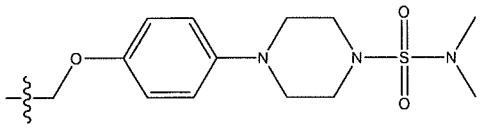
R^{10} is -C_3H_6O-R^{13},

wherein R^{13} is  , tetraline, or naphthyl optionally substituted with fluorine;

R^{11} is H, Cl, F or methyl,

R^{12} is 

, or

wherein **R^{20}** is Me, -CH_2-O-bromobenzaldehyde, or  .

30. The compound of any one of claims 1-29 wherein **Z_2** is N and  is a single bond.

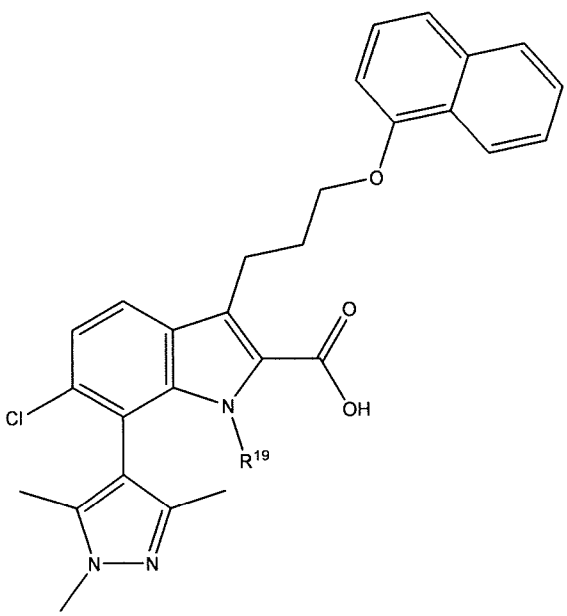
31. The compound of any one of claims 1-29 wherein **Z_2** is C and  is a double bond.

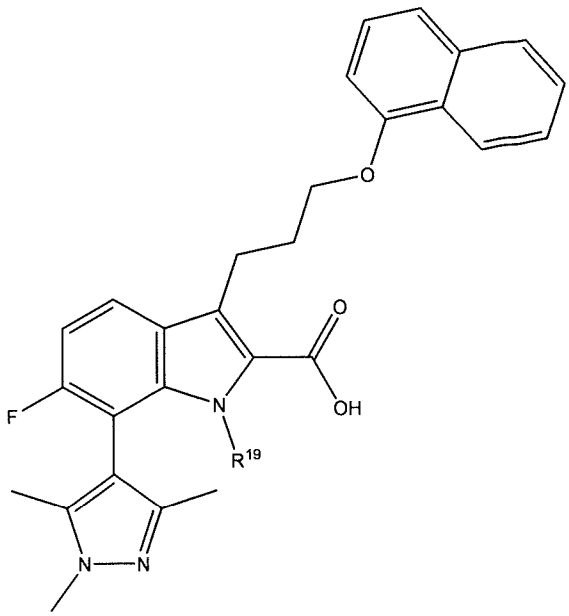
32. The compound of any one of claims 1-31, wherein **R^{11}** is hydrogen.

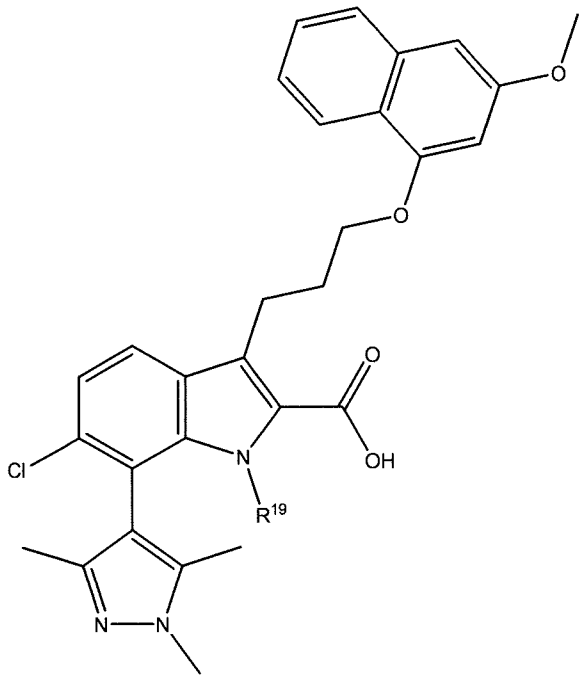
33. The compound of any one of claims 1-31, wherein **R^{11}** is halogen or C_1-C_6 alkyl.

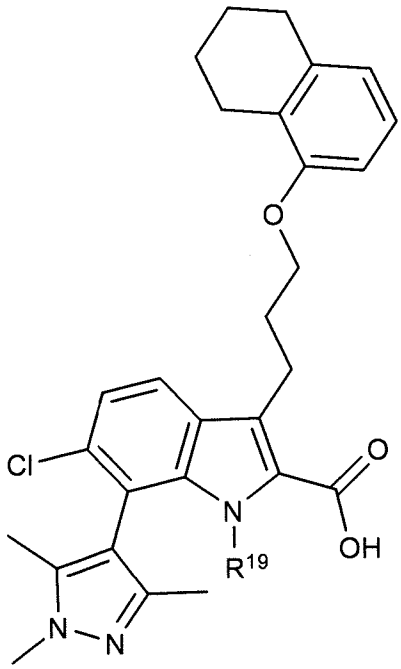
34. The compound of claim 33, wherein **R^{11}** is halogen.

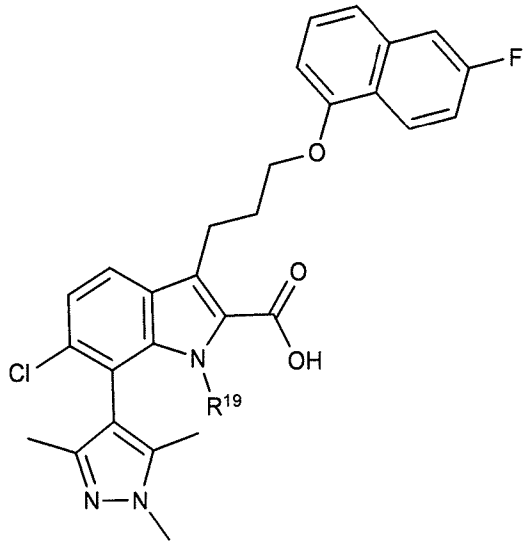
35. The compound of any one of claims 1-34, wherein **[MCL-1 ligand moiety]** is selected from:

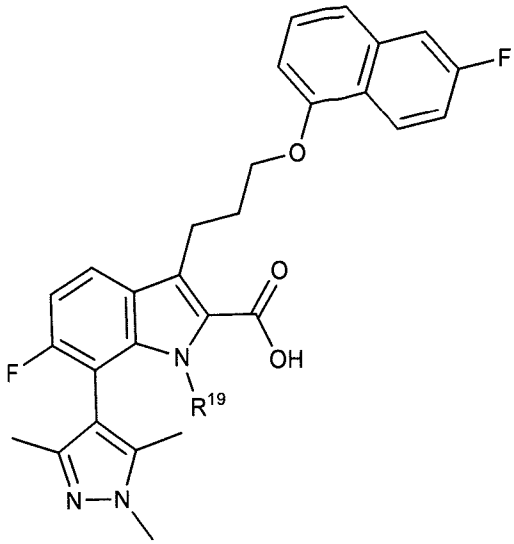


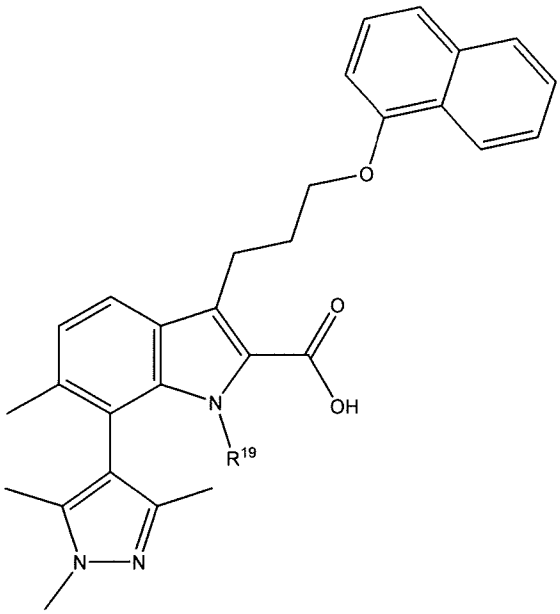


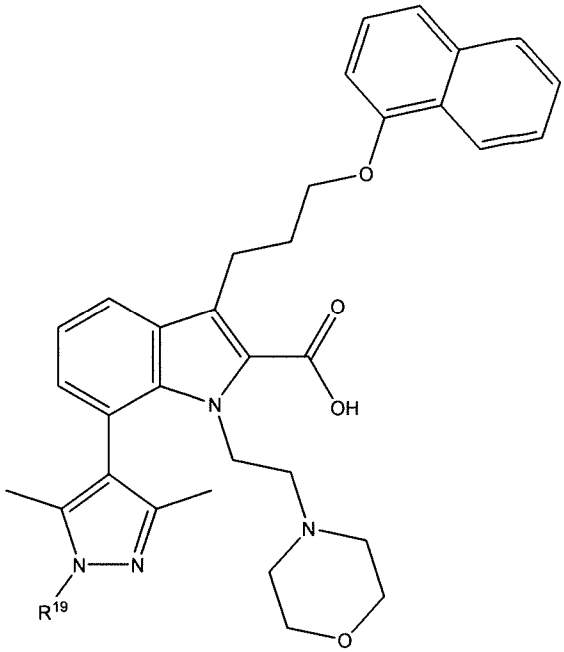


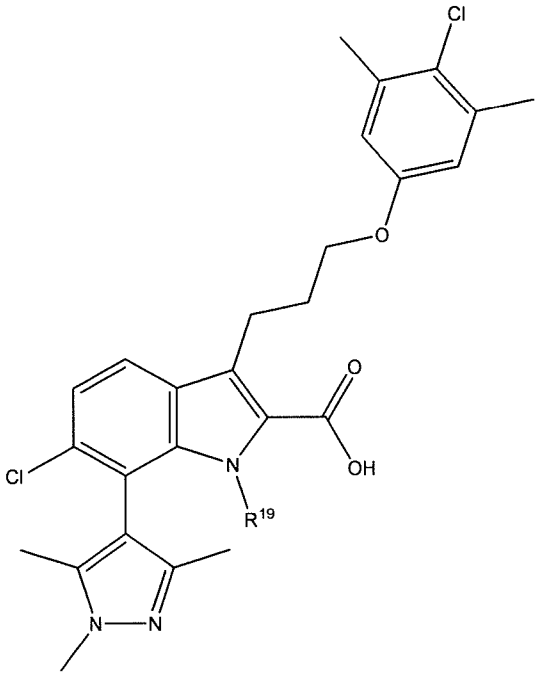
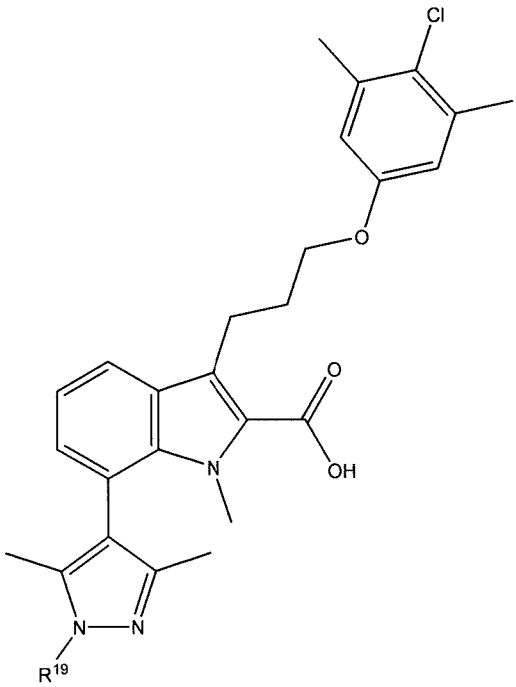
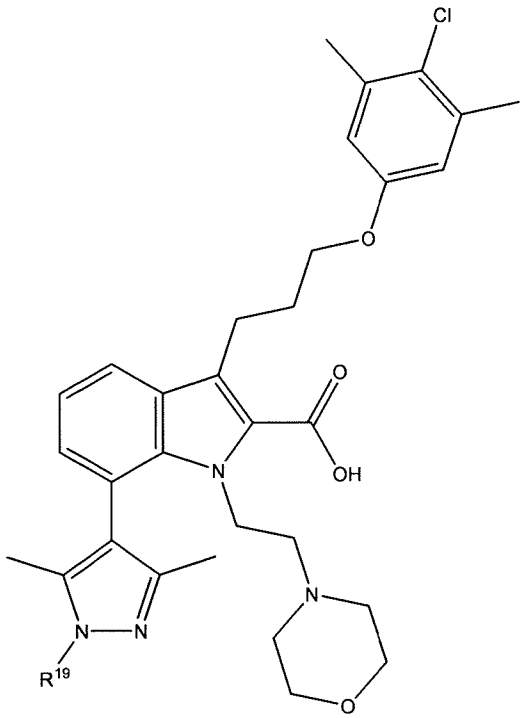
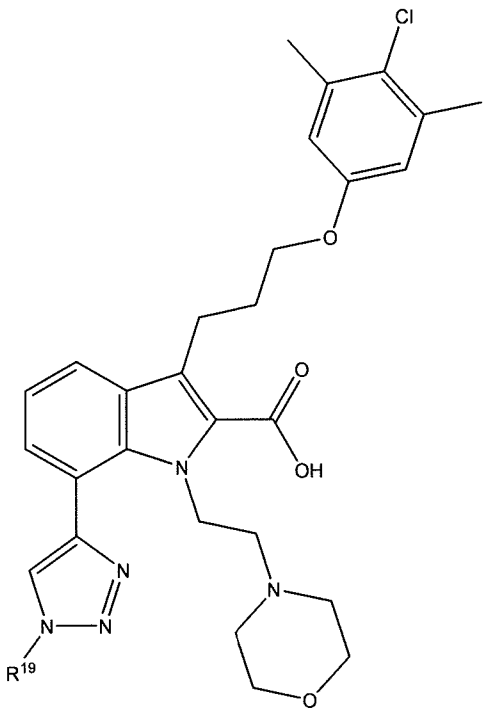


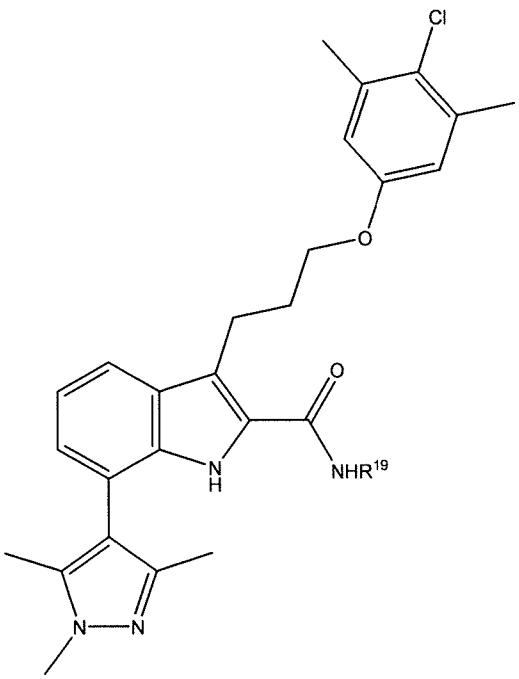

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Cl
N
R19
N
N

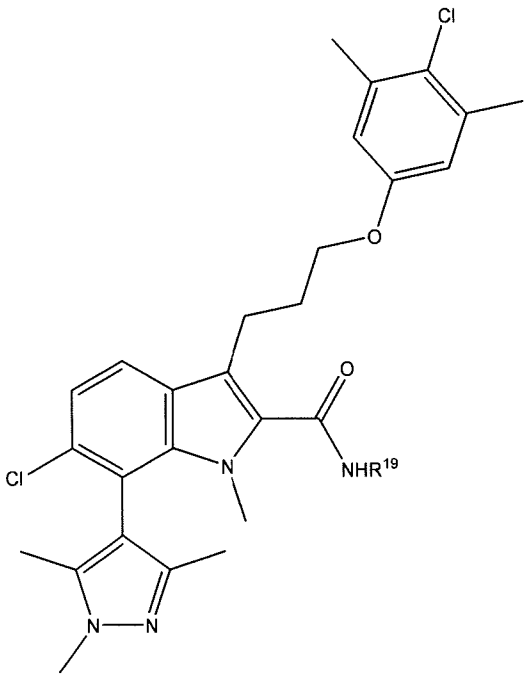

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R19
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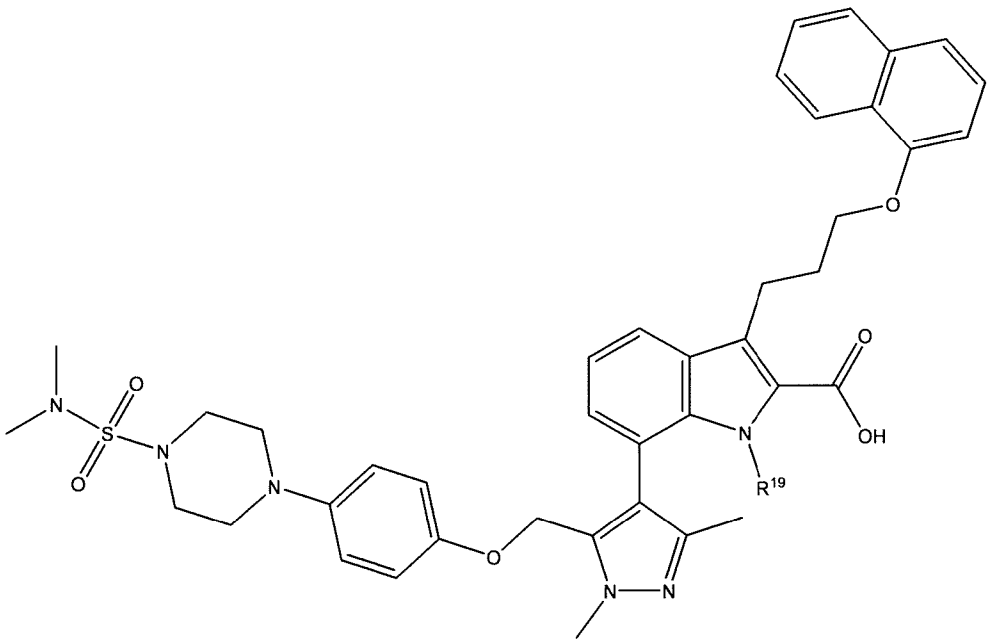

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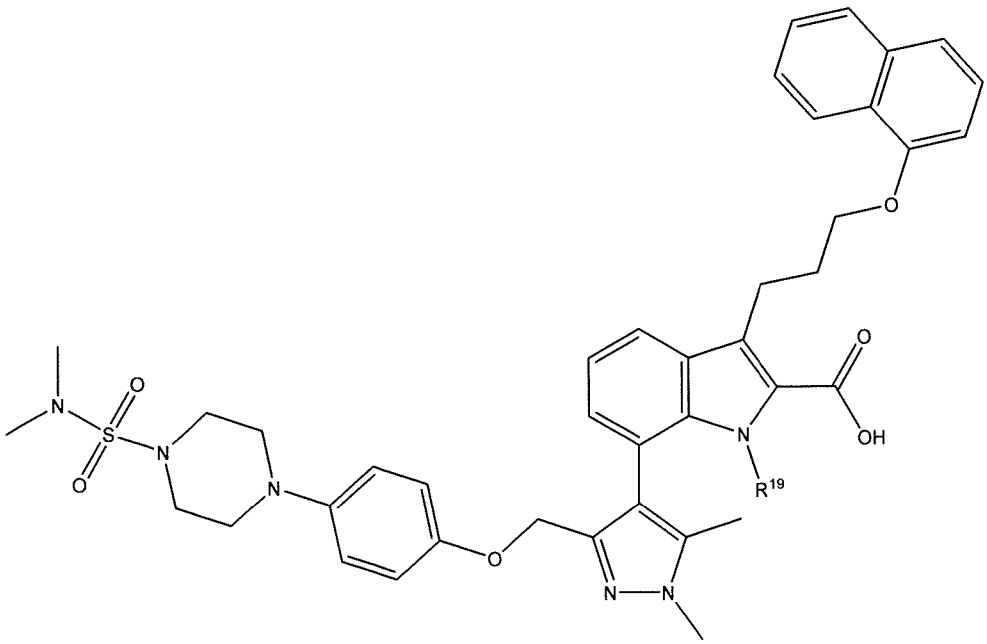

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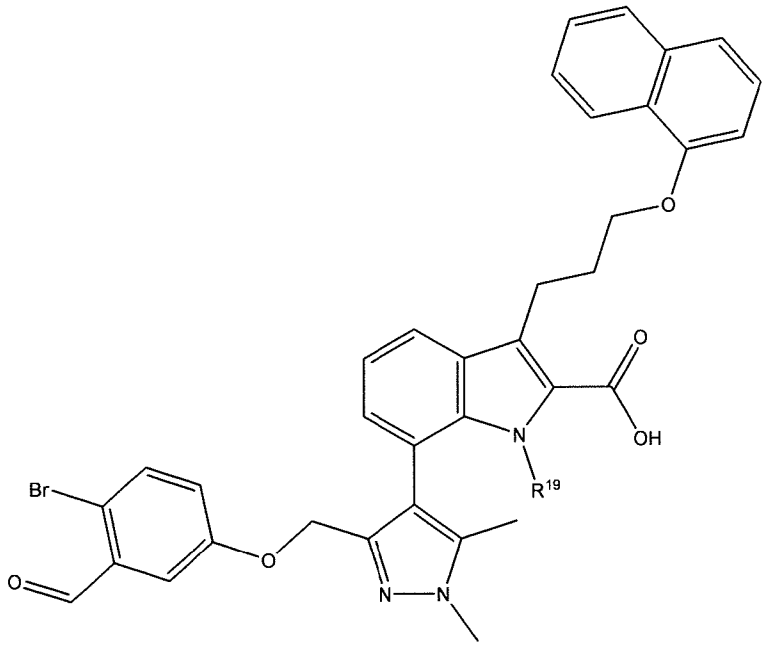





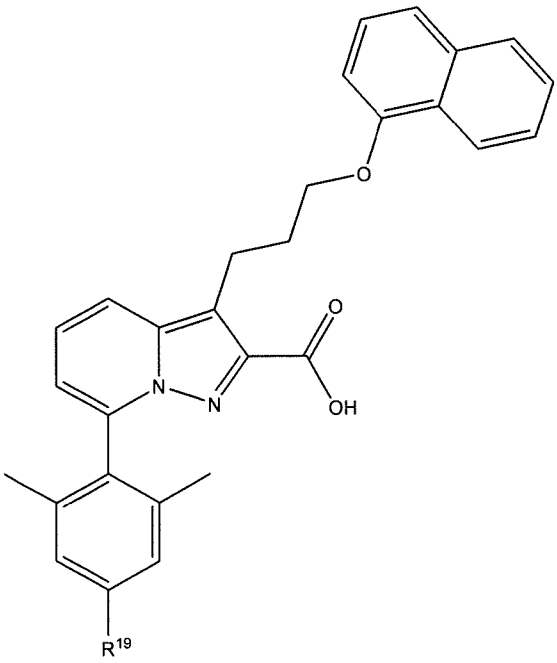


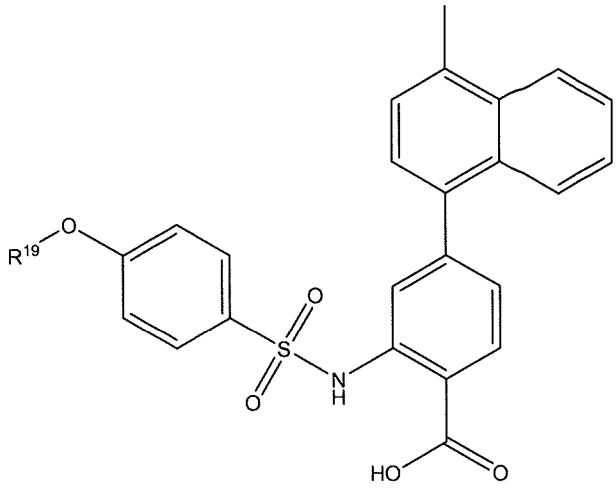


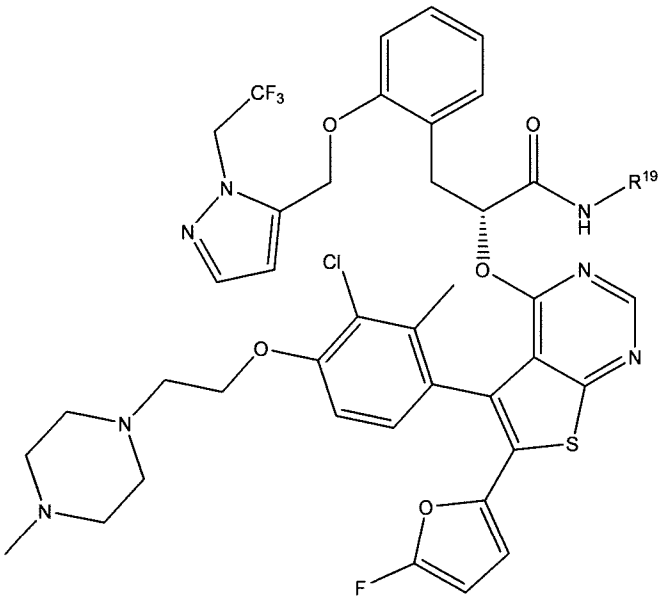




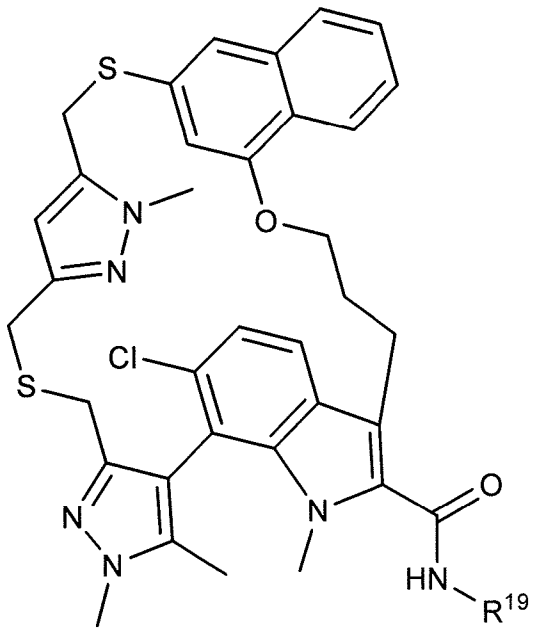




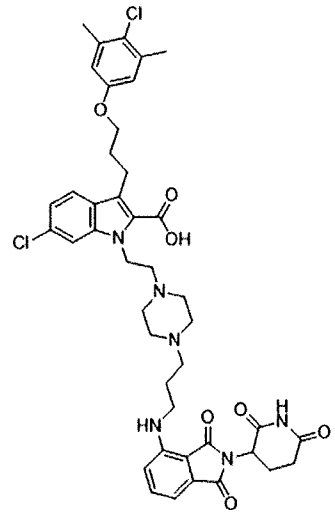
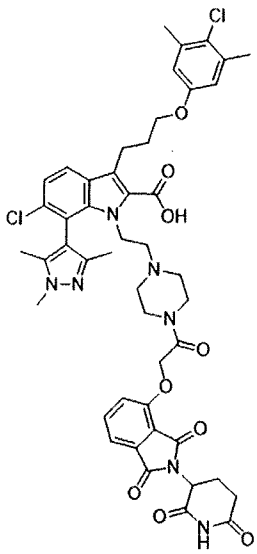
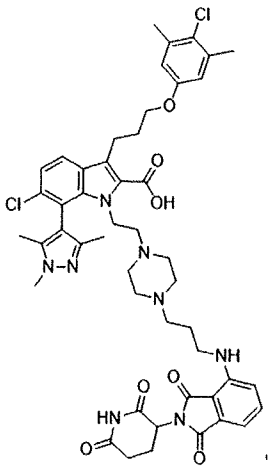


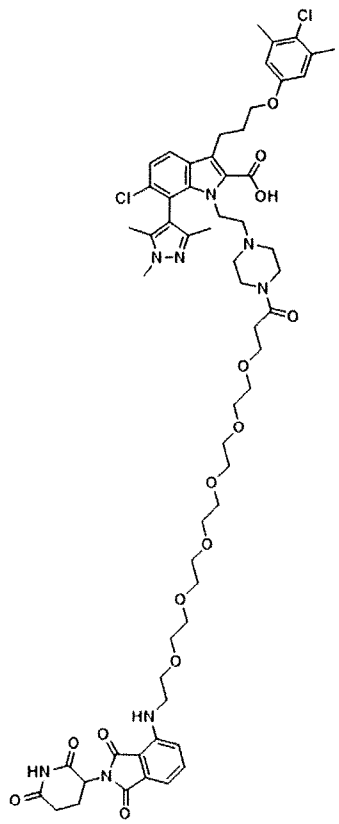
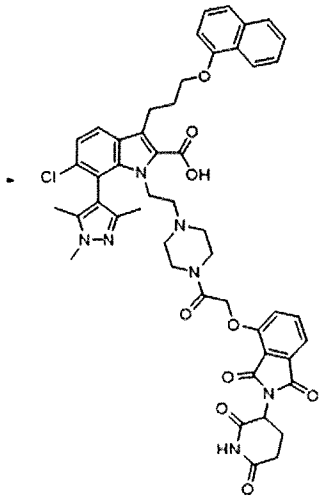
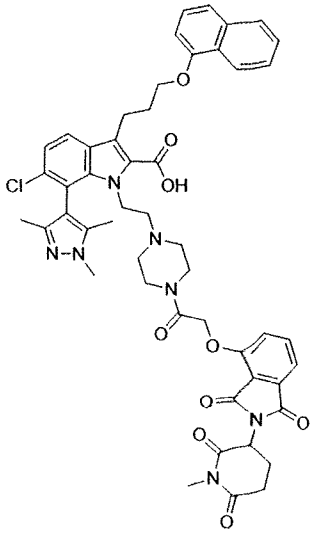
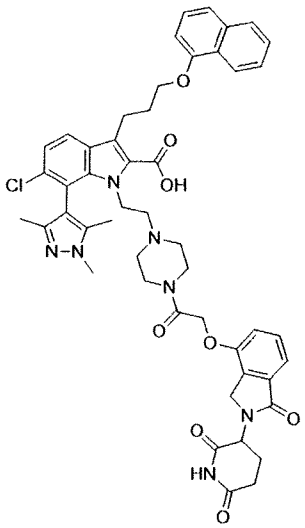
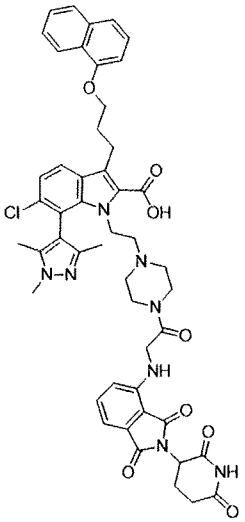
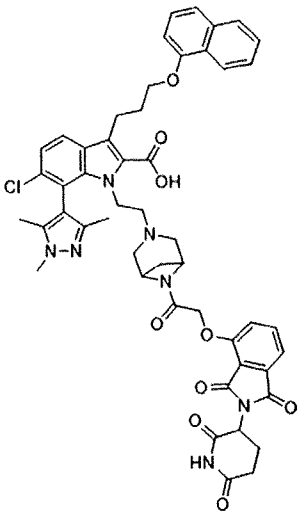


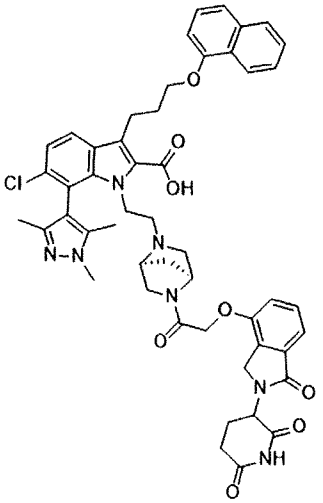
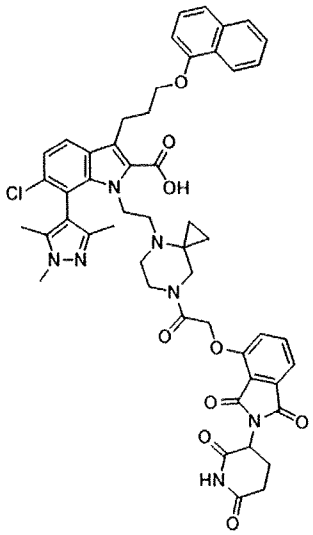
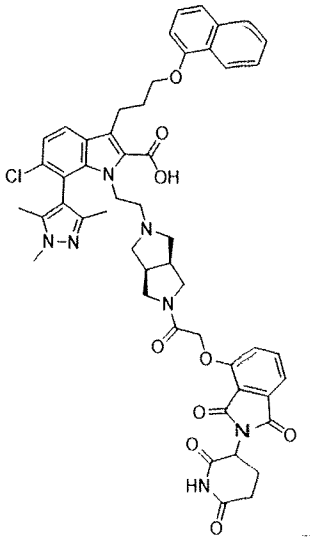
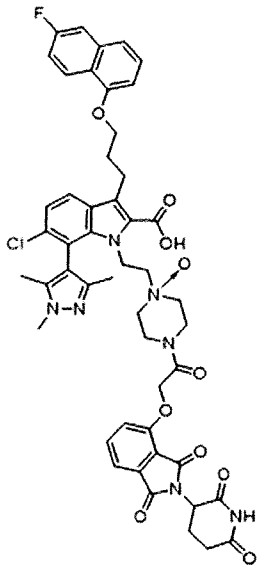
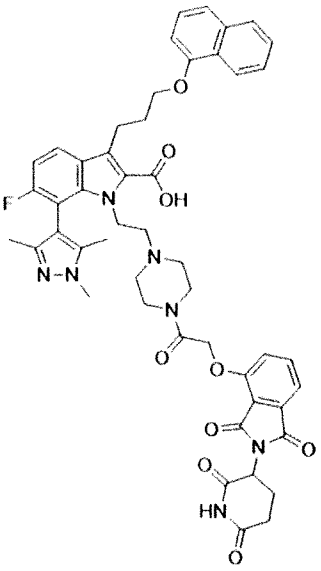
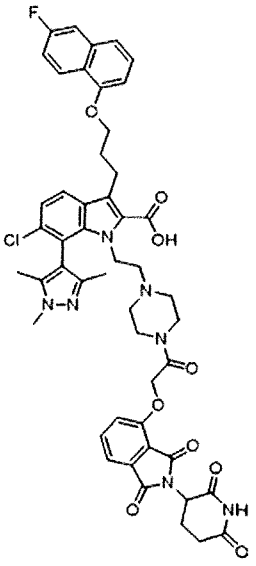
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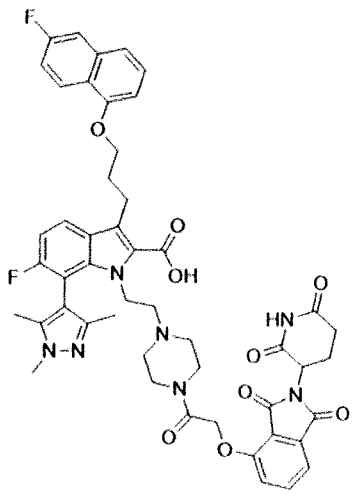
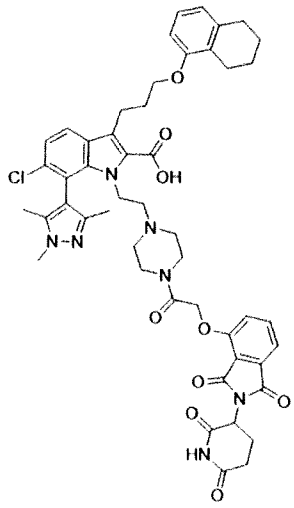
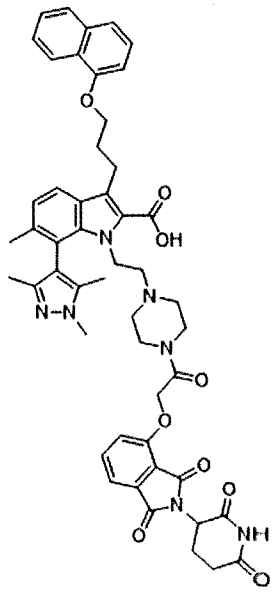
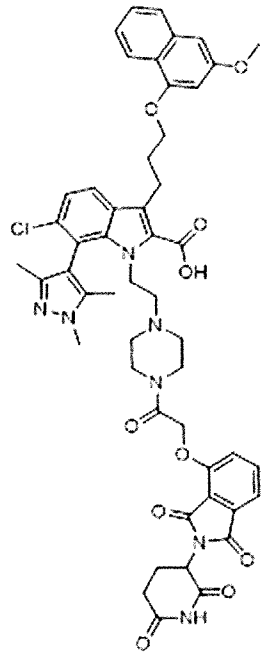
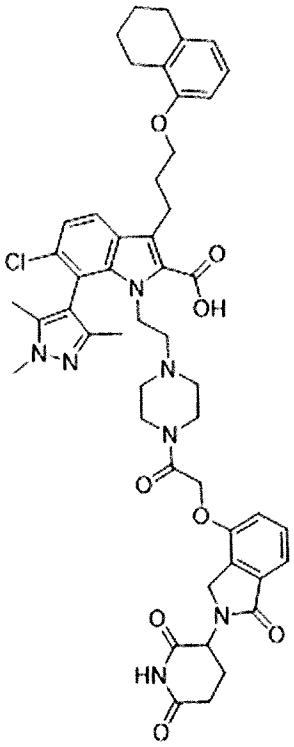
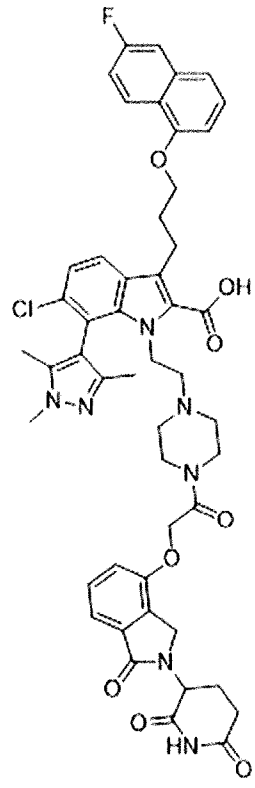


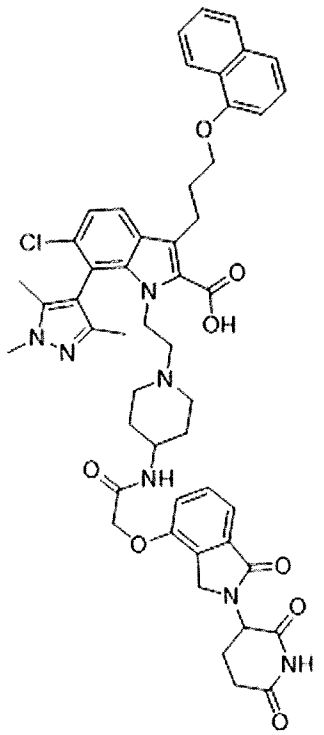
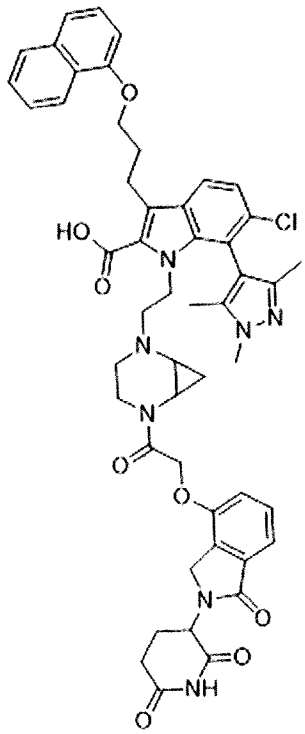
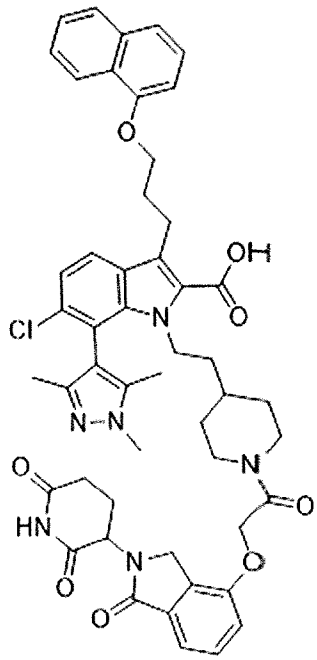
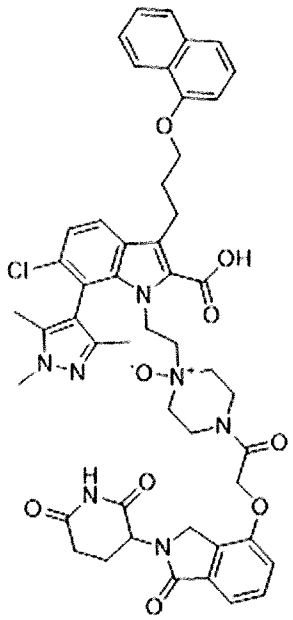
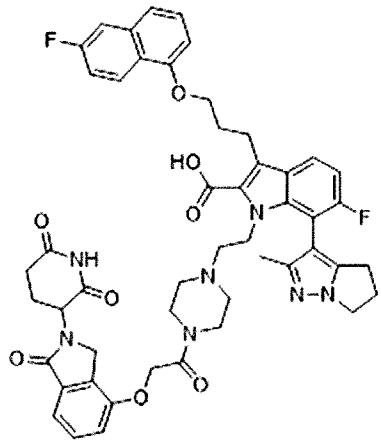
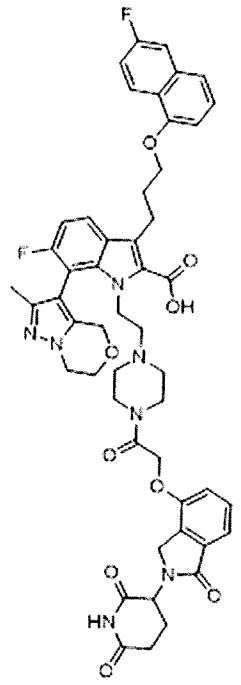
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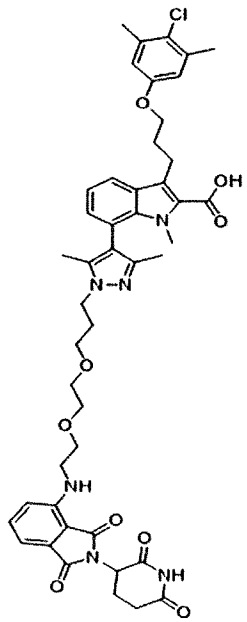
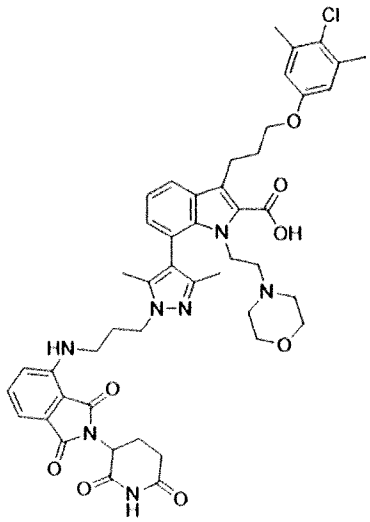
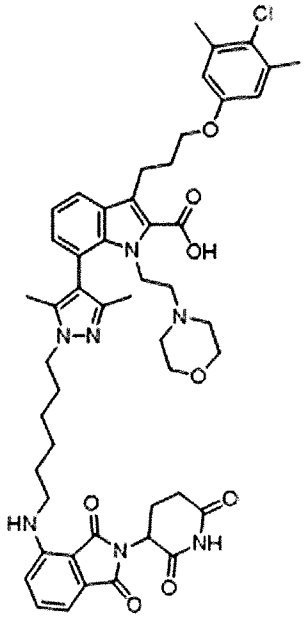
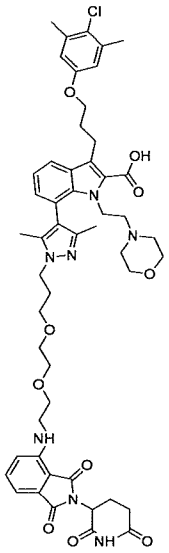
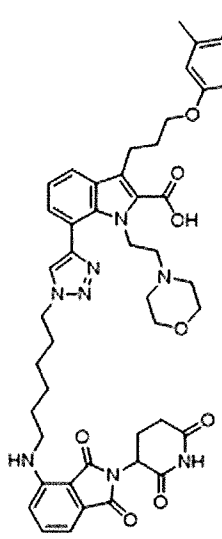
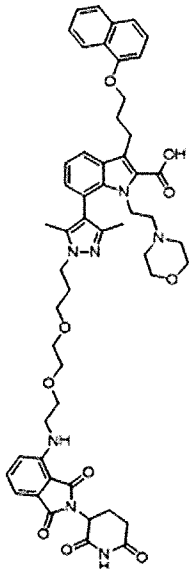
		
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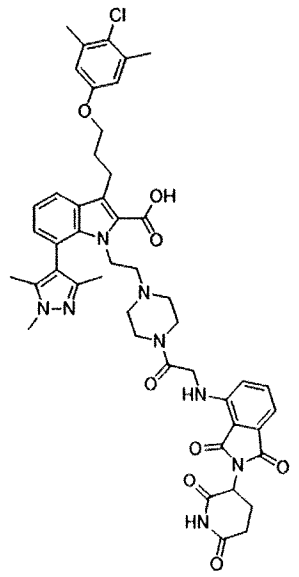
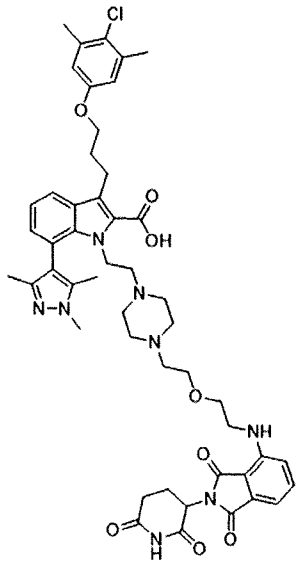
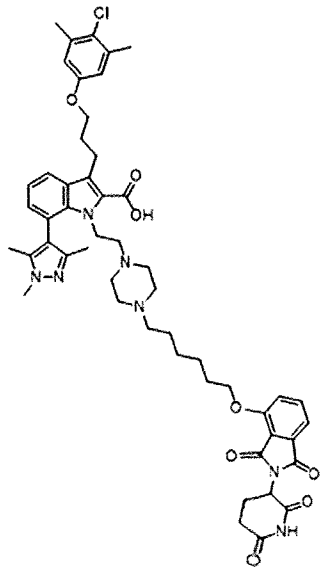
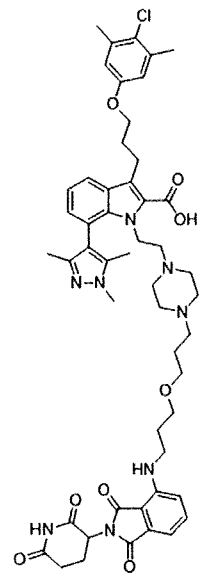
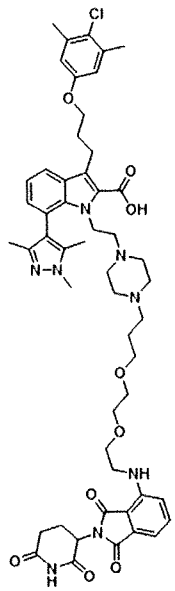
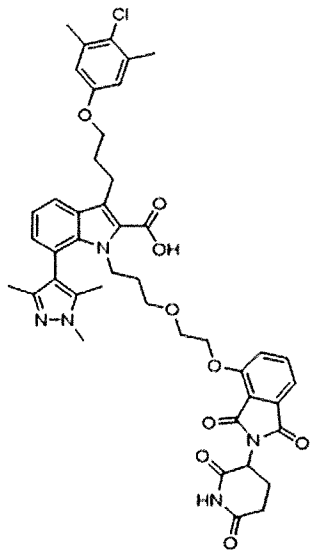
		
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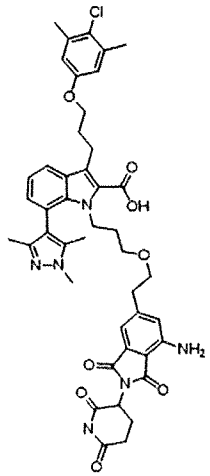
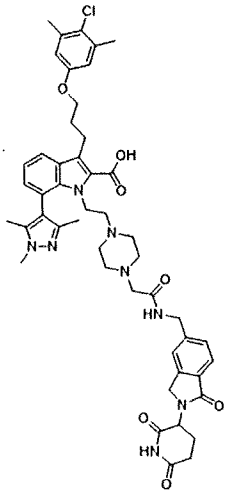
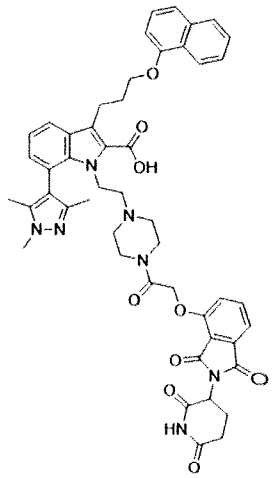
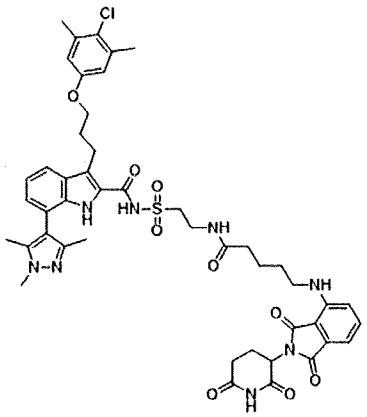
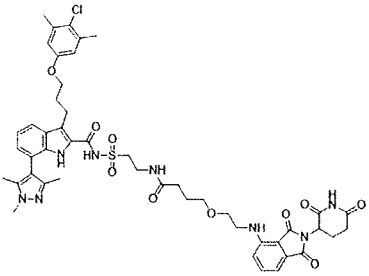
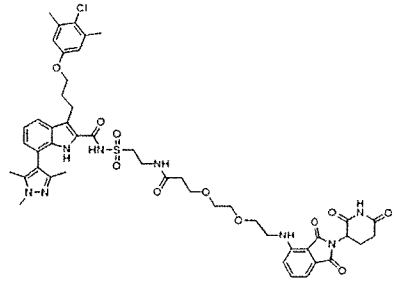
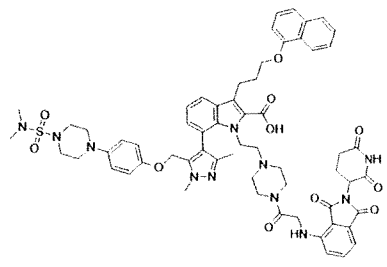
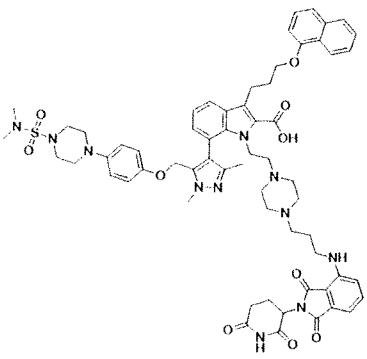
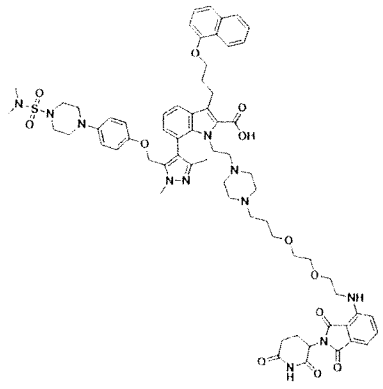
		
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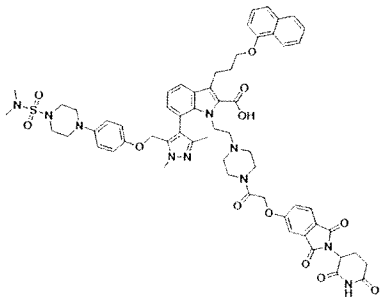
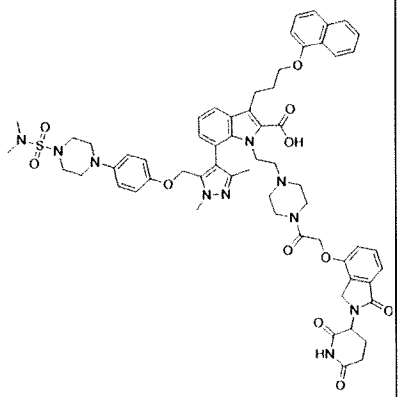
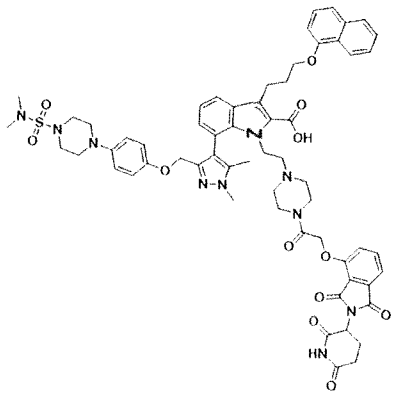
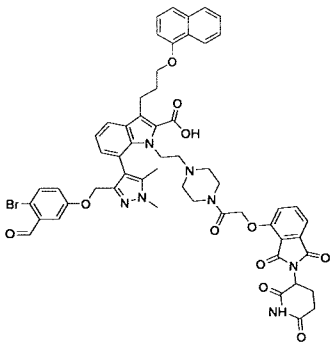
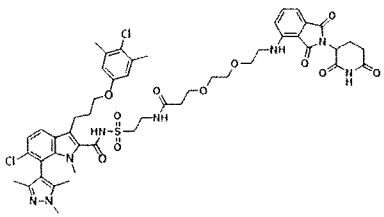
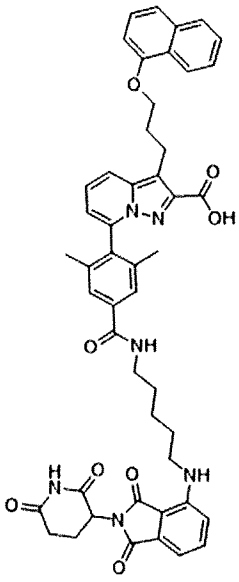
		
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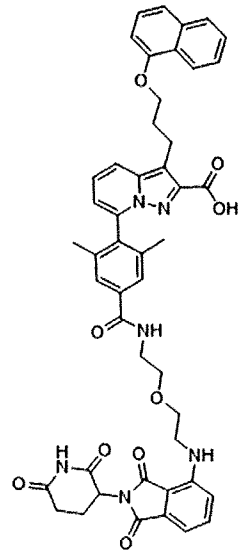
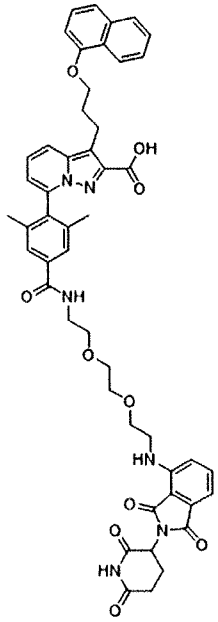
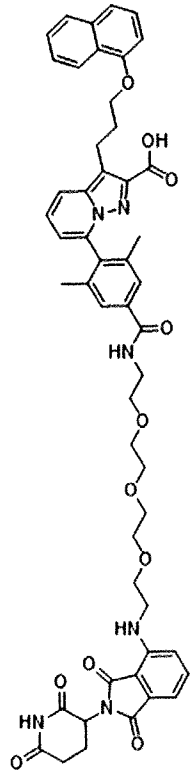
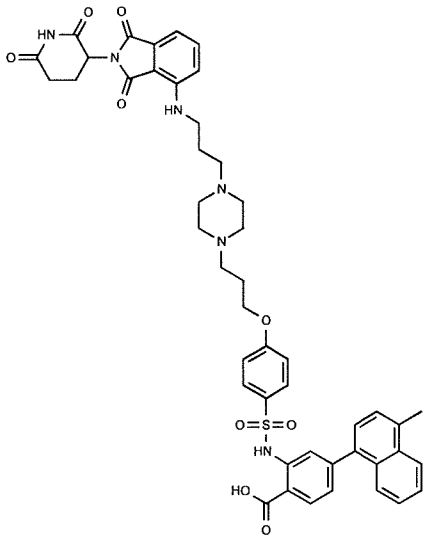
		
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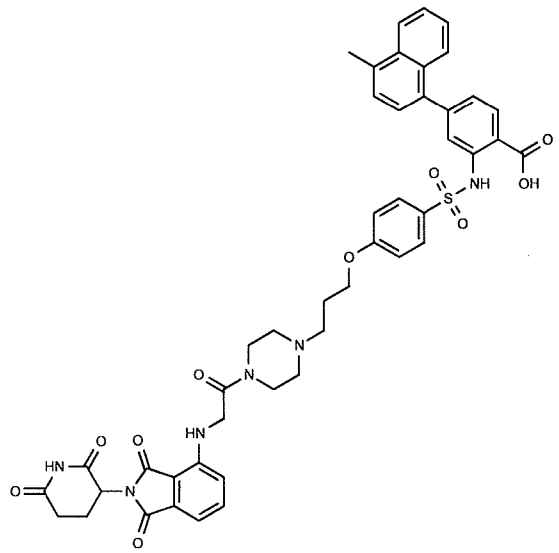
		
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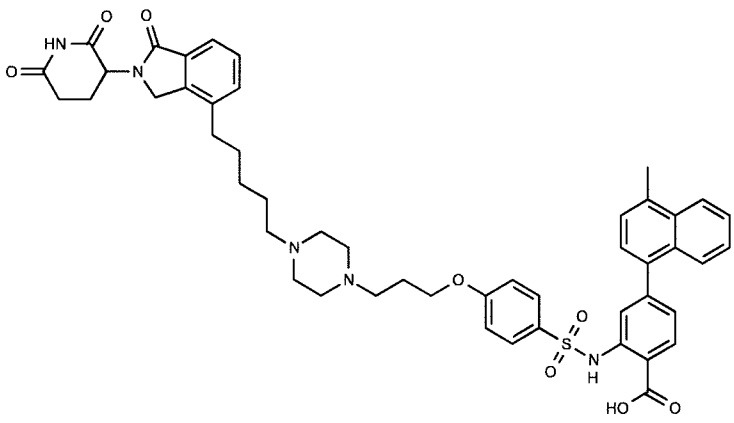
		
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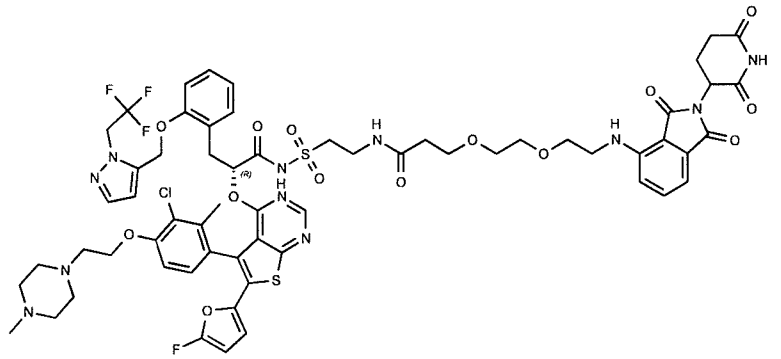
		
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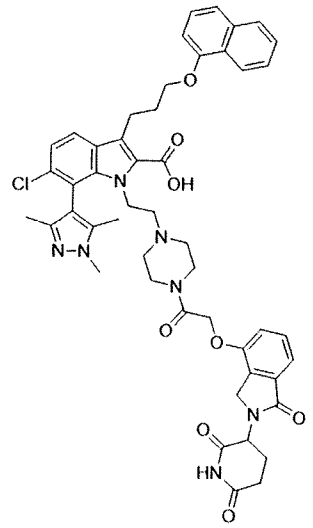
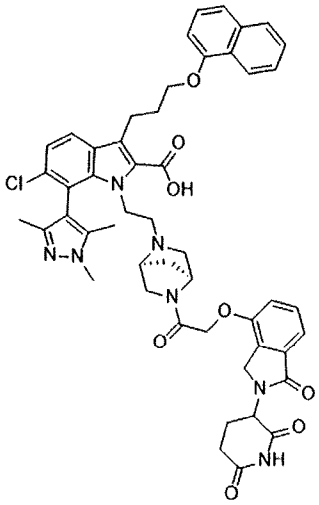
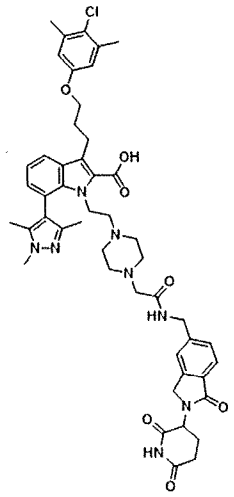
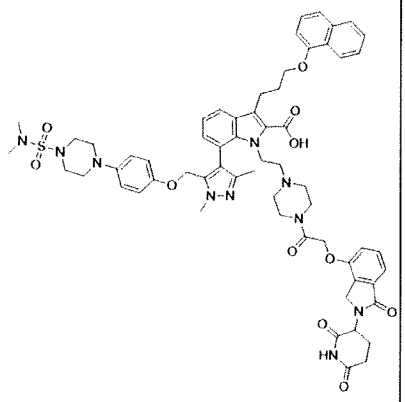
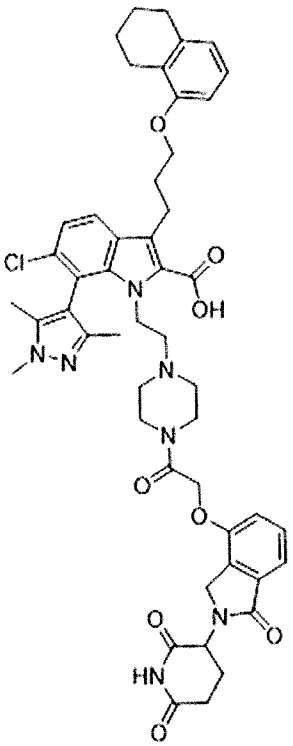
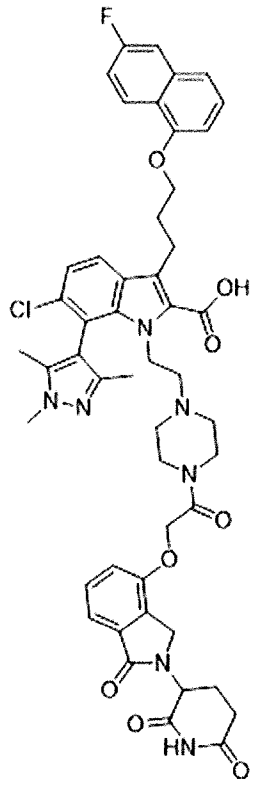
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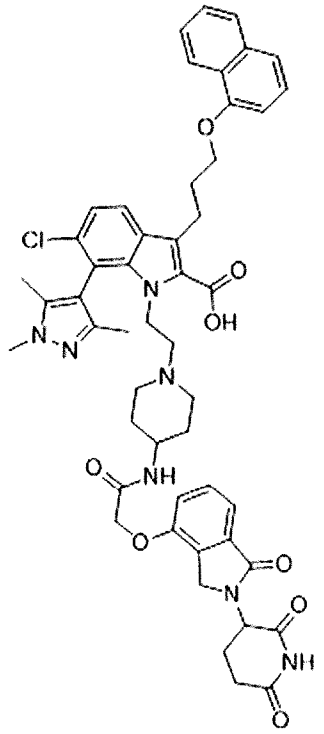
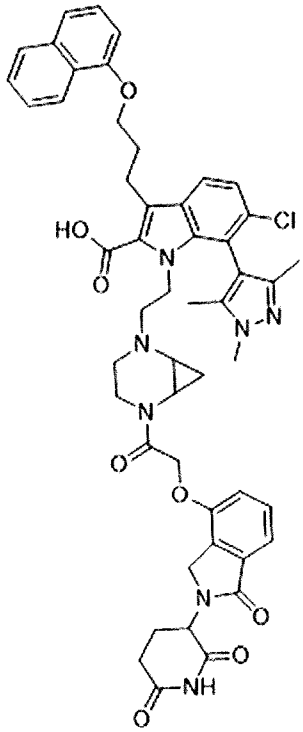
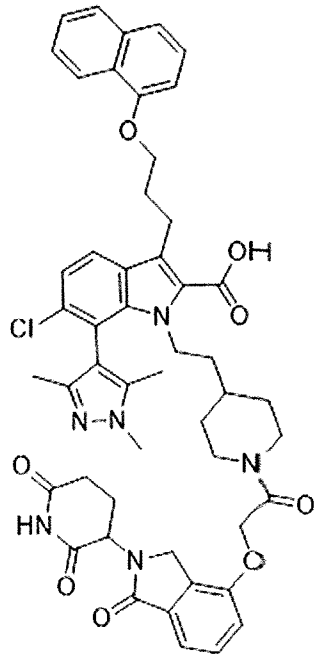
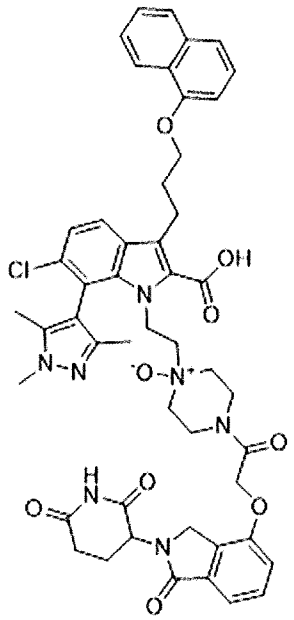
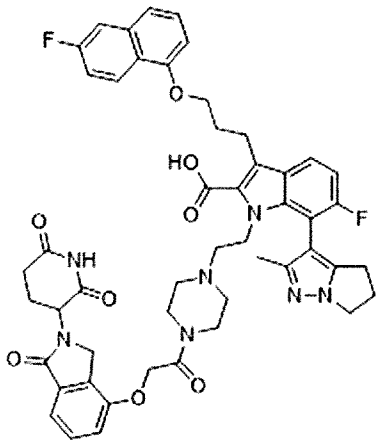
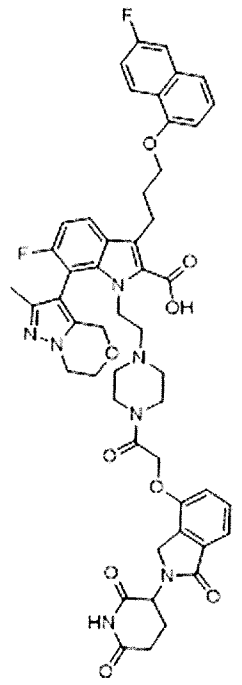


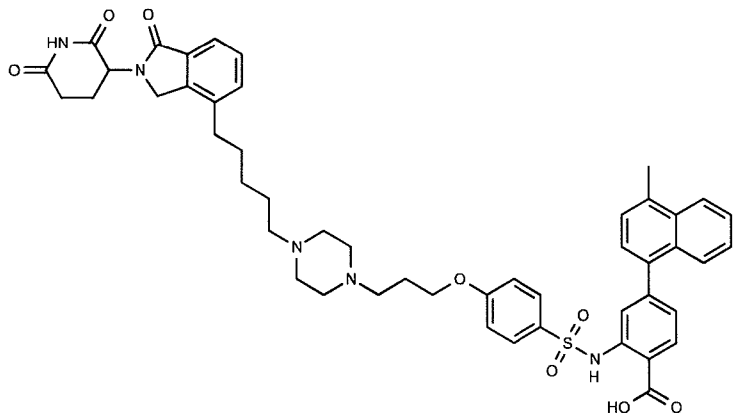
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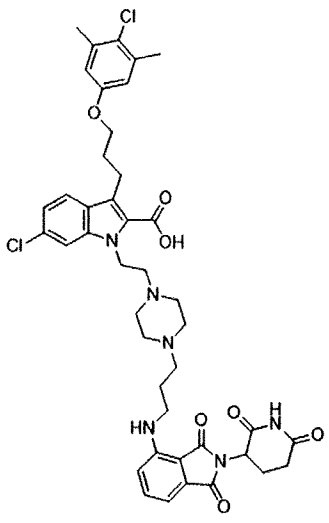
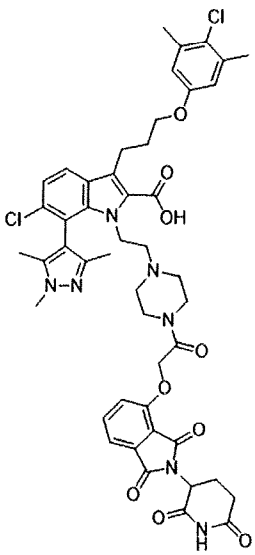
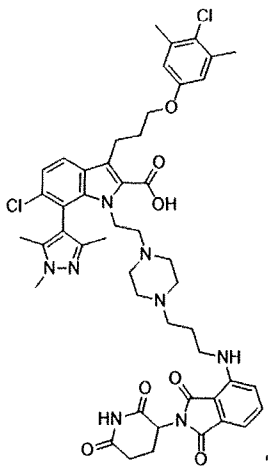
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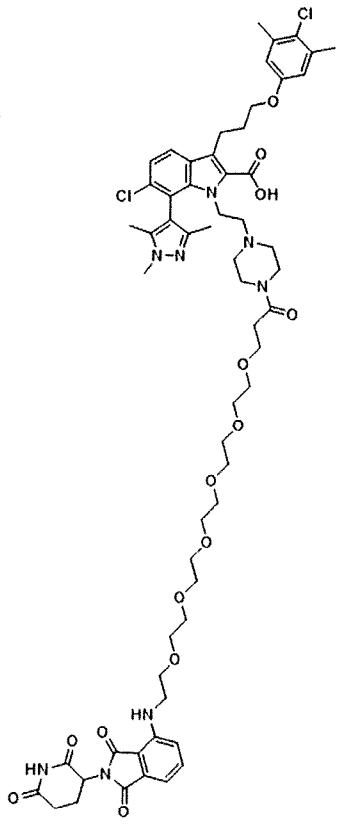
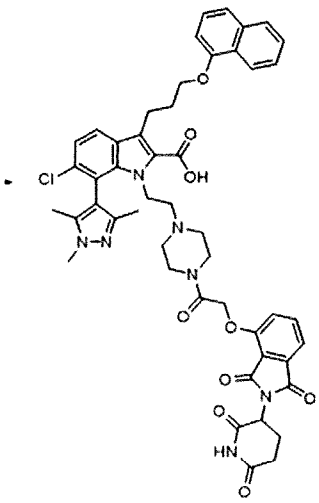
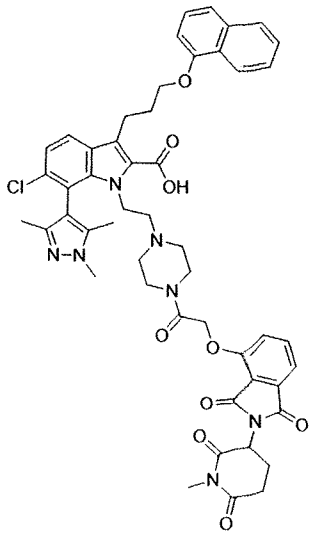
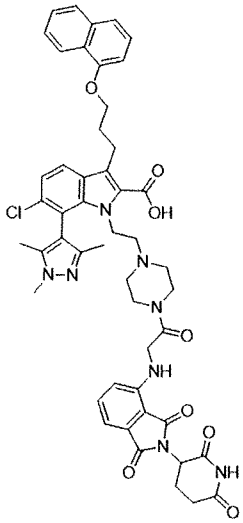
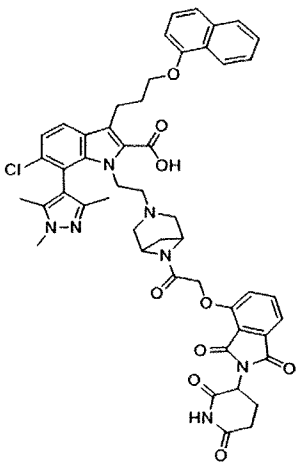
		
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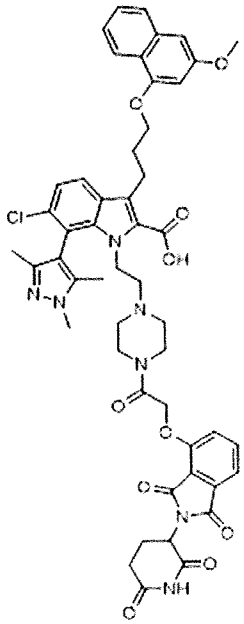
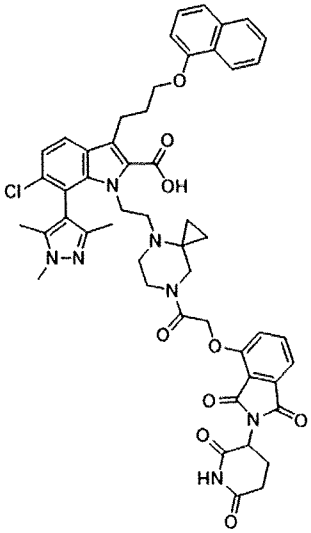
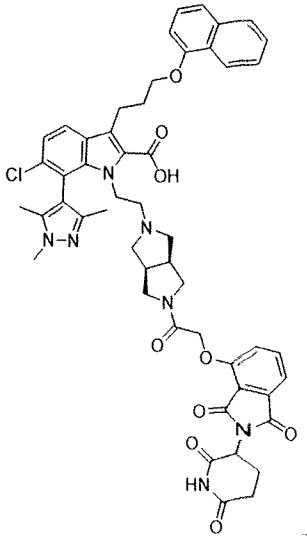
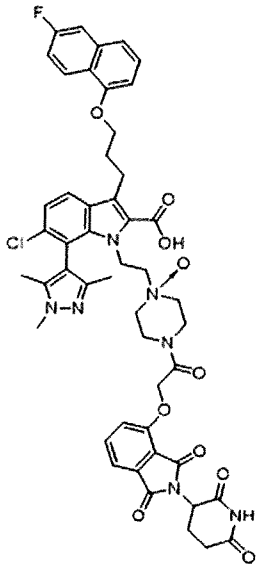
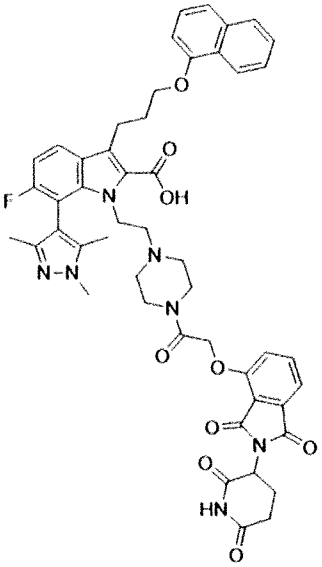
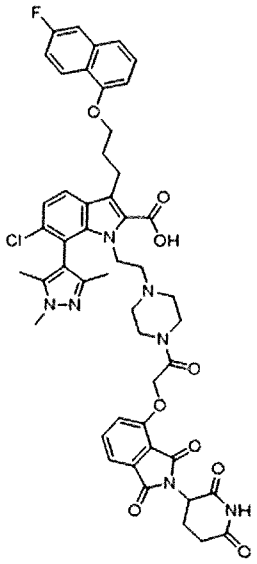
		
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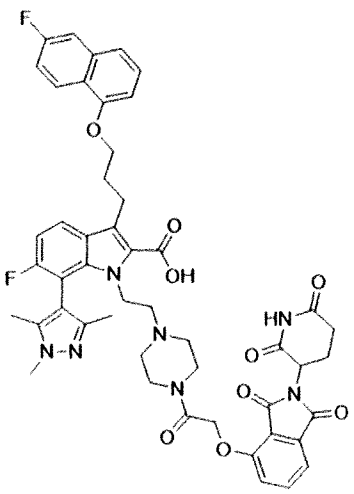
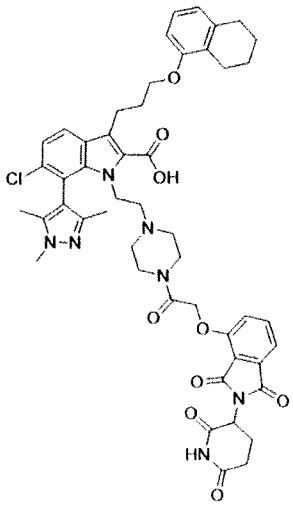
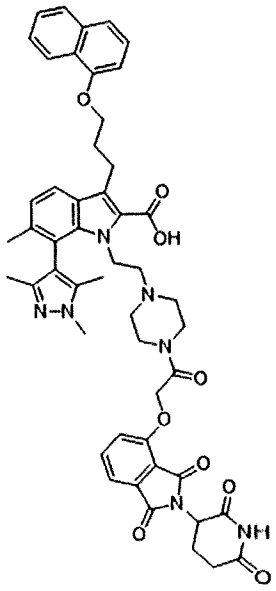
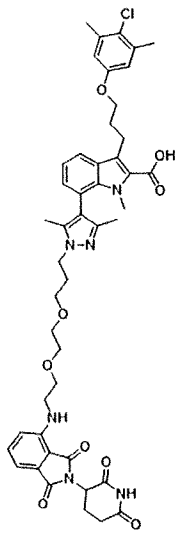
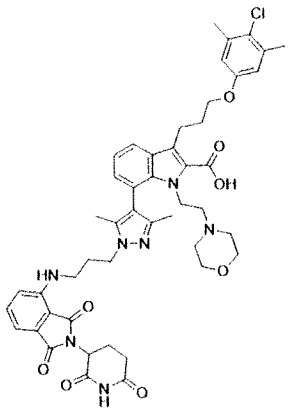
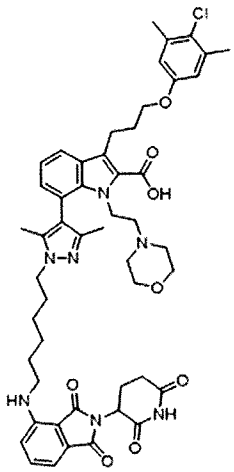

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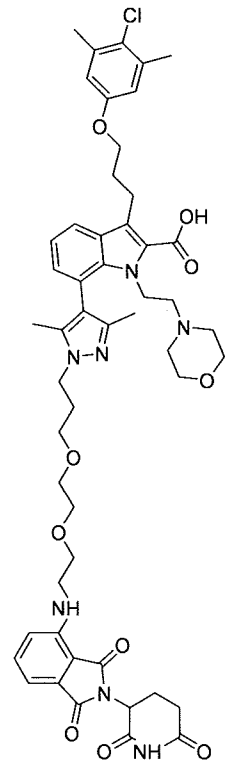
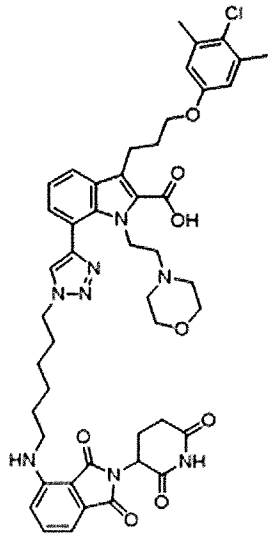
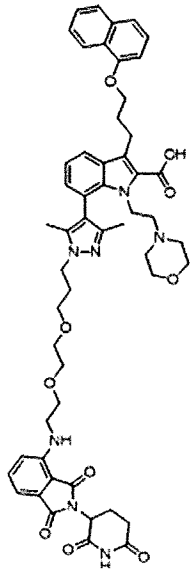
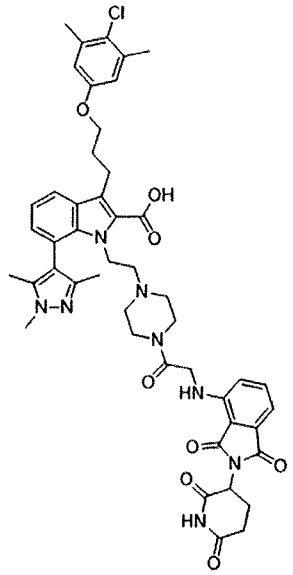
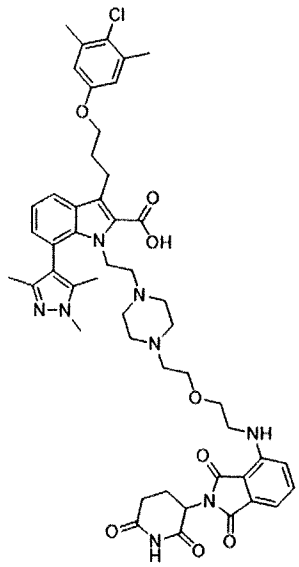
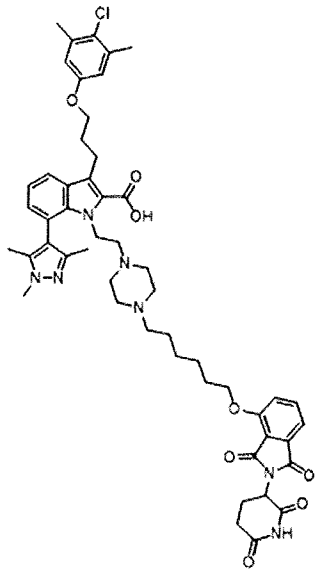
38. The compound of claim 36, which is selected from:

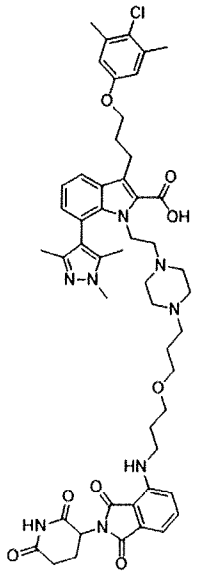
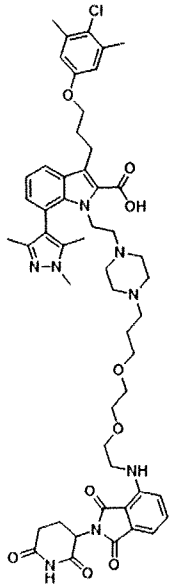
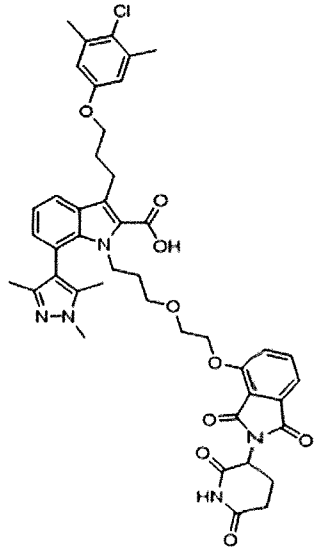
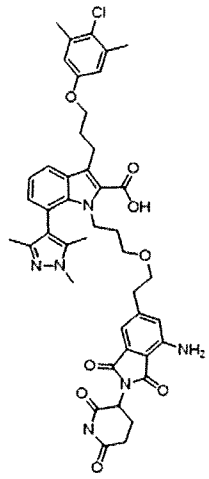
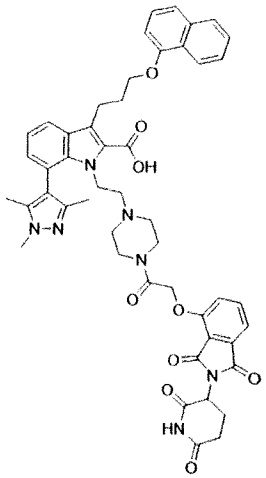
		
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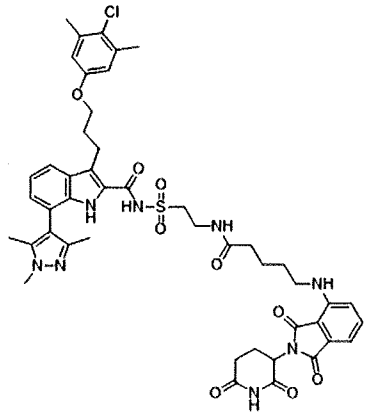
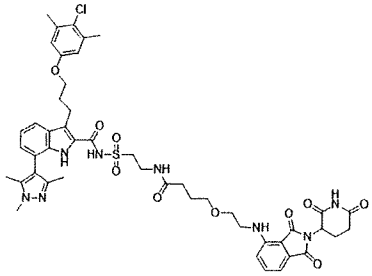
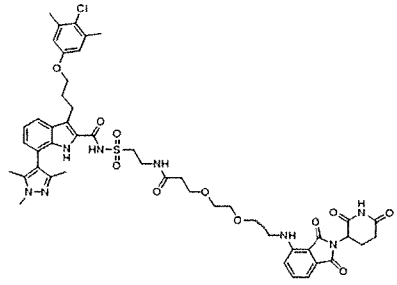
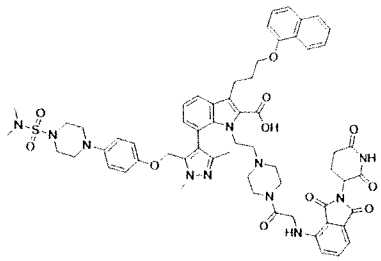
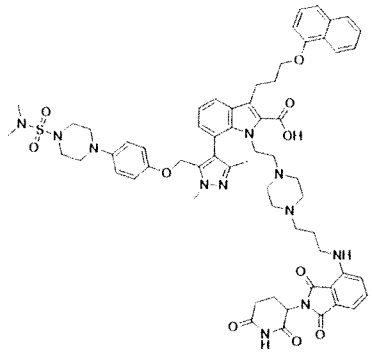
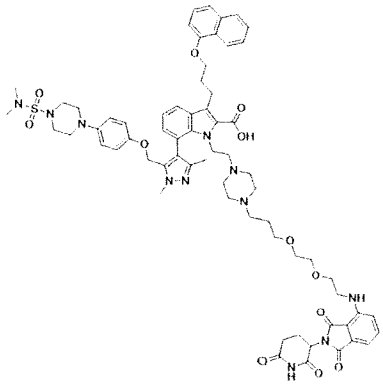
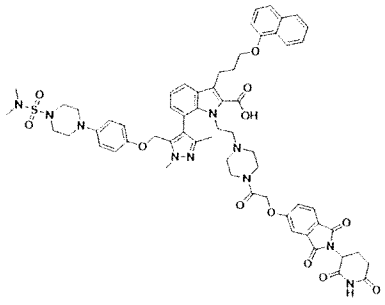
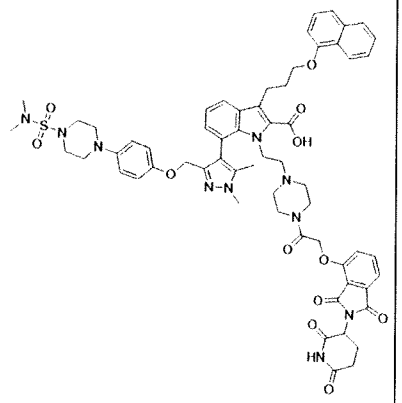
		
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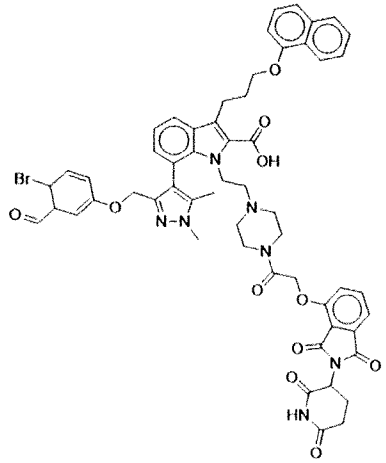
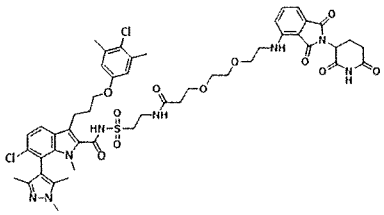
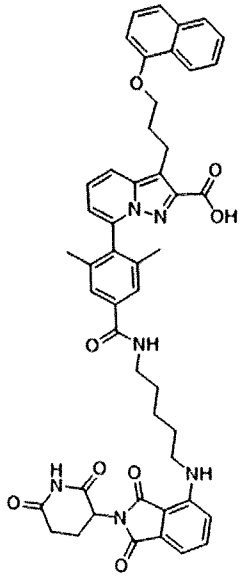
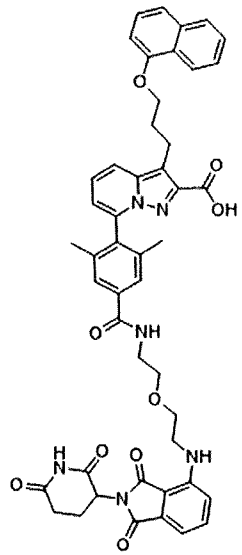
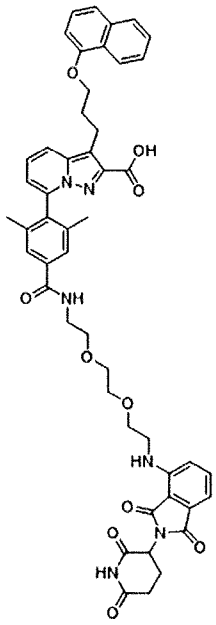
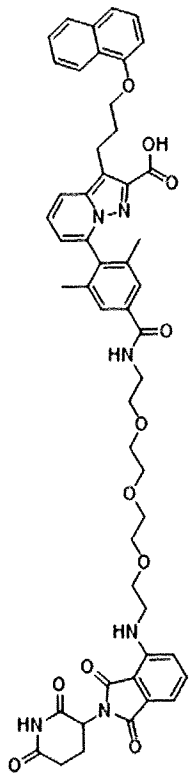
		
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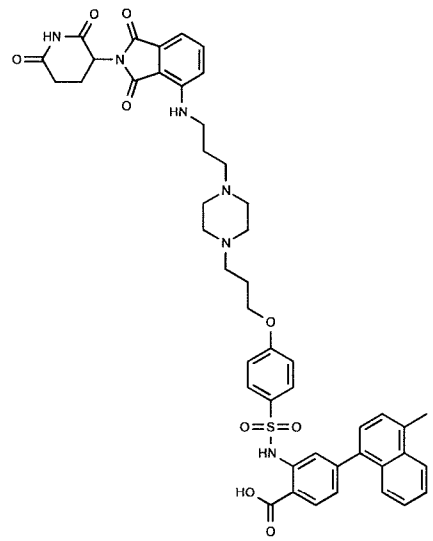
		
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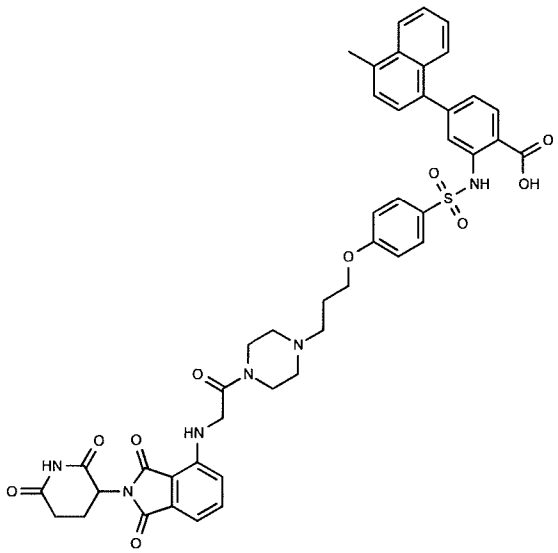
		
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242	*243*	*244*
		
245	246	247
		
248		250

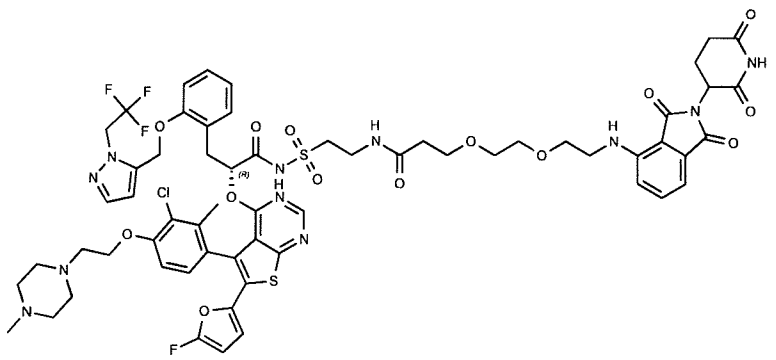
		
251	*252*	253
		
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257



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261	

39. The compound of any one of claims 1-38, wherein each alkyl, alkenyl, alkynyl, aryl, heteroaryl and benzyl is unsubstituted.

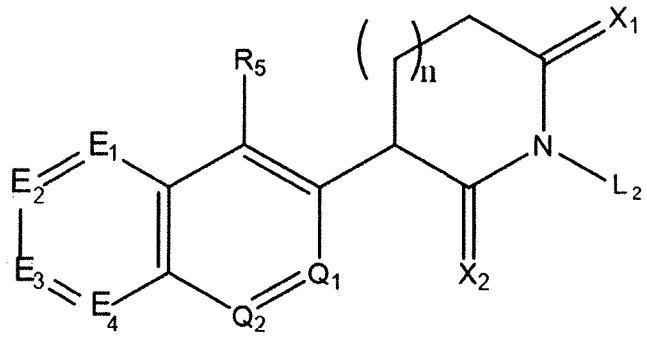
40. A compound of formula (I)

[MCL-1 ligand moiety] – [linker] – [ligase ligand moiety] (I)

or a salt, solvate, hydrate, isomer or prodrug thereof,

wherein **[ligase ligand moiety]** is:

(a) Formula (IV)



(IV)

wherein:

each of X_1 and X_2 is independently O or S;

each of Q_1 and Q_2 is independently N or CR^5, wherein at least one of Q_1 and Q_2 is N;

each of E_1, E_2, E_3 and E_4 is independently N or CR';

n is 0, 1 or 2;

L_2 is hydrogen, alkyl, alkenyl, aryl, heteroaryl, benzyl, haloalkyl, haloalkenyl, -C(O)R''', -C(O)OR''', $-C(O)NH_2$, -C(O)NHR''', -C(O)NR'''$_2$, -OR''', -NR'''$_2$, or $-S(O)_2$R''';

each R^5 is independently hydrogen, halogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, benzyl, haloalkyl, haloalkenyl, $-NH_2$, -NHR''', -NR'''$_2$, -NR'''C(O)R''', -NR'''C(O)OR''', $-NO_2$, -CN, -C(O)R''', -C(O)OR''', $-C(O)NH_2$, -C(O)NHR''', -C(O)NR'''$_2$, -OR''', -OC(O)R''', -OC(O)OR''', $-OC(O)NH_2$, -OC(O)NHR''', -OC(O)NR'''$_2$, -SR''', $-S(O)_2$R''', $-S(O)_2$OR''', $-S(O)_2NH_2$, $-S(O)_2$NHR''', $-S(O)_2$NR'''$_2$; -O-**R^{21}**, -NH-**R^{21}**, -C(O)-NH-**R^{21}**, or $-CH_2$-NH-C(O)-**R^{21}**;

each R' is independently hydrogen, halogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, benzyl, haloalkyl, haloalkenyl, $-NH_2$, -NHR''', -NR'''$_2$, -NR'''C(O)R''', -NR'''C(O)OR''', $-NO_2$,

-CN, -C(O)R''', -C(O)OR''', -C(O)NH_2, -C(O)NHR''', -C(O)NR'''_2, -OR''', -OC(O)R''', -OC(O)OR''', -OC(O)NH_2, -OC(O)NHR''', -OC(O)NR'''_2, -SR''', -$S(O)_2$R''', -$S(O)_2$OR''', $S(O)_2NH_2$, -$S(O)_2$NHR''', -$S(O)_2NR'''_2$, -O-**R^{21}**, -NH-**R^{21}**, -C(O)-NH-**R^{21}**, or -CH_2-NH-C(O)-**R^{21}**;

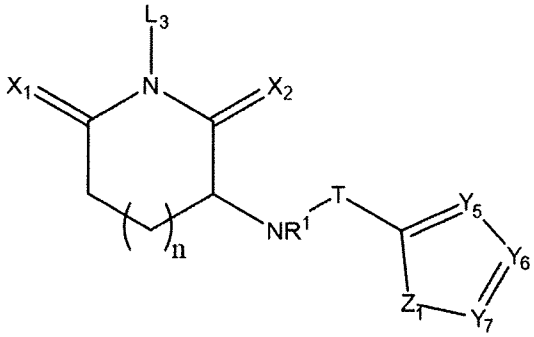
and

each R''' is independently hydrogen, alkyl, alkenyl, aryl, heteroaryl, or benzyl;

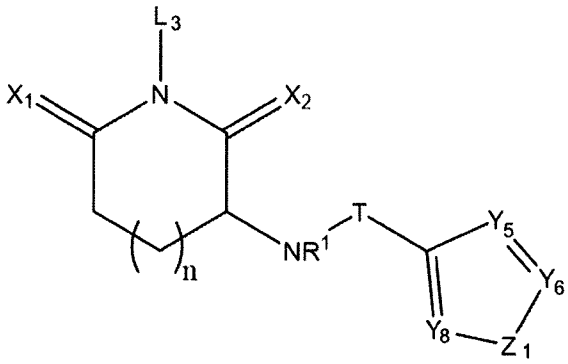
wherein **R^{21}** is a bond connected to **R^{18}** of the linker, and wherein Formula (IV) contains a single **R^{21}**;

or

(b) Formula (Va) or (Vb):



(Va)



(Vb)

or a pharmaceutically acceptable salt or tautomer thereof,

wherein

each of X_1 and X_2 is independently O or S;

Z_1 is O, S or NR^6;

T is is C=O or SO_2;

R^1 is hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, aryl, heteroaryl, or benzyl;

each of Y_5, Y_6, Y_7, and Y_8 is independently N or CR^7,

wherein at least one of Y_5, Y_6 and Y_7 in Formula (Va) is CR^7, and at least one of Y_5, Y_5 and Y_8 in Formula (Vb) is CR^7;

n is 0, 1 or 2;

L_3 is hydrogen, alkyl, alkenyl, aryl, heteroaryl, benzyl, haloalkyl, haloalkenyl, -C(O)R'''', -CH_2C(O)OR'''', -C(O)OR'''', -C(O)NH_2, -C(O)NHR'''', -C(O)NR''''_2, -OR'''', -NR''''_2, or -$S(O)_2$R'''';

each R^7 is independently hydrogen, halogen, alkyl, cycloalkyl, heterocycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, heteroaryl, benzyl, haloalkyl, haloalkenyl, -NH_2, -NHR'''', -NR''''_2, -$CH_2NR''''_2$, -NR''''C(O)R'''', -NR''''C(O)$CH_2NR''''_2$, -NR''''C(O)CH_2-heterocycloalkyl, -NR''''C(O)CH(OH)R'''', -CH_2NR''''C(O)OR'''', -NR''''C(O)OR'''', -NR''''SO_2R'''', -NO_2, -CN, -C(O)R'''', -C(O)OR'''', -C(O)NH_2, -C(O)NHR'''', -C(O)NR''''_2, -OR'''', -OC(O)R'''', -OC(O)OR'''', -OC(O)NH_2, -OC(O)NHR'''', -OC(O)NR''''_2, --NHC(S)NHR'''', SR'''', or -$S(O)_2$R'''',-$S(O)_2$OR'''', -$S(O)_2NH_2$, -$S(O)_2$NHR'''', -$S(O)_2NR''''_2$, -O-**R^{21}**, -NH-**R^{21}**, -C(O)-NH-**R^{21}**, or -CH_2-NH-C(O)-**R^{21}**;

each R'''' is independently hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, aryl, heteroaryl, or benzyl;

R^6 is hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, heteroaryl, benzyl, haloalkyl, haloalkenyl, -NH_2, -NHR'''', -NR''''_2, -NR''''C(O)R'''', -N[C(O)R''''$]_2$, -NR''''C(O)OR'''', -NO_2, -CN, -C(O)R'''', -C(O)OR'''', -C(O)NH_2, -C(O)NHR'''', -C(O)NR''''_2, -OR'''', -OC(O)R'''', -OC(O)OR'''', -OC(O)NH_2, -OC(O)NHR'''', -OC(O)NR''''_2, -SR'''', or -$S(O)_2$R'''',-$S(O)_2$OR'''', -$S(O)_2NH_2$, -$S(O)_2$NHR'''', -$S(O)_2NR''''_2$, -**R^{21}**, -C(O)-NH-**R^{21}**, or -CH_2-NH-C(O)-**R^{21}**;

wherein **R^{21}** is a bond connected to **R^{18}** of the linker, and wherein formula (Va) and formula (Vb) each contain a single **R^{21}**;

wherein when Z_1 is O, then Y_6 is CR^7 and

wherein when the compound is of Formula (Va), then

(i) when each of Y_5, Y_6 and Y_7 is CR^7, then at least one of R^7 is not H;

(ii) when Z_1 is NR^6, then Y_6 and Y_7 are CR^7;

(iii) when Z_1 is S, then Y_5 is not C-OMe and Y_6 is not C-OMe;

(iv) when Z_1 is S and Y_5 is C-NHCOMe, then Y_7 is not C-CH_2NR''''C(O)OR'''';

(v) when Z_1 is S and Y_5 is N, then Y_6 is not C-H, C-aryl or C-C(O)OR''''; and

(vi) when Z_1 is S and Y_6 is N, then Y_7 is C-NH_2, C-NHR'''', C-NR''''_2, C-NR''''C(O)OR'''', C-CH_2NR''''C(O)OR'''', C-haloalkyl, C-^{t}Butyl, C-OR'''', C-COOR'''' or C-SR''''; wherein when Y_7 is C-NH_2, C-NHR'''' or C-NR''''_2, then Y_5 is C-H;

and when the compound is of Formula (Vb), then:

(vii) when each of Y_5, Y_6 and Y_8 is CR^7, then at least one of R^7 is not H;

(viii) when Z_1 is S, then Y_5 is not C-COOH or C-NHC(O)Me, and Y_8 is not C-Br;

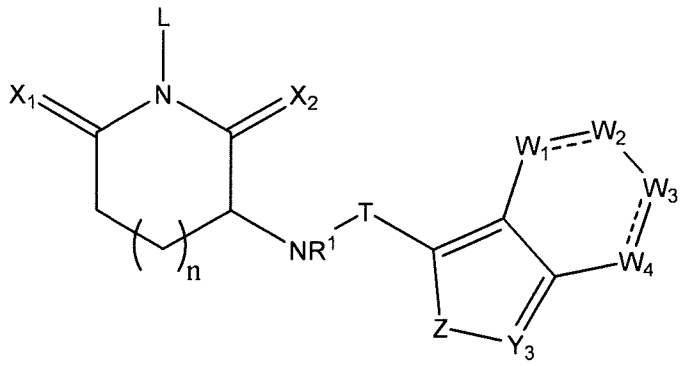
(ix) when Z_1 is S and Y_6 is C-Br, then Y_8 is C-OR''''

(x) when Z_1 is S, Y_5 is N and Y_6 is C-H or C-NH_2, then Y_8 is not C-H

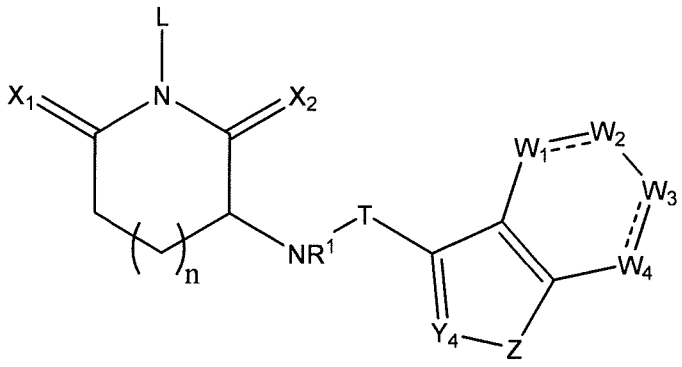
(xi) when Z_1 is S and Y_5 is N, then Y_6 is not C- halogen, C-alkyl, C-cycloalkyl, C-aryl, C-heteroaryl, C-CH_2NH_2, C-COOalkyl, or C-NHC(O)alkyl; (xii) when Z_1 is NR^6, then Y_5, Y_6 and Y_8 are CR^7.

or

(c) Formula (IIa) or (IIb):



(IIa)



(IIb)

wherein

each of X_1 and X_2 is independently O or S;

Z is O, S or NR^2;

T is C=O or SO_2;

Y_3 is N or CR;

Y_4 is N or CR;

 indicates a single or double bond, wherein

when each  is a double bond, each of W_1, W_2, W_3 and W_4 is independently N or CR^a, wherein at least one of W_1, W_2, W_3 and W_4 is N, and

when each  is a single bond, W_1, W_2, W_3 and W_4 are each CR^a_2 and Y_4 is CR;

n is 0, 1 or 2;

L is hydrogen, alkyl, alkenyl, aryl, heteroaryl, benzyl, haloalkyl, haloalkenyl, $-C(O)R^h$, $-C(O)OR^h$, $-C(O)NH_2$, $-C(O)NHR^h$, $-C(O)NR^h_2$, $-OR^h$, $-NR^h_2$, or $-S(O)_2R^h$;

each R is independently hydrogen, halogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, heteroaryl, benzyl, haloalkyl, haloalkenyl, $-NH_2$, $-NHR^h$, $-NR^h_2$, $-NR^hC(O)R^h$, $-NR^hC(O)CH_2R^h$, $-NR^hC(O)CH(OH)R^h$, $-NR^hC(O)OR^h$, $-NR^hSO_2R^h$, $-NO_2$, -CN, $-C(O)R^h$, $-C(O)OR^h$, $-C(O)NH_2$, $-C(O)NHR^h$, $-C(O)NR^h_2$, $-OR^h$, $-OC(O)R^h$, $-OC(O)OR^h$, $-OC(O)NH_2$, $-OC(O)NHR^h$, $-OC(O)NR^h_2$, $-SR^h$, or $-S(O)_2R^h$,$-S(O)_2OR^h$, $-S(O)_2NH_2$, $-S(O)_2NHR^h$, or $-S(O)_2NR^h_2$;

each R^a is independently hydrogen, halogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, heteroaryl, benzyl, haloalkyl, haloalkenyl, $-NH_2$, $-NHR^h$, $-NR^h_2$, $-NR^hC(O)R^h$, $-NR^hC(O)CH(OH)R^h$, $-NR^hC(O)OR^h$, $-NR^hSO_2R^h$, $-NO_2$, -CN, $-C(O)R^h$, $-C(O)OR^h$, $-C(O)NH_2$, $-C(O)NHR^h$, $-C(O)NR^h_2$, $-OR^h$, $-OC(O)R^h$, $-OC(O)OR^h$, $-OC(O)NH_2$, $-OC(O)NHR^h$, $-OC(O)NR^h_2$, $-SR^h$, $-S(O)_2R^h$, $-S(O)_2OR^h$, $-S(O)_2NH_2$, $-S(O)_2NHR^h$, $-S(O)_2NR^h_2$, $-O-\mathbf{R^{21}}$, $-NH-\mathbf{R^{21}}$, $-C(O)-NH-\mathbf{R^{21}}$, or $-CH_2-NH-C(O)-\mathbf{R^{21}}$;

each R^h is independently hydrogen, alkyl, cycloalkyl, heterocycloalkyl, alkenyl, cycloalkenyl, aryl, heteroaryl, or benzyl;

R^2 is hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, heteroaryl, benzyl, haloalkyl, haloalkenyl, $-NH_2$, $-NHR^h$, $-NR^h_2$, $-NR^hC(O)R^h$, $-N[C(O)R^h]_2$, $-NR^hC(O)OR^h$, $-NO_2$, -CN, $-C(O)R^h$, $-C(O)OR^h$, $-C(O)NH_2$, $-C(O)NHR^h$, $-C(O)NR^h_2$, $-OR^h$, $-OC(O)R^h$, $-OC(O)OR^h$, $-OC(O)NH_2$, $-OC(O)NHR^h$, $-OC(O)NR^h_2$, $-SR^h$, $-S(O)_2R^h$,$-S(O)_2OR^h$, $-S(O)_2NH_2$, $-S(O)_2NHR^h$, or $-S(O)_2NR^h_2$; and

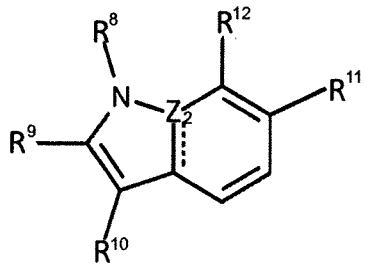
R^1 is hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, aryl, heteroaryl, or benzyl;

$\mathbf{R^{21}}$ is a bond connected to $\mathbf{R^{18}}$ of the linker, and wherein formula (IIa) and formula (IIb) each contain a single $\mathbf{R^{21}}$;

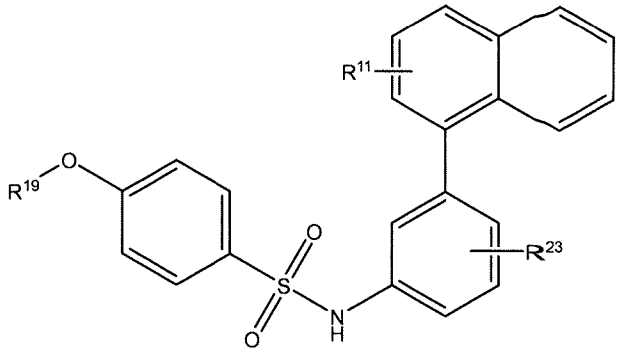
wherein when each is a double bond, Z is NR^2, R^2 is hydrogen, and each R^a is hydrogen, then W_4 is CR^a;

wherein

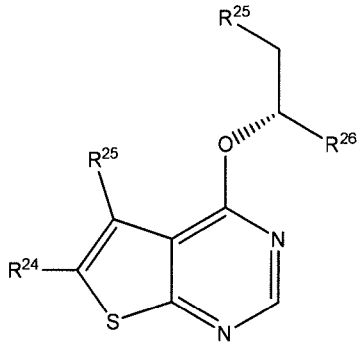
[MCL-1 ligand moiety] is a compound of Formula (A), Formula (B) or Formula (C)



(A)



(B)



(C)

wherein

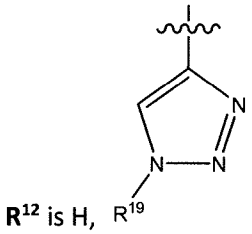
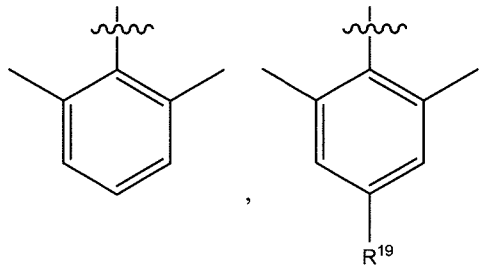
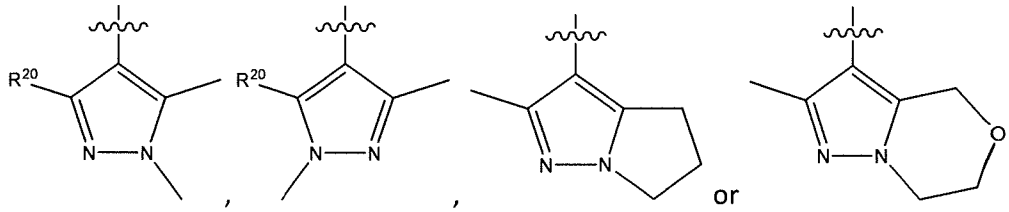
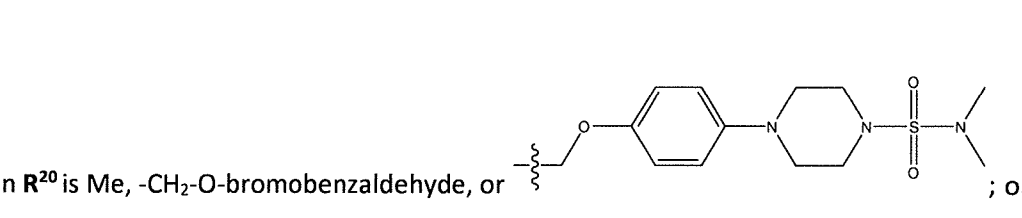
 is a single bond or a double bond;

$\mathbf{R^8}$ is H, $\mathbf{R^{19}}$, or C_1-C_6 alkyl optionally substituted with morpholine;

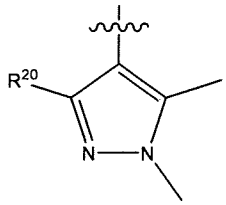
$\mathbf{R^9}$ is -C(O)OH, -C(O)OC_1-C_6alkyl, -C(O)NH_2, -C(O)O$\mathbf{R^{19}}$ or -C(O)NH$\mathbf{R^{19}}$,

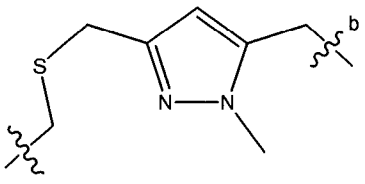
$\mathbf{R^{10}}$ is -$C_{2\text{-}5}$alkyl-O-R^{13}, wherein R^{13} is phenyl, naphthyl or tetraline, wherein the phenyl, naphthyl or tetraline is optionally substituted with at least one substituent selected from halogen, C_1-C_6 alkyl and -O(C_1-C_6 alkyl); or wherein the naphthyl is optionally substituted with -O- or -S-,

$\mathbf{R^{11}}$ is H, halogen or C_1-C_6 alkyl,

R^{12} is H,  ,  ,  ,  or

wherein **R^{20}** is Me, -CH$_2$-O-bromobenzaldehyde, or ; or when

R^{12} is  and **R^{10}** is -O-naphthyl substituted with -O- or -S-, then **R^{20}** is

 , wherein  indicates attachment to -O- or -S- of **R^{10}**;

and wherein

R^{19} is a bond connected to **R^{14}** of the linker;

R^{23} is -C(O)OH or -C(O)OC$_1$-C$_6$alkyl;

Z_2 is N or C, wherein when Z_2 is N, then  is a single bond; and when Z_2 is C, then  is a double bond,

R^{24} is furan optionally substituted with at least one halogen,

each R^{25} is independently phenyl substituted with $-OR^{28}$ and optionally further substituted with at least one substituent selected from halogen and C_1-C_6 alkyl;

R^{26} is $-C(O)OR^{19}$ or $-C(O)NHR^{19}$; and

each R^{28} is independently $-C_{1-3}$alkyl-(N-alkyl piperazine) or $-C_{1-3}$alkyl-(N-haloalkylpyrazole)

and wherein each of Formula (A), Formula (B) and Formula (C) contains a single R^{19};

and wherein **[linker]** has the following formula

R^{14}-R^{15}-R^{16}-R^{17}-R^{18}

wherein

R^{14} is $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, -C(O)-, $-SO_2-$ or is absent

R^{15} is cycloalkyl, heterocycloalkyl, aryl, heteroaryl, $-C_{1-6}$ alkyl-NH-, -cycloalkyl-NH- or is absent

R^{16} is $-C_{1-6}$ alkyl, -C(O)-, -C(O)-NH-, -C(O)O-, $-CH_2$-C(O)-, $-CH_2$-C(O)-NH-, $-CH_2$-C(O)O- or is absent

R^{17} is $-CH_2(C_2H_4-O)_y$, $(C_2H_4-O)_x$, $(C_3H_6-O)_x$, or is absent

x is 1-10

y is 2-10

R^{18} is $-C_{1-6}$ alkyl, heterocycloalkyl, or is absent

wherein at least one of R^{14}-R^{18} is present.

41. The compound of claim 40, wherein each alkyl, alkenyl, alkynyl, aryl, heteroaryl and benzyl groups is unsubstituted.

42. The compound of any one of claims 40-41, wherein each R is independently hydrogen, halogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, heteroaryl, benzyl, haloalkyl, haloalkenyl, $-NH_2$, -NHR'''', $-NR''''_2$, -NR''''C(O)R'''', -NR''''C(O)CH(OH)R'''', -NR''''C(O)OR'''', $-NR''''SO_2R''''$, $-NO_2$, -CN,-C(O)R'''', -C(O)OR'''', $-C(O)NH_2$, -C(O)NHR'''', $-C(O)NR''''_2$, -OR'''', -OC(O)R'''', -OC(O)OR'''', $-OC(O)NH_2$, -

$OC(O)NHR''''$, $-OC(O)NR''''_2$, $-SR''''$, or $-S(O)_2R''''$, $-S(O)_2OR''''$, $-S(O)_2NH_2$, $-S(O)_2NHR''''$, or $-S(O)_2NR''''_2$, -O-$\mathbf{R^{21}}$, -NH-$\mathbf{R^{21}}$, -C(O)-NH-$\mathbf{R^{21}}$, or $-CH_2$-NH-C(O)-$\mathbf{R^{21}}$.

43. The compound of any one of claims 40-42, wherein R^1 is hydrogen.

44. The compound of any one of claims 40-43, wherein R^6 is hydrogen.

45. The compound of any one of claims 40-44, wherein when Z_1 is S in Formula (Vb), then Y_5 is not C- $NHC(O)R''''$ or $-C(O)OR''''$.

46. The compound of any one of claims 40-45, wherein Z_1 is NR^6.

47. The compound of any one of claims 40-46, wherein **[ligase ligand moiety]** is of Formula (Va) and Y_5, Y_6 and Y_7 are each CR^7.

48. The compound of claim 47, wherein

Y_5 is -C-$NHC(O)R''''$,

Y_6 is CH, and

Y_7 is CH or CCl.

49. The compound of claim 48, wherein:

L_3 is hydrogen;

Z_1 is S;

R^1 is hydrogen;

T is C=O; and

Y_7 is CH.

50. The compound of any one of claims 40-46, wherein the compound is of Formula (Vb) and Y_5, Y_6 and Y_8 are each CR^7.

51. The compound of claim 50, wherein:

L_3 is hydrogen;

Z_1 is S;

R^1 is H;

T is C=O;

Y_5 is CH, C-OR'''', CCl, C-CN, or C-NHC(O)R'''';

Y_6 is CH, CCl, C-alkyl, C-cycloalkyl, or C-haloalkyl; and

Y_8 is CH, C-OR'''', C-NHC(O)R'''', C-NHC(O)OR'''', C-NHR'''', $C\text{-}NH_2$, or $C\text{-}NHSO_2R''''$;

wherein, when Y_5 is CCl, then Y_6 is CH, C-alkyl, C-cycloalkyl, or C-haloalkyl;

optionally wherein each R'''' is independently alkyl, cycloalkyl, aryl or benzyl.

52. The compound of claim 51, wherein:

Y_5 is CH;

Y_6 is CH or CCl; and

Y_8 is C-OR'''' or $C\text{-}NH_2$, optionally C-OMe or $C\text{-}NH_2$.

53. The compound of any one of claims 40-52, wherein Z is NR^2.

54. The compound of any one of claims 40-52, wherein Z is S.

55. The compound of any one of claims 40-54, wherein each  is a double bond.

56. The compound of any one of claims 40-55, wherein L is hydrogen.

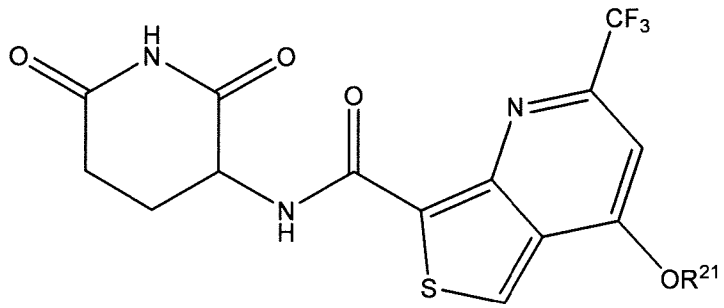
57. The compound of claim 55 or 56, wherein one of W_1, W_2, W_3 and W_4 is N, and the remaining three of W_1, W_2, W_3 and W_4 are each CR^a; optionally wherein W_4 is CR^a.

58. The compound of claim 55 or 56, wherein two of W_1, W_2, W_3 and W_4 is N, and the remaining two of W_1, W_2, W_3 and W_4 are each CR^a.

59. The compound of claim 55 or 56, wherein one of W_1, W_2, W_3 and W_4 is CR^a, and the remaining three of W_1, W_2, W_3 and W_4 are each N.

60. The compound of any one of claims 40-59, wherein each R is independently hydrogen, halogen or -$NR^hC(O)R^h$.

61 The compound of any one of claims 40-60, wherein **[ligase ligand moiety]** is:



62. The compound of any one of claims 40-61, wherein E_1, E_2, E_3 and E_4 are each CR'.

63. The compound of any one of claims 40-62, wherein one of E_1, E_2, E_3 and E_4 is N and the remaining three of E_1, E_2, E_3 and E_4 are each CR'.

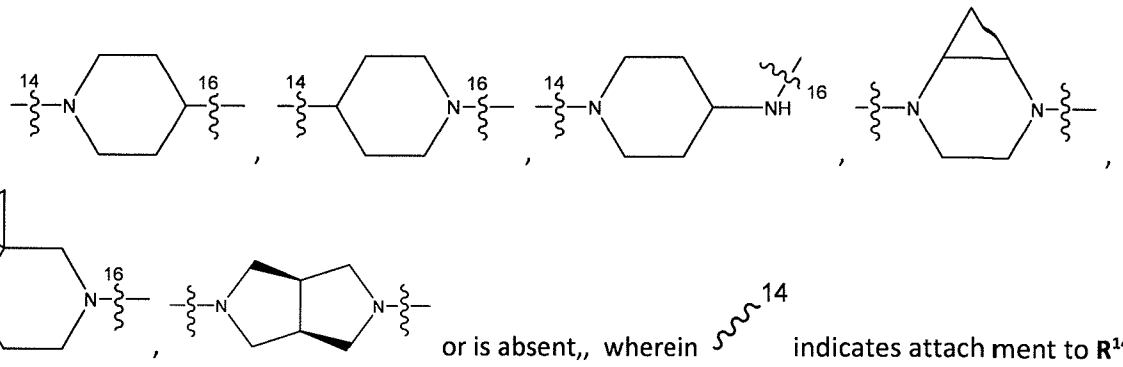
64. The compound of any one of claims 40-63, wherein Q_1 is CR^5

65. The compound of any one of claims 40-63, wherein Q_2 is CR^5

66. The compound of any one of claims 40-65, wherein

R^{14} is -C_{1-6} alkyl, -SO_2- or is absent

R^{15} is piperazine, bridged piperazine, piperazine N-oxide, piperazine cation, -C_{1-6} alkyl-NH-,



or is absent,, wherein indicates attach ment to **R**^{14} and  indicates attachment to **R**^{16},

R^{16} is -C_{1-6} alkyl, -C(O)-, -C(O)-NH-, -CH_2-C(O)-NH- or is absent

R^{17} is -$CH_2(C_2H_4\text{-}O)_y$, $(C_2H_4\text{-}O)_x$, $(C_3H_6\text{-}O)_x$, or is absent

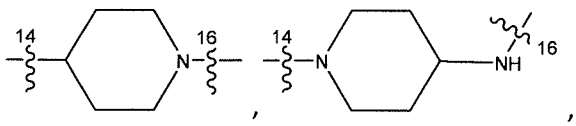
x is 1-6

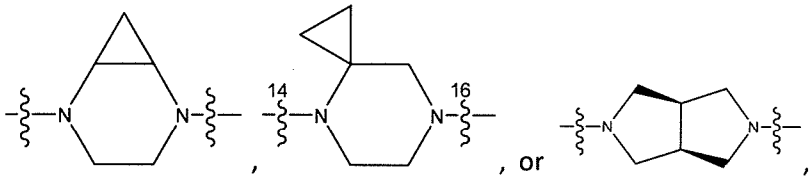
y is 2-6

R^{18} is -C_{1-6} alkyl, piperazine, or is absent

wherein at least one of R^{14}-R^{18} is present

67. The compound of any one of claims 40-66, wherein **R**^{18} is -C_{1-6} alkyl or is absent.

68. The compound of any one of claims 40-67, wherein when **R**^{15} is piperazine, bridged piperazine, piperazine N-oxide, piperazine cation, -C_{1-6} alkyl-NH-, 

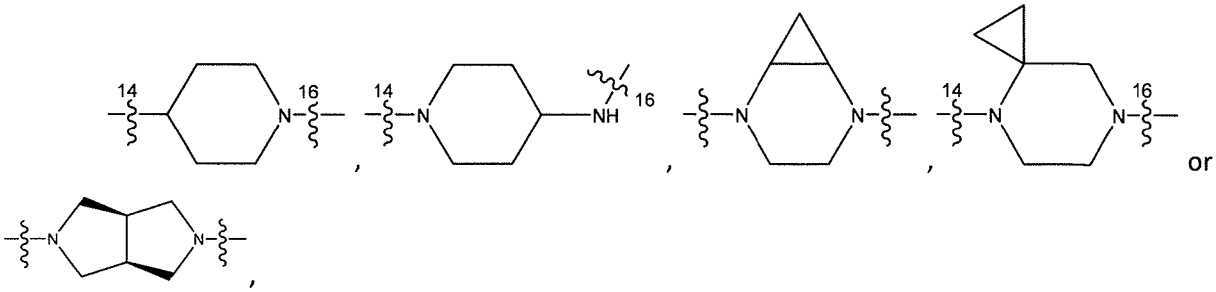


then **R**^{14} is -C_{1-6} alkyl.

69. The compound of any one of claims 40-68, wherein

R^{14} is -C_{1-6} alkyl,

R^{15} is piperazine, bridged piperazine, piperazine N-oxide,



,

$\mathbf{R^{16}}$ is -C(O)-, -CH_2-C(O)-NH-, or is absent

$\mathbf{R^{17}}$ is -$CH_2(C_2H_4\text{-}O)_y$, $(C_2H_4\text{-}O)_x$, $(C_3H_6\text{-}O)_x$, or is absent

$\mathbf{R^{18}}$ is -$C_{1\text{-}6}$ alkyl,

wherein when $\mathbf{R^{16}}$ and $\mathbf{R^{17}}$ are absent, $\mathbf{R^{18}}$ is -$C_{3\text{-}6}$ alkyl.

70. The compound of claim 69, wherein

$\mathbf{R^{14}}$ is -C_2 alkyl,

x is 1, 2 or 6

y is 2.

71. The compound of claim 69, wherein

$\mathbf{R^{15}}$ is piperazine,

$\mathbf{R^{16}}$ is -C(O)-,

$\mathbf{R^{17}}$ is absent.

72. The compound of claim 71, wherein

$\mathbf{R^{14}}$ is -C_2 alkyl,

$\mathbf{R^{18}}$ is -$C_{1\text{-}2}$ alkyl.

73. The compound of any one of claims 40-67, wherein when $\mathbf{R^{14}}$ is -SO_2-, at least two of $\mathbf{R^{15}}$-$\mathbf{R^{18}}$ are present, and at least one of $\mathbf{R^{15}}$-$\mathbf{R^{18}}$ is not $C_{1\text{-}6}$ alkyl.

74. The compound of any one of claims 40-67, wherein

$\mathbf{R^{14}}$ is -SO_2-

$\mathbf{R^{15}}$ is -$C_{1\text{-}6}$ alkyl-NH-

$\mathbf{R^{16}}$ is -C(O)-

$\mathbf{R^{17}}$ is $-CH_2(C_2H_4-O)_y$, $(C_2H_4-O)_x$ or is absent

$\mathbf{R^{18}}$ is $-C_{2-4}$ alkyl.

75. The compound of claim 74, wherein

$\mathbf{R^{15}}$ is $-C_2$alkyl-NH-

x is 1 or 2

y is 1

$\mathbf{R^{18}}$ is $-C_{2-4}$ alkyl

76. The compound of any one of claims 40-67 wherein

$\mathbf{R^{14}}$ is absent

$\mathbf{R^{15}}$ is absent

$\mathbf{R^{16}}$ is -C(O)-NH-, or is absent

$\mathbf{R^{17}}$ is $-CH_2(C_2H_4-O)_y$, $(C_2H_4-O)_x$, $(C_3H_6-O)_x$, or is absent

$\mathbf{R^{18}}$ is $-C_{1-6}$ alkyl.

77. The compound of any one of claims 40-76, wherein at least one of $\mathbf{R^{14}}$-$\mathbf{R^{18}}$ is not $-C_{1-6}$ alkyl.

78. The compound of claim 76 or claim 77, wherein

x is 1, 2 or 3

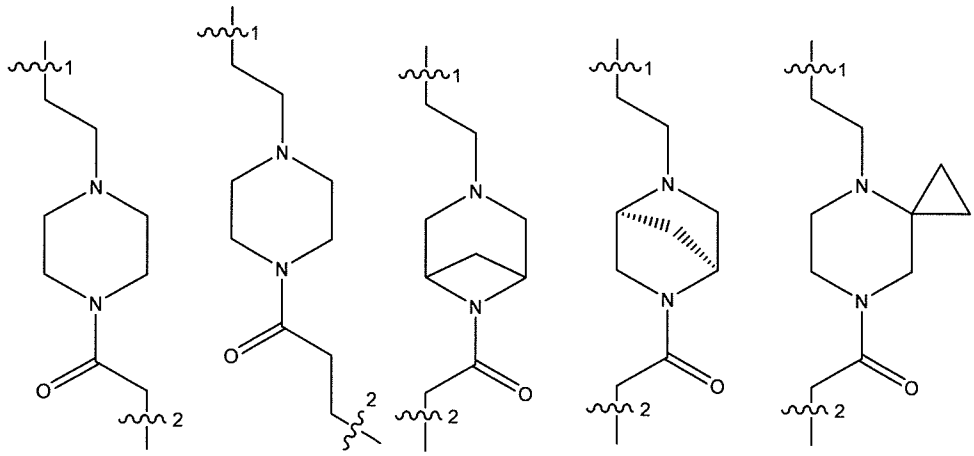
y is 2

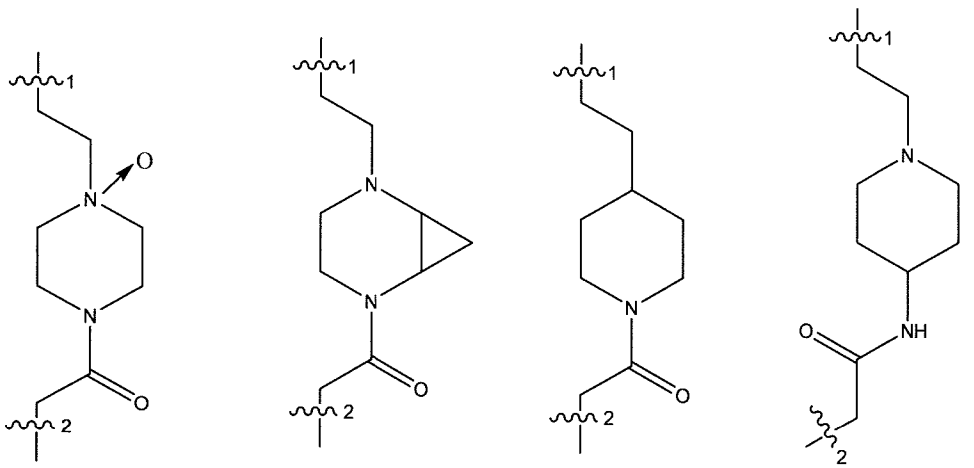
$\mathbf{R^{18}}$ is $-C_{2-6}$ alkyl.

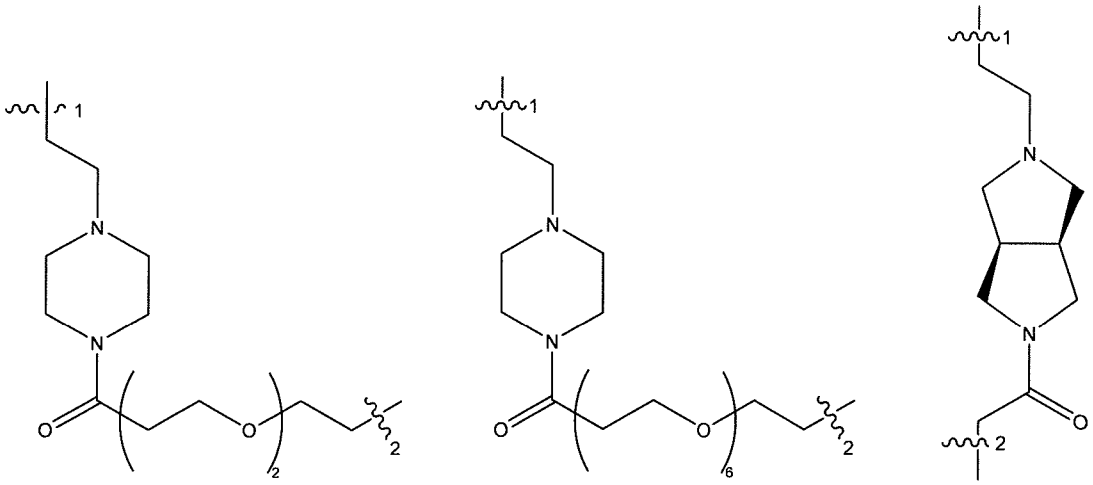
79. The compound of any one of claims 40-78, wherein when $\mathbf{R^{15}}$ is $-C_{1-6}$ alkyl-NH-, at least one of $\mathbf{R^{16}}$-$\mathbf{R^{18}}$ is present.

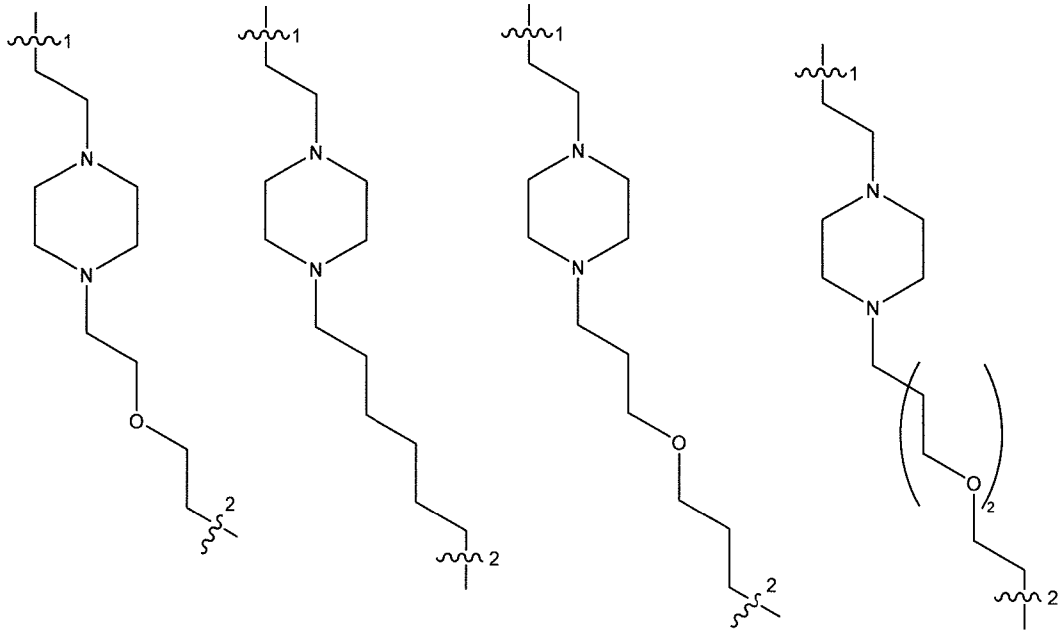
80. The compound of any one of claims 40-79 wherein when $\mathbf{R^{17}}$ is $-CH_2(C_2H_4-O)_y$, $(C_2H_4-O)_x$ or $(C_3H_6-O)_x$, at least one of $\mathbf{R^{14}}$-$\mathbf{R^{16}}$ and $\mathbf{R^{18}}$ is present, wherein at least one of $\mathbf{R^{14}}$ and $\mathbf{R^{18}}$ is not $-C_{1-6}$ alkyl.

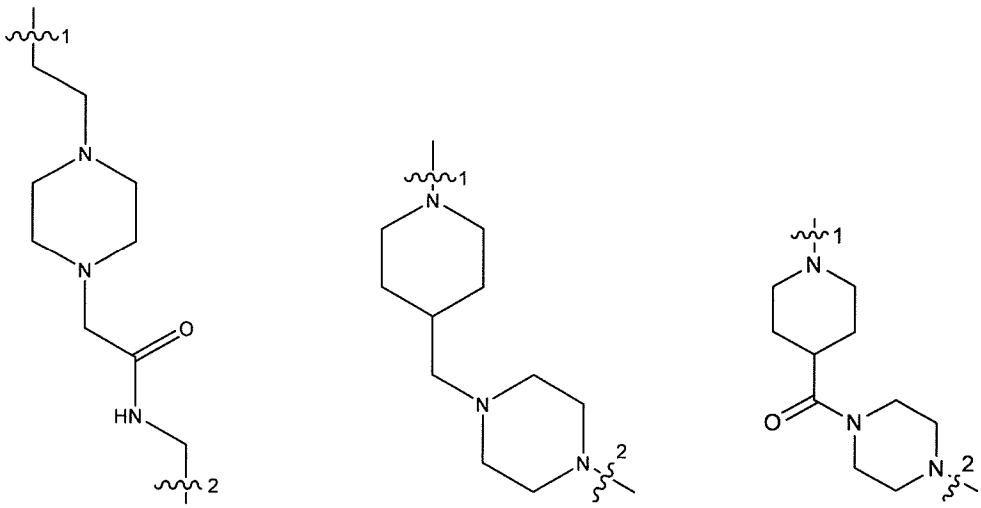
81. The compound of any one of claims 40-80, wherein **[linker]** is selected from

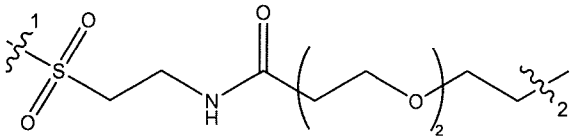


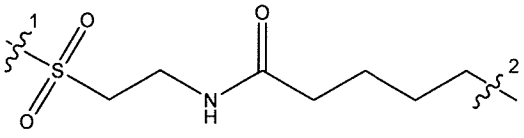


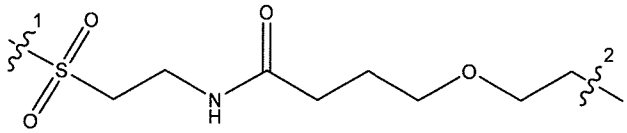


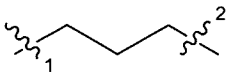


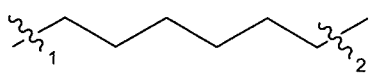


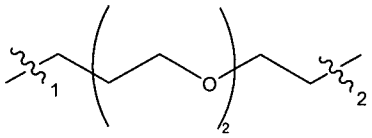


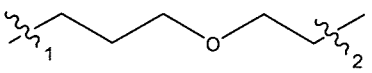


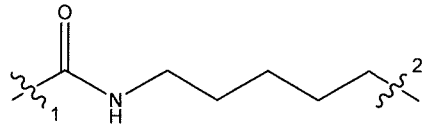


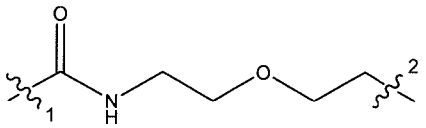


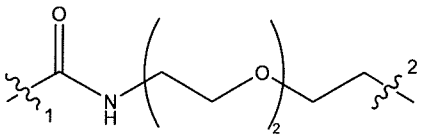




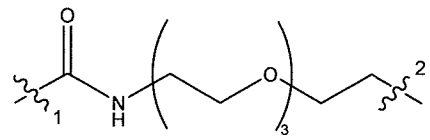








and

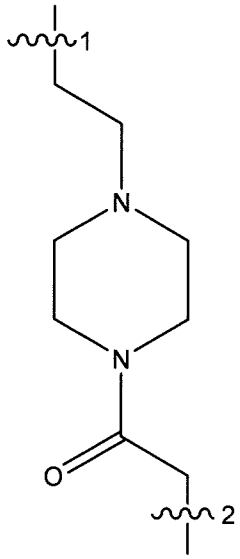


wherein

 indicates attachment to **[MCL-1 ligand moiety]** and

 indicates attachment to **[ligase ligand moiety].**

82. The compound of any one of claims 40-81, wherein **[linker]** is



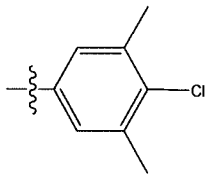
wherein



indicates attachment to **[MCL-1 ligand moiety]** and



indicates attachment to **[ligase ligand moiety].**

83. The compound of any one of claims 40-82 wherein when $\mathbf{R^8}$ is H, $\mathbf{R^{13}}$ is 

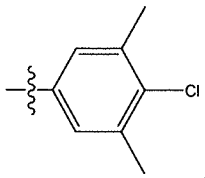
.

84. The compound of any one of claims 40-83, wherein

$\mathbf{R^8}$ is H, $\mathbf{R^{19}}$, methyl, or -CH_2CH_2-morpholine;

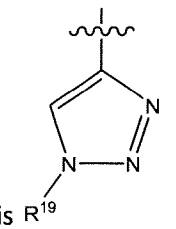
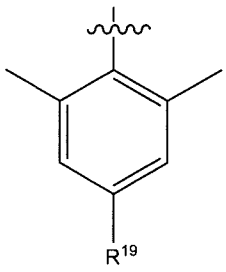
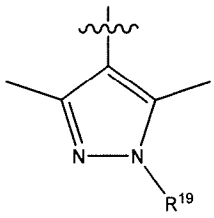
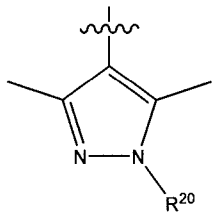
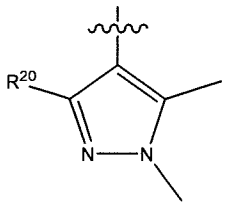
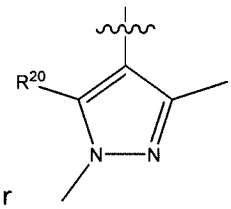
$\mathbf{R^9}$ is -C(O)OH or -C(O)NH$\mathbf{R^{19}}$,

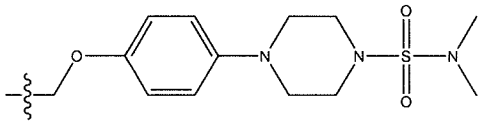
$\mathbf{R^{10}}$ is -C_3H_6O-R^{13},

wherein $\mathbf{R^{13}}$ is 

, tetraline, or naphthyl optionally substituted with fluorine;

$\mathbf{R^{11}}$ is H, Cl, F or methyl,

R12 is  ,  ,  ,  ,  ,  , or

wherein **R20** is Me, -CH_2-O-bromobenzaldehyde, or  .

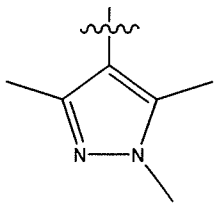
85. The compound of claim 84, wherein

R8 is **R19** or methyl;

R10 is -C_3H_6O-R^{13}, wherein **R13** is naphthyl optionally substituted with fluorine;

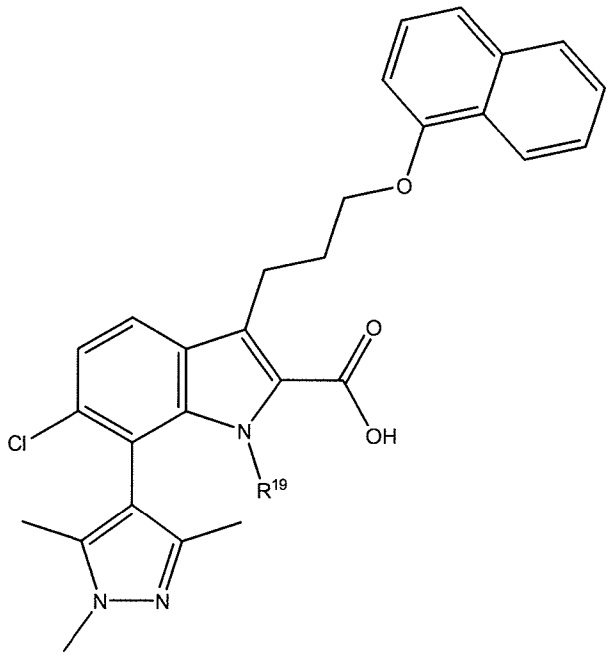
R11 is Cl or F,

R12 is

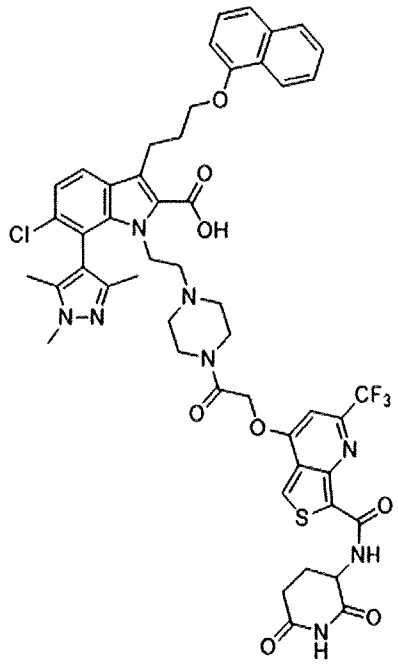
 .

86. The compound of any one of claims 40-85 wherein Z_2 is C and  is a double bond.

87. The compound of any one of claims 40-86, wherein **[MCL-1 ligand moiety]** is



88. The compound of claim 40, wherein the compound is:



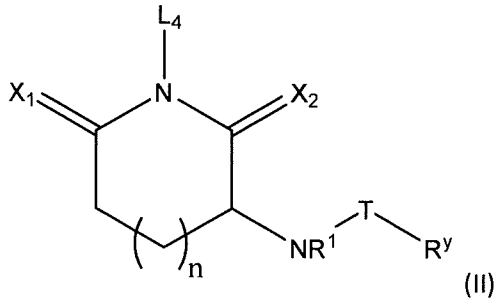
89. A compound of formula (I)

[MCL-1 ligand moiety] – [linker] – [ligase ligand moiety] (I)

or a salt, solvate, hydrate, isomer or prodrug thereof,

wherein **[ligase ligand moiety]** is:

(a) Formula (II):



(II)

wherein:

each of X_1 and X_2 is independently O or S;

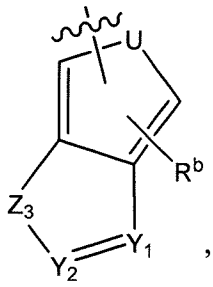
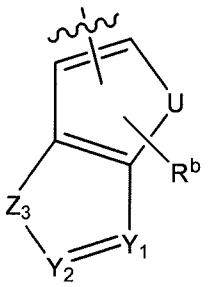
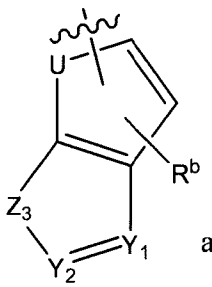
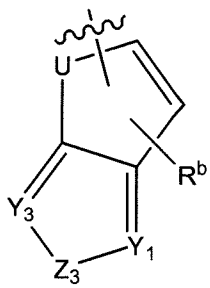
T is C=O or SO_2;

R^1 is hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, aryl, heteroaryl, or benzyl;

n is 0, 1 or 2;

L_4 is hydrogen, alkyl, alkenyl, aryl, heteroaryl, benzyl, haloalkyl, haloalkenyl, -C(O)H, -C(O)R'',-C(O)OH, -C(O)OR'', $-C(O)NH_2$, -C(O)NHR'', $-C(O)NR''_2$, -OH, -OR'', $-NH_2$, -NHR'', $-NR''_2$, $-S(O)_2H$ or $-S(O)_2R''$;

R^y is selected from


,

,

and


wherein  indicates attachment to T,

Z_3 is O, S or NR^3;

U is O, S, NR^b or CR^b_2;

each of Y_1, Y_2 and Y_3 is independently N or CR^d;

each R^d is independently hydrogen, halogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, heteroaryl, benzyl, haloalkyl, haloalkenyl, $-NH_2$, -NHR'', $-NR''_2$, -NHC(O)R'', -NR''C(O)R'', NHC(O)CH(OH)R'', -NR''C(O)CH(OH)R'', -NHC(O)OR'', -NR''C(O)OR'', $-NHSO_2R''$, $-NR''SO_2R''$, $-NO_2$, -CN, -C(O)H, C(O)R'', -C(O)OH, -C(O)OR'', $-C(O)NH_2$, -C(O)NHR'', $-C(O)NR''_2$,-OH, -OR'', -OC(O)H, -OC(O)R'', -OC(O)OH,-OC(O)OR'', $-OC(O)NH_2$, -OC(O)NHR'', $-OC(O)NR''_2$, -SH, -SR'', $-S(O)_2H$, $-S(O)_2R''$, $-S(O)_2OH$, $-S(O)_2OR''$, $-S(O)_2NH_2$, $-S(O)_2NHR''$, $-S(O)_2NR''_2$, -O-$\mathbf{R^{21}}$, -NH-$\mathbf{R^{21}}$, -C(O)-NH-$\mathbf{R^{21}}$, or $-CH_2$-NH-C(O)-$\mathbf{R^{21}}$;

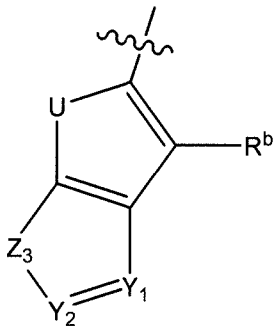
each R^b is independently hydrogen, halogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, heteroaryl, benzyl, haloalkyl, haloalkenyl, $-NH_2$, -NHR'', $-NR''_2$, -NHC(O)R'', -NR''C(O)R'', NHC(O)CH(OH)R'', -NR''C(O)CH(OH)R'', -NHC(O)OR'', -NR''C(O)OR'', $-NHSO_2R''$, $-NR''SO_2R''$, $-NO_2$, -CN, -C(O)H, C(O)R'', -C(O)OH, -C(O)OR'', $-C(O)NH_2$, -C(O)NHR'', $-C(O)NR''_2$,-OH, -OR'', -OC(O)H, -OC(O)R'', -OC(O)OH,-OC(O)OR'', $-OC(O)NH_2$, -OC(O)NHR'', $-OC(O)NR''_2$, -SH, -SR'', $-S(O)_2H$, $-S(O)_2R''$, $-S(O)_2OH$, $-S(O)_2OR''$, $-S(O)_2NH_2$, $-S(O)_2NHR''$, or $-S(O)_2NR''_2$;

each R^3 is independently hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, heteroaryl, benzyl, haloalkyl, haloalkenyl, $-NH_2$, -NHR'', $-NR''_2$, -NHC(O)R'', -NR''C(O)R'', NHC(O)CH(OH)R'', -NR''C(O)CH(OH)R'', -NHC(O)OR'', -NR''C(O)OR'', $-NHSO_2R''$, $-NR''SO_2R''$, $-NO_2$, -CN, -C(O)H, C(O)R'', -C(O)OH, -C(O)OR'', $-C(O)NH_2$, -C(O)NHR'', $-C(O)NR''_2$,-OH, -OR'', -OC(O)H, -OC(O)R'', -OC(O)OH,-OC(O)OR'', $-OC(O)NH_2$, -OC(O)NHR'', $-OC(O)NR''_2$, -SH, -SR'', $-S(O)_2H$, $-S(O)_2R''$, $-S(O)_2OH$, $-S(O)_2OR''$, $-S(O)_2NH_2$, $-S(O)_2NHR''$, $-S(O)_2NR''_2$, -$\mathbf{R^{21}}$, -C(O)-NH-$\mathbf{R^{21}}$, or $-CH_2$-NH-C(O)-$\mathbf{R^{21}}$;

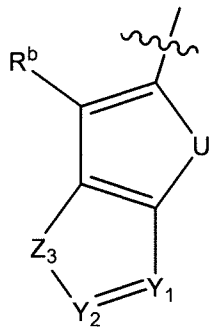
each R'' is independently alkyl, cycloalkyl, alkenyl, cycloalkenyl, aryl, heteroaryl, or benzyl;

$\mathbf{R^{21}}$ is a bond connected to $\mathbf{R^{18}}$ of the linker, wherein Formula (II) contains a single $\mathbf{R^{21}}$;

wherein,

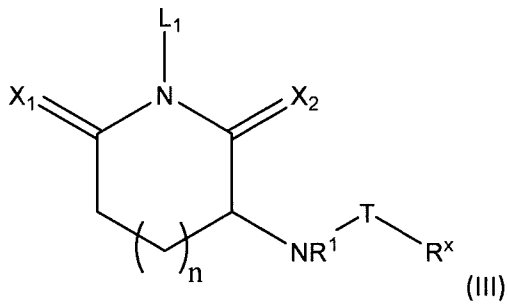


(i) when R^y is then Y_2 is CR^d; and

(ii) when R^y is  , then R^b in CR^b_2 is not hydrogen

or

(b) Formula (III):



(III)

wherein:

each of X_1 and X_2 is independently O or S;

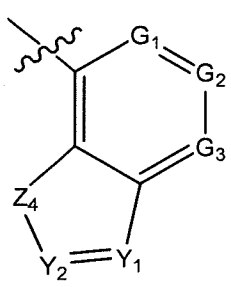
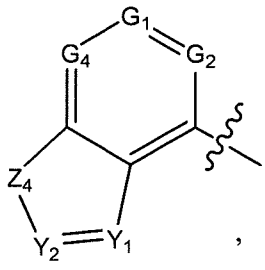
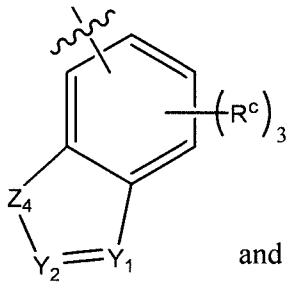
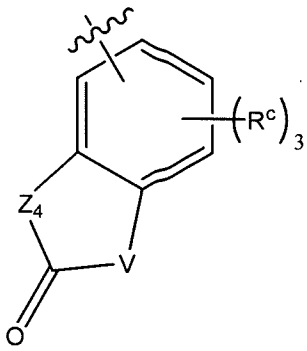
T is C=O or SO_2;

R^1 is hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, aryl, heteroaryl, or benzyl;

n is 0, 1 or 2;

L_1 is hydrogen, alkenyl, aryl, heteroaryl, benzyl, haloalkyl, haloalkenyl, -C(O)H, -C(O)R'',-C(O)OH, -C(O)OR'', $-CH_2C(O)OR''$, $-C(O)NH_2$, -C(O)NHR'', $-C(O)NR''_2$, -OH, -OR'', $-NH_2$, -NHR'', $-NR''_2$, $-S(O)_2H$ or $-S(O)_2R''$;

R^x is selected from




and


wherein ~~~ indicates attachment to T,

Z_4 is O, S or NR^4;

V is CR^f_2, NR^4 or S;

each of G_1, G_2, G_3 and G_4 is independently N or CR^c,

each of Y_1 and Y_2 is independently N or CR^f,

each R^f is independently hydrogen, halogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, fused aryl-cycloalkyl, fused aryl-heterocycloalkyl, heteroaryl, heteroaryl substituted with at least one aryl group, benzyl, haloalkyl, haloalkenyl, $-NH_2$, -NHR'', $-NR''_2$, -NHC(O)R'', -NR''C(O)R'', NHC(O)CH(OH)R'', -NR''C(O)CH(OH)R'', -NHC(O)OR'', -NR''C(O)OR'', $-NHSO_2R''$, $-NR''SO_2R''$, $-NO_2$, -CN, -C(O)H, C(O)R'', -C(O)OH, -C(O)OR'', $-C(O)NH_2$, -C(O)NHR'', $-C(O)NR''_2$,-OH, -OR'', -OC(O)H, -OC(O)R'', -OC(O)OH,-OC(O)OR'', $-OC(O)NH_2$, -OC(O)NHR'', $-OC(O)NR''_2$, -SH, -SR'', $-S(O)_2H$, $-S(O)_2R''$, $-S(O)_2OH$, $-S(O)_2OR''$, $-S(O)_2NH_2$, $-S(O)_2NHR''$, $-S(O)_2NR''_2$, - $\mathbf{R^{21}}$,-O-$\mathbf{R^{21}}$, -NH-$\mathbf{R^{21}}$, -C(O)-NH-$\mathbf{R^{21}}$, or $-CH_2$-NH-C(O)-$\mathbf{R^{21}}$; or when Y_1 and Y_2 are CR^f then each R^f, together with the carbon atom to which it is attached, forms a 5- or 6- membered ring;

each R^c is independently hydrogen, halogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, aryl substituted with at least one –OR'', heteroaryl, benzyl, haloalkyl, haloalkenyl, $-NH_2$, -NHR'', $-NR''_2$, $-CH_2NH_2$, -NHC(O)R'', -NR''C(O)R'', NHC(O)CH(OH)R'', -NR''C(O)CH(OH)R'', -NHC(O)OR'', -NR''C(O)OR'', $-NHSO_2R''$, $-NR''SO_2R''$, $-NO_2$, -CN, -C(O)H, C(O)R'', -C(O)OR'', $-C(O)NH_2$, -C(O)NHR'', $-C(O)NR''_2$,-OH, -OR'', -OC(O)H, -OC(O)R'', -OC(O)OH,-OC(O)OR'', $-OC(O)NH_2$, -OC(O)NHR'', $-OC(O)NR''_2$, -SH, -SR'', $-S(O)_2H$, $-S(O)_2R''$, $-S(O)_2OH$, $-S(O)_2OR''$, $-S(O)_2NH_2$, $-S(O)_2NHR''$, $-S(O)_2NR''_2$, -O-$\mathbf{R^{21}}$, -NH-$\mathbf{R^{21}}$, -C(O)-NH-$\mathbf{R^{21}}$, or $-CH_2$-NH-C(O)-$\mathbf{R^{21}}$;

each R^4 is independently hydrogen, halogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, heteroaryl, benzyl, haloalkyl, haloalkenyl, -C(O)H, C(O)R'', -C(O)OH, -C(O)OR'', $-C(O)NH_2$, -C(O)NHR'', -

$C(O)NR''_2$, -OH, -OR'', $-NH_2$, -NHR'', $-NR''_2$, $-S(O)_2H$, $-S(O)_2R''$, - $\mathbf{R^{21}}$, -C(O)-NH-$\mathbf{R^{21}}$, or $-CH_2$-NH-C(O)-$\mathbf{R^{21}}$; and

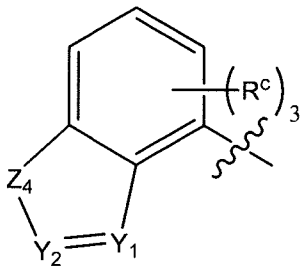
each R'' is independently alkyl, cycloalkyl, alkenyl, cycloalkenyl, aryl, heteroaryl, or benzyl;

$\mathbf{R^{21}}$ is a bond connected to $\mathbf{R^{18}}$ of the linker, wherein Formula (III) contains a single $\mathbf{R^{21}}$;

wherein, when n = 2, each R^c is hydrogen, and each of G_1, G_2, G_3 and G_4 is CR^c, then $C=X_1$ may be replaced by CH;

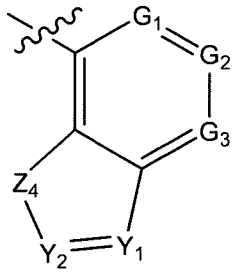
and wherein:

(i) when R^x is

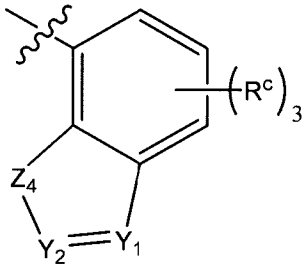


and Z_4 is NH, then L_1 is hydrogen, $-CH_2C(O)OR''$, or -OR'';

(ii) when R^x is

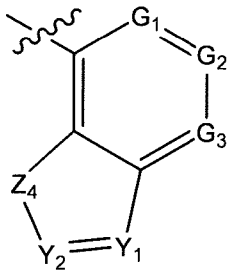


or



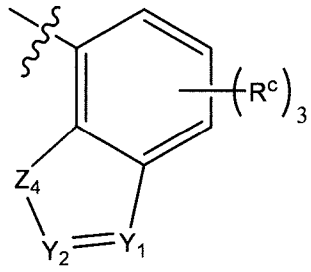
, Z_4 is NR^4, Y_1 is CR^f, and Y_2 is N, then R^4 is not alkyl and at least one of R^2 and R is not H;

(iii) when R^x is



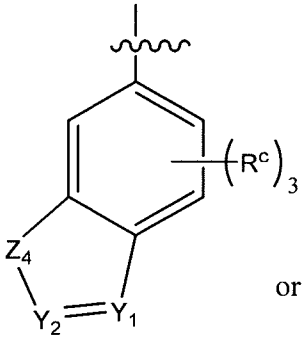
, Z_4 is NR^4, and Y_1 and Y_2 are CR^f, then at least one of G_1, G_2 and G_3 is N;

(iv) when Z_4 is NR^4, and Y_1 and Y_2 are CR^f, then R^x is not

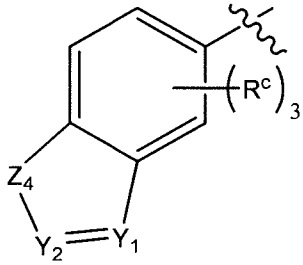


;

(v) when R^x is

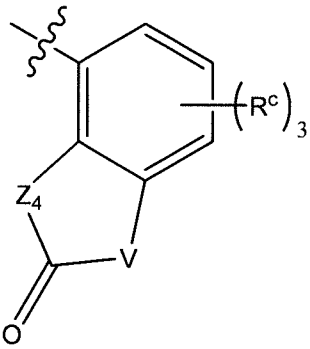


or

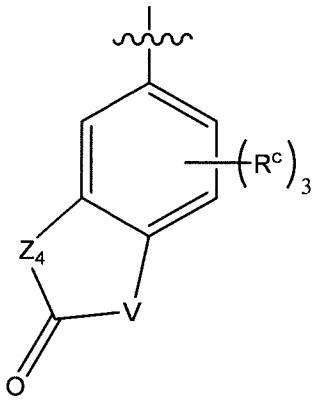


, Z_4 is NR^4, and Y_1 or Y_2 is N, then R^4 is not alkyl;

(vi) when R^x is

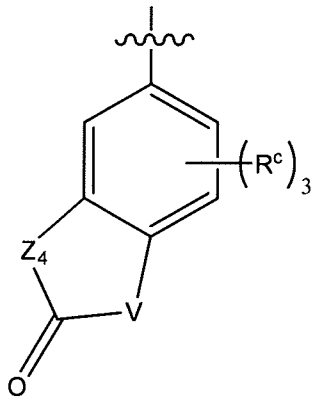


or

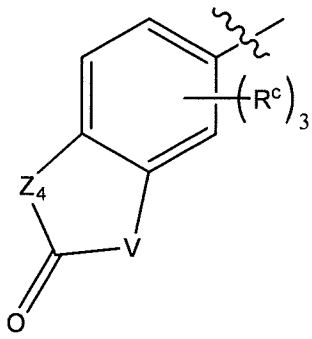


, then n = 1 or 2; and

(vii) when R^x is



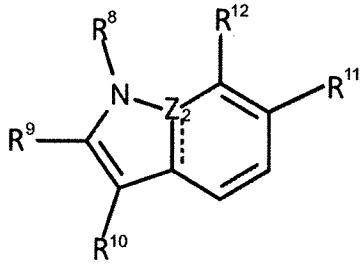
or



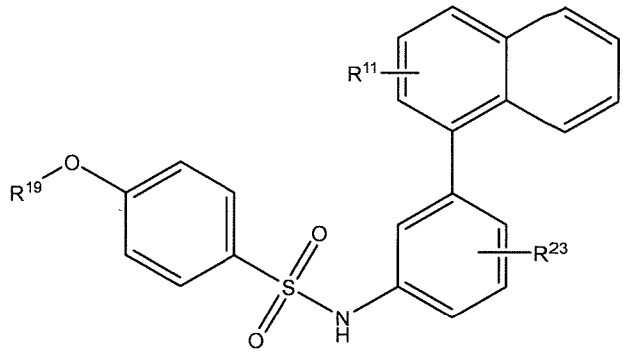
, then Z_4 = O or S

wherein

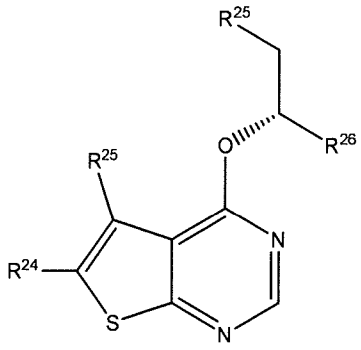
[MCL-1 ligand moiety] is a compound of Formula (A), Formula (B) or Formula (C)



(A)



(B)



(C)

wherein

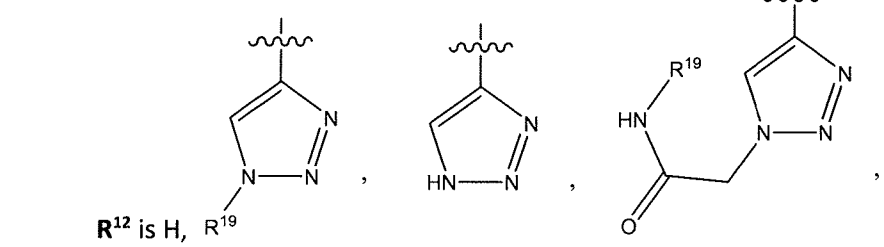
 is a single bond or a double bond;

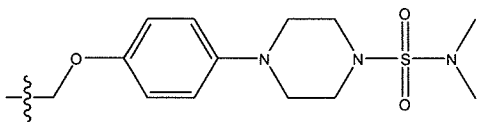
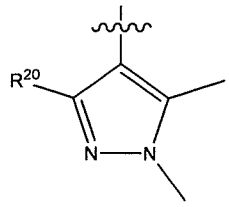
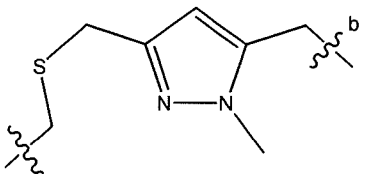
R^{8} is H, **R**^{19}, or C_1-C_6 alkyl optionally substituted with morpholine;

R^{9} is -C(O)OH, -C(O)OC_1-C_6alkyl; -C(O)NH_2; -C(O)O**R**^{19} or -C(O)NH**R**^{19},

R^{10} is -$C_{2\text{-}5}$alkyl-O-R^{13}, wherein R^{13} is phenyl, naphthyl or tetraline, wherein the phenyl, naphthyl or tetraline is optionally substituted with at least one substituent selected from halogen, C_1-C_6 alkyl and -O(C_1-C_6 alkyl); or wherein the naphthyl is optionally substituted with -O- or -S-,

R^{11} is H, halogen or C_1-C_6 alkyl,

R^{12} is H, 

wherein R^{20} is Me, -CH_2-O-bromobenzaldehyde, or  ; or when R^{12} is  and R^{10} is -O-naphthyl substituted with -O- or -S-, then R^{20} is  , wherein  indicates attachment to -O- or -S- of R^{10};

and wherein

R^{19} is a bond connected to R^{14} of the linker;

R^{23} is -C(O)OH or -C(O)OC_1-C_6alkyl;

Z_2 is N or C, wherein when Z_2 is N, then  is a single bond; and when Z_2 is C, then  is a double bond,

R^{24} is furan optionally substituted with at least one halogen,

each R^{25} is independently phenyl substituted with -OR^{28} and optionally further substituted with at least one substituent selected from halogen and C_1-C_6 alkyl;

R^{26} is -C(O)OR^{19} or -C(O)NHR^{19}; and

each R^{28} is independently -C_{1-3}alkyl-(N-alkyl piperazine) or -C_{1-3}alkyl-(N-haloalkylpyrazole)

and wherein each of Formula (A), Formula (B) and Formula (C) contains a single R^{19};

and wherein **[linker]** has the following formula

R^{14}-R^{15}-R^{16}-R^{17}-R^{18}

wherein

R^{14} is -C_{1-6} alkyl, -C_{2-6} alkenyl, -C_{2-6} alkynyl, -C(O)-, -SO_2- or is absent

R^{15} is cycloalkyl, heterocycloalkyl, aryl, heteroaryl, -C_{1-6} alkyl-NH-, -cycloalkyl-NH- or is absent

R^{16} is -C_{1-6} alkyl, -C(O)-, -C(O)-NH-, -C(O)O-, -CH_2-C(O)-, -CH_2-C(O)-NH-, -CH_2-C(O)O- or is absent

R^{17} is -$CH_2(C_2H_4\text{-}O)_y$, $(C_2H_4\text{-}O)_x$, $(C_3H_6\text{-}O)_x$, or is absent

x is 1-10

y is 2-10

R^{18} is -C_{1-6} alkyl, heterocycloalkyl, or is absent

wherein at least one of R^{14}-R^{18} is present

90. The compound of claim 89, wherein each alkyl, alkenyl, alkynyl, aryl, heteroaryl and benzyl is unsubstituted.

91. The compound of any one of claims 89-90, wherein in Formula (III):

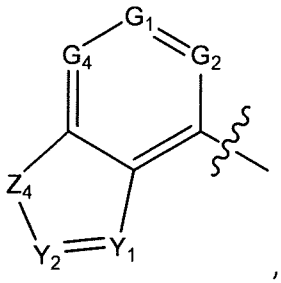
each of X_1 and X_2 is O;

T is C=O;

R^1 is hydrogen,

L_1 is hydrogen,

R^x is



,

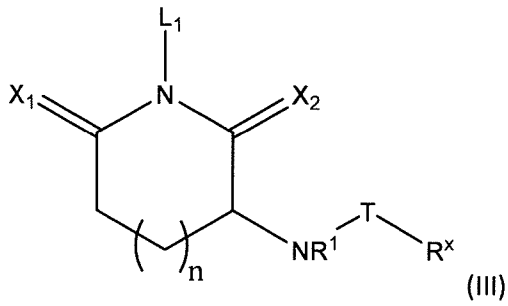
Z_4 is NR^4;

each of G_1, G_2 and G_4 is CR^c,

Y_1 is N, and

Y_2 is CR^f, wherein R^f is not hydrogen.

92. The compound of any one of claims 89-91 wherein **[ligase ligand moiety]** is Formula (III):



(III)

93. The compound of any one of claims 89-92, wherein one of R^c is -O-**R**^{21}, -NH-**R**^{21}, -C(O)-NH-**R**^{21}, or -CH_2-NH-C(O)-**R**^{21}.

94. The compound of any one of claims 89-93, wherein G_1 is C-O-**R**^{21}, C-NH-**R**^{21}, C-C(O)-NH-**R**^{21}, or C-CH_2-NH-C(O)-**R**^{21}.

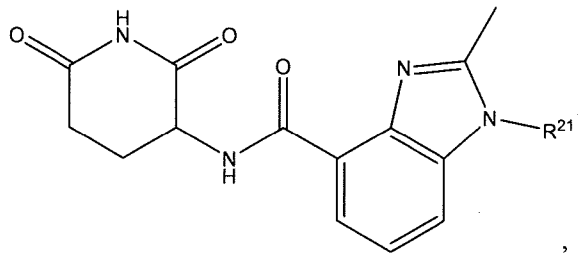
95. The compound of any one of claims 89-93, wherein G_2 is C-O-**R**^{21}, C-NH-**R**^{21}, C-C(O)-NH-**R**^{21}, or C-CH_2-NH-C(O)-**R**^{21}.

96. The compound of any one of claims 89-92, wherein R^4 is **R**^{21}, -C(O)-NH-**R**^{21}, or -CH_2-NH-C(O)-**R**^{21}.

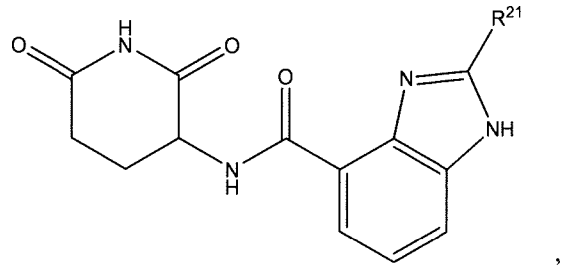
97. The compound of any one of claims 89-92, wherein one of R^f is - **R**^{21}, -O-**R**^{21}, -NH-**R**^{21}, -C(O)-NH-**R**^{21}, or -CH_2-NH-C(O)-**R**^{21}.

98. The compound of claim 97, wherein Y_2 is C-**R**^{21}, CO-**R**^{21}, C-NH-**R**^{21}, C-C(O)-NH-**R**^{21}, or C-CH_2-NH-C(O)-**R**^{21}.

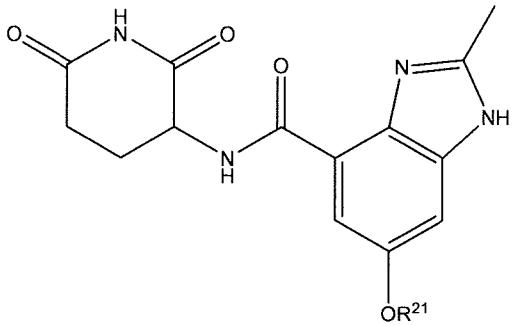
99. The compound of any one of claims 89-98, wherein **[ligase ligand moiety]** is selected from



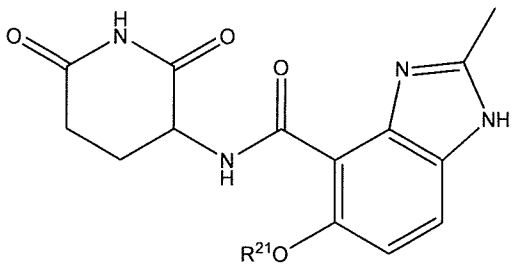
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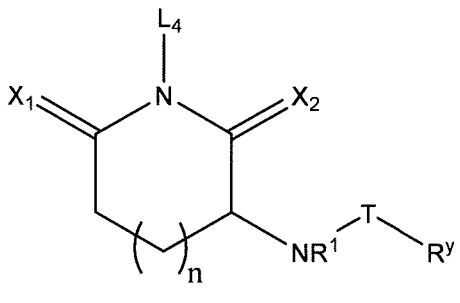


and



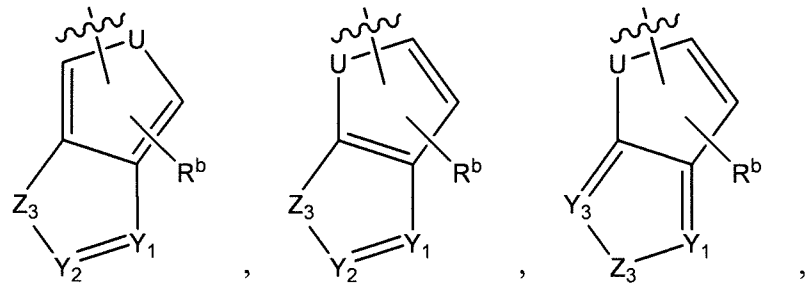
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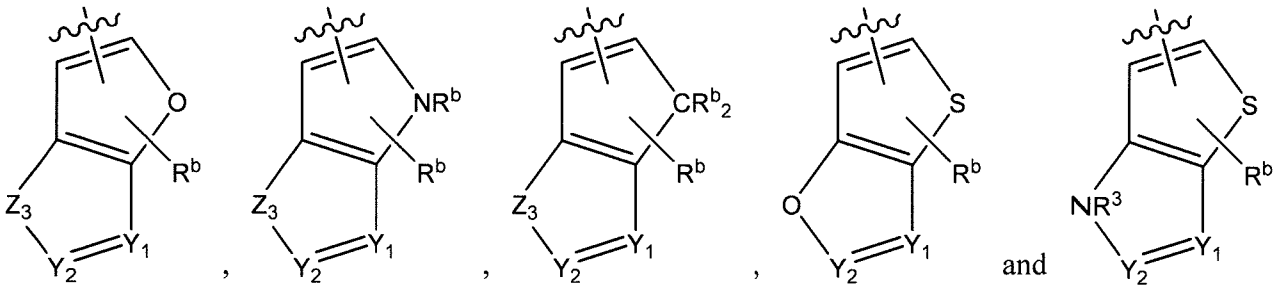
100. The compound of any one of claims 89-90, wherein **[ligase ligand moiety]** is of Formula (II):



(II)

101. The compound of any one of claims 89-90 and 100, wherein R^y is selected from





and

102. The compound of any one of claims 89-90 and 100-101, wherein

Z_3 is S or NR^3;

U is O or S;

each of Y_1, Y_2 and Y_3 is independently N or CR^d.

103. The compound of any one of claims 89-90 and 101-102, wherein R^b is hydrogen or alkyl.

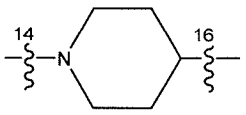
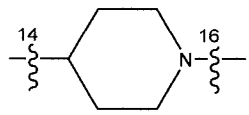
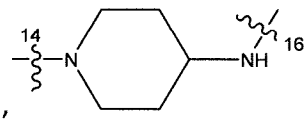
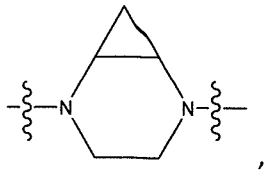
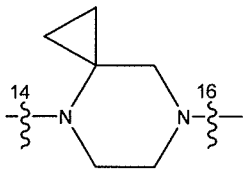
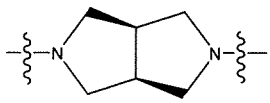
104. The compound of any one of claims 89-90 and 101-103, wherein R^3 is hydrogen, alkyl, cycloalkyl, -$\mathbf{R^{21}}$, -C(O)-NH-$\mathbf{R^{21}}$, or -CH_2-NH-C(O)-$\mathbf{R^{21}}$.

105. The compound of any one of claims 89-90 and 101-104, wherein each R^d is independently hydrogen, alkyl, -O-$\mathbf{R^{21}}$, -NH-$\mathbf{R^{21}}$, -C(O)-NH-$\mathbf{R^{21}}$, or -CH_2-NH-C(O)-$\mathbf{R^{21}}$.

106. The compound of any one of claims 89-105, wherein

$\mathbf{R^{14}}$ is -C_{1-6} alkyl, -SO_2- or is absent

R^{15} is piperazine, bridged piperazine, piperazine N-oxide, piperazine cation, -C_{1-6} alkyl-NH-,







or is absent, wherein  indicates attachment to **R**^{14} and  indicates attachment to **R**^{16},

R^{16} is -C_{1-6} alkyl, -C(O)-, -C(O)-NH-, -CH_2-C(O)-NH- or is absent

R^{17} is -$CH_2(C_2H_4\text{-}O)_y$, $(C_2H_4\text{-}O)_x$, $(C_3H_6\text{-}O)_x$, or is absent

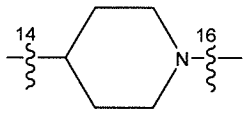
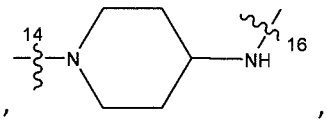
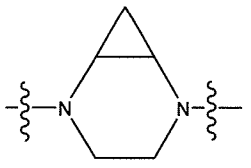
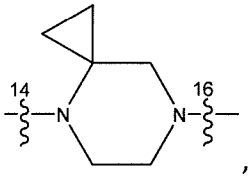
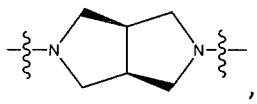
x is 1-6

y is 2-6

R^{18} is -C_{1-6} alkyl, piperazine, or is absent

wherein at least one of R^{14}-R^{18} is present.

107. The compound of any one of claims 89-106, wherein **R**^{18} is -C_{1-6} alkyl or is absent.

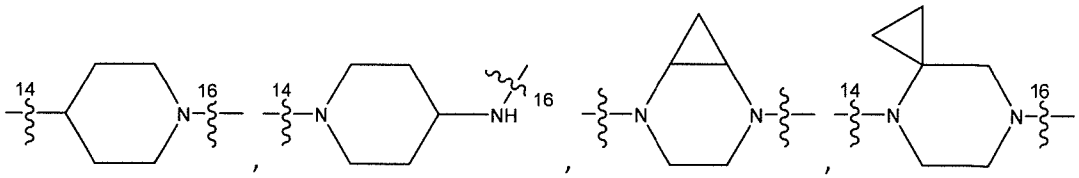
108. The compound of any one of claims 89-107, wherein when **R**^{15} is piperazine, bridged piperazine, piperazine N-oxide, piperazine cation, -C_{1-6} alkyl-NH-, 



, or  ,

then **R**^{14} is -C_{1-6} alkyl.

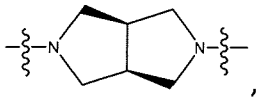
109. The compound of any one of claims 89-108, wherein

R^{14} is -C_{1-6} alkyl,

R^{15} is piperazine, bridged piperazine, piperazine N-oxide,



or



,

R^{16} is -C(O)-, $-CH_2$-C(O)-NH-, or is absent

R^{17} is $-CH_2(C_2H_4\text{-}O)_y$, $(C_2H_4\text{-}O)_x$, $(C_3H_6\text{-}O)_x$, or is absent

R^{18} is $-C_{1\text{-}6}$ alkyl.

wherein when R^{16} and R^{17} are absent, R^{18} is $-C_{3\text{-}6}$ alkyl.

110. The compound of claim 109, wherein

R^{14} is $-C_2$ alkyl,

x is 1, 2 or 6

y is 2.

111. The compound of claim 109, wherein

R^{15} is piperazine,

R^{16} is -C(O)-,

R^{17} is – absent.

112. The compound of claim 111, wherein

R^{14} is $-C_2$ alkyl,

R^{18} is $-C_{1\text{-}2}$ alkyl.

113. The compound of any one of claims 89-108, wherein when R^{14} is $-SO_2$-, at least two of R^{15}-R^{18} are present, and at least one of R^{15}-R^{18} is not $C_{1\text{-}6}$ alkyl.

114. The compound of any one of claims 89-108, wherein

R^{14} is $-SO_2$-

R^{15} is $-C_{1\text{-}6}$ alkyl-NH-

$\mathbf{R^{16}}$ is -C(O)-

$\mathbf{R^{17}}$ is $-CH_2(C_2H_4\text{-}O)_y$, $(C_2H_4\text{-}O)_x$ or is absent

$\mathbf{R^{18}}$ is $-C_{2\text{-}4}$ alkyl.

115. The compound of claim 114, wherein

$\mathbf{R^{15}}$ is $-C_2$alkyl-NH-

x is 1 or 2

y is 1

$\mathbf{R^{18}}$ is $-C_{2\text{-}4}$ alkyl

116. The compound of any one of claims 89-108, wherein

$\mathbf{R^{14}}$ is absent

$\mathbf{R^{15}}$ is absent

$\mathbf{R^{16}}$ is -C(O)-NH-, or is absent

$\mathbf{R^{17}}$ is $-CH_2(C_2H_4\text{-}O)_y$, $(C_2H_4\text{-}O)_x$, $(C_3H_6\text{-}O)_x$, or is absent

$\mathbf{R^{18}}$ is $-C_{1\text{-}6}$ alkyl.

117. The compound of any one of claims 89-116, wherein at least one of $\mathbf{R^{14}}$-$\mathbf{R^{18}}$ is not $-C_{1\text{-}6}$ alkyl.

118. The compound of claim 116 or 117, wherein

x is 1, 2 or 3

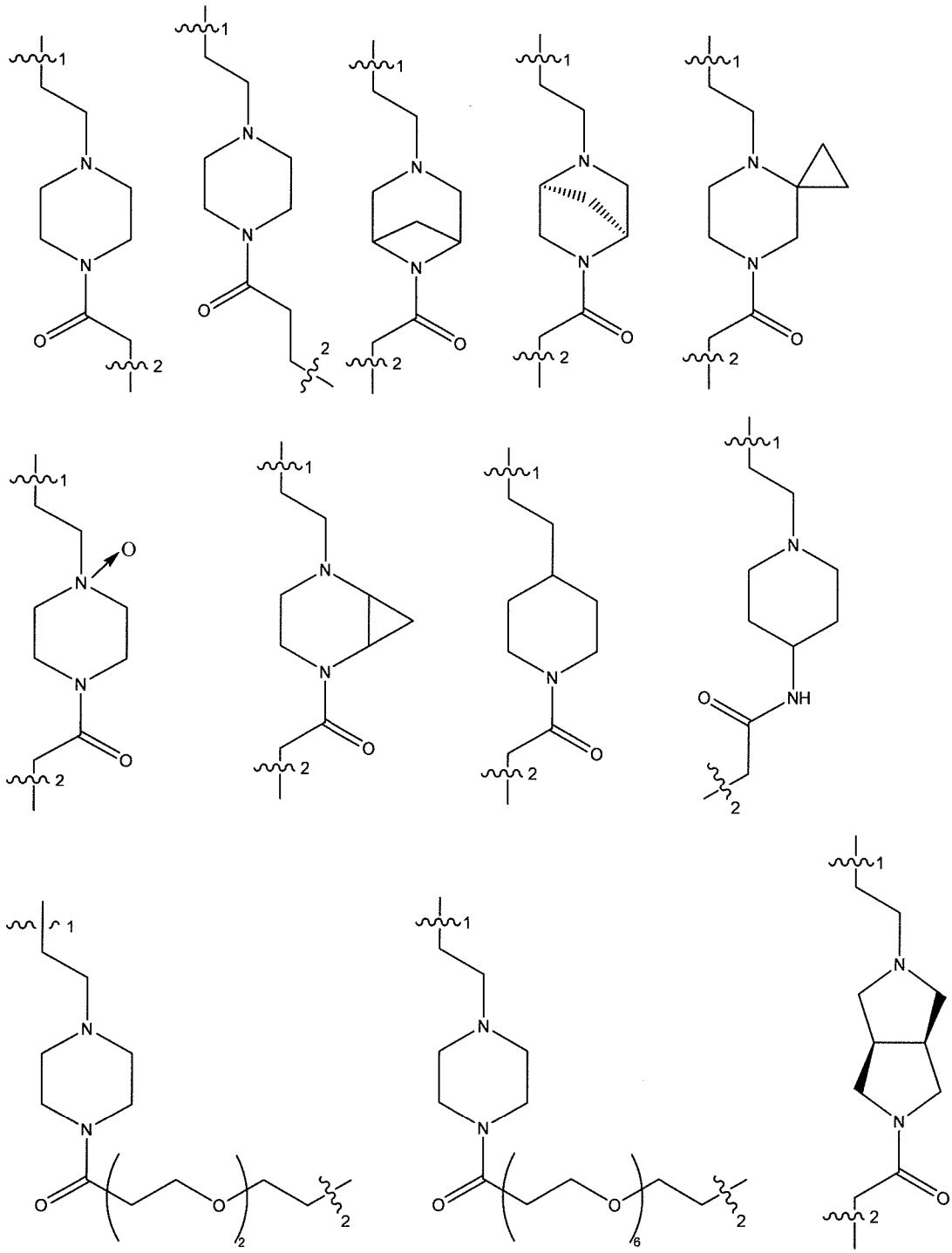
y is 2

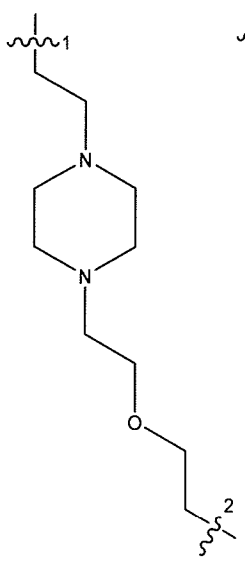
$\mathbf{R^{18}}$ is $-C_{2\text{-}6}$ alkyl.

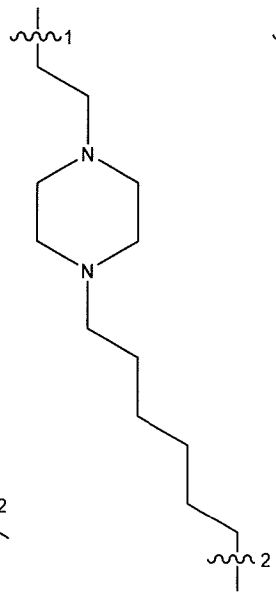
119. The compound of any one of claims 89-118, wherein when $\mathbf{R^{15}}$ is $-C_{1\text{-}6}$ alkyl-NH-, at least one of $\mathbf{R^{16}}$-$\mathbf{R^{18}}$ is present.

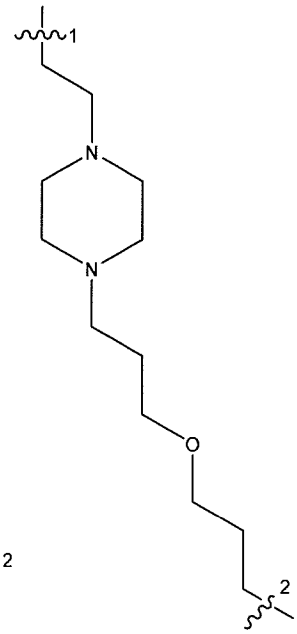
120. The compound of any one of claims 89-119 wherein when $\mathbf{R^{17}}$ is $-CH_2(C_2H_4\text{-}O)_y$, $(C_2H_4\text{-}O)_x$ or $(C_3H_6\text{-}O)_x$, at least one of $\mathbf{R^{14}}$-$\mathbf{R^{16}}$ and $\mathbf{R^{18}}$ is present, wherein at least one of $\mathbf{R^{14}}$ and $\mathbf{R^{18}}$ is not $-C_{1\text{-}6}$ alkyl.

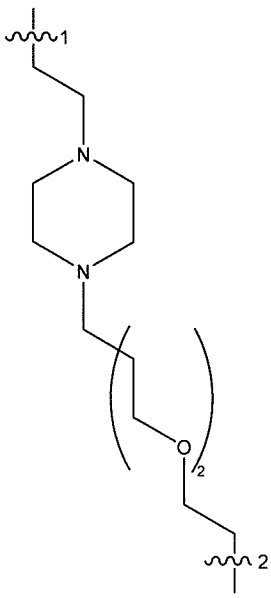
121. The compound of any one of claims 89-120, wherein **[linker]** is selected from

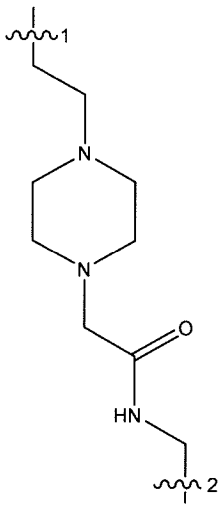


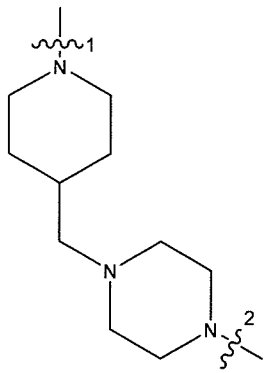


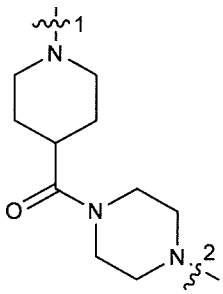


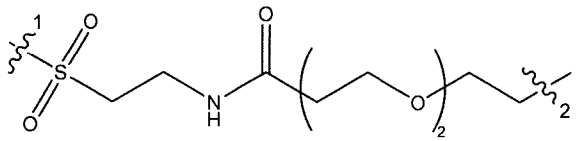


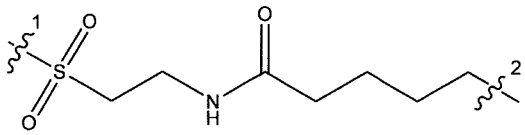


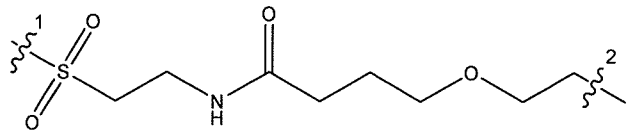


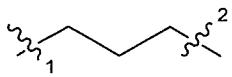


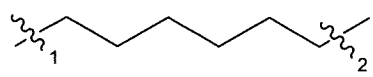


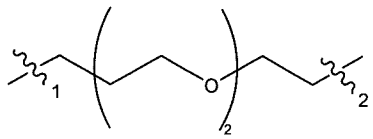


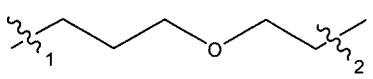


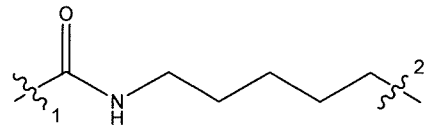


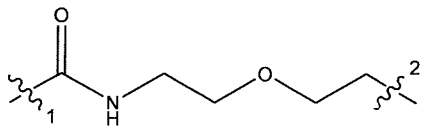


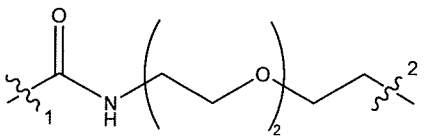




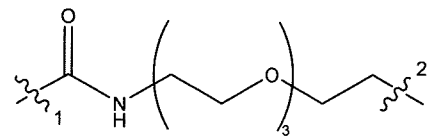








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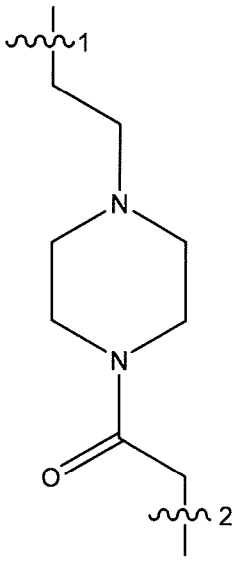


wherein

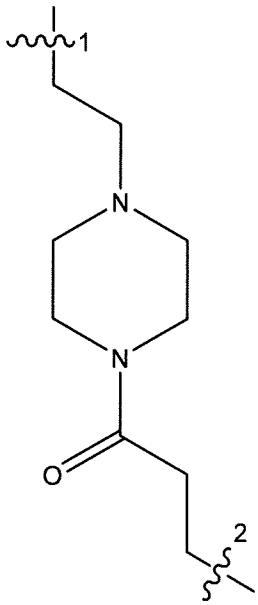
 indicates attachment to **[MCL-1 ligand moiety]** and

 indicates attachment to **[ligase ligand moiety].**

122. The compound of any one of claims 89-121, wherein **[linker]** is selected from



and



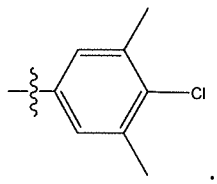
wherein



indicates attachment to **[MCL-1 ligand moiety]** and



indicates attachment to **[ligase ligand moiety].**

123. The compound of any one of claims 89-122 wherein when $\mathbf{R^8}$ is H, $\mathbf{R^{13}}$ is 

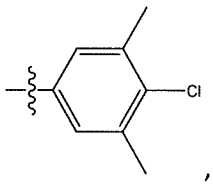
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124. The compound of any one of claims 87-120, wherein

$\mathbf{R^8}$ is H, $\mathbf{R^{19}}$, methyl, or -CH_2CH_2-morpholine;

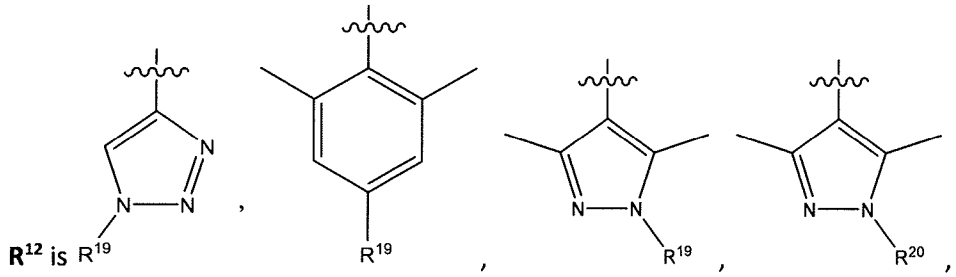
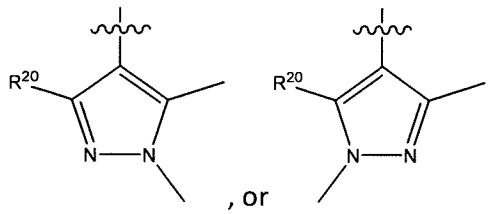
$\mathbf{R^9}$ is -C(O)OH or -C(O)NH$\mathbf{R^{19}}$,

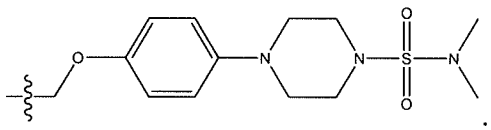
$\mathbf{R^{10}}$ is -C_3H_6O-R^{13},

wherein $\mathbf{R^{13}}$ is 

, tetraline or naphthyl optionally substituted with fluorine;

$\mathbf{R^{11}}$ is H, Cl, F or methyl,

R^{12} is  , or 

wherein **R^{20}** is Me, -CH_2-O-bromobenzaldehyde, or  .

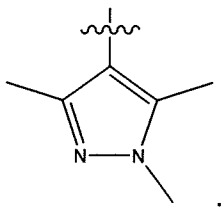
125. The compound of claim 124, wherein

R^{8} is **R^{19}** or methyl;

R^{10} is -C_3H_6O-R^{13}, wherein **R^{13}** is naphthyl optionally substituted with fluorine;

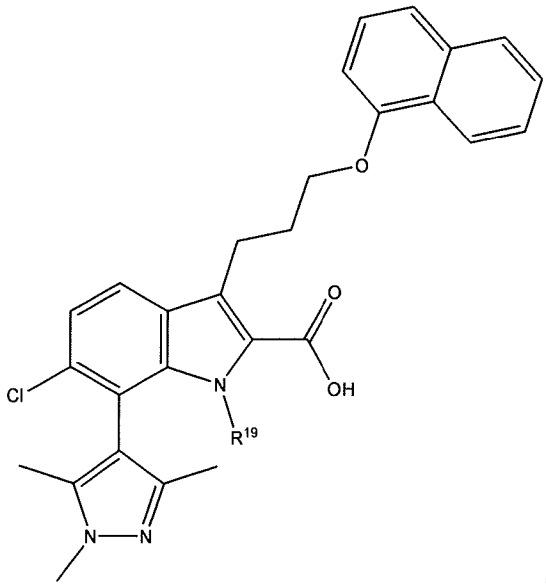
R^{11} is Cl or F,

R^{12} is

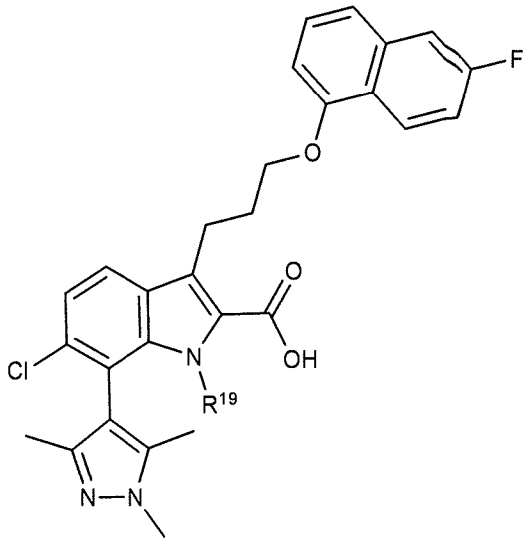
 .

126. The compound of any one of claims 89-125 wherein **Z_2** is C and  is a double bond.

127. The compound of any one of claims 89-126, wherein **[MCL-1 ligand moiety]** is

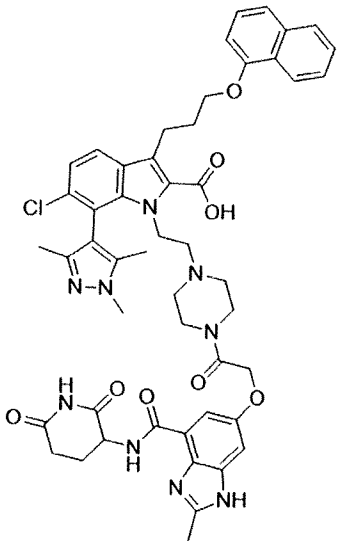


or



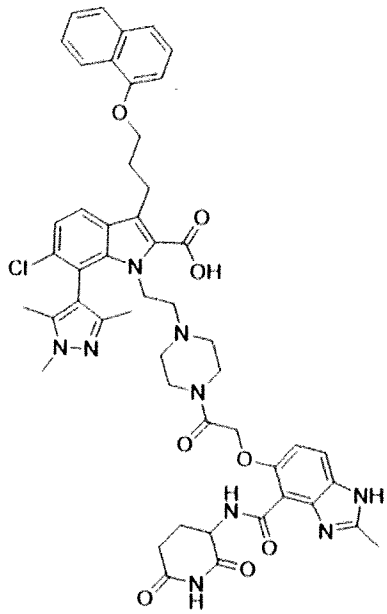
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128. The compound of claim 127, wherein the compound is selected from:



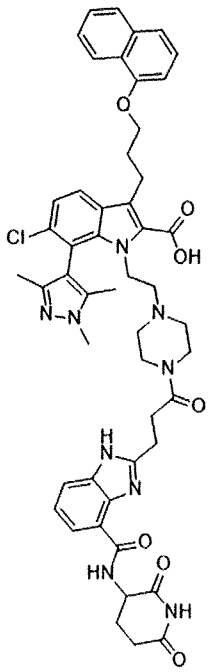
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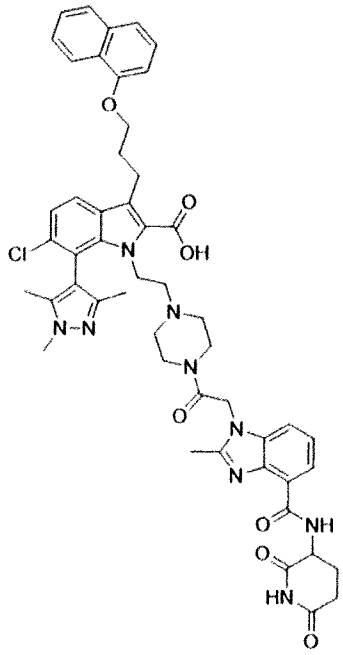


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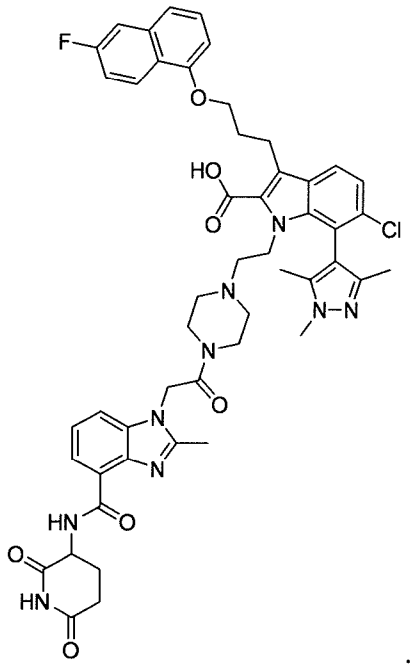


,



and

265 266



.

268

129. The compound of any preceding claim, wherein T is C=O.

130. The compound of any one of claims 1-128, wherein T is SO_2.

131. The compound of any preceding claim, wherein X_1 and X_2 are O.

132. The compound of any one of claims 1-130, wherein X_1 is O and X_2 is S.

133. The compound of any one of claims 1-130, wherein X_1 is S and X_2 is O.

134. The compound of any one of claims 1-130, wherein X_1 and X_2 are S.

135. The compound of any preceding claim, wherein n is 0.

136. The compound of any one of claims 1-134, wherein n is 1 or 2.

137. The compound of claim 136, wherein n is 1.

138. The compound of claim 136, wherein n is 2.

139. The compound of any preceding claim, wherein **[MCL-1 ligand moiety]** is a compound of Formula (A), and wherein $\mathbf{R^{10}}$ is $-C_{2\text{-}5}$alkyl-O-R^{13},

140. The compound of any preceding claim, wherein $\mathbf{R^{10}}$ is $-C_3H_6$-O-R^{13},

141. A pharmaceutical composition comprising a compound of any one of claims 1-140.

142. The compound of any one of claims 1-140 or the pharmaceutical composition of claim 141, for use in medicine.

143. The compound of any one of claims 1-140 or the pharmaceutical composition of claim 141, for use in the treatment of cancer.

144. The compound or composition for use of claim 143, wherein the cancer is selected from breast cancer, triple negative breast cancer, colorectal cancer, pancreatic cancer, skin cancer, melanoma, ovarian cancer, kidney cancer, lung cancer, small-cell lung cancer, non-small-cell lung cancer, lymphoma, non-Hodgkin's lymphoma, multiple myeloma, cervical cancer, leukaemia, chronic lymphocytic leukaemia (CLL), acute myeloid leukaemia (AML), chronic myelogenous leukemia (CML), acute lymphoblastic leukaemia (ALL), bladder cancer, and prostate cancer.

145. The compound or composition for use of claim 144, wherein the cancer is multiple myeloma or acute myeloid leukaemia.

146. A method of treating cancer in a subject in need thereof, the method comprising administering to the subject an effective amount of a compound according to any one of claims 1-140, or a pharmaceutical composition according to claim 141.

147. The method of claim 146, wherein the cancer is selected from breast cancer, triple negative breast cancer, colorectal cancer, pancreatic cancer, skin cancer, melanoma, ovarian cancer, kidney cancer, lung cancer, small-cell lung cancer, non-small-cell lung cancer, lymphoma, non-Hodgkin's lymphoma, multiple myeloma, cervical cancer, leukaemia, chronic lymphocytic leukaemia (CLL), acute myeloid leukaemia (AML), chronic myelogenous leukemia (CML), acute lymphoblastic leukaemia (ALL), bladder cancer, and prostate cancer.

148. The method of claim 147, wherein the cancer is multiple myeloma acute myeloid leukaemia.

149. The method of any one of claims 146-148, wherein the administration does not result in cytotoxicity in cardiomyocytes in the subject.

150. The method of any one of claims 145-148, further comprising administering at least one additional active agent to the subject.

151. The method of claim 150, wherein the at least one additional active agent is an anti-cancer agent selected from eribulin; fulvestrant; midostaurin; an immune checkpoint inhibitor selected

from anti-pd-1 antibody, anti-pd-l1 antibody, and anti pd-1/pd-l1 interaction inhibitor; nivolumab; pembrolizumab; atezolizumab; pidilizumab; carfilzomib; venetoclax; cytarabine; anthracyclines; a taxane compound; and hypomethylating agents.

152. The compound of any one of claims 1-140 or the pharmaceutical composition of claim 141, for use in reversing resistance to chemotherapy or targeted cancer therapies.

153. A method of reversing resistance to chemotherapy or targeted cancer therapies in a subject in need thereof, the method comprising administering to the subject an effective amount of a compound according to any one of claims 1-140, or a pharmaceutical composition according to claim 141.

154. A combined preparation of a compound of any one of claims 1-140 and at least one additional active agent, for simultaneous, separate or sequential use in therapy.

155. The combined preparation of claim 154, wherein the at least one additional active agent is an anti-cancer agent selected from eribulin; fulvestrant; midostaurin; an immune checkpoint inhibitor selected from anti-pd-1 antibody, anti-pd-l1 antibody, and anti pd-1/pd-l1 interaction inhibitor; nivolumab; pembrolizumab; atezolizumab; pidilizumab; carfilzomib; venetoclax; cytarabine; anthracyclines; a taxane compound; and hypomethylating agents.

156. The combined preparation of any one of claims 154-155 wherein the therapy is the treatment of cancer.

157. A compound of formula (X):

[MCL-1 inhibitor] – L – [cereblon binding moiety] (X)

wherein L is a bond or a linker compound.

158. A method of reducing the cardiac cytotoxicity of an MCL-1 inhibitor, comprising coupling a cereblon binding moiety to the MCL-1 inhibitor.

159. The compound of claim 157 or the method of claim 158, wherein the cereblon binding moiety is a **[ligase ligand moiety]** as defined in any one of claims 1-138.

160. The compound or method of any one of claims 157-159, wherein the MCL-1 inhibitor is an **[MCL-1 binding moiety]** as defined in any one of claims 1-138.

161. The compound or method of any one of claims 157-160, wherein the cereblon binding moiety is coupled to the MCL-1 inhibitor by a linker compound, wherein the linker compound is covalently attached to the cereblon binding moiety and the MCL-1 inhibitor.

162. The compound or method of any one of claims 157-161, wherein the linker compound is a **[linker]** as defined in any one of claims 1-138.

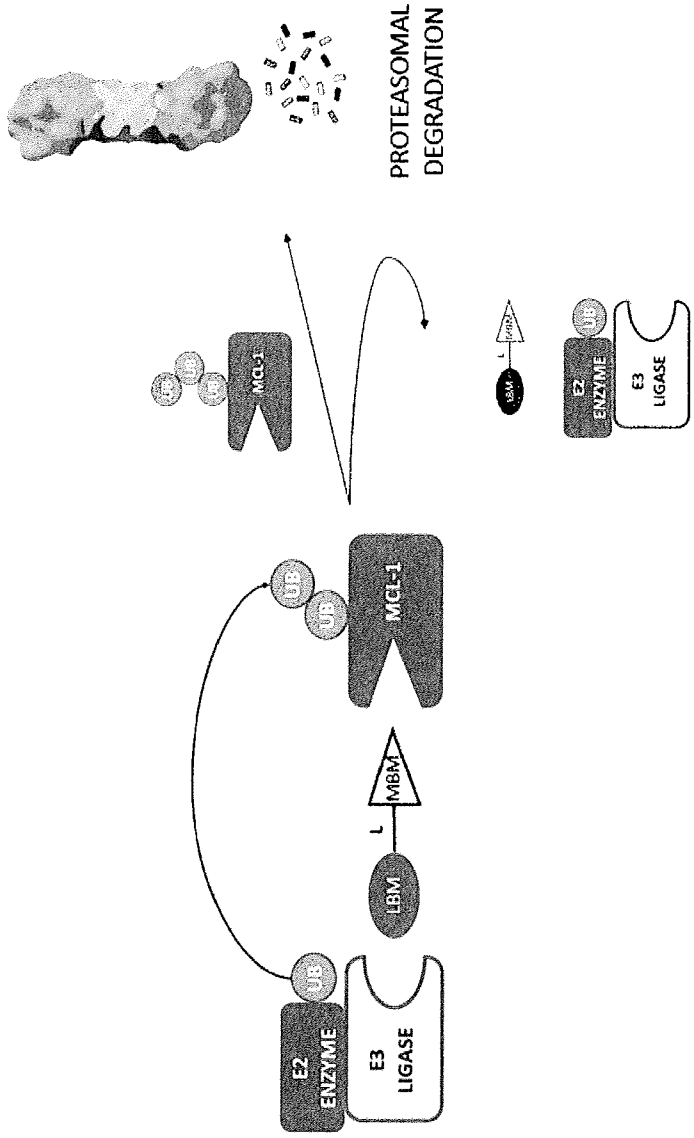
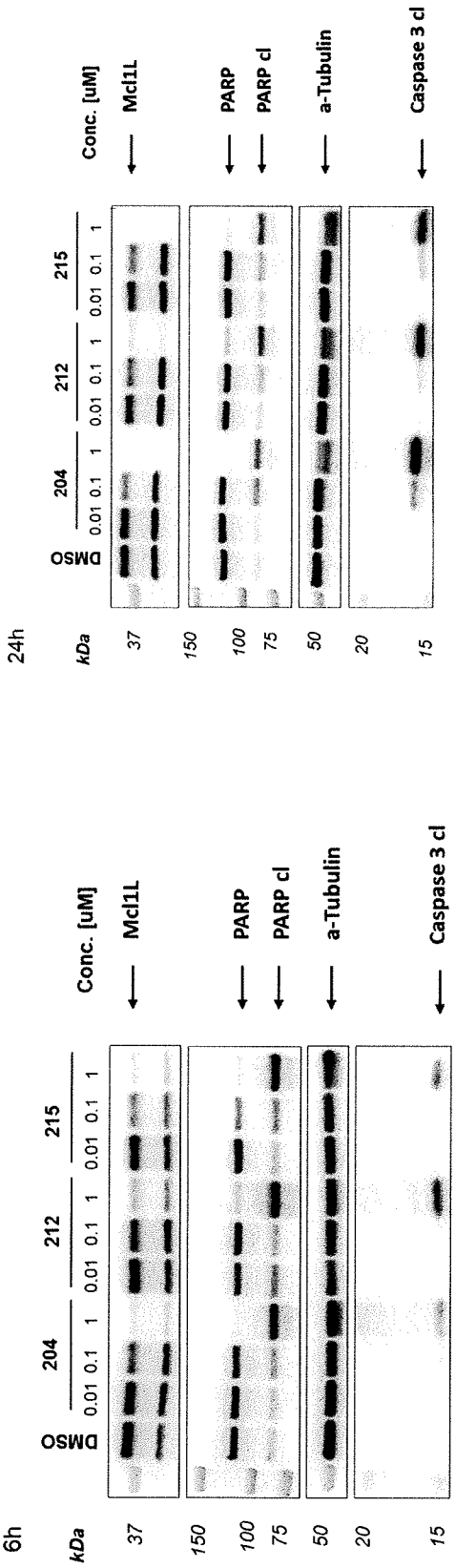


FIG. 1

605

FIG. 2


6h
24h
kDa
37
150
100
75
50
20
15
DMSO
0.01 0.1 1
204
0.01 0.1 1
212
0.01 0.1 1
215
Conc. [uM]
Mcl1L
PARP
PARP cl
a-Tubulin
Caspase 3 cl

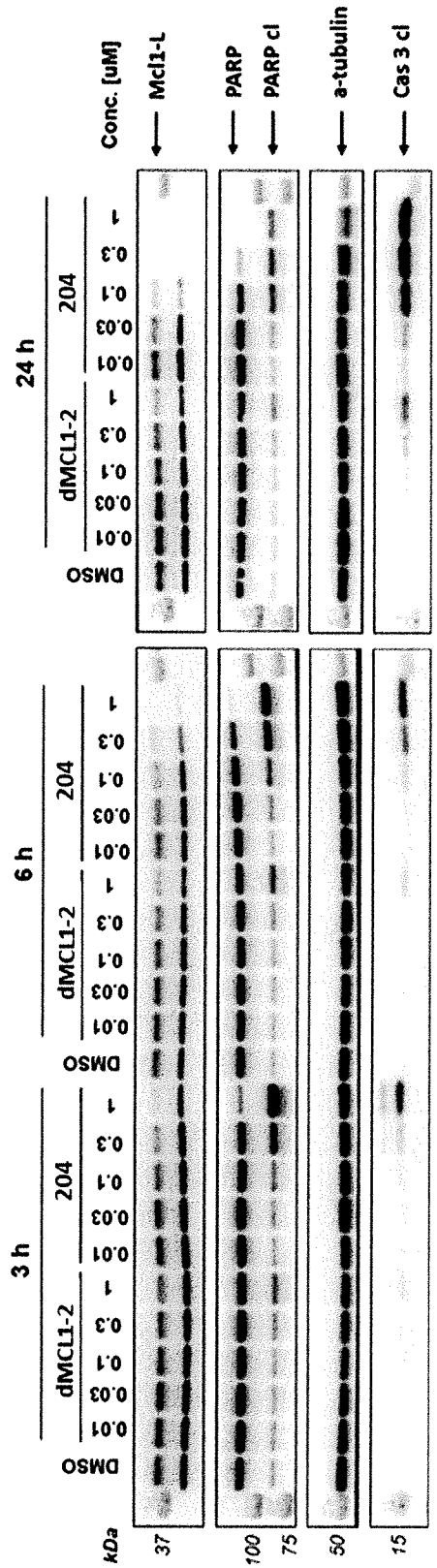

3 h
6 h
24 h
DMSO
dMCL1-2
204
0.01
0.03
0.1
0.3
1
Conc. [uM]
Mcl1-L
PARP
PARP cl
a-tubulin
Cas 3 cl
kDa
37
100
75
50
15

FIG. 3A

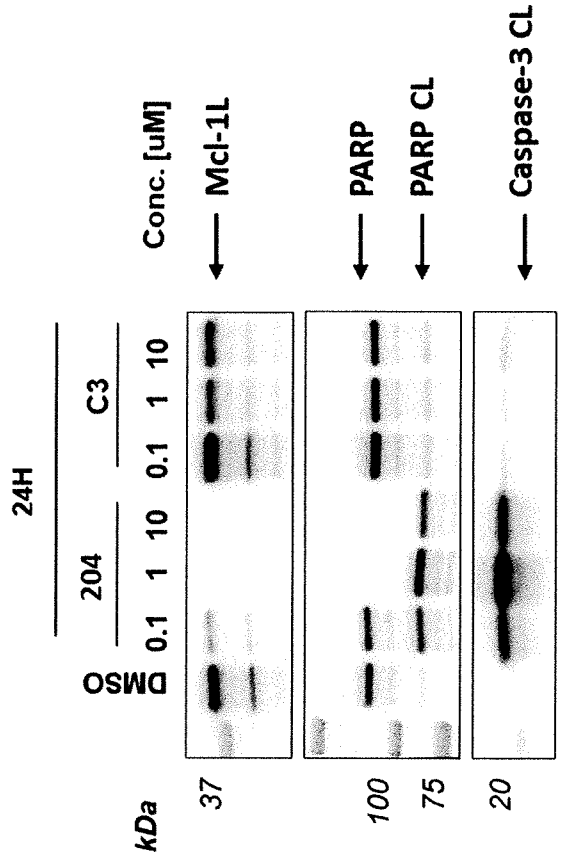

24H
DMSO
204
C3
0.1 1 10 0.1 1 10
Conc. [uM]
Mcl-1L
PARP
PARP CL
Caspase-3 CL
kDa
37
100
75
20

FIG. 3B

608

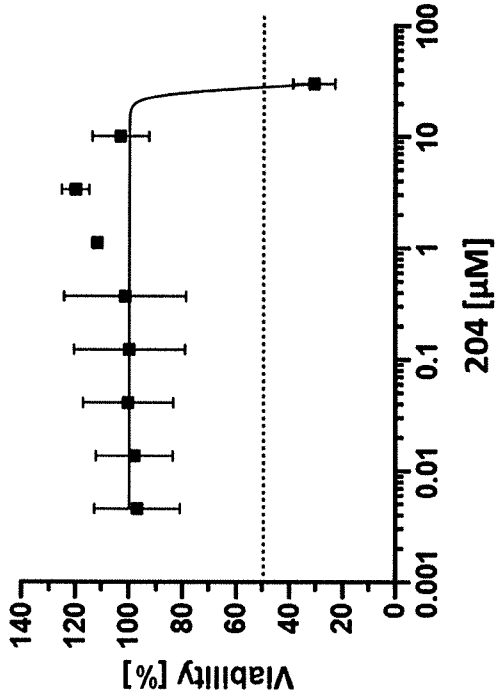


FIG. 4B

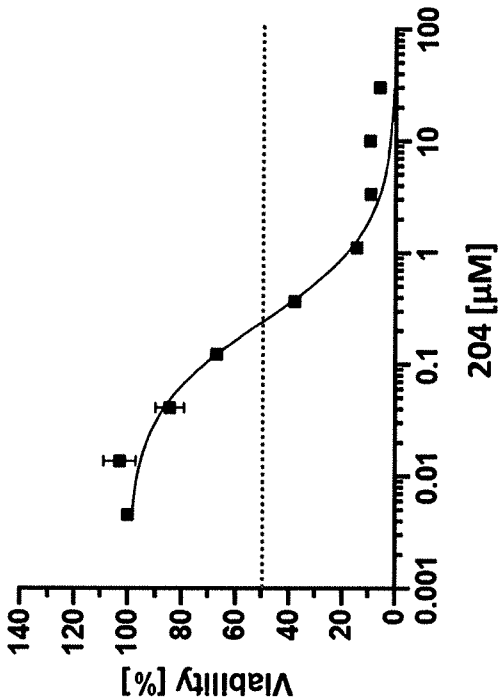


FIG. 4A

609

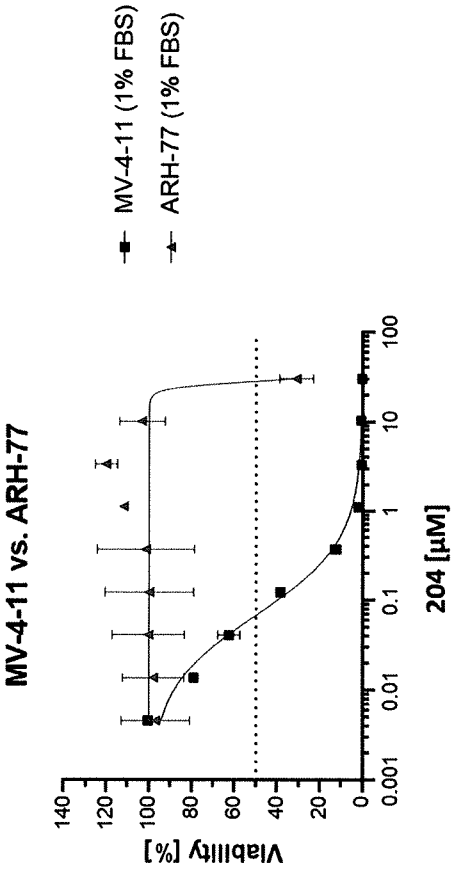

MV-4-11 vs. ARH-77
MV-4-11 (1% FBS)
ARH-77 (1% FBS)
Viability [%]
140
120
100
80
60
40
20
0
0.001
0.01
0.1
1
10
100
204 [µM]

FIG. 4D

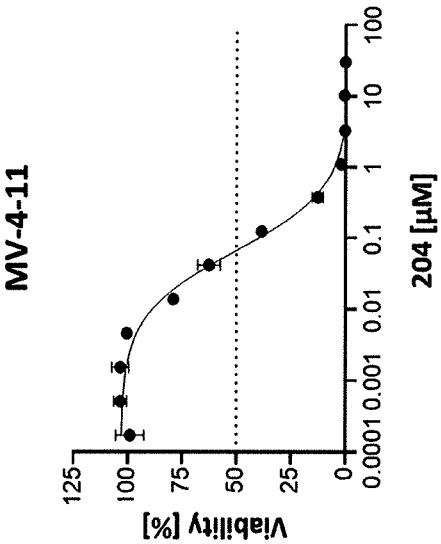

MV-4-11
Viability [%]
125
100
75
50
25
0
0.0001
0.001
0.01
0.1
1
10
100
204 [µM]

FIG. 4C

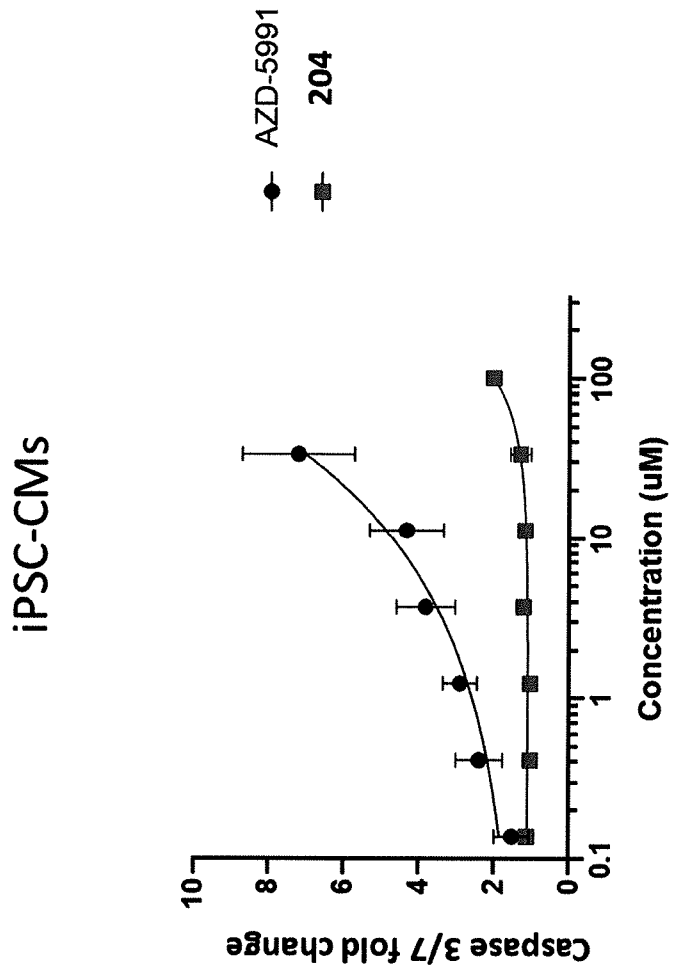

iPSC-CMs
AZD-5991
204
Caspase 3/7 fold change
10
8
6
4
2
0
0.1
1
10
100
Concentration (uM)

FIG. 5

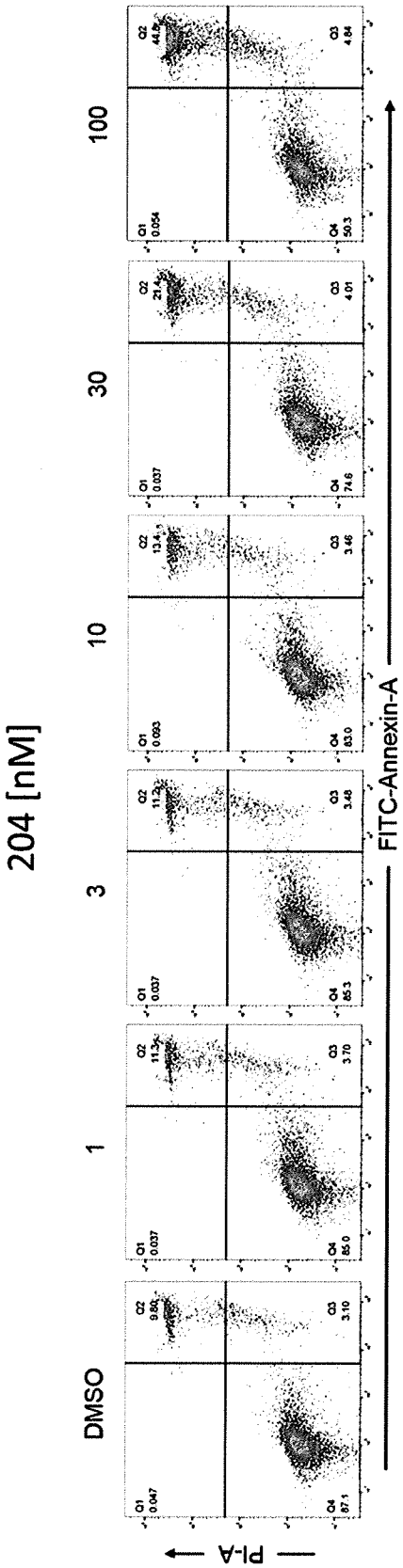


FIG. 6

INTERNATIONAL SEARCH REPORT

International application No
PCT/PL2021/000030

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/14 C07D401/04 C07D471/04 C07D513/04 C07D515/18
A61P35/00 A61K31/4439
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61P A61K

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PAPATZIMAS ET AL.: "From Inhibition to Degradation: Targeting the Antiapoptotic Protein Myeloid Cell Leukemia 1 (MCL1)", J. MED. CHEM., vol. 62, no. 11, 22 May 2019 (2019-05-22), pages 5522-5540, XP055880351, US ISSN: 0022-2623, DOI: 10.1021/acs.jmedchem.9b00455 cited in the application	1-39, 129-157, 159-162
Y	Title; abstract; page 5524, figure 3; page 5529, section "conclusions".	1-162

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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

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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

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

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance;; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 March 2022	25/03/2022

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	Weisbrod, Thomas

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

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WANG ET AL.: "Proteolysis Targeting Chimeras for the Selective Degradation of Mcl-1/Bcl-2 Derived from Nonselective Target Binding Ligands", J. MED. CHEM., vol. 62, no. 17, 7 August 2019 (2019-08-07), pages 8152-8163, XP055880355, US ISSN: 0022-2623, DOI: 10.1021/acs.jmedchem.9b00919 cited in the application Title; abstract; page 8153, figure 1b: compounds H1-H5, C1-C6.	157, 159-162
X	WU ET AL.: "Ubiquitination and deubiquitination of MCL1 in cancer: deciphering chemoresistance mechanisms and providing potential therapeutic options", CELL DEATH & DISEASE, vol. 11:556, 22 July 2020 (2020-07-22), pages 1-11, XP055881173, DOI: 10.1038/s41419-020-02760-y Retrieved from the Internet: URL:https://www.nature.com/articles/s41419-020-02760-y.pdf>	158
Y	Page 8, section "Application of PROTACs": "PROTAC technology exhibits advantages of reducing on-target toxicity, which provides insight into minimization of undesirable cardiotoxicity [...] caused by MCL1 depletion via exploration of specific E3 ligases that are rarely expressed in cardiomyocytes [...]".	158
X	HE ET AL.: "Proteolysis targeting chimeras (PROTACs) are emerging therapeutics for hematologic malignancies", JOURNAL OF HEMATOLOGY & ONCOLOGY, vol. 13:103, 27 July 2020 (2020-07-27), pages 1-24, XP055751965, DOI: 10.1186/s13045-020-00924-z Page 6, table 2: last entry, target Mcl-1, compound dMCL1-2; page 8, left column, last line to right column, line 5: "There are reported Mcl-1 PROTACs [45, 58], dMCL1-2 as a representative, which degrades Mcl-1 in OPM2 and MM.1S MM cell lines. It is worth looking into the possibility to design tissue-specific PROTACs to reduce the on-target toxicity of Mcl-1 inhibition in the heart."	158-162

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2

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CHEN, FLETCHER: "Mcl-1 inhibitors: a patent review", EXP. OPIN. THER. PATENTS, vol. 27, no. 2, February 2017 (2017-02), pages 163-178, XP055811306, GB ISSN: 1354-3776, DOI: 10.1080/13543776.2017.1249848 Retrieved from the Internet: URL:https://www.tandfonline.com/doi/pdf/10.1080/13543776.2017.1249848?needAccess=true> Pages 166, 168, 169.	1-39, 129-156
Y	WO 2008/131000 A2 (ABBOTT LAB [US]; ELMORE STEVEN W [US] ET AL.) 30 October 2008 (2008-10-30) Title; abstract; claims; examples.	1-39, 129-156
Y	BRUNCKO ET AL.: "Structure-Guided Design of a Series of MCL-1 Inhibitors with High Affinity and Selectivity", J. MED. CHEM., vol. 58, no. 5, 26 February 2015 (2015-02-26), pages 2180-2194, XP055540622, US ISSN: 0022-2623, DOI: 10.1021/jm501258m the whole document	1-39, 129-156
Y	WO 2015/031608 A1 (UNIV VANDERBILT [US]) 5 March 2015 (2015-03-05) Abstract; claims; pages 65-76: table 1.	1-39, 129-156
Y	TRON ET AL.: "Discovery of Mcl-1-specific inhibitor AZD5991 and preclinical activity in multiple myeloma and acute myeloid leukemia", NATURE COMMUNICATIONS, vol. 9, no. 1, 17 December 2018 (2018-12-17), pages 1-14, XP055663493, DOI: 10.1038/s41467-018-07551-w Abstract; page 3, table 1: compounds 2-8.	1-39, 129-156
X	WO 2017/184995 A1 (BIOVENTURES LLC [US]) 26 October 2017 (2017-10-26)	157, 159-161
Y	Title; abstract; paragraphs 2, 4, 16, 161; claims: in particular claim 1, R1 on page 242 and R2 on pages 244-245; claim 14; and claim 15, page 259.	1-39, 129-156

-/--

2

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	PETROS ET AL.: "Fragment-based discovery of potent inhibitors of the anti-apoptotic MCL-1 protein", BIOORG. MED. CHEM. LETT., vol. 24, no. 6, 14 February 2014 (2014-02-14), pages 1484-1488, XP028625292, ISSN: 0960-894X, DOI: 10.1016/J.BMCL.2014.02.010 Title; abstract; tables 2 and 3: compounds 14, 15, 17, 24.	1-27, 35-39, 129-138, 141-162
Y	US 2015/175623 A1 (KOTSCHY ANDRÁS [HU] ET AL) 25 June 2015 (2015-06-25) Paragraphs 1-2; pages 200-201, example A, in particular, page 201, paragraph 2392; claim 1, formula (I); claims 20-27.	1-27,35, 36,38, 39, 129-138, 141-162
Y	KOTSCHY ET AL.: "The MCL1 inhibitor S63845 is tolerable and effective in diverse cancer models", NATURE, vol. 538, no. 7626, 19 October 2016 (2016-10-19), pages 477-482, XP055571783, London ISSN: 0028-0836, DOI: 10.1038/nature19830 Title; abstract; figure 1a: structure of compound S63845.	1-27,35, 36,38, 39, 129-138, 141-162
A	US 2018/215731 A1 (CREW ANDREW P [US] ET AL) 2 August 2018 (2018-08-02) Title; claims, in particular pages 418 and 420: formula (f), and page 423: formula (y).	40-42, 60, 62-87, 131-162
Y	WO 2017/161119 A1 (MOFFITT CANCER CENT & RES INST INC H LEE) 21 September 2017 (2017-09-21) Title; abstract; claims; pages 128, 177, 190, 220: compounds MA6-116, SG4-144, SG5-031, MA5-178.	40-162
Y	US 2020/207783 A1 (NORCROSS ROGER [CH] ET AL) 2 July 2020 (2020-07-02) Abstract; claims; examples 7, 8, 12, 13, 16, 17, 18, 21, 24, 25, 34, 42, 49, 69, 70.	40-162

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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.
E	WO 2021/105334 A1 (CAPTOR THERAPEUTICS S A [PL]) 3 June 2021 (2021-06-03) Title; abstract; claims; examples, e.g. page 110, example 85 corresponding with the ligase ligand moiety of formula (IIa) in the compound of current claim 88; pages 32-40, test results.	89
E	WO 2021/105335 A1 (CAPTOR THERAPEUTICS S A [PL]) 3 June 2021 (2021-06-03) Title; abstract; claims; pages 121-131: examples.	40,89

INTERNATIONAL SEARCH REPORT

International application No.
PCT/PL2021/000030

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims;; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 28-34(completely); 1-27, 35-39, 129-162(partially)

relating to compounds of the formulae (I) and (X) wherein the ligase binding moiety of formula (I) and the cereblon binding moiety of formula (X) both are represented by the ligase moieties shown on page 512 of claim 1 and wherein the MCL-1 ligand moiety is represented by Formula (A) shown in claim 1.

1.1. claims: 1-7, 9, 14-39, 129-162(all partially)

relating to compounds of the formulae (I) and (X) wherein the ligase binding moiety of formula (I) and the cereblon binding moiety of formula (X) both are represented by the first ligase moiety shown on page 512 of claim 1 and wherein the MCL-1 ligand moiety is represented by Formula (A) shown in claim 1.

1.2. claims: 1-6, 8-10, 12-39, 129-162(all partially)

relating to compounds of the formulae (I) and (X) wherein the ligase binding moiety of formula (I) and the cereblon binding moiety of formula (X) both are represented by the second and fourth ligase moieties shown on page 512 of claim 1 and wherein the MCL-1 ligand moiety is represented by Formula (A) shown in claim 1.

1.3. claims: 1-5, 10, 11, 13-37, 39, 129-162(all partially)

relating to compounds of the formulae (I) and (X) wherein the ligase binding moiety of formula (I) and the cereblon binding moiety of formula (X) both are represented by the third ligase moiety shown on page 512 of claim 1 and wherein the MCL-1 ligand moiety is represented by Formula (A) shown in claim 1.

---

2. claims: 1-27, 35-39, 129-138, 141-162(all partially)

relating to compounds of the formulae (I) and (X) wherein the ligase binding moiety of formula (I) and the cereblon binding moiety of formula (X) both are represented by the ligase moieties shown on page 512 of claim 1 and wherein wherein the MCL-1 ligand moiety is represented by Formula (B) shown in claim 1.

---

3. claims: 1-27, 35, 36, 38, 39, 129-138, 141-162(all partially)

relating to compounds of the formulae (I) and (X) wherein the ligase binding moiety of formula (I) and the cereblon binding moiety of formula (X) both are represented by the

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

ligase moieties shown on page 512 of claim 1 and wherein the MCL-1 ligand moiety is represented by Formula (C) shown in claim 1.

---

4. claims: 62-65(completely); 40-42, 60, 66-87, 131-162(partially)

relating to compounds of the formulae (I) and (X) wherein the ligase binding moiety of formula (I) and the cereblon binding moiety of formula (X) both are represented by formula (IV) as shown on page 558 of claim 40.

---

5. claims: 43-59, 61, 88-128(completely); 40-42, 60, 66-87, 129-162(partially)

relating to compounds of the formulae (I) and (X) wherein the ligase binding moiety of formula (I) and the cereblon binding moiety of formula (X) both are represented by one of the formulae (Va), (Vb), (IIa), (IIb) as shown on pages 559 and 561 of claim 40 or one of the formulae (II), (III) as shown on pages 578 and 580 of claim 89.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/PL2021/000030

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/PL2021/000030

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