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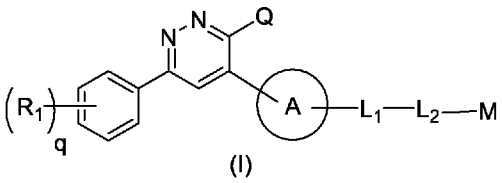

(I)

(57) Abstract: The present disclosure provides amino-substituted pyridazine compounds of formula (I), which are therapeutically useful as SMARCA2 and/or SMARCA4 degraders. These compounds are useful in the treatment and/or delaying progression of disease or disorder dependent upon SMARCA2 and/or SMARCA4 in a subject. The present disclosure also provides pharmaceutical compositions comprising at least one of the compounds of formula (I) or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof.

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AMINO-SUBSTITUTED PYRIDAZINE COMPOUNDS AS SMARCA2 AND/OR SMARCA4 DEGRADERS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of Indian provisional application number 202341074562, filed on November 1, 2023, the specification of which is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

The present disclosure relates to an amino-substituted pyridazine compounds and a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof which are useful as SMARCA2/4 degraders and for the treatment of disease or disorder dependent on SMARCA2/4. The present disclosure also relates to a method of preparation of the said pyridazine compounds and pharmaceutical compositions comprising the said compounds.

BACKGROUND OF THE INVENTION

One of the most significant findings from the cancer genome profiling is the discovery of frequent mutations in various subunits of the mammalian SWI/SNF (SWItch/Sucrose Non-Fermentable) chromatin remodelling complex. Approximately 20% of human cancers are associated with somatic mutations in subunits of the SWI/SNF complex, a chromatin remodelling complex that influences gene regulation by disrupting histone-DNA contacts (PNAS February 25, 2014. 111 (8) 3128-3133).

SWI/SNF complexes contain either of two closely related and evolutionarily conserved catalytic ATPase subunits: Brahma (BRM/SMARCA2) or Brahma-related gene 1 (BRG1/SMARCA4). They share approximately 75% identity at the protein level. Although BRG1- and BRM-containing complexes show some redundancy, they may function distinctively. In human cancer, BRG1 seems to be one of the most frequently mutated subunit genes, whereas the BRM gene is rarely mutated. BRG1/SMARCA4 mutations occurring in ~10–15% of lung adenocarcinomas. BRM/SMARCA2 is essential for the growth of tumour cells that harbour loss of function mutations in BRG1/SMARCA4. Depletion of BRM in BRG1-deficient cancer cells leads to a cell cycle arrest, induction of senescence, and increased levels of global H3K9me31 (PNAS February 25, 2014, 111 (8), 3128-3133).

In some tumour types, mutations within the SWI/SNF complex lead to context specific vulnerabilities such as the requirement of SMARCA2 for survival of tumour cells lacking

SMARCA4. This finding of SMARCA2/4 synthetic lethal relationship translates in vivo which emphasizes SMARCA2 as a promising therapeutic target for the treatment of SMARCA4-deficient cancers. Moreover, the SMARCA4-deficient patient population generally lacks targetable oncogenes (such as mutant EGFR or ALK translocations), which further emphasizes the potential of developing SMARCA2 inhibitors. Characterization of SMARCA4 function in tumours with high SMARCA4 levels, shows effects on signalling pathways that result in increased proliferation and survival. SMARCA4 knockdown in tumours that show elevated levels known to inhibit proliferation and other cancer cell properties. Studies have also shown that SMARCA4 knockdown/modulation increases sensitivity to known chemotherapeutic agents, thereby indicating that SMARCA4 targeting could also be an adjuvant therapy to existing chemotherapeutic approaches (PNAS February 25, 2014. 111 (8) 3128-3133; J Pathol. 2016 Feb; 238(3): 389–400).

Contrary to genetic silencing of SMARCA2 leading to potent anti-proliferative activity in SMARCA4-deficient cancer cell lines, PFI-3, a selective cell permeable SMARCA2/4 bromodomain inhibitor capable of binding to SMARCA2 and SMARCA4 bromodomain, fails to display an antiproliferative phenotype which indicates that bromodomain function of SMARCA2/4 is dispensable for tumor cell proliferation, while the catalytic ATPase activity is essential (Cancer Res. 2015 Sep 15; 75(18): 3865–3878). In order to mimic the phenotype achieved by genetic silencing, approaches that lead to reduction or complete elimination of SMARCA2/4 may be needed.

The ubiquitin-proteasome system (UPS) is a major pathway that regulates the levels of intracellular proteins and provides a fine balance between protein synthesis and degradation required for normal maintenance of cellular function, including proliferation, differentiation, and cell death. Ubiquitination is a post-translational modification, where a small protein, ubiquitin, is covalently attached to lysine residues on a substrate protein carried out sequentially by a cascade of enzymatic reactions involving an intimate collaboration between E1 activating, E2 conjugating and E3 ligating enzymes and subsequent degradation of the tagged proteins (J. Biosci. 31(1), March 2006, 137–155; Expert Opin Ther Targets. 2013 September; 17(9): 1091–1108 and Cell Research (2016) 26:484-498).

Proteolysis targeting chimeras are the heterobifunctional molecules contain a ligand for a target protein of interest connected via a linker to a ligand for an E3 ubiquitin ligase. Upon such bi-functional molecule-mediated heterodimerization of the two bound proteins, the target protein is ubiquitinated and degraded by the proteasome in cells. Many such bi-functional

molecules have been developed to recruit E3 ubiquitin ligases to a variety of substrates using high-affinity ligands for the protein of interest. Proteins effectively degraded using these approaches include RIPK2 and ERRα, BRD4, BRD9, BCR/Abl and Abl and Erα (Cell Chemical Biology 25, 78–87, January 18, 2018). E3 ubiquitin ligases (of which over 600 are known in humans) confer substrate specificity for ubiquitination and are more attractive therapeutic targets than general proteasome inhibitors due to their specificity for certain protein substrates.

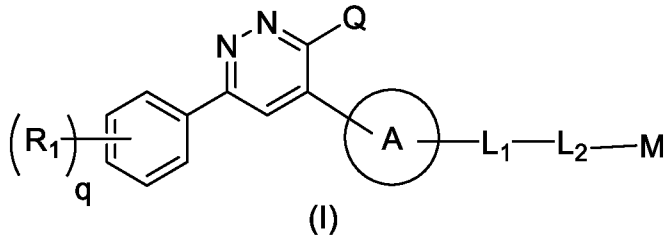
Small molecule ligands targeting the bromodomains of SMARCA2 and SMARCA4 have been reported (Gerstenberger et al., Journal of Medicinal Chemistry 2016, 59, 4800-4811; Hoffman et al., PNAS, 2014b, 777, 3128-3133; Sutherell et al., 2016, Journal of Medicinal Chemistry 59, 5095-5101; WO2016138114). Although cells lacking SMARCA4 activity are vulnerable to the loss of SMARCA2 (Hoffman et al., 2014a, PNAS 777, 3128-3133), SMARCA2/4 inhibitors have failed to phenocopy these anti-proliferative effects (Vangamudi et al., 2015). In agreement with this, re-expression of SMARCA2 variants in cells, where the endogenous protein had been suppressed, showed that an intact bromodomain is not required to maintain proliferation (Vangamudi et al., 2015, Cancer Research 75, 3865-3878). SMARCA2/4BD inhibitors are thus precluded from use for the treatment of SMARCA4 mutant cancers but could provide attractive ligands for PROTAC conjugation.

It is therefore reasoned that a PROTAC targeting the non-functional bromodomain of SMARCA2/4 should offer an opportunity to exploit the vulnerability of SMARCA2 in SMARCA4 mutated cancer cells for therapeutic purposes. The principle of conjugation of a suitable SMARCA ligand with an E3 ligase binder has been described in WO 2016/105518; WO2017/007612 and WO2017/011371. However, in none of the publications a concrete example and corresponding degradation of SMARCA proteins has been demonstrated.

SUMMARY OF THE INVENTION

Provided herein an amino-substituted pyridazine compounds and pharmaceutical compositions thereof that are useful as SMARCA2/4 degraders and for the treatment of disease or disorder dependent on or mediated by SMARCA2/4.

In one aspect, the present disclosure provides a compound of formula (I):



(I)

or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof;

wherein,

R_1 at each occurrence, independently, is hydroxy, halo(C_1-C_6)alkyl, (C_1-C_6)alkoxy, halogen, (C_1-C_6)alkyl, amino or cyano;

q is 0, 1, 2 or 3;

Q is hydroxy, (C_1-C_6)alkoxy, amino or (C_1-C_6)alkylamino;

A is phenylenyl or 6-membered heteroarylenyl; wherein the phenylenyl and heteroarylenyl independently, are unsubstituted or substituted with 1, 2 or 3 occurrence(s) of Ra;

Ra represents halogen, (C_1-C_6)alkyl or halo(C_1-C_6)alkyl;

L_1 is -(3- to 12-membered heterocycloalkylenyl)-, *-(3- to 12-membered heterocycloalkylenyl)-(3- to 8-membered cycloalkylenyl)-, -(3- to 12-membered heterocycloalkylenyl)-(3- to 12-membered heterocycloalkylenyl)-, or *-N(Rx)-(3- to 12-membered heterocycloalkylenyl)-; wherein the heterocycloalkylenyl and cycloalkylenyl independently is unsubstituted or substituted with 1, 2 or 3 occurrence(s) of Rd; wherein the asterisk mark represents the point of attachment with ring A;

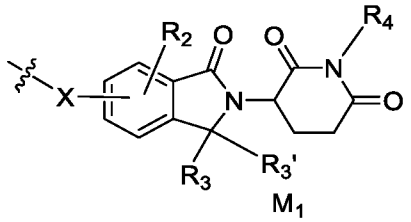
L_2 is a bond, -(3- to 8-membered cycloalkylenyl)-, -(3- to 10-membered heterocycloalkylenyl)-, *-$(CRxRy)_n$-(3- to 8-membered cycloalkylenyl)-, *-$(CRxRy)_n$-(3- to 10-membered heterocycloalkylenyl)-, *-(3- to 10-membered heterocycloalkylenyl)-$(CRxRy)_n$-; wherein the cycloalkylenyl and heterocycloalkylenyl, independently is unsubstituted or substituted with 1, 2 or 3 occurrence(s) of Rd; wherein the asterisk mark represents the point of attachment with L_1;

Rx and Ry, independently, is hydrogen or (C_1-C_6)alkyl;

n is 1, 2 or 3;

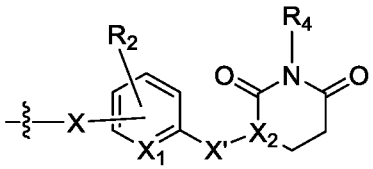
Rd at each occurrence, independently, is (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, halogen, hydroxy or (C_1-C_6)alkoxy;

M is M_1 or M_2;



M_1

or



M_2 ;

wherein,

X and X' independently, is a bond, -N(Rz)- or -O-;

Rz is hydrogen or (C_1-C_6)alkyl;

X_1 and X_2, at each occurrence, independently, is N or CH;

R_2 is hydrogen, halogen, halo(C_1-C_6)alkyl or (C_1-C_6)alkyl;

R_3 and R_3' independently are hydrogen; or R_3 and R_3' together represent an oxo group; and

R_4 is hydrogen or (C_1-C_6)alkyl.

In another aspect, the present disclosure provides a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof, and a pharmaceutically acceptable carrier or an excipient.

In another aspect, the present disclosure provides a method of degrading a target protein in a subject comprising, administering to the subject in need thereof, a therapeutically effective amount of the compound of formula (I) or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof.

In another aspect, the present disclosure provides a method of treating a condition of a disease or a disorder comprising, administering a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof to an individual, e.g., a human, in need thereof. The disease or disorder is treatable by degradation of SMARCA2/4, for example, a cancer, a chronic autoimmune disorder, an inflammatory condition, a proliferative disorder, sepsis or a viral infection.

In another aspect, the present disclosure provides a compound of formula (I) or a pharmaceutical acceptable salt or a stereoisomer or a tautomer thereof, for use as a medicament.

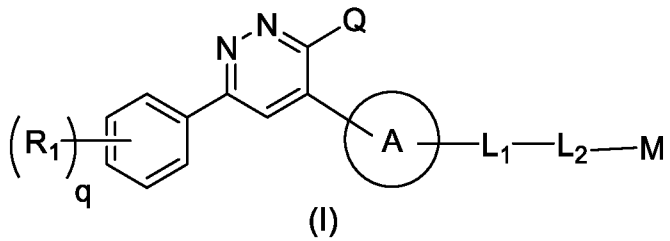
In another aspect, the present disclosure provides the use of a compound of formula (I) or a pharmaceutical acceptable salt or a stereoisomer or a tautomer thereof, in the manufacture of a medicament for the treatment of a disease or disorder dependent upon SMARCA2 and/or SMARCA4; wherein the disease or disorder is cancer.

DETAILED DESCRIPTION OF THE INVENTION

The present disclosure provides amino-substituted pyridazine compounds, referred as a compound of formula (I), which are useful as SMARCA2/4 degraders and for the treatment of conditions dependent on or mediated by SMARCA2/4. The present disclosure further provides pharmaceutical compositions comprising the said compound or a stereoisomer or a tautomer thereof as therapeutic agents.

Each embodiment is provided by way of explanation of the invention and not by way of limitation of the invention. In fact, it will be apparent to those skilled in the art that various modifications and variations can be made to the compounds, compositions and methods described herein without departing from the scope or spirit of the invention. For instance, features illustrated or described as part of one embodiment can be applied to another embodiment to yield a still further embodiment. Thus, it is intended that the present invention includes such modifications and variations and their equivalents. Other objects, features and aspects of the present invention are disclosed in or are obvious from, the following detailed description. It is to be understood by one of ordinary skill in the art that the present discussion is a description of exemplary embodiments only and is not to be construed as limiting the broader aspects of the present invention.

In one embodiment, the present disclosure provides a compound of formula (I),



(I)

or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof;

wherein,

R_1 at each occurrence, independently, is hydroxy, halo(C_1-C_6)alkyl, (C_1-C_6)alkoxy, halogen, (C_1-C_6)alkyl, amino or cyano;

q is 0, 1, 2 or 3;

Q is hydroxy, (C_1-C_6)alkoxy, amino or (C_1-C_6)alkylamino;

A is phenylenyl or 6-membered heteroarylenyl; wherein the phenylenyl and heteroarylenyl independently, are unsubstituted or substituted with 1, 2 or 3 occurrence(s) of Ra;

Ra represents halogen, (C_1-C_6)alkyl or halo(C_1-C_6)alkyl;

L_1 is -(3- to 12-membered heterocycloalkylenyl)-, *-(3- to 12-membered heterocycloalkylenyl)-(3- to 8-membered cycloalkylenyl)-, -(3- to 12-membered heterocycloalkylenyl)-(3- to 12-membered heterocycloalkylenyl)-, or *-N(Rx)-(3- to 12-membered heterocycloalkylenyl)-; wherein the heterocycloalkylenyl and cycloalkylenyl independently is unsubstituted or substituted with 1, 2 or 3 occurrence(s) of Rd; wherein the asterisk mark represents the point of attachment with ring A;

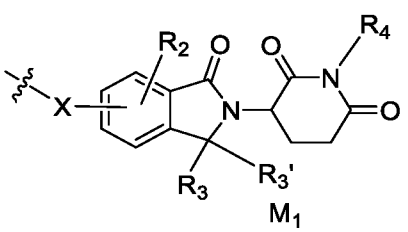
L_2 is a bond, -(3- to 8-membered cycloalkylenyl)-, -(3- to 10-membered heterocycloalkylenyl)-, *-$(CRxRy)_n$-(3- to 8-membered cycloalkylenyl)-, *-$(CRxRy)_n$-(3- to 10-membered heterocycloalkylenyl)-, *-(3- to 10-membered heterocycloalkylenyl)-$(CRxRy)_n$-; wherein the cycloalkylenyl and heterocycloalkylenyl, independently is unsubstituted or substituted with 1, 2 or 3 occurrence(s) of Rd; wherein the asterisk mark represents the point of attachment with L_1;

Rx and Ry, independently, is hydrogen or (C_1-C_6)alkyl;

n is 1, 2 or 3;

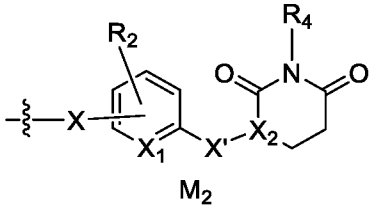
Rd at each occurrence, independently, is (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, halogen, hydroxy or (C_1-C_6)alkoxy;

M is M_1 or M_2;



M_1

or



M_2 ;

wherein,

X and X' independently, is a bond, -N(Rz)- or -O-;

Rz is hydrogen or (C_1-C_6)alkyl;

X_1 and X_2, at each occurrence, independently, is N or CH;

R_2 is hydrogen, halogen, halo(C_1-C_6)alkyl or (C_1-C_6)alkyl;

R_3 and R_3' independently are hydrogen; or R_3 and R_3' together represent an oxo group; and

R_4 is hydrogen or (C_1-C_6)alkyl.

In one embodiment, R_1 is hydroxy or halo(C_1-C_6)alkyl.

In one embodiment, R_1 is -OH or -CF_3.

In one embodiment, R_1 is halo(C_1-C_6)alkyl.

In one embodiment, R_1 is -CF_3.

In one embodiment, q is 1, 2, or 3.

In one embodiment, q is 1.

In one embodiment, Q is hydroxy, amino or (C_1-C_6)alkylamino.

In one embodiment, Q is -NH_2, -$NHCH_3$ or -OH.

In one embodiment, Q is amino or (C_1-C_6)alkylamino.

In one embodiment, Q is amino or hydroxy.

In one embodiment, Q is (C_1-C_6)alkylamino.

In one embodiment, Q is -NH_2, or -OH.

In one embodiment, Q is -$NHCH_3$ or -OH.

In one embodiment, Q is -NH_2.

In one embodiment, Q is -$NHCH_3$.

In one embodiment, Q is -OH.

In one embodiment, ring A is phenylenyl; wherein phenylenyl is unsubstituted or substituted with 1 or 2 occurrence(s) of Ra.

In one embodiment, ring A is phenylenyl; wherein phenylenyl is unsubstituted.

In one embodiment, ring A is 6-membered heteroarylenyl; wherein the heteroarylenyl is pyridinylenyl, pyrimidinylenyl, triazinylenyl, or pyrazinylenyl.

In one embodiment, ring A is 6-membered heteroarylenyl; wherein the heteroarylenyl is unsubstituted.

In one embodiment, Ra is halogen or (C_1-C_6)alkyl.

In one embodiment, Ra is -F or methyl.

In one embodiment, Ra is halogen.

In one embodiment, Ra is (C_1-C_6)alkyl.

In one embodiment, Ra is F.

In one embodiment, Ra is methyl.

In one embodiment, L_1 is -(3- to 12-membered heterocycloalkylenyl)- *-(3- to 12-membered heterocycloalkylenyl)-(3- to 8-membered cycloalkylenyl)-, or *-N(Rx)-(3- to 12-membered heterocycloalkylenyl)-; wherein the heterocycloalkylenyl and cycloalkylenyl independently is unsubstituted or substituted with 1, 2 or 3 occurrence(s) of Rd; wherein the asterisk mark represents the point of attachment with ring A.

In one embodiment, L_1 is -(6- to 10-membered heterocycloalkylenyl)-, *-(6- to 10-membered heterocycloalkylenyl)-(6- to 8-membered cycloalkylenyl)-, -(3- to 12-membered heterocycloalkylenyl)-(6- to 8-membered heterocycloalkylenyl)-, or *-N(Rx)-(6- to 10-membered heterocycloalkylenyl)-; wherein the heterocycloalkylenyl and cycloalkylenyl independently is unsubstituted or substituted with 1, 2 or 3 occurrence(s) of Rd; wherein the asterisk mark represents the point of attachment with ring A.

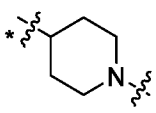
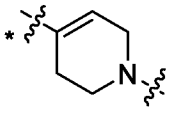
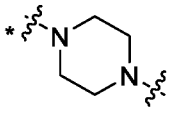
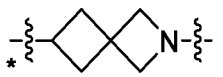
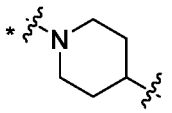
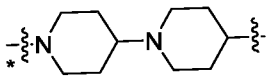
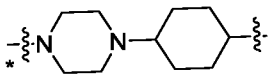
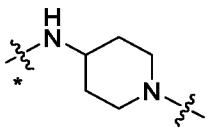
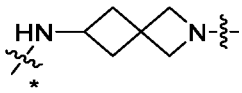
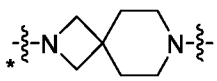
In one embodiment, Rd at each occurrence, independently, is (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, halogen, hydroxy, or (C_1-C_6)alkoxy.

In one embodiment, Rd at each occurrence, independently, is halogen.

In one embodiment, Rd at each occurrence, independently, is fluorine.

In one embodiment, Rx is hydrogen or (C_1-C_6)alkyl.

In one embodiment, Rx is hydrogen.

In one embodiment, L_1 is  ,  ,  ,  ,  ,  ,  ,  ,  ,  , or  ; wherein the asterisk mark indicates the point of attachment towards ring A.

In one embodiment, L_2 is a bond, -(3- to 8-membered cycloalkylenyl)-, -(3- to 10-membered heterocycloalkylenyl), *-$(CRxRy)_n$-(3- to 8-membered cycloalkylenyl)-, *-$(CRxRy)_n$-(3- to 10-membered heterocycloalkylenyl)-, *-(3- to 10-membered heterocycloalkylenyl)-$(CRxRy)_n$-; wherein the cycloalkylenyl and heterocycloalkylenyl, at each occurrence, independently is unsubstituted or substituted with 1, 2 or 3 occurrence(s) of Rd; wherein the asterisk mark represents the point of attachment with L_1.

In one embodiment, L_2 is a bond, -(3- to 8-membered cycloalkylenyl)-, -(3- to 10-membered heterocycloalkylenyl)-, *-$(CRxRy)_n$-(3- to 8-membered cycloalkylenyl)- or *-$(CRxRy)_n$-(3- to 10-membered heterocycloalkylenyl)-; wherein the cycloalkylenyl and heterocycloalkylenyl independently is substituted with 1, 2 or 3 occurrences of Rd; wherein the asterisk mark represents the point of attachment with L_1.

In one embodiment, L_2 is a bond, -(4- to 8-membered cycloalkylenyl)-, -(4- to 8-membered heterocycloalkylenyl), *-$(CRxRy)_n$-(4- to 8-membered cycloalkylenyl)-, *-$(CRxRy)_n$-(4- to 8-membered heterocycloalkylenyl)-, *-(4- to 8-membered heterocycloalkylenyl)-$(CRxRy)_n$-; wherein the cycloalkylenyl and heterocycloalkylenyl, at each occurrence, independently is unsubstituted or substituted with 1, 2 or 3 occurrence(s) of Rd; wherein the asterisk mark represents the point of attachment with L_1.

In one embodiment, Rd at each occurrence, independently, is $(C_1$-$C_6)$alkyl, halo$(C_1$-$C_6)$alkyl, or halogen.

In one embodiment, Rd at each occurrence, independently, is halogen.

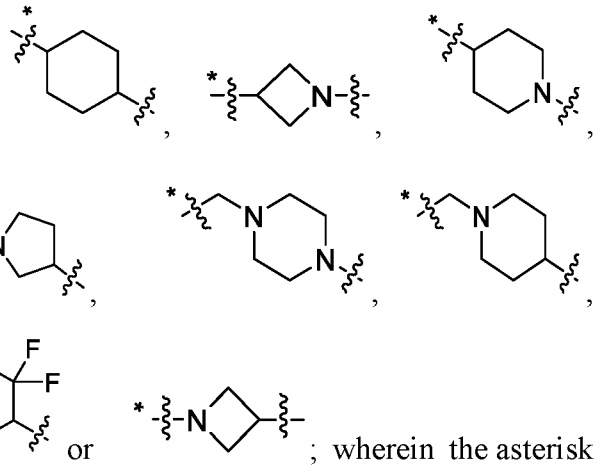
In one embodiment, Rd at each occurrence, independently, is fluorine.

In one embodiment, Rx and Ry, independently, is hydrogen or $(C_1$-$C_6)$alkyl.

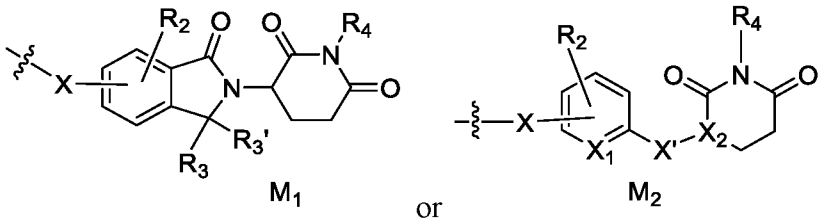
In one embodiment, Rx and Ry is hydrogen.

In one embodiment, n represents 1, 2, or 3.

In one embodiment, n represents 1.

In one embodiment, L_2 is a bond,  ; wherein the asterisk mark indicates the point of attachment towards L_1.

In one embodiment, M is M_1 or M_2:



M_1 or M_2.

In one embodiment, Rz is hydrogen or $(C_1\text{-}C_6)$alkyl.

In one embodiment, Rz is hydrogen or $-CH_3$.

In one embodiment, Rz is hydrogen.

In one embodiment, Rz is $(C_1\text{-}C_6)$alkyl.

In one embodiment, Rz is $-CH_3$.

In one embodiment, X and X', independently, is a bond, -NH-, $-N(C_1\text{-}C_6)$alkyl, or -O-.

In one embodiment, X and X', independently, is a bond, -NH-, -N(methyl)-, -O-.

In one embodiment, X and X', independently, is a bond, -NH-, or -N(methyl)-.

In one embodiment, X and X', independently, is a bond, or -NH-.

In one embodiment, X and X', independently is -NH- or $-N(C_1\text{-}C_6)$alkyl.

In one embodiment, X and X' is a bond.

In one embodiment, X and X' is -NH-.

In one embodiment, X and X' is -N(methyl)-.

In one embodiment, X and X' is -O-.

In one embodiment, X_1 and X_2, independently, is -N- or -CH-.

In one embodiment, X_1 and X_2, is -CH-.In one embodiment, R_2 is hydrogen, halogen, or halo(C_1-C_6)alkyl.

In one embodiment, R_2 is halogen or halo(C_1-C_6)alkyl.

In one embodiment, R_2 is hydrogen, fluorine, or -CF_3.

In one embodiment, R_2 is fluorine or -CF_3.

In one embodiment, R_2 is fluorine or chlorine.

In one embodiment, R_2 is hydrogen.

In one embodiment, R_2 is fluorine.

In one embodiment, R_2 is halo(C_1-C_6)alkyl.

In one embodiment, R_2 is -CF_3.

In one embodiment, R_2 is (C_1-C_6)alkyl.

In one embodiment, R_3 and $R_{3'}$ independently are hydrogen.

In one embodiment, R_3 and $R_{3'}$ together represent an oxo group.

In one embodiment, R_4 is hydrogen or (C_1-C_6)alkyl.

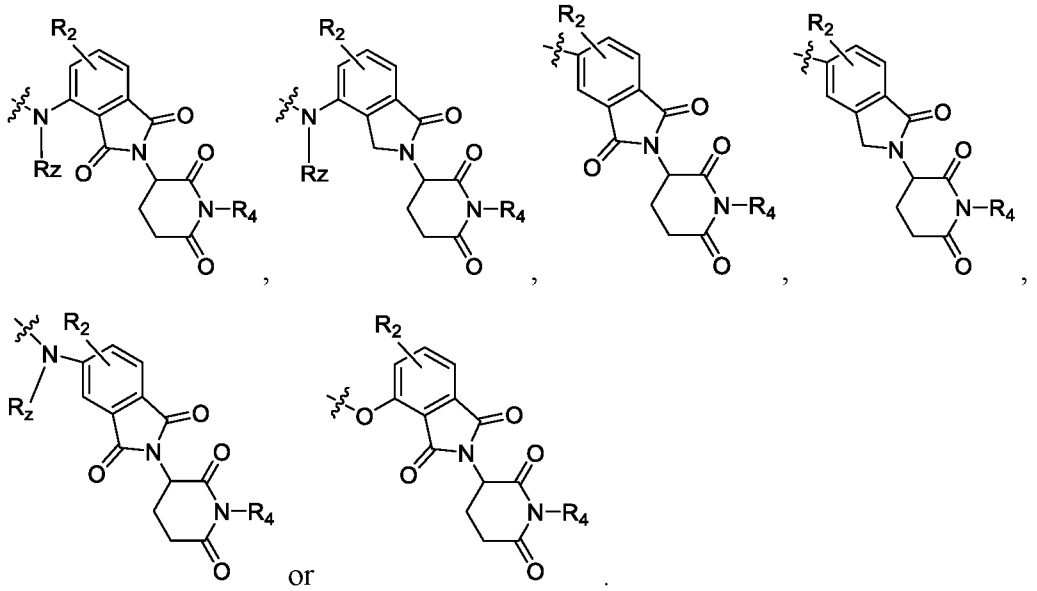
In one embodiment, R_4 is hydrogen or methyl.

In one embodiment, R_4 is hydrogen.

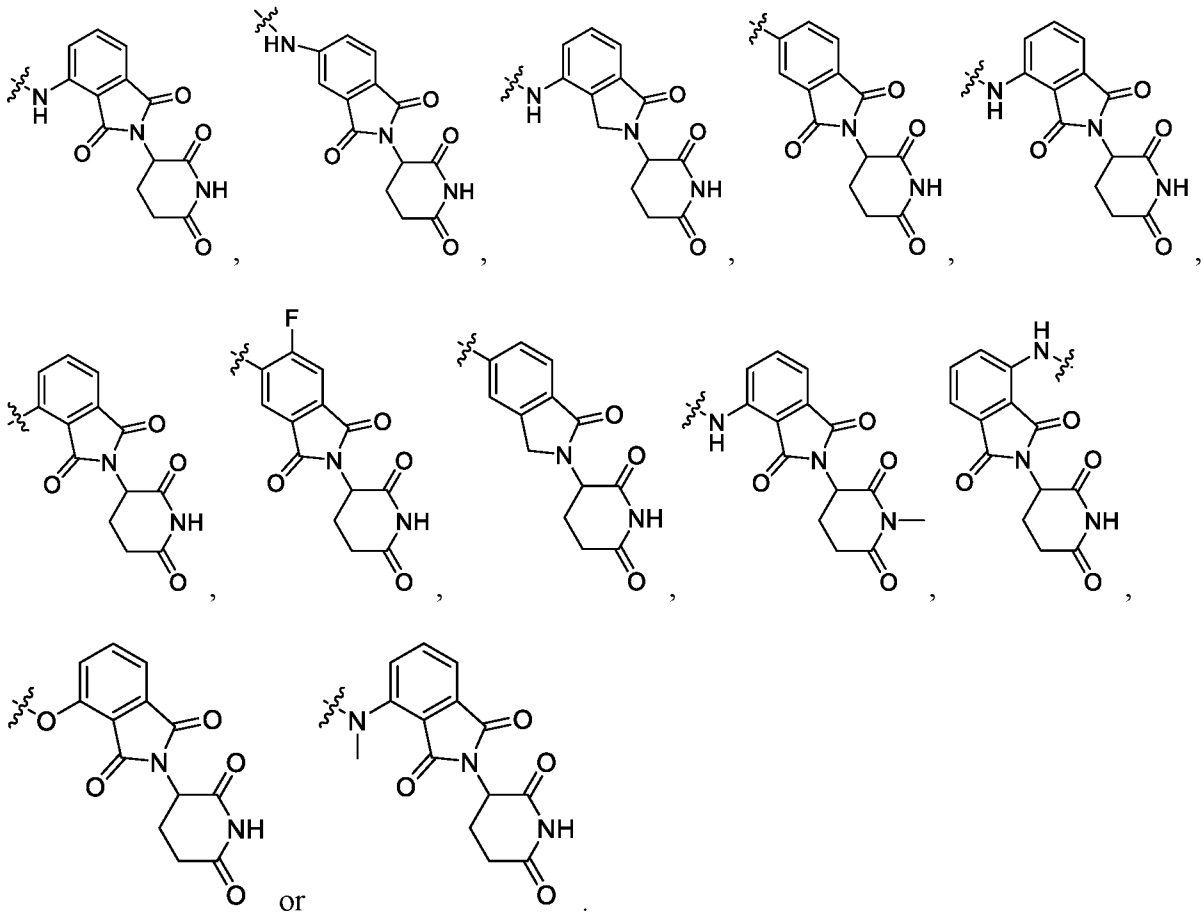
In one embodiment, R_4 is (C_1-C_6)alkyl.

In one embodiment, R_4 is methyl.

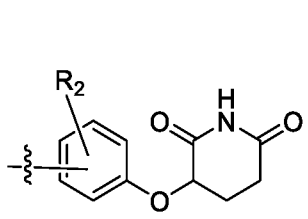
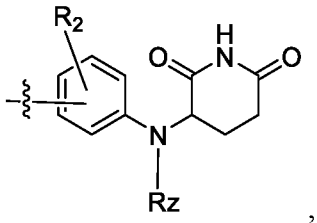
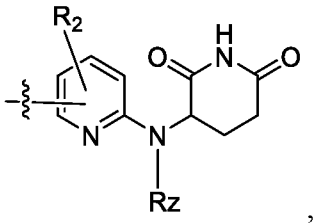
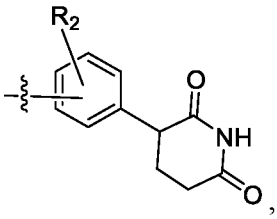
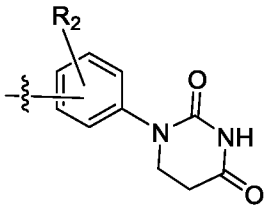
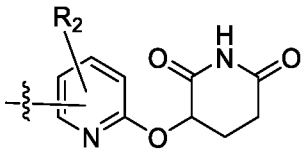
In one embodiment, M_1 is a group of formula



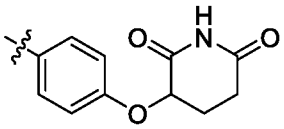
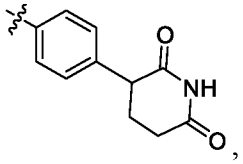
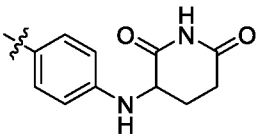
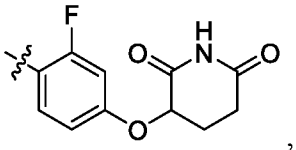
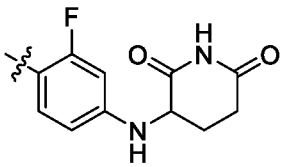
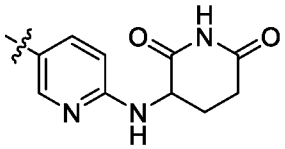
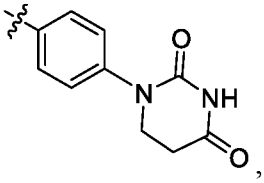
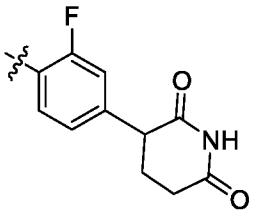
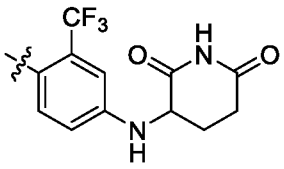
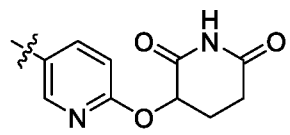
In one embodiment, M_1 is



In one embodiment, M_2 is a group of formula

In one embodiment, M_2 is

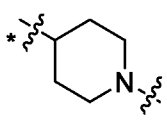
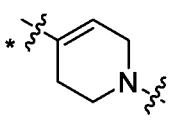
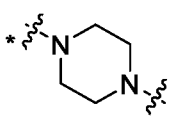











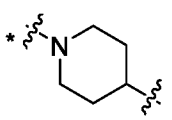
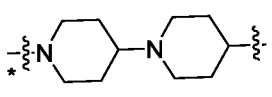
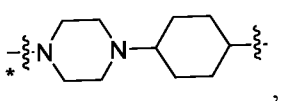
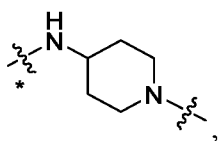
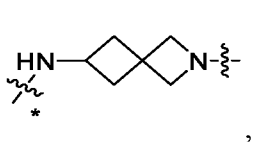
or .

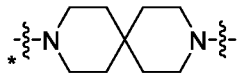
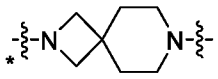
In one embodiment, R_1 is hydroxy or halo(C_1-C_6)alkyl;

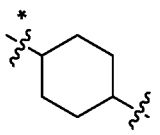
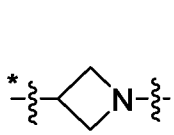
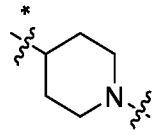
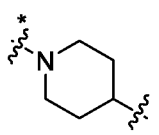
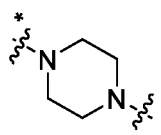
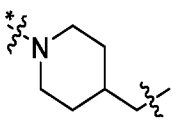
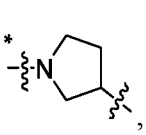
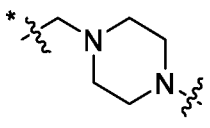
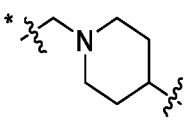
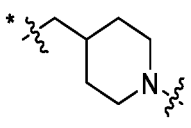
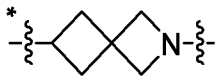
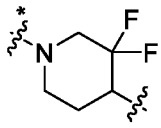
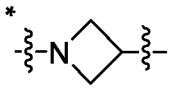
Q is amino or hydroxy, (C_1-C_6)alkylamino;

ring A is phenylenyl;

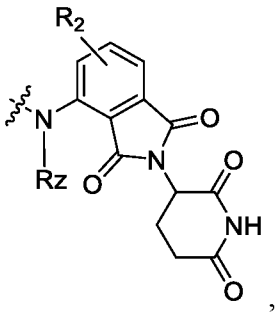
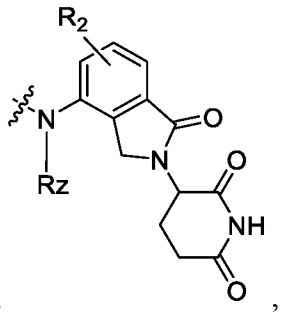
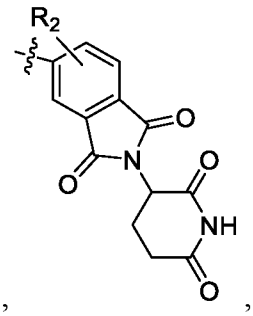
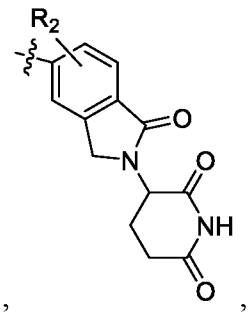
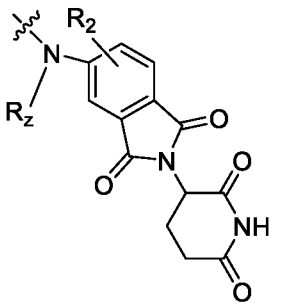
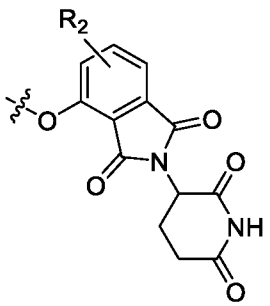
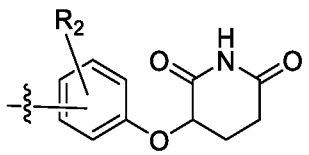
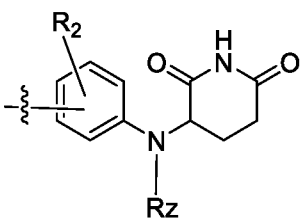
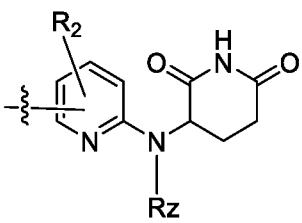
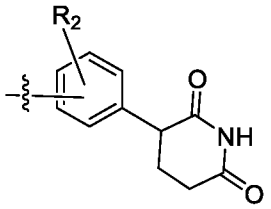
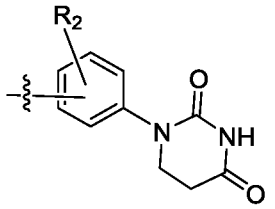
L_1 is 



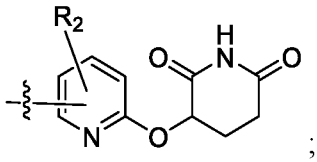






 or  ; wherein the asterisk mark indicates the point of attachment towards ring A;

L_2 is a bond,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  or  ; wherein the asterisk indicates the point of attachment towards L_1; and

M is

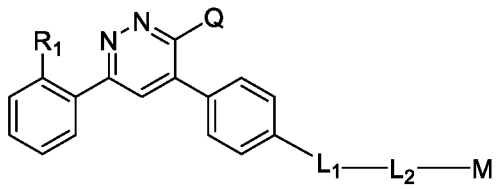
 ,  ,  ,  ,  ,  ,  ,  ,  ,  , 

or  ;

R_2 is hydrogen, halogen or halo(C_1-C_6)alkyl; and

R_3 and R_3' independently are hydrogen; or R_3 and R_3' together represent an oxo group.

In one embodiment, the present disclosure provides a compound of formula (IA):



(IA)

or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof, wherein R_1, Q, L_1, L_2, and M are as described in classes and subclasses herein, both singly and in combination.

In one embodiment, R_1 at each occurrence independently is hydroxy or halo(C_1-C_6)alkyl.

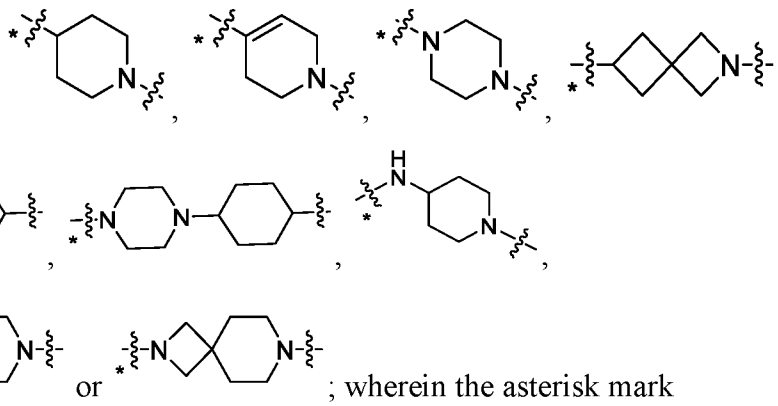
In one embodiment, R_1 at each occurrence independently is hydroxy.

In one embodiment, R_1 at each occurrence independently is halo(C_1-C_6)alkyl.

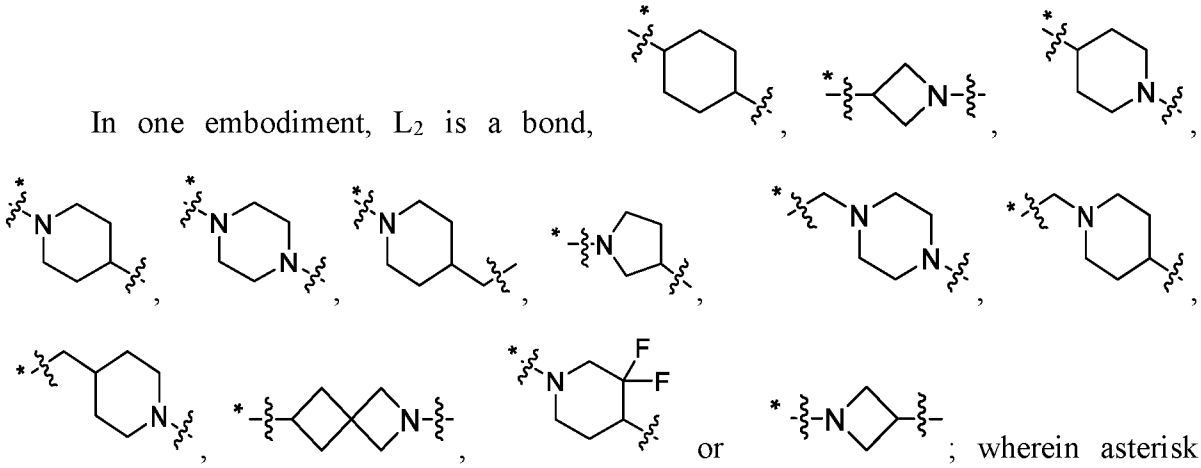
In one embodiment, R_1 at each occurrence, independently, is -OH or -CF_3.

In one embodiment, Q is hydroxy, amino or (C_1-C_6)alkylamino.

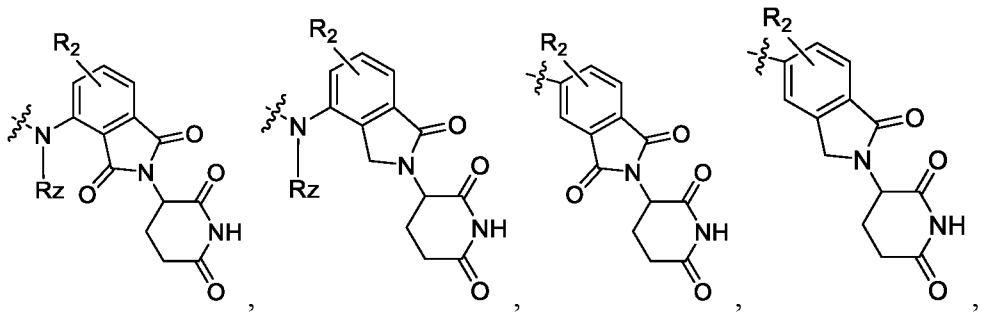
In one embodiment, L_1 is -(6- to 10-membered heterocycloalkylenyl)-, *-(6- to 10-membered heterocycloalkylenyl)-(6- to 8-membered cycloalkylenyl)-, -(3- to 12-membered heterocycloalkylenyl)-(6- to 8-membered heterocycloalkylenyl)-, or *-N(Rx)-(6- to 10-membered heterocycloalkylenyl)-; wherein the heterocycloalkylenyl and cycloalkylenyl independently is unsubstituted or substituted with 1, 2 or 3 occurrence(s) of Rd; wherein the asterisk mark represents the point of attachment with ring A.

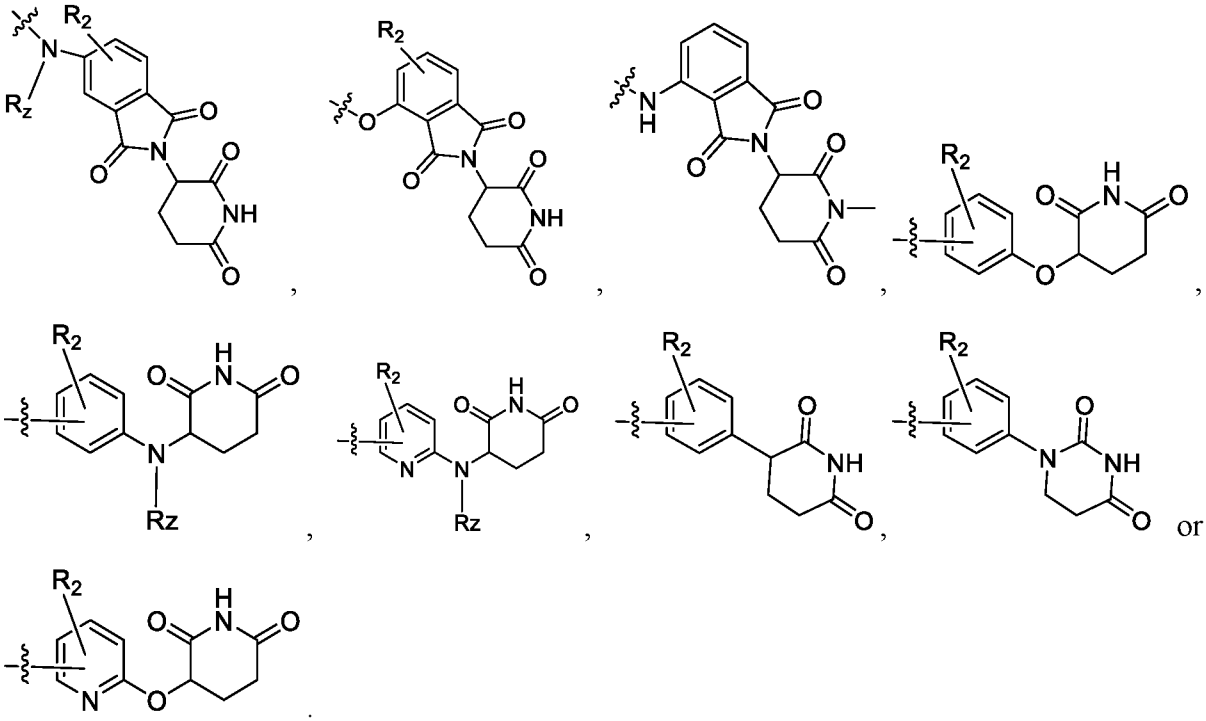
In one embodiment, L_1 is  ; wherein the asterisk mark indicates the point of attachment towards ring A.

In one embodiment, wherein L_2 is a bond, -(4- to 8-membered cycloalkylenyl)-, -(4- to 8-membered heterocycloalkylenyl), *-$(CRxRy)_n$-(4- to 8-membered cycloalkylenyl)-, *-$(CRxRy)_n$-(4- to 8-membered heterocycloalkylenyl)-, *-(4- to 8-membered heterocycloalkylenyl)-$(CRxRy)_n$-; wherein the cycloalkylenyl and heterocycloalkylenyl, at each occurrence, independently is unsubstituted or substituted with 1, 2 or 3 occurrence(s) of Rd; wherein the asterisk mark represents the point of attachment with L_1.

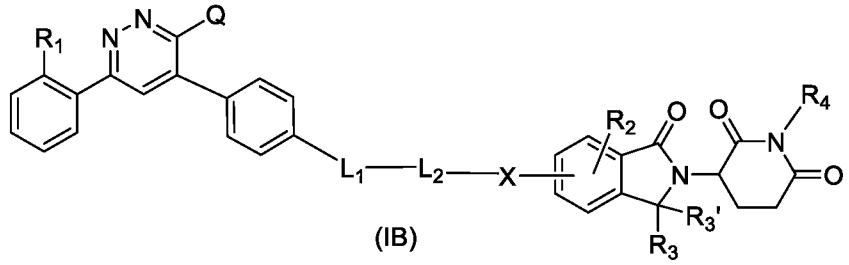
In one embodiment, L_2 is a bond,  ; wherein asterisk mark indicates the point of attachment towards L_1.

In one embodiment, M is





In one embodiment, the present disclosure provides a compound of formula (IB):



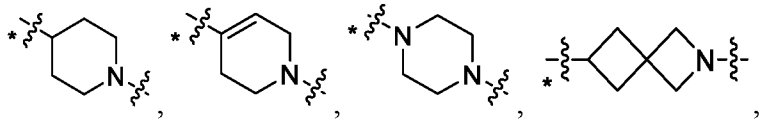
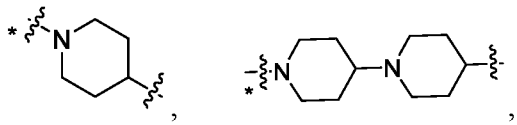
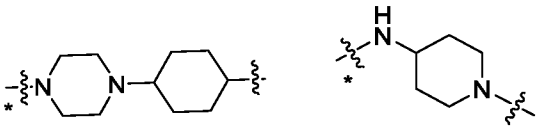
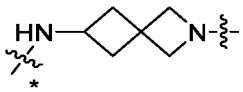
(IB)

or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof, wherein R_1, Q, L_1, L_2, X, R_2, R_3, R_3' and R_4 are as described in classes and subclasses herein, both singly and in combination.

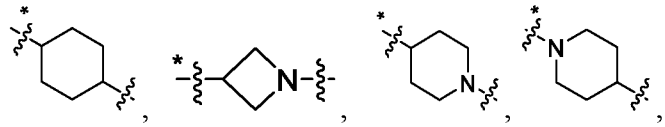
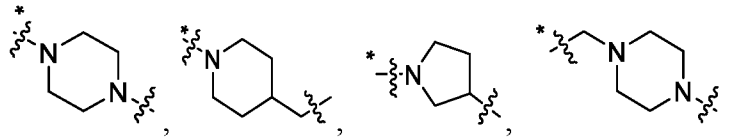
In one embodiment, R_1 at each occurrence independently is hydroxy or halo(C_1-C_6)alkyl.

In one embodiment, Q is hydroxy, amino or (C_1-C_6)alkylamino.

In one embodiment, L_1 is -(6- to 10-membered heterocycloalkylenyl)-, *-(6- to 10-membered heterocycloalkylenyl)-(6- to 8-membered cycloalkylenyl)-, -(3- to 12-membered heterocycloalkylenyl)-(6- to 8-membered heterocycloalkylenyl)-, or *-N(Rx)-(6- to 10-membered heterocycloalkylenyl)-; wherein the heterocycloalkylenyl and cycloalkylenyl independently is unsubstituted or substituted with 1, 2 or 3 occurrence(s) of Rd; wherein the asterisk mark represents the point of attachment with ring A.

In one embodiment, L_1 is  ,  ,  ,  ; wherein the asterisk mark indicates the point of attachment towards ring A.

In one embodiment, wherein L_2 is a bond, -(4- to 8-membered cycloalkylenyl)-, -(4- to 8-membered heterocycloalkylenyl), *-$(CRxRy)_n$-(4- to 8-membered cycloalkylenyl)-, *-$(CRxRy)_n$-(4- to 8-membered heterocycloalkylenyl)-, *-(4- to 8-membered heterocycloalkylenyl)-$(CRxRy)_n$-; wherein the cycloalkylenyl and heterocycloalkylenyl, at each occurrence, independently is unsubstituted or substituted with 1, 2 or 3 occurrence(s) of Rd; wherein the asterisk mark represents the point of attachment with L_1.

In one embodiment, L_2 is a bond,  ,  ; wherein the asterisk mark indicates the point of attachment towards L_1.

In one embodiment, X is a bond, -NH-, -N(CH_3)- or -O-.

In one embodiment, X is a bond.

In one embodiment, X is -NH-.

In one embodiment, X is -N(CH_3)-.

In one embodiment, X is -O-.

In one embodiment, R_2 at each occurrence, independently, is hydrogen, halogen or halo(C_1-C_6)alkyl.

In one embodiment, R_2 is hydrogen or fluorine.

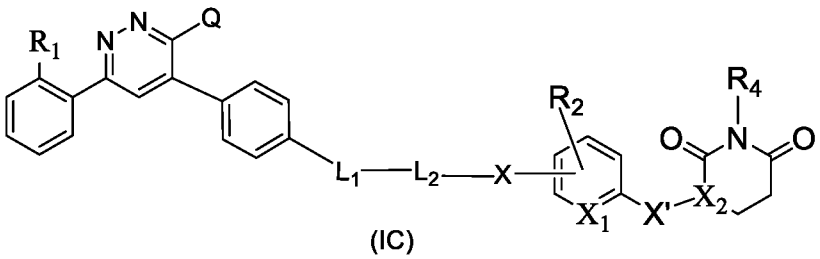
In one embodiment, R_3 and R_3' are hydrogen.

In one embodiment, R_3 and R_3' together represent an oxo group.

In one embodiment, R_4 is hydrogen or (C_1-C_6)alkyl.

In one embodiment, R_4 is hydrogen or methyl.

In one embodiment, the present disclosure provides a compound of formula (IC):



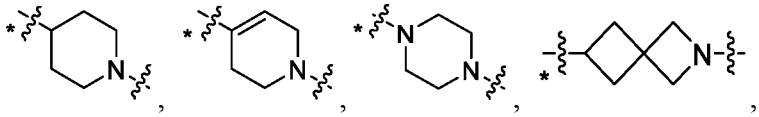
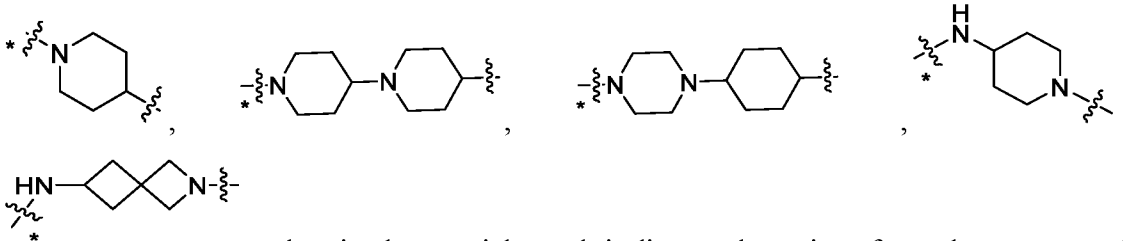
(IC)

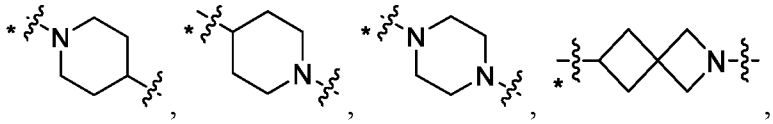
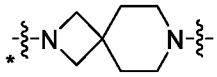
or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof, wherein R_1, Q, L_1, L_2, X, R_2, R_4, X_1, X_2, and X' are as described in classes and subclasses herein, both singly and in combination.

In one embodiment, R_1 at each occurrence independently is hydroxy or halo(C_1-C_6)alkyl.

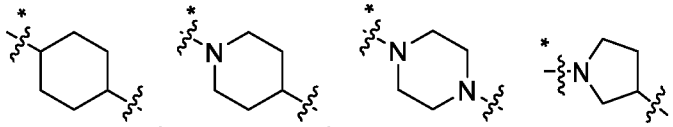
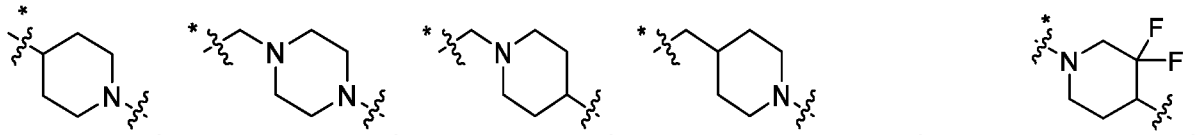
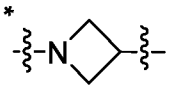
In one embodiment, Q is hydroxy, amino or (C_1-C_6)alkylamino.

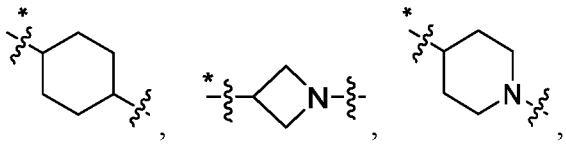
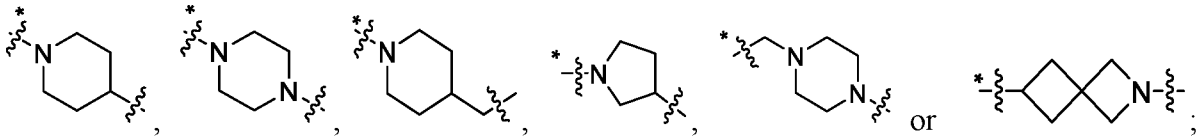
In one embodiment, L_1 is -(6- to 10-membered heterocycloalkylenyl)-, *-(6- to 10-membered heterocycloalkylenyl)-(6- to 8-membered cycloalkylenyl)-, -(3- to 12-membered heterocycloalkylenyl)-(6- to 8-membered heterocycloalkylenyl)-, or *-N(Rx)-(6- to 10-membered heterocycloalkylenyl)-; wherein the heterocycloalkylenyl and cycloalkylenyl independently is unsubstituted or substituted with 1, 2 or 3 occurrence(s) of Rd; wherein the asterisk mark represents the point of attachment with ring A.

In one embodiment, L_1 is  ,  , or ; wherein the asterisk mark indicates the point of attachment towards ring A.

In one embodiment, L_1 is  ,  or  ; wherein the asterisk mark indicates the point of attachment towards ring A.

In one embodiment, wherein L_2 is a bond, -(4- to 8-membered cycloalkylenyl)-, -(4- to 8-membered heterocycloalkylenyl), *-$(CRxRy)_n$-(4- to 8-membered cycloalkylenyl)-, *-$(CRxRy)_n$-(4- to 8-membered heterocycloalkylenyl)-, *-(4- to 8-membered heterocycloalkylenyl)-$(CRxRy)_n$-; wherein the cycloalkylenyl and heterocycloalkylenyl, at each occurrence, independently is unsubstituted or substituted with 1, 2 or 3 occurrence(s) of Rd; wherein the asterisk mark represents the point of attachment with L_1.

In one embodiment, L_2 is a bond,  ,  or  ; wherein the asterisk mark indicates the point of attachment towards L_1.

In one embodiment, L_2 is a bond,  ,  or ; wherein the asterisk mark indicates the point of attachment towards L_1.

In one embodiment, X' is a bond, -NH- or -O-.

In one embodiment, X' is a bond.

In one embodiment, X' is -NH-.

In one embodiment, X', is -N(CH_3)-

In one embodiment, X' is -O-.

In one embodiment, X_1 and X_2 are CH.

In one embodiment, X_1 and X_2 are N.

In one embodiment, R_2 is hydrogen, halogen, or halo(C_1-C_6)alkyl.

In one embodiment, R_2 is hydrogen, fluorine, or -CF_3.

In one embodiment, R_2 is hydrogen or fluorine.

In one embodiment, R_2 is hydrogen.

In one embodiment, R_2 is fluorine.

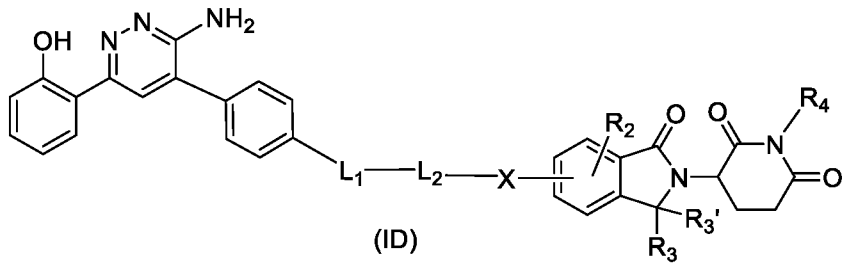
In one embodiment, R_2 is -CF_3.

In one embodiment, R_4 is hydrogen or (C_1-C_4)alkyl.

In one embodiment, R_4 is hydrogen or methyl.

In one embodiment, R_4 is hydrogen.

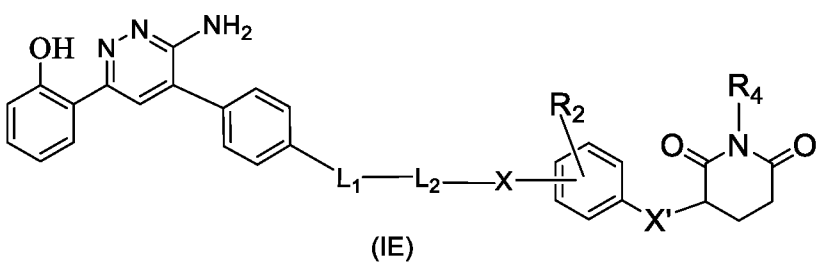
In one embodiment, the present disclosure provides a compound of formula (ID):



(ID)

or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof, wherein L_1, L_2, X, R_2, R_3, R_3' and R_4 are as described in classes and subclasses herein, both singly and in combination.

In one embodiment, the present disclosure provides a compound of formula (IE):



(IE)

or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof, wherein L_1, L_2, X, R_2, and R_4 are as described in classes and subclasses herein, both singly and in combination.

In one embodiment, the present disclosure provides compound of formula (I), wherein

R_1 is hydroxy or halo(C_1-C_6)alkyl;

Q is hydroxy, amino or (C_1-C_6)alkylamino;

A is phenylenyl; wherein phenylenyl is unsubstituted or substituted with 1 or 2 occurrence(s) of Ra;

L_1 is -(3- to 12-membered heterocycloalkylenyl)- *-(3- to 12-membered heterocycloalkylenyl)-(3- to 8-membered cycloalkylenyl)-, or *-N(Rx)-(3- to 12-membered heterocycloalkylenyl)-; wherein the heterocycloalkylenyl and cycloalkylenyl independently is unsubstituted or substituted with 1, 2 or 3 occurrence(s) of Rd; wherein the asterisk mark represents the point of attachment with ring A;

L_2 is a bond, -(3- to 8-membered cycloalkylenyl)-, -(3- to 10-membered heterocycloalkylenyl)-, *-$(CRxRy)_n$-(3- to 8-membered cycloalkylenyl)- or *-$(CRxRy)_n$-(3- to 10-membered heterocycloalkylenyl)-; wherein the cycloalkylenyl and heterocycloalkylenyl independently is substituted with 1, 2 or 3 occurrences of Rd; wherein the asterisk mark represents the point of attachment with L_1;

Rd is halogen;

Rx and Ry, independently, is hydrogen or (C_1-C_6)alkyl;

R_3 and $R_{3'}$ together represent an oxo group; and

R_2 is hydrogen, halogen, or halo(C_1-C_6)alkyl.

In one embodiment, the present disclosure provides compound of formula (I), wherein

R_1 is -OH or -CF_3;

Q is amino;

A is phenylenyl;

L_1 is -(6- to 10-membered heterocycloalkylenyl)-, *-(6- to 10-membered heterocycloalkylenyl)-(6- to 8-membered cycloalkylenyl)-, -(3- to 12-membered heterocycloalkylenyl)-(6- to 8-membered heterocycloalkylenyl)-, or *-N(Rx)-(6- to 10-

membered heterocycloalkylenyl)-; wherein the heterocycloalkylenyl and cycloalkylenyl independently is unsubstituted or substituted with 1, 2 or 3 occurrence(s) of Rd; wherein the asterisk mark represents the point of attachment with ring A;

L_2 is a bond, -(4- to 8-membered cycloalkylenyl)-, -(4- to 8-membered heterocycloalkylenyl), *-$(CRxRy)_n$-(4- to 8-membered cycloalkylenyl)-, *-$(CRxRy)_n$-(4- to 8-membered heterocycloalkylenyl)-, *-(4- to 8-membered heterocycloalkylenyl)-$(CRxRy)_n$-; wherein the cycloalkylenyl and heterocycloalkylenyl, at each occurrence, independently is unsubstituted or substituted with 1, 2 or 3 occurrence(s) of Rd; wherein the asterisk mark represents the point of attachment with L_1;

Rx and Ry are hydrogen;

Rd is fluorine;

X and X', independently, is a bond, -NH;

X_1 and X_2 are -CH-; and

R_3 and $R_{3'}$ together represent an oxo group.

PHARMACEUTICAL COMPOSITIONS

In one embodiment, the present disclosure provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof.

In another embodiment, the present disclosure provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof, and at least one pharmaceutically acceptable carrier or pharmaceutically acceptable excipients.

In another embodiment, the present disclosure provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof, and a pharmaceutically acceptable carrier or an excipient.

In one embodiment, the pharmaceutically acceptable excipients (such as a carrier or a diluent) or be diluted by a carrier or enclosed within a carrier which can be in the form of a capsule, sachet, paper, or other container.

In one embodiment, Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and

elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, com, germ, olive, castor and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring and perfuming agents.

Injectable preparations, for example, sterile injectable aqueous, or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

In order to prolong the effect of a drug, it is often desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this application with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

Solid compositions of a similar type may also be employed as fillers in soft and hard filled gelatine capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

The active compounds can also be in micro-encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, draggers, capsules, pills and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, including but not limited to tableting lubricants and other tableting aids such a magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents.

Dosage forms for topical or transdermal administration of a compound of this application include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulation, ear drops, eye ointments, powders and solutions are also contemplated as being within the scope of this application.

The ointments, pastes, creams and gels may contain, in addition to an active compound of this application, excipients such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

Powders and sprays can contain, in addition to the compounds of this application, excipients such as lactose, talc, silicic acid, aluminium hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants such as chlorofluorohydrocarbons.

Transdermal patches have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by dissolving or dispensing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

Administration of the disclosed compounds and pharmaceutical compositions can be accomplished via any mode of administration for therapeutic agents. These modes include systemic or local administration such as oral, nasal, parenteral, intravenous, transdermal, subcutaneous, vaginal, buccal, rectal or topical administration modes.

Depending on the intended mode of administration, the disclosed compounds or pharmaceutical compositions can be in solid, semi-solid or liquid dosage form, such as, for example, injectables, tablets, suppositories, pills, time-release capsules, elixirs, tinctures, emulsions, syrups, powders, liquids, suspensions, or the like, sometimes in unit dosages and consistent with conventional pharmaceutical practices. Likewise, they can also be administered in intravenous (both bolus and infusion), intraperitoneal, subcutaneous or intramuscular form and all using forms well known to those skilled in the pharmaceutical arts.

Illustrative pharmaceutical compositions are tablets and gelatine capsules comprising one or more compounds of the present disclosure and a pharmaceutically acceptable carrier, such as, but not limited to, a) a diluent, e.g., purified water, triglyceride oils, such as hydrogenated or partially hydrogenated vegetable oil, or mixtures thereof, corn oil, olive oil, sunflower oil, safflower oil, fish oils, such as EPA or DHA, or their esters or triglycerides or mixtures thereof, omega-3 fatty acids or derivatives thereof, lactose, dextrose, sucrose, mannitol, sorbitol, cellulose, sodium, saccharin, glucose and/or glycine; b) a lubricant, e.g., silica, talcum, stearic acid, its magnesium or calcium salt, sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and/or polyethylene glycol; for tablets also; c) a binder, e.g., magnesium aluminium silicate, starch paste, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, magnesium carbonate, natural sugars such as glucose or beta- lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, waxes and/or polyvinylpyrrolidone, if desired; d) a disintegrant, e.g., starches, agar, methyl cellulose, bentonite, xanthan gum, alginic acid or its sodium salt, or effervescent mixtures; e) absorbent, colorant, flavorant and sweetener; f) an emulsifier or dispersing agent, such as Tween 80, Labrasol, HPMC, DOSS, caproyl 909, labrafac, labrafil, peceol, transcutol, capmul MCM, capmul PG-12, captex 355, gelucire, vitamin E TGPS or other acceptable emulsifier; and/or g) an agent that enhances absorption of the compound such as cyclodextrin, hydroxypropyl-cyclodextrin, PEG400, PEG200.

Liquid, particularly injectable, compositions can, for example, be prepared by dissolution, dispersion, etc. For example, one or more disclosed compound is dissolved in or mixed with a pharmaceutically acceptable solvent such as, for example, water, saline, aqueous dextrose, glycerol, ethanol and the like, to thereby form an injectable isotonic solution or suspension. Proteins such as albumin, chylomicron particles, or serum proteins can be used to solubilize the disclosed compounds.

One or more disclosed compounds or compositions can be delivered by parental administration. The parental injectable administration is generally used for subcutaneous, intramuscular or intravenous injections and infusions. Injectables can be prepared in conventional forms, either as liquid solutions or suspensions or solid forms suitable for dissolving in liquid prior to injection.

In one embodiment, the present disclosure provides a pharmaceutical composition comprising a compound of formula (I), for use in degrading a target protein in a subject wherein the target protein is SMARCA2 and/or SMARCA4.

In one embodiment, the subject is afflicted with a disease or disorder dependent upon SMARCA2 and/or SMARCA4.

In one embodiment, the subject is afflicted with a disease or disorder dependent upon SMARCA2 and/or SMARCA4, wherein the disease or disorder is cancer.

In one embodiment, the present disclosure provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or a stereoisomer thereof, for use in treating or preventing cancers selected from the group consisting of hematologic cancers, lung cancer, non-small cell lung cancer, acoustic neuroma, acute leukemia, acute lymphocytic leukemia, acute myelocytic leukemia, adenocarcinoma, angiosarcoma, astrocytoma, myelomonocytic leukemia, promyelocytic leukemia, acute T-cell leukemia, basal cell carcinoma, bile duct carcinoma, bladder cancer, brain cancer, breast cancer, bronchogenic carcinoma, cervical cancer, chondrosarcoma, chordoma, choriocarcinoma, chronic leukemia, chronic lymphocytic leukemia, chronic myelocytic leukemia, granulocytic leukemia, chronic myelogenous leukemia, colon cancer, colorectal cancer, craniopharyngioma, cystadenocarcinoma, diffuse large B-cell lymphoma, dysproliferative changes, dysplasias, metaplasias, embryonal carcinoma, endometrial cancer, endotheliosarcoma, ependymoma, epithelial carcinoma, erythroleukemia, esophageal cancer, estrogen-receptor positive breast cancer, essential thrombocythemia, Ewing's tumor, fibrosarcoma, follicular lymphoma, germ cell testicular cancer, glioma, glioblastoma, gliosarcoma, heavy chain disease, head and neck cancer, hemangioblastoma, hepatoma, hepatocellular cancer, hormone insensitive prostate cancer, leiomyosarcoma, leukemia, liposarcoma, liver cancer, lymphagioendotheliosarcoma, lymphangiosarcoma, lymphoblastic leukemia, lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, Burkitt's lymphoma, malignancies and hyperproliferative disorders of the bladder, breast, colon, lung, ovaries,

pancreas, prostate, skin and uterus, lymphoid malignancies of T-cell or B-cell origin, medullary carcinoma, medulloblastoma, melanoma, meningioma, mesothelioma, multiple myeloma, myelogenous leukemia, myeloma, myxosarcoma, neuroblastoma, NUT midline carcinoma (NMC), oligodendroglioma, oral cancer, osteogenic sarcoma, ovarian cancer, pancreatic cancer, papillary adenocarcinomas, papillary carcinoma, pinealoma, polycythemia vera, prostate cancer, rectal cancer, renal cell carcinoma, retinoblastoma, malignant rhabdoid tumor (MRT), rhabdomyosarcoma, sarcoma, sebaceous gland carcinoma, seminoma, skin cancer, small cell lung carcinoma, solid tumors, carcinomas, sarcomas, small cell lung cancer, stomach cancer, squamous cell carcinoma, synovioma, sweat gland carcinoma, thyroid cancer, Waldenstrom's macroglobulinemia, testicular tumors, uterine cancer or Wilms' tumor.

In one embodiment, the present disclosure provides a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof for treating diseases or conditions or disorders that are dependent upon or mediated by SMARCA2 and/or SMARCA4.

In one embodiment, the present disclosure provides a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof for treating a disease that has altered SMARCA2/4 including mutations and overexpression.

In one embodiment, the present disclosure provides a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof for treating a disease wherein degradation of SMARCA2/4 proteins provides a benefit, e.g., cancer.

In one embodiment, the present disclosure provides a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof for treating a disease dependent upon altered activity of SWI/SNF complex with or without chromatic remodeling activities.

METHODS AND/OR USES:

In one embodiment, the present disclosure provides, a method of degrading a target protein in a subject comprising administering to a subject in need thereof, a therapeutically effective amount of the compound of formula (I) or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof.

In one embodiment, the target protein is SMARCA2 and/or SMARCA4.

In one embodiment, the present disclosure provides, a method of treating or delaying progression of a disease or disorder dependent upon SMARCA2 and/or SMARCA4 in a subject comprising administering to the subject, in need thereof, a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof.

In one embodiment, the present disclosure provides a method for treating diseases or disorders dependent upon at least one of SMARCA2 and SMARCA4 in a subject comprising administering to the subject in need thereof a therapeutically effective amount of a compound formula (I) or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof.

In one embodiment, diseases or disorders that are dependent upon SMARCA2 and/or SMARCA4, is cancer.

In one embodiment, the present disclosure provides a method of inhibiting tumor growth in a subject afflicted with cancer comprising administering a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof to the subject, in need thereof.

In any one of the preceding embodiments, cancer is selected from hematologic cancers, lung cancer, non-small cell lung cancer, acoustic neuroma, acute leukemia, acute lymphocytic leukemia, acute myelocytic leukemia, adenocarcinoma, angiosarcoma, astrocytoma, myelomonocytic leukemia, promyelocytic leukemia, acute T-cell leukemia, basal cell carcinoma, bile duct carcinoma, bladder cancer, brain cancer, breast cancer, bronchogenic carcinoma, cervical cancer, chondrosarcoma, chordoma, choriocarcinoma, chronic leukemia, chronic lymphocytic leukemia, chronic myelocytic leukemia, granulocytic leukemia, chronic myelogenous leukemia, colon cancer, colorectal cancer, craniopharyngioma, cystadenocarcinoma, diffuse large B-cell lymphoma, dysproliferative changes, dysplasias, metaplasias, embryonal carcinoma, endometrial cancer, endotheliosarcoma, ependymoma, epithelial carcinoma, erythroleukemia, esophageal cancer, estrogen-receptor positive breast cancer, essential thrombocythemia, Ewing's tumor, fibrosarcoma, follicular lymphoma, germ cell testicular cancer, glioma, glioblastoma, gliosarcoma, heavy chain disease, head and neck cancer, hemangioblastoma, hepatoma, hepatocellular cancer, hormone insensitive prostate cancer, leiomyosarcoma, leukemia, liposarcoma, liver cancer, lymphagioendotheliosarcoma, lymphangiosarcoma, lymphoblastic leukemia, lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, Burkitt's lymphoma, malignancies and hyperproliferative disorders of

the bladder, breast, colon, lung, ovaries, pancreas, prostate, skin and uterus, lymphoid malignancies of T-cell or B-cell origin, medullary carcinoma, medulloblastoma, melanoma, meningioma, mesothelioma, multiple myeloma, myelogenous leukemia, myeloma, myxosarcoma, neuroblastoma, NUT midline carcinoma (NMC), oligodendroglioma, oral cancer, osteogenic sarcoma, ovarian cancer, pancreatic cancer, papillary adenocarcinomas, papillary carcinoma, pinealoma, polycythemia vera, prostate cancer, rectal cancer, renal cell carcinoma, retinoblastoma, malignant rhabdoid tumor (MRT), rhabdomyosarcoma, sarcoma, sebaceous gland carcinoma, seminoma, skin cancer, small cell lung carcinoma, solid tumors, carcinomas, sarcomas, small cell lung cancer, stomach cancer, squamous cell carcinoma, synovioma, sweat gland carcinoma, thyroid cancer, Waldenstrom's macroglobulinemia, testicular tumors, uterine cancer or Wilms' tumor.

In one embodiment, the cancer dependent upon SMARCA2 and/or SMARCA4 is lung cancer such as NSCLC, i.e., non-small cell lung cancer.

In one embodiment, the cancer dependent upon SMARCA2 and/or SMARCA4 is melanoma.

In one embodiment, the present disclosure provides, a compound of formula (I) or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof, for use as a medicament.

In one embodiment, the present disclosure provides, a compound of formula (I) or a pharmaceutical acceptable salt or a stereoisomer or a tautomer thereof, for use in the treatment of a disease or disorder dependent upon SMARCA2 and/or SMARCA4.

In one embodiment, a disease or disorder dependent upon SMARCA2 and/or SMARCA4 is cancer.

In one embodiment, the present disclosure provides the use of a compound of formula (I) or a pharmaceutical acceptable salt or a stereoisomer or a tautomer thereof, in the manufacture of a medicament for the treatment of a disease or disorder dependent upon SMARCA2 and/or SMARCA4.

In one embodiment, the present disclosure provides a compound represented by formula (I) or a pharmaceutical acceptable salt or a stereoisomer or a tautomer thereof, for use in the treatment of a disease or disorder dependent upon SMARCA2 and/or SMARCA4, wherein the disease or disorder is cancer.

In one embodiment, the disease or disorder is cancer selected from hematologic cancers, lung cancer, non-small cell lung cancer, acoustic neuroma, acute leukemia, acute lymphocytic leukemia, acute myelocytic leukemia, adenocarcinoma, angiosarcoma, astrocytoma, myelomonocytic leukemia, promyelocytic leukemia, acute T-cell leukemia, basal cell carcinoma, bile duct carcinoma, bladder cancer, brain cancer, breast cancer, bronchogenic carcinoma, cervical cancer, chondrosarcoma, chordoma, choriocarcinoma, chronic leukemia, chronic lymphocytic leukemia, chronic myelocytic leukemia, granulocytic leukemia, chronic myelogenous leukemia, colon cancer, colorectal cancer, craniopharyngioma, cystadenocarcinoma, diffuse large B-cell lymphoma, dysproliferative changes, dysplasias, metaplasias, embryonal carcinoma, endometrial cancer, endotheliosarcoma, ependymoma, epithelial carcinoma, erythroleukemia, esophageal cancer, estrogen-receptor positive breast cancer, essential thrombocythemia, Ewing's tumor, fibrosarcoma, follicular lymphoma, germ cell testicular cancer, glioma, glioblastoma, gliosarcoma, heavy chain disease, head and neck cancer, hemangioblastoma, hepatoma, hepatocellular cancer, hormone insensitive prostate cancer, leiomyosarcoma, leukemia, liposarcoma, liver cancer, lymphagioendotheliosarcoma, lymphangiosarcoma, lymphoblastic leukemia, lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, Burkitt's lymphoma, malignancies and hyperproliferative disorders of the bladder, breast, colon, lung, ovaries, pancreas, prostate, skin and uterus, lymphoid malignancies of T-cell or B-cell origin, medullary carcinoma, medulloblastoma, melanoma, meningioma, mesothelioma, multiple myeloma, myelogenous leukemia, myeloma, myxosarcoma, neuroblastoma, NUT midline carcinoma (NMC), oligodendroglioma, oral cancer, osteogenic sarcoma, ovarian cancer, pancreatic cancer, papillary adenocarcinomas, papillary carcinoma, pinealoma, polycythemia vera, prostate cancer, rectal cancer, renal cell carcinoma, retinoblastoma, malignant rhabdoid tumor (MRT), rhabdomyosarcoma, sarcoma, sebaceous gland carcinoma, seminoma, skin cancer, small cell lung carcinoma, solid tumors, carcinomas, sarcomas, small cell lung cancer, stomach cancer, squamous cell carcinoma, synovioma, sweat gland carcinoma, thyroid cancer, Waldenstrom's macroglobulinemia, testicular tumors, uterine cancer or Wilms' tumor.

In one embodiment, the present disclosure provides, a preparation of compound of formula (I).

Definitions

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in art to which the subject matter herein

belongs. As used in the specification and the appended claims, unless specified to the contrary, the following terms have the meaning indicated in order to facilitate the understanding of the present invention.

The singular forms "a", "an" and "the" encompass plural references unless the context clearly indicates otherwise.

As used herein, the terms "optional" or "optionally" mean that the subsequently described event or circumstance may occur or may not occur, and that the description includes instances where the event or circumstance occurs as well as instances in which it does not. For example, "optionally substituted alkyl" refers to an event or circumstance where the alkyl is substituted as well as the event or circumstance where the alkyl is not substituted.

The term "substituted" refers to moieties having substituents replacing hydrogen on one or more carbons of the backbone. It will be understood that "substitution" or "substituted with" includes the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent and that the substitution results in a stable compound, e.g., which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc. As used herein, the term "substituted" is contemplated to include all permissible substituents of organic compounds. In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and non-aromatic substituents of organic compounds. The permissible substituents can be one or more and the same or different for appropriate organic compounds. For purposes of this invention, the heteroatoms such as nitrogen may have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valences of the heteroatoms. Substituents can include any substituents described herein, for example, a halogen, a hydroxyl, a carbonyl (such as a carboxyl, an alkoxycarbonyl, a formyl or an acyl), a thiocarbonyl (such as a thioester, a thioacetate or a thioformate), an alkoxyl, an oxo, a phosphoryl, a phosphate, a phosphonate, a phosphinate, an amino, an amido, an amidine, an imine, a cyano, a nitro, an azido, a sulfhydryl, an alkylthio, a sulfate, a sulfonate, a sulfamoyl, a sulfonamido, a sulfonyl, a heteroaryl, a heterocyclyl, an aralkyl or an aromatic or heteroaromatic moiety. It will be understood by those skilled in the art that substituents can themselves be substituted, if appropriate.

As used herein, the term "alkyl" refers to saturated aliphatic groups, including but not limited to C_1-C_{10} straight-chain alkyl groups or C_3-C_{10} branched-chain alkyl groups.

Preferably, "alkyl" group refers to C_1-C_6 straight-chain alkyl groups or C_3-C_6 branched-chain alkyl groups. In one embodiment, the "alkyl" group refers to C_1-C_4 straight-chain alkyl groups. Examples of "alkyl" include, but are not limited to, methyl, ethyl, 1-propyl, 2-propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, 1-pentyl, 2-pentyl, 3-pentyl, neo-pentyl, 1-hexyl, 2-hexyl, 3-hexyl, 1-heptyl, 2-heptyl, 3-heptyl, 4-heptyl, 1-octyl, 2-octyl, 3-octyl and 4-octyl. Accordingly, examples of "alkylenyl" include, but are not limited to, $-CH_2-$, $-CH_2CH_2-$, $-CH(CH_3)CH_2-$, $-CH_2CH_2CH_2CH_2-$, $-CH(CH_3)CH_2CH_2CH_2-$ and $-CH_2CH(CH_3)CH_2CH_2-$, The "alkyl" group may be optionally substituted.

The term "halo" is used herein interchangeably with the term "halogen" to mean F, Cl, Br or I atoms.

As used herein, the term "amino" refers to an $-NH_2$ group.

As used herein, the term "alkylamino" refers to an amino group substituted with one or more "alkyl" group, wherein the alkyl group and amino group is as defined above. Examples of "alkylamino" groups include but are not limited to $-NHCH_3$, $-NHCH_2CH_3$, $-N(CH_3)_2$, $-N(CH_3)(CH_2CH_3)$ and the like.

As used herein, the term "haloalkyl" refers to alkyl substituted with one or more halogen atoms, wherein the halo and alkyl groups are as defined above. In one embodiment, haloalkyl contains (C_1-C_6)alkyl and preferably (C_1-C_4)alkyl. Examples of "haloalkyl" include but are not limited to fluoromethyl, difluoromethyl, chloromethyl, trifluoromethyl, and 2,2,2-trifluoroethyl.

As used herein, the term "hydroxyalkyl" refers to an alkyl group, as defined above, wherein one or more of the alkyl group's hydrogen atoms have been replaced with hydroxyl group. In one embodiment, hydroxyalkyl contains (C_1-C_6)alkyl and preferably (C_1-C_4)alkyl. Examples of hydroxyalkyl moieties include but are not limited to $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH_2CH(OH)CH_2OH$, $-CH_2CH(OH)CH_3$, $-CH(CH_3)CH_2OH$.

As used herein, the term "cycloalkylenyl" refers to a divalent cycloalkyl group as defined herein. The term "cycloalkyl" means C_3-C_{10} saturated cyclic hydrocarbon ring. A cycloalkyl may be a single ring, which typically contains from 3 to 7 carbon ring atoms. Examples of single ring cycloalkyls include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. A cycloalkyl may alternatively be polycyclic or contain more than one ring. Examples of polycyclic cycloalkyls include bridged, fused and

spirocyclic carbocyclyls. Accordingly, examples of 'cycloalkylenyl' include, but not limited to, cyclopropylenyl, cyclobutylenyl, cyclopentylenyl, cyclohexylenyl and cycloheptylenyl.

As used herein, the term "heterocycloalkylenyl" refers to a divalent heterocycloalkyl group as defined herein. The term "heterocycloalkyl" refers to a non-aromatic, saturated or partially saturated, bridged bicyclic, spirocyclic, monocyclic or polycyclic ring system of 3 to 15 member, unless the ring size is specifically mentioned, having at least one heteroatom or heterogroup selected from O, N, S, S(O), $S(O)_2$, NH or C(O) with the remaining ring atoms being independently selected from the group consisting of carbon, oxygen, nitrogen and sulfur. The term "heterocycloalkyl" or "heterocyclyl" also refers to the bridged bicyclic ring system having at least one heteroatom or hetero group selected from O, N, S, S(O), $S(O)_2$, NH and C(O). Examples of "heterocycloalkyl" include, but not limited to, azetidinyl, oxetanyl, imidazolidinyl, pyrrolidinyl, oxazolidinyl, thiazolidinyl, pyrazolidinyl, tetrahydrofuranyl, piperidinyl, dihydropyridinyl, piperazinyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl, 1,4-dioxanyl, dioxidothiomorpholinyl, oxapiperazinyl, oxapiperidinyl, tetrahydrofuryl, tetrahydropyranyl, tetrahydrothiophenyl, dihydropyranyl, indolinyl, indolinylmethyl, isoindolinyl, oxoisoindolinyl, dioxoisoindolinyl, aza-bicyclooctanyl, diazabicyclooctanyl, azocinyl, chromanyl, isochromanyl, xanthenyl and 2-oxa-6-azaspiro[3.3]heptanyl. Accordingly, examples of 'heterocycloalkylenyl' include, but not limited to, azetidinylenyl, oxetanylenyl, pyrrolidinylenyl, piperidinylenyl and piperazinylenyl. Attachment of a heterocyclyl substituent can occur via either a carbon atom or a heteroatom.

A heterocyclyl group can be optionally substituted with one or more suitable groups by one or more aforesaid groups. Preferably "heterocycloalkyl" refers to 5- to 6-membered ring (unless the ring size is specifically mentioned) selected from the group consisting of imidazolidinyl, pyrrolidinyl, oxazolidinyl, thiazolidinyl, pyrazolidinyl, tetrahydrofuranyl, piperidinyl, piperazinyl, tetrahydropyranyl, morpholinyl and thiomorpholinyl. All heterocyclyl are optionally substituted by one or more aforesaid groups.

As used herein, the term "heterocycloalkenylenyl" refers to a divalent heterocycloalkenyl group as defined herein. The term "heterocycloalkenyl" alone or in combination with other term(s) means a partially unsaturated ring system containing a total of 4 to 14 ring atoms, unless the ring size is specifically mentioned. At least one of the ring atoms is a heteroatom (i.e., O, N or S), with the remaining ring atoms/groups being independently selected from C, N, O or S. A heterocycloalkenyl may be a single-ring (monocyclic) or multiple rings (bicyclic, tricyclic or polycyclic) fused together or linked covalently. Preferably, "heterocycloalkenyl" is a 4- to

7-membered ring, unless the ring size is specifically mentioned. The rings may contain from 1 to 4 additional heteroatoms selected from N, O and S, wherein the N atom is optionally quarternized. Any suitable ring position of the heterocycloalkenyl moiety may be covalently linked to the defined chemical structure. Examples of "heterocycloalkenyl" include but not limited to pyrroline, pyrazoline, tetrahydropyridine, tetrahydropyrazine, tetrahydropyrimidine, tetrahydropyridazine tetrahydro azepine and the like. Heterocycloalkenyl group may be optionally further substituted.

As used herein, the term "heteroarylenyl" refers to a divalent heteroaryl group as defined herein. The term "heteroaryl" alone or in combination with other term(s) means a completely unsaturated ring system containing a total of 5 to 14 ring atoms, unless the ring size is specifically mentioned. At least one of the ring atoms is a heteroatom (i.e., O, N or S), with the remaining ring atoms/groups being independently selected from C, N, O or S. A heteroaryl may be a single-ring (monocyclic) or multiple rings (bicyclic, tricyclic or polycyclic) fused together or linked covalently. Preferably, "heteroaryl" is a 5- to 6-membered ring, unless the ring size is specifically mentioned. The rings may contain from 1 to 4 additional heteroatoms selected from N, O and S, wherein the N atom is optionally quarternized. Any suitable ring position of the heteroaryl moiety may be covalently linked to the defined chemical structure. Examples of "heteroaryl" include but not limited to furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, cinnolinyl, isoxazolyl, thiazolyl, isothiazolyl, 1H-tetrazolyl, oxadiazolyl, triazolyl, pyridyl (pyridinyl), 3-fluoropyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzofuranyl, benzothienyl, benzotriazinyl, phthalazinyl, thianthrene, dibenzofuranyl, dibenzothienyl, benzimidazolyl, indolyl, isoindolyl, indazolyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, purinyl, pteridinyl, 9H-carbazolyl, α-carbolinyl, indolizinyl, benzoisothiazolyl, benzoxazolyl, pyrrolopyridyl, furopyridinyl, purinyl, benzothiadiazolyl, benzooxadiazolyl, benzotriazolyl, benzotriadiazolyl, carbazolyl, dibenzothienyl, acridinyl and the like. Accordingly, examples of 'heteroarylenyl' include, but not limited to, furanylenyl, thienylenyl, pyrrolylenyl, pyrazolylenyl, imidazolylenyl, oxazolylenyl, isoxazolylenyl, thiazolylenyl, isothiazolylenyl, 1H-tetrazolylenyl, oxadiazolylenyl, triazolylenyl, pyridylenyl (pyridinylenyl), pyrimidinylenyl, pyrazinylenyl, pyridazinylenyl, 1,2,3-triazinylenyl, 1,2,4-triazinylenyl and 1,3,5-triazinylenyl. Heteroaryl group may be optionally further substituted.

As used herein, the term "amino" refers to an $-NH_2$ group.

As used herein, the term “hydroxy” or “hydroxyl” alone or in combination with other term(s) means –OH.

As used herein, the term “oxo” refers to =O group.

As used herein, the term “alkoxy” refers to the group -O-alkyl, where alkyl groups are as defined above. Exemplary C_1-C_{10} alkoxy groups include but are not limited to methoxy, ethoxy, n-propoxy, n-butoxy or t-butoxy. An alkoxy group can be optionally substituted with one or more suitable groups.

The term “aryl”, as employed herein as such or as part of another group, refers to a monocyclic, bicyclic or polycyclic aromatic hydrocarbon ring system of 6 to 14 carbon atoms. Examples of aryl groups include, but are not limited to phenyl, naphthyl, biphenyl, anthryl, biphenylenyl and acenaphthyl. Preferred aryl group is phenyl.

The term “heteroatom” as used herein designates a sulfur, nitrogen or oxygen atom.

As used herein, the term 'compound(s)' comprise(s) the compound(s) disclosed in the present invention.

The term “salt/salts” refers to the salts derived from appropriate bases include alkali metal (e.g., sodium and potassium), alkaline earth metal (e.g., magnesium), ammonium and $N^+(C_{1-4}$ alkyl$)_4$ salts.

As used herein, the term “comprise” or “comprising” is generally used in the sense of include, that is to say permitting the presence of one or more features or components.

As used herein, the term “or” means “and/or” unless stated otherwise.

As used herein, the term “including” as well as other forms, such as “include”, “includes” and “included” is not limiting.

As used herein, the term “composition” is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

As used herein, the term “pharmaceutical composition” refers to a composition(s) containing a therapeutically effective amount of at least one compound of formula (I) or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier.

The pharmaceutical composition(s) usually contain(s) about 1% to 99%, for example, about 5% to 75% or from about 10% to about 30% by weight of the compound of formula (I)

or (II) or pharmaceutically acceptable salts thereof. The amount of the compound of formula (I) or pharmaceutically acceptable salts thereof in the pharmaceutical composition(s) can range from about 1 mg to about 1000 mg or from about 2.5 mg to about 500 mg or from about 5 mg to about 250 mg or in any range falling within the broader range of 1 mg to 1000 mg or higher or lower than the aforementioned range.

The term "tautomer" refers to compounds in which hydrogen atoms are transposed to other parts of the molecules and the chemical bonds between the atoms of the molecules are consequently rearranged. Compounds of the present invention, free form and salts thereof, may exist in multiple tautomeric forms. It is understood that all tautomeric forms, insofar as they may exist, are included within the invention. For example, pyridine or pyridyl can be optionally substituted by oxo to form a respective pyridone or pyridon-yl and may include its tautomeric form such as a respective hydroxy-pyridine or hydroxy-pyridyl, provided said tautomeric form may be obtainable.

As used herein, "pharmaceutically acceptable carrier, diluent or excipient" includes without limitation any adjuvant, carrier, excipient, glidant, sweetening agent, diluent, preservative, dye/colorant, flavor enhancer, surfactant, wetting agent, dispersing agent, suspending agent, stabilizer, isotonic agent, solvent, surfactant or emulsifier that has been approved by the United States Food and Drug Administration as being acceptable for use in humans or domestic animals.

The term "administer," "administering," or "administration" as used in this disclosure refers to either directly administering one or more disclosed compounds or a pharmaceutically acceptable salt of one or more disclosed compounds or a composition comprising one or more disclosed compounds to a subject or administering an analog of the compound or a pharmaceutically acceptable salt of the compound or composition to the subject, which can form an equivalent amount of active compound within the subject's body.

The term "carrier" as used in this disclosure, encompasses carriers, excipients and diluents and means a material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material, involved in carrying or transporting a pharmaceutical agent from one organ or portion of the body to another organ or portion of the body of a subject.

As used herein, the term "treat", "treating" and "treatment" refer to a method of alleviating or abrogating a disease and/or its attendant symptoms.

As used herein, the term “prevent”, “preventing” and “prevention” refer to a method of preventing the onset of a disease and/or its attendant symptoms or barring a subject from acquiring a disease. As used herein, “prevent”, “preventing” and “prevention” also include delaying the onset of a disease and/or its attendant symptoms and reducing a subject's risk of acquiring a disease.

As used herein, the term “subject” that may be interchangeable with ‘patient’, refers to an animal, preferably a mammal and most preferably a human.

As used herein, the term, “therapeutically effective amount” refers to an amount of a compound of formula (I) or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof; or a composition comprising the compound of formula (I) or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof, effective in producing the desired therapeutic response in a particular patient suffering from a diseases or disorder, in particular their use in diseases or disorder associated with cancer. Particularly, the term “therapeutically effective amount” includes the amount of the compound of formula (I) or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof, when administered, that induces a positive modification in the disease or disorder to be treated or is sufficient to prevent development of or alleviate to some extent, one or more of the symptoms of the disease or disorder being treated in a subject. In respect of the therapeutic amount of the compound, the amount of the compound used for the treatment of a subject is low enough to avoid undue or severe side effects, within the scope of sound medical judgment can also be considered. The therapeutically effective amount of the compound or composition will be varied with the particular condition being treated, the severity of the condition being treated or prevented, the duration of the treatment, the nature of concurrent therapy, the age and physical condition of the end user, the specific compound or composition employed the particular pharmaceutically acceptable carrier utilized.

The term “pharmaceutically acceptable salt” refers to a product obtained by reaction of the compound of the present invention with a suitable acid or a base. Pharmaceutically acceptable salts of the compounds of this invention include those derived from suitable inorganic bases such as Li, Na, K, Ca, Mg, Fe, Cu, Al, Zn and Mn salts; Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, isonicotinate, acetate, lactate, salicylate, citrate, tartrate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucaronate,

saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, 4-methylbenzenesulfonate or p-toluenesulfonate salts and the like. Certain compounds of the invention (compound of formula (I)) can form pharmaceutically acceptable salts with various organic bases such as lysine, arginine, guanidine, diethanolamine or metformin. Suitable base salts include, but are not limited to, aluminum, calcium, lithium, magnesium, potassium, sodium or zinc salts.

"Pharmaceutically acceptable" means that, which is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable and includes that which is acceptable for veterinary as well as human pharmaceutical use.

The present disclosure also provides methods for formulating the disclosed compounds as for pharmaceutical administration.

In a preferred embodiment, when such pharmaceutical compositions are for human administration, particularly for invasive routes of administration (i.e., routes, such as injection or implantation, that circumvent transport or diffusion through an epithelial barrier), the aqueous solution is pyrogen-free or substantially pyrogen-free. The excipients can be chosen, for example, to effect delayed release of an agent or to selectively target one or more cells, tissues or organs. The pharmaceutical composition can be in dosage unit form such as tablet, capsule (including sprinkle capsule and gelatin capsule), granule, lyophile for reconstitution, powder, solution, syrup, suppository, injection or the like. The composition can also be present in a transdermal delivery system, e.g., a skin patch. The composition can also be present in a solution suitable for topical administration, such as an eye drop.

The term "cancer" is used throughout the specification to refer to the pathological process that results in the formation and growth of a cancerous or malignant neoplasm, i.e., abnormal tissue that grows by cellular proliferation, often more rapidly than normal and continues to grow after the stimuli that initiated the new growth cease. Malignant neoplasms show partial or complete lack of structural organization and functional coordination with the normal tissue and most invade surrounding tissues, metastasize to several sites and are likely to recur after attempted removal and to cause the death of the patient unless adequately treated. As used herein, the term neoplasia is used to describe all cancerous disease states and embraces or encompasses the pathological process associated with malignant hematogenous, ascitic and solid tumors. Exemplary cancers which may be treated by the present compounds either alone

or in combination with at least one additional anti-cancer agent include squamous-cell carcinoma, basal cell carcinoma, adenocarcinoma, hepatocellular carcinomas, hematologic cancers and renal cell carcinomas, cancer of the bladder, bowel, breast, cervix, colon, esophagus, head, kidney, liver, lung, neck, ovary, pancreas, prostate and stomach; leukemias; benign and malignant lymphomas, particularly Burkitt's lymphoma and Non-Hodgkin's lymphoma; benign and malignant melanomas; myeloproliferative diseases; sarcomas, including Ewing's sarcoma, hemangiosarcoma, Kaposi's sarcoma, liposarcoma, myosarcomas, peripheral neuroepithelioma, synovial sarcoma, gliomas, astrocytomas, oligodendrogliomas, ependymomas, gliobastomas, neuroblastomas, ganglioneuromas, gangliogliomas, medulloblastomas, pineal cell tumors, meningiomas, meningeal sarcomas, neurofibromas and Schwannomas; bowel cancer, breast cancer, prostate cancer, cervical cancer, uterine cancer, lung cancer, ovarian cancer, testicular cancer, thyroid cancer, astrocytoma, esophageal cancer, pancreatic cancer, stomach cancer, liver cancer, colon cancer, melanoma; carcinosarcoma, Hodgkin's disease, Wilms' tumor and teratocarcinomas. Additional cancers which may be treated using compounds according to the present invention include, for example, T-lineage Acute lymphoblastic Leukemia (T-ALL), T- lineage lymphoblastic Lymphoma (T-LL), Peripheral T-cell lymphoma, Adult T-cell Leukemia, Pre-B ALL, Pre-B Lymphomas, Large B-cell Lymphoma, Burkitts Lymphoma, B-cell ALL, Philadelphia chromosome positive ALL and Philadelphia chromosome positive CML.

The term “stereoisomers” refers to any enantiomers, diastereoisomers or geometrical isomers of the compounds of formula (I), wherever they are chiral or when they bear one or more double bonds. When the compounds of the formula (I) and related formulae are chiral, they can exist in racemic or in optically active form. It should be understood that the invention encompasses all stereochemical isomeric forms, including diastereomeric, enantiomeric and epimeric forms, as well as *d*-Isomers and *l*-Isomers and mixtures thereof. Individual stereoisomers of compounds can be prepared synthetically from commercially available starting materials which contain chiral centres or by preparation of mixtures of enantiomeric products followed by separation such as conversion to a mixture of diastereomers followed by separation or recrystallization, chromatographic techniques, direct separation of enantiomers on chiral chromatographic columns or any other appropriate method known in the art. Starting compounds of particular stereochemistry are either commercially available or can be made and resolved by techniques known in the art. Additionally, the compounds of the present invention

may exist as geometric Isomers. The present invention includes all cis, trans, syn, anti, entgegen (E), and zusammen (Z) Isomers as well as the appropriate mixtures thereof.

The term “enantiomers” refers to a pair of stereoisomers which are non-superimposable mirror images of one another. The term “enantiomer” refers to a single member of this pair of stereoisomers. The term “racemic” refers to a 1 : 1 mixture of a pair of enantiomers. The disclosure includes enantiomers of the compounds described herein. Each compound herein disclosed includes all the enantiomers that conform to the general structure of the compound. The compounds may be in a racemic or enantiomerically pure form or any other form in terms of stereochemistry. In some embodiments the compounds are the (,S)-enantiomer.

The term “diastereomers” refers to the set of stereoisomers which cannot be made superimposable by rotation around single bonds. For example, cis- and trans- double bonds, endo- and exo- substitution on bicyclic ring systems and compounds containing multiple stereogenic centres with different relative configurations are considered to be diastereomers. The term “diastereomer” refers to any member of this set of compounds. In some examples presented, the synthetic route may produce a single diastereomer or a mixture of diastereomers. The disclosure includes diastereomers of the compounds described herein.

The compounds of the present disclosure may be used as single drug or as a pharmaceutical composition in which the compound is mixed with various pharmacologically acceptable materials.

The compounds of the disclosure are typically administered in the form of a pharmaceutical composition. Such compositions can be prepared using procedures well known in the pharmaceutical art and comprise at least one compound of the disclosure. The pharmaceutical composition of the present patent application comprises one or more compounds described herein and one or more pharmaceutically acceptable excipients. Typically, the pharmaceutically acceptable excipients are approved by regulatory authorities or are generally regarded as safe for human or animal use. The pharmaceutically acceptable excipients include, but are not limited to, carriers, diluents, glidants and lubricants, preservatives, buffering agents, chelating agents, polymers, gelling agents, viscosifying agents and solvents.

The pharmaceutical composition can be administered by oral, parenteral or inhalation routes. Examples of the parenteral administration include administration by injection, percutaneous, transmucosal, transnasal and transpulmonary administrations.

Examples of suitable carriers include, but are not limited to, water, salt solutions, alcohols, polyethylene glycols, peanut oil, olive oil, gelatin, lactose, terra alba, sucrose, dextrin, magnesium carbonate, sugar, amylose, magnesium stearate, talc, gelatin, agar, pectin, acacia, stearic acid, lower alkyl ethers of cellulose, silicic acid, fatty acids, fatty acid amines, fatty acid monoglycerides and diglycerides, fatty acid esters and polyoxyethylene.

The pharmaceutical composition may also include one or more pharmaceutically acceptable auxiliary agents, wetting agents, suspending agents, preserving agents, buffers, sweetening agents, flavouring agents, colorants or any combination of the foregoing.

The pharmaceutical compositions may be in conventional forms, for example, tablets, capsules, solutions, suspensions, injectables or products for topical application. Further, the pharmaceutical composition of the present invention may be formulated so as to provide desired release profile.

Administration of the compounds of the disclosure, in pure form or in an appropriate pharmaceutical composition, can be carried out using any of the accepted routes of administration of pharmaceutical compositions. The route of administration may be any route which effectively transports the active compound of the patent application to the appropriate or desired site of action. Suitable routes of administration include, but are not limited to oral, nasal, buccal, dermal, intradermal, transdermal, parenteral, rectal, subcutaneous, intravenous, intraurethral, intramuscular or topical.

Solid oral formulations include, but are not limited to, tablets, capsules (soft or hard gelatin), dragees (containing the active ingredient in powder or pellet form), troches and lozenges.

Liquid formulations include, but are not limited to, syrups, emulsions and sterile injectable liquids, such as suspensions or solutions.

Topical dosage forms of the compounds include ointments, pastes, creams, lotions, powders, solutions, eye or ear drops, impregnated dressings and may contain appropriate conventional additives such as preservatives, solvents to assist drug penetration.

The pharmaceutical compositions of the present patent application may be prepared by conventional techniques known in literature.

Suitable doses of the compounds for use in treating the disease or disorder described herein can be determined by those skilled in the relevant art. Therapeutic doses are generally

identified through a dose ranging study in humans based on preliminary evidence derived from the animal studies. Doses must be sufficient to result in a desired therapeutic benefit without causing unwanted side effects. Mode of administration, dosage forms and suitable pharmaceutical excipients can also be well used and adjusted by those skilled in the art. All changes and modifications are envisioned within the scope of the present patent application.

According to one embodiment, the compounds of the present disclosure can also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the present disclosure also embraces isotopically-labeled variants of the present disclosure which are identical to those recited herein, but for the fact that one or more atoms of the compound are replaced by an atom having the atomic mass or mass number different from the predominant atomic mass or mass number usually found in nature for the atom. All isotopes of any particular atom or element as specified are contemplated within the scope of the compounds of the disclosure and their uses. Exemplary isotopes that can be incorporated into compounds of the disclosure include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulfur, fluorine, chlorine and iodine, such as ^{2}H ("D"), ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{13}N, ^{15}N, ^{15}O, ^{17}O, ^{18}O, ^{32}P, ^{33}P, ^{35}S, ^{18}F, ^{36}Cl, ^{123}I and ^{125}I. Isotopically labeled compounds of the present disclosure can generally be prepared by following procedures analogous to those disclosed in the schemes and/or in the examples herein below, by substituting an isotopically labeled reagent for a non-isotopically labeled reagent.

EXPERIMENTAL

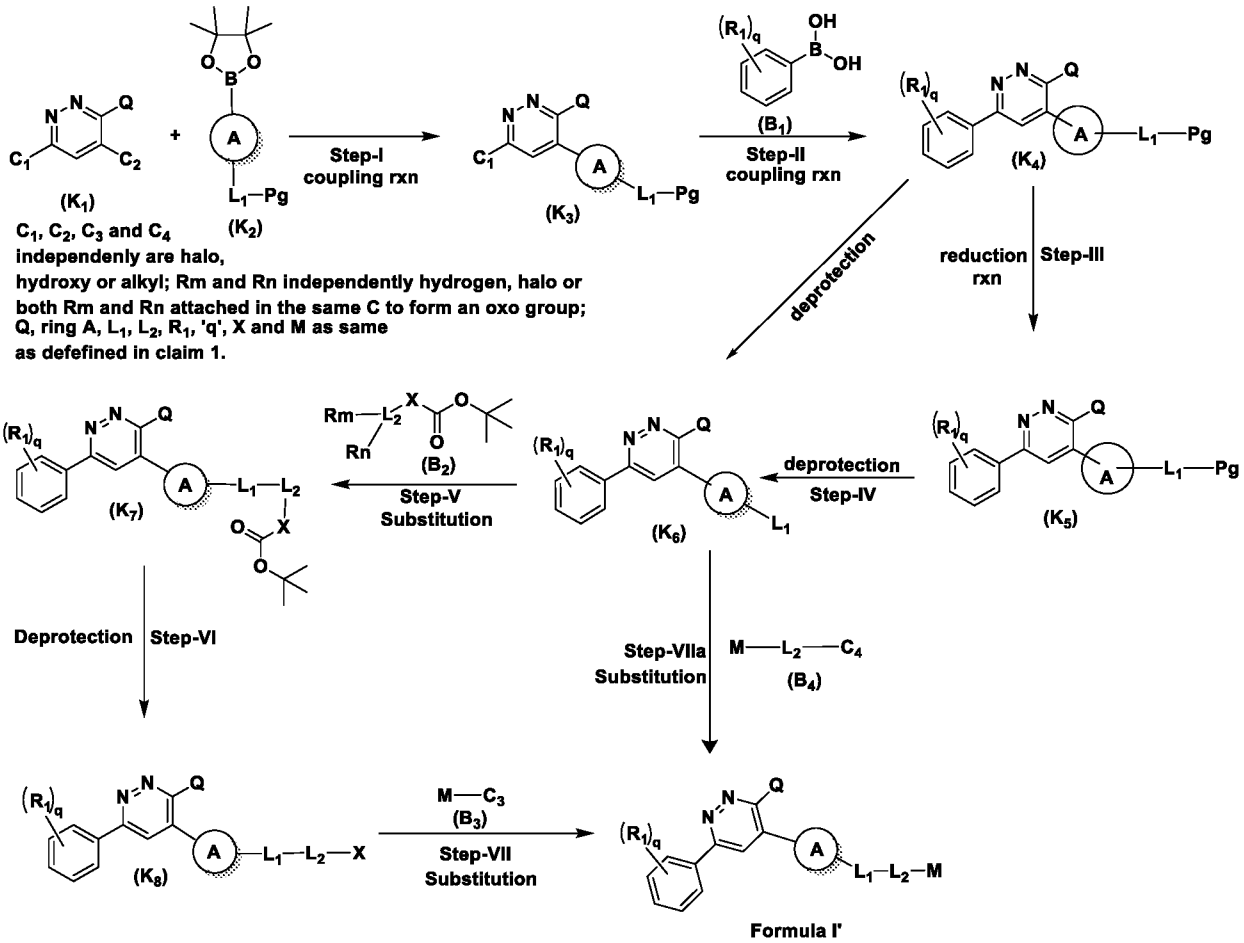
The abbreviations used in the entire specification is summarized below with their meaning.

MeOH – Methanol, EtOH – Ethanol, DCM – Dichloromethane, DMF – N,N-Dimethylformamide, EtOAc – Ethyl acetate, THF – Tetrahydrofuran, DME- 1,2-Dimethoxyethane, DMSO- Dimethyl sulfoxide DIPEA- N,N-Diisopropylethylamine, NCS- N-chloro succinimide, HATU – (1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluoro phosphate), KOAc – Potassium acetate, Na_2SO_4 - Sodium sulphate, Na_2CO_3 – Sodium carbonate, K_2CO_3 – Potassium carbonate, Cs_2CO_3-Cesium carbonate, KO^{t}Bu- Potassium tert-butoxide, TEA – Triethyl amine; DEA- Diethyl amine, $LiOH{\cdot}H_2O$ – Lithium hydroxide monohydrate; EDC.HCl – 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide. hydrochloride, DAST- diethylaminosulfur trifluoride, PPTs- Pyridinium p-toluenesulfonate, NaH – Sodium hydride, NH_4OH- Ammonium hydroxide, NaOH – Sodium hydroxide, HCl – Hydrochloric acid, $Pd(pph_3)_2Cl_2$. DCM –Bis(triphenylphosphine)-

palladium(II) dichloride Dichloromethane complex; $Pd(OAc)_2$ – Palladium (II) acetate, mL – Milliliter, TLC – Thin layer chromatography, RT or rt – Room temperature, h – Hour, N – Normality, M – Molarity, ^{1}HNMR – Proton nuclear magnetic resonance, DMSO-d_6 – Deuterated Dimethyl sulfoxide, $CDCl_3$ – Deuterated chloroform, CD_3OD- Deuterated Methanol, s – Singlet, d – Doublet, t –Triplet, m – Multiplet, H – Proton, MHz – Mega hertz, Hz – Hertz, Ppm – Parts per million, Bs – Broad singlet, HPLC – High-performance liquid chromatography, LCMS – Liquid chromatography Mass spectroscopy, g – Gram, mmol – Milli mol and °C – degree centigrade.

General scheme – I:

Certain compounds of the present disclosure can be made by following the process as given in General scheme-I.

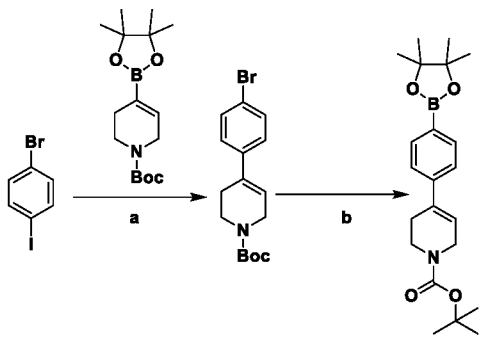


The general scheme-I for the synthesis of compound represented by formula (I') is depicted in the above scheme. The compound of formula (K_1) is reacted with the compound of formula (K_2) in a suitable solvent and suitable coupling reagent to yield compound of formula (K_3) which upon further reaction with a compound of formula (B_1) in the presence of suitable

coupling reagent and solvent can provide a compound of formula (K_4). The compound of formula (K_4) undergoes a reduction reaction to result in compound of formula (K_5) which further deprotected with a suitable deprotection reagent and solvent to yield compound of formula (K_6). In another way, the compound of formula (K_4) undergoes deprotection in the presence of a suitable reagent and solvent to yield the compound of formula (K_6). The compound of formula (K_6) reacts with the compound of formula (B_2) with suitable solvent in high temperature to result in an amide compound of formula (K_7) which further can undergo deprotection reaction in the presence of a suitable reagent and solvent to provide a compound of formula (K_8). The compound of formula (K_8) can undergo substitution reaction with the compound of formula (B_3) to result in the compound of formula (I'). In other hand the compound of formula (K_6) undergoes substitution reaction with compound of formula (B_4) to result in compound of formula (I').

PREPARATION OF INTERMEDIATES AND COMPOUNDS

Intermediate 1: Synthesis of tert-butyl 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-3,6-dihydropyridine-1(2H)-carboxylate.



Int-1

Step-a: Synthesis of tert-butyl 4-(4-bromophenyl)-3,6-dihydropyridine-1(2H)-carboxylate

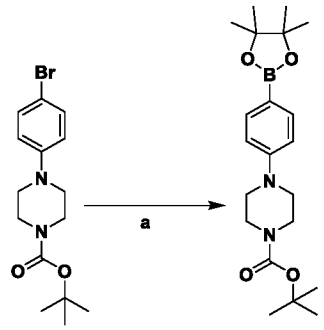
To a stirred solution of 1-Bromo-4-iodobenzene (5g, 17.67 mmol), tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (5.46g, 17.67 mmol) in 1,4-dioxane (80 mL) and water (20 mL) was added K_2CO_3 (7.32g, 53 mmol) and degassed with nitrogen for 10 min followed by $Pd(dppf)_2Cl_2$.DCM (1.44 g, 1.76 mmol) was added and the reaction mixture was heated for 16 h at 100 °C in sealed tube. Once the reaction was completed (monitored by TLC), the reaction mixture was diluted with EtOAc. The

combined organic layer was washed with water, brine, dried over anhydrous sodium sulphate and concentrated under vacuum to give the residue which was purified by combi flash column chromatography using 20% ethyl acetate in hexane as eluent to afford the title compound as off-white solid (5g, 83%). ^{1}H NMR (400 MHz, DMSO-d6): δ 7.53 (d, J = 8 Hz, 2H), 7.39 (d, J = 8 Hz, 2H), 6.20 (s, 1H), 3.98 (bs, 2H), 3.52 (t, J = 5.2 Hz, 2H), 2.43 (bs, 2H), 1.42 (s, 9H); LC-MS: m/z 338.0 (M+H).

Step-b: Synthesis of tert-butyl 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-3,6-dihydropyridine-1(2H)-carboxylate (Intermediate 1)

To a stirred solution of tert-butyl 4-(4-bromophenyl)-3,6-dihydropyridine-1(2H)-carboxylate (5g, 14.78 mmol) in dioxane (20 mL) was added bis pinacolato diboron (4.12g, 16.26 mmol) and KOAc (4.34g, 44.3 mmol) at RT and degassed with nitrogen for 10 min then $Pd(dppf)_2Cl_2$.DCM (1.2g, 1.47 mmol) was added to the reaction mixture and heated at 100 °C for 16 h. Once the reaction was completed (monitored by TLC), the reaction mixture was diluted with EtOAc. The combined organic layer was washed with water, brine, dried over anhydrous sodium sulphate, and concentrated under vacuum to give the residue which was purified by combi flash column chromatography using 35-40% ethyl acetate in hexane as eluent to afford the title compound as off-white solid (4.4g, 77 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, J = 10.8 Hz, 2H), 7.34 (d, J = 10.8 Hz, 2H), 6.08 (s, 1H), 4.07 (bs, 2H), 3.61 (m, 2H), 2.52 (m, 2H), 1.47 (s, 9H), 1.32 (s, 12H).

Intermediate-2: Synthesis of tert-butyl 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperazine-1-carboxylate

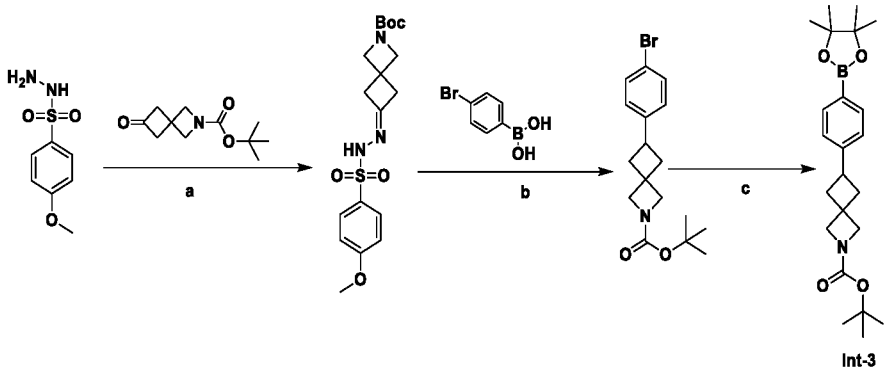


Int-2

To a stirred solution of tert-butyl 4-(4-bromophenyl)piperazine-1-carboxylate (5g, 14.65 mmol) in dioxane (80 mL) was added bis pinacolato diboron (4.46 g, 17.58 mmol) and KOAc (4.31g, 43.95 mmol) at RT. The reaction mixture was degassed with nitrogen for 5 min then $Pd(dppf)_2Cl_2$.DCM (1.19g, 1.46 mmol) was added into the reaction mixture and heated at

100 °C for 16 h. Once the reaction was completed (monitored by TLC), the reaction mixture was diluted with EtOAc. The combined organic layer was washed with water and brine, dried over anhydrous sodium sulphate, and concentrated under vacuum to give the residue which was purified by combi flash column chromatography using 15-20% ethyl acetate in hexane as eluent to afford the title compound as off-white solid (5.1g, 89.6 %). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.51 (d, J = 8.4 Hz, 2H), 6.90 (d, J = 8.4 Hz, 2H), 3.43 (bs, 4H), 3.18 (bs, 4H), 1.41 (s, 9H), 1.25 (s, 12H); LC-MS: m/z 389 (M+H).

Intermediate 3: Synthesis of Tert-butyl 6-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-2-azaspiro[3.3]heptane-2-carboxylate



Step-a: Synthesis of tert-butyl 6-(2-((4-methoxyphenyl)sulfonyl)hydrazineylidene)-2-azaspiro[3.3]heptane-2-carboxylate

To a stirred solution of 4-Methoxybenzenesulfonohydrazide (1.5g, 7.41 mmol), Tert-butyl 6-oxo-2-azaspiro[3.3]heptane-2-carboxylate (1.56g, 7.41 mmol) in toluene (30 mL) and the reaction mixture was heated for 16 h at 50 °C in a sealed tube. Once the reaction was completed (monitored by TLC), reaction mass was concentrated under vacuum to give the residue which was purified by combi flash column chromatography using 35% ethyl acetate in hexane as eluent to afford the title compound as white solid (2.8g, 95%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.21 (bs, 1H), 7.68 (d, J = 8.4 Hz, 2H), 7.05 (d, J = 8.4 Hz, 2H), 3.82 (bs, 4H), 3.78 (s, 3H), 2.95 (m, 4H), 1.31 (s, 9H); LC-MS: m/z 394.1 (M-H).

Step-b: Synthesis of Tert-butyl 6-(4-bromophenyl)-2-azaspiro[3.3]heptane-2-carboxylate

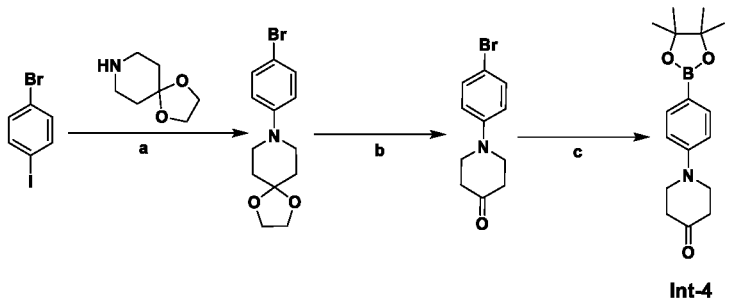
To a stirred solution of Tert-butyl 6-(2-((4-methoxyphenyl)sulfonyl)hydrazineylidene)-2-azaspiro[3.3]heptane-2-carboxylate (2.8g, 7.08 mmol), (4-Bromophenyl)boronic acid (2.13g, 10.6 mmol) in dioxane (60 mL) was added Cs_2CO_3 (4.6g, 14.16 mmol) and degassed

with nitrogen for 30 min. Then the reaction mixture was heated for 16 h at 110 °C in sealed tube. Once the reaction was completed (monitored by TLC), the reaction mixture was diluted with EtOAc and filtered. Filtrate was concentrated under vacuum to give the residue which was purified by combi flash column chromatography using 20% ethyl acetate in hexane as eluent to afford the title compound as a colourless liquid (1.3g, 52%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.38 (d, J = 8.4 Hz, 2H), 7.01 (d, J = 8.4 Hz, 2H), 4.02 (s, 2H), 3.81 (s, 2H), 3.18 (m, 1H), 2.54 (m, 2H), 2.21 (m, 2H), 1.42 (s, 9H).

Step-c: Synthesis of tert-butyl 6-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-2-azaspiro[3.3]heptane-2-carboxylate (Intermediate 3)

To a stirred solution of Tert-butyl 6-(4-bromophenyl)-2-azaspiro[3.3]heptane-2-carboxylate (1.3g, 3.69 mmol) in dioxane (35 mL) was added bis pinacolato diboron (1.4g, 5.53 mmol) and KOAc (0.90 g, 9.22 mmol) at RT and degassed with nitrogen for 5 min then $Pd(dppf)_2Cl_2$.DCM (0.30g, 0.36 mmol) was added into the reaction mixture and heated at 110 °C for 16 h. Once the reaction was completed (monitored by TLC), the reaction mixture was diluted with EtOAc. The combined organic layer was washed with water, brine, dried over anhydrous sodium sulphate, and concentrated under vacuum to afford the title compound as creamy sticky solid (0.3g, 93 %). LC-MS: m/z 300.1 [(M-100)+H)].

Intermediate 4: Synthesis of 1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl) piperidin-4-one



Int-4

Step-a: Synthesis of 8-(4-bromophenyl)-1,4-dioxa-8-azaspiro[4.5]decane

To a stirred solution of 1-Bromo-4-iodobenzene (10g, 35.3 mmol), 1,4-dioxa-8-azaspiro[4.5]decane (5.06 g, 35.3 mmol) in DMSO (100 mL) were added K_2CO_3 (9.77g, 70.69 mmol) and L-proline (1.62g, 14.1 mmol) and degassed with nitrogen for 10 min followed by CuI (1.34g, 7.06 mmol) was added and the reaction mixture was heated at 90 °C for 16 h in sealed tube. Once the reaction was completed (monitored by TLC), the reaction mixture was

diluted with EtOAc. The combined organic layer was washed with water, brine, dried over anhydrous sodium sulphate and concentrated under vacuum to give the residue which was purified by combi flash column chromatography using 10% ethyl acetate in hexane as eluent to afford the title compound as off-white solid (7g, 66%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.31 (d, J = 9.2 Hz, 2H), 6.90 (d, J = 9.2 Hz, 2H), 3.90 (s, 4H), 3.27-3.24 (m, 4H), 1.68-1.65 (m, 4H); LC-MS: m/z 297.9 (M+H).

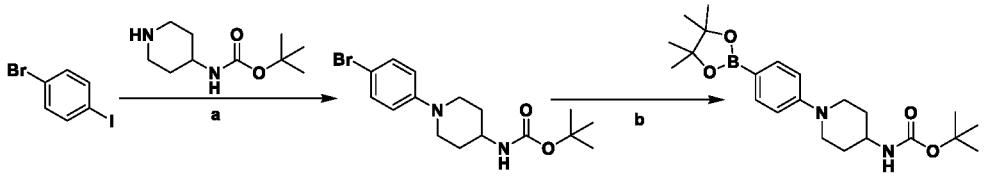
Step-b: Synthesis of 1-(4-bromophenyl)piperidin-4-one

To a stirred solution of 8-(4-bromophenyl)-1,4-dioxa-8-azaspiro[4.5]decane (7g, 13.41 mmol) in THF (50 mL) was added 1(N) aq HCl (50 mL) at 0 °C and then slowly brought to RT and the and the reaction mixture was heated for 6 h at 80 °C. Once the reaction was completed (monitored by TLC), the reaction mixture was basified with $NaHCO_3$ and extracted with EtOAc. The combined organic layer was washed with water, brine, dried over anhydrous sodium sulphate and concentrated under vacuum to give the residue which was purified by combi flash column chromatography using 10% ethyl acetate in hexane as eluent to afford the title compound as off-white solid (4g, 66%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.35 (d, J = 8.8 Hz, 2H), 6.97 (d, J = 8.8 Hz, 2H), 3.60-3.57 (m, 4H), 2.40-2.37 (m, 4H); LC-MS: m/z 254 (M+H).

Step-c: Synthesis of 1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidin-4-one (Intermediate 4)

To a stirred solution of 1-(4-bromophenyl)piperidin-4-one (4g, 15.74 mmol) in dioxane (80 mL) was added bis pinacolato diboron (5.99 g, 23.60 mmol) and KOAc (4.63g, 47.22 mmol) at RT and degassed with nitrogen for 10 min then $Pd(dppf)_2Cl_2$.DCM (1.28 g, 1.57 mmol) was added into the reaction mixture and heated at 100 °C for 16 h. Once the reaction was completed (monitored by TLC), the reaction mixture was diluted with EtOAc. The combined organic layer was washed with water, brine, dried over anhydrous sodium sulphate and concentrated under vacuum to give the residue which was purified by combi flash column chromatography using 15% ethyl acetate in hexane as eluent to afford the title compound as off-white solid (4g, 84 %). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.53 (d, J = 8.4 Hz, 2H), 6.97 (d, J = 8.4 Hz, 2H), 3.68-3.65 (m, 4H), 2.40-2.37 (m, 4H), 1.26 (s, 12 H); LC-MS: m/z 302.05 (M+H).

Intermediate 5: Synthesis of tert-butyl (1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidin-4-yl)carbamate



Int-5

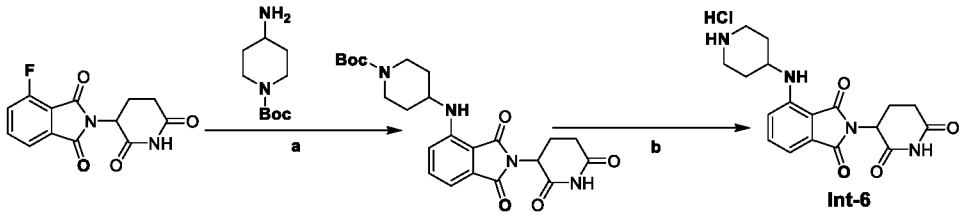
Step-a: Synthesis of tert-butyl (1-(4-bromophenyl)piperidin-4-yl)carbamate

To a stirred solution of 1-Bromo-4-iodobenzene (1g, 3.53 mmol), tert-butyl piperidin-4-ylcarbamate (0.85g, 4.24 mmol) in 1,4-dioxane (10 mL) was added Cs_2CO_3 (2.3g, 7.07 mmol) and degassed with nitrogen for 10 min followed by $Pd_2(dba)3$ (0.16g, 0.17 mmol) and xantphos (0.20g, 0.35 mmol) were added and the reaction mixture was heated for 16 h at 100 ºC in sealed tube. Once the reaction was completed (monitored by TLC), the reaction mixture was diluted with EtOAc. The combined organic layer was washed with water, brine, dried over anhydrous sodium sulphate and concentrated under vacuum to give the residue which was purified by combi flash column chromatography using 20% ethyl acetate in hexane as eluent to afford the title compound as off-white solid (0.85g, 69%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.30 (d, J = 8.8 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 3.65-3.58 (m, 2H), 3.40 (bs, 1H), 2.78-2.65 (m, 2H), 1.82-1.73 (m, 2H), 1.48-1.40 (m, 2H), 1.38 (s, 9H).

Step-b: Synthesis of tert-butyl (1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidin-4-yl)carbamate (Intermediate 5)

To a stirred solution of tert-butyl (1-(4-bromophenyl)piperidin-4-yl)carbamate (0.85g, 2.39 mmol) in dioxane (15 mL) was added bis pinacolato diboron (0.91 g, 3.58 mmol) and KOAc (0.7g, 7.17 mmol) at RT and degassed with nitrogen for 10 min then $Pd(dppf)_2Cl_2$.DCM (0.19g, 0.29 mmol) was added into the reaction mixture and heated at 100 ºC for 16 h. Once the reaction was completed (monitored by TLC), the reaction mixture was diluted with EtOAc. The combined organic layer was washed with water, brine, dried over anhydrous sodium sulphate and concentrated under vacuum to give the residue which was purified by combi flash column chromatography using 35-40% ethyl acetate in hexane as eluent to afford the title compound as off-white solid (0.45g, 46 %). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.48 (d, J = 8.8 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 3.78-3.71 (m, 2H), 3.43 (bs, 1H), 2.84-2.76 (m, 2H), 1.79-1.72 (m, 2H), 1.45-1.39 (m, 2H), 1.38 (s, 9H), 1.25 (s, 12 H); LC-MS: m/z 403.3 (M+H).

Intermediate 6: Synthesis of 2-(2,6-dioxopiperidin-3-yl)-4-(piperidin-4-ylamino) isoindoline-1,3-dione hydrochloride



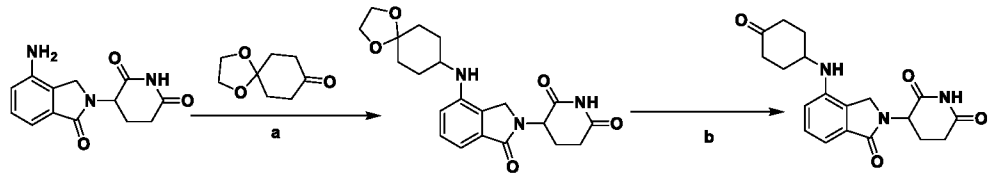
Step a: Synthesis of tert-butyl 4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)piperidine-1-carboxylate

To a stirred solution of 2-(2,6-dioxopiperidin-3-yl)-4-fluoroisoindoline-1,3-dione (0.5g, 1.81 mmol) and tert-butyl 4-aminopiperidine-1-carboxylate (0.36g, 1.81 mmol) in DMSO (5 mL) was added DIPEA (1.17 g, 9.05 mmol) and heated at 130°C for 4 hrs. Once the reaction was completed (monitored by TLC), reaction mixture was quenched with cold water and stirred for 30 mins, the solid so formed was filtered and dried under vacuum to afford title compound as off-white solid (0.4g, 48 %). ^{1}H NMR (400 MHz, DMSO-d_6): d 11.11 (bs, 1H), 7.59 (t, J = 7.2 Hz, 1H), 7.21 (d, J = 8.8 Hz, 1H), 7.05 (d, J = 7.2 Hz, 1H), 6.27 (d, J = 8.0 Hz, 1H), 5.06 (dd, J = 5.2, 12.8 Hz, 1H), 3.98 - 3.84 (m, 2H), 3.82 - 3.70 (m, 1H), 3.05 - 2.82 (m, 3H), 2.65 - 2.52 (m, 2H), 2.07 - 1.99 (m, 1H), 1.97 - 1.86 (m, 2H), 1.40 (s, 9H), 1.40 - 1.33 (m, 2H); LC-MS: m/z 356.9 (M-100).

Step-b: Synthesis of 2-(2,6-dioxopiperidin-3-yl)-4-(piperidin-4-ylamino)isoindoline-1,3-dione hydrochloride (Intermediate 6)

To a stirred solution of tert-butyl 4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)piperidine-1-carboxylate (0.4 g, 0.87 mmol) in DCM (5 mL) was added 4(N) dioxane HCl (2 mL) at 0 °C and then slowly brought to RT and stirred at RT for 3 h. Reaction mixture was evaporated under reduced pressure, the resultant residue was washed with diethyl ether and dried under vacuum to afford the title compound as yellowish solid (0.4 g, crude). ^{1}H NMR (400 MHz, DMSO-d6): d 11.10 (s, 1H), 8.95-8.85 (m, 1H), 8.70 – 8.58 (m, 1H), 7.62 (t, J = 7.2 Hz, 1H), 7.24 (d, J = 8.8 Hz, 1H), 7.09 (d, J = 7.2 Hz, 1H), 6.29 (d, J = 8.4 Hz, 1H), 5.06 (dd, J = 5.2, 12.8 Hz, 1H), 3.92-3.82 (m, 1H), 3.38 - 3.25 (m, 2H), 3.05 - 2.85 (m, 3H), 2.61 - 2.52 (m, 1H), 2.13 - 1.97 (m, 3H), 1.75 - 1.61 (m, 2H), 1.29 - 1.23 (m, 1H); LC-MS: m/z 356.9 (M+H).

Intermediate 7: Synthesis of 3-(1-oxo-4-((4-oxocyclohexyl)amino)isoindolin-2-yl) piperidine-2,6-dione



Int-7

Step-a: Synthesis of 3-(4-((1,4-dioxaspiro[4.5]decan-8-yl)amino)-1-oxoisoindolin-2-yl) piperidine-2,6-dione

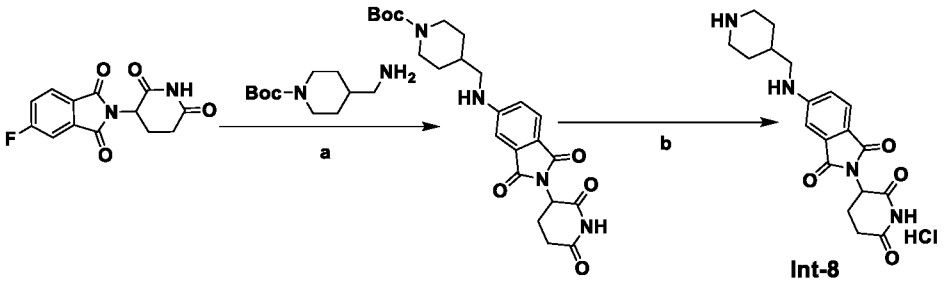
To a stirred solution of 3-(4-amino-1-oxoisoindolin-2-yl)piperidine-2,6-dione (0.5 g, 1.92 mmol) and 1,4-dioxaspiro[4.5]decan-8-one (0.3 g, 0.92 mmol) in MeOH (12 mL) was added acetic acid (0.1 mL) at 0 °C to the reaction mixture. The reaction mixture was stirred at rt for 2h. Then the reaction mixture was cooled to 0 °C and sodium cyano borohydride (0.36 g, 5.78 mmol) was added and the reaction mixture was stirred for 12h at RT. Reaction was monitored by TLC. After completion of the reaction the reaction mixture was extracted in 10% MeOH in DCM and saturated ammonium chloride wash was given to the organic layer followed by saturated sodium chloride wash. The organic layer dried over anhydrous sodium sulphate and then concentrated under reduced pressure and the resultant residue. The crude compound was purified by combi flash column chromatography and eluted in 5% MeOH/DCM to afford the title compound as yellow solid (0.2g, 26 %). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.01 (s, 1H), 7.28 (t, J = 7.2 Hz, 1H), 6.91 (d, J = 6.8 Hz, 1H), 6.81 (d, J = 8 Hz, 1H), 5.34 (d, J = 7.6 Hz, 1H), 5.12-5.10 (m, 1H), 4.24-4.09 (m, 2H), 3.86 (s, 4H), 3.84-3.80 (m, 1H), 3.58-3.51 (m, 1H), 3.48-3.42 (m, 1H), 2.97-2.87 (m, 1H), 2.32-2.27 (m, 1H), 2.06-2.02 (m, 1H), 1.90-1.88 (m, 1H), 1.66-1.40 (m, 6H). LCMS: m/z 400.0 (M+H).

Step-b: Synthesis of 3-(1-oxo-4-((4-oxocyclohexyl)amino)isoindolin-2-yl)piperidine-2,6-dione (Intermediate 7)

To a stirred solution of tert-butyl 3-(4-((1,4-dioxaspiro[4.5]decan-8-yl)amino)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (0.25g, 0.62 mmol) in THF (10 mL) was added 2 N aq. hydrochloride (2 mL) at 0 °C and then slowly brought to RT and stirred for 12 h. The reaction mixture was evaporated under reduced pressure, and the resultant residue was washed with diethyl ether and dried under vacuum to afford the title compound as yellowish solid (0.2g, 89.9%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.01 (s, 1H), 7.30 (t, J = 8 Hz, 1H), 6.96 (d, J = 7.6 Hz, 1H), 6.92 (d, J = 7.6 Hz, 1H), 5.46 (d, J = 7.2 Hz, 1H), 5.17-5.11 (m, 1H), 4.27-4.13

(m, 2H), 3.94-3.91 (m, 1H), 3.65-3.62 (m, 1H), 3.42-3.38 (m, 1H), 2.95-2.85 (m, 1H), 2.65-2.56 (m, 1H), 2.39-2.12 (m, 4H), 1.91-1.88 (m, 2H), 1.55-1.35 (m, 2H); LCMS: m/z 356.2 (M+H).

Intermediate 8: Synthesis of 2-(2,6-dioxopiperidin-3-yl)-5-((piperidin-4-ylmethyl)amino) isoindoline-1,3-dione hydrochloride



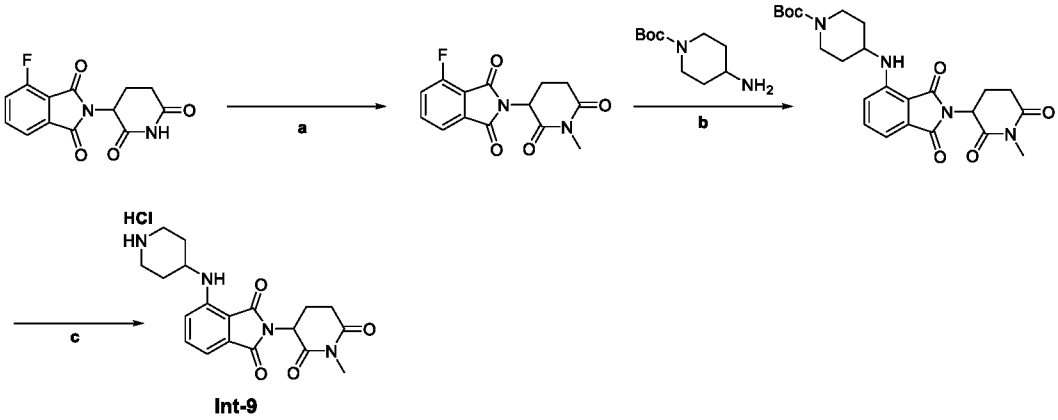
Step-a: Synthesis of tert-butyl 4-(((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl) amino)methyl)piperidine-1-carboxylate

To a stirred solution of 2-(2,6-dioxopiperidin-3-yl)-5-fluoroisoindoline-1,3-dione (0.4g, 1.44 mmol), tert-butyl 4-(aminomethyl)piperidine-1-carboxylate (0.34g, 1.59 mmol) in DMSO (4 mL) were added DIPEA (0.93 g, 7.23 mmol) and the reaction mixture was microwaved at 130 °C for 1h in microwave. Once the reaction was completed (monitored by TLC), the reaction mixture was quenched to ice water, solid formed was filtered and dried to give crude product which was purified by combi flash column chromatography using 6% methanol in DCM as eluent to afford the title compound as off-white solid (0.25g, 36%); LC-MS: m/z 469.1 (M-H).

Step-b: Synthesis of 2-(2,6-dioxopiperidin-3-yl)-5-((piperidin-4-ylmethyl)amino) isoindoline-1,3-dione hydrochloride (Intermediate 8)

To a stirred solution of tert-butyl 4-(((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)amino)methyl)piperidine-1-carboxylate (0.15g, 0.31 mmol) in DCM (1.5 mL) was added dioxane HCl (1.5 mL) at 0 °C and then slowly brought to RT and the reaction mixture was stirred at RT for 1h. Once the reaction was completed (monitored by TLC) the reaction mixture was evaporated under reduced pressure, the resultant residue was washed with diethyl ether and dried under vacuum to afford the title compound as yellow solid (0.117g, 99%); LC-MS: m/z 371.2 (M+H).

Intermediate 9: Synthesis of 2-(1-methyl-2,6-dioxopiperidin-3-yl)-4-(piperidin-4-ylamino)isoindoline-1,3-dione hydrochloride



Int-9

Step-a: Synthesis of 4-fluoro-2-(1-methyl-2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione

To a stirred solution 2-(2,6-dioxopiperidin-3-yl)-4-fluoroisoindoline-1,3-dione (0.5 g, 1.88 mmol) in DMF (20 mL) was added K_2CO_3 (0.75g, 5.43 mmol) and followed by MeI (0.38g, 2.71 mmol) to the reaction mixture and stirred at RT for 12h. The reaction was monitored by TLC. After completion of the reaction the reaction mixture was poured into ice water to obtain the solid, was filtered and washed with water to afford the title compound as a light-yellow solid (0.5g, 95.17 %). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.98-7.93 (m, 1H), 7.80-7.72 (m, 2H), 5.25-5.20 (m, 1H), 2.99 (s, 3H), 2.97-2.91 (m, 1H), 2.79-2.75 (m, 1H), 2.59-2.54 (m, 1H), 2.10-2.06 (m, 1H).

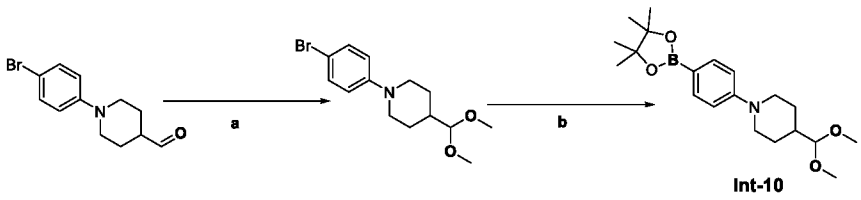
Step-b: Synthesis of tert-butyl 4-((2-(1-methyl-2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)piperidine-1-carboxylate

To a stirred solution of 4-fluoro-2-(1-methyl-2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (0.5 g, 1.72 mmol), tert-butyl 4-aminopiperidine-1-carboxylate (0.34 g, 1.72 mmol) DMSO (4 mL) was added DIPEA (1.11 g, 8.61 mmol) to the reaction mixture at rt and stirred at 130 °C in microwave for 1h. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was poured into ice water to get the precipitate, filtered, and washed with water to afford the title compound as a yellow solid. (0.7 g, 98.6%) ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.60 (t, J = 7.2 Hz. 1H), 7.22 (d, J = 8.8 Hz, 1H), 7.06 (d, J = 6.8 Hz, 1H), 6.27 (d, J = 8.4 Hz, 1H), 5.14-5.10 (m, 1H), 3.92-3.88 (m, 2H), 3.74 (bs, 1H), 3.01 (s, 3H), 2.97-2.91 (m, 2H), 2.77-2.73 (m, 1H), 2.54-2.50 (m, 2H), 2.05-2.03 (m, 1H), 1.93-1.90 (m, 2H), 1.40 (s, 9H), 0.97 (bs, 2H); LC-MS: m/z 371.2 (M-100).

Step-c: Synthesis of 2-(1-methyl-2,6-dioxopiperidin-3-yl)-4-(piperidin-4-ylamino) isoindoline-1,3-dione hydrochloride (Intermediate 9)

To a stirred solution of tert-butyl 4-((2-(1-methyl-2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)piperidine-1-carboxylate (0.3 g, 0.63 mmol) in DCM (2 mL) was added 4M HCl in dioxane (5 mL) to the reaction mixture at 0 °C and stirred at rt for 2h. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was evaporated completely to get a crude compound, washed with diethyl ether to afford the title compound as a yellow solid (0.23g, 97.3%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.99 (bs, 1H), 8.77-8.75 (m, 1H), 7.62 (t, J = 7.6 Hz, 1H), 7.25 (d, J = 8.8 Hz, 1H), 7.10 (d, J = 6.8 Hz, 1H), 6.29 (d, J = 8.0 Hz, 1H), 5.16-5.11 (m, 1H), 3.89-3.87 (m, 1H), 3.60-3.51 (m, 1H), 3.37-3.30 (m, 2H), 3.01 (s, 3H), 2.99-2.90 (m, 1H), 2.78-2.74 (m, 1H), 2.58-2.55 (m, 1H), 2.11-2.03 (m, 2H), 1.74-1.66 (m, 2H), 1.30-1.23 (m, 2H); LC-MS: m/z 371.2 (M+H).

Intermediate 10: Synthesis of 4-(dimethoxymethyl)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidine



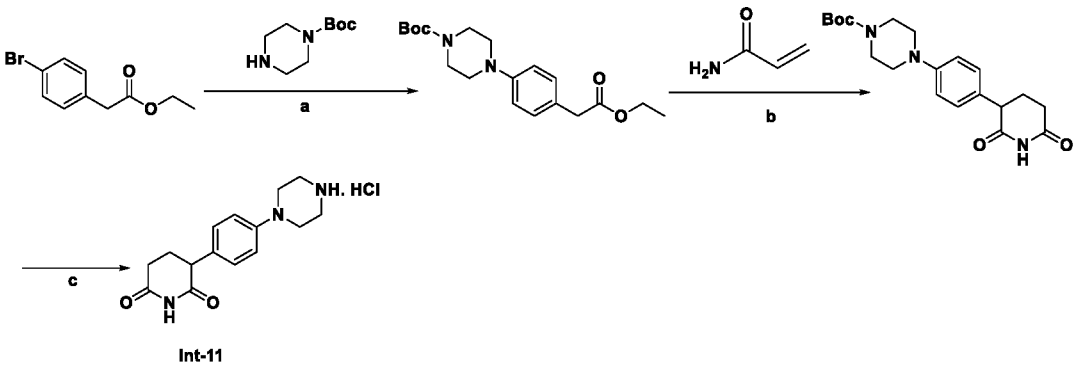
Step-a: Synthesis of 1-(4-bromophenyl)-4-(dimethoxymethyl)piperidine

To a stirred solution of 1-(4-bromophenyl)piperidine-4-carbaldehyde (synthesized following ref: WO2020/51564) (3.2 g, 11.93 mmol) in MeOH (50 mL) were added trimethoxymethane (6.33 g, 59.67 mmol) and 4-methylbenzenesulfonic acid hydrate (0.064 g, 0.33 mmol) and stirred at RT for 12h. The reaction was monitored by TLC. Reaction mixture was quenched in bicarbonate solution and extracted with DCM. The organic layer was collected, followed by washing with brine solution dried over $Na2SO_4$ to get crude compound. The crude compound was purified by combi flash column chromatography and eluted in 20% hexane/ethyl acetate to afford the title compound as a light-yellow solid (1.1g, 28 %). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.30 (d, J = 9.2 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 4.06 (d, J = 6.8 Hz, 1H), 3.67 (d, J = 12.4 Hz, 2H), 3.25 (s, 6H), 2.60 (dt, J = 11.6, 2 Hz, 2H), 1.78-1.72 (m, 1H), 1.68 (d, J = 12.4 Hz, 2H), 1.35-1.16 (m, 2H). LC-MS: m/z 314 (M+H).

Step-b: Synthesis of 4-(dimethoxymethyl)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidine (Intermediate 10)

To a stirred solution of 1-(4-bromophenyl)-4-(dimethoxymethyl)piperidine (1.1g, 3.5 mmol) in dioxane (35 mL) was added bis pinacolato diboron (1.15 g, 4.55 mmol) and KOAc (1.03 g, 10.5 mmol) at RT and degassed with nitrogen for 10 min then $Pd(dppf)_2Cl_2$.DCM (0.28 g, 0.35 mmol) was added into the reaction mixture and heated at 100 °C for 12 h. Once the reaction was completed (monitored by TLC), the reaction mixture was diluted with EtOAc. The combined organic layer was washed with water, brine, dried over anhydrous sodium sulphate and concentrated under vacuum to give the residue which was purified by combi flash column chromatography using 20-30% ethyl acetate in hexane as eluent to afford the title compound as pale yellowing solid (1.25g, 98.8 %). ^{1}H NMR (400 MHz, CDCl3): δ 7.67 (d, J = 8.8 Hz, 2H), 6.86 (d, J = 9.2 Hz, 2H), 4.05 (d, J = 6.8 Hz, 1H), 3.81 (d, J = 12.4 Hz, 2H), 3.35 (s, 6H), 2.71 (dt, J = 12, 2.4 Hz, 2H), 1.81 (d, J = 12 Hz, 2H), 1.80-1.74 (m, 1H), 1.48-1.38 (m, 2H), 1.31 (s, 12H); LC-MS: m/z 361.3 (M+H).

Intermediate 11: Synthesis of 3-(4-(piperazin-1-yl)phenyl)piperidine-2,6-dione hydrochloride



Int-11

Step-a: Synthesis of tert-butyl 4-(4-(2-ethoxy-2-oxoethyl)phenyl)piperazine-1-carboxylate

To a stirred solution of ethyl 2-(4-bromophenyl)acetate (2g, 8.22 mmol), tert-butyl piperazine-1-carboxylate (1.53 g, 8.22 mmol) in toluene (15 mL) was added Cs_2CO_3 (5.36 g, 16.45 mmol) and degassed with nitrogen for 10 min followed by Ru-Phos Pd-G2 (0.32g, 0.41 mmol) was added and the reaction mixture was heated for 12 h at 110 °C in sealed tube. Once the reaction was completed (monitored by TLC), the reaction mixture was dissolved in 10% MeOH/DCM and passed through celite. Filtrate was concentrated under reduced pressure to

obtain crude compound. Crude compound was purified by combi flash column chromatography using 20-25% ethyl acetate in hexane as eluent to afford the title compound as off-white solid (2.1 g, 73.2%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.10 (d, *J* = 8.4 Hz, 2H), 6.89 (d, *J* = 8.4 Hz, 2H), 4.04 (q, J = 7.2 Hz, 2H), 3.52 (s, 2H), 3.43 (m, 4H), 3.05 (m, 4H), 1.41 (s, 9H), 1.16 (t, J = 7.2 Hz, 3H); LC-MS: m/z 349.2 (M+H).

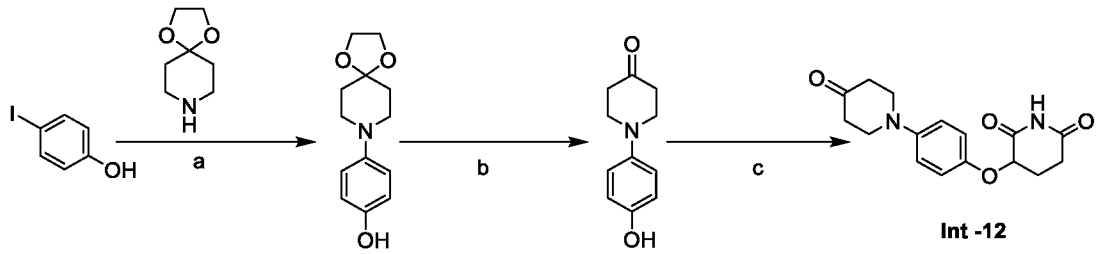
Step-b: Synthesis of tert-butyl 4-(4-(2,6-dioxopiperidin-3-yl)phenyl)piperazine-1-carboxylate

To a stirred solution of tert-butyl 4-(4-(2-ethoxy-2-oxoethyl)phenyl)piperazine-1-carboxylate (2 g, 5.74 mmol) and acrylamide (0.36 g, 5.16 mmol) were taken in THF (20 mL) was added KO^{t}Bu (0.70 g, 6.31 mmol) and the reaction mixture was heated for 12 h at 50 °C. Once the reaction was completed (monitored by TLC), the reaction mixture was quenched with ice cold water and extracted with EtOAc. The combined organic layer was washed with water, brine, dried over anhydrous sodium sulphate and concentrated under vacuum to give the residue which was purified by combi flash column chromatography using 40-60% ethyl acetate in hexane as eluent to afford the title compound as off-white solid (0.82 g, 38%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.77 (s, 1H), 7.06 (d, *J* = 8.8 Hz, 2H), 6.90 (d, *J* = 8.8 Hz, 2H), 3.73 (m, 1H), 3.44 (m, 4H), 3.06 (m, 4H), 2.69-2.54 (m, 1H), 2.48-2.42 (m, 1H), 2.18-2.07 (m, 1H), 2.03-1.95 (m, 1H), 1.41 (s, 9H); LC-MS: m/z 374.3 (M+H).

Step-c: Synthesis of 3-(4-(piperazin-1-yl)phenyl)piperidine-2,6-dione hydrochloride (Intermediate 11)

To a stirred solution of tert-butyl 4-(4-(2,6-dioxopiperidin-3-yl)phenyl)piperazine-1-carboxylate (0.82 g, 2.19 mmol) in DCM (10 mL) was added 4(N) dioxane HCl (10 mL) at 0 °C and then slowly brought to RT and stirred at RT for 16 h. The reaction mixture was evaporated under reduced pressure, the resultant residue was washed with diethyl ether and dried under vacuum to afford the title compound as yellowish solid (0.8 g, crude). ^{1}H NMR (400 MHz, DMSO-d6): d 10.78 (s, 1H), 9.35 (bs, 2H), 7.10 (d, *J* = 8.4 Hz, 2H), 6.96 (d, *J* = 8.4 Hz, 2H), 3.78-3.74 (m, 1H), 3.37 (m, 4H), 3.19 (m, 4H), 2.69-2.56 (m, 1H), 2.47-2.41 (m, 1H), 2.21-2.09 (m, 1H), 2.05-1.95 (m, 1H); LC-MS: m/z 274.2 (M+H).

Intermediate 12: Synthesis of 3-(4-(4-oxopiperidin-1-yl)phenoxy)piperidine-2,6-dione



Step-a: Synthesis of 4-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)phenol

To a stirred solution of 4-iodophenol (5g, 28.89 mmol), 1,4-dioxa-8-azaspiro[4.5]decane (4.13 g, 28.89 mmol) in DMSO (50 mL) were added K_2CO_3 (7.98 g, 57.80 mmol) and L-proline (1.33g, 11.56 mmol) and degassed with nitrogen for 10 min followed by CuI (1.10g, 5.78 mmol) was added and the reaction mixture was heated at 90 °C for 12 h in sealed tube. Once the reaction was completed (monitored by TLC), the reaction mixture was diluted with EtOAc. The combined organic layer was washed with water, brine, dried over anhydrous sodium sulphate and concentrated under vacuum to give the residue which was purified by combi flash column chromatography using 40% ethyl acetate in hexane as eluent to afford the title compound as off-white solid (1.5g, 22%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.82 (s, 1H), 6.79 (d, J = 8.8 Hz, 2H), 6.63 (d, J = 8.8 Hz, 2H), 3.89 (s, 4H), 3.05-3.02 (m, 4H), 1.72-1.69 (m, 4H); LC-MS: m/z 236.1.

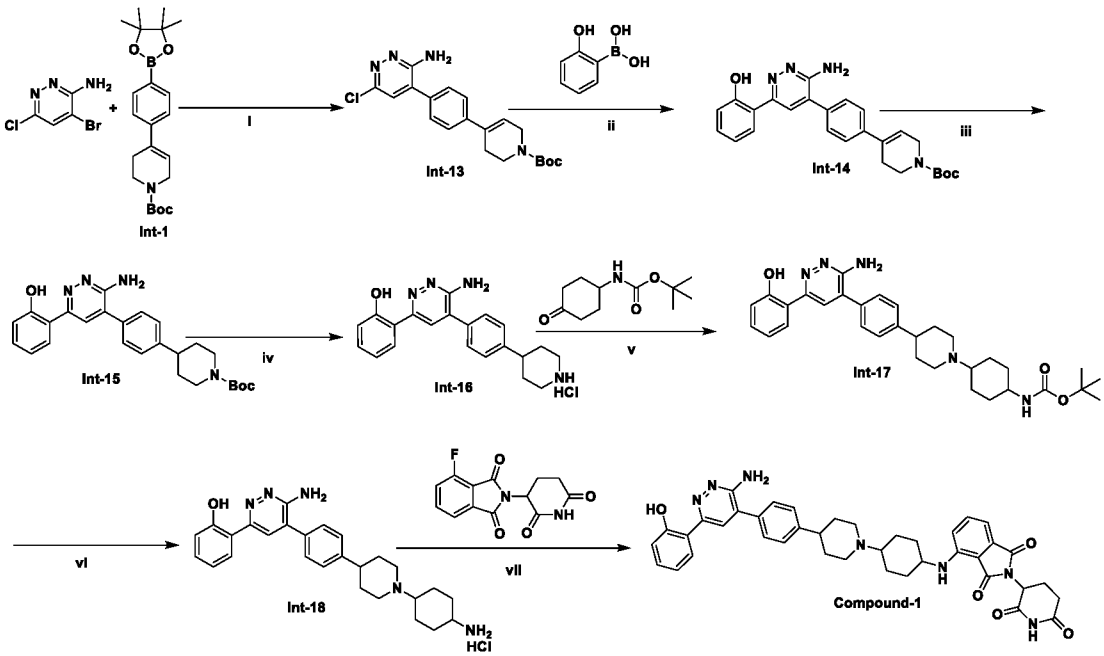
Step-b: Synthesis of 1-(4-hydroxyphenyl)piperidin-4-one

To a stirred solution of 4-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)phenol (1.5g, 13.41 mmol) in THF (30 mL) was added 2(N) aq HCl (50 mL) at 0 °C and then slowly brought to RT and the reaction mixture was heated for 9 h at 70 °C. Once the reaction was completed (monitored by TLC), the reaction mixture was basified with $NaHCO_3$ and extracted with EtOAc. The combined organic layer was washed with water, brine, dried over anhydrous sodium sulphate and concentrated under vacuum to give the residue which was purified by combi flash column chromatography using 10% ethyl acetate in hexane as eluent to afford the title compound as off-white solid (0.7g, 57%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.86 (s, 1H), 6.88 (d, J = 8.8 Hz, 2H), 6.67 (d, J = 8.8 Hz, 2H), 3.39-3.34 (m, 4H), 2.44-2.39 (m, 4H); LC-MS: m/z 192.1 (M+H).

Step-c: Synthesis of 3-(4-(4-oxopiperidin-1-yl)phenoxy)piperidine-2,6-dione (Intermediate 12)

To a stirred solution of 1-(4-hydroxyphenyl)piperidin-4-one (1.2g, 6.27 mmol) in DMF (30 mL) was added NaH (0.37g, 15.68 mmol) at 0 °C temperature and stirred for 30 mins. Now 3-bromopiperidine-2,6-dione (1.80 g, 9.41 mmol) was added in the reaction mixture and stirred at RT for 1h After completion of the reaction, the reaction mixture was poured in ice cold water and extracted with 2 X 100 mL of ethyl acetate, evaporated to afford the title compound as colourless solid (1.2g, 63 %). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.89 (s, 1H), 6.99-6.89 (m, 4H), 5.05-5.01 (m, 1H), 3.48-3.33 (m, 4H), 2.67-2.55 (m, 2H), 2.49-2.41 (m, 4H), 2.20-1.99 (m, 2H), LCMS: m/z 303.2 (M+H).

Example-I: Synthesis of 4-((4-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)phenyl)piperidin-1-yl)cyclohexyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (Compound 1)



Step-i: Synthesis of tert-butyl 4-(4-(3-amino-6-chloropyridazin-4-yl)phenyl)-3,6-dihydropyridine-1(2H)-carboxylate (Intermediate-13)

To a stirred solution of 4-bromo-6-chloropyridazin-3-amine (4.4g, 11.41 mmol), tert-butyl 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-3,6-dihydropyridine-1(2H)-carboxylate (2.38g, 11.41 mmol) in 1,4-dioxane (80 mL) and water (10 mL) was added K_2CO_3 (4.73g, 34.25 mmol) and degassed with nitrogen for 10 min. followed by $Pd(dppf)_2Cl_2$.DCM (0.93g, 1.14 mmol) was added and the reaction mixture was heated for 4h at 70 °C in a sealed

tube. Once the reaction was completed (monitored by TLC), the reaction mixture was diluted with EtOAc. The combined organic layer was washed with water, brine, dried over anhydrous sodium sulphate, and concentrated under vacuum to get crude product which was purified by combi flash column chromatography using 2-3% methanol in DCM as eluent to afford the title compound as white solid (3.2g, 72%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.59-7.52 (m, 4H), 7.36 7.36 (s, 1H), 6.39 (bs, 2H), 6.26 (s, 1H), 4.02 (bs, 2H), 3.56 (m, 2H), 2.50 (m, 2H), 1.43 (s, 9H); LC-MS: m/z 387.1 (M+H).

Step-ii: Synthesis of tert-butyl 4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)phenyl)-3,6-dihydropyridine-1(2H)-carboxylate (Intermediate-14)

To a stirred solution of tert-butyl 4-(4-(3-amino-6-chloropyridazin-4-yl)phenyl)-3,6-dihydropyridine-1(2H)-carboxylate (3g, 7.75 mmol), (2-hydroxyphenyl)boronic acid (1.60g, 11.6 mmol) in 1,4-dioxane (50 mL) and water (13 mL) was added K_2CO_3 (3.21g, 23.26 mmol) and degassed with nitrogen for 10 min. followed by $Pd(dppf)_2Cl_2$.DCM (0.63g, 0.77 mmol) was added and the reaction mixture was heated for 4h at 100 °C in a sealed tube. Once the reaction was completed (monitored by TLC), the reaction mixture was diluted with EtOAc. The combined organic layer was washed with water, and brine, dried over anhydrous sodium sulphate, and concentrated under vacuum to give the residue which was purified by combi flash column chromatography using 3-4% methanol in DCM as eluent to afford the title compound as off white solid (0.18g, 52%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.62 (s, 1H), 8.01 (s, 1H), 7.95 (d, J = 10.4 Hz, 1H), 7.62 (bs, 4H), 7.25 (m, 1H), 6.94-6.87 (m, 2H), 6.49 (bs, 2H), 6.28 (s, 1H), 4.04 (bs, 2H), 3.57 (m, 2H), 2.55 (m, 2H), 1.44 (s, 9H). LC-MS: m/z 445.3 (M+H).

Step-iii: Synthesis of tert-butyl 4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl) phenyl)piperidine-1-carboxylate (Intermediate-15)

To a stirred solution of tert-butyl 4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)phenyl)-3,6-dihydropyridine-1(2H)-carboxylate (2.6g, 5.84 mmol) in ethanol (30 mL) and THF (30 mL) was added 10% Pd-C (1g) at 0 °C and then reaction mixture was stirred under hydrogen atmosphere for 12 h. After completion of the reaction, the reaction mixture was filtered with celite bed and washed with 10% MeOH in DCM. The filtrate was concentrated under reduced pressure to afford the title compound as pale yellow solid (2.2g, 84%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.59 (s, 1H), 7.96 (s, 1H), 7.90 (d, J = 10.8 Hz, 1H), 7.53 (d, J = 8 Hz, 2H), 7.39 (d, J = 8 Hz, 2H), 7.22-7.18 (m, 1H), 6.88-6.81 (m, 2H), 6.41 (bs, 2H), 4.07-4.04

(m, 2H), 3.12 (d, *J* = 48 Hz, 1H), 2.85-2.70 (m, 2H), 1.77-1.69 (m, 2H), 1.56-1.44 (m, 2H), 1.38 (s, 9H); LC-MS: m/z 447.2 (M+H).

Step-iv: Synthesis of 2-(6-amino-5-(4-(piperidin-4-yl)phenyl)pyridazin-3-yl)phenol hydrochloride (Intermediate-16)

To a stirred solution of tert-butyl 4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)phenyl)piperidine-1-carboxylate (1g, 2.17 mmol) in DCM (5 mL) was added 4 N dioxane hydrochloride (10 mL) at 0 °C and then slowly brought to RT and stirred for 1h. The reaction mixture was evaporated under reduced pressure, the resultant residue was washed with diethyl ether and dried under vacuum to afford the title compound as yellow solid (0.75g, crude). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.26-9.40 (m, 1H), 8.37 (bs, 1H), 8.19 (s, 1H), 7.65 (d, *J* = 7.6 Hz, 2H), 7.50 (d, *J* = 7.6 Hz, 2H), 7.39 (t, *J* = 7.6 Hz, 1H), 7.15 (d, *J* = 8.4 Hz, 1H), 7.00 (t, *J* = 7.6 Hz, 1H), 6.41 (bs, 2H), 3.45-3.60 (m, 2H), 3.08-2.97 (m, 2H), 2.05-1.95 (m, 4H); LC-MS: m/z 347.2 (M+H).

Step-v: Synthesis of tert-butyl (4-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl) phenyl)piperidin-1-yl)cyclohexyl)carbamate (Intermediate-17)

To a stirred solution of 2-(6-amino-5-(4-(piperidin-4-yl)phenyl)pyridazin-3-yl)phenol hydrochloride (0.5g, 1.44 mmol) and tert-butyl (4-oxocyclohexyl)carbamate (0.30g, 1.44 mmol) in 9mL THF:DMSO (2:1) mixture was added KOAc (0.29g, 4.32 mmol) and acetic acid (0.2 mL) and molecular sieves (4A°) and the reaction mixture was stirred at 45 °C for 4 h. Then the reaction mixture was cooled to 0 °C and sodium tri acetoxy borohydride (0.91g, 4.32 mmol) was added and the reaction mixture was stirred for 4 h at RT. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was extracted in DCM, and saturated ammonium chloride wash was given to the organic layer followed by saturated sodium chloride wash. The organic layer dried over anhydrous sodium sulphate and then concentrated under reduced pressure and the resultant residue was washed with diethyl ether and dried under vacuum to afford the title compound as off white solid (0.5g, 64 %). ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.57 (bs, 1H), 10.55 (bs, 1H), 8.00 (s, 1H), 7.94 (d, *J* = 7.2 Hz, 1H), 7.62 (d, *J* = 6.4 Hz, 2H), 7.43 (d, *J* = 8 Hz, 1H), 7.25 (t, *J* = 8 Hz, 1H), 7.03 (bs, 1H), 6.93-6.88 (m, 3H), 6.48 (bs, 2H), 3.68 (bs, 1H), 3.50-3.42 (m, 2H), 3.22-3.16 (m, 2H), 3.01-2.92 (m, 1H), 2.30 -1.96 (m, 5H), 1.95-1.85 (m, 2H), 1.84-1.73 (m, 2H), 1.60-1.48 (m, 2H), 1.40 (s, 9H), 1.39-1.33 (m, 2H); LCMS: m/z 544.3 (M+H).

Step-vi: Synthesis of 2-(6-amino-5-(4-(1-(4-aminocyclohexyl)piperidin-4-yl)phenyl) pyridazin-3-yl)phenol hydrochloride (Intermediate-18)

To a stirred solution of tert-butyl (4-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)phenyl)piperidin-1-yl)cyclohexyl)carbamate (0.7g, 1.28 mmol) in DCM (7 mL), followed by adding 4 N dioxane hydrochloride (7 mL) at 0 °C and then slowly brought to RT and stirred for 4 h. The reaction mixture was evaporated under reduced pressure, the resultant residue was washed with diethyl ether and dried under vacuum to afford the title compound as a yellowish solid (0.56g, 98%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.98 (bs, 1H), 8.30 (bs, 1H), 8.14 (bs, 2H), 8.12 (s, 1H), 7.68 (d, *J* = 7.6 Hz, 1H), 7.62 (d, *J* = 8 Hz, 2H), 7.47 (d, *J* = 8 Hz, 2H), 7.45 (t, *J* = 7.6 Hz, 1H), 7.04 (d, *J* = 7.6 Hz, 1H), 6.96 (t, *J* = 7.6 Hz, 1H), 3.53-3.34 (m, 2H), 3.22-2.91 (m, 4H), 2.35-2.27 (m, 2H), 2.12-1.93 (m, 6H), 1.68-1.54 (m, 2H), 1.50-1.36 (m, 2H), 1.36-1.34 (m, 1H):LC-MS: m/z 442.1 (M-H).

Step-vii: Synthesis of 4-((4-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)phenyl) piperidin-1-yl)cyclohexyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (Compound 1)

To a stirred solution of 2-(6-amino-5-(4-(1-(4-aminocyclohexyl)piperidin-4-yl)phenyl)pyridazin-3-yl)phenol hydrochloride (0.55g, 1.24 mmol) in DMSO (5 mL), DIPEA (0.64g, 4.96 mmol) was added and stirred for 5 mins. 2-(2,6-dioxopiperidin-3-yl)-4-fluoroisoindoline-1,3-dione (0.34g, 1.24 mmol) was added to the reaction mixture and heated at 130 °C for 12h. After completion of the reaction, the reaction mixture was poured in ice cold water and stirred for 30 minutes and filtered through Buchner funnel to get crude as a solid. The crude product was purified first by combi flash column chromatography using 3-4% methanol in DCM to afford the title compound as yellow solid as a racemic mixture (0.2g, 23 %)**:** ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.6 (bs, 1H), 11.10 (d, J = 3.6 Hz, 1H), 8.00 (s, 1H), 7.95 (d, J = 8 Hz, 1H), 7.58 (m, 3H), 7.44 (d, J = 8 Hz, 2H), 7.22 (t, J = 7.6 Hz, 1H), 7.16 (d, J = 8 Hz, 1H), 7.05 (t, J = 7.6 Hz, 1H), 6.92 (d, J = 8 Hz, 1H), 6.87 (t, J = 8 Hz, 1H), 6.48 (d, J = 8 Hz, 0.5H), 6.44 (bs, 2H), 6.28 (d, J = 8 Hz, 0.5H), 5.11-5.02 (m, 1H), 3.87 (bs, 0.5H), 3.53 (bs, 0.5H), 3.35 (bs, 2H), 3.09-2.83 (m, 3H), 2.62-2.54 (m, 3H), 2.42-2.16 (m, 3H), 2.11-1.97 (m, 2H), 1.92-1.76 (m, 4H), 1.75-1.62 (m, 4H), 1.60-1.45 (m, 1H): LC-MS: m/z 700.1 (M+H).

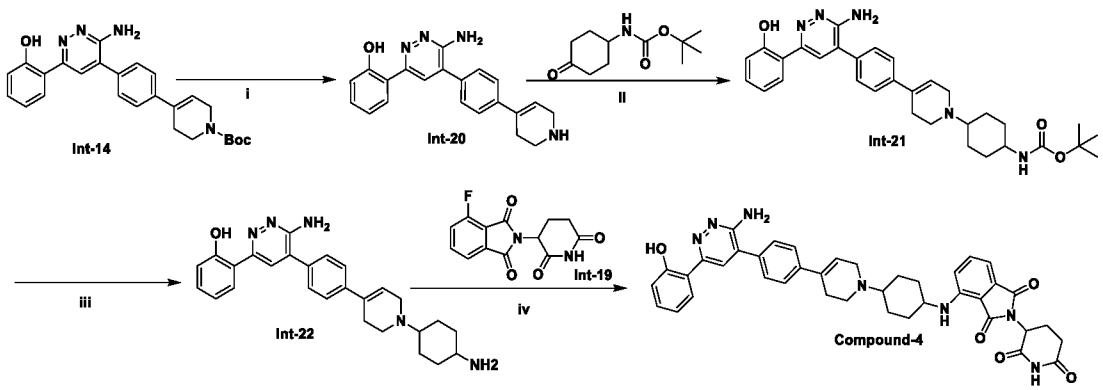
Compounds 2 and 3: Stereoisomers of Compound 1 (Stereoisomer 1a and Stereoisomer 1b)

Compounds 2 and 3 were obtained by HPLC of Compound 1 using the following method COLUMN:Waters X bridge, c18 (250 ×21.2mm), 5µ, Eluent A = 5 mm ammonium acetate in Water, Eluent B % = ACN, Flow 18ml/min.

Compound 2 (Stereoisomer-1a of compound 1): ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.72 (bs, 1H), 11.15 (s, 1H), 8.05 (s, 1H), 7.99 (d, J = 8 Hz, 1H), 7.65-7.60 (m, 3H), 7.47 (d, J = 8.4 Hz, 2H), 7.28 (t, J = 8 Hz, 1H), 7.21 (d, J = 8 Hz, 1H), 7.07 (d, J = 6.8 Hz, 1H), 6.96 (d, J = 8 Hz, 1H), 6.91 (t, J = 8 Hz, 1H), 6.48 (bs, 2H), 6.21 (d, J = 8 Hz, 1H), 5.11-5.06 (m, 1H), 3.54 (bs, 1H), 3.40 (bs, 2H), 3.02-2.99 (m, 2H), 2.91-2.88 (m, 1H), 2.64-2.54 (m, 3H), 2.44-2.36 (m,2H), 2.16-2.02 (m, 2H), 1.94-1.83 (m, 3H), 1.78-1.60 (m, 3H), 1.58-1.44 (m, 2H) 1.42-1.31 (m, 2H): LC-MS: m/z 700.5 (M+H).

Compound 3 (Stereoisomer-1b of compound 1): ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.70 (bs, 1H), 11.15 (s, 1H), 8.04 (s, 1H), 7.99 (d, J = 7.6 Hz, 1H), 7.65 (d, J= 8 Hz, 1H), 7.61 (d, J= 8 Hz, 2H), 7.48 (d, J = 8.4 Hz, 2H), 7.28 (t, J = 7.6 Hz, 1H), 7.20 (d, J = 8 Hz, 1H), 7.09 (d, J = 7.2 Hz, 1H), 6.96 (d, J = 8 Hz, 1H), 6.91 (t, J = 7.6 Hz, 1H), 6.52 (d, J = 8.4 Hz, 1H), 6.48 (bs, 2H), 5.14-5.09 (m, 1H), 3.90 (bs, 1H), 3.45 (bs, 2H), 3.12-3.05 (m, 2H), 2.94-2.85 (m, 1H), 2.64-2.55 (m, 3H), 2.43-2.36 (m, 2H), 2.32-2.25 (m, 2H), 2.11-2.05 (m, 1H), 1.92-1.81 (m, 4H), 1.78-1.68 (m, 4H), 1.65-1.59 (m, 1H); LC-MS: m/z 700.5 (M+H).

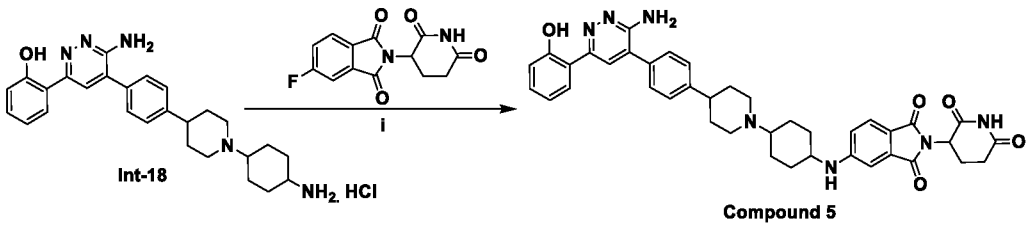
Example-II: Synthesis of 4-((4-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl) phenyl)-3,6-dihydropyridin-1(2H)-yl)cyclohexyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (Compound 4)



Intermediates 20 to 22 and Compound-4 were prepared by a procedure similar to the one described in Example-I with appropriate variations in reactants, quantities of reagents, protections and deprotections, solvents, and reaction conditions. ^{1}H NMR (400 MHz, DMSO-

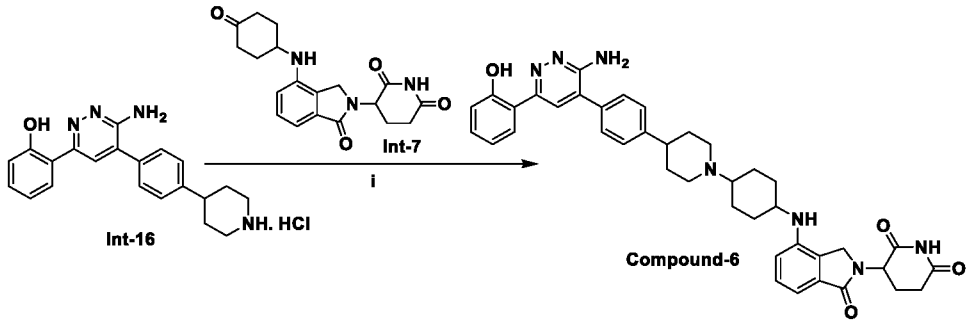
d_6): δ 13.62 (bs, 1H), 11.10 (s, 1H), 8.01 (s, 1H), 7.94 (d, J = 8 Hz, 1H), 7.58 (bs, 4H), 7.35 (t, J = 7.6 Hz, 1H), 7.20-7.04 (m, 3H), 6.92 (d, J = 8 Hz, 1H), 6.87 (t, J = 8 Hz, 1H), 6.47 (d, J = 8 Hz, 0.5H), 6.48 (bs, 2H), 6.32 (bs, 1H), 6.19 (d, J = 8 Hz, 0.5H), 5.09-5.03 (m, 1H), 3.88 (bs, 0.5H), 3.54 (bs, 0.5H), 3.27 (m, 3H), 2.93-2.75 (m, 3H), 2.62-2.52 (m, 3H), 2.12-1.90 (m, 4H), 1.92-1.35 (m, 7H): LC-MS: m/z 698.05 (M+H).

Example-III: Synthesis of 5-((4-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl) phenyl)piperidin-1-yl)cyclohexyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (Compound 5)



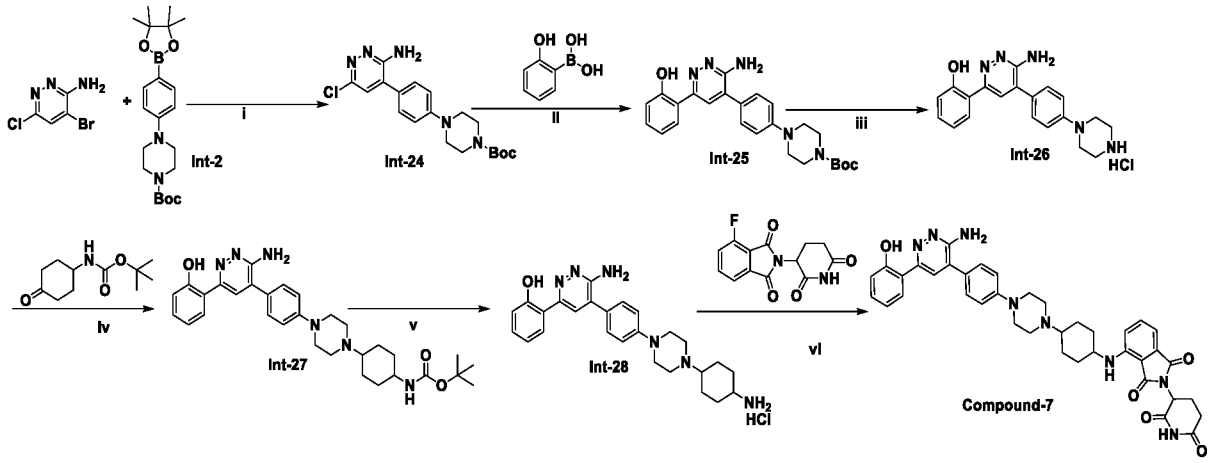
To a stirred solution of 2-(6-amino-5-(4-(1-(4-aminocyclohexyl)piperidin-4-yl)phenyl)pyridazin-3-yl)phenol hydrochloride (0.12g, 0.27 mmol) in DMSO (1 mL) was added DIPEA (0.35g, 2.70 mmol)) and stirred for 5 mins. 2-(2,6-dioxopiperidin-3-yl)-4-fluoroisoindoline-1,3-dione (0.075 g, 0.27 mmol) was added to the reaction mixture and heated at 130°C for 12h. After completion of the reaction, the reaction mixture was poured into ice cold water and stirred for 30 minutes and filtered through Buchner funnel to get crude product (as a solid). The crude product was purified first by combi flash column chromatography using 3-4% methanol in DCM system followed by prep HPLC, pure fractions were dried under lyophilization to afford the title compound as off white solid (18mg, 9.5 %). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.06 (s, 1H), 9.66 (bs, 1H), 9.58 (bs, 1H), 8.02 (s, 1H), 7.90 (d, J = 8 Hz, 1H), 7.64-7.59 (m, 4H), 7.43 (d, J = 7.6 Hz, 2H), 7.26 (t, J = 8 Hz, 1H), 7.07 (bs, 1H), 7.05-6.87 (m, 3H), 6.73 (bs, 2H), 5.07-4.98 (m, 1H), 3.85 (m, 1H), 3.24- 3.16 (m, 2H), 3.05-2.82 (m, 3H), 2.62-2.45 (m, 4H), 2.18-1.80 (m, 10H), 1.79-1.65 (m, 3H): LC-MS: m/z 698.4 (M-H).

Example-IV: Synthesis of 3-(4-((4-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl) phenyl)piperidin-1-yl)cyclohexyl)amino)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (Compound 6)



To a stirred solution of 2-(6-amino-5-(4-(piperidin-4-yl)phenyl)pyridazin-3-yl)phenol hydrochloride (0.06g, 0.16 mmol) and 3-(1-oxo-4-((4-oxocyclohexyl)amino)isoindolin-2-yl)piperidine-2,6-dione (0.30g, 1.44 mmol) in methanol (2 ml) was added a pre-mixture solution of $ZnCl_2$ (0.08 g, 0.05 mmol) and sodium cyanoborohydride (0.008 g, 0.12 mmol) in methanol (1 mL), and the reaction mixture was stirred at RT for 12 h. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was quenched to ice water and the solid formed was filtered and dried. Filtrate was taken and extracted with 20% MeOH in DCM. The organic layer was collected washed with brine solution dried over Na_2SO_4 and concentrated to get crude product. The Crude product was purified first by combi flash column chromatography using 3-4% methanol in DCM system followed by prep HPLC, pure fractions were dried under lyophilization to afford the title compound as light yellow solid (0.02g, 17 %). ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.62 (bs, 1H), 11.02 (s, 1H), 8.31 (s, 1H), 7.99 (s, 1H), 7.94 (d, J= 7.6 Hz, 1H), 7.58 (d, J= 8.4 Hz, 2H), 7.43 (d, J = 8 Hz, 1H), 7.29-7.18 (m, 3H), 6.91-6.86 (m, 2H), 6.80 (d, J = 8 Hz, 1H), 6.65 (bs, 1H), 6.44 (bs, 2H), 5.33-5.32 (m, 1H), 5.21 (d, J= 6.4Hz, 1H), 5.15-5.11 (m, 1H), 4.31-4.16 (m, 2H), 3.58-3.50 (m, 2H), 3.17-3.11 (m, 2H), 2.93-2.88 (m, 2H), 2.60-2.53 (m, 2H), 2.30-2.11 (m, 2H), 2.08-2.02 (m, 3H), 1.89-1.75 (m, 3H), 1.70-1.59 (m, 3H), 1.46-1.45 (m, 2H).: LC-MS: m/z 684.2 (M-H).

Example-V: Synthesis of 4-((4-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl) phenyl)piperidin-1-yl)cyclohexyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (Compound 7)



Step-i: Synthesis of tert-butyl 4-(4-(3-amino-6-chloropyridazin-4-yl)phenyl)piperazine-1-carboxylate (Intermediate-24)

To a stirred solution of 4-bromo-6-chloropyridazin-3-amine (1.6g, 7.72 mmol), tert-butyl 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperazine-1-carboxylate (2g, 5.15 mmol) in 1,4-dioxane (30 mL) and water (5 mL) was added K_2CO_3 (1.77g, 12.8 mmol) and degassed with nitrogen for 10 min, followed by adding $Pd(dppf)_2Cl_2$.DCM (0.42g, 0.52 mmol) and the reaction mixture was heated at 120 °C in sealed tube for 16h. Once the reaction was completed (monitored by TLC), the reaction mixture was diluted with EtOAc. The combined organic layer was washed with water, brine, dried over anhydrous sodium sulphate and concentrated under vacuum to get crude product which was purified by combi flash column chromatography using 80% EtOAc in Hexane as eluent to afford the title compound as off white solid (0.98g, 48.8%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.48 (d, J= 8.8 Hz, 2H), 7.32 (s, 1H), 7.10 (d, J= 8.8 Hz, 2H), 6.32 (bs, 2H), 3.50 (m, 4H), 3.25 (m, 4H), 1.46 (s, 9H); LC-MS: m/z 390.1 (M+H).

Step-ii: Synthesis of tert-butyl 4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl) phenyl)piperazine-1-carboxylate (Intermediate-25)

To a stirred solution of tert-butyl 4-(4-(3-amino-6-chloropyridazin-4-yl)phenyl)piperazine-1-carboxylate (0.98g, 2.51 mmol), (2-hydroxyphenyl)boronic acid (0.69g, 5.02 mmol) in 1,4-dioxane (15 mL) and water (3 mL) was added K_2CO_3 (0.86g, 6.28 mmol) and degassed with nitrogen for 15 min, followed by adding $Pd(dppf)_2Cl_2$.DCM (0.20g,

0.25 mmol) and the reaction mixture was heated at 120 °C in a sealed tube for 16h. Once the reaction was completed (monitored by TLC), the reaction mixture was diluted with EtOAc. The combined organic layer was washed with water, brine, dried over anhydrous sodium sulphate and concentrated under vacuum to give the residue which was purified by combi flash column chromatography using 60% EtOAc in Hexane as eluent to afford the title compound as off white solid (0.6g, 53%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.78 (s, 1H), 7.99-7.96 (m, 2H), 7.58 (d, J= 8.8 Hz, 2H), 7.28 (dt, J = 7.6, 1.6 Hz, 1H), 7.14 (d, J= 8.8 Hz, 2H), 6.96-6.90 (m, 2H), 6.43 (bs, 2H), 3.52 (m, 4H), 3.27 (m, 4H), 1.47 (s, 9H); LC-MS: m/z 448.0 (M+H).

Step-iii: Synthesis of 2-(6-amino-5-(4-(piperazin-1-yl)phenyl)pyridazin-3-yl)phenol hydrochloride (Intermediate-26)

To a stirred solution of tert-butyl 4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)phenyl)piperazine-1-carboxylate (0.68 g, 1.53 mmol) in DCM (3 mL) was added 4 N dioxane hydrochloride (3 mL) at 0 °C and then slowly brought to RT and stirred for 1h. The reaction mixture was evaporated under reduced pressure, the resultant residue was washed with diethyl ether and dried under vacuum to afford the title compound as yellowish solid (0.58 g, 99%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.36 (bs, 2H), 8.22 (bs, 1H), 8.13 (s, 1H), 7.66 (d, *J* = 6.8 Hz, 1H), 7.59 (d, *J* = 7.6 Hz, 2H), 7.40 (t, *J* = 7.2 Hz, 1H), 7.22 (d, *J* = 8.8 Hz, 2H), 7.10 (t, *J* = 8.4 Hz, 1H), 7.01 (t, *J* = 7.6 Hz, 1H), 3.58 (m, 4H), 3.25 (m, 4H); LC-MS: m/z 348.2 (M+H).

Step-iv: Synthesis of tert-butyl (4-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl) phenyl)piperidin-1-yl)cyclohexyl)carbamate (Intermediate-27)

To a stirred solution of 2-(6-amino-5-(4-(piperazin-1-yl)phenyl)pyridazin-3-yl)phenol hydrochloride (0.3g, 0.78 mmol) and tert-butyl (4-oxocyclohexyl)carbamate (0.16g, 0.78 mmol) in 4.5mL THF:DMSO (2:1) mixture was added KOAc (0.23g, 2.34 mmol) and acetic acid (0.16 mL) and molecular sieves (4A°) and the reaction mixture was stirred at 45°C for 4 hours. Then the reaction mixture was cooled to 0°C and sodium triacetoxy borohydride (0.48g, 2.34 mmol) was added and the reaction mixture was stirred for 4h at RT. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was extracted in DCM and saturated ammonium chloride wash was given to the organic layer followed by saturated sodium chloride wash. The organic layer was dried over anhydrous sodium sulphate and then concentrated under reduced pressure and the resultant residue was washed with diethyl ether and dried under vacuum to afford the title compound as off white solid (0.14g, 32.9 %).

^{1}H NMR (400 MHz, DMSO-d_6): δ 13.72 (bs, 1H), 10.18 (bs, 1H), 7.98 (s, 1H), 7.96 (d, *J* = 8.0 Hz, 1H), 7.60 (bs, 2H), 7.28 (t, *J* = 7.6 Hz, 1H), 7.25-7.14 (m, 2H), 6.98-6.91 (m, 2H), 6.45 (bs, 2H), 4.05 (bs, 2H), 3.70 (m, 1H), 3.59 (bs, 2H), 3.26 (m, 4H), 2.69-2.62 (m, 1H), 1.94-1.78 (m, 4H), 1.61-1.48 (m, 4H), 1.44 (s, 9H); LCMS: m/z 545.3 (M+H).

Step-v: Synthesis of 2-(6-amino-5-(4-(4-(4-aminocyclohexyl)piperazin-1-yl)phenyl) pyridazin-3-yl)phenol hydrochloride (Intermediate-28)

To a stirred solution of tert-butyl (4-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)phenyl)piperidin-1-yl)cyclohexyl)carbamate (0.14g, 0.25 mmol) in DCM (2 mL) was added 4 N dioxane hydrochloride (2 mL) at 0 °C and then slowly brought to RT and stirred for 4 h. The reaction mixture was evaporated under reduced pressure, the resultant residue was washed with diethyl ether and dried under vacuum to afford the title compound as yellowish solid (0.14g, crude). LCMS: m/z 445.3 (M+H).

Step-vi: Synthesis of 4-((4-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)phenyl) piperidin-1-yl)cyclohexyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (Compound 7)

To a stirred solution of 2-(6-amino-5-(4-(4-(4-aminocyclohexyl)piperazin-1-yl) phenyl)pyridazin-3-yl)phenol hydrochloride (0.14g, 0.29 mmol) in DMSO (1.5 mL) was added DIPEA (0.11g, 0.87 mmol)) and stirred for 5 mins, 2-(2,6-dioxopiperidin-3-yl)-4-fluoroisoindoline-1,3-dione (0.08g, 0.29 mmol) was added to the reaction mixture and heated at 130 °C for 16h. After completion of the reaction, the reaction mixture was poured in ice cold water and stirred for 30 minutes and filtered through Buchner funnel to get crude product (as a solid). The crude product was purified first by combi flash column chromatography using 3-4% methanol in DCM system followed by prep HPLC, pure fractions were dried under lyophilization to afford the title compound as yellow solid (0.08g, 36 %). ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.74 (bs, 1H), 11.11 (s, 1H), 7.94 (m, 2H), 7.58 (t, J = 7.6 Hz, 1H), 7.52 (d, J = 8.4 Hz, 2H), 7.24 (t, J = 7.6 Hz, 1H), 7.16 (d, J = 8.8 Hz, 1H), 7.09 (d, J = 9.2 Hz, 2H), 7.06-7.02 (m, 1H), 6.91 (d, J = 8.4 Hz, 1H), 6.87 (d, J = 8 Hz, 1H), 6.44 (d, J = 8 Hz, 0.5H), 6.38 (bs, 2H), 6.18 (d, J = 8 Hz, 0.5H), 5.11-5.02 (m, 1H), 3.87 (bs, 0.5H), 3.54 (bs, 0.5H), 3.26 (bs, 4H), 2.93-2.84 (m, 2H), 2.66 (bs, 4H), 2.60-2.53 (m, 2H), 2.35-2.20 (m, 1H), 2.11-2.01 (m, 2H), 1.92-1.35 (m, 6H): LC-MS: m/z 701.3 (M+H).

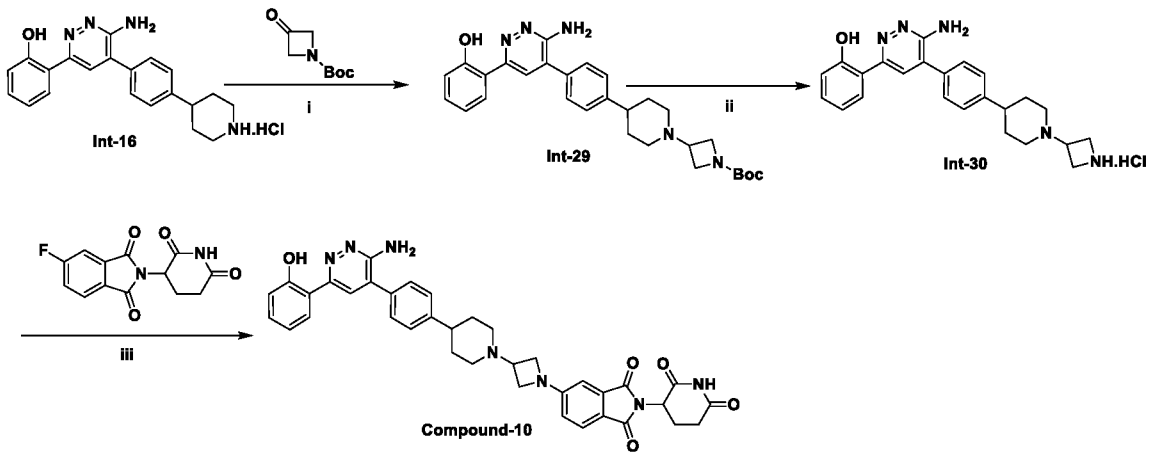
Compounds 8 and 9: Stereoisomers of Compound 7 (Stereoisomer 7a and Stereoisomer 7b)

Compounds 8 and 9 were obtained by HPLC of Compound 7 using following method COLUMN: Waters , xselect ,c18 (250 ×19mm) 5µ, Eluent A = 5 mm ammonium acetate in Water, Eluent B % = ACN. Flow 15ml/min.

Compound 8 (Stereoisomer-7a of Compound 7): ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.74 (bs, 1H), 11.10 (s, 1H), 7.94 (m, 2H), 7.58 (t, J = 7.6 Hz, 1H), 7.52 (d, J = 8.4 Hz, 2H), 7.23 (t, J = 7.6 Hz, 1H), 7.18 (d, J = 8.8 Hz, 1H), 7.09 (d, J = 9.2 Hz, 2H), 7.06 (d, J = 8 Hz, 1H), 6.91 (d, J = 8.4 Hz, 1H), 6.87 (d, J = 8 Hz, 1H), 6.39 (bs, 2H), 6.18 (d, J = 8 Hz, 1H), 5.08-5.02 (m, 1H), 3.53 (bs, 1H), 3.30-3.22 (m, 4H), 2.95-2.83 (m, 2H), 2.67 (bs, 4H), 2.62-2.53 (m, 2H), 2.10-1.85 (m, 5H), 1.52-1.30 (m, 4H): LC-MS: m/z 701.2 (M+H).

Compound 9 (Stereoisomer-7b of Compound 7): ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.75 (bs, 1H), 11.11 (s, 1H), 7.95-7.93 (m, 2H), 7.59 (t, J = 7.2 Hz, 1H), 7.52 (d, J = 8 Hz, 2H), 7.24 (t, J = 7.6 Hz, 1H), 7.16 (d, J = 8.8 Hz, 1H), 7.09 (d, J = 8.4 Hz, 2H), 7.05 (d, J = 8.8 Hz, 1H), 6.91 (d, J = 8.4 Hz, 1H), 6.87 (d, J = 8 Hz, 1H), 6.45 (d, J = 8 Hz, 1H), 6.38 (bs, 2H), 5.10-5.02 (m, 1H), 3.85 (bs, 1H), 3.26 (bs, 4H), 2.94-2.82 (m, 2H), 2.66 (bs, 4H), 2.57-2.50 (m, 2H), 2.32 (m, 1H), 2.08-1.95 (m, 2H), 1.85-1.45 (m, 6H): LC-MS: m/z 701.2 (M+H).

Example-VI: Synthesis of 5-(3-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl) phenyl)piperidin-1-yl)azetidin-1-yl)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (Compound 10)



Step-i: Synthesis of tert-butyl 3-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl) phenyl)piperidin-1-yl)azetidine-1-carboxylate (Intermediate-29)

To a stirred solution of 2-(6-amino-5-(4-(piperazin-1-yl)phenyl)pyridazin-3-yl)phenol hydrochloride (0.2g, 0.57 mmol) and tert-butyl 3-oxoazetidine-1-carboxylate (0.109g, 0.63 mmol) in 3 mL THF:DMSO (2:1) mixture was added KOAc (0.17g, 1.73 mmol) and acetic acid (0.2 mL) and molecular sieves (4A°) and the reaction mixture was stirred at 45 °C for 4 hours. Then the reaction mixture was cooled to 0 °C and sodium cyanoborohydride (0.109 g, 1.73 mmol) was added and the reaction mixture was stirred for 12h at RT. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was extracted in 10% MeOH/DCM and brine wash was given to the organic layer and dried over anhydrous sodium sulphate and then concentrated under reduced pressure to get the crude product. The crude product was purified by combi flash column chromatography by eluting 2-3% MeOH/DCM to afford the title compound as a light yellow solid (0.19g, 65%). LCMS: m/z 502.2 (M+H).

Step-ii: Synthesis of 2-(6-amino-5-(4-(1-(azetidin-3-yl)piperidin-4-yl)phenyl)pyridazin-3-yl)phenol hydrochloride (Intermediate-30)

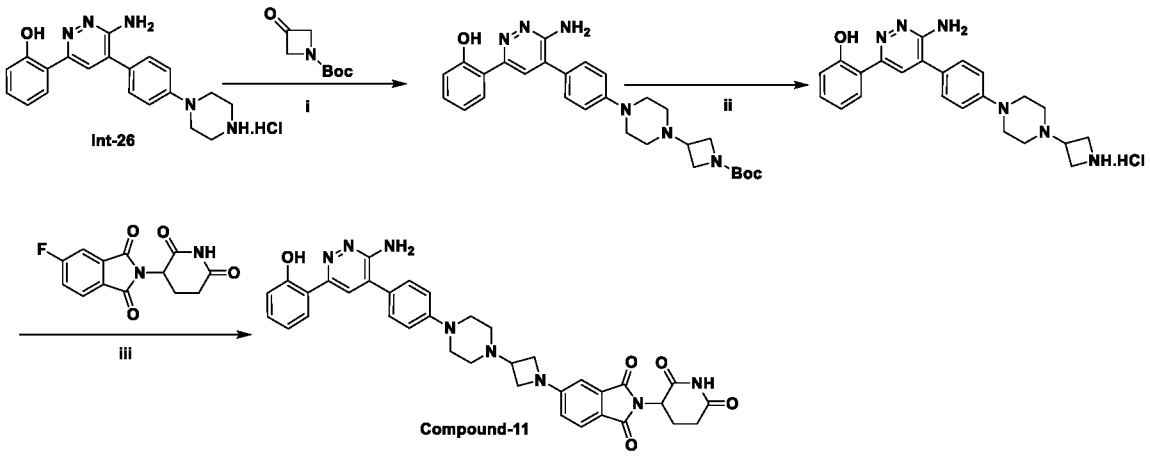
To a stirred solution of tert-butyl 3-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)phenyl)piperidin-1-yl)azetidine-1-carboxylate (0.17g, 0.34 mmol) in DCM (1 mL) was added 4 N dioxane hydrochloride (5 mL) at 0 °C and then slowly brought to RT and stirred for 2 h. The reaction mixture was evaporated under reduced pressure, the resultant residue was washed with diethyl ether and dried under vacuum to afford the title compound as yellowish solid (0.17g, crude). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.56 (bs, 1H), 9.93 (bs, 1H), 9.19 (bs, 1H), 8.24 (bs, 1H), 8.14 (s, 1H), 7.64 (d, J= 8.4 Hz, 3H), 7.49 (d, J= 8 Hz, 2H), 7.37-7.34 (m, 1H), 7.08 (d, J= 6.8 Hz, 1H), 6.96 (t, J= 7.2 Hz, 1H), 4.61-4.54 (m, 2H), 4.33-4.30 (m, 1H), 4.12 (bs, 2H), 3.52-3.49 (m, 3H), 3.04-2.93 (m, 2H), 2.53 (bs, 2H), 2.20-2.04 (m, 2H); LCMS: m/z 402.05 (M+H).

Step-iii: Synthesis of 5-(3-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)phenyl) piperidin-1-yl)azetidin-1-yl)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (Compound 10)

To a stirred solution of 2-(6-amino-5-(4-(1-(azetidin-3-yl)piperidin-4-yl)phenyl)pyridazin-3-yl)phenol hydrochloride (0.1g, 0.24 mmol) in DMSO (1 mL) was added DIPEA (0.22g, 1.75 mmol) and stirred for 5 mins. 2-(2,6-dioxopiperidin-3-yl)-5-fluoroisoindoline-1,3-dione (0.076g, 0.27 mmol) was added in the microwave vessel and the

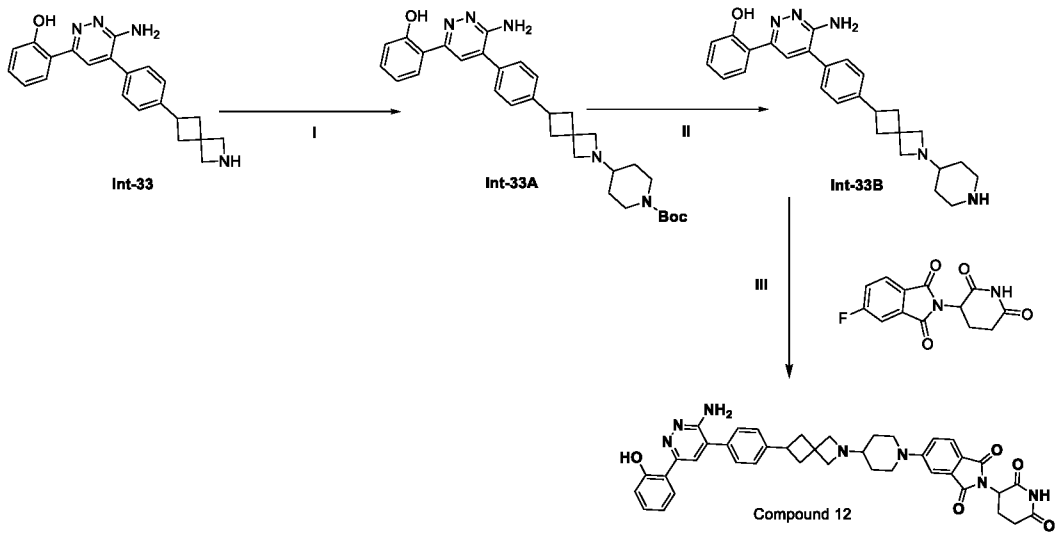
reaction mixture was heated at 120 °C for 1h. After completion of the reaction, the reaction mixture was poured into ice cold water and stirred for 30 minutes and filtered through Buchner funnel to get crude product as a solid. The crude product was purified by combi flash column chromatography using 2-3% methanol in DCM to afford the title compound as light yellow solid (0.05g, 30.5 %). ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.63 (bs, 1H), 11.07 (s, 1H), 8.00 (s, 1H), 7.94 (d, J = 7.6 Hz, 1H), 7.66 (d, J= 8.4 Hz, 1H), 7.57 (d, J= 8 Hz, 2H), 7.44 (d, J = 8.4 Hz, 2H), 7.24 (t, J = 7.2 Hz, 1H), 6.92-6.85 (m, 2H), 6.81 (s, 1H), 6.68-6.66 (dd, J = 8, 1.6 Hz 1H), 6.45 (bs, 2H), 5.08-5.03 (m, 1H), 4.16-4.12 (m, 2H), 3.89-3.86 (m, 2H), 3.37 (m, 1H), 2.98 (d, J = 10 Hz, 2H), 2.95-2.85 (m, 1H), 2.64-2.49 (m, 3H), 2.07-1.98 (m, 3H), 1.86-1.83 (m, 2H), 1.73-1.70 (m, 2H); LC-MS: m/z 658.3 (M+H).

Example-VII: Synthesis of 5-(3-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl) phenyl)piperazin-1-yl)azetidin-1-yl)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (Compound 11)



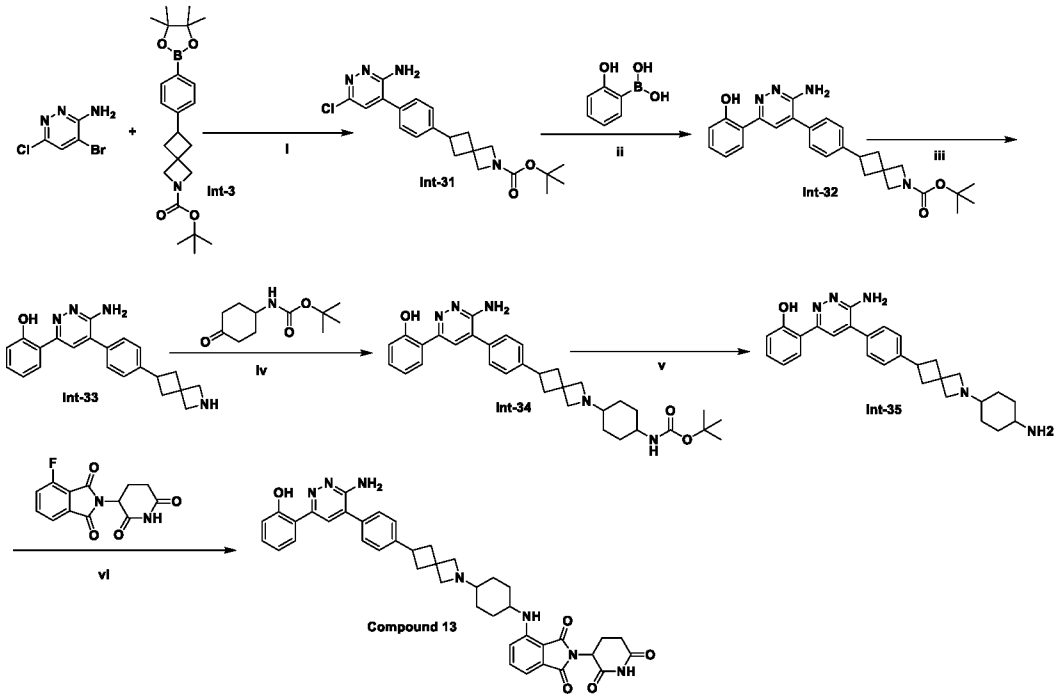
Compound-11 was prepared by procedure similar to the one described in Example-VI with appropriate variations in reactants, quantities of reagents, protections and deprotections, solvents and reaction conditions. ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.74 (bs, 1H), 11.07 (s, 1H), 7.94 (s, 1H), 7.93 (d, J = 3.6 Hz, 1H), 7.66 (d, J = 8.4 Hz, 1H), 7.53 (d, J = 8.4 Hz, 1H), 7.24 (t, J = 7.6 Hz, 1H), 7.11 (d, J = 8 Hz, 2H), 6.92-6.88 (m, 2H), 6.82 (bs, 1H), 6.67 (d, J = 8 Hz, 2H), 6.38 (bs, 2H), 5.09-5.06 (m, 1H), 4.15-4.08 (m, 3H), 3.93 (m, 1H), 3.42 (m, 1H), 3.36 (bs, 4H), 2.92-2.85 (m, 2H), 2.55 (bs, 4H), 2.03-1.97 (m, 2H): LC-MS: m/z 659.3 (M+H).

Example-VIII: Synthesis of 5-(4-(6-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl) phenyl)-2-azaspiro[3.3]heptan-2-yl)piperidin-1-yl)-2-(2,6-dioxopiperidin-3-yl) isoindoline-1,3-dione (Compound 12)



Compound-12 was prepared by a procedure similar to the one described in Example-VII with appropriate variations in reactants, quantities of reagents, protections and deprotections, solvents, and reaction conditions. ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.61 (s, 1H), 11.07 (s, 1H), 7.97 (s, 1H), 7.92 (d, J = 8.0 Hz, 1H), 7.66-7.63 (m, 1H), 7.55 (d, J = 8.0 Hz, 2H), 7.38 (d, J = 8.0 Hz, 2H), 7.30 (s, 1H), 7.25-7.21 (m, 2H), 6.92-6.85 (m, 2H), 6.43 (bs, 2H), 5.07-5.03 (m, 1H), 3.87-3.83 (m, 2H), 3.50-3.41 (m, 1H), 3.31-3.27 (m, 2H), 3.11-3.07 (m, 3H), 2.91-2.82 (m, 2H), 2.66-2.58 (m, 2H), 2.24-2.19 (m, 3H), 2.05-1.98 (m, 1H), 1.71-1.68 (m, 2H), 1.28-1.20 (m, 4H): LC-MS: m/z 698.5 (M+H).

Example-IX: Synthesis of 4-((4-(6-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl) phenyl)-2-azaspiro[3.3]heptan-2-yl)cyclohexyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (Compound 13)



Step-i: Synthesis of tert-butyl 6-(4-(3-amino-6-chloropyridazin-4-yl)phenyl)-2-azaspiro [3.3]heptane-2-carboxylate (Intermediate-31)

To a stirred solution of 4-bromo-6-chloropyridazin-3-amine (0.62g, 3.00 mmol), tert-butyl6-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-2-azaspiro[3.3]heptane-2-carboxylate (0.80g, 2.00 mmol) in 1,4-dioxane (10 mL) and water (2 mL) was added K_2CO_3 (0.69g, 5.00 mmol) and degassed with nitrogen for 10 min, followed by adding $Pd(dppf)Cl_2$.DCM (0.16g, 0.20 mmol) and the reaction mixture was heated for 16 h at 100 ºC in a sealed tube. Once the reaction was completed (monitored by TLC), the reaction mixture was diluted with EtOAc. The combined organic layer was washed with water, brine, dried over anhydrous sodium sulphate, and concentrated under vacuum to get crude product which was purified by combi flash column chromatography using 60-80% Ethyl acetate in hexane to afford the title compound as white solid (0.35g, 42%). ^{1}H NMR (400 MHz, DMSO-d_6): d 7.47 (d, J= 8.4 Hz, 2H), 7.35 (d, J= 8.4 Hz, 2H), 7.32 (s, 1H), 6.33 (bs, 2H), 3.99 (bs, 2H), 3.77 (bs, 2H), 3.47-3.42 (m, 1H), 2.60-2.51 (m, 2H), 2.29-2.23 (m, 2H), 1.37 (s, 9H); LC-MS: m/z 401.1 (M+H).

Step-ii: Synthesis of tert-butyl 6-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl) phenyl)-2-azaspiro[3.3]heptane-2-carboxylate (Intermediate-32)

To a stirred solution of tert-butyl 6-(4-(3-amino-6-chloropyridazin-4-yl)phenyl)-2-azaspiro[3.3]heptane-2-carboxylate (0.35g, 0.87 mmol), (2-hydroxyphenyl)boronic acid (0.24g, 1.74 mmol) in 1,4-dioxane (5 mL) and water (2 mL) was added K_2CO_3 (0.30g, 2.18 mmol) and degassed with nitrogen for 10 min, followed by adding $Pd(dppf)_2Cl_2$.DCM (0.07g, 0.08 mmol) and the reaction mixture was heated for 16 h at 120 °C in a sealed tube. Once the reaction was completed (monitored by TLC), the reaction mixture was diluted with EtOAc. The combined organic layer was washed with water, brine, dried over anhydrous sodium sulphate, and concentrated under vacuum to give the residue which was purified by combi flash column chromatography using 80-100% ethyl acetate in hexane to afford the title compound as off white solid (0.20g, 50%). ^{1}H NMR (400 MHz, DMSO-d_6): d 13.61 (s, 1H), 7.98 (s, 1H), 7.93 (d, *J* = 8 Hz, 1H), 7.57 (d, *J* = 8 Hz, 2H), 7.39 (d, *J* = 8 Hz, 2H), 7.24 (t, *J* = 7.6 Hz, 1H), 6.93-6.88 (m, 2H), 6.44 (bs, 2H), 4.00 (bs, 2H), 3.79 (bs, 2H), 3.48-3.41 (m, 1H), 2.62-2.54 (m, 2H), 2.31-2.28 (m, 2H), 1.37 (s, 9H). LC-MS: m/z 459.2 (M+H).

Step-iii: Synthesis of 2-(5-(4-(2-azaspiro[3.3]heptan-6-yl)phenyl)-6-aminopyridazin-3-yl) phenol (Intermediate-33)

To a stirred solution of tert-butyl 6-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)phenyl)-2-azaspiro[3.3]heptane-2-carboxylate (0.20g, 0.43 mmol) in DCM (2 mL) was added Trifluoroacetic acid (1 mL) at 0 °C and then slowly brought to RT and stirred for 1 h. The reaction mixture was evaporated under reduced pressure, the resultant residue was washed with diethyl ether and dried under vacuum to afford the title compound as a yellowish solid (0.15g, crude). ^{1}H NMR (400 MHz, DMSO-d_6): d 8.65 (bs, 1H), 8.04 (s, 1H), 7.78 (d, *J* = 7.6 Hz, 1H), 7.57 (d, *J* = 8 Hz, 2H), 7.42 (d, *J* = 8 Hz, 2H), 7.31 (t, *J* = 7.6 Hz, 1H), 6.98-6.93 (m, 2H), 6.44 (bs, 2H), 4.13 (t, J = 6.4 Hz, 2H), 3.91 (t, J = 6.4 Hz, 2H), 3.50-3.43 (m, 1H), 2.64 (dt, J = 9.6, 2.8 Hz, 2H), 2.34 (dt, J = 9.6, 2.8 Hz, 2H); LC-MS: m/z 359.2 (M+H).

Step-iv: Synthesis of tert-butyl (4-(6-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl) phenyl)-2-azaspiro[3.3]heptan-2-yl)cyclohexyl)carbamate (Intermediate-34)

To a stirred solution of 2-(5-(4-(2-azaspiro[3.3]heptan-6-yl)phenyl)-6-aminopyridazin-3-yl)phenol (0.15g, 0.41 mmol) and tert-butyl (4-oxocyclohexyl)carbamate (0.08g, 0.41 mmol) in 9 mL THF:DMSO (2:1) mixture was added KOAc (0.08g, 0.83 mmol) and acetic acid (0.1 mL) and molecular sieves (4A°) and the reaction mixture was stirred at 45 °C for 4 hours. Then

the reaction mixture was cooled to 0°C and sodium triacetoxy borohydride (0.17g, 0.83 mmol) was added and the reaction mixture was stirred for 16 h at RT. The reaction was monitored by TLC. After completion of the reaction the reaction mixture was extracted in DCM and saturated ammonium chloride wash was given to the organic layer followed by saturated sodium chloride wash. The organic layer dried over anhydrous sodium sulphate and then concentrated under reduced pressure, and the resultant residue was washed with diethyl ether and dried under vacuum to afford the title compound as off white solid (0.10g, 43%). ^{1}H NMR (400 MHz, DMSO-d_6): d 13.59 (s, 1H), 7.97 (s, 1H), 7.92 (d, *J* = 8 Hz, 1H), 7.57 (d, *J* = 8 Hz, 2H), 7.40 (d, *J* = 8 Hz, 2H), 7.25 (t, *J* = 8.4 Hz, 1H), 6.93-6.86 (m, 2H), 6.44 (bs, 2H), 4.31-4.20 (, 1H), 4.15-3.97 (m, 2H), 3.52-3.41 (m, 2H), 3.25-3.30 (m, 2H), 3.05-2.95 (m, 1H), 2.62-2.55 (m, 2H), 2.31-2.15 (m, 3H), 1.88-1.75 (m, 2H), 1.65-1.43 (m, 6H), 1.37 (s, 9H). LCMS: m/z 556.3 (M+H).

Step-v: Synthesis of 2-(6-amino-5-(4-(2-(4-aminocyclohexyl)-2-azaspiro[3.3]heptan-6-yl) phenyl)pyridazin-3-yl)phenol (Intermediate-35)

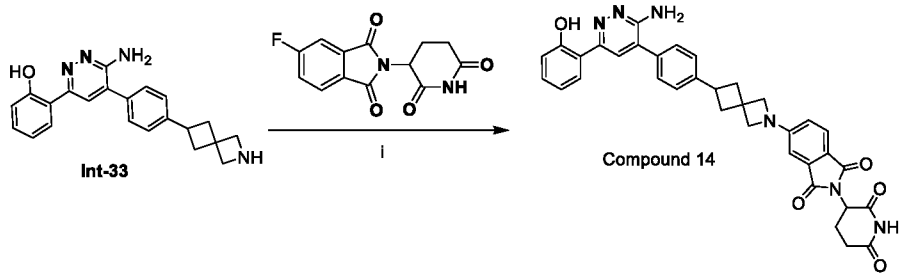
To a stirred solution of tert-butyl (4-(6-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)phenyl)-2-azaspiro[3.3]heptan-2-yl)cyclohexyl)carbamate (0.10g, 0.18 mmol) in DCM (2 mL) was added Trifluoroacetic acid (0.2 mL) at 0 °C and then slowly brought to RT and stirred for 1 h. The reaction mixture was evaporated under reduced pressure, the resultant residue was washed with diethyl ether and dried under vacuum to afford the title compound as a yellowish solid (0.08g, 98%); LC-MS: m/z 456.2 (M+H).

Step-vi: Synthesis of 4-((4-(6-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)phenyl)-2-azaspiro[3.3]heptan-2-yl)cyclohexyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (Compound 13)

To a stirred solution of 2-(6-amino-5-(4-(2-(4-aminocyclohexyl)-2-azaspiro[3.3]heptan-6-yl)phenyl)pyridazin-3-yl)phenol (0.10g, 0.21 mmol) in DMSO (3 mL) was added DIPEA (0.14g, 1.09 mmol) and stirred for 5 mins. 2-(2,6-dioxopiperidin-3-yl)-4-fluoroisoindoline-1,3-dione (0.06 g, 0.21 mmol) was added to the reaction mixture and heated at 130 °C for 4h. After completion of the reaction, the reaction mixture was poured into ice cold water and stirred for 30 minutes and filtered through Buchner funnel to get crude product as a solid. The crude product was purified first by combi flash column chromatography using 3-4% methanol in DCM system followed by prep HPLC, pure fractions were dried under lyophilization to afford the title compound as yellow solid (0.01 g, 7 %). ^{1}H NMR (400 MHz,

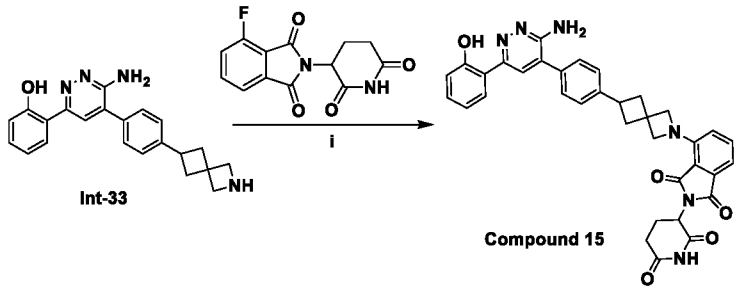
DMSO- d_6): δ 13.62 (s, 1H), 11.10 (s, 1H), 7.98 (s, 1H), 7.93 (d, J = 8.0 Hz, 1H), 7.61-7.55 (m, 3H), 7.39 (d, J = 8.0 Hz, 2H), 7.24 (t, J = 7.2 Hz, 1H), 7.08 (d, J = 8.8 Hz, 1H), 7.04 (d, J = 8.0 Hz, 1H), 6.93-6.88 (m, 2H), 6.44 (bs, 2H), 6.32 (d, J = 8.0 Hz, 0.5H), 6.18 (d, J = 8.0 Hz, 0.5H), 5.08-5.02 (m, 1H), 3.73 (bs, 1H), 3.62-3.50 (m, 2H), 3.25 (bs, 2H), 3.13 (bs, 2H), 2.93-2.84 (m, 2H), 2.61-2.55 (m, 2H), 2.31-2.19 (m, 2H), 2.11-1.95 (m, 3H), 1.75-1.60 (m, 3H), 1.57-1.32 (m, 4H). LC-MS: m/z 710.32 (M-H).

Example-X: Synthesis of 5-(6-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)phenyl)-2-azaspiro[3.3]heptan-2-yl)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (Compound 14)



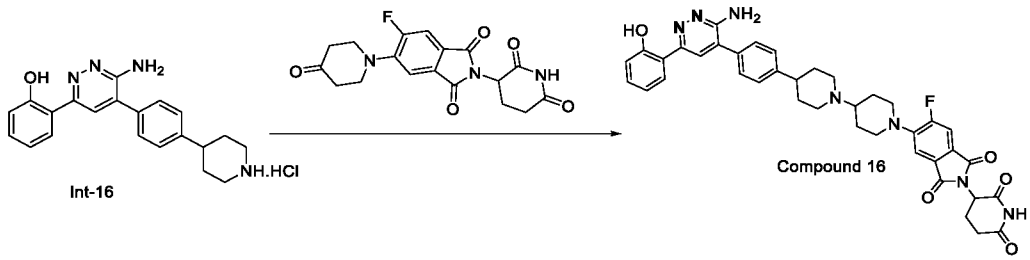
To a stirred solution of 2-(5-(4-(2-azaspiro[3.3]heptan-6-yl)phenyl)-6-aminopyridazin-3-yl)phenol (0.05 mg, 0.13 mmol) in DMSO (2 mL) was added DIPEA (0.054 g, 0.41 mmol)) and stirred for 5 mins. 2-(2,6-dioxopiperidin-3-yl)-4-fluoroisoindoline-1,3-dione (0.046g, 1.24 mmol) was added to the reaction mixture and heated at 130 °C for 6h. After completion of the reaction, the reaction mixture was poured into ice cold water and stirred for 30 minutes and filtered through Buchner funnel to get crude product as a solid. The crude product was purified first by combi flash column chromatography using 2.5% methanol in DCM system followed by prep HPLC, pure fractions were dried under lyophilization to afford the title compound as yellow solid (0.005g, 5.8 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.48 (s, 1H), 8.09 (s, 1H), 7.73 (s, 1H), 7.66-7.60 (m, 2H), 7.50 (d, J = 8.0 Hz, 2H), 7.39 (d, J = 8.0 Hz, 2H), 7.29 (t, J = 4.5 Hz, 1H), 7.08 (d, J = 8.4 Hz, 1H), 6.90 (t, J = 6.0 Hz, 1H), 6.80-6.79 (m, 1H), 6.53 (d, J = 8.0 Hz, 1H), 4.98-4.94 (m, 2H), 4.21 (s, 2H), 4.00 (s, 2H), 3.62-3.55 (m, 1H), 2.92-2.85 (m, 1H), 2.81-2.70 (m, 3H), 2.50-2.35 (m, 2H), 2.15-2.10 (m, 1H). LC-MS: m/z 615.2 (M+H).

Example-XI: Synthesis of 4-(6-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)phenyl)-2-azaspiro[3.3]heptan-2-yl)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (Compound 15)



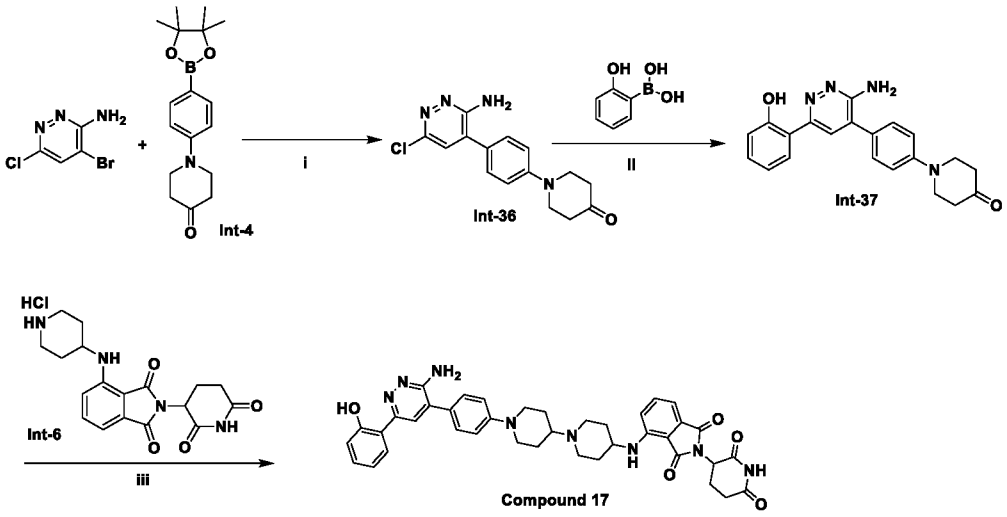
Compound 15 was prepared by procedure similar to the one described in Example-X with appropriate variations in reactants, quantities of reagents, protections and deprotections, solvents and reaction conditions. ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.62 (s, 1H), 11.08 (s, 1H), 7.99 (s, 1H), 7.96 (d, J – 8.0 Hz, 1H), 7.59-7.56 (m, 3H), 7.44 (d, J = 8.0 Hz, 2H), 7.25 (d, J = 8.0 Hz, 1H), 7.13 (d, J = 6.8 Hz, 1H), 6.93-6.88 (m, 2H), 6.80 (d, J = 8.8 Hz, 1H), 6.45 (bs, 2H), 5.09-5.02 (m, 1H), 4.38 (s, 2H), 4.17 (s, 2H), 3.55-3.50 (m, 1H), 2.99-2.82 (m 1H), 2.70-2.60 (m, 4H), 2.40-2.36 (m, 2H), 2.10-1.98 (m, 1H). LC-MS: m/z 614.95 (M+H).

Example-XII: Synthesis of 5-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)phenyl)-[1,4'-bipiperidin]-1'-yl)-2-(2,6-dioxopiperidin-3-yl)-6-fluoroisoindoline-1,3-dione (Compound 16)



Compound 16 was prepared by procedure similar to the one described in Example-IV with appropriate variations in reactants, quantities of reagents, protections and deprotections, solvents and reaction conditions. ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.64 (s, 1H), 11.11 (s, 1H), 8.01 (s, 1H), 7.96 (dd, J = 8.4, 1.6 Hz, 1H), 7.72 (d, J = 7.6 Hz, 1H), 7.58 (d, J = 8.0 Hz, 2H), 7.47- 7.43 (m, 3H), 7.23 (t, J = 7.6 Hz, 1H), 6.93-6.88 (m, 2H), 6.45 (bs, 2H), 5.14-5.07 (m, 1H), 3.69 (d, J = 11.6 Hz, 2H), 3.05 (bs, 2H), 2.96-2.84 (m, 3H), 2.65-2.55 (m, 3H), 2.36-2.22 (m, 2H), 2.10-2.01 (m, 2H), 1.96-1.80 (m, 4H), 1.75-1.59 (m, 4H). LC-MS: m/z 704.5 (M+H).

Example-XIII: Synthesis of 4-((1'-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl) phenyl)-[1,4'-bipiperidin]-4-yl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (Compound 17)



Step-i: Synthesis of 1-(4-(3-amino-6-chloropyridazin-4-yl)phenyl)piperidin-4-one (Intermediate 36)

To a stirred solution of 4-bromo-6-chloropyridazin-3-amine (8.3g, 39.84 mmol), 1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidin-4-one (10.0g, 33.20 mmol) in 1,4-dioxane (80 mL) and water (10 mL) was added K_2CO_3 (13.76g, 99.6 mmol) and degassed with nitrogen for 10 min, followed by adding $Pd(dppf)_2Cl_2$.DCM (2.71g, 3.32 mmol) and the reaction mixture was heated at 100 °C in sealed tube for 16 h. Once the reaction was completed (monitored by TLC), the reaction mixture was diluted with EtOAc. The combined organic layer was washed with water, brine, dried over anhydrous sodium sulphate and concentrated under vacuum to get crude product which was purified by combi flash column chromatography using 70-90% EtOAc in hexane as eluent to afford the title compound as white solid (5.0g, 50%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.47 (d, J = 8.8 Hz, 2H), 7.29 (s, 1H), 7.13 (d, J = 9.2 Hz, 2H), 6.28 (bs, 2H), 3.71 (t, J = 6.0 Hz, 4H), 2.43 (t, J = 6.4 Hz, 4H); LC-MS: m/z 302.95 (M+H).

Step-ii: Synthesis of 1-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)phenyl)piperidin-4-one (Intermediate 37)

To a stirred solution of 1-(4-(3-amino-6-chloropyridazin-4-yl)phenyl)piperidin-4-one (11g, 36.33 mmol), (2-hydroxyphenyl)boronic acid (7.01g, 50.86 mmol) in 1,4-dioxane (50 mL) and water (13 mL) was added K_2CO_3 (15.0g, 138.2 mmol) and degassed with nitrogen for 10 min, followed by adding $Pd(dppf)_2Cl_2$.DCM (2.96 g, 3.63 mmol) and the reaction mixture

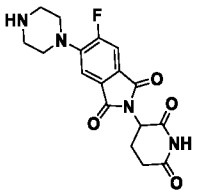
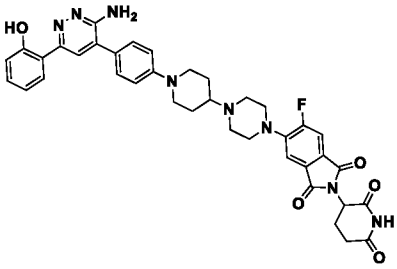
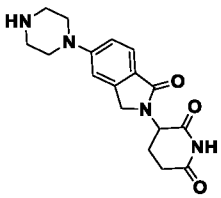
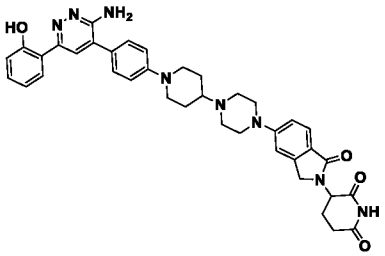
was heated for 4 h at 120 ºC in a sealed tube. Once the reaction was completed (monitored by TLC), the reaction mixture was diluted with EtOAc. The combined organic layer was washed with water, brine, dried over anhydrous sodium sulphate and concentrated under vacuum to give the residue which was purified by combi flash column chromatography using 90 - 100% EtOAc in hexane as eluent to afford the title compound as off white solid (7.0g, 54%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.7 (s, 1H), 7.92 (m, 2H), 7.53 (d, J = 8.8 Hz, 2H), 7.21 (t, J = 7.6 Hz, 1H), 7.14 (d, J = 8.4 Hz, 2H), 6.89-6.83 (m, 2H), 6.36 (bs, 2H), 3.73 (t, J = 5.6 Hz, 4H), 2.45 (t, J = 5.6 Hz, 4H). LC-MS: m/z 361.0 (M+H).

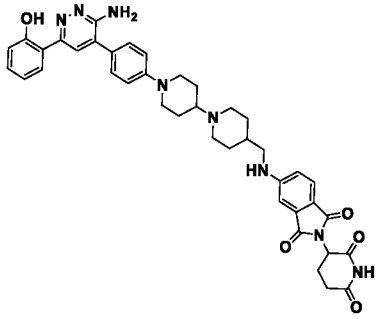
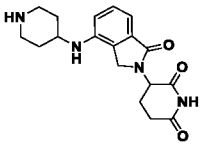
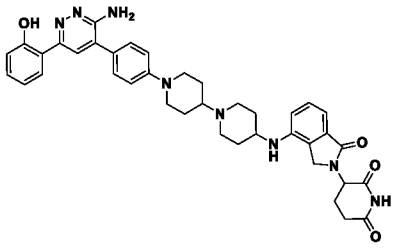
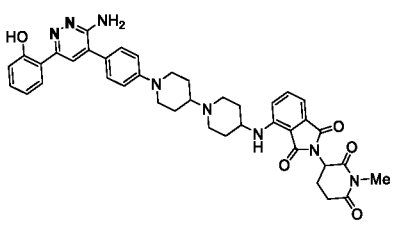
Step-iii: Synthesis of 4-((1'-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)phenyl)-[1,4'-bipiperidin]-4-yl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (Compound 17)

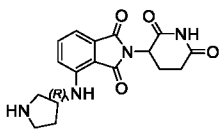
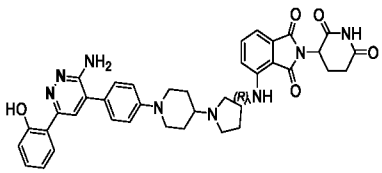
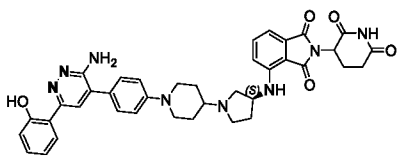
To a stirred solution of 1-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)phenyl)piperidin-4-one (0.10g, 0.27 mmol) and 2-(2,6-dioxopiperidin-3-yl)-4-(piperidin-4-ylamino)isoindoline-1,3-dione hydrochloride (0.13g, 0.33 mmol) in 9mL THF:DMSO (2:1) mixture was added KOAc (0.082g, 0.83 mmol) and acetic acid (0.2 mL) and molecular sieves (4A°) and the reaction mixture was stirred at 45 °C for 4h. Then the reaction mixture was cooled to 0 °C and sodium triacetoxy borohydride (0.17g, 0.83 mmol) was added and the reaction mixture was stirred at RT for 16h. The reaction was monitored by TLC. After completion of the reaction the reaction mixture was extracted in DCM and saturated ammonium chloride wash was given to the organic layer followed by saturated sodium chloride wash. The organic layer dried over anhydrous sodium sulphate and then concentrated under reduced pressure and the resultant residue was washed with diethyl ether and dried under vacuum to afford the title compound as off white solid (0.02g, 11 %). ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.76 (s, 1H), 11.10 (s, 1H), 7.97 (d, J = 7.2 Hz, 1H), 7.94 (s, 1H), 7.58 (t, J = 7.2 Hz, 1H), 7.51 (d, J = 8.4 Hz, 2H), 7.24 (t, J = 7.2 Hz, 1H), 7.17 (d, J = 8.0 Hz, 1H), 7.10-7.03 (m, 3H), 6.93-6.86 (m, 2H), 6.38 (bs, 2H), 6.24 (d, J = 8.0 Hz, 1H), 5.08-5.03 (m, 1H), 3.90 (d, J = 8.0 Hz, 2H), 3.57 (bs, 1H), 2.94-2.71 (m, 5H), 2.69-2.54 (m, 2H), 2.43-2.31 (m, 3H), 2.17-1.80 (m, 5H), 1.60-1.38 (m, 4H); LCMS: m/z 699.2 (M-H).

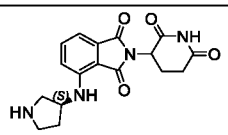
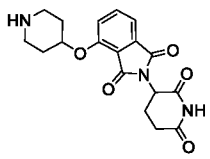
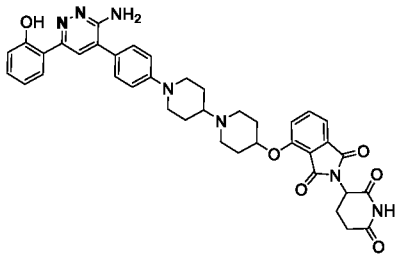
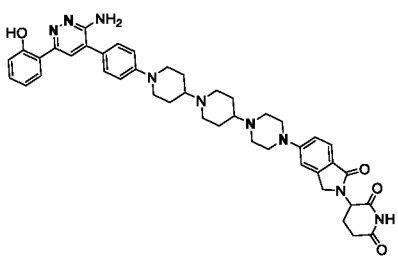
The compounds 18-27 listed in below **Table-1** were prepared by procedure similar to the one described in **Example-XIII** with appropriate variations in reactants, quantities of reagents, protections and deprotections, solvents and reaction conditions. The characterization data of the compounds are summarized herein the below table.

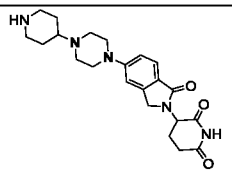
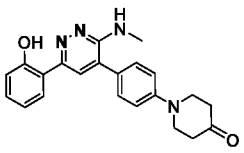
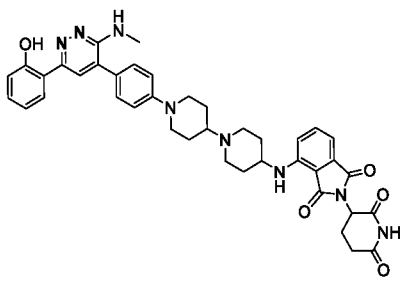
Table-1:

Comp. No	Intermediate	Structure	Characterization Data
18	Int-37 & 		^{1}H NMR (400 MHz, DMSO-d_6): δ 13.80 (s, 1H), 11.12 (s, 1H), 7.94 (t, J = 6.8 Hz, 2H), 7.74 (d, J = 8.0 Hz, 1H), 7.52 (d, J = 8.8 Hz, 2H), 7.48 (d, J = 8.0 Hz, 1H), 7.35 (d, J = 8.0 Hz, 1H), 7.10 (d, J = 8.8 Hz, 2H), 6.92-6.88 (m, 2H), 6.28 (bs, 2H), 5.12-5.08 (m, 1H), 3.90 (d, J = 8.0 Hz, 2H), 3.60-3.50 (m, 1H), 3.26 (d, J = 6.0 Hz, 4H), 2.80 (d, J = 8.0 Hz, 2H), 2.72-2.65 (m, 4H), 2.55-2.54 (m, 2H), 2.15-2.00 (m, 1H), 1.85-1.78 (m, 2H), 1.60-1.55 (m, 3H). LCMS: m/z 706.2 (M+H).
19	Int-37 & 		^{1}H NMR (400 MHz, DMSO-d_6): δ 13.76 (s, 1H), 10.95 (s, 1H), 7.95 (t, J = 6.8 Hz, 2H), 7.50 (d, J = 8.8 Hz, 2H), 7.24 (t, J = 7.2 Hz, 2H), 7.11-7.07 (m, 4H), 6.92-6.87 (m, 2H), 6.38 (bs, 2H), 5.08-5.02 (m, 1H), 4.36-4.18 (m, 2H), 3.90 (d, J = 8.0 Hz, 2H), 3.27 (bs, 4H), 2.91-2.75 (m, 3H), 2.67 (bs, 4H), 2.54-2.39 (m, 2H),

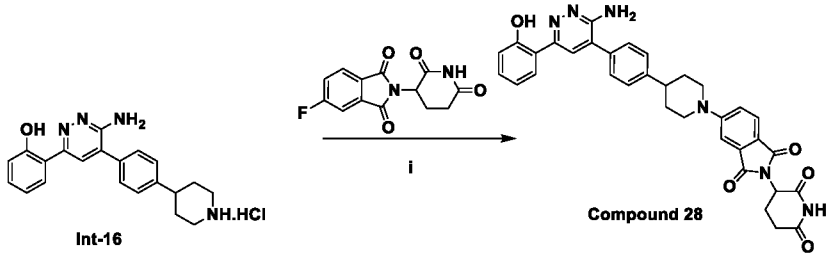
			2.01-1.88 (m, 4H), 1.56-1.52 (m, 2H). LCMS: m/z 671.3 (M-H).
20	Int-37 & Int-8		LCMS: m/z 715.5 (M+H).
21	Int-37 & 		^{1}H NMR (400 MHz, DMSO-d_6): δ 7.95 (d, J = 7.2 Hz, 1H), 7.94 (s, 1H), 7.50 (d, J = 8 Hz, 2H), 7.31- 7.23(m, 2H), 7.09 (d, J = 8.0 Hz, 2H), 6.92 (d, J = 7.6 Hz, 2H), 6.88 (d, J = 7.6 Hz, 1H), 6.81 (d, J = 7.6 Hz, 1H), 6.38 (bs, 2H), 5.35 (d, J = 7.6 Hz, 1H), 5.15-5.07 (m, 1H), 4.28-4.14 (m, 2H), 3.91 (d, J = 8.0 Hz, 2H), 3.52 (bs, 2H), 2.95-2.87 (m, 2H), 2.82- 2.74 (m, 2H), 2.67-2.54 (m, 2H), 2.35-2.26 (m, 2H), 2.16-1.85 (m, 5H), 1.61-1.39 (m, 4H); LC-MS: m/z 688.3 (M+H).
22	Int-37 & Int-9		^{1}H NMR (400 MHz, DMSO-d_6): δ 13.72 (bs, 1H), 7.95-7.93 (m, 2H), 7.63-7.61 (m, 1H), 7.54 (d, J = 8 Hz, 2H), 7.27-7.11 (m, 5H), 6.93-6.87

			(m, 2H), 6.38 (bs, 2H), 6.28 (bs, 1H), 5.16-5.11 (m, 1H), 3.98 (bs, 2H), 3.68 (bs, 1H), 3.26 (bs, 2H), 3.02 (s, 3H), 2.98-2.90 (m, 1H), 2.84-2.74 (m, 3H), 2.55 (bs, 4H), 2.06-2.03 (m, 4H), 1.85-1.43 (m, 5H); LC-MS: m/z 715.5 (M+H).
23	Int-37 & 		1H NMR (400 MHz, DMSO): δ 13.77 (s, 1H), 11.09 (s, 1H), 7.95 (d, J = 7.2 Hz, 1H), 7.94 (s, 1H), 7.60 (t, J = 8.0 Hz, 1H), 7.52 (d, J = 8.8 Hz, 2H), 7.25 (t, J = 7.2 Hz, 1H), 7.14 (d, J = 8.8 Hz, 1H), 7.10-7.06 (m, 3H), 6.93-6.87 (m, 2H), 6.41 (d, J = 8.0 Hz, 1H), 6.38 (bs, 2H), 5.07-5.02 (m, 1H), 4.21 (bs, 1H), 3.80 (dd, J = 12.8, 5 Hz, 2H), 2.91-2.82 (m, 4H), 2.67-2.44 (m, 5H), 2.35-2.26 (m, 2H), 2.05-1.88 (m, 3H), 1.63 (bs, 1H), 1.18-1.45 (m, 2H); LC-MS: m/z 687.3 (M-H).
24	Int-37 &		1H NMR (400 MHz, DMSO): δ 13.78 (s, 1H), 11.10 (s, 1H), 7.95 (d, J = 7.2 Hz, 1H), 7.94 (s, 1H), 7.61 (t, J = 8 Hz, 1H), 7.52 (d, J =

			8.4 Hz, 2H), 7.25 (t, J = 7.2 Hz, 1H), 7.14 (d, J = 8.8 Hz, 1H), 7.10-7.06 (m, 3H), 6.93-6.87 (m, 2H), 6.42 (d, J = 7.6 Hz, 1H), 6.39 (bs, 2H), 5.07-5.02 (m, 1H), 4.23 (bs, 1H), 3.81 (dd, J = 12.8, 5 Hz, 2H), 2.91-2.82 (m, 4H), 2.69-2.45 (m, 5H), 2.34-2.25 (m, 2H), 2.05-1.88 (m, 3H), 1.64 (bs, 1H), 1.17-1.47 (m, 2H); LC-MS: m/z 685.2 (M-H).
25	Int-37 & 		1H NMR (400 MHz, DMSO): δ 13.69 (s, 1H), 11.11 (s, 1H), 7.92 (m, 2H), 7.83 (bs, 1H), 7.61 (bs, 1H), 7.53 (d, J = 8.4 Hz, 2H), 7.24 (t, J = 7.6 Hz, 1H), 7.12 (d, J = 7.2 Hz, 2 H), 6.92-6.86 (m, 2H), 6.37 (bs, 2H), 5.14-5.05 (m, 1H), 4.01 (d, J = 7.2 Hz, 2H), 3.44 (bs, 1H), 3.25-3.13 (m, 1H), 2.95-2.74 (m, 4H), 2.68-2.50 (m, 6H), 2.22-1.95 (m, 6H), 1.82-1.65 (m, 2H); LC-MS: m/z 702.5 (M+H).
26	Int-37 &		1H NMR (400 MHz, DMSO): δ 13.75 (s, 1H), 10.93 (s, 1H), 7.95-7.92 (m, 2H), 7.50 (d, J = 8.8 Hz, 2H), 7.23 (t, J = 7.6 Hz, 2H), 7.09-

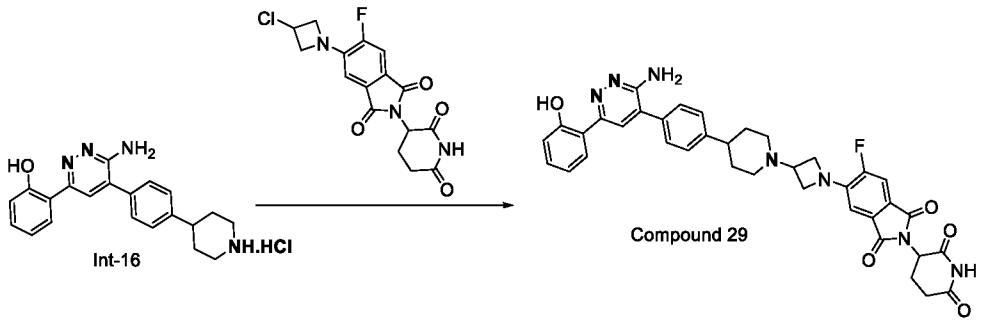
			7.02 (m, 4H), 6.91-6.85 (m, 2H), 6.37 (bs, 2H), 5.05-5.01 (m, 1H), 4.31 (d, J = 16.8 Hz, 1H), 4.18 (d, J = 16.8 Hz, 1H), 3.87 (d, J = 12.0 Hz, 2H), 2.93 (bs, 4H), 2.97-2.83 (m, 3H), 2.81-2.68 (m, 2H), 2.61 (bs, 4H), 2.56-2.51 (m, 2H), 2.41-2.28 (m, 2H), 2.24-2.05 (m, 2H), 2.01-1.75 (m, 5H), 1.58-1.33 (m, 4H); LC-MS: m/z 756.6 (M-H).
27	Int-6 & 		1H NMR (400 MHz, DMSO): δ 13.98 (s, 1H), 11.09 (s, 1H), 7.93 (d, J = 7.2 Hz, 1H), 7.87 (s, 1H), 7.58 (t, J = 8 Hz, 1H), 7.45 (d, J = 8.8 Hz, 2H), 7.26-7.15 (m, 2H), 7.08 (d, J = 8.8 Hz, 2H), 7.03 (d, J = 7.2 Hz, 1H), 6.92-6.85 (m, 2H), 6.41 (d, J = 8.8 Hz, 1H), 6.24 (d, J = 8.0 Hz, 1H), 5.06-5.02 (m, 1H), 3.90 (d, J = 8.0 Hz, 2H), 3.56 (bs, 1H), 2.92 (d, J= 3.6Hz, 3H), 2.88-2.73 (m, 4H), 2.65-2.55 (m, 3H), 2.42-2.31 (m, 3H), 2.22-1.81 (m, 5H), 1.58-1.41 (m, 4H); LC-MS: m/z 715.2 (M+H).

Example-XIV: Synthesis of 5-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)phenyl) piperidin-1-yl)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (Compound 28)



To a stirred solution of 2-(6-amino-5-(4-(piperidin-4-yl)phenyl)pyridazin-3-yl)phenol hydrochloride (0.10g, 0.28 mmol) in DMSO (2 mL) was added DIPEA (0.11g, 0.86 mmol)) and stirred for 5 mins. 2-(2,6-dioxopiperidin-3-yl)-4-fluoroisoindoline-1,3-dione (0.08 g, 0.28 mmol) was added to the reaction mixture and heated at 130 °C for 4h. After completion of the reaction, the reaction mixture was poured into ice cold water and stirred for 30 minutes and filtered through Buchner funnel to get crude product as a solid. The crude product was purified first by combi flash column chromatography using 3-4% methanol in DCM system to afford the title compound as off white solid (0.05g, 27.8 %). ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.62 (s, 1H), 11.08 (s, 1H), 8.00 (s, 1H), 7.94 (d, J = 8.4 Hz, 1H), 7.70-7.68 (m, 1H), 7.58 (d, J = 8.0 Hz, 2H), 7.45 (d, J = 7.6 Hz, 2H), 7.39 (s, 1H), 7.34 (d, J = 8.0 Hz, 1H), 7.25 (t, J = 8.0 Hz, 1H), 6.93-6.87 (m, 2H), 6.45 (bs, 2H), 5.12-5.02 (m, 1H), 4.28-4.21 (m, 2H), 3.11 (t, J = 5.6 Hz, 2H), 3.00-2.85 (m, 2H), 2.70-2.20 (m, 2H), 2.05-2.00 (m, 1H), 1.98-1.90 (m, 2H), 1.80-1.72 (m, 2H). LC/MS: m/z 603.2 (M+H).

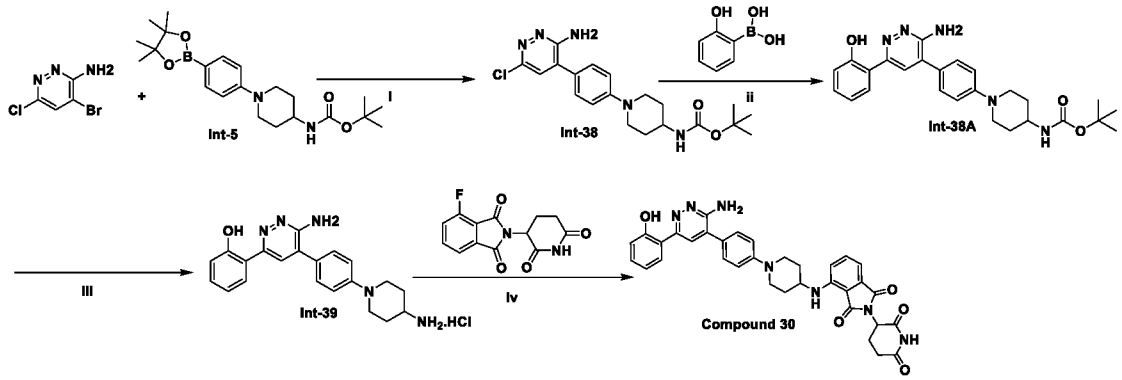
Example-XV: Synthesis of 5-(3-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl) phenyl)piperidin-1-yl)azetidin-1-yl)-2-(2,6-dioxopiperidin-3-yl)-6-fluoroisoindoline-1,3-dione (Compound 29)



Compound 29 was prepared by procedure similar to the one described in Example-XIV with appropriate variations in reactants, quantities of reagents, protections and deprotections, solvents and reaction conditions. ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.64 (s, 1H), 11.10 (s,

1H), 8.01 (s, 1H), 7.95 (dd, J = 1.6 & 8.0 Hz, 1H), 7.64-7.58 (m, 3H), 7.45 (d, J = 8.0 Hz, 2H), 7.27-7.23 (m, 1H), 6.96-6.94 (m, 3H), 6.46 (s, 2H), 5.08 (dd, J = 5.6 & 13.2 Hz, 1H), 4.30-4.25 (m, 3H), 4.02 (t, J = 6.0 Hz, 2H), 3.00-2.97 (m, 2H), 2.90-2.80 (m, 1H), 2.51-2.50 (m, 2H), 2.04-1.98 (m, 4H), 1.86-1.84 (m, 2H), 1.74-1.72 (m, 2H). LC/MS: m/z 676.5 (M+H).

Example-XVI: Synthesis of 4-((1-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl) phenyl)piperidin-4-yl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (Compound 30)



Step-i: Synthesis of tert-butyl (1-(4-(3-amino-6-chloropyridazin-4-yl)phenyl)piperidin-4-yl)carbamate (Intermediate 38)

To a stirred solution of 4-bromo-6-chloropyridazin-3-amine (0.24g, 1.19 mmol), tert-butyl (1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidin-4-yl)carbamate (0.40 g, 0.99 mmol) in 1,4-dioxane (10 mL) and water (1 mL) was added K_2CO_3 (0.41g, 2.98 mmol) and degassed with nitrogen for 10 min, followed by adding $Pd(dppf)_2Cl_2$.DCM (0.08g, 0.09 mmol) and the reaction mixture was heated for 16 h at 100 °C in sealed tube. Once the reaction was completed (monitored by TLC), the reaction mixture was diluted with EtOAc. The combined organic layer was washed with water, brine, dried over anhydrous sodium sulphate, and concentrated under vacuum to get crude product which was purified by combi flash column chromatography using 70-90% EtOAc in hexane as eluent to afford the title compound as white solid (0.28g, 59%). ^{1}H NMR (400 MHz, DMSO-d_6): d 7.42 (d, J = 8.8 Hz, 2H), 7.27 (s, 1H), 7.03 (d, J = 9.2 Hz, 2H), 6.89-6.85 (m, 1H), 6.26 (bs, 2H), 3.75 (t, J = 7.6 Hz, 2H), 3.47 (bs, 1H), 2.70 (t, J = 6.8 Hz, 2H), 1.78-1.75 (m, 2H), 1.48-1.42 (m, 2H), 1.38 (s, 9H); LC-MS: m/z 404.0 (M+H).

Step-ii: Synthesis of tert-butyl (1-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl) phenyl)piperidin-4-yl)carbamate (Intermediate 38A)

To a stirred solution of tert-butyl (1-(4-(3-amino-6-chloropyridazin-4-yl)phenyl)piperidin-4-yl)carbamate (0.28g, 0.69 mmol) and (2-hydroxyphenyl)boronic acid (0.124g, 0.90 mmol) in 1,4-dioxane (4 mL) and water (0.4 mL) was added K_2CO_3 (0.28g, 2.07 mmol) and degassed with nitrogen for 10 min, followed by adding $Pd(dppf)_2Cl_2$.DCM (0.057g, 0.06 mmol) and the reaction mixture was heated at 120 ºC in a sealed tube for 4h. Once the reaction was completed (monitored by TLC), the reaction mixture was diluted with EtOAc. The combined organic layer was washed with water, brine, dried over anhydrous sodium sulphate, and concentrated under vacuum to give the residue which was purified by combi flash column chromatography using 90 - 100% EtOAc in hexane as eluent to afford the title compound as off white solid (0.15g, 47%). ^{1}H NMR (400 MHz, DMSO-d_6): d 13.80 (s, 1H), 7.95 (d, J = 5.6 Hz, 2H), 7.56 (d, J = 8.6 Hz, 2H), 7.24 (t, J = 7.6 Hz, 2H), 7.18 (d, J = 8.4 Hz, 1H), 6.92-6.86 (m, 3H), 6.40 (s, 2H), 3.74 (t, J = 7.6 Hz, 2H), 3.47 (bs, 1H), 2.82 (t, J = 6.8 Hz, 2H), 1.78-1.75 (m, 2H), 1.48-1.42 (m, 2H), 1.38 (s, 9H). LC-MS: m/z 462.05 (M+H).

Step-iii: Synthesis of 2-(6-amino-5-(4-(4-aminopiperidin-1-yl)phenyl)pyridazin-3-yl) phenol hydrochloride (Intermediate 39)

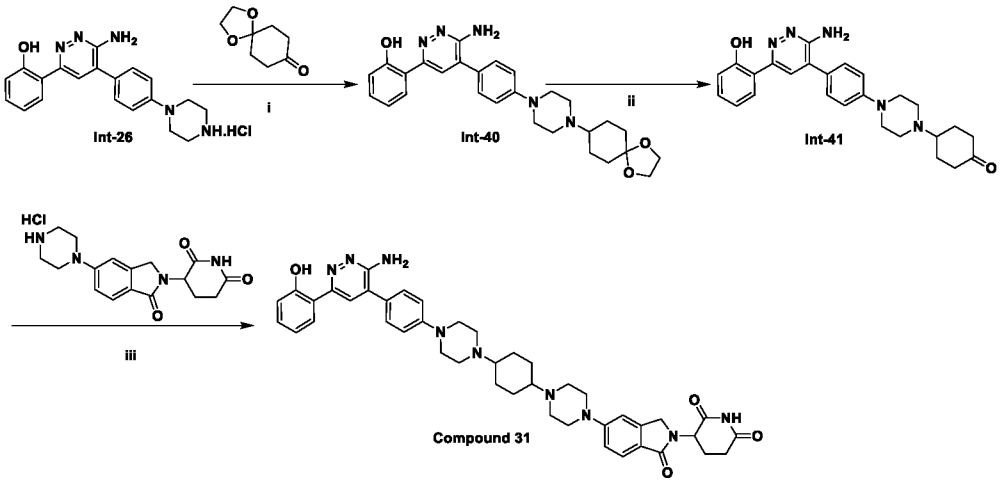
To a stirred solution of tert-butyl (1-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)phenyl)piperidin-4-yl)carbamate (0.15g, 0.32 mmol) in DCM (2 mL) was added 4 M dioxane hydrochloride (2 mL) at 0 ºC and then slowly brought to RT and stirred for 4 h. The reaction mixture was evaporated under reduced pressure, and the resultant residue was washed with diethyl ether and dried under vacuum to afford the title compound as a yellowish solid (0.15g, crude). ^{1}H NMR (400 MHz, DMSO-d_6): d 8.23 (bs, 3H), 8.07 (s, 1H), 7.61 (d, J = 5.6 Hz, 1H), 7.52 (d, J = 8.6 Hz, 2H), 7.35 (t, J = 7.6 Hz, 1H), 7.16 (d, J = 8.4 Hz, 2H), 7.07 (d, J = 8.4 Hz, 1H), 6.98 (t, J = 7.6 Hz, 1H), 3.95 (t, J = 7.6 Hz, 2H), 3.47 (bs, 1H), 2.93 (t, J = 6.8 Hz, 2H), 1.99-1.97 (m, 2H), 1.58-1.52 (m, 2H). LC-MS: m/z 362.00 (M+H).

Step-iv: Synthesis of 4-((1-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)phenyl) piperidin-4-yl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (Compound 30)

To a stirred solution of 2-(6-amino-5-(4-(4-aminopiperidin-1-yl)phenyl)pyridazin-3-yl)phenol hydrochloride (0.15g, 0.37 mmol) in DMSO (2 mL) was added DIPEA (0.14g, 1.13 mmol)) and stirred for 5 mins. 2-(2,6-dioxopiperidin-3-yl)-4-fluoroisoindoline-1,3-dione (0.12g, 0.45 mmol) was added in the reaction mixture and heated at 130ºC for 4h. After

completion of the reaction, the reaction mixture was poured into ice cold water and stirred for 30 minutes and filtered through Buchner funnel to get crude product as a solid. The crude product was purified first by combi flash column chromatography using 3-4% methanol in DCM system followed by prep HPLC. The pure fractions were dried under lyophilization to afford the title compound as yellow solid (0.02g, 9 %). ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.76 (s, 1H), 11.10 (s, 1H), 7.95-7.94 (m, 2H), 7.62 (t, J = 8 Hz, 1H), 7.53 (d, J = 8 Hz, 2H), 7.28-7.22 (m, 2H), 7.13 (d, J = 8 Hz, 2H), 7.07 (d, J = 7.2 Hz, 1H), 6.92—6.86 (m, 2H), 6.39 (bs, 2H), 6.30 (d, J = 7.6 Hz, 1H), 5.07-5.03 (m, 1H), 3.91—3.80 (m, 3H), 3.06 (t, J = 10.8 Hz, 2H), 2.94-2.84 (m, 1H), 2.60-2.51 (m, 2H), 2.08-2.01 (m, 3H), 1.66-1.55 (m, 2H): LC-MS: m/z 618.2 (M+H).

Example-XVII: Synthesis of 3-(5-(4-(4-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)phenyl)piperazin-1-yl)cyclohexyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (Compound 31)



Step-i: Synthesis of 2-(5-(4-(4-(1,4-dioxaspiro[4.5]decan-8-yl)piperazin-1-yl)phenyl)-6-aminopyridazin-3-yl)phenol (Intermediate 40)

To a stirred solution of 2-(6-amino-5-(4-(piperazin-1-yl)phenyl)pyridazin-3-yl)phenol hydrochloride (0.10g, 0.28 mmol) and 1,4-dioxaspiro[4.5]decan-8-one (0.05g, 0.31 mmol) in 1.5 mL THF:DMSO (2:1) mixture was added KOAc (0.085g, 0.86 mmol) and acetic acid (0.1 mL) and molecular sieves (4A°) and the reaction mixture was stirred at 45 °C for 4h. Then the reaction mixture was cooled to 0 °C, and sodium triacetoxy borohydride (0.183g, 0.86 mmol) was added and the reaction mixture was stirred at RT for 16 h. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was extracted in 10% MeOH/DCM, and brine wash was given to the organic layer. The organic layer was dried over

anhydrous sodium sulphate and then concentrated under reduced pressure to get the crude product. The crude product was purified by combi flash column chromatography by eluting 5-6% MeOH/DCM to afford the title compound as a light yellow solid (0.08g, 57 %). ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.63 (bs, 1H), 7.93-7.92 (m, 2H), 7.53 (d, J = 8.8 Hz, 2H), 7.27-7.25 (m, 1H), 7.08 (d, J= 8.8 Hz, 2H), 6.92-6.89 (m, 2H), 6.38 (bs, 2H), 3.84 (s, 4H), 3.22-3.21 (m, 4H), 2.63-2.61 (m, 4H), 2.36-2.34 (m, 1H), 1.73-1.71 (m, 4H), 1.59-1.42 (m, 4H); LCMS: m/z 488.2 (M+H).

Step-ii: Synthesis of 4-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)phenyl) piperazin-1-yl)cyclohexan-1-one (Intermediate 41)

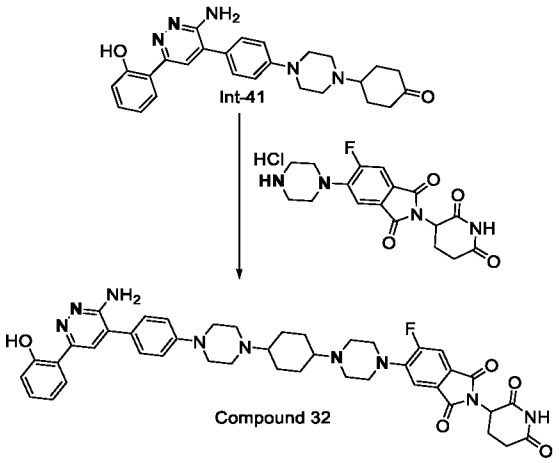
To a stirred solution of 2-(5-(4-(4-(1,4-dioxaspiro[4.5]decan-8-yl)piperazin-1-yl)phenyl)-6-aminopyridazin-3-yl)phenol (0.08g, 0.16 mmol) in THF (4 mL) was added 3 N aq. HCl solution (4 mL) to the reaction mixture at RT and stirred at the same temperature for 2h. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was basified using K_2CO_3 and extracted in 10% MeOH/DCM. The organic layer was washed with brine solution and dried over anhydrous sodium sulphate and then concentrated under reduced pressure to afford the title compound as a light yellow solid. (0.07g, crude) ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.75 (bs, 1H), 7.95-7.94 (m, 2H), 7.53 (d, J = 8.4 Hz, 2H), 7.24-7.22 (m, 1H), 7.10 (d, J= 8.4 Hz, 2H), 6.92-6.86 (m, 2H), 6.39 (bs, 2H), 3.63-3.56 (m, 1H), 3.32-3.25 (m, 4H), 2.69-2.66 (m, 4H), 2.35-2.30 (m, 4H), 2.00-1.97 (m, 2H), 1.82-1.75 (m, 2H). LCMS: m/z 444.05 (M+H).

Step-iii: Synthesis of 3-(5-(4-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl) phenyl)piperazin-1-yl)cyclohexyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (Compound 31)

To a stirred solution of 4-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)phenyl)piperazin-1-yl)cyclohexan-1-one (0.176g, 0.39 mmol) and 3-(1-oxo-5-(piperazin-1-yl)isoindolin-2-yl)piperidine-2,6-dione hydrochloride (0.13g, 0.39 mmol) in 4.5 mL THF:DMSO (2:1) mixture was added KOAc (0.117g, 1.18 mmol) and acetic acid (0.2 mL) and molecular sieves (4A°) and the reaction mixture was stirred at 45 °C for 4h. Then the reaction mixture was cooled to 0 °C and sodium cyanoborohydride (0.075g, 1.18 mmol) was added and the reaction mixture was stirred at RT for 12h. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was poured into ice water to obtain the solid, filtered and washed with water to get the crude product. The crude product was purified by

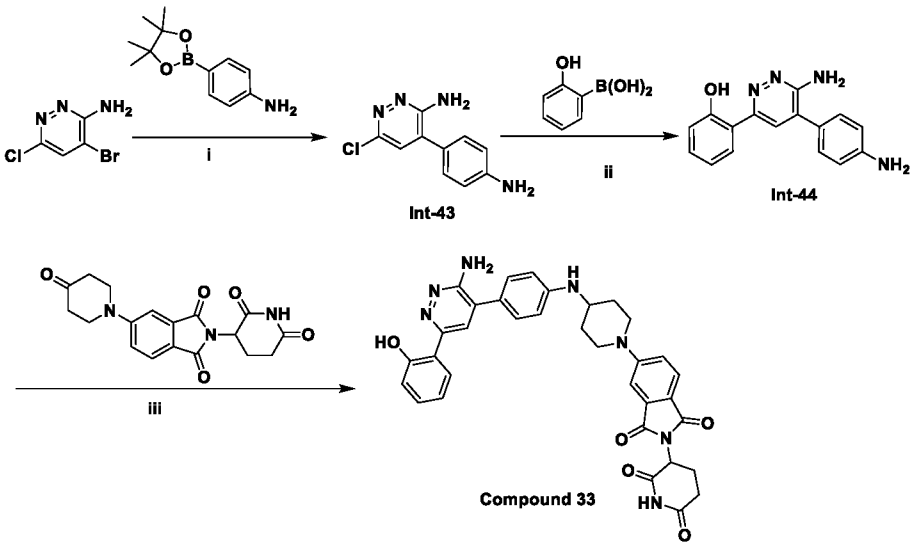
preparative HPLC to afford the title compound as a light yellow solid (0.045g, 15 %). ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.75 (bs, 1H), 10.94 (bs, 1H), 7.95-7.94 (m, 2H), 7.53 (d, J = 8 Hz, 2H), 7.24-7.22 (m, 2H), 7.09 (d, J= 8 Hz, 2H), 7.04 (s, 1H), 6.92-6.88 (m, 3H), 6.38 (bs, 2H), 5.33-5.31 (m, 1H), 506-5.02 (m, 2H), 4.34 (d, J = 16.4Hz, 1H), 4.22 (d, J = 16.8 Hz, 1H), 4.09-4.08 (m, 1H), 3.19 (bs, 8H), 3.17 (d, J = 5.6Hz, 1H), 2.89-2.85 (m, 2H), 2.59 (bs, 4H), 2.32 (m, 2H), 2.23-2.21 (m, 2H), 1.98-1.96 (m, 2H), 1.85-1.82 (m, 3H), 1.47-1.45 (m, 3H); LC-MS: m/z 756.5 (M+H).

Example-XVIII: Synthesis of 5-(4-(4-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)phenyl)piperazin-1-yl)cyclohexyl)piperazin-1-yl)-2-(2,6-dioxopiperidin-3-yl)-6-fluoroisoindoline-1,3-dione (Compound 32)



Compound 32 was prepared by a procedure similar to the one described in Example-XVII with appropriate variations in reactants, quantities of reagents, protections and deprotections, solvents, and reaction conditions. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.12 (s, 1H), 9.78 (bs, 1H), 9.60 (bs, 1H), 7.99 (s, 1H), 7.87-7.82 (m, 2H), 7.59 (d, J = 8 Hz, 2H), 7.30 (t, J = 7.6 Hz, 1H), 7.20 (d, J = 8.0 Hz, 2H), 6.97-6.91 (m, 3H), 5.15-5.08 (m, 1H), 4.05 (bs, 2H), 3.84 (bs, 2H), 3.65 (bs, 4H), 3.45-3.3 (m, 8H), 3.25-3.06 (m, 2H), 2.92-2.85 (m, 2H), 2.65-2.54 (m, 2H), 2.35-2.26 (m, 2H), 2.15-1.96 (m, 3H), 1.91-1.84 (m, 2H), 1.58-1.52 (m, 2H). LC-MS: m/z 788.2 (M+H).

Example-XIX: Synthesis of 5-(4-((4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl) phenyl)amino)piperidin-1-yl)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (Compound 33)



Step-i: Synthesis of 4-(4-aminophenyl)-6-chloropyridazin-3-amine (Intermediate-43)

To a stirred solution of 4-bromo-6-chloropyridazin-3-amine (2g, 9.61 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (2.3g, 10.5 mmol) in 1,4-dioxane (40 mL) and water (4 mL) was added K_2CO_3 (3.97g, 28.8 mmol) and degassed with nitrogen for 15 min, followed by adding $Pd(dppf)_2Cl_2$.DCM (0.78g, 0.96 mmol) and the reaction mixture was heated for 16 h at 100 °C in a sealed tube. Once the reaction was completed (monitored by TLC), the reaction mixture was diluted with EtOAc. The combined organic layer was washed with water, brine, dried over anhydrous sodium sulphate, and concentrated under vacuum to give the residue which was purified by combi flash column chromatography using 35% ethyl acetate in hexane as eluent to afford the title compound as pale brown solid (1.3g, 64%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.29 (d, J = 8.8 Hz, 2H), 7.24 (s, 1H), 6.69 (d, J = 8.8 Hz, 2H), 6.23 (bs, 2H), 5.59 (bs, 2H); LC-MS: m/z 221.0 (M+H).

Step-ii: Synthesis of 2-(6-amino-5-(4-aminophenyl)pyridazin-3-yl)phenol (Intermediate 44)

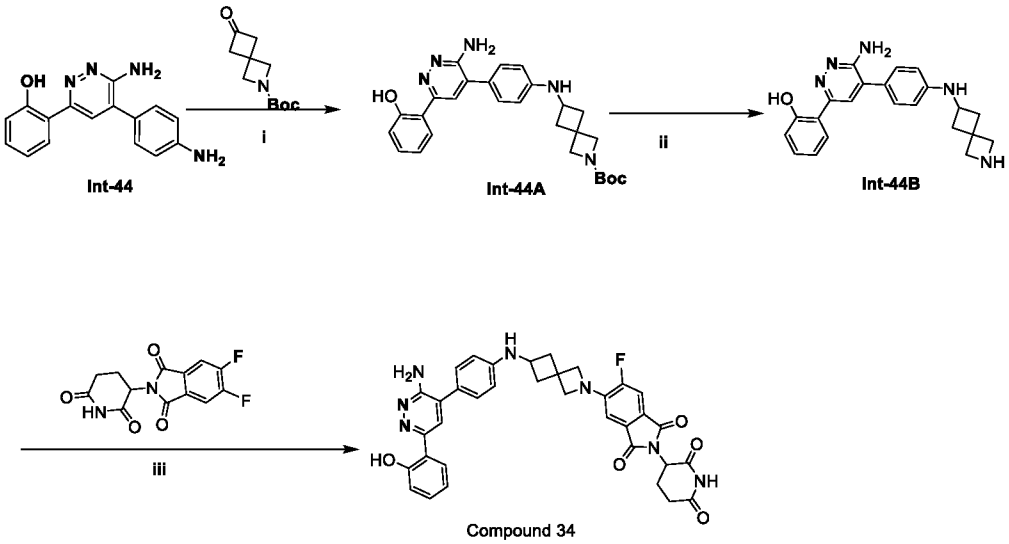
To a stirred solution of 4-(4-aminophenyl)-6-chloropyridazin-3-amine (1g, 4.53 mmol), 2-hydroxyphenyl boronic acid (0.68g, 4.98 mmol) in 1,4-dioxane (25 mL) and water (5 mL) was added K_2CO_3 (1.87g, 13.6 mmol) and degassed with nitrogen for 10 min, followed by adding $Pd(dppf)_2Cl_2$.DCM (0.37g, 0.45 mmol) and the reaction mixture was heated for 6h at 120 °C in a sealed tube. Once the reaction was completed (monitored by TLC), the reaction

mixture was diluted with 10% MeOH/DCM. The combined organic layer was washed with water, brine, dried over anhydrous sodium sulphate, and concentrated under vacuum to give the residue which was purified by combi flash column chromatography using 60-70% ethyl acetate in hexane as eluent to afford the title compounds as a light brown solid (0.6g, 47.5%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.85 (bs, 1H), 7.94 (d, *J* = 7.2 Hz, 1H), 7.88 (s, 1H), 7.36 (d, J = 8.4 Hz, 2H), 7.25 (t, J = 7.6Hz, 1H), 6.91-6.86 (m, 2H), 6.71 (d, J = 8.8 Hz, 2H), 6.32 (bs, 2H), 5.54 (bs, 2H); LC-MS: m/z 279.0 (M+H).

Step-iii: Synthesis of 5-(4-((4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)phenyl) amino)piperidin-1-yl)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (Compound 33)

To a stirred solution of 2-(6-amino-5-(4-aminophenyl)pyridazin-3-yl)phenol (0.04g, 0.14 mmol) and 2-(2,6-dioxopiperidin-3-yl)-5-(4-oxopiperidin-1-yl)isoindoline-1,3-dione(0.05g, 0.14 mmol) (synthesized using Ref WO2020/81450) in 1.5mL THF:DMSO (2:1) mixture was added KOAc (0.042g, 0.42 mmol) and acetic acid (0.1 mL) and molecular sieves (4A°) and the reaction mixture was stirred at 45 °C for 4 hours. Then the reaction mixture was cooled to 0 °C and sodium cyanoborohydride (0.027g, 0.42 mmol) was added and the reaction mixture was stirred for 16h at RT. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was poured into ice water to obtain the precipitate, filtered, and washed with water to get the crude, which was further purified prep HPLC to afford the title compound as yellow solid (0.020g, 23%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.84 (s, 1H), 11.08 (s, 1H), 7.94 (d, J = 7.2 Hz, 1H), 7.90 (s, 1H), 7.68 (d, J = 8.8 Hz, 1H), 7.42 (d, J = 8.4 Hz, 2H), 7.37 (bs, 1H), 7.32-7.22 (m, 2H), 6.93-6.86 (m, 2H), 6.77 (d, J = 8.8 Hz, 2H), 6.34 (bs, 2H), 6.05 (d, J = 8.0 Hz, 1H), 5.11-5.04 (m, 1H), 3.04 (d, J = 8.0 Hz, 2H), 3.67 (m, 1H), 3.28-3.15 (m, 2H), 2.93-2.82 (m, 1H), 2.62-2.55 (m, 2H), 2.08-1.95 (m, 3H), 1.52-1.40 (m, 2H); LC-MS: m/z 618.0 (M+H).

Example-XX: Synthesis of 5-(6-((4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)phenyl) amino)-2-azaspiro[3.3]heptan-2-yl)-2-(2,6-dioxopiperidin-3-yl)-6-fluoroisoindoline-1,3-dione (Compound 34)



Step-i Synthesis of tert-butyl 6-((4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)phenyl) amino)-2-azaspiro[3.3]heptane-2-carboxylate (Intermediate-44A)

To a stirred solution of 2-(6-amino-5-(4-aminophenyl)pyridazin-3-yl)phenol (0.05g, 0.18 mmol) and tert-butyl 6-oxo-2-azaspiro[3.3]heptane-2-carboxylate (0.076g, 0.36 mmol) in methanol (5mL), was added acetic acid (0.022g, 0.36 mmol) and the reaction mixture was stirred at RT for 3 h. Then the reaction mixture was cooled to 0°C and sodium cyanoborohydride (0.023g, 0.36 mmol) was added and the reaction mixture was stirred for 18h at RT. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was quenched with cold water and extracted in EtOAc, organic layer was dried over anhydrous sodium sulphate and then concentrated under reduced pressure to get the crude, which was further purified by combi flash column chromatography using 5-8% methanol in DCM to afford the title compound brownish solid (0.08g, 93.8 %). LCMS: m/z 474.2 (M+H).

Step-ii: Synthesis of 2-(5-(4-((2-azaspiro[3.3]heptan-6-yl)amino)phenyl)-6-amino pyridazin-3-yl)phenol (Intermediate 44B)

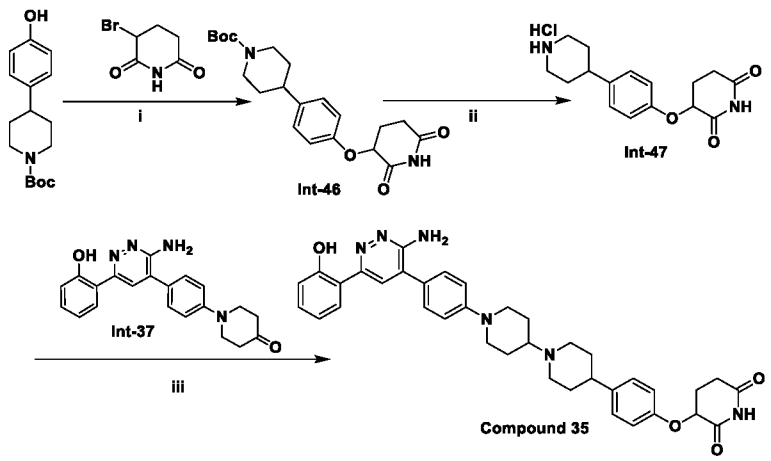
To a stirred solution of tert-butyl 6-((4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)phenyl)amino)-2-azaspiro[3.3]heptane-2-carboxylate (0.07g, 0.148 mmol) in DCM (2 mL) was added trifluoro acetic acid (0.1 mL) at 0 °C and then slowly brought to RT and stirred for 1 h. The reaction mixture was evaporated under reduced pressure, the resultant residue was

washed with diethyl ether and dried under vacuum to afford the title compound as a yellowish solid (0.0.7g, crude). LC-MS: m/z 374.2 (M+H).

Step-iii: Synthesis of 5-(6-((4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)phenyl) amino)-2-azaspiro[3.3]heptan-2-yl)-2-(2,6-dioxopiperidin-3-yl)-6-fluoroisoindoline-1,3-dione (Compound 34)

To a stirred solution of 2-(5-(4-((2-azaspiro[3.3]heptan-6-yl)amino)phenyl)-6-aminopyridazin-3-yl)phenol (0.07g, 0.187 mmol) in DMSO (2 mL) was added DIPEA (0.173g, 1.33 mmol)) and stirred for 5 mins. 2-(2,6-dioxopiperidin-3-yl)-5,6-difluoroisoindoline-1,3-dione (0.055g, 0.187 mmol) was added to the reaction mixture and heated at 120 °C for 1h. After completion of the reaction, the reaction mixture was poured into ice cold water and stirred for 30 minutes and filtered through Buchner funnel to get crude product as a solid. The crude product was purified by Prep TLC using 3% methanol in DCM system to afford the title compound yellow solid (0.03g, 24.7 %). ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.84 (s, 1H), 11.09 (s, 1H), 7.94 (dd, J = 7.2 Hz, 1.6 Hz 1H), 7.90 (s, 1H), 7.61 (d, J = 7.2 Hz, 1H), 7.43 (d, J = 8.8 Hz, 2H), 7.24 (dt, J = 7.2, 1.6 Hz, 1H), 6.92-6.88 (m, 3H), 6.77 (d, J = 8.8 Hz, 2H), 6.42 (d, J = 8.0 Hz, 1H), 6.34 (bs, 2H), 5.10-5.03 (m, 1H), 4.28 (bs, 2H), 4.16 (bs, 2H), 3.89-3.82 (m, 1H), 2.92-2.84 (m, 1H), 2.77-2.71 (m, 2H), 2.62-2.55 (m, 1H), 2.15-2.08 (m, 2H), 2.05-1.96 (m, 2H); LCMS: m/z 648.2 (M+H).

Example-XXI: Synthesis of 3-(4-(1'-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl) phenyl)-[1,4'-bipiperidin]-4-yl)phenoxy)piperidine-2,6-dione (Compound 35)



Step-i: Synthesis of tert-butyl 4-(4-((2,6-dioxopiperidin-3-yl)oxy)phenyl)piperidine-1-carboxylate (Intermediate-46)

To a stirred solution of tert-butyl 4-(4-hydroxyphenyl)piperidine-1-carboxylate (synthesized using Ref. chem comm 2018, 54,46,-49) (2.0g, 7.21 mmol) in DMF (20 mL) was added NaH (0.43g, 18.02 mmol) at 0°C temperature and stirred for 30 mins. Now 3-bromopiperidine-2,6-dione (1.66 g, 8.65 mmol) was added to the reaction mixture and stirred at RT for 2h After completion of the reaction the reaction mixture was poured into ice cold water and extracted with 2 X 100 mL of ethyl acetate, evaporated to get crude product. The crude product was purified first by combi flash column chromatography using 20-30% ethyl acetate in hexane to afford the title compound as colourless solid (1.1g, 39 %). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.91 (s, 1H), 7.14 (d, J = 8.8 Hz, 2H), 6.93 (d, J = 8.4 Hz, 2H), 5.15-5.13 (m, 1H), 4.10-3.90 (m, 2H), 2.84-2.72 (m, 2H), 2.68-2.55 (m, 2H), 2.20-2.11 (m, 3H), 1.73-1.69 (m, 2H), 1.51-1.42 (m, 2H), 1.41 (s, 9H). LCMS: m/z 387.1 (M-H).

Step-ii: Synthesis of 3-(4-(piperidin-4-yl)phenoxy)piperidine-2,6-dione hydrochloride (Intermediate-47)

To a stirred solution of tert-butyl 4-(4-((2,6-dioxopiperidin-3-yl)oxy)phenyl) piperidine-1-carboxylate (1.1g, 2.83 mmol) in DCM (10 mL) was added 4 N dioxane hydrochloride (10 mL) at 0 °C and then slowly brought to RT and stirred for 4h. The reaction mixture was evaporated under reduced pressure, the resultant residue was washed with diethyl ether and dried under vacuum to afford the title compound as a yellowish solid (0.81g, crude). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.93 (s, 1H), 8.91 (bs, 1H), 8.71 (bs, 1H), 7.13 (d, J = 8.8 Hz, 2H), 6.97 (d, J = 8.4 Hz, 2H), 5.18-5.15 (m, 1H), 3.34-3.31 (m, 2H), 2.98-2.93 (m, 2H), 2.78-2.68 (m, 2H), 2.63-2.61 (m, 1H), 2.17-2.12 (m, 2H), 1.91-1.87 (m, 2H), 1.85-1.78 (m, 2H). LCMS: m/z 289.1 (M+H).

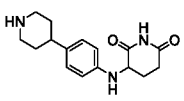
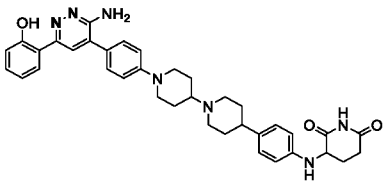
Step-iii: Synthesis of 3-(4-(1'-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)phenyl)-[1,4'-bipiperidin]-4-yl)phenoxy)piperidine-2,6-dione (Compound 35)

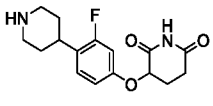
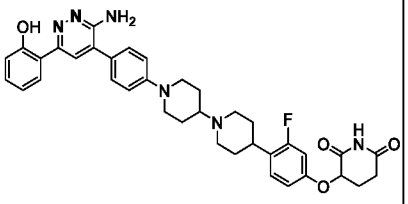
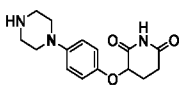
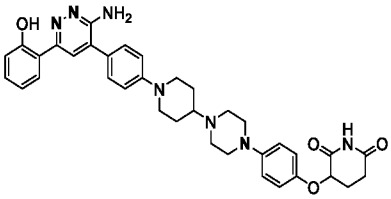
To a stirred solution of 3-(4-(piperidin-4-yl)phenoxy)piperidine-2,6-dione (0.20g, 0.69 mmol) and 1-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)phenyl)piperidin-4-one hydrochloride (0.25g, 0.69 mmol) in 9 mL THF:DMSO (2:1) mixture was added KOAc (0.20g, 2.08 mmol) and acetic acid (0.2 mL) and molecular sieves (4A°) and the reaction mixture was stirred at 45 °C for 4h. Then the reaction mixture was cooled to 0°C and sodium triacetoxy borohydride (0.4 g, 2.08 mmol) was added and the reaction mixture was stirred at RT for 16h.

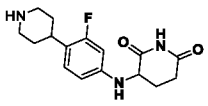
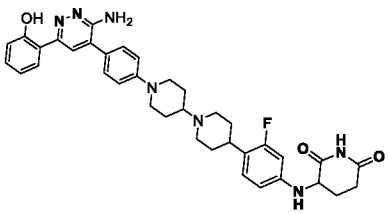
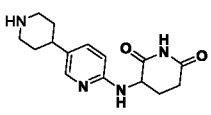
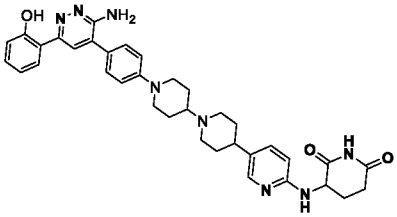
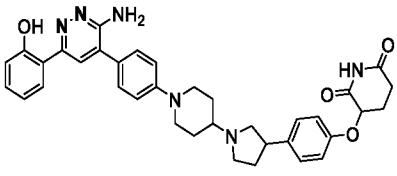
The reaction was monitored by TLC. After completion of the reaction the reaction mixture was extracted in DCM and saturated ammonium chloride wash was given to the organic layer followed by saturated sodium chloride wash. The organic layer was dried over anhydrous sodium sulphate and then concentrated under reduced pressure and the resultant residue was washed with diethyl ether and dried under vacuum to afford the title compound as a light yellow solid (0.03g, 7 %). ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.76 (s, 1H), 10.90 (s, 1H), 7.94 (d, J = 7.2 Hz, 1H), 7.93(s, 1H), 7.50 (d, J = 8.8 Hz, 2H), 7.23 (dt, J = 8.4, 1.6 Hz, 1H), 7.14 (d, J = 8.8 Hz, 2H), 7.07 (d, J = 8.8 Hz, 2H), 6.92-6.85 (m, 4H), 6.37 (bs, 2H), 5.15-5.11 (m, 1H), 3.89 (d, J = 12.4 Hz, 2H), 2.98 (d, J = 10 Hz, 2H), 2.82-2.55 (m, 4H), 2.48-2.35 (m, 2H), 2.30-2.05 (m, 4H), 1.87-1.82 (m, 2H), 1.76-1.67 (m, 2H), 1.61-1.48 (m, 4H). LCMS: m/z 633.05 (M+H).

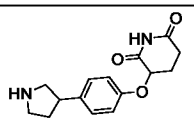
The compounds 36 to 41 listed in below **Table-2** were prepared by procedure similar to the one described in **Example-XXI** with appropriate variations in reactants, quantities of reagents, protections and deprotections, solvents and reaction conditions. The characterization data of the compounds are summarized herein the below table.

Table-2:

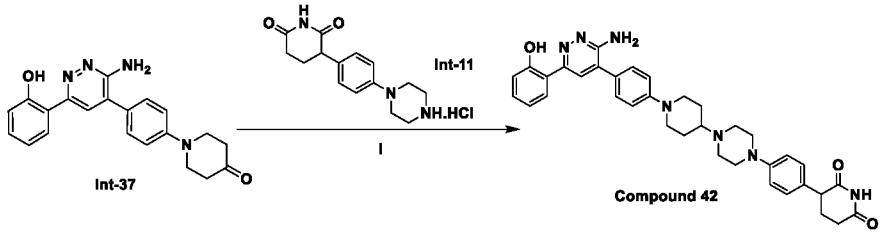
Comp. No	Intermediate	Structure	Characterization Data
36	Int-37 & 		^{1}H NMR (400 MHz, DMSO-d6): δ 10.77 (s, 1H), 9.12 (s, 1H), 7.95 (s, 1H), 7.86 (d, J = 7.2 Hz, 1H), 7.54 (d, J = 8.8 Hz, 2H), 7.27 (t, J = 7.2 Hz, 1H), 7.14 (d, J = 8.8 Hz, 2H), 6.95-6.88 (m, 3H), 6.63 (d, J = 8.4 Hz, 3H), 5.77 (bs, 1H), 4.27 (d, J = 6.8 Hz, 1H), 4.04 (d, J = 12 Hz, 2H), 3.56 (d, J = 12 Hz, 2H), 3.15-3.06 (m, 2H), 2.85-2.63 (m, 4H), 2.62-2.53 (m, 3H), 2.22-1.95 (m, 5H), 1.91-

			1.71 (m, 4H). LC-MS: m/z 632.4 (M+H).
37	Int-37 & 		^{1}H NMR (400 MHz, DMSO): δ 13.76 (s, 1H), 10.93 (s, 1H), 7.94-7.93 (m, 2H), 7.50 (d, J = 8.0 Hz, 2H), 7.20 (d, J = 8.0 Hz, 2H), 7.08 (d, J = 8.0 Hz, 2H), 6.91-6.77 (m, 4H), 6.37 (bs, 2H), 5.22-5.19 (m, 1H), 3.91-3.89 (m, 2H), 2.98 (d, J = 6.8 Hz, 2H), 2.77 (t, J = 8.0 Hz, 2H), 2.69-2.61 (m, 3H), 2.31-2.16 (m, 4H), 1.87-1.84 (m, 3H), 1.68-1.65 (m, 4H), 1.56-1.54 (m, 2H)
38	Int-37 & 		^{1}H NMR (400 MHz, DMSO-d_6): δ 13.77 (s, 1H), 10.89 (s, 1H), 7.95 (m, 2H), 7.52 (d, J = 8 Hz, 2H), 7.25 (t, J = 7.2 Hz, 1H), 7.10 (d, J = 8.8 Hz, 2H), 6.95-6.85 (m, 6H), 6.39 (bs, 2H), 5.03-4.99 (m, 1H), 3.90 (d, J = 10.8 hz, 2H), 3.03 (bs, 4H), 2.84-2.71 (m, 2H), 2.65 (bs, 4H), 2.63-2.53 (m, 2H), 2.21-2.03 (m, 3H), 1.97-1.86 (m, 2H), 1.61-1.46 (m, 2H). LC-MS: m/z 634.2 (M+H).

39	Int-37 & 		^{1}H NMR (400 MHz, DMSO-d6): δ 13.55 (s, 1H), 11.80 (s, 1H), 7.96-7.94 (m, 2H), 7.53 (d, J = 12.0 Hz, 2H), 7.27-7.23 (m, 1H), 7.11-7.09 (m, 2H), 7.01-6.99 (m, 1H), 6.93-6.87 (m, 2H), 6.46-6.39 (m, 4H), 6.01 (bs, 1H), 4.32-4.30 (m, 1H), 3.93-3.89 (m, 2H), 3.01-2.95 (m, 2H), 2.82-2.70 (m, 3H), 2.62-2.55 (m, 2H), 2.30-2.20 (m, 2H), 2.10-2.01 (m, 2H), 1.90-1.85 (m, 3H), 1.70-1.50 (m, 6H).
40	Int-37 & 		^{1}H NMR (400 MHz, DMSO-d_6): δ 10.98 (s, 1H), 9.35 (bs, 1H), 8.01 (s, 1H), 7.84 (d, J = 2.0 Hz, 1H), 7.78 (d, J = 7.6 Hz, 1H), 7.59-7.54 (m, 3H), 7.35-7.31 (m, 2H), 7.17 (d, J = 8.8 Hz, 2H), 7.01-6.93 (m, 3H), 6.87 (bs, 1H), 4.73 (t, J = 5.2 Hz, 1H), 4.09-4.06 (m, 3H), 3.51-3.48 (m, 4H), 3.13-3.10 (m, 2H), 2.85 (t, J = 12.4 Hz, 3H), 2.17-2.11 (m, 2H), 2.09-2.03 (m, 4H), 1.87-1.75 (m, 4H).
41	Int-37 &		^{1}H NMR (400 MHz, DMSO-d_6): δ 13.78 (s, 1H), 10.92 (s, 1H), 7.96 (d, J = 7.2 Hz, 1H), 7.95 (s, 1H), 7.53 (d, J = 8.8 Hz,

			2H), 7.25-7.22 (m, 3H), 7.11 (d, J = 8.8 Hz, 2H), 6.96-6.89 (m, 4H), 6.40 (bs, 2H), 5.19-5.15 (m, 1H), 3.84 (bs, 2H), 3.34 (bs, 4H), 2.92-2.69 (m, 3H), 2.67-2.55 (m, 3H), 2.31-1.94 (m, 5H), 1.87-1.72 (m, 1H), 1.68-1.55 (m, 2H); LCMS: m/z 619.05 (M+H).

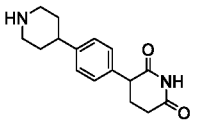
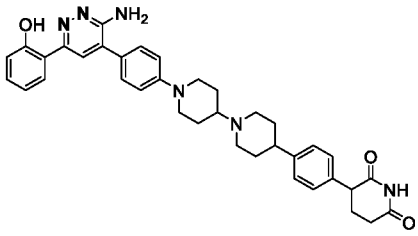
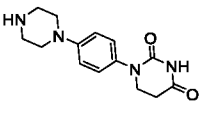
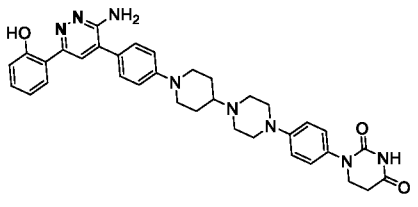
Example-XXII: Synthesis of 3-(4-(4-(1-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)phenyl)piperidin-4-yl)piperazin-1-yl)phenyl)piperidine-2,6-dione (Compound 42)

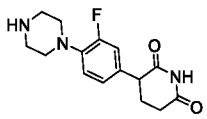
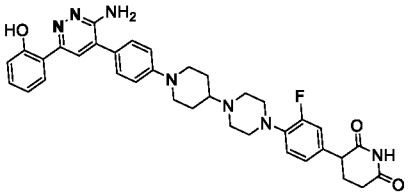
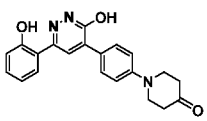
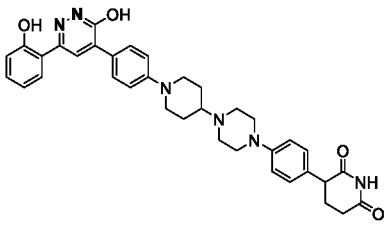


To a stirred solution of 1-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)phenyl)piperidin-4-one (0.13g, 0.36 mmol) and 3-(4-(piperazin-1-yl)phenyl)piperidine-2,6-dione hydrochloride (synthesized using Ref. WO2021/83949) (0.10g, 0.366mmol) in 9mL THF:DMSO (2:1) mixture was added KOAc (0.108g, 1.09 mmol) and acetic acid (0.2 mL) and molecular sieves (4A°) and the reaction mixture was stirred at 45 °C for 4h. Then the reaction mixture was cooled to 0 °C and sodium tri acetoxy borohydride (0.23g, 1.09 mmol) was added and the reaction mixture was stirred at RT for 16h. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was extracted in DCM and saturated ammonium chloride wash was given to the organic layer followed by saturated sodium chloride wash. The organic layer dried over anhydrous sodium sulphate and then concentrated under reduced pressure, and the resultant residue was washed with diethyl ether and dried under vacuum to afford the title compound as an off white solid (0.02g, 9 %). ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.77 (s, 1H), 10.78 (s, 1H), 7.96 (d, *J* = 7.6 Hz, 1H), 7.94 (s, 1H), 7.52 (d, *J* = 8.4 Hz, 2H), 7.25 (dt, *J* = 8, 1.6 Hz, 1H), 7.10 (d, *J* = 8.8 Hz, 2H), 7.05 (d, *J* = 8.8 Hz, 2H), 6.93-6.87 (m, 3H), 6.39 (bs, 2H), 3.95-3.85 (m, 2H), 3.74-3.70 (m, 1H), 3.11 (bs, 4H), 2.85-2.78 (m, 2H), 2.66 (bs, 4H), 2.64-2.57 (m, 1H), 2.48-2.42 (m, 3H), 2.15-1.98 (m, 2H), 1.95-1.88 (m, 2H), 1.58-1.48 (m, 2H); LCMS: m/z 618.15 (M+H).

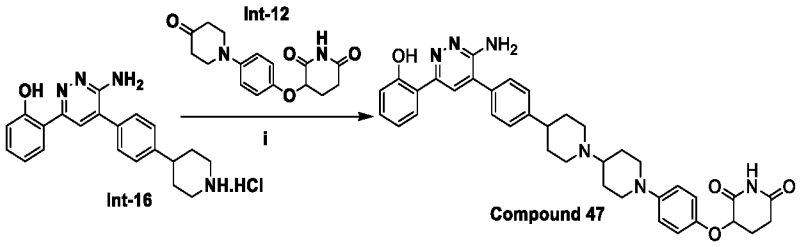
The compounds 43 to 46 listed in below **Table-3** were prepared by procedure similar to the one described in **Example-XXII** with appropriate variations in reactants, quantities of reagents, protections and deprotections, solvents and reaction conditions. The characterization data of the compounds are summarized herein the below table.

Table-3:

Comp. No	Intermediate	Structure	Characterization Data
43	Int-37 & 		^{1}H NMR (400 MHz, DMSO-d_6): δ 13.77 (s, 1H), 10.83 (s, 1H), 7.98-7.88 (m, 2H), 7.96-7.94 (m, 2H), 7.53 (d, J = 8.4 Hz, 2H), 7.27-7.10 (m, 7H), 6.39 (s, 2H), 3.93-3.89 (m, 2H), 3.83-3.80 (m, 1H), 3.08-2.98 (m, 2H), 2.83-2.77 (m, 2H), 2.68-2.63 (m, 2H), 2.60-2.55 (m, 2H), 2.33-2.15 (m, 3H), 2.05-2.02 (m, 2H), 1.99-1.60 (m, 7H); LCMS: m/z 617.4 (M+H).
44	Int-37 & 		^{1}H NMR (400 MHz, DMSO-d_6): δ 13.78 (s, 1H), 10.28 (s, 1H), 7.96 (d, J = 1.6 Hz, 1H), 7.95 (s, 1H), 7.53 (d, J = 8.4 Hz 2H), 7.27-7.23 (m, 1H), 7.15 (d, J = 9.2 Hz, 2H), 7.11 (d, J = 8.8 Hz, 2H), 6.95-6.87 (m, 4H), 6.41 (s, 2H), 3.91 (d, J = 12.4 Hz, 2H), 3.70 (t, J = 6.6 Hz, 2H), 3.14 (s, 4H), 2.81 (t, J = 11.6 Hz, 2H), 2.70-2.67 (m,

			6H), 2.53 (s, 1H), 1.93 (d, J = 10.4 Hz, 2H), 1.56-1.53 (m, 2H); LCMS: m/z 619.4 (M+H).
45	Int-37 & 		^{1}H NMR (400 MHz, DMSO-d_6): δ 13.78 (s, 1H), 10.82 (s, 1H), 7.96 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.94 (s, 1H), 7.52 (d, *J* = 8.8 Hz, 2H), 7.25 (dt, *J* = 8.4, 1.6 Hz, 1H), 7.11 (d, *J* = 9.2 Hz, 2H), 7.06-6.87 (m, 5H), 6.41 (bs, 2H), 3.90 (d, J= 12.4 Hz, 2H), 3.82-3.78 (m, 1H), 3.01 (bs, 4H), 2.83-2.78 (m, 2H), 2.68 (bs, 4H), 2.63-2.59 (m, 1H), 2.47-2.45 (m, 2H), 2.27-2.16 (m, 1H), 2.05-1.87 (m, 3H), 1.62-1.53 (m, 2H); LCMS: m/z 618.15 (M+H).
46	Int-11 & 		^{1}H NMR (400 MHz, DMSO-d_6): δ 13.13 (s, 1H), 10.78 (s, 1H), 10.33 (s, 1H), 8.00 (s, 1H), 7.91 (d, J = 9.2 Hz, 2H), 7.65-7.63 (m, 1H), 7.31-7.26 (m, 1H), 7.06-7.01 (m, 4H), 6.98-6.96 (m, 4H), 3.92 (d, J = 12.0 Hz, 2H), 3.75-3.71 (m, 1H), 3.16 (s, 4H), 2.81 (t, J = 11.4 Hz, 2H), 2.67 (s, 4H), 2.55-2.50 (m, 1H), 2.22-2.10 (m, 1H), 2.03-1.99 (m, 2H), 1.90 (d, J = 9.6 Hz, 2H), 1.55-1.52 (m, 3H); LCMS: m/z 619.5 (M+H).

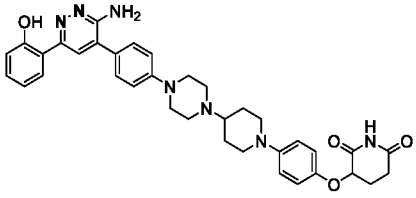
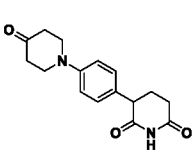
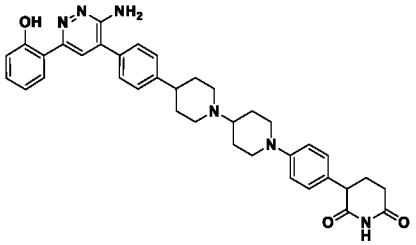
Example-XXIII: Synthesis of 3-(4-(4-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)phenyl)-[1,4'-bipiperidin]-1'-yl)phenoxy)piperidine-2,6-dione (Compound 47)

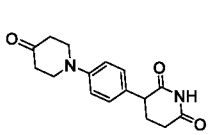
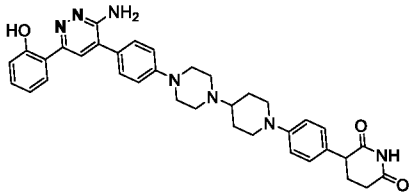


To a stirred solution of 2-(6-amino-5-(4-(piperidin-4-yl)phenyl)pyridazin-3-yl)phenol hydrochloride (0.3g, 0.99 mmol) and 3-(4-(4-oxopiperidin-1-yl)phenoxy)piperidine-2,6-dione (0.344g, 0.99 mmol) in 9mL THF:DMSO (2:1) mixture was added KOAc (0.29g, 2.97 mmol) and acetic acid (0.1 mL) and molecular sieves (4Ao) and the reaction mixture was stirred at 70°C for 18 Hours. Then the reaction mixture was cooled to 0°C and sodium tri-acetoxyborohydride (0.63g, 2,97 mmol) was added and the reaction mixture was stirred for 12h at RT. The reaction was monitored by TLC. After completion of the reaction the reaction mixture was poured into ice water to obtain the precipitate, filtered and washed with water to get the crude product. The crude product was purified by column chromatography using 5-10 % MeOH in DCM to afford the title compound as light brown solid (0.063g, 10%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.62 (s, 1H), 11.08 (s, 1H), 8.00 (s, 1H), 7.94 (d, J = 8.4 Hz, 1H), 7.70-7.68 (m, 1H), 7.58 (d, J = 8.0 Hz, 2H), 7.45 (d, J = 7.6 Hz, 2H), 7.39 (s, 1H), 7.34 (d, J = 8.0 Hz, 1H), 7.25 (t, J = 8.0 Hz, 1H), 6.93-6.87 (m, 2H), 6.45 (bs, 2H), 5.12-5.02 (m, 1H), 4.28-4.21 (m, 2H), 3.11 (t, J = 5.6 Hz, 2H), 3.00-2.85 (m, 2H), 2.70-2.20 (m, 2H), 2.05-2.00 (m, 1H), 1.98-1.90 (m, 2H), 1.80-1.72 (m, 2H). LC/MS: m/z 603.2 (M+H).

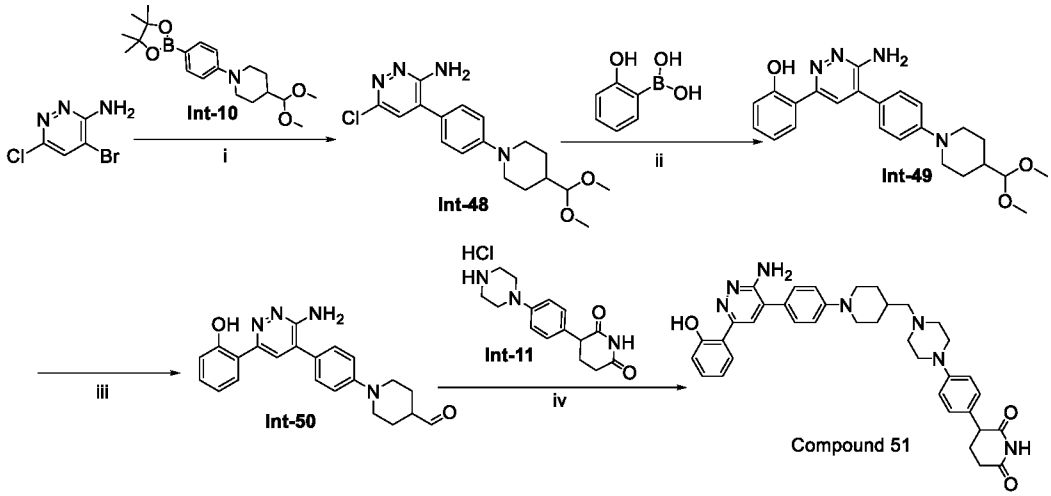
The compounds 48 to 50 listed in below **Table-4** were prepared by procedure similar to the one described in **Example-XXIII** with appropriate variations in reactants, quantities of reagents, protections and deprotections, solvents, and reaction conditions. The characterization data of the compounds are summarized herein in the below table.

Table-4:

Comp. No	Intermediate	Structure	Characterization Data
48	Int-26 & Int-12		^{1}H NMR (400 MHz, DMSO-d6): δ 13.77 (s, 1H), 10.91 (s, 1H), 7.96 (dd, J = 8, 1.6 Hz, 1H), 7.95 (s, 1H), 7.53 (d, J = 8.8 Hz, 2H), 7.25 (dt, J = 7.2, 1.2 Hz, 1H), 7.10 (d, J = 8.8 Hz, 2H), 6.95-6.86 (m, 6H), 6.41 (bs, 2H), 5.03-5.00 (m, 1H), 3.55-3.46 (m, 2H), 3.26 (m, 4H), 2.68 (m, 4H), 2.64-2.57 (m, 3H), 2.41-2.31 (m, 2H), 2.21-1.98 (m, 2H), 1.94-1.86 (m, 2H), 1.62-1.53 (m, 2H). LC-MS: m/z 634.5(M+H).
49	Int-16 & 		^{1}H NMR (400 MHz, DMSO-d_6): δ 10.95 (bs, 1H), 10.82 (s, 1H), 8.16 (s, 1H), 8.11 (s, 1H), 7.69-7.64 (m, 3H), 7.50 (d, *J* = 8.4 Hz, 2H), 7.25 (dt, *J* = 8.4, 1.6 Hz, 1H), 7.14 (d, *J* = 7.6 Hz, 2H), 7.07 (d, *J* = 7.6 Hz, 2H), 7.00 (t, J = 7.2Hz, 1H), 3.88-3.77 (m, 3H), 3.65-3.55 (m, 3H), 3.25-3.12 (m, 3H), 3.09-2.98 (m,1H), 2.84 (bs, 2H), 2.72-2.62 (m, 1H), 2.36-2.12 (m, 5H), 2.10-1.88 (m,

			5H); LCMS: m/z 617.5 (M+H).
50	Int-26 & 		^{1}H NMR (400 MHz, DMSO-d6): δ 13.79 (s, 1H), 10.83 (s, 1H), 7.95 (m, 2H), 7.53 (d, J = 8.4 Hz, 2H), 7.25 (dt, J = 7.2, 1.2 Hz, 1H), 7.09 (d, J = 8.8 Hz, 2H), 7.04 (d, J = 8.4 Hz, 2H), 6.96-6.85 (m, 4H), 6.41 (bs, 2H), 3.78-3.71 (m, 3H), 3.26 (bs, 3H), 3.17 (d, J = 5.2 Hz, 2H), 2.74-2.58 (m, 7H), 2.55-2.38 (m, 1H), 2.19-2.11 (m, 1H), 2.06-1.86 (m, 3H), 1.61-1.49 (m, 2H). LC-MS: m/z 618.5 (M+H).

Example XXIV: Synthesis of 3-(4-(4-((1-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)phenyl)piperidine-2,6-dione (Compound 51)



Step-i: Synthesis of 6-chloro-4-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)pyridazin-3-amine (Intermediate 48)

To a stirred solution of 4-bromo-6-chloropyridazin-3-amine (1.25 g, 3.45 mmol), 4-(dimethoxymethyl)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidine (0.72 g, 3.45 mmol) in 1,4-dioxane (16 mL) and water (4 mL) was added K_2CO_3 (1.43g, 10.38 mmol) and degassed with nitrogen for 10 min, followed by adding $Pd(dppf)_2Cl_2$.DCM (0.28g, 0.34 mmol) and the reaction mixture was heated for 6h at 70 °C in a sealed tube. Once the reaction was completed (monitored by TLC), the reaction mixture was diluted with EtOAc. The combined organic layer was washed with water, brine, dried over anhydrous sodium sulphate, and concentrated under vacuum to get crude product which was purified by combi flash column chromatography using 5-8% methanol in DCM as eluent to afford the title compound as light brown solid (0.75g, 59.7%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.41 (d, *J* = 8.8 Hz, 2H), 7.26 (s, 1H), 7.02 (d, *J* = 8.8 Hz, 2H), 6.25 (bs, 2H), 4.07 (d, J = 6.8 Hz, 1H), 3.83 (d, J = 12.8 Hz, 2H), 3.26 (s, 6H), 2.71 (dt, J = 12, 2.4 Hz, 2H), 1.84-1.76 (m, 1H), 1.70 (d, J = 13.2 Hz, 2H), 1.35-1.22 (m, 2H); LC-MS: m/z 363.2 (M+H).

Step-ii: Synthesis of 2-(6-amino-5-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl) pyridazin-3-yl)phenol (Intermediate 49)

To a stirred solution of 6-chloro-4-(4-(4-(dimethoxymethyl)piperidin-1-yl)phenyl)pyridazin-3-amine (0.23 g, 0.63 mmol), (2-hydroxyphenyl)boronic acid (0.13 g, 0.95 mmol) in 1,4-dioxane (3 mL) and water (0.75 mL) was added K_2CO_3 (0.26g, 1.9 mmol) and degassed with nitrogen for 10 min, followed by adding $Pd(dppf)_2Cl_2$.DCM (0.045 g, 0.06 mmol) and the reaction mixture was microwaved for 1h at 110 °C in a microwave. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was dissolved in 10%MeOH/DCM and passed through celite, and filtrate was concentrated under reduced pressure to give the residue which was purified by combi flash column chromatography using 60-70 % ethyl acetate in hexene as eluent to afford the title compound as light brown solid (0.19 g, 71%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.78 (s, 1H), 7.95 (d, *J* = 6.4 Hz, 1H), 7.94 (s, 1H), 7.51(d, *J* = 8.8 Hz, 2H), 7.25 (m, 1H), 7.07 (d, *J* = 6.4 Hz, 1H), 6.93-6.86 (m, 2H), 6.38 (bs, 2H), 4.09 (d, J = 6.8 Hz, 1H), 3.86 (d, J = 12.8 Hz, 2H), 3.28 (s, 6H), 2.74 (dt, J = 12, 2.4 Hz, 2H), 1.85-1.78 (m, 1H), 1.73 (d, J = 13.2 Hz, 2H), 1.38-1.26 (m, 2H); LC-MS: m/z 421.3 (M+H).

Step-iii: Synthesis of 1-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)phenyl) piperidine-4-carbaldehyde (Intermediate 50)

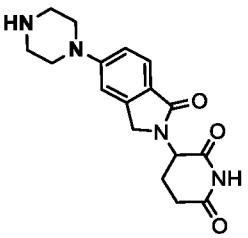
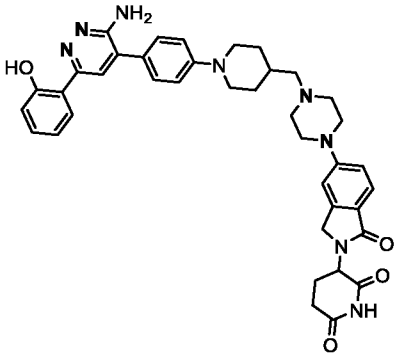
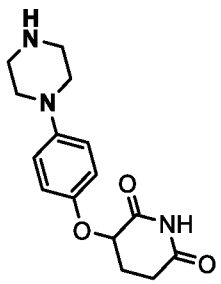
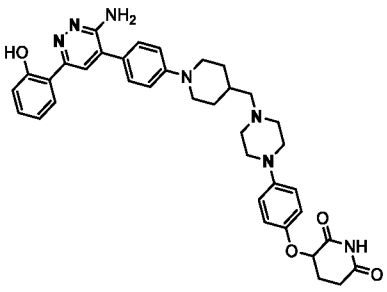
To a stirred solution of 1-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)phenyl)piperidine-4-carbaldehyde (0.19g, 0.42 mmol) in THF (3 mL) was added 3 N aq. hydrochloride (0.5 mL) at 0 °C and then slowly brought to RT and stirred for 6 h. The reaction mixture was quenched with ice water and pH was adjusted to pH-8 by the addition of K_2CO_3 solid pinch-wise. Then the reaction mass was extracted with 10%MeOH in DCM organic layer, washed with brine solution dried over Na_2SO_4, and concentrated to afford the title compound as orange solid (0.168 g, 99%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.75 (s, 1H), 9.63 (s, 1H), 7.94 (d, J = 5.6 Hz, 1H), 7.93 (s, 1H), 7.51(d, J = 8.8 Hz, 2H), 7.23 (m, 1H), 7.08 (d, J = 6.4 Hz, 1H), 6.93-6.85 (m, 2H), 6.37 (bs, 2H), 3.75 (d, J = 12.8 Hz, 2H), 2.98 (dt, J = 12.8, 2.4 Hz, 2H), 1.95-1.90 (m, 2H), 1.77-1.70 (m, 1H), 1.62-1.52 (m, 2H); LCMS: m/z 375.2 (M+H).

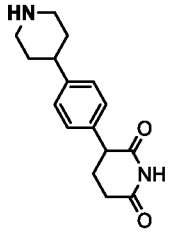
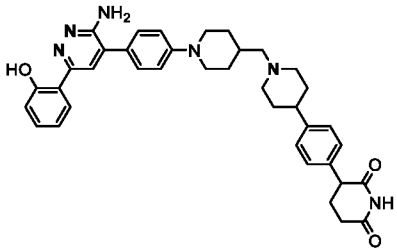
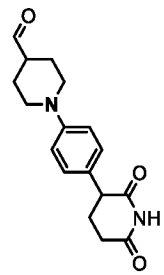
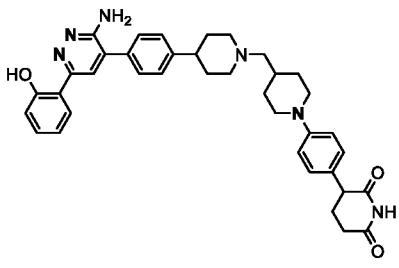
Step-iv: 3-(4-(4-((1-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)phenyl)piperidine-2,6-dione (Compound 51)

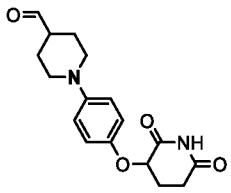
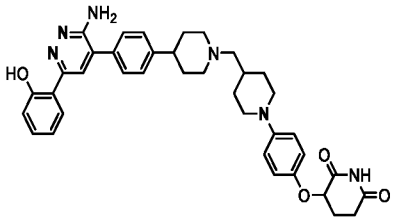
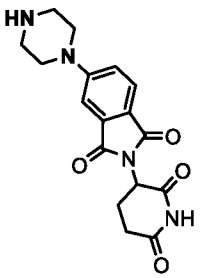
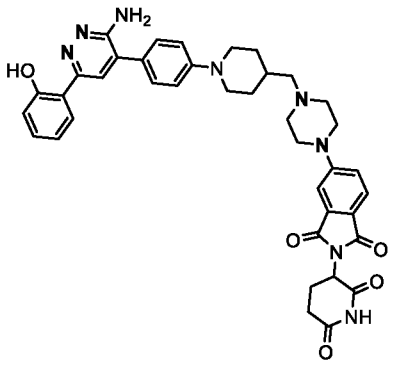
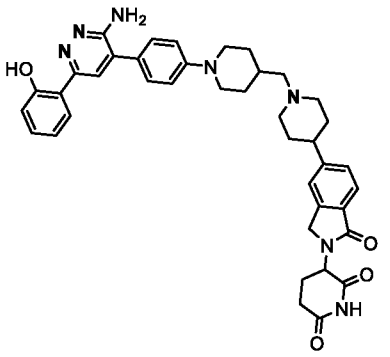
To a stirred solution of 1-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)phenyl) piperidine-4-carbaldehyde (0.05g, 0.134 mmol) and 2-(2,6-dioxopiperidin-3-yl)-5-(4-oxopiperidin-1-yl)isoindoline-1,3-dione (0.037g, 0.134 mmol) in 1.5mL THF:DMSO (2:1) mixture was added KOAc (0.04g, 0.04 mmol) and acetic acid (0.05 mL) and molecular sieves (4A°) and the reaction mixture was stirred at 40 °C for 4 hours. Then the reaction mixture was cooled to 0 °C and sodium cyanoborohydride (0.025g, 0.40 mmol) was added and the reaction mixture was stirred for 16h at RT. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was poured into ice water to obtain the precipitate, filtered, and washed with water to get the crude, which was further purified prep HPLC to afford the title compound as a light yellow solid (0.030g, 35%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.73 (bs, 1H), 10.77 (s, 1H), 7.93 (bs, 2H), 7.51 (d, J = 8.4 Hz, 2H), 7.24 (t, J = 7.2 Hz, 1H), 7.14-7.03 (m, 4H), 6.95-6.85 (m, 4H), 6.37 (bs, 2H), 3.85 (d, J = 11.2 Hz, 2H), 3.73 (d, J = 6.8 Hz,, 1H), 3.10 (bs, 4H), 2.85-2.55 (m, 5H), 2.48-2.39 (m, 3H), 2.27-1.95 (m, 3H), 1.88-1.75 (m, 2H), 1.33-1.15 (m, 4H); LC-MS: m/z 632.5 (M+H).

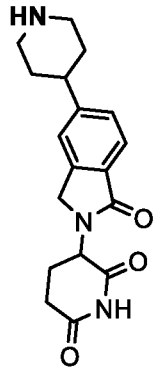
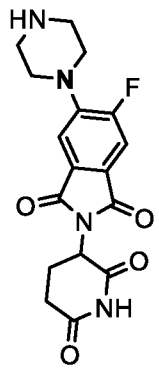
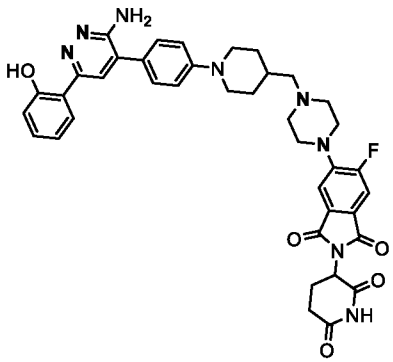
The compounds 52 to 55 and 71 to 74 listed in below **Table-5** were prepared by a procedure similar to the one described in **Example-XXIV** with appropriate variations in reactants, quantities of reagents, protections and deprotections, solvents, and reaction conditions. The characterization data of the compounds are summarized herein the below table.

Table-5:

Comp. No	Intermediate	Structure	Characterization Data
52	Int-50 & 		^{1}H NMR (400 MHz, DMSO-d_6): δ 13.73 (bs, 1H), 11.95 (s, 1H), 7.94 (bs, 2H), 7.58-7.48 (m, 3H), 7.28-7.22 (m, 1H), 7.15-7.04 (m, 4H), 6.93-6.88 (m, 2H), 6.39 (bs, 2H), 5.10-5.03 (m, 1H), 4.40-4.18 (m, 2H), 3.92-3.82 (m, 2H), 3.28 (bs, 6H), 2.94-2.86 (m, 1H), 2.83-2.75 (m, 2H), 2.63-2.55 (m, 3H), 2.43-2.27 (m, 3H), 2.02-1.76 (m, 4H), 1.35-1.27 (m, 2H); LC-MS: m/z 685.2 (M-H).
53	Int-50 & 		^{1}H NMR (400 MHz, DMSO-d_6): δ 13.65 (bs, 1H), 10.89 (s, 1H), 9.35 (bs, 1H), 7.92 (bs, 2H), 7.51 (bs, 2H), 7.23 (bs, 1H), 7.09 (m, 2H), 6.97-6.83 (m, 5H), 6.40 (bs, 2H), 5.09-4.98 (m, 1H), 3.86 (bs, 2H), 3.71-3.53 (m, 2H), 3.13 (bs, 3H), 3.06-2.92 (m, 2H), 2.87-2.75 (m, 2H), 2.71-2.57 (m, 2H), 2.22-1.98 (m, 4H), 1.84 (m, 2H), 1.37-1.25 (m, 4H); LC-MS: m/z 648.5 (M-H).

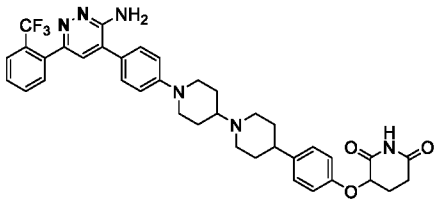
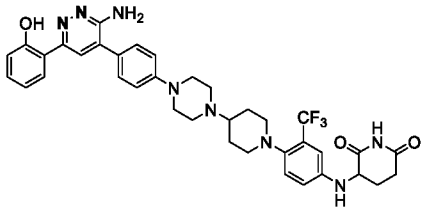
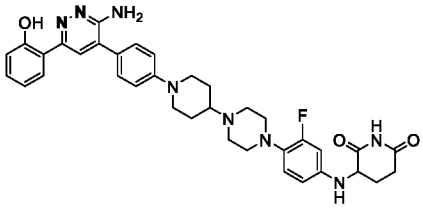
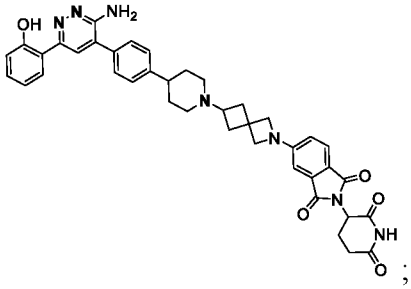
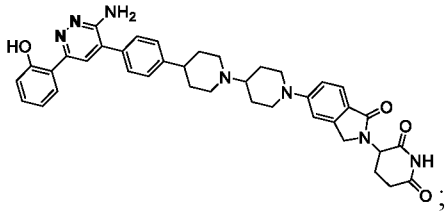
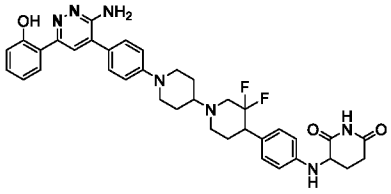
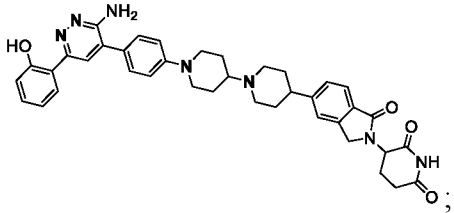
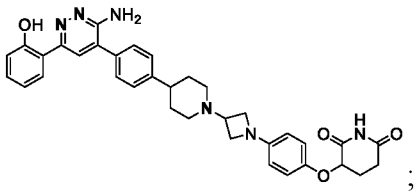
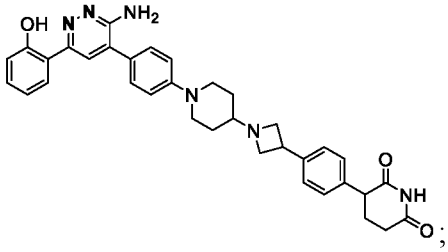
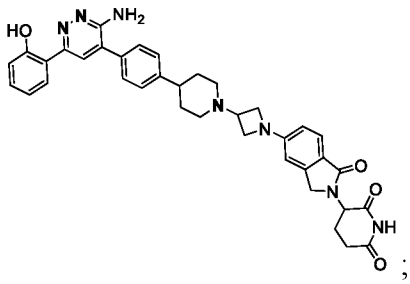
54	Int-50 & 		^{1}H NMR (400 MHz, DMSO-d_6): δ 13.78 (bs, 1H), 10.83 (s, 1H), 7.95 (dd, J = 7.2, 1.6 Hz, 1H), 7.94 (s, 1H), 7.52 (d, J = 8.8 Hz, 2H), 7.27 (dt, J = 6.8, 1.2 Hz, 1H), 7.22 (d, J = 8.4 Hz, 2H), 7.14 (d, J = 8.0 Hz, 2H), 7.09 (d, J = 8.8 Hz, 2H), 6.93-6.87 (m, 2H), 6.40 (bs, 2H), 3.89-3.78 (m, 3H), 2.97 (d, J = 11.2 Hz, 2H), 2.84-2.60 (m, 3H), 2.24-2.12 (m, 3H), 2.08-1.96 (m, 3H), 1.87-1.60 (m, 7H), 1.28-1.15 (m, 4H); LC-MS: m/z 631.5 (M+H).
55	Int-16 & 		^{1}H NMR (400 MHz, DMSO-d_6): δ 13.65 (bs, 1H), 10.78 (s, 1H), 8.01 (s, 1H), 7.95 (dd, J = 8.0, 1.6 Hz, 1H), 7.57 (d, J = 8.0 Hz, 2H), 7.44 (d, J = 8.4 Hz, 2H), 7.24 (dt, J = 7.2, 1.2 Hz, 1H), 7.03 (d, J = 8.8 Hz, 2H), 6.93-6.85 (m, 4H), 6.46 (bs, 2H), 3.73-3.50 (m, 3H), 2.99 (d, J = 11.2 Hz, 2H), 2.67-2.54 (m, 3H), 2.21-2.08 (m, 3H), 2.05-1.97 (m, 3H), 1.85-1.64 (m, 7H), 1.27-1.17 (m, 4H); LC-MS: m/z 631.5 (M+H).

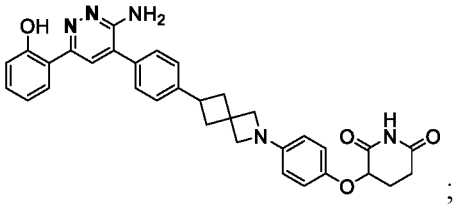
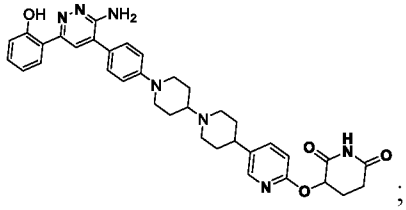
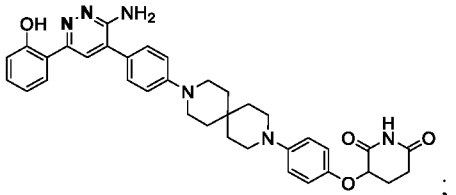
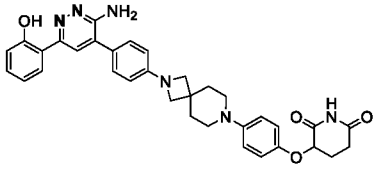
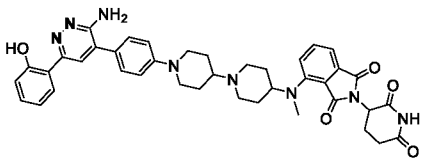
71	Int-16 & 		LC-MS: m/z 647.33 (M+H). HPLC purity:95.8 %
72	Int-50 & 		^{1}H NMR (400 MHz, DMSO-d_6): δ 13.77 (s, 1H), 11.08 (s, 1H), 7.96-7.94 (m, 2H), 7.69 (d, J = 8.4 Hz, 1H), 7.52 (d, J = 8.8 Hz, 2H), 7.36 (s, 1H), 7.28-7.27 (m, 2H), 7.09 (d, J = 8.8 Hz, 2H), 6.93-6.91 (m, 2H), 6.38 (s, 2H), 5.10-5.06 (m, 1H), 3.86 (d, J = 12.4 Hz, 2H), 3.46 (bs, 4H), 2.91-2.75 (m, 3H), 2.57-2.50 (m, 4H), 2.23 (d, J = 6.8 Hz, 2H), 2.08-1.98 (m, 2H), 1.89-1.71 (m, 3H), 1.25-1.15 (m, 3H); LC-MS: m/z 701.3 (M-H).
73	Int-50 &		^{1}H NMR (400 MHz, DMSO-d_6): δ 13.75 (s, 1H), 10.98 (s, 1H), 7.96-7.94 (m, 2H), 7.65 (d, J = 8.4 Hz, 1H), 7.52 (d, J = 9.2 Hz, 3H), 7.41 (d, J = 6.8 Hz, 1H), 7.27-7.23 (m, 1H), 7.09 (d, J = 8.8 Hz, 2H), 6.93-6.87 (m, 2H), 6.38 (s, 2H), 5.13-5.08 (m, 1H),

			4.45-4.27 (m, 2H), 3.86 (d, J = 12.4 Hz, 2H), 2.98-2.89 (m, 3H), 2.82-2.71 (m, 2H), 2.69-2.56 (m, 2H), 2.42-2.35 (m, 1H), 2.12 (d, J = 6.8 Hz, 2H), 2.08-1.95 (m, 3H), 1.87-1.62 (m, 6H), 1.28-1.20 (m, 3H); LC-MS: m/z 686.34 (M-H).
74	Int-50 & 		^{1}H NMR (400 MHz, DMSO-d_6): δ 13.76 (s, 1H), 11.11 (s, 1H), 7.96-7.94 (m, 2H), 7.73 (d, J = 8.4 Hz, 1H), 7.52 (d, J = 8.8 Hz, 2H), 7.46 (d, J = 8.6 Hz, 1H), 7.28-7.27 (m, 1H), 7.09 (d, J = 8.8 Hz, 2H), 6.93-6.91 (m, 2H), 6.38 (s, 2H), 5.10-5.06 (m, 1H), 3.86 (d, J = 12.4 Hz, 2H), 3.27 (bs, 4H), 2.91-2.75 (m, 3H), 2.52 (bs, 4H), 2.23 (d, J = 6.8 Hz, 2H), 2.08-1.98 (m, 2H), 1.89-1.71 (m, 3H), 1.25-1.15 (m, 3H); LC-MS: m/z 719.2 (M-H).

Although the present disclosure has been illustrated by certain of the preceding examples, it is not to be construed as being limited thereby; but rather, the present disclosure encompasses the generic area as hereinbefore disclosed. Various modifications and embodiments can be made without departing from the spirit and scope thereof. For example, the compounds in the Table-6 below which can be prepared by following similar procedure as described in above Schemes/Examples with suitable modifications known to the one ordinary skilled in the art are also included in the scope of the present disclosure.

Table-6:

Comp. No.	Structure	Comp. No.	Structure
56	 ;	57	 ;
58	 ;	59	 ;
60	 ;	61	 ;
62	 ;	63	 ;
64	 ;	65	 ;

66	 ;	67	 ;
68	 ;	69	 or
70			

Example-P1: Determination of Anti proliferative activity of compounds in cell line SK-MEL-5 by Cell Titer Glo®(Promega) assay

Cells were seeded into 96-well plates and the plates were incubated at 37°C in incubator overnight. The next day, compounds were diluted 3-fold to cover the 9-point concentration range in DMSO. Intermediate plate dilution was prepared in media followed with compound treatment in cells. Retreatment of cells with compound dilutions was performed on Day 4 and assay was terminated on day 8 for SK-MEL-5 cells using 100 µl of CellTiter-Glo and the plate was kept on orbital shaker for 20 minutes at RT. Luminescence signal was recorded on VICTOR5 instrument. Percent inhibition of proliferation was calculated at each concentration and plotted against the compound concentration. EC_{50} value was calculated using GraphPad® software.

Selected compounds of the present disclosure were screened in the above-mentioned assay procedures for determination of EC_{50} (SK-MEL-5) values and the results are summarized into groups A, B and C in below table-7. Herein the group "A" refers to EC_{50} values ≤100 nM, "B" refers to EC_{50} values >100 nM to ≤500 nM and "C" refers to EC_{50} values >500 nM.

Table-7:

Group	Compounds
A	1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 13, 17, 19, 20, 21, 24, 26, 28, 30, 31, 32, 33, 35, 36, 37, 38, 39, 41, 42, 43, 45, 47, 49, 50, 51, 52, 53, 54, 55, 71, 72 and 73.
B	14, 18, 25, 34 and 74.
C	9, 11, 15, 16, 22, 23, 27, 29, 23 25, 44, 46 and 48.

Example-P2: Determination of Anti proliferative activity of compounds in cell lines MV-4-11 by Cell Titer Glo®(promega) assay:

MV-4-11 (CRL-9591™) cells were seeded in 96 well plate flat black clear bottom plates using complete DMEM Medium. Next day, compounds listed in the present disclosure were added to cells from 10 mM stocks made in DMSO. Each concentration of compound was tested in triplicate with DMSO concentration at a final percentage not exceeding 0.3 in the cells. After the incubation of MV-4-11 cells with compound for 3 days; assay was terminated using 100 µl of CellTiter Glo® reagent. Luminescence readings were taken in Victor-5 instrument. Percent inhibition of proliferation was calculated using formula, % inhibition =100-(luminescence value of test/luminescence value of DMSO control) * 100. EC_{50} was calculated using graph pad prism software.

Selected compounds of the present disclosure were screened in the above-mentioned assay procedures for determination of EC_{50} (MV-4-11) values and the results are summarized into groups A, B and C in below table-8. Herein the group "A" refers to EC_{50} values ≤100 nM and "B" refers to EC_{50} values >100 nM.

Table-8:

Group	Compounds
A	1, 2, 3, 4, 5, 6, 7, 8, 12, 13, 14, 17, 21, 25, 30, 31, 35, 36, 37, 39, 42, 43, 45, 49, 50, 51, 52, 54, 55, 72, 73 and 74.
B	9, 10, 11, 15, 16, 18, 19, 20, 22, 23, 24, 26, 27, 28, 29, 32, 33, 34, 38, 40, 41, 44, 46, 47, 48, 53, 71.

Example-P3: Determination of SMARCA2 and SMARCA4 degradation in MV-4-11 cells by Western blot.

MV-4-11 (CRL-9591™) cells were plated in 6 well plates using complete Dulbecco's Modified Eagle's Medium. On the third day, selected compounds of the present disclosure were added to cells from 10 mM stocks made in DMSO. Each concentration of compound was tested with DMSO not exceeding the final percentage of 0.1 in the cells. Cells were incubated with the compound for 16 hours followed by harvesting with 1X RIPA lysis buffer containing protease inhibitor cocktail. An equal amount of protein was loaded on SDS-PAGE gel for electrophoresis. Western blot was carried out for detection of either SMARCA2 (Cell signalling technologies, catalogue number #11966) or SMARCA4 antibody (Cell signalling technologies, catalogue number #52251). Beta-Tubulin antibody (Cell signalling technologies, catalogue number # 86298) was used as loading control. Percentage of SMARCA2 or SMARCA4 degradation was calculated using the formula % Degradation = 100 - [(normalized band intensity in treated sample/normalized band intensity in DMSO sample) * 100.

Selected compounds of the present disclosure were screened in the above-mentioned assay procedures for determination of percent degradation and the results are summarized in below table-9.

Table-9:

Compound No	Percent degradation (at 100 nM)	
	SMARCA2	SMARCA4
2	99.9	96.8
3	98.2	98.7
4	96.6	80.9
5	95.3	86.2
6	98.7	97.8
8	95.0	82.3
10	59.8	60.6
11	81.2	74.1
12	97.8	97.8
16	100.0	92.2
17	99.1	100.1

19	93.2	81.3
24	96.5	69.6
25	68.7	45.7
26	98.6	96.9
28	73.1	62.1
30	91.6	82.3
32	75.3	53.7
33	87.1	75.4
35	99.8	99.9
36	97.3	81.2
37	97.7	96.8
38	69.5	34.0
39	98.9	99.1
42	93.7	94.3
43	97.2	93.2
49	98.4	95.3
51	95.8	89.4
52	98.8	98.7
53	71.0	50.2
54	95.3	93.3
71	94.0	96.0
72	97.7	84.0
73	100.0	99.6
74	99.0	94.0

Incorporation by Reference

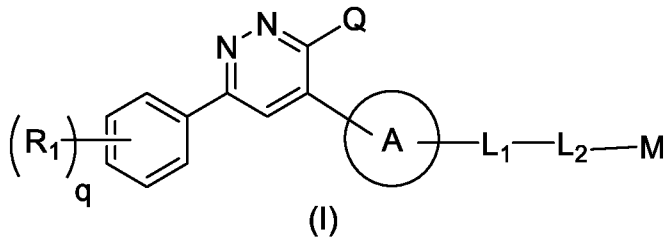
All publications and patents mentioned herein are hereby incorporated by reference in their entirety as if each individual publication or patent were specifically and individually indicated to be incorporated by reference. In case of conflict, the present application, including any definitions herein, will control.

Equivalents

While specific embodiments of the subject disclosure have been discussed, the above specification is illustrative and not restrictive. Many variations of the disclosure will become apparent to those skilled in the art upon review of this specification and the claims below. The full scope of the disclosure should be determined by reference to the claims, along with such variations.

Claims:

1. A compound of formula (I)



(I)

or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof;

wherein,

R_1 at each occurrence, independently, is hydroxy, halo(C_1-C_6)alkyl, (C_1-C_6)alkoxy, halogen, (C_1-C_6)alkyl, amino or cyano;

q is 0, 1, 2 or 3;

Q is hydroxy, (C_1-C_6)alkoxy, amino or (C_1-C_6)alkylamino;

A is phenylenyl or 6-membered heteroarylenyl; wherein the phenylenyl and heteroarylenyl independently, are unsubstituted or substituted with 1, 2 or 3 occurrence(s) of Ra;

Ra represents halogen, (C_1-C_6)alkyl or halo(C_1-C_6)alkyl;

L_1 is -(3- to 12-membered heterocycloalkylenyl)-, *-(3- to 12-membered heterocycloalkylenyl)-(3- to 8-membered cycloalkylenyl)-, -(3- to 12-membered heterocycloalkylenyl)-(3- to 12-membered heterocycloalkylenyl)-, or *-N(Rx)-(3- to 12-membered heterocycloalkylenyl)-; wherein the heterocycloalkylenyl and cycloalkylenyl independently is unsubstituted or substituted with 1, 2 or 3 occurrence(s) of Rd; wherein the asterisk mark represents the point of attachment with ring A;

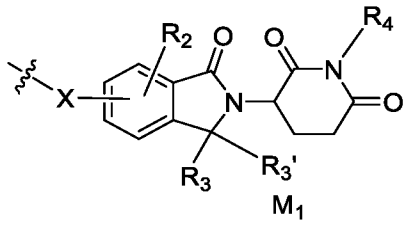
L_2 is a bond, -(3- to 8-membered cycloalkylenyl)-, -(3- to 10-membered heterocycloalkylenyl)-, *-$(CRxRy)_n$-(3- to 8-membered cycloalkylenyl)-, *-$(CRxRy)_n$-(3- to 10-membered heterocycloalkylenyl)-, *-(3- to 10-membered heterocycloalkylenyl)-$(CRxRy)_n$-; wherein the cycloalkylenyl and heterocycloalkylenyl, independently is unsubstituted or substituted with 1, 2 or 3 occurrence(s) of Rd; wherein the asterisk mark represents the point of attachment with L_1;

Rx and Ry, independently, is hydrogen or (C_1-C_6)alkyl;

n is 1, 2 or 3;

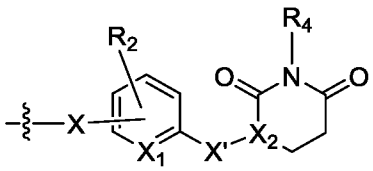
Rd at each occurrence, independently, is (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, halogen, hydroxy or (C_1-C_6)alkoxy;

M is M_1 or M_2;



M_1

or



M_2 ;

wherein,

X and X' independently, is a bond, -N(Rz)- or -O-;

Rz is hydrogen or (C_1-C_6)alkyl;

X_1 and X_2, at each occurrence, independently, is N or CH;

R_2 is hydrogen, halogen, halo(C_1-C_6)alkyl or (C_1-C_6)alkyl;

R_3 and R_3' independently are hydrogen; or R_3 and R_3' together represent an oxo group; and

R_4 is hydrogen or (C_1-C_6)alkyl.

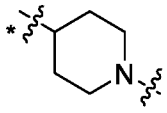
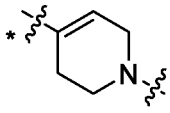
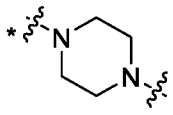
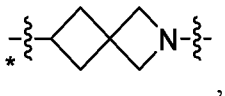
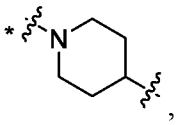
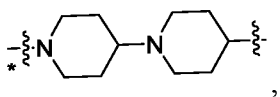
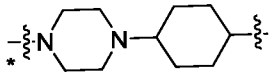
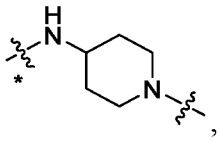
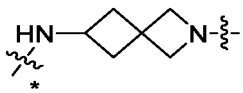
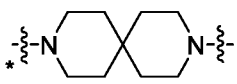
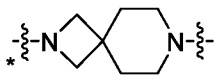
2. The compound of claim 1, wherein R_1 is hydroxy or halo(C_1-C_6)alkyl.

3. The compound of claim 1, wherein R_1 is -OH or -CF_3.

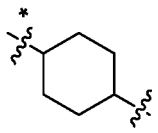
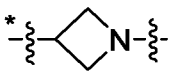
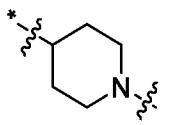
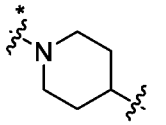
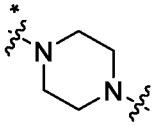
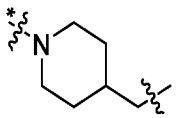
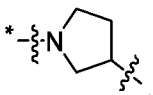
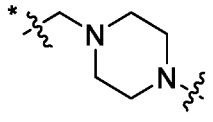
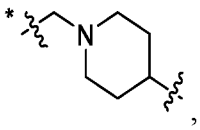
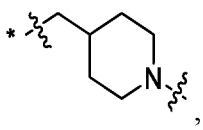
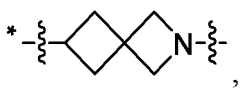
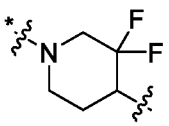
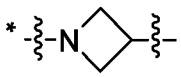
4. The compound of claim 1, wherein Q is hydroxy, amino or (C_1-C_6)alkylamino.

5. The compound of claim 1, wherein Q is -NH_2, -$NHCH_3$ or -OH.

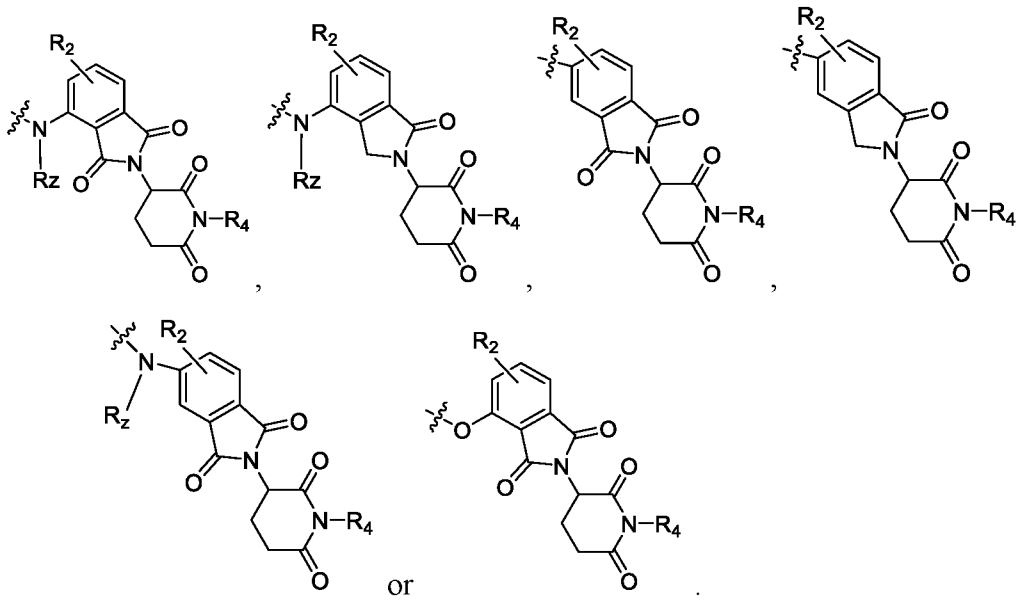
6. The compound of claim 1, wherein L_1 is -(3- to 12-membered heterocycloalkylenyl)-*-(3- to 12-membered heterocycloalkylenyl)-(3- to 8-membered cycloalkylenyl)-, or *-N(Rx)-(3- to 12-membered heterocycloalkylenyl)-; wherein the heterocycloalkylenyl and cycloalkylenyl independently is unsubstituted or substituted with 1, 2 or 3 occurrence(s) of Rd; wherein the asterisk mark represents the point of attachment with ring A.

7. The compound of claims 1 and 6, wherein L_1 is  ,  ,  ,  ,  ,  ,  ,  ,  ,  , or  ; wherein the asterisk mark indicates the point of attachment towards ring A.

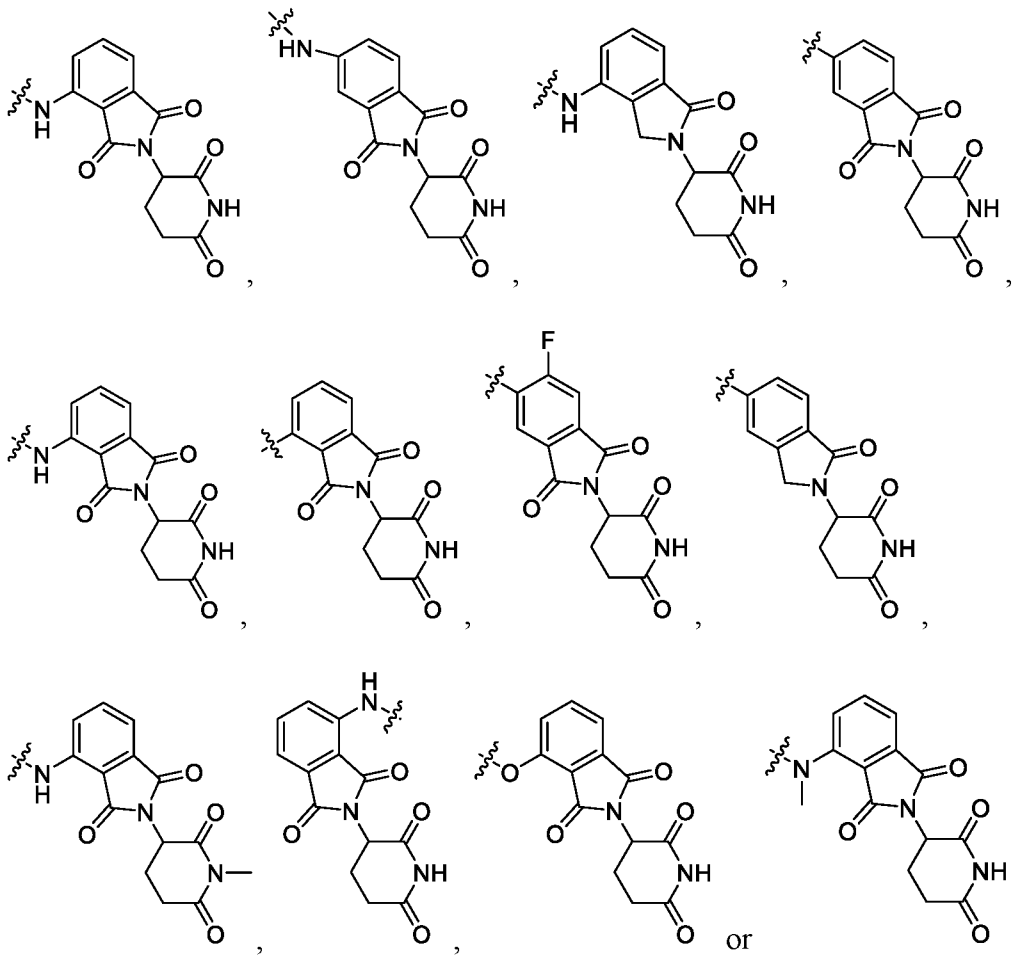
8. The compound of claim 1, wherein L_2 is a bond, -(3- to 8-membered cycloalkylenyl)-, -(3- to 10-membered heterocycloalkylenyl)-, *-$(CRxRy)_n$-(3- to 8-membered cycloalkylenyl)- or *-$(CRxRy)_n$-(3- to 10-membered heterocycloalkylenyl)-; wherein the cycloalkylenyl and heterocycloalkylenyl independently is substituted with 1, 2 or 3 occurrences of Rd; wherein the asterisk mark represents the point of attachment with L_1.

9. The compound of claim 1 and 8, wherein L_2 is a bond,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  or  ; wherein the asterisk mark indicates the point of attachment towards L_1.

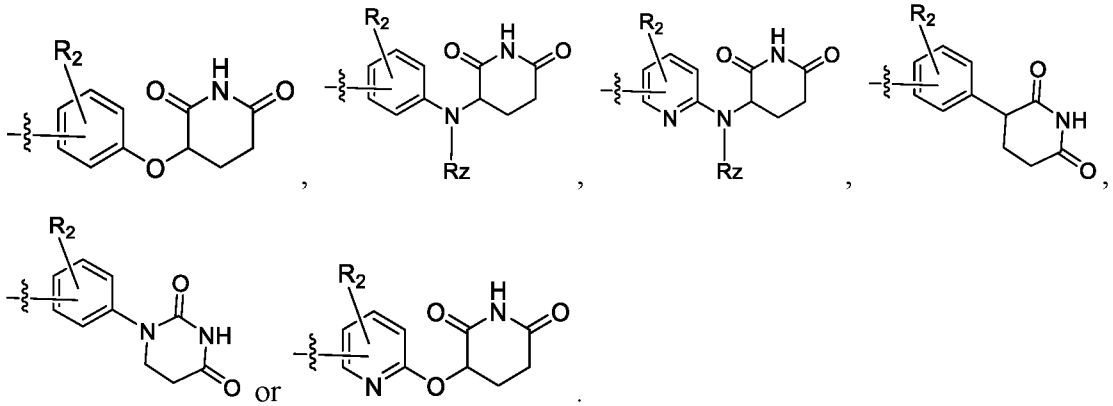
10. The compound of claim 1, wherein M_1 is a group of formula



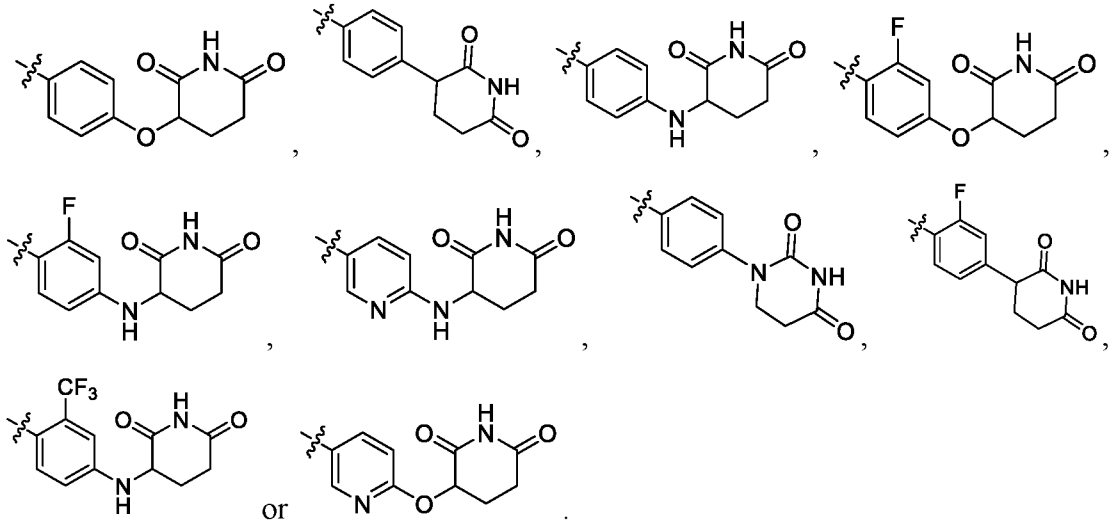
11. The compound of claim 10, wherein M_1 is



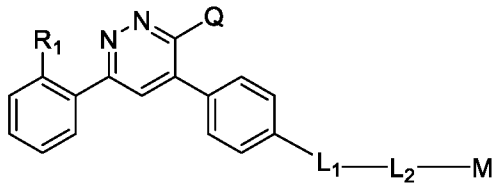
12. The compound of claim 1, wherein M_2 is a group of formula



13. The compound of claim 12, wherein M_2 is



14. The compound of claim 1, having a formula (IA):

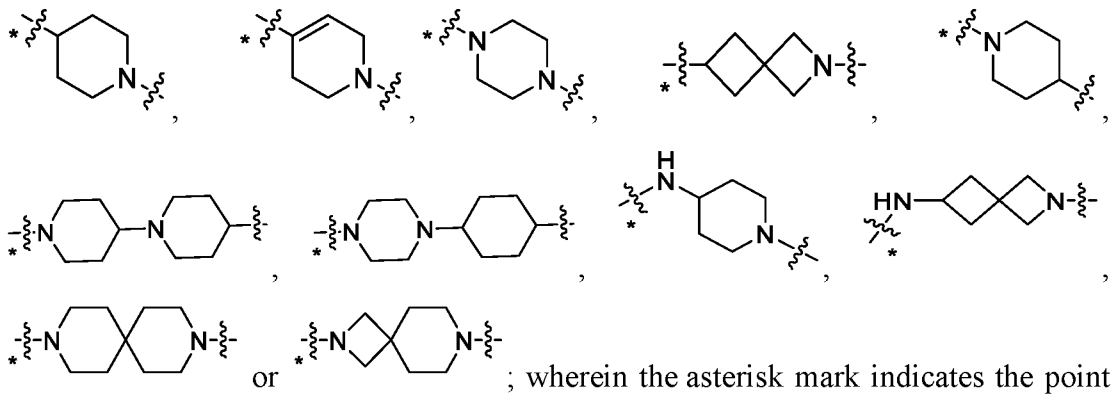


(IA)

or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof.

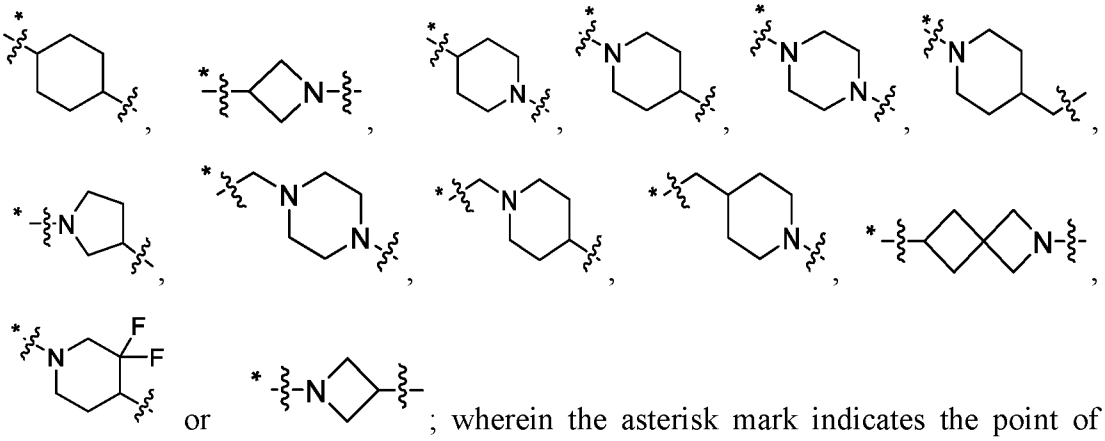
15. The compound of claim 14, wherein R_1 at each occurrence independently is hydroxy or halo(C_1-C_6)alkyl.

16. The compound of claim 14, wherein L_1 is



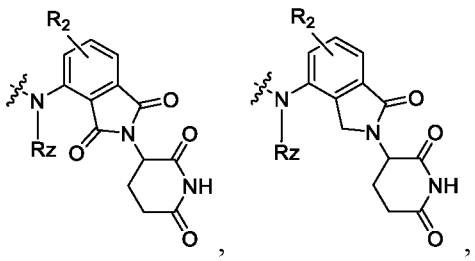
; wherein the asterisk mark indicates the point of attachment towards ring A.

17. The compound of claim 14, wherein L_2 is a bond,

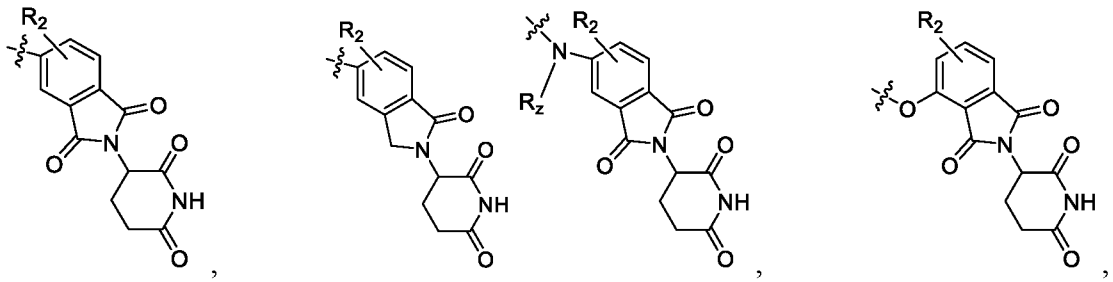


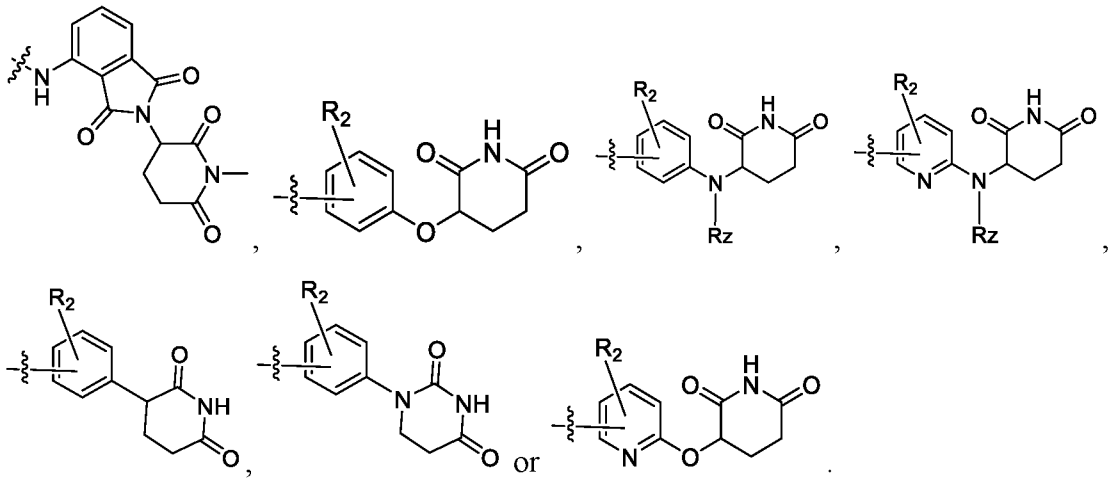
; wherein the asterisk mark indicates the point of attachment towards L_1.

18. The compound of claim 14, wherein M is

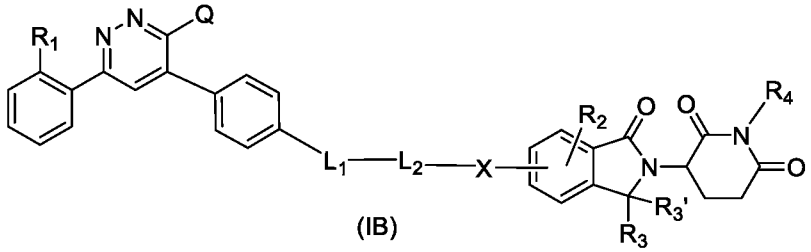


,





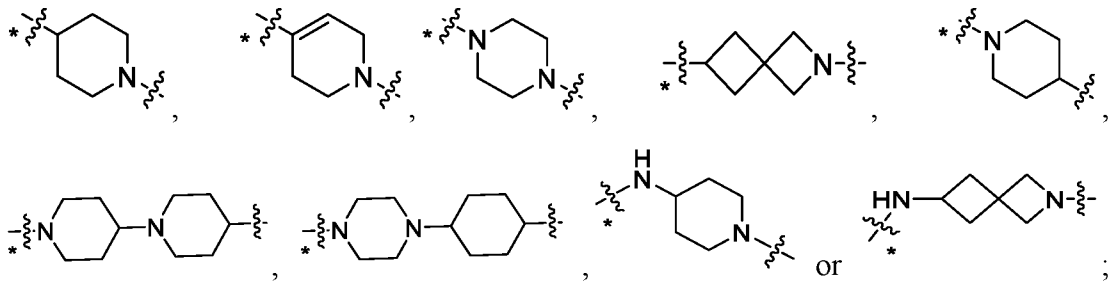
19. The compound of claim 1, having a formula (IB):



(IB)

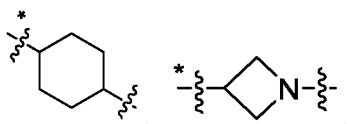
or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof.

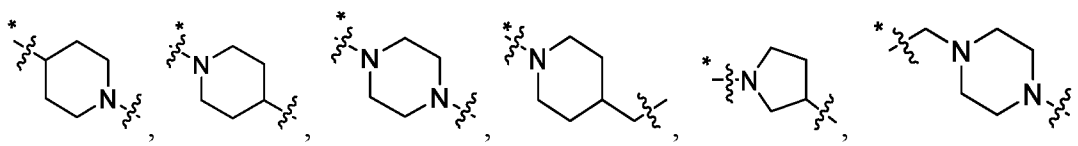
20. The compound of claim 19, wherein L_1 is

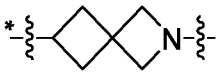


wherein the asterisk mark indicates the point of attachment towards ring A.

21. The compound of claim 19, wherein L_2 is a bond,





or  ; wherein the asterisk mark indicates the point of attachment towards L_1.

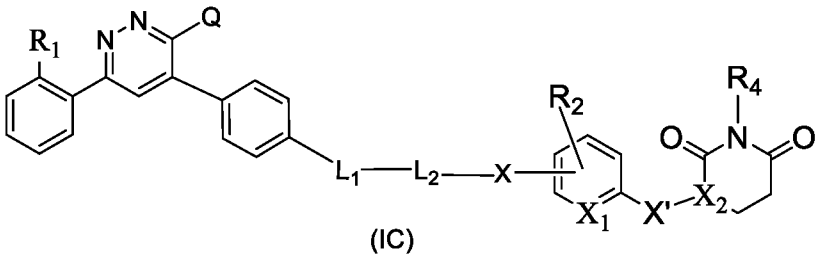
22. The compound of claim 19, wherein X is a bond, -NH- or -O-.

23. The compound of claim 19, wherein R_2 is hydrogen or fluorine.

24. The compound of claim 19, wherein R_3 and R_3' independently are hydrogen or R_3 and R_3' together represent an oxo group.

25. The compound of claim 19, wherein R_4 is hydrogen or methyl.

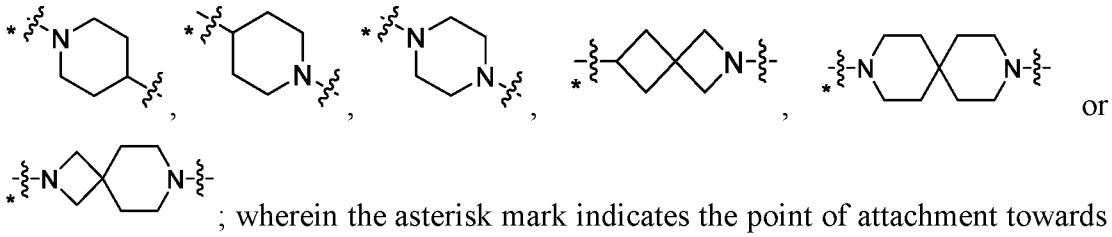
26. The compound of claim 1, having a formula (IC):



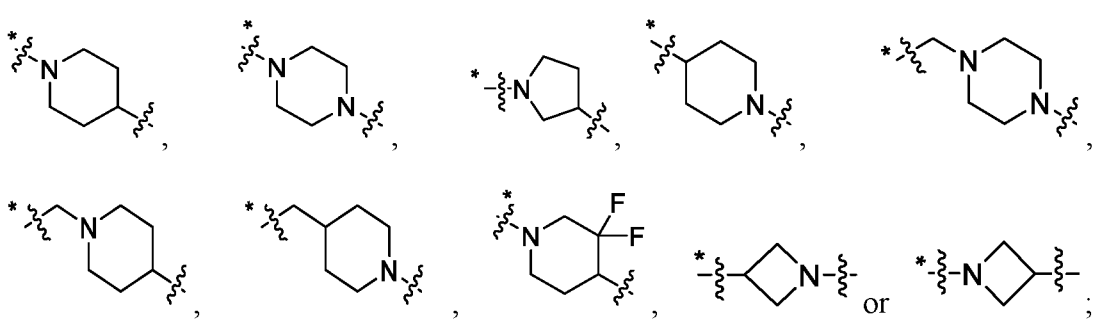
(IC)

or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof.

27. The compound of claim 26, wherein L_1 is

 ; wherein the asterisk mark indicates the point of attachment towards ring A.

28. The compound of claim 26, wherein L_2 is

 ; wherein the asterisk mark indicates the point of attachment towards L_1.

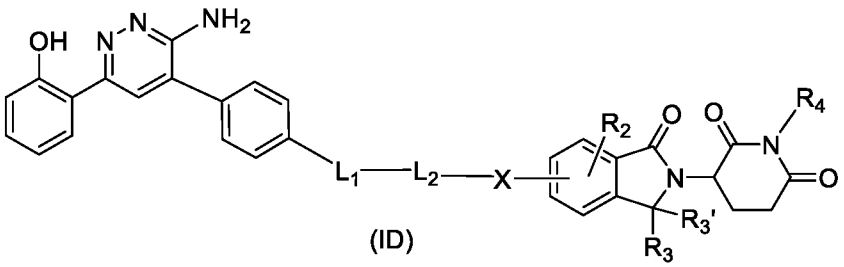
29. The compound of claim 26, wherein X and X', independently, is a bond, -NH- or -O-.

30. The compound of claim 26, wherein R_2 is hydrogen, fluorine, or $-CF_3$.

31. The compound of claim 26, wherein X_1 and X_2, independently, is CH.

32. The compound of claim 26, wherein R_4 is hydrogen.

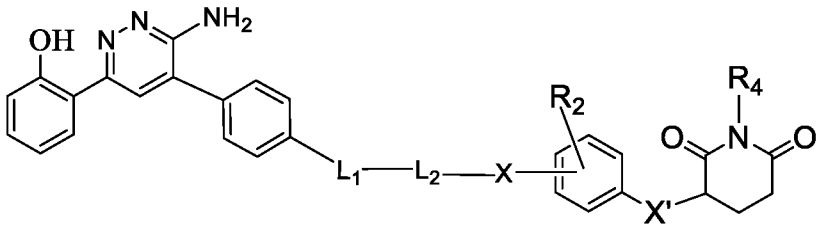
33. The compound of claim 1, having a formula (ID):



(ID)

or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof.

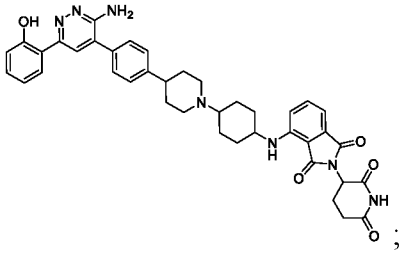
34. The compound of claim 1, having a formula (IE):

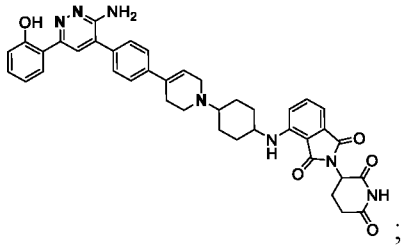
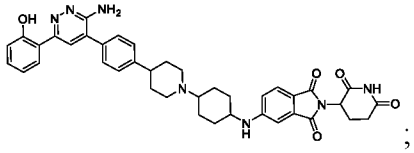
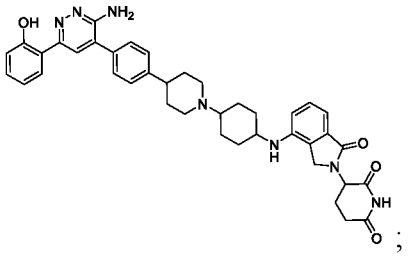
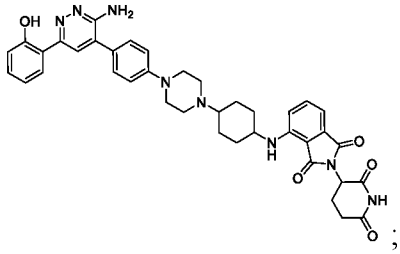
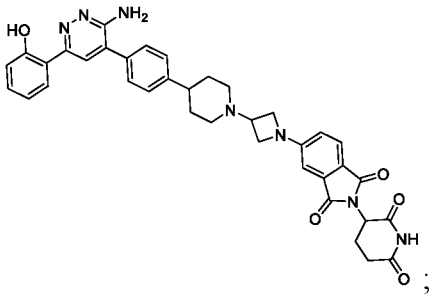
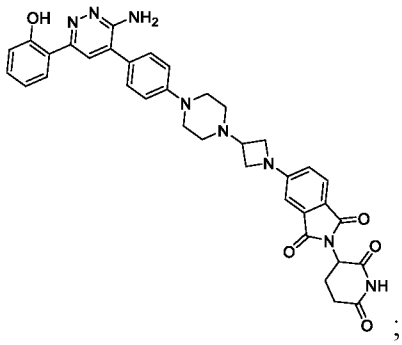
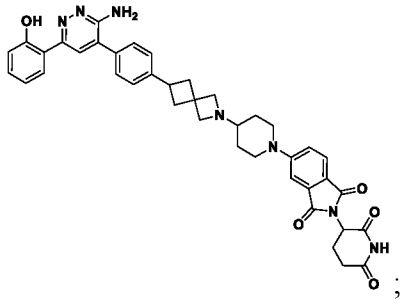


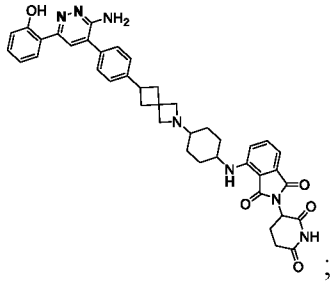
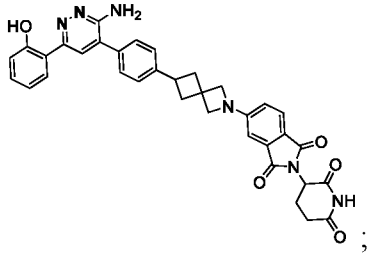
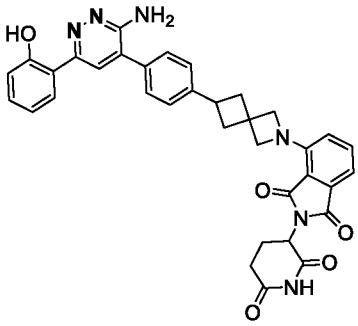
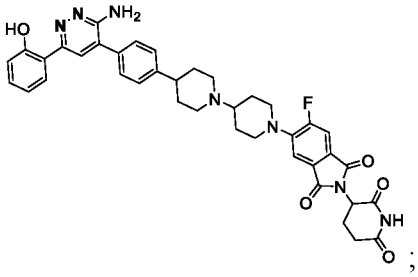
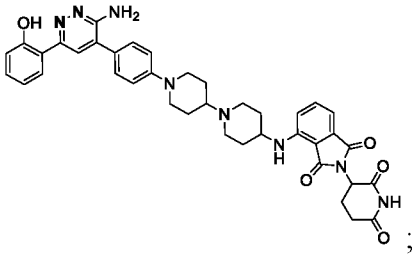
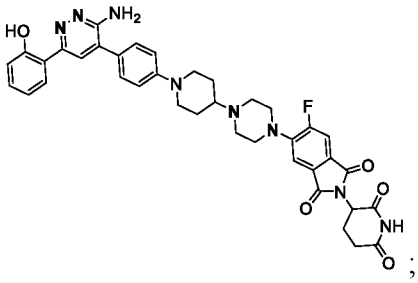
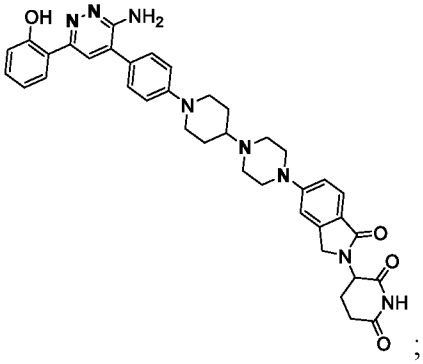
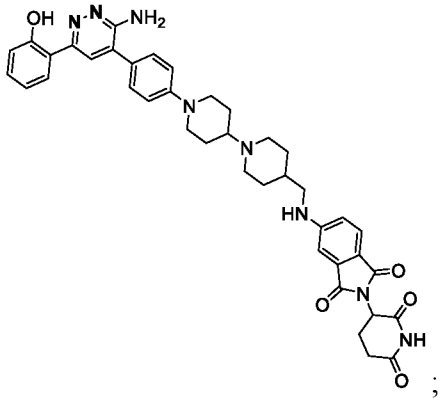
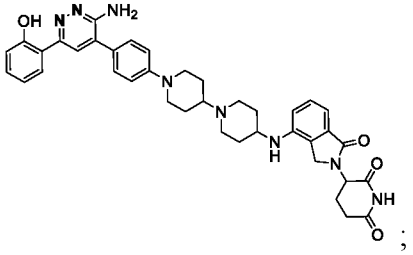
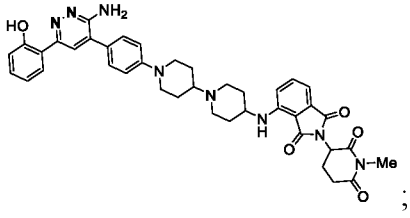
(IE)

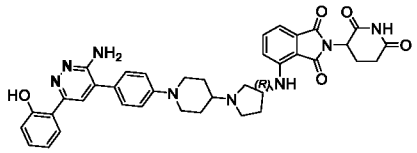
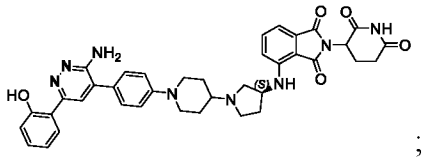
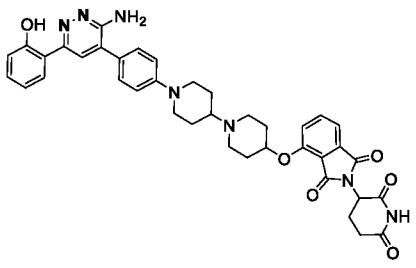
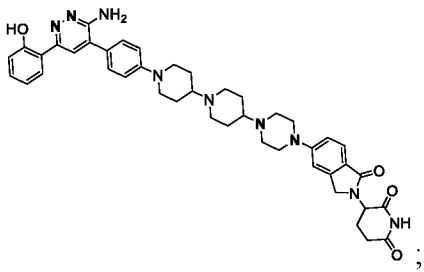
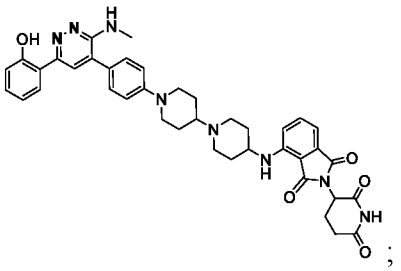
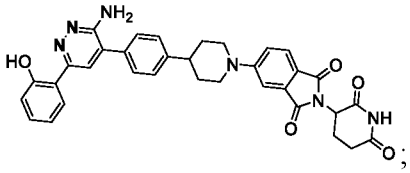
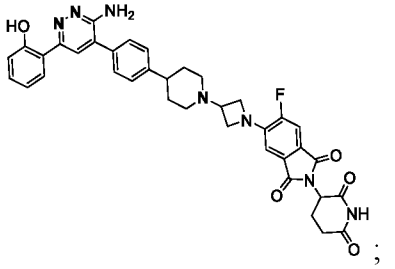
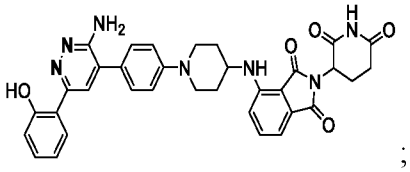
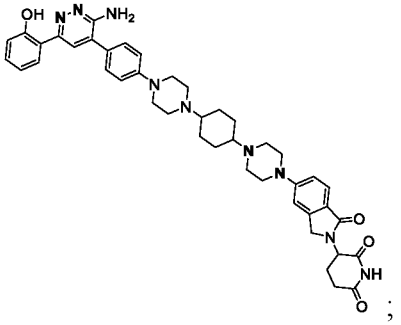
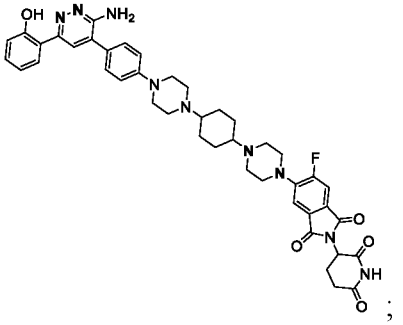
or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof.

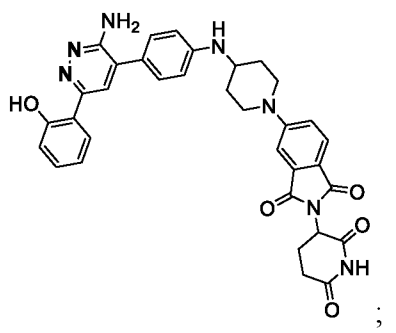
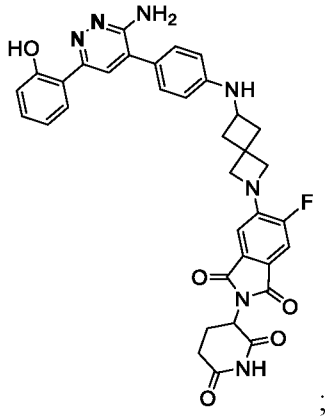
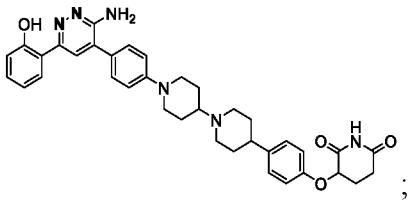
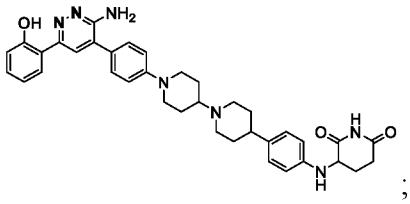
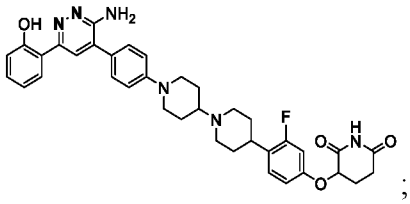
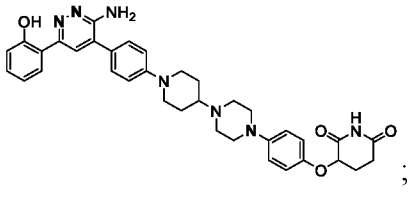
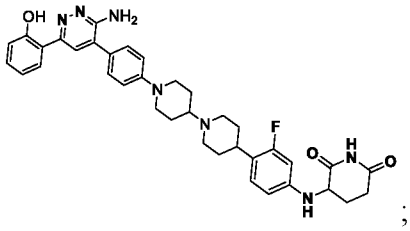
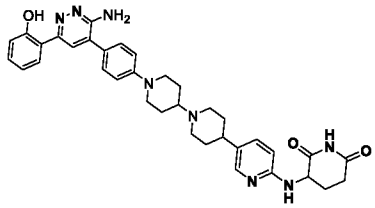
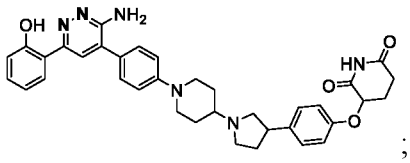
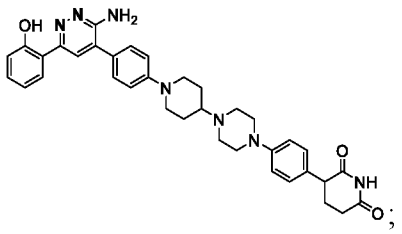
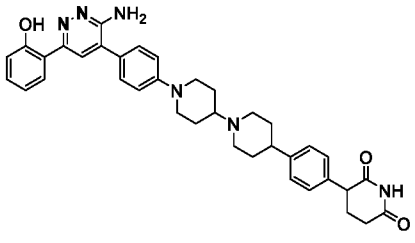
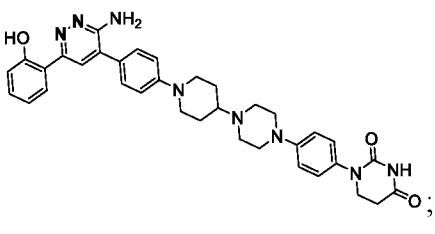
35. The compound of claims 1-34, wherein the compound of formula (I) is selected from:

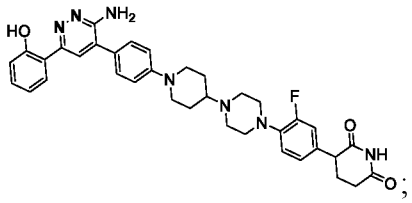
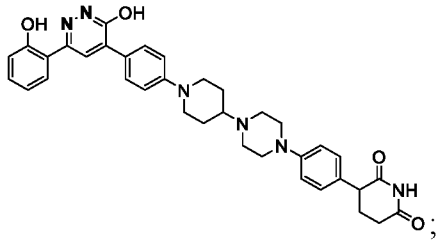
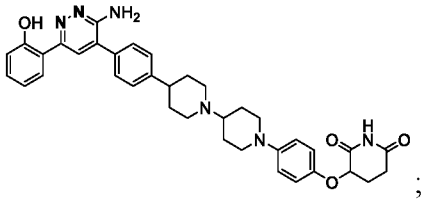
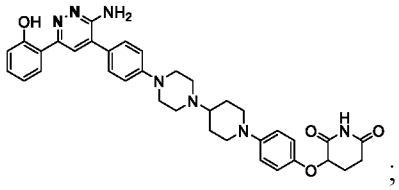
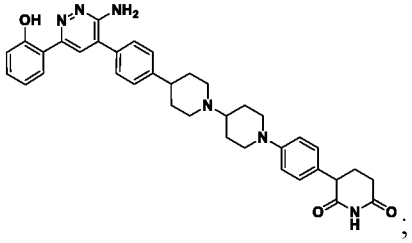
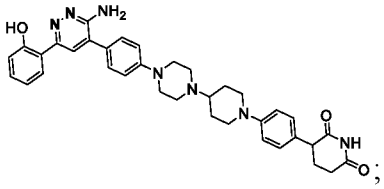
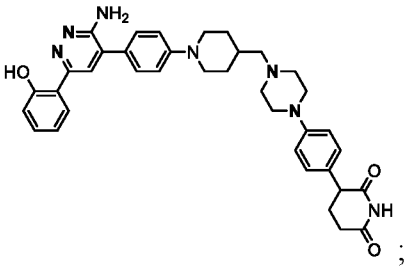
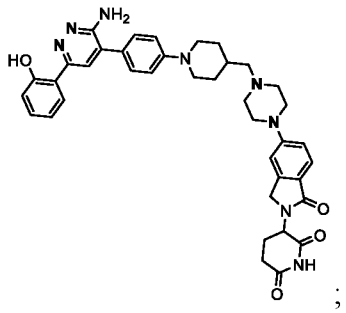
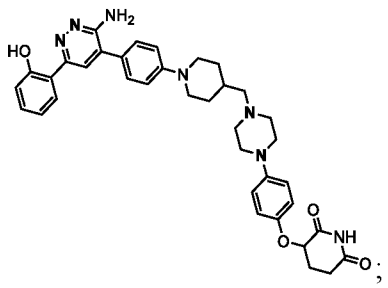
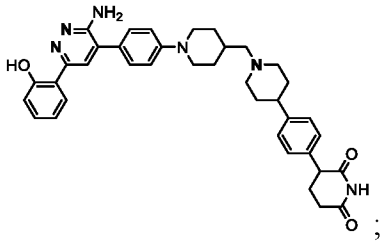
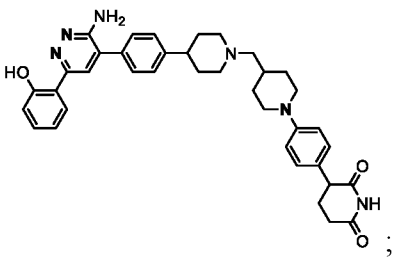
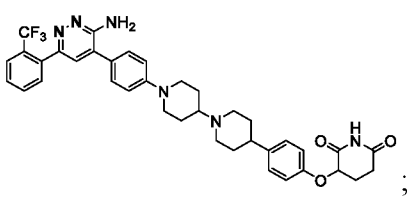
Comp. No.	Structure	Comp. No.	Structure
1	 ;	2	Stereoisomer 1a of Compound 1;

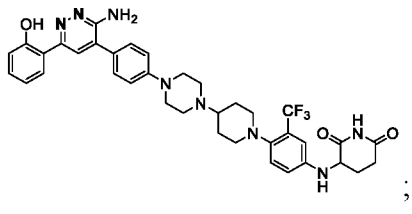
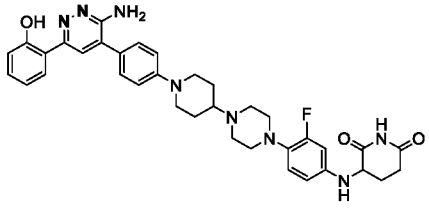
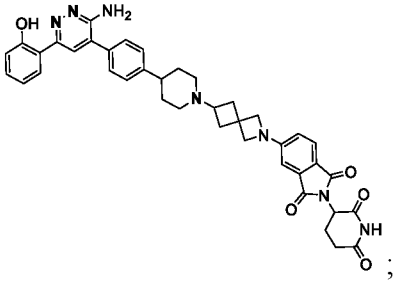
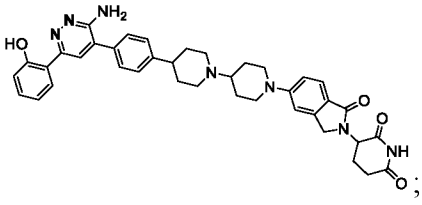
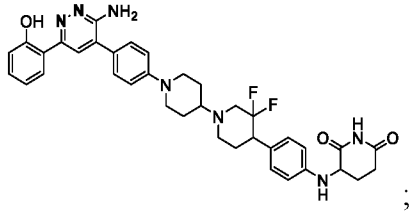
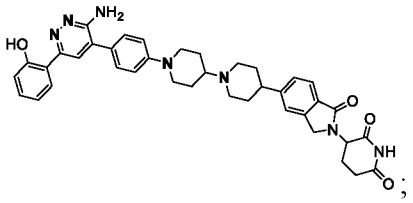
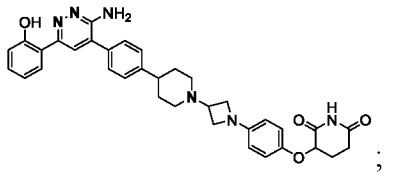
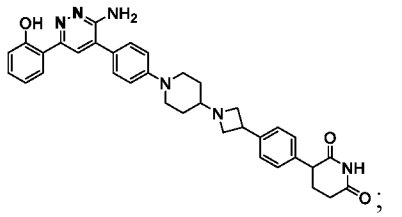
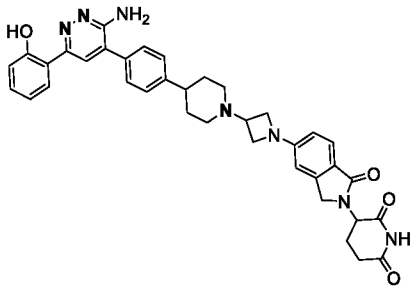
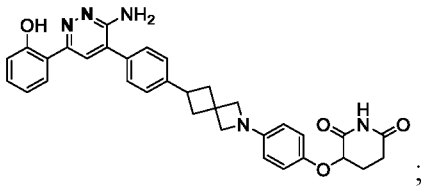
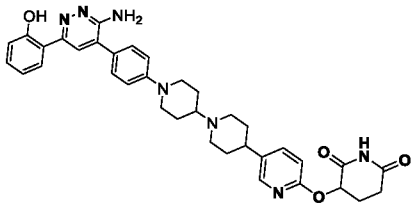
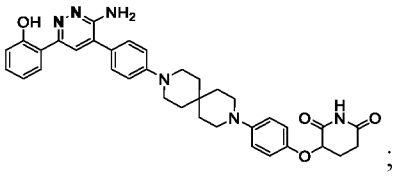
3	Stereoisomer 1b of Compound 1;	4	 ;
5	 ;	6	 ;
7	 ;	8	Stereoisomer 7a of Compound 7;
9	Stereoisomer 7b of Compound 7;	10	 ;
11	 ;	12	 ;

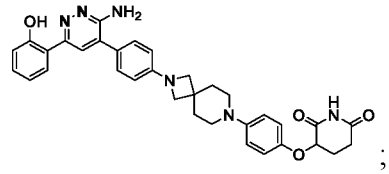
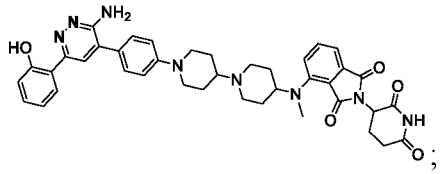
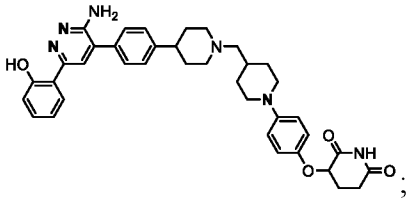
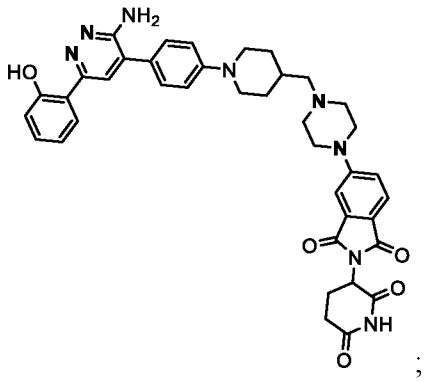
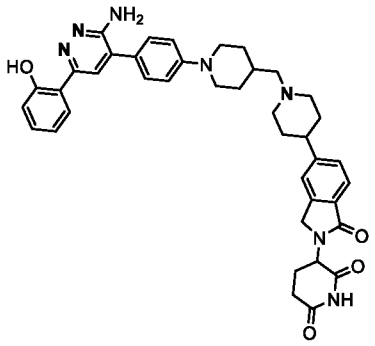
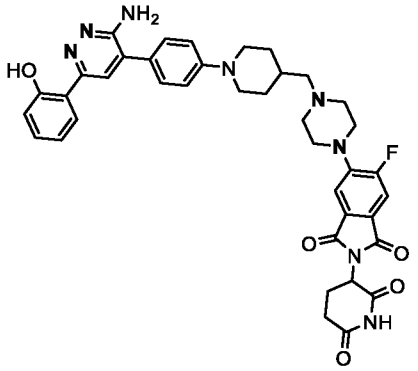
13	 ;	14	 ;
15	 ;	16	 ;
17	 ;	18	 ;
19	 ;	20	 ;
21	 ;	22	 ;

23	 ;	24	 ;
25	 ;	26	 ;
27	 ;	28	 ;
29	 ;	30	 ;
31	 ;	32	 ;

33	 ;	34	 ;
35	 ;	36	 ;
37	 ;	38	 ;
39	 ;	40	 ;
41	 ;	42	 ;
43	 ;	44	 ;

45	 ;	46	 ;
47	 ;	48	 ;
49	 ;	50	 ;
51	 ;	52	 ;
53	 ;	54	 ;
55	 ;	56	 ;

57	 ;	58	 ;
59	 ;	60	 ;
61	 ;	62	 ;
63	 ;	64	 ;
65	 ;	66	 ;
67	 ;	68	 ;

69	 ;	70	 ;
71	 ;	72	 ;
73	 or	74	

or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof.

36. A pharmaceutical composition comprising the compound of any one of claims 1 to 35 or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof, and a pharmaceutically acceptable carrier or an excipient.

37. The pharmaceutical composition of claims 1 to 36, for use in degrading a target protein in a subject, wherein the target protein is SMARCA2 and/or SMARCA4.

38. The pharmaceutical composition for use of claim 37, wherein the subject is afflicted with a disease or disorder dependent upon SMARCA2 and/or SMARCA4.

39. The pharmaceutical composition for use of claim 38, wherein the disease or disorder is cancer selected from hematologic cancers, lung cancer, non-small cell lung cancer, acoustic neuroma, acute leukemia, acute lymphocytic leukemia, acute myelocytic leukemia, adenocarcinoma, angiosarcoma, astrocytoma, myelomonocytic leukemia, promyelocytic leukemia, acute T-cell leukemia, basal cell carcinoma, bile duct

carcinoma, bladder cancer, brain cancer, breast cancer, bronchogenic carcinoma, cervical cancer, chondrosarcoma, chordoma, choriocarcinoma, chronic leukemia, chronic lymphocytic leukemia, chronic myelocytic leukemia, granulocytic leukemia, chronic myelogenous leukemia, colon cancer, colorectal cancer, craniopharyngioma, cystadenocarcinoma, diffuse large B-cell lymphoma, dysproliferative changes, dysplasias, metaplasias, embryonal carcinoma, endometrial cancer, endotheliosarcoma, ependymoma, epithelial carcinoma, erythroleukemia, esophageal cancer, estrogen-receptor positive breast cancer, essential thrombocythemia, Ewing's tumor, fibrosarcoma, follicular lymphoma, germ cell testicular cancer, glioma, glioblastoma, gliosarcoma, heavy chain disease, head and neck cancer, hemangioblastoma, hepatoma, hepatocellular cancer, hormone insensitive prostate cancer, leiomyosarcoma, leukemia, liposarcoma, liver cancer, lymphagioendotheliosarcoma, lymphangiosarcoma, lymphoblastic leukemia, lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, Burkitt's lymphoma, malignancies and hyperproliferative disorders of the bladder, breast, colon, lung, ovaries, pancreas, prostate, skin and uterus, lymphoid malignancies of T-cell or B-cell origin, medullary carcinoma, medulloblastoma, melanoma, meningioma, mesothelioma, multiple myeloma, myelogenous leukemia, myeloma, myxosarcoma, neuroblastoma, NUT midline carcinoma (NMC), oligodendroglioma, oral cancer, osteogenic sarcoma, ovarian cancer, pancreatic cancer, papillary adenocarcinomas, papillary carcinoma, pinealoma, polycythemia vera, prostate cancer, rectal cancer, renal cell carcinoma, retinoblastoma, malignant rhabdoid tumor (MRT), rhabdomyosarcoma, sarcoma, sebaceous gland carcinoma, seminoma, skin cancer, small cell lung carcinoma, solid tumors, carcinomas, sarcomas, small cell lung cancer, stomach cancer, squamous cell carcinoma, synovioma, sweat gland carcinoma, thyroid cancer, Waldenstrom's macroglobulinemia, testicular tumors, uterine cancer or Wilms' tumor.

40. A method of degrading a target protein in a subject comprising, administering to a subject in need thereof, a therapeutically effective amount of the compound according to any one of claims 1 to 35 or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof.

41. The method of claim 40, wherein the target protein is SMARCA2 and/or SMARCA4.

42. A method of treating a disease or a disorder dependent upon at least one of SMARCA2 and SMARCA4 in a subject comprising, administering to the subject in need thereof, a

therapeutically effective amount of a compound according to any one of claims 1 to 35 or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof.

43. The method of claim 42, wherein the disease or disorder dependent upon SMARCA2 and/or SMARCA4 is cancer, selected from hematologic cancers, lung cancer, non-small cell lung cancer, acoustic neuroma, acute leukemia, acute lymphocytic leukemia, acute myelocytic leukemia, adenocarcinoma, angiosarcoma, astrocytoma, myelomonocytic leukemia, promyelocytic leukemia, acute T-cell leukemia, basal cell carcinoma, bile duct carcinoma, bladder cancer, brain cancer, breast cancer, bronchogenic carcinoma, cervical cancer, chondrosarcoma, chordoma, choriocarcinoma, chronic leukemia, chronic lymphocytic leukemia, chronic myelocytic leukemia, granulocytic leukemia, chronic myelogenous leukemia, colon cancer, colorectal cancer, craniopharyngioma, cystadenocarcinoma, diffuse large B-cell lymphoma, dysproliferative changes, dysplasias, metaplasias, embryonal carcinoma, endometrial cancer, endotheliosarcoma, ependymoma, epithelial carcinoma, erythroleukemia, esophageal cancer, estrogen-receptor positive breast cancer, essential thrombocythemia, Ewing's tumor, fibrosarcoma, follicular lymphoma, germ cell testicular cancer, glioma, glioblastoma, gliosarcoma, heavy chain disease, head and neck cancer, hemangioblastoma, hepatoma, hepatocellular cancer, hormone insensitive prostate cancer, leiomyosarcoma, leukemia, liposarcoma, liver cancer, lymphagioendotheliosarcoma, lymphangiosarcoma, lymphoblastic leukemia, lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, Burkitt's lymphoma, malignancies and hyperproliferative disorders of the bladder, breast, colon, lung, ovaries, pancreas, prostate, skin and uterus, lymphoid malignancies of T-cell or B-cell origin, medullary carcinoma, medulloblastoma, melanoma, meningioma, mesothelioma, multiple myeloma, myelogenous leukemia, myeloma, myxosarcoma, neuroblastoma, NUT midline carcinoma (NMC), oligodendroglioma, oral cancer, osteogenic sarcoma, ovarian cancer, pancreatic cancer, papillary adenocarcinomas, papillary carcinoma, pinealoma, polycythemia vera, prostate cancer, rectal cancer, renal cell carcinoma, retinoblastoma, malignant rhabdoid tumor (MRT), rhabdomyosarcoma, sarcoma, sebaceous gland carcinoma, seminoma, skin cancer, small cell lung carcinoma, solid tumors, carcinomas, sarcomas, small cell lung cancer, stomach cancer, squamous cell carcinoma, synovioma, sweat gland carcinoma, thyroid cancer, Waldenstrom's macroglobulinemia, testicular tumors, uterine cancer or Wilms' tumor.

44. A compound of claims 1 to 35, for use as a medicament.

45. A compound according to any one of claims 1 to 35, for use in the treatment of a disease or disorder dependent upon SMARCA2 and/or SMARCA4, wherein the disease or disorder is cancer.

46. Use of a compound of formula (I) or a pharmaceutical acceptable salt or a stereoisomer or a tautomer thereof according to any one of claims 1 to 35, in the manufacture of a medicament for the treatment of a disease or disorder dependent upon SMARCA2 and/or SMARCA4; wherein the disease or disorder is cancer.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2024/060683

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/14 A61P35/00 A61K31/501
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)
A61P A61K C07D

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2021/083949 A1 (HOFFMANN LA ROCHE [CH]; HOFFMANN LA ROCHE [US] ET AL.) 6 May 2021 (2021-05-06)	1-46
Y	claim 1	1-46

Y	WO 2019/195201 A1 (ARVINAS OPERATIONS INC [US]; GENENTECH INC [US]) 10 October 2019 (2019-10-10) claim 3	1-46

Y	WO 2020/251969 A1 (KYMERA THERAPEUTICS INC [US]) 17 December 2020 (2020-12-17) Table 1 starting at page 98: compounds with 3-amino-6-(o-hydroxy)phenyl-pyridazine moiety First structure of claim 6	1-46

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

☒ 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

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"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
31 March 2025	22/04/2025

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	Panday, Narendra

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2024/060683

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