

**BIFUNCTIONAL COMPOUNDS CONTAINING 2,5-SUBSTITUTED PYRIMIDINE
DERIVATIVES FOR DEGRADING CYCLIN-DEPENDENT KINASE 2 AND CYCLIN-
DEPENDENT KINASE 4 VIA UBIQUITIN PROTEASOME PATHWAY**

5 Cross-reference to Related Applications

This PCT International Patent Application claims the benefit of U.S. Provisional Application No. 63/603,095, filed on November 27, 2023; U.S. Provisional Application No. 63/611,727, filed on December 18, 2023; and U.S. Provisional Application No. 63/563,922, filed on March 11, 2024; the
10 entire contents of each of these applications are hereby incorporated by reference.

Field of the disclosure

The present disclosure provides certain bifunctional compounds containing 2,5-substituted pyrimidine derivatives that cause degradation of Cyclin-dependent kinase 2 (CDK2) and Cyclin-
15 dependent kinase 2 (CDK4) via ubiquitin proteasome pathway and are therefore useful for the treatment of diseases mediated by CDK2 and/or CDK4. Also provided are pharmaceutical compositions containing such compounds and processes for preparing such compounds.

Background

20 Cyclin-dependent kinases (CDKs) are essential cellular serine/threonine kinases that play an important role in orchestrating signaling events, such as DNA replication and protein synthesis, to ensure faithful eukaryotic cell division and proliferation. The regulation of CDK activity is tightly controlled by the fluctuating levels of various cyclins, which form heterodimeric complexes with CDKs to activate them. Out of the 21 identified CDKs, CDK1/Cyclin B, CDK2/Cyclin E,
25 CDK2/Cyclin A, CDK4/Cyclin D, CDK6/Cyclin D complexes are well known to be vital regulators of cell cycle progression. Other CDKs are involved in regulating gene transcription, DNA repair, differentiation, and apoptosis (*see* Morgan, D. O. *Annu. Rev. Cell. Dev. Biol.* (1997) 13: 261-291).

In the canonical model of cell cycle, mitogenic signaling upregulates D-type cyclins, which directly bind and activate CDK4/6. Active CDK4/6-cyclin D complexes partially phosphorylate Rb,
30 disrupting the Rb/E2F interaction and de-repressing E2F activity, leading to upregulation of cyclin E, a CDK2 activator. Cdk2-cyclin E further hyper-phosphorylates Rb, releasing E2F to transcribe genes required for S-phase entry. During S-phase, cyclin E is degraded and CDK2 forms a complex with cyclin A to promote phosphorylation of substrates essential for DNA replication and inactivation of E2F, completing S-phase (Asghar et al. *Nat. Rev. Drug. Discov.* (2015) 14: 130-146). CDK1-Cyclin
35 A and CDK1-Cyclin B complexes are activated in late S and G2 phases to drive the transition into

and completion of mitosis, respectively (Katsuno et al., 2009; Lindqvist et al., 2009; Lohka et al., 1988).

Due to their crucial roles in regulating cell cycle and other essential cellular processes, increased activity or temporally abnormal activation of CDKs has been shown to promote tumorigenesis and disease progression (Cordon-Cardo C. *Am. J. Pathol.* (1995) 147:545-560; Karp JE, Broder S. *Nat. Med.* (1995) 1:309-320; Hall M, Peters G. *Adv. Cancer Res.* (1996) 68:67-108). Genetic changes in CDK-cyclin complexes and the proteins that regulate them are widespread in various cancers and are often associated with poor clinical outcomes. Common alterations include amplifications/overexpression of cyclin D, cyclin E, CDK4 and CDK6; loss of Rb; deficiency in CDK inhibitory regulators such as p16, p21, p27, and loss-of-function mutations in FBXW7, a component of SCF^{Fbw7} ubiquitin E3 ligase responsible for cyclin E degradation. (Smalley et al. *Cancer Res.* (2008) 68: 5743-52).

Over the last two decades, there has been significant interest in developing CDK inhibitors for therapeutic purposes. In combination with endocrine therapies, selective reversible inhibitors of CDK4 and CDK6 e.g., palbociclib, ribociclib, and abemaciclib have revolutionized the therapeutic management for hormone receptor-positive (HR+) metastatic breast cancer (MBC). Ongoing clinical trials are also investigating these CDK4/6 inhibitors as single agents or in combination with other therapeutics for various cancers. (O'Leary et al. *Nature Reviews* (2016) 13:417-430).

Despite their significant clinical efficacy in ER-positive metastatic breast cancer, CDK4/6 inhibitors have some limitations. One major drawback is the development of primary or acquired resistance over time. An important mechanism of resistance involves the abnormal activation of CDK2. This can occur due to an overactivated CDK2/Cyclin E complex caused by elevated Cyclin E expression (Asghar, U. et al. *Clin. Cancer Res.* (2017) 23:5561) or formation of the noncanonical CDK2/cyclin D1 complex in response to CDK4/6 inhibition (Herrera-Abreu MT et al, *Cancer Res.* (2006) 15: 2301), which bypasses the need for CDK4/6 for cell cycle reentry. Additionally, CDK4/6 inhibitors palbociclib and ribociclib exhibit relatively high hematological toxicity, primarily neutropenia. CDK6 is highly expressed in the blood system and plays a role in regulating the growth of hematopoietic cells. Therefore, it is generally believed that the inhibition of CDK6 leads to neutropenia as breast cancer cells mainly depend on CDK4 for proliferation. Abemaciclib exhibits weaker inhibition of CDK6 than CDK4, resulting in lower hematological toxicity.

Considering these factors, developing a small molecule inhibitor or a proteolysis-targeting chimeric molecule (PROTAC) that specifically targets both CDK4 and CDK2 could represent a therapeutic opportunity with reduced toxicity and improved overall therapeutic efficacy.

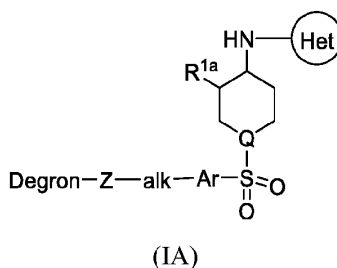
PROTACs are bifunctional molecules comprised of target protein-recruitment moiety and a ligand for E3 ligase, connected by a biocompatible linker. PROTACs bring the protein of interest and the E3 ligase into close proximity and induce ubiquitination and subsequent degradation of the target protein by proteasome.

5 Compared to small molecule drugs that typically bind disease-relevant proteins and inhibit their function, PROTACs display several unique and attractive features that make them desirable drug candidates. For example, PROTACs have been shown to be more selective than their inhibitor counterparts, potentially reducing off-target toxicity. Moreover, PROTACs can perform multiple rounds of target ubiquitination and degradation. Due to this catalytic mode of action, PROTACs can
 10 function at sub-stoichiometric receptor occupancies. The E3 ligases used in PROTACs mainly include cereblon (CRBN), Von Hippel–Lindau-containing complex (VHL), inhibitor of apoptosis protein (IAP), and mouse double minute 2 (MDM2).

Therefore, PROTACs that could recruit both CDK2 and CDK4 to a ubiquitin ligase, and thereby causing ubiquitylation and proteasomal degradation of both CDK2 and CDK4 are desirable.
 15 The present disclosure fulfills this and related needs.

Summary

In a first aspect, provided is a method of degrading CDK2 and CDK4 proteins via ubiquitin proteasome pathway, comprising contacting a cell with a compound of Formula (IA):
 20



where:

Q is CH or N;
 25 R^{1a} is hydrogen, deuterium, alkyl, halo, haloalkyl, alkoxy, hydroxy, or cyano;
 Het is selected from 1) a 5- or 6-membered heteroaryl ring containing one or two nitrogen ring atoms, where the 5- or 6-membered heteroaryl ring is optionally fused to heterocycl^{1A} or spiro heterocycl^{1A}, 2) a 9- or 10-membered fused bicyclic heteroaryl ring containing one to five nitrogen ring atoms, where the 9- or 10-membered fused bicyclic heteroaryl ring is optionally fused to
 30 heterocycl^{1A} or unsaturated heterocycl^{1A}, and 3) partially saturated 9- or 10-membered fused

bicyclic heteroaryl optionally fused to a 5-membered heteroaryl^A containing one or two nitrogen ring atoms, wherein at least one nitrogen ring atom of the 5- or 6-membered heteroaryl, the 9- or 10-membered fused bicyclic heteroaryl, and the partially saturated 9- or 10-membered fused bicyclic heteroaryl is ortho to the carbon atom of the Het ring that forms a bond to -NH- and each ring in Het is substituted with R^x, R^y, and R^z where R^x and R^y are independently selected from hydrogen, alkyl, alkoxy, halo, haloalkyl, haloalkoxy, hydroxy, cyano, cyanoalkyl, cyanoalkoxy, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, and alkylcarbonylamino and R^z is hydrogen, alkyl, alkenyl, alkynyl, halo, hydroxy, cycloalkyl, bridged cycloalkyl, cycloalkylalkyl, spirocycloalkyl, phenyl, heteroaryl, heterocyclyl, bridged heterocyclyl, spiroheterocyclyl, or fused heterocyclyl
 5 is substituted with R^x, R^y, and R^z where R^x and R^y are independently selected from hydrogen, alkyl, alkoxy, halo, haloalkyl, haloalkoxy, hydroxy, cyano, cyanoalkyl, cyanoalkoxy, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, and alkylcarbonylamino and R^z is hydrogen, alkyl, alkenyl, alkynyl, halo, hydroxy, cycloalkyl, bridged cycloalkyl, cycloalkylalkyl, spirocycloalkyl, phenyl, heteroaryl, heterocyclyl, bridged heterocyclyl, spiroheterocyclyl, or fused heterocyclyl
 10 wherein each aforementioned R^z ring is optionally substituted with 1 to 3 substituents independently selected from hydrogen, alkyl, cycloalkyl, halo, cyano, hydroxy, or amino;

Degron is an E3 ubiquitin ligase ligand; and

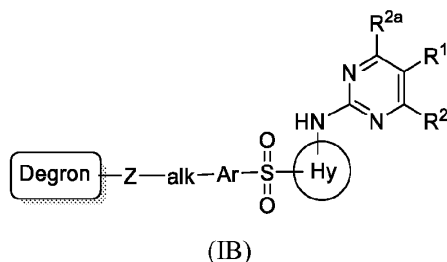
Z is -O-, -NR³- (where R³ is hydrogen or alkyl), alkynylene, cycloalkylene, phenylene, monocyclic heteroarylene, unsaturated heterocyclylene, heterocyclylene, bridged heterocyclylene, or
 15 spiro heterocyclylene where each ring is substituted with R^d and R^e independently selected from hydrogen, deuterium, alkyl, alkoxy, halo, haloalkyl, haloalkoxy, and cyano;

alk is C₃ to C₆ alkenylene substituted with R^f selected from hydrogen, fluoro, and cyano; C₃ to C₆ alkylene or C₃ to C₆ heteroalkylene wherein the C₃ to C₆ alkylene and C₃ to C₆ heteroalkylene are substituted with R^g, R^h, and Rⁱ where R^g is hydrogen, deuterium or halo, R^h is hydrogen, deuterium, cycloalkyl, cycloalkoxy, bridged cycloalkyl, halo, haloalkoxy, alkoxy, hydroxy, cyano, cyanoalkyl, cyanoalkoxy, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylcarbonylamino, phenyl, heteroaryl, heterocyclyl, heterocyclxyloxy, heterocyclcarbonyl, or
 20 bridged heterocyclyl (where cycloalkyl, either by itself or as part of cycloalkoxy, bridged cycloalkyl, phenyl, heteroaryl, heterocyclyl, either by itself or as part of heterocyclxyloxy or heterocyclcarbonyl, and bridged heterocyclyl are substituted with R⁷ and R⁸ independently selected from hydrogen, deuterium, alkyl, alkoxy, halo, haloalkyl, haloalkoxy, hydroxy, alkylcarbonyl, alkyloxy carbonyl, amino, alkylamino, dialkylamino, and cyano); or when R^g and R^h are attached to the same carbon or to adjacent carbon atoms of the linear portion of the C₃ to C₆ alkylene or C₃ to C₆ heteroalkylene, R^g and R^h together with the carbon atom(s) to which they are attached can form
 25 cycloalkylene or heterocyclylene (where the cycloalkylene and heterocyclylene formed by R^g and R^h are substituted with R⁹ and R¹⁰ independently selected from hydrogen, deuterium, alkyl, alkoxy, halo, haloalkyl, haloalkoxy, hydroxy, alkylcarbonyl, alkyloxy carbonyl, amino, alkylamino, dialkylamino, and cyano), and Rⁱ is hydrogen or halo; and the linear portion of C₃ to C₆ alkenylene, C₃ to C₆ alkylene, and C₃ to C₆ heteroalkylene, attaching Ar and Z, contains at least three atoms;

Ar is phenylene, monocyclic heteroarylene, heterocyclylene, bridged heterocyclylene, or spiro heterocyclylene, where each of the aforementioned rings is substituted with R^j , R^k , and R^m independently selected from hydrogen, deuterium, alkyl, alkoxy, halo, haloalkyl, haloalkoxy, and cyano; or

5 a pharmaceutically acceptable salt thereof.

In a second aspect, provided is a compound of Formula (IB):



wherein:

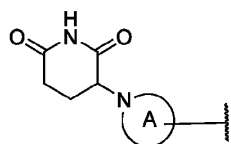
10 R^1 is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyloxy (wherein cycloalkyl, either alone or as part of cycloalkoxy, is substituted with one to three halo), halo, haloalkyl, haloalkoxy, alkoxy, aryloxy, or cyano;

R^2 and R^{2a} are independently hydrogen or deuterium;

Hy is cycloalkylene, arylene, heteroarylene, heterocyclylene, bicyclic heterocyclylene, spiro
15 heterocyclylene, bridged heterocyclylene, or fused heterocyclylene, where each of the aforementioned rings is substituted with R^a , R^b , and R^c independently selected from hydrogen, deuterium, alkyl, halo, haloalkyl, alkoxy, hydroxy, and cyano;

Degron is an E3 ubiquitin ligase ligand selected from:

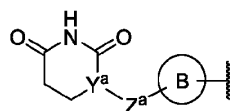
(a) a group of formula (i):



20

(i); or

(b) a group of formula (ii):



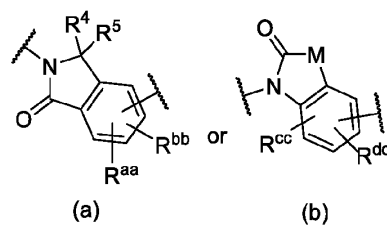
(ii);

25

Y^a is CH or N;

Z^a is a bond, $-\text{CH}_2-$, $-\text{NH}-$, $-\text{O}-$, or $-\text{NHC(O)}-$ where NH of $-\text{NHC(O)}-$ is attached to Y^a ;

ring A is a group of formula (a) or (b):



5 where:

R^{aa} , R^{bb} , R^{cc} , and R^{dd} are independently selected from hydrogen, alkyl, alkoxy, halo, haloalkyl, haloalkoxy, and cyano;

R^4 and R^5 are independently hydrogen or alkyl; or R^4 and R^5 together with the carbon to which they are attached form $>\text{C}=\text{O}$;

10 M is $-\text{O}-$ or $-\text{NR}^6-$; and

R^6 is hydrogen or alkyl;

ring B is phenylene, cyclylaminylene, a 5- or 6-membered monocyclic heteroarylene, or a 9- or 10-membered fused bicyclic heteroarylene, wherein each heteroarylene ring contains one to three ring atoms that are heteroatoms independently selected from nitrogen, oxygen or sulfur and further wherein the phenylene, cyclylaminylene, and each heteroarylene are independently substituted with R^{ee} and R^{ff} independently selected from hydrogen, alkyl, cycloalkyl, alkoxy, halo, haloalkyl, haloalkoxy, and cyano; and

Z is $-\text{O}-$, $-\text{NR}^3-$ (where R^3 is hydrogen or alkyl), alkynylene, cycloalkylene, phenylene, monocyclic heteroarylene, unsaturated heterocyclylene, heterocyclylene, bridged heterocyclylene, or spiro heterocyclylene and where each ring is substituted with R^d and R^e independently selected from hydrogen, deuterium, alkyl, alkoxy, halo, haloalkyl, haloalkoxy, and cyano;

alk is C_3 to C_6 alkenylene substituted with R^f selected from hydrogen, fluoro, and cyano; C_3 to C_6 alkylene or C_3 to C_6 heteroalkylene wherein the C_3 to C_6 alkylene and C_3 to C_6 heteroalkylene are substituted with R^g , R^h , and R^i where R^g is hydrogen, deuterium or halo, R^h is hydrogen, deuterium, cycloalkyl, cycloalkyloxy, bridged cycloalkyl, halo, haloalkoxy, alkoxy, hydroxy, cyano, cyanoalkyl, cyanoalkyloxy, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylcarbonylamino, phenyl, heteroaryl, heterocyclyl, heterocyclyloxy, heterocyclylcarbonyl, or bridged heterocyclyl (where cycloalkyl, either by itself or as part of cycloalkyloxy, bridged cycloalkyl, phenyl, heteroaryl, heterocyclyl, either by itself or as part of heterocyclyloxy or heterocyclylcarbonyl, and bridged heterocyclyl are substituted with R^7 and R^8 independently selected

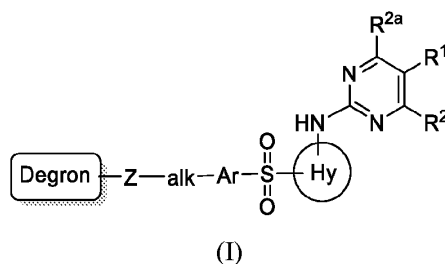
from hydrogen, deuterium, alkyl, alkoxy, halo, haloalkyl, haloalkoxy, hydroxy, alkylcarbonyl, alkyloxycarbonyl, amino, alkylamino, dialkylamino, and cyano); or when R^g and R^h are attached to the same carbon or to adjacent carbon atoms of the linear portion of the C_3 to C_6 alkylene or C_3 to C_6 heteroalkylene, R^g and R^h together with the carbon atom(s) to which they are attached can form

5 cycloalkylene or heterocyclylene (where the cycloalkylene and heterocyclylene formed by R^g and R^h are substituted with R^9 and R^{10} independently selected from hydrogen, deuterium, alkyl, alkoxy, halo, haloalkyl, haloalkoxy, hydroxy, alkylcarbonyl, alkyloxycarbonyl, amino, alkylamino, dialkylamino, and cyano), and R^i is hydrogen or halo; and the linear portion of C_3 to C_6 alkenylene, C_3 to C_6 alkylene, and C_3 to C_6 heteroalkylene, attaching Ar and Z, contains at least three atoms;

10 Ar is phenylene, monocyclic heteroarylene, heterocyclylene, unsaturated heterocyclylene^x, bridged heterocyclylene, or spiro heterocyclylene, where each of the aforementioned ring is substituted with R^j , R^k , and R^m independently selected from hydrogen, deuterium, alkyl, alkoxy, halo, haloalkyl, haloalkoxy, and cyano; or

a pharmaceutically acceptable salt thereof.

15 In a first embodiment of the second aspect, the compound of Formula (IB) is a compound of Formula (I):



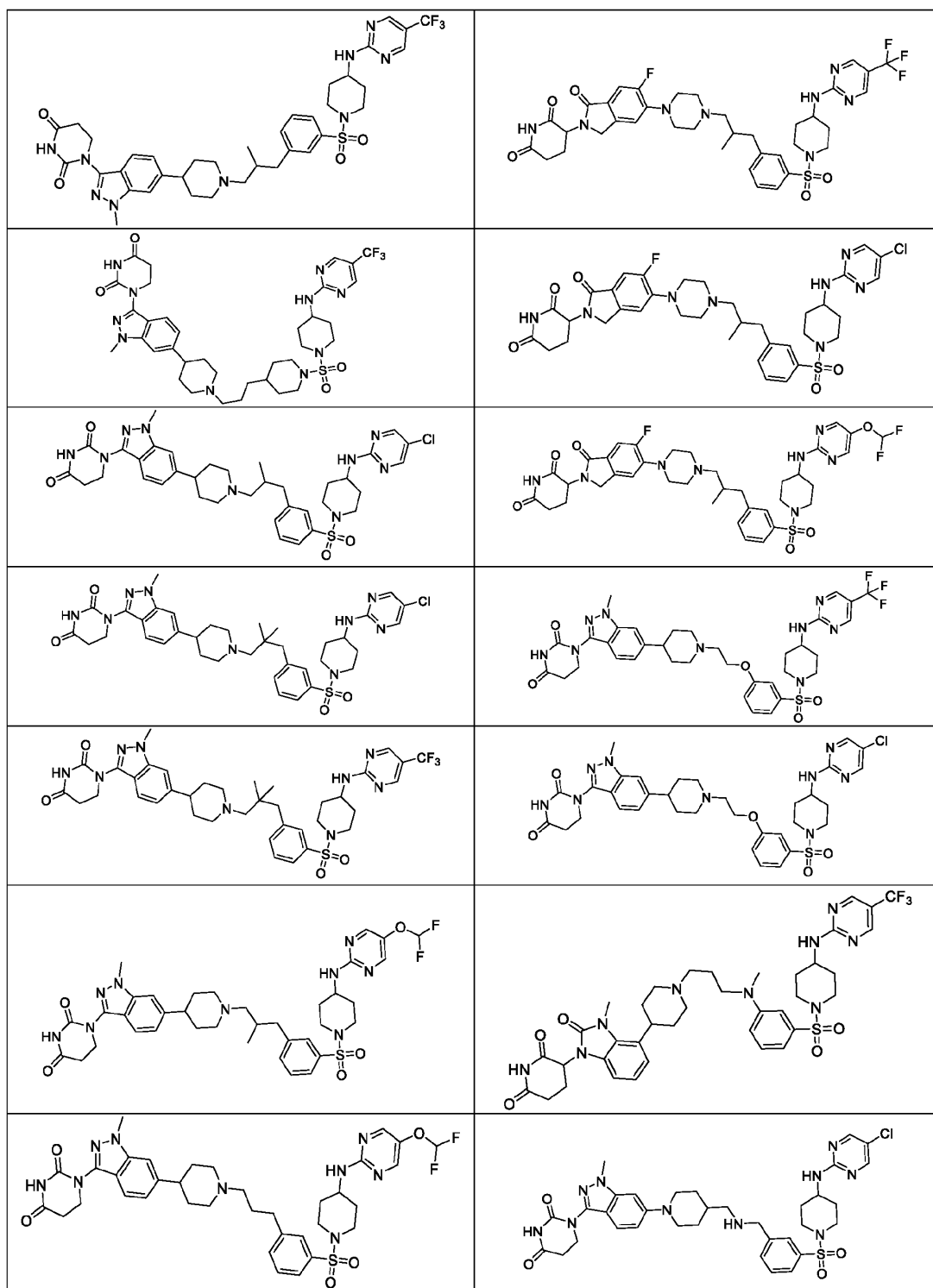
wherein:

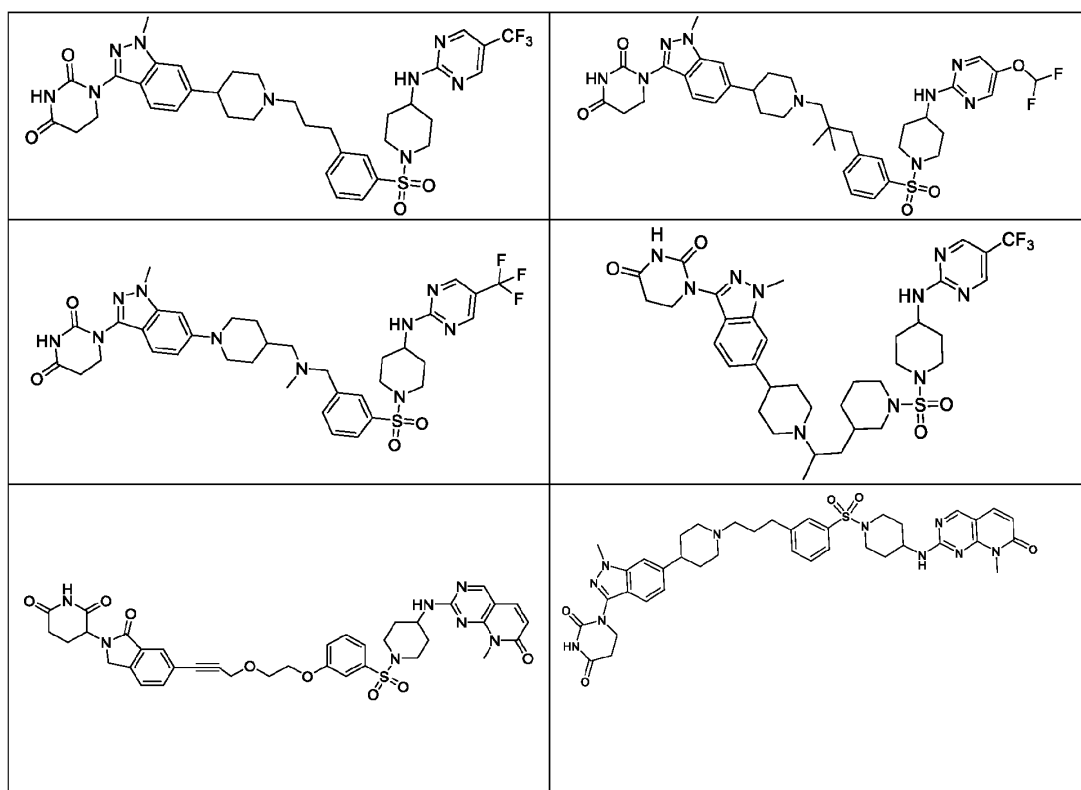
20 Ar is phenylene, monocyclic heteroarylene, heterocyclylene, bridged heterocyclylene, or spiro heterocyclylene, where each of the aforementioned rings is substituted with R^j , R^k , and R^m independently selected from hydrogen, deuterium, alkyl, alkoxy, halo, haloalkyl, haloalkoxy, and cyano; and other groups are as defined in Formula (IB); or

a pharmaceutically acceptable salt thereof.

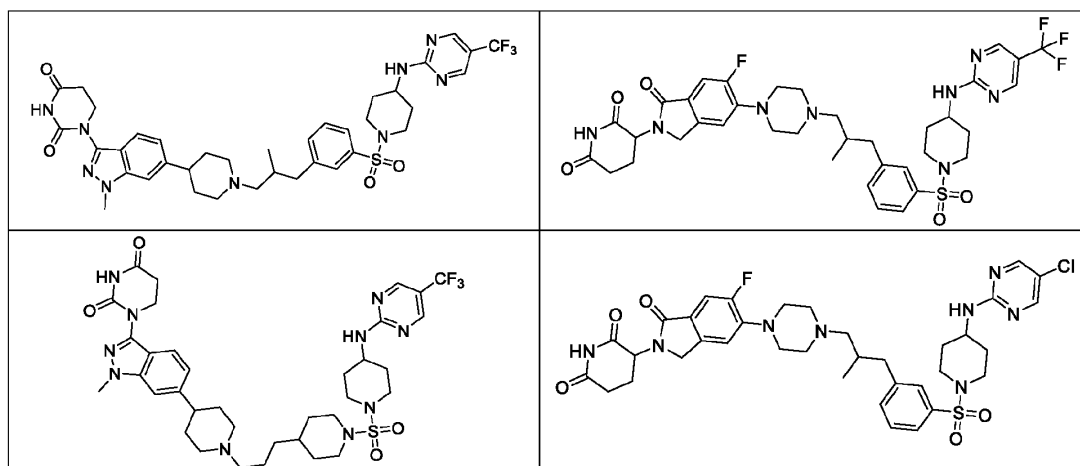
25 Compounds of Formula (I) are a subset of compounds of Formula (IB).

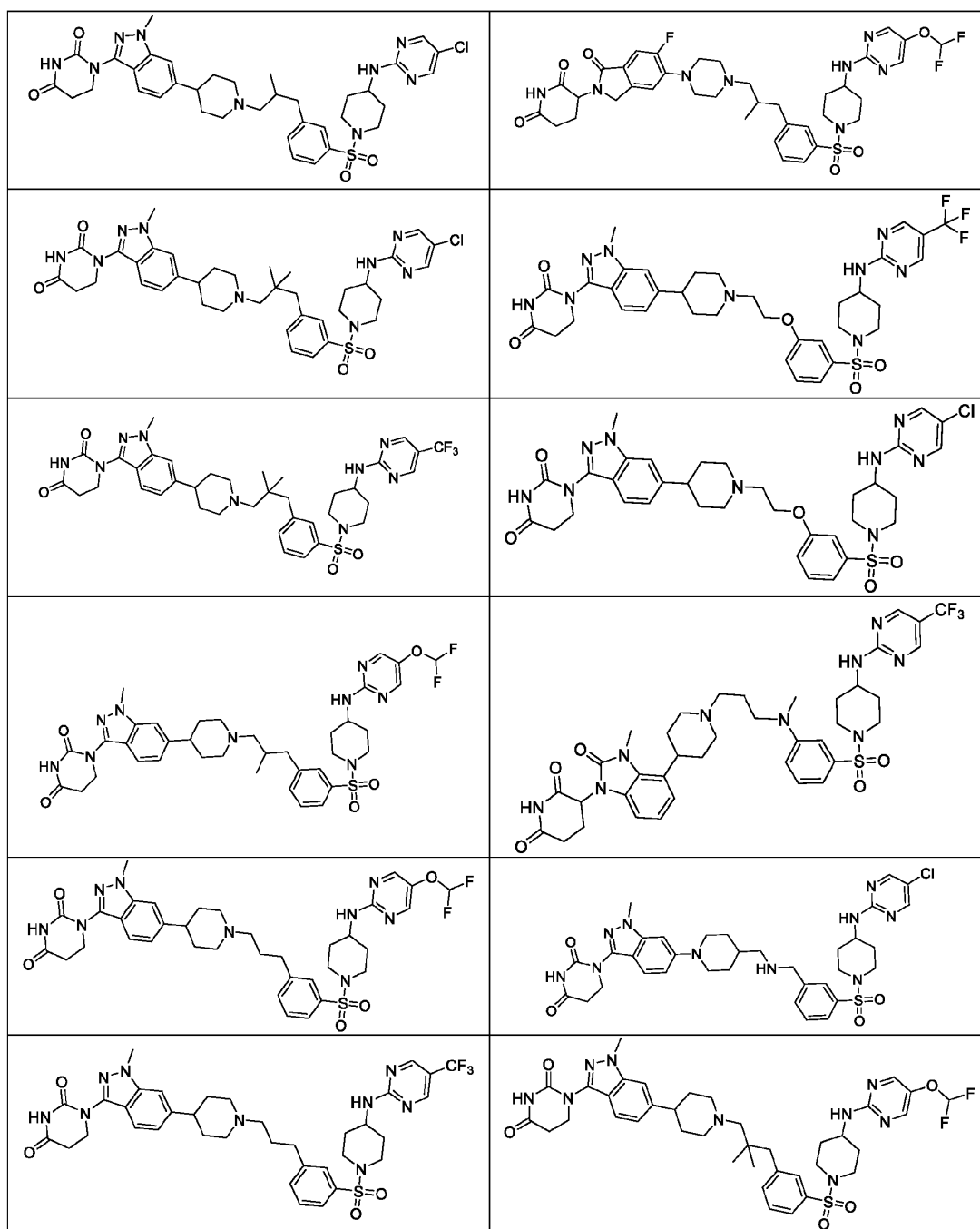
In a first embodiment of the first aspect, the compound of Formula (IA) is not:

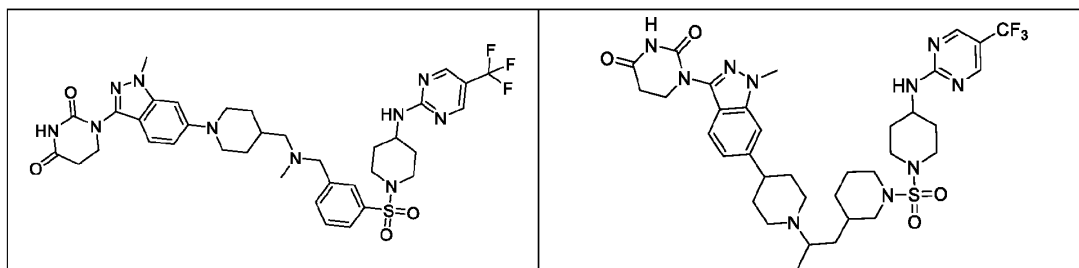




In a second embodiment of the second aspect and the first embodiment thereof, the compound of Formula (IB) or (I) is not:







In a third aspect, provided is a pharmaceutical composition comprising a compound of Formula (IA), (IB), or Formula (I) (or any of the embodiments thereof described herein), or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable excipient.

In a fourth aspect, provided is a method of treating a disease mediated by CDK2 and/or CDK4 in a patient, preferably the patient is in need of such treatment, which method comprises administering to the patient, preferably a patient in need of such treatment, a therapeutically effective amount of a compound of Formula (IA), (IB), or a compound of Formula (I) (or any of the embodiments thereof described herein below), or a pharmaceutically acceptable salt thereof; or a pharmaceutical composition thereof disclosed herein. In a first embodiment of the fourth aspect, the disease is cancer. In a second sub-embodiment of the fourth aspect the disease is cancer selected from lung cancer (*e.g.*, adenocarcinoma, small cell lung cancer, non-small cell lung carcinomas, parvicellular and non-parvicellular carcinoma, bronchial carcinoma, bronchial adenoma, and/or pleuropulmonary blastoma), skin cancer (*e.g.*, melanoma, squamous cell carcinoma, Kaposi sarcoma, and/or Merkel cell skin cancer), bladder cancer, breast cancer, cervical cancer, colorectal cancer, cancer of the small intestine (such as appendiceal carcinoma), colon cancer, rectal cancer, cancer of the anus, endometrial cancer, gastric cancer, head and neck cancer (*e.g.*, cancers of the larynx, hypopharynx, nasopharynx, oropharynx, lips, and/or mouth), liver cancer (*e.g.*, hepatocellular carcinoma and/or cholangiocellular carcinoma), cholangiocarcinoma, ovarian cancer, prostate cancer, testicular cancer, uterine cancer, esophageal cancer, gall bladder cancer, pancreatic cancer (*e.g.*, exocrine pancreatic carcinoma), stomach cancer, thyroid cancer, parathyroid cancer, bone cancer, biliary tract cancer, vaginal cancer, astrocytoma, liposarcomas, glioblastoma, neuroblastoma and/or kidney cancer. In a third embodiment of the fourth aspect, the cancers are those that are resistant to CDK4/6 inhibitors through CDK2-mediated mechanisms *e.g.*, breast cancer. In a fourth embodiment of the fourth aspect, the disease is an autoimmune disease or a condition associated with an autoimmune disease, which method comprises administering to the patient, preferably a patient in need of such treatment, a therapeutically effective amount of a compound of Formula (I) (or any of the embodiments thereof described herein below), or a pharmaceutically acceptable salt thereof. In

some embodiments, the autoimmune disease or condition associated with an autoimmune disease is selected from rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), primary Sjogren's syndrome (pSS), multiple sclerosis (MS), Crohn's disease (CD), uveitis, pemphigus vulgaris, and sepsis. In a fifth embodiment of the fourth aspect, the disease is gout.

5 In a fifth aspect, provided is a method of treating noise-induced, chemotherapy-induced (cisplatin-induced), antibiotic-induced, or age-related hearing loss, which method comprises administering to a patient, preferably a patient in need of such treatment, a therapeutically effective amount of a compound of Formula (I) (or any of the embodiments thereof described herein), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof as disclosed
10 therein. In some embodiments, the amount of hearing loss is reduced when compared to an age-matched control. In some embodiments, the hearing loss is prevented when compared to an age-matched control.

 In a sixth aspect, provided is a compound of Formula (IA), (IB), or a compound of Formula (I) (or any of the embodiments thereof described herein), or a pharmaceutically acceptable salt
15 thereof for use in therapy. In one embodiment of the sixth aspect, the compound of Formula (IA) or a compound of Formula (I) (or any embodiments thereof disclosed herein), or a pharmaceutically acceptable salt thereof is for use in the treatment of one or more of diseases disclosed in the fourth or fifth aspect above.

 In a seventh aspect, provided is the use of a compound of Formula (IA), (IB), or a compound
20 of Formula (I) (or any of the embodiments thereof described herein), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a disease in a patient in which the activity of CDK2 and/or CDK4 contributes to the pathology and/or symptoms of the disease. In one embodiment of the seventh aspect, the disease is one or more of diseases disclosed in the fourth and/or fifth aspects above.

25 In an eighth aspect, provided is a method of degrading CDK2 and/or CDK4 in a cell via ubiquitin proteasome pathway which method comprises contacting the cell with a compound of Formula (IA), (IB), or (I) (or embodiments thereof as disclosed herein). In one embodiment of the first and seventh aspects, the CDK2 and/or CDK4 are degraded in vitro. In another embodiment of the first and seventh aspects, the CDK2 and/or CDK4 are degraded in vivo. In yet another
30 embodiment of the first and seventh aspects, the CDK2 and/or CDK4 are degraded in a cell of a patient.

 It has been surprisingly discovered that PROTACS targeting CDKs containing -Z-alk-Ar¹-linker degrade CDK2 and CDK4 selectively over CDK1 and/or CDK6.

In the aforementioned aspects involving the treatment of cancer, further embodiments are provided comprising administering the compound of first aspect and of Formula (I), or a pharmaceutically acceptable salt thereof (or any embodiments thereof disclosed herein) or the pharmaceutical composition of the third aspect, in combination with at least one additional anticancer agent. When combination therapy is used, the agents can be administered simultaneously or sequentially.

Detailed Description

Definitions:

Unless otherwise stated, the following terms used in the specification and claims are defined for the purposes of this Application and have the following meaning:

Terms ending “ene” refer to the divalent radicals of the corresponding monovalent radicals unless stated otherwise. For example, alkylene is divalent radical of alkyl, alkenylene is a divalent radical of alkenyl, and heterocyclylene is divalent radical of heterocyclyl.

“Alkyl” means a linear or branched saturated monovalent hydrocarbon radical of one to six carbon atoms, *e.g.*, methyl, ethyl, propyl, 2-propyl, butyl, pentyl, and the like.

“Alkenyl” means a linear or branched monovalent hydrocarbon radical of two to six carbon atoms containing a double bond *e.g.*, ethenyl, propenyl, 2-propenyl, butenyl, pentenyl, and the like.

“Alkynyl” means a linear or branched monovalent hydrocarbon radical of two to six carbon atoms containing a triple bond *e.g.*, ethynyl, propynyl, 2-propynyl, butynyl, and the like.

“Alkylene” means a linear or branched saturated divalent hydrocarbon radical of one to six carbon atoms unless otherwise stated. When alkylene contains three to six carbon atoms it is also referred to herein as C3 to C6 alkylene. Examples include, but are not limited to, methylene, ethylene, propylene, 1-methylpropylene, 2-methylpropylene, butylene, pentylene, and the like.

“Alkynylene” means a linear or branched divalent hydrocarbon radical of two to six carbon atoms containing a triple bond, *e.g.*, $\text{---}\equiv\text{---}$, $\text{---C}\equiv\text{---CH}_2\text{---}$, and the like.

“Alkoxy” means a ---OR^p radical where R^p is alkyl as defined above, *e.g.*, methoxy, ethoxy, propoxy, or 2-propoxy, *n*-, *iso*-, or *tert*-butoxy, and the like.

“Alkoxycarbonyl” or “alkyloxycarbonyl” means a ---C(O)OR^p radical where R^p is alkyl as defined above, *e.g.*, methoxycarbonyl, ethoxycarbonyl, and the like.

“Alkylcarbonylamino” means a $\text{---NR}^{p'}\text{C(O)R}^p$ radical where R^p is alkyl and $R^{p'}$ is H or alkyl, as defined above, *e.g.*, methylcarbonylamino, ethylcarbonylamino, and the like.

“Alkylcarbonyl” means a ---C(O)R^p radical where R^p is as defined herein, *e.g.*, methylcarbonyl, ethylcarbonyl and the like.

“Amino” means -NH_2 .

“Aminocarbonyl” means -C(O)NH_2 .

“Alkylaminocarbonyl” means -C(O)NHR^P radical where R^P is alkyl as defined above e.g., methylaminocarbonyl, ethylaminocarbonyl, propylaminocarbonyl, and the like.

5 “Alkylcarbonylamino” means -NHC(O)R^P radical where R^P is alkyl as defined above e.g., methylcarbonylamino, ethylcarbonylamino, propylcarbonylamino, and the like.

“Alkylsulfonyl” means -NHS(O)_2R^P radical where R^P is alkyl as defined above e.g., methylsulfonylamino, ethylsulfonylamino, and the like.

10 “Dialkylaminocarbonyl” means $\text{-C(O)NR}^{P1}R^P$ radical where R^P and R^{P1} are independently alkyl as defined above e.g., dimethylaminocarbonyl, diethylaminocarbonyl, dipropylaminocarbonyl, and the like.

“Alkylamino” means -NHR^P radical where R^P is alkyl as defined above e.g., methylamino, ethylamino, propylamino, and the like.

15 “Aryl” means a monovalent monocyclic or bicyclic aromatic hydrocarbon radical of 6 to 10 ring atoms e.g., phenyl or naphthyl.

“Arylene” means a divalent aryl (as defined above) radical e.g., phenylene or naphthylene.

“Aryloxy” means a -O-R^P radical where R^P is aryl as defined above e.g., phenyloxy (or phenoxy), or naphthyloxy.

20 “Bicyclic heterocyclylene” means a saturated divalent fused bicyclic group of 8 to 12 ring atoms in which one, two, or three ring atoms are heteroatoms independently selected from N, NH, O, and S(O)_n , where n is an integer selected from 0 to 2, the remaining ring atoms being carbon, unless stated otherwise. Additionally, one or two ring carbon atoms of the bicyclic heterocyclylene ring can optionally be replaced by a -CO- group. More specifically the term bicyclic heterocyclylene includes, but is not limited to, isoindolin-diyl, decahydro-2,6-naphthyridin-diyl, 25 octahydrocyclopenta[c]pyrrol-diyl, octahydro-1H-pyrrolo[3,4-c]pyridin-diyl, hexahydrofuro[3,2-b]furan-3,6-diyl, and the like. When the heterocyclylene ring is unsaturated it can contain one or two ring double bonds provided that the ring is not aromatic.

30 “Bridged cycloalkyl” means a saturated monovalent bicyclic ring having 5 to 8 ring carbon ring atoms in which two non-adjacent ring atoms are linked by a $(\text{CR}^P\text{R}^P)_n$ group where n is an integer selected from 1 to 3 and R^P and R^P are independently H or methyl (also may be referred to herein as “bridging” group). Examples include, but are not limited to, bicyclo[1.1.1]pent-1-yl, bicyclo[2.2.1]heptyl, preferably, bicyclo[2.2.1]hept-2-yl, and the like.

“Bridged heterocyclyl” means a saturated monovalent bicyclic ring having 5 to 9 ring carbon ring atoms in which two non-adjacent ring atoms are linked by a $(\text{CR}^P\text{R}^P)_n$ group where n is an

integer selected from 1 to 3 and R^P and $R^{P'}$ are independently H or methyl (also may be referred to herein as “bridging” group) and further wherein one or two ring carbon atoms, including an atom in the bridging group, is replaced by a heteroatom selected from N, NH, O, and $S(O)_n$, where n is an integer selected from 0 to 2. Bridged heterocyclyl is optionally substituted with one or two

5 substituents independently selected from alkyl, halo, alkoxy, hydroxy, and cyano unless stated otherwise. Examples include, but are not limited to, 3,8-diazabicyclo[3.2.1]octanyl, 7-oxabicyclo[2.2.1]heptanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 3,6-diazabicyclo-[3.1.1]heptanyl, 2,5-diazabicyclo[2.2.2]octanyl, 3,8-diazabicyclo[3.2.1]octanyl, 6-azabicyclo[3.1.1]heptanyl, 8-azabicyclo[3.2.1]octanyl, and the like.

10 “Bridged heterocyclylene” means a saturated divalent bicyclic ring having 5 to 9 ring carbon ring atoms in which two non-adjacent ring atoms are linked by a $(CR^P R^{P'})_n$ group where n is an integer selected from 1 to 3 and R^P and $R^{P'}$ are independently H or methyl (also may be referred to herein as “bridging” group) and further wherein one or two ring carbon atoms, including an atom in the bridging group, is replaced by a heteroatom selected from N, NH, O, and $S(O)_n$, where n is an

15 integer selected from 0 to 2. Bridged heterocyclylene is optionally substituted with one or two substituents independently selected from alkyl, halo, alkoxy, hydroxy, and cyano unless stated otherwise. Examples include, but are not limited to, 3,8-diazabicyclo[3.2.1]octa-3,8-diyl, 7-oxabicyclo[2.2.1]heptan-diyl, 2,5-diazabicyclo[2.2.1]heptan-diyl, 3,6-diazabicyclo-[3.1.1]heptan-diyl, 2,5-diazabicyclo[2.2.2]octan-diyl, 3,8-diazabicyclo[3.2.1]octan-diyl, 6-azabicyclo[3.1.1]heptan-

20 diyl, 8-azabicyclo[3.2.1]octan-diyl, and the like.

“Cycloalkyl” means a monocyclic saturated monovalent hydrocarbon radical of three to ten carbon atoms. Examples include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like.

25 “Cycloalkylalkyl” means an alkyl group, as defined above, substituted with cycloalkyl as defined above. Examples include, but are not limited to, cyclopropylmethyl, cyclopropylethyl, cyclobutylmethyl, cyclobutylethyl, cyclopentylmethyl, cyclopentylethyl, cyclohexylmethyl, cyclohexylethyl, and the like.

“Cycloalkyloxy or cycloalkoxy” means a $-OR^P$ radical where R^P is cycloalkyl as defined above. Examples include, but are not limited to, cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, 30 cyclohexyloxy, and the like.

“Cycloalkylene” means a divalent saturated hydrocarbon radical of three to six carbon atoms, otherwise *e.g.*, 1,1-cyclopropylene, 1,1-cyclobutylene, 1,4-cyclohexylene, and the like.

“Carbonyl” means $-C(O)-$.

“Carboxy” means $-COOH$.

“Cyclalaminy” means a saturated monovalent monocyclic ring of 4 to 8 ring atoms in which one or two ring atoms are nitrogen, the remaining ring atoms being carbon. More specifically, the term cyclalaminy includes, but is not limited to, pyrrolidiny, piperidiny, piperaziny, and the like.

“Cyclalaminylene” means a saturated divalent monocyclic ring of 4 to 8 ring atoms in which one or two ring atoms are nitrogen, the remaining ring atoms being carbon. More specifically, the term cyclalaminylene includes, but is not limited to, pyrrolidinylene, piperidin-diyl, homopiperidin-diyl, piperazin-diyl, and the like.

“Cyanoalkyl” means alkyl as defined above that is substituted with a cyano e.g., cyanomethyl, cyanoethyl, and the like.

“Cyanoalkyloxy” means an -OR^P radical where R^P is cyanoalkyl as defined above, e.g., cyanomethyloxy, cyanoethyloxy, and the like.

“Deuterium” means refers to ²H or D.

“Dialkylamino” means a -NR^PR^P radical where each R^P is alkyl as defined above and are independently selected, e.g., dimethylamino, methylethylamino, n-propylmethylamino, 2-propylmethylamino, *n*-, *iso*-, or *tert*-butylmethylamino, and the like.

“Fused heterocycl” means a monovalent bicyclic ring in which two adjacent ring atoms of a saturated monocyclic ring of 4 to 7 ring atoms having one or two heteroatoms independently selected from N, NH, O, and S(O)_n (where n is 0, 1, or 2) and the remaining ring atoms being carbon, are fused to two adjacent ring members of a phenyl, or a five or six membered heteroaryl, each as defined herein, unless stated otherwise. The nitrogen atom is optionally oxidized and further wherein one of the carbon ring atoms of the saturated monocyclic ring is optionally replaced by a -C(=O)-group. Representative examples include, but are not limited to, 1,2,3,4-tetrahydroquinoliny, 3,4-dihydro-2H-benzo[b][1,4]oxazinyl, 3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazinyl, 4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazinyl, and the like.

“Fused heterocyclylene” means a divalent bicyclic ring in which two adjacent ring atoms of a saturated monocyclic ring of 4 to 7 ring atoms having one or two heteroatoms independently selected from N, NH, O, and S(O)_n (where n is 0, 1, or 2) and the remaining ring atoms being carbon, are fused to two adjacent ring members of a phenyl, or a five or six membered heteroaryl, each as defined herein, unless stated otherwise. The nitrogen atom is optionally oxidized and further wherein one of the carbon ring atoms of the saturated monocyclic ring is optionally replaced by a -C(=O)-group. The fused heterocyclylene can be attached at any two atoms of the ring. Representative examples include, but are not limited to, 1,2,3,4-tetrahydroquinolin-1,4-diyl, 3,4-dihydro-2H-benzo[b][1,4]oxazin-5,8-diyl, 3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-diyl, 4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-diyl, and the like.

“Halo” means fluoro, chloro, bromo, or iodo, *e.g.*, fluoro or chloro.

“Haloalkyl” means alkyl radical as defined above, which is substituted with one or more halogen atoms, *e.g.*, one to five halogen atoms, such as fluorine or chlorine, including those substituted with different halogens, *e.g.*, -CH₂Cl, -CF₃, -CHF₂, -CH₂CF₃, -CF₂CF₃,

5 -CF(CH₃)₂, and the like. When the alkyl is substituted with only fluoro, it can be referred to in this Application as fluoroalkyl.

“Haloalkoxy” means an -OR^p radical where R^p is haloalkyl as defined above *e.g.*, -OCF₃, -OCHF₂, and the like. When R^p is haloalkyl where the alkyl is substituted with only fluoro (in some examples, one or more fluoro), it is referred to in this Application as fluoroalkoxy.

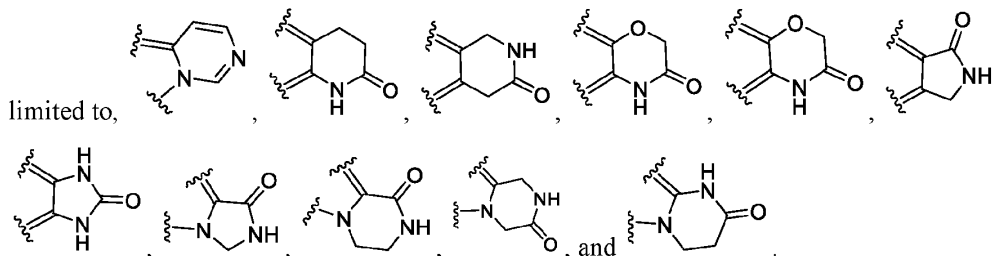
10 “Heteroaryl” means a monovalent monocyclic or fused bicyclic aromatic radical of 5 to 10 ring atoms where one or more, (in one embodiment, one, two, or three), ring atoms are heteroatom selected from N, NH, O, and S, the remaining ring atoms being carbon, unless otherwise stated. Representative examples include, but are not limited to, pyrrolyl, thienyl, thiazolyl, imidazolyl, furanyl, indolyl, isoindolyl, indazolyl, imidazo[1,2-a]pyridinyl, imidazo[1,2-a]pyrazinyl, oxazolyl, 15 isoxazolyl, oxadiazolyl, benzothiazolyl, benzoxazolyl, quinolinyl, isoquinolinyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazolyl, tetrazolyl, and the like. As defined herein, the terms “heteroaryl” and “aryl” are mutually exclusive. When the heteroaryl ring contains 5- or 6 ring atoms and is a monocyclic ring, it is also referred to herein as “five or six” or “5-or 6”-membered monocyclic heteroaryl, or “5- or 6-membered heteroaryl”. When the heteroaryl ring contains 9- or 20 10 ring atoms, it is also referred to herein as 9-or 10-membered fused bicyclic heteroaryl.

“5-Membered heteroaryl^A” means a monocyclic aromatic radical of 5 ring atoms where one or two ring atoms are nitrogen and the remaining ring atoms being carbon, unless otherwise stated. Representative examples include, but are not limited to, pyrrolyl, imidazolyl, pyrazolyl, and the like. As defined herein, the terms “heteroaryl” and “aryl” are mutually exclusive.

25 “Heteroarylene” means a divalent heteroaryl radical as defined above, unless stated otherwise. Representative examples include, but are not limited to, benzimidazoldiyl *e.g.*, benzimidazole-1,5-diyl, and the like. When the heteroarylene ring contains 5- or 6 ring atoms and is a monocyclic ring, it is also referred to herein as “monocyclic heteroarylene” or as “5-or 6-membered monocyclic heteroarylene” *e.g.*, pyrazolyl-diyl (pyrazolyl-1.3-diyl, pyrazolyl-1.4-diyl, 30 pyrazolyl-1.5-diyl and the like) and imidazol-diyl (imidazol-1,2-diyl, imidazol-1,4-diyl, imidazol-1,5-diyl). When the heteroarylene ring contains 9- or 10 ring atoms and is a fused bicyclic ring, it is also referred to herein as 9-or 10-membered fused bicyclic heteroarylene.

“Heterocyclyl^A” means a saturated monocyclic ring having five or six ring atoms in which one or two ring atoms are selected from N, NH, O, S(O)_n, where n is an integer selected from 0 to 2,

, the remaining ring atoms being C. Additionally, one or two ring carbon atoms in the heterocyclyl^A ring can optionally be replaced by a -C(=O)- group. Representative examples include, but are not



- 5 “Heterocyclyl” means a saturated, monovalent, monocyclic group of 4 to 8 ring atoms in which one or two ring atoms are heteroatom independently selected from N, NH, O, and S(O)_n, where n is an integer selected from 0 to 2, the remaining ring atoms being C, unless stated otherwise. Additionally, one or two ring carbon atoms in the heterocyclylene ring can optionally be replaced by a -C(=O)- group. More specifically, the term heterocyclyl includes, but is not limited to, oxetanyl, piperidinyl, piperazinyl, pyrrolidinyl, azetidiny, and the like.

“Heterocyclylcarbonyl” means a -C(O)R group where R is heterocyclyl as defined herein. More specifically, the term heterocyclyl includes, but is not limited to, piperidinylcarbonyl, piperazinylcarbonyl, pyrrolidinylcarbonyl, azetidiny carbonyl, and the like.

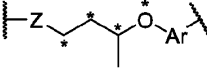
- 15 “Heterocycloxy” means an -OR group where R is heterocyclyl as defined herein. More specifically, the term heterocyclyl includes, but is not limited to, piperidinyloxy, piperazinyloxy, pyrrolidinyloxy, azetidinyloxy, and the like.

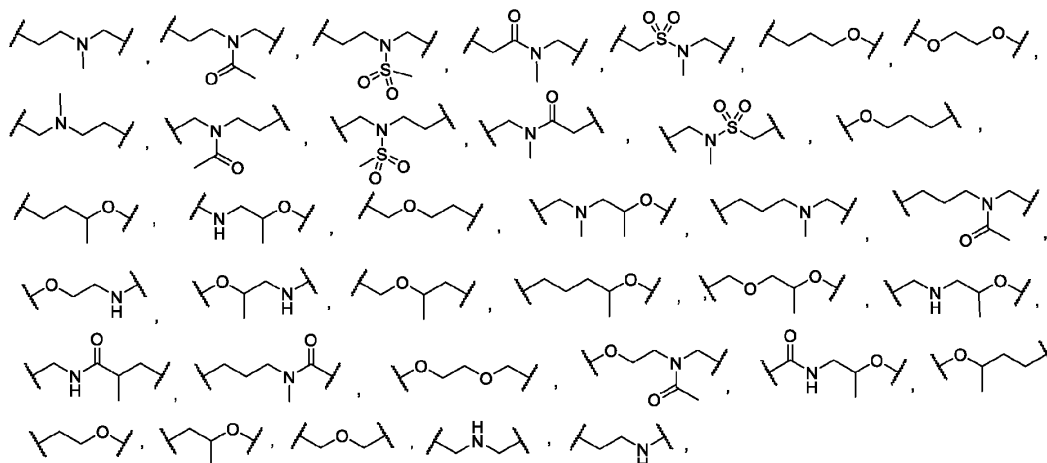
- “Heterocyclylene” means a saturated, divalent, monocyclic group of 4 to 8 ring atoms in which one or two ring atoms are heteroatom independently selected from N, NH, O, and S(O)_n, where n is an integer selected from 0 to 2, the remaining ring atoms being C, unless stated otherwise. Additionally, one or two ring carbon atoms in the heterocyclylene ring can optionally be replaced by

a -C(=O)- group. More specifically, the term heterocyclylene includes, but is not limited to, , piperidin-1,4-diyl, azetidin-1,3-diyl, and the like.

- 25 “C₃ to C₆ heteroalkylene” means is a linear or branched saturated divalent hydrocarbon radical of three to six carbon atoms where (a) one carbon atom of the linear portion of the divalent hydrocarbon radical is replaced by X^a where X^a is -O-, -S-, -SO-, -SO₂-, -CO-, or -NR^q- or (b) two adjacent carbon atoms of the linear portion of the divalent hydrocarbon radical are replaced by X^{a1} where X^{a1} is -NR^qCO-, -CONR^q-, -NR^qSO-, -SONR^q-, -NR^qSO₂-, or -SO₂NR^q- (where each R^q is hydrogen, alkyl, alkylcarbonyl, or alkylsulfonyl) and furthermore an additional carbon atom, that is not adjacent to X^a and X^{a1} in the linear portion of the C₃ to C₆ heteroalkylene of (a) and (b) above

can be replaced by X^y where X^y is -O- or -NR^{q1}- (where each R^{q1} is hydrogen, alkyl, alkylcarbonyl, or alkylsulfonyl), provided that the linear portion of C₃ to C₆ heteroalkylene attaching Z and Ar contains at least three atoms. For sake of clarity, as used in this definition, the linear portion of the C₃ to C₆ heteroalkylene means the consecutive atoms of the C₃ to C₆ heteroalkylene connecting Z and

- Ar e.g., in the structure , the atoms with * form the linear portion of C₅ heteroalkylene. When the C₃ to C₆ heteroalkylene contains only one or two -O-, it can be referred to herein as “oxoalkylene.” When the C₃ to C₆ heteroalkylene contains only one or two -NR^{q1}- and/or -NR^{q1}-, it can be referred to herein as “aminylalkylene.” When the C₃ to C₆ heteroalkylene contains only -S-, it can be referred to herein as “sulfanylalkylene.” When the C₃ to C₆ heteroalkylene contains only -SO-, it can be referred to herein as “sulfinylalkylene.” When the C₃ to C₆ heteroalkylene contains only -SO₂-, it can be referred to herein as “sulfonylalkylene.” Representative examples, of C₃ to C₆ heteroalkylene include, *e.g.*,



and the like.

- 15 “Phenylene” means divalent phenyl.

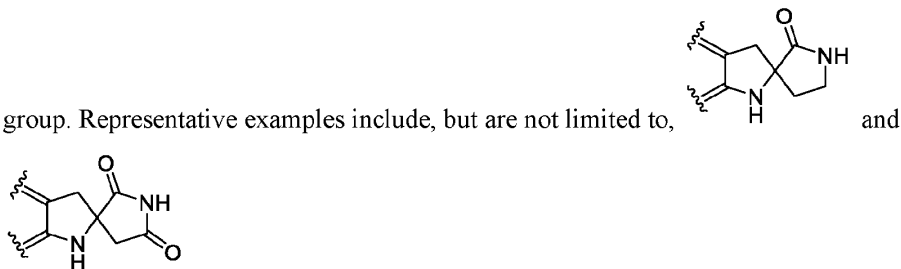
- 20 “Partially saturated 9- or 10-membered fused bicyclic heteroaryl” means a monovalent bicyclic ring in which two adjacent atoms of a five or six membered heteroaryl ring containing one or two nitrogen ring atoms are fused to two adjacent atoms of a five or six membered cycloalkyl or a five or six membered saturated ring of 5 or 6-ring atoms wherein one, two, or three ring atoms are heteroatoms selected from N and O and the remaining ring atoms being carbon. The partially saturated 9- or 10-membered fused bicyclic heteroaryl is attached to -NH- of Formula (IA) via the heteroaryl portion of the fused bicyclic heteroaryl. Representative examples include, but are not limited to, 5,6,7,8-tetrahydroquinolinyl, 5,6,7,8-tetrahydroquinazolinyl, 5,6,7,8-

tetrahydropyrido[2,3-d]pyrimidinyl, 7,8-dihydro-5H-pyrano[4,3-d]pyrimidinyl, 3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazinyl, 4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazinyl, and the like.

The phrase “optionally” or “optional” as used herein means that the subsequently described event or circumstance may but need not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, the phrase “alkylene optionally substituted with halo” is intended to cover alkylene that is unsubstituted and alkylene that is substituted with halo.

“Spirocycloalkyl” means a saturated bicyclic monovalent hydrocarbon radical of three to ten carbon atoms where the rings are connected through only one carbon atom, and where the connecting atom is also called the spiroatom, most often a quaternary carbon (“spiro carbon”). Representative examples include, but are not limited to, spiro[2.2]pentanyl, spiro[2.5]octanyl, spiro[4.5]decanyl, spiro[5.5]undecanyl, and the like.

“Spiro heterocyclyl^A” means a saturated bicyclic ring having 9 to 10 ring atoms in which one, two, or three ring atoms are selected from N, O, S(O)_n, where n is an integer selected from 0 to 2, the remaining ring atoms being C and the rings are connected through only one atom, the connecting atom is also called the spiroatom, most often a quaternary carbon (“spiro carbon”). Additionally, one or two ring carbon atoms in the spiro heterocyclyl ring can optionally be replaced by a $-C(=O)-$ group. Representative examples include, but are not limited to,



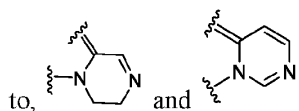
“Spiroheterocyclyl” means a saturated bicyclic monovalent ring having 6 to 10 ring atoms in which one, two, or three ring atoms are heteroatom selected from N, O, and S(O)_n, where n is an integer selected from 0 to 2, the remaining ring atoms being C and the rings are connected through only one atom, the connecting atom is also called the spiroatom, most often a quaternary carbon (“spiro carbon”). Spiro heterocyclylene is optionally substituted with one or two substituents independently selected from alkyl, halo, alkoxy, hydroxy, and cyano, unless stated otherwise. Representative examples include, but are not limited to, 2-azaspiro[3.3]heptanyl, 2,6-diazaspiro[3.3]heptanyl, 1,7-diazaspiro[3.5]nonanyl, 2,7-diazaspiro[3.5]nonanyl, 3,9-diazaspiro[5.5]undecanyl, and the like.

“Spiro heterocyclylene” means a saturated bicyclic divalent ring having 6 to 10 ring atoms in which one, two, or three ring atoms are heteroatom selected from N, O, and S(O)_n, where n is an

integer selected from 0 to 2, the remaining ring atoms being C and the rings are connected through only one atom, the connecting atom is also called the spiroatom, most often a quaternary carbon (“spiro carbon”). Spiro heterocyclylene is optionally substituted with one or two substituents independently selected from alkyl, halo, alkoxy, hydroxy, and cyano, unless stated otherwise.

- 5 Representative examples include, but are not limited to, 2-azaspiro[3.3]heptan-diyl, 2,6-diazaspiro[3.3]heptan-diyl, 1,7-diazaspiro[3.5]nonan-diyl, 2,7-diazaspiro[3.5]nonan-diyl, 3,9-diazaspiro[5.5]undecan-diyl, and the like.

“Unsaturated heterocyclyl^A” means monocyclic nonaromatic group of 6 to 8 ring atoms having one or two double bonds and in which one or two ring atoms are heteroatom independently selected from N, O, and S(O)_n, where n is an integer selected from 0 to 2, the remaining ring atoms being C, unless stated otherwise. Additionally, one or two ring carbon atoms in the heterocyclyl ring can optionally be replaced by a –C(=O)– group. Representative examples include, but are not limited



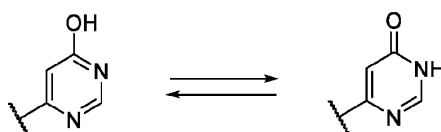
“Unsaturated heterocyclylene” means divalent, monocyclic nonaromatic group of 6 to 8 ring atoms having one or two double bonds and in which one or two ring atoms are heteroatom independently selected from N, O, and S(O)_n, where n is an integer selected from 0 to 2, the remaining ring atoms being C, unless stated otherwise. Additionally, one or two ring carbon atoms in the heterocyclylene ring can optionally be replaced by a –C(=O)– group.

“Unsaturated heterocyclylene^X” means divalent, monocyclic nonaromatic heterocyclylene group of 5 to 8 ring atoms having one, two, or three double bonds and in which one or two ring atoms are heteroatom(s) independently selected from N, O, and S(O)_n, where n is an integer selected from 0 to 2, the remaining ring atoms being C, unless stated otherwise. Additionally, one or two ring carbon atoms in the heterocyclylene ring can optionally be replaced by a –C(=O)– group.

The present disclosure also includes protected derivatives of compounds of Formula (I) (or any embodiments thereof disclosed herein), or a pharmaceutically acceptable salt thereof. For example, when compounds of Formula (I) contain groups such as hydroxy, carboxy, or any group containing a nitrogen atom(s), these groups can be protected with suitable protecting groups. A comprehensive list of suitable protective groups can be found in T.W. Greene, *Protective Groups in Organic Synthesis*, 5th Ed., John Wiley & Sons, Inc. (2014), the disclosure of which is incorporated herein by reference in its entirety. The protected derivatives of compounds of the present disclosure can be prepared by methods well known in the art.

The present disclosure also includes polymorphic forms and deuterated forms of the compound of Formula (I) (or any embodiments thereof disclosed herein), or a pharmaceutically acceptable salt thereof.

Certain compounds of the present disclosure can exist as tautomers and/or geometric isomers. All possible tautomers and *cis* and *trans* isomers, as individual forms and mixtures thereof are within the scope of this disclosure. For example, a compound of Formula (IA), (IB), or (I) having a hydroxy substituted pyridyl ring can exist as a tautomer as shown below:



The term “prodrug” refers to a compound that is made more active in vivo. Certain compounds Formula (I) (and any embodiment thereof disclosed herein including specific compounds) may also exist as prodrugs, as described in *Hydrolysis in Drug and Prodrug Metabolism: Chemistry, Biochemistry, and Enzymology* (Testa, Bernard and Mayer, Joachim M. Wiley-VHCA, Zurich, Switzerland 2003). Prodrugs of the compounds described herein are structurally modified forms of the compound that readily undergo chemical changes under physiological conditions to provide the active compound. Prodrugs are often useful because, in some situations, they may be easier to administer than the compound, or parent drug. They may, for instance, be bioavailable by oral administration whereas the parent drug is not. A wide variety of prodrug derivatives are known in the art, such as those that rely on hydrolytic cleavage or oxidative activation of the prodrug. An example, without limitation, of a prodrug would be a compound which is administered as an ester (the “prodrug”), but then is metabolically hydrolyzed to the carboxylic acid, the active entity. Additional examples include peptidyl derivatives of a compound.

A “pharmaceutically acceptable salt” of a compound means a salt that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent compound. Such salts include:

acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as formic acid, acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic

acid, camphorsulfonic acid, glucoheptonic acid, 4,4'-methylenebis-(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, and the like; or

5 salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, *e.g.*, an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, tromethamine, *N*-methylglucamine, and the like. It is understood that the pharmaceutically acceptable salts are non-toxic. Additional information on suitable pharmaceutically acceptable salts can be found in
10 *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, PA, 1985, which is incorporated herein by reference in its entirety.

The compounds of Formula (IB) or (I) (and any embodiment thereof disclosed herein including specific compounds) may have asymmetric centers. Compounds of Formula (IB) or (I) (and any embodiment thereof disclosed herein including specific compounds) containing an
15 asymmetrically substituted atom may be isolated in optically active or racemic forms. Individual stereoisomers of compounds can be prepared synthetically from commercially available starting materials which contain chiral centers 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
20 chromatographic columns, or any other appropriate method known in the art. All chiral, diastereomeric, all mixtures of chiral or diastereomeric forms, and racemic forms are within the scope of this disclosure, unless the specific stereochemistry or isomeric form is specifically indicated. It will also be understood by a person of ordinary skill in the art that when a compound is denoted as (R) stereoisomer, it may contain the corresponding (S) stereoisomer as an impurity
25 and vice versa.

Certain compounds of Formula (IB) or (I) (and any embodiment thereof disclosed herein including specific compounds) can exist as tautomers and/or geometric isomers. All possible tautomers and *cis* and *trans* isomers, as individual forms and mixtures thereof are within the scope of this disclosure. Additionally, as used herein the term alkyl includes all the possible isomeric
30 forms of said alkyl group albeit only a few examples are set forth. Furthermore, when the cyclic groups such as aryl is substituted, it includes all the positional isomers albeit only a few examples are set forth. Furthermore, all hydrates of a compound of Formula (IB) or (I) (and any embodiment thereof disclosed herein including specific compounds) are within the scope of this disclosure.

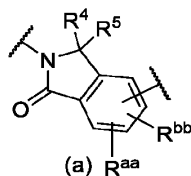
The compounds of Formula (IB) or (I) (and any embodiment thereof disclosed herein including specific compounds) may also contain unnatural amounts of isotopes at one or more of the atoms that constitute such compounds. Unnatural amounts of an isotope may be defined as ranging from the amount found in nature to an amount 100% of the atom in question. that differ
5 only in the presence of one or more isotopically enriched atoms. Exemplary isotopes that can be incorporated into compounds of the present disclosure, such as a compound of Formula (IB) or (I) (and any embodiment thereof disclosed herein including specific compounds) include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, fluorine, chlorine, and iodine, such as ^2H , ^3H , ^{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 , respectively.
10 Isotopically labeled compounds (*e.g.*, those labeled with ^3H and ^{14}C) can be useful in compound or substrate tissue distribution assays. Tritiated (*i.e.*, ^3H) and carbon-14 (*i.e.*, ^{14}C) isotopes can be useful for their ease of preparation and detectability. Further, substitution with (or isotopically enriched for) heavier isotopes such as deuterium (*i.e.*, ^2H) may afford certain therapeutic advantages resulting from greater metabolic stability (*e.g.*, increased in vivo half-life or reduced
15 dosage requirements). In some embodiments, in compounds of Formula (I) (and any embodiment thereof disclosed herein including specific compounds, including in Table 1 below, one or more hydrogen atoms are replaced by ^2H or ^3H , or one or more carbon atoms are replaced by ^{13}C - or ^{14}C -enriched carbon. Positron emitting isotopes such as ^{15}O , ^{13}N , ^{11}C , and ^{15}F are useful for positron emission tomography (PET) studies to examine substrate receptor occupancy. Isotopically labeled
20 compounds can generally be prepared by following procedures analogous to those disclosed in the Schemes or in the Examples herein, by substituting an isotopically labeled reagent for a non-isotopically labeled reagent.

A “pharmaceutically acceptable carrier or excipient” means a carrier or an excipient that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither
25 biologically nor otherwise undesirable, and includes a carrier or an excipient that is acceptable for veterinary use as well as human pharmaceutical use.

“A pharmaceutically acceptable carrier/excipient” as used in the specification and claims includes both one and more than one such excipient. The term “about,” as used herein, is intended to qualify the numerical values which it modifies, denoting such a value as variable within a margin of
30 error. When no particular margin of error, such as a standard deviation to a mean value given in a chart or table of data, is recited, the term “about” should be understood to mean that range which would encompass $\pm 10\%$, preferably $\pm 5\%$, the recited value and the range is included.

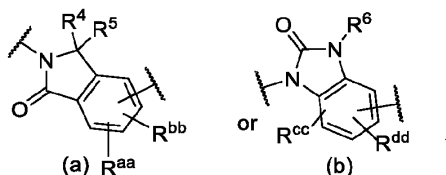
Certain structures provided herein are drawn with one or more floating substituents. Unless provided otherwise or otherwise clear from the context, the substituent(s) may be present on any

atom of the ring to which it is attached, where chemically feasible and valency rules permitting. For



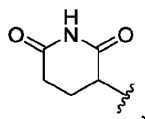
example, in the structure: (a) R^{aa}, the R^{aa} substituent, and similarly the R^{bb} substituent, can replace hydrogen of any CH that is part of the benzo portion of the bicyclic ring that is not already substituted with R^{bb} (in the case of R^{aa}), and similarly with R^{aa} (in the case of R^{bb}).

- 5 Additionally, as used throughout the application, including in the embodiments, when a group is drawn out as divalent, the left bond of the divalent group is attached to the group which is to its left in the remainder of the molecule, and the right bond of the divalent group is attached to the group which is to its right in the remainder of the molecule. For example, in the following divalent groups:



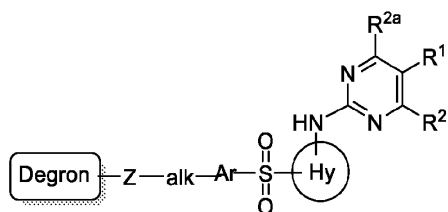
10

of E3 ubiquitin ligase ligand group of formula (i), the  bond on the left of (a) and (b) is attached to the following ring:

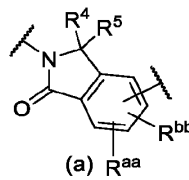
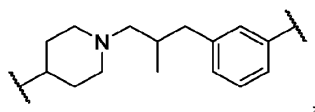


and the  on the right side of (a) and (b) is attached to Z of the Formula (I) structure:

15



Similarly, for -Z-alk-Ar-, the bond on left side (i.e., Z) is attached to the group on its left side i.e., ring A of formula (i) or ring B of formula (ii) and the bond on right side (i.e., Ar is attached to -SO₂- that is attached to an atom of Hy. For example, when -Z-alk-Ar- a group of formula:



and ring A of Degron of formula (i) is a group of formula (a) R^{aa} , the --- bond of

piperidinyl is attached to benzo portion of ring (a) and the --- bond of phenyl is attached to $\text{---SO}_2\text{---}$ that is attached to Hy.

5 The term “disease” as used herein is intended to be generally synonymous, and is used interchangeably with, the terms “disorder,” “syndrome,” and “condition” (as in medical condition), in that all reflect an abnormal condition of the human or animal body or of one of its parts that impairs normal functioning, is typically manifested by distinguishing signs and symptoms, and causes the human or animal to have a reduced duration or quality of life.

10 The term “combination therapy” means the administration of two or more therapeutic agents to treat a disease or disorder described in the present disclosure. Such administration encompasses co-administration of these therapeutic agents in a substantially simultaneous manner, such as in a single capsule having a fixed ratio of active ingredients or in multiple, separate capsules for each active ingredient. In addition, such administration also encompasses use of each type of therapeutic agent in a sequential manner. In either case, the treatment regimen will provide beneficial effects of the drug combination in treating the conditions or disorders described herein.

15 The term “patient” is generally synonymous with the term “subject” and includes all mammals including humans. Examples of patients include humans, livestock such as cows, goats, sheep, pigs, and rabbits, and companion animals such as dogs, cats, rabbits, and horses. Preferably, the patient is a human.

20 “Treating” or “treatment” of a disease includes:

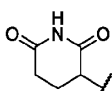
- (1) preventing the disease, *i.e.*, causing the clinical symptoms of the disease not to develop in a mammal that may be exposed to or predisposed to the disease but does not yet experience or display symptoms of the disease;
- 25 (2) inhibiting the disease, *i.e.*, delaying, arresting (stabilizing), or reducing the development or severity of the disease or its clinical symptoms; or
- (3) relieving the disease, *i.e.*, causing regression of the disease or its clinical symptoms.

In one embodiment, treating or treatment of a disease includes inhibiting the disease, *i.e.*, delaying, arresting or reducing the development or severity of the disease or its clinical symptoms; or relieving the disease, *i.e.*, causing regression of the disease or its clinical symptoms.

A “therapeutically effective amount” means the amount of a compound of the present disclosure and/or a pharmaceutically acceptable salt thereof that, when administered to a patient for treating a disease, is sufficient to affect such treatment for the disease. The “therapeutically effective amount” will vary depending on the compound, the disease and its severity and the age, weight, etc., of the mammal to be treated.

A “condition associated with an autoimmune disease” means a condition that a patient with an autoimmune disease is susceptible to, *e.g.*, sepsis, or a condition that is caused by the autoimmune disease, *e.g.*, uveitis.

The compounds of Formula (IB) or (I) can also inhibit CDK2 and CDK4. The term “inhibiting” and “reducing,” or any variation of these terms in relation of CDK2 and CDK4, includes any measurable decrease or complete inhibition of enzymatic activity of CDK2 and CDK4, respectively, to achieve a desired result. For example, there may be a decrease of about, at most about, or at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 99%, or more, or any range derivable therein, reduction of CDK2 and CDK4 activities, compared to its normal activity. In some embodiments, the CDK2 and CDK4 activity is reduced by at least 40% in the presence of a compound disclosed herein in the Summary, Embodiments, and Compound Table 1 disclosed herein, as compared to an equivalent sample comprising CDK2 or CDK4, respectively, in the absence of said compound. The inhibitory activity of a compound of Formula (IB) or (I) can also be measured using Biological Example 1, by converting a compound of Formula (IB) or (I) to a corresponding compound of Formula (IB) or (I) that cannot be degraded by the ubiquitin proteasome pathway *e.g.*, by methylating the nitrogen atom

in  group of ligase ligand (i) or (ii) present in the compound of Formula (IB) or (I).

The term “degrading” and “degrade,” or any variation of these terms in relation of CDK2, CDK4, and CDK1, means any measurable decrease in the concentration of CDK2, CDK4, and CDK1, respectively, in a sample over time. For example, there may be a decrease of about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 99%, or more, or any range derivable therein, in CDK2 and CDK4 concentration in a sample containing CDK2 and CDK4, respectively and a compound disclosed herein in the Summary, Embodiments, and Compound Table 1 disclosed herein as compared to an equivalent sample

comprising CDK2 or CDK4, in the absence of said compound. The % degradation can be determined as described in Biological Example 2 below. In one embodiment, the decrease in the concentration of CDK2 and CDK4 is $\geq 20\%$. In one embodiment, the decrease in the concentration of CDK2 and CDK4 is $\geq 40\%$. In one embodiment, the decrease in the concentration of CDK2 and CDK4 is $\geq 50\%$. In one embodiment, the decrease in the concentration of CDK2 and CDK4 is $\geq 60\%$. In one embodiment, the decrease in the concentration of CDK2 and CDK4 is $\geq 70\%$. In one embodiment, the decrease in the concentration of CDK2 and CDK4 is $\geq 80\%$.

“E3 ubiquitin ligase” refers to a family of proteins that operate in conjunction with E1 ubiquitin-activating enzyme and E2 ubiquitin-conjugating enzyme, assist or directly catalyze the covalent ligation of ubiquitin to a lysine residue of a substrate protein. E3 ubiquitin ligases directly bind to substrate proteins and thus confer substrate specificity for the ubiquitination process. Ubiquitination can serve as a versatile signal mark for substrate proteins, which are targeted to degradation by proteasome or other regulations ranging from translocation to transcription. The cereblon (CRBN) and von Hippel-Lindau (VHL) proteins are substrate recognition subunits of two ubiquitously expressed and biologically important Cullin RING E3 ubiquitin ligase complexes. Cereblon forms an E3 ubiquitin ligase complex with damaged DNA binding protein 1 (DDB1), Cullin-4A (CUL4A), and regulator of cullins 1 (ROC1). VHL is part of the E3 ligase complex VCB, which also consists of elongins B and C, Cul2 and Rbx1.

Embodiments:

Embodiment A

In embodiments A1A to A207, the present disclosure includes:

A1A. In embodiment A1A, provided is a compound of Formula (IB), or a pharmaceutically acceptable salt thereof, as described in the second aspect of the Summary or a second embodiment thereof.

A1. In embodiment A1, provided is a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as described in the first embodiment of the second aspect of the Summary or a first embodiment thereof.

A2. In embodiment A2, the compound of embodiment A1A or A1, or a pharmaceutically acceptable salt thereof, is wherein R^1 is halo.

A3. In embodiment A3, the compound of embodiment A1A or A1, or a pharmaceutically acceptable salt thereof, is wherein R^1 is haloalkyl or haloalkoxy.

A4. In embodiment A4, the compound of embodiment A1A, A1, or A3, or a pharmaceutically acceptable salt thereof, is wherein R^1 is haloalkyl.

A5. In embodiment A5, the compound of embodiment A1A, A1, or A3, or a pharmaceutically acceptable salt thereof, is wherein R¹ is haloalkoxy.

A6. In embodiment A6, the compound of any one of embodiments A1A to A5, or a pharmaceutically acceptable salt thereof, is wherein R¹ is chloro, bromo, fluoro, difluoromethyl, trifluoromethyl, difluoroethyl, trifluoroethyl, difluoromethoxy, trifluoromethoxy, difluoroethoxy, or trifluoroethoxy unless stated otherwise.

A7. In embodiment A7, the compound of any one of embodiments A1A to A6, or a pharmaceutically acceptable salt thereof, is wherein R¹ is chloro, bromo, difluoromethyl, trifluoromethyl, difluoromethoxy, or trifluoromethoxy unless stated otherwise.

10 A8. In embodiment A8, the compound of any one of embodiments A1A, A1, A2, A6, and A7, or a pharmaceutically acceptable salt thereof, is wherein R¹ is chloro or bromo.

A9. In embodiment A9, the compound of any one of embodiments A1A, A1, A3, A4, A6, and A7, or a pharmaceutically acceptable salt thereof, is wherein R¹ is difluoromethyl or trifluoromethyl.

15 A10. In embodiment A10, the compound of any one of embodiments A1A, A1, A3, A4, A6, A7, and A9, or a pharmaceutically acceptable salt thereof, is wherein R¹ is trifluoromethyl.

A11. In embodiment A11, the compound of any one of embodiments A1A, A1, A3, and A5 to A7, or a pharmaceutically acceptable salt thereof, is wherein R¹ is difluoromethoxy or trifluoromethoxy.

20 A12. In embodiment A12, the compound of any one of embodiments A1A, A1, A3, A5 to A7, and A11, or a pharmaceutically acceptable salt thereof, is wherein R¹ is difluoromethoxy.

A13. In embodiment A13, the compound of embodiment A1A or A1, or a pharmaceutically acceptable salt thereof, is wherein R¹ is alkyl, alkenyl, or alkynyl.

A14. In embodiment A14, the compound of embodiment A1A, A1 or A13, or a pharmaceutically acceptable salt thereof, is wherein R¹ is methyl, ethyl, propyl, vinyl, propenyl, ethynyl, or propynyl.

A15. In embodiment A15, the compound of embodiment A1A, A1, A13, or A14, or a pharmaceutically acceptable salt thereof, is wherein R¹ is methyl, ethyl, or propyl.

30 A16. In embodiment A16, the compound of embodiment A1A, A1, A13, or A14, or a pharmaceutically acceptable salt thereof, is wherein R¹ is vinyl, propenyl, ethynyl, or propynyl.

A17. In embodiment A17, the compound of embodiment A1A or A1, or a pharmaceutically acceptable salt thereof, is wherein R¹ is alkoxy.

A18. In embodiment A18, the compound of embodiment A1A, A1, or A17, or a pharmaceutically acceptable salt thereof, is wherein R¹ is methoxy, ethoxy, or propoxy.

A19. In embodiment A19, the compound of embodiment A1A or A1, or a pharmaceutically acceptable salt thereof, is wherein R^1 is aryloxy, preferably phenoxy.

A20. In embodiment A20, the compound of embodiment A1A or A1, or a pharmaceutically acceptable salt thereof, is wherein R^1 is cyano.

5 A21. In embodiment A21, the compound of embodiment A1A or A1, or a pharmaceutically acceptable salt thereof, is wherein R^1 is cycloalkyl, preferably cyclopropyl.

A22. In embodiment A22, the compound of embodiment A1A or A1, or a pharmaceutically acceptable salt thereof, is wherein R^1 is cycloalkyl substituted with one to three halo, preferably fluorocyclopropyl or difluorocyclopropyl.

10 A22a. In embodiment A22a, the compound of embodiment A1A or A1, or a pharmaceutically acceptable salt thereof, is wherein R^1 is cycloalkyloxy, preferably cyclopropyloxy.

A22b. In embodiment A22b, the compound of embodiment A1A or A1, or a pharmaceutically acceptable salt thereof, is wherein R^1 is cycloalkyloxy substituted with one to three halo, preferably fluorocyclopropyloxy or difluorocyclopropyloxy.

15 A23. In embodiment A23, the compound of any one of embodiments A1A to A22b, or a pharmaceutically acceptable salt thereof, is wherein R^2 and R^{2a} are hydrogen.

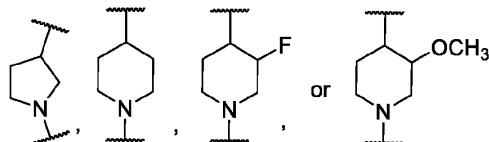
A24. In embodiment A24, the compound of any one of embodiments A1A to A22b, or a pharmaceutically acceptable salt thereof, is wherein one of R^2 and R^{2a} is deuterium and the other of R^2 and R^{2a} is hydrogen or both R^2 and R^{2a} are deuterium.

20 A25. In embodiment A25, the compound of any one of embodiments A1A to A24, or a pharmaceutically acceptable salt thereof, is wherein Hy is heterocyclylene, phenylene, spiro heterocyclylene, bridged heterocyclylene, or cycloalkylene, wherein each of the aforementioned rings is substituted with R^a , R^b , and R^c where R^a and R^b are independently selected from hydrogen, deuterium, alkyl, halo, haloalkyl, alkoxy, hydroxy, and cyano, and R^c is hydrogen.

25 A26. In embodiment A26, the compound of any one of embodiments A1A to A25, or a pharmaceutically acceptable salt thereof, is wherein Hy is heterocyclylene substituted with R^a , R^b , and R^c where R^a and R^b are independently selected from hydrogen, deuterium, alkyl, halo, haloalkyl, alkoxy, hydroxy, and cyano, and R^c is hydrogen.

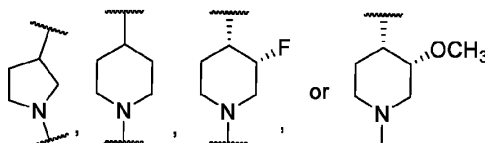
30 A27. In embodiment A27, the compound of any one of embodiments A1A to A26, or a pharmaceutically acceptable salt thereof, is wherein the heterocyclylene of Hy is pyrrolidin-1,3-diyl, or piperidin-1,4-diyl, each ring being substituted with R^a , R^b , and R^c where R^a and R^b are independently hydrogen, deuterium, methyl, fluoro, methoxy, or hydroxy, R^c is hydrogen, and $-SO_2-$ is attached to the nitrogen atom of the piperidin-1,4-diyl or pyrrolidin-1,3-diyl ring of Hy.

A28. In embodiment A28, the compound of any one of embodiments A1A to A27, or a pharmaceutically acceptable salt thereof, is wherein the heterocyclylene of Hy is:



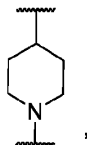
where the N atom of the pyrrolidin-1,3-diyl or piperidin-1,4-diyl rings is attached to -SO₂-

5 A29. In embodiment A29, the compound of any one of embodiments A1A to A28, or a pharmaceutically acceptable salt thereof, is wherein the heterocyclylene of Hy is:



where the N atom of the pyrrolidin-1,3-diyl or piperidin-1,4-diyl rings is attached to -SO₂-.

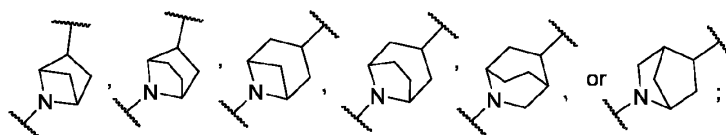
10 A29a. In embodiment A29a, the compound of any one of embodiments A1A to A29, or a pharmaceutically acceptable salt thereof, is wherein the heterocyclylene of Hy is:



where the N atom of the piperidin-1,4-diyl ring is attached to -SO₂-.

A30. In embodiment A30, the compound of any one of embodiments A1A to A25, or a pharmaceutically acceptable salt thereof, is wherein Hy is bridged heterocyclylene substituted with
15 R^a, R^b, and R^c where R^c is hydrogen.

A31. In embodiment A31, the compound of any one of embodiments A1A to A25 and A30, or a pharmaceutically acceptable salt thereof, is wherein the bridged heterocyclylene of Hy is a ring of formula:



20 where each ring is substituted with R^a, R^b, and R^c where R^c is hydrogen, and the nitrogen atom of each ring is attached to -SO₂-.

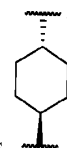
A32. In embodiment A32, the compound of embodiment A30 or A31, or a pharmaceutically acceptable salt thereof, is wherein R^a and R^b are independently hydrogen, deuterium, methyl, fluoro, methoxy, or hydroxy.

A33. In embodiment A33, the compound of embodiment A30, A31 or A32, or a pharmaceutically acceptable salt thereof, is wherein R^b is hydrogen.

A34. In embodiment A34, the compound of any one of embodiments A1A to A25, or a pharmaceutically acceptable salt thereof, is wherein Hy is cycloalkylene substituted with R^a , R^b , and R^c where R^a is deuterium, methyl, fluoro, methoxy, or hydroxy and R^b and R^c are hydrogen.

A35. In embodiment A35, the compound of any one of embodiments A1A to A25 and A34, or a pharmaceutically acceptable salt thereof, is wherein the cycloalkylene of Hy is cyclohexylene.

A36. In embodiment A36, the compound of any one of embodiments A1A to A25, A34,



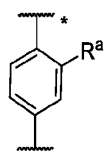
and A35, or a pharmaceutically acceptable salt thereof, is wherein the cycloalkylene of Hy is

where  denotes bond to NH and  denotes bond of $-SO_2-$.

A37. In embodiment A37, the compound of any one of embodiments A1A to A25, or a pharmaceutically acceptable salt thereof, is wherein Hy is arylene wherein the arylene is phenylene substituted with R^a , R^b , and R^c where R^a and R^b are independently selected from hydrogen, deuterium, alkyl, halo, haloalkyl, alkoxy, hydroxy, and cyano, and R^c is hydrogen.

A38. In embodiment A38, the compound of any one of embodiments A1A to A25, or a pharmaceutically acceptable salt thereof, is wherein Hy is spiro heterocyclylene (preferably, 2-azaspiro[3.3]heptan-2-yl) substituted with R^a , R^b , and R^c where R^a and R^b are independently selected from hydrogen, deuterium, alkyl, halo, haloalkyl, alkoxy, hydroxy, and cyano, and R^c is hydrogen.

A39. In embodiment A39, the compound of embodiment A37, or a pharmaceutically acceptable salt thereof, is wherein the phenylene of Hy is 1,4-phenylene according to structure

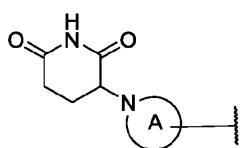


where  denotes bond to NH and  denotes bond to $-SO_2-$ where R^a is hydrogen, fluoro, methyl or methoxy and R^b is hydrogen.

A39a. In embodiment A39a, the compound of any one of embodiments A1A to A24, or a pharmaceutically acceptable salt thereof, is wherein Hy is fused heterocyclylene substituted with R^a , R^b , and R^c where R^a and R^b are independently selected from hydrogen, deuterium, alkyl, halo, haloalkyl, alkoxy, hydroxy, and cyano, and R^c is hydrogen.

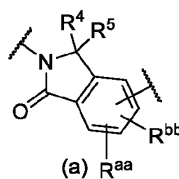
A39b. In embodiment A39b, the compound of any one of embodiments A1A to A24, or a pharmaceutically acceptable salt thereof, is wherein Hy is bicyclic heterocyclylene substituted with R^a , R^b , and R^c where R^a and R^b are independently selected from hydrogen, deuterium, alkyl, halo, haloalkyl, alkoxy, hydroxy, and cyano, and R^c is hydrogen.

- 5 A40. In embodiment A40, the compound of any one of embodiments A1A to A39b, or a pharmaceutically acceptable salt thereof, is wherein the Degron is an E3 ubiquitin ligase ligand of formula (i):



(i).

- 10 A41. In embodiment A41, the compound of any one of embodiments A1A to A40, or a pharmaceutically acceptable salt thereof, is wherein the ring A of the E3 ubiquitin ligase ligand of formula (i) is a group of formula (a):



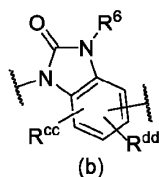
- 15 A42. In embodiment A42, the compound of any one of embodiments A1A to A41, or a pharmaceutically acceptable salt thereof, is wherein R^4 and R^5 are independently hydrogen or alkyl.

A43. In embodiment A43, the compound of any one of embodiments A1A to A42, or a pharmaceutically acceptable salt thereof, is wherein R^4 and R^5 are hydrogen.

A44. In embodiment A44, the compound of any one of embodiments A1A to 42, or a pharmaceutically acceptable salt thereof, is wherein R^4 is hydrogen and R^5 is methyl.

- 20 A45. In embodiment A45, the compound of any one of embodiments A1A to A41, or a pharmaceutically acceptable salt thereof, is wherein R^4 and R^5 together with the carbon to which they are attached form $>C=O$.

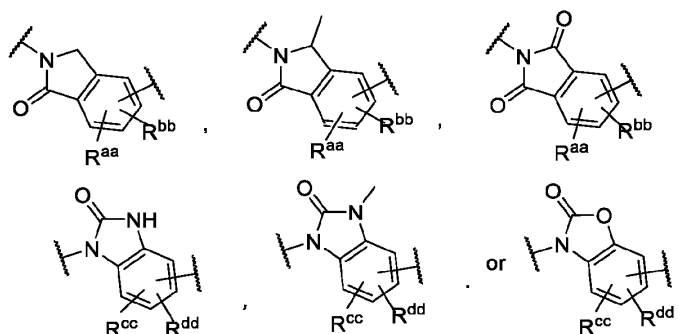
- 25 A46. In embodiment A46, the compound of any one of embodiments A1A to A40, or a pharmaceutically acceptable salt thereof, is wherein the ring A of the E3 ubiquitin ligase ligand of formula (i) is a group of formula (b):



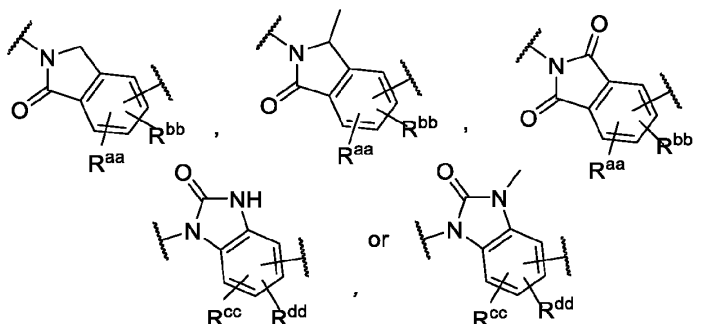
A47. In embodiment A47, the compound of any one of embodiments A1A to A40 and A46, or a pharmaceutically acceptable salt thereof, is wherein R⁶ is hydrogen.

A48. In embodiment A48, the compound of any one of embodiments A1A to A40 and A46, or a pharmaceutically acceptable salt thereof, wherein R⁶ is alkyl, preferably methyl.

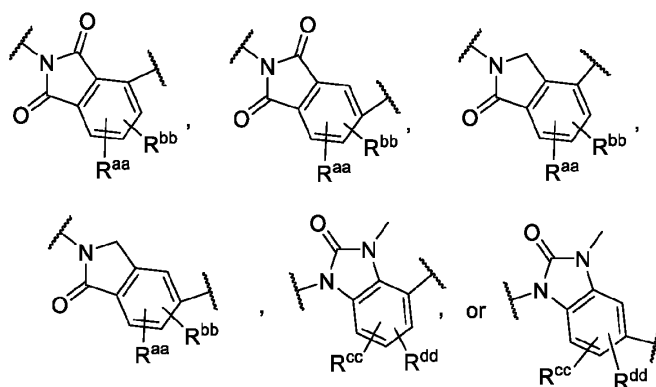
A49. In embodiment A49, the compound of any one of embodiments A1A to A48, or a pharmaceutically acceptable salt thereof, is wherein the ring A of the E3 ubiquitin ligase ligand of formula (i) is:



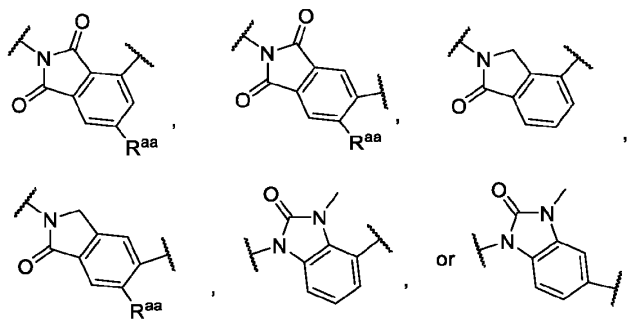
A50. In embodiment A50, the compound of any one of embodiments A1A to A49, or a pharmaceutically acceptable salt thereof, is wherein the ring A of the E3 ubiquitin ligase ligand of formula (i) is:



A51. In embodiment A51, the compound of any one of embodiments A1A to A50, or a pharmaceutically acceptable salt thereof, is wherein ring A of the E3 ubiquitin ligase ligand of formula (i) is:

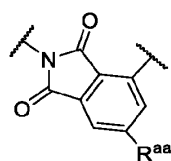


A52. In embodiment A52, the compound of any one of embodiments A1A to A51, or a pharmaceutically acceptable salt thereof, is wherein ring A of the E3 ubiquitin ligase ligand of
 5 formula (i) is:



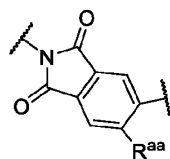
i.e., where R^{bb} , R^{cc} , and R^{dd} are hydrogen.

A52a. In embodiment A52a, the compound of any one of embodiments A1A to A52, or a pharmaceutically acceptable salt thereof, is wherein ring A of the E3 ubiquitin ligase ligand of
 10 formula (i) is:



i.e., where R^{bb} is hydrogen.

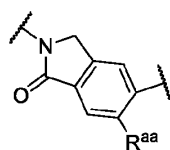
A53. In embodiment A53, the compound of any one of embodiments A1A to A52, or a pharmaceutically acceptable salt thereof, is wherein ring A of the E3 ubiquitin ligase ligand of
 15 formula (i) is:



i.e., where R^{bb} is hydrogen.

A54. In embodiment A54, the compound of any one of embodiments A1A to A52, or a pharmaceutically acceptable salt thereof, is wherein ring A of the E3 ubiquitin ligase ligand of

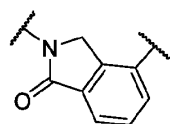
5 formula (i) is:



i.e., where R^{bb} is hydrogen.

A55. In embodiment A55, the compound of any one of embodiments A1A to A52, or a pharmaceutically acceptable salt thereof, is wherein ring A of the E3 ubiquitin ligase ligand of

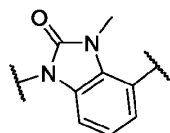
10 formula (i) is:



i.e., where R^{aa} and R^{bb} is hydrogen.

A56. In embodiment A56, the compound of any one of embodiments A1A to A52, or a pharmaceutically acceptable salt thereof, is wherein ring A of the E3 ubiquitin ligase ligand of

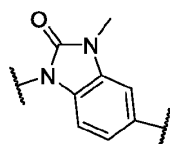
15 formula (i) is:



i.e., where R^{cc} , and R^{dd} are hydrogen.

A57. In embodiment A57, the compound of any one of embodiments A1A to A52, or a pharmaceutically acceptable salt thereof, is wherein ring A of the E3 ubiquitin ligase ligand of

20 formula (i) is:



i.e., where R^{cc} , and R^{dd} are hydrogen.

A58. In embodiment A58, the compound of any one of embodiments A1A to A54, or a pharmaceutically acceptable salt thereof, is wherein R^{aa} , R^{bb} , R^{cc} , and R^{dd} are independently selected from hydrogen, alkyl, alkoxy, halo, haloalkyl, and haloalkoxy, unless stated otherwise i.e., in embodiments A52 to A54, R^{bb} , R^{cc} , and R^{dd} are hydrogen.

5 A59. In embodiment A59, the compound of any one of embodiments A1A to A54, or a pharmaceutically acceptable salt thereof, is wherein R^{aa} , R^{bb} , R^{cc} , and R^{dd} are independently selected from hydrogen, alkyl, alkoxy, halo, haloalkyl, and cyano, unless stated otherwise.

A60. In embodiment A60, the compound of any one of embodiments A1A to A54, A58, and A59, or a pharmaceutically acceptable salt thereof, is wherein R^{aa} , R^{bb} , R^{cc} , and R^{dd} are
10 independently selected from hydrogen, methyl, methoxy, ethoxy, fluoro, trifluoromethyl, difluoromethyl, and trifluoromethoxy, unless stated otherwise.

A61. In embodiment A61, the compound of any one of embodiments A1A to A54, and A58 to A60, or a pharmaceutically acceptable salt thereof, is wherein R^{aa} , R^{bb} , R^{cc} , and R^{dd} are
independently selected from hydrogen and methyl, unless stated otherwise.

15 A62. In embodiment A62, the compound of any one of embodiments A1A to A54, and A58 to A60, or a pharmaceutically acceptable salt thereof, is wherein R^{aa} , R^{bb} , R^{cc} , and R^{dd} are independently selected from hydrogen and methoxy, unless stated otherwise.

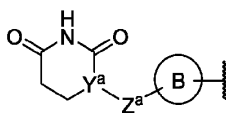
A63. In embodiment A63, the compound of any one of embodiments A1A to A54, and A58 to A60, or a pharmaceutically acceptable salt thereof, is wherein R^{aa} , R^{bb} , R^{cc} , and R^{dd} are
20 independently selected from hydrogen and fluoro, unless stated otherwise.

A64. In embodiment A64, the compound of any one of embodiments A1A to A54, and A58 to A60, or a pharmaceutically acceptable salt thereof, is wherein R^{aa} , R^{bb} , R^{cc} , and R^{dd} are independently selected from hydrogen, trifluoromethyl, and difluoromethyl, unless stated otherwise.

A65. In embodiment A65, the compound of any one of embodiments A1A to A54, A58, and A60, or a pharmaceutically acceptable salt thereof, is wherein R^{aa} , R^{bb} , R^{cc} , and R^{dd} are
25 independently selected from hydrogen and trifluoromethoxy, unless stated otherwise.

A66. In embodiment A66, the compound of any one of embodiments A1A to A54, and A58 to A60, or a pharmaceutically acceptable salt thereof, is wherein R^{aa} , R^{bb} , R^{cc} , and R^{dd} are independently selected from hydrogen, fluoro, and trifluoromethyl, unless stated otherwise.

A67. In embodiment A67, the compound of any one of embodiments A1A to A39b, or a pharmaceutically acceptable salt thereof, is wherein the Degron is an E3 ubiquitin ligase ligand of formula (ii):



(ii).

A68. In embodiment A68, the compound of any one of embodiments A1A to A39b and A41 to A67, or a pharmaceutically acceptable salt thereof, is wherein Y^a is CH.

A69. In embodiment A69, the compound of any one of embodiments A1A to A39b and A41 to A67, or a pharmaceutically acceptable salt thereof, is wherein Y^a is N.

A70. In embodiment A70, the compound of any one of embodiments A1A to A39b and A41 to A69, or a pharmaceutically acceptable salt thereof, is wherein Z^a is a bond, -NH-, -O-, or -NHC(O)-.

A71. In embodiment A71, the compound of any one of embodiments A1A to A39b and A41 to A70, or a pharmaceutically acceptable salt thereof, is wherein Z^a is a bond, -NH-, or -NHC(O)-.

A72. In embodiment A72, the compound of any one of embodiments A1A to A39b and A41 to A71, or a pharmaceutically acceptable salt thereof, is wherein Z^a is a bond.

A73. In embodiment A73, the compound of any one of embodiments A1A to A39b and A41 to A71, or a pharmaceutically acceptable salt thereof, is wherein Z^a is -NH-, or -NHC(O)-.

A74. In embodiment A74, the compound of any one of embodiments A1A to A39b, A41 to A71, and A73, or a pharmaceutically acceptable salt thereof, is wherein Z^a is -NH-.

A74a. In embodiment A74a, the compound of any one of embodiments A1A to A39b, A41 to A71, and A73, or a pharmaceutically acceptable salt thereof, is wherein Z^a is -NHC(O)-.

A75. In embodiment A75, the compound of any one of embodiments A1A to A39b and A41 to A74a, or a pharmaceutically acceptable salt thereof, is wherein ring B is phenylene substituted with R^{ee} and R^{ff} .

A76. In embodiment A76, the compound of any one of embodiments A1A to A39b, and A41 to A74a, or a pharmaceutically acceptable salt thereof, is wherein ring B is cyclylaminylene substituted with R^{ee} and R^{ff} .

A77. In embodiment A77, the compound of any one of embodiments A1A to A39b and A41 to A74a, or a pharmaceutically acceptable salt thereof, is wherein ring B is 5- or 6-membered monocyclic heteroarylene or a 9- or 10-membered fused bicyclic heteroarylene, wherein each

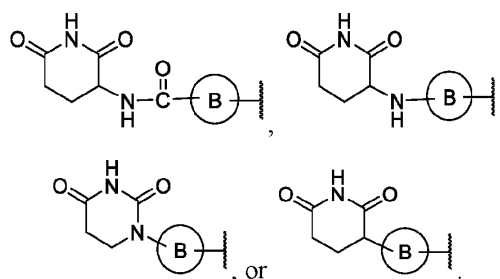
heteroarylene ring contains one to three nitrogen ring atoms and each ring is substituted with R^{ee} and R^{ff} .

A78. In embodiment A78, the compound of any one of embodiments A1A to A39b, A41 to A74a, and A77, or a pharmaceutically acceptable salt thereof, is wherein ring B is 5- or 6-membered monocyclic heteroarylene containing one or two nitrogen ring atoms substituted with R^{ee} and R^{ff} .

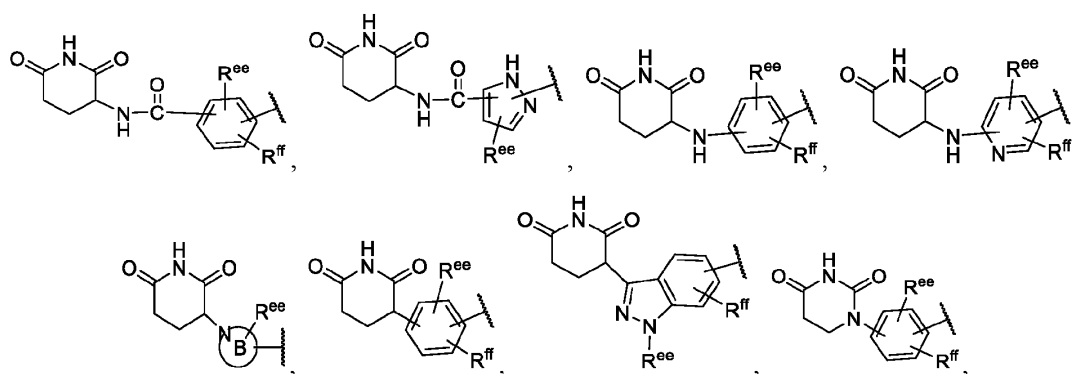
A79. In embodiment A79, the compound of any one of embodiments A1A to A39b, A41 to A74a, and A77, or a pharmaceutically acceptable salt thereof, is wherein ring B is a 9- or 10-membered fused bicyclic heteroarylene containing one to three nitrogen ring atoms and substituted with R^{ee} and R^{ff} .

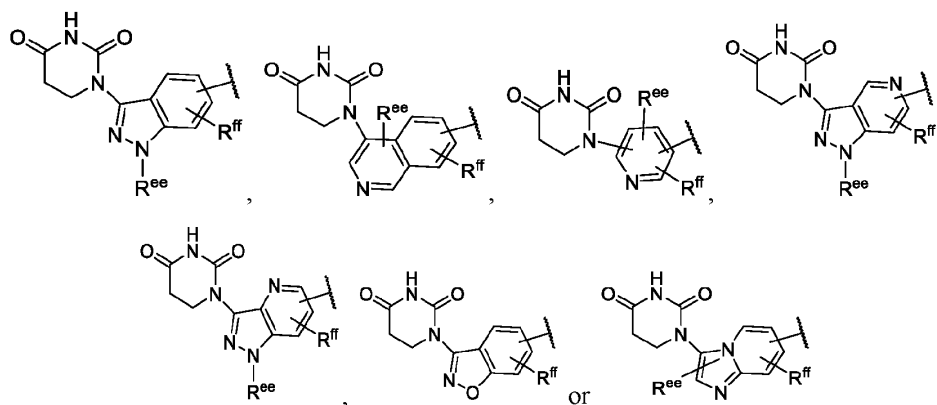
A80. In embodiment A80, the compound of any one of embodiments A1A to A39b, A41 to A74a, A77, and A79, or a pharmaceutically acceptable salt thereof, is wherein ring B is a 9- or 10-membered fused bicyclic heteroarylene containing one or two nitrogen ring atoms and substituted with R^{ee} and R^{ff} .

A81. In embodiment A81, the compound of any one of embodiments A1A to A39b and A41 to A80, or a pharmaceutically acceptable salt thereof, is wherein the E3 ubiquitin ligase ligand of formula (ii) is:



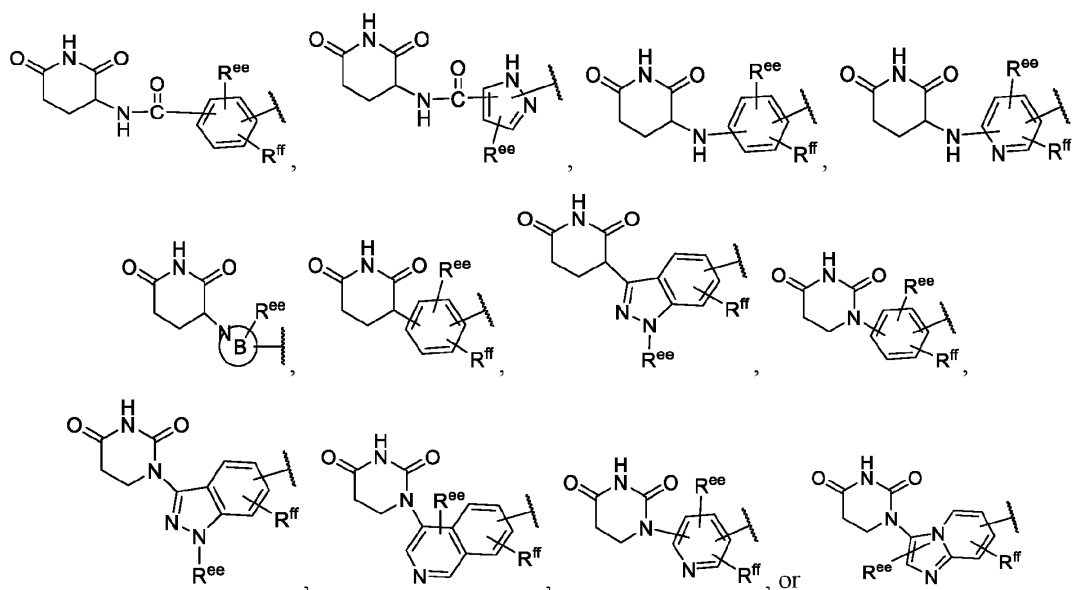
A82-1. In embodiment A82-1, the compound of any one of embodiments A1A to A39b and A41 to A81, or a pharmaceutically acceptable salt thereof, is wherein the E3 ubiquitin ligase ligand of formula (ii) is:





where ring B is cyclolaminylene. For sake of clarity, it is to be understood that R^{ee} and/or R^{ff} are/is hydrogen when they are/is not drawn out in a structure.

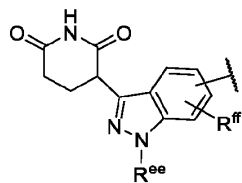
- 5 A82. In embodiment A82, the compound of any one of embodiments A1A to A39b and A41 to A82-1, or a pharmaceutically acceptable salt thereof, is wherein the E3 ubiquitin ligase ligand of formula (ii) is:



10

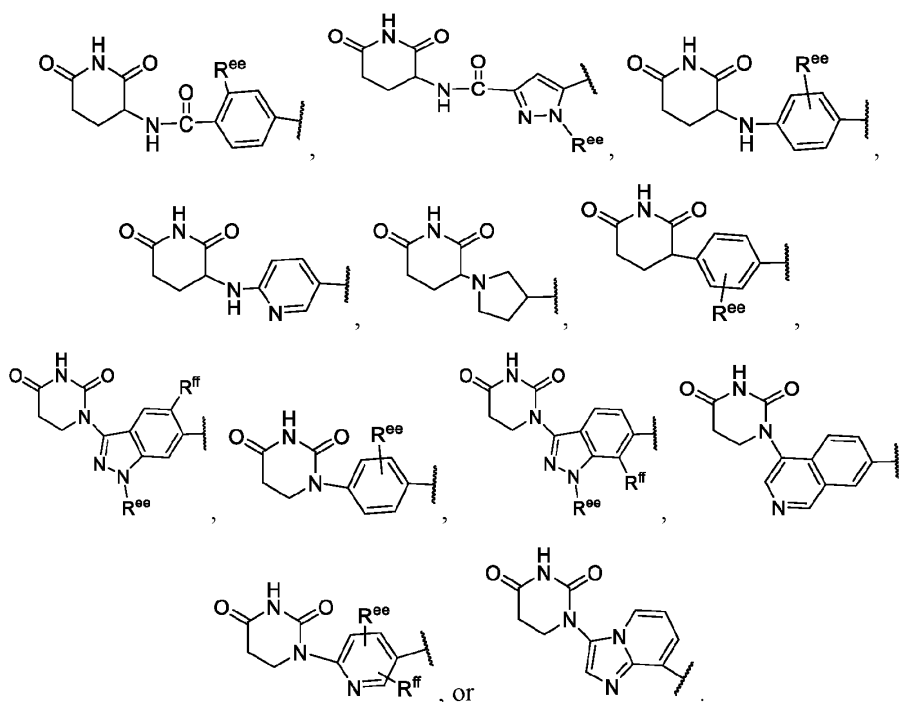
where ring B is cyclolaminylene.

A82A. In embodiment A82A, the compound of any one of embodiments A1A to A39b and A41 to A82, or a pharmaceutically acceptable salt thereof, is wherein the E3 ubiquitin ligase ligand



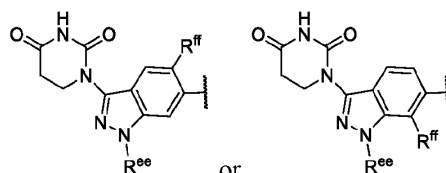
of formula (ii) is

A83. In embodiment A83, the compound of any one of embodiments A1A to A39b and A41 to A82, or a pharmaceutically acceptable salt thereof, is wherein the E3 ubiquitin ligase ligand of formula (ii) is:



10

A83A. In embodiment A83A, the compound of any one of embodiments A1A to A39b and A41 to A82, and A83, or a pharmaceutically acceptable salt thereof, is wherein the E3 ubiquitin



ligase ligand of formula (ii) is

or

15

A84. In embodiment A84, the compound of any one of embodiments A1A to A39b and A41 to A83A, or a pharmaceutically acceptable salt thereof, is wherein each R^{ee} and R^{ff} are

independently selected from hydrogen, alkyl, alkoxy, halo, cyano, haloalkyl, and haloalkoxy unless stated otherwise.

A85. In embodiment A85, the compound of any one of embodiments A1A to A39b and A41 to A84, or a pharmaceutically acceptable salt thereof, is wherein R^{ee} and R^{ff} are independently
5 selected from hydrogen, alkyl, cycloalkyl, alkoxy, halo, haloalkyl, and cyano unless stated otherwise.

A86. In embodiment A86, the compound of any one of embodiments A1A to A39b and A41 to A85, or a pharmaceutically acceptable salt thereof, is wherein R^{ee} and R^{ff} are independently
10 selected from hydrogen, methyl, ethyl, isopropyl, cyclopropyl, methoxy, ethoxy, fluoro, chloro, trifluoromethyl, 2,2,2-trifluoroethyl, difluoromethyl, difluoromethoxy, trifluoromethoxy, and cyano unless stated otherwise.

A87. In embodiment A87, the compound of any one of embodiments A1A to A39b and A41 to A86, or a pharmaceutically acceptable salt thereof, is wherein R^{ee} and R^{ff} are independently
selected from hydrogen, methyl, ethyl, and isopropyl unless stated otherwise.

A88. In embodiment A88, the compound of any one of embodiments A1A to A39b and
15 A41 to A86, or a pharmaceutically acceptable salt thereof, is wherein R^{ee} and R^{ff} are independently selected from hydrogen and methoxy unless stated otherwise.

A89. In embodiment A89, the compound of any one of embodiments A1A to A39b and A41 to A86, or a pharmaceutically acceptable salt thereof, is wherein R^{ee} and R^{ff} are independently
selected from hydrogen, methyl, ethyl, isopropyl, chloro, and fluoro unless stated otherwise.

20 A90. In embodiment A90, the compound of any one of embodiments A1A to A39b, A41 to A86, or a pharmaceutically acceptable salt thereof, is wherein one of R^{ee} and R^{ff} is hydrogen or fluoro and the other of R^{ee} and R^{ff} is selected from hydrogen, trifluoromethyl, 2,2,2-trifluoroethyl, and difluoromethyl unless stated otherwise.

A91. In embodiment A91, the compound of any one of embodiments A1A to A39b and
25 A41 to A86, or a pharmaceutically acceptable salt thereof, is wherein R^{ee} and R^{ff} are independently selected from hydrogen, difluoromethoxy, and trifluoromethoxy unless stated otherwise.

A92. In embodiment A92, the compound of any one of embodiments A1A to A39b and A41 to A86, or a pharmaceutically acceptable salt thereof, is wherein R^{ee} and R^{ff} are independently
selected from hydrogen, chloro, fluoro, and trifluoromethyl unless stated otherwise.

30 A93. In embodiment A93, the compound of any one of embodiments A1A to A39b and A41 to A86, or a pharmaceutically acceptable salt thereof, is wherein R^{ee} and R^{ff} are hydrogen.

A94. In embodiment A94, the compound of any one of embodiments A1A to A39b and A41 to A86, or a pharmaceutically acceptable salt thereof, is wherein R^{ee} and R^{ff} are chloro unless
stated otherwise.

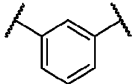
A95. In embodiment A95, the compound of any one of embodiments A1A to A39b and A41 to A86, or a pharmaceutically acceptable salt thereof, is wherein R^{ee} and R^{ff} are fluoro unless stated otherwise.

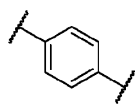
A96. In embodiment A96, the compound of any one of embodiments A1A to A39b and A41 to A86, or a pharmaceutically acceptable salt thereof, is wherein R^{ee} and R^{ff} are independently trifluoromethyl or 2,2,2-trifluoroethyl unless stated otherwise.

A97a. In embodiment A97a, the compound of any one of embodiments A1A and A2 to A96, or a pharmaceutically acceptable salt thereof, is wherein Ar is phenylene, monocyclic heteroarylene, bridged heterocyclylene, heterocyclylene, or unsaturated heterocyclylene^x, where each ring is substituted with R^j , R^k , and R^m where R^m is hydrogen.

A97. In embodiment A97, the compound of any one of embodiments A1A to A97a, or a pharmaceutically acceptable salt thereof, is wherein Ar is phenylene, monocyclic heteroarylene, bridged heterocyclylene, or heterocyclylene, where each ring is substituted with R^j , R^k , and R^m where R^m is hydrogen.

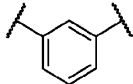
A98. In embodiment A98, the compound of any one of embodiments A1A to A97, or a

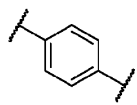
pharmaceutically acceptable salt thereof, is wherein -Ar- is phenylene of formula  or



(i.e., Ar is phenylene where alk and SO₂ are attached at meta position or para position of the phenylene ring) substituted with R^j , R^k , and R^m where R^j and R^k are independently selected from hydrogen, alkyl, alkoxy, halo, cyano, haloalkyl, and haloalkoxy and R^m is hydrogen.

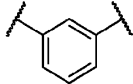
A99. In embodiment A99, the compound of any one of embodiments A1A to A98, or a

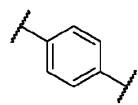
pharmaceutically acceptable salt thereof, is wherein the phenylene of -Ar- is  or



substituted with R^j , R^k , and R^m where R^j and R^k are independently selected from hydrogen, deuterium, methyl, methoxy, fluoro, chloro, cyano, difluoromethyl, trifluoromethyl, difluoromethoxy, and trifluoromethoxy and R^m is hydrogen.

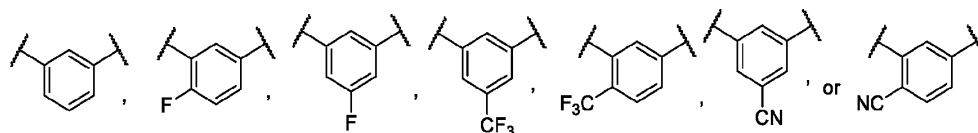
A100. In embodiment A100, the compound of any one of embodiments A1A to A99, or a

pharmaceutically acceptable salt thereof, is wherein the phenylene of -Ar- is  or



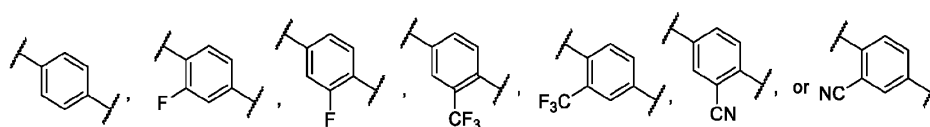
substituted with R^j , R^k , and R^m where R^j and R^k independently selected from hydrogen, fluoro, cyano, or trifluoromethyl and R^m is hydrogen.

A101-1. In embodiment A101-1, the compound of any one of embodiments A1A to A100, or a pharmaceutically acceptable salt thereof, is wherein the phenylene of -Ar- is



5

A101. In embodiment A101, the compound of any one of embodiments A1A to A100, or a pharmaceutically acceptable salt thereof, is wherein the phenylene of -Ar- is



A102. In embodiment A102, the compound of any one of embodiments A1A to A97, or a pharmaceutically acceptable salt thereof, is wherein -Ar- is monocyclic heteroarylene (such as imidazol-1,5-diyl, pyridin-2,4-diyl, pyridin-2,6-diyl, pyridin-2,5-diyl, or pyridin-3,5-diyl) substituted with R^j , R^k , and R^m where R^j and R^k are independently selected from hydrogen, alkyl, alkoxy, halo, haloalkyl, cyano, and haloalkoxy and R^m is hydrogen.

A103. In embodiment A103, the compound of any one of embodiments A1A to A97, and A99 to A102, or a pharmaceutically acceptable salt thereof, is wherein the monocyclic heteroarylene of -Ar- is imidazol-2,5-diyl, pyridin-2,4-diyl, pyridin-2,6-diyl, pyridin-2,5-diyl, or pyridin-3,5-diyl, each ring substituted with R^j , R^k , and R^m where R^j and R^k are independently selected from hydrogen, methyl, methoxy, fluoro, chloro, difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, difluoromethoxy, and trifluoromethoxy and R^m is hydrogen.

A104. In embodiment A104, the compound of any one of embodiments A1A to A97 and A99 to A103, or a pharmaceutically acceptable salt thereof, is wherein the monocyclic heteroarylene of -Ar- is imidazol-2,5-diyl, pyridin-2,4-diyl, pyridin-2,6-diyl, or pyridin-3,5-diyl, each ring substituted with R^j , R^k , and R^m where R^j and R^k are independently selected from hydrogen, methyl, methoxy, fluoro, chloro, difluoromethyl, trifluoromethyl, difluoromethoxy, and trifluoromethoxy and R^m is hydrogen.

A105. In embodiment A105, the compound of any one of embodiments A1A to A97, or a pharmaceutically acceptable salt thereof, is wherein -Ar- is heterocyclylene substituted with R^j , R^k , and R^m where R^j and R^k are independently selected from hydrogen, methyl, methoxy, fluoro, chloro,

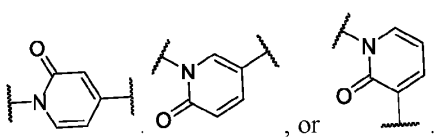
difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, difluoromethoxy, and trifluoromethoxy and R^m is hydrogen.

A106. In embodiment A106, the compound of any one of embodiments A1A to A97, A99 to A101, and A103 to A105, or a pharmaceutically acceptable salt thereof, is wherein the

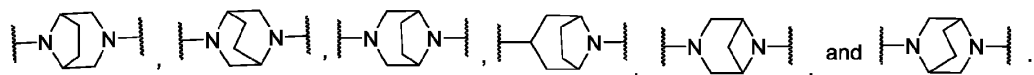
5 heterocyclylene of -Ar- is divalent azetidiny, pyrrolidinyl, piperazinyl, or piperidinyl. A107. In embodiment A107, the compound of any one of embodiments A1A to A97, or a pharmaceutically acceptable salt thereof, is wherein -Ar- is bridged heterocyclylene.

10 A108a. In embodiment A108a, the compound of any one of embodiments A1A and A2 to A97a, or a pharmaceutically acceptable salt thereof, is wherein Ar is unsaturated heterocyclylene^x substituted with R^j , R^k , and R^m where R^m is hydrogen.

A108b. In embodiment A108b, the compound of any one of embodiments A1A and A2 to A97a, A99 to A101, A103, A104, A106, and 108a, or a pharmaceutically acceptable salt thereof, is

wherein the unsaturated heterocyclylene^x is , or

15 A108. In embodiment A108, the compound of any one of embodiments A1A to A97, A99 to A101, A103, A104, A106, and A107 or a pharmaceutically acceptable salt thereof, is wherein the bridged heterocyclylene of -Ar- is selected from:



20 A109. In embodiment A109, the compound of any one of embodiments A1A to A108, or a pharmaceutically acceptable salt thereof, is wherein Z is cycloalkylene selected from cyclopropylene, cyclobutylene, cyclopentylene, and cyclohexylene and substituted as defined therein.

A110. In embodiment A110, the compound of any one of embodiments A1A to A109, or a pharmaceutically acceptable salt thereof, is wherein the cycloalkylene of Z is independently selected from 1,3-cyclopentylene, 1,3-cyclohexylene, and 1,4-cyclohexylene.

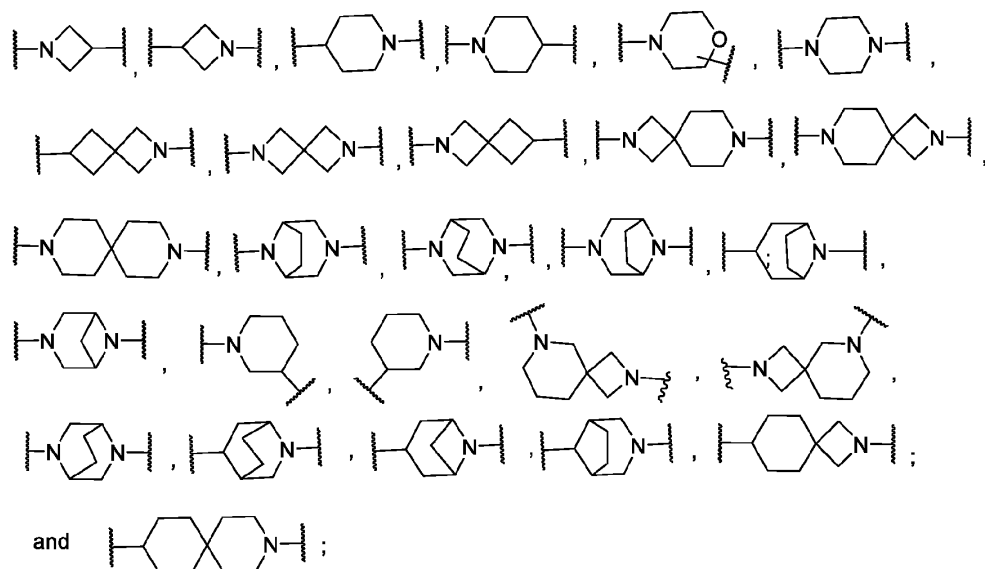
25 A111. In embodiment A111, the compound of any one of embodiments A1A to A108 and A110, or a pharmaceutically acceptable salt thereof, is wherein Z is phenylene or monocyclic heteroarylene (such as imidazoldiyl, pyridindiyl and pyrimidindiyl) and substituted with R^d and R^e as defined therein.

A112. In embodiment A112, the compound of any one of embodiments A1A to A108, and A111, or a pharmaceutically acceptable salt thereof, is wherein Z is monocyclic heteroaryl selected from imidazol-2,5-diyl, pyridin-2,4-diyl, pyridin-2,6-diyl, and pyridin-3,5-diyl.

A113. In embodiment A113, the compound of any one of embodiments A1A to A108 and
5 A111, or a pharmaceutically acceptable salt thereof, is wherein Z is 1,3-phenylene or 1,4-phenylene.

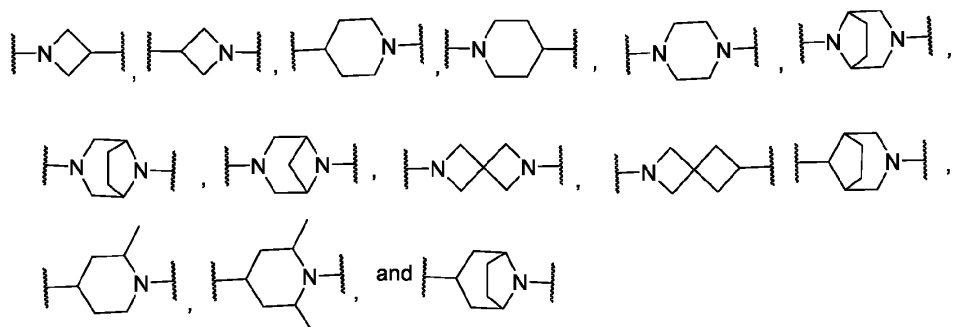
A114. In embodiment A114, the compound of any one of embodiments A1A to A108, or a pharmaceutically acceptable salt thereof, is wherein Z is heterocyclylene, bridged heterocyclylene, or spiro heterocyclylene, each ring substituted with R^d and R^e as defined therein.

A115. In embodiment A115, the compound of any one of embodiments A1A to A108 and
10 A114, or a pharmaceutically acceptable salt thereof, is wherein the heterocyclylene, bridged
heterocyclylene, and spiro heterocyclylene of Z are selected from:



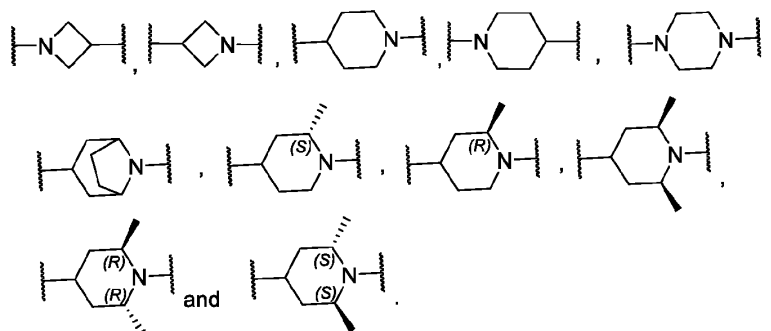
wherein each ring is substituted with R^d and R^e independently selected from hydrogen, deuterium, alkyl, and halo.

15 A116. In embodiment A116, the compound of any one of embodiments A1A to A108, A114, and A115, or a pharmaceutically acceptable salt thereof, is wherein the heterocyclene, bridged heterocyclene, and spiro heterocyclene of Z are independently selected from:

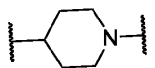


respectively.

A117. In embodiment A117, the compound of any one of embodiments A1A to A108 and A114 to A116, or a pharmaceutically acceptable salt thereof, is wherein Z is heterocyclylene selected from:

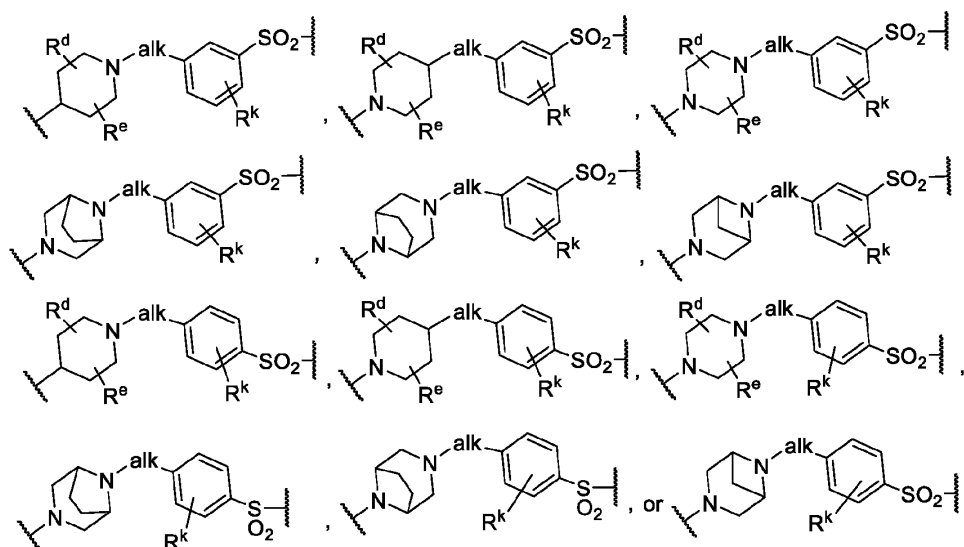


A118. In embodiment A118, the compound of any one of embodiments A1A to A108 and A114 to A117, or a pharmaceutically acceptable salt thereof, is wherein Z is heterocyclylene,



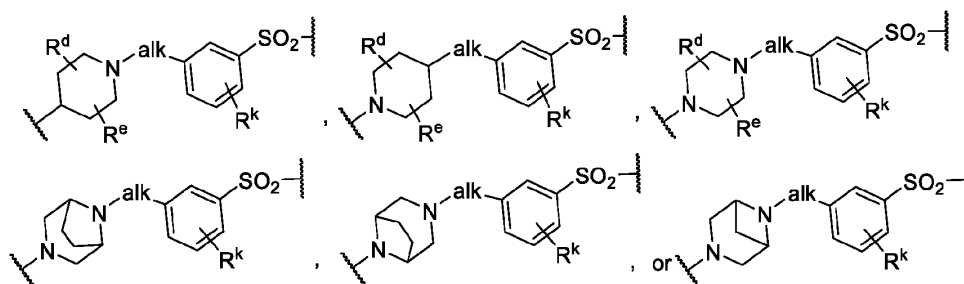
10 A119. In embodiment A119, the compound of any one of embodiments A1A to A108 or a pharmaceutically acceptable salt thereof, is wherein Z is -O-, -NH-, or -NCH₃-.

A120. In embodiment A120, the compound of any one of embodiments A1A to A98 and A114, or a pharmaceutically acceptable salt thereof, is wherein -Z-alk-Ar-SO₂- is:



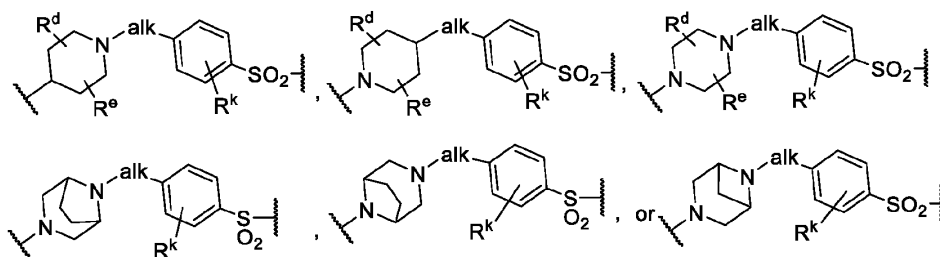
wherein each R^d , R^e , and R^k are independently selected from hydrogen, alkyl, halo, haloalkyl, haloalkoxy, alkoxy, and cyano and R^j is hydrogen.

A121. In embodiment A121, the compound of any one of embodiments A1A to A98, A114, and A120, or a pharmaceutically acceptable salt thereof, is wherein -Z-alk-Ar-SO₂- is:



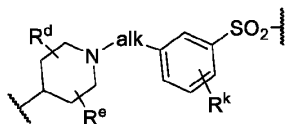
wherein each R^d , R^e , and R^k are independently selected from hydrogen, alkyl, halo, haloalkyl, haloalkoxy, alkoxy, and cyano and R^j is hydrogen.

A122. In embodiment A122, the compound of any one of embodiments A1A to A98, A114, and A120, or a pharmaceutically acceptable salt thereof, is wherein -Z-alk-Ar-SO₂- is:



wherein each R^d , R^e , and R^k are independently selected from hydrogen, alkyl, halo, haloalkyl, haloalkoxy, alkoxy, and cyano and R^j is hydrogen.

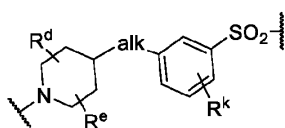
A123. In embodiment A123, the compound of any one of embodiments A1A to A98, A114, A120, and A121, or a pharmaceutically acceptable salt thereof, is wherein -Z-alk-Ar-SO₂- is:



5

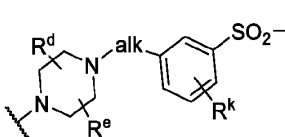
wherein R^d , R^e , and R^k are as defined therein.

A124. In embodiment A124, the compound of any one of embodiments A1A to A98, A114, A120, and A121, or a pharmaceutically acceptable salt thereof, is wherein -Z-alk-Ar-SO₂- is:



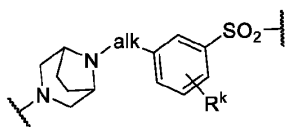
10 wherein R^d , R^e , and R^k are as defined therein.

A125. In embodiment A125, the compound of any one of embodiments A1A to A98, A114, A120, and A121, or a pharmaceutically acceptable salt thereof, is wherein -Z-alk-Ar-SO₂- is:



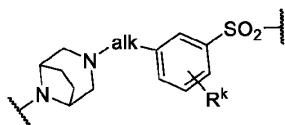
wherein R^d , R^e , and R^k are as defined therein.

15 A126. In embodiment A126, the compound of any one of embodiments A1A to A98, A114, A120, and A121, or a pharmaceutically acceptable salt thereof, is wherein -Z-alk-Ar-SO₂- is:



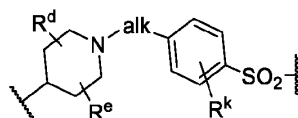
wherein R^d , R^e , and R^k are as defined therein.

20 A127. In embodiment A127, the compound of any one of embodiments A1A to A98, A114, A120, and A121, or a pharmaceutically acceptable salt thereof, is wherein -Z-alk-Ar-SO₂- is:



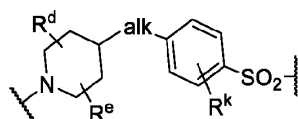
wherein R^d , R^e , and R^k are as defined therein.

A128. In embodiment A128, the compound of any one of embodiments A1A to A98, A114, A120, and A122, or a pharmaceutically acceptable salt thereof, is wherein -Z-alk-Ar-SO₂- is:



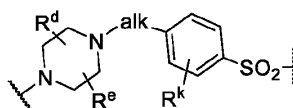
wherein R^d, R^e, and R^k are as defined therein.

5 A129. In embodiment A129, the compound of any one of embodiments A1A to A98, A114, A120, and A122, or a pharmaceutically acceptable salt thereof, is wherein -Z-alk-Ar-SO₂- is:



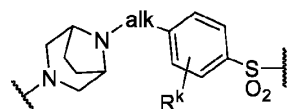
wherein R^d, R^e, and R^k are as defined therein.

10 A130. In embodiment A130, the compound of any one of embodiments A1A to A98, A114, A120, and A122, or a pharmaceutically acceptable salt thereof, is wherein -Z-alk-Ar-SO₂- is:



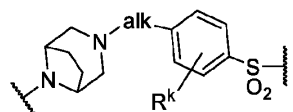
wherein R^d, R^e, and R^k are as defined therein.

A131. In embodiment A131, the compound of any one of embodiments A1A to A98, A114, A120, and A122, or a pharmaceutically acceptable salt thereof, is wherein -Z-alk-Ar-SO₂- is:



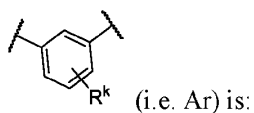
15 wherein R^d, R^e, and R^k are as defined therein.

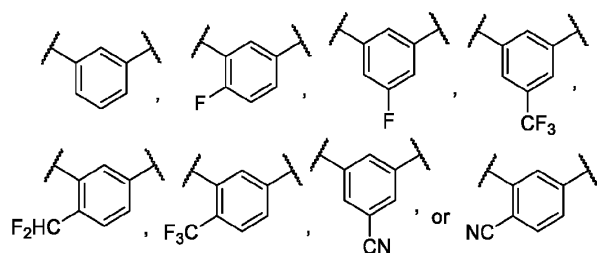
A132. In embodiment A132, the compound of any one of embodiments A1A to A98, A114, A120, and A122, or a pharmaceutically acceptable salt thereof, is wherein -Z-alk-Ar-SO₂- is:



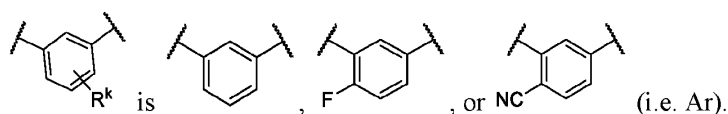
20 wherein R^d, R^e, and R^k are as defined therein.

A133. In embodiment A133, the compound of any one of embodiments A1A to A98, A114, A120, A121, and A123 to A127, or a pharmaceutically acceptable salt thereof, is wherein





A134. In embodiment A134, the compound of any one of embodiments A1A to A98, A114, A120, A121, A123 to A127, and A133, or a pharmaceutically acceptable salt thereof, is wherein



5 A135. In embodiment A135, the compound of any one of embodiments A1A to A134, or a pharmaceutically acceptable salt thereof, is wherein alk is C₃ to C₆ alkenylene substituted with R^f where R^f is hydrogen.

A136. In embodiment A136, the compound of any one of embodiments A1A to A134, or a pharmaceutically acceptable salt thereof, is wherein alk is C₃ to C₆ alkenylene substituted with R^f where R^f is fluoro or cyano.

A137. In embodiment A137, the compound of any one of embodiments A1A to A134, or a pharmaceutically acceptable salt thereof, is wherein alk is C₃ to C₆ alkylene substituted with R^g, R^h, and Rⁱ where R^g, R^h, and Rⁱ are hydrogen.

15 A138. In embodiment A138, the compound of any one of embodiments A1A to A134, or a pharmaceutically acceptable salt thereof, is wherein alk is C₃ to C₆ alkylene substituted with R^g, R^h, and Rⁱ where R^g, R^h, and Rⁱ are hydrogen or halo, provided at least one of R^g, R^h, and Rⁱ is halo.

A139. In embodiment A139, the compound of embodiment A138, or a pharmaceutically acceptable salt thereof, is wherein the halo of the at least one of R^g, R^h, and Rⁱ is fluoro.

20 A140. In embodiment A140, the compound of any one of embodiments A1A to A134, or a pharmaceutically acceptable salt thereof, is wherein alk is C₃ to C₆ alkylene substituted with R^g, R^h, and Rⁱ where R^h is other than hydrogen and Rⁱ is hydrogen or when R^g and R^h are attached to the same carbon or to adjacent carbon atoms of the linear portion of the C₃ to C₆ alkylene, R^g and R^h together with the carbon atom(s) to which they are attached can form cycloalkylene or heterocyclylene where the cycloalkylene and heterocyclylene formed by R^g and R^h are substituted
25 with R⁹ and R¹⁰.

A141. In embodiment A141, the compound of any one of embodiments A140, or a pharmaceutically acceptable salt thereof, is wherein alk is C₃ to C₆ alkylenes substituted with R^g, R^h, and Rⁱ where R^h is other than hydrogen and Rⁱ is hydrogen.

5 A142. In embodiment A142, the compound of any one of embodiments A1A to A141, or a pharmaceutically acceptable salt thereof, is wherein the C₃ to C₆ alkenylene and C₃ to C₆ alkylene of alk are linear alkenylene and alkylene, respectively and substituted as defined therein.

A143. In embodiment A143, the compound of any one of embodiments A1A to A136 and A140 to A142, or a pharmaceutically acceptable salt thereof, is wherein the linear C₃ to C₆ alkenylene of alk is -CH=C(R^f)CH₂- and the linear alkylene of C₃ to C₆ alkylene of alk is -CH₂CH(R^h)CH₂-, -CH₂CH₂CH(R^h)-, -CH₂C(R^g)(R^h)CH₂-, -CH₂CH₂C(R^g)(R^h)- where R^h is other than hydrogen and Rⁱ is hydrogen.

A144. In embodiment A144, the compound of any one of embodiments A1A to A134 and A140 to A143, or a pharmaceutically acceptable salt thereof, is wherein the linear C₃ to C₆ alkylene of alk is -CH₂CH(R^h)CH₂- where R^h is other than hydrogen and Rⁱ is hydrogen.

15 A145. In embodiment A145, the compound of any one of embodiments A1A to A134 and A140 to A144, or a pharmaceutically acceptable salt thereof, is wherein R^g of linear C₃ to C₆ alkylene of alk is hydrogen, deuterium, or halo and R^h of linear C₃ to C₆ alkylene of alk is halo, haloalkoxy, cycloalkyl, cycloalkyloxy, alkoxy, hydroxy, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylcarbonylamino, cyano, cyanoalkyloxy, phenyl, heteroaryl, heterocyclyl, or bridged heterocyclyl, each ring substituted as defined therein unless stated otherwise.

20 A146. In embodiment A146, the compound of any one of embodiments A1A to A134 and A140 to A145, or a pharmaceutically acceptable salt thereof, is wherein R^g of linear C₃ to C₆ alkylene of alk is hydrogen and R^h of linear C₃ to C₆ alkylene of alk is halo, haloalkoxy, cycloalkyl, cycloalkyloxy, alkoxy, hydroxy, dialkylaminocarbonyl, alkylcarbonylamino, cyano, phenyl, heteroaryl, heterocyclyl, or bridged heterocyclyl, each ring substituted as defined therein.

A147. In embodiment A147, the compound of any one of embodiments A1A to A134 and A140 to A146, or a pharmaceutically acceptable salt thereof, is wherein R^g of linear C₃ to C₆ alkylene of alk is hydrogen and R^h of linear C₃ to C₆ alkylene of alk is halo, haloalkoxy, alkoxy, hydroxy, dialkylaminocarbonyl, cyano, heterocyclyl, or heteroaryl, each ring substituted as defined therein.

30 A148. In embodiment A148, the compound of any one of embodiments A1A to A134 and A140 to A147, or a pharmaceutically acceptable salt thereof, is wherein the heteroaryl, heterocyclyl, and bridged heterocyclyl of R^h of linear C₃ to C₆ alkylene of alk, when present, are five or six membered ring and each ring is substituted as defined therein.

A149. In embodiment A149, the compound of any one of embodiments A1A to A134 and A140 to A148, or a pharmaceutically acceptable salt thereof, is wherein R^g of linear C_3 to C_6 alkylene of alk is hydrogen, deuterium, or fluoro unless stated otherwise and R^h of linear C_3 to C_6 alkylene of alk is fluoro, cyclopropyl, cyclobutyl, cyclopropyloxy, cyclobutyloxy, difluoromethoxy, trifluoromethoxy, methoxy, ethoxy, hydroxy, cyano, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, diethylaminocarbonyl, methylcarbonylamino, ethylcarbonylamino, phenyl, pyrazolyl, furanyl, thiazolyl, pyridinyl, pyrrolidinyl, 2-oxopyrrolidinyl, piperidinyl, piperazinyl, or tetrahydrofuranyl, where each ring of R^h is substituted with R^7 and R^8 independently selected from hydrogen, deuterium, methyl, methoxy, fluoro, difluoromethyl, trifluoromethyl, difluoromethoxy, trifluoromethyl, hydroxy, amino, methylamino, dimethylamino and cyano, unless stated otherwise.

A149A. In embodiment A149A, the compound of any one of embodiments A1A to A134 and A140 to A149, or a pharmaceutically acceptable salt thereof, is wherein R^g of linear C_3 to C_6 alkylene of alk is hydrogen, deuterium, or fluoro, unless stated otherwise and R^h of linear C_3 to C_6 alkylene of alk is fluoro, cyclopropyl, cyclopropyloxy, difluoromethoxy, trifluoromethoxy, methoxy, ethoxy, hydroxy, cyano, methylaminocarbonyl, dimethylaminocarbonyl, methylcarbonylamino, phenyl, pyrazol-1-yl, pyrazol-4-yl, pyridin-4-yl, pyrrolidin-1-yl, 2-oxopyrrolidin-1-yl, where each ring of R^h is substituted with R^7 and R^8 independently selected from hydrogen, deuterium, methyl, or fluoro, unless stated otherwise.

A150. In embodiment A150, the compound of any one of embodiments A1A to A134, or a pharmaceutically acceptable salt thereof, is wherein alk is branched C_4 to C_6 alkylene substituted with R^g , R^h , and R^i as defined therein.

A151. In embodiment A151, the compound of any one of embodiments A1A to A138 and A150, or a pharmaceutically acceptable salt thereof, is wherein the C_3 to C_6 alkenylene and C_3 to C_6 alkylene of alk are branched C_4 to C_6 alkenylene and C_4 to C_6 alkylene, respectively, where the C_4 to C_6 alkylene is substituted with R^g , R^h , and R^i as defined therein.

A152. In embodiment A152, the compound of any one of embodiments A1A to A138, A150, and A151, or a pharmaceutically acceptable salt thereof, is wherein the branched C_4 to C_6 alkenylene of alk is $-CH_2CH_2C(CH_3)=C(R^f)-$, $-CH_2C(CH_3)=C(R^f)-$, or $-CH_2C(=CH_2)CH_2-$ and the branched C_4 to C_6 alkylene of alk is $-CH_2C(CH_3)(R^h)CH_2-$, $-CH_2C(C_2H_5)(R^h)CH_2-$, $-CH_2CH(CH_2R^h)CH_2-$, $-CH_2CH(CH_2CH_2R^h)CH_2-$, $-CH_2C(CH_3)(CH_2R^h)CH_2-$, $-CH_2C(C_2H_5)(CH_2R^h)CH_2-$, $-CH_2C(CH_3)(CH_2CH_2R^h)CH_2-$, $-CH_2CH(CH_3)CH(CH_2R^h)-$, $-CH_2CH_2C(CH_3)(CH_2R^h)-$, $-CH_2CH(CH_3)C(R^g)(R^h)-$, $-CH_2CH(C_2H_5)C(R^g)(R^h)-$, $-CH_2CH(C(R^g)(R^h)(R^i))CH(CH_3)-$, $-CH_2C(CH_3)C(R^g)(R^h)(R^i)CH(CH_3)-$

, -CH₂CH(C(R^g)(R^h)(Rⁱ))CH₂-, -CH₂CH₂CH(C(R^g)(R^h)(Rⁱ))- , -CH₂CH₂CH(C(R^g)(R^h)(Rⁱ))CH₂-,
or -CH₂CH₂CH₂CH(C(R^g)(R^h)(Rⁱ))- where R^g, R^h, and Rⁱ are as defined therein.

A153. In embodiment A153, the compound of any one of embodiments A1A to A138 and
A150 to 152, or a pharmaceutically acceptable salt thereof, is wherein the branched C₄ to C₆
5 alkenylene of alk is -CH₂C(CH₃)=C(R^f)- or -CH₂C(=)CH₂- and the branched C₄ to C₆ alkenylene of alk
is -CH₂C(CH₃)(R^h)CH₂-, -CH₂CH(CH₂R^h)CH₂-, -CH₂CH(CH₂CH₂R^h)CH₂-
, -CH₂CH(C(R^g)(R^h)(Rⁱ))CH₂-, -CH₂CH₂CH(C(R^g)(R^h)(Rⁱ))CH₂-,
or -CH₂CH₂CH₂CH(C(R^g)(R^h)(Rⁱ))- where R^g, R^h, and Rⁱ are as defined therein.

A154. In embodiment A154, the compound of any one of embodiments A1A to A138 and
10 A150 to A153, or a pharmaceutically acceptable salt thereof, is wherein the R^g and Rⁱ of branched C₄
to C₆ alkenylene of alk are independently hydrogen or halo (unless stated otherwise) and R^h of
branched C₄ to C₆ alkenylene of alk is hydrogen, halo, haloalkoxy, cycloalkyl, cycloalkyloxy, alkoxy,
hydroxy, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylcarbonylamino, cyano,
cyanoalkyloxy, phenyl, heteroaryl, heterocyclyl, heterocyclyloxy, heterocyclylcarbonyl, or bridged
15 heterocyclyl (unless stated otherwise), each ring of R^h is substituted as defined therein.

A155. In embodiment A155, the compound of any one of embodiments A1A to A138 and
A150 to A154, or a pharmaceutically acceptable salt thereof, is wherein the R^g and Rⁱ of branched C₄
to C₆ alkenylene of alk are hydrogen or fluoro (unless stated otherwise) and R^h of branched C₄ to C₆
alkylene of alk is hydrogen, halo, cycloalkyl, cycloalkyloxy, alkoxy, hydroxy, alkylaminocarbonyl,
20 dialkylaminocarbonyl, alkylcarbonylamino, cyano, phenyl, heteroaryl, heterocyclyl, heterocyclyloxy,
heterocyclylcarbonyl, or bridged heterocyclyl (unless stated otherwise), each ring of R^h is substituted
as defined therein.

A156. In embodiment A156, the compound of any one of embodiments A1A to A138 and
A150 to A155, or a pharmaceutically acceptable salt thereof, is wherein R^g and Rⁱ of branched C₄ to
25 C₆ alkenylene of alk are hydrogen or fluoro (unless stated otherwise) and R^h of branched C₄ to C₆
alkylene of alk is hydrogen, halo, alkoxy, hydroxy, dialkylaminocarbonyl, cyano, or heteroaryl
substituted as defined therein.

A157. In embodiment A157, the compound of any one of embodiments A1A to A138 and
A150 to A155, or a pharmaceutically acceptable salt thereof, is wherein alk is branched C₄ to C₆
30 alkenylene substituted as defined therein and the heteroaryl, heterocyclyl, by itself or as part of
heterocyclyloxy, heterocyclylcarbonyl, and bridged heterocyclyl of branched C₄ to C₆ alkenylene of
alk, when present, are five or six membered ring and each ring of R^h is substituted as defined therein.

A158. In embodiment A158, the compound of any one of embodiments A1A to A138 and
A150 to A157, or a pharmaceutically acceptable salt thereof, is R^g and Rⁱ of branched C₄ to C₆

alkylene of alk are independently hydrogen, deuterium, or fluoro (unless stated otherwise) and R^h of branched C₄ to C₆ alkylene of alk, when present and unless stated otherwise, is hydrogen, deuterium, fluoro, cyclopropyl, cyclobutyl, cyclopropyloxy, cyclobutyloxy, difluoromethoxy, trifluoromethoxy, methoxy, ethoxy, hydroxy, cyano, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, diethylaminocarbonyl, methylcarbonylamino, ethylcarbonylamino, phenyl, pyrazolyl, thiazolyl, furanyl, pyridinyl, pyrrolidinyl, 2-oxopyrrolidinyl, piperidinyl, piperazinyl, or tetrahydrofuranyl, where each ring of R^h is substituted with R⁷ and R⁸ independently selected from hydrogen, deuterium, methyl, methoxy, fluoro, difluoromethyl, trifluoromethyl, difluoromethoxy, trifluoromethyl, hydroxy, amino, methylamino, dimethylamino and cyano, unless stated otherwise.

10 A158A. In embodiment A158A, the compound of any one of embodiments A1A to A138 and A150 to A158, or a pharmaceutically acceptable salt thereof, is wherein R^g and Rⁱ of branched C₄ to C₆ alkylene of alk, when present and unless stated otherwise, is hydrogen or fluoro and R^h of branched C₄ to C₆ alkylene of alk, when present and unless stated otherwise, is hydrogen, fluoro, hydroxy, methoxy, cyano, pyrazolyl-1-yl, or methylaminocarbonyl.

15 A159. In embodiment A159, the compound of any one of embodiments A1A to A134 and A140, or a pharmaceutically acceptable salt thereof, is wherein alk is C₃ to C₆ alkylene substituted with R^g, R^h, and Rⁱ where R^g and R^h are attached to the same carbon or to adjacent carbon atoms of the linear portion of the C₃ to C₆ alkylene and R^g and R^h together with the carbon atom(s) to which they are attached can form cycloalkylene or heterocyclylene where the cycloalkylene and
20 heterocyclylene formed by R^g and R^h are substituted with R⁹ and R¹⁰.

A160. In embodiment A160, the compound of any one of embodiments A1A to A134, A140, and A159, or a pharmaceutically acceptable salt thereof, is wherein alk is C₃ to C₆ alkylene substituted with R^g, R^h, and Rⁱ where R^g and R^h are attached to the same carbon atom of the linear portion of C₃ to C₆ alkylene and together with the carbon atom to which they are attached can form
25 cycloalkylene substituted with R⁹ and R¹⁰.

A161. In embodiment A161, the compound of any one of embodiments A1A to A134, A140, and A159, or a pharmaceutically acceptable salt thereof, is wherein alk is C₃ to C₆ alkylene substituted with R^g, R^h, and Rⁱ where R^g and R^h are attached to the same carbon atom of the linear portion of the C₃ to C₆ alkylene and together with the carbon atom to which they are attached can
30 form heterocyclylene substituted with R⁹ and R¹⁰.

A162. In embodiment A162, the compound of any one of embodiments A1A to A134, A140, and A159, or a pharmaceutically acceptable salt thereof, is wherein alk is C₃ to C₆ alkylene substituted with R^g, R^h, and Rⁱ where R^g and R^h are attached to adjacent carbon atoms of the linear

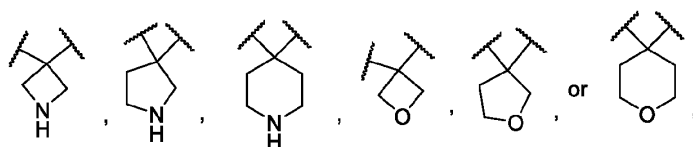
portion of the C₃ to C₆ alkylene and together with the carbon atoms to which they are attached can form cycloalkylene substituted with R⁹ and R¹⁰.

A163. In embodiment A163, the compound of any one of embodiments A1A to A134, A140, and A159, or a pharmaceutically acceptable salt thereof, is wherein alk is C₃ to C₆ alkylene substituted with R^g, R^h, and Rⁱ where R^g and R^h are attached to adjacent same carbon atoms of the linear portion of the C₃ to C₆ alkylene and together with the carbon atoms to which they are attached can form heterocyclylene substituted with R⁹ and R¹⁰.

A164. In embodiment A164, the compound of any one of embodiments A1A to A134, A140, and A159 to A161, or a pharmaceutically acceptable salt thereof, is wherein R^g and R^h are attached to the same carbon atom of the linear portion C₃ to C₆ alkylene and together with the carbon atom to which they are attached can form cycloalkylene of formula:

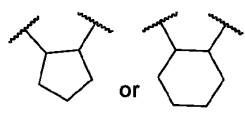


or heterocyclylene of formula:

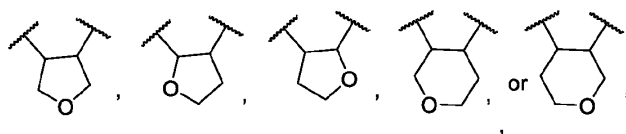


where each ring is substituted with R⁹ and R¹⁰, preferably R⁹ is hydrogen, halo, methyl or ethyl and R¹⁰ is hydrogen.

A165. In embodiment A165, the compound of any one of embodiments A1A to A134, A140, A159, A162, and A163, or a pharmaceutically acceptable salt thereof, is wherein R^g and R^h are attached to adjacent carbon atoms of the linear portion of the C₃ to C₆ alkylene and together with the carbon atoms to which they are attached can form cycloalkylene of formula:



or heterocyclylene of formula:



where each ring is substituted with R⁹ and R¹⁰, preferably R⁹ is hydrogen, halo, methyl or ethyl and R¹⁰ is hydrogen.

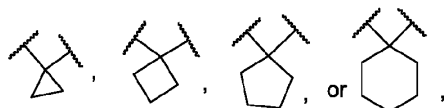
A166. In embodiment A166, the compound of any one of embodiments A1A to A134, or a pharmaceutically acceptable salt thereof, is wherein alk is C₃ to C₆ heteroalkylene substituted with R^g, R^h, and Rⁱ.

5 A167. In embodiment A167, the compound of any one of embodiments A1A to A134 and A166, or a pharmaceutically acceptable salt thereof, is wherein alk is C₃ to C₆ heteroalkylene substituted with R^g, R^h, and Rⁱ where R^g, R^h, and Rⁱ are hydrogen.

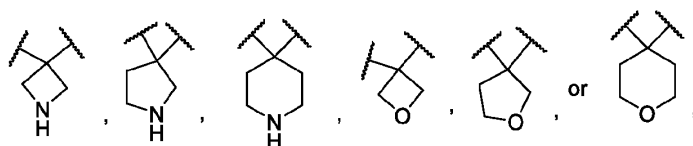
A168. In embodiment A168, the compound of any one of embodiments A1A to A134 and A166, or a pharmaceutically acceptable salt thereof, is wherein alk is C₃ to C₆ heteroalkylene substituted with R^g, R^h, and Rⁱ where R^g, R^h, and Rⁱ are hydrogen or halo, provided at least one of
10 R^g, R^h, and Rⁱ is halo.

A169. In embodiment A169, the compound of any one of embodiments A1A to A134 and A166, or a pharmaceutically acceptable salt thereof, is wherein alk is C₃ to C₆ heteroalkylene substituted with R^g, R^h, and Rⁱ where R^h is other than hydrogen and Rⁱ is hydrogen, or when R^g and R^h are attached to the same carbon or to adjacent carbon atoms of the linear portion of the C₃ to C₆
15 heteroalkylene, R^g and R^h together with the carbon atom to which they are attached can form cycloalkylene or heterocyclylene where the cycloalkylene and heterocyclylene are substituted with R⁹ and R¹⁰.

A169a. In embodiment A169a, the compound of any one of embodiments A1A to A134 and A169, or a pharmaceutically acceptable salt thereof, is wherein R^g and R^h are attached to the same
20 carbon atom of the linear portion of the C₃ to C₆ heteroalkylene and together with the carbon atom to which they are attached can form cycloalkylene of formula:

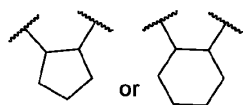


or heterocyclylene of formula:

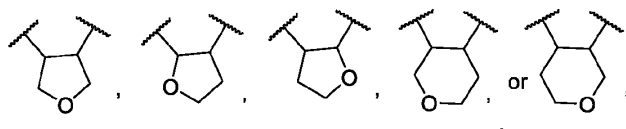


25 where each ring is substituted with R⁹ and R¹⁰, preferably R⁹ is hydrogen, halo, methyl or ethyl and R¹⁰ is hydrogen.

A169b. In embodiment A169b, the compound of any one of embodiments A1A to A134 and A169, or a pharmaceutically acceptable salt thereof, is wherein R^g and R^h are attached to adjacent
30 carbon atoms of the linear portion of the C₃ to C₆ heteroalkylene and together with the carbon atoms to which they are attached can form cycloalkylene of formula:



or heterocyclene of formula:



where each ring is substituted with R^9 and R^{10} , preferably R^9 is hydrogen, halo, methyl or ethyl and R^{10} is hydrogen.

A170. In embodiment A170, the compound of any one of embodiments A1A to A134, A166, and A169, or a pharmaceutically acceptable salt thereof, is wherein alk is C_3 to C_6 heteroalkylene substituted with R^g , R^h , and R^i where R^h is other than hydrogen and R^i is hydrogen.

A171. In embodiment A171, the compound of any one of embodiments A1A to A134, A142 to A149A, A151 to A156, A158, A158A, and A166 to A170, or a pharmaceutically acceptable salt thereof, is wherein the C_3 to C_6 heteroalkylene of alk is linear C_3 to C_6 heteroalkylene and for the sake of clarity, since this embodiment is only characterizing that the C_3 to C_6 heteroalkylene of alk is linear in nature, it is understood the linear C_3 to C_6 heteroalkylene is substituted with R^g , R^h , and R^i as provided in the referred to embodiments.

A172. In embodiment A172, the compound of any one of embodiments A1A to A134, A142 to A149A, A152 to A156, A158, A158A, and A166 to A169, A170, and A171, or a pharmaceutically acceptable salt thereof, is wherein the linear C_3 to C_6 heteroalkylene of alk is $-CH_2CH_2X^aCH_2-$, $-CH_2X^aCH_2CH_2-$, $-CH_2CH_2CH_2X^a-$, $-X^aCH_2CH_2CH_2-$, $-X^yCH_2CH_2X^a-$, $-X^yCH_2CH_2X^aCH_2-$, $-CH_2CH_2CH_2X^aCH_2-$, $-CH_2X^aCH_2-$, $-X^aCH_2CH_2-$, $-CH_2CH_2X^a-$, $-CH_2CONR^qCH_2-$, $-CH_2SO_2NR^qCH_2-$, $-CH_2NR^qCOCH_2-$, $-CH_2NR^qSO_2CH_2-$, $-CH_2CH_2CH_2NR^qCO-$, $-CH_2CONR^q-$, $-CH_2SO_2NR^q-$, $-CH_2NR^qCO-$, $-CH_2NR^qSO_2-$, $-CONR^qCH_2-$, $-SO_2NR^qCH_2-$, $-NR^qCOCH_2-$, or $-NR^qSO_2CH_2-$ substituted with R^g , R^h , and R^i as defined therein and X^a is $-NR^q-$, $-O-$, $-S-$, $-SO-$, $-SO_2-$, or $-CO-$.

A173. In embodiment A173, the compound of any one of embodiments A1A to A134, A142 to A149A, A151 to A156, A158, A158A, and A166 to A172, or a pharmaceutically acceptable salt thereof, is wherein R^q is hydrogen, methyl, ethyl, methylcarbonyl, or methylsulfonyl.

A174. In embodiment A174, the compound of any one of embodiments A1A to A134, A142 to A149A, A151 to A156, A158, A158A, A166 to A169, and A170 to A173, or a pharmaceutically acceptable salt thereof, is wherein the linear C_3 to C_6 heteroalkylene of alk is

-CH₂X^aCH₂-, -X^aCH₂CH₂-, -CH₂CH₂X^a-, -CH₂CH(R^h)X^a-, -X^aCH(R^h)CH₂-, -CH₂CONR^q-,
 -CH₂SO₂NR^q-, -CH₂NR^qCO-, -CH₂NR^qSO₂-, -CONR^qCH₂-, -SO₂NR^qCH₂-, -NR^qCOCH₂-, or
 -NR^qSO₂CH₂- where X^a is -S-, -SO₂-, -O-, or -NR^q-.

A175. In embodiment A175, the compound of any one of embodiments A1A to A134, A142
 5 to A149A, A151 to A156, A158, A158A, A166 to A169, and A170 to A174, or a pharmaceutically
 acceptable salt thereof, is wherein the linear C₃ to C₆ heteroalkylene of alk is
 -CH₂CH₂CH₂X^a- or -CH₂CH₂X^a.

A176. In embodiment A176, the compound of any one of embodiments A1A to A134, A142
 to A149A, A151 to A156, A158, A158A, A166 to A169, and A170 to A175, or a pharmaceutically
 10 acceptable salt thereof, is wherein R^s of linear C₃ to C₆ heteroalkylene of alk is hydrogen or halo
 (unless stated otherwise) and R^h of linear C₃ to C₆ heteroalkylene of alk is (unless stated otherwise)
 hydrogen, halo, haloalkoxy, cycloalkyl, cycloalkyloxy, alkoxy, hydroxy, aminocarbonyl,
 alkylaminocarbonyl, dialkylaminocarbonyl, alkylcarbonylamino, cyano, cyanoalkyloxy, phenyl,
 heteroaryl, heterocyclyl, or bridged heterocyclyl, each ring substituted as defined therein and Rⁱ is
 15 hydrogen.

A177. In embodiment A177, the compound of any one of embodiments A1A to A134, A142
 to A149A, A151 to A156, A158, A158A, A166 to A169, and A170 to A176, or a pharmaceutically
 acceptable salt thereof, is wherein R^s of linear C₃ to C₆ heteroalkylene of alk is hydrogen or fluoro
 (unless stated otherwise) and R^h of linear C₃ to C₆ heteroalkylene of alk (unless stated otherwise) is
 20 hydrogen halo, haloalkoxy, alkoxy, hydroxy, dialkylaminocarbonyl, cyano, or heteroaryl substituted
 as defined therein.

A178. In embodiment A178, the compound of any one of embodiments A1A to A134, A142
 to A149A, A151 to A156, A158, A158A, A166 to A169, and A170 to A177, or a pharmaceutically
 acceptable salt thereof, is wherein the heteroaryl, heterocyclyl, and bridged heterocyclyl of R^h of
 25 linear C₃ to C₆ heteroalkylene of alk, when present, are five or six membered ring and each ring is
 substituted as defined therein.

A179. In embodiment A179, the compound of any one of embodiments A1A to A134, A142
 to A149A, A151 to A156, A158, A158A, A166 to A169, and A170 to A178, or a pharmaceutically
 acceptable salt thereof, is wherein R^s of linear C₃ to C₆ heteroalkylene of alk, when present and
 30 unless stated otherwise, is hydrogen, deuterium, or fluoro, and R^h of linear C₃ to C₆ heteroalkylene of
 alk, when present and unless stated otherwise, is hydrogen, deuterium, fluoro, cyclopropyl,
 cyclobutyl, cyclopropyloxy, cyclobutyloxy, difluoromethoxy, trifluoromethoxy, methoxy, ethoxy,
 hydroxy, cyano, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl,
 diethylaminocarbonyl, methylcarbonylamino, ethylcarbonylamino, phenyl, pyrazolyl, thiazolyl,

furanyl, pyridinyl, pyrrolidinyl, 2-oxopyrrolidinyl, piperidinyl, piperazinyl, tetrahydrofuranyl, each ring substituted with R⁷ and R⁸ independently selected from hydrogen, deuterium, methyl, methoxy, fluoro, difluoromethyl, trifluoromethyl, difluoromethoxy, trifluoromethyl, hydroxy, amino, methylamino, dimethylamino, and cyano.

5 A180. In embodiment A180, the compound of any one of embodiments A1A to A134, A142 to A149A, A151 to A156, A158, A158A, A166 to A169, and A170 to A179, or a pharmaceutically acceptable salt thereof, is wherein R^g of linear C₃ to C₆ heteroalkylene of alk is hydrogen and R^h of linear C₃ to C₆ heteroalkylene of alk is fluoro, cyclopropyl, cyclopropyloxy, difluoromethoxy, trifluoromethoxy, methoxy, ethoxy, hydroxy, cyano, methylaminocarbonyl, dimethylaminocarbonyl, methylcarbonylamino, phenyl, pyrazol-1-yl, pyrazol-4-yl, pyridin-4-yl, pyrrolidin-1-yl, 10 2-oxopyrrolidin-1-yl, each ring substituted with R⁷ and R⁸ independently selected from hydrogen, deuterium, methyl, or fluoro.

A181. In embodiment A181, the compound of any one of embodiments A172 to A180, or a pharmaceutically acceptable salt thereof, is wherein X^a is -NR^q-, -O-, -S-, or -SO₂-, preferably -NR^q-, 15 -O-, or -S-.

A182. In embodiment A182, the compound of any one of embodiments A172 to A181, or a pharmaceutically acceptable salt thereof, is wherein X^a is -NR^q- where R^q is hydrogen or methyl.

A183. In embodiment A183, the compound of any one of embodiments A172 to A181, or a pharmaceutically acceptable salt thereof, is wherein X^a is -O-.

20 A184. In embodiment A184, the compound of any one of embodiments A172 to A181, or a pharmaceutically acceptable salt thereof, is wherein X^a is -S-.

A185. In embodiment A185, the compound of any one of embodiments A172 to A184, or a pharmaceutically acceptable salt thereof, is wherein X^y is -O-.

A186. In embodiment A186, the compound of any one of embodiments A172 to A184, or a 25 pharmaceutically acceptable salt thereof, is wherein X^y is -NH- or -NCH₃-.

A187. In embodiment A187, the compound of any one of embodiments A1A to 134, A166 to A169, and A170, or a pharmaceutically acceptable salt thereof, is wherein the C₃ to C₆ heteroalkylene of alk is branched C₄ to C₆ heteroalkylene and for the sake of clarity, since this embodiment is only characterizing that the C₄ to C₆ heteroalkylene of alk is branched in nature, it is 30 understood the branched C₄ to C₆ heteroalkylene is substituted with R^g, R^h, and Rⁱ as provided in the referred to embodiments.

A188. In embodiment A188, the compound of any one of embodiments A1A to A134, A166 to A169, A170, and A187, or a pharmaceutically acceptable salt thereof, is wherein the branched C₄ to C₆ heteroalkylene of alk is -CH₂X^aCH(CH₃)CH₂-,

-CH₂X^yCH₂CH(CH₃)X^a-, -CH₂CH₂CH(CH₃)X^a-, -X^aCH(CH₃)CH₂CH₂-, -X^yCH₂CH(CH₃)X^a-,
 -X^yCH(CH₃)CH₂X^a-, -CH₂CH₂CH₂CH(CH₃)X^a-, -X^aCH(CH₂R^h)CH₂-, -CH₂CH(CH₂R^h)X^a-,
 -X^aCH(CH₂CH₂R^h)CH₂-, -CH₂CH(CH₂CH₂R^h)X^a-, -CH₂C(CH₃)(CH₃)X^a-, -X^aC(CH₃)(CH₃)CH₂-,
 -CH(CH₃)CH(CH₃)X^a-, -CONR^qCH₂CH(CH₃)X^a-, -CH₂NR^qCOCH(CH₃)CH₂-, or

5 -NR^qCOCH(CH₃)CH₂- where X^a is -NR^q-, -O-, -S-, -SO-, -SO₂-, or -CO-.

A189. In embodiment A189, the compound of any one of embodiments A1A to 134, A166 to A169, A170, A187, and A188, or a pharmaceutically acceptable salt thereof, is wherein the branched C₄ to C₆ heteroalkylene of alk is -CH₂C(CH₃)(CH₃)X^a-, -CH(CH₃)(CHCH₃)X^a-,
 -X^aCH(CH₂CH₂R^h)CH₂-, -CH₂CH(CH₂CH₂R^h)X^a-, -X^aCH(CH₂R^h)CH₂-, or -CH₂CH(CH₂R^h)X^a-.

10 A190. In embodiment A190, the compound of any one of embodiments A1A to 134, A166 to A169, A170, A173, and A187 to A189, or a pharmaceutically acceptable salt thereof, is wherein the R^g and Rⁱ of branched C₄ to C₆ heteroalkylene of alk are hydrogen or halo (unless stated otherwise) and R^h of branched C₄ to C₆ heteroalkylene of alk is hydrogen, halo, haloalkoxy, cycloalkyl, cycloalkyloxy, alkoxy, hydroxy, aminocarbonyl, alkylaminocarbonyl,
 15 dialkylaminocarbonyl, alkylcarbonylamino, cyano, cyanoalkyloxy, phenyl, heteroaryl, heterocyclyl, heterocyclyloxy, heterocyclylcarbonyl, or bridged heterocyclyl substituted as defined therein.

A191. In embodiment A191, the compound of any one of embodiments A1A to 134, A166 to A169, A170, A173, and A187 to A190, or a pharmaceutically acceptable salt thereof, is wherein the R^g and Rⁱ of branched C₄ to C₆ heteroalkylene of alk are hydrogen or fluoro (unless stated otherwise) and R^h (unless stated otherwise) is hydrogen, halo, cycloalkyl, cycloalkyloxy, alkoxy,
 20 hydroxy, alkylaminocarbonyl, dialkylaminocarbonyl, alkylcarbonylamino, cyano, phenyl, heteroaryl, heterocyclyl, heterocyclyloxy, heterocyclylcarbonyl, or bridged heterocyclyl, substituted as defined therein.

A192. In embodiment A192, the compound of any one of embodiments A1A to 134, A166 to A169, A170, A173, and A187 to A191, or a pharmaceutically acceptable salt thereof, is wherein R^g and Rⁱ are hydrogen and R^h is hydrogen, heteroaryl, alkylaminocarbonyl, or cyano.
 25

A193. In embodiment A193, the compound of any one of embodiments A1A to 134, A166 to A169, A170, A173, and A187 to A192, or a pharmaceutically acceptable salt thereof, is wherein the heteroaryl, heterocyclyl of branched C₄ to C₆ heteroalkylene of alk, by itself or as part of
 30 heterocyclyloxy, heterocyclylcarbonyl, and bridged heterocyclyl, when present, are five or six membered ring and each ring is substituted as defined therein.

A194. In embodiment A194, the compound of any one of embodiments A1A to 134, A166 to A169, A170, A173, and A187 to A193, or a pharmaceutically acceptable salt thereof, is wherein R^h of branched C₄ to C₆ heteroalkylene of alk, when present and unless stated otherwise, is

hydrogen, deuterium, fluoro, cyclopropyl, cyclobutyl, cyclopropyloxy, cyclobutyloxy, difluoromethoxy, trifluoromethoxy, methoxy, ethoxy, hydroxy, cyano, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, diethylaminocarbonyl, methylcarbonylamino, ethylcarbonylamino, phenyl, pyrazolyl, thiazolyl, furanyl, pyrrolidinyl, pyridinyl, piperidinyl, piperazinyl, tetrahydrofuranyl, each ring substituted with R⁷ and R⁸ independently selected from hydrogen, deuterium, methyl, methoxy, fluoro, difluoromethyl, trifluoromethyl, difluoromethoxy, trifluoromethyl, hydroxy, amino, methylamino, dimethylamino and cyano.

A195. In embodiment A195, the compound of any one of embodiments A188 to A194, or a pharmaceutically acceptable salt thereof, is wherein X^a is -NR^q-, -O-, -S-, or -SO₂-, preferably -NR^q- or -O-.

A196. In embodiment A196, the compound of any one of embodiments A188 to A195, or a pharmaceutically acceptable salt thereof, is wherein X^a is -NR^q- where R^q is hydrogen or methyl.

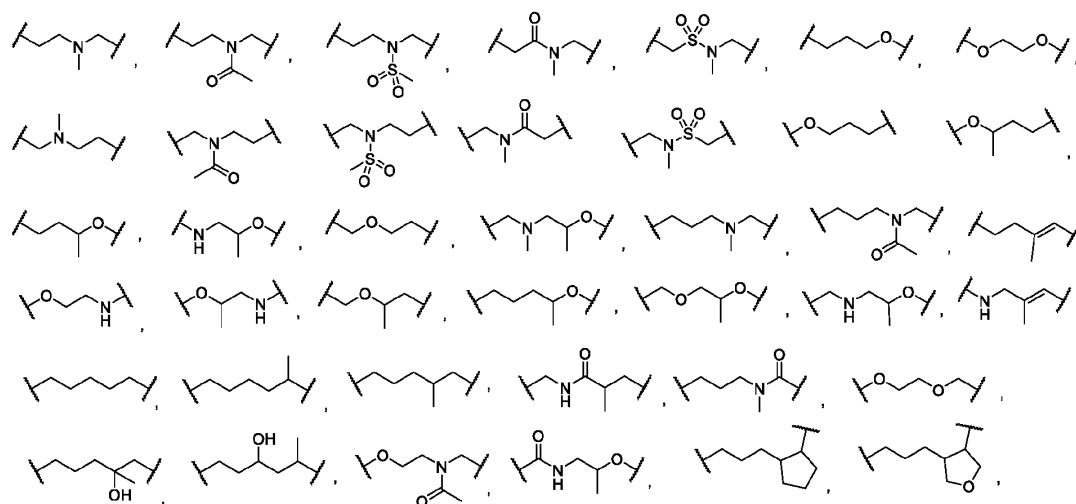
A197. In embodiment A197, the compound of any one of embodiments A188 to A195, or a pharmaceutically acceptable salt thereof, is wherein X^a is -O-.

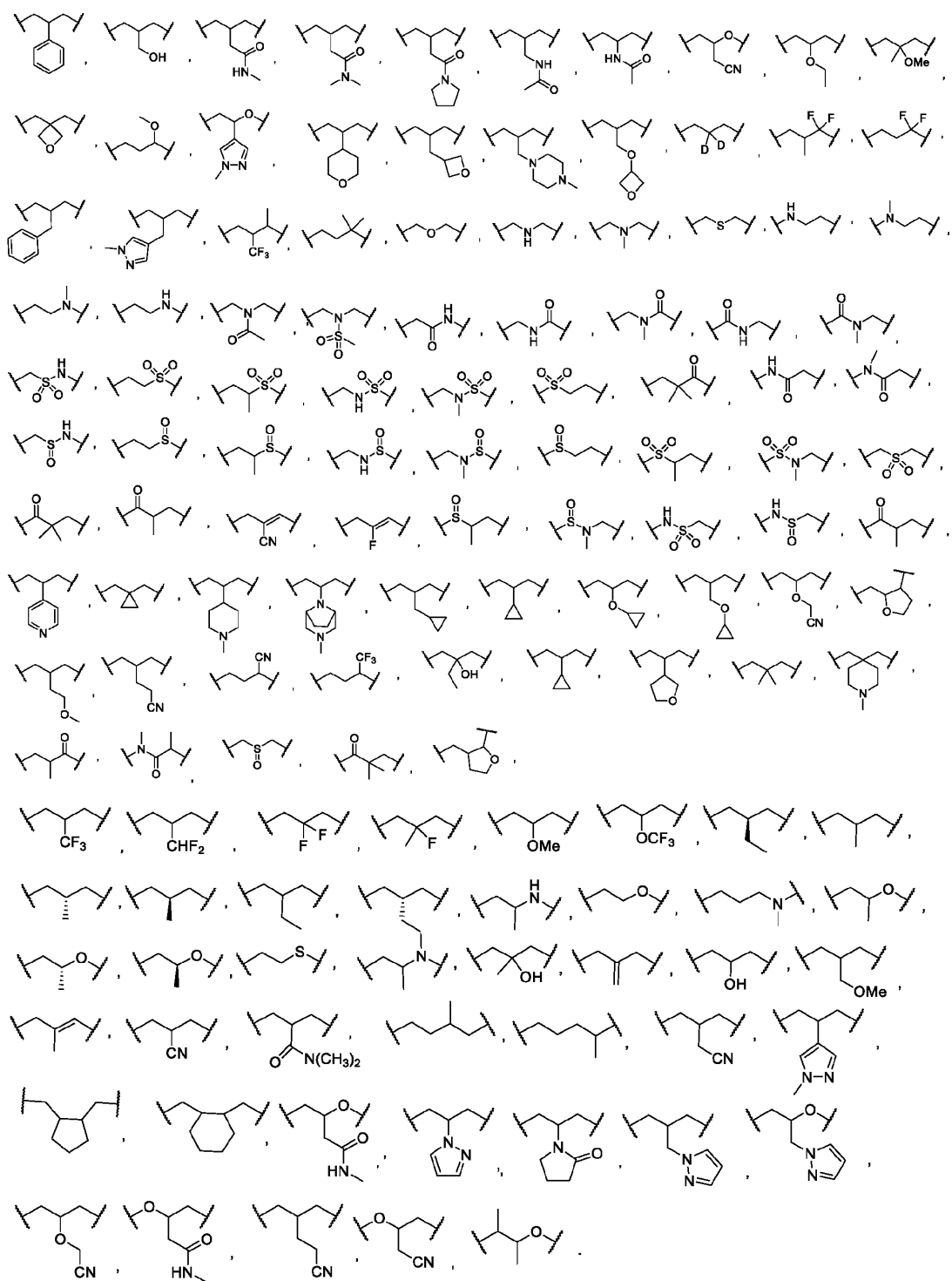
A198. In embodiment A198, the compound of any one of embodiments A188 to A195, or a pharmaceutically acceptable salt thereof, is wherein X^a is -S-.

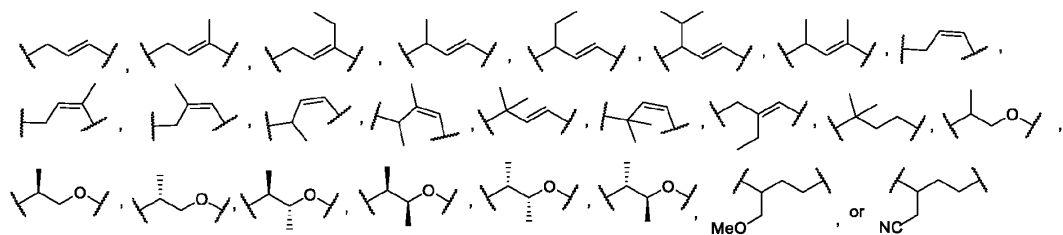
A199. In embodiment A199, the compound of any one of embodiments A188 to A198, or a pharmaceutically acceptable salt thereof, is wherein X^y is -O-.

A200. In embodiment A200, the compound of any one of embodiments A188 to A198, or a pharmaceutically acceptable salt thereof, is wherein X^y is -NH- or -NCH₃-.

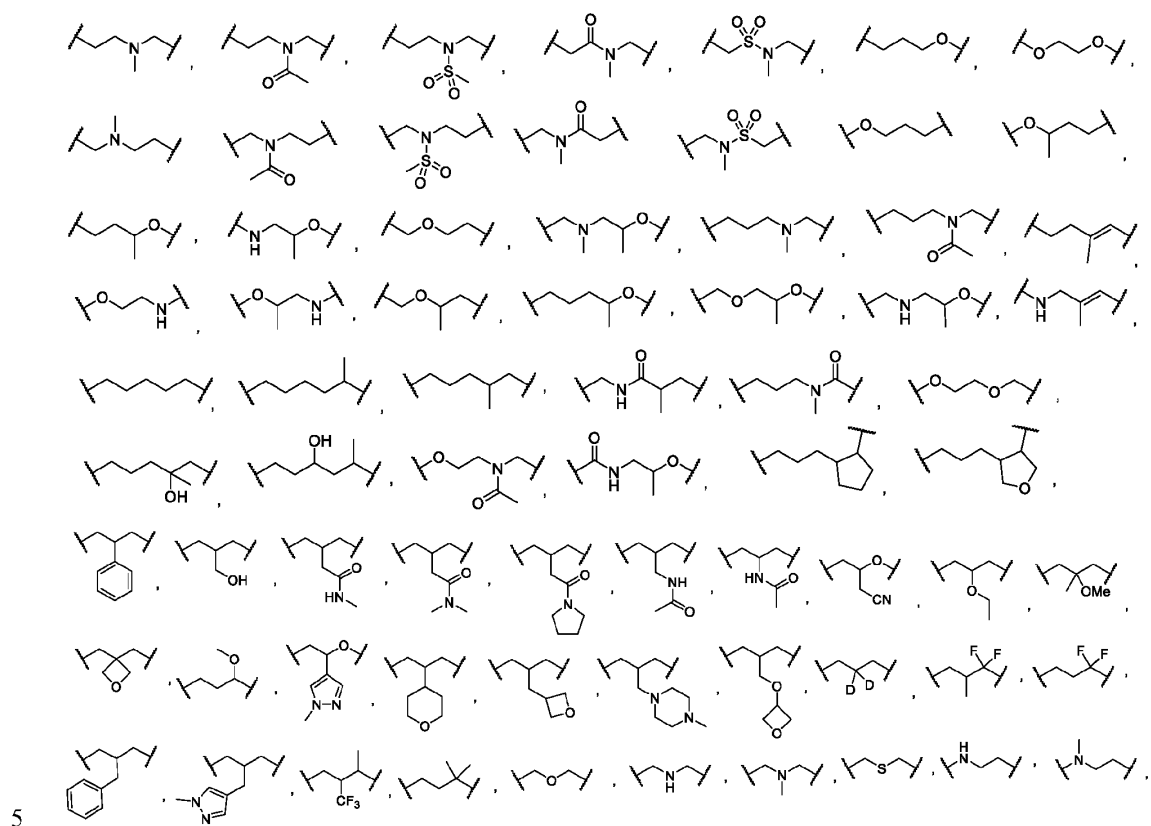
A201a. In embodiment A201a, the compound of any one of embodiments A1A to A200, or a pharmaceutically acceptable salt thereof, is wherein alk is:



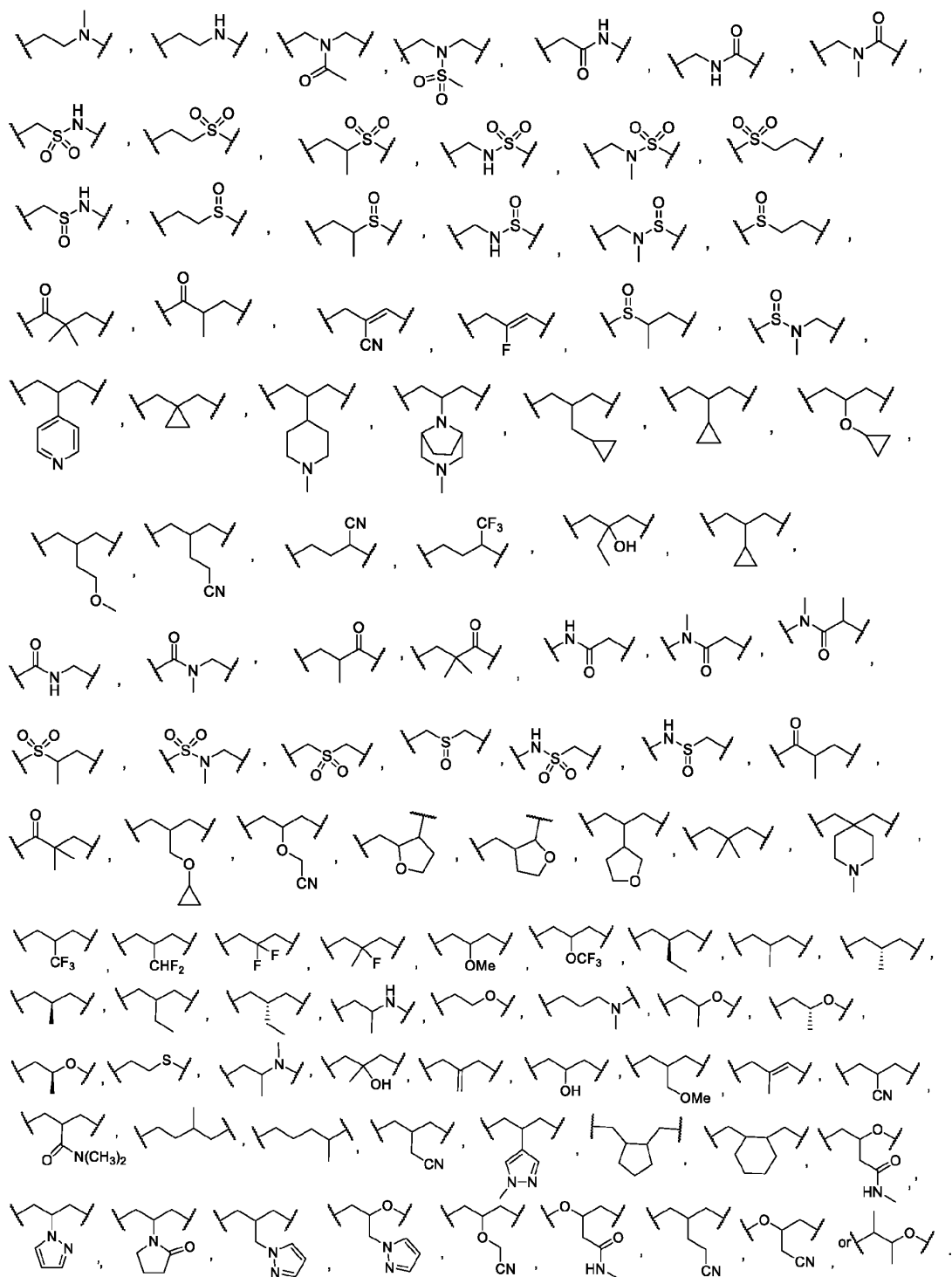




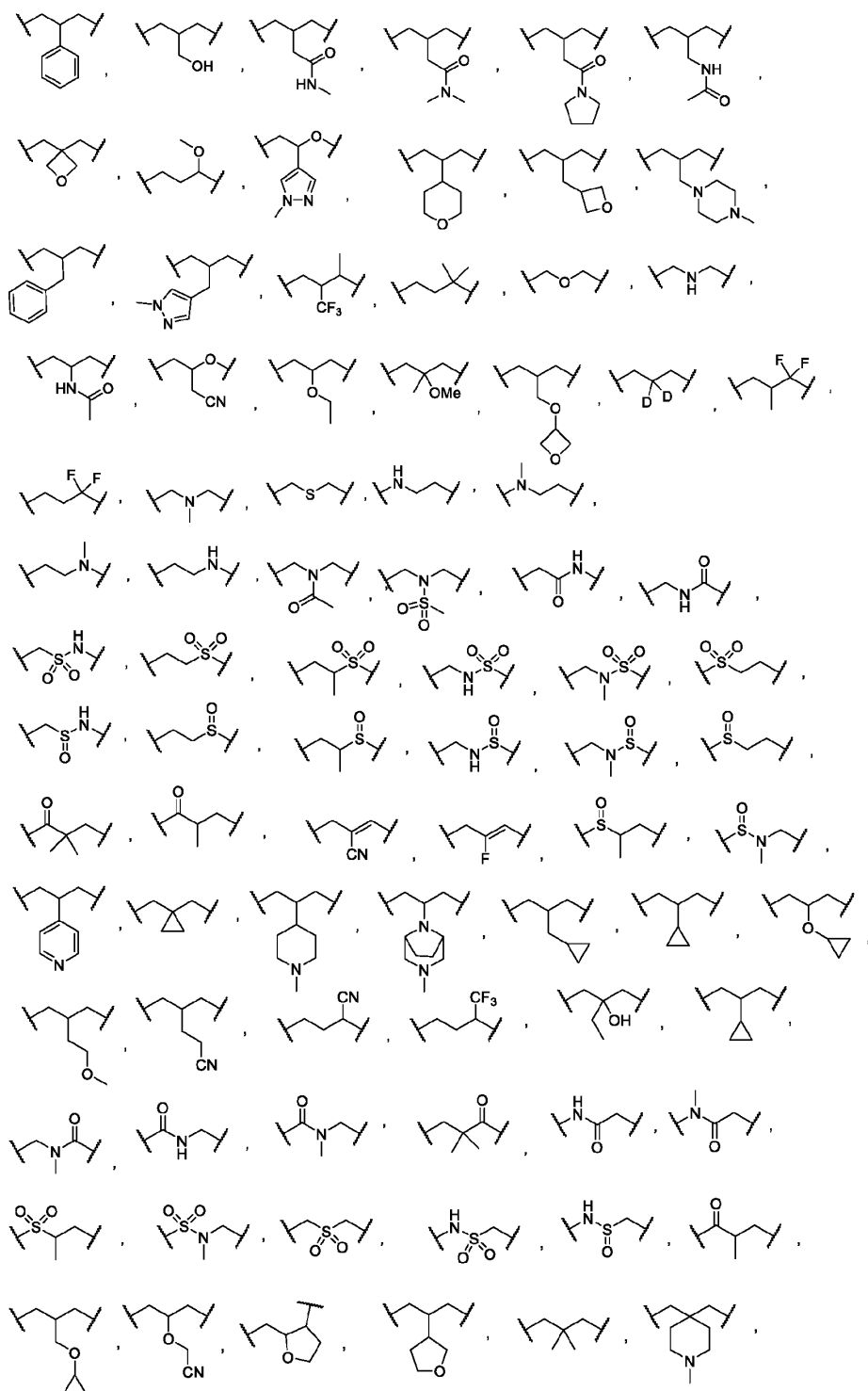
A201. In embodiment A201, the compound of any one of embodiments A1A to A200a, or a pharmaceutically acceptable salt thereof, is wherein alk is:

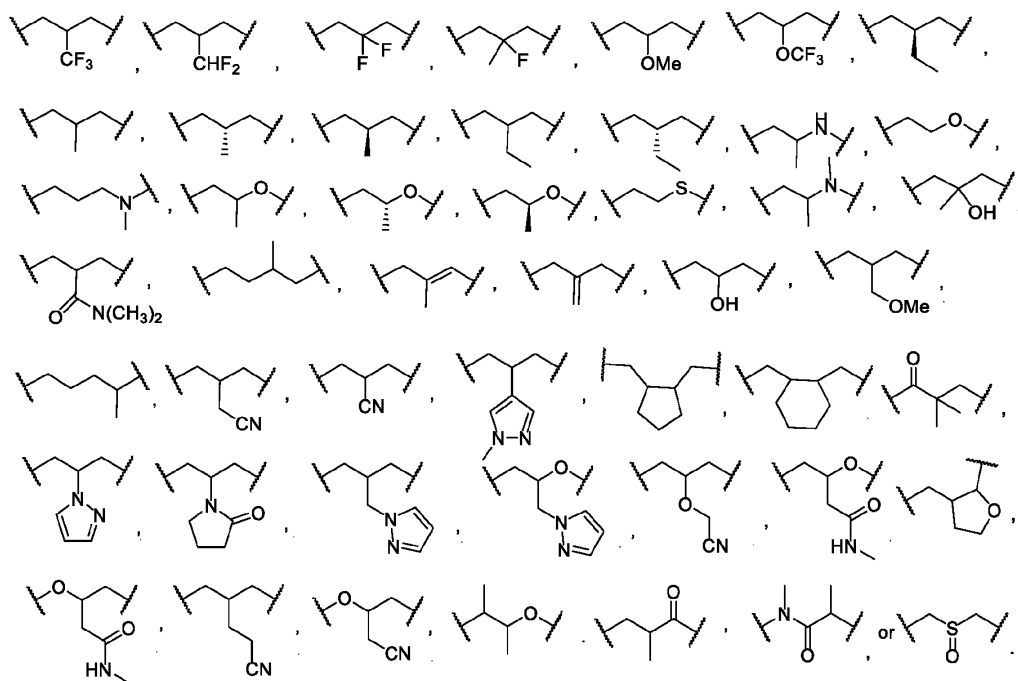


5

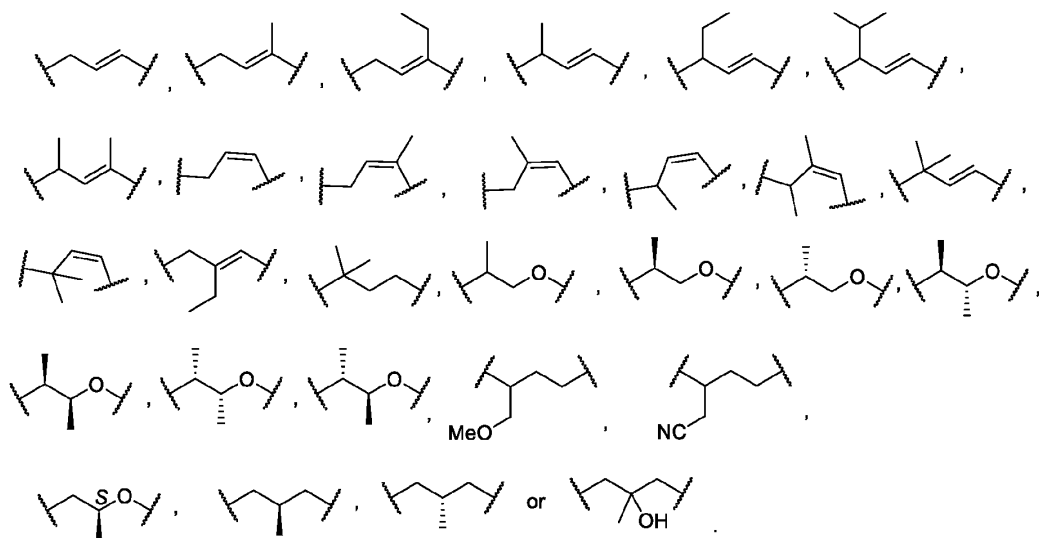


A202. In embodiment A202, the compound of any one of embodiments A1A to A201, or a pharmaceutically acceptable salt thereof, is wherein alk is:

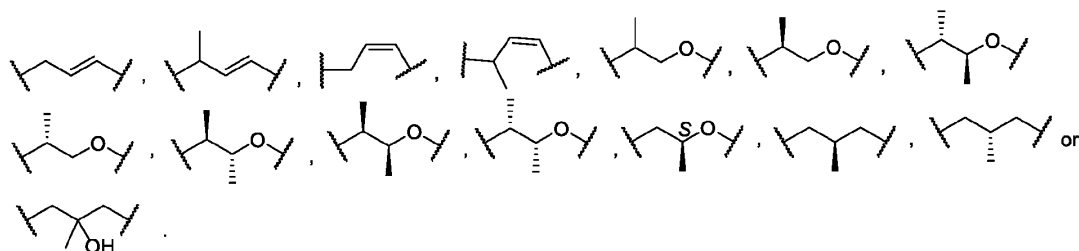




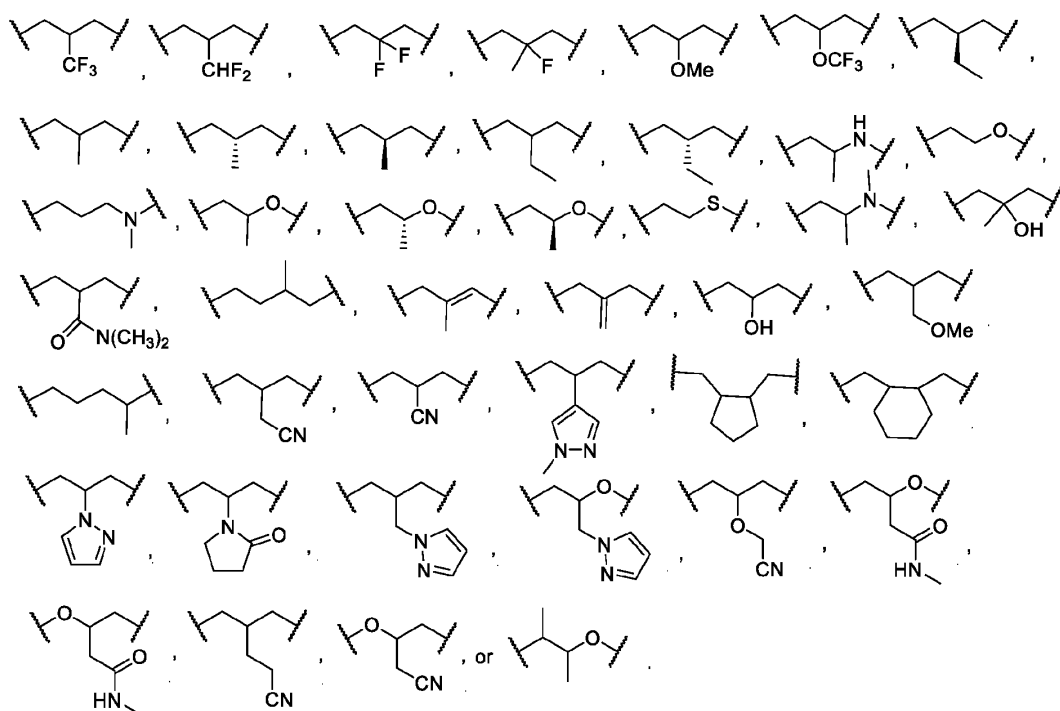
A203a. In embodiment A203a, the compound of any one of embodiments A1A to A202, or a pharmaceutically acceptable salt thereof, is wherein alk is:



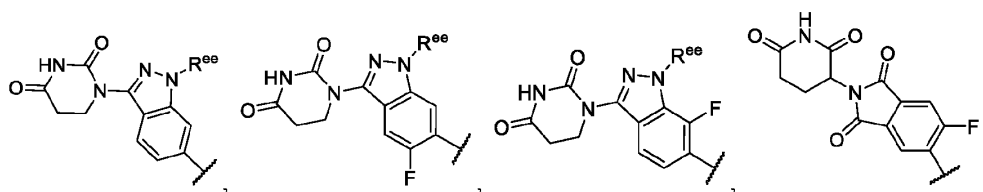
A203b. In embodiment A203b, the compound of any one of embodiments A1A to 203a, or a pharmaceutically acceptable salt thereof, is wherein alk is:

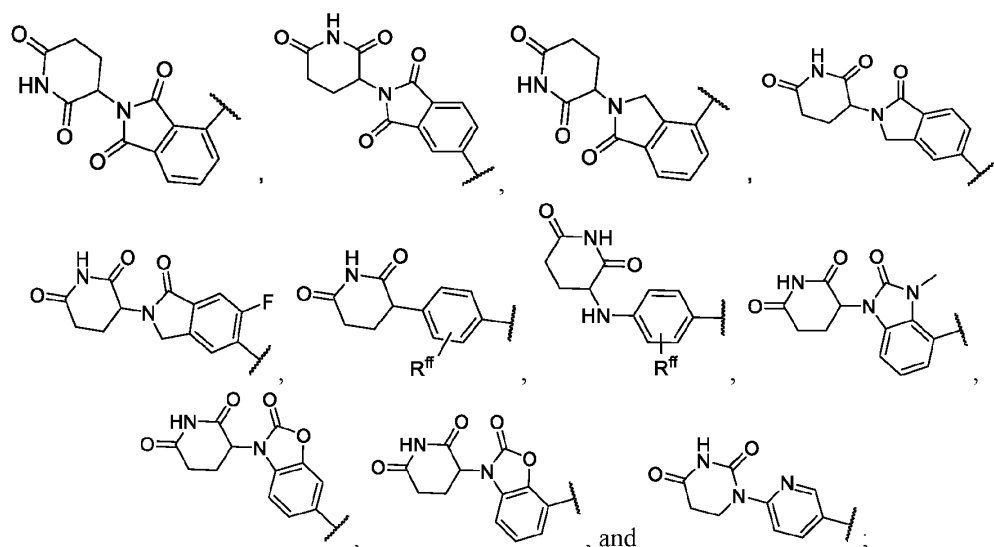


A203. In embodiment A203, the compound of any one of embodiments A1A to A202, or a pharmaceutically acceptable salt thereof, is wherein alk is:



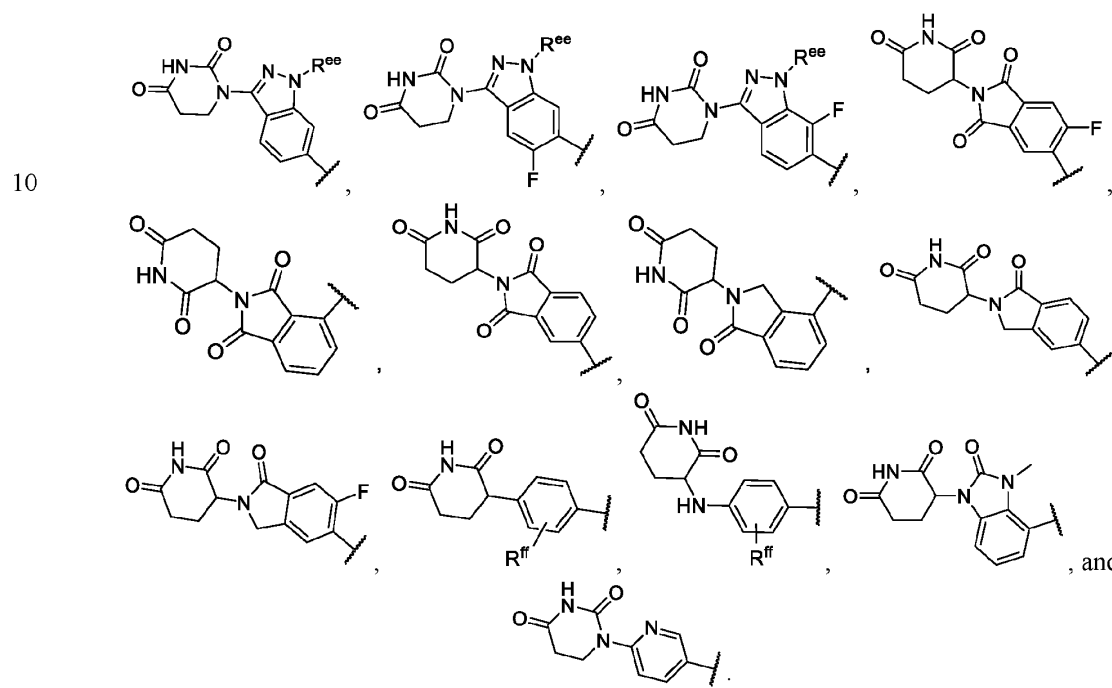
A204. In embodiment A204, the compound of any one of embodiments A1A to A203, or a pharmaceutically acceptable salt thereof, is wherein Degron is the E3 ubiquitin ligase ligand selected from:





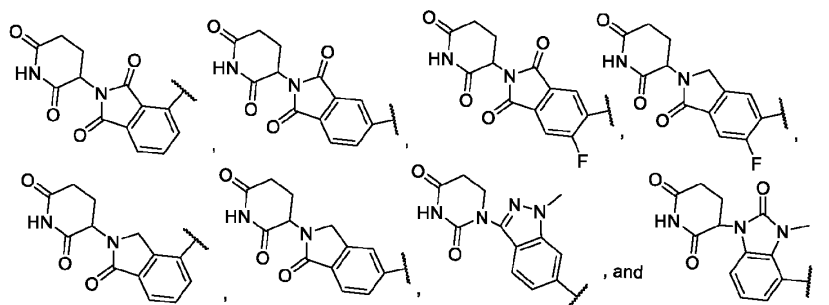
5 where R^{ee} is hydrogen, methyl, ethyl, cyclopropyl, or 2,2,2-trifluoroethyl and R^{ff} is hydrogen, methyl, cyclopropyl, fluoro, cyano, methoxy, difluoromethoxy, trifluoromethoxy, or trifluoromethyl.

A205. In embodiment A205, the compound of any one of embodiments A1A to A204, or a pharmaceutically acceptable salt thereof, is wherein Degron is the E3 ubiquitin ligase ligand selected from:

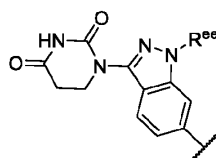


15 where R^{ee} is hydrogen, methyl, ethyl, cyclopropyl, or 2,2,2-trifluoroethyl and R^{ff} is hydrogen, methyl, cyclopropyl, fluoro, cyano, methoxy, difluoromethoxy, trifluoromethoxy, or trifluoromethyl.

A206. In embodiment A206, the compound of any one of embodiments A1A to A205, or a pharmaceutically acceptable salt thereof, is wherein Degron is the E3 ligase ligand selected from:



A207. In embodiment A207, the compound of any one of embodiments A1A A39b, A67, A69 to A72, A77, A79 to A93, A97a to A205, or a pharmaceutically acceptable salt thereof, is



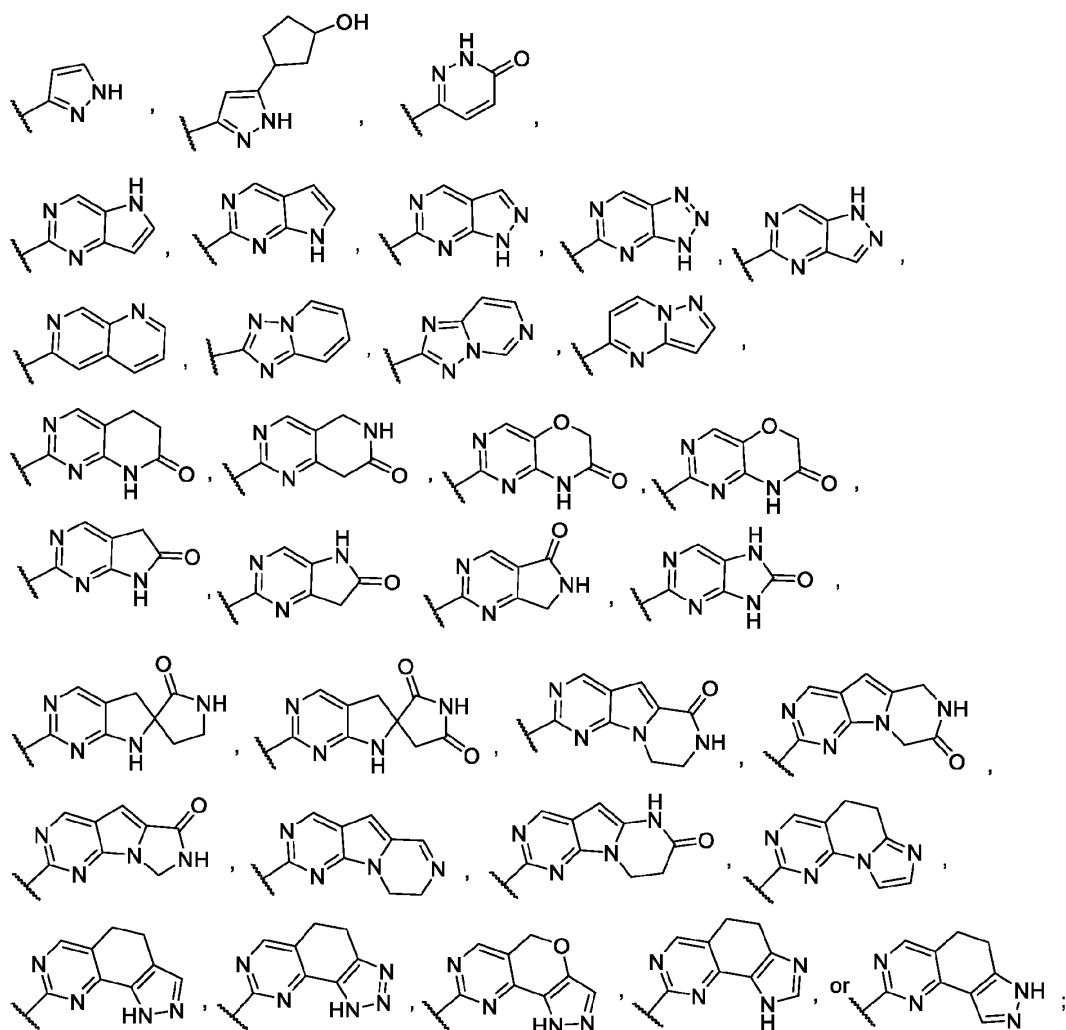
wherein Degron is the E3 ubiquitin ligase ligand is where each R^{ee} is hydrogen, methyl, ethyl, cyclopropyl, or 2,2,2-trifluoroethyl, preferably methyl and R^{ff} is hydrogen, methyl, cyclopropyl, fluoro, cyano, methoxy, difluoromethoxy, trifluoromethoxy, or trifluoromethyl.

“Unless stated otherwise” as used in the embodiments means that when an embodiment refers to more than one preceding embodiment of varying scopes, only those groups that fall within the scope of group(s) recited in a preceding embodiment(s) should be selected from the embodiment referring thereto. For example, of the groups recited in embodiment A6, while all the recited groups in A6 should be selected for embodiment A1, only fluoro, chloro, and bromo should be selected for embodiment A2 as scope of A2 is limited to halo; and only difluoromethyl, trifluoromethyl, difluoroethyl, and trifluoroethyl should be selected for embodiment A4 as scope of A4 is limited to haloalkyl.

Embodiment B:

B1. In embodiment B1, provided is a compound of Formula (IA), or a pharmaceutically acceptable salt thereof, as described in the first aspect of the Summary and/or first embodiment thereof.

B2. In embodiment B2, provided is a compound of Formula (IA), or a pharmaceutically acceptable salt thereof, wherein HET in Formula (IA) is:



5 where each of the above rings is substituted with R^x , R^y , and R^z .

B3. In embodiment B3, provided is a compound of embodiment B1 or B2, or a pharmaceutically acceptable salt thereof, wherein Q is CH.

B4. In embodiment B4, provided is a compound of embodiment B1 or B2, or a pharmaceutically acceptable salt thereof, wherein Q is N.

10 B5. In embodiment B5, provided is a compound of any one of embodiments B1 to B4, or a pharmaceutically acceptable salt thereof, wherein R^{1a} is hydrogen.

B6. In embodiment B6, provided is a compound of any one of embodiments B1 to B4, or a pharmaceutically acceptable salt thereof, wherein R^{1a} is deuterium.

15 B7. In embodiment B7, provided is a compound of any one of embodiments B1 to B4, or a pharmaceutically acceptable salt thereof, wherein R^{1a} is alkyl, preferably methyl or ethyl.

B8. In embodiment B8, provided is a compound of any one of embodiments B1 to B4, or a pharmaceutically acceptable salt thereof, wherein R^{1a} is halo, preferably fluoro.

B9. In embodiment B9, provided is a compound of any one of embodiments B1 to B4, or a pharmaceutically acceptable salt thereof, wherein R^{1a} is haloalkyl, preferably trifluoromethyl.

5 B10. In embodiment B10, provided is a compound of any one of embodiments B1 to B4, or a pharmaceutically acceptable salt thereof, wherein R^{1a} is alkoxy, preferably methoxy.

B11. In embodiment B11, provided is a compound of any one of embodiments B1 to B4, or a pharmaceutically acceptable salt thereof, wherein R^{1a} is hydroxy.

10 B12. In embodiment B12, provided is a compound of any one of embodiments B1 to B4, or a pharmaceutically acceptable salt thereof, wherein R^{1a} is cyano.

B13 to B73. In embodiments B13 to B73, provided is a compound of any one of embodiments B1 to B12, or a pharmaceutically acceptable salt thereof, wherein Degron is as provided in any one of embodiments A40 to A96 and A204 to A207.

15 B74 to B84. In embodiments B74 to B84, provided is a compound of any one of embodiments B1 to B73, or a pharmaceutically acceptable salt thereof, wherein Z is as provided in any one of embodiments A109 to A119.

B85 to B97. In embodiments B85 to B97, provided is a compound of any one of embodiments B1 to B84, or a pharmaceutically acceptable salt thereof, wherein -Z-alk-Ar-SO₂- is as provided in any one of embodiments A120 to A132.

20 B98 to B166. In embodiments B98 to B166, provided is a compound of any one of embodiments B1 to B97, or a pharmaceutically acceptable salt thereof, wherein alk is as provided in any one of embodiments A135 to A203.

B167 to B190. In embodiments B167 to B190, provided is a compound of any one of embodiments B1 to B166, or a pharmaceutically acceptable salt thereof, wherein Ar is as provided in
25 any one of embodiments A97 to A108 and A133 to A134.

Embodiment C:

C1. In embodiment C1, provided is a compound of Formula (I) or a pharmaceutically acceptable salt as defined in the Summary; or a pharmaceutically acceptable salt thereof.

30 C2. In embodiment C2, the compound of embodiment C1, or a pharmaceutically acceptable salt thereof, wherein R¹ is halo.

C3. In embodiment C3, the compound of embodiment C1, or a pharmaceutically acceptable salt thereof, wherein R¹ is haloalkyl or haloalkoxy.

C4. In embodiment C4, the compound of embodiment C1 and C3, or a pharmaceutically acceptable salt thereof, wherein R^1 is haloalkyl.

C5. In embodiment C5, the compound of embodiment C1 and C3, or a pharmaceutically acceptable salt thereof, wherein R^1 is haloalkoxy.

5 C6. In embodiment C6, the compound of embodiment C1 or C2, or a pharmaceutically acceptable salt thereof, wherein R^1 is chloro or bromo.

C7. In embodiment C7, the compound of embodiments C1, C3, or C4, or a pharmaceutically acceptable salt thereof, wherein R^1 is difluoromethyl or trifluoromethyl.

10 C8. In embodiment C8, the compound of any one of embodiments C1, C3, and C5, or a pharmaceutically acceptable salt thereof, wherein R^1 is difluoromethoxy or trifluoromethoxy.

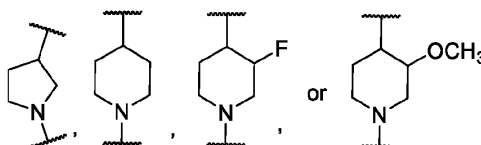
C9. In embodiment C9, the compound of embodiment C1, or a pharmaceutically acceptable salt thereof, wherein R^1 is methyl, ethyl, propyl, vinyl, propenyl, ethynyl, or propynyl.

C10. In embodiment C10, the compound of any one of embodiments C1 to C9, or a pharmaceutically acceptable salt thereof, wherein R^2 and R^{2a} are hydrogen.

15 C11. In embodiment C11, the compound of any one of embodiments C1 to C9, or a pharmaceutically acceptable salt thereof, wherein one of R^2 and R^{2a} is deuterium and the other of R^2 and R^{2a} is hydrogen, or both R^2 and R^{2a} are deuterium.

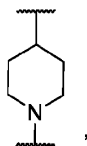
20 C12. In embodiment C12, the compound of any one of embodiments C1 to C11, or a pharmaceutically acceptable salt thereof, wherein Hy is heterocyclylene substituted with R^a , R^b , and R^c where R^a and R^b are independently selected from hydrogen, deuterium, alkyl, halo, haloalkyl, alkoxy, hydroxy, and cyano, and R^c is hydrogen.

C13. In embodiment C13, the compound of any one of embodiments C1 to C12, or a pharmaceutically acceptable salt thereof, wherein the heterocyclylene of Hy is:



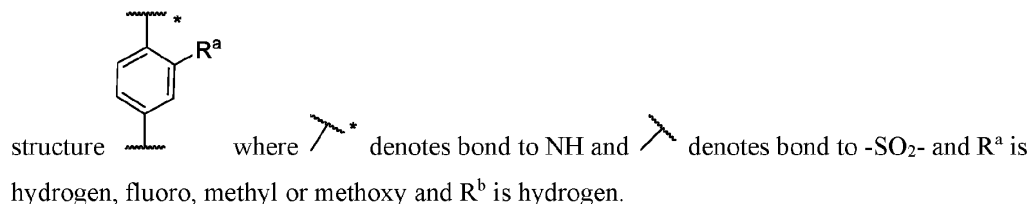
25 where the N atom of the pyrrolidine-1,3-diyl or piperidine-1,4-diyl rings is attached to $-SO_2-$.

C14. In embodiment C14, the compound of any one of embodiments C1 to C13, or a pharmaceutically acceptable salt thereof, wherein the heterocyclylene of Hy is:

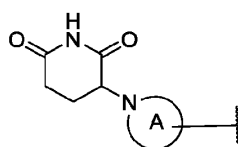


where the N atom of the piperidine-1,4-diyl ring is attached to $-SO_2-$.

C15. In embodiment C15, the compound of any one of embodiments C1 to C11, or a pharmaceutically acceptable salt thereof, wherein the phenylene of Hy is 1,4-phenylene according to

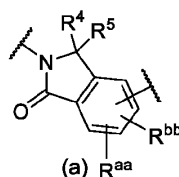


- 5 C16. In embodiment C16, the compound of any one of embodiments C1 to C15, or a pharmaceutically acceptable salt thereof, wherein the Degron is an E3 ubiquitin ligase ligand of formula (i):

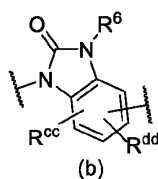


(i).

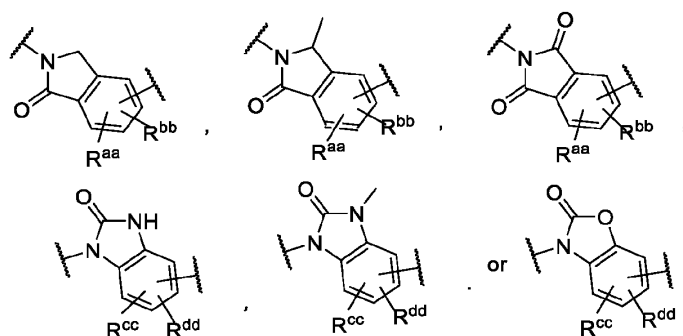
- 10 C17. In embodiment C17, the compound of any one of embodiments C1 to C16, or a pharmaceutically acceptable salt thereof, wherein the ring A of the E3 ubiquitin ligase ligand of formula (i) is a group of formula (a):



- 15 C18. In embodiment C18, the compound of any one of embodiments C1 to C16, or a pharmaceutically acceptable salt thereof, wherein the ring A of the E3 ubiquitin ligase ligand of formula (i) is a group of formula (b):

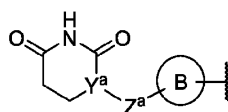


- 20 C19. In embodiment C19, the compound of any one of embodiments C1 to C18, or a pharmaceutically acceptable salt thereof, wherein the ring A of the E3 ubiquitin ligase ligand of formula (i) is:



C20. In embodiment C20, the compound of any one of embodiments C1 to C19, or a pharmaceutically acceptable salt thereof, wherein R^{aa} and R^{bb} , R^{cc} , and R^{dd} are independently
5 selected from hydrogen, methyl, methoxy, ethoxy, fluoro, trifluoromethyl, difluoromethyl, and trifluoromethoxy.

C21. In embodiment C21, the compound of any one of embodiments C1 to C15, or a pharmaceutically acceptable salt thereof, wherein the Degron is an E3 ubiquitin ligase ligand of formula (ii):



(ii).

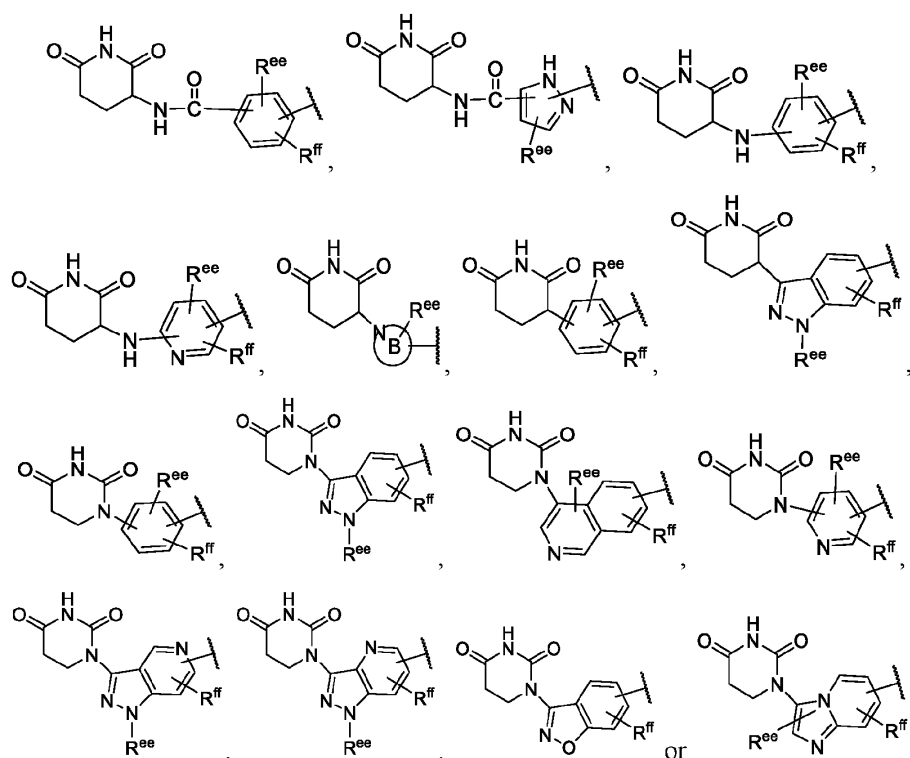
C22. In embodiment C22, the compound of any one of embodiments C1 to C15 and 17 to 21, or a pharmaceutically acceptable salt thereof, wherein Y^a is CH.

C23. In embodiment C23, the compound of any one of embodiments C1 to C15 and C17
15 to C21, or a pharmaceutically acceptable salt thereof, wherein Y^a is N.

C24. In embodiment C24, the compound of any one of embodiments C1 to C15 and C17 to C23, or a pharmaceutically acceptable salt thereof, wherein Z^a is a bond, -NH-, -O-, or -NHC(O)-.

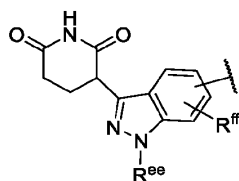
C25. In embodiment C25, the compound of any one of embodiments C1 to C15 and C17 to C24, or a pharmaceutically acceptable salt thereof, wherein ring B is 5- or 6-membered
20 monocyclic heteroarylene or a 9- or 10-membered fused bicyclic heteroarylene, wherein each heteroarylene ring contains one to three nitrogen ring atoms and each ring of ring B is substituted with R^{ee} and R^{ff} .

C26. In embodiment C26, the compound of any one of embodiments C1 to C15 and C17 to C25, or a pharmaceutically acceptable salt thereof, wherein the E3 ubiquitin ligase ligand of formula
25 (ii) is:



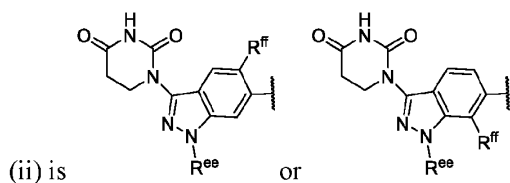
5 where ring B is cyclylaminylene.

C27. In embodiment C27, the compound of any one of embodiments C1 to C15 and C17 to C26, or a pharmaceutically acceptable salt thereof, wherein the E3 ubiquitin ligase ligand of



formula (ii) is

10 C28. In embodiment C28, the compound of any one of embodiments C1 to C15 and C17 to C27, or a pharmaceutically acceptable salt thereof, wherein the E3 ubiquitin ligase ligand of formula



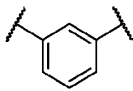
(ii) is

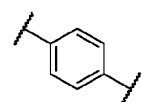
or

C29. In embodiment C29, the compound of any one of embodiments C1 to C15 and C17 to C28, or a pharmaceutically acceptable salt thereof, wherein R^{ee} and R^{ff} are independently selected from hydrogen, methyl, ethyl, isopropyl, cyclopropyl, methoxy, ethoxy, fluoro, chloro, trifluoromethyl, 2,2,2-trifluoroethyl, difluoromethyl, difluoromethoxy, trifluoromethoxy, and cyano.

C30. In embodiment C30, the compound of any one of embodiments C1 to C29, or a pharmaceutically acceptable salt thereof, wherein Ar is phenylene, monocyclic heteroaryl, bridged heterocyclylene, or heterocyclylene, where each ring of Ar is substituted with R^j , R^k , and R^m where R^m is hydrogen.

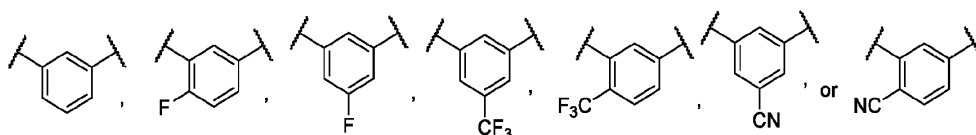
5 C31. In embodiment C31, the compound of any one of embodiments C1 to C30, or a

pharmaceutically acceptable salt thereof, wherein Ar is phenylene of formula  or

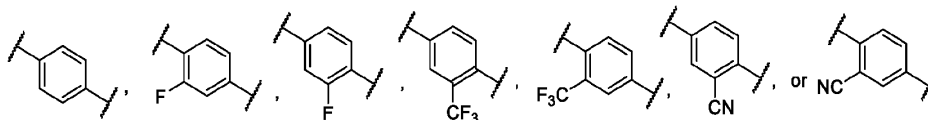


substituted with R^j , R^k , and R^m where R^j and R^k are independently selected from hydrogen, alkyl, alkoxy, halo, cyano, haloalkyl, and haloalkoxy and R^m is hydrogen.

10 C32. In embodiment C32, the compound of any one of embodiments C1 to C31, or a pharmaceutically acceptable salt thereof, wherein the phenylene of Ar is



C33. In embodiment C33, the compound of any one of embodiments C1 to C31, or a pharmaceutically acceptable salt thereof, wherein the phenylene of Ar is

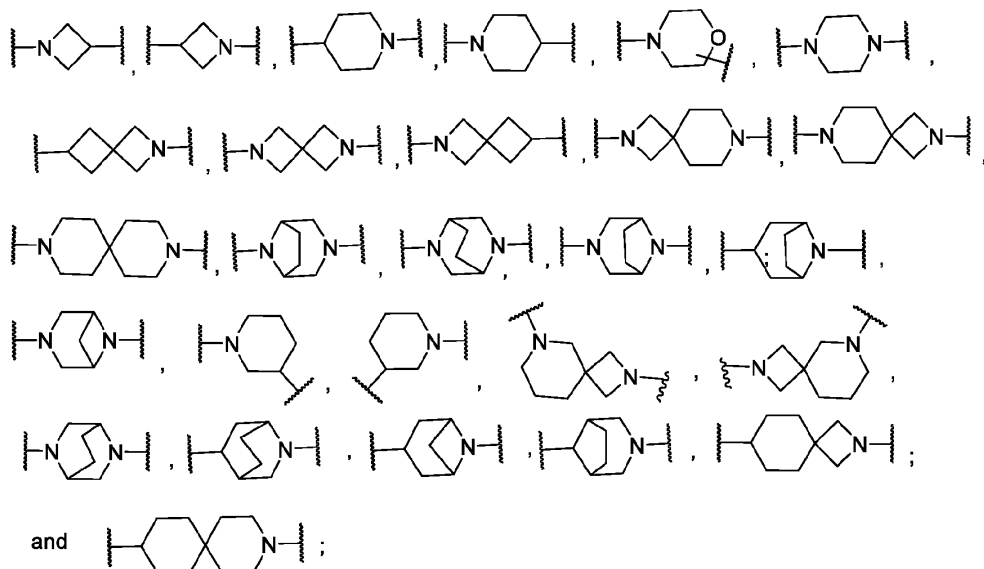


15 C34. In embodiment C34, the compound of any one of embodiments C1 to C30, or a pharmaceutically acceptable salt thereof, wherein Ar is monocyclic heteroaryl (such as imidazol-1,5-diyl, pyridin-2,4-diyl, pyridin-2,6-diyl, pyridin-2,5-diyl, or pyridin-3,5-diyl) substituted with R^j , R^k , and R^m where R^j and R^k are independently selected from hydrogen, alkyl, alkoxy, halo, haloalkyl, cyano, and haloalkoxy and R^m is hydrogen.

20 C35. In embodiment C35, the compound of any one of embodiments C1 to C30, or a pharmaceutically acceptable salt thereof, wherein Ar is heterocyclylene substituted with R^j , R^k , and R^m where R^j and R^k are independently selected from hydrogen, methyl, methoxy, fluoro, chloro, difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, difluoromethoxy, and trifluoromethoxy and R^m is hydrogen.

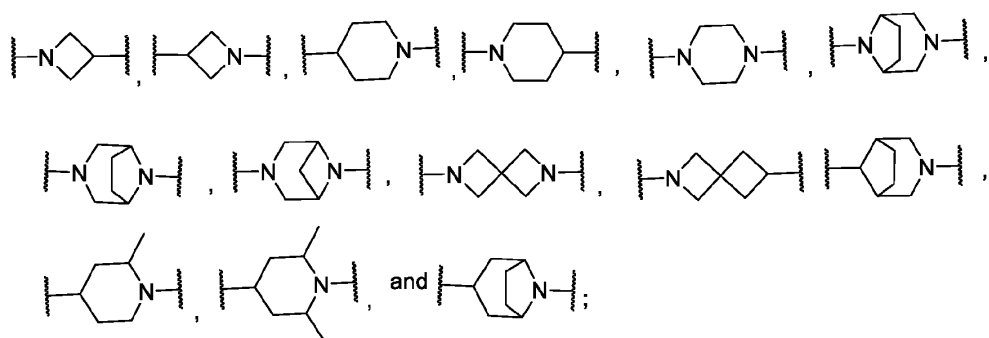
C36. In embodiment C36, the compound of any one of embodiments C1 to C35, or a pharmaceutically acceptable salt thereof, wherein Z is heterocyclylene, bridged heterocyclylene, or spiro heterocyclylene, where each ring of Z is substituted with R^d and R^e.

C37. In embodiment C37, the compound of any one of embodiments C1 to C36, or a
5 pharmaceutically acceptable salt thereof, wherein the heterocyclylene, bridged heterocyclylene, and
spiro heterocyclylene of Z are selected from:



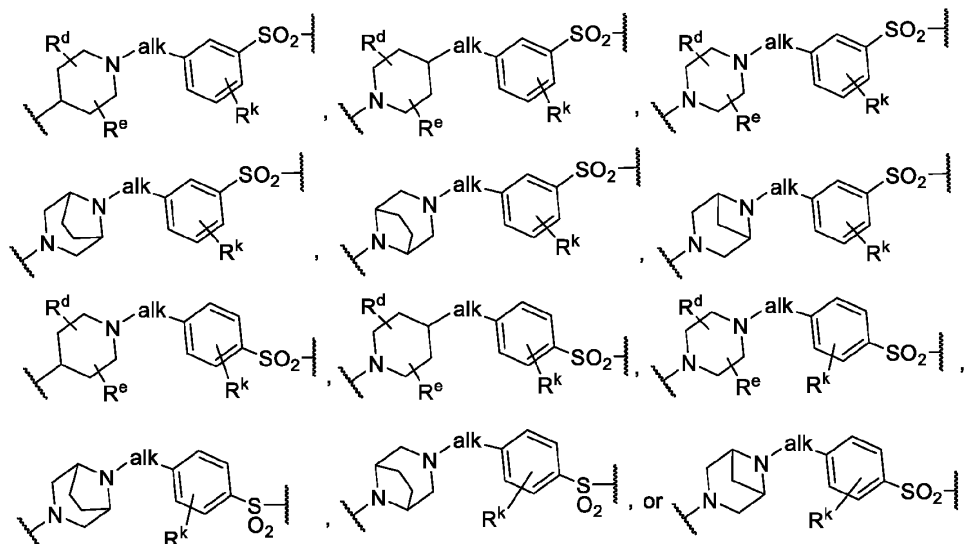
respectively, and wherein each of the above rings is substituted with R^d and R^e independently selected from hydrogen, deuterium, alkyl, and halo.

10 C38. In embodiment C38, the compound of any one of embodiments C1 to C37, or a pharmaceutically acceptable salt thereof, wherein the heterocyclylene, bridged heterocyclylene, and spiro heterocyclylene of Z are independently selected from:



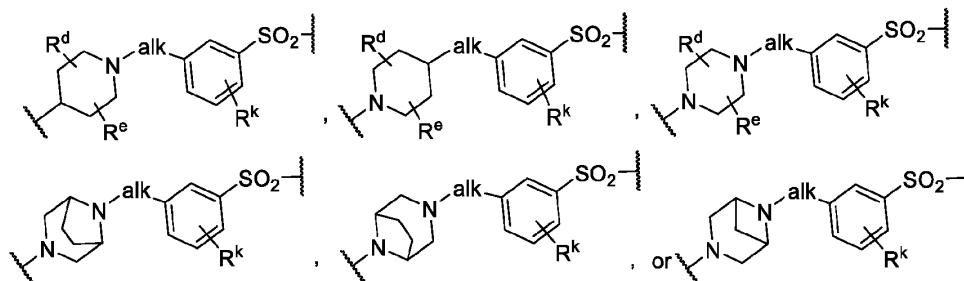
respectively.

C39. In embodiment C39, the compound of any one of embodiments C1 to C31 and C36 to C38, or a pharmaceutically acceptable salt thereof, wherein -Z-alk-Ar-SO₂- is:



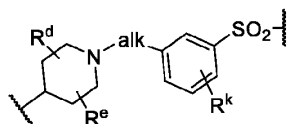
wherein each R^d, R^e, and R^k are independently selected from hydrogen, alkyl, halo, haloalkyl, haloalkoxy, alkoxy, and cyano and R^j is hydrogen.

C40. In embodiment C40, the compound of any one of embodiments C1 to C31 and C36 to C39, or a pharmaceutically acceptable salt thereof, wherein -Z-alk-Ar-SO₂- is:

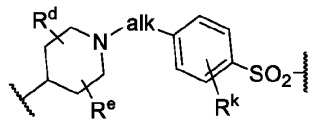


wherein each R^d, R^e, and R^k are independently selected from hydrogen, alkyl, halo, haloalkyl, haloalkoxy, alkoxy, and cyano and R^j is hydrogen.

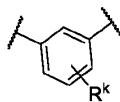
C41. In embodiment C41, the compound of any one of embodiments C1 to C31 and C36 to C40, or a pharmaceutically acceptable salt thereof, wherein -Z-alk-Ar-SO₂- is:

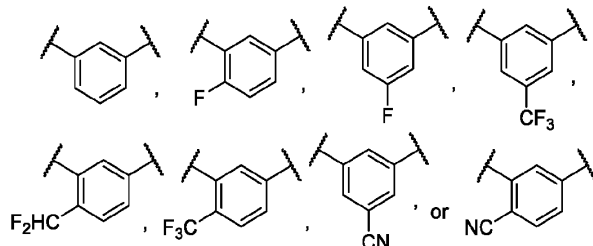


C42. In embodiment C42, the compound of any one of embodiments C1 to C31 and C36 to C39, or a pharmaceutically acceptable salt thereof, wherein -Z-alk-Ar-SO₂- is:



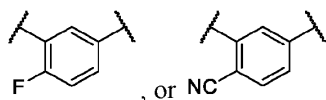
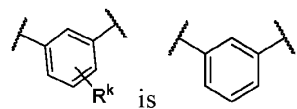
C43. In embodiment C43, the compound of any one of embodiments C39, C40, and C41,

5 or a pharmaceutically acceptable salt thereof, wherein  is:



C44. In embodiment C44, the compound of any one of embodiments C39, C40, C41, and

C43, or a pharmaceutically acceptable salt thereof, wherein



10 C45. In embodiment C45, the compound of any one of embodiments C1 to C44, or a pharmaceutically acceptable salt thereof, wherein alk is C₃ to C₆ alkenylene substituted with R^f where R^f is hydrogen.

C46. In embodiment C46, the compound of any one of embodiments C1 to C44, or a pharmaceutically acceptable salt thereof, wherein alk is C₃ to C₆ alkenylene substituted with R^f where R^f is fluoro or cyano.

C47. In embodiment C47, the compound of any one of embodiments C1 to C44, or a pharmaceutically acceptable salt thereof, wherein alk is C₃ to C₆ alkylene substituted with R^g, R^h, and Rⁱ where R^g, R^h, and Rⁱ are hydrogen.

20 C48. In embodiment C48, the compound of any one of embodiments C1 to 4C4, or a pharmaceutically acceptable salt thereof, wherein alk is C₃ to C₆ alkylene substituted with R^g, R^h, and Rⁱ where R^g, R^h, and Rⁱ are hydrogen or halo provided at least one of R^g, R^h, and Rⁱ is halo.

C49. In embodiment C49, the compound of any one of embodiments C1 to C44, or a pharmaceutically acceptable salt thereof, wherein alk is C₃ to C₆ alkylene substituted with R^g, R^h, and Rⁱ where R^h is other than hydrogen and Rⁱ is hydrogen or when R^g and R^h are attached to the same carbon or to adjacent carbon atoms of the linear portion of the C₃ to C₆ alkylene, R^g and R^h together with the carbon atom to which they are attached can form cycloalkylene or heterocyclylene where the cycloalkylene and heterocyclylene formed by R^g and R^h are substituted with R⁹ and R¹⁰.

C50. In embodiment C50, the compound of any one of embodiments C1 to C44 and C49, or a pharmaceutically acceptable salt thereof, wherein alk is C₃ to C₆ alkylene substituted with R^g, R^h, and Rⁱ where R^h is other than hydrogen and Rⁱ is hydrogen. In an embodiment, the compound of embodiment C49, or a pharmaceutically acceptable salt thereof, is wherein alk is C₃ to C₆ alkylene substituted with R^g, R^h, and Rⁱ where R^h is other than hydrogen and Rⁱ is hydrogen.

C51. In embodiment C51, the compound of any one of embodiments C1 to C50, or a pharmaceutically acceptable salt thereof, wherein the C₃ to C₆ alkenylene and C₃ to C₆ alkylene of alk are linear C₃ to C₆ alkenylene and linear C₃ to C₆ alkylene, respectively, where alk is substituted with R^g, R^h, and Rⁱ.

C52. In embodiment C52, the compound of any one of embodiments C1 to C46 and 49 to 51, or a pharmaceutically acceptable salt thereof, wherein the linear C₃ to C₆ alkenylene of alk is -CH=C(R^f)CH₂- and the linear alkylene of C₃ to C₆ alkylene of alk is -CH₂CH(R^h)CH₂-, -CH₂CH₂CH(R^h)-, -CH₂C(R^g)(R^h)CH₂-, -CH₂CH₂C(R^g)(R^h)- where R^h is other than hydrogen and Rⁱ is hydrogen.

C53. In embodiment C53, the compound of any one of embodiments C1 to C44 and C49 to C52, or a pharmaceutically acceptable salt thereof, wherein the linear C₃ to C₆ alkylene of alk is -CH₂CH(R^h)CH₂- where R^h is other than hydrogen and Rⁱ is hydrogen.

C54. In embodiment C54, the compound of any one of embodiments C1 to C44 and C49 to C53, or a pharmaceutically acceptable salt thereof, wherein R^g of linear C₃ to C₆ alkylene of alk is hydrogen, deuterium, or halo and R^h of linear C₃ to C₆ alkylene of alk is halo, haloalkoxy, cycloalkyl, cycloalkyloxy, alkoxy, hydroxy, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylcarbonylamino, cyano, cyanoalkyloxy, phenyl, heteroaryl, heterocyclyl, or bridged heterocyclyl, each ring of R^h is substituted with R⁷ and R⁸.

C55. In embodiment C55, the compound of any one of embodiments C1 to C44 and C49 to C54, or a pharmaceutically acceptable salt thereof, wherein R^g of linear C₃ to C₆ alkylene of alk is hydrogen and R^h of linear C₃ to C₆ alkylene of alk is halo, haloalkoxy, cycloalkyl, cycloalkyloxy, alkoxy, hydroxy, dialkylaminocarbonyl, alkylcarbonylamino, cyano, phenyl, heteroaryl, heterocyclyl, or bridged heterocyclyl, each ring of R^h is substituted with R⁷ and R⁸.

C56. In embodiment C56, the compound of any one of embodiments C1 to C44 and C49 to C55, or a pharmaceutically acceptable salt thereof, wherein R^g of linear C₃ to C₆ alkylene of alk is hydrogen and R^h of linear C₃ to C₆ alkylene of alk is halo, haloalkoxy, alkoxy, hydroxy, dialkylaminocarbonyl, cyano, heterocyclyl, or heteroaryl, each ring of R^h is substituted with R⁷ and R⁸.

C57. In embodiment C57, the compound of any one of embodiments C1 to C44 and C49 to C56, or a pharmaceutically acceptable salt thereof, wherein the heteroaryl, heterocyclyl, and bridged heterocyclyl of R^h of linear C₃ to C₆ alkylene of alk, when present, are five or six membered ring and each ring of R^h is substituted with R⁷ and R⁸.

C58. In embodiment C58, the compound of any one of embodiments C1 to C44 and C49 to C57, or a pharmaceutically acceptable salt thereof, wherein R^g of linear C₃ to C₆ alkylene of alk is hydrogen, deuterium, or fluoro (unless stated otherwise, e.g. where R^g is hydrogen as stated in embodiments C55 and C56) and R^h of linear C₃ to C₆ alkylene of alk is fluoro, cyclopropyl, cyclobutyl, cyclopropyloxy, cyclobutyloxy, difluoromethoxy, trifluoromethoxy, methoxy, ethoxy, hydroxy, cyano, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, diethylaminocarbonyl, methylcarbonylamino, ethylcarbonylamino, phenyl, pyrazolyl, furanyl, thiazolyl, pyridinyl, pyrrolidinyl, 2-oxopyrrolidinyl, piperidinyl, piperazinyl, or tetrahydrofuranyl, each ring of R^h is substituted with R⁷ and R⁸ independently selected from hydrogen, deuterium, methyl, methoxy, fluoro, difluoromethyl, trifluoromethyl, difluoromethoxy, trifluoromethyl, hydroxy, amino, methylamino, dimethylamino and cyano, unless stated otherwise.

C59. In embodiment C59, the compound of any one of embodiments C1 to C44 and C49 to C58, or a pharmaceutically acceptable salt thereof, wherein R^g of linear C₃ to C₆ alkylene of alk is hydrogen and R^h of linear C₃ to C₆ alkylene of alk is fluoro, cyclopropyl, cyclopropyloxy, difluoromethoxy, trifluoromethoxy, methoxy, ethoxy, hydroxy, cyano, methylaminocarbonyl, dimethylaminocarbonyl, methylcarbonylamino, phenyl, pyrazol-1-yl, pyrazol-4-yl, pyridin-4-yl, pyrrolidin-1-yl, or 2-oxopyrrolidin-1-yl, each ring of R^h is substituted with R⁷ and R⁸ independently selected from hydrogen, deuterium, methyl, and fluoro, unless stated otherwise.

C60. In embodiment C60, the compound of any one of embodiments C1 to C44, or a pharmaceutically acceptable salt thereof, wherein alk is branched C₄ to C₆ alkylene substituted with R^g, R^h, and Rⁱ.

C61. In embodiment C61, the compound of any one of embodiments C1 to C46 and C60, or a pharmaceutically acceptable salt thereof, wherein the C₃ to C₆ alkenylene and C₃ to C₆ alkylene of alk are branched C₄ to C₆ alkenylene and C₄ to C₆ alkylene, respectively.

C62. In embodiment C62, the compound of any one of embodiments C1 to C46, C60, and C61, or a pharmaceutically acceptable salt thereof, wherein the branched C₄ to C₆ alkenylene of alk is -CH₂CH₂C(CH₃)=C(R^f)-, -CH₂C(CH₃)=C(R^f)-, or -CH₂C(=CH₂)CH₂- and the branched C₄ to C₆ alkylene of alk is -CH₂C(CH₃)(R^h)CH₂-, -CH₂C(C₂H₅)(R^h)CH₂-,

- 5 -CH₂CH(CH₂R^h)CH₂-, -CH₂CH(CH₂CH₂R^h)CH₂-, -CH₂C(CH₃)(CH₂R^h)CH₂-,
 -CH₂C(C₂H₅)(CH₂R^h)CH₂-, -CH₂C(CH₃)(CH₂CH₂R^h)CH₂-, -CH₂CH(CH₃)CH(CH₂R^h)-,
 -CH₂CH₂C(CH₃)(CH₂R^h)-, -CH₂CH(CH₃)C(R^s)(R^h)-, -CH₂CH(C₂H₅)C(R^s)(R^h)-,
 -CH₂CH(C(R^s)(R^h)(Rⁱ))CH(CH₃)-, -CH₂C(CH₃)(C(R^s)(R^h)(Rⁱ))CH(CH₃)-,
 -CH₂CH(C(R^s)(R^h)(Rⁱ))CH₂-, -CH₂CH₂CH(C(R^s)(R^h)(Rⁱ))-, -CH₂CH₂CH(C(R^s)(R^h)(Rⁱ))CH₂-,
 10 or -CH₂CH₂CH₂CH(C(R^s)(R^h)(Rⁱ))-.

C63. In embodiment C63, the compound of any one of embodiments C1 to C46 and C60 to C62, or a pharmaceutically acceptable salt thereof, wherein the branched C₄ to C₆ alkenylene of alk is -CH₂C(CH₃)=C(R^f)- or -CH₂C(=)CH₂- and the branched C₄ to C₆ alkylene of alk is -CH₂C(CH₃)(R^h)CH₂-, -CH₂CH(CH₂R^h)CH₂-, -CH₂CH(CH₂CH₂R^h)CH₂-,
 15 -CH₂CH(C(R^s)(R^h)(Rⁱ))CH₂-, -CH₂CH₂CH(C(R^s)(R^h)(Rⁱ))CH₂-, or
 -CH₂CH₂CH₂CH(C(R^s)(R^h)(Rⁱ))-.

- C64. In embodiment C64, the compound of any one of embodiments C1 to C44 and C60 to C63, or a pharmaceutically acceptable salt thereof, wherein the R^s and Rⁱ of branched C₄ to C₆ alkylene of alk are independently hydrogen or halo (unless stated otherwise) and R^h of branched C₄ to C₆ alkylene of alk is hydrogen, halo, haloalkoxy, cycloalkyl, cycloalkyloxy, alkoxy, hydroxy, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylcarbonylamino, cyano, cyanoalkyloxy, phenyl, heteroaryl, heterocyclyl, heterocyclyloxy, heterocyclylcarbonyl, or bridged heterocyclyl, each ring of R^h is substituted with R⁷ and R⁸.
- 20

- C65. In embodiment C65, the compound of any one of embodiments C1 to C44 and C60 to C64, or a pharmaceutically acceptable salt thereof, wherein the R^s and Rⁱ of branched C₄ to C₆ alkylene of alk are hydrogen or fluoro (unless stated otherwise) and R^h of branched C₄ to C₆ alkylene of alk is hydrogen, halo, cycloalkyl, cycloalkyloxy, alkoxy, hydroxy, alkylaminocarbonyl, dialkylaminocarbonyl, alkylcarbonylamino, cyano, phenyl, heteroaryl, heterocyclyl, heterocyclyloxy, heterocyclylcarbonyl, or bridged heterocyclyl, each ring of R^h is substituted with R⁷ and R⁸.
- 25

- C66. In embodiment C66, the compound of any one of embodiments C1 to C44 and C60 to C65, or a pharmaceutically acceptable salt thereof, wherein R^s and Rⁱ of branched C₄ to C₆ alkylene of alk are hydrogen or fluoro and R^h of branched C₄ to C₆ alkylene of alk is hydrogen, halo, alkoxy, hydroxy, dialkylaminocarbonyl, cyano, or heteroaryl substituted with R⁷ and R⁸.
- 30

C67. In embodiment C67, the compound of any one of embodiments C1 to C44 and C60 to C66, or a pharmaceutically acceptable salt thereof, wherein the heteroaryl, heterocyclyl, by itself or as part of heterocyclyloxy, heterocyclylcarbonyl, and bridged heterocyclyl of branched C₄ to C₆ alkylene of alk, when present, are five or six membered ring and each ring of R^h is substituted with R⁷ and R⁸.

C68. In embodiment C68, the compound of any one of embodiments C1 to C44 and C60 to C67, or a pharmaceutically acceptable salt thereof, is R^g and Rⁱ of branched C₄ to C₆ alkylene of alk are (unless stated otherwise) hydrogen, deuterium, or fluoro and R^h of branched C₄ to C₆ alkylene of alk, unless stated otherwise, is hydrogen, deuterium, fluoro, cyclopropyl, cyclobutyl, cyclopropyloxy, cyclobutyloxy, difluoromethoxy, trifluoromethoxy, methoxy, ethoxy, hydroxy, cyano, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, diethylaminocarbonyl, methylcarbonylamino, ethylcarbonylamino, phenyl, pyrazolyl, thiazolyl, furanyl, pyridinyl, pyrrolidinyl, 2-oxopyrrolidinyl, piperidinyl, piperazinyl, tetrahydrofuranyl, each ring of R^h is substituted with R⁷ and R⁸ independently selected from hydrogen, deuterium, methyl, methoxy, fluoro, difluoromethyl, trifluoromethyl, difluoromethoxy, trifluoromethyl, hydroxy, amino, methylamino, dimethylamino and cyano, unless stated otherwise.

C69. In embodiment C69, the compound of any one of embodiments C1 to C44 and C60 to C68, or a pharmaceutically acceptable salt thereof, wherein R^g and Rⁱ of branched C₄ to C₆ alkylene of alk, unless stated otherwise, is hydrogen or fluoro and R^h of branched C₄ to C₆ alkylene of alk, is hydrogen, fluoro, hydroxy, methoxy, cyano, pyrazolyl-1-yl, or methylaminocarbonyl.

C70. In embodiment C70, the compound of any one of embodiments C1 to C44 and C49, or a pharmaceutically acceptable salt thereof, wherein alk is C₃ to C₆ alkylene substituted with R^g, R^h, and Rⁱ where R^g and R^h are attached to the same carbon or to adjacent carbon atoms of the linear portion of the C₃ to C₆ alkylene and R^g and R^h together with the carbon atom(s) to which they are attached can form cycloalkylene or heterocyclylene where the cycloalkylene and heterocyclylene formed by R^g and R^h are substituted with R⁹ and R¹⁰.

C71. In embodiment C71, the compound of any one of embodiments C1 to C44, C49, and C70, or a pharmaceutically acceptable salt thereof, wherein alk is C₃ to C₆ alkylene substituted with R^g, R^h, and Rⁱ where R^g and R^h are attached to the same carbon atom of the linear portion of the C₃ to C₆ alkylene and together with the carbon atom to which they are attached can form cycloalkylene substituted with R⁹ and R¹⁰.

C72. In embodiment C72, the compound of any one of embodiments C1 to C44, C49, and C70, or a pharmaceutically acceptable salt thereof, wherein alk is C₃ to C₆ alkylene substituted with R^g, R^h, and Rⁱ where R^g and R^h are attached to the same carbon atom of the linear portion of the C₃ to

C₆ alkylene and together with the carbon atom to which they are attached can form heterocyclylene substituted with R⁹ and R¹⁰.

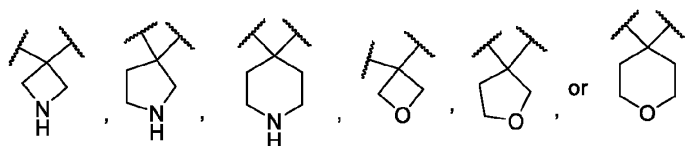
C73. In embodiment C73, the compound of any one of embodiments C1 to C44, C49, and C70, or a pharmaceutically acceptable salt thereof, wherein alk is C₃ to C₆ alkylene substituted with R^g, R^h, and Rⁱ where R^g and R^h are attached to adjacent carbon atoms of the linear portion of the C₃ to C₆ alkylene and together with the carbon atoms to which they are attached can form cycloalkylene substituted with R⁹ and R¹⁰.

C74. In embodiment C74, the compound of any one of embodiments C1 to C44, C49, and C70, or a pharmaceutically acceptable salt thereof, wherein alk is C₃ to C₆ alkylene substituted with R^g, R^h, and Rⁱ where R^g and R^h are attached to adjacent same carbon atom of the linear portion of the C₃ to C₆ alkylene and together with the carbon atom to which they are attached can form heterocyclylene substituted with R⁹ and R¹⁰.

C75. In embodiment C75, the compound of any one of embodiments C1 to C44, C49, and C70 to C72, or a pharmaceutically acceptable salt thereof, wherein R^g and R^h are attached to the same carbon atom of the linear portion of the C₃ to C₆ alkylene and together with the carbon atom to which they are attached can form cycloalkylene of formula:

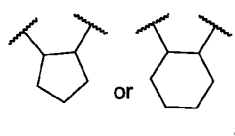


or heterocyclylene of formula:

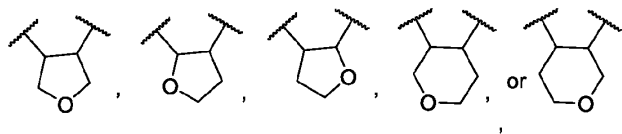


where each of the above rings substituted with R⁹ and R¹⁰, preferably R⁹ is hydrogen, halo, methyl or ethyl and R¹⁰ is hydrogen.

C76. In embodiment C76, the compound of any one of embodiments C1 to C44, C49, C70, C73, and C74, or a pharmaceutically acceptable salt thereof, wherein R^g and R^h are attached to adjacent carbon atoms of the linear portion of the C₃ to C₆ alkylene and together with the carbon atoms to which they are attached can form cycloalkylene of formula:



and heterocyclylene of formula:



where each of the above rings is substituted with R^9 and R^{10} , preferably R^9 is hydrogen, halo, methyl, or ethyl and R^{10} is hydrogen.

C77. In embodiment C77, the compound of any one of embodiments C1 to C44, or a
 5 pharmaceutically acceptable salt thereof, wherein the alk is C_3 to C_6 heteroalkylene substituted with R^g , R^h , and R^i .

C78. In embodiment C78, the compound of any one of embodiments C1 to C44 and C77,
 or a pharmaceutically acceptable salt thereof, wherein the alk is C_3 to C_6 heteroalkylene substituted
 with R^g , R^h , and R^i where R^g , R^h , and R^i are hydrogen.

10 C79. In embodiment C79, the compound of any one of embodiments C1 to C44 and C77,
 or a pharmaceutically acceptable salt thereof, wherein the alk is C_3 to C_6 heteroalkylene substituted
 with R^g , R^h , and R^i where R^g , R^h , and R^i are hydrogen or halo, provided at least one of R^g , R^h , and R^i
 is halo.

C80. In embodiment C80, the compound of any one of embodiments C1 to C44 and C77,
 15 or a pharmaceutically acceptable salt thereof, wherein alk is C_3 to C_6 heteroalkylene substituted with
 R^g , R^h , and R^i where R^h is other than hydrogen and R^i is hydrogen or when R^g and R^h are attached to
 the same carbon or to adjacent carbon atoms of the linear portion of the C_3 to C_6 alkylene, R^g and R^h
 together with the carbon atom(s) to which they are attached can form cycloalkylene or
 heterocyclylene where the cycloalkylene and heterocyclylene formed by R^g and R^h are substituted
 20 with R^9 and R^{10} .

C81. In embodiment C81, the compound of any one of embodiments C1 to C44 and C80,
 or a pharmaceutically acceptable salt thereof, wherein alk is C_3 to C_6 heteroalkylene substituted with
 R^g , R^h , and R^i where R^h is other than hydrogen and R^i is hydrogen.

C82. In embodiment C82, the compound of any one of embodiments C1 to C44 and C77 to
 25 C81, or a pharmaceutically acceptable salt thereof, wherein the C_3 to C_6 heteroalkylene of alk is
 linear C_3 to C_6 heteroalkylene and for the sake of clarity, since this embodiment is only
 characterizing that the C_3 to C_6 heteroalkylene of alk is linear in nature, it is understood the linear C_3
 to C_6 heteroalkylene is substituted with R^g , R^h , and R^i as provided in the referred to embodiments.

C83. In embodiment C83, the compound of any one of embodiments C1 to C44, C51 to
 30 C59, C62 to C69, and C77 to C82, or a pharmaceutically acceptable salt thereof, wherein the linear
 C_3 to C_6 heteroalkylene of alk is $-CH_2CH_2X^aCH_2-$, $-CH_2X^aCH_2CH_2-$, $-CH_2CH_2CH_2X^a-$,
 $-X^aCH_2CH_2CH_2-$, $-X^yCH_2CH_2X^a-$, $-X^yCH_2CH_2X^aCH_2-$, $-CH_2CH_2CH_2X^aCH_2-$, $-CH_2X^aCH_2-$,

-X^aCH₂CH₂-, -CH₂CH₂X^a-, -CH₂CONR^qCH₂-, -CH₂SO₂NR^qCH₂-, -CH₂NR^qCOCH₂-,
 -CH₂NR^qSO₂CH₂-, -CH₂CH₂CH₂NR^qCO-, -CH₂CONR^q-, -CH₂SO₂NR^q-, -CH₂NR^qCO-,
 -CH₂NR^qSO₂-, -CONR^qCH₂-, -SO₂NR^qCH₂-, -NR^qCOCH₂-, or -NR^qSO₂CH₂ substituted with R^g, R^h,
 and Rⁱ as defined therein and X^a is -NR^q-, -O-, -S-, -SO-, -SO₂-, or -CO-.

5 C84. In embodiment C84, the compound of any one of embodiments C1 to C44, C51 to C59, C62 to C69, and C77 to C83, or a pharmaceutically acceptable salt thereof, wherein R^q is hydrogen, methyl, ethyl, methylcarbonyl, or methylsulfonyl.

C85. In embodiment C85, the compound of any one of embodiments C1 to C44, C51 to C59, C62 to C69, and C77 to C84, or a pharmaceutically acceptable salt thereof, wherein the linear
 10 C₃ to C₆ heteroalkylene of alk is -CH₂X^aCH₂-, -X^aCH₂CH₂-, -CH₂CH₂X^a-, -CH₂CH(R^h)X^a-,
 -X^aCH(R^h)CH₂-, -CH₂CONR^q-, -CH₂SO₂NR^q-, -CH₂NR^qCO-, -CH₂NR^qSO₂-, -CONR^qCH₂-,
 -SO₂NR^qCH₂-, -NR^qCOCH₂-, or -NR^qSO₂CH₂- where X^a is -S-, -SO₂-, -O-, or -NR^q-.

C86. In embodiment C86, the compound of any one of embodiments C1 to C44, C51 to C59, C62 to C69, and C77 to C85, or a pharmaceutically acceptable salt thereof, wherein the linear
 15 C₃ to C₆ heteroalkylene of alk is -CH₂CH₂CH₂X^a- or -CH₂CH₂X^a.

C87. In embodiment C87, the compound of any one of embodiments C1 to C44, C51 to C59, C62 to C69, and C77 to C86, or a pharmaceutically acceptable salt thereof, wherein R^g of linear
 C₃ to C₆ heteroalkylene of alk is hydrogen or halo (unless stated otherwise) and R^h of linear C₃ to C₆
 heteroalkylene of alk is (unless stated otherwise) hydrogen, halo, haloalkoxy, cycloalkyl,
 20 cycloalkyloxy, alkoxy, hydroxy, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl,
 alkylcarbonylamino, cyano, cyanoalkyloxy, phenyl, heteroaryl, heterocyclyl, or bridged heterocyclyl,
 each ring of R^h is substituted with R⁷ and R⁸ and Rⁱ is hydrogen.

C88. In embodiment C88, the compound of any one of embodiments C1 to C44, C51 to C59, C62 to C69, and C77 to C87, or a pharmaceutically acceptable salt thereof, wherein R^g of linear
 25 C₃ to C₆ heteroalkylene of alk is hydrogen fluoro (unless stated otherwise) and R^h of linear C₃ to C₆
 heteroalkylene of alk (unless stated otherwise) is hydrogen halo, haloalkoxy, alkoxy, hydroxy,
 dialkylaminocarbonyl, cyano, or heteroaryl substituted with R⁷ and R⁸.

C89. In embodiment C89, the compound of any one of embodiments C1 to C44, C51 to C59, C62 to C69, and C77 to C88, or a pharmaceutically acceptable salt thereof, wherein the
 30 heteroaryl, heterocyclyl, and bridged heterocyclyl of R^h of linear C₃ to C₆ heteroalkylene of alk,
 when present, are five or six membered ring and each ring of R^h is substituted with R⁷ and R⁸.

C90. In embodiment C90, the compound of any one of embodiments C1 to C44, C51 to C59, C62 to C69, and C77 to C89, or a pharmaceutically acceptable salt thereof, wherein R^g of linear
 C₃ to C₆ heteroalkylene of alk, when present and unless stated otherwise, is hydrogen, deuterium, or

fluoro, and R^h of linear C₃ to C₆ heteroalkylene of alk, when present and unless stated otherwise, is hydrogen, deuterium, fluoro, cyclopropyl, cyclobutyl, cyclopropyloxy, cyclobutyloxy, difluoromethoxy, trifluoromethoxy, methoxy, ethoxy, hydroxy, cyano, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, diethylaminocarbonyl, methylcarbonylamino, ethylcarbonylamino, phenyl, pyrazolyl, thiazolyl, furanyl, pyridinyl, pyrrolidinyl, 2-oxopyrrolidinyl, piperidinyl, piperazinyl, or tetrahydrofuranyl, each ring of R^h is substituted with R⁷ and R⁸ independently selected from hydrogen, deuterium, methyl, methoxy, fluoro, difluoromethyl, trifluoromethyl, difluoromethoxy, trifluoromethyl, hydroxy, amino, methylamino, dimethylamino and cyano.

- 10 C91. In embodiment C91, the compound of any one of embodiments C1 to C44, C51 to C59, C62 to C69, and C77 to C90, or a pharmaceutically acceptable salt thereof, wherein R^g of linear C₃ to C₆ heteroalkylene of alk is hydrogen and R^h of linear C₃ to C₆ heteroalkylene of alk is fluoro, cyclopropyl, cyclopropyloxy, difluoromethoxy, trifluoromethoxy, methoxy, ethoxy, hydroxy, cyano, methylaminocarbonyl, dimethylaminocarbonyl, methylcarbonylamino, phenyl, pyrazol-1-yl, 15 pyrrazol-4-yl, pyridin-4-yl, pyrrolidin-1-yl, or 2-oxopyrrolidin-1-yl, each ring of R^h is substituted with R⁷ and R⁸ independently selected from hydrogen, deuterium, methyl, and fluoro.

C92. In embodiment C92, the compound of any one of embodiments C77 to C91, or a pharmaceutically acceptable salt thereof, wherein X^a is -NR^q-, -O-, -S-, or -SO₂-, preferably -NR^q-, -O-, or -S-.

- 20 C93. In embodiment C93, the compound of any one of embodiments C77 to C92, or a pharmaceutically acceptable salt thereof, wherein X^a is -NR^q- where R^q is hydrogen or methyl.

C94. In embodiment C94, the compound of any one of embodiments C77 to C92, or a pharmaceutically acceptable salt thereof, wherein X^a is -O-.

- 25 C95. In embodiment C95, the compound of any one of embodiments C77 to C92, or a pharmaceutically acceptable salt thereof, wherein X^a is -S-.

C96. In embodiment C96, the compound of any one of embodiments C77 to C95, or a pharmaceutically acceptable salt thereof, wherein X^y is -O-.

C97. In embodiment C97, the compound of any one of embodiments C77 to C95, or a pharmaceutically acceptable salt thereof, wherein X^y is -NH- or -NCH₃-.

- 30 C98. In embodiment C98, the compound of any one of embodiments C1 to C44 and C77 to C81, or a pharmaceutically acceptable salt thereof, wherein the C₃ to C₆ heteroalkylene of alk is branched C₄ to C₆ heteroalkylene and for the sake of clarity, since this embodiment is only characterizing that the C₄ to C₆ heteroalkylene of alk is branched in nature, it is understood the

branched C₄ to C₆ heteroalkylene is substituted with R^g, R^h, and Rⁱ as provided in the referred to embodiments.

C99. In embodiment C99, the compound of any one of embodiments C1 to C44 and C77 to C81, and C98, or a pharmaceutically acceptable salt thereof, wherein the branched C₄ to C₆ heteroalkylene of alk is -CH₂X^aCH(CH₃)CH₂-, -CH₂X^yCH₂CH(CH₃)X^a-, -CH₂CH₂CH(CH₃)X^a-, -X^aCH(CH₃)CH₂CH₂-, -X^yCH₂CH(CH₃)X^a-, -X^yCH(CH₃)CH₂X^a-, -CH₂CH₂CH₂CH(CH₃)X^a-, -X^aCH(CH₂R^h)CH₂-, -CH₂CH(CH₂R^h)X^a-, -X^aCH(CH₂CH₂R^h)CH₂-, -CH₂CH(CH₂CH₂R^h)X^a-, -CH₂C(CH₃)(CH₃)X^a-, -X^aC(CH₃)(CH₃)CH₂-, -CH(CH₃)CH(CH₃)X^a-, -CONR^zCH₂CH(CH₃)X^a-, -CH₂NR^qCOCH(CH₃)CH₂-, or -NR^qCOCH(CH₃)CH₂- where X^a is -NR^q-, -O-, -S-, -SO-, -SO₂-, or -CO-.

C100. In embodiment C100, the compound of any one of embodiments C1 to C44, C77 to C81, C98, and C99, or a pharmaceutically acceptable salt thereof, wherein the branched C₄ to C₆ heteroalkylene of alk is -CH₂C(CH₃)(CH₃)X^a-, -CH(CH₃)(CHCH₃)X^a-, -X^aCH(CH₂CH₂R^h)CH₂-, -CH₂CH(CH₂CH₂R^h)X^a-, -X^aCH(CH₂R^h)CH₂-, or -CH₂CH(CH₂R^h)X^a-.

C101. In embodiment C101, the compound of any one of embodiments C1 to C44, C77 to C81, and C98 to C100, or a pharmaceutically acceptable salt thereof, wherein the R^g and Rⁱ of branched C₄ to C₆ heteroalkylene of alk are hydrogen or halo (unless stated otherwise) and R^h of branched C₄ to C₆ heteroalkylene of alk is hydrogen, halo, haloalkoxy, cycloalkyl, cycloalkyloxy, alkoxy, hydroxy, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylcarbonylamino, cyano, cyanoalkyloxy, phenyl, heteroaryl, heterocyclyl, heterocyclyloxy, heterocyclylcarbonyl, or bridged heterocyclyl each ring of R^h is substituted with R⁷ and R⁸.

C102. In embodiment C102, the compound of any one of embodiments C1 to C44, C77 to C81, and C98 to C101, or a pharmaceutically acceptable salt thereof, wherein the R^g and Rⁱ of branched C₄ to C₆ heteroalkylene of alk are hydrogen or fluoro (unless stated otherwise) and R^h (unless stated otherwise) is hydrogen, halo, cycloalkyl, cycloalkyloxy, alkoxy, hydroxy, alkylaminocarbonyl, dialkylaminocarbonyl, alkylcarbonylamino, cyano, phenyl, heteroaryl, heterocyclyl, heterocyclyloxy, heterocyclylcarbonyl, or bridged heterocyclyl, each ring of R^h is substituted with R⁷ and R⁸.

C103. In embodiment C103, the compound of any one of embodiments C1 to C44, C77 to C81, and C98 to C102, or a pharmaceutically acceptable salt thereof, wherein R^g and Rⁱ are hydrogen and R^h is hydrogen, heteroaryl, alkylaminocarbonyl, or cyano.

C104. In embodiment C104, the compound of any one of embodiments C1 to C44, C77 to C81, and C98 to C103, or a pharmaceutically acceptable salt thereof, wherein the heteroaryl, heterocyclyl of branched C₄ to C₆ heteroalkylene of alk, by itself or as part of heterocyclyloxy,

heterocyclylcarbonyl, and bridged heterocyclyl, when present, are five or six membered ring, each ring of R^h is substituted with R⁷ and R⁸.

C105. In embodiment C105, the compound of any one of embodiments C1 to C44, C77 to C81, and C98 to C104, or a pharmaceutically acceptable salt thereof, wherein R^h of branched C₄ to C₆ heteroalkylene of alk, when present and unless stated otherwise, is hydrogen, deuterium, fluoro, cyclopropyl, cyclobutyl, cyclopropyloxy, cyclobutyloxy, difluoromethoxy, trifluoromethoxy, methoxy, ethoxy, hydroxy, cyano, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, diethylaminocarbonyl, methylcarbonylamino, ethylcarbonylamino, phenyl, pyrazolyl, thiazolyl, furanyl, pyrrolidinyl, pyridinyl, piperidinyl, piperazinyl, tetrahydrofuranyl, each ring of R^h is substituted with R⁷ and R⁸ independently selected from hydrogen, deuterium, methyl, methoxy, fluoro, difluoromethyl, trifluoromethyl, difluoromethoxy, trifluoromethyl, hydroxy, amino, methylamino, dimethylamino and cyano.

C106. In embodiment C106, the compound of any one of embodiments C98 to C105, or a pharmaceutically acceptable salt thereof, wherein X^a is -NR^q-, -O-, -S-, or -SO₂-, preferably -NR^q- or -O-.

C107. In embodiment C107, the compound of any one of embodiments C98 to C106, or a pharmaceutically acceptable salt thereof, wherein X^a is -NR^q- where R^q is hydrogen or methyl.

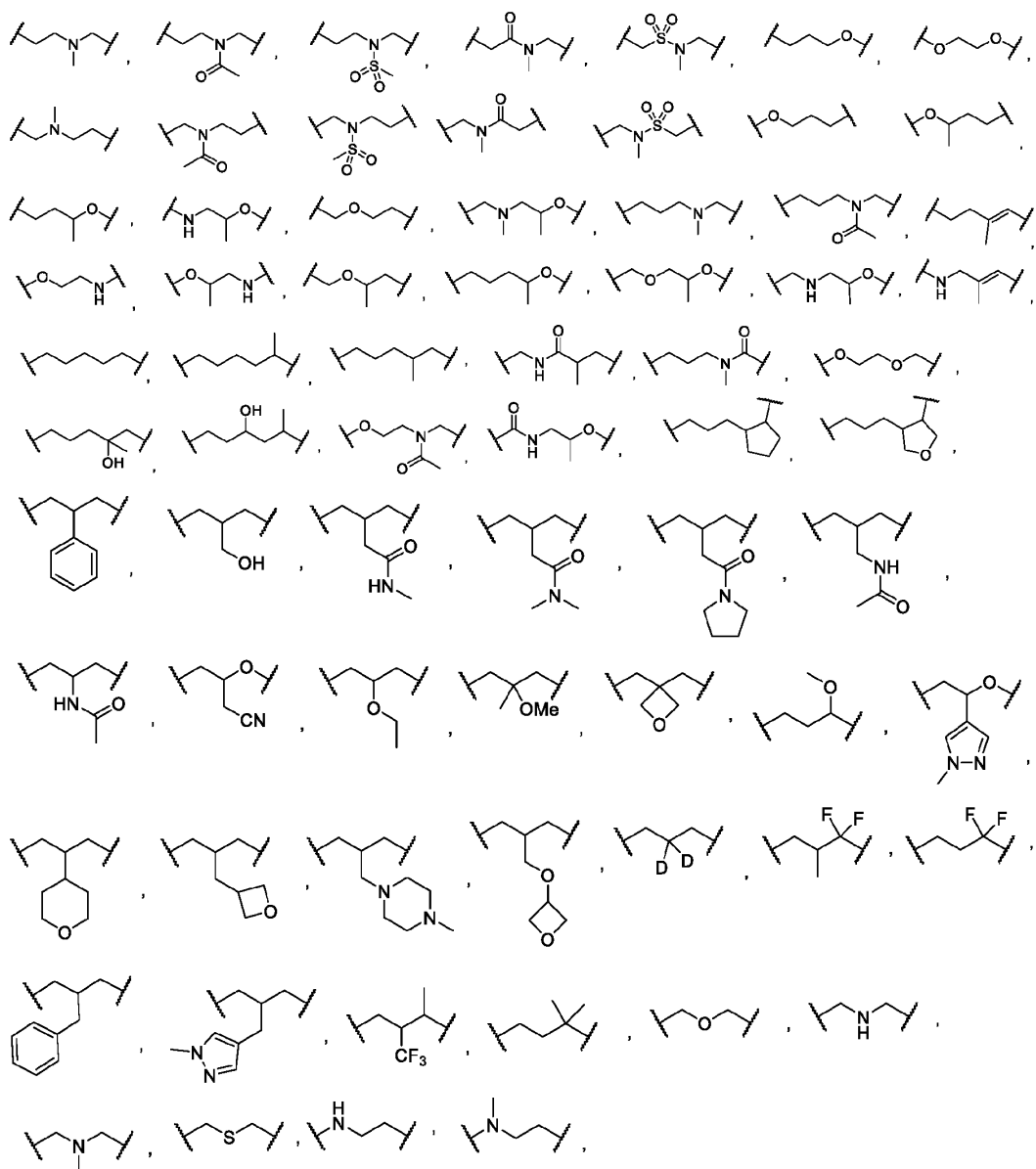
C108. In embodiment C108, the compound of any one of embodiments C98 to C106, or a pharmaceutically acceptable salt thereof, wherein X^a is -O-.

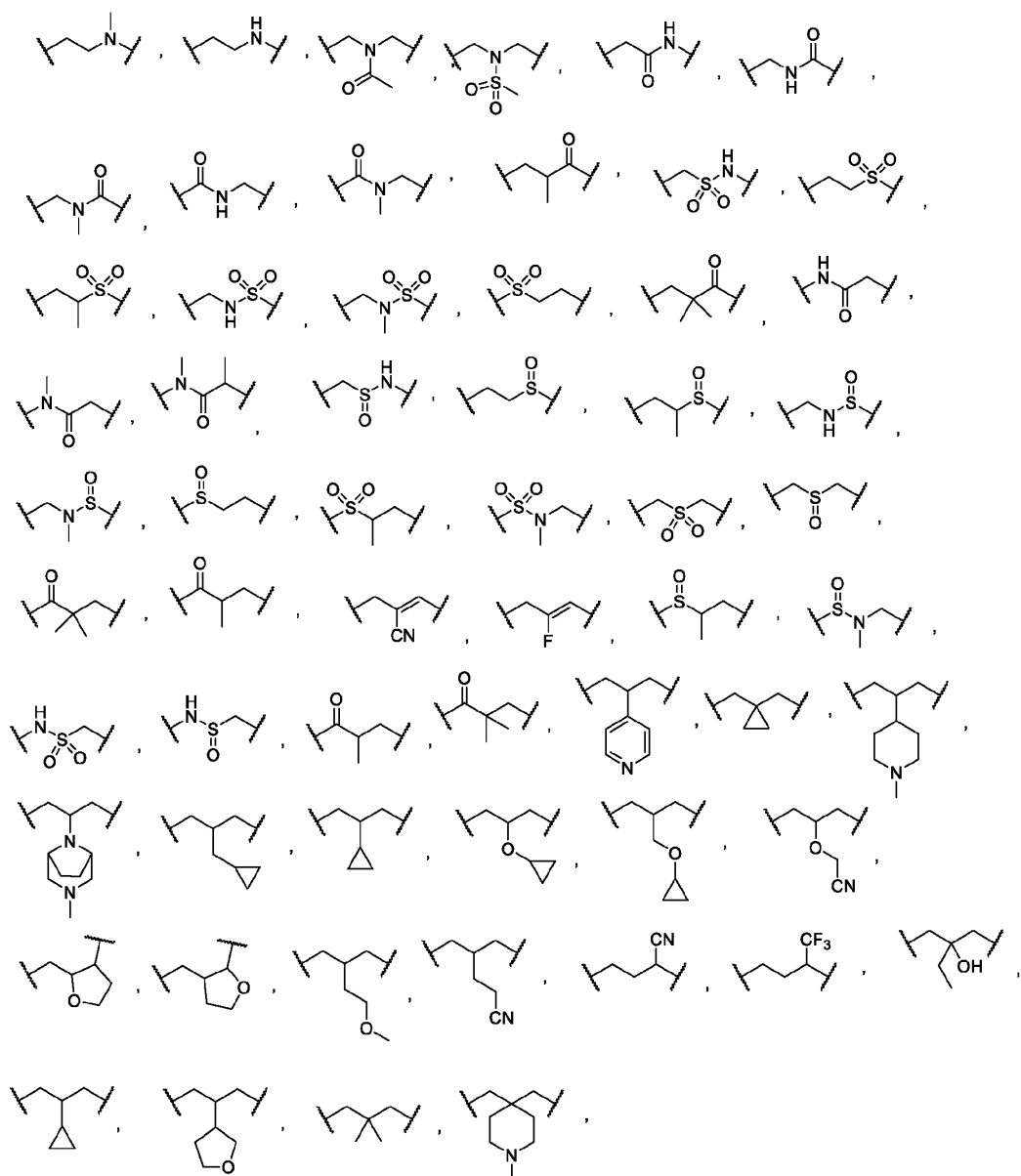
C109. In embodiment C109, the compound of any one of embodiments C98 to C106, or a pharmaceutically acceptable salt thereof, wherein X^a is -S-.

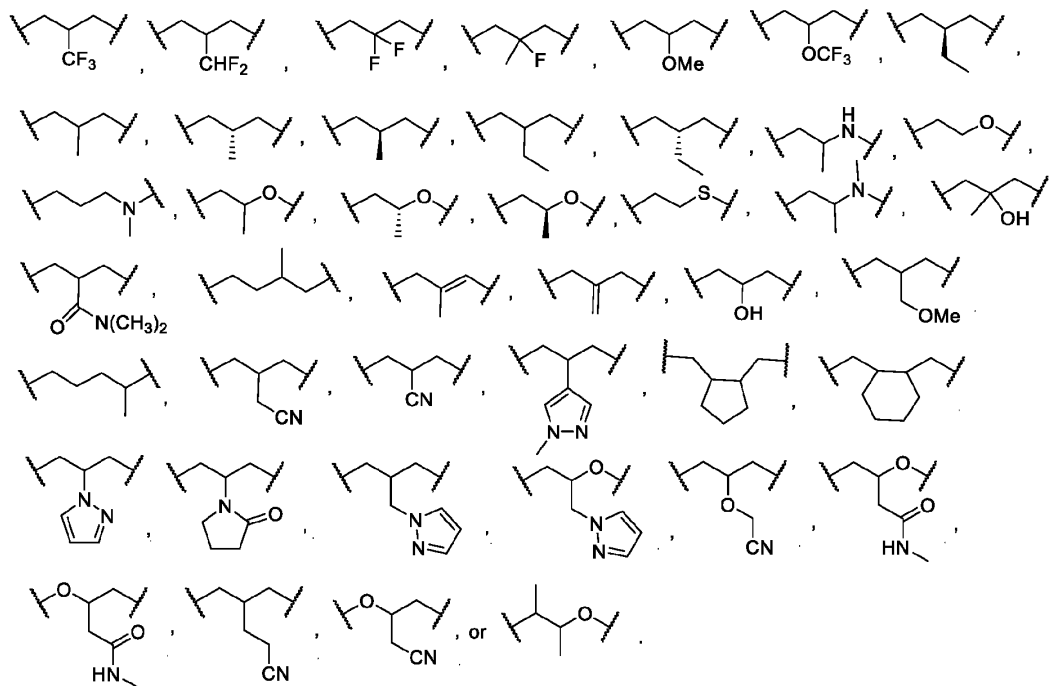
C110. In embodiment C110, the compound of any one of embodiments C98 to C109, or a pharmaceutically acceptable salt thereof, wherein X^y is -O-.

C111. In embodiment C111, the compound of any one of embodiments C98 to C109, or a pharmaceutically acceptable salt thereof, wherein X^y is -NH- or -NCH₃-.

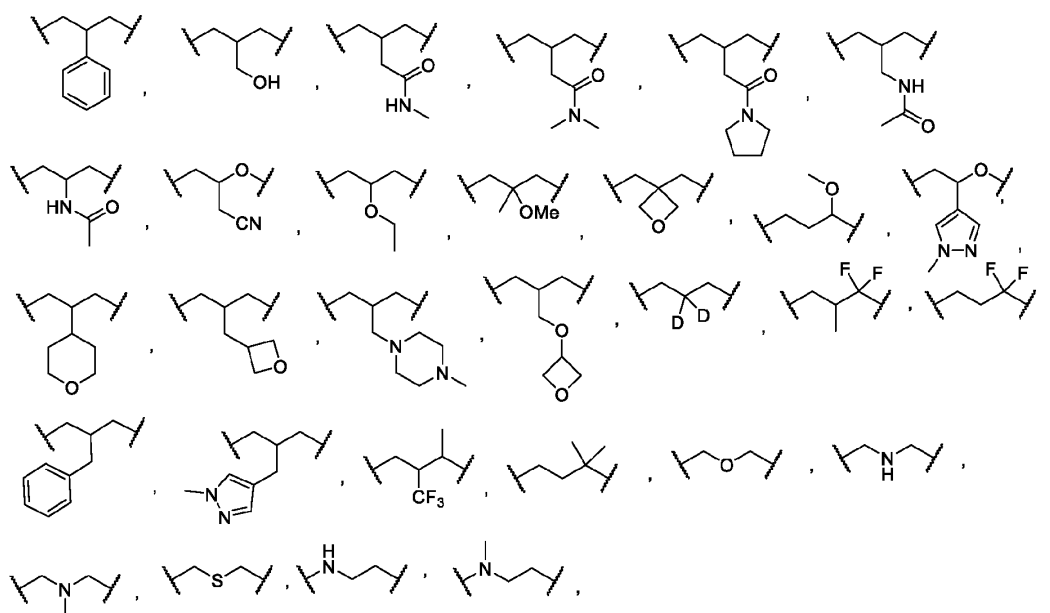
C112. In embodiment C112, the compound of any one of embodiments C1 to C111, or a pharmaceutically acceptable salt thereof, wherein alk is:

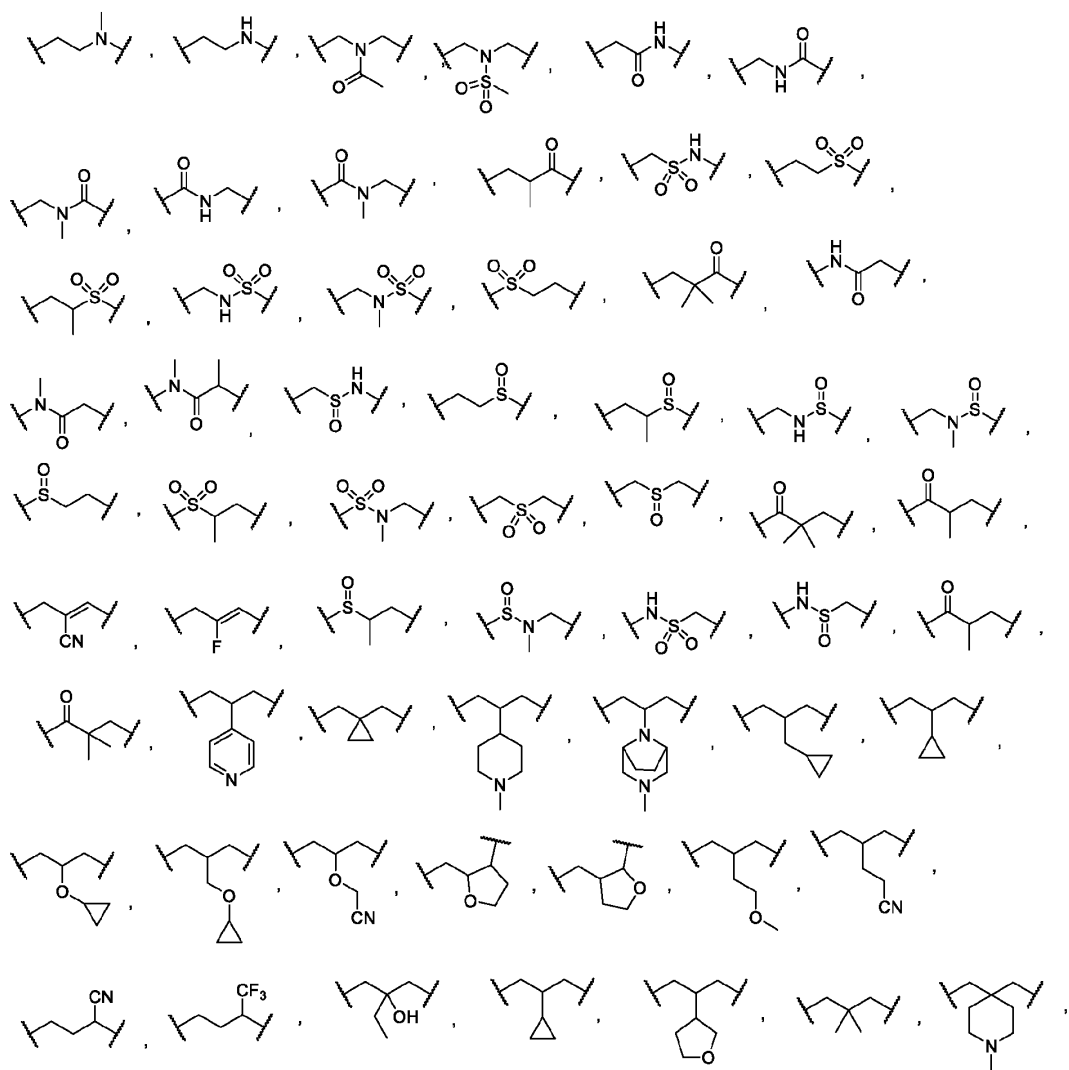


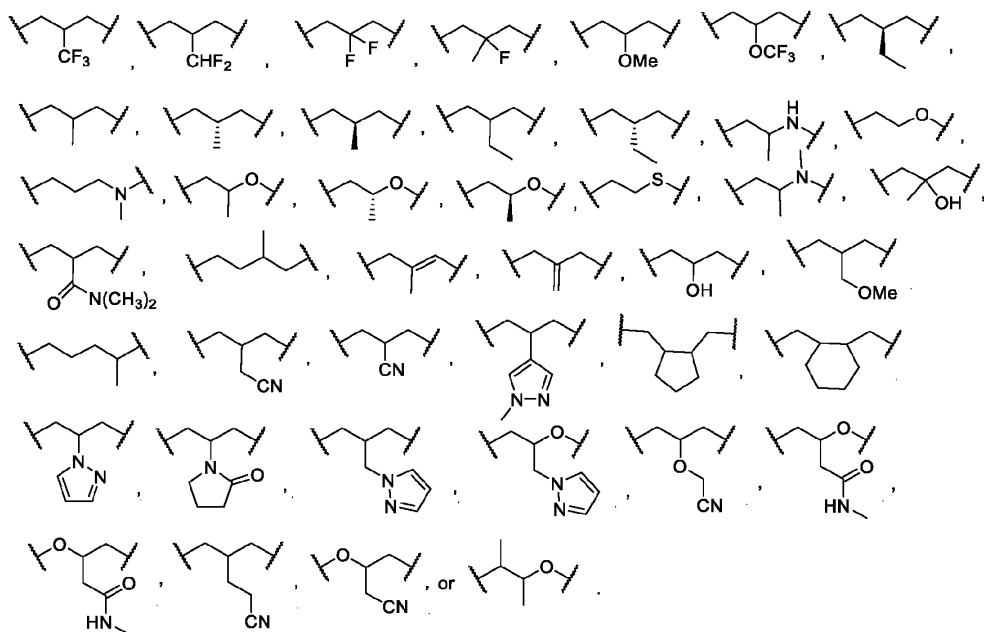




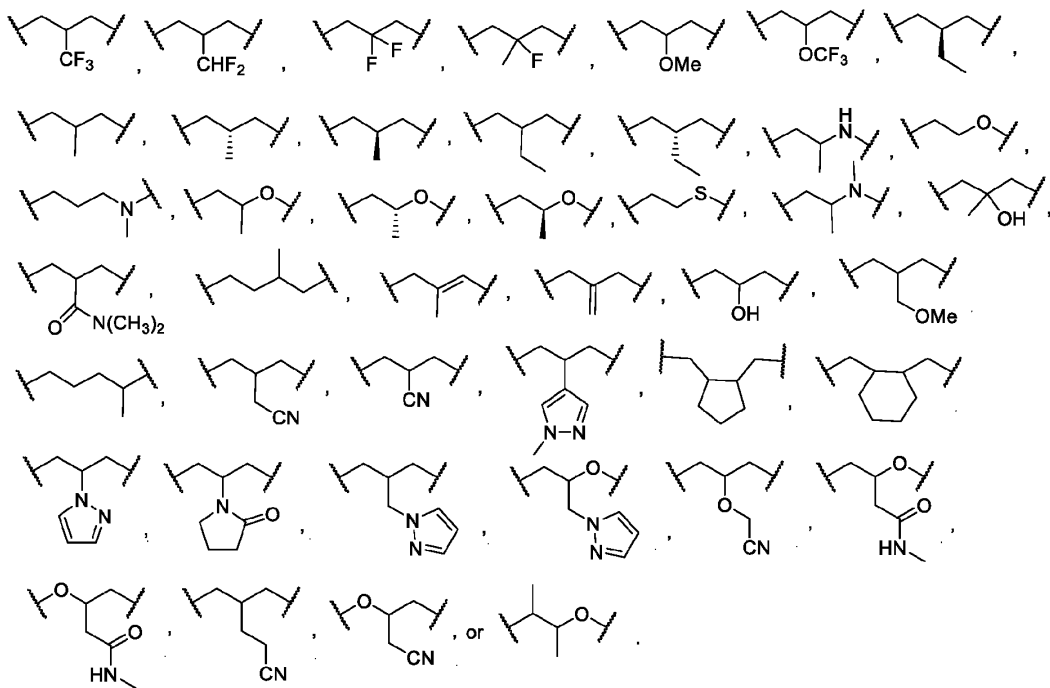
C113. In embodiment C113, the compound of any one of embodiments C1 to C112, or a pharmaceutically acceptable salt thereof, wherein alk is:



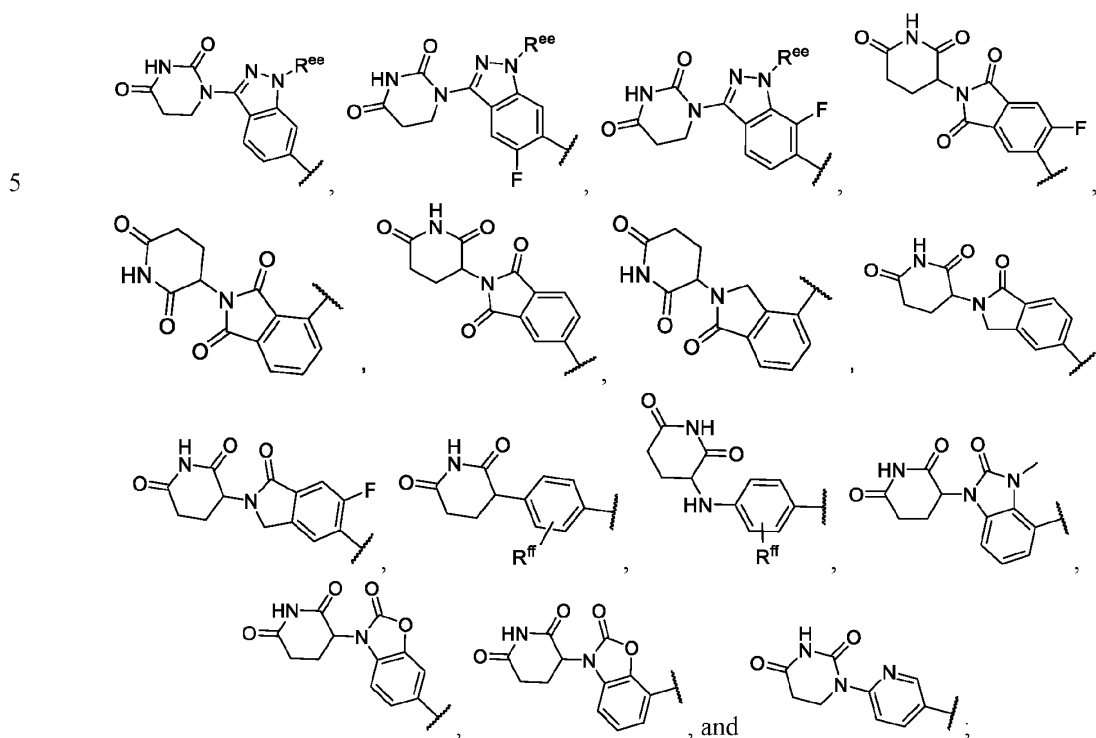




C114. In embodiment C114, the compound of any one of embodiments C1 to C113, or a pharmaceutically acceptable salt thereof, wherein alk is:

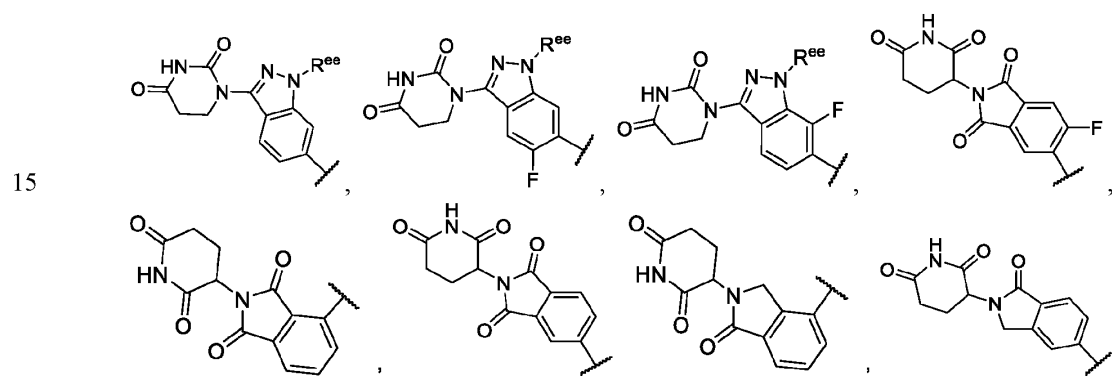


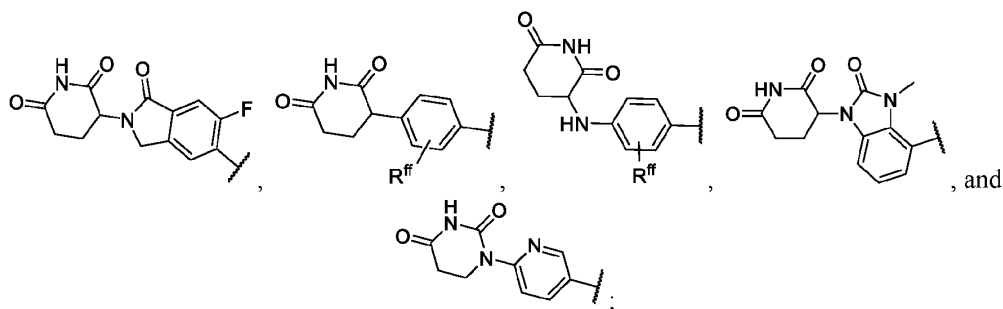
C115. In embodiment C115, the compound of any one of embodiments C1 to C114, or a pharmaceutically acceptable salt thereof, wherein Degron is the E3 ubiquitin ligase ligand selected from:



where R^{ee} is hydrogen, methyl, ethyl, cyclopropyl, or 2,2,2-trifluoroethyl and R^{ff} is hydrogen, methyl, cyclopropyl, fluoro, cyano, methoxy, difluoromethoxy, trifluoromethoxy, or trifluoromethyl.

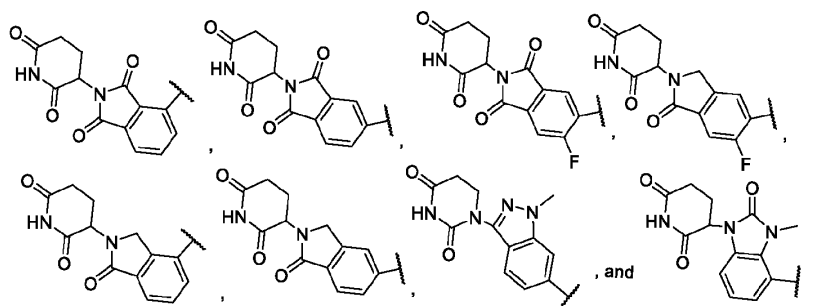
C116. In embodiment C116, the compound of any one of embodiments C1 to C115, or a pharmaceutically acceptable salt thereof, wherein Degron is the E3 ubiquitin ligase ligand selected from:



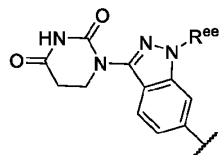


where R^{ee} is hydrogen, methyl, ethyl, cyclopropyl, or 2,2,2-trifluoroethyl and R^{ff} is hydrogen,
 5 methyl, cyclopropyl, fluoro, cyano, methoxy, difluoromethoxy, trifluoromethoxy, or trifluoromethyl.

C117. In embodiment C117, the compound of any one of embodiments C1 to C116, or a
 pharmaceutically acceptable salt thereof, wherein Degron is the E3 ligase ligand selected from:



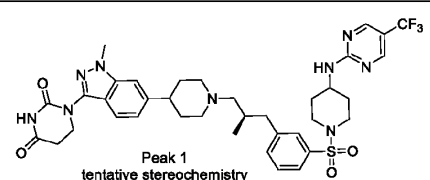
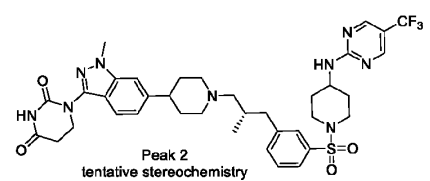
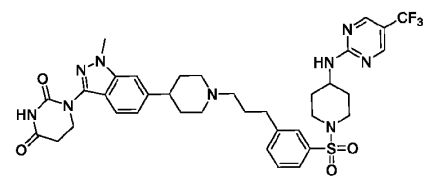
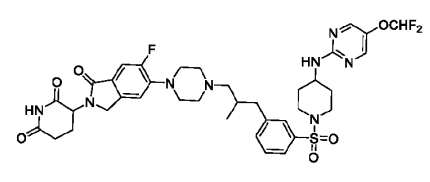
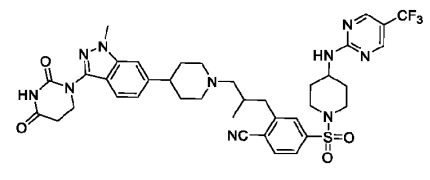
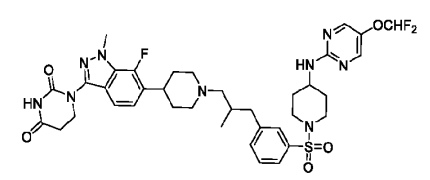
C118. In embodiment C118, the compound of any one of embodiments C1 to C116, or a
 10 pharmaceutically acceptable salt thereof, wherein Degron is the E3 ubiquitin ligase ligand is



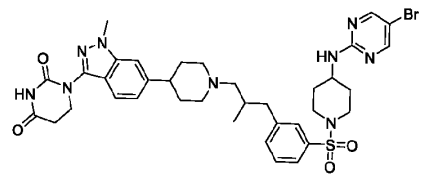
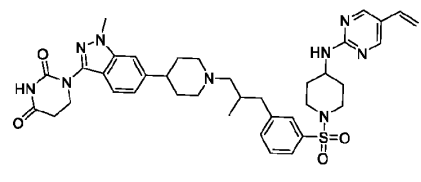
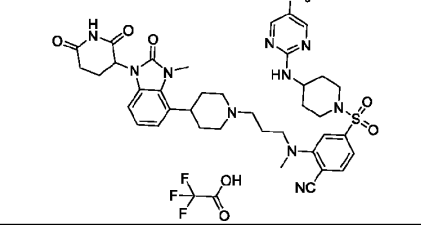
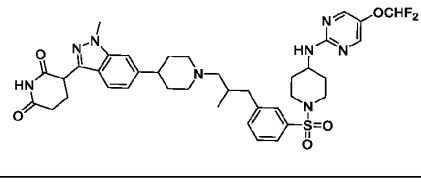
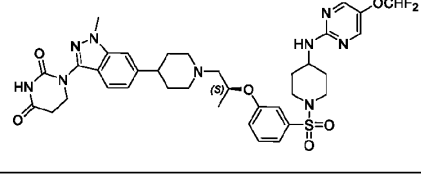
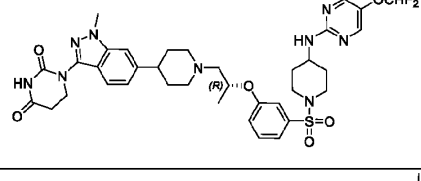
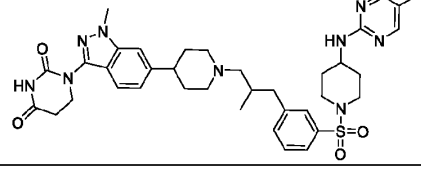
where each R^{ee} is hydrogen, methyl, ethyl, cyclopropyl, or 2,2,2-trifluoroethyl,
 preferably methyl.

Representative compounds of first aspect and Formula (I) are shown in Compound Table 1 below:

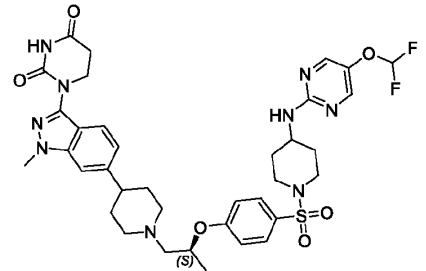
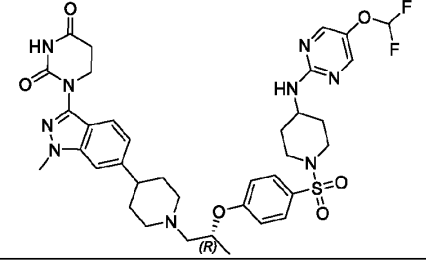
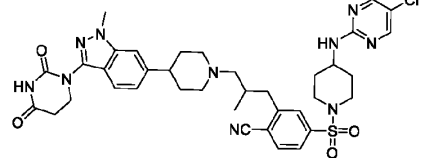
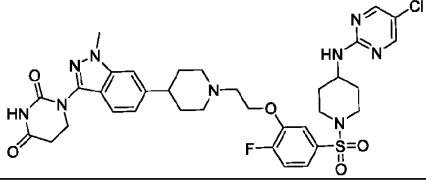
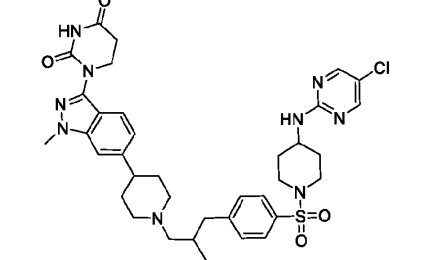
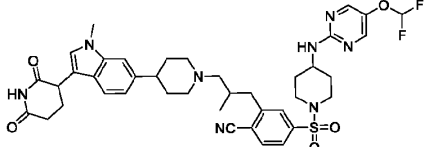
Table 1

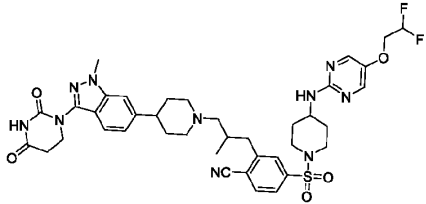
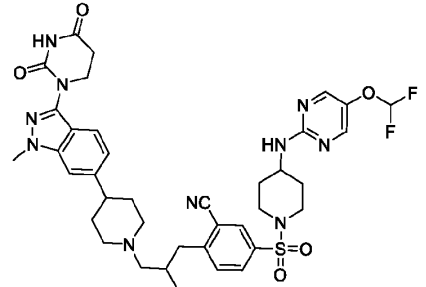
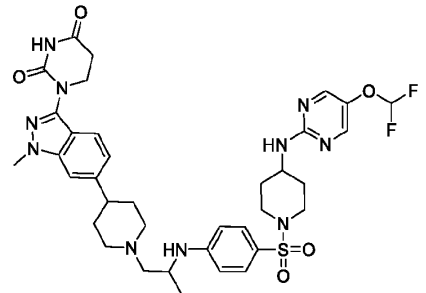
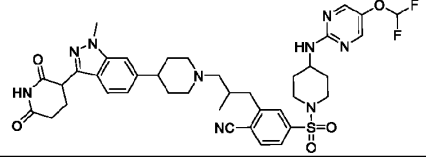
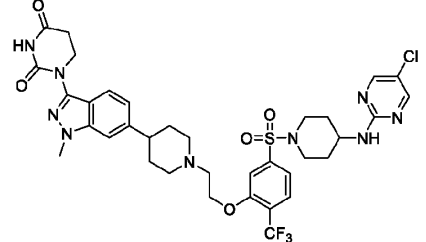
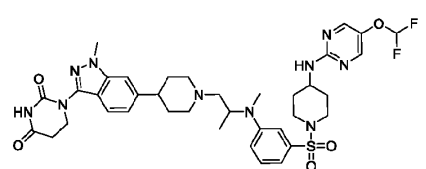
CPD #	Structure	Name	MS (ES, m/z): [M+1] ⁺
1		(R)-1-(1-methyl-6-(1-(2-methyl-3-(3-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)propyl)piperidin-4-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	768.3
2		(S)-1-(1-methyl-6-(1-(2-methyl-3-(3-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)propyl)piperidin-4-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	768.3
4		1-(1-methyl-6-(1-(3-(3-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)propyl)piperidin-4-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	754.1
7		3-(5-(4-(3-(3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-2-methylpropyl)piperazin-1-yl)-6-fluoro-1-oxoisindolin-2-yl)piperidine-2,6-dione	785.1
9		2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-methylpropyl)-4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzonitrile	793.1
10		1-(6-(1-(3-(3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-2-methylpropyl)piperidin-4-yl)-7-fluoro-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	784.0

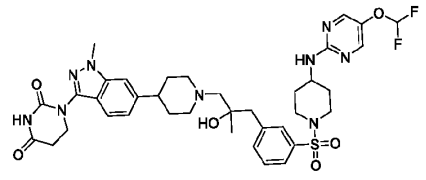
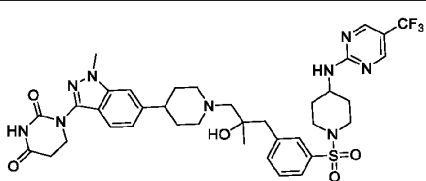
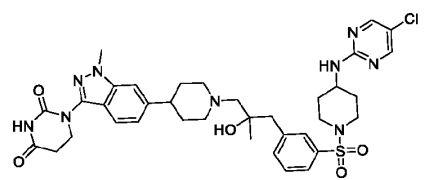
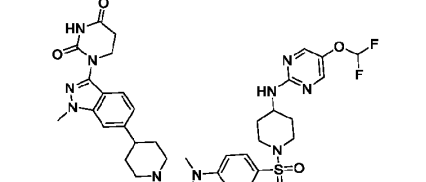
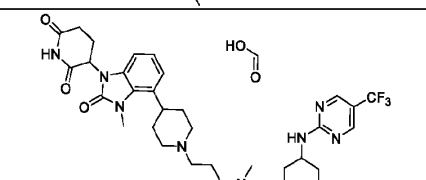
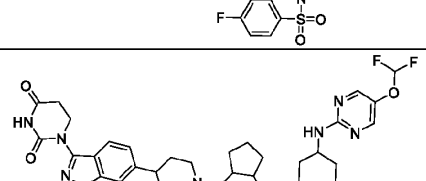
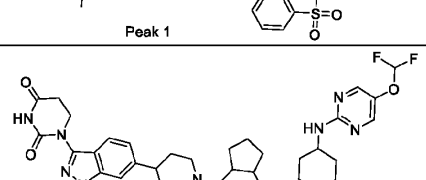
CPD #	Structure	Name	MS (ES, m/z): [M+1] ⁺
11		1-(6-(1-(3-(4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	767.1
12		1-(1-methyl-6-(1-(2-(3-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzyl)butyl)piperidin-4-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	782.0
13		1-(6-(1-(2-(3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzyl)butyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	780.3
14		(R)-1-(6-(1-(3-(3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	766.6
15		(S)-1-(6-(1-(3-(3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	766.6
16		4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-methylpropyl)benzonitrile	791.2
17		1-(1-methyl-6-(1-(2-methyl-3-(3-((4-((5-(trifluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)propyl)piperidin-4-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	784.4

CPD #	Structure	Name	MS (ES, m/z): [M+1] ⁺
18		1-(6-(1-(3-(3-((4-((5-bromopyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)di-hydropyrimidine-2,4(1H,3H)-dione	780.3
19		1-(1-methyl-6-(1-(2-methyl-3-(3-((4-((5-vinylpyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)propyl)piperidin-4-yl)-1H-indazol-3-yl)di-hydropyrimidine-2,4(1H,3H)-dione	726.4
20		2-((3-(4-(1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)piperidin-1-yl)propyl)(methyl)amino)-4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzonitrile 2,2,2-trifluoroacetate	823.3
21		3-(6-(1-(3-(3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)piperidine-2,6-dione	765.3
22		(S)-1-(6-(1-(2-(3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenoxy)propyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)di-hydropyrimidine-2,4(1H,3H)-dione	768.2
23		(R)-1-(6-(1-(2-(3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenoxy)propyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)di-hydropyrimidine-2,4(1H,3H)-dione	768.4
24		1-(6-(1-(3-(3-((4-((5-ethylpyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)di-hydropyrimidine-2,4(1H,3H)-dione	728.4

CPD #	Structure	Name	MS (ES, m/z): [M+1] ⁺
25		1-(6-(1-(3-(5-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-fluorophenyl)-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl) dihydropyrimidine-2,4(1H,3H)-dione	784.3
26		3-(3-methyl-4-(1-(3-(methyl(2-(trifluoromethyl)-5-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)amino)propyl)piperidin-4-yl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione 2,2,2-trifluoroacetate	866.3
27		4-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(2-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)ethoxy)benzonitrile	747.2
28		1-(6-(1-(3-(3-((4-((5-isopropylpyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl) dihydropyrimidine-2,4(1H,3H)-dione	742.5
29		1-(6-(1-(2-((3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)amino)propyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl) dihydropyrimidine-2,4(1H,3H)-dione	767.4
30		1-(6-(1-(2-((3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)thio)propyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl) dihydropyrimidine-2,4(1H,3H)-dione	784.4

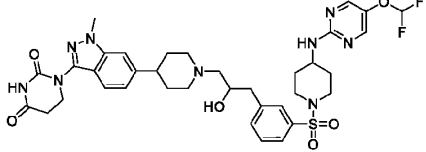
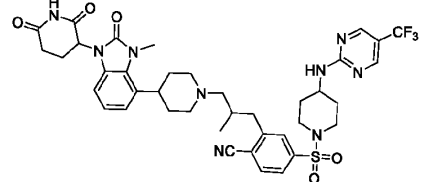
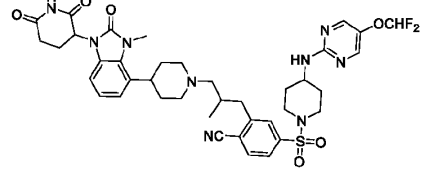
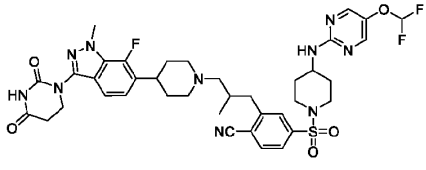
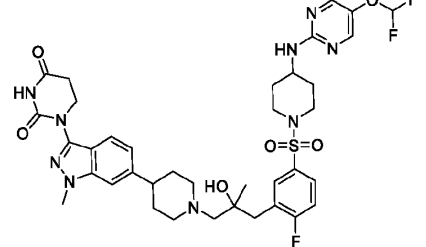
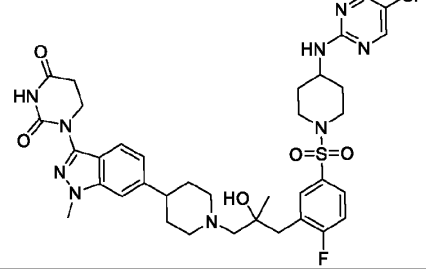
CPD #	Structure	Name	MS (ES, m/z): [M+1] ⁺
31		(S)-1-(6-(1-(2-(4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenoxy)propyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	768.3
32		(R)-1-(6-(1-(2-(4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenoxy)propyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	768.3
33		4-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-methylpropyl)benzonitrile	759.3
34		1-(6-(1-(2-(5-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-fluorophenoxy)ethyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	740.2
35		1-(6-(1-(3-(4-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	734.2
36		4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indol-6-yl)piperidin-1-yl)-2-methylpropyl)benzonitrile	789.3

CPD #	Structure	Name	MS (ES, m/z): [M+1] ⁺
37		4-((4-((5-(2,2-difluoroethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-methylpropyl)benzonitrile	805.3
38		5-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-methylpropyl)benzonitrile	791.3
39		1-(6-(1-(2-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)amino)propyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl) dihydropyrimidine-2,4(1H,3H)-dione	767.4
40		4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-methylpropyl)benzonitrile	790.3
41		1-(6-(1-(2-(5-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(trifluoromethyl)phenoxy)ethyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl) dihydropyrimidine-2,4(1H,3H)-dione	790.2
42		1-(6-(1-(2-((3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)(methyl)amino)propyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl) dihydropyrimidine-2,4(1H,3H)-dione	781.2

CPD #	Structure	Name	MS (ES, m/z): [M+1] ⁺
43		1-(6-(1-(3-(3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-2-hydroxy-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	782.4
44		1-(6-(1-(2-hydroxy-2-methyl-3-(3-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)propyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	784.2
45		1-(6-(1-(3-(3-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-2-hydroxy-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	750.4
46		1-(6-(1-(2-((4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)(methyl)amino)propyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	781.4
47		3-(4-(1-(3-((2-fluoro-5-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)(methyl)amino)propyl)piperidin-4-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione formate	816.3
48		1-(6-(1-((2-(3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)cyclopentyl)methyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	792.3
49		1-(6-(1-((2-(3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)cyclopentyl)methyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	792.3

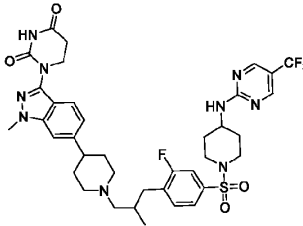
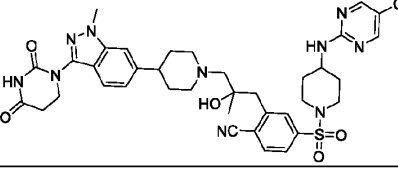
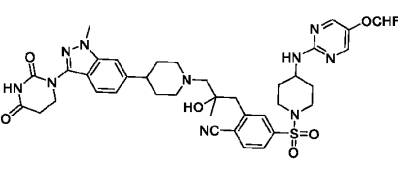
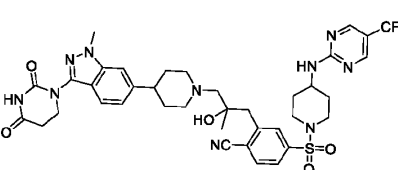
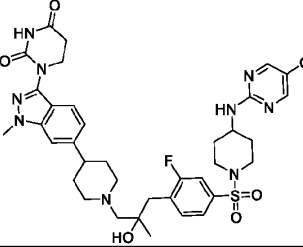
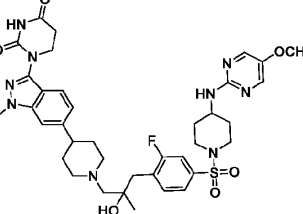
CPD #	Structure	Name	MS (ES, m/z): [M+1] ⁺
50		1-(6-(1-((2-(3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)cyclohexyl)methyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione formate	806.3
51		1-(6-(1-(3-(4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-fluorophenyl)-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	784.2
52		2-(3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzyl)-3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-N,N-dimethylpropanamide	823.3
53		4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)-3,3-difluoropiperidin-1-yl)-2-methylpropyl)benzonitrile formate	827.2
54		4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-(2,2,2-trifluoroethyl)-1H-indazol-6-yl)piperidin-1-yl)-2-methylpropyl)benzonitrile	859.3
55		2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-methylpropyl)-4-((4-((5-(trifluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzonitrile	809.3

CPD #	Structure	Name	MS (ES, m/z): [M+1] ⁺
56		4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(4-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-methylbutyl)benzonitrile	805.4
57		4-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)piperidin-1-yl)-2-methylpropyl)benzonitrile	774.2
58		4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(2-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)ethoxy)benzonitrile	779.2
59		(S)-4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-methylpropyl)benzonitrile	791.2
60		(R)-4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-methylpropyl)benzonitrile	791.2
61		(E)-4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-methylprop-1-en-1-yl)benzonitrile	789.4
62		1-(6-(1-(2-(3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzyl)allyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)benzonitrile	764.4

CPD #	Structure	Name	MS (ES, m/z): [M+1] ⁺
		yl) dihydropyrimidine-2,4(1H,3H)-dione	
63		1-(6-(1-(3-(3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-2-hydroxypropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl) dihydropyrimidine-2,4(1H,3H)-dione	768.3
64		2-(3-(4-(1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)piperidin-1-yl)-2-methylpropyl)-4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzonitrile	808.2
65		4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)piperidin-1-yl)-2-methylpropyl)benzonitrile	806.3
66		4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-7-fluoro-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-methylpropyl)benzonitrile	809.3
67		1-(6-(1-(3-(5-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-fluorophenyl)-2-hydroxy-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl) dihydropyrimidine-2,4(1H,3H)-dione	800.3
68		1-(6-(1-(3-(5-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-fluorophenyl)-2-hydroxy-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl) dihydropyrimidine-2,4(1H,3H)-dione	768.2

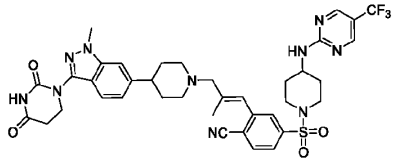
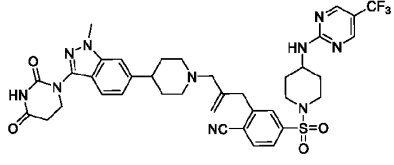
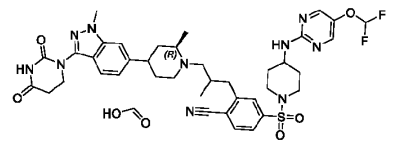
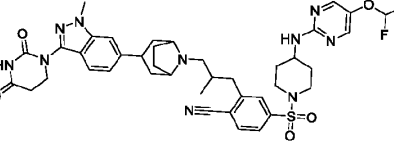
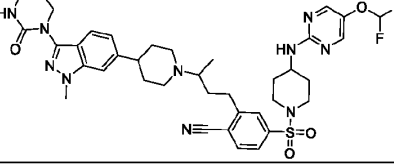
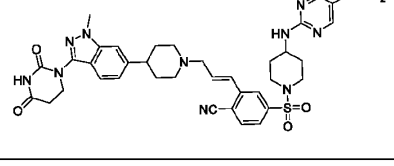
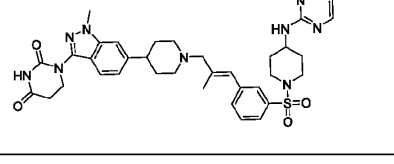
CPD #	Structure	Name	MS (ES, m/z): [M+1] ⁺
69		1-(6-(1-(3-(2-fluoro-5-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-2-hydroxy-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	802.3
70		1-(6-(1-(3-(3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)butyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	766.3
71		3-(3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzyl)-4-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)butanenitrile	791.3
72		1-(6-(1-(3-(3-((4-((5-(chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-5-fluorophenyl)-2-hydroxy-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	768.2
73		1-(6-(1-(3-(3-fluoro-5-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-2-hydroxy-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	802.3
74		1-(6-(1-(3-(3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-5-fluorophenyl)-2-hydroxy-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	800.3

CPD #	Structure	Name	MS (ES, m/z): [M+1] ⁺
75		5-(1-(3-(2-cyano-5-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-2-methylpropyl)piperidin-4-yl)-N-(2,6-dioxopiperidin-3-yl)picolinamide	780.3
76		3-(4-(1-(3-(3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-2-methylpropyl)piperidin-4-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione	781.2
77		5-(1-(3-(5-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-cyanophenyl)-2-methylpropyl)piperidin-4-yl)-N-(2,6-dioxopiperidin-3-yl)picolinamide	748.2
78		4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-((1-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)propan-2-yl)oxy)benzonitrile	793.4
79		5-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-methylpropyl)benzonitrile	758.9
80		1-(6-(1-(3-(5-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(trifluoromethyl)phenyl)-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	833.9
81		1-(6-(1-(3-(4-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-fluorophenyl)-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	751.9

CPD #	Structure	Name	MS (ES, m/z): [M+1] ⁺
82		1-(6-(1-(3-(2-fluoro-4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	785.9
83		4-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-hydroxy-2-methylpropyl)benzonitrile	775.3
84		4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-hydroxy-2-methylpropyl)benzonitrile	807.4
85		2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-hydroxy-2-methylpropyl)-4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzonitrile	809.3
86		1-(6-(1-(3-(4-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-fluorophenyl)-2-hydroxy-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	768.4
87		1-(6-(1-(3-(4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-fluorophenyl)-2-hydroxy-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	800.6

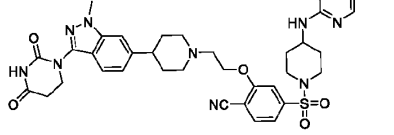
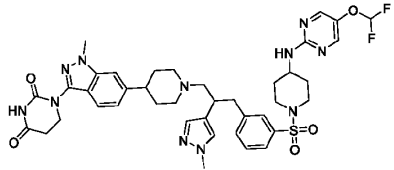
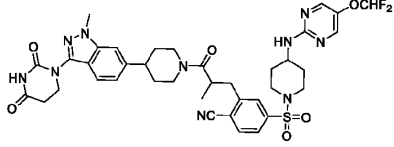
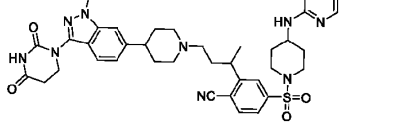
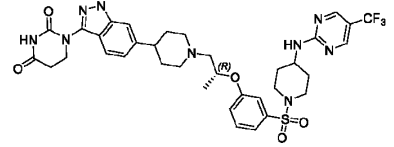
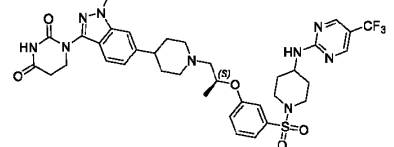
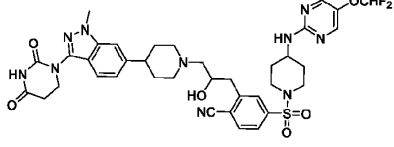
CPD #	Structure	Name	MS (ES, m/z): [M+1] ⁺
88		1-(6-(1-(3-(2-fluoro-4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-2-hydroxy-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl) dihydropyrimidine-2,4(1H,3H)-dione	802.4
89		1-(6-(1-(2-hydroxy-2-methyl-3-(2-(trifluoromethyl)-4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)propyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl) dihydropyrimidine-2,4(1H,3H)-dione	852.4
90		1-(6-(1-(2-(5-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(trifluoromethyl)phenoxy)ethyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl) dihydropyrimidine-2,4(1H,3H)-dione	821.9
91		1-(6-(1-(3-(4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(trifluoromethyl)phenyl)-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl) dihydropyrimidine-2,4(1H,3H)-dione	834.0
92		1-(6-(1-(3-(4-((5-(5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(trifluoromethyl)phenyl)-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl) dihydropyrimidine-2,4(1H,3H)-dione	801.9
93		1-(1-methyl-6-(1-(2-methyl-3-(2-(trifluoromethyl)-4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)propyl)piperidin-4-yl)-1H-indazol-3-yl) dihydropyrimidine-2,4(1H,3H)-dione	835.9

CPD #	Structure	Name	MS (ES, m/z): [M+1] ⁺
94		1-(6-(1-(3-(4-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-2-hydroxy-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	750.2
95		1-(6-(1-(3-(4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-2-hydroxy-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	782.2
96		1-(6-(1-(2-hydroxy-2-methyl-3-(4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)propyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	784.2
97		1-(6-(1-(3-(4-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(trifluoromethyl)phenyl)-2-hydroxy-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	818.3
98		1-(6-(1-(3-(4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(trifluoromethyl)phenyl)-2-hydroxy-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	850.6
99		(E)-4-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-methylprop-1-en-1-yl)benzonitrile	757.5
100		4-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(2-((4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-methylprop-1-en-1-yl)benzonitrile	757.5

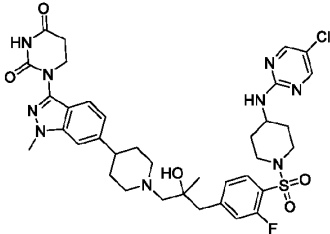
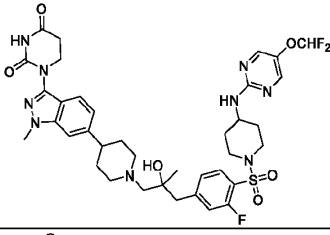
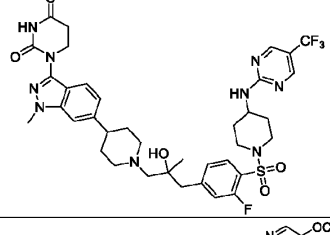
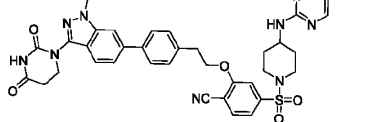
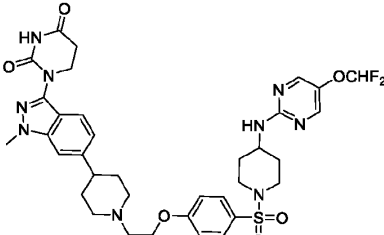
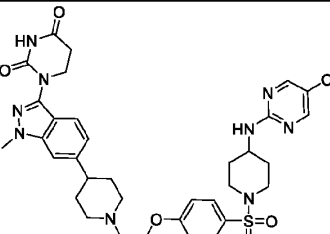
CPD #	Structure	Name	MS (ES, m/z): [M+1] ⁺
		yl)piperidin-1-yl)methyl)allyl)benzonitrile	
101		(E)-2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-methylprop-1-en-1-yl)-4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzonitrile	791.5
102		2-(2-((4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)allyl)-4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzonitrile	791.5
103		4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-((2R)-4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)-2-methylpiperidin-1-yl)-2-methylpropyl)benzonitrile formate	805.0
104		4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(3-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-methylpropyl)benzonitrile	817.2
105		4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)butyl)benzonitrile	791.3
106		(E)-4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)prop-1-en-1-yl)benzonitrile	775.1
107		(E)-1-(6-(1-(3-(3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-2-methylallyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	764.3

CPD #	Structure	Name	MS (ES, m/z): [M+1] ⁺
108		(E)-1-(1-methyl-6-(1-(2-methyl-3-(3-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)allyl)piperidin-4-yl)-1H-indazol-3-yl) dihydropyrimidine-2,4(1H,3H)-dione	766.3
109		(E)-4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)but-1-en-1-yl)benzonitrile	789.1
110		(E)-4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-methylbut-1-en-1-yl)benzonitrile	803.2
111		(E)-4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-3-methylbut-1-en-1-yl)benzonitrile	803.4
112		(E)-2-(3-(4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-methylprop-1-en-1-yl)-4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzonitrile	790.4
113		(E)-1-(6-(1-(3-(2-(difluoromethyl)-5-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)allyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl) dihydropyrimidine-2,4(1H,3H)-dione	802.1
114		(Z)-4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)prop-1-en-1-yl)benzonitrile	775.1

CPD #	Structure	Name	MS (ES, m/z): [M+1] ⁺
115		1-(6-(1-(3-(5-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(difluoromethyl)phenyl)-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	816.1
116		4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-((2S,6S)-4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)-2,6-dimethylpiperidin-1-yl)-2-methylpropyl)benzonitrile formate	819.3
117		4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-((2-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)ethyl)amino)benzonitrile	778.4
118		4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)-2-oxopyridin-1(2H)-yl)-2-methylpropyl)benzonitrile	801.2
119		1-(6-(1-(2-(5-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenoxy)ethyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione 2,2,2-trifluoroacetate	774.2
120		2-(3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzyl)-3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-N-methylpropanamide	809.4
121		1-(6-(1-(2-(5-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-fluorophenoxy)ethyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	772.2

CPD #	Structure	Name	MS (ES, m/z): [M+1] ⁺
122		2-(2-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)ethoxy)-4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzonitrile	781.2
123		1-(6-(1-(3-(3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-2-(1-methyl-1H-pyrazol-4-yl)propyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	832.3
124		4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-methyl-3-oxopropyl)benzonitrile	805.3
125		4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(4-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)butan-2-yl)benzonitrile	791.2
126		(R)-1-(1-methyl-6-(1-(2-(3-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenoxy)propyl)piperidin-4-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	770.4
127		(S)-1-(1-methyl-6-(1-(2-(3-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenoxy)propyl)piperidin-4-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	770.4
128		4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-hydroxypropyl)benzonitrile	793.2

CPD #	Structure	Name	MS (ES, m/z): [M+1] ⁺
129		2-(3-(3-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-methylpropyl)-4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzonitrile	819.3
130		4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-((2S)-4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)-2-methylpiperidin-1-yl)-2-methylpropyl)benzonitrile	805.3
131		4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-((2-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)ethyl)(methyl)amino)benzonitrile	792.4
132		4-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-((2-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)ethyl)(methyl)amino)benzonitrile	760.4
133		2-(3-(3-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)ethyl)(methyl)amino)-4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzonitrile	794.4
134		4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-((2-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)ethyl)thio)benzonitrile	795.5
135		(R)-4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-((1-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)propan-2-yl)oxy)benzonitrile	795.4
136		(S)-4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-((1-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)propan-2-yl)oxy)benzonitrile	795.4

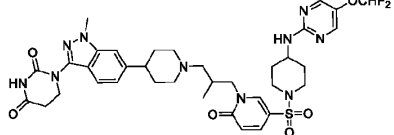
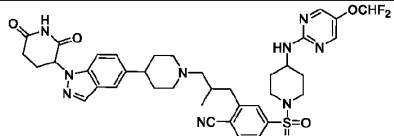
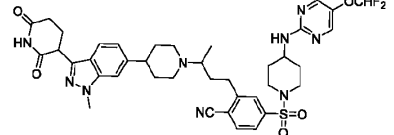
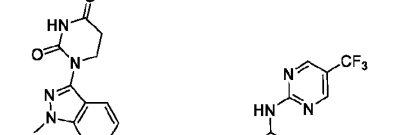
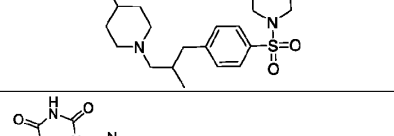
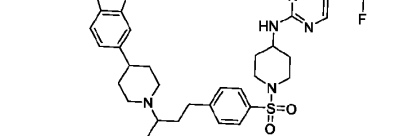
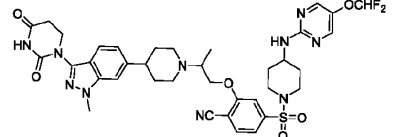
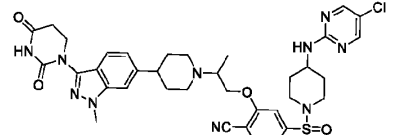
CPD #	Structure	Name	MS (ES, m/z): [M+1] ⁺
		methyl-1H-indazol-6-yl)piperidin-1-yl)propan-2-yl)oxy)benzonitrile	
137		1-(6-(1-(3-(4-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-3-fluorophenyl)-2-hydroxy-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	768.2
138		1-(6-(1-(3-(4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-3-fluorophenyl)-2-hydroxy-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	800.3
139		1-(6-(1-(3-(3-fluoro-4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-2-hydroxy-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	802.2
140		4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)phenethoxy)benzonitrile	772.2
141		1-(6-(1-(2-(4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenoxy)ethyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	754.4
142		1-(6-(1-(2-(4-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenoxy)ethyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	722.3

CPD #	Structure	Name	MS (ES, m/z): [M+1] ⁺
143		1-(1-methyl-6-(1-(2-(4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenoxy)ethyl)piperidin-4-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	756.4
144		4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(2-((2R)-4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)-2-methylpiperidin-1-yl)ethoxy)benzonitrile	793.2
145		2-(3-((2R)-4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)-2-methylpiperidin-1-yl)-2-methylpropyl)-4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzonitrile	807.2
146		2-(3-((2S)-4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)-2-methylpiperidin-1-yl)-2-methylpropyl)-4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzonitrile	807.2
147		4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(7-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)-3-oxa-9-azabicyclo[3.3.1]nonan-9-yl)-2-methylpropyl)benzonitrile	833.3
148		4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)-3-methylphenethoxy)benzonitrile	786.2
149		1-(6-(1-(3-(2-(difluoromethyl)-5-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	818.1

CPD #	Structure	Name	MS (ES, m/z): [M+1] ⁺
		yl) dihydropyrimidine-2,4(1H,3H)-dione	
150		1-(6-(1-(3-(5-((4-(5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(difluoromethyl)phenyl)-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl) dihydropyrimidine-2,4(1H,3H)-dione	784.1
151		4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(2-((2S)-4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)-2-methylpiperidin-1-yl)ethoxy)benzonitrile	793.2
152		1-(6-(1-(3-(2-bromo-5-((4-(5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl) dihydropyrimidine-2,4(1H,3H)-dione	844.1
153		1-(6-(1-(2-(5-((4-(5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(difluoromethyl)phenoxy)ethyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl) dihydropyrimidine-2,4(1H,3H)-dione	804.1
154		4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(6-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)-2-azaspiro[3.3]heptan-2-yl)-2-methylpropyl)benzonitrile	803.3
155		4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(3-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)azetidin-1-yl)-2-methylpropyl)benzonitrile	763.3
156		2-(3-cyano-2-((4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)propyl)-4-((4-(5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzonitrile	816.3

CPD #	Structure	Name	MS (ES, m/z): [M+1] ⁺
157		1-(6-(1-(3-(3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenoxy)propyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione formate	768.3
158		4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)propoxy)benzonitrile	793.3
159		1-(6-(1-((1-((3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenoxy)methyl)cyclopropyl)methyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	794.3
160		1-(6-(1-(3-(2-chloro-5-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	800.1
161		1-(6-(1-(3-(3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-3,3-difluoropropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	788.3

CPD #	Structure	Name	MS (ES, m/z): [M+1] ⁺
162		2-(4-cyano-3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)butyl)-4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl sulfonamide	816.4
163		4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl sulfonamide-2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperazin-1-yl)-2-methylpropyl)benzonitrile	792.3
164		4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl sulfonamide-2-(3-(3-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-2-methylpropyl)benzonitrile	818.4
165		1-(6-(1-(4-(5-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(difluoromethyl)phenyl)butan-2-yl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	816.2
166		4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl sulfonamide-2-((1-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-3-methoxypropan-2-yl)oxy)benzonitrile	823.3
167		3-(6-(1-(3-(5-((4-(5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(difluoromethyl)phenyl)-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)piperidine-2,6-dione	815.2
168		1-(6-(1-(2-(3-((4-(5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzyl)-3,3,3-trifluoropropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	820.3

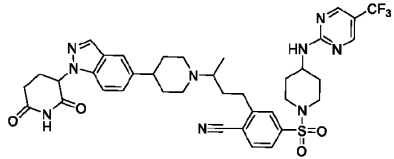
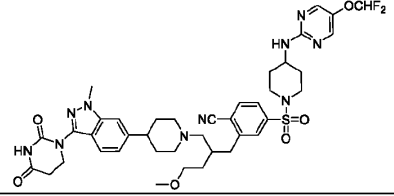
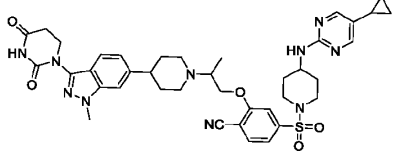
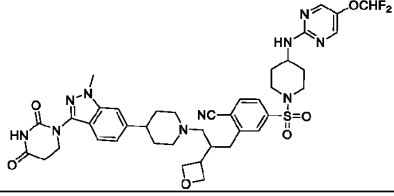
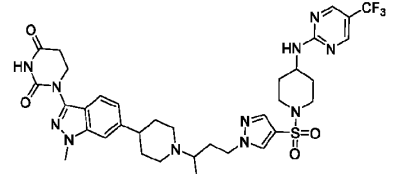
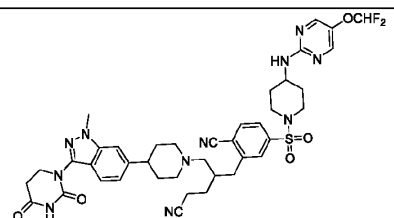
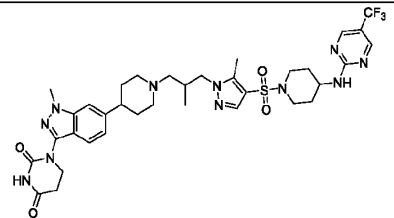
CPD #	Structure	Name	MS (ES, m/z): [M+1] ⁺
169		1-(6-(1-(3-(5-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-oxopyridin-1(2H)-yl)-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	783.2
170		4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(1-(2,6-dioxopiperidin-3-yl)-1H-indazol-5-yl)piperidin-1-yl)-2-methylpropyl)benzonitrile	776.2
171		4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)butyl)benzonitrile	790.2
172		1-(1-methyl-6-(1-(2-methyl-3-(4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)propyl)piperidin-4-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	768.2
173		1-(6-(1-(4-(4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)butan-2-yl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	766.2
174		4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(2-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)propoxy)benzonitrile	793.1
175		4-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(2-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)propoxy)benzonitrile	761.1
176		2-(2-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)propoxy)-4-((4-((5-(trifluoromethyl)pyrimidin-2-	795.1

CPD #	Structure	Name	MS (ES, m/z): [M+1] ⁺
		yl)amino)piperidin-1-yl)sulfonyl)benzonitrile	
177		1-(6-(1-(3-(4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-1-methyl-1H-imidazol-2-yl)-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	770.4
178		1-(6-(1-(2-(3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzyl)-4,4,4-trifluorobutyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	834.1
179		3-(6-(1-(4-(5-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(difluoromethyl)phenyl)butan-2-yl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)piperidine-2,6-dione	815.3
180		1-(6-(1-(3-(3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-3,3-difluoro-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	802.5
181		4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(2-(4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)ethoxy)benzonitrile	778.4
182		2-(2-(4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)ethoxy)-4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzonitrile	780.4
183		1-(6-(4-(((3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzyl)(methylamino)methyl)cyclohexyl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione formate	766.2

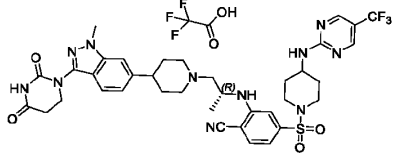
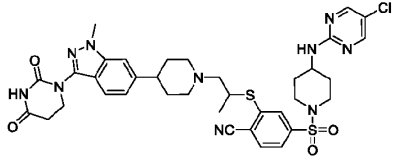
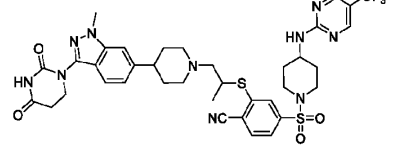
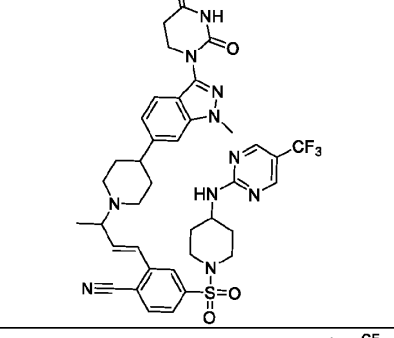
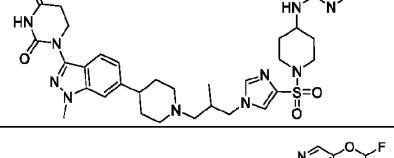
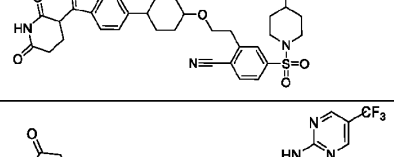
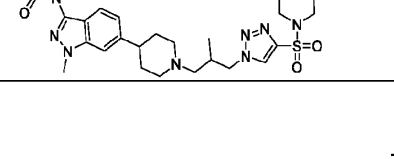
CPD #	Structure	Name	MS (ES, m/z): [M+1] ⁺
184		4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)piperidin-1-yl)butyl)benzonitrile	791.1
185		1-(6-(1-(3-(4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(difluoromethyl)phenyl)-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	816.1
186		4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-((2S)-3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-methylbutyl)benzonitrile	805.5
187		1-(6-(1-(4-(3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-2-methylbutan-2-yl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	780.5
188		4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)piperidin-1-yl)butyl)benzonitrile	806.2
189		1-(6-(1-(3-(4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-1H-pyrazol-1-yl)-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	756.2
190		4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-5-yl)piperidin-1-yl)butyl)benzonitrile	805.1
191		4-((4-((5-(cyclopropyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-methylpropyl)benzonitrile	765.2

CPD #	Structure	Name	MS (ES, m/z): [M+1] ⁺
192		4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(2-(4-(1-(2,6-dioxopiperidin-3-yl)-1H-indazol-5-yl)piperidin-1-yl)propoxy)benzonitrile	778.1
193		4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-3-methylbutyl)benzonitrile	805.4
194		1-(6-(1-(3-(3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-2,2-difluoropropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	788.5
195		4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2,2-difluoropropyl)benzonitrile	813.3
196		4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-pentyl)benzonitrile	805.5
197		4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(4-((2,6-dioxopiperidin-3-yl)amino)phenyl)piperidin-1-yl)-2-methylpropyl)benzonitrile	751.2
198		4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(3-((2,6-dioxopiperidin-3-yl)amino)phenyl)piperidin-1-yl)-2-methylpropyl)benzonitrile	751.2
199		4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(1-(2,6-dioxopiperidin-3-yl)-3-methyl-1H-indazol-5-yl)piperidin-1-yl)-2-methylpropyl)benzonitrile	790.2

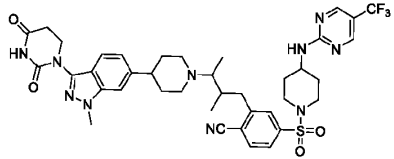
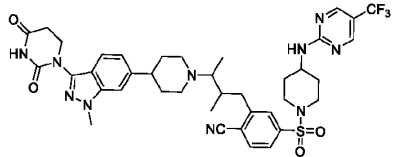
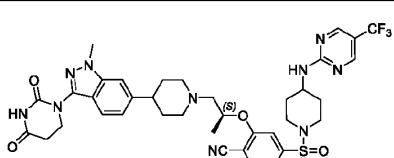
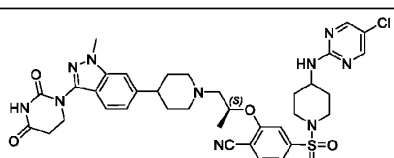
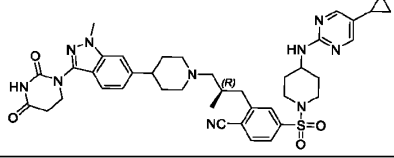
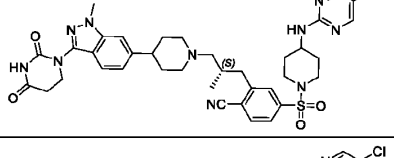
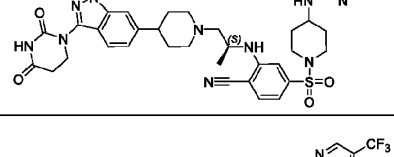
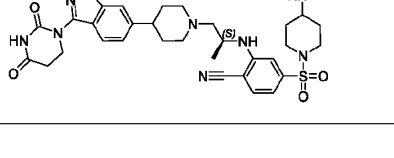
CPD #	Structure	Name	MS (ES, m/z): [M+1] ⁺
200		1-(6-(1-(4-(5-((4-(5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-oxopyridin-1(2H)-yl)butan-2-yl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl) dihydropyrimidine-2,4(1H,3H)-dione	783.1
201		4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-(methoxymethyl)propyl)benzonitrile	821.6
202		4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-4,4,4-trifluorobutyl)benzonitrile	845.5
203		4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,6-dioxopiperidin-3-yl)-1-(2,2,2-trifluoroethyl)-1H-indazol-6-yl)piperidin-1-yl)-2-methylpropyl)benzonitrile formate	858.1
204		4-((4-((5-((difluoromethylthio)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-methylpropyl)benzonitrile	807.1
205		1-(6-(1-(3-(4-((4-(5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-oxopyridin-1(2H)-yl)-2-methylpropyl)-piperidin-4-yl)-1-methyl-1H-indazol-3-yl) dihydropyrimidine-2,4(1H,3H)-dione	783.2
206		2-(3-(4-(1-cyclopropyl-3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1H-indazol-6-yl)piperidin-1-yl)-2-methylpropyl)-4-((4-(5-(difluoromethoxy)pyrimidin-2-yl)amino)-piperidin-1-yl)sulfonyl)benzonitrile	817.2

CPD #	Structure	Name	MS (ES, m/z): [M+1] ⁺
207		2-(3-(4-(1-(2,6-dioxopiperidin-3-yl)-1H-indazol-5-yl)piperidin-1-yl)butyl)-4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)-piperidin-1-yl)sulfonyl)benzonitrile	778.1
208		4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(2-((4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)-4-methoxybutyl)benzonitrile	835.3
209		4-((4-((5-(cyclopropyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(2-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-propoxy)benzonitrile	767.1
210		4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-(oxetan-3-yl)propyl)benzonitrile	833.5
211		1-(1-methyl-6-(1-(4-(4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-1H-pyrazol-1-yl)butan-2-yl)-piperidin-4-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	758.1
212		2-(4-cyano-2-((4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)butyl)-4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzonitrile	830.5
213		1-(1-methyl-6-(1-(2-methyl-3-(5-methyl-4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-1H-pyrazol-1-yl)propyl)piperidin-4-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	772.2

CPD #	Structure	Name	MS (ES, m/z): [M+1] ⁺
214		1-(1-methyl-6-(1-(2-methyl-3-(3-methyl-4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-1H-pyrazol-1-yl)propyl)piperidin-4-yl)-1H-indazol-3-yl) dihydropyrimidine-2,4(1H,3H)-dione	772.2
215		4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(1-(2,6-dioxopiperidin-3-yl)-1H-benzo[d][1,2,3]triazol-5-yl)-piperidin-1-yl)-2-methylpropyl)-benzonitrile	777.2
216		1-(1-methyl-6-(1-(2-methyl-3-(3-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-1H-pyrazol-1-yl)propyl)piperidin-4-yl)-1H-indazol-3-yl) dihydropyrimidine-2,4(1H,3H)-dione	758.1
217		1-(6-(1-(1-(2-fluoro-5-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-phenoxy)propan-2-yl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl) dihydropyrimidine-2,4(1H,3H)-dione	788.1
218		(R)-4-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-((1-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)propan-2-yl)oxy)benzonitrile	761.4
219		(R)-2-((1-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)propan-2-yl)oxy)-4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-benzonitrile	793.4
220		(R)-4-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-((1-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)propan-2-yl)amino)-benzonitrile 2,2,2-trifluoroacetate	760.4

CPD #	Structure	Name	MS (ES, m/z): [M+1] ⁺
221		(R)-2-((1-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)propan-2-yl)amino)-4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzonitrile 2,2,2-trifluoroacetate	794.4
222		4-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-((1-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)propan-2-yl)thio)benzonitrile	777.2
223		2-((1-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)propan-2-yl)thio)-4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzonitrile	811.3
224		(E)-2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)but-1-en-1-yl)-4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzonitrile	791.1
225		1-(1-methyl-6-(1-(2-methyl-3-(4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-1H-imidazol-1-yl)propyl)piperidin-4-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	758.2
226		4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(2-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-6-yl)cyclohexyl)oxy)-ethyl)benzonitrile	777.5
227		1-(1-methyl-6-(1-(2-methyl-3-(4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-1H-1,2,3-triazol-1-yl)propyl)piperidin-4-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	759.1

CPD #	Structure	Name	MS (ES, m/z): [M+1] ⁺
		yl)dihydropyrimidine-2,4(1H,3H)-dione	
228		N-(2-cyano-5-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-2-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-acetamide 2,2,2-trifluoroacetate	792.3
229		4-((4-((5-(2,2-difluorocyclopropyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-methylpropyl)-benzonitrile	801.2
230		2-(4-cyano-2-((4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)butyl)-4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-benzonitrile	832.5
231		4-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(4-cyano-2-((4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)butyl)-benzonitrile	798.5
232		2-(2-cyclopropyl-3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)propyl)-4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-benzonitrile	817.5
233		1-(1-methyl-6-(1-(2-methyl-3-(4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)-sulfonyl)-1H-pyrazol-1-yl)-propyl)piperidin-4-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	758.2

CPD #	Structure	Name	MS (ES, m/z): [M+1] ⁺
234	 Separated diastereomer	2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-methylbutyl)-4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzonitrile	807.2
235	 Separated diastereomer	2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-methylbutyl)-4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzonitrile	807.2
236	 Separated diastereomer	(S)-2-((1-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)propan-2-yl)oxy)-4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzonitrile	795.4
237	 Separated diastereomer	(S)-4-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-((1-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)propan-2-yl)oxy)benzonitrile	761.4
238	 Separated diastereomer	(R)-4-((4-((5-cyclopropylpyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-methylpropyl)-benzonitrile	765.3
239	 Separated diastereomer	(S)-4-((4-((5-cyclopropylpyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-methylpropyl)-benzonitrile	765.3
240	 Separated diastereomer	(S)-4-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-((1-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)propan-2-yl)amino)-benzonitrile	760.2
241	 Separated diastereomer	(S)-2-((1-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)propan-2-yl)amino)-4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzonitrile	794.3

CPD #	Structure	Name	MS (ES, m/z): [M+1] ⁺
242		1-(6-(1-(1-(2-chloro-5-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenoxy)propan-2-yl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione	804.1
243		4-((4-((5-cyclopropylpyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-((1-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)butan-2-yl)oxy)benzonitrile	781.3
244		4-((4-((5-cyclopropylpyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-((2-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)ethyl)amino)benzonitrile	752.6
245		2-((1-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)butan-2-yl)oxy)-4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzonitrile	809.4
246		(S)-1-(6-(1-(3-(5-((4-((5-cyclopropylpyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(difluoromethyl)phenyl)-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydro-pyrimidine-2,4(1H,3H)-dione	790.3
247		1-(6-(1-(2-(2-chloro-5-((4-((5-cyclopropylpyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenoxy)propyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydro-pyrimidine-2,4(1H,3H)-dione formate	776.3
248		1-(6-(1-(1-(2-chloro-5-((4-((5-cyclopropylpyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenoxy)propan-2-yl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione formate	776.3

CPD #	Structure	Name	MS (ES, m/z): [M+1] ⁺
249		1-(6-(1-(1-(5-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)-sulfonyl)-2-(difluoromethyl)phenoxy)propan-2-yl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl) dihydropyrimidine-2,4(1H,3H)-dione	818.1
250		2-(2-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)butoxy)-4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzonitrile	809.4

Contemplated compounds are disclosed in Table 2 below:

5

Table 2

General Synthetic Scheme

10

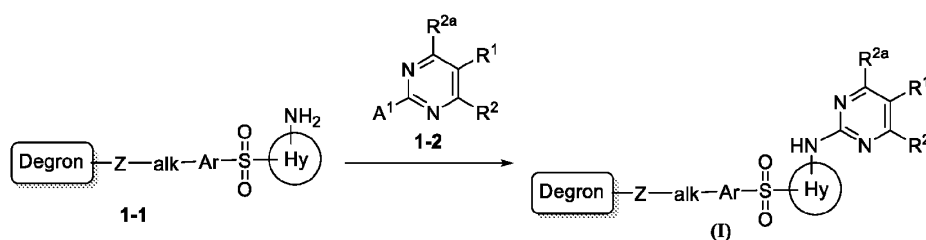
Compounds Formula (I) (and any embodiment thereof disclosed herein including specific compounds) can be made by the methods depicted in the reaction schemes shown below.

The starting materials and reagents used in preparing these compounds are either available from commercial suppliers such as Aldrich Chemical Co., (Milwaukee, Wis.), Bachem (Torrance, Calif.), or Sigma (St. Louis, Mo.) or are prepared by methods known to those skilled in the art following procedures set forth in references such as Fieser and Fieser's Reagents for Organic
 5 Synthesis, Volumes 1-17 (John Wiley and Sons, 1991); Rodd's Chemistry of Carbon Compounds, Volumes 1-5 and Supplementals (Elsevier Science Publishers, 1989); Organic Reactions, Volumes 1-40 (John Wiley and Sons, 1991), March's Advanced Organic Chemistry, (John Wiley and Sons, 4th Edition) and Larock's Comprehensive Organic Transformations (VCH Publishers Inc., 1989). These schemes are merely illustrative of some methods by which the compounds Formula (I) (and
 10 any embodiment thereof disclosed herein including specific compounds) can be synthesized, and various modifications to these schemes can be made and will be suggested to one skilled in the art reading this disclosure. The starting materials and the intermediates, and the final products of the reaction may be isolated and purified if desired using conventional techniques, including but not limited to filtration, distillation, crystallization, chromatography and the like. Such materials may be
 15 characterized using conventional means, including physical constants and spectral data.

Unless specified to the contrary, the reactions described herein take place at atmospheric pressure over a temperature range from about -78°C to about 150°C , such as from about 0°C to about 125°C and further such as at about room (or ambient) temperature, *e.g.*, about 20°C .

Compounds of Formula (I), where Degron is an E3 ligase ligand of formula (i) and (ii) and
 20 Hy, R^1 , R^2 , R^{2a} , Ar, alk, and Z are as defined in the Summary or an embodiment thereof hereinabove, can be prepared as described in Scheme 1 below.

Scheme 1

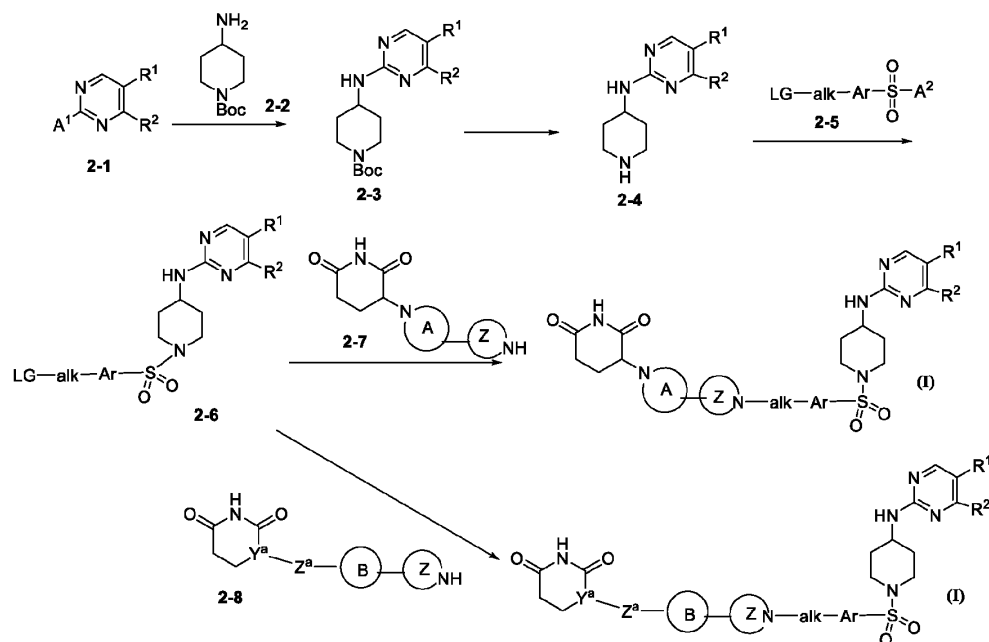


Treatment of a pyrimidine of formula **1-2** where A^1 is a halogen such as chlorine, or bromine,
 25 with an amine of formula **1-1** where Degron, Hy, R^1 , R^2 , R^{2a} , Ar, alk, and Z are as defined in the Summary or an embodiment thereof hereinabove, under suitable conditions such as acidic, basic or transition metal catalyzed reaction conditions well known in the art, provides a compound of Formula (I).

Alternatively, a compound of Formula (I) such as where R^1 , R^2 , Ar, and alk are as defined in the Summary or an embodiment thereof, R^{2a} is hydrogen, Hy is 1,4-piperidindiy, Degron is a group of formula (i) or (ii), and Z is heterocyclylene, bridged heterocyclylene, or spiro heterocyclylene, each ring containing at least one nitrogen atom, can be synthesized as illustrated and described in

5 Scheme 2 below.

Scheme 2



Treatment of a pyrimidine of formula 2-1 where A^1 is a halogen such as chlorine, or bromine and R^1 and R^2 are defined in the Summary or an embodiment thereof hereinabove, with a piperidine amine of formula 2-2 under conditions well known in the art, such as in the presence of DIPEA in

10 tert-butanol at elevated temperature, provides a compound of formula 2-3. An amine compound of formula 2-4, prepared by removal of the Boc protecting group of 2-3 in the presence of an acid, such as TFA, is converted to a sulfonamide compound of formula 2-6 by treating it with a sulfonyl halide of formula 2-5 where A^2 is halogen such as chlorine and LG is a suitable leaving group such as halo

15 or methylsulfonyl and Ar and alk are as defined in the Summary or an embodiment thereof hereinabove. Treatment of a compound of formula 2-6 with an amine compound of formula 2-7

where $\text{Z}'\text{NH}$ is heterocyclyl, bridged heterocyclyl, or spiro heterocyclyl, each ring containing at least one nitrogen atom and ring A is defined as in the Summary or an embodiment thereof hereinabove or with a compound of formula 2-8 where Y^a , Z^a , and ring B are as defined in the

Summary and $\text{Z}'\text{NH}$ is as defined in compound **2-7**, under basic conditions such as in the presence of DIPEA, provides a compound of Formula (I).

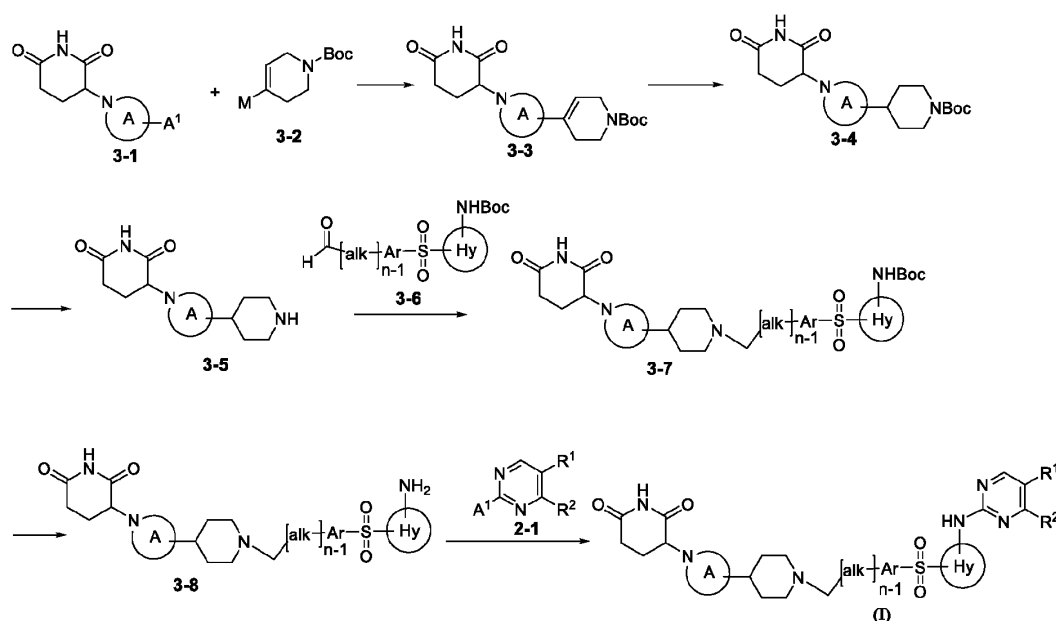
Compounds of formula **2-1**, **2-5**, **2-7**, and **2-8** are either commercially available or they can be prepared by methods known in the art.

5

Alternatively, a compound of Formula (I) such as where R^1 , R^2 , Ar, and alk are as defined in the Summary or an embodiment thereof, R^{2a} is hydrogen, 1,4-piperidindyl, Degron is a group of formula (i) and Degron of formula (i) or (ii) and Z is heterocyclylene containing at least one nitrogen atoms such as 4-piperidin-1-yl, can be synthesized as illustrated and described in Scheme 3 below.

10

Scheme 3



Cross coupling of a compound of formula **3-1**, where A^1 is a halogen and ring A as defined in the Summary or an embodiment thereof hereinabove, with a tetrahydropiperidinyl of formula **3-2** where M is a metal, such as boronic ester or zinc, provides a compound of formula **3-3**. The reaction typically proceeds in the presence of a palladium catalyst; for example, when M is a boronic ester, a Suzuki reaction is conducted in the presence of $\text{Pd}(\text{dppf})\text{Cl}_2$ and Na_2CO_3 , in 1,4-dioxane and water.

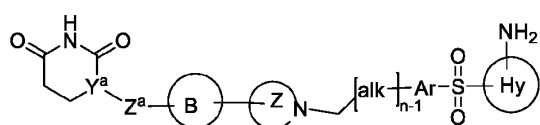
Reduction of the double bond in compound **3-3** under conditions well known in the art, such as in the presence of a palladium catalyst and under hydrogen atmosphere, provides compound of formula **3-4**. Removal of the Boc protection group of **3-4** under acidic conditions provides an amine compound of formula **3-5**. Reaction of **3-5** with an aldehyde of formula **3-6** where Ar and $-\text{CH}_2-$

20

[alk]_{n-1} is alk, each as defined in the Summary or an embodiment thereof hereinabove, under conditions well known in the art in the presence of a reducing agent, such as NaBH(OAc)₃, in a suitable solvent, such as DCM, where Hy is as defined in the Summary or an embodiment thereof hereinabove and -CH₂-(alk)_{n-1} is alk as defined in the Summary or an embodiment thereof

- 5 hereinabove, provides compound of formula 3-7. Removal of the Boc protecting group in compound 3-7 using an acid like TFA provides an amine compound of formula 3-8. Treatment of compound 3-8 with a compound of formula 2-1 under suitable conditions such as acidic, basic or transition metal catalyzed reaction conditions well known in the art, provides a compound of Formula (I).

- 10 Proceeding as described in Scheme 3 above, but replacing a compound of formula 3-5 with a compound of formula 2-8, will provide a compound of formula

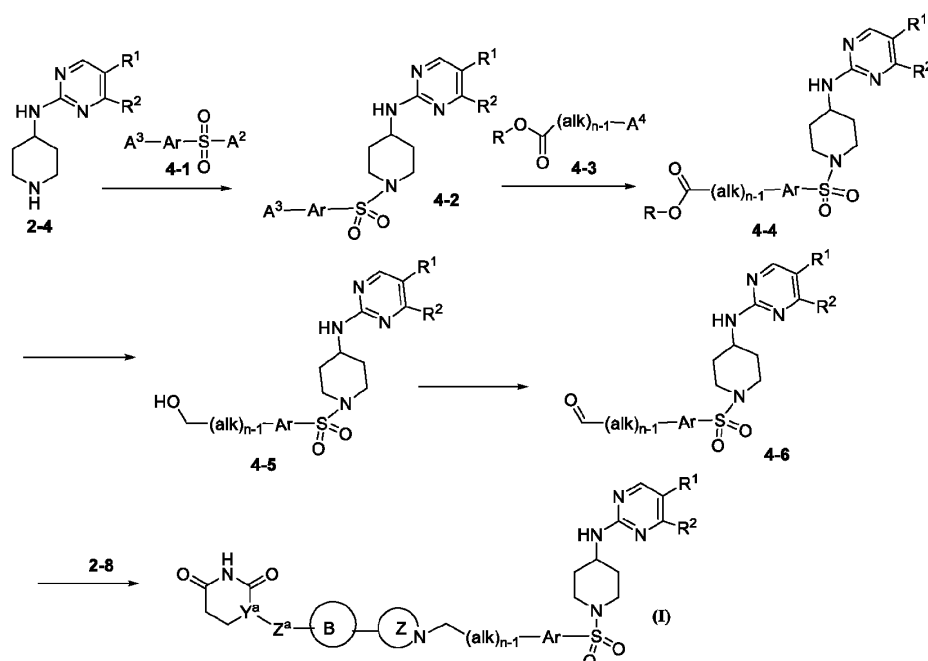


which can then be converted into a compound of

Formula (I) where the Degron is a group of formula (ii) or any embodiment thereof.

- 15 A compound of Formula (I) or embodiments thereof where R¹, R², Ar are as defined in the Summary or an embodiment thereof, R^{2a} is hydrogen, Hy is heterocyclene such as 1,4-piperidindyl, alk is C₃ to C₆ alkylene substituted with R^g, R^h, and Rⁱ (or an embodiment thereof), Degron is a group of formula (ii) and Z is heterocyclene, bridged heterocyclene, or spiro heterocyclene, each ring containing at least one nitrogen atom, can be also synthesized as illustrated and described in Scheme 4 below.

Scheme 4

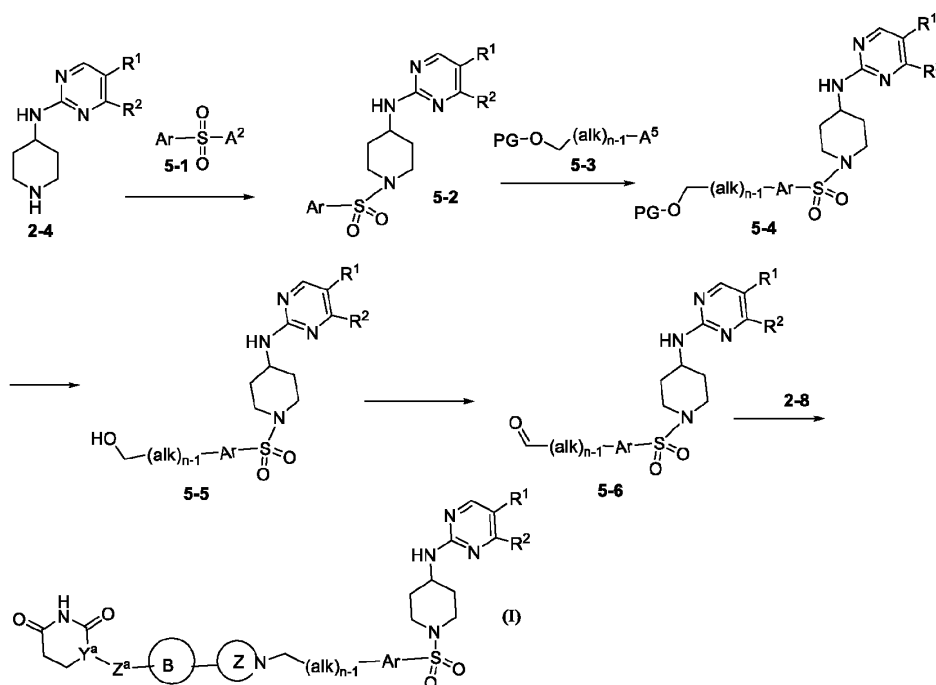


An amine compound of formula 2-4 is converted to a sulfonamide compound of formula 4-2 by treating it with a sulfonyl halide of formula 4-1 where A^2 is halogen such as chlorine and A^3 is a suitable halogen such as bromine and Ar is as defined in the Summary or an embodiment thereof hereinabove. Treatment of a compound of formula 4-2 with an ester of formula 4-3 where R is alkyl, $(alk)_{n-1}$ is C_2 to C_5 alkylene substituted with R^g , R^h , and R^i , A^4 is halogen such as iodo, under reductive coupling conditions known in the art, such as in the presence of a combination of Mn, $NiCl_2(DME)$, pyridine-2-carboxamide hydrochloride and NaI, provides a compound of formula 4-4 which can be converted to an alcohol of formula 4-5 in the presence of a reducing agent, such as DIBAL-H. An aldehyde compound of formula 4-6, synthesized by oxidation of 4-5 with a suitable oxidant, such as Dess-Martin periodinane, can be treated with a compound of formula 2-8 under reductive amination conditions to yield a compound of Formula (I) where $-CH_2-[alk]_{n-1}$ is C_3 to C_6 alkylene substituted with R^g , R^h , and R^i (or an embodiment thereof).

A compound of Formula (I) or embodiments thereof where R^1 and R^2 are as defined in the Summary or an embodiment thereof, Ar is monocyclic heteroaryl, heterocyclylene, unsaturated heterocyclylene^x or an embodiment thereof, R^{2a} is hydrogen, Hy is heterocyclylene such as 1,4-piperidindyl, Degron is a group of formula (ii), and alk is C_3 to C_6 alkylene substituted with R^g ,

R^h , and R^i (or an embodiment thereof) can be synthesized as illustrated and described in Scheme 5 below.

Scheme 5

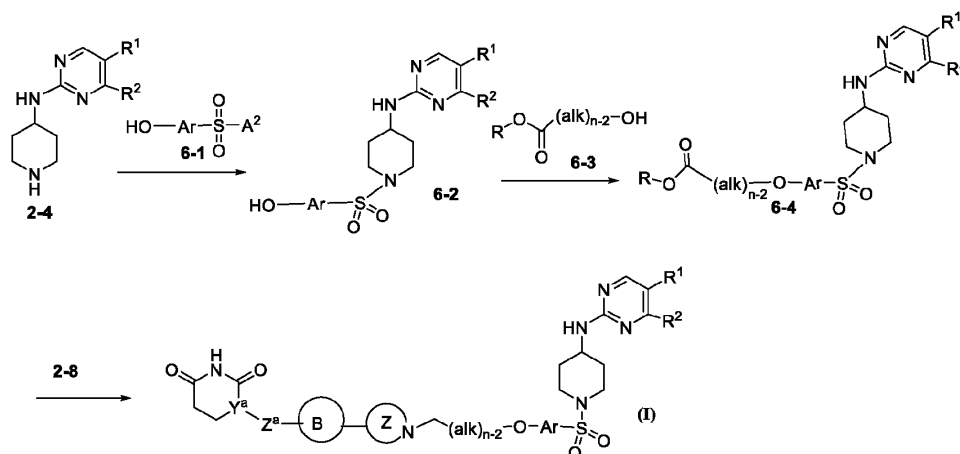


- 5 An amine compound of formula 2-4 is converted to a sulfonamide compound of formula 5-2 by treating it with a sulfonyl halide of formula 5-1 where A^2 is halogen such as chlorine and Ar is monocyclic heteroarylene, heterocyclylene, unsaturated heterocyclylene^x or an embodiment thereof hereinabove. Treatment of a compound of formula 5-2 with a compound of formula 5-3, where PG is a suitable oxygen protecting group, (alk)_{n-1} is C₂ to C₅ alkylene substituted with R^g , R^h , and R^i , and
- 10 A^5 is a suitable leaving group, such as halogen or mesylate, in the presence of a base at elevated temperature, provides a compound of formula 5-4. Compound of formula 5-4 can be converted to an alcohol of formula 5-5 by removing the protecting group with methods known in the art. An aldehyde of formula 5-6, synthesized by oxidation of 5-5 with a suitable oxidant, such as Dess-Martin periodinane, can be treated with a compound of formula 2-8 under reductive amination
- 15 conditions to yield a compound of Formula (I) where -CH₂-(alk)_{n-1} is C₃ to C₆ alkylene substituted with R^g , R^h , and R^i (or an embodiment thereof).

- A compound of Formula (I) or embodiments thereof where R^1 and R^2 are as defined in the Summary or an embodiment thereof, Ar is aryl or monocyclic heteroaryl or an embodiment thereof,
- 20 R^{2a} is hydrogen, Hy is heterocyclylene such as 1,4-piperidindiyl, Degron is a group of formula (ii), and

alk is C₃ to C₆ heteroalkylene substituted with R^g, R^h (of an embodiment thereof), and Rⁱ that attached to Ar via oxygen atom of heteroalkylene can be synthesized as illustrated and described in Scheme 6 below.

Scheme 6

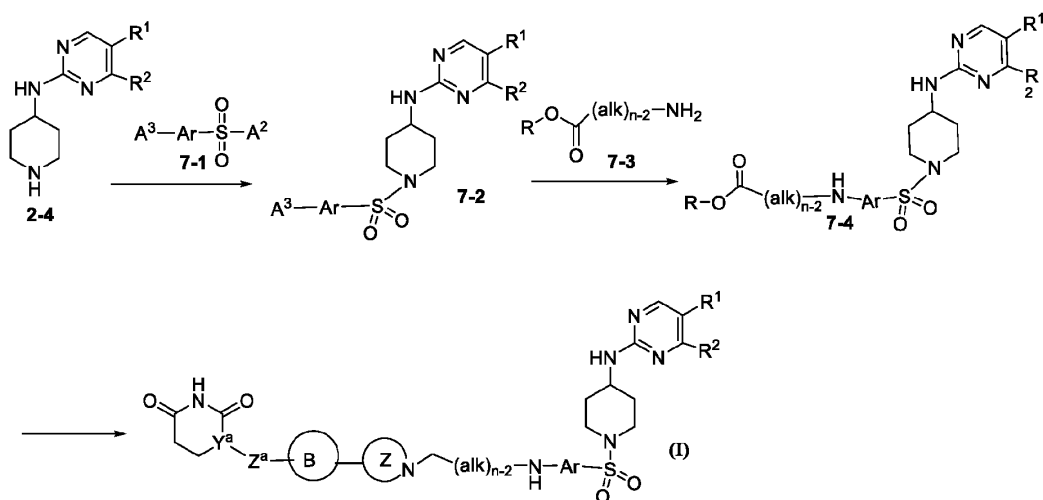


5

An amine compound of formula 2-4 is converted to a sulfonamide compound of formula 6-2 by treating it with a sulfonyl halide of formula 6-1 where A² is halogen such as chlorine and Ar is as defined in the Summary or an embodiment thereof hereinabove. Treatment of a compound of formula 6-2 with an alcohol of formula 6-3, where R is alkyl, under Mitsunobu reaction conditions known in the art, provides a compound of formula 6-4 which can be converted to compound of Formula (I) where -CH₂-(alk)_{n-2}-O- is C₃ to C₆ heteroalkylene substituted with R^g, R^h, and Rⁱ (of an embodiment thereof), by proceeding analogously as described in Scheme 4.

A compound of Formula (I) or embodiments thereof where R¹ and R² are as defined in the Summary or an embodiment thereof, Ar is aryl or monocyclic heteroaryl or an embodiment thereof, R^{2a} is hydrogen, Hy is heterocyclene such as 1,4-piperidindiyl, Degron is a group of formula (ii), and alk is C₃ to C₆ heteroalkylene substituted with R^g, R^h, and Rⁱ (of an embodiment thereof) that attached to Ar via nitrogen atom of heteroalkylene can be synthesized as illustrated and described in Scheme 7 below.

Scheme 7



An amine compound of formula 2-4 is converted to a sulfonamide compound of formula 7-2 by treating it with a sulfonyl halide of formula 7-1 where A² is halogen such as chlorine and A³ is a suitable halogen such as bromine and Ar is as defined in the Summary or an embodiment thereof
 5 hereinafter. Treatment of a compound of formula 7-2 with an amine of formula 7-3, where R is alkyl, under Buchwald coupling reaction conditions known in the art, provides a compound of formula 7-4 which can be converted to compound of Formula (I) where -CH₂-[alk]_{n-2}-NH- is C₃ to C₆ heteroalkylene substituted with R^g, R^h, and Rⁱ (or an embodiment thereof), by proceeding
 10 analogously as described in Scheme 4.

Utility

The compound of Formula (I) (and any embodiment thereof disclosed herein including specific compounds) could cause degradation of CDK2 and CDK4 proteins and hence are useful in
 15 the treatment of diseases mediated by CDK2 and/or CDK4.

Increasing evidence suggests that overactivated CDK2 and/or CDK4 leads to abnormal cell cycle regulation and proliferation in cancer cells. While CDK2/4 mutations are rarely found, the kinase activity of CDK4/Cyclin D, CDK2/Cyclin E or CDK2/Cyclin A complexes is elevated via several mechanisms in human cancers. Aberrations of CDK4/cyclin D regulation have been
 20 identified in many human cancers. For example, amplification or overexpression of cyclin D1 has been found in many cancers, including breast invasive ductal carcinoma, invasive breast carcinoma, bladder urothelial carcinoma, breast invasive lobular carcinoma, and lung adenocarcinoma. Translocation of cyclin D1 Amplification of CDK4 is common in liposarcoma. CDK4 amplification has also been observed at lower frequency in other solid tumors and hematologic malignancies. Loss

of the CDK4 inhibitor p16 (CDKN2A) is also a common event in many cancers, including glioblastoma multiforme, head and neck squamous cell carcinoma, pancreatic adenocarcinoma, esophageal adenocarcinoma, mesothelioma, lung squamous cell carcinoma, bladder urothelial carcinoma, skin cutaneous melanoma, diffuse large B-cell lymphoma, cholangiocarcinoma, lung
5 adenocarcinoma, and stomach adenocarcinoma.

Cyclin E has been found to be frequently amplified in cancers, for example, in uterine cancer, ovarian cancer, stomach cancer, and breast cancer. In some cancer types, loss-of-function mutations in FBXW7 or overexpression of USP28, which control the turnover of cyclin E, leads to cyclin E overexpression and CDK2 activation. Alternatively, certain cancer cells express a hyperactive,
10 truncated form of cyclin E or cyclin A. In addition, cyclin A amplification and overexpression have also been reported in various cancers such as hepatocellular carcinomas, colorectal and breast cancers. In some tumors, catalytic activity of CDK2 is increased following loss of the expression or alteration of the location of the endogenous CDK2 inhibitor p27 or p21, or overexpression of SKP2, a negative regulator of p27. In addition, CDC25A and CDC25B, protein phosphatases responsible
15 for the dephosphorylations that activate the CDK2, are overexpressed in various tumors. These various mechanisms of CDK2 activation have been validated using cancer cells or mouse cancer models. Furthermore, CDK2/cyclin E phosphorylates oncogenic Myc to oppose ras-induced senescence, highlighting the importance of CDK2 in myc/ras-induced tumorigenesis. Inactivation of CDK2 has been shown to be synthetically lethal to myc over-expressing cancer cells. In aneuploid
20 cancer cells, for example KRAS-mutant lung cancer, CDK2 inhibition resulted in anaphase catastrophe and apoptosis. Moreover, inhibiting CDK2 effectively induced granulocytic differentiation in AML cell lines and arrested tumor growth in AML mice models.

CDK2 activation as a result of cyclin E amplification or overexpression has also been identified as a key primary or acquired resistance pathway to HR+ or HER2+ breast cancers treated
25 by CDK4/6 inhibitors or trastuzumab. Accordingly, compounds of Formula (I) can be used in combination with CDK4/6 inhibitors or anti-HER2 therapies for the treatment of cancers that become refractory to CDK4/6 inhibitors or anti-HER2 therapies.

Therefore, a compound of this disclosure may be useful for treating tumors characterized by
30 1) overexpression of CDK2 and/or CDK4; 2) amplification /overexpression of cyclin D, cyclin E or cyclin A; 3) hyperphosphorylation of CDK2 (Thr160) or CDK4 (Thr172); 4) loss-of-function of mutation in FBXW7, depletion of AMBRA1, overexpression of USP28, or amplification/overexpression of CDC25A or/and CDC25B; 5) expression of truncated cyclin E or cyclin A, 6) dysregulation of p16, p21 or p27, or overexpression of SKP2; 7) hyperactive

MYC/RAS; 8) Aneuploid cancers; 9) CDK4 and/or CDK6 inhibitor refractory cancers; and 10) amplification and/or overexpression of CCNE1.

Accordingly, also provided herein are additional embodiments D1 to D20:

- D1. In embodiment D1, provided is a method of treating a patient having cancer other than HR+/HER2- wherein the cancer is characterized by one or more of:
- (i) amplification of CDK2 gene;
 - (ii) amplification of CDK4 gene;
 - (iii) overexpression of CDK2 protein;
 - (iv) overexpression of CDK4 protein;
 - (v) amplification of CCNE genes;
 - (vi) overexpression of cyclin E proteins;
 - (vii) amplification of CCND genes;
 - (viii) overexpression cyclin D proteins;
 - (ix) overexpression of cyclin A proteins;
 - (x) hyperphosphorylation of CDK2 (Thr160) protein;
 - (xi) hyperphosphorylation of CDK4 (Thr172) protein;
 - (xii) loss-of-function mutation in FBXW7 protein;
 - (xiii) deletion of AMBRA1 gene;
 - (xiv) overexpression of USP28 protein;
 - (xv) overexpression of CDC25A protein;
 - (xvi) overexpression of CDC25B protein;
 - (xvii) expression of truncated cyclin E protein;
 - (xviii) expression of truncated cyclin A protein;
 - (xix) loss of function mutations of p15 protein;
 - (xx) loss of function mutations of p16 protein;
 - (xxi) loss of function mutations of p21 protein;
 - (xxii) loss of function mutations of p27 protein;
 - (xxiii) loss of CDKN2A gene;
 - (xxiv) loss of CDKN2B gene;
 - (xxv) loss of CDKN1A gene;
 - (xxvi) loss of CDKN1B gene;
 - (xxvii) overexpression of SKP2 protein;
 - (xxviii) hyperactive MYC pathway;
 - (xxix) hyperactive RAS pathway;

(xxx) mutation of retinoblastoma gene; and

(xxxi) loss of retinoblastoma gene;

the method comprising administering a therapeutically effective amount of a compound of Formula (IB) or (I) (or an embodiment thereof), to a patient in need thereof.

5 D2. In embodiment D2, provided is method of treating a patient having cancer other than HR+/HER2-, the method comprising:

(A) determining whether the patient has cancer that is characterized by at least one of:

- (i) amplification of CDK2 gene;
- (ii) amplification of CDK4 gene;
- 10 (iii) overexpression of CDK2 protein;
- (iv) overexpression of CDK4 protein;
- (v) amplification of CCNE genes;
- (vi) overexpression of cyclin E proteins;
- (vii) amplification of CCND genes;
- 15 (viii) overexpression cyclin D proteins;
- (ix) overexpression of cyclin A proteins;
- (x) hyperphosphorylation of CDK2 (Thr160) protein;
- (xi) hyperphosphorylation of CDK4 (Thr172) protein;
- (xii) loss-of-function mutation in FBXW7 protein;
- 20 (xiii) deletion of AMBRA1 gene;
- (xiv) overexpression of USP28 protein;
- (xv) overexpression of CDC25A protein;
- (xvi) overexpression of CDC25B protein;
- (xvii) expression of truncated cyclin E protein;
- 25 (xviii) expression of truncated cyclin A protein;
- (xix) loss of function mutations of p15 protein;
- (xx) loss of function mutations of p16 protein;
- (xxi) loss of function mutations of p21 protein;
- (xxii) loss of function mutations of p27 protein;
- 30 (xxiii) loss of CDKN2A gene;
- (xxiv) loss of CDKN2B gene;
- (xxv) loss of CDKN1A gene;
- (xxvi) loss of CDKN1B gene;
- (xxvii) overexpression of SKP2 protein;

- (xxviii) hyperactive MYC pathway;
- (xxix) hyperactive RAS pathway;
- (xxx) mutation of retinoblastoma gene; and
- (xxxi) loss of retinoblastoma gene; and

5 (b) administering a therapeutically effective amount of a compound of Formula (IB) or (I) (or an embodiment thereof) to the patient who is determined to have a cancer that is characterized by at least one of (a)(i)-(a)(xxxi).

D3. In embodiment D3, provided is a method of identifying a patient having a cancer, other than HR+/HER2-, who may benefit from treatment a compound of Formula (IB) or (I) (or an
10 embodiment thereof), the method comprising:

(A) determining whether the patient has cancer that is characterized by at least one of:

- (i) amplification of CDK2 gene;
- (ii) amplification of CDK4 gene;
- (iii) overexpression of CDK2 protein;
- 15 (iv) overexpression of CDK4 protein;
- (v) amplification of CCNE genes;
- (vi) overexpression of cyclin E proteins;
- (vii) amplification of CCND genes;
- (viii) overexpression cyclin D proteins;
- 20 (ix) overexpression of cyclin A proteins;
- (x) hyperphosphorylation of CDK2 (Thr160) protein;
- (xi) hyperphosphorylation of CDK4 (Thr172) protein;
- (xii) loss-of-function mutation in FBXW7 protein;
- (xiii) deletion of AMBRA1 gene;
- 25 (xiv) overexpression of USP28 protein;
- (xv) overexpression of CDC25A protein;
- (xvi) overexpression of CDC25B protein;
- (xvii) expression of truncated cyclin E protein;
- (xviii) expression of truncated cyclin A protein;
- 30 (xix) loss of function mutations of p15 protein;
- (xx) loss of function mutations of p16 protein;
- (xxi) loss of function mutations of p21 protein;
- (xxii) loss of function mutations of p27 protein;
- (xxiii) loss of CDKN2A gene;

- (xxiv) loss of CDKN2B gene;
- (xxv) loss of CDKN1A gene;
- (xxvi) loss of CDKN1B gene;
- (xxvii) overexpression of SKP2 protein;
- 5 (xxviii) hyperactive MYC pathway;
- (xxix) hyperactive RAS pathway;
- (xxx) mutation of retinoblastoma gene; and
- (xxxi) loss of retinoblastoma gene

10 wherein the determining identifies the patient as one who may benefit from treatment with a compound of Formula (IB) or (I) (or an embodiment thereof). In a sub-embodiment of embodiment D3, the method further comprises administering a therapeutically effective amount of a compound of Formula (IB) or (I) to the patient who is identified as one who may benefit from treatment with a compound of Formula (IB) or (I) (or an embodiment thereof).

15 D4. In embodiment D4, the method of embodiment D2 or D3, is wherein the presence of at least one of the following:

- (i) amplification of CDK2 gene;
- (ii) amplification of CDK4 gene;
- (iii) overexpression of CDK2 protein;
- (iv) overexpression of CDK4 protein;
- 20 (v) amplification of CCNE genes;
- (vi) overexpression of cyclin E proteins;
- (vii) amplification of CCND genes;
- (viii) overexpression cyclin D proteins;
- (ix) overexpression of cyclin A proteins;
- 25 (x) hyperphosphorylation of CDK2 (Thr160) protein;
- (xi) hyperphosphorylation of CDK4 (Thr172) protein;
- (xii) loss-of-function mutation in FBXW7 protein;
- (xiii) deletion of AMBRA1 gene;
- (xiv) overexpression of USP28 protein;
- 30 (xv) overexpression of CDC25A protein;
- (xvi) overexpression of CDC25B protein;
- (xvii) expression of truncated cyclin E protein;
- (xviii) expression of truncated cyclin A protein;
- (xix) loss of function mutations of p15 protein;

- (xx) loss of function mutations of p16 protein;
 - (xxi) loss of function mutations of p21 protein;
 - (xxii) loss of function mutations of p27 protein;
 - (xxiii) loss of CDKN2A gene;
 - 5 (xxiv) loss of CDKN2B gene;
 - (xxv) loss of CDKN1A gene;
 - (xxvi) loss of CDKN1B gene;
 - (xxvii) overexpression of SKP2 protein;
 - (xxviii) hyperactive MYC pathway;
 - 10 (xxix) hyperactive RAS pathway;
 - (xxx) mutation of retinoblastoma gene; and
 - (xxxi) loss of retinoblastoma gene;
- is assessed by histological and/or genetic analysis of a cancer sample obtained from the patient.
- 15 D5. In embodiment D5, the method of embodiment D4 is wherein the amplification, deletion, mutation, and loss of one or more of CDK2 gene, CDK4 gene, CCNE genes, CCND genes, AMBRA1 gene, CDKN2A gene, CDKN2B gene, CDKN1A gene, CDKN1B gene, and retinoblastoma gene in the cancer sample is determined by whole genome sequencing, exome sequencing, targeted gene sequencing, or a combination thereof.
- 20 D6. In embodiment D6, the method of embodiment D4 or D5 is wherein the amplification, deletion, mutation, and loss of one or more of CDK2 gene, CDK4 gene, CCNE genes, CCND genes, AMBRA1 gene, CDKN2A gene, CDKN2B gene, CDKN1A gene, CDKN1B gene, and retinoblastoma gene in the cancer sample is different from wild type CDK2 gene, CDK4 gene, CCNE genes, CCND genes, AMBRA1 gene, CDKN2A gene, CDKN2B gene, CDKN1A gene,
- 25 CDKN1B gene, and retinoblastoma gene, respectively.
- D7. In embodiment D7, the method of any one of embodiments D2 to D4 is wherein the expression level of one of more of AMBRA1 gene, CDKN2A gene, CDKN2B gene, CDKN1A gene, CDKN1B gene, and retinoblastoma gene and the protein that each of the gene codes for in the cancer sample is below the reference expression level of the corresponding one or more AMBRA1 gene,
- 30 CDKN2A gene, CDKN2B gene, CDKN1A gene, CDKN1B gene, and retinoblastoma gene and the protein each of the gene codes for.
- D7A. In embodiment D7A, the method of any one of embodiments D2 to D4 is wherein the expression level of one of more of CDK2 gene, CDK4 gene, CCNE genes, CCND genes and the protein each of the gene codes for, USP28 protein, CDC25A protein, CDC25B protein, and SKP2

protein, in the cancer sample is higher than the reference expression level of the corresponding one or more CDK2 gene, CDK4 gene, CCNE genes, CCND genes, CDKN2B gene, CDKN1A gene, and CDKN1B gene the protein each of the gene codes for, USP28 protein, CDC25A protein, CDC25B protein, and SKP2 protein.

5 D8. In embodiment D8, the method of embodiment D7 to D7A is wherein the reference expression level of each of the gene and each of the protein is determined from a population of patients having the same cancer.

D9. In embodiment D9, the method of embodiment D7 to D8 is wherein the expression level and the reference expression level are a nucleic acid expression level and the nucleic acid
10 expression level is an mRNA expression level.

D10. In embodiment D10, the method of embodiment D9 is wherein the mRNA expression level is determined by RNA-seq, QuantiGene RNA Assay, Nanostring, RT-qPCR, qPCR, multiplex qPCR or RT-qPCR, microarray analysis, SAGE, MassARRAY technique, or ISH, or a combination thereof.

15 D11. In embodiment D11, the method of embodiment D7 to D8 is wherein the expression level and the reference expression level are a protein expression level.

D12. In embodiment D12, the method of embodiment D11 is wherein the protein expression level is determined by immunohistochemistry (IHC), Western blot, enzyme-linked immunosorbent assay (ELISA), AlphaLISA immunoassay, immunoprecipitation,
20 immunofluorescence, electrochemiluminescence detection, homogeneous time resolved fluorescence (HTRF) assay, radioimmunoassay, or mass spectrometry.

D13. In embodiment D13, the method of any one of embodiments D4 to D12 is wherein the cancer sample is a tissue sample, a cell sample, a whole blood sample, a plasma sample, a serum sample, or a combination thereof.

25 D14. In embodiment D14, the method of embodiment D13 is wherein the tissue sample is a tumor tissue sample.

D15. In embodiment D15, provided is a method of treating cancer in a patient in need thereof, comprising:

(A) determining whether the patient will respond to CDK2 and/or CDK4-based therapy, by
30 measuring the expression level of at least one of:

- (i) amplification of CDK2 gene;
- (ii) amplification of CDK4 gene;
- (iii) overexpression of CDK2 protein;
- (iv) overexpression of CDK4 protein;

- (v) amplification of CCNE genes;
 - (vi) overexpression of cyclin E proteins;
 - (vii) amplification of CCND genes;
 - (viii) overexpression cyclin D proteins;
 - 5 (ix) overexpression of cyclin A proteins;
 - (x) hyperphosphorylation of CDK2 (Thr160) protein;
 - (xi) hyperphosphorylation of CDK4 (Thr172) protein;
 - (xii) loss-of-function mutation in FBXW7 protein;
 - (xiii) loss of AMBRA1 gene;
 - 10 (xiv) overexpression of USP28 protein;
 - (xv) overexpression of CDC25A protein;
 - (xvi) overexpression of CDC25B protein;
 - (xvii) expression of truncated cyclin E protein;
 - (xviii) expression of truncated cyclin A protein;
 - 15 (xix) loss of function mutations of p15 protein;
 - (xx) loss of function mutations of p16 protein;
 - (xxi) loss of function mutations of p21 protein;
 - (xxii) loss of function mutations of p27 protein;
 - (xxiii) loss of CDKN2A gene;
 - 20 (xxiv) loss of CDKN2B gene;
 - (xxv) loss of CDKN1A gene;
 - (xxvi) loss of CDKN1B gene;
 - (xxvii) overexpression of SKP2 protein;
 - (xxviii) hyperactive MYC pathway;
 - 25 (xxix) hyperactive RAS pathway;
 - (xxx) mutation of retinoblastoma gene; and
 - (xxxi) loss of retinoblastoma gene;
- in a patient sample; and
- (B) comparing the expression level measured in the patient sample in (A) with a
- 30 corresponding reference expression level derived from subject(s) with cancer who are responsive to the treatment; or
- (C) comparing the expression level measured in the patient sample in (A) with a corresponding reference expression level derived from cancer-free subject(s); and

(D) administering to the patient a therapeutically effective amount of a compound of Formula (IB) or (I) or a pharmaceutically acceptable salt thereof when the expression level measured in the patient sample in (A) and the corresponding reference expression level in (B) are similar or when the expression level measured in the patient sample in (A) is lower than the corresponding reference expression level in (C).

D16. In embodiment D16, provided is the method or use of any one of embodiments D2 to D15, wherein a plurality of (A)(i)-(A)(viii) are measured.

D17. In embodiment D17, provided is a method or use of any one of embodiments D7 to D11, and D16, wherein the reference level is an age-matched reference level.

D18. In embodiment D18, provided is a method or use of any one of embodiments D7 to D11, and D16, wherein the reference level is a BMI-matched reference level.

D19. In embodiment D19, provided is a method or use of any one of embodiments D7 to D11, and D16, wherein the reference level is a sex-matched reference level.

D20. In embodiment D20, provided is a method of any one of embodiments D7 to D11, and D16, wherein the reference level is a smoking/non-smoking matched reference level.

D21. In embodiment D21, provided is a method of any one of embodiments D7 to D11, and D16, wherein the reference level controls are for more than one parameter (e.g. two, three, four, five, or more parameters) as provided in embodiments D17 to D21.

D22. In embodiment D22, provided is a method of any one of embodiments D7 to D11, and D16 to D21, wherein the reference level is determined by measuring the level in a population of individuals.

In a first embodiment of embodiment D22, the term “population of individuals” means one or more individuals.

In a second embodiment of embodiment D22, the population of individuals comprises multiple individuals. In another embodiment, the term “multiple” means at least 2 (such as at least 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, or 30) individuals. In another embodiment, the population of individuals comprises at least 10 individuals.

In a third embodiment of embodiment D22, the population of individuals consists of one individual.

D23. In embodiment D23, the method of any one of embodiments D1 to D22 is wherein the cancer is a solid cancer.

As used above, polypeptides and nucleic acid that have different amino acid or nucleotide sequence, respectively, compared to their wild-type sequence are referred to as a “mutant” or “mutants”. Mutants include amplification, insertions, deletions, substitutions, transversions,

truncations, and/or inversions at one or more locations in the amino acid or nucleotide sequence, respectively, compared to the wild-type sequence. The mutant polypeptides include a polypeptide having a certain percent, e.g., at least about 80%, 85%, 90%, 95%, or 99%, of sequence identity with the wild type polypeptide or protein. Mutants may have 1, 2, 3, 4, 5, 10, 15, 20, 30, or more amino acid substitutions, additions, or deletions, or any integral value within the range of 1-100, compared to the wild-type sequence. The term “mutation” of a retinoblastoma gene refers to one or more changes in the nucleotide sequence of the retinoblastoma gene and the consequence may be loss of or reduced function of the retinoblastoma protein.

Gene deletion is a mutation in which a part of a sequence of DNA is left out during DNA replication. Any number of nucleotides can be deleted, from a single base to an entire piece of a gene.

“Loss of gene” means that a specific gene is completely missing from an organism's DNA. Loss of a gene results in a lack of protein that the gene encodes.

“Cancer sample” refers to a sample derived from, obtained by, generated from, provided from, taken from, or removed from a patient; or from fluid or tissue from the patient. Cancer samples include, but are not limited to synovial fluid, whole blood, blood serum, blood plasma, urine, sputum, tissue, saliva, tears, hair, spinal fluid, tissue section(s) obtained by biopsy, cell(s), or any combination thereof that are placed in or adapted to tissue culture, sweat, mucous, fecal material, gastric fluid, abdominal fluid, amniotic fluid, cyst fluid, peritoneal fluid, pancreatic juice, prostate milk, lung lavage, marrow, gastric acid, bile, semen, pus, aqueous humor, transudate, and the like including derivatives, portions and combinations of the foregoing. In some embodiments, cancer samples include, but are not limited, to blood and/or plasma. In some embodiments, cancer samples include, but are not limited, to urine or stool. Cancer samples include, but are not limited, to saliva. Cancer samples include, but are not limited, to tissue dissections and tissue biopsies. Cancer samples include, but are not limited, samples that can provide nucleic acids for analysis. Cancer samples include, but are not limited, any derivative or fraction of the aforementioned cancer samples.

Truncated proteins in the context of the present disclosure may, typically, comprise a sequence of a protein, which is, with regard to its amino acid sequence (or its encoding nucleic acid molecule), N-terminally, C-terminally and/or intrasequentially truncated compared to the amino acid sequence of the original (native) protein (or its encoded nucleic acid molecule). Such truncation may thus occur either on the amino acid level or correspondingly on the nucleic acid level. A “truncated” protein may be encoded by mature mRNA lacking one or part of an exon, or more exons of the gene responsible for the full-length protein, and still has, at least to some extent, the functions of the full-

length protein encoded by the normal gene corresponding to the gene. A “truncated” protein may also be introduced when the full-length protein is cleaved post-translationally by proteases.

“Truncation” of the cyclin E, also known as low molecular weight (LMW) cyclin E, refers to a version of cyclin E protein that the N-terminus 40 amino acids were deleted by protease.

- 5 “Truncation” or LMW cyclin E binds to CDK2 more efficiently than the full-length form of cyclin E, thus resulting in increased CDK2 activity.

- Hyperphosphorylation refers to a process where a protein is excessively phosphorylated, or has too many phosphate groups added to it as compared to the wild -type protein. When CDK2 is excessively phosphorylated at T160 site, it can lead to uncontrolled cell cycle progression and potential tumor development. When CDK4 is excessively phosphorylated at T172 site, it can lead to uncontrolled cell cycle progression and potential tumor development.
- 10

As used herein above, Cyclin E genes refers to cyclin E1 and cyclin E2 genes; cyclin E genes refers to CCNE1 and CCNE2 genes, Cyclin D genes refers to cyclin D1, cyclin D2 and cyclin D3 genes, and CCND genes refers to CCND1, CCND2 and CCND3.

- 15 In some embodiments, the term “wild type” denotes the most common, typical phenotype in a natural healthy population. In some embodiments, the term “wild type” denotes an organism or gene locus that predominates in natural or normal populations. In some embodiments, the cancer is ovarian cancer (e.g. serous, clear cell, endometrioid, and mucinous ovarian carcinomas), uterine cancer (e.g. endometrial cancer and uterine sarcoma), stomach cancer (i.e. gastric cancer), lung cancer (e.g., adenocarcinoma, small cell lung cancer and non-small cell lung carcinomas, parvicellular and non-parvicellular carcinoma, bronchial carcinoma, bronchial adenoma, pleuropulmonary blastoma), renal cancer (e.g. clear cell renal cell carcinomas, papillary renal cell carcinomas, and chromophobe renal cell carcinomas), brain cancer (including astrocytoma, meningioma and glioblastoma), neuroblastoma, paraganglioma, pheochromocytoma, pancreatic neuroendocrine tumors, somatostatinomas, hemangioblastomas, gastrointestinal stromal tumors, pituitary tumors, leiomyomas, leiomyosarcomas, polycythaemia, retinal cancers, hereditary leiomyomatosis, enal cell cancer, astrocytoma, skin cancer (e.g. melanoma, squamous cell carcinoma, Kaposi sarcoma, Merkel cell skin cancer), bladder cancer (including bladder urothelial carcinoma), cervical cancer, colorectal cancer (e.g., cancer of the small intestine, colon cancer, rectal cancer, cancer of the anus), head and neck cancer (e.g., cancers of the larynx, hypopharynx, nasopharynx, oropharynx, lips, tongue and mouth), liver cancer (e.g., hepatocellular carcinoma and cholangiocellular carcinoma), prostate cancer, testicular cancer, gall bladder cancer, pancreatic cancer (e.g. exocrine pancreatic carcinoma and neuroendocrine pancreatic cancer), thyroid cancer, and parathyroid cancer, fallopian tube cancer, peritoneal cancer, vaginal cancer, biliary tract cancer,
- 20
- 25
- 30

esophageal cancer (e.g. esophageal squamous cell carcinoma and esophageal adenocarcinoma), sarcoma (e.g. liposarcoma and osteosarcoma), bone cancer, chondrosarcoma, leukemia (including acute myeloid leukemia, acute lymphocytic leukemia, chronic myelogenous leukemia, and chronic lymphocytic leukemia), lymphoma (e.g. non-Hodgkin lymphoma NHL including mantle cell

5 lymphoma, MCL and Hodgkin lymphoma) and multiple myeloma.

In other embodiments, the cancer is breast cancer, including, *e.g.*, ER-positive/HR-positive breast cancer, HER2-negative breast cancer; ER-positive/HR-positive breast cancer, HER2-positive breast cancer; ER-negative/HR-negative, HER2-positive breast cancer, triple negative breast cancer (TNBC); or inflammatory breast cancer. In some embodiments, the breast cancer is endocrine
10 resistant breast cancer, anti-HER2 therapy (e.g. trastuzumab) resistant breast cancer, or breast cancer demonstrating primary or acquired resistance to CDK4/CDK6 inhibition. In some embodiments, the breast cancer is advanced or metastatic breast cancer. In some embodiments of each of the foregoing, the breast cancer is characterized by amplification or overexpression of CCNE1 and/or CCNE2.

Besides cancer, compounds of Formula (I) as described in the Summary as described in the
15 first aspect (or any of the embodiments thereof herein above) are useful in treating autoimmune diseases autoimmune diseases e.g., rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), primary Sjogren's syndrome (pSS), multiple sclerosis (MS), Crohn's disease (CD), gout, uveitis, pemphigus vulgaris, and sepsis, and can also be used as a promising preventive treatment for noise-, cisplatin-, or antibiotic-induced or age-related hearing loss.

20

Testing

CDK2/4 degradation activities of the compounds of the present disclosure can be tested using the *in vitro* assays described in Biological Examples below.

25

Pharmaceutical Compositions

In general, the compounds Formula (I) (unless stated otherwise, reference to compound/compounds of Formula (I) wherein includes any embodiments thereof described herein or a pharmaceutically acceptable salt thereof) will be administered in a therapeutically effective amount by any of the accepted modes of administration for agents that serve similar utilities. Therapeutically
30 effective amounts of compounds of Formula (I) (and any embodiment thereof disclosed herein including specific compounds) may range from about 0.01 to about 500 mg per kg patient body weight per day, which can be administered in single or multiple doses. A suitable dosage level may be from about 0.1 to about 250 mg/kg per day; about 0.5 to about 100 mg/kg per day. A suitable dosage level may be about 0.01 to about 250 mg/kg per day, about 0.05 to about 100 mg/kg per day,

or about 0.1 to about 50 mg/kg per day. Within this range the dosage can be about 0.05 to about 0.5, about 0.5 to about 5 or about 5 to about 50 mg/kg per day. For oral administration, the compositions can be provided in the form of tablets containing about 1.0 to about 1000 milligrams of the active ingredient, particularly about 1, 5, 10, 15, 20, 25, 50, 75, 100, 150, 200, 250, 300, 400, 500, 600, 750, 800, 900, and 1000 milligrams of the active ingredient. The actual amount of the compound of Formula (I) (or any embodiment thereof disclosed herein including specific compounds), *i.e.*, the active ingredient, will depend upon numerous factors such as the severity of the disease to be treated, the age and relative health of the patient, the potency of the compound being utilized, the route and form of administration, and other factors.

In general, compounds Formula (I) (and any embodiment thereof disclosed herein including specific compounds) will be administered as pharmaceutical compositions by any one of the following routes: oral, systemic (*e.g.*, transdermal, intranasal or by suppository), or parenteral (*e.g.*, intramuscular, intravenous or subcutaneous) administration. The preferred manner of administration is oral using a convenient daily dosage regimen, which can be adjusted according to the degree of affliction. Compositions can take the form of tablets, pills, capsules, semisolids, powders, sustained release formulations, solutions, suspensions, elixirs, aerosols, or any other appropriate compositions.

The choice of formulation depends on various factors such as the mode of drug administration (*e.g.*, for oral administration, formulations in the form of tablets, pills or capsules, including enteric coated or delayed release tablets, pills or capsules are preferred) and the bioavailability of the drug substance.

The compositions are comprised of in general, a compound of Formula (I) (or any embodiment thereof disclosed herein including specific compounds) in combination with at least one pharmaceutically acceptable excipient. Acceptable excipients are generally non-toxic, aid administration, and do not adversely affect the therapeutic benefit of the compound of Formula (I) (or any embodiment thereof disclosed herein including specific compounds). Such excipient may be any solid, liquid, semi-solid or, in the case of an aerosol composition, gaseous excipient that is generally available to one of skill in the art.

Solid pharmaceutical excipients include starch, cellulose, talc, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, magnesium stearate, sodium stearate, glycerol monostearate, sodium chloride, dried skim milk and the like. Liquid and semisolid excipients may be selected from glycerol, propylene glycol, water, ethanol and various oils, including those of petroleum, animal, vegetable or synthetic origin, *e.g.*, peanut oil, soybean oil, mineral oil, sesame oil, etc. Preferred liquid carriers, particularly for injectable solutions, include water, saline, aqueous dextrose, and glycols.

The compounds of Formula (I) (and any embodiment thereof disclosed herein including specific compounds) may be formulated for parenteral administration by injection, *e.g.*, by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, *e.g.*, in ampoules or in multi-dose containers, with an added preservative. The compositions may take
5 such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in powder form or in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example, saline or sterile pyrogen-free water, immediately prior to use.
10 Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

Formulations for parenteral administration include aqueous and non-aqueous (oily) sterile injection solutions of the active compounds which may contain antioxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and
15 aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or
20 agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

In addition to the formulations described previously, the compounds of Formula (I) (and any embodiment thereof disclosed herein including specific compounds) may also be formulated as a depot preparation. Such long -acting formulations may be administered by implantation (for example
25 subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

For buccal or sublingual administration, the compositions may take the form of tablets,
30 lozenges, pastilles, or gels formulated in conventional manner. Such compositions may comprise the active ingredient in a flavored basis such as sucrose and acacia or tragacanth.

The compounds of Formula (I) (and any embodiment thereof disclosed herein including specific compounds) may also be formulated in rectal compositions such as suppositories or

retention enemas, *e.g.*, containing conventional suppository bases such as cocoa butter, polyethylene glycol, or other glycerides.

Certain compounds of Formula (I) (and any embodiment thereof disclosed herein including specific compounds) may be administered topically, that is by non-systemic

5 administration. This includes the application of a compound of Formula (I) (or any embodiment thereof disclosed herein including specific compounds) externally to the epidermis or the buccal cavity and the instillation of such a compound into the ear, eye and nose, such that the compound does not significantly enter the blood stream. In contrast, systemic administration refers to oral, intravenous, intraperitoneal and intramuscular administration.

10 Formulations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin to the site of inflammation such as gels, liniments, lotions, creams, ointments or pastes, and drops suitable for administration to the eye, ear or nose. The active ingredient for topical administration may comprise, for example, from 0.001% to 10% w/w (by weight) of the formulation. In certain embodiments, the active ingredient may comprise as much as 15 10% w/w. In other embodiments, it may comprise less than 5% w/w. In certain embodiments, the active ingredient may comprise from 2% w/w to 5% w/w. In other embodiments, it may comprise from 0.1% to 1% w/w of the formulation.

For administration by inhalation, compounds of Formula (I) (and any embodiment thereof disclosed herein including specific compounds) may be conveniently delivered from an insufflator, 20 nebulizer pressurized packs or other convenient means of delivering an aerosol spray. Pressurized packs may comprise a suitable propellant such as dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. Alternatively, for administration by inhalation or insufflation, the compounds of Formula (I) (and any embodiment 25 thereof disclosed herein including specific compounds) may take the form of a dry powder composition, for example a powder mix of the compound and a suitable powder base such as lactose or starch. The powder composition may be presented in unit dosage form, in for example, capsules, cartridges, gelatin or blister packs from which the powder may be administered with the aid of an inhalator or insufflator. Other suitable pharmaceutical excipients and their formulations are described 30 in Remington's Pharmaceutical Sciences, edited by E. W. Martin (Mack Publishing Company, 20th ed., 2000).

The level of the compound of Formula (I) (or any embodiment thereof disclosed herein including specific compounds) in a formulation can vary within the full range employed by those skilled in the art. Typically, the formulation will contain, on a weight percent (wt. %) basis, from

about 0.01-99.99 wt. % of a compound of Formula (I) (or any embodiment thereof disclosed herein including specific compounds) based on the total formulation, with the balance being one or more suitable pharmaceutical excipients. For example, the compound is present at a level of about 1-80 wt%.

5 Combinations and Combination Therapies

The compounds of Formula (I) (and any embodiment thereof disclosed herein including specific compounds) may be used in combination with one or more other drugs in the treatment of diseases or conditions for which compounds of Formula (I) (and any embodiment thereof disclosed herein including specific compounds) or the other drugs may have utility. Such other drug(s) may be administered, by a route and in an amount commonly used therefore, contemporaneously or sequentially with a compound of Formula (I) (or any embodiment thereof disclosed herein including specific compounds). When a compound of Formula (I) (or any embodiment thereof disclosed herein including specific compounds) is used contemporaneously with one or more other drugs, a pharmaceutical composition in unit dosage form containing such other drugs and the compound of Formula (I) (or any embodiment thereof disclosed herein including specific compounds) is preferred. However, the combination therapy may also include therapies in which the compound of Formula (I) (or any embodiment thereof disclosed herein including specific compounds) and one or more other drugs are administered on different overlapping schedules. It is also contemplated that when used in combination with one or more other active ingredients, the compounds of Formula (I) (and any embodiment thereof disclosed herein including specific compounds) and the other active ingredients may be used in lower doses than when each is used singly.

Accordingly, the pharmaceutical compositions of the present disclosure also include those that contain one or more other drugs, in addition to a compound of Formula (I) (or any embodiment thereof disclosed herein including specific compounds).

25 The above combinations include combinations of a compound of Formula (I) (or any embodiment thereof disclosed herein including specific compounds) not only with one other drug, but also with two or more other active drugs. Likewise, a compound of Formula (I) (or any embodiment thereof disclosed herein including specific compounds) may be used in combination with other drugs that are used in the prevention, treatment, control, amelioration, or reduction of risk of the diseases or conditions for which a compound of Formula (I) (or any embodiment thereof disclosed herein including specific compounds) is useful. Such other drugs may be administered, by a route and in an amount commonly used therefore, contemporaneously or sequentially with a compound of Formula (I) (or any embodiment thereof disclosed herein including specific compounds). When a compound of Formula (I) (or any embodiment thereof disclosed herein

including specific compounds) is used contemporaneously with one or more other drugs, a pharmaceutical composition containing such other drugs in addition to the compound of Formula (I) (or any embodiment thereof disclosed herein including specific compounds) can be used.

Accordingly, the pharmaceutical compositions of the present disclosure also include those that also contain one or more other active ingredients, in addition to a compound of Formula (I) (or any embodiment thereof disclosed herein including specific compounds). The weight ratio of the compound of this disclosure to the second active ingredient may be varied and will depend upon the effective dose of each ingredient. Generally, an effective dose of each will be used.

Where the subject in need is suffering from or at risk of suffering from cancer, the subject can be treated with a compound of Formula (I) (or any embodiment thereof disclosed herein including specific compounds) in any combination with one or more other anti-cancer agents including but not limited to: MAP kinase pathway (RAS/RAF/MEK/ERK) inhibitors including but not limited to: Vemurafanib (PLX4032), Dabrafenib, Encorafenib (LGX818), TQ-B3233, XL-518 (Cas No. 1029872-29-4, available from ACC Corp); trametinib, selumetinib (AZD6244), TQ-B3234, PD184352, PD325901, TAK-733, pimasertinib, binimetinib, refametinib, cobimetinib (GDC-0973), AZD8330, BVD-523, LTT462, Ulixertinib, AMG510, ARS853, and any RAS inhibitors disclosed in patents WO2016049565, WO2016164675, WO2016168540, WO2017015562, WO2017058728, WO2017058768, WO2017058792, WO2017058805, WO2017058807, WO2017058902, WO2017058915, WO2017070256, WO2017087528, WO2017100546, WO2017172979, WO2017201161, WO2018064510, WO2018068017, WO2018119183;

CSF1R inhibitors (PLX3397, LY3022855, etc.) and CSF1R antibodies (IMC-054, RG7155) TGF beta receptor kinase inhibitor such as LY2157299;

BTK inhibitor such as ibrutinib; BCR-ABL inhibitors: Imatinib (Gleevec®); Inilotinib hydrochloride; Nilotinib (Tasigna®); Dasatinib (BMS-345825); Bosutinib (SKI-606); Ponatinib (AP24534); Bafetinib (INNO406); Danusertib (PHA-739358), AT9283 (CAS 1133385-83-7); Saracatinib (AZD0530); and N-[2-[(1S,4R)-6-[[4-cyclobutylarmno)-5-(trifluoromethyl)-2-pyrimidinyl]amino]-1, 2,3,4-tetrahydronaphthalen-1,4-imin-9-yl]-2-oxoethyl]-acetamide (PF-03814735, CAS 942487-16-3);

ALK inhibitors: PF-2341066 (XALKOPJ ®; crizotinib); 5-chloro-N4-(2-(isopropyl-sulfonyl)phenyl)-N2-(2-methoxy-4-(4-(4-methylpiperazin-1-yl)piperidin-1-yl)phenyl)pyrimidine-2,4-diamine; GSK1838705 A; CH5424802; Ceritinib (ZYGADIA); TQ-B3139, TQ-B3101 PI3K inhibitors: 4-[2-(1H-indazol-4-yl)-6-[[4-(methylsulfonyl)piperazin-1-yl]methyl]thieno[3,2-d]-pyrimidin-4-yl]morpholine (also known as GDC 0941 and described in PCT Publication Nos. WO 09/036082 and WO 09/055730), 2-methyl-2-[4-[3-methyl-2-oxo-8-(quinolin-3-yl)-2,3-dihydro-

imidazo[4,5-c]quinolin-1-yl]phenyl]propionitrile (also known as BEZ 235 or NVP-BEZ 235, and described in PCT Publication No. WO 06/122806);

Vascular Endothelial Growth Factor (VEGF) receptor inhibitors: Bevacizumab (sold under the trademark Avastin® by Genentech/Roche), axitinib, (N-methyl-2-[[3-[(E)-2-pyridin-2-ylethenyl]-1H-indazol-6-yl]sulfanyl]benzamide, also known as AG013736, and described in PCT Publication No. WO 01/002369), Brivanib Alaninate ((S)-((R)-1-(4-(4-fluoro-2-methyl-1H-indol-5-yloxy)-5-methylpyrrolo[2,1-f][1,2,4]triazin-6-yloxy)propan-2-yl)2-aminopropanoate, also known as BMS-582664), motesanib (N-(2,3-dihydro-3,3-dimethyl-1H-indol-6-yl)-2-[(4-pyridinyl-methyl)amino]-3-pyridinecarboxamide, and described in PCT Publication No. WO 02/066470), pasireotide (also known as SOM230, and described in PCT Publication No. WO 02/010192), sorafenib (sold under the tradename Nexavar®); AL-2846 MET inhibitor such as foretinib, carbosantinib, or crizotinib;

FLT3 inhibitors - sunitinib malate (sold under the tradename Sutent® by Pfizer); PKC412 (midostaurin); tanutinib, sorafenib, lestaurtinib, KW-2449, quizartinib (AC220) and crenolanib;

Epidermal growth factor receptor (EGFR) inhibitors: Gefitinib (sold under the tradename Iressa®), N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[[3-(3"-tetrahydro-3-furanyl)oxy]-6-quinazolinyl]-4(dimethylamino)-2-butenamide, sold under the tradename Tovok® by Boehringer Ingelheim), cetuximab (sold under the tradename Erbitux® by Bristol-Myers Squibb), panitumumab (sold under the tradename Vectibix® by Amgen);

HER2 receptor inhibitors: Trastuzumab (sold under the trademark Herceptin® by Genentech/Roche), neratinib (also known as HKI-272, (2E)-N-[4-[[3-chloro-4-[(pyridin-2-yl)methoxy]phenyl]amino]-3-cyano-7-ethoxyquinolin-6-yl]-4-(dimethylamino)but-2-enamide, and described PCT Publication No. WO 05/028443), lapatinib or lapatinib ditosylate (sold under the trademark Tykerb® by GlaxoSmithKline); Trastuzumab emtansine (in the United States, ado-trastuzumab emtansine, trade name Kadcyla) - an antibody-drug conjugate consisting of the monoclonal antibody trastuzumab (Herceptin) linked to the cytotoxic agent mertansine (DM1); Trastuzumab deruxtecan (trade name Enhertu);

HER dimerization inhibitors: Pertuzumab (sold under the trademark Omnitarg®, by Genentech);

CD20 antibodies: Rituximab (sold under the trademarks Riuxan® and MabThera® by Genentech/Roche), tositumomab (sold under the trademarks Bexxar® by GlaxoSmithKline), ofatumumab (sold under the trademark Arzerra® by GlaxoSmithKline);

Tyrosine kinase inhibitors: Erlotinib hydrochloride (sold under the trademark Tarceva® by Genentech/Roche), Linifanib (N-[4-(3-amino-1H-indazol-4-yl)phenyl]-N'-(2-fluoro-5-

methylphenyl)urea, also known as ABT 869, available from Genentech), sunitinib malate (sold under the tradename Sutent® by Pfizer), bosutinib (4-[(2,4-dichloro-5-methoxyphenyl)amino]-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinoline-3-carbonitrile, also known as SKI-606, and described in US Patent No. 6,780,996), dasatinib (sold under the tradename Sprycel® by Bristol-Myers Squibb), armala (also known as pazopanib, sold under the tradename Votrient® by GlaxoSmithKline), imatinib and imatinib mesylate (sold under the tradenames Gilvec® and Gleevec® by Novartis);

DNA Synthesis inhibitors: Capecitabine (sold under the trademark Xeloda® by Roche), gemcitabine hydrochloride (sold under the trademark Gemzar® by Eli Lilly and Company), nelarabine ((2R,3S,4R,5R)-2-(2-amino-6-methoxy-purin-9-yl)-5-(hydroxymethyl)oxolane-3,4-diol, sold under the tradenames Arranon® and Atriance® by GlaxoSmithKline);

Antineoplastic agents: oxaliplatin (sold under the tradename Eloxatin® by Sanofi-Aventis and described in US Patent No. 4,169,846);

Human Granulocyte colony-stimulating factor (G-CSF) modulators: Filgrastim (sold under the tradename Neupogen® by Amgen);

Immunomodulators: Afutuzumab (available from Roche®), pegfilgrastim (sold under the tradename Neulasta® by Amgen), lenalidomide (also known as CC-5013, sold under the tradename Revlimid®), thalidomide (sold under the tradename Thalomid®);

CD40 inhibitors: Dacetuzumab (also known as SGN-40 or huS2C6, available from Seattle Genetics, Inc); Pro-apoptotic receptor agonists (PARAs): Dulanermin (also known as AMG-951, available from Amgen/Genentech);

Hedgehog antagonists: 2-chloro-N-[4-chloro-3-(2-pyridinyl)phenyl]-4-(methylsulfonyl)-benzamide (also known as GDC-0449, and described in PCT Publication No. WO 06/028958);

Phospholipase A2 inhibitors: Anagrelide (sold under the tradename Agrylin®);

BCL-2 inhibitors: 4-[4-[[2-(4-chlorophenyl)-5,5-dimethyl-1-cyclohexen-1-yl]methyl]-1-piperazinyl]-N-[[4-[[[(1R)-3-(4-morpholinyl)-1-[(phenylthio)methyl]propyl]amino]-3-[(trifluoromethyl)sulfonyl]phenyl]sulfonyl]benzamide (also known as ABT-263 and described in PCT Publication No. WO 09/155386);

MCL-1 inhibitors: MIK665, S64315, AMG 397, and AZD5991;

Aromatase inhibitors: Exemestane (sold under the trademark Aromasin® by Pfizer), letrozole (sold under the tradename Femara® by Novartis), anastrozole (sold under the tradename Arimidex®);

Topoisomerase I inhibitors: Irinotecan (sold under the trademark Camptosar® by Pfizer), topotecan hydrochloride (sold under the tradename Hycamtin® by GlaxoSmithKline);

Topoisomerase II inhibitors: etoposide (also known as VP-16 and Etoposide phosphate, sold under the tradenames Toposar®, VePesid® and Etopophos®), teniposide (also known as VM-26, sold under the tradename Vumon®);

mTOR inhibitors: Temsirolimus (sold under the tradename Torisel® by Pfizer),
 5 ridaforolimus (formally known as deferolimus, (1R,2R,4S)-4-[(2R)-2[(1R,9S,12S,15R,16E,18R,19R,21R, 23S,24E,26E,28Z,30S,32S,35R)-1,18-dihydroxy-19,30- dimethoxy-15, 17, 21, 23, 29, 35-hexamethyl-2,3, 10, 14,20-pentaoxo-11, 36-dioxa-4- azatricyclo[30.3.1.0 4' 9] hexatriaconta-16,24,26,28-tetraen-12-yl]propyl]-2-methoxycyclohexyl dimethylphosphinate, also known as AP23573 and MK8669, and described in PCT Publication No. WO 03/064383), everolimus (sold
 10 under the tradename Afinitor® by Novartis);

Proteasome inhibitor such as carfilzomib, MLN9708, delanzomib, or bortezomib;

BET inhibitors such as INCB054329, OTX015, and CPI-0610;

LSD1 inhibitors such as GSK2979552, and INCB059872;

KAT6 inhibitors such as PF-07248144;

15 HIF-2 α inhibitors such as PT2977, PT2385, imdatifan, and casdatifan;

Osteoclastic bone resorption inhibitors: 1-Hydroxy-2-imidazol-1-yl-phosphonoethyl) phosphonic acid monohydrate (sold under the tradename Zometa® by Novartis); CD33 Antibody Drug Conjugates: Gemtuzumab ozogamicin (sold under the tradename Mylotarg® by Pfizer/Wyeth);

CD22 Antibody Drug Conjugates: Inotuzumab ozogamicin (also referred to as CMC-544 and
 20 WAY-207294, available from Hangzhou Sage Chemical Co., Ltd.);

CD20 Antibody Drug Conjugates: Ibritumomab tiuxetan (sold under the tradename Zevalin®);

Somatostatin analogs: octreotide (also known as octreotide acetate, sold under the tradenames Sandostatin® and Sandostatin LAR®);

25 Synthetic Interleukin-11 (IL-11): oprelvekin (sold under the tradename Neumega® by Pfizer/Wyeth);

Synthetic erythropoietin: Darbepoetin alfa (sold under the tradename Aranesp® by Amgen);

Receptor Activator for Nuclear Factor κ B (RANK) inhibitors: Denosumab (sold under the tradename Prolia® by Amgen);

30 Thrombopoietin mimetic peptibodies: Romiplostim (sold under the tradename Nplate® by Amgen);

Cell growth stimulators: Palifermin (sold under the tradename Kepivance® by Amgen);

Anti-Insulin-like Growth Factor-1 receptor (IGF-1R) antibodies: Figitumumab (also known as CP-751,871, available from ACC Corp), robatumumab (CAS No. 934235-44-6);

Anti-CS1 antibodies: Elotuzumab (HuLuc63, CAS No. 915296-00-3);

CD52 antibodies: Alemtuzumab (sold under the tradename Campath®);

Histone deacetylase inhibitors (HDI): Voninostat (sold under the tradename Zolinza® by Merck);

- 5 Alkylating agents: Temozolomide (sold under the tradenames Temodar® and Temodal® by Schering-Plough/Merck), dactinomycin (also known as actinomycin-D and sold under the tradename Cosmegen®), melphalan (also known as L-PAM, L-sarcolysin, and phenylalanine mustard, sold under the tradename Alkeran®), altretamine (also known as hexamethylmelamine (HMM), sold under the tradename Hexalen®), carmustine (sold under the tradename BiCNU®), bendamustine
10 (sold under the tradename Treanda®), busulfan (sold under the tradenames Busulfex® and Myleran®), carboplatin (sold under the tradename Paraplatin®), lomustine (also known as CCNU, sold under the tradename CeeNU®), cisplatin (also known as CDDP, sold under the tradenames Platinol® and Platinol®-AQ), chlorambucil (sold under the tradename Leukeran®), cyclophosphamide (sold under the tradenames Cytoxan® and Neosar®), dacarbazine (also known as
15 DTIC, DIC and imidazole carboxamide, sold under the tradename DTIC-Dome®), altretamine (also known as hexamethylmelamine (HMM) sold under the tradename Hexalen®), ifosfamide (sold under the tradename Ifex®), procarbazine (sold under the tradename Matulane®), mechlorethamine (also known as nitrogen mustard, mustine and mechloroethamine hydrochloride, sold under the tradename Mustargen®), streptozocin (sold under the tradename Zanosar®), thiotepa (also known as
20 thiophosphoamide, TESPA and TSPA, sold under the tradename Thioplex®; Biologic response modifiers: bacillus calmette-guerin (sold under the tradenames theraCys® and TICE® BCG), denileukin diftitox (sold under the tradename Ontak®);

- Anti-tumor antibiotics: doxorubicin (sold under the tradenames Adriamycin® and Rubex®), bleomycin (sold under the tradename lenoxane®), daunorubicin (also known as dauorubicin
25 hydrochloride, daunomycin, and rubidomycin hydrochloride, sold under the tradename Cerubidine®), daunorubicin liposomal (daunorubicin citrate liposome, sold under the tradename DaunoXome®), mitoxantrone (also known as DHAD, sold under the tradename Novantrone®), epirubicin (sold under the tradename Ellence™), idarubicin (sold under the tradenames Idamycin®, Idamycin PFS®), mitomycin C (sold under the tradename Mutamycin®);

- 30 Anti-microtubule agents: Estramustine (sold under the tradename Emcyl®);

Cathepsin K inhibitors: Odanacatib (also known as MK-0822, N-(1-cyanocyclopropyl)-4-fluoro-N-2-{(1S)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)biphenyl-4-yl]ethyl}-L-leucinamide, available from Lanzhou Chon Chemicals, ACC Corp., and ChemieTek, and described in PCT Publication no.

WO 03/075836); Epothilone B analogs: Ixabepilone (sold under the tradename Lxemptra® by Bristol-Myers Squibb);

- Heat Shock Protein (HSP) inhibitors: Tanespimycin (17-allylamino-17-demethoxygeldanamycin, also known as KOS-953 and 17-AAG, available from SIGMA, and described in US Patent No. 4,261,989), NVP-HSP990, AUY922, AT13387, STA-9090, Debio 0932, KW-2478, XL888, CNF2024, TAS-116

TpoR agonists: Eltrombopag (sold under the tradenames Promacta® and Revolade® by GlaxoSmithKline);

- Anti-mitotic agents: Docetaxel (sold under the tradename Taxotere® by Sanofi-Aventis);
10 Adrenal steroid inhibitors: aminoglutethimide (sold under the tradename Cytadren®);

Anti-androgens: Nilutamide (sold under the tradenames Nilandron® and Anandron®), bicalutamide (sold under tradename Casodex®), flutamide (sold under the tradename Fulexin™);

Androgens: Fluoxymesterone (sold under the tradename Halotestin®);

- CDK (CDK1, CDK2, CDK3, CDK5, CDK7, CDK8, CDK9, CDK11/12, or CDK16)
15 inhibitors including but not limited to Alvocidib (pan-CDK inhibitor, also known as flovopirdol or HMR-1275, 2-(2-chlorophenyl)-5,7-dihydroxy-8-[(3S,4R)-3-hydroxy-1-methyl-4-piperidinyl]-4-chromenone, and described in US Patent No. 5,621,002);

CDK4/6 inhibitors pabociclib, ribociclib, abemaciclib, and Trilaciclib; CDK9 inhibitors AZD 4573, P276-00, AT7519M, TP-1287; CDK2/4/6 inhibitor such as PF-06873600;

- 20 SHP-2 inhibitor such as TNO155;

MDM2/MDMX, MDM2/p53 and/or MDMX/p53 modulators;

Gonadotropin-releasing hormone (GnRH) receptor agonists: Leuprolide or leuprolide acetate (sold under the tradenames Viadure® by Bayer AG, Eligard® by Sanofi-Aventis and Lupron® by Abbott Lab);

- 25 Taxane anti-neoplastic agents: Cabazitaxel (1-hydroxy-7, 10 -dimethoxy-9-oxo-5,20-epoxytax-11-ene-2a,4,13a-triyl-4-acetate-2-benzoate-13-[(2R,3S)-3-{[(tert-butoxy)carbonyl]amino}-2-hydroxy-3-phenylpropanoate), larotaxel ((2α,3ξ,4α,5β,7α,10β,13α)-4,10-bis(acetyloxy)-13-({(2R,3S)-3-[(tert-butoxycarbonyl) amino]-2-hydroxy-3-phenylpropanoyl}oxy)-1-hydroxy-9-oxo-5,20-epoxy-7,19-cyclotax-11-en-2-yl benzoate);

- 30 5HT1a receptor agonists: Xaliproden (also known as SR57746, 1-[2-(2-naphthyl)ethyl]-4-[3-(trifluoromethyl)phenyl]-1,2,3,6-tetrahydropyridine, and described in US Patent No. 5,266,573);

HPC vaccines: Cervarix® sold by GlaxoSmithKline, Gardasil® sold by Merck; Iron Chelating agents: Deferasinox (sold under the tradename Exjade® by Novartis);

Anti-metabolites: Claribine (2-chlorodeoxyadenosine, sold under the tradename leustatin®), 5-fluorouracil (sold under the tradename Adrucil®), 6-thioguanine (sold under the tradename Purinethol®), pemetrexed (sold under the tradename Alimta®), cytarabine (also known as arabinosylcytosine (Ara-C), sold under the tradename Cytosar-U®), cytarabine liposomal (also known as Liposomal Ara-C, sold under the tradename DepoCyt™), decitabine (sold under the tradename Dacogen®), hydroxyurea (sold under the tradenames Hydrea®, Droxia™ and Mylocel™), fludarabine (sold under the tradename Fludara®), floxuridine (sold under the tradename FUDR®), cladribine (also known as 2-chlorodeoxyadenosine (2-CdA) sold under the tradename Leustatin™), methotrexate (also known as amethopterin, methotrexate sodium (MTX), sold under the tradenames Rheumatrex® and Trexall™), pentostatin (sold under the tradename Nipent®);

Bisphosphonates: Pamidronate (sold under the tradename Aredia®), zoledronic acid (sold under the tradename Zometa®); Demethylating agents: 5-azacitidine (sold under the tradename Vidaza®), decitabine (sold under the tradename Dacogen®);

Plant Alkaloids: Paclitaxel protein-bound (sold under the tradename Abraxane®), vinblastine (also known as vinblastine sulfate, vincalkebblastine and VLB, sold under the tradenames Alkaban-AQ® and Velban®), vincristine (also known as vincristine sulfate, LCR, and VCR, sold under the tradenames Oncovin® and Vincasar Pfs®), vinorelbine (sold under the tradename Navelbine®), paclitaxel (sold under the tradenames Taxol and Onxal™);

Retinoids: Ali tretinoin (sold under the tradename Panretin®), tretinoin (all-trans retinoic acid, also known as ATRA, sold under the tradename Vesanoid®), Isotretinoin (13-cis-retinoic acid, sold under the tradenames Accutane®, Amnesteem®, Claravis®, Clarus®, Decutan®, Isotane®, Izotech®, Oratane®, Isotret®, and Sotret®), bexarotene (sold under the tradename Targretin®);

Glucocorticosteroids: Hydrocortisone (also known as cortisone, hydrocortisone sodium succinate, hydrocortisone sodium phosphate, and sold under the tradenames Ala-Cort®, Hydrocortisone Phosphate, Solu-Cortef®, Hydrocort Acetate® and Lanacort®), dexamethazone ((8S,9R,10S,11S,13S,14S,16R,17R)-9-fluoro-11,17-dihydroxy-17-(2-hydroxyacetyl)-10,13,16-trimethyl-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-3-one), prednisolone (sold under the tradenames Delta-Cortel®, Orapred®, Pediapred® and Prelone®), prednisone (sold under the tradenames Deltasone®, Liquid Red®, Meticorten® and Orasone®), methylprednisolone (also known as 6-Methylprednisolone, Methylprednisolone Acetate, Methylprednisolone Sodium Succinate, sold under the tradenames Duralone®, Medralone®, Medrol®, M-Prednisol® and Solu-Medrol®);

Cytokines: interleukin-2 (also known as aldesleukin and IL-2, sold under the tradename Proleukin®), interleukin-11 (also known as oprevelkin, sold under the tradename Neumega®), alpha

interferon alfa (also known as IFN-alpha, sold under the tradenames Intron® A, and Roferon-A®);

Estrogen receptor downregulators: Fulvestrant (sold under the tradename Faslodex®);

Anti-estrogens: tamoxifen (sold under the tradename Novaldex®); Toremifene (sold under the tradename Fareston®);

5 Selective estrogen receptor modulators (SERMs): Raloxifene (sold under the tradename Evista®);

Estrogen receptor PROTACs: Vepdegestrant (ARV-471);

Leutinizing hormone releasing hormone (LHRH) agonists: Goserelin (sold under the tradename Zoladex®); Progesterones: megestrol (also known as megestrol acetate, sold under the tradename Megace®);

Miscellaneous cytotoxic agents: Arsenic trioxide (sold under the tradename Trisenox®), asparaginase (also known as L-asparaginase, Erwinia L-asparaginase, sold under the tradenames Elspar® and Kidrolase®);

One or more immune checkpoint inhibitors CD27, CD28, CD40, CD122, CD96, CD73, CD39, CD47, OX40, GITR, CSF1R, JAK, PI3K delta, PI3K gamma, TAM kinase, arginase, CD137 (also known as 4-1BB), ICOS, A2AR, A2BR, HIF-2 α , B7-H3, B7-H4, BTLA, CTLA-4, LAG3, TIM3, VISTA, CD96, TIGIT, PD-1, PD-L1 and PD-L2. In some embodiments, the immune checkpoint molecule is a stimulatory checkpoint molecule selected from CD27, CD28, CD40, ICOS, OX40, GITR, CD137 and STING. In some embodiments, the immune checkpoint molecule is an inhibitory checkpoint molecule selected from B7-H3, B7-H4, BTLA, CTLA-4, IDO, TDO, Arginase, KIR, LAG3, PD-1, TIM3, CD96, TIGIT and VISTA. In some embodiments, the compounds provided herein can be used in combination with one or more agents selected from KIR inhibitors, TIGIT inhibitors, LAIR1 inhibitors, CD160 inhibitors, 2B4 inhibitors and TGFR beta inhibitors.

25 In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of PD-1, *e.g.*, an anti-PD-1 monoclonal antibody. In some embodiments, the anti-PD-1 monoclonal antibody is nivolumab, pembrolizumab (also known as MK-3475), pidilizumab, SHR-1210, PDR001, or AMP-224. In some embodiments, the anti-PD-1 monoclonal antibody is nivolumab, or pembrolizumab or PDR001. In some embodiments, the anti-PD1 antibody is pembrolizumab.

30 In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of PD-L1, *e.g.*, an anti-PD-L1 monoclonal antibody. In some embodiments, the anti-PD-L1 monoclonal antibody is BMS-935559, MEDI4736, MPDL3280A (also known as RG7446), or MSB0010718C. In some embodiments, the anti-PD-L1 monoclonal antibody is MPDL3280A (atezolizumab) or MEDI4736 (durvalumab).

In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of CTLA-4, *e.g.*, an anti-CTLA-4 antibody. In some embodiments, the anti-CTLA-4 antibody is ipilimumab or tremelimumab. In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of LAG3, *e.g.*, an anti-LAG3 antibody. In some embodiments, the anti-LAG3 antibody is BMS-986016 or LAG525. In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of GITR, *e.g.*, an anti-GITR antibody. In some embodiments, the anti-GITR antibody is TRX518 or, MK-4166, INCAGN01876 or MK-1248. In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of OX40, *e.g.*, an anti-OX40 antibody or OX40L fusion protein. In some embodiments, the anti-OX40 antibody is MEDI0562 or, INCAGN01949, GSK2831781, GSK-3174998, MOXR-0916, PF-04518600 or LAG525. In some embodiments, the OX40L fusion protein is MEDI6383

Compounds of Formula (I) (and any embodiment thereof disclosed herein including specific compounds) can also be used to increase or enhance an immune response, including increasing the immune response to an antigen; to improve immunization, including increasing vaccine efficacy; and to increase inflammation. In some embodiments, the compounds of the invention can be used to enhance the immune response to vaccines including, but not limited, *Listeria* vaccines, oncolytic viral vaccines, and cancer vaccines such as GVAX® (granulocyte-macrophage colony-stimulating factor (GM-CSF) gene-transfected tumor cell vaccine). Anti-cancer vaccines include dendritic cells, synthetic peptides, DNA vaccines and recombinant viruses. Other immune-modulatory agents also include those that block immune cell migration such as antagonists to chemokine receptors, including CCR2 and CCR4; Sting agonists and Toll receptor agonists.

Other anti-cancer agents also include those that augment the immune system such as adjuvants or adoptive T cell transfer. Compounds of this application may be effective in combination with CAR (Chimeric antigen receptor) T cell treatment as a booster for T cell activation.

A compound of Formula (I) (or any embodiment thereof disclosed herein including specific compounds) can also be used in combination with the following adjunct therapies: anti-nausea drugs: NK-1 receptor antagonists: Casopitant (sold under the tradenames Rezonic® and Zunrisa® by GlaxoSmithKline); and

Cytoprotective agents: Amifostine (sold under the tradename Ethiol®), leucovorin (also known as calcium leucovorin, citrovorum factor and folinic acid).

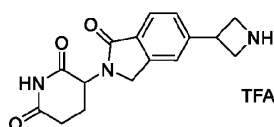
Examples

The following preparations of Intermediates (References) and compounds of Formula (I) (Examples) are given to enable those skilled in the art to more clearly understand and to practice the

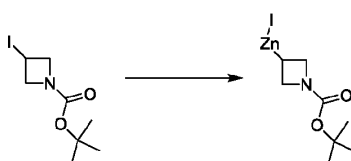
present disclosure. They should not be considered as limiting the scope of the disclosure, but merely as being illustrative and representative thereof.

Reference 1

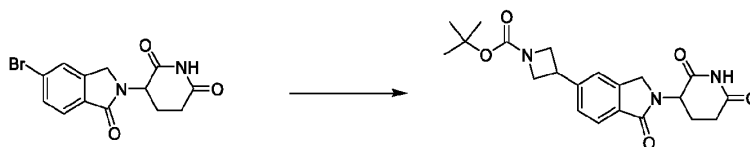
- 5 Synthesis of 3-(5-(azetidin-3-yl)-1-oxoisindolin-2-yl)piperidine-2,6-dione 2,2,2-trifluoroacetate



Step 1: (1-(tert-Butoxycarbonyl)azetidin-3-yl)zinc(II) iodide

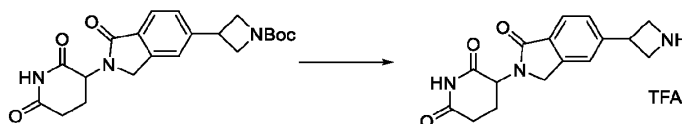


- To a mixture of Zn dust (300 mg, 4.59 mmol, 1.30 eq.) in DMA (3.0 mL) was added
 10 1,2-dibromoethene (66 mg, 0.35 mmol, 0.10 eq.) and the mixture was stirred at 65 °C under N₂ for
 30 min. The mixture was allowed to cool to rt and TMSCl (38 mg, 0.35 mmol, 0.10 eq.) was added.
 After stirring the mixture for 30 min, a solution of tert-butyl 3-iodoazetidine-1-carboxylate (1.00 g,
 3.53 mmol, 1.00 eq.) in DMA (1.0 mL) was added dropwise. The mixture was stirred at 65 °C under
 N₂ for 2 h, and then cooled to rt. The solution was used in next step without further purification.
 15 Step 2: tert-Butyl 3-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)azetidine-1-carboxylate



- A solution of (1-(tert-butoxycarbonyl)azetidin-3-yl)zinc(II) iodide (600 mg, 1.72 mmol, 3.00
 eq.) in DMA was slowly added to a mixture of 3-(5-bromo-1-oxoisindolin-2-yl)piperidine-2,6-
 dione (185 mg, 0.57 mmol, 1.00 eq.), CuI (12 mg, 0.06 mmol, 0.10 eq.), Pd(dppf)Cl₂ (44 mg, 0.06
 20 mmol, 0.10 eq.) in DMA (2.0 mL). The mixture was stirred at 90 °C under N₂ overnight. The
 mixture was concentrated and purified by column chromatography on silica gel (EtOAc) to give the
 title compound as a brown solid.

Step 3: 3-(5-(Azetidin-3-yl)-1-oxoisindolin-2-yl)piperidine-2,6-dione 2,2,2-trifluoroacetate

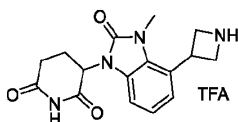


To a solution of tert-butyl 3-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)azetidine-1-carboxylate (44 mg, 0.11 mmol, 1.00 eq.) in DCM (1.0 mL) was added TFA (0.2 mL) dropwise and the solution was stirred for 3 h. The resulting mixture was concentrated to give the title product as a brown oil.

5

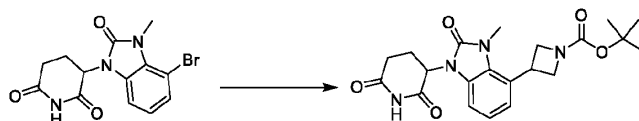
Reference 2

Synthesis of 3-(4-(azetidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione 2,2,2-trifluoroacetate



Step 1: tert-Butyl 3-(1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]-imidazol-4-yl)azetidine-1-carboxylate

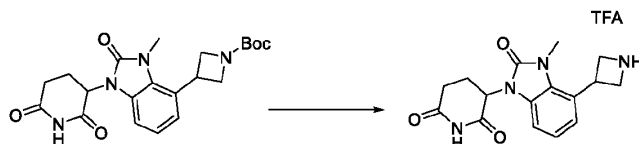
10



A solution of (1-(tert-butoxycarbonyl)azetidin-3-yl)zinc (II) iodide (600 mg, 1.72 mmol, 3.00 eq.) in DMA was slowly added to a mixture of 3-(4-bromo-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione (193 mg, 0.57 mmol, 1.00 eq.) in DMA (2.0 mL) CuI (12 mg, 0.06 mmol, 0.10 eq.) and Pd(dppf)Cl₂ (44 mg, 0.06 mmol, 0.10 eq.). The mixture was stirred at 90 °C under N₂ overnight. The mixture was concentrated and purified by column chromatography on silica gel (EtOAc) to afford the title compound as a yellow solid.

15

Step 2: 3-(4-(Azetidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione 2,2,2-trifluoroacetate



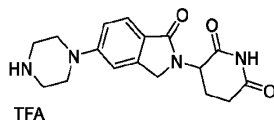
20

To a solution of tert-butyl 3-(1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)azetidine-1-carboxylate (23 mg, 0.055 mmol, 1.00 eq.) in DCM (1.0 mL) was added TFA (0.2 mL) dropwise and the solution was stirred at rt for 3 h. The resulting mixture was concentrated to give the title compound as a brown oil.

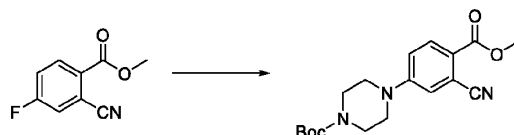
25

Reference 3

Synthesis of 3-(1-Oxo-5-(piperazin-1-yl)isoindolin-2-yl)piperidine-2,6-dione 2,2,2-trifluoroacetate



Step 1: tert-Butyl 4-(3-cyano-4-(methoxycarbonyl)phenyl)piperazine-1-carboxylate

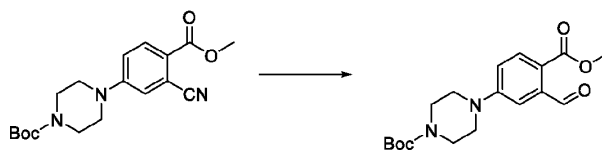


5

To a stirred solution of methyl 2-cyano-4-fluorobenzoate (10.00 g, 55.80 mmol, 1.00 eq.) in DMSO (150.0 mL) was added tert-butyl piperazine-1-carboxylate (11.40 g, 61.38 mmol, 1.10 eq.) and DIEA (34.70 g, 268.96 mmol, 4.80 eq.), and the resulting mixture was stirred at 110 °C for 12 h. The mixture was diluted with water and extracted with EtOAc, and the combined organic layers was washed with brine, dried over Na₂SO₄. After filtration, the filtrate was concentrated and purified by silica gel column chromatography eluting with PE/EtOAc (3:1) to give the title compound as yellow solid.

10

Step 2: tert-Butyl 4-(3-formyl-4-(methoxycarbonyl)phenyl)piperazine-1-carboxylate

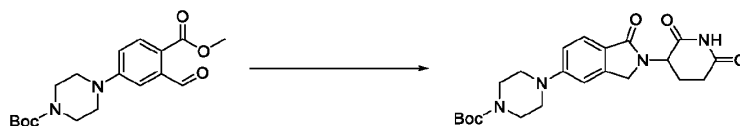


15

A mixture of tert-butyl 4-(3-cyano-4-(methoxycarbonyl)phenyl)piperazine-1-carboxylate (8.00 g, 23.20 mmol, 1.00 eq.), NaH₂PO₄·H₂O (5.20 g, 48.70 mmol, 2.10 eq.) and Raney-Ni (5.10 g) in pyridine:H₂O:AcOH=2:1:1 (80.0 mL) was stirred at 70 °C for 12 h. The mixture was adjusted pH=7~8 with aq. NaHCO₃, and the mixture was filtered, and extracted with EtOAc. The organic layer was washed with brine, dried over Na₂SO₄. After filtration, the filtrate was concentrated and the residue was purified by silica gel column chromatography eluting with PE/EtOAc (3:1) to give the title compound as yellow solid.

20

Step 3: tert-Butyl 4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)piperazine-1-carboxylate

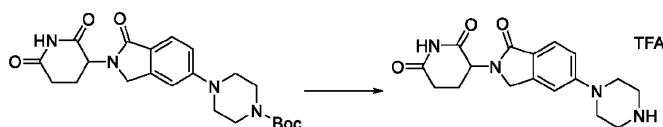


A mixture of 3-aminopiperidine-2,6-dione hydrochloride (2.60 g, 15.50 mmol, 1.20 eq.) DIEA (4.03 g, 31.22 mmol, 2.42 eq.), AcOH (10.63 g, 188.76 mmol, 13.78 eq.) and tert-butyl 4-(3-

25

formyl-4-(methoxycarbonyl)phenyl)piperazine-1-carboxylate (4.50 g, 12.90 mmol, 1.00 eq.) in DCM (50.0 mL) was stirred at 35 °C for 4 h. Then NaBH(OAc)₃ (8.20 g, 38.70 mmol, 3.00 eq.) was added the above mixture, and the mixture was stirred at 40 °C for 12 h. The mixture was diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried over Na₂SO₄. After filtration, the filtrate was concentrated, and the residue was purified by silica gel column chromatography eluting with PE/EtOAc (1:2) to give the title compound as white solid.

Step 4: 3-(1-Oxo-5-(piperazin-1-yl)isoindolin-2-yl)piperidine-2,6-dione 2,2,2-trifluoroacetate



To a solution of tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)piperazine-1-carboxylate (72 mg, 0.17 mmol, 1.00 eq.) in DCM (4.0 mL) was added TFA (1.0 mL). The resulting mixture was stirred at rt for 2 h and then concentrated to give the title compound as yellow oil.

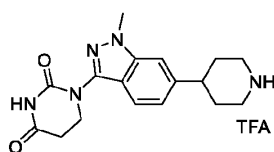
The following reference compounds were synthesized by proceeding analogously as described in Reference 3.

Ref#	structure
Ref. 4	

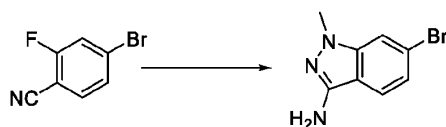
15

Reference 5

Synthesis of 1-(1-methyl-6-(piperidin-4-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione 2,2,2,2,2-trifluoroacetate



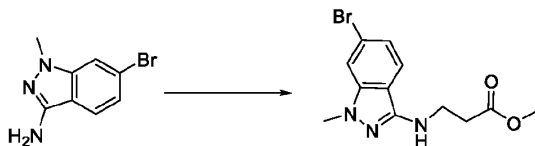
Step 1: 6-Bromo-1-methyl-1H-indazol-3-amine



To a stirred solution of 4-bromo-2-fluorobenzonitrile (10 g, 0.05 mol, 1.00 eq.) in EtOH (50.0 mL) was added methylhydrazine (57 g, 0.50 mol, 10.00 eq.) and the mixture was stirred at

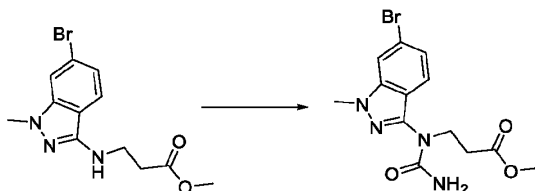
100°C 30 h in sealed tube. Then the mixture was concentrated, and diluted water. The mixture was filtered to give the title compound as pale yellow solid.

Step 2: Methyl 3-((6-bromo-1-methyl-1H-indazol-3-yl)amino)propanoate



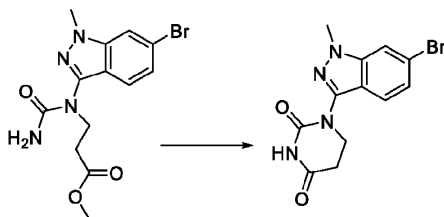
5 Methyl acrylate (209.00 g, 2.43 mol, 10.00 eq.) was added to a solution of 6-bromo-1-methyl-1H-indazol-3-amine (55.00 g, 0.24 mol, 1.00 eq.), DBU (55.00 g, 0.36 mol, 1.50 eq.), lactic acid (33.00 g, 0.36 mol, 1.50 eq.) at 0 °C, and the mixture was stirred at 90 °C 20 h under N₂. The mixture was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel (EtOAc:PE = 0 to 100%) to give the title compound as yellow solid.

10 Step 3: Methyl 3-(1-(6-bromo-1-methyl-1H-indazol-3-yl)ureido)propanoate



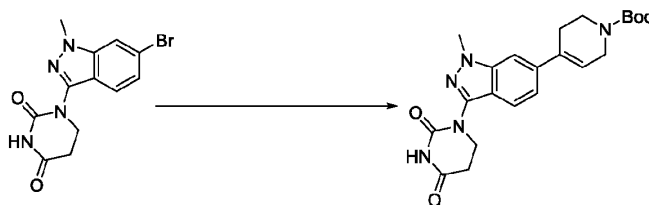
NaOCN (26.00 g, 0.32 mol, 2.00 eq.) was added to a solution of methyl 3-((6-bromo-1-methyl-1H-indazol-3-yl)amino)propanoate (50.00 g, 0.16 mol, 1.00 eq.) in AcOH (500.0 mL), and the mixture was stirred at 80 °C 20 h under N₂. The mixture was diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried over Na₂SO₄. After filtration, the filtrate was concentrated to give the title compound as yellow solid.

Step 4: 1-(6-Bromo-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione



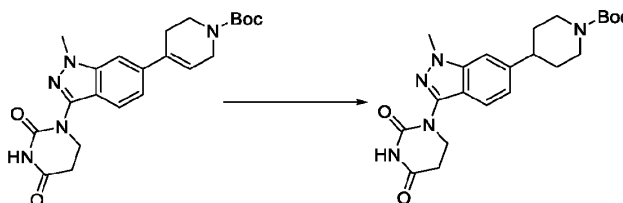
20 To a solution of methyl 3-(1-(6-bromo-1-methyl-1H-indazol-3-yl)ureido)propanoate (56.00 g, 0.16 mol, 1.00 eq.) in MeCN (500.0 mL) was added Tirton-B (7.90 g, 0.05 mol, 0.30 eq.) and stirred at rt for 20 h under N₂. The mixture was concentrated, then diluted with water. The mixture was filtered and solid was washed with water, air dried to give the title compound as pale yellow solid.

Step 5: tert-Butyl 4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)-5,6-dihydropyridine-1(2H)-carboxylate



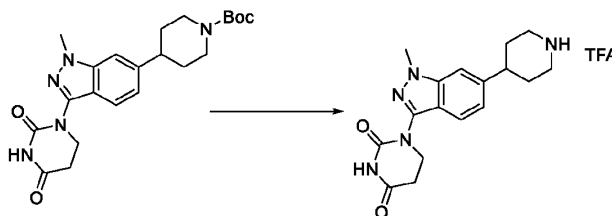
To a mixture of 1-(6-bromo-1-methyl-1H-indazol-3-yl)di-hydropyrimidine-2,4(1H,3H)-dione (1.10 g, 3.41 mmol, 1.00 eq.) in 1,4-dioxane/H₂O (10 mL/1 mL) was added tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyridine-1(2H)-carboxylate (1.60 g, 5.11 mmol, 1.50 eq.), K₃PO₄ (2.20 g, 10.22 mmol, 3.00 eq.) and X-Phos-Pd G3 (289 mg, 0.34 mmol, 0.10 eq.), and the mixture was stirred at 60 °C under N₂ for 3 h. The mixture was diluted with DCM, and the organic layer was washed with brine, dried over Na₂SO₄. After filtration, the filtrate was concentrated, and the residue was purified by column chromatography on silica gel (DCM:MeOH = 20 : 1) to give the title compound as yellow solid.

Step 6: tert-Butyl 4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidine-1-carboxylate



A mixture of tert-butyl 4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)-5,6-dihydropyridine-1(2H)-carboxylate (300 mg, 0.71 mmol, 1.00 eq.), Pd/C (150 mg, 50% wt) and Pd(OH)₂ (150 mg, 50% wt) in THF (20.0 mL) was stirred under H₂ at 50 °C and 50 psi overnight. The mixture was filtered and the filtrate was concentrated and purified by column chromatography on silica gel (PE:EtOAc = 1 : 1) to give the title compound as yellow solid.

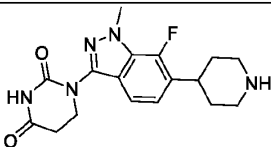
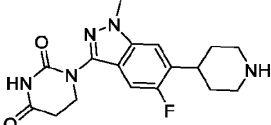
Step 7: 1-(1-Methyl-6-(piperidin-4-yl)-1H-indazol-3-yl)di-hydropyrimidine-2,4(1H,3H)-dione 2,2,2-trifluoroacetate



A mixture of tert-butyl 4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidine-1-carboxylate (100 mg, 0.25 mmol, 1.00 eq.) in TFA/DCM (0.5 mL/2.0 mL) was stirred at rt for 2 h. The mixture was concentrated to give the title compound as brown oil.

The following Reference compounds were synthesized by proceeding analogously as described in

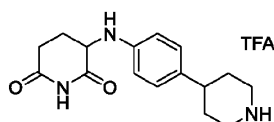
5 Reference 5.

Ref#	structure
Ref 6	
Ref 7	

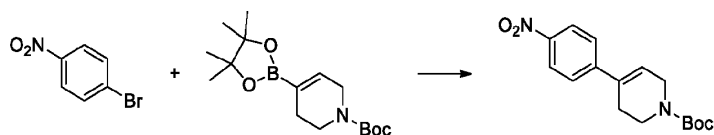
Reference 8

Synthesis of 3-((4-(Piperidin-4-yl)phenyl)amino)piperidine-2,6-dione 2,2,2-trifluoroacetate

10



Step 1: tert-Butyl 4-(4-nitrophenyl)-5,6-dihydropyridine-1(2H)-carboxylate

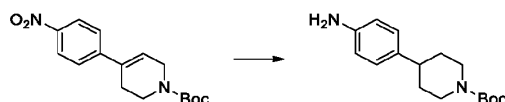


15

A mixture of 1-bromo-4-nitrobenzene (1.0 g, 4.95 mmol, 1.00 eq), tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyridine-1(2H)-carboxylate (2.30 g, 7.43 mmol, 1.50 eq.), K₂CO₃ (1.37 g, 9.90 mmol, 2.00 eq.), and Pd(dppf)Cl₂ (724 mg, 0.99 mmol, 0.20 eq) in dioxane/H₂O (15 mL, 5/1) was stirred at 100 °C for 4 h. The mixture was filtered and extracted with EtOAc. The combined organic layers were dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated. The residue was purified by silica flash column PE/EtOAc (10:1) to give the title compound as yellow solid.

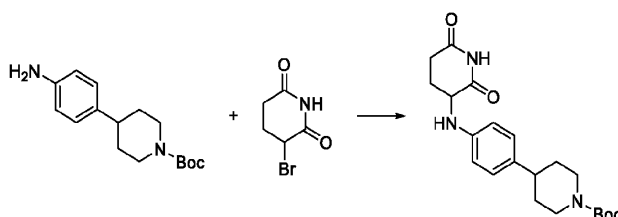
20

Step 2: tert-Butyl 4-(4-aminophenyl)piperidine-1-carboxylate



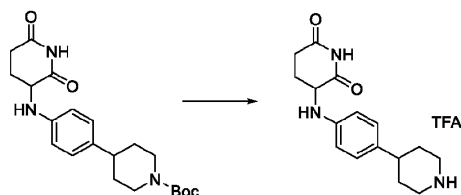
A mixture of tert-butyl 4-(4-nitrophenyl)-5,6-dihydropyridine-1(2H)-carboxylate (1.20 g, 3.95 mmol, 1.00 eq.), Pd/C (360 mg, 10% w/w) in MeOH/THF (30 mL, 1:1) was stirred at 45 °C under H₂ overnight. The mixture was filtered, and the filtrate was concentrated. The residue was purified by silica flash column PE/EtOAc (3:1) to give the title compound as yellow solid.

5 Step 3: tert-Butyl 4-(4-((2,6-dioxopiperidin-3-yl)amino)phenyl)piperidine-1-carboxylate



A mixture of tert-butyl 4-(4-aminophenyl)piperidine-1-carboxylate (332 mg, 1.20 mmol, 1.00 eq.), 3-bromopiperidine-2,6-dione (242 mg, 1.26 mmol, 1.05 eq.) and NaHCO₃ (302 mg, 3.60 mmol, 3.00 eq.) in DMF (4.0 mL) was stirred at 70 °C overnight. The mixture was diluted with water and
 10 extracted with EtOAc. The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and then concentrated. The residue was purified by silica flash column PE/EtOAc (1:1) to give the title compound as yellow solid.

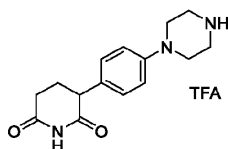
Step 4: 3-((4-(Piperidin-4-yl)phenyl)amino)piperidine-2,6-dione 2,2,2-trifluoroacetate



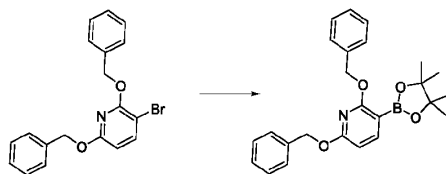
15 TFA (0.5 mL) was added to a mixture of tert-butyl 4-(4-((2,6-dioxopiperidin-3-yl)amino)phenyl)piperidine-1-carboxylate (100 mg, 0.26 mmol, 1.00 eq.) in DCM (2.0 mL) and the mixture was stirred at rt for 2 h. The mixture was concentrated to give the title compound as a yellow solid.

Reference 9

20 Synthesis of 3-(4-(piperazin-1-yl)phenyl)piperidine-2,6-dione 2,2,2-trifluoroacetate

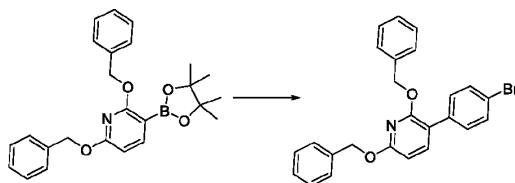


Step 1: 2,6-Bis(benzyloxy)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine



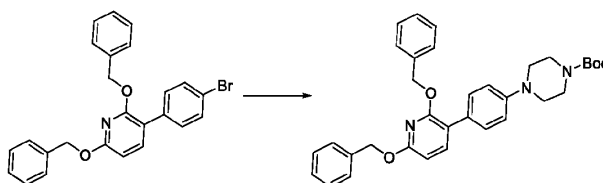
A mixture of 2,6-bis(benzyloxy)-3-bromopyridine (19.00 g, 0.05 mol, 1.00 eq.), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (19.60 g, 0.08 mol, 1.50 eq.), KOAc (10.00 g, 0.10 mol, 2.00 eq.), and Pd(dppf)Cl₂ (3.7 g, 5.00 mmol, 0.10 eq.) in 1,4-dioxane (200.0 mL) was stirred at 100 °C for 25 h under N₂. The mixture was diluted with water and extracted with EtOAc, and the combined organic layer was washed with brine, dried over Na₂SO₄. After filtration, the filtrate was concentrated and the residue was purified by silica gel column chromatography eluting with EtOAc:PE= 0 to 100% to give the title compound as yellow solid.

Step 4: 2,6-Bis(benzyloxy)-3-(4-bromophenyl)pyridine



A mixture of 2,6-bis(benzyloxy)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (4.42 g, 10.60 mmol, 1.20 eq.), 1-bromo-4-iodobenzene (2.50 g, 8.83 mol, 1.00 eq.), K₃PO₄ (5.63 g, 26.50 mmol, 3.00 eq.), and Pd(PPh₃)₄ (510 mg, 0.44 mmol, 0.05 eq.) in 1,4-dioxane/H₂O=10:1 (40.0 mL) was stirred at 100 °C for 16 h under N₂. The mixture was diluted with water and extracted with EtOAc, and the combined organic layer was washed with brine, dried over Na₂SO₄. After filtration, the filtrate was concentrated and the residue was purified by silica gel column chromatography eluting with EtOAc:PE= 0 to 100% to give the title compound as yellow solid.

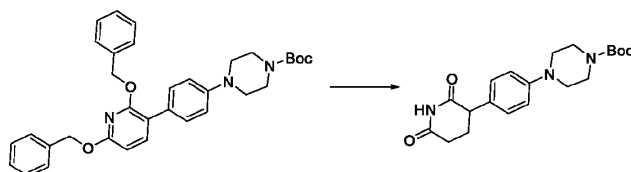
Step 5: tert-Butyl 4-(4-(2,6-bis(benzyloxy)pyridin-3-yl)phenyl)piperazine-1-carboxylate



A mixture of 2,6-bis(benzyloxy)-3-(4-bromophenyl)pyridine (500 mg, 1.12 mmol, 1.00 eq.), tert-butyl piperazine-1-carboxylate (417 mg, 2.24 mmol, 2.00 eq.), Cs₂CO₃ (730 mg, 2.24 mmol, 2.00 eq.), Pd₂(dba)₃ (51 mg, 0.06 mmol, 0.05 eq.), and RuPhos (52 mg, 0.11 mmol, 0.10 eq.) in toluene (15.0 mL) was stirred at 110 °C for 20 h under N₂. The mixture was diluted with water and

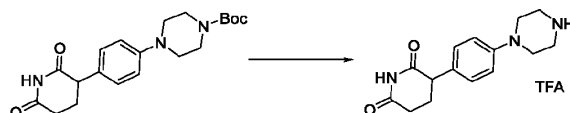
extracted with EtOAc, and the combined organic layer was washed with brine, dried over Na₂SO₄. After filtration, the filtrate was concentrated and the residue was purified by silica gel column chromatography eluting with EtOAc:PE= 0 to 100% to give the title compound as yellow solid.

Step 6: tert-Butyl 4-(4-(2,6-dioxopiperidin-3-yl)phenyl)piperazine-1-carboxylate



A mixture of tert-butyl 4-(4-(2,6-bis(benzyloxy)pyridin-3-yl)phenyl)piperazine-1-carboxylate (260 mg, 0.47 mmol, 1.00 eq.), 10% Pd/C (260 mg) in EtOAc (5.0 mL) and 1,4-dioxane (5.0 mL) was stirred at rt for 20 h under H₂. The mixture was filtered and the filtrate was concentrated to give the title compound as yellow oil.

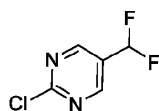
Step 7: 3-(4-(Piperazin-1-yl)phenyl)piperidine-2,6-dione 2,2,2-trifluoroacetate



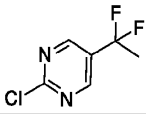
TFA (0.5 mL) was added to a stirred solution of tert-butyl 4-(4-(2,6-dioxopiperidin-3-yl)phenyl)piperazine-1-carboxylate (160 mg, 0.43 mmol, 1.00 eq.) in DCM (2.0 mL) and the mixture was stirred at rt for 2 h under N₂. The mixture was concentrated to give the title compound as yellow oil.

Reference 10

Synthesis of 2-chloro-5-(difluoromethyl)pyrimidine

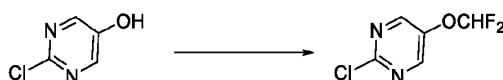


To a solution of 2-chloropyrimidine-5-carbaldehyde (250 mg, 1.60 mmol, 1.00 eq.) in DCM (3.0 mL) was added DAST (45 mg, 31.93 mmol, 20.00 eq.) at 0 °C and the mixture was stirred at r.t overnight. The mixture was diluted with water and extracted DCM. The organic layer was washed with brine, dried over Na₂SO₄. After filtration, the filtrate was concentrated, and the residue was purified by flash chromatography (PE:EtOAc=10:1) to give the title compound as a white solid. The following Reference compound was prepared by proceeding analogously as described in Reference 10.

Ref#	Structure
Ref. 10a	

Reference 11

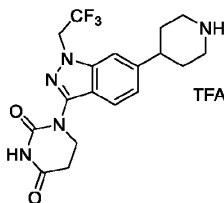
Synthesis of 2-chloro-5-(difluoromethoxy)pyrimidine



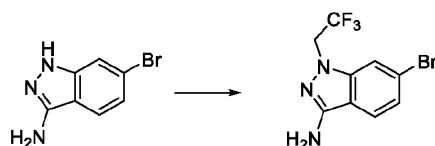
- 5 A mixture of 2-chloropyrimidin-5-ol (1.00 g, 7.69 mmol, 1.00 eq.), methyl 2-chloro-2,2-difluoroacetate (3.32 g, 23.08 mmol, 3.00 eq.) and Cs₂CO₃ (3.01 g, 9.23 mmol, 1.20 eq.) in DMF (10.0 mL) was stirred at 100 °C under N₂ 1h. The mixture was poured into water, and the resulting mixture was extracted with DCM. The combined organic layers was dried over Na₂SO₄. After filtration, the filtrate was concentrated and the residue was purified by column chromatography on silica gel (PE : EtOAc =20:1) give the title compound as yellow oil.
- 10

Reference 12

Synthesis of 1-(6-(piperidin-4-yl)-1-(2,2,2-trifluoroethyl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione 2,2,2-trifluoroacetate

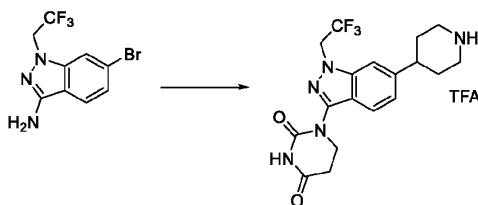


- 15 Step 1: 6-Bromo-1-(2,2,2-trifluoroethyl)-1H-indazol-3-amine



- NaH (2.10 g, 52.83 mmol, 2.00 eq.) was added to a stirred solution of 6-bromo-1H-indazol-3-amine (5.60 g, 26.42 mmol, 1.00 eq.) in DMF (20.0 mL) at 0 °C and the mixture was stirred at 0 °C for 1h. 2,2,2-Trifluoroethyl trifluoromethanesulfonate (6.7 g, 29.06 mmol, 1.10 eq.) was added and the mixture was stirred at rt for 3 h under N₂. The mixture was poured into cold water and filtered. The solid was washed with water and dried to give the title compound as yellow solid.
- 20

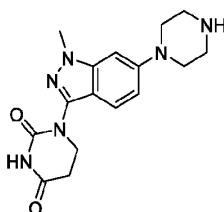
Step 2: 1-(6-(Piperidin-4-yl)-1-(2,2,2-trifluoroethyl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione 2,2,2-trifluoroacetate



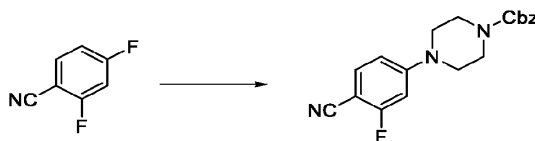
The title compound was synthesized by proceeding analogously as described in Reference 5,
5 Steps 2-7.

Reference 13

Synthesis of 1-(1-methyl-6-(piperazin-1-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione



Step 1: Benzyl 4-(4-cyano-3-fluorophenyl)piperazine-1-carboxylate

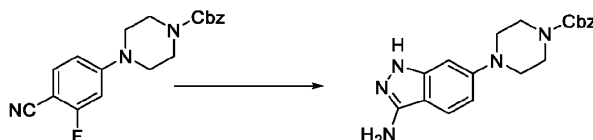


10

A mixture of 2,4-difluorobenzonitrile (18.95 g, 136.20 mmol, 1.50 eq.), benzyl piperazine-1-carboxylate (20 g, 90.80 mmol, 1.00 eq.) and potassium carbonate (25.10 g, 181.6 mmol, 2.00 eq.) in ACN (200.0 mL) was stirred at 80 °C under N₂ for 16 h. The mixture was filtered, and the filtrate was concentrated. The residue was purified by silica gel column chromatography eluting with

15 PE/EtOAc (3:1) to give the title compound as white solid.

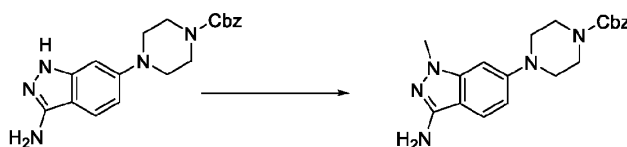
Step 2: Benzyl 4-(3-amino-1H-indazol-6-yl)piperazine-1-carboxylate



20

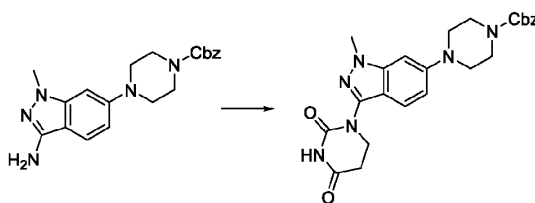
A mixture of benzyl 4-(4-cyano-3-fluorophenyl)piperazine-1-carboxylate (11.00 g, 32.40 mmol, 1.00 eq.) and N₂H₄/H₂O (10.14g, 161.99 mmol, 5.00 eq) in BuOH (100.0 mL) was stirred at 100 °C under N₂ for 16 h. The mixture was concentrated and purified by flash chromatography to give the title compound as yellow solid.

Step 3: Benzyl 4-(3-amino-1-methyl-1H-indazol-6-yl)piperazine-1-carboxylate



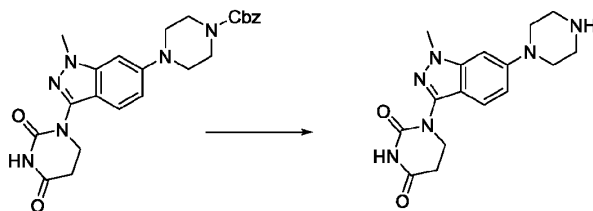
To a solution of benzyl 4-(3-amino-1H-indazol-6-yl)piperazine-1-carboxylate (4.00 g, 11.40 mmol, 1.00 eq.) in dry DMF (50.0 mL) at 0 °C was added NaH (0.91 g, 22.80 mmol, 2.00 eq.) under N₂, and the mixture was stirred at rt for 30 min. The mixture was cooled to 0 °C, CH₃I (1.78 g, 12.54 mmol, 1.10 eq.) in dry DMF (10.0 mL) was added dropwise, and the mixture was stirred for 3 h. The mixture was quenched with water, extracted with EtOAc. The combined organic layers were washed with brine, dried with Na₂SO₄. After filtration, the filtrate was concentrated and the residue was purified by silica gel column chromatography eluting with DCM/MeOH = (50:1) to give the title compound as yellow solid.

Step 4: Benzyl 4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)-piperazine-1-carboxylate



The title compound was synthesized by proceeding analogously as described in Reference 5, Steps 2-4.

Step 5: 1-(1-Methyl-6-(piperazin-1-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione



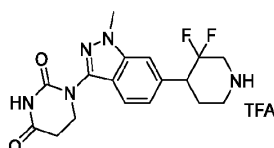
A mixture of benzyl 4-[3-(2,4-dioxo-1,3-diazinan-1-yl)-1-methylindazol-6-yl]piperazine-1-carboxylate (500 mg, 1.08 mmol, 1.00 eq.), 10% Pd/C (400 mg) and ammonium formate (682 mg, 10.81 mmol, 10.00 eq.) in MeOH (20.0 mL) was stirred at 60 °C under N₂ for 16 h. The mixture was filtered and the filtrate was concentrated to give the title compound as white solid.

The following Reference compound was synthesized by proceeding analogously as described in Reference 13.

Ref#	Structure
Ref.14	

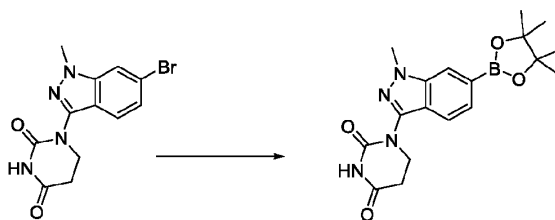
Reference 15

Synthesis of 1-(6-(3,3-difluoropiperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione 2,2,2,2,2-trifluoroacetate



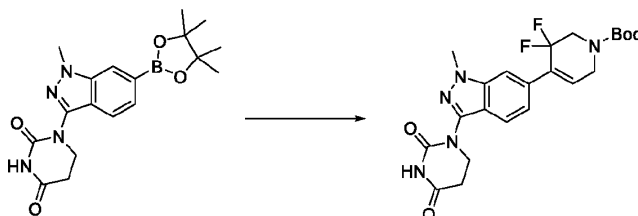
5

Step 1: 1-(1-Methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione



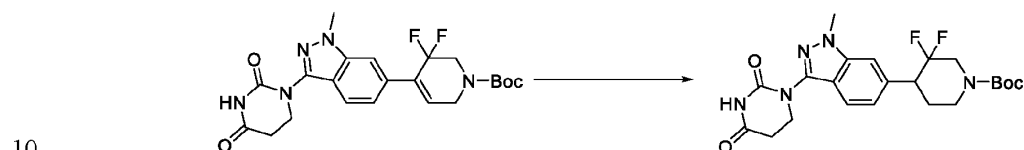
A mixture of 1-(6-bromo-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (626 mg, 2.00 mmol, 1.00 eq.), 4,4,4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (762 mg, 3.00 mmol, 1.50 eq.), KOAc (589 mg, 6.00 mmol, 3.00 eq.) and Pd(dppf)Cl₂ (146 mg, 0.20 mmol, 0.10 eq.) in 1,4-dioxane (10 mL) was stirred at 85 °C under N₂ overnight. The mixture was filtered and the filtrate was concentrated. The residue was purified by column chromatography on silica gel (DCM:MeOH = 100 : 1) to give the title compound as a yellow solid.

Step 2: tert-Butyl 4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)-3,3-difluoro-3,6-dihydropyridine-1(2H)-carboxylate



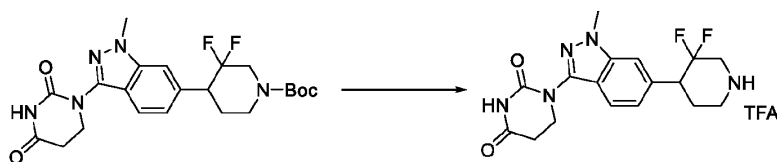
A mixture of 1-(1-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (800 mg, 2.00 mmol, 1.00 eq.), tert-butyl 3,3-difluoro-4-(((trifluoromethyl)sulfonyl)oxy)-3,6-dihydropyridine-1(2H)-carboxylate (1.10 g, 3.00 mmol, 1.50 eq.), Na₂CO₃ (636 mg, 6.00 mmol, 3.00 eq.), Pd(dppf)Cl₂ (146 mg, 0.20 mmol, 0.1 eq.) and H₂O (2.5 mL) in 1,4-dioxane (10.0 mL) was stirred at 55 °C under N₂ overnight. The mixture was filtered and the filtrate was concentrated. The residue was purified by column chromatography on silica gel (DCM:MeOH = 120 : 1) to give the title compound as a yellow solid.

Step 3: tert-Butyl 4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)-3,3-difluoropiperidine-1-carboxylate



A mixture of tert-butyl 4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)-3,3-difluoro-3,6-dihydropyridine-1(2H)-carboxylate (940 mg, 2.00 mmol, 1.00 eq.), 10% Pd/C (900mg) and Pd(OH)₂ (900mg) in MeOH (10.0 mL) was stirred at 50 °C under H₂ (50 PSI) overnight. The mixture was filtered, and the filtrate was concentrated. The residue was purified by column chromatography on silica gel (DCM:MeOH = 1 : 1) to give the title as yellow solid.

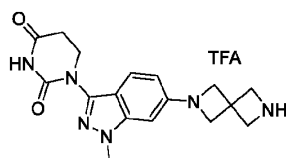
Step 4: 1-(6-(3,3-Difluoropiperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione 2,2,2,2,2-trifluoroacetate



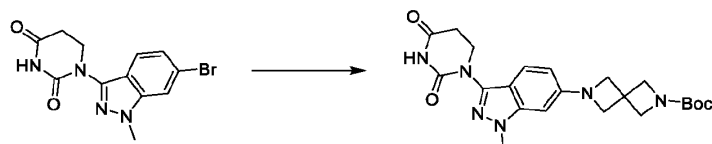
A mixture of tert-butyl 4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)-3,3-difluoropiperidine-1-carboxylate (102 mg, 0.22 mmol, 1.00 eq.) in TFA/DCM (0.5 mL/2.0 mL) was stirred at rt for 2h. The mixture was concentrated to give the title compound as brown oil.

Reference 16

Synthesis of tert-butyl 6-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)-2,6-diazaspiro[3.3]heptane-2-carboxylate 2,2,2-trifluoroacetate

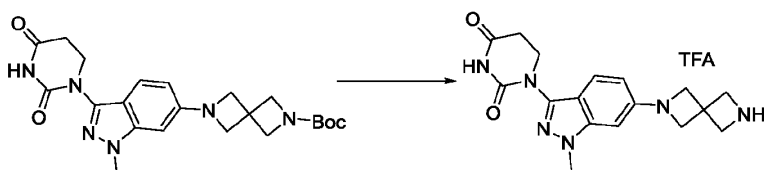


Step 1: tert-Butyl 6-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)-2,6-diazaspiro[3.3]heptane-2-carboxylate



A mixture of 1-(6-bromo-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (300 mg, 0.93 mmol, 1.00 eq.), tert-butyl 2,6-diazaspiro[3.3]heptane-2-carboxylate (570 mg, 2.32 mmol, 2.50 eq.), t-BuOK (627 mg, 5.6 mmol, 6.00 eq.), t-BuBrettphos Pd G3 (81 mg, 0.093 mmol, 0.10 eq.) and t-BuXphos (76 mg, 0.186 mmol, 0.20 eq.) in 1,4-dioxane (6 mL) was stirred at 100 °C under N₂ for 3 h. The mixture was diluted with DCM and the organic layer was washed with water and brine, dried over Na₂SO₄. After filtration, the filtrate was concentrated, and the residue was purified by column chromatography on silica gel (DCM:MeOH = 20 : 1) to give the title compound as yellow solid.

Step 2: 1-(1-Methyl-6-(2,6-diazaspiro[3.3]heptan-2-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione 2,2,2,2,2-trifluoroacetate

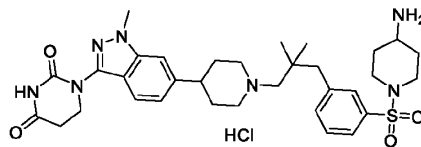


A mixture of tert-butyl 6-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)-2,6-diazaspiro[3.3]heptane-2-carboxylate (90 mg, 0.204 mmol, 1.00 eq.) in TFA/DCM (0.5 mL/2 mL) was stirred at rt for 2 h. The mixture was concentrated to give the title compound as brown oil.

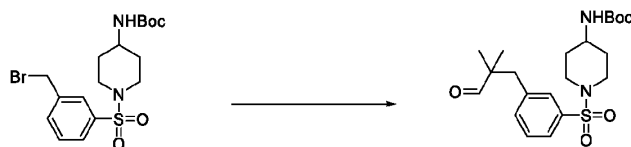
20

Reference 17

Synthesis of 1-(6-(1-(3-(3-((4-aminopiperidin-1-yl)sulfonyl)phenyl)-2,2-dimethylpropyl) piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione hydrochloride

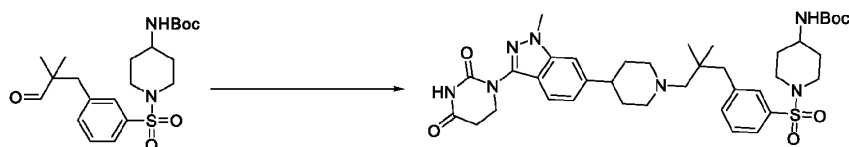


Step 1: tert-Butyl (1-((3-(2,2-dimethyl-3-oxopropyl)phenyl)sulfonyl)piperidin-4-yl)carbamate



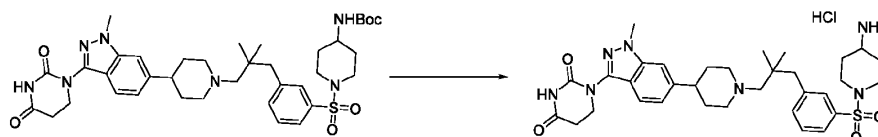
A mixture of tert-butyl N-[1-[3-(bromomethyl)phenyl]sulfonyl-4-piperidyl]carbamate (1.0 g, 2.31 mmol), 2-methylpropanal (416 mg, 5.77 mmol), tetrabutylammonium iodide (85.24 mg, 0.23 mmol) and sodium hydroxide (323.06 mg, 8.08 mmol) in 1,4-dioxane (10 mL) was heated to 70 °C and stirred for 3 h under argon atmosphere. After cooling, the mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with water, brine, and dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated and the residue was purified by silica gel chromatography, eluted with ethyl acetate/petroleum ether (0~20% with 5% dichloromethane) to afford the title compound as a white solid.

Step 2: tert-Butyl (1-((3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2,2-dimethylpropyl)phenyl)sulfonyl)piperidin-4-yl)carbamate



Titanium tetraisopropoxide (1.24 g, 4.37 mmol) was added to a mixture of tert-butyl (1-((3-(2,2-dimethyl-3-oxopropyl)phenyl)sulfonyl)piperidin-4-yl)carbamate (530 mg, 1.25 mmol) and 1-(1-methyl-6-(piperidin-4-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione hydrochloride (408.7 mg, 1.25 mmol) in anhydrous N-methyl-2-pyrrolidone (5.3 mL), and the mixture was heated to 90 °C for 3 h under argon atmosphere. The mixture was cooled to rt and sodium cyanoborohydride (274.56 mg, 4.37 mmol) was added, and the mixture was stirred at 25 °C for 1 h. The mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with water, brine, dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated and the residue was purified by silica gel chromatography, eluted with methanol/dichloromethane (0~5%) to afford the title compound as a white solid.

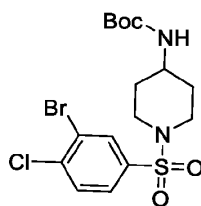
Step 3: 1-(6-(1-(3-(3-((4-Aminopiperidin-1-yl)sulfonyl)phenyl)-2,2-dimethylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione hydrochloride



To a stirred solution of tert-butyl (1-((3-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2,2-dimethylpropyl)phenyl) sulfonyl)piperidin-4-yl)carbamate (280 mg, 0.38 mmol) in dichloromethane (3 mL) was added 4 M hydrogen chloride in dioxane (1.5 mL) at 0 °C and stirred for 1 h. The mixture was concentrated under reduced pressure to afford the title compound as a white solid.

Reference 18

Synthesis of tert-butyl (1-((3-bromo-4-chlorophenyl)sulfonyl)piperidin-4-yl)carbamate

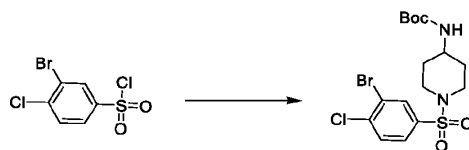


Step 1: 3-Bromo-4-chlorobenzenesulfonyl chloride



To a stirred solution of 3-bromo-4-chloroaniline (5.00 g, 24.22 mmol, 1.00 eq.) in con. HCl (50.0 mL) were added NaNO₂ (3.34 g, 48.44 mmol, 2.00 eq.) at 0 °C, followed by copper sulfate pentahydrate (0.60 g, 2.42 mmol, 0.10 eq.) and then NaHSO₃(aq.) (25.20 g, 242.20 mmol, 10.00 eq.) at 0 °C. The reaction mixture was stirred at 0 °C under nitrogen for 1 h. The reaction mixture was extracted with EA. The combined organic layers were washed with brine and the organic layer was dried over anhydrous Na₂SO₄. After filtration and concentration, the residue was purified by silica gel column chromatography (PE : EA = 10 : 1) to give the title compound as a brown oil.

Step 2: tert-Butyl (1-((3-bromo-4-chlorophenyl)sulfonyl)piperidin-4-yl)carbamate

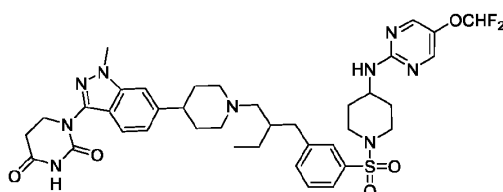


To a stirred solution of tert-butyl piperidin-4-ylcarbamate (3.97 g, 19.83 mmol, 1.15 eq.) and TEA (6.98 g, 68.96 mmol, 4.00 eq.) in DCM (50.0 mL) was added 3-bromo-4-chlorobenzenesulfonyl chloride (5.00 g, 17.24 mmol, 1.00 eq.) slowly at 0 °C. The resulting mixture was stirred at rt under nitrogen for 1 h, diluted with water and extracted with DCM. The combined organic layers were washed with brine and the organic layer was dried over anhydrous Na₂SO₄.

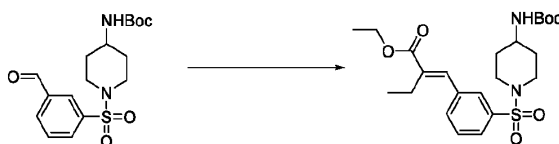
After filtration and concentration, the residue was purified by silica gel column chromatography (DCM:MeOH = 20 : 1) to give the title compound as a yellow solid.

Example 1

- 5 Synthesis of 1-(6-(1-(2-(3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)-sulfonyl)benzyl)butyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione



- Step 1: Ethyl (E)-2-(3-((4-((tert-butoxycarbonyl)amino)piperidin-1-yl)sulfonyl)benzylidene)-butanoate



- Ethyl 2-(diethoxyphosphoryl)butanoate (412 mg, 1.63 mmol, 1.20 eq.) was added to a stirred solution of NaH (60 % in mineral oil, 82 mg, 2.04 mmol, 1.50 eq.) in THF (10.0 mL) at 0 °C and this mixture was stirred at 0 °C for 30 min. Then tert-butyl (1-((3-formylphenyl)sulfonyl)piperidin-4-yl)carbamate (500 mg, 1.36 mmol, 1.00 eq.) in THF (10.0 mL) was added. This mixture was stirred at 0 °C for 30 min, and then slowly warmed to rt and stirred for 12 h. The mixture was quenched with H₂O at 0 °C, and extracted with EtOAc. The combined organic layers was washed with brine, and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel, eluting with DCM:MeOH (0~5 %), to afford the title compound as a white solid.

Step 2: Ethyl 2-(3-((4-((tert-butoxycarbonyl)amino)piperidin-1-yl)sulfonyl)benzyl)butanoate



- A mixture of ethyl (E)-2-(3-((4-((tert-butoxycarbonyl)amino)piperidin-1-yl)sulfonyl)benzylidene)butanoate (400 mg, 0.86 mmol, 1.00 eq.), 10% Pd/C (200 mg) in

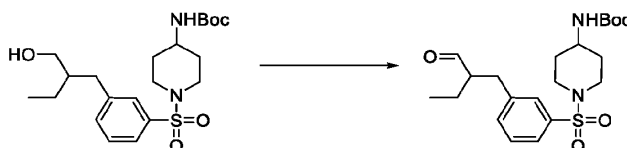
MeOH (10.0 mL) was stirred at rt under 1 atm H₂ for 12h. The mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with DCM:MeOH (0~5 %) to afford the title compound as a pale yellow oil.

5 Step 3: tert-Butyl (1-((3-(2-(hydroxymethyl)butyl)phenyl)sulfonyl)piperidin-4-yl)carbamate



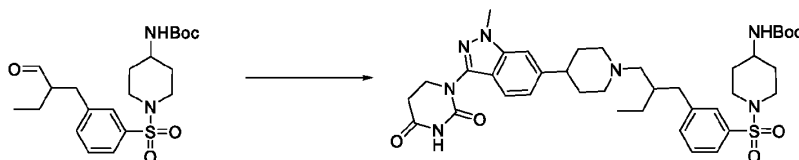
LiAlH₄ (2.5 M in THF, 1.15 mL, 2.88 mmol, 3.00 eq.) was added to a stirred solution of ethyl 2-(3-((4-((tert-butoxycarbonyl)amino)piperidin-1-yl)sulfonyl)benzyl)-butanoate (450 mg, 0.96 mmol, 1.00 eq.) in THF (20.0 mL) at -10 °C, and the mixture was stirred for 3h. The mixture was diluted with DCM, quenched with H₂O, and the resulting mixture was stirred at rt for 30 min. The mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with DCM:MeOH (0~5 %), to afford the title compound as a pale yellow solid.

Step 4: tert-Butyl (1-((3-(2-formylbutyl)phenyl)sulfonyl)piperidin-4-yl)carbamate



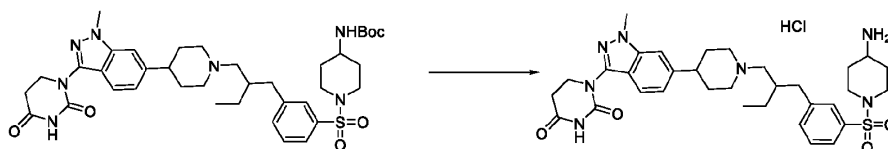
To a stirred solution of tert-butyl (1-((3-(2-(hydroxymethyl)butyl)phenyl)sulfonyl)-piperidin-4-yl)carbamate (150 mg, 0.35 mmol, 1.00 eq.) in DCM (7.0 mL) was added Dess-Martin periodinane (223 mg, 0.53 mmol, 1.50 eq.) at 0 °C and the mixture was stirred under N₂ for 2h. The mixture was filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with DCM: MeOH (0~2 %), to afford the title compound as a pale yellow solid.

Step 5: tert-Butyl (1-((3-(2-((4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)butyl)phenyl)sulfonyl)piperidin-4-yl)carbamate



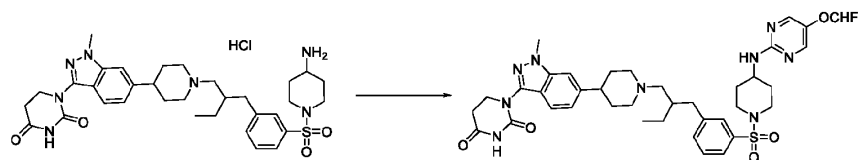
NaBH(OAc)₃ (180 mg, 0.85 mmol, 2.5 eq.) in DMA (2.0 mL) was added to a mixture of 1-(1-methyl-6-(piperidin-4-yl)-1H-indazol-3-yl) dihydropyrimidine-2,4(1H,3H)-dione hydrochloride (127 mg, 0.35 mmol, 1.00 eq.), TEA (106 mg, 1.05 mmol, 3.00 eq.) and tert-butyl (1-((3-(2-formylbutyl)phenyl)sulfonyl)piperidin-4-yl)carbamate (149 mg, 0.35 mmol, 1.00 eq.) in DMA (6.0 mL) at 0 °C, and the mixture was stirred at rt for 12h. The mixture was diluted with water and extracted with EtOAc. The combined organic layers was washed with brine, and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel, eluting with DCM:MeOH (0~5 %), to afford the title compound as a pale yellow solid.

Step 6: 1-(6-(1-(2-(3-((4-Aminopiperidin-1-yl)sulfonyl)benzyl)butyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl) dihydropyrimidine-2,4(1H,3H)-dione hydrochloride



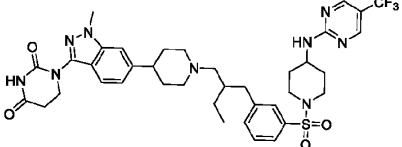
HCl in EtOAc (2 M, 5.0 mL) was added to tert-butyl (1-((3-(2-((4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)butyl)-phenyl)sulfonyl)piperidin-4-yl)carbamate (170 mg, 0.23 mmol, 1.00 eq.) at rt and it was allowed to stir for 3h. The mixture was concentrated under reduced pressure to afford the title compound as a pale yellow solid.

Step 7: 1-(6-(1-(2-(3-((4-((5-(Difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzyl)butyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl) dihydropyrimidine-2,4(1H,3H)-dione



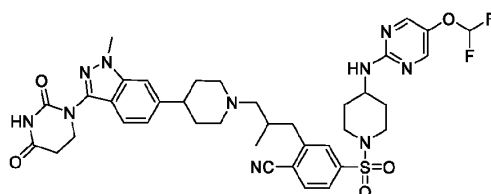
A mixture of 1-(6-(1-(2-(3-((4-aminopiperidin-1-yl)sulfonyl)benzyl)butyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl) dihydropyrimidine-2,4(1H,3H)-dione hydrochloride (155 mg, 0.23 mmol, 1.00 eq.), DIEA (149 mg, 1.15 mmol, 5.00 eq.), CsF (70 mg, 0.46 mmol, 2.00 eq.) and 2-chloro-5-(difluoromethoxy)pyrimidine (83 mg, 0.46 mmol, 2.00 eq.) in DMSO (7.0 mL) was stirred at 50 °C under N₂ for 12h. The mixture was diluted with water and extracted with EtOAc. The combined organic layers was washed with brine, and the organic layer was dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by *prep*-HPLC, to afford the title compound as a white solid. MS (ES, m/z): [M+1]⁺ = 780.4

The following compounds were synthesized by proceeding analogously as described in Example 1.

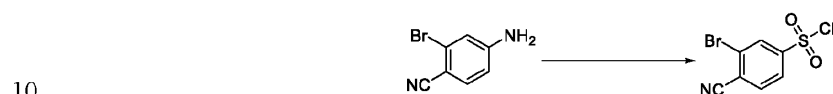
Ex#	Structure
Ex. 2	

Example 3

- 5 Synthesis of 4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-methylpropyl)benzonitrile

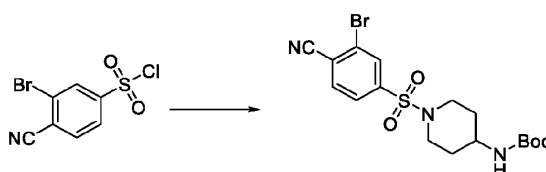


Step 1: 3-Bromo-4-cyanobenzenesulfonyl chloride



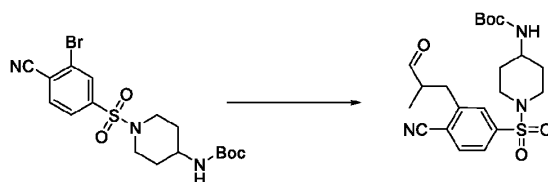
- A mixture of 4-amino-2-bromobenzonitrile (5.0 g, 25.38 mmol, 1.00 eq.) in conc. HCl/H₂O (60.0 mL/225.0 mL) was warmed to 90 °C until fully dissolved. The mixture was cooled to 0~5 °C. A solution of NaNO₂ (1.9 g, 27.54 mmol, 1.08 eq.) in H₂O (5 mL) was added dropwise to above mixture then followed by addition of CuCl (0.2 g, 2.02 mmol, 0.08 eq.) in SOCl₂/H₂O (8.0 mL/50.0 mL) dropwise at 0~5 °C. The resulting mixture was stirred at 0~5 °C for 1 h. The mixture was diluted with water and extracted with EtOAc. The combined organic layers was washed with water, brine, and the organic layer was dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography, eluting with PE:EtOAc = 4: 1 to afford the title compound as a white oil.

- 20 Step 2: tert-Butyl (1-((3-bromo-4-cyanophenyl)sulfonyl)piperidin-4-yl)carbamate



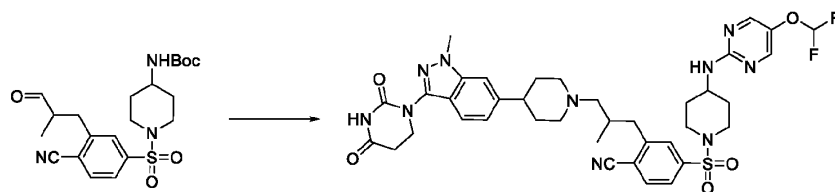
3-Bromo-4-cyanobenzenesulfonyl chloride (500 mg, 1.79 mmol, 1.00 eq.) in DCM (5.0 mL) was added to a stirred solution of tert-butyl piperidin-4-ylcarbamate (359.2 mg, 1.79 mmol, 1.00 eq.) and TEA (542.4 mg, 5.37 mmol, 3.00 eq.) in DCM (5.0 mL) dropwise at 0 °C. The mixture was stirred at rt for 2h. The mixture was poured into water and extracted with DCM. The combined organic layer was washed with water and brine, dried over Na₂SO₄. After filtration, the filtrate was concentrated and the residue was purified by flash chromatography to give the title compound as brown solid.

Step 3: tert-Butyl (1-((4-cyano-3-(2-methyl-3-oxopropyl)phenyl)sulfonyl)piperidin-4-yl)-carbamate



To a stirred solution of tert-butyl (1-((3-bromo-4-cyanophenyl)sulfonyl)piperidin-4-yl)-carbamate (400 mg, 0.90 mmol, 1.00 eq.) in DMF (8.0 mL) was added 2-(di-tert-butylphosphaneyl)-1-phenyl-1H-indole (20 mg, 0.06 mmol, 0.06 eq.), N-cyclohexyl-N-methylcyclohexanamine (194.4 mg, 1.17 mmol, 1.1 eq.), 2-methylprop-2-en-1-ol (130 mg, 1.8 mmol, 2.00 eq.) and Pd₂(dba)₃ (16.8 mg, 0.02 mmol, 0.02 eq.). The mixture was purged with N₂ and stirred at 100 °C for 5h. The mixture was poured into water, extracted with EtOAc, and the combined organic layers was washed with water and brine, dried over Na₂SO₄. After filtration, the filtrate was concentrated and the residue was purified by flash chromatography to give the title compound as white solid.

Step 4: 4-((4-((5-(Difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-methylpropyl)benzonitrile



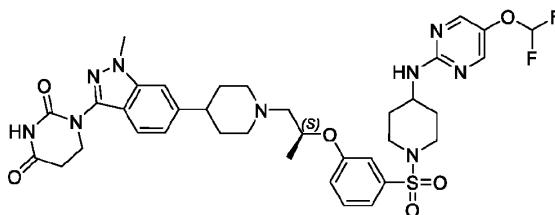
The title compound was synthesized by proceeding analogously as described in Example 1, Step 5-7. MS (ES, m/z): [M+1]⁺ = 791.3.

The following compounds were synthesized by proceeding analogously as described in Example 3.

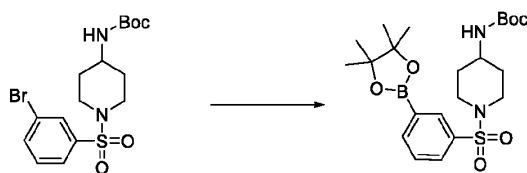
Ex#	Structure
Ex. 4	
Ex. 5	

Example 6

- 5 Synthesis of (S)-1-(6-(1-(2-(3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenoxy)propyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione



- Step 1: tert-Butyl (1-((3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)sulfonyl)piperidin-4-yl)carbamate



- To a stirred solution of tert-butyl (1-((3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)sulfonyl)piperidin-4-yl)carbamate (5 g, 11.92 mmol, 1 eq.) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (3.03 g, 11.92 mmol, 1 eq.) in 1,4-dioxane (50 mL) was added Pd(dppf)Cl₂ (0.87 g, 1.19 mmol, 0.1 eq.) and AcOK (3.51 g, 35.77 mmol, 3 eq.) at rt under nitrogen atmosphere, and the resulting mixture was stirred for 2 h at 80 °C. The mixture was quenched with water and extracted with EtOAc. The combined

organic layers were washed with water and brine, dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure to afford the title compound as a yellow solid.

Step 2: tert-Butyl (1-((3-hydroxyphenyl)sulfonyl)piperidin-4-yl)carbamate

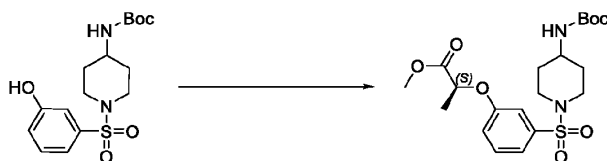
5



To a stirred solution of tert-butyl (1-((3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-phenyl)sulfonyl)piperidin-4-yl) carbamate (9 g, 19.3 mmol, 1 eq.) in ACN (90 mL) was added H₂O₂ (30%, 45 mL) at rt. The resulting mixture was stirred for 10 min at room temperature. The mixture was quenched with sat. Na₂SO₃ solution at 0 °C and the resulting mixture was extracted with EtOAc. The combined organic layers was washed with water and brine, dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with EtOAc/PE (0-50%) to afford the title compound as a white solid.

15

Step 3: Methyl (S)-2-(3-((4-((tert-butoxycarbonyl)amino)piperidin-1-yl)sulfonyl)phenoxy)-propanoate

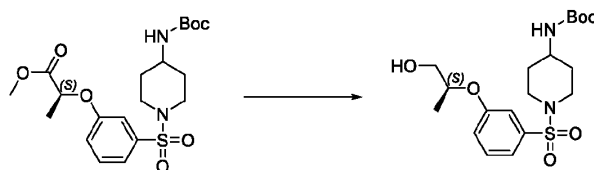


20

To a stirred mixture of tert-butyl (1-((3-hydroxyphenyl)sulfonyl)piperidin-4-yl)carbamate (2 g, 5.6 mmol, 1.0 eq.), PPh₃ (2.2 g, 8.4 mmol, 1.5 eq.) and methyl (2S)-2-hydroxypropanoate (600 mg, 5.78 mmol, 1.03 eq.) in THF (20 mL) was added DIAD (1.36 g, 6.73 mmol, 1.20 eq.) dropwise at 0 °C under nitrogen atmosphere. The mixture was stirred for 2 h at room temperature. The mixture was quenched with water and the resulting mixture was extracted with EtOAc. The combined organic layers were washed with water and brine, dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with EtOAc/PE (0-25%) to afford the title compound as a white solid.

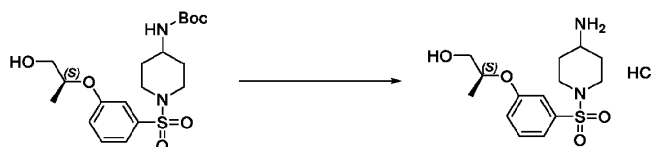
25

Step 4: tert-Butyl (S)-2-(3-((3-((1-hydroxypropan-2-yl)oxy)phenyl)sulfonyl)piperidin-4-yl)-carbamate



To a stirred solution of methyl (S)-2-(3-((3-((tert-butoxycarbonyl)amino)piperidin-1-yl)sulfonyl)phenoxy)propanoate (1.6 g, 3.62 mmol, 1.0 eq.) in THF (16 mL) was added 2 M LiAlH₄ in THF (3.6 mL, 7.2 mmol, 2 eq.) dropwise at 0 °C. The resulting mixture was stirred for 2 h at 0 °C. The mixture was quenched with water and 15% NaOH aq. The resulting mixture was diluted with EtOAc, and filtered. The filtrate was concentrated under reduced pressure to give the title compound as a yellow solid.

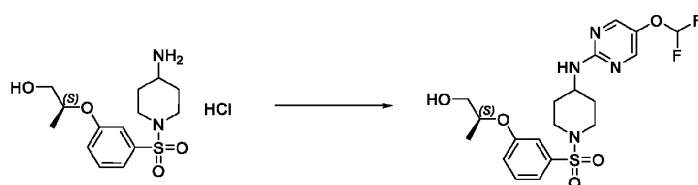
Step 5: (S)-2-(3-((4-Aminopiperidin-1-yl)sulfonyl)phenoxy)propan-1-ol hydrochloride



10

To a stirred solution of tert-butyl (S)-2-(3-((3-((1-hydroxypropan-2-yl)oxy)phenyl)sulfonyl)-piperidin-4-yl)carbamate (1 g, 2.4 mmol, 1.0 eq.) in DCM (10 mL) was added 4 M HCl in 1,4-dioxane (5 mL) dropwise at room temperature. The resulting mixture was stirred for 2 h. The mixture was concentrated under reduced pressure to afford the title compound as a light yellow solid.

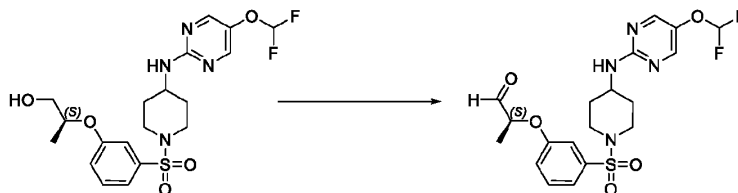
Step 6: (S)-2-(3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-phenoxy)propan-1-ol



To a stirred solution of (S)-2-(3-((4-aminopiperidin-1-yl)sulfonyl)phenoxy)propan-1-ol hydrochloride (760 mg, 2.16 mmol, 1.0 eq.) and 2-chloro-5-(difluoromethoxy)pyrimidine (391 mg, 2.16 mmol, 1.0 eq.) in DMSO (7 mL) was added DIEA (560 mg, 4.32 mmol, 2.0 eq.), and the mixture was stirred for 16 h at 90 °C. The mixture was quenched with water and the mixture was extracted with EtOAc. The combined organic layers were washed with water, brine, and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with EtOAc/PE (0-50%) to afford the title compound as a light yellow solid.

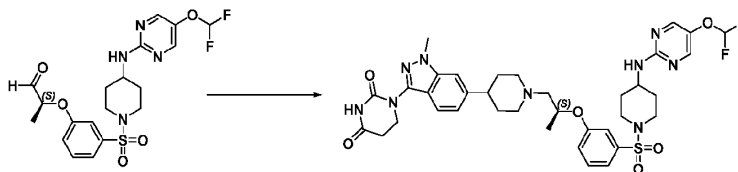
25

Step 7: (S)-2-(3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenoxy)propanal



To a stirred solution of (S)-2-(3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenoxy)propan-1-ol (200 mg, 0.44 mmol, 1.0 eq.) and DIEA (338 mg, 2.62 mmol, 6.0 eq.) in DCM (1 mL) was added SO₃-pyridine (278 mg, 1.74 mmol, 4.0 eq.) in DMSO (1 mL) dropwise at -5~0 °C under nitrogen atmosphere, and the mixture was stirred for 10 min at 0 °C. The mixture was quenched by addition of water and the mixture was extracted with EtOAc. The combined organic layers were washed with water, brine, and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with EtOAc/PE (0-30%) to afford the title compound as a light yellow solid.

Step 8: (S)-1-(6-(1-(2-(3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenoxy)propyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione



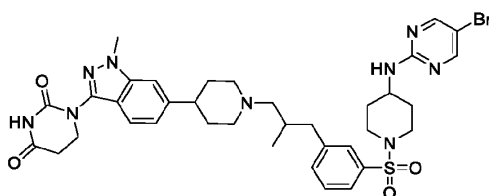
To a stirred mixture of 1-(1-methyl-6-(piperidin-4-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione hydrochloride (80 mg, 0.22 mmol, 1.0 eq.) and TEA (44 mg, 0.44 mmol, 2.0 eq.) in DMAc (1 mL) was added (S)-2-(3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenoxy)propanal (100 mg, 0.22 mmol, 1.0 eq.) in portions at 0°C. The resulting mixture was stirred for 30 min at room temperature, followed by addition of NaBH(OAc)₃ (104 mg, 0.49 mmol, 2.25 eq.) in portions at 0°C. The resulting mixture was stirred for 2 h at rt. The mixture was concentrated, and the residue was purified by prep-HPLC to afford the title compound as an off-white solid. MS (ES, m/z): [M+H]⁺ = 768.2.

The following compounds were synthesized by proceeding analogously as described in Example 6.

Ex#	Structure
Ex. 7	
Ex. 8	
Ex. 9	

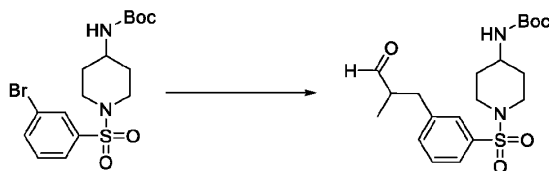
Example 10

Synthesis of 1-(6-(1-(3-(3-((4-((5-bromopyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl) dihydropyrimidine-2,4(1H,3H) dione



5

Step 1: tert-Butyl (1-((3-(2-methyl-3-oxopropyl)phenyl)sulfonyl)piperidin-4-yl)carbamate

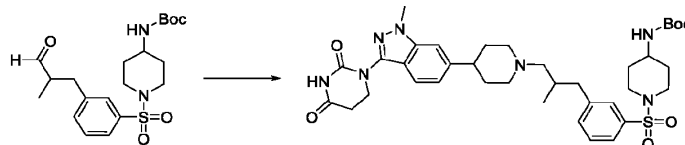


A solution of tert-butyl (1-((3-(2-methyl-3-oxopropyl)phenyl)sulfonyl)piperidin-4-yl)carbamate (5.1 g, 12.2 mmol, 1.0 eq.), Pd(AcO)₂ (0.27 g, 1.2 mmol, 0.1 eq.), 2-methylprop-2-en-1-ol (2.6 g, 36.5 mmol, 3.0 eq.), NaHCO₃ (2 g, 24.3 mmol, 2.0 eq.) and tetrabutylammonium bromide (19.6 g, 60.8 mmol, 5.0

10

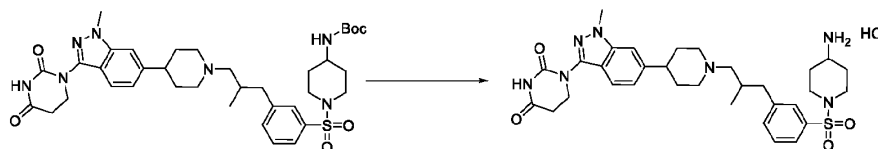
eq.) in DMF (51 mL) was stirred for 3 h at 100°C under nitrogen atmosphere. The resulting mixture was diluted with EtOAc and the organic layer was washed with water and brine, dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with EtOAc/PE (0-25%) to afford the title compound as a light yellow solid.

Step 2: tert-Butyl (1-((3-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-methylpropyl)phenyl)sulfonyl)piperidin-4-yl)carbamate



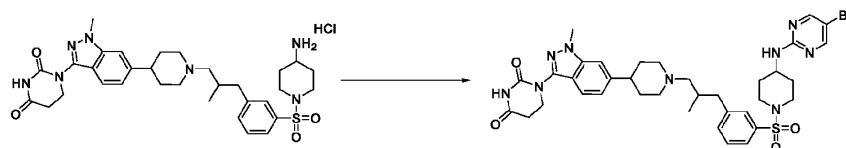
To a stirred solution of 1-(1-methyl-6-(piperidin-4-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione hydrochloride (4.06 g, 11.2 mmol, 1.0 eq.) in DMAc (46 mL) was added TEA (5.7 g, 56 mmol, 5.0 eq.) at 0 °C. The resulting mixture was stirred for 5 min at rt. To the above mixture was added tert-butyl (1-((3-(2-methyl-3-oxopropyl)phenyl)sulfonyl)piperidin-4-yl)carbamate (4.6 g, 11.2 mmol, 1.0 eq.). The resulting mixture was stirred for 1 h at rt. Then NaBH(AcO)₃ (5.3 g, 25.2 mmol, 2.25 eq.) was added in portions at 0°C and stirred for 2 h at rt. The mixture was diluted with H₂O and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with EtOAc/PE (0-100%) to afford the title compound as a white solid.

Step 3: 1-(6-(1-(3-(3-((4-Aminopiperidin-1-yl)sulfonyl)phenyl)-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione hydrochloride



To a stirred solution of tert-butyl (1-((3-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-methylpropyl)phenyl)sulfonyl)piperidin-4-yl)-carbamate (3.7 g, 5.1 mmol, 1.0 eq.) in DCM (37 mL) was added 4M HCl in 1,4-dioxane (18 mL) dropwise at 0 °C. The resulting mixture was stirred for 1 h at rt. The mixture was concentrated under reduced pressure to give the title compound as a light yellow solid.

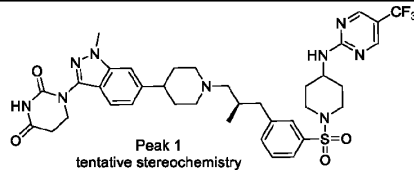
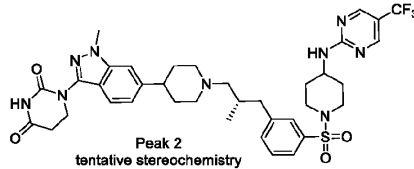
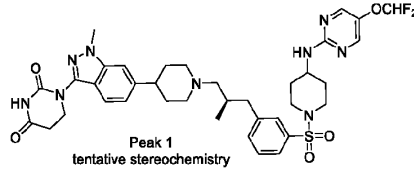
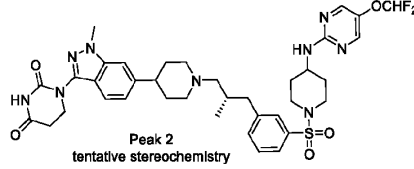
Step 4: 1-(6-(1-(3-(3-((4-((5-Bromopyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H) dione



To a stirred solution of 1-(6-(1-(3-(3-((4-aminopiperidin-1-yl)sulfonyl)phenyl)-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione hydrochloride (100 mg, 0.15 mmol, 1.0 eq.) in DMSO (1 mL) was added DIEA (120 mg, 0.91 mmol, 6.0 eq.) at rt, and the mixture was stirred for 5 min. To the above mixture was added 5-bromo-2-chloropyrimidine (45 mg, 0.23 mmol, 1.5 eq.), and the mixture was stirred for 16 h at 120 °C. The mixture was concentrated and the residue was purified by prep-HPLC to afford the title compound as a white solid. MS (ES, m/z): $[M+H]^+ = 778.3$.

The following compounds were synthesized by proceeding analogously as described in Example 10.

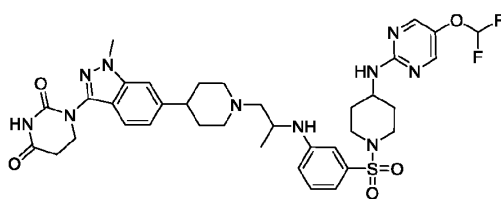
Ex#	Structure
Ex. 11	
Ex. 12	
Ex. 13	
Ex. 14	

Ex#	Structure
Ex.15*	
Ex.16*	
Ex.17*	
Ex.18*	
* The single enantiomers were prepared by chiral separation of the racemic material.	

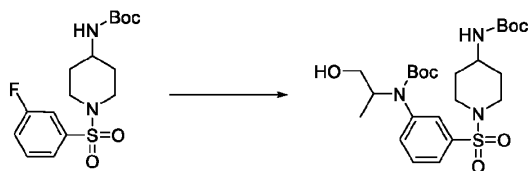
Example 19

Synthesis of 1-(6-(1-(2-((3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)-sulfonyl)phenyl) amino) propyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl) dihydropyrimidine-2,4(1H,3H)-dione

5

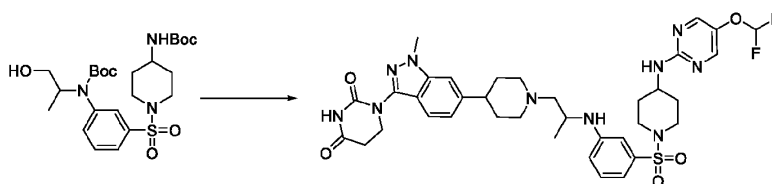


Step 1: tert-Butyl (3-((4-((tert-butoxycarbonyl)amino)piperidin-1-yl)sulfonyl)phenyl)(1-hydroxypropan-2-yl)carbamate



A solution of tert-butyl (1-((3-fluorophenyl)sulfonyl)piperidin-4-yl)carbamate (5 g, 13.95 mmol, 1.0 eq.) and 2-aminopropan-1-ol (4.19 g, 55.8 mmol, 4.0 eq.), NaOH (2.79 g, 69.75 mmol, 5.0 eq.) in DMSO (50 mL) was stirred for 2 h at 80 °C under nitrogen atmosphere. The mixture was diluted with water and the mixture was extracted with EtOAc. The combined organic layers were washed with water and brine, dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. To the above residue was added Boc₂O (6.5 g, 28 mmol, 2.0 eq.) in MeOH (45 mL) and the mixture was stirred for 16 h at rt. The mixture was diluted with water and the resulting mixture was extracted with EtOAc. The combined organic layers were washed with water and brine, dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with EtOAc/PE (0-25%) to afford the title compound as a yellow solid.

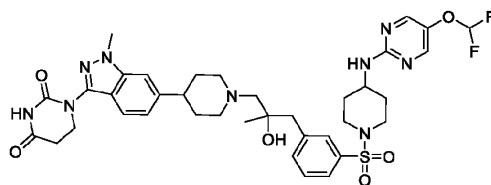
Step 2: 1-(6-(1-(2-((3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)amino)propyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl) dihydropyrimidine-2,4(1H,3H)-dione



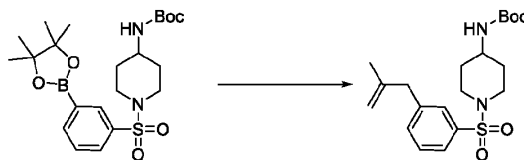
The title compound was synthesized by proceeding analogously as described in Example 6, Steps 5-8. MS (ES, m/z): [M+H]⁺ = 767.4.

Example 20

Synthesis of 1-(6-(1-(3-(3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-2-hydroxy-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl) dihydropyrimidine-2,4(1H,3H)-dione

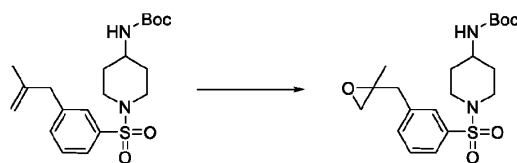


Step 1: tert-Butyl (1-((3-(2-methylallyl)phenyl)sulfonyl)piperidin-4-yl)carbamate



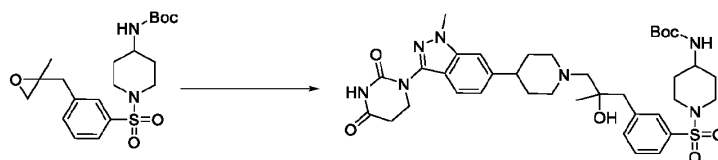
A mixture of tert-butyl (1-((3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)sulfonyl)piperidin-4-yl)carbamate (3.3 g, 7.1 mmol, 1.0 eq.), 3-bromo-2-methylprop-1-ene (1.91 g, 14.2 mmol, 2.0 eq.), Pd(PPh₃)₂Cl₂ (497 mg, 0.7 mmol, 0.1 eq.) and Na₂CO₃ (2.25 g, 21.2 mmol, 3.0 eq.) in THF (30 mL) and H₂O (3 mL) was stirred for 4 h at 65 °C under nitrogen atmosphere. The resulting mixture was diluted with water and extracted with DCM. The combined organic layers were washed with water and brine, dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with EtOAc/PE (0-30%) to afford the title compound as a yellow solid.

Step 2: tert-Butyl (1-((3-((2-methyloxiran-2-yl)methyl)phenyl)sulfonyl)piperidin-4-yl)carbamate



To a stirred solution of tert-butyl (1-((3-(2-methylallyl)phenyl)sulfonyl)piperidin-4-yl)carbamate (810 mg, 2.1 mmol, 1.0 eq.) in DCM (10 mL) was added m-CPBA (834 mg, 4.1 mmol, 2.0 eq., 85%) in portions at 0 °C. The resulting mixture was stirred for 4 h at rt. The reaction was quenched with aq NaHCO₃ at 0 °C, and the resulting mixture was extracted with EtOAc. The combined organic layers were washed with water and brine, dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with EtOAc/PE (0~100%) to afford the title compound as a light yellow solid.

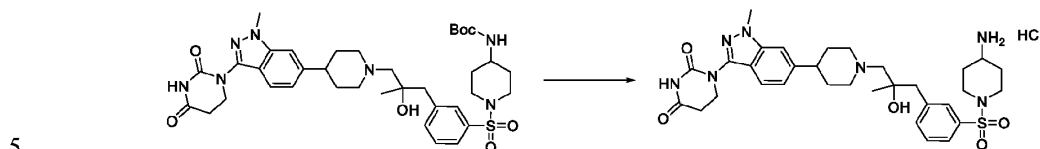
Step 3: tert-Butyl (1-((3-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-hydroxy-2-methylpropyl)phenyl)sulfonyl)piperidin-4-yl)carbamate



To a stirred solution of tert-butyl (1-((3-((2-methyloxiran-2-yl)methyl)phenyl)sulfonyl)piperidin-4-yl)carbamate (650 mg, 1.6 mmol, 1.0 eq.) and 1-(1-methyl-6-(piperidin-4-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione hydrochloride (634 mg, 1.76 mmol, 1.1 eq.) in EtOH (6 mL) was added TEA (240 mg, 2.4 mmol, 1.5 eq.) and the mixture was stirred for 24 h at 80 °C. The mixture was diluted with water and extracted with EtOAc. The combined organic layers were washed with water and brine, and the organic layer was dried over anhydrous Na₂SO₄. After

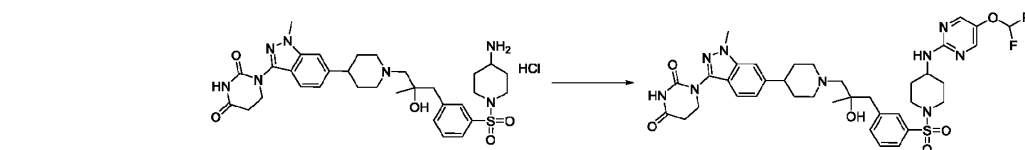
filtration, the filtrate was concentrated under reduced pressure. The residue was purified by trituration with EtOAc/PE (1:3) to afford the title compound as a white solid.

Step 4: 1-(6-(1-(3-(3-((4-Aminopiperidin-1-yl)sulfonyl)phenyl)-2-hydroxy-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione hydrochloride



To a stirred solution of tert-butyl (1-((3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-hydroxy-2-methylpropyl)phenyl)sulfonyl)piperidin-4-yl)carbamate (700 mg, 1 mmol, 1.0 eq.) in DCM (3 mL) was added 4 M HCl in 1,4-dioxane (3 mL) dropwise, and the mixture was stirred for 2 h. The resulting mixture was concentrated under vacuum to afford the title compound as a light yellow solid.

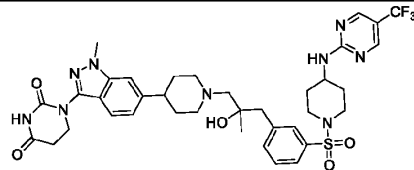
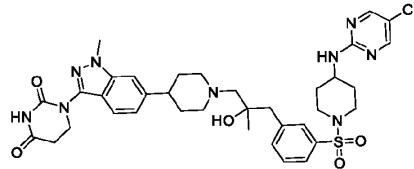
Step 5: 1-(6-(1-(3-(3-((5-(Difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-2-hydroxy-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione



To a stirred mixture of 1-(6-(1-(3-(3-((4-aminopiperidin-1-yl)sulfonyl)phenyl)-2-hydroxy-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione hydrochloride (90 mg, 0.14 mmol, 1.0 eq.) and 2-chloro-5-(difluoromethoxy)pyrimidine (38 mg, 0.2 mmol, 1.5 eq.) in DMSO (0.45 mL) was added DIEA (0.45 mL), and the resulting mixture was stirred for 16 h at 100°C under nitrogen atmosphere. The mixture was diluted with water and extracted with EtOAc. The combined organic layers were washed with water, brine, and the organic layer was dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by prep-HPLC to afford the title compound as a light-yellow solid. MS (ES, m/z): [M+H]⁺ = 782.4.

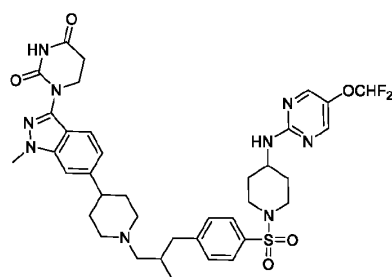
The following compounds were synthesized by proceeding analogously as described in Example 20.

25

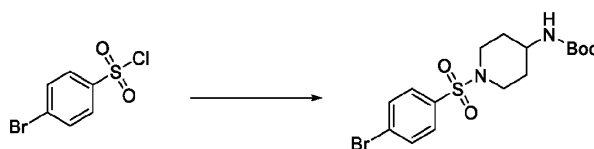
Ex#	Structure
Ex. 21	
Ex. 22	

Example 23

Synthesis of 1-(6-(1-(3-(4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl) dihydropyrimidine-2,4(1H,3H)-dione

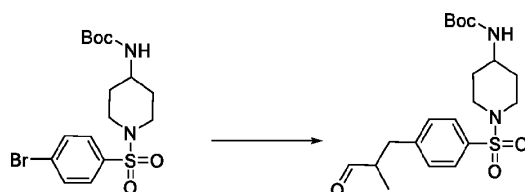


Step 1: tert-Butyl (1-((4-bromophenyl)sulfonyl)piperidin-4-yl)carbamate



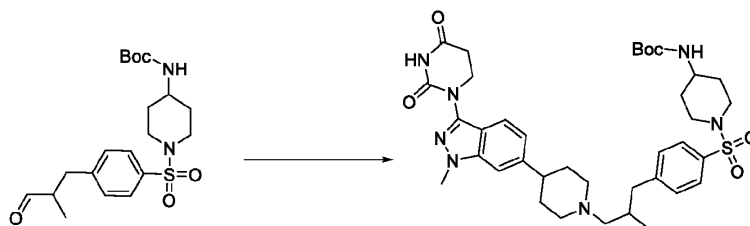
To a stirred solution of 4-bromobenzenesulfonyl chloride (10.0 g, 39.14 mmol, 1.00 eq.) in DCM (20.0 mL) was added tert-butyl piperidin-4-ylcarbamate (9.41 g, 46.96 mmol, 1.20 eq.) and TEA (7.92 g, 78.27 mmol, 2.00 eq.) at 0 °C, and the mixture was stirred at rt for 2h. The mixture was diluted with water and extracted with DCM. The combined organic layers was washed with water, brine, and the organic layer was dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography, eluting with PE:EtOAc=4:1, to afford the title compound as a white solid.

Step 2: tert-Butyl (1-((4-(2-methyl-3-oxopropyl)phenyl)sulfonyl)piperidin-4-yl)carbamate



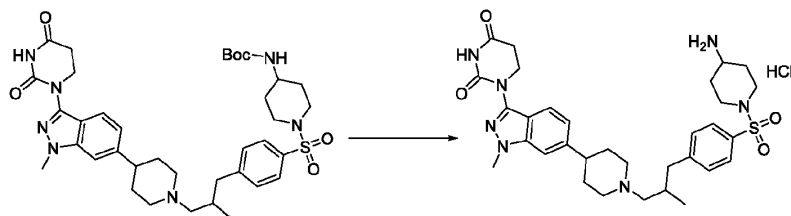
A mixture of tert-butyl (1-((4-bromophenyl)sulfonyl)piperidin-4-yl)carbamate (500 mg, 1.20 mmol, 1.00 eq.), NaHCO₃ (201 mg, 2.39 mmol, 2.00 eq.), tetrabutylammonium bromide (77.1 mg, 0.239 mmol, 0.2 eq.), 2-methylprop-2-en-1-ol (172.4 mg, 2.39 mmol, 2.00 eq.) and Pd(OAc)₂ (6 mg, 0.0239 mmol, 0.02 eq.) in DMF (10.0 mL) was stirred at 100 °C for 12 h under N₂. The mixture was poured into water, extracted with EtOAc. The combined organic layer was washed with water and brine, dried over Na₂SO₄. After filtration, the filtrate was concentrated and the residue was purified by flash chromatography to give the title compound as a white solid.

Step 3: tert-Butyl (1-((4-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-methylpropyl)phenyl)sulfonyl)piperidin-4-yl)carbamate



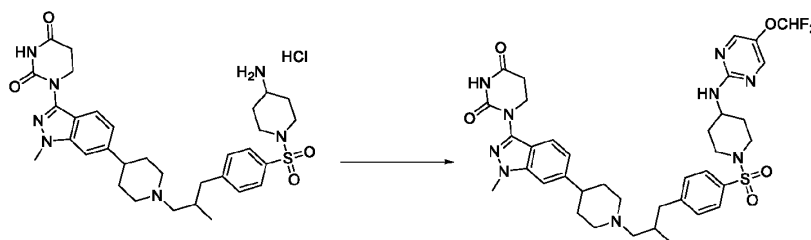
To a stirred solution of tert-butyl (1-((4-(2-methyl-3-oxopropyl)phenyl)sulfonyl)piperidin-4-yl)carbamate (150 mg, 0.366 mmol, 1.00 eq.), 1-(1-methyl-6-(piperidin-4-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione hydrochloride (133 mg, 0.366 mmol, 1.00 eq.) and TEA (110.9 mg, 1.1 mmol, 3.00 eq.) in DMA (2.0 ml) was added NaBH(OAc)₃ (187.7 mg, 0.886 mmol, 2.5 eq.) at 0 °C and the mixture was stirred at 0 °C for 2h. The mixture was poured into water, extracted with EtOAc. The combined organic layer was washed with water and brine, dried over Na₂SO₄. After filtration, the filtrate was concentrated and the residue was purified by flash chromatography to give the title compound as white solid.

Step 4: 1-(6-(1-(3-(4-((4-Aminopiperidin-1-yl)sulfonyl)phenyl)-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione hydrochloride



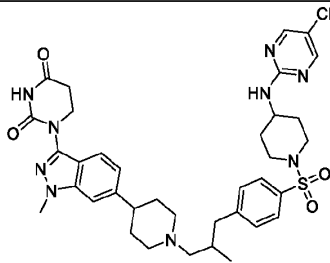
HCl in EtOAc (2 M, 2.0 mL) was added to tert-butyl (1-((4-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-methylpropyl)phenyl)sulfonyl)-piperidin-4-yl)carbamate (110 mg, 0.15 mmol, 1.00 eq.) and the mixture was stirred at rt for 2h. The mixture was concentrated under reduced pressure to give the title compound as brown oil.

Step 5: 1-(6-(1-(3-(4-((5-(Difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione



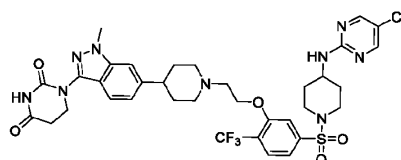
A mixture of 1-(6-(1-(3-(4-((4-aminopiperidin-1-yl)sulfonyl)phenyl)-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione hydrochloride (94.8 mg, 0.15 mmol, 1.00 eq.), CsF (151.9 mg, 0.76 mmol, 5.00 eq.), DIEA (98 mg, 0.76 mmol, 5.00 eq.) and 2-chloro-5-(difluoromethoxy) pyrimidine (27.4 mg, 0.152 mmol, 1.00 eq.) in DMSO (2.0 mL) was stirred at 50 °C for 12 h under N₂. The mixture was diluted with water and extracted with EtOAc. The combined organic layers were washed with water, brine, and the organic layer was dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated and the residue was purified by flash chromatography to afford the title compound as a white solid. MS (ES, m/z): [M+1]⁺ = 766.3.

The following compounds were synthesized by proceeding analogously as described in Example 23.

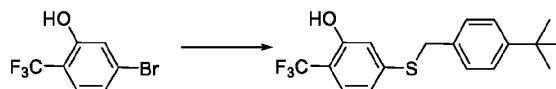
Ex#	Structure
Ex. 24	

Example 25

- 5 Synthesis of 1-(6-(1-(2-(5-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(trifluoromethyl)phenoxy)ethyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione



Step 1: 5-((4-(tert-Butyl)benzyl)thio)-2-(trifluoromethyl)phenol



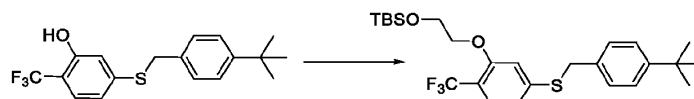
10

To a stirred solution of 5-bromo-2-(trifluoromethyl)phenol (1.00 g, 4.15 mmol, 1.00 eq.) in 1,4-dioxane (10.0 mL) was added (4-(tert-butyl)phenyl)methanethiol (972 mg, 5.40 mmol, 1.30 eq.), Pd₂(dba)₃ (385 mg, 0.42 mmol, 0.10 eq.), DIEA (1.61 g, 12.45 mmol, 3.00 eq.) and XantPhos (486 mg, 0.84 mmol, 0.20 eq.) and the mixture was stirred at 100 °C for 12 h. The mixture was diluted with water and extracted with DCM. The combined organic layers was washed with water, brine, and the organic layer was dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with PE/EtOAc=20:1, to afford the title compound as a yellow solid.

15

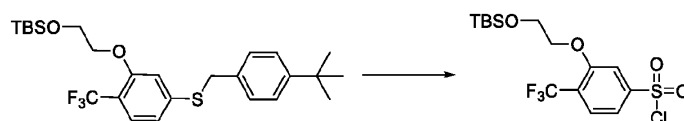
Step 2: tert-Butyl(2-(5-((4-(tert-butyl)benzyl)thio)-2-(trifluoromethyl)phenoxy)ethoxy)dimethylsilane

20



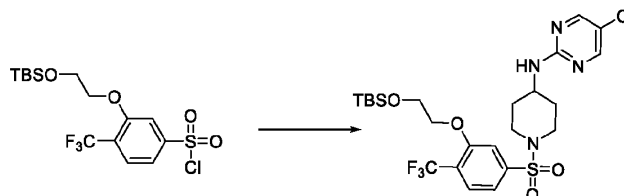
To a stirred solution of 5-((4-(tert-butyl)benzyl)thio)-2-(trifluoromethyl)phenol (801 mg, 2.36 mmol, 1.00 eq.), 2-((tert-butyldimethylsilyl)oxy)ethan-1-ol (415 mg, 2.36 mmol, 1.00 eq.) in THF (10.0 mL) was added triphenylphosphine (1.24 g, 4.72 mmol, 2.00 eq.) and stirred at 0 °C for 15 min. Then DIAD was added (953 mg, 4.72 mmol, 2.00 eq.) at 0 °C and the mixture was stirred for 3 h. The mixture was diluted with water and extracted with DCM. The combined organic layers was washed with water, brine, and the organic layer was dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with PE/EtOAc=20:1, to afford the title compound as a yellow solid.

Step 3: 3-(2-((tert-Butyldimethylsilyl)oxy)ethoxy)-4-(trifluoromethyl)benzenesulfonyl chloride



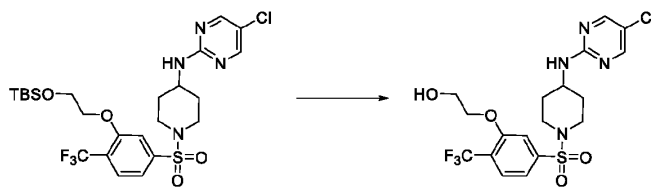
To a stirred solution of tert-butyl(2-(5-((4-(tert-butyl)benzyl)thio)-2-(trifluoromethyl)phenoxy)ethoxy)dimethylsilane (637 mg, 1.28 mmol, 1.00 eq.) in AcOH (1.0 mL) and ACN/H₂O (3.0 mL/0.4 mL) was added 1,3-dichloro-5,5-dimethylimidazolidine-2,4-dione (504 mg, 2.56 mmol, 2.00 eq.) at rt and the mixture was stirred for 12 h. The mixture was diluted with water and extracted with DCM. The combined organic layers was washed with water, brine, and the organic layer was dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure to afford the title compound as a white solid.

Step 4: N-(1-((3-(2-((tert-Butyldimethylsilyl)oxy)ethoxy)-4-(trifluoromethyl)phenyl)-sulfonyl)-piperidin-4-yl)-5-chloropyrimidin-2-amine

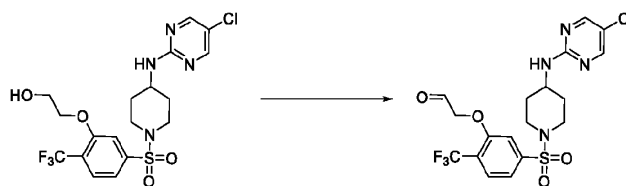


To a stirred solution of 5-chloro-N-(piperidin-4-yl)pyrimidin-2-amine (349 mg, 1.41 mmol, 1.10 eq.) and TEA (388 mg, 3.84 mmol, 3.00 eq.) in DCM (5.0 mL) was added 3-(2-((tert-butyldimethylsilyl)oxy)ethoxy)-4-(trifluoromethyl)benzenesulfonyl chloride (535 mg, 1.28 mmol, 1.00 eq.) at rt and the mixture was stirred for 12 h. The mixture was diluted with water and extracted with DCM. The combined organic layers was washed with water, brine, and the organic layer was dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with EtOAc:PE (0 to 100%), to afford the title compound as a white solid.

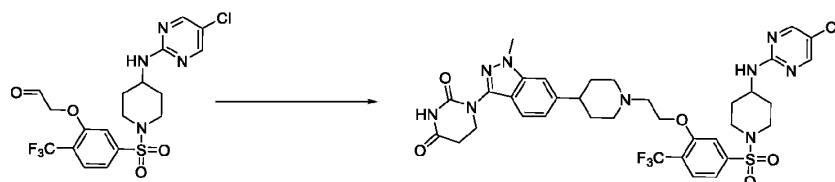
Step 5: 2-(5-((4-((5-Chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(trifluoromethyl)phenoxy)ethan-1-ol



- TBAF (1.0 M in THF, 2.00 mL) was added to a stirred solution of N-(1-((3-(2-((tert-butyldimethylsilyl)oxy)ethoxy)-4-(trifluoromethyl)phenyl)sulfonyl)piperidin-4-yl)-5-chloropyrimidin-2-amine (120 mg, 0.20 mmol, 1.00 eq.) at rt and the mixture was stirred for 3 h. The mixture was diluted with water and extracted with DCM. The combined organic layers was washed with water, brine, and the organic layer was dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure to afford the title compound as a white solid.
- Step 6: 2-(5-((4-((5-Chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(trifluoromethyl)phenoxy)acetaldehyde



- To a stirred solution of 2-(5-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(trifluoromethyl)phenoxy)ethan-1-ol (100 mg, 0.21 mmol, 1.00 eq.) in DCM (5.0 mL) was added Dess-Martin periodinane (134 mg, 0.32 mmol, 1.50 eq.) at rt and the mixture was stirred for 5 h. The mixture was diluted with water and extracted with DCM. The combined organic layers was washed with water, brine, and the organic layer was dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure to afford the title compound as a yellow oil.
- Step 7: 1-(6-(1-(2-(5-((4-((5-Chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(trifluoromethyl)phenoxy)ethyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione

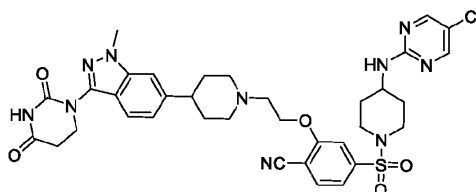


To a stirred mixture of 2-(5-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(trifluoromethyl)phenoxy)acetaldehyde (100 mg, 0.21 mmol, 1.00 eq) in DMA (2.0 mL) was added

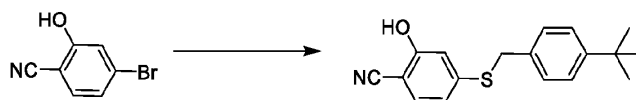
1-(1-methyl-6-(piperidin-4-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione hydrochloride (83 mg, 0.23 mmol, 1.10 eq.), TEA (64 mg, 0.63 mmol, 3.00 eq.), NaBH(OAc)₃ (108 mg, 0.51 mmol, 2.5 eq.) at 0°C and the resulting mixture was stirred for 12h. The mixture was diluted with water and extracted with DCM. The combined organic layers was washed with water, brine, and the organic layer was dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with DCM/MeOH (20:1) to afford the title compound as a white solid. MS (ES, m/z): [M+1]⁺ = 790.2.

Example 26

Synthesis of 4-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(2-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)ethoxy)benzonitrile

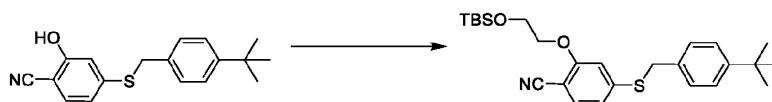


Step 1: 4-((4-(tert-Butyl)benzyl)thio)-2-hydroxybenzonitrile



A mixture of 4-bromo-2-hydroxybenzonitrile (3.10 g, 15.7 mmol, 1.00 eq.), (4-tert-butylphenyl)methanethiol (3.11 g, 17.2 mmol, 1.10 eq.), Pd₂(dba)₃ (1.44 g, 1.57 mmol, 0.10 eq.) and XantPhos (1.82 g, 3.14 mmol, 0.20 eq.), DIEA (6.09 g, 47.1 mmol, 3.00 eq.) in 1,4-dioxane (40.0 mL) was stirred at 100 °C under N₂ for 16h. The mixture was filtrated, and the filtrate was concentrated. The residue was purified by column chromatography on silica gel (PE:EtOAc = 30 : 1) to give the title compound as yellow solid.

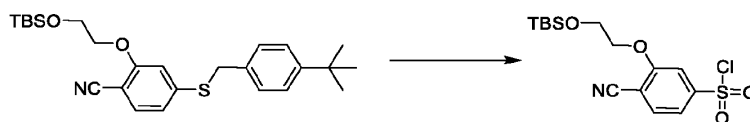
Step 2: 4-((4-(tert-Butyl)benzyl)thio)-2-(2-((tert-butyldimethylsilyl)oxy)ethoxy)benzonitrile



To a stirred solution of 4-((4-(tert-butyl)benzyl)thio)-2-hydroxybenzonitrile (1.00 g, 3.4 mmol, 1.00 eq.), 2-((tert-butyldimethylsilyl)oxy)ethanol (0.66 g, 3.7 mmol, 1.10 eq.) and triphenylphosphine (1.78 g, 6.8 mmol, 2.00 eq.) in THF (25.0 mL) was added diisopropyl azodicarboxylate (1.38 g, 6.8 mmol, 2.00 eq.) slowly at 0 °C. The mixture was stirred at rt under N₂ for 3h. The mixture was diluted with water and extracted with EtOAc. The combined organic layers

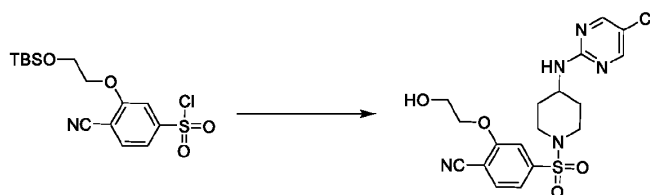
was washed with brine and the organic layer was dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated and the residue was purified by silica gel column chromatography (PE:EtOAc = 20 : 1) to give the title compound as light yellow oil.

Step 3: 3-(2-((tert-Butyldimethylsilyl)oxy)ethoxy)-4-cyanobenzenesulfonyl chloride



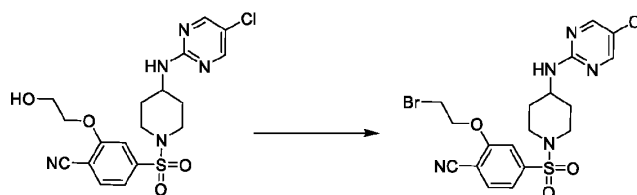
To a stirred solution of 4-((4-(tert-butyl)benzyl)thio)-2-(2-((tert-butyldimethylsilyl)oxy)ethoxy)benzonitrile (910 mg, 2.00 mmol, 1.00 eq.) in ACN (15.0 mL)/water (2.0 mL) was added AcOH (5.0 mL). Then 1,3-dichloro-5,5-dimethylimidazolidine-2,4-dione (786.8 mg, 3.99 mmol, 2.00 eq.) was added at 0 °C and the mixture was stirred at rt for 3h. The mixture was diluted with water and extracted with EtOAc. The combined organic layers was washed with brine and the organic layer was dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated to give the title compound as yellow oil.

Step 4: 4-((4-((5-Chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(2-hydroxyethoxy)benzonitrile



The title compound was synthesized by proceeding analogously as described in Example 25, Step 4-5.

Step 5: 2-(2-Bromoethoxy)-4-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-benzonitrile

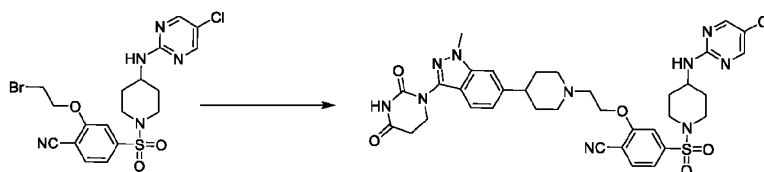


To a stirred solution of 4-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(2-hydroxyethoxy)benzonitrile (100 mg, 0.23 mmol, 1.00 eq.) and tetrabromomethane (90.9 mg, 0.27 mmol, 1.20 eq.) in DCM (5.0 mL) was added triphenylphosphine (95.9 mg, 0.37 mmol, 1.60 eq.) at rt and the mixture was stirred for 3 h. The mixture was diluted with water and extracted with DCM.

The combined organic layers was washed with brine and the organic layer was dried over anhydrous

Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (DCM:MeOH = 20:1) to give the title compound as white solid.

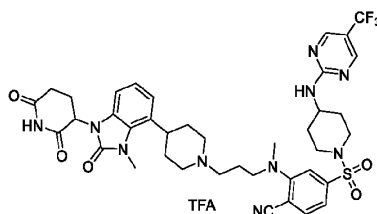
Step 6: 4-((4-((5-Chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(2-(4-(3-(2,4-dioxo-
5 tetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)ethoxy)benzonitrile



To a stirred solution of 1-(1-methyl-6-(piperidin-4-yl)-1H-indazol-3-yl)dihydro-pyrimidine-2,4(1H,3H)-dione hydrochloride (20 mg, 0.06 mmol, 1.00 eq.) and 2-(2-bromo-ethoxy)-4-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzonitrile (27.5 mg, 0.06 mmol, 1.00 eq.) in
10 DMSO (1.0 mL) were added K₂CO₃ (22.8 mg, 0.17 mmol, 3.00 eq.) and KI (18.3 mg, 0.11 mmol, 2.00 eq.) at rt and the mixture was stirred at 70 °C under N₂ for 16 h. The mixture was diluted with water and extracted with EtOAc. The combined organic layers was washed with brine and the organic layer was dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by prep-TLC (DCM:MeOH=15:1) to give the title
15 compound as white solid. MS (ES, m/z): [M+1]⁺ = 747.2.

Example 27

Synthesis of 2-((3-(4-(1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]-imidazol-4-yl)piperidin-1-yl)propyl)(methyl)amino)-4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzonitrile 2,2,2-trifluoroacetate
20



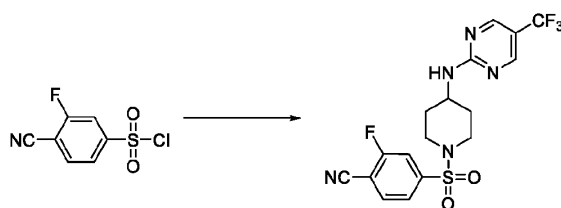
Step 1: 4-Cyano-3-fluorobenzenesulfonyl chloride



A mixture of 4-amino-2-fluorobenzonitrile (4.80 g, 35.29 mmol, 1.00 eq.) in conc. HCl (60.0
25 mL) and H₂O (20.0 mL) turned clear after heating at 80 °C, then the mixture was cooled to 0 °C. A

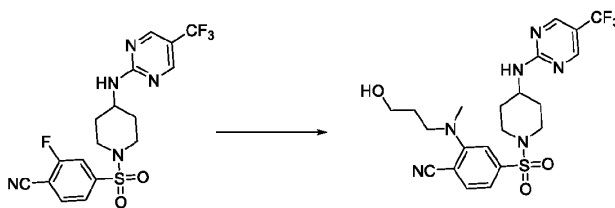
solution of NaNO₂ (2.64 g, 38.11 mmol, 1.08 eq.) in H₂O (60.0 mL) was slowly added to the above mixture at 0 °C, and the mixture was stirred for 15min. Then a solution of CuCl (280 mg, 2.82 mmol, 0.08 eq.) in H₂O (60.0 mL) was added slowly, followed by addition of SOCl₂ (10.0 mL) at 0 °C. The mixture was stirred at 0 °C for 30 min. The mixture was diluted with water and extracted with EtOAc. The combined organic layers was washed with water, brine, and the organic layer was dried over anhydrous Na₂SO₄. After filtration, the organic layer was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with (PE:EtOAc=2:1), to afford the title compound as a yellow solid.

Step 2: 2-Fluoro-4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-benzonitrile



To a stirred solution of N-(piperidin-4-yl)-5-(trifluoromethyl)pyrimidin-2-amine hydrochloride (1.28 g, 4.56 mmol, 1.00 eq.) in DCM (15.0 mL) was added TEA (1.38 g, 13.68 mmol, 3.00 eq.) and 3-bromo-4-cyanobenzenesulfonyl chloride (1.00 g, 4.56 mmol, 1.00 eq.) at 0 °C and the mixture was stirred for 3h. The mixture was diluted with water and extracted with EtOAc. The combined organic layers was washed with water, brine, and the organic layer was dried over anhydrous Na₂SO₄. After filtration, the organic layer was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with (DCM:MeOH=40:1), to afford the title compound as a yellow solid.

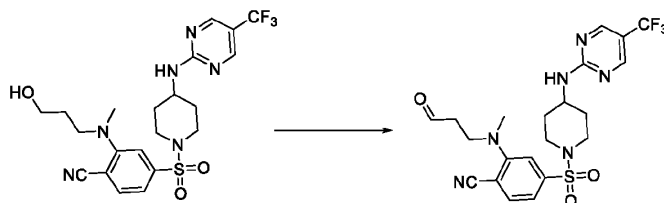
Step 3: 2-((3-Hydroxypropyl)(methyl)amino)-4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)-piperidin-1-yl)sulfonyl)benzonitrile



To a stirred solution of 2-fluoro-4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)-piperidin-1-yl)sulfonyl)benzonitrile (500 mg, 1.17 mmol, 1.00 eq.) in DMSO (8.0 mL) was added 3-(methylamino)propan-1-ol (312 mg, 3.51 mmol, 3.00 eq.) and potassium carbonate (484 mg, 3.51 mmol, 3.00 eq.) and the mixture was stirred at 100 °C for 3h. The mixture was diluted with water and

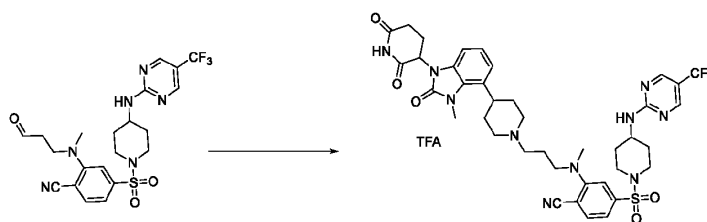
extracted with EtOAc. The combined organic layers was washed with water, brine, and the organic layer was dried over anhydrous Na₂SO₄. After filtration, the organic layer was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with (DCM:MeOH=50:1), to afford the title compound as a yellow solid.

- 5 Step 4: 2-(Methyl(3-oxopropyl)amino)-4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzonitrile



- To a stirred solution of 2-((3-hydroxypropyl)(methyl)amino)-4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzonitrile (130 mg, 0.26 mmol, 1.00 eq.) in DCM (3.0 mL) was added Dess-Martin periodinane (165 mg, 0.39 mmol, 1.50 eq.) at 0 °C and the mixture was stirred for 2h. The mixture was diluted with water and extracted with EtOAc. The combined organic layers was washed with water, brine, and the organic layer was dried over anhydrous Na₂SO₄. After filtration, the organic layer was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with (PE:EtOAc=5:1), to afford the title compound as a yellow oil.

Step 5: 2-((3-(4-(1-(2,6-Dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)piperidin-1-yl)propyl)(methyl)amino)-4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)-piperidin-1-yl)sulfonyl)benzonitrile 2,2,2-trifluoroacetate

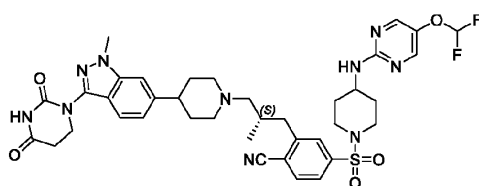


- To a mixture of 2-(methyl(3-oxopropyl)amino)-4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzonitrile (150 mg, 0.30 mmol, 1.00 eq.) and 3-(3-methyl-2-oxo-4-(piperidin-4-yl)-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione hydrochloride (113.4 mg, 0.30 mmol, 1.00 eq.) in DCM (5.0 mL) was added NaBH(OAc)₃ (154 mg, 0.73 mmol, 2.50 eq.) and TEA (91 mg, 0.90 mmol, 3.00 eq.) at 0 °C and the mixture was stirred at rt for 12h. The mixture was diluted with water and extracted with EtOAc. The combined organic layers was washed with brine, and the organic layer was dried over anhydrous Na₂SO₄. After filtration, the filtrate was

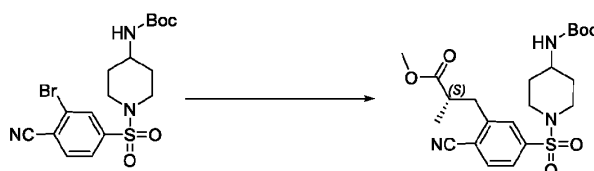
concentrated under reduced pressure, and the residue was purified by *prep*-HPLC to afford the title compound as a white solid as its TFA salt. MS (ES, *m/z*): $[M+1]^+ = 823.3$

Example 28

- 5 Synthesis of (S)-4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-methylpropyl)benzonitrile

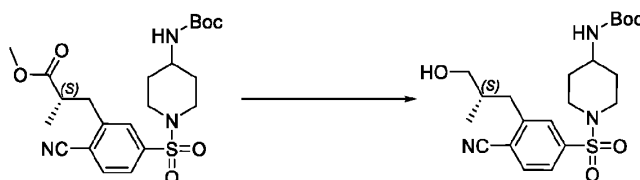


- Step 1: Methyl (S)-3-(5-((4-((tert-butoxycarbonyl)amino)piperidin-1-yl)sulfonyl)-2-cyanophenyl)-2-methyl propanoate



- To a solution of tert-butyl N-[1-(3-bromo-4-cyanobenzenesulfonyl)piperidin-4-yl]carbamate (1 g, 2.25 mmol, 1.00 eq.), pyridine-2-carboximidamide hydrochloride (40 mg, 0.23 mmol, 0.1 eq.), NaI (84 mg, 0.56 mmol, 0.25 eq.), NiCl₂(dme) (50 mg, 0.23 mmol, 0.1 eq.) in DMA (10 mL) and methyl (2R)-3-bromo-2-methylpropanoate (610 mg, 3.38 mmol, 1.5 eq.) was added Mn powder (250 mg, 4.5 mmol, 2.0 eq.) under nitrogen atmosphere. The resulting mixture was stirred for 3 h at 40 °C under nitrogen atmosphere. The reaction was quenched with water. The resulting mixture was extracted with EtOAc. The combined organic layers were washed with water and brine, dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with EtOAc/PE (0~100%) to afford the title compound as a light yellow solid.

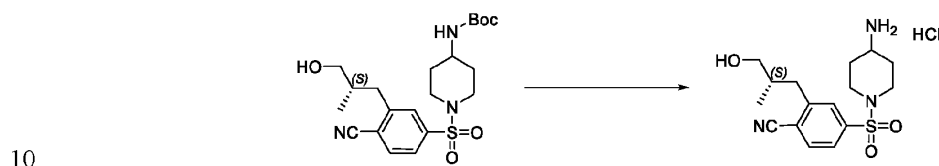
Step 2: tert-Butyl (S)-[1-((4-cyano-3-(3-hydroxy-2-methylpropyl)phenyl)sulfonyl)piperidin-4-yl]carbamate



To a stirred solution of methyl (S)-3-(5-((4-((tert-butoxycarbonyl)amino)piperidin-1-yl)sulfonyl)-2-cyanophenyl)-2-methyl propanoate (800 mg, 1.72 mmol, 1.0 eq.) in THF (8 mL) were added 1 M LiAlH₄ in THF (2.4 mL, 2.4 mmol, 1.40 eq.) dropwise at -60 °C under nitrogen atmosphere. The resulting mixture was stirred for 30 min at -60~-40 °C under nitrogen atmosphere.

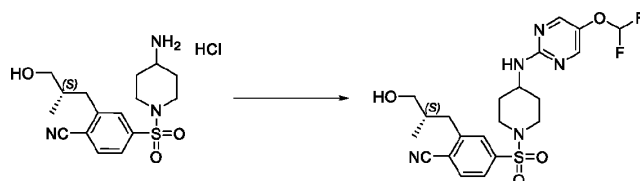
- 5 The reaction was quenched with water, 15% NaOH(aq.) and water at 0 °C. The resulting mixture was dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure to afford the title compound as a light yellow solid.

Step 3: (S)-4-((4-Aminopiperidin-1-yl)sulfonyl)-2-(3-hydroxy-2-methylpropyl)benzonitrile hydrochloride



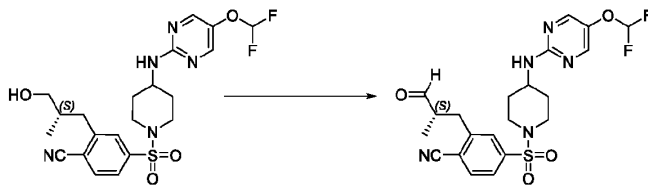
- To a stirred solution of tert-butyl (S)-1-((4-cyano-3-(3-hydroxy-2-methylpropyl)phenyl)sulfonyl)piperidin-4-yl)carbamate (500 mg, 1.14 mmol, 1.0 eq.) in DCM (3 mL) were added 4M HCl in 1,4-dioxane (3 mL). The resulting mixture was stirred for 1 h at room temperature. The resulting mixture was concentrated under reduced pressure to afford the title compound as a light yellow solid.
- 15

Step 4: (S)-4-((4-((5-(Difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-hydroxy-2-methyl propyl)benzonitrile



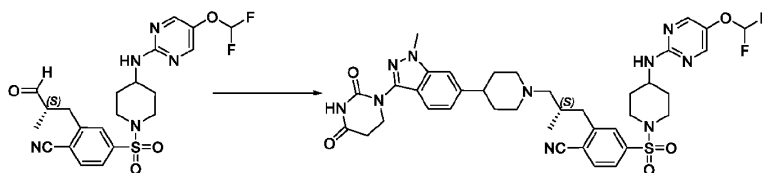
- To a stirred mixture of (S)-4-((4-aminopiperidin-1-yl)sulfonyl)-2-(3-hydroxy-2-methylpropyl)benzonitrile hydrochloride (500 mg, 1.48 mmol, 1 eq.) and DIEA (580 mg, 4.49 mmol, 3.03 eq.) in DMSO (5 mL) was added 2-chloro-5-(difluoromethoxy)pyrimidine (400 mg, 2.22 mmol, 1.50 eq.) at room temperature. The resulting mixture was stirred overnight at 100 °C under nitrogen atmosphere. The mixture was quenched by the addition of water. The resulting mixture was extracted with EtOAc. The combined organic layers were washed with water and brine, dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with EtOAc/PE (0-30%) to afford the title compound as an off-white solid.
- 20
- 25

Step 5: (S)-4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(2-methyl-3-oxopropyl)benzonitrile



To a stirred solution of (S)-4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-hydroxy-2-methylpropyl) benzonitrile (170 mg, 0.35 mmol, 1.0 eq.) and DIEA (274 mg, 2.12 mmol, 6.0 eq.) in DCM (2 mL) was added SO₃-pyridine (225 mg, 1.4 mmol, 4.0 eq.) in DMSO (2 mL) dropwise at -5~0 °C under nitrogen atmosphere. The resulting mixture was stirred for 10 min at 0 °C under nitrogen atmosphere. The mixture was quenched with water. The resulting mixture was extracted with EtOAc. The combined organic layers were washed with water and brine, dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with EtOAc/PE (0 - 30%) to afford the title compound as a light yellow oil.

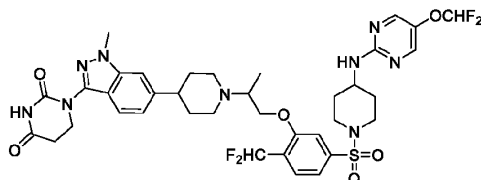
Step 6: (S)-4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-methylpropyl)benzonitrile



To a stirred mixture of 1-(1-methyl-6-(piperidin-4-yl)-1H-indazol-3-yl)dihydro-pyrimidine-2,4(1H,3H)-dione (76 mg, 0.23 mmol, 1.0 eq.) and TEA (47 mg, 0.46 mmol, 2.0 eq.) in DMAc (1 mL) was added (S)-4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(2-methyl-3-oxopropyl)benzonitrile (110 mg, 0.23 mmol, 1 eq.) in portions at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 30 min at room temperature. To the above mixture was added NaBH(OAc)₃ (110 mg, 0.52 mmol, 2.25 eq.) in portions at 0-5 °C under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 0-5 °C. The reaction was quenched with water. The resulting mixture was extracted with EtOAc. The combined organic layers were washed with water and brine, dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by prep-HPLC to afford the title compound as an off-white solid. MS (ES, m/z): [M+H]⁺ = 791.2.

Example 29

Synthesis of 1-(6-(1-(1-(5-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)-sulfonyl)-2-(difluoromethyl)phenoxy)propan-2-yl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl) dihydropyrimidine-2,4(1H,3H)-dione



5

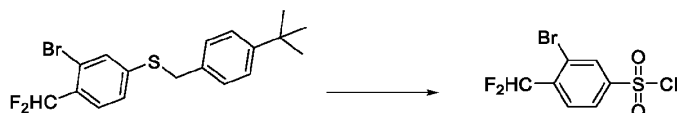
Step 1: (3-Bromo-4-(difluoromethyl)phenyl)(4-(tert-butyl)benzyl)sulfane



To a stirred solution of (4-(tert-butyl)phenyl)methanethiol (3.00 g, 16.67 mmol, 1.50 eq.) in DMF (50.0 mL) was added NaH (60 % in oil, 667 mg, 16.67 mmol, 1.50 eq.) in portion at 0 °C. The mixture was stirred at rt under nitrogen for 1 h. 2-Bromo-1-(difluoromethyl)-4-fluorobenzene (2.50 g, 11.11 mmol, 1.00 eq.) was added to this mixture and the resulting mixture was stirred at rt for 2 h. The reaction mixture was quenched with water and extracted with EA. The combined organic layers were washed with brine and the organic layer was dried over anhydrous Na₂SO₄. After filtration and concentration, the residue was purified by column chromatography on silica gel (PE) to give the title compound as a yellow oil.

15

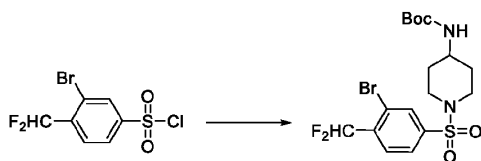
Step 2: 3-Bromo-4-(difluoromethyl)benzenesulfonyl chloride



To a stirred solution of (3-bromo-4-(difluoromethyl)phenyl)(4-(tert-butyl)benzyl)sulfane (4.20 g, 10.90 mmol, 1.00 eq.) in ACN (40.0 mL) was added AcOH (3.27 g, 54.50 mmol, 5.00 eq.), H₂O (981 mg, 54.50 mmol, 5.00 eq.) and NCS (7.27 g, 54.50 mmol, 5.00 eq.) in portions at 0 °C. The reaction mixture was stirred at rt for 2 h, quenched with water and extracted with EA. The combined organic layers were washed with brine and the organic layer was dried over anhydrous Na₂SO₄, concentrated to give the crude title compound as a white solid.

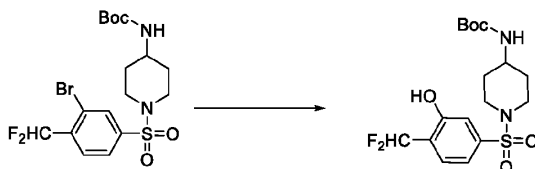
20

Step 3: tert-Butyl (1-((3-bromo-4-(difluoromethyl)phenyl)sulfonyl)piperidin-4-yl)carbamate



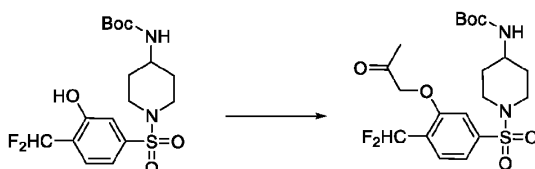
To a stirred mixture of tert-butyl piperidin-4-ylcarbamate (2.20 g, 10.98 mmol, 1.00 eq.) in DCM (20.0 mL) were added TEA (3.33 g, 32.94 mmol, 3.00 eq.), and then a solution of 3-bromo-4-(difluoromethyl)benzenesulfonyl chloride (3.35 g, 10.98 mmol, 1.00 eq.) in DCM (30.0 mL) slowly at 0 °C. The reaction mixture was stirred at rt for 3 h, quenched with water and extracted with DCM. The combined organic layers were washed with brine and the organic layer was dried over anhydrous Na₂SO₄. After filtration and concentration, the residue was purified by column chromatography on silica gel (PE:EA = 6:1) to give the title compound as a yellow solid.

Step 4: tert-Butyl (1-((4-(difluoromethyl)-3-hydroxyphenyl)sulfonyl)piperidin-4-yl)carbamate



To a stirred mixture of tert-butyl (1-((3-bromo-4-(difluoromethyl)phenyl)sulfonyl)-piperidin-4-yl)carbamate (2.34 g, 4.99 mmol, 1.00 eq.) in dioxane (30.0 mL) were added 4,4,4',4',5,5',5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.90 g, 7.49 mmol, 1.50 eq.), Pd(dppf)Cl₂ (366 mg, 0.50 mmol, 0.10 eq.) and KOAc (1.47 g, 14.97 mmol, 3.00 eq.). The reaction mixture was stirred at 100 °C under N₂ for 3 h, cooled and then H₂O₂ (30%, 1.70 g, 15.0 mmol, 3.00 eq.) was added at rt. After stirring for 2 h, the reaction mixture was quenched with water and extracted with EA. The combined organic layers were washed with brine and the organic layer was dried over anhydrous Na₂SO₄. The residue was purified by column chromatography on silica gel (DCM : MeOH = 120:1) to give the title compound as a yellow oil.

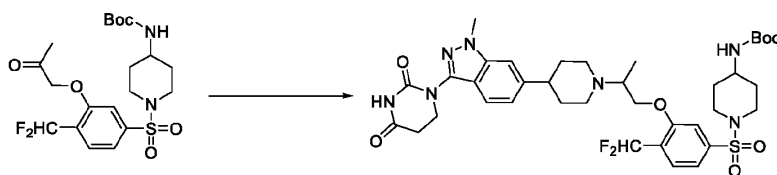
Step 5: tert-Butyl (1-((4-(difluoromethyl)-3-(2-oxopropoxy)phenyl)sulfonyl)piperidin-4-yl)carbamate



To a stirred solution of tert-butyl (1-((4-(difluoromethyl)-3-hydroxyphenyl)sulfonyl)-piperidin-4-yl)carbamate (244 mg, 0.60 mmol, 1.00 eq.) in DMF (5.0 mL) were added 1-

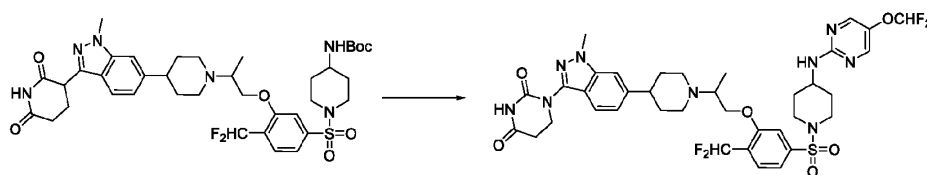
chloropropan-2-one (110 mg, 1.20 mmol, 2.00 eq.), K_2CO_3 (248 mg, 1.80 mmol, 3.00 eq.) and KI (100 mg, 0.60 mmol, 1.00 eq.). The reaction mixture was stirred at 80 °C under N_2 for 5 h, cooled, quenched with water and extracted with EA. The combined organic layers were washed with brine and the organic layer was dried over anhydrous Na_2SO_4 . After filtration and concentration, the residue was purified by column chromatography on silica gel (DCM : MeOH = 30:1) to give the title compound as a yellow solid.

Step 6: tert-Butyl (1-((4-(difluoromethyl)-3-(2-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)propoxy)phenyl)sulfonyl)piperidin-4-yl)carbamate



To a stirred solution of tert-butyl (1-((4-(difluoromethyl)-3-(2-oxopropoxy)phenyl)sulfonyl)piperidin-4-yl)carbamate (50 mg, 0.10 mmol, 1.00 eq.) in MeOH/THF (1.0 mL/1.0 mL) were added 1-(1-methyl-6-(piperidin-4-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (33 mg, 0.10 mmol, 1.00 eq.), trimethoxymethane (11 mg, 0.10 mmol, 1.00 eq.), TEA (20 mg, 0.20 mmol, 2.00 eq.) and $NaBH_3CN$ (13 mg, 0.20 mmol, 2.00 eq.). The reaction mixture was stirred at 70 °C under N_2 for 16 h, cooled, quenched with water and extracted with EA. The combined organic layers were washed with brine and the organic layer was dried over anhydrous Na_2SO_4 . After filtration and concentration, the residue was purified by column chromatography on silica gel (DCM : MeOH = 20:1) to give the title compound as a yellow solid.

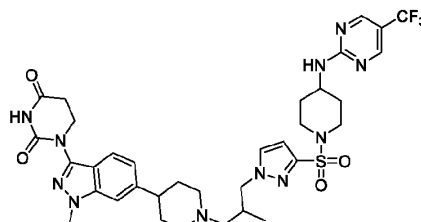
Step 7: 1-(6-(1-(1-(5-((4-((5-(Difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(difluoromethyl)phenoxy)propan-2-yl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione



The title compound was synthesized by proceeding analogously as described in Example 23, Steps 4-5, to afford the title compounds as a yellow solid. MS (ES, m/z): $[M+1]^+ = 818.1$.

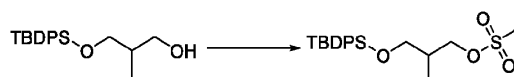
Example 30

Synthesis of 1-(1-methyl-6-(1-(2-methyl-3-(3-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)-piperidin-1-yl)sulfonyl)-1H-pyrazol-1-yl)propyl)piperidin-4-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione



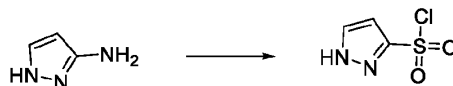
5

Step 1: 3-((tert-Butyldiphenylsilyl)oxy)-2-methylpropyl methanesulfonate



To a stirred solution of 3-((tert-butyldiphenylsilyl)oxy)-2-methylpropan-1-ol (8.10 g, 24.70 mmol, 1.00 eq.) in DCM (90.0 mL) were added TEA (5.00 g, 49.40 mmol, 2.00 eq.) and MsCl (4.22 g, 37.05 mmol, 1.50 eq.) at rt and the resulting mixture was stirred for 16 h. The reaction mixture was diluted with water and extracted with EA. The combined organic layers were washed with brine, and the organic layer was dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure and purified by column chromatography (PE: EA= 10: 1) to afford the title compound as a colorless oil.

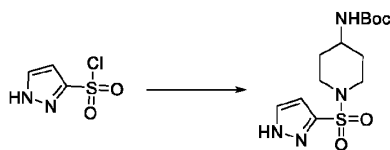
15 Step 3: 1H-Pyrazole-3-sulfonyl chloride



To a stirred solution of 1H-pyrazole-3-amine (1.00 g, 12.04 mmol, 1.00 eq.) in con. HCl (10.0 mL) was added a solution of NaNO₂ (2.49 g, 36.12 mmol, 3.00 eq.) in water (10.0 mL) at 0 °C under N₂ and the resulting mixture was stirred at 0 °C for 15 min, then to the mixture were added a solution of CuSO₄·5H₂O (300 mg, 1.20 mmol, 0.10 eq.) in con. HCl (2.0 mL) and then a solution of NaHSO₃ (12.53 g, 120.40 mmol, 10.00 eq.) in water (10.0 mL) at 0 °C. After stirring at 0 °C for 30 min, the reaction mixture was diluted with water and extracted with EA. The combined organic layers were washed with water, brine, and then dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated to afford the title compound as a brown oil.

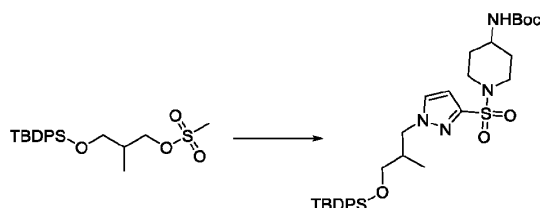
20

Step 4: tert-Butyl (1-((1H-pyrazol-3-yl)sulfonyl)piperidin-4-yl)carbamate



To a stirred solution of tert-butyl piperidin-4-ylcarbamate (1.14 g, 5.67 mmol, 1.50 eq.) and TEA (1.15 g, 11.34 mmol, 3.00 eq.) in DCM (5.0 ml) was added a solution of 1H-pyrazole-3-sulfonyl chloride (630 mg, 3.78 mmol, 1.00 eq.) in DCM (5.0 mL) at 0 °C, and the resulting mixture was stirred for 2 h. The reaction mixture was diluted with water and extracted with EA. The combined organic layers were washed with water, brine, and the organic layer was dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure and purified by *prep*-HPLC to afford the title compound as a white solid.

Step 5: tert-Butyl (1-((1-(3-((tert-butyldiphenylsilyl)oxy)-2-methylpropyl)-1H-pyrazol-3-yl)sulfonyl)piperidin-4-yl)carbamate



To a stirred solution of tert-butyl (1-((1H-pyrazol-3-yl)sulfonyl)piperidin-4-yl)carbamate (200 mg, 0.61 mmol, 1.00 eq.) in DMF (6.0 mL) were added 3-((tert-butyldiphenylsilyl)oxy)-2-methylpropyl methanesulfonate (246 mg, 0.61 mmol, 1.00 eq.) and Cs₂CO₃ (395 mg, 1.22 mmol, 2.00 eq.) at 50 °C, and the resulting mixture was stirred for 16 h. The reaction mixture was diluted with water and extracted with EA. The combined organic layers were washed with water, brine, and the organic layer was dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure and purified by column chromatography (PE: EA= 1: 1) to afford the title compound as a white solid.

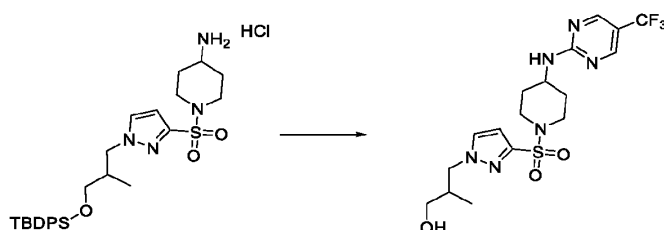
Step 6: 1-((1-(3-((tert-Butyldiphenylsilyl)oxy)-2-methylpropyl)-1H-pyrazol-3-yl)sulfonyl)-piperidin-4-amine hydrochloride



To a stirred solution of tert-butyl (1-((1-(3-((tert-butyldiphenylsilyl)oxy)-2-methylpropyl)-1H-pyrazol-3-yl)sulfonyl)piperidin-4-yl)carbamate (130 mg, 0.20 mmol, 1.00 eq.) in EA (2.0 mL)

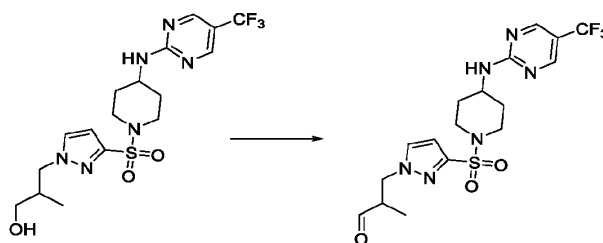
was added EA/HCl (2.0 mL) at 40 °C, and the resulting mixture was stirred for 2 h. The reaction mixture was concentrated under reduced pressure to afford the title compound (117 mg, crude) as a white solid.

Step 7: 2-Methyl-3-(3-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-1H-pyrazol-1-yl)propan-1-ol



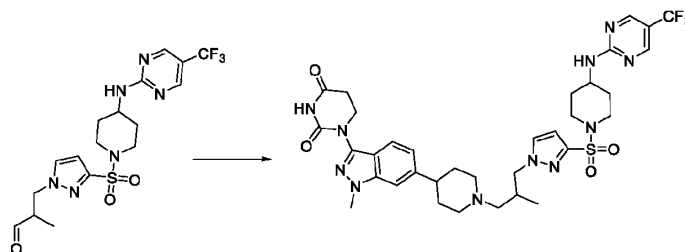
To a stirred solution of 1-((1-(3-((tert-butylidiphenylsilyl)oxy)-2-methylpropyl)-1H-pyrazol-3-yl)sulfonyl)piperidin-4-amine hydrochloride (60 mg, 0.10 mmol, 1.00 eq.) in DMSO (2.0 mL) were added 2-chloro-5-(trifluoromethyl)pyrimidine (36 mg, 0.20 mol, 2.00 eq.), DIEA (65 mg, 0.50 mmol, 5.00 eq.) and CsF (76 mg, 0.50 mmol, 5.00 eq.) at 50 °C, and the resulting mixture was stirred for 16 h. The reaction mixture was diluted with water and extracted with EA. The combined organic layers were washed with water, brine, and the organic layer was dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure and purified by prep-TLC (DCM: MeOH= 20 : 1) to afford the title compound as a white solid.

Step 8: 2-Methyl-3-(3-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-1H-pyrazol-1-yl)propanal



To a stirred solution of 2-methyl-3-(3-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-1H-pyrazol-1-yl)propan-1-ol (40 mg, 0.090 mmol, 1.00 eq.) in DCM (2.0 mL) was added Dess-Martin periodinane (57 mg, 0.13 mmol, 1.44 eq.) at rt, and the resulting mixture was stirred for 2 h. The reaction mixture was purified by column chromatography (DCM: MeOH= 10: 1) to afford the title compound as a white solid.

Step 9: 1-(1-Methyl-6-(1-(2-methyl-3-(3-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-1H-pyrazol-1-yl)propyl)piperidin-4-yl)-1H-indazol-3-yl) dihydropyrimidine-2,4(1H,3H)-dione



- 5 To a stirred solution of 1-(1-methyl-6-(piperidin-4-yl)-1H-indazol-3-yl) dihydropyrimidine-2,4(1H,3H)-dione (35 mg, 0.11 mmol, 1.22 eq.) in DMA (2.0 mL) were added 2-methyl-3-(3-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-1H-pyrazol-1-yl)propanal (40 mg, 0.090 mmol, 1.00 eq.), TEA (27 mg, 0.27 mmol, 3.00 eq.) and NaBH(OAc)₃ (46 mg, 0.22 mmol, 2.44 eq.) at rt, and the resulting mixture was stirred for 3 h. The reaction mixture was diluted with
- 10 water and extracted with EA. The combined organic layers were washed with water, brine, and the organic layer was dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure and the residue was purified by column chromatography (DCM: MeOH= 15: 1) to afford the title compound as a white solid. MS (ES, m/z): [M+1]⁺ = 758.1

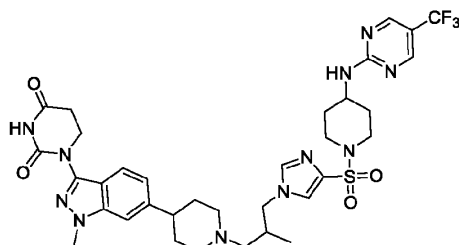
The following examples were synthesized by proceeding analogously as described in

- 15 Example 30.

Ex.#	Structure	Procedure
31		1H-pyrazole-3-sulfonyl chloride was replaced by 3-methyl-1H-pyrazole-4-sulfonyl chloride in Step 4.
32		1H-pyrazole-3-sulfonyl chloride was replaced by 5-methyl-1H-pyrazole-4-sulfonyl chloride in Step 4.

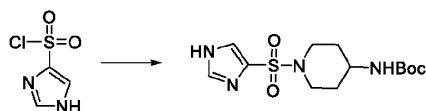
Example 33

Synthesis of 1-(1-methyl-6-(1-(2-methyl-3-(4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-1H-imidazol-1-yl)propyl)piperidin-4-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione



5

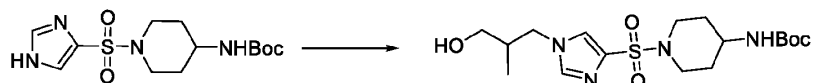
Step 1: tert-Butyl N-[1-(1H-imidazole-4-sulfonyl)piperidin-4-yl]carbamate



To a stirred mixture of 1H-imidazole-4-sulfonyl chloride (250 mg, 1.50 mmol, 1.00 eq.) in DCM (10.0 mL) were added tert-butyl N-(piperidin-4-yl)carbamate (300 mg, 1.50 mmol, 1.00 eq.) and TEA (455 mg, 4.50 mmol, 3.00 eq.), and the resulting mixture was stirred at 25 °C for 1 h under N₂. The reaction mixture was diluted with water and extracted with EA. The combined organic layers were washed with water, brine, dried over anhydrous Na₂SO₄, filtered and concentrated to give the title compound as a yellow solid.

Step 2: tert-Butyl N-{1-[1-(3-hydroxy-2-methylpropyl)imidazole-4-sulfonyl]piperidin-4-yl}carbamate

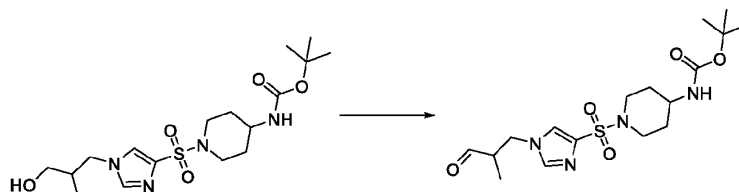
15



To a stirred mixture of 3-bromo-2-methylpropan-1-ol (344 mg, 2.25 mmol, 1.50 eq.) in MeCN (10.0 mL) were added tert-butyl N-[1-(1H-imidazole-4-sulfonyl)piperidin-4-yl]carbamate (495 mg, 1.50 mmol, 1.00 eq.), KI (498 mg, 3.00 mmol, 2.00 eq.) and K₂CO₃ (622 mg, 4.50 mmol, 3.00 eq.), and the resulting mixture was stirred at 70 °C for 2 days under N₂. The reaction mixture was diluted with water and extracted with EA. The combined organic layers were washed with water, brine, dried over anhydrous Na₂SO₄, and concentrated to give the title compound as a yellow solid.

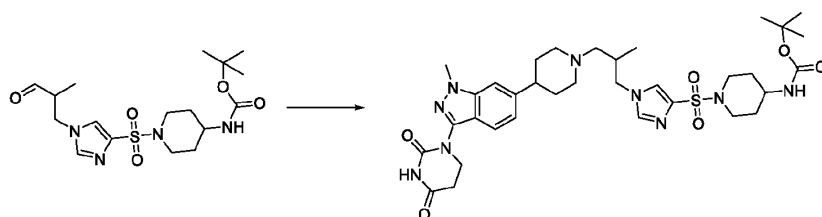
25

Step 3: tert-Butyl N-{1-[1-(2-methyl-3-oxopropyl)imidazole-4-sulfonyl]piperidin-4-yl} carbamate



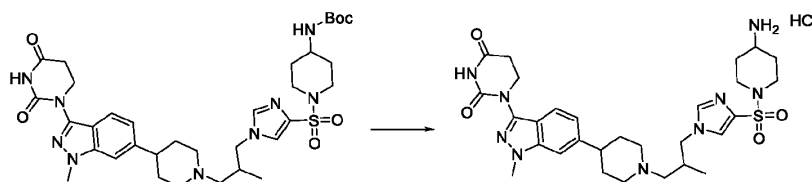
To a stirred mixture of tert-butyl N-{1-[1-(3-hydroxy-2-methylpropyl)imidazole-4-sulfonyl]piperidin-4-yl} carbamate (600 mg, 1.49 mmol, 1.00 eq.) in DCM (15.0 mL) was added Dess-Martin periodinane (948 mg, 2.34 mmol, 1.50 eq.), and the resulting mixture was stirred at 25 °C for 1 h. The reaction mixture was diluted with water and extracted with EA. The combined organic layers were washed with water, brine, dried over anhydrous Na₂SO₄, and concentrated to give the title compound as a yellow oil.

Step 4: tert-Butyl N-(1-{1-[2-({4-[3-(2,4-dioxo-1,3-diazinan-1-yl)-1-methylindazol-6-yl]piperidin-1-yl}methyl)propyl]imidazole-4-sulfonyl}piperidin-4-yl)carbamate



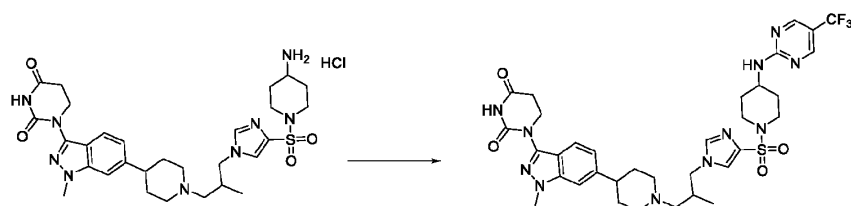
To a stirred mixture of 1-[1-methyl-6-(piperidin-4-yl)indazol-3-yl]-1,3-diazinane-2,4-dione (1226 mg, 3.75 mmol, 2.50 eq.) in DCM (10.0 mL) were added tert-butyl N-{1-[1-(2-methyl-3-oxopropyl)imidazole-4-sulfonyl]piperidin-4-yl} carbamate (600 mg, 1.50 mmol, 1.00 eq.), TEA (455 mg, 4.49 mmol, 3.00 eq.) and NaBH(OAc)₃ (794 mg, 3.75 mmol, 2.50 eq.), and the resulting mixture was stirred at 40 °C for 3 h. The reaction mixture was diluted with water and extracted with EA. The combined organic layers were washed with water, brine, dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by flash column chromatography (EA:PE=0~100%) to give the title compound as a yellow solid.

Step 5: 1-(6-(1-(3-(4-((4-Aminopiperidin-1-yl)sulfonyl)-1H-imidazol-1-yl)-2-methylpropyl)-piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione hydrogen chloride



A mixture of tert-butyl (1-((1-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-methylpropyl)-1H-imidazol-4-yl)sulfonyl)piperidin-4-yl)carbamate (230 mg, 0.32 mmol, 1.00 eq.) in EA/HCl (5.0 mL) was stirred at 40 °C for 2 h. The reaction mixture was concentrated to give the title compound as an off-white solid.

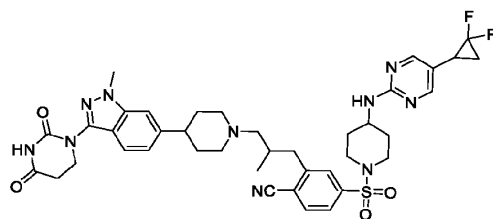
- 5 Step 6: 1-(1-Methyl-6-(1-(2-methyl-3-(4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-1H-imidazol-1-yl)propyl)piperidin-4-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione



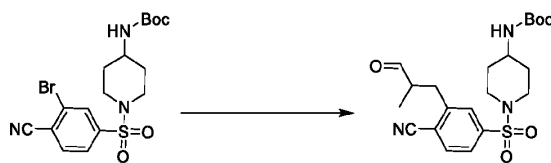
- To a stirred mixture of 2-chloro-5-(trifluoromethyl)pyrimidine (28 mg, 0.154 mmol, 1.00 eq) in DMSO (3.0 mL) were added 1-(6-(1-(3-(4-((4-aminopiperidin-1-yl)sulfonyl)-1H-imidazol-1-yl)-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione hydrogen chloride (100 mg, 0.154 mmol, 1.00 eq.), CsF (117 mg, 0.77 mmol, 5.00 eq.) and DIEA (99 mg, 0.77 mmol, 5.00 eq.), and the resulting mixture was stirred at 50 °C for 12 h. The reaction mixture was diluted with water and extracted with EA. The combined organic layers were washed with water, brine, dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by flash column chromatography (DCM:MeOH=0~100%) to give the title compound as a white solid. MS (ES, m/z): [M+1]⁺ = 758.3.

Example 34

- Synthesis of 4-((4-((5-(2,2-difluorocyclopropyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-methylpropyl)benzonitrile

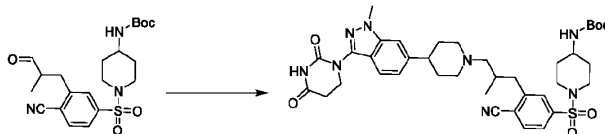


Step 1: tert-Butyl (1-((4-cyano-3-(2-methyl-3-oxopropyl)phenyl)sulfonyl)piperidin-4-yl)-carbamate



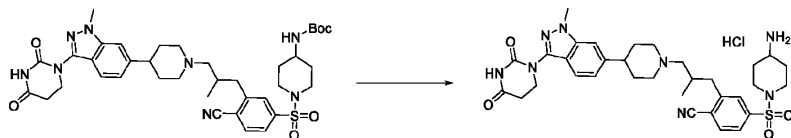
To a stirred solution of tert-butyl (1-((3-bromo-4-cyanophenyl)sulfonyl)piperidin-4-yl)-carbamate (600 mg, 1.35 mmol, 1.00 eq.) in DMF (6.0 mL) were added 1-hydroxypropan-2-one (588 mg, 8.10 mmol, 6.00 eq.), Pd₂(dba)₃ (27 mg, 0.029 mmol, 0.021 eq.), 2-(di-tert-butylphosphaneyl)-1-phenyl-1H-indole (27 mg, 0.080 mmol, 0.059 eq.) and N-cyclohexyl-N-methylcyclohexanamine (291 mg, 1.49 mmol, 1.10 eq.), and the resulting mixture was stirred for 7 h at 100 °C under N₂. The reaction mixture was cooled, diluted with water and extracted with EA. The combined organic layers were washed with water, brine, and the organic layer was dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with (DCM:MeOH= 120:1), to afford the title compound as a yellow oil.

Step 2: tert-Butyl (1-((4-cyano-3-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-methylpropyl)phenyl)sulfonyl)piperidin-4-yl)-carbamate



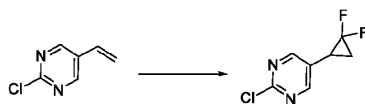
To a stirred solution of 1-[1-methyl-6-(piperidin-4-yl)indazol-3-yl]-1,3-diazinane-2,4-dione hydrochloride (546 mg, 1.50 mmol, 1.00 eq.) in DMA (10.0 mL) were added TEA (455 mg, 4.50 mmol, 3.00 eq.), tert-butyl (1-((4-cyano-3-(2-methyl-3-oxopropyl)phenyl)sulfonyl)piperidin-4-yl)-carbamate (980 mg, 2.25 mmol, 1.50 eq.) and sodium triacetoxyborohydride (769 mg, 3.63 mmol, 2.42 eq.) at 0 °C. The reaction mixture was stirred at 0 °C to 25 °C under nitrogen for 4 h. The reaction mixture was quenched with water and extracted with EA. The combined organic layers were washed with brine and the organic layer was dried over anhydrous Na₂SO₄. The residue was purified by silica gel column chromatography (DCM:MeOH = 50 : 1) to give the title compound as a yellow solid.

Step 3: 4-((4-Aminopiperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-methylpropyl)benzonitrile hydrogen chloride



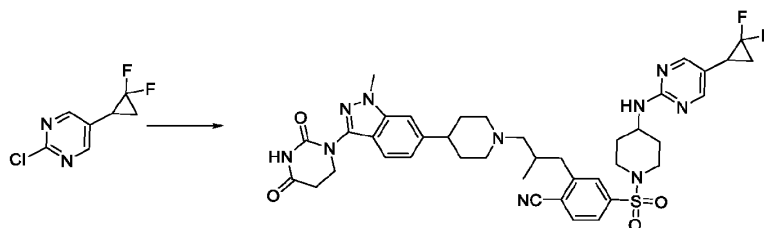
To a stirred mixture of tert-butyl (1-((4-cyano-3-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-methylpropyl)phenyl)sulfonyl)piperidin-4-yl)carbamate (100 mg, 0.13 mmol, 1.00 eq.) in EA (1.0 mL) was added EA/HCl (1.0 mL), and the resulting mixture was stirred at rt for 2 h. The reaction mixture was concentrated to give the title compound as a white solid.

Step 4: tert-Butyl 2-chloro-5-(2,2-difluorocyclopropyl)pyrimidine.



To a stirred solution of 2-chloro-5-vinylpyrimidine (100 mg, 0.71 mmol, 1.00 eq.) in toluene (2.0 mL) were added (bromodifluoromethyl)trimethylsilane (432 mg, 2.13 mmol, 3.00 eq.) and TBAB (14 mg, 0.043 mmol, 0.061 eq.), and the resulting mixture was stirred at 110 °C for 2 h. The reaction mixture was cooled, diluted with water and extracted with EA. The combined organic layers were washed with brine, and the organic layer was dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure and purified by column chromatography (PE : EA= 10 : 1) to afford the title compound as a white solid.

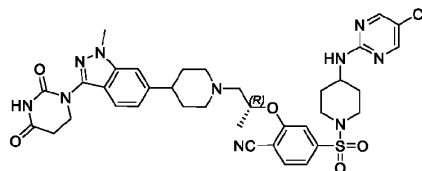
Step 5: 4-((4-((5-(2,2-Difluorocyclopropyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-methylpropyl)benzonitrile



To a stirred solution of 4-((4-aminopiperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-methylpropyl)benzonitrile hydrogen chloride (61 mg, 0.089 mmol, 1.00 eq.) in DMSO (2.0 mL) were added tert-butyl 2-chloro-5-(2,2-difluorocyclopropyl)pyrimidine (51 mg, 0.27 mol, 3.00 eq.), DIEA (58 mg, 0.45 mmol, 5.00 eq.) and CsF (68 mg, 0.45 mmol, 5.00 eq.), and the resulting mixture was stirred at 50 °C for 16 h. The reaction mixture was diluted with water and extracted with EA. The combined organic layers were washed with water, brine, and the organic layer was dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure and purified by *prep*-TLC (DCM: MeOH= 15: 1) to afford the title compound as a white solid. MS (ES, m/z): [M+1]⁺ = 801.4.

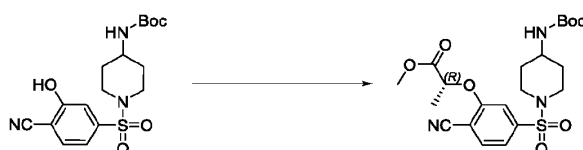
Example 35

Synthesis of (R)-4-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-((1-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)propan-2-yl)oxy)benzonitrile



5

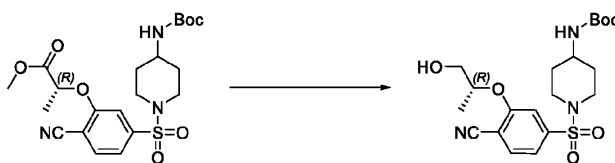
Step 1: Methyl (R)-2-(5-((4-((tert-butoxycarbonyl)amino)piperidin-1-yl)sulfonyl)-2-cyano-phenoxy)propanoate



To a stirred solution of tert-butyl (1-((4-cyano-3-hydroxyphenyl)sulfonyl)piperidin-4-yl)-carbamate (2.0 g, 5.24 mmol, 1.00 eq.), methyl (S)-2-hydroxypropanoate (0.55 g, 5.24 mmol, 1.00 eq.) and PPh₃ (2.06 g, 7.87 mmol, 1.50 eq.) in THF (20 mL) was added DIAD (1.27 g, 6.29 mmol, 1.20 eq.) dropwise at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 2 h at room temperature. The reaction mixture was diluted with EA and washed with water and brine, dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography to obtain the title compound as a light yellow solid.

15

Step 2: tert-Butyl (R)-1-((4-cyano-3-((1-hydroxypropan-2-yl)oxy)phenyl)sulfonyl)piperidin-4-yl)carbamate



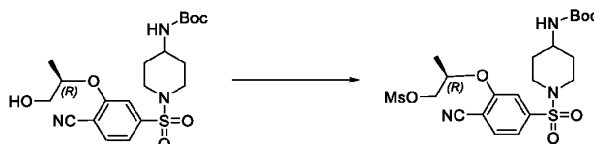
20

To a stirred solution of methyl (R)-2-(5-((4-((tert-butoxycarbonyl)amino)piperidin-1-yl)sulfonyl)-2-cyano-phenoxy)propanoate (660 mg, 1.41 mmol, 1.00 eq.) in MeOH (6.6 mL) was added NaBH₄ (160 mg, 4.24 mmol, 3.00 eq.) in portions at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 1 h at room temperature under nitrogen atmosphere. The reaction mixture was quenched with sat. NH₄Cl (aq.) at room temperature. The resulting mixture was extracted with EA. The combined organic layers were washed with water and brine, dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by

25

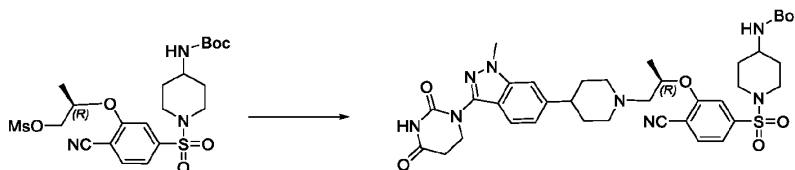
silica gel column chromatography, eluted with EA/PE (0-70%), to afford the title compound as a white solid.

Step 3: (R)-2-(5-((4-((tert-butoxycarbonyl)amino)piperidin-1-yl)sulfonyl)-2-cyanophenoxy)propyl methanesulfonate



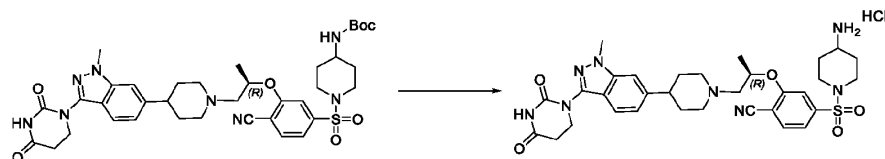
To a stirred solution of tert-butyl (R)-1-((4-cyano-3-((1-hydroxypropan-2-yl)oxy)-phenyl)sulfonyl)piperidin-4-yl)carbamate (500 mg, 1.14 mmol, 1.00 eq.) and TEA (345 mg, 3.41 mmol, 3.00 eq.) in DCM (5 mL) was added MsCl (170 mg, 1.48 mmol, 1.30 eq.) in portions at 0 °C under nitrogen atmosphere. The resulting mixture was stirred at room temperature for 2 h. The reaction mixture was quenched with water at room temperature and extracted with DCM. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure to obtain the crude title compound as a brown solid.

Step 4: tert-Butyl (R)-1-((4-cyano-3-((1-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)propan-2-yl)oxy)phenyl)sulfonyl)piperidin-4-yl)carbamate



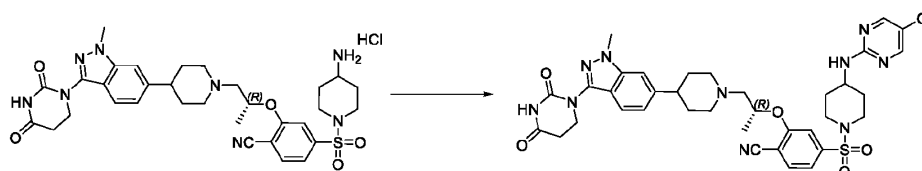
A mixture of (R)-2-(5-((4-((tert-butoxycarbonyl)amino)piperidin-1-yl)sulfonyl)-2-cyanophenoxy)propyl methanesulfonate (477 mg, 0.92 mmol, 1.00 eq.), 1-(1-methyl-6-(piperidin-4-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione hydrochloride (0.40 g, 1.11 mmol, 1.20 eq.), KI (0.31 g, 1.84 mmol, 2.00 eq.) and DIEA (0.60 g, 4.61 mmol, 5.00 eq.) in CH₃CN (5.0 mL) was stirred overnight at 80 °C. The reaction mixture was cooled, diluted with water and extracted with EA. The combined organic layers were washed with brine, and dried over anhydrous Na₂SO₄. The mixture was filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with THF/PE (0-50%), to afford the title compound as a white solid.

Step 5: (R)-4-((4-aminopiperidin-1-yl)sulfonyl)-2-((1-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)propan-2-yl)oxy)benzonitrile hydrogen chloride



To a stirred solution of tert-butyl (R)-1-((4-cyano-3-((1-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)propan-2-yl)oxy)phenyl)sulfonyl)piperidin-4-yl)carbamate (270 mg, 0.36 mmol, 1.00 eq.) in DCM (2.0 mL) was added 4.0 M HCl in dioxane (1.0 mL) dropwise at room temperature. After stirring for 3 h, the resulting mixture was concentrated to afford the title compound.

Step 6: (R)-4-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-((1-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)propan-2-yl)oxy)benzonitrile



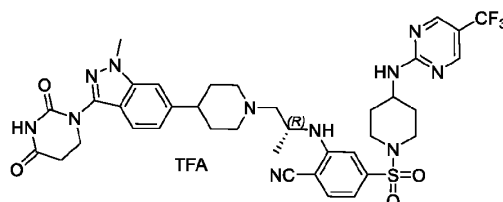
A mixture of ((R)-4-((4-aminopiperidin-1-yl)sulfonyl)-2-((1-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)propan-2-yl)oxy)-benzonitrile hydrochloride (100 mg, 0.154 mmol, 1.00 eq.), 2,5-dichloropyrimidine (0.03 g, 0.231 mmol, 1.50 eq.), CsF (0.05 g, 0.308 mmol, 2.00 eq.) and DIEA (0.06 g, 0.462 mmol, 3.00 eq.) in DMSO (1.0 mL) was stirred for 16 h at 80 °C. The resulting mixture was cooled, filtered and the filter cake was washed with DMSO. The filtrate was concentrated and the residue was purified by prep-HPLC to afford the title compound as a white solid. MS (ES, m/z): $[M+H]^+ = 761.4$.

The following compounds were synthesized by proceeding analogously as described in Example 35.

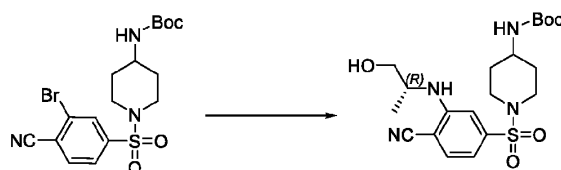
Ex.#	Structure	Procedure
36		2,5-dichloropyrimidine was replaced by 2-chloro-5-(trifluoromethyl)-pyrimidine in Step 6.

Example 37

Synthesis of (R)-2-((1-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)-piperidin-1-yl)propan-2-yl)amino)-4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzonitrile trifluoroacetate

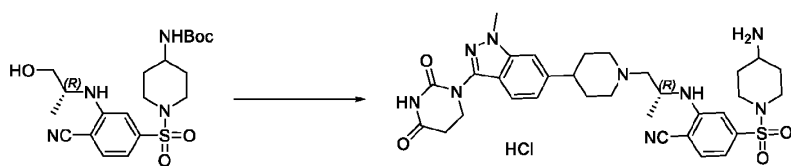


- 5 Step 1: tert-Butyl (R)-1-((4-cyano-3-((1-hydroxypropan-2-yl)amino)phenyl)sulfonyl)piperidin-4-yl)carbamate



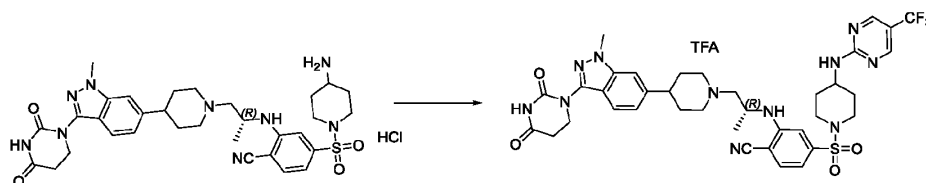
- A solution of tert-butyl 1-((3-bromo-4-cyanophenyl)sulfonyl)piperidin-4-yl)carbamate (5.0 g, 11.25 mmol, 1.00 eq.), (2R)-2-aminopropan-1-ol (1.27 g, 16.91 mmol, 1.50 eq.), XantPhos (1.30 g, 2.25 mmol, 0.20 eq.), Pd₂(dba)₃ (1.03 g, 1.125 mmol, 0.10 eq.) and Cs₂CO₃ (11.0 g, 33.76 mmol, 3.00 eq.) in 1, 4-dioxane (50 mL) was stirred at 100 °C for 3 h under nitrogen atmosphere. The reaction mixture was cooled, diluted with water and extracted with EA. The combined organic layers were washed with water and brine, dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with EA/PE (0-50%), to afford the title compound as a yellow solid.

Step 2: (R)-4-((4-aminopiperidin-1-yl)sulfonyl)-2-((1-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)propan-2-yl)amino)benzonitrile hydrochloride



- The title compound was synthesized by proceeding analogously as described in Example 35, Steps 3-5.

Step 3: (R)-2-((1-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)-piperidin-1-yl)propan-2-yl)amino)-4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzonitrile trifluoroacetate



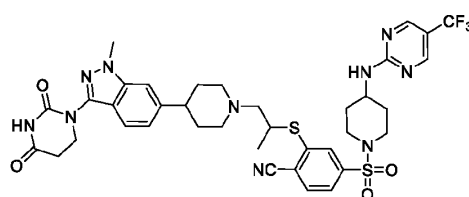
To a stirred solution of (R)-4-((4-aminopiperidin-1-yl)sulfonyl)-2-((1-(4-(3-(2,4-dioxo-
tetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)propan-2-yl)amino)-
benzonitrile hydrochloride (100 mg, 0.15 mmol, 1 equiv) and DIEA (113 mg, 0.88 mmol, 6 equiv)
5 and CsF (44 mg, 0.29 mmol, 2 equiv) in DMSO (1 mL) were added 2-chloro-5-(trifluoromethyl)-
pyrimidine (40 mg, 0.22 mmol, 1.5 equiv) in portions at room temperature under nitrogen
atmosphere. The resulting mixture was stirred at 80 °C for an additional 16 h. The crude product was
purified by prep-HPLC to afford the title compound. MS (ES, m/z): [M+H]⁺ = 794.4.

The following examples were synthesized by proceeding analogously as described in
10 Example 37.

Ex.#	Structure	Procedure
38		2-chloro-5-(trifluoromethyl)pyrimidine was replaced by 2,5-dichloropyrimidine in Step 3.

Example 39

Synthesis of 2-((1-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)-
piperidin-1-yl)propan-2-yl)thio)-4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-
15 yl)sulfonyl)benzonitrile



Step 1: Methyl 2-((5-((4-((tert-butoxycarbonyl)amino)piperidin-1-yl)sulfonyl)-2-cyanophenyl)-
thio)propanoate



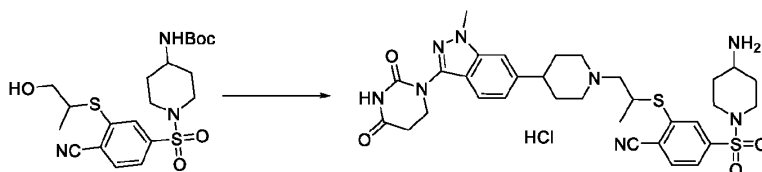
A solution of tert-butyl (1-((3-bromo-4-cyanophenyl)sulfonyl)piperidin-4-yl)carbamate (5.0 g, 11.25 mmol, 1.00 eq.), methyl 2-sulfanylpropanoate (1.49 g, 12.37 mmol, 1.10 eq.), $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ (1.16 g, 1.125 mmol, 0.10 eq.), XantPhos (0.65 g, 1.125 mmol, 0.10 eq.) and DIEA (4.36 g, 33.76 mmol, 3.00 eq.) in dioxane (50 mL) was stirred for 4 h at 100 °C under nitrogen atmosphere. The reaction mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with EA/PE (0-40%), to afford the title compound as a yellow solid.

Step 2: tert-Butyl (1-((4-cyano-3-((1-hydroxypropan-2-yl)thio)phenyl)sulfonyl)piperidin-4-yl)carbamate



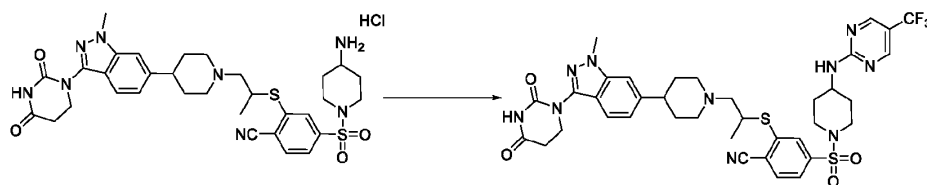
To a stirred mixture of methyl 2-((5-((4-((tert-butoxycarbonyl)amino)piperidin-1-yl)sulfonyl)-2-cyanophenyl)thio)propanoate (3.6 g, 7.44 mmol, 1.00 eq.) in THF (10 mL) and MeOH (10 mL) were added NaBH_4 (1.4 g, 37.01 mmol, 4.97 eq.) and CaCl_2 (2.05 g, 18.47 mmol, 2.48 eq.) at 0 °C under nitrogen atmosphere. The resulting mixture was stirred at room temperature for 4 h under nitrogen atmosphere. The reaction mixture was quenched with sat. NH_4Cl (aq.) at 0 °C and extracted with EA. The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with EA/PE (0-50%), to afford the title compound as a light yellow solid.

Step 3: 4-((4-Aminopiperidin-1-yl)sulfonyl)-2-((1-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)propan-2-yl)thio)benzonitrile hydrochloride



The title compound was synthesized by proceeding analogously as described in Example 35, Steps 3-5.

Step 4: 2-((1-(4-(3-(2,4-Dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)propan-2-yl)thio)-4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzonitrile



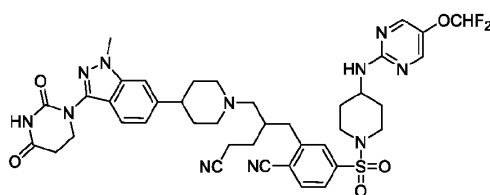
To a stirred solution of 4-((4-aminopiperidin-1-yl)sulfonyl)-2-((1-(4-(3-(2,4-dioxo-
tetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)propan-2-yl)thio)-
benzonitrile (150 mg, 0.214 mmol, 1 equiv) and DIEA (165 mg, 1.284 mmol, 6 equiv) and CsF (65
5 mg, 0.428 mmol, 2 equiv) in DMSO (1.5 mL) were added 2-chloro-5-(trifluoromethyl)-pyrimidine
(77 mg, 0.428 mmol, 2 equiv) in portions at room temperature under nitrogen atmosphere. The
resulting mixture was stirred at 80°C for additional 16 h. The mixture was concentrated and the
residue was purified by prep-HPLC to afford the title compound. MS (ES, m/z): $[M+H]^+ = 811.3$.

The following examples were synthesized by proceeding analogously as described in
10 Example 39.

Ex.#	Structure	Procedure
40		2-chloro-5-(trifluoromethyl)-pyrimidine was replaced by 2,5-dichloropyrimidine in Step 4.

Example 41

Synthesis of 2-(4-cyano-2-((4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-
6-yl)piperidin-1-yl)methyl)butyl)-4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-
15 yl)sulfonyl)benzonitrile



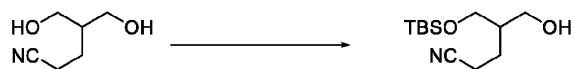
Step 1: 5-Hydroxy-4-(hydroxymethyl)pentanenitrile



To a stirred solution of diethyl 2-(2-cyanoethyl)propanedioate (4.26 g, 20.00 mmol, 1.00 eq.)
20 in anhydrous methanol (100 mL) at 0 °C was added NaBH₄ (3.8 g, 100.45 mmol, 5.00 eq.) in
portions. This resulting mixture was stirred at 25 °C for 16 h. The reaction mixture was quenched

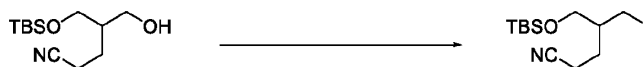
with 6 M aqueous hydrogen chloride and then concentrated under reduced pressure. The residue was filtered through a silica gel pad and the pad was washed with ethyl acetate/methanol=10/1. The filtrate was dried over anhydrous Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure to afford the crude title compound as a yellow oil.

5 Step 2: 5-((tert-Butyldimethylsilyl)oxy)-4-(hydroxymethyl)pentanenitrile



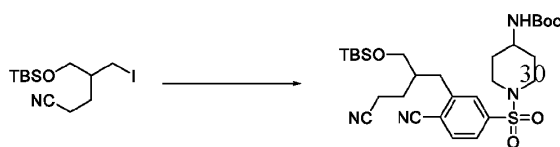
To a stirred solution of 5-hydroxy-4-(hydroxymethyl)pentanenitrile (517 mg, 4.00 mmol, 1.25 eq.) in anhydrous THF (8.0 mL) at 0 °C was added sodium hydride (60% in oil, 160 mg, 4.00 mmol, 1.25 eq.) in portions. The resulting mixture was stirred at 0 °C under argon atmosphere for 10 min, then a solution of TBSCl (480 mg, 3.20 mmol, 1.00 eq.) in anhydrous THF (5.0 mL) was added dropwise. The reaction mixture was stirred at rt for 16 h. The reaction mixture was quenched with saturated NH₄Cl solution, diluted with water, and extracted with EA. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with EA/PE (0-30%). to afford the title compound as a yellow oil.

Step 3: 5-((tert-Butyldimethylsilyl)oxy)-4-(iodomethyl)pentanenitrile



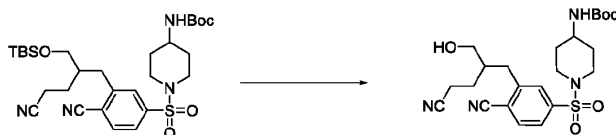
To a stirred solution of triphenylphosphine (1.22 g, 4.65 mmol, 1.30 eq.) and imidazole (341 mg, 5.01 mmol, 1.40 eq.) in anhydrous DCM (20 mL) was added iodine (1.09 mg, 4.29 mmol, 1.20 eq.) at 0 °C under argon atmosphere. After stirring at rt for 10 min, a solution of 5-((tert-butyldimethylsilyl)oxy)-4-(hydroxymethyl)pentanenitrile (870 mg, 3.57 mmol, 1.00 eq.) in anhydrous DCM (10 mL) was added. The resulting mixture was stirred at rt for 2 h, filtered, quenched with water and extracted with DCM. The combined organic layers were washed with brine, and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with EA/PE (0-10%), to afford the title compound as a yellow oil.

Step 4: tert-Butyl (1-((3-(2-(((tert-butyldimethylsilyl)oxy)methyl)-4-cyanobutyl)-4-cyanophenyl)-sulfonyl)piperidin-4-yl)carbamate



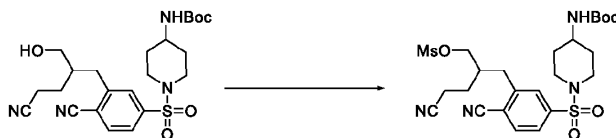
To a stirred solution of 5-((tert-butyldimethylsilyl)oxy)-4-(iodomethyl)pentanenitrile (348 mg, 0.99 mmol, 1.46 eq.) in anhydrous DMAc (5.0 mL) were added Mn (148 mg, 2.69 mmol, 3.96 eq.), tert-butyl N-[1-(3-bromo-4-cyano-phenyl)sulfonyl-4-piperidyl]carbamate (300 mg, 0.68 mmol, 1.00 eq.) and NiCl₂(DME) (30 mg, 0.14 mmol, 0.21 eq.), pyridine-2-carboxamide hydrochloride (21 mg, 0.14 mmol, 0.21 eq.) and NaI (25 mg, 0.17 mmol, 0.25 eq.). The resulting mixture was stirred at 45 °C under argon atmosphere in a sealed tube for 16 h, quenched with water, and extracted with EA. The combined organic layers were washed with brine, and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with EA/PE (0-25%), to afford the title compound as a white solid.

Step 5: tert-Butyl (1-((4-cyano-3-(4-cyano-2-(hydroxymethyl)butyl)phenyl)sulfonyl)piperidin-4-yl)carbamate



To a stirred solution of tert-butyl (1-((3-(2-(((tert-butyldimethylsilyl)oxy)methyl)-4-cyanobutyl)-4-cyanophenyl)sulfonyl)piperidin-4-yl)carbamate (120 mg, 0.20 mmol, 1.00 eq.) in anhydrous THF (10 mL) was added TABF (0.41 mL, 0.41 mmol, 2.05 eq.). After stirring at 25 °C for 16 h, the reaction mixture was concentrated under reduced pressure. The residue was diluted with water, and extracted with EA. The combined organic layers were washed with brine, and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with EA/PE (0-50%), to afford the title compound as a white solid.

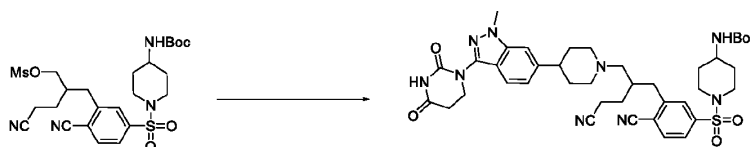
Step 6: 2-(5-((4-((tert-Butoxycarbonyl)amino)piperidin-1-yl)sulfonyl)-2-cyanobenzyl)-4-cyanobutyl methanesulfonate



To a stirred solution of tert-butyl (1-((4-cyano-3-(4-cyano-2-(hydroxymethyl)butyl)phenyl)sulfonyl)piperidin-4-yl)carbamate (70 mg, 0.15 mmol, 1.00 eq.) and TEA (65 mg, 0.59 mmol, 3.93 eq.) in anhydrous DCM (10.0 mL) at 0 °C was added methanesulfonyl anhydride (51 mg, 0.29 mmol, 1.93 eq.) in portions. After stirring at 25 °C for 2 h, the reaction mixture was quenched with water, and extracted with DCM. The combined organic layers were washed with

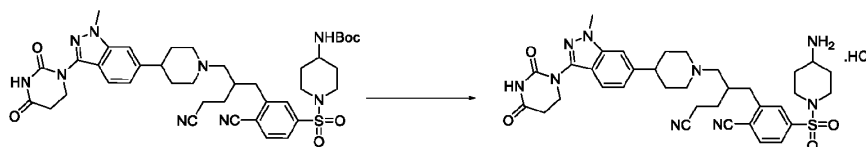
brine, and dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with MeOH/DCM (0-3%), to afford the title compound as a white solid.

Step 7: tert-Butyl (1-((4-cyano-3-(4-cyano-2-((4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)butyl)phenyl)sulfonyl)piperidin-4-yl)carbamate



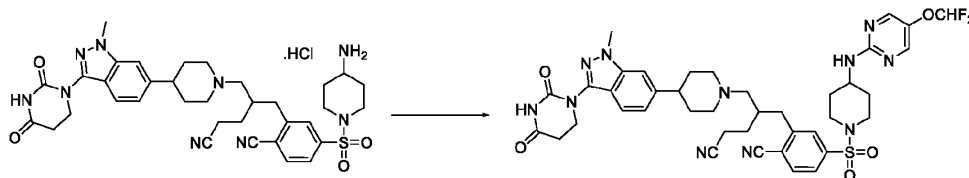
To a stirred solution of 1-[1-methyl-6-(4-piperidyl)indazol-3-yl]hexahydropyrimidine-2,4-dione hydrochloride (46 mg, 0.13 mmol, 1.00 eq.), 2-(5-((4-((tert-butoxycarbonyl) amino)piperidin-1-yl)sulfonyl)-2-cyanobenzyl)-4-cyanobutyl methanesulfonate (70 mg, 0.13 mmol, 1.00 eq.) and NaI (38 mg, 0.25 mmol, 1.92 eq.) in anhydrous MeCN (7.0 mL) was added DIPEA (56 mg, 0.50 mmol, 3.85 eq.). After stirring at 100 °C for 16 h, the reaction mixture was cooled, diluted with water, and extracted with EA. The combined organic layers were washed with brine, and dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with MeOH/DCM (0-3%), to afford the title compound as a white solid.

Step 8: 4-((4-Aminopiperidin-1-yl)sulfonyl)-2-(4-cyano-2-((4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)butyl)benzonitrile hydrochloride



To a solution of tert-butyl (1-((4-cyano-3-(4-cyano-2-((4-(3-(2,4-dioxotetrahydro-pyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)butyl)phenyl)sulfonyl)-piperidin-4-yl)carbamate (15 mg, 0.02 mmol) in anhydrous DCM (5 mL), was added 4 M HCl/1,4-dioxane (0.5 mL, 2 mmol) dropwise at 0 °C. This mixture was stirred at 25 °C for 2 h. The resulting mixture was concentrated under reduced pressure to afford the title compound as a yellow solid.

Step 9: 2-(4-Cyano-2-((4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)butyl)-4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzonitrile



- 5 To a solution of 2-chloro-5-(difluoromethoxy)pyrimidine (7 mg, 0.04 mmol), 4-((4-aminopiperidin-1-yl)sulfonyl)-2-(4-cyano-2-((4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)butyl)benzonitrile hydrochloride (13 mg, 0.018 mmol) and CsF (6 mg, 0.04 mmol) in DMSO (2 mL), was added DIPEA (10 mg, 0.07 mmol). The mixture was stirred at 90 °C for 6 h. The resulting mixture was purified by C18 column
- 10 chromatography, eluted with MeCN/water (0-50%, 0.05% NH₄HCO₃) to afford the title compound as an off-white solid. MS (ES, m/z): [M+H]⁺ = 830.5.

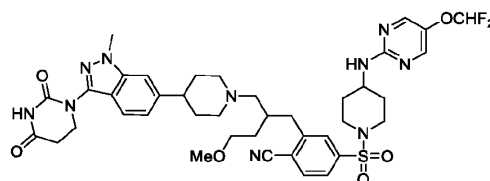
The following examples were synthesized by proceeding analogously as described in Example 41.

Ex.#	Structure	Procedure
42		2-chloro-5-(difluoromethoxy)-pyrimidine was replaced by 2-chloro-5-(trifluoromethyl)-pyrimidine in Step 9.

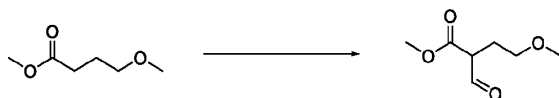
15

Example 43

Synthesis of 4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(2-((4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)-4-methoxybutyl)benzonitrile



Step 1: Methyl 2-formyl-4-methoxybutanoate



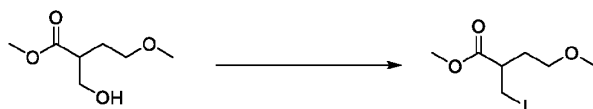
To a stirred solution of N-isopropylpropan-2-amine (2.43g, 24.01 mmol, 1.20 eq.) in anhydrous THF (40 mL) at -78 °C was added nBuLi (2.5 M, 9.6 mL, 24.00 mmol, 1.20 eq.). After stirring at -78 °C under argon atmosphere for 30 min, methyl 4-methoxybutanoate (2.64 g, 20.00 mmol, 1.00 eq.) was added. The resulting mixture was stirred at -78 °C for 1 h and ethyl formate (1.78 g, 24.00 mmol, 1.20 eq.) was added. After stirring at -78 °C for 3 h, the reaction mixture was warmed to rt slowly and then stirred at rt for 16 h. The reaction mixture was quenched with saturated NH₄Cl solution, and extracted with EA. The combined organic layers were washed with brine and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with EA/PE (0-40%), to afford the title compound as a yellow oil.

Step 2: Methyl 2-(hydroxymethyl)-4-methoxybutanoate



To a stirred solution of methyl 2-formyl-4-methoxybutanoate (800 mg, 4.99 mmol, 1.00 eq.) in anhydrous methanol (10 mL) and THF (10 mL) at 0 °C was added NaBH₄ (190 mg, 4.99 mmol, 1.00 eq.) in portions. After stirring at 0 °C for 1 h, the reaction mixture was quenched with water, and extracted with EA. The combined organic layers were washed with brine, and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with EA/PE (0-40%), to afford the title compound as a yellow oil.

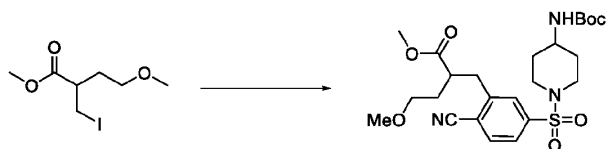
Step 3: Methyl 2-(iodomethyl)-4-methoxybutanoate



To a stirred solution of triphenylphosphine (776 mg, 2.96 mmol, 1.20 eq.) and imidazole (210 mg, 3.08 mmol, 1.25 eq.) in anhydrous DCM (20 mL) was added iodine (689 mg, 2.71 mmol, 1.10 eq.) at 0 °C under argon atmosphere. The resulting mixture was stirred at rt under argon atmosphere for 10 min and a solution of methyl 2-(hydroxymethyl)-4-methoxybutanoate (400 mg, 2.47 mmol, 1.00 eq.) in anhydrous DCM (10 mL) was added. After stirring at rt for 2 h, the reaction mixture was filtered, quenched with water and then extracted with DCM. The combined organic

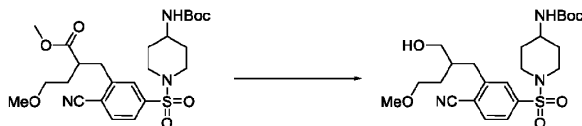
layers were washed with brine and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with EA/PE (0-5%), to afford the title compound as a yellow oil.

Step 4: Methyl 2-(5-((4-((tert-butoxycarbonyl)amino)piperidin-1-yl)sulfonyl)-2-cyanobenzyl)-4-methoxybutanoate



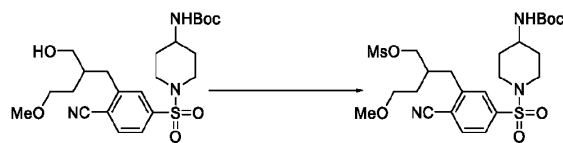
To a stirred solution of methyl 2-(iodomethyl)-4-methoxybutanoate (460 mg, 1.69 mmol, 1.64 eq.) in anhydrous DMAc (7.5 mL) were added Mn (227 mg, 4.12 mmol, 4.00 eq.), tert-butyl N-[1-(3-bromo-4-cyano-phenyl)sulfonyl-4-piperidyl]carbamate (458 mg, 1.03 mmol, 1.00 eq.), NiCl₂(DME) (45 mg, 0.21 mmol, 0.20 eq.), NaI (39 mg, 0.26 mmol, 0.25 eq.) and pyridine-2-carboxamide hydrochloride (33 mg, 0.21 mmol, 0.20 eq.) at 25 °C. The resulting mixture was stirred at 45 °C under argon atmosphere in a sealed tube for 16 h. The reaction mixture was quenched with water, and extracted with EA. The combined organic layers were washed with brine and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with EA/PE (0-20%), to afford the title compound as a white solid.

Step 5: tert-Butyl (1-((4-cyano-3-(2-(hydroxymethyl)-4-methoxybutyl)phenyl)sulfonyl)piperidin-4-yl)carbamate



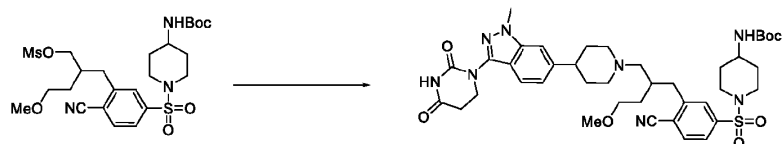
To a stirred solution of methyl 2-[[5-[[4-(tert-butoxycarbonylamino)-1-piperidyl]sulfonyl]-2-cyano-phenyl]methyl]-4-methoxy-butanoate (340 mg, 0.67 mmol, 1.00 eq.) and CaCl₂ (222 mg, 2.00 mmol, 3.00 eq.) in anhydrous ethanol (3.0 mL) and THF (9.0 mL) at 0 °C was added NaBH₄ (254 mg, 6.67 mmol, 10.00 eq.) was added in portions. After stirring at 25 °C for 16 h, the reaction mixture was quenched with water, and extracted with EA. The combined organic layers were washed with brine and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with MeOH/DCM (0-2%), to afford the title compound as a white solid.

Step 6: 2-(5-((4-((tert-Butoxycarbonyl)amino)piperidin-1-yl)sulfonyl)-2-cyanobenzyl)-4-methoxybutyl methanesulfonate



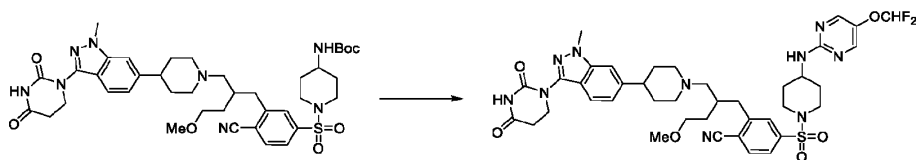
To a stirred solution of tert-butyl (1-((4-cyano-3-(2-(hydroxymethyl)-4-methoxybutyl)phenyl)sulfonyl)piperidin-4-yl)carbamate (240 mg, 0.50 mmol, 1.00 eq.) and TEA (166 mg, 1.49 mmol, 2.98 eq.) in anhydrous DCM (20 mL) at 0 °C was added methanesulfonic anhydride (139 mg, 0.80 mmol, 1.20 eq.). After stirring at 25 °C for 1 h, the reaction mixture was quenched with water, and extracted with DCM. The combined organic layers were washed with brine, and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure to afford the crude title compound as a white solid.

Step 7: tert-Butyl (1-((4-cyano-3-(2-((4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)-4-methoxybutyl)phenyl)sulfonyl)piperidin-4-yl)carbamate



To a stirred solution of 1-[1-methyl-6-(4-piperidyl)indazol-3-yl]hexahydropyrimidine-2,4-dione hydrochloride (130 mg, 0.36 mmol, 1.00 eq.), 2-(5-((4-((tert-butoxycarbonyl)amino)piperidin-1-yl)sulfonyl)-2-cyanobenzyl)-4-methoxybutyl methanesulfonate (250 mg, 0.45 mmol, 1.25 eq.) and NaI (134 mg, 0.89 mmol, 2.47 eq.) in anhydrous MeCN (20 mL) at 25 °C was added DIPEA (248 mg, 2.23 mmol, 6.19 eq.). After stirring at 90 °C for 24 h, the reaction mixture was cooled, diluted with water, and extracted with EA. The combined organic layers were washed with brine, and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with MeOH/DCM (0-3%), to afford the title compound as a yellow oil.

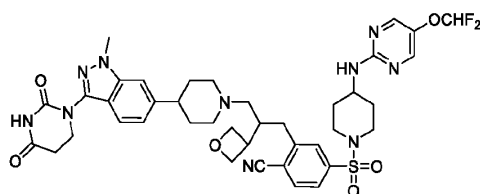
Step 8: 4-((4-((5-(Difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(2-((4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)-4-methoxybutyl)benzonitrile



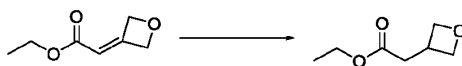
The title compound was synthesized by proceeding analogously as described in Example 23, Steps 4-5, to afford the title compound as a white solid. (ES, m/z): [M+H]⁺ = 835.5.

Example 44

Synthesis of 4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-(oxetan-3-yl)propyl)benzonitrile

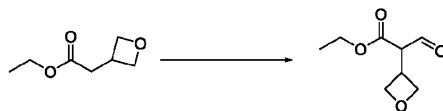


Step 1: Ethyl 2-(oxetan-3-yl)acetate



To a stirred solution of ethyl 2-(oxetan-3-ylidene)acetate (5 g, 35.17 mmol, 1.00 eq.) in anhydrous ethanol (150 mL) at 25 °C was added 10% Pd/C (500 mg). The resulting mixture was stirred at 25 °C under 1 atm hydrogen atmosphere for 24 h. The reaction mixture was filtered through celite, and the filtrate was concentrated under reduced pressure to afford the crude title compound as a yellow oil.

Step 2: Ethyl 2-(oxetan-3-yl)-3-oxopropanoate



To a stirred solution of N-isopropylpropan-2-amine (2.43 g, 24.01 mmol, 1.20 eq.) in anhydrous THF (80 mL) at -78 °C was added n-BuLi (2.5 M, 9.6 mL, 24.00 mmol, 1.20 eq.) dropwise. The resulting mixture was stirred at -78 °C under argon atmosphere for 30 min, a solution of ethyl 2-(oxetan-3-yl)acetate (2.88 g, 20.00 mmol, 1.00 eq.) in anhydrous THF (2.0 mL) then was added. After stirring at -78 °C for 1 h, ethyl formate (2.22 g, 30.00 mmol, 1.50 eq.) was added. This reaction mixture was stirred at -78 °C for 3 h, warmed to 25 °C slowly and then stirred at 25 °C for 16 h. The reaction mixture was quenched with EtOH and then adjusted to pH=6 with acetic acid. The resulting mixture was diluted with water and extracted with EA. The combined organic layers were washed with brine and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with EA/PE (0-40%), to afford the title compound as a yellow oil.

Step 3: Ethyl 3-hydroxy-2-(oxetan-3-yl)propanoate



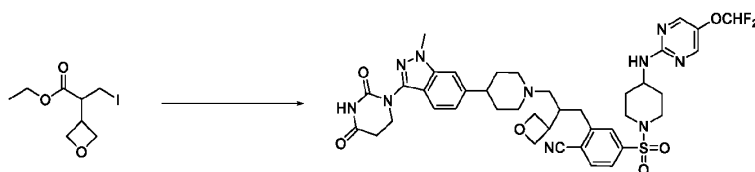
To a stirred solution of ethyl 2-(oxetan-3-yl)-3-oxopropanoate (260 mg, 1.51 mmol, 1.00 eq.) in anhydrous ethanol (5.0 mL) and THF (5.0 mL) at 0 °C was added NaBH₄ (115 mg, 3.02 mmol, 2.00 eq.) in portions. The reaction mixture was stirred at 0 °C for 1 h, and then concentrated under reduced pressure. The residue was treated with water and adjusted to pH=6 with acetic acid. The resulting mixture was extracted with EA. The combined organic layers were washed with brine and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure to afford the title compound as a yellow oil.

Step 4: Ethyl 2-(iodomethyl)-4-methoxybutanoate



To a stirred solution of triphenylphosphine (199 mg, 0.76 mmol) and imidazole (54 mg, 0.79 mmol, 1.14 eq.) in anhydrous DCM (20 mL) at 0 °C under argon atmosphere was added iodine (192 mg, 0.76 mmol, 1.10 eq.). The resulting mixture was stirred at rt under argon atmosphere for 10 min, a solution of ethyl 3-hydroxy-2-(oxetan-3-yl)propanoate (120 mg, 0.69 mmol, 1.00 eq.) in anhydrous DCM (10 mL) then was added. After stirring at rt for 2 h, the reaction mixture was filtered, quenched with water, and extracted with DCM. The combined organic layers were washed with brine and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with EA/PE (0-20%), to afford the title compound as a yellow oil.

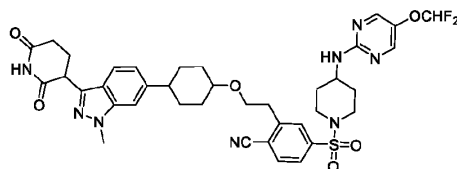
Step 5: 4-((4-((5-(Difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-(oxetan-3-yl)propyl)benzonitrile



The title compound was synthesized by proceeding analogously as described in Example 43, Steps 4-8 to afford the title compound as a yellow solid. MS (ES, m/z): [M+H]⁺ = 833.5.

Example 45

Synthesis of 4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-6-yl)cyclohexyl)oxy)ethyl)benzonitrile



Step 1: 4-((4-Aminopiperidin-1-yl)sulfonyl)-2-bromobenzonitrile hydrochloride



5

To a stirred solution of tert-butyl N-[1-(3-bromo-4-cyano-phenyl)sulfonyl-4-piperidyl]-carbamate (400 mg, 0.90 mmol, 1.00 eq.) in anhydrous DCM (10.0 mL) and methanol (5.0 mL) at 0 °C was added 4.0 M HCl/1,4-dioxane (5.0 mL, 20.0 mmol, 22.2 eq.) dropwise. The resulting mixture was stirred at 25 °C for 4 h. The reaction mixture was concentrated under reduced pressure to afford the crude title compound as a white solid.

10

Step 2: Benzyl (1-((3-bromo-4-cyanophenyl)sulfonyl)piperidin-4-yl)carbamate

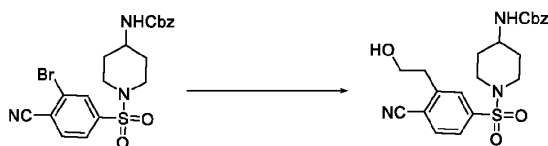


15

To a stirred mixture of 4-((4-aminopiperidin-1-yl)sulfonyl)-2-bromobenzonitrile (340 mg, 0.89 mmol, 1.00 eq.) and NaHCO₃ (662 mg, 7.88 mmol, 8.85 eq.) in THF (20 mL) and water (10 mL) at 0 °C was added CbzCl (0.18 mL, 1.26 mmol, 1.42 eq.) dropwise. The resulting mixture was stirred at 25 °C for 2 h. The reaction mixture was diluted with water and extracted with DCM. The combined organic layers were washed with brine and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with MeOH/DCM (0-3%), to afford the title compound as a white solid.

20

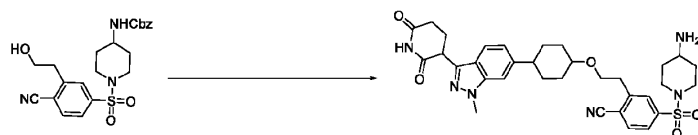
Step 3: Benzyl (1-((4-cyano-3-(2-hydroxyethyl)phenyl)sulfonyl)piperidin-4-yl)carbamate



To a stirred solution of benzyl (1-((3-bromo-4-cyanophenyl)sulfonyl)piperidin-4-yl)-carbamate (350 mg, 0.73 mmol, 1.00 eq.) in anhydrous DMAc (5.0 mL) at 25 °C were added Mn

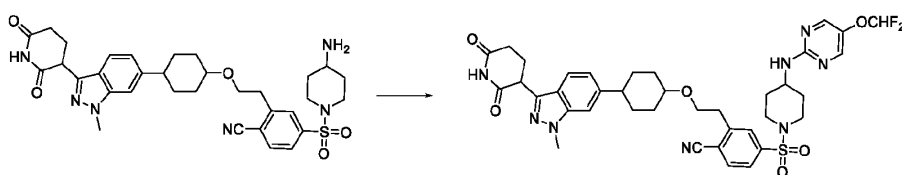
(161 mg, 2.93 mmol, 4.01 eq.), 2-iodoethanol (377 mg, 2.19 mmol, 3.00 eq.), $\text{NiCl}_2(\text{DME})$ (32 mg, 0.15 mmol, 0.21 eq.), pyridine-2-carboxamide hydrochloride (23 mg, 0.15 mmol, 0.21 eq.) and NaI (27 mg, 0.18 mmol, 0.25 eq.). The resulting mixture was stirred at 45 °C under argon atmosphere in a sealed tube for 16 h. The reaction mixture was treated with water, and extracted with EA. The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with EA/PE (0-40%), to afford the title compound as a white solid.

Step 4: 4-((4-Aminopiperidin-1-yl)sulfonyl)-2-(2-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-6-yl)cyclohexyl)oxy)ethyl)benzonitrile



To a stirred solution of 3-[1-methyl-6-(4-oxocyclohexyl)indazol-3-yl]piperidine-2,6-dione (105 mg, 0.31 mmol, 1.15 eq.), benzyl (1-((4-cyano-3-(2-hydroxyethyl)phenyl)sulfonyl) piperidin-4-yl)carbamate (120 mg, 0.27 mmol, 1.00 eq.) and phenylsilane (100 mg, 0.93 mmol, 3.44 eq.) in MeCN (10 mL) was added TMSOTf (26 mg, 0.12 mmol, 0.44 eq.) at 25 °C under argon atmosphere. The resulting mixture was stirred at 25 °C for 16 h. The reaction mixture was quenched with sat. aqueous sodium bicarbonate and extracted with EA. The combined organic layers were washed with brine, and dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with MeOH/DCM (0-5%), to afford the title compound as a yellow oil.

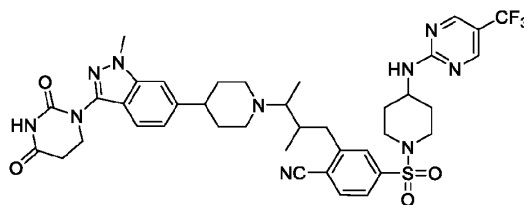
Step 5: 4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(2-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-6-yl)cyclohexyl)oxy)ethyl)benzonitrile



To a stirred solution of 4-((4-aminopiperidin-1-yl)sulfonyl)-2-(2-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-6-yl)cyclohexyl)oxy)ethyl)benzonitrile (50 mg, 0.056 mmol, 1.00 eq.), 2-chloro-5-(difluoromethoxy)pyrimidine (20 mg, 0.11 mmol, 1.96 eq.) and CsF (17 mg, 0.11 mmol, 1.96 eq.) in DMSO (2.0 mL) was added DIPEA (29 mg, 0.22 mmol, 3.93 eq.). The resulting mixture was stirred at 90 °C for 3 h. The reaction mixture was purified by C18 column chromatography, eluted with MeCN/water (0-50%, 0.05% NH_4HCO_3), to afford the title compound as a white solid. MS (ES, m/z): $[\text{M}+\text{H}]^+ = 777.5$.

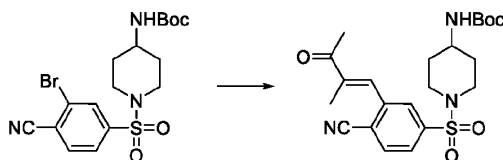
Example 46

Synthesis of 2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-methylbutyl)-4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzonitrile



5

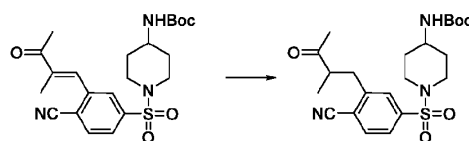
Step 1: tert-Butyl (E)-1-((4-cyano-3-(2-methyl-3-oxobut-1-en-1-yl)phenyl)sulfonyl)piperidin-4-yl)carbamate



3-Methylbut-3-en-2-one (2.84 g, 33.75 mmol, 3.00 eq.), tri-*o*-tolylphosphine (1.38 g, 4.53 mmol, 0.40 eq.), NaOAc (2.77 g, 33.75 mmol, 3.00 eq.) and Pd(OAc)₂ (1.26 g, 5.63 mmol, 0.50 eq.) were added successively to a solution of tert-butyl N-1-((3-bromo-4-cyanophenyl)sulfonyl)piperidin-4-yl)carbamate (5.00 g, 11.25 mmol, 1.00 eq.) in DMF (20.0 mL). The reaction mixture was stirred at 100 °C for 3 h under microwave irradiation. The mixture was filtered, diluted with water and extracted with EA. The combined organic layers were dried over Na₂SO₄, filtered, and concentrated. The residue was purified by silica column (PE/EA = 3/1) to give the title compound as a yellow solid.

15

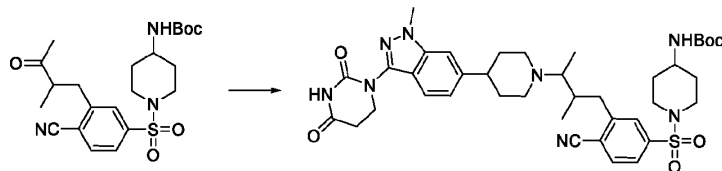
Step 2: tert-Butyl (1-((4-cyano-3-(2-methyl-3-oxobutyl)phenyl)sulfonyl)piperidin-4-yl)carbamate



20

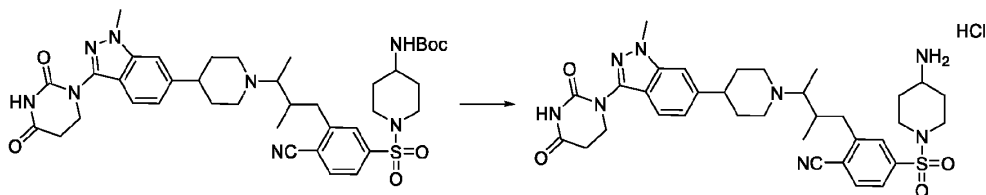
A mixture of tert-butyl N-1-((4-cyano-3-((1E)-2-methyl-3-oxobut-1-en-1-yl)benzene)sulfonyl)piperidin-4-yl)carbamate (1.40 g, 3.13 mmol, 1.00 eq.) and 10% Pd/C (400 mg) in MeOH (10.0 mL) was stirred at rt under H₂ (15 psi) for 12 h. The reaction mixture was filtrated and concentrated to give the title compound as a yellow solid.

Step 3: tert-Butyl (1-((4-cyano-3-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-methylbutyl)phenyl)sulfonyl)piperidin-4-yl)carbamate



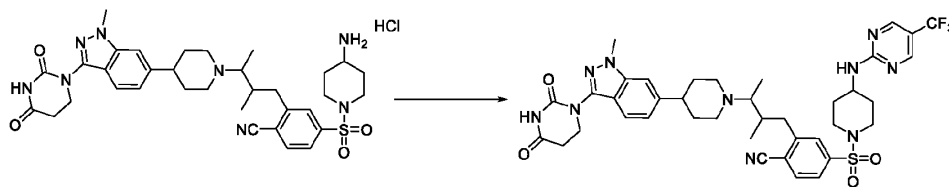
To a stirred solution of tert-butyl N-(1-([4-cyano-3-(2-methyl-3-oxobutyl)benzene]-sulfonyl)piperidin-4-yl)carbamate (1.40 g, 3.13 mmol, 1.00 eq.) in DMA (10.0 mL) were added 1-[1-methyl-6-(piperidin-4-yl)indazol-3-yl]-1,3-diazinane-2,4-dione (1.0 g, 3.05 mmol, 1.00 eq.), AcOH (0.3 mL) and NaBH₃CN (590 mg, 9.39 mmol, 3.00 eq.). The resulting mixture was stirred at 70 °C for 4 days. The reaction mixture was diluted with DCM, and organic layer was washed with brine and then concentrated. The residue was purified by silica flash column (DCM/MeOH = 20/1) to give the title compound as a yellow solid.

Step 4: 4-((4-Aminopiperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-methylbutyl)benzonitrile hydrochloride



A mixture of tert-butyl N-(1-([4-cyano-3-(3-{4-[3-(2,4-dioxo-1,3-diazinan-1-yl)-1-methylindazol-6-yl]piperidin-1-yl}-2-methylbutyl)benzene]sulfonyl)piperidin-4-yl)carbamate (130 mg, 0.17 mmol, 1.00 eq.) and EA/HCl (2.0 mL) in EA (2.0 mL) was stirred at rt for 3 h. The reaction mixture was concentrated to give the title compound as a yellow solid.

Step 5: 2-(3-(4-(3-(2,4-Dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-methylbutyl)-4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-benzonitrile



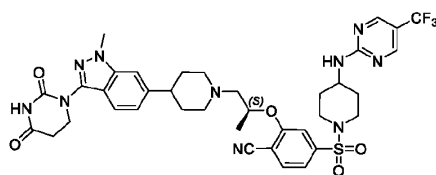
A mixture of 4-(4-aminopiperidine-1-sulfonyl)-2-(3-{4-[3-(2,4-dioxo-1,3-diazinan-1-yl)-1-methylindazol-6-yl]piperidin-1-yl}-2-methylbutyl)benzonitrile hydrochloride (30 mg, 0.043 mmol, 1.00 eq), 2,5-dichloropyrimidine (37 mg, 0.20 mmol, 4.65 eq.), CsF (30 mg, 0.20 mmol, 4.65 eq.)

and DIEA (26 mg, 0.20 mmol, 4.65 eq.) in DMSO (1.5 mL) was stirred at 65°C under N₂ overnight. The reaction mixture was cooled, diluted with DCM and washed with water. The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was purified by *prep*-HPLC to give the title compound as a white solid and separated into two diastereomers. MS (ES, m/z): [M+1]⁺ = 807.2.

5

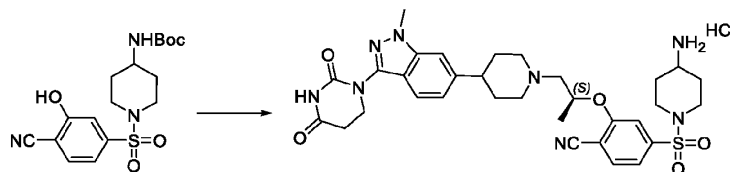
Example 47

Synthesis of (S)-2-((1-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)propan-2-yl)oxy)-4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzonitrile



10

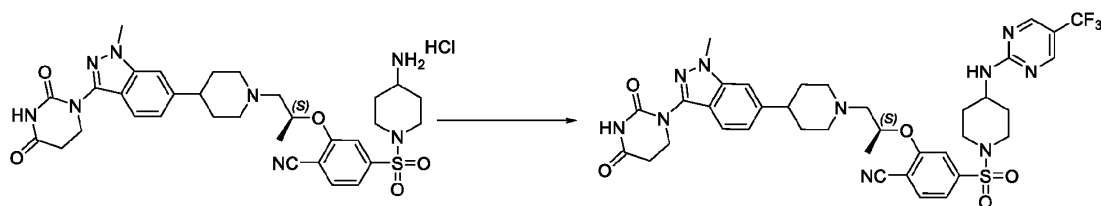
Step 1: (S)-4-((4-aminopiperidin-1-yl)sulfonyl)-2-((1-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)propan-2-yl)oxy)benzonitrile hydrochloride



The title compound was synthesized by proceeding analogously as described in Example 35,

Step 1-5, replacing methyl (S)-2-hydroxypropanoate with methyl (R)-2-hydroxypropanoate in Step 1.

Step 2: (S)-2-((1-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)propan-2-yl)oxy)-4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzonitrile

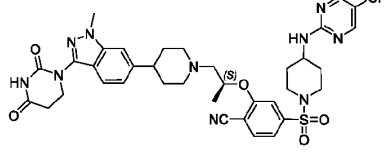


20

A mixture of (S)-4-((4-aminopiperidin-1-yl)sulfonyl)-2-((1-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)propan-2-yl)oxy)benzonitrile hydrochloride (40 mg, 0.06 mmol, 1 eq.), 2-chloro-5-(trifluoromethyl)pyrimidine (16

mg, 0.09 mmol, 1.5 eq.) and DIEA (23 mg, 0.18 mmol, 3 eq.) in DMSO (1 mL) was stirred at 80 °C for 16 h. The mixture was purified by prep-HPLC to afford the title compound as a white solid.

The following compounds were synthesized by proceeding analogously as described in Example 47.

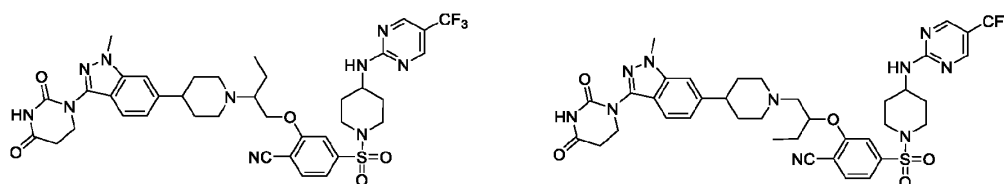
Ex.	Structure	procedure
48		2,5-dichloropyrimidine replaced 2-chloro-5-(trifluoromethyl)pyrimidine in Step 2.

5

Example 49

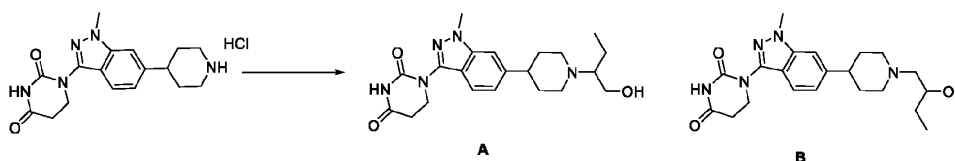
Synthesis of 2-(2-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)butoxy)-4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzonitrile & 2-((1-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)butan-2-yl)oxy)-4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzonitrile

10



Step 1: 1-(6-(1-(1-Hydroxybutan-2-yl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydro-pyrimidine-2,4(1H,3H)-dione (**A**) & 1-(6-(1-(2-hydroxybutyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydro-pyrimidine-2,4(1H,3H)-dione (**B**)

15

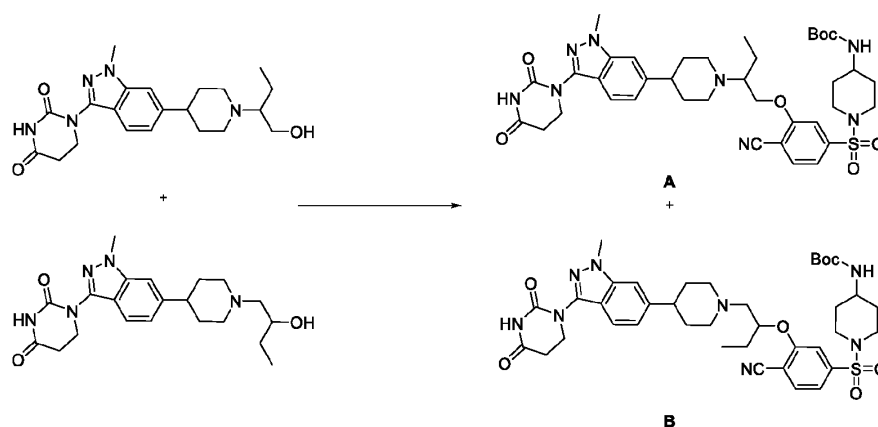


To a stirred solution of 1-(1-methyl-6-(piperidin-4-yl)-1H-indazol-3-yl)dihydro-pyrimidine-2,4(1H,3H)-dione hydrochloride (500 mg, 1.4 mmol, 1 eq.), AcOH (99 mg, 1.6 mmol, 1.2 eq.), MgSO₄ (827 mg, 6.9 mmol, 5 eq.) and 1-hydroxybutan-2-one (605 mg, 6.9 mmol, 5 equiv) in DMF (5 mL) was added NaBH(OAc)₃ (2.3 g, 11 mmol, 8 equiv) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred at room temperature for additional 16 h. The mixture was diluted with H₂O and basified to pH 10-11 with NH₃·H₂O. The

20

resulting mixture was extracted with DCM. The combined organic layers were washed with water and brine, dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / THF (0-100%) to afford the title compounds as a white solid.

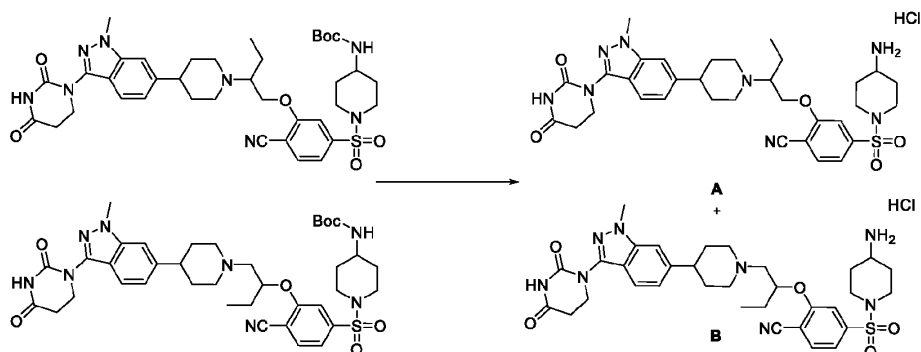
- 5 Step 2: tert-Butyl (1-((4-cyano-3-(2-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)butoxy)phenyl)sulfonyl)piperidin-4-yl)carbamate (**A**) & tert-butyl (1-((4-cyano-3-((1-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)butan-2-yl)oxy)phenyl)sulfonyl)piperidin-4-yl)carbamate (**B**)



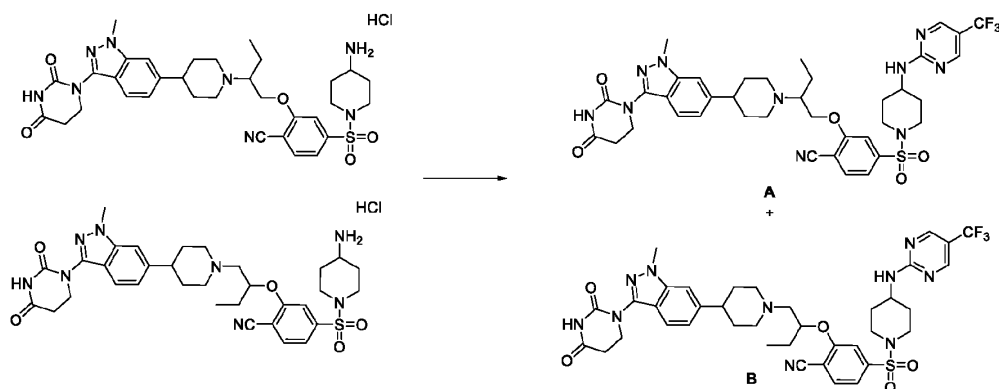
- 10 To a stirred solution of a mixture of tert-butyl (1-((4-cyano-3-(2-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)butoxy)phenyl)sulfonyl)piperidin-4-yl)carbamate & tert-butyl (1-((4-cyano-3-((1-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)butan-2-yl)oxy)phenyl)sulfonyl)piperidin-4-yl)carbamate (300 mg, 0.75 mmol, 1 eq.), tert-butyl (1-((4-cyano-3-hydroxyphenyl)sulfonyl)piperidin-4-yl)carbamate (286 mg, 0.75 mmol, 1 eq.) and PPh₃ (236.4 mg, 0.9 mmol, 1.2 eq.) in THF (3 mL) was added DIAD (304 mg, 1.5 mmol, 2 eq.) at room temperature under nitrogen atmosphere. The resulting mixture was stirred at room temperature for additional 1h. The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with EA/PE (0-100%) to afford the title compounds as a yellow solid.
- 20

Step 3: 4-((4-Aminopiperidin-1-yl)sulfonyl)-2-(2-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)butoxy)benzonitrile hydrochloride (**A**) & 4-((4-

aminopiperidin-1-yl)sulfonyl)-2-((1-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)butan-2-yl)oxy)benzonitrile hydrochloride (**B**)



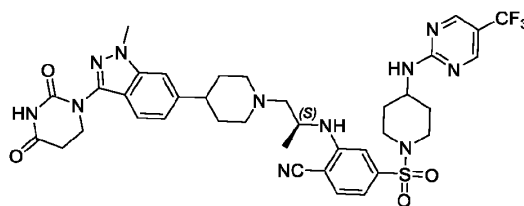
- To a stirred solution of a mixture of tert-butyl (1-((4-cyano-3-(2-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)butoxy)phenyl)sulfonyl)piperidin-4-yl)carbamate & tert-butyl (1-((4-cyano-3-((1-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)butan-2-yl)oxy)phenyl)sulfonyl)piperidin-4-yl)carbamate (420 mg, 0.551 mmol, 1 equiv) in DCM (1 mL) was added 4 M HCl in 1,4-dioxane (1 mL) dropwise at room temperature under nitrogen atmosphere. The resulting mixture was stirred at room temperature for additional 1h. The mixture was concentrated under vacuum to give the title compounds as a yellow solid.
- Step 4: 2-(2-(4-(3-(2,4-Dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)butoxy)-4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzonitrile (**A**) & 2-((1-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)butan-2-yl)oxy)-4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzonitrile (**B**)



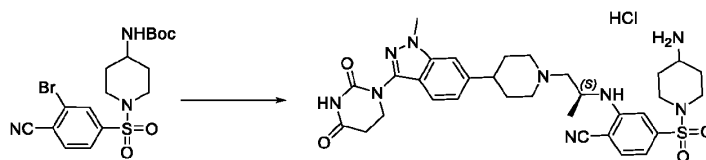
To a stirred solution of a mixture of 4-((4-aminopiperidin-1-yl)sulfonyl)-2-(2-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)butoxy)benzonitrile hydrochloride & 4-((4-aminopiperidin-1-yl)sulfonyl)-2-((1-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)butan-2-yl)oxy)benzonitrile hydrochloride (80 mg, 0.114 mmol, 1 eq.) and DIEA (88.7 mg, 0.7 mmol, 6 eq.) in DMSO (2 mL) was added 2-chloro-5-(trifluoromethyl)pyrimidine (32 mg, 0.2 mmol, 1.5 eq.) at room temperature under nitrogen atmosphere. The resulting mixture was stirred at room temperature for additional 16 h. The crude mixture was purified by prep-HPLC to afford the title compound A as a white solid. MS (ES, m/z): $[M+H]^+ = 809.4$. And afford the title compound B as a white solid. MS (ES, m/z): $[M+H]^+ = 809.4$.

Example 50

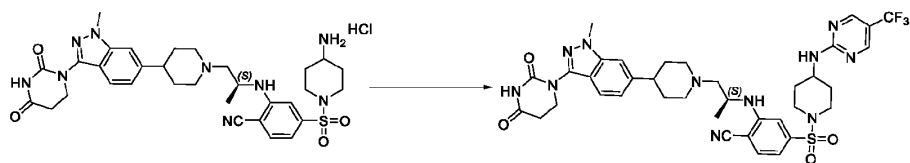
Synthesis of (S)-2-((1-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)propan-2-yl)amino)-4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzonitrile



Step 1: (S)-4-((4-aminopiperidin-1-yl)sulfonyl)-2-((1-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)propan-2-yl)amino)benzonitrile hydrochloride



The title compound was synthesized by proceeding analogously as described in Example 37, Step 1-2, replacing (2R)-2-aminopropan-1-ol with (2S)-2-aminopropan-1-ol in Step 1. Step 2: (S)-2-((1-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)propan-2-yl)amino)-4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzonitrile



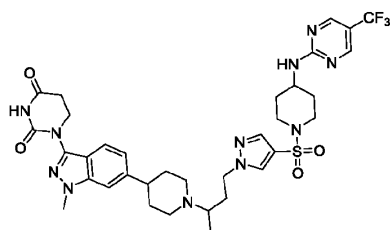
To a stirred solution of (S)-4-((4-aminopiperidin-1-yl)sulfonyl)-2-((1-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)propan-2-yl)amino)benzonitrile hydrochloride (100 mg, 0.15 mmol, 1 eq.) and DIEA (113 mg, 0.9 mmol, 6 eq.) in DMSO (1 mL) were added 2-chloro-5-(trifluoromethyl)pyrimidine (40 mg, 0.22 mmol, 1.5 eq.) at room temperature under nitrogen atmosphere. The resulting mixture was stirred at 80 °C for additional 16 h. The crude mixture was purified by prep-HPLC to afford the title compound as a white solid. MS (ES, m/z): [M+H]⁺ = 794.3.

The following compounds were synthesized by proceeding analogously as described in Example 50.

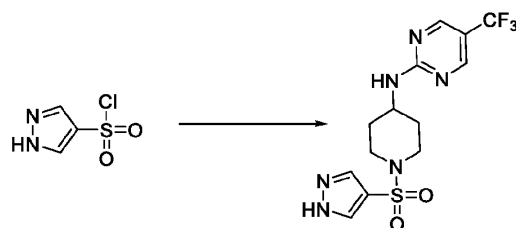
Ex.	Structure	procedure
51		2,5-dichloropyrimidine replaced 2-chloro-5-(trifluoromethyl)pyrimidine in Step 2.

Example 52

Synthesis of 1-(1-methyl-6-(1-(4-(4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-1H-pyrazol-1-yl)butan-2-yl)piperidin-4-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione

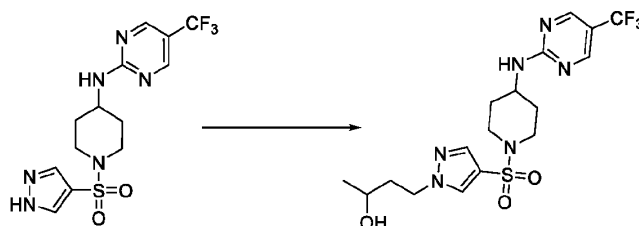


Step 1: N-(1-((1H-pyrazol-4-yl)sulfonyl)piperidin-4-yl)-5-(trifluoromethyl)pyrimidin-2-amine



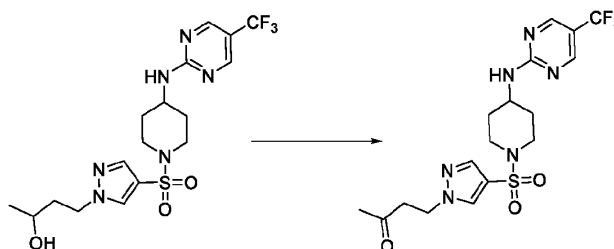
To a solution of N-(piperidin-4-yl)-5-(trifluoromethyl)pyrimidin-2-amine hydrochloride (424 mg, 1.50 mmol, 1.50 eq.) and TEA (303 mg, 3.00 mmol, 3.00 eq.) in DCM (10.0 mL) was added 1H-pyrazole-4-sulfonyl chloride (166 mg, 1.00 mmol, 1.00 eq.) in portion at 0 °C. The mixture was stirred at r.t. for 2 h. Then the mixture was quenched with water and extracted with DCM. The combined organic layers were washed with brine and the organic layer was dried over anhydrous Na₂SO₄. It was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (PE:EA = 5:1) to give the title compound as yellow solid.

Step 2: 4-(4-((4-((5-(Trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-1H-pyrazol-1-yl)butan-2-ol



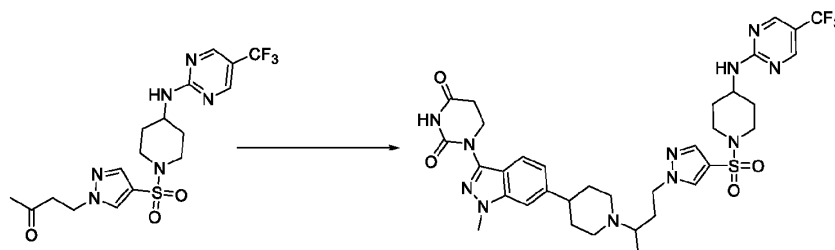
To a solution of N-(1-((1H-pyrazol-4-yl)sulfonyl)piperidin-4-yl)-5-(trifluoromethyl)pyrimidin-2-amine (200 mg, 0.53 mmol, 1.00 eq.) in DMF (5.0 mL) was added NaH (60 % in mineral oil, 64 mg, 1.60 mmol, 3.00 eq.) at 0 °C and stirred for 0.5 h. Then 4-bromobutan-2-ol (121 mg, 0.80 mmol, 1.5 eq.) was added to the mixture at 0 °C. The mixture was stirred at r.t for 2 h. Then the mixture was quenched with water and extracted with EA. The combined organic layers were washed with brine and the organic layer was dried over anhydrous Na₂SO₄. It was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (PE:EA = 3:1) to give the title compound as yellow solid.

Step 3: 4-(4-((4-((5-(Trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-1H-pyrazol-1-yl)butan-2-one



To a mixture of 4-(4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-1H-pyrazol-1-yl)butan-2-ol (200 mg, 0.45 mmol, 1.00 eq.) in DCM (10.0 mL) was added Dess-Martin periodinane (286 mg, 0.68 mmol, 1.50 eq.) at 0 °C. The mixture was stirred at 25 °C for 3 h. Then the mixture was quenched with water and extracted with DCM. The combined organic layers were washed with brine and the organic layer was dried over anhydrous Na₂SO₄. It was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (PE:EA = 5:1) to give the title compound as yellow solid.

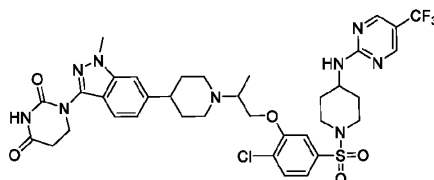
Step 4: 1-(1-Methyl-6-(1-(4-(4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-1H-pyrazol-1-yl)butan-2-yl)piperidin-4-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione



To a mixture of 4-(4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-1H-pyrazol-1-yl)butan-2-one (90 mg, 0.20 mmol, 1.00 eq.), 1-(1-methyl-6-(piperidin-4-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (198 mg, 0.61 mmol, 3.00 eq.) and AcOH (0.3 mL) in DMA (10.0 mL) was added NaBH₃CN (38 mg, 0.61 mmol, 3.00 eq.). The reaction mixture was stirred at 90 °C under N₂ for 16 h. Then the mixture was quenched with water and extracted with EA. The combined organic layers were washed with brine and the organic layer was dried over anhydrous Na₂SO₄. It was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by prep-TLC (DCM : MeOH = 20:1) to give the title compound as white solid. MS (ES, m/z): [M+1]⁺ = 758.1.

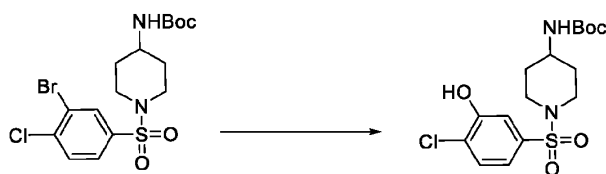
Example 53

Synthesis of 1-(6-(1-(1-(2-chloro-5-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenoxy)propan-2-yl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione



5

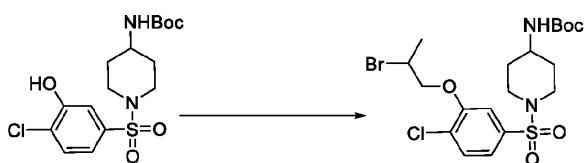
Step 1: tert-Butyl (1-((4-chloro-3-hydroxyphenyl)sulfonyl)piperidin-4-yl)carbamate



To a mixture of tert-butyl (1-((3-bromo-4-chlorophenyl)sulfonyl)piperidin-4-yl)carbamate (1.00 g, 2.21 mmol, 1.00 eq.), bis(pinacolato)diboron (842 mg, 3.32 mmol, 1.5 eq.) and KOAc (650 mg, 6.63 mmol, 3.00 eq.) in dioxane (20.0 mL) was added Pd(dppf)Cl₂ (161 mg, 0.22 mmol, 0.10 eq.). The mixture was stirred at 100 °C under N₂ for 3 h. To the mixture was added 30% H₂O₂ solution (225 mg, 6.63 mmol, 3.00 eq.) at 25 °C. The mixture was stirred at 25 °C for 0.5 h. Then the mixture was quenched with water and extracted with EA. The combined organic layers were washed with brine and dried over anhydrous Na₂SO₄. It was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (PE:EA = 5:1) to give the title compound as yellow solid.

15

Step 2: tert-Butyl (1-((3-(2-bromopropoxy)-4-chlorophenyl)sulfonyl)piperidin-4-yl)carbamate

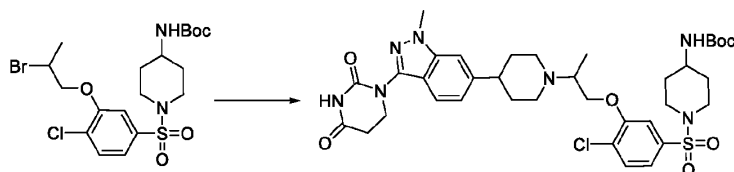


To a mixture of tert-butyl (1-((4-chloro-3-hydroxyphenyl)sulfonyl)piperidin-4-yl)carbamate (700 mg, 1.79 mmol, 1.00 eq.), 2-bromopropan-1-ol (741 mg, 5.37 mmol, 3.00 eq.) and PPh₃ (1.41 g, 5.37 mmol, 3.00 eq.) in THF (30.0 mL) was added DIAD (1.09 g, 5.37 mmol, 3.00 eq.) at 0 °C under N₂. The mixture was stirred at 25 °C under N₂ for 16 h. Then the mixture was quenched with water and extracted with EA. The combined organic layers were washed with brine and dried over anhydrous Na₂SO₄. It was filtered and the filtrate was concentrated under reduced pressure. The

20

residue was purified by column chromatography on silica gel (DCM : MeOH = 100:1) to give the title compound as yellow solid.

Step 3: tert-Butyl (1-((4-chloro-3-(2-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)propoxy)phenyl)sulfonyl)piperidin-4-yl)carbamate

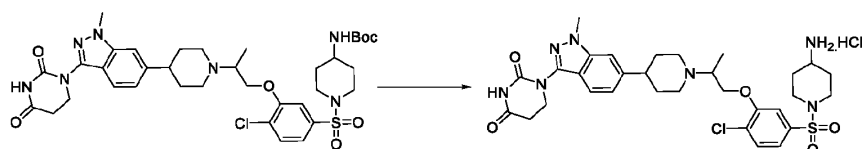


5

To a mixture of tert-butyl (1-((3-(2-bromopropoxy)-4-chlorophenyl)sulfonyl)piperidin-4-yl)carbamate (200 mg, 0.39 mmol, 1.00 eq.), 1-(1-methyl-6-(piperidin-4-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (128 mg, 0.39 mmol, 1.00 eq.), and KI (195 mg, 1.18 mmol, 3eq.) in ACN (10.0 mL) was added K₂CO₃ (163 mg, 1.18 mmol, 3.0 eq.). The mixture was stirred at 80 °C for 16 h. Then the mixture was quenched with water and extracted with EA. The combined organic layers were washed with brine and dried over anhydrous Na₂SO₄. It was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (DCM : MeOH = 30:1) to afford the title compound as yellow solid.

Step 4: 1-(6-(1-(1-(5-((4-Aminopiperidin-1-yl)sulfonyl)-2-chlorophenoxy)propan-2-yl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione hydrochloride

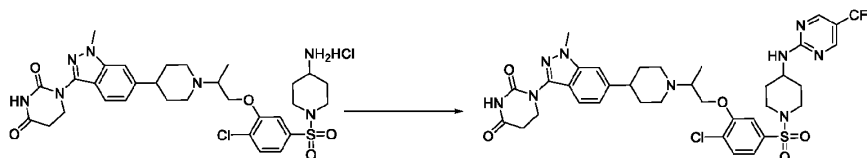
15



To a mixture of tert-butyl (1-((4-chloro-3-(2-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)propoxy)phenyl)sulfonyl)piperidin-4-yl)carbamate (20 mg, 0.03 mmol, 1.00 eq.) in EA (1.0 mL) was added 4 M HCl in EA (1.0 mL). The mixture was stirred at 25 °C for 3 h. Then the mixture was concentrated to afford the title compound as yellow solid.

20

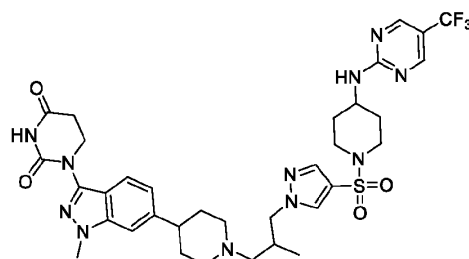
Step 5: 1-(6-(1-(1-(2-Chloro-5-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenoxy)propan-2-yl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione



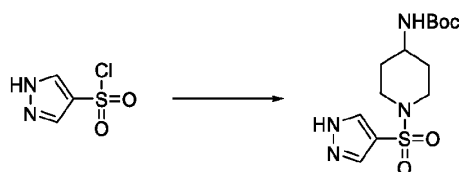
To a solution of 1-(6-(1-(1-(5-((4-aminopiperidin-1-yl)sulfonyl)-2-chlorophenoxy)propan-2-yl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione hydrochloride (20 mg, 0.03 mmol, 1.00 eq.) in DMSO (2.0 mL) was added 2-chloro-5-(trifluoromethyl)pyrimidine (17 mg, 0.09 mmol, 3.00 eq.), DIEA (19 mg, 0.15 mmol, 5.00 eq.) and CsF (14 mg, 0.15 mmol, 5.00 eq.). The mixture was stirred at 50 °C under N₂ for 16 h. Then the mixture was quenched with water and extracted with EA. The combined organic layers were washed with brine and the organic layer was dried over anhydrous Na₂SO₄. It was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by prep-HPLC (ACN in H₂O(0.1% FA)) to afford the title compound as white solid. MS (ES, m/z): [M+1]⁺ = 804.1.

Example 54

Synthesis of 1-(1-methyl-6-(1-(2-methyl-3-(4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-1H-pyrazol-1-yl)propyl)piperidin-4-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione

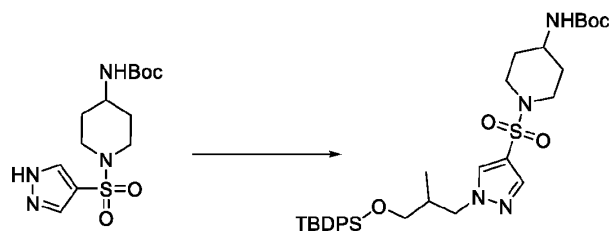


Step 1: tert-Butyl (1-((1H-pyrazol-4-yl)sulfonyl)piperidin-4-yl)carbamate



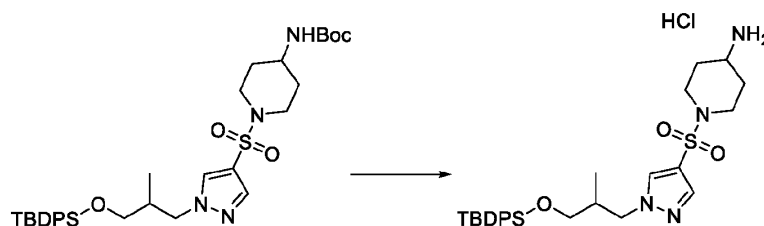
To a solution of tert-butyl piperidin-4-ylcarbamate (1.20 g, 5.99 mmol, 1.00 eq.) in DCM (40.0 mL) was added TEA (1.82 g, 17.97 mmol, 3.00 eq.) and 1H-pyrazole-4-sulfonyl chloride (998 mg, 5.99 mmol, 1.00 eq.) in DCM (20.0 mL) dropwise at 0 °C. The mixture was stirred at 25 °C under N₂ for 2 h. The mixture was poured into water and extracted with EA. The combined organic layers was dried over Na₂SO₄, and filtered. The filtrate was concentrated to give the title compound as white solid.

Step 2: tert-Butyl (1-((1-(3-((tert-butyldiphenylsilyl)oxy)-2-methylpropyl)-1H-pyrazol-4-yl)sulfonyl)piperidin-4-yl)carbamate



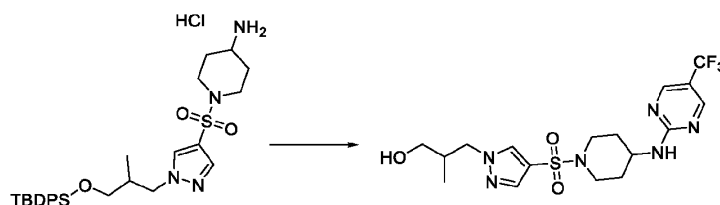
To a stirred solution of 3-((tert-butyldiphenylsilyl)oxy)-2-methylpropyl methanesulfonate (406 mg, 1.00 mmol, 1.00 eq.) in DMF (10.0 mL) was added Cs₂CO₃ (652 mg, 2.00 mmol, 2.00 eq.) and tert-butyl (1-((1H-pyrazol-4-yl)sulfonyl)piperidin-4-yl)carbamate (330 mg, 1.00 mmol, 1.00 eq.), the mixture was stirred at 50 °C for 16 h. The mixture was diluted with water and extracted with EA. The combined organic layers were washed with water, brine, and the organic layer was dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (PE:EA=3:1) to afford the title compound as white solid.

Step 3: 1-((1-(3-((tert-Butyldiphenylsilyl)oxy)-2-methylpropyl)-1H-pyrazol-4-yl)sulfonyl)-piperidin-4-amine hydrochloride



A mixture of tert-butyl (1-((1-(3-((tert-butyldiphenylsilyl)oxy)-2-methylpropyl)-1H-pyrazol-4-yl)sulfonyl)piperidin-4-yl)carbamate (120 mg, 0.19 mmol, 1.00 eq.) and 4 M HCl in EA (2.0 mL) was stirred at r.t under N₂ for 2 h. The mixture was concentrated to give the title compound as an off-white solid.

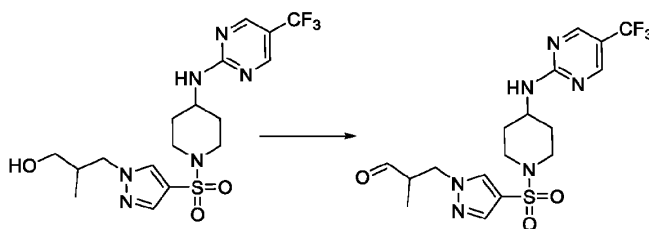
Step 4: 2-Methyl-3-(4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-1H-pyrazol-1-yl)propan-1-ol



To a solution of 1-((1-(3-((tert-butyldiphenylsilyl)oxy)-2-methylpropyl)-1H-pyrazol-4-yl)sulfonyl)piperidin-4-amine hydrochloride (110 mg, 0.19 mmol, 1.00 eq.) in DMSO (6.0 mL) was

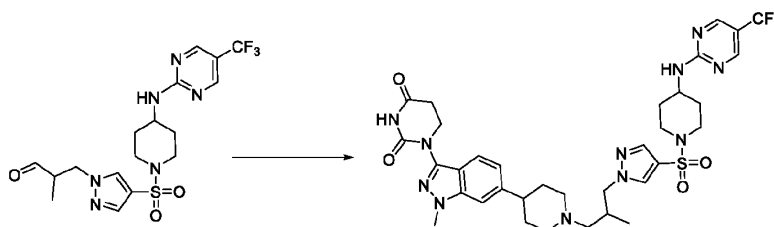
added DIEA (123 mg, 0.94 mmol, 5.00 eq.), CsF (143 mg, 0.94 mmol, 5.00 eq.) and 2-chloro-5-(trifluoromethyl)pyrimidine (35 mg, 0.19 mmol, 1.00 eq.). The mixture was stirred at 50 °C under N₂ for 12 h. The mixture was poured into water and extracted with EA. The combined organic layers were washed with water, brine, and the organic layer was dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was concentrated and purified by flash chromatography (PE:EA=1:1) to afford the title compound as white solid.

Step 5: 2-Methyl-3-(4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-1H-pyrazol-1-yl)propanal



To a stirred solution of 2-methyl-3-(4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-1H-pyrazol-1-yl)propan-1-ol (40 mg, 0.09 mmol, 1.00 eq.) in DCM (5.0 mL) was added Dess-Martin periodinane (76 mg, 0.18 mmol, 2.00 eq.) at 0 °C, the mixture was stirred for 2 h at r.t. under N₂. The mixture was filtered and concentrated to give the title compound as an off-white solid.

Step 6: 1-(1-Methyl-6-(1-(2-methyl-3-(4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-1H-pyrazol-1-yl)propyl)piperidin-4-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione

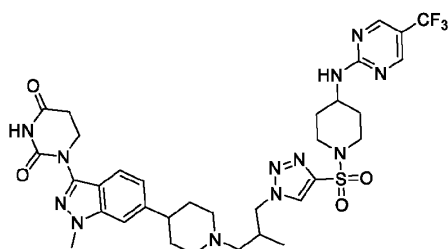


To a mixture of 1-(1-methyl-6-(piperidin-4-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (28 mg, 0.09 mmol, 1.00 eq.) in DMA (3.0 mL) was added 2-methyl-3-(4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-1H-pyrazol-1-yl)propanal (39 mg, 0.09 mmol, 1.00 eq.), TEA (27 mg, 0.27 mmol, 3.00 eq.), NaBH(OAc)₃ (47 mg, 0.22 mmol, 2.40 eq.) and the mixture was stirred at r.t. for 1 h under N₂. The mixture was poured into water and extracted with EA. The combined organic layers were washed with water, brine, and the organic layer was dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure.

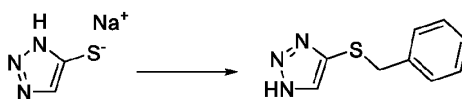
The residue was purified by flash column chromatography (DCM:MeOH=0~100%) to give the title compound as a white solid. MS (ES, m/z): $[M+1]^+ = 758.3$.

Example 55

- 5 Synthesis of 1-(1-methyl-6-(1-(2-methyl-3-(4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-1H-1,2,3-triazol-1-yl)propyl)piperidin-4-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione



Step 1: 4-(Benzylthio)-1H-1,2,3-triazole



10

To a stirred solution of sodium 1H-1,2,3-triazole-5-thiolate (1.00 g, 8.12 mmol, 1.00 eq.) in DCM (10.0 mL) was added (bromomethyl)benzene (1.39 g, 8.12 mmol, 1.00 eq.) at r.t. The resulting mixture was stirred at r.t. overnight. The mixture was diluted with DCM, and the mixture was washed with water and brine. The organic layer was dried over Na₂SO₄. After filtration, the filtrate was concentrated and the residue was purified by column chromatography on silica gel (PE:EA = 8 : 1) to give the title compound as white solid.

15

Step 2: 4-(Benzylthio)-1-(3-((tert-butyldiphenylsilyl)oxy)-2-methylpropyl)-1H-1,2,3-triazole

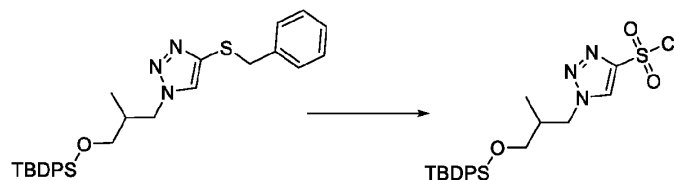


20

To a stirred solution of 4-(benzylthio)-1H-1,2,3-triazole (200 mg, 1.05 mmol, 1.00 eq.) in DMF (5.0 mL) was added Cs₂CO₃ (681 mg, 2.10 mmol, 2.00 eq.) and 3-((tert-butyldiphenylsilyl)oxy)-2-methylpropyl methanesulfonate (425 mg, 1.05 mmol, 1.00 eq.). The resulting mixture was stirred at 50 °C for 16 h. The mixture was diluted with EA, and the mixture was washed with water and brine. The organic layer was dried over Na₂SO₄. After filtration, the

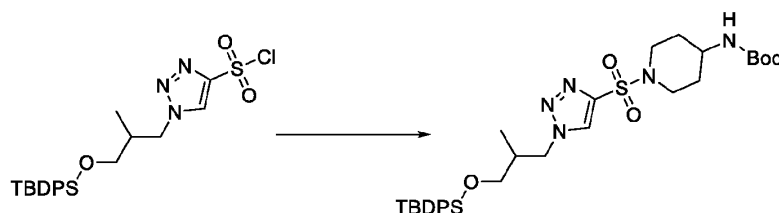
filtrate was concentrated and the residue was purified by column chromatography on silica gel (PE:EA = 5 : 1) to give the title compound as white solid.

Step 3: 1-(3-(((tert-Butyldiphenylsilyl)oxy)-2-methylpropyl)-1H-1,2,3-triazole-4-sulfonyl chloride



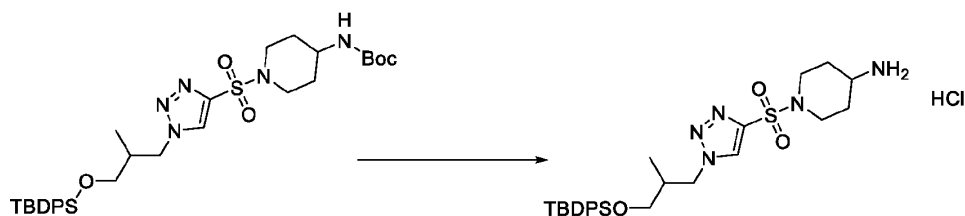
- 5 To a solution of 4-(benzylthio)-1-(3-(((tert-butyldiphenylsilyl)oxy)-2-methylpropyl)-1H-1,2,3-triazole (100 mg, 0.20 mmol, 1.00 eq.) in CAN (3.0 mL), AcOH (0.5 mL) and H₂O (0.5 mL) was added DCDMH (79 mg, 0.40 mmol, 2.00 eq.) at 0 °C and the mixture was stirred at r.t. for 2 h under N₂. The mixture was diluted with EA, and the mixture was washed with water and brine. The organic layer was dried over Na₂SO₄. After filtration, the filtrate was concentrated and the residue was
- 10 purified by column chromatography on silica gel (PE:EA = 6 : 1) to give the title compound as colorless oil.

Step 4: tert-Butyl (1-((1-(3-(((tert-butyldiphenylsilyl)oxy)-2-methylpropyl)-1H-1,2,3-triazol-4-yl)sulfonyl)piperidin-4-yl)carbamate



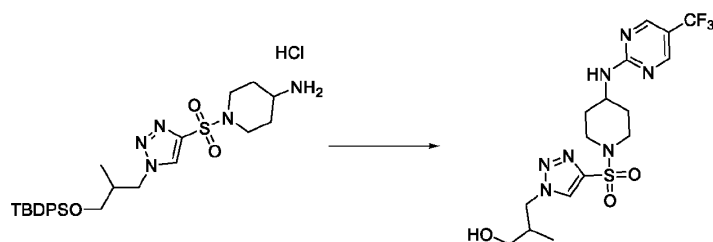
- 15 To a mixture of 1-(3-(((tert-butyldiphenylsilyl)oxy)-2-methylpropyl)-1H-1,2,3-triazole-4-sulfonyl chloride (95 mg, 0.20 mmol, 1.00 eq.) in DCM (3.0 mL) was added tert-butyl piperidin-4-ylcarbamate (50 mg, 0.24 mmol, 1.20 eq.) and TEA (40 mg, 0.40 mmol, 2.00 eq.) at 0 °C. The mixture was stirred at r.t. under N₂ for 2 h. The mixture was diluted with DCM, and the organic layer was washed with water and brine. The organic layer was dried over Na₂SO₄. After filtration, the
- 20 filtrate was concentrated and the residue was purified by column chromatography on silica gel (PE:EA = 10 : 1) to give the title compound as white solid.

Step 5: 1-((1-(3-((tert-Butyldiphenylsilyl)oxy)-2-methylpropyl)-1H-1,2,3-triazol-4-yl)sulfonyl)-piperidin-4-amine hydrochloride



A mixture of tert-butyl 1-((1-(3-((tert-butyl-diphenylsilyl)oxy)-2-methylpropyl)-1H-1,2,3-triazol-4-yl)sulfonyl)piperidin-4-yl)carbamate (300 mg, 0.47 mmol, 1.00 eq.) in EA (2.0 mL) was added 4 M HCl in EA (2.0 mL). The mixture was stirred at r.t. for 2h, and the mixture was concentrated to give the title compound as white solid.

Step 6: 2-Methyl-3-(4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-1H-1,2,3-triazol-1-yl)propan-1-ol



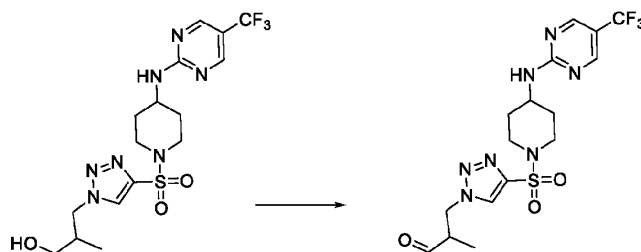
10

To a mixture of 1-((1-(3-((tert-butyl-diphenylsilyl)oxy)-2-methylpropyl)-1H-1,2,3-triazol-4-yl)sulfonyl)piperidin-4-amine hydrochloride (330 mg, 0.57 mmol, 1.00 eq.) in DMSO (3.0 mL) was added 2-chloro-5-(trifluoromethyl)pyrimidine (152 mg, 0.86 mmol, 1.50 eq.), DIEA (357 mg, 2.85 mmol, 5.00 eq.) and CsF (421 mg, 2.85 mmol, 5.00 eq.) at r.t. The mixture was stirred at 60 °C under N₂ for 16 h. The mixture was diluted with EA, and the organic layer was washed with water and brine. The organic layer was dried over Na₂SO₄. After filtration, the filtrate was concentrated and the residue was purified by column chromatography on silica gel (PE:EA = 2 : 1) to give the title compound as white solid.

15

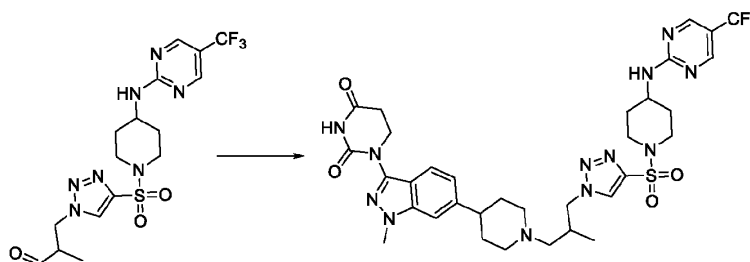
Step 7: 2-Methyl-3-(4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-1H-1,2,3-triazol-1-yl)propanal

20



A mixture of 2-methyl-3-(4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-1H-1,2,3-triazol-1-yl)propan-1-ol (110 mg, 0.24 mmol, 1.00 eq.), Dess-Martin periodinane (204 mg, 0.48 mmol, 2.00 eq.) in DCM (8.0 mL) was stirred at r.t. for 3 h. The mixture was filtered and the filtrate was concentrated and purified by column chromatography on silica gel (DCM:MeOH = 30 : 1) to give the title compound as white solid.

Step 8: 1-(1-Methyl-6-(1-(2-methyl-3-(4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-1H-1,2,3-triazol-1-yl)propyl)piperidin-4-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione



To a stirred solution of 1-(1-methyl-6-(piperidin-4-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (124 mg, 0.38 mmol, 2.00 eq.), 2-methyl-3-(4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-1H-1,2,3-triazol-1-yl)propanal (87 mg, 0.19 mmol, 1.00 eq.) and TEA (58 mg, 0.57 mmol, 3.00 eq.) in DMA (5.0 mL) was added $\text{NaBH}(\text{OAc})_3$ (102 mg, 0.48 mmol, 2.50 eq.) at 0 °C and the mixture was stirred at r.t. for 16 h. The mixture was poured into water, extracted with EA. The combined organic layer was dried over Na_2SO_4 . After filtration, the filtrate was concentrated and the residue was purified by *prep*-HPLC to give the title product as white solid. MS (ES, m/z): $[\text{M}+1]^+ = 759.1$.

Biological Examples

Biological Example 1

Phospho-Rb Measurement in Cells

Phosphorylation of RB protein at S807/811 were measured using HTRF phospho-RB cellular kits (Cat# 64RBS807PEG) from Cisbio.

On Day 1, adherent cells, such as OVCAR3 (CDK2-dependent cell line) and T47D (CDK4-dependent) were seeded into 96-well tissue-culture treated plates at 20,000 cells/well in 200 μL and incubated overnight at 37 °C in CO_2 atmosphere. On Day 2, the cells were treated with test compounds at concentrations from 0.3 to 3,000 nM using HP D300 digital dispenser. Twenty-four hours after compound treatment, cell culture media of the adherent cells is removed by flicking the plate and tapping the plate against clean paper towel. 30 μL 1X lysis buffer was supplemented from

the kit was added to each well of adherent cells. For suspension cells, 13.3 μ L 1X lysis buffer was directly added to 40 μ L of cell in 384-well plates. The plates were then incubated at room temperature on shaker for 30 min. After homogenization by pipetting up and down, 8 μ L cell lysate from cell culture plate was transferred to 384-well small volume white detection plate. 2 μ L

5 premixed detection solution was added and the plate was covered with sealer. To prepare the detection solution, d2 conjugated-phospho-RB antibody and Eu-cryptate conjugated phosphor-RB antibody were diluted into detection buffer following manufacturer's instruction. Detection plates were incubated for 4 h at room temperature and read on ClarioStar (BMG Labtech) in TR-FRET mode (665 nM and 620 nM). The TR-FRET ratio (665 nM/620 nM) was plotted against the

10 compound concentration and normalized to DMSO controls. Half maximal inhibition concentration (IC_{50}) values were calculated with a four-parameter logistic fit using GraphPad Prism (version 9; La Jolla, CA).

In the table below, AA indicates a IC_{50} of less than 1 nM; A indicates a IC_{50} of greater than or equal to 1 nM but less than or equal to 100 nM; B indicates a IC_{50} of greater than 100 nM but less

15 than or equal to 500 nM; C indicates a IC_{50} of greater than 500 nM but less than or equal to 2.5 μ M; D indicates a IC_{50} of greater than 2.5 μ M but less than or equal to 5.0 μ M; E indicates a IC_{50} of greater than 3 μ M.

CPD #	pRB_ OVCAR3 _24h (nM)	pRb_ T47D_ 24h (nM)	CPD #	pRB_ OVCAR3 _24h (nM)	pRb_ T47D_ 24h (nM)
1	A	A	54	A	A
2	A	NT	55	A	A
4	A	NT	56	B	A
7	C	NT	57	A	A
9	A	NT	58	A	A
10	A	NT	59	A	AA
11	A	NT	60	A	AA
12	A	NT	61	A	A
13	A	NT	62	A	A
14	A	A	63	A	A
15	A	A	64	A	A
16	A	A	65	A	A
17	A	A	66	A	AA
18	A	A	67	A	A
19	A	A	68	A	A
20	A	A	69	A	AA
21	A	A	70	A	A
22	B	B	71	A	AA
23	A	A	72	A	A

CPD #	pRB_ OVCAR3 _24h (nM)	pRb_ T47D_ 24h (nM)	CPD #	pRB_ OVCAR3 _24h (nM)	pRb_ T47D_ 24h (nM)
24	A	A	73	A	A
25	A	A	74	A	A
26	B	A	75	B	A
27	B	B	76	A	A
28	A	A	77	C	B
29	A	A	78	B	A
30	A	A	79	A	A
31	B	C	80	A	A
32	B	A	81	A	A
33	A	A	82	A	A
34	A	A	83	A	A
35	A	A	84	A	A
36	A	A	85	A	A
37	C	B	86	A	AA
38	A	A	87	A	AA
39	A	B	88	A	AA
40	A	AA	89	B	A
41	A	B	90	A	A
42	A	A	91	A	A
43	A	A	92	B	A
44	A	A	93	B	A
45	A	A	94	A	AA
46	A	A	95	A	AA
47	A	A	96	A	AA
48	A	A	97	B	A
49	A	A	98	B	A
50	A	A	99	B	B
51	A	A	100	B	A
52	A	A	101	A	A
53	B	NT	102	A	A
107	A	A	103	A	A
109	A	A	104	A	AA
111	C	B	105	A	A
113	A	A	106	A	B
115	A	A	108	A	A
117	A	A	110	A	C
119	A	A	112	A	AA
121	A	A	114	A	A
123	A	A	116	A	A
125	B	A	118	C	D
127	B	A	120	A	A
129	B	A	122	A	A
131	B	A	124	C	C
133	A	A	126	A	A
135	A	A	128	A	A

CPD #	pRB_ OVCAR3 _24h (nM)	pRb_ T47D_ 24h (nM)	CPD #	pRB_ OVCAR3 _24h (nM)	pRb_ T47D_ 24h (nM)
137	B	AA	130	B	A
139	A	AA	132	B	A
141	C	B	134	B	A
143	B	A	136	B	A
145	A	AA	138	B	A
147	E	A	140	E	E
149	A	A	142	B	A
151	A	A	144	A	A
153	A	A	146	A	AA
155	B	A	148	E	E
157	B	A	150	B	A
159	C	E	152	A	A
161	A	A	154	C	B
163	C	B	156	A	A
165	A	A	158	B	A
167	A	AA	160	A	AA
169	A	AA	162	B	C
171	A	AA	164	B	B
173	A	A	166	C	A
175	A	A	168	C	B
177	E	E	170	A	AA
179	A	AA	172	A	AA
181	A	AA	174	A	A
183	B	A	176	A	AA
185	A	A	178	A	A
187	A	A	180	B	A
189	A	A	182	A	AA
191	A	AA	184	A	A
193	A	A	186	A	A
195	C	D	188	A	A
197	B	A	190	B	A
199	A	AA	192	A	A
201	A	AA	194	C	B
203	A	AA	196	A	A
205	A	AA	198	C	C
207	A	AA	200	A	A
208	A	A	202	E	E
209	A	A	204	A	A
210	>1 μ M	>1 μ M	206	A	AA
211	A	AA	230	A	AA
212	A	AA	231	A	A
213	A	AA	232	A	A
214	B	A	233	A	AA
215	A	AA	234	A	A
216	A	A	235	C	A

CPD #	pRB_ OVCAR3 _24h (nM)	pRb_ T47D _24h (nM)	CPD #	pRB_ OVCAR3 _24h (nM)	pRb_ T47D _24h (nM)
217	A	A	236	>1 μ M	>1 μ M
218	A	A	237	C	>1 μ M
219	A	A	238	A	AA
220	B	A	239	A	A
221	A	A	240	>3 μ M	>3 μ M
222	B	A	241	C	C
223	B	A	242	C	A
224	A	A	243	B	A
225	A	A	244	A	B
226	A	A	245	B	A
227	A	A	246	A	A
228	B	C	247	B	A
229	A	A	248	A	A

Biological Example 2

High-throughput Measurement of Cellular Endogenous CDK1/2/4/6

Effects of compounds on cellular CDK levels were monitored by a high-throughput HTRF
 5 assay.

To determine half maximal degradation concentration (DC_{50}) and maximum degradation level (D_{max}) values of compounds, cellular CDK level was measured in 96-well format using HTRF total CDK cellular kit (CDK1, Cat# 64CDK1TPEG; CDK2 Cat# 64CDK2TPEG; CDK4 Cat# 64CDK4TPEG; CDK6, Cat# 64CDK6TPEG) from Cisbio/Revvity.

10 On Day 1, cells were seeded into 96-well tissue-culture treated plates at 20,000 cells/well in 200 μ L and incubated overnight at 37°C in CO₂ atmosphere. On Day 2 cells were treated with compounds at concentration ranging from 0.1 to 1,000 nM using HP D300 digital dispenser. 6 or 24 hours after compound treatment, cell culture media was removed by flicking the plate and tapping the plate against clean paper towel. Immediately 30 μ L 1X lysis buffer was supplemented from the
 15 kit and added to each well and the plate is incubated at room temperature on shaker for 30 min. After homogenization by pipetting up and down, 8 μ L cell lysate from 96-well cell culture plate was transferred to 384-well small volume white detection plate. 2 μ L premixed detection solution was added and the plate is covered with sealer. To prepare the detection solution, d2 conjugated-CDK antibody and Eu-cryptate conjugated CDK antibody were diluted into detection buffer following
 20 manufacturer's instruction. Detection plates were incubated overnight at room temperature and read on ClarioStar (BMG Labtech) in TR-FRET mode (665 nM and 620 nM). The TR-FRET ratio (665 nM/620 nM) was plotted against the compound concentration and normalized to DMSO controls

(0% degradation) and lysis buffer controls (100% degradation). Half maximal degradation concentration (DC_{50}) (0% degradation) and lysis buffer controls (100% degradation) values were calculated with a four-parameter logistic fit using GraphPad Prism (version 9; La Jolla, CA).

In the table below, A indicates a DC_{50} of greater than or equal to 0.1 nM but less than or equal to 10 nM; B indicates a DC_{50} of greater than 10 nM but less than or equal to 100 nM; C indicates a DC_{50} of greater than 100 nM but less than or equal to 1 μ M; and D indicates a DC_{50} of greater than 1 μ M nM but less than or equal to 5 μ M. NT means not tested.

CPD #	CDK2 DC50_ OVCAR3 6h (nM)
1	B
2	B
3	A
4	A
9	A
10	B
11	A
12	B
13	A
14	B
15	A
16	A
17	B
18	A
19	A
20	A
21	A

Formulation Examples

The following are representative pharmaceutical formulations containing a compound of the present disclosure.

Tablet Formulation

The following ingredients are mixed intimately and pressed into single scored tablets.

Ingredient	Quantity per tablet (mg)
compound Formula (I)	400
cornstarch	50
croscarmellose sodium	25
lactose	120

magnesium stearate

5

Capsule Formulation

The following ingredients are mixed intimately and loaded into a hard-shell gelatin capsule.

Ingredient	Quantity per capsule (mg)
Compound Formula (I)	200
lactose spray dried	148
magnesium stearate	2

Injectable Formulation

Compound of Formula (I) in 2% HPMC, 1% Tween 80 in DI water, pH 2.2 with MSA, q.s. to at least 20 mg/mL

Inhalation Composition

To prepare a pharmaceutical composition for inhalation delivery, 20 mg of a compound of Formula (I) is mixed with 50 mg of anhydrous citric acid and 100 mL of 0.9% sodium chloride solution. The mixture is incorporated into an inhalation delivery unit, such as a nebulizer, which is suitable for inhalation administration.

Topical Gel Composition

To prepare a pharmaceutical topical gel composition, 100 mg of a compound of Formula (I) is mixed with 1.75 g of hydroxypropyl cellulose, 10 mL of propylene glycol, 10 mL of isopropyl myristate and 100 mL of purified alcohol USP. The resulting gel mixture is then incorporated into containers, such as tubes, which are suitable for topical administration.

Ophthalmic Solution Composition

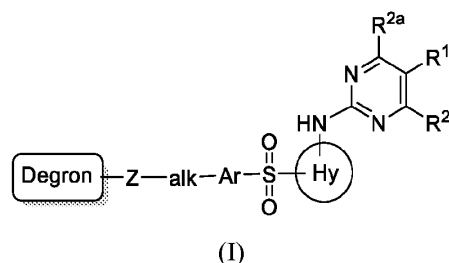
To prepare a pharmaceutical ophthalmic solution composition, 100 mg of a compound of Formula (I) is mixed with 0.9 g of NaCl in 100 mL of purified water and filtered using a 0.2 micron filter. The resulting isotonic solution is then incorporated into ophthalmic delivery units, such as eye drop containers, which are suitable for ophthalmic administration.

Nasal spray solution

To prepare a pharmaceutical nasal spray solution, 10 g of a compound of Formula (I) is mixed with 30 mL of a 0.05M phosphate buffer solution (pH 4.4). The solution is placed in a nasal administrator designed to deliver 100 μ L of spray for each application.

What is Claimed:

1. A compound of Formula (I):



5 wherein:

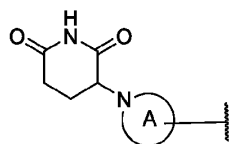
R^1 is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyloxy (wherein cycloalkyl, either alone or as part of cycloalkoxy, is substituted with one to three halo), halo, haloalkyl, haloalkoxy, alkoxy, aryloxy, or cyano;

R^2 and R^{2a} are independently hydrogen or deuterium;

10 Hy is cycloalkylene, arylene, heteroarylene, heterocyclylene, bicyclic heterocyclylene, spiro heterocyclylene, bridged heterocyclylene, or fused heterocyclylene, where each of the aforementioned rings is substituted with R^a , R^b , and R^c independently selected from hydrogen, deuterium, alkyl, halo, haloalkyl, alkoxy, hydroxy, and cyano;

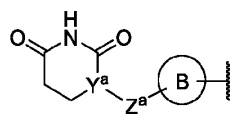
Degron is an E3 ubiquitin ligase ligand selected from:

- 15 (a) a group of formula (i):



(i); or

- (b) a group of formula (ii):



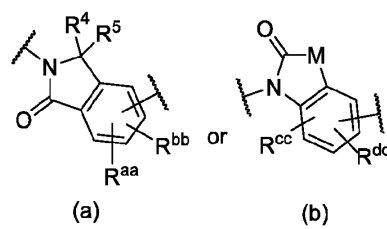
(ii);

Y^a is CH or N;

Z^a is a bond, $-CH_2-$, $-NH-$, $-O-$, or $-NHC(O)-$ where NH of $-NHC(O)-$ is attached

to Y^a ;

ring A is a group of formula (a) or (b):



where:

R^{aa} , R^{bb} , R^{cc} , and R^{dd} are independently selected from hydrogen, alkyl, alkoxy, halo, haloalkyl, haloalkoxy, and cyano;

R^4 and R^5 are independently hydrogen or alkyl; or R^4 and R^5 together with the carbon to which they are attached form $>C=O$;

M is $-O-$ or $-NR^6-$;

R^6 is hydrogen or alkyl;

ring B is phenylene, cyclylaminylene, 5- or 6-membered monocyclic heteroarylene, or 9- or 10-membered fused bicyclic heteroarylene, wherein each heteroarylene ring contains one to three ring atoms that are heteroatoms independently selected from nitrogen, oxygen or sulfur and further wherein the phenylene, cyclylaminylene, and each heteroarylene are independently substituted with R^{ee} and R^{ff} independently selected from hydrogen, alkyl, cycloalkyl, alkoxy, halo, haloalkyl, haloalkoxy, and cyano; and

Z is $-O-$, $-NR^3-$ (where R^3 is hydrogen or alkyl), alkynylene, cycloalkylene, phenylene, monocyclic heteroarylene, unsaturated heterocyclylene, heterocyclylene, bridged heterocyclylene, or spiro heterocyclylene and where each ring is substituted with R^d and R^e independently selected from hydrogen, deuterium, alkyl, alkoxy, halo, haloalkyl, haloalkoxy, and cyano;

alk is C_3 to C_6 alkenylene substituted with R^f selected from hydrogen, fluoro, and cyano; C_3 to C_6 alkylene or C_3 to C_6 heteroalkylene wherein the C_3 to C_6 alkylene and C_3 to C_6 heteroalkylene are substituted with R^g , R^h , and R^i where R^g is hydrogen, deuterium or halo, R^h is hydrogen, deuterium, cycloalkyl, cycloalkyloxy, bridged cycloalkyl, halo, haloalkoxy, alkoxy, hydroxy, cyano, cyanoalkyl, cyanoalkyloxy, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylcarbonylamino, phenyl, heteroaryl, heterocyclyl, heterocyclyloxy, heterocyclylcarbonyl, or bridged heterocyclyl (where cycloalkyl, either by itself or as part of cycloalkyloxy, bridged cycloalkyl, phenyl, heteroaryl, heterocyclyl, either by itself or as part of heterocyclyloxy or heterocyclylcarbonyl, and bridged heterocyclyl are substituted with R^7 and R^8 independently selected from hydrogen, deuterium, alkyl, alkoxy, halo, haloalkyl, haloalkoxy, hydroxy, alkylcarbonyl, alkyloxycarbonyl, amino, alkylamino, dialkylamino, and cyano); or when R^g and R^h are attached to

the same carbon or to adjacent carbon atoms of linear portion of the C₃ to C₆ alkylene or C₃ to C₆ heteroalkylene, R^g and R^h together with the carbon atom(s) to which they are attached can form cycloalkylene or heterocyclylene (where the cycloalkylene and heterocyclylene formed by R^g and R^h are substituted with R⁹ and R¹⁰ independently selected from hydrogen, deuterium, alkyl, alkoxy, halo, haloalkyl, haloalkoxy, hydroxy, alkylcarbonyl, alkyloxycarbonyl, amino, alkylamino, dialkylamino, and cyano), and Rⁱ is hydrogen or halo; and the linear portion of C₃ to C₆ alkenylene, C₃ to C₆ alkylene, and C₃ to C₆ heteroalkylene, attaching Ar and Z, contains at least three atoms; and

Ar is phenylene, monocyclic heteroarylene, heterocyclylene bridged heterocyclylene, or spiro heterocyclylene, where each of the aforementioned ring is substituted with R^j, R^k, and R^m independently selected from hydrogen, deuterium, alkyl, alkoxy, halo, haloalkyl, haloalkoxy, and cyano; or

a pharmaceutically acceptable salt thereof.

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R¹ is halo.

3. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R¹ is haloalkyl.

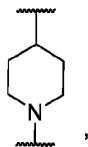
4. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R¹ is haloalkoxy.

5. The compound of any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, wherein R¹ is chloro, bromo, difluoromethyl, trifluoromethyl, difluoromethoxy, or trifluoromethoxy.

6. The compound of any one of claims 1 to 5, or a pharmaceutically acceptable salt thereof, wherein R² and R^{2a} are hydrogen.

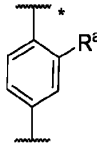
7. The compound of any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof, wherein Hy is heterocyclylene substituted with R^a, R^b, and R^c where R^a and R^b are independently selected from hydrogen, deuterium, alkyl, halo, haloalkyl, alkoxy, hydroxy, and cyano, and R^c is hydrogen.

8. The compound of any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, wherein the heterocyclylene of Hy is:

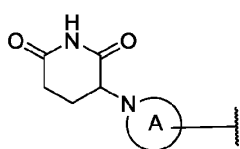


where the N atom of the piperidin-1,4-diyl ring is attached to -SO₂-.

9. The compound of any one of claims 1 to 7, or a pharmaceutically acceptable salt

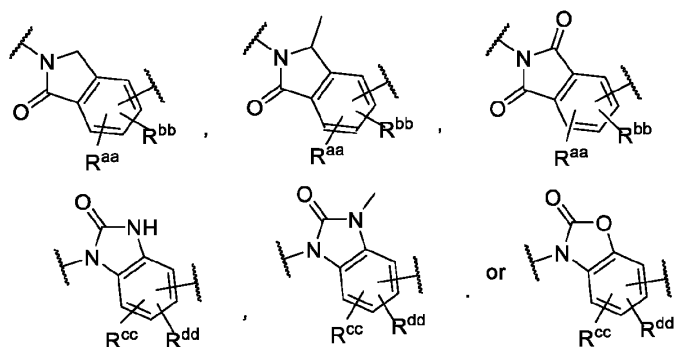
thereof, wherein the phenylene of Hy is 1,4-phenylene according to structure  where  denotes bond to NH and  denotes bond to -SO₂- and R^a is hydrogen, fluoro, methyl or methoxy and R^b is hydrogen.

10. The compound of any one of claims 1 to 9, or a pharmaceutically acceptable salt thereof, wherein the Degron is an E3 ubiquitin ligase ligand of formula (i):



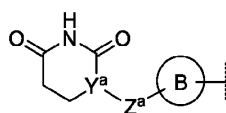
(i).

11. The compound of any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof, wherein the ring A of the E3 ubiquitin ligase ligand of formula (i) is:



12. The compound of any one of claims 1 to 11, or a pharmaceutically acceptable salt thereof, wherein R^{aa} and R^{bb}, R^{cc}, and R^{dd} are independently selected from hydrogen, methyl, methoxy, ethoxy, fluoro, trifluoromethyl, difluoromethyl, and trifluoromethoxy.

13. The compound of any one of claims 1 to 9, or a pharmaceutically acceptable salt thereof, wherein the Degron is an E3 ubiquitin ligase ligand of formula (ii):



(ii).

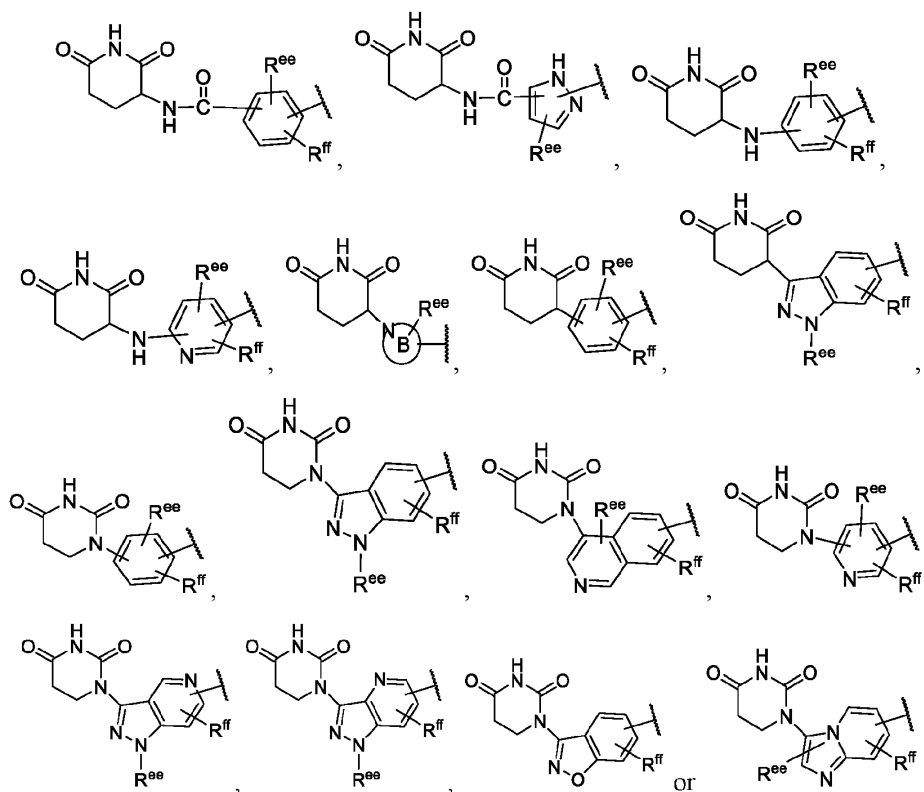
14. The compound of any one of claims 1 to 9 and 13, or a pharmaceutically acceptable salt thereof, wherein Y^a is CH.

15. The compound of any one of claims 1 to 9 and 13, or a pharmaceutically acceptable salt thereof, wherein Y^a is N.

16. The compound of any one of claims 1 to 9, and 13 to 15, or a pharmaceutically acceptable salt thereof, wherein Z^a is a bond, -NH-, -O-, or -NHC(O)-.

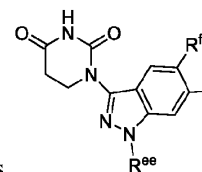
17. The compound of any one of claims 1 to 9 and 13 to 16, or a pharmaceutically acceptable salt thereof, wherein ring B is 5- or 6-membered monocyclic heteroaryl or a 9- or 10-membered fused bicyclic heteroaryl, wherein each heteroaryl ring contains one to three nitrogen ring atoms and each ring of ring B is substituted with R^{ee} and R^{ff} .

18. The compound of any one of claims 1 to 9 and 13 to 17, or a pharmaceutically acceptable salt thereof, wherein the E3 ubiquitin ligase ligand of formula (ii) is:

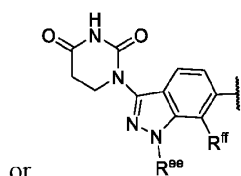


where ring B is cyclaminylene.

19. The compound of any one of claims 1 to 9 and 13 to 18, or a pharmaceutically



acceptable salt thereof, wherein the E3 ubiquitin ligase ligand of formula (ii) is



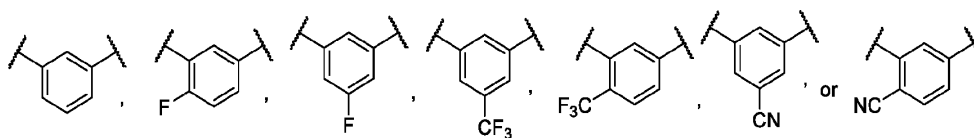
20. The compound of any one of claims 1 to 9 and 13 to 19, or a pharmaceutically acceptable
5 salt thereof, wherein R^{ee} and R^{ff} are independently selected from hydrogen, methyl, ethyl, isopropyl, cyclopropyl, methoxy, ethoxy, fluoro, chloro, trifluoromethyl, 2,2,2-trifluoroethyl, difluoromethyl, difluoromethoxy, trifluoromethoxy, and cyano.

21. The compound of any one of claims 1 to 20, or a pharmaceutically acceptable salt
10 thereof, wherein Ar is phenylene, monocyclic heteroarylene, bridged heterocyclylene, or heterocyclylene, where each ring of Ar is substituted with R^j , R^k , and R^m where R^m is hydrogen.

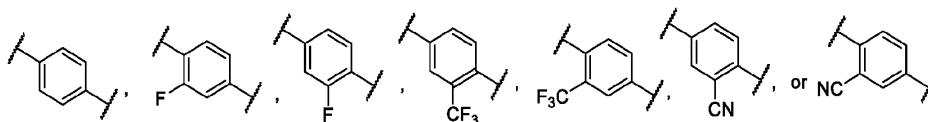
22. The compound of any one of claims 1 to 21, or a pharmaceutically acceptable salt

thereof, wherein -r- is phenylene of formula or substituted with R^j , R^k , and R^m where R^j and R^k are independently selected from hydrogen, alkyl, alkoxy, halo, cyano, haloalkyl, and haloalkoxy and R^m is hydrogen.

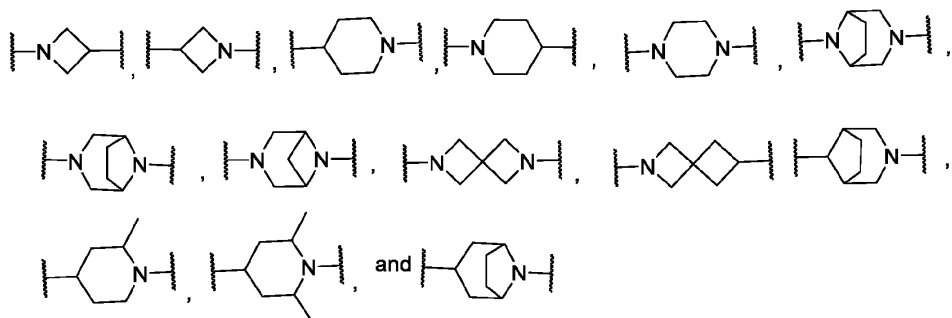
15 23. The compound of any one of claims 1 to 22, or a pharmaceutically acceptable salt thereof, wherein the phenylene of Ar is



24. The compound of any one of claims 1 to 22, or a pharmaceutically acceptable salt thereof, wherein the phenylene of Ar is

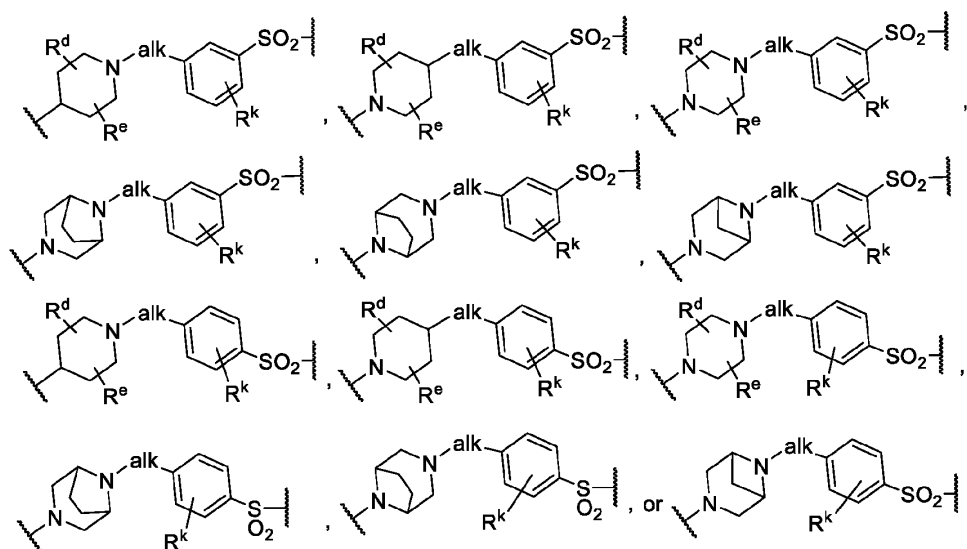


20



respectively.

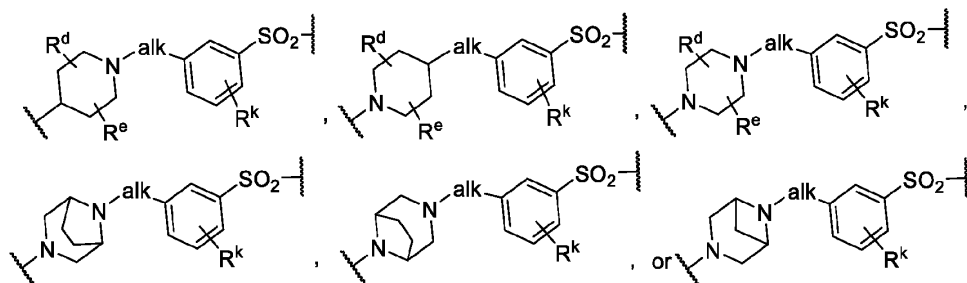
30. The compound of any one of claims 1 to 22 and 27 to 29, or a pharmaceutically acceptable salt thereof, wherein -Z-alk-Ar-SO₂- is:



5

wherein each R^d, R^e, and R^k are independently selected from hydrogen, alkyl, halo, haloalkyl, haloalkoxy, alkoxy, and cyano and R^j is hydrogen.

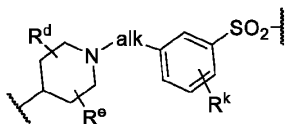
31. The compound of any one of claims 1 to 22 and 27 to 30, or a pharmaceutically acceptable salt thereof, wherein -Z-alk-Ar-SO₂- is:



10

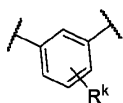
wherein each R^d, R^e, and R^k are independently selected from hydrogen, alkyl, halo, haloalkyl, haloalkoxy, alkoxy, and cyano and R^j is hydrogen.

32. The compound of any one of claims 1 to 22 and 27 to 31, or a pharmaceutically acceptable salt thereof, wherein -Z-alk-Ar-SO₂- is:

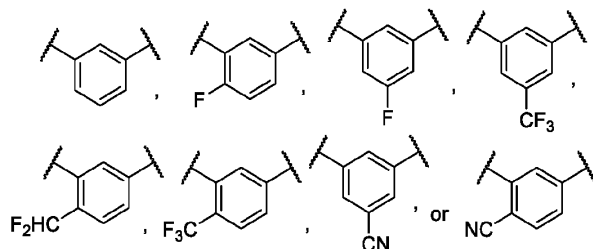


5

33. The compound of any one of claims 30, 31, and 32, or a pharmaceutically acceptable



salt thereof, wherein is:



34. The compound of any one of claims 1 to 33, or a pharmaceutically acceptable salt thereof, wherein alk is C₃ to C₆ heteroalkylene substituted with R^g, R^h, and Rⁱ.

35. The compound of any one of claims 1 to 34, or a pharmaceutically acceptable salt thereof, wherein alk is C₃ to C₆ heteroalkylene substituted with R^g, R^h, and Rⁱ where R^g, R^h, and Rⁱ are hydrogen.

36. The compound of any one of claims 1 to 35, or a pharmaceutically acceptable salt thereof, wherein the C₃ to C₆ heteroalkylene of alk is branched C₄ to C₆ heteroalkylene.

37. The compound of any one of claims 1 to 36, or a pharmaceutically acceptable salt thereof, wherein the branched C₄ to C₆ heteroalkylene of alk is -CH₂X^aCH(CH₃)CH₂-, -CH₂X^yCH₂CH(CH₃)X^a-, -CH₂CH₂CH(CH₃)X^a-, -X^aCH(CH₃)CH₂CH₂-, -X^yCH₂CH(CH₃)X^a-, -X^yCH(CH₃)CH₂X^a-, -CH₂CH₂CH₂CH(CH₃)X^a-, -X^aCH(CH₂R^h)CH₂-, -CH₂CH(CH₂R^h)X^a-, -X^aCH(CH₂CH₂R^h)CH₂-, -CH₂CH(CH₂CH₂R^h)X^a-, -CH₂C(CH₃)(CH₃)X^a-, -X^aC(CH₃)(CH₃)CH₂-, -CH(CH₃)CH(CH₃)X^a-, -CONR^zCH₂CH(CH₃)X^a-, -CH₂NR^qCOCH(CH₃)CH₂-, or -NR^qCOCH(CH₃)CH₂- where X^a is -NR^q-, -O-, -S-, -SO-, -SO₂-, or -CO-.

38. The compound of any one of claims 1 to 37, or a pharmaceutically acceptable salt thereof, wherein the branched C₄ to C₆ heteroalkylene of alk is -CH₂C(CH₃)(CH₃)X^a-,

-CH(CH₃)(CHCH₃)X^a-, -X^aCH(CH₂CH₂R^h)CH₂-, -CH₂CH(CH₂CH₂R^h)X^a-, -X^aCH(CH₂R^h)CH₂-, or -CH₂CH(CH₂R^h)X^a-.

39. The compound of any one of claims 36 to 38, or a pharmaceutically acceptable salt thereof, wherein X^a is -NR^q- where R^q is hydrogen or methyl.

5 40. The compound of any one of claims 36 to 38, or a pharmaceutically acceptable salt thereof, wherein X^a is -O-.

41. The compound of any one of claims 36 to 38, or a pharmaceutically acceptable salt thereof, wherein X^y is -O- or -NH- or -NCH₃-.

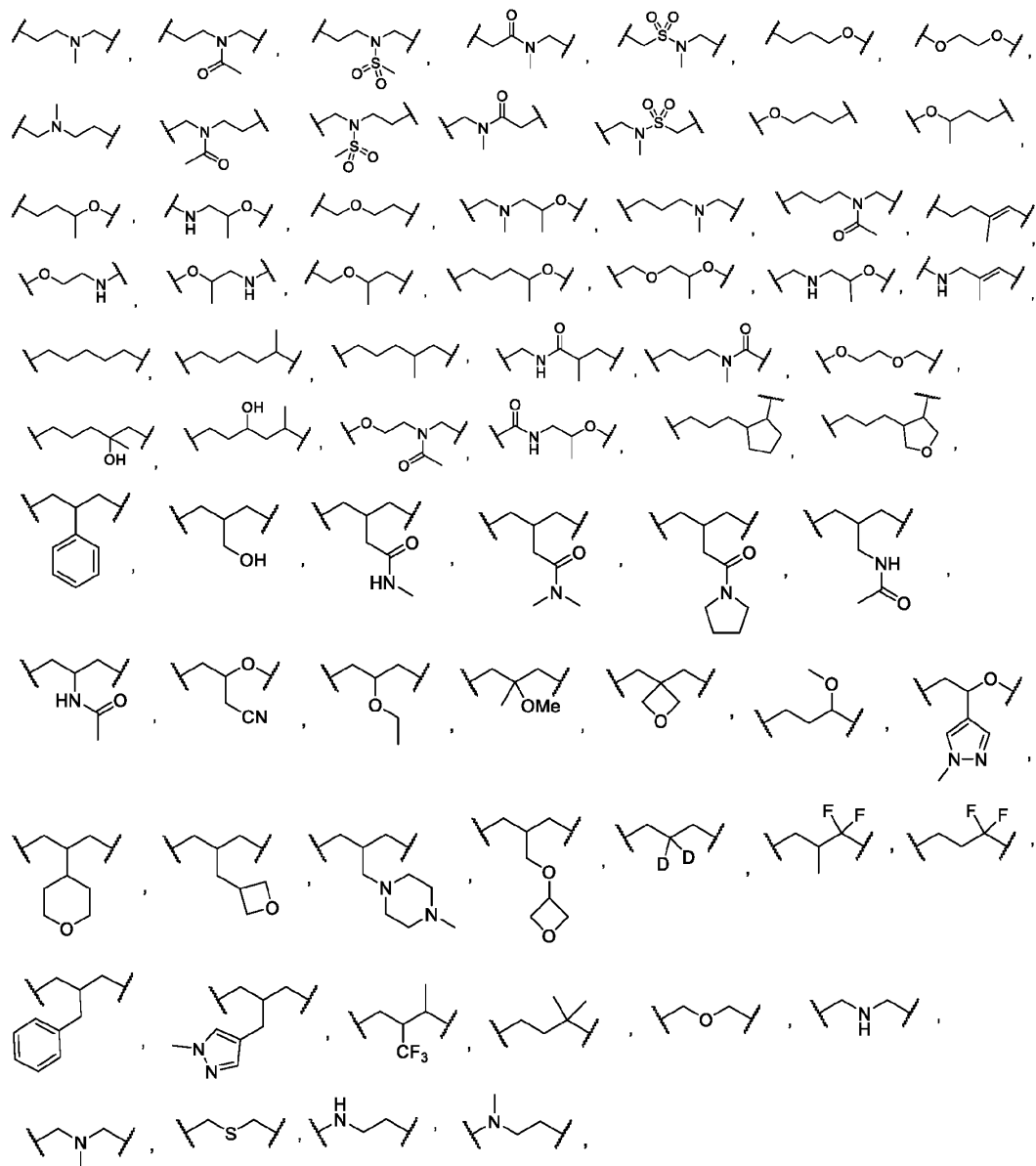
42. The compound of any one of claims 1 to 33, or a pharmaceutically acceptable salt
10 thereof, wherein alk is a linear C₃ to C₆ alkylene substituted with R^g, R^h, and Rⁱ where R^g, R^h, and Rⁱ are hydrogen.

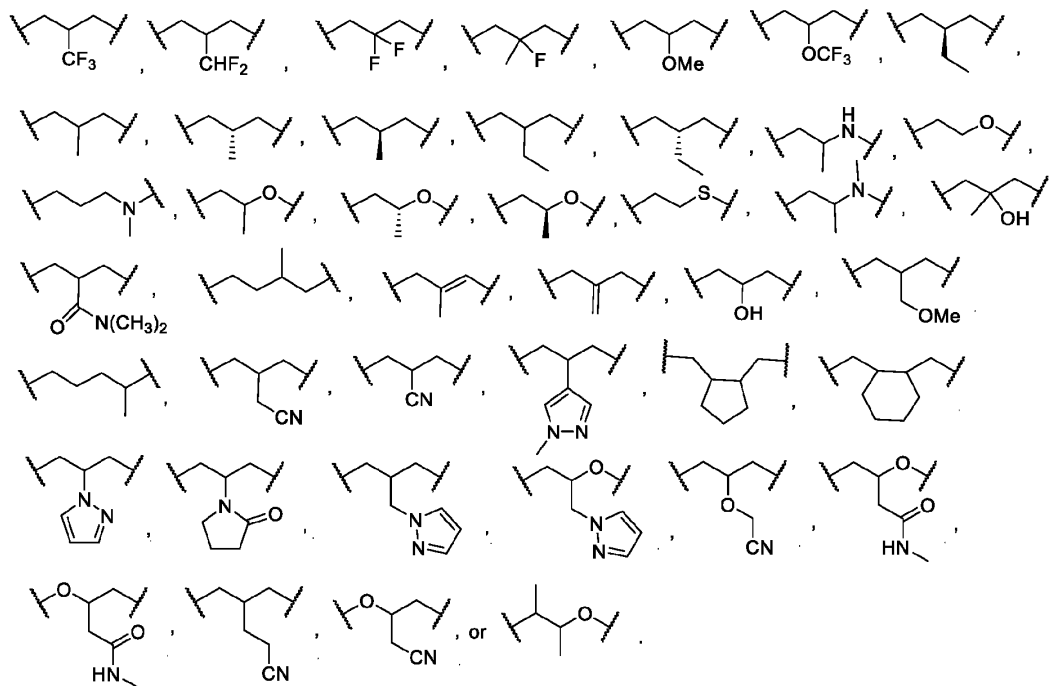
43. The compound of any one of claims 1 to 33, or a pharmaceutically acceptable salt thereof, wherein alk is branched C₄ to C₆ alkylene substituted with R^g, R^h, and Rⁱ where R^g, R^h, and Rⁱ are hydrogen.

15 44. The compound of any one of claims 1 to 33, and 43, or a pharmaceutically acceptable salt thereof, wherein the branched C₄ to C₆ alkylene of alk is -CH₂C(CH₃)(R^h)CH₂-,
-CH₂C(C₂H₅)(R^h)CH₂-, -CH₂CH(CH₂R^h)CH₂-, -CH₂CH(CH₂CH₂R^h)CH₂-,
-CH₂C(CH₃)(CH₂R^h)CH₂-, -CH₂C(C₂H₅)(CH₂R^h)CH₂-, -CH₂C(CH₃)(CH₂CH₂R^h)CH₂-,
-CH₂CH(CH₃)CH(CH₂R^h)-, -CH₂CH₂C(CH₃)(CH₂R^h)-, -CH₂CH(CH₃)C(R^g)(R^h)-,
20 -CH₂CH(C₂H₅)C(R^g)(R^h)-, -CH₂CH(C(R^g)(R^h)(Rⁱ))CH(CH₃)-,
-CH₂C(CH₃)(C(R^g)(R^h)(Rⁱ))CH(CH₃)-, -CH₂CH(C(R^g)(R^h)(Rⁱ))CH₂-,
-CH₂CH₂CH(C(R^g)(R^h)(Rⁱ))-, -CH₂CH₂CH(C(R^g)(R^h)(Rⁱ))CH₂-, or -CH₂CH₂CH₂CH(C(R^g)(R^h)(Rⁱ))-.

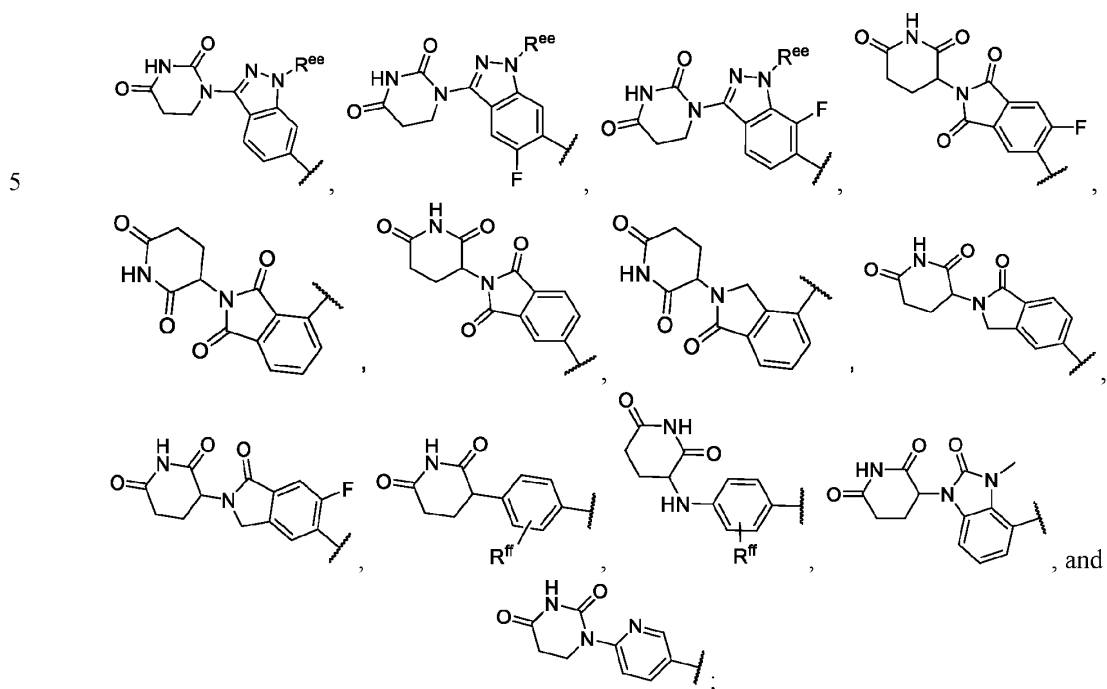
45. The compound of any one of claims 1 to 33, 43, and 44, or a pharmaceutically acceptable salt thereof, wherein the branched C₄ to C₆ alkylene of alk is
25 -CH₂C(CH₃)(R^h)CH₂-, -CH₂CH(CH₂R^h)CH₂-, -CH₂CH(CH₂CH₂R^h)CH₂-,
-CH₂CH(C(R^g)(R^h)(Rⁱ))CH₂-, -CH₂CH₂CH(C(R^g)(R^h)(Rⁱ))CH₂-, or
-CH₂CH₂CH₂CH(C(R^g)(R^h)(Rⁱ))-.

46. The compound of any one of claims 1 to 45, or a pharmaceutically acceptable salt thereof, wherein alk is:





47. The compound of any one of claims 1 to 46, or a pharmaceutically acceptable salt thereof, wherein Degron is the E3 ubiquitin ligase ligand selected from:



where R^{ee} is hydrogen, methyl, ethyl, cyclopropyl, or 2,2,2-trifluoroethyl and R^{ff} is hydrogen, methyl, cyclopropyl, fluoro, cyano, methoxy, difluoromethoxy, trifluoromethoxy, or trifluoromethyl.

48. A compound selected from:

(R)-1-(1-methyl-6-(1-(2-methyl-3-(3-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)propyl)piperidin-4-yl)-1H-indazol-3-yl) dihydropyrimidine-2,4(1H,3H)-dione
(S)-1-(1-methyl-6-(1-(2-methyl-3-(3-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)propyl)piperidin-4-yl)-1H-indazol-3-yl) dihydropyrimidine-2,4(1H,3H)-dione
1-(1-methyl-6-(1-(3-(3-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)propyl)piperidin-4-yl)-1H-indazol-3-yl) dihydropyrimidine-2,4(1H,3H)-dione
3-(5-(4-(3-(3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-2-methylpropyl)piperazin-1-yl)-6-fluoro-1-oxoisindolin-2-yl)piperidine-2,6-dione
2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-methylpropyl)-4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzonitrile
1-(6-(1-(3-(3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-2-methylpropyl)piperidin-4-yl)-7-fluoro-1-methyl-1H-indazol-3-yl) dihydropyrimidine-2,4(1H,3H)-dione
1-(6-(1-(3-(4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl) dihydropyrimidine-2,4(1H,3H)-dione
1-(1-methyl-6-(1-(2-(3-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzyl)butyl)piperidin-4-yl)-1H-indazol-3-yl) dihydropyrimidine-2,4(1H,3H)-dione
1-(6-(1-(2-(3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzyl)butyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl) dihydropyrimidine-2,4(1H,3H)-dione
(R)-1-(6-(1-(3-(3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl) dihydropyrimidine-2,4(1H,3H)-dione
(S)-1-(6-(1-(3-(3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl) dihydropyrimidine-2,4(1H,3H)-dione
4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-methylpropyl)benzonitrile
1-(1-methyl-6-(1-(2-methyl-3-(3-((4-((5-(trifluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)propyl)piperidin-4-yl)-1H-indazol-3-yl) dihydropyrimidine-2,4(1H,3H)-dione
1-(6-(1-(3-(3-((4-((5-bromopyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl) dihydropyrimidine-2,4(1H,3H)-dione
1-(1-methyl-6-(1-(2-methyl-3-(3-((4-((5-vinylpyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)propyl)piperidin-4-yl)-1H-indazol-3-yl) dihydropyrimidine-2,4(1H,3H)-dione
2-((3-(4-(1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzof[d]imidazol-4-yl)piperidin-1-yl)propyl)(methyl)amino)-4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzonitrile 2,2,2-trifluoroacetate
3-(6-(1-(3-(3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)piperidine-2,6-dione

(S)-1-(6-(1-(2-(3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenoxy)propyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione
(R)-1-(6-(1-(2-(3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenoxy)propyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione
1-(6-(1-(3-(3-((4-((5-ethylpyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione
1-(6-(1-(3-(5-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-fluorophenyl)-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione
3-(3-methyl-4-(1-(3-(methyl(2-(trifluoromethyl)-5-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)amino)propyl)piperidin-4-yl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione 2,2,2-trifluoroacetate
4-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(2-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)ethoxy)benzonitrile
1-(6-(1-(3-(3-((4-((5-isopropylpyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione
1-(6-(1-(2-((3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)amino)propyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione
1-(6-(1-(2-((3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)thio)propyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione
(S)-1-(6-(1-(2-(4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenoxy)propyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione
(R)-1-(6-(1-(2-(4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenoxy)propyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione
4-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-methylpropyl)benzonitrile
1-(6-(1-(2-(5-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-fluorophenoxy)ethyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione
1-(6-(1-(3-(4-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione
4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indol-6-yl)piperidin-1-yl)-2-methylpropyl)benzonitrile
4-((4-((5-(2,2-difluoroethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-methylpropyl)benzonitrile
5-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-methylpropyl)benzonitrile
1-(6-(1-(2-((4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)amino)propyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione

4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-methylpropyl)benzonitrile
1-(6-(1-(2-(5-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(trifluoromethyl)phenoxy)ethyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione
1-(6-(1-(2-((3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)(methyl)amino)propyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione
1-(6-(1-(3-(3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-2-hydroxy-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione
1-(6-(1-(2-hydroxy-2-methyl-3-(3-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)propyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione
1-(6-(1-(3-(3-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-2-hydroxy-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione
1-(6-(1-(2-((4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)(methyl)amino)propyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione
3-(4-(1-(3-((2-fluoro-5-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)(methyl)amino)propyl)piperidin-4-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione formate
1-(6-(1-((2-(3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)cyclopentyl)methyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione
1-(6-(1-((2-(3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)cyclopentyl)methyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione
1-(6-(1-((2-(3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)cyclohexyl)methyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione formate
1-(6-(1-(3-(4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-fluorophenyl)-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione
2-(3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzyl)-3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-N,N-dimethylpropanamide
4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)-3,3-difluoropiperidin-1-yl)-2-methylpropyl)benzonitrile formate
4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-(2,2,2-trifluoroethyl)-1H-indazol-6-yl)piperidin-1-yl)-2-methylpropyl)benzonitrile
2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-methylpropyl)-4-((4-((5-(trifluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzonitrile
4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(4-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-methylbutyl)benzonitrile

4-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)piperidin-1-yl)-2-methylpropyl)benzonitrile
4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(2-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)ethoxy)benzonitrile
(S)-4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-methylpropyl)benzonitrile
(R)-4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-methylpropyl)benzonitrile
(E)-4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-methylprop-1-en-1-yl)benzonitrile
1-(6-(1-(2-(3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzyl)allyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione
1-(6-(1-(3-(3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-2-hydroxypropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione
2-(3-(4-(1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)piperidin-1-yl)-2-methylpropyl)-4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzonitrile
4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)piperidin-1-yl)-2-methylpropyl)benzonitrile
4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-7-fluoro-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-methylpropyl)benzonitrile
1-(6-(1-(3-(5-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-fluorophenyl)-2-hydroxy-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione
1-(6-(1-(3-(5-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-fluorophenyl)-2-hydroxy-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione
1-(6-(1-(3-(2-fluoro-5-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-2-hydroxy-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione
1-(6-(1-(3-(3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)butyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione
3-(3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzyl)-4-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)butanenitrile
1-(6-(1-(3-(3-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-5-fluorophenyl)-2-hydroxy-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione
1-(6-(1-(3-(3-fluoro-5-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-2-hydroxy-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione

1-(6-(1-(3-(3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-5-fluorophenyl)-2-hydroxy-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione
5-(1-(3-(2-cyano-5-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-2-methylpropyl)piperidin-4-yl)-N-(2,6-dioxopiperidin-3-yl)picolinamide
3-(4-(1-(3-(3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-2-methylpropyl)piperidin-4-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione
5-(1-(3-(5-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-cyanophenyl)-2-methylpropyl)piperidin-4-yl)-N-(2,6-dioxopiperidin-3-yl)picolinamide
4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-((1-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)propan-2-yl)oxy)benzonitrile
5-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-methylpropyl)benzonitrile
1-(6-(1-(3-(5-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(trifluoromethyl)phenyl)-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione
1-(6-(1-(3-(4-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-fluorophenyl)-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione
1-(6-(1-(3-(2-fluoro-4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione
4-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-hydroxy-2-methylpropyl)benzonitrile
4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-hydroxy-2-methylpropyl)benzonitrile
2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-hydroxy-2-methylpropyl)-4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzonitrile
1-(6-(1-(3-(4-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-fluorophenyl)-2-hydroxy-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione
1-(6-(1-(3-(4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-fluorophenyl)-2-hydroxy-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione
1-(6-(1-(3-(2-fluoro-4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-2-hydroxy-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione
1-(6-(1-(2-hydroxy-2-methyl-3-(2-(trifluoromethyl)-4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)propyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione
1-(6-(1-(2-(5-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(trifluoromethyl)phenoxy)ethyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione

1-(6-(1-(3-(4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(trifluoromethyl)phenyl)-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl) dihydropyrimidine-2,4(1H,3H)-dione
1-(6-(1-(3-(4-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(trifluoromethyl)phenyl)-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl) dihydropyrimidine-2,4(1H,3H)-dione
1-(1-methyl-6-(1-(2-methyl-3-(2-(trifluoromethyl)-4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)propyl)piperidin-4-yl)-1H-indazol-3-yl) dihydropyrimidine-2,4(1H,3H)-dione
1-(6-(1-(3-(4-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-2-hydroxy-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl) dihydropyrimidine-2,4(1H,3H)-dione
1-(6-(1-(3-(4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-2-hydroxy-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl) dihydropyrimidine-2,4(1H,3H)-dione
1-(6-(1-(2-hydroxy-2-methyl-3-(4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)propyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl) dihydropyrimidine-2,4(1H,3H)-dione
1-(6-(1-(3-(4-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(trifluoromethyl)phenyl)-2-hydroxy-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl) dihydropyrimidine-2,4(1H,3H)-dione
1-(6-(1-(3-(4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(trifluoromethyl)phenyl)-2-hydroxy-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl) dihydropyrimidine-2,4(1H,3H)-dione
(E)-4-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-methylprop-1-en-1-yl)benzonitrile
4-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(2-((4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)allyl)benzonitrile
(E)-2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-methylprop-1-en-1-yl)-4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzonitrile
2-(2-((4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)allyl)-4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzonitrile
4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-((2R)-4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)-2-methylpiperidin-1-yl)-2-methylpropyl)benzonitrile formate
4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(3-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-methylpropyl)benzonitrile
4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)butyl)benzonitrile
(E)-4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)prop-1-en-1-yl)benzonitrile
(E)-1-(6-(1-(3-(3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-2-methylallyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl) dihydropyrimidine-2,4(1H,3H)-dione

(E)-1-(1-methyl-6-(1-(2-methyl-3-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)allyl)piperidin-4-yl)-1H-indazol-3-yl) dihydropyrimidine-2,4(1H,3H)-dione
(E)-4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)but-1-en-1-yl)benzonitrile
(E)-4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-methylbut-1-en-1-yl)benzonitrile
(E)-4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-3-methylbut-1-en-1-yl)benzonitrile
(E)-2-(3-(4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-methylprop-1-en-1-yl)-4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzonitrile
(E)-1-(6-(1-(3-(2-(difluoromethyl)-5-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)allyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl) dihydropyrimidine-2,4(1H,3H)-dione
(Z)-4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)prop-1-en-1-yl)benzonitrile
1-(6-(1-(3-(5-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(difluoromethyl)phenyl)-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl) dihydropyrimidine-2,4(1H,3H)-dione
4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-((2S,6S)-4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)-2,6-dimethylpiperidin-1-yl)-2-methylpropyl)benzonitrile formate
4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-((2-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)ethyl)amino)benzonitrile
4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)-2-oxopyridin-1(2H)-yl)-2-methylpropyl)benzonitrile
1-(6-(1-(2-(2-fluoro-5-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenoxy)ethyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl) dihydropyrimidine-2,4(1H,3H)-dione 2,2,2-trifluoroacetate
2-(3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzyl)-3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-N-methylpropanamide
1-(6-(1-(2-(5-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-fluorophenoxy)ethyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl) dihydropyrimidine-2,4(1H,3H)-dione
2-(2-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)ethoxy)-4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzonitrile
1-(6-(1-(3-(3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-2-(1-methyl-1H-pyrazol-4-yl)propyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl) dihydropyrimidine-2,4(1H,3H)-dione
4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-methyl-3-oxopropyl)benzonitrile

4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(4-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)butan-2-yl)benzonitrile
(R)-1-(1-(1-methyl-6-(1-(2-(3-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenoxy)propyl)piperidin-4-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione
(S)-1-(1-(1-methyl-6-(1-(2-(3-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenoxy)propyl)piperidin-4-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione
4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-hydroxypropyl)benzonitrile
2-(3-(3-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)-8-azabicyclo[3.2.1]octan-8-yl)-2-methylpropyl)-4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzonitrile
4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-((2S)-4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)-2-methylpiperidin-1-yl)-2-methylpropyl)benzonitrile
4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-((2-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)ethyl)(methyl)amino)benzonitrile
4-((4-((5-(chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-((2-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)ethyl)(methyl)amino)benzonitrile
2-((2-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)ethyl)(methyl)amino)-4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzonitrile
4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-((2-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)ethyl)thio)benzonitrile
(R)-4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-((1-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)propan-2-yl)oxy)benzonitrile
(S)-4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-((1-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)propan-2-yl)oxy)benzonitrile
1-(6-(1-(3-(4-((4-((5-(chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-3-fluorophenyl)-2-hydroxy-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione
1-(6-(1-(3-(4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-3-fluorophenyl)-2-hydroxy-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione
1-(6-(1-(3-(3-fluoro-4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-2-hydroxy-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione
4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)phenethoxy)benzonitrile
1-(6-(1-(2-(4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenoxy)ethyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione

1-(6-(1-(2-(4-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenoxy)ethyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl) dihydropyrimidine-2,4(1H,3H)-dione
1-(1-methyl-6-(1-(2-(4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenoxy)ethyl)piperidin-4-yl)-1H-indazol-3-yl) dihydropyrimidine-2,4(1H,3H)-dione
4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(2-((2R)-4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)-2-methylpiperidin-1-yl)ethoxy)benzonitrile
2-(3-((2R)-4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)-2-methylpiperidin-1-yl)-2-methylpropyl)-4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzonitrile
2-(3-((2S)-4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)-2-methylpiperidin-1-yl)-2-methylpropyl)-4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzonitrile
4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(7-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)-3-oxa-9-azabicyclo[3.3.1]nonan-9-yl)-2-methylpropyl)benzonitrile
4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)-3-methylphenethoxy)benzonitrile
1-(6-(1-(3-(2-(difluoromethyl)-5-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl) dihydropyrimidine-2,4(1H,3H)-dione
1-(6-(1-(3-(5-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(difluoromethyl)phenyl)-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl) dihydropyrimidine-2,4(1H,3H)-dione
4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(2-((2S)-4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)-2-methylpiperidin-1-yl)ethoxy)benzonitrile
1-(6-(1-(3-(2-bromo-5-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl) dihydropyrimidine-2,4(1H,3H)-dione
1-(6-(1-(2-(5-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(difluoromethyl)phenoxy)ethyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl) dihydropyrimidine-2,4(1H,3H)-dione
4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(6-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)-2-azaspiro[3.3]heptan-2-yl)-2-methylpropyl)benzonitrile
4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(3-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)azetidin-1-yl)-2-methylpropyl)benzonitrile
2-(3-cyano-2-((4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)propyl)-4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzonitrile
1-(6-(1-(3-(3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenoxy)propyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl) dihydropyrimidine-2,4(1H,3H)-dione formate
4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)propoxy)benzonitrile

1-(6-(1-((1-((3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenoxy)methyl)cyclopropyl)methyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione
1-(6-(1-(3-(2-chloro-5-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione
1-(6-(1-(3-(3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-3,3-difluoropropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione
2-(4-cyano-3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)butyl)-4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzonitrile
4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperazin-1-yl)-2-methylpropyl)benzonitrile
4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(3-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl)-2-methylpropyl)benzonitrile
1-(6-(1-(4-(5-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(difluoromethyl)phenyl)butan-2-yl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione
4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-((1-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-3-methoxypropan-2-yl)oxy)benzonitrile
3-(6-(1-(3-(5-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(difluoromethyl)phenyl)-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)piperidine-2,6-dione
1-(6-(1-(2-(3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzyl)-3,3,3-trifluoropropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione
1-(6-(1-(3-(5-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-oxopyridin-1(2H)-yl)-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione
4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(1-(2,6-dioxopiperidin-3-yl)-1H-indazol-5-yl)piperidin-1-yl)-2-methylpropyl)benzonitrile
4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)butyl)benzonitrile
1-(1-methyl-6-(1-(2-methyl-3-(4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)propyl)piperidin-4-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione
1-(6-(1-(4-(4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)butan-2-yl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione
4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(2-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)propoxy)benzonitrile
4-((4-((5-(chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(2-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)propoxy)benzonitrile
2-(2-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)propoxy)-4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzonitrile

1-(6-(1-(3-(4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-1-methyl-1H-imidazol-2-yl)-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl) dihydropyrimidine-2,4(1H,3H)-dione
1-(6-(1-(2-(3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzyl)-4,4,4-trifluorobutyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl) dihydropyrimidine-2,4(1H,3H)-dione
3-(6-(1-(4-(5-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(difluoromethyl)phenyl)butan-2-yl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl) piperidine-2,6-dione
1-(6-(1-(3-(3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-3,3-difluoro-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl) dihydropyrimidine-2,4(1H,3H)-dione
4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(2-(4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)ethoxy)benzonitrile
2-(2-(4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)ethoxy)-4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzonitrile
1-(6-(4-(((3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzyl)(methyl)amino)methyl)cyclohexyl)-1-methyl-1H-indazol-3-yl) dihydropyrimidine-2,4(1H,3H)-dione formate
4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)piperidin-1-yl)butyl)benzonitrile
1-(6-(1-(3-(4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(difluoromethyl)phenyl)-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl) dihydropyrimidine-2,4(1H,3H)-dione
4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-((2S)-3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-methylbutyl)benzonitrile
1-(6-(1-(4-(3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-2-methylbutan-2-yl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl) dihydropyrimidine-2,4(1H,3H)-dione
4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)piperidin-1-yl)butyl)benzonitrile
1-(6-(1-(3-(4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-1H-pyrazol-1-yl)-2-methylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl) dihydropyrimidine-2,4(1H,3H)-dione
4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-5-yl)piperidin-1-yl)butyl)benzonitrile
4-((4-((5-(cyclopropyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-methylpropyl)benzonitrile
4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(2-(4-(1-(2,6-dioxopiperidin-3-yl)-1H-indazol-5-yl)piperidin-1-yl)propoxy)benzonitrile
4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-3-methylbutyl)benzonitrile
1-(6-(1-(3-(3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-2,2-difluoropropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl) dihydropyrimidine-2,4(1H,3H)-dione

4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2,2-difluoropropyl)benzonitrile
4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)pentyl)benzonitrile
4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(4-((2,6-dioxopiperidin-3-yl)amino)phenyl)piperidin-1-yl)-2-methylpropyl)benzonitrile
4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(3-((2,6-dioxopiperidin-3-yl)amino)phenyl)piperidin-1-yl)-2-methylpropyl)benzonitrile
4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(1-(2,6-dioxopiperidin-3-yl)-3-methyl-1H-indazol-5-yl)piperidin-1-yl)-2-methylpropyl)benzonitrile
1-(6-(1-(4-(5-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-oxopyridin-1(2H)-yl)butan-2-yl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione
4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-(methoxymethyl)propyl)benzonitrile
4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-4,4,4-trifluorobutyl)benzonitrile
4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,6-dioxopiperidin-3-yl)-1-(2,2,2-trifluoroethyl)-1H-indazol-6-yl)piperidin-1-yl)-2-methylpropyl)benzonitrile formate
4-((4-((5-(difluoromethylthio)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-methylpropyl)benzonitrile
1-(6-(1-(3-(4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-oxopyridin-1(2H)-yl)-2-methylpropyl)-piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione
2-(3-(4-(1-cyclopropyl-3-(2,4-dioxo-tetrahydropyrimidin-1(2H)-yl)-1H-indazol-6-yl)piperidin-1-yl)-2-methylpropyl)-4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)-piperidin-1-yl)sulfonyl)benzonitrile
2-(3-(4-(1-(2,6-dioxopiperidin-3-yl)-1H-indazol-5-yl)piperidin-1-yl)butyl)-4-((4-((5-(trifluoro-methyl)pyrimidin-2-yl)amino)-piperidin-1-yl)sulfonyl)benzonitrile
4-((4-((5-(difluoromethoxy)-pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(2-((4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)-4-methoxybutyl)benzonitrile
4-((4-((5-cyclopropylpyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(2-(4-(3-(2,4-dioxotetrahydro-pyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-propoxy)benzonitrile
4-((4-((5-(difluoromethoxy)-pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-(oxetan-3-yl)propyl)benzonitrile
1-(1-methyl-6-(1-(4-(4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-1H-pyrazol-1-yl)butan-2-yl)-piperidin-4-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione
2-(4-cyano-2-((4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)butyl)-4-((4-((5-(difluoromethoxy)-pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzonitrile

1-(1-methyl-6-(1-(2-methyl-3-(5-methyl-4-((4-((5-(trifluoromethyl)-pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-1H-pyrazol-1-yl)propyl)piperidin-4-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione
1-(1-methyl-6-(1-(2-methyl-3-(3-methyl-4-((4-((5-(trifluoromethyl)-pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-1H-pyrazol-1-yl)propyl)piperidin-4-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione
4-((4-((5-(difluoromethoxy)-pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(3-(4-(1-(2,6-dioxopiperidin-3-yl)-1H-benzo-[d][1,2,3]triazol-5-yl)-piperidin-1-yl)-2-methylpropyl)-benzonitrile
1-(1-methyl-6-(1-(2-methyl-3-(3-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-1H-pyrazol-1-yl)propyl)piperidin-4-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione
1-(6-(1-(1-(2-fluoro-5-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-phenoxy)propan-2-yl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione
(R)-4-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-((1-(4-(3-(2,4-dioxotetrahydro-pyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)propan-2-yl)oxy)benzonitrile
(R)-2-((1-(4-(3-(2,4-dioxotetra-hydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)propan-2-yl)oxy)-4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-benzonitrile
(R)-4-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-((1-(4-(3-(2,4-dioxotetra-hydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)propan-2-yl)amino)-benzonitrile 2,2,2-trifluoroacetate
(R)-2-((1-(4-(3-(2,4-dioxotetra-hydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)propan-2-yl)amino)-4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzonitrile 2,2,2-trifluoroacetate
4-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-((1-(4-(3-(2,4-dioxotetra-hydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)propan-2-yl)thio)benzonitrile
2-((1-(4-(3-(2,4-dioxotetra-hydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)propan-2-yl)thio)-4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-benzonitrile
(E)-2-(3-(4-(3-(2,4-dioxotetra-hydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)but-1-en-1-yl)-4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-benzonitrile
1-(1-methyl-6-(1-(2-methyl-3-(4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)-sulfonyl)-1H-imidazol-1-yl)-propyl)piperidin-4-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione
4-((4-((5-(difluoromethoxy)-pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(2-((4-(3-(2,6-dioxopiperidin-3-yl)-1-methyl-1H-indazol-6-yl)cyclohexyl)oxy)-ethyl)benzonitrile
1-(1-methyl-6-(1-(2-methyl-3-(4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)-sulfonyl)-1H-1,2,3-triazol-1-yl)propyl)piperidin-4-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione
N-(2-cyano-5-((4-((5-(difluoro-methoxy)pyrimidin-2-yl)amino)-piperidin-1-yl)sulfonyl)phenyl)-2-(4-(3-(2,4-dioxotetrahydro-pyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-acetamide 2,2,2-trifluoroacetate
4-((4-((5-(2,2-difluorocyclo-propyl)pyrimidin-2-yl)amino)-piperidin-1-yl)sulfonyl)-2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-methylpropyl)-benzonitrile

2-(4-cyano-2-((4-(3-(2,4-dioxo-tetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)butyl)-4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-benzonitrile
4-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(4-cyano-2-((4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)butyl)-benzonitrile
2-(2-cyclopropyl-3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)propyl)-4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-benzonitrile
1-(1-methyl-6-(1-(2-methyl-3-(4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)-sulfonyl)-1H-pyrazol-1-yl)-propyl)piperidin-4-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione
2-(3-(4-(3-(2,4-dioxotetrahydro-pyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-methylbutyl)-4-((4-((5-(trifluoro-methyl)pyrimidin-2-yl)amino)-piperidin-1-yl)sulfonyl)benzonitrile
2-(3-(4-(3-(2,4-dioxotetrahydro-pyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-methylbutyl)-4-((4-((5-(trifluoro-methyl)pyrimidin-2-yl)amino)-piperidin-1-yl)sulfonyl)benzonitrile
(S)-2-((1-(4-(3-(2,4-dioxo-tetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)propan-2-yl)oxy)-4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-benzonitrile
(S)-4-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-((1-(4-(3-(2,4-dioxotetrahydro-pyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)propan-2-yl)oxy)benzonitrile
(R)-4-((4-((5-cyclopropylpyrimidin-2-yl)amino)piperidin-1-yl)-sulfonyl)-2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-methylpropyl)-benzonitrile
(S)-4-((4-((5-cyclopropylpyrimidin-2-yl)amino)piperidin-1-yl)-sulfonyl)-2-(3-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)-2-methylpropyl)-benzonitrile
(S)-4-((4-((5-chloropyrimidine-2-yl)amino)piperidin-1-yl)sulfonyl)-2-((1-(4-(3-(2,4-dioxotetra-hydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)propan-2-yl)amino)-benzonitrile
(S)-2-((1-(4-(3-(2,4-dioxotetra-hydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)propan-2-yl)amino)-4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-benzonitrile
1-(6-(1-(1-(2-chloro-5-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)-sulfonyl)phenoxy)propan-2-yl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione
4-((4-((5-cyclopropylpyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-((1-(4-(3-(2,4-dioxotetra-hydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)butan-2-yl)oxy)benzonitrile
4-((4-((5-cyclopropylpyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-((2-(4-(3-(2,4-dioxotetrahydro-pyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)ethyl)amino)benzonitrile
2-((1-(4-(3-(2,4-dioxotetrahydro-pyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)butan-2-yl)oxy)-4-((4-((5-(trifluoromethyl)-pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzonitrile

(S)-1-(6-(1-(3-(5-((4-((5-cyclopropylpyrimidin-2-yl)amino)-piperidin-1-yl)sulfonyl)-2-(difluoromethyl)phenyl)-2-methyl-propyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl) dihydro-pyrimidine-2,4(1H,3H)-dione
1-(6-(1-(2-(2-chloro-5-((4-((5-cyclopropylpyrimidin-2-yl)amino)-piperidin-1-yl)sulfonyl)phenoxy)-propyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl) dihydro-pyrimidine-2,4(1H,3H)-dione formate
1-(6-(1-(1-(2-chloro-5-((4-((5-cyclopropylpyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-phenoxy)propan-2-yl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl) dihydro-pyrimidine-2,4(1H,3H)-dione formate
1-(6-(1-(1-(5-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)-sulfonyl)-2-(difluoromethyl)phenoxy)propan-2-yl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl) dihydro-pyrimidine-2,4(1H,3H)-dione
2-(2-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)butoxy)-4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzonitrile and
2-((1-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)butan-2-yl)oxy)-4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzonitrile

or a pharmaceutically acceptable salt thereof.

49. A pharmaceutical composition comprising a compound of any one of claims 1 to 48, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

50. A method of treating a disease mediated by CDK2 in a patient which method
5 comprises administering to the patient in recognized need thereof, a therapeutically effective amount of a compound of any one of claims 1 to 48, or a pharmaceutical composition of claim 49.

51. A method of treating cancer in a patient which method comprises administering to the patient in need thereof, a therapeutically effective amount a compound of any one of claims 1 to 48, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 49.

10 52. The method of claim 51, wherein the compound of any one of claims 1 to 48 or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of 49 is administered in combination with at least one other anticancer agent.