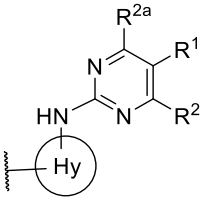
Summary

Provided herein is a compound for use in the degradation and/or inhibition of CDK2 wherein the compound comprises a CDK2 binding moiety of Formula (A1):



(A1)

wherein:

R^1 is alkyl, alkenyl, alkynyl, alkylthio, pentafluorothio, halo, haloalkyl, haloalkylthio, haloalkoxy, alkoxy, amino, alkylamino, dialkylamino, cyano, cycloalkyl, cycloalkoxy, cycloalkylalkyl, bridged cycloalkyl, bridged cycloalkoxy, bridged cycloalkylalkyl, cyanoalkyl, cyanoalkoxy, alkoxyalkyl, aminoalkyl, aminoalkoxy, alkylaminoalkyl, dialkylaminoalkyl, alkylaminoalkoxy, dialkylaminoalkoxy, acyl, azidocarbonyl, alkoxycarbonyl, alkylcarbonylamino, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, substituted sulfonyl, substituted sulfinyl, substituted ureido, aryl, aralkyl, aryloxy, heteroaryl, heteroaralkyl, heteroaryloxy, heterocyclyl, heterocyclylalkyl, heterocyclyloxy, fused heterocyclyl, fused heterocyclyloxy, or fused heterocyclylalkyl, wherein cycloalkyl, by itself or as part of cycloalkoxy and cycloalkylalkyl, aryl, by itself or as part of aralkyl and aryloxy, heteroaryl, by itself or as part of heteroaralkyl and heteroaryloxy, heterocyclyl, by itself or as part of heterocyclylalkyl and heterocyclyloxy, bridged cycloalkyl, alone or as part of bridged cycloalkoxy and bridged cycloalkylalkyl, and fused heterocyclyl, by itself or as part of fused heterocyclylalkyl and fused heterocyclyloxy, are substituted with one, two, or three substituents independently selected from hydrogen, alkyl, alkoxy, halo, haloalkyl, haloalkoxy, and cyano;

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

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; or

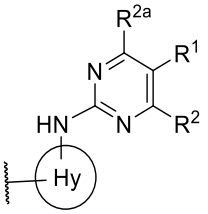
a pharmaceutically acceptable salt thereof;

wherein the compound of Formula (A1) degrades and/or inhibits CDK2 and the degradation of CDK2 is via ubiquitin proteasome pathway.

In an example, the compound of Formula (A1) degrades CDK2 via ubiquitin proteasome pathway.

In an example, the compound of Formula (A1) inhibits CDK2.

Provided herein is also a compound for use in the degradation of CDK2 wherein the compound comprises a CDK2 binding moiety of Formula (A):



(A)

wherein:

R^1 is alkyl, alkenyl, alkynyl, cycloalkyl, halo, haloalkyl, haloalkoxy, alkoxy, aryloxy, cyano, or cycloalkyl where the cycloalkyl is substituted with one to three halo;

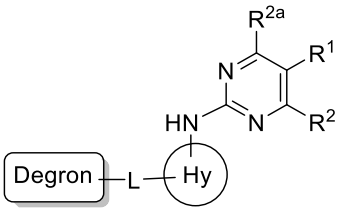
R^2 and R^{2a} are independently hydrogen or deuterium; and

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; or

a pharmaceutically acceptable salt thereof;

wherein the degradation of CDK2 is via ubiquitin proteasome pathway.

Provided herein is also the compound of Formulae (A1) and (A) for use in the degradation of CDK2 as described above are as according to Formula (I):



(I)

wherein:

R^1 is as defined therein;

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

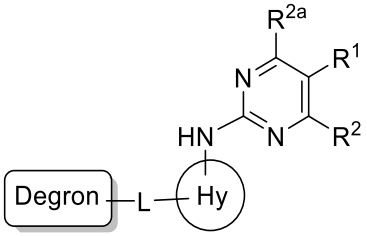
Hy is cycloalkylene, arylene, heteroarylene, heterocyclylene, bicyclic heterocyclylene, spiro heterocyclylene, bridged heterocyclylene, or fused heterocyclylene, where each of the aforementioned rings is substituted with R^a, R^b, and R^c independently selected from hydrogen, deuterium, alkyl, halo,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

L is a linker; and

Degron is an E3 ubiquitin ligase ligand; or

a pharmaceutically acceptable salt thereof.

Provided herein is also a compound of Formula (Ia):



(Ia)

wherein

R^1 is alkyl, alkenyl, alkynyl, alkylthio, pentafluorothio, halo, haloalkyl, haloalkylthio, haloalkoxy, alkoxy, amino, alkylamino, dialkylamino, cyano, cycloalkyl, cycloalkoxy, cycloalkylalkyl, bridged cycloalkyl, bridged cycloalkoxy, bridged cycloalkylalkyl, cyanoalkyl, cyanoalkoxy, alkoxyalkyl, aminoalkyl, aminoalkoxy, alkylaminoalkyl, dialkylaminoalkyl, alkylaminoalkoxy, dialkylaminoalkoxy, acyl, azidocarbonyl, alkoxycarbonyl, alkylcarbonylamino, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, substituted sulfonyl, substituted sulfinyl, substituted ureido, aryl, aralkyl, aryloxy, heteroaryl, heteroaralkyl, heteroaryloxy, heterocyclyl, heterocyclylalkyl, heterocyclyloxy, fused heterocyclyl, fused heterocyclyloxy, or fused heterocyclylalkyl, wherein cycloalkyl, by itself or as part of cycloalkoxy and cycloalkylalkyl, aryl, by itself or as part of aralkyl and aryloxy, heteroaryl, by itself or as part of heteroaralkyl and heteroaryloxy, heterocyclyl, by itself or as part of heterocyclylalkyl and heterocyclyloxy, bridged cycloalkyl, alone or as part of bridged cycloalkoxy and bridged cycloalkylalkyl, and fused heterocyclyl, by itself or as part of fused heterocyclylalkyl and fused heterocyclyloxy, are substituted with one, two, or three substituents independently selected from hydrogen, alkyl, alkoxy, halo, haloalkyl, haloalkoxy, and cyano;

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

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;

Z^4 is a bond, alkylene, alkynylene, -(alkylene-NR")-, -(NR"-alkylene)-, -O-, -C(O)-, -NR"-, -(O-alkylene)$_d$-, -(alkylene-O)$_d$-, cycloalkylene, -(alkylene)-cycloalkylene-, -cycloalkylene-(alkylene)-, spiro cyclolalkylene, phenylene, heteroarylene, heterocyclylene, -(alkylene)-heterocyclylene-, -heterocyclylene-(alkylene)-, fused heterocyclylene, bridged heterocyclylene, -(alkylene)-bridged heterocyclylene-, -bridged heterocyclylene-(alkylene)-, spiro heterocyclylene, -(alkylene)-spiro heterocyclylene, or -spiro heterocyclylene-(alkylene)-, where each ring, by itself or as part of another group, is substituted with R^o and R^p independently selected from hydrogen, deuterium, alkyl, alkoxy, halo, haloalkyl, haloalkoxy, cyano, hydroxy, amino, alkylamino, and dialkylamino;

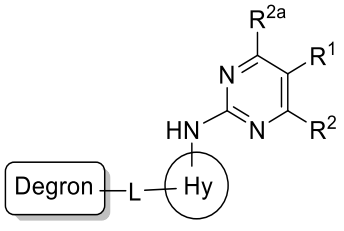
Z^5 is a bond, -alkylene, -NR"-, -O-, -C(O)-, -S(O)$_2$-, -NR'(CO)-, -C(O)NR-, phenylene, monocyclic heteroarylene, or heterocycylene, where each ring is substituted with R^q and R^r independently selected from hydrogen, deuterium, alkyl, alkoxy, halo, haloalkyl, haloalkoxy, cyano, hydroxy, amino, alkylamino, and dialkylamino; and

Z^6 is a bond, alkylene, -NR"-, -O-, -(alkylene-O)-, -C(O)-, -S(O)$_2$-, -NR'(CO)-, or -C(O)NR-;

where each R, R' and R" is independently hydrogen or alkyl, each a, b, c, and d is independently an integer selected from 1 to 6, and each alkylene of -Z^1-, -Z^2-, -Z^3-, -Z^4-, -Z^5- and -Z^6-, by itself or as part of another group, is independently substituted with R^s and R^t where R^s is hydrogen or deuterium and R^t is hydrogen, deuterium, haloalkyl, hydroxy, alkoxy, cyano, cycloalkyl, heterocyclyl, aryl, or monocyclic heteroaryl, wherein cycloalkyl, heterocyclyl, aryl, monocyclic heteroaryl are substituted with one or two substituents independently selected from hydrogen, alkyl, alkoxy, halo, haloalkyl, haloalkoxy, or cyano; provided that at least one of -Z^1-Z^2-Z^3-Z^4-Z^5-Z^6- is not a bond;

or a pharmaceutically acceptable salt thereof.

In one aspect, provided is a compound of Formula (Ia):



(Ia)

wherein:

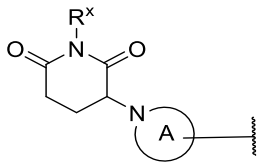
R^1 is C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, halo, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy, aryloxy, cyano, or cycloalkyl where the cycloalkyl is substituted with one to three halo;

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

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, C_1-C_6-alkyl, halo, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, hydroxy, and cyano;

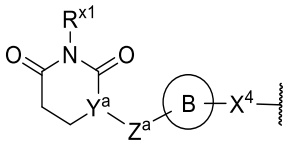
Degron is an E3 ubiquitin ligase ligand selected from:

(a) a group of formula (i):



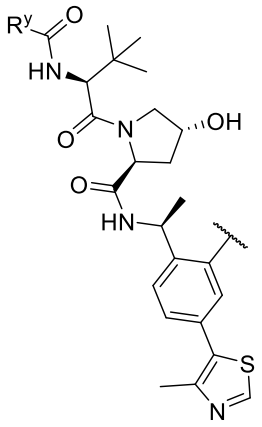
(i);

(b) a group of formula (ii):



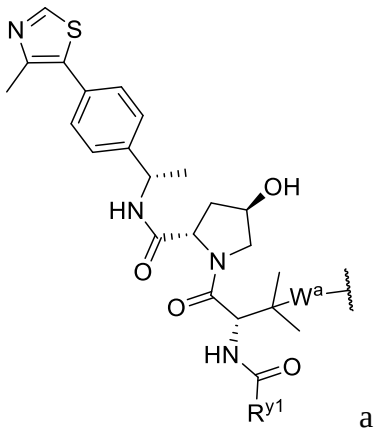
(ii);

(c) a group of formula (iii):



(iii);

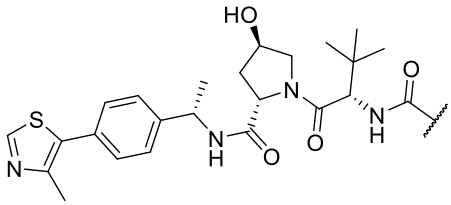
(d) a group of formula (iv):



a

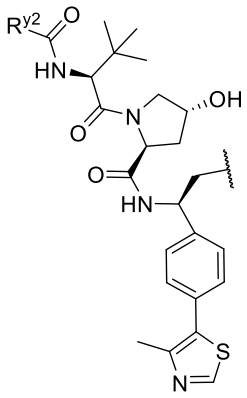
(iv);

(e) a group of formula (v):



(v); and

(f) a group of formula (vi):



(vi);

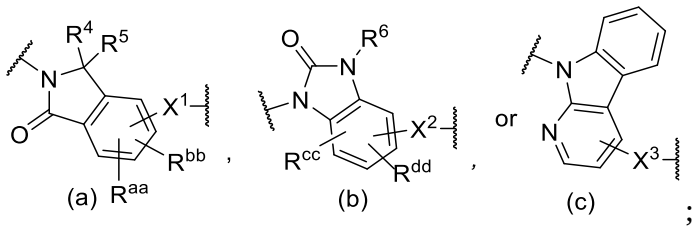
where:

R^x and R^{x1} are each hydrogen;

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), (b), or (c):



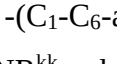
where:

R^{aa}, R^{bb}, R^{cc}, and R^{dd} are independently selected from hydrogen, C_1-C_6-alkyl, C_1-C_6-alkoxy, halo, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, 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; and

R^6 is hydrogen or C_1-C_6-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 nitrogen ring atoms and further wherein the phenylene, cyclylaminylene, and each heteroarylene are independently substituted with R^{ee} and R^{ff} independently selected from hydrogen, C_1-C_6-alkyl, cycloalkyl, C_1-C_6-alkoxy, halo, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, and cyano; and

X^1, X^2, X^3, and X^4 are independently a bond, -C_1-C_6-alkylene-, -O-, -(O-C_1-C_6-alkylene)-, -(C_1-C_6-alkylene-O)-, -(NR^{gg}-C_1-C_6-alkylene)-, -(C_1-C_6-alkylene-NR^{hh})-, , -NH-, -N(C_1-C_6-alkyl)-, –C(=O)-, –NR^{jj}C(=O)-, or –C(=O)NR^{kk}- where R^{gg}, R^{hh}, R^{jj}, and R^{kk} are independently hydrogen, C_1-C_6-alkyl, or cycloalkyl and each C_1-C_6-alkylene, itself or as part of another group, is optionally substituted with one or two fluoro;

R^y, R^{y1}, and R^{y2} are independently C_1-C_6-alkyl, hydroxy-C_1-C_6-alkyl, cycloalkyl or heterocyclyl wherein cycloalkyl and heterocyclyl are substituted with R^d and R^f selected from hydrogen, halo, cyano, C_1-C_6-alkylcarbonyl, and C_1-C_6-alkylcarbonylamino; and

W^a is bond, O, S, or C_1-C_6-alkylene; and

L is -Z^1-Z^2-Z^3-Z^4-Z^5-Z^6- where:

Z^1 is a bond, C_1-C_6-alkylene, -C(O)NR-, -NR'(CO)-, -$S(O)_2$NR-, -NR'$S(O)_2$-, -(O-C_1-C_6-alkylene)$_a$-, -(C_1-C_6-alkylene-O)$_a$-, phenylene, monocyclic heteroarylene, or heterocyclylene, where each ring is substituted with R^h and R^i independently selected from hydrogen, deuterium, C_1-C_6-alkyl, C_1-C_6-alkoxy, halo, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, cyano, hydroxy, amino, C_1-C_6-alkylamino, and di-C_1-C_6-alkylamino;

Z^2 is a bond, C_1-C_6-alkylene, C_2-C_6-alkynylene, -C(O)-, -C(O)N(R)-, -NR'(CO)-, -(O-C_1-C_6-alkylene)$_b$-, -(C_1-C_6-alkylene-O)$_b$-, -O(CH_2)$_7$-, -O(CH_2)$_8$-, cycloalkylene, or -heterocyclylene,

where each ring is substituted with R^j and R^k independently selected from hydrogen, deuterium, C_1-C_6-alkyl, alkoxy, halo, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, cyano, hydroxy, amino, C_1-C_6-alkylamino, and di-C_1-C_6-alkylamino;

Z^3 is a bond, C_1-C_6-alkylene, C_2-C_6-alkynylene, -C(O)NR-, -NR'(CO)-, -O-, -NR"-, -(O-C_1-C_6-alkylene)$_c$-, -(C_1-C_6-alkylene-O)$_c$-, cycloalkylene, spiro cyclolalkylene, phenylene, -(C_1-C_6-alkylene)-phenylene-, -phenylene-(C_1-C_6-alkylene)-, monocyclic heteroarylene, -(C_1-C_6-alkylene)-monocyclic heteroarylene-, -monocyclic heteroarylene-(C_1-C_6-alkylene)-, heterocyclylene, -(C_1-C_6-alkylene)-heterocyclylene-, -heterocyclylene-(C_1-C_6-alkylene)-, bicyclic heterocyclylene, bridged heterocyclylene, -(C_1-C_6-alkylene)-bridged heterocyclylene-, -bridged heterocyclylene-(C_1-C_6-alkylene)-, fused heterocyclylene, spiro heterocyclylene, -(C_1-C_6-alkylene)-spiro heterocyclylene-, -spiro heterocyclylene-(C_1-C_6-alkylene)-, or 11 to 13 membered spiro heterocyclylene, where each ring, by itself or as part of another group, is substituted with R^m and R^n independently selected from hydrogen, deuterium, C_1-C_6-alkyl, C_1-C_6-alkoxy, halo, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, cyano, hydroxy, amino, C_1-C_6-alkylamino, and di-C_1-C_6-alkylamino;

Z^4 is a bond, C_1-C_6-alkylene, C_2-C_6-alkynylene, -(C_1-C_6-alkylene-NR")-, -(NR"-C_1-C_6-alkylene)-, -O-, -C(O)-, -NR"-, -(O-C_1-C_6-alkylene)$_d$-, -(C_1-C_6-alkylene-O)$_d$-, cycloalkylene, -(C_1-C_6-alkylene)-cycloalkylene-, -cycloalkylene-(C_1-C_6-alkylene)-, spiro cyclolalkylene, phenylene, heteroarylene, heterocyclylene, -(C_1-C_6-alkylene)-heterocyclylene-, -heterocyclylene-(C_1-C_6-alkylene)-, fused heterocyclylene, bridged heterocyclylene, -(C_1-C_6-alkylene)-bridged heterocyclylene-, -bridged heterocyclylene-(C_1-C_6-alkylene)-, spiro heterocyclylene, -(C_1-C_6-alkylene)-spiro heterocyclylene, or -spiro heterocyclylene-(C_1-C_6-alkylene)-, where each ring, by itself or as part of another group, is substituted with R^o and R^p independently selected from hydrogen, deuterium, C_1-C_6-alkyl, C_1-C_6-alkoxy, halo, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, cyano, hydroxy, amino, C_1-C_6-alkylamino, and di-C_1-C_6-alkylamino;

Z^5 is a bond, -C_1-C_6-alkylene, -NR"-, -O-, -C(O)-, -S(O)$_2$-, -NR'(CO)-, -C(O)NR-, phenylene, monocyclic heteroarylene, or heterocycylene, where each ring is substituted with R^q and R^r independently selected from hydrogen, deuterium, C_1-C_6-alkyl, C_1-C_6-alkoxy, halo, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, cyano, hydroxy, amino, C_1-C_6-alkylamino, and di-C_1-C_6-alkylamino; and

Z^6 is -S(O)$_2$-;

where each R, R' and R" is independently hydrogen or C_1-C_6-alkyl, each a, b, c, and d is independently an integer selected from 1 to 6, and each C_1-C_6-alkylene of -Z^1-, -Z^2-, -Z^3-, -Z^4-, and -Z^5-, by itself or as part of another group, is independently substituted with R^s and R^t where R^s

is hydrogen or deuterium and R^t is hydrogen, deuterium, halo-C_1-C_6-alkyl, hydroxy, C_1-C_6-alkoxy, cyano, cycloalkyl, heterocyclyl, aryl, or monocyclic heteroaryl, wherein cycloalkyl, heterocyclyl, aryl, monocyclic heteroaryl are substituted with one or two substituents independently selected from hydrogen, C_1-C_6-alkyl, C_1-C_6-alkoxy, halo, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, or cyano; or

a pharmaceutically acceptable salt thereof.

Provided herein is also a method of treating a disease mediated by CDK2 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 (A1), Formula (A), Formula (I) or a compound of Formula (Ia) as defined herein (or any of the examples thereof described herein), or a pharmaceutically acceptable salt thereof. (For the sake of clarity, the phrase “any of the embodiments thereof described herein” or “any of the examples thereof described herein” includes embodiments or examples of the compound of Formula (A1), Formula (A), Formula (I)and Formula (Ia) disclosed herein, unless stated otherwise.) In an example, the disease is cancer.

In another aspect, provided is use of a compound as defined herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein in the manufacture of a medicament for the treatment of cancer.

In an example, the disease is cancer selected from lung cancer (*e.g.,* adenocarcinoma, small cell lung cancer and 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, 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), ovarian cancer, prostate cancer, testicular cancer, uterine cancer, esophageal cancer, gall bladder cancer, pancreatic cancer (*e.g.*, exocrine pancreatic carcinoma), stomach cancer, thyroid cancer, and parathyroid cancer. In an example, the cancers are those that are resistant to CDK4/6 inhibitors through CDK2-mediated mechanisms e.g., breast cancer. In an example, 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 (A1), Formula (A), Formula (I) or a compound of Formula (Ia) (or any of the examples thereof described herein), or a pharmaceutically acceptable salt thereof. In some examples, 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 an example, the disease is gout. In an example, the therapeutically effective amount of a compound of Formulas (A1), (A), (I), or (Ia) (or any example thereof disclosed herein including specific compounds), or a pharmaceutically acceptable salt thereof, is administered in a pharmaceutical composition.

In another aspect, provided is a compound as defined herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein for use in therapy.

Provided is also 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 (A1), Formula (A), Formula (I), or a compound of Formula (Ia) as defined herein (or any of the examples thereof described herein), or a pharmaceutically acceptable salt thereof. In an example, the amount of hearing loss is reduced when compared to an age-matched control. In some examples, the hearing loss is prevented when compared to an age-matched control.

In another aspect, provided is a pharmaceutical composition comprising a compound of Formula (A1), Formula (A), Formula (I) or a compound of Formula (Ia) as defined herein (or any of the examples thereof described herein), or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable excipient.

Provided is also a compound of Formula (A1), Formula (A), Formula (I) or a compound of Formula (Ia) as defined herein (or any of the examples thereof described herein), or a pharmaceutically acceptable salt thereof for use as a medicament. In an example, the compound of Formula (A1), Formula (A), Formula (I) or Formula (Ia) as defined herein (or any examples thereof disclosed herein), or a pharmaceutically acceptable salt thereof is useful for the treatment of one or more of diseases disclosed above.

Provided is also the use of a compound of Formula (A1), Formula (A), Formula (I) or a compound of Formula (Ia) as defined herein (or any of the examples 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 contributes to the pathology and/or symptoms of the disease. In an example, the disease is one or more of diseases disclosed above.

Provided is also a method of degrading CDK2 in a cell via ubiquitin proteasome pathway which method comprises contacting the cell with a compound comprising a 2,5-disubstituted pyrimidinyl moiety wherein said moiety binds to CDK2, or a pharmaceutically acceptable salt thereof. In an example, the 2,5-disubstituted pyrimidinyl moiety is a moiety of Formula(Ia) as defined herein (or examples thereof as disclosed herein, including specific compounds). In another example, the CDK2 is degraded in a cell in a patient.

In an example, CDK2 is selectively degraded over CDK1. In another example, CDK2 is selectively degraded over CDK1 and CDK4 and/or CDK6.

In the aforementioned involving the treatment of cancer, further examples are provided comprising administering the compound of Formula (A1), Formula (A), Formula (I), and Formula (Ia), or a pharmaceutically acceptable salt thereof (or any examples thereof disclosed herein) or the pharmaceutical composition as defined herein, 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:

alkoxy, hydroxy, and cyano, unless stated otherwise. Representative examples include, but are not limited to, spiro[3,5]nonandiyl *e.g.*, spiro[3.5]nonane-2,7-diyl, 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. 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.

"11 to 13 membered spiro heterocyclylene" means a saturated bicyclic divalent ring having 11 to 13 ring atoms in which one, two, or three ring atoms are heteroatom(s) 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"). The 11 to 13 membered 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, diazaspiro[5.5]undecan-diyl, 1-oxa-diazaspiro[5.5]undecan-diyl, and the like.

"Pentafluorothio" means an $-SF_5$.

"Sulfinyl" means an -S(O)- group.

"Substituted sulfinyl" means an $-S(O)R^z$ where R^z is alkyl as defined above e.g., methyl or ethylsulfinyl.

"Sulfonyl" means an $-S(O)_2-$ group.

"Substituted sulfonyl" means an $-S(O)_2R^z$ where R^z is alkyl as defined above e.g., methyl or ethylsulfonyl.

"Thioether" means an -S- group.

"Thioureido" means an -NHC(S)NH- group.

"Ureido" means an -NHC(O)NH- group.

"Substituted ureido" means an $-NHC(O)NR^zR^{z'}$ where R^z is hydrogen or alkyl and $R^{z'}$ is alkyl, as defined above e.g., -NHC(O)NHmethyl, $-NHC(O)NMe_2$, and the like.

The present disclosure also includes protected derivatives of compounds of Formula (A1), Formula (A), Formula (I), or Formula (Ia) (or any embodiments thereof disclosed herein), or a pharmaceutically acceptable salt thereof. For example, when compounds of Formula (Ia) 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 (A1), Formula (A), Formula (I), or Formula (Ia) (or any embodiments thereof disclosed herein), or a pharmaceutically acceptable salt thereof.

The term "prodrug" refers to a compound that is made more active in vivo. Certain compounds Formulas (A1), (A), (I), or (Ia) (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-

"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;

(2) inhibiting the disease, *i.e.*, delaying, arresting, 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 (A1), Formula (A), Formula (I), and Formula (Ia) and embodiments thereof, can also inhibit CDK2. The term "inhibiting" and "reducing," or any variation of these terms in relation of CDK2, includes any measurable decrease or complete inhibition 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 activity, compared to normal.

The term "degrading" and "degrade," or any variation of these terms in relation of CDK2 and CDK1, means any measurable decrease in the concentration of CDK2 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 concentration in a sample containing CDK2, and a compound disclosed herein in the Summary, Embodiments, and Compound Table 1 disclosed herein (including a compound of Formula (A1), (A), (I), or (Ia)) as compared to an equivalent sample comprising CDK2, 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 ≥ 40%. In one embodiment, the decrease in the concentration of CDK2 ≥ 50%. In one embodiment, the decrease in the concentration of CDK2 ≥ 60%. In one embodiment, the decrease in the concentration of CDK2 ≥ 70%. In one embodiment, the decrease in the concentration of CDK2 ≥ 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.

"E3 ubiquitin ligase ligand" means a small molecule ligand (i.e., having a molecular weight of below 2,000, 1,000, 500, or 200 Daltons), which is capable of binding to an E3 ubiquitin ligase or a subunit of E3 ligase, such as Cereblon, VHL, IAP, or MDM2.

Embodiments:

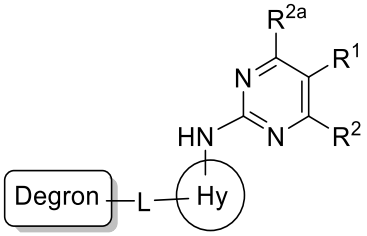
In embodiments A1A to A190, the present disclosure includes:

A1A. In embodiment A1A, provided is a compound of Formula (A1), or a pharmaceutically acceptable salt for use as described in the Summary.

A1. In embodiment A1, provided is a compound of Formula (A), or a pharmaceutically acceptable salt for use as described in the Summary.

A2. In embodiment A2, provided is a compound of Formula (I) or a pharmaceutically acceptable salt for use as described in the Summary.

A3-1. In embodiment A3-1, the compound for use of embodiment A1A, A1, or A2, or a pharmaceutically acceptable salt thereof, is wherein the compound of Formula (A1), (A), or (I) is according to Formula (Ia1):



(Ia1)

wherein:

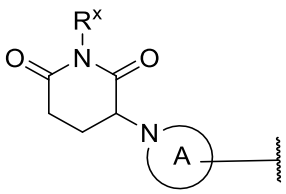
R^1 is as defined in Formula (A1), Formula (A), Formula (I), respectively;

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

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

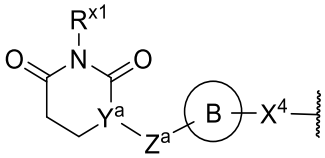
Degron is an E3 ubiquitin ligase ligand selected from:

(a) a group of formula (i):

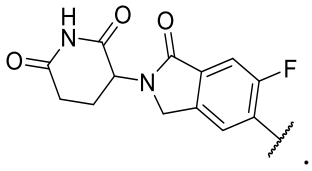


(i);

(b) a group of formula (ii):



(ii);

A189. In embodiment A189, the compound for use of any one of embodiments A3-1 to A96 and A97 to A186, or a pharmaceutically acceptable salt thereof, is wherein Degron is the E3 ubiquitin ligase ligand is .

A190. In embodiment A190, the compound for use of any one of embodiments A3-1 to A185, or a pharmaceutically acceptable salt thereof, is wherein R^x and R^{x1} are hydrogen.

For sake of clarity, embodiment A includes combination of embodiments A and subembodiments thereof.

For sake of clarity, when an embodiment refers to more than one preceding embodiments of varying scopes, the scope of the preceding embodiments control i.e., 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 A8, while all the recited groups in A8 should be selected for embodiment A1, only fluoro, chloro, and bromo should be selected for embodiment A5 as scope of R^1 in A5 is limited to halo; and only difluoromethyl, trifluoromethyl, difluoroethyl, and trifluoroethyl should be selected for embodiment A6 as scope of R^1 in A6 is limited to haloalkyl.

Additional embodiments B1-157 are:

B1A. In embodiment B1A, the compound of Formula (A1) for use, or a pharmaceutically acceptable salt thereof, is wherein the compound (or any one of the embodiments thereof disclosed in the Summary) further comprises a linker attached to the Hy of CDK2 binding moiety of formula (A1).

B1. In embodiment B1, the compound of Formula (A) for use, or a pharmaceutically acceptable salt thereof, is wherein the compound further comprises a linker attached to the Hy of CDK2 binding moiety of formula (A).

B2-1 to B2-40. In embodiments B2-1 to B2-40, the compound for use of embodiment B1 is wherein the moiety of formula (A) is as disclosed in embodiments A4-50 and A4 to A39b respectively, or a pharmaceutically acceptable salt thereof.

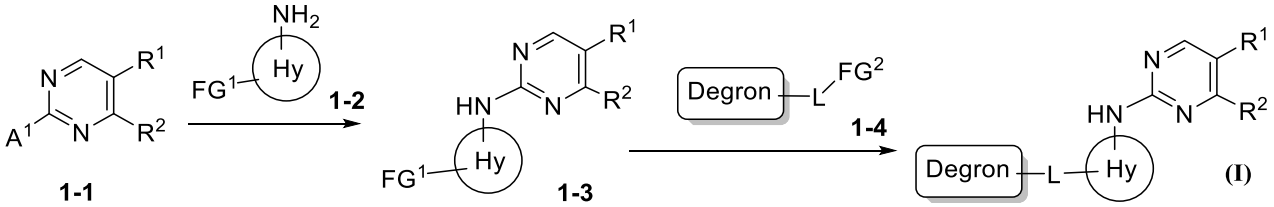
B2-41 to B2-112. In embodiments B2-41 to B2-110, the compound for use of embodiment B1A is wherein the moiety of formula (A1) is as disclosed in embodiments A4-1 to A4-50, A4, and A23 to A39b respectively, or a pharmaceutically acceptable salt thereof.

Inc., 1989). These schemes are merely illustrative of some methods by which the compounds Formulas (A1), (A), (I), or (Ia) (and 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 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 ºC to about 150 ºC, such as from about 0 ºC to about 125 ºC and further such as at about room (or ambient) temperature, *e.g.*, about 20 ºC.

Compounds of Formula (Ia), where Degron is an E3 ligase ligand of formula (i)-(vi) where R^{2a} is hydrogen, ring Hy, R^1, R^2, and L are as defined for Formula (Ia), can be prepared as described in Scheme 1 below.

Scheme 1



Treatment of a pyrimidine of formula **1-1** where A^1 is a halogen such as chlorine, or bromine, with an amine of formula **1-2**, where Hy is as defined in the Summary and FG^1 is a suitable functional group such as an acid or amine, under conditions well known in the art (such as in the presence of TEA and $ZnCl_2$ in tert-butanol), provides a compound of formula **1-3**. A compound of formula **1-4** with a suitable functional group (FG^2), such as acid, amine, or alkylhalide, reacts with FG^1 in **1-3** to afford compound of Formula (Ia). For example, the reaction is a peptide coupling reaction, where the resulting amide bond is part of L as defined in the Summary, and FG^1 and FG^2 are a combination of carboxylic acid and an amine, in the presence of suitable coupling reagents, such as a combination of HATU and DIPEA in DMF.

Alternatively, a compound of Formula (Ia) such as where R^{2a} is hydrogen, Hy is 1,4-piperidindiyl, Degron is a group of formula (i) and L is attached to Degron (i) via heterocyclylene and Hy via -SO_2-, can be synthesized as illustrated and described in Scheme 2.

leukemia (including acute myeloid leukemia, acute lymphocytic leukemia, chronic myelogenous leukemia and chronic lymphocytic leukemia), lymphoma (e.g. non-Hodgkin lymphoma NHL including mantel cell lymphoma, MCL and Hodgkin lymphoma) and multiple myeloma.
In some embodiments, the cancer is hepatocellular carcinomas, colorectal and breast cancers. In some embodiments, the cancer is ovarian cancer. In some such embodiments, the ovarian cancer is characterized by amplification or overexpression of CCNE1 and/or CCNE2.

In some 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 resistant breast cancer, anti-HER2 therapy (i.e., 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 CCNE2, and/or CCNA2. In some embodiments, the cancer is characterized by Rb deficiency and/or SKP2 amplification.

In some embodiments, the cancer can be lung cancer including NSCLC and SCLC. In some embodiments, the lung cancer can be characterized by Rb deficiency and/or SKP2 amplification.

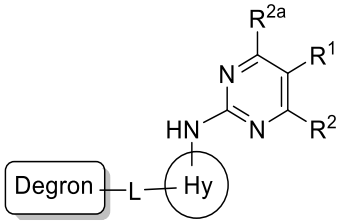
In addition, compounds of this disclosure can also be useful in treating Ewing sarcoma, liposarcoma, osteosarcoma, rhabdomyosarcoma, neuroblastoma, medulloblastoma and AL in pediatric patients.

Besides cancer, CDK2 upregulation is also implicated in autoimmume 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. As such compounds of this disclosure as described in the Summary as described for Formula (A1) (or any of the embodiments thereof herein above) are useful in treating above autoimmune diseases. Pharmacologic inhibition or genetic deletion of CDK2 has also been shown to preserve hearing function in animal models treated with cisplatin or noise (*see* Teitz T. et al., *J Exp Med*. 2018 Apr 2;215(4):1187-1203). Therefore, in addition to anti-tumor therapies, CDK2 inhibition can also be used as a promising preventive treatment for noise-, cisplatin-, or antibiotic-induced or age-related hearing loss.

Testing

What is Claimed:

1. A compound of Formula (Ia):



(Ia)

wherein:

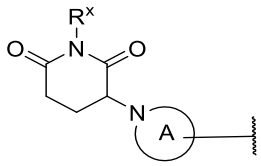
R^1 is C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, halo, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy, aryloxy, cyano, or cycloalkyl where the cycloalkyl is substituted with one to three halo;

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

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, C_1-C_6-alkyl, halo, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, hydroxy, and cyano;

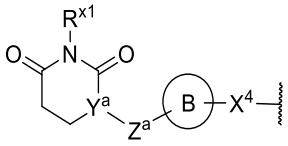
Degron is an E3 ubiquitin ligase ligand selected from:

(a) a group of formula (i):



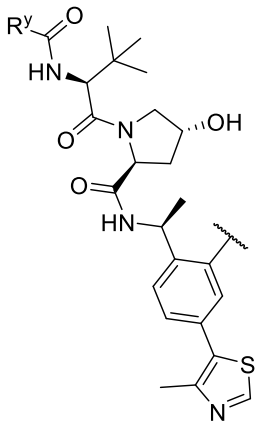
(i);

(b) a group of formula (ii):



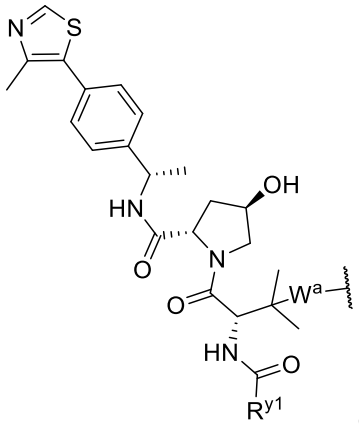
(ii);

(c) a group of formula (iii):



(iii);

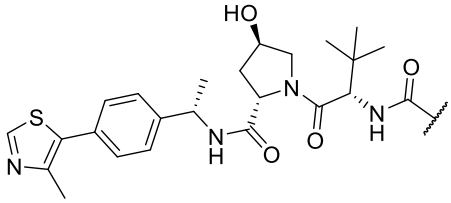
(d) a group of formula (iv):



a

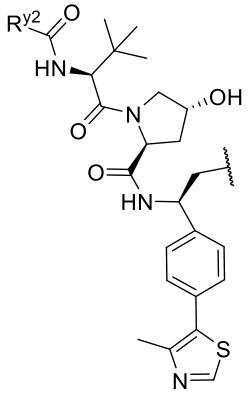
(iv);

(e) a group of formula (v):



(v); and

(f) a group of formula (vi):



(vi);

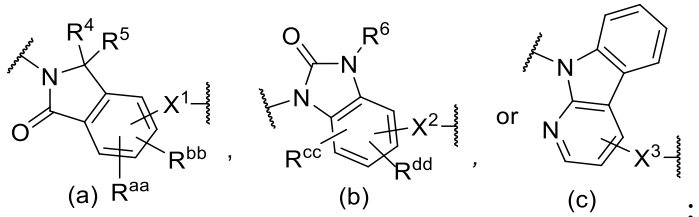
where:

R^x and R^{x1} are each hydrogen;

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), (b), or (c):



;

where:

R^{aa}, R^{bb}, R^{cc}, and R^{dd} are independently selected from hydrogen, C_1-C_6-alkyl, C_1-C_6-alkoxy, halo, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, 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; and

R^6 is hydrogen or C_1-C_6-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 nitrogen ring atoms and further wherein the phenylene, cyclylaminylene, and each heteroarylene are independently substituted with R^{ee} and R^{ff} independently selected from hydrogen, C_1-C_6-alkyl, cycloalkyl, C_1-C_6-alkoxy, halo, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, and cyano; and

X^1, X^2, X^3, and X^4 are independently a bond, -C_1-C_6-alkylene-, -O-, -(O-C_1-C_6-alkylene)-, -(C_1-C_6-alkylene-O)-, -(NR^{gg}-C_1-C_6-alkylene)-, -(C_1-C_6-alkylene-NR^{hh})-, , -

NH-, -N(C_1-C_6-alkyl)-, –C(=O)-, –NR^{jj}C(=O)-, or –C(=O)NR^{kk}- where R^{gg}, R^{hh}, R^{jj}, and R^{kk} are independently hydrogen, C_1-C_6-alkyl, or cycloalkyl and each C_1-C_6-alkylene, itself or as part of another group, is optionally substituted with one or two fluoro;

R^y, R^{y1}, and R^{y2} are independently C_1-C_6-alkyl, hydroxy-C_1-C_6-alkyl, cycloalkyl or heterocyclyl wherein cycloalkyl and heterocyclyl are substituted with R^d and R^f selected from hydrogen, halo, cyano, C_1-C_6-alkylcarbonyl, and C_1-C_6-alkylcarbonylamino; and

W^a is bond, O, S, or C_1-C_6-alkylene; and

L is -Z^1-Z^2-Z^3-Z^4-Z^5-Z^6- where:

Z^1 is a bond, C_1-C_6-alkylene, -C(O)NR-, -NR'(CO)-, -$S(O)_2$NR-, -NR'$S(O)_2$-, -(O-C_1-C_6-alkylene)$_a$-, -(C_1-C_6-alkylene-O)$_a$-, phenylene, monocyclic heteroarylene, or heterocyclylene, where each ring is substituted with R^h and R^i independently selected from hydrogen, deuterium, C_1-C_6-alkyl, C_1-C_6-alkoxy, halo, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, cyano, hydroxy, amino, C_1-C_6-alkylamino, and di-C_1-C_6-alkylamino;

Z^2 is a bond, C_1-C_6-alkylene, C_2-C_6-alkynylene, -C(O)-, -C(O)N(R)-, -NR'(CO)-, -(O-C_1-C_6-alkylene)$_b$-, -(C_1-C_6-alkylene-O)$_b$-, -O(CH_2)$_7$-, -O(CH_2)$_8$-, cycloalkylene, or -heterocyclylene, where each ring is substituted with R^j and R^k independently selected from hydrogen, deuterium, C_1-C_6-alkyl, alkoxy, halo, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, cyano, hydroxy, amino, C_1-C_6-alkylamino, and di-C_1-C_6-alkylamino;

Z^3 is a bond, C_1-C_6-alkylene, C_2-C_6-alkynylene, -C(O)NR-, -NR'(CO)-, -O-, -NR"-, -(O-C_1-C_6-alkylene)$_c$-, -(C_1-C_6-alkylene-O)$_c$-, cycloalkylene, spiro cyclolalkylene, phenylene, -(C_1-C_6-alkylene)-phenylene-, -phenylene-(C_1-C_6-alkylene)-, monocyclic heteroarylene, -(C_1-C_6-alkylene)-monocyclic heteroarylene-, -monocyclic heteroarylene-(C_1-C_6-alkylene)-, heterocyclylene, -(C_1-C_6-alkylene)-heterocyclylene-, -heterocyclylene-(C_1-C_6-alkylene)-, bicyclic heterocyclylene, bridged heterocyclylene, -(C_1-C_6-alkylene)-bridged heterocyclylene-, -bridged heterocyclylene-(C_1-C_6-alkylene)-, fused heterocyclylene, spiro heterocyclylene, -(C_1-C_6-alkylene)-spiro heterocyclylene-, -spiro heterocyclylene-(C_1-C_6-alkylene)-, or 11 to 13 membered spiro heterocyclylene, where each ring, by itself or as part of another group, is substituted with R^m and R^n independently selected from hydrogen, deuterium, C_1-C_6-alkyl, C_1-C_6-alkoxy, halo, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, cyano, hydroxy, amino, C_1-C_6-alkylamino, and di-C_1-C_6-alkylamino;

Z^4 is a bond, C_1-C_6-alkylene, C_2-C_6-alkynylene, -(C_1-C_6-alkylene-NR")-, -(NR"-C_1-C_6-alkylene)-, -O-, -C(O)-, -NR"-, -(O-C_1-C_6-alkylene)$_d$-, -(C_1-C_6-alkylene-O)$_d$-, cycloalkylene, -(C_1-C_6-alkylene)-cycloalkylene-, -cycloalkylene-(C_1-C_6-alkylene)-, spiro cyclolalkylene, phenylene, heteroarylene, heterocyclylene, -(C_1-C_6-alkylene)-heterocyclylene-, -heterocyclylene-(C_1-C_6-

alkylene)-, fused heterocyclylene, bridged heterocyclylene, -(C_1-C_6-alkylene)-bridged heterocyclylene-, -bridged heterocyclylene-(C_1-C_6-alkylene)-, spiro heterocyclylene, -(C_1-C_6-alkylene)-spiro heterocyclylene, or -spiro heterocyclylene-(C_1-C_6-alkylene)-, where each ring, by itself or as part of another group, is substituted with R^o and R^p independently selected from hydrogen, deuterium, C_1-C_6-alkyl, C_1-C_6-alkoxy, halo, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, cyano, hydroxy, amino, C_1-C_6-alkylamino, and di-C_1-C_6-alkylamino;

Z^5 is a bond, -C_1-C_6-alkylene, -NR"-, -O-, -C(O)-, -$S(O)_2$-, -NR'(CO)-, -C(O)NR-, phenylene, monocyclic heteroarylene, or heterocycylene, where each ring is substituted with R^q and R^r independently selected from hydrogen, deuterium, C_1-C_6-alkyl, C_1-C_6-alkoxy, halo, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, cyano, hydroxy, amino, C_1-C_6-alkylamino, and di-C_1-C_6-alkylamino; and

Z^6 is -$S(O)_2$-;

where each R, R' and R" is independently hydrogen or C_1-C_6-alkyl, each a, b, c, and d is independently an integer selected from 1 to 6, and each C_1-C_6-alkylene of -Z^1-, -Z^2-, -Z^3-, -Z^4-, and -Z^5-, by itself or as part of another group, is independently substituted with R^s and R^t where R^s is hydrogen or deuterium and R^t is hydrogen, deuterium, halo-C_1-C_6-alkyl, hydroxy, C_1-C_6-alkoxy, cyano, cycloalkyl, heterocyclyl, aryl, or monocyclic heteroaryl, wherein cycloalkyl, heterocyclyl, aryl, monocyclic heteroaryl are substituted with one or two substituents independently selected from hydrogen, C_1-C_6-alkyl, C_1-C_6-alkoxy, halo, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, or cyano; or

a pharmaceutically acceptable salt thereof.

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^1 is halo, halo-C_1-C_6-alkyl, or halo-C_1-C_6-alkoxy.

3. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein R^1 is halo.

4. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein R^1 is halo-C_1-C_6-alkoxy.

5. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^1 is chloro, bromo, fluoro, difluoromethyl, trifluoromethyl, difluoroethyl, trifluoroethyl, difluoromethoxy, trifluoromethoxy, difluoroethoxy, or trifluoroethoxy.

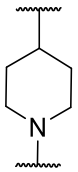
6. The compound of any one of claims 1 to 3 and 5, or a pharmaceutically acceptable salt thereof, wherein R^1 is chloro or bromo.

7. The compound of any one of claims 1, 2, 4, and 5, or a pharmaceutically acceptable salt thereof, wherein R^1 is difluoromethyl or trifluoromethyl.

8. The compound of any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, wherein both R^2 and R^{2a} are hydrogen.

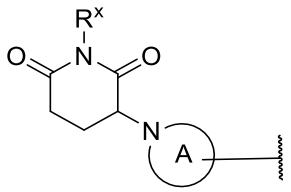
9. The compound of any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof, wherein Hy is heterocyclylene substituted with R^a, R^b, and R^c where R^a and R^b are independently selected from hydrogen, deuterium, C_1-C_6-alkyl, halo, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, and hydroxy and R^c is hydrogen.

10. The compound of any one of claims 1 to 9, or a pharmaceutically acceptable salt thereof, wherein the heterocyclylene of Hy is:



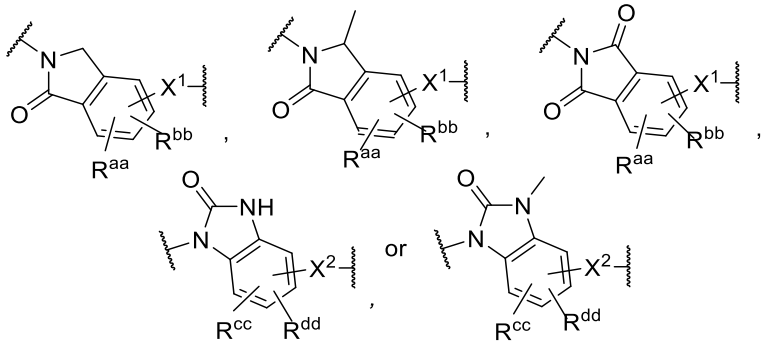
where the N atom of piperidin-1,4-diyl rings is attached to L.

11. The compound of any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof, wherein the Degron is an E3 ubiquitin ligase ligand of formula (i):



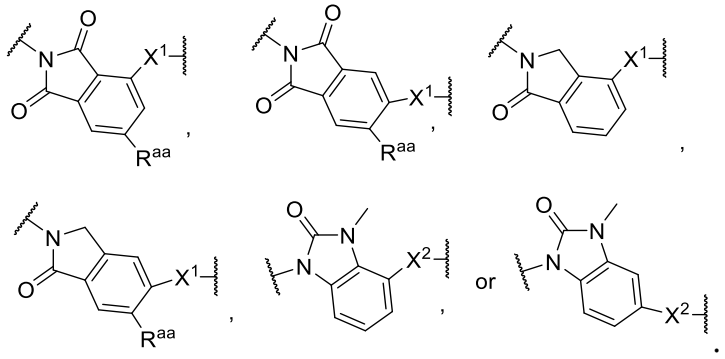
(i).

12. The compound of any one of claims 1 to 11, or a pharmaceutically acceptable salt thereof, wherein the ring A of the E3 ubiquitin ligase ligand of formula (i) is:



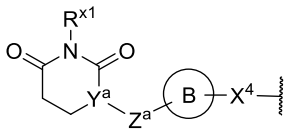
.

13. The compound of any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof, wherein ring A of the E3 ubiquitin ligase ligand of formula (i) is:



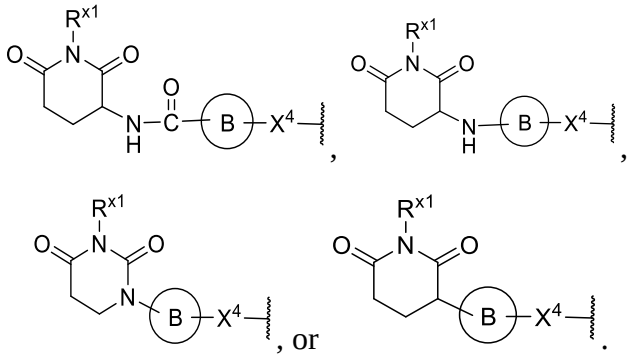
14. The compound of any one of claims 1 to 13, or a pharmaceutically acceptable salt thereof, wherein R^{aa}, R^{bb}, R^{cc}, and R^{dd} are independently selected from hydrogen, C_1-C_6-alkyl, C_1-C_6-alkoxy, halo, halo-C_1-C_6-alkyl, and halo-C_1-C_6-alkoxy.

15. The compound of any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof, wherein the Degron is an E3 ubiquitin ligase ligand of formula (ii):



(ii).

16. The compound of any one of claims 1 to 10 and 15, or a pharmaceutically acceptable salt thereof, wherein the E3 ubiquitin ligase ligand of formula (ii) is:



17. The compound of any one of claims 1 to 16, or a pharmaceutically acceptable salt thereof, wherein X^1, X^2, X^3, and X^4 are each a bond.

18. The compound of any one of claims 1 to 17, or a pharmaceutically acceptable salt thereof, wherein Z^5 is phenylene, monocyclic heteroarylene, or heterocycylene, where each ring is substituted with R^q and R^r.

19. The compound of any one of claims 1 to 16, or a pharmaceutically acceptable salt thereof, wherein:

X^1, X^2, X^3, X^4, and Z^1 are each a bond;

Z^2 is a bond, C_1-C_6-alkylene, cycloalkylene, or heterocyclylene, where each ring is substituted with R^j and R^k;

Z^3 is a bond, C_1-C_6-alkylene, -C(O)NR-, -NR'(CO)-, -O-, -NR"-, cycloalkylene, phenylene, monocyclic heteroarylene, heterocyclylene, bicyclic heterocyclylene, bridged heterocyclylene, fused heterocyclylene, or spiro heterocyclylene, where each ring is substituted with R^m and R^n;

Z^4 is a bond, C_1-C_6-alkylene, -O-, cycloalkylene, phenylene, monocyclic heteroarylene, heterocyclylene, fused heterocyclylene, or spiro heterocyclylene, where each ring is substituted with R^o and R^p; and

Z^5 is phenylene, monocyclic heteroarylene, or heterocycylene, where each ring is substituted with R^q and R^r; and

wherein each C_1-C_6-alkylene in Z^2, Z^3, and Z^4 is independently substituted with R^s and R^t.

20. The compound of any one of claims 1 to 16 and 19, or a pharmaceutically acceptable salt thereof, wherein:

X^1, X^2, X^3, X^4, Z^1, and Z^2 are each a bond;

Z^3 is cycloalkylene, phenylene, monocyclic heteroarylene, heterocyclylene, bicyclic heterocyclylene, bridged heterocyclylene, fused heterocyclylene, or spiro heterocyclylene, where each ring is substituted with R^m and R^n;

Z^4 is a bond, C_1-C_6-alkylene, -O-, cycloalkylene, phenylene, monocyclic heteroarylene, heterocyclylene, fused heterocyclylene, or spiro heterocyclylene, where each ring is substituted with R^o and R^p independently selected from hydrogen, deuterium, C_1-C_6-alkyl, C_1-C_6-alkoxy, hydroxy, cyano, halo, halo-C_1-C_6-alkyl, and halo-C_1-C_6-alkoxy; and

Z^5 is phenylene, monocyclic heteroarylene, or heterocycylene, where each ring is substituted with R^q and R^r; and

wherein C_1-C_6-alkylene in Z^4 is substituted with R^s and R^t.

21. The compound of any one of claims 1 to 16, 19, and 20, or a pharmaceutically acceptable salt thereof, wherein:

X^1, X^2, X^3, X^4, Z^1, and Z^2 are each a bond;

Z^3 is heterocyclylene, bicyclic heterocyclylene, bridged heterocyclylene, fused heterocyclylene, or spiro heterocyclylene, where each ring is substituted with R^m and R^n

independently selected from hydrogen, deuterium, C_1-C_6-alkyl, C_1-C_6-alkoxy, hydroxy, cyano, halo, halo-C_1-C_6-alkyl, and halo-C_1-C_6-alkoxy;

Z^4 is C_1-C_6-alkylene, -O-, cycloalkylene, monocyclic heteroarylene, heterocyclylene, fused heterocyclylene, or spiro heterocyclylene, where each ring is substituted with R^o and R^p independently selected from hydrogen, deuterium, C_1-C_6-alkyl, C_1-C_6-alkoxy, hydroxy, cyano, halo, halo-C_1-C_6-alkyl, and halo-C_1-C_6-alkoxy; and

Z^5 is phenylene, monocyclic heteroarylene, or heterocycylene, where each ring is substituted with R^q and R^r independently selected from hydrogen, deuterium, C_1-C_6-alkyl, C_1-C_6-alkoxy, hydroxy, cyano, halo, halo-C_1-C_6-alkyl, and halo-C_1-C_6-alkoxy; and

wherein C_1-C_6-alkylene in Z^4 is substituted with R^s and R^t.

22. The compound of any one of claims 1 to 16 and 19 to 21, or a pharmaceutically acceptable salt thereof, wherein:

X^1, X^2, X^3, and X^4, Z^1, and Z^2 are each a bond;

Z^3 is heterocyclylene, bridged heterocyclylene, or spiro heterocyclylene, where each ring is substituted with R^m and R^n independently selected from hydrogen, deuterium, C_1-C_6-alkyl, C_1-C_6-alkoxy, hydroxy, cyano, halo, halo-C_1-C_6-alkyl, and halo-C_1-C_6-alkoxy;

Z^4 is C_1-C_6-alkylene, -O-, cycloalkylene, or heterocyclylene, where each ring is substituted with R^o and R^p independently selected from hydrogen, deuterium, C_1-C_6-alkyl, C_1-C_6-alkoxy, halo, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, cyano, and hydroxy; and

Z^5 is phenylene, monocyclic heteroarylene, or heterocycylene, where each ring is substituted with R^q and R^r independently selected from hydrogen, deuterium, C_1-C_6-alkyl, C_1-C_6-alkoxy, hydroxy, cyano, halo, halo-C_1-C_6-alkyl, and halo-C_1-C_6-alkoxy; and

wherein C_1-C_6-alkylene in Z^4 is substituted with R^s and R^t.

23. The compound of any one of claims 1 to 16 and 19 to 22, or a pharmaceutically acceptable salt thereof, wherein:

X^1, X^2, X^3, X^4, Z^1, and Z^2 are each a bond;

Z^3 is heterocyclylene, bridged heterocyclylene, or spiro heterocyclylene, where each ring is substituted with R^m and R^n independently selected from hydrogen, deuterium, C_1-C_6-alkyl, C_1-C_6-alkoxy, hydroxy, cyano, halo, halo-C_1-C_6-alkyl, and halo-C_1-C_6-alkoxy;

Z^4 is C_1-C_6-alkylene or -O-; and

Z^5 is phenylene or monocyclic heteroarylene, each ring substituted with R^q and R^r independently selected from hydrogen, deuterium, C_1-C_6-alkyl, C_1-C_6-alkoxy, hydroxy, cyano, halo, halo-C_1-C_6-alkyl, and halo-C_1-C_6-alkoxy; and

wherein C_1-C_6-alkylene in Z^4 is substituted with R^s and R^t.

24. The compound of any one of claims 1 to 16 and 19, or a pharmaceutically acceptable salt thereof, wherein:

X^1, X^2, X^3, X^4, and Z^1 are each a bond;

Z^2 is cycloalkylene or heterocyclylene, where each ring is substituted with R^j and R^k independently selected from hydrogen, deuterium, C_1-C_6-alkyl, C_1-C_6-alkoxy, halo, halo-C_1-C_6-alkyl, and halo-C_1-C_6-alkoxy;

Z^3 is cycloalkylene, phenylene, monocyclic heteroarylene, heterocyclylene, bicyclic heterocyclylene, bridged heterocyclylene, fused heterocyclylene, or spiro heterocyclylene, where each ring is substituted with R^m and R^n independently selected from hydrogen, deuterium, C_1-C_6-alkyl, C_1-C_6-alkoxy, hydroxy, cyano, halo, halo-C_1-C_6-alkyl, and halo-C_1-C_6-alkoxy;

Z^4 is a bond, C_1-C_6-alkylene, or -O-; and

Z^5 is phenylene, monocyclic heteroarylene, or heterocycylene, where each ring is substituted with R^q and R^r independently selected from hydrogen, deuterium, C_1-C_6-alkyl, C_1-C_6-alkoxy, hydroxy, cyano, halo, halo-C_1-C_6-alkyl, and halo-C_1-C_6-alkoxy; and

wherein C_1-C_6-alkylene in Z^4 is substituted with R^s and R^t.

25. The compound of any one of claims 1 to 16, or a pharmaceutically acceptable salt thereof, wherein:

X^1, X^2, X^3, X^4, and Z^1 are each a bond;

Z^2 is heterocyclylene substituted with R^j and R^k;

Z^3 is a bond, C_1-C_6-alkylene, or -O-;

Z^4 is heterocyclylene, bridged heterocyclylene, or spiro heterocyclylene, where each ring is substituted with R^o and R^p; and

Z^5 is phenylene or monocyclic heteroarylene, each ring substituted with R^q and R^r; and

wherein C_1-C_6-alkylene in Z^3 is substituted with R^s and R^t.

26. The compound of any one of claims 1 to 16, or a pharmaceutically acceptable salt thereof, wherein:

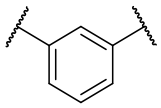
X^1, X^2, X^3, X^4, Z^1 and Z^2 are each a bond;

Z^3 is C_1-C_6-alkylene, phenylene, -(C_1-C_6-alkylene)-phenylene-, -phenylene-(C_1-C_6-alkylene)-, monocyclic heteroarylene, -(C_1-C_6-alkylene)-monocyclic heteroarylene-, -monocyclic heteroarylene-(C_1-C_6-alkylene)-, heterocyclylene, -(C_1-C_6-alkylene)-heterocyclylene-, -heterocyclylene- (C_1-C_6-alkylene)-, bridged heterocyclylene, -(C_1-C_6-alkylene)-bridged heterocyclylene-, -bridged heterocyclylene-(C_1-C_6-alkylene)-, spiro heterocyclylene, -(C_1-C_6-alkylene)-spiro heterocyclylene-, or -spiro heterocyclylene-(C_1-C_6-alkylene), where each ring, by itself or as part of another group, is substituted with R^m and R^n;

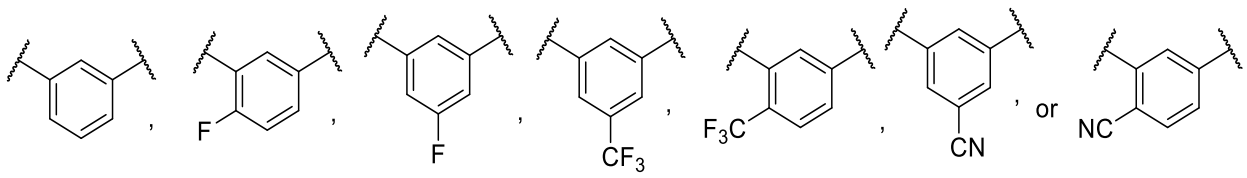
Z^4 is C_1-C_6-alkylene, -(C_1-C_6-alkylene-NR")-, -(NR"-C_1-C_6-alkylene)-, -O-, -NR"-, -(O-C_1-C_6-alkylene)$_d$-, -(C_1-C_6-alkylene-O)$_d$-, cycloalkylene, -(C_1-C_6-alkylene)-cycloalkylene-, -cycloalkylene-(C_1-C_6-alkylene)-, spiro cyclolalkylene, phenylene, heteroarylene, heterocyclylene, -(C_1-C_6-alkylene)-heterocyclylene-, -heterocyclylene-(C_1-C_6-alkylene)-, fused heterocyclylene, bridged heterocyclylene, -(C_1-C_6-alkylene)-bridged heterocyclylene-, -bridged heterocyclylene-(C_1-C_6-alkylene)-, spiro heterocyclylene, -(C_1-C_6-alkylene)-spiro heterocyclylene, or -spiro heterocyclylene-(C_1-C_6-alkylene)-, where each ring, by itself or as part of another group, is substituted with R^o and R^p;

Z^5 is phenylene, monocyclic heteroarylene, or heterocycylene, where each ring is substituted with R^q and R^r; and

each alkylene in Z^3 and Z^4, itself or as part of another group, is independently substituted with R^s and R^t.

27. The compound of any one of claims 1 to 26, or a pharmaceutically acceptable salt thereof, wherein -Z^5- is  substituted with R^q and R^r independently selected from hydrogen, deuterium, C_1-C_6-alkyl, C_1-C_6-alkoxy, halo, halo-C_1-C_6-alkyl, and halo-C_1-C_6-alkoxy.

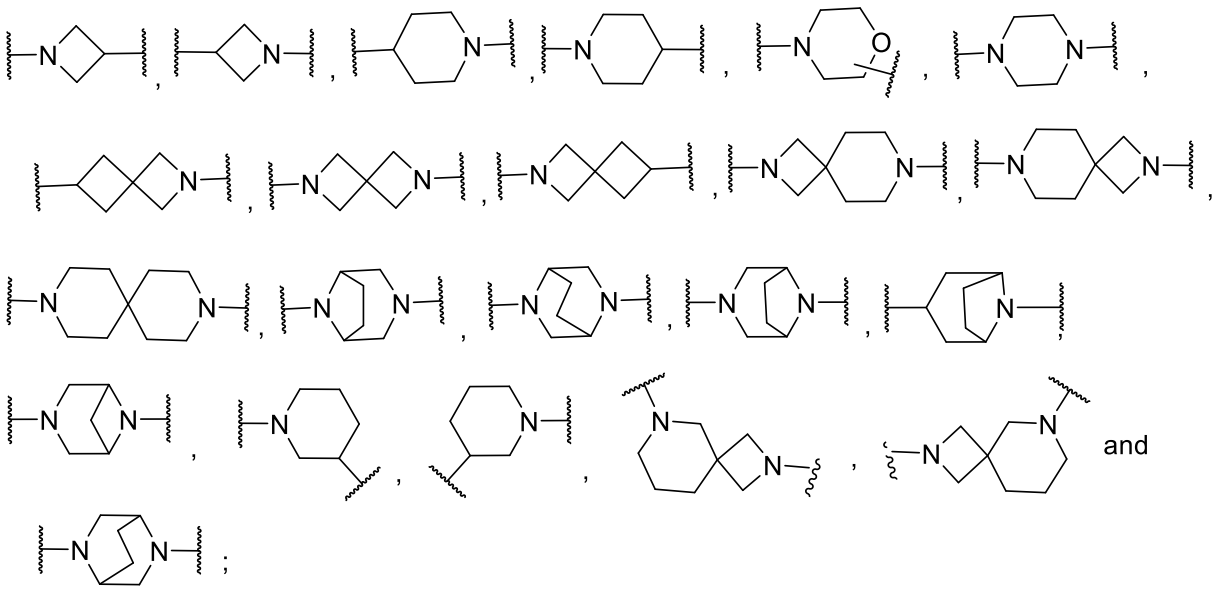
28. The compound of any one of claims 1 to 27, or a pharmaceutically acceptable salt thereof, wherein -Z^5- is



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29. The compound of any one of claims 1 to 26, or a pharmaceutically acceptable salt thereof, wherein -Z^5- is monocyclic heteroarylene substituted with R^q and R^r independently selected from hydrogen, C_1-C_6-alkyl, C_1-C_6-alkoxy, halo, halo-C_1-C_6-alkyl, and halo-C_1-C_6-alkoxy.

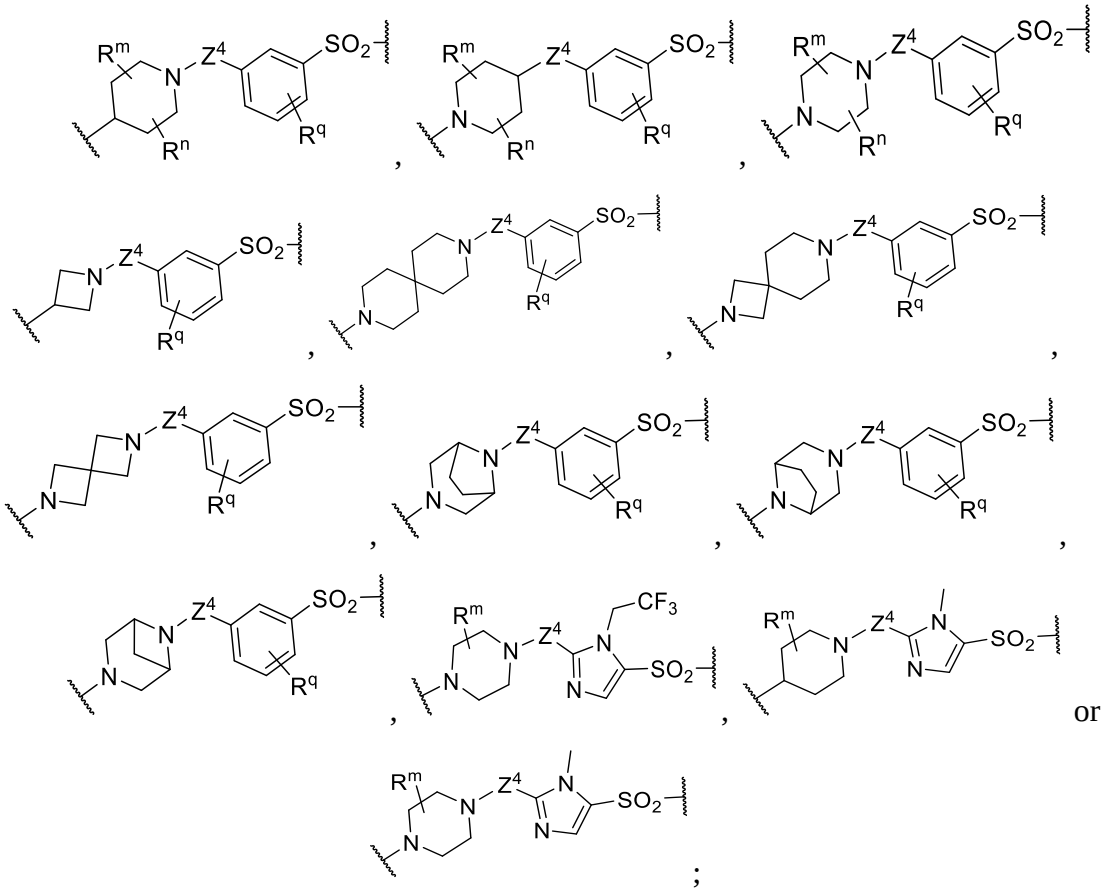
30. The compound of any one of claims 1 to 29, or a pharmaceutically acceptable salt thereof, wherein each heterocyclylene, bridged heterocyclylene, and spiro heterocyclylene, of Z^1, Z^2, Z^3, Z^4, and Z^5, when present, are independently selected from:



and

wherein each ring is optionally substituted with 1, 2, or 3 fluoro.

31. The compound of any one of claims 1 to 24 and 26, or a pharmaceutically acceptable salt thereof, wherein -Z^3-Z^4-Z^5-Z^6- is:



or

;

wherein each R^m, R^n, and R^q are independently selected from hydrogen, C_1-C_6-alkyl, halo, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy, and cyano.

32. The compound of any one of claims 1 to 24, 26 to 29, and 31, or a pharmaceutically acceptable salt thereof, wherein Z^4 is alkylene substituted with R^s and R^t where R^s and R^t are hydrogen.

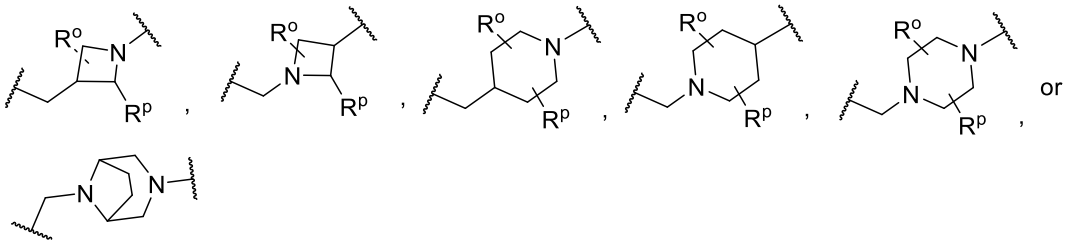
33. The compound of any one of claims 1 to 24, 26 to 29, and 31, or a pharmaceutically acceptable salt thereof, wherein Z^4 is -O-.

34. The compound of any one of claims 1 to 24, 26 to 29, and 31, or a pharmaceutically acceptable salt thereof, wherein Z^4 is alkylene substituted with R^s and R^t where R^s is hydrogen or deuterium and R^t is hydrogen, deuterium, halo-C_1-C_6-alkyl, hydroxy, C_1-C_6-alkoxy, or cyano.

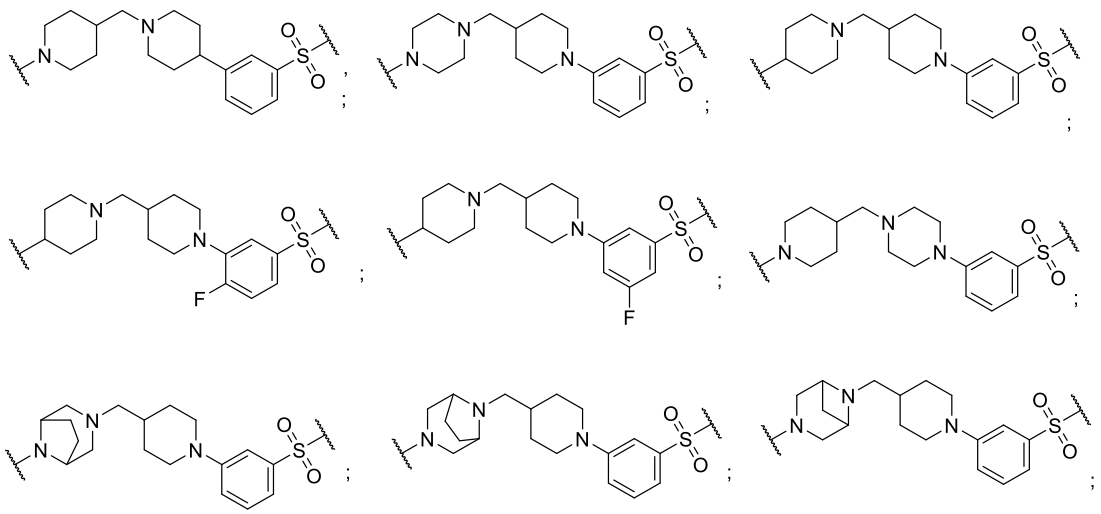
35. The compound of any one of 1 to 18, 26 to 29, and 31, or a pharmaceutically acceptable salt thereof, wherein Z^4 is –(C_1-C_6-alkylene)-heterocyclylene- where heterocyclylene is substituted with R^o and R^p.

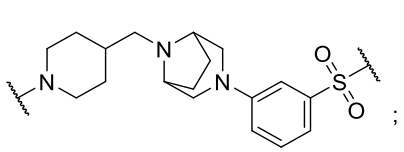
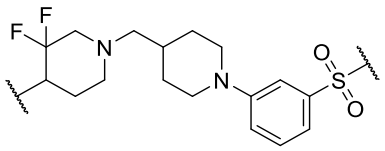
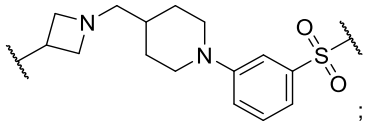
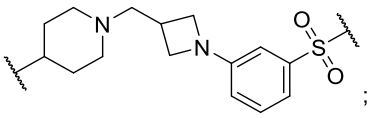
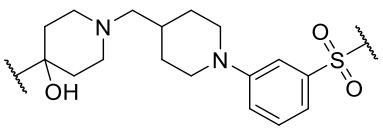
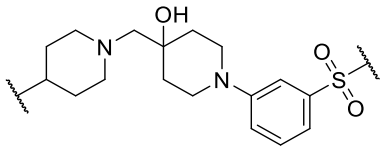
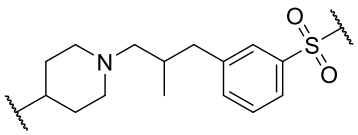
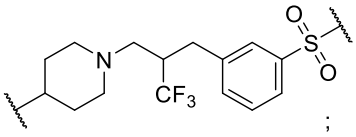
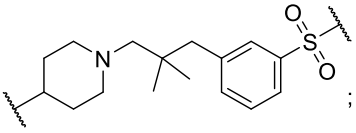
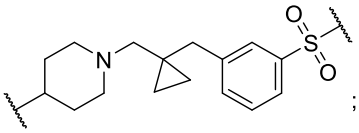
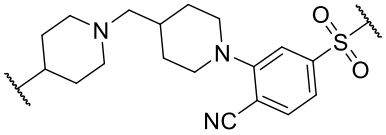
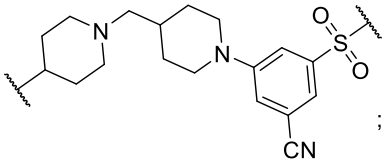
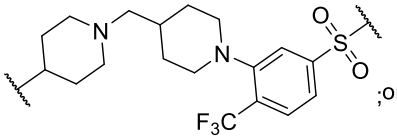
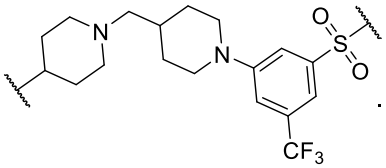
36. The compound of any one of 1 to 18, 26 to 29, 31, and 35, or a pharmaceutically acceptable salt thereof, wherein Z^4 is –(CH_2)-heterocyclylene- where heterocyclylene is substituted with R^o and R^p.

37. The compound of any one of 1 to 18, 26 to 29, 31, 35, and 36, or a pharmaceutically acceptable salt thereof, wherein Z^4 is:

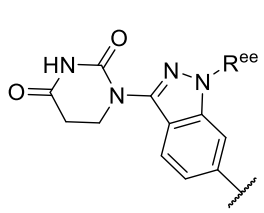
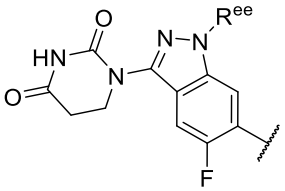
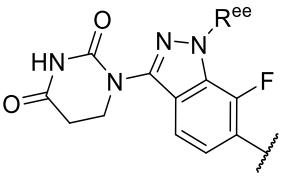
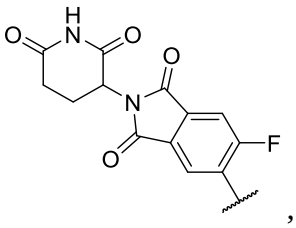
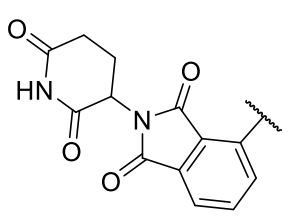
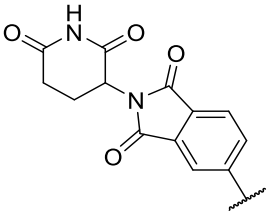
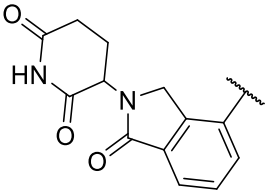
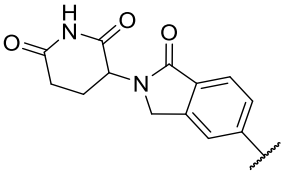
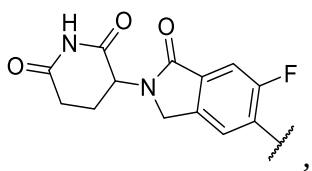
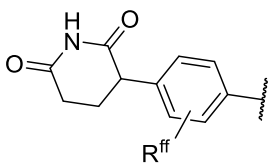
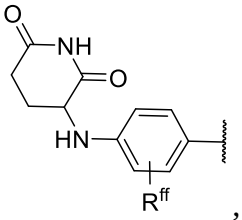
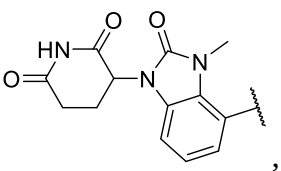
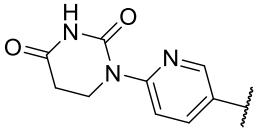


38. The compound of any one of 1 to 18, 26 to 28, 31, and 36 to 37, or a pharmaceutically acceptable salt thereof, wherein -Z^3-Z^4-Z^5-Z^6- is:



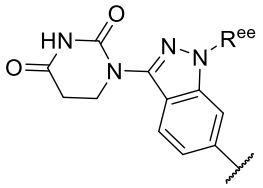

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;or

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39. The compound of any one of claims 1 to 38, or a pharmaceutically acceptable salt thereof, wherein Degron is the E3 ubiquitin ligase ligand selected from:


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

40. The compound of claim 39, or a pharmaceutically acceptable salt thereof, wherein Degron is the E3 ubiquitin ligase ligand is:



41. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from:

1-(1-methyl-6-(1-(3-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzyl)-piperidin-4-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(7-fluoro-1-methyl-6-(1-(3-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzyl)-piperidin-4-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(6-(3,3-difluoro-1-(3-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)-piperidin-1-yl)sulfonyl)benzyl)-piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-methyl-6-(6-(3-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzyl)-2,6-diazaspiro[3.3]heptan-2-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-(2,2,2-trifluoroethyl)-6-(1-(3-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)-piperidin-1-yl)sulfonyl)benzyl)-piperidin-4-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-methyl-6-(1-(3-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)-piperidin-1-yl)sulfonyl)phenethyl)piperidin-4-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

N-((R)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)-carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)-1-(3-((4-((5-(trifluoro-methyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzyl)piperidine-4-carboxamide;

(2S,4R)-1-((R)-2-(1-fluorocyclopropane-1-carboxamido)-3-methyl-3-(((1-(3-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)-piperidin-1-yl)sulfonyl)benzyl)piperidin-4-yl)methyl)thio)butanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)-ethyl)pyrrolidine-2-carboxamide;

(2S,4R)-1-((S)-3,3-dimethyl-2-(2-(1-(3-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-benzyl)piperidin-4-yl)acetamido)butanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide;

1-(1-methyl-6-(1-(3-(((1r,4r)-4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)-cyclohexyl)sulfonyl)benzyl)piperidin-4-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(6-(1-(3-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzyl)-piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-methyl-6-(4-(3-((4-((5-(trifluoro-methyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzyl)piperazin-1-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(6-(1-(3-((4-((5-(difluoromethyl)-pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(6-(1-(3-(((3R,4S)-3-fluoro-4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)-piperidin-1-yl)sulfonyl)benzyl)-piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-methyl-6-(1-((1-((4-((5-(trifluoro-methyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(5-fluoro-1-methyl-6-(1-(3-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)-piperidin-1-yl)sulfonyl)benzyl)piperidin-4-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(6-(1-(3-((4-((5-(1,1-difluoroethyl)-pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(6-(1-((1-((3-fluoro-4-((5-(trifluoro-methyl)pyrimidin-2-yl)amino)phenyl)-sulfonyl)piperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-methyl-6-(1-((1-(((1r,4r)-4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)-cyclohexyl)sulfonyl)piperidin-3-yl)methyl)piperidin-4-yl)-1H-indazol-3-yl)dihydro-pyrimidine-2,4(1H,3H)-dione;

1-(1-methyl-6-(1-((1-(((1r,4r)-4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)-cyclohexyl)sulfonyl)piperidin-4-yl)methyl)-piperidin-4-yl)-1H-indazol-3-yl)-dihydropyrimidine-2,4(1H,3H)-dione;

1-(6-(1-(3-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzyl)-piperidin-4-yl)-1-(2,2,2-trifluoroethyl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

5-(4-(3-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzyl)-piperazin-1-yl)-2-(2,6-dioxopiperidin-3-yl)-6-fluoroisoindoline-1,3-dione;

1-(6-(1-(3-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzyl)-piperidin-4-yl)-5-fluoro-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(6-(1-(3-((4-((5-bromopyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzyl)-piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(6-(4-(3-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzyl)-piperazin-1-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(6-(1-(3-((4-((5-fluoropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzyl)-piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(6-(1-(3-(((3R,4S)-4-((5-chloropyrimidin-2-yl)amino)-3-fluoropiperidin-1-yl)sulfonyl)benzyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(6-(1-(3-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzyl)-piperidin-4-yl)-7-fluoro-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

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-(6-(1-(1-(3-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-2,2-difluoroethyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-methyl-6-(1-(2-(1-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)-piperidin-1-yl)sulfonyl)piperidin-3-yl)ethyl)piperidin-4-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(6-(1-(3-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzyl)-3,3-difluoropiperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

3-(5-(4-(3-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzyl)-piperazin-1-yl)-6-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione;

1-(6-(1-(3-((4-((5-(difluoromethoxy)-pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-benzyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-methyl-6-(1-(3-(1-((4-((5-(trifluoro-methyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)piperidin-4-yl)propyl)piperidin-4-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(6-(1-(1-(3-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-ethyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(6-(1-((1-(3-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-piperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-methyl-6-(1-((1-(3-((4-((5-(trifluoro-methyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

3-(1-oxo-5-(4-(3-((4-((5-(trifluoromethyl)-pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenoxy)piperidin-1-yl)isoindolin-2-yl)piperidine-2,6-dione;

3-(6-fluoro-1-oxo-5-(4-(3-((4-((5-(trifluoro-methyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzyl)piperazin-1-yl)isoindolin-2-yl)piperidine-2,6-dione;

3-(5-(4-(3-((4-((5-(difluoromethoxy)-pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-benzyl)piperazin-1-yl)-6-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione;

3-(1-oxo-5-(4-(3-(3-((4-((5-(trifluoro-methyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenoxy)azetidin-1-yl)piperidin-1-yl)isoindolin-2-yl)piperidine-2,6-dione;

1-(6-(6-(3-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzyl)-2,6-diazaspiro[3.3]heptan-2-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-methyl-6-(1-((1-methyl-5-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)-piperidin-1-yl)sulfonyl)-1H-imidazol-2-yl)methyl)piperidin-4-yl)-1H-indazol-3-yl)dihydro-pyrimidine-2,4(1H,3H)-dione;

3-(1-oxo-5-(1-(3-((4-((5-(trifluoromethyl)-pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzyl)azetidin-3-yl)isoindolin-2-yl)piperidine-2,6-dione;

1-(1-methyl-6-(1-(3-((4-((5-(trifluoro-methyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzyl)azetidin-3-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

3-(5-(1-(3-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzyl)-azetidin-3-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione;

1-(1-methyl-6-(4-((1-(3-((4-((5-(trifluoro-methyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(6-(4-((1-(3-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-piperidin-4-yl)methyl)piperazin-1-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-methylpropyl)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)-2,2-dimethylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(6-(1-(2,2-dimethyl-3-(3-((4-((5-(trifluoro-methyl)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-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzyl)-azetidin-3-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(6-(1-(3-((4-((5-methoxypyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzyl)-piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-methyl-6-(1-(3-((4-((5-vinylpyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzyl)-piperidin-4-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(6-(1-(3-(((1r,4r)-4-((5-chloropyrimidin-2-yl)amino)cyclohexyl)sulfonyl)-benzyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-methyl-6-(1-(3-((4-((5-methyl-pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzyl)piperidin-4-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(6-(1-(3-((4-((5-ethylpyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzyl)-piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(6-(4-(3-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzyl)-piperazin-1-yl)-1-(2,2,2-trifluoroethyl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(6-(1-(4-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzyl)-piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-methyl-6-(1-(4-((4-((5-(trifluoro-methyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzyl)piperidin-4-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-methyl-6-(1-(3-((4-((5-phenoxy-pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzyl)piperidin-4-yl)-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-methylpropyl)-piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydro-pyrimidine-2,4(1H,3H)-dione;

1-(6-(4-(3-(((1r,4r)-4-((5-chloropyrimidin-2-yl)amino)cyclohexyl)sulfonyl)benzyl)-piperazin-1-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(6-(1-(3-((4-((5-(difluoromethoxy)-pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzyl)piperidin-4-yl)-1-(2,2,2-trifluoroethyl)-1H-indazol-3-yl)dihydro-pyrimidine-2,4(1H,3H)-dione;

1-(7-chloro-6-(1-((1-(3-((4-((5-chloro-pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)piperidin-4-yl)methyl)-piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

2-(2,6-dioxopiperidin-3-yl)-5-fluoro-6-(4-(3-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzyl)-piperazin-1-yl)isoindoline-1,3-dione;

1-(1-methyl-6-(1-(3-((4-((5-(trifluoro-methyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzyl)azetidin-3-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

3-(5-(4-(3-((4-((5-(difluoromethoxy)-pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzyl)piperazin-1-yl)-6-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione;

1-(6-(1-(3-((4-((5-(difluoromethoxy)-pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzyl)-3,3-difluoropiperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

3-(1-oxo-5-(4-(3-((4-((5-(trifluoromethyl)-pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzyl)piperazin-1-yl)isoindolin-2-yl)piperidine-2,6-dione;

1-(6-(1-(3-((4-((5-(difluoromethoxy)-pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzyl)piperidin-4-yl)-5-fluoro-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

3-((4-(4-(3-((4-((5-(trifluoromethyl)-pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzyl)piperazin-1-yl)phenyl)amino)piperidine-2,6-dione;

5-(4-((1-(3-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-piperidin-4-yl)methyl)piperazin-1-yl)-2-(2,6-dioxopiperidin-3-yl)-6-fluoroisoindoline-1,3-dione;

2-(2,6-dioxopiperidin-3-yl)-5-fluoro-6-(4-((1-(3-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-piperidin-4-yl)methyl)piperazin-1-yl)isoindoline-1,3-dione;

1-(6-(1-(3-((4-((5-(difluoromethoxy)-pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzyl)azetidin-3-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(4-(4-(3-((4-((5-(trifluoromethyl)-pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-benzyl)piperazin-1-yl)phenyl)dihydropyrimidine-2,4(1H,3H)-dione;

3-(3-methyl-2-oxo-4-(1-(3-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzyl)-piperidin-4-yl)-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione;

1-(6-(4-((3-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzyl)-amino)piperidin-1-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-methyl-6-(4-((3-((4-((5-(trifluoro-methyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzyl)amino)piperidin-1-yl)-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)propyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-methyl-6-(1-(3-(3-((4-((5-(trifluoro-methyl)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-(4-((methyl(3-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)-piperidin-1-yl)sulfonyl)benzyl)amino)-methyl)piperidin-1-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(7-chloro-1-methyl-6-(1-((1-(3-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)-piperidin-1-yl)sulfonyl)phenyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(6-(3,3-difluoro-1-((1-(3-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)-piperidin-1-yl)sulfonyl)phenyl)piperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydro-pyrimidine-2,4(1H,3H)-dione;

1-(1-(2,2,2-trifluoroethyl)-6-(1-((1-(3-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-piperidin-4-yl)methyl)piperidin-4-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

3-(1-oxo-5-(4-(3-(3-((4-((5-(trifluoro-methyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenoxy)azetidin-1-yl)piperidin-1-yl)isoindolin-2-yl)piperidine-2,6-dione;

1-(6-(1-(3-((4-((5-(difluoromethoxy)-pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzyl)piperidin-4-yl)-7-fluoro-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(7-fluoro-1-methyl-6-(1-((1-(3-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)-piperidin-1-yl)sulfonyl)phenyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(6-(1-((1-(3-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-piperidin-4-yl)methyl)piperidin-4-yl)-7-fluoro-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

3-(6-fluoro-5-(4-(2-methyl-3-(3-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)-piperidin-1-yl)sulfonyl)phenyl)propyl)-piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione;

3-(5-(4-(3-(3-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-2-methylpropyl)piperazin-1-yl)-6-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione;

3-(5-(4-((1-(3-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione;

1-(6-(1-((1-(3-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-piperidin-4-yl)methyl)piperidin-4-yl)-5-fluoro-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(5-fluoro-1-methyl-6-(1-((1-(3-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)-piperidin-1-yl)sulfonyl)phenyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

3-(6-fluoro-1-oxo-5-(4-((1-(3-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)-piperidin-1-yl)sulfonyl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)isoindolin-2-yl)piperidine-2,6-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-oxoisoindolin-2-yl)piperidine-2,6-dione;

3-(5-(4-((1-(3-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-piperidin-4-yl)methyl)piperazin-1-yl)-6-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione;

1-(6-(3-((1-(3-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-piperidin-4-yl)methyl)-3,8-diaza-bicyclo[3.2.1]octan-8-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

3-(5-(4-(3-(3-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenoxy)-azetidin-1-yl)piperidin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione;

3-(5-(4-((1-(3-((4-((5-(difluoromethoxy)-pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)piperidin-4-yl)methyl)-piperazin-1-yl)-6-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione;

3-(3-methyl-2-oxo-4-(1-((1-(3-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)-piperidin-1-yl)sulfonyl)phenyl)piperidin-4-yl)methyl)piperidin-4-yl)-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione;

1-(1-methyl-6-(1-((1-(3-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)-piperidin-1-yl)sulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(4-(4-((1-(3-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-piperidin-4-yl)methyl)piperazin-1-yl)phenyl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(5-fluoro-1-methyl-6-(4-((1-(3-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)-piperidin-1-yl)sulfonyl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(6-(4-((1-(3-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-piperidin-4-yl)methyl)piperazin-1-yl)-5-fluoro-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(6-(1-((1-(3-((4-((5-(difluoromethoxy)-pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)piperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(4-(4-((1-(3-((4-((5-(trifluoromethyl)-pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)phenyl)-dihydropyrimidine-2,4(1H,3H)-dione;

1-(6-(8-((1-(3-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-piperidin-4-yl)methyl)-3,8-diaza-bicyclo[3.2.1]octan-3-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-methyl-6-(1-((1-(3-((4-((5-(trifluoro-methoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(6-(4-((1-(3-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-piperidin-4-yl)methyl)-2-methylpiperazin-1-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(S)-1-(6-(4-((1-(3-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-piperidin-4-yl)methyl)-2-methylpiperazin-1-yl)-1-methyl-1H-indazol-3-yl)dihydro-pyrimidine-2,4(1H,3H)-dione;

1-(1-methyl-6-(1-((1-(3-((4-((5-(trifluoro-methyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)piperidin-4-yl)methyl)-azetidin-3-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

3-(6-fluoro-1-oxo-5-(1-((1-(3-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)-piperidin-1-yl)sulfonyl)phenyl)piperidin-4-yl)methyl)piperidin-4-yl)isoindolin-2-yl)piperidine-2,6-dione;

3-(5-(1-((1-(3-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-piperidin-4-yl)methyl)piperidin-4-yl)-6-fluoro-1-oxoisoindolin-2-yl)piperidine-2,6-dione;

3-(4-(1-((1-(3-((4-((5-(difluoromethoxy)-pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)piperidin-4-yl)methyl)-piperidin-4-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione;

1-(6-(1-((3'-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-[1,1'-biphenyl]-4-yl)methyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-methyl-6-(1-(2-(3-((4-((5-(trifluoro-methyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenoxy)ethyl)piperidin-4-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(6-(1-(2-(3-((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-(6-(6-((1-(3-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-piperidin-4-yl)methyl)-3,6-diazabicyclo-[3.1.1]heptan-3-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-methyl-6-(6-((1-(3-((4-((5-(trifluoro-methyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)piperidin-4-yl)methyl)-3,6-diazabicyclo[3.1.1]heptan-3-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(6-((2S,6R)-4-((1-(3-((4-((5-chloro-pyrimidin-2-yl)amino)piperidin-1-yl)-sulfonyl)phenyl)piperidin-4-yl)methyl)-2,6-dimethylpiperazin-1-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

3-(4-(1-(3-((4-((5-(difluoromethoxy)-pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzyl)piperidin-4-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione;

1-(6-(1-((1-(3-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-azetidin-3-yl)methyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-methyl-6-(1-((5-((4-((5-(trifluoro-methyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)pyridin-3-yl)methyl)piperidin-4-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(6-(1-((1-(3-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-1H-pyrazol-4-yl)methyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(6-(1-((2-(3-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-2-azaspiro[3.3]heptan-6-yl)methyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

3-((4-(4-((1-(3-((4-((5-(trifluoromethyl)-pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)phenyl)amino)-piperidine-2,6-dione;

1-(6-(1-((1-(3-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-piperidin-4-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(S)-1-(6-(1-((1-(3-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-pyrrolidin-3-yl)methyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(6-(1-((1-(3-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-azepan-4-yl)methyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-methyl-5-(1-((1-(3-((4-((5-(trifluoro-methyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)piperidin-4-yl)methyl)-piperidin-4-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(6-(4-((4-(3-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-piperazin-1-yl)methyl)piperidin-1-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(6-(1-(4-(1-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)piperidin-4-yl)benzyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(6-(1-((1-(5-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-fluorophenyl)piperidin-4-yl)methyl)-piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(6-(1-((1-(2-fluoro-5-((4-((5-(trifluoro-methyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)piperidin-4-yl)methyl)-piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(6-(1-((1-(3-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-pyrrolidin-3-yl)methyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-methyl-7-(1-((1-(3-((4-((5-(trifluoro-methyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)piperidin-4-yl)methyl)-piperidin-4-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-methyl-6-(1-(3-((6-((5-(trifluoro-methyl)pyrimidin-2-yl)amino)-2-azaspiro[3.3]-heptan-2-yl)sulfonyl)benzyl)-piperidin-4-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(6-(1-((1-(3-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-5-fluorophenyl)piperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydro-pyrimidine-2,4(1H,3H)-dione;

4-((4-((5-chloropyrimidin-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)methyl)-piperidin-1-yl)benzonitrile;

1-(6-(1-((1-(3-fluoro-5-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)piperidin-4-yl)methyl)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-(4-((4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-7-fluoro-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)piperidin-1-yl)benzonitrile;

4-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(4-((4-(1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)piperidin-1-yl)methyl)piperidin-1-yl)benzonitrile;

2-(4-((4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)piperidin-1-yl)-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-((4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-5-fluoro-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)piperidin-1-yl)benzonitrile;

1-(1-methyl-6-(1-(3-((3-((5-(trifluoromethyl)pyrimidin-2-yl)amino)azetidin-1-yl)sulfonyl)benzyl)piperidin-4-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(6-(1-((4-(3-((4-((5-chloropyrimidin-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 2,2,2-trifluoroacetate;

1-(6-(1-(4-(1-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)piperidin-3-yl)benzyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(6-(1-((1-(4-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-piperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(6-(4-((1-(3-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-piperidin-4-yl)methyl)-2,2-dimethylpiperazin-1-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

3-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-5-(4-((4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)-piperidin-1-yl)benzonitrile 2,2,2-trifluoroacetate;

2-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-4-(4-((4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)-piperidin-1-yl)benzonitrile;

1-(6-(1-((1-(3-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-4-hydroxypiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(6-(1-((1-(1-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)piperidin-4-yl)-1H-pyrazol-4-yl)methyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(3-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-4-((4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)-piperidine-4-carbonitrile;

1-(1-methyl-6-(1-((1-(4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(6-(4-((3-(3-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-3,8-diazabicyclo[3.2.1]octan-8-yl)methyl)piperidin-1-yl)-1-methyl-1H-indazol-3-yl)dihydro-pyrimidine-2,4(1H,3H)-dione;

3-(3-methyl-2-oxo-6-(1-((1-(3-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)-piperidin-1-yl)sulfonyl)phenyl)piperidin-4-yl)methyl)piperidin-4-yl)-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-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)piperidin-1-yl)methyl)benzonitrile;

1-(6-(1-((1-(3-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-5-(trifluoromethyl)phenyl)piperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-methyl-6-(1-((1-(3-((6-((5-(trifluoromethyl)pyrimidin-2-yl)amino)-2-azaspiro[3.3]heptan-2-yl)sulfonyl)phenyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

3-(4-(1-((1-(3-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-5-(trifluoromethyl)phenyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione;

3-(4-(1-((1-(3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-5-fluorophenyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione;

1-(6-(1-((1-(3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-5-fluorophenyl)piperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydro-pyrimidine-2,4(1H,3H)-dione;

3-(4-(1-((1-(3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-5-(trifluoromethyl)phenyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione;

3-(3-methyl-2-oxo-5-(1-((1-(3-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)-piperidin-1-yl)sulfonyl)phenyl)piperidin-4-yl)methyl)piperidin-4-yl)-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione;

1-(1-methyl-6-(1-((1-(3-((3-((5-(trifluoromethyl)pyrimidin-2-yl)amino)azetidin-1-yl)sulfonyl)phenyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-methyl-6-((4-(3-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)piperazin-1-yl)methyl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

3-(4-(1-((1-(3-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-5-fluorophenyl)piperidin-4-yl)methyl)piperidin-4-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione;

2-(4-((4-(1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]-imidazol-4-yl)piperidin-1-yl)methyl)piperidin-1-yl)-4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzonitrile;

1-(3-(1-((1-(3-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-piperidin-4-yl)methyl)piperidin-4-yl)phenyl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-methyl-6-(1-((2-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)pyridin-4-yl)methyl)piperidin-4-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

3-(4-(1-(3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-5-fluorobenzyl)piperidin-4-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione;

4-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(4-((4-(2-(2,6-dioxopiperidin-3-yl)-6-fluoro-1,3-dioxoisoindolin-5-yl)piperazin-1-yl)methyl)piperidin-1-yl)benzonitrile;

1-(6-(1-((1-(3-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-fluorophenyl)piperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

2-(4-((4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-7-fluoro-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)piperidin-1-yl)-4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzonitrile;

1-(6-(1-((1-(3-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-4-fluorophenyl)piperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydro-pyrimidine-2,4(1H,3H)-dione;

3-(3-methyl-4-(1-(3-(methyl(3-((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;

1-(6-(4-((8-(3-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-3,8-diazabicyclo[3.2.1]octan-3-yl)methyl)piperidin-1-yl)-1-methyl-1H-indazol-3-yl)dihydro-pyrimidine-2,4(1H,3H)-dione;

4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(4-((4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-7-fluoro-1-methyl-1H-indazol-6-yl)piperidin-1-yl)methyl)piperidin-1-yl)benzonitrile;

1-(6-(1-((1-(3-((4-((5-fluoropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-piperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(8-(1-((1-(3-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-piperidin-4-yl)methyl)piperidin-4-yl)isoquinolin-4-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(6-(1-((1-(3-((4-((5-(difluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)piperidin-4-yl)methyl)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-(1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)piperidin-1-yl)methyl)benzonitrile;

1-(6-(1-((1-(3-((4-((5-bromopyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-piperidin-4-yl)methyl)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-(4-((4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)piperazin-1-yl)methyl)piperidin-1-yl)benzonitrile;

Rac-1-(6-(1-((1-(3-(((3R,4S)-4-((5-chloropyrimidin-2-yl)amino)-3-fluoropiperidin-1-yl)sulfonyl)phenyl)piperidin-4-yl)methyl)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-(4-((4-(1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)piperazin-1-yl)methyl)piperidin-1-yl)benzonitrile;

4-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(4-((4-(1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)piperidin-1-yl)methyl)piperidin-1-yl)benzonitrile;

2-(4-((4-(1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)piperidin-1-yl)methyl)piperidin-1-yl)-4-((4-((5-(trifluoromethyl)-pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzonitrile;

1-(6-(1-((1-(3-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-4-methylpiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-methyl-6-(1-((1-(3-((4-((5-vinylpyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-phenyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

4-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(4-((4-(1-(2,6-dioxopiperidin-3-yl)-6-fluoro-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)piperidin-1-yl)methyl)piperidin-1-yl)benzonitrile;

1-(6-(1-((1-(3-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-phenyl)piperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)pyrimidine-2,4(1H,3H)-dione;

1-(1-methyl-6-(1-((1-(3-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-indazol-3-yl)pyrimidine-2,4(1H,3H)-dione;

1-(1-methyl-6-(1-((1-(3-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-pyrazolo[4,3-b]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(8-(1-((1-(3-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-piperidin-4-yl)methyl)piperidin-4-yl)imidazo[1,2-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

4-((4-((5-chloropyrimidin-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)methyl)-4-hydroxypiperidin-1-yl)benzonitrile;

1-(6-(1-((1-(3-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-piperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1H-pyrazolo[4,3-b]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

4-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-2-(4-((4-(1-(2,6-dioxopiperidin-3-yl)-5-fluoro-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)piperidin-1-yl)methyl)piperidin-1-yl)benzonitrile;

2-(4-((4-(1-(2,6-dioxopiperidin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]-imidazol-4-yl)piperazin-1-yl)methyl)piperidin-1-yl)-4-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzonitrile;

1-(6-(1-((1-(3-(((3R,4S)-4-((5-chloropyrimidin-2-yl)amino)-3-methoxypiperidin-1-yl)sulfonyl)phenyl)piperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydro-pyrimidine-2,4(1H,3H)-dione;

Rac-1-(6-(1-((1-(3-(((3R,4R)-4-((5-chloropyrimidin-2-yl)amino)-3-methoxypiperidin-1-yl)sulfonyl)phenyl)piperidin-4-yl)methyl)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-(4-((4-(1-(2,6-dioxopiperidin-3-yl)-7-fluoro-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)piperidin-1-yl)methyl)piperidin-1-yl)benzonitrile;

Rac-1-(6-(1-((1-(3-(((3R,4S)-3-fluoro-4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)piperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(6-(4-((4-(3-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-piperazin-1-yl)methyl)cyclohexyl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

N-(2,6-dioxopiperidin-3-yl)-5-(1-((1-(3-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)piperidin-4-yl)methyl)piperidin-4-yl)picolinamide;

1-(6-(1-(3-(3-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)prop-2-yn-1-yl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(6-(1-((1-(3-(((1R,5S)-3-((5-chloropyrimidin-2-yl)amino)-8-azabicyclo[3.2.1]octan-8-yl)sulfonyl)phenyl)piperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(6-(1-((1-(3-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-piperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1H-pyrazolo[4,3-c]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

Rac-1-(6-(1-((1-(3-(((1R,5S,8s)-8-((5-chloropyrimidin-2-yl)amino)-3-azabicyclo-[3.2.1]octan-3-yl)sulfonyl)phenyl)piperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-methyl-6-(3-(4-(3-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)piperazin-1-yl)prop-1-yn-1-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(6-(3-(4-(3-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-phenyl)piperazin-1-yl)prop-1-yn-1-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-methyl-6-(1-(4-((3-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)ethynyl)benzyl)piperidin-4-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(6-(1-(4-((3-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-ethynyl)benzyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(6-(1-((1-(3-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-2-oxopiperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-methyl-6-(3-(4-(3-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)piperazin-1-yl)propyl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

N-(2,6-dioxopiperidin-3-yl)-2-fluoro-4-(1-((1-(3-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)piperidin-4-yl)methyl)piperidin-4-yl)benzamide;

4-(1-((1-(3-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-piperidin-4-yl)methyl)piperidin-4-yl)-N-(2,6-dioxopiperidin-3-yl)-2-fluorobenzamide;

1-(1-methyl-6-(4-((4-(3-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)piperidin-1-yl)methyl)cyclohexyl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(6-(1-((1-(3-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-piperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)-4-thioxotetrahydropyrimidin-2(1H)-one;

1-(6-(1-((1-(3-(((1r,4r)-4-((5-chloropyrimidin-2-yl)amino)cyclohexyl)sulfonyl)-phenyl)piperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(6-(1-(4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-benzyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(6-(1-(4-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzyl)piperidin-4-yl)-7-fluoro-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-methyl-6-(1-((1-(3-((4-((5-(2,2,2-trifluoroethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(6-(1-((1-(3-((4-((5-isopropylpyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-phenyl)piperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-methyl-6-(1-((1-(3-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)phenyl)-sulfonyl)phenyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

3-(6-(1-((1-(3-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-piperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)piperidine-2,6-dione;

3-(5-(4-((4-(3-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)piperazin-1-yl)methyl)piperidin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione;

3-(1-oxo-5-(4-((4-(3-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)piperazin-1-yl)methyl)piperidin-1-yl)isoindolin-2-yl)piperidine-2,6-dione;

1-(6-(1-((1-(3-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)piperidin-4-yl)methyl)azetidin-3-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

3-(1-methyl-6-(1-((1-(3-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)piperidin-4-yl)methyl)piperidin-4-yl)-1H-indol-3-yl)piperidine-2,6-dione;

1-(6-(1-((1-(3-((4-((5-isopropoxypyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-phenyl)piperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

3-(6-(1-((1-(3-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)-phenyl)piperidin-4-yl)methyl)piperidin-4-yl)-1-methyl-1H-indol-3-yl)piperidine-2,6-dione;

(R)-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)pyrrolidin-1-yl)benzonitrile;

(S)-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)pyrrolidin-1-yl)benzonitrile;

(S)-1-(6-(1-((1-(3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)piperidin-3-yl)methyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(6-(1-((1-(3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)piperidin-3-yl)methyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(S)-1-(6-(1-((1-(3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)pyrrolidin-2-yl)methyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(R)-1-(6-(1-((1-(3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)piperidin-2-yl)methyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

(S)-1-(6-(1-((1-(3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)piperidin-2-yl)methyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(6-(4-(((3-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzyl)amino)methyl)piperidin-1-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(6-(4-((3-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzyl)(methyl)amino)piperidin-1-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-methyl-6-(1-(3-((4-((5-(trifluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzyl)piperidin-4-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(1-methyl-6-(1-(1-(1-((4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)piperidin-3-yl)propan-2-yl)piperidin-4-yl)-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(6-(1-(3-((4-((5-(chlorodifluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

1-(7-chloro-6-(1-(3-((4-((5-chloropyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)benzyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione; and

1-(6-(1-(3-(3-((4-((5-(difluoromethoxy)pyrimidin-2-yl)amino)piperidin-1-yl)sulfonyl)phenyl)-2,2-dimethylpropyl)piperidin-4-yl)-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

or a pharmaceutically acceptable salt thereof.

42. A pharmaceutical composition comprising a compound of any one of claims 1 to 41, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

43. Use of a compound of any one of claims 1 to 41, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 42 in the manufacture of a medicament for the treatment of cancer.

44. The use of claim 43 wherein the compound of any one of claims 1 to 42 or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of 44 is to be administered in combination with at least one other anticancer agent.

45. The use of claim 43 or 44 wherein the cancer is lung cancer, skin cancer, bladder cancer, breast cancer, cervical cancer, colorectal cancer, cancer of the small intestine, colon cancer, rectal cancer, cancer of the anus, endometrial cancer, gastric cancer, head and neck cancer, liver cancer, ovarian cancer, prostate cancer, testicular cancer, uterine cancer, esophageal cancer, gall bladder cancer, pancreatic cancer, stomach cancer, thyroid cancer, or parathyroid cancer.

46. A compound of any one of claims 1 to 41, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 42 for use in therapy.