BIFUNCTIONAL ANDROGEN RECEPTOR COMPOUNDS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Patent Application No. 63/589,861, filed October 12, 2023, and U.S. Provisional Patent Application No. 63/636,293, filed April 19, 2024, which are incorporated herein by reference in their entireties.

FIELD OF THE INVENTION

[0001] Described herein are heterobifunctional small molecules, methods of making, pharmaceutical compositions and medicaments comprising such heterobifunctional small molecules, and methods of using such heterobifunctional small molecules are described herein, in the treatment of diseases and conditions, such as cancer, autoimmune diseases, and inflammatory diseases.

BACKGROUND OF THE INVENTION

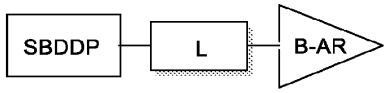
[0002] Cellular homeostasis, a key hallmark of living organisms, arises from interactions between biomolecules, such as protein (e.g., enzyme) and substrate interactions, within and outside the cell. Conventionally, the function of a particular protein in a particular disease state has been investigated and controlled through the use of monofunctional molecules (e.g., an inhibitor), which occupy the active site of the disease protein, thereby forming binary complexes that inhibit or downregulate activity of the disease proteins. Such monofunctional molecules have provided a conceptual pathway toward many FDA-approved drugs as a means for treating the disease state.

[0003] However, many monofunctional molecules lack specificity for the disease proteins in question leading to undesired toxicities or lack of efficacy, or the disease proteins adapts to the monofunctional molecules thereby leading to resistance. An alternative approach with monofunctional molecules is to target the coregulator or coactivator proteins of the disease proteins. However, such coregulator or coactivator proteins are typically present in every cell, healthy or diseased, and inhibiting their activity typically leads to narrower therapeutic indices.

[0004] Described herein are heterobifunctional small molecules that engage the androgen receptor (AR) and a disease-dependent protein, thereby forming ternary complexes only in the disease cells that express both proteins and leading to loss of function of the disease-dependent protein. The heterobifunctional small molecules described herein comprise at least one silent binder to the disease-dependent protein and at least one binder to AR. Such heterobifunctional small molecules offer a new means for treatment of diseases or conditions, with a wider therapeutic index and offer novel therapeutic targets vis a vis expansion of the disease proteins, such as AR.

SUMMARY OF THE INVENTION

[0005] In some embodiments, disclosed herein is a heterobifunctional conditional inhibitor compound of Formula (I),or a pharmaceutically acceptable salt or solvate thereof:



wherein:

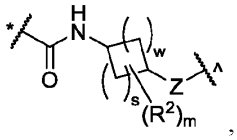
SBDDP is a silent binder of a disease-dependent protein (DDP);

L is an optional linker; wherein L is covalently attached at a position of SBDDP that is solvent exposed when SBDDP binds to the DDP;

B-AR is a binder of the androgen receptor (AR), wherein B-AR comprises:

1) a head group that occupies the ligand-binding domain (LBD) of AR and is covalently attached to a core moiety; and

2) an optional tail moiety covalently attached to the core moiety; wherein the core comprises an optionally substituted cycloalkyl having the structure of Formula (C):



, Formula (C);

the head group is covalently attached to Z at position (^);

the optional tail moiety comprises a ring D that is covalently attached to the amide (*), wherein ring D is a 5-, 6-, 8-, 9- or 10-membered aryl or a 5-, 6-, 8-, 9- or 10-membered heteroaryl that is optionally substituted with s R^3;

wherein:

s is 1, 2, or 3; w is 2 or 3;

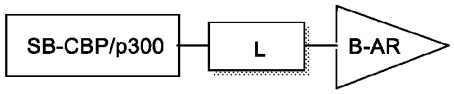
m is 0, 1, 2, 3, or 4;

Z is -O- or -NR^5-; and R^2 and R^3 is described herein;

wherein L is covalently attached to the core moiety at position (*) if the optional tail moiety is absent, or L is covalently attached to the tail moiety if present;

wherein DDP and AR are both expressed in a cell of interest (COI), and wherein the relative abundance of the AR in the COI is greater than the relative abundance of the DDP in the COI; or the COI is a diseased cell, and the AR is overexpressed, overactive, or both overexpressed and overactive, or amplified in the diseased cell as compared to when the COI is a non-diseased cell.

[0006] In some embodiments, disclosed herein is a heterobifunctional compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof:



wherein:

SB-CBP/p300 is a silent binder of human CREB-binding protein (CBP) or human E1A-binding protein p300 (p300) (CBP/p300);

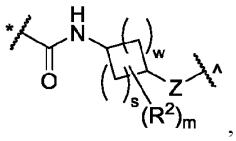
L is an optional linker; wherein L is covalently attached at a position of SB-CBP/p300 that is solvent

exposed when SB binds to CBP/p300;

B-AR is a binder of the androgen receptor (AR), wherein the B-AR comprises:

1) a head group that occupies the ligand-binding domain (LBD) of AR and is covalently attached to a core moiety; and

2) an optional tail moiety covalently attached to the core moiety; wherein the core comprises an optionally substituted cycloalkyl having the structure of Formula (C):



, Formula (C);

wherein:

s is 1, 2, or 3; w is 2 or 3;

m is 0, 1, 2, 3, or 4;

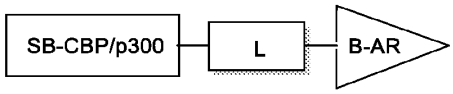
the head group is covalently attached to Z at position (^);

the optional tail moiety comprises a ring D that is covalently attached to the amide (*), wherein ring D is a 5-, 6-, 8-, 9- or 10-membered aryl or a 5-, 6-, 8-, 9- or 10-membered heteroaryl that is optionally substituted with s R^3;

Z is -O- or -NR^5-; and R^2 and R^3 is described herein;

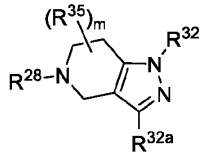
wherein L is covalently attached to the core moiety at position (*) if the optional tail moiety is absent, or L is covalently attached to the tail moiety if present.

[0007] In some embodiments, disclosed herein is a heterobifunctional conditional inhibitor compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof:



SB-CBP/p300 is a silent binder of the bromodomain of human CREB-binding protein (CBP) or human E1A-binding protein p300 (p300) (CBP/p300), wherein the binder of CBP/p300 comprises:

- an acetyl-lysine mimetic moiety that binds in the acetyl-lysine (KAc) binding site of the bromodomain of human CREB-binding protein (CBP) or human E1A-binding protein p300 (p300) (CBP/p300) and has the structure:



R^{28} is -C(=O)CH_3, -C(=O)CH_2CH_3, -C(=O)NH_2, -C(=O)NH(CH_3); or -C(=O)NH(CH_2CH_3);

R^{32} is a moiety that occupies the BC Loop region of the bromodomain of CBP/p300;

R^{32a} is a moiety that occupies the lipophilic shelf (LPF) region of the bromodomain of CBP/p300;

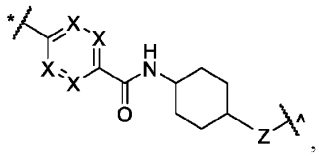
each R^{35} is independently hydrogen, C_1-C_4alkyl, or C_1-C_4fluoroalkyl;

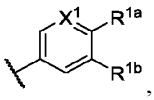
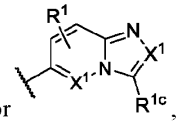
m is 0, 1, 2, 3, or 4;

L is an optional linker, wherein L is covalently attached to the R^{32} group, or at the position occupied by R^{32}, or the R^{32a} group;

B-AR is a binder of the androgen receptor (AR), wherein the B-AR comprises:

- a head group that occupies the ligand-binding domain (LBD) of AR and is covalently attached to a core with a tail moiety covalently attached to the core moiety; wherein B-AR has the structure of Formula (D):


, Formula (D);

wherein head group is  , or  , and the the head group is covalently attached to Z at position (^), and L is attached at position *;

Z is -O-, -NH- or -N(C_1-C_4alkyl)-;

each X^1 is independently -CR^1- or -N-;

R^{1a} is -CN, -NO_2, -C(=O)R^5, -C(=O)OR^5, or -C(=O)$N(R^5)_2$;

R^{1b} is hydrogen, halogen, substituted or unsubstituted C_1-C_4alkyl, C_1-C_4fluoroalkyl, -CN, -OH, or -OR^4;

R^{1c} is hydrogen, halogen, C_1-C_4alkyl, C_1-C_4fluoroalkyl, or -CN;

each R^1 is independently hydrogen, halogen, substituted or unsubstituted C_1-C_4alkyl, C_1-C_4fluoroalkyl, -CN, -OH, or -OR^4;

each X is independently -CR^3- or -N-;

each R^3 is independently hydrogen, halogen, substituted or unsubstituted C_1-C_4alkyl, C_1-C_4fluoroalkyl, -CN, -OH, -OR^4, or -$N(R^5)_2$.

each R^4 is independently substituted or unsubstituted C_1-C_4alkyl, or C_1-C_4fluoroalkyl;

each R^5 is independently hydrogen, substituted or unsubstituted C_1-C_4alkyl, C_1-C_4fluoroalkyl; and

each s is 1, 2, or 3.

[0008] In some embodiments, disclosed herein is a stable ternary complex comprising:

a. one or more disease-dependent proteins (DDPs);
b. Androgen Receptor (AR); and
c. heterobifunctional conditional inhibitor compound as described herein;

wherein DDP and AR are present in a cell of interest (COI) and the relative abundance of the AR in the COI is greater than the relative abundance of the DDP in the COI.

[0009] In some embodiments, the DDP is CREB-binding protein (CBP)/p300.

[0010] In some embodiments, disclosed herein is a stable ternary complex comprising:

a. CBP/p300;
b. Androgen receptor (AR); and
c. heterobifunctional conditional inhibitor compound as described herein;

wherein CBP/p300 and DP are present in a cell of interest (COI) and the relative abundance of the DP in the COI is greater than the relative abundance of CBP/p300 in the COI.

[0011] In another aspect, described herein is a method of selectively inhibiting the activity of a disease-dependent protein (DDP) in a cell of interest (COI) of a mammal comprising administering a heterobifunctional compound as described herein, or a pharmaceutically acceptable salt or solvate thereof, wherein the COI expresses the androgen receptor (AR). In some embodiments, the heterobifunctional compound as described herein, or a pharmaceutically acceptable salt or solvate thereof, inhibits the activity of the DDP in the COI but does not inhibit the activity of the DDP in cells expressing the DDP and not expressing the AR. In some embodiments, the AR is overexpressed, overactive or both overexpressed and overactive in the COI. In some embodiments, the DDP is CREB-binding protein (CBP)/p300.

[0012] In another aspect, described herein is a method of treating cancer in a mammal comprising administering to the mammal a therapeutically effective amount of a compound as described herein, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the cancer is a hormone dependent cancer. In some embodiments, the cancer is prostate cancer.

[0013] In another aspect, described herein is a method of treating an androgen receptor dependent or androgen receptor mediated disease or condition in mammal comprising administering to the mammal a therapeutically effective amount of a compound as described herein, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the androgen receptor dependent or androgen receptor mediated disease or condition is selected from benign prostate hyperplasia, hirsutism, adenomas and neoplasms of the prostate, benign or malignant tumor cells containing the androgen receptor, prostate cancer, breast cancer, endometrial cancer, and uterine cancer.

[0014] Also described herein is a pharmaceutical composition comprising a heterobifunctional compound described herein, or a pharmaceutically acceptable salt, or solvate thereof, and at least one pharmaceutically acceptable excipient. In some embodiments, the pharmaceutical composition is formulated for administration to a mammal by oral administration, intravenous administration, or subcutaneous administration. In some embodiments, the pharmaceutical composition is formulated for administration to a mammal by oral administration. In some embodiments, the pharmaceutical composition is in the form of a tablet, a pill, a capsule, a liquid, or a suspension.

[0015] In one aspect, the heterobifunctional compounds described herein, or a pharmaceutically acceptable salt, or solvate thereof, are used in the treatment of diseases or conditions, such as cancer, autoimmune diseases, and inflammatory diseases. In some embodiments, the disease or condition is cancer. In some embodiments, the cancer comprises altered DP expression levels. In some embodiments, the cancer comprises altered androgen receptor expression levels. In some embodiments, altered DP expression levels

comprises overexpressed DP, overactive DP, amplified DP, or combinations thereof.

[0016] In any of the embodiments disclosed herein, the mammal is a human. In some embodiments, compounds disclosed herein are orally administered to a human.

[0017] Other objects, features and advantages of the compounds, methods and compositions described herein will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating specific embodiments, are given by way of illustration only, since various changes and modifications within the spirit and scope of the instant disclosure will become apparent to those skilled in the art from this detailed description.

BRIEF DESCRIPTION OF THE FIGURES

[0018] **FIG. 1** shows the ternary complex formation assay for **Compound 16** and **Compound 101**.

[0019] **FIG. 2** shows the normalized bioluminescence resonance energy transfer (BRET) response as a function of compound concentration for GNE-781.

DETAILED DESCRIPTION OF THE INVENTION

[0020] Normally, human cells grow and multiply through cell division to form new cells as the body needs them. Every cell in humans includes a collection of genes and proteins, many of which are required for survival and proliferation, and impairment of these genes and proteins leads to loss of fitness or cell death.

[0021] When cells grow old or become damaged, they die and new cells take their place. Sometimes this orderly process breaks down, and abnormal or damaged cells grow and multiply when they shouldn't. In the context of disease states, such as cancerous, autoimmune, or inflammatory states, certain proteins drive the disorderly growth and multiplication of abnormal or damaged cells.

[0022] Conventional monofunctional molecules (e.g., activators, inhibitors) form binary complexes with a target protein. In these binary complexes, the activators or inhibitors target a functional site, either orthosterically or allosterically, to modulate the target protein.

[0023] Many desired cellular changes cannot be accomplished through inhibition alone. Another class of molecules, i.e., bifunctional molecules, have been developed that operate by inducing proximity between the target proteins to form ternary complexes, which evokes a number of functions beyond inhibition.

[0024] Bifunctional molecules have primarily been utilized for their potential to simultaneously engage two macromolecular targets to form ternary complexes that in turn result in new and unique biological and cellular activities. The bifunctional molecules have seen promise in the applications of chemical induced dimerization, the inhibition of protein-protein interactions (PPIs), the degradation of target proteins, the simultaneous catalysis of two or more enzymatic processes, and the promotion or inhibition of protein aggregation. However, bifunctional molecules are not limited to the simultaneous engagement of targets. These molecules can be rationally designed from two functional chemical moieties for various dual functions such as the dual inhibition of synergistic proteins in diseases, targeted drug delivery, and activity-based profiling. Such applications have been proposed to replace combination therapies.

[0025] In ternary complexes, the bifunctional molecules can bind to various sites, including active or allosteric sites. While conventional inhibitors are occupancy driven, bifunctional molecules are often event driven. As a result, conventional inhibitors are stoichiometric, while bifunctional molecules can be sub-stoichiometric and catalytic. Furthermore, conventional inhibitors require strong binding affinities, whereas bifunctional molecules may exhibit low-to-moderate binding affinities to targeted proteins, as some ternary complexes rely on cooperativity. Compared with protein inhibitors, which can globally affect protein targets, these bifunctional molecules can be used to localize enzymatic activity to a given target. In addition, binary complexes have a saturation binding effect, where at high concentrations, the binding site is occupied. In contrast, ternary complexes can exhibit a hook effect, where high concentrations of the small molecule can saturate the two binding partners into individual binary complexes, resulting in loss of efficacy at a higher dose. Mathematical frameworks to describe the three-body equilibria have been developed to support experimental and theoretical findings of these ternary complexes (E.F. Douglass Jr., et al., A comprehensive mathematical model for three-body binding equilibria, *J. Am. Chem. Soc.*, 135 (2013), pp. 6092-6099).

[0026] Cancer cells show extensive alterations in protein expression levels, which are drivers of their malignant transformation. Proteins with altered expression levels in cancer are involved in protein synthesis and degradation, signaling and metabolic pathways, DNA repair, apoptosis, and other cellular processes, whose alterations cause tumor development and progression.

[0027] A key component of successful drug development is the assessment of the therapeutic index (TI), the ratio of the dose or exposure of a drug required to elicit the desired therapeutic effect compared with the dose or exposure at which toxicity becomes limiting. While drugs with a high TI effectively kill cancer cells with manageable toxicities, drugs with a low TI cause significant side effects at or below efficacious doses. Cytotoxic chemotherapies, which typically target proliferating cells, generally have low TIs.

[0028] The modulation of disease protein levels is an effective anticancer target, which is achieved by targeting of up-regulated proteins in cancer, such as, but not limited to, androgen receptor, estrogen receptor, epidermal growth factor receptor 2 (HER2), and vascular endothelial growth factor (VEGF). The development of targeted therapeutics, typically monofunctional molecules, has provided alternative routes to achieving high TIs by either targeting cancer dysregulated genes with limited requirements for homeostasis in adults (e.g., ABL, KIT, TRK, ALK), or by developing mutation-biased inhibitors (e.g., $KRAS^{G12C}$).

[0029] However, targeting proteins that are required for survival and proliferation of cancer cells (i.e., disease-dependent proteins), such as cell cycle regulators, mitotic kinases, and epigenetic regulators, results in cellular loss of fitness or cell death of cancer cells, but the same proteins are also targeted in healthy cells. The result is a low TI drug that either fails approval by regulatory agencies or has limited use in treatment.

[0030] Described herein is a novel treatment modality for treating cancers, and other disease states. The novel heterobifunctional compounds described herein comprise at least two different monofunctional compounds, one that targets a disease protein and the other that targets a disease-dependent protein, with an optional linker connecting the two together. The targeting of the disease-dependent protein is achieved with a silent binder, such that the binding of the silent binder to the disease-dependent protein in the diseased cell

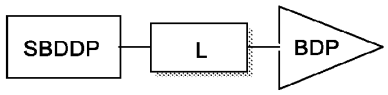
(i.e., cancer cell) or healthy cells leads to minimal or no inhibition of the disease-dependent protein. When the binder of the disease protein binds to its target and the silent binder binds with its target, inhibition of disease-dependent protein is the result. The novel heterobifunctional compounds described herein are therapeutics with a high TI.

[0031] Protein pairs for the heterobifunctional compounds described herein can be chosen from resources such as, but not limited to: The Cancer Genome Atlas (TCGA), TCGA Pan-Cancer project, The Cancer Cell Line Encyclopedia (CCLE) consortium, the Genomics of Drug Sensitivity in Cancer (GDSC), Clinical Proteomic Tumour Analysis Consortium (CPTAC), Protein Interaction Network Analysis (PINA) platform , protein-protein interaction (PPI) network based on computational methods have been used to identify disease-specific genes, modules, and cancer-subtype subnetworks (Kann MG. Protein interactions and disease: computational approaches to uncover the etiology of diseases. *Brief Bioinform.* 2007;8:333–46), Proteomics Database (PD), Dependency Map (DepMap), and Protein Abundance Database (PAXdb).

Heterobifunctional Inhibitors

[0032] In some embodiments disclosed herein is a heterobifunctional inhibitor. In some embodiments, the heterobifunctional inhibitor is a heterobifunctional conditional inhibitor.

[0033] In some embodiments, the heterobifunctional conditional inhibitor compound is a compound of Formula (I):



wherein:

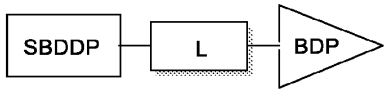
SB is a silent binder of a disease-dependent protein (DDP);

L is an optional linker; and

BDP is a binder of a disease protein (DP), wherein the DP is the androgen receptor.

[0034] In some embodiments disclosed herein is a stable ternary complex comprising:

a. one or more disease-dependent proteins (DDPs);
b. a disease protein (DP), wherein the DP is the androgen receptor; and
c. heterobifunctional conditional inhibitor compound of Formula (I):



wherein:

SBDDP is a silent binder of a disease-dependent protein (DDP);

L is an optional linker; and

BDP is a binder of a disease protein (DP), wherein the DP is the androgen receptor;

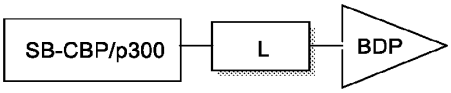
wherein DDP and DP are present in a cell of interest (COI) and the relative abundance of the DP in the COI is greater than the relative abundance of the DDP in the COI

[0035] In some embodiments disclosed herein is a stable ternary complex comprising:

a. CBP/p300;

b. a disease protein (DP), wherein the DP is the androgen receptor; and

c. heterobifunctional conditional inhibitor compound of Formula (II):



wherein:

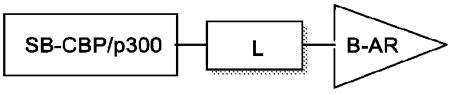
SB-CBP/p300 is a silent binder of CBP/p300;

L is an optional linker; and

BDP is a binder of a disease protein (DP);

wherein CBP/p300 and DP are present in a cell of interest (COI) and the relative abundance of the DP in the COI is greater than the relative abundance of CBP/p300 in the COI.

[0036] In some embodiments disclosed herein is a compound of Formula (III):



wherein:

SB-CBP/p300 is a silent binder of CBP/p300;

L is an optional linker; and

B-AR is a binder of the androgen receptor (AR).

[0037] In some embodiments, disclosed herein is a heterobifunctional compound of Formula (Ia), comprising:

a. a binder of human CREB-binding protein (CBP) or human E1A-binding protein p300 (p300) (CBP/p300);

b. a binder of a disease protein (DP), wherein the DP is the androgen receptor; and

c. an optional linker covalently connecting a) to b);

wherein the optional linker is covalently attached at a position of a) that is solvent exposed when a) binds to CBP/p300.

[0038] In some embodiments, wherein SBDDP binds to the DDP and inhibits the activity of the DDP in the COI if the BDP simultaneously binds to the AR and the relative abundance of AR in the COI is greater than the DDP in the COI.

[0039] In some embodiments, BDP is a non-silent binder or silent binder of a disease protein (DP). In some embodiments, BDP is a non-silent binder of AR. In some embodiments, BDP is a silent binder of a disease protein AR.

[0040] In some embodiments, DDP and AR are both expressed in a cell of interest (COI). In some embodiments, CBP/p300 and AR are both expressed in a cell of interest (COI). In some embodiments, CBP/p300 and AR are both expressed in a cell of interest (COI).

[0041] In some embodiments, the relative abundance of AR in the COI is greater than the relative abundance of the DDP in the COI. In some embodiments, the relative abundance of AR in the COI is greater than the relative abundance of the DDP in the COI by a factor of at least about 2, at least about 5, at least about 10, at least about 50, at least about 100, or about least about 250. In some embodiments, the relative abundance of AR in the COI is greater than the relative abundance of the DDP in the COI by a factor of at least about 100. In some embodiments, the relative abundance of AR in the COI is greater than the relative abundance of CBP/p300 in the COI. In some embodiments, the relative abundance of AR in the COI is greater than the relative abundance of CBP/p300 in the COI by a factor of at least about 2, at least about 5, at least about 10, at least about 50, at least about 100, or about least about 250. In some embodiments, the relative abundance of AR in the COI is greater than the relative abundance of CBP/p300 in the COI by a factor of at least about 100. In some embodiments, the relative abundance of AR in the COI is greater than the relative abundance of the CBP/p300 in the COI. In some embodiments, the relative abundance of AR in the COI is greater than the relative abundance of CBP/p300 in the COI by a factor of at least about 2, at least about 5, at least about 10, at least about 50, at least about 100, or about least about 250. In some embodiments, the relative abundance of AR in the COI is greater than the relative abundance of CBP/p300 in the COI by a factor of at least about 100.

[0042] In some embodiments, the COI is a diseased cell, and AR is overexpressed, overactive, or both overexpressed and overactive, or amplified in the diseased cell as compared to when the COI is a non-diseased cell. In some embodiments, the COI is a diseased cell, and AR is overexpressed in the diseased cell as compared to when the COI is a non-diseased cell. In some embodiments, the COI is a diseased cell, and AR is overactive in the diseased cell as compared to when the COI is a non-diseased cell. In some embodiments, the COI is a diseased cell, and AR is overexpressed and overactive in the diseased cell as compared to when the COI is a non-diseased cell. In some embodiments, the COI is a diseased cell, and AR is amplified in the diseased cell as compared to when the COI is a non-diseased cell. In some embodiments, COI is a diseased cell, and AR is overexpressed, overactive, or both overexpressed and overactive, or amplified in the diseased cell as compared to when the COI is a non-diseased cell.

[0043] In some embodiments, the activity of the DDP is reduced or inhibited by the compound of Formula (I), (II), or (III) when the DDP and AR are both expressed in the same COI and the relative abundance of the AR in the COI is greater than the relative abundance of the DDP in the COI. In some embodiments, the activity of the DDP is reduced by the compound of Formula (I), (II), or (III) when the DDP and AR are both expressed in the same COI and the relative abundance of the AR in the COI is greater than the relative abundance of the DDP in the COI. In some embodiments, the activity of the DDP is inhibited by the compound of Formula (I), (II), or (III) when the DDP and AR are both expressed in the same COI and the relative abundance of the AR in the COI is greater than the relative abundance of the DDP in the COI.

[0044] In some embodiments, the activity of the CBP/p300 is reduced or inhibited by the compound of Formula (Ia) when the CBP/p300 and AR are both expressed in the same COI and the relative abundance of

the AR in the COI is greater than the relative abundance of the CBP/p300 in the COI.

[0045] In some embodiments, the activity of CBP/p300 is reduced or inhibited by the compound of Formula (III) when CBP/p300 and AR are both expressed in the same COI and the relative abundance of the AR in the COI is greater than the relative abundance of the CBP/p300 in the COI.

[0046] In some embodiments, the activity of the DDP is unaltered by the compound of Formula (I), (II), or (III) when the DDP and AR are not both expressed in the same COI and/or the relative abundance of the AR in the COI is not greater than the relative abundance of the DDP in the COI.

[0047] In some embodiments, the activity of the CBP/p300 is unaltered by the compound of Formula (Ia) when the CBP/p300 and AR are not both expressed in the same COI and/or the relative abundance of the AR in the COI is not greater than the relative abundance of the CBP/p300 in the COI.

[0048] In some embodiments, the activity of CBP/p300 is unaltered by the compound of Formula (III) when CBP/p300 and AR are not both expressed in the same COI and/or the relative abundance of the AR in the COI is not greater than the relative abundance of the CBP/p300 in the COI.

[0049] In some embodiments, the DP is the androgen receptor (AR) and the BDP is an AR binder. In some embodiments, the DP is the androgen receptor (AR) and the BDP is an AR antagonist or agonist.

Cell of Interest (COI)

[0050] In some embodiments, the COI is a diseased cell where inhibition of disease-dependent protein (DDP) is desirable. In some embodiments, the COI is a diseased cell. In some embodiments, the cell of interest is a cancer cell. In some embodiments, the cancer cell is associated with a carcinoma, sarcoma, leukemia, lymphoma, myeloma, or the central nervous system. In some embodiments, the cancer cell is associated with a carcinoma, for example, squamous cell carcinoma, adenocarcinoma, transitional cell carcinoma, or basal cell carcinoma. In some embodiments, the cancer cell is an epithelial cell, for example, a squamous cell, adenomatous cell, transitional cell, or basal cell. In some embodiments, the cancer cell is associated with a sarcoma, for example, bone sarcoma or soft tissue sarcoma. In some embodiments, the cancer cell is a bone cell, cartilage cell, or muscle cell. In some embodiments, the cancer cell is associated with a leukemia. In some embodiments, the cancer cell is a white blood cell. In some embodiments, the cancer cell is associated with a lymphoma or myeloma. In some embodiments, the cancer cell is a white blood cell or plasma cell. In some embodiments, the cancer cell is associated with the central nervous system, for example, the brain or spinal cord. In some embodiments, the cancer cell is a glial cell.

[0051] In some embodiments, the COI is a cell associated with head and neck cancer, laryngeal and hypopharyngeal cancer, nasal cavity and paranasal sinuses cancer, nasopharyngeal cancer, oral cavity (mouth) and oropharyngeal (throat) cancer, or salivary gland cancer. In some embodiments, the COI is a cell associated with anal cancer, bile duct cancer, colorectal cancer, esophagus cancer, gallbladder cancer, gastrointestinal neuroendocrine tumors, gastrointestinal stromal tumor, liver cancer pancreatic cancer, pancreatic neuroendocrine tumor, small intestine cancer, or stomach cancer. In some embodiments, the COI is a cell associated with associated with bladder cancer, kidney cancer, or Wilms tumor. In some

embodiments, the COI is a cell associated with lung cancer, lung carcinoid tumor, or malignant mesothelioma. In some embodiments, the COI is a cell associated with breast cancer. In some embodiments, the COI is a cell associated with cervical cancer, endometrial cancer, ovarian cancer, penile cancer, prostate cancer, testicular cancer, uterine sarcoma, vaginal cancer, or vulvar cancer. In some embodiments, the COI is a cell associated with adrenal cancer, gastrointestinal neuroendocrine tumors, lung carcinoid tumor, pancreatic neuroendocrine tumor, pituitary tumors, or thyroid cancer. In some embodiments, the COI is a cell associated with skin cancer, basal and squamous cell skin cancer, Kaposi sarcoma, lymphoma of the skin, melanoma skin cancer, or Merkel cell skin cancer. In some embodiments, the COI is a cell associated with bone cancer, Ewing family of tumors, osteosarcoma, rhabdomyosarcoma, or soft tissue sarcoma. In some embodiments, the COI is a cell associated with eye cancer or retinoblastoma. In some embodiments, the COI is a cell associated with brain and spinal cord tumors or neuroblastoma. In some embodiments, the COI is a cell associated with leukemia, acute lymphocytic leukemia, acute myeloid leukemia, chronic lymphocytic leukemia, chronic myeloid leukemia, chronic myelomonocytic leukemia, lymphoma, non-Hodgkin lymphoma, Hodgkin-lymphoma, multiple myeloma, myelodysplastic syndromes, thymus cancer, or Waldenstrom macroglobulinemia.

[0052] In some embodiments, the COI is a cell associated with prostate cancer or breast cancer. In some embodiments, the COI is a cell associated with prostate cancer, luminal breast cancer, and luminal androgen receptor triple-negative breast cancer.

Disease-Dependent Protein (DDP)

[0053] "Disease-dependent protein" or "DDP" refers to any one of the proteins expressed in cell of interest that is/are required for cell functioning and/or maintenance and/or survival in a particular disease. That is, the indicated disease is dependent on the disease-dependent protein to survive. In some embodiments, a cell of interest includes one type of DDP. In some embodiments, a cell of interest expresses more than one type of DDPs, and each type of DDPs performs functions distinct from any other type of DDPs in the cell of interest. In some embodiments, a cell of interest expresses more than one type of DDPs, and each type of DDPs performs functions substantially the same or overlapping with at least one other type of DDPs in the cell of interest.

[0054] In some embodiments, the disease-dependent protein (DDP) is AT-Hook containing transcription factor 1 (AHCTF1), Anaphase promoting complex subunit 1 (ANAPC1), ANAPC4, ANAPC5, Ataxia-telangiectasia mutated (ATM), Ataxia telangiectasia and Rad3-related protein (ATR), Aurora Kinase A (AurkA), Aurora Kinase B (AurkB), Bromodomain-containing protein 4 (BRD4), Bromodomain PHD finger transcription factor (BPTF), BUB1 mitotic checkpoint serine/threonine kinase B (BUB1B), CREB-binding protein (CBP)/p300, Cell division cycle 7-related protein kinase (CDC7), CDC16, CDC23, CDC27, CDC45, Centromere protein W (CENPW), Chromatin assembly factor 1 subunit b (CHAF1B), Chromodomain helicase DNA binding protein 4 (CHD4), Checkpoint kinase 1 (CHK1), CHK2, Cleavage factor polyribonucleotide kinase subunit 1 (CLP1), CWC22, Cyclin-dependent kinase 1 (CDK1), CDK2,

CDK4, CDK5, CDK6, CDK9, CDK11a, Cytoskeleton associated protein 5 (CKAP5), DDB1 and CUL4 associated factor 1 (DCAF1), DEAD-box helicase 1 (DBR1), DDX10, DDX41, DDX47, DDX54, DDX56, Dehydrodolichyl diphosphate synthase subunit (DHDDS), Deoxyhypusine synthase (DHPS), DEAH-box helicase 8 (DHX8), DONSON, DNA methyltransferase 1(DNMT1), Denticleless E3 ubiquitin protein ligase homolog (DTL), histone acetyltransferase P300 (EP300), E1A binding protein P400 (EP400), Extra spindle pole bodies like 1, separase (ESPL1)/separin, F-Box Protein 5 (FBXO5), Gem nuclear organelle associated protein 5 (GEMIN5), GINS2, GPN-Loop GTPase 3 (GPN3), HAUS augmin like complex subunit 1 (HAUS1), HAUS6, Host cell factor C1 (HCFC1), Histone deacetylase 1 (HDAC1), HDAC2, HDAC3, HEAT repeat containing 1 (HEATR1), Integrator complex subunit 11 (INTS11), Lysine acetyltransferase 8 (KAT8)/MYST1, Kinesin family member 11 (KIF11), KIF18A, KIF23, Mitotic arrest deficient 2 like 1 (MAD2A/MAD2L1), MAK16, Microtubule associate serine/threonine kinase like (MASTL), Midasin AAA ATPase 1 (MDN1), Mediator complex subunit 14 (MED14), MED11, MED28, Mitogen-activated protein kinase 1 (MEK1), MEK2, MIS18A, Methyl methanesulfonate-sensitivity protein 22-like (MMS22L), Myc, Mammalian target of rapamycin (MTOR), Neuronal precursor cell-expressed developmentally down-regulated protein 8 (NEDD8), NIP7, Nucleolar complex associated 4 homolog (NOC4L), Nucleolar protein 6 (NOL6), Notchless homolog 1 (NLE1), NUF2, Nucleoporin 205 (NUP205), NUS1, Opa interacting protein 5 (OIP5), Programmed cell death 11 (PDCD11), Phosphatidylinositol-3 kinase (PI3K), Polo-like kinase 1 (PLK1), DNA polymerase alpha 1, catalytic subunit (POLA1), DNA polymerase delta 1, catalytic subunit (POLD1), DNA polymerase epsilon, catalytic subunit (POLE), DNA polymerase epsilon, subunit 2 (POLE2), Peptidylprolyl isomerase domain and WD repeat containing 1 (PPWD1), Protein regulator of cytokinesis 1 (PRC1), DNA primase subunit 1 (PRIM1)/DNA PRIMASE, Protein arginine methyltransferase 5 (PRMT5), 20S proteasome subunits, RAD51, Rac GTPase activating protein 1 (RACGAP1), Ribonucleoside-diphosphate reductase subunit M1 (RRM1), Ribonucleic acid export 1 (RAE1), RNA polymerase I subunit B (POLR1B), RNA polymerase II subunit J (POLR2J), RNA polymerase II associated protein 1 (RPAP1), RNA guanylyltransferase and 5'-phosphatase (RNGTT), Splicing factor 3b subunit 1 (SF3B1), SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily A, member 2/4 (SMARCA2/4), Small nuclear RNA activating complex polypeptide 5 (SNAPC5), Structural maintenance of chromosomes 4 (SMC4), SMG1, SGO1, Steroid receptor coactivator 1 (SRC1), SRC2, SRC3, SLU7, SPC24, SPT6H, SPT5H, Symplekin scaffold protein (SYMPK), TIMELESS, Thioredoxin like 4a (TXNL4A), Tonsoku-like, DNA repair protein (TONSL), Topoisomerase II alpha (TOP2A), TPX2, Transformation/transcription domain associated protein (TRRAP), Trafficking protein particle complex subunit 8 (TRAPPC8), TSR2, Ubiquitously expressed transcript protein (UXT), URB1, UTP15, UTP20, Ubiquitin specific peptidase like 1 (USPL1), Vacuolar protein-sorting-associated protein 25 (VPS25), WD repeat-containing protein 3 (WDR3), WDR5, WDR12, WDR43, WDR46, WDR70, WD74, WEE1, WW domain binding protein 11 (WBP11), Xeroderma pigmentosum group A-binding protein 2 (XAB2), or Exportin 1 (XPO1).

[0055] In some embodiments, the disease-dependent protein (DDP) is Ataxia-telangiectasia mutated

(ATM), Ataxia telangiectasia and Rad3-related protein (ATR), Aurora Kinase A (AurkA), AurkB, Cell division cycle 7-related protein kinase (CDC7), Checkpoint kinase 1 (CHK1), CHK2, Cyclin-dependent kinase 1 (CDK1), CDK2, CDK4, CDK5, CDK6, CDK9, DNA methyltransferase 1 (DNMT1), Exportin 1 (XPO1), Histone deacetylase 1 (HDAC1), HDAC2, HDAC3, kinesin family member 11 (KIF11), Mitogen-activated protein kinase kinase 1 (MEK1), MEK2, Myc, neuronal precursor cell-expressed developmentally down-regulated protein 8 (NEDD8), SMARCA2, SMARCA4, CREB-binding protein (CBP)/p300, WD repeat-containing protein 5 (WDR5), DDB1- and CUL4-associated factor 1 (DCAF1), phosphatidylinositol-3 kinase (PI3K), Protein arginine methyltransferase 5 (PRMT5), splicing factor 3b subunit 1 (SF3B1), WEE1, 20S proteasome subunits, Steroid Receptor Coactivator 1 (SRC1), SRC2, or SRC3. In some embodiments, DDP is Aurora Kinase A (AurkA), Checkpoint kinase 1 (CHK1), CHK2, CDK4, CDK6, Myc, SMARCA2, SMARCA4, CREB-binding protein (CBP)/p300, WD repeat-containing protein 5 (WDR5), DDB1- and CUL4-associated factor 1 (DCAF1), phosphatidylinositol-3 kinase (PI3K), or WEE1. In some embodiments, DDP is Aurora Kinase A (AurkA), Checkpoint kinase 1 (CHK1), CHK2, CDK4, CDK6, Myc, SMARCA2, SMARCA4, CREB-binding protein (CBP)/p300, WD repeat-containing protein 5 (WDR5), DDB1- and CUL4-associated factor 1 (DCAF1), phosphatidylinositol-3 kinase (PI3K), or WEE1. In some embodiments, the DDP is CBP/p300 or SMARCA2/4. In some embodiments, DDP is CBP/p300. In some embodiments, the DDP is SMARCA 2/4.

[0056] In some embodiments, when the disease protein is the androgen receptor (AR), then the DDP is an AR coactivator or coregulator. Androgens, functioning through the AR, are essential for the normal development and maintenance of the prostate. Androgen-bound AR functions as a transcription factor to regulate genes involved in an array of physiological processes. The transcriptional activity of AR is affected by coregulators that influence a number of functional properties of AR, including ligand selectivity and DNA binding capacity. As the promoter of target genes, coregulators participate in DNA modification, either directly through modification of histones or indirectly by the recruitment of chromatin-modifying complexes, as well as functioning in the recruitment of the basal transcriptional machinery. Aberrant coregulator activity due to mutation or altered expression levels may be a contributing factor in the progression of diseases related to AR activity, such as prostate cancer.

[0057] The progression of prostate cancer is also sensitive to androgens. Surgical and/or pharmacological androgen ablation remain the predominant form of treatment for advanced prostate cancer. Androgen ablation therapy is often combined with treatment with nonsteroidal antiandrogens, such as hydroxyflutamide, to block residual adrenal androgen action. While 70–80% of patients initially respond to androgen ablation therapy, tumors ultimately become resistant and may, in fact, proliferate in response to antiandrogens. Because AR is generally expressed in prostate tumors and their metastases, aberrant regulation of AR activity by coregulators may contribute to prostate cancer progression or the acquired agonist effect of antiandrogens.

[0058] In addition, androgen-independent activation of the AR is a well-known phenomenon and can occur via several different mechanisms, including activation by interleukins. For example, interleukin-6 (IL-

6) has been shown to activate AR-dependent gene expression in the absence of androgens. Activation of the AR and AR target gene expression by IL-6 requires p300 and its HAT activity. Similar to IL-6, interleukin-4 (IL-4) activates the AR, increases CBP/p300 protein expression, and enhances the interaction of CBP/p300 with the AR at the KLK3 promoter. Therefore, CBP/p300 appears to be crucial for AR transcriptional activity in both the presence and absence of androgens.

[0059] In some embodiments, AR coactivators or coactivator or coregulator is AKT1, AurkA, BAG family molecular chaperone regulator 1 (BAG1), beta-catenin, Breast cancer type 1 susceptibility protein (BRCA1), BRD4, C-jun, calmodulin 1, caveolin 1, CDK4/6, CDK9, Cytochrome C oxidase subunit 5b (COX5B), CBP/p300, CD1, CDK7, Dachshund family transcription factor 1 (DACH1), Death domain associated protein (Daxx), DCAF1, L-3,4-dihydroxyphenylalanine (L-DOPA), EF-hand calcium-binding domain-containing protein 6 (EFCAB6), Epidermal growth factor receptor (EGFR), Forkhead Box O1 (FOXO1), Glyceraldehyde-3-Phosphate Dehydrogenase (GAPDH), gelsolin, guanine nucleotide-binding protein subunit beta-2-like 1 (GNB2L1), Glycogen synthase kinase 3 beta (GSK3B), HDAC1, Heat shock protein 90 alpha family class a member 1 (HSP90AA1), HTATIP, MAGEA11, MED1, Myc, MYST2, Nuclear receptor coactivator 1 (NCOA1), NCOA2, NCOA3, NCOA4, NCOA6, Nuclear receptor corepressor 2 (NCOR2), Non-POU domain-containing octamer-binding protein (NONO), Proliferation-associated protein 2G4 (PA2G4), P21 (RAC1) Activated kinase 6 (PAK6), POZ/BTB and at hook containing zinc finger 1 (PATZ1), Protein Inhibitor Of Activated STAT 2 (PIAS2), Pre-MRNA Processing Factor 6 (PRPF6), Phosphatase And Tensin Homolog (PTEN), RAD9A, RAN binding protein 9 (RANBP9), Ring finger and CHY zinc finger domain containing 1 (RCHY1), Retinoblastoma protein, Ring finger protein 4 (RNF4), RNF14, Spliceosome associated factor 3, U4/U6 recycling protein (SART3), Sirtuin 1 (SIRT1), SMAD3, SMARCA2/4, small heterodimer partner, Src, Sex determining region Y (SRY), STAT3, Supervillin (SVIL), Testicular receptor 2, Testicular receptor 4, Transforming growth factor beta 1 induced transcript 1 (TGFB1I1), TATA element modulatory factor 1 (TMF1), Tripartite motif containing 68 (TRIM68), Ubiquitin conjugating enzyme E2 I (UBE2I), Ubiquitously expressed prefoldin like chaperone (UXT), WEE1, and Zinc finger MIZ-type containing 1 (ZMIZ1).

Silent Binder of a Disease-Dependent Protein (SBDDP)

[0060] "Silent-binder" refers to a compound (or fragment of a heterobifunctional compound) that binds to a target protein and does not substantially alter protein function. In some embodiments, a silent binder does not result in functional activation or inhibition of the target protein.

[0061] It is understood that some silent binders may, upon binding to a target protein, result in or induce some measurable or detectable effect on protein function. However, in such instances the measurable altered protein function is not detrimental to the ordinary functioning of the target protein at concentrations relevant for inducing inhibition of the target protein.

[0062] It is also understood that the silent binder to a target protein does not substantially alter protein function when it is incorporated into the heterobifunctional conditional inhibitor compounds disclosed herein

unless the non-silent binder (NSB) component of the heterobifunctional conditional inhibitor compound also simultaneously binds to the disease protein (DP) in the same cell.

[0063] In some embodiments, a silent binder may be silent because it binds to a domain of a target protein that is not a relevant domain for the activity of the target protein. In other embodiments, a silent binder may be silent because it an allosteric binder of the target protein. In other embodiments, a silent binder may be silent because its incorporation into a heterobifunctional compound reduces the activity of the binder as compared to when it is not incorporated into a heterobifunctional compound. For example, a compound may be a modulator of a target protein when it is not a component of a heterobifunctional compound but becomes a silent binder of the target protein by virtue of its incorporation into a heterobifunctional compounds disclosed herein.

[0064] "Binder of a disease protein" or "BDP" refers to a compound (or fragment of a heterobifunctional compound) that binds to a target disease protein and: 1) does not substantially alter protein function; or 2) substantially alters protein function. In some embodiments, a binder of a disease protein when incorporated into the heterobifunctional compounds disclosed herein does not substantially alter protein function of the disease protein. In some embodiments, a binder of a disease protein when incorporated into the heterobifunctional compounds disclosed herein does not substantially alter protein function of the disease protein unless the silent binder component of the heterobifunctional conditional compound also simultaneously binds to a disease-dependent protein in the same cell.

[0065] "Non-silent binder" or "NSB" refers to a compound (or fragment of a heterobifunctional compound) that binds to a target disease protein and substantially alters protein function. NSBs include, but are not limited to, agonist, inverse agonist, antagonist, neutral antagonist, silent antagonist, competitive antagonist, irreversible antagonist, reversible antagonist, inhibitor, irreversible inhibitor, reversible inhibitor, allosteric modulator, negative allosteric modulator, and positive allosteric modulator.

[0066] Silent Antagonist is a drug that attenuates the effects of agonists or inverse agonists, producing a functional reduction in signal transduction. Affects only ligand-dependent receptor activation and displays no intrinsic activity itself. Also known as a neutral antagonist.

[0067] Agonist is a drug that binds to and activates a receptor. Can be full, partial or inverse. A full agonist has high efficacy, producing a full response while occupying a relatively low proportion of receptors. A partial agonist has lower efficacy than a full agonist. It produces sub-maximal activation even when occupying the total receptor population, therefore cannot produce the maximal response, irrespective of the concentration applied. An inverse agonist produces an effect opposite to that of an agonist yet binds to the same receptor binding-site as an agonist.

[0068] Allosteric Modulator is a drug that binds to a receptor at a site distinct from the active site. Induces a conformational change in the receptor, which alters the affinity of the receptor for the endogenous ligand. Positive allosteric modulators increase the affinity, whilst negative allosteric modulators decrease the affinity.

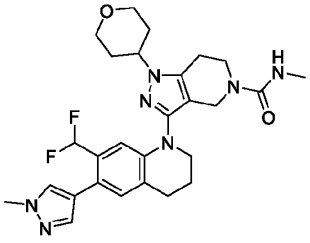
[0069] Antagonist is a drug that attenuates the effect of an agonist. Can be competitive or non-

competitive, each of which can be reversible or irreversible. A competitive antagonist binds to the same site as the agonist but does not activate it, thus blocks the agonist's action. A non-competitive antagonist binds to an allosteric (non-agonist) site on the receptor to prevent activation of the receptor. A reversible antagonist binds non-covalently to the receptor, therefore can be "washed out". An irreversible antagonist binds covalently to the receptor and cannot be displaced by either competing ligands or washing.

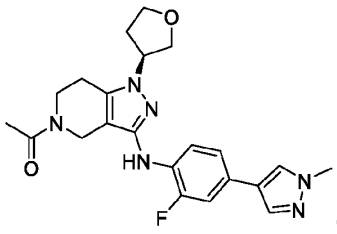
[0070] Efficacy describes the way that agonists vary in the response they produce when they occupy the same number of receptors. High efficacy agonists produce their maximal response while occupying a relatively low proportion of the total receptor population. Lower efficacy agonists do not activate receptors to the same degree and may not be able to produce the maximal response (see Agonist, Partial).

[0071] In some embodiments, SBDDP is a CBP/p300 binder. In some embodiments, SBDDP is a CBP/p300 bromodomain binder. In some embodiments, SBDDP is a CBP/p300 histone acetyltransferase (HAT) domain binder. In some embodiments, SBDDP is a CBP/p300 bromodomain binder comprising a benzimidazole, piperidine, benzodiazepinone, indole, oxazolidinedione, barbituric skeleton, thiobarbituric skeleton, or alkaloid. In some embodiments, SBDDP is a CBP/p300 binder as described in Zhang-Xu He, *et al., European Journal of Medicinal Chemistry*, Volume 209, 2021, 112861, which is incorporated by reference for such CBP/p300 binder. In some embodiments, SBDDP is a CBP/p300 binder as any one of compounds 1 to 75 as described in Zhang-Xu He, *et al., European Journal of Medicinal Chemistry*, Volume 209, 2021, 112861, which is incorporated by reference for such CBP/p300 binders.

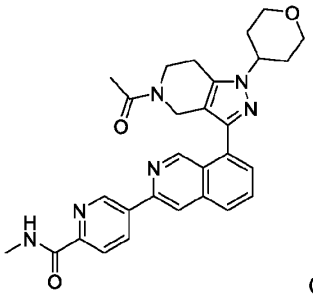
[0072] In some embodiments, SBDDP has one of the following structures:



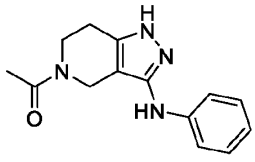
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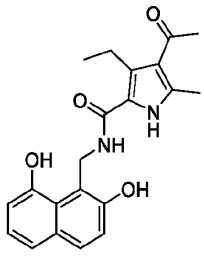
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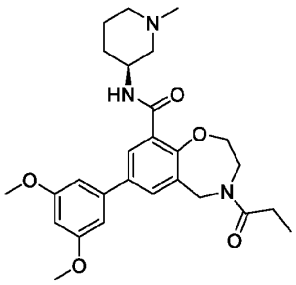
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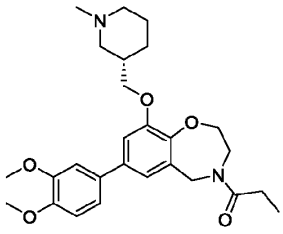
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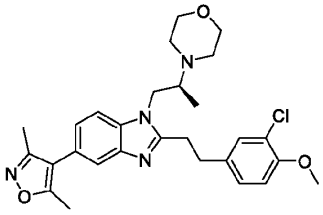
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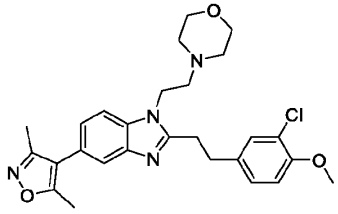
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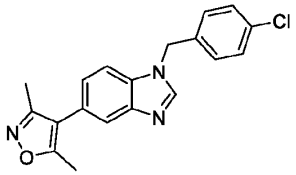
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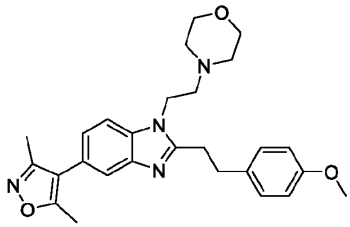
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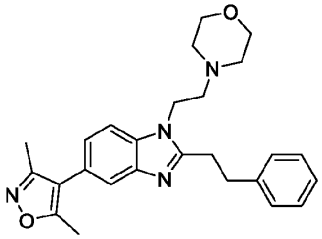
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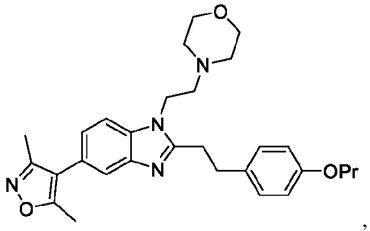
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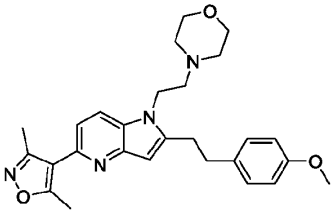
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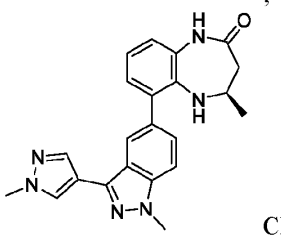
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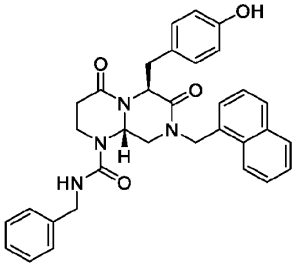
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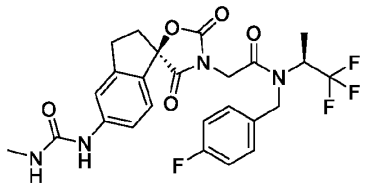
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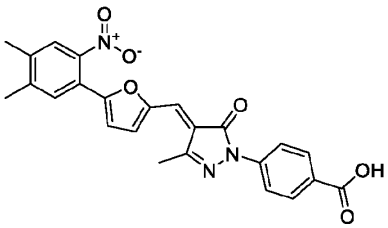
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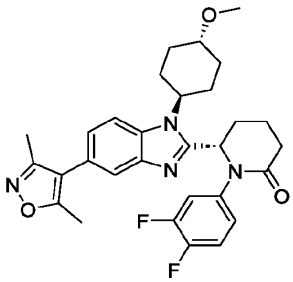
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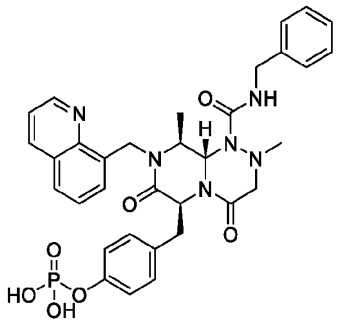
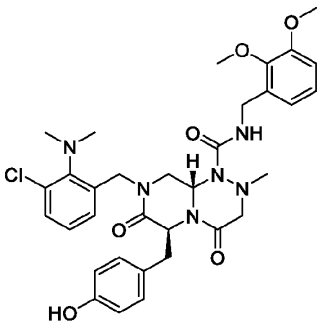
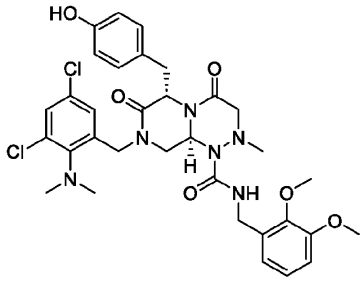
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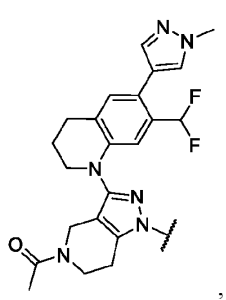
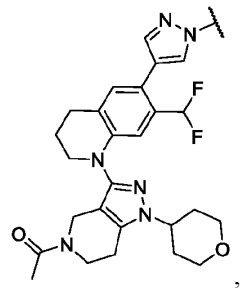
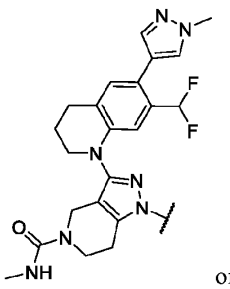
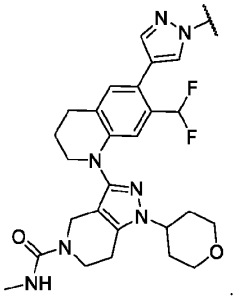
C646,



inobrodib (CCS1477),


PRI-724,

YH249, or

YH250.

[0073] In some embodiments, SBDDP has one of the following structures:


,

,

or

.

Disease Protein (DP)

[0074] In some embodiments, the DP is a protein selectively expressed in a cancer or COI.

[0075] In some embodiments, the DP is a nuclear hormone receptor protein. In some embodiments, the DP is a nuclear hormone receptor, for example, androgen receptor (AR), estrogen receptor (ER), retinoic acid receptor (RAR), vitamin D receptor (VDR), glucocorticoid receptor (GR), mineralocorticoid receptor (MR), or progesterone receptor (PR). In some embodiments, the DP is AR or ER. In some embodiments, the DP is AR.

[0076] In some embodiments, the DP is AR.

Binder of a Disease Protein (BDP)

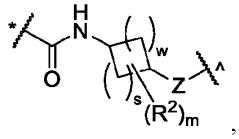
[0077] In some embodiments, the BDP is a non-silent binder of a DP. In some embodiments, the BDP is a silent binder of AR.

[0078] In some embodiments, the AR is a binder of the androgen receptor (AR), wherein B-AR comprises:

1) a head group that occupies the ligand-binding domain (LBD) of AR and is covalently attached to a core moiety, wherein the core comprises an optionally substituted cyclohexyl; and

2) an optional tail moiety covalently attached to the core moiety.

[0079] In some embodiments, the core comprises an optionally substituted cycloalkyl having the structure of Formula (C):


, Formula (C);

wherein: the head group is covalently attached to Z at position (^); the optional tail moiety comprises a ring D that is covalently attached to the amide (*), each R^2 is $-CH_3$; wherein ring D is a 5-, 6-, 8-, 9- or 10-membered aryl or a 5-, 6-, 8-, 9- or 10-membered heteroaryl that is optionally substituted with s R^3; Z is -O- or -NH- or -N(alkyl)-.

[0080] In some embodiments, the head moiety of the AR antagonist forms hydrogen bonds with the side chains of Gln 711 and Arg752 of the LBD of AR.

[0081] In some embodiments, the head group of B-AR comprises 4-cyanophenyl; 3-fluoro-4-cyanophenyl; 3-chloro-4-cyanophenyl; 3-methoxy-4-cyanophenyl; 3-methyl-4-cyanophenyl; 3-trifluroromethyl-4-cyanophenyl; 3-trifluroromethoxy-4-cyanophenyl; 5-fluoro-6-cyanopyridin-3-yl; 5-chloro-6-cyanopyridin-3-yl; 5-methoxy-6-cyanopyridin-3-yl; 5-methyl-6-cyanopyridin-3-yl; 5-trifluroromethyl-6-cyanopyridin-3-yl; 5-trifluroromethoxy-6-cyanopyridin-3-yl; [1,2,4]triazolo[4,3-b]pyridazin-6-yl; or 3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl.

[0082] In some embodiments, the head group and core of B-AR is:

N-(4-(3-fluoro-4-cyanophenoxy)cyclohexyl)acetamide-*;

N-(4-(3-chloro-4-cyanophenoxy)cyclohexyl)acetamide-*;

N-(4-(3-methoxy-4-cyanophenoxy)cyclohexyl)acetamide-*;

N-(4-(3-methyl-4-cyanophenoxy)cyclohexyl)acetamide-*;

N-(4-(3-trifluroromethyl-4-cyanophenoxy)cyclohexyl)acetamide-*;

N-(4-(3-trifluroromethoxy-4-cyanophenoxy)cyclohexyl)acetamide-*;

N-(4-((5- fluoro-6-cyanopyridin-3-yl)oxy)cyclohexyl)acetamide-*;

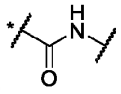
N-(4-((5-chloro-6-cyanopyridin-3-yl)oxy)cyclohexyl)acetamide-*;

N-(4-((5-methoxy -6-cyanopyridin-3-yl)oxy)cyclohexyl)acetamide-*;

N-(4-((5-methyl -6-cyanopyridin-3-yl)oxy)cyclohexyl)acetamide-*;

N-(4-((5-trifluroromethyl -6-cyanopyridin-3-yl)oxy)cyclohexyl)acetamide-*; or

N-(4-((5-trifluroromethoxy-6-cyanopyridin-3-yl)oxy)cyclohexyl)-2,2,4,4-tetramethylcyclobutyl)acetamide-*;

wherein acetamide-* is  .

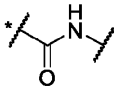
[0083] In some embodiments, the head group and core of B-AR is:

N-(4-(3-chloro-4-cyanophenoxy)cyclohexyl)acetamide-*;

N-(4-(3-methoxy-4-cyanophenoxy)cyclohexyl)acetamide-*;

N-(4-(3-methyl-4-cyanophenoxy)cyclohexyl)acetamide-*; or

N-(4-(3-trifluroromethyl-4-cyanophenoxy)cyclohexyl)acetamide-*;

wherein acetamide-* is  .

[0084] In some embodiments, the BDP is an AR antagonist.

[0085] In some embodiments, B-AR further comprises a tail moiety that is covalently attached to position (*), wherein the tail moiety is a ring D that is phenyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, triazolyl, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, indolyl, isoindolyl, indolizinyl, benzimidazolyl, napthyl, quinolyl, isoquinolyl, quinoxalinyl, quinazolinyl, indazolyl, or benzotriazolyl; wherein ring D is optionally substituted with s R^3; s is 1, 2, or 3; each R^3 is independently hydrogen, F, Cl, Br, I, $-CH_3$, $-CH_2CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2CH_2F$, $-CH_2CHF_2$, $-CH_2CF_3$, -OH, $-OCF_3$, $-OCH_3$, $-OCH_2CH_3$, -CN, $-C(=O)NH_2$, or $-C(=O)NH(CH_3)$.

Representative Approaches to Designing Heterobifunctional Compounds

[0086] The heterobifunctional compounds described herein include three component parts: the ligand that binds the target protein (i.e., the disease protein), the ligand that binds to the disease-dependent protein (DDP), and the linker. Crystal structures of many of these proteins are known and the binding interactions of each component within its respective binding site can be visualized with suitable modeling software. In addition, computer modeling can also be performed to determine the placement of the two proteins relative to one another.

[0087] The Protein Data Bank (PDB) is a database for the three-dimensional structural data of large biological molecules, such as proteins and nucleic acids (*Nucleic Acids Res*. 2019 Jan 8;47(D1):D520-D528. doi: 10.1093/nar/gky949). The data is submitted by biologists and biochemists from around the world, are freely accessible on the Internet via the websites of its member organizations (e.g. PDBe - www.pdbe.org, PDBj - www.pdbj.org, RCSB - www.rcsb.org/pdb, and BMRB - www.bmrb.wisc.edu). The PDB is overseen by an organization called the Worldwide Protein Data Bank - wwPDB - www.wwpdb.org.

[0088] In some embodiments, searching on the PDB database and manipulating of protein 3D models is performed with PyMOL. PyMOL is a user-sponsored molecular visualization system on an open-source foundation, maintained and distributed by Schrödinger. Other PDB database search engines and molecular visualization system are contemplated.

[0089] Model of ligand docking in candidate proteins, and modelling of ternary complexes can be built in the Rosetta software suite (Leaver-Fay A, et al., ROSETTA3: an object-oriented software suite for the simulation and design of macromolecules. Methods Enzymol. 2011; 487:545-74).

[0090] Novel silent binders can be identified for DDPs using methods known in the art, such as fragment-based lead discovery (FBLD) (Kirsch P.; *et al.,* Concepts and Core Principles of Fragment-Based Drug Design. Molecules 2019, 24 (23), 4309; Lamoree B.; et al. Current perspectives in fragment-based lead discovery (FBLD). *Essays Biochem.* 2017, 61 (5), 453–464; Erlanson D. A.; *et al.* Fragment-Based Drug Discovery. *J. Med. Chem.* 2004, 47 (14), 3463–3482; Shuker S. B.; et al. Discovering high-affinity ligands for proteins: SAR by NMR. Science 1996, 274 (5292), 1531–1534), DNA-Encoded Library (DEL) approaches and traditional high-throughput screening (HTS) methods.

[0091] Screening libraries used in FBLD are composed of small molecules called fragments that are broadly compliant with what is now widely recognized as the rule-of-three (Ro3) (Congreve M.; et al., 'Rule of Three' for fragment-based lead discovery?. *Drug Discovery Today* 2003, 8 (19), 876–877; Jhoti H.; et al., The 'rule of three' for fragment-based drug discovery: where are we now?. Nat. Rev. Drug Discovery 2013, 12 (8), 644–644). The small size and simplicity of fragments enables a minimalist approach to drug discovery, whereby a vast chemical space can be efficiently covered using libraries of only a few hundred molecules. This makes fragment screening appealing to industry and academic investigators alike and represents a very accessible, cost-effective, and sustainable approach to hit discovery. Furthermore, unlike conventional libraries used for HTS, fragment libraries are not biased toward previously explored targets. This makes FBLD an indispensable method for assessing the ligandability of novel proteins' binding sites, including PPI sites.

[0092] In some embodiments, the small size of fragments, however, results in them having weak binding affinities to proteins. For this reason, fragments tend to be screened at high concentrations using biophysical techniques such as nuclear magnetic resonance (NMR), surface plasmon resonance (SPR), differential scanning fluorimetry (DSF; also known as thermal shift assay (TSA)), and X-ray crystallography. Weak binders can be skillfully optimized into bespoke potent ligands for proteins via fragment growing, merging, and hybridizing methodologies. However, the successful pursuit of such approaches is often contingent on the determination of the binding mode of the fragment hits to the target protein, typically using X-ray crystallographic methods and/or ^{15}N 2D-NMR experiments and/or cryogenic electron microscopy (cryo-EM) (Saur M.; *et al.*, Fragment-based drug discovery using cryo-EM. *Drug Discovery Today* 2020, 25 (3), 485–490).

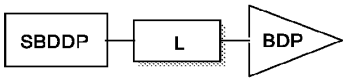
[0093] DEL is achieved through combinatorial chemistry and DNA-encoding techniques. With library modularity, DELs can be built in a time-saving and labor-saving way. This technology can construct and screen unprecedented scale combinatorial compound libraries (hundreds of billions scale) and discover numerous high-affinity ligands with high efficiency and low cost through protein target affinity screening and high-throughput sequencing and decoding (Buller *et al.*, (2010). Drug discovery with DNA-encoded chemical libraries. *Bioconjug. Chem.* 21 (9), 1571–15802010; Kalliokoski T. (2015). Price-focused analysis of commercially available building blocks for combinatorial library synthesis. *ACS Comb. Sci.* 17 (10), 600–607; Goodnow et al., (2017). DNA-Encoded chemistry: Enabling the deeper sampling of chemical space. *Nat. Rev. Drug Discov.* 16 (2), 131–147). DEL can be used to create compound libraries with higher

molecular weight. Empirically, such DEL libraries appear well suited for discovering ligands for protein-protein interaction (PPI) targets, which are increasingly needed for hits.

[0094] Linkers can be designed and assessed as well. Capturing the breadth of viable linker conformations is much akin to modeling the flexibility of drug-like molecules when docking them to proteins. For this purpose, the OMEGA software (Hawkins PC, et al., Comparison of shape-matching and docking as virtual screening tools. *J Med Chem*. 2007; 50:74-82; Hawkins PC, Nicholls A. Conformer generation with OMEGA: learning from the data set and the analysis of failures. *J Chem Inf Model*. 2012; 52:2919-36).

Compounds

[0095] In some embodiments, the heterobifunctional conditional inhibitor compound is a compound of Formula (I):



wherein:

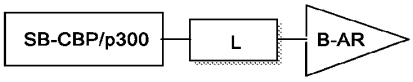
SB is a silent binder of a disease-dependent protein (DDP);

L is an optional linker; and

BDP is a binder of a disease protein (DP).

[0096] In some embodiments, the BDP is an AR antagonist.

[0097] In some embodiments disclosed herein are heterobifunctional conditional inhibitor compounds of Formula (III):



wherein:

SB-CBP/p300 is a silent binder of CBP/p300;

L is an optional linker; and

B-AR is a binder of the androgen receptor (AR).

[0098] In some embodiments, disclosed herein is a heterobifunctional compound of Formula (Ia), comprising:

a. a binder of human CREB-binding protein (CBP) or human E1A-binding protein p300 (p300) (CBP/p300);
b. a binder of a disease protein (DP); and
c. an optional linker covalently connecting a) to b);

wherein the optional linker is covalently attached at a position of a) that is solvent exposed when a) binds to CBP/p300.

[0099] In some embodiments, the binder of CBP/p300 binds in the acetyl-lysine (Kac) binding site of the bromodomain CBP/p300. In some embodiments, the binder of CBP/p300 comprises an acetyl-lysine

mimetic moiety that binds in the acetyl-lysine (KAc) binding site of the bromodomain of human CREB-binding protein (CBP) or human E1A-binding protein p300 (p300) (CBP/p300).

[00100] In some embodiments, the optional linker is covalently attached at a position of a) that is solvent exposed when a) binds the KAc binding site of the bromodomain of CBP/p300.

[00101] In some embodiments, the moiety comprising an acetyl-lysine mimetic makes or mimics a hydrogen bond interaction to Asn1168 in the Asn-binding pocket of the bromodomain of CBP, or makes or mimics a hydrogen bond interaction to Asn1132 in the Asn-binding pocket of the bromodomain of p300.

[00102] In some embodiments, a) further comprises a moiety that interacts with Arg1173 in the bromodomain of CBP or Asn1137 in the bromodomain of p300.

[00103] In some embodiments, wherein a) further comprises:

1) a moiety that occupies the lipophilic shelf (LPF) region of the bromodomain of CBP/p300; or

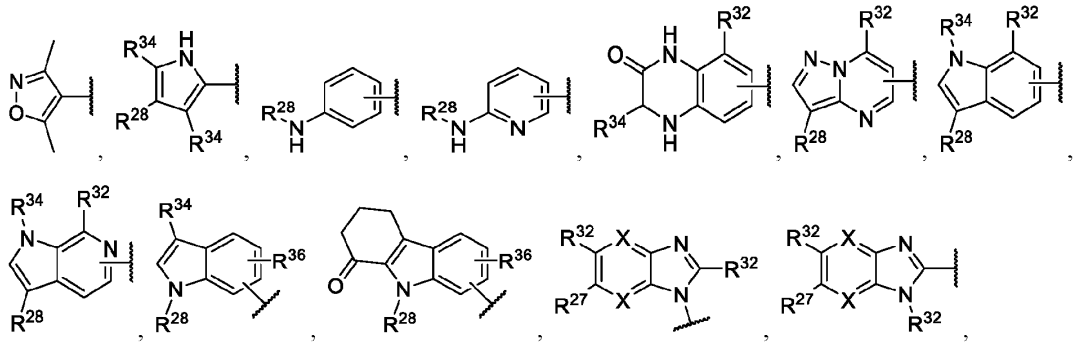
2) a moiety that occupies the BC Loop region of the bromodomain of CBP/p300; or

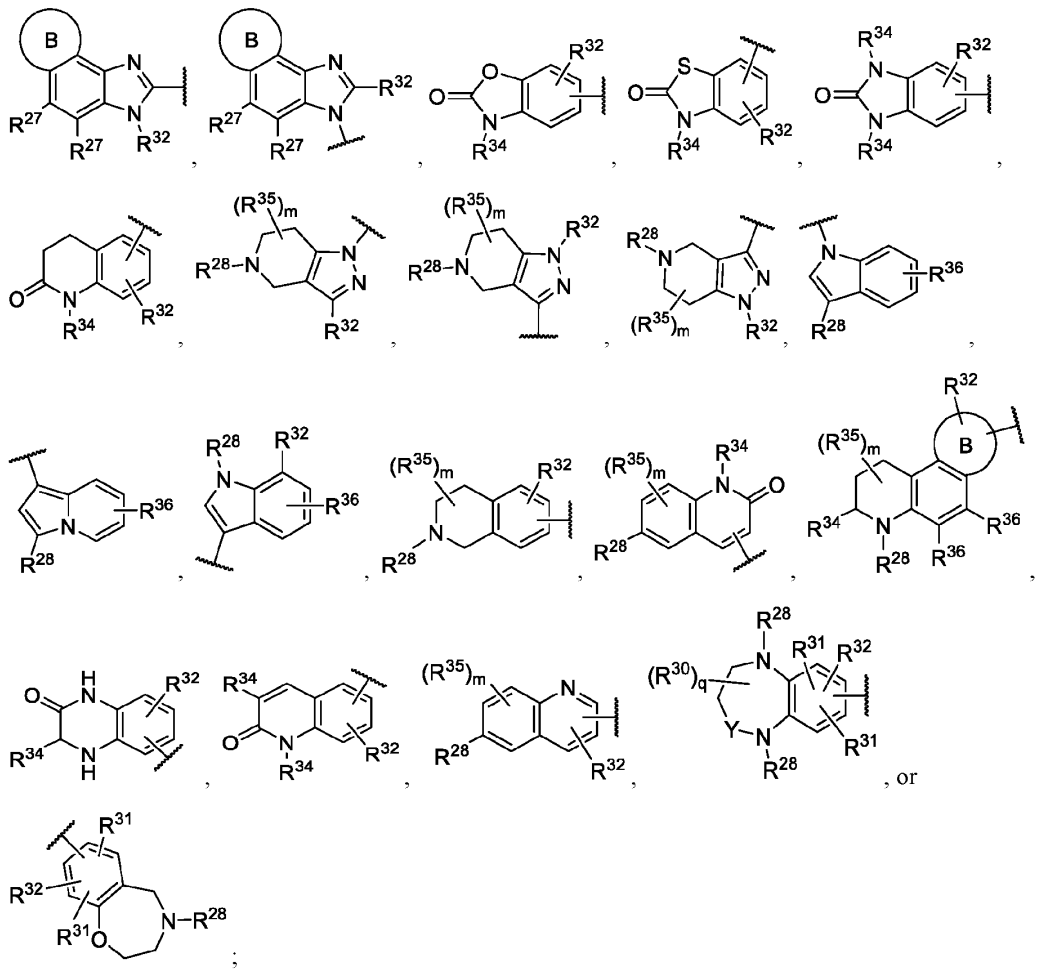
3) both 1) and 2).

[00104] In some embodiments, wherein the moiety comprising an acetyl-lysine mimetic comprises a moiety selected from pyrrolidonyl, phenyl, pyridinyl, pyridinonyl, triazolyl, pyrrolyl, isoxazolyl, pyrazolyl, quinolinyl, tetrahydroquinolinyl, isoquinolinyl, tetrahydroisoquinolinyl, quinazolonyl, quinazolinyl, dihydroquinazolinonyl, imidazo[4,5-c]quinolinyl fused to a dimethylisoxazolyl, triazolophthalazinyl, indolizinyl, benzoimidazolyl, isoxazole-indolizinyl, thienodiazepine-indolizinyl, benzodiazepine-indolizinyl, 5-isoxazolylbenzimidazolyl, 6-isoxazolylbenzimidazolyl, 7-isoxazolo-quinolinyl, diazobenzyl, triazolophthalazinyl, isoxazoloquinolinyl, 2-thiazolidinonyl, triazolopyrimidinyl, thienodiazepinyl, benzodiazepinyl, benzotriazepinyl, triazolobenzodiazepinyl, triazolothienodiazepinyl, triazolothienodiazepinyl, and isoxazole-azepinyl.

[00105] In some embodiments, the optional linker of c) is covalently attached to a) on: the acetyl-lysine mimetic moiety; or the moiety that occupies the lipophilic shelf (LPF) region of the bromodomain of CBP/p300, if present; or the moiety that occupies the BC Loop region of the bromodomain of CBP/p300, if present; wherein the optional linker of c) is covalently attached to a) at a position that does not interfere with the binding of the acetyl-lysine mimetic moiety in the acetylated lysine (KAc) binding site of CBP/p300.

[00106] In some embodiments, the moiety comprising an acetyl-lysine mimetic comprises a moiety selected from:





each R^{32} is independently an optional moiety that occupies the lipophilic shelf (LPF) region of the bromodomain of CBP/p300;

or each R^{32} is independently an optional moiety that occupies the BC Loop region of the bromodomain of CBP/p300;

 is the point of attachment to the optional linker that covalently connects a) to b);

or  is R^{32} and the optional linker that covalently connects a) to b) is attached to R^{32};

each R^{28} is independently hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, -C(=O)R^b, or -C(=O)N(R^b)$_2$;

each R^{34} is independently hydrogen or substituted or unsubstituted C_1-C_6alkyl;

each R^{35} is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, or substituted or unsubstituted 3- to 8-membered heterocycloalkyl, -CN, -OH, -OR^a, or -N(R^b)$_2$;

m is 0, 1, 2, 3, or 4;

each R^{27} is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -CN, -NO_2, -OH, -OR^a, $OC(=O)R^a$, -$OC(=O)N(R^b)_2$, -$OC(=O)OR^a$, -$OC(=O)N(R^b)_2$, -SR^b, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2OR^b$, -$S(=O)_2N(R^b)_2$, -$N(R^b)_2$, -$NR^bC(=O)N(R^b)_2$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^a$, -$NR^bS(=O)_2R^a$, -$C(=O)R^b$, -$C(=O)OR^b$, or -$C(=O)N(R^b)_2$;

Y is -$C(R^{30})_2$- or C(=O);each R^{30} is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, -CN, -NO_2, -OH, -OR^a, $OC(=O)R^a$, -$OC(=O)N(R^b)_2$, -$OC(=O)OR^a$, -SR^b, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2OR^b$, -$S(=O)_2N(R^b)_2$, -$N(R^b)_2$, -$NR^bC(=O)N(R^b)_2$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^a$, -$NR^bS(=O)_2R^a$, -$C(=O)R^b$, -$C(=O)OR^b$, or -$C(=O)N(R^b)_2$;

q is 0, 1, 2, 3, or 4;

each R^{31} is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, -CN, -NO_2, -OH, -OR^a, $OC(=O)R^a$, -$OC(=O)N(R^b)_2$, -$OC(=O)OR^a$, -SR^b, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2OR^b$, -$S(=O)_2N(R^b)_2$, -$N(R^b)_2$, -$NR^bC(=O)NR^b$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^a$, -$NR^bS(=O)_2R^a$, -$C(=O)R^b$, -$C(=O)OR^b$, or -$C(=O)N(R^b)_2$;

each R^{36} is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, -CN, -OH, -OR^a, or -$N(R^b)_2$;

Ring B is a fused substituted or unsubstituted 5 or 6 membered heterocycloalkyl;

each R^a is independently substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted monocyclic 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted monocyclic heteroaryl;

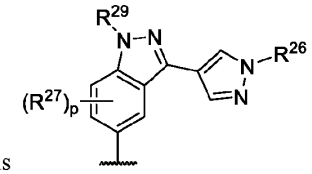
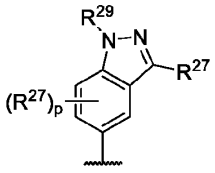
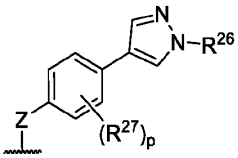
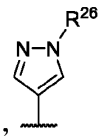
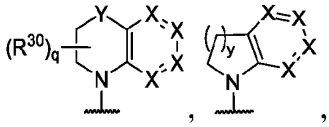
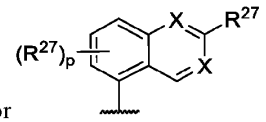
each R^b is independently hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted monocyclic 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted monocyclic heteroaryl;

or two R^b on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle.

[00107] In some embodiments, the moiety that occupies the lipophilic shelf (LPF) region of the bromodomain of CBP/p300 is R^{32}, wherein:

R^{32} is hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_2-C_6alkenyl, substituted or unsubstituted C_2-C_6alkynyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or

unsubstituted C_3-C_{12}cycloalkyl, substituted or unsubstituted 3- to 12-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

or R^{32} is  ,  ,  ,  ,  ,  ;

y is 1 or 2;

Z is -NR^c-, -O-, or -S-;

R^c is hydrogen or substituted or unsubstituted C_1-C_6alkyl;

R^{26} is hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, or substituted or unsubstituted 3- to 8-membered heterocycloalkyl;

each X is independently -CR^{27}- or -N-;

each R^{27} is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -CN, -NO_2, -OH, -OR^a, $OC(=O)R^a$, -$OC(=O)N(R^b)_2$, -$OC(=O)OR^a$, -$OC(=O)N(R^b)_2$, -SR^b, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2OR^b$, -$S(=O)_2N(R^b)_2$, -$N(R^b)_2$, -$NR^bC(=O)N(R^b)_2$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^a$, -$NR^bS(=O)_2R^a$, -$C(=O)R^b$, -$C(=O)OR^b$, or -$C(=O)N(R^b)_2$;

p is 0, 1, 2, or 3;

R^{28} is hydrogen or substituted or unsubstituted C_1-C_6alkyl;

R^{29} is hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, or substituted or unsubstituted 3- to 8-membered heterocycloalkyl;

Y is -$C(R^{30})_2$- or $N(R^{28})$-;

each R^{30} is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, -CN, -NO_2, -OH, -OR^a, $OC(=O)R^a$, -$OC(=O)N(R^b)_2$, -$OC(=O)OR^a$, -SR^b, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2OR^b$, -$S(=O)_2N(R^b)_2$, -$N(R^b)_2$, -$NR^bC(=O)N(R^b)_2$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^a$, -$NR^bS(=O)_2R^a$, -$C(=O)R^b$, -$C(=O)OR^b$, or -$C(=O)N(R^b)_2$;

q is 0, 1, 2, 3, or 4;

or R^{32} is -L-C;

L is substituted or unsubstituted C_1-C_6alkyl or substituted or unsubstituted C_1-C_6heteroalkyl;

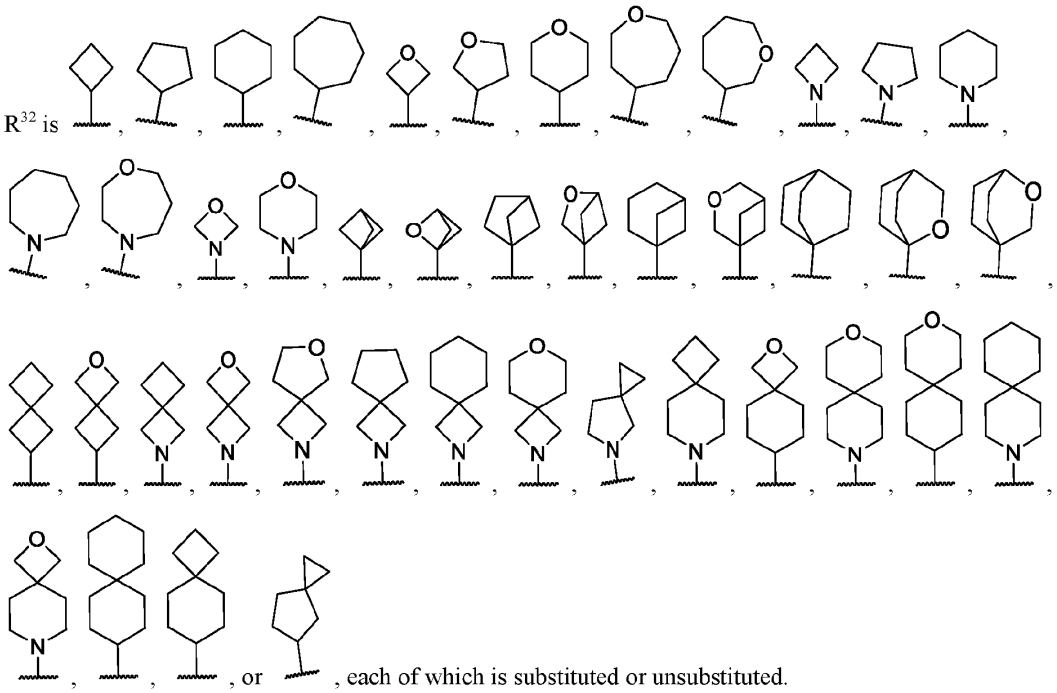
C is substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

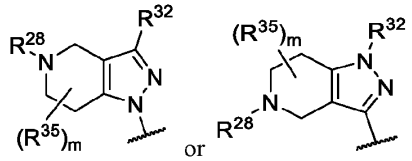
each R^a is independently substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted monocyclic 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted monocyclic heteroaryl;

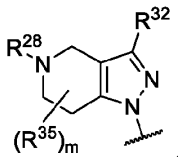
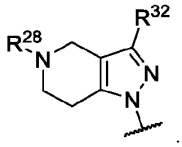
each R^b is independently hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted monocyclic 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted monocyclic heteroaryl;

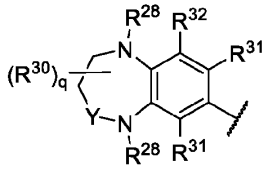
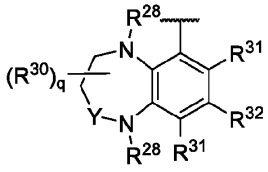
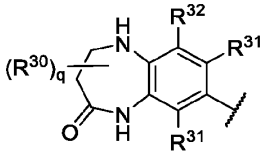
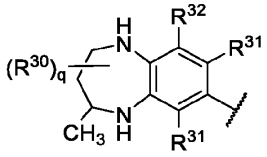
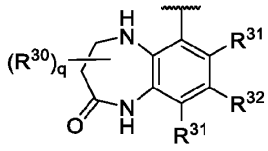
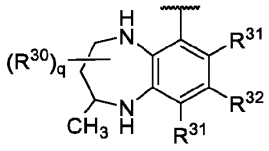
or two R^b on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle.

[00108] In some embodiments, the moiety that occupies the BC Loop region of the bromodomain of CBP/p300 is R^{32}, wherein:

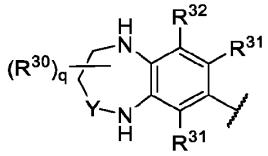
R^{32} is  , each of which is substituted or unsubstituted.

[00109] In some embodiments, the moiety comprising an acetyl-lysine mimetic comprises  or . In some embodiments, the moiety comprising an acetyl-lysine

mimetic comprises  . In some embodiments, the moiety comprising an acetyl-lysine mimetic comprises  .

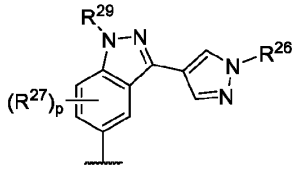
[00110] In some embodiments, the moiety comprising an acetyl-lysine mimetic comprises  or  . In some embodiments, the moiety comprising an acetyl-lysine mimetic comprises  ,  ,  , or  .

[00111] In some embodiments, the moiety comprising an acetyl-lysine mimetic comprises

 ;

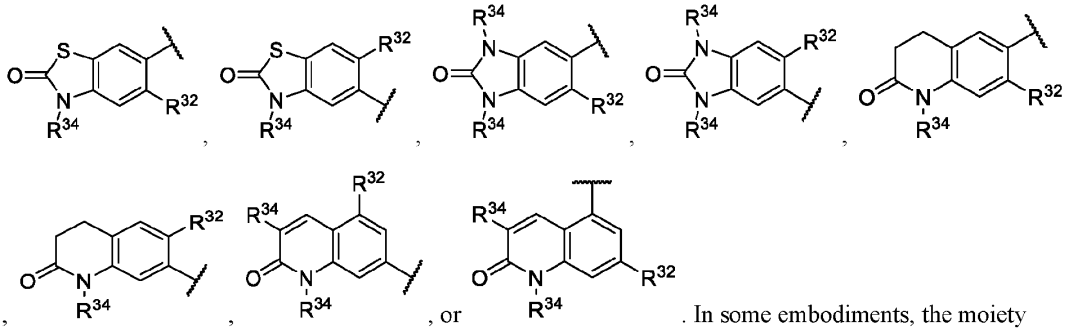
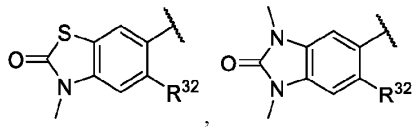
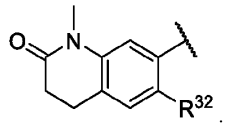
wherein:

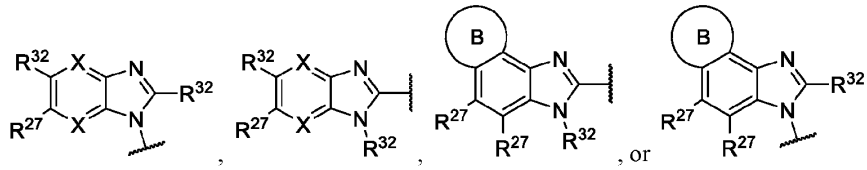
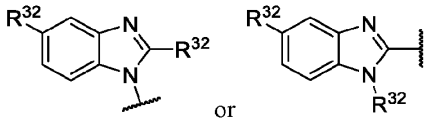
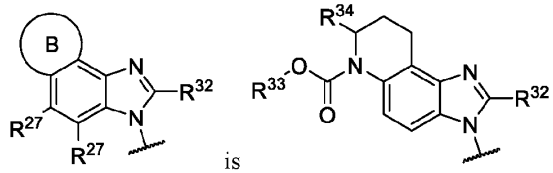
each R^{28} is independently hydrogen or substituted or unsubstituted C_1-C_6alkyl;

R^{32} is  ; and

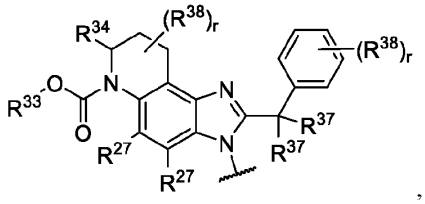
each R^{27} is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, -CN, -NO_2, -OH, -OR^a, $OC(=O)R^a$, -$OC(=O)N(R^b)_2$, -$OC(=O)OR^a$, -SR^b, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2OR^b$, -$S(=O)_2N(R^b)_2$, -

$N(R^b)_2$, $-NR^bC(=O)N(R^b)_2$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^a$, $-NR^bS(=O)_2R^a$, $-C(=O)R^b$, $-C(=O)OR^b$, or $-C(=O)N(R^b)_2$.

[00112] In some embodiments, the moiety comprising an acetyl-lysine mimetic comprises  . In some embodiments, the moiety comprising an acetyl-lysine mimetic comprises  , or  .

[00113] In some embodiments, the moiety comprising an acetyl-lysine mimetic comprises  . In some embodiments, the moiety comprising an acetyl-lysine mimetic comprises the moiety comprising an acetyl-lysine mimetic comprises  or . In some embodiments,  is .

[00114] In some embodiments, the moiety comprising an acetyl-lysine mimetic comprises



,

wherein:

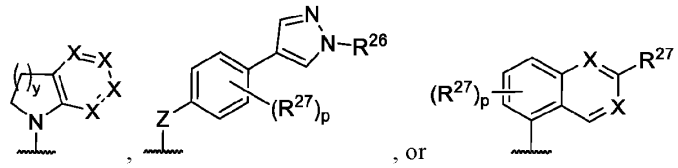
each R^{27} is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, -CN, -OH, -OR^a, or -$N(R^b)_2$;

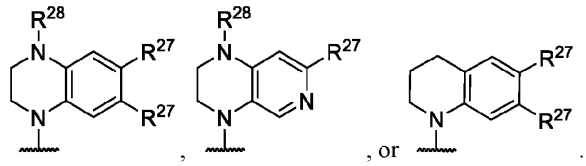
R^{33} is hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, or substituted or unsubstituted C_1-C_6heteroalkyl;

R^{34} is hydrogen or substituted or unsubstituted C_1-C_6alkyl;

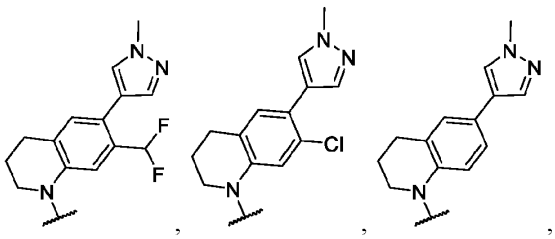
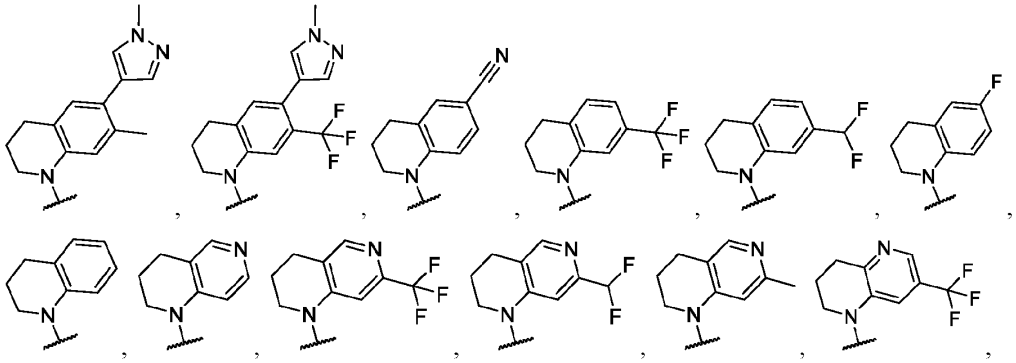
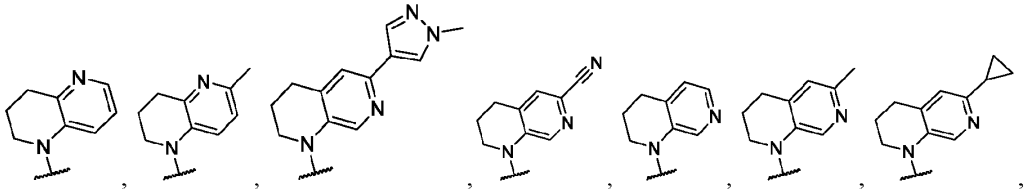
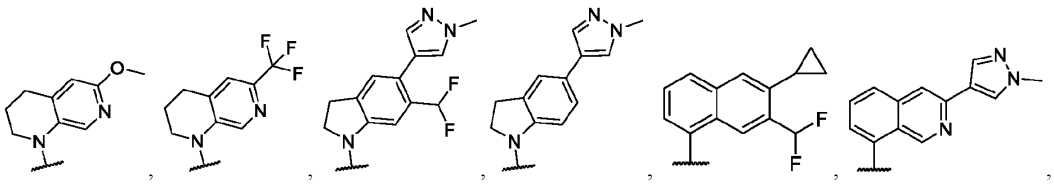
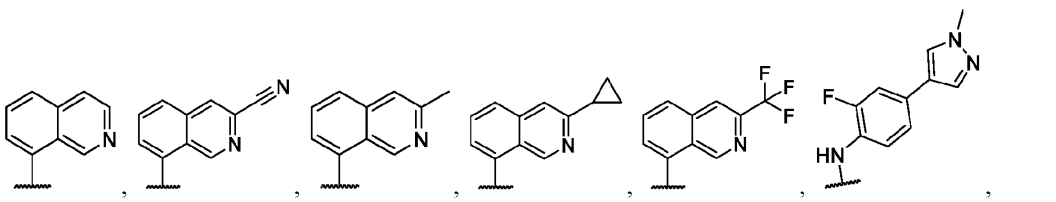
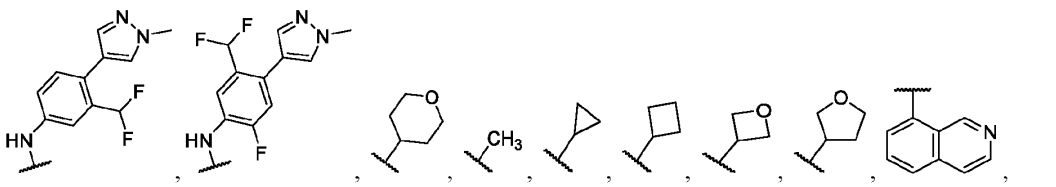
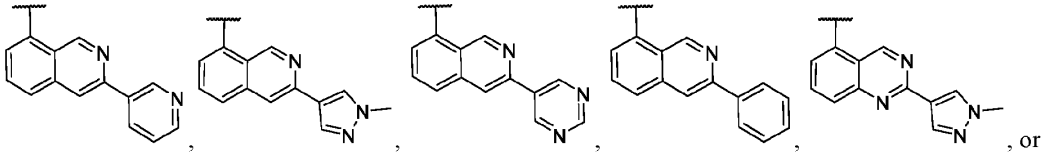
each R^{38} is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted 3- to 8-membered heterocycloalkyl, -CN, -NO_2, -OH, -OR^a, -$OC(=O)R^a$, -$OC(=O)N(R^b)_2$, -$OC(=O)OR^a$, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2OR^b$, -$S(=O)_2N(R^b)_2$, -$N(R^b)_2$, -$NR^bC(=O)N(R^b)_2$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^a$, -$NR^bS(=O)_2R^a$, -$C(=O)R^b$, -$C(=O)OR^b$, or -$C(=O)N(R^b)_2$;

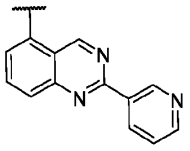
r is 0, 1, 2, 3, or 4;

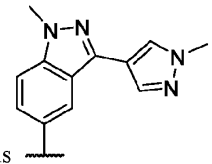
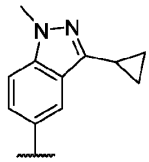
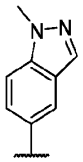
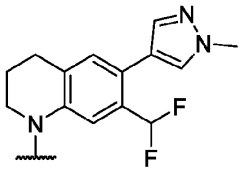
[00115] In some embodiments, R^{32} is  ; each R^{27} is independently hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -CN, -OH, or -OR^a; and each R^a is independently substituted or unsubstituted C_1-C_6alkyl.

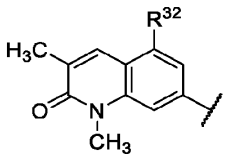
[00116] In some embodiments, R^{32} is  .

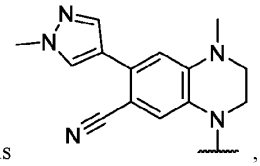
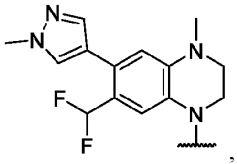
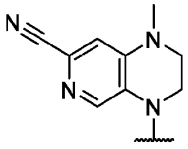
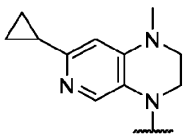
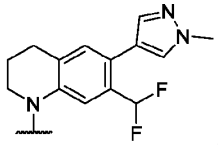
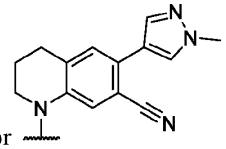
[00117] In some embodiments, each R^{27} is independently hydrogen, -CH_3, -CH_2CH_3, -F, -CHF_2, -CF_3, -CN, -OH, -OCH_3, cyclopropyl, cyclobutyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, phenyl, pyrazolyl, 1-methyl pyrazolyl, pyridinyl, or pyrimidinyl.

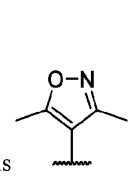
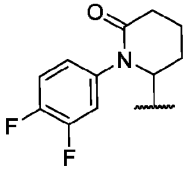
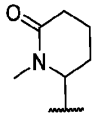
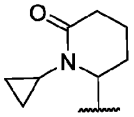
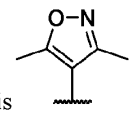
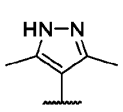
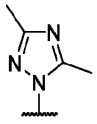
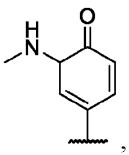
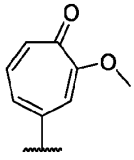
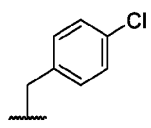
[00118] In some embodiments, R^{32} is  ,  ,  ,  ,  ,  ,  , or

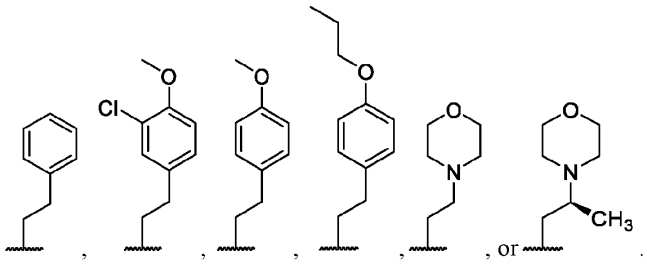

.

[00119] In some embodiments, R^{32} is  ,  ,  , or  .

[00120] In some embodiments, R^{32} is  .

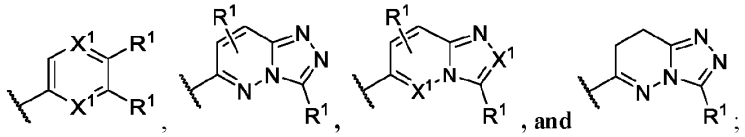
[00121] In some embodiments, R^{32} is  ,  ,  ,  ,  , or  .

[00122] In some embodiments, R^{32} is  ,  ,  , or  . In some embodiments, R^{32} is  ,  ,  ,  ,  ,  ,



[00123] In some embodiments, B-AR is a non-steroidal AR ligand or a steroidal AR ligand.

[00124] In some embodiments, B-AR comprises a head group and an optional core, wherein the head group is selected from:



each X^1 is independently $-CR^1-$ or -N-;

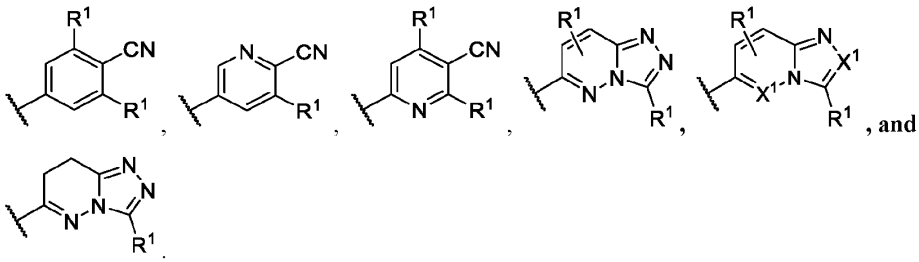
each R^1 is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted 3- to 8-membered heterocycloalkyl, -CN, -NO_2, -OH, $-OR^4$, $OC(=O)R^4$, $-OC(=O)N(R^5)_2$, $-OC(=O)OR^5$, $-OC(=O)NR^5$, -SH, $-SR^4$, $-S(=O)R^4$, $-S(=O)_2R^5$, $-S(=O)_2OR^4$, $-S(=O)_2N(R^5)_2$, $-N(R^5)_2$, $-NR^5C(=O)NR^5$, $-NR^5C(=O)R^4$, $-NR^5C(=O)OR^5$, $-NR^5S(=O)_2R^5$, $-C(=O)R^5$, $-C(=O)OR^5$, or $-C(=O)N(R^5)_2$.

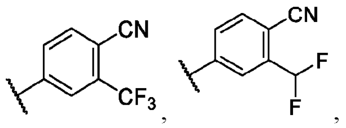
each R^4 is independently substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted monocyclic 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted monocyclic heteroaryl;

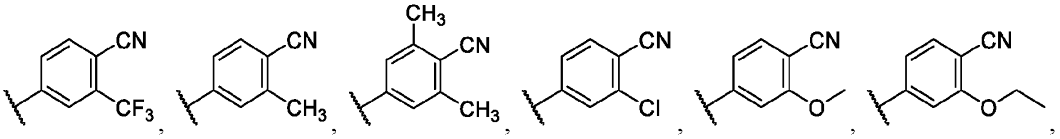
each R^5 is independently hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted monocyclic 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted monocyclic heteroaryl;

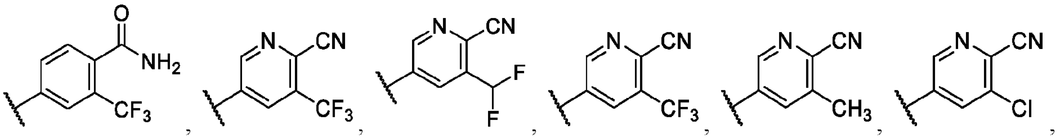
or two R^5 on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle.

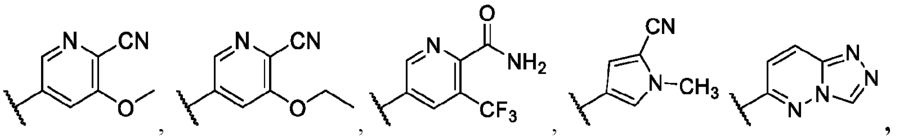
[00125] In some embodiments, the head group is selected from:

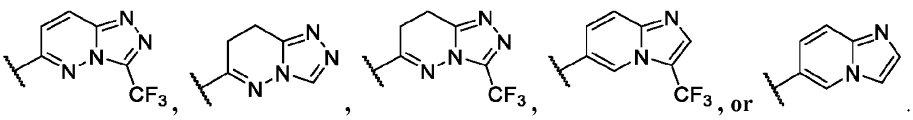


[00126] In some embodiments, the head group is selected from: 

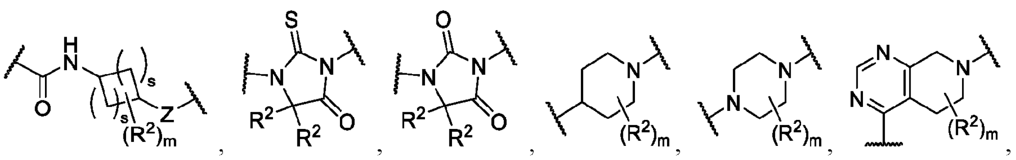


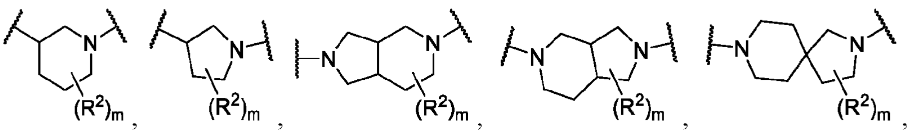


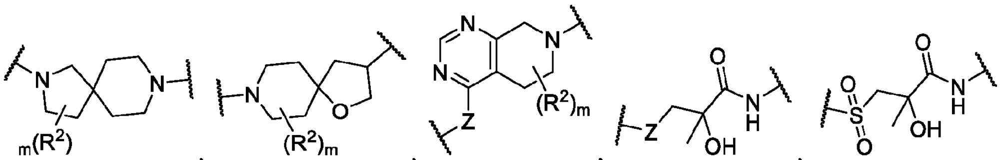




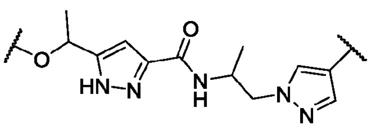
[00127] In some embodiments, the optional core comprises a group selected from:







, and



;

Z is -O- or -NR^5-;

each R^2 is independently hydrogen, halogen, substituted or unsubstituted C$_1$-C$_6$alkyl, substituted or unsubstituted C$_1$-C$_6$fluoroalkyl, substituted or unsubstituted C$_1$-C$_6$heteroalkyl, -CN, -NO$_2$, -OH, -OR^4, OC(=O)R^4, -S(=O)R^4, -S(=O)$_2$R^5, -S(=O)$_2$N(R^5)$_2$, -N(R^5)$_2$, -NR^{5}C(=O)NR^5, -NR^{5}C(=O)R^4, -C(=O)R^5, -

$C(=O)OR^5$, or $-C(=O)N(R^5)_2$; or

two R^2 on the same carbon atom are taken together with the carbon atom to which they are attached to form a substituted or unsubstituted C_3-C_8cycloalkyl or a substituted or unsubstituted monocyclic 3- to 8-membered heterocycloalkyl;

m is 0, 1, 2, 3, or 4;

each s is independently 1, 2, or 3;

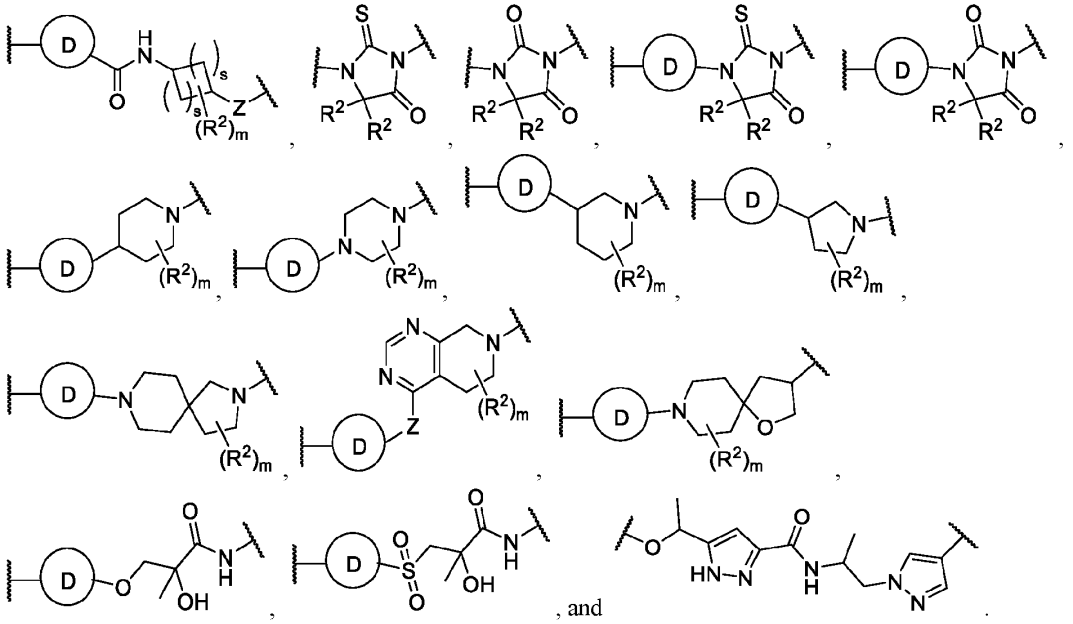
each R^4 is independently substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted monocyclic 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted monocyclic heteroaryl;

each R^5 is independently hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted monocyclic 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted monocyclic heteroaryl;

or two R^5 on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle.

[00128] In some embodiments, the optional core further comprises a ring D that is a 5-, 6-, 8-, 9- or 10-membered aryl or a 5-, 6-, 8-, 9- or 10-membered heteroaryl that is optionally substituted with s R^3; each R^3 is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, -CN, -OH, $-OR^4$, or $-N(R^5)_2$.

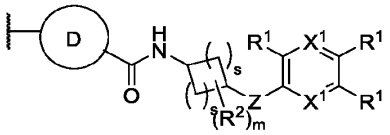
[00129] In some embodiments, the optional core comprises a group selected from:



, and .

[00130] In some embodiments, B-AR has the structure of Formula (IIIa), or a pharmaceutically acceptable

salt or solvate thereof:



Formula (IIIa)

wherein:

each X is independently -CR^3- or -N-;

each X^1 is independently -CR^1- or -N-;

Z is -O- or -NR^5-;

each R^1 is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted 3- to 8-membered heterocycloalkyl, -CN, -NO_2, -OH, -OR^4, $OC(=O)R^4$, -$OC(=O)N(R^5)_2$, -$OC(=O)OR^5$, -$OC(=O)NR^5$, -SH, -SR^4, -$S(=O)R^4$, -$S(=O)_2R^5$, -$S(=O)_2OR^4$, -$S(=O)_2N(R^5)_2$, -$N(R^5)_2$, -$NR^5C(=O)NR^5$, -$NR^5C(=O)R^4$, -$NR^5C(=O)OR^5$, -$NR^5S(=O)_2R^5$, -$C(=O)R^5$, -$C(=O)OR^5$, or -$C(=O)N(R^5)_2$;

each R^2 is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, -CN, -NO_2, -OH, -OR^4, $OC(=O)R^4$, -$S(=O)R^4$, -$S(=O)_2R^5$, -$S(=O)_2N(R^5)_2$, -$N(R^5)_2$, -$NR^5C(=O)NR^5$, -$NR^5C(=O)R^4$, -$C(=O)R^5$, -$C(=O)OR^5$, or -$C(=O)N(R^5)_2$;

ring D that is a 5-, 6-, 8-, 9- or 10-membered aryl or a 5-, 6-, 8-, 9- or 10-membered heteroaryl that is optionally substituted with s R^3;

R^3 is hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, -CN, -OH, -OR^4, or -$N(R^5)_2$;

n is 0, 1, 2, 3, 4, or 5;

m is 0, 1, 2, 3, or 4;

each s is independently 1, 2, or 3;

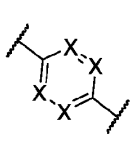
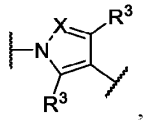
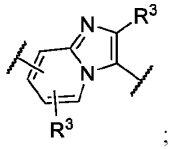
each R^4 is independently substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted monocyclic 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted monocyclic heteroaryl;

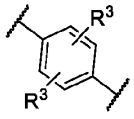
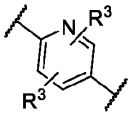
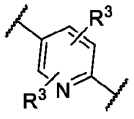
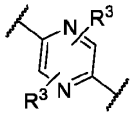
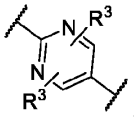
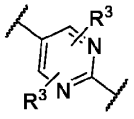
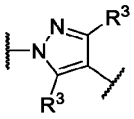
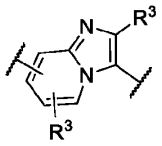
each R^5 is independently hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted monocyclic 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted monocyclic heteroaryl;

or two R^5 on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle.

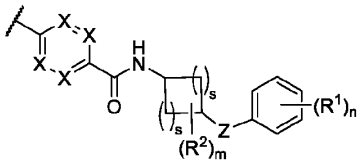
[00131] In some embodiments, ring D is phenyl, naphthyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl,

triazinyl, pyrrolyl, thiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, imidazolyl, pyrazolyl, isothiazolyl, triazolyl, and tetrazolyl, wherein each ring D is optionally susbstitued substituted with s R^3.

[00132] In some embodiments, ring D is  ,  , or  ; each X is independently -CR^3- or -N-.

[00133] In some embodiments, ring D is  ,  ,  ,  ,  ,  ,  , or  .

[00134] In some embodiments, B-AR has the structure of Formula (IIIa), or a pharmaceutically acceptable salt or solvate thereof:



Formula (IIIa)

wherein:

each X is independently -CR^3- or -N-;

Z is -O- or -NR^5-;

each R^1 is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted 3- to 8-membered heterocycloalkyl, -CN, -NO_2, -OH, -OR^4, OC(=O)R^4, -OC(=O)N(R^5)$_2$, -OC(=O)OR^5, -OC(=O)NR^5, -SH, -SR^4, -S(=O)R^4, -S(=O)$_2$$R^5$, -S(=O)$_2OR^4$, -S(=O)$_2$N($R^5$)$_2$, -N($R^5$)$_2$, -N$R^5$C(=O)N$R^5$, -N$R^5$C(=O)$R^4$, -N$R^5$C(=O)O$R^5$, -N$R^5$S(=O)$_2$$R^5$, -C(=O)$R^5$, -C(=O)O$R^5$, or -C(=O)N($R^5$)$_2$;

each R^2 is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, -CN, -NO_2, -OH, -OR^4, OC(=O)R^4, -S(=O)R^4, -S(=O)$_2$$R^5$, -S(=O)$_2$N($R^5$)$_2$, -N($R^5$)$_2$, -N$R^5$C(=O)N$R^5$, -N$R^5$C(=O)$R^4$, -C(=O)$R^5$, -C(=O)O$R^5$, or -C(=O)N($R^5$)$_2$;

R^3 is hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, -CN, -OH, -OR^4, or -N(R^5)$_2$;

n is 0, 1, 2, 3, 4, or 5;

m is 0, 1, 2, 3, or 4;

each s is independently 1, 2, or 3;

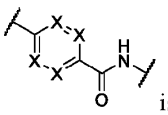
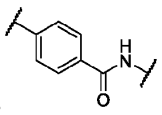
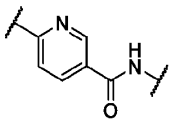
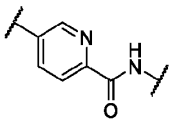
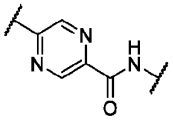
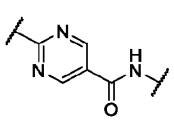
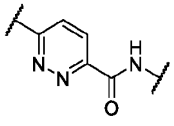
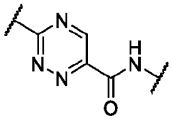
each R^4 is independently substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted monocyclic 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted monocyclic heteroaryl;

each R^5 is independently hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted monocyclic 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted monocyclic heteroaryl;

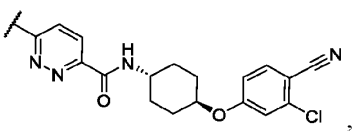
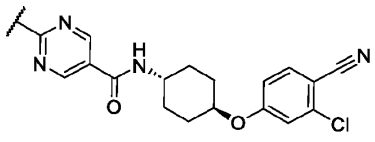
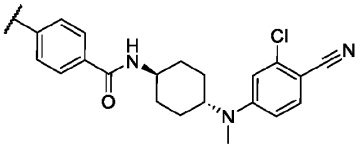
or two R^5 on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle.

[00135] In some embodiments, m is 4 and each R^2 is substituted or unsubstituted C_1-C_6alkyl. In some embodiments, m is 4 and each R^2 is -CH_3. In some embodiments, two R^2 on the same carbon atom are taken together with the carbon atom to which they are attached to form a substituted or unsubstituted cyclobutyl, substituted or unsubstituted cyclopentyl, substituted or unsubstituted cyclohexyl, substituted or unsubstituted oxetanyl, substituted or unsubstituted tetrahydrofuranyl, substituted or unsubstituted tetrahydropyranyl, substituted or unsubstituted azetidine, substituted or unsubstituted pyrrolidinyl, or a substituted or unsubstituted piperidinyl. In some embodiments, two R^2 on the same carbon atom are taken together with the carbon atom to which they are attached to form a substituted or unsubstituted cyclobutyl.

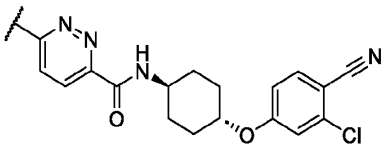
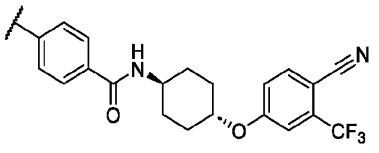
[00136] In some embodiments, n is 2 and one R^1 is halogen and the other R^1 is -CN. In some embodiments, n is 2 and one R^1 is -Cl and the other R^1 is -CN.

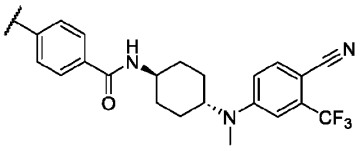
[00137] In some embodiments,  is  ,  ,  ,  ,  ,  , or  .

[00138] In some embodiments, B-AR has one of the following structures:

 ,  , or  , or a pharmaceutically acceptable salt or solvate thereof.

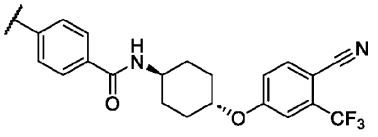
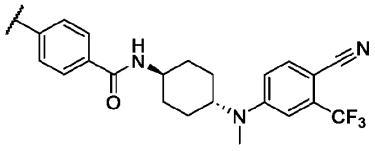
[00139] In some embodiments, B-Ar has one of the following structures:



, or

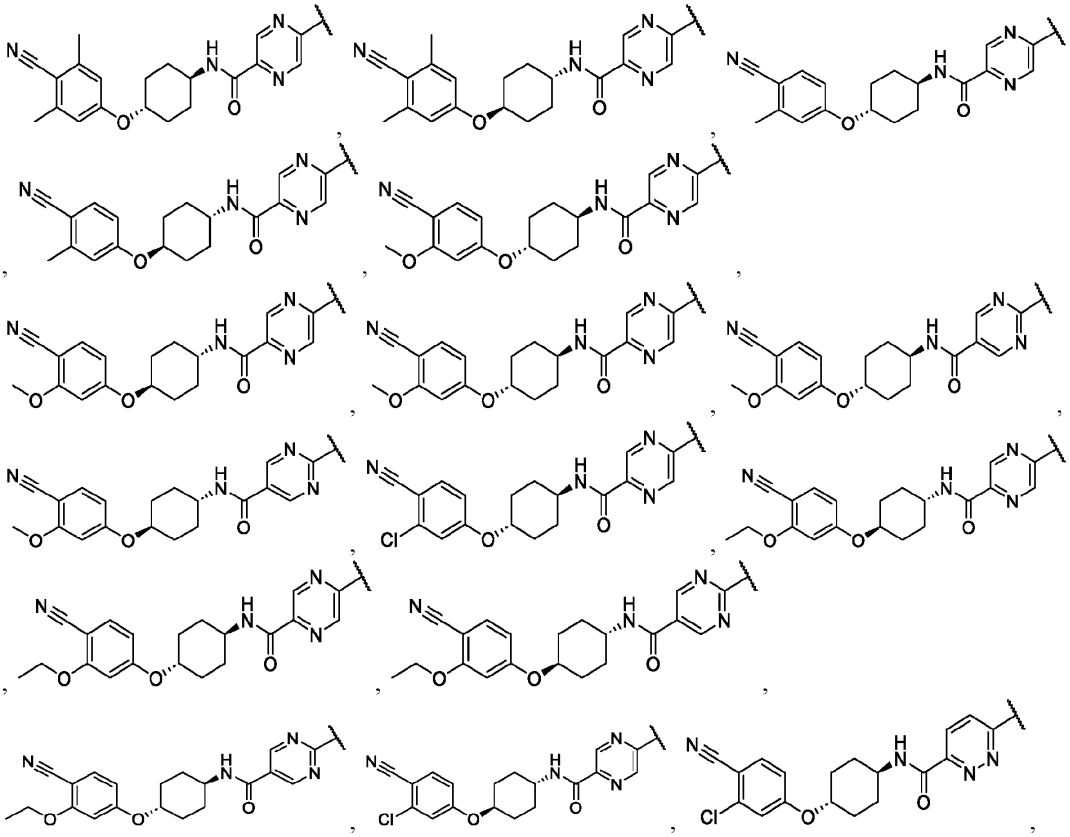

, or a pharmaceutically acceptable salt or solvate thereof.

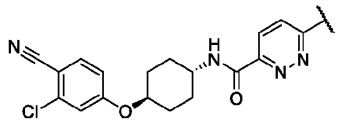
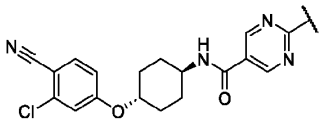
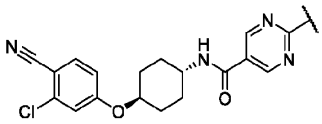
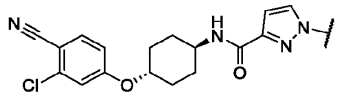
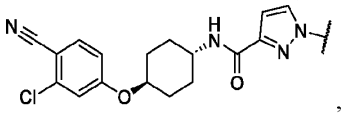
[00140] In some embodiments, the BDP is an AR antagonist.

[00141] In some embodiments, the BDP has one of the following structures:


or


[00142] In some embodiments, the BDP has one of the following structures:




,

,

,

, or

,
or a pharmaceutically acceptable salt or solvate thereof.

[00143] In some embodiments, the linker is absent.

[00144] In some embodiments, the linker has a prescribed length thereby linking the SBDDP and the BDP while allowing an appropriate distance therebetween.

[00145] In some embodiments, the linker is flexible. In some embodiments, the linker is rigid.

[00146] In some embodiments, the linker comprises a linear structure. In some embodiments, the linker comprises a non-linear structure. In some embodiments, the linker comprises a branched structure. In some embodiments, the linker comprises a cyclic structure.

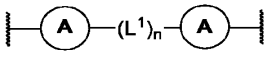
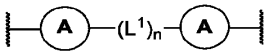
[00147] In some embodiments, the use of trivalent linkers allow for the preparation of heterotrifunctional compounds comprising one silent binder to a DDP and two binders to a disease protein, or two silent binders to a DDP and one binder to a disease protein, thereby simultaneously binding a disease protein and a DDP and forming a productive ternary complex. In some embodiments, such heterotrifunctional compounds would result in more sustained and more potent anticancer activity.

[00148] In some embodiments, the linker comprises one or more linear structures, one or more non-linear structures, one or more branched structures, one or more cyclic structures, one or more flexible moieties, one or more rigid moieties, or combinations thereof.

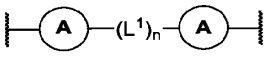
[00149] In some embodiments, the linker comprises one or more amino acid residues. In some embodiments, the linker comprises 1 to 3, 1 to 5, 1 to 10, 5 to 10, or 5 to 20 amino acid residues. In some embodiments, one or more amino acids of the linker are unnatural amino acids. In some embodiments, the linker comprises a peptide linkage. The peptide linkage comprises L-amino acids and/or D-amino acids.

[00150] In some embodiments, the linker has 1 to 100 atoms, 1 to 50 atoms, 1 to 30 atoms, 1 to 20 atoms, 1 to 15 atoms, 1 to 10 atoms, or 1 to 5 atoms in length. In some embodiments, the linker has 1 to 10 atoms in length. In some embodiments, the linker has 1 to 20 atoms in length.

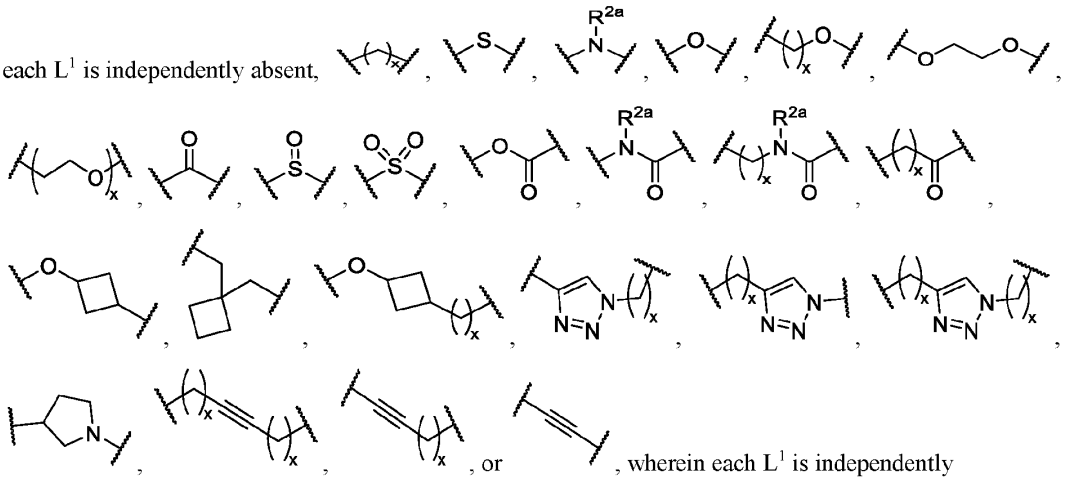
[00151] In some embodiments, the linker comprises flexible and/or rigid regions.

[00152] In some embodiments, the linker is L, wherein L is absent or  . In some embodiments, L is absent. In some embodiments, L is  .

[00153] In some embodiments, L comprises substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted 3- to 10-membered heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or combinations thereof.

[00154] In some embodiments, L is absent or  , wherein:

each A is independently absent, substituted or unsubstituted monocyclic C_3-C_{10}cycloalkyl, substituted or unsubstituted bridged bicyclic C_3-C_{10}cycloalkyl, substituted or unsubstituted fused bicyclic C_3-C_{10}cycloalkyl, substituted or unsubstituted spiro bicyclic C_3-C_{10}cycloalkyl, substituted or unsubstituted monocyclic 3- to 10-membered heterocycloalkyl, substituted or unsubstituted bridged bicyclic 3- to 10-membered heterocycloalkyl, substituted or unsubstituted fused bicyclic 3- to 10-membered heterocycloalkyl, substituted or unsubstituted spiro bicyclic 3- to 10-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, wherein each A is independently unsubstituted or substituted with x R^{2b};

each L^1 is independently absent,  , wherein each L^1 is independently unsubstituted or substituted with x R^{2b};

n is 1, 2, 3, 4, 5, or 6;

each x is independently 1, 2, 3, 4, 5, 6, 7, or 8;

each R^{2a} is independently hydrogen or substituted or unsubstituted C_1-C_6alkyl; and

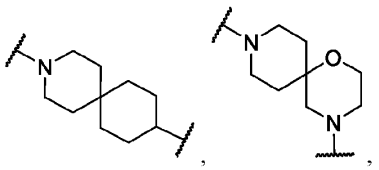
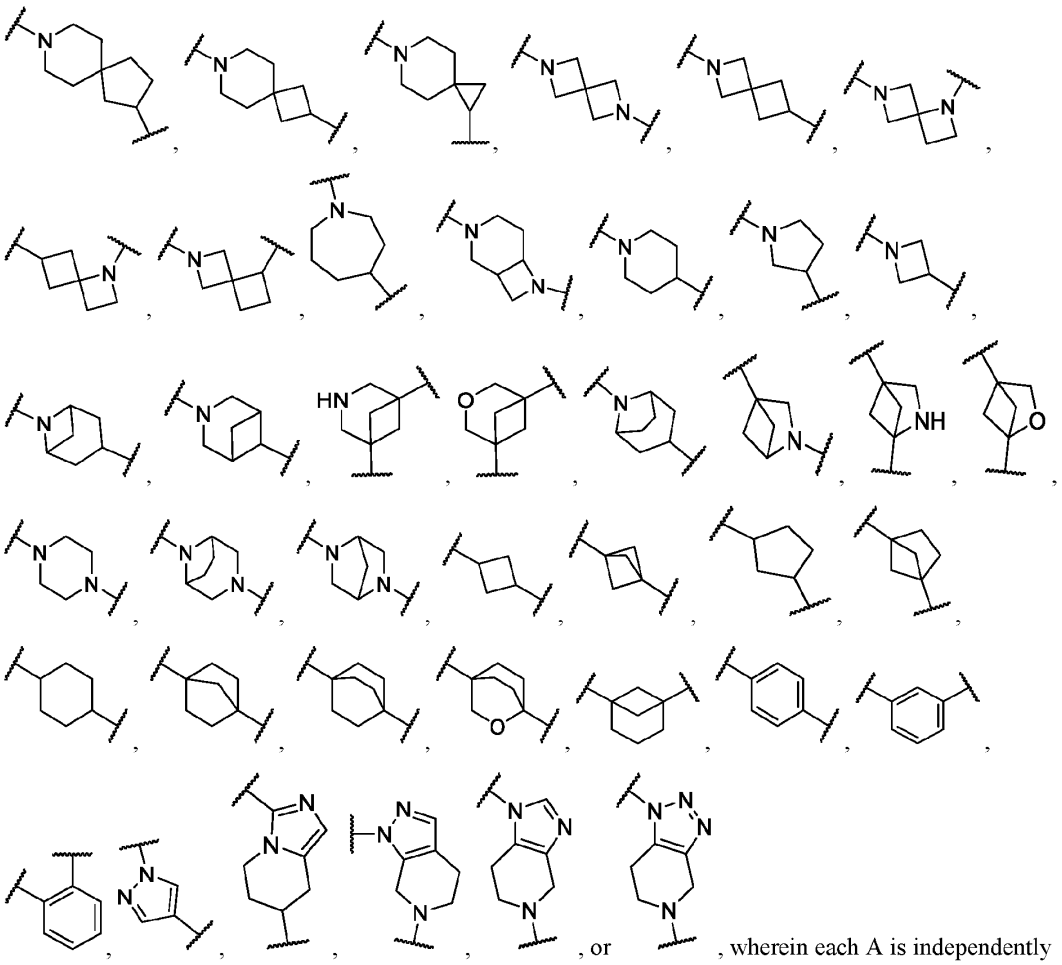
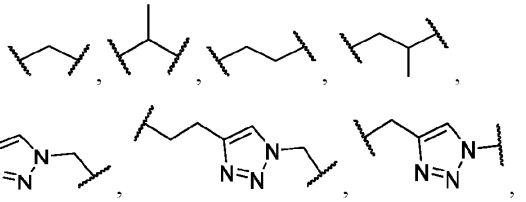
each R^{2b} is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -CN, -NO_2, -OH, -OR^a, -$OC(=O)R^a$, -$OC(=O)N(R^b)_2$, -$OC(=O)OR^a$, -SR^b, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2OR^b$, -$S(=O)_2N(R^b)_2$, -$N(R^b)_2$, -$NR^bC(=O)N(R^b)_2$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^a$, -$NR^bS(=O)_2R^a$, -$C(=O)R^b$, -$C(=O)OR^b$, or -$C(=O)N(R^b)$;

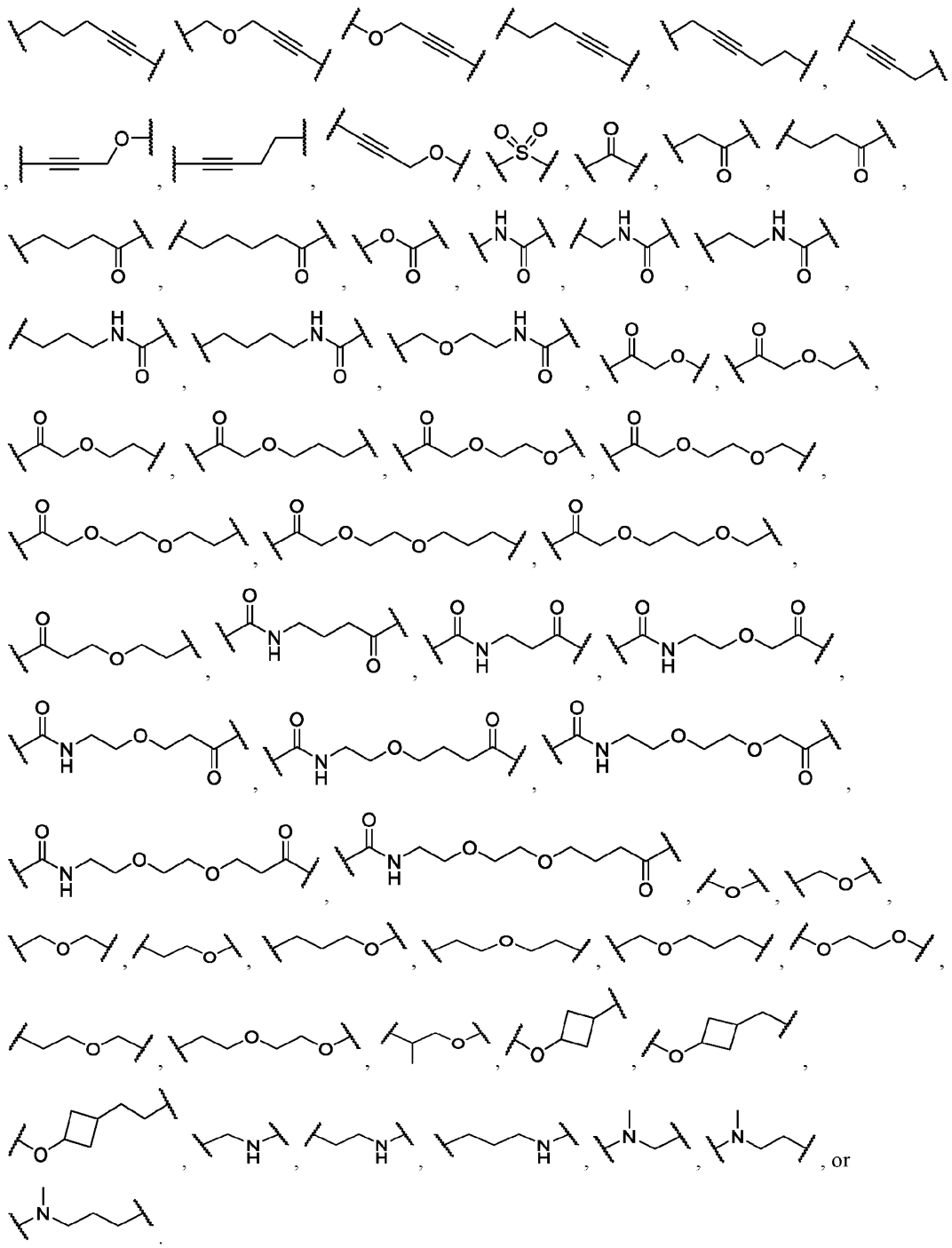
each R^a is independently substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted monocyclic 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted monocyclic heteroaryl;

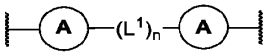
each R^b is independently hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-

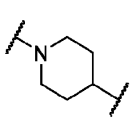
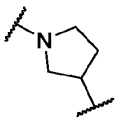
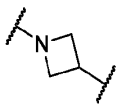
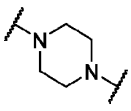
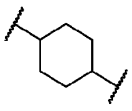
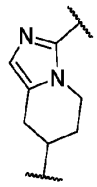
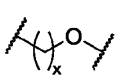
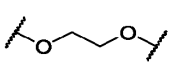
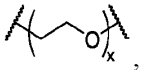
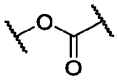
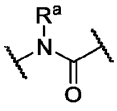
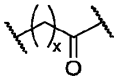
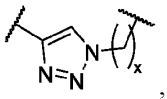
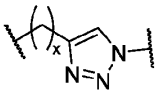
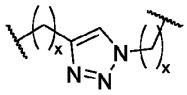
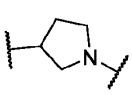
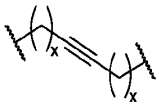
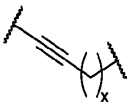
C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted monocyclic 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted monocyclic heteroaryl;

or two R^b on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle.

[00155] In some embodiments, each A is independently absent,  ,  , , , , , or , wherein each A is independently unsubstituted or substituted with x R^{2b}; $(L^1)_n$ is absent,  .



[00156] In some embodiments, L is absent or  , wherein:

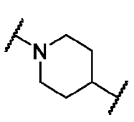
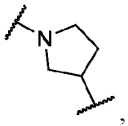
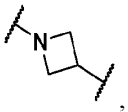
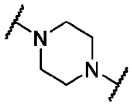
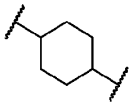
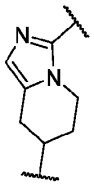
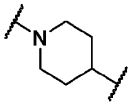
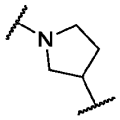
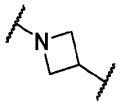
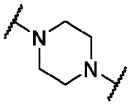
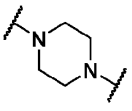
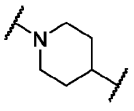
each A is independently absent,  ,  ,  ,  ,  , or  ; each L^1 is independently absent,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , or ;

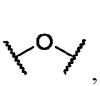
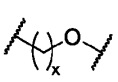
n is 1, 2, or 3;

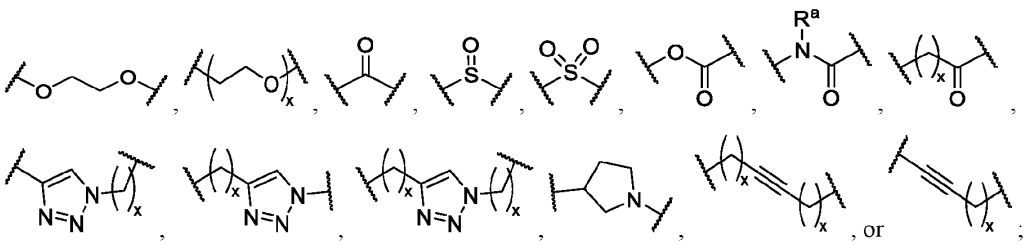
each x is independently 1, 2, 3, 4, 5, or 6;

each R^a is independently hydrogen or substituted or unsubstituted C_1-C_6alkyl; and

each R^b is independently hydrogen, halogen, or substituted or unsubstituted C_1-C_6alkyl.

[00157] In some embodiments, each A is independently absent, absent,  ,  ,  ,  ,  , or  . In some embodiments, each A is independently  ,  ,  , or  . In some embodiments, each A is independently absent,  , or  .

[00158] In some embodiments, each absent,  ,  ,  ,  ,  ,



n is 1, 2, or 3;

each x is independently 1, 2, 3, 4, 5, or 6;

each R^a is independently hydrogen or substituted or unsubstituted C_1-C_6alkyl; and

each R^b is independently hydrogen, halogen, or substituted or unsubstituted C_1-C_6alkyl.

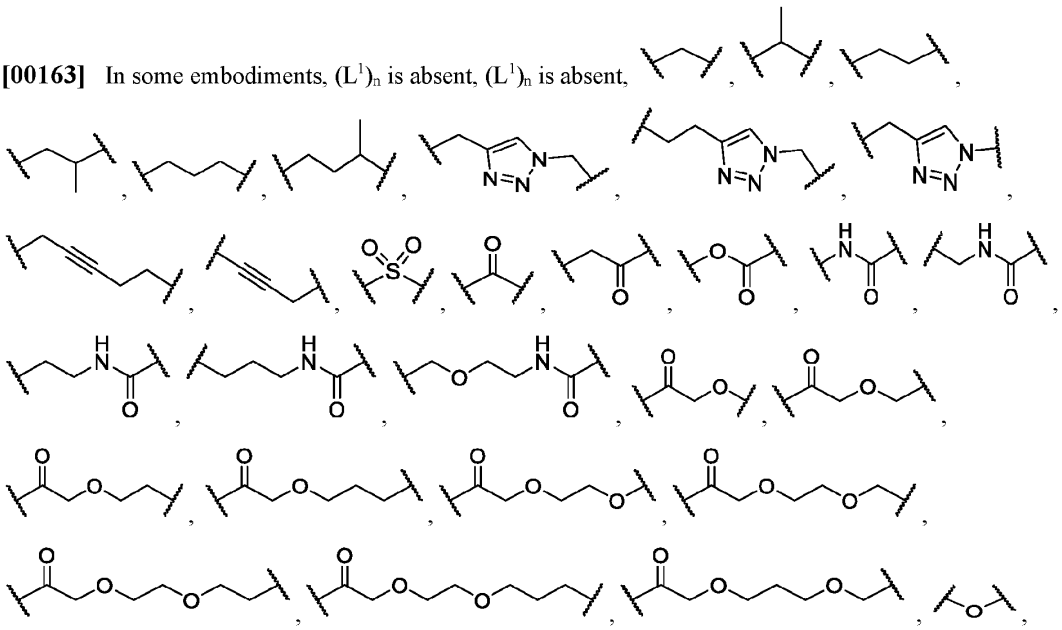
[00159] In some embodiments, n is 1. In some embodiments, n is 2. In some embodiments, n is 3.

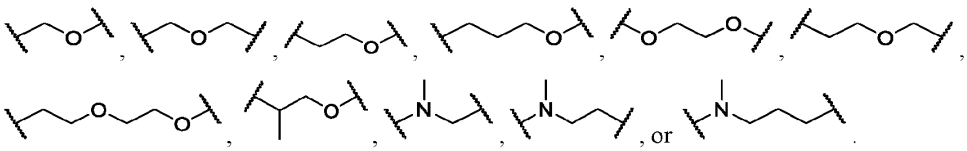
[00160] In some embodiments, x is 1. In some embodiments, x is 2. In some embodiments, x is 3. In some embodiments, x is 4. In some embodiments, x is 5. In some embodiments, x is 6.

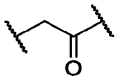
[00161] In some embodiments, R^a is hydrogen. In some embodiments, each R^a is independently substituted or unsubstituted C_1-C_6alkyl. In some embodiments, each R^a is independently hydrogen, methyl, ethyl, propyl, iso-propyl, n-butyl, iso-butyl, or tert-butyl. In some embodiments, each R^a is independently hydrogen or methyl. In some embodiments, R^a is methyl.

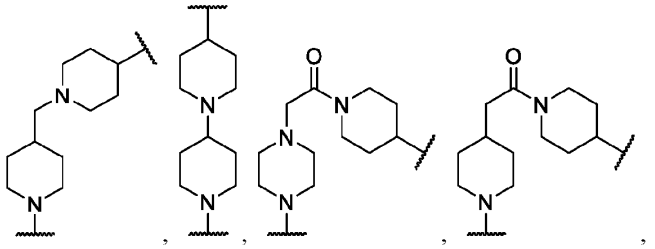
[00162] In some embodiments, R^b is hydrogen. In some embodiments, each R^b is independently substituted or unsubstituted C_1-C_6alkyl. In some embodiments, each R^b is independently hydrogen, methyl, ethyl, propyl, iso-propyl, n-butyl, iso-butyl, or tert-butyl. In some embodiments, each R^b is independently hydrogen or methyl. In some embodiments, R^b is methyl.

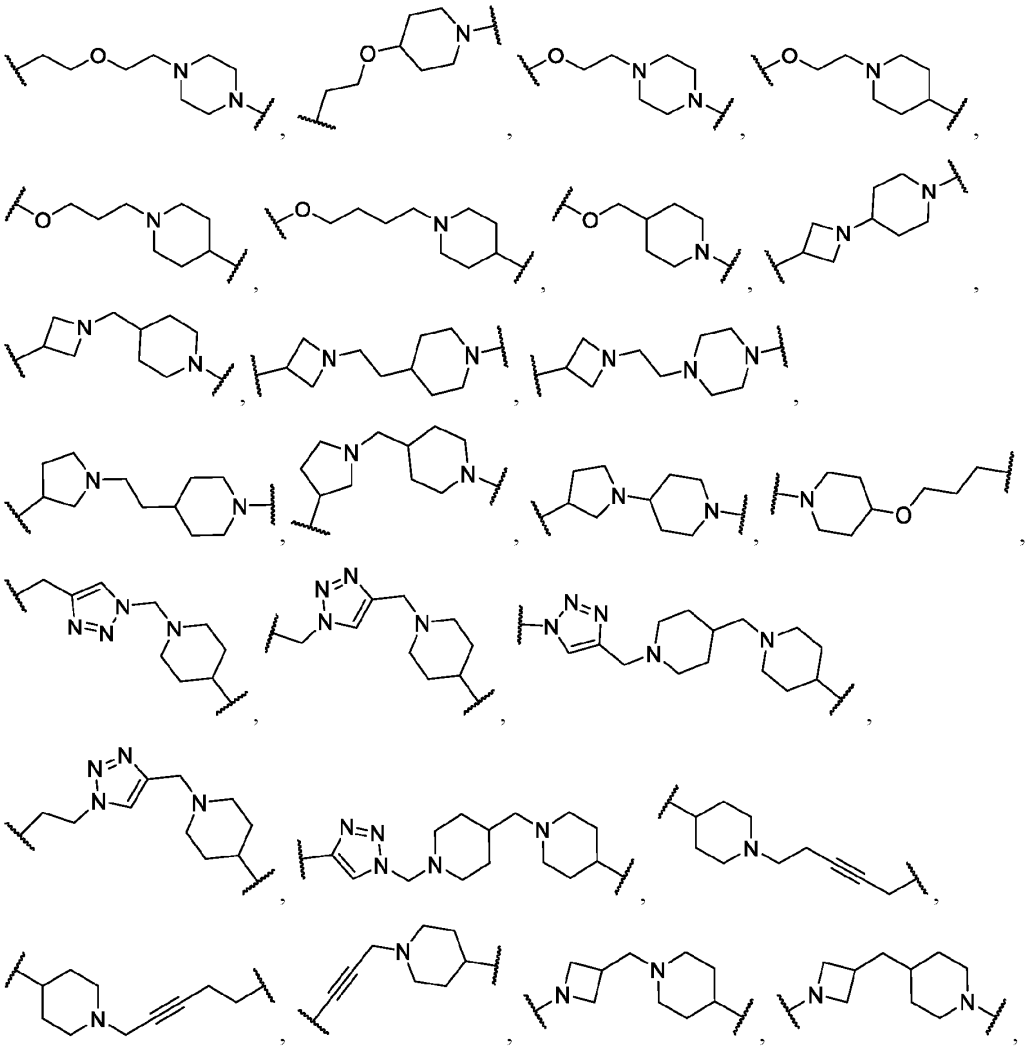
[00163] In some embodiments, $(L^1)_n$ is absent, $(L^1)_n$ is absent,

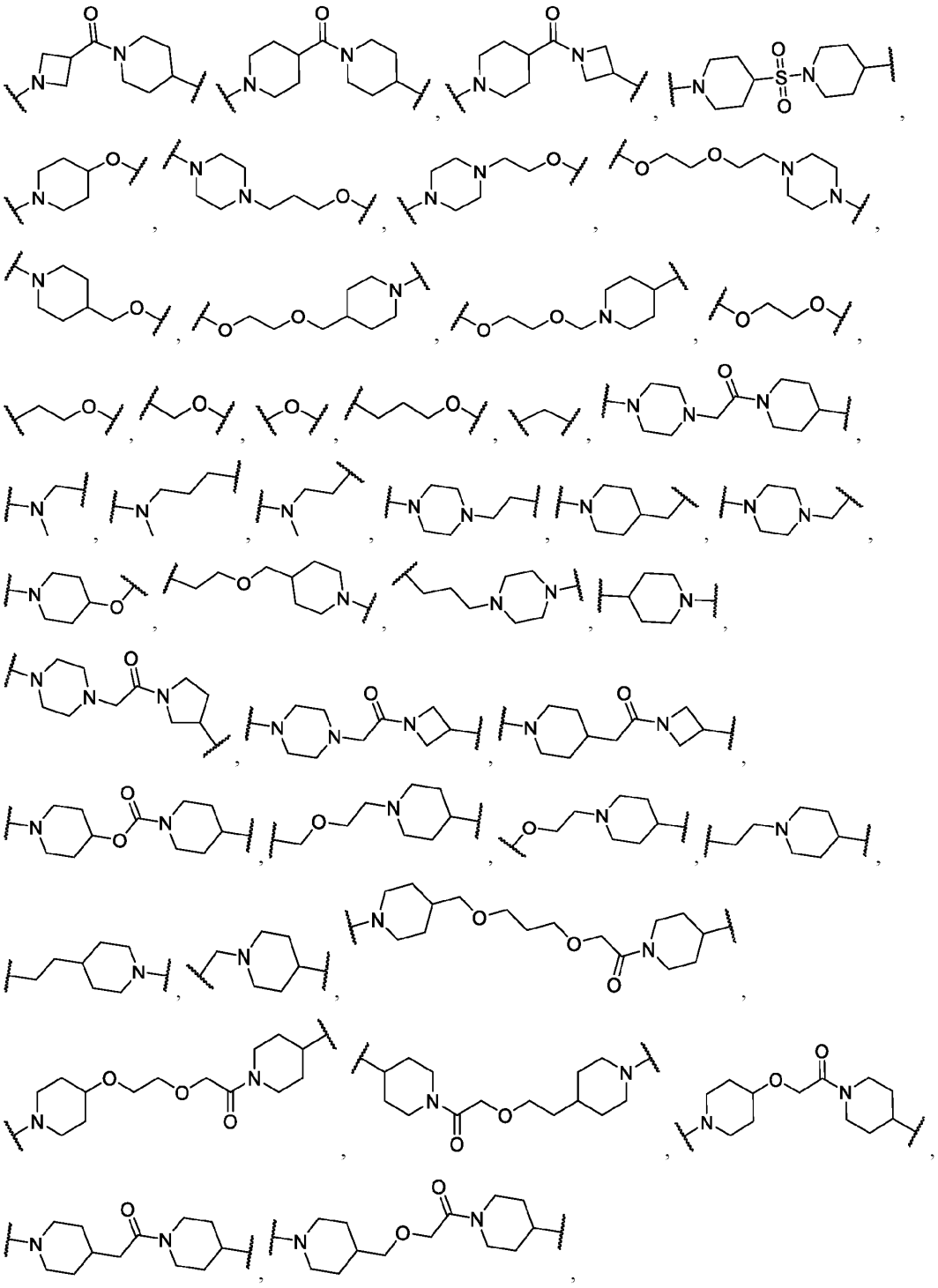


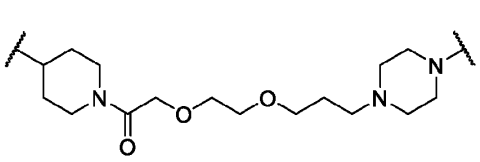
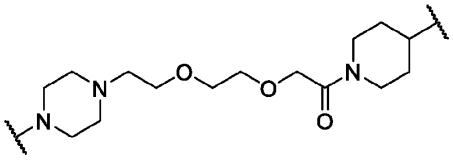
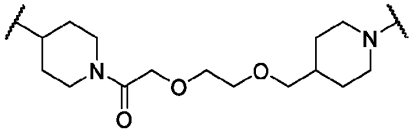
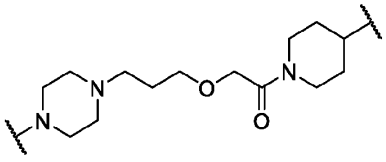
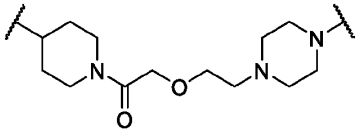
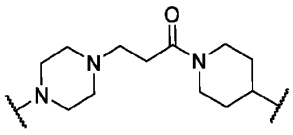
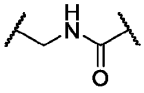
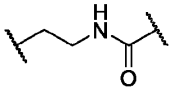
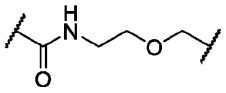
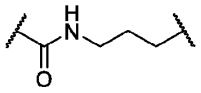
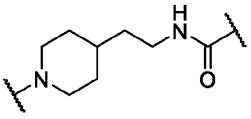
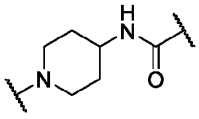
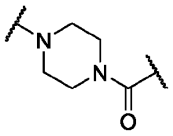
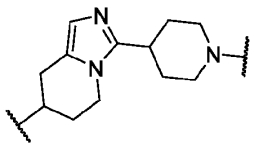
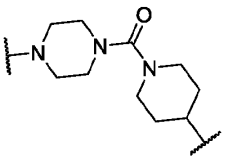
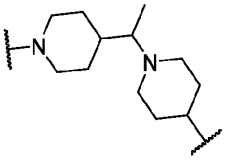
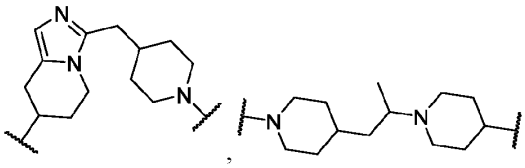


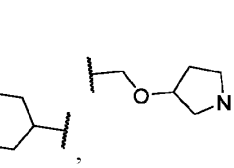
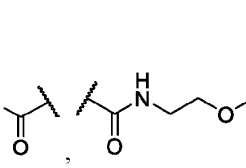
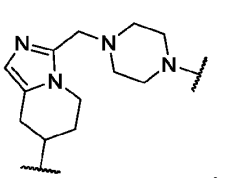
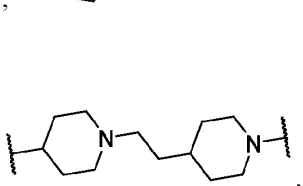
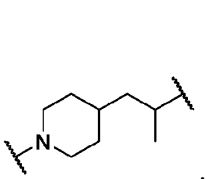
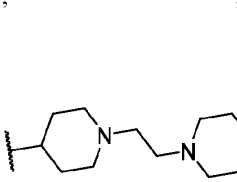
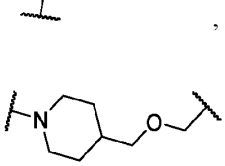
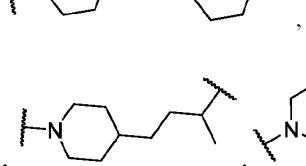
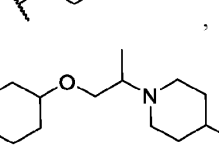
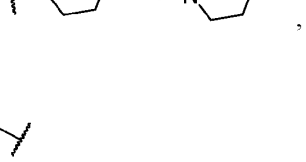
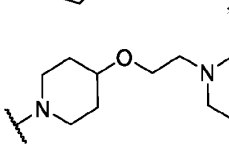
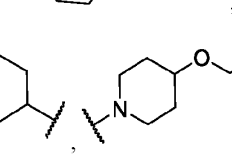
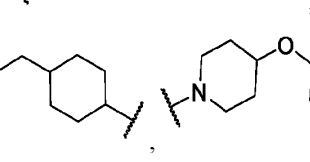
[00164] . In some embodiments, $(L^1)_n$ is absent,  , or  .

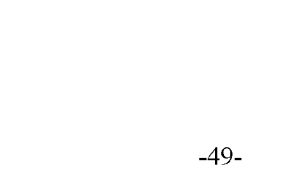
[00165] In some embodiments, L is  ,



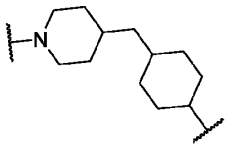


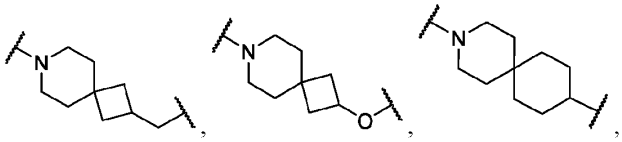
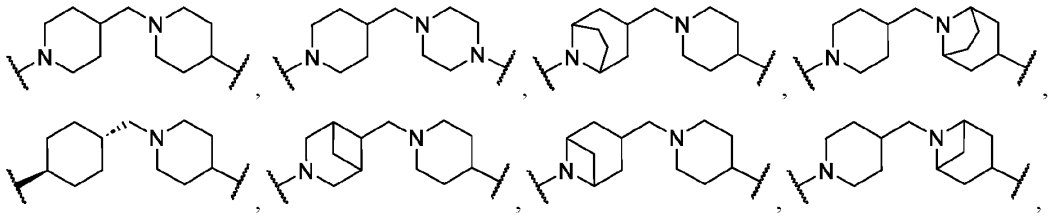
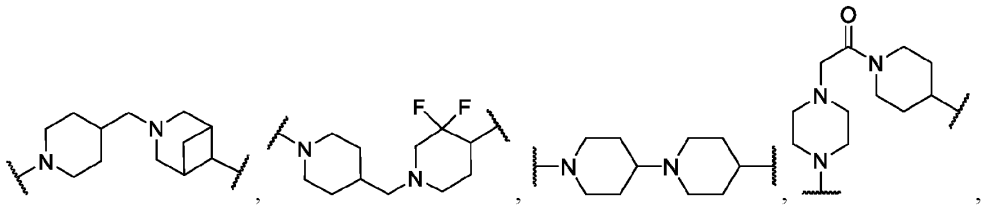
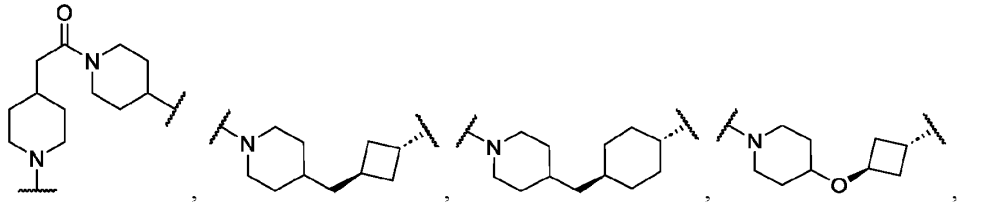
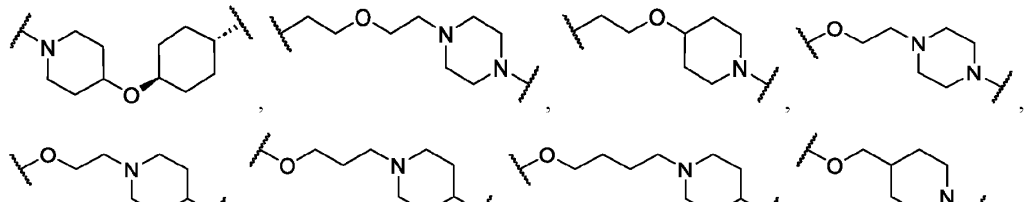
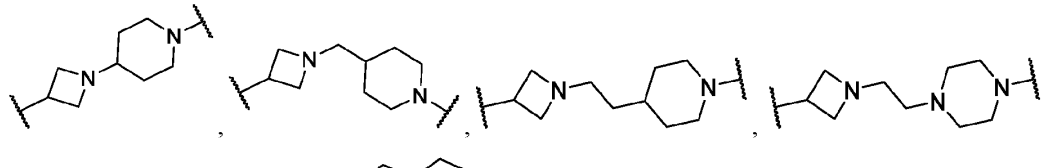
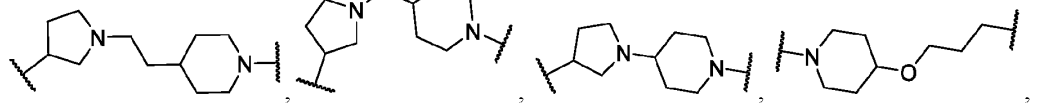

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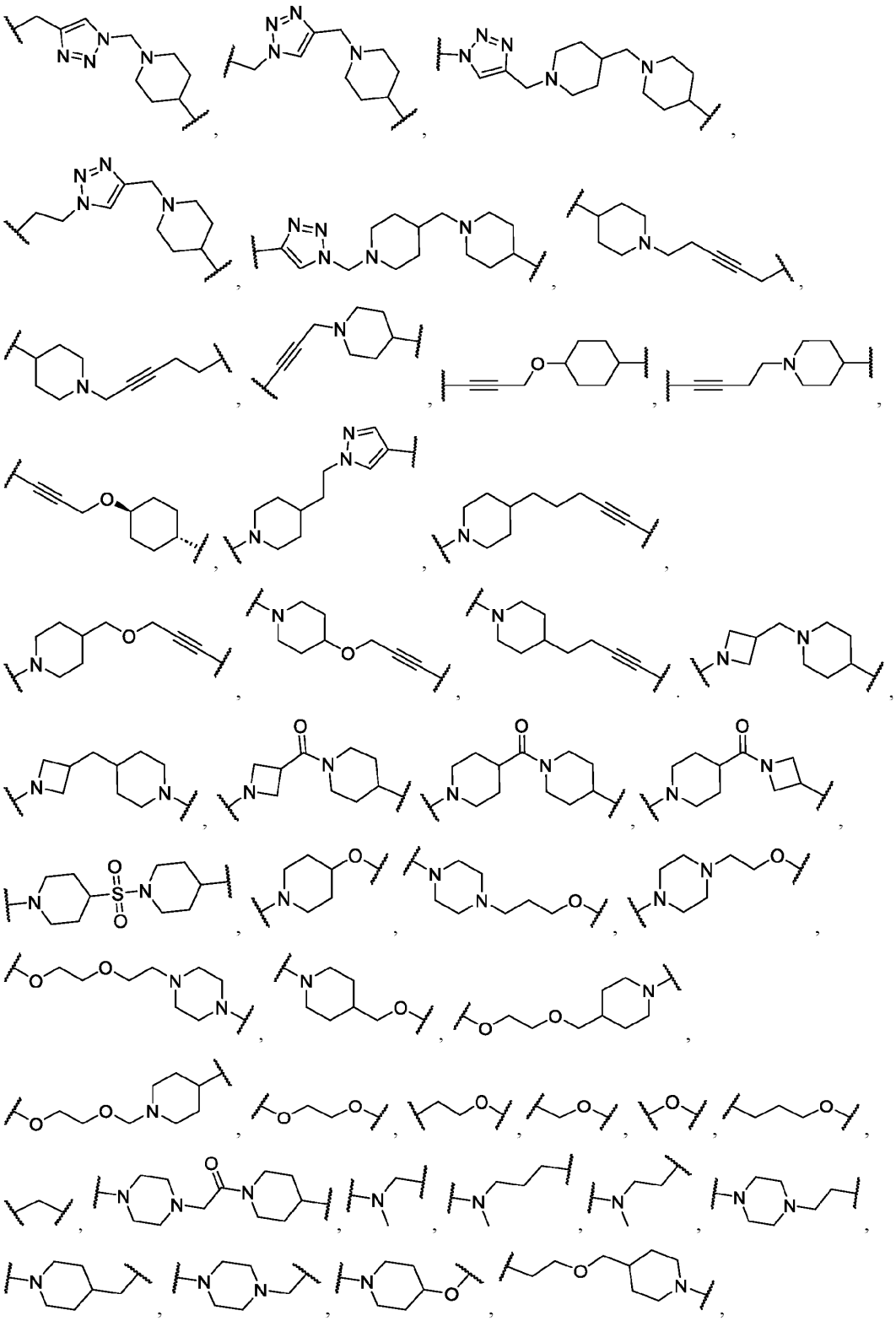
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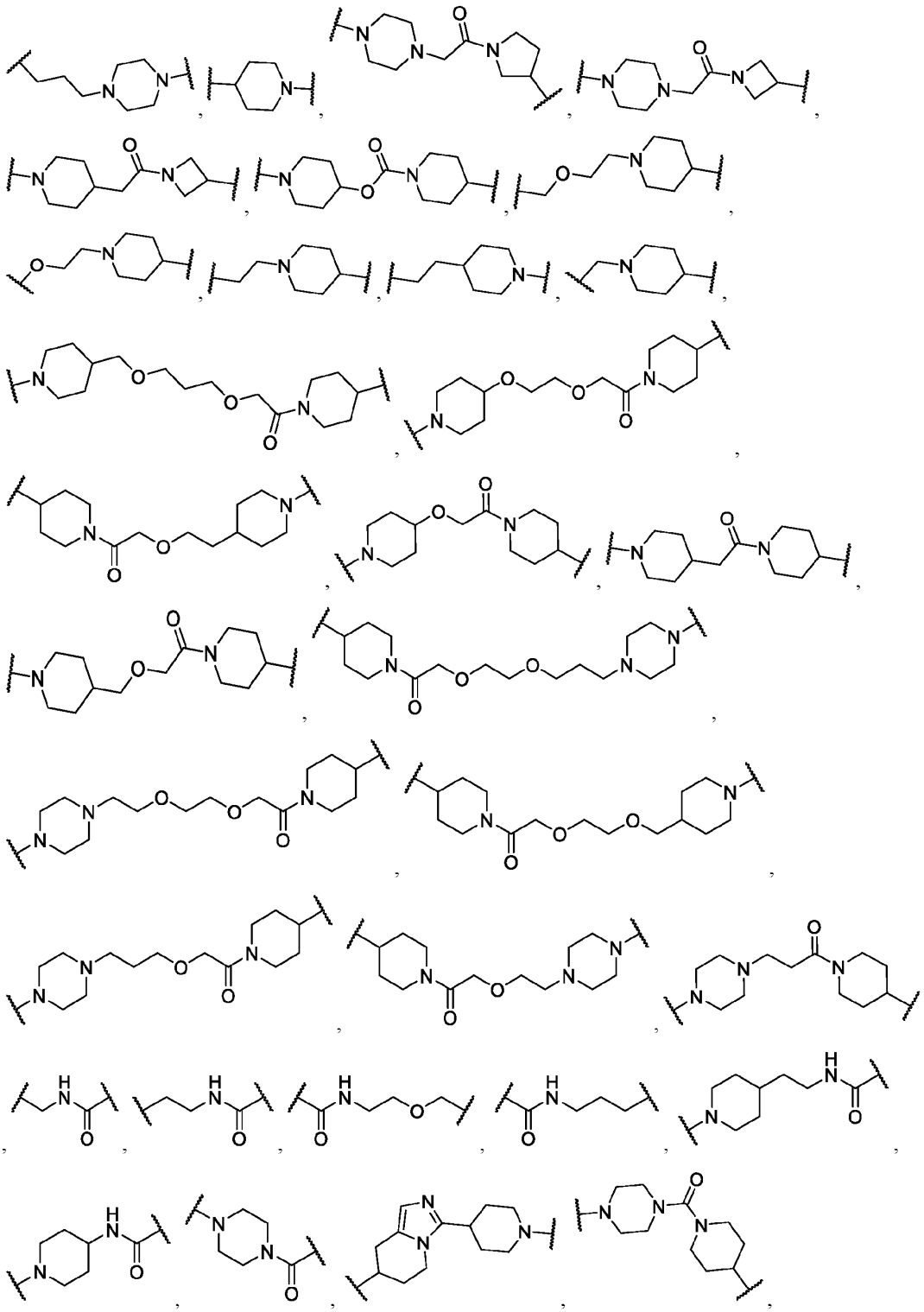
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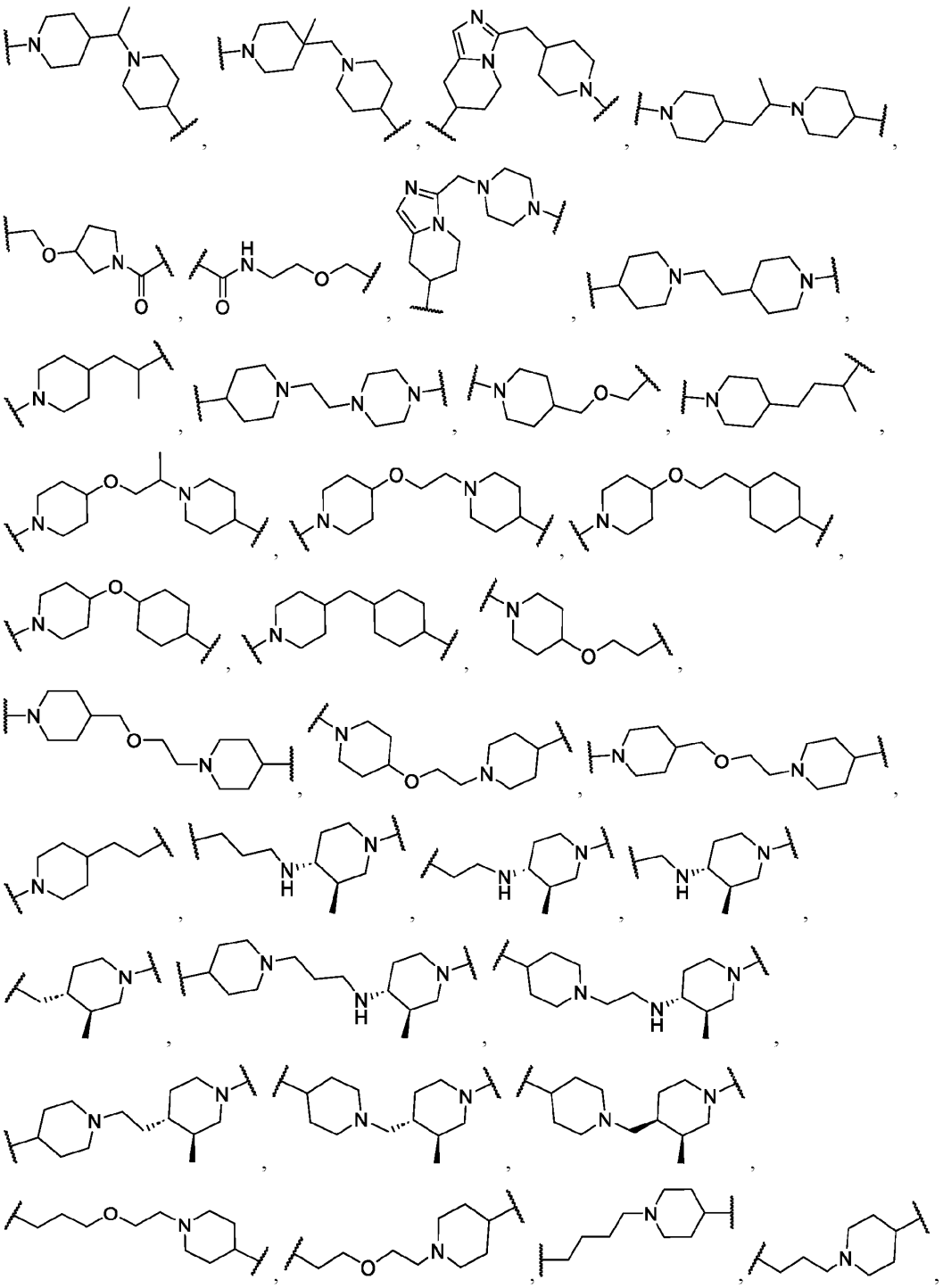
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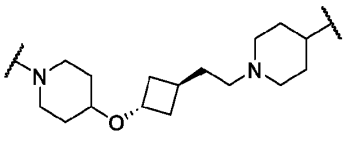
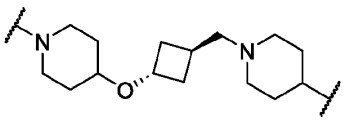
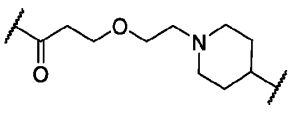
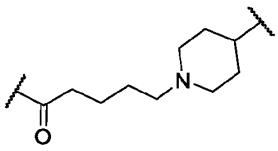
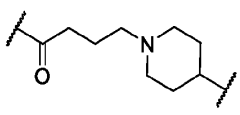
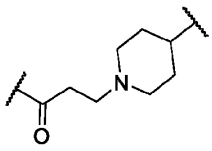
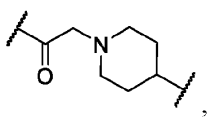
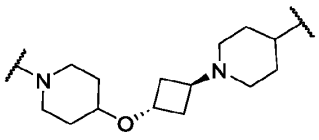
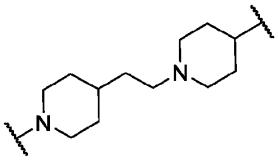
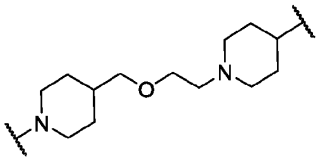
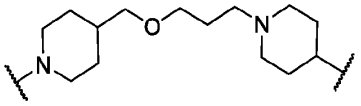
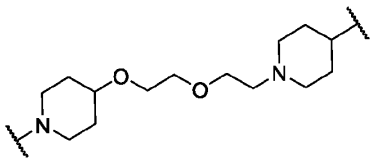
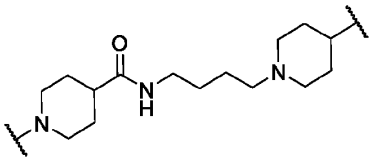
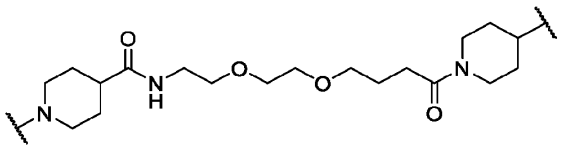
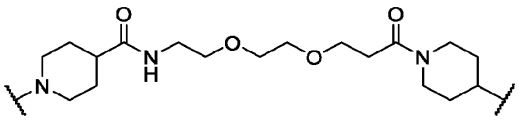
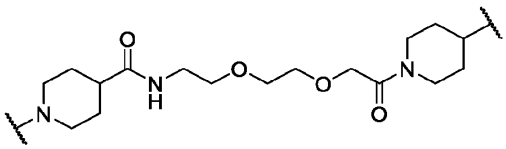
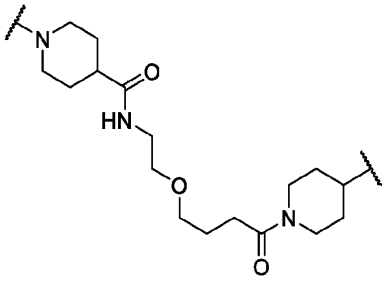
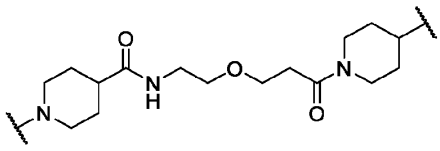
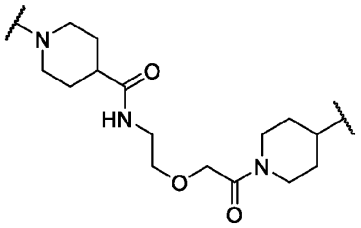
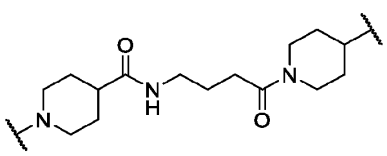

, or a pharmaceutically acceptable salt or solvate thereof.

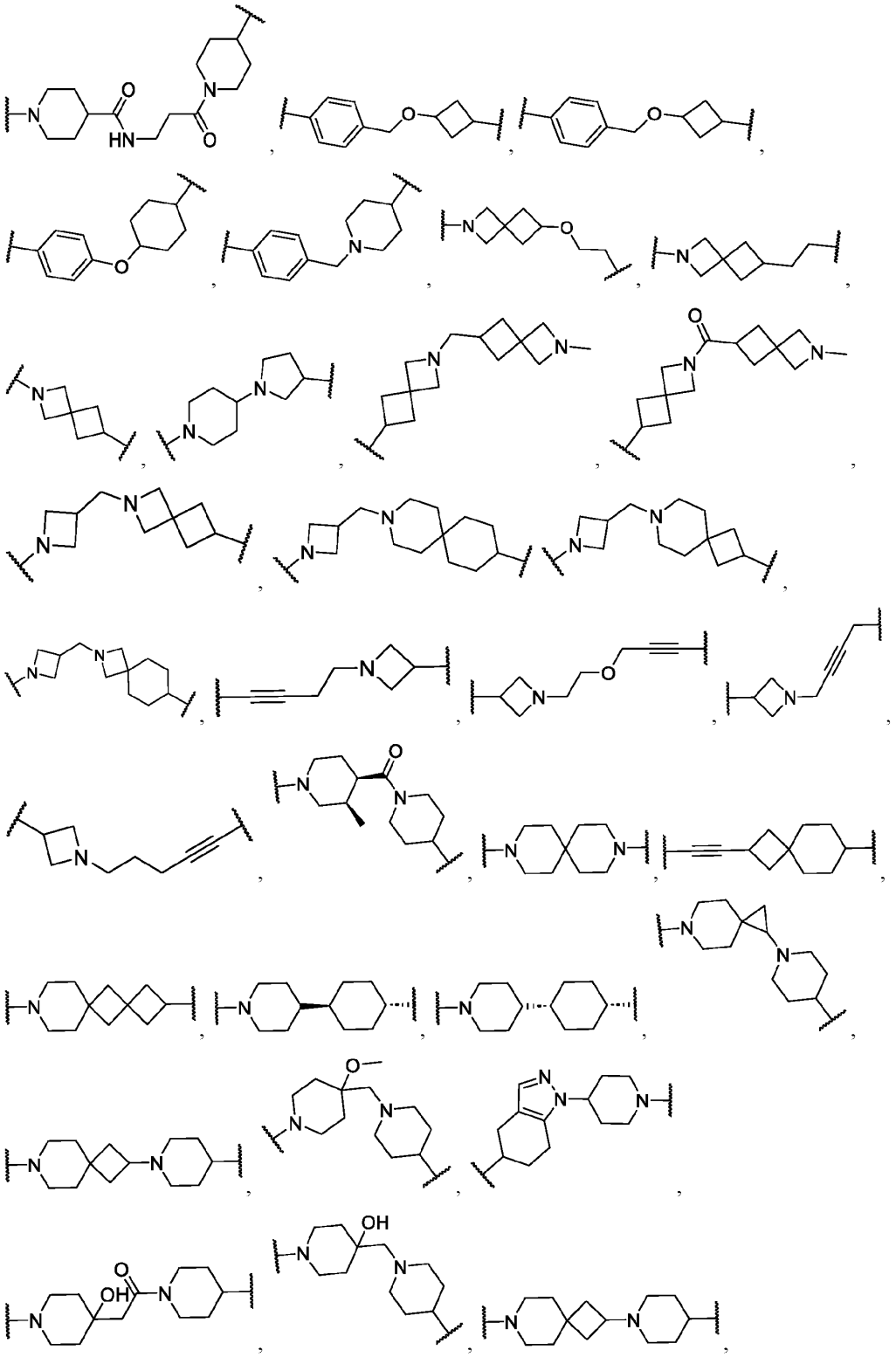
[00166] In some embodiments, L is 







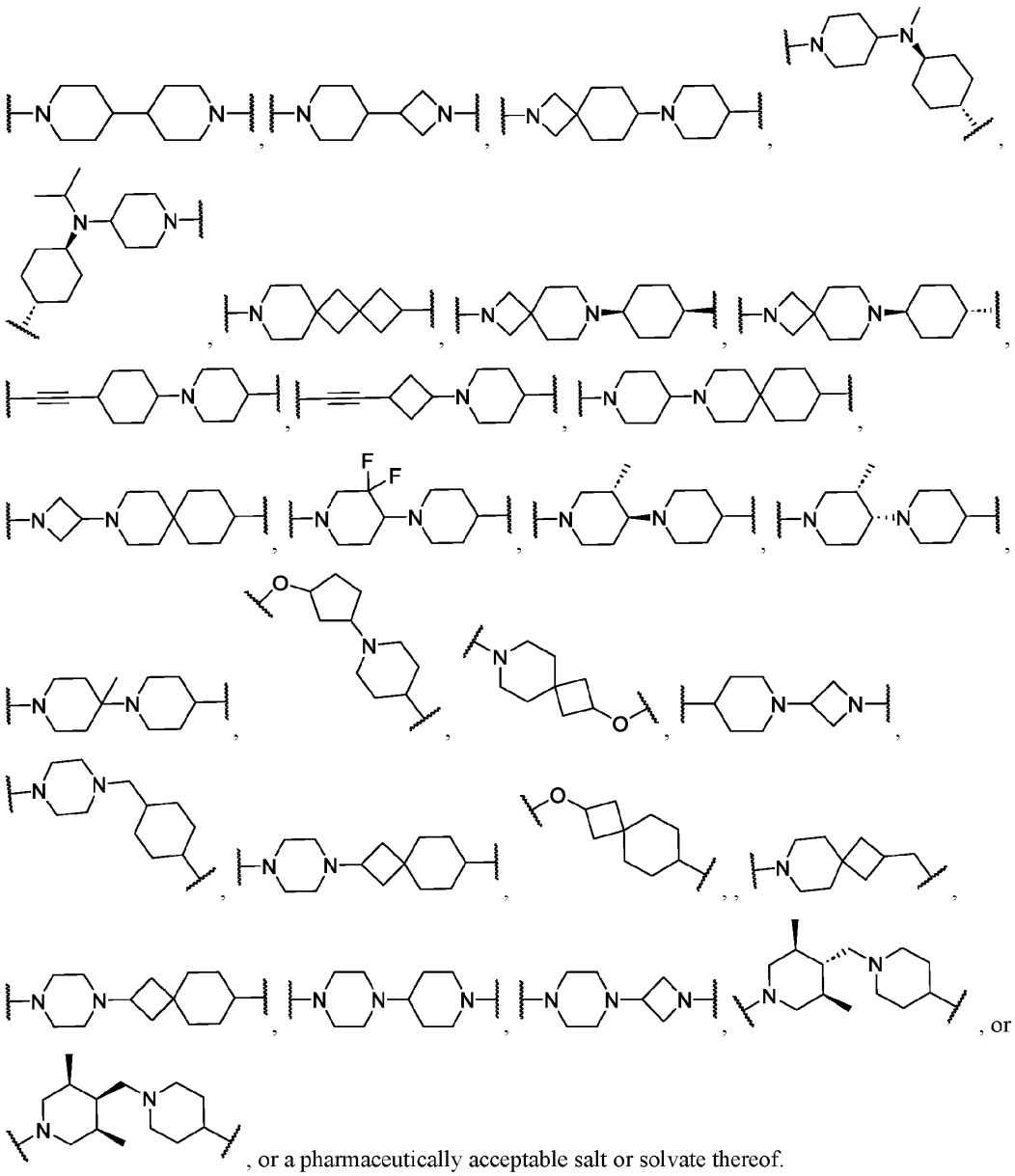






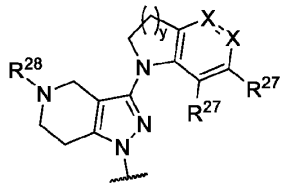

























, or a pharmaceutically acceptable salt or solvate thereof.

[00167] In some embodiments, SB-CBP/p300 has the structure of Formula (IIIb), or a pharmaceutically acceptable salt or solvate thereof:



Formula (IIIb)

wherein:

each X is independently -CR^{27}- or -N-;

each R^{27} is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6cycloalkyl, or substituted or unsubstituted 3- to 8-membered heterocycloalkyl, -CN, -NO_2, -OH, -OR^a, $OC(=O)R^a$, -$OC(=O)N(R^b)_2$, -$OC(=O)OR^b$, -$OC(=O)NR^b$, -SH, -SR^a, -$S(=O)R^a$, -$S(=O)_2R^b$, -$S(=O)_2OR^a$, -$S(=O)_2N(R^b)_2$, -$N(R^b)_2$, -NR^b $C(=O)NR^b$, -N $R^bC(=O)R^a$, -$NR^bC(=O)OR^b$, -$NR^bS(=O)_2R^b$, -$C(=O)R^b$, -$C(=O)OR^b$, or -$C(=O)N(R^b)_2$;

p is 0, 1, 2, or 3;

R^{28} is hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, -$C(=O)R^b$, or -$C(=O)N(R^b)_2$;

y is 1 or 2;

each R^a is independently substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted monocyclic 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted monocyclic heteroaryl;

each R^b is independently hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted monocyclic 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted monocyclic heteroaryl;

or two R^b on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle.

[00168] In some embodiments, SB-CBP/p300 has the structure of Formula (IIIb), or a pharmaceutically acceptable salt or solvate thereof, wherein:

each X is independently -CR^{27}- or -N-;

each R^{27} is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -CN, -NO_2, -OH, -OR^a, $OC(=O)R^a$, -$OC(=O)N(R^b)_2$, -$OC(=O)OR^a$, -$OC(=O)N(R^b)_2$, -SR^b, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2OR^b$, -$S(=O)_2N(R^b)_2$, -$N(R^b)_2$, -$NR^bC(=O)N(R^b)_2$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^a$, -$NR^bS(=O)_2R^a$, -$C(=O)R^b$, -$C(=O)OR^b$, or -$C(=O)N(R^b)_2$;

p is 0, 1, 2, or 3;

R^{28} is hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, -$C(=O)R^b$, or -$C(=O)N(R^b)_2$;

y is 1 or 2;

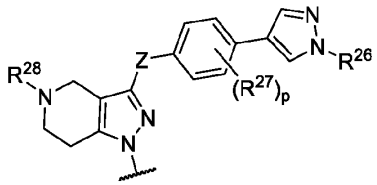
each R^a is independently substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-

C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted monocyclic 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted monocyclic heteroaryl;

each R^b is independently hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted monocyclic 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted monocyclic heteroaryl;

or two R^b on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle.

[00169] In some embodiments, SB-CBP/p300 has the structure of Formula (IIIc), or a pharmaceutically acceptable salt or solvate thereof:



Formula (IIIc)

wherein:

R^6 is hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, or substituted or unsubstituted 3- to 8-membered heterocycloalkyl;

each R^{27} is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, -CN, -NO_2, -OH, -OR^a, $OC(=O)R^a$, -$OC(=O)N(R^b)_2$, -$OC(=O)OR^b$, -$OC(=O)NR^b$, -SH, -SR^a, -$S(=O)R^a$, -$S(=O)_2R^b$, -$S(=O)_2OR^a$, -$S(=O)_2N(R^b)_2$, -$N(R^b)_2$, -$NR^bC(=O)NR^b$, -$NR^bC(=O)R^a$, -NR^b $C(=O)OR^b$, -$NR^bS(=O)_2R^b$, -$C(=O)R^b$, -$C(=O)OR^b$, or -$C(=O)N(R^b)_2$;

p is 0, 1, 2, or 3;

R^{28} is hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, -$C(=O)R^b$, or -$C(=O)N(R^b)_2$;

Z is -NR^c-, -O-, or -S-;

R^c is hydrogen or substituted or unsubstituted C_1-C_6alkyl;

each R^a is independently substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted monocyclic 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted monocyclic heteroaryl;

each R^b is independently hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-

C_6cycloalkyl, substituted or unsubstituted monocyclic 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted monocyclic heteroaryl;

or two R^b on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle.

[00170] In some embodiments, SB-CBP/p300 has the structure of Formula (IIIc), or a pharmaceutically acceptable salt or solvate thereof, wherein:

R^{26} is hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, or substituted or unsubstituted 3- to 8-membered heterocycloalkyl;

each R^{27} is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -CN, -NO_2, -OH, -OR^a, $OC(=O)R^a$, -$OC(=O)N(R^b)_2$, -$OC(=O)OR^a$, -$OC(=O)N(R^b)_2$, -SR^b, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2OR^b$, -$S(=O)_2N(R^b)_2$, -$N(R^b)_2$, -$NR^bC(=O)N(R^b)_2$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^a$, -$NR^bS(=O)_2R^a$, -$C(=O)R^b$, -$C(=O)OR^b$, or -$C(=O)N(R^b)_2$;

p is 0, 1, 2, or 3;

R^{28} is hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, -$C(=O)R^a$, or -$C(=O)N(R^b)_2$;

Z is -NR^c-, -O-, or -S-;

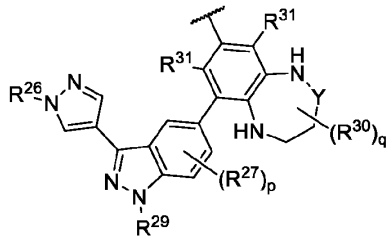
R^c is hydrogen or substituted or unsubstituted C_1-C_6alkyl;

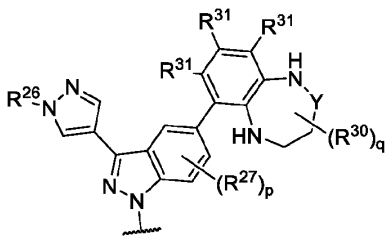
each R^a is independently substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted monocyclic 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted monocyclic heteroaryl;

each R^b is independently hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted monocyclic 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted monocyclic heteroaryl;

or two R^b on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle.

[00171] In some embodiments, SB-CBP/p300 has the structure of Formula (IIId-1) or (IIId-2), or a pharmaceutically acceptable salt or solvate thereof:



Formula (IIId-1) or  Formula (IIId-2)

wherein:

R^6 is hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, or substituted or unsubstituted 3- to 8-membered heterocycloalkyl;

each R^{27} is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, -CN, -NO_2, -OH, -OR^a, $OC(=O)R^a$, $-OC(=O)N(R^b)_2$, $-OC(=O)OR^b$, $-OC(=O)NR^b$, -SH, -SR^a, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2OR^a$, $-S(=O)_2N(R^b)_2$, $-N(R^b)_2$, $-NR^bC(=O)NR^b$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-NR^bS(=O)_2R^b$, $-C(=O)R^b$, $-C(=O)OR^b$, or $-C(=O)N(R^b)_2$;

p is 0, 1, 2, or 3;

R^9 is hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, or substituted or unsubstituted 3- to 8-membered heterocycloalkyl;

each R^{10} is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, -CN, -NO_2, -OH, -OR^a, $OC(=O)R^a$, $-OC(=O)N(R^b)_2$, $-OC(=O)OR^b$, $-OC(=O)NR^b$, -SH, -SR^a, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2OR^a$, $-S(=O)_2N(R^b)_2$, $-N(R^b)_2$, $-NR^bC(=O)NR^b$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-NR^bS(=O)_2R^b$, $-C(=O)R^b$, $-C(=O)OR^b$, or $-C(=O)N(R^b)_2$;

q is 0, 1, 2, 3, or 4;

each R^{11} is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, -CN, -NO_2, -OH, -OR^a, $OC(=O)R^a$, $-OC(=O)N(R^b)_2$, $-OC(=O)OR^b$, $-OC(=O)NR^b$, -SH, -SR^a, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2OR^a$, $-S(=O)_2N(R^b)_2$, $-N(R^b)_2$, $-NR^bC(=O)NR^b$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-NR^bS(=O)_2R^b$, $-C(=O)R^b$, $-C(=O)OR^b$, or $-C(=O)N(R^b)_2$;

Y is $-C(R^{10})_2-$ or C(=O);

each R^a is independently substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted monocyclic 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted monocyclic heteroaryl;

each R^b is independently hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-

C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted monocyclic 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted monocyclic heteroaryl;

or two R^b on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle.

[00172] In some embodiments, SB-CBP/p300 has the structure of Formula (IIId-1) or (IIId-2), or a pharmaceutically acceptable salt or solvate thereof, wherein:

R^{26} is hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, or substituted or unsubstituted 3- to 8-membered heterocycloalkyl;

each R^{27} is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -CN, -NO_2, -OH, -OR^a, $OC(=O)R^a$, -$OC(=O)N(R^b)_2$, -$OC(=O)OR^a$, -$OC(=O)N(R^b)_2$, -SR^b, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2OR^b$, -$S(=O)_2N(R^b)_2$, -$N(R^b)_2$, -$NR^bC(=O)N(R^b)_2$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^a$, -$NR^bS(=O)_2R^a$, -$C(=O)R^b$, -$C(=O)OR^b$, or -$C(=O)N(R^b)_2$;

p is 0, 1, 2, or 3;

R^{29} is hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, or substituted or unsubstituted 3- to 8-membered heterocycloalkyl;

each R^{30} is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, -CN, -NO_2, -OH, -OR^a, $OC(=O)R^a$, -$OC(=O)N(R^b)_2$, -$OC(=O)OR^a$, -SR^b, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2OR^b$, -$S(=O)_2N(R^b)_2$, -$N(R^b)_2$, -$NR^bC(=O)N(R^b)_2$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^a$, -$NR^bS(=O)_2R^a$, -$C(=O)R^b$, -$C(=O)OR^b$, or -$C(=O)N(R^b)_2$;

q is 0, 1, 2, 3, or 4;

each R^{31} is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, -CN, -NO_2, -OH, -OR^a, $OC(=O)R^a$, -$OC(=O)N(R^b)_2$, -$OC(=O)OR^a$, -SR^b, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2OR^b$, -$S(=O)_2N(R^b)_2$, -$N(R^b)_2$, -$NR^bC(=O)NR^b$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^a$, -$NR^bS(=O)_2R^a$, -$C(=O)R^b$, -$C(=O)OR^b$, or -$C(=O)N(R^b)_2$;

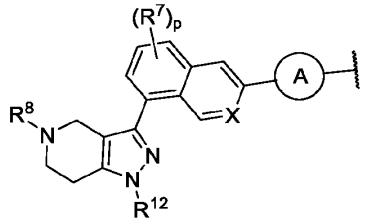
Y is -$C(R^{30})_2$- or C(=O);

each R^a is independently substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted monocyclic 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted monocyclic heteroaryl;

each R^b is independently hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted monocyclic 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted monocyclic heteroaryl;

or two R^b on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle.

[00173] In some embodiments, SB-CBP/p300 has the structure of Formula (IIIe), or a pharmaceutically acceptable salt or solvate thereof:



Formula (IIIe)

wherein:

X is -CR^{27}- or -N-;

each R^{27} is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, -CN, -NO_2, -OH, -OR^a, $OC(=O)R^a$, -$OC(=O)N(R^b)_2$, -$OC(=O)OR^b$, -$OC(=O)NR^b$, -SH, -SR^a, -$S(=O)R^b$, -$S(=O)_2R^b$, -$S(=O)_2OR^a$, -$S(=O)_2N(R^b)_2$, -$N(R^b)_2$, -$NR^bC(=O)NR^b$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^b$, -$NR^bS(=O)_2R^b$, -$C(=O)R^b$, -$C(=O)OR^b$, or -$C(=O)N(R^b)_2$;

p is 0, 1, 2, or 3;

R^{28} is hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, -$C(=O)R^b$, or -$C(=O)N(R^b)_2$;

R^{12} is hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, or substituted or unsubstituted 3- to 8-membered heterocycloalkyl;

Ring A is absent or substituted or unsubstituted 3- to 8-membered heterocycloalkyl;

each R^a is independently substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted monocyclic 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted monocyclic heteroaryl;

each R^b is independently hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted monocyclic 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted monocyclic heteroaryl;

or two R^b on the same N atom are taken together with the N atom to which they are attached to form a

substituted or unsubstituted N-containing heterocycle.

[00174] In some embodiments, SB-CBP/p300 has the structure of Formula (IIIe), or a pharmaceutically acceptable salt or solvate thereof, wherein:

X is $-CR^{27}-$ or -N-;

each R^{27} is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -CN, $-NO_2$, -OH, $-OR^a$, $OC(=O)R^a$, $-OC(=O)N(R^b)_2$, $-OC(=O)OR^a$, $-OC(=O)N(R^b)_2$, $-SR^b$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2OR^b$, $-S(=O)_2N(R^b)_2$, $-N(R^b)_2$, $-NR^bC(=O)N(R^b)_2$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^a$, $-NR^bS(=O)_2R^a$, $-C(=O)R^b$, $-C(=O)OR^b$, or $-C(=O)N(R^b)_2$;

p is 0, 1, 2, or 3;

R^{28} is hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, $-C(=O)R^b$, or $-C(=O)N(R^b)_2$;

R^{32} is hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, or substituted or unsubstituted 3- to 8-membered heterocycloalkyl;

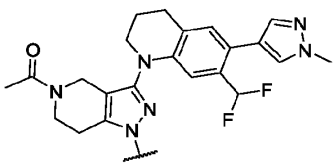
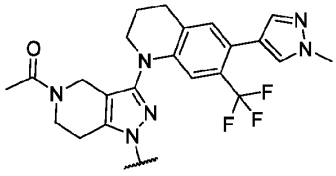
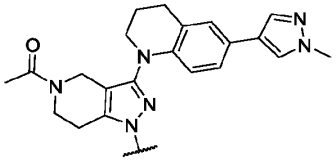
Ring A is absent or substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

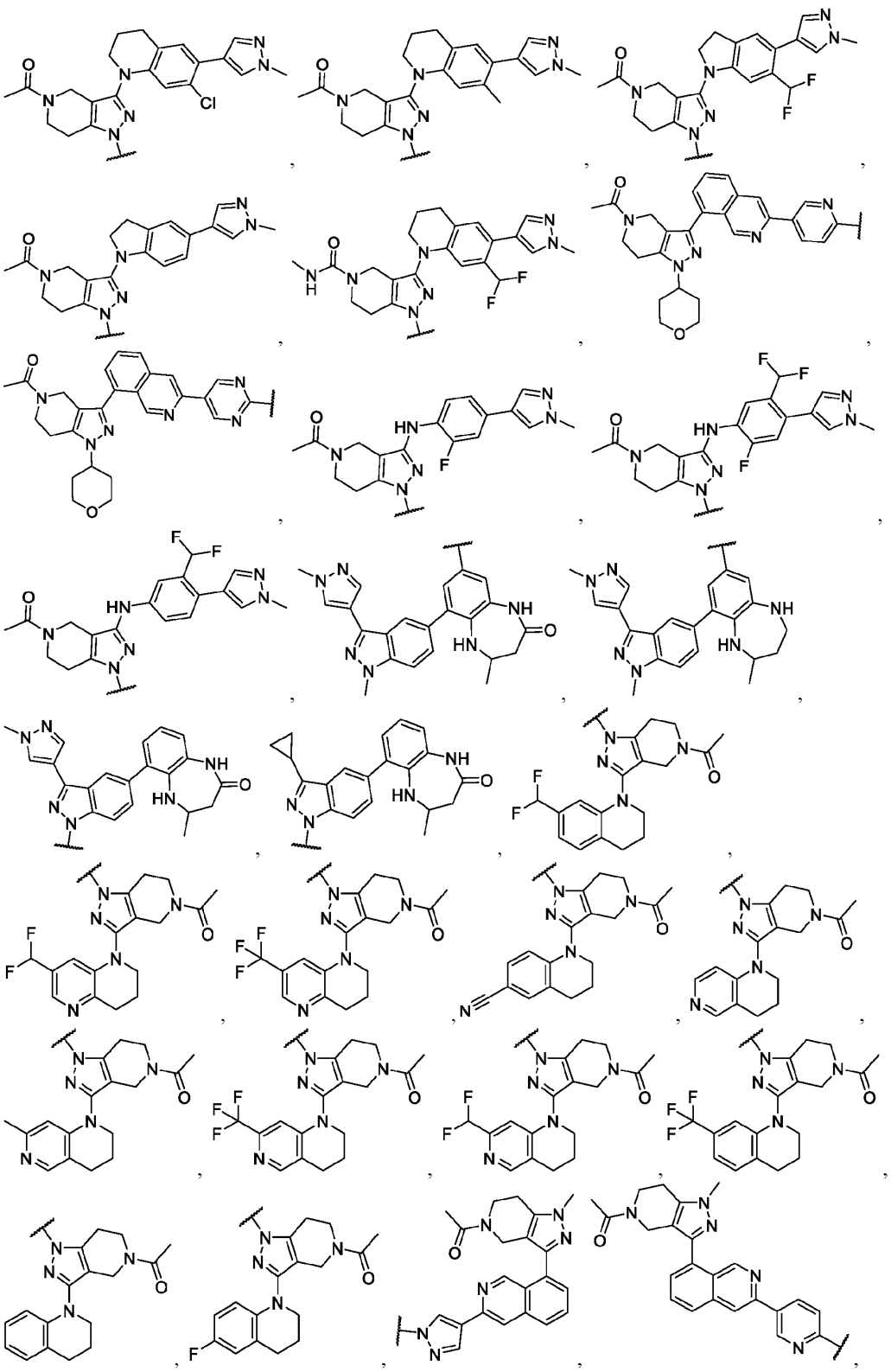
each R^a is independently substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted monocyclic 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted monocyclic heteroaryl;

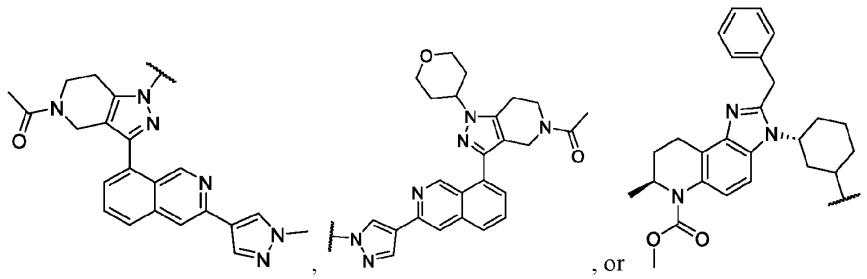
each R^b is independently hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted monocyclic 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted monocyclic heteroaryl;

or two R^b on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle.

[00175] In some embodiments, SB-CBP/p300 has one of the following structures:


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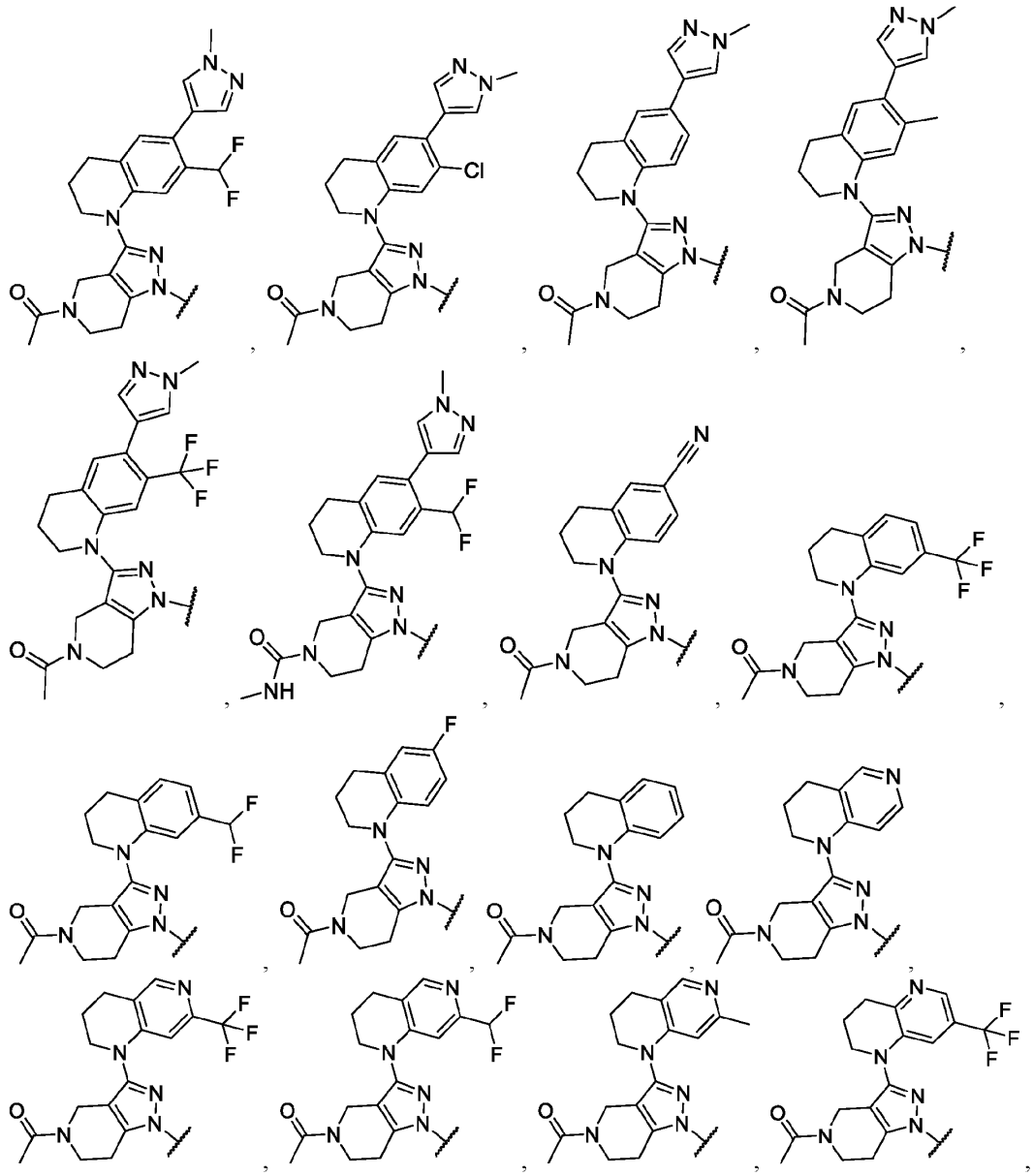


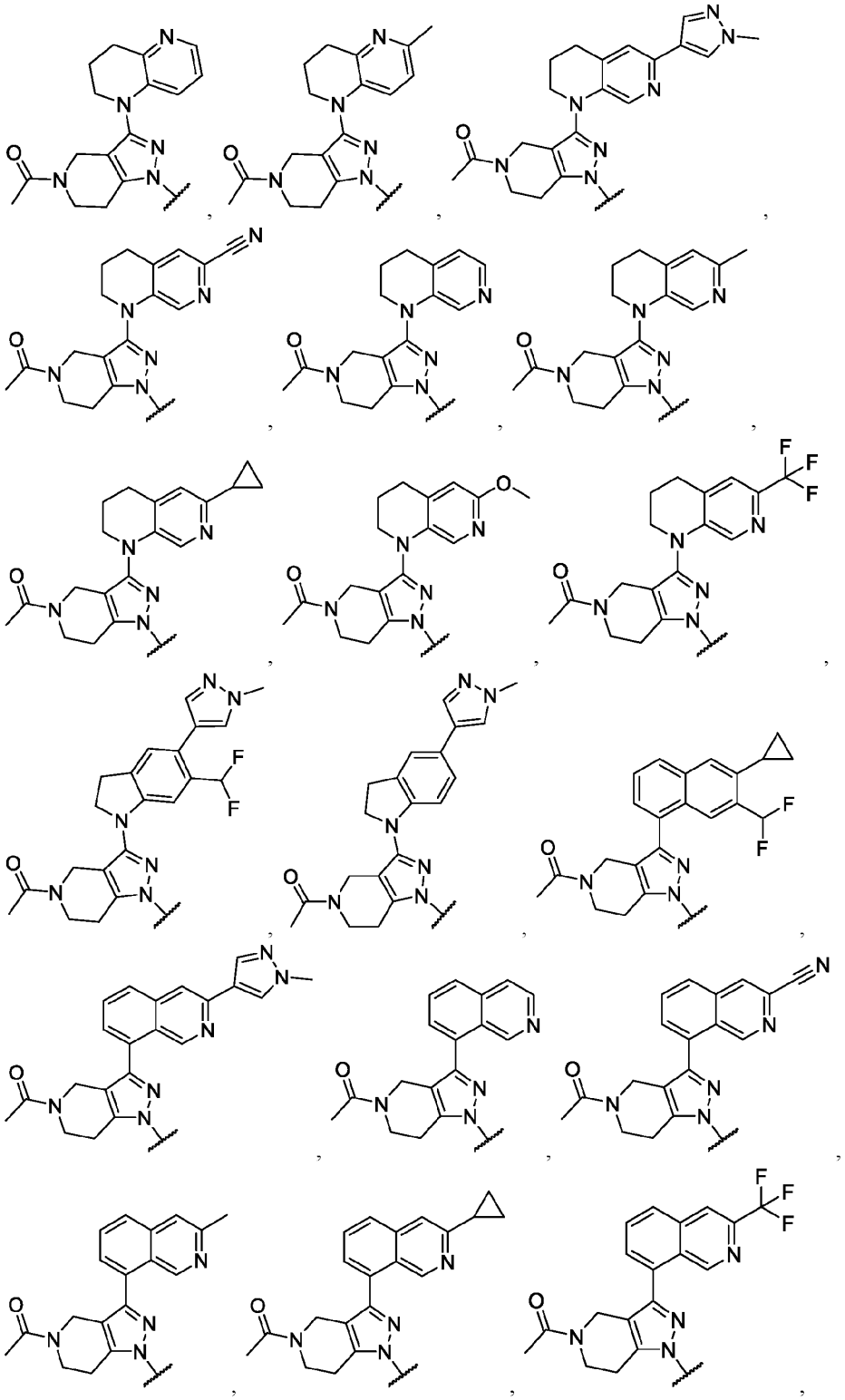


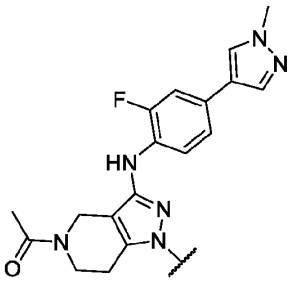
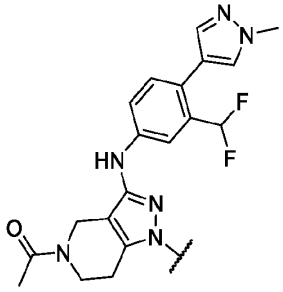
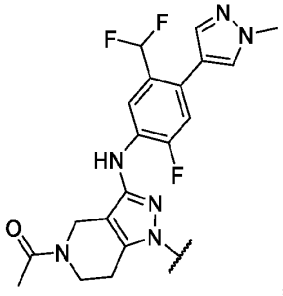
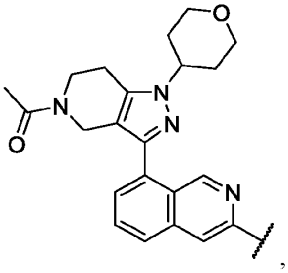
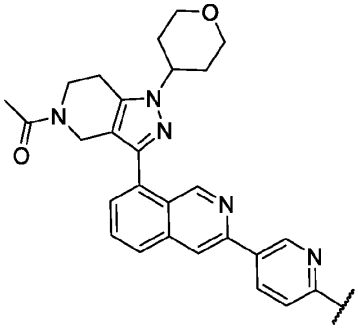
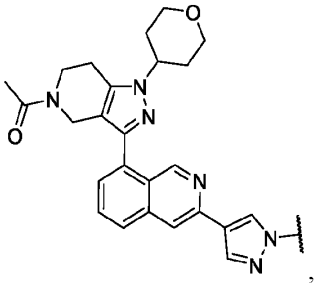
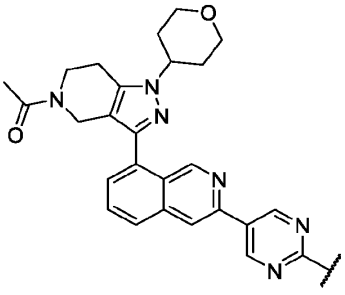
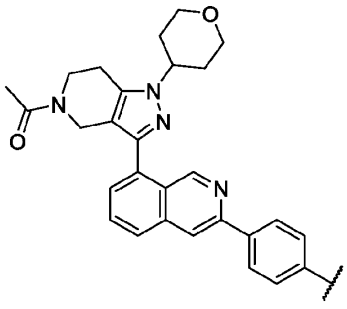
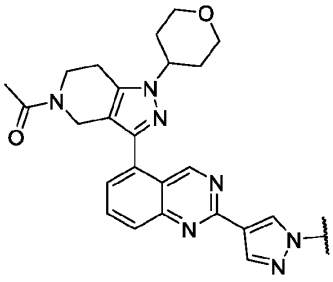
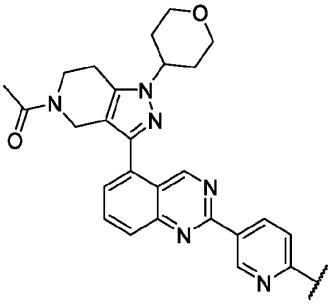
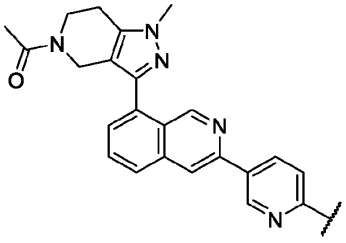
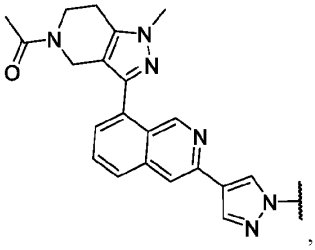
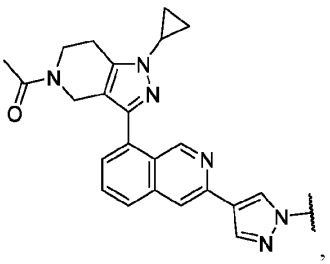
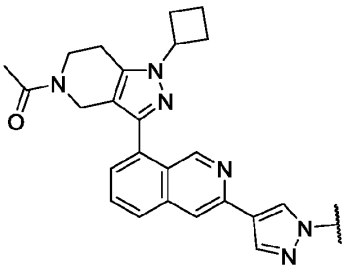
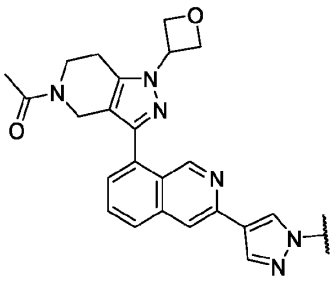
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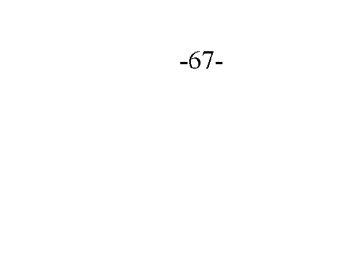
or a pharmaceutically acceptable salt or solvate thereof.

[00176] In some embodiments, SB-CBP/p300 has one of the following structures:

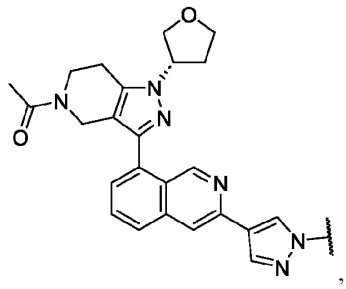
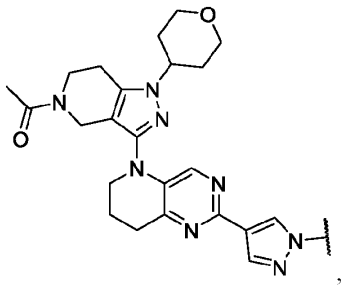
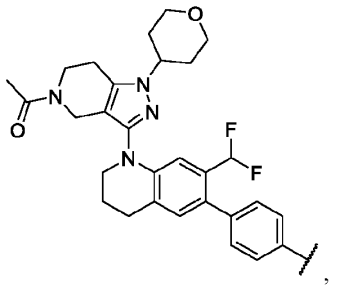
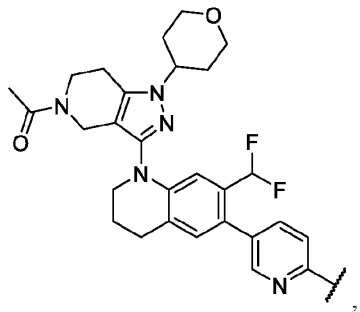
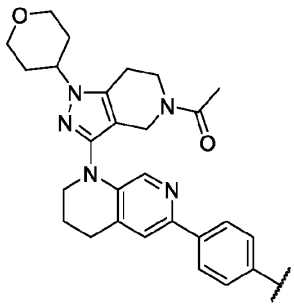
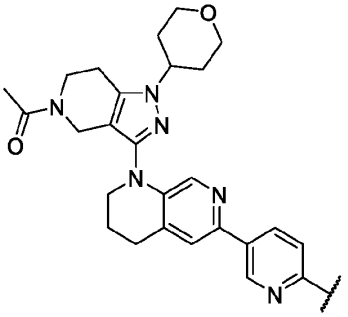
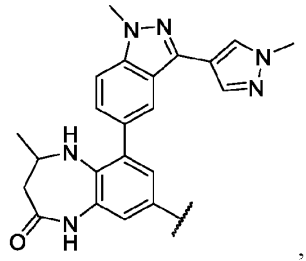
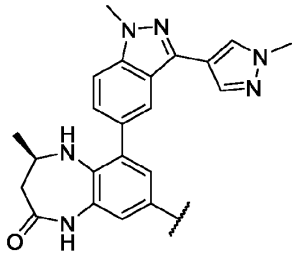
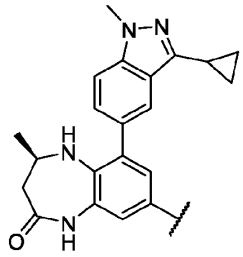
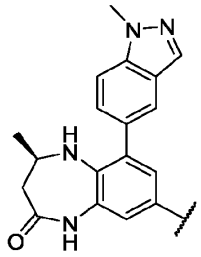
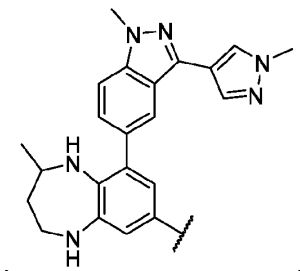
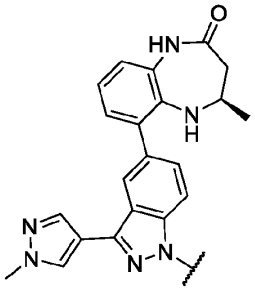
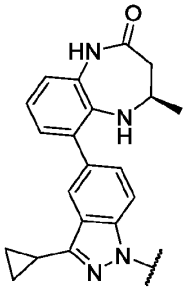
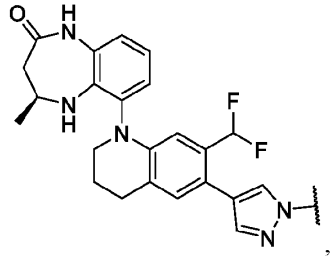
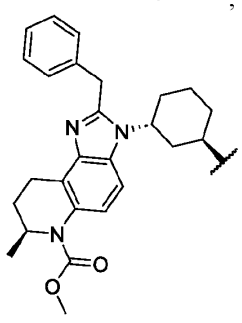
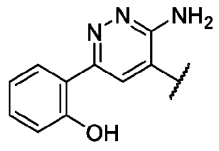
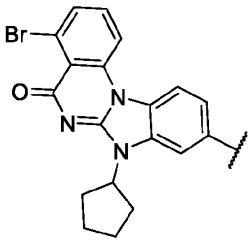


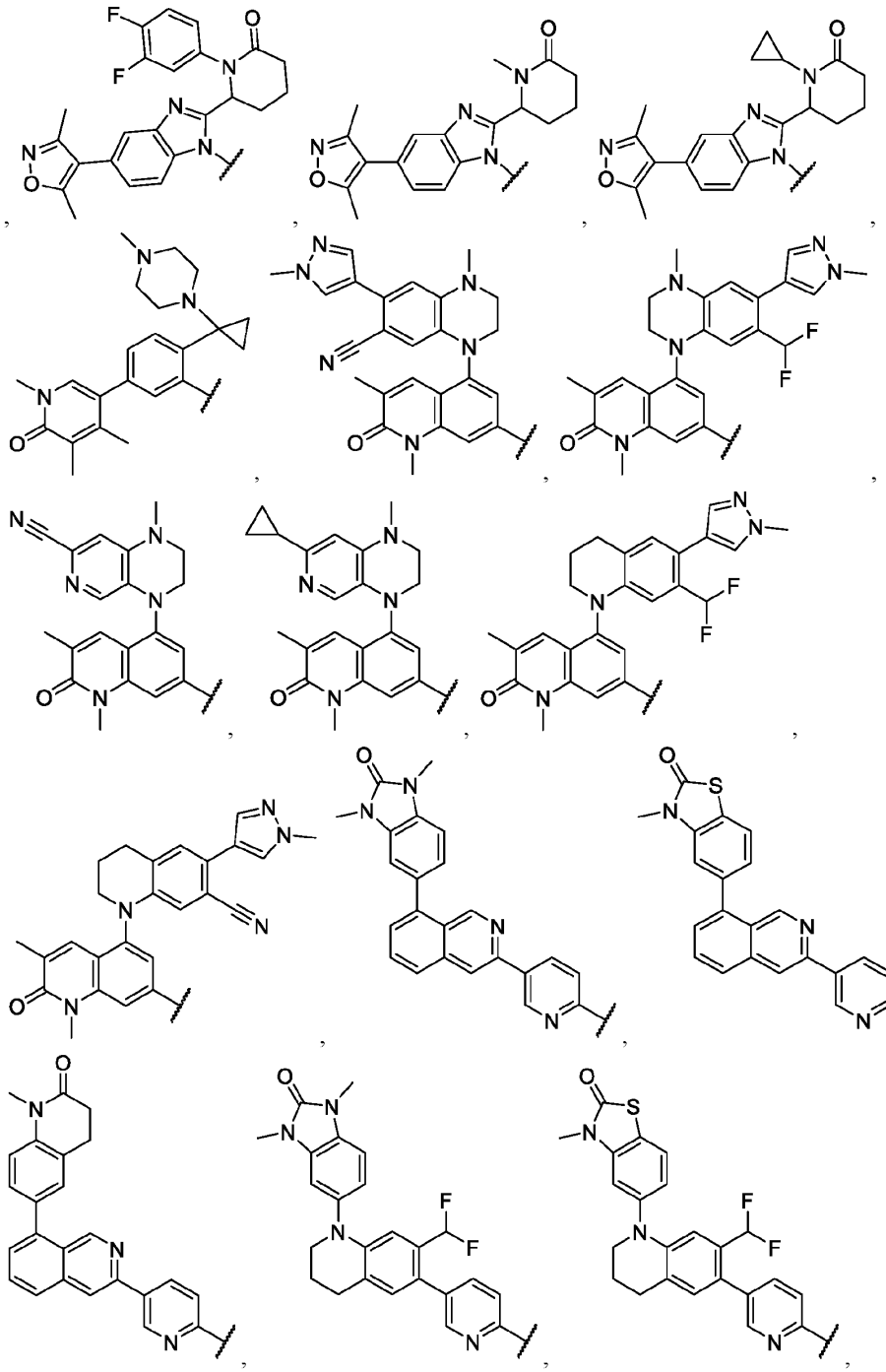


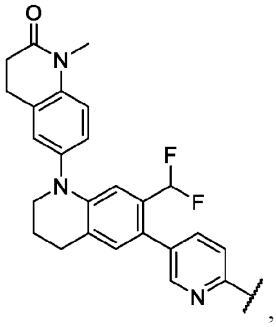
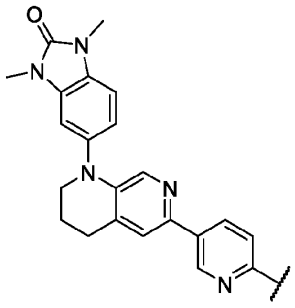
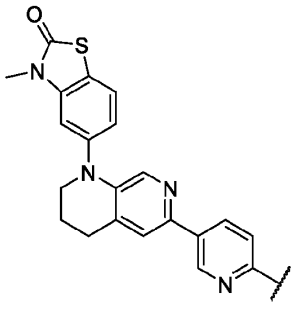
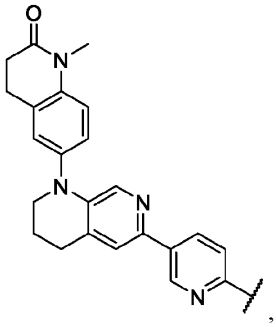

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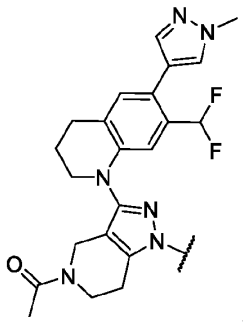
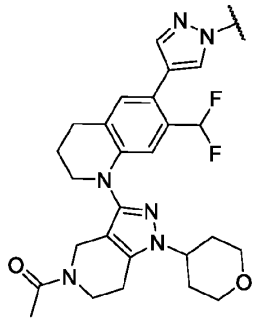
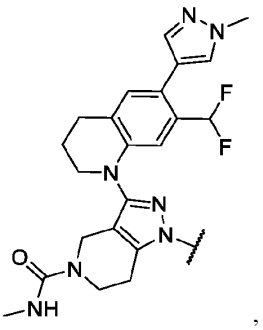
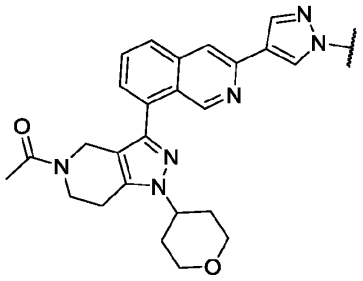
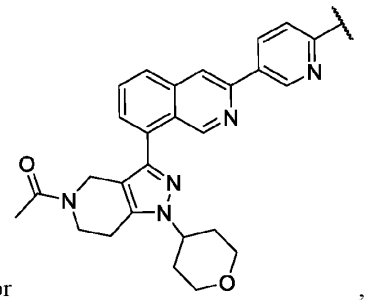





















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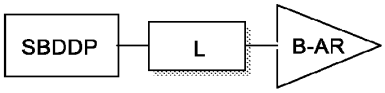
or a pharmaceutically acceptable salt or solvate thereof.

[00177] In some embodiments, SB-CBP/p300 has one of the following structures:


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, or

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or a pharmaceutically acceptable salt or solvate thereof.

[00178] Embodiment 1. A heterobifunctional conditional inhibitor compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof:



wherein:

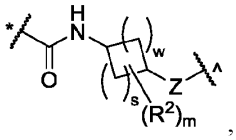
SBDDP is a silent binder of a disease-dependent protein (DDP);

L is an optional linker; wherein L is covalently attached at a position of SBDDP that is solvent exposed when SBDDP binds to the DDP;

B-AR is a binder of the androgen receptor (AR), wherein B-AR comprises:

1) a head group that occupies the ligand-binding domain (LBD) of AR and is covalently attached to a core moiety; and

2) an optional tail moiety covalently attached to the core moiety; wherein the core comprises an optionally substituted cycloalkyl having the structure of Formula (C):



, Formula (C);

the head group is covalently attached to Z at position (^);

the optional tail moiety comprises a ring D that is covalently attached to the amide (*), wherein ring D is a 5-, 6-, 8-, 9- or 10-membered aryl or a 5-, 6-, 8-, 9- or 10-membered heteroaryl that is optionally substituted with s R^3;

wherein:

s is 1, 2, or 3; w is 2 or 3;

m is 0, 1, 2, 3, or 4;

Z is -O- or -NR^5-;

each R^2 is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, -CN, -NO_2, -OH, -OR^4, OC(=O)R^4, -S(=O)R^4, -$S(=O)_2R^5$, -$S(=O)_2N(R^5)_2$, -$N(R^5)_2$, -$NR^5C(=O)NR^5$, -$NR^5C(=O)R^4$, -$C(=O)R^5$, -$C(=O)OR^5$, or -$C(=O)N(R^5)_2$; or

two R^2 on the same carbon atom are taken together with the carbon atom to which they are attached to form a substituted or unsubstituted C_3-C_8cycloalkyl or a substituted or unsubstituted monocyclic 3- to 8-membered heterocycloalkyl;

each R^3 is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, -CN, -OH, -OR^4, or -$N(R^5)_2$.

each R^4 is independently substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted monocyclic 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted monocyclic heteroaryl;

each R^5 is independently hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted monocyclic 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted monocyclic heteroaryl;

or two R^5 on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle; and

wherein L is covalently attached to the core moiety at position (*) if the optional tail moiety is absent, or L is covalently attached to the tail moiety if present;

wherein DDP and AR are both expressed in a cell of interest (COI), and wherein the relative abundance of the AR in the COI is greater than the relative abundance of the DDP in the COI; or the COI is a diseased cell, and the AR is overexpressed, overactive, or both overexpressed and overactive, or amplified in the diseased cell as compared to when the COI is a non-diseased cell.

[00179] Embodiment 2. The compound of embodiment 1, or a pharmaceutically acceptable salt or solvate thereof, wherein DDP is Ataxia-telangiectasia mutated (ATM), Ataxia telangiectasia and Rad3-related protein (ATR), Aurora Kinase A (AurkA), AurkB, Cell division cycle 7-related protein kinase (CDC7), Checkpoint kinase 1 (CHK1), CHK2, Cyclin-dependent kinase 1 (CDK1), CDK2, CDK4, CDK5, CDK6, CDK9, DNA methyltransferase 1 (DNMT1), Exportin 1 (XPO1), Histone deacetylase 1 (HDAC1), HDAC2, HDAC3, kinesin family member 11 (KIF11), Mitogen-activated protein kinase kinase 1 (MEK1), MEK2, Myc, neuronal precursor cell-expressed developmentally down-regulated protein 8 (NEDD8), SMARCA2/4, CREB-binding protein (CBP)/p300, WD repeat-containing protein 5 (WDR5), DDB1- and CUL4-associated factor 1 (DCAF1), phosphatidylinositol-3 kinase (PI3K), Protein arginine methyltransferase 5 (PRMT5), splicing factor 3b subunit 1 (SF3B1), WEE1, 20S proteasome subunits, Steroid Receptor Coactivator 1 (SRC1), SRC2, or SRC3.

[00180] Embodiment 3. The compound of embodiment 1 or embodiment 2, or a pharmaceutically acceptable salt or solvate thereof, wherein DDP is Aurora Kinase A (AurkA), Checkpoint kinase 1 (CHK1), CHK2, CDK4, CDK6, Myc, SMARCA2/4, CREB-binding protein (CBP)/p300, WD repeat-containing protein 5 (WDR5), DDB1- and CUL4-associated factor 1 (DCAF1), phosphatidylinositol-3 kinase (PI3K), or WEE1.

[00181] Embodiment 4. The compound of any one of embodiments 1-3, or a pharmaceutically acceptable salt or solvate thereof, wherein DDP is CREB-binding protein (CBP)/p300.

[00182] Embodiment 5. The compound of embodiment 4, or a pharmaceutically acceptable salt or solvate thereof, wherein SBDDP binds in the acetyl-lysine (KAc) binding site of the bromodomain of CBP/p300.

[00183] Embodiment 6. The compound of embodiment 4, or a pharmaceutically acceptable salt or solvate thereof, wherein the SBDDP comprises an acetyl-lysine mimetic moiety that binds in the acetyl-lysine (KAc) binding site of the bromodomain of CBP/p300.

[00184] Embodiment 7. The compound of embodiment 6, or a pharmaceutically acceptable salt or solvate

thereof, wherein:

the moiety comprising an acetyl-lysine mimetic makes or mimics a hydrogen bond interaction to Asn1168 in the Asn-binding pocket of the bromodomain of CBP, or makes or mimics a hydrogen bond interaction to Asn1132 in the Asn-binding pocket of the bromodomain of p300; and

the head group of B-AR forms hydrogen bonds with the side chains of Gln 711 and Arg752 of the LBD of AR.

[00185] Embodiment 8. The compound of any one of embodiments 1-7, or a pharmaceutically acceptable salt or solvate thereof, wherein: SBDDP further comprises a moiety that interacts with Arg1173 in the bromodomain of CBP or Asn1137 in the bromodomain of p300.

[00186] Embodiment 9. The compound of any one of embodiments 1-8, or a pharmaceutically acceptable salt or solvate thereof, wherein SBDDP further comprises:

1) a moiety that occupies the lipophilic shelf (LPF) region of the bromodomain of CBP/p300; or

2) a moiety that occupies the BC Loop region of the bromodomain of CBP/p300; or

3) both 1) and 2).

[00187] Embodiment 10. The compound of any one of embodiments 6-9, or a pharmaceutically acceptable salt or solvate thereof, wherein the moiety comprising an acetyl-lysine mimetic comprises a moiety selected from pyrrolidonyl, phenyl, pyridinyl, pyridinonyl, triazolyl, pyrrolyl, isoxazolyl, pyrazolyl, quinolinyl, tetrahydroquinolinyl, isoquinolinyl, tetrahydroisoquinolinyl, quinazolonyl, quinazolinyl, dihydroquinazolinonyl, imidazo[4,5-c]quinolinyl fused to a dimethylisoxazolyl, triazolophthalazinyl, indolizinyl, benzoimidazolyl, isoxazole-indolizinyl, thienodiazepine-indolizinyl, benzodiazepine-indolizinyl, 5-isoxazolylbenzimidazolyl, 6-isoxazolylbenzimidazolyl, 7-isoxazolo-quinolinyl, diazobenzyl, triazolophthalazinyl, isoxazoloquinolinyl, 2-thiazolidinonyl, triazolopyrimidinyl, thienodiazepinyl, benzodiazepinyl, benzotriazepinyl, triazolobenzodiazepinyl, triazolothienodiazepinyl, triazolothienodiazepinyl, and isoxazole-azepinyl.

[00188] Embodiment 11. The compound of embodiment 9 or 10, or a pharmaceutically acceptable salt or solvate thereof, wherein L is covalently attached to SBDDP on:

- the acetyl-lysine mimetic moiety; or
- the moiety that occupies the lipophilic shelf (LPF) region of the bromodomain of CBP/p300, if present; or
- the moiety that occupies the BC Loop region of the bromodomain of CBP/p300, if present;

wherein L is covalently attached to SBDDP at a position that does not interfere with the binding of the acetyl-lysine mimetic moiety in the acetylated lysine (KAc) binding site of CBP/p300.

[00189] Embodiment 12. The compound of any one of embodiments 1-11, or a pharmaceutically acceptable salt or solvate thereof, wherein:

the head group of B-AR comprises 4-cyanophenyl; 3-fluoro-4-cyanophenyl; 3-chloro-4-cyanophenyl; 3-methoxy-4-cyanophenyl; 3-methyl-4-cyanophenyl; 3-trifluroromethyl-4-cyanophenyl; 3-trifluroromethoxy-4-cyanophenyl; 5-fluoro-6-cyanopyridin-3-yl; 5-chloro-6-cyanopyridin-3-yl; 5-

methoxy-6-cyanopyridin-3-yl; 5-methyl-6-cyanopyridin-3-yl; 5-trifluroromethyl-6-cyanopyridin-3-yl; 5-trifluroromethoxy-6-cyanopyridin-3-yl; [1,2,4]triazolo[4,3-b]pyridazin-6-yl; or 3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl; and

each R^2 is $-CH_3$.

[00190] Embodiment 13. The compound of any one of embodiments 1-12, or a pharmaceutically acceptable salt or solvate thereof, wherein the acetyl-lysine mimetic moiety that binds in the acetyl-lysine (KAc) binding site of the bromodomain of CBP/p300 comprises:

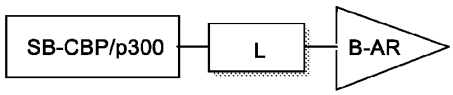
1-(1,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridin-5-yl)ethan-1-one; or N-methyl-1,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxamide; wherein the acetyl-lysine mimetic moiety optionally further comprises:

1) a moiety at the 1-position of the 1,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridin-5-yl group that occupies the lipophilic shelf (LPF) region of the bromodomain of CBP/p300; or

2) a moiety that at the 3-position of the 1,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridin-5-yl group occupies the BC Loop region of the bromodomain of CBP/p300; or

3) both 1) and 2).

[00191] Embodiment 14. A heterobifunctional conditional inhibitor compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof:



wherein:

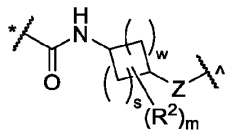
SB-CBP/p300 is a silent binder of human CREB-binding protein (CBP) or human E1A-binding protein p300 (p300) (CBP/p300);

L is an optional linker; wherein L is covalently attached at a position of SB-CBP/p300 that is solvent exposed when SB binds to CBP/p300;

B-AR is a binder of the androgen receptor (AR), wherein the B-AR comprises:

1) a head group that occupies the ligand-binding domain (LBD) of AR and is covalently attached to a core moiety; and

2) an optional tail moiety covalently attached to the core moiety; wherein the core comprises an optionally substituted cycloalkyl having the structure of Formula (C):



, Formula (C);

wherein:

s is 1, 2, or 3; w is 2 or 3;

m is 0, 1, 2, 3, or 4;

the head group is covalently attached to Z at position (^);

the optional tail moiety comprises a ring D that is covalently attached to the amide (*), wherein ring D is a 5-, 6-, 8-, 9- or 10-membered aryl or a 5-, 6-, 8-, 9- or 10-membered heteroaryl that is optionally substituted with s R^3;

Z is -O- or -NR^5-;

each R^2 is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, -CN, -NO_2, -OH, -OR^4, $OC(=O)R^4$, $-S(=O)R^4$, $-S(=O)_2R^5$, $-S(=O)_2N(R^5)_2$, $-N(R^5)_2$, $-NR^5C(=O)NR^5$, $-NR^5C(=O)R^4$, $-C(=O)R^5$, $-C(=O)OR^5$, or $-C(=O)N(R^5)_2$; or

two R^2 on the same carbon atom are taken together with the carbon atom to which they are attached to form a substituted or unsubstituted C_3-C_8cycloalkyl or a substituted or unsubstituted monocyclic 3- to 8-membered heterocycloalkyl;

each R^3 is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, -CN, -OH, -OR^4, or -$N(R^5)_2$.

each R^4 is independently substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted monocyclic 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted monocyclic heteroaryl;

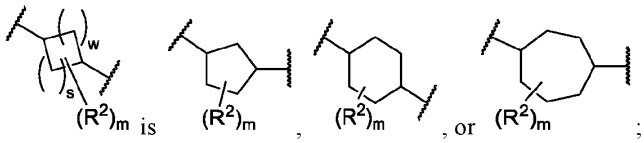
each R^5 is independently hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted monocyclic 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted monocyclic heteroaryl;

or two R^5 on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle; and

wherein L is covalently attached to the core moiety at position (*) if the optional tail moiety is absent, or L is covalently attached to the tail moiety if present.

[00192] Embodiment 15. The compound of any one of embodiments 1-11 or 14, or a pharmaceutically acceptable salt or solvate thereof, wherein: the head group of B-AR forms hydrogen bonds with the side chains of Gln 711 and Arg752 of the LBD of AR.

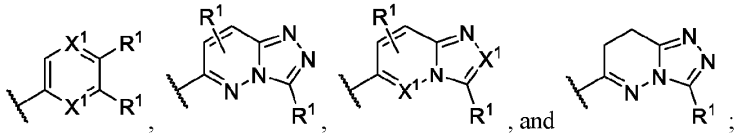
[00193] Embodiment 16. The compound of any one of embodiments 1-11 or 14, or a pharmaceutically acceptable salt or solvate thereof, wherein:



each R^2 is independently hydrogen, $-CH_3$, $-CH_2F$, $-CHF_2$, or $-CF_3$.

[00194] Embodiment 17. The compound of any one of embodiments 1-11 or 14, or a pharmaceutically acceptable salt or solvate thereof, wherein B-AR comprises a head group and an optional core, wherein the

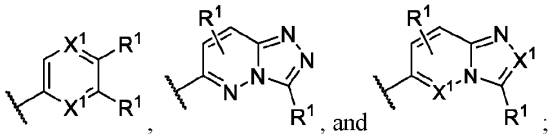
head group is selected from:



each X^1 is independently -CR^1- or -N-;

each R^1 is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted 3- to 8-membered heterocycloalkyl, -CN, -NO_2, -OH, -OR^4, $OC(=O)R^4$, -$OC(=O)N(R^5)_2$, -$OC(=O)OR^5$, -$OC(=O)NR^5$, -SH, -SR^4, -$S(=O)R^4$, -$S(=O)_2R^5$, -$S(=O)_2OR^4$, -$S(=O)_2N(R^5)_2$, -$N(R^5)_2$, -$NR^5C(=O)NR^5$, -$NR^5C(=O)R^4$, -$NR^5C(=O)OR^5$, -$NR^5S(=O)_2R^5$, -$C(=O)R^5$, -$C(=O)OR^5$, or -$C(=O)N(R^5)_2$.

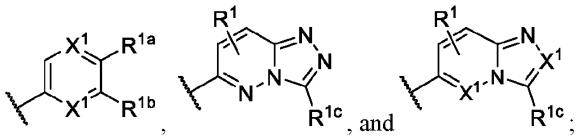
[00195] Embodiment 18. The compound of any one of embodiments 1-11 or 14, or a pharmaceutically acceptable salt or solvate thereof, wherein B-AR comprises a head group and an optional core, wherein the head group is selected from:



one X^1 is -CR^1- and the other X^1 is -CR^1- or -N-;

each R^1 is independently hydrogen, F, Cl, Br, I, -CH_3, -CD_3, -CH_2CH_3, -CH_2F, -CHF_2, -CF_3, -CH_2CH_2F, -CH_2CHF_2, - CH_2CF_3, -OH, -OCF_3, -OCH_3, -OCD_3, -OCH_2CH_3, -CN, -$C(=O)NH_2$ - $C(=O)NH(CH_3)$or -$C(=O)NH(CD_3)$.

[00196] Embodiment 19. The compound of any one of embodiments 1-11 or 14, or a pharmaceutically acceptable salt or solvate thereof, wherein B-AR comprises a head group and an optional core, wherein the head group is selected from:



each X^1 is independently -CR^1- or -N-;

R^{1a} is -CN, -NO_2, -$C(=O)R^5$, -$C(=O)OR^5$, or -$C(=O)N(R^5)_2$;

R^{1b} is hydrogen, halogen, C_1-C_4alkyl, C_1-C_4fluoroalkyl, -CN, -OH, -OR^4, or -SR^4;

R^{1c} is hydrogen, halogen, C_1-C_4alkyl, C_1-C_4fluoroalkyl, or -CN;

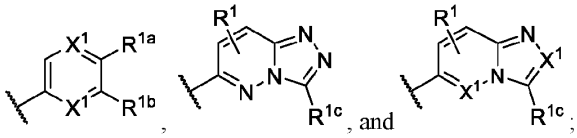
each R^1 is independently hydrogen, halogen, C_1-C_4alkyl, C_1-C_4fluoroalkyl, -CN, -OH, or -OR^4;

each R^4 is independently C_1-C_4alkyl, or C_1-C_4fluoroalkyl;

each R^5 is independently hydrogen, C_1-C_4alkyl, or C_1-C_4fluoroalkyl.

[00197] Embodiment 20. The compound of any one of embodiments 1-11 or 14, or a pharmaceutically

acceptable salt or solvate thereof, wherein B-AR comprises a head group and an optional core, wherein the head group is selected from:



one X^1 is $-CR^1-$ and the other X^1 is $-CR^1-$ or -N-;

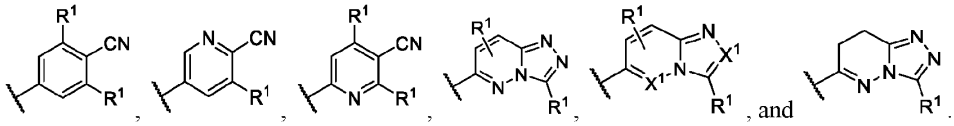
R^{1a} is -CN, $-NO_2$, $-C(=O)NH_2$ or $-C(=O)NH(CH_3)$;

R^{1b} is hydrogen, F, Cl, Br, I, $-CH_3$, $-CH_2CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, -OH, $-OCF_3$, $-OCH_3$, $-OCH_2CH_3$, or -CN;

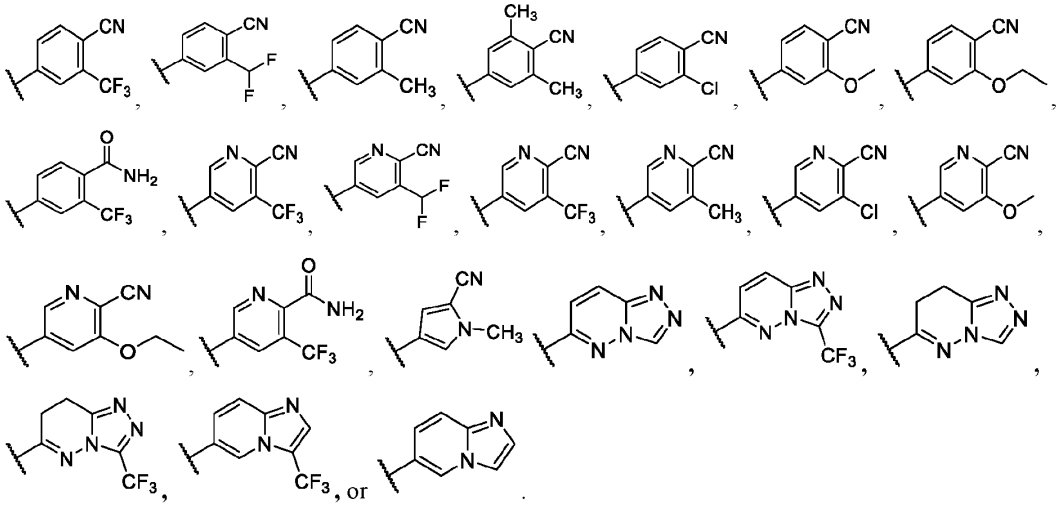
each R^{1c} is hydrogen, F, Cl, Br, $-CH_3$, $-CH_2F$, $-CHF_2$, or $-CF_3$;

each R^1 is independently hydrogen, F, Cl, Br, I, $-CH_3$, $-CH_2CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2CH_2F$, $-CH_2CHF_2$, $-CH_2CF_3$, -OH, $-OCF_3$, $-OCH_3$, or $-OCH_2CH_3$.

[00198] Embodiment 21. The compound of any one of embodiments 1-11, 14, or 20, or a pharmaceutically acceptable salt or solvate thereof, wherein B-AR comprises a head group and an optional core, wherein the head group is selected from:

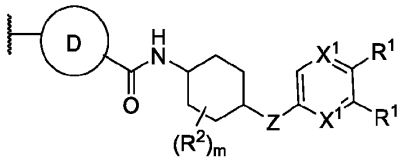


[00199] Embodiment 22. The compound of any one of embodiments 1-11 or 14, or a pharmaceutically acceptable salt or solvate thereof, wherein B-AR comprises a head group and an optional core, wherein the head group is selected from:



[00200] Embodiment 23. The compound of any one of embodiments 1-11 or 14-20, or a pharmaceutically acceptable salt or solvate thereof, wherein B-AR has the structure of Formula (IIa), or a pharmaceutically

acceptable salt or solvate thereof:



Formula (IIa)

wherein:

each X^1 is independently -CR^1- or -N-;

Z is -O- or -NR^5-;

each R^1 is independently hydrogen, F, Cl, Br, I, -CH_3, -CH_2CH_3, -CH_2F, -CHF_2, -CF_3, -CH_2CH_2F, -CH_2CHF_2, -CH_2CF_3, -OH, -OCF_3, -OCH_3, -OCH_2CH_3, -CN, -C(=O)NH_2 or -C(=O)$NH(CH_3)$;

each R^2 is C_1-C_6alkyl;

ring D that is a 5-, 6-, 8-, 9- or 10-membered aryl or a 5-, 6-, 8-, 9- or 10-membered heteroaryl that is optionally substituted with s R^3;

each R^3 is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, -CN, -OH, -OR^4, or -$N(R^5)_2$;

m is 0, 1, 2, 3, or 4;

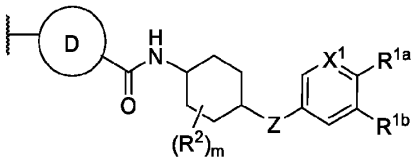
s is 1, 2, or 3.

[00201] Embodiment 24. The compound of embodiment 23, or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutically acceptable salt or solvate thereof:

one X^1 is -CR^1- and the other X^1 is -CR^1- or -N-;

each R^2 is -CH_3.

[00202] Embodiment 25. The compound of any one of embodiments 1-11 or 14-20, or a pharmaceutically acceptable salt or solvate thereof, wherein B-AR has the structure of Formula (IIIa), or a pharmaceutically acceptable salt or solvate thereof:



Formula (IIIa)

wherein:

X^1 is -CR^1- or -N-;

Z is -O- or -NR^5-;

R^{1a} is -CN, -NO_2, -C(=O)R^5, -C(=O)OR^5, or -C(=O)$N(R^5)_2$;

R^{1b} is hydrogen, halogen, C_1-C_4alkyl, C_1-C_4fluoroalkyl, -CN, -OH, or -OR^4;

R^1 is hydrogen, halogen, C_1-C_4alkyl, C_1-C_4fluoroalkyl, -CN, -OH, or -OR^4;

each R^2 is $-CH_3$;

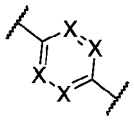
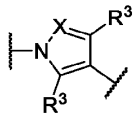
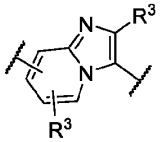
ring D that is a 5-, 6-, 8-, 9- or 10-membered aryl or a 5-, 6-, 8-, 9- or 10-membered heteroaryl that is optionally substituted with s R^3;

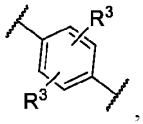
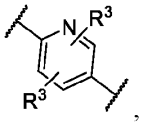
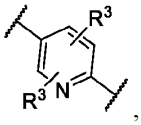
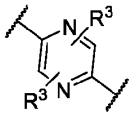
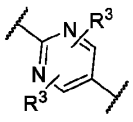
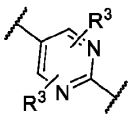
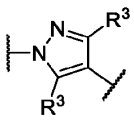
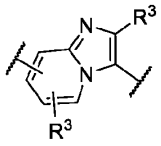
each R^3 is independently hydrogen, halogen, substituted or unsubstituted C_1-C_4alkyl, C_1-C_4fluoroalkyl, -CN, -OH, $-OR^4$, or $-N(R^5)_2$;

each R^4 is independently C_1-C_4alkyl, or C_1-C_4fluoroalkyl;

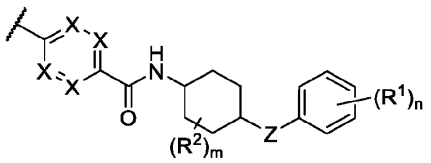
each R^5 is independently hydrogen, C_1-C_4alkyl, or C_1-C_4fluoroalkyl.

[00203] Embodiment 26. The compound of any one of embodiments 23-25, or a pharmaceutically acceptable salt or solvate thereof, wherein ring D is phenyl, naphthyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, triazinyl, pyrrolyl, thiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, imidazolyl, pyrazolyl, isothiazolyl, triazolyl, and tetrazolyl, wherein each ring D is optionally substituted with s R^3.

[00204] Embodiment 27. The compound of any one of embodiments 23-25, or a pharmaceutically acceptable salt or solvate thereof, wherein ring D is  ,  , or  ; and each X is independently $-CR^3$- or -N-.

[00205] Embodiment 28. The compound of any one of embodiments 23-25, or a pharmaceutically acceptable salt or solvate thereof, wherein ring D is  ,  ,  ,  ,  ,  ,  , or  .

[00206] Embodiment 29. The compound of any one of embodiments 1-11 or 14-20, or a pharmaceutically acceptable salt or solvate thereof, wherein B-AR has the structure of Formula (IVa), or a pharmaceutically acceptable salt or solvate thereof:



Formula (IVa)

wherein:

each X is independently $-CR^3$- or -N-;

Z is -O- or $-NR^5$-;

n is 2 and one R^1 is halogen, $-CH_3$, $-OCH_3$, or $-CF_3$, and the other R^1 is -CN;

each R^2 is $-CH_3$;

each R^3 is independently hydrogen, halogen, substituted or unsubstituted C_1-C_4alkyl, C_1-C_4fluoroalkyl, -CN, -OH, $-OR^4$, or $-N(R^5)_2$;

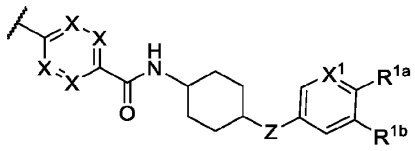
each R^4 is independently C_1-C_4alkyl, or C_1-C_4fluoroalkyl;

each R^5 is independently hydrogen, C_1-C_4alkyl, or C_1-C_4fluoroalkyl.

[00207] Embodiment 30. The compound of embodiment 20, or a pharmaceutically acceptable salt or solvate thereof, wherein:

one R^1 is -Cl, $-CH_3$, $-OCH_3$, or $-CF_3$, and the other R^1 is -CN.

[00208] Embodiment 31. The compound of any one of embodiments 1-11 or 14-20, or a pharmaceutically acceptable salt or solvate thereof, wherein B-AR has the structure of Formula (Va), or a pharmaceutically acceptable salt or solvate thereof:



Formula (Va)

wherein:

each X is independently $-CR^3-$ or -N-;

Z is -O- or $-NR^5-$;

X^1 is $-CR^1-$ or -N-;

R^{1a} is -CN;

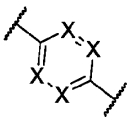
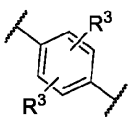
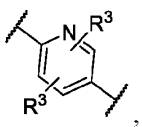
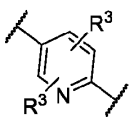
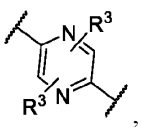
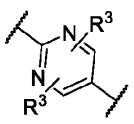
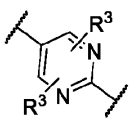
R^{1b} is hydrogen, F, Cl, Br, I, $-CH_3$, $-CH_2CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, -OH, $-OCF_3$, $-OCH_3$, or -CN;

R^1 is hydrogen, F, Cl, Br, I, $-CH_3$, $-CH_2CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2CF_3$, -OH, $-OCF_3$, $-OCH_3$, $-OCH_2CH_3$, or $-OCH_2CF_3$;

each R^3 is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, -CN, -OH, $-OR^4$, or $-N(R^5)_2$;

each R^4 is independently substituted or unsubstituted C_1-C_6alkyl, or C_1-C_6fluoroalkyl;

each R^5 is independently hydrogen, substituted or unsubstituted C_1-C_6alkyl, C_1-C_6fluoroalkyl.

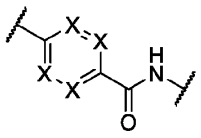
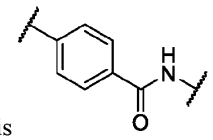
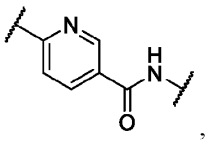
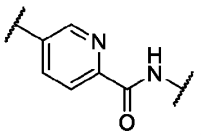
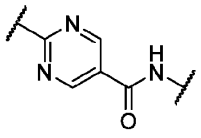
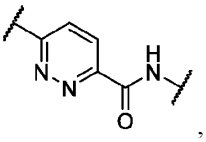
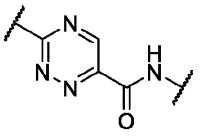
[00209] Embodiment 32. The compound of any one of embodiments 29-31, or a pharmaceutically acceptable salt or solvate thereof, wherein  is  ,  ,  ,  ,  , or  .

[00210] Embodiment 33. The compound of any one of embodiments 1-32, or a pharmaceutically

acceptable salt or solvate thereof, wherein:

each R^3 is independently hydrogen, F, Cl, Br, I, $-CH_3$, $-CH_2CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2CH_2F$, $-CH_2CHF_2$, $-CH_2CF_3$, -OH, $-OCF_3$, $-OCH_3$, $-OCH_2CH_3$, -CN, $-C(=O)NH_2$, or $-C(=O)NH(CH_3)$.

[00211] Embodiment 34. The compound of any one of embodiments 29-33, or a pharmaceutically acceptable salt or solvate thereof, wherein:


is

,

,

,

,

, or

.

[00212] Embodiment 35. The compound of any one of embodiments 1-11 or 14, or a pharmaceutically acceptable salt or solvate thereof, wherein the head group and core of B-AR is:

N-(4-(3-fluoro-4-cyanophenoxy)cyclohexyl)acetamide-*;

N-(4-(3-chloro-4-cyanophenoxy)cyclohexyl)acetamide-*;

N-(4-(3-methoxy-4-cyanophenoxy)cyclohexyl)acetamide-*;

N-(4-(3-methyl-4-cyanophenoxy)cyclohexyl)acetamide-*;

N-(4-(3-trifluroromethyl-4-cyanophenoxy)cyclohexyl)acetamide-*;

N-(4-(3-trifluroromethoxy-4-cyanophenoxy)cyclohexyl)acetamide-*;

N-(4-((5- fluoro-6-cyanopyridin-3-yl)oxy)cyclohexyl)acetamide-*;

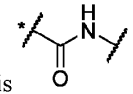
N-(4-((5-chloro-6-cyanopyridin-3-yl)oxy)cyclohexyl)acetamide-*;

N-(4-((5-methoxy -6-cyanopyridin-3-yl)oxy)cyclohexyl)acetamide-*;

N-(4-((5-methyl -6-cyanopyridin-3-yl)oxy)cyclohexyl)acetamide-*;

N-(4-((5-trifluroromethyl -6-cyanopyridin-3-yl)oxy)cyclohexyl)acetamide-*; or

N-(4-((5-trifluroromethoxy-6-cyanopyridin-3-yl)oxy)cyclohexyl)-2,2,4,4-tetramethylcyclobutyl)acetamide-*;

wherein acetamide-* is 
.

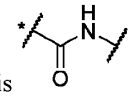
[00213] Embodiment 36. The compound of any one of embodiments 1-11 or 14, or a pharmaceutically acceptable salt or solvate thereof, wherein the head group and core of B-AR is:

N-(4-(3-chloro-4-cyanophenoxy)cyclohexyl)acetamide-*;

N-(4-(3-methoxy-4-cyanophenoxy)cyclohexyl)acetamide-*;

N-(4-(3-methyl-4-cyanophenoxy)cyclohexyl)acetamide-*; or

N-(4-(3-trifluroromethyl-4-cyanophenoxy)cyclohexyl)acetamide-*;

wherein acetamide-* is  .

[00214] Embodiment 37. The compound of embodiment 35 or 36, or a pharmaceutically acceptable salt or solvate thereof, wherein B-AR further comprises a tail moiety that is covalently attached to position (*), wherein the tail moiety is a ring D that is phenyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, triazolyl, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, indolyl, isoindolyl, indolizinyl, benzimidazolyl, napthyl, quinolyl, isoquinolyl, quinoxalinyl, quinazolinyl, indazolyl, or benzotriazolyl; wherein ring D is optionally substituted with s R^3;

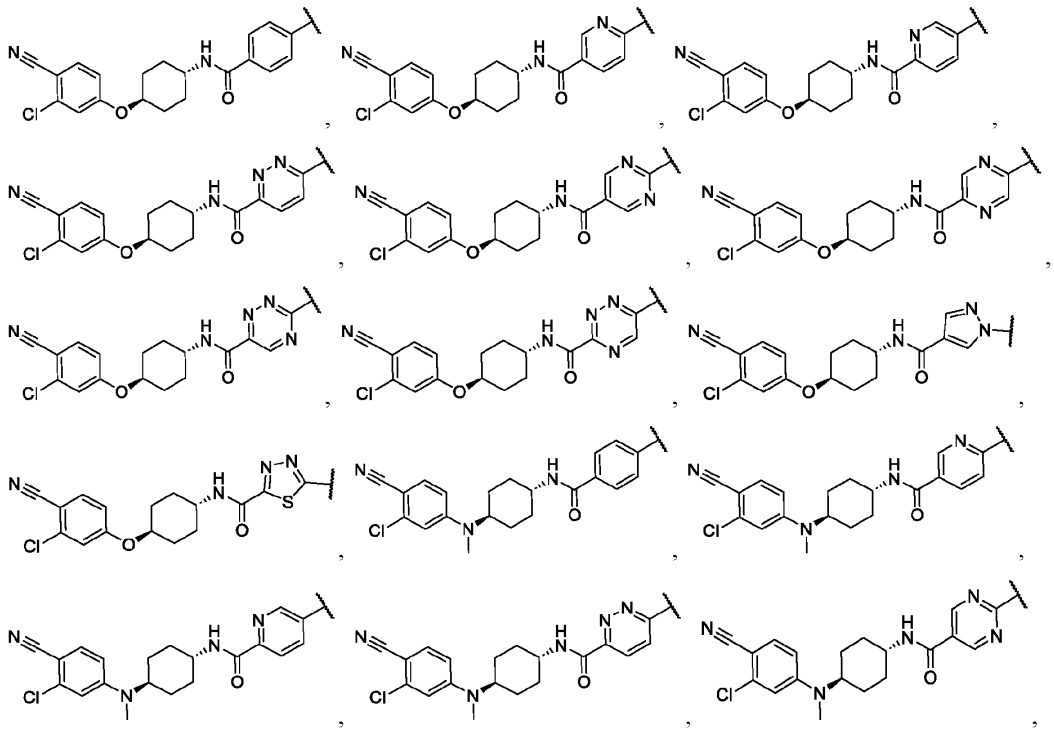
s is 1, 2, or 3;

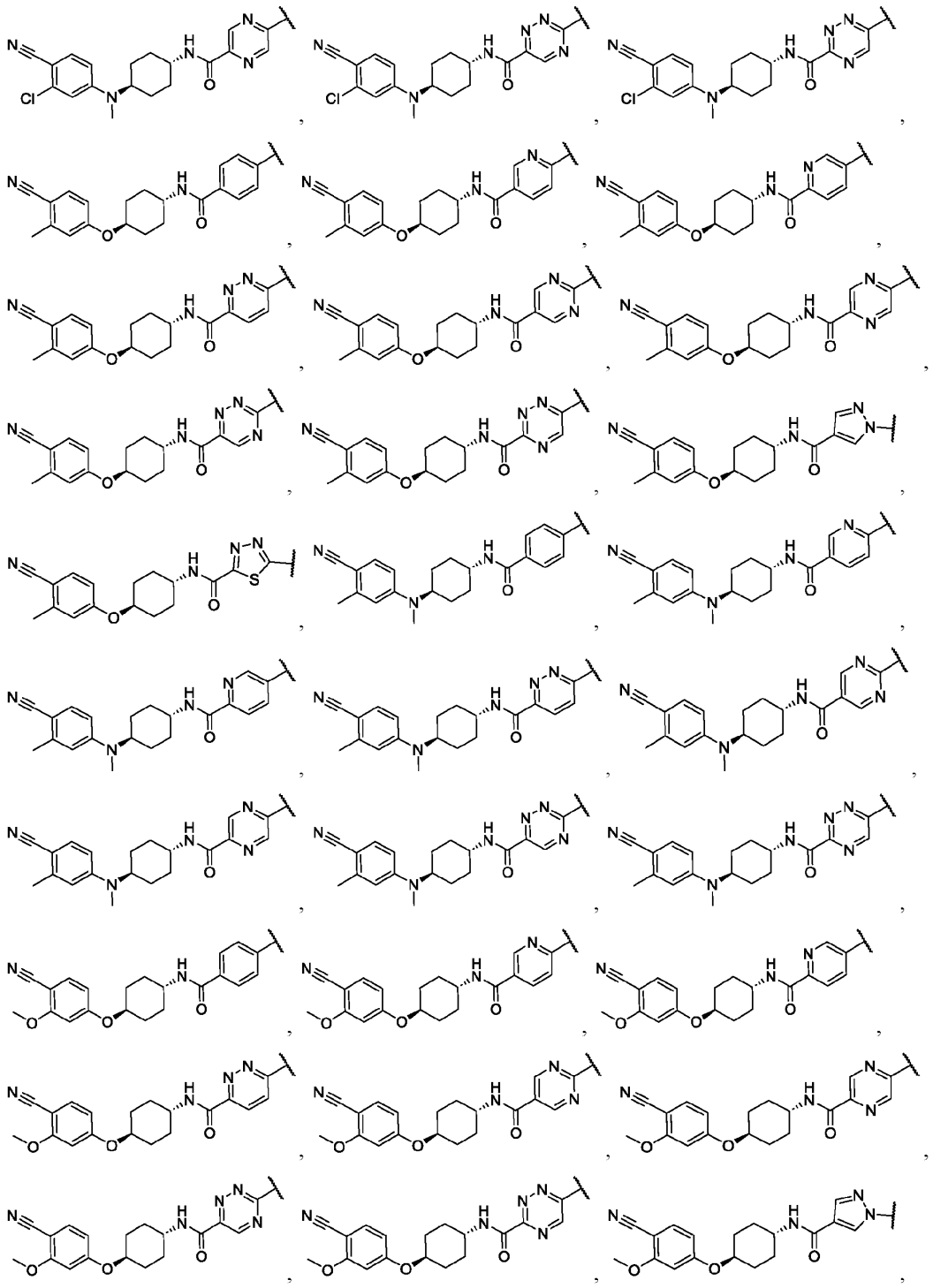
each R^3 is independently hydrogen, F, Cl, Br, I, $-CH_3$, $-CH_2CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2CH_2F$, $-CH_2CHF_2$, $-CH_2CF_3$, -OH, $-OCF_3$, $-OCH_3$, $-OCH_2CH_3$, -CN, $-C(=O)NH_2$, or $-C(=O)NH(CH_3)$.

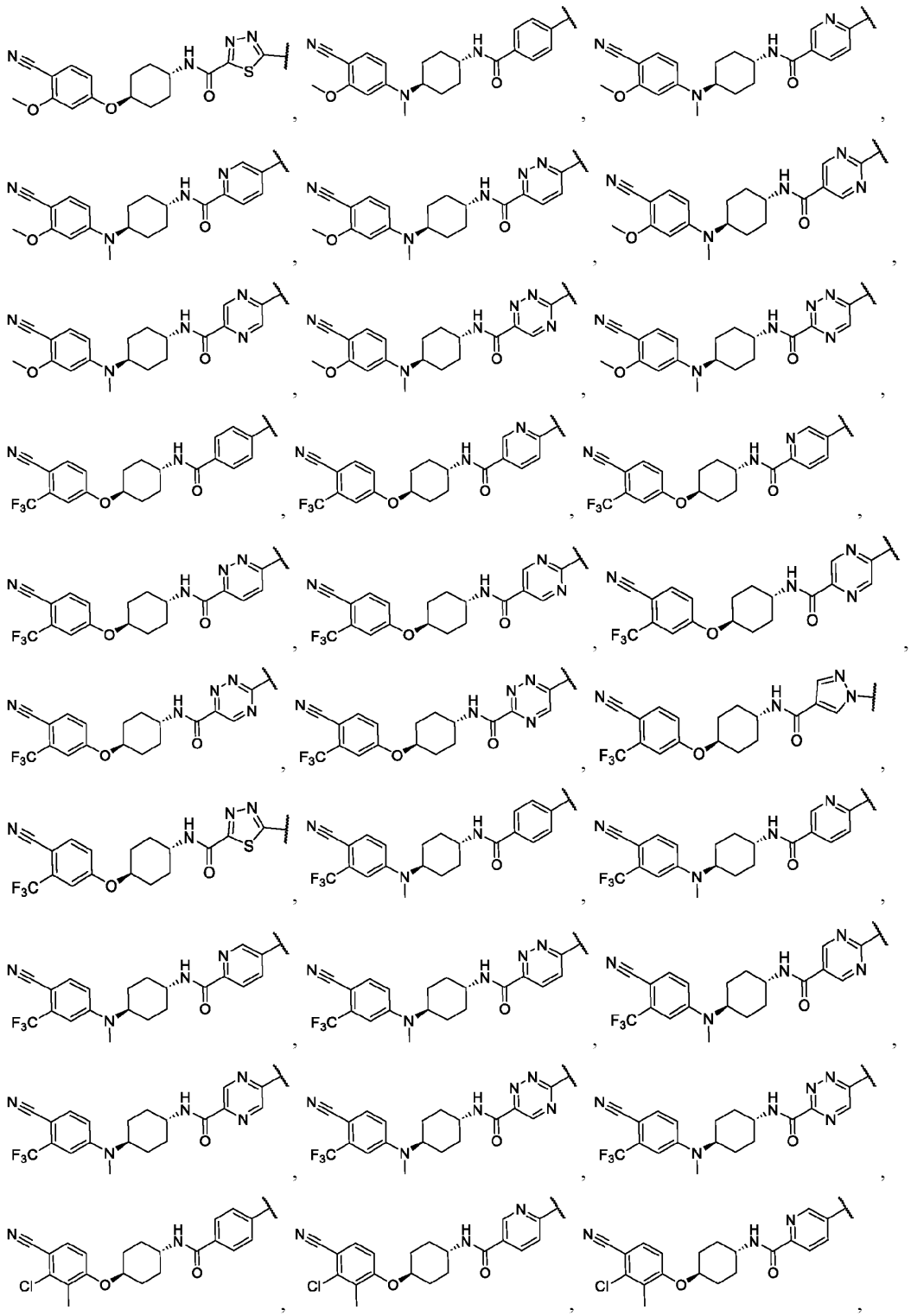
[00215] Embodiment 38. The compound of embodiment 35 or 36, or a pharmaceutically acceptable salt or solvate thereof, wherein ring D is phenyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, or triazinyl; wherein ring D is optionally substituted with s R^3; s is 1, 2, or 3;

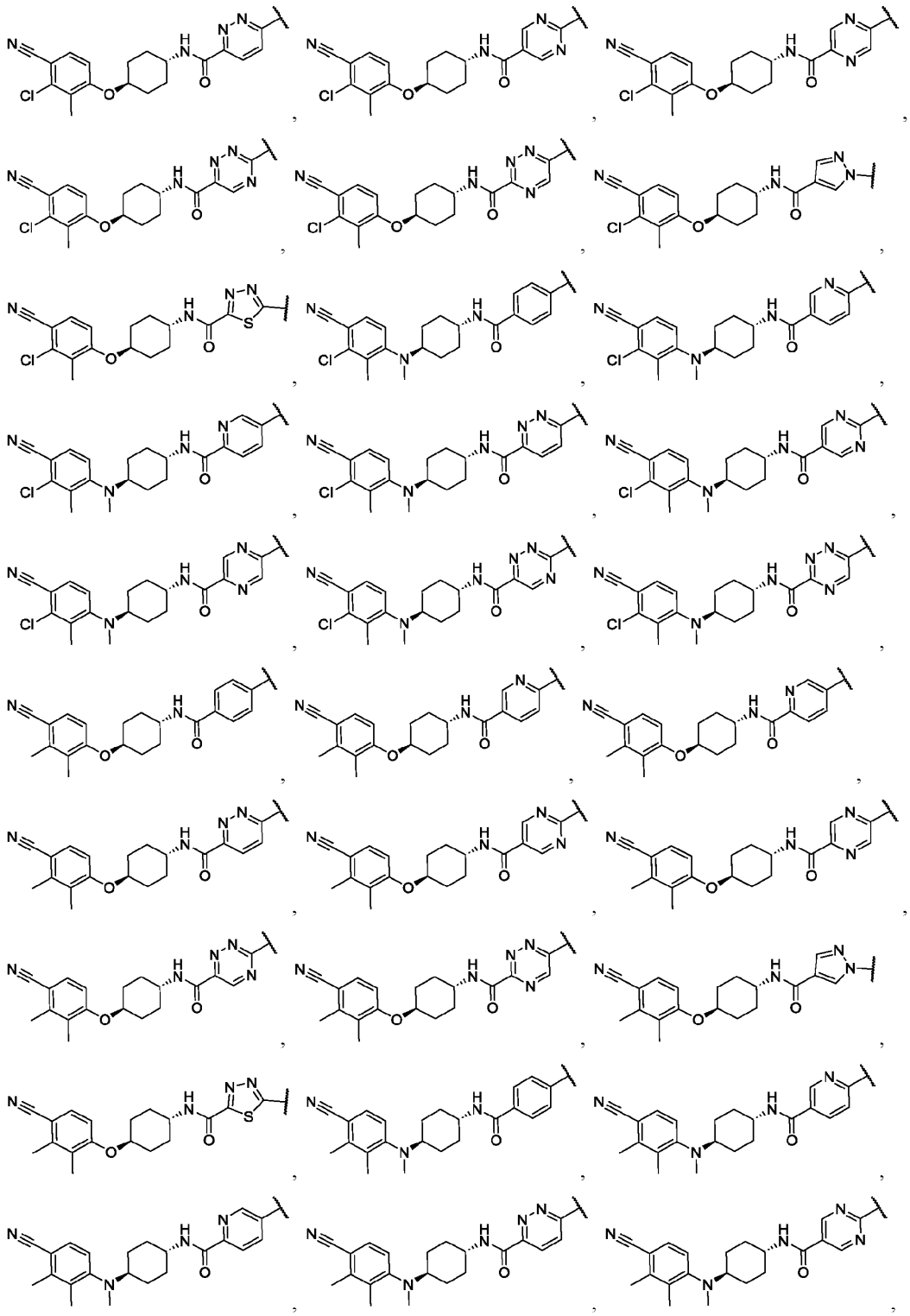
each R^3 is independently hydrogen, F, Cl, Br, I, $-CH_3$, $-CH_2CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2CH_2F$, $-CH_2CHF_2$, $-CH_2CF_3$, -OH, $-OCF_3$, $-OCH_3$, $-OCH_2CH_3$, or -CN.

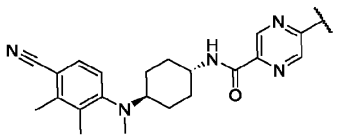
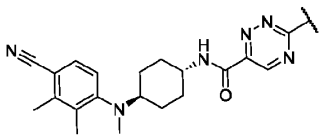
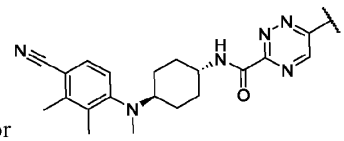
[00216] Embodiment 39. The compound of embodiment 1-11 or 14, or a pharmaceutically acceptable salt or solvate thereof, wherein B-AR has one of the following structures:









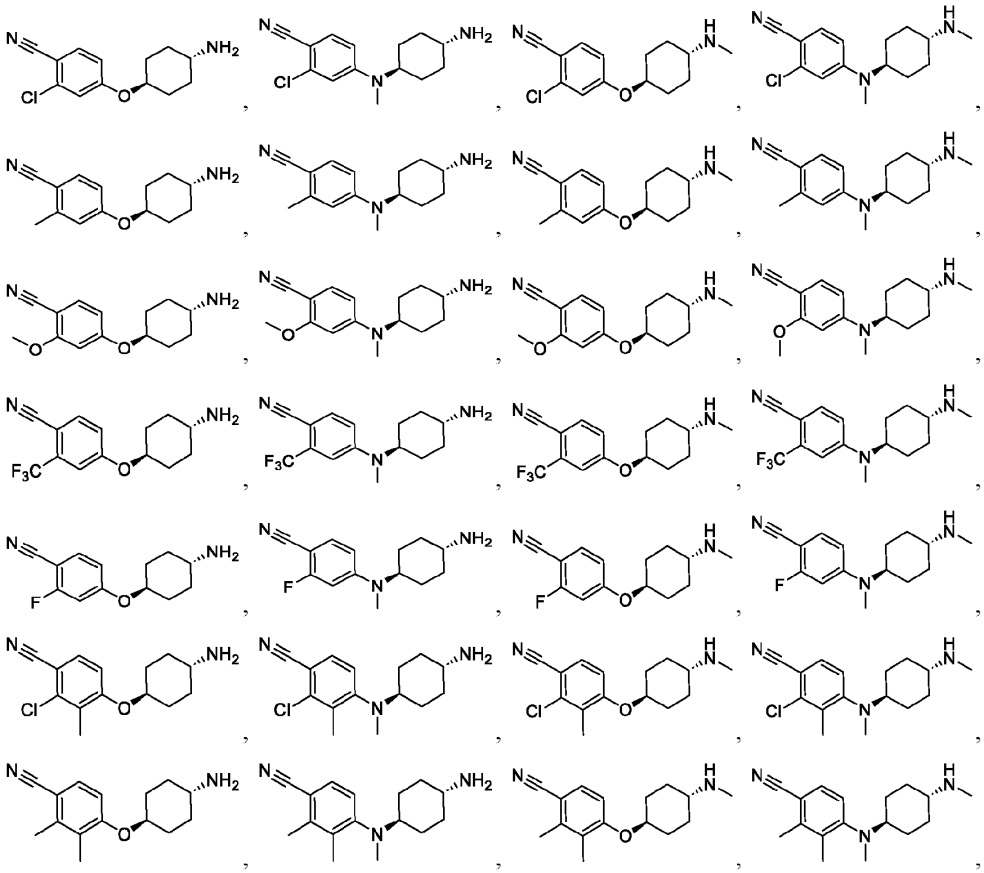
[00217] Embodiment 39a. The compound of embodiment 39, or a pharmaceutically acceptable salt or solvate thereof, wherein B-AR has one of the following structures of embodiment 39, wherein is halide. is halide.

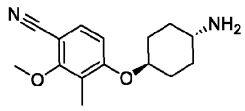
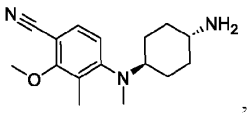
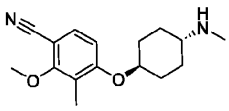
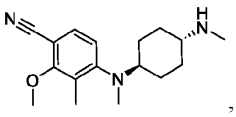
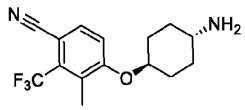
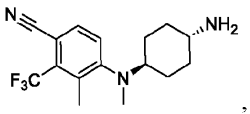
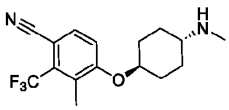
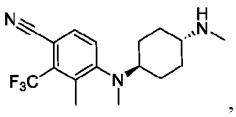
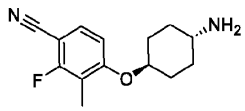
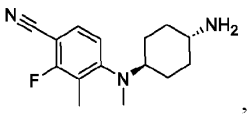
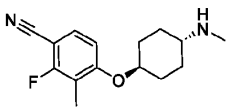
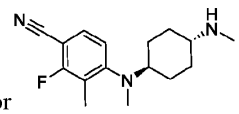
[00218] Embodiment 39b. The compound of embodiment 39a, or a pharmaceutically acceptable salt or solvate thereof, wherein B-AR has one of the following structures of embodiment 39a, wherein is Cl, Br or I.

[00219] Embodiment 39c. The compound of embodiment 39a, or a pharmaceutically acceptable salt or solvate thereof, wherein B-AR has one of the following structures of embodiment 39a, wherein is Cl.

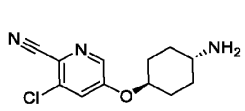
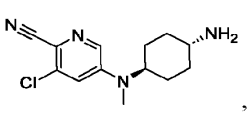
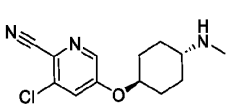
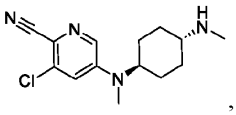
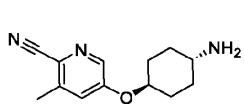
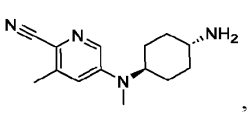
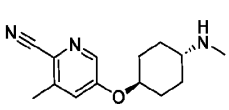
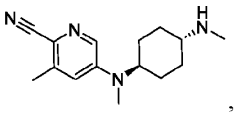
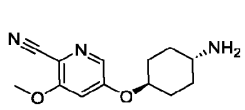
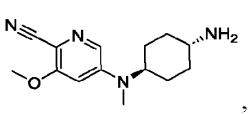
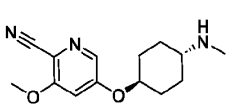
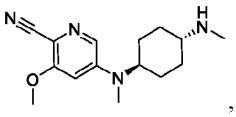
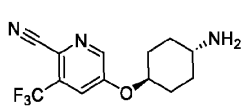
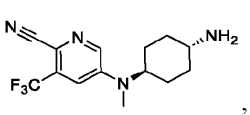
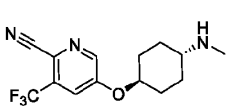
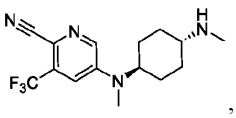
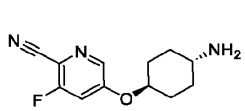
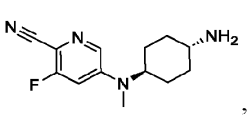
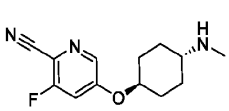
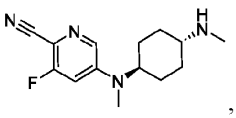
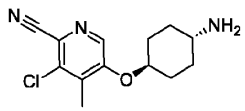
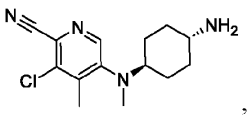
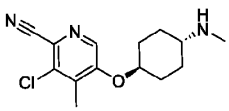
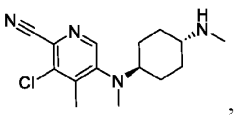
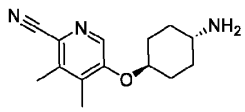
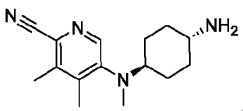
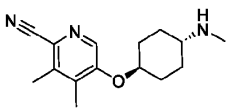
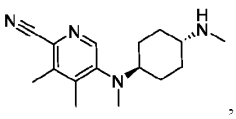
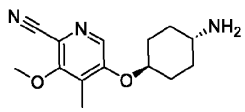
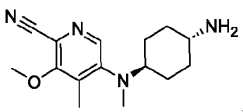
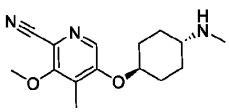
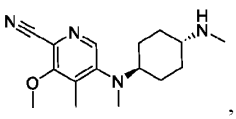
[00220] Embodiment 39d. The compound of embodiment 39a, or a pharmaceutically acceptable salt or solvate thereof, wherein B-AR has one of the following structures of embodiment 39a, wherein is H.

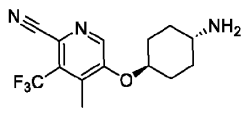
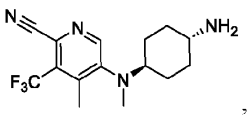
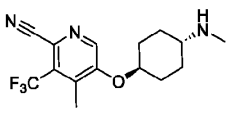
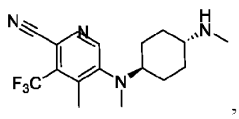
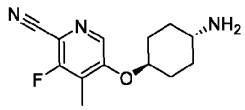
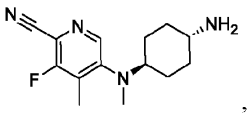
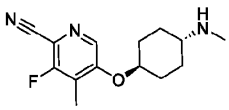
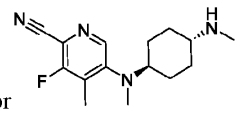
[00221] Embodiment 39e. A compound, or a pharmaceutically acceptable salt or solvate thereof, that has one of the following structures:















, or .

[00222] Embodiment 39f. A compound, or a pharmaceutically acceptable salt or solvate thereof, that has one of the following structures:


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, or

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[00223] Embodiment 40. The compound of any one of embodiments 14-39, or a pharmaceutically acceptable salt or solvate thereof, wherein SB-CBP/p300 binds in the acetyl-lysine (KAc) binding site of the bromodomain of CBP/p300.

[00224] Embodiment 41. The compound of any one of embodiments 14-39, or a pharmaceutically acceptable salt or solvate thereof, wherein SB-CBP/p300 comprises an acetyl-lysine mimetic moiety that binds in the acetyl-lysine (KAc) binding site of the bromodomain of CBP/p300.

[00225] Embodiment 42. The compound of embodiment 41, or a pharmaceutically acceptable salt or solvate thereof, wherein L is covalently attached at a position of a) that is solvent exposed when a) binds the KAc binding site of the bromodomain of CBP/p300.

[00226] Embodiment 43. The compound of embodiment 41, or a pharmaceutically acceptable salt or solvate thereof, wherein the moiety comprising an acetyl-lysine mimetic makes or mimics a hydrogen bond interaction to Asn1168 in the Asn-binding pocket of the bromodomain of CBP, or makes or mimics a hydrogen bond interaction to Asn1132 in the Asn-binding pocket of the bromodomain of p300; and the head group of B-AR forms hydrogen bonds with the side chains of Gln 711 and Arg 752 of the LBD of AR.

[00227] Embodiment 44. The compound of any one of embodiments 14-43, or a pharmaceutically acceptable salt or solvate thereof, wherein SB-CBP/p300 further comprises a moiety that interacts with Arg1173 in the bromodomain of CBP or Asn1137 in the bromodomain of p300.

[00228] Embodiment 45. The compound of any one of embodiments 14-44, or a pharmaceutically acceptable salt or solvate thereof, wherein SB-CBP/p300 further comprises:

1) a moiety that occupies the lipophilic shelf (LPF) region of the bromodomain of CBP/p300; or

2) a moiety that occupies the BC Loop region of the bromodomain of CBP/p300; or

3) both 1) and 2).

[00229] Embodiment 46. The compound of embodiment 41-45, or a pharmaceutically acceptable salt or solvate thereof, wherein the moiety comprising an acetyl-lysine mimetic comprises a moiety selected from pyrrolidonyl, phenyl, pyridinyl, pyridinonyl, triazolyl, pyrrolyl, isoxazolyl, pyrazolyl, quinolinyl, tetrahydroquinolinyl, isoquinolinyl, tetrahydroisoquinolinyl, quinazolonyl, quinazolinyl, dihydroquinazolinonyl, imidazo[4,5-c]quinolinyl fused to a dimethylisoxazolyl, triazolophthalazinyl, indolizinyl, benzoimidazolyl, isoxazole-indolizinyl, thienodiazepine-indolizinyl, benzodiazepine-indolizinyl, 5-isoxazolylbenzimidazolyl, 6-isoxazolylbenzimidazolyl, 7-isoxazolo-quinolinyl, diazobenzyl, triazolophthalazinyl, isoxazoloquinolinyl, 2-thiazolidinonyl, triazolopyrimidinyl, thienodiazepinyl, benzodiazepinyl, benzotriazepinyl, triazolobenzodiazepinyl, triazolothienodiazepinyl,

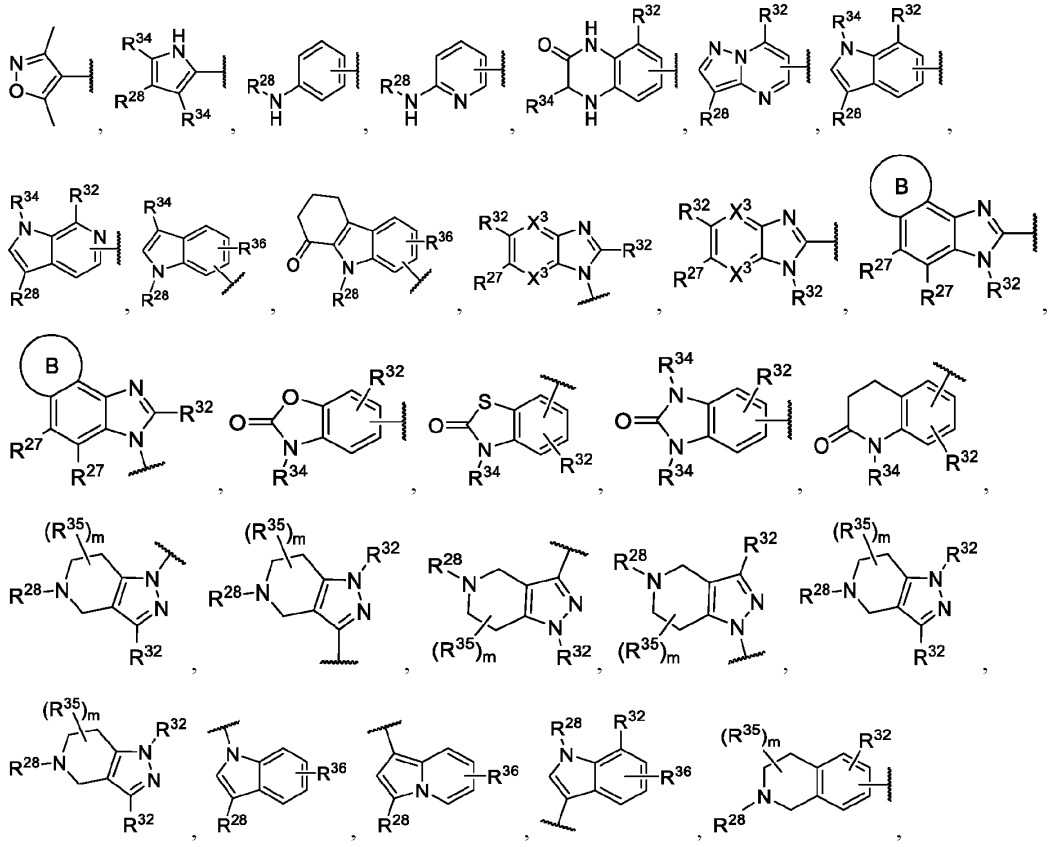
triazolothienodiazepinyl, and isoxazole-azepinyl.

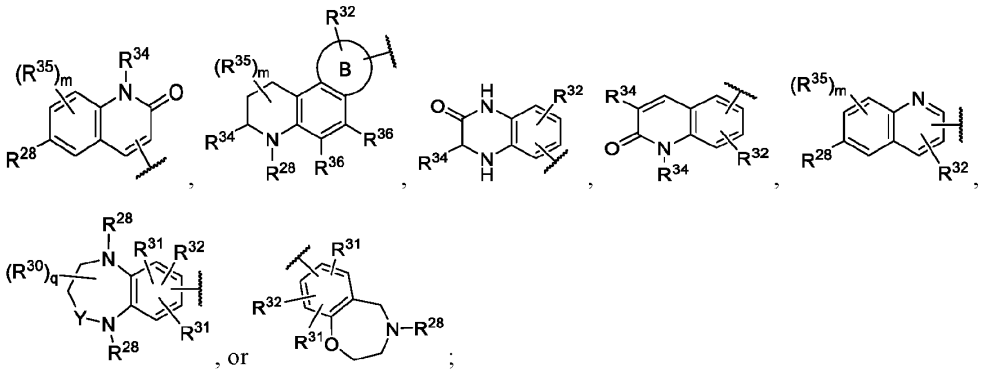
[00230] Embodiment 47. The compound of embodiment 45 or 46, or a pharmaceutically acceptable salt or solvate thereof, wherein L is covalently attached to SB-CBP/p300 on:

- the acetyl-lysine mimetic moiety; or
- the moiety that occupies the lipophilic shelf (LPF) region of the bromodomain of CBP/p300, if present; or
- the moiety that occupies the BC Loop region of the bromodomain of CBP/p300, if present;

wherein L is covalently attached to SB-p300/CBP at a position that does not interfere with the binding of the acetyl-lysine mimetic moiety in the acetylated lysine (KAc) binding site of CBP/p300.

[00231] Embodiment 48. The compound of any one of embodiments 1-47, or a pharmaceutically acceptable salt or solvate thereof, wherein the moiety comprising an acetyl-lysine mimetic comprises a moiety selected from:





, or ;

each R^{32} is independently an optional moiety that occupies the lipophilic shelf (LPF) region of the bromodomain of CBP/p300;

or each R^{32} is independently an optional moiety that occupies the BC Loop region of the bromodomain of CBP/p300;

⊣ is the point of attachment to L that covalently connects SB-CBP/p300 to B-AR;

or R^{32} comprises ⊣ and L that covalently connects SB-CBP/p300 to B-AR is attached to R^{32};

each R^{28} is independently hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, -C(=O)R^b, or -C(=O)N(R^b)$_2$;

each R^{34} is independently hydrogen or substituted or unsubstituted C_1-C_6alkyl;

each R^{35} is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, or substituted or unsubstituted 3- to 8-membered heterocycloalkyl, -CN, -OH, -OR^a, or -N(R^b)$_2$;

m is 0, 1, 2, 3, or 4;

each R^{27} is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -CN, -NO_2, -OH, -OR^a, OC(=O)R^a, -OC(=O)N(R^b)$_2$, -OC(=O)OR^a, -OC(=O)N(R^b)$_2$, -SR^b, -S(=O)R^a, -S(=O)$_2R^a$, -S(=O)$_2$OR^b, -S(=O)$_2$N(R^b)$_2$, -N(R^b)$_2$, -NR^bC(=O)N(R^b)$_2$, -NR^bC(=O)R^a, -NR^bC(=O)OR^a, -NR^bS(=O)$_2R^a$, -C(=O)R^b, -C(=O)OR^b, or -C(=O)N(R^b)$_2$;

Y is -C(R^{30})$_2$- or C(=O);

each X^3 is independently CR^{27} or N;

each R^{30} is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, -CN, -NO_2, -OH, -OR^a, OC(=O)R^a, -OC(=O)N(R^b)$_2$, -OC(=O)OR^a, -SR^b, -S(=O)R^a, -S(=O)$_2R^a$, -S(=O)$_2$OR^b, -S(=O)$_2$N(R^b)$_2$, -N(R^b)$_2$, -NR^bC(=O)N(R^b)$_2$, -NR^bC(=O)R^a, -NR^bC(=O)OR^a, -NR^bS(=O)$_2R^a$, -C(=O)R^b, -C(=O)OR^b, or

$-C(=O)N(R^b)_2$;

q is 0, 1, 2, 3, or 4;

each R^{31} is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, -CN, $-NO_2$, -OH, $-OR^a$, $OC(=O)R^a$, $-OC(=O)N(R^b)_2$, $-OC(=O)OR^a$, $-SR^b$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2OR^b$, $-S(=O)_2N(R^b)_2$, $-N(R^b)_2$, $-NR^bC(=O)NR^b$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^a$, $-NR^bS(=O)_2R^a$, $-C(=O)R^b$, $-C(=O)OR^b$, or $-C(=O)N(R^b)_2$;

each R^{36} is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, -CN, -OH, $-OR^a$, or $-N(R^b)_2$;

Ring B is a fused substituted or unsubstituted 5 or 6 membered heterocycloalkyl;

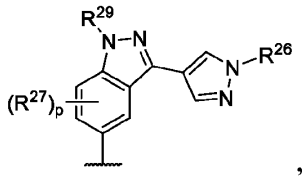
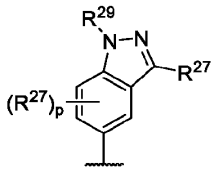
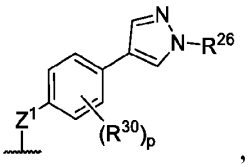
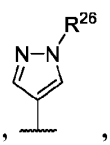
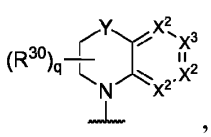
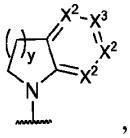
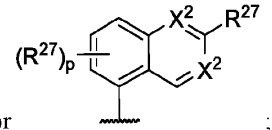
each R^a is independently substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted monocyclic 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted monocyclic heteroaryl;

each R^b is independently hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted monocyclic 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted monocyclic heteroaryl;

or two R^b on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle.

[00232] Embodiment 49. The compound of embodiment 45-48, or a pharmaceutically acceptable salt or solvate thereof, wherein the moiety that occupies the lipophilic shelf (LPF) region of the bromodomain of CBP/p300 is R^{32}, wherein:

R^{32} is hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_2-C_6alkenyl, substituted or unsubstituted C_2-C_6alkynyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{12}cycloalkyl, substituted or unsubstituted 3- to 12-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

or R^{32} is  ,  ,  ,  ,  ,  , or  ;

y is 1 or 2;

Z^1 is -NR^c-, -O-, or -S-;

R^c is hydrogen or substituted or unsubstituted C_1-C_6alkyl;

R^{26} is hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, or substituted or unsubstituted 3- to 8-membered heterocycloalkyl;

each X^2 is independently -CR^{30}- or -N-;

each X^3 is independently -CR^{27}- or -N-;

each R^{27} is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -CN, -NO_2, -OH, -OR^a, $OC(=O)R^a$, -$OC(=O)N(R^b)_2$, -$OC(=O)OR^a$, -$OC(=O)N(R^b)_2$, -SR^b, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2OR^b$, -$S(=O)_2N(R^b)_2$, -$N(R^b)_2$, -$NR^bC(=O)N(R^b)_2$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^a$, -$NR^bS(=O)_2R^a$, -$C(=O)R^b$, -$C(=O)OR^b$, or -$C(=O)N(R^b)_2$;

p is 0, 1, 2, or 3;

R^{28} is hydrogen or substituted or unsubstituted C_1-C_6alkyl;

R^{29} is hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, or substituted or unsubstituted 3- to 8-membered heterocycloalkyl;

Y is -$C(R^{30})_2$- or $N(R^{28})$-;

each R^{30} is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, -CN, -NO_2, -OH, -OR^a, $OC(=O)R^a$, -$OC(=O)N(R^b)_2$, -$OC(=O)OR^a$, -SR^b, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2OR^b$, -$S(=O)_2N(R^b)_2$, -$N(R^b)_2$, -$NR^bC(=O)N(R^b)_2$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^a$, -$NR^bS(=O)_2R^a$, -$C(=O)R^b$, -$C(=O)OR^b$, or -$C(=O)N(R^b)_2$;

q is 0, 1, 2, 3, or 4;

or R^{32} is -L-C;

L is substituted or unsubstituted C_1-C_6alkyl or substituted or unsubstituted C_1-C_6heteroalkyl;

C is substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

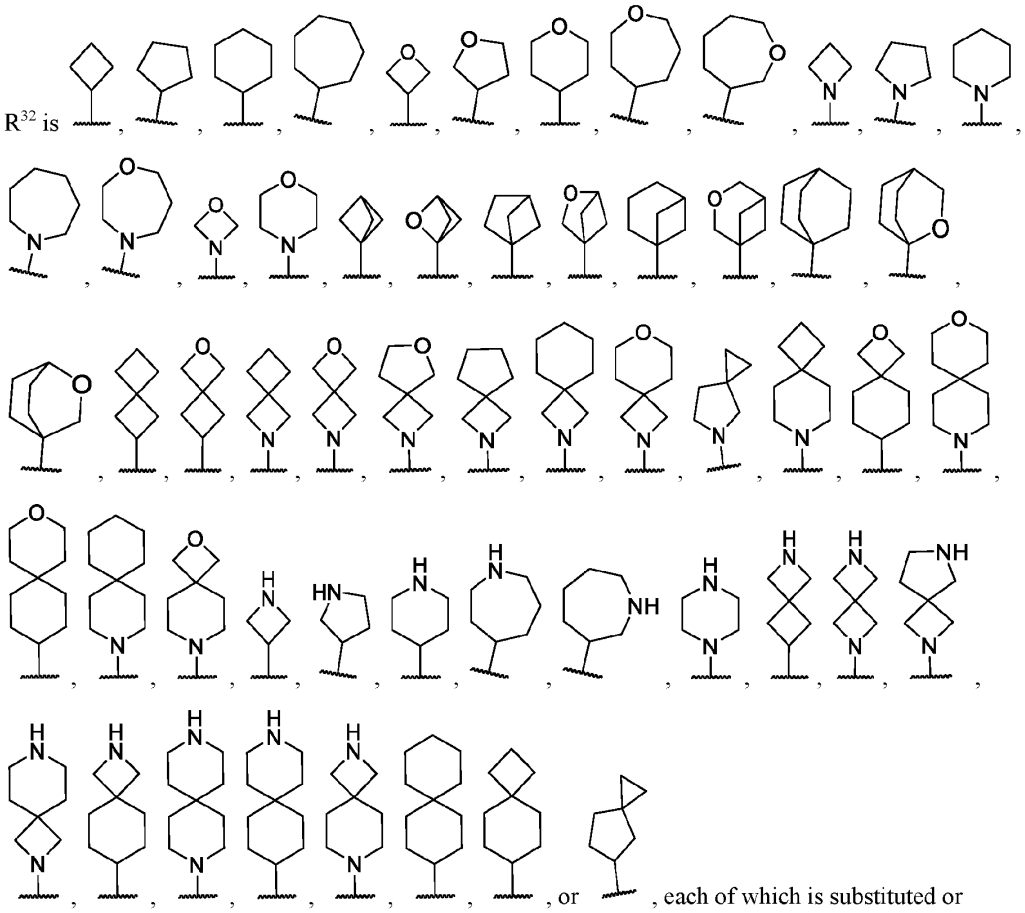
each R^a is independently substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted monocyclic 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted monocyclic heteroaryl;

each R^b is independently hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted monocyclic 3- to 8-membered heterocycloalkyl, substituted

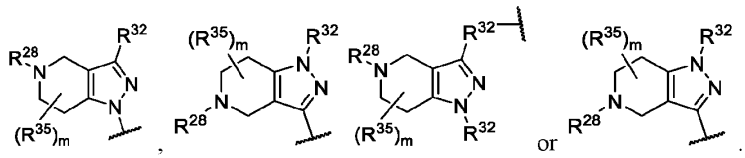
or unsubstituted aryl, or substituted or unsubstituted monocyclic heteroaryl;

or two R^b on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle.

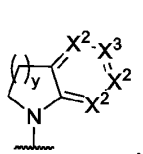
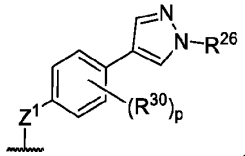
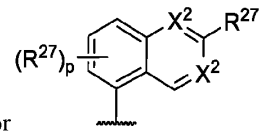
[00233] Embodiment 50. The compound of any one of embodiments 45-49, or a pharmaceutically acceptable salt or solvate thereof, wherein the moiety that occupies the BC Loop region of the bromodomain of CBP/p300 is R^{32}, wherein:

R^{32} is  , each of which is substituted or unsubstituted.

[00234] Embodiment 51. The compound of any one of embodiments 41-50, or a pharmaceutically acceptable salt or solvate thereof, wherein the moiety comprising an acetyl-lysine mimetic comprises



[00235] Embodiment 52. The compound of embodiment 51, or a pharmaceutically acceptable salt or solvate thereof, wherein:

R^{32} is  ,  , or  ;

R^{27} is hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -CN, -OH, or -OR^a; and

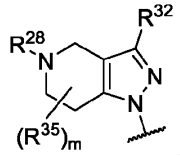
each R^{27} is independently hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, -CN, -OH, or -OR^a; and

each R^a is independently substituted or unsubstituted C_1-C_6alkyl.

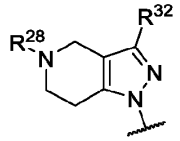
[00236] Embodiment 53. The compound of embodiment 52, or a pharmaceutically acceptable salt or solvate thereof, wherein:

each R^{27} is independently hydrogen, -CH_3, -CH_2CH_3, -F, -CHF_2, -CF_3, -CN, -OH, -OCH_3, cyclopropyl, cyclobutyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, phenyl, pyrazolyl, 1-methyl pyrazolyl, pyridinyl, or pyrimidinyl.

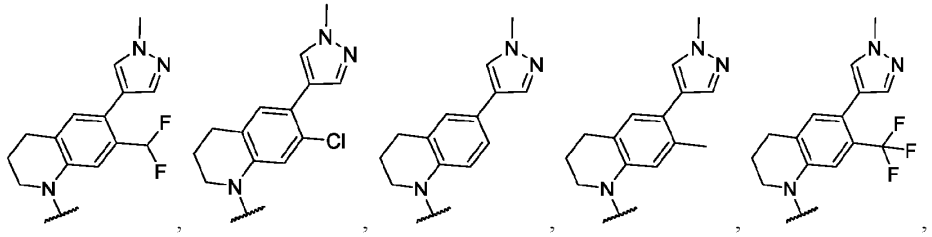
[00237] Embodiment 54. The compound of any one of embodiments 51-53, or a pharmaceutically acceptable salt or solvate thereof, wherein the moiety comprising an acetyl-lysine mimetic comprises

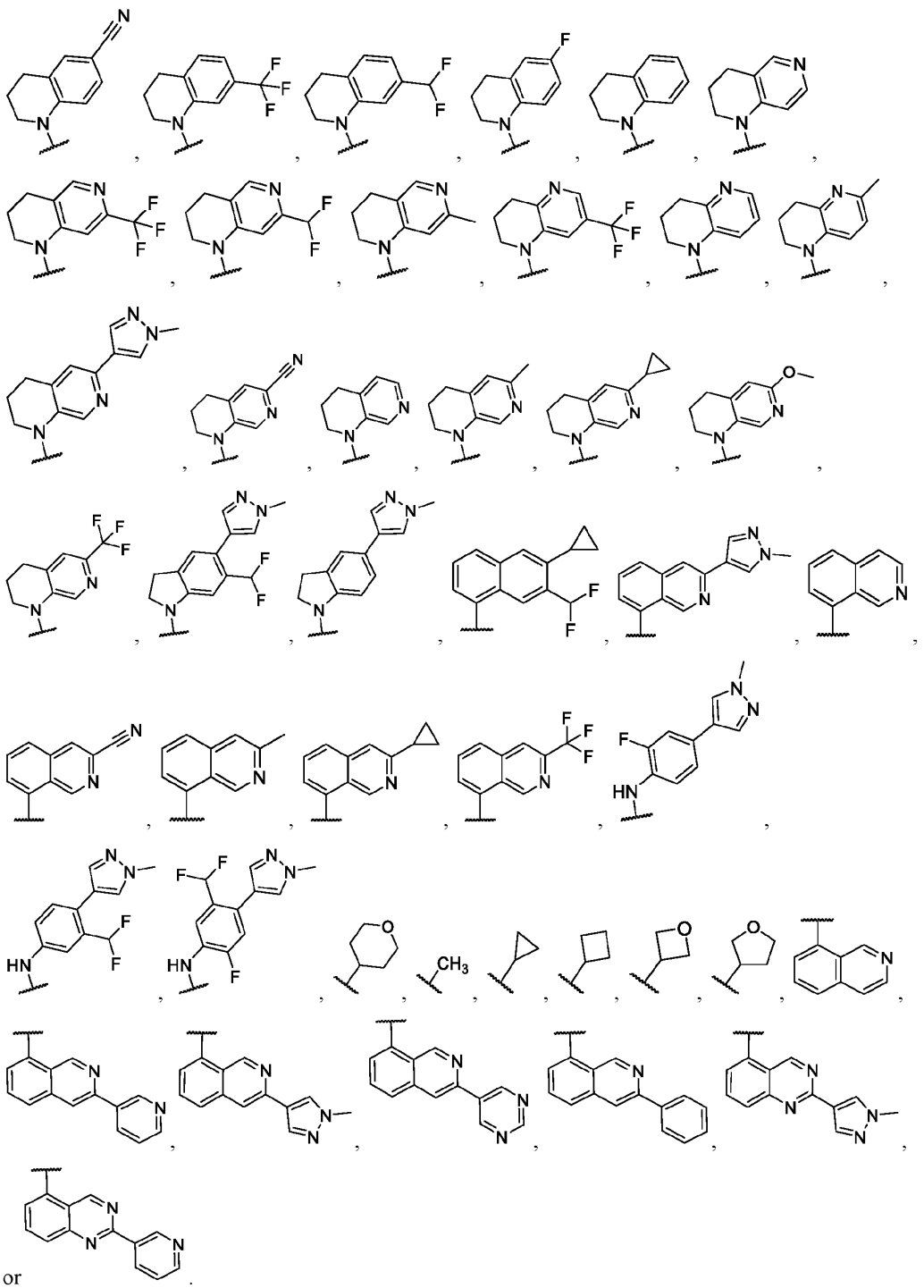


[00238] Embodiment 55. The compound of any one of embodiments 51-53, or a pharmaceutically acceptable salt or solvate thereof, wherein the moiety comprising an acetyl-lysine mimetic comprises



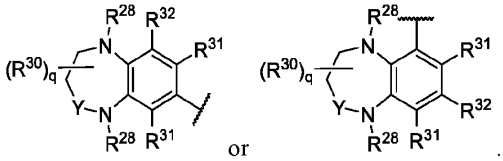
[00239] Embodiment 56. The compound of any one of embodiments 51-55, or a pharmaceutically acceptable salt or solvate thereof, wherein:

R^{32} is 

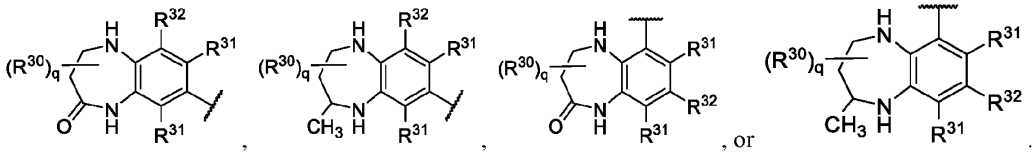


or .

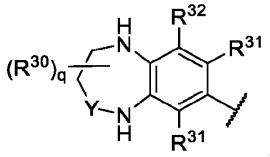
[00240] Embodiment 57. The compound of any one of embodiments 41-50, or a pharmaceutically acceptable salt or solvate thereof, wherein the moiety comprising an acetyl-lysine mimetic comprises

 or .

[00241] Embodiment 58. The compound of embodiment 57, or a pharmaceutically acceptable salt or solvate thereof, wherein the moiety comprising an acetyl-lysine mimetic comprises

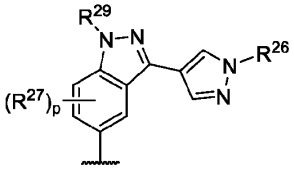
 , , , or .

[00242] Embodiment 59. The compound of embodiment 57, or a pharmaceutically acceptable salt or solvate thereof, wherein the moiety comprising an acetyl-lysine mimetic comprises

 ;

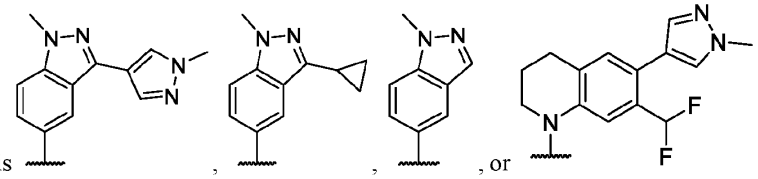
wherein:

each R^{28} is independently hydrogen or substituted or unsubstituted C_1-C_6alkyl;

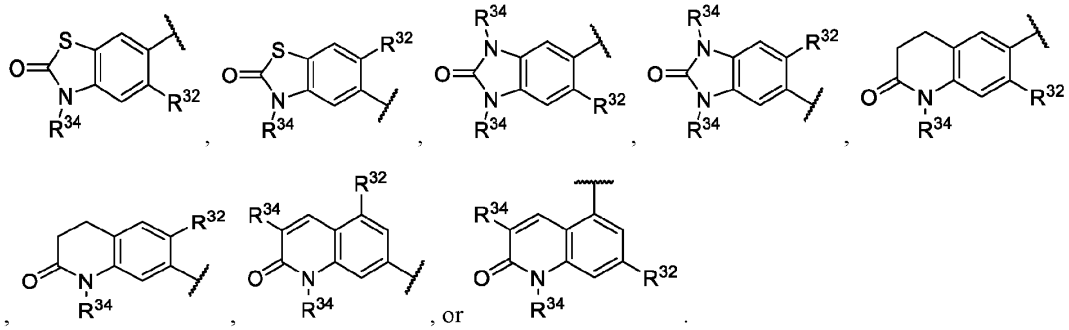
R^{32} is  ; and

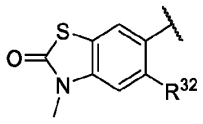
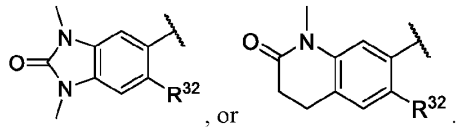
each R^{27} is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, -CN, -NO_2, -OH, -OR^a, $OC(=O)R^a$, -$OC(=O)N(R^b)_2$, -$OC(=O)OR^a$, -SR^b, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2OR^b$, -$S(=O)_2N(R^b)_2$, -$N(R^b)_2$, -$NR^bC(=O)N(R^b)_2$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^a$, -$NR^bS(=O)_2R^a$, -$C(=O)R^b$, -$C(=O)OR^b$, or -$C(=O)N(R^b)_2$.

[00243] Embodiment 60. The compound of any one of embodiments 57-59, or a pharmaceutically acceptable salt or solvate thereof, wherein:

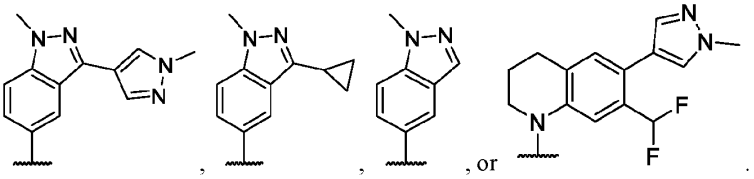
R^{32} is  .

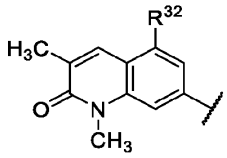
[00244] Embodiment 61. The compound of any one of embodiments 41-50, or a pharmaceutically acceptable salt or solvate thereof, wherein the moiety comprising an acetyl-lysine mimetic comprises



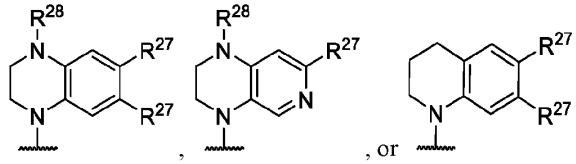
[00245] Embodiment 62. The compound of embodiment 61, or a pharmaceutically acceptable salt or solvate thereof, wherein the moiety comprising an acetyl-lysine mimetic comprises  ,  .

[00246] Embodiment 63. The compound of any one of embodiments 61-62, or a pharmaceutically acceptable salt or solvate thereof, wherein:

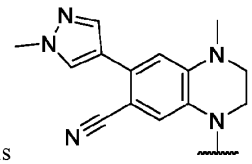
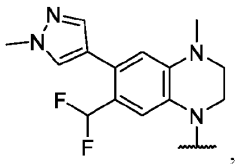
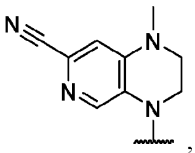
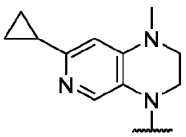
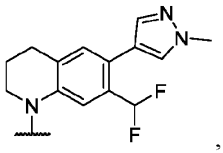
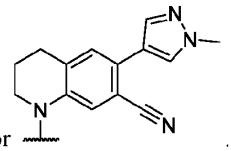
R^{32} is  .

[00247] Embodiment 64. The compound of embodiment 61, or a pharmaceutically acceptable salt or solvate thereof, wherein the moiety comprising an acetyl-lysine mimetic comprises:  .

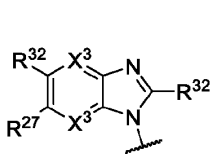
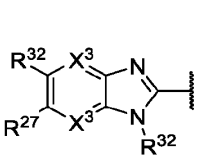
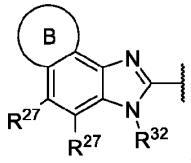
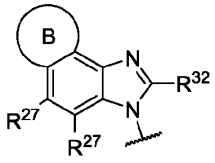
[00248] Embodiment 65. The compound of embodiment 61 or 64, or a pharmaceutically acceptable salt or solvate thereof, wherein:

R^{32} is  .

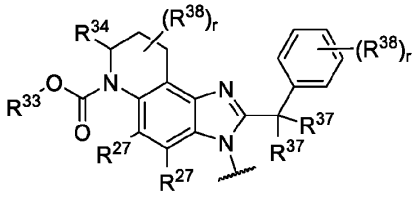
[00249] Embodiment 66. The compound of any one of embodiments 61, 62, 64, or 65, or a pharmaceutically acceptable salt or solvate thereof, wherein:

R^{32} is  ,  ,  ,  ,  , or  .

[00250] Embodiment 67. The compound of any one of embodiments 41-50, or a pharmaceutically acceptable salt or solvate thereof, wherein the moiety comprising an acetyl-lysine mimetic comprises

 ,  ,  , or  .

[00251] Embodiment 68. The compound of embodiment 67, or a pharmaceutically acceptable salt or solvate thereof, wherein the moiety comprising an acetyl-lysine mimetic comprises

 , wherein:

each R^{27} is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, -CN, -OH, -OR^a, or -$N(R^b)_2$;

R^{33} is hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, or substituted or unsubstituted C_1-C_6heteroalkyl;

R^{34} is hydrogen or substituted or unsubstituted C_1-C_6alkyl;

each R^{37} is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, -CN, -OH, -OR^a, or -$N(R^b)_2$;

each R^{38} is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted 3- to 8-membered heterocycloalkyl, -CN, -NO_2, -OH, -OR^a, -$OC(=O)R^a$, -$OC(=O)N(R^b)_2$, -$OC(=O)OR^a$, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2OR^b$, -$S(=O)_2N(R^b)_2$, -$N(R^b)_2$, -$NR^bC(=O)N(R^b)_2$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^a$, -$NR^bS(=O)_2R^a$, -$C(=O)R^b$, -$C(=O)OR^b$, or -$C(=O)N(R^b)_2$;

each R^a is independently substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-

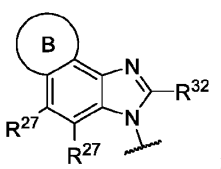
C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted monocyclic 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted monocyclic heteroaryl;

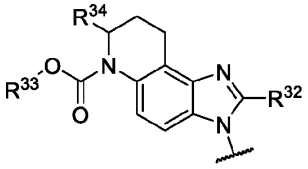
each R^b is independently hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted monocyclic 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted monocyclic heteroaryl;

or two R^b on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle;

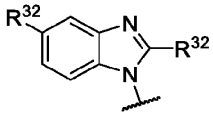
r is 0, 1, 2, 3, or 4;

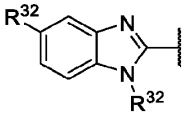
[00252] Embodiment 69. The compound of embodiment 67, or a pharmaceutically acceptable salt or solvate thereof, wherein:



is 

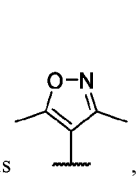
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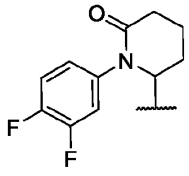
[00253] Embodiment 70. The compound of embodiment 67, or a pharmaceutically acceptable salt or solvate thereof, wherein the moiety comprising an acetyl-lysine mimetic comprises 

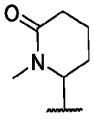
or 

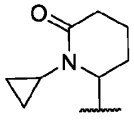
.

[00254] Embodiment 71. The compound of any one of embodiments 67-70, or a pharmaceutically acceptable salt or solvate thereof, wherein:

R^{32} is 

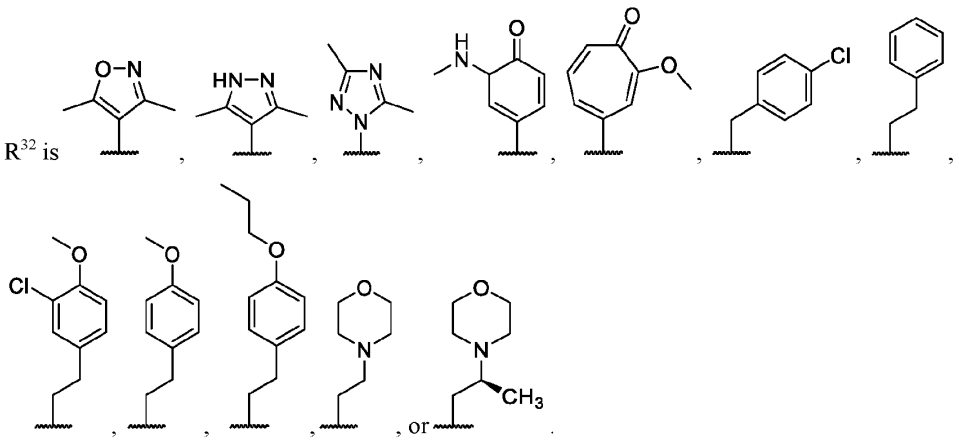
, 

, 

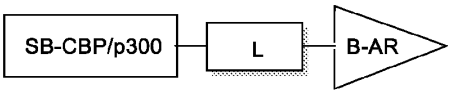
, or 

.

[00255] Embodiment 72. The compound of any one of embodiments 67-70, or a pharmaceutically acceptable salt or solvate thereof, wherein:

R^{32} is 

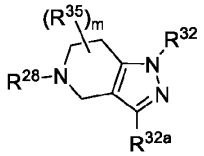
[00256] Embodiment 73. A heterobifunctional conditional inhibitor compound of Formula (I) or a pharmaceutically acceptable salt or solvate thereof:



wherein:

SB-CBP/p300 is a silent binder of the bromodomain of human CREB-binding protein (CBP) or human E1A-binding protein p300 (p300) (CBP/p300), wherein the binder of CBP/p300 comprises:

- an acetyl-lysine mimetic moiety that binds in the acetyl-lysine (KAc) binding site of the bromodomain of human CREB-binding protein (CBP) or human E1A-binding protein p300 (p300) (CBP/p300) and has the structure:



R^{28} is -C(=O)CH_3, -C(=O)CH_2CH_3, -C(=O)NH_2, -C(=O)NH(CH_3); or -C(=O)NH(CH_2CH_3);

R^{32} is a moiety that occupies the BC Loop region of the bromodomain of CBP/p300;

R^{32a} is a moiety that occupies the lipophilic shelf (LPF) region of the bromodomain of CBP/p300;

each R^{35} is independently hydrogen, C_1-C_4alkyl, or C_1-C_4fluoroalkyl;

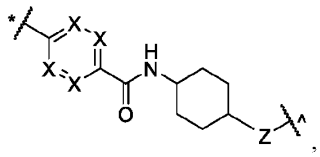
m is 0, 1, 2, 3, or 4;

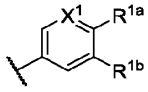
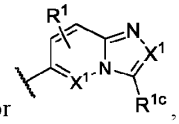
L is an optional linker;

wherein L is covalently attached to the R^{32} group, or at the position occupied by R^{32}, or the R^{32a} group;

B-AR is a binder of the androgen receptor (AR), wherein the B-AR comprises:

- a head group that occupies the ligand-binding domain (LBD) of AR and is covalently attached to a core with a tail moiety covalently attached to the core moiety; wherein B-AR has the structure of Formula (D):


, Formula (D);

wherein head group is  , or  , and the the head group is covalently attached to Z at position (^), and L is attached at position *;

Z is -O-, -NH- or -N(C_1-C_4alkyl)-;

each X^1 is independently -CR^1- or -N-;

R^{1a} is -CN, -NO_2, -C(=O)R^5, -C(=O)OR^5, or -C(=O)$N(R^5)_2$;

R^{1b} is hydrogen, halogen, substituted or unsubstituted C_1-C_4alkyl, C_1-C_4fluoroalkyl, -CN, -OH, or -OR^4;

R^{1c} is hydrogen, halogen, C_1-C_4alkyl, C_1-C_4fluoroalkyl, or -CN;

each R^1 is independently hydrogen, halogen, substituted or unsubstituted C_1-C_4alkyl, C_1-C_4fluoroalkyl, -CN, -OH, or -OR^4;

each X is independently -CR^3- or -N-;

each R^3 is independently hydrogen, halogen, substituted or unsubstituted C_1-C_4alkyl, C_1-C_4fluoroalkyl, -CN, -OH, -OR^4, or -$N(R^5)_2$.

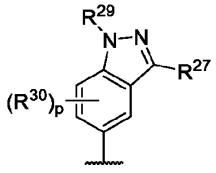
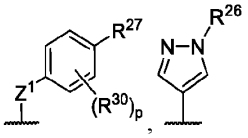
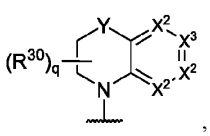
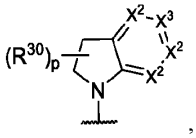
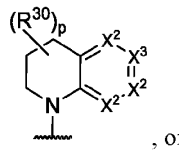
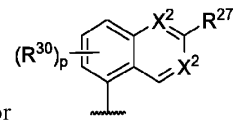
each R^4 is independently substituted or unsubstituted C_1-C_4alkyl, or C_1-C_4fluoroalkyl;

each R^5 is independently hydrogen, substituted or unsubstituted C_1-C_4alkyl, C_1-C_4fluoroalkyl; and

each s is 1, 2, or 3.

[00257] Embodiment 74. The compound of embodiment 73, or a pharmaceutically acceptable salt or solvate thereof, wherein:

R^{32} is hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_3-C_{12}cycloalkyl, or substituted or unsubstituted 3- to 12-membered heterocycloalkyl;

R^{32a} is  ,  ,  ,  ,  , or  ;

at least one X^2 is -CR^{30}- and at most two X^2 are -N-;

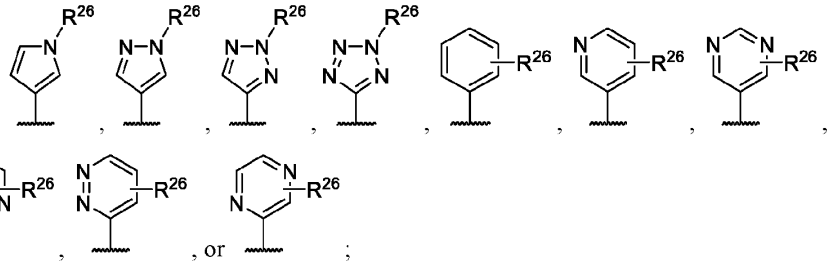
Z^1 is -NR^c- or -O-;

R^c is hydrogen or C_1-C_6alkyl;

R^{26} is hydrogen, substituted or unsubstituted C_1-C_4alkyl, C_1-C_4fluoroalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, or substituted or unsubstituted 3- to 8-membered heterocycloalkyl;

X^3 is -CR^{27}- or -N-;

R^{27} is hydrogen, halogen, substituted or unsubstituted C_1-C_4alkyl, C_1-C_4fluoroalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted 3- to 8-membered heterocycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted monocyclic heteroaryl, -CN, -OH, -OR^a, -$N(R^b)_2$, -$NR^bC(=O)R^a$, -$C(=O)R^b$, -$C(=O)OR^b$, or -$C(=O)N(R^b)_2$;

or R^{27} is  ;

p is 0, 1, 2, or 3;

R^{29} is hydrogen, substituted or unsubstituted C_1-C_4alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, or substituted or unsubstituted 3- to 8-membered heterocycloalkyl;

Y is -$C(R^{30})_2$- or $N(R^{28})$-;

each R^{30} is independently hydrogen, halogen, C_1-C_4alkyl, C_1-C_4fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, -CN, -OH, or -OR^a;

q is 0, 1, 2, 3, or 4;

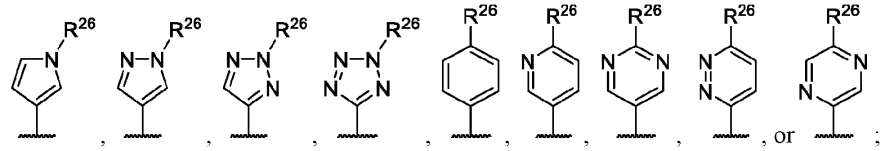
each R^a is independently C_1-C_4alkyl, C_1-C_6fluoroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted monocyclic 3- to 6-membered heterocycloalkyl, substituted or unsubstituted phenyl, or substituted or unsubstituted monocyclic heteroaryl;

each R^b is independently hydrogen, C_1-C_4alkyl, C_1-C_4fluoroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted monocyclic 3- to 6-membered heterocycloalkyl, substituted or unsubstituted phenyl, or substituted or unsubstituted monocyclic heteroaryl;

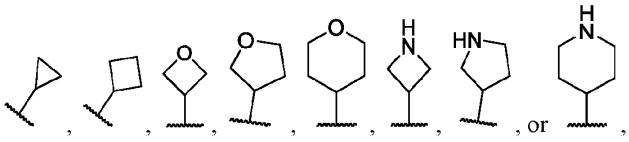
or two R^b on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle.

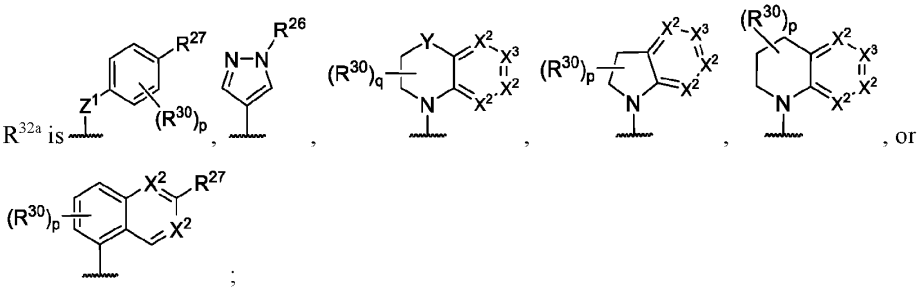
[00258] Embodiment 75. The compound of any one of embodiments 73-74, or a pharmaceutically acceptable salt or solvate thereof, wherein:

R^{27} is hydrogen, halogen, C_1-C_4alkyl, C_1-C_4fluoroalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted 3- to 8-membered heterocycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted monocyclic 5- or 6-membered heteroaryl, -CN, -OH, -OR^a, -$N(R^b)_2$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^a$, -$NR^bS(=O)_2R^a$, -$C(=O)R^b$, -$C(=O)OR^b$, or -$C(=O)N(R^b)_2$;

or R^{27} is  ;

[00259] Embodiment 76. The compound of any one of embodiments 73-75, or a pharmaceutically acceptable salt or solvate thereof, wherein:

R^{32} is  , each of which is unsubstituted or substituted with F, Cl, Br, $-CH_3$, $-CD_3$, $-CH_2CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2CH_2F$, $-CH_2CHF_2$, $-CH_2CF_3$, -CN, $-C(=O)CH_3$, $-C(=O)CH_2CH_3$, $-C(=O)CH_2F$, $-C(=O)CHF_2$, $-C(=O)CF_3$, $-C(=O)CH_2CH_2F$, $-C(=O)CH_2CHF_2$, $-C(=O)CH_2CF_3$, $-C(=O)CD_3$, or $-SO_2CH_3$, $-SO_2CH_2CH_3$, $-SO_2CD_3$, or $-SO_2CH_2CD_3$.

R^{32a} is  ;

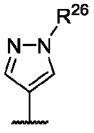
at least one X^2 is $-CR^{30}-$ and at most two X^2 are -N-;

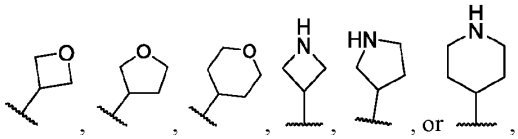
each R^{27} is independently hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -CN, -OH, or $-OR^a$; and

each R^a is independently substituted or unsubstituted C_1-C_6alkyl.

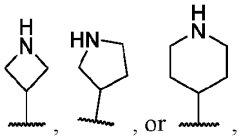
[00260] Embodiment 77. The compound of any one of embodiments 73-76, or a pharmaceutically acceptable salt or solvate thereof, wherein:

R^{27} is hydrogen, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH_2(CH_3)_2$, $-(CH_3)_3$, -F, $-CHF_2$, $-CF_3$, -CN, -OH, $-OCH_3$, cyclopropyl, cyclobutyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, unsubstituted or substituted phenyl, unsubstituted or substituted pyrazolyl, unsubstituted or substituted pyridinyl, or unsubstituted or substituted pyrimidinyl; or

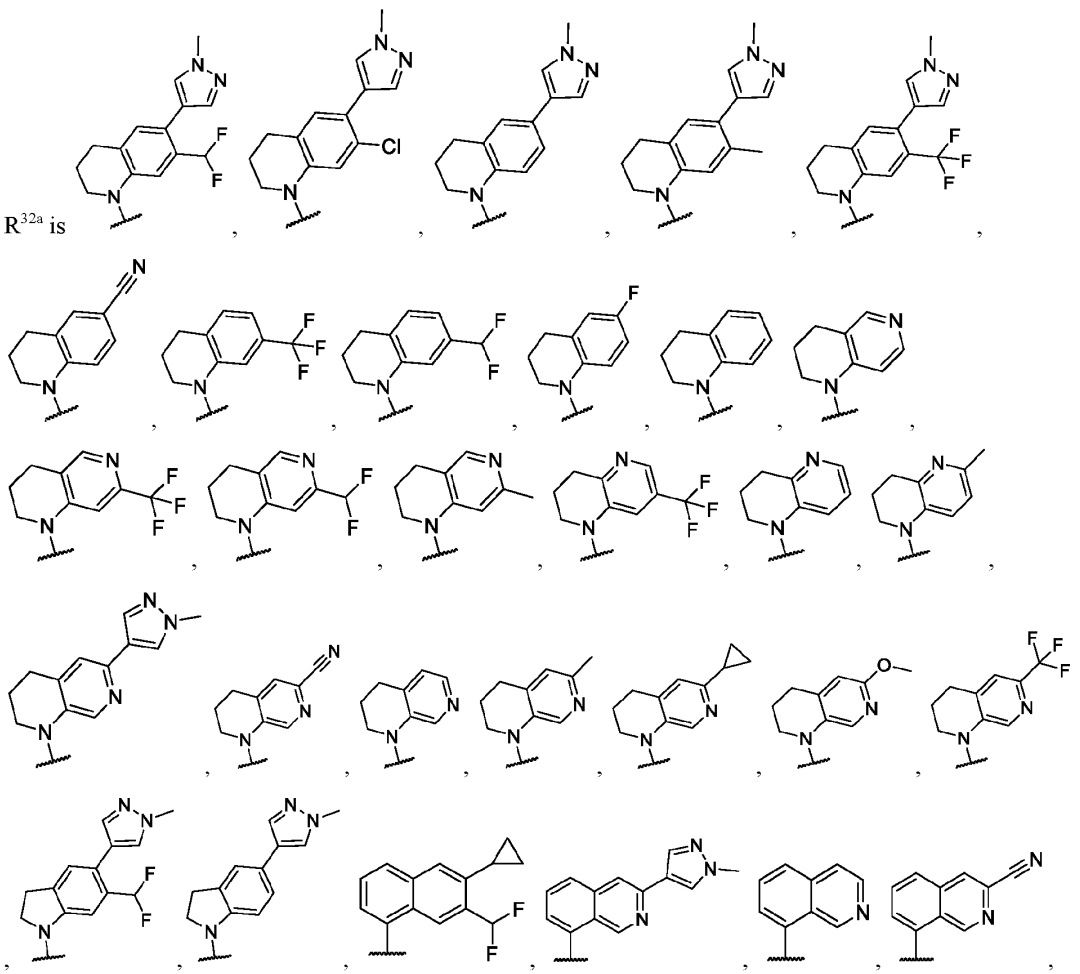
R^{27} is  ;

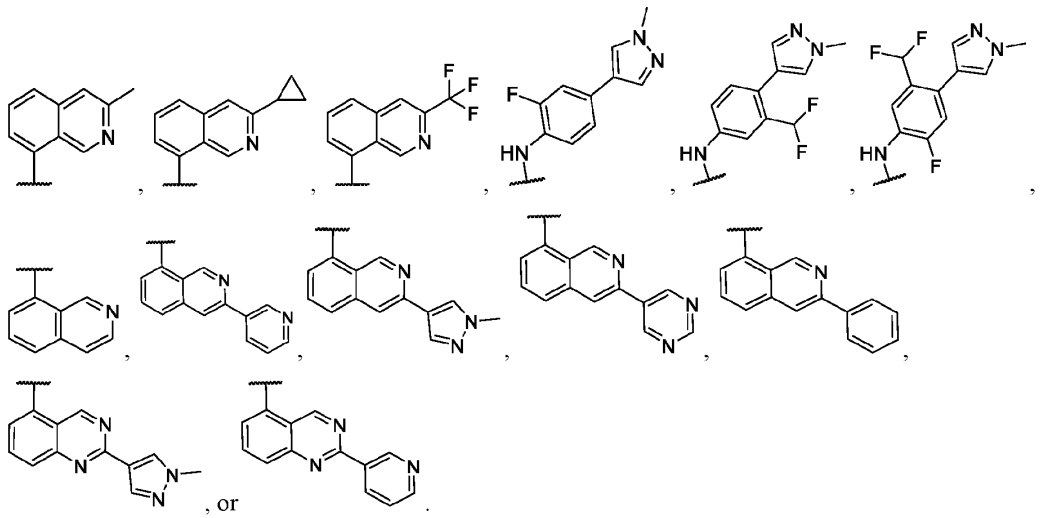
R^{32} is  , each of which is unsubstituted or substituted with F, Cl, Br, $-CH_3$, $-CD_3$, $-CH_2CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, CN, $-C(=O)CH_3$, $-C(=O)CH_2F$, $-C(=O)CHF_2$, $-C(=O)CF_3$, $-C(=O)CD_3$.

[00261] Embodiment 78. The compound of embodiment 73-77, or a pharmaceutically acceptable salt or solvate thereof, wherein:

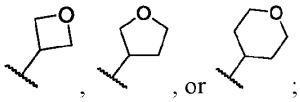
R^{32} is  , wherein the optional linker is covalently attached to the nitrogen of R^{32} group;

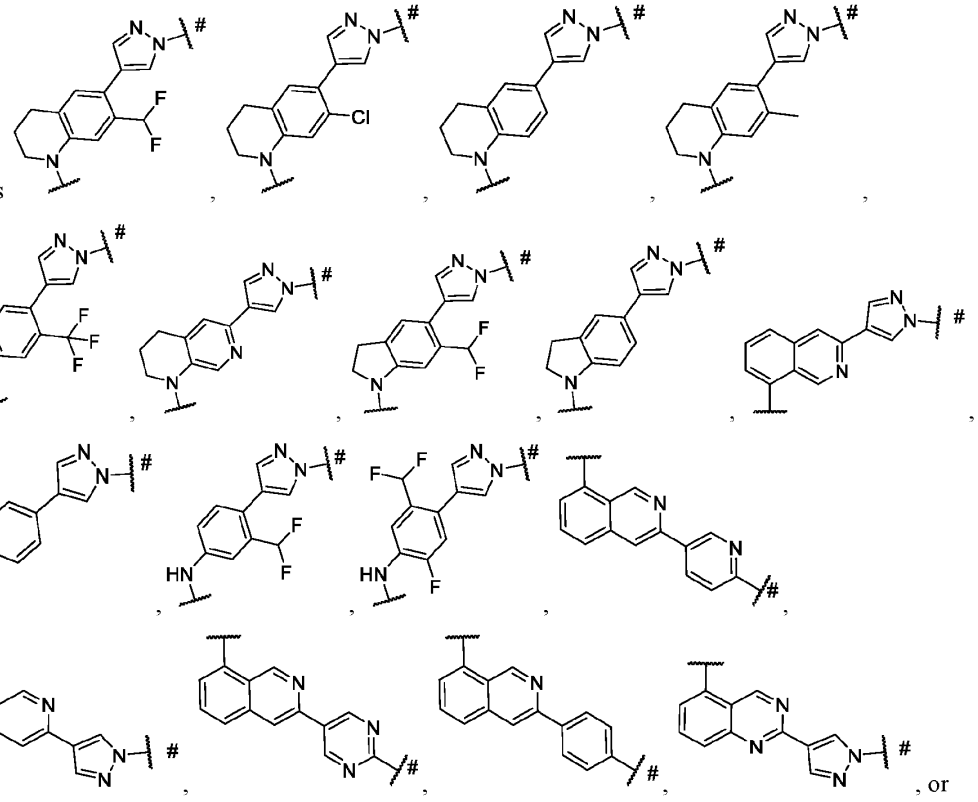
or R^{32} is absent and L is covalently attached to the acetyl-lysine mimetic moiety at the position occupied by R^{32}; and

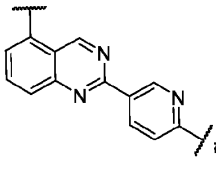
R^{32a} is 



[00262] Embodiment 79. The compound of any one of embodiments 73-78, or a pharmaceutically acceptable salt or solvate thereof, wherein:

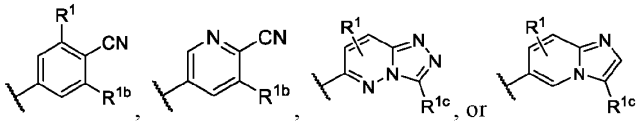
R^{32} is  ;

R^{32a} is 


, wherein

 is the point of attachment to the optional linker.

[00263] Embodiment 80. The compound of embodiment 73, or a pharmaceutically acceptable salt or solvate thereof, wherein the head group is:

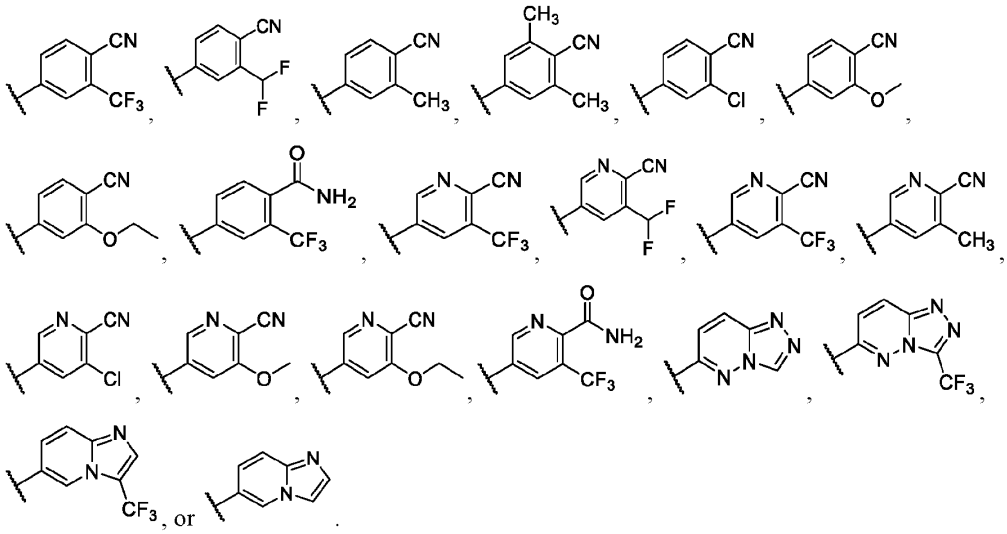


R^{1b} is hydrogen, F, Cl, Br, I, $-CH_3$, $-CD_3$, $-CH_2CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, -OH, $-OCF_3$, $-OCH_3$, $-OCH_2CH_3$, $-OCD_3$, $-OCH_2CD_3$, or -CN;

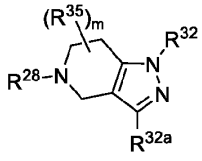
each R^{1c} is hydrogen, F, Cl, Br, $-CH_3$, $-CD_3$, $-CH_2F$, $-CHF_2$, or $-CF_3$;

each R^1 is independently hydrogen, F, Cl, Br, I, $-CH_3$, $-CD_3$, $-CH_2CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2CH_2F$, $-CH_2CHF_2$, $-CH_2CF_3$, -OH, $-OCF_3$, $-OCH_3$, $-OCD_3$, or $-OCH_2CH_3$.

[00264] Embodiment 81. The compound of embodiment 73, or a pharmaceutically acceptable salt or solvate thereof, wherein the head group is selected from:



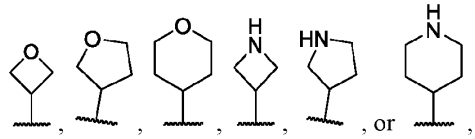
[00265] Embodiment 82. The compound of any one of embodiments 14-81, or a pharmaceutically acceptable salt or solvate thereof, wherein:

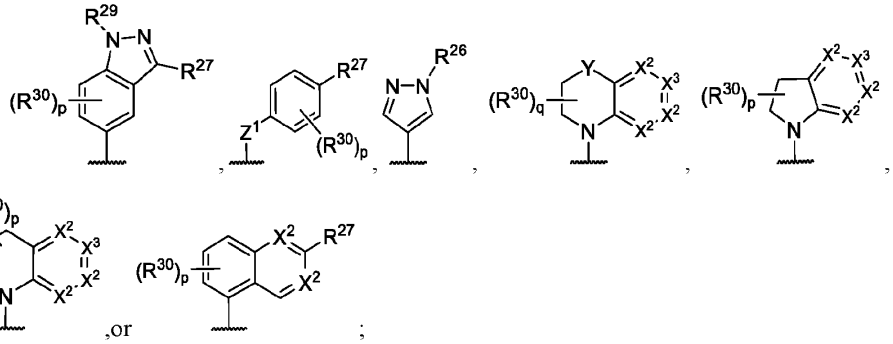
SB-CBP/p300 has the structure: 

R^{28} is -C(=O)CH_3 or -C(=O)NH(CH_3);

each R^{35} is independently hydrogen, -CH_3, -CH_2F, -CHF_2, -CF_3;

m is 0, 1, or 2;

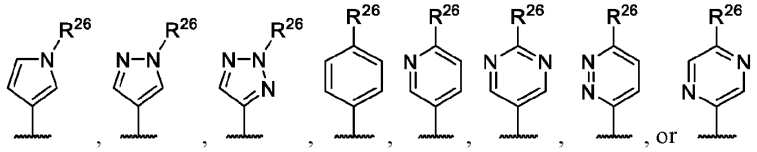
R^{32} is  , each of which is unsubstituted or substituted with F, -CH_3, -CH_2F, -CHF_2, or -CF_3;

R^{32a} is  ;

at least one X^2 is -CR^{30}- and at most two X^2 are -N-;

R^{26} is hydrogen, C_1-C_4alkyl, C_1-C_4fluoroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, or substituted or unsubstituted 3- to 6-membered heterocycloalkyl;

R^{27} is hydrogen, halogen, C_1-C_4alkyl, C_1-C_4fluoroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted 3- to 6-membered heterocycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted monocyclic 5- or 6-membered heteroaryl, -CN, -OH, -OR^a, or -$N(R^b)_2$;

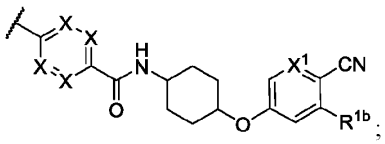
or R^{27} is  ;

each R^{30} is independently hydrogen, halogen, C_1-C_4alkyl, C_1-C_4fluoroalkyl, -CN, -OH, or -OR^a;

R^a is C_1-C_4alkyl;

each R^b is independently hydrogen or C_1-C_6alkyl;

wherein L is covalently attached to the R^{32} group, or at the position occupied by R^{26}, or at the position occupied by R^{27};

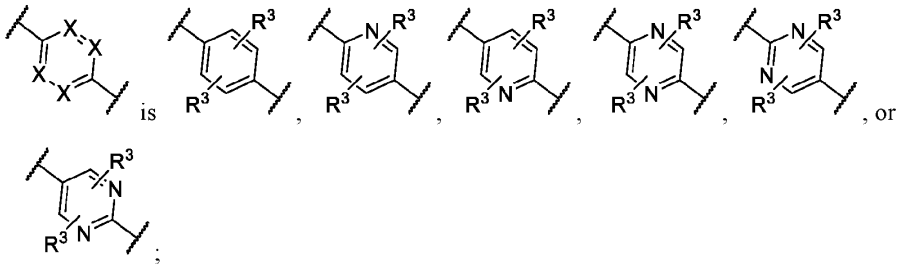
B-AR has the structure:  ;

each X is independently -CR^3- or -N-;

X^1 is -CR^1- or -N-;

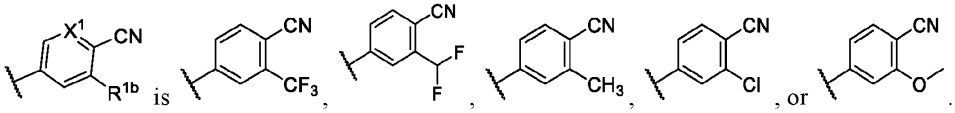
R^{1b} is hydrogen, F, Cl, -CH_3, -CH_2F, -CHF_2, -CF_3, or -OCF_3,

R^1 is hydrogen, F, Cl, -CH_3, -CH_2F, -CHF_2, or -CF_3;

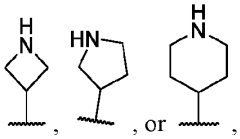


each R^3 is independently hydrogen, F, Cl, Br, -CH_3, -CH_2F, -CHF_2, -CF_3, -OH, -OCF_3, -OCH_3, or -CN.

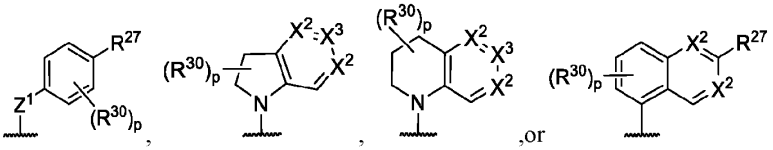
[00266] Embodiment 83. The compound of embodiment 82, or a pharmaceutically acceptable salt or solvate thereof, wherein:



[00267] Embodiment 84. The compound of any one of embodiments 82-83, or a pharmaceutically acceptable salt or solvate thereof, wherein:

R^{32} is  , wherein the optional linker is covalently attached to the nitrogen of R^{32} group;

or R^{32} is absent and the optional linker is covalently attached to the acetyl-lysine mimetic moiety at the position occupied by R^{32};

R^{32a} is  ;

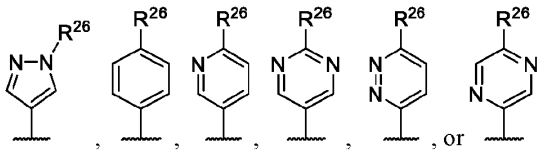
at least one X^2 is -CR^{30}- and at most two X^2 are -N-;

X^3 is -CR^{27}- or -N-;

Z^1 is -NH- or -O-;

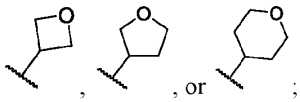
R^{26} is hydrogen, C_1-C_4alkyl, C_1-C_4fluoroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, or substituted or unsubstituted 3- to 6-membered heterocycloalkyl;

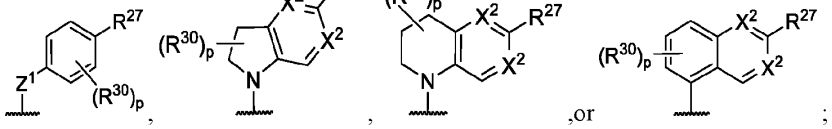
R^{27} is hydrogen, halogen, C_1-C_4alkyl, C_1-C_4fluoroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted 3- to 6-membered heterocycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted monocyclic 5- or 6-membered heteroaryl, -CN, -OH, -OR^a, or -$N(R^b)_2$;

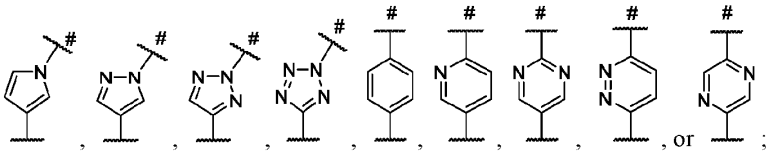
or R^{27} is  ; and

each R^{30} is independently hydrogen, halogen, C_1-C_4alkyl, C_1-C_4fluoroalkyl, -CN, -OH, or -OR^a.

[00268] Embodiment 85. The compound of any one of embodiments 82-84, or a pharmaceutically acceptable salt or solvate thereof, wherein:

R^{32} is  ;

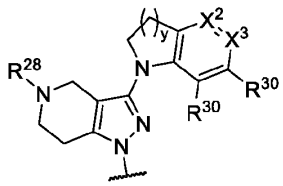
R^{32a} is  ;

R^{27} is  ;

Z^1 is -NH- or -O-;

 is the point of attachment to the optional linker.

[00269] Embodiment 86. The compound of any one of embodiments 14-81, or a pharmaceutically acceptable salt or solvate thereof, wherein SB-CBP/p300 has the structure of Formula (IIIb):



Formula (IIIb)

wherein:

X^2 is -CR^{30}- or -N-;

X^3 is $-CR^{27}-$ or -N-;

each R^{27} is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -CN, $-NO_2$, -OH, $-OR^a$, $OC(=O)R^a$, $-OC(=O)N(R^b)_2$, $-OC(=O)OR^a$, $-OC(=O)N(R^b)_2$, $-SR^b$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2OR^b$, $-S(=O)_2N(R^b)_2$, $-N(R^b)_2$, $-NR^bC(=O)N(R^b)_2$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^a$, $-NR^bS(=O)_2R^a$, $-C(=O)R^b$, $-C(=O)OR^b$, or $-C(=O)N(R^b)_2$;

R^{28} is hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, $-C(=O)R^b$, or $-C(=O)N(R^b)_2$;

each R^{30} is independently hydrogen, halogen, C_1-C_4alkyl, C_1-C_4fluoroalkyl, -CN, -OH, or $-OR^a$;

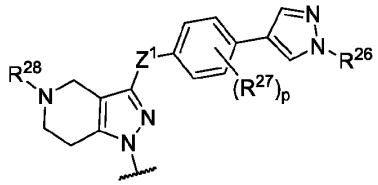
y is 1 or 2;

each R^a is independently substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted monocyclic 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted monocyclic heteroaryl;

each R^b is independently hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted monocyclic 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted monocyclic heteroaryl;

or two R^b on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle.

[00270] Embodiment 87. The compound of any one of embodiments 14-81, or a pharmaceutically acceptable salt or solvate thereof, wherein SB-CBP/p300 has the structure of Formula (IIIc):



Formula (IIIc)

wherein:

R^{26} is hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, or substituted or unsubstituted 3- to 8-membered heterocycloalkyl;

each R^{27} is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted 3- to 8-membered heterocycloalkyl,

substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -CN, -NO_2, -OH, -OR^a, $OC(=O)R^a$, -$OC(=O)N(R^b)_2$, -$OC(=O)OR^a$, -$OC(=O)N(R^b)_2$, -SR^b, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2OR^b$, -$S(=O)_2N(R^b)_2$, -$N(R^b)_2$, -$NR^bC(=O)N(R^b)_2$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^a$, -$NR^bS(=O)_2R^a$, -$C(=O)R^b$, -$C(=O)OR^b$, or -$C(=O)N(R^b)_2$;

p is 0, 1, 2, or 3;

R^{28} is hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, -$C(=O)R^a$, or -$C(=O)N(R^b)_2$;

Z^1 is -NR^c-, -O-, or -S-;

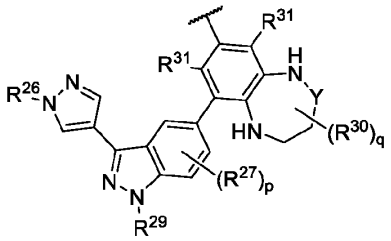
R^c is hydrogen or substituted or unsubstituted C_1-C_6alkyl;

each R^a is independently substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted monocyclic 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted monocyclic heteroaryl;

each R^b is independently hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted monocyclic 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted monocyclic heteroaryl;

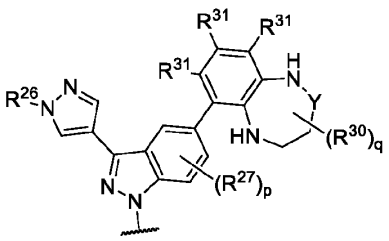
or two R^b on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle.

[00271] Embodiment 88. The compound of any one of embodiments 14-81, or a pharmaceutically acceptable salt or solvate thereof, wherein SB-CBP/p300 has the structure of Formula (IIId-1) or (IIId-2):



Formula (IIId-1)

or



Formula (IIId-2)

wherein:

R^{26} is hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, or substituted or unsubstituted 3- to 8-membered heterocycloalkyl;

each R^{27} is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -CN, -NO_2, -OH, -OR^a,

$OC(=O)R^a$, $-OC(=O)N(R^b)_2$, $-OC(=O)OR^a$, $-OC(=O)N(R^b)_2$, $-SR^b$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2OR^b$, $-S(=O)_2N(R^b)_2$, $-N(R^b)_2$, $-NR^bC(=O)N(R^b)_2$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^a$, $-NR^bS(=O)_2R^a$, $-C(=O)R^b$, $-C(=O)OR^b$, or $-C(=O)N(R^b)_2$;

p is 0, 1, 2, or 3;

R^{29} is hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, or substituted or unsubstituted 3- to 8-membered heterocycloalkyl;

each R^{30} is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, -CN, $-NO_2$, -OH, $-OR^a$, $OC(=O)R^a$, $-OC(=O)N(R^b)_2$, $-OC(=O)OR^a$, $-SR^b$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2OR^b$, $-S(=O)_2N(R^b)_2$, $-N(R^b)_2$, $-NR^bC(=O)N(R^b)_2$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^a$, $-NR^bS(=O)_2R^a$, $-C(=O)R^b$, $-C(=O)OR^b$, or $-C(=O)N(R^b)_2$;

q is 0, 1, 2, 3, or 4;

each R^{31} is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, -CN, $-NO_2$, -OH, $-OR^a$, $OC(=O)R^a$, $-OC(=O)N(R^b)_2$, $-OC(=O)OR^a$, $-SR^b$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2OR^b$, $-S(=O)_2N(R^b)_2$, $-N(R^b)_2$, $-NR^bC(=O)NR^b$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^a$, $-NR^bS(=O)_2R^a$, $-C(=O)R^b$, $-C(=O)OR^b$, or $-C(=O)N(R^b)_2$;

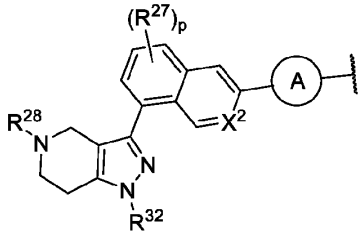
Y is $-C(R^{30})_2-$ or C(=O);

each R^a is independently substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted monocyclic 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted monocyclic heteroaryl;

each R^b is independently hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted monocyclic 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted monocyclic heteroaryl;

or two R^b on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle.

[00272] Embodiment 89. The compound of any one of embodiments 14-81, or a pharmaceutically acceptable salt or solvate thereof, wherein SB-CBP/p300 has the structure of Formula (IIIe):



Formula (IIIe)

wherein:

X^2 is $-CR^{27}-$ or -N-;

each R^{27} is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -CN, $-NO_2$, -OH, $-OR^a$, $OC(=O)R^a$, $-OC(=O)N(R^b)_2$, $-OC(=O)OR^a$, $-OC(=O)N(R^b)_2$, $-SR^b$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2OR^b$, $-S(=O)_2N(R^b)_2$, $-N(R^b)_2$, $-NR^bC(=O)N(R^b)_2$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^a$, $-NR^bS(=O)_2R^a$, $-C(=O)R^b$, $-C(=O)OR^b$, or $-C(=O)N(R^b)_2$;

p is 0, 1, 2, or 3;

R^{28} is hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, $-C(=O)R^b$, or $-C(=O)N(R^b)_2$;

R^{32} is hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, or substituted or unsubstituted 3- to 8-membered heterocycloalkyl;

Ring A is absent or substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

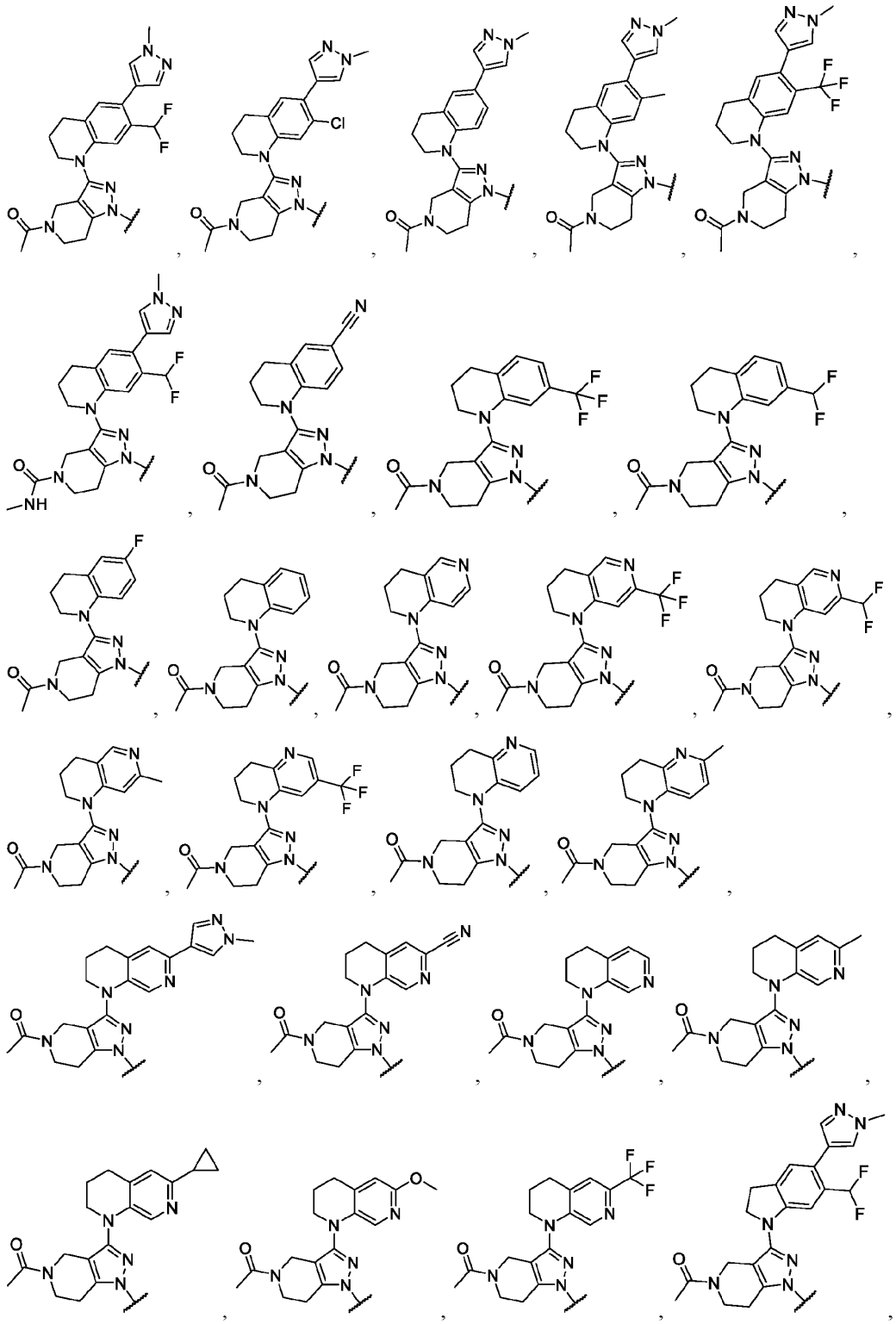
each R^a is independently substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted monocyclic 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted monocyclic heteroaryl;

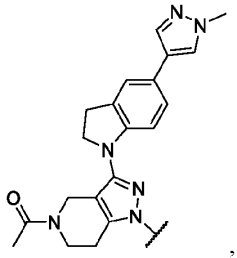
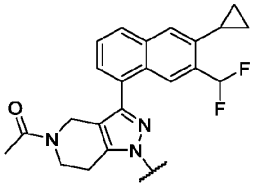
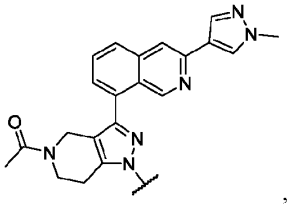
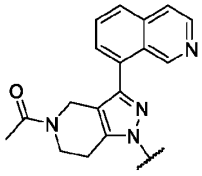
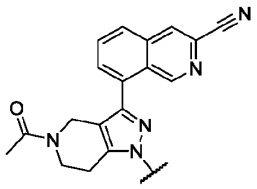
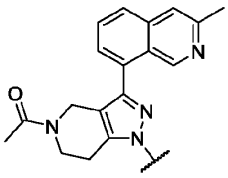
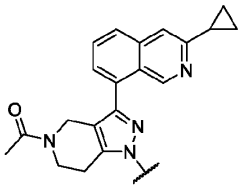
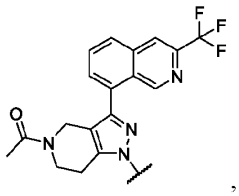
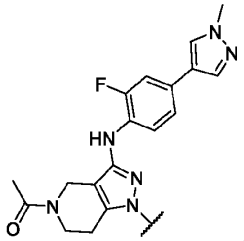
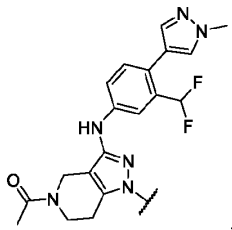
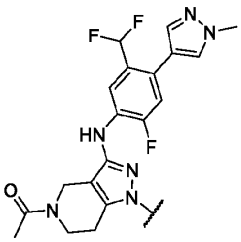
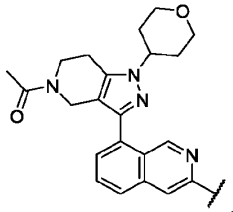
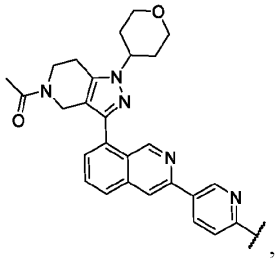
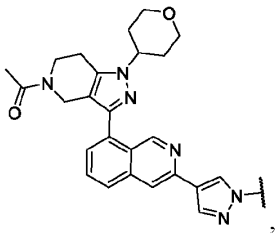
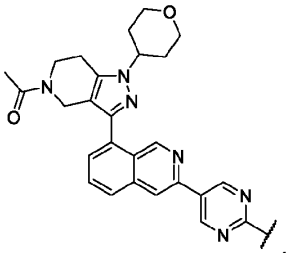
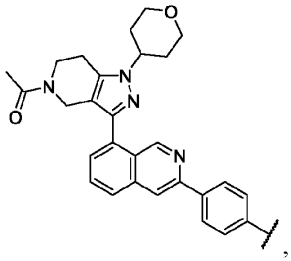
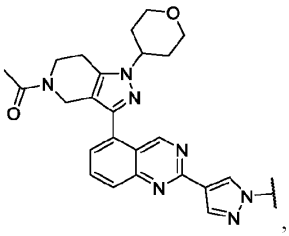
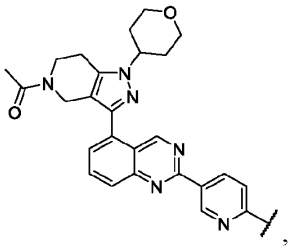
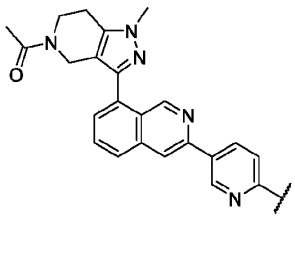
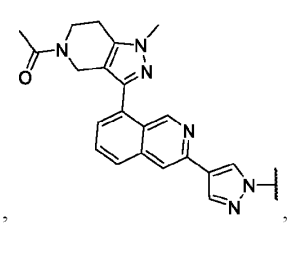
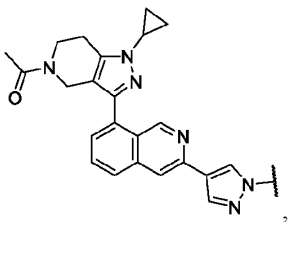
each R^b is independently hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted monocyclic 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted monocyclic heteroaryl;

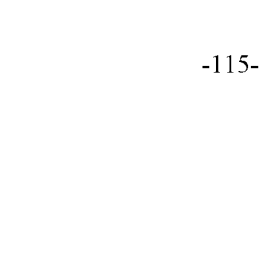
or two R^b on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle.

[00273] Embodiment 90. The compound of any one of embodiments 14-89, or a pharmaceutically

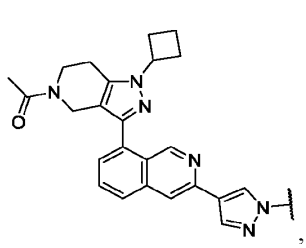
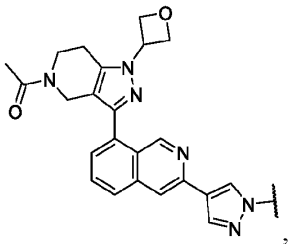
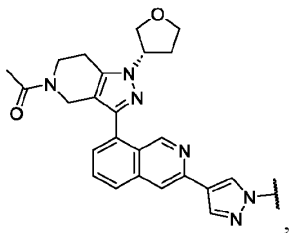
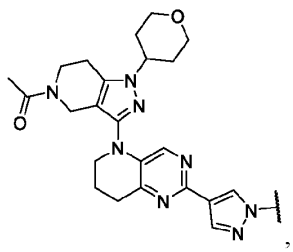
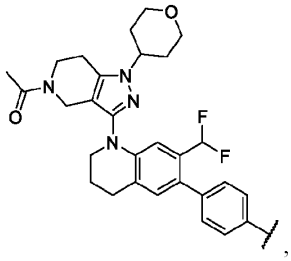
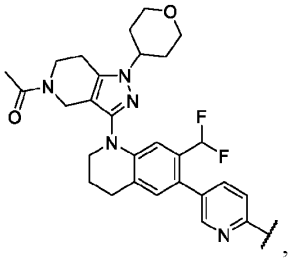
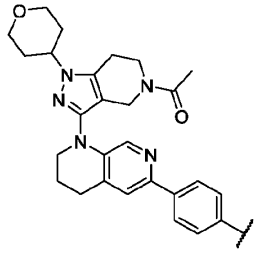
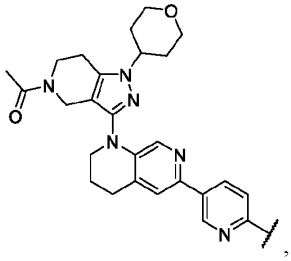
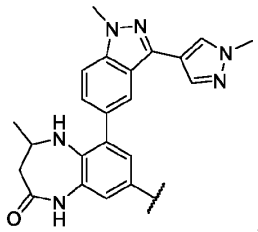
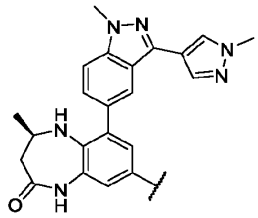
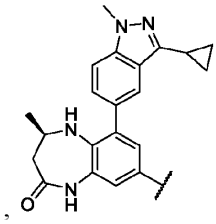
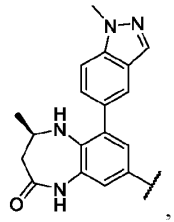
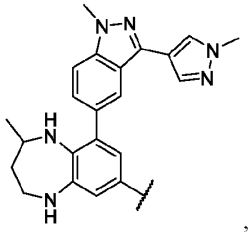
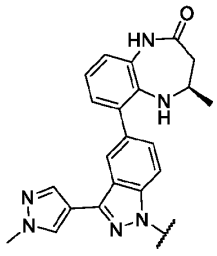
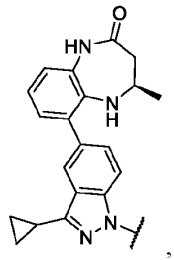
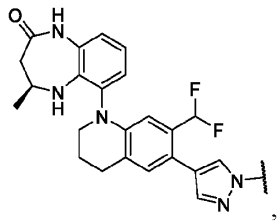
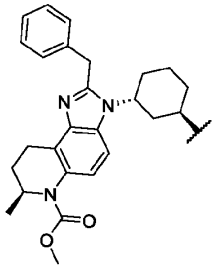
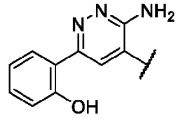
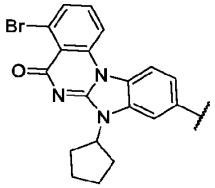
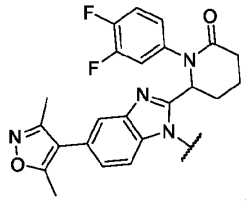
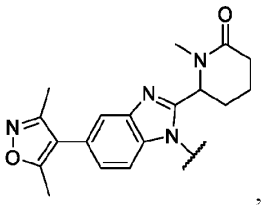
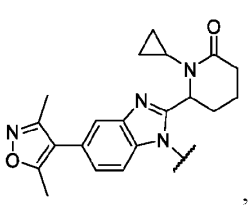
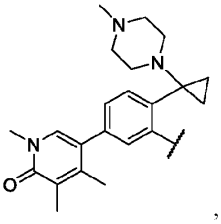
acceptable salt or solvate thereof, wherein SB-CBP/p300 has one of the following structures:

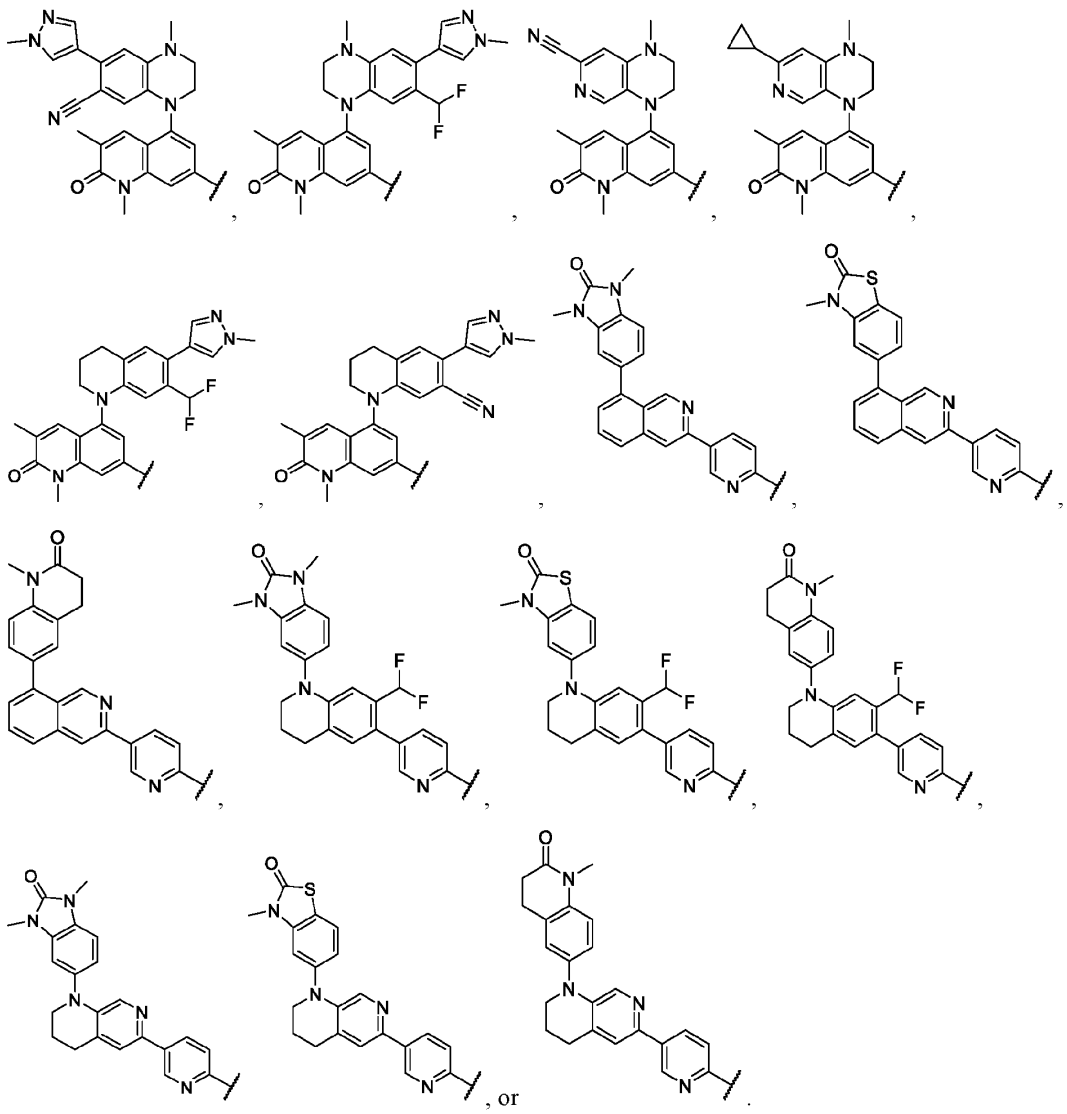



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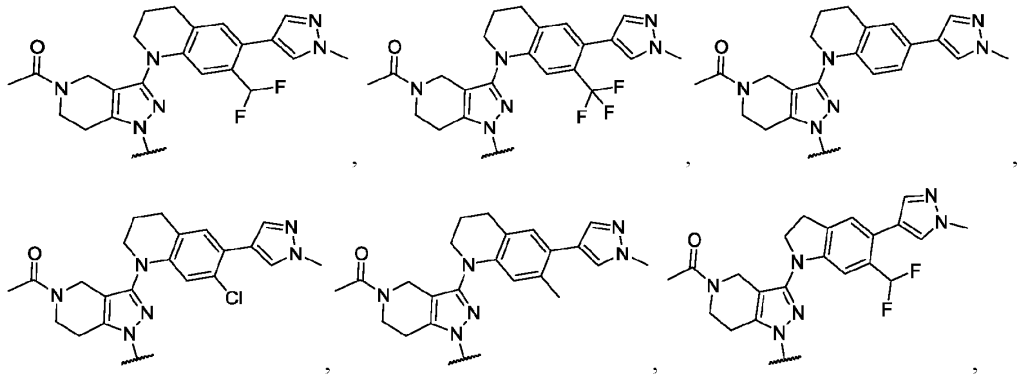
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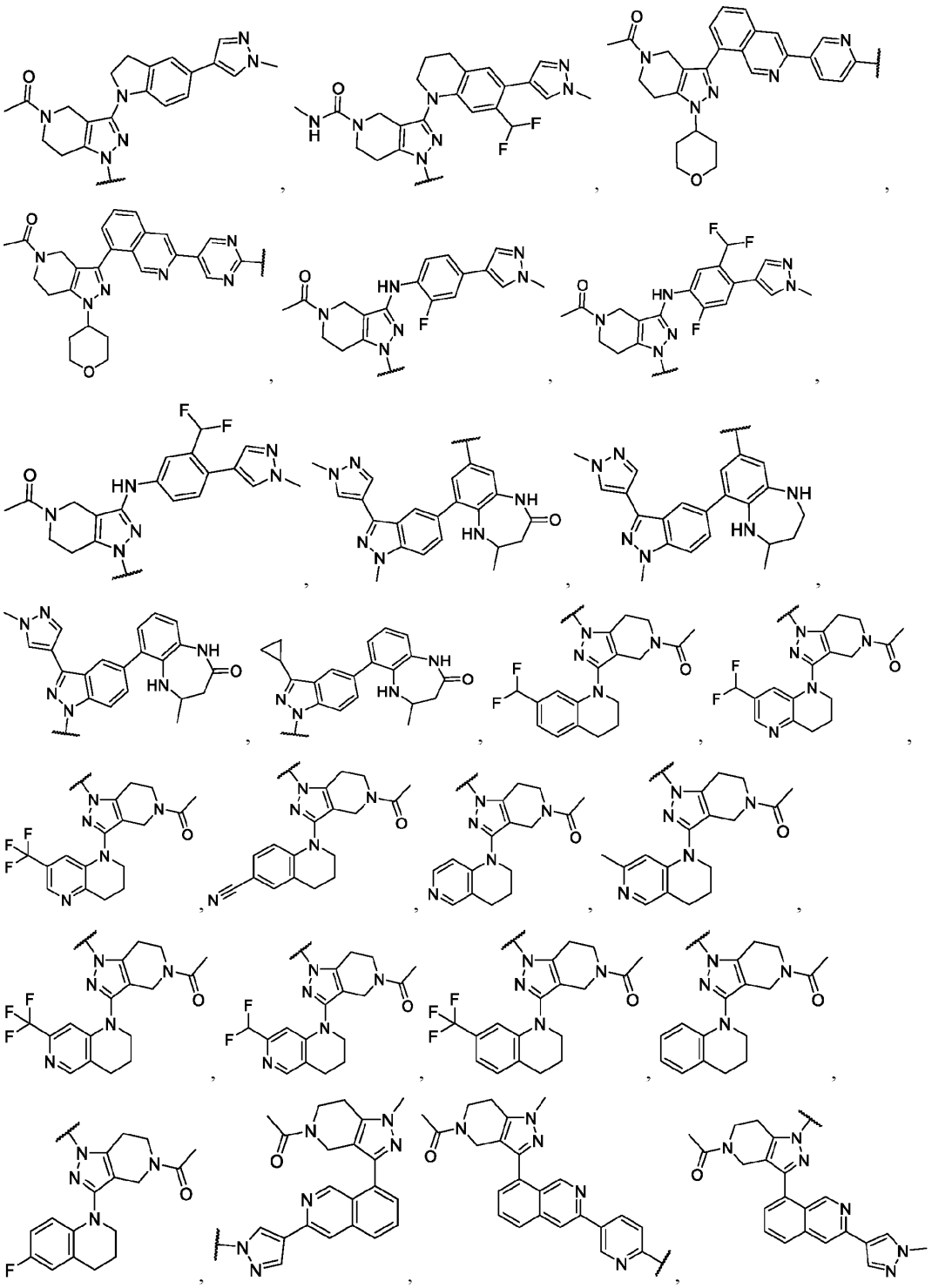
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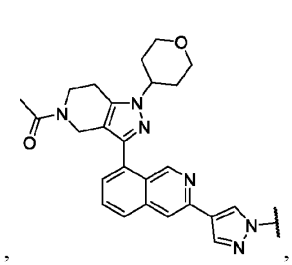
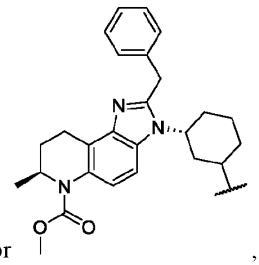

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[00274] Embodiment 91. The compound of any one of embodiments 14-89, wherein SB-CBP/p300 has one of the following structures:

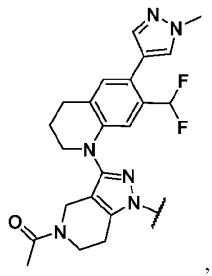
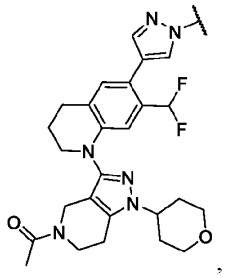
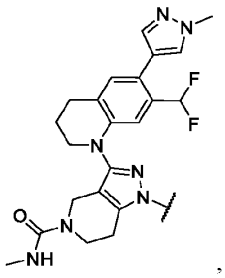
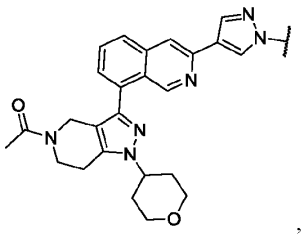
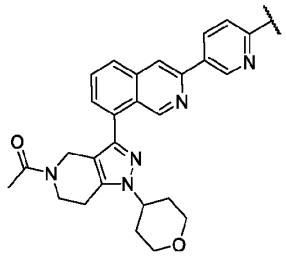




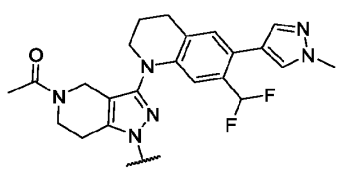
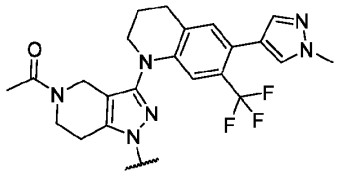
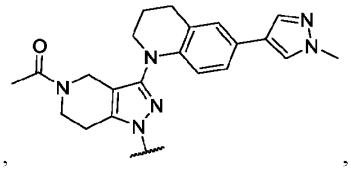
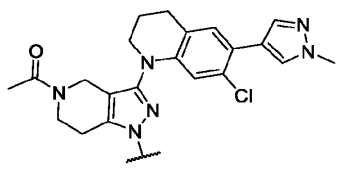
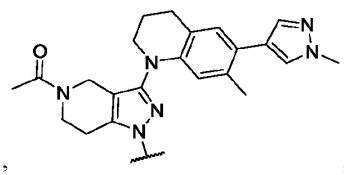
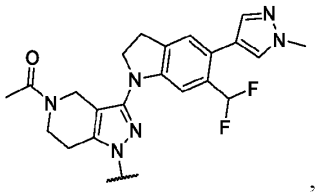

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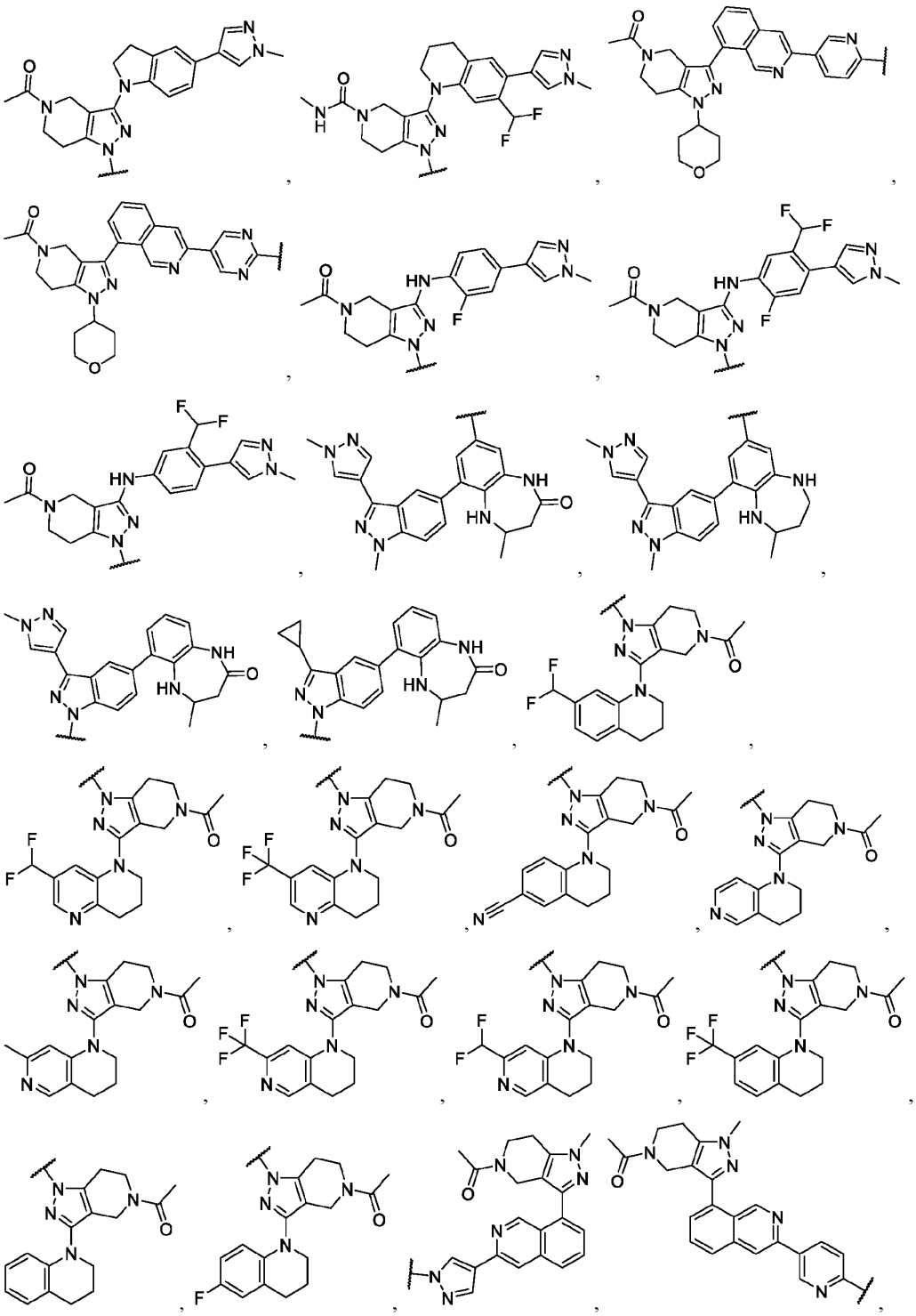
or a pharmaceutically acceptable salt or solvate thereof.

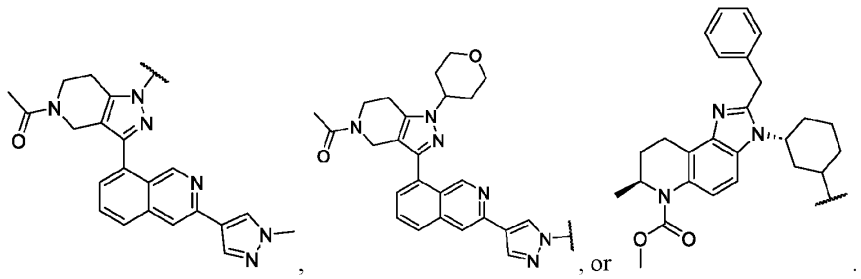
[00275] Embodiment 92. The compound of any one of embodiments 14-89, or a pharmaceutically acceptable salt or solvate thereof, wherein SB-CBP/p300 has one of the following structures:


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, or 
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[00276] Embodiment 93. The compound of any one of embodiments 14-89, or a pharmaceutically acceptable salt or solvate thereof, wherein SB-CBP/p300 has one of the following structures:

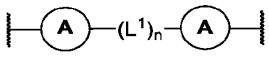

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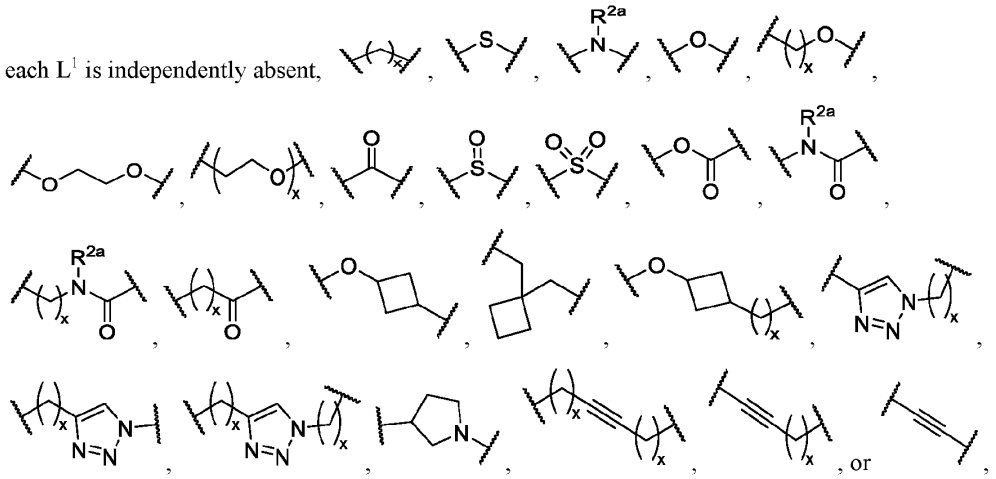


[00277] Embodiment 94. The compound of any one of embodiments 1-93, or a pharmaceutically acceptable salt or solvate thereof, wherein L is absent.

[00278] Embodiment 95. The compound of any one of embodiments 1-93, or a pharmaceutically acceptable salt or solvate thereof, wherein L comprises substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted 3- to 10-membered heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or combinations thereof.

[00279] Embodiment 96. The compound of any one of embodiments 1-93, or a pharmaceutically acceptable salt or solvate thereof, wherein L is absent or  , wherein:

each A is independently absent, substituted or unsubstituted monocyclic C_3-C_{10}cycloalkyl, substituted or unsubstituted bridged bicyclic C_3-C_{10}cycloalkyl, substituted or unsubstituted fused bicyclic C_3-C_{10}cycloalkyl, substituted or unsubstituted spiro bicyclic C_3-C_{10}cycloalkyl, substituted or unsubstituted monocyclic 3- to 10-membered heterocycloalkyl, substituted or unsubstituted bridged bicyclic 3- to 10-membered heterocycloalkyl, substituted or unsubstituted fused bicyclic 3- to 10-membered heterocycloalkyl, substituted or unsubstituted spiro bicyclic 3- to 10-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, wherein each A is independently unsubstituted or substituted with x R^{2b};

each L^1 is independently absent, 

wherein each L^1 is independently unsubstituted or substituted with x R^{2b};

n is 1, 2, 3, 4, 5, or 6;

each x is independently 1, 2, 3, 4, 5, 6, 7, or 8;

each R^{2a} is independently hydrogen or substituted or unsubstituted C_1-C_6alkyl; and

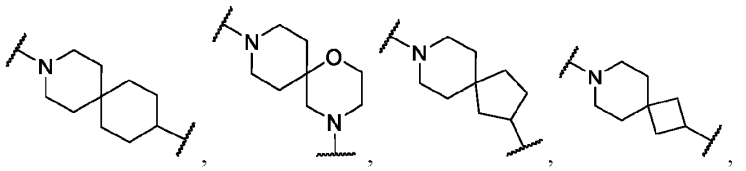
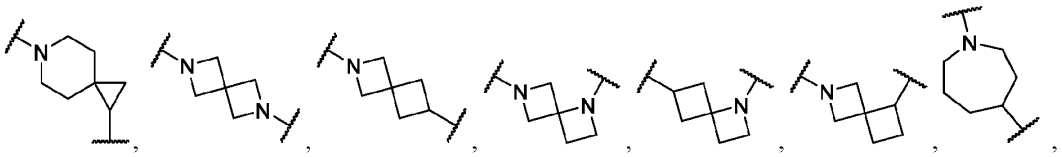
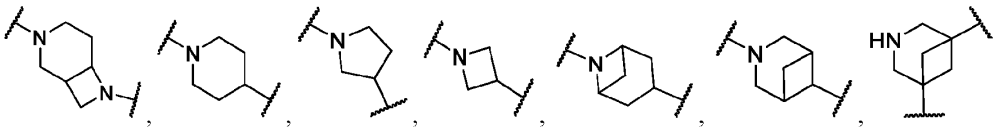
each R^{2b} is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -CN, -NO_2, -OH, -OR^a, -$OC(=O)R^a$, -$OC(=O)N(R^b)_2$, -$OC(=O)OR^a$, -SR^b, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2OR^b$, -$S(=O)_2N(R^b)_2$, -$N(R^b)_2$, -$NR^bC(=O)N(R^b)_2$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^a$, -$NR^bS(=O)_2R^a$, -$C(=O)R^b$, -$C(=O)OR^b$, or -$C(=O)N(R^b)$;

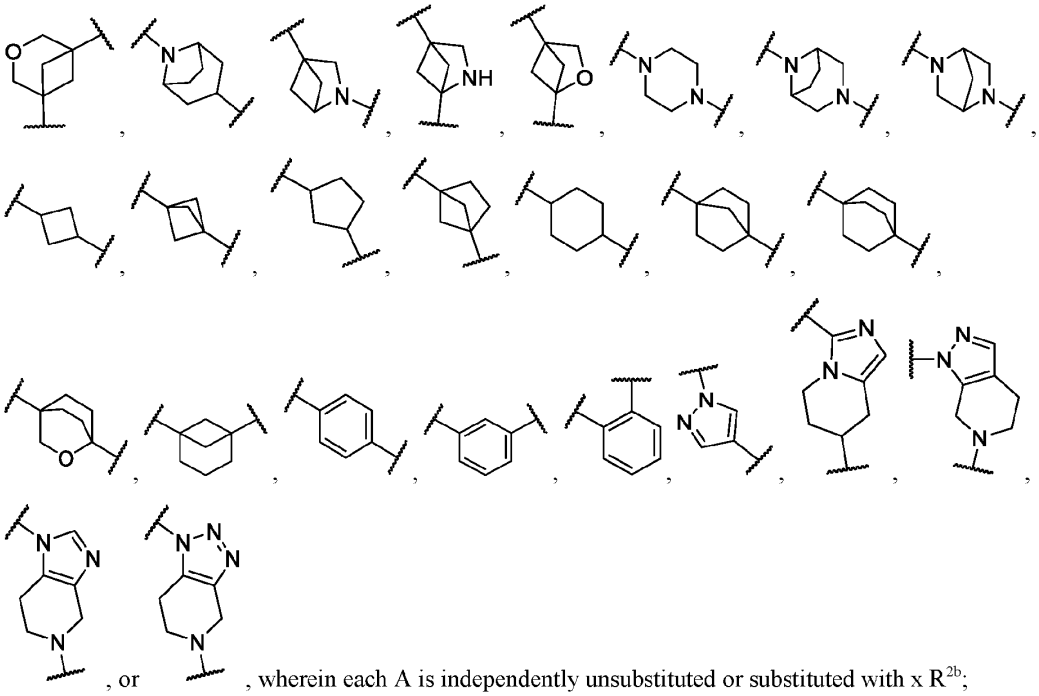
each R^a is independently substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted monocyclic 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted monocyclic heteroaryl;

each R^b is independently hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted monocyclic 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted monocyclic heteroaryl;

or two R^b on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle.

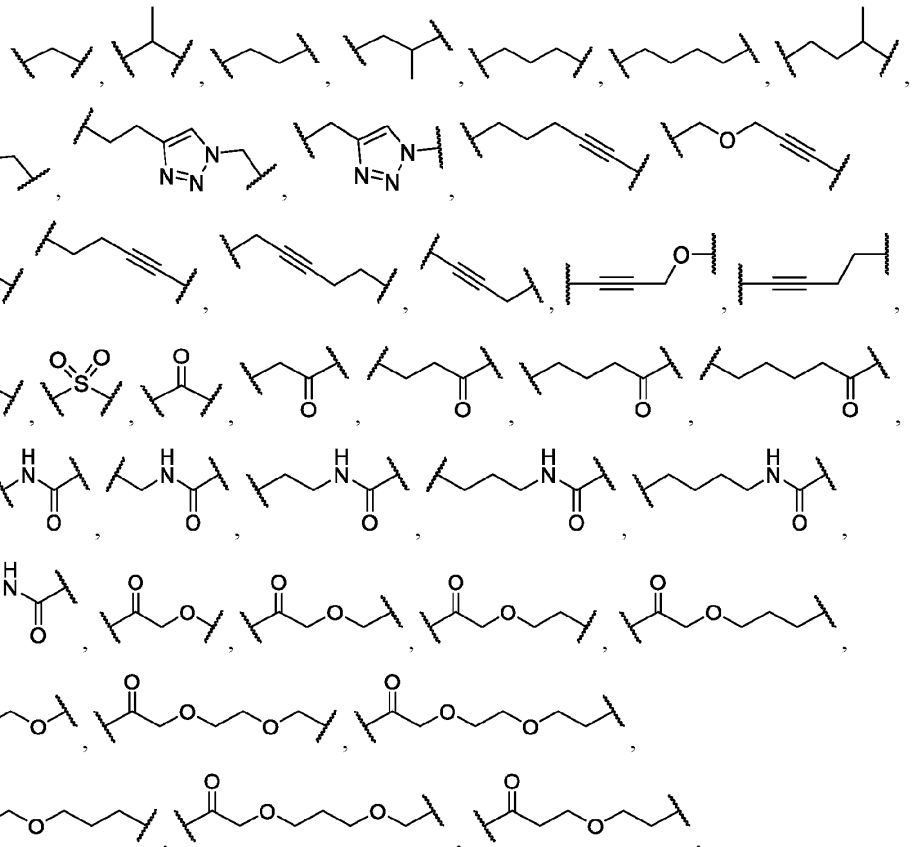
[00280] Embodiment 97. The compound of embodiment 96, or a pharmaceutically acceptable salt or solvate thereof, wherein:

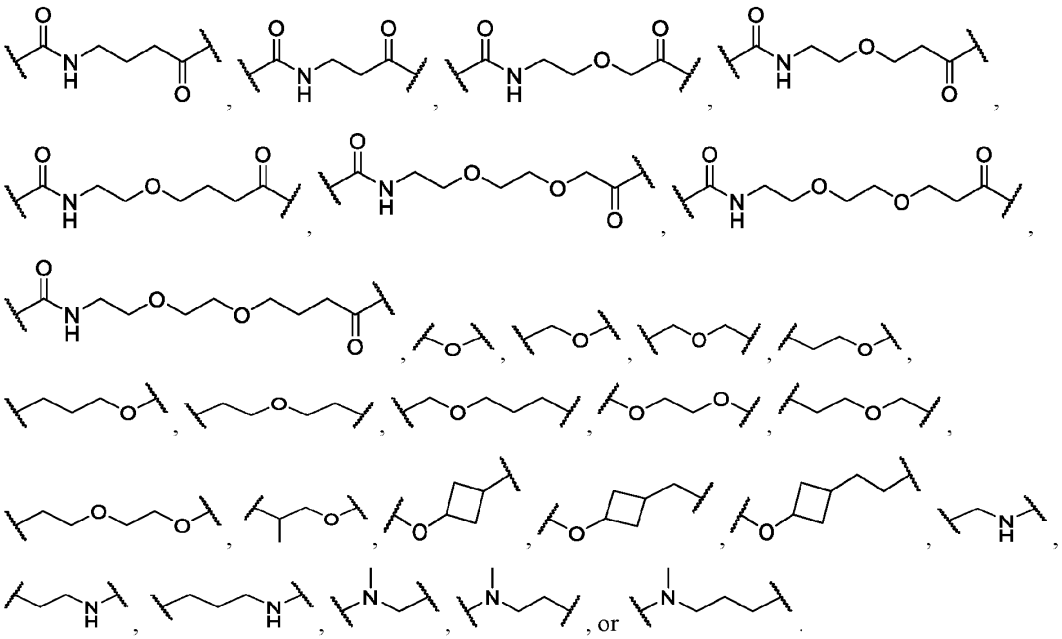
each A is independently absent, 



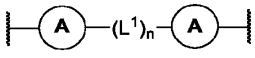


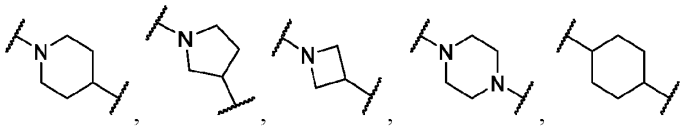
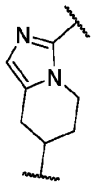
, or , wherein each A is independently unsubstituted or substituted with x R^{2b};

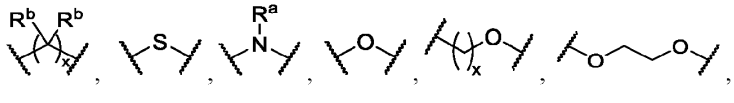
$(L^1)_n$ is absent,

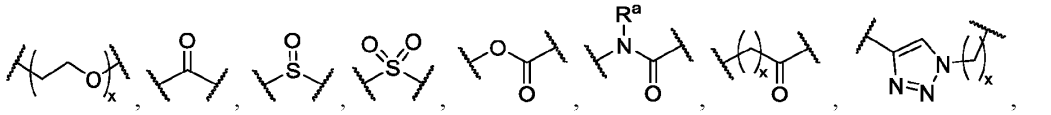


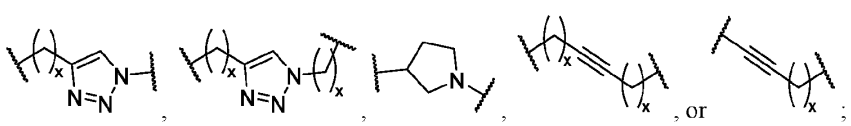


[00281] Embodiment 98. The compound of any one of embodiments 1-93, or a pharmaceutically acceptable salt or solvate thereof, wherein L is absent or  wherein:

each A is independently absent,  , or  ;

each L^1 is independently absent, 



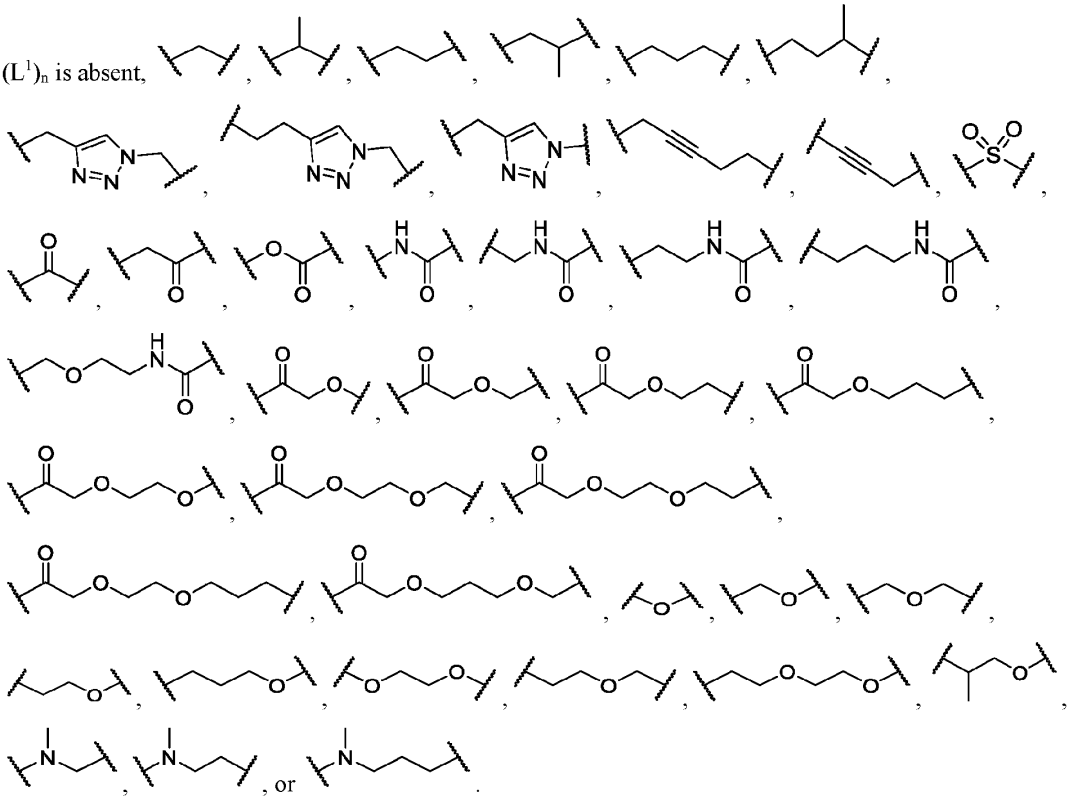
 , or ;

n is 1, 2, or 3; each x is independently 1, 2, 3, 4, 5, or 6;

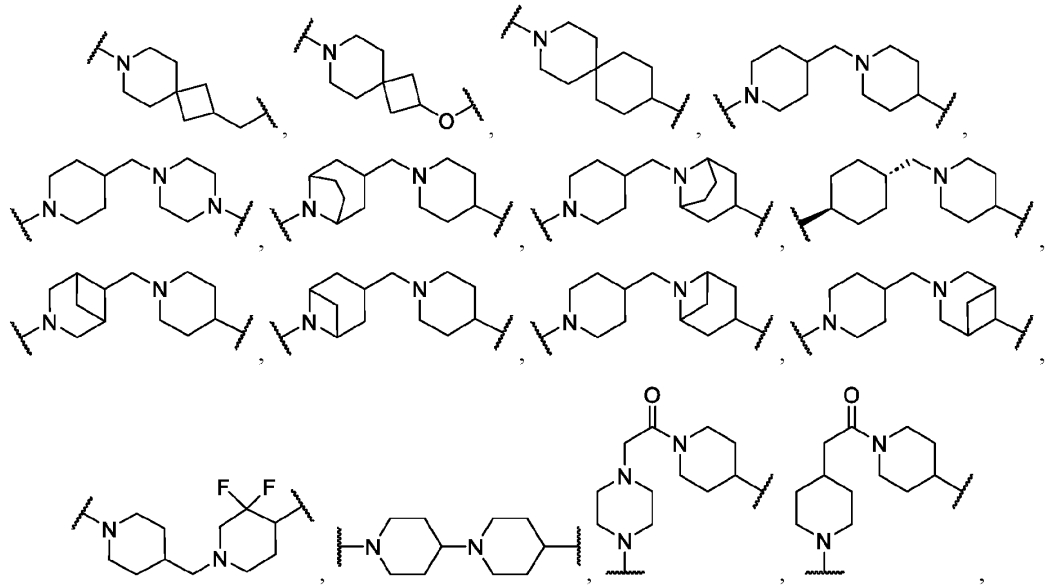
each R^a is independently hydrogen or substituted or unsubstituted C_1-C_6alkyl; and

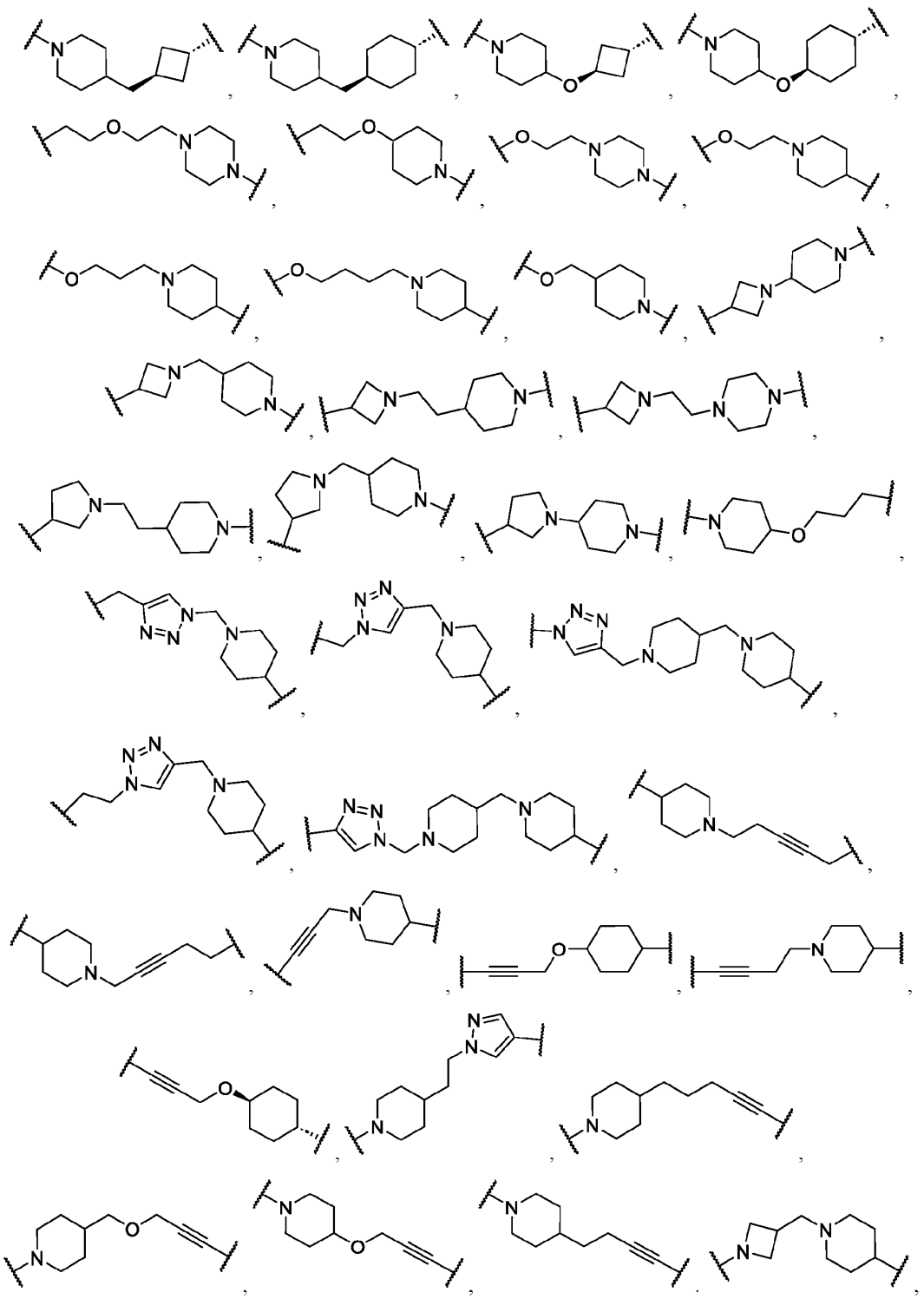
each R^b is independently hydrogen, halogen, or substituted or unsubstituted C_1-C_6alkyl.

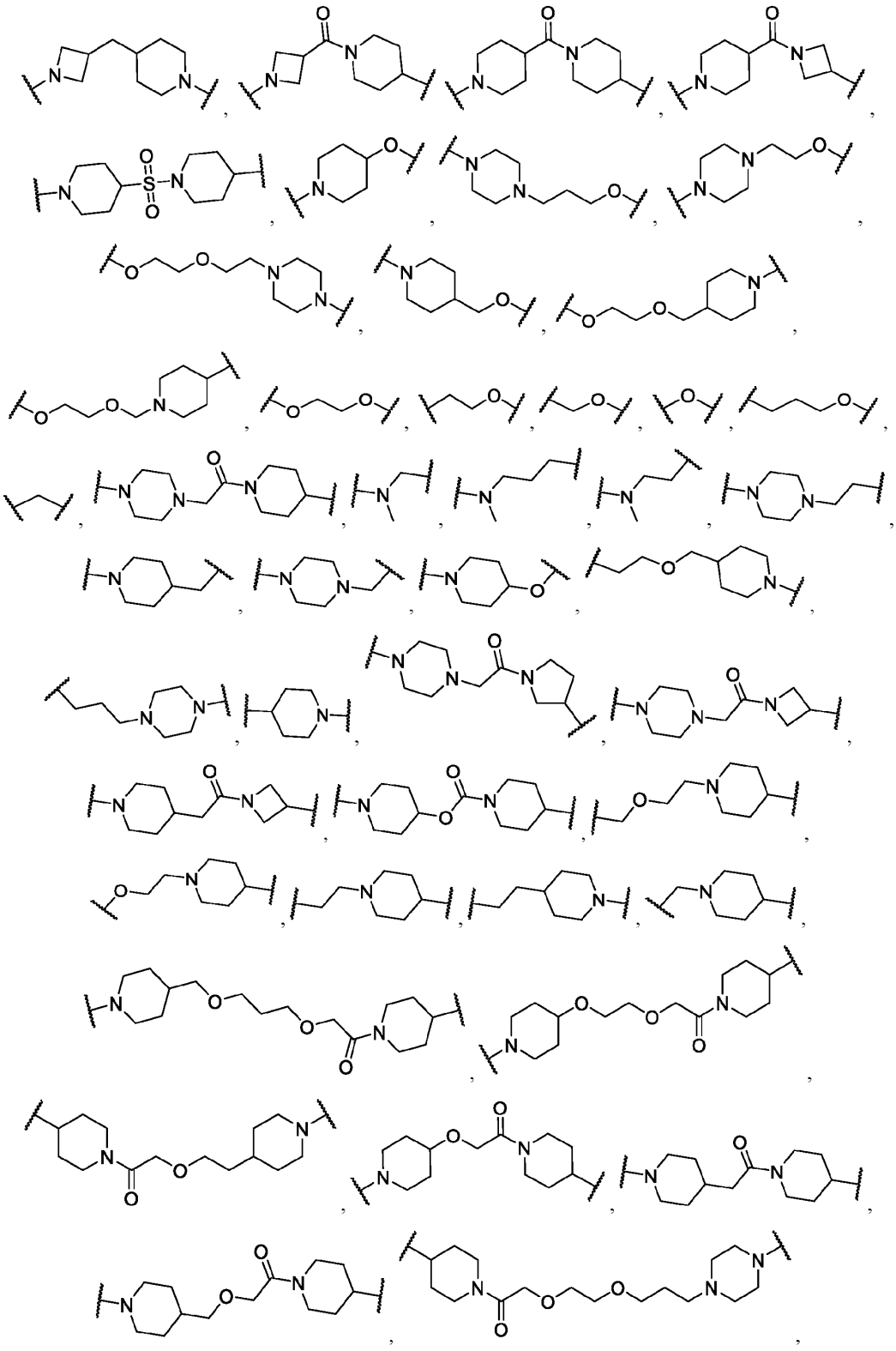
[00282] Embodiment 99. The compound of any one of embodiments 96-98, or a pharmaceutically acceptable salt or solvate thereof, wherein:

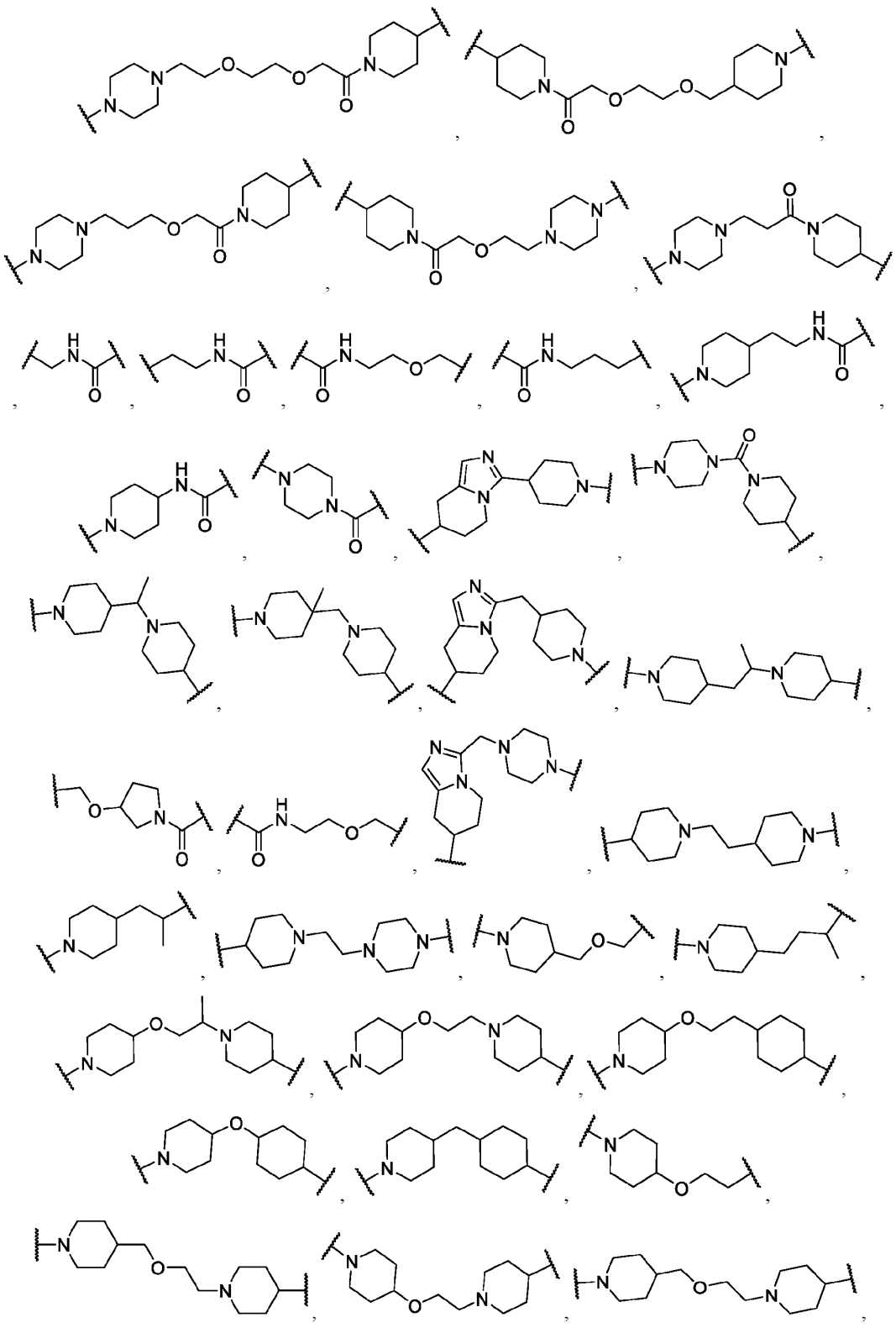
$(L^1)_n$ is absent,  , or .

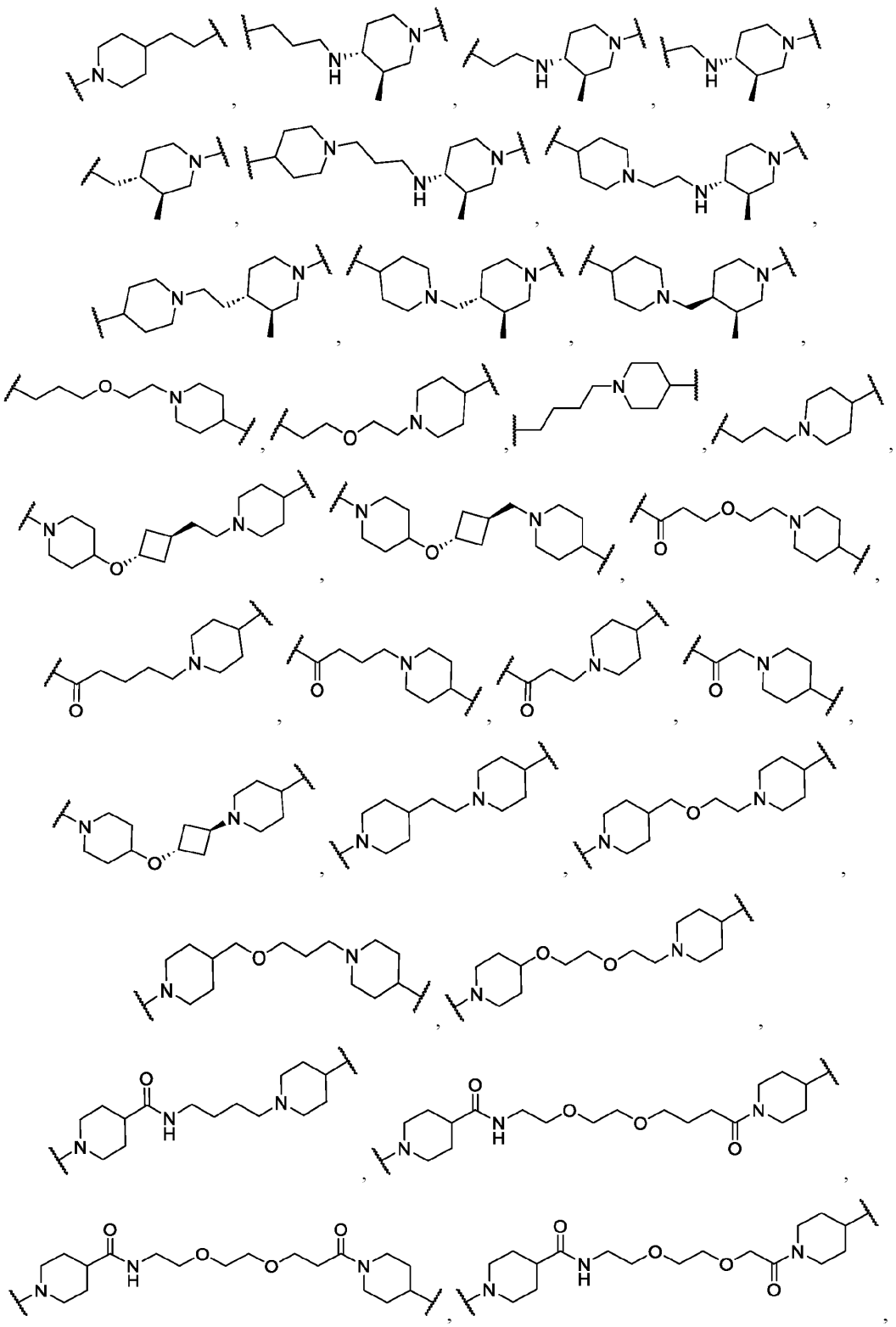
[00283] Embodiment 100. The compound of any one of embodiments 1-99, or a pharmaceutically acceptable salt or solvate thereof, wherein L has one of the following structures:

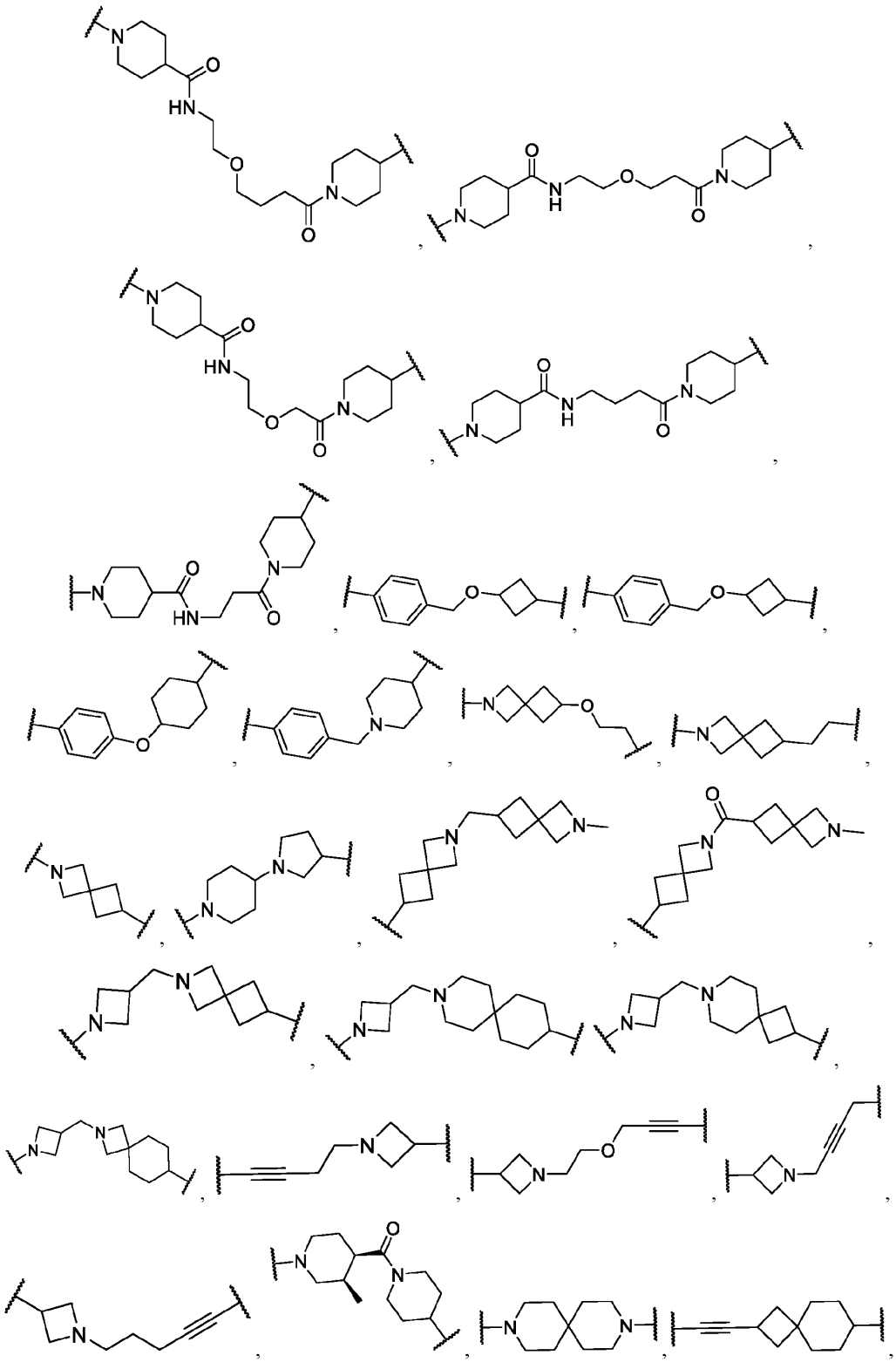


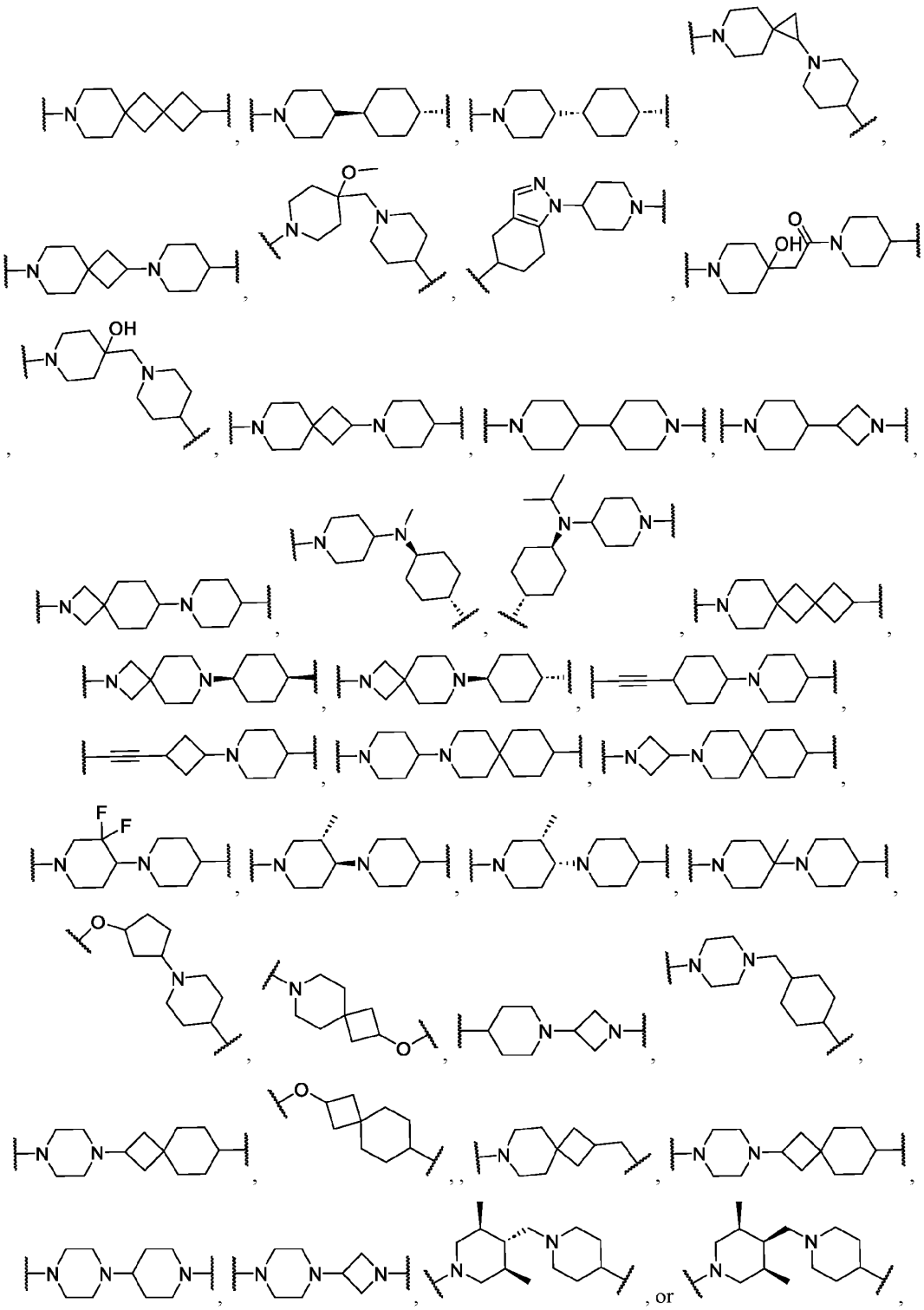






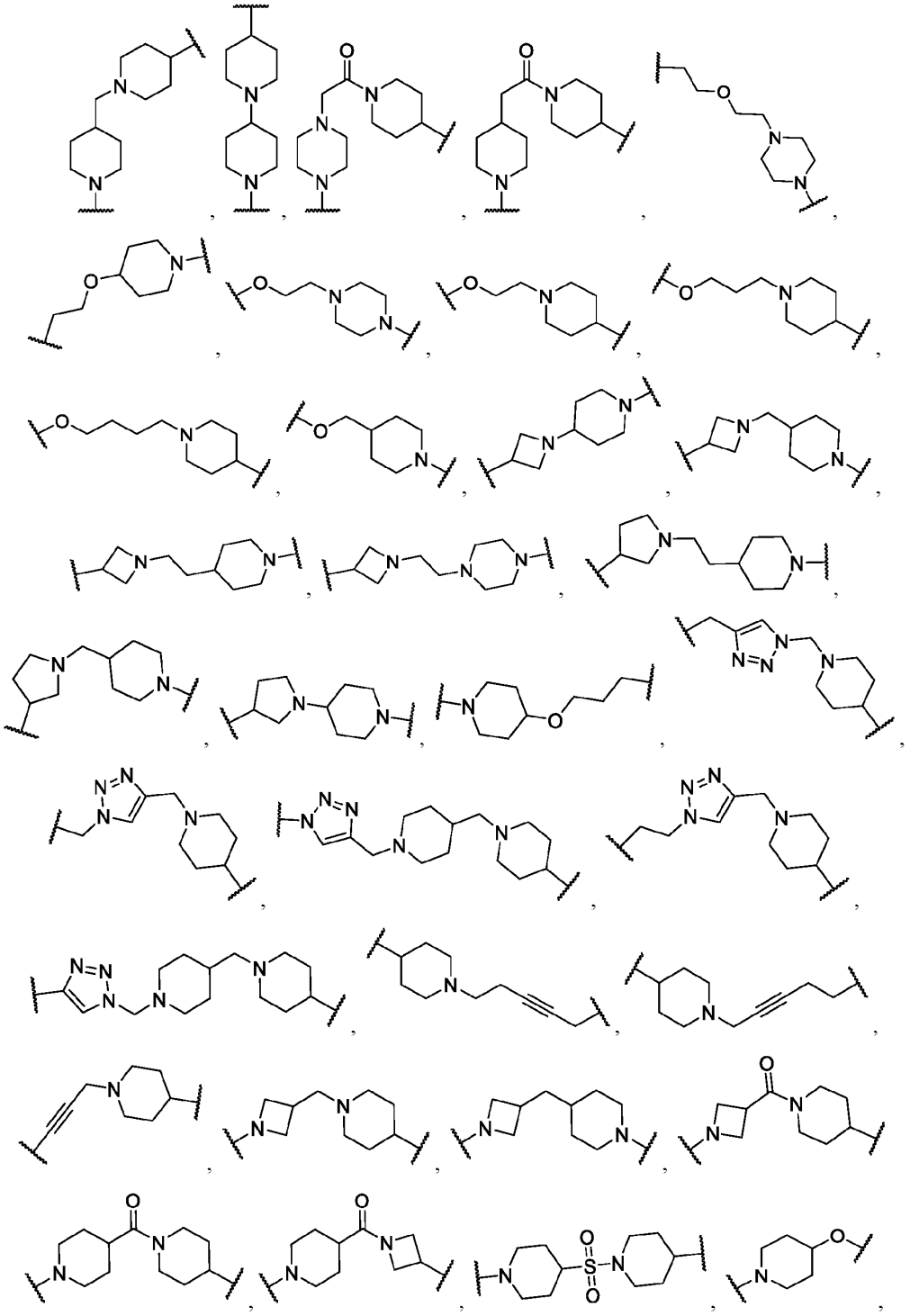


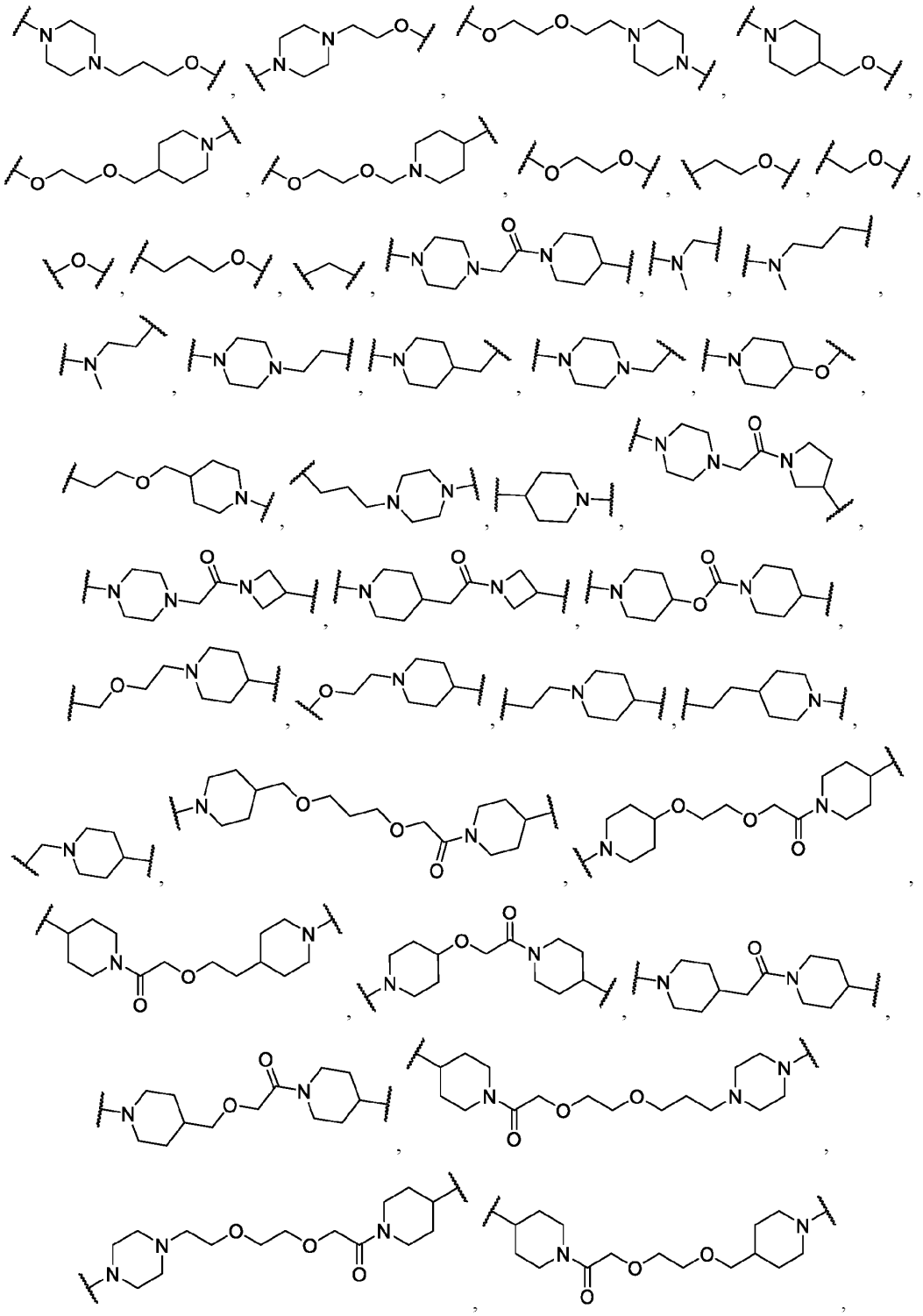


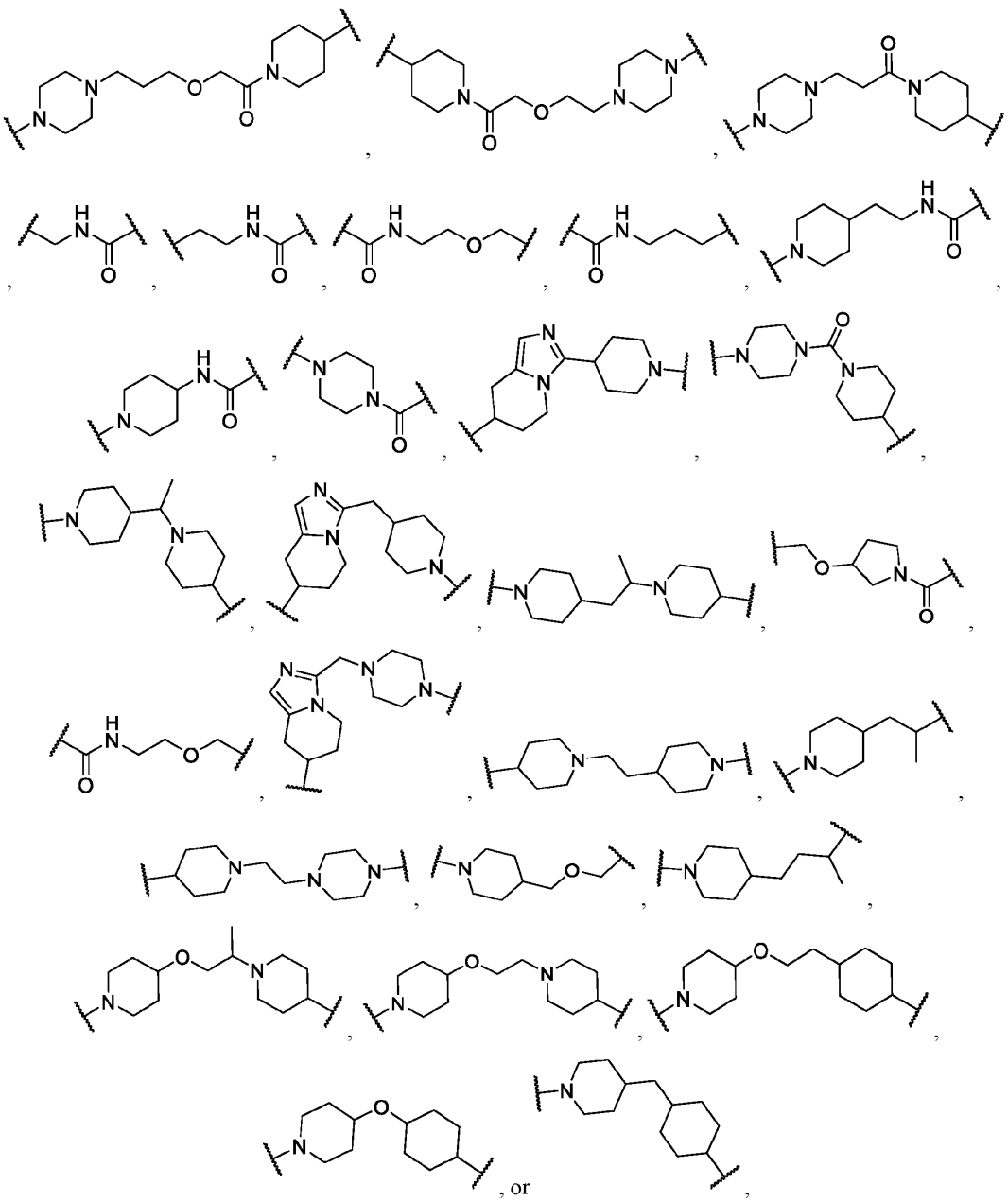


or a pharmaceutically acceptable salt or solvate thereof.

[00284] Embodiment 101. The compound of any one of embodiments 1-99, or a pharmaceutically acceptable salt or solvate thereof, wherein L has one of the following structures:







, or

or a pharmaceutically acceptable salt or solvate thereof.

[00285] Embodiment 102. A compound of Table 1, or a pharmaceutically acceptable salt or solvate thereof.

[00286] Embodiment 103. A stable ternary complex comprising:

a. one or more disease-dependent proteins (DDPs);

b. Androgen Receptor (AR); and

c. heterobifunctional conditional inhibitor compound of any one of embodiments 1-102;

wherein DDP and AR are present in a cell of interest (COI) and the relative abundance of the AR in the COI is greater than the relative abundance of the DDP in the COI.

[00287] Embodiment 104. The stable ternary complex of embodiment 103, wherein DDP is Ataxia-telangiectasia mutated (ATM), Ataxia telangiectasia and Rad3-related protein (ATR), Aurora Kinase A (AurkA), AurkB, Cell division cycle 7-related protein kinase (CDC7), Checkpoint kinase 1 (CHK1), CHK2, Cyclin-dependent kinase 1 (CDK1), CDK2, CDK4, CDK5, CDK6, CDK9, DNA methyltransferase 1 (DNMT1), Exportin 1 (XPO1), Histone deacetylase 1 (HDAC1), HDAC2, HDAC3, kinesin family member 11 (KIF11), Mitogen-activated protein kinase kinase 1 (MEK1), MEK2, Myc, neuronal precursor cell-expressed developmentally down-regulated protein 8 (NEDD8), SMARCA2/4, CREB-binding protein (CBP)/p300, WD repeat-containing protein 5 (WDR5), DDB1- and CUL4-associated factor 1 (DCAF1), phosphatidylinositol-3 kinase (PI3K), Protein arginine methyltransferase 5 (PRMT5), splicing factor 3b subunit 1 (SF3B1), WEE1, 20S proteasome subunits, Steroid Receptor Coactivator 1 (SRC1), SRC2, or SRC3.

[00288] Embodiment 105. The stable ternary complex of embodiment 103, wherein DDP is Aurora Kinase A (AurkA), Checkpoint kinase 1 (CHK1), CHK2, CDK4, CDK6, Myc, SMARCA2/4, CREB-binding protein (CBP)/p300, WD repeat-containing protein 5 (WDR5), DDB1- and CUL4-associated factor 1 (DCAF1), phosphatidylinositol-3 kinase (PI3K), or WEE1.

[00289] Embodiment 106. The stable ternary complex of embodiment 103, wherein the DDP is CREB-binding protein (CBP)/p300.

[00290] Embodiment 107. A stable ternary complex comprising:

d. CBP/p300;

e. Androgen receptor (AR); and

f. heterobifunctional conditional inhibitor compound of any one of embodiments 1-102;

wherein CBP/p300 and DP are present in a cell of interest (COI) and the relative abundance of the DP in the COI is greater than the relative abundance of CBP/p300 in the COI.

[00291] Embodiment 108. A method of selectively inhibiting the activity of a disease-dependent protein (DDP) in a cell of interest (COI) of a mammal comprising administering a heterobifunctional compound of any one of embodiments 1-102, or a pharmaceutically acceptable salt or solvate thereof, wherein the COI expresses the androgen receptor (AR).

[00292] Embodiment 109. The method of embodiment 108, wherein the heterobifunctional compound of any one of embodiments 1-102, or a pharmaceutically acceptable salt or solvate thereof, inhibits the activity of the DDP in the COI but does not inhibit the activity of the DDP in cells expressing the DDP and not expressing the AR.

[00293] Embodiment 110. The method of embodiment 108, wherein the AR is overexpressed, overactive or both overexpressed and overactive in the COI.

[00294] Embodiment 111. The method of any one of embodiments 108-110, wherein DDP is Ataxia-telangiectasia mutated (ATM), Ataxia telangiectasia and Rad3-related protein (ATR), Aurora Kinase A

(AurkA), AurkB, Cell division cycle 7-related protein kinase (CDC7), Checkpoint kinase 1 (CHK1), CHK2, Cyclin-dependent kinase 1 (CDK1), CDK2, CDK4, CDK5, CDK6, CDK9, DNA methyltransferase 1 (DNMT1), Exportin 1 (XPO1), Histone deacetylase 1 (HDAC1), HDAC2, HDAC3, kinesin family member 11 (KIF11), Mitogen-activated protein kinase kinase 1 (MEK1), MEK2, Myc, neuronal precursor cell-expressed developmentally down-regulated protein 8 (NEDD8), SMARCA2/4, CREB-binding protein (CBP)/p300, WD repeat-containing protein 5 (WDR5), DDB1- and CUL4-associated factor 1 (DCAF1), phosphatidylinositol-3 kinase (PI3K), Protein arginine methyltransferase 5 (PRMT5), splicing factor 3b subunit 1 (SF3B1), WEE1, 20S proteasome subunits, Steroid Receptor Coactivator 1 (SRC1), SRC2, or SRC3.

[00295] Embodiment 112. The method of any one of embodiments 108-111, wherein DDP is Aurora Kinase A (AurkA), Checkpoint kinase 1 (CHK1), CHK2, CDK4, CDK6, Myc, SMARCA2/4, CREB-binding protein (CBP)/p300, WD repeat-containing protein 5 (WDR5), DDB1- and CUL4-associated factor 1 (DCAF1), phosphatidylinositol-3 kinase (PI3K), or WEE1.

[00296] Embodiment 113. The method of any one of embodiments 108-111, wherein the DDP is CREB-binding protein (CBP)/p300.

[00297] Embodiment 114. A method of treating cancer in a mammal comprising administering to the mammal a heterobifunctional compound of any one of embodiments 1-102.

[00298] Embodiment 115. A method of treating cancer in a mammal comprising administering to the mammal a therapeutically effective amount of a compound of any one of embodiments 1-102, or a pharmaceutically acceptable salt or solvate thereof.

[00299] Embodiment 116. The method of embodiment 115, wherein the cancer is a hormone dependent cancer.

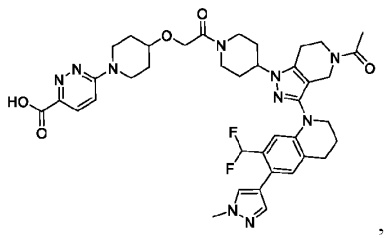
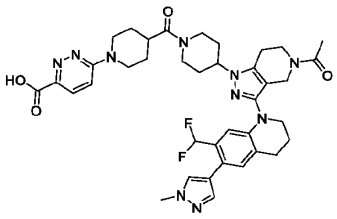
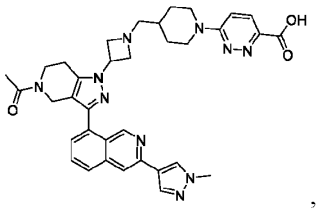
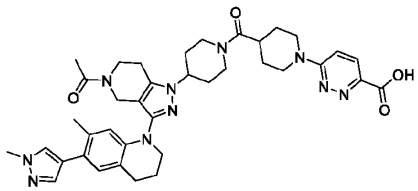
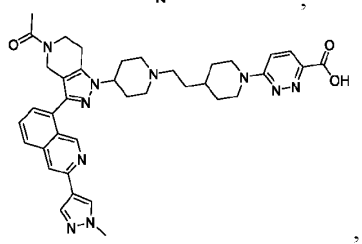
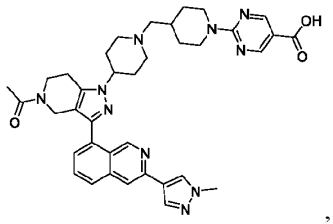
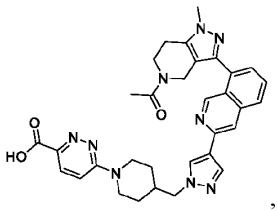
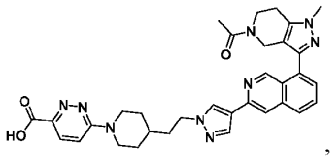
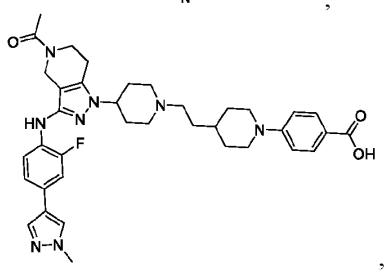
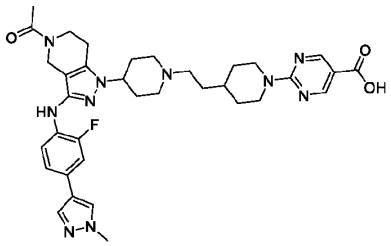
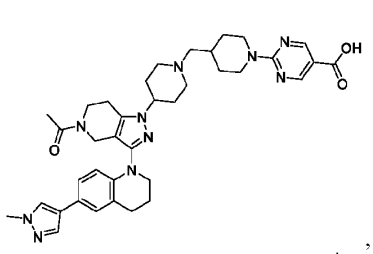
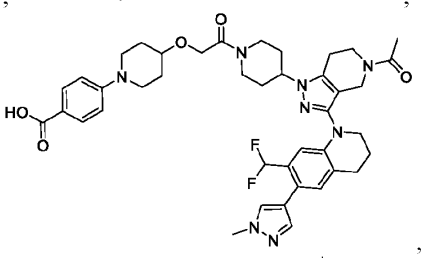
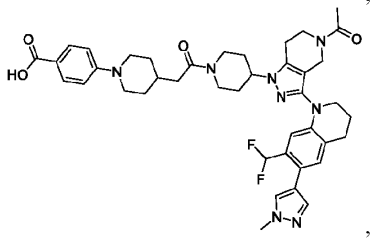
[00300] Embodiment 117. The method of embodiment 115, wherein the cancer is prostate cancer.

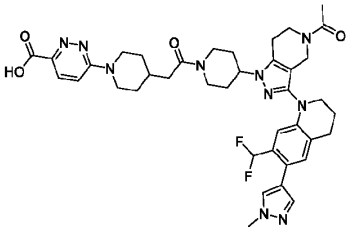
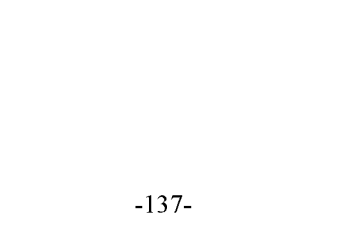
[00301] Embodiment 118. A method of treating an androgen receptor dependent or androgen receptor mediated disease or condition in mammal comprising administering to the mammal a therapeutically effective amount of a compound according to any one of embodiments 1-102, or a pharmaceutically acceptable salt or solvate thereof.

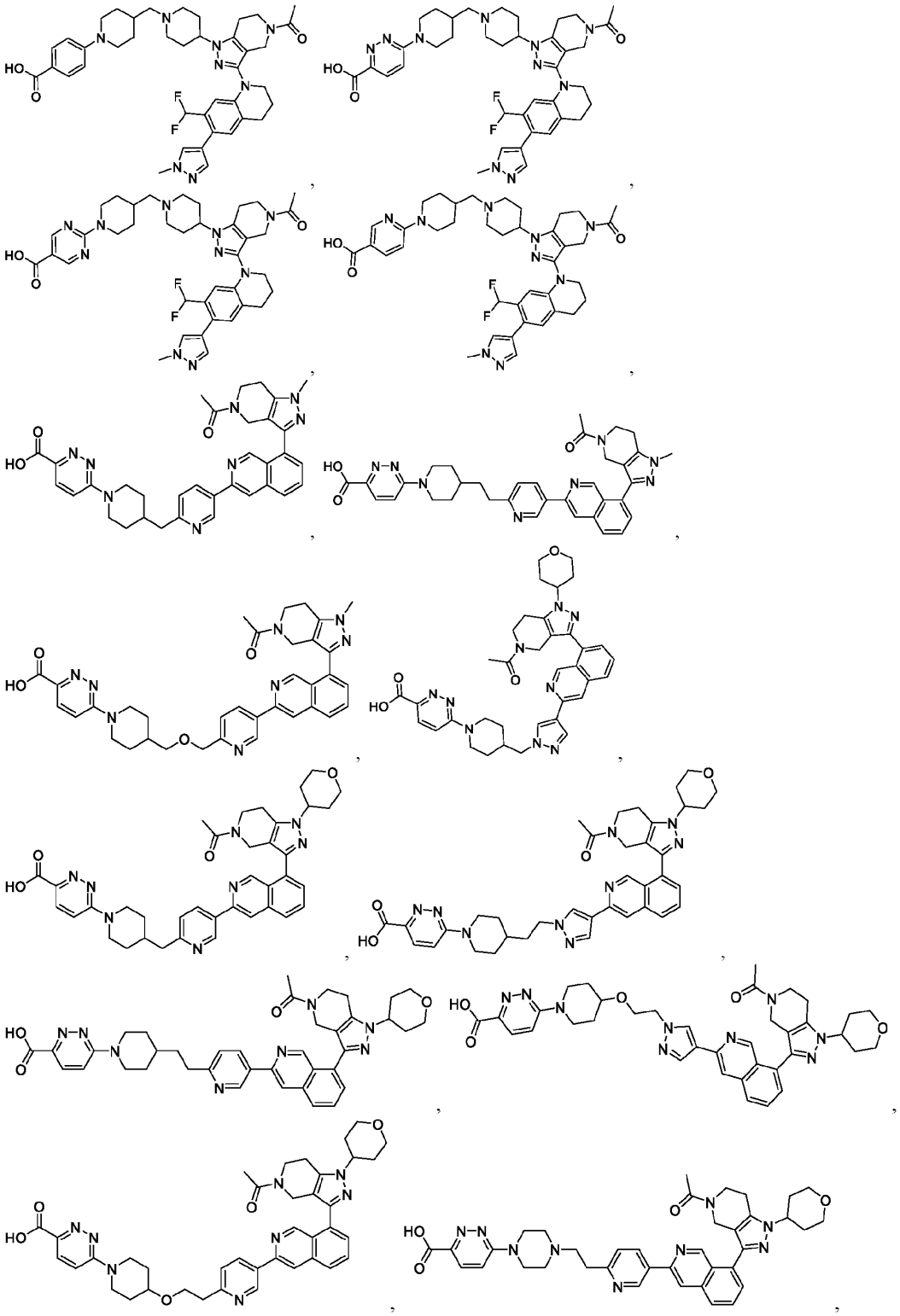
[00302] Embodiment 119. The method of embodiment 118, wherein androgen receptor dependent or androgen receptor mediated disease or condition is selected from benign prostate hyperplasia, hirsutism, adenomas and neoplasms of the prostate, benign or malignant tumor cells containing the androgen receptor, prostate cancer, breast cancer, endometrial cancer, and uterine cancer.

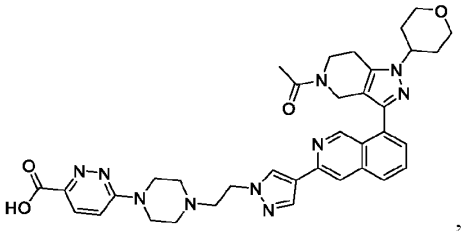
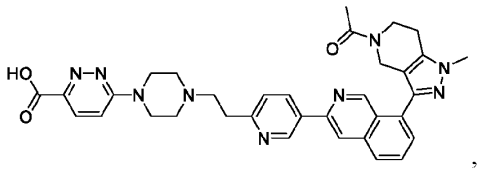
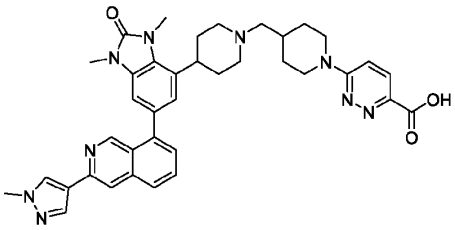
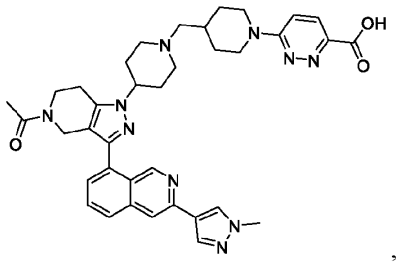
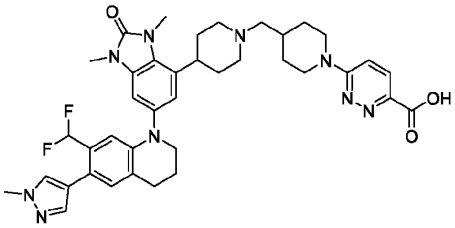
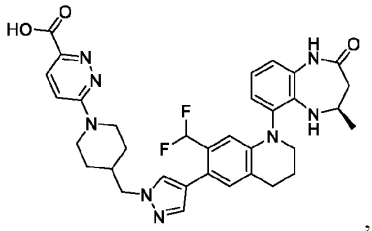
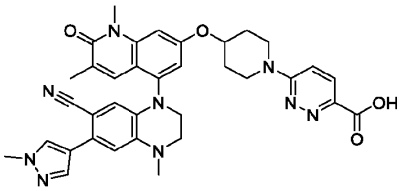
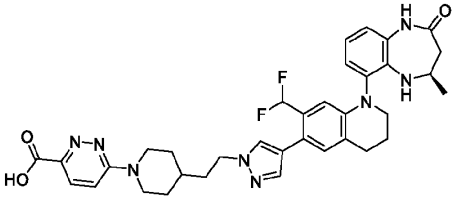
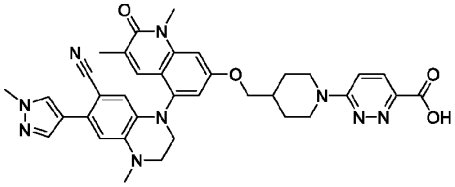
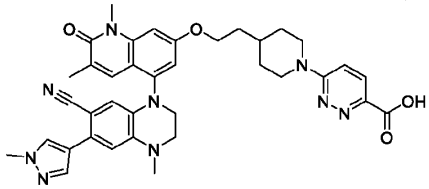
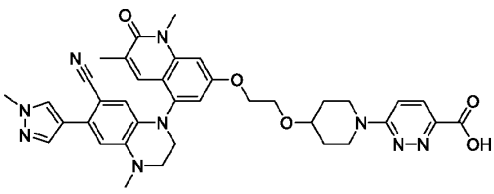
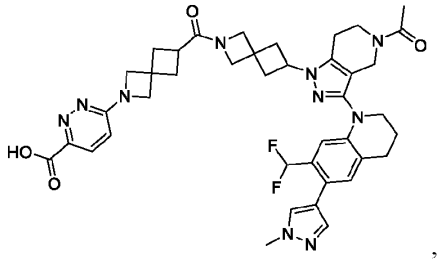
[00303] Embodiment 120. A pharmaceutical composition comprising a compound of any one of embodiments 1-102, or a pharmaceutically acceptable salt or solvate thereof, and at least one pharmaceutically acceptable excipient.

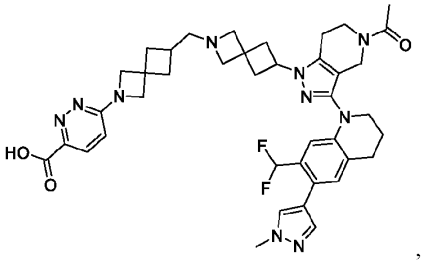
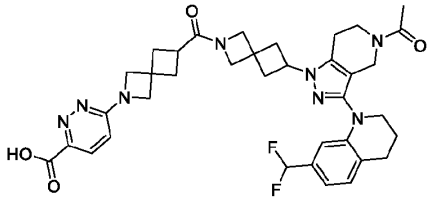
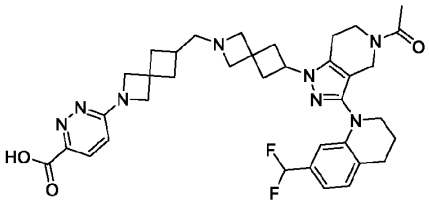
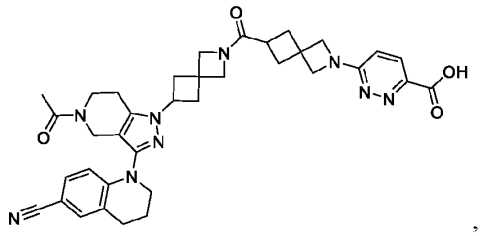
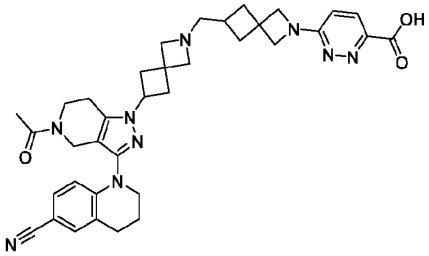
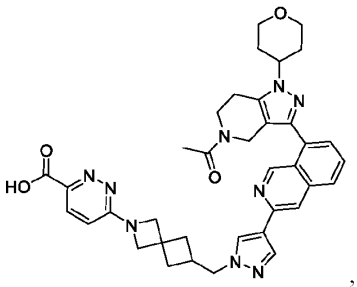
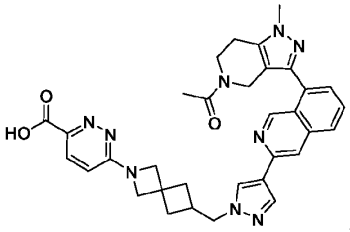
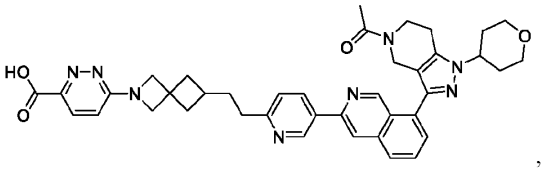
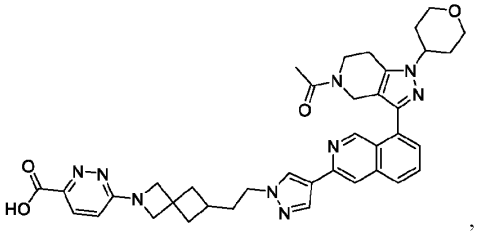
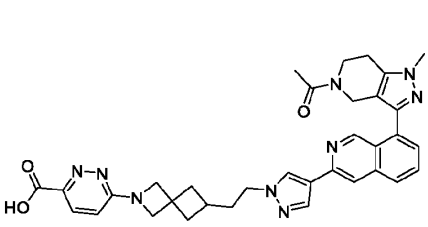
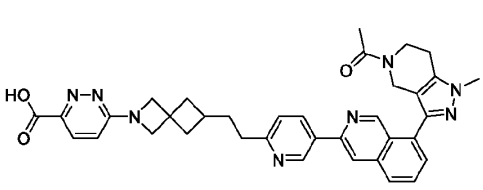
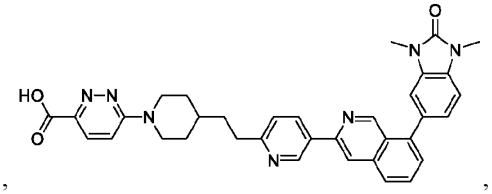
[00304] Embodiment 121. A compound, or a pharmaceutically acceptable salt or solvate thereof, that has one of the following structures:


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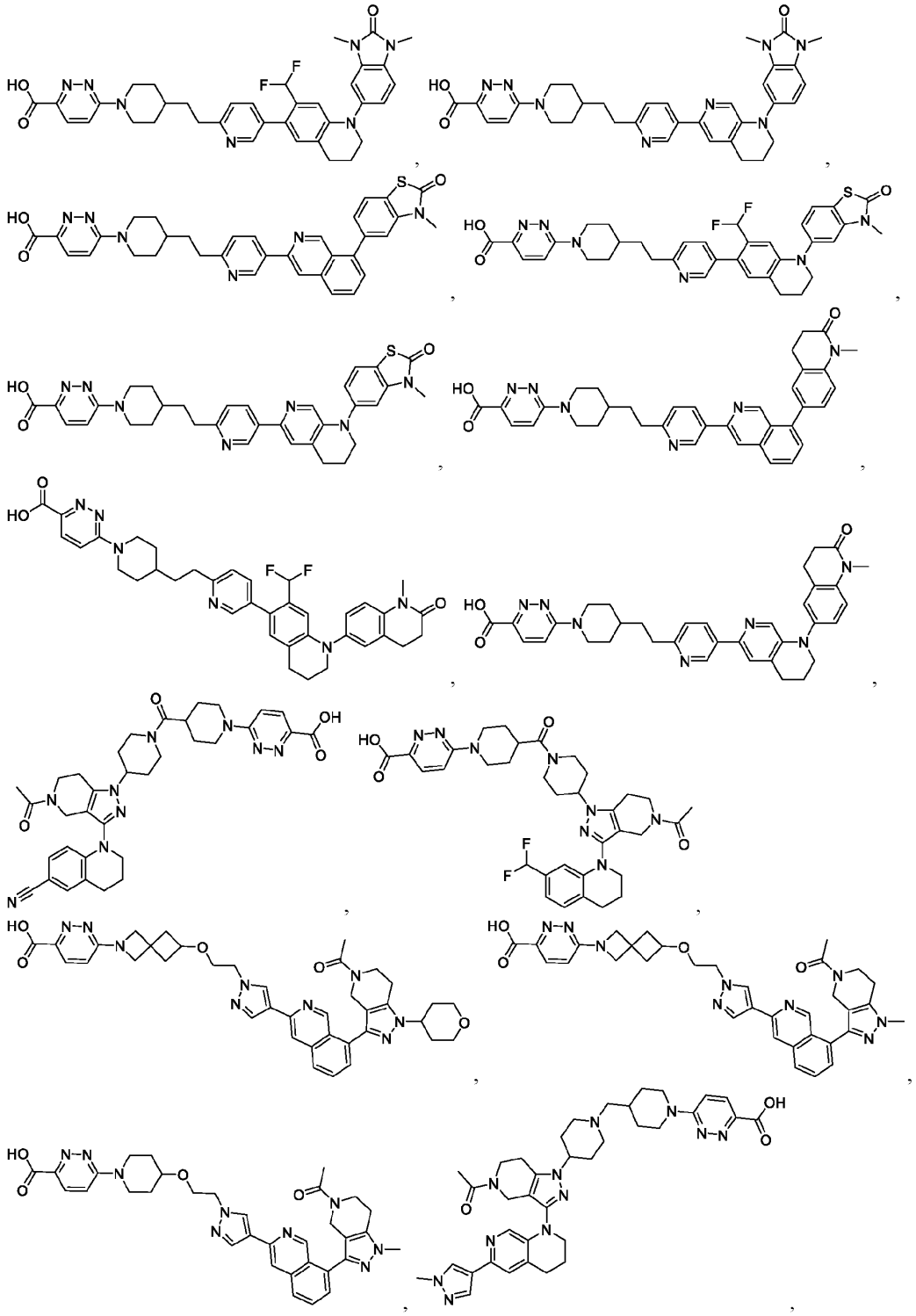


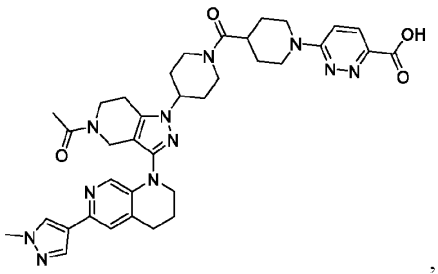
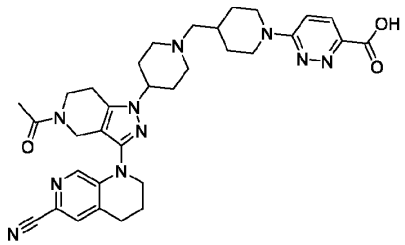
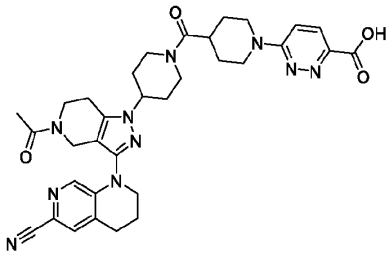
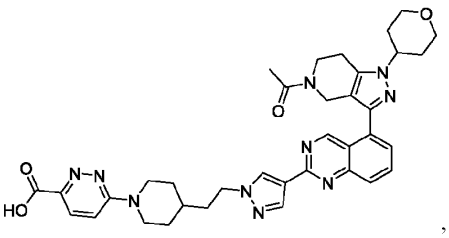
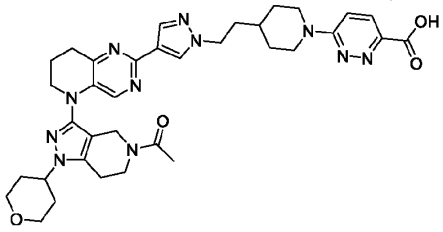
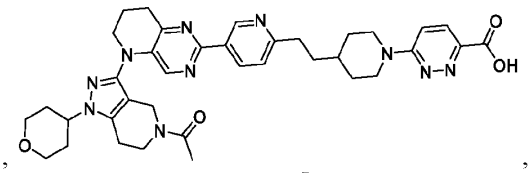
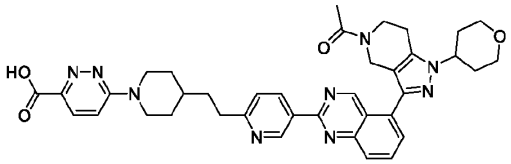
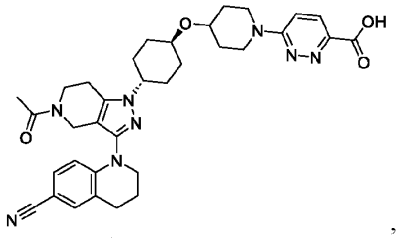
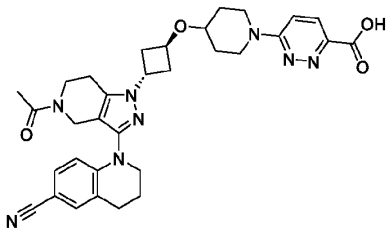
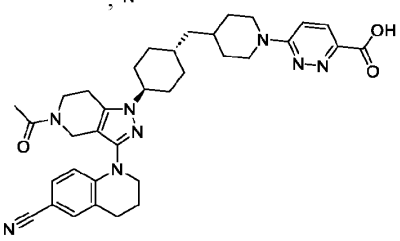
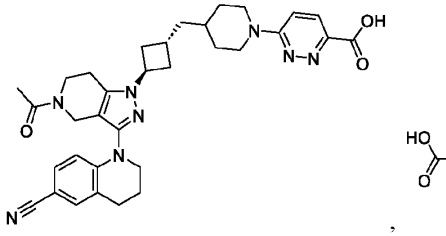
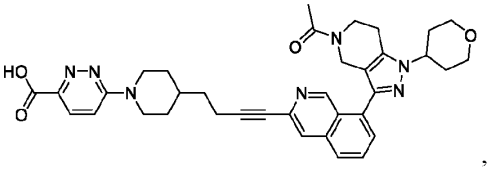

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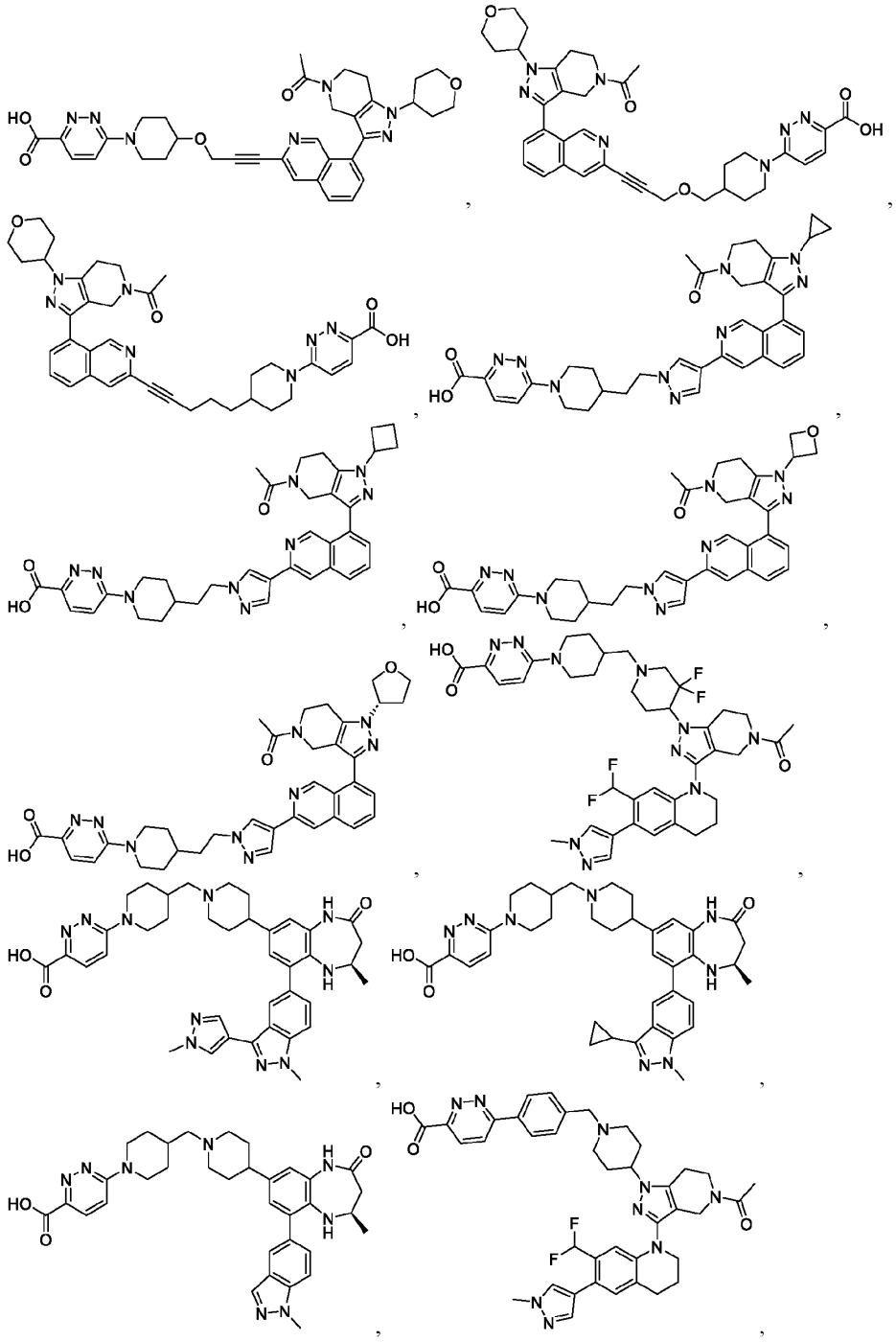

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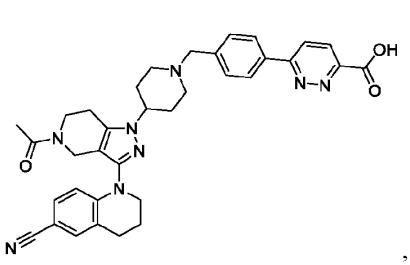
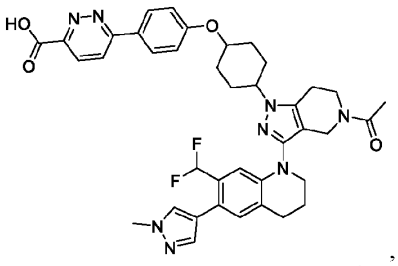
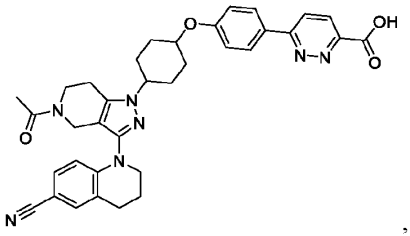
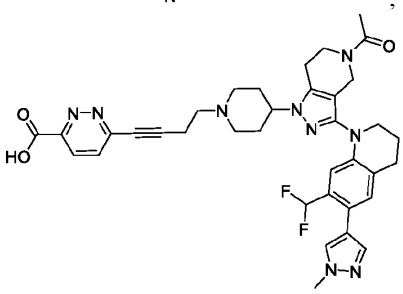
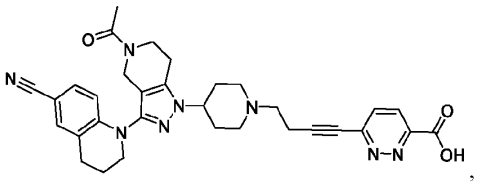
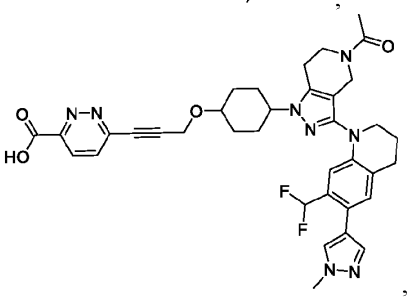
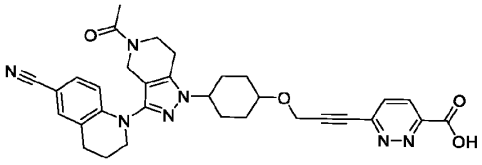
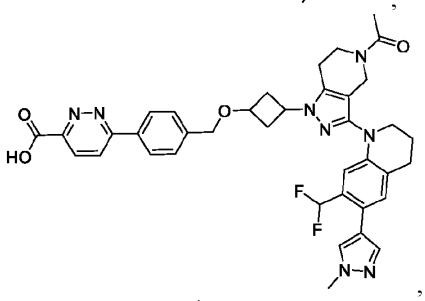
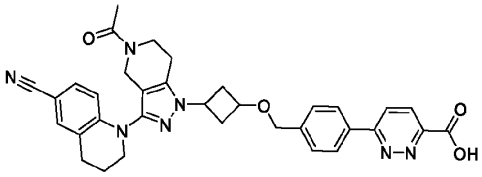
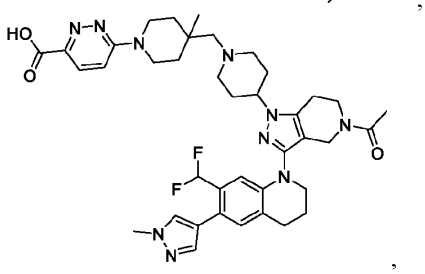
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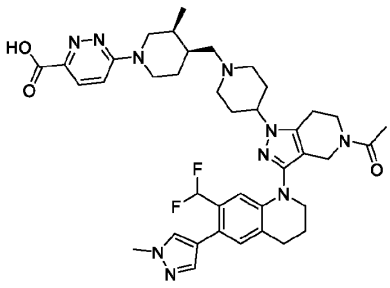
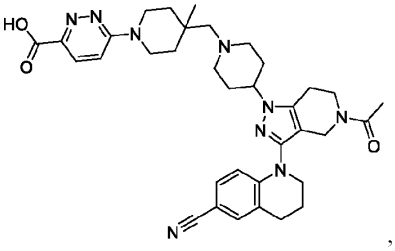
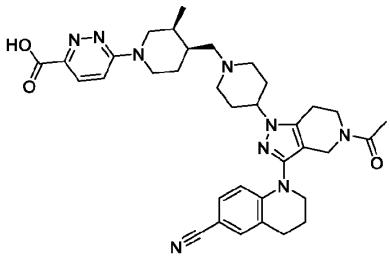
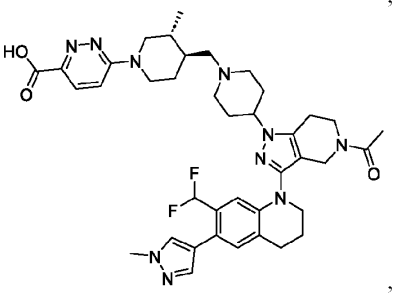
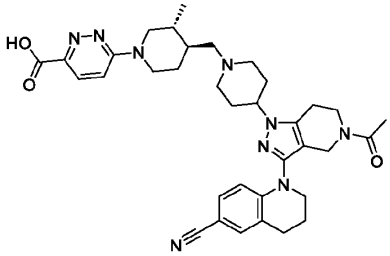
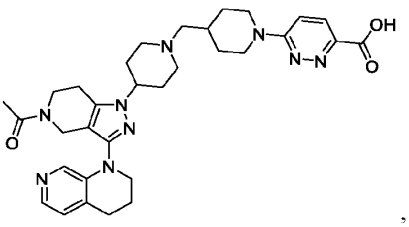
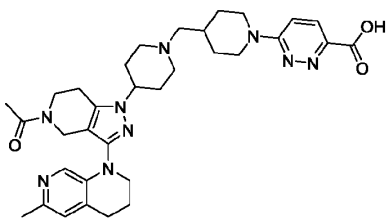
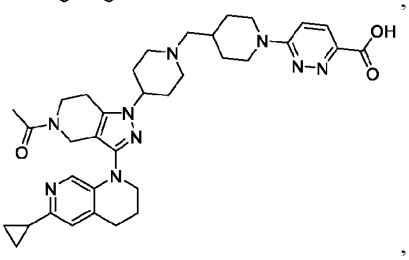
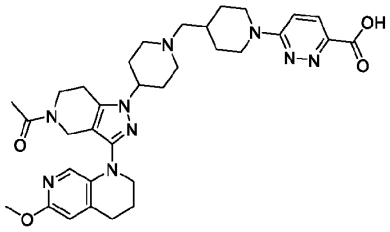
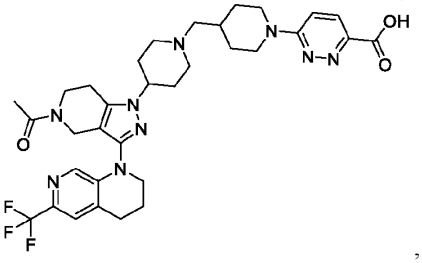

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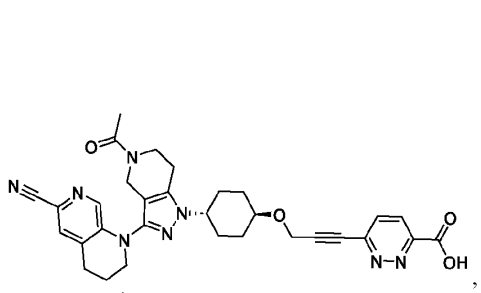
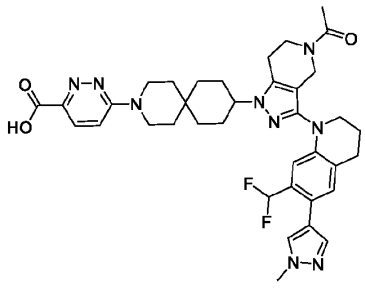
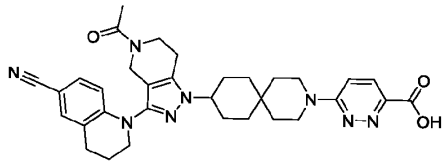
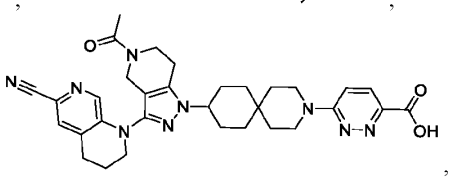
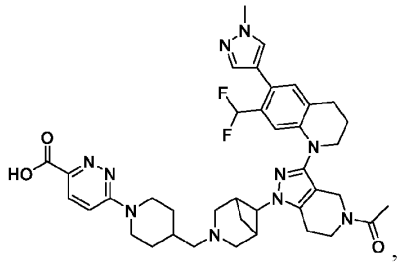
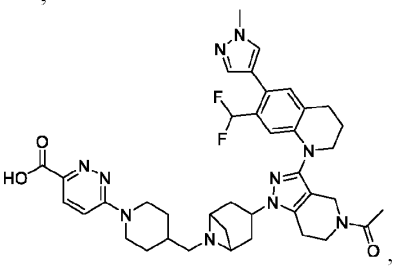
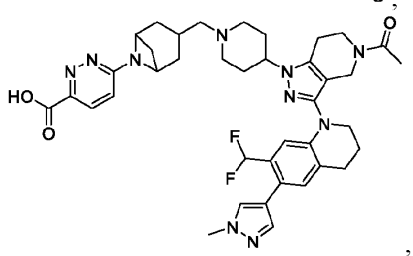
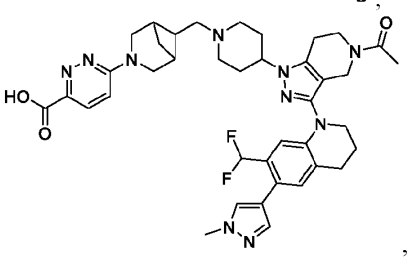
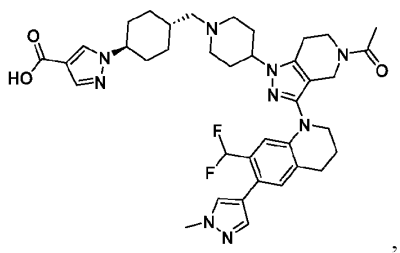
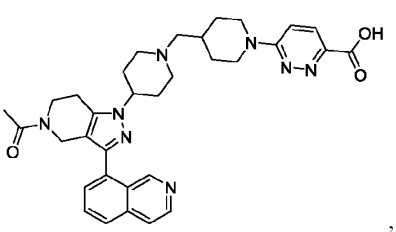
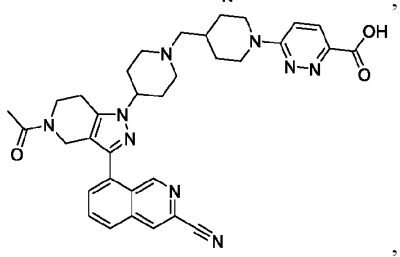
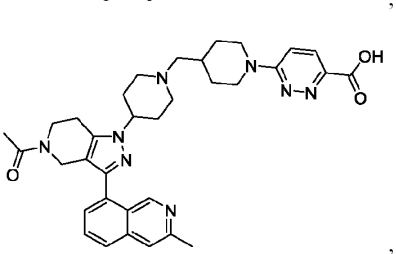


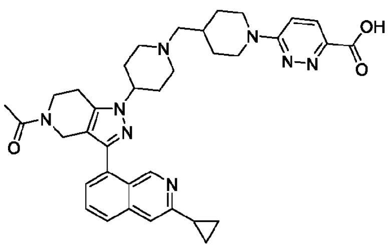
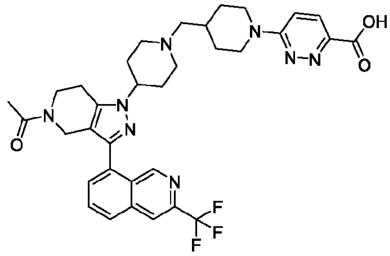
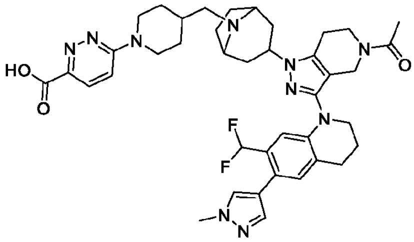
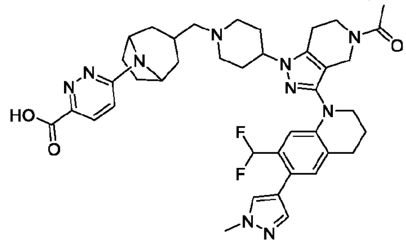
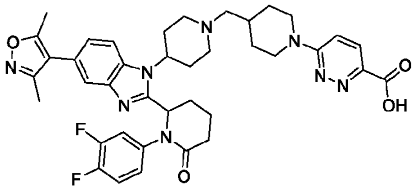
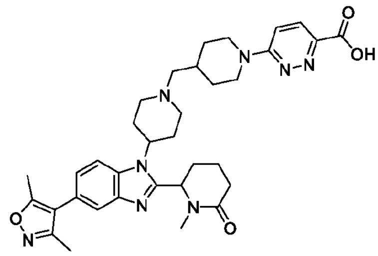
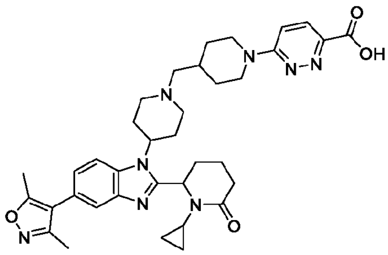
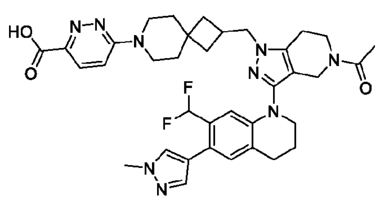
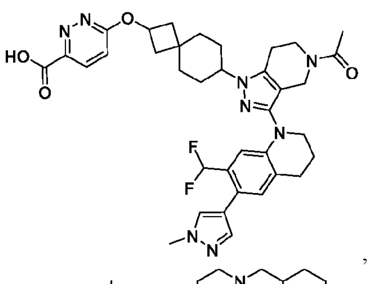
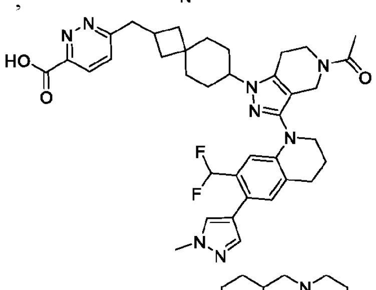
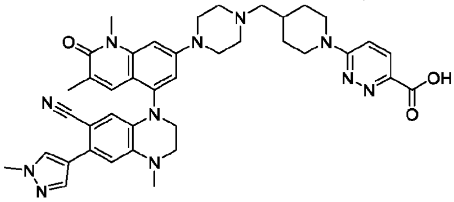
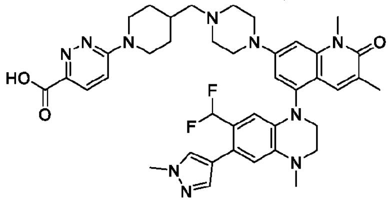

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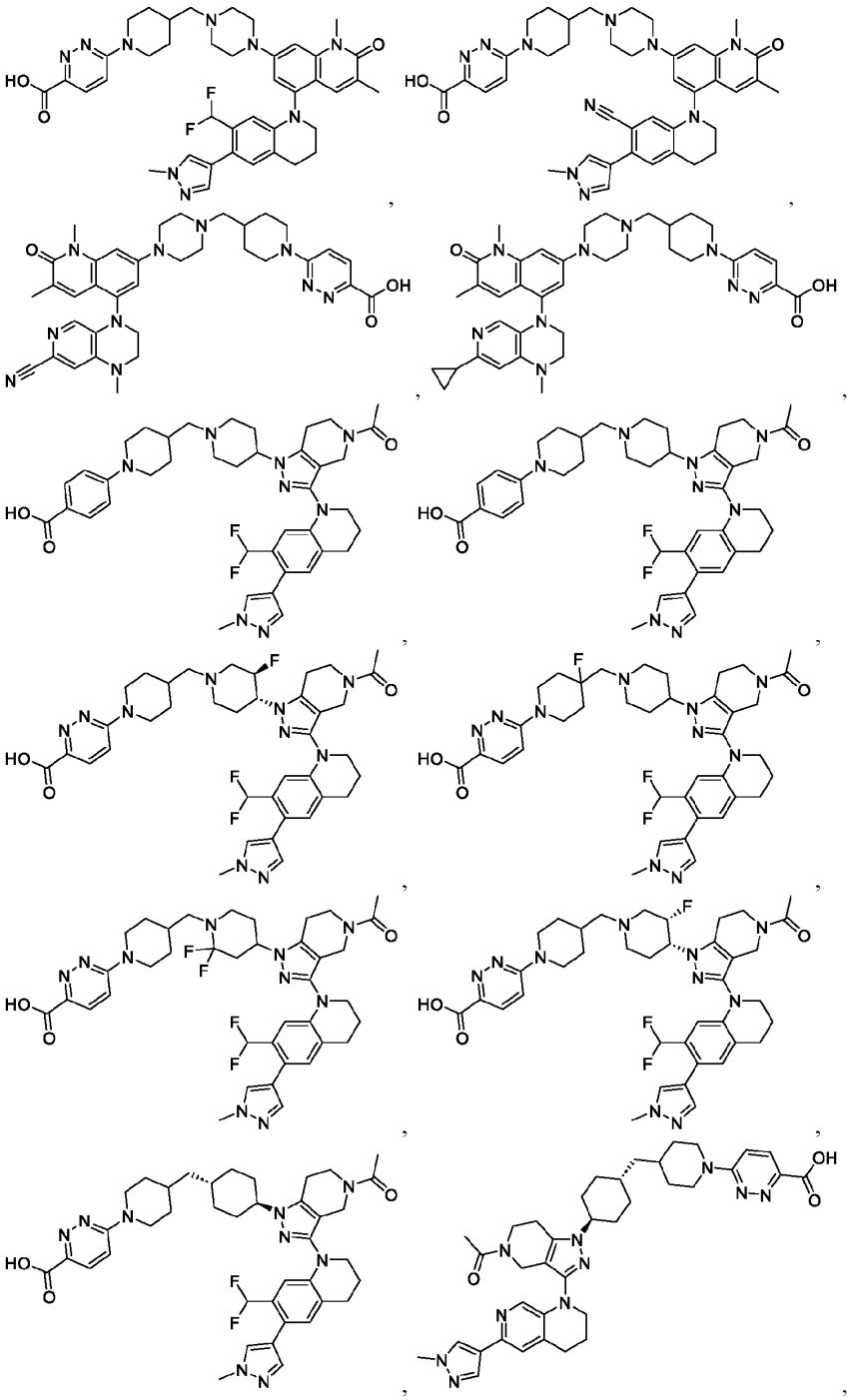
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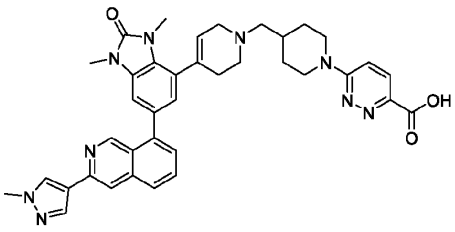
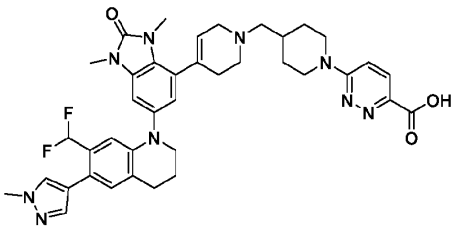
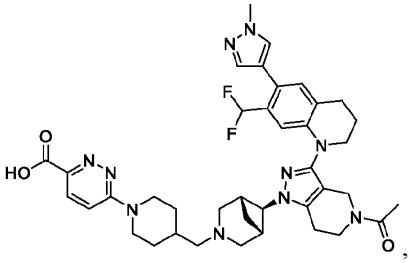
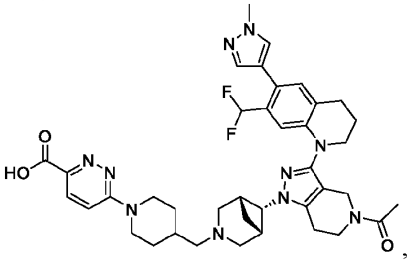
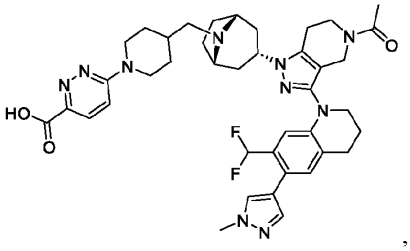
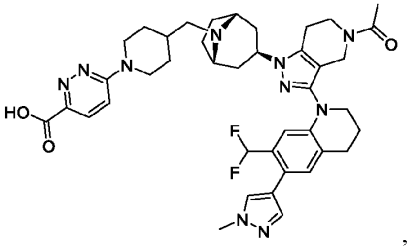
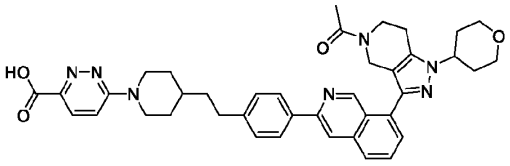
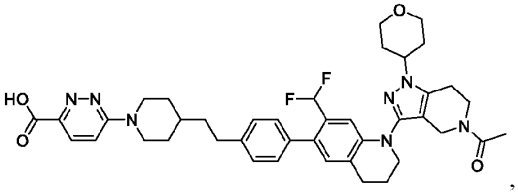
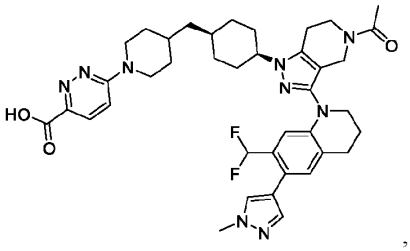
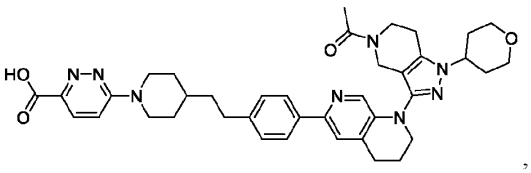
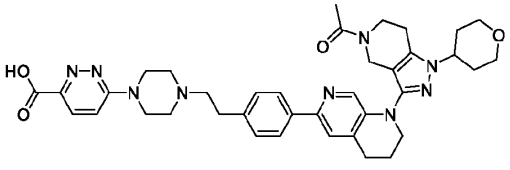
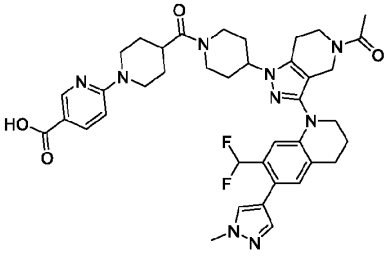
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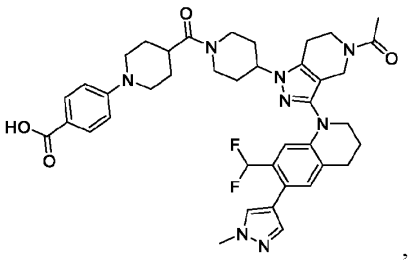
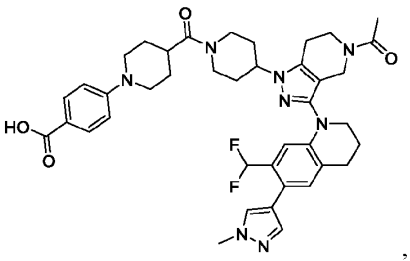
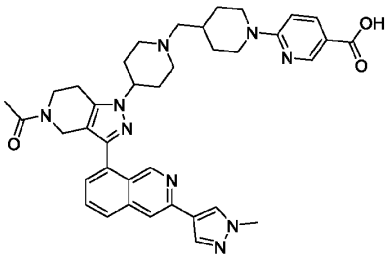
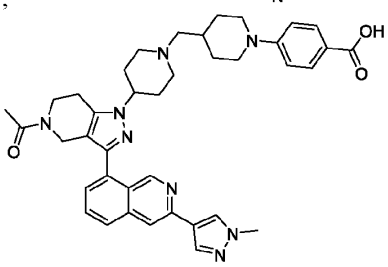
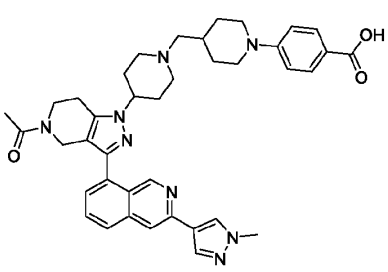
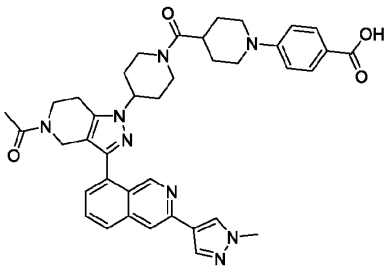
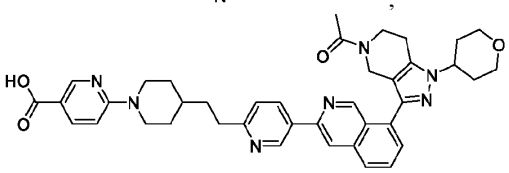
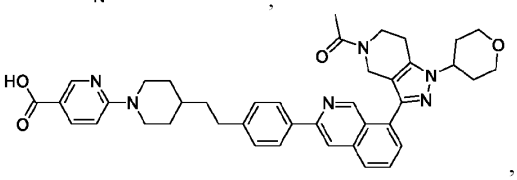
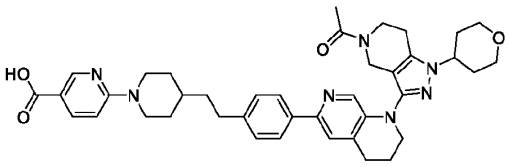
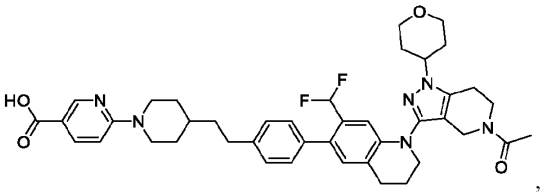
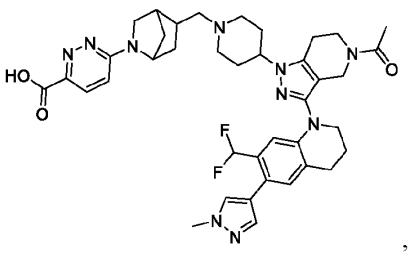
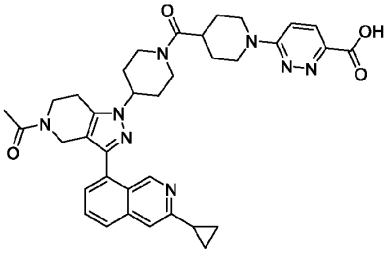

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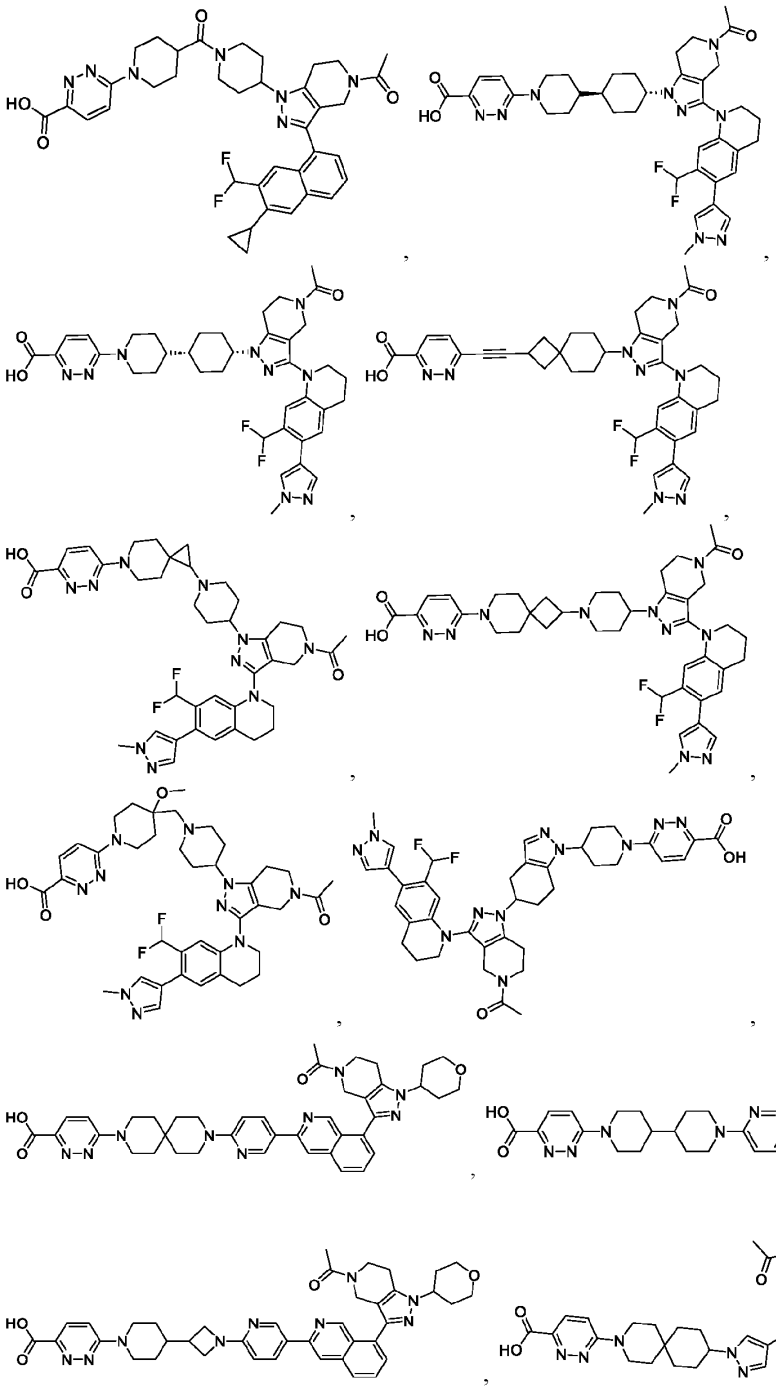

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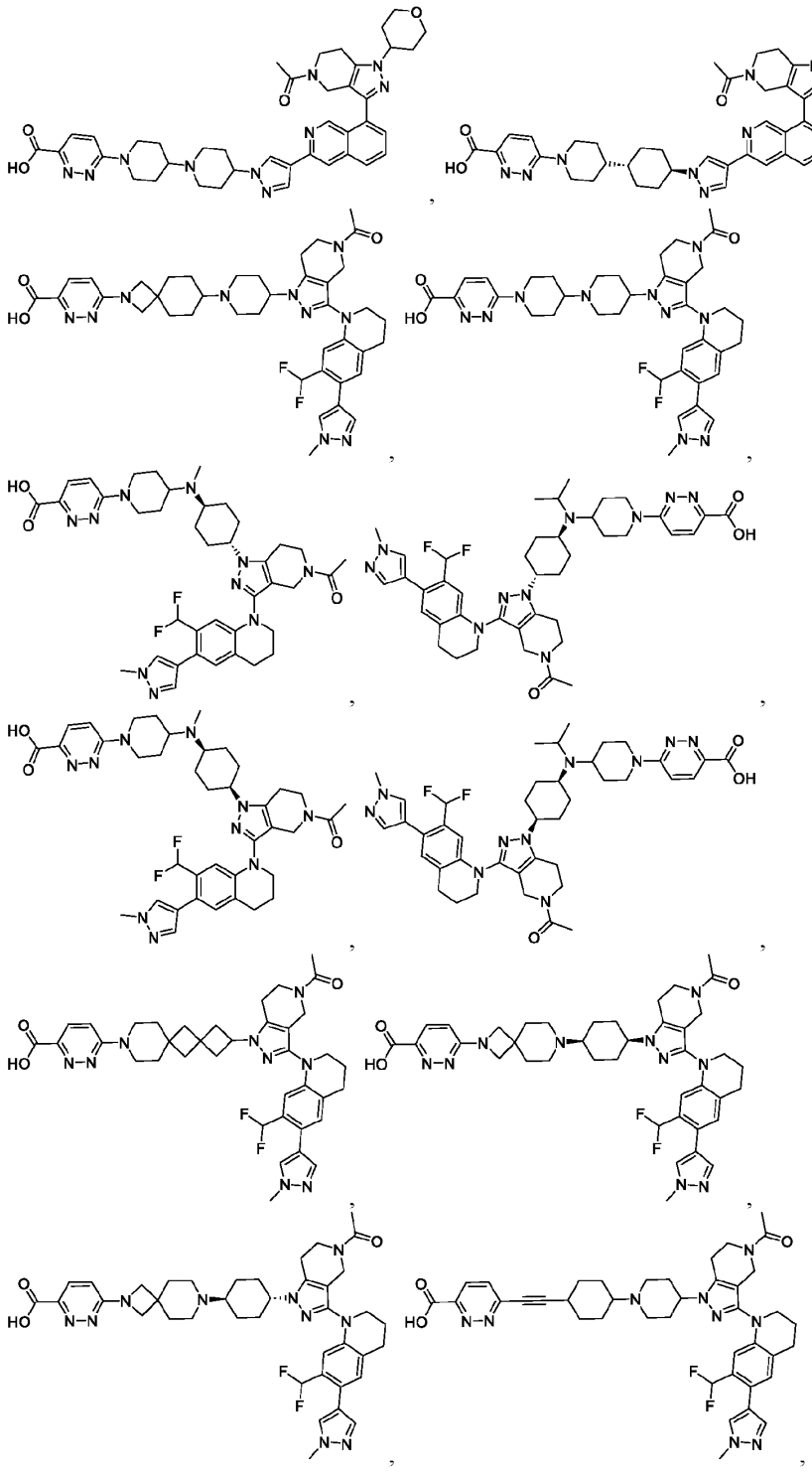

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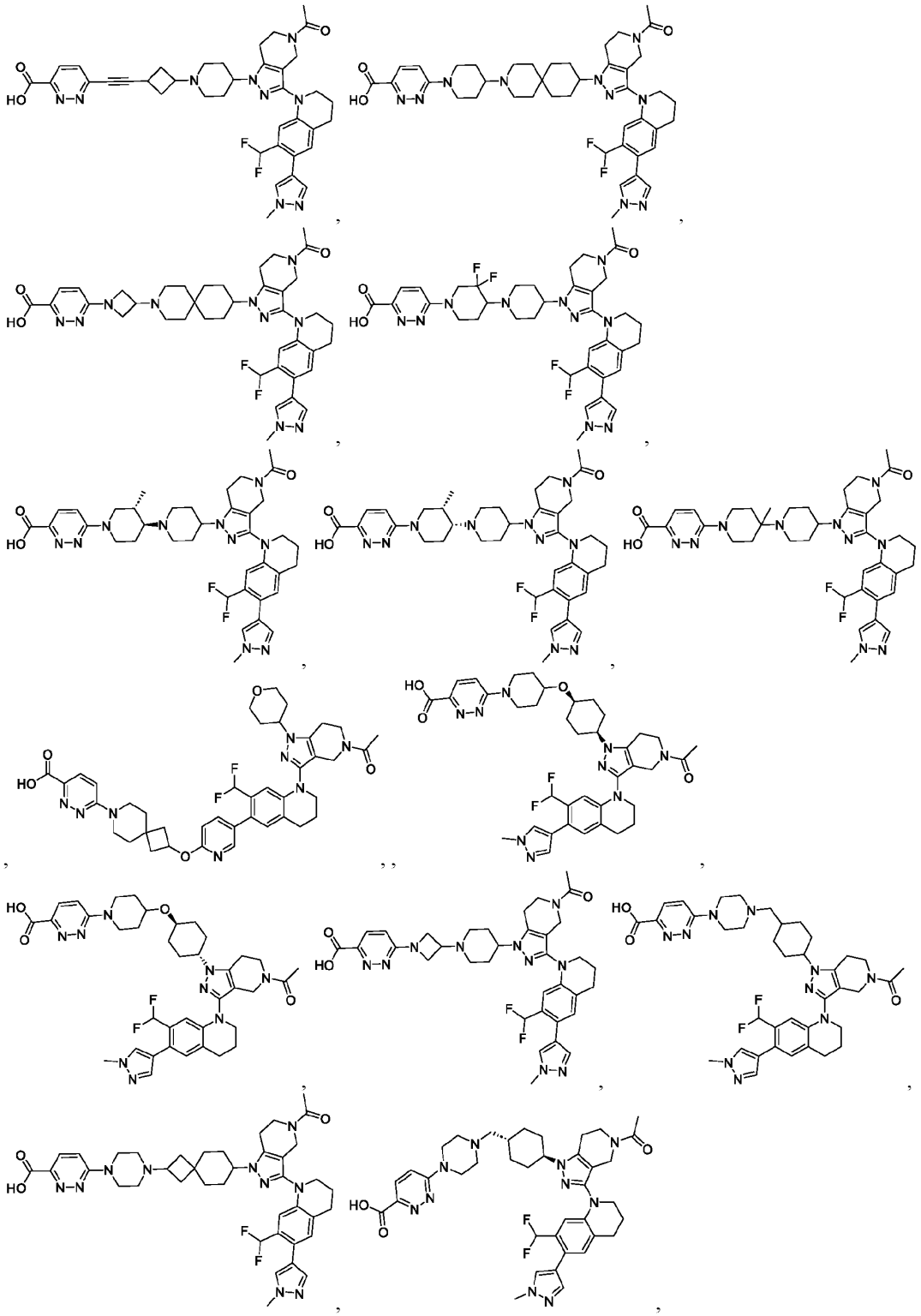


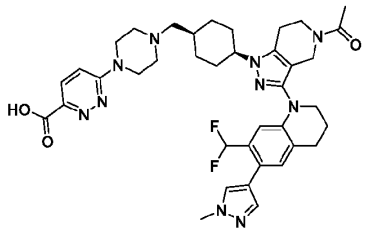
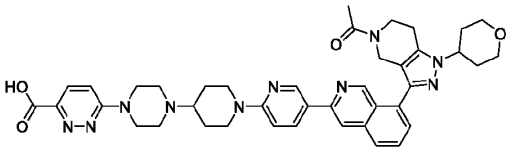
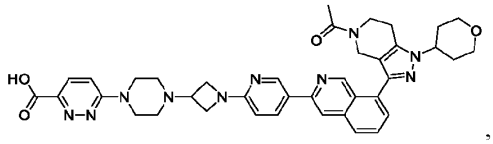
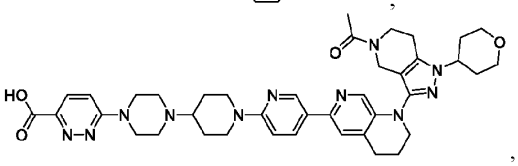
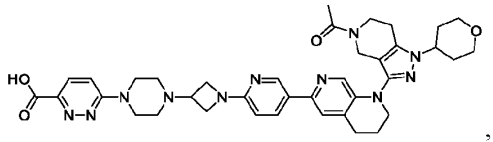
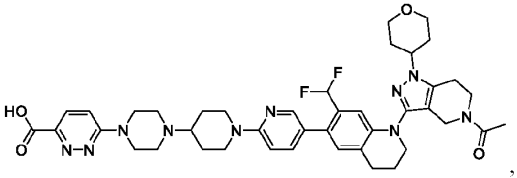
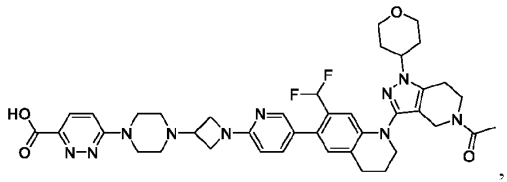
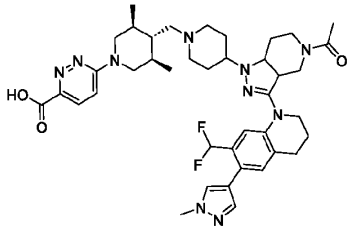
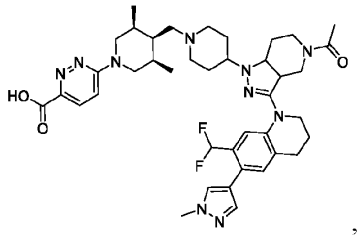
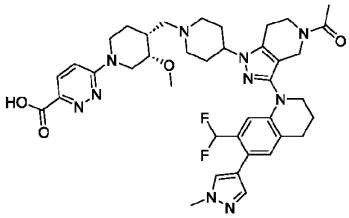
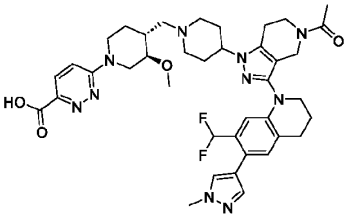
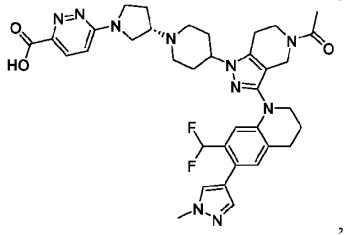
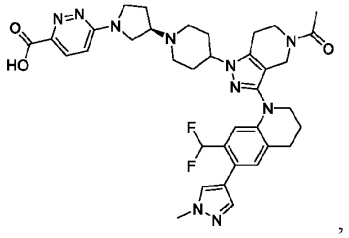
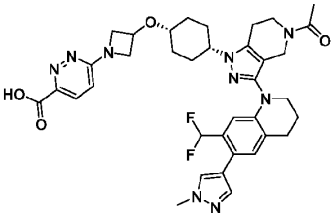
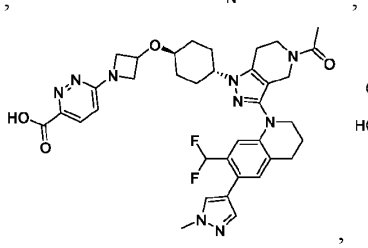
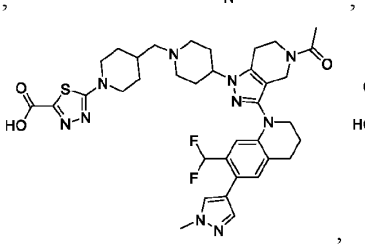
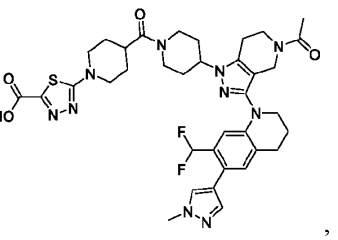

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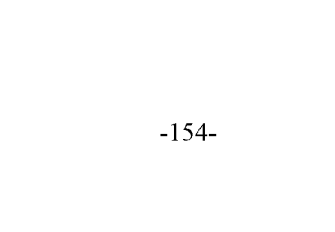

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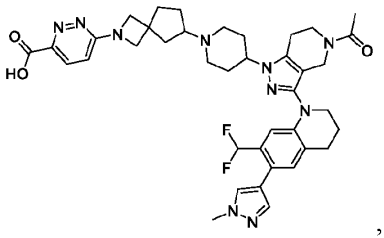
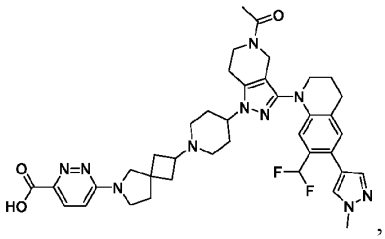
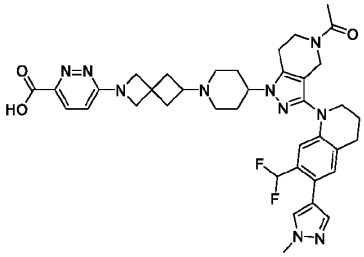
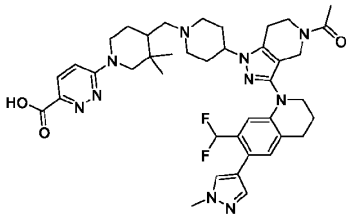
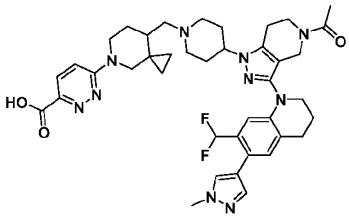
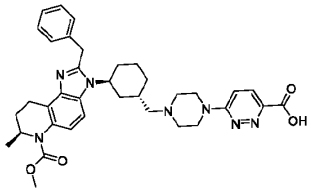
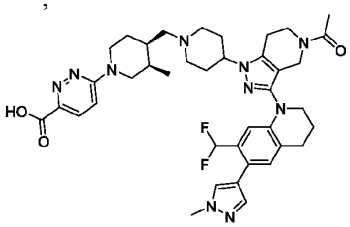
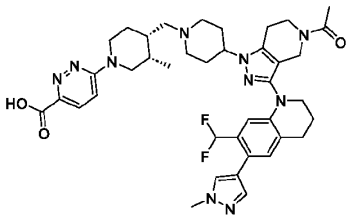
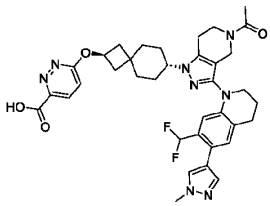
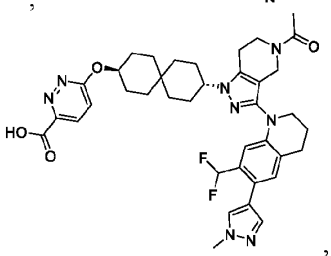
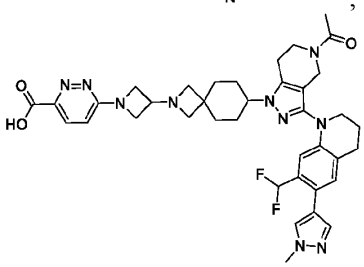
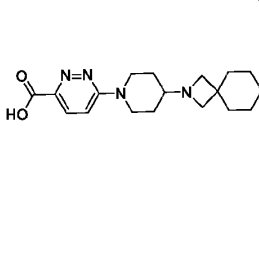
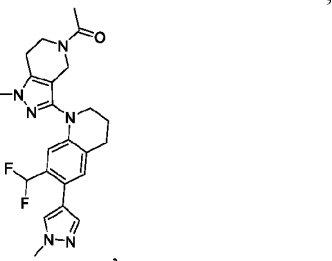
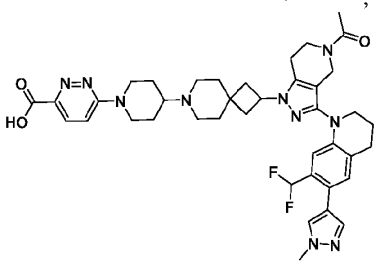
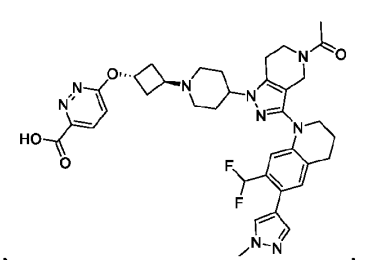


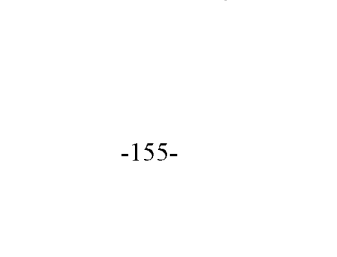


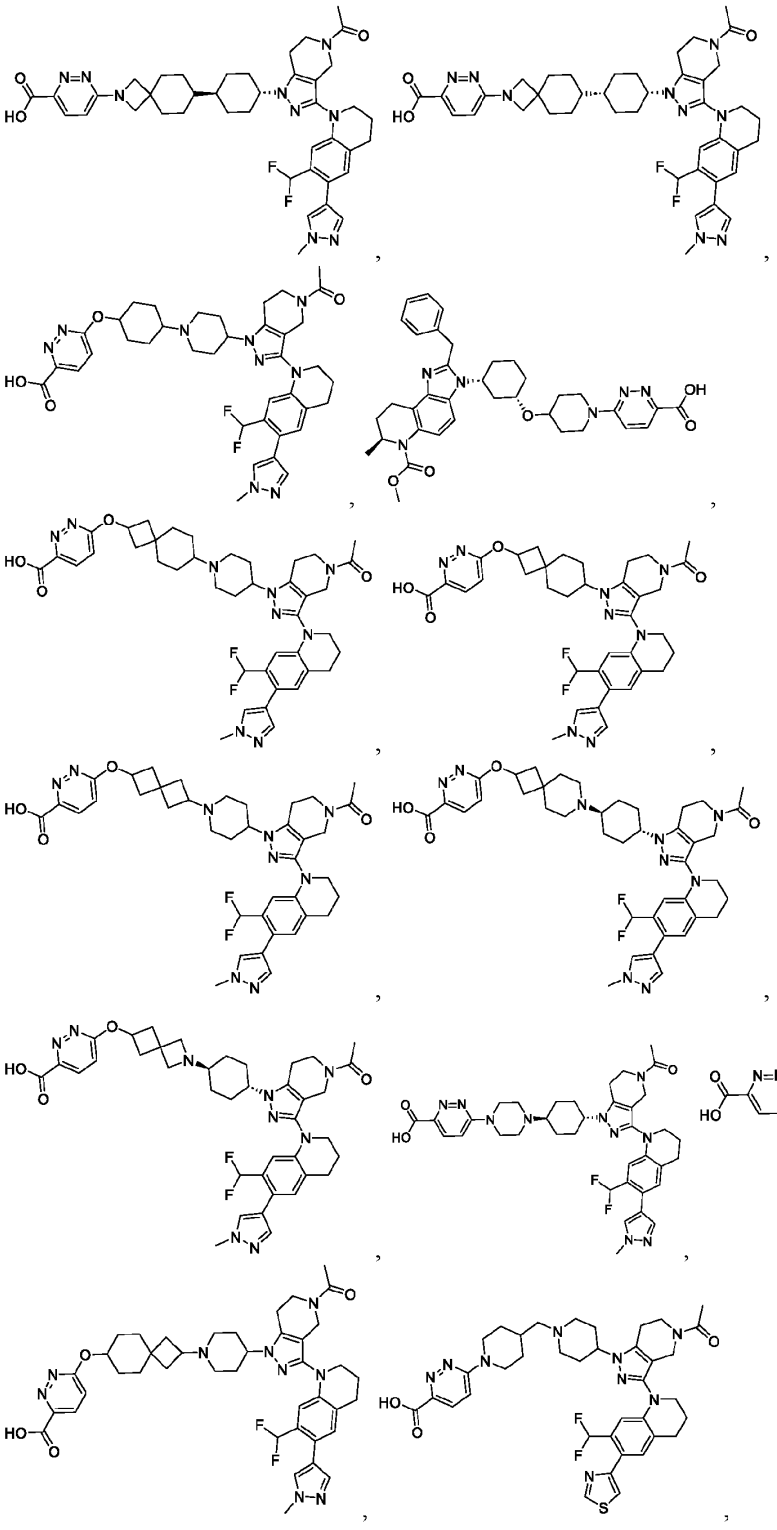

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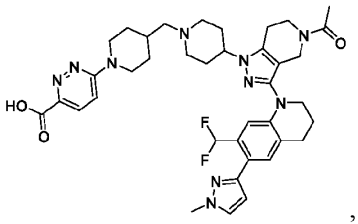
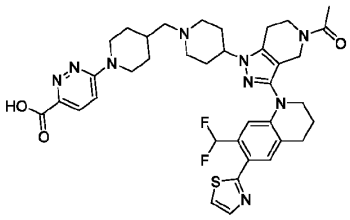
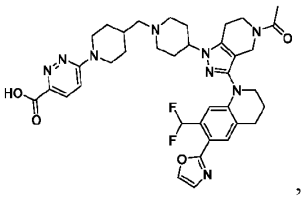
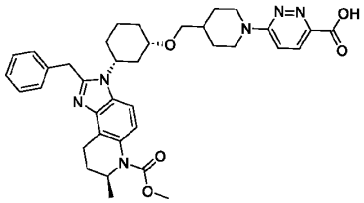
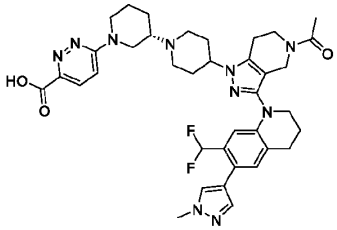
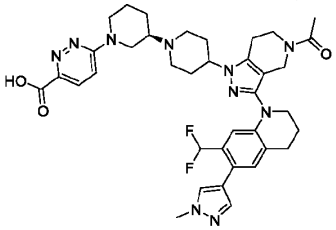
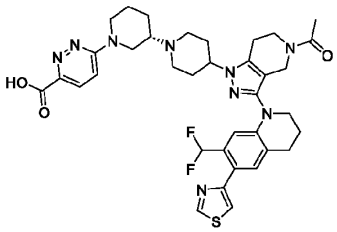
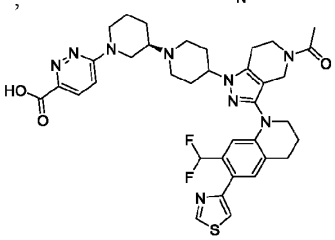
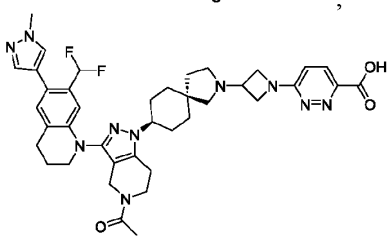
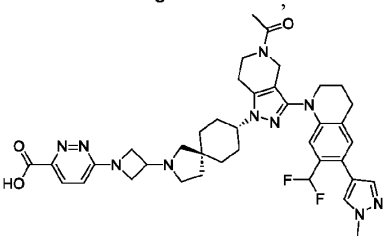
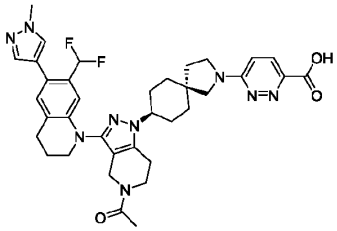
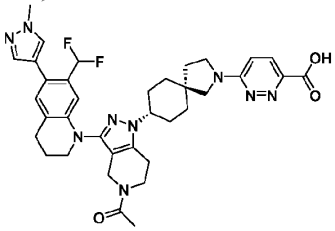
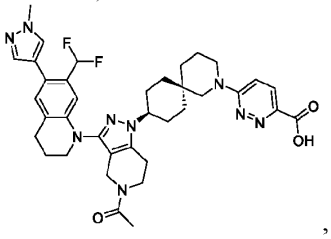
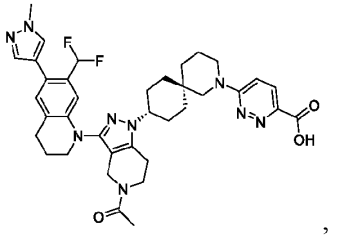
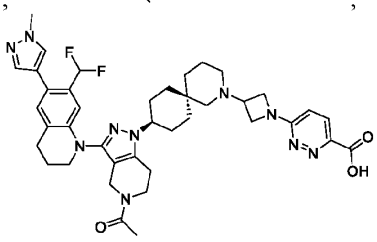
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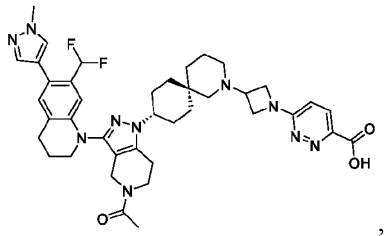
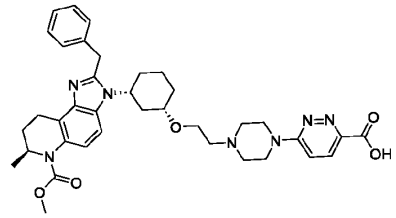
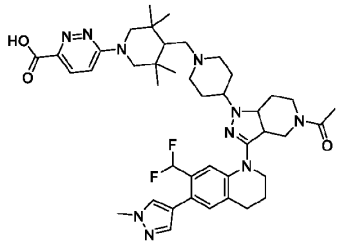
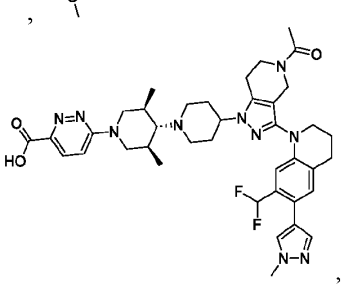
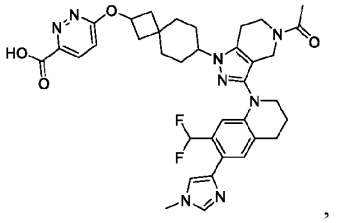
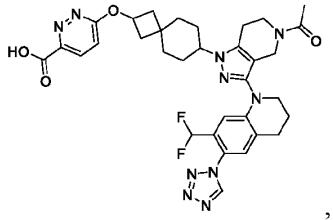
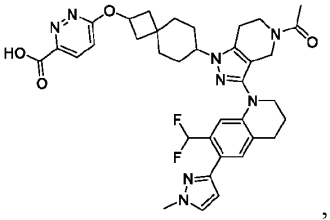
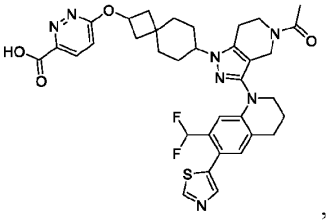
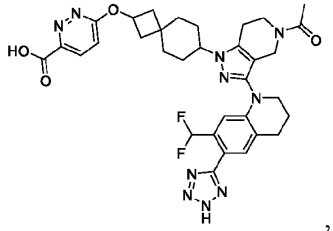
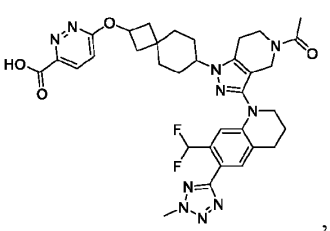
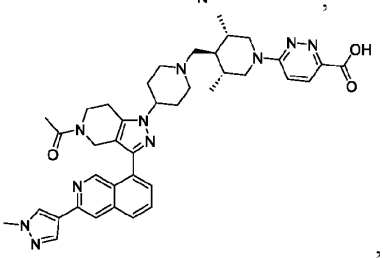
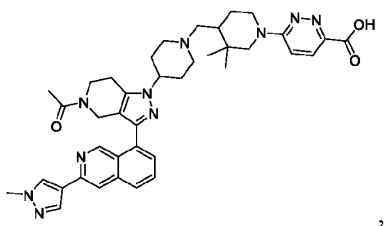
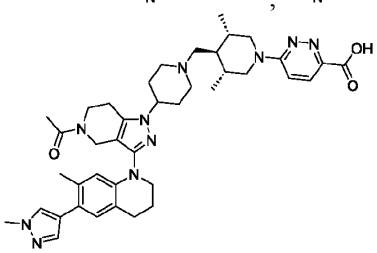
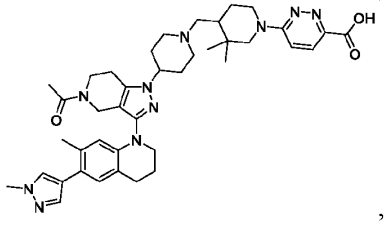
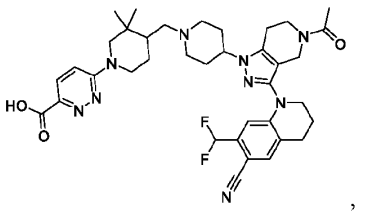
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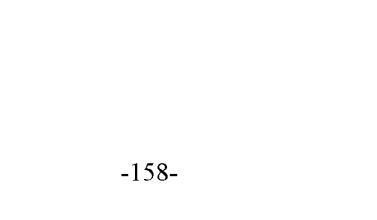

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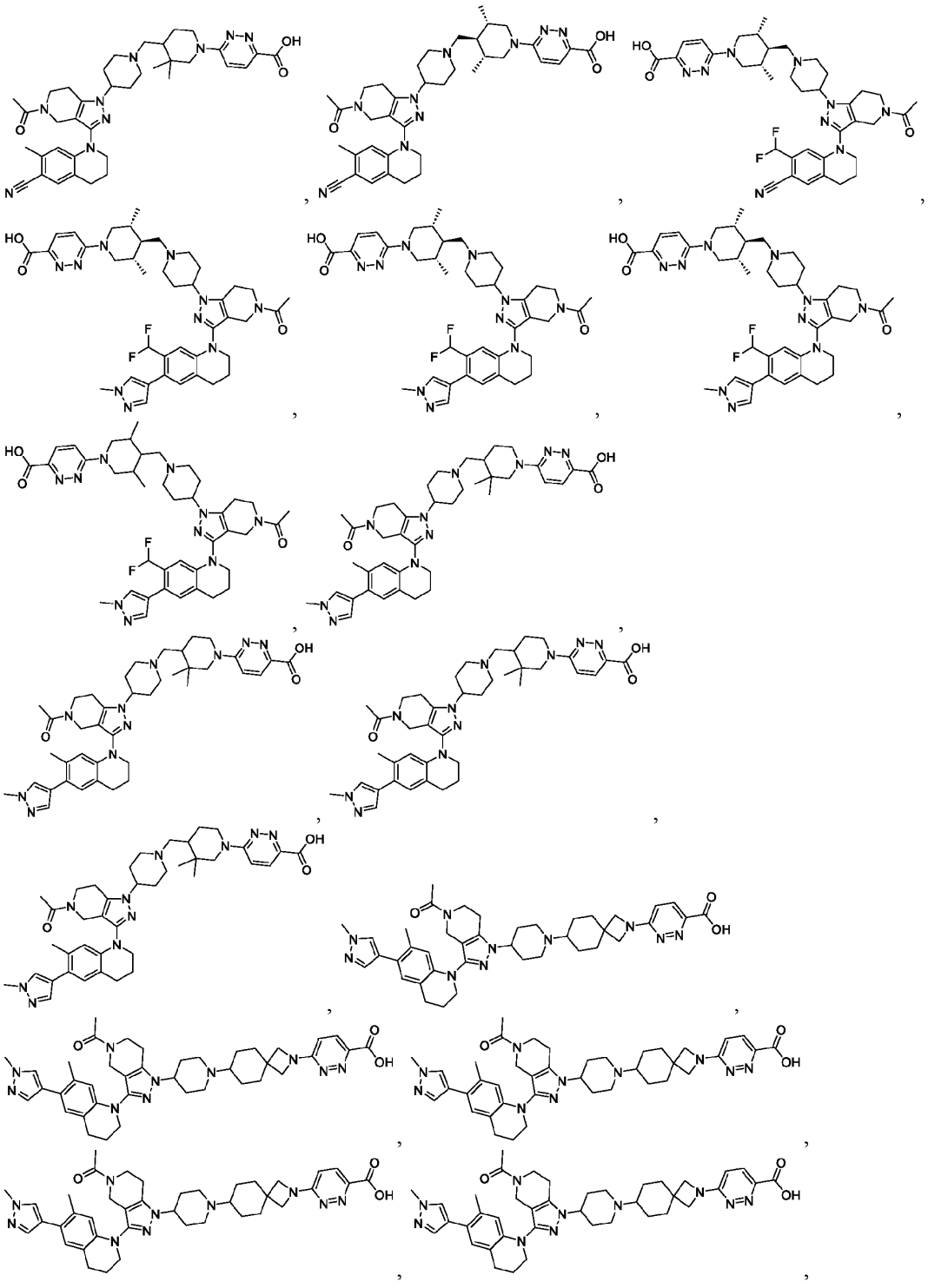
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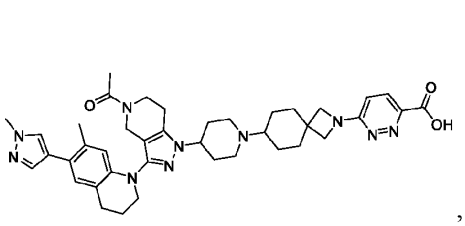
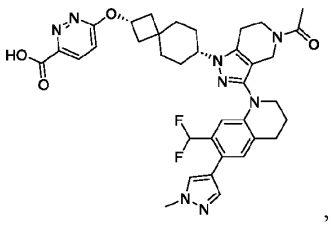
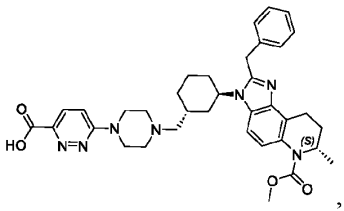
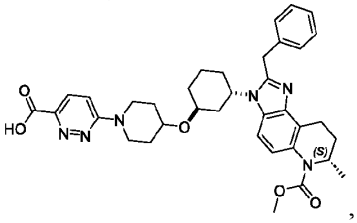
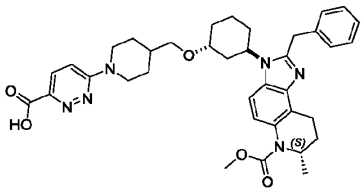
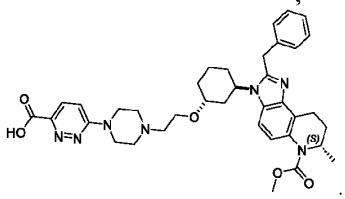



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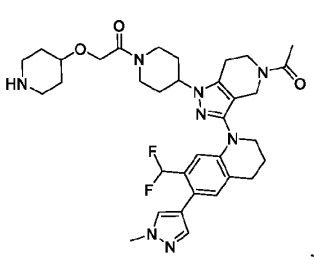
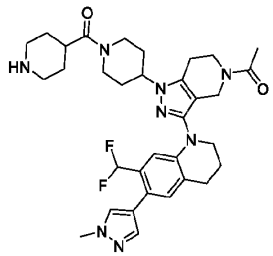
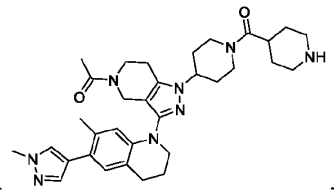
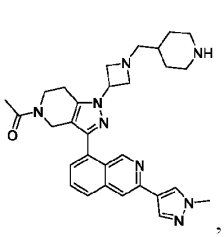
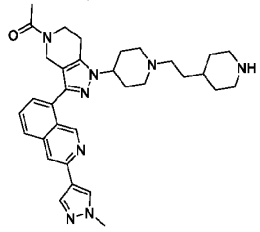
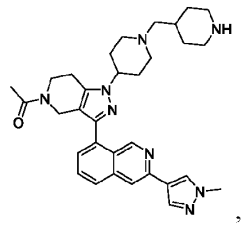
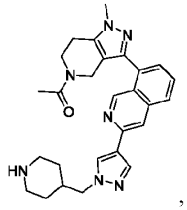


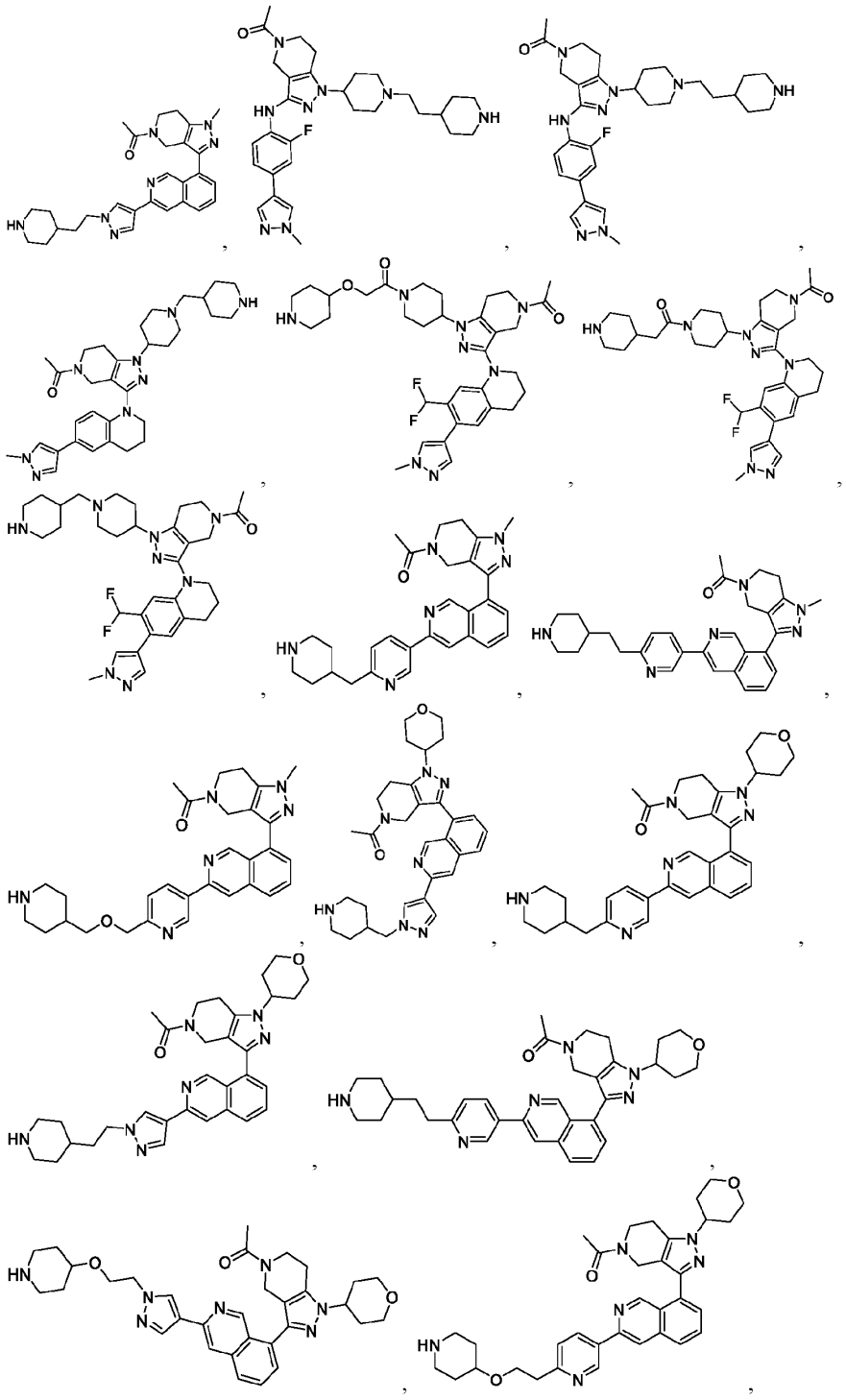

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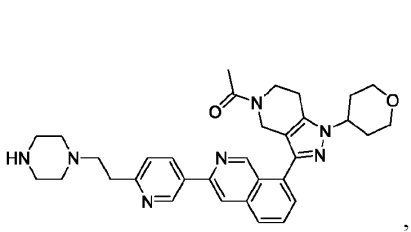
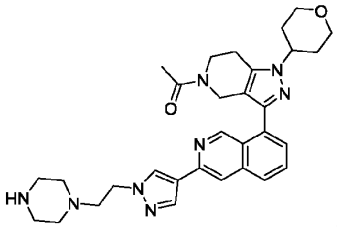
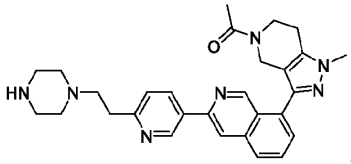
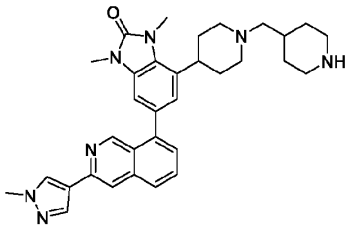
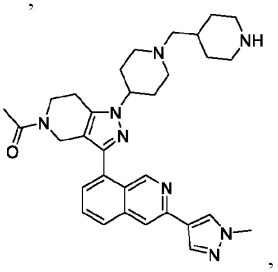
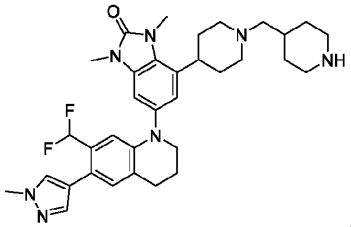
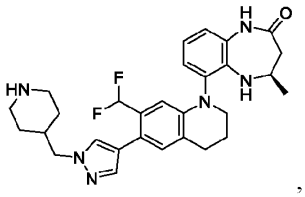
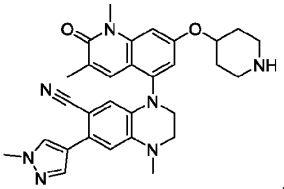
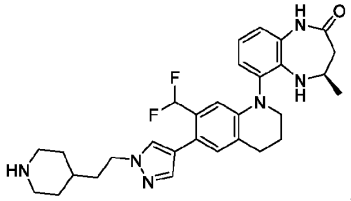
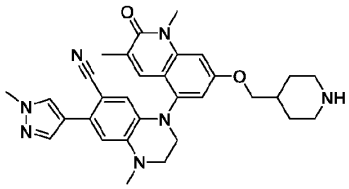
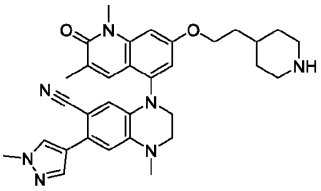
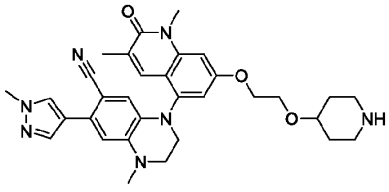
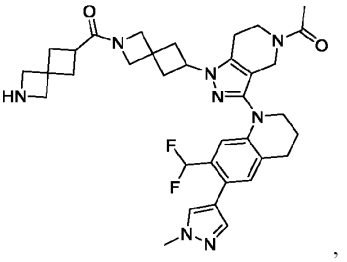
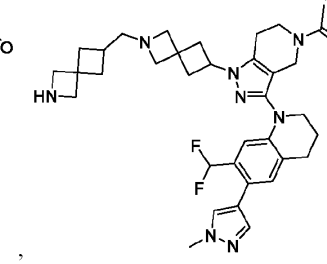
[00305] Embodiment 122. A compound, or a pharmaceutically acceptable salt or solvate thereof, prepared by an amide coupling of the compound of embodiment 39e and the compound of embodiment 121.

[00306] Embodiment 123. A compound, or a pharmaceutically acceptable salt or solvate thereof, prepared by an amide coupling of the compound of embodiment 39f and the compound of embodiment 121.

[00307] Embodiment 124. A compound, or a pharmaceutically acceptable salt or solvate thereof, that has one of the following structures:

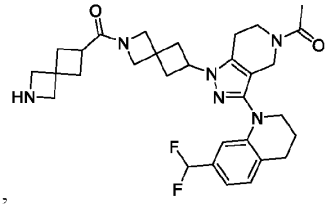
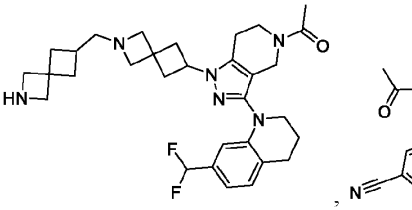
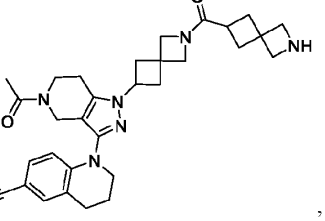

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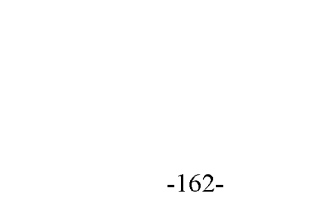
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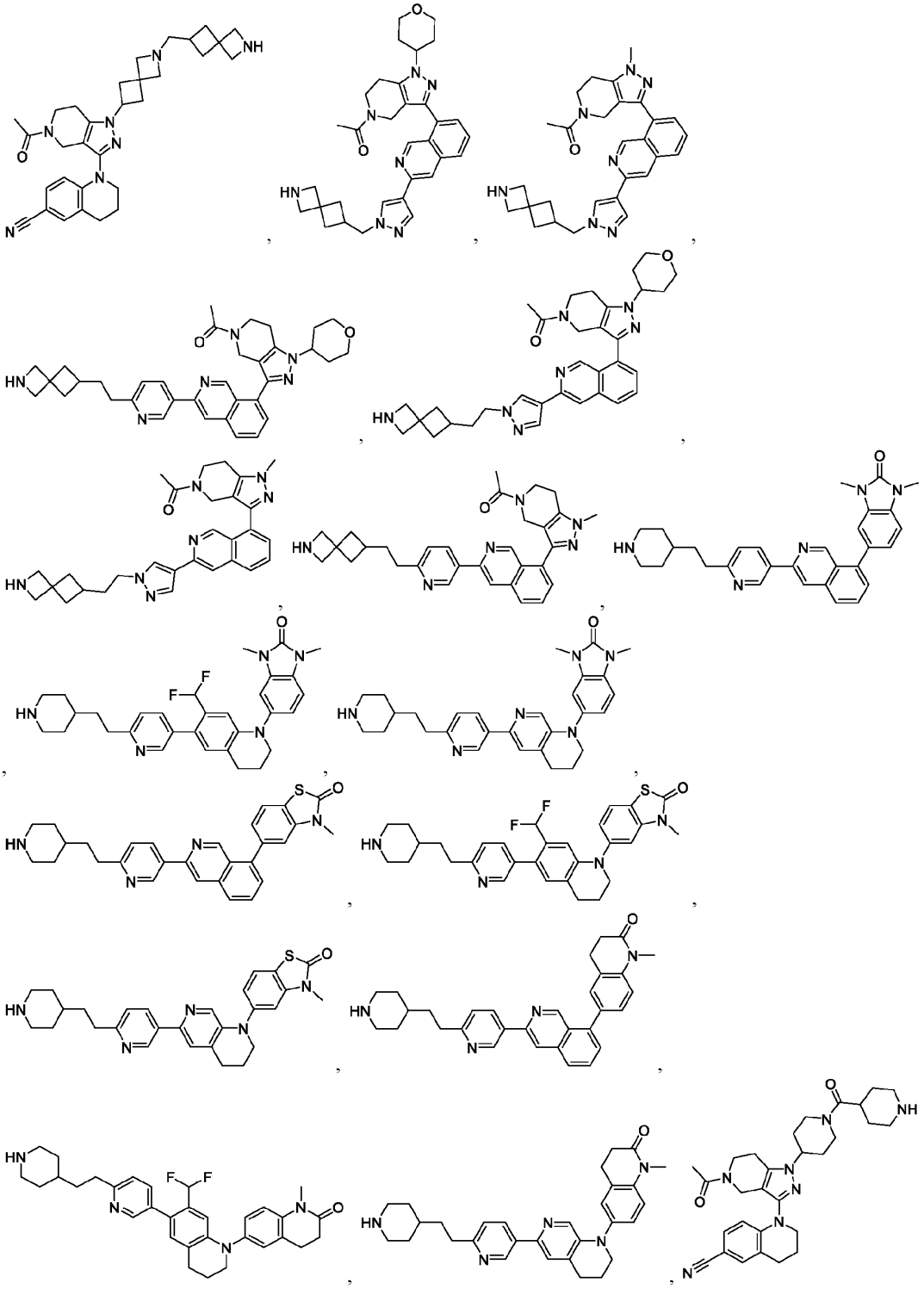
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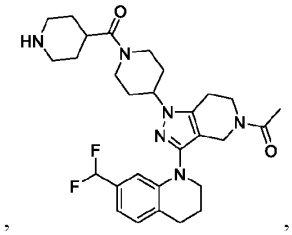
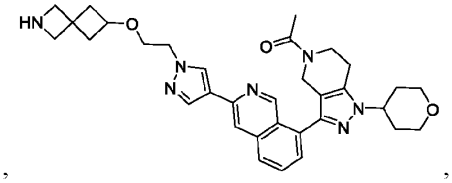
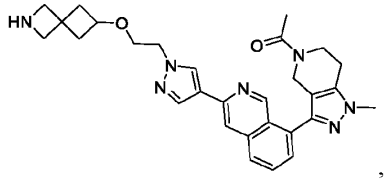
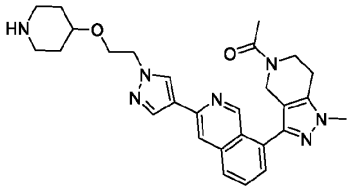
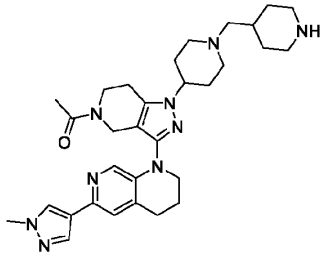
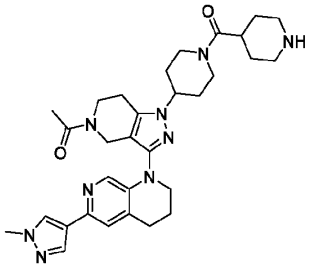
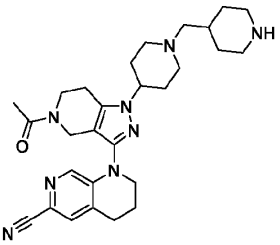
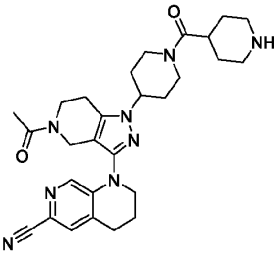
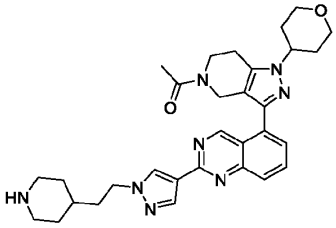
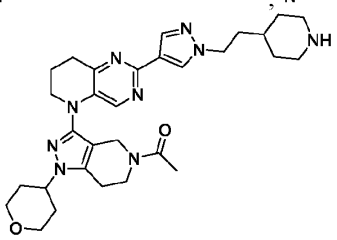
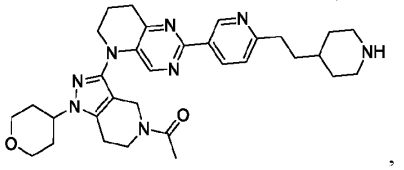
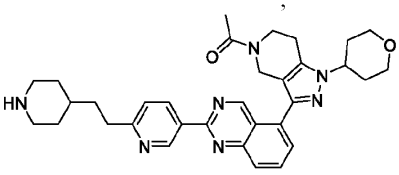
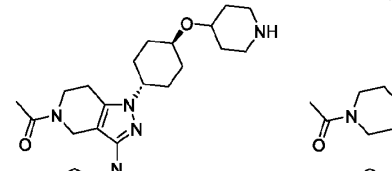
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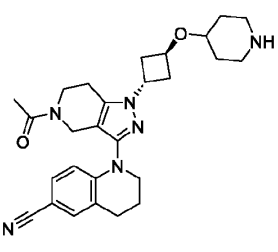
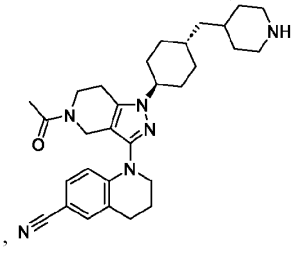
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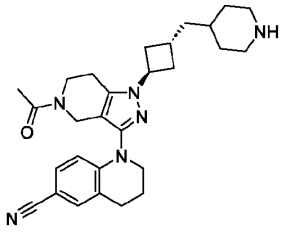
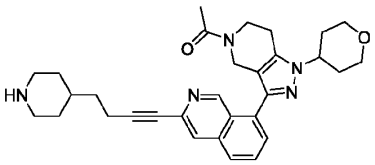
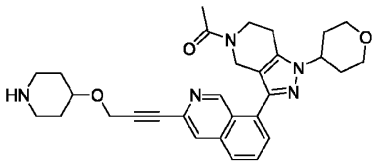
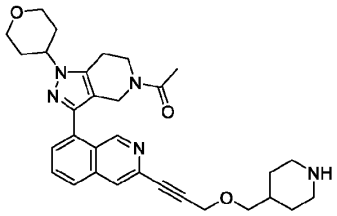
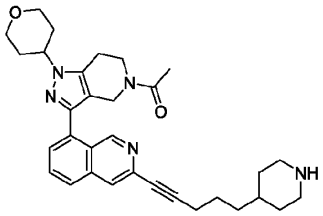
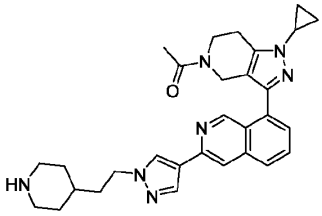
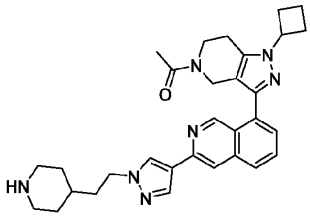
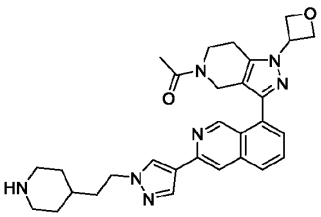
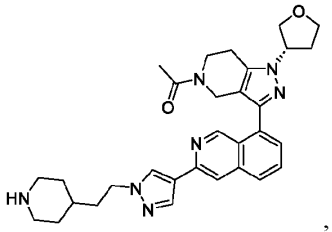
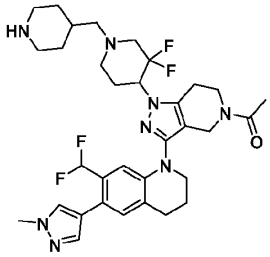
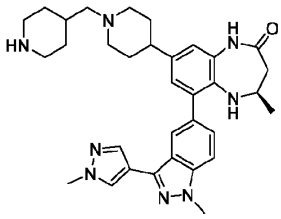
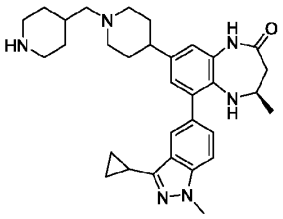
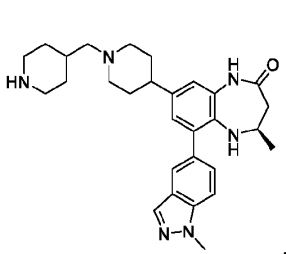
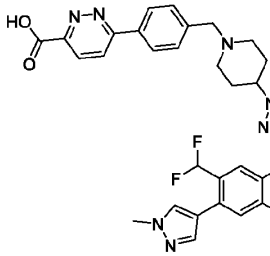
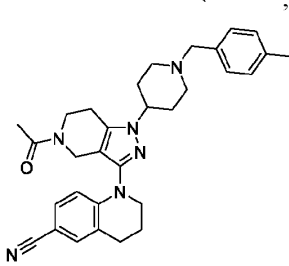
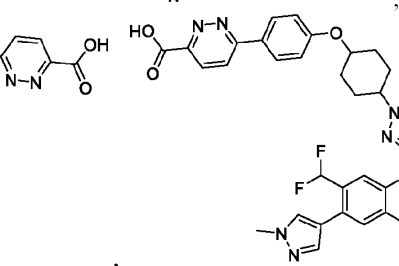
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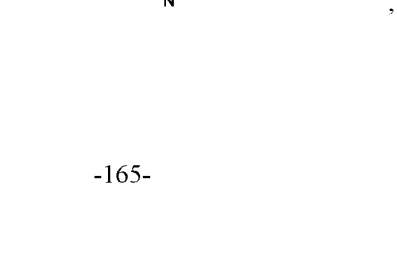


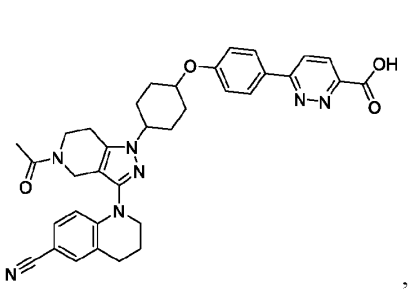
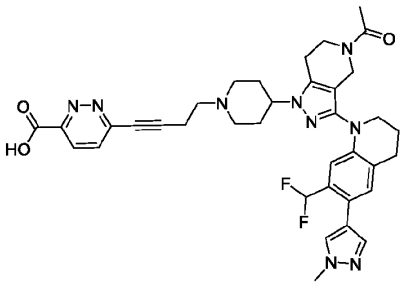
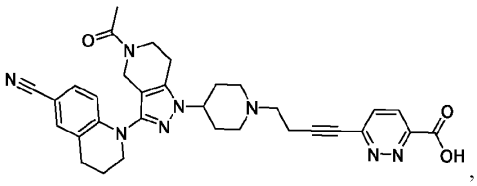
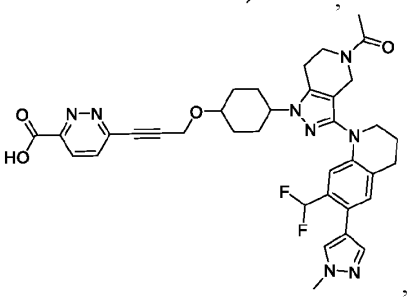
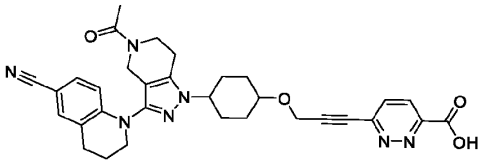
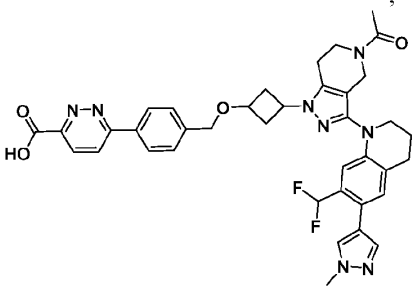
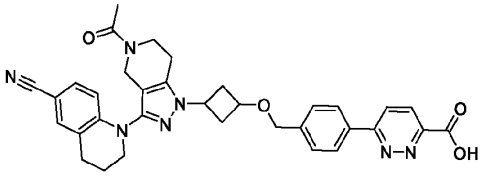
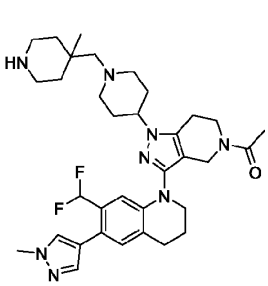
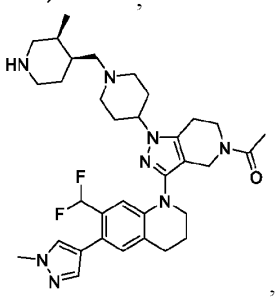
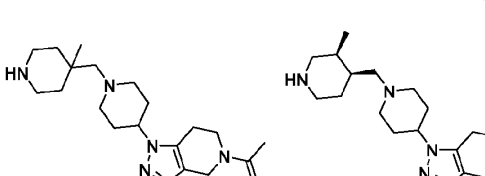
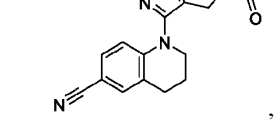
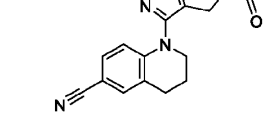
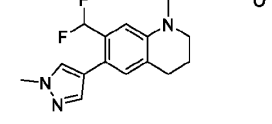

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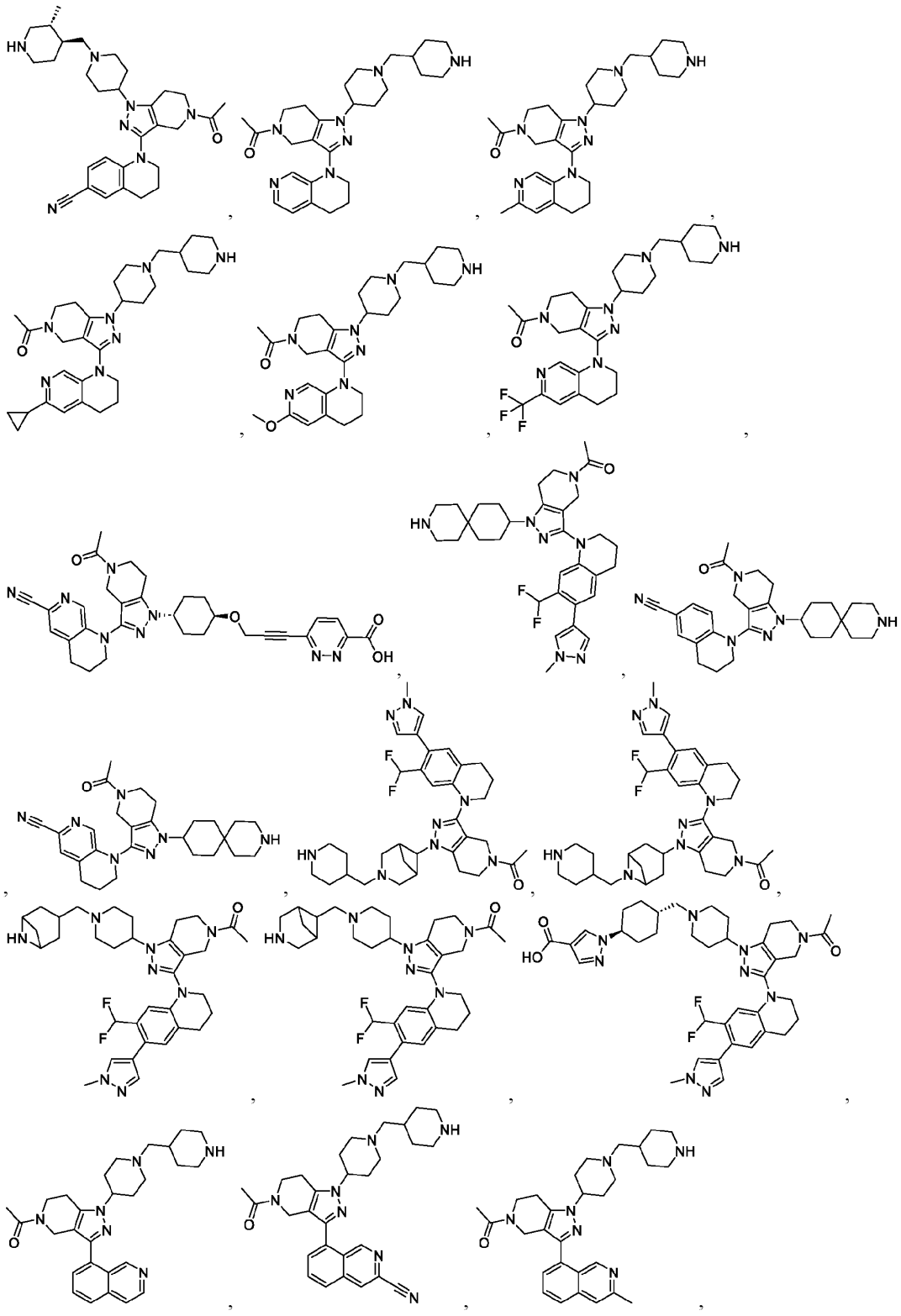
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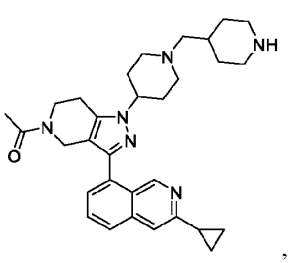
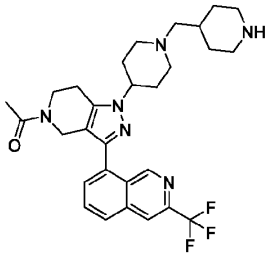
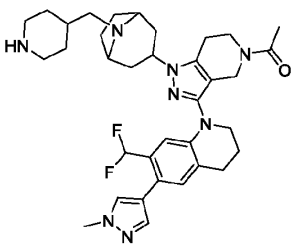
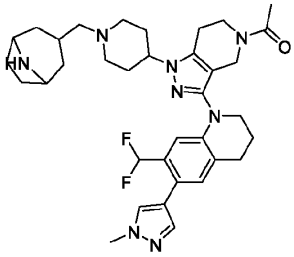
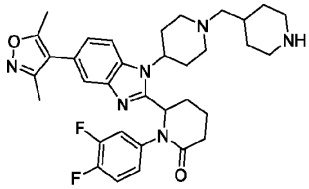
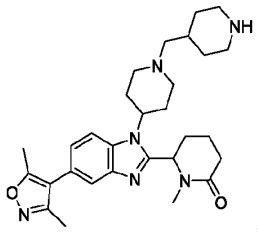
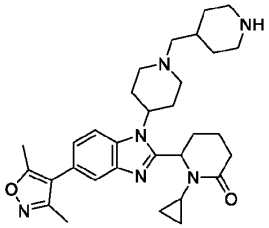
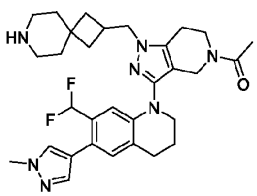
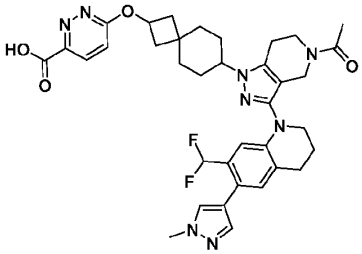
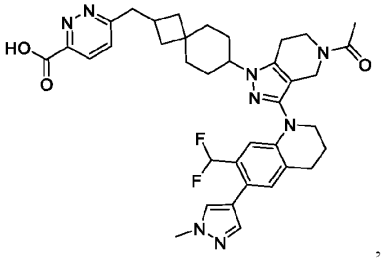
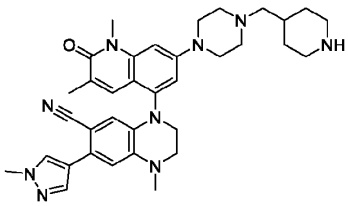
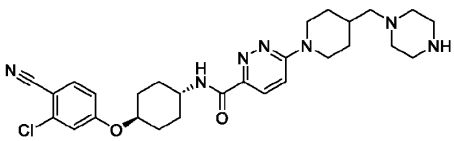
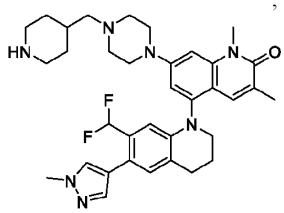
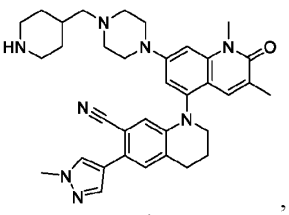
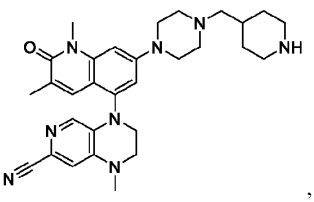
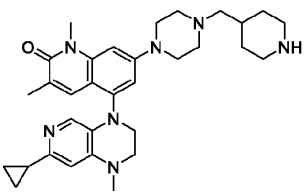
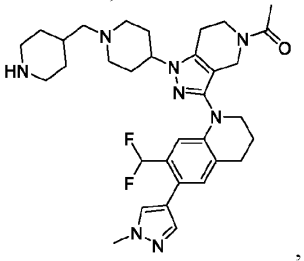
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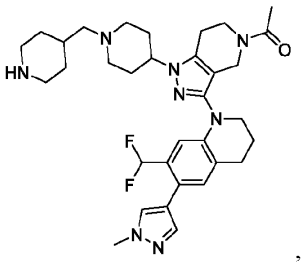
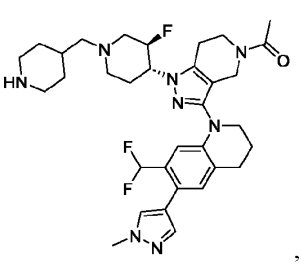
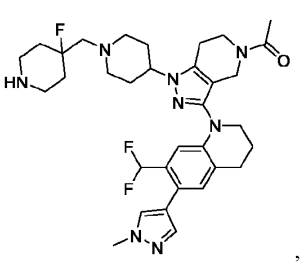
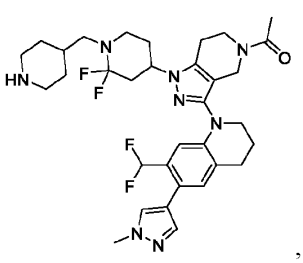
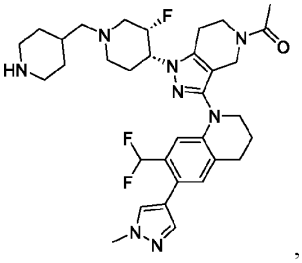
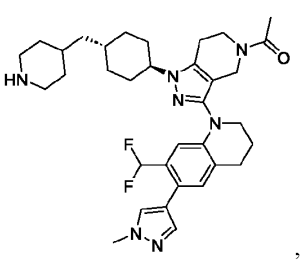
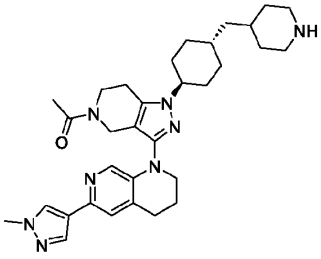
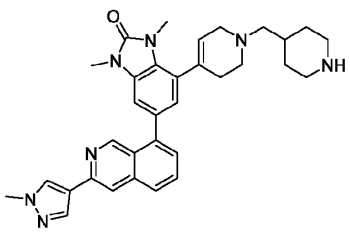
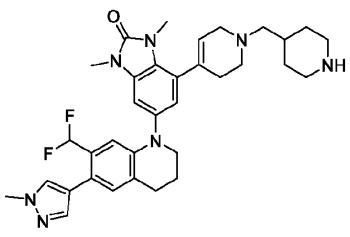
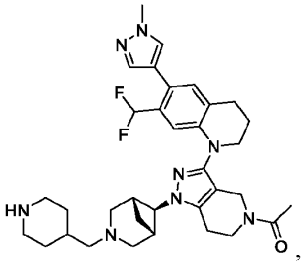
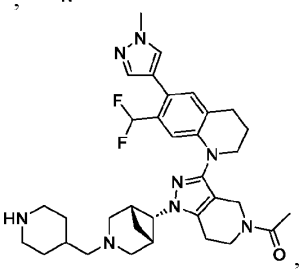
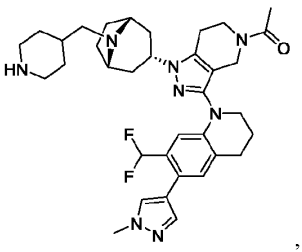
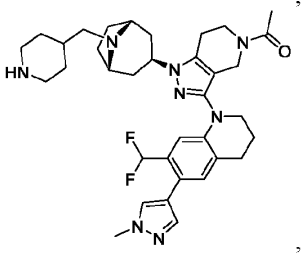
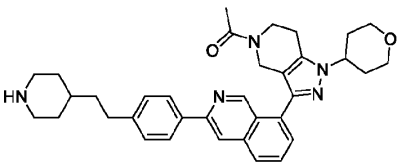
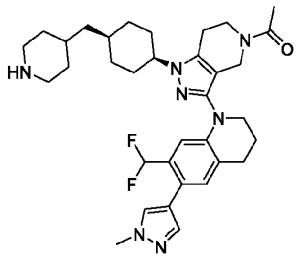
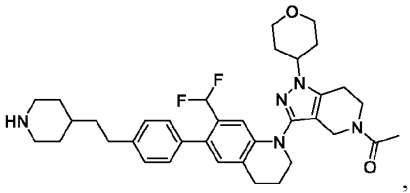

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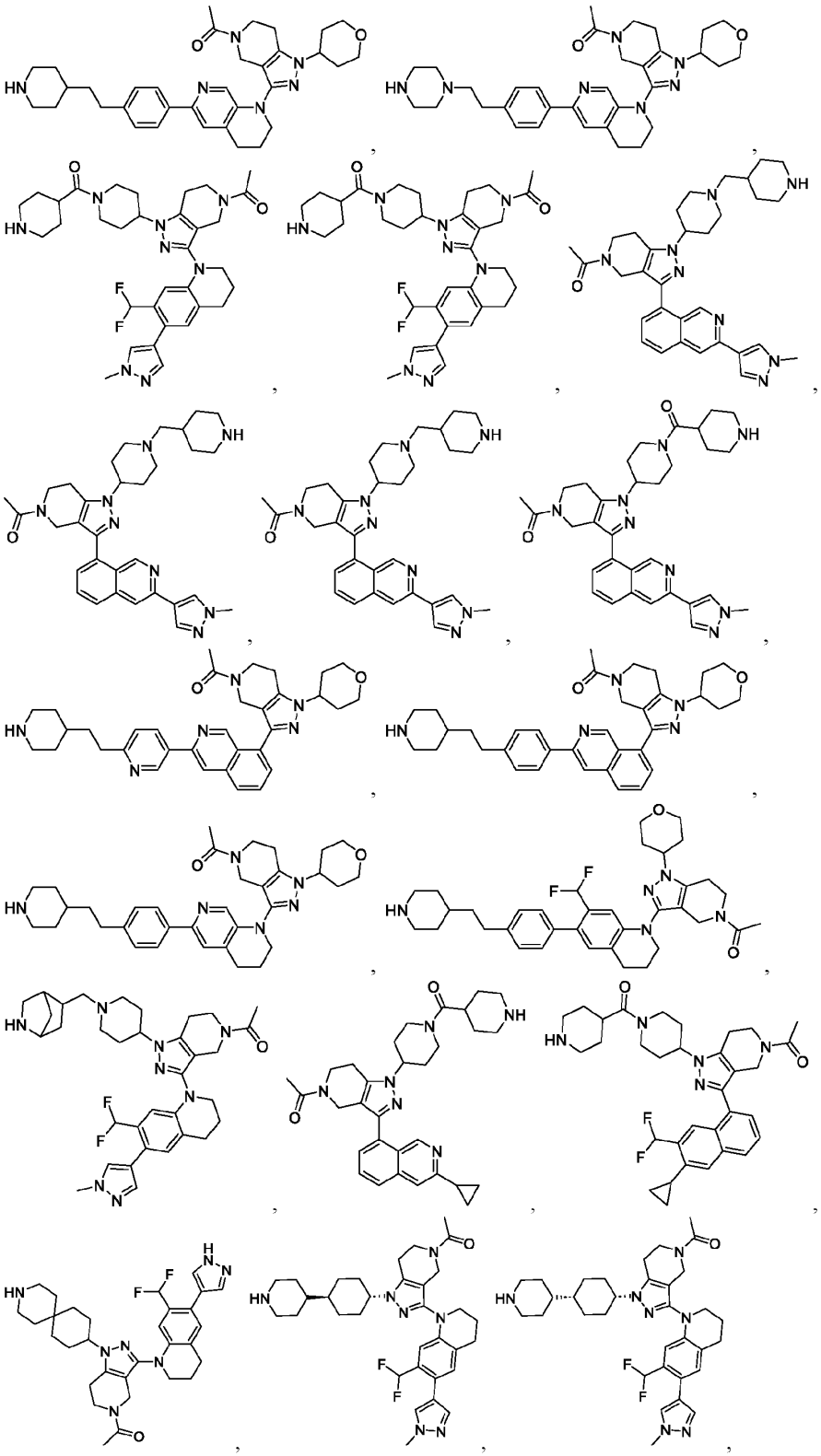
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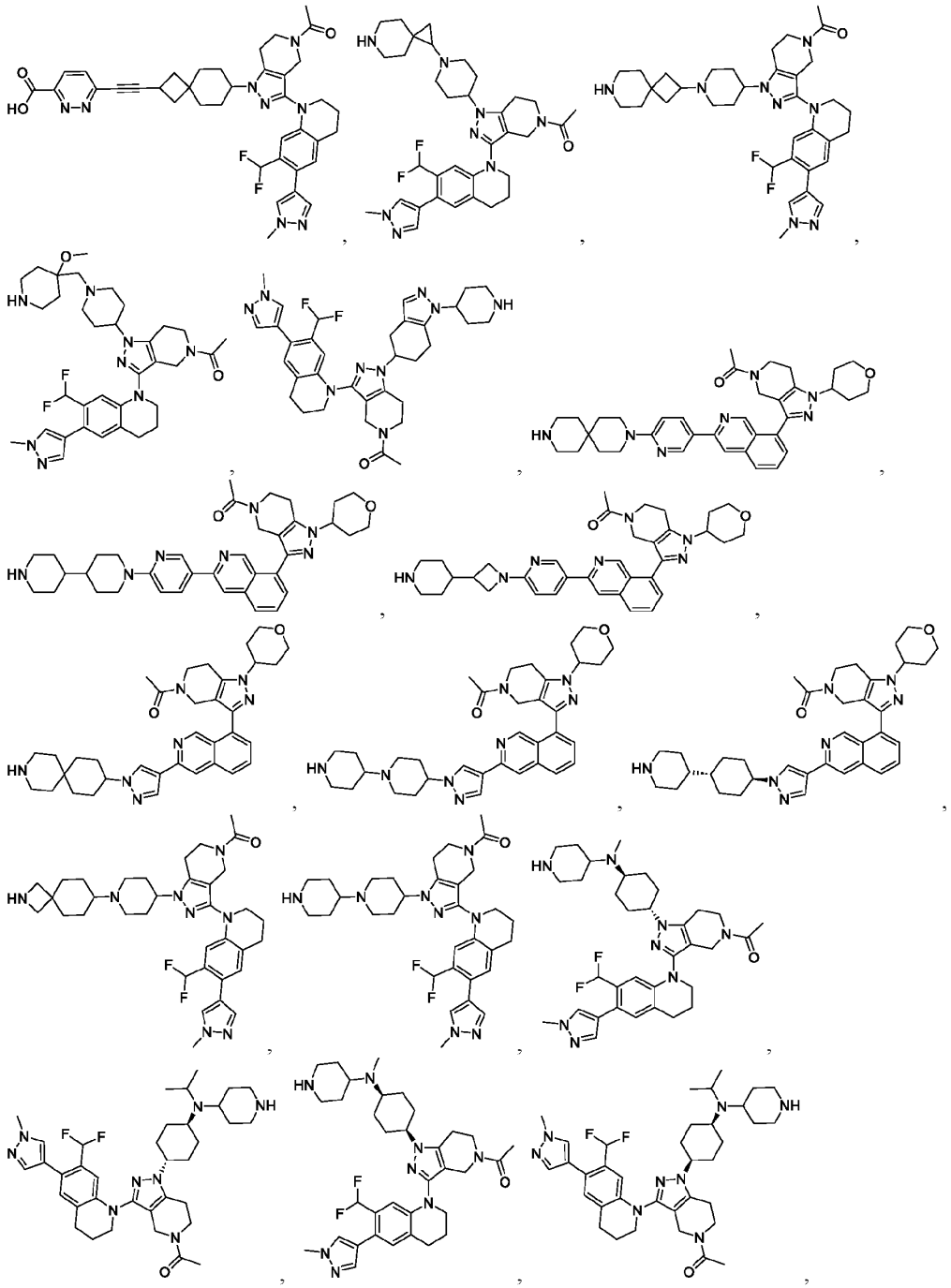

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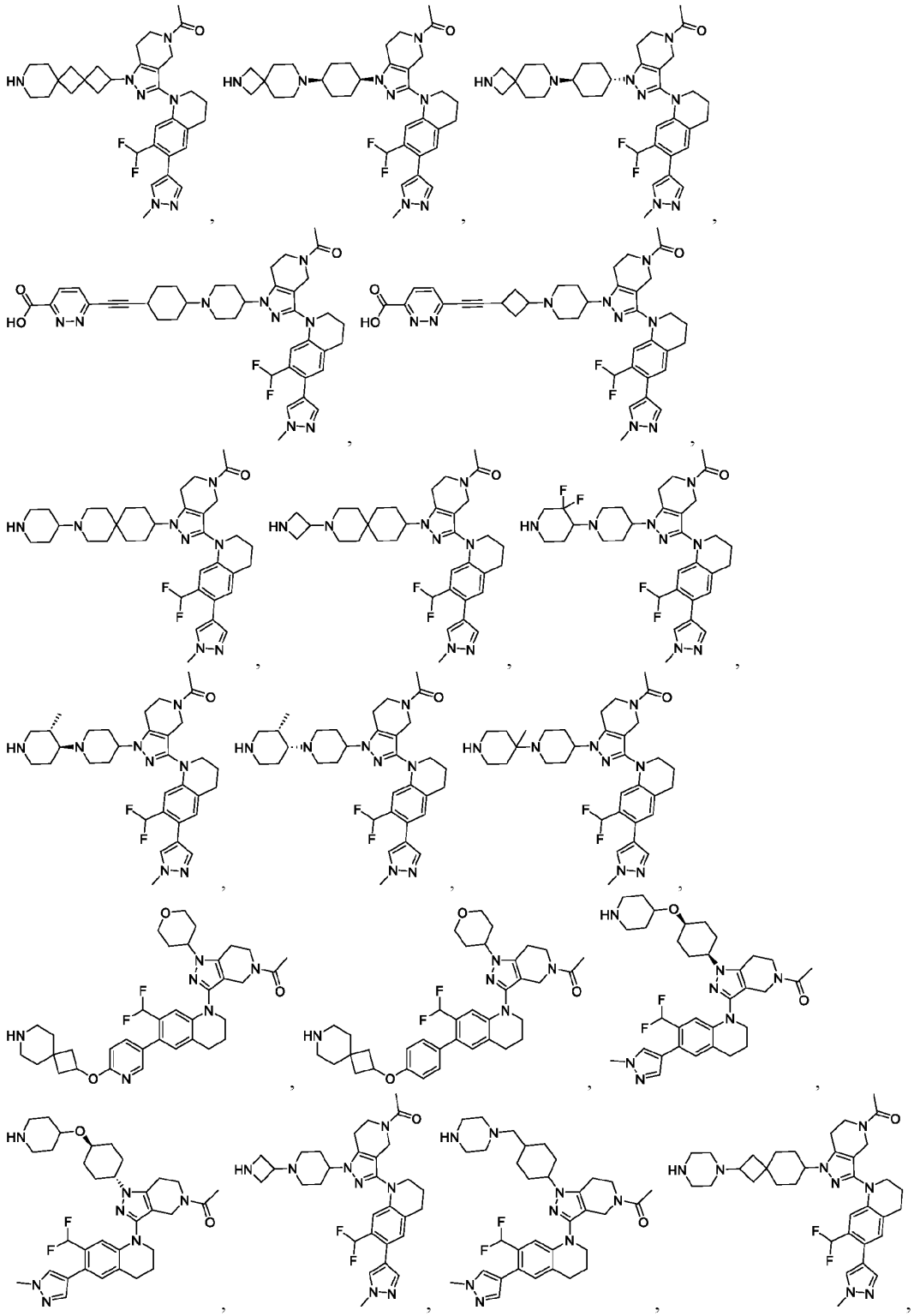


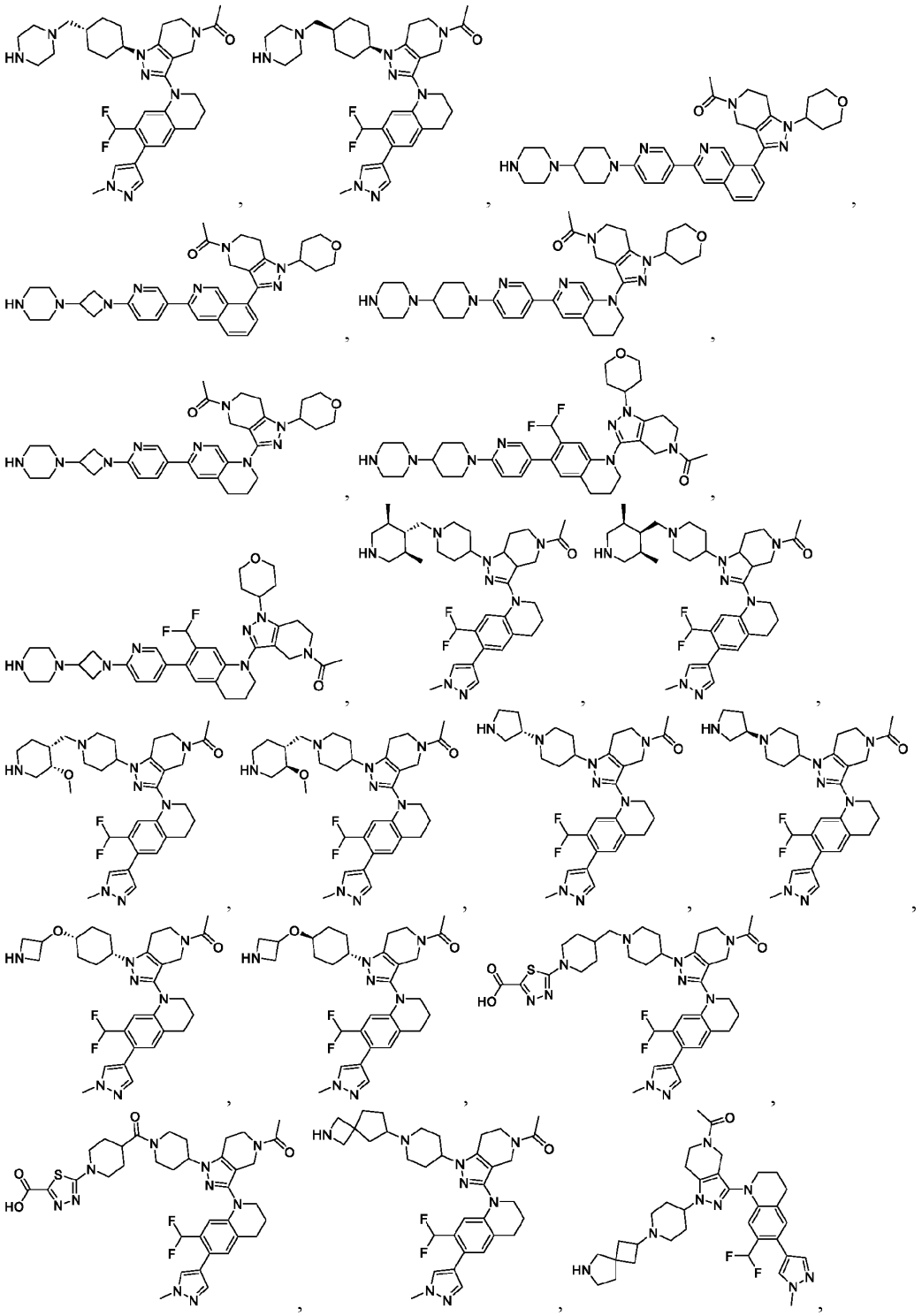

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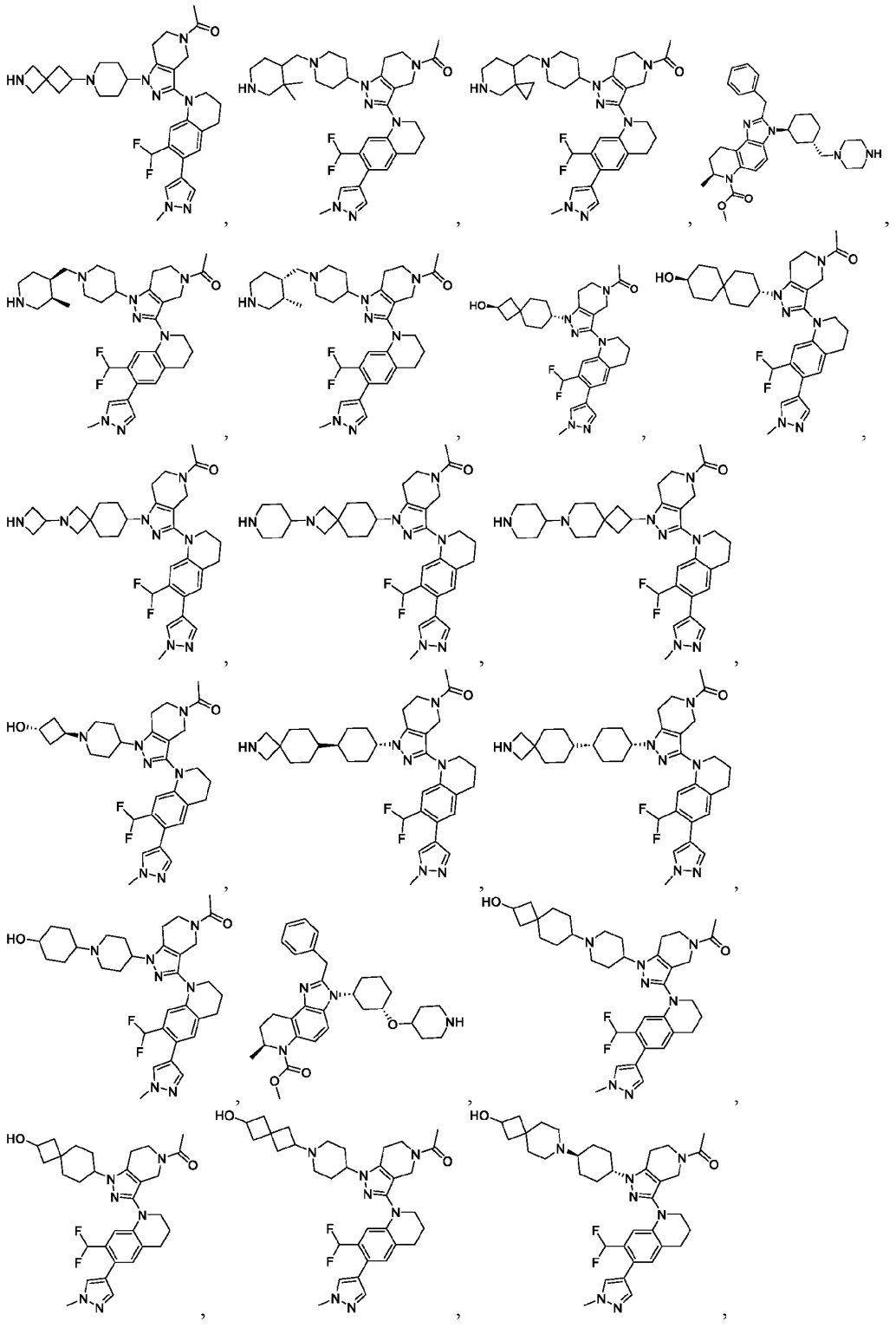

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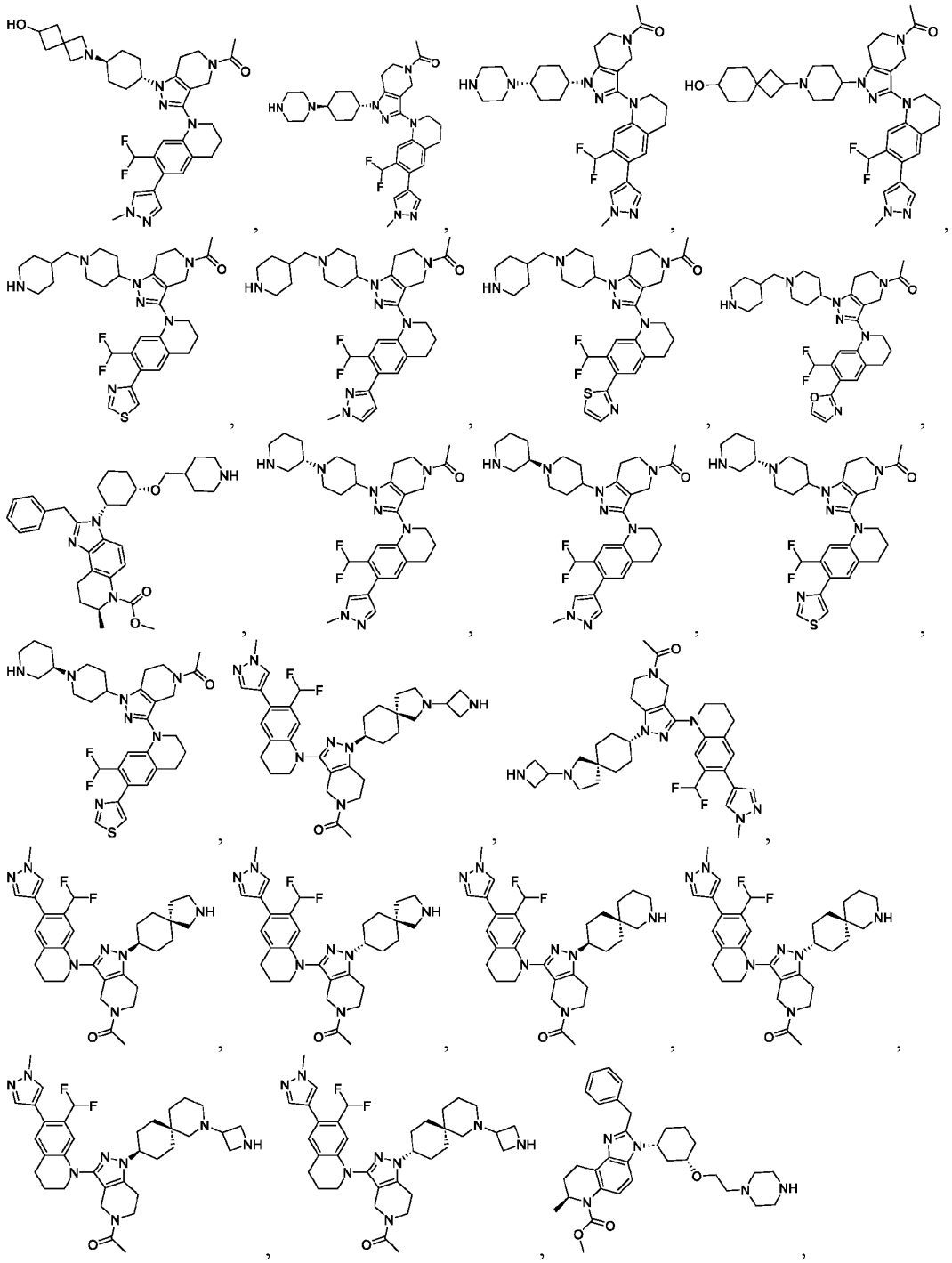


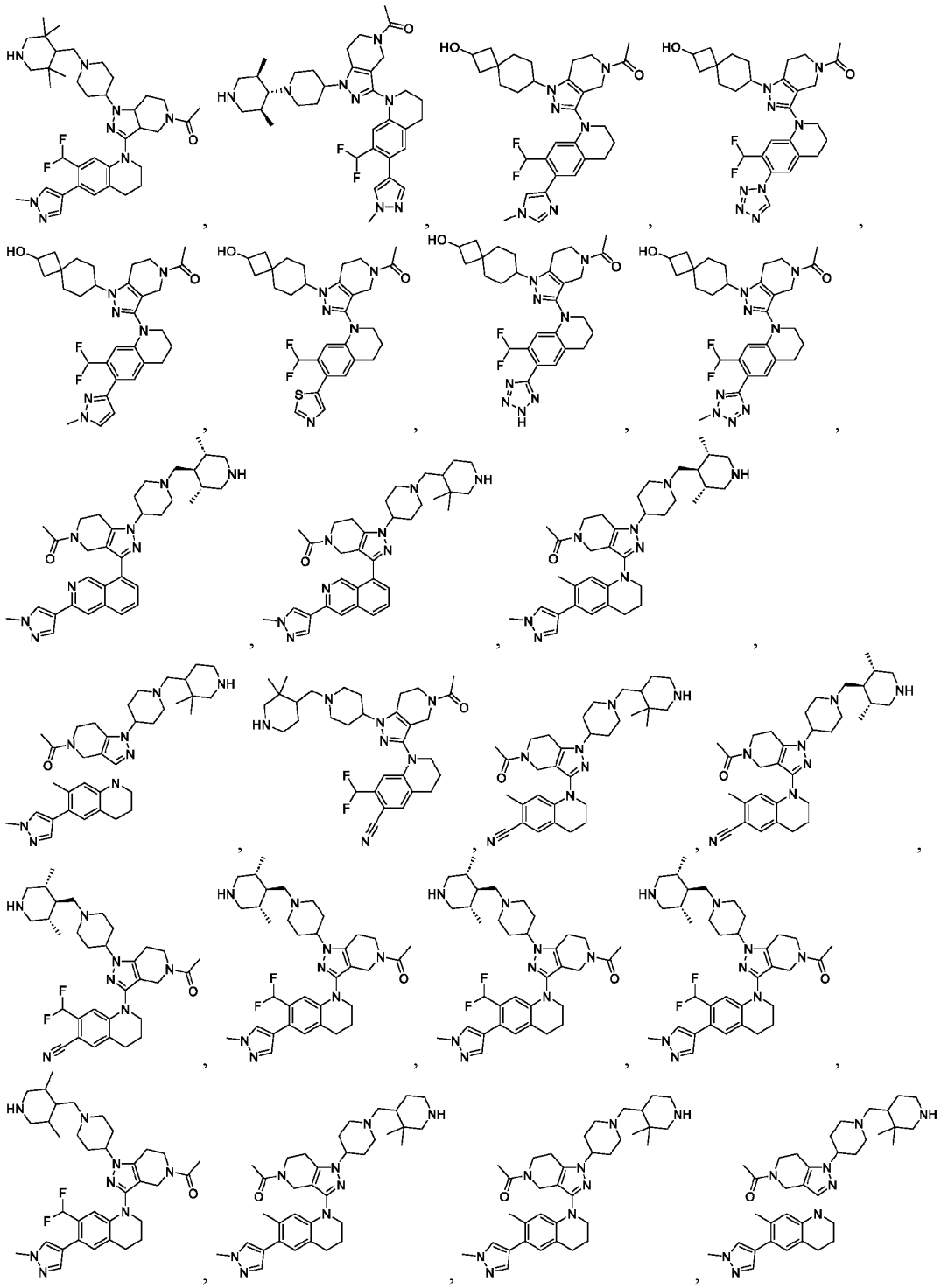


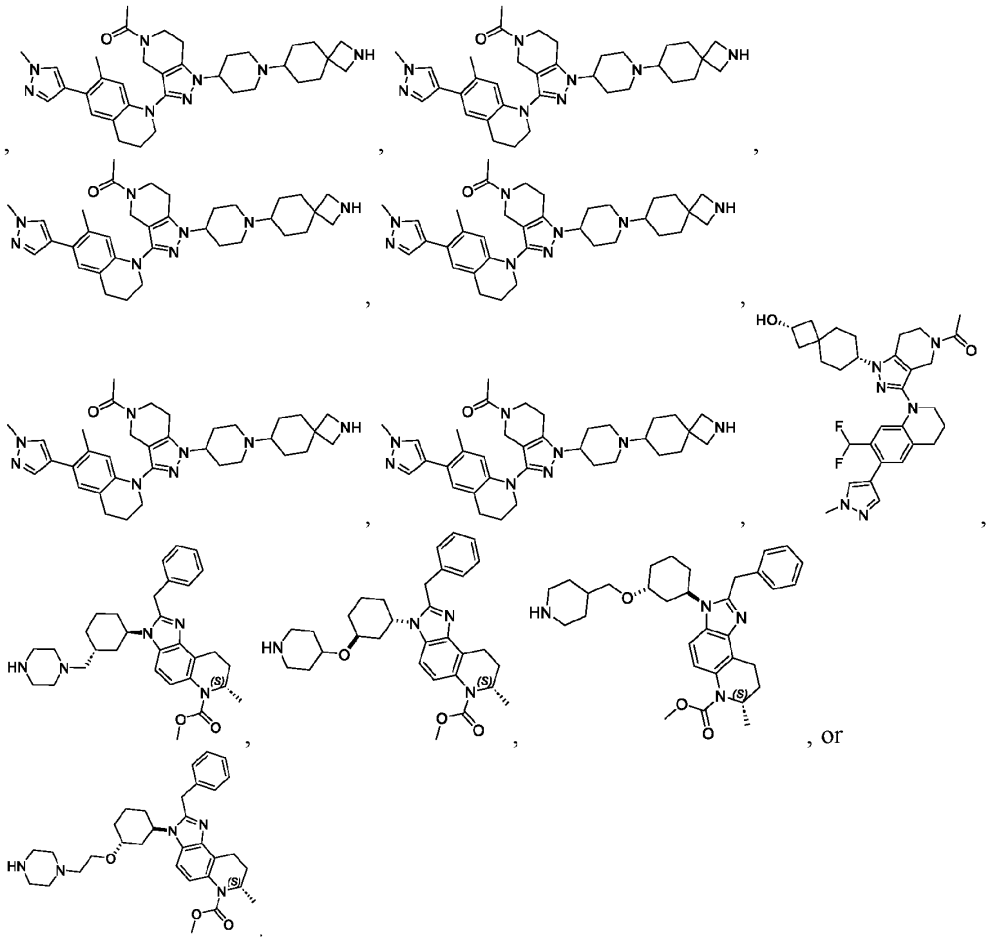




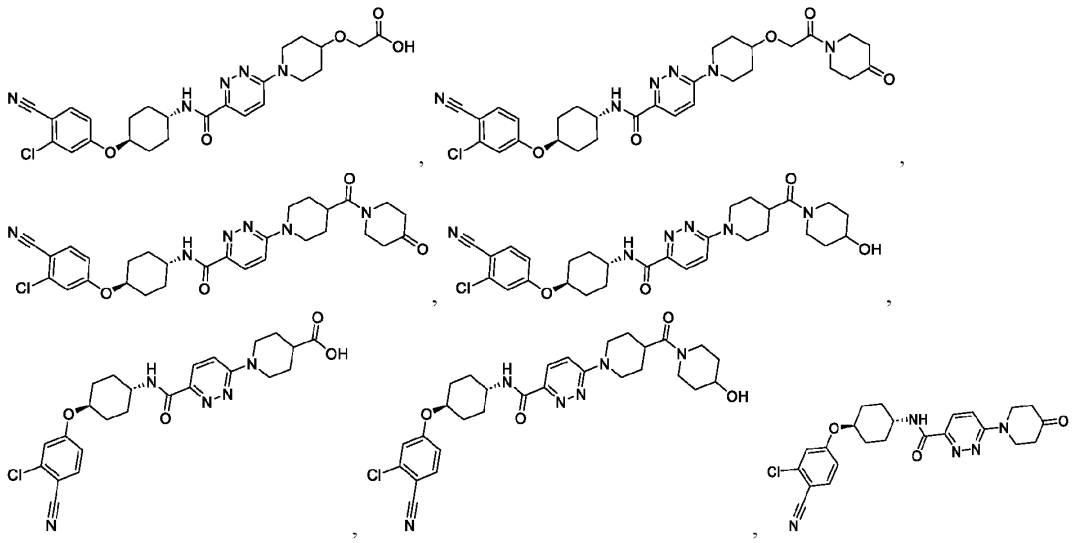


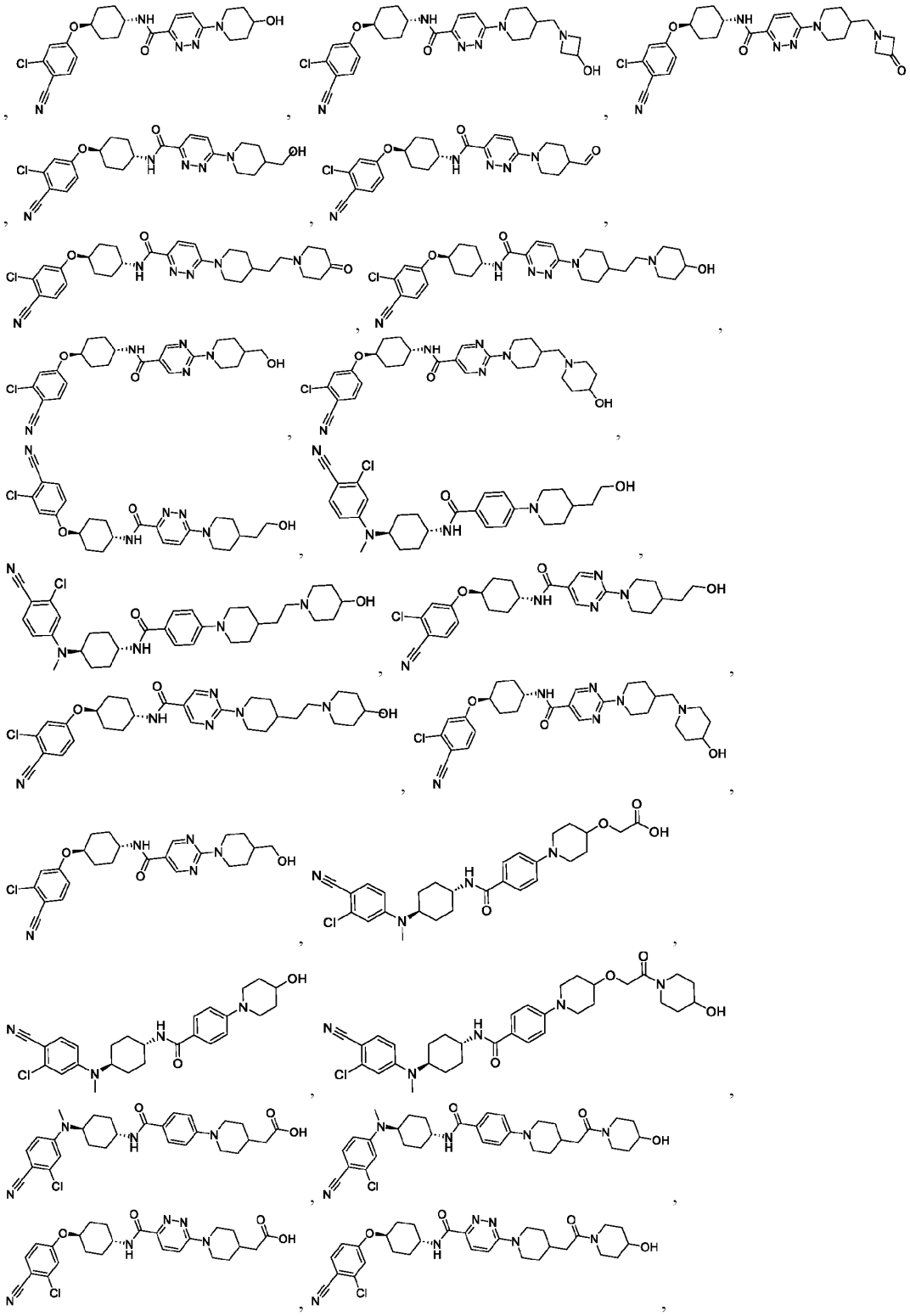


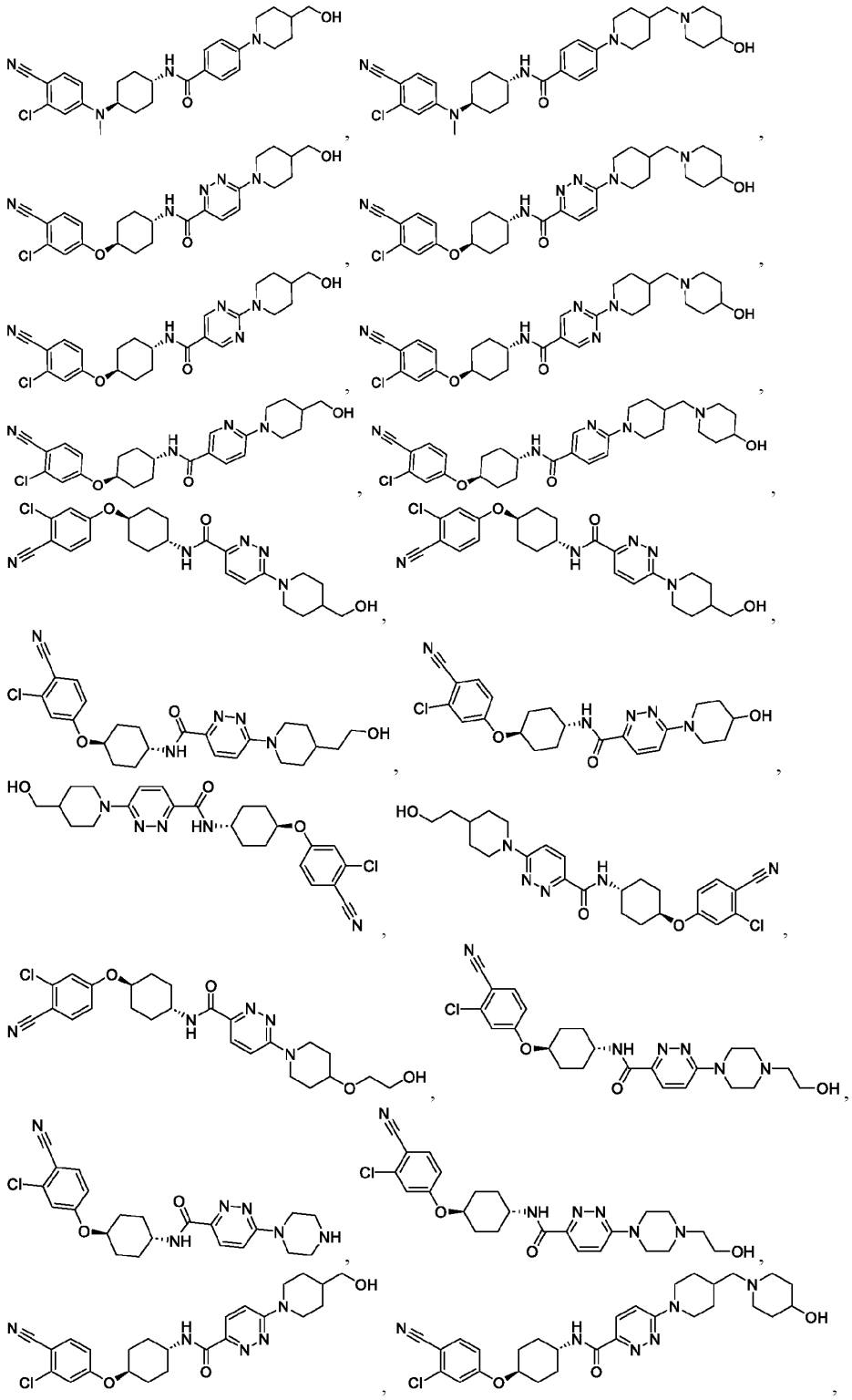


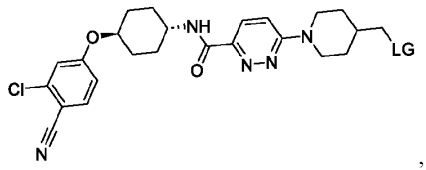
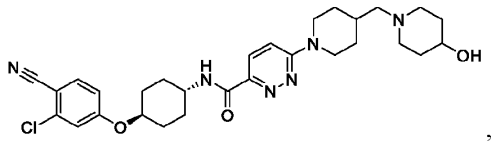
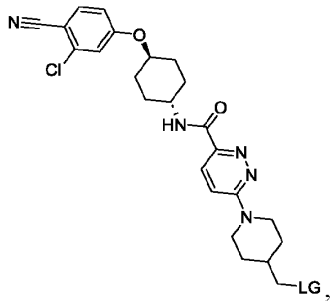
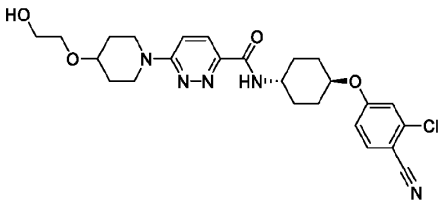
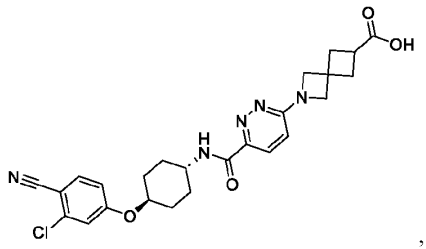
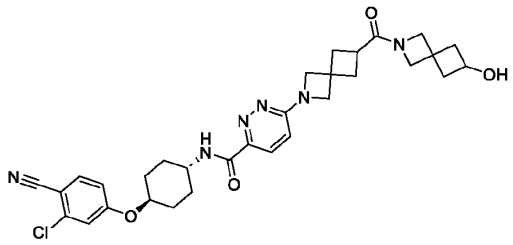
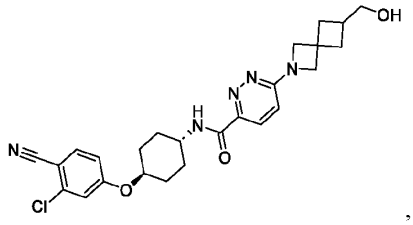
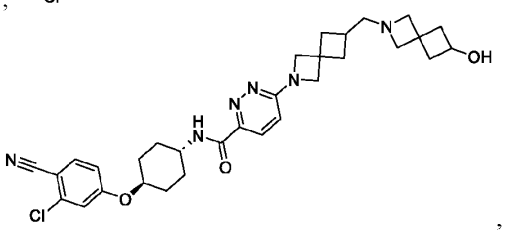
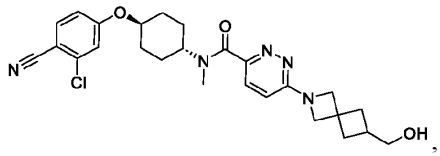
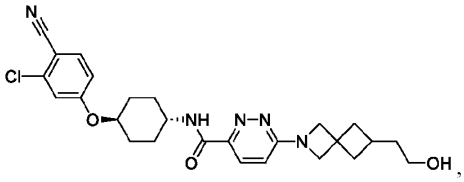
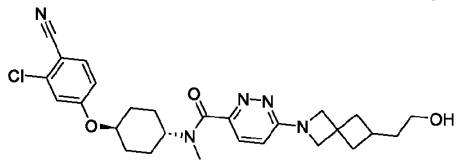
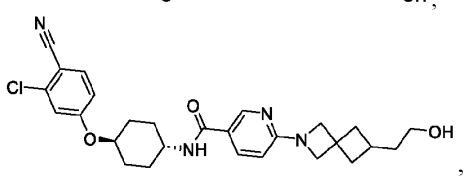
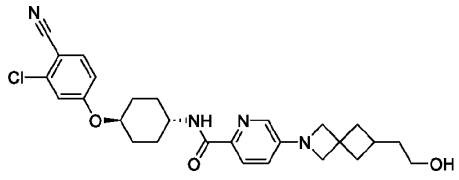
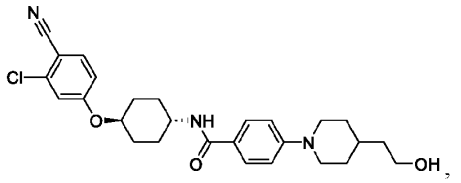


[00308] Embodiment 125. A compound, or a pharmaceutically acceptable salt or solvate thereof, that has one of the following structures:



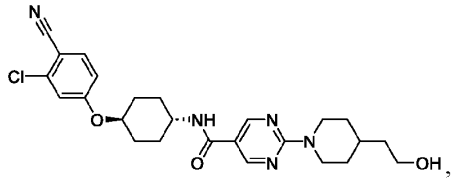
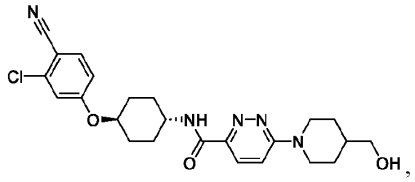
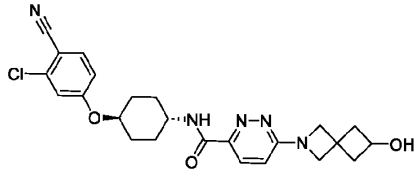
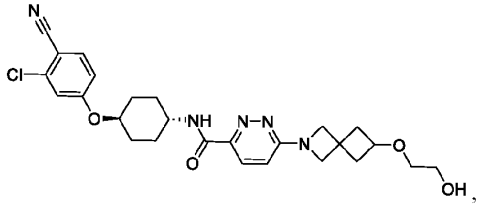
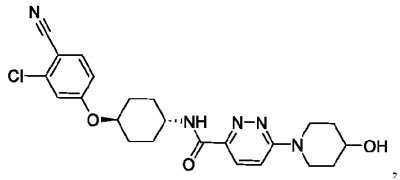
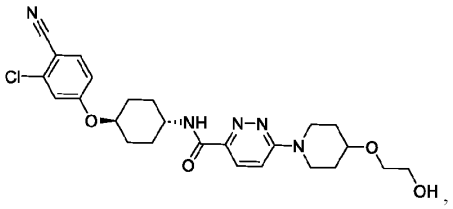
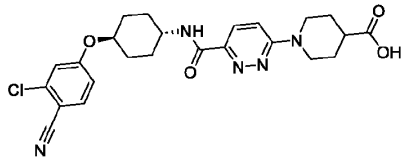
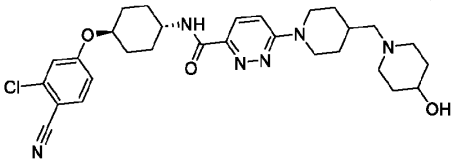
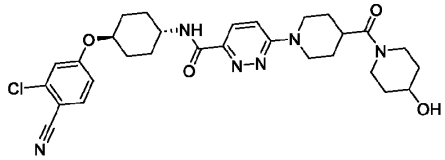
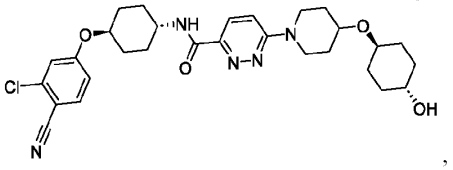
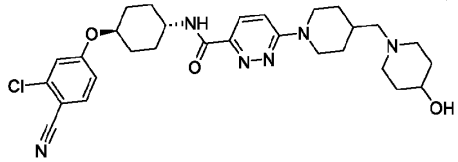
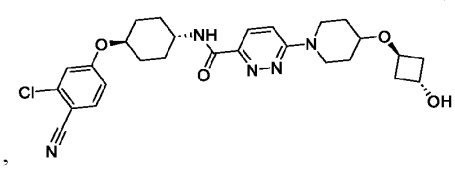
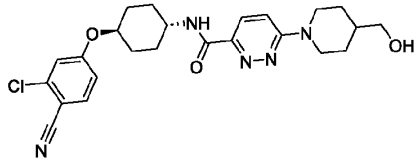
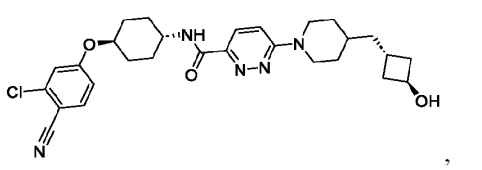
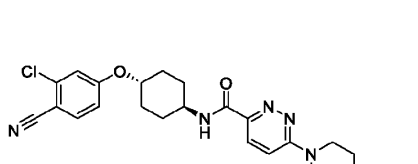
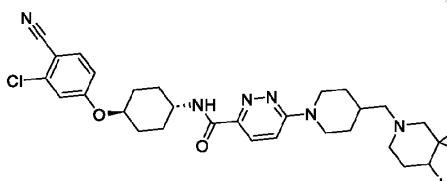





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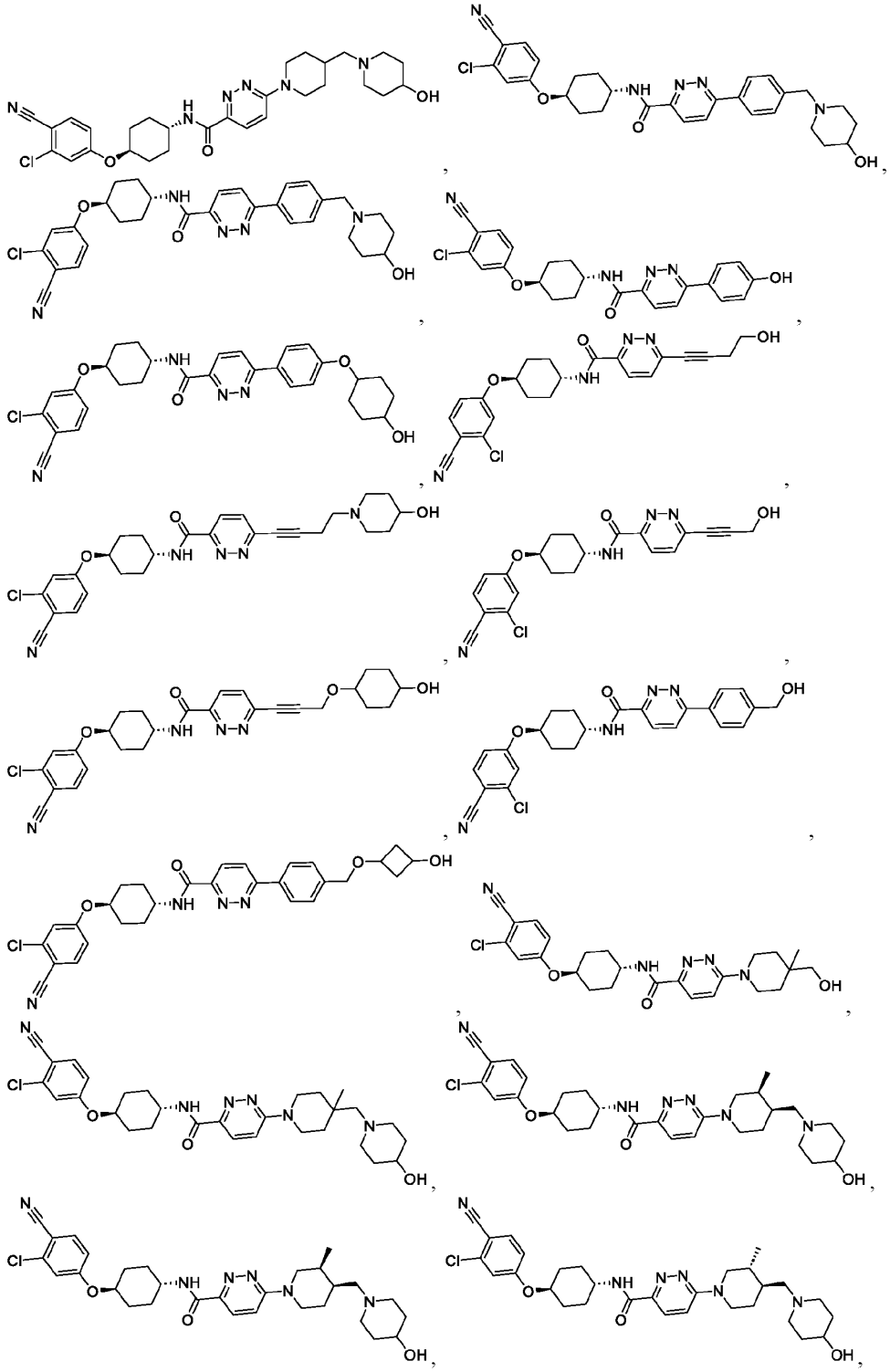
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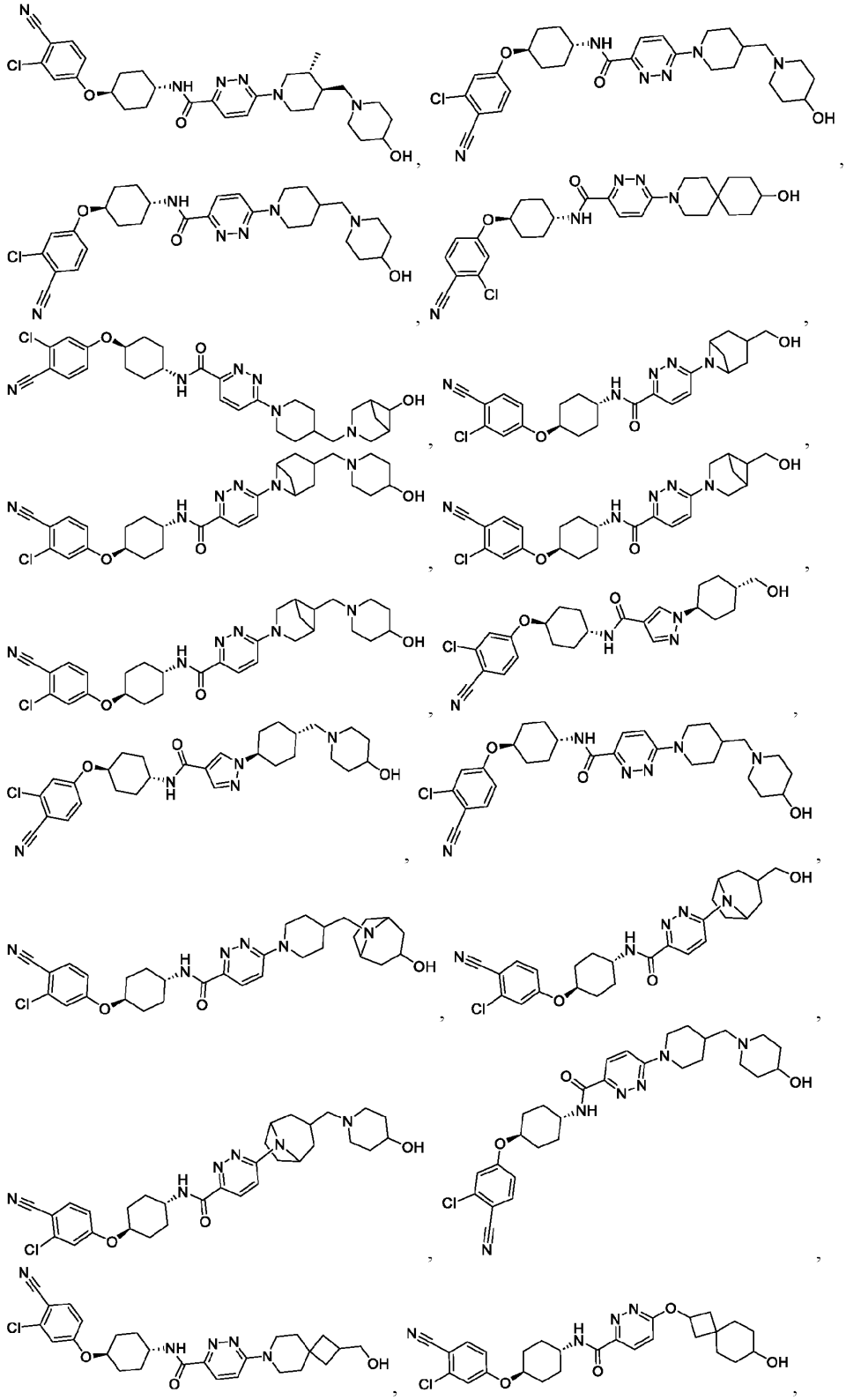
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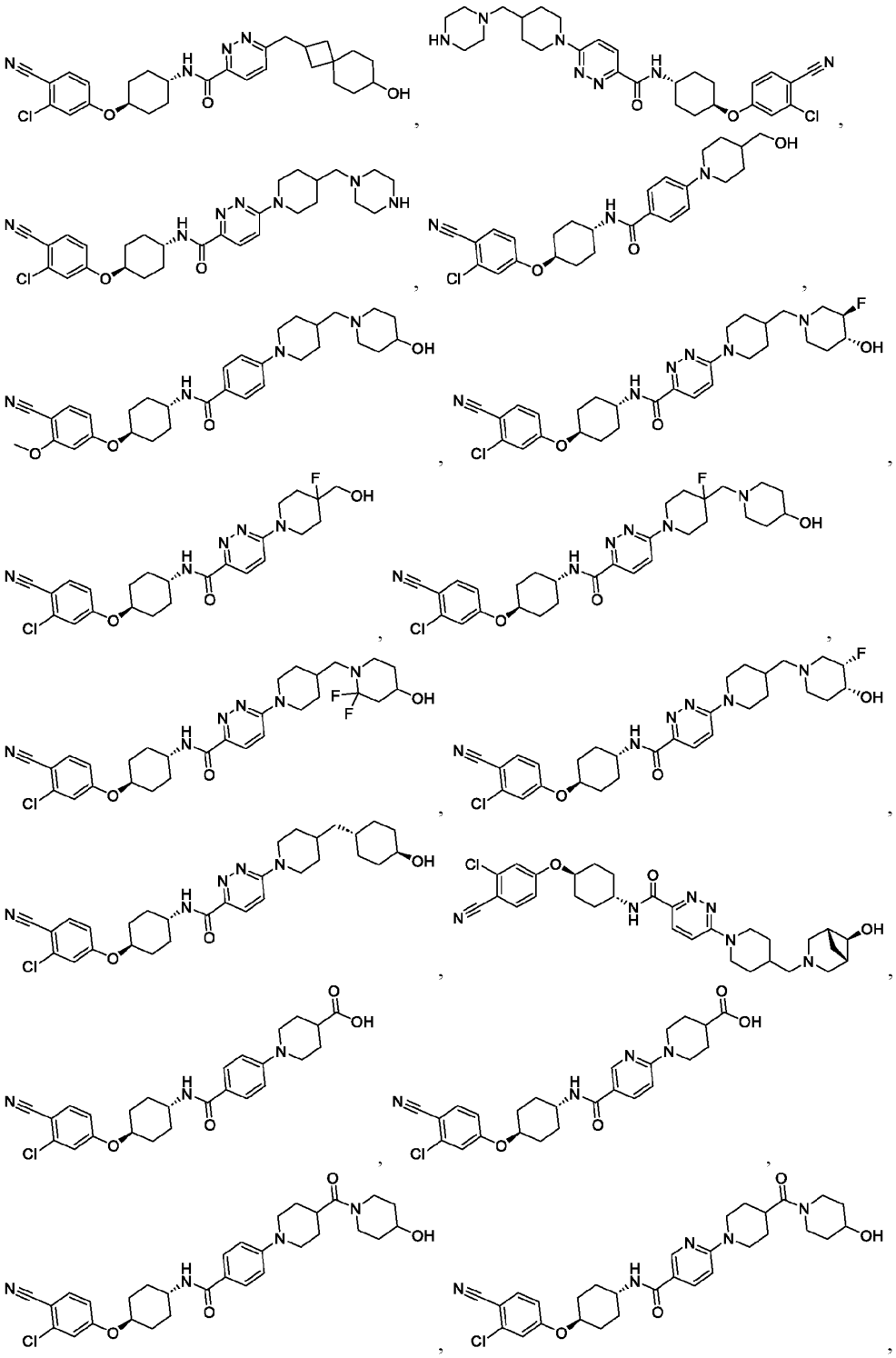
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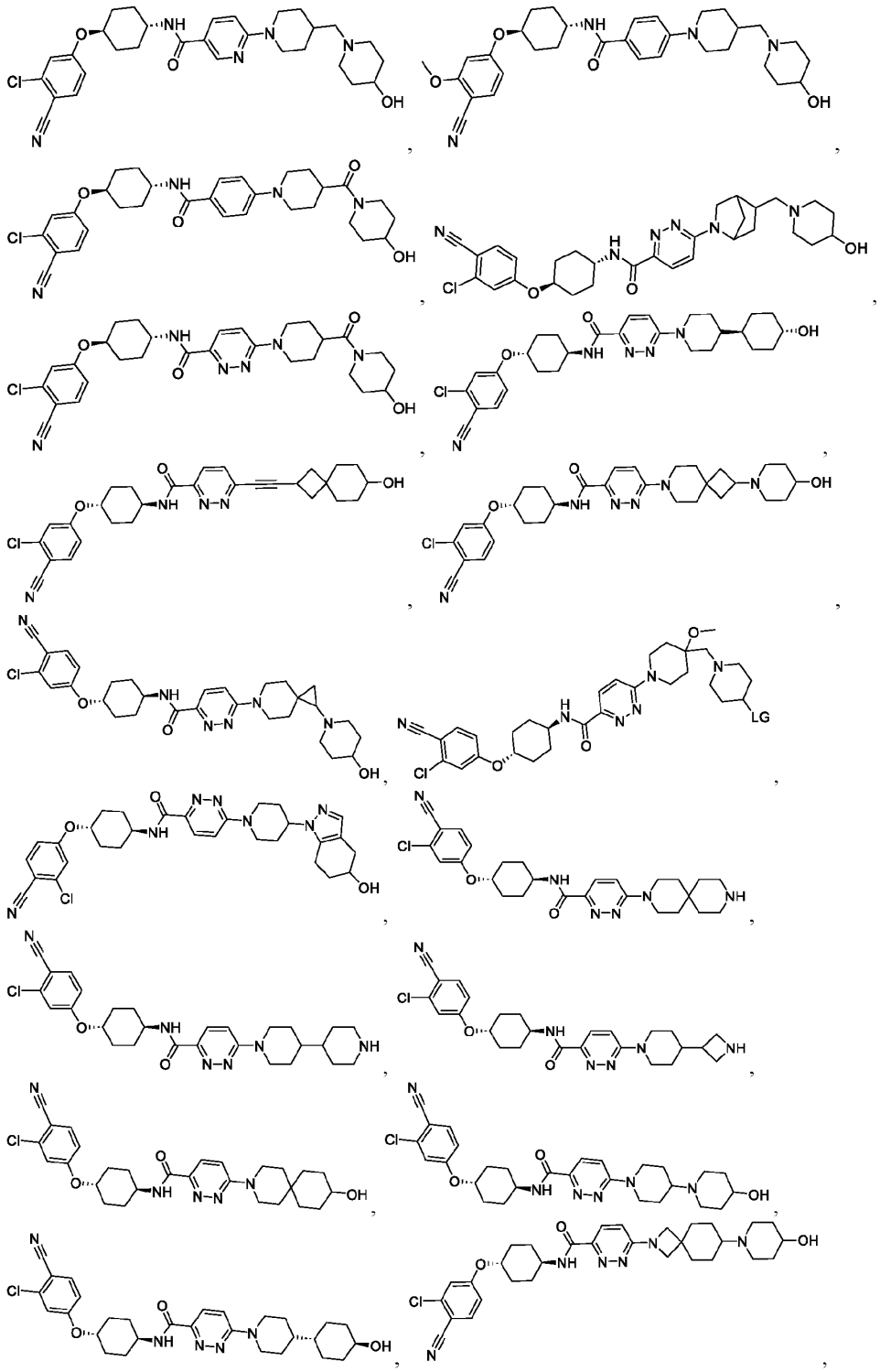
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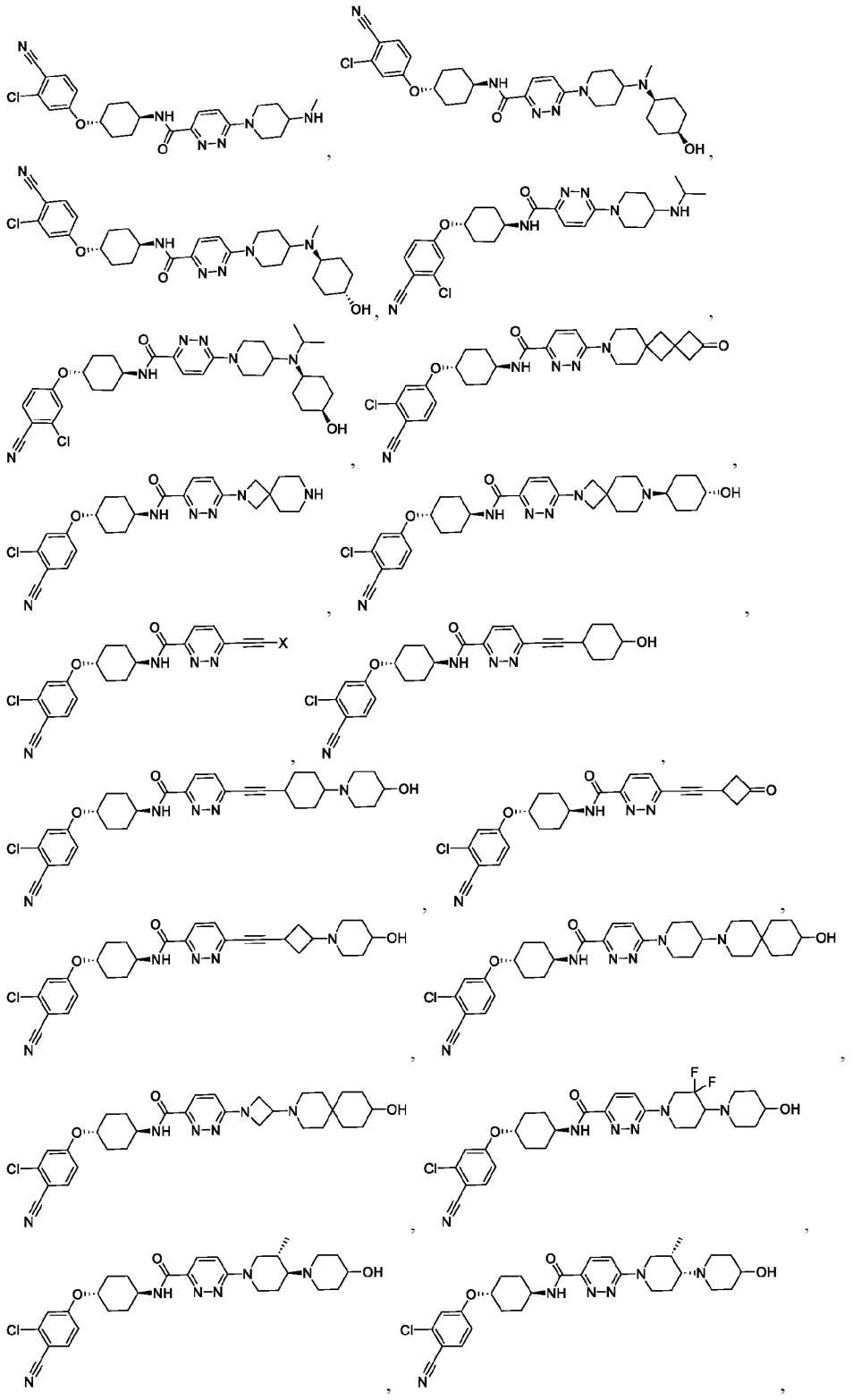
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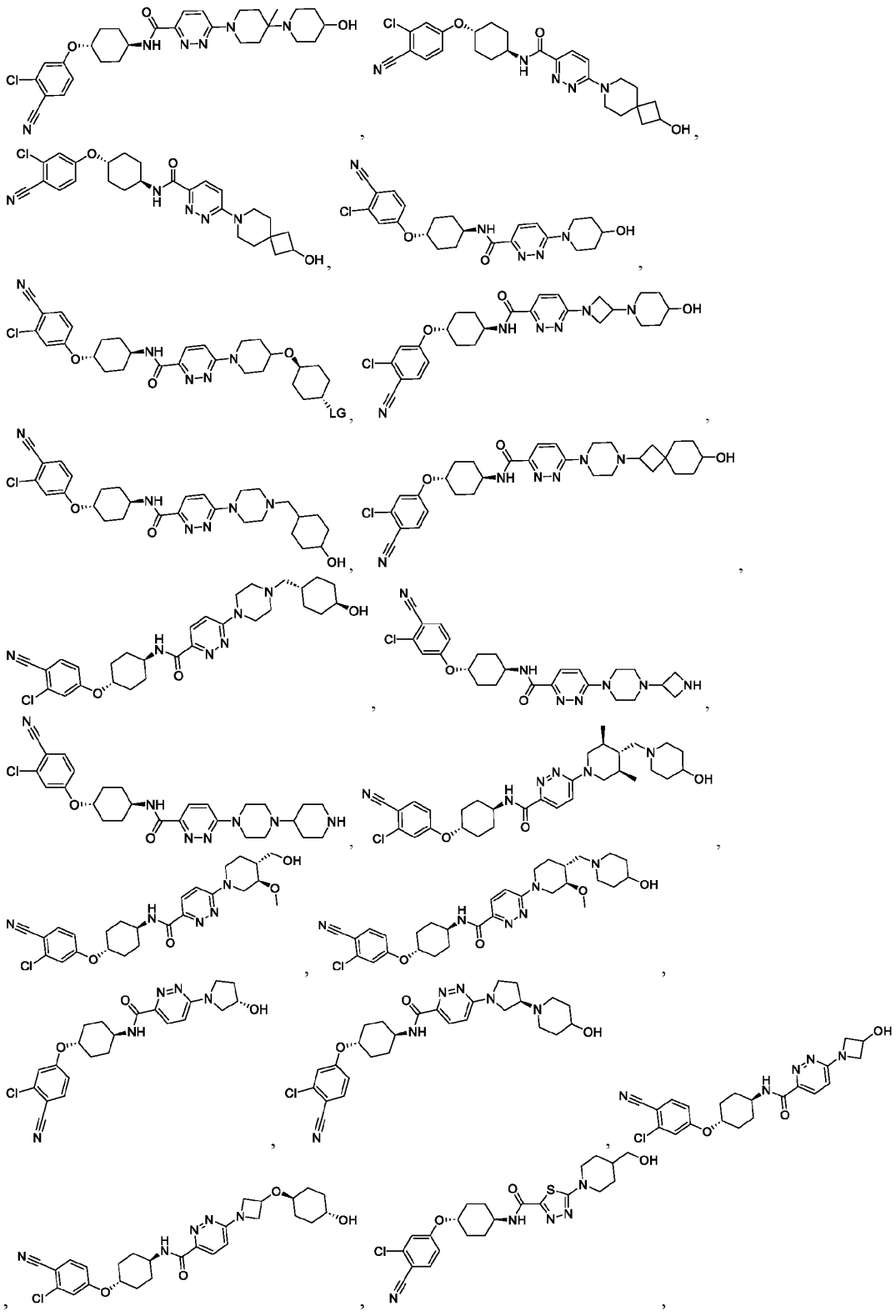


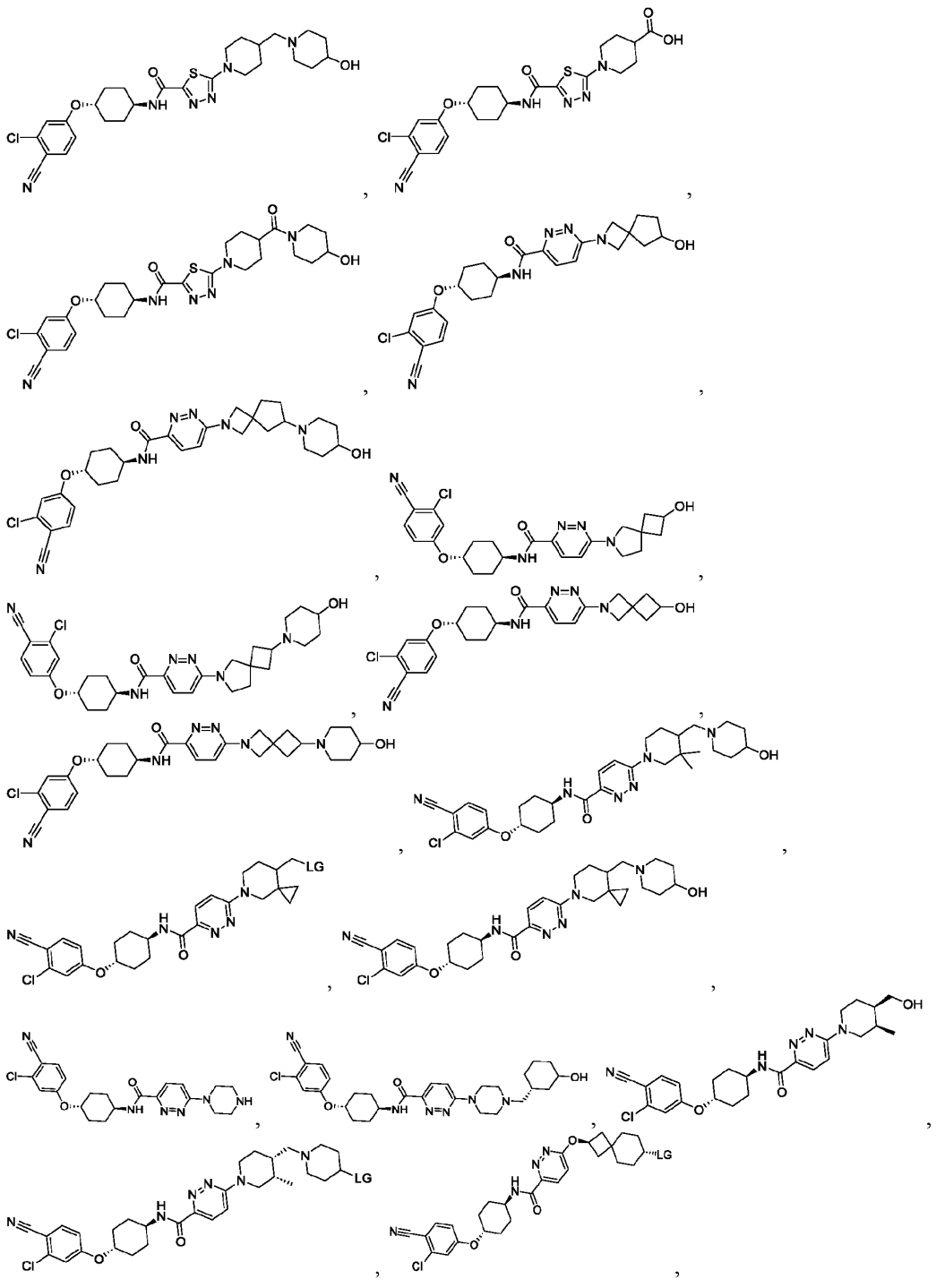


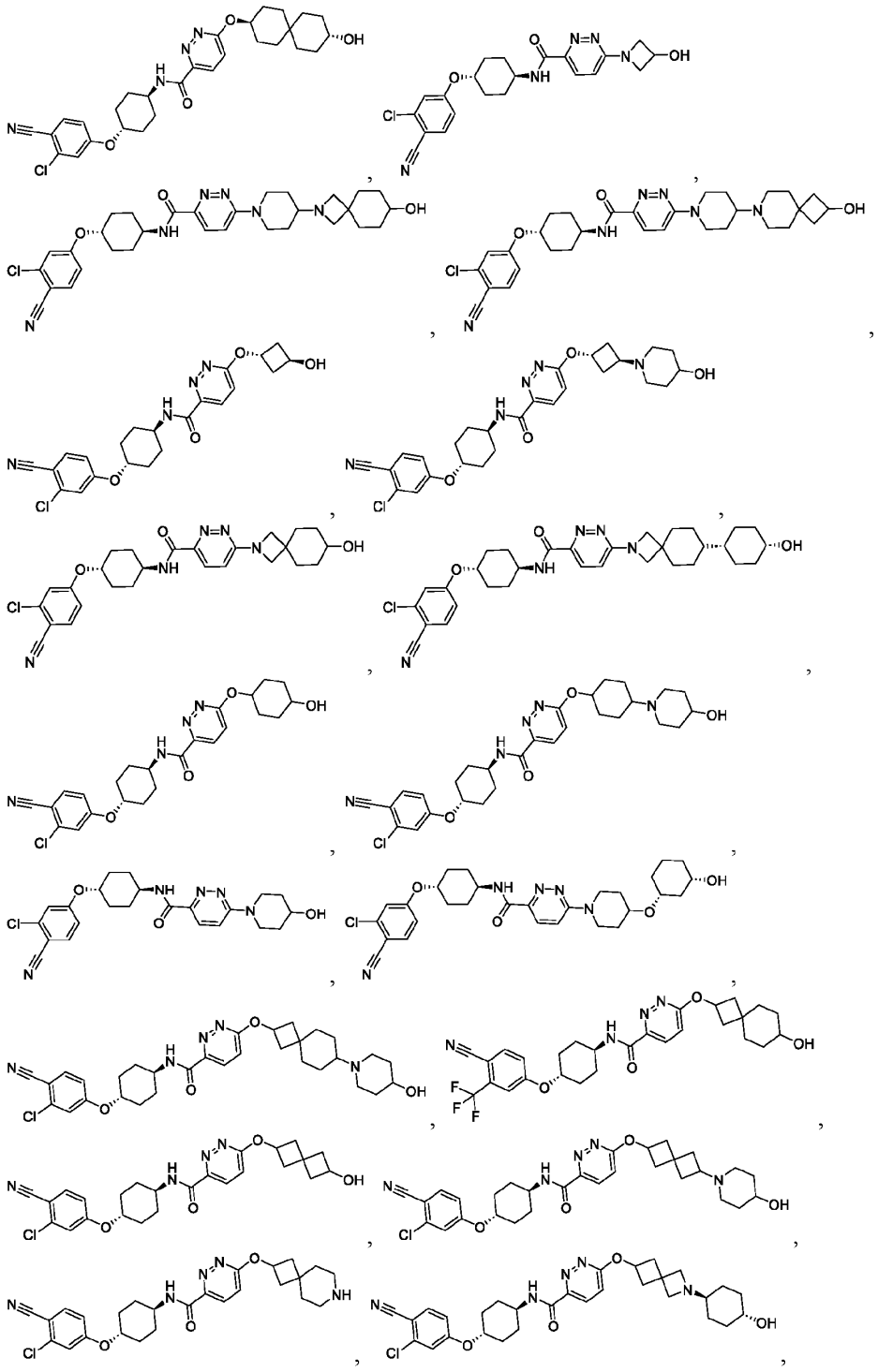


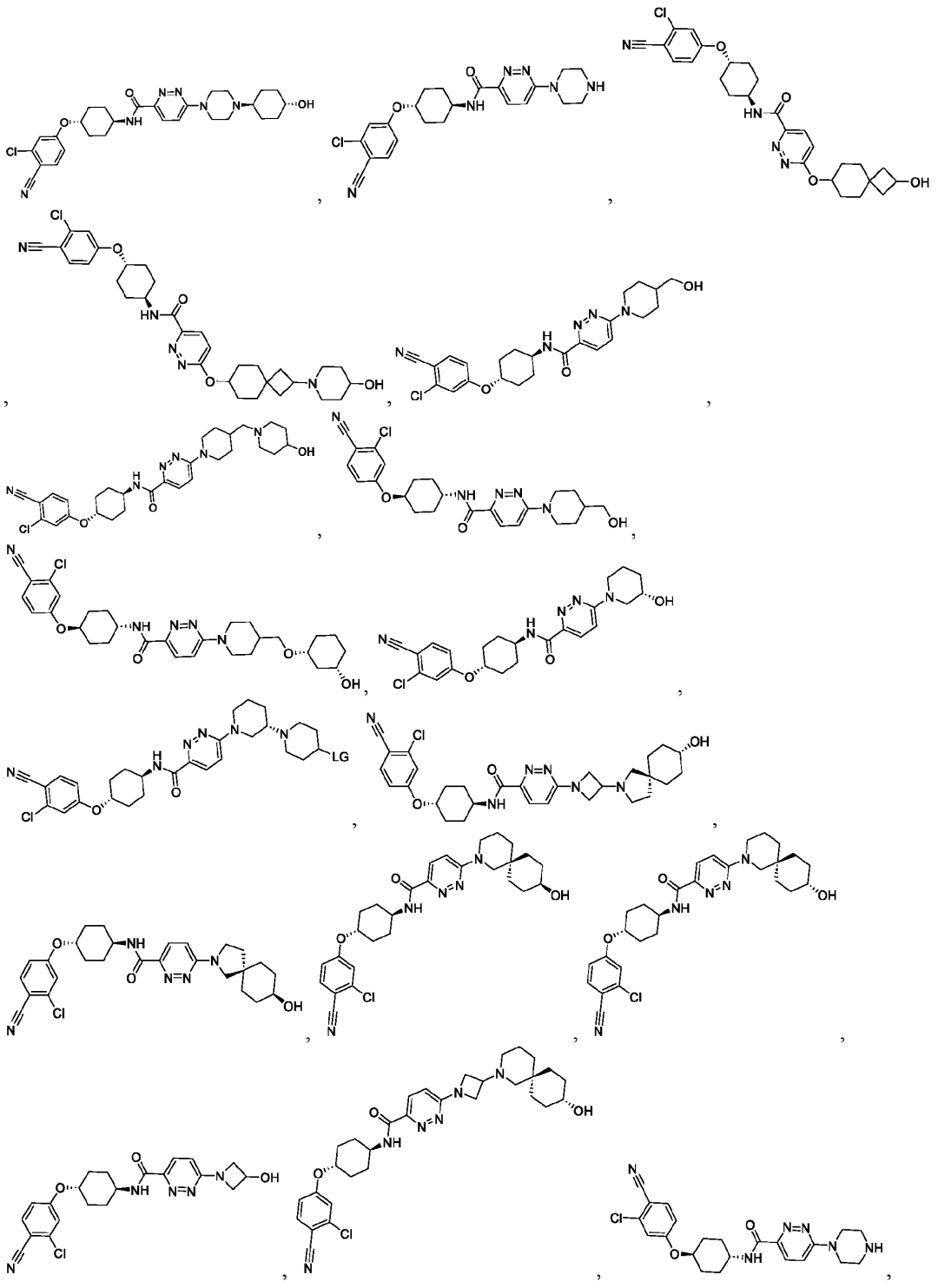


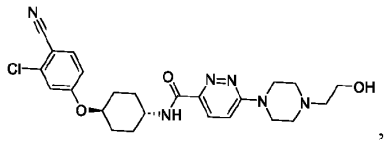
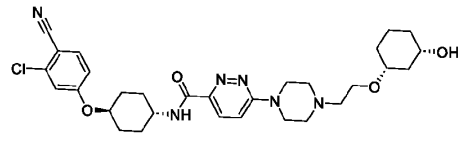
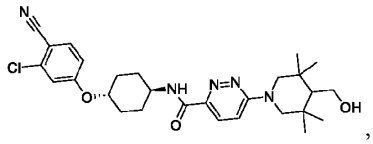
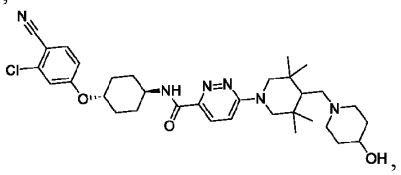
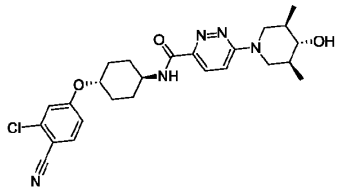
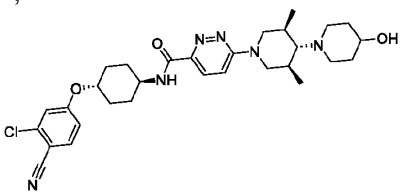
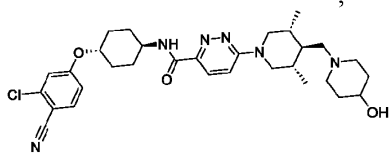
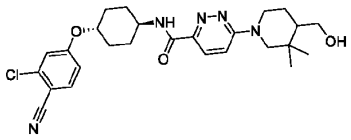
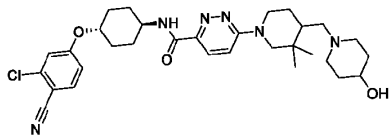
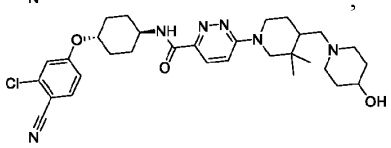
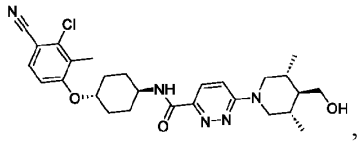
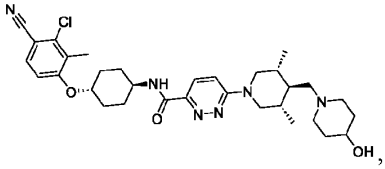
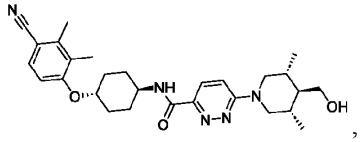
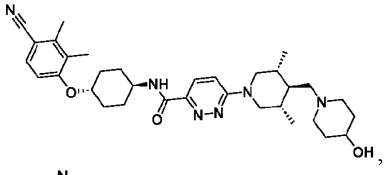
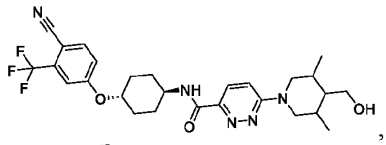
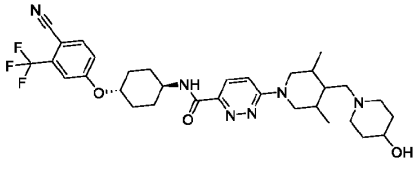
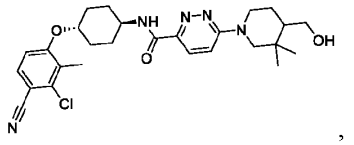
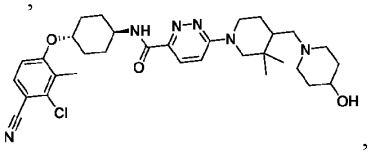
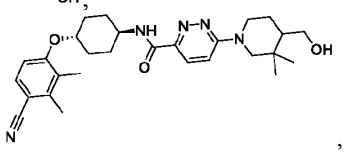
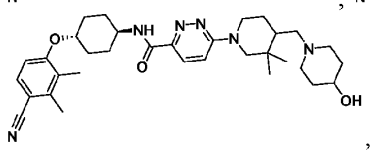
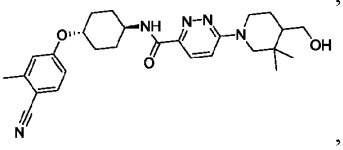


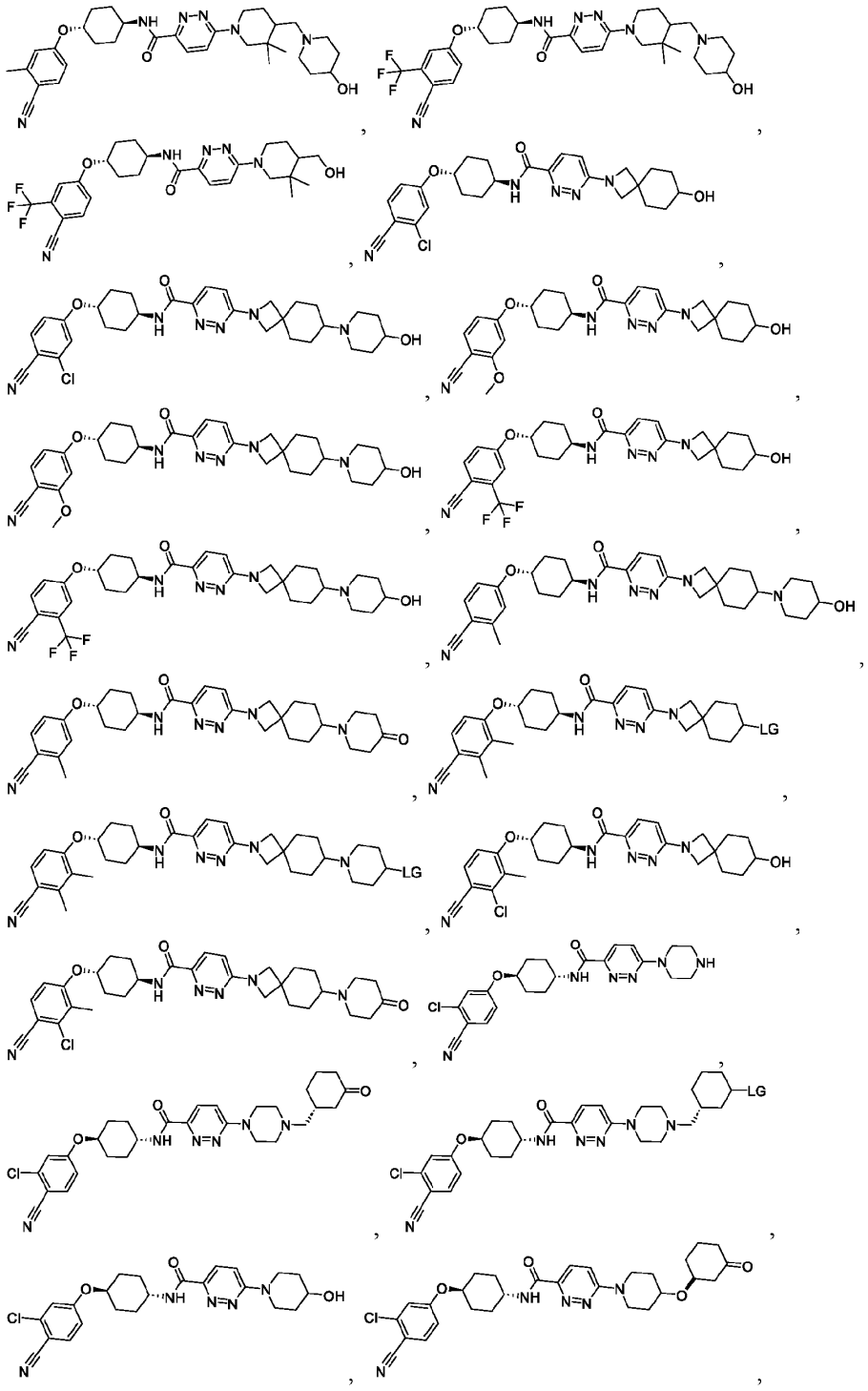


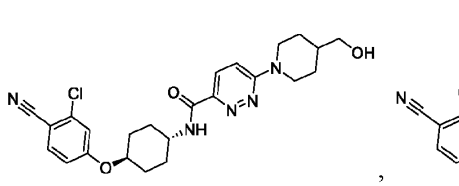
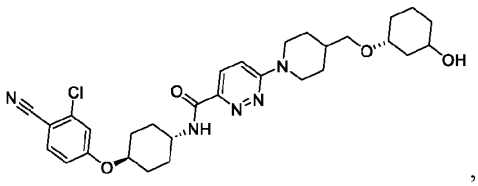
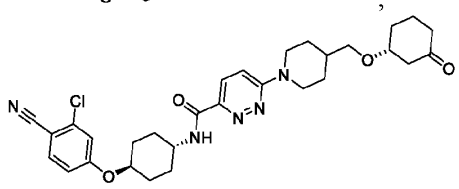
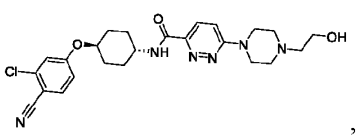
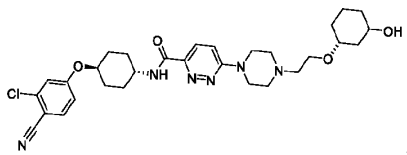
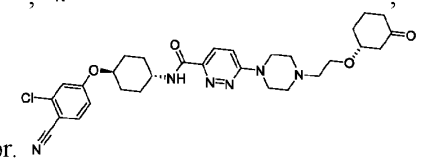




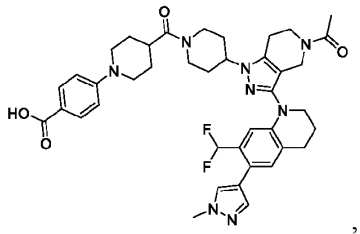
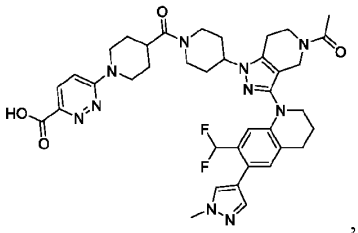
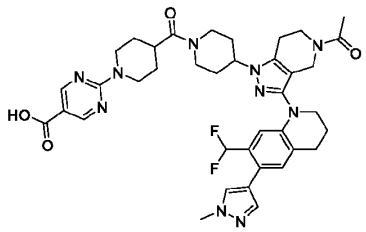
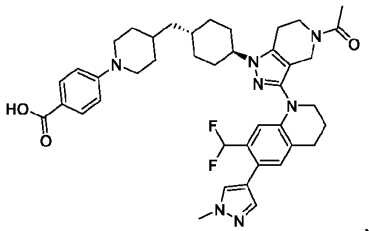
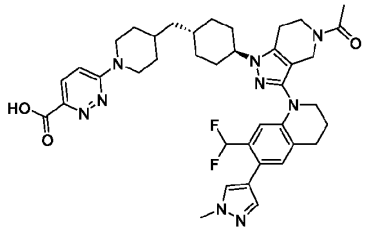
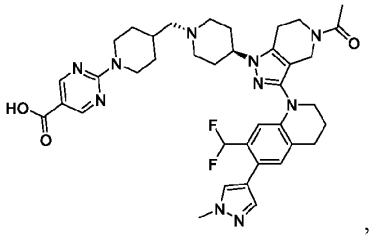


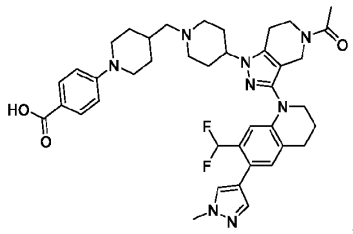
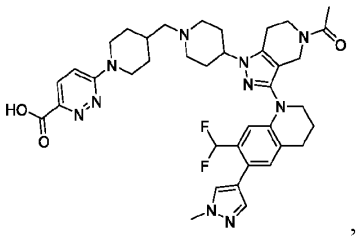
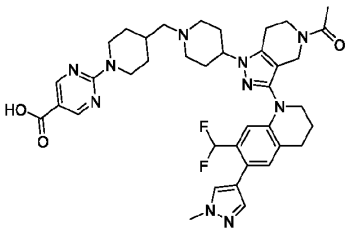
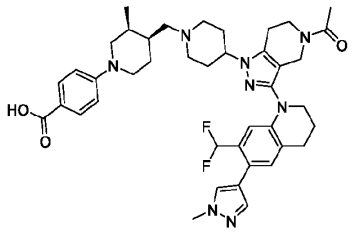
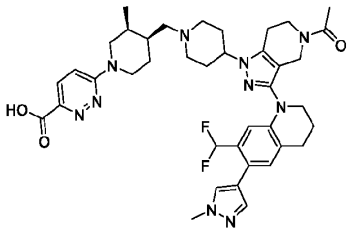
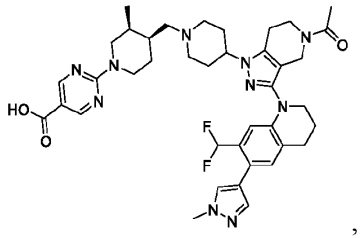
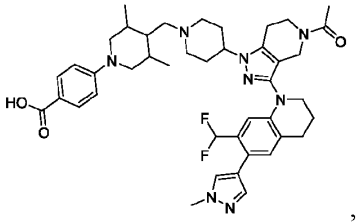
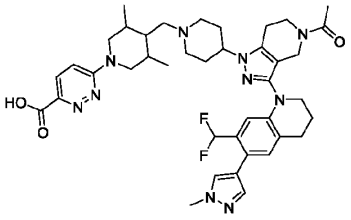
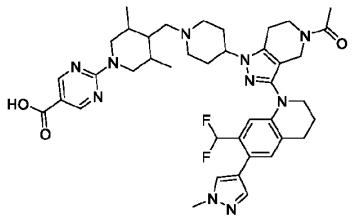
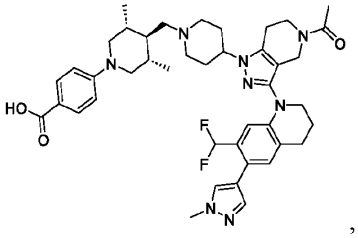
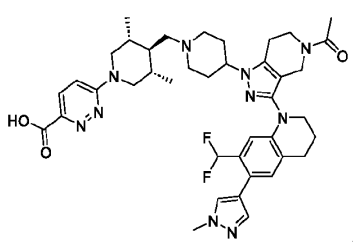
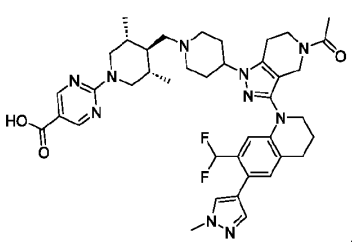
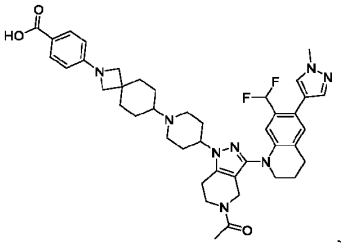
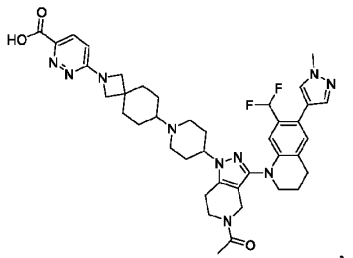
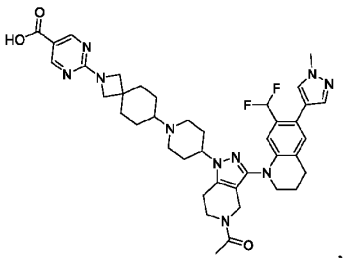
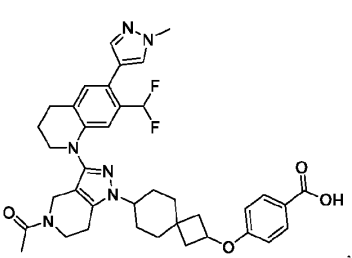

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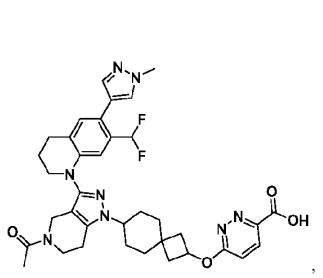
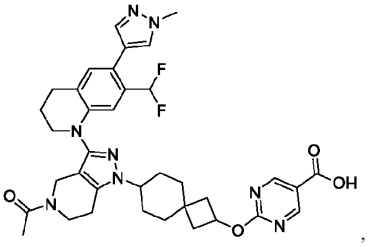
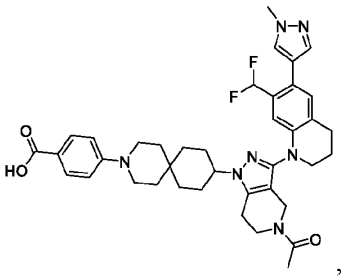
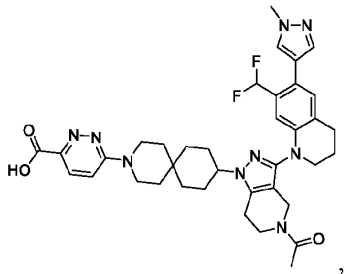
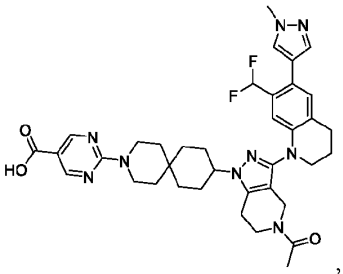
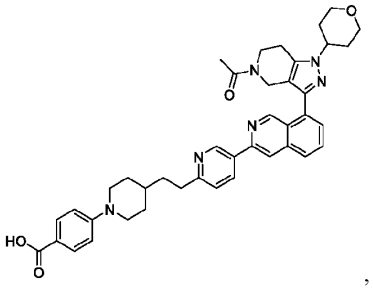
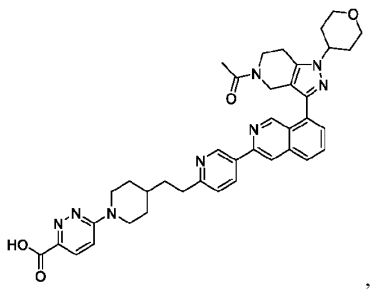
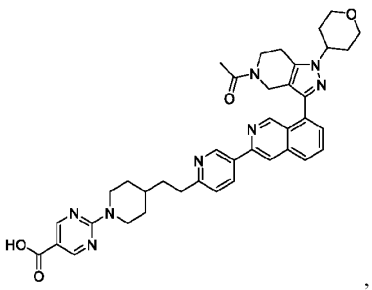
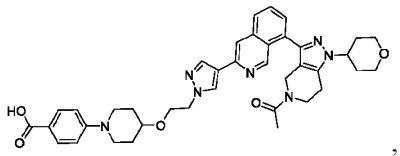
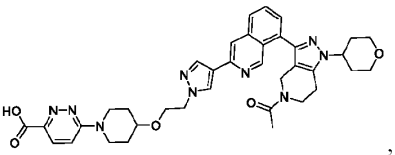
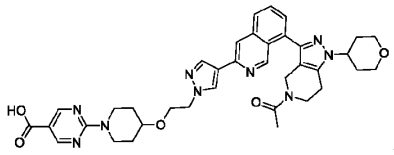



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[00309] Embodiment 121a. A compound, or a pharmaceutically acceptable salt or solvate thereof, that has one of the following structures:


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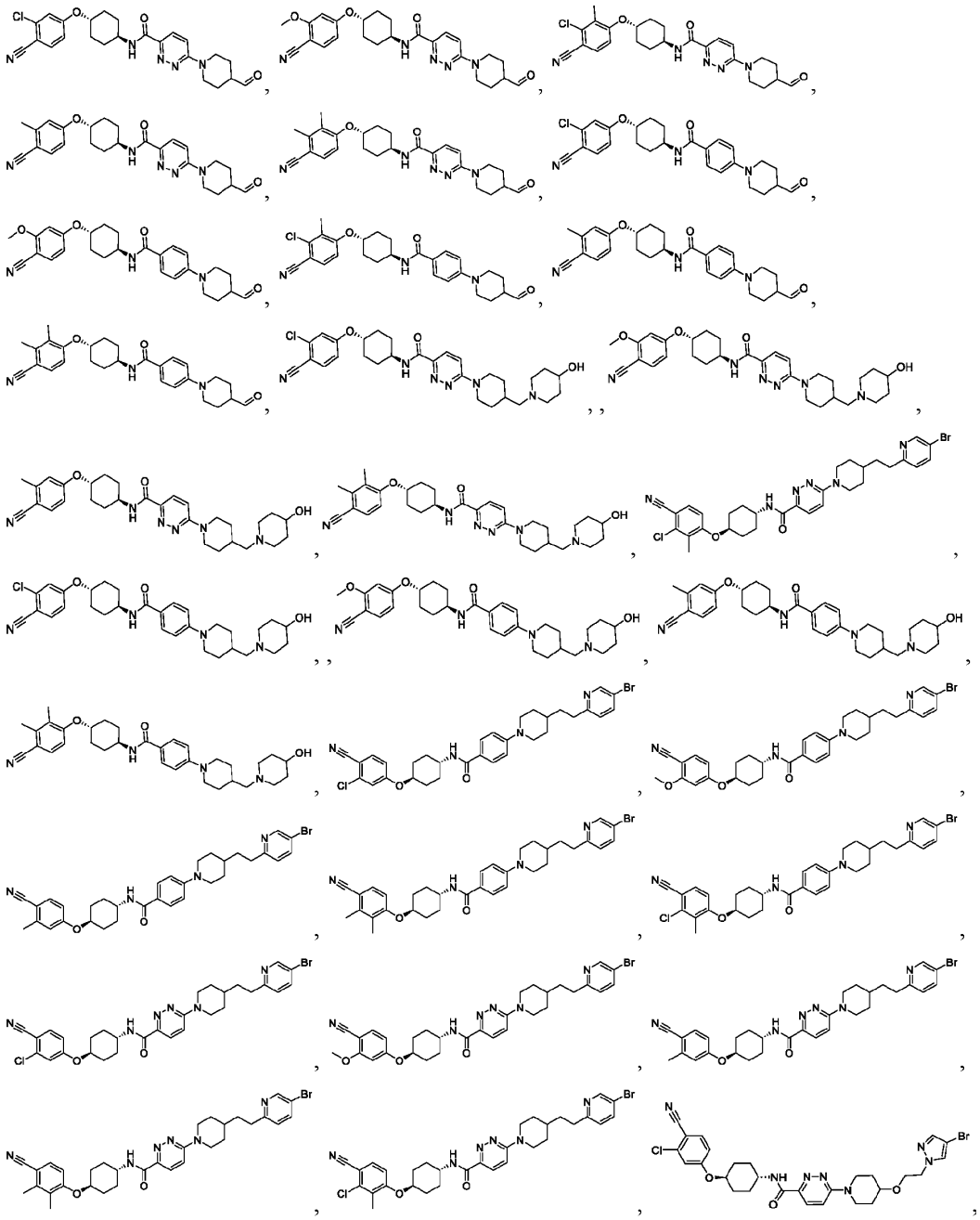
[00310] Embodiment 122. A compound, or a pharmaceutically acceptable salt or solvate thereof, prepared by an amide coupling of the compound of embodiment 39e and the compound of embodiment 121.

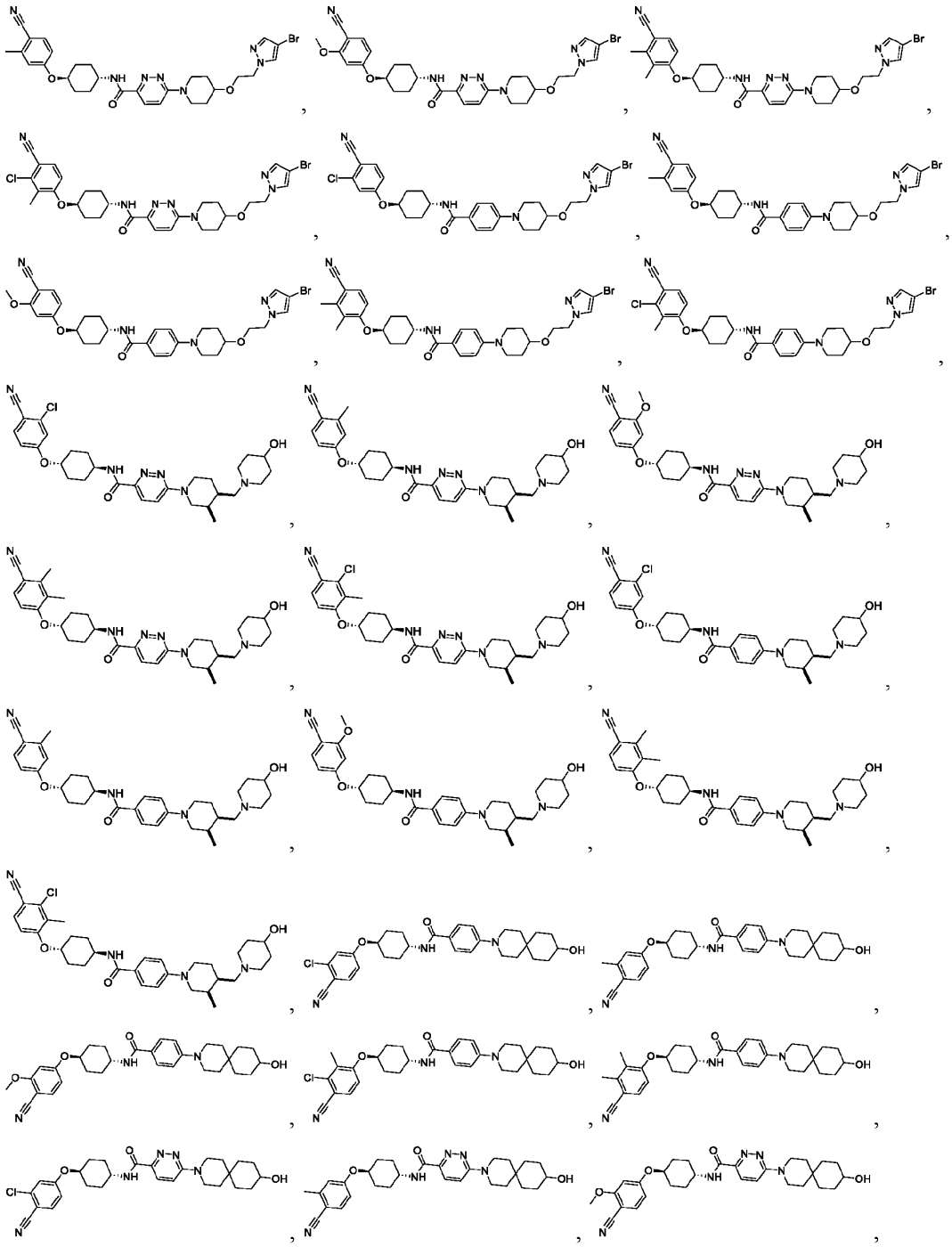
[00311] Embodiment 122a. A compound, or a pharmaceutically acceptable salt or solvate thereof, prepared by an amide coupling of the compound of embodiment 39f and the compound of embodiment 121.

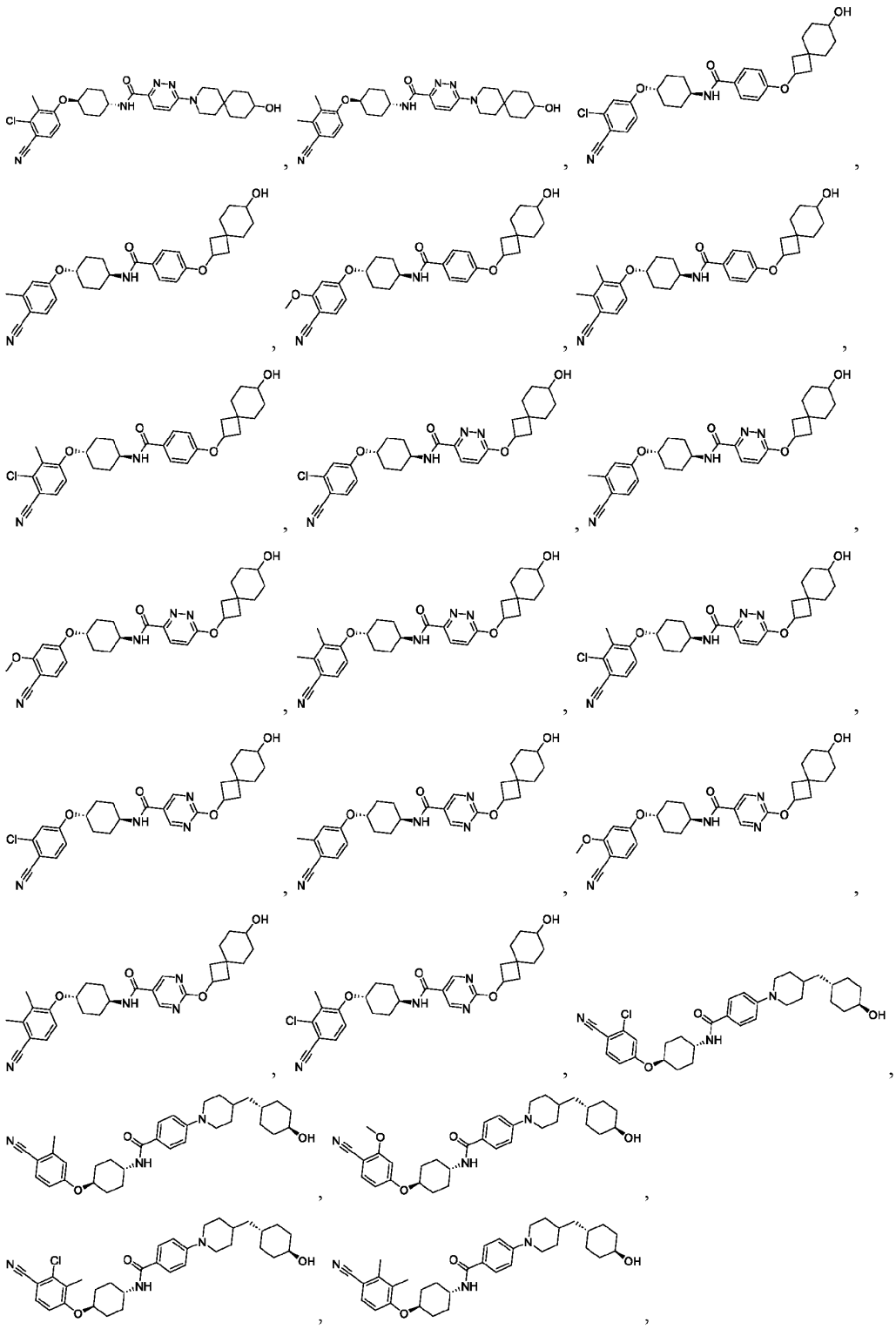
[00312] Embodiment 123c. A compound, or a pharmaceutically acceptable salt or solvate thereof, prepared by an amide coupling of the compound of embodiment 39e and the compound of embodiment 121a.

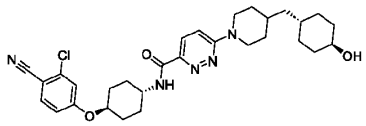
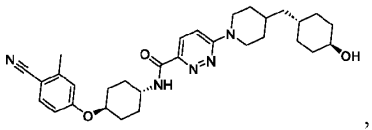
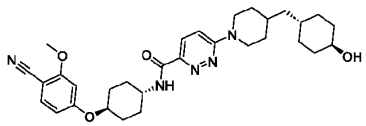
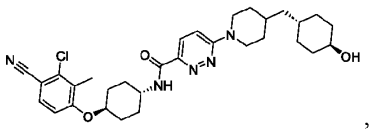
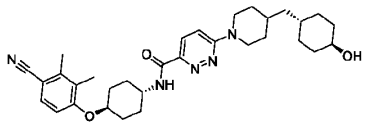
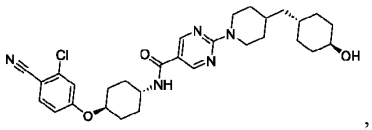
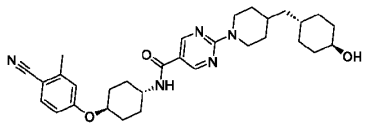
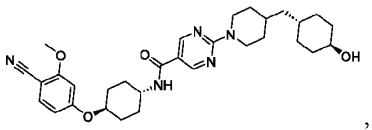
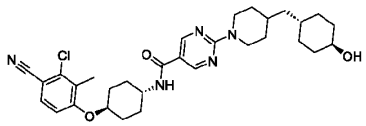
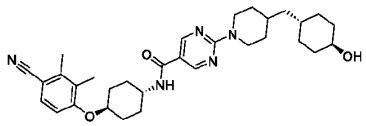
[00313] Embodiment 123d. A compound, or a pharmaceutically acceptable salt or solvate thereof, prepared by an amide coupling of the compound of embodiment 39f and the compound of embodiment 121a.

[00314] Embodiment 124. A compound, or a pharmaceutically acceptable salt or solvate thereof, that has one of the following structures:



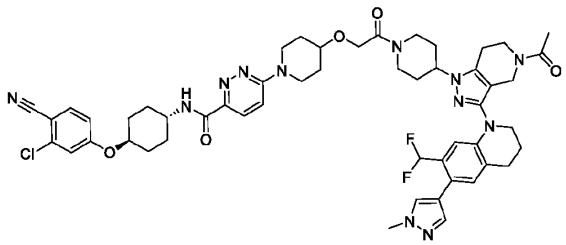
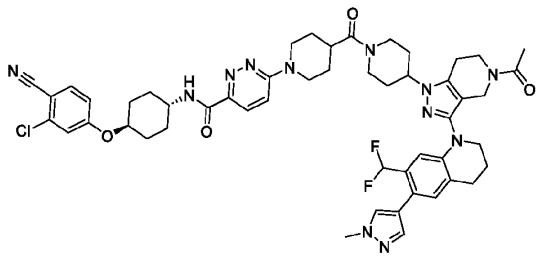


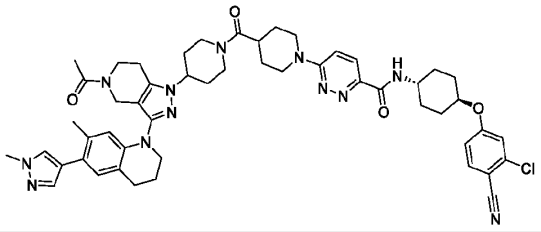
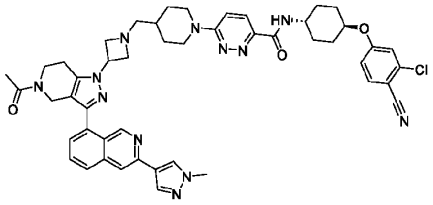
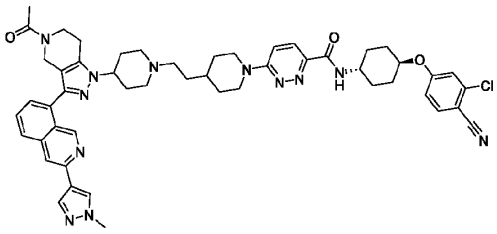
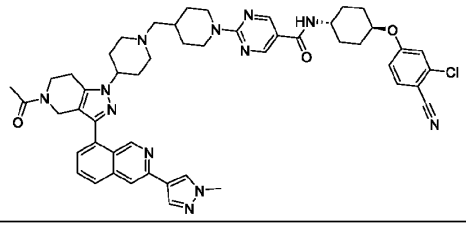
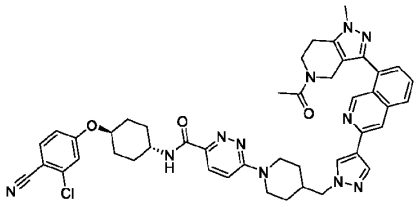
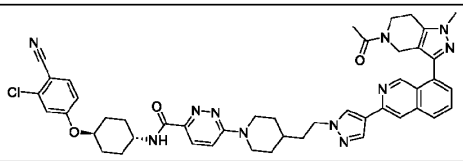
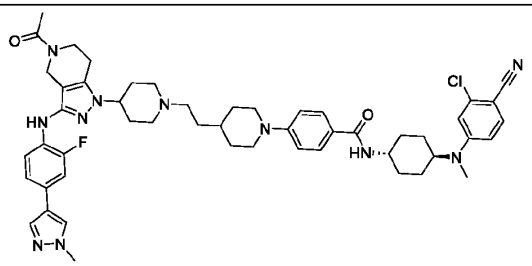


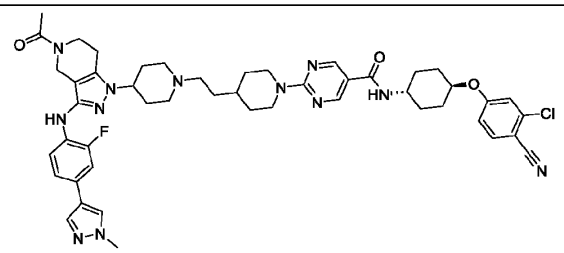
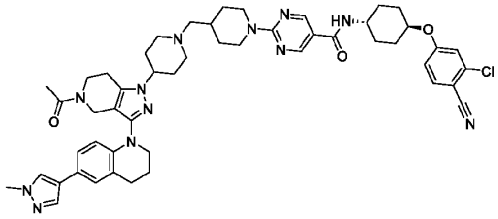
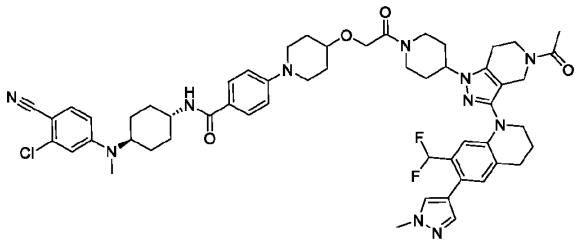
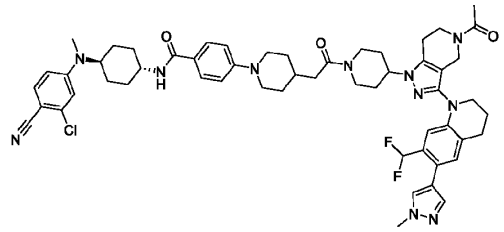
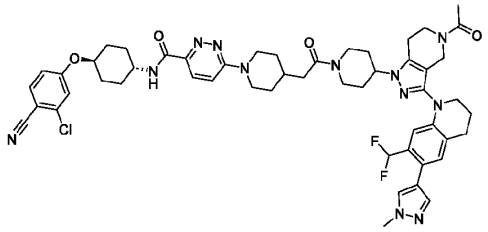
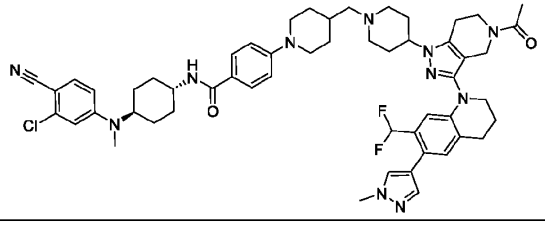

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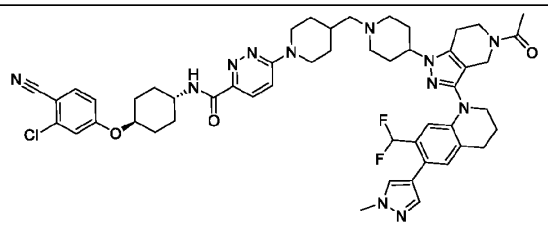
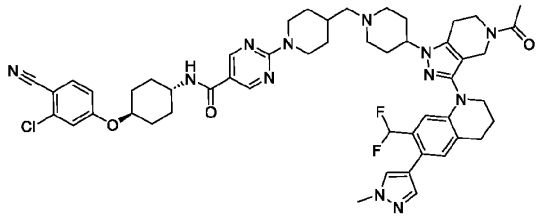
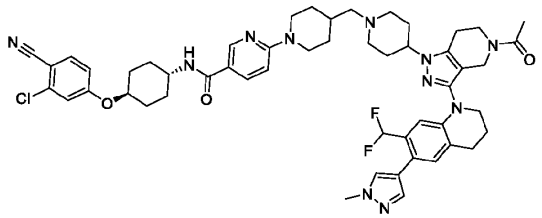
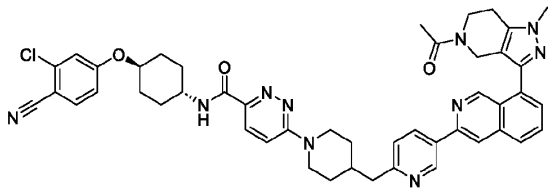
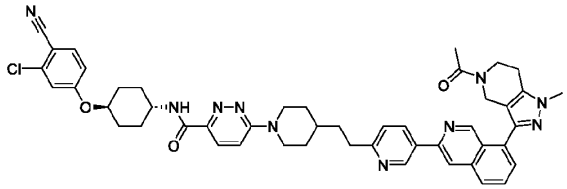
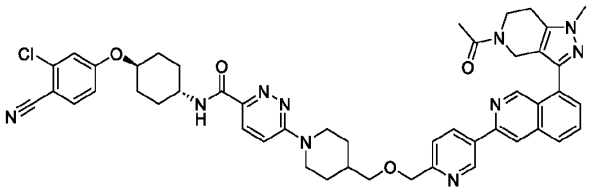
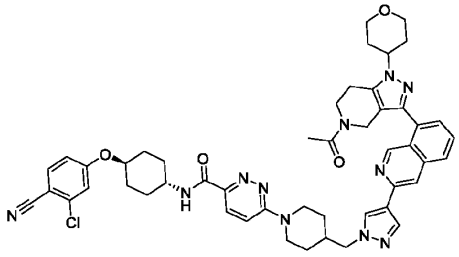
[00315] In some embodiments, the compound is a compound of Table 1, or a pharmaceutically acceptable salt or solvate thereof:

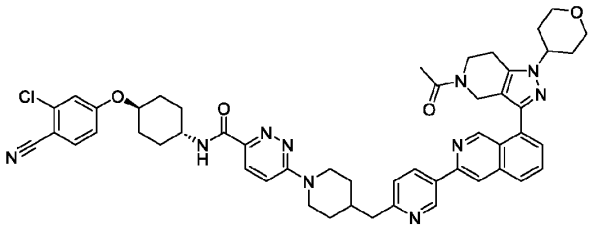
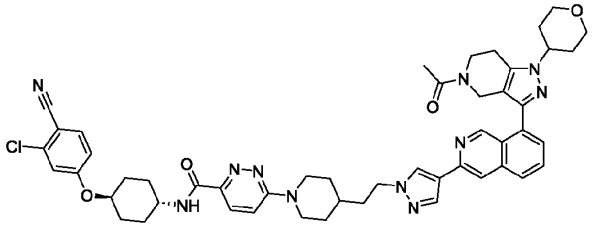
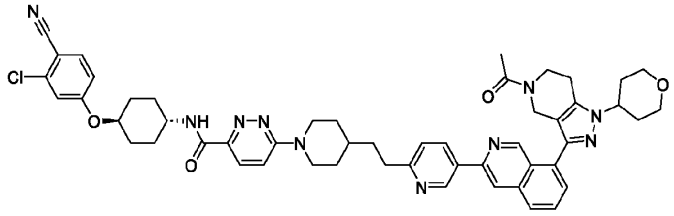
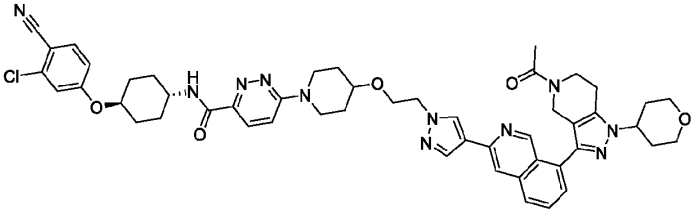
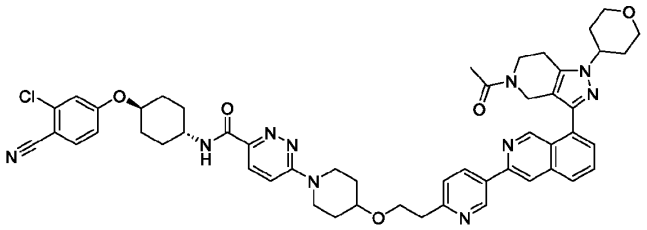
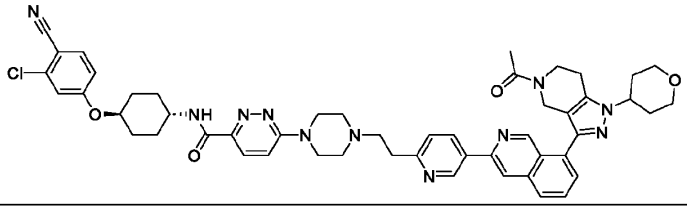
Table 1

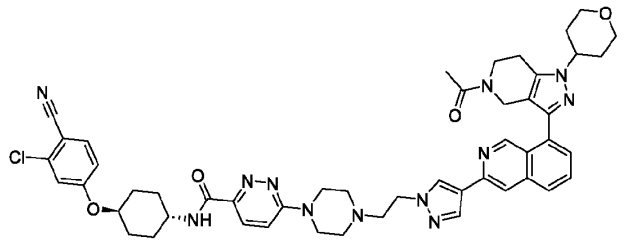
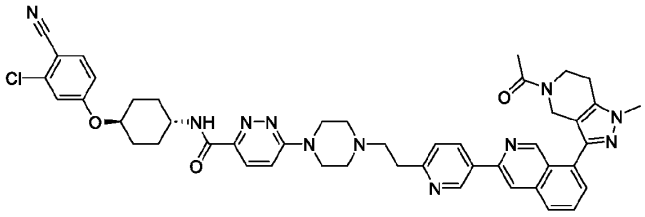
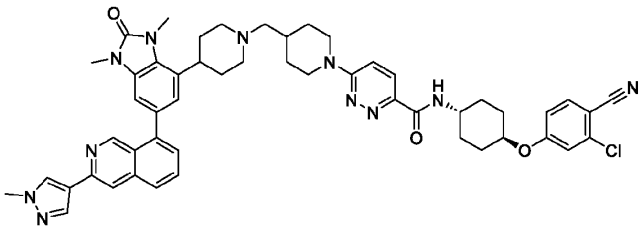
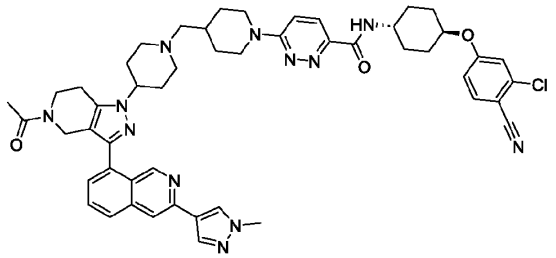
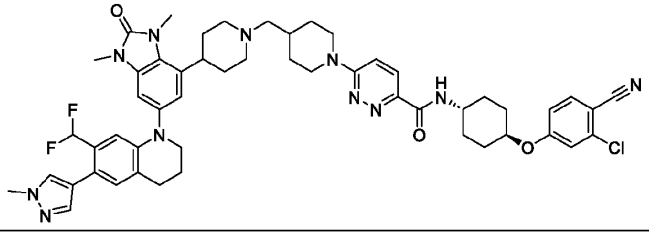
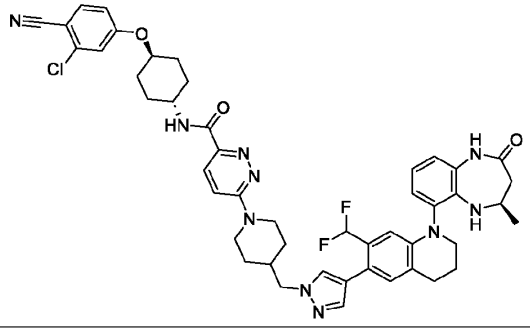
Compound	Structure
1	
2	

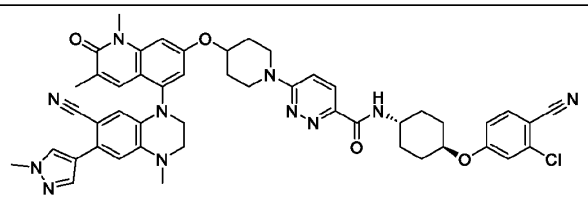
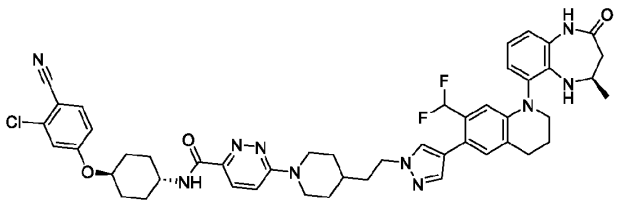
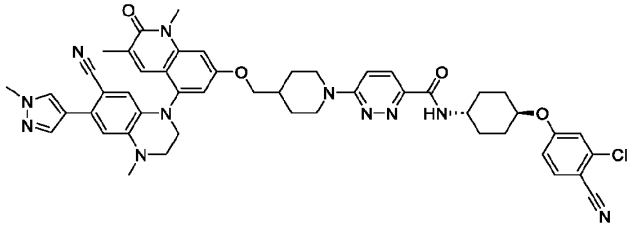
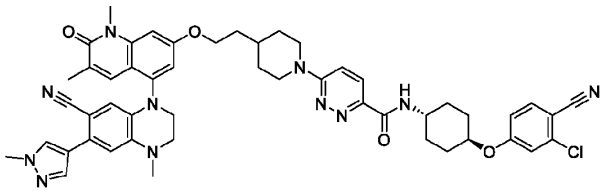
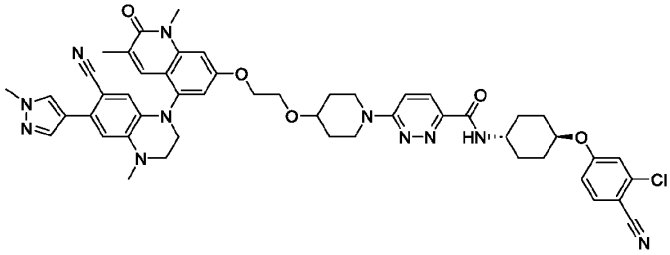
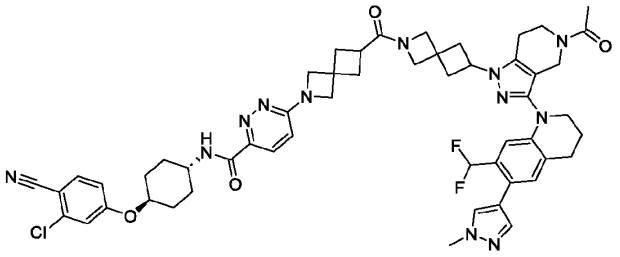
Compound	Structure
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4	
5	
6	
7	
8	
9	

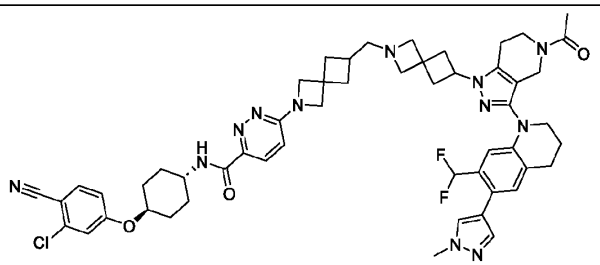
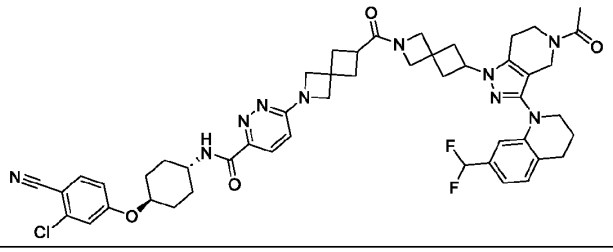
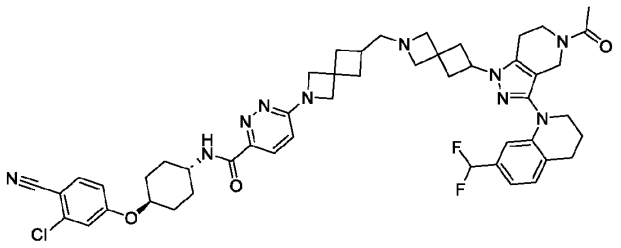
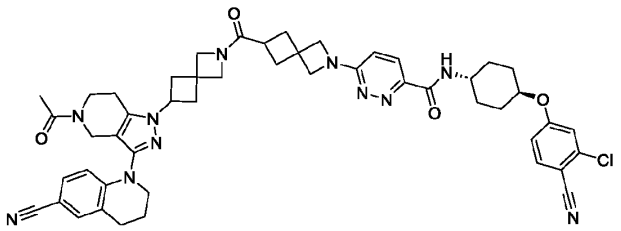
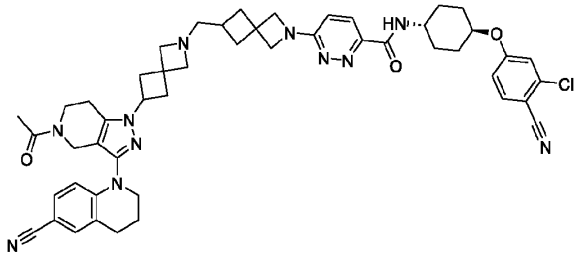
Compound	Structure
10	
11	
12	
13	
14	
15	

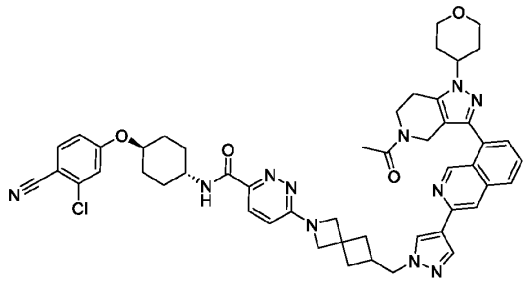
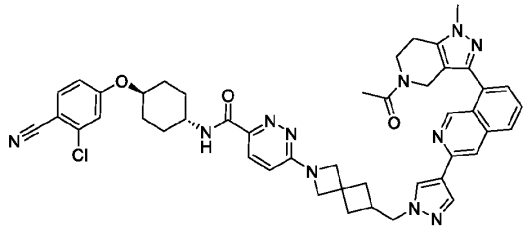
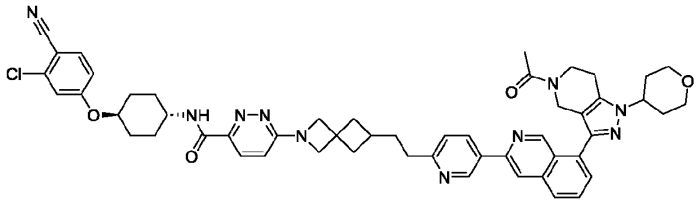
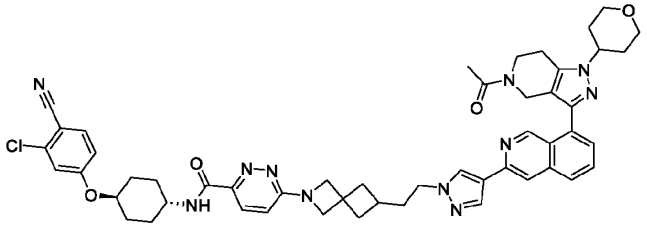
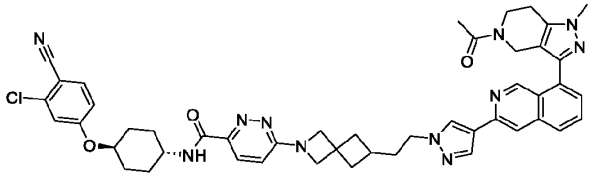
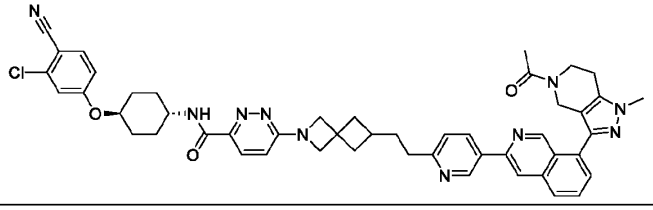
Compound	Structure
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17	
18	
19	
20	
21	
22	

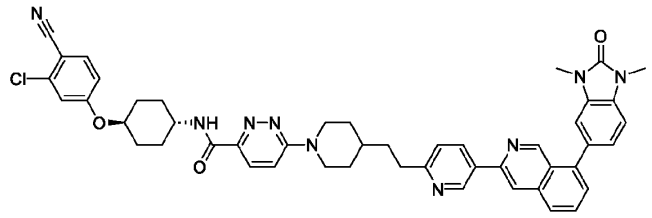
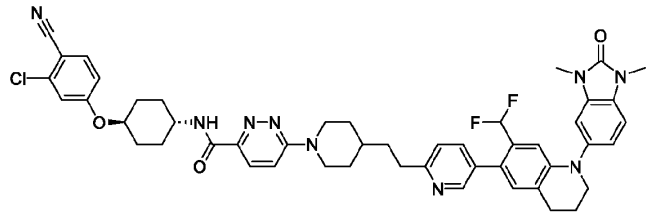
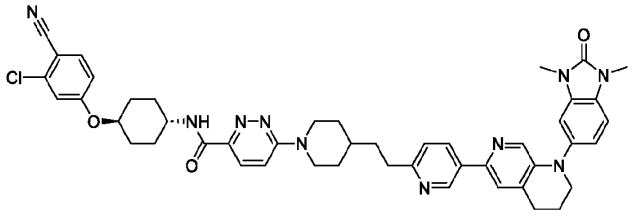
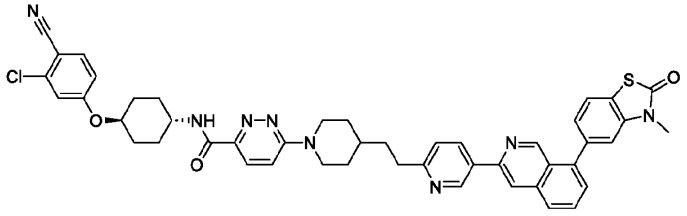
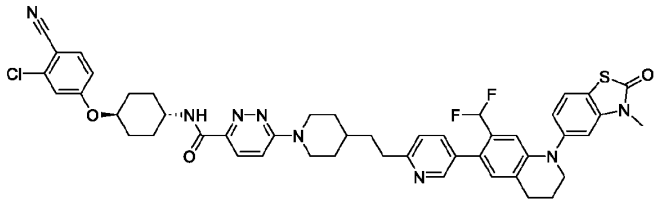
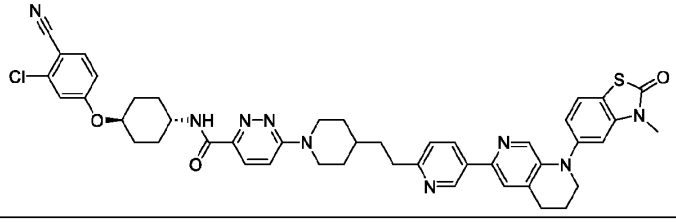
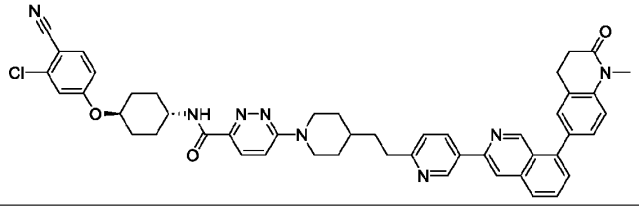
Compound	Structure
23	
24	
25	
26	
27	
28	

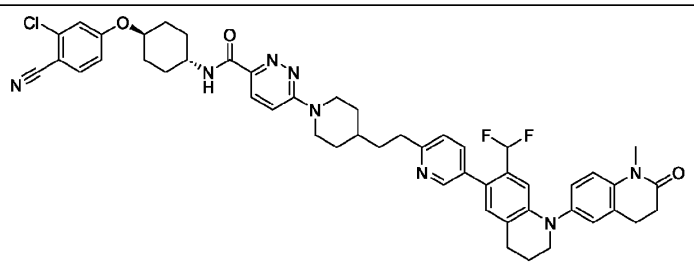
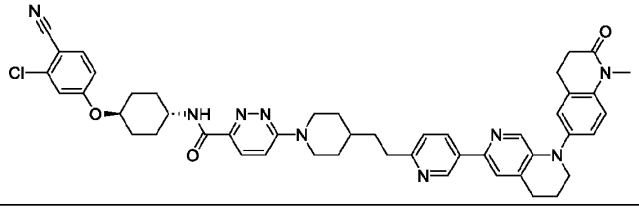
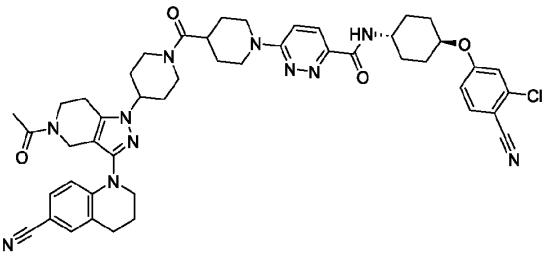
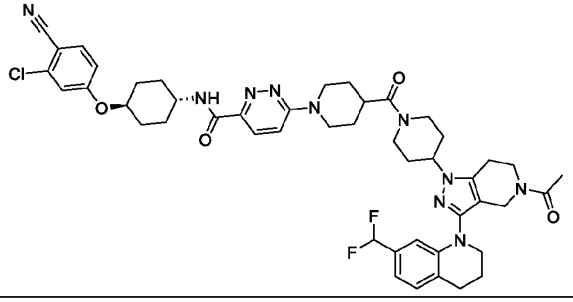
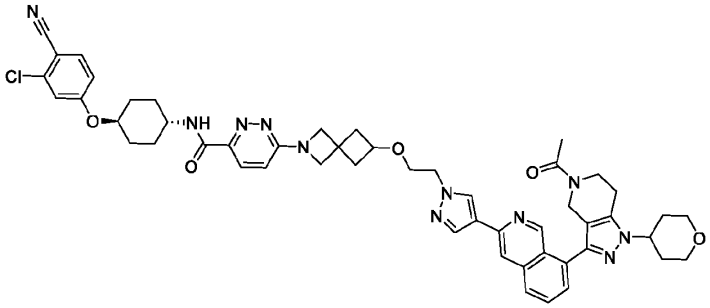
Compound	Structure
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30	
31	
32	
33	
34	

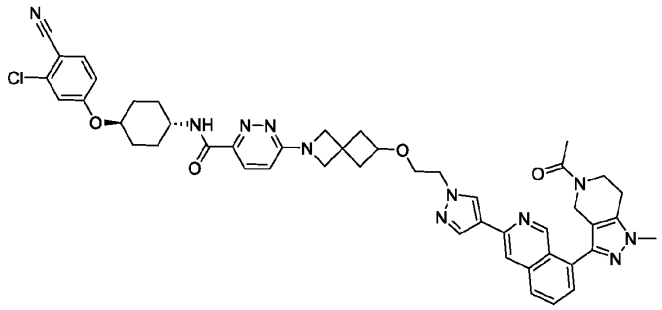
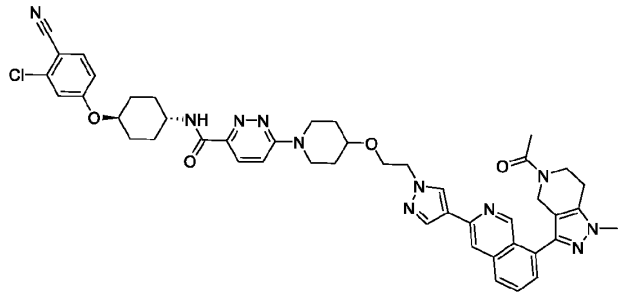
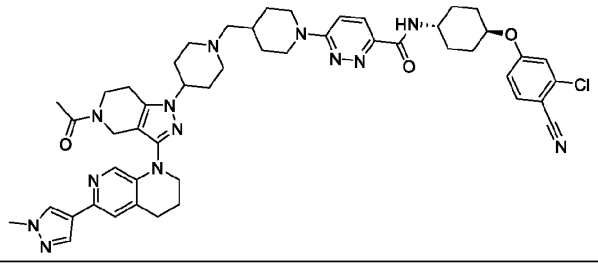
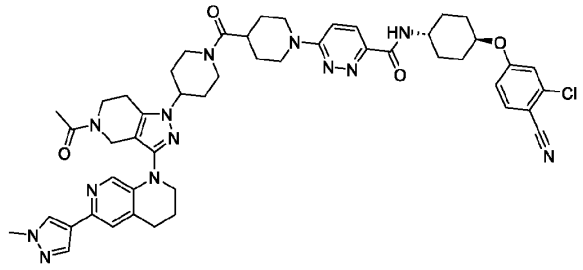
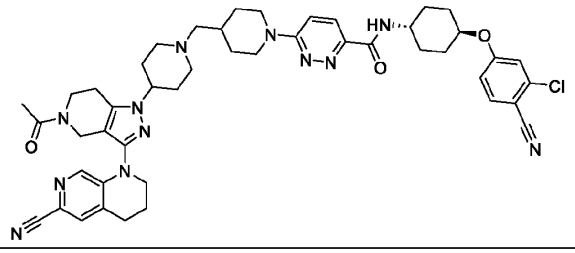
Compound	Structure
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36	
37	
38	
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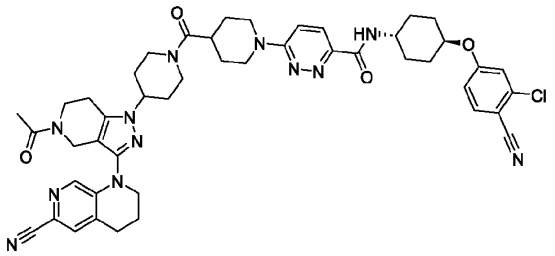
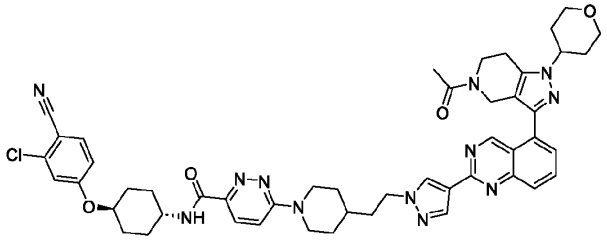
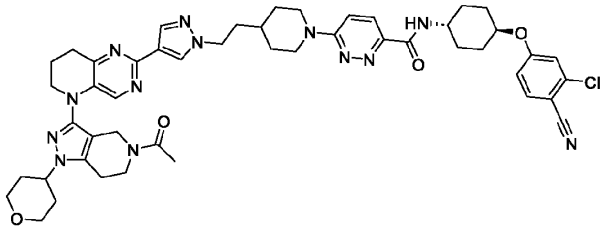
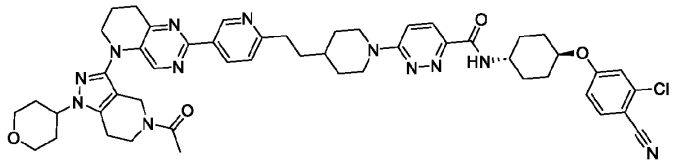
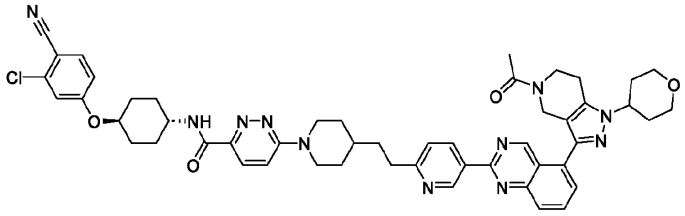
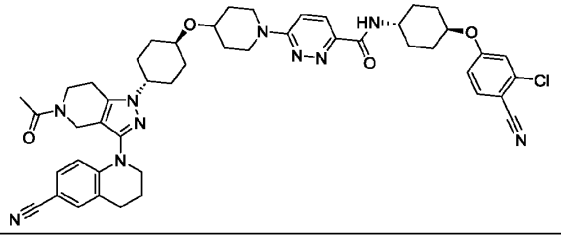
Compound	Structure
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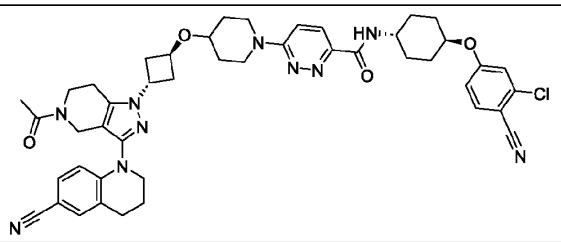
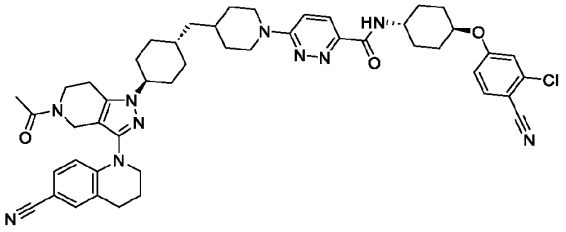
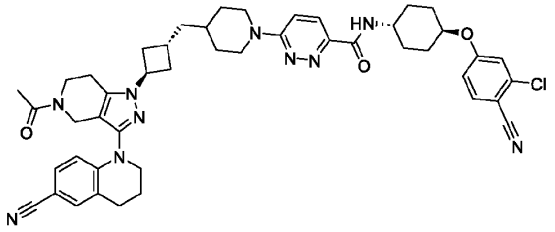
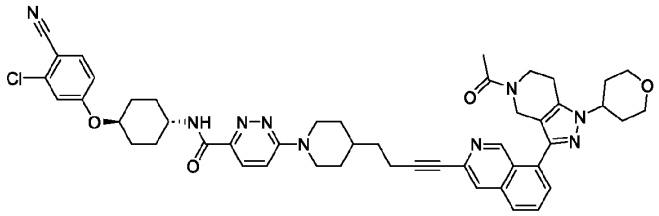
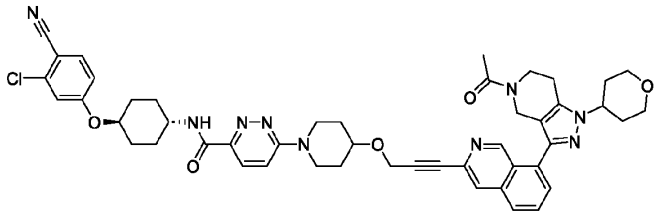
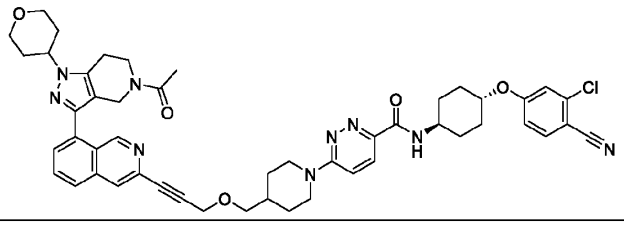
Compound	Structure
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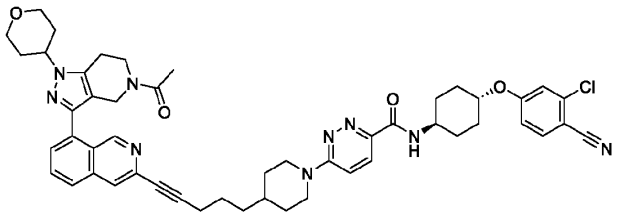
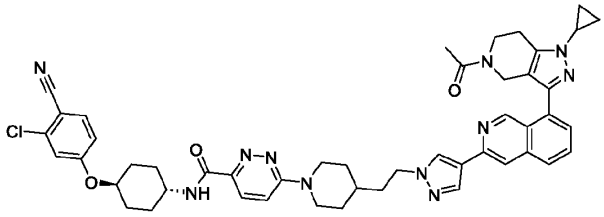
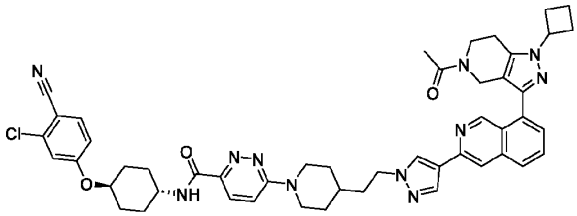
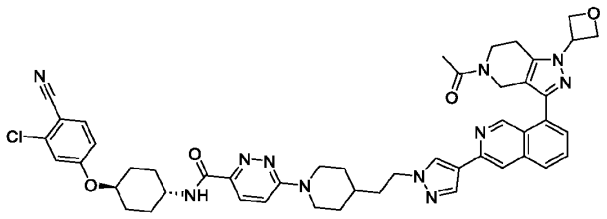
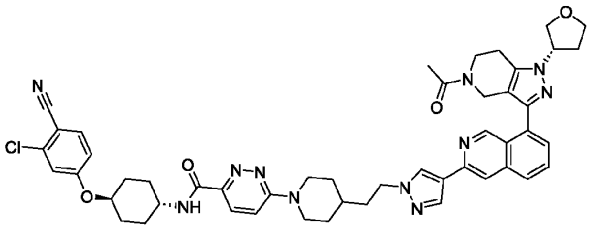
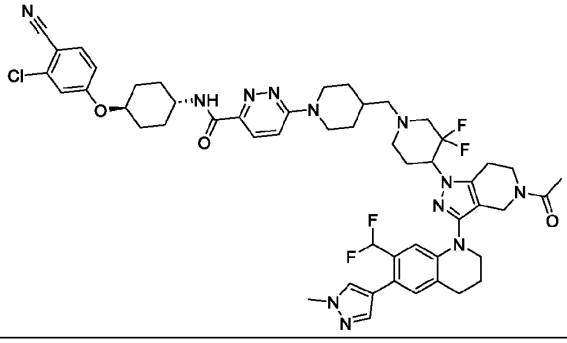
Compound	Structure
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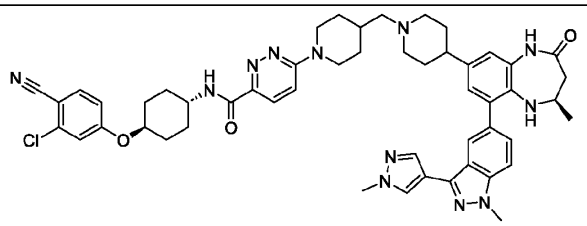
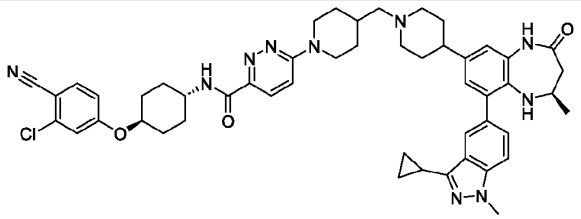
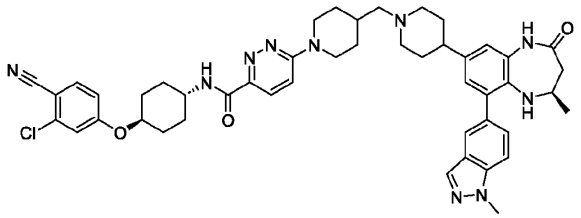
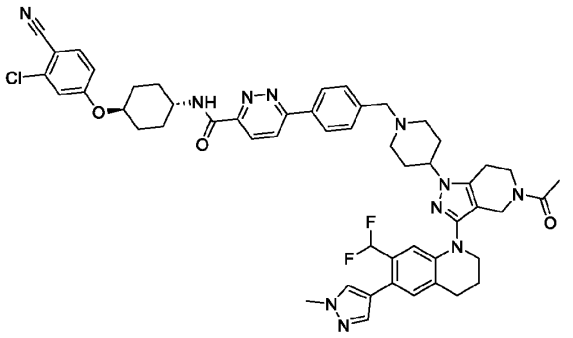
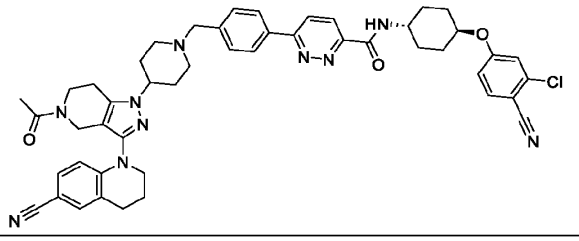
Compound	Structure
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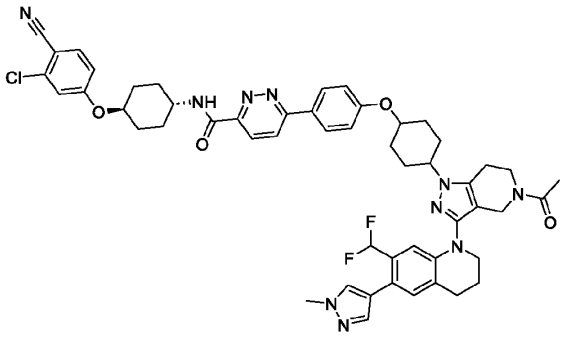
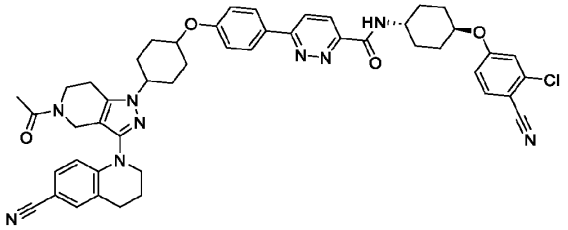
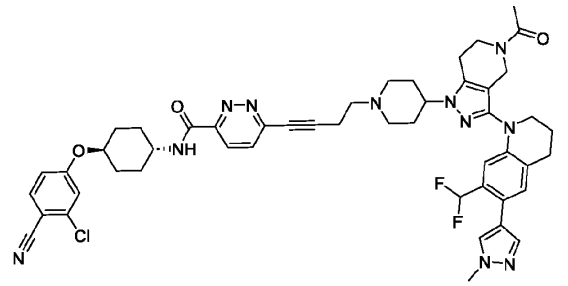
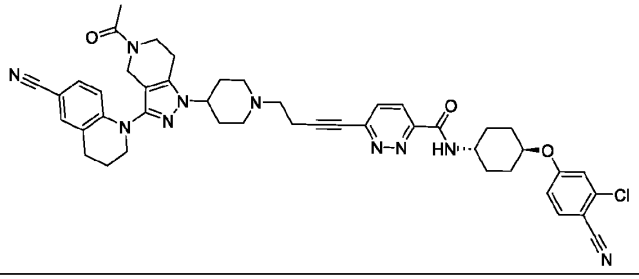
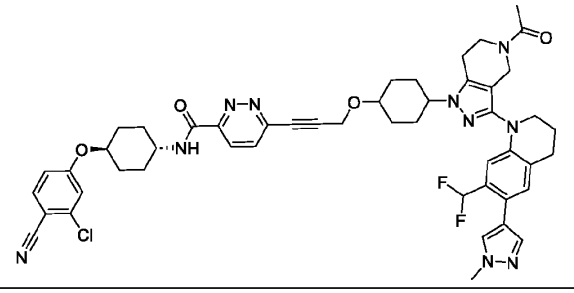
Compound	Structure
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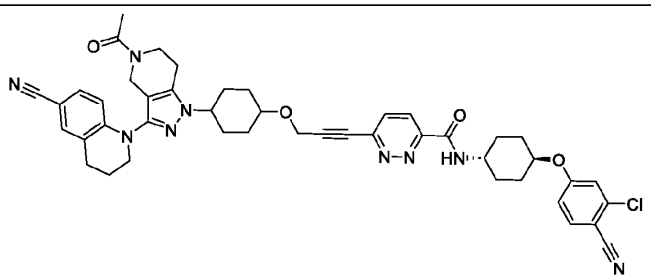
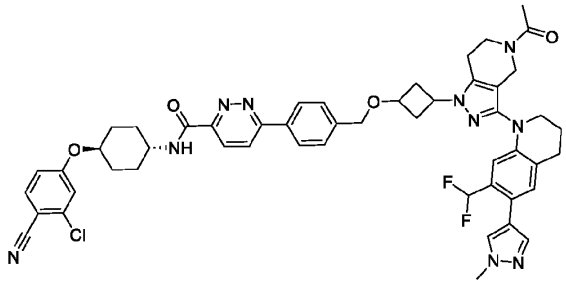
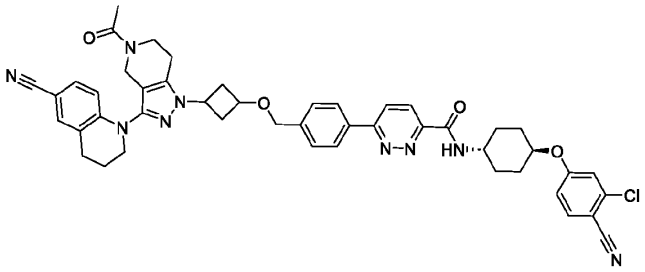
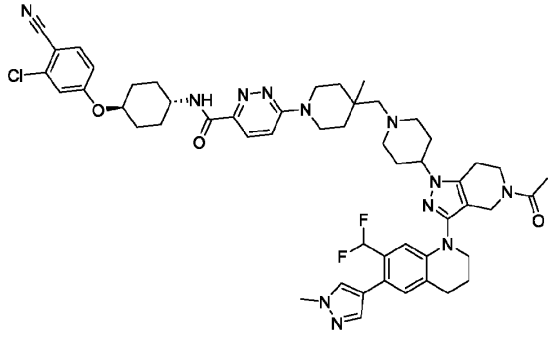
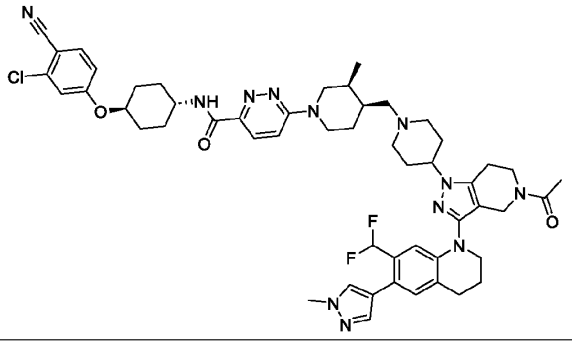
Compound	Structure
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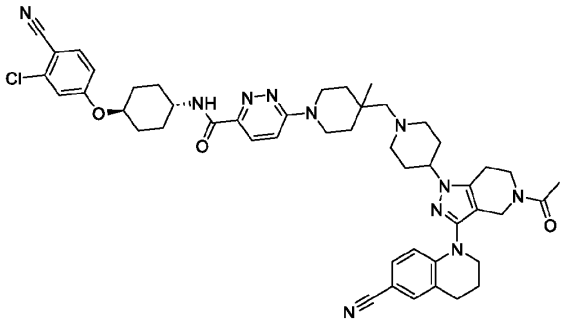
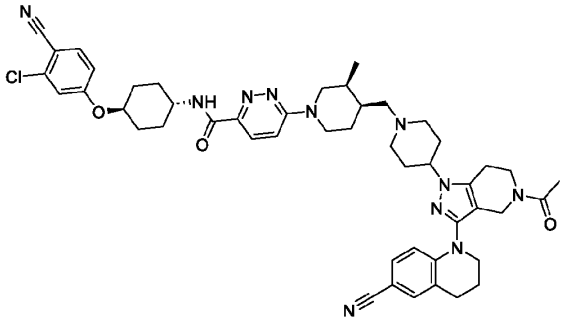
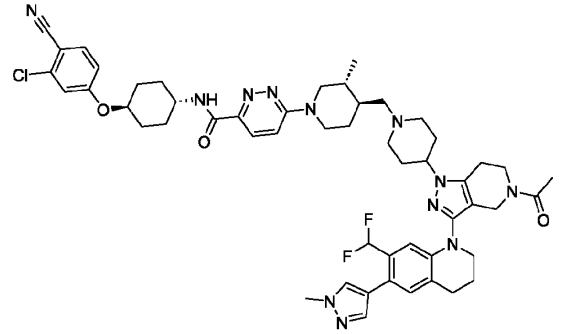
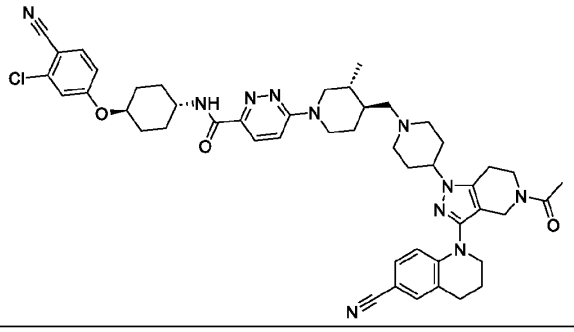
Compound	Structure
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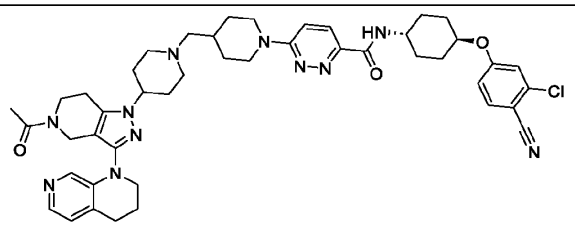
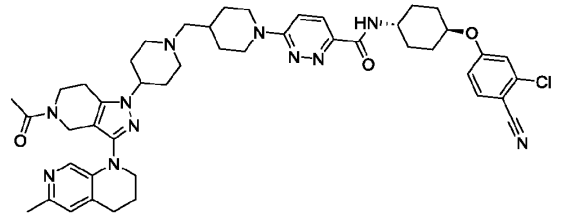
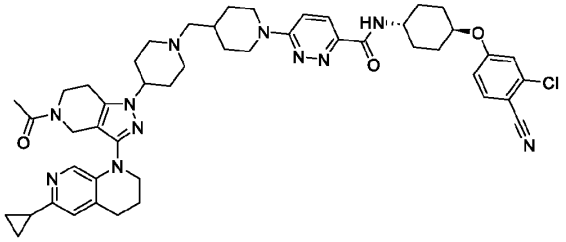
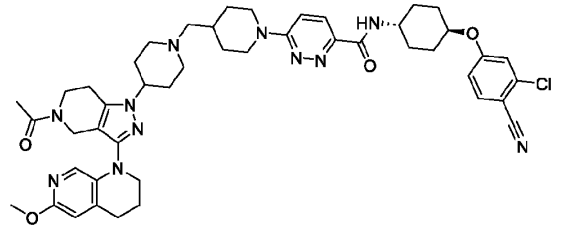
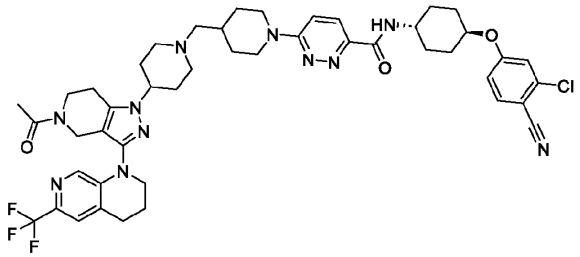
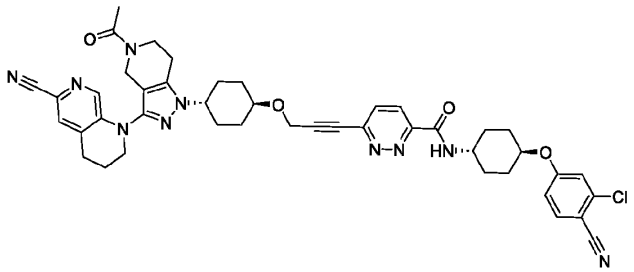
Compound	Structure
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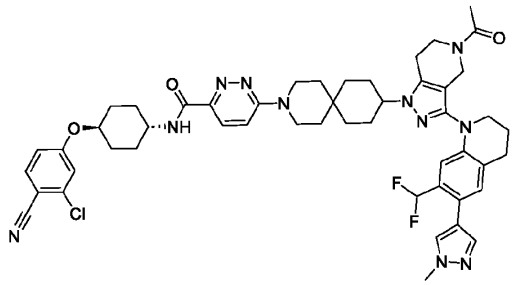
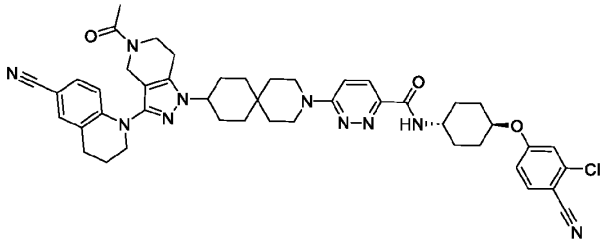
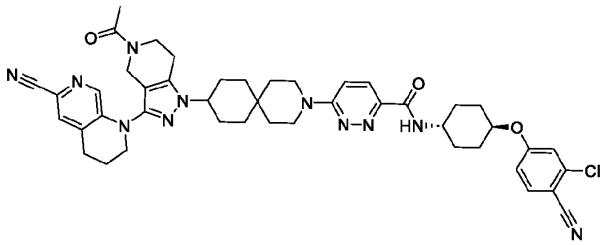
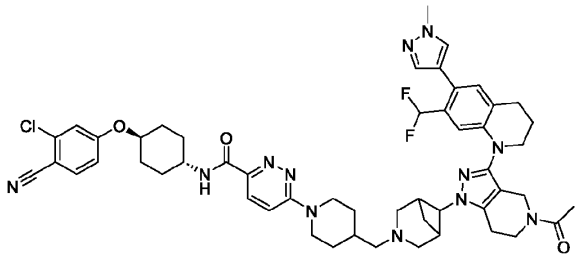
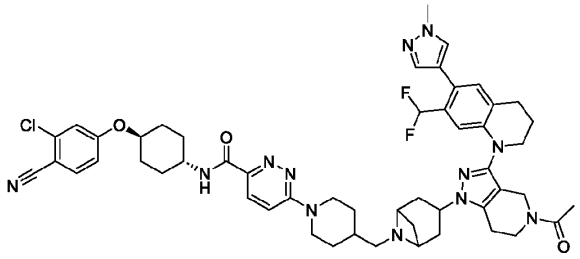
Compound	Structure
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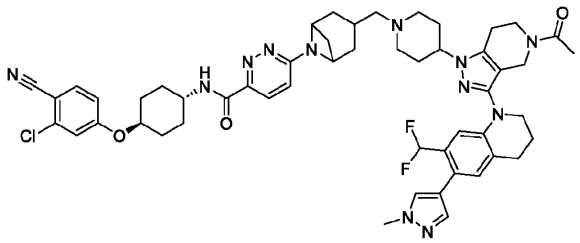
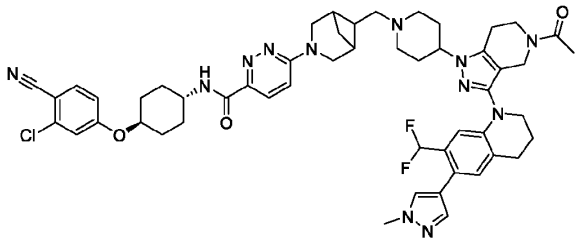
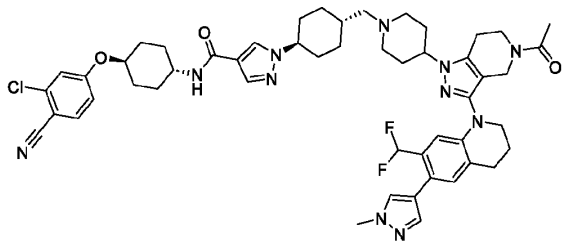
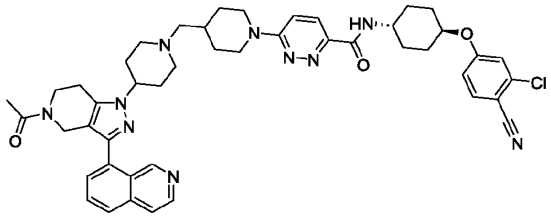
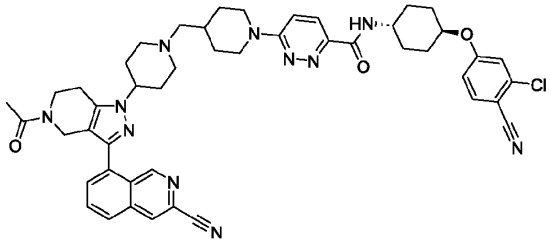
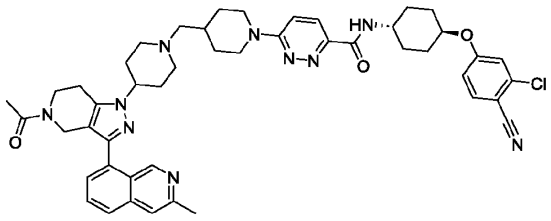
Compound	Structure
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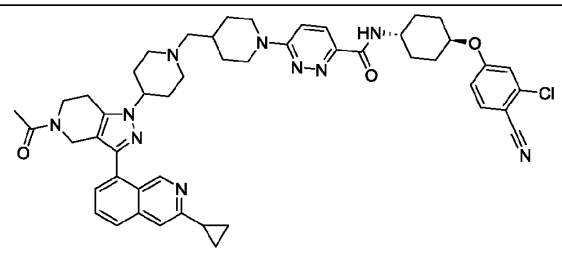
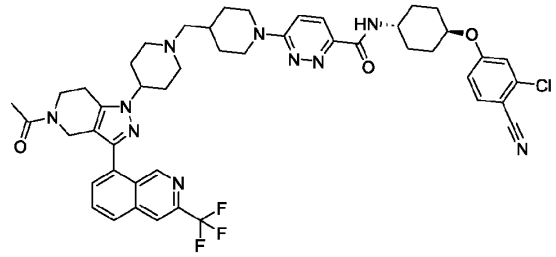
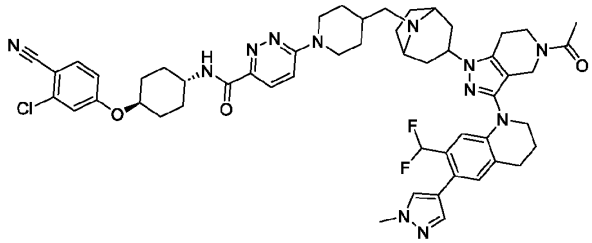
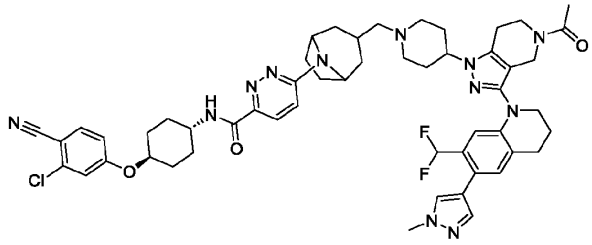
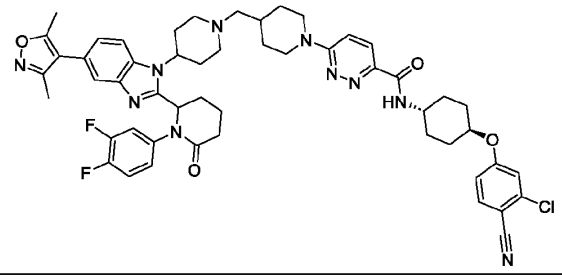
Compound	Structure
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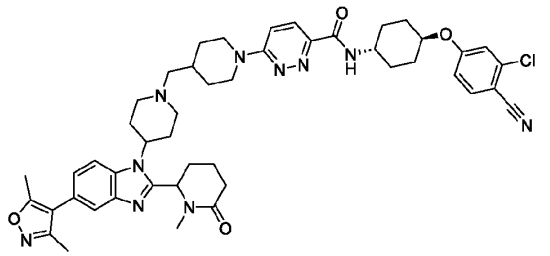
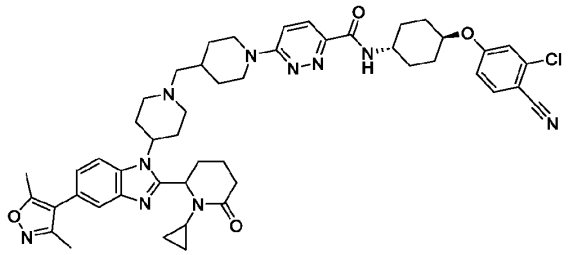
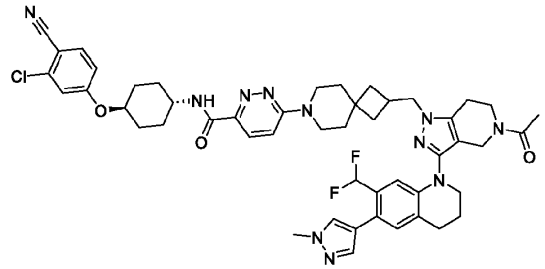
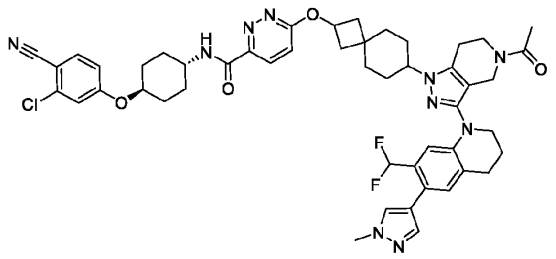
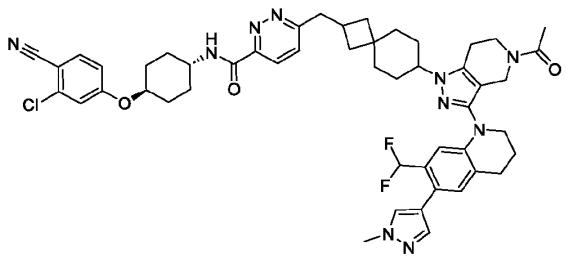
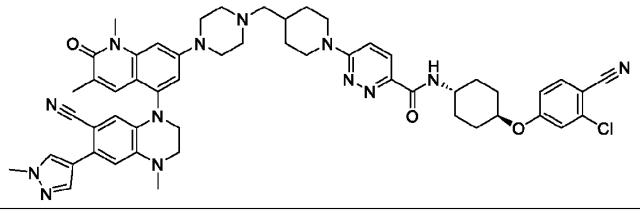
Compound	Structure
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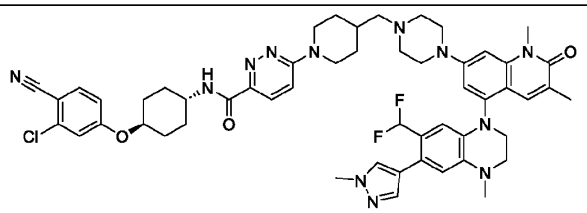
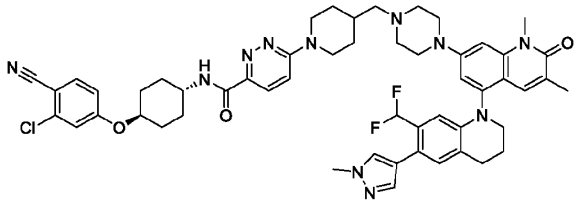
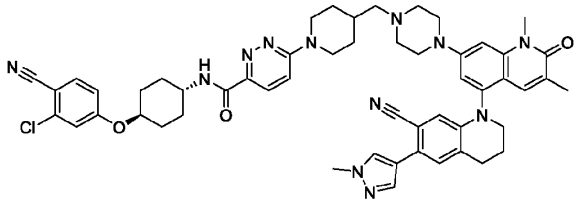
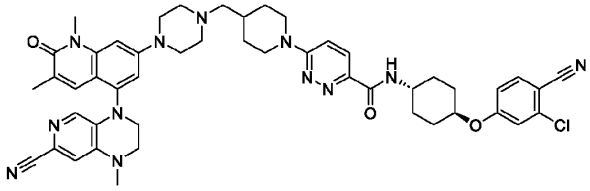
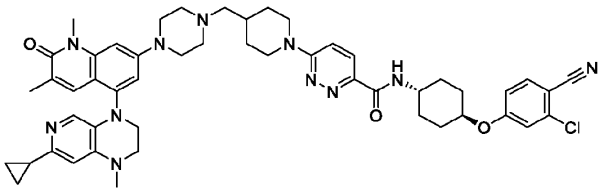
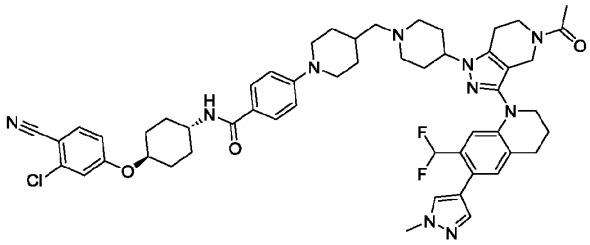
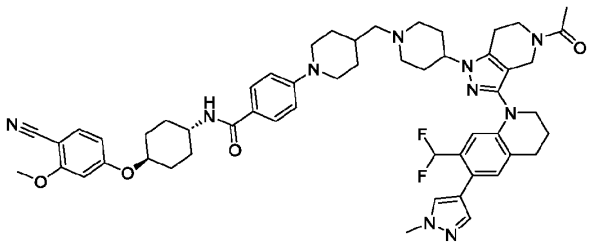
Compound	Structure
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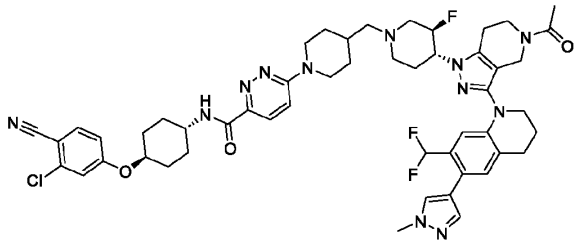
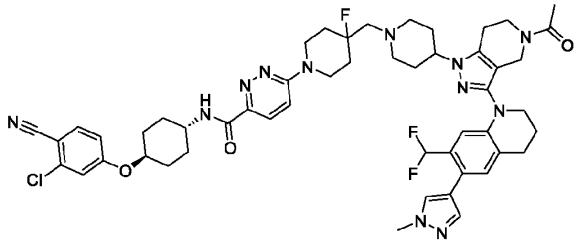
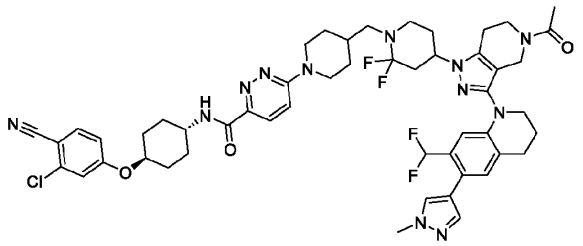
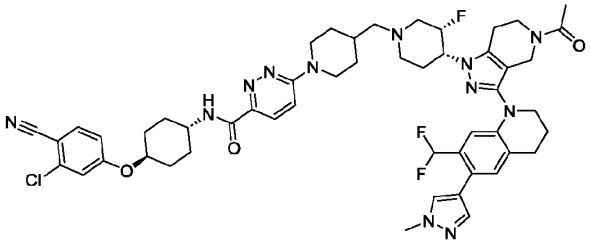
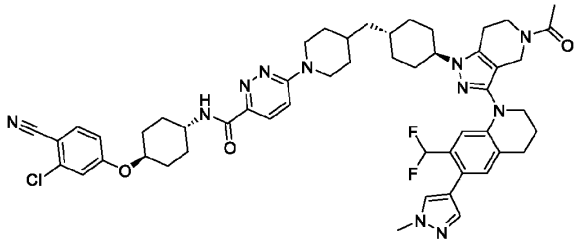
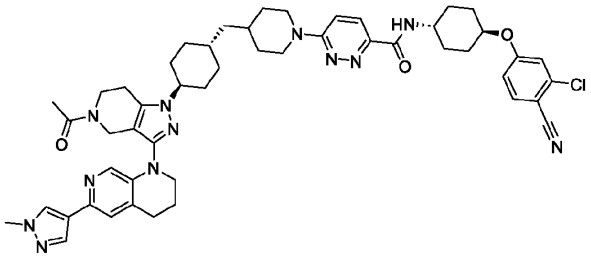
Compound	Structure
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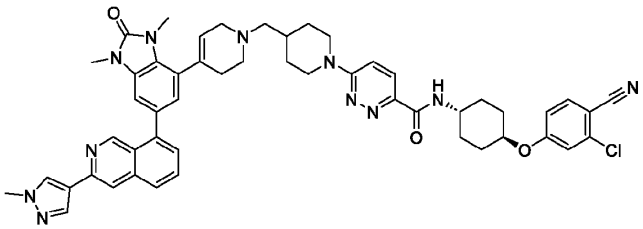
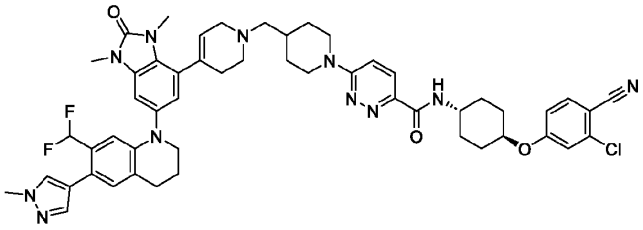
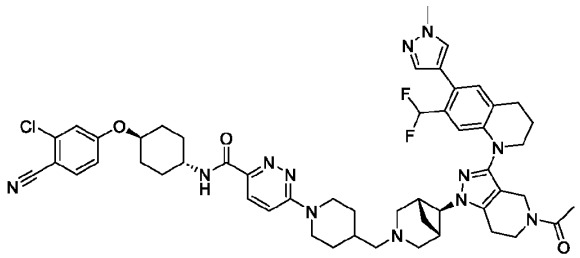
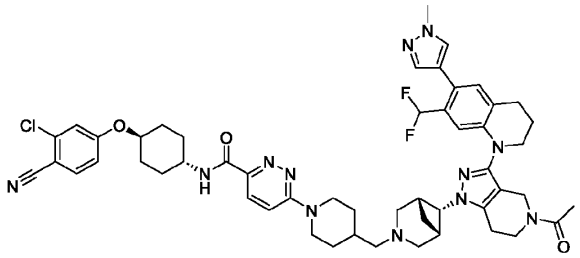
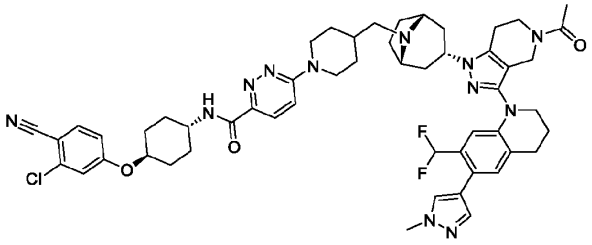
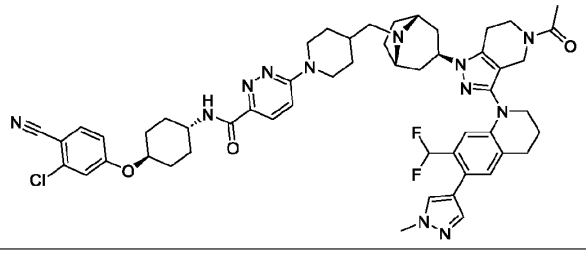
Compound	Structure
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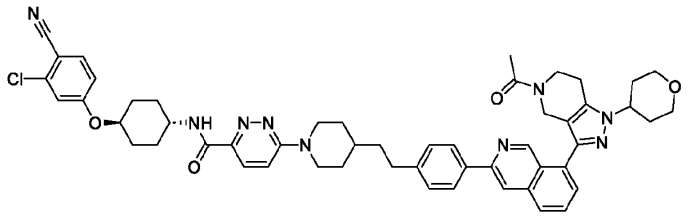
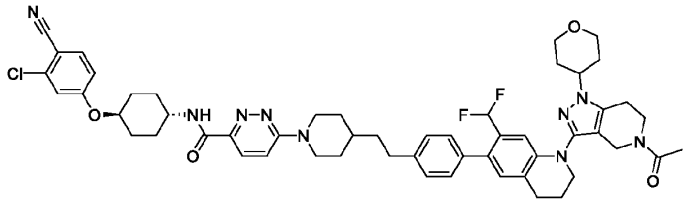
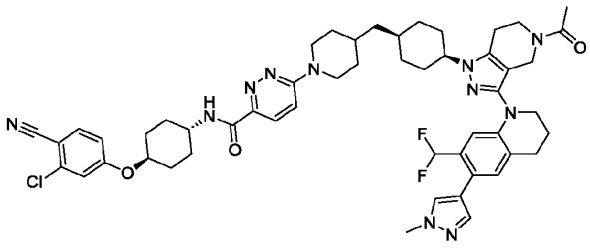
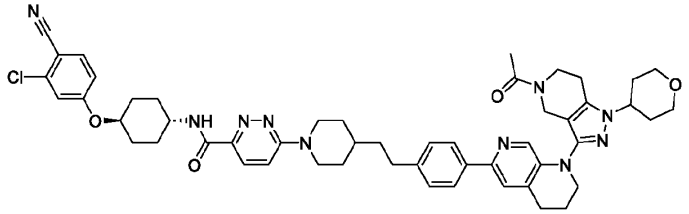
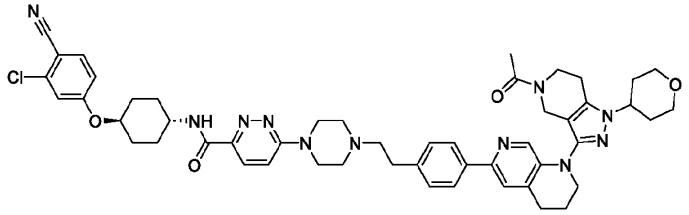
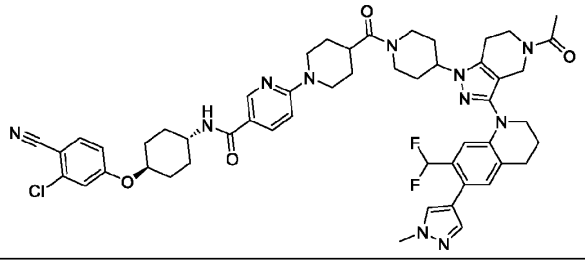
Compound	Structure
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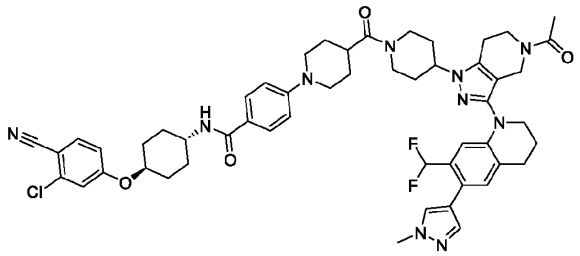
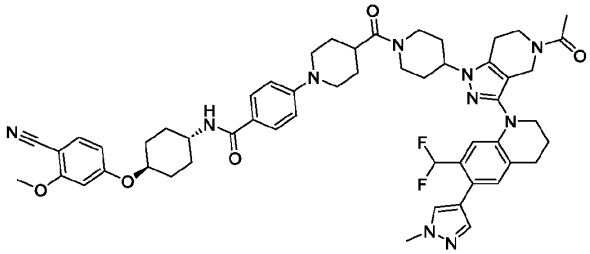
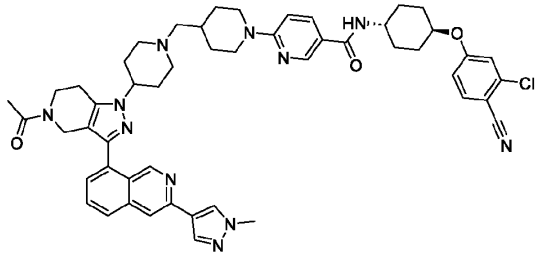
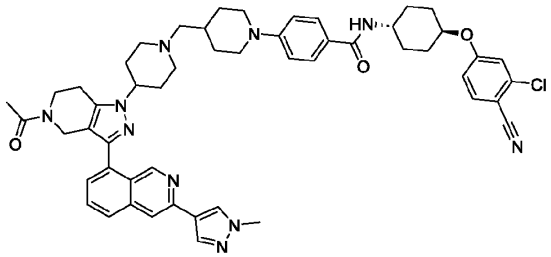
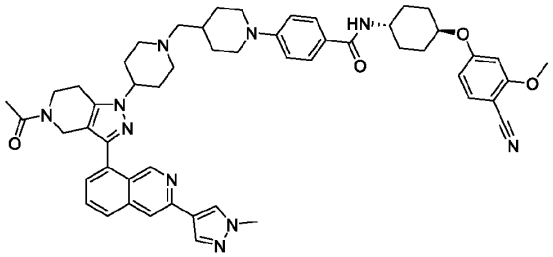
Compound	Structure
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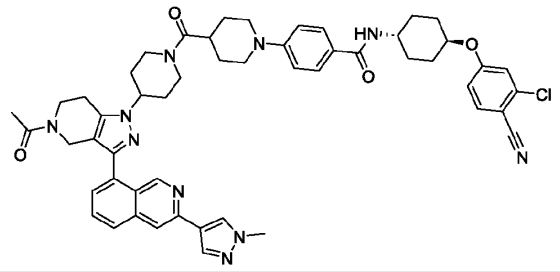
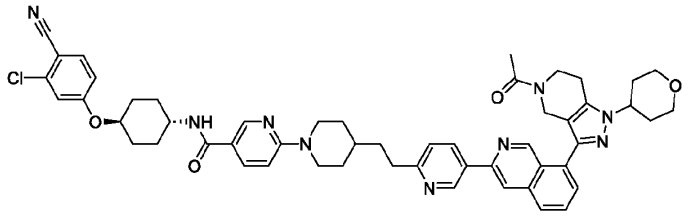
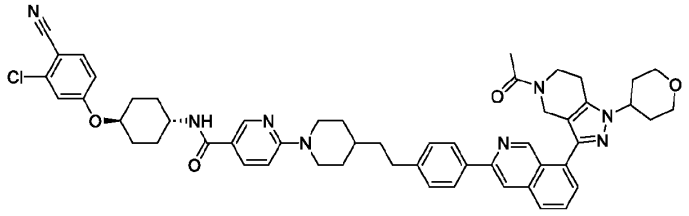
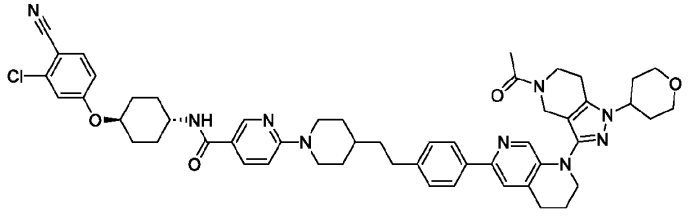
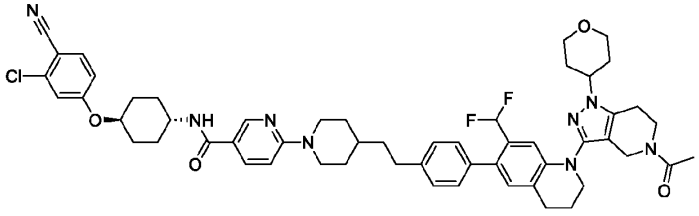
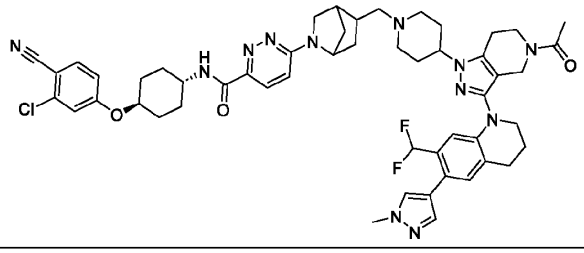
Compound	Structure
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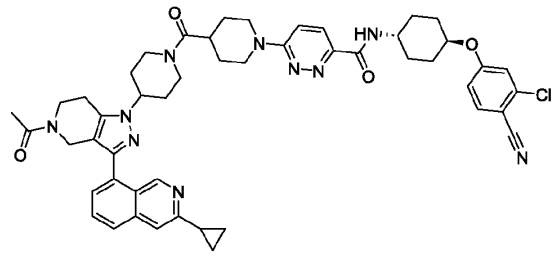
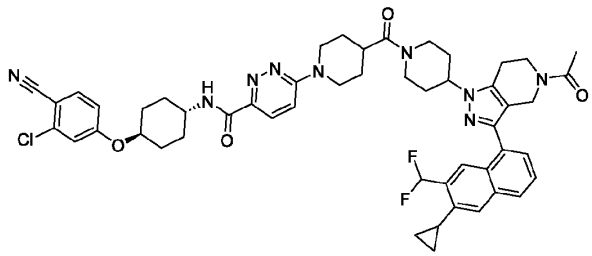
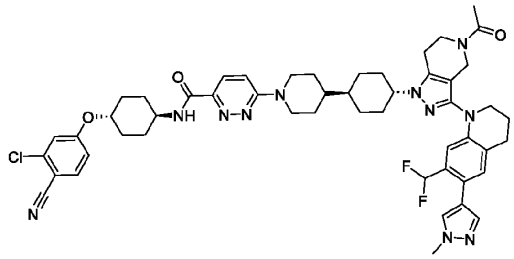
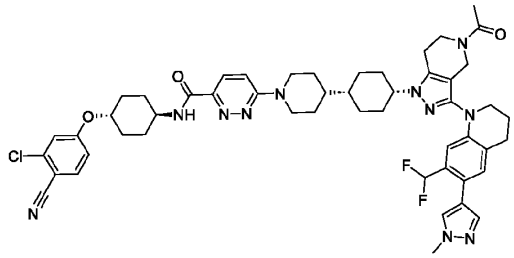
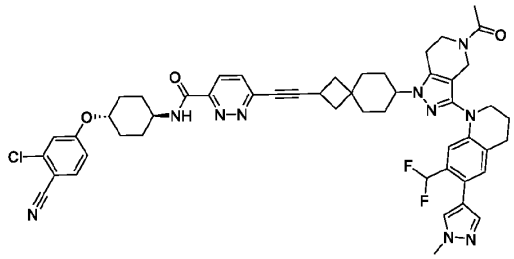
Compound	Structure
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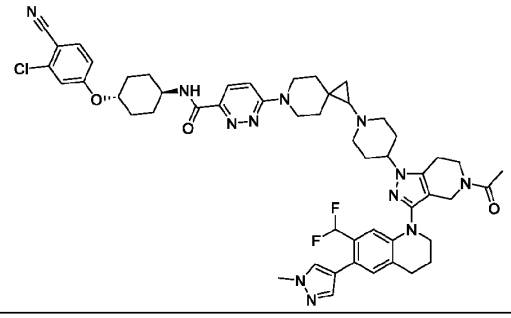
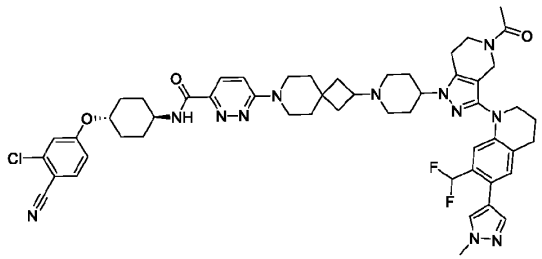
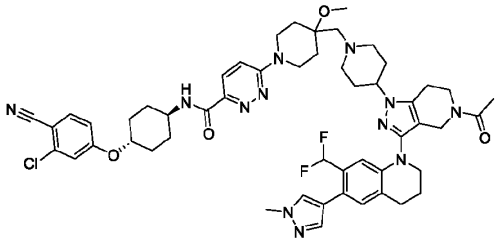
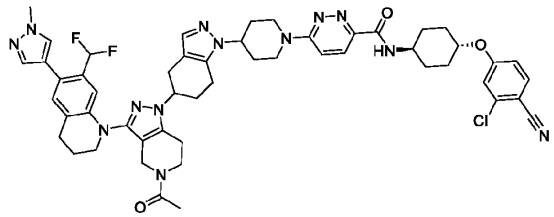
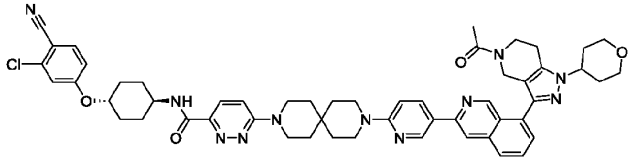
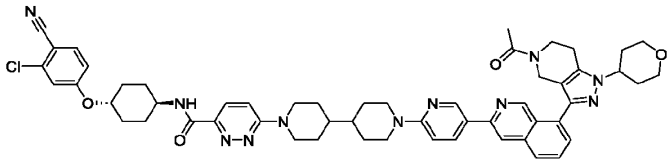
Compound	Structure
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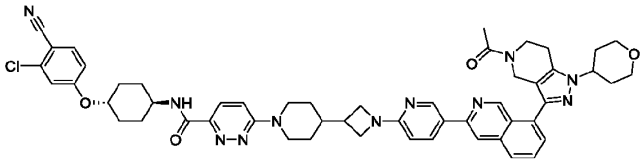
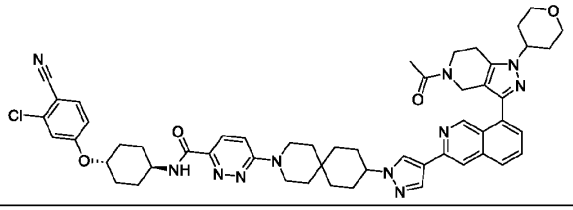
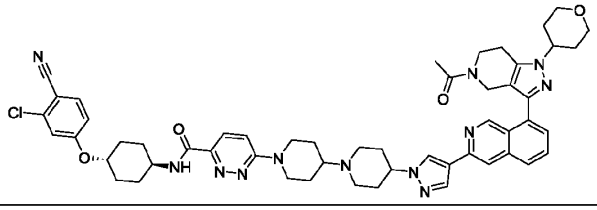
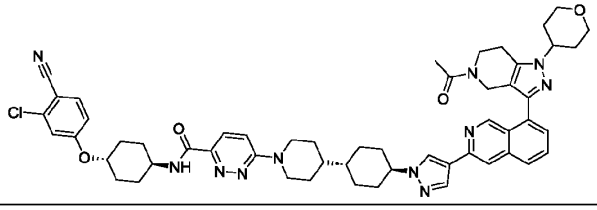
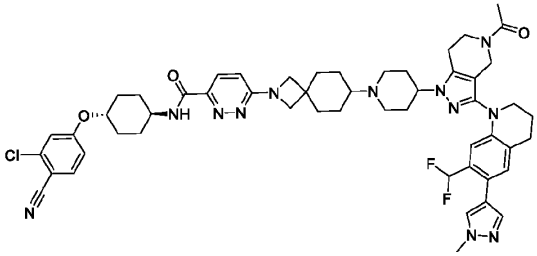
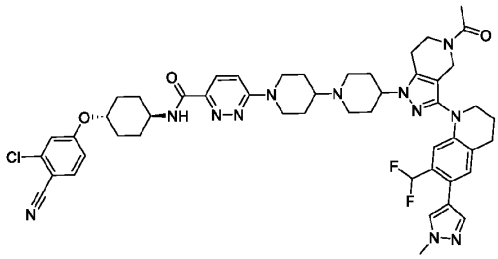
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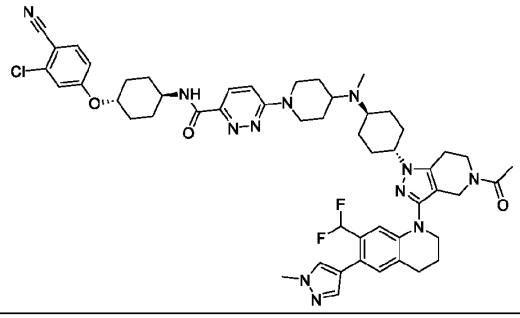
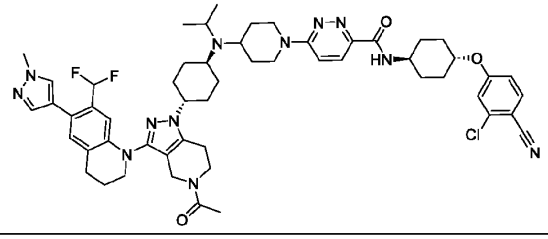
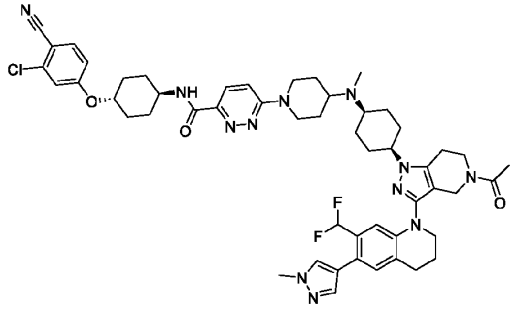
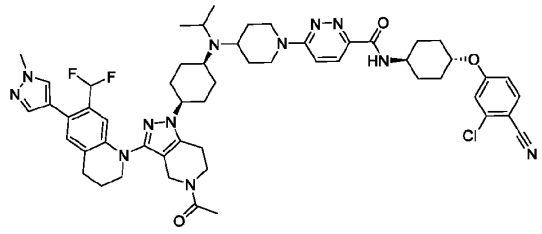
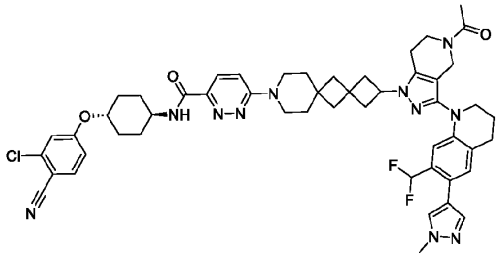
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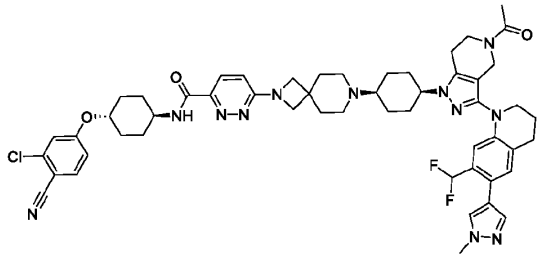
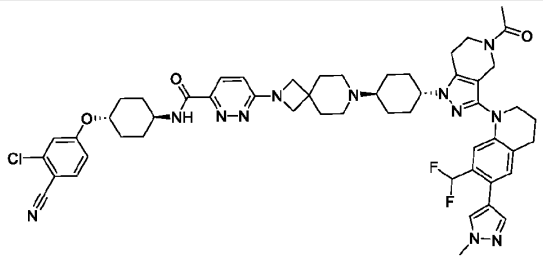
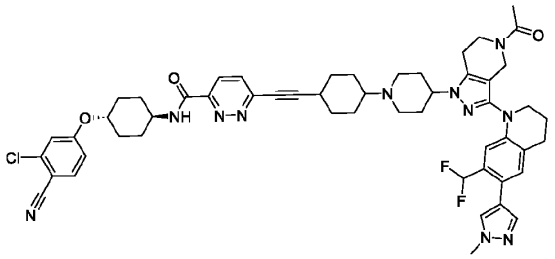
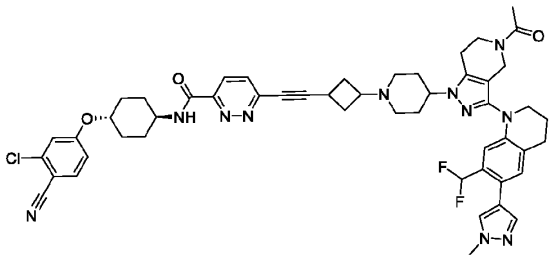
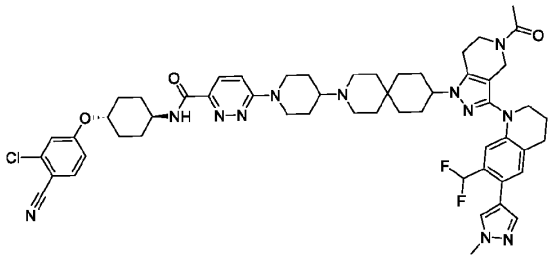
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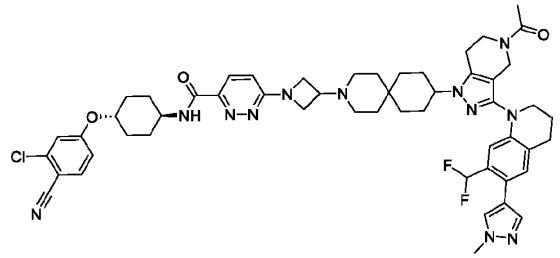
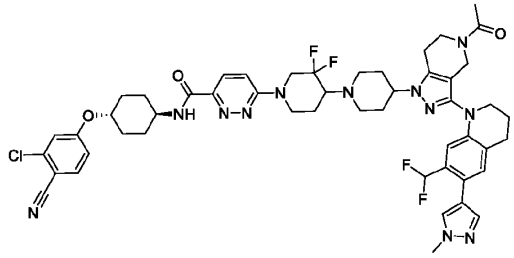
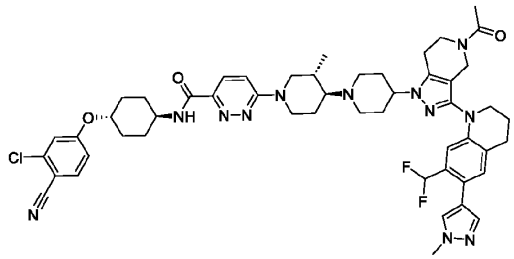
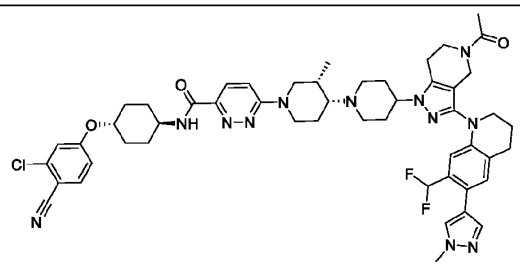
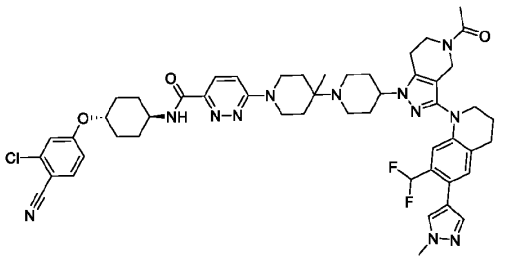
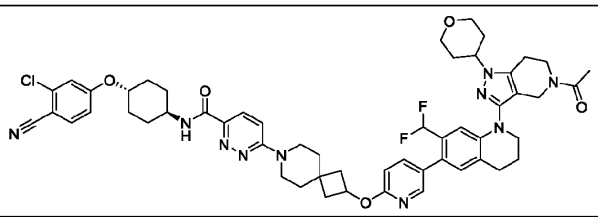
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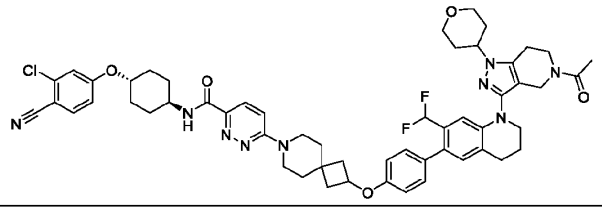
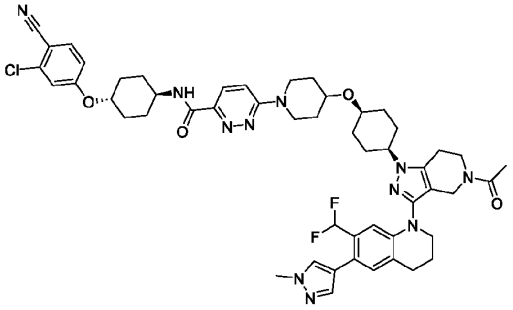
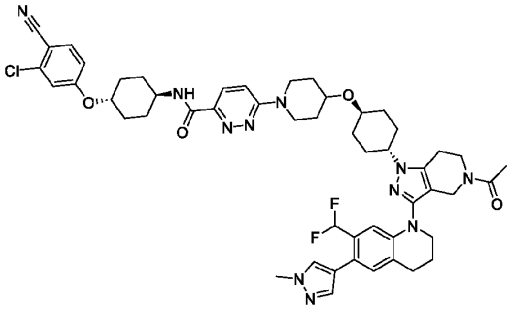
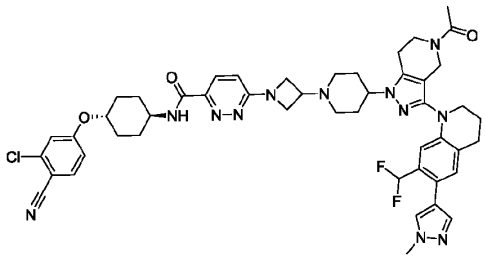
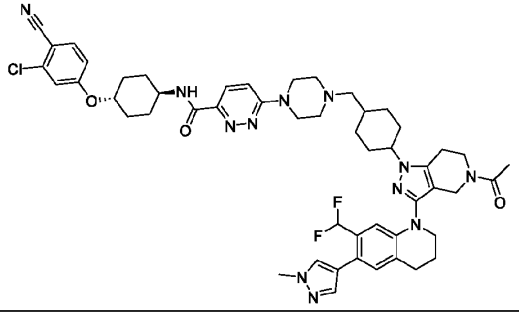
Compound	Structure
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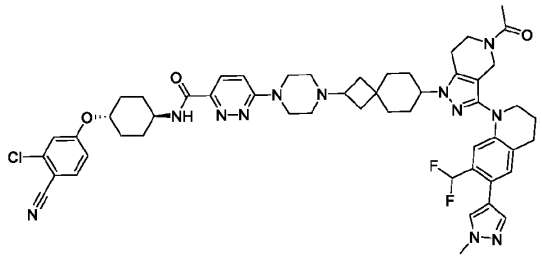
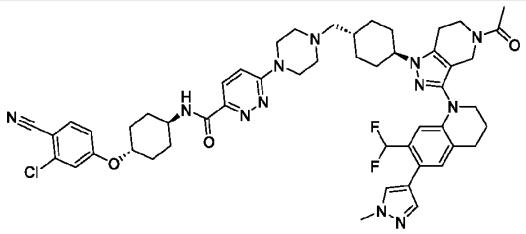
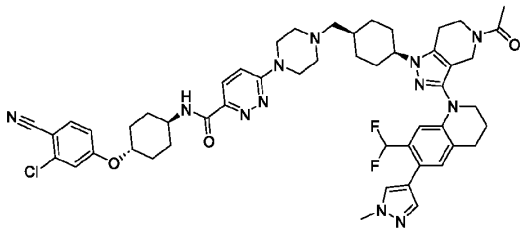
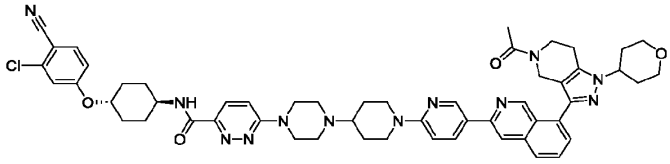
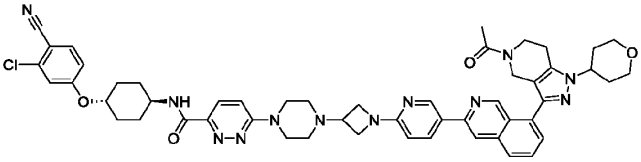
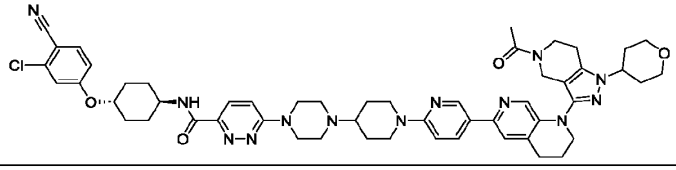
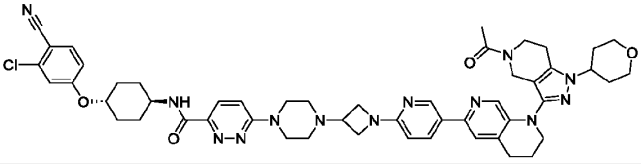
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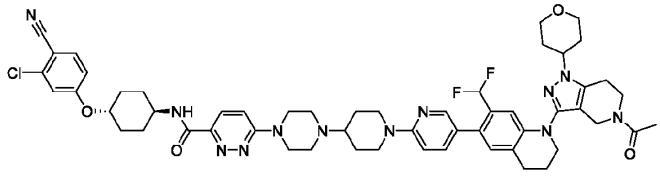
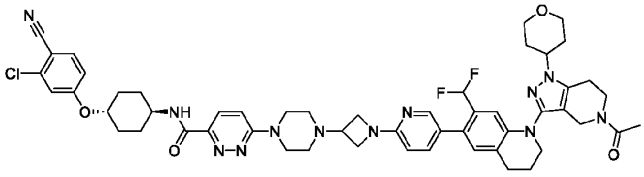
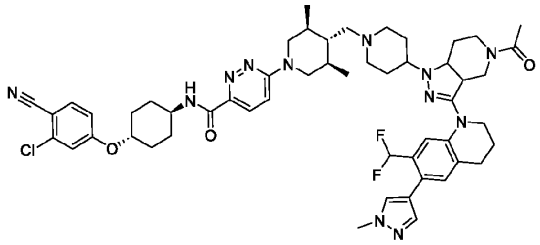
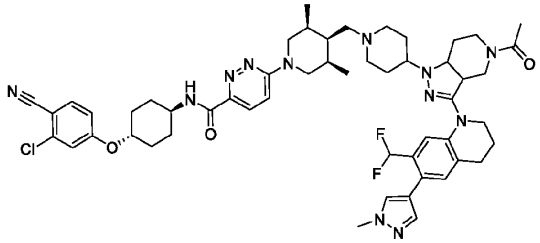
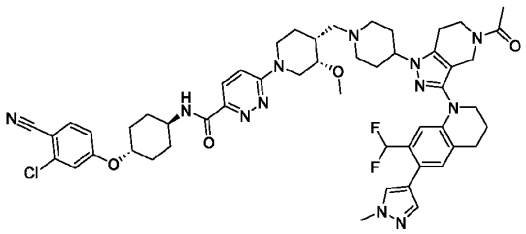
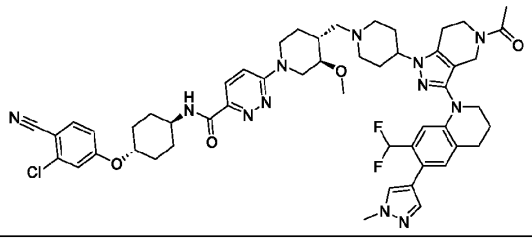
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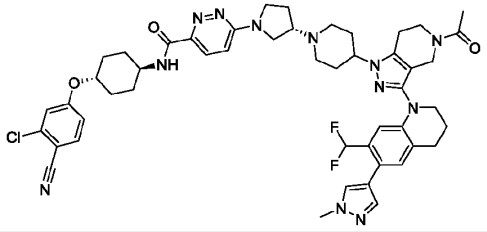
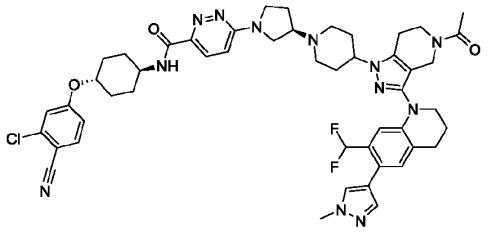
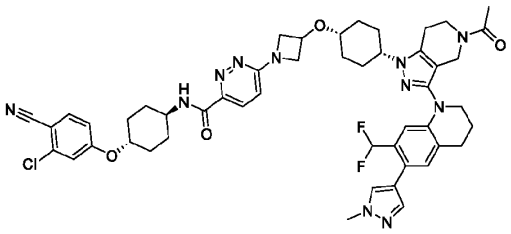
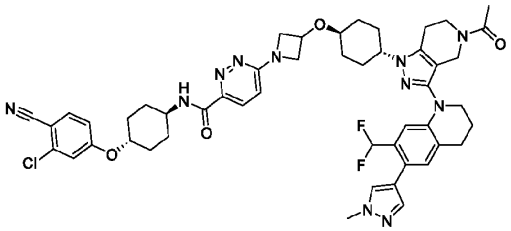
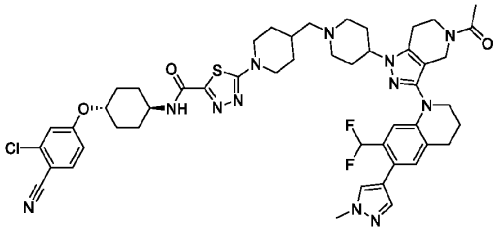
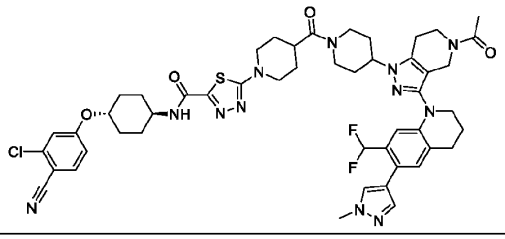
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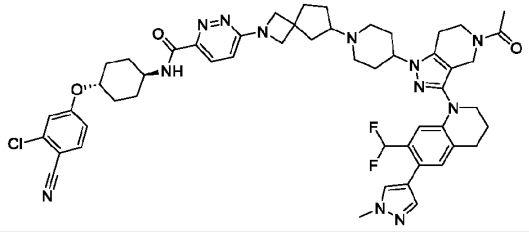
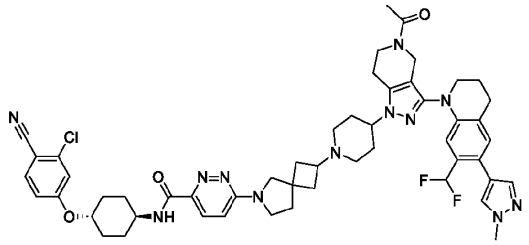
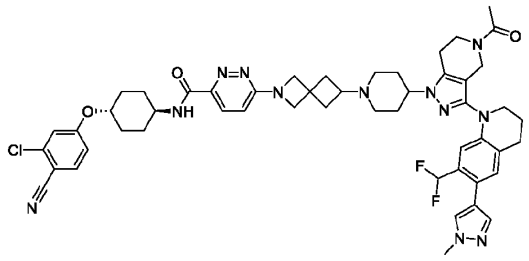
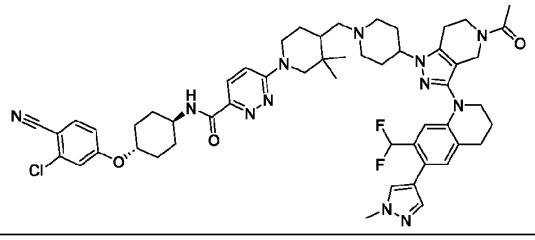
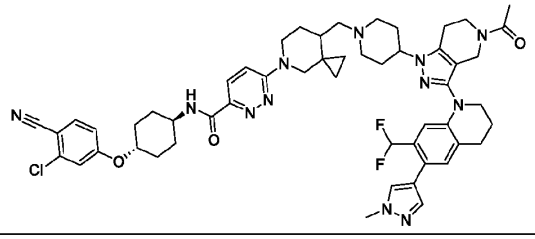
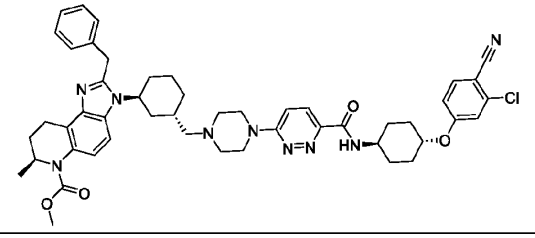
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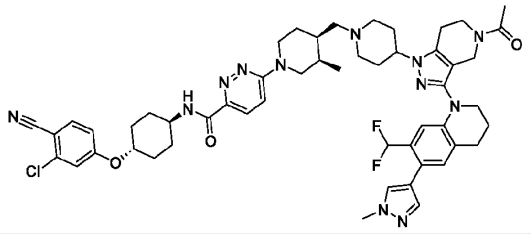
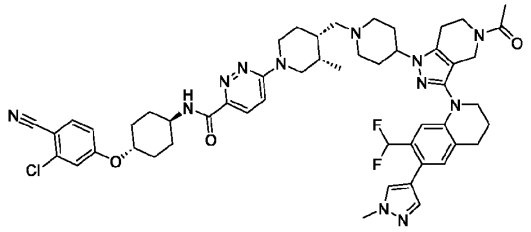
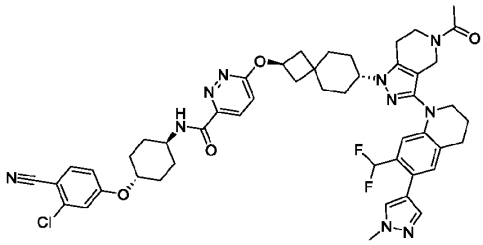
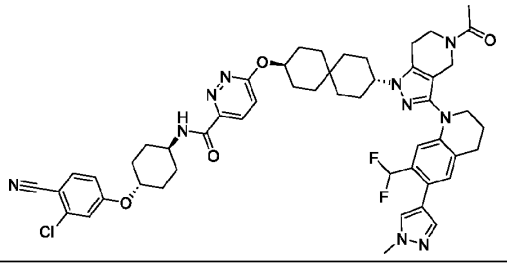
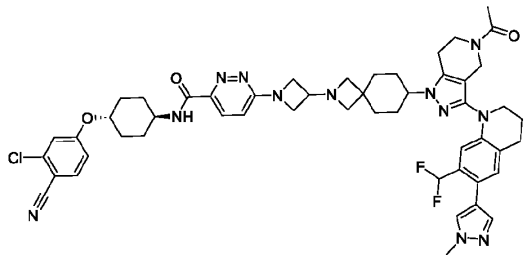
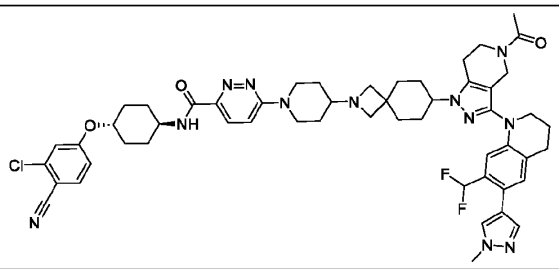
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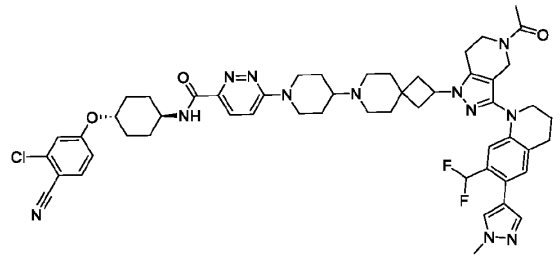
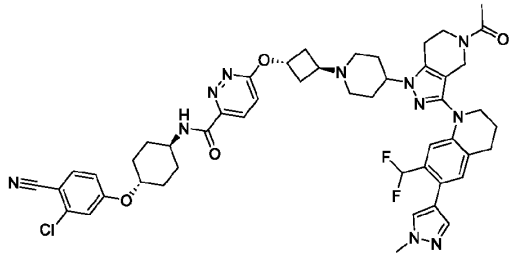
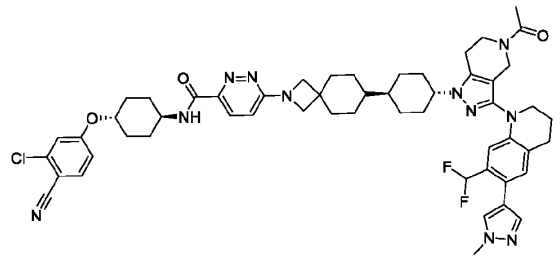
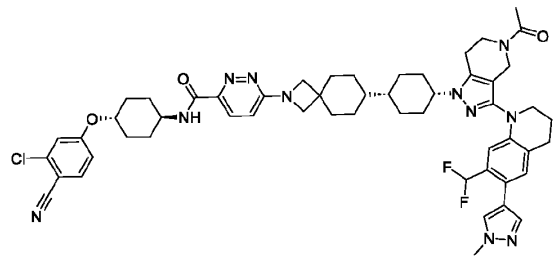
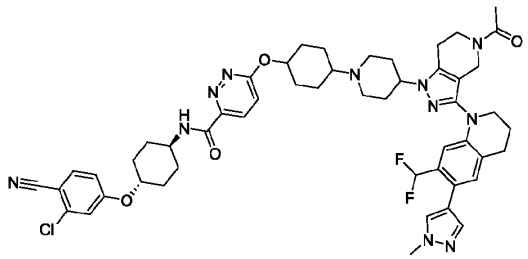
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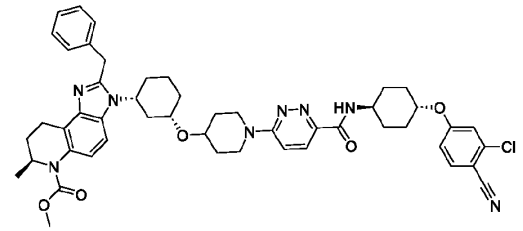
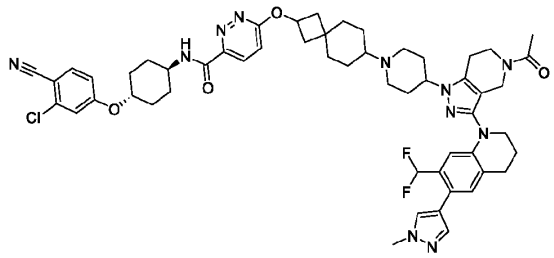
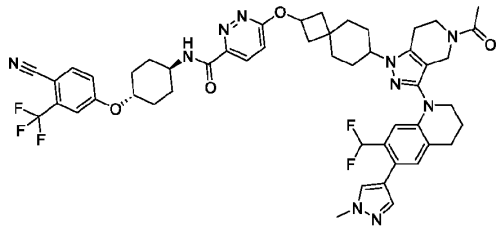
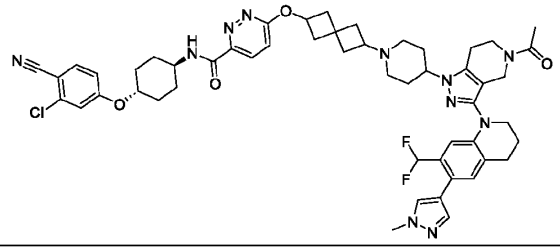
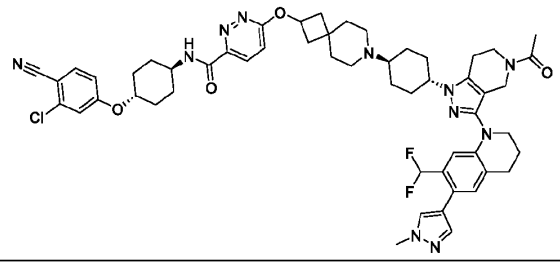
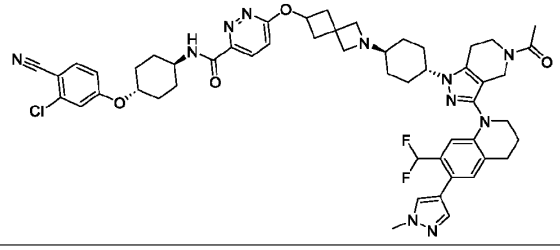
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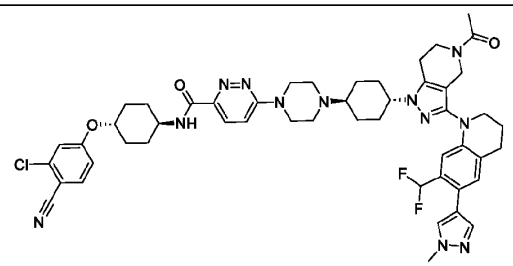
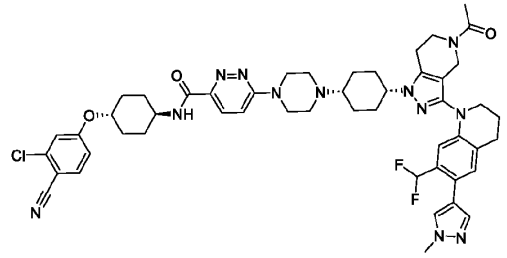
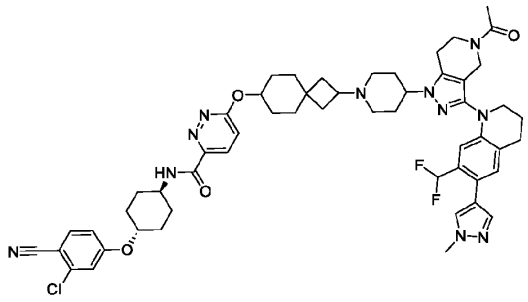
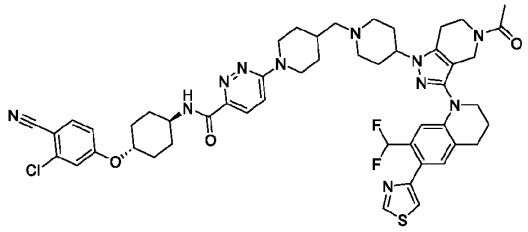
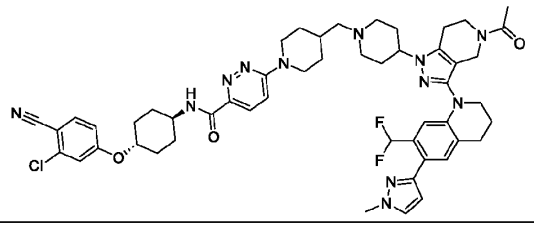
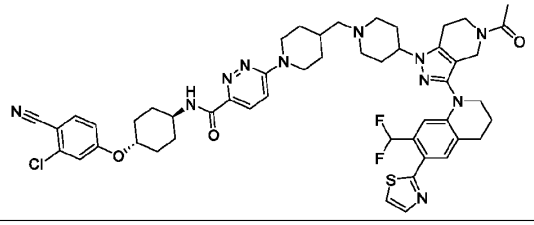
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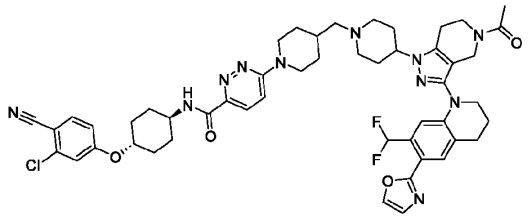
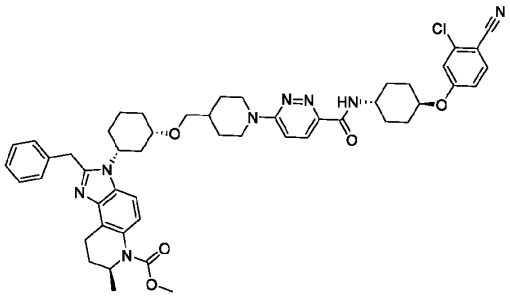
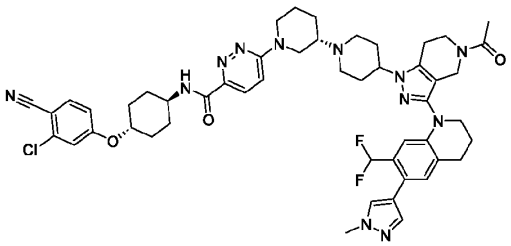
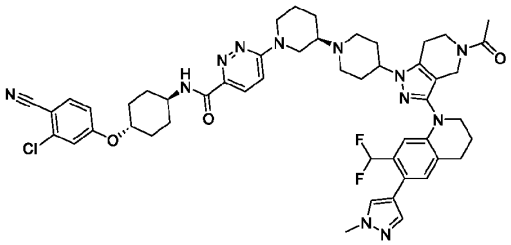
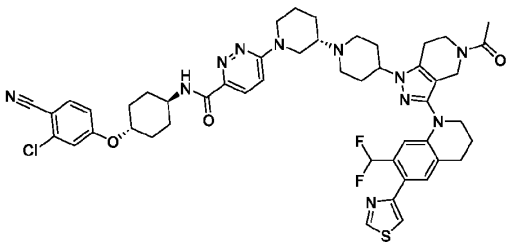
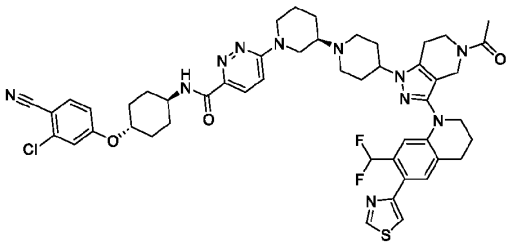
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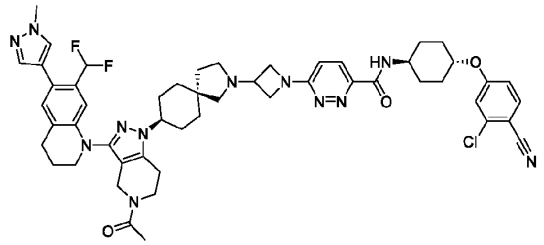
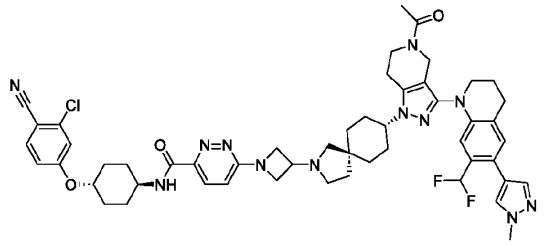
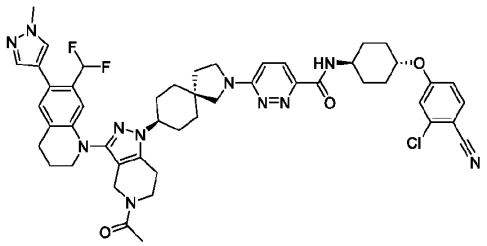
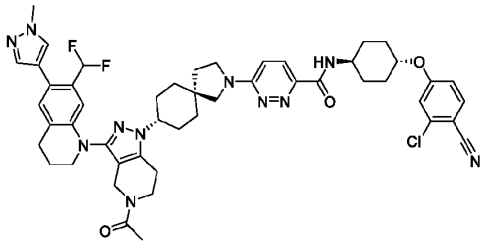
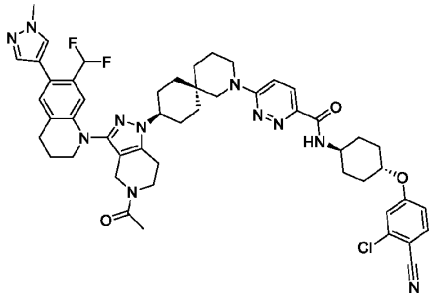
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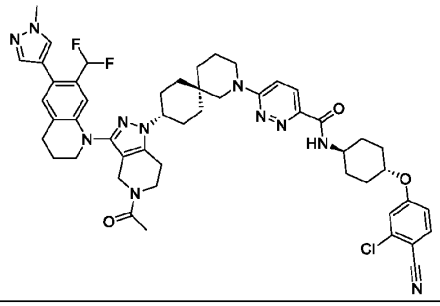
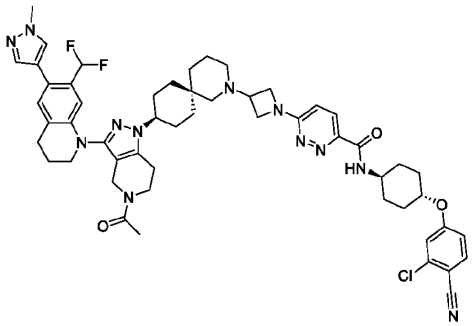
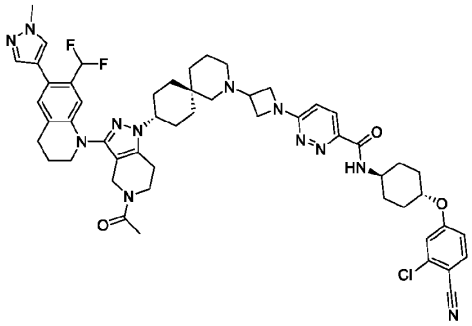
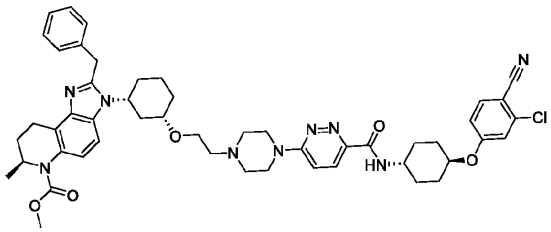
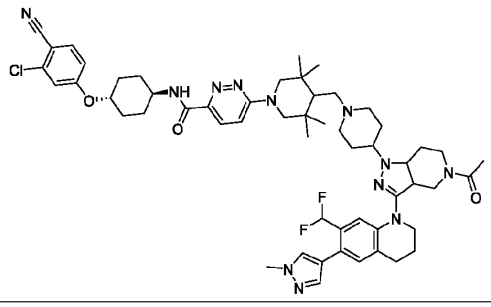
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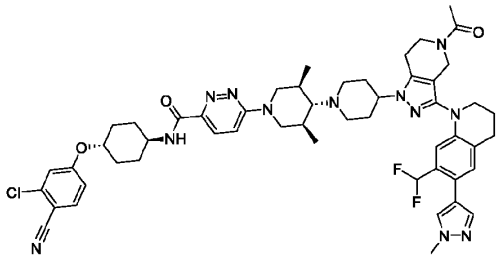
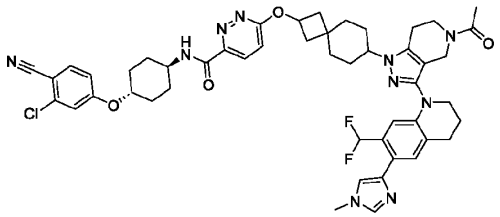
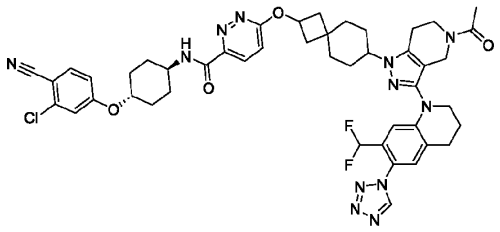
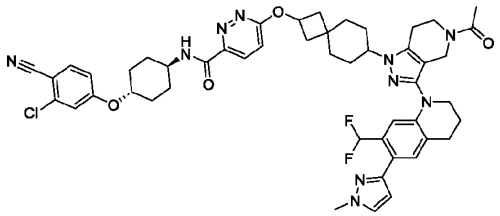
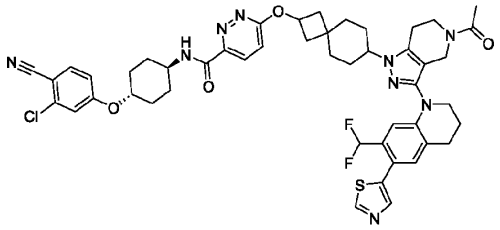
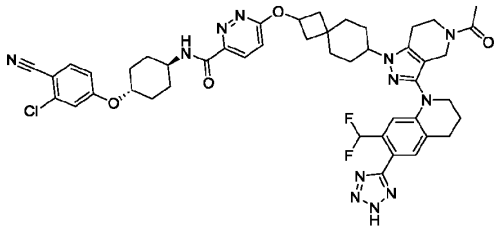
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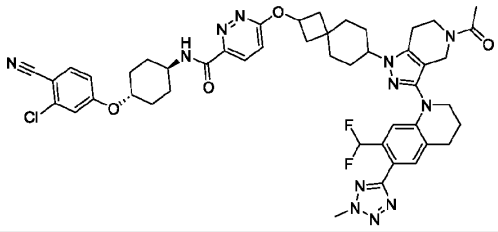
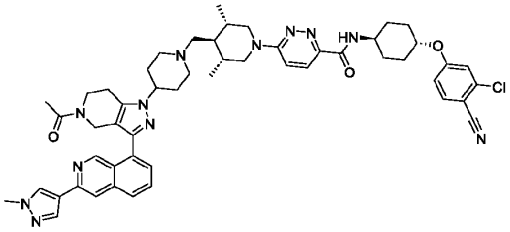
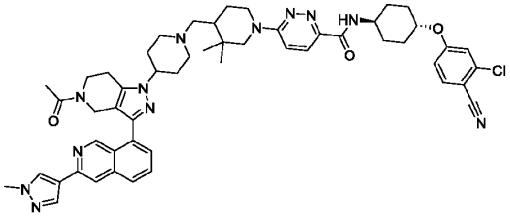
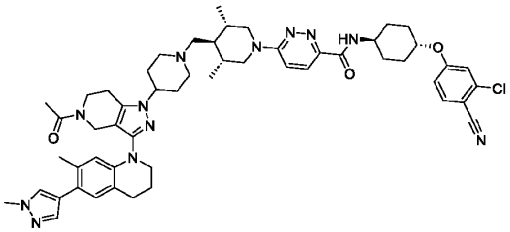
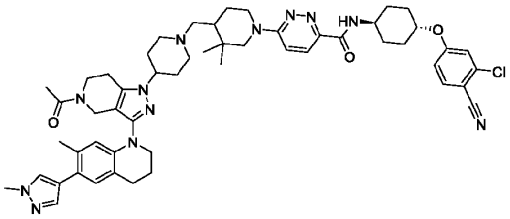
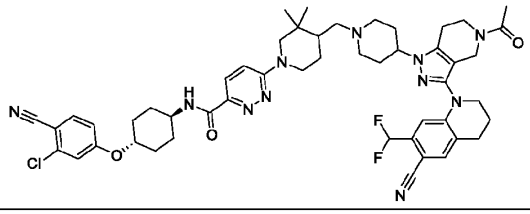
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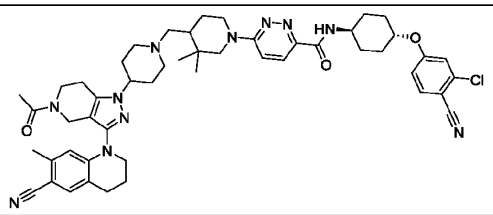
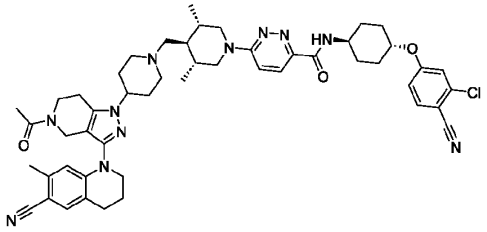
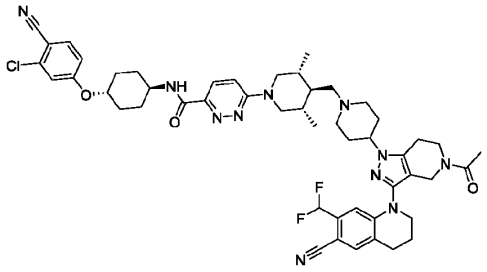
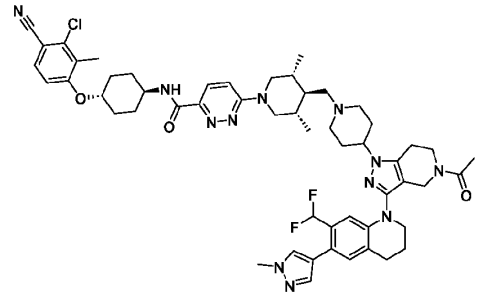
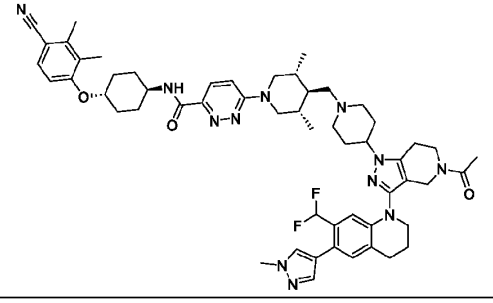
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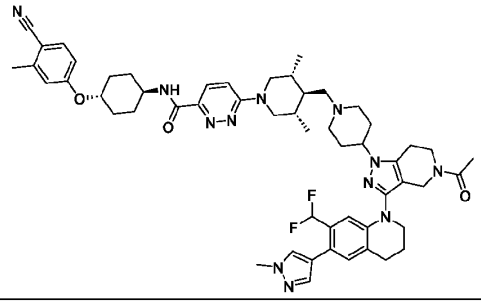
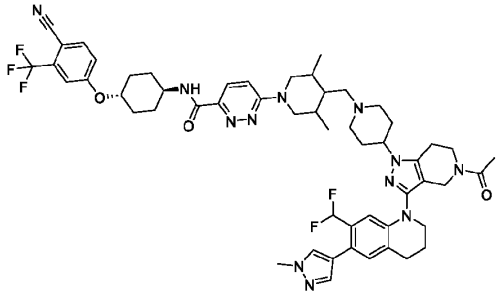
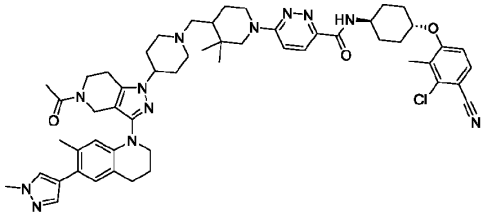
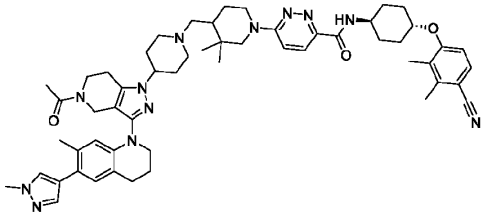
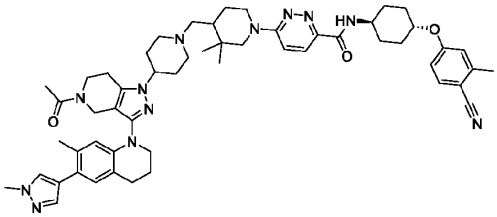
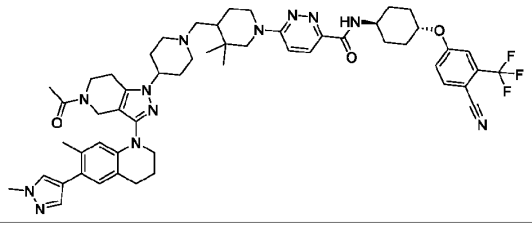
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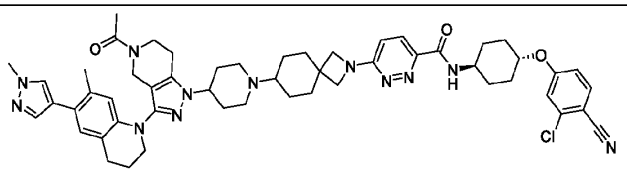
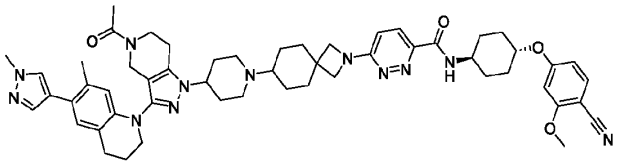
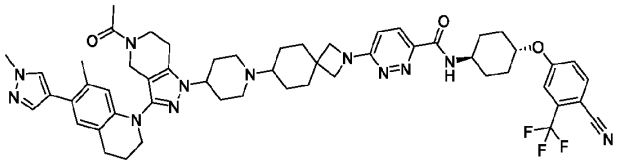
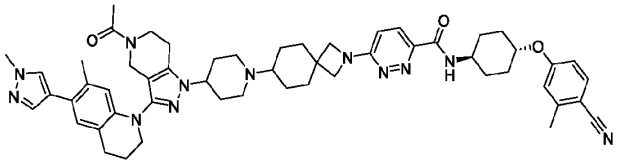
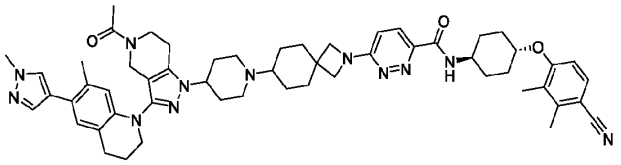
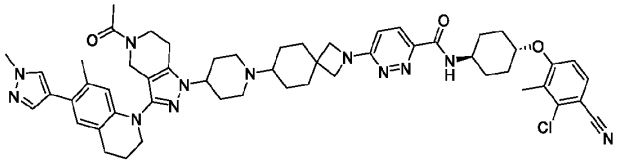
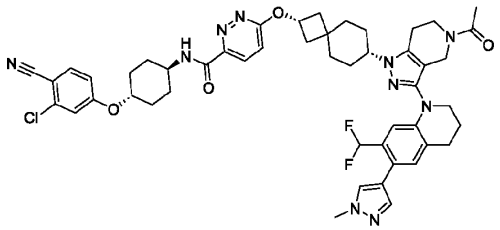
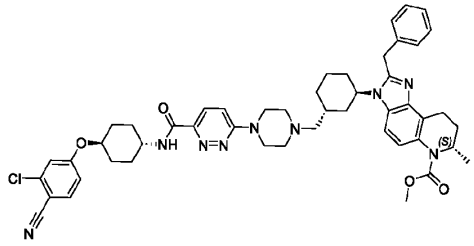
Compound	Structure
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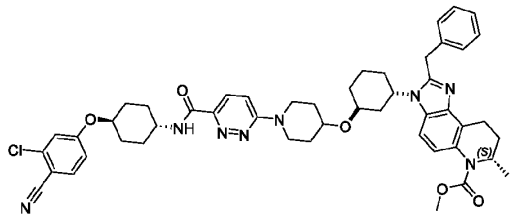
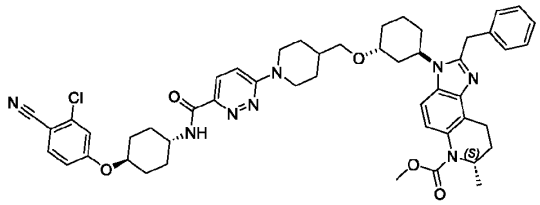
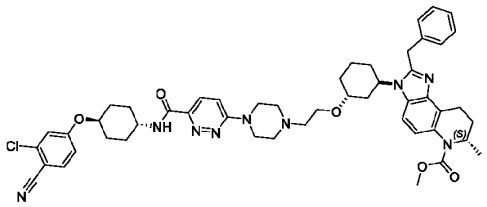
Compound	Structure
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Compound	Structure
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Compound	Structure
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Compound	Structure
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Compound	Structure
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Compound	Structure
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Further Forms of Compounds

[00316] In one aspect, compounds described herein are in the form of pharmaceutically acceptable salts. As well, active metabolites of these compounds having the same type of activity are included in the scope of the present disclosure. In addition, the compounds described herein can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. The solvated forms of the compounds presented herein are also considered to be disclosed herein.

[00317] "Pharmaceutically acceptable," as used herein, refers a material, such as a carrier or diluent, which does not abrogate the biological activity or properties of the compound, and is relatively nontoxic, i.e., the material is administered to an individual without causing undesirable biological effects or interacting in a deleterious manner with any of the components of the composition in which it is contained.

[00318] The term "pharmaceutically acceptable salt" refers to a form of a therapeutically active agent that consists of a cationic form of the therapeutically active agent in combination with a suitable anion, or in alternative embodiments, an anionic form of the therapeutically active agent in combination with a suitable cation. Handbook of Pharmaceutical Salts: Properties, Selection and Use. International Union of Pure and Applied Chemistry, Wiley-VCH 2002. S.M. Berge, L.D. Bighley, D.C. Monkhouse, J. Pharm. Sci. 1977, 66, 1-19. P. H. Stahl and C. G. Wermuth, editors, *Handbook of Pharmaceutical Salts: Properties, Selection and Use*, Weinheim/Zürich:Wiley-VCH/VHCA, 2002. Pharmaceutical salts typically are more soluble and more rapidly soluble in stomach and intestinal juices than non-ionic species and so are useful in solid dosage forms. Furthermore, because their solubility often is a function of pH, selective dissolution in one or another

part of the digestive tract is possible and this capability can be manipulated as one aspect of delayed and sustained release behaviors. Also, because the salt-forming molecule can be in equilibrium with a neutral form, passage through biological membranes can be adjusted.

[00319] In some embodiments, pharmaceutically acceptable salts are obtained by reacting a compound disclosed herein with an acid. In some embodiments, the compound disclosed herein (i.e. free base form) is basic and is reacted with an organic acid or an inorganic acid. Inorganic acids include, but are not limited to, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid, and metaphosphoric acid. Organic acids include, but are not limited to, 1-hydroxy-2-naphthoic acid; 2,2-dichloroacetic acid; 2-hydroxyethanesulfonic acid; 2-oxoglutaric acid; 4-acetamidobenzoic acid; 4-aminosalicylic acid; acetic acid; adipic acid; ascorbic acid (L); aspartic acid (L); benzenesulfonic acid; benzoic acid; camphoric acid (+); camphor-10-sulfonic acid (+); capric acid (decanoic acid); caproic acid (hexanoic acid); caprylic acid (octanoic acid); carbonic acid; cinnamic acid; citric acid; cyclamic acid; dodecylsulfuric acid; ethane-1,2-disulfonic acid; ethanesulfonic acid; formic acid; fumaric acid; galactaric acid; gentisic acid; glucoheptonic acid (D); gluconic acid (D); glucuronic acid (D); glutamic acid; glutaric acid; glycerophosphoric acid; glycolic acid; hippuric acid; isobutyric acid; lactic acid (DL); lactobionic acid; lauric acid; maleic acid; malic acid (- L); malonic acid; mandelic acid (DL); methanesulfonic acid; naphthalene-1,5-disulfonic acid; naphthalene-2-sulfonic acid; nicotinic acid; oleic acid; oxalic acid; palmitic acid; pamoic acid; phosphoric acid; proprionic acid; pyroglutamic acid (- L); salicylic acid; sebacic acid; stearic acid; succinic acid; sulfuric acid; tartaric acid (+ L); thiocyanic acid; toluenesulfonic acid (*p*); and undecylenic acid.

[00320] In some embodiments, pharmaceutically acceptable salts are obtained by reacting a compound disclosed herein with a base. In some embodiments, the compound disclosed herein is acidic and is reacted with a base. In such situations, an acidic proton of the compound disclosed herein is replaced by a metal ion, e.g., lithium, sodium, potassium, magnesium, calcium, or an aluminum ion. In some cases, compounds described herein coordinate with an organic base, such as, but not limited to, ethanolamine, diethanolamine, triethanolamine, tromethamine, meglumine, N-methylglucamine, dicyclohexylamine, tris(hydroxymethyl)methylamine. In other cases, compounds described herein form salts with amino acids such as, but not limited to, arginine, lysine, and the like. Acceptable inorganic bases used to form salts with compounds that include an acidic proton, include, but are not limited to, aluminum hydroxide, calcium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium hydroxide, lithium hydroxide, and the like. In some embodiments, the compounds provided herein are prepared as a sodium salt, calcium salt, potassium salt, magnesium salt, meglumine salt, N-methylglucamine salt or ammonium salt.

[00321] It should be understood that a reference to a pharmaceutically acceptable salt includes the solvent addition forms. In some embodiments, solvates contain either stoichiometric or non-stoichiometric amounts of a solvent, and are formed during the process of crystallization with pharmaceutically acceptable solvents such as water, ethanol, and the like. Hydrates are formed when the solvent is water, or alcoholates are formed when the solvent is alcohol. Solvates of compounds described herein are conveniently prepared or

formed during the processes described herein. In addition, the compounds provided herein optionally exist in unsolvated as well as solvated forms.

[00322] The methods and formulations described herein include the use of *N*-oxides (if appropriate), or pharmaceutically acceptable salts of compounds having the structure disclosed herein, as well as active metabolites of these compounds having the same type of activity.

[00323] In some embodiments, sites on the organic radicals (e.g. alkyl groups, aromatic rings) of compounds disclosed herein are susceptible to various metabolic reactions. Incorporation of appropriate substituents on the organic radicals will reduce, minimize, or eliminate this metabolic pathway. In specific embodiments, the appropriate substituent to decrease or eliminate the susceptibility of the aromatic ring to metabolic reactions is, by way of example only, a halogen, deuterium, an alkyl group, a haloalkyl group, or a deuteroalkyl group.

[00324] In another embodiment, the compounds described herein are labeled isotopically (e.g. with a radioisotope) or by another other means, including, but not limited to, the use of chromophores or fluorescent moieties, bioluminescent labels, or chemiluminescent labels.

[00325] Compounds described herein include isotopically-labeled compounds, which are identical to those recited in the various formulae and structures presented herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into the present compounds include isotopes of hydrogen, carbon, nitrogen, oxygen, sulfur, fluorine chlorine, iodine, phosphorus, such as, for example, ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{35}S, ^{18}F, ^{36}Cl, ^{123}I, ^{124}I, ^{125}I, ^{131}I, ^{32}P and ^{33}P. In one aspect, isotopically-labeled compounds described herein, for example those into which radioactive isotopes such as ^{3}H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. In one aspect, substitution with isotopes such as deuterium affords certain therapeutic advantages resulting from greater metabolic stability, such as, for example, increased *in vivo* half-life or reduced dosage requirements.

[00326] In some embodiments, the compounds disclosed herein possess one or more stereocenters and each stereocenter exists independently in either the R or S configuration. In some embodiments, the compound disclosed herein exists in the R configuration. In some embodiments, the compound disclosed herein exists in the S configuration. The compounds presented herein include all diastereomeric, individual enantiomers, atropisomers, and epimeric forms as well as the appropriate mixtures thereof. The compounds and methods provided herein include all cis, trans, syn, anti, entgegen (E), and zusammen (Z) isomers as well as the appropriate mixtures thereof.

[00327] Individual stereoisomers are obtained, if desired, by methods such as, stereoselective synthesis and/or the separation of stereoisomers by chiral chromatographic columns or the separation of diastereomers by either non-chiral or chiral chromatographic columns or crystallization and recrystallization in a proper solvent or a mixture of solvents. In certain embodiments, compounds disclosed herein are prepared as their individual stereoisomers by reacting a racemic mixture of the compound with an optically active resolving agent to form a pair of diastereoisomeric compounds/salts, separating the diastereomers and recovering the

optically pure individual enantiomers. In some embodiments, resolution of individual enantiomers is carried out using covalent diastereomeric derivatives of the compounds described herein. In another embodiment, diastereomers are separated by separation/resolution techniques based upon differences in solubility. In other embodiments, separation of stereoisomers is performed by chromatography or by the forming diastereomeric salts and separation by recrystallization, or chromatography, or any combination thereof. Jean Jacques, Andre Collet, Samuel H. Wilen, "Enantiomers, Racemates and Resolutions", John Wiley And Sons, Inc., 1981. In some embodiments, stereoisomers are obtained by stereoselective synthesis.

[00328] In some embodiments, compounds described herein are prepared as prodrugs. A "prodrug" refers to an agent that is converted into the parent drug *in vivo*. Prodrugs are often useful because, in some situations, they are easier to administer than the parent drug. They are, for instance, bioavailable by oral administration whereas the parent is not. Further or alternatively, the prodrug also has improved solubility in pharmaceutical compositions over the parent drug. In some embodiments, the design of a prodrug increases the effective water solubility. An example, without limitation, of a prodrug is a compound described herein, which is administered as an ester (the "prodrug") but then is metabolically hydrolyzed to provide the active entity. A further example of a prodrug is a short peptide (polyaminoacid) bonded to an acid group where the peptide is metabolized to reveal the active moiety. In certain embodiments, upon *in vivo* administration, a prodrug is chemically converted to the biologically, pharmaceutically, or therapeutically active form of the compound. In certain embodiments, a prodrug is enzymatically metabolized by one or more steps or processes to the biologically, pharmaceutically, or therapeutically active form of the compound.

[00329] Prodrugs of the compounds described herein include, but are not limited to, esters, ethers, carbonates, thiocarbonates, N-acyl derivatives, N-acyloxyalkyl derivatives, N-alkyloxyacyl derivatives, quaternary derivatives of tertiary amines, N-Mannich bases, Schiff bases, amino acid conjugates, phosphate esters, and sulfonate esters. See for example Design of Prodrugs, Bundgaard, A. Ed., Elseview, 1985 and Method in Enzymology, Widder, K. *et al.*, Ed.; Academic, 1985, vol. 42, p. 309-396; Bundgaard, H. "Design and Application of Prodrugs" in A Textbook of Drug Design and Development, Krosgaard-Larsen and H. Bundgaard, Ed., 1991, Chapter 5, p. 113-191; and Bundgaard, H., Advanced Drug Delivery Review, 1992, 8, 1-38, each of which is incorporated herein by reference. In some embodiments, a hydroxyl group in the compounds disclosed herein is used to form a prodrug, wherein the hydroxyl group is incorporated into an acyloxyalkyl ester, alkoxycarbonyloxyalkyl ester, alkyl ester, aryl ester, phosphate ester, sugar ester, ether, and the like. In some embodiments, a hydroxyl group in the compounds disclosed herein is a prodrug wherein the hydroxyl is then metabolized in vivo to provide a carboxylic acid group. In some embodiments, a carboxyl group is used to provide an ester or amide (i.e. the prodrug), which is then metabolized in vivo to provide a carboxylic acid group. In some embodiments, compounds described herein are prepared as alkyl ester prodrugs.

Certain Terminology

[00330] Unless otherwise stated, the following terms used in this application have the definitions given

below. The use of the term "including" as well as other forms, such as "include", "includes," and "included," is not limiting.

[00331] As used herein, C_1-C_x includes C_1-C_2, C_1-C_3 . . . C_1-C_x. By way of example only, a group designated as "C_1-C_4" indicates that there are one to four carbon atoms in the moiety, i.e. groups containing 1 carbon atom, 2 carbon atoms, 3 carbon atoms or 4 carbon atoms. Thus, by way of example only, "C_1-C_4 alkyl" indicates that there are one to four carbon atoms in the alkyl group, *i.e.*, the alkyl group is selected from among methyl, ethyl, propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, and *t*-butyl.

[00332] The term "acyl," as used herein refers to the group -C(=O)-R, where R is alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroaryl, heterocycle, or any other moiety were the atom attached to the carbonyl is carbon. An "acetyl" group refers to a $-C(=O)CH_3$ group.

[00333] The term "alkenyl," as used herein refers to a straight-chain or branched-chain hydrocarbon radical having one or more double bonds and containing from 2 to 20 carbon atoms. In certain embodiments, alkenyl includes 2 to 6 carbon atoms. The term "alkenylene" refers to a divalent alkenyl. In some embodiments, an alkenyl is selected from ethenyl (*i.e.*, vinyl), propenyl (*i.e.*, allyl), butenyl, pentenyl, pentadienyl, and the like. Non-limiting examples of an alkenyl group include $-CH=CH_2$, $-C(CH_3)=CH_2$, $-CH=CHCH_3$, $-C(CH_3)=CHCH_3$, and $-CH_2CH=CH_2$.

[00334] The term "alkoxy" refers to a (alkyl)-O- group, where alkyl is as defined herein. In some embodiments, the alkoxy group is a C_1-C_6alkoxy, which refers to a (C_1-C_6alkyl)-O- group. Examples of alkyl groups include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy, and the like.

[00335] An "alkyl" group refers to an aliphatic hydrocarbon group. In some embodiments, the alkyl is a straight-chain or branched-chain aliphatic hydrocarbon group containing from 1 to 20 carbon atoms. In certain embodiments, alkyl includes 1 to 10 carbon atoms. In further embodiments, the alkyl includes 1 to 8 carbon atoms. Examples of alkyl radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexyl, octyl, nonyl, and the like. In some embodiments, an alkyl is a C_1-C_6alkyl. In one aspect the alkyl is methyl, ethyl, propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, or t-butyl. The term "alkylene" refers to a divalent alkyl, such as methylene ($-CH_2-$). In some embodiments, an alkylene is a C_1-C_6alkylene. In other embodiments, an alkylene is a C_1-C_4alkylene. Typical alkylene groups include, but are not limited to, $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2-$, and the like.

[00336] The term "amino," as used herein refers to -NRR', wherein R and R' are independently selected from hydrogen, alkyl, acyl, heteroalkyl, aryl, cycloalkyl, heteroaryl, and heterocycloalkyl, any of which may themselves be optionally substituted. Additionally, R and R' may combine to form heterocycloalkyl, either of which may be optionally substituted. In one aspect, "amino" as used herein refers to an $-NH_2$ group.

[00337] The term "alkynyl," as used herein refers to a straight-chain or branched chain hydrocarbon radical having one or more triple bonds and containing from 2 to 20 carbon atoms. In certain embodiments, said alkynyl comprises from 2 to 6 carbon atoms. In further embodiments, said alkynyl comprises from 2 to 4 carbon atoms. In one embodiment, an alkenyl group has the formula -C≡C-R, wherein R refers to the

remaining portions of the alkynyl group. In some embodiments, R is H or an alkyl. In some embodiments, an alkynyl is selected from ethynyl, propynyl, butynyl, pentynyl, hexynyl, and the like. Non-limiting examples of an alkynyl group include -C≡CH, -C≡CCH$_3$ -C≡CCH$_2$CH$_3$, -CH$_2$C≡CH. The term "alkynylene" refers to a carbon-carbon triple bond attached at two positions such as ethynylene (-C≡C-). Examples of alkynyl radicals include ethynyl, propynyl, hydroxypropynyl, butyn-1-yl, butyn-2-yl, pentyn-1-yl, 3-methylbutyn-1-yl, hexyn-2-yl, and the like. Unless otherwise specified, the term "alkynyl" may include "alkynylene" groups.

[00338] The term "aromatic" refers to a planar ring having a delocalized π-electron system containing 4n+2 π electrons, where n is an integer. The term "aromatic" includes both carbocyclic aryl ("aryl", *e.g.*, phenyl) and heterocyclic aryl (or "heteroaryl" or "heteroaromatic") groups (*e.g.*, pyridine). The term includes monocyclic or fused-ring polycyclic (*i.e.*, rings which share adjacent pairs of carbon atoms) groups.

[00339] The term "carbocyclic" or "carbocycle" refers to a ring or ring system where the atoms forming the backbone of the ring are all carbon atoms. The term thus distinguishes carbocyclic from "heterocyclic" rings or "heterocycles" in which the ring backbone contains at least one atom which is different from carbon. In some embodiments, at least one of the two rings of a bicyclic carbocycle is aromatic. In some embodiments, both rings of a bicyclic carbocycle are aromatic. Carbocycles include aryls and cycloalkyls.

[00340] The term "aryl" as used herein means a carbocyclic aromatic system containing one, two or three rings wherein such polycyclic ring systems are fused together. The term "aryl" embraces aromatic groups such as phenyl, naphthyl, anthracenyl, and phenanthryl. In one aspect, aryl is phenyl or a naphthyl. In some embodiments, an aryl is a phenyl. In some embodiments, an aryl is a phenyl, naphthyl, indanyl, indenyl, or tetrahyodronaphthyl. In some embodiments, an aryl is a C$_6$-C$_{10}$aryl. Depending on the structure, an aryl group is a monoradical or a diradical (i.e., an arylene group).

[00341] The terms "benzo" and "benz," as used herein refer to fused bicyclic or polyclic ring system that is formed with benzene as one of the rings. Examples include benzofuran, benzothiophene, and benzimidazole.

[00342] The term "cycloalkyl," as used herein refers to a saturated or partially saturated monocyclic, bicyclic or tricyclic alkyl group wherein each cyclic moiety contains from 3 to 12 carbon atom ring members and which may optionally be a benzo fused ring system which is optionally substituted as defined herein. In some embodiments, cycloalkyl groups include groups having from 3 to 10 ring atoms. In certain embodiments, said cycloalkyl will comprise from 5 to 7 carbon atoms. In certain embodiments, said cycloalkyl will comprise from 3 to 6 carbon atoms. Examples of such cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, tetrahydronaphthyl, indanyl, octahydronaphthyl, 2,3-dihydro-1H-indenyl, adamantly, and the like. "Bicyclic" and "tricyclic" as used herein are intended to include both fused ring systems, such as decahydronaphthalene, octahydronaphthalene as well as the multicyclic (multicentered) saturated or partially unsaturated type. The latter type of isomer is exemplified in general by, bicyclo[1,1,1]pentane, camphor, adamantane, and bicyclo[3,2,1]octane. In some embodiments, a cycloalkyl is a C$_3$-C$_6$cycloalkyl. In some embodiments, a cycloalkyl is a C$_3$-C$_4$cycloalkyl.

[00343] The term "heterocycle" or "heterocyclic" refers to heteroaromatic rings (also known as heteroaryls) and heterocycloalkyl rings containing one to four heteroatoms in the ring(s), where each heteroatom in the ring(s) is selected from O, S and N, wherein each heterocyclic group has from 3 to 10 atoms in its ring system, and with the proviso that any ring does not contain two adjacent O or S atoms. Non-aromatic heterocyclic groups (also known as heterocycloalkyls) include rings having 3 to 10 atoms in its ring system and aromatic heterocyclic groups include rings having 5 to 10 atoms in its ring system. The heterocyclic groups include benzo-fused ring systems. Examples of non-aromatic heterocyclic groups are pyrrolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, oxazolidinonyl, tetrahydropyranyl, dihydropyranyl, tetrahydrothiopyranyl, piperidinyl, morpholinyl, thiomorpholinyl, thioxanyl, piperazinyl, aziridinyl, azetidinyl, oxetanyl, thietanyl, homopiperidinyl, oxepanyl, thiepanyl, oxazepinyl, diazepinyl, thiazepinyl, 1,2,3,6-tetrahydropyridinyl, pyrrolin-2-yl, pyrrolin-3-yl, indolinyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, dithianyl, dithiolanyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, 3-azabicyclo[3.1.0]hexanyl, 3-azabicyclo[4.1.0]heptanyl, 3H-indolyl, indolin-2-onyl, isoindolin-1-onyl, isoindoline-1,3-dionyl, 3,4-dihydroisoquinolin-1(2H)-onyl, 3,4-dihydroquinolin-2(1H)-onyl, isoindoline-1,3-dithionyl, benzo[d]oxazol-2(3H)-onyl, 1H-benzo[d]imidazol-2(3H)-onyl, benzo[d]thiazol-2(3H)-onyl, and quinolizinyl. Examples of aromatic heterocyclic groups are pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indolizinyl, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridinyl, purinyl, oxadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, and furopyridinyl. The foregoing groups are either C-attached (or C-linked) or *N*-attached where such is possible. For instance, a group derived from pyrrole includes both pyrrol-1-yl (*N*-attached) or pyrrol-3-yl (C-attached). Further, a group derived from imidazole includes imidazol-1-yl or imidazol-3-yl (both *N*-attached) or imidazol-2-yl, imidazol-4-yl or imidazol-5-yl (all C-attached). The heterocyclic groups include benzo-fused ring systems. Non-aromatic heterocycles are optionally substituted with one or two oxo (=O) moieties, such as pyrrolidin-2-one. In some embodiments, at least one of the two rings of a bicyclic heterocycle is aromatic. In some embodiments, both rings of a bicyclic heterocycle are aromatic.

[00344] The terms "heteroaryl" or, alternatively, "heteroaromatic" refers to an aryl group that includes one or more ring heteroatoms selected from nitrogen, oxygen and sulfur. In some embodiments, the term "heteroaryl," as used herein refers to a 3 to 15 membered unsaturated heteromonocyclic ring, or a fused monocyclic, bicyclic, or tricyclic ring system in which at least one of the fused rings is aromatic, which contains at least one atom selected from N, O, and S. In certain embodiments, said heteroaryl will comprise from 1 to 4 heteroatoms as ring members. In further embodiments, said heteroaryl will comprise from 1 to 2 heteroatoms as ring members. In certain embodiments, said heteroaryl will comprise from 5 to 7 atoms. The term also embraces fused polycyclic groups wherein heterocyclic rings are fused with aryl rings, wherein heteroaryl rings are fused with other heteroaryl rings, wherein heteroaryl rings are fused with

heterocycloalkyl rings, or wherein heteroaryl rings are fused with cycloalkyl rings. Examples of heteroaryl groups include pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, triazolyl, furyl, thienyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, thiadiazolyl, isothiazolyl, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, quinoxalinyl, quinazolinyl, indazolyl, benzotriazolyl, benzodioxolyl, benzopyranyl, benzoxazolyl, benzoxadiazolyl, benzothiazolyl, benzothiadiazolyl, benzofuranyl, benzothienyl, chromonyl, coumarinyl, benzopyranyl, tetrahydroquinolinyl, tetrazolopyridazinyl, tetrahydroisoquinolinyl, thienopyridinyl, furopyridinyl, pyrrolopyridinyl, and the like. Exemplary tricyclic heterocyclic groups include carbazolyl, benzidolyl, phenanthrolinyl, dibenzofuranyl, acridinyl, phenanthridinyl, xanthenyl, and the like. In some embodiments, a heteroaryl contains 0-4 N atoms in the ring. In some embodiments, a heteroaryl contains 1-4 N atoms in the ring. In some embodiments, a heteroaryl contains 1 O atom in the ring. In some embodiments, a heteroaryl contains 1 S atom in the ring. In some embodiments, a heteroaryl contains 1-4 N atoms, 0-1 O atoms, and 0-1 S atoms in the ring. In some embodiments, heteroaryl is a C_1-C_9heteroaryl. In some embodiments, monocyclic heteroaryl is a C_1-C_5heteroaryl. In some embodiments, monocyclic heteroaryl is a 5-membered or 6-membered heteroaryl. In some embodiments, bicyclic heteroaryl is a C_6-C_9heteroaryl.

[00345] A "heterocycloalkyl" group refers to a cycloalkyl group that includes at least one heteroatom selected from nitrogen, oxygen and sulfur. In some embodiments, the term "heterocycloalkyl" as used herein each refer to a saturated, partially unsaturated, or fully unsaturated (but nonaromatic) monocyclic, bicyclic, or tricyclic heterocyclic group containing at least one heteroatom as a ring member, wherein each said heteroatom may be independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, said hetercycloalkyl will comprise from 1 to 4 heteroatoms as ring members. In further embodiments, said hetercycloalkyl will comprise from 1 to 2 heteroatoms as ring members. In certain embodiments, said hetercycloalkyl will comprise from 3 to 8 ring members in each ring. In further embodiments, said hetercycloalkyl will comprise from 3 to 7 ring members in each ring. In yet further embodiments, said hetercycloalkyl will comprise from 5 to 6 ring members in each ring. "Heterocycloalkyl" and "heterocycle" are intended to include sulfones, sulfoxides, N-oxides of tertiary nitrogen ring members, and carbocyclic fused and benzo fused ring systems; additionally, both terms also include systems where a heterocycle ring is fused to an aryl group, as defined herein, or an additional heterocycle group. Examples of heterocycle groups include aziridinyl, azetidinyl, 1,3-benzodioxolyl, dihydroisoindolyl, dihydroisoquinolinyl, dihydrocinnolinyl, dihydrobenzodioxinyl, dihydro[1,3]oxazolo[4,5-b]pyridinyl, benzothiazolyl, dihydroindolyl, dihydropyridinyl, 1,3-dioxanyl, 1,4-dioxanyl, 1,3-dioxolanyl, isoindolinyl, morpholinyl, piperazinyl, pyrrolidinyl, tetrahydropyridinyl, piperidinyl, thiomorpholinyl, and the like. The heterocycle groups may be optionally substituted unless specifically prohibited. In one aspect, a heterocycloalkyl is a C_2-C_{10}heterocycloalkyl. In another aspect, a heterocycloalkyl is a C_4-C_{10}heterocycloalkyl. In some embodiments, a heterocycloalkyl is monocyclic or bicyclic. In some embodiments, a heterocycloalkyl is monocyclic and is a 3, 4, 5, 6, 7, or 8-membered ring. In some embodiments, a heterocycloalkyl is monocyclic and is a 3, 4, 5, or 6-membered ring. In some embodiments, a heterocycloalkyl is monocyclic

and is a 3 or 4-membered ring. In some embodiments, a heterocycloalkyl contains 1-2 N atoms in the ring. In some embodiments, a heterocycloalkyl contains 1-2 O atoms. In some embodiments, a heterocycloalkyl contains 1 S atom. In some embodiments, a heterocycloalkyl contains 0-2 N atoms, 0-2 O atoms and 0-1 S atoms in the ring.

[00346] The term "carbamate," as used herein refers to an ester of carbamic acid (-NHCOO-) which may be attached to the parent molecular moiety from either the nitrogen or acid end, and which may be optionally substituted as defined herein.

[00347] The term "carboxyl" or "carboxy," as used herein, refers to -C(=O)OH or the corresponding "carboxylate" anion, such as is in a carboxylic acid salt.

[00348] The term "cyano," as used herein refers to -CN.

[00349] The term "ester," as used herein refers to a carboxy group bridging two moieties linked at carbon atoms.

[00350] The term "ether," as used herein refers to an oxy group bridging two moieties linked at carbon atoms.

[00351] The term "halo," or "halogen," as used herein refers to fluorine, chlorine, bromine, or iodine. In some embodiments, halo is fluoro, chloro, or bromo.

[00352] The term "haloalkyl," as used herein refers to an alkyl radical having the meaning as defined above wherein one or more hydrogens are replaced with a halogen. Specifically embraced are monohaloalkyl, dihaloalkyl and polyhaloalkyl radicals. A monohaloalkyl radical, for one example, may have an iodo, bromo, chloro or fluoro atom within the radical. Dihalo and polyhaloalkyl radicals may have two or more of the same halo atoms or a combination of different halo radicals. Examples of haloalkyl radicals include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl. "Haloalkylene" refers to a haloalkyl group attached at two or more positions. Examples include fluoromethylene (-CFH-), difluoromethylene (-CF_2 -), chloromethylene (-CHCl-), and the like. In one aspect, a haloalkyl is a C_1-C_6haloalkyl. In another aspect, a haloalkyl is a C_1-C_4haloalkyl.

[00353] The term "haloalkoxy," as used herein refers to a haloalkyl group attached to the parent molecular moiety through an oxygen atom. In one aspect, the haloalkoxy is a C_1-C_6haloalkoxy, which refers to a (C_1-C_6haloalkyl)-O- group. In another aspect, the haloalkoxy is a C_1-C_4haloalkoxy, which refers to a (C_1-C_4haloalkyl)-O- group.

[00354] The term "heteroalkyl" refers to an alkyl wherein 1 or more carbon atoms are replaced with a heteroatom. In some embodiments, "heteroalkyl" refers to an alkyl wherein 1 or more carbon atoms are replaced with one or more heteroatoms that are independently selected from NH, -N(alkyl), O, S, S(=O) and $S(=O)_2$. The attachment of the heteroatom(s) to the remainder of the compound is at a carbon atoms of the heteroalkyl. In some embodiments, up to two heteroatoms may be consecutive, such as, for example, -CH_2-NH-OCH_3. In some embodiments, "heteroalkyl" is an "alkoxyalkyl", "alkylthioalkyl", or "alkylaminoalkyl".

"Alkoxyalkyl" refers to an alkyl in which one hydrogen atom is replaced by an alkoxy group, as defined herein. In some embodiments, an alkoxyalkyl is a (C_1-C_6alkoxy)-C_1-C_6alkyl. Typical alkoxyalkyl groups include, but are not limited to, -CH_2OCH_3, -$CH_2CH_2OCH_3$, -$CH_2CH_2CH_2OCH_3$, -$CH_2CH_2CH_2CH_2OCH_3$, -$CH_2OCH_2CH_3$, -$CH_2CH_2OCH_2CH_3$, -$CH_2CH_2CH_2OCH_2CH_3$, -$CH_2CH_2CH_2CH_2OCH_2CH_3$, and the like. "Alkylthioalkyl" refers to an alkyl in which one hydrogen atom is replaced by an alkylthio group, as defined herein. In some embodiments, an alkoxyalkyl is a (C_1-C_6 alkylthio)-C_1-C_6alkyl. Typical alkoxyalkyl groups include, but are not limited to, -CH_2SCH_3, -$CH_2CH_2SCH_3$, -$CH_2CH_2CH_2SCH_3$, -$CH_2CH_2CH_2CH_2SCH_3$, -$CH_2SCH_2CH_3$, -$CH_2CH_2SCH_2CH_3$, -$CH_2CH_2CH_2SCH_2CH_3$, -$CH_2CH_2CH_2CH_2SCH_2CH_3$, and the like. "Alkylaminoalkyl" refers to an alkyl in which one hydrogen atom is replaced by an alkylamino group, as defined herein. In some embodiments, an alkoxyalkyl is a (C_1-C_6alkylamino)-C_1-C_6alkyl. Typical alkoxyalkyl groups include, but are not limited to, -CH_2NHCH_3, -$CH_2CH_2NHCH_3$, -$CH_2CH_2CH_2NHCH_3$, -$CH_2CH_2CH_2CH_2NHCH_3$, -$CH_2NHCH_2CH_3$, -$CH_2CH_2NHCH_2CH_3$, -$CH_2CH_2CH_2NHCH_2CH_3$, -$CH_2CH_2CH_2CH_2NHCH_2CH_3$, and the like.

[00355] The term "hydroxy," or "hydroxyl," as used herein refers to -OH.

[00356] The term "hydroxyalkyl," as used herein refers to a hydroxy group attached to the parent molecular moiety through an alkyl group. In some embodiments, a hydroxyalkyl is a C_1-C_4hydroxyalkyl. Typical hydroxyalkyl groups include, but are not limited to, -CH_2OH, -CH_2CH_2OH, -$CH_2CH_2CH_2OH$, -$CH_2CH_2CH_2CH_2OH$, and the like.

[00357] The phrase "linear chain of atoms" refers to the longest straight chain of atoms independently selected from carbon, nitrogen, oxygen and sulfur.

[00358] The term "nitro," as used herein refers to -NO_2.

[00359] The term "oxo," as used herein refers to =O.

[00360] The terms "sulfonate," "sulfonic acid," and "sulfonic," as used herein refer the -SO_3H group and its anion as the sulfonic acid is used in salt formation.

[00361] The term "sulfanyl," as used herein refers to -S-.

[00362] The term "sulfinyl," as used herein refers to -S(=O)-.

[00363] The term "sulfonyl," as used herein refers to a -$S(=O)_2$-, -$S(=O)_2R$, or -$S(=O)_2R$- group, with R as defined herein.

[00364] Any definition herein may be used in combination with any other definition to describe a composite structural group. By convention, the trailing element of any such definition is that which attaches to the parent moiety. For example, the composite group alkylamido would represent an alkyl group attached to the parent molecule through an amido group, and the term alkoxyalkyl would represent an alkoxy group attached to the parent molecule through an alkyl group.

[00365] When a group is defined to be "null," what is meant is that said group is absent.

[00366] In some embodiments, the term "optionally substituted" or "substituted" means that the referenced group is optionally substituted with one or more additional group(s) individually and independently selected from halogen, -CN, -NH_2, -NH(alkyl), -$N(alkyl)_2$, -OH, -CO_2H, -CO_2alkyl, -

$C(=O)NH_2$, -C(=O)NH(alkyl), $-C(=O)N(alkyl)_2$, $-S(=O)_2NH_2$, $-S(=O)_2NH(alkyl)$, $-S(=O)_2N(alkyl)_2$, alkyl, cycloalkyl, fluoroalkyl, heteroalkyl, alkoxy, fluoroalkoxy, heterocycloalkyl, aryl, heteroaryl, aryloxy, alkylthio, arylthio, alkylsulfoxide, arylsulfoxide, alkylsulfone, and arylsulfone. In some other embodiments, optional substituents are independently selected from halogen, -CN, $-NH_2$, $-NH(CH_3)$, $-N(CH_3)_2$, -OH, $-CO_2H$, $-CO_2(C_1$-C_4alkyl), $-C(=O)NH_2$, $-C(=O)NH(C_1$-C_4alkyl), $-C(=O)N(C_1$-C_4alkyl$)_2$, $-S(=O)_2NH_2$, $-S(=O)_2NH(C_1$-C_4alkyl), $-S(=O)_2N(C_1$-C_4alkyl$)_2$, C_1-C_4alkyl, C_3-C_6cycloalkyl, C_1-C_4fluoroalkyl, C_1-C_4heteroalkyl, C_1-C_4alkoxy, C_1-C_4fluoroalkoxy, $-SC_1$-C_4alkyl, $-S(=O)C_1$-C_4alkyl, and $-S(=O)_2C_1$-C_4alkyl. In some embodiments, optional substituents are independently selected from halogen, -CN, $-NH_2$, -OH, $-NH(CH_3)$, $-N(CH_3)_2$, $-CH_3$, $-CH_2CH_3$, $-CHF_2$, $-CF_3$, $-OCH_3$, $-OCHF_2$, and $-OCF_3$. In some embodiments, substituted groups are substituted with one or two of the preceding groups. In some embodiments, an optional substituent on an aliphatic carbon atom (acyclic or cyclic) includes oxo (=O).

[00367] The term "bond" refers to a covalent linkage between two atoms, or two moieties when the atoms joined by the bond are considered to be part of larger substructure. A bond may be single, double, or triple unless otherwise specified. A dashed line between two atoms in a drawing of a molecule indicates that an additional bond may be present or absent at that position.

[00368] The term "disease" or "disorder" as used herein refers to any condition that impairs the normal functioning of the body, such as a functional abnormality or disturbance that impairs normal functioning.

[00369] The term "combination therapy" means the administration of two or more therapeutic agents to treat a therapeutic condition or disorder described in the present disclosure.

[00370] The phrase "therapeutically effective" is intended to qualify the amount of active ingredients used in the treatment of a disease or disorder or on the effecting of a clinical endpoint.

[00371] The term "therapeutically acceptable" refers to those compounds (or salts, prodrugs, tautomers, zwitterionic forms, etc.) which are suitable for use in contact with the tissues of patients without undue toxicity, irritation, and allergic response, are commensurate with a reasonable benefit/risk ratio, and are effective for their intended use.

[00372] As used herein, "treating," "treatment," and the like means ameliorating a disease, so as to reduce, ameliorate, or eliminate its cause, its progression, its severity, or one or more of its symptoms, or otherwise beneficially alter the disease in a subject. In certain embodiments, reference to "treating" or "treatment" of a subject at risk for developing a disease, or at risk of disease progression to a worse state, is intended to include prophylaxis. Prevention of a disease may involve complete protection from disease or may involve prevention of disease progression. Prevention of diseases may also mean prevention of progression of a disease to a later stage of the disease.

[00373] The term "patient" is generally synonymous with the term "subject" and includes all mammals including humans. Examples of patients include humans, non-human primates such as chimpanzees, and other apes and monkey species; livestock such as cows, goats, sheep, pigs, and rabbits, and companion animals such as dogs, cats, rabbits, and horses. Preferably, the patient is a human.

Pharmaceutical Compositions and Formulations

[00374] Formulations may be prepared by any suitable method, typically by uniformly mixing the active compound(s) with liquids or finely divided solid carriers, or both, in the required proportions and then, if necessary, forming the resulting mixture into a desired shape.

[00375] Conventional excipients, such as binding agents, fillers, acceptable wetting agents, tableting lubricants and disintegrants may be used in tablets and capsules for oral administration. Liquid preparations for oral administration may be in the form of solutions, emulsions, aqueous or oily suspensions and syrups. Alternatively, the oral preparations may be in the form of dry powder that can be reconstituted with water or another suitable liquid vehicle before use. Additional additives such as suspending or emulsifying agents, non-aqueous vehicles (including edible oils), preservatives and flavorings and colorants may be added to the liquid preparations. Parenteral dosage forms may be prepared by dissolving the compound provided herein in a suitable liquid vehicle and filter sterilizing the solution before filling and sealing an appropriate vial or ampule. These are just a few examples of the many appropriate methods well known in the art for preparing dosage forms.

[00376] A compound of the present invention can be formulated into pharmaceutical compositions using techniques well known to those in the art. Suitable pharmaceutically-acceptable carriers, outside those mentioned herein, are known in the art; for example, see Remington, The Science and Practice of Pharmacy, 20th Edition, 2000, Lippincott Williams & Wilkins, (Editors: Gennaro *et. al.*).

[00377] The compounds provided herein, together with a conventional adjuvant, carrier, or diluent, may thus be placed into the form of pharmaceutical formulations and unit dosages thereof and in such form may be employed as solids, such as tablets or filled capsules, or liquids such as solutions, suspensions, emulsions, elixirs, gels or capsules filled with the same, all for oral use, or in the form of sterile injectable solutions for parenteral (including subcutaneous) use. Such pharmaceutical compositions and unit dosage forms thereof may comprise conventional ingredients in conventional proportions, with or without additional active compounds or principles and such unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed.

[00378] For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, capsule, suspension or liquid. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient. Examples of such dosage units are capsules, tablets, powders, granules or a suspension, with conventional additives such as lactose, mannitol, corn starch or potato starch; with binders such as crystalline cellulose, cellulose derivatives, acacia, corn starch or gelatins; with disintegrators such as corn starch, potato starch or sodium carboxymethyl-cellulose; and with lubricants such as talc or magnesium stearate. The active ingredient may also be administered by injection as a composition wherein, for example, saline, dextrose or water may be used as a suitable pharmaceutically acceptable carrier.

[00379] Compounds provided herein or a salt, solvate, or hydrate thereof can be used as active ingredients in pharmaceutical compositions. The term "active ingredient", defined in the context of a "pharmaceutical

composition", refers to a component of a pharmaceutical composition that provides the primary pharmacological effect, as opposed to an "inactive ingredient" which would generally be recognized as providing no pharmaceutical benefit.

[00380] The dose when using the compounds provided herein can vary within wide limits and as is customary and is known to the physician or other clinician, it is to be tailored to the individual conditions in each individual case. It depends, for example, on the nature and severity of the illness to be treated, on the condition of the patient, on the compound employed or on whether an acute or chronic disease state is treated, or prophylaxis conducted, or on whether further active compounds are administered in addition to the compounds provided herein. Representative doses include, but are not limited to, about 0.001 mg to about 5000 mg, about 0.001 mg to about 2500 mg, about 0.001 mg to about 1000 mg, about 0.001 mg to about 500 mg, about 0.001 mg to about 250 mg, about 0.001 mg to 100 mg, about 0.001 mg to about 50 mg and about 0.001 mg to about 25 mg. Multiple doses may be administered during the day, especially when relatively large amounts are deemed to be needed, for example 2, 3, or 4 doses. Depending on the individual and as deemed appropriate from the healthcare provider it may be necessary to deviate upward or downward from the doses described herein.

[00381] The amount of active ingredient, or an active salt or derivative thereof, required for use in treatment will vary not only with the particular salt selected but also with the route of administration, the nature of the condition being treated and the age and condition of the patient and will ultimately be at the discretion of the attendant physician or clinician. In general, one skilled in the art understands how to extrapolate *in vivo* data obtained in a model system, typically an animal model, to another, such as a human. In some circumstances, these extrapolations may merely be based on the weight of the animal model in comparison to another, such as a mammal, preferably a human, however, more often, these extrapolations are not simply based on weights, but rather incorporate a variety of factors. Representative factors include the type, age, weight, sex, diet and medical condition of the patient, the severity of the disease, the route of administration, pharmacological considerations such as the activity, efficacy, pharmacokinetic and toxicology profiles of the particular compound employed, whether a drug delivery system is utilized, on whether an acute or chronic disease state is being treated, or prophylaxis conducted, or on whether further active compounds are administered in addition to the compounds provided herein and as part of a drug combination. The dosage regimen for treating a disease condition with the compounds and/or compositions provided herein is selected in accordance with a variety of factors as cited above. Thus, the actual dosage regimen employed may vary widely and therefore may deviate from a preferred dosage regimen and one skilled in the art will recognize that dosage and dosage regimen outside these typical ranges can be tested and, where appropriate, may be used in the methods provided herein.

[00382] Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water-propylene glycol solutions. For example, parenteral injection liquid preparations can be formulated as solutions in aqueous polyethylene glycol solution. Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing

or wetting agents and suspending agents.

[00383] Aqueous formulations suitable for oral use can be prepared by dissolving or suspending the active component in water and adding suitable colorants, flavors, stabilizing and thickening agents, as desired.

[00384] Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

[00385] For topical administration to the epidermis the compounds provided herein may be formulated as ointments, creams, or lotions, or as a transdermal patch.

[00386] Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilizing agents, dispersing agents, suspending agents, thickening agents, or coloring agents.

[00387] The pharmaceutical preparations are preferably in unit dosage forms. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

Methods of Dosing and Treatment Regimens

[00388] In one embodiment, the compounds disclosed herein, or a pharmaceutically acceptable salt thereof, are used in the preparation of medicaments for the treatment of diseases or conditions in a mammal. Methods for treating any of the diseases or conditions described herein in a mammal in need of such treatment, involves administration of pharmaceutical compositions that include at least one compound disclosed herein, or a pharmaceutically acceptable salt, active metabolite, prodrug, or pharmaceutically acceptable solvate thereof, in therapeutically effective amounts to said mammal.

[00389] In certain embodiments, the compositions containing the compound(s) described herein are administered for prophylactic and/or therapeutic treatments. In certain therapeutic applications, the compositions are administered to a patient already suffering from a disease or condition, in an amount sufficient to cure or at least partially arrest at least one of the symptoms of the disease or condition. Amounts effective for this use depend on the severity and course of the disease or condition, previous therapy, the patient's health status, weight, and response to the drugs, and the judgment of the treating physician. Therapeutically effective amounts are optionally determined by methods including, but not limited to, a dose escalation and/or dose ranging clinical trial.

[00390] In prophylactic applications, compositions containing the compounds described herein are administered to a patient susceptible to or otherwise at risk of a particular disease, disorder, or condition. Such an amount is defined to be a "prophylactically effective amount or dose." In this use, the precise

amounts also depend on the patient's state of health, weight, and the like. When used in patients, effective amounts for this use will depend on the severity and course of the disease, disorder or condition, previous therapy, the patient's health status and response to the drugs, and the judgment of the treating physician. In one aspect, prophylactic treatments include administering to a mammal, who previously experienced at least one symptom of the disease being treated and is currently in remission, a pharmaceutical composition comprising a compound disclosed herein, or a pharmaceutically acceptable salt thereof, in order to prevent a return of the symptoms of the disease or condition.

[00391] In certain embodiments wherein the patient's condition does not improve, upon the doctor's discretion the administration of the compounds are administered chronically, that is, for an extended period of time, including throughout the duration of the patient's life in order to ameliorate or otherwise control or limit the symptoms of the patient's disease or condition.

[00392] Once improvement of the patient's conditions has occurred, a maintenance dose is administered if necessary. Subsequently, in specific embodiments, the dosage or the frequency of administration, or both, is reduced, as a function of the symptoms, to a level at which the improved disease, disorder or condition is retained. In certain embodiments, however, the patient requires intermittent treatment on a long-term basis upon any recurrence of symptoms.

[00393] The amount of a given agent that corresponds to such an amount varies depending upon factors such as the particular compound, disease condition and its severity, the identity (*e.g.*, weight, sex) of the subject or host in need of treatment, but nevertheless is determined according to the particular circumstances surrounding the case, including, *e.g.*, the specific agent being administered, the route of administration, the condition being treated, and the subject or host being treated.

[00394] In general, however, doses employed for adult human treatment are typically in the range of 0.01 mg-2000 mg per day. In one embodiment, the desired dose is conveniently presented in a single dose or in divided doses administered simultaneously or at appropriate intervals, for example as two, three, four or more sub-doses per day.

[00395] In one embodiment, the daily dosages appropriate for the compound disclosed herein, or a pharmaceutically acceptable salt thereof, described herein are from about 0.01 to about 50 mg/kg per body weight. In some embodiments, the daily dosage or the amount of active in the dosage form are lower or higher than the ranges indicated herein, based on a number of variables in regard to an individual treatment regime. In various embodiments, the daily and unit dosages are altered depending on a number of variables including, but not limited to, the activity of the compound used, the disease or condition to be treated, the mode of administration, the requirements of the individual subject, the severity of the disease or condition being treated, and the judgment of the practitioner.

[00396] Toxicity and therapeutic efficacy of such therapeutic regimens are determined by standard pharmaceutical procedures in cell cultures or experimental animals, including, but not limited to, the determination of the LD_{50} and the ED_{50}. The dose ratio between the toxic and therapeutic effects is the therapeutic index and it is expressed as the ratio between LD_{50} and ED_{50}. In certain embodiments, the data

obtained from cell culture assays and animal studies are used in formulating the therapeutically effective daily dosage range and/or the therapeutically effective unit dosage amount for use in mammals, including humans. In some embodiments, the daily dosage amount of the compounds described herein lies within a range of circulating concentrations that include the ED_{50} with minimal toxicity. In certain embodiments, the daily dosage range and/or the unit dosage amount varies within this range depending upon the dosage form employed and the route of administration utilized.

[00397] In any of the aforementioned aspects are further embodiments in which the effective amount of the compound disclosed herein, or a pharmaceutically acceptable salt thereof, is: (a) systemically administered to the mammal; and/or (b) administered orally to the mammal; and/or (c) intravenously administered to the mammal; and/or (d) administered by injection to the mammal; and/or (e) administered topically to the mammal; and/or (f) administered non-systemically or locally to the mammal.

[00398] In any of the aforementioned aspects are further embodiments comprising single administrations of the effective amount of the compound, including further embodiments in which (i) the compound is administered once a day; or (ii) the compound is administered to the mammal multiple times over the span of one day.

[00399] In any of the aforementioned aspects are further embodiments comprising multiple administrations of the effective amount of the compound, including further embodiments in which (i) the compound is administered continuously or intermittently: as in a single dose; (ii) the time between multiple administrations is every 6 hours; (iii) the compound is administered to the mammal every 8 hours; (iv) the compound is administered to the mammal every 12 hours; (v) the compound is administered to the mammal every 24 hours. In further or alternative embodiments, the method comprises a drug holiday, wherein the administration of the compound is temporarily suspended or the dose of the compound being administered is temporarily reduced; at the end of the drug holiday, dosing of the compound is resumed. In one embodiment, the length of the drug holiday varies from 2 days to 1 year.

[00400] In certain instances, it is appropriate to administer at least one compound disclosed herein, or a pharmaceutically acceptable salt thereof, in combination with one or more other therapeutic agents.

[00401] As used above, and throughout the description of the invention, the following abbreviations, unless otherwise indicated, shall be understood to have the following meanings:

ACN or MeCN	acetonitrile
Ac	acetyl
Ac_2O	acetic anhydride
AcOH	acetic acid
AIBN	azobisisobutyronitrile
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthalene
Bn	benzyl
BOC or Boc	*tert*-butyl carbamate
Boc_2O	di-tert-butyl decarbonate or Boc anhydride

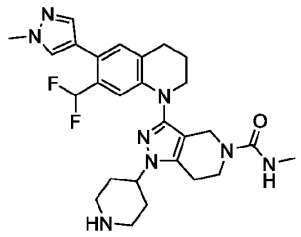
BPO	benzoyl peroxide
BrettPhos Pd G3	[(2-Di-cyclohexylphosphino-3,6-dimethoxy-2′,4′,6′- triisopropyl-1,1′-biphenyl)-2-(2′-amino-1,1′ -biphenyl)]palladium(II) methanesulfonate methanesulfonate
t-Bu	*tert*-butyl
C Phos Pd G3	[(2-Dicyclohexylphosphino-2′,6′-bis(N,N-dimethylamino) -1,1′-biphenyl)-2-(2′-amino-1,1′-biphenyl)] palladium(II) methanesulfonate
Cy	cyclohexyl
DBA or dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	dichloroethane ($ClCH_2CH_2Cl$)
DCM	dichloromethane (CH_2Cl_2)
DIPEA or DIEA	diisopropylethylamine
DMAP	4-(*N,N*-dimethylamino)pyridine
DMF	dimethylformamide
DMA	*N,N*-dimethylacetamide
DMSO	dimethylsulfoxide
Dppf	1,1'-bis(diphenylphosphino)ferrocene
EEDQ	2-Ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline
eq	equivalent(s)
Et	ethyl
Et_2O	diethyl ether
EtOH	ethanol
EtOAc	ethyl acetate
FA	formic acid
HATU	1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5- b]pyridinium 3-oxid hexafluorophosphate
HPLC	high performance liquid chromatography
H_2O	water
K_2CO_3	potassium carbonate
LAH	lithium aluminum anhydride
LCMS	liquid chromatography mass spectrometry
Me	methyl
MeOH	methanol
MS	mass spectrometry
MsCl	mesyl chloride
Na_2CO_3	sodium carbonate

$NaBH(OAc)_3$	sodium triacetoxyborohydride
NaH	sodium hydride
Na_2SO_4	sodium sulfate
NBS	N-bromo succinamide
NMP	*N*-methyl-pyrrolidin-2-one
NMR	nuclear magnetic resonance
$Pd(dppf)Cl_2$	(1,1'-Bis(diphenylphosphino)ferrocene)palladium(II) dichloride
Ph	phenyl
Pin	pinacolato
Prep-HPLC	preparative high performance liquid chromatography
i-Pr	*iso*-propyl
RP-HPLC	reverse phase-high pressure liquid chromatography
RuPhos Pd G3	(2-Dicyclohexylphosphino-2′,6′-diisopropoxy-1,1′-biphenyl)[2-(2′-amino-1,1′-biphenyl)]palladium(II) methanesulfonate
TBS	*tert*-butyldimethylsilyl
TFA	trifluoroacetic acid
TEA	triethylamine
THF	tetrahydrofuran
TsCl	tosyl chloride
TLC	thin layer chromatography

EXAMPLES

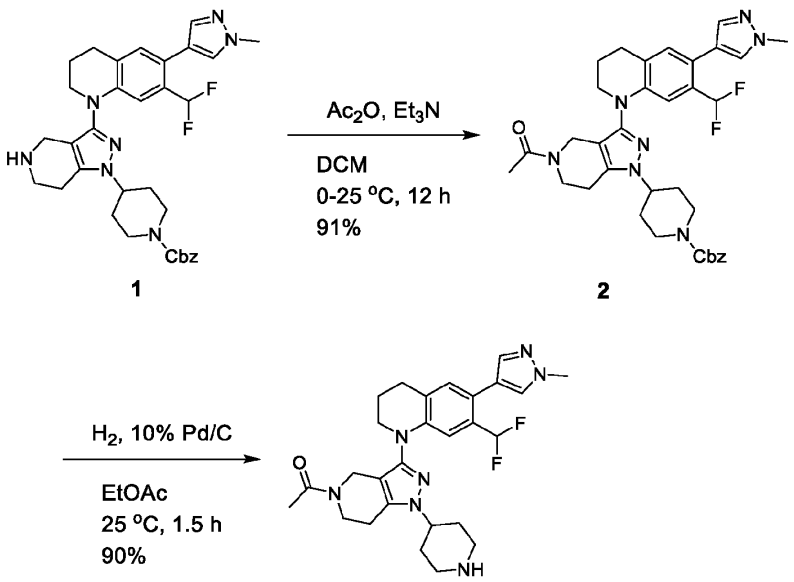
[00402] The following examples are provided for illustrative purposes only and not to limit the scope of the claims provided herein.

[00403] **Compound A** was prepared according to the procedure described in WO 2022/42707 A1.



Compound A

[00404] **Compound C** was prepared according to the following procedure:



1 2

Compound C

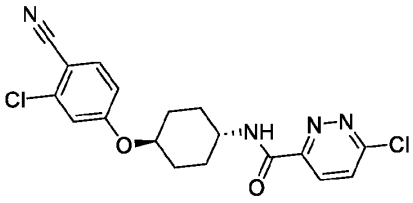
[00405] **1** was prepared according to the procedure described in WO 2022/42707 A1.

[00406] To a solution of benzyl 4-[3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-4,5,6,7-tetrahydropyrazolo[4,3-c]pyridin-1-yl]piperidine-1-carboxylate (0.250 g, 349 μmol, 1.0 eq, TFA) in DCM (0.5 mL) was added TEA (106 mg, 1.05 mmol, 146 μL, 3.0 eq) and Ac_2O (53.5 mg, 524 μmol, 49.2 μL, 1.5 eq) at 0 °C .The mixture was stirred at 25 °C for 12 h. The mixture was poured into ice-water (20 mL). The aqueous phase was extracted with dichloromethane (15 mL × 3). The combined organic phase was washed with brine (10 mL × 2), dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. The residue was purified by *prep*-TLC (silica, dichloromethane /methyl alcohol= 10/1). Compound benzyl 4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]piperidine-1-carboxylate (0.21 g, 316 μmol, 91% yield) was obtained as a light yellow solid. LC-MS: MS (ESI^+): t_R = 0.980 min, m/z = 644.3 [M + H^+]

[00407] Pd/C (0.110 g, 10% Pd on carbon, w/w) was added into a 100 mL single-necked round bottom flask under N_2, and then EtOAc (10 mL) was added at 25 °C under N_2. After addition, benzyl 4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]piperidine-1-carboxylate (0.210 g, 326 μmol, 1.0 eq) was added under N_2. The suspension was degassed under vacuum and purged with H_2 several times. The mixture was stirred under H_2 (15 psi) at 25 °C for 1.5 h. The reaction mixture was filtered and washed with MeOH (20 mL x 3). The collected filtrate was concentrated to give a residue. The residue was used for the next step without further purification. Compound 1-[3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-1-(4-piperidyl)-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]ethanone (0.15 g, 294 μmol, 90% yield) was obtained as a white solid. LC-MS: MS (ESI^+): t_R = 0.429 min, m/z = 510.3 [M + H^+]

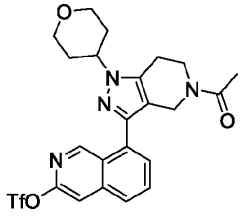
[00408] **Compound D** was prepared according to the procedure described in Journal of Medicinal

Chemistry, 2023, 66, 7, 4784 – 4801 and WO2021/231174 A1.



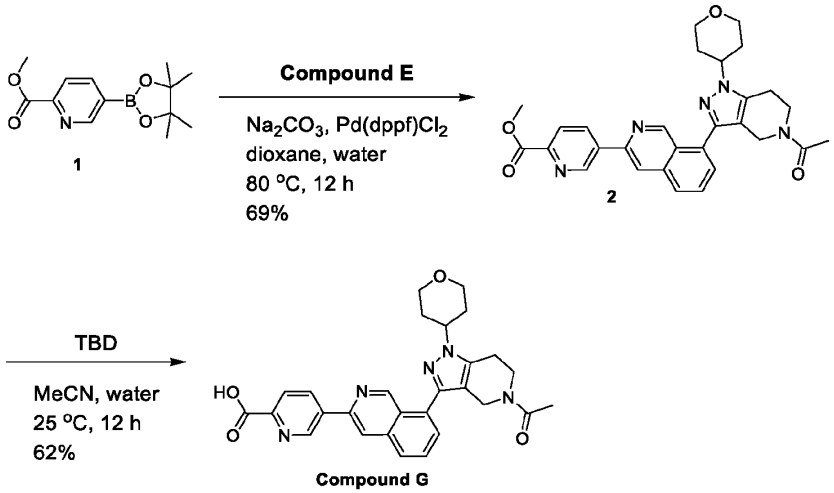
Compound D

[00409] **Compound E** was prepared according to the procedure described in WO 2017/205538 A1.



Compound E

[00410] **Compound G** was prepared according to the following procedure:

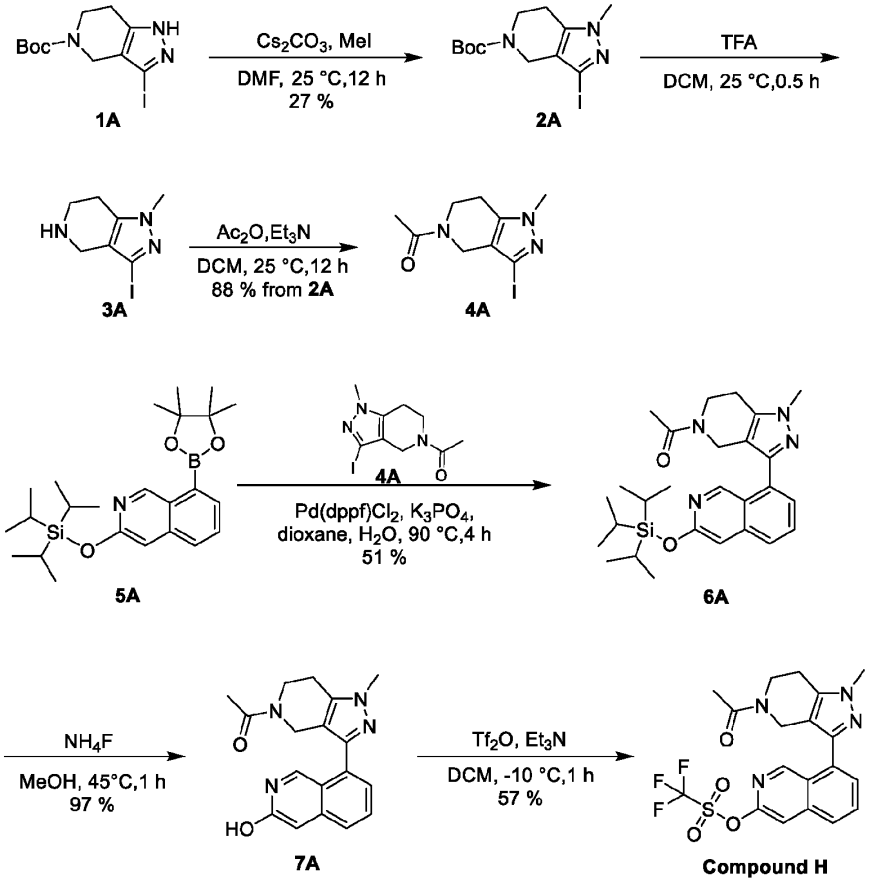


[00411] To a solution of methyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-2-carboxylate (0.15 g, 570.13 μmol, 1 eq) and Na_2CO_3 (120.86 mg, 1.14 mmol, 2 eq) and $Pd(dppf)Cl_2$ (41.72 mg, 57.01 μmol, 0.1 eq) in dioxane (5 mL) and H_2O (0.5 mL) was added [8-(5-acetyl-1-tetrahydropyran-4-yl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-3-yl)-3-isoquinolyl] trifluoromethanesulfonate (299 mg, 570 μmol, 1.0 eq). The mixture was stirred at 80 °C for 12 h. The mixture was poured into H_2O (100 mL) and extracted with ethyl acetate (100 mL × 2). The combined organics were washed with brine (200 mL × 2), dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuum. The residue was purified by column chromatography (silica, petroleum ether/ethyl acetate = 50/1 to 0/1, DCM/MeOH = 50/1 to 20/1). Compound methyl 5-[8-(5-acetyl-1-tetrahydropyran-4-yl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-3-yl)-3-

isoquinolyl]pyridine-2-carboxylate (0.20 g, 390.95 μmol, 68% yield) was obtained as a yellow solid. LC-MS: MS (ESI^+): t_R = 0.468 min, m/z = 512.2 [M + H^+]

[00412] To a solution of methyl 5-[8-(5-acetyl-1-tetrahydropyran-4-yl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-3-yl)-3-isoquinolyl]pyridine-2-carboxylate (0.20 g, 391 μmol, 1.0 eq) in MeCN (3 mL) and H_2O (1 mL) was added 3,4,6,7,8,9-hexahydro-2H-pyrimido[1,2-a]pyrimidine (109 mg, 782 μmol, 2.0 eq). The mixture was stirred at 25 °C for 12 h. The mixture was added 1 M HCl (0.10 mL) and extracted with DCM (100 mL × 2). The combined organic phase was washed with brine (100 mL × 2), dried with anhydrous sodium sulfate, filtered and concentrated in vacuum. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150*25mm* 10um;mobile phase: [water(HCl)-ACN];gradient:13%-43% B over 10 min). Compound 5-[8-(5-acetyl-1-tetrahydropyran-4-yl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-3-yl)-3-isoquinolyl]pyridine-2-carboxylic acid (0.12 g, 241 μmol, 62% yield) was obtained as a yellow solid. LC-MS: MS (ESI^+): t_R = 0.477 min, m/z = 498.3 [M + Na^+]

[00413] **Compound H** was prepared according to the following procedure:



[00414] Synthesis of **5A** was reported in WO2021/231174, 2021, A1.

[00415] A mixture of tert-butyl 3-iodo-1,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-5-carboxylate (15.0 g,

42.96 mmol, 1 eq) , Cs_2CO_3 (41.9 g, 128.88 mmol, 3.0 eq) in DMF (150 mL) was degassed and purged with N_2 for 3 times, and then added MeI (9.15 g, 64.44 mmol, 4.01 mL, 1.5 eq), the mixture was stirred at 25 °C for 1 2h under N_2. The reaction mixture was quenched by addition water 1000 mL, and then extracted with ethyl acetate (300 mL × 3). The combined organic layers were washed with brine (300 mL × 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=10/1 to 2/1). Compound tert-butyl 3-iodo-1-methyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridine-5-carboxylate (4.3 g, 11.84 mmol, 27 % yield) was obtained as a white solid.

[00416] **1H NMR** (400 MHz, DMSO-d_6): δ = 4.09 (s, 2H), 3.69 (s, 3H), 3.59 (t, J = 5.6 Hz, 2H), 2.64 (t, J = 5.6 Hz, 2H), 1.41 (s, 9H)

[00417] **LC-MS:** MS (ESI^+): t_R = 0.521 min, m/z = 364.1 [M + H^+]

[00418] To a solution of tert-butyl 3-iodo-1-methyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridine-5-carboxylate (4.30 g, 11.84 mmol, 1.0 eq) in DCM (20 mL) was added TFA (15.35 g, 134.62 mmol, 10 mL, 11.3 eq). The mixture was stirred at 25 °C for 0.5 h. The reaction mixture was concentrated in vacuo to give the crude product. Compound 3-iodo-1-methyl-4,5,6,7-tetrahydropyrazolo[4,3-c]pyridine (4.46 g) was obtained as a white solid and directly used in the next step without further purification.

[00419] **LC-MS:** MS (ESI^+): t_R = 0.218 min, m/z = 263.1 [M + H^+]

[00420] To a solution of 3-iodo-1-methyl-4,5,6,7-tetrahydropyrazolo[4,3-c]pyridine (4.46 g, 11.83 mmol, 1.0 eq) in DCM (40 mL) was added Et_3N (3.59 g, 35.48 mmol, 4.94 mL, 3.0 eq), Ac_2O (1.81 g, 17.74 mmol, 1.67 mL, 1.5 eq). The mixture was stirred at 25 °C for 12 h. The reaction mixture was concentrated in vacuo to give the crude product. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=10/1 to 0/1). Compound 1-(3-iodo-1-methyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl)ethanone (3.20 g, 10.49 mmol, 88 % yield over two steps) was obtained as a white solid.

[00421] **LC-MS:** MS (ESI^+): t_R = 0.378 min, m/z = 306.1 [M + H^+]

[00422] A mixture of 1-(3-iodo-1-methyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl)ethanone (3.00 g, 9.83 mmol, 1.0 eq), triisopropyl-[[8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-isoquinolyl]oxy]silane (7.00 g, 11.46 mmol, 1.1 eq), $Pd(dppf)Cl_2$ (359 mg, 491.62 μmol, 0.05 eq), K_3PO_4 (7.30 g, 34.41 mmol, 3.5 eq) and water (50 mL) in dioxane (80 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 90 °C for 4 h under N_2. The reaction mixture was quenched by addition water 500 mL, and then extracted with DCM (100 mL × 3). The combined organic layers were washed with brine (100 mL × 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, dichloromethane: methanol=100/1 to 20/1). Compound 1-[1-methyl-3-(3-triisopropylsilyloxy-8-isoquinolyl)-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]ethanone (2.43 g, 5.08 mmol, 51 % yield) was obtained as a white solid.

[00423] **LC-MS:** MS (ESI^+): t_R = 0.893 min, m/z = 479.3 [M + H^+]

[00424] To a solution of 1-[1-methyl-3-(3-triisopropylsilyloxy-8-isoquinolyl)-6,7-dihydro-4H-

pyrazolo[4,3-c]pyridin-5-yl]ethanone (2.43 g, 5.08 mmol, 1.0 eq) in MeOH (20 mL) was added NH_4F (1.88 g, 50.76 mmol, 10.0 eq). The mixture was stirred at 45 °C for 1 h. The reaction mixture was filtered and concentrated under reduced pressure to give a residue The residue was purified by column chromatography (SiO_2, dichloromethane : methanol=50/1 to 10/1). Compound 1-[3-(3-hydroxy-8-isoquinolyl)-1-methyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]ethanone (1.6 g, 4.96 mmol, 97 % yield) was obtained as a yellow solid.

[00425] **1H NMR** (400 MHz, DMSO-d_6): δ = 10.97 (br s, 1H), 9.44 - 9.21 (m, 1H), 7.70 - 7.63 (m, 1H), 7.63 - 7.55 (m, 1H), 7.28 - 7.17 (m, 1H), 6.90 (s, 1H), 4.48 (s, 2H), 3.89 - 3.72 (m, 5H), 2.92 - 2.71 (m, 2H), 2.14 - 1.94 (m, 3H)

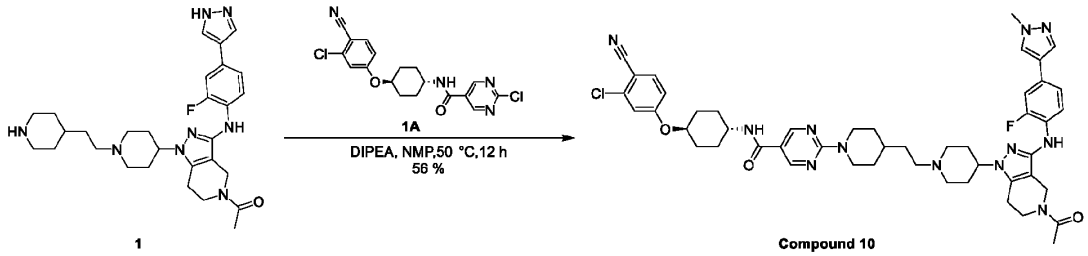
[00426] **LC-MS:** MS (ESI^+): t_R = 0.368 min, m/z = 323.2 [$M + H^+$]

[00427] To a solution of 1-[3-(3-hydroxy-8-isoquinolyl)-1-methyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]ethanone (1.60 g, 4.96 mmol, 1.0 eq) in DCM (20 mL) was added Et_3N (1.51 g, 14.89 mmol, 2.07 mL, 3.0 eq), and added Tf_2O (2.10 g, 7.45 mmol, 1.23 mL, 1.5 eq). The mixture was stirred at -10 °C for 1 h. The reaction mixture was quenched by addition water 200 mL, and then extracted with DCM (50 mL × 3). The combined organic layers were washed with brine (50 mL × 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, dichloromethane : methanol=50/1 to 10/1). Compound [8-(5-acetyl-1-methyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-3-yl)-3-isoquinolyl] trifluoromethanesulfonate (1.3 g, 2.86 mmol, 57 % yield) was obtained as a yellow solid.

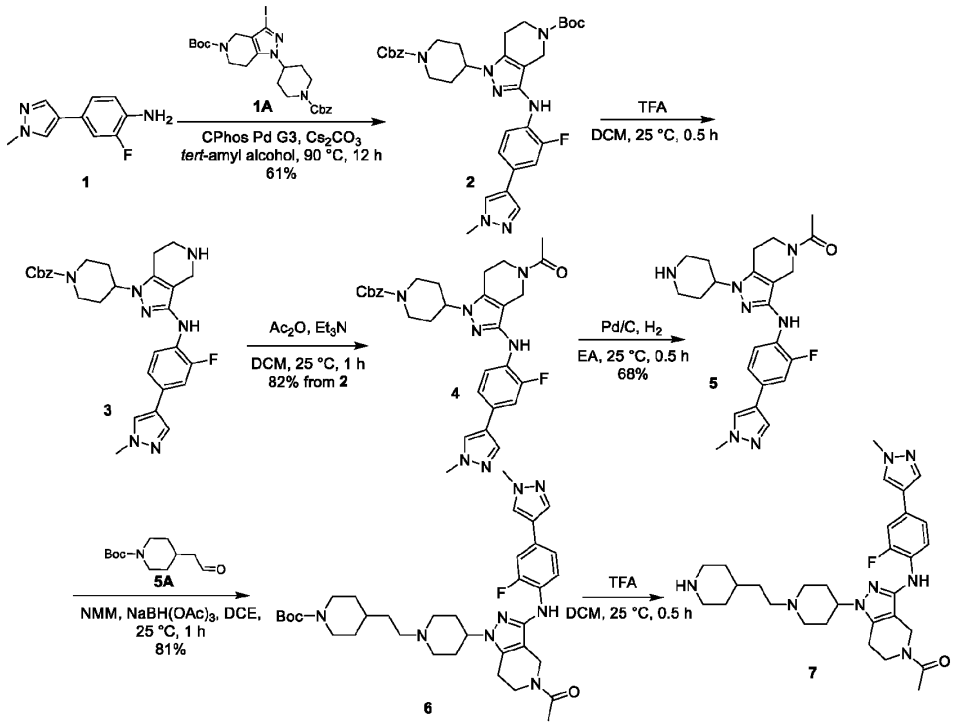
[00428] **1H NMR** (400 MHz, DMSO-d_6): δ = 9.82 - 9.76 (m, 1H), 8.21 (s, 1H), 8.14 (d, J = 8.4 Hz, 1H), 8.04 - 7.96 (m, 1H), 7.82 - 7.71 (m, 1H), 4.56 (s, 2H), 3.89 - 3.76 (m, 5H), 2.93 - 2.74 (m, 2H), 2.16 - 1.98 (m, 3H)

[00429] **LC-MS:** MS (ESI^+): t_R = 0.521 min, m/z = 455.2 [$M + H^+$]

[00430] **Example 1**: Synthesis of 2-[4-[2-[4-[5-acetyl-3-[2-fluoro-4-(1-methylpyrazol-4-yl)anilino]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]ethyl]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyrimidine-5-carboxamide (**Compound 10**)



[00431] Synthesis of **1**:



[00432] To a solution of 2-fluoro-4-(1-methylpyrazol-4-yl)aniline (500 mg, 2.6 mmol, 1.0 eq)、Cs_2CO_3 (1.70 g, 5.2 mmol, 2.0 eq) and tert-butyl 1-(1-benzyloxycarbonyl-4-piperidyl)-3-iodo-6,7-dihydro-4H-pyrazolo[4,3-c]pyridine-5-carboxylate (1.48 g, 1.6 mmol, 1.0 eq) in 2-methylbutan-2-ol (20 mL) was added Cphos Pd G_3 (105 mg, 130 μmol, 0.05 eq). The mixture was stirred at 90 °C for 12 h under nitrogen atomsphere. The mixture was filtered and washed with ethyl acetate (200 mL), dried with anhydrous sodium sulfate and concentrated in vacuum. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate=50/1 to 3/1). Compound tert-butyl 1-(1-benzyloxycarbonyl-4-piperidyl)-3-[2-fluoro-4-(1-methylpyrazol-4-yl)anilino]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridine-5-carboxylate (1.00 g, 1.6 mmol, 61% yield) was obtained as a yellow solid.

[00433] To a solution of tert-butyl 1-(1-benzyloxycarbonyl-4-piperidyl)-3-[2-fluoro-4-(1-methylpyrazol-4-yl)anilino]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridine-5-carboxylate (1.00 g, 1.5 mmol, 1.0 eq) in DCM (10 mL) was added TFA (10 mL, 85.0 *eq*). The mixture was stirred at 25 °C for 0.5 h. The mixture was concentrated in vacuum. Compound benzyl 4-[3-[2-fluoro-4-(1-methylpyrazol-4-yl)anilino]-4,5,6,7-tetrahydropyrazolo[4,3-c]pyridin-1-yl]piperidine-1-carboxylate (800 mg) was obtained as a yellow oil and directly used in the next step without further purification.

[00434] To a solution of benzyl 4-[3-[2-fluoro-4-(1-methylpyrazol-4-yl)anilino]-4,5,6,7-tetrahydropyrazolo[4,3-c]pyridin-1-yl]piperidine-1-carboxylate (800 mg, 1.5 mmol, 1.0 eq) and Et_3N (458 mg, 4.5 mmol, 630 uL, 3.0 eq) in DCM (10 mL) was added Ac_2O (154 mg, 1.5 mmol, 141 μL, 1.0 eq). The mixture was stirred at 25 °C for 1 h under nitrogen atmosphere. The mixture was poured into water (100 mL) and extracted with dichloromethane (100 mL × 2). The combined organic phase was washed with brine

(200 mL × 2), dried with anhydrous sodium sulfate, filtered and concentrated in vacuum. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate=50/1 to 1/2). Compound benzyl 4-[5-acetyl-3-[2-fluoro-4-(1-methylpyrazol-4-yl)anilino]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]piperidine-1-carboxylate (707 mg, 1.2 mmol, 82% yield over two steps) was obtained as a yellow solid.

[00435] To a solution of benzyl 4-[5-acetyl-3-[2-fluoro-4-(1-methylpyrazol-4-yl)anilino]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]piperidine-1-carboxylate (707 mg, 1.2 mmol, 1.0 eq) in ethyl acetate (10 mL) was added Pd/C (141 mg, 132 umol, 10% purity) under N_2 atmosphere. The suspension was degassed and purged with H_2 for 3 times. The mixture was stirred at 25 °C for 12 h under H_2 atmosphere. The mixture was filtered and washed with dichloromethane/methanol (10/1, 200 mL), concentrated in vacuum. The residue was purified by prep-HPLC (SiO_2, column: YMC-Actus Triart C18 150*30mm*7um;mobile phase: [water(FA)-ACN];gradient:18%-48% B over 10 min). Compound 1-[3-[2-fluoro-4-(1-methylpyrazol-4-yl)anilino]-1-(4-piperidyl)-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]ethanone (370 mg, 845 umol, 68% yield) was obtained as a yellow solid.

[00436] To a solution of 1-[3-[2-fluoro-4-(1-methylpyrazol-4-yl)anilino]-1-(4-piperidyl)-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]ethanone (200 mg, 457 μmol, 1.0 eq)、NMM (138 mg, 1.3 mmol, 150 μL, 3.0 eq) and tert-butyl 4-(2-oxoethyl)piperidine-1-carboxylate (103 mg, 457 μmol, 1.0 eq) in DCE (2 mL), stirred for 0.5 h. The mixture was added $NaBH(OAc)_3$ (193 mg, 914 μmol, 2.0 eq), stirred at 25 °C for 0.5 h. The mixture was poured into water (100 mL) and extracted with dichloromethane (100 mL × 2). The combined organic phase was washed with brine (100 mL × 2), dried with anhydrous sodium sulfate, filtered and concentrated in vacuum. The residue was purified by prep-TLC(SiO_2, dichloromethane/methanol=10/1). Compound tert-butyl 4-[2-[4-[5-acetyl-3-[2-fluoro-4-(1-methylpyrazol-4-yl)anilino]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]ethyl]piperidine-1-carboxylate (240 mg, 369 μmol, 81% yield) was obtained as a white solid.

[00437] To a solution of tert-butyl 4-[2-[4-[5-acetyl-3-[2-fluoro-4-(1-methylpyrazol-4-yl)anilino]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]ethyl]piperidine-1-carboxylate (120 mg, 184 μmol, 1.0 eq) in DCM (2 mL) was added TFA (451 mg, 3.9 mmol, 293 μL, 21.0 *eq*). The mixture was stirred at 25 °C for 0.5 h. The mixture was concentrated in vacuum. Compound 1-[3-[2-fluoro-4-(1-methylpyrazol-4-yl)anilino]-1-[1-[2-(4-piperidyl)ethyl]-4-piperidyl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]ethanone (100 mg) was obtained as a yellow oil and directly used in the next step without further purification.

[00438] Synthesis of **Compound 10**:

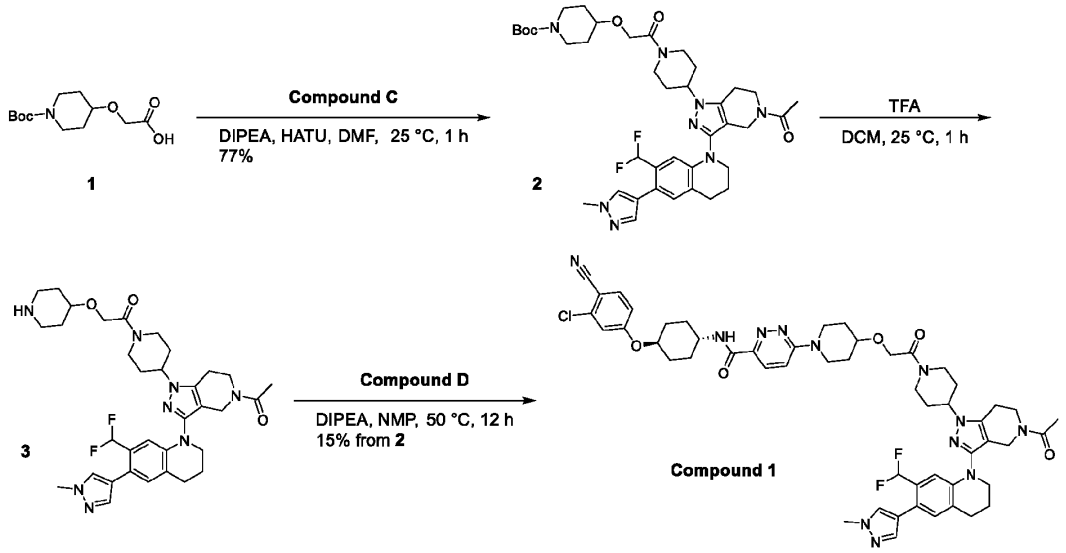
[00439] To a solution of 1-[3-[2-fluoro-4-(1-methylpyrazol-4-yl)anilino]-1-[1-[2-(4-piperidyl)ethyl]-4-piperidyl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]ethanone (122 mg, 184.09 μmol, 1.0 eq), 2-chloro-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyrimidine-5-carboxamide (72 mg, 184.09 μmol, 1.0 eq) in NMP (2 mL) was added DIPEA (443 mg, 3.43 mmol, 598.04 μL, 18.6 eq). The mixture was stirred at 50 °C for 12 h. The reaction mixture was quenched by addition water 30 mL, and then extracted with ethyl acetate (30 mL × 3). The combined organic layers were washed with brine (30 mL × 3), dried over Na_2SO_4, filtered and

concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (FA condition;column: Welch Xtimate C18 150*25mm*5um;mobile phase: [water(FA)-ACN];gradient:28%-48% B over 10 min). Compound 2-[4-[2-[4-[5-acetyl-3-[2-fluoro-4-(1-methylpyrazol-4-yl)anilino]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]ethyl]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyrimidine-5-carboxamide (93.79 mg, 103.63 μmol, 56% yield) was obtained as a white solid.

[00440] **^{1}H NMR** (400 MHz, CHLOROFORM-*d*): δ = 8.66 (s, 2H), 8.50 (s, 1H), 7.78 - 7.48 (m, 4H), 7.19 - 7.07 (m, 2H), 6.98 (d, J = 2.4 Hz, 1H), 6.83 (dd, J = 2.4, 8.8 Hz, 1H), 5.97 (br dd, J = 8.0, 12.4 Hz, 1H), 5.82 (dd, J = 2.8, 10.0 Hz, 1H), 4.82 (br d, J = 13.2 Hz, 2H), 4.46 (s, 1H), 4.33 - 4.23 (m, 2H), 4.07 - 3.88 (m, 5H), 3.74 (br t, J = 5.6 Hz, 1H), 3.28 - 3.13 (m, 2H), 2.91 (br t, J = 12.0 Hz, 2H), 2.77 (br t, J = 5.2 Hz, 1H), 2.70 (br t, J = 5.6 Hz, 1H), 2.62 - 2.53 (m, 3H), 2.41 - 2.24 (m, 4H), 2.22 - 2.12 (m, 7H), 2.08 - 1.95 (m, 2H), 1.80 (br d, J = 11.6 Hz, 2H), 1.72 - 1.51 (m, 5H), 1.49 - 1.36 (m, 2H), 1.26 - 1.13 (m, 2H)

[00441] **LC-MS:** MS (ESI$^+$): t_R = 2.178 min, m/z = 903.5 [M + H$^+$].

[00442] **Example 2**: Synthesis of 6-[4-[2-[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]-2-oxo-ethoxy]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide (**Compound 1**)



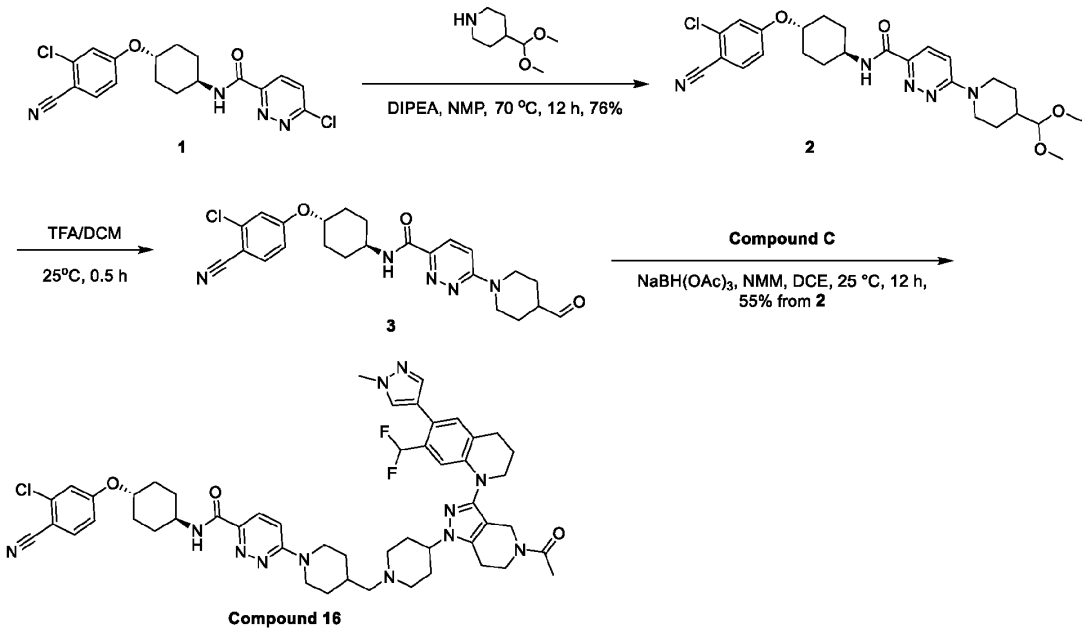
[00443] **1** was prepared according to the procedure described in WO2017/89390 A1. To a solution of 2-[(1-tert-butoxycarbonyl-4-piperidyl)oxy]acetic acid (38.2 mg, 147 μmol, 1.0 eq), 1-[3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-1-(4-piperidyl)-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]ethanone (75.0 mg, 147.2 μmol, 1.0 eq), DIPEA (57.1 mg, 442 μmol, 80 μL, 3.0 eq) in DMF (2 mL) was added HATU (67.2 mg, 177 μmol, 1.2 eq) and stirred at 25 °C for 1 h. The residue was diluted with H_2O (20 mL) and extracted with ethyl acetate (10 mL × 3). The residue was purified by prep-TLC (SiO_2, DCM: MeOH = 10:1). Compound tert-butyl 4-[2-[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-

methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]-2-oxo-ethoxy]piperidine-1-carboxylate (85.0 mg, 113 μmol, 77% yield) was obtained as a white solid. LC-MS: MS (ESI^+): t_R = 0.586 min, m/z = 751.7 [M + H^+]

[00444] To a solution of tert-butyl 4-[2-[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]-2-oxo-ethoxy]piperidine-1-carboxylate (85.0 mg, 113 μmol, 1.0 eq) in DCM (2 mL) was added TFA (1.54 g, 13.5 mmol, 1 mL, 119 eq) and stirred at 25 °C for 1 h. The reaction mixture was concentrated under reduced pressure to give a residue. Compound 1-[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]-2-(4-piperidyloxy)ethanone (86 mg) as a white solid was directly used into the next step without further purification. LC-MS: MS (ESI^+): t_R = 0.488 min, m/z = 651.6 [M + H^+]

[00445] To a solution of 1-[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]-2-(4-piperidyloxy)ethanone (86.0 mg), 6-chloro-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide (46.3 mg, 118 μmol, 1.1 eq) in NMP (0.5 mL) was added DIPEA (41.7 mg, 323 μmol, 56.2 μL, 3.0 eq) .The mixture was stirred at 50 °C for 12 h. The reaction mixture was quenched by addition water 10 mL and extracted with DCM (20 mL × 3). The orange phase was washed with brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a residue. The residue was purified by reversed-phase HPLC (column: Phenomenex luna C18 150× 25mm× 10um; mobile phase: [water (FA)-ACN]; gradient: 47%-77% B over 10 min). Compound 6-[4-[2-[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]-2-oxo-ethoxy]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide (**Compound 1**, 15.9 mg, 15.6 μmol, 15% yield over two steps) was obtained as a yellow solid. LC-MS: MS (ESI^+): t_R = 2.863 min, m/z = 1005.4 [M + H+]. ^1H NMR (400 MHz, DMSO-d_6) δ = 8.67 - 8.50 (m, 1H), 7.85 (d, *J* = 8.4 Hz, 1H), 7.79 (d, *J* = 9.6 Hz, 1H), 7.74 (s, 1H), 7.49 (s, 1H), 7.39 (s, 1H), 7.34 (d, *J* = 9.2 Hz, 1H), 7.18 - 7.07 (m, 2H), 6.95 - 6.61 (m, 2H), 4.62 - 4.48 (m, 1H), 4.46 - 4.31 (m, 2H), 4.29 - 4.20 (m, 2H), 4.19 - 4.14 (m, 1H), 4.13 - 4.04 (m, 3H), 4.01 - 3.92 (m, 1H), 3.86 (s, 4H), 3.78 - 3.64 (m, 3H), 3.56 (br d, *J* = 5.6 Hz, 2H), 3.44 - 3.38 (m, 2H), 3.24 - 3.11 (m, 1H), 2.90 - 2.69 (m, 5H), 2.16 - 2.04 (m, 4H), 2.01 - 1.84 (m, 10H), 1.83 - 1.73 (m, 1H), 1.70 - 1.58 (m, 2H), 1.57 - 1.42 (m, 4H)

[00446] **Example 3**: Synthesis of 6-[4-[[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]methyl]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide **(Compound 16)**



1 2 3

Compound 16

[00447] To a solution of 6-chloro-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide (150 mg, 383.39 μmol, 1.0 eq) in NMP (3 mL) was added DIPEA (396 mg, 3.07 mmol, 534.23 μL, 8.0 eq) and 4-(dimethoxymethyl)piperidine (73 mg, 460.06 μmol, 1.2 eq). The mixture was stirred at 70 °C for 12 h. The mixture was poured into water (50 mL). The aqueous phase was extracted with ethyl acetate (30 mL × 2). The combined organic phase was washed with brine (50 mL × 3), dried with anhydrous sodium sulfate, filtered, and concentrated in vacuum. The residue was purified by prep-TLC (SiO_2, Petroleum ether: Ethyl acetate=1: 1). Compound N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]-6-[4-(dimethoxymethyl)-1-piperidyl]pyridazine-3-carboxamide (150 mg, 291.82 μmol, 76% yield) was obtained as a yellow solid.

[00448] **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.96 (d, J = 9.6 Hz, 1H), 7.88 (d, J = 8.4 Hz, 1H), 7.56 (d, J = 8.8 Hz, 1H), 7.02 - 6.94 (m, 2H), 6.86 (dd, J = 2.4, 8.8 Hz, 1H), 4.53 (d, J = 13.2 Hz, 2H), 4.38 - 4.27 (m, 1H), 4.11 - 3.99 (m, 2H), 3.38 (s, 6H), 3.04 - 2.97 (m, 2H), 2.38 (t, J = 8.0 Hz, 3H), 2.18 (t, J = 9.6 Hz, 4H), 1.70 - 1.64 (m, 2H), 1.50 - 1.33 (m, 4H)

[00449] **LC-MS:** MS (ESI^+): t_R = 0.533 min, m/z = 514.3 [M + H^+]

[00450] To a solution of N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]-6-[4-(dimethoxymethyl)-1-piperidyl]pyridazine-3-carboxamide (150 mg, 291.82 μmol, 1.0 eq) in DCM (5 mL) was added TFA (7.68 g, 67.31 mmol, 5.00 mL, 230.67 eq). The mixture was stirred at 25 °C for 0.5 h. The reaction mixture was concentrated under reduced pressure to give the product. Compound N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]-6-(4-formyl-1-piperidyl)pyridazine-3-carboxamide (130 mg) was obtained as a yellow oil and directly used in the next step without further purification.

[00451] **LC-MS:** MS (ESI^+): t_R = 0.509 min, m/z = 468.3 [M + H^+]

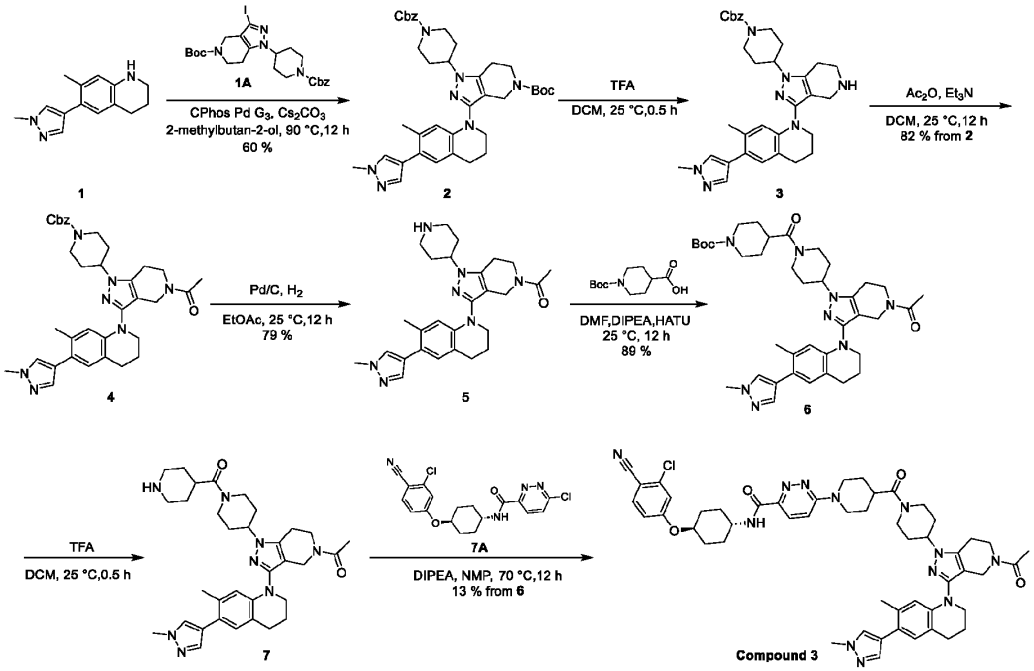
[00452] To a solution of N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]-6-(4-formyl-1-piperidyl)pyridazine-3-carboxamide (130 mg, 277.81 μmol, 1.5 eq) in DCE (5 mL) was added NMM (298

mg, 2.95 mmol, 323.93 μL, 16.37 eq) and 1-[3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-1-(4-piperidyl)-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]ethanone (100 mg, 179.98 μmol, 1.0 eq, FA) .$NaBH(OAc)_3$ (114 mg, 539.94 μmol, 3.0 eq) was added and the mixture was stirred at 25 °C for 12 h. The mixture was poured into water (50 mL). The aqueous phase was extracted with ethyl acetate (30 mL × 2). The combined organic phase was washed with brine (50 mL × 3), dried with anhydrous sodium sulfate, filtered and concentrated in vacuum. The residue was purified by prep-TLC (SiO_2, Dichloromethane: Methanol=15: 1). The residue was purified by prep-HPLC (column: Phenomenex luna C18 150*25mm* 10um; mobile phase: [water (FA) - ACN]; gradient: 25% - 55% B over 1 min) to give desired compound. Then it was lyophilized. Compound 6-[4-[[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]methyl]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide (96.74 mg, 99.30 μmol, 55% yield over two steps) was obtained as a white solid.

[00453] **1H NMR** (400 MHz, $CDCl_3$) δ = 8.31 - 8.28 (m, 1H), 7.97 (d, J = 9.6 Hz, 1H), 7.88 (d, J = 8.0 Hz, 1H), 7.59 - 7.52 (m, 2H), 7.41 (d, J = 6.4 Hz, 1H), 7.07 - 6.96 (m, 3H), 6.91 - 6.84 (m, 2H), 6.69 - 6.37 (m, 1H), 4.50 (d, J = 13.2 Hz, 2H), 4.40 - 4.21 (m, 2H), 4.15 - 4.05 (m, 2H), 3.98 - 3.89 (m, 5H), 3.79 - 3.67 (m, 3H), 3.15 - 3.00 (m, 4H), 2.88 (td, J = 5.6, 11.0 Hz, 2H), 2.81 (t, J = 5.6 Hz, 1H), 2.75 (t, J = 5.6 Hz, 1H), 2.28 (d, J = 12.4 Hz, 4H), 2.24 - 2.11 (m, 7H), 2.06 (s, 2H), 1.96 (d, *J* = 13.2 Hz, 4H), 1.76 - 1.62 (m, 5H), 1.53 - 1.43 (m, 2H), 1.32 - 1.21 (m, 2H)

[00454] **LC-MS:** MS (ESI^+): t_R = 2.172 min, m/z = 961.5 [$M + H^+$]

[00455] **Example 4**: Synthesis of 6-[4-[4-[5-acetyl-3-[7-methyl-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]piperidine-1-carbonyl]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide (**Compound 3**)



[00456] A mixture of 7-methyl-6-(1-methylpyrazol-4-yl)-1,2,3,4-tetrahydroquinoline (450 mg, 1.98 mmol, 1 eq) , tert-butyl 1-(1-benzyloxycarbonyl-4-piperidyl)-3-iodo-6,7-dihydro-4H-pyrazolo[4,3-c]pyridine-5-carboxylate (1.12 g, 1.98 mmol, 1.0 eq), Cphos Pd G_3 (159 mg, 197.97 μmol, 0.1 eq), Cs_2CO_3 (1.94 g, 5.94 mmol, 3.0 eq) in 2-methylbutan-2-ol (15 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 90 °C for 12 h under N_2. The reaction mixture was concentrated in vacuo to give the crude product. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=10/1 to 0/1). Compound tert-butyl 1-(1-benzyloxycarbonyl-4-piperidyl)-3-[7-methyl-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridine-5-carboxylate (800 mg, 1.20 mmol, 60 % yield) was obtained as a white solid.

[00457] **LC-MS:** MS (ESI^+): t_R = 0.634 min, m/z = 666.5 [M + H^+]

[00458] To a solution of tert-butyl 1-(1-benzyloxycarbonyl-4-piperidyl)-3-[7-methyl-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridine-5-carboxylate (800 mg, 1.20 mmol, 1.0 eq) in DCM (10 mL) was added TFA (1.64 g, 14.36 mmol, 1.07 mL, 11.9 eq). The mixture was stirred at 25 °C for 0.5 h. The reaction mixture was concentrated in vacuo to give the crude product. Compound benzyl 4-[3-[7-methyl-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-4,5,6,7-tetrahydropyrazolo[4,3-c]pyridin-1-yl]piperidine-1-carboxylate (816 mg) was obtained as a white solid and directly used in the next step without further purification.

[00459] **LC-MS:** MS (ESI^+): t_R = 0.481 min, m/z = 566.5 [M + H^+]

[00460] To a solution of benzyl 4-[3-[7-methyl-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-4,5,6,7-tetrahydropyrazolo[4,3-c]pyridin-1-yl]piperidine-1-carboxylate (816 mg, 1.20 mmol, 1.0 eq) in DCM (10 mL) was added Et3N (364 mg, 3.60 mmol, 501.27 μL, 3.0 eq), Ac_2O (183 mg, 1.80 mmol, 169.12

μL, 1.5 eq). The mixture was stirred at 0-25 °C for 12 h. The reaction mixture was concentrated in vacuo to give the crude product. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=10/1 to 0/1). Compound benzyl 4-[5-acetyl-3-[7-methyl-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]piperidine-1-carboxylate (600 mg, 987.26 μmol, 82 % yield over two steps) was obtained as a white solid.

[00461] **LC-MS:** MS (ESI^+): t_R = 0.548 min, m/z = 608.5 [M + H^+]

[00462] To a solution of benzyl 4-[5-acetyl-3-[7-methyl-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]piperidine-1-carboxylate (600 mg, 987.26 μmol, 1.0 eq) in ethyl acetate (10 mL) was added palladium on carbon (300 mg, 281.90 μmol, 0.3 eq) under N_2. The suspension was degassed and purged with H_2 for 3 times. The mixture was stirred under H_2 (15 Psi) at 25 °C for 12 h. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (FA condition;column: Phenomenex luna C18 150*25mm* 10um;mobile phase: [water(HCl)-ACN];gradient:10%-40% B over 10 min). Compound 1-[3-[7-methyl-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-1-(4-piperidyl)-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]ethanone (400 mg, 784.20 μmol, 79 % yield) was obtained as a white solid.

[00463] **LC-MS:** MS (ESI^+): t_R = 0.414 min, m/z = 474.4 [M + H^+]

[00464] To a solution of 1-[3-[7-methyl-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-1-(4-piperidyl)-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]ethanone (100 mg, 196.05 μmol, 1.0 eq) in DMF (3 mL) was added DIPEA (76 mg, 588.15 μmol, 102.44 μL, 3.0 eq), 1-tert-butoxycarbonylpiperidine-4-carboxylic acid (44 mg, 196.05 μmol, 1.0 eq) and HATU (149 mg, 392.10 μmol, 2.0 eq). The mixture was stirred at 25 °C for 12 h. The reaction mixture was quenched by addition water 50 mL, and then extracted with DCM (20 mL × 3). The combined organic layers were washed with brine (30 mL × 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, DCM: MeOH = 20:1). Compound tert-butyl 4-[4-[5-acetyl-3-[7-methyl-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]piperidine-1-carbonyl]piperidine-1-carboxylate (120 mg, 175.22 μmol, 89 % yield) was obtained as a white solid.

[00465] **LC-MS:** MS (ESI^+): t_R = 0.537 min, m/z = 685.5 [M + H^+]

[00466] To a solution of tert-butyl 4-[4-[5-acetyl-3-[7-methyl-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]piperidine-1-carbonyl]piperidine-1-carboxylate (120 mg, 175.22 μmol, 1.0 eq) in DCM (2 mL) was added TFA (767 mg, 6.73 mmol, 0.5 mL, 38.4 eq). The mixture was stirred at 25 °C for 0.5 h. The reaction mixture was concentrated in vacuo to give the crude product. Compound 1-[3-[7-methyl-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-1-[1-(piperidine-4-carbonyl)-4-piperidyl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]ethanone (122 mg) was obtained as a white solid and directly used in the next step without further purification.

[00467] **LC-MS:** MS (ESI^+): t_R = 0.417 min, m/z = 585.5 [M + H^+]

[00468] To a solution of 1-[3-[7-methyl-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-1-[1-(piperidine-4-carbonyl)-4-piperidyl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]ethanone (122 mg, 174.59

μmol, 1.0 eq), 6-chloro-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide (68 mg, 174.59 μmol, 1.0 eq) in NMP (2 mL) was added DIPEA (371 mg, 2.87 mmol, 0.5 mL, 16.4 eq). The mixture was stirred at 70 °C for 12 h. The reaction mixture was quenched by addition water 50 mL, and then extracted with ethyl acetate (20 mL × 3). The combined organic layers were washed with brine (30 mL × 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (FA condition; column: Welch Xtimate C18 150*25mm*5um;mobile phase: [water(FA)-ACN];gradient:45%-75% B over 10 min).

[00469] Compound 6-[4-[4-[5-acetyl-3-[7-methyl-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]piperidine-1-carbonyl]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide (22.89 mg, 23.89 μmol, 13 % yield over two steps) was obtained as a white solid.

[00470] **1H NMR** (400 MHz, CHLOROFORM-d): δ = 8.00 (d, J = 9.6 Hz, 1H), 7.87 (d, J = 8.0 Hz, 1H), 7.62 - 7.47 (m, 2H), 7.42 - 7.34 (m, 1H), 7.07 - 6.92 (m, 3H), 6.86 (dd, J = 2.4, 8.8 Hz, 1H), 6.37 (s, 1H), 4.75 (br dd, J = 2.8, 13.2 Hz, 1H), 4.60 - 4.44 (m, 2H), 4.40 - 4.23 (m, 2H), 4.19 - 4.11 (m, 3H), 4.09 - 4.01 (m, 1H), 3.97 - 3.90 (m, 4H), 3.84 - 3.55 (m, 3H), 3.34 - 3.12 (m, 3H), 2.94 - 2.71 (m, 6H), 2.33 - 2.12 (m, 10H), 2.11 - 2.01 (m, 6H), 1.99 - 1.85 (m, 5H), 1.68 (br s, 1H), 1.53 - 1.44 (m, 2H).

[00471] **LC-MS:** MS (ESI^+): t_R = 2.736 min, m/z = 470.4 [M / 2]

[00472] The compounds below were prepared in a similar manner as described in Example 4.

Compound	Name	^1H NMR ($CDCl_3$)	LC-MS [M + H^+]
11	2-[4-[[4-[5-acetyl-3-[6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]methyl]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyrimidine-5-carboxamide	δ = 8.66 (s, 2H), 7.69 - 7.62 (m, 1H), 7.57 (d, J = 8.8 Hz, 1H), 7.51 - 7.44 (m, 1H), 7.19 - 6.96 (m, 3H), 6.89 - 6.81 (m, 1H), 6.51 (d, J = 8.4 Hz, 1H), 5.66 (d, J = 8.0 Hz, 1H), 4.90 - 4.78 (m, 2H), 4.35 - 4.24 (m, 2H), 4.11 (s, 2H), 3.95 - 3.87 (m, 5H), 3.77 - 3.62 (m, 3H), 3.06 - 2.69 (m, 8H), 2.34 - 2.14 (m, 9H), 2.13 - 2.00 (m, 6H), 1.93 - 1.76 (m, 5H), 1.46 - 1.33 (m, 3H), 1.28 - 1.06 (m, 3H)	911.6
12	4-[4-[2-[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]-2-oxo-ethoxy]-1-piperidyl]-N-[4-(3-chloro-4-cyano-N-methyl-anilino)cyclohexyl]benzamide	(DMSO-d6) δ = 8.21 (s, 1H), 7.93 (d, *J* = 7.6 Hz, 1H), 7.77 - 7.67 (m, 3H), 7.59 (d, *J* = 9.2Hz, 1H), 7.49 (s, 1H), 7.09 (s, 1H), 6.95 - 6.88 (m, 3H), 6.85 - 6.80 (m, 1H), 6.80 - 6.62 (m, 2H), 4.47 - 4.29 (m, 2H), 4.27 - 4.08 (m, 4H), 4.00 - 3.92 (m, 1H), 3.85 (s, 3H), 3.82 - 3.66 (m, 4H), 3.62 - 3.53 (m, 5H), 3.20 - 3.13 (m, 1H), 2.98 (br t, *J* = 10.4 Hz, 2H), 2.89 - 2.73 (m, 8H), 2.07 (s, 2H), 1.94 (br d, *J* = 14.4 Hz, 10H), 1.82 - 1.62 (m, 5H), 1.60 - 1.47 (m, 4H)	1016.6
13	4-[4-[2-[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-	δ = 7.66 (d, 2H, J=8.8 Hz), 7.53 (d, 1H, J=6.0 Hz), 7.4-7.5 (m, 2H), 7.0-	1000.5

Compound	Name	^{1}H NMR ($CDCl_3$)	LC-MS [M + H$^+$]
	4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]-2-oxo-ethyl]-1-piperidyl]-N-[4-(3-chloro-4-cyano-N-methyl-anilino)cyclohexyl]benzamide	7.1 (m, 1H), 6.9-7.0 (m, 3H), 6.73 (d, 1H, J=2.4 Hz), 6.4-6.7 (m, 2H), 5.89 (dd, 1H, J=4.2, 7.6 Hz), 4.7-4.8 (m, 1H), 4.1-4.3 (m, 3H), 3.96 (d, 3H, J=2.4 Hz), 3.7-3.9 (m, 3H), 3.6-3.7 (m, 3H), 3.20 (t, 1H, J=12.4 Hz), 2.7-2.9 (m, 10H), 2.32 (d, 2H, J=6.4 Hz), 2.25 (d, 2H, J=11.2 Hz), 2.18 (s, 2H), 2.0-2.1 (m, 8H), 1.7-1.9 (m, 8H), 1.3-1.5 (m, 5H)	
14	6-[4-[2-[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]-2-oxo-ethyl]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	δ=7.97 (d, *J*=9.60 Hz, 1 H) 7.87 (d, *J*=8.00 Hz, 1 H) 7.57 (d, *J*=8.40 Hz, 1 H) 7.51 - 7.55 (m, 1 H) 7.35 - 7.45 (m, 1 H) 7.06 (s, 1 H) 7.01 (s, 1 H) 6.98 (d, *J*=9.60 Hz, 1 H) 6.84 - 6.90 (m, 2 H) 6.37 - 6.69 (m, 1 H) 4.71 - 4.84 (m, 1 H) 4.45 - 4.59 (m, 2 H) 4.31 - 4.39 (m, 1 H) 4.29 (br s, 1 H) 4.13 (s, 2 H) 4.00 - 4.09 (m, 2 H) 3.96 (d, *J*=2.00 Hz, 3 H) 3.90 (br t, *J*=6.40 Hz, 1 H) 3.73 - 3.81 (m, 1 H) 3.65 - 3.73 (m, 2 H) 3.20 (br t, *J*=12.00 Hz, 1 H) 3.09 (br t, *J*=12.40 Hz, 2 H) 2.84 - 2.96 (m, 2 H) 2.70 - 2.83 (m, 3 H) 2.29 - 2.36 (m, 2 H) 2.13 - 2.25 (m, 7 H) 2.09 (br d, *J*=5.60 Hz, 2 H) 2.06 (s, 2 H) 2.03 (br d, *J*=4.80 Hz, 1 H) 1.96 (br d, *J*=13.20 Hz, 3 H) 1.69 (br d, *J*=12.00 Hz, 2 H) 1.62 - 1.66 (m, 1 H) 1.46 (br d, *J*=12.00 Hz, 2 H) 1.25 - 1.37 (m, 2 H).	989.5
17	2-[4-[[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]methyl]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyrimidine-5-carboxamide	δ = 8.66 (s, 2H), 7.60 - 7.51 (m, 2H), 7.41 (d, J = 6.4 Hz, 1H), 7.05 (d, J = 17.6 Hz, 1H), 7.01 - 6.89 (m, 2H), 6.83 – 6.86 (m, 1H), 6.39 - 6.69 (m, 1H), 6.11 - 5.86 (m, 1H), 4.85 (d, J = 12.4 Hz, 2H), 4.40 - 4.27 (m, 2H), 4.26 - 4.10 (m, 2H), 4.00 – 4.08 (m, 1H), 3.96 (d, J = 1.6 Hz, 3H), 3.91 (t, J = 5.6 Hz, 1H), 3.80 - 3.73 (m, 1H), 3.65 – 3.71 (m, 2H), 3.54 - 3.23 (m, 2H), 3.00 - 2.78 (m, 6H), 2.78 - 2.51 (m, 3H), 2.31 - 2.13 (m, 8H), 2.12 - 1.95 (m, 7H), 1.70 - 1.58 (m, 4H), 1.52 - 1.43 (m, 2H), 1.23 (d, J = 1.2 Hz, 2H)	961.6
18	6-[4-[[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]methyl]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridine-3-carboxamide	δ = 8.52 (d, J = 2.4 Hz, 1H), 7.92 - 7.80 (m, 1H), 7.62 - 7.47 (m, 2H), 7.41 (d, J = 6.4 Hz, 1H), 7.10 - 6.95 (m, 2H), 6.93 - 6.80 (m, 2H), 6.73 - 6.32 (m, 2H), 5.87 - 5.68 (m, 1H), 4.48 - 4.36 (m, 2H), 4.35 - 4.23 (m, 2H), 4.18 - 4.00 (m, 2H), 3.99 - 3.85 (m, 5H), 3.80 - 3.61 (m, 3H), 3.06 -	960.6

Compound	Name	^{1}H NMR ($CDCl_3$)	LC-MS [M + H$^+$]
		2.72 (m, 8H), 2.31 - 2.13 (m, 9H), 2.13 - 2.02 (m, 5H), 1.96 - 1.83 (m, 3H), 1.76 - 1.61 (m, 4H), 1.49 - 1.35 (m, 3H), 1.29 - 1.10 (m, 2H)	
61	6-[4-[4-[5-acetyl-3-(6-cyano-3,4-dihydro-2H-quinolin-1-yl)-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]piperidine-1-carbonyl]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	(DMSO-d_6) δ = 8.59 (d, *J* = 8.4 Hz, 1H), 7.93 - 7.76 (m, 2H), 7.44 - 7.35 (m, 3H), 7.34 - 7.25 (m, 1H), 7.20 - 7.09 (m, 1H), 6.49 - 6.34 (m, 1H), 4.60 - 4.32 (m, 5H), 4.23 - 4.07 (m, 3H), 3.91 - 3.74 (m, 2H), 3.73 - 3.68 (m, 1H), 3.63 - 3.58 (m, 2H), 3.28 - 3.03 (m, 4H), 2.90 - 2.66 (m, 5H), 2.15 - 2.06 (m, 4H), 2.01 - 1.85 (m, 8H), 1.77 - 1.45 (m, 9H).	870.4
62	6-[4-[4-[5-acetyl-3-[7-(difluoromethyl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]piperidine-1-carbonyl]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	(DMSO-d6) δ = 8.60 (d, *J* = 8.0 Hz, 1H), 7.88 - 7.79 (m, 2H), 7.41 - 7.33 (m, 2H), 7.16 - 7.09 (m, 2H), 6.98 - 6.60 (m, 3H), 4.61 - 4.44 (m, 4H), 4.41 - 4.28 (m, 1H), 4.23 - 4.05 (m, 3H), 3.94 - 3.80 (m, 1H), 3.79 - 3.67 (m, 2H), 3.60 - 3.53 (m, 2H), 3.29 - 3.19 (m, 1H), 3.18 - 3.03 (m, 3H), 2.90 - 2.85 (m, 1H), 2.82 (br t, *J* = 5.6 Hz, 2H), 2.78 - 2.72 (m, 1H), 2.16 - 2.06 (m, 4H), 1.98 - 1.85 (m, 8H), 1.80 - 1.44 (m, 10H)	895.5
66	rac-6-(4-((4-(5-acetyl-3-(6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydro-1,7-naphthyridin-1(2H)-yl)-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridin-1-yl)piperidin-1-yl)methyl)piperidin-1-yl)-N-((1r,4r)-4-(3-chloro-4-cyanophenoxy)cyclohexyl)pyridazine-3-carboxamide	(DMSO-d_6) δ = 8.58 (br d, J = 8.4 Hz, 1H), 8.14 (s, 1H), 8.03 (s, 1H), 7.85 (d, J = 8.8 Hz, 1H), 7.82-7.65 (m, 3H), 7.39 (d, J = 2.4 Hz, 1H), 7.32 (br d, J = 9.6 Hz, 1H), 7.29 (s, 1H), 7.13 (dd, J = 8.9, 2.4 Hz, 1H), 4.60-4.40 (m, 3H), 4.25-4.13 (m, 2H), 4.07-3.95 (m, 1H), 3.84 (s, 3H), 3.78-3.65 (m, 2H), 3.61-3.50 (m, 2H), 3.07-2.89 (m, 4H), 2.86-2.75 (m, 3H), 2.73-2.64 (m, 1H), 2.19 (br d, J = 6.4 Hz, 2H), 2.15-1.99 (m, 8H), 1.97-1.91 (m, 2H), 1.91-1.75 (m, 7H), 1.63 (br d, J = 13.2 Hz, 2H), 1.56-1.45 (m, 2H), 1.16-1.04 ppm (m, 2H).	912.6
67	6-[4-[4-[5-acetyl-3-[6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-1,7-naphthyridin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]piperidine-1-carbonyl]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	(DMSO-d_6) δ = 8.59 (d, J = 8.0Hz, 1H), 8.23-8.06 (m, 1H), 7.94-7.83 (m, 2H), 7.82-7.72 (m, 2H), 7.39 (d, J = 2.4 Hz, 1H), 7.34 (d, J = 10 Hz, 1H), 7.13 (dd, J = 8.9, 2.4 Hz, 1H), 4.61-4.43 (m, 4H), 4.36 (br d, J = 4.4 Hz, 1H), 4.30-4.09 (m, 3H), 3.87 (s, 3H), 3.82-3.67 (m, 2H), 3.66-3.51 (m, 2H), 3.16-3.04 (m, 3H), 2.88 (br s, 3H), 2.81-2.65 (m, 2H), 2.11 (br s, 1H), 2.09 (s, 3H), 2.03-1.95 (m, 4H), 1.95-	926.4

Compound	Name	^{1}H NMR ($CDCl_3$)	LC-MS [M + H$^+$]
		1.85 (m, 4H), 1.80-1.64 (m, 4H), 1.64-1.41 ppm (m, 6H).	
77	6-[4-[[3-[5-acetyl-3-(6-cyano-3,4-dihydro-2H-quinolin-1-yl)-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]cyclobutyl]methyl]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	(DMSO-d_6): δ = 8.60 (br d, J = 8.4 Hz, 1H), 7.86 (d, J = 8.8 Hz, 1H), 7.79 (d, J = 9.2 Hz, 1H), 7.46 - 7.37 (m, 2H), 7.36 - 7.27 (m, 2H), 7.17 - 7.07 (m, 1H), 6.52 - 6.39 (m, 1H), 4.92 - 4.77 (m, 1H), 4.62 - 4.41 (m, 3H), 4.19 - 4.06 (m, 2H), 3.92 - 3.79 (m, 1H), 3.76 - 3.57 (m, 4H), 2.97 (br t, J = 12.4 Hz, 2H), 2.86 - 2.56 (m, 6H), 2.47 - 2.36 (m, 1H), 2.16 - 2.05 (m, 6H), 2.02 - 1.93 (m, 3H), 1.89 (br d, J = 10.4 Hz, 2H), 1.74 (br d, J = 12.4 Hz, 2H), 1.69 - 1.44 (m, 7H), 1.21 - 1.05 (m, 2H)	820.6
94	6-[4-[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]but-1-ynyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	δ = 8.24 (d, J = 8.8 Hz, 1H), 8.09 (d, J = 8.4 Hz, 1H), 7.68 (d, J = 8.8 Hz, 1H), 7.60 - 7.52 (m, 2H), 7.44 - 7.37 (m, 1H), 7.07 - 6.99 (m, 2H), 6.91 - 6.83 (m, 2H), 6.70 - 6.35 (m, 1H), 4.40 - 4.30 (m, 1H), 4.25 (s, 1H), 4.16 - 4.09 (m, 2H), 4.02 - 3.93 (m, 4H), 3.92 (d, J = 5.6 Hz, 1H), 3.80 - 3.67 (m, 3H), 3.14 (s, 2H), 2.90 - 2.73 (m, 8H), 2.30 (t, J = 7.6 Hz, 4H), 2.26 - 2.18 (m, 4H), 2.11 - 2.07 (m, 1H), 2.00 - 1.91 (m, 2H), 1.79 - 1.65 (m, 6H), 1.60 - 1.52 (m, 2H)	916.6
100	6-[4-[[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]methyl]-4-methyl-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	(DMSO-d6) δ = 8.58 (d, J = 8.4 Hz, 1H), 7.85 (d, J = 8.8 Hz, 1H), 7.81 - 7.73 (m, 2H), 7.49 (s, 1H), 7.39 (d, J = 2.4 Hz, 1H), 7.32 (d, J = 9.6 Hz, 1H), 7.16 - 7.06 (m, 2H), 6.95 - 6.62 (m, 2H), 4.61 - 4.44 (m, 1H), 4.20 - 4.08 (m, 2H), 4.06 - 3.94 (m, 3H), 3.86 (s, 3H), 3.77 - 3.65 (m, 2H), 3.62 - 3.54 (m, 2H), 3.42 (br t, J = 10.4 Hz, 2H), 2.83 (br s, 5H), 2.72 (br s, 1H), 2.41 (br t, J = 11.2 Hz, 2H), 2.23 (br s, 2H), 2.14 - 1.83 (m, 12H), 1.81 - 1.73 (m, 2H), 1.66 - 1.57 (m, 2H), 1.56 - 1.45 (m, 4H), 1.41 - 1.30 (m, 2H), 1.00 (s, 3H)	975.6
102	6-[4-[[4-[5-acetyl-3-(6-cyano-3,4-dihydro-2H-quinolin-1-yl)-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]methyl]-4-methyl-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	δ = 7.97 (d, J = 9.6 Hz, 1H), 7.87 (br d, J = 8.4 Hz, 1H), 7.57 (d, J = 8.8 Hz, 1H), 7.27 - 7.13 (m, 2H), 7.01 (d, J = 2.4 Hz, 1H), 6.97 (d, J = 9.6 Hz, 1H), 6.86 (dd, J = 2.4, 8.8 Hz, 1H), 6.41 (dd, J = 3.6, 8.4 Hz, 1H), 4.29 (s, 2H), 4.17 - 4.00 (m, 4H), 3.91 (s, 2H), 3.75 (br t, J = 5.6 Hz, 1H), 3.67 (td, J = 5.6, 12.0 Hz, 2H), 3.49 - 3.32 (m, 2H),	870.5

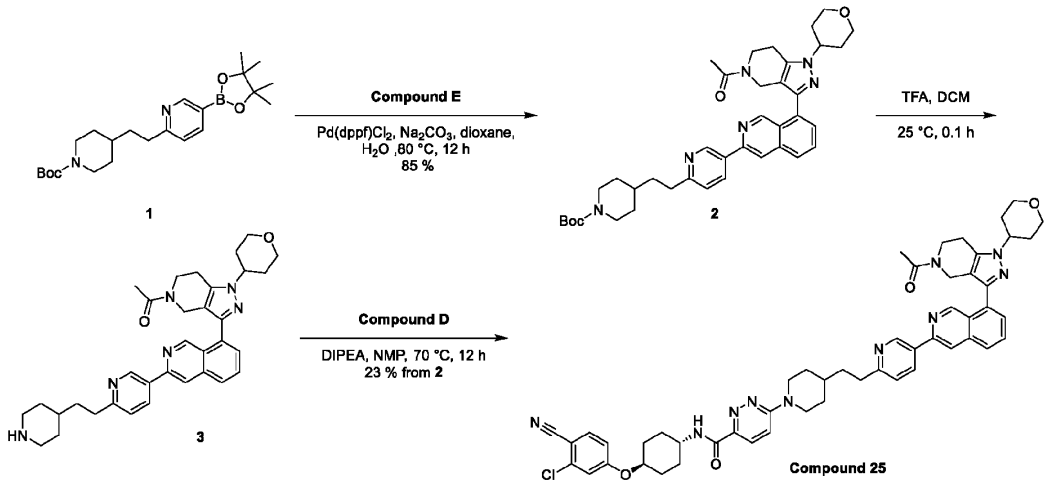
Compound	Name	^{1}H NMR ($CDCl_3$)	LC-MS [M + H$^+$]
		3.04 - 2.87 (m, 2H), 2.87 - 2.78 (m, 3H), 2.73 (br t, J = 5.6 Hz, 1H), 2.45 (br s, 2H), 2.25 (br s, 3H), 2.22 - 2.12 (m, 6H), 2.12 - 1.98 (m, 4H), 1.85 - 1.76 (m, 2H), 1.75 - 1.58 (m, 5H), 1.54 - 1.39 (m, 4H), 1.05 (br s, 2H)	
106	6-[4-[[4-[5-acetyl-3-(3,4-dihydro-2H-1,7-naphthyridin-1-yl)-6,7-dihydro-4Hpyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]methyl]-1-piperidyl]-N-[4-(4-chloro-3-cyanophenoxy)cyclohexyl]pyridazine-3-carboxamide	δ = 8.33 - 8.11 (m, 1H), 7.97 (d, J = 10.0 Hz, 1H), 7.94 - 7.76 (m, 2H), 7.56 (d, J = 8.8 Hz, 1H), 7.30 (d, J = 5.2 Hz, 1H), 7.05 - 6.92 (m, 2H), 6.90 - 6.81 (m, 1H), 4.51 (d, J = 13.6 Hz, 2H), 4.43 (s, 1H), 4.42 - 4.30 (m, 2H), 4.25 (s, 1H), 4.12 - 3.98 (m, 1H), 3.97 - 3.76 (m, 2H), 3.75 - 3.61 (m, 2H), 3.47 (d, J = 4.8 Hz, 2H), 3.28 - 3.13 (m, 1H), 3.08 - 2.96 (m, 4H), 2.93 - 2.68 (m, 4H), 2.35 (s, 4H), 2.20 (s, 5H), 2.17 - 2.05 (m, 5H), 2.00 (d, J = 12 Hz, 2H), 1.75 - 1.62 (m, 2H), 1.60 - 1.43 (m, 2H), 1.43 - 1.19 (m, 3H).	920.6
107	6-[4-[[4-[5-acetyl-3-(6-methyl-3,4-dihydro-2H-1,7-naphthyridin-1-yl)-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]methyl]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	1.17 - 1.31 (m, 2 H) 1.40 - 1.52 (m, 2 H) 1.63 - 1.75 (m, 2 H) 1.81 - 1.97 (m, 5 H) 1.99 - 2.10 (m, 3 H) 2.11 - 2.23 (m, 8 H) 2.25 - 2.28 (m, 2 H) 2.41 (s, 3 H) 2.72 (br t, J=5.63 Hz, 1 H) 2.77 - 2.88 (m, 3 H) 2.96 - 3.11 (m, 4 H) 3.62 - 3.69 (m, 2 H) 3.73 (br t, J=5.63 Hz, 1 H) 3.80 - 3.97 (m, 3 H) 4.01 - 4.09 (m, 1 H) 4.14 (s, 1 H) 4.27 - 4.37 (m, 2 H) 4.49 (br d, J=13.13 Hz, 2 H) 6.79 - 6.89 (m, 2 H) 6.94 - 7.04 (m, 2 H) 7.56 (d, J=8.76 Hz, 1 H) 7.79 (d, J=14.76 Hz, 1 H) 7.87 (d, J=8.25 Hz, 1 H) 7.96 (d, J=9.63 Hz, 1 H).	846.6
108	6-[4-[[4-[5-acetyl-3-(6-cyclopropyl-3,4-dihydro-2H-1,7-naphthyridin-1-yl)-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]methyl]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	δ = 8.39 (s, 1H), 7.96 (d, J = 9.2 Hz, 1H), 7.87 (d, J = 8.0 Hz, 1H), 7.74 (d, J = 12.4 Hz, 1H), 7.56 (d, J = 8.8 Hz, 1H), 7.04 - 6.93 (m, 2H), 6.85 (dd, J = 2.4, 8.8 Hz, 1H), 6.75 (d, J = 13.6 Hz, 1H), 4.49 (br d, J = 13.6 Hz, 2H), 4.39 - 4.25 (m, 2H), 4.15 - 3.98 (m, 2H), 3.97 - 3.82 (m, 2H), 3.72 (br t, J = 6.0 Hz, 1H), 3.68 - 3.58 (m, 2H), 3.03 (br t, J = 11.2 Hz, 4H), 2.88 - 2.63 (m, 4H), 2.34 - 2.14 (m, 11H), 2.13 - 2.01 (m, 4H), 2.00 - 1.80 (m, 6H), 1.77 - 1.59 (m, 2H), 1.54 - 1.37 (m, 2H), 1.32 - 1.15 (m, 2H), 1.00 - 0.76 (m, 4H).	872.6
109	6-[4-[[4-[5-acetyl-3-(6-methoxy-3,4-dihydro-2H-1,7-naphthyridin-1-yl)-6,7-dihydro-4H-pyrazolo[4,3-	*δ* = 7.96 (d, J = 9.6 Hz, 1H), 7.87 (d, J = 8.0 Hz, 1H), 7.56 (d, J = 8.8 Hz, 1H), 7.41 (s, 1H), 7.04 - 6.95 (m, 2H),	862.6

Compound	Name	^{1}H NMR ($CDCl_3$)	LC-MS [M + H$^+$]
	c]pyridin-1-yl]-1-piperidyl]methyl]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	6.86 (dd, J = 2.4, 8.8 Hz, 1H), 6.46 (d, J = 13.6 Hz, 1H), 4.50 (br d, J = 13.6 Hz, 2H), 4.38 - 4.26 (m, 2H), 4.13 - 4.02 (m, 2H), 3.91 - 3.80 (m, 5H), 3.75 - 3.58 (m, 3H), 3.10 - 2.96 (m, 4H), 2.84 - 2.68 (m, 4H), 2.30 - 2.14 (m, 10H), 2.10 - 2.00 (m, 5H), 1.97 - 1.82 (m, 5H), 1.76 - 1.63 (m, 2H), 1.52 - 1.40 (m, 2H), 1.31 - 1.17 (m, 2H)	
118	6-[6-[[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c] pyridin-1-yl]-1-piperidyl] methyl]-3-azabicyclo [3.1.1] heptan-3-yl]-N-[4-(3-chloro-4-cyano-phenoxy) cyclohexyl] pyridazine-3-carboxamide	(400 MHz, DMSO-d_6): δ = 8.60 (d, *J* = 8.4 Hz, 1H), 8.17 (s, 1H), 7.91 - 7.82 (m, 2H), 7.75 (s, 1H), 7.50 (s, 1H), 7.39 (d, *J* = 2.0 Hz, 1H), 7.17 - 7.04 (m, 3H), 6.95 - 6.63 (m, 2H), 4.61 - 4.47 (m, 1H), 4.21 - 4.08 (m, 2H), 4.07 - 3.95 (m, 1H), 3.93 - 3.80 (m, 5H), 3.79 - 3.64 (m, 4H), 3.58 (br s, 1H), 3.04 - 2.88 (m, 2H), 2.87 - 2.70 (m, 4H), 2.69 - 2.56 (m, 2H), 2.42 (br s, 1H), 2.28 (br d, *J* = 6.4 Hz, 1H), 2.11 (br s, 2H), 2.10 - 2.06 (m, 3H), 2.06 - 1.86 (m, 9H), 1.86 - 1.75 (m, 2H), 1.74 - 1.58 (m, 2H), 1.57 - 1.47 (m, 2H), 1.46 - 1.38 (m, 1H).	973.7
126	6-[3-[[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]methyl]-8-azabicyclo[3.2.1] octan-8-yl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	δ = 7.96 (d, J = 9.2 Hz, 1H), 7.89 (br d, J = 8.4 Hz, 1H), 7.61 - 7.51 (m, 2H), 7.41 (d, J = 6.8 Hz, 1H), 7.10 - 6.98 (m, 2H), 6.92 - 6.77 (m, 3H), 6.72 - 6.34 (m, 1H), 4.88 - 4.52 (m, 2H), 4.38 - 4.29 (m, 1H), 4.25 (s, 1H), 4.15 - 4.01 (m, 2H), 3.96 (s, 3H), 3.90 (br t, J = 5.2 Hz, 2H), 3.79 - 3.65 (m, 3H), 2.97 (br s, 2H), 2.91 - 2.84 (m, 2H), 2.82 - 2.69 (m, 2H), 2.27 - 2.03 (m, 18H), 1.95 - 1.83 (m, 4H), 1.78 - 1.61 (m, 4H), 1.57 - 1.34 (m, 4H)	987.6
139	4-[4-[[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c] pyridin-1-yl]-1-piperidyl] methyl]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy) cyclohexyl] benzamide	(DMSO-d_6): *δ* = 7.98 - 7.91 (m, 1H), 7.88 - 7.82 (m, 1H), 7.75 (s, 1H), 7.74 - 7.68 (m, 1H), 7.50 (s, 1H), 7.41 - 7.34 (m, 1H), 7.16 - 7.08 (m, 2H), 6.94 - 6.64 (m, 4H), 4.59 - 4.46 (m, 1H), 4.21 - 4.08 (m, 2H), 4.07 - 3.96 (m, 1H), 3.90 - 3.71 (m, 7H), 3.70 - 3.67 (m, 1H), 3.65 - 3.53 (m, 2H), 2.97 - 2.69 (m, 8H), 2.24 - 2.14 (m, 2H), 2.13 - 1.94 (m, 11H), 1.92 - 1.70 (m, 7H), 1.58 - 1.43 (m, 4H), 1.24 - 1.09 (m, 2H).	959.7
140	4-[4-[[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-	(DMSO-d_6) δ = 8.17 (s, 1H), 7.94 (m, 1H), 7.80 - 7.65 (m, 3H), 7.61 (m, 1H), 7.50 (s, 1H), 7.10 (s, 1H), 6.91 (m, 2H), 6.86 - 6.60 (m, 4H), 4.54 -	954.51

Compound	Name	^{1}H NMR ($CDCl_3$)	LC-MS [M + H$^+$]
	c]pyridin-1-yl]-1-piperidyl]methyl]-1-piperidyl]-N-[4-(4-cyano-3-methoxy-phenoxy)cyclohexyl]benzamide	4.39 (m, 1H), 4.20 - 4.09 (m, 2H), 4.01 (s, 1H), 3.91 - 3.78 (m, 9H), 3.75 - 3.67 (m, 2H), 3.62 - 3.56 (m, 2H), 2.94 (s, 2H), 2.88 - 2.69 (m, 6H), 2.19 (m, 2H), 2.14 - 1.94 (m, 10H), 1.94 - 1.64 (m, 8H), 1.50 (m, 4H), 1.16 (m, 2H).	
141	6-[4-[[(3R,4R)-4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-3-fluoro-1-piperidyl]methyl]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	(DMSO-d6) δ = 8.65 - 8.54 (m, 1H), 8.42 (s, 1H), 7.85 (d, *J* = 8.8 Hz, 1H), 7.82 - 7.74 (m, 2H), 7.51 (s, 1H), 7.39 (d, *J* = 2.4 Hz, 1H), 7.32 (br d, *J* = 10.0 Hz, 1H), 7.17 - 7.09 (m, 2H), 6.97 - 6.63 (m, 2H), 4.94 - 4.67 (m, 1H), 4.61 - 4.38 (m, 3H), 4.27 - 4.12 (m, 2H), 4.17 - 4.02 (m, 1H), 3.87 (s, 4H), 3.78 - 3.68 (m, 1H), 3.72 - 3.55 (m, 3H), 3.07 - 2.95 (m, 2H), 2.94 - 2.68 (m, 5H), 2.31 - 2.22 (m, 2H), 2.16 - 1.80 (m, 12H), 1.68 - 1.58 (m, 2H), 1.56 - 1.46 (m, 2H), 1.16 - 1.04 (m, 2H)	979.4
152	6-[4-[[(1R,5S)-3-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-8-azabicyclo[3.2.1]octan-8-yl]methyl]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	δ=8.00 (d, *J*=9.60 Hz, 1 H) 7.86 (br d, *J*=8.00 Hz, 1 H) 7.57 (d, *J*=8.80 Hz, 1 H) 7.53 (d, *J*=4.80 Hz, 1 H) 7.41 (d, *J*=5.20 Hz, 1 H) 7.05 (br d, *J*=19.60 Hz, 1 H) 7.01 (s, 1 H) 6.98 - 7.01 (m, 1 H) 6.82 - 6.92 (m, 2 H) 6.36 - 6.69 (m, 1 H) 4.56 (br d, *J*=13.20 Hz, 3 H) 4.27 - 4.38 (m, 2 H) 4.16 (s, 1 H) 4.03 - 4.10 (m, 1 H) 3.96 (s, 3 H) 3.89 (br t, *J*=5.60 Hz, 1 H) 3.74 (br t, *J*=5.60 Hz, 2 H) 3.61 - 3.71 (m, 3 H) 3.42 - 3.60 (m, 1 H) 3.14 (br t, *J*=12.00 Hz, 2 H) 2.83 - 2.94 (m, 2 H) 2.69 - 2.82 (m, 3 H) 2.40 - 2.68 (m, 3 H) 2.21 (br s, 4 H) 2.13 - 2.20 (m, 6 H) 2.10 (br d, *J*=5.20 Hz, 2 H) 1.96 - 2.08 (m, 4 H) 1.63 - 1.76 (m, 3 H) 1.38 - 1.54 (m, 4 H).	987.6
158	6-[4-[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]piperidine-1-carbonyl]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridine-3-carboxamide	(DMSO-d_6) δ = 8.62 - 8.55 (m, 1H), 8.12 - 8.04 (m, 1H), 8.00 - 7.90 (m, 1H), 7.90 - 7.80 (m, 1H), 7.79 - 7.72 (m, 1H), 7.49 (s, 1H), 7.42 - 7.36 (m, 1H), 7.17 - 7.08 (m, 2H), 6.95 - 6.65 (m, 3H), 4.59 - 4.45 (m, 2H), 4.40 - 4.29 (m, 3H), 4.24 - 4.06 (m, 3H), 3.86 (s, 3H), 3.83 - 3.65 (m, 3H), 3.63 - 3.53 (m, 2H), 3.28 - 3.18 (m, 1H), 3.10 - 2.95 (m, 3H), 2.90 - 2.80 (m, 3H), 2.78 - 2.65 (m, 2H), 2.20 - 2.05 (m, 4H), 2.04 - 1.85 (m, 8H), 1.80 - 1.64 (m, 3H), 1.57 - 1.45 (m, 6H)	974.4

Compound	Name	^{1}H NMR ($CDCl_3$)	LC-MS [M + H$^+$]
219	6-[4-[[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c] pyridin-1-yl]-1-piperidyl] methyl]-3-methoxy-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy) cyclohexyl] pyridazine-3-carboxamide	(DMSO-d6) δ = 8.59 (d, J = 8.4 Hz, 1H), 7.86 (d, J = 8.8 Hz, 1H), 7.81 - 7.73 (m, 2H), 7.51 (s, 1H), 7.40 (d, J = 2.4 Hz, 1H), 7.34 (d, J = 9.4 Hz, 1H), 7.17 - 7.10 (m, 2H), 6.96 - 6.64 (m, 2H), 4.90 - 4.77 (m, 1H), 4.60 - 4.47 (m, 2H), 4.20 - 4.11 (m, 2H), 4.09 - 3.98 (m, 1H), 3.92 - 3.83 (m, 4H), 3.78 - 3.67 (m, 2H), 3.63 - 3.55 (m, 2H), 3.23 (s, 3H), 3.08 - 2.88 (m, 5H), 2.88 - 2.72 (m, 4H), 2.24 - 1.95 (m, 14H), 1.93 - 1.83 (m, 4H), 1.70 - 1.59 (m, 2H), 1.56 - 1.41 (m, 4H)	991.6
220	6-[4-[[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]methyl]-3-methoxy-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	δ = 8.00 (d, J = 9.6 Hz, 1H), 7.86 (d, J = 8.4 Hz, 1H), 7.57 (d, J = 8.8 Hz, 1H), 7.54 (d, J = 5.2 Hz, 1H), 7.41 (d, J = 6.4 Hz, 1H), 7.06 - 6.97 (m, 3H), 6.92 - 6.83 (m, 2H), 6.69 - 6.37 (m, 1H), 4.73 (s, 1H), 4.36 - 4.29 (m, 1H), 4.28 - 4.12 (m, 2H), 4.11 - 4.02 (m, 2H), 3.96 (d, J = 2.0 Hz, 3H), 3.91 (t, J = 5.6 Hz, 2H), 3.79 - 3.66 (m, 3H), 3.46 (s, 3H), 3.18 (t, J = 12.0 Hz, 1H), 3.14 - 3.00 (m, 3H), 3.00 - 2.91 (m, 1H), 2.87 (td, J = 6.0, 11.6 Hz, 2H), 2.83 - 2.73 (m, 2H), 2.73 - 2.61 (m, 1H), 2.34 - 2.02 (m, 15H), 2.00 - 1.79 (m, 3H), 1.75 - 1.68 (m, 2H), 1.52 - 1.41 (m, 2H), 1.40 - 1.30 (m, 1H)	991.7

[00473] **Example 5**: Synthesis of 6-[4-[2-[5-[8-(5-acetyl-1-tetrahydropyran-4-yl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-3-yl)-3-isoquinolyl]-2-pyridyl]ethyl]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide **(Compound 25)**



[00474] Preparation of **1**:

[00475] To a solution of 9-BBN (0.5 M, 85.19 mL, 3.0 *eq*) was added tert-butyl 4-vinylpiperidine-1-carboxylate (3 g, 14.20 mmol, 1.0 *eq*),the mixture was stirred at 60 °C for 1 h.Then it was cooled to room temperture. 2,5-dibromopyridine (3.36 g, 14.20 mmol, 1.0 *eq*), Pd(dppf)Cl_2.CH_2Cl_2 (347 mg, 425.94 μmol, 0.03 *eq*), K_2CO_3 (7.85 g, 56.79 mmol, 4.0 *eq*), DMF (100 mL) and H_2O (10 mL) was added.The mixture was stirred at 60 °C for 12 h.The reaction mixture was quenched by addition ice water 100 mL, and then extracted with ethyl acetate (200 mL × 3). The combined organic layers were washed with brine (100 mL × 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue.The residue was purified by prep-HPLC (column: Phenomenex luna C18 150*40mm* 15um;mobile phase: [water(FA)-ACN];gradient:55%-85% B over 15 min). Compound tert-butyl 4-[2-(5-bromo-2-pyridyl)ethyl]piperidine-1-carboxylate (5.1 g, 13.81 mmol, 97% yield) was obtained as a yellow oil.

[00476] **LC-MS:** MS (ESI^+): t_R = 0.590 min, m/z = 315.5 [M + H^+]

[00477] To a solution of tert-butyl 4-[2-(5-bromo-2-pyridyl)ethyl]piperidine-1-carboxylate (900 mg, 2.44 mmol, 1 *eq*) in dioxane (10 mL) was added BPD (928 mg, 3.66 mmol, 1.5 *eq*), KOAc (717 mg, 7.31 mmol, 3.0 *eq*) and Pd(dppf)Cl_2 (53 mg, 73.11 μmol, 0.03 *eq*). The mixture was stirred at 80 °C for 12 h .The mixture was diluted with water (80 mL) and extracted with ethyl acetate (100 mL x 3). The combined organic layers were washed with brine (80 mL x 3), dried over anhydrous sodium sulfate, filtered and concentrated in vacuum.The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~90% Ethyl acetate/Petroleum ethergradient @ 80 mL/min).Compound tert-butyl 4-[2-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-pyridyl]ethyl]piperidine-1-carboxylate (300 mg, 720.53 μmol, 29% yield) was obtained as a yellow solid.

[00478] **LC-MS:** MS (ESI^+): t_R = 0.452 min, m/z = 335.3 [M - 82 + H^+]

[00479] Preparation of **Compound 25**:

[00480] To a solution of tert-butyl 4-[2-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-pyridyl]ethyl]piperidine-1-carboxylate (119 mg, 285.98 μmol, 1.5 *eq*) and [8-(5-acetyl-1-tetrahydropyran-4-yl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-3-yl)-3-isoquinolyl] trifluoromethanesulfonate (100 mg, 190.65 μmol, 1.0 *eq*) in dioxane (5 mL) and H_2O (0.5 mL) was added K_2CO_3 (79 mg, 571.96 μmol, 3.0 *eq*) and Pd(dppf)Cl_2 (13 mg, 19.07 μmol, 0.1 *eq*).The mixture was stirred at 80 °C for 12 h . The mixture was diluted with water (20 mL) and extracted with ethyl acetate (30 mL x 3). The combined organic layers were washed with brine (20 mL x 3), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuum. The residue was purified by prep-TLC (SiO_2, DCM: MeOH = 15:1). Compound tert-butyl 4-[2-[5-[8-(5-acetyl-1-tetrahydropyran-4-yl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-3-yl)-3-isoquinolyl]-2-pyridyl]ethyl]piperidine-1-carboxylate (108 mg, 162.45 μmol, 85% yield) was obtained as a yellow solid.

[00481] **LC-MS:** MS (ESI^+): t_R = 0.495 min, m/z = 665.4 [M + H^+]

[00482] To a solution of tert-butyl 4-[2-[5-[8-(5-acetyl-1-tetrahydropyran-4-yl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-3-yl)-3-isoquinolyl]-2-pyridyl]ethyl]piperidine-1-carboxylate (108 mg, 162.45 μmol, 1.0 *eq*) in DCM (3 mL) was added TFA (4.61 g, 40.39 mmol, 3 mL, 248.62 *eq*). The mixture was stirred

at 25 °C for 0.1 h. The mixture was concentrated in vacuo. Compound 1-[3-[3-[6-[2-(4-piperidyl)ethyl]-3-pyridyl]-8-isoquinolyl]-1-tetrahydropyran-4-yl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]ethanone (90 mg) was obtained as a yellow solid and directly used in the next step without further purification.

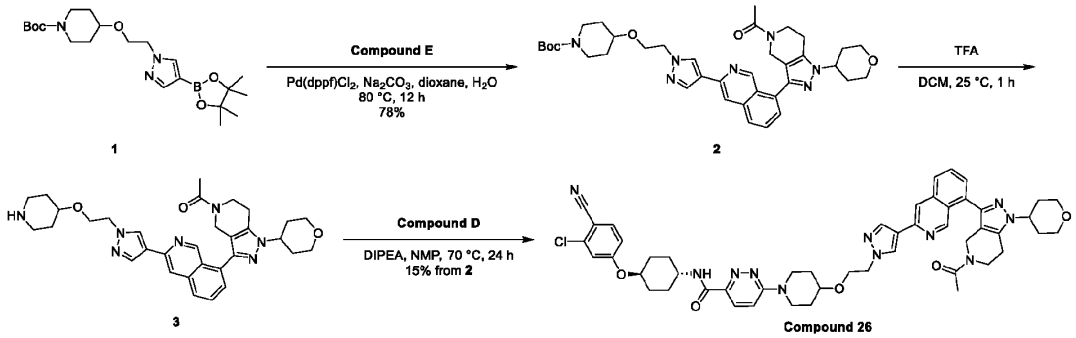
[00483] **LC-MS:** MS (ESI^+): t_R = 0.399 min, m/z = 565.3 [M + H^+]

[00484] To a solution of 1-[3-[3-[6-[2-(4-piperidyl)ethyl]-3-pyridyl]-8-isoquinolyl]-1-tetrahydropyran-4-yl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]ethanone (90 mg, 159.37 μmol, 1.0 *eq*) in NMP (3 mL) was added DIPEA (102 mg, 796.86 μmol, 138.80 μL, 5.0 *eq*) and 6-chloro-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide (62 mg, 159.37 μmol, 1.0 *eq*) .The mixture was stirred at 70 °C for 12 h . The mixture was diluted with water (20 mL) and extracted with ethyl acetate (30 mL x 3). The combined organic layers were washed with brine (20 mL x 3), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuum. The residue was purified by prep-HPLC (column: YMC-Actus Triart C18 150*30mm*7um;mobile phase: [water(FA)-ACN];gradient:35%-65% B over 10 min). Compound 6-[4-[2-[5-[8-(5-acetyl-1-tetrahydropyran-4-yl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-3-yl)-3-isoquinolyl]-2-pyridyl]ethyl]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide (34.01 mg, 36.95 μmol, 23% yield over two steps) was obtained as an off-white solid.

[00485] **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 9.85 (d, *J* = 6.3 Hz, 1H), 9.25 (br s, 1H), 8.40 (dt, *J* = 2.3, 7.9 Hz, 1H), 8.17 - 8.09 (m, 1H), 8.02 - 7.86 (m, 3H), 7.83 - 7.73 (m, 1H), 7.65 - 7.55 (m, 2H), 7.33 (dd, *J* = 4.8, 7.9 Hz, 1H), 7.05 - 6.95 (m, 2H), 6.88 (dd, *J* = 2.3, 8.8 Hz, 1H), 4.69 (s, 1H), 4.60 - 4.46 (m, 3H), 4.39 - 4.26 (m, 2H), 4.19 (br d, *J* = 11.6 Hz, 2H), 4.13 - 4.01 (m, 2H), 3.88 (br t, *J* = 5.7 Hz, 1H), 3.59 (br t, *J* = 12.1 Hz, 2H), 3.12 - 3.01 (m, 2H), 3.01 - 2.92 (m, 3H), 2.89 (br t, *J* = 5.6 Hz, 1H), 2.54 - 2.40 (m, 2H), 2.25 - 2.16 (m, 5H), 2.10 (s, 1H), 2.02 - 1.94 (m, 4H), 1.87 - 1.79 (m, 3H), 1.70 (br s, 2H), 1.53 - 1.45 (m, 2H), 1.42 - 1.27 (m, 3H)

[00486] **LC-MS:** MS (ESI^+): t_R=2.508 min, m/z=460.1 [M/2+H^+]

[00487] **Example 6**: Synthesis of 6-[4-[2-[4-[8-(5-acetyl-1-tetrahydropyran-4-yl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-3-yl)-3-isoquinolyl]pyrazol-1-yl]ethoxy]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide **(Compound 26)**



[00488] Preparation of **1**:

[00489] To a solution of tert-butyl 4-(2-methylsulfonyloxyethoxy)piperidine-1-carboxylate (800 mg, 2.47

mmol, 1.0 eq) in DMF (15 mL) was added K_2CO_3 (1.03 g, 7.42 mmol, 3.0 eq), 1,4,7,10,13,16-hexaoxacyclooctadecane (65 mg, 247.37 μmol, 0.1 eq) and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (480 mg, 2.47 mmol, 1.0 eq). The mixture was stirred at 80 °C for 12 h. The mixture was poured into water (100 mL). The aqueous phase was extracted with ethyl acetate (100 mL × 2). The combined organic phase was washed with brine (80 mL × 2), dried with anhydrous sodium sulfate, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (10% - 50% ethyl acetate in petroleum ether). Compound tert-butyl 4-[2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazol-1-yl]ethoxy]piperidine-1-carboxylate (670 mg, 1.59 mmol, 64% yield) was obtained as a colorless gum.

[00490] **LC-MS:** MS (ESI^+): t_R = 0.564 min, m/z = 422.3 [M + H^+]

[00491] Preparation of **Compound 26**:

[00492] A mixture of tert-butyl 4-[2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazol-1-yl]ethoxy]piperidine-1-carboxylate (120 mg, 285.98 μmol, 1.5 eq), [8-(5-acetyl-1-tetrahydropyran-4-yl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-3-yl)-3-isoquinolyl] trifluoromethanesulfonate (100 mg, 190.65 μmol, 1.0 eq), $Pd(dppf)Cl_2$ (14 mg, 19.07 μmol, 0.1 eq), Na_2CO_3 (61 mg, 571.96 μmol, 3.0 eq) and H_2O (0.4 mL) in dioxane (4 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 80 °C for 12 h under N_2 atmosphere. The mixture was concentrated in vacuum. The residue was purified by silica gel chromatography (0% - 10% methanol in dichloromethane). Compound tert-butyl 4-[2-[4-[8-(5-acetyl-1-tetrahydropyran-4-yl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-3-yl)-3-isoquinolyl]pyrazol-1-yl]ethoxy]piperidine-1-carboxylate (100 mg, 149.30 μmol, 78% yield) was obtained as a yellow gum.

[00493] **LC-MS:** MS (ESI^+): t_R = 0.485 min, m/z = 670.4 [M + H^+]

[00494] To a solution of tert-butyl 4-[2-[4-[8-(5-acetyl-1-tetrahydropyran-4-yl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-3-yl)-3-isoquinolyl]pyrazol-1-yl]ethoxy]piperidine-1-carboxylate (100 mg, 149.30 μmol, 1.0 eq) in DCM (3 mL) was added TFA (1.54 g, 13.46 mmol, 1 mL). The mixture was stirred at 25 °C for 1 h. The mixture was concentrated under reduced pressure. Compound 1-[3-[3-[1-[2-(4-piperidyloxy)ethyl]pyrazol-4-yl]-8-isoquinolyl]-1-tetrahydropyran-4-yl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]ethanone (100 mg) was obtained as a yellow gum and directly used in the next step without further purification.

[00495] **LC-MS:** MS (ESI^+): t_R = 0.388 min, m/z = 570.4 [M + H^+]

[00496] To a solution of 1-[3-[3-[1-[2-(4-piperidyloxy)ethyl]pyrazol-4-yl]-8-isoquinolyl]-1-tetrahydropyran-4-yl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]ethanone (100 mg) in NMP (2 mL) was added DIPEA (95 mg, 731.29 μmol, 127 μL, 5.0 eq) and 6-chloro-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide (57 mg, 146.26 μmol, 1.0 eq). The mixture was stirred at 70 °C for 24 h. The mixture was poured into water (30 mL). The aqueous phase was extracted with ethyl acetate (30 mL × 2). The combined organic phase was washed with brine (30 mL × 2), dried with anhydrous sodium sulfate, filtered, and concentrated in vacuum. The residue was purified by prep-Thin-layer chromatography (SiO_2, dichloromethane:methanol = 15:1) and further purified by prep-HPLC (column:

Welch Xtimate C18 150*25mm*5um; mobile phase: [water (FA)-ACN]; gradient: 33%-63% B over 10 min). Compound 6-[4-[2-[4-[8-(5-acetyl-1-tetrahydropyran-4-yl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-3-yl)-3-isoquinolyl]pyrazol-1-yl]ethoxy]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide (20.91 mg, 22.62 μmol, 15% yield over two steps) was obtained as a white solid.

[00497] **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 9.81 - 9.58 (m, 1H), 8.15 (br s, 1H), 8.11 (s, 1H), 7.91 (dd, J = 2.4, 9.6 Hz, 1H), 7.88 - 7.73 (m, 3H), 7.73 - 7.63 (m, 1H), 7.56 (d, J = 8.8 Hz, 1H), 7.54 - 7.43 (m, 1H), 7.01 (d, J = 2.4 Hz, 1H), 6.92 (dd, J = 4.0, 9.6 Hz, 1H), 6.86 (dd, J = 2.4, 8.8 Hz, 1H), 4.69 - 4.46 (m, 2H), 4.39 (br t, J = 4.8 Hz, 2H), 4.35 - 4.23 (m, 2H), 4.17 (br d, J = 12.0 Hz, 2H), 4.08 - 3.99 (m, 2H), 3.95 (t, J = 5.2 Hz, 2H), 3.93 - 3.77 (m, 3H), 3.65 - 3.49 (m, 5H), 2.97 - 2.82 (m, 2H), 2.52 - 2.37 (m, 2H), 2.24 - 2.06 (m, 7H), 1.96 (br d, J = 13.2 Hz, 2H), 1.92 - 1.84 (m, 2H), 1.75 - 1.68 (m, 4H), 1.50 - 1.39 (m, 2H).

[00498] **LC-MS:** MS (ESI^+): t_R = 2.459 min, m/z = 924.1 [$M + H^+$]

[00499] The compounds below were prepared in a similar manner as described in Example 6.

Compound	Name	^{1}H NMR ($CDCl_3$)	LC-MS [$M + H^+$]
7	6-[4-[[4-[8-(5-acetyl-1-methyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-3-yl)-3-isoquinolyl]pyrazol-1-yl]methyl]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	δ = 9.77 - 9.59 (m, 1H), 8.10 (d, *J* = 1.7 Hz, 2H), 7.96 - 7.99 (m, 1H), 7.91 - 7.77 (m, 3H), 7.73 (t, *J* = 7.2 Hz, 1H), 7.60 - 7.48 (m, 2H), 7.04 - 6.95 (m, 2H), 6.84 - 6.87 (m, 1H), 4.63 (s, 1H), 4.55 (d, *J* = 13.2 Hz, 2H), 4.46 (s, 1H), 4.36 - 4.27 (m, 1H), 4.11 (d, *J* = 7.2 Hz, 2H), 4.09 - 3.98 (m, 2H), 3.90 (d, *J* = 3.2 Hz, 3H), 3.84 (t, *J* = 6.0 Hz, 1H), 3.04 (t, *J* = 11.6 Hz, 2H), 2.94 - 2.79 (m, 2H), 2.47 - 2.30 (m, 1H), 2.23 - 2.15 (m, 5H), 2.06 (s, 1H), 1.85 (s, 1H), 1.72 - 1.64 (m, 4H), 1.51 - 1.37 (m, 4H)	824.4
8	6-[4-[2-[4-[8-(5-acetyl-1-methyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-3-yl)-3-isoquinolyl]pyrazol-1-yl]ethyl]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	δ = 9.79 - 9.62 (m, 1H), 8.19 - 8.05 (m, 2H), 8.00 - 7.93 (m, 1H), 7.91 - 7.77 (m, 3H), 7.76 - 7.67 (m, 1H), 7.60 - 7.47 (m, 2H), 7.03 - 6.93 (m, 2H), 6.84 - 6.87 (m, 1H), 4.63 (s, 1H), 4.55 - 4.41 (m, 3H), 4.38 - 4.23 (m, 3H), 4.10 - 3.98 (m, 2H), 3.90 (d, J = 3.6 Hz, 3H), 3.84 (t, J = 5.6 Hz, 1H), 3.02 (t, J = 12.0 Hz, 2H), 2.89 (t, J = 5.6 Hz, 1H), 2.83 (t, J = 5.6 Hz, 1H), 2.24 - 2.11 (m, 6H), 2.06 (s, 2H), 1.94 - 1.86 (m, 4H), 1.69 (d, J = 11.6 Hz, 2H), 1.52 - 1.42 (m, 2H), 1.39 - 1.28 (m, 2H).	838.4
19	6-[4-[[5-[8-(5-acetyl-1-methyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-3-yl)-3-isoquinolyl]-2-pyridyl]methyl]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-	δ = 9.79 (d, J = 9.6 Hz, 1H), 9.29 (s, 1H), 8.42 (br d, J = 4.8 Hz, 1H), 8.13 (d, J = 10.4 Hz, 1H), 8.00 - 7.84 (m, 3H), 7.78 (td, J = 8.8, 12.0 Hz, 1H), 7.64 - 7.54 (m, 2H), 7.31 - 7.27 (m, 1H), 7.04 - 6.93 (m, 2H), 6.86 (dd, J = 2.4, 8.8 Hz,	835.5

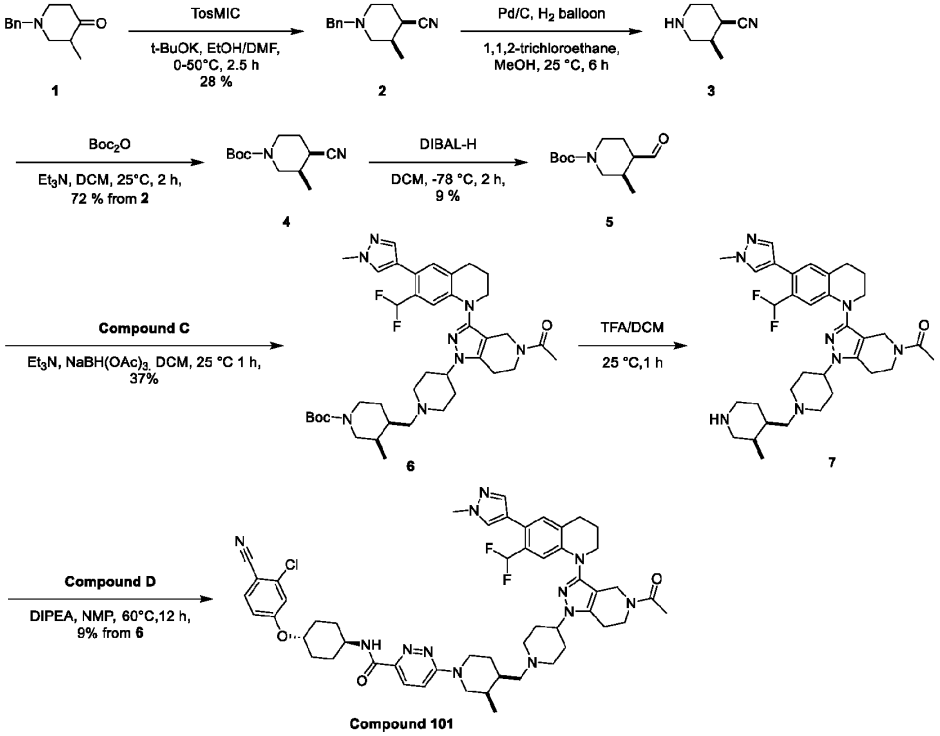
Compound	Name	^{1}H NMR ($CDCl_3$)	LC-MS [M + H$^+$]
	3-carboxamide	1H), 4.64 (s, 1H), 4.57 - 4.45 (m, 3H), 4.38 - 4.27 (m, 1H), 4.11 - 3.99 (m, 2H), 3.92 (d, J = 3.2 Hz, 3H), 3.85 (t, J = 5.6 Hz, 1H), 3.04 (br t, J = 11.2 Hz, 2H), 2.95 - 2.79 (m, 4H), 2.23 - 2.06 (m, 7H), 1.87 (br d, J = 12.0 Hz, 2H), 1.70 - 1.64 (m, 3H), 1.52 - 1.39 (m, 4H).	
20	6-[4-[2-[5-[8-(5-acetyl-1-methyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-3-yl)-3-isoquinolyl]-2-pyridyl]ethyl]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	δ = 9.80 (d, *J* = 11.0 Hz, 1H), 9.28 (s, 1H), 8.53 - 8.37 (m, 1H), 8.13 (d, *J* = 10.0 Hz, 1H), 8.02 - 7.85 (m, 3H), 7.79 (td, *J* = 7.7, 11.3 Hz, 1H), 7.66 - 7.55 (m, 2H), 7.40 - 7.32 (m, 1H), 7.05 - 6.96 (m, 2H), 6.88 (dd, *J* = 2.4, 8.8 Hz, 1H), 4.65 (s, 1H), 4.60 - 4.45 (m, 3H), 4.41 - 4.29 (m, 1H), 4.15 - 4.00 (m, 2H), 3.93 (d, *J* = 3.3 Hz, 3H), 3.87 (t, *J* = 5.8 Hz, 1H), 3.11 - 2.95 (m, 4H), 2.94 - 2.83 (m, 2H), 2.32 - 2.12 (m, 6H), 2.08 (s, 1H), 1.98 (br d, *J* = 12.0 Hz, 2H), 1.87 - 1.80 (m, 2H), 1.71 (br d, *J* = 12.6 Hz, 3H), 1.53 - 1.46 (m, 2H), 1.40 - 1.31 (m, 2H)	849.7
21	6-[4-[[5-[8-(5-acetyl-1-methyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-3-yl)-3-isoquinolyl]-2-pyridyl]methoxymethyl]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	δ = 9.80 (br d, J = 12.4 Hz, 1H), 9.28 (br s, 1H), 8.49 (br s, 1H), 8.14 (br d, J = 9.2 Hz, 1H), 8.04 - 7.85 (m, 3H), 7.83 - 7.71 (m, 1H), 7.68 - 7.51 (m, 3H), 7.05 - 6.93 (m, 2H), 6.86 (br d, J = 8.0 Hz, 1H), 4.74 (br s, 2H), 4.64 (br s, 1H), 4.55 (br d, J = 12.4 Hz, 2H), 4.48 (br s, 1H), 4.38 - 4.26 (m, 1H), 4.13 - 3.99 (m, 2H), 3.95 - 3.82 (m, 4H), 3.50 (br s, 2H), 3.09 (br t, J = 11.7 Hz, 2H), 2.95 - 2.80 (m, 2H), 2.28 - 2.13 (m, 6H), 2.07 (br s, 2H), 2.02 - 1.93 (m, 2H), 1.71 - 1.63 (m, 2H), 1.51 - 1.35 (m, 4H)	865.6
22	6-[4-[[4-[8-(5-acetyl-1-tetrahydropyran-4-yl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-3-yl)-3-isoquinolyl]pyrazol-1-yl]methyl]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	δ = 9.70 (d, J = 7.2 Hz, 1H), 8.14 - 8.03 (m, 2H), 7.98 (d, J = 9.6 Hz, 1H), 7.90 - 7.76 (m, 3H), 7.75 - 7.65 (m, 1H), 7.58 - 7.46 (m, 2H), 7.03 - 6.94 (m, 2H), 6.85 (dd, J = 2.4, 8.8 Hz, 1H), 4.65 (s, 1H), 4.55 (br d, J = 13.6 Hz, 2H), 4.49 (s, 1H), 4.36 - 4.24 (m, 2H), 4.19 - 3.99 (m, 6H), 3.85 (br t, J = 5.6 Hz, 1H), 3.57 (br t, J = 12.0 Hz, 2H), 3.04 (br t, J = 11.6 Hz, 2H), 2.93 (br t, J = 5.6 Hz, 1H), 2.86 (br t, J = 6.0 Hz, 1H), 2.49 - 2.35 (m, 3H), 2.23 - 2.06 (m, 8H), 1.98 (br s, 2H), 1.83 (br d, J = 12.0 Hz, 2H), 1.68 - 1.63 (m, 1H), 1.51 - 1.35 (m, 4H).	894.5
23	6-[4-[[5-[8-(5-acetyl-1-tetrahydropyran-4-yl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-3-yl)-3-isoquinolyl]-2-pyridyl]methyl]-1-piperidyl]-N-[4-(3-chloro-4-cyano-	δ = 9.84 (d, 1H, J=5.2 Hz), 9.27 (d, 1H, J=2.4 Hz), 8.37 (dt, 1H, J=2.4, 7.8 Hz), 8.11 (d, 1H, J=10.8 Hz), 7.8-8.0 (m, 3H), 7.77 (td, 1H, J=7.7, 12.0 Hz), 7.5-7.6 (m, 2H), 7.3-7.3 (m, 1H), 6.9-7.1 (m, 2H), 6.86 (dd, 1H, J=2.4, 8.8 Hz), 4.67	453.1 [M/2 + H$^+$];

Compound	Name	^{1}H NMR ($CDCl_3$)	LC-MS [M + H$^+$]
	phenoxy)cyclohexyl]pyridazine-3-carboxamide	(s, 1H), 4.4-4.6 (m, 3H), 4.2-4.4 (m, 2H), 4.17 (d, 2H, J=11.6 Hz), 4.0-4.1 (m, 2H), 3.86 (t, 1H, J=5.6 Hz), 3.58 (t, 2H, J=12.0 Hz), 3.04 (t, 2H, J=12.0 Hz), 2.94 (t, 1H, J=6.0 Hz), 2.8-2.9 (m, 3H), 2.4-2.6 (m, 2H), 2.1-2.3 (m, 6H), 1.98 (d, 2H, J=12.8 Hz), 1.86 (br d, 2H, J=11.6 Hz), 1.6-1.8 (m, 4H), 1.3-1.5 (m, 4H)	
24	6-[4-[2-[4-[8-(5-acetyl-1-tetrahydropyran-4-yl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-3-yl)-3-isoquinolyl]pyrazol-1-yl]ethyl]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	δ = 9.6-9.8 (m, 1H), 8.0-8.3 (m, 2H), 7.7-8.0 (m, 5H), 7.5-7.6 (m, 2H), 6.9-7.0 (m, 2H), 6.8-6.9 (m, 1H), 4.67 (s, 1H), 4.4-4.6 (m, 3H), 4.2-4.4 (m, 4H), 4.17 (d, 2H, J=11.6 Hz), 4.0-4.1 (m, 2H), 3.8-3.9 (m, 1H), 3.57 (t, 2H, J=11.6 Hz), 2.8-3.2 (m, 4H), 2.3-2.6 (m, 2H), 2.1-2.2 (m, 5H), 2.08 (s, 1H), 1.9-2.0 (m, 6H), 1.7-1.8 (m, 2H), 1.4-1.5 (m, 3H), 1.2-1.4 (m, 3H)	908.6
27	6-[4-[2-[5-[8-(5-acetyl-1-tetrahydropyran-4-yl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-3-yl)-3-isoquinolyl]-2-pyridyl]ethoxy]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	δ = 9.85 (d, 1H, J=5.6 Hz), 9.28 (s, 1H), 8.46 (d, 1H, J=8.0 Hz), 8.12 (d, 1H, J=8.8 Hz), 7.8-8.0 (m, 3H), 7.78 (td, 1H, J=7.7, 10.0 Hz), 7.5-7.7 (m, 2H), 7.44 (d, 1H, J=8.0 Hz), 6.9-7.1 (m, 2H), 6.86 (dd, 1H, J=2.4, 8.8 Hz), 4.67 (s, 1H), 4.51 (s, 1H), 4.2-4.4 (m, 2H), 4.17 (d, 2H, J=11.6 Hz), 4.0-4.1 (m, 2H), 3.9-4.0 (m, 4H), 3.86 (t, 1H, J=5.6 Hz), 3.68 (d, 1H, J=2.0 Hz), 3.5-3.6 (m, 4H), 3.1-3.3 (m, 2H), 2.8-3.0 (m, 2H), 2.4-2.5 (m, 2H), 2.1-2.2 (m, 6H), 1.9-2.0 (m, 5H), 1.6-1.7 (m, 4H), 1.4-1.5 (m, 2H)	935.5
28	6-[4-[2-[5-[8-(5-acetyl-1-tetrahydropyran-4-yl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-3-yl)-3-isoquinolyl]-2-pyridyl]ethyl]piperazin-1-yl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	δ = 9.84 (d, J = 4.4 Hz, 1H), 9.28 - 9.21 (m, 1H), 8.45 - 8.36 (m, 1H), 8.14 - 7.99 (m, 2H), 7.96 - 7.85 (m, 2H), 7.77 (td, J = 7.6, 11.6 Hz, 1H), 7.63 - 7.55 (m, 2H), 7.44 - 7.35 (m, 1H), 7.03 - 6.96 (m, 2H), 6.86 (dd, J = 2.4, 8.8 Hz, 1H), 4.72 - 4.64 (m, 1H), 4.55 - 4.49 (m, 1H), 4.42 - 4.13 (m, 5H), 4.12 - 3.76 (m, 7H), 3.58 (t, J = 12.0 Hz, 2H), 3.28 - 3.11 (m, 2H), 3.01 - 2.73 (m, 6H), 2.51 - 2.41 (m, 2H), 2.23 - 2.18 (m, 4H), 2.04 - 1.91 (m, 3H), 1.90 - 1.76 (m, 2H), 1.69 - 1.59 (m, 2H), 1.56 - 1.40 (m, 3H)	920.6
29	6-[4-[2-[4-[8-(5-acetyl-1-tetrahydropyran-4-yl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-3-yl)-3-isoquinolyl]pyrazol-1-yl]ethyl]piperazin-1-yl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	(DMSO-d6) δ = 9.82 (s, 1H), 8.63 (br d, J = 8.2 Hz, 1H), 8.46 (s, 1H), 8.12 (d, J = 7.6 Hz, 2H), 7.94 - 7.75 (m, 4H), 7.62 - 7.47 (m, 1H), 7.43 - 7.31 (m, 2H), 7.13 (dd, J = 2.4, 8.8 Hz, 1H), 4.60 - 4.44 (m, 4H), 4.40 - 4.29 (m, 2H), 4.02 (br d, J = 10.4 Hz, 2H), 3.87 - 3.77 (m, 3H), 3.70 (br s, 4H), 3.57 - 3.48 (m, 2H), 2.99 - 2.82 (m, 4H), 2.68 - 2.58 (m, 4H), 2.13 -	909.5

Compound	Name	^{1}H NMR ($CDCl_3$)	LC-MS [M + H$^+$]
		2.07 (m, 5H), 2.02 (s, 1H), 1.99 - 1.86 (m, 4H), 1.70 - 1.46 (m, 4H), 1.23 (s, 1H)	
30	6-[4-[2-[5-[8-(5-acetyl-1-methyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-3-yl)-3-isoquinolyl]-2-pyridyl]ethyl]piperazin-1-yl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	δ = 9.78 (d, J = 9.2 Hz, 1H), 9.31 - 9.22 (m, 1H), 8.45 - 8.36 (m, 1H), 8.11 (d, J = 11.2 Hz, 1H), 8.07 - 7.98 (m, 1H), 7.96 - 7.84 (m, 2H), 7.82 - 7.72 (m, 1H), 7.64 - 7.55 (m, 2H), 7.43 - 7.35 (m, 1H), 7.05 - 6.98 (m, 2H), 6.86 (dd, J = 2.4, 8.8 Hz, 1H), 4.64 (s, 1H), 4.51 - 4.45 (m, 1H), 4.37 - 4.30 (m, 1H), 4.12 - 3.98 (m, 3H), 3.98 - 3.81 (m, 7H), 3.38 - 3.01 (m, 4H), 2.98 (s, 6H), 2.25 - 2.15 (m, 6H), 1.74 - 1.64 (m, 3H), 1.53 - 1.45 (m, 2H)	850.7
65	6-[4-[2-[4-[8-(5-acetyl-1-methyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-3-yl)-3-isoquinolyl]pyrazol-1-yl]ethoxy]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	1.34 - 1.34 (m, 1 H) 1.40 - 1.50 (m, 2 H) 1.63 - 1.73 (m, 4 H) 1.88 (td, J=8.63, 3.50 Hz, 2 H) 2.06 (s, 2 H) 2.17 - 2.22 (m, 4 H) 2.83 (br t, J=5.69 Hz, 1 H) 2.89 (br t, J=5.63 Hz, 1 H) 3.51 - 3.65 (m, 3 H) 3.81 - 3.93 (m, 6 H) 3.95 (t, J=5.19 Hz, 2 H) 3.98 - 4.06 (m, 2 H) 4.28 - 4.43 (m, 3 H) 4.47 (s, 1 H) 4.63 (s, 1 H) 6.86 (dd, J=8.76, 2.38 Hz, 1 H) 6.92 (dd, J=9.57, 4.31 Hz, 1 H) 7.00 (d, J=2.25 Hz, 1 H) 7.48 - 7.60 (m, 2 H) 7.67 - 7.89 (m, 4 H) 7.92 (dd, J=9.51, 1.38 Hz, 1 H) 8.11 (s, 2 H) 9.57 - 9.80 (m, 1 H).	854.1
71	6-[4-[2-[4-[5-(5-acetyl-1-tetrahydropyran-4-yl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-3-yl)quinazolin-2-yl]pyrazol-1-yl]ethyl]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	δ = 10.15 - 9.92 (m, 1H), 8.42 - 8.22 (m, 2H), 8.02 - 7.80 (m, 4H), 7.60 - 7.43 (m, 2H), 7.05 - 6.93 (m, 2H), 6.91 - 6.82 (m, 1H), 4.77 - 4.54 (m, 2H), 4.50 (d, *J* = 12.4 Hz, 2H), 4.37 - 4.23 (m, 4H), 4.21 - 4.12 (m, 2H), 4.10 - 3.98 (m, 2H), 3.93 - 3.79 (m, 1H), 3.64 - 3.52 (m, 2H), 3.51 - 3.47 (m, 1H), 3.09 - 2.97 (m, 2H), 2.97 - 2.82 (m, 2H), 2.52 - 2.36 (m, 2H), 2.22 (s, 2H), 2.18 (s, 3H), 2.12 (s, 1H), 1.99 - 1.88 (m, 6H), 1.70 (s, 2H), 1.51 - 1.42 (m, 2H), 1.38 - 1.28 (m, 2H)	909.4
72	6-[4-[2-[4-[5-(5-acetyl-1-tetrahydropyran-4-yl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-3-yl)-7,8-dihydro-6H-pyrido[3,2-d]pyrimidin-2-yl]pyrazol-1-yl]ethyl]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	(DMSO-d_6): δ = 8.58 (d, *J* = 8.0 Hz, 1H), 8.23 (s, 1H), 8.11 - 8.02 (m, 1H), 7.90 - 7.82 (m, 2H), 7.79 (d, *J* = 9.6 Hz, 1H), 7.39 (d, *J* = 2.4 Hz, 1H), 7.33 (d, *J* = 10.0 Hz, 1H), 7.18 - 7.09 (m, 1H), 4.60 - 4.51 (m, 1H), 4.49 - 4.41 (m, 2H), 4.34 - 4.17 (m, 5H), 4.02 - 3.92 (m, 2H), 3.90 - 3.81 (m, 1H), 3.79 - 3.69 (m, 2H), 3.63 - 3.54 (m, 2H), 3.45 (br t, *J* = 11.6 Hz, 2H), 3.02 - 2.71 (m, 6H), 2.17 - 2.03 (m, 6H), 2.01 - 1.77 (m, 11H), 1.69 - 1.58 (m, 2H), 1.57 - 1.44 (m, 3H), 1.23 - 1.11 (m, 2H)	914.4

Compound	Name	^{1}H NMR ($CDCl_3$)	LC-MS [M + H$^+$]
73	6-[4-[2-[5-[5-(5-acetyl-1-tetrahydropyran-4-yl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-3-yl)quinazolin-2-yl]-2-pyridyl]ethyl]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	δ = 10.15 (s, 1H), 9.81 - 9.73 (m, 1H), 9.09 - 8.68 (m, 1H), 8.13 - 8.05 (m, 1H), 8.02 - 7.93 (m, 2H), 7.88 (d, *J* = 8.4 Hz, 1H), 7.67 - 7.53 (m, 2H), 7.49 - 7.32 (m, 1H), 7.04 - 6.94 (m, 2H), 6.84 - 6.8 (m, 1H), 4.77 - 4.57 (m, 2H), 4.53 (d, *J* = 13.6 Hz, 2H), 4.38 - 4.26 (m, 2H), 4.24 - 4.16 (m, 2H), 4.12 - 4.00 (m, 2H), 3.87 (t, *J* = 60 Hz, 1H), 3.59 (t, *J* = 12.0 Hz, 2H), 3.16 - 2.96 (m, 4H), 2.96 - 2.85 (m, 2H), 2.52 - 2.39 (m, 2H), 2.23 (s, 2H), 2.21 - 2.15 (m, 3H), 2.12 (s, 2H), 2.02 - 1.94 (m, 4H), 1.88 - 1.79 (m, 2H), 1.75 - 1.65 (m, 3H), 1.52 - 1.45 (m, 2H), 1.41 - 1.31 (m, 2H)	920.4
82	6-[4-[2-[4-[8-(5-acetyl-1-cyclopropyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-3-yl)-3-isoquinolyl]pyrazol-1-yl]ethyl]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	δ ppm 9.52 - 9.74 (m, 1 H) 9.52 - 9.75 (m, 1 H) 8.07 (s, 2 H) 7.96 (m, 1 H) 7.75 - 7.92 (m, 3 H) 7.61 - 7.74 (m, 1 H) 7.56 (d, *J*=8.8 Hz, 1 H) 7.43 - 7.53 (m, 1 H) 6.94 - 7.05 (m, 2 H) 6.86 (m, 1 H) 4.61 (s, 1 H) 4.39 - 4.57 (m, 3 H) 4.21 - 4.39 (m, 3 H) 3.93 - 4.15 (m, 2 H) 3.83 (t, *J*=5.6 Hz, 1 H) 3.46 (m, 1 H) 2.90 - 3.11 (m, 4 H) 2.12 - 2.25 (m, 1 H) 2.12 - 2.28 (m, 5 H) 2.05 - 2.06 (m, 1 H) 2.06 (s, 1 H) 1.87 - 1.99 (m, 4 H) 1.64 - 1.74 (m, 5 H) 1.41 - 1.52 (m, 2 H) 1.25 - 1.40 (m, 4 H) 1.05 - 1.15 (m, 2 H)	864.4
83	6-[4-[2-[4-[8-(5-acetyl-1-cyclobutyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-3-yl)-3-isoquinolyl]pyrazol-1-yl]ethyl]-1-piperidyl]-N-[4-(3-chloro-4-cyanophenoxy) cyclohexyl]pyridazine-3-carboxamide	9.64 - 9.87 (m, 1 H) 8.02 - 8.28 (m, 2 H) 7.96 (d, *J*=9.6 Hz, 1 H) 7.77 - 7.92 (m, 3 H) 7.65 - 7.76 (m, 1 H) 7.45 - 7.62 (m, 2 H) 6.92 - 7.05 (m, 2 H) 6.86 (m, 1 H) 4.60 - 4.84 (m, 2 H) 4.41 - 4.56 (m, 3 H) 4.23 - 4.40 (m, 3 H) 3.93 - 4.13 (m, 2 H) 3.81 (t, *J*=5.6 Hz, 1 H) 2.95 - 3.12 (m, 2 H) 2.74 - 2.94 (m, 4 H) 2.38 - 2.55 (m, 2 H) 2.17 - 2.27 (m, 4 H) 2.06 (s, 1 H) 1.86 - 1.98 (m, 6 H) 1.63 - 1.76 (m, 5 H) 1.30 - 1.50 (m, 4 H)	878.4
84	6-[4-[2-[4-[8-[5-acetyl-1-(oxetan-3-yl)-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-3-yl]-3-isoquinolyl]pyrazol-1-yl]ethyl]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	δ = 9.95 - 9.69 (m, 1H), 8.34 - 8.14 (m, 1H), 8.13 - 8.04 (m, 1H), 8.00 - 7.94 (m, 1H), 7.94 - 7.83 (m, 3H), 7.82 - 7.71 (m, 1H), 7.66 - 7.51 (m, 2H), 7.03 - 6.93 (m, 2H), 6.90 - 6.82 (m, 1H), 5.52 - 5.40 (m, 1H), 5.38 - 5.27 (m, 2H), 5.05 (m, 2H), 4.70 - 4.60 (m, 1H), 4.55 - 4.42 (m, 3H), 4.37 - 4.22 (m, 3H), 4.13 - 3.95 (m, 2H), 3.89 - 3.77 (m, 1H), 3.10 - 2.96 (m, 2H), 2.93 - 2.74 (m, 2H), 2.26 - 2.12 (m, 6H), 2.07 (s, 2H), 1.97 - 1.90 (m, 4H), 1.54 - 1.40 (m, 3H), 1.38 - 1.23 (m, 3H)	880.5

[00500] **Example 7**: Synthesis of 6-[4-[[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c] pyridin-1-yl]-1-piperidyl] methyl]-3-methyl-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy) cyclohexyl] pyridazine-3-carboxamide (**Compound 101**)



[00501] To a solution of tert-butyl 3-methyl-4-oxo-piperidine-1-carboxylate (10.00 g, 46.0 mmol, 1.0 eq) in DMF (100 mL) was added t-BuOK (1 M, 140 mL, 3.0 eq) at 0 °C, the resulting mixture was stirred at 0 °C for 15 min. After addition, the mixture was added a solution of 1-(isocyanomethylsulfonyl)-4-methyl-benzene (14.00 g, 70.0 mmol, 1.5 eq) and EtOH (7 mL) at this temperature. The resulting mixture was stirred at 50 °C for 2 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/THF=20/1). Compound 1-benzyl-3-methyl-piperidine-4-carbonitrile (3.00 g, 14.0 mmol, 28 % yield) was obtained as a white solid.

[00502] **^{1}H NMR** (400 MHz, DMSO-d_6) δ = 7.45 - 7.15 (m, 5H), 3.46 (s, 2H), 2.70 - 2.55 (m, 2H), 2.22 - 2.07 (m, 1H), 1.96 - 1.68 (m, 4H), 0.95 (br d, *J* = 5.6 Hz, 3H).

[00503] To a solution of 1-benzyl-3-methyl-piperidine-4-carbonitrile (3.00 g, 14.0 mmol, 1.0 *eq*), 1,1,2-trichloroethane (1.88 g, 14.1 mmol, 1.31 mL, 1.0 *eq*) in MeOH (60 mL) was added Pd/C (1.50 g, 1.41 mmol, 10% purity, 0.1 *eq*) under N_2 atmosphere. The suspension was degassed and purged with H_2 for 3 times. The mixture was stirred under H_2 balloon (15 psi) at 25 °C for 6 h. The reaction mixture was concentrated under reduced pressure to give a residue. Compound 3-methylpiperidine-4-carbonitrile (1.70 g) was obtained as a colorless oil and directly used in the next step without further purification.

[00504] **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 3.85 - 3.53 (m, 2H), 3.37 (br d, *J* = 12.0 Hz, 1H),

3.22 - 3.01 (m, 2H), 2.92 - 2.76 (m, 1H), 2.56 - 2.30 (m, 2H), 2.24 - 2.12 (m, 1H), 1.18 (d, J = 6.8 Hz, 3H).

[00505] To a solution of 3-methylpiperidine-4-carbonitrile (1.70 g), Et_3N (4.36 g, 43.1 mmol, 6 mL, 3.2 *eq*) in DCM (20 mL) was added Boc_2O (3.33 g, 15.2 mmol, 3.5 mL, 1.1 eq). The mixture was stirred at 25 °C for 12 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=10/1 to 1/1). Compound tert-butyl 4-cyano-3-methyl-piperidine-1-carboxylate (2.20 g, 9.81 mmol, 72% yield over two steps) was obtained as a colorless oil.

[00506] **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 4.03 - 3.63 (m, 2H), 3.21 - 3.09 (m, 1H), 3.03 - 2.64 (m, 2H), 2.00 - 1.91 (m, 1H), 1.88 - 1.81 (m, 1H), 1.80 - 1.67 (m, 1H), 1.46 (s, 9H), 1.09 (d, J = 6.8 Hz, 3H).

[00507] To a solution of tert-butyl 4-cyano-3-methyl-piperidine-1-carboxylate (2.2 g, 9.81 mmol, 1.0 *eq*) in DCM (20 mL) was added DIBAL-H (1 M, 29 mL, 3.0 *eq*) at -78 °C under N_2. The mixture was stirred at -78 °C for 2 h. The mixture was poured into $Na_2SO_4.10H_2O$ at 0 °C. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=50/1 to 15/1). Compound tert-butyl 4-formyl-3-methyl-piperidine-1-carboxylate (201 mg, 884 µmol, 9 % yield) was obtained as a colorless oil.

[00508] **LC-MS:** MS (ESI+): t_R = 0.558 min, m/z = 172.1 [M - tBu+]

[00509] To a solution of tert-butyl 4-formyl-3-methyl-piperidine-1-carboxylate (50 mg, 220 µmol, 1.1 *eq*), 1-[3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-1-(4-piperidyl)-6,7-dihydro-4H-pyrazolo[4,3-c] pyridin-5-yl]ethanone (100 mg, 196 µmol, 1.0 *eq*) in DCM (1 mL) and was added Et_3N (145 mg, 1.44 mmol, 200 µL, 7.3 *eq*) at 25 °C for 0.1 h. The mixture was added $NaBH(OAc)_3$ (130 mg, 613 µmol, 3.1 *eq*) stirred at 25 °C for 1 h. The mixture was poured into saturated ammonium chloride (5 mL) and ice water 5 mL at 0 °C, extracted with DCM (20 mL × 3), The orange phase was washed with brine 10 mL, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give residue. The crude product was purified by reversed-phase HPLC (column: Phenomenex luna C18 150 × 25mm × 10um; mobile phase: [water (FA)-ACN]; gradient:22%-52% B over 10 min). Compound tert-butyl 4-[[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c] pyridin-1-yl]-1-piperidyl] methyl]-3-methyl-piperidine-1-carboxylate (52 mg, 72.1 µmol, 37% yield) was obtained as a white solid.

[00510] **LC-MS:** MS (ESI^+): t_R = 0.538 min, m/z = 721.6 [$M + H^+$].

[00511] To a solution of tert-butyl 4-[[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c] pyridin-1-yl]-1-piperidyl] methyl]-3-methyl-piperidine-1-carboxylate (52 mg, 72.1 µmol, 1.0 *eq*) in DCM (0.5 mL) was added TFA (260 µL). The mixture was stirred at 25 °C for 1 h. The reaction mixture was concentrated under reduced pressure to give a residue. Compound 1-[3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-1-[1-[(3-methyl-4-piperidyl) methyl]-4-piperidyl]-6,7-dihydro-4H-pyrazolo[4,3-c] pyridin-5-yl] ethanone (45 mg) was obtained as a yellow solid and directly used in the next step without further purification.

[00512] **LC-MS:** MS (ESI^+): t_R = 0.473 min, m/z = 621.6 [$M + H^+$].

[00513] To a solution of 1-[3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-1-[1-[(3-methyl-4-piperidyl)methyl]-4-piperidyl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]ethanone (45 mg), 6-chloro-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide (32 mg, 81.8 μmol, 1.1 *eq*) in NMP (0.5 mL) was added DIPEA (69 mg, 535 μmol, 93.3 μL, 7.4 *eq*). The mixture was stirred at 60 °C for 12 h. The mixture was poured into saturated ammonium chloride (10 mL) and ice water 10 mL at 0 °C, extracted with Ethyl acetate (20 mL × 3). The orange phase was washed with brine 10 mL, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give residue. The crude product was purified by reversed-phase HPLC (column: Phenomenex luna C18 150 × 25mm × 10um; mobile phase: [water (FA)-ACN]; gradient:29%-59% B over 10 min). Compound 6-[4-[[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c] pyridin-1-yl]-1-piperidyl] methyl]-3-methyl-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy) cyclohexyl] pyridazine-3-carboxamide (6.48 mg, 6.51 μmol, 9% yield over two steps) was obtained as an off-white solid.

[00514] **^{1}H NMR** (400 MHz, DMSO-d_6) δ = 8.61 - 8.52 (m, 1H), 8.13 (s, 1H), 7.85 (d, *J* = 8.8 Hz, 1H), 7.81 - 7.72 (m, 2H), 7.50 (s, 1H), 7.39 (d, *J* = 2.0 Hz, 1H), 7.35 - 7.29 (m, 1H), 7.19 - 7.08 (m, 2H), 6.97 - 6.62 (m, 2H), 4.60 - 4.49 (m, 1H), 4.48 - 4.40 (m, 1H), 4.36 - 4.27 (m, 1H), 4.21 - 4.10 (m, 2H), 4.07 - 3.99 (m, 1H), 3.87 (s, 3H), 3.75 - 3.66 (m, 2H), 3.62 - 3.56 (m, 2H), 3.23 - 3.17 (m, 1H), 3.08 - 2.99 (m, 2H), 2.97 - 2.91 (m, 1H), 2.90 - 2.81 (m, 4H), 2.76 - 2.72 (m, 1H), 2.24 - 2.19 (m, 1H), 2.17 - 1.94 (m, 14H), 1.93 - 1.82 (m, 4H), 1.69 - 1.58 (m, 2H), 1.57 - 1.38 (m, 4H), 0.78 (br d, *J* = 6.0 Hz, 3H)。

[00515] **LC-MS:** MS (ESI$^+$): t_R = 2.212 min, m/z = 975.4 [M + H$^+$].

[00516] **SFC:** t_R = 2.639 min, 48%, t_R = 3.154 min, 52 %

[00517] The compounds below were prepared in a similar manner as described in Example 7.

Compound	Name	^{1}H NMR ($CDCl_3$)	LC-MS [M + H$^+$]
103	6-[4-[[4-[5-acetyl-3-(6-cyano-3,4-dihydro-2H-quinolin-1-yl)-6,7-dihydro-4H-pyrazolo[4,3-c] pyridin-1-yl]-1-piperidyl] methyl]-3-methyl-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy) cyclohexyl] pyridazine-3-carboxamide	(DMSO-d_6) δ = 8.55 (d, *J* = 8.4 Hz, 1H), 7.85 (d, *J* = 8.8 Hz, 1H), 7.76 (d, *J* = 9.6 Hz, 1H), 7.45 - 7.35 (m, 2H), 7.35 - 7.26 (m, 2H), 7.18 - 7.09 (m, 1H), 6.49 - 6.36 (m, 1H), 4.62 - 4.39 (m, 2H), 4.30 (br d, *J* = 13.6 Hz, 1H), 4.21 - 3.99 (m, 3H), 3.93 - 3.81 (m, 1H), 3.78 - 3.67 (m, 2H), 3.64 - 3.53 (m, 2H), 3.25 - 3.17 (m, 1H), 3.05 (br t, *J* = 11.4 Hz, 2H), 2.93 - 2.77 (m, 4H), 2.73 (br t, *J* = 5.4 Hz, 1H), 2.30 - 1.74 (m, 19H), 1.71 - 1.59 (m, 2H), 1.58 - 1.39 (m, 4H), 0.78 (br d, *J* = 6.4 Hz, 3H)	870.6
104	6-[4-[[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]methyl]-3-methyl-1-	(DMSO-d6) δ = 8.57 (br d, *J* = 8.0 Hz, 1H), 8.14 (s, 1H), 7.85 (d, *J* = 8.8 Hz, 1H), 7.81 - 7.73 (m, 2H), 7.50 (s, 1H), 7.38 (d, *J* = 2.4 Hz, 1H), 7.33 (d, *J* = 9.6 Hz, 1H), 7.16 - 7.07 (m, 2H), 6.96 - 6.62 (m, 2H), 4.59 - 4.48 (m, 1H), 4.43 (br d, *J* = 13.2 Hz, 1H), 4.37 - 4.27 (m, 1H),	975.4

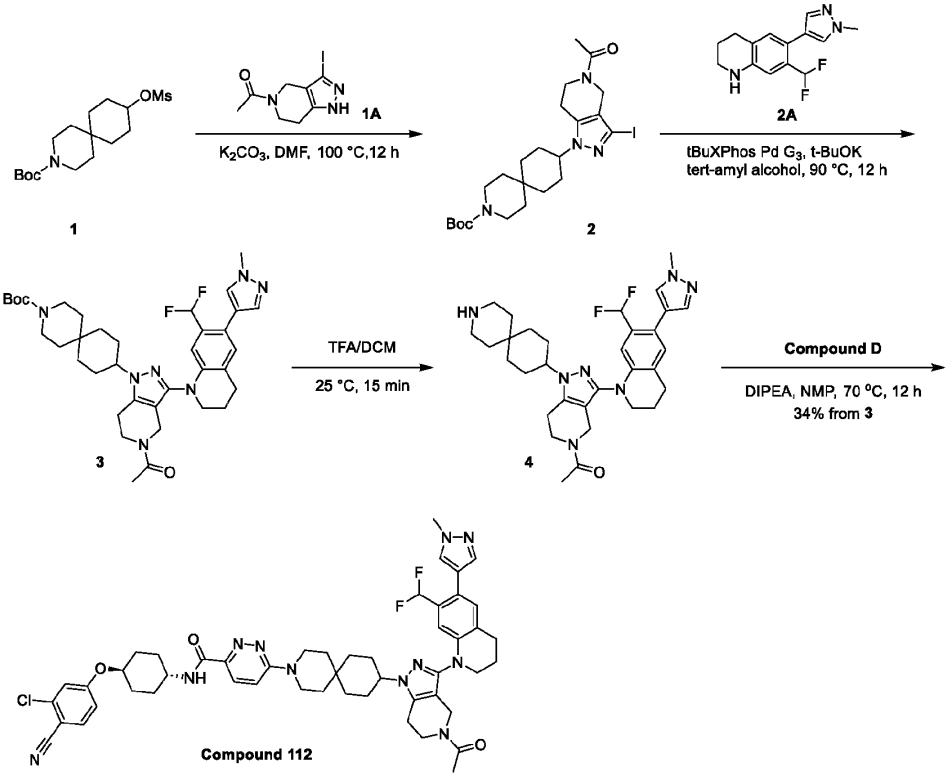
Compound	Name	^{1}H NMR ($CDCl_3$)	LC-MS [M + H$^+$]
	piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	4.20 - 4.08 (m, 2H), 4.07 - 3.96 (m, 1H), 3.92 - 3.79 (m, 4H), 3.77 - 3.64 (m, 2H), 3.63 - 3.53 (m, 2H), 3.09 - 2.96 (m, 2H), 2.84 (br d, *J* = 4.8 Hz, 4H), 2.77 - 2.62 (m, 2H), 2.46 - 2.38 (m, 1H), 2.18 - 1.81 (m, 14H), 1.70 - 1.56 (m, 2H), 1.56 - 1.43 (m, 3H), 1.41 - 1.28 (m, 1H), 1.18 - 1.04 (m, 1H), 0.97 (br d, *J* = 6.4 Hz, 3H)	
105	6-[4-[[4-[5-acetyl-3-(6-cyano-3,4-dihydro-2H-quinolin-1-yl)-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]methyl]-3-methyl-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	(DMSO-d6) δ = 8.58 (br d, *J* = 8.0 Hz, 1H), 8.15 (s, 1H), 7.85 (d, *J* = 8.8 Hz, 1H), 7.79 (d, *J* = 9.6 Hz, 1H), 7.43 - 7.37 (m, 2H), 7.37 - 7.27 (m, 2H), 7.16 - 7.11 (m, 1H), 6.47 - 6.37 (m, 1H), 4.60 - 4.49 (m, 1H), 4.48 - 4.39 (m, 1H), 4.38 - 4.27 (m, 1H), 4.21 - 4.09 (m, 2H), 4.08 - 3.97 (m, 1H), 3.93 - 3.79 (m, 1H), 3.78 - 3.65 (m, 2H), 3.64 - 3.54 (m, 2H), 3.10 - 2.94 (m, 2H), 2.88 - 2.78 (m, 4H), 2.77 - 2.65 (m, 2H), 2.46 - 2.38 (m, 1H), 2.17 - 2.05 (m, 6H), 2.02 - 1.79 (m, 11H), 1.70 - 1.57 (m, 2H), 1.57 - 1.44 (m, 3H), 1.41 - 1.29 (m, 1H), 1.18 - 1.04 (m, 1H), 0.97 (br d, *J* = 6.4 Hz, 3H)	870.4
230	6-[4-[[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]methyl]-3,3-dimethyl-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	δ = 7.94 (d, J = 9.6 Hz, 1H), 7.86 (d, J = 8.4 Hz, 1H), 7.59 - 7.51 (m, 2H), 7.44 - 7.38 (m, 1H), 7.07 - 6.99 (m, 2H), 6.95 (d, J = 9.6 Hz, 1H), 6.90 - 6.83 (m, 2H), 6.70 - 6.35 (m, 1H), 4.48 (d, J = 12.4 Hz, 1H), 4.38 - 4.24 (m, 2H), 4.22 - 4.11 (m, 2H), 4.10 - 4.00 (m, 1H), 3.99 - 3.89 (m, 5H), 3.79 - 3.65 (m, 3H), 3.11 (d, J = 10.0 Hz, 1H), 3.03 - 2.93 (m, 2H), 2.92 - 2.72 (m, 5H), 2.50 - 2.39 (m, 1H), 2.27 (d, J = 8.4 Hz, 2H), 2.22 - 2.13 (m, 6H), 2.12 - 2.00 (m, 6H), 1.96 - 1.89 (m, 3H), 1.74 - 1.57 (m, 3H), 1.52 - 1.37 (m, 3H), 1.07 (s, 3H), 0.83 (s, 3H)	989.7
231	6-[8-[[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]methyl]-5-azaspiro[2.5]octan-5-yl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	δ = 8.25 (s, 1H), 7.96 (d, J = 9.4 Hz, 1H), 7.84 (br d, J = 8.0 Hz, 1H), 7.58 - 7.51 (m, 2H), 7.41 (d, J = 5.8 Hz, 1H), 7.08 - 6.98 (m, 2H), 6.96 - 6.82 (m, 3H), 6.69 - 6.38 (m, 1H), 4.38 - 4.26 (m, 2H), 4.18 - 4.00 (m, 3H), 3.96 (s, 3H), 3.93 - 3.50 (m, 9H), 3.36 - 3.04 (m, 2H), 2.97 - 2.71 (m, 5H), 2.30 - 1.99 (m, 15H), 1.96 - 1.87 (m, 2H), 1.67 - 1.62 (m, 2H), 1.51 - 1.41 (m, 2H), 0.50 (br s, 4H)	987.4
233	6-[(3R,4R)-4-[[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-	(DMSO-d6) δ = 8.60 - 8.53 (m, 1H), 8.14 (s, 1H), 7.86 (d, J = 8.8 Hz, 1H), 7.76 (t, J = 4.8 Hz, 2H), 7.50 (s, 1H), 7.39 (d, J = 2.4 Hz, 1H), 7.32 (d, J = 9.8 Hz, 1H), 7.17 - 7.09 (m, 2H), 6.96 - 6.63 (m, 2H), 4.59 - 4.40 (m, 2H), 4.38 - 4.27	973.4

Compound	Name	^{1}H NMR ($CDCl_3$)	LC-MS [M + H$^+$]
	piperidyl]methyl]-3-methyl-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	(m, 1H), 4.21 - 4.09 (m, 2H), 4.08 - 3.97 (m, 1H), 3.91 - 3.82 (m, 4H), 3.78 - 3.66 (m, 2H), 3.64 - 3.56 (m, 2H), 3.22 - 3.19 (m, 1H), 3.06 - 2.91 (m, 3H), 2.85 (br d, J = 5.4 Hz, 3H), 2.78 - 2.70 (m, 1H), 2.25 - 2.17 (m, 2H), 2.12 - 1.96 (m, 13H), 1.91 - 1.81 (m, 4H), 1.69 - 1.59 (m, 2H), 1.56 - 1.41 (m, 4H), 0.78 (br d, J = 6.4 Hz, 3H)	
234	6-[(3S,4S)-4-[[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]methyl]-3-methyl-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy) cyclohexyl] pyridazine-3-carboxamide	(DMSO-d6) δ = 10.70 - 9.79 (m, 1H), 8.57 (br d, J = 8.0 Hz, 1H), 7.86 (d, J = 8.8 Hz, 1H), 7.80 - 7.73 (m, 2H), 7.51 (s, 1H), 7.39 (d, J = 2.4 Hz, 1H), 7.33 (d, J = 9.6 Hz, 1H), 7.18 - 7.09 (m, 2H), 6.98 - 6.62 (m, 2H), 4.59 - 4.51 (m, 1H), 4.49 - 4.42 (m, 1H), 4.37 - 4.27 (m, 1H), 4.19 - 4.11 (m, 2H), 4.08 - 4.00 (m, 1H), 3.88 (s, 4H), 3.76 - 3.69 (m, 2H), 3.62 - 3.58 (m, 2H), 3.22 - 3.19 (m, 1H), 3.09 - 2.96 (m, 3H), 2.95 - 2.84 (m, 4H), 2.22 - 1.96 (m, 15H), 1.89 (br d, J = 13.2 Hz, 4H), 1.70 - 1.58 (m, 2H), 1.57 - 1.39 (m, 4H), 0.78 (br d, J = 6.4 Hz, 3H)	975.7
282	6-[4-[[4-[5-acetyl-3-[7-methyl-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]methyl]-3,3-dimethyl-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	δ = 8.28 (s, 1H), 7.95 (d, J = 9.6 Hz, 1H), 7.86 (br d, J = 8.0 Hz, 1H), 7.62 - 7.50 (m, 2H), 7.42 - 7.33 (m, 1H), 7.04 - 6.93 (m, 3H), 6.86 (dd, J = 2.4, 8.8 Hz, 1H), 6.38 (s, 1H), 4.51 - 4.39 (m, 1H), 4.37 - 4.19 (m, 3H), 4.13 (s, 1H), 4.11 - 3.98 (m, 2H), 3.98 - 3.87 (m, 5H), 3.75 (br t, J = 5.6 Hz, 1H), 3.69 - 3.61 (m, 2H), 3.03 - 2.94 (m, 1H), 2.89 - 2.67 (m, 6H), 2.40 - 2.12 (m, 13H), 2.10 - 1.94 (m, 7H), 1.74 - 1.61 (m, 4H), 1.52 - 1.38 (m, 3H), 1.07 (s, 3H), 0.84 (s, 3H)	953.6
283	6-[4-[[4-[5-acetyl-3-[6-cyano-7-(difluoromethyl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]methyl]-3,3-dimethyl-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	δ = 8.25 (s, 1H), 7.94 (d, J = 9.6 Hz, 1H), 7.86 (d, J = 8.4 Hz, 1H), 7.57 (d, J = 8.8 Hz, 1H), 7.34 (d, J = 11.0 Hz, 1H), 7.03 - 6.93 (m, 2H), 6.92 - 6.59 (m, 3H), 4.57 - 4.42 (m, 1H), 4.39 - 4.26 (m, 2H), 4.25 - 4.11 (m, 2H), 4.10 - 4.00 (m, 1H), 3.99 - 3.88 (m, 2H), 3.81 - 3.67 (m, 3H), 3.13 (br s, 1H), 3.03 - 2.92 (m, 2H), 2.91 - 2.73 (m, 5H), 2.51 - 2.40 (m, 1H), 2.35 - 2.25 (m, 2H), 2.25 - 2.12 (m, 8H), 2.12 - 2.05 (m, 4H), 2.04 - 1.99 (m, 1H), 1.94 (br d, J = 2.4 Hz, 2H), 1.68 - 1.55 (m, 3H), 1.52 - 1.38 (m, 3H), 1.06 (s, 3H), 0.83 (s, 3H)	934.5
286	6-[4-[[4-[5-acetyl-3-[6-cyano-7-(difluoromethyl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]methyl]-3,5-	(DMSO-d_6) δ = 8.58 (d, *J* = 8.4 Hz, 1H), 7.85 (d, *J* = 8.8 Hz, 1H), 7.77 (d, *J* = 9.6 Hz, 1H), 7.58 (s, 1H), 7.39 (d, *J* = 2.4 Hz, 1H), 7.34 (d, *J* = 9.6 Hz, 1H), 7.17 - 6.84 (m, 2H), 6.82 - 6.70 (m, 1H), 4.61 -	934.6

Compound	Name	^{1}H NMR ($CDCl_3$)	LC-MS [M + H$^+$]
	dimethyl-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	4.46 (m, 1H), 4.26 - 4.13 (m, 2H), 4.11 - 3.97 (m, 1H), 3.92 - 3.69 (m, 5H), 3.67 - 3.59 (m, 2H), 3.32 - 3.27 (m, 2H), 3.10 - 2.96 (m, 2H), 2.92 - 2.82 (m, 3H), 2.79 - 2.71 (m, 1H), 2.38 - 2.26 (m, 2H), 2.13 - 1.83 (m, 18H), 1.69 - 1.57 (m, 2H), 1.56 - 1.45 (m, 2H), 1.05 - 0.91 (m, 6H)	
291	6-[4-[[4-[5-acetyl-3-[7-methyl-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]methyl]-3,3-dimethyl-1-piperidyl]-N-[4-(3-chloro-4-cyano-2-methyl-phenoxy)cyclohexyl]pyridazine-3-carboxamide	δ = 7.94 (d, J = 9.6 Hz, 1H), 7.87 (d, J = 8.2 Hz, 1H), 7.57 - 7.52 (m, 1H), 7.48 (d, J = 8.8 Hz, 1H), 7.40 - 7.34 (m, 1H), 7.02 - 6.92 (m, 2H), 6.83 (d, *J* = 8.8 Hz, 1H), 6.40 - 6.36 (m, 1H), 4.53 - 4.44 (m, 1H), 4.40 - 4.31 (m, 1H), 4.29 (s, 1H), 4.24 - 4.16 (m, 1H), 4.13 (s, 1H), 4.11 - 4.03 (m, 1H), 3.96 - 3.93 (m, 3H), 3.93 - 3.87 (m, 2H), 3.78 - 3.61 (m, 3H), 3.20 - 3.07 (m, 1H), 3.04 - 2.91 (m, 2H), 2.87 - 2.77 (m, 4H), 2.77 - 2.72 (m, 1H), 2.51 - 2.39 (m, 1H), 2.30 (s, 5H), 2.24 (s, 3H), 2.22 - 2.14 (m, 7H), 2.09 - 1.99 (m, 6H), 1.97 - 1.86 (m, 2H), 1.72 - 1.66 (m, 2H), 1.64 - 1.55 (m, 1H), 1.53 - 1.41 (m, 3H), 1.07 (s, 3H), 0.84 (s, 3H).	967.7
292	6-[4-[[4-[5-acetyl-3-[7-methyl-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]methyl]-3,3-dimethyl-1-piperidyl]-N-[4-(4-cyano-2,3-dimethyl-phenoxy)cyclohexyl]pyridazine-3-carboxamide	δ = 7.94 (d, J = 9.4 Hz, 1H), 7.88 (d, J = 8.2 Hz, 1H), 7.58 - 7.52 (m, 1H), 7.43 (d, J = 8.8 Hz, 1H), 7.40 - 7.34 (m, 1H), 7.05 - 6.90 (m, 2H), 6.78 (d, J = 8.6 Hz, 1H), 6.38 (s, 1H), 4.53 - 4.43 (m, 1H), 4.39 - 4.01 (m, 5H), 3.98 - 3.86 (m, 5H), 3.80 - 3.71 (m, 1H), 3.70 - 3.59 (m, 2H), 3.19 - 3.07 (m, 1H), 3.05 - 2.90 (m, 2H), 2.89 - 2.69 (m, 5H), 2.52 - 2.36 (m, 4H), 2.35 - 2.11 (m, 15H), 2.09 - 1.98 (m, 6H), 1.97 - 1.85 (m, 2H), 1.82 - 1.74 (m, 1H), 1.66 - 1.54 (m, 2H), 1.53 - 1.38 (m, 3H), 1.07 (s, 3H), 0.84 (s, 3H)	947.8
293	6-[4-[[4-[5-acetyl-3-[7-methyl-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]methyl]-3,3-dimethyl-1-piperidyl]-N-[4-(4-cyano-3-methyl-phenoxy)cyclohexyl]pyridazine-3-carboxamide	δ = 7.94 (d, J = 9.6 Hz, 1H), 7.86 (d, J = 8.4 Hz, 1H), 7.58 - 7.48 (m, 2H), 7.40 - 7.34 (m, 1H), 7.02 - 6.92 (m, 2H), 6.83 - 6.74 (m, 2H), 6.42 - 6.36 (m, 1H), 4.55 - 4.43 (m, 1H), 4.38 - 4.25 (m, 2H), 4.23 - 4.15 (m, 1H), 4.13 (s, 1H), 4.11 - 4.00 (m, 1H), 3.96 - 3.93 (m, 3H), 3.93 - 3.86 (m, 2H), 3.80 - 3.61 (m, 3H), 3.16 - 3.06 (m, 1H), 3.03 - 2.89 (m, 2H), 2.87 - 2.71 (m, 5H), 2.51 (s, 3H), 2.46 - 2.37 (m, 1H), 2.34 - 2.23 (m, 5H), 2.22 - 2.10 (m, 7H), 2.09 - 1.97 (m, 6H), 1.95 - 1.86 (m, 2H), 1.69 - 1.53 (m, 3H), 1.51 - 1.37 (m, 3H), 1.07 (s, 3H), 0.83 (s, 3H)	933.8

[00518] **Example 8**: Synthesis of 6-[9-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-

dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-3-azaspiro[5.5]undecan-3-yl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide (**Compound 112**)



[00519] Synthesis of 1 was the reported of. Medicinal Chemistry Letters, 2016, vol. 7, # 4, p. 397 - 402]

[00520] Synthesis of **2A** was reported in **WO2016/86200, 2016, A1.**

[00521] Preparation of **1A:**

[00522] To a solution of 3-iodo-4, 5, 6, 7-tetrahydro-1H- pyrazolo [4, 3-c] pyridine (10.40 g, 28.0 mmol, 1.0 eq, TFA) in DCM (150 mL) was added Et_3N (14.50 g, 143 mmol, 20.0 mL, 5.0 eq) and acetic anhydride (2.60 g, 25 mmol, 2.4 mL, 0.9 eq) at 0 °C. The mixture was stirred at 0 °C for 1 h. The mixture was poured into iced water (50 mL). The aqueous phase was extracted with dichloromethane (30 mL × 3). The combined organic phase was washed with brine (30 mL × 2), dried with anhydrous sodium sulfate, filtered and concentrated under vacuum. The crude product was triturated with EtOAc/PE (1/1, 30 mL) at 25 °C for 30 min. Compound 1-(3-iodo-1,4,6,7-tetrahydropyrazolo[4,3-c]pyridin-5-yl)ethanone (5.40 g, 18.0 mmol, 64% yield) was obtained as a white solid.

[00523] **LC-MS:** MS (ESI+): t_R = 0.508 min, m/z = 292.0 [M + H^+].

[00524] Preparation of **Compound 112:**

[00525] To a solution of tert-butyl 9-methylsulfonyloxy-3-azaspiro[5.5]undecane-3-carboxylate (2.39 g, 6.87 mmol, 2 eq) ,1-(3-iodo-1,4,6,7-tetrahydropyrazolo[4,3-c]pyridin-5-yl)ethanone (1.00 g, 3.44 mmol, 1 eq) in DMF (30 mL) was added K_2CO_3 (1.42 g, 10.31 mmol, 3.0 eq). The mixture was stirred at 100 °C for

12 h. The residue was diluted with water 500 mL and extracted with ethyl acetate 600 mL. The combined organic layers were washed with brine 400mL, dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=20/1 to 0/1- dichloromethane: ethyl acetate = 1:1). Compound tert-butyl 9-(5-acetyl-3-iodo-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl)-3-azaspiro[5.5]undecane-3-carboxylate (500mg, 921.74 μmol, 26% yield)was obtained as a white solid.

[00526] **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 4.2-4.5 (m, 2H), 3.6-4.0 (m, 3H), 3.38 (q, 4H, J=6.0 Hz), 2.6-2.8 (m, 2H), 2.2-2.2 (m, 3H), 2.0-2.2 (m, 2H), 1.86 (d, 2H, J=13.6 Hz), 1.73 (d, 2H, J=11.2 Hz), 1.6-1.7 (m, 2H), 1.46 (s, 9H), 1.3-1.4 (m, 2H), 1.2-1.3 (m, 2H)

[00527] **LC-MS:** MS (ESI^+): t_R = 0.569 min, m/z = 543.2 [$M + H^+$]

[00528] To a solution of tert-butyl 9-(5-acetyl-3-iodo-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl)-3-azaspiro[5.5]undecane-3-carboxylate (300 mg, 553.04 μmol, 1.0 eq), 7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-1,2,3,4-tetrahydroquinoline (146 mg, 553.04 μmol, 1.0 eq) in 2-methylbutan-2-ol (3 mL) was added tBuXPhos Pd G_3 (100 mg, 125.89 μmol, 2.28e-1 eq) and t-BuOK (1 M, 1.66 mL, 3.0 eq). The mixture was stirred at 90 °C for 12 h. The residue was diluted with water 500 mL and extracted with ethyl acetate 600 mL. The combined organic layers were washed with brine 400mL, dried over sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=20/1 to 0/1- dichloromethane: ethyl acetate =1:1). Compound tert-butyl 9-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-3-azaspiro[5.5]undecane-3-carboxylate (110 mg, 162.28 μmol, 29% yield) was obtained as a white solid.

[00529] **LC-MS:** MS (ESI^+): t_R = 0.597 min, m/z = 678.4 [$M + H^+$]

[00530] To a solution of tert-butyl 9-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-3-azaspiro[5.5]undecane-3-carboxylate (130 mg, 191.79 μmol, 1.0 eq) in DCM (3 mL) was added TFA (219 mg, 1.92 mmol, 142.47 μL, 10.0 eq). The mixture was stirred at 25 °C for 15 min. The residue was filtered and concentrated under reduced pressure to give a residue. The residue was used to next step without purification. Compound 1-[1-(3-azaspiro[5.5]undecan-9-yl)-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]ethanone (120 mg) was obtained as a colorless oil and directly used in the next step without further purification.

[00531] **LC-MS:** MS (ESI^+): t_R = 0.432 min, m/z = 578.3 [$M + H^+$]

[00532] To a solution of 1-[1-(3-azaspiro[5.5]undecan-9-yl)-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]ethanone (120 mg), 6-chloro-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide (150 mg, 383.39 μmol, 1.8 eq) in NMP (2 mL) was added DPIEA (268 mg, 2.08 mmol, 361.80 μL, 10.0 eq). The mixture was stirred at 70 °C for 12h. The residue was diluted with water 100 mL and extracted with ethyl acetate 60mL. The combined organic layers were washed with brine 40mL, dried over sodium sulfate, filtered, and concentrated

under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, DCM: MeOH = 15:1). The residue was purified by prep-HPLC (column: Welch Xtimate C18 150*25mm*5um; mobile phase: [water(FA)-ACN]; gradient:53%-83% B over 10 min). Compound 6-[9-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-3-azaspiro[5.5]undecan-3-yl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide (67.29 mg, 72.07 μmol, 34% yield over two steps) was obtained as an off-white solid.

[00533] **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.98 (d, 1H, J=9.6 Hz), 7.88 (d, 1H, J=8.0 Hz), 7.5-7.6 (m, 2H), 7.4-7.4 (m, 1H), 7.4-7.4 (m, 1H), 6.9-7.1 (m, 4H), 6.86 (dd, 1H, J=2.3, 8.8 Hz), 6.3-6.7 (m, 1H), 4.3-4.4 (m, 2H), 4.14 (s, 1H), 4.0-4.1 (m, 1H), 3.9-4.0 (m, 5H), 3.7-3.8 (m, 7H), 2.7-2.9 (m, 4H), 2.1-2.2 (m, 7H), 2.0-2.1 (m, 4H), 1.95 (d, 2H, J=13.2 Hz), 1.83 (s, 4H), 1.7-1.8 (m, 2H), 1.63 (dd, 1H, J=1.6, 12.4 Hz), 1.4-1.5 (m, 2H), 1.3-1.4 (m, 2H)

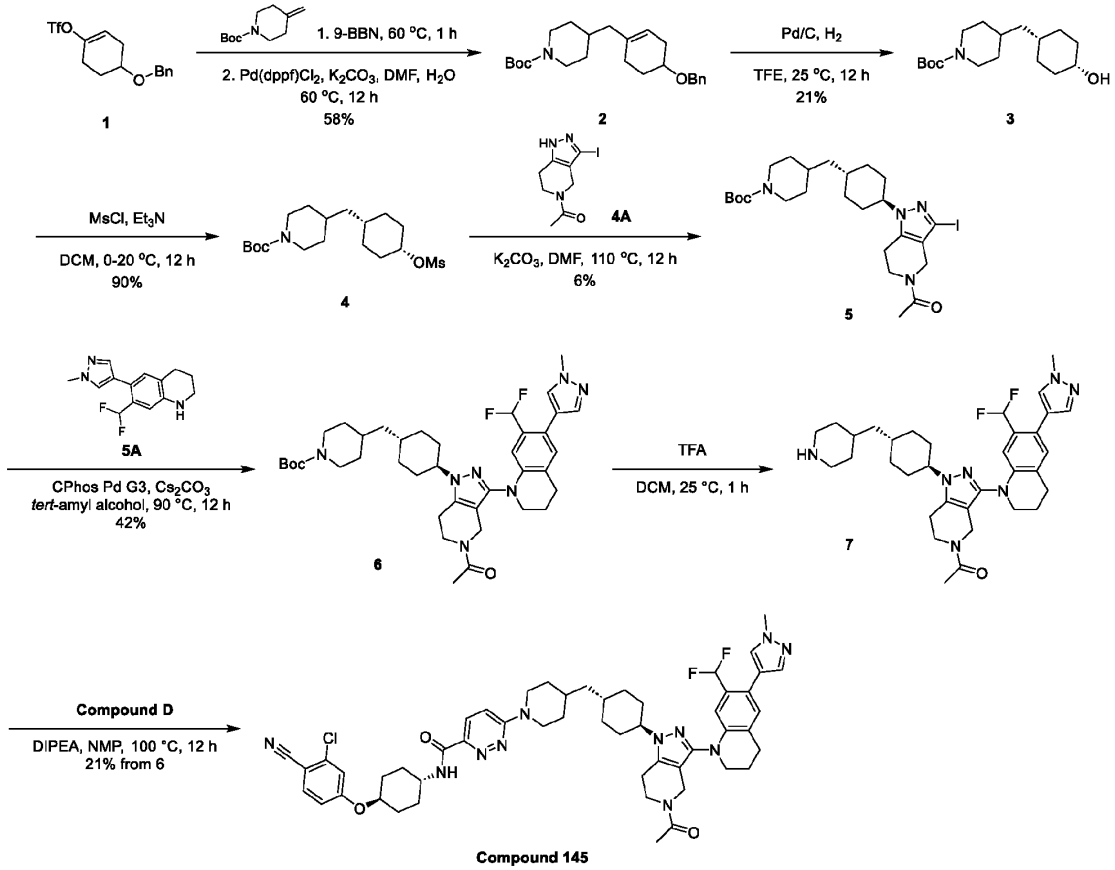
[00534] **LC-MS:** MS (ESI^+): t_R = 2.989 min, m/z = 932.7 [M + H^+]

[00535] The compounds below were prepared in a similar manner as described in Example 8.

Compound	Name	^{1}H NMR ($CDCl_3$)	LC-MS [M + H^+]
113	6-[9-[5-acetyl-3-(6-cyano-3,4-dihydro-2H-quinolin-1-yl)-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-3-azaspiro[5.5]undecan-3-yl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	(DMSO-d6) δ = 8.59 (d, J = 8.4 Hz, 1H), 7.83 (dd, J = 9.2, 19.6 Hz, 2H), 7.39 (dd, J = 2.0, 6.4 Hz, 2H), 7.35 - 7.24 (m, 2H), 7.13 (dd, J = 2.4, 8.8 Hz, 1H), 6.46 - 6.33 (m, 1H), 4.62 - 4.42 (m, 1H), 4.13 (br s, 2H), 4.05 (br d, J = 4.4 Hz, 1H), 3.92 - 3.80 (m, 1H), 3.79 - 3.64 (m, 6H), 3.64 - 3.54 (m, 2H), 2.87 - 2.78 (m, 3H), 2.72 (br s, 1H), 2.15 - 2.06 (m, 4H), 2.01 - 1.82 (m, 9H), 1.79 - 1.70 (m, 2H), 1.69 - 1.58 (m, 4H), 1.57 - 1.47 (m, 2H), 1.44 (br s, 2H), 1.38 - 1.28 (m, 2H)	827.4
179	6-[9-[5-[8-(5-acetyl-1-tetrahydropyran-4-yl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-3-yl)-3-isoquinolyl]-2-pyridyl]-3,9-diazaspiro[5.5]undecan-3-yl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	δ = 9.79-9.72 (m, 1 H) 8.92 (dd, *J*=5.2, 2.4 Hz, 1 H) 8.32 (d, *J*=5.6 Hz, 1 H) 8.02-7.96 (m, 2 H) 7.89 (d, *J*=8.0 Hz, 1 H) 7.88-7.81 (m, 1 H) 7.76-7.68 (m, 1 H) 7.57 (d, *J*=8.8 Hz, 1 H) 7.55-7.47 (m, 1 H) 7.03-6.98 (m, 2 H) 6.87 (dd, *J*=8.8, 2.4 Hz, 1 H) 6.82 (d, *J*=9.2 Hz, 1 H) 4.66 (s, 1 H) 4.49 (s, 1 H) 4.38-4.24 (m, 2 H) 4.22-4.14 (m, 2 H) 4.13-3.99 (m, 2 H) 3.85 (t, *J*=6.0 Hz, 1 H) 3.83-3.78 (m, 4 H) 3.70 (d, *J*=5.6 Hz, 4 H) 3.58 (t, *J*=12.0 Hz, 2 H) 2.94 (t, *J*=5.6 Hz, 1 H) 2.87 (t, *J*=5.6 Hz, 1 H) 2.53-2.38 (m, 2 H) 2.22 (s, 2 H) 2.19 (s, 2 H) 2.08 (s, 1 H) 1.98 (d, *J*=13.2 Hz, 2 H) 1.78-1.69 (m, 12 H) 1.53-1.47 (m, 2 H)	960.5
191	6-[2-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-9-azadispiro	(DMSO-*d*$_6$) δ = 8.59 (d, J = 8.4 Hz, 1H), 7.85 (d, J = 8.8 Hz, 1H), 7.81 - 7.74 (m, 2H), 7.50 (s, 1H), 7.39 (d, J = 2.4 Hz, 1H), 7.34 (d, J = 9.8 Hz, 1H), 7.15 - 7.09 (m, 2H), 6.94 - 6.64 (m, 2H), 4.67 - 4.48 (m, 2H), 4.18 - 4.06 (m, 2H), 3.89 -	944.6

Compound	Name	^{1}H NMR ($CDCl_3$)	LC-MS [M + H$^+$]
	[3.1.56.14] dodecan-9-yl]-N-[4-(3-chloro-4-cyano-phenoxy) cyclohexyl] pyridazine-3-carboxamide	3.83 (m, 4H), 3.71 - 3.57 (m, 8H), 2.86 - 2.79 (m, 3H), 2.14 - 2.02 (m, 7H), 2.02 - 1.84 (m, 9H), 1.71 - 1.42 (m, 10H), 1.23 (s, 1H)	

[00536] **Example 9**: Synthesis of 6-[4-[[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]cyclohexyl]methyl]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide **(Compound 145)**



[00537] Synthesis of **1** was reported in Journal of the American Chemical Society, 2001, vol. 123, # 27, p. 6724 - 6725.

[00538] Synthesis of **5A** was reported in WO2022/42707, 2022, A1.

[00539] A mixture of tert-butyl 4-methylenepiperidine-1-carboxylate (13.80 g, 69.93 mmol, 1.2 eq) in 9-BBN (0.5 M, 151.52 mL, 1.3 eq) was stirred at 60 °C for 1 h under N_2 atmosphere. After cooling the reactants, (4-benzyloxycyclohexen-1-yl) trifluoromethanesulfonate (19.60 g, 58.28 mmol, 1.0 eq), $Pd(dppf)Cl_2$ (4.26 g, 5.83 mmol, 0.1 eq), K_2CO_3 (12.08 g, 87.42 mmol, 1.5 eq), DMF (200 mL) and H_2O (20 mL) were added and the mixture was stirred at 60 °C for 12 h. NaOH (150 mL, 1 M) was added and the

mixture was poured into water (400 mL). The aqueous phase was extracted with ethyl acetate (400 mL × 2). The combined organic phase was washed with brine (400 mL × 3), dried with anhydrous sodium sulfate, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (0% - 5% ethyl acetate in petroleum ether). Compound tert-butyl 4-[(4-benzyloxycyclohexen-1-yl)methyl]piperidine-1-carboxylate (13.00 g, 33.72 mmol, 58% yield) was obtained as a yellow oil.

[00540] **LC-MS:** MS (ESI^+): t_R = 0.699 min, m/z = 408.3 [M + Na^+]

[00541] To a solution of tert-butyl 4-[(4-benzyloxycyclohexen-1-yl)methyl]piperidine-1-carboxylate (8.00 g, 20.75 mmol, 1.0 eq) in TFE (80 mL) was added Pd/C (2.00 g, 10% Pd on carbon, w/w) under N_2 atmosphere. The suspension was degassed and purged with H_2 for 3 times. The mixture was stirred under H_2 (50 Psi) at 25 °C for 12 h. The mixture was filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (5% - 40% ethyl acetate in petroleum ether). Compound tert-butyl 4-[(4-hydroxycyclohexyl)methyl]piperidine-1-carboxylate (1.32 g, 4.44 mmol, 21% yield) was obtained as a white solid.

[00542] **LC-MS:** MS (ESI^+): t_R = 0.554 min, m/z = 242.0 [M - 55]

[00543] **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 4.07 (br d, J = 13.2 Hz, 2H), 4.00 - 3.93 (m, 1H), 2.75 - 2.60 (m, 2H), 1.75 - 1.66 (m, 2H), 1.62 (br d, J = 10.8 Hz, 2H), 1.59 - 1.52 (m, 2H), 1.52 - 1.48 (m, 2H), 1.46 (s, 9H), 1.43 - 1.40 (m, 2H), 1.38 - 1.32 (m, 2H), 1.16 (t, J = 6.8 Hz, 2H), 1.05 (dq, J = 4.4, 12.4 Hz, 2H).

[00544] To a solution of tert-butyl 4-[(4-hydroxycyclohexyl)methyl]piperidine-1-carboxylate (1.44 g, 4.84 mmol, 1.0 eq) and MsCl (940 mg, 8.21 mmol, 1.69 eq) in DCM (15 mL) was added Et_3N (1.47 g, 14.52 mmol, 3.0 eq) at 0 °C. The mixture was stirred at 20 °C for 12 h. The mixture was poured into ice-water (100 mL). The aqueous phase was extracted with dichloromethane (100 mL × 2). The combined organic phase was washed with brine (80 mL × 2), dried with anhydrous sodium sulfate, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (10% - 30% ethyl acetate in petroleum ether). Compound tert-butyl 4-[(4-methylsulfonyloxycyclohexyl)methyl]piperidine-1-carboxylate (1.64 g, 4.37 mmol, 90% yield) was obtained as a colorless gum.

[00545] To a solution of tert-butyl 4-[(4-methylsulfonyloxycyclohexyl)methyl]piperidine-1-carboxylate (1.64 g, 4.37 mmol, 1.0 eq) in DMF (20 mL) was added K_2CO_3 (1.81 g, 13.10 mmol, 3.0 eq) and 1-(3-iodo-1,4,6,7-tetrahydropyrazolo[4,3-c]pyridin-5-yl)ethanone (1.27 g, 4.37 mmol, 1.0 eq). The mixture was stirred at 110 °C for 12 h. The mixture was poured into water (100 mL). The aqueous phase was extracted with ethyl acetate (100 mL × 2). The combined organic phase was washed with brine (100 mL × 2), dried with anhydrous sodium sulfate, filtered and concentrated in vacuum. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150*40mm* 15um; mobile phase: [water (FA)-ACN]; gradient: 58%-88% B over 15 min). Compound tert-butyl 4-[[4-(5-acetyl-3-iodo-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl)cyclohexyl]methyl]piperidine-1-carboxylate (150 mg, 262.93 μmol, 6% yield) was obtained as a white solid.

[00546] **LC-MS:** MS (ESI^+): t_R = 0.612 min, m/z = 571.3 [M + H^+]

[00547] **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 4.43 - 4.21 (m, 2H), 4.16 - 3.98 (m, 2H), 3.95 - 3.65 (m, 3H),

2.85 - 2.51 (m, 4H), 2.19 (s, 3H), 2.05 - 1.76 (m, 6H), 1.66 - 1.57 (m, 3H), 1.55 - 1.37 (m, 11H), 1.15 (t, J = 7.2 Hz, 2H), 1.08 - 0.98 (m, 3H).

[00548] A mixture of tert-butyl 4-[[4-(5-acetyl-3-iodo-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl)cyclohexyl]methyl]piperidine-1-carboxylate (120 mg, 210.34 μmol, 1.0 eq), 7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-1,2,3,4-tetrahydroquinoline (83 mg, 315.51 μmol, 1.5 eq), CPHOS PD G3 (17 mg, 21.03 μmol, 0.1 eq) and Cs_2CO_3 (206 mg, 631.02 μmol, 3.0 eq) in 2-methylbutan-2-ol (3 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 90 °C for 12 h under N_2 atmosphere. The mixture was poured into water (50 mL). The aqueous phase was extracted with ethyl acetate (50 mL × 2). The combined organic phase was washed with brine (40 mL × 2), dried with anhydrous sodium sulfate, filtered and concentrated in vacuum. The residue was purified by prep-Thin-layer chromatography (SiO_2, dichloromethane : methanol = 15:1). Compound tert-butyl 4-[[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]cyclohexyl]methyl]piperidine-1-carboxylate (62 mg, 87.83 μmol, 42% yield) was obtained as a yellow solid.

[00549] **LC-MS:** MS (ESI^+): t_R = 0.647 min, m/z = 706.4 [$M + H^+$]

[00550] To a solution of tert-butyl 4-[[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]cyclohexyl]methyl]piperidine-1-carboxylate (70 mg, 99.17 μmol, 1.0 eq) in DCM (5 mL) was added TFA (3.07 g, 26.93 mmol, 2 mL). The mixture was stirred at 25 °C for 1 h. The mixture was concentrated under reduced pressure. Compound 1-[3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-1-[4-(4-piperidylmethyl)cyclohexyl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]ethanone (70 mg) was obtained as a yellow gum and directly used in the next step without further purification.

[00551] **LC-MS:** MS (ESI^+): t_R = 0.463 min, m/z = 606.4 [$M + H^+$]

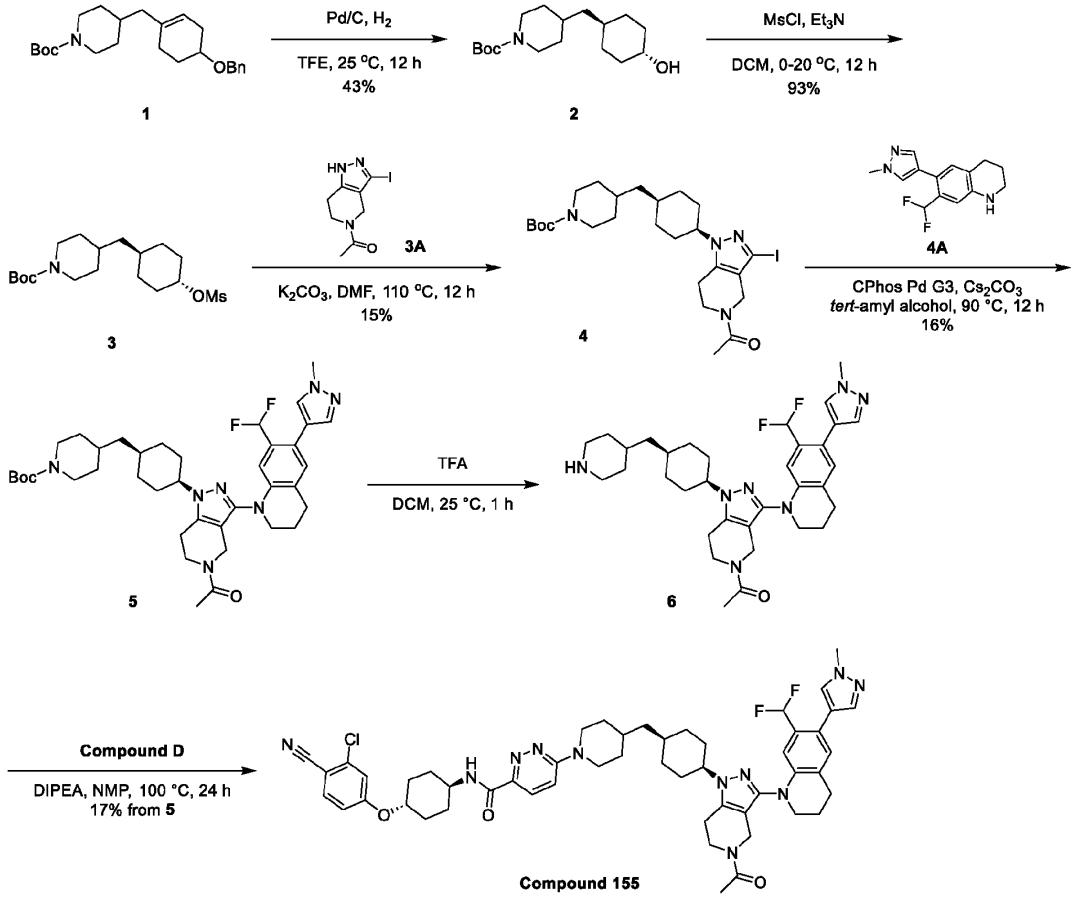
[00552] To a solution of 1-[3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-1-[4-(4-piperidylmethyl)cyclohexyl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]ethanone (70 mg) in NMP (2 mL) was added DIPEA (75 mg, 583.51 μmol, 6.0 eq) and 6-chloro-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide (76 mg, 194.50 μmol, 2.0 eq). The mixture was stirred at 100 °C for 12 h. The mixture was poured into water (30 mL). The aqueous phase was extracted with ethyl acetate (30 mL × 2). The combined organic phase was washed with brine (30 mL × 2), dried with anhydrous sodium sulfate, filtered and concentrated in vacuum. The residue was purified by prep-Thin-layer chromatography (SiO_2, dichloromethane : methanol = 15:1) and further purified by prep-HPLC (column: Welch Xtimate C18 150*25mm*5um; mobile phase: [water (FA)-ACN]; gradient: 58%-88% B over 10 min). Compound 6-[4-[[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]cyclohexyl]methyl]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide (19.34 mg, 19.93 μmol, 21% yield over two steps) was obtained as a white solid.

[00553] **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.97 (d, J = 9.6 Hz, 1H), 7.88 (d, J = 8.0 Hz, 1H), 7.57 (d, J =

8.8 Hz, 1H), 7.55 - 7.52 (m, 1H), 7.45 - 7.37 (m, 1H), 7.07 - 6.95 (m, 3H), 6.90 - 6.83 (m, 2H), 6.69 - 6.37 (m, 1H), 4.51 (br d, J = 13.6 Hz, 2H), 4.38 - 4.29 (m, 1H), 4.28 - 4.11 (m, 2H), 4.10 - 4.01 (m, 1H), 3.96 (d, J = 2.0 Hz, 3H), 3.91 (br t, J = 6.0 Hz, 2H), 3.81 - 3.61 (m, 3H), 3.08 - 2.99 (m, 2H), 2.91 - 2.84 (m, 2H), 2.82 - 2.71 (m, 2H), 2.23 - 2.03 (m, 10H), 2.01 - 1.89 (m, 5H), 1.83 (br d, J = 12.8 Hz, 2H), 1.75 - 1.66 (m, 3H), 1.52 - 1.41 (m, 3H), 1.27 - 1.18 (m, 4H), 1.15 - 1.02 (m, 2H).

[00554] **LC-MS:** MS (ESI^+): t_R = 3.197 min, m/z = 960.6 [M + H^+]

[00555] **Example 10**: Synthesis of 6-[4-[[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]cyclohexyl]methyl]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide **(Compound 155)**



[00556] To a solution of tert-butyl 4-[(4-benzyloxycyclohexen-1-yl)methyl]piperidine-1-carboxylate (2.65 g, 6.87 mmol, 1.0 eq) in TFE (20 mL) was added Pd/C (0.80 g, 10% Pd on carbon, w/w) under N_2 atmosphere. The suspension was degassed and purged with H_2 for 3 times. The mixture was stirred under H_2 (50 Psi) at 25 °C for 12 h. The mixture was filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150*40mm* 15um; mobile phase: [water (FA)-ACN]; gradient: 40%-70% B over 22 min). Compound tert-butyl 4-[(4-

hydroxycyclohexyl)methyl]piperidine-1-carboxylate (880 mg, 2.96 mmol, 43% yield) was obtained as a yellow solid.

[00557] **LC-MS:** MS (ESI^+): t_R = 0.527 min, m/z = 242.2 [M - 55]

[00558] **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 4.07 (br d, J = 1.2 Hz, 2H), 3.55 (tt, J = 4.4, 10.8 Hz, 1H), 2.67 (br t, J = 12.4 Hz, 2H), 2.03 - 1.92 (m, 2H), 1.79 - 1.71 (m, 2H), 1.62 (br d, J = 12.8 Hz, 2H), 1.51 - 1.48 (m, 1H), 1.46 (s, 9H), 1.35 - 1.28 (m, 1H), 1.28 - 1.19 (m, 2H), 1.14 - 1.08 (m, 2H), 1.08 - 0.99 (m, 2H), 0.99 - 0.86 (m, 2H).

[00559] To a solution of tert-butyl 4-[(4-hydroxycyclohexyl)methyl]piperidine-1-carboxylate (880 mg, 2.96 mmol, 1.0 eq) and MsCl (580 mg, 5.06 mmol, 1.71 eq) in DCM (10 mL) was added Et_3N (898 mg, 8.88 mmol, 1.24 mL, 3.0 eq) at 0 °C. The mixture was stirred at 20 °C for 12 h. The mixture was poured into ice-water (100 mL). The aqueous phase was extracted with dichloromethane (100 mL × 2). The combined organic phase was washed with brine (80 mL × 2), dried with anhydrous sodium sulfate, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (10% - 30% ethyl acetate in petroleum ether). Compound tert-butyl 4-[(4-methylsulfonyloxycyclohexyl)methyl]piperidine-1-carboxylate (1.03 g, 2.74 mmol, 93% yield) was obtained as a white solid.

[00560] To a solution of tert-butyl 4-[(4-methylsulfonyloxycyclohexyl)methyl]piperidine-1-carboxylate (1.03 g, 2.74 mmol, 1.0 eq) in DMF (10 mL) was added K_2CO_3 (1.14 g, 8.23 mmol, 3.0 eq) and 1-(3-iodo-1,4,6,7-tetrahydropyrazolo[4,3-c]pyridin-5-yl)ethanone (798 mg, 2.74 mmol, 1.0 eq). The mixture was stirred at 110 °C for 12 h. The mixture was poured into water (100 mL). The aqueous phase was extracted with ethyl acetate (100 mL × 2). The combined organic phase was washed with brine (100 mL × 3), dried with anhydrous sodium sulfate, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (50% - 100% ethyl acetate in petroleum ether) and further purified by prep-HPLC (column: Phenomenex luna C18 150*40mm* 15um; mobile phase: [water (FA)-ACN]; gradient: 58%-88% B over 15 min). Compound tert-butyl 4-[[4-(5-acetyl-3-iodo-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl)cyclohexyl]methyl]piperidine-1-carboxylate (235 mg, 407.80 μmol, 15% yield) was obtained as a yellow solid.

[00561] **LC-MS:** MS (ESI^+): t_R = 0.622 min, m/z = 571.4 [$M + H^+$]

[00562] **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 4.44 - 4.21 (m, 2H), 4.08 (br d, J = 2.8 Hz, 2H), 3.96 - 3.68 (m, 3H), 2.84 - 2.51 (m, 4H), 2.19 (s, 3H), 2.14 - 2.01 (m, 2H), 1.82 (br s, 1H), 1.73 - 1.63 (m, 7H), 1.62 - 1.55 (m, 2H), 1.46 (s, 9H), 1.42 - 1.35 (m, 2H), 1.15 - 1.02 (m, 2H).

[00563] A mixture of tert-butyl 4-[[4-(5-acetyl-3-iodo-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl)cyclohexyl]methyl]piperidine-1-carboxylate (200 mg, 350.57 μmol, 1.0 eq), 7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-1,2,3,4-tetrahydroquinoline (111 mg, 420.68 μmol, 1.2 eq), CPHOS PD G3 (28 mg, 35.06 μmol, 0.1 eq) and Cs_2CO_3 (343 mg, 1.05 mmol, 3.0 eq) in 2-methylbutan-2-ol (5 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 90 °C for 12 h under N_2 atmosphere. The mixture was poured into water (50 mL). The aqueous phase was extracted with dichloromethane (50 mL × 2). The combined organic phase was washed with brine (50 mL × 2), dried with anhydrous sodium sulfate,

filtered and concentrated in vacuum. The residue was purified by prep-Thin-layer chromatography (SiO_2, dichloromethane : methanol = 20:1) and further purified by prep-HPLC (column: Welch Xtimate C18 150*25mm*5um; mobile phase: [water (FA)-ACN]; gradient: 70%-90% B over 10 min). Compound tert-butyl 4-[[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]cyclohexyl]methyl]piperidine-1-carboxylate (40 mg, 56.67 μmol, 16% yield) was obtained as a light yellow solid.

[00564] **LC-MS:** MS (ESI^+): t_R = 0.634 min, m/z = 706.5 [M + H^+]

[00565] To a solution of tert-butyl 4-[[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]cyclohexyl]methyl]piperidine-1-carboxylate (40 mg, 56.67 μmol, 1.0 eq) in DCM (3 mL) was added TFA (1.54 g, 13.46 mmol, 1 mL). The mixture was stirred at 25 °C for 1 h. The mixture was concentrated under reduced pressure. Compound 1-[3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-1-[4-(4-piperidylmethyl)cyclohexyl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]ethanone (40 mg) was obtained as a yellow gum and directly used in the next step without further purification.

[00566] **LC-MS:** MS (ESI^+): t_R = 0.465 min, m/z = 606.4 [M + H^+]

[00567] To a solution of 1-[3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-1-[4-(4-piperidylmethyl)cyclohexyl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]ethanone (40 mg) in NMP (2 mL) was added DIPEA (36 mg, 277.86 μmol, 5.0 eq) and 6-chloro-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide (43 mg, 111.14 μmol, 2.0 eq). The mixture was stirred at 100 °C for 24 h. The mixture was poured into water (30 mL). The aqueous phase was extracted with ethyl acetate (30 mL × 2). The combined organic phase was washed with brine (30 mL × 2), dried with anhydrous sodium sulfate, filtered and concentrated in vacuum. The residue was purified by prep-Thin-layer chromatography (SiO_2, dichloromethane : methanol = 15:1) and further purified by prep-HPLC (column: Welch Xtimate C18 150*25mm*5um; mobile phase: [water (FA)-ACN]; gradient: 60%-90% B over 10 min). Compound 6-[4-[[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]cyclohexyl]methyl]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide (9.09 mg, 9.37 μmol, 17% yield over two steps) was obtained as a white solid.

[00568] **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.96 (d, J = 9.6 Hz, 1H), 7.87 (d, J = 8.0 Hz, 1H), 7.59 - 7.52 (m, 2H), 7.41 (d, J = 6.4 Hz, 1H), 7.06 - 6.99 (m, 2H), 6.99 - 6.91 (m, 2H), 6.86 (dd, J = 2.4, 8.8 Hz, 1H), 6.69 - 6.36 (m, 1H), 4.50 (br d, J = 13.2 Hz, 2H), 4.37 - 4.30 (m, 1H), 4.29 - 4.13 (m, 2H), 4.10 - 4.02 (m, 1H), 3.96 (s, 3H), 3.96 - 3.92 (m, 1H), 3.90 (br t, J = 6.0 Hz, 1H), 3.78 - 3.65 (m, 3H), 3.03 (br t, J = 12.0 Hz, 2H), 2.88 (td, J = 6.0, 11.6 Hz, 2H), 2.82 - 2.71 (m, 2H), 2.23 - 2.04 (m, 11H), 1.91 - 1.82 (m, 3H), 1.76 (br d, J = 11.6 Hz, 4H), 1.72 - 1.62 (m, 5H), 1.51 - 1.40 (m, 4H), 1.30 - 1.23 (m, 2H).

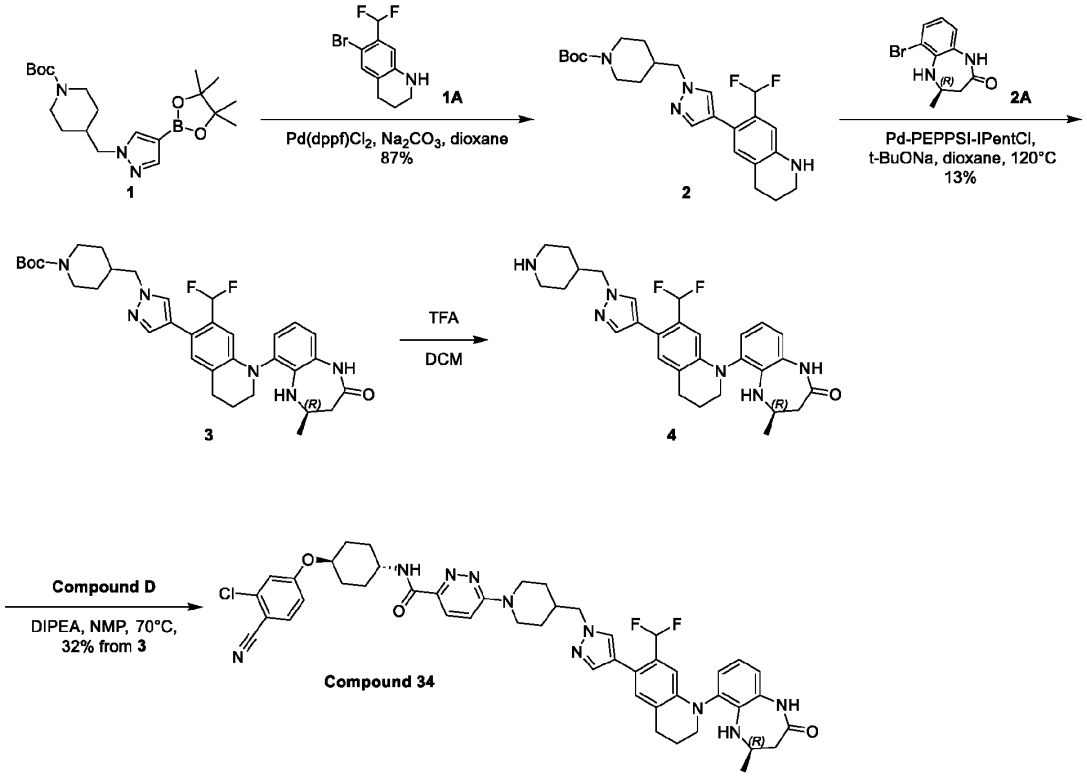
[00569] **LC-MS:** MS (ESI^+): t_R = 3.152 min, m/z = 960.6 [M + H^+]

[00570] The compounds below were prepared in a similar manner as described in Example 10.

Compound	Name	^{1}H NMR ($CDCl_3$)	LC-MS [M + H$^+$]
146	6-[4-[[4-[5-acetyl-3-[6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-1,7-naphthyridin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]cyclohexyl]methyl]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	δ = 7.96 (d, *J* = 9.6 Hz, 1H), 7.88 (d, *J* = 8.4 Hz, 1H), 7.84 - 7.79 (m, 2H), 7.57 (d, *J* = 8.8 Hz, 1H), 7.16 - 7.10 (m, 1H), 7.01 (d, *J* = 2.4 Hz, 1H), 6.97 (d, *J* = 9.6 Hz, 1H), 6.86 (dd, *J* = 2.4, 8.8 Hz, 1H), 4.56 - 4.45 (m, 2H), 4.38 - 4.29 (m, 2H), 4.19 - 4.15 (m, 1H), 4.10 - 4.01 (m, 1H), 3.75 - 3.64 (m, 3H), 3.08 - 2.99 (m, 2H), 2.91 - 2.83 (m, 2H), 2.79 (br t, *J* = 5.4 Hz, 1H), 2.75 - 2.70 (m, 1H), 2.25 - 2.14 (m, 6H), 2.12 - 2.05 (m, 4H), 2.01 - 1.88 (m, 6H), 1.86 - 1.78 (m, 3H), 1.77 - 1.70 (m, 4H), 1.52 - 1.44 (m, 4H), 1.29 - 1.23 (m, 3H), 1.23 - 1.17 (m, 3H), 1.13 - 1.04 (m, 2H)	911.5
172	6-[4-[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]cyclohexyl]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	δ = 7.97 (d, *J* = 9.5 Hz, 1H), 7.88 (d, *J* = 8.3 Hz, 1H), 7.57 (d, *J* = 8.8 Hz, 1H), 7.54 - 7.52 (m, 1H), 7.42 - 7.38 (m, 1H), 7.05 - 6.96 (m, 3H), 6.88 - 6.84 (m, 2H), 6.68 - 6.36 (m, 1H), 4.56 (d, *J* = 13.0 Hz, 2H), 4.38 - 4.28 (m, 1H), 4.26 (s, 1H), 4.12 (s, 1H), 4.10 - 4.02 (m, 1H), 3.95 (d, *J* = 2.1 Hz, 3H), 3.93 - 3.85 (m, 2H), 3.77 - 3.65 (m, 3H), 3.00 (t, *J* = 11.9 Hz, 2H), 2.87 (td, *J* = 6.0, 12.0 Hz, 2H), 2.80 (t, *J* = 5.4 Hz, 1H), 2.74 (t, *J* = 5.6 Hz, 1H), 2.23 - 2.15 (m, 5H), 2.11 - 2.04 (m, 4H), 2.04 - 1.94 (m, 6H), 1.88 (d, *J* = 11.3 Hz, 2H), 1.71 (s, 1H), 1.53 - 1.44 (m, 3H), 1.43 - 1.11 (m, 6H)	946.5
173	6-[4-[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]cyclohexyl]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	*δ* = 7.96 (d, J = 9.6 Hz, 1H), 7.88 (d, J = 8.4 Hz, 1H), 7.56 (d, J = 8.8 Hz, 1H), 7.54 (d, J = 5.2 Hz, 1H), 7.41 (d, J = 6.4 Hz, 1H), 7.07 - 6.97 (m, 3H), 6.95 (d, J = 2.0 Hz, 1H), 6.86 (dd, J = 2.4, 8.8 Hz, 1H), 6.69 - 6.37 (m, 1H), 4.53 (d, J = 13.2 Hz, 2H), 4.38 - 4.31 (m, 1H), 4.31 - 4.13 (m, 2H), 4.10 - 3.99 (m, 2H), 3.95 (d, J = 2.8 Hz, 3H), 3.91 (t, J = 5.6 Hz, 1H), 3.82 - 3.61 (m, 3H), 3.03 (t, J = 12.4 Hz, 2H), 2.93 - 2.84 (m, 2H), 2.82 - 2.70 (m, 2H), 2.23 - 2.05 (m, 11H), 1.97 (d, J = 11.6 Hz, 4H), 1.86 (dd, J = 4.0, 9.2 Hz, 1H), 1.81 - 1.74 (m, 2H), 1.71 - 1.67 (m, 2H), 1.60 - 1.54 (m, 2H), 1.50 - 1.40 (m, 2H), 1.38 - 1.31 (m, 1H), 1.27 - 1.17 (m, 2H)	946.5
177	6-[4-[[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo [4,3-c] pyridin-1-yl]-1-piperidyl] methyl]-4-methoxy-1-	(DMSO-d_6) δ = 8.62 - 8.55 (m, 1H), 8.22 (s, 1H), 7.87 - 7.78 (m, 2H), 7.75 (s, 1H), 7.49 (s, 1H), 7.41 - 7.37 (m, 1H), 7.34 (d, *J* = 9.6 Hz, 1H), 7.16 - 7.08 (m, 2H), 6.94 - 6.63 (m, 2H), 4.60 - 4.47 (m, 1H), 4.18 - 4.07 (m, 4H), 4.01 - 3.94 (m, 1H), 3.90 - 3.82 (m, 4H), 3.75 -	991.6

Compound	Name	^{1}H NMR ($CDCl_3$)	LC-MS [M + H$^+$]
	piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy) cyclohexyl] pyridazine-3-carboxamide	3.66 (m, 2H), 3.61 - 3.55 (m, 2H), 3.34 (s, 2H), 3.18 (s, 3H), 3.04 - 2.97 (m, 2H), 2.84 (s, 3H), 2.76 - 2.65 (m, 1H), 2.42 (s, 2H), 2.31 - 2.21 (m, 2H), 2.14 - 2.05 (m, 4H), 2.03 - 1.93 (m, 5H), 1.92 - 1.84 (m, 3H), 1.84 - 1.75 (m, 3H), 1.67 - 1.47 (m, 6H)	
178	6-[4-[5-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-4,5,6,7-tetrahydroindazol-1-yl]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	δ = 8.02 (d, J = 9.6 Hz, 1H), 7.88 (d, J = 8.4 Hz, 1H), 7.62 - 7.51 (m, 2H), 7.41 (d, J = 6.8 Hz, 1H), 7.30 (d, J = 2.8 Hz, 1H), 7.10 - 6.99 (m, 3H), 6.94 - 6.83 (m, 2H), 6.72 - 6.35 (m, 1H), 4.78 - 4.60 (m, 2H), 4.41 - 4.20 (m, 4H), 4.17 - 4.05 (m, 2H), 4.01 - 3.92 (m, 3H), 3.99 - 3.86 (m, 1H), 3.82 - 3.62 (m, 3H), 3.25 (t, J = 12.6 Hz, 2H), 3.18 - 3.08 (m, 1H), 3.00 - 2.74 (m, 7H), 2.59 - 2.45 (m, 1H), 2.33 - 2.26 (m, 2H), 2.23 - 2.14 (m, 5H), 2.13 - 2.05 (m, 5H), 1.79 - 1.67 (m, 4H), 1.53 - 1.44 (m, 2H)	984.6

[00571] **Example 11**: Synthesis of N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]-6-[4-[[4-[7-(difluoromethyl)-1-[(4R)-4-methyl-2-oxo1,3,4,5-tetrahydro-1,5-benzodiazepin-6-yl]-3,4-dihydro-2H-quinolin-6-yl]pyrazol-1-yl]methyl]-1- piperidyl]pyridazine-3-carboxamide **(Compound 34)**



[00572] Synthesis of **1A** was described in the report of US2019/308978, 2019, A1

[00573] Synthesis of **2A** was described in the report of Journal of Medicinal Chemistry, 2021, vol. 64, # 14, p. 10102 - 10123

[00574] To a solution of tert-butyl 4-[[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazol-1-yl]methyl]piperidine-1- carboxylate (1.94 g, 4.96 mmol, 1.3 eq) in dioxane (30 mL) and H_2O (3 mL) was added Na_2CO_3 (950.04 mg, 11.45 mmol, 3 eq) and 6-bromo-7-(difluoromethyl)-1,2,3,4-tetrahydroquinoline (1.0 g, 3.82 mmol, 1 eq) and $Pd(dppf)Cl_2$ (279.18 mg, 381.54 μmol, 0.1 eq). The mixture was stirred at 80°C for 12 h under N_2 atmosphere. The reaction mixture was diluted with H_2O (50 mL) and extracted with DCM (50 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether: Ethyl acetate = 1: 0 to 0: 1 and Dichloromethane: Methanol = 1: 0 to 1: 1). Compound tert-butyl 4-[[4-[7-(difluoromethyl)-1,2,3,4-tetrahydroquinolin-6-yl]pyrazol-1-yl]methyl]piperidine-1- carboxylate (1.6 g, 3.31 mmol, 87% yield) was obtained as a yellow solid.

[00575] **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 7.55 (s, 1H), 7.38 (s, 1H), 6.97 (s, 1H), 6.81 (s, 1H), .6.67 - 6.37 (m, 1H), 4.18 - 3.98 (m, 6H), 3.40 - 3.30 (m, 2H), 2.82 - 2.66 (m, 4H), 2.15 - 2.08 (m, 1H), 1.97 - 1.95 (m, 1H), 1.56 (s, 4H), 1.25 (s, 9H).

[00576] **LC-MS:** MS (ESI^+): t_R = 0.553 min, m/z = 447.2 [$M + H^+$]

[00577] To a solution of tert-butyl 4-[[4-[7-(difluoromethyl)-1,2,3,4-tetrahydroquinolin-6-yl]pyrazol-1-yl]methyl]piperidine1-carboxylate (1.0 g, 2.24 mmol, 1 eq) in dioxane (20 mL) was added Pd-PEPPSI-IPentCl (192.72 mg, 223.95 μmol, 0.1 eq) and rac-(4R)-6-bromo-4-methyl-1,3,4,5-tetrahydro-1,5-benzodiazepin-2-one (856.97 mg, 3.36 mmol, 1.5 eq) and t-BuONa (645.64 mg, 6.72 mmol, 3 eq). The mixture was stirred at 120°C for 12 h under N_2 atmosphere. The reaction mixture was diluted with H_2O (20 mL) and extracted with DCM (30 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150*25mm* 10um;mobile phase: [water(FA)-ACN];gradient:55%-75% B over 15 min). Compound tert-butyl 4-[[4-[7-(difluoromethyl)-1-[rac-(4R)-4-methyl-2-oxo-1,3,4,5-tetrahydro-1,5-benzodiazepin-6- yl]-3,4-dihydro-2H-quinolin-6-yl]pyrazol-1-yl]methyl]piperidine-1-carboxylate (180 mg, 281.28 μmol, 13% yield) was obtained as a yellow solid.

[00578] **LC-MS:** MS (ESI^+): t_R = 0.593 min, m/z = 521.3 [$M - 100^-$]

[00579] To a solution of tert-butyl 4-[[4-[7-(difluoromethyl)-1-[rac-(4R)-4-methyl-2-oxo-1,3,4,5-tetrahydro-1,5- benzodiazepin-6-yl]-3,4-dihydro-2H-quinolin-6-yl]pyrazol-1-yl]methyl]piperidine-1-carboxylate (160 mg, 257.76 μmol, 1 eq) in DCM (4 mL) was added TFA (6.14 g, 53.85 mmol, 4.00 mL, 208.91 eq). The mixture was stirred at 20°C for 0.5 h. The reaction mixture was concentrated under reduced pressure to give a residue. Compound rac-(4R)-6-[7-(difluoromethyl)-6-[1-(4-piperidylmethyl)pyrazol-4-yl]-3,4-dihydro-2H-quinolin-1-yl]-4- methyl-1,3,4,5-tetrahydro-1,5-benzodiazepin-2-one (134 mg) was obtained as a yellow oil and directly used in the next step without further purification.

[00580] **LC-MS:** MS (ESI^+): t_R = 0.439 min, m/z = 521.4 [$M + H^+$]

[00581] To a solution of (4R)-6-[7-(difluoromethyl)-6-[1-(4-piperidylmethyl)pyrazol-4-yl]-3,4-dihydro-2H-quinolin-1-yl]-4- methyl-1,3,4,5-tetrahydro-1,5-benzodiazepin-2-one (134 mg, 257.39 μmol, 1 eq) and 6-chloro-N-[4-(3-chloro-4- cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide (151.05 mg, 386.08 μmol, 1.5 eq) in NMP (2 mL) was added DIPEA (498.98 mg, 3.86 mmol, 672.48 μL, 15 eq). The mixture was stirred at 70°C for 12 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150*25mm* 10um; mobile phase: [water(FA)-ACN];gradient:58%-88% B over 1 min). Compound N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]-6-[4-[[4-[7-(difluoromethyl)-1-[(4R)-4-methyl-2-oxo1,3,4,5-tetrahydro-1,5-benzodiazepin-6-yl]-3,4-dihydro-2H-quinolin-6-yl]pyrazol-1-yl]methyl]-1- piperidyl]pyridazine-3-carboxamide (74.32 mg, 82.18 μmol, 32% yield over two steps) was obtained as a yellow solid.

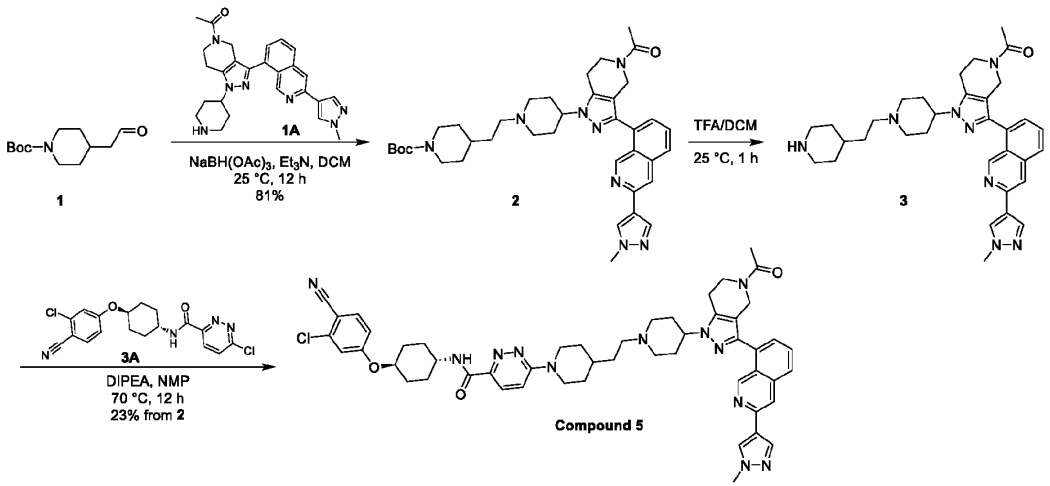
[00582] **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 9.64 (d, J = 4.8 Hz, 1H), 8.60 (d, J = 8.4 Hz, 1H), 7.87 - 7.76 (m, 2H), 7.74 (s, 1H), 7.51 (s, 1H), 7.41 - 7.30 (m, 2H), 7.15 - 7.06 (m, 2H), 6.97 - 6.86 (m, 2H), 6.85 - 6.78 (m, 1H), 6.78 - 6.51 (m, 1H), 6.29 (d, J = 5.2 Hz, 1H), 4.79 - 4.57 (m, 1H), 4.56 - 4.38 (m, 3H), 4.05 (d, J = 6.8 Hz, 2H), 3.95 - 3.81 (m, 2H), 3.60 - 3.38 (m, 2H), 3.09 - 2.86 (m, 4H), 2.85 - 2.51 (m, 1H), 2.35 - 2.13 (m, 3H), 2.11 - 1.97 (m, 3H), 1.89 (d, J = 10.4 Hz, 2H), 1.68 - 1.56 (m, 4H), 1.55 - 1.46 (m, 2H), 1.30 - 1.10 (m, 4H), 1.08 (d, J = 6.4 Hz, 1H).

[00583] **LC-MS:** MS (ESI$^+$): t_R = 2.075 min, m/z = 875.5 [M + H$^+$]

[00584] The compounds below were prepared in a similar manner as described in Example 11.

Compound	Name	^{1}H NMR ($CDCl_3$)	LC-MS [M + H$^+$]
36	N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]-6-[4-[2-[4-[7-(difluoromethyl)-1-[(4R)-4-methyl-2-oxo-1,3,4,5-tetrahydro-1,5-benzodiazepin-6-yl]-3,4-dihydro-2H-quinolin-6-yl]pyrazol-1-yl]ethyl]-1-piperidyl]pyridazine-3-carboxamide	δ = 8.00 (d, 1H, J=9.6 Hz), 7.86 (d, 1H, J=8.4 Hz), 7.5-7.6 (m, 3H), 7.44 (s, 1H), 7.09 (s, 1H), 6.9-7.1 (m, 3H), 6.8-6.9 (m, 3H), 6.3-6.6 (m, 2H), 4.51 (d, 2H, J=13.2 Hz), 4.2-4.4 (m, 4H), 3.9-4.1 (m, 2H), 3.3-3.7 (m, 2H), 2.9-3.1 (m, 4H), 2.4-2.8 (m, 2H), 2.1-2.2 (m, 6H), 1.9-1.9 (m, 4H), 1.6-1.7 (m, 3H), 1.4-1.5 (m, 2H), 1.2-1.4 (m, 5H)	889.5

[00585] **Example 12**: Synthesis of 6-[4-[2-[4-[5-acetyl-3-[3-(1-methylpyrazol-4-yl)-8-isoquinolyl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]ethyl]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide **(Compound 5)**



[00586] tert-butyl 4-(2-oxoethyl)piperidine-1-carboxylate (150 mg, 659 μmol, 1.5 eq) was added to the mixture of 1-[3-[3-(1-methylpyrazol-4-yl)-8-isoquinolyl]-1-(4-piperidyl)-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]ethanone (200 mg, 439 μmol, 1.0 eq) and Et_3N (444 mg, 4.39 mmol, 10.0 eq) in DCM (5 mL) and stirred at 25 °C for 0.5 h. $NaBH(OAc)_3$ (465 mg, 2.20 mmol, 5.0 eq) was added to the above reaction mixture and stirred at 25 °C for 12 h under N_2. The mixture was poured into water (20 mL). The aqueous phase was extracted with ethyl acetate (20 mL × 3), dried with anhydrous sodium sulfate, filtered and concentrated under vacuum. The residue was purified by prep-TLC (SiO_2, DCM: MeOH = 15:1). Compound tert-butyl 4-[2-[4-[5-acetyl-3-[3-(1-methylpyrazol-4-yl)-8-isoquinolyl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]ethyl]piperidine-1-carboxylate (250 mg, 356 μmol, 81% yield) was obtained as a yellow oil.

[00587] **LC-MS:** MS (ESI^+): t_R = 0.509 min, m/z = 667.6 [$M + H^+$]

[00588] To a solution of tert-butyl 4-[2-[4-[5-acetyl-3-[3-(1-methylpyrazol-4-yl)-8-isoquinolyl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]ethyl]piperidine-1-carboxylate (150 mg, 225 μmol, 1.0 eq) in DCM (2 mL) was added TFA (1.07 g, 9.42 mmol, 41.9 eq) .The mixture was stirred at 25 °C for 1 h under N_2. The mixture was concentrated to give a residue. Compound 1-[3-[3-(1-methylpyrazol-4-yl)-8-isoquinolyl]-1-[1-[2-(4-piperidyl)ethyl]-4-piperidyl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]ethanone (150 mg) as a yellow oil and directly used in the next step without further purification.

[00589] **LC-MS:** MS (ESI^+): t_R = 0.440 min, m/z = 567.4 [$M + H^+$]

[00590] To a solution of 1-[3-[3-(1-methylpyrazol-4-yl)-8-isoquinolyl]-1-[1-[2-(4-piperidyl)ethyl]-4-piperidyl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]ethanone (150 mg, 220 μmol, 1.0 eq) and 6-chloro-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide (103 mg, 264 μmol, 1.2 eq) in NMP (2 mL) was added DIPEA (85 mg, 661 μmol, 3.0 eq) .The mixture was stirred at 70 °C for 12 h under N_2. The mixture was poured into water (20 mL). The aqueous phase was extracted with ethyl acetate (20 mL × 3), dried with anhydrous sodium sulfate, filtered and concentrated under vacuum. This residue was purified by prep-HPLC (column: Phenomenex luna C18 150 × 25mm × 10um;mobile phase: [water(FA)-

ACN];gradient:31%-61% B over 10 min) to give 6-[4-[2-[4-[5-acetyl-3-[3-(1-methylpyrazol-4-yl)-8-isoquinolyl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]ethyl]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide (49.78 mg, 50.5 μmol, 23% yield over two steps) was obtained as a off-white solid.

[00591] **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 9.70 (d, J = 7.6 Hz, 1H), 8.41 (s, 1H), 8.09 - 7.99 (m, 2H), 7.96 (d, J = 9.6 Hz, 1H), 7.87 (d, J = 8.4 Hz, 1H), 7.83 - 7.76 (m, 2H), 7.73 - 7.65 (m, 1H), 7.56 (d, J = 8.8 Hz, 1H), 7.52 - 7.42 (m, 1H), 4.66 (s, 1H), 4.55 - 4.40 (m, 3H), 4.39 - 4.27 (m, 1H), 4.26 - 4.11 (m, 1H), 4.10 - 3.95 (m, 5H), 3.84 (m, 1H), 3.36 - 3.15 (m, 2H), 3.03 (m, 2H), 2.95 - 2.80 (m, 2H), 2.73 - 2.53 (m, 2H), 2.47 - 2.28 (m, 4H), 2.27 - 2.12 (m, 8H), 2.10 - 2.01 (m, 4H), 1.92 - 1.80 (m, 3H), 1.76 - 1.62 (m, 3H), 1.51 - 1.41 (m, 2H), 1.35 - 1.21 (m, 2H)

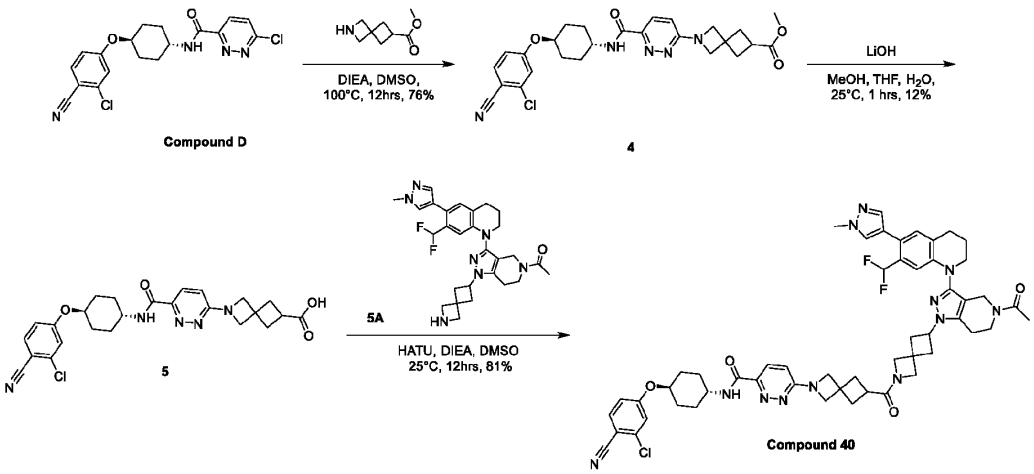
[00592] **LC-MS:** MS (ESI$^+$): t_R = 1.906 min, m/z = 921.5 [M + H$^+$]

[00593] The compounds below were prepared in a similar manner as described in Example 12.

Compound	Name	^{1}H NMR ($CDCl_3$)	LC-MS [M + H$^+$]
4	6-[4-[[3-[5-acetyl-3-[3-(1-methylpyrazol-4-yl)-8-isoquinolyl]-6,7-dihydro-4H-pyrazolo[4,3-c] pyridin-1-yl] azetidin-1-yl] methyl]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy) cyclohexyl] pyridazine-3-carboxamide	(DMSO-d6) δ = 9.76 (s, 1H), 8.58 (br d, J = 8.4 Hz, 1H), 8.36 (s, 1H), 8.10 (d, J = 8.8 Hz, 2H), 7.91 (d, J = 8.0 Hz, 1H), 7.85 (d, J = 8.8 Hz, 1H), 7.83 - 7.75 (m, 2H), 7.62 - 7.50 (m, 1H), 7.39 (d, J = 2.4 Hz, 1H), 7.32 (br d, J = 9.6 Hz, 1H), 7.18 - 7.09 (m, 1H), 5.02 (br t, J = 7.2 Hz, 1H), 4.61 - 4.37 (m, 5H), 3.91 (s, 3H), 3.88 - 3.72 (m, 5H), 3.54 - 3.45 (m, 2H), 3.06 - 2.96 (m, 2H), 2.93 - 2.78 (m, 2H), 2.43 (br d, J = 6.4 Hz, 2H), 2.16 - 2.05 (m, 4H), 1.99 (s, 1H), 1.94 - 1.77 (m, 4H), 1.72 - 1.57 (m, 3H), 1.56 - 1.45 (m, 2H), 1.22 - 1.07 (m, 2H)	879.4
32	6-[4-[[4-[5-acetyl-3-[3-(1-methylpyrazol-4-yl)-8-isoquinolyl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]methyl]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	(DMSO-d_6): δ = 9.85 (s, 1H), 8.54 (s, 1H), 8.37 (s, 1H), 8.10 (d, J = 2.0 Hz, 2H), 7.90-7.83 (m, 2H), 7.82-7.75 (m, 2H), 7.60-7.48 (m, 1H), 7.39 (d, J = 2.4 Hz, 1H), 7.34-7.29 (m, 1H), 7.15 (s, 1H), 4.60-4.55 (m, 2H), 4.55-4.43 (m, 3H), 4.24 (s, 1H), 3.92 (s, 3H), 3.89-3.77 (m, 3H), 3.08-2.90 (m, 6H), 2.24-2.19 (m, 2H), 2.18-2.05 (m, 8H), 2.02 (s, 1H), 2.00-1.94 (m, 2H), 1.93-1.80 (m, 5H), 1.69-1.53 (m, 2H), 1.56-1.44 (m, 2H), 1.19-1.05 ppm (m, 2H).	1056.83
120	6-[4-[[4-[5-acetyl-3-(8-isoquinolyl)-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]methyl]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	δ ppm 1.25 (q, J=12.05 Hz, 2 H) 1.41 - 1.53 (m, 2 H) 1.63 - 1.74 (m, 2 H) 1.87 - 2.01 (m, 4 H) 2.05 - 2.23 (m, 10 H) 2.27 - 2.44 (m, 4 H) 2.85 (br t, J=5.57 Hz, 1 H) 2.92 (br t, J=5.38 Hz, 1 H) 2.98 - 3.18 (m, 4 H) 3.84 (br t, J=5.63 Hz, 1 H) 3.97 - 4.14 (m, 3 H) 4.28 - 4.38 (m, 1 H) 4.45 - 4.56 (m, 3 H) 4.65 (s, 1 H) 6.86	827.5

Compound	Name	^{1}H NMR ($CDCl_3$)	LC-MS [M + H$^+$]
		(dd, J=8.76, 2.38 Hz, 1 H) 6.95 - 7.04 (m, 2 H) 7.54 - 7.63 (m, 2 H) 7.68 - 7.78 (m, 2 H) 7.80 - 7.91 (m, 2 H) 7.96 (d, J=9.63 Hz, 1 H) 8.56 (dd, J=13.88, 5.63 Hz, 1 H) 9.76 (br d, J=9.63 Hz, 1 H)	
121	6-[4-[[4-[5-acetyl-3-(3-cyano-8-isoquinolyl)-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]methyl]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	δ = 9.93 (s, 1H), 8.19 (d, J = 7.6 Hz, 1H), 7.96 (d, J = 9.6 Hz, 1H), 7.94 - 7.83 (m, 3H), 7.80 - 7.67 (m, 1H), 7.56 (d, J = 8.8 Hz, 1H), 7.05 - 6.94 (m, 2H), 6.86 (dd, J = 2.4, 8.8 Hz, 1H), 4.68 (s, 1H), 4.60 - 4.42 (m, 3H), 4.38 - 4.28 (m, 1H), 4.18 - 3.96 (m, 3H), 3.85 (br t, J = 6.0 Hz, 1H), 3.16 - 2.99 (m, 4H), 2.92 (br t, J = 5.6 Hz, 1H), 2.85 (br t, J = 5.6 Hz, 1H), 2.46 - 2.25 (m, 6H), 2.23 - 2.07 (m, 8H), 2.07 - 1.91 (m, 4H), 1.75 - 1.62 (m, 2H), 1.53 - 1.38 (m, 2H), 1.26 (q, J = 11.6 Hz, 2H).	852.5
122	-[4-[[4-[5-acetyl-3-(3-methyl-8-isoquinolyl)-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]methyl]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	δ = 9.73 (d, J = 8.8 Hz, 1H), 7.96 (d, J = 9.6 Hz, 1H), 7.87 (d, J = 8.0 Hz, 1H), 7.79 - 7.62 (m, 2H), 7.60 - 7.44 (m, 3H), 7.06 - 6.94 (m, 2H), 6.85 (dd, J = 2.4, 8.8 Hz, 1H), 4.66 (s, 1H), 4.69 - 4.60 (m, 1H), 4.55 - 4.44 (m, 3H), 4.38 - 4.27 (m, 1H), 4.11 - 3.96 (m, 3H), 3.83 (br t, J = 5.6 Hz, 1H), 3.09 - 2.98 (m, 4H), 2.97 - 2.79 (m, 3H), 2.71 (d, J = 6.0 Hz, 3H), 2.45 - 2.34 (m, 2H), 2.31 - 2.26 (m, 2H), 2.25 - 2.14 (m, 7H), 2.07 (s, 2H), 2.04 - 1.92 (m, 4H), 1.76 - 1.61 (m, 2H), 1.53 - 1.39 (m, 2H), 1.32 - 1.17 (m, 2H)	841.6
123	6-[4-[[4-[5-acetyl-3-(3-cyclopropyl-8-isoquinolyl)-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]methyl]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	δ = 9.61 (d, J = 6.8 Hz, 1H), 7.96 (d, J = 9.6 Hz, 1H), 7.87 (d, J = 8.0 Hz, 1H), 7.74 - 7.61 (m, 2H), 7.56 (d, J = 8.8 Hz, 1H), 7.49 (d, J = 10.8 Hz, 1H), 7.43 (dd, J = 6.8, 18.8 Hz, 1H), 7.03 - 6.94 (m, 2H), 6.85 (dd, J = 2.4, 8.8 Hz, 1H), 4.63 (s, 1H), 4.54 - 4.44 (m, 3H), 4.37 - 4.26 (m, 1H), 4.10 - 3.96 (m, 3H), 3.82 (br t, J = 6.0 Hz, 1H), 3.13 - 2.98 (m, 4H), 2.90 (br t, J = 5.6 Hz, 1H), 2.83 (br t, J = 6.0 Hz, 1H), 2.49 - 2.23 (m, 6H), 2.23 - 2.05 (m, 10H), 1.96 (br d, J = 12.8 Hz, 3H), 1.74 - 1.63 (m, 2H), 1.52 - 1.39 (m, 2H), 1.24 (q, J = 11.2 Hz, 2H), 1.13 - 1.00 (m, 4H).	867.6

[00594] **Example 13**: Synthesis of 6-[6-[6-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-2-azaspiro[3.3]heptane-2-carbonyl]-2-azaspiro[3.3]heptan-2-yl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide **(Compound 40)**



[00595] To a solution of 6-chloro-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide (300 mg, 766.77 μmol, 1.0 eq) and methyl 2-azaspiro[3.3]heptane-6-carboxylate (373 mg, 766.77 μmol, 1.0 eq, 2.9 TFA) in DMSO (10 mL) was added DIEPA (2.30 mmol, 400.67 μL, 3.0 eq). The mixture was stirred at 100 °C for 12hr and then the mixture was poured into water (30 mL). The aqueous phase was extracted with ethyl acetate 150 mL (15 mL × 3), the combined organic layers were washed with brine (15 mL *3), dried with anhydrous sodium sulfate, filtered and concentrated under vacuum. The desired compound methyl 2-[6-[[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]carbamoyl]pyridazin-3-yl]-2-azaspiro[3.3]heptane-6-carboxylate (324 mg, 581.20 μmol, 76% yield) was obtained as a brown solid.

[00596] **LC-MS:** MS (ESI^+): t_R = 0.565 min, m/z = 510.3 [M + H^+]

[00597] To a solution of methyl 2-[6-[[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]carbamoyl]pyridazin-3-yl]-2-azaspiro[3.3]heptane-6-carboxylate (50 mg, 98.04 μmol, 1.0 eq) in THF (1 mL) and H_2O (0.5 mL) was added $LiOH.H_2O$ (41 mg, 980.42 μmol, 10.0 eq). The mixture was stirred at 25 °C for 1hr and then concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150*25mm* 10um;mobile phase: [water(FA)-ACN];gradient:30%-60% B over 10 min). Compound 2-[6-[[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]carbamoyl]pyridazin-3-yl]-2-azaspiro[3.3]heptane-6-carboxylic acid (6 mg, 11.72 μmol, 12% yield) was obtained as a white solid.

[00598] **LC-MS:** MS (ESI^+): t_R = 0.542 min, m/z = 496.3 [M + H^+]

[00599] To a solution of 2-[6-[[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]carbamoyl]pyridazin-3-yl]-2-azaspiro[3.3]heptane-6-carboxylic acid (11 mg, 22.18 umol, 1.1 eq) , 1-[1-(2-azaspiro[3.3]heptan-6-yl)-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]ethanone (11 mg, 20.16 μmol, 1.0 eq) ,DIPEA (60.49 μmol, 10.54 μL, 3.0 eq) in DMSO (1 mL) was added HATU (9 mg, 24.20 μmol, 1.2 eq). The mixture was stirred at 25 °C for 12 hr and then the mixture was poured into water (10 mL). The aqueous phase was extracted with ethyl acetate 24 mL (8 mL × 3), dried with anhydrous sodium sulfate, filtered and concentrated under vacuum. The residue was purified by prep-HPLC (column: Welch Xtimate C18 150*25mm*5um;mobile phase: [water(FA)-ACN];gradient:48%-78% B over 10 min). Compound 6-[6-[6-[5-acetyl-3-[7-(difluoromethyl)-6-(1-

methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-2-azaspiro[3.3]heptane-2-carbonyl]-2-azaspiro[3.3]heptan-2-yl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide (16.44 mg, 16.25 μmol, 81% yield) was obtained as a white solid.

[00600] **^{1}H NMR** (400 MHz, DMSO-d_6) δ = 8.54 (br d, J = 8.1 Hz, 1H), 8.45-8.40 (m, 1H), 7.89-7.78 (m, 2H), 7.76 (s, 1H), 7.50 (s, 1H), 7.38 (d, J = 2.4 Hz, 1H), 7.16-7.08 (m, 2H), 6.96-6.64 (m, 3H), 4.74-4.46 (m, 2H), 4.15 (br d, J = 10.4 Hz, 3H), 4.08 (br d, J = 16.0 Hz, 2H), 4.03 (br d, J = 4.4 Hz, 2H), 3.96 (br s, 1H), 3.90-3.81 (m, 5H), 3.76-3.65 (m, 2H), 3.64-3.54 (m, 2H), 3.31-3.22 (m, 2H), 3.05 -2.93 (m, 1H), 2.83-2.76 (m, 2H), 2.67-2.62 (m, 4H), 2.40-2.31 (m, 4H), 2.15-2.05 (m, 4H), 2.00-1.93 (m, 3H), 1.93-1.84 (m, 2H), 1.70-1.53 (m, 2H), 1.56-1.43 ppm (m, 2H).

[00601] **LC-MS:** MS (ESI$^+$): t_R = 2.677 min, m/z = 493.51 [M + H$^+$]

[00602] The compounds below were prepared in a similar manner as described in Example 13.

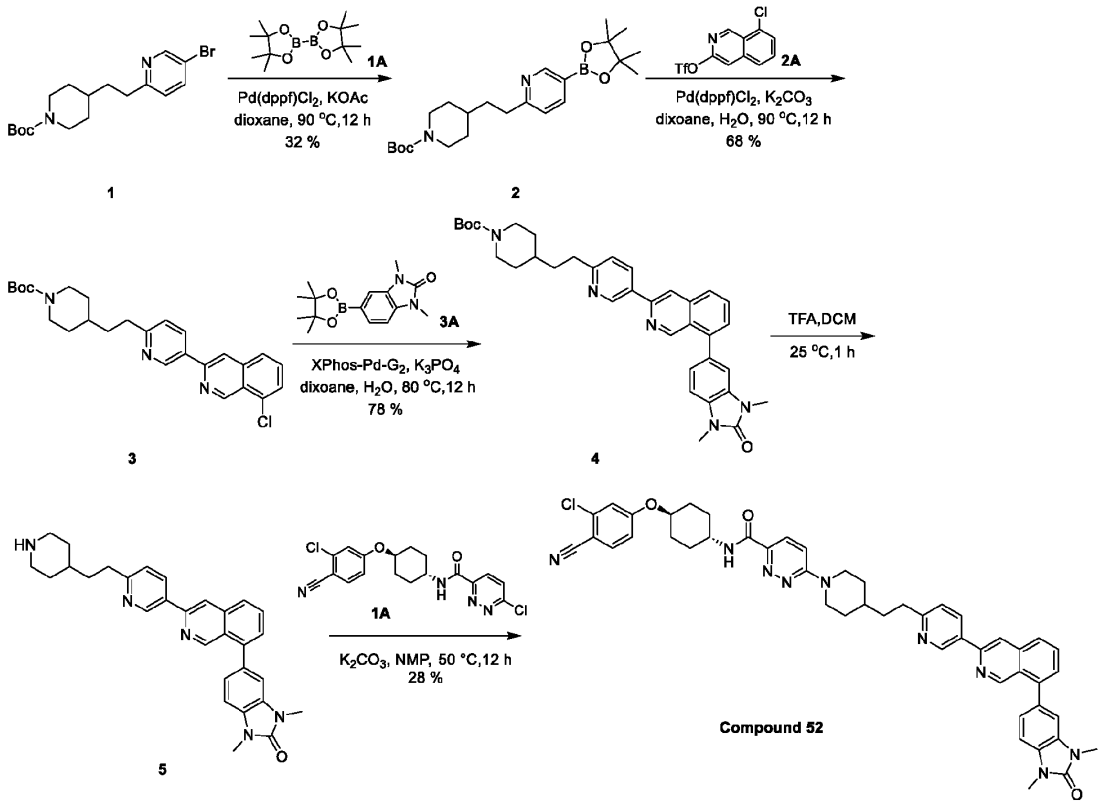
Compound	Name	^{1}H NMR ($CDCl_3$)	LC-MS [M + H$^+$]
41	6-[6-[[6-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c] pyridin-1-yl]-2-azaspiro [3.3] heptan-2-yl] methyl]-2-azaspiro [3.3] heptan-2-yl]-N-[4-(3-chloro-4-cyano-phenoxy) cyclohexyl] pyridazine-3-carboxamide	δ = 8.02 - 7.94 (m, 1H), 7.87 (br d, *J* = 8.0 Hz, 1H), 7.61 - 7.51 (m, 2H), 7.41 (d, *J* = 5.6 Hz, 1H), 7.09 - 6.98 (m, 2H), 6.96 - 6.90 (m, 1H), 6.89 - 6.83 (m, 1H), 6.73 - 6.35 (m, 2H), 4.51 - 4.39 (m, 1H), 4.38 - 4.28 (m, 1H), 4.28 - 4.16 (m, 2H), 4.14 - 4.03 (m, 4H), 3.99 - 3.93 (m, 3H), 3.91 - 3.85 (m, 1H), 3.75 - 3.55 (m, 6H), 2.94 - 2.81 (m, 4H), 2.74 - 2.65 (m, 5H), 2.50 - 2.32 (m, 3H), 2.25 - 2.12 (m, 6H), 2.12 - 1.99 (m, 7H), 1.71 (br s, 3H), 1.51 - 1.43 (m, 2H).	985.6
42	6-[6-[6-[5-acetyl-3-[7-(difluoromethyl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-2-azaspiro[3.3]heptane-2-carbonyl]-2-azaspiro[3.3]heptan-2-yl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	(DMSO-d6) δ = 8.54 (d, *J* = 8.0 Hz, 1H), 8.22 (s, 1H), 7.89 - 7.76 (m, 2H), 7.38 (d, *J* = 2.4 Hz, 1H), 7.17 - 7.07 (m, 2H), 6.98 - 6.62 (m, 4H), 4.73 - 4.59 (m, 1H), 4.58 - 4.47 (m, 1H), 4.16 (br d, *J* = 6.0 Hz, 3H), 4.11 - 3.99 (m, 5H), 3.96 (s, 1H), 3.90 - 3.79 (m, 2H), 3.75 - 3.64 (m, 2H), 3.63 - 3.54 (m, 2H), 3.05 - 2.92 (m, 1H), 2.84 - 2.75 (m, 3H), 2.64 (br d, *J* = 7.6 Hz, 5H), 2.40 - 2.30 (m, 4H), 2.15 - 2.02 (m, 4H), 1.98 - 1.85 (m, 5H), 1.68 - 1.46 (m, 4H)	919.4
43	-[6-[[6-[5-acetyl-3-[7-(difluoromethyl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c] pyridin-1-yl]-2-azaspiro [3.3] heptan-2-yl] methyl]-2-azaspiro [3.3] heptan-2-yl]-N-[4-(3-chloro-4-cyano-	(DMSO-d_6): δ = 8.53 (d, *J* = 8.0 Hz, 1H), 8.37 (s, 1H), 7.89 - 7.76 (m, 2H), 7.38 (d, *J* = 2.4 Hz, 1H), 7.18 - 7.08 (m, 2H), 6.98 - 6.61 (m, 4H), 4.64 - 4.45 (m, 2H), 4.13 (s, 2H), 4.10 - 4.04 (m, 2H), 4.01 (s, 2H), 3.90 - 3.79 (m, 1H), 3.75 - 3.63 (m, 2H), 3.62 - 3.54 (m,	905.4

Compound	Name	^{1}H NMR ($CDCl_3$)	LC-MS [M + H$^+$]
	phenoxy) cyclohexyl] pyridazine-3-carboxamide	2H), 3.20 (br s, 2H), 3.11 - 3.05 (m, 2H), 2.87 - 2.73 (m, 3H), 2.69 - 2.63 (m, 1H), 2.58 - 2.51 (m, 4H), 2.39 - 2.33 (m, 2H), 2.31 - 2.23 (m, 2H), 2.18 - 2.10 (m, 2H), 2.09 - 2.02 (m, 3H), 2.00 - 1.83 (m, 7H), 1.69 - 1.57 (m, 2H), 1.57 - 1.43 (m, 2H)	
44	6-[6-[6-[5-acetyl-3-(6-cyano-3,4-dihydro-2H-quinolin-1-yl)-6,7-dihydro-4H-pyrazolo[4,3-c] pyridin-1-yl]-2-azaspiro [3.3] heptane-2-carbonyl]-2-azaspiro [3.3] heptan-2-yl]-N-[4-(3-chloro-4-cyano-phenoxy) cyclohexyl] pyridazine-3-carboxamide	(DMSO-d_6) δ = 8.55 (d, J = 8.0 Hz, 1H), 7.89 - 7.77 (m, 2H), 7.46 - 7.36 (m, 2H), 7.34 - 7.26 (m, 1H), 7.17 - 7.09 (m, 1H), 6.87 - 6.78 (m, 1H), 6.49 - 6.36 (m, 1H), 4.71 - 4.62 (m, 1H), 4.58 - 4.48 (m, 1H), 4.19 - 4.01 (m, 8H), 3.96 (s, 1H), 3.90 - 3.79 (m, 2H), 3.75 - 3.65 (m, 2H), 3.65 - 3.57 (m, 2H), 3.03 - 2.94 (m, 1H), 2.84 - 2.76 (m, 3H), 2.73 - 2.58 (m, 5H), 2.42 - 2.29 (m, 4H), 2.14 - 2.04 (m, 4H), 2.00 - 1.85 (m, 5H), 1.69 - 1.45 (m, 4H).	894.4
45	6-[6-[[6-[5-acetyl-3-(6-cyano-3,4-dihydro-2H-quinolin-1-yl)-6,7-dihydro-4H-pyrazolo[4,3-c] pyridin-1-yl]-2-azaspiro [3.3] heptan-2-yl] methyl]-2-azaspiro [3.3] heptan-2-yl]-N-[4-(3-chloro-4-cyano-phenoxy) cyclohexyl] pyridazine-3-carboxamide	(METHANOL-d4) δ = 7.94 - 7.86 (m, 1H), 7.72 - 7.65 (m, 1H), 7.34 (s, 1H), 7.28 - 7.18 (m, 2H), 7.08 - 7.01 (m, 1H), 6.85 - 6.79 (m, 1H), 6.49 - 6.38 (m, 1H), 4.73 - 4.60 (m, 2H), 4.60 - 4.41 (m, 2H), 4.26 - 4.19 (m, 4H), 4.08 (s, 2H), 3.99 - 3.93 (m, 1H), 3.90 - 3.83 (m, 1H), 3.82 (s, 1H), 3.72 - 3.64 (m, 2H), 3.45 - 3.39 (m, 2H), 2.89 - 2.81 (m, 3H), 2.75 - 2.62 (m, 5H), 2.55 (d, J = 6.8 Hz, 2H), 2.42 - 2.35 (m, 2H), 2.34 - 2.27 (m, 1H), 2.23 - 2.15 (m, 4H), 2.10 - 1.98 (m, 7H), 1.69 - 1.58 (m, 4H).	902.6 [M + 23]
46	6-[6-[[4-[8-(5-acetyl-1-tetrahydropyran-4-yl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-3-yl)-3-isoquinolyl]pyrazol-1-yl]methyl]-2-azaspiro[3.3]heptan-2-yl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	δ = 9.86 - 9.63 (m, 1H), 8.09 (s, 1H), 7.98 - 7.94 (m, 1H), 7.91 - 7.62 (m, 4H), 7.60 - 7.44 (m, 2H), 7.01 (d, J = 2.4 Hz, 1H), 6.90 - 6.80 (m, 1H), 6.58 - 6.53 (m, 1H), 4.75 - 4.46 (m, 2H), 4.38 - 4.28 (m, 2H), 4.27 - 4.22 (m, 4H), 4.21 - 4.15 (m, 2H), 4.14 - 4.10 (m, 2H), 4.07 - 3.97 (m, 2H), 3.85 (m, 1H), 3.57 (m, 2H), 3.01 - 2.81 (m, 3H), 2.53 - 2.39 (m, 4H), 2.25 - 2.20 (m, 4H), 2.19 - 2.08 (m, 5H), 2.03 - 1.94 (m, 2H), 1.70 - 1.64 (m, 2H), 1.50 - 1.44 (m, 2H)	906.5
47	6-[6-[[4-[8-(5-acetyl-1-methyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-3-yl)-3-isoquinolyl]pyrazol-1-yl]methyl]-2-azaspiro[3.3]heptan-2-yl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-	δ = 9.89 - 9.55 (m, 1H), 8.10 (s, 1H), 7.97 (dd, J = 1.6, 9.2 Hz, 1H), 7.93 - 7.79 (m, 3H), 7.79 - 7.69 (m, 1H), 7.63 - 7.48 (m, 2H), 7.02 (d, J = 2.3 Hz, 1H), 6.87 (dd, J = 2.4, 8.8 Hz, 1H), 6.57 (d, J = 9.3 Hz, 1H), 4.65 (s, 1H), 4.52 - 4.45 (m, 1H), 4.38 - 4.31 (m, 1H), 4.30 -	836.6

Compound	Name	^{1}H NMR ($CDCl_3$)	LC-MS [M + H$^+$]
	3-carboxamide	4.19 (m, 4H), 4.13 (s, 2H), 4.10 - 4.00 (m, 2H), 3.92 (d, *J* = 4.0 Hz, 3H), 3.86 (br t, *J* = 5.9 Hz, 1H), 2.99 - 2.79 (m, 3H), 2.56 - 2.44 (m, 2H), 2.25 - 2.14 (m, 7H), 2.08 (s, 1H), 1.82 - 1.65 (m, 4H), 1.52 - 1.42 (m, 2H)	
48	6-[6-[2-[5-[8-(5-acetyl-1-tetrahydropyran-4-yl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-3-yl)-3-isoquinolyl]-2-pyridyl]ethyl]-2-azaspiro[3.3]heptan-2-yl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	δ = 9.76 (d, *J* = 6.1 Hz, 1H), 9.17 (s, 1H), 8.33 (s, 1H), 8.03 (d, *J* = 10.4 Hz, 1H), 7.90 - 7.77 (m, 3H), 7.74 - 7.63 (m, 1H), 7.56 - 7.45 (m, 2H), 7.23 (d, *J* = 8.0 Hz, 1H), 6.93 (d, *J* = 2.4 Hz, 1H), 6.76 - 6.79 (m, 1H), 6.46 (d, *J* = 9.2 Hz, 1H), 4.65 - 4.39 (m, 2H), 4.24 (d, *J* = 10.8 Hz, 2H), 4.16 - 4.07 (m, 4H), 4.02 (s, 2H), 3.99 - 3.91 (m, 2H), 3.78 (t, *J* = 5.6 Hz, 1H), 3.50 (t, *J* = 12.0 Hz, 2H), 2.87 (t, *J* = 5.6 Hz, 1H), 2.82 - 2.71 (m, 3H), 2.42 - 2.29 (m, 4H), 2.28 - 2.20 (m, 1H), 2.14 (s, 3H), 2.07 (d, *J* = 3.6 Hz, 2H), 2.01 (s, 2H), 1.94 - 1.84 (m, 6H), 1.65 - 1.57 (m, 2H), 1.45 - 1.34 (m, 2H)	931.4
49	6-[6-[2-[4-[8-(5-acetyl-1-tetrahydropyran-4-yl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-3-yl)-3-isoquinolyl]pyrazol-1-yl]ethyl]-2-azaspiro[3.3]heptan-2-yl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine3-carboxamide	δ = 10.02 - 9.54 (m, 1H), 8.08 (s, 2H), 7.97 - 7.91 (m, 1H), 7.91 - 7.67 (m, 4H), 7.64 - 7.40 (m, 3H), 7.02 (d, J = 1.6 Hz, 1H), 6.8.7 (d, J = 8.8 Hz, 1H), 6.54 (d, J = 8.8 Hz, 1H), 4.68 (s, 1H), 4.51 (s, 1H), 4.41 - 4.27 (m, 2H), 4.27 - 4.14 (m, 6H), 4.13 - 3.99 (m, 4H), 3.87 (d, J = 2.8 Hz, 1H), 3.67 - 3.51 (m, 2H), 3.05 - 2.79 (m, 2H), 2.56 - 3.38 (m, 4H), 2.37 - 2.13 (m, 6H), 2.10 (s, 3H), 2.04 - 1.88 (m, 4H), 1.74 - 1.68 (m, 2H), 1.98 - 1.91 (m, 2H), 1.52 - 1.40 (m, 2H).	920.6
50	6-[6-[2-[4-[8-(5-acetyl-1-methyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-3-yl)-3-isoquinolyl]pyrazol-1- yl]ethyl]-2-azaspiro[3.3]heptan-2-yl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	δ = 10.05 - 9.40 (m, 1H), 8.09 (s, 2H), 7.97 - 7.91 (m, 1H), 7.91 - 7.76 (m, 3H), 7.76 - 7.66 (m, 1H), 7.60 - 7.47 (m, 2H), 7.02 (d, J = 2.0 Hz, 1H), 6.92 - 6.80 (s, 1H), 6.54 (d, J = 9.2 Hz, 1H), 4.64 (s, 1H), 4.47 (s, 1H), 4.40 - 4.28 (m, 1H), 4.20 (s, 2H), 4.19 - 4.13 (m, 2H), 4.09 (s, 2H), 4.07 - 3.98 (m, 2H), 3.91 (d, J = 2.8 Hz, 3H), 3.88 - 3.80 (m, 1H), 2.98 - 2.79 (m, 2H), 2.49 - 2.38 (m, 2H), 2.34 - 2.26 (m, 1H), 2.16 - 2.11 (m, 6H), 2.10 - 2.05 (m, 3H), 1.98 - 1.91 (m, 2H), 1.74 - 1.66 (m, 2H), 1.54 - 1.41 (m, 2H).	850.5
51	6-[6-[2-[5-[8-(5-acetyl-1-methyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-3-yl)-3-isoquinolyl]-2-pyridyl]ethyl]-2-azaspiro[3.3]heptan-2-yl]-N-[4-	δ = 9.78 (d, J = 10.8 Hz, 1H), 9.25 (s, 1H), 8.41 (br d, J = 5.6 Hz, 1H), 8.11 (d, J = 10.8 Hz, 1H), 7.98 - 7.84 (m, 3H), 7.77 (td, J = 8.4, 12.4 Hz, 1H), 7.64 - 7.53 (m, 2H), 7.33 - 7.28 (m,	861.5

Compound	Name	^{1}H NMR ($CDCl_3$)	LC-MS [M + H$^+$]
	(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	1H), 7.00 (d, J = 2.0 Hz, 1H), 6.86 (dd, J = 2.4, 8.8 Hz, 1H), 6.54 (d, J = 9.2 Hz, 1H), 4.64 (s, 1H), 4.47 (s, 1H), 4.37 - 4.28 (m, 1H), 4.21 (s, 2H), 4.11 - 3.98 (m, 4H), 3.92 (d, J = 3.2 Hz, 3H), 3.85 (t, J = 6.0 Hz, 1H), 2.90 (br t, J = 6.0 Hz, 1H), 2.84 (br t, J = 6.8 Hz, 3H), 2.46 - 2.37 (m, 2H), 2.34 - 2.26 (m, 1H), 2.22 - 2.06 (m, 7H), 2.00 - 1.90 (m, 4H), 1.73 - 1.64 (m, 2H), 1.51 - 1.40 (m, 2H).	
63	6-[6-[2-[4-[8-(5-acetyl-1-tetrahydropyran-4-yl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-3-yl)-3-isoquinolyl]pyrazol-1-yl]ethoxy]-2-azaspiro[3.3]heptan-2-yl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	δ = 9.76 (br d, J = 3.2 Hz, 1H), 8.30 - 8.12 (m, 1H), 8.12 (s, 1H), 7.92 - 7.80 (m, 3H), 7.80 - 7.60 (m, 2H), 7.59 - 7.47 (m, 2H), 7.00 (d, J = 2.4 Hz, 1H), 6.85 (dd, J = 2.4, 8.8 Hz, 1H), 6.55 - 6.00 (m, 1H), 4.69 - 4.48 (m, 2H), 4.39 - 4.25 (m, 4H), 4.20 - 4.11 (m, 4H), 4.07 - 3.93 (m, 5H), 3.85 (br t, J = 5.6 Hz, 1H), 3.79 (br d, J = 3.6 Hz, 2H), 3.57 (br t, J = 12.0 Hz, 2H), 2.97 - 2.83 (m, 2H), 2.59 - 2.50 (m, 2H), 2.49 - 2.38 (m, 2H), 2.22 - 2.05 (m, 9H), 1.97 (br d, J = 12.4 Hz, 2H), 1.73 - 1.68 (m, 2H), 1.49 - 1.39 (m, 2H).	936.7
64	6-[6-[2-[4-[8-(5-acetyl-1-methyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-3-yl)-3-isoquinolyl]pyrazol-1-yl]ethoxy]-2-azaspiro[3.3]heptan-2-yl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	δ = 9.88 - 9.56 (m, 1H), 8.32 - 8.12 (m, 1H), 8.12 (s, 1H), 7.90 - 7.81 (m, 3H), 7.81 - 7.63 (m, 2H), 7.59 - 7.49 (m, 2H), 7.00 (d, J = 2.4 Hz, 1H), 6.85 (dd, J = 2.4, 8.8 Hz, 1H), 6.51 - 6.10 (m, 1H), 4.65 - 4.45 (m, 2H), 4.36 (br t, J = 4.4 Hz, 2H), 4.34 - 4.27 (m, 1H), 4.14 (d, J = 5.6 Hz, 2H), 4.06 - 3.98 (m, 4H), 3.95 (dt, J = 3.2, 6.4 Hz, 1H), 3.90 (d, J = 4.0 Hz, 3H), 3.84 (br t, J = 5.6 Hz, 1H), 3.81 - 3.73 (m, 2H), 2.90 (br t, J = 5.6 Hz, 1H), 2.82 (br t, J = 5.6 Hz, 1H), 2.59 - 2.49 (m, 2H), 2.22 - 2.03 (m, 9H), 1.73 - 1.68 (m, 2H), 1.50 - 1.39 (m, 2H).	866.6

[00603] **Example 14**: Synthesis of N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]-6-[4-[2-[5-[8-(1,3-dimethyl-2-oxo-benzimidazol-5-yl)-3-isoquinolyl]-2-pyridyl]ethyl]-1-piperidyl]pyridazine-3-carboxamide **(Compound 52)**



[00604] To a solution of tert-butyl 4-[2-(5-bromo-2-pyridyl)ethyl]piperidine-1-carboxylate (3.80 g, 10.20 mmol, 1.0 eq) in dioxane (72 mL) was added Pd(dppf)Cl2 (752 mg, 1.00 mmol, 0.1 eq), KOAc (3.03 g, 30.81 mmol, 3.0 eq) and 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (5.23 g, 20.50 mmol, 2.0 eq). The mixture was stirred to 90 °C for 12 h under N2. The reaction mixture was diluted with water (15 mL) and extracted with EtOAc (15 mL * 3). The combined organic layers were washed with sat. NaCl (20 mL * 3), dried over Na2SO4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=50/1 to 5/1). Compound tert-butyl 4-[2-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-pyridyl]ethyl]piperidine-1-carboxylate (1.40 g, 3.30 mmol, 32 % yield) was obtained as a black solid.

[00605] LC-MS: MS (ESI+): tR = 0.808 min, m/z = 416.2 [M + H+]

[00606] To a solution of tert-butyl 4-[2-(5-bromo-2-pyridyl)ethyl]piperidine-1-carboxylate (3.80 g, 10.20 mmol, 1.0 eq) in dioxane (72 mL) was added Pd(dppf)Cl2 (752 mg, 1.00 mmol, 0.1 eq), KOAc (3.03 g, 30.81 mmol, 3.0 eq) and 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (5.23 g, 20.50 mmol, 2.0 eq). The mixture was stirred to 90 °C for 12 h under N2. The reaction mixture was diluted with water (15 mL) and extracted with EtOAc (15 mL * 3). The combined organic layers were washed with sat. NaCl (20 mL * 3), dried over Na2SO4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography

(petroleum ether/ethyl acetate=50/1 to 5/1). Compound tert-butyl 4-[2-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-pyridyl]ethyl]piperidine-1-carboxylate (1.40 g, 3.30 mmol, 32 % yield) was obtained as a black solid.

[00607] LC-MS: MS (ESI+): tR = 0.808 min, m/z = 416.2 [M + H+]

[00608] To a solution of tert-butyl 4-[2-[5-(8-chloro-3-isoquinolyl)-2-pyridyl]ethyl]piperidine-1-carboxylate (240 mg, 530 μmol, 1.0 eq) and 1,3-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzimidazol-2-one (198 mg, 690 μmol, 1.3 eq) in dioxane (5 mL) and H2O (1.5 mL) was added K3PO4 (338 mg, 1.50 mmol, 3.0 eq) and XPhos-Pd-G2 (41 mg, 53 μmol, 0.1 eq) under N2 atmosphere. The mixture was stirred at 80 °C for 12 h under N2 atmosphere. The residue was diluted with H2O (15 ml) and extracted with EA (10 mL * 3). The combined organic layers were washed with sat. NaCl (10 mL * 3), dried over Na2SO4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate= 10/1 to 0/1). Compound tert-butyl 4-[2-[5-[8-(1,3-dimethyl-2-oxo-benzimidazol-5-yl)-3-isoquinolyl]-2-pyridyl]ethyl]piperidine-1-carboxylate (240 mg, 415 μmol, 78 % yield) was obtained as a white solid.

[00609] LC-MS: MS (ESI+): tR = 0.555 min, m/z = 577.3 [M + H+]

[00610] To a solution of tert-butyl 4-[2-[5-[8-(1,3-dimethyl-2-oxo-benzimidazol-5-yl)-3-isoquinolyl]-2-pyridyl]ethyl]piperidine-1-carboxylate (240 mg, 415 μmol, 1.0 eq) in DCM (3 mL) was added TFA (1.54 g, 13.40 mmol, 1.0 mL, 32.4 eq). The mixture was stirred at 25 °C for 1 h. The reaction mixture was concentrated under reduced pressure to give a crude product. Compound 1,3-dimethyl-5-[3-[6-[2-(4-piperidyl)ethyl]-3-pyridyl]-8-isoquinolyl]benzimidazol-2-one (198 mg) was obtained as a yellow oil and directly used in the next step without further purification.

[00611] LC-MS: MS (ESI+): tR = 0.434 min, m/z = 477.2 [M + H+]

[00612] A mixture of 1,3-dimethyl-5-[3-[6-[2-(4-piperidyl)ethyl]-3-pyridyl]-8-isoquinolyl]benzimidazol-2-one (99 mg, 207 μmol, 1.0 *eq*), 6-chloro-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide (81 mg, 207 μmol, 1.0 *eq*) and K_2CO_3 (85 mg, 621 μmol, 3.0 *eq*) in NMP (1.5 mL) was stirred at 50 °C for 12 h. The mixture was filtered and concentrated to give a residue. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150*25mm* 10um; mobile phase: [water (FA)-ACN]; gradient: 50%-80% B over 10 min). Compound N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]-6-[4-[2-[5-[8-(1,3-dimethyl-2-oxo-benzimidazol-5-yl)-3-isoquinolyl]-2-pyridyl]ethyl]-1-piperidyl]pyridazine-3-carboxamide (50 mg, 28 % yield) was obtained as a white solid.

[00613] **^{1}H NMR** (400 MHz, DMSO-d_6) δ = 9.37 - 9.28 (m, 2H), 8.60 - 8.54 (m, 2H), 8.46 (s, 1H), 8.19 (s, 1H), 8.04 (m, 1H), 7.90 - 7.76 (m, 3H), 7.61 (s, 1H), 7.45 - 7.40 (m, 2H), 7.37 (s, 1H), 7.35 - 7.25 (m, 3H), 7.12 (m, 1H), 4.60 - 4.42 (m, 3H), 3.93 - 3.77 (m, 1H), 3.42 - 3.40 (m, 3H), 3.39 (s, 3H), 2.97 (s, 2H), 2.85 (s, 2H), 2.09 (m, 2H), 1.87 (m, 4H), 1.74 - 1.57 (m, 5H), 1.56 - 1.43 (m, 2H), 1.25 - 1.12 (m, 2H).

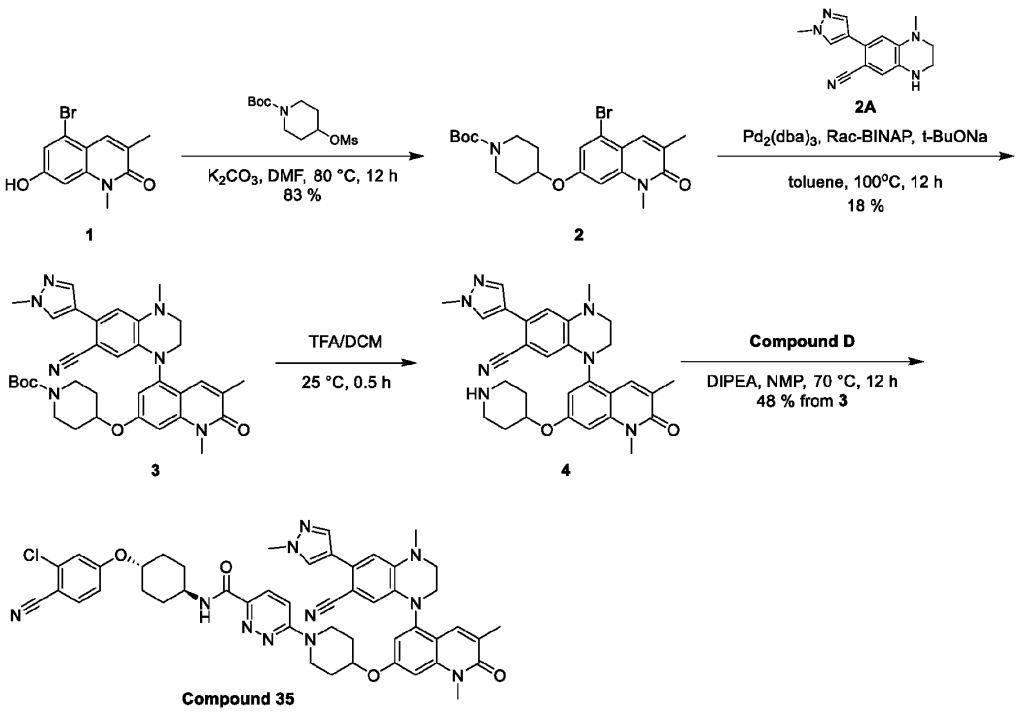
[00614] **LC-MS:** MS (ESI^+): t_R = 1.973 min, m/z = 831.3 [M + H^+]

[00615] The compounds below were prepared in a similar manner as described in Example 14

Compound	Name	^{1}H NMR ($CDCl_3$)	LC-MS [M + H$^+$]
53	N-[4-(3-chloro-4-cyano-phenoxy) cyclohexyl]-6-[4-[2-[5-[7-(difluoromethyl)-1-(1,3-dimethyl-2-oxo-benzimidazol-5-yl)-3,4-dihydro-2H-quinolin-6-yl]-2-pyridyl] ethyl]-1-piperidyl] pyridazine-3-carboxamide	δ = 8.64 - 8.52 (m, 1H), 8.43 - 8.31 (m, 1H), 7.88 - 7.82 (m, 1H), 7.82 - 7.77 (m, 1H), 7.63 (s, 1H), 7.41 - 7.37 (m, 1H), 7.36 - 7.30 (m, 2H), 7.21 (s, 1H), 7.19 - 7.16 (m, 1H), 7.15 (s, 1H), 7.04 - 6.99 (m, 2H), 6.73 - 6.43 (m, 2H), 4.56 - 4.46 (m, 3H), 3.91 - 3.80 (m, 1H), 3.64 - 3.58 (m, 2H), 3.02 - 2.79 (m, 7H), 2.15 - 2.00 (m, 5H), 1.94 - 1.78 (m, 5H), 1.71 - 1.58 (m, 6H), 1.57 - 1.40 (m, 3H), 1.31 - 1.05 (m, 3H).	886.4
54	N-[4-(3-chloro-4-cyano-phenoxy) cyclohexyl]-6-[4-[2-[5-[1-(1,3-dimethyl-2-oxo-benzimidazol-5-yl)-3,4-dihydro-2H-1,7-naphthyridin-6-yl]-2-pyridyl] ethyl]-1-piperidyl] pyridazine-3-carboxamide	δ = 9.04 - 8.95 (m, 1H), 8.63 - 8.52 (m, 1H), 8.19 - 8.10 (m, 1H), 7.88 - 7.81 (m, 1H), 7.81 - 7.75 (m, 1H), 7.69 (s, 1H), 7.64 (s, 1H), 7.40 - 7.36 (m, 1H), 7.35 - 7.24 (m, 2H), 7.22 - 7.16 (m, 2H), 7.15 - 7.11 (m, 1H), 7.04 - 6.99 (m, 1H), 4.57 - 4.44 (m, 3H), 3.95 - 3.76 (m, 1H), 3.67 - 3.57 (m, 2H), 3.35 (s, 3H), 3.00 - 2.87 (m, 4H), 2.83 - 2.74 (m, 2H), 2.13 - 1.77 (m, 9H), 1.70 - 1.30 (m, 8H), 1.30 - 1.05 (m, 3H).	837.5
55	N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]-6-[4-[2-[5-[8-(3-methyl-2-oxo-1,3-benzothiazol-5-yl)-3-isoquinolyl]-2-pyridyl]ethyl]-1-piperidyl]pyridazine-3-carboxamide	δ = 9.41 (s, 1 H) 9.22 - 9.33 (m, 1 H) 8.42 - 8.65 (m, 1 H) 8.14 - 8.23 (m, 1 H) 7.93 - 8.04 (m, 2 H) 7.78 - 7.91 (m, 2 H) 7.55 - 7.63 (m, 3 H) 7.34 - 7.47 (m, 2 H) 7.19 - 7.23 (m, 1 H) 6.97 - 7.03 (m, 2 H) 6.83 - 6.91 (m, 1 H) 4.53 (m, 2 H) 4.27 - 4.39 (m, 1 H) 4.00 - 4.15 (m, 1 H) 3.51 (s, 3 H) 3.05 (m, 4 H) 2.13 - 2.23 (m, 4 H) 1.97 (m, 2 H) 1.80 - 1.87 (m, 2 H) 1.64 - 1.74 (m, 4 H) 1.45 - 1.51 (m, 2 H) 1.32 - 1.40 (m, 2 H)	835.3
56	N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]-6-[4-[2-[5-[7-(difluoromethyl)-1-(3-methyl-2-oxo-1,3-benzothiazol-5-yl)-3,4-dihydro-2H-quinolin-6-yl]-2-pyridyl]ethyl]-1-piperidyl]pyridazine-3-carboxamide	δ = 8.53 (d, J = 1.2 Hz, 1H), 8.05 - 7.94 (m, 1H), 7.88 (d, J = 8.4 Hz, 1H), 7.67 (m, 1H), 7.57 (d, J = 8.8 Hz, 1H), 7.46 (d, J = 8.4 Hz, 1H), 7.14 - 7.07 (m, 1H), 7.05 - 6.98 (m, 4H), 6.89 - 6.83 (m, 1H), 6.51 - 6.14 (m, 1H), 4.53 (m, 2H), 4.39 - 4.26 (m, 1H), 4.07 (m, 1H), 3.76 - 3.65 (m, 2H), 3.43 (s, 3H), 3.06 (m, 2H), 2.98 - 2.92 (m, 4H), 2.85 (s, 1H), 2.27 - 2.08 (m, 6H), 1.96 (m, 2H), 1.85 - 1.75 (m, 3H), 1.70 - 1.62 (m, 2H), 1.40 (br s, 5H)	889.5
57	N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]-6-[4-[2-[5-[1-(3-methyl-2-oxo-1,3-benzothiazol-5-yl)-3,4-dihydro-2H-1,7-naphthyridin-6-yl]-2-pyridyl]ethyl]-1-piperidyl]pyridazine-3-carboxamide	δ = 9.00 (d, J = 2.0 Hz, 1H), 8.21 (m, 1H), 8.10 (s, 1H), 7.96 (d, J = 9.6 Hz, 1H), 7.88 (d, J = 8.4 Hz, 1H), 7.57 (d, J = 8.8 Hz, 1H), 7.48 - 7.40 (m, 2H), 7.25 (m, 1H), 7.14 - 7.07 (m, 1H), 7.04 - 6.93 (m, 3H), 6.90 - 6.83 (m, 1H), 4.51 (m, 2H), 4.39 - 4.26 (m, 1H), 4.17 - 3.97 (m, 1H), 3.79 - 3.67 (m, 2H), 3.44 (s, 3H), 3.07 - 2.98 (m, 2H), 2.98 - 2.88 (m, 4H), 2.25 - 2.09 (m, 6H), 2.06 - 2.01 (m, 1H),	840.4

Compound	Name	^{1}H NMR ($CDCl_3$)	LC-MS [M + H$^+$]
		1.94 (m, 2H), 1.82 - 1.72 (m, 3H), 1.52 - 1.44 (m, 2H), 1.41 - 1.24 (m, 3H)	
58	N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]-6-[4-[2-[5-[8-(1-methyl-2-oxo-3,4-dihydroquinolin-6-yl)-3-isoquinolyl]-2-pyridyl]ethyl]-1-piperidyl]pyridazine-3-carboxamide	(DMSO-d_6): δ = 9.34 (s, 1H), 9.32 (d, J = 2.0 Hz, 1H), 8.62 - 8.55 (m, 2H), 8.54 - 8.48 (m, 1H), 8.13 (s, 1H), 8.05 (d, J = 8.4 Hz, 1H), 7.90 - 7.83 (m, 2H), 7.80 (d, J = 9.6 Hz, 1H), 7.60 (d, J = 7.2 Hz, 1H), 7.53 - 7.45 (m, 3H), 7.39 (d, J = 2.4 Hz, 1H), 7.34 (d, J = 9.6 Hz, 1H), 7.29 (d, J = 8.8 Hz, 1H), 7.13 (d, J = 2.4, 8.8 Hz, 1H), 4.57 - 4.44 (m, 3H), 3.91 - 3.79 (m, 1H), 3.35 (s, 3H), 3.03 - 2.94 (m, 4H), 2.88 (t, J = 7.6 Hz, 2H), 2.68 - 2.62 (m, 2H), 2.13 - 2.06 (m, 2H), 1.92 - 1.83 (m, 4H), 1.73 - 1.59 (m, 5H), 1.55 - 1.47 (m, 2H), 1.25 - 1.15 (m, 2H)	831.6
59	N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]-6-[4-[2-[5-[7-(difluoromethyl)-1-(1-methyl-2-oxo-3,4-dihydroquinolin-6-yl)-3,4-dihydro-2H-quinolin-6-yl]-2-pyridyl]ethyl]-1-piperidyl]pyridazine-3-carboxamide	(DMSO-d_6): δ = 8.58 (d, J = 8.3 Hz, 1H), 8.42 - 8.37 (m, 1H), 7.85 (d, J = 8.8 Hz, 1H), 7.80 (d, J = 9.6 Hz, 1H), 7.61 (d, J = 2.2, 8.0 Hz, 1H), 7.41 - 7.38 (m, 1H), 7.36 - 7.31 (m, 2H), 7.21 - 7.12 (m, 4H), 7.05 (s, 1H), 6.79 - 6.47 (m, 2H), 4.57 - 4.46 (m, 3H), 3.91 - 3.80 (m, 1H), 3.62 - 3.56 (m, 2H), 3.28 (s, 3H), 3.03 - 2.94 (m, 2H), 2.91 - 2.85 (m, 4H), 2.84 - 2.79 (m, 2H), 2.59 - 2.54 (m, 2H), 2.14 - 2.06 (m, 2H), 2.04 - 1.97 (m, 2H), 1.92 - 1.83 (m, 4H), 1.70 - 1.59 (m, 5H), 1.56 - 1.47 (m, 2H), 1.24 - 1.14 (m, 2H)	885.6
60	N-[4-(3-chloro-4-cyano-phenoxy) cyclohexyl]-6-[4-[2-[5-[1-(1-methyl-2-oxo-3,4-dihydroquinolin-6-yl)-3,4-dihydro-2H-1,7-naphthyridin-6-yl]-2-pyridyl] ethyl]-1-piperidyl] pyridazine-3-carboxamide	(DMSO-d_6): δ = 9.01 (d, J = 2.0 Hz, 1H), 8.58 (d, J = 8.4 Hz, 1H), 8.28 - 8.09 (m, 1H), 7.90 - 7.83 (m, 2H), 7.79 (d, J = 9.6 Hz, 1H), 7.67 (s, 1H), 7.39 (d, J = 2.4 Hz, 1H), 7.36 - 7.27 (m, 2H), 7.24 - 7.18 (m, 2H), 7.17 - 7.09 (m, 2H), 4.62 - 4.41 (m, 3H), 3.95 - 3.76 (m, 1H), 3.66 - 3.56 (m, 2H), 3.27 (s, 3H), 3.02 - 2.92 (m, 2H), 2.88 (br t, J = 7.2 Hz, 4H), 2.79 (br t, J = 7.4 Hz, 2H), 2.56 (t, J = 7.4 Hz, 2H), 2.10 (br d, J = 10.6 Hz, 2H), 2.04 - 1.96 (m, 2H), 1.92 - 1.80 (m, 4H), 1.70 - 1.58 (m, 5H), 1.56 - 1.46 (m, 2H), 1.24 - 1.12 (m, 2H).	836.6

[00616] **Example 15**: Synthesis of N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]-6-[4-[[5-[7-cyano-4-methyl-6-(1-methylpyrazol-4-yl)-2,3-dihydroquinoxalin-1-yl]-1,3-dimethyl-2-oxo-7-quinolyl]oxy]-1-piperidyl]pyridazine-3-carboxamide (**Compound 35**)



[00617] Synthesis of **1** was reported in WO2022/53967, 2022, A1.

[00618] Synthesis of **2A** was reported in WO2016/55028, 2016, A1.

[00619] To a solution of 5-bromo-7-hydroxy-1,3-dimethyl-quinolin-2-one (300 mg, 1.12 mmol, 1.0 eq) and tert-butyl 4-methylsulfonyloxypiperidine-1-carboxylate (313 mg, 1.12 mmol, 1.0 eq) in DMF (10 mL) was added K_2CO_3 (464 mg, 3.36 mmol, 3.0 eq). The reaction mixture was stirred at 80 °C for 12 h. The reaction mixture was quenched by addition water (10 mL) at 25 °C, and then diluted with water (20 mL) and extracted with ethyl acetate (50 mL × 3). The combined organic layers were washed with brine (30 mL × 3), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~50% Ethylacetate/Petroleum ethergradient @ 100 mL/min). The desired compound tert-butyl 4-[(5-bromo-1,3-dimethyl-2-oxo-7-quinolyl)oxy]piperidine-1-carboxylate (420 mg, 930.54 μmol, 83% yield) was obtained as off-white solid.

[00620] **^{1}H NMR** (400 MHz, DMSO-d_6) δ = 7.82 (s, 1H), 7.28 (d, J = 2.0 Hz, 1H), 6.99 (d, J = 1.6 Hz, 1H), 4.83 (td, J = 4.0, 7.6 Hz, 1H), 3.75 - 3.58 (m, 5H), 3.28 - 3.15 (m, 2H), 2.13 (s, 3H), 1.99 - 1.87 (m, 2H), 1.63 - 1.49 (m, 2H), 1.41 (s, 9H)

[00621] **LC-MS:** MS (ESI^+): t_R = 0.644 min, m/z = 453.1 [$M + H^+$]

[00622] To a solution of tert-butyl 4-[(5-bromo-1,3-dimethyl-2-oxo-7-quinolyl)oxy]piperidine-1-carboxylate (400 mg, 886.22 μmol, 1.0 eq) and 1-methyl-7-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinoxaline-6-carbonitrile (269 mg, 1.06 mmol, 1.2 eq) in toluene (10 mL) was added $Pd_2(dba)_3$ (81 mg, 88.62 μmol, 0.1 eq), [1-(2-diphenylphosphanyl-1-naphthyl)-2-naphthyl]-diphenyl-phosphane (166 mg,

265.87 μmol, 0.3 eq) and t-BuONa (256 mg, 2.66 mmol, 3.0 eq). The reaction mixture was stirred at 100 °C under N_2 for 12 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0 ~ 90% Ethylacetate/Petroleum ethergradient @ 100 mL/min). The residue was purified by prep-HPLC (FA condition: column: Phenomenex luna C18 150*25mm* 10um; mobile phase: [water (FA) - ACN]; gradient: 55% - 85% B over 1 min). The desired tert-butyl 4-[[5-[7-cyano-4-methyl-6-(1-methylpyrazol-4-yl)-2,3-dihydroquinoxalin-1-yl]-1,3-dimethyl-2-oxo-7-quinolyl]oxy]piperidine-1-carboxylate (100 mg, 160.32 μmol, 18% yield) was obtained as a yellow solid.

[00623] **LC-MS:** MS (ESI^+): t_R = 0.588 min, m/z = 623.3 [M + H^+]

[00624] To a solution of tert-butyl 4-[[5-[7-cyano-4-methyl-6-(1-methylpyrazol-4-yl)-2,3-dihydroquinoxalin-1-yl]-1,3-dimethyl-2-oxo-7-quinolyl]oxy]piperidine-1-carboxylate (170 mg, 200.23 μmol, 1.0 eq) in DCM (5 mL) was added TFA (114 mg, 1.00 mmol, 74.37 μL, 5.0 eq). The reaction mixture was stirred at 25 °C for 0.5 h. The reaction mixture was concentrated under reduced pressure to give a residue. Compound4-[1,3-dimethyl-2-oxo-7-(4-piperidyloxy)-5-quinolyl]-1-methyl-7-(1-methylpyrazol-4-yl)-2,3-dihydroquinoxaline-6-carbonitrile (130 mg) was obtained as yellow oil and directly used in the next step without further purification.

[00625] **LC-MS:** MS (ESI^+): t_R = 0.439 min, m/z = 524.4 [M + H^+]

[00626] To a solution of 4-[1,3-dimethyl-2-oxo-7-(4-piperidyloxy)-5-quinolyl]-1-methyl-7-(1-methylpyrazol-4-yl)-2,3-dihydroquinoxaline-6-carbonitrile (130 mg, 203.87 μmol, 1.0 eq) and DIPEA (263 mg, 2.04 mmol, 355.11 μL, 10.0 eq) in NMP (4 mL) was added 6-chloro-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide (160 mg, 407.75 μmol, 2.0 eq). The reaction mixture was stirred at 70 °C for 12 h under N_2. The reaction mixture was quenched by addition water (10 mL) at 25 °C, and then diluted with water (20 mL) and extracted with ethyl acetate (30 mL × 3). The combined organic layers were washed with brine (30 mL × 3), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (silica, DCM: MeOH = 20: 1). The residue was purified by prep-HPLC (FA condition：column: Phenomenex luna C18 150*25mm* 10um; mobile phase: [water (FA) - ACN]; gradient: 60% - 90% B over 1 min). The desired compound N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]-6-[4-[[5-[7-cyano-4-methyl-6-(1-methylpyrazol-4-yl)-2,3-dihydroquinoxalin-1-yl]-1,3-dimethyl-2-oxo-7-quinolyl]oxy]-1-piperidyl]pyridazine-3-carboxamide (88.05 mg, 99.08 μmol, 48% yield over two steps) was obtained as a yellow solid.

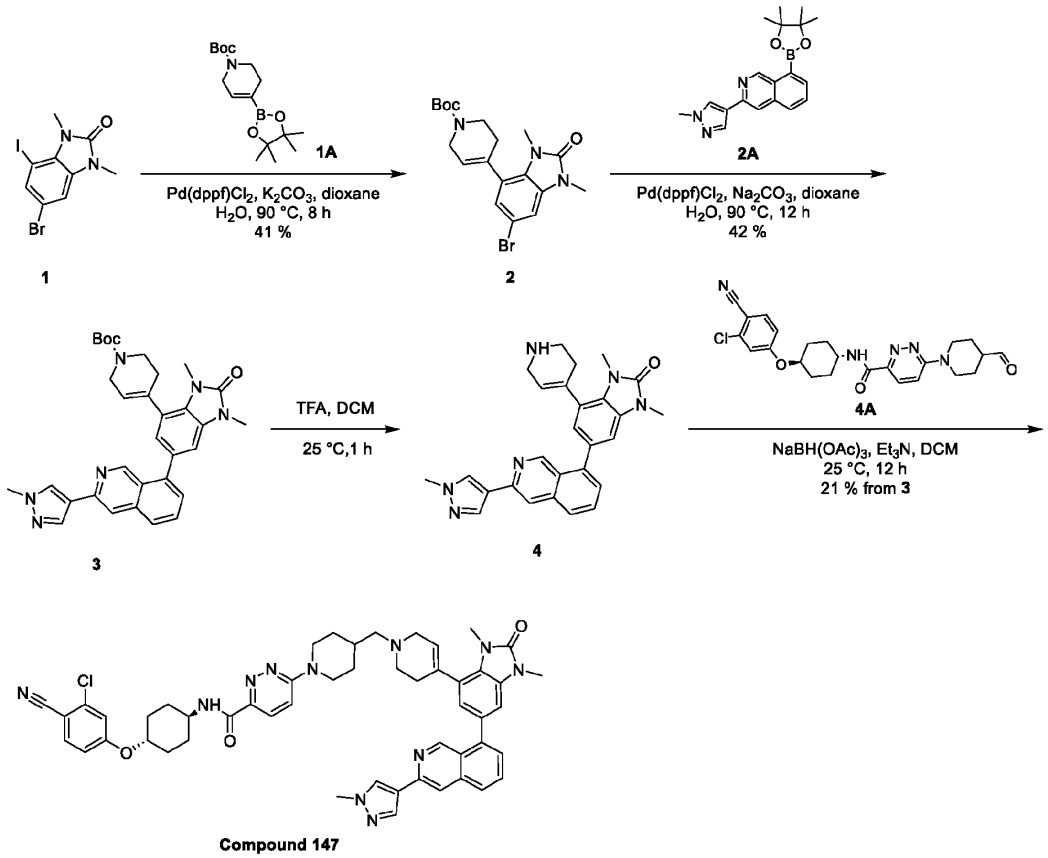
[00627] **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8.03 (d, J = 9.6 Hz, 1H), 7.91 - 7.84 (m, 2H), 7.77 (s, 1H), 7.61 - 7.54 (m, 2H), 7.09 - 6.99 (m, 2H), 6.91 - 6.79 (m, 2H), 6.71 (d, J = 2.0 Hz, 1H), 6.66 (s, 1H), 6.25 (s, 1H), 4.82 - 4.69 (m, 1H), 4.40 - 4.26 (m, 1H), 4.15 - 3.93 (m, 6H), 3.92 - 3.85 (m, 2H), 3.84 - 3.73 (m, 5H), 3.66 - 3.57 (m, 1H), 3.55 - 3.46 (m, 1H), 3.12 (s, 3H), 2.25 - 2.09 (m, 9H), 2.03 (br d, J = 2.9 Hz, 2H), 1.78 - 1.67 (m, 2H), 1.52 - 1.41 (m, 2H)

[00628] **LC-MS:** MS (ESI^+): t_R = 3.120 min, m/z = 878.7 [M + H^+]

[00629] The compounds below were prepared in a similar manner as described in Example 15.

Compound	Name	^{1}H NMR ($CDCl_3$)	LC-MS [M + H$^+$]
37	N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]-6-[4-[[5-[7-cyano-4-methyl-6-(1-methylpyrazol-4-yl)-2,3-dihydroquinoxalin-1-yl]-1,3-dimethyl-2-oxo-7-quinolyl]oxymethyl]-1-piperidyl]pyridazine-3-carboxamide	δ=8.03 (d, *J*=9.60 Hz, 1 H) 7.84 - 7.92 (m, 2 H) 7.76 (s, 1 H) 7.54 - 7.60 (m, 2 H) 7.07 (br d, *J*=9.60 Hz, 1 H) 7.01 (d, *J*=2.40 Hz, 1 H) 6.86 (dd, *J*=8.80, 2.40 Hz, 1 H) 6.75 (d, *J*=1.60 Hz, 1 H) 6.67 (d, *J*=2.00 Hz, 1 H) 6.65 (s, 1 H) 6.23 (s, 1 H) 4.64 (br dd, *J*=12.00, 2.00 Hz, 2 H) 4.21 - 4.40 (m, 1 H) 4.03 - 4.15 (m, 1 H) 3.92 - 3.99 (m, 5 H) 3.79 (br d, *J*=8.00 Hz, 2 H) 3.77 (s, 3 H) 3.56 - 3.64 (m, 1 H) 3.45 - 3.52 (m, 1 H) 3.17 (br d, *J*=1.20 Hz, 2 H) 3.13 (br s, 3 H) 2.19 (br d, *J*=0.80 Hz, 4 H) 2.18 (br s, 2 H) 2.04 - 2.11 (m, 2 H) 1.69 (br d, *J*=12.40 Hz, 4 H) 1.44 - 1.53 (m, 4 H).	892.5
38	N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]-6-[4-[2-[[5-[7-cyano-4-methyl-6-(1-methylpyrazol-4-yl)-2,3-dihydroquinoxalin-1-yl]-1,3-dimethyl-2-oxo-7-quinolyl]oxy]ethyl]-1-piperidyl]pyridazine-3-carboxamide	δ = 7.98 (d, J = 9.6 Hz, 1H), 7.92 - 7.84 (m, 2H), 7.76 (s, 1H), 7.61 - 7.52 (m, 2H), 7.05 - 6.97 (m, 2H), 6.86 (dd, J = 2.4, 8.8 Hz, 1H), 6.76 (d, J = 1.6 Hz, 1H), 6.71 - 6.62 (m, 2H), 6.23 (s, 1H), 4.55 (br d, J = 12.8 Hz, 2H), 4.38 - 4.28 (m, 1H), 4.14 (br t, J = 6.0 Hz, 2H), 4.10 - 4.01 (m, 1H), 3.95 (s, 3H), 3.87 - 3.75 (m, 5H), 3.60 (br dd, J = 3.6, 7.8 Hz, 1H), 3.55 - 3.44 (m, 1H), 3.17 - 3.04 (m, 5H), 2.26 - 2.12 (m, 7H), 1.97 (br d, J = 10.4 Hz, 3H), 1.84 (q, J = 6.0 Hz, 2H), 1.71 - 1.64 (m, 2H), 1.51 - 1.33 (m, 4H)	906.7
39	N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]-6-[4-[2-[[5-[7-cyano-4-methyl-6-(1-methylpyrazol-4-yl)-2,3-dihydroquinoxalin-1-yl]-1,3-dimethyl-2-oxo-7-quinolyl]oxy]ethoxy]-1-piperidyl]pyridazine-3-carboxamide	(DMSO-d6) δ = 8.59 (d, J = 8.4 Hz, 1H), 8.06 (s, 1H), 7.90 - 7.74 (m, 3H), 7.59 (s, 1H), 7.39 (d, J = 2.4 Hz, 1H), 7.33 (d, J = 9.6 Hz, 1H), 7.13 (dd, J = 2.4, 8.8 Hz, 1H), 6.96 (d, J = 1.6 Hz, 1H), 6.88 (d, J = 2.0 Hz, 1H), 6.70 (s, 1H), 5.92 (s, 1H), 4.60 - 4.46 (m, 1H), 4.35 - 4.24 (m, 2H), 4.14 - 3.99 (m, 2H), 3.89 - 3.82 (m, 6H), 3.78 (s, 1H), 3.66 (s, 3H), 3.49 (br d, J = 1.2 Hz, 2H), 3.44 - 3.35 (m, 2H), 3.07 (s, 3H), 2.10 (br d, J = 9.6 Hz, 2H), 2.05 (s, 3H), 1.97 - 1.85 (m, 4H), 1.69 - 1.57 (m, 2H), 1.56 - 1.44 (m, 4H), 1.23 (s, 1H)	922.5

[00630] **Example 16**: Synthesis of N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]-6-[4-[[4-[1,3-dimethyl-6-[3-(1-methylpyrazol-4-yl)-8-isoquinolyl]-2-oxo-benzimidazol-4-yl]-3,6-dihydro-2H-pyridin-1-yl]methyl]-1-piperidyl]pyridazine-3-carboxamide (**Compound 147**)



[00631] Synthesis of **1** was reported in Journal of Organic Chemistry, 2018, vol. 83, # 17, p. 10627 - 10635.

[00632] Synthesis of **2A** was reported in Journal of Bioorganic and Medicinal Chemistry Letters, 2018, vol. 28, # 1, p. 15 - 23.

[00633] Synthesis of **4A** was reported in Journal of Journal of Medicinal Chemistry, 2023, vol. 66, # 7, p. 4784 - 4801.

[00634] To a solution of 6-bromo-4-iodo-1,3-dimethyl-benzimidazol-2-one (4.00 g, 10.90 mmol, 1.0 *eq*) and tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyridine-1-carboxylate (6.74 g, 21.80 mmol, 2.0 *eq*) in dioxane (82 mL) and H_2O (16 mL) was added K_2CO_3 (3.77 g, 27.25 mmol, 2.5 eq) and $Pd(dppf)Cl_2$ (1.20 g, 1.63 mmol, 0.1 *eq*) under N_2 atmosphere. The mixture was stirred at 90 °C for 8 h under N_2 atmosphere. The residue was diluted with H_2O (50 mL) and extracted with EtOAc (60 mL * 3). The combined organic layers were washed with sat. NaCl (80 mL * 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate= 10/1 to 1/1). Compound tert-butyl 4-(6-bromo-1,3-dimethyl-2-oxo-benzimidazol-4-yl)-3,6-dihydro-2H-pyridine-1-carboxylate (1.90 g, 4.50 mmol, 41 % yield) was obtained as a yellow oil.

[00635] **LC-MS:** MS (ESI^+): t_R = 0.913 min, m/z = 421.1 [$M + H^+$]

[00636] To a solution of tert-butyl 4-(6-bromo-1,3-dimethyl-2-oxo-benzimidazol-4-yl)-3,6-dihydro-2H-pyridine-1-carboxylate (200 mg, 473 μmol, 1.0 *eq*) and 3-(1-methylpyrazol-4-yl)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoquinoline (190 mg, 568 μmol, 1.2 *eq*) in dioxane (4 mL) and H_2O (0.4 mL) was added Pd(dppf)Cl_2 (34 mg, 47 μmol, 0.1 *eq*) and Na_2CO_3 (150 mg, 1.45 mmol, 3.0 *eq*) under N_2 atmosphere. The mixture was stirred at 90 °C for 12 h under N_2 atmosphere. The residue was diluted with H_2O (10 mL) and extracted with EtOAc (15 mL * 3). The combined organic layers were washed with sat. NaCl (20 mL * 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, EA: MeOH = 10:1). Compound tert-butyl 4-[1,3-dimethyl-6-[3-(1-methylpyrazol-4-yl)-8-isoquinolyl]-2-oxo-benzimidazol-4-yl]-3,6-dihydro-2H-pyridine-1-carboxylate (112 mg, 203 μmol, 42 % yield) was obtained as a yellow oil.

[00637] **LC-MS:** MS (ESI^+): t_R = 0.581 min, m/z = 550.2 [M + H^+]

[00638] To a solution of tert-butyl 4-[1,3-dimethyl-6-[3-(1-methylpyrazol-4-yl)-8-isoquinolyl]-2-oxo-benzimidazol-4-yl]-3,6-dihydro-2H-pyridine-1-carboxylate (56 mg, 101 μmol, 1.0 *eq*) in DCM (3 mL) was added TFA (1.54 g, 13.46 mmol, 1.0 mL, 132.3 *eq*). The mixture was stirred at 25 °C for 1 h. The mixture was concentrated to give a residue. Compound 1,3-dimethyl-6-[3-(1-methylpyrazol-4-yl)-8-isoquinolyl]-4-(1,2,3,6-tetrahydropyridin-4-yl)benzimidazol-2-one (45 mg) was obtained as a yellow oil and directly used in the next step without further purification.

[00639] **LC-MS:** MS (ESI^+): t_R = 0.622 min, m/z = 450.2 [M + H^+]

[00640] To a solution of 1,3-dimethyl-6-[3-(1-methylpyrazol-4-yl)-8-isoquinolyl]-4-(1,2,3,6-tetrahydropyridin-4-yl)benzimidazol-2-one (45 mg) in DCM (1 mL) was added N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]-6-(4-formyl-1-piperidyl)pyridazine-3-carboxamide (46 mg, 99 μmol, 1.0 *eq*), Et_3N (30 mg, 299 μmol, 41.7 μL, 3.0 *eq*) and $NaBH(OAc)_3$ (42 mg, 199 μmol, 2.0 *eq*). The mixture was stirred at 25 °C for 12 h. The mixture was filtered and concentrated to give a residue. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150*25mm* 10um;mobile phase: [water(FA)-ACN];gradient:26%-56% B over 10 min). The residue was purified by prep-HPLC (column: Waters Xbridge 150*25mm* 5um;mobile phase: [water(NH_4HCO_3)-ACN];gradient:45%-65% B over 10 min). Compound N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]-6-[4-[[4-[1,3-dimethyl-6-[3-(1-methylpyrazol-4-yl)-8-isoquinolyl]-2-oxo-benzimidazol-4-yl]-3,6-dihydro-2H-pyridin-1-yl]methyl]-1-piperidyl]pyridazine-3-carboxamide (20 mg, 21 % yield over two steps) was obtained as a white solid.

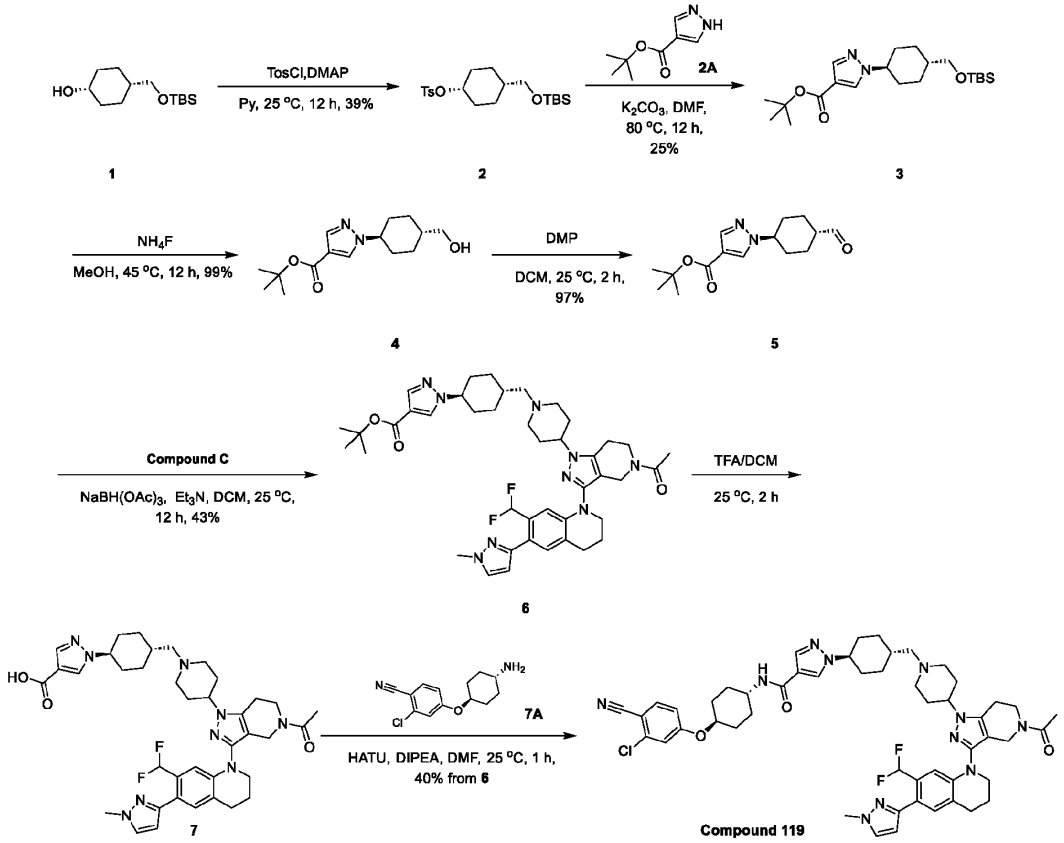
[00641] **^{1}H NMR** (400 MHz, DMSO-d_6) δ = 9.24 (s, 1H), 8.64 - 8.54 (m, 1H), 8.33 (s, 1H), 8.10 (m, 2H), 7.78 (s, 4H), 7.48 (S.1 Hz, 1H), 7.34 (s, 3H), 7.09 (s, 1H), 6.98 (S 1H), 5.87 - 5.71 (m, 1H), 4.60 - 4.40 (m, 3H), 3.91 (s, 4H), 3.44 - 3.38 (m, 6H), 3.15 - 2.96 (m, 4H), 2.68 - 2.63 (m, 2H), 2.56 - 2.52 (m, 2H), 2.36 - 2.24 (m, 2H), 2.16 - 2.04 (m, 2H), 1.99 - 1.80 (m, 5H), 1.70 - 1.57 (m, 2H), 1.57 - 1.44 (m, 2H), 1.25 - 1.05 (m, 2H).

[00642] **LC-MS:** MS (ESI^+): t_R = 1.599 min, m/z = 901.3 [M + H^+]

[00643] The compounds below were prepared in a similar manner as described in Example 16.

Compound	Name	^{1}H NMR ($CDCl_3$)	LC-MS [M + H$^+$]
148	N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]-6-[4-[[4-[1,3-dimethyl-6-[3-(1-methylpyrazol-4-yl)-8-isoquinolyl]-2-oxo-benzimidazol-4-yl]-3,6-dihydro-2H-pyridin-1-yl]methyl]-1-piperidyl]pyridazine-3-carboxamide	(DMSO-d_6) δ = 8.52 (s, 1H), 7.91 - 7.75 (m, 2H), 7.74 - 7.71 (m, 1H), 7.48 (s, 1H), 7.39 - 7.35 (m, 1H), 7.34 - 7.28 (m, 1H), 7.13 (s, 1H), 7.10 - 7.03 (m, 2H), 6.71 (s, 3H), 5.69 (s, 1H), 4.58 - 4.42 (m, 3H), 3.86 (s, 4H), 3.61 (m, 2H), 3.39 - 3.33 (m, 3H), 3.31 (s, 3H), 3.11 - 2.96 (m, 4H), 2.90 - 2.82 (m, 2H), 2.70 - 2.60 (m, 2H), 2.42 - 2.36 (m, 2H), 2.33 - 2.27 (m, 2H), 2.14 - 2.07 (m, 2H), 2.04 - 1.98 (m, 2H), 1.96 - 1.80 (m, 5H), 1.70 - 1.59 (m, 2H), 1.57 - 1.46 (m, 2H), 1.14 (m, 2H).	955.4

[00644] **Example 17**: Synthesis of 1-[4-[[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-3-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo [4,3-c]pyridin-1-yl]-1-piperidyl]methyl]cyclohexyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl] pyrazole-4-carboxamide **(Compound 119)**



[00645] Synthesis of **1** was reported in WO2022/161414, 2022, A1.

[00646] Synthesis of **2A** was reported in WO2017/87858, 2017, A1.

[00647] Synthesis of **7A** was reported in MedChemComm, 2016, vol. 7, # 5, p. 813 – 819.

[00648] To a mixtuer of 4-[[tert-butyl(dimethyl)silyl]oxymethyl]cyclohexanol (2.80 g, 11.5 mmol, 1.0 eq) in Py (50 mL) was added DMAP (280 mg, 2.30 mmol, 0.2 eq) and TosCl (2.80 g, 14.7 mmol, 1.3 eq). The mixture was stirred at 25 °C for 12 h under N_2 atmosphere. The reaction mixture was quenched by addition water 100 mL, and then extracted with ethyl acetate (30 mL × 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether: Ethyl acetate= 1:0 to 20:1). Compound [4-[[tert-butyl(dimethyl)silyl]oxymethyl]cyclohexyl] 4-methylbenzenesulfonate (1.80 g, 4.52 mmol, 39% yield) was obtained as a Colorless oil.

[00649] **^{1}H NMR** (400 MHz, CHLOROFORM-*d*) δ ppm 7.80 (d, *J*=8.4 Hz, 2 H) 7.33 (d, *J*=8.0 Hz, 2 H) 4.76 (s, 1 H) 3.40 (d, *J*=6.4 Hz, 2 H) 2.45 (s, 3 H) 1.88 (m, 2 H) 1.41 - 1.61 (m, 5 H) 1.17 - 1.41 (m, 2 H) 0.88 (s, 9 H) 0.03 (s, 6 H).

[00650] A mixture of tert-butyl 1H-pyrazole-4-carboxylate (900 mg, 5.35 mmol, 1.2 eq), [4-[[tert-butyl(dimethyl)silyl]oxymethyl]cyclohexyl] 4-methylbenzenesulfonate (1.80 g, 4.52 mmol, 1.0 eq), K_2CO_3 (1.80 g, 13.0 mmol, 2.9 eq) in DMF (40 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 80 °C for 12 h under N_2 atmosphere. The reaction mixture was quenched by addition water 250 mL, and then extracted with ethyl acetate (30 mL × 3). The combined organic layers were washed with brine (30 mL × 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether: Ethyl acetate=1:0 to 5:1). Compound tert-butyl 1-[4-[[tert-butyl(dimethyl)silyl]oxymethyl]cyclohexyl]pyrazole-4-carboxylate (450 mg, 1.14 mmol, 25% yield) was obtained as a colorless oil.

[00651] **LC-MS:** MS (ESI^+): t_R = 0.768 min, m/z = 395.2 [$M + H^+$]

[00652] A mixture of tert-butyl 1-[4-[[tert-butyl(dimethyl)silyl]oxymethyl]cyclohexyl]pyrazole-4-carboxylate (400 mg, 1.01 mmol, 1.0 eq), NH_4F (400 mg, 10.8 mmol, 10.7 eq) in MeOH (20 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 45 °C for 12 h under N_2 atmosphere. Afterwards, the reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by column chromatography (SiO_2, Dichloromethane: Methanol=30:1 to 10:1). Compound tert-butyl 1-[4-(hydroxymethyl)cyclohexyl]pyrazole-4-carboxylate (280 mg, 999 μmol, 99% yield) was obtained as a yellow solid.

[00653] **LC-MS:** MS (ESI^+): t_R = 0.527 min, m/z = 281.2 [$M + H^+$]

[00654] A mixture of tert-butyl 1-[4-(hydroxymethyl)cyclohexyl]pyrazole-4-carboxylate (280 mg, 999 μmol, 1.0 eq), DMP (560 mg, 1.32 mmol, 1.3 eq) in DCM (10 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 25 °C for 2 h under N_2 atmosphere. Afterwards, the reaction mixture was quenched by addition saturated eq.$NaHCO_3$ (50 mL) and saturated eq.Na_2SO_3 (50 mL) at 0 °C, and then extracted with DCM (40 mL × 3). The combined organic layers were washed with brine (40 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether: Ethyl acetate=1:0 to 0:1). Compound tert-butyl 1-(4-formylcyclohexyl)pyrazole-4-carboxylate (270 mg, 970 μmol, 97% yield) was obtained as a yellow

solid.

[00655] **LC-MS:** MS (ESI^+): t_R = 0.552 min, m/z = 279.2 [M + H^+]

[00656] To a solution of 1-[3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-1-(4-piperidyl)-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]ethanone (100 mg, 196 μmol, 1.0 eq), tert-butyl 4-formylpiperidine-1-carboxylate (50 mg, 234 μmol, 1.2 eq) and Et_3N (218 mg, 2.16 mmol, 11.0 eq) in DCM (5 mL) was added $NaBH(OAc)_3$ (210 mg, 991 μmol, 5.1 eq). The mixture was stirred at 25 °C for 12 h, and then the mixture was diluted with DCM (100 mL), washed with water (15 mL × 2), brine (15 mL), dried with anhydrous sodium sulfate, filtered and concentrated under vacuum. The residue was purified by prep-TLC (SiO_2, ethyl acetate: MeOH= 10:1). Compound tert-butyl 4-[[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]methyl]piperidine-1-carboxylate (61 mg, 84.9 μmol, 43% yield) was obtained as a yellow oil.

[00657] **LC-MS:** MS (ESI^+): t_R = 0.527 min, m/z = 772.5 [M + H^+]

[00658] A mixture of tert-butyl 1-[4-[[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-3-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]methyl]cyclohexyl] pyrazole-4-carboxylate (80 mg, 104 μmol, 1.0 eq), TFA (480 mg, 4.00 mmol, 40.0 eq) in DCM (10 mL) was stirred at 25 °C for 2 h. The reaction mixture was concentrated under reduced pressure to give a residue. Compound 1-[4-[[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-3-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]methyl]cyclohexyl]pyrazole-4-carboxylic acid (85 mg) was obtained as a white solid and directly used in the next step without further purification.

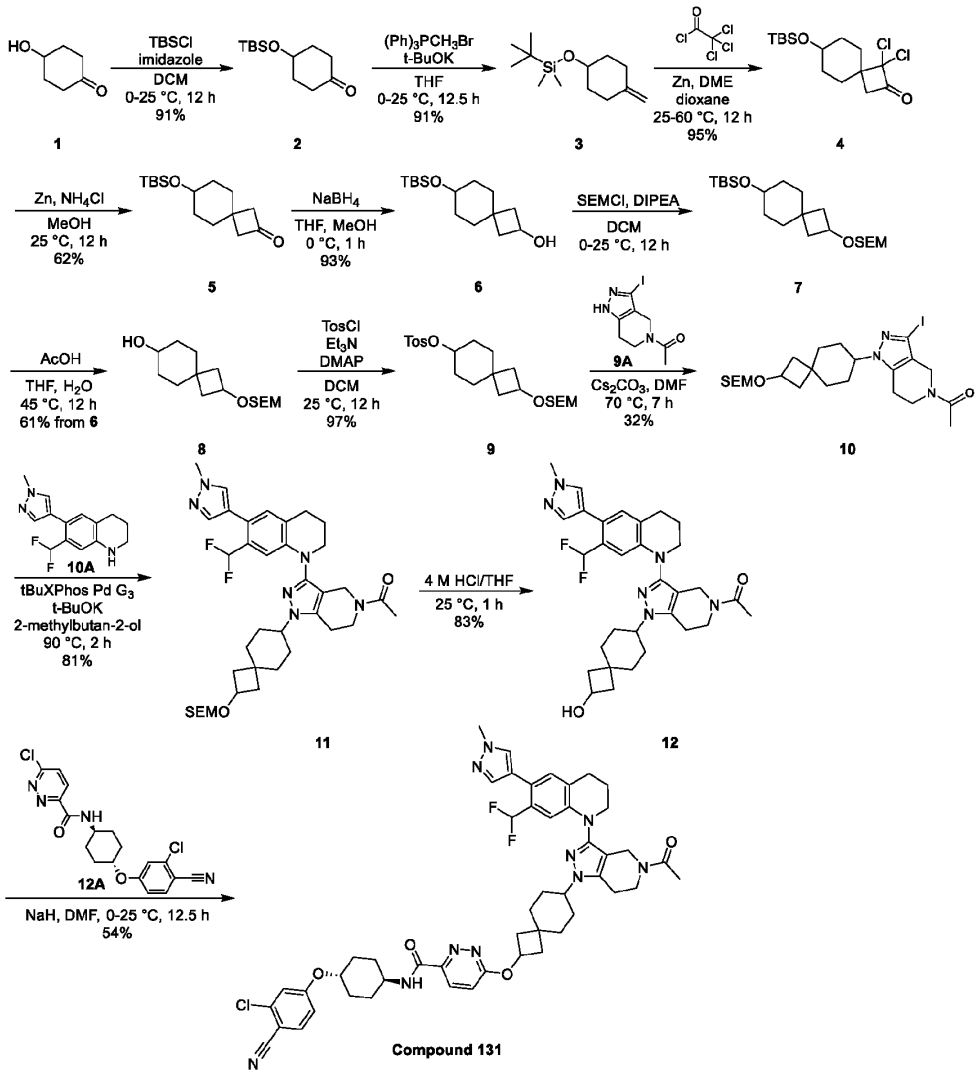
[00659] **LC-MS:** MS (ESI^+): t_R = 0.452 min, m/z = 716.4 [M + H^+]

[00660] To a solution of 1-[4-[[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-3-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]methyl]cyclohexyl]pyrazole-4-carboxylic acid (70 mg, 84.4 μmol, 1.0 eq) and 4-(4-aminocyclohexoxy)-2-chloro-benzonitrile (50 mg, 200 μmol, 2.4 eq) in DMF (5 mL) was added HATU (50 mg, 132 μmol, 1.6 eq) and DIPEA (109 mg, 844 μmol, 10.0 eq) and stirred at 25 °C for 1 h. The mixture was diluted with ethyl acetate (100 mL), washed with water (20 mL × 2), brine (20 mL), dried with anhydrous sodium sulfate, filtered and concentrated under vacuum. The crude product was purified by reversed-phase HPLC (column: Phenomenex luna C18 150 × 25mm × 10um; mobile phase: [water (FA)-ACN]; gradient: 29%-59% B over 10 min). Compound 1-[4-[[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-3-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo [4,3-c]pyridin-1-yl]-1-piperidyl]methyl]cyclohexyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl] pyrazole-4-carboxamide (32.31 mg, 33.8 μmol, 40% yield over two steps) was obtained as an off-white solid.

[00661] **^{1}H NMR** (400 MHz, CHLOROFORM-*d*) δ ppm 7.91 (s, 1 H) 7.70 (s, 1 H) 7.51 - 7.60 (m, 2 H) 7.41 (d, *J*=6.8 Hz, 1 H) 6.98 - 7.08 (m, 2 H) 6.82 - 6.92 (m, 2 H) 6.36 - 6.70 (m, 1 H) 5.58 (d, *J*=7.6 Hz, 1 H) 4.20 - 4.37 (m, 2 H) 4.09 - 4.18 (m, 2 H) 4.02 (m, 1 H) 3.87 - 3.99 (m, 5 H) 3.65 - 3.82 (m, 3 H) 2.93 - 3.12 (m, 2 H) 2.78 - 2.93 (m, 3 H) 2.75 (m, 1 H) 2.12 - 2.34 (m, 13 H) 2.01 - 2.11 (m, 6 H) 1.89 - 1.99 (m, 2 H) 1.80 - 1.89 (m, 2 H) 1.61 - 1.80 (m, 6 H) 1.34 - 1.46 (m, 2 H) 1.03 - 1.19 (m, 2 H)

[00662] **LC-MS:** MS (ESI^+): t_R = 2.191 min, m/z = 948.6 [M + H^+]

[00663] **Example 18**: Synthesis of 6-((7-(5-acetyl-3-(7-(difluoromethyl)-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinolin-1(2H)-yl)-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridin-1-yl)spiro[3.5]nonan-2-yl)oxy)-N-((1SR,4SR)-4-(3-chloro-4-cyanophenoxy)cyclohexyl)pyridazine-3-carboxamide (**Compound 131**)



[00664] Synthesis of **9A** was reported in Journal of Medicinal Chemistry, 2024, vol. 67, # 7, p. 5275 – 5304

[00665] Synthesis of **10A** was reported in Cell Chemical Biology, 2021, vol. 28, # 4, p. 503 - 12,514

[00666] Synthesis of **12A** was reported in European Journal of Medicinal Chemistry, 2024, vol. 271, art.

no. 116400.

[00667] To a solution of 4-hydroxycyclohexanone (25.00 g, 219 mmol, 1.0 eq) and imidazole (29.97 g, 440 mmol, 2.0 eq) in DCM (500 mL) and then tert-butyldimethylsilyl chloride (34.66 g, 230 mmol, 1.1 eq) was added in portions at 0 °C. The mixture was stirred at 25 °C for 12 h under N_2. The mixture was poured into iced water (500 mL). The aqueous phase was extracted with DCM (500 mL × 3). The combined organic phase was washed with brine (200 mL × 2), dried with anhydrous sodium sulfate, filtered and concentrated under vacuum. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate=1/0). The desired compound 4-[tert-butyl(dimethyl)silyl]oxycyclohexanone (45.50 g, 199 mmol, 91% yield) was obtained as colourless oil.

[00668] **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 4.15 - 4.12 (m, 1H), 2.84 - 2.55 (m, 2H), 2.32 - 2.15 (m, 2H), 2.05 - 1.83 (m, 4H), 0.96 - 0.87 (m, 9H), 0.15 - 0.05 (m, 6H)

[00669] To a solution of methyl(triphenyl)phosphonium;bromide (70.38 g, 197 mmol, 1.5 eq) in THF (200 mL) was added t-BuOK (1.0 M, 197 mL, 1.5 eq) at 0 °C under N_2 atmosphere. The mixture was stirred at 0 °C for 0.5 h, and then 4-[tert-butyl(dimethyl)silyl]oxycyclohexanone (30.00 g, 132 mmol, 1.0 eq) in THF (50 mL) was added. The mixture was stirred at 25 °C for 12 h under N_2 atmosphere. The reaction mixture was quenched by addition water 100 mL, and then diluted with water 100 mL and extracted with ethyl acetate (300 mL × 3). The combined organic layers were washed with brine (100 mL × 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The crude product was triturated with petroleum ether 200 mL at 25 °C for 30 min. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate=1/ 0 to 50/1). The desired compound tert-butyl-dimethyl-(4-methylenecyclohexoxy)silane (27.00 g, 119 mmol, 91% yield) was obtained as colourless oil.

[00670] **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 4.61 (s, 2H), 3.86 - 3.82 (m, 1H), 2.47 - 2.27 (m, 2H), 2.07 - 2.00 (m, 2H), 1.77 - 1.70 (m, 2H), 1.57 - 1.48 (m, 2H), 0.91 - 0.88 (m, 9H), 0.06 (s, 5H)

[00671] To a mixture of tert-butyl-dimethyl-(4-methylenecyclohexoxy)silane (25.18 g, 111 mmol, 1.0 eq) and Zn (44.31 g, 678 mmol, 6.1 eq) in dioxane (400 mL) was added 2,2,2-trichloroacetyl chloride (40.44 g, 222 mmol, 2.0 eq), DME (20.04 g, 222 mmol, 2.0 eq) in dioxane (50 mL) at 60 °C. After the mixture was stirred at 25 °C for 12 h under N_2 atmosphere. The mixture was poured into saturated $NaHCO_3$ (150 mL) and the solid was filtered off. The filtrate was extracted with ethyl acetate (300 mL × 3). The organic phase was washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate=1/0 to 50/1). The desired compound 7-[tert-butyl(dimethyl)silyl]oxy-3,3-dichloro-spiro[3.5]nonan-2-one (35.70 g, 106 mmol, 95% yield) was obtained as yellow oil.

[00672] To a mixture of 7-[tert-butyl(dimethyl)silyl]oxy-3,3-dichloro-spiro[3.5]nonan-2-one (38.74 g, 115 mmol, 1.0 eq) and NH_4Cl (61.43 g, 1.15 mol, 10.0 eq) in MeOH (500 mL) was added Zn (38.20 g, 584 mmol, 5.1 eq) at 25 °C. After the mixture was stirred at 25 °C for 12 h. The mixture was poured into saturated $NaHCO_3$ (200 mL) and the solid was filtered off. The filtrate was extracted with ethyl acetate (200 mL × 3). The organic phase was washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated

under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate=1/0 to 50/1). The desired compound 7-[tert-butyl(dimethyl)silyl]oxyspiro[3.5]nonan-2-one (19.00 g, 70.8 mmol, 62% yield) was obtained as colourless oil.

[00673] **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 3.84 - 3.64 (m, 1H), 2.75 (d, *J* = 3.6 Hz, 4H), 1.83 (d, *J* = 8.0 Hz, 2H), 1.77 - 1.65 (m, 2H), 1.60 - 1.51 (m, 2H), 1.50 - 1.37 (m, 2H), 0.90 (s, 9H), 0.06 (s, 6H)

[00674] To a solution of 7-[tert-butyl(dimethyl)silyl]oxyspiro[3.5]nonan-2-one (38.00 g, 142 mmol, 1.0 eq) in THF (300 mL) and MeOH (100 mL) was added $NaBH_4$ (6.22 g, 164 mmol, 1.2 eq) at 0 °C. The mixture was stirred at 0 °C for 1 h under N_2 atmosphere. The reaction mixture was quenched with saturated aqueous NH_4Cl 150 mL at 0 °C dropwise under N_2 atmosphere. And the resulting mixture was extracted with ethyl acetate (300 mL × 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate=20/1 to 5/1). The desired compound 7-[tert-butyl(dimethyl)silyl]oxyspiro[3.5]nonan-2-ol (35.70 g, 132 mmol, 93% yield) was obtained as colourless oil.

[00675] **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 4.26 (d, *J* = 5.2 Hz, 1H), 3.59 (d, *J* = 3.2 Hz, 1H), 2.31 - 2.25 (m, 1H), 2.19 - 2.13 (m, 1H), 1.69 - 1.58 (m, 6H), 1.40 - 1.24 (m, 4H), 0.88 (s, 9H), 0.04 (s, 6H)

[00676] To a solution of 7-[tert-butyl(dimethyl)silyl]oxyspiro[3.5]nonan-2-ol (17.00 g, 62.9 mmol, 1.0 eq) in DCM (340 mL) was added DIPEA (32.49 g, 251 mmol, 4.0 eq) and (2-trimethylethylsilylethoxy)methyl chloride (31.44 g, 189 mmol, 3.0 eq) at 0 °C. The mixture was stirred at 25 °C for 12 h under N_2 atmosphere. The reaction mixture was quenched by addition water 20 mL, and then diluted with water 20 mL and extracted with DCM (50 mL × 3). The combined organic layers were washed with water (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. Compound tert-butyl-dimethyl-[2-(2-trimethylsilylethoxymethoxy)spiro[3.5]nonan-7-yl]oxy-silane (26.00 g) was obtained as colourless oil and directly used in the next step without further purification

[00677] To a solution of tert-butyl-dimethyl-[2-(2-trimethylsilylethoxymethoxy)spiro[3.5]nonan-7-yl]oxy-silane (26.00 g) in THF (65 mL) and H_2O (65 mL) was added AcOH (136.37 g, 2.27 mol, 35.0 eq). The mixture was stirred at 45 °C for 12 h. Adjust the PH to 7-8 with NaOH aq. and then concentrate the system, extracted with DCM (100 mL × 3), wash with water (50 mL × 2),dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate=100/1 to 5/1). The desired compound 2-(2-trimethylsilylethoxymethoxy)spiro[3.5]nonan-7-ol (11.40 g, 39.8 mmol, 61% yield over two steps) was obtained as yellow oil.

[00678] **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 4.63 (s, 2H), 4.16 (t, *J* = 7.2 Hz, 1H), 3.66 - 3.54 (m, 3H), 2.31 - 2.19 (m, 1H), 2.16 - 2.06 (m, 1H), 1.80 - 1.70 (m, 3H), 1.68 - 1.63 (,m, 3H), 1.45 - 1.30 (m, 4H), 0.97 - 0.89 (m, 2H), 0.02 (s, 9H)

[00679] To a solution of 2-(2-trimethylsilylethoxymethoxy)spiro[3.5]nonan-7-ol (11.40 g, 39.8 mmol, 1.0 eq) in DCM (220 mL) was added Et_3N (20.13 g, 199 mmol, 5.0 eq), DMAP (972 mg, 7.96 mmol, 0.2 eq)

and p-toluenesulfonyl chloride (22.76 g, 119 mmol, 3.0 eq). The mixture was stirred at 25 °C for 12 h. The reaction mixture was diluted with DCM 200 mL, and then washed by water (50 mL × 2). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate=100/1 to 10/1). The desired compound [2-(2-trimethylsilylethoxymethoxy)spiro[3.5]nonan-7-yl] 4-methylbenzenesulfonate (17.00 g, 38.6 mmol, 97% yield) was obtained as yellow oil.

[00680] **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 7.85 - 7.74 (m, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 4.60 (s, 2H), 4.48 (t, *J* = 7.6 Hz, 1H), 4.22 - 4.03 (m, 1H), 3.67 - 3.54 (m, 2H), 2.45 (s, 3H), 2.21 - 2.15 (m, 1H), 2.13 - 2.07 (m, 1H), 1.73 - 1.60 (m, 8H), 1.43 - 1.30 (m, 2H), 0.98 - 0.86 (m, 2H), 0.08 - -0.03 (m, 9H)

[00681] To a solution of [2-(2-trimethylsilylethoxymethoxy)spiro[3.5]nonan-7-yl] 4-methylbenzenesulfonate (10.00 g, 22.7 mmol, 1.0 eq), 1-(3-iodo-1,4,6,7-tetrahydropyrazolo[4,3-c]pyridin-5-yl)ethanone (6.61 g, 22.7 mmol, 1.0 eq) in DMF (165 mL) was added Cs_2CO_3 (59.15 g, 182 mmol, 8.0 eq). The mixture was stirred at 70 °C for 7 h. The reaction mixture was quenched by addition water 1000 mL at 0 °C, and then diluted extracted with ethyl acetate (300 mL × 3). The combined organic layers were washed with brine (200 mL × 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (neutral condition; column: Welch Ultimate XB-CN 250 × 70 × 10um;mobile phase: [Hexane-EtOH（0.1% $NH_3.H_2O$）];gradient:10%-50% B over 15 min). The desired compound 1-[3-iodo-1-[2-(2-trimethylsilylethoxymethoxy)spiro[3.5]nonan-7-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]ethanone (4.00 g, 7.15 mmol, 32% yield) was obtained as off-white solid

[00682] **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 4.63 (s, 2H), 4.42 - 4.22 (m, 2H), 4.20 - 4.13 (m, 1H), 3.70 (t, *J* = 5.6 Hz, 3H), 3.65 - 3.57 (m, 2H), 2.78 - 2.59 (m, 2H), 2.43 - 2.35 (m, 1H), 2.18 (s, 3H), 2.15 - 2.09 (m, 1H), 2.03 - 1.90 (m, 2H), 1.84 - 1.71 (m, 6H), 1.56 - 1.39 (m, 2H), 0.99 - 0.89 (m, 2H), 0.05 - 0.00 (m, 9H)

[00683] To a solution of 1-[3-iodo-1-[2-(2-trimethylsilylethoxymethoxy)spiro[3.5]nonan-7-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]ethanone (4.00 g, 7.15 mmol, 1.0 eq), 7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-1,2,3,4-tetrahydroquinoline (1.88 g, 7.15 mmol, 1.0 eq), tBuXPhos Pd G3 (1.14 g, 1.43 mmol, 0.2 eq) in 2-methylbutan-2-ol (80 mL) was added t-BuOK (1.0 M, 16.7 mL, 2.4 eq). The mixture was stirred at 90 °C for 2 h under N_2. The reaction mixture was diluted with DCM 300 mL, and then washed by water (50 mL × 2). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO; 40 g SepaFlash Silica Flash Column, Eluent of 0~100% ethyl acetate/petroleum ethergradient @ 50 mL/min). The desired compound 1-[3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-1-[2-(2-trimethylsilylethoxymethoxy)spiro[3.5]nonan-7-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]ethanone (4.00 g, 5.76 mmol, 81% yield) was obtained as yellow solid.

[00684] **LC-MS:** MS (ESI^+): t_R = 0.723 min, m/z = 695.3 [M + H^+]

[00685] To a solution of 1-[3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-1-[2-(2-trimethylsilylethoxymethoxy)spiro[3.5]nonan-7-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-

yl]ethanone (5.90 g, 8.49 mmol, 1.0 eq) in THF (60 mL) was added HCl (4.0 M, 60 mL, 28.3 eq). The mixture was stirred at 25 °C for 1 h. Adjust the PH to 9-10 with NaOH aq. and then concentrate the system, extracted with DCM (50 mL × 3), wash with water (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate=1/1 to 0/1). The desired compound 1-[3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-1-(2-hydroxyspiro[3.5]nonan-7-yl)-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]ethanone (4.00 g, 7.08 mmol, 83% yield) was obtained as off-white solid.

[00686] **LC-MS:** MS (ESI^+): t_R = 0.911 min, m/z = 565.3 [M + H^+]

[00687] To a solution of 1-[3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-1-(2-hydroxyspiro[3.5]nonan-7-yl)-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]ethanone (4.00 g, 7.08 mmol, 1.0 eq) in DMF (50 mL) was added NaH (567 mg, 60% w/w, 14.2 mmol, 2.0 eq). The mixture was stirred at 0 °C for 0.5 h under N_2 atmosphere. And then 6-chloro-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide (3.33 g, 8.50 mmol, 1.2 eq) was added at 0 °C. The mixture was stirred at 25 °C for 12 h under N_2 atmosphere. The reaction mixture was quenched with saturated aqueous NH_4Cl (50 mL) solution at 0 °C dropwise under N_2 atmosphere. And the resulting mixture was extracted with ethyl acetate (60 mL × 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by prep-HPLC (FA condition;column: Phenomenex luna C18 (250 × 70mm,10 um);mobile phase: [water(FA)-ACN];gradient:58%-88% B over 20 min). The desired compound 6-[7-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]spiro[3.5]nonan-2-yl]oxy-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide (3585.8 mg, 3.85 mmol, 54% yield) was obtained as yellow solid.

[00688] **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 8.12 (d, J = 9.2 Hz, 1H), 7.99 (s, 1H), 7.84 (d, J = 8.0 Hz, 1H), 7.53 - 7.42 (m, 2H), 7.39 - 7.30 (m, 1H), 7.02 (d, J = 9.2 Hz, 1H), 6.99 - 6.90 (m, 2H), 6.84 - 6.76 (m, 2H), 6.62 - 6.28 (m, 1H), 5.38 (t, J = 7.2 Hz, 1H), 4.30 - 4.21 (m, 1H), 4.20 - 4.03 (m, 2H), 4.02 - 3.94 (m, 1H), 3.92 - 3.78 (m, 5H), 3.75 - 3.58 (m, 3H), 2.82 - 2.76 (m, 2H), 2.74 - 2.60 (m, 3H), 2.47 - 2.36 (m, 1H), 2.16 - 2.07 (m, 5H), 2.04 - 1.91 (m, 8H), 1.89 - 1.75 (m, 4H), 1.67 - 1.59 (m, 4H), 1.45 - 1.36 (m, 2H)

[00689] **LC-MS:** MS (ESI^+): t_R = 3.662 min, m/z = 919.5 [M + H^+]

[00690] **Preparation of Compound 235**

[00691] 6-[7-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]spiro[3.5]nonan-2-yl]oxy-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide (3.00 g, 3.26 mmol, 1.0 eq) was separated by SFC (column: DAICEL CHIRALPAK AD(250mm × 30mm,10um);mobile phase: [CO_2-ACN/i-PrOH(0.1% NH_3H_2O)];B%:35%, isocratic elution mode). The desired compound 6-((7-(5-acetyl-3-(7-(difluoromethyl)-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinolin-1(2H)-yl)-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridin-1-yl)spiro[3.5]nonan-2-yl)oxy)-N-((1SR,4SR)-4-(3-chloro-4-cyanophenoxy)cyclohexyl)pyridazine-3-

carboxamide (975.11 mg, 1.06 mmol, 32% yield) was obtained as yellow solid.

[00692] **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 8.19 (d, *J* = 9.2 Hz, 1H), 7.91 (d, *J* = 8.4 Hz, 1H), 7.62 - 7.49 (m, 2H), 7.40 (d, *J* = 6.8 Hz, 1H), 7.09 (d, *J* = 9.2 Hz, 1H), 7.06 - 6.97 (m, 2H), 6.92 - 6.80 (m, 2H), 6.72 - 6.34 (m, 1H), 5.45 (t, *J* = 7.2 Hz, 1H), 4.40 - 4.29 (m, 1H), 4.28 - 4.10 (m, 2H), 4.09 - 4.00 (m, 1H), 3.99 - 3.84 (m, 5H), 3.83 - 3.65 (m, 3H), 2.89 - 2.83 (m, 2H), 2.82 - 2.65 (m, 3H), 2.51 - 2.45 (m, 1H), 2.23 - 2.13 (m, 5H), 2.12 - 1.98 (m, 8H), 1.97 - 1.81 (m, 4H), 1.70 - 1.54 (m, 4H), 1.54 - 1.41 (m, 2H)

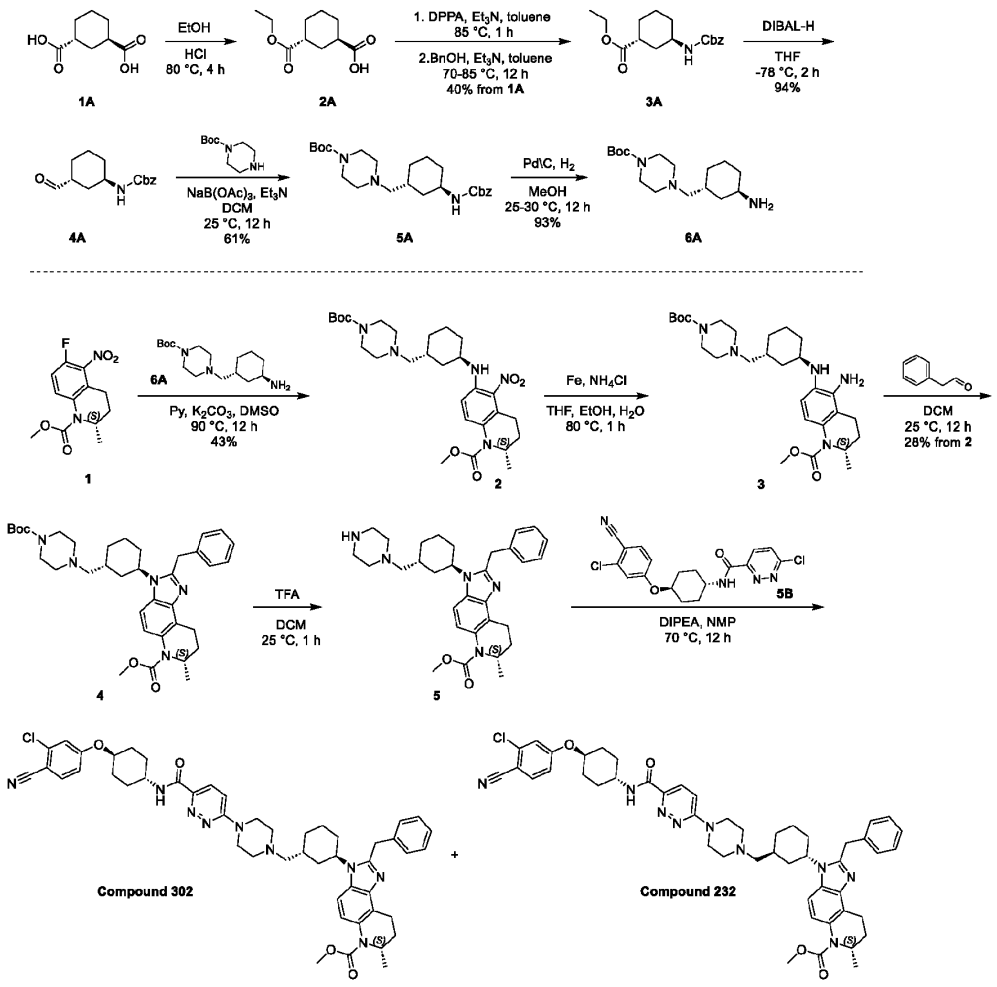
[00693] **LC-MS:** MS (ESI$^+$): t_R = 3.655 min, m/z = 919.6 [M + H$^+$]

[00694] **Preparation of Compound 301**

[00695] 6-[7-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]spiro[3.5]nonan-2-yl]oxy-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide (3.00 g, 3.26 mmol, 1.0 eq) was separated by SFC (column: DAICEL CHIRALPAK AD(250mm × 30mm,10um);mobile phase: [CO_2-ACN/i-PrOH(0.1% NH_3H_2O)];B%:35%, isocratic elution mode). The desired compound 6-((7-(5-acetyl-3-(7-(difluoromethyl)-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinolin-1(2H)-yl)-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridin-1-yl)spiro[3.5]nonan-2-yl)oxy)-N-((1SR,4SR)-4-(3-chloro-4-cyanophenoxy)cyclohexyl)pyridazine-3-carboxamide (1086.15 mg, 1.17 mmol, 36 yield) was obtained as yellow solid.

[00696] **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 8.19 (d, *J* = 9.2 Hz, 1H), 7.91 (d, *J* = 8.0 Hz, 1H), 7.61 - 7.50 (m, 2H), 7.46 - 7.36 (m, 1H), 7.09 (d, *J* = 9.2 Hz, 1H), 7.06 - 6.96 (m, 2H), 6.92 - 6.82 (m, 2H), 6.70 - 6.33 (m, 1H), 5.45 (t, *J* = 7.2 Hz, 1H), 4.41 - 4.28 (m, 1H), 4.27 - 4.10 (m, 2H), 4.09 - 3.99 (m, 1H), 3.98 - 3.84 (m, 5H), 3.83 - 3.64 (m, 3H), 2.89 - 2.84 (m, 2H), 2.82 - 2.65 (m, 3H), 2.52 - 2.46 (m, 1H), 2.24 - 2.15 (m, 5H), 2.11 - 1.98 (m, 8H), 1.97 - 1.82 (m, 4H), 1.71 - 1.54 (m, 4H), 1.53 - 1.41 (m, 2H)
LC-MS: MS (ESI$^+$): t_R = 3.655 min, m/z = 919.6 [M + H$^+$]

[00697] **Example 19:** Synthesis of methyl (7S)-2-benzyl-3-[(1R,3R)-3-[[4-[6-[[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]carbamoyl]pyridazin-3-yl]piperazin-1-yl]methyl]cyclohexyl]-7-methyl-8,9-dihydro-7H-imidazo[4,5-f]quinoline-6-carboxylate **(Compound 302)** and methyl (7S)-2-benzyl-3-[(1S,3S)-3-[[4-[6-[[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]carbamoyl]pyridazin-3-yl]piperazin-1-yl]methyl]cyclohexyl]-7-methyl-8,9-dihydro-7H-imidazo[4,5-f]quinoline-6-carboxylate **(Compound 232)**



[00698] Synthesis of **1A** was reported in WO2022/87636, 2022, A1.

[00699] Synthesis of **1** was reported in US2022/88005, 2022, A1.

[00700] Synthesis of **5B** was reported in European Journal of Medicinal Chemistry, 2024, vol. 271, art. no. 116400.

[00701] To a mixture of (1R,3R)-cyclohexane-1,3-dicarboxylic acid (4.00 g, 23.2 mmol, 1.0 eq) in HCl (100 mL) was added EtOH (1.07 g, 23.2 mmol, 1.0 eq). The reaction mixture was stirred at 80 °C for 4 h. under N_2. The mixture was poured into ice-water (150 mL). The aqueous phase was extracted with ethyl acetate (60 mL × 3). The combined organic phase was dried with anhydrous sodium sulfate, filtered and concentrated under vacuum. Compound (1R,3R)-3-ethoxycarbonylcyclohexanecarboxylic acid (4.60 g) was obtained as a yellow oil and directly used in the next step without further purification.

[00702] **LC-MS:** MS (ESI^+): t_R = 0.407 min, m/z = 199.2 [M - H^+]

[00703] (1R,3R)-3-ethoxycarbonylcyclohexanecarboxylic acid (4.60 g, 23.0 mmol, 1.0 eq) was dissolved in toluene (80 mL) and treated with Et_3N (7.27 g, 71.9 mmol, 10 mL, 3.1 eq) and diphenyl phosphoryl azide (7.65 g, 27.8 mmol, 6 mL, 1.2 eq). The resulting solution was heated to 85 °C and stirred for 1 h. After

cooling to 70 °C, BnOH (3.76 g, 34.8 mmol, 3.6 mL, 1.5 eq) was added, and the mixture was heated to 85 °C for 12 h. The mixture was poured into water (200 mL) and adjusted PH=10 with saturated sodium carbonate. The aqueous phase was extracted with ethyl acetate (50 mL × 3). The combined organic phase was washed with brine (80 mL), dried with anhydrous sodium sulfate, filtered and concentrated under vacuum. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=30/1 to 10/1). Compound ethyl (1R,3R)-3-(benzyloxycarbonylamino)cyclohexanecarboxylate (2.80 g, 9.2 mmol, 40% yield over two steps) was obtained as a colorless oil.

[00704] **LC-MS:** MS (ESI^+): t_R = 0.595 min, m/z = 306.2 [M + H^+]

[00705] To a solution of ethyl (1R,3R)-3-(benzyloxycarbonylamino)cyclohexanecarboxylate (600 mg, 1.96 mmol, 1.0 eq) in THF (40 mL) was added dropwise diisobutylalumane (1 M, 7.0 mL, 3.6 eq) at -78 °C under N_2. The reaction mixture was stirred at -78 °C for 2 h under N_2 .Then the reaction was quenched with aqueous ammonium chloride (10 mL) at -78 °C under N_2, diluted with water (50 mL). The result mixture was extracted with ethyl acetate (25 mL × 3), and the organic layers were washed with brine (40 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduce pressure. Compound benzyl N-[(1R,3R)-3-formylcyclohexyl]carbamate (500 mg) was obtained as a colorless oil and directly used in the next step without further purification.

[00706] To a solution of benzyl N-[(1R,3R)-3-formylcyclohexyl]carbamate (500 mg, 1.91 mmol, 1.0 eq) and tert-butyl piperazine-1-carboxylate (563 mg, 3.02 mmol, 1.6 eq) in DCM (10 mL) was added dropwise Et_3N (1.94 g, 19.1 mmol, 2.7 mL, 10.0 eq) and $NaBH(OAc)_3$ (2.03 g, 9.57 mmol, 5.0 eq). The reaction mixture was stirred at 25 °C for 12 h. The mixture was poured into iced water (40 mL). The aqueous phase was extracted with dichloromethane (20 mL × 3). The combined organic phase was washed with brine (20 mL), dried with anhydrous sodium sulfate, filtered and concentrated under vacuum. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 3/1 to 1/1). Compound tert-butyl 4-[[(1R,3R)-3-(benzyloxycarbonylamino)cyclohexyl]methyl]piperazine-1-carboxylate (500 mg, 1.16 mmol, 61% yield over two steps) was obtained as a colorless oil.

[00707] **LC-MS:** MS (ESI^+): t_R = 0.763 min, m/z = 432.3 [M + H^+]

[00708] Pd/C (0.3 g, 10% Pd on carbon, w/w) was added into a 30 mL single-necked round bottom flask under N_2, and then MeOH (10 mL) was added at 25 °C under N_2. After addition, tert-butyl 4-[[(1R,3R)-3-(benzyloxycarbonylamino)cyclohexyl]methyl]piperazine-1-carboxylate (500 mg, 1.16 mmol, 1.0 eq) was added under N_2. The suspension was degassed under vacuum and purged with H_2 several times. The mixture was stirred under H_2 (50 psi) at 30 °C for 12 h. The reaction mixture was filtered and washed with DCM/MeOH (10/1, 30 mL × 3). The collected filtrate was concentrated to give a residue. Compound tert-butyl 4-[[(1R,3R)-3-aminocyclohexyl]methyl]piperazine-1-carboxylate (320 mg) was obtained as a colorless oil and directly used in the next step without further purification.

[00709] To a solution of methyl (2S)-6-fluoro-2-methyl-5-nitro-3,4-dihydro-2H-quinoline-1-carboxylate (229 mg, 854 μmol, 1.0 eq) and tert-butyl 4-[[(1R,3R)-3-aminocyclohexyl]methyl]piperazine-1-carboxylate

(320 mg) in DMSO (5 mL) was added pyridine (203 mg, 2.56 mmol, 207 μL, 3.0 eq) and K_2CO_3 (236 mg, 1.71 mmol, 2.0 eq). The reaction mixture was stirred at 90 °C for 12 h. The mixture was poured into iced water (60 mL). The aqueous phase was extracted with ethyl acetate (25 mL × 3). The combined organic phase was washed with brine (30 mL × 2), dried with anhydrous sodium sulfate, filtered and concentrated under vacuum. The residue was purified by prep-TLC (petroleum ether/ethyl acetate = 1/1). Compound methyl (2S)-6-[[(1R,3R)-3-[(4-tert-butoxycarbonylpiperazin-1-yl)methyl]cyclohexyl]amino]-2-methyl-5-nitro-3,4-dihydro-2H-quinoline-1-carboxylate (203 mg, 367 μmol, 43% yield over two steps) was obtained as a red gum.

[00710] **LC-MS:** MS (ESI^+): t_R = 0.562 min, m/z = 546.5 [M + H^+]

[00711] To a mixture of methyl (2S)-6-[[(1R,3R)-3-[(4-tert-butoxycarbonylpiperazin-1-yl)methyl]cyclohexyl]amino]-2-methyl-5-nitro-3,4-dihydro-2H-quinoline-1-carboxylate (203 mg, 367 μmol, 1.0 eq) and NH_4Cl (200 mg, 3.74 mmol, 10.2 eq) in EtOH (3 mL) and THF (3 mL) and H_2O (1 mL) was added Fe (180 mg, 3.22 mmol, 184 μL, 8.8 eq). The reaction mixture was stirred at 80 °C for 1 h under N_2. The reaction mixture was filtered and washed with ethyl acetate (20 mL × 2). The collected filtrate was concentrated to give a residue. Compound methyl (2S)-5-amino-6-[[(1R,3R)-3-[(4-tert-butoxycarbonylpiperazin-1-yl)methyl]cyclohexyl]amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylate (205 mg) was obtained as a colorless oil and directly used in the next step without further purification.

[00712] **LC-MS:** MS (ESI^+): t_R = 0.494 min, m/z = 516.5 [M + H^+]

[00713] To a mixture of methyl (2S)-5-amino-6-[[(1R,3R)-3-[(4-tert-butoxycarbonylpiperazin-1-yl)methyl]cyclohexyl]amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylate (205 mg) in DCM (10 mL) was added 2-phenylacetaldehyde (150 mg, 1.25 mmol, 97.4 μL, 3.2 eq). The reaction mixture was stirred at 25 °C for 12 h under N_2. The mixture was concentrated to give a residue. The residue was purified by prep-TLC (petroleum ether/ethyl acetate = 1/1). Compound methyl (7S)-2-benzyl-3-[(1R,3R)-3-[(4-tert-butoxycarbonylpiperazin-1-yl)methyl]cyclohexyl]-7-methyl-8,9-dihydro-7H-imidazo[4,5-f]quinoline-6-carboxylate (70 mg, 108 μmol, 28% yield over two steps) was obtained as a colorless gum.

[00714] **LC-MS:** MS (ESI^+): t_R = 0.502 min, m/z = 616.6 [M + H^+]

[00715] To a mixture of methyl (7S)-2-benzyl-3-[(1R,3R)-3-[(4-tert-butoxycarbonylpiperazin-1-yl)methyl]cyclohexyl]-7-methyl-8,9-dihydro-7H-imidazo[4,5-f]quinoline-6-carboxylate (70 mg, 114 μmol, 1.0 eq) in DCM (5 mL) was added TFA (4.61 g, 40.4 mmol, 3 mL, 355.3 eq). The reaction mixture was stirred at 25 °C for 1 h. The mixture was concentrated to give a residue. The residue was used for the next step without further purification. Compound methyl (7S)-2-benzyl-7-methyl-3-[(1R,3R)-3-(piperazin-1-ylmethyl)cyclohexyl]-8,9-dihydro-7H-imidazo[4,5-f]quinoline-6-carboxylate (70 mg) was obtained as a brown gum and directly used in the next step without further purification.

[00716] **LC-MS:** MS (ESI^+): t_R = 0.462 min, 470 min, m/z = 516.5 [M + H^+]

[00717] To a mixture of methyl (7S)-2-benzyl-7-methyl-3-[(1R,3R)-3-(piperazin-1-ylmethyl)cyclohexyl]-8,9-dihydro-7H-imidazo[4,5-f]quinoline-6-carboxylate (70 mg) in NMP (3 mL) was added DIPEA (742 mg, 5.74 mmol, 1 mL, 51.7 eq) and 6-chloro-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-

carboxamide (65 mg, 167 μmol, 1.5 eq). The reaction mixture was stirred at 70 °C for 12 h. The mixture was diluted with EtOAc (100 mL), washed with water (15 mL × 2), brine (15 mL), dried with anhydrous sodium sulfate, filtered and concentrated under vacuum. The residue was purified by prep-TLC (ethyl acetate /methyl alcohol=60/1) to give crude product **Compound 302** and **Compound 232**.

[00718] The crude product **Compound 302** was purified by semi-preparative reverse phase HPLC (column: Phenomenex Luna C18 150 × 25mm × 10um;mobile phase: [water(FA)-ACN];gradient:21%-51% B over 10 min). Compound methyl (7S)-2-benzyl-3-[(1R,3R)-3-[[4-[6-[[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]carbamoyl]pyridazin-3-yl]piperazin-1-yl]methyl]cyclohexyl]-7-methyl-8,9-dihydro-7H-imidazo[4,5-f]quinoline-6-carboxylate (5.46 mg, 6.27 μmol, 6% yield) was obtained as a white solid.

[00719] **^{1}H NMR** (400 MHz, CHLOROFORM-*d*) δ = 8.02 (d, *J*=9.6 Hz, 1 H) 7.88 (d, *J*=8.0 Hz, 1 H) 7.57 (d, *J*=8.8 Hz, 1 H) 7.37 - 7.46 (m, 1 H) 7.28 - 7.36 (m, 3 H) 7.21 - 7.25 (m, 1 H) 7.17 (m, 2 H) 7.01 (d, *J*=2.4 Hz, 1 H) 6.98 (m, 1 H) 6.86 (m, 1 H) 4.74 - 4.90 (m, 1 H) 4.28 - 4.53 (m, 3 H) 4.01 - 4.24 (m, 2 H) 3.80 (s, 3 H) 3.74 (d, *J*=3.6 Hz, 4 H) 3.21 - 3.35 (m, 1 H) 3.01 - 3.14 (m, 1 H) 2.43 - 2.57 (m, 4 H) 2.02 - 2.37 (m, 10 H) 1.66 - 1.82 (m, 6 H) 1.42 - 1.56 (m, 5 H) 1.26 - 1.37 (m, 1 H) 1.19 (m, 3 H).

[00720] **LC-MS:** MS (ESI$^+$): t_R = 1.57 min, m/z = 870.3 [M + H$^+$]

[00721] The crude product **Compound 232** was purified by semi-preparative reverse phase HPLC (column: Phenomenex Luna C18 150 × 25mm × 10um;mobile phase: [water(FA)-ACN];gradient:22%-52% B over 10 min). Compound methyl (7S)-2-benzyl-3-[(1S,3S)-3-[[4-[6-[[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]carbamoyl]pyridazin-3-yl]piperazin-1-yl]methyl]cyclohexyl]-7-methyl-8,9-dihydro-7H-imidazo[4,5-f]quinoline-6-carboxylate (3.47 mg, 3.94 μmol, 4% yield) was obtained as a white solid.

[00722] **^{1}H NMR** (400 MHz, CHLOROFORM-*d*) δ =7.96 - 8.03 (m, 1 H) 7.83 - 7.91 (m, 1 H) 7.57 (d, *J*=8.8 Hz, 1 H) 7.39 - 7.49 (m, 1 H) 7.29 (d, *J*=8.0 Hz, 4 H) 7.22 - 7.25 (m, 2 H) 6.99 - 7.04 (m, 1 H) 6.92 - 6.98 (m, 1 H) 6.86 (m, 1 H) 4.75 - 4.95 (m, 1 H) 4.40 - 4.61 (m, 1 H) 4.26 - 4.40 (m, 2 H) 3.98 - 4.21 (m, 2 H) 3.80 (s, 3 H) 3.56 - 3.76 (m, 4 H) 3.19 - 3.36 (m, 1 H) 3.01 - 3.17 (m, 1 H) 2.32 - 2.46 (m, 4 H) 2.13 - 2.30 (m, 7 H) 2.00 - 2.13 (m, 2 H) 1.86 - 1.93 (m, 1 H) 1.70 - 1.81 (m, 6 H) 1.40 - 1.53 (m, 5 H) 1.24 - 1.30 (m, 1 H) 1.19 (d, *J*=6.8 Hz, 3 H).

[00723] **LC-MS:** MS (ESI$^+$): t_R = 1.584 min, m/z = 870.3 [M + H$^+$]

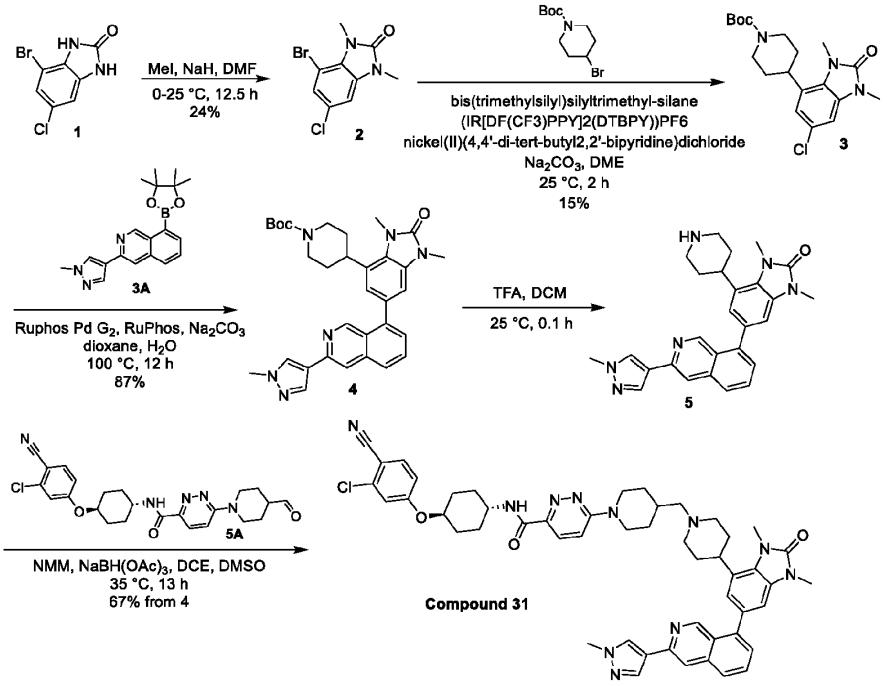
[00724] The compounds below were prepared in a similar manner as described in Example 19.

Compound	Name	^{1}H NMR ($CDCl_3$)	LC-MS [M + H$^+$]
303	methyl (7S)-2-benzyl-3-[3-[[1-[6-[[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]carbamoyl]pyridazin-3-yl]-4-piperidyl]oxy]cyclohexyl]-7-methyl-8,9-dihydro-7H-imidazo[4,5-f]quinoline-6-carboxylate	δ = 8.07 - 7.98 (m, 1H), 7.93 - 7.86 (m, 1H), 7.61 - 7.54 (m, 1H), 7.46 - 7.36 (m, 1H), 7.25 (s, 3H), 7.18 (s, 3H), 7.05 - 7.00 (m, 2H), 6.91 - 6.83 (m, 1H), 4.87 - 4.76 (m, 1H), 4.67 - 4.54 (m, 1H), 4.49 - 4.21 (m, 3H), 4.15 - 3.89 (m, 4H), 3.79 (d, *J* = 2.0 Hz, 3H), 3.68 - 3.51 (m, 3H), 3.37 - 3.18 (m, 1H), 3.13 - 2.98 (m, 1H), 2.28	871.6

Compound	Name	^{1}H NMR ($CDCl_3$)	LC-MS [M + H$^+$]
		- 2.15 (m, 5H), 2.10 - 1.99 (m, 1H), 1.94 - 1.82 (m, 3H), 1.81 - 1.68 (m, 5H), 1.58 - 1.50 (m, 4H), 1.49 - 1.36 (m, 3H), 1.28 - 1.13 (m, 4H)	
304	methyl (7S)-2-benzyl-3-[(1S,3S)-3-[[1-[6-[[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]carbamoyl]pyridazin-3-yl]-4-piperidyl]methoxy]cyclohexyl]-7-methyl-8,9-dihydro-7H-imidazo[4,5-f]quinoline-6-carboxylate	δ = 8.00 (d, *J*=9.6 Hz, 1 H) 7.88 (d, *J*=8.0 Hz, 1 H) 7.57 (d, *J*=8.8 Hz, 1 H) 7.44 - 7.36 (m, 1 H) 7.26 - 7.21 (m, 3 H) 7.20 - 7.12 (m, 3 H) 7.05 - 7.00 (m, 2 H) 6.86 (m, 1 H) 4.93 - 4.68 (m, 1 H) 4.66 - 4.46 (m, 3 H) 4.44 - 4.21 (m, 3 H) 4.15 – 3.99 (m, 1 H) 3.82 - 3.70 (m, 4 H) 3.35 - 3.15 (m, 2 H) 3.14 – 2.94 (m, 4 H) 2.33 - 2.12 (m, 7 H) 2.09 - 2.01 (m, 1 H) 1.98 - 1.84 (m, 5 H) 1.78 - 1.72 (m, 2 H) 1.57 - 1.45 (m, 5 H) 1.30 (m, 4 H) 1.18 (m, 3 H)	885.6
305	methyl (7S)-2-benzyl-3-[3-[2-[4-[6-[[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]carbamoyl]pyridazin-3-yl]piperazin-1-yl]ethoxy]cyclohexyl]-7-methyl-8,9-dihydro-7H-imidazo[4,5-f]quinoline-6-carboxylate	δ = 8.05 - 7.99 (m, 1H), 7.92 - 7.84 (m, 1H), 7.61 - 7.53 (m, 1H), 7.43 - 7.35 (m, 1H), 7.26 - 7.17 (m, 5H), 7.05 - 6.94 (m, 2H), 6.91 - 6.80 (m, 1H), 4.85 - 4.77 (m, 1H), 4.55 (s, 1H), 4.41 (d, *J* = 3.6 Hz, 1H), 4.47 - 4.26 (m, 2H), 4.08 (s, 1H), 3.79 (s, 8H), 3.57 - 3.23 (m, 3H), 3.07 (s, 1H), 2.77 - 2.58 (m, 6H), 2.28 - 2.13 (m, 6H), 2.09 - 1.86 (m, 3H), 1.80 - 1.72 (m, 2H), 1.55 - 1.43 (m, 4H), 1.56 - 1.24 (m, 4H), 1.19 - 1.16 (m, 3H)	900.5
257	methyl (7S)-2-benzyl-3-[(1R,3S)-3-[[1-[6-[[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]carbamoyl]pyridazin-3-yl]-4-piperidyl]methoxy]cyclohexyl]-7-methyl-8,9-dihydro-7H-imidazo[4,5-f]quinoline-6-carboxylate	δ = 7.92 - 7.86 (m, 1H), 7.81 - 7.74 (m, 1H), 7.51 - 7.47 (m, 1H), 7.34 - 7.27 (m, 1H), 7.27 - 7.20 (m, 2H), 7.15 - 7.10 (m, 4H), 6.93 (s, 3H), 6.81 - 6.76 (m, 1H), 4.78 - 4.68 (m, 1H), 4.48 - 4.32 (m, 3H), 4.31 - 4.16 (m, 3H), 4.01 - 3.90 (m, 2H), 3.73 - 3.67 (m, 3H), 3.24 - 3.15 (m, 1H), 3.12 - 3.05 (m, 1H), 3.02 - 2.85 (m, 5H), 2.23 - 2.16 (m, 1H), 2.15 - 2.04 (m, 5H), 1.98 - 1.89 (m, 3H), 1.79 - 1.69 (m, 6H), 1.41 - 1.36 (m, 3H), 1.29 - 1.22 (m, 4H), 1.13 - 1.07 (m, 6H)	885.6
270	methyl (7S)-2-benzyl-3-[3-[2-[4-[6-[[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]carbamoyl]pyridazin-3-yl]piperazin-1-yl]ethoxy]cyclohexyl]-7-methyl-8,9-dihydro-7H-imidazo[4,5-f]quinoline-6-carboxylate	δ = 8.00 (d, *J* = 9.6 Hz, 1H), 7.87 (d, *J* = 8.4 Hz, 1H), 7.57 (d, *J* = 8.8 Hz, 1H), 7.40 (d, *J* = 8.8 Hz, 1H), 7.32 - 7.29 (m, 1H), 7.27 - 7.19 (m, 4H), 7.03 - 6.93 (m, 2H), 6.87 – 6.84 (m, 1H), 4.90 - 4.73 (m, 1H), 4.47 - 4.27 (m, 3H), 4.11	900.5

Compound	Name	^{1}H NMR ($CDCl_3$)	LC-MS [M + H$^+$]
		- 4.01 (m, 2H), 3.80 - 3.73 (m, 7H), 3.51 - 3.23 (m, 3H), 3.13 - 3.01 (m, 2H), 2.67 - 2.54 (m, 6H), 2.28 - 2.14 (m, 5H), 2.06 - 1.96 (m, 3H), 1.89 - 1.75 (m, 5H), 1.57 - 1.37 (m, 4H), 1.26 - 1.11 (m, 5H)	

[00725] **Example 20:** Synthesis of N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]-6-[4-[[4-[1,3-dimethyl-6-[3-(1-methylpyrazol-4-yl)-8-isoquinolyl]-2-oxo-benzimidazol-4-yl]-1-piperidyl]methyl]-1-piperidyl]pyridazine-3-carboxamide (**Compound 31**)



[00726] Synthesis of **1** was reported in WO2008/75109, 2008, A1.

[00727] Synthesis of **3A** was reported in US2019/308978, 2019, A1.

[00728] Synthesis of **5A** was reported in WO2021/127443, 2021, A1

[00729] To a solution of 4-bromo-6-chloro-1,3-dihydrobenzimidazol-2-one (5.80 g, 23.44 mmol, 1 *eq*) in DMF (60 mL) was added NaH (2.34 g, 58.59 mmol, 60% purity, 2.5 *eq*) at 0 °C. After addition, the mixture was stirred at this temperature for 0.5 h, and then MeI (8.32 g, 58.59 mmol, 3.65 mL, 2.5 *eq*) was added dropwise at 0 °C. The resulting mixture was stirred at 25 °C for 12 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (100 mL) solution at 0 °C dropwise. And the resulting mixture was extracted with ethyl acetate (50 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash silica gel chromatography (ISCO®;

40 g SepaFlash® Silica Flash Column, Eluent of 0~10%dichloromethane/methanol ethergradient @ 80 mL/min). Compound 4-bromo-6-chloro-1,3-dimethyl-benzimidazol-2-one (1.60 g, 5.81 mmol, 24% yield) was obtained as a yellow solid.

[00730] **^{1}H NMR** (400 MHz, DMSO-d_6): δ = 7.40 (d, J = 2.0 Hz, 1H), 7.33 (d, J = 1.9 Hz, 1H), 3.63 (s, 3H), 3.36 (s, 3H) .

[00731] **LC-MS:** MS (ESI$^+$): t_R = 0.540 min, m/z = 274.9 [M + H$^+$]

[00732] 4-bromo-6-chloro-1,3-dimethyl-benzimidazol-2-one,1 eq,1 g; tert-butyl 4-bromopiperidine-1-carboxylate,1.5 eq,1.43 g; bis(trimethylsilyl)silyltrimethyl-silane,1.1 eq,0.99 g; (IR[DF(CF3)PPY]2(DTBPY))PF6,0.01 eq,0.04 g; nickel(II)(4,4'-di-tert-butyl-2,2'-bipyridine)dichloride,0.01 eq,0.01 g; Na_2CO_3,2 eq,0.76 g in DME （20 mL） . The volume of flow reactor 1 {1/8" FEP coil,395 nm,120 W} was {10 mL}. The residence time of flow reactor 1 was {120 min}. Set the bath at {25°C} for flow reactor 1. The flow rate of Pump 1 was adjusted to {20 mL/min} for solution 1. The mixture was collected with a bottle The Pump 1 was started. The reaction mixture was collected after running 120 mins. Take a sample for analysis after 120mins, Stop collecting the reaction mixture after 120 mins.

[00733] **LC-MS:** MS (ESI$^+$): t_R = 0.666 min, m/z = 531.3 [M - 55]

[00734] **^{1}H NMR** (400 MHz, DMSO-d_6): δ = 7.16 (d, J = 1.9 Hz, 1H), 6.96 (d, J = 1.8 Hz, 1H), 4.07 (d, J = 9.9 Hz, 2H), 3.57 (s, 3H), 3.30 (s, 3H), 2.92 - 2.85 (m, 1H), 2.54 (s, 2H), 1.78 (d, J = 12.1 Hz, 2H), 1.57 (dq, J = 4.1, 12.4 Hz, 2H), 1.42 (s, 9H) .

[00735] A mixture of 3-(1-methylpyrazol-4-yl)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoquinoline (381 mg, 568.60 μmol, 1.2 *eq*), tert-butyl 4-(6-chloro-1,3-dimethyl-2-oxo-benzimidazol-4-yl)piperidine-1-carboxylate (180 mg, 473.83 μmol, 1 *eq*), Na_2CO_3 (150 mg, 1.42 mmol, 3 *eq*), RuPhos (22 mg, 47.38 μmol, 0.1 *eq*) ，Ruphos Pd G_2 (36 mg, 47.38 μmol, 0.1 *eq*) and H_2O (1 mL) in dioxane (5 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 100 °C for 12 h under N_2 atmosphere. The mixture was diluted with water (50 mL) and extracted with ethyl acetate (60 mL x 3). The combined organic layers were washed with brine (50 mL x 3), dried over anhydrous sodium sulfate, filtered and concentrated in vacuum. The residue was purified by prep-TLC (SiO_2, DCM: MeOH = 15:1). Compound tert-butyl 4-[1,3-dimethyl-6-[3-(1-methylpyrazol-4-yl)-8-isoquinolyl]-2-oxo-benzimidazol-4-yl]piperidine-1-carboxylate (230 mg, 416.17 μmol, 87% yield) was obtained as a yellow solid.

[00736] **LC-MS:** MS (ESI$^+$): t_R = 0.512 min, m/z = 553.3 [M + H$^+$]

[00737] To a solution of tert-butyl 4-[1,3-dimethyl-6-[3-(1-methylpyrazol-4-yl)-8-isoquinolyl]-2-oxo-benzimidazol-4-yl]piperidine-1-carboxylate (120 mg, 217.13 μmol, 1 eq) in DCM (2 mL) was added TFA (3.07 g, 26.93 mmol, 2 mL, 124.00 eq) .The mixture was stirred at 25 °C for 0.1 h. The mixture was concentrated in vacuo. Compound 1,3-dimethyl-6-[3-(1-methylpyrazol-4-yl)-8-isoquinolyl]-4-(4-piperidyl)benzimidazol-2-one (98 mg) was obtained as a yellow oil and directly used in the next step without further purification.

[00738] **LC-MS:** MS (ESI$^+$): t_R = 0.392 min, m/z = 453.2 [M + H$^+$]

[00739] To a solution of 1,3-dimethyl-6-[3-(1-methylpyrazol-4-yl)-8-isoquinolyl]-4-(4-piperidyl)benzimidazol-2-one (95 mg, 209.92 μmol, 1 eq) in DMSO (1 mL)was added NMM (424 mg, 4.20 mmol, 461.59 μL, 20 eq). After addition, the mixture was stirred at 35 °C for 0.5 h,and N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]-6-(4-formyl-1-piperidyl)pyridazine-3-carboxamide (98 mg, 209.92 μmol, 1 eq) in DCE (1 mL) was added at 35 °C for 0.5 h. And then $NaBH(OAc)_3$ (133 mg, 629.77 μmol, 3 eq) was added at 35 °C. The resulting mixture was stirred at 35°C for 12 h. The mixture was diluted with water (20 mL) and extracted with dichloromethane(30 mL x 3). The combined organic layers were washed with brine (20 mL x 3), dried over anhydrous sodium sulfate, filtered and concentrated in vacuum. The mixture was purified by prep-HPLC (column: Phenomenex luna C18 150*25mm* 10um;mobile phase: [water(FA)-ACN];gradient:23%-53% B over 10 min). Compound N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]-6-[4-[[4-[1,3-dimethyl-6-[3-(1-methylpyrazol-4-yl)-8-isoquinolyl]-2-oxo-benzimidazol-4-yl]-1-piperidyl]methyl]-1-piperidyl]pyridazine-3-carboxamide (129.64 mg, 140.69 μmol, 67% yield over two steps) was obtained as a white solid.

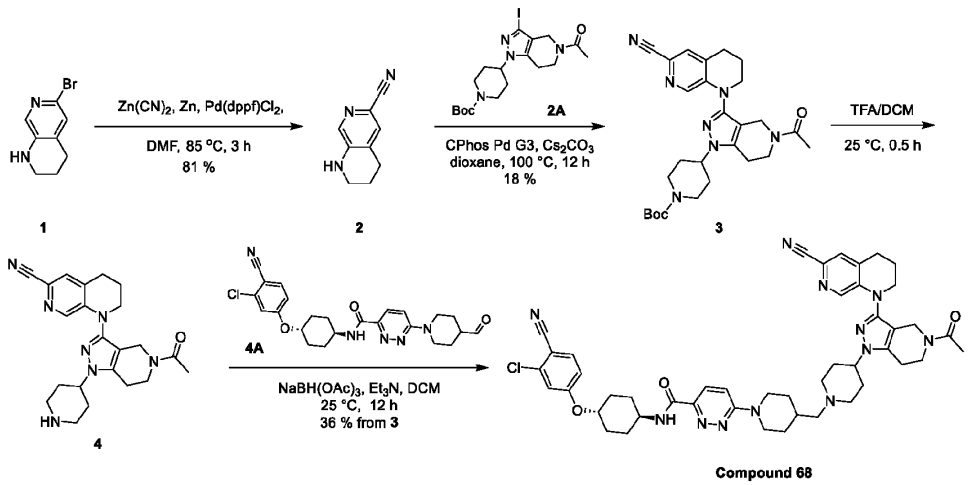
[00740] **1H NMR** (400 MHz, DMSO-d_6): δ = 9.23 (s, 1H), 8.55 (d, J = 8.3 Hz, 1H), 8.35 (s, 1H), 8.13 (s, 1H), 8.09 (s, 1H), 7.90 (d, J = 8.4 Hz, 1H), 7.85 (d, J = 8.9 Hz, 1H), 7.82 - 7.75 (m, 2H), 7.52 (d, J = 6.4 Hz, 1H), 7.38 (d, J = 2.3 Hz, 1H), 7.30 (d, J = 9.6 Hz, 1H), 7.27 (d, J = 1.1 Hz, 1H), 7.19 - 7.10 (m, 2H), 4.59 - 4.49 (m, 1H), 4.45 (br d, J = 13.0 Hz, 2H), 3.92 (s, 3H), 3.88 - 3.80 (m, 1H), 3.66 (s, 3H), 3.39 (s, 3H), 3.36 - 3.32 (m, 1H), 3.06 - 2.92 (m, 4H), 2.20 (br d, J = 6.8 Hz, 2H), 2.15 - 2.05 (m, 4H), 1.94 - 1.77 (m, 9H), 1.68 - 1.58 (m, 2H), 1.56 - 1.44 (m, 2H), 1.17 - 1.02 (m, 2H)

[00741] **LC-MS:** MS (ESI^+): t_R = 2.313 min, m/z = 904.5 [M + H^+]

[00742] The compounds below were prepared in a similar manner as described in Example 20.

Compound	Name	^{1}H NMR (DMSO-d6)	LC-MS [M + H^+]
33	N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]-6-[4-[[4-[6-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-1,3-dimethyl-2-oxo-benzimidazol-4-yl]-1-piperidyl]methyl]-1-piperidyl]pyridazine-3-carboxamide	δ = 8.60 (d, J = 8.5 Hz, 1H), 7.86 (d, J = 8.8 Hz, 1H), 7.79 (d, J = 9.5 Hz, 1H), 7.75 (s, 1H), 7.49 (s, 1H), 7.40 (d, J = 2.4 Hz, 1H), 7.32 (d, J = 9.8 Hz, 1H), 7.14 (dd, J = 2.4, 8.8 Hz, 1H), 7.10 (s, 1H), 7.00 (d, J = 1.8 Hz, 1H), 6.91 (d, J = 1.6 Hz, 1H), 6.88 (s, 2H), 4.59 - 4.51 (m, 1H), 4.50 - 4.40 (m, 2H), 3.92 - 3.83 (m, 4H), 3.66 - 3.61 (m, 2H), 3.59 (s, 3H), 3.31 (s, 3H), 3.26 - 3.19 (m, 1H), 3.06 - 2.91 (m, 4H), 2.87 (br t, J = 5.8 Hz, 2H), 2.18 (br d, J = 6.8 Hz, 2H), 2.16 - 2.07 (m, 3H), 2.06 - 2.01 (m, 3H), 1.93 - 1.78 (m, 7H), 1.73 - 1.59 (m, 4H), 1.56 - 1.47 (m, 2H), 1.16 - 1.03 (m, 2H)	958.6

[00743] **Example 21:** Synthesis of 6-[4-[[4-[5-acetyl-3-(6-cyano-3,4-dihydro-2H-1,7-naphthyridin-1-yl)-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]methyl]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide **(Compound 68)**



[00744] Synthesis of **1** was reported in WO2019/89412, 2019, A1

[00745] Synthesis of **4A** was reported in WO2021/127443, 2021, A1

[00746] A mixture of 6-bromo-1,2,3,4-tetrahydro-1,7-naphthyridine (450 mg, 2.11 mmol, 1.0 *eq*), $Zn(CN)_2$ (410 mg, 3.49 mmol, 221 μL, 1.6 *eq*), Zn (180 mg, 2.75 mmol, 1.3 *eq*) and $Pd(dppf)Cl_2$ (154 mg, 211 μmol, 0.1 *eq*) in DMF (9 mL) was stirred at 85 °C for 3 h under N_2. The reaction mixture was diluted with water (30 mL) and adjusted to pH about 12 with sat.Na_2CO_3. The mixture was extracted with EtOAc (40 mL * 3). The combined organic layers were washed with brine (50 mL * 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 20/1 to 1/1). Compound 1,2,3,4-tetrahydro-1,7-naphthyridine-6-carbonitrile (274 mg, 1.72 mmol, 81% yield) was obtained as a white solid.

[00747] **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.82 (s, 1H), 7.21 (s, 1H), 4.87 - 4.50 (m, 1H), 3.58 - 3.36 (m, 2H), 2.90 - 2.65 (m, 2H), 2.06 - 1.88 (m, 2H).

[00748] **LC-MS:** MS (ESI^+): t_R = 0.598 min, m/z = 160.5 [$M + H^+$]

[00749] To a mixture of tert-butyl 4-(5-acetyl-3-iodo-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl)piperidine-1-carboxylate (500 mg, 1.05 mmol, 1.0 *eq*) and 1,2,3,4-tetrahydro-1,7-naphthyridine-6-carbonitrile (201 mg, 1.26 mmol, 1.2 *eq*) in dioxane (10 mL) was added CPhos Pd G3 (169 mg, 210 μmol, 0.2 *eq*) and Cs_2CO_3 (1.03 g, 3.16 mmol, 3.0 *eq*), the mixture was stirred at 100 °C for 12 h under N_2. The reaction mixture was diluted with water (20 mL) and extracted with EtOAc (30 mL * 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Ethyl acetate/MeOH =100/1 to 10/1) to give a crude product, then the crude product was purified by prep-HPLC (column: Phenomenex luna C18 150*25mm* 10um; mobile phase: [water (FA)-ACN]; gradient: 40%-70% B over 10 min). Compound tert-butyl 4-[5-acetyl-3-(6-cyano-3,4-dihydro-2H-1,7-naphthyridin-1-yl)-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]piperidine-1-carboxylate (100 mg, 197 μmol, 18% yield) was obtained as a white solid.

[00750] **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.88 - 7.79 (m, 1H), 7.34 - 7.28 (m, 1H), 4.46 - 4.14 (m, 4H), 4.13 - 4.00 (m, 1H), 3.98 - 3.83 (m, 1H), 3.82 - 3.59 (m, 3H), 3.01 - 2.61 (m, 6H), 2.28 - 2.02 (m, 7H), 1.92 - 1.79 (m, 2H), 1.47 (s, 9H).

[00751] **LC-MS:** MS (ESI^+): t_R = 1.954 min, m/z = 506.2 [$M + H^+$]

[00752] To a mixture of tert-butyl 4-[5-acetyl-3-(6-cyano-3,4-dihydro-2H-1,7-naphthyridin-1-yl)-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]piperidine-1-carboxylate (50 mg, 98 μmol, 1.0 *eq*) in DCM (2 mL) was added TFA (1.54 g, 13.4 mmol, 1 mL, 136.1 *eq*), the mixture was stirred at 25 °C for 0.5 h. The mixture was concentrated to give a crude product. Compound 1-[5-acetyl-1-(4-piperidyl)-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-3-yl]-3,4-dihydro-2H-1,7-naphthyridine-6-carbonitrile (40 mg) was obtained as a yellow solid and directly used into the next step without further purification.

[00753] **LC-MS:** MS (ESI^+): t_R = 0.572 min, m/z = 406.4 [$M + H^+$]

[00754] To a mixture of 1-[5-acetyl-1-(4-piperidyl)-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-3-yl]-3,4-dihydro-2H-1,7-naphthyridine-6-carbonitrile (40 mg) and Et_3N (49 mg, 493 μmol, 68 μL, 5.0 *eq*) in DCM (1 mL) was added N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]-6-(4-formyl-1-piperidyl)pyridazine-3-carboxamide (50 mg, 108 μmol, 1.1 *eq*) and $NaBH(OAc)_3$ (62 mg, 295 μmol, 3.0 *eq*), the mixture was stirred at 25 °C for 12 h. The mixture was concentrated to give a residue. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150*25mm* 10um; mobile phase: [water (FA)-ACN]; gradient: 25%-55% B over 10 min). Compound 6-[4-[[4-[5-acetyl-3-(6-cyano-3,4-dihydro-2H-1,7-naphthyridin-1-yl)-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]methyl]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide (31.1 mg, 36.2 μmol, 36% yield over two steps) was obtained as a white solid.

[00755] **^{1}H NMR** (400 MHz, DMSO-d_6) δ = 8.66 - 8.54 (m, 1H), 7.89 - 7.76 (m, 3H), 7.62 (s, 1H), 7.39 (d, J = 2.4 Hz, 1H), 7.32 (d, J = 9.6 Hz, 1H), 7.06 (s, 1H), 4.60 - 4.41 (m, 3H), 4.31 - 4.17 (m, 2H), 4.11 - 3.99 (m, 1H), 3.92 - 3.80 (m, 1H), 3.78 - 3.67 (m, 2H), 3.67 - 3.57 (m, 2H), 3.06 - 2.90 (m, 4H), 2.89 - 2.71 (m, 4H), 2.22 - 2.15 (m, 2H), 2.14 - 1.93 (m, 11H), 1.93 - 1.78 (m, 7H), 1.70 - 1.57 (m, 2H), 1.57 - 1.44 (m, 2H), 1.20 - 1.02 (m, 2H).

[00756] **LC-MS:** MS (ESI^+): t_R = 2.288 min, m/z = 857.4 [$M + H^+$]

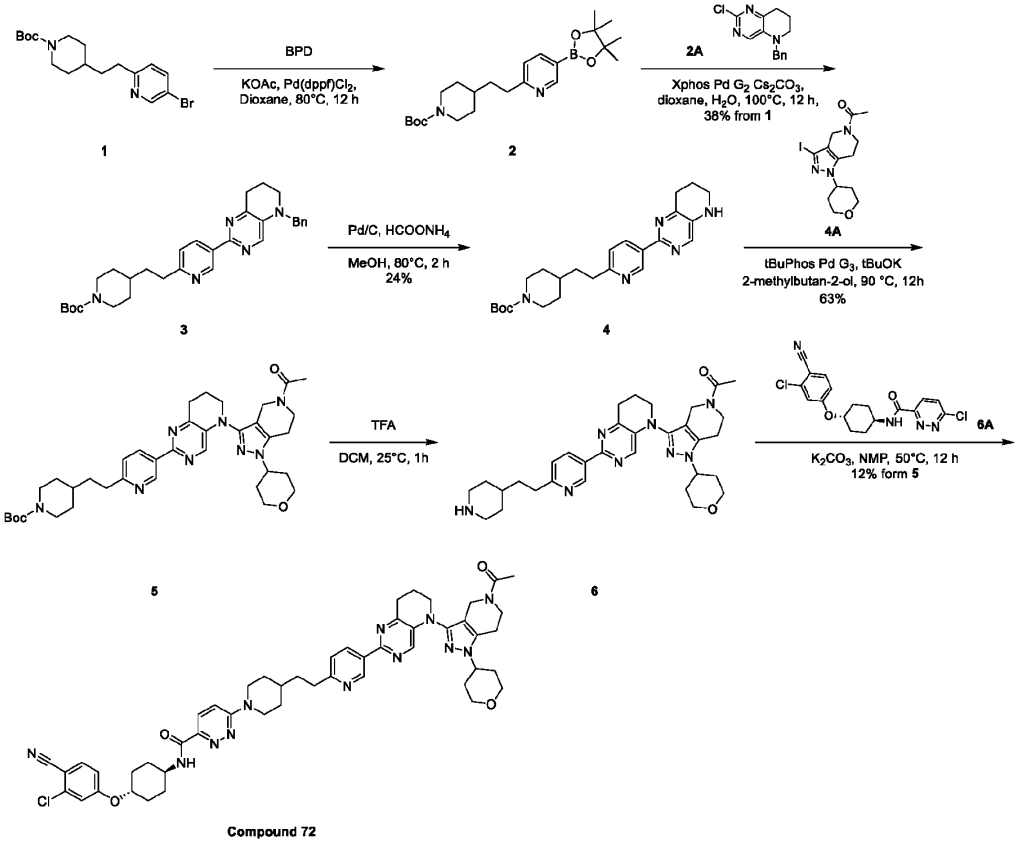
[00757] The compounds below were prepared in a similar manner as described in Example 21.

Compound	Name	^{1}H NMR (DMSO-d_6)	LC-MS [$M + H^+$]
69	6-[4-[4-[5-acetyl-3-(6-cyano-3,4-dihydro-2H-1,7-naphthyridin-1-yl)-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]piperidine-1-carbonyl]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	δ = 8.70 - 8.55 (m, 1H), 7.92 - 7.71 (m, 3H), 7.62 (s, 1H), 7.44 - 7.34 (m, 2H), 7.17 - 7.08 (m, 1H), 4.58 - 4.33 (m, 5H), 4.30 - 4.09 (m, 3H), 3.90 - 3.68 (m, 3H), 3.65 - 3.58 (m, 2H), 3.26 - 3.01 (m, 4H), 2.94 - 2.64 (m, 5H), 2.15 - 2.05 (m, 4H), 2.04 - 1.82 (m, 8H), 1.80 - 1.71 (m, 2H), 1.70 - 1.45 (m, 7H)	871.4
110	6-[4-[[4-[5-acetyl-3-[6-(trifluoromethyl)-3,4-dihydro-2H-	($CDCl_3$) δ = 8.04 - 7.91 (m, 2H), 7.87 (d, J = 8.4 Hz, 1H), 7.57 (d, J = 8.8	900.6

Compound	Name	^{1}H NMR (DMSO-d_6)	LC-MS [M + H$^+$]
	1,7-naphthyridin-1- yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]methyl]-1-piperidyl]-N-[4- (4-chloro-3-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	Hz, 1H), 7.31 (s, 1H), 7.04 - 6.93 (m, 2H), 6.91 - 6.82 (m, 1H), 4.51 (d, J = 13.2 Hz, 2H), 4.43 - 4.31 (m, 2H), 4.21 (s, 1H), 4.12 - 4.02 (m, 1H), 4.02 - 3.81 (m, 2H), 3.77 - 3.64 (m, 3H), 3.23 - 2.97 (m, 4H), 2.97 - 2.62 (m, 5H), 2.31 - 2.19 (m, 5H), 2.14 - 2.05 (m, 5H), 2.04- 1.78 (m, 5H), 1.75 - 1.58 (m, 6H), 1.52 - 1.43 (m, 2H), 1.33 - 1.16 (m, 2H)	
142	6-[4-[[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]methyl]-4-fluoro-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	δ = 8.04 - 7.98 (m, 1H), 7.91 - 7.84 (m, 1H), 7.61 - 7.50 (m, 2H), 7.45 - 7.38 (m, 1H), 7.08 - 6.97 (m, 3H), 6.92 - 6.82 (m, 2H), 6.69 - 6.34 (m, 1H), 4.42 - 4.22 (m, 4H), 4.16 - 4.11 (m, 1H), 4.10 - 4.01 (m, 1H), 3.99 - 3.93 (m, 3H), 3.92 - 3.83 (m, 2H), 3.80 - 3.65 (m, 3H), 3.50 - 3.39 (m, 2H), 3.13 - 3.02 (m, 2H), 2.93 - 2.83 (m, 2H), 2.82 - 2.70 (m, 2H), 2.63 - 2.50 (m, 2H), 2.39 - 2.24 (m, 4H), 2.24 - 2.15 (m, 5H), 2.10 - 2.04 (m, 5H), 1.90 - 1.80 (m, 2H), 1.78 - 1.65 (m, 5H), 1.54 - 1.41 (m, 2H)	979.4
144	6-[4-[[(3S,4R)-4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c] pyridin-1-yl]-3-fluoro-1-piperidyl] methyl]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy) cyclohexyl] pyridazine-3-carboxamide	δ = 8.59 (d, J = 8.0 Hz, 1H), 8.40 (s, 1H), 7.86 (d, J = 8.8 Hz, 1H), 7.80 (d, J = 9.6 Hz, 1H), 7.76 (s, 1H), 7.51 (s, 1H), 7.39 (d, J = 2.4 Hz, 1H), 7.34 (d, J = 9.6 Hz, 1H), 7.18 - 7.10 (m, 2H), 6.97 - 6.62 (m, 2H), 4.98 - 4.79 (m, 1H), 4.61 - 4.33 (m, 4H), 4.31 - 3.94 (m, 2H), 3.92 - 3.74 (m, 5H), 3.63 - 3.54 (m, 3H), 3.17 - 2.98 (m, 4H), 2.95 - 2.75 (m, 4H), 2.61 - 2.53 (m, 1H), 2.42 - 2.31 (m, 1H), 2.24 (br d, J = 5.6 Hz, 3H), 2.15 - 2.06 (m, 4H), 2.01 - 1.80 (m, 9H), 1.71 - 1.58 (m, 2H), 1.57 - 1.45 (m, 2H), 1.20 - 1.04 (m, 2H)	979.4
161	6-[4-[[4-[5-acetyl-3-[3-(1-methylpyrazol-4-yl)-8-isoquinolyl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]methyl]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridine-3-carboxamide	($CDCl_3$) δ = 9.81 - 9.66 (m, 1H), 8.57 - 8.46 (m, 1H), 8.45 - 8.25 (m, 1H), 8.10 - 8.00 (m, 2H), 7.90 - 7.75 (m, 3H), 7.74 - 7.64 (m, 1H), 7.59 - 7.53 (m, 1H), 7.52 - 7.44 (m, 1H), 7.03 - 6.96 (m, 1H), 6.88 - 6.80 (m, 1H), 6.67 - 6.58 (m, 1H), 5.91 - 5.77 (m, 1H), 4.82 - 4.55 (m, 1H), 4.52 - 4.46 (m, 1H), 4.45 - 4.35 (m, 2H), 4.33 - 4.22 (m, 1H), 4.15 - 3.97 (m, 6H), 3.91 - 3.75 (m, 1H), 3.20 - 3.04 (m, 3H), 2.94 - 2.82 (m, 4H), 2.47 - 2.28 (m, 5H), 2.24 - 2.15 (m, 5H), 2.12 - 1.96 (m, 4H), 1.94 - 1.79 (m, 3H),	906.4

Compound	Name	^{1}H NMR (DMSO-d_6)	LC-MS [M + H$^+$]
		1.73 - 1.59 (m, 2H), 1.48 - 1.33 (m, 2H), 1.27 - 1.13 (m, 2H)	

[00758] **Example 22:** Synthesis of -[4-[2-[5-[5-(5-acetyl-1-tetrahydropyran-4-yl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-3-yl)-7,8-dihydro-6H-pyrido[3,2-d]pyrimidin-2-yl]-2-pyridyl]ethyl]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide **(Compound 72)**



[00759] Synthesis of **1** was reported in WO2023/38500 A1.

[00760] Synthesis of **4A** was reported in Journal of Medicinal Chemistry, 2023, vol. 66, # 12, p. 8178 - 8199.

[00761] Synthesis of **6A** was reported in WO2021/127443 A1.

[00762] A mixture of tert-butyl 4-[2-(5-bromo-2-pyridyl)ethyl]piperidine-1-carboxylate (2.00 g, 5.42 mmol, 1.0 eq), BPD (2.06 g, 8.12 mmol, 1.5 eq), Pd(dppf)Cl_2 (119 mg, 162 μmol, 0.03 eq), KOAc (1.59 g, 16.25 mmol, 3.0 eq) in dioxane (20 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 80 °C for 12 h under N_2 atmosphere. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, DCM/MeOH = 1/0 to 10/1) to give tert-butyl 4-[2-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-

pyridyl]ethyl]piperidine-1-carboxylate (1.90 g) as a white solid and used into the next step without further purification.

[00763] **LC-MS:** MS (ESI^+): t_R= 0.505 min, m/z = 335.2 [M - 81]

[00764] A mixture of tert-butyl 4-[2-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-pyridyl]ethyl]piperidine-1-carboxylate (1.15 g), 5-benzyl-2-chloro-7,8-dihydro-6H-pyrido[3,2-d]pyrimidine (600 mg, 2.31 mmol, 1.0 eq), Xphos Pd G2 (364 mg, 462 μmol, 0.2 eq) and Cs_2CO_3 (2.26 g, 6.93 mmol, 3.0 eq) in dioxane (12 mL) and H_2O (1.2 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 100 °C for 12 h under N_2 atmosphere. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate= 1/0 to 0/1) to give tert-butyl 4-[2-[5-(5-benzyl-7,8-dihydro-6H-pyrido[3,2-d]pyrimidin-2-yl)-2-pyridyl]ethyl]piperidine-1-carboxylate (496 mg, 894 μmol, 38% yield over two steps) as a white solid.

[00765] **LC-MS:** MS (ESI^+): t_R = 0.579 min, m/z = 514.5 [M + H^+]

[00766] To a solution of tert-butyl 4-[2-[5-(5-benzyl-7,8-dihydro-6H-pyrido[3,2-d]pyrimidin-2-yl)-2-pyridyl]ethyl]piperidine-1-carboxylate (496 mg, 966 μmol, 1.0 eq) in MeOH (20 mL) was added Pd/C (473 mg, 444 μmol, 10% purity, 0.5 eq) and $HCOONH_4$ (189 mg, 3.00 mmol, 3.1 eq) under N_2 atmosphere. The suspension was degassed and purged with N_2 for 3 times. The mixture was stirred under N_2 at 80 °C for 2 h. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, Petroleum ether : Ethyl acetate = 10:1) to give tert-butyl 4-[2-[5-(5,6,7,8-tetrahydropyrido[3,2-d]pyrimidin-2-yl)-2-pyridyl]ethyl]piperidine-1-carboxylate (100 mg, 232 μmol, 24% yield) as a white solid.

[00767] **LC-MS:** MS (ESI^+): t_R = 0.798 min, m/z = 424.3 [M + H^+]

[00768] To a solution tert-butyl 4-[2-[5-(5,6,7,8-tetrahydropyrido[3,2-d]pyrimidin-2-yl)-2-pyridyl]ethyl]piperidine-1-carboxylate (100 mg, 236 μmol, 1.0 eq), 1-(3-iodo-1-tetrahydropyran-4-yl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl)ethanone (125 mg, 331 μmol, 1.4 eq) in 2-methylbutan-2-ol (4 mL) was added tBuXPhos Pd G3 (25 mg, 31.47 μmol, 0.1 eq) and tBuOK (1 M, 0.5 mL, 2.1 eq). The mixture was stirred at 90 °C for 12 h under N_2. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, DCM/MeOH = 10/1) to give tert-butyl 4-[2-[5-[5-(5-acetyl-1-tetrahydropyran-4-yl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-3-yl)-7,8-dihydro-6H-pyrido[3,2-d]pyrimidin-2-yl]-2-pyridyl]ethyl]piperidine-1-carboxylate (118 mg, 150 μmol, 63% yield) as a white solid.

[00769] **LC-MS:** MS (ESI^+): t_R = 0.844 min, m/z = 671.5 [M + H^+]

[00770] To a solution of tert-butyl 4-[2-[5-[5-(5-acetyl-1-tetrahydropyran-4-yl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-3-yl)-7,8-dihydro-6H-pyrido[3,2-d]pyrimidin-2-yl]-2-pyridyl]ethyl]piperidine-1-carboxylate (118 mg, 176 μmol, 1.0 eq) in DCM (1 mL) was added TFA (1 mL). The mixture was stirred at 25 °C for 1 h. The reaction mixture was concentrated to give 1-[3-[2-[6-[2-(4-piperidyl)ethyl]-3-pyridyl]-7,8-dihydro-6H-pyrido[3,2-d]pyrimidin-5-yl]-1-tetrahydropyran-4-yl-6,7-dihydro-4H-pyrazolo[4,3-

c]pyridin-5-yl]ethanone (100 mg) as a white solid and used into the next step without further purification.

[00771] **LC-MS:** MS (ESI^+): t_R = 0.702 min, m/z = 571.5 [M + H^+]

[00772] To a solution of 1-[3-[2-[6-[2-(4-piperidyl)ethyl]-3-pyridyl]-7,8-dihydro-6H-pyrido[3,2-d]pyrimidin-5-yl]-1-tetrahydropyran-4-yl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]ethanone (100 mg), 6-chloro-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide (75 mg, 192 μmol, 1.1 eq) in NMP (1 mL) was added K_2CO_3 (75 mg, 543 μmol, 3.1 eq) and the mixture was stirred at 50 °C for 12 h under N_2. The reaction was diluted with water (10 mL) and the resulting mixture was extracted with ethyl acetate (20 mL × 2). The combined organic layers were dried over Na_2SO_4 and concentrated to give the residue. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150*25mm* 10um;mobile phase: [water(FA)-ACN];gradient:35%-65% B over 10 min) to give 6-[4-[2-[5-[5-(5-acetyl-1-tetrahydropyran-4-yl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-3-yl)-7,8-dihydro-6H-pyrido[3,2-d]pyrimidin-2-yl]-2-pyridyl]ethyl]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide (20.66 mg, 21.45 μmol, 12% yield over two steps) as a yellow solid.

[00773] **^{1}H NMR** (400 MHz, DMSO-d6): δ = 9.25 (d, J = 2.0 Hz, 1H), 8.62 - 8.55 (m, 1H), 8.44 - 8.37 (m, 1H), 8.20 - 8.12 (m, 1H), 7.85 (d, J = 8.8 Hz, 1H), 7.79 (d, J = 9.6 Hz, 1H), 7.39 (d, J = 2.4 Hz, 1H), 7.34 (d, J = 4.5, 8.8 Hz, 2H), 7.13 (d, J = 2.4, 8.8 Hz, 1H), 4.58 - 4.52 (m, 1H), 4.49 (d, J = 13.6 Hz, 2H), 4.36 - 4.30 (m, 1H), 4.30 - 4.26 (m, 2H), 3.96 (d, J = 11.2 Hz, 2H), 3.89 - 3.82 (m, 1H), 3.79 - 3.71 (m, 2H), 3.67 - 3.60 (m, 2H), 3.46 (t, J = 11.8 Hz, 2H), 3.02 - 2.98 (m, 2H), 2.98 - 2.91 (m, 2H), 2.89 - 2.80 (m, 3H), 2.75 (d, J = 4.0 Hz, 1H), 2.13 - 2.06 (m, 6H), 2.03 - 1.99 (m, 2H), 1.98 - 1.79 (m, 8H), 1.68 - 1.61 (m, 4H), 1.55 - 1.47 (m, 2H), 1.23 - 1.14 (m, 2H).

[00774] **LC-MS:** MS (ESI^+): t_R = 2.115 min, m/z = 925.4 [M + H^+]

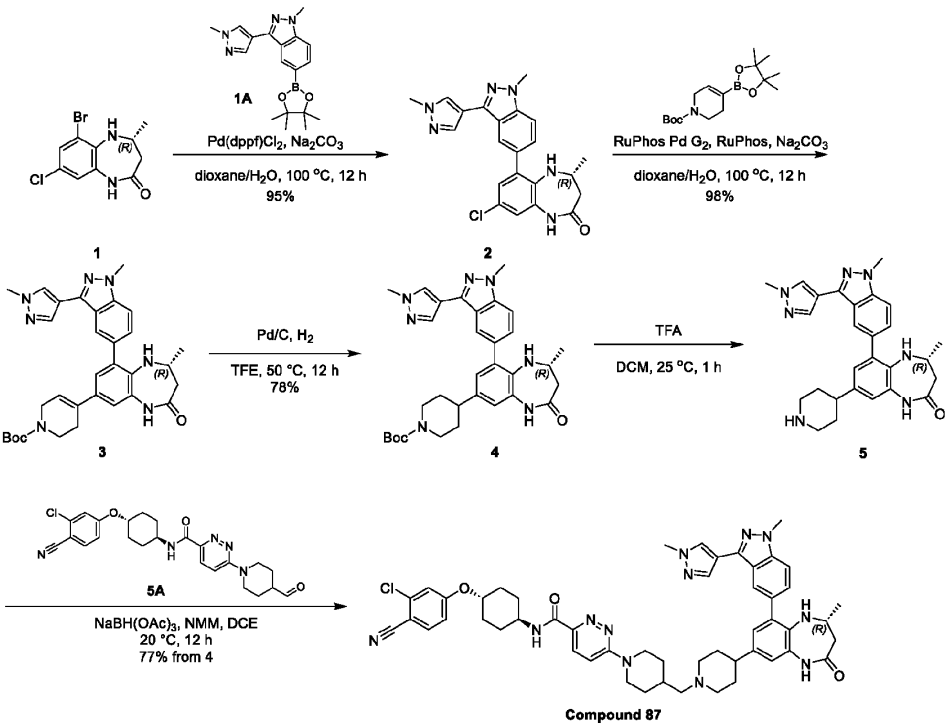
[00775] The compounds below were prepared in a similar manner as described in Example 22.

Compound	Name	^{1}H NMR ($CDCl_3$)	LC-MS [M + H^+]
85	6-[4-[2-[4-[8-[5-acetyl-1-[(3S)-tetrahydrofuran-3-yl]-6,7-dihydro-4H-pyrazolo[4,3-c] pyridin-3-yl]-3-isoquinolyl] pyrazol-1-yl] ethyl]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy) cyclohexyl] pyridazine-3-carboxamide	(DMSO-d_6) δ = 9.77 (s, 1H), 8.59 (d, J = 8.4 Hz, 1H), 8.45 (s, 1H), 8.11 (d, J = 3.6 Hz, 2H), 7.91 - 7.87 (m, 1H), 7.85 (d, J = 8.8 Hz, 1H), 7.82 - 7.72 (m, 2H), 7.54 (s, 1H), 7.39 (d, J = 2.0 Hz, 1H), 7.34 (d, J = 9.6 Hz, 1H), 7.18 - 7.10 (m, 1H), 5.13 - 5.05 (m, 1H), 4.54 (br s, 3H), 4.48 (br d, J = 12.8 Hz, 2H), 4.29 - 4.21 (m, 2H), 4.15 - 4.03 (m, 2H), 4.01 - 3.93 (m, 1H), 3.93 - 3.79 (m, 4H), 3.01 - 2.93 (m, 3H), 2.43 - 2.35 (m, 3H), 2.15 - 2.07 (m, 4H), 2.01 (s, 1H), 1.92 - 1.80 (m, 6H), 1.69 - 1.57 (m, 3H), 1.56 - 1.48 (m, 2H), 1.27 - 1.15 (m, 2H)	894.4
153	6-[4-[2-[4-[8-(5-acetyl-1-tetrahydropyran-4-yl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-3-yl)-3-isoquinolyl]phenyl]ethyl]-1-piperidyl]-N-[4-(3-chloro-4-cyano-	δ = 9.81 (d, J = 13.2 Hz, 1H), 8.11 - 8.03 (m, 3H), 7.97 (d, J = 9.6 Hz, 1H), 7.92 - 7.82 (m, 2H), 7.79 - 7.68 (m, 1H), 7.61 - 7.50 (m, 2H), 7.38 - 7.31 (m, 2H), 7.05 - 6.95 (m, 2H), 6.89 -	918.5

Compound	Name	^{1}H NMR ($CDCl_3$)	LC-MS [M + H$^+$]
	phenoxy)cyclohexyl]pyridazine-3-carboxamide	6.82 (m, 1H), 4.67 (s, 1H), 4.58 - 4.45 (m, 3H), 4.39 - 4.23 (m, 2H), 4.17 (d, J = 12.0 Hz, 2H), 4.11 - 3.99 (m, 2H), 3.85 (m, 1H), 3.58 (m, 2H), 3.03 (m, 2H), 2.97 - 2.83 (m, 2H), 2.81 - 2.72 (m, 2H), 2.55 - 2.37 (m, 2H), 2.23 - 2.15 (m, 5H), 2.08 (s, 2H), 1.95 (m, 4H), 1.64 - 1.55 (m, 3H), 1.53 - 1.41 (m, 3H), 1.39 - 1.25 (m, 3H)	
154	6-[4-[2-[4-[1-(5-acetyl-1-tetrahydropyran-4-yl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-3-yl)-7-(difluoromethyl)-3,4-dihydro-2H-quinolin-6-yl]phenyl]ethyl]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	δ = 7.97 (d, *J* = 9.6 Hz, 1H), 7.88 (d, *J* = 8.0 Hz, 1H), 7.57 (d, *J* = 8.8 Hz, 1H), 7.27 - 7.19 (m, 4H), 7.06 - 6.95 (m, 3H), 6.92 - 6.83 (m, 2H), 6.46 (d, *J* = 9.2 Hz, 1H), 4.52 (d, *J* = 13.2 Hz, 2H), 4.39 - 4.23 (m, 2H), 4.19 - 4.03 (m, 5H), 3.92 (t, *J* = 5.6 Hz, 1H), 3.82 - 3.68 (m, 3H), 3.59 - 3.50 (m, 2H), 3.05 (t, *J* = 12.0 Hz, 2H), 2.95 - 2.80 (m, 3H), 2.79 - 2.67 (m, 3H), 2.32 (d, *J* = 11.2 Hz, 2H), 2.24 - 2.15 (m, 5H), 2.13 - 2.01 (m, 4H), 1.98 - 1.85 (m, 4H), 1.76 - 1.66 (m, 5H), 1.51 - 1.40 (m, 2H), 1.33 (d, *J* = 10.8 Hz, 2H)	972.7
156	6-[4-[2-[4-[1-(5-acetyl-1-tetrahydropyran-4-yl-6,7-dihydro-4H-pyrazolo[4,3- c]pyridin-3-yl)-3,4-dihydro-2H-1,7-naphthyridin-6-yl]phenyl]ethyl]-1-piperidyl]-N-[4-(3- chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	δ = 7.99 - 7.93 (m, 1H), 7.91 (s, 1H), 7.88 (d, J = 8.0 Hz, 1H), 7.83 - 7.74 (m, 2H), 7.56 (d, J = 8.8 Hz, 1H), 7.37 (d, J = 16.0 Hz, 1H), 7.26 - 7.19 (m, 2H), 7.01 (d, J = 2.4 Hz, 1H), 6.97 (d, J = 9.6 Hz, 1H), 6.89 - 6.83 (m, 1H), 4.50 (d, J = 12.8 Hz, 2H), 4.38 - 4.27 (m, 2H), 4.20 - 4.09 (m, 4H), 4.08 - 4.00 (m, 1H), 3.91 (t, J = 6.0 Hz, 1H), 3.80 - 3.63 (m, 3H), 3.52 (t, J = 12.0 Hz, 2H), 3.08 - 2.95 (m, 2H), 2.94 - 2.86 (m, 2H), 2.82 (t, J = 5.2 Hz, 1H), 2.78 - 2.67 (m, 3H), 2.38 - 2.26 (m, 2H), 2.22 - 2.16 (m, 4H), 2.15 - 2.08 (m, 3H), 1.88 (t, J = 15.2 Hz, 6H), 1.74 - 1.60 (m, 5H), 1.51 - 1.40 (m, 2H), 1.35 - 1.24 (m, 2H)	923.6
157	6-[4-[2-[4-[1-(5-acetyl-1-tetrahydropyran-4-yl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-3-yl)-3,4-dihydro-2H-1,7-naphthyridin-6-yl]phenyl]ethyl]piperazin-1-yl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	(DMSO-d_6) δ = 8.62 (d, *J* = 8.1 Hz, 1H), 7.91 - 7.86 (m, 2H), 7.85 (d, *J* = 1.4 Hz, 2H), 7.83 (d, *J* = 3.4 Hz, 1H), 7.59 (s, 1H), 7.40 (d, *J* = 2.4 Hz, 1H), 7.37 (d, *J* = 9.6 Hz, 1H), 7.28 (d, *J* = 8.4 Hz, 2H), 7.14 (dd, *J* = 2.4, 8.8 Hz, 1H), 4.62 - 4.48 (m, 1H), 4.36 - 4.26 (m, 1H), 4.25 - 4.17 (m, 2H), 4.01 - 3.93 (m, 2H), 3.91 - 3.83 (m, 1H), 3.78 (d, *J* = 6.1 Hz, 1H), 3.73 (d, *J* = 4.8 Hz, 5H), 3.63 - 3.57 (m, 2H), 3.47 (t, *J* = 12.1 Hz, 2H), 2.90 - 2.85 (m, 3H), 2.84 - 2.78 (m, 2H), 2.75 (t, *J* = 5.8 Hz, 1H), 2.64 - 2.57 (m, 6H), 2.15	924.6

Compound	Name	^{1}H NMR ($CDCl_3$)	LC-MS [M + H$^+$]
		- 2.07 (m, 4H), 2.04 - 1.95 (m, 5H), 1.91 (d, *J* = 10.8 Hz, 2H), 1.87 - 1.81 (m, 2H), 1.70 - 1.60 (m, 2H), 1.57 - 1.47 (m, 2H)	
166	6-[4-[2-[4-[8-(5-acetyl-1-tetrahydropyran-4-yl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-3-yl)-3-isoquinolyl]phenyl]ethyl]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridine-3-carboxamide	δ = 9.81 (d, J = 14.8 Hz, 1H), 8.53 (d, J = 2.4 Hz, 1H), 8.11 - 8.01 (m, 3H), 7.93 - 7.81 (m, 2H), 7.79 - 7.67 (m, 1H), 7.60 - 7.50 (m, 2H), 7.38 - 7.31 (m, 2H), 7.00 (d, J = 2.4 Hz, 1H), 6.90 - 6.77 (m, 1H), 6.64 (d, J = 9.2 Hz, 1H), 5.78 (d, J = 7.6 Hz, 1H), 4.67 (s, 1H), 4.50 (s, 1H), 4.42 (d, J = 12.8 Hz, 2H), 4.34 - 4.23 (m, 2H), 4.21 - 4.12 (m, 2H), 4.10 - 3.97 (m, 2H), 3.85 (s, 1H), 3.57 (s, 2H), 2.99 - 2.83 (m, 4H), 2.75 (s, 2H), 2.54 - 2.37 (m, 2H), 2.26 - 2.18 (m, 4H), 2.17 - 2.13 (m, 1H), 2.08 (s, 2H), 1.83 (s, 6H), 1.68 - 1.63 (m, 3H), 1.47 - 1.35 (m, 2H), 1.33 - 1.22 (m, 2H)	917.6
167	6-[4-[2-[4-[1-(5-acetyl-1-tetrahydropyran-4-yl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-3-yl)-3,4-dihydro-2H-1,7-naphthyridin-6-yl]phenyl]ethyl]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridine-3-carboxamide	δ 8.52 (d, *J*=2.4 Hz, 1 H) 7.91 (s, 1 H) 7.90 - 7.84 (m, 1 H) 7.86 (m, 1 H) 7.78 (m, 1 H) 7.56 (d, *J*=8.8 Hz, 1 H) 7.37 (d, *J*=12.4 Hz, 1 H) 7.23 (m, 2 H) 6.99 (d, *J*=2.0 Hz, 1 H) 6.85 (m, 1 H) 6.62 (d, *J*=8.8 Hz, 1 H) 5.80 (m, 1 H) 4.40 (m, 2 H) 4.36 - 4.23 (m, 2 H) 4.22 - 4.08 (m, 4 H) 4.08 – 3.97 (m, 1 H) 3.91 (m, 1 H) 3.81 - 3.66 (m, 3 H) 3.52 (m, 2 H) 2.97 - 2.88 (m, 3 H) 2.86 - 2. 78 (m, 2 H) 2. 78 - 2.65 (m, 3 H) 2. 38 - 2.27 (m, 2 H) 2. 26 - 2.08 (m, 8 H) 2.06 (s, 2 H) 1. 87 - 1.76 (m, 6 H) 1.68 (m, 2 H) 1. 49 - 1.34 (m, 2 H) 1.30 - 1.20 (m, 2 H)	922.7
168	6-[4-[2-[4-[1-(5-acetyl-1-tetrahydropyran-4-yl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-3-yl)-7-(difluoromethyl)-3,4-dihydro-2H-quinolin-6-yl]phenyl]ethyl]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridine-3-carboxamide	δ = 8.57 - 8.42 (m, 1H), 8.04 - 7.89 (m, 1H), 7.57 (d, J = 8.8 Hz, 1H), 7.26 - 7.17 (m, 4H), 7.05 - 6.94 (m, 2H), 6.92 - 6.81 (m, 2H), 6.73 (dd, J = 4.0, 9.2 Hz, 1H), 6.63 - 6.26 (m, 1H), 6.03 - 5.89 (m, 1H), 4.47 - 4.35 (m, 2H), 4.35 - 4.22 (m, 2H), 4.18 - 4.10 (m, 4H), 4.08 - 3.98 (m, 1H), 3.92 (t, J = 5.6 Hz, 1H), 3.83 - 3.66 (m, 3H), 3.53 (t, J = 12.0 Hz, 2H), 2.99 (t, J = 13.2 Hz, 2H), 2.94 - 2.80 (m, 3H), 2.77 (t, J = 5.6 Hz, 1H), 2.74 - 2.63 (m, 2H), 2.31 (dq, J = 4.0, 12.8 Hz, 2H), 2.22 - 2.15 (m, 5H), 2.09 - 2.05 (m, 3H), 1.94 - 1.84 (m, 5H), 1.73 - 1.59 (m, 5H), 1.50 - 1.38 (m, 2H), 1.35 - 1.24 (m, 2H)	971.5

[00776] **Example 23:** Synthesis of N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]-6-[4-[[4-[(4R)-4-methyl-6-[1-methyl-3-(1-methylpyrazol-4-yl)indazol-5-yl]-2-oxo-1,3,4,5-tetrahydro-1,5-benzodiazepin-8-yl]-1-piperidyl]methyl]-1-piperidyl]pyridazine-3-carboxamide (**Compound 87**)



[00777] Synthesis of **1** was reported in WO2016/55028, 2016, A1.

[00778] Synthesis of **1A** was reported in ACS Medicinal Chemistry Letters, 2016, vol. 7, # 5, p. 531 - 536.

[00779] Synthesis of **5A** was reported in WO2021/127443, 2021, A1.

[00780] A mixture of (4R)-6-bromo-8-chloro-4-methyl-1,3,4,5-tetrahydro-1,5-benzodiazepin-2-one (180 mg, 621.64 μmol, 1.0 eq), 1-methyl-3-(1-methylpyrazol-4-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indazole (231 mg, 683.81 μmol, 1.1 eq), $Pd(dppf)Cl_2$ (46 mg, 62.16 μmol, 0.1 eq), Na_2CO_3 (132 mg, 1.24 mmol, 2.0 eq) and H_2O (1.6 mL) in dioxane (8 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 100 °C for 12 h under N_2 atmosphere. The mixture was poured into water (70 mL). The aqueous phase was extracted with ethyl acetate (70 mL × 2). The combined organic phase was washed with brine (70 mL × 2), dried with anhydrous sodium sulfate, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (50% - 100% ethyl acetate in petroleum ether). Compound (4R)-8-chloro-4-methyl-6-[1-methyl-3-(1-methylpyrazol-4-yl)indazol-5-yl]-1,3,4,5-tetrahydro-1,5-benzodiazepin-2-one (250 mg, 593.97 μmol, 95% yield) was obtained as a light yellow solid.

[00781] **LC-MS:** MS (ESI^+): t_R = 0.499 min, m/z = 421.2 [M + H^+]

[00782] A mixture of (4R)-8-chloro-4-methyl-6-[1-methyl-3-(1-methylpyrazol-4-yl)indazol-5-yl]-1,3,4,5-tetrahydro-1,5-benzodiazepin-2-one (225 mg, 534.58 μmol, 1.0 eq), tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyridine-1-carboxylate (331 mg, 1.07 mmol, 2.0 eq), Na_2CO_3 (170 mg,

1.60 mmol, 3.0 eq), Ruphos Pd G_2 (42 mg, 53.46 μmol, 0.1 eq), RuPhos (25 mg, 53.46 μmol, 0.1 eq) and H_2O (1 mL) in dioxane (5 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 100 °C for 12 h under N_2 atmosphere. The mixture was poured into water (80 mL). The aqueous phase was extracted with ethyl acetate (80 mL × 2). The combined organic phase was washed with brine (80 mL × 2), dried with anhydrous sodium sulfate, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (50% - 100% ethyl acetate in petroleum ether). Compound tert-butyl 4-[(4R)-4-methyl-6-[1-methyl-3-(1-methylpyrazol-4-yl)indazol-5-yl]-2-oxo-1,3,4,5-tetrahydro-1,5-benzodiazepin-8-yl]-3,6-dihydro-2H-pyridine-1-carboxylate (300 mg, 528.47 μmol, 98% yield) was obtained as a yellow solid.

[00783] **LC-MS:** MS (ESI^+): t_R = 0.547 min, m/z = 568.4 [M + H^+]

[00784] To a solution of tert-butyl 4-[(4R)-4-methyl-6-[1-methyl-3-(1-methylpyrazol-4-yl)indazol-5-yl]-2-oxo-1,3,4,5-tetrahydro-1,5-benzodiazepin-8-yl]-3,6-dihydro-2H-pyridine-1-carboxylate (140 mg, 246.62 μmol, 1.0 eq) in TFE (10 mL) was added Pd/C (100 mg, 10% Pd on carbon, w/w) under N_2 atmosphere. The suspension was degassed and purged with H_2 for 3 times. The mixture was stirred under H_2 (50 Psi) at 50 °C for 12 h. The mixture was filtered and concentrated under reduced pressure. The residue was purified by prep-Thin-layer chromatography (SiO_2, dichloromethane : methanol = 13:1). Compound tert-butyl 4-[(4R)-4-methyl-6-[1-methyl-3-(1-methylpyrazol-4-yl)indazol-5-yl]-2-oxo-1,3,4,5-tetrahydro-1,5-benzodiazepin-8-yl]piperidine-1-carboxylate (110 mg, 193.09 μmol, 78% yield) was obtained as a white solid.

[00785] **LC-MS:** MS (ESI^+): t_R = 0.535 min, m/z = 570.5 [M + H^+]

[00786] To a solution of tert-butyl 4-[(4R)-4-methyl-6-[1-methyl-3-(1-methylpyrazol-4-yl)indazol-5-yl]-2-oxo-1,3,4,5-tetrahydro-1,5-benzodiazepin-8-yl]piperidine-1-carboxylate (140 mg, 245.75 μmol, 1.0 eq) in DCM (5 mL) was added TFA (3.07 g, 26.93 mmol, 2 mL). The mixture was stirred at 25 °C for 1 h. The mixture was concentrated under reduced pressure. Compound (4R)-4-methyl-6-[1-methyl-3-(1-methylpyrazol-4-yl)indazol-5-yl]-8-(4-piperidyl)-1,3,4,5-tetrahydro-1,5-benzodiazepin-2-one (140 mg) was obtained as a yellow gum and directly used in the next step without further purification.

[00787] **LC-MS:** MS (ESI^+): t_R = 0.400 min, m/z = 470.4 [M + H^+]

[00788] To a solution of (4R)-4-methyl-6-[1-methyl-3-(1-methylpyrazol-4-yl)indazol-5-yl]-8-(4-piperidyl)-1,3,4,5-tetrahydro-1,5-benzodiazepin-2-one (140 mg) in DCE (5 mL) was added NMM (97 mg, 959.56 μmol, 4.0 eq) and N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]-6-(4-formyl-1-piperidyl)pyridazine-3-carboxamide (112 mg, 239.89 μmol, 1.0 eq). The mixture was stirred at 20 °C for 5 min. Then $NaBH(OAc)_3$ (102 mg, 479.78 μmol, 2.0 eq) was added and the mixture was stirred at 20 °C for another 12 h. The mixture was poured into water (50 mL). The aqueous phase was extracted with dichloromethane (50 mL × 2). The combined organic phase was washed with brine (50 mL × 2), dried with anhydrous sodium sulfate, filtered and concentrated in vacuum. The residue was purified by prep-Thin-layer chromatography (SiO_2, dichloromethane : methanol = 10:1) and further purified by prep-HPLC (column: Phenomenex luna C18 150*25mm*10um; mobile phase: [water (FA)-ACN]; gradient: 23%-53% B over 10 min). Compound N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]-6-[4-[[4-[(4R)-4-methyl-6-[1-methyl-3-(1-methylpyrazol-4-

yl)indazol-5-yl]-2-oxo-1,3,4,5-tetrahydro-1,5-benzodiazepin-8-yl]-1-piperidyl]methyl]-1-piperidyl]pyridazine-3-carboxamide (171.94 mg, 184.72 μmol, 77% yield over two steps) was obtained as a yellow solid.

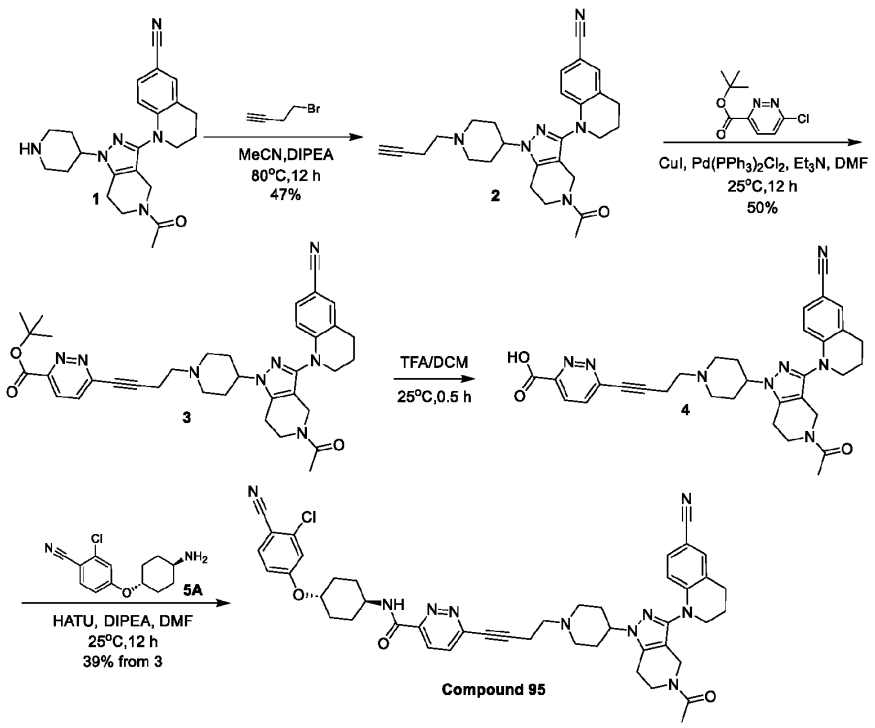
[00789] **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.01 (s, 1H), 7.96 (d, J = 9.6 Hz, 1H), 7.90 (s, 1H), 7.87 (br d, J = 8.0 Hz, 1H), 7.79 (s, 1H), 7.73 (s, 1H), 7.56 (d, J = 8.8 Hz, 1H), 7.48 (d, J = 8.8 Hz, 1H), 7.38 (dd, J = 1.2, 8.8 Hz, 1H), 7.00 (d, J = 2.4 Hz, 1H), 6.97 (d, J = 9.6 Hz, 1H), 6.95 (d, J = 2.0 Hz, 1H), 6.85 (dd, J = 2.4, 8.8 Hz, 1H), 6.81 (d, J = 1.6 Hz, 1H), 4.50 (br d, J = 13.2 Hz, 2H), 4.36 - 4.28 (m, 1H), 4.13 (s, 3H), 4.13 - 4.01 (m, 2H), 4.00 (s, 3H), 3.96 - 3.91 (m, 1H), 3.19 (br d, J = 11.2 Hz, 2H), 3.04 (br t, J = 12.0 Hz, 2H), 2.76 (dd, J = 4.4, 13.2 Hz, 1H), 2.52 (dt, J = 4.8, 10.4 Hz, 1H), 2.48 - 2.37 (m, 3H), 2.28 - 2.13 (m, 6H), 2.05 - 1.86 (m, 7H), 1.74 - 1.63 (m, 2H), 1.51 - 1.41 (m, 2H), 1.36 - 1.25 (m, 2H), 1.16 (d, J = 6.4 Hz, 3H).

[00790] **LC-MS:** MS (ESI^+): t_R = 2.376 min, m/z = 921.6 [$M + H^+$]

[00791] The compounds below were prepared in a similar manner as described in Example 23.

Compound	Name	^{1}H NMR ($CDCl_3$)	LC-MS [$M + H^+$]
88	N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]-6-[4-[[4-[(4R)-6-(3- cyclopropyl-1-methyl-indazol-5-yl)-4-methyl-2-oxo-1,3,4,5-tetrahydro-1,5-benzodiazepin-8-yl]-1-piperidyl]methyl]-1-piperidyl]pyridazine-3-carboxamide	δ = 12.30 - 11.08 (m, 1H), 8.76 - 8.49 (m, 1H), 8.04 (d, J = 9.6 Hz, 1H), 7.83 (d, J = 8.0 Hz, 1H), 7.67 (s, 1H), 7.56 (d, J = 8.4 Hz, 1H), 7.44 - 7.38 (m, 1H), 7.30 (d, J = 8.8 Hz, 1H), 7.09 (d, J = 9.2 Hz, 1H), 7.00 (d, J = 2.0 Hz, 1H), 6.93 (s, 1H), 6.89 - 6.82 (m, 2H), 4.52 (d, J = 12.8 Hz, 2H), 4.32 (t, J = 9.6 Hz, 1H), 3.98 - 3.91 (m, 1H), 3.85 (d, J = 10.4 Hz, 2H), 3.74 - 3.24 (m, 1H), 3.12 (t, J = 12.0 Hz, 3H), 2.99 (d, J = 5.2 Hz, 2H), 2.88 - 2.68 (m, 4H), 2.53 - 2.43 (m, 1H), 2.30 (d, J = 9.6 Hz, 3H), 2.22 - 2.13 (m, 6H), 2.11 - 1.99 (m, 4H), 1.73 - 1.64 (m, 2H), 1.57 - 1.32 (m, 5H), 1.18 (d, J = 6.4 Hz, 3H), 1.13 - 0.92 (m, 5H)	881.6
89	N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]-6-[4-[[4-[(4R)-4-methyl-6-(1-methylindazol-5-yl)-2-oxo-1,3,4,5-tetrahydro-1,5-benzodiazepin-8-yl]-1-piperidyl]methyl]-1-piperidyl]pyridazine-3-carboxamide	δ = 8.03 (s, 1H), 7.98 (d, J = 9.6 Hz, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.67 (s, 1H), 7.56 (d, J = 8.8 Hz, 2H), 7.50 (d, J = 8.8 Hz, 1H), 7.35 (d, J = 8.4 Hz, 1H), 7.04 - 6.95 (m, 2H), 6.93 - 6.84 (m, 2H), 6.78 (s, 1H), 4.52 (d, J = 13.6 Hz, 2H), 4.36 - 4.29 (m, 1H), 4.14 (s, 3H), 4.10 - 4.02 (m, 1H), 3.97 - 3.89 (m, 1H), 3.56 - 3.38 (m, 2H), 3.06 (t, J = 12.0 Hz, 2H), 2.78 - 2.72 (m, 1H), 2.66 - 2.52 (m, 3H), 2.52 - 2.34 (m, 3H), 2.23 - 2.13 (m, 5H), 2.05 - 1.95 (m, 5H), 1.74 - 1.64 (m, 3H), 1.53 - 1.45 (m, 2H), 1.45 - 1.29 (m, 3H), 1.17 (d, J = 6.0 Hz, 3H)	841.5

[00792] **Example 24:** Synthesis of 6-[4-[4-[5-acetyl-3-(6-cyano-3,4-dihydro-2H-quinolin-1-yl)-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]but-1-ynyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide **(Compound 95)**



[00793] Synthesis of **5A** was reported in WO2021/231927 A1

[00794] To a solution of 1-[5-acetyl-1-(4-piperidyl)-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-3-yl]-3,4-dihydro-2H-quinoline-6-carbonitrile (375 mg, 927.05 μmol, 1.0 eq) in MeCN (5 mL) was added DIPEA (359 mg, 2.78 mmol, 3.0 eq) and 4-bromobut-1-yne (160 mg, 1.21 mmol, 1.3 eq). The mixture was stirred at 80 °C for 12 h. The collected fractions were concentrated to remove most of the organic volatiles. The pH of the aqueous phase was adjusted to 5~6 by addition of formic acid. The residue was purified by semi-preparative reverse phase HPLC(column: Phenomenex luna C18 150*25mm* 10um;mobile phase: [water(FA)-ACN];gradient:5%-35% B over 15 min) Compound 1-[5-acetyl-1-(1-but-3-ynyl-4-piperidyl)-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-3-yl]-3,4-dihydro-2H-quinoline-6-carbonitrile (200 mg, 438.04 μmol, 47% yield) was obtained as a white solid.

[00795] **LC-MS:** MS (ESI^+): t_R = 0.402 min, m/z = 457.2 [$M + H^+$]

[00796] To a solution of 1-[5-acetyl-1-(1-but-3-ynyl-4-piperidyl)-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-3-yl]-3,4-dihydro-2H-quinoline-6-carbonitrile (200 mg, 438.04 μmol, 1.0 eq) ,tert-butyl 6-chloropyridazine-3-carboxylate (141 mg, 657.06 μmol, 1.5 eq), Et_3N (88 mg, 876.08 μmol, 2.0 eq), CuI (8 mg, 43.80 μmol, 0.1 eq) and $Pd(PPh_3)_2Cl_2$ (6 mg, 8.76 μmol, 0.02 eq) in DMF (5 mL) and stirred at 25 °C for 12 h. The mixture was added water (20 mL) and the mixture was extracted with ethyl acetate (20 mL × 3). The combined organic phase was washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified by prep-TLC (SiO_2,DCM: MeOH= 20:1). Compound tert-butyl 6-[4-[4-[5-acetyl-3-(6-cyano-3,4-dihydro-2H-quinolin-1-yl)-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]but-1-ynyl]pyridazine-3-carboxylate (140 mg, 220.55 μmol, 50% yield) was obtained as a

yellow oil.

[00797] **LC-MS:** MS (ESI^+): t_R = 0.452 min, m/z = 635.4 [M + H^+]

[00798] To a solution of tert-butyl 6-[4-[4-[5-acetyl-3-(6-cyano-3,4-dihydro-2H-quinolin-1-yl)-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]but-1-ynyl]pyridazine-3-carboxylate (140 mg, 220.55 μmol, 1.0 eq) in DCM (2 mL) was added TFA (3.0 g, 26.93 mmol, 2 mL, 122.0 eq). The mixture was stirred at 25 °C for 12 h. Compound 6-[4-[4-[5-acetyl-3-(6-cyano-3,4-dihydro-2H-quinolin-1-yl)-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]but-1-ynyl]pyridazine-3-carboxylic acid (120 mg, 207.37 μmol, 94% yield) was obtained as a yellow oil and directly used in the next step without further purification.

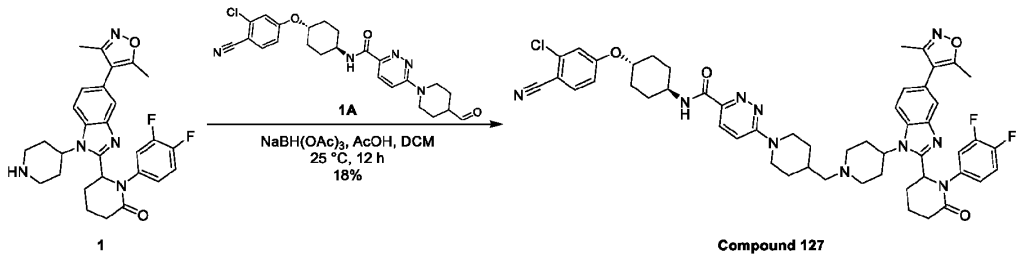
[00799] **LC-MS:** MS (ESI^+): t_R = 0.477 min, m/z = 444.1 [M + H^+]

[00800] To a solution of 6-[4-[4-[5-acetyl-3-(6-cyano-3,4-dihydro-2H-quinolin-1-yl)-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]but-1-ynyl]pyridazine-3-carboxylic acid (120 mg, 207.37 μmol, 1.0 eq) in DMF (3 mL) was added DIPEA (268 mg, 2.07 mmol,10.0 eq) ,4-(4-aminocyclohexoxy)-2-chloro-benzonitrile (77 mg, 311.06 μmol, 1.5 eq) and HATU (236 mg, 622.12 μmol, 3.0 eq). The mixture was stirred at 25 °C for 12 h. The mixture was added water (20 mL) and the mixture was extracted with ethyl acetate (20 mL × 3). The combined organic phase was washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified by semi-preparative reverse phase HPLC(column: Welch Xtimate C18 150*25mm*5um;mobile phase: [water(FA)-ACN];gradient:30%-50% B over 10 min) .Compound 6-[4-[4-[5-acetyl-3-(6-cyano-3,4-dihydro-2H-quinolin-1-yl)-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]but-1-ynyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide (68 mg, 82.67 μmol, 39% yield over two steps) was obtained as a yellow solid

[00801] **^{1}H NMR** (400 MHz, DMSO-d6) δ = 9.13 (d, J = 8.4 Hz, 1H), 8.26 - 8.05 (m, 1H), 8.00 - 7.77 (m, 2H), 7.39 (d, J = 2.4 Hz, 2H), 7.35 - 7.23 (m, 1H), 7.14 (dd, J = 2.4, 8.8 Hz, 1H), 6.55 - 6.36 (m, 1H), 4.62 - 4.44 (m, 1H), 4.18 - 4.10 (m, 2H), 3.96 - 3.85 (m, 1H), 3.82 - 3.66 (m, 2H), 3.65 - 3.53 (m, 2H), 3.32 (s, 5H), 3.17 - 2.93 (m, 2H), 2.92 - 2.76 (m, 5H), 2.74 (br d, J = 4.8 Hz, 2H), 2.28 - 2.19 (m, 1H), 2.13 (br s, 1H), 2.10 (br d, J = 0.8 Hz, 1H), 2.08 (s, 2H), 1.97 (s, 2H), 1.94 (br dd, J = 6.4, 12.4 Hz, 3H), 1.89 (br s, 2H), 1.76 - 1.64 (m, 2H), 1.59 - 1.45 (m, 2H)

[00802] **LC-MS:** MS (ESI^+): t_R = 2.439 min, m/z = 811.4 [M + H^+]

[00803] **Example 25:** Synthesis of N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]-6-[4-[[4-[2-[1-(3,4-difluorophenyl)-6-oxo-2-piperidyl]-5-(3,5-dimethylisoxazol-4-yl)benzimidazol-1-yl]-1-piperidyl]methyl]-1-piperidyl]pyridazine-3-carboxamide (**Compound 127**)



[00804] Synthesis of **1** was reported in Journal of Medicinal Chemistry, 2024, vol. 67, # 4, p. 2466 - 2486

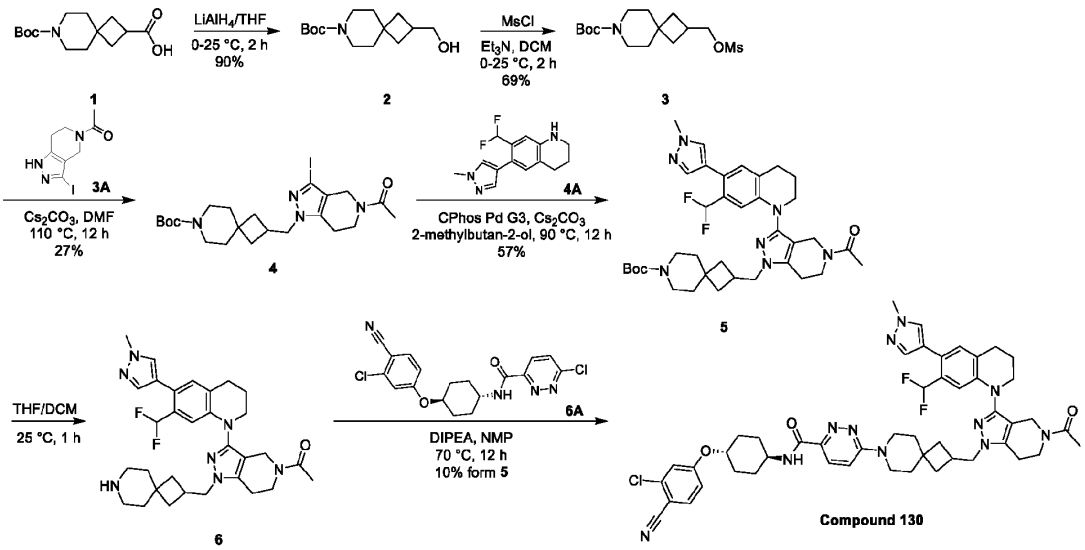
[00805] Synthesis of **1A** was reported in WO2021/127443, 2021, A1

[00806] To a solution of 1-(3,4-difluorophenyl)-6-[5-(3,5-dimethylisoxazol-4-yl)-1-(4-piperidyl)benzimidazol-2-yl]piperidin-2-one (60 mg, 119 μmol, 1.0 eq), N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]-6-(4-formyl-1-piperidyl)pyridazine-3-carboxamide (111 mg, 237 μmol, 2.0 eq) in DCM (3 mL) was added AcOH (14 mg, 237 μmol, 2.0 eq). The mixture was stirred at 25 °C for 0.5 h. And then $NaBH(OAc)_3$ (126 mg, 593 μmol, 5.0 eq) was added. The mixture was stirred at 25 °C for 11.5 h. The reaction mixture was quenched by addition water 20 mL, and then extracted with ethyl acetate (30 mL × 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (neutral condition; column: Waters xbridge 150 × 25mm 10um; mobile phase: [water (NH_4HCO_3)-ACN]; gradient:62%-82% B over 8 min). The desired compound N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]-6-[4-[[4-[2-[1-(3,4-difluorophenyl)-6-oxo-2-piperidyl]-5-(3,5-dimethylisoxazol-4-yl)benzimidazol-1-yl]-1-piperidyl]methyl]-1-piperidyl]pyridazine-3-carboxamide (20.49 mg, 21.22 μmol, 18% yield) was obtained as white solid.

[00807] **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 8.00 (d, *J* = 9.6 Hz, 1H), 7.89 (d, *J* = 8.4 Hz, 1H), 7.71 (d, *J* = 1.2 Hz, 1H), 7.65 - 7.52 (m, 2H), 7.19 - 7.11 (m, 2H), 7.10 - 6.97 (m, 4H), 6.89 - 6.86 (m, 1H), 5.32 - 5.21 (m, 1H), 4.56 (d, *J* = 13.2 Hz, 2H), 4.40 - 4.29 (m, 1H), 4.16 - 3.94 (m, 2H), 3.15 - 2.98 (m, 4H), 2.81 (d, *J* = 2.4 Hz, 1H), 2.74 - 2.63 (m, 1H), 2.61 - 2.40 (m, 6H), 2.34 (s, 3H), 2.29 (d, *J* = 7.2 Hz, 3H), 2.25 - 2.13 (m, 6H), 2.08 - 1.87 (m, 5H), 1.79 - 1.67 (m, 3H), 1.54 - 1.45 (m, 2H), 1.35 - 1.25 (m, 3H)

[00808] **LC-MS:** MS (ESI^+): t_R = 2.089 min, m/z = 957.4 [$M + H^+$].

[00809] **Example 26:** Synthesis of 6-[2-[[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]methyl]-7-azaspiro[3.5]nonan-7-yl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide (**Compound 130**)



[00810] Synthesis of **3A** was was reported in Journal of Medicinal Chemistry, 2024, vol. 67, # 7, p. 5275 – 5304.

[00811] Synthesis of **4A** was reported in Journal of Cell Chemical Biology, 2021, vol. 28, # 4, p. 503 - 12,514.

[00812] Synthesis of **6A** was reported in Journal of European Journal of Medicinal Chemistry, 2024, vol. 271, art. no. 116400.

[00813] To a solution of 7-tert-butoxycarbonyl-7-azaspiro[3.5]nonane-2-carboxylic acid (2.00 g, 7.43 mmol, 1.0 eq) in THF (40 mL) was added $LiAlH_4$ (1 M, 8.91 mL, 1.2 eq) at 0 °C for 1 h under N_2.The mixture was stirred at 25 °C for 1 h under N_2. The reaction mixture was quenched with 5 mL water at 0 °C and then quenched with (10 mL) 15% aqueous NaOH solution at 0 °C. The resulting mixture was quenched with (15 mL) water. The reaction mixture was concentrated under reduced pressure to remove THF and then diluted with 50 mL ethyl acetate and washed by water (30 mL × 3), then the organic phase was dried over anhydrous with Na_2SO_4, evaporated in vacuum. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=10/1 to 2/1). Compound tert-butyl 2-(hydroxymethyl)-7-azaspiro[3.5]nonane-7-carboxylate (1.92 g, 6.70 mmol, 90% yield) was obtained as a yellow oil.

[00814] **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 3.59 (d, J = 6.8 Hz, 2H), 3.39 - 3.31 (m, 2H), 3.30 - 3.20 (m, 2H), 2.53 - 2.39 (m, 1H), 1.97 - 1.84 (m, 2H), 1.47 (s, 6H), 1.44 (s, 9H)

[00815] To a mixture of tert-butyl 2-(hydroxymethyl)-7-azaspiro[3.5]nonane-7-carboxylate (1.92 g, 6.7 mmol, 1.0 eq) in DCM (20 mL) was added Et_3N (2.26 g, 22.3 mmol, 3.0 eq) and MsCl (2.50 g, 21.8 mmol, 2.9 eq) at 0 °C. The mixture was stirred at 25 °C for 2 h under N_2. The reaction mixture was poured into iced water 50 mL at 0 °C, and then extracted with DCM (20 mL × 3). The combined organic layers were washed with brine 20 mL, dried over Na_2SO_4, concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=10/1 to 4/1). Compound tert-butyl 2-(methylsulfonyloxymethyl)-7-azaspiro[3.5]nonane-7-carboxylate (1.81 g, 5.13 mmol, 69% yield)

was obtained as a colorless oil.

[00816] **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 4.17 (d, J = 6.4 Hz, 2H), 3.37 - 3.30 (m, 2H), 3.29 - 3.20 (m, 2H), 3.13 (s, 2H), 3.00 (s, 3H), 2.73 - 2.59 (m, 1H), 2.01 - 1.88 (m, 2H), 1.64 - 1.54 (m, 4H), 1.43 (s, 9H)

[00817] To a solution of tert-butyl 2-(methylsulfonyloxymethyl)-7-azaspiro[3.5]nonane-7-carboxylate (900 mg, 2.70 mmol, 1.0 eq) and 1-(3-iodo-1,4,6,7-tetrahydropyrazolo[4,3-c]pyridin-5-yl)ethanone (943 mg, 3.24 mmol, 1.2 eq) in DMF (20 mL) was added Cs_2CO_3 (2.64 g, 8.10 mmol, 3.0 eq). The mixture was stirred at 110 °C for 12 h under N_2. The mixture was poured into water (50 mL). The aqueous phase was extracted with ethyl acetate (50 mL × 3), dried with anhydrous sodium sulfate, concentrated under vacuum. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150 × 40mm × 15um; mobile phase: [water(FA)-ACN]; gradient: 55%-85% B over 10 min) and purified by prep-TLC (SiO_2, DCM/MeOH = 25/1). Compound tert-butyl 2-[(5-acetyl-3-iodo-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl)methyl]-7-azaspiro[3.5]nonane-7-carboxylate (400 mg, 719 μmol, 27% yield) was obtained as a white solid.

[00818] **LC-MS:** MS (ESI^+): t_R = 0.611 min, m/z = 429.2 [M - 99]

[00819] To a solution of tert-butyl 2-[(5-acetyl-3-iodo-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl)methyl]-7-azaspiro[3.5]nonane-7-carboxylate (200 mg, 378 μmol, 1.0 eq) and 7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-1,2,3,4-tetrahydroquinoline (120 mg, 454 μmol, 1.2 eq) in 2-methylbutan-2-ol (5 mL) was added Cphos Pd G3 (61 mg, 75.7 μmol, 0.2 eq) and Cs_2CO_3 (370 mg, 1.14 mmol, 3.0 eq). The mixture was stirred at 90 °C for 12 h under N_2. The mixture was poured into water (30 mL). The aqueous phase was extracted with ethyl acetate (30 mL × 3), dried with anhydrous sodium sulfate, concentrated under vacuum. The residue was purified by prep-TLC (SiO_2, petroleum ether /ethyl acetate = 0/1). Compound tert-butyl 2-[[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]methyl]-7-azaspiro[3.5]nonane-7-carboxylate (153 mg, 215 μmol, 57% yield) was obtained as a yellow oil.

[00820] **LC-MS:** MS (ESI^+): t_R = 0.643 min, m/z = 664.6 [$M + H^+$]

[00821] To a solution of tert-butyl 2-[[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]methyl]-7-azaspiro[3.5]nonane-7-carboxylate (153 mg, 215 μmol, 1.0 eq) in DCM (1 mL) was added TFA (768 mg, 6.73 mmol, 29.8 eq). The mixture was stirred at 25 °C for 0.5 h. The reaction mixture was concentrated. Compound 1-[1-(7-azaspiro[3.5]nonan-2-ylmethyl)-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]ethanone (150 mg) as a yellow oil and directly used in the next step without further purification.

[00822] **LC-MS:** MS (ESI^+): t_R = 0.501 min, m/z = 564.5 [$M + H^+$]

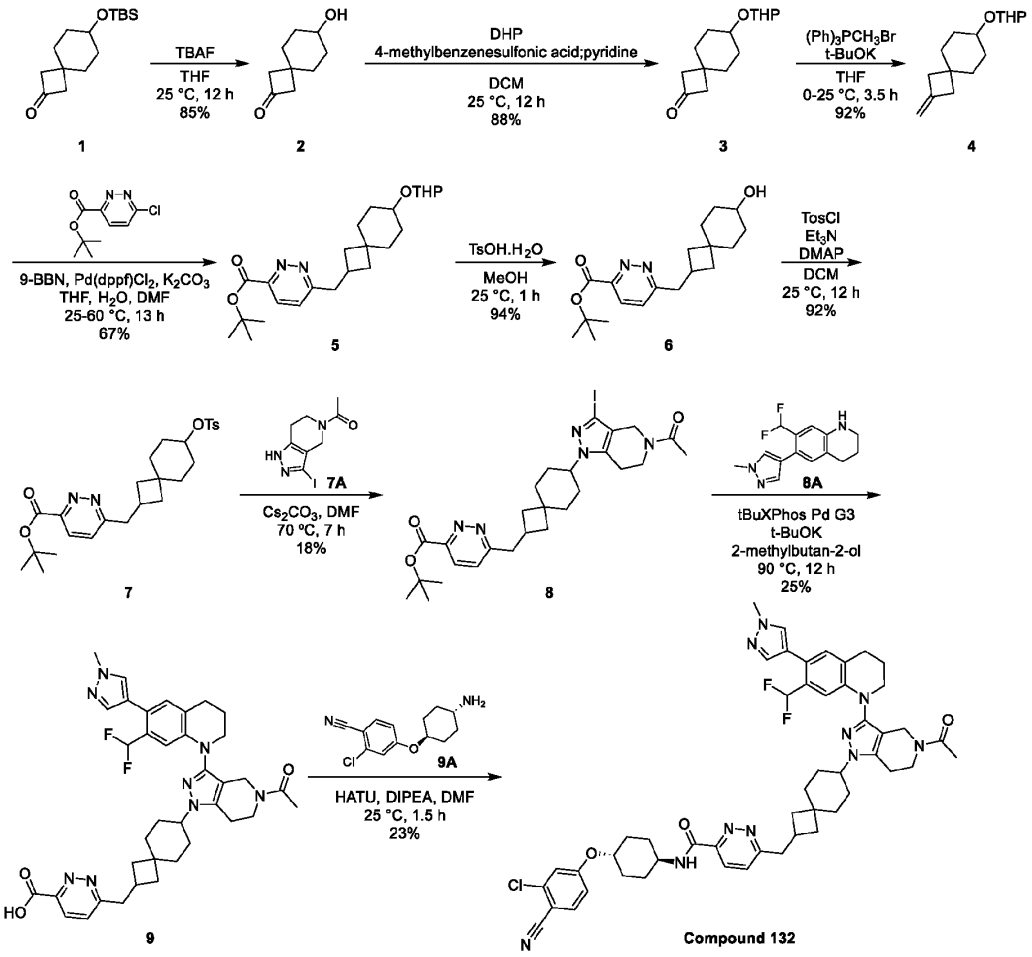
[00823] To a solution of 1-[1-(7-azaspiro[3.5]nonan-2-ylmethyl)-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]ethanone (150 mg) and 6-chloro-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide (130 mg, 332 μmol, 1.5 eq) in NMP (2 mL) was added DIPEA (86 mg, 664 μmol, 3.0 eq). The mixture was stirred at

70 °C for 12 h under N_2. The mixture was poured into water (20 mL). The aqueous phase was extracted with ethyl acetate (20 mL × 3), dried with anhydrous sodium sulfate, concentrated under vacuum. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150 × 25mm × 10um; mobile phase: [water(FA)-ACN]; gradient: 53%-83% B over 10 min) to give 6-[2-[[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]methyl]-7-azaspiro[3.5]nonan-7-yl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide (21.15 mg, 22.9 μmol, 10% yield over two steps,) was obtained as a yellow solid.

[00824] **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 8.07 (s, 1H), 8.02 - 7.95 (m, 1H), 7.88 - 7.81 (m, 1H), 7.60 - 7.50 (m, 2H), 7.43 - 7.37 (m, 1H), 7.09 - 6.97 (m, 3H), 6.92 - 6.83 (m, 2H), 6.72 - 6.34 (m, 1H), 4.39 - 4.25 (m, 2H), 4.18 (s, 1H), 4.11 - 3.99 (m, 3H), 3.98 - 3.86 (m, 4H), 3.82 - 3.59 (m, 7H), 2.95 - 2.68 (m, 5H), 2.22 - 2.14 (m, 5H), 2.12 - 2.02 (m, 6H), 1.78 - 1.67 (m, 6H), 1.65 - 1.60 (m, 2H), 1.54 - 1.41 (m, 2H)

[00825] **LC-MS:** MS (ESI$^+$): t_R = 2.981 min, m/z = 918.5 [M + H$^+$]

[00826] **Example 27:** Synthesis of 6-[[7-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]spiro[3.5]nonan-2-yl]methyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide (**Compound 132**)



[00827] Synthesis of **7A** was reported in Journal of Medicinal Chemistry, 2024, vol. 67, # 7, p. 5275 – 5304

[00828] Synthesis of **8A** was reported in Cell Chemical Biology, 2021, vol. 28, # 4, p. 503 - 12,514

[00829] Synthesis of **8A** was reported in MedChemComm, 2016, vol. 7, # 5, p. 813 – 819

[00830] To a solution of 7-[tert-butyl(dimethyl)silyl]oxyspiro[3.5]nonan-2-one (4.40 g, 16.4 mmol, 1.0 eq) in THF (44 mL) was added tetrabutyl ammonium fluoride (1.0 M, 24.6 mL, 1.5 eq). The mixture was stirred at 25 °C for 12 h under N_2 atmosphere. The reaction mixture was quenched by addition water 20 mL, and then diluted with water 40 mL and extracted with ethyl acetate (50 mL × 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate=10/1 to 1/1). The desired compound 7-hydroxyspiro[3.5]nonan-2-one (2.15 g, 13.9 mmol, 85% yield) was obtained as off-white solid.

[00831] **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 3.82 - 3.70 (m, 1H), 2.78 (s, 4H), 1.94 - 1.77 (m, 4H), 1.70 - 1.61 (m, 2H), 1.49 - 1.36 (m, 3H)

[00832] To a solution of 7-hydroxyspiro[3.5]nonan-2-one (1.06 g, 6.85 mmol, 1.0 eq), 4-methylbenzenesulfonic acid;pyridine (345 mg, 1.37 mmol, 0.2 eq) in DCM (25 mL) was added 3,4-dihydro-2H-pyran (1.15 g, 13.7 mmol, 2.0 eq). The mixture was stirred at 25 °C for 12 h under N_2 atmosphere. The reaction mixture was quenched by addition water 20 mL, and then diluted with water 20 mL and extracted with ethyl acetate (50 mL × 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate=50/1 to 10/1). The desired compound 7-tetrahydropyran-2-yloxyspiro[3.5]nonan-2-one (1.44 g, 6.04 mmol, 88% yield) was obtained as colourless oil.

[00833] **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 4.77 - 4.69 (m, 1H), 3.95 - 3.89 (m, 1H), 3.78 - 3.67 (m, 1H), 3.55 - 3.46 (m, 1H), 2.77 (s, 4H), 1.86 (s, 3H), 1.76 - 1.65 (m, 2H), 1.64 - 1.48 (m, 8H), 1.46 - 1.34 (m, 1H)

[00834] To a solution of methyl(triphenyl)phosphonium;bromide (2.81 g, 7.85 mmol, 1.3 eq) in THF (14 mL) was added t-BuOK (1.0 M, 7.85 mL, 1.3 eq) at 0 °C under N_2 atmosphere. The mixture was stirred at 0 °C for 0.5 h. And then 7-tetrahydropyran-2-yloxyspiro[3.5]nonan-2-one (1.44 g, 6.04 mmol, 1.0 eq) in THF (14 mL) was added at 0 °C. The mixture was stirred at 25 °C for 3 h under N_2 atmosphere. The reaction mixture was quenched by addition water 20 mL, and then diluted with water 20 mL and extracted with ethyl acetate (50 mL × 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate=100/1 to 50/1). The desired compound 2-(2-methylenespiro[3.5]nonan-7-yl)oxytetrahydropyran (1.32 g, 5.57 mmol, 92% yield) was obtained as colourless oil.

[00835] **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 4.80 (d, J = 2.0 Hz, 2H), 4.75 - 4.68 (m, 1H), 3.97 - 3.87 (m, 1H), 3.66 - 3.56 (m, 1H), 3.54 - 3.45 (m, 1H), 2.38 (d, J = 11.2 Hz, 4H), 1.92 - 1.70 (m, 6H), 1.56 - 1.26 (m, 8H)

[00836] 2-(2-methylenespiro[3.5]nonan-7-yl)oxytetrahydropyran (1.32 g, 5.57 mmol, 1.0 eq) and 9-BBN (0.5 M, 13.4 mL, 1.2 eq) in THF (14 mL) was stirred at 60 °C for 1 h under N_2 atmosphere. After cooled to 25 °C, tert-butyl 6-chloropyridazine-3-carboxylate (1.44 g, 6.69 mmol, 1.2 eq), K_2CO_3 (1.16 g, 8.36 mmol, 1.5 eq) and $Pd(dppf)Cl_2$ (815 mg, 1.11 mmol, 0.2 eq) in H_2O (2.8 mL) and DMF (14 mL) was added, then the mixture was stirred at 60 °C for 12 h under N_2 atmosphere. The mixture was poured into iced water (40 mL). The aqueous phase was extracted with ethyl acetate (50 mL × 3). The combined organic phase was washed with brine (30 mL × 2), dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate=50/1 to 5/1). The desired compound tert-butyl 6-[(7-tetrahydropyran-2-yloxyspiro[3.5]nonan-2-yl)methyl]pyridazine-3-carboxylate (1.57 g, 3.76 mmol, 67% yield) was obtained as yellow solid.

[00837] **LC-MS:** MS (ESI^+): t_R = 0.661 min, m/z = 417.4 [$M + H^+$]

[00838] To a solution of tert-butyl 6-[(7-tetrahydropyran-2-yloxyspiro[3.5]nonan-2-yl)methyl]pyridazine-

3-carboxylate (1.47 g, 3.52 mmol, 1.0 eq) in MeOH (15 mL) was added $TsOH \cdot H_2O$ (669 mg, 3.52 mmol, 1.0 eq). The mixture was stirred at 25 °C for 1 h. The reaction mixture was quenched by addition water 20 mL, and then diluted with water 20 mL and extracted with ethyl acetate (50 mL × 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate=10/1 to 1/1). The desired compound tert-butyl 6-[(7-hydroxyspiro[3.5]nonan-2-yl)methyl]pyridazine-3-carboxylate (1.10 g, 3.30 mmol, 94% yield) was obtained as yellow oil.

[00839] **LC-MS:** MS (ESI^+): t_R = 0.869 min, m/z = 333.2 [$M + H^+$]

[00840] To a solution of tert-butyl 6-[(7-hydroxyspiro[3.5]nonan-2-yl)methyl]pyridazine-3-carboxylate (1.10 g, 3.30 mmol, 1.0 eq) in DCM (20 mL) was added Et_3N (1.67 g, 16.5 mmol, 5.0 eq), DMAP (40 mg, 330 μmol, 0.1 eq) and p-toluenesulfonyl chloride (1.89 g, 9.89 mmol, 3.0 eq). The mixture was stirred at 25 °C for 12 h. The reaction mixture was quenched by addition water 20 mL, and then diluted with water 30 mL and extracted with ethyl acetate (50 mL × 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate=10/1 to 2/1). The desired compound tert-butyl 6-[[7-(p-tolylsulfonyloxy)spiro[3.5]nonan-2-yl]methyl]pyridazine-3-carboxylate (1.48 g, 3.04 mmol, 92% yield) was obtained as brown oil.

[00841] **LC-MS:** MS (ESI^+): t_R = 0.939 min, m/z = 487.3 [$M + H^+$]

[00842] To a solution of tert-butyl 6-[[7-(p-tolylsulfonyloxy)spiro[3.5]nonan-2-yl]methyl]pyridazine-3-carboxylate (1.08 g, 2.22 mmol, 1.0 eq) in DMF (15 mL) was added 1-(3-iodo-1,4,6,7-tetrahydropyrazolo[4,3-c]pyridin-5-yl)ethanone (775 mg, 2.66 mmol, 1.2 eq) and Cs_2CO_3 (2.89 g, 8.88 mmol, 4.0 eq). The mixture was stirred at 70 °C for 7 h. The reaction mixture was quenched by addition water 20 mL at 0 °C, and then diluted with water 40 mL and extracted with ethyl acetate (50 mL × 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (FA condition; column: Phenomenex luna C18 150 × 40mm × 15um; mobile phase: [water(FA)-ACN];gradient:53%-83% B over 10 min). The residue was purified by prep-TLC (SiO_2, DCM/MeOH = 20/1). The desired compound tert-butyl 6-[[7-(5-acetyl-3-iodo-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl)spiro[3.5]nonan-2-yl]methyl]pyridazine-3-carboxylate (240 mg, 396 μmol, 18% yield) was obtained as white solid.

[00843] **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 8.02 (d, *J* = 8.8 Hz, 1H), 7.37 (d, *J* = 8.8 Hz, 1H), 4.45 - 4.19 (m, 2H), 3.91 - 3.66 (m, 3H), 3.16 (d, *J* = 7.6 Hz, 2H), 2.79 - 2.61 (m, 3H), 2.25 - 2.09 (m, 4H), 1.99 - 1.84 (m, 4H), 1.76 - 1.71 (m, 3H), 1.66 (s, 9H), 1.62 - 1.53 (m, 2H), 1.51 - 1.36 (m, 2H)

[00844] To a solution of tert-butyl 6-[[7-(5-acetyl-3-iodo-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl)spiro[3.5]nonan-2-yl]methyl]pyridazine-3-carboxylate (240 mg, 396 μmol, 1.0 eq), 7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-1,2,3,4-tetrahydroquinoline (125 mg, 475 μmol, 1.2 eq), [2-(2-aminophenyl)phenyl]-methylsulfonyloxy-palladium;ditert-butyl-[2-(2,4,6-triisopropylphenyl)phenyl]phosphane (63 mg, 79 μmol, 0.2 eq) in 2-methylbutan-2-ol (5 mL) was added t-BuOK (1.0 M, 939 μL, 2.4 eq). The mixture was stirred at

90 °C for 12 h under N_2. The reaction mixture was quenched by addition water 20 mL, and then extracted with ethyl acetate (50 mL × 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (FA condition; column: Phenomenex luna C18 150 × 25mm × 10um; mobile phase: [water (FA)-ACN];gradient:40%-70% B over 10 min). The residue was purified by prep-HPLC (neutral condition; column: Waters xbridge 150 × 25mm 10um; mobile phase: [water (NH_4HCO_3)-ACN];gradient:28%-48% B over 8 min). The desired compound 6-[[7-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]spiro[3.5]nonan-2-yl]methyl]pyridazine-3-carboxylic acid (68 mg, 99 μmol, 25% yield) was obtained as off-white solid.

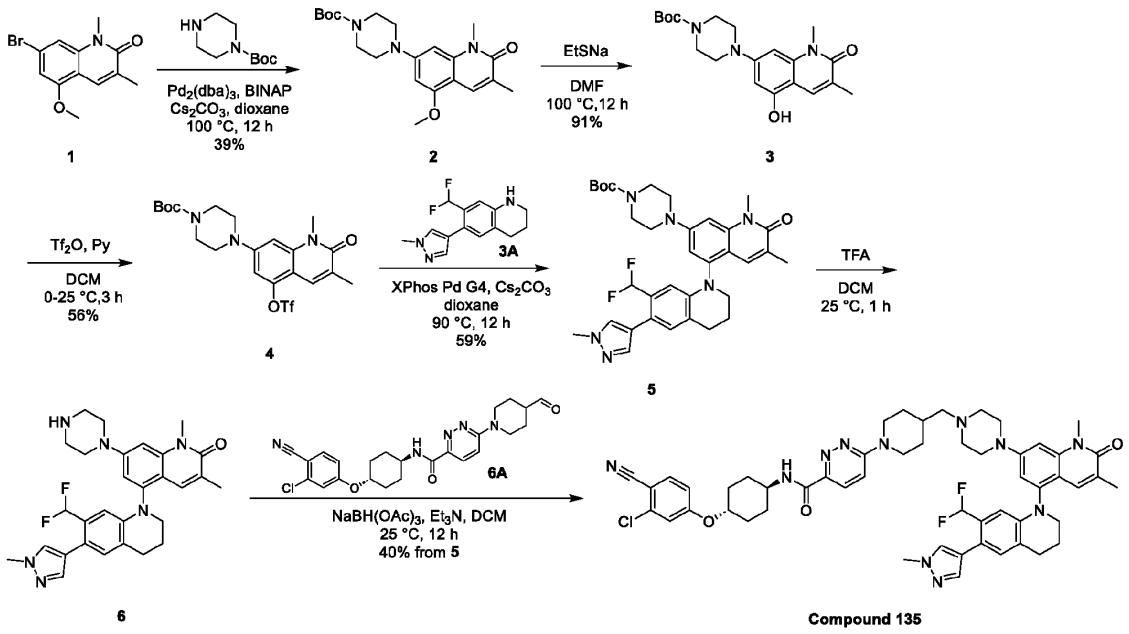
[00845] **LC-MS:** MS (ESI^+): t_R = 0.897 min, m/z = 685.3 [M + H^+]

[00846] To a solution of 6-[[7-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]spiro[3.5]nonan-2-yl]methyl]pyridazine-3-carboxylic acid (68 mg, 99 μmol, 1.0 eq), HATU (57 mg, 149 μmol, 1.5 eq) in DMF (1 mL). The mixture was stirred at 25 °C for 0.5 h. And then 4-(4-aminocyclohexoxy)-2-chloro-benzonitrile (37 mg, 149 μmol, 1.5 eq) and DIPEA (39 mg, 298 μmol, 3.0 eq) in DMF (1 mL) was added. The mixture was stirred at 25 °C for 1 h. The reaction mixture was quenched by addition water 20 mL, and then extracted with ethyl acetate (50 mL × 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, DCM/MeOH = 10/1). The residue was purified by prep-HPLC (FA condition; column: Phenomenex luna C18 150 × 25mm × 10um; mobile phase: [water (FA)-ACN];gradient:58%-88% B over 10 min). The desired compound 6-[[7-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]spiro[3.5]nonan-2-yl]methyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide (21.34 mg, 23.21 μmol, 23% yield) was obtained as yellow solid.

[00847] **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 8.21 (d, *J* = 8.8 Hz, 1H), 8.13 (d, *J* = 8.0 Hz, 1H), 8.09 - 8.00 (m, 1H), 7.61 - 7.51 (m, 2H), 7.46 (d, *J* = 8.8 Hz, 1H), 7.43 - 7.36 (m, 1H), 7.08 - 6.95 (m, 2H), 6.91 - 6.82 (m, 2H), 6.70 - 6.33 (m, 1H), 4.40 - 4.30 (m, 1H), 4.27 - 4.05 (m, 3H), 3.95 (d, *J* = 2.0 Hz, 3H), 3.90 - 3.65 (m, 5H), 3.17 (d, *J* = 7.6 Hz, 2H), 2.89 - 2.83 (m, 2H), 2.81 - 2.68 (m, 3H), 2.25 - 2.14 (m, 6H), 2.10 - 2.03 (m, 4H), 2.02 - 1.90 (m, 4H), 1.85 - 1.70 (m, 6H), 1.57 - 1.38 (m, 5H)

LC-MS: MS (ESI^+): t_R = 2.920 min, m/z = 917.4 [M + H^+]

[00848] **Example 28:** Synthesis of N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]-6-[4-[[4-[5-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-1,3-dimethyl-2-oxo-7-quinolyl]piperazin-1-yl]methyl]-1-piperidyl]pyridazine-3-carboxamide (**Compound 135**)



[00849] Synthesis of **1** was reported in WO2022/53967 A1.

[00850] Synthesis of **3A** was reported in Journal of Cell Chemical Biology, 2021, vol. 28, # 4, p. 503 - 12,514

[00851] Synthesis of **6A** was reported in EP3957633 A1.

[00852] A mixture of 7-bromo-5-methoxy-1,3-dimethyl-quinolin-2-one (1.00 g, 3.54 mmol, 1.0 eq), Cs_2CO_3 (3.00 g, 9.21 mmol, 2.6 eq), [1-(2-diphenylphosphanyl-1-naphthyl)-2-naphthyl]-diphenyl-phosphane (1.32 g, 1.06 mmol, 0.3 eq), $Pd_2(dba)_3$ (649 mg, 709 μmol, 0.2 eq) and tert-butyl piperazine-1-carboxylate (1.00 g, 5.37 mmol, 1.5 eq) in dioxane (20 mL) was stirrd at 100 °C for 12 h. under N_2.The reaction mixture was filtered and washed with EtOAc (20 mL × 3). The collected filtrate was concentrated to give a residue. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=3/1 to 1/1). Compound tert-butyl 4-(5-methoxy-1,3-dimethyl-2-oxo-7-quinolyl)piperazine-1-carboxylate (400 mg, 1.03 mmol, 39% yield) was obtained as a brown solid.

[00853] **LC-MS:** MS (ESI^+): t_R = 0.915 min, m/z = 388.1 [$M + H^+$]

[00854] To a solution of tert-butyl 4-(5-methoxy-1,3-dimethyl-2-oxo-7-quinolyl)piperazine-1-carboxylate (400 mg, 1.03 mmol, 1.0 eq) in DMF (20 mL) was added ethylsulfanylsodium (2.40 g, 28.5 mmol, 27.6 eq) and stirred at 100 °C for 12 h. The reaction mixture was quenched by iced water (50 mL), and extracted with EtOAc (25 mL × 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=3/1 to 1/1). Compound tert-butyl 4-(5-hydroxy-1,3-dimethyl-2-oxo-7-quinolyl)piperazine-1-carboxylate (350 mg, 937 μmol, 91% yield) was obtained as a light yellow solid.

[00855] **LC-MS:** MS (ESI^+): t_R = 0.557 min, m/z = 374.3 [$M + H^+$]

[00856] To a solution of tert-butyl 4-(5-hydroxy-1,3-dimethyl-2-oxo-7-quinolyl)piperazine-1-carboxylate

(350 mg, 937 μmol, 1.0 eq) and pyridine (259 mg, 3.28 mmol, 265 μL, 3.5 eq) in DCM (20 mL) was added Tf_2O (599 mg, 2.12 mmol, 350 μL, 2.3 eq) at 0 °C and stirred at 25 °C for 3 h under N_2. The mixture was poured into iced water (30 mL). It was filtered, the filtrate was extracted with DCM (20 mL × 3). The combined organic phase was washed with brine (20 mL), dried with anhydrous sodium sulfate, filtered and concentrated under vacuum. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=10/1 to 3/1). Compound tert-butyl 4-[1,3-dimethyl-2-oxo-5-(trifluoromethylsulfonyloxy)-7-quinolyl]piperazine-1-carboxylate (280 mg, 521 μmol, 56% yield) was obtained as a yellow solid.

[00857] **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.60 (s, 1 H) 6.74 (d, *J*=2.0 Hz, 1 H) 6.62 (d, *J*=1.6 Hz, 1 H) 3.70 (s, 3 H) 3.59 - 3.67 (m, 4 H) 3.24 - 3.36 (m, 4 H) 2.26 (s, 3 H) 1.50 (s, 9 H)

[00858] **LC-MS:** MS (ESI^+): t_R = 0.663 min, m/z = 506.2 [M + H^+]

[00859] To a mixture of tert-butyl 4-[1,3-dimethyl-2-oxo-5-(trifluoromethylsulfonyloxy)-7-quinolyl]piperazine-1-carboxylate (150 mg, 297 μmol, 1.0 eq) and 7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-1,2,3,4-tetrahydroquinoline (94 mg, 356 μmol, 1.2 eq) in dioxane (8 mL) was added Xphos Pd G4 (51 mg, 59.4 μmol, 0.2 eq) and Cs_2CO_3 (290 mg, 890 μmol, 3.0 eq). The reaction mixture was stirred at 90 °C for 12 h under N_2. The reaction mixture was filtered and washed with EtOAc (20 mL × 2). The collected filtrate was concentrated to give a residue. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=3/1 to 0/1) to give a crude product. The crude product was purified by prep-TLC (petroleum ether/ethyl acetate =1/3). Compound tert-butyl 4-[5-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-1,3-dimethyl-2-oxo-7-quinolyl]piperazine-1-carboxylate (120 mg, 176 μmol, 59 % yield) was obtained as a white solid.

[00860] **LC-MS:** MS (ESI^+): t_R = 1.059 min, m/z = 619.4 [M + H^+]

[00861] To a mixture of tert-butyl 4-[5-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-1,3-dimethyl-2-oxo-7-quinolyl]piperazine-1-carboxylate (120 mg, 176 μmol, 1.0 eq) in DCM (4 mL) was added TFA (3.07 g, 26.9 mmol, 2 mL, 138.8 eq). The reaction mixture was stirred at 25 °C for 1 h. The mixture was concentrated to give a residue. Compound 5-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-1,3-dimethyl-7-piperazin-1-yl-quinolin-2-one (150 mg) was obtained as a brown gum and directly used in the next step without further purification.

[00862] **LC-MS:** MS (ESI^+): t_R = 0.812min, m/z = 519.3 [M + H^+]

[00863] To a mixture of 5-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-1,3-dimethyl-7-piperazin-1-yl-quinolin-2-one (150 mg) in DCM (10 mL) was added Et_3N (240 mg, 2.37 mmol, 330 μL, 10 eq), N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]-6-(4-formyl-1-piperidyl)pyridazine-3-carboxamide (150 mg, 321 μmol, 1.4 eq) and $NaBH(OAc)_3$ (251 mg, 1.19 mmol, 5.0 eq). The reaction mixture was stirred at 25 °C for 12 h. The mixture was poured into iced water (50 mL). The aqueous phase was extracted with dichloromethane (30 mL × 3). The combined organic phase was washed with brine (30 mL), dried with anhydrous sodium sulfate, filtered and concentrated under vacuum. The residue was purified by semi-preparative reverse phase HPLC (column: Agela DuraShell C18 150 × 25mm × 5um; mobile phase:

[water (FA)-ACN]; gradient:31%-61% B over 10 min). Compound N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]-6-[4-[[4-[5-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-1,3-dimethyl-2-oxo-7-quinolyl]piperazin-1-yl]methyl]-1-piperidyl]pyridazine-3-carboxamide (92.99 mg, 94.85 μmol, 40% yield over two steps) was obtained as a yellow solid.

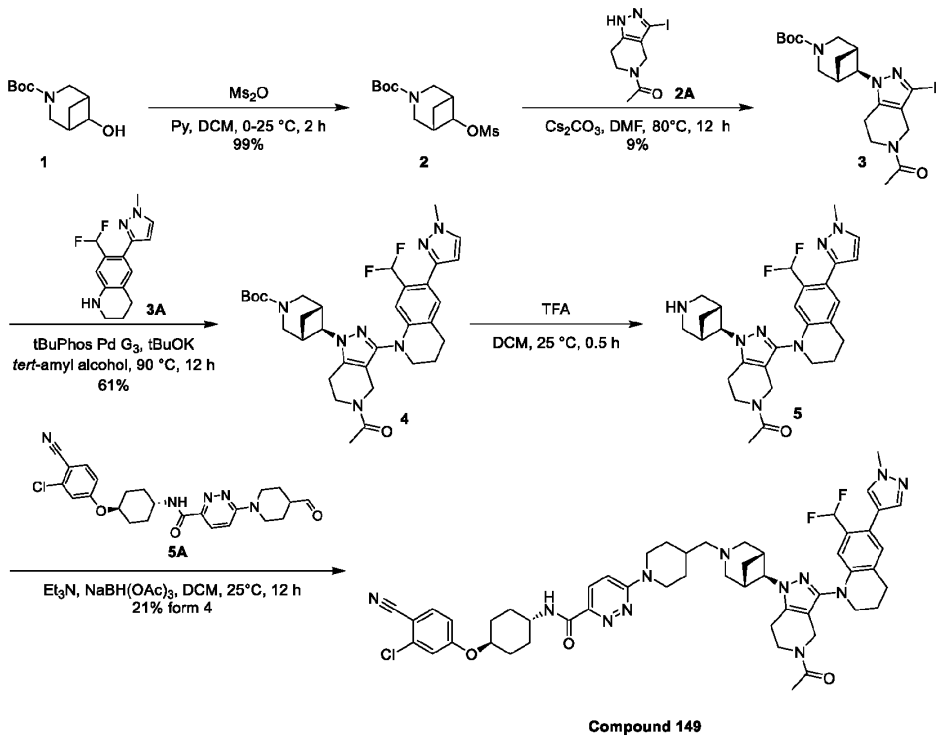
[00864] **^{1}H NMR** (400 MHz, CHLOROFORM-*d*) δ = 7.98 (d, *J*=9.2 Hz, 1 H) 7.87 (d, *J*=8.4 Hz, 1 H) 7.50 - 7.59 (m, 3 H) 7.41 (s, 1 H) 7.09 (s, 1 H) 6.95 - 7.02 (m, 2 H) 6.86 (m, 1 H) 6.77 (s, 1 H) 6.65 (s, 1 H) 6.29 - 6.58 (m, 2 H) 4.52 (m, 2 H) 4.28 - 4.38 (m, 1 H) 4.00 - 4.13 (m, 1 H) 3.95 (s, 3 H) 3.76 (s, 3 H) 3.59 (t, *J*=5.6 Hz, 2 H) 3.25 - 3.40 (m, 4 H) 2.96 - 3.12 (m, 4 H) 2.61 (s, 4 H) 2.26 - 2.34 (m, 2 H) 2.12 - 2.24 (m, 9 H) 1.85 - 2.02 (m, 3 H) 1.66 - 1.77 (m, 2 H) 1.40 - 1.54 (m, 2 H) 1.20 - 1.36 (m, 2 H).

[00865] **LC-MS:** MS (ESI$^+$): t_R = 1.954 min, m/z = 970.6 [M + H$^+$];

[00866] The compounds below were prepared in a similar manner as described in Example 28.

Compound	Name	^{1}H NMR ($CDCl_3$)	LC-MS [M + H$^+$]
138	N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]-6-[4-[[4-[5-(7-cyclopropyl-1-methyl-2,3-dihydropyrido[3,4-b]pyrazin-4-yl)-1,3-dimethyl-2-oxo-7-quinolyl]piperazin-1-yl]methyl]-1-piperidyl]pyridazine-3-carboxamide	δ = 7.97 (d, *J*=9.6 Hz, 1 H) 7.87 (d, *J*=8.4 Hz, 1 H) 7.56 (d, *J*=8.8 Hz, 1 H) 7.45 (s, 1 H) 6.95 - 7.04 (m, 3 H) 6.86 (m, 1 H) 6.58 - 6.68 (m, 2 H) 6.14 (s, 1 H) 4.52 (m, 2 H) 4.27 - 4.39 (m, 1 H) 3.99 - 4.13 (m, 1 H) 3.81 - 3.94 (m, 1 H) 3.73 (s, 4 H) 3.56 (m, 2 H) 3.31 (s, 4 H) 3.15 (s, 3 H) 3.06 (m, 2 H) 2.60 (m, 4 H) 2.29 (m, 2 H) 2.14 - 2.22 (m, 7 H) 1.87 - 1.98 (m, 3 H) 1.65 - 1.73 (m, 2 H) 1.43 - 1.52 (m, 2 H) 1.26 - 1.29 (m, 2 H) 1.03 - 1.12 (m, 2 H) 0.90 - 0.98 (m, 2 H) 0.82 - 0.89 (m, 1 H).	896.4

[00867] **Example 29:** Synthesis of N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]-6-[4-[[rac-(1S,5R)-6-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-3-azabicyclo[3.1.1]heptan-3-yl]methyl]-1-piperidyl]pyridazine-3-carboxamide **(Compound 149)**



Compound 149

[00868] Synthesis of **1** was reported in WO2020/249064 A1

[00869] Synthesis of **2A** was reported in Journal of Medicinal Chemistry, 2024, vol. 67, # 7, p. 5275 – 5304

[00870] Synthesis of **3A** was reported in Cell Chemical Biology, 2021, vol. 28, # 4, p. 503 - 12,514.

[00871] Synthesis of **5A** was reported in WO2021/231174 A1

[00872] To a solution of tert-butyl 6-hydroxy-3-azabicyclo[3.1.1]heptane-3-carboxylate (430 mg, 2.02 mmol, 1.0 *eq*) in DCM (10.0 mL) was added methylsulfonyl methanesulfonate (654 mg, 3.76 mmol, 1.9 *eq*) and Py (493 mg, 6.23 mmol, 500 µL, 3.1 *eq*) at 0 °C. After stirred at 25 °C for 2 h under N_2. The reaction mixture was diluted with DCM (10 mL), washed with saturated $NaHCO_3$, dried over dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=10/1 to 2/1). Compound tert-butyl 6-methylsulfonyloxy-3-azabicyclo[3.1.1]heptane-3-carboxylate (580 mg, 1.99 mmol, 99% yield) was obtained as a white solid.

[00873] **^{1}H NMR:** δ = 4.87 (t, *J* = 5.6 Hz, 1H), 3.76 - 3.54 (m, 4H), 3.05 (s, 3H), 2.85 - 2.72 (m, 2H), 1.75 - 1.68 (m, 1H), 1.58 (br s, 1H), 1.50 (s, 9H)

[00874] To a solution of 1-(3-iodo-1,4,6,7-tetrahydropyrazolo[4,3-c]pyridin-5-yl)ethanone (350 mg, 1.20 mmol, 1.0 *eq*) and tert-butyl 6-methylsulfonyloxy-3-azabicyclo[3.1.1]heptane-3-carboxylate (580 mg, 1.99 mmol, 1.7 *eq*) in DMF (6.0 mL) was added Cs_2CO_3 (800 mg, 2.46 mmol, 2.0 *eq*) and the mixture was stirred at 80 °C for 12 h. The reaction mixture was filtered and concentrated under reduced pressure to give a

residue. The residue was purified by prep-HPLC (FA condition;column: Phenomenex luna C18 150*25mm* 10um;mobile phase: [water(FA)-ACN];gradient:43%-73% B over 10 min). Compound tert-butyl (1R, 5S)-6-(5-acetyl-3-iodo-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl)-3-azabicyclo[3.1.1]heptane-3-carboxylate (50 mg, 103 μmol, 9% yield) was obtained as a white solid.

[00875] **^{1}H NMR** (400 MHz, DMSO-d_6) δ = 4.78 - 4.61 (m, 1H), 4.35 - 4.10 (m, 2H), 3.90 - 3.58 (m, 4H), 3.35 (br d, *J* = 13.6 Hz, 1H), 3.31 - 3.17 (m, 1H), 2.96 - 2.66 (m, 2H), 2.10 (s, 3H), 1.57 - 1.31 (m, 11H), 0.92 - 0.81 (m, 1H), 0.72 - 0.59 (m, 1H)

[00876] To a solution of tert-butyl (1R,5S)-6-(5-acetyl-3-iodo-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl)-3-azabicyclo[3.1.1]heptane-3-carboxylate (90 mg, 185 μmol, 1.0 *eq*), 7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-1,2,3,4-tetrahydroquinoline (100 mg, 380 μmol, 2.1 *eq*) in tert-amyl alcohol (4.0 mL) was added [2-(2-aminophenyl)phenyl]-methylsulfonyloxy-palladium;ditert-butyl-[2-(2,4,6-triisopropylphenyl)phenyl]phosphane (30 mg, 37.77 μmol, 0.2 *eq*) and t-BuOK (1 M, 450 μL, 2.4 *eq*). The mixture was stirred at 90 °C for 12 h under N_2. The reaction mixture was diluted with **Ethyl acetate** (150 mL), washed with brine 50 mL, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, Petroleum ether/Ethyl acetate = 0/1). Compound tert-butyl (1R,5S)-6-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-3-azabicyclo[3.1.1]heptane-3-carboxylate (70 mg, 113 μmol, 61% yield) was obtained as a white solid.

[00877] **^{1}H NMR** (400 MHz, DMSO-d_6) δ = 7.75 (s, 1H), 7.49 (s, 1H), 7.10 (s, 1H), 6.96 - 6.60 (m, 2H), 4.76 - 4.61 (m, 1H), 4.30 - 4.05 (m, 2H), 3.86 (s, 3H), 3.73 - 3.50 (m, 4H), 3.31 - 3.19 (m, 2H), 2.99 - 2.76 (m, 4H), 2.08 (s, 2H), 2.02 - 1.90 (m, 4H), 1.39 (br s, 10H), 0.96 - 0.84 (m, 1H), 0.71 - 0.59 (m, 1H)

[00878] To a solution of tert-butyl (1R,5S)-6-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-3-azabicyclo[3.1.1]heptane-3-carboxylate (70 mg, 113 μmol, 1.0 *eq*) in DCM (1 mL) was added TFA (0.5 mL) and the mixture was stirred at 25 °C for 0.5 h under N_2. The reaction mixture was concentrated under reduced pressure to give a residue. Then to the residue was added dichloromethane/Methanol (10/1) 50 mL, and adjusted the pH to 7-8 with ammonium hydroxide, dried over anhydrous sodium sulfate, filtered and concentrated in vacuum to give a residue. The crude product 1-[1-[(1R,5S)-3-azabicyclo[3.1.1]heptan-6-yl]-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]ethanone (58 mg) was obtained as a white solid and used into the next step without further purification.

[00879] **LC-MS:** MS (ESI^+): t_R = 0.454 min, m/z = 522.4 [$M + H^+$]

[00880] To a solution of1-[1-[(1R,5S)-3-azabicyclo[3.1.1]heptan-6-yl]-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]ethanone (58 mg), N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]-6-(4-formyl-1-piperidyl)pyridazine-3-carboxamide (52 mg, 111 μmol, 1.0 *eq*) in DCM (5 mL) was added Et_3N (73 mg, 718 μmol, 100 μL, 6.5 *eq*) and $NaBH(OAc)_3$ (70 mg, 330 μmol, 3.0 *eq*). The mixture was stirred at 25 °C for 12 h under N_2. The reaction mixture was diluted with DCM (20 mL), washed with saturated $NaHCO_3$, dried over Na_2SO_4, filtered and

concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (FA condition; column: Phenomenex luna C18 150*25mm* 10um; mobile phase: [water (FA)-ACN]; gradient: 29%-59% B over 10 min). Compound N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]-6-[4-[[rac-(1S,5R)-6-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-3-azabicyclo[3.1.1]heptan-3-yl]methyl]-1-piperidyl]pyridazine-3-carboxamide (23.47 mg, 24 μmol, 21% yield over two steps) was obtained as a white solid.

[00881] **^{1}H NMR** (400 MHz, DMSO-d_6) δ = 8.57 (d, *J* = 8.0 Hz, 1H), 7.85 (d, *J* = 8.4 Hz, 1H), 7.79 - 7.71 (m, 2H), 7.48 (s, 1H), 7.39 (d, *J* = 2.4 Hz, 1H), 7.28 - 7.19 (m, 1H), 7.17 - 7.11 (m, 1H), 7.09 (s, 1H), 6.97 - 6.62 (m, 2H), 4.81 - 4.68 (m, 1H), 4.59 - 4.50 (m, 1H), 4.48 - 4.39 (m, 1H), 4.37 - 4.03 (m, 3H), 3.98 - 3.74 (m, 5H), 3.70 - 3.52 (m, 3H), 3.02 - 2.77 (m, 7H), 2.61 - 2.51 (m, 2H), 2.24 (br d, *J* = 11.6 Hz, 1H), 2.16 - 2.05 (m, 6H), 2.00 - 1.85 (m, 7H), 1.78 (br d, *J* = 12.4 Hz, 1H), 1.69 - 1.58 (m, 2H), 1.56 - 1.44 (m, 2H), 1.42 - 1.27 (m, 2H), 1.13 - 0.96 (m, 2H), 0.83 - 0.73 (m, 1H), 0.61 - 0.49 (m, 1H)

[00882] **LC-MS:** MS (ESI$^+$): t_R = 2.235 min, m/z=973.4 [M + H$^+$]

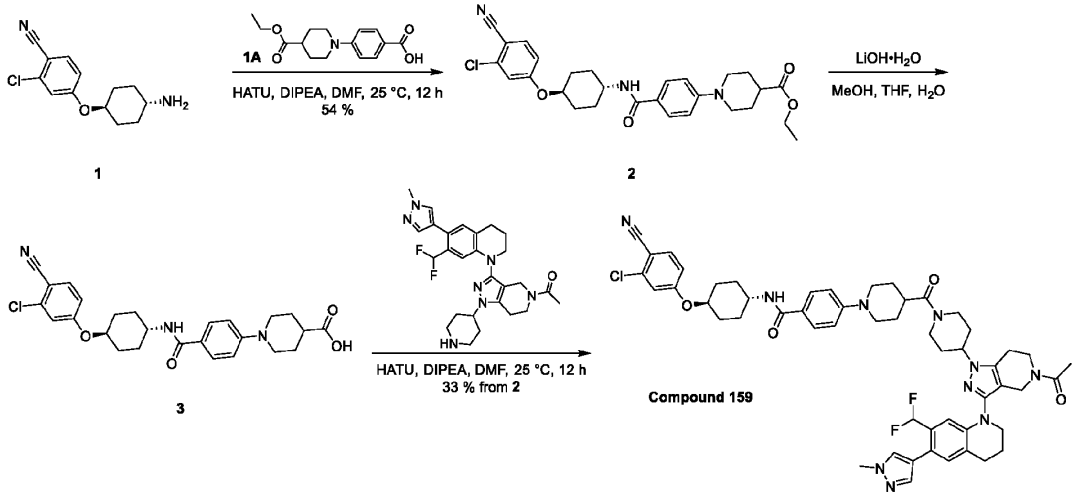
[00883] **SFC:** t_R = 1.848 min, 48%; t_R = 2.382 min ; 52%.

[00884] The compounds below were prepared in a similar manner as described in Example 29.

Compound	Name	^{1}H NMR (DMSO-d_6)	LC-MS [M + H$^+$]
150	N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]-6-[4-[[rac-(1R,5S)-6-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-3-azabicyclo[3.1.1]heptan-3-yl]methyl]-1-piperidyl]pyridazine-3-carboxamide	δ = 8.65 - 8.56 (m, 1H), 7.86 (d, *J* = 8.4 Hz, 1H), 7.82 - 7.72 (m, 2H), 7.50 (s, 1H), 7.39 (d, *J* = 2.0 Hz, 1H), 7.31 (d, *J* = 9.6 Hz, 1H), 7.17 - 7.08 (m, 2H), 6.95 - 6.62 (m, 2H), 4.62 - 4.36 (m, 4H), 4.24 - 4.11 (m, 2H), 3.91 - 3.81 (m, 4H), 3.75 - 3.64 (m, 1H), 3.63 - 3.54 (m, 2H), 3.07 - 2.90 (m, 3H), 2.89 - 2.65 (m, 4H), 2.64 - 2.55 (m, 2H), 2.27 - 2.15 (m, 1H), 2.15 - 2.04 (m, 6H), 2.02 - 1.94 (m, 3H), 1.93 - 1.86 (m, 2H), 1.84 - 1.71 (m, 2H), 1.70 - 1.58 (m, 3H), 1.56 - 1.45 (m, 2H), 1.32 - 1.20 (m, 3H), 1.11 - 0.96 (m, 2H), 0.77 - 0.64 (m, 1H), 0.55 - 0.46 (m, 1H)	973.4
169	6-[5-[[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]methyl]-2-azabicyclo [2.2.1] heptan-2-yl]-N-[4-(3-chloro-4-cyano-phenoxy) cyclohexyl] pyridazine-3-carboxamide	δ = 8.56 - 8.44 (m, 1H), 7.86 (d, J = 8.4 Hz, 1H), 7.81 - 7.71 (m, 2H), 7.51 (s, 1H), 7.39 (d, J = 2.4 Hz, 1H), 7.17 - 7.08 (m, 2H), 6.99 - 6.60 (m, 3H), 4.78 - 4.42 (m, 2H), 4.24 - 4.09 (m, 2H), 4.07 - 3.96 (m, 1H), 3.94 - 3.81 (m, 4H), 3.78 - 3.67 (m, 2H), 3.63 - 3.57 (m, 2H), 3.52 - 3.47 (m, 1H), 3.05 - 2.92 (m, 2H), 2.85 (br s, 3H), 2.77 - 2.63 (m, 2H), 2.39 - 2.31 (m, 1H), 2.24 - 1.93 (m, 13H), 1.93 - 1.78 (m, 5H), 1.75 - 1.60 (m, 4H), 1.59 - 1.47 (m, 2H), 1.40 - 1.01 (m, 1H)	973.4

[00885] **Example 30:** Synthesis of 4-[4-[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]piperidine-1-carbonyl]-1-piperidyl]-

N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]benzamide (**Compound 159**)



[00886] Synthesis of **1** was reported in WO2021/231927, 2021, A1

[00887] Synthesis of **1A** was reported in WO2023/242598, 2023, A1

[00888] To a solution of 4-(4-ethoxycarbonyl-1-piperidyl)benzoic acid (300 mg, 1.08 mmol, 1.0 *eq*) and 4-(4-aminocyclohexoxy)-2-chloro-benzonitrile (310 mg, 1.08 mmol, 1.0 *eq*) in DMF (3 mL) was added HATU (617 mg, 1.62 mmol, 1.5 *eq*) and DIPEA (699 mg, 5.41 mmol, 942 µL, 5.0 *eq*). The mixture was stirred at 25 °C for 12 h. The residue was diluted with water (10 mL) and extracted with EtOAc (10 mL * 3). The combined organic layers were washed with brine (10 mL * 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, Petroleum ether/Ethyl acetate = 1/1). Compound ethyl 1-[4-[[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]carbamoyl]phenyl]piperidine-4-carboxylate (300 mg, 588 µmol, 54% yield) was obtained as a white solid.

[00889] **LC-MS:** MS (ESI^+): t_R = 0.617 min, m/z = 510.2 [$M + H^+$]

[00890] To a solution of ethyl 1-[4-[[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]carbamoyl]phenyl]piperidine-4-carboxylate (300 mg, 588 µmol, 1.0 *eq*) in THF (2 mL) was added $LiOH.H_2O$ (74 mg, 1.76 mmol, 3.0 *eq*) and MeOH (1 mL) and H_2O (1 mL). The mixture was stirred at 25 °C for 1 h. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. Compound 1-[4-[[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]carbamoyl]phenyl]piperidine-4-carboxylic acid (189 mg) was obtained as a white solid and directly used into the next step without further purification.

[00891] **LC-MS:** MS (ESI^+): t_R = 0.840 min, m/z = 482.2 [$M + H^+$]

[00892] To a solution of 1-[3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-1-(4-piperidyl)-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]ethanone (70 mg, 137 µmol, 1.0 *eq*) and 1-[4-[[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]carbamoyl]phenyl]piperidine-4-carboxylic acid (72 mg) in DMF (1 mL) was added HATU (78 mg, 206 µmol, 1.5 *eq*) and DIPEA (88 mg, 686 µmol, 119 µL,

5.0 *eq*). The mixture was stirred at 25 °C for 12 h. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150*25mm* 10um; mobile phase: [water (FA)-ACN]; gradient: 52%-82% B over 10 min). Compound 4-[4-[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]piperidine-1-carbonyl]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]benzamide (45.93 mg, 45.90 μmol, 33% yield over two steps) was obtained as a white solid.

[00893] **^{1}H NMR** (400 MHz, DMSO-d_6) δ = 8.13 - 7.92 (m, 1H), 7.90 - 7.82 (m, 1H), 7.79 - 7.68 (m, 3H), 7.49 (s, 1H), 7.43 - 7.35 (m, 1H), 7.18 - 7.06 (m, 2H), 6.99 - 6.90 (m, 2H), 6.85 - 6.58 (m, 2H), 4.61 - 4.43 (m, 2H), 4.41 - 4.28 (m, 1H), 4.23 - 4.09 (m, 3H), 3.92 - 3.85 (m, 5H), 3.81 - 3.68 (m, 3H), 3.62 - 3.54 (m, 3H), 3.28 - 3.18 (m, 1H), 2.95 - 2.82 (m, 6H), 2.79 - 2.66 (m, 2H), 2.14 - 2.03 (m, 4H), 1.99 - 1.85 (m, 8H), 1.74 - 1.63 (m, 4H), 1.56 - 1.41 (m, 4H).

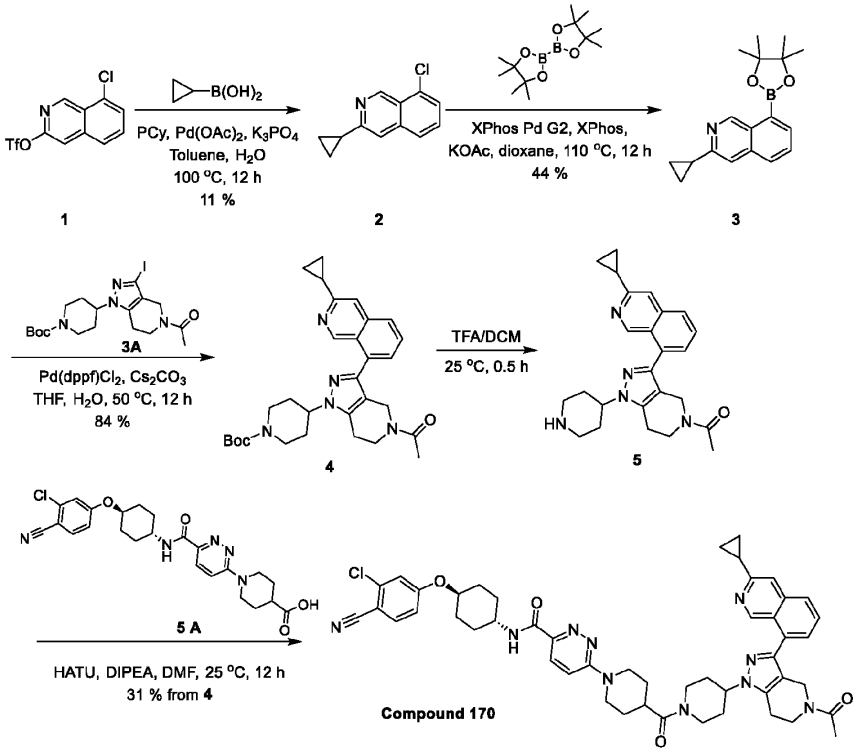
[00894] **LC-MS:** MS (ESI$^+$): t_R = 2.514 min, m/z = 973.4 [M + H$^+$]

[00895] The compounds below were prepared in a similar manner as described in Example 30.

Compound	Name	^{1}H NMR (DMSO-d_6)	LC-MS [M + H$^+$]
160	4-[4-[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]piperidine-1-carbonyl]-1-piperidyl]-N-[4-(4-cyano-3-methoxy-phenoxy)cyclohexyl]benzamide	δ = 8.01 - 7.90 (m, 1H), 7.83 - 7.68 (m, 3H), 7.64 - 7.56 (m, 1H), 7.49 (s, 1H), 7.14 - 7.05 (m, 1H), 7.02 - 6.88 (m, 2H), 6.87 - 6.59 (m, 4H), 4.61 - 4.43 (m, 2H), 4.40 - 4.29 (m, 1H), 4.23 - 4.08 (m, 3H), 3.95 - 3.45 (m, 14H), 3.28 - 3.15 (m, 1H), 3.01- 2.62 (m, 9H), 2.16 - 2.05 (m, 4H), 2.00 - 1.85 (m, 8H), 1.72 - 1.66 (m, 3H), 1.56 - 1.42 (m, 4H)	969.4
162	4-[4-[[4-[5-acetyl-3-[3-(1-methylpyrazol-4-yl)-8-isoquinolyl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]methyl]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]benzamide	($CDCl_3$) δ = 9.81 - 9.68 (m, 1H), 8.45 - 8.35 (m, 1H), 8.10 - 7.98 (m, 2H), 7.85 - 7.74 (m, 2H), 7.73 - 7.62 (m, 3H), 7.58 - 7.43 (m, 2H), 7.01 - 6.95 (m, 1H), 6.93 - 6.78 (m, 3H), 6.00 - 5.84 (m, 1H), 4.72 - 4.61 (m, 1H), 4.52 - 4.45 (m, 1H), 4.32 - 4.22 (m, 1H), 4.11 - 3.96 (m, 6H), 3.88 - 3.73 (m, 3H), 3.28 - 3.01 (m, 3H), 2.96 - 2.75 (m, 4H), 2.49 (s, 2H), 2.34 - 2.24 (m, 3H), 2.23 - 2.13 (m, 6H), 2.11 - 1.96 (m, 4H), 1.89 (d, *J* = 12.8 Hz, 2H), 1.70 - 1.60 (m, 2H), 1.46 - 1.24 (m, 4H)	905.7
163	4-[4-[[4-[5-acetyl-3-[3-(1-methylpyrazol-4-yl)-8-isoquinolyl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]methyl]-1-piperidyl]-N-[4-(4-cyano-3-methoxy-phenoxy)cyclohexyl]benzamide	δ = 9.85 (s, 1H), 8.37 (s, 1H), 8.23 - 8.11 (m, 2H), 7.95 - 7.85 (m, 2H), 7.82 - 7.65 (m, 3H), 7.63 - 7.42 (m, 2H), 6.98 - 6.85 (m, 2H), 6.76 - 6.64 (m, 2H), 4.62 - 4.41 (m, 3H), 4.22 - 4.12 (m, 1H), 3.92 - 3.78 (m, 10H), 3.12 - 2.87 (m, 4H), 2.85 - 2.71 (m, 4H), 2.63 - 2.55 (m, 2H), 2.23 - 2.08 (m, 10H), 2.01 - 1.70 (m, 8H), 1.60 - 1.40 (m, 4H), 1.30 - 1.05 (m, 2H).	901.4

Compound	Name	^{1}H NMR (DMSO-d_6)	LC-MS [M + H$^+$]
164	4-[4-[4-[5-acetyl-3-[3-(1-methylpyrazol-4-yl)-8-isoquinolyl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]piperidine-1-carbonyl]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]benzamide	($CDCl_3$) δ = 9.79 - 9.56 (m, 1H), 8.10 - 8.00 (m, 2H), 7.88 - 7.76 (m, 2H), 7.75 - 7.62 (m, 3H), 7.59 - 7.54 (m, 1H), 7.53 - 7.44 (m, 1H), 7.04 - 6.96 (m, 1H), 6.92 - 6.81 (m, 3H), 5.94 - 5.78 (m, 1H), 4.90 - 4.77 (m, 1H), 4.74 - 4.58 (m, 1H), 4.54 - 4.45 (m, 1H), 4.35 - 4.25 (m, 2H), 4.23 - 4.10 (m, 1H), 4.09 - 3.97 (m, 5H), 3.87 (d, *J* = 8.8 Hz, 3H), 3.38 - 3.21 (m, 1H), 2.95 - 2.69 (m, 6H), 2.54 - 2.33 (m, 1H), 2.29 - 2.12 (m, 8H), 2.08 (s, 3H), 2.01 - 1.91 (m, 3H), 1.72 - 1.63 (m, 2H), 1.48 - 1.34 (m, 2H)	919.4

[00896] **Example 31:** Synthesis of 6-[4-[4-[5-acetyl-3-(3-cyclopropyl-8-isoquinolyl)-6,7-dihydro-4H-pyrazolo[4,3-c] pyridin-1-yl] piperidine1-carbonyl]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy) cyclohexyl] pyridazine-3-carboxamide **(Compound 170)**



[00897] Synthesis of **1** was reported in WO2023/220741 A1

[00898] Synthesis of **5A** was reported in WO2022/204184 A1.

[00899] To a solution of (8-chloro-3-isoquinolyl) trifluoromethanesulfonate (4.10 g, 13.2 mmol, 1.0 eq) and cyclopropylboronicacid (1.69 g, 19.7 mmol, 1.5 eq) in toluene (60 mL) and H_2O (6 mL) and was added

PCy_3 (368 mg, 1.32 mmol, 426 μL, 0.1 eq), $Pd(OAc)_2$ (147 mg, 657 μmol, 0.05 eq) and K_3PO_4 (9.77 g, 46.5 mmol, 3.5 eq). The mixture was stirred at 100 °C for 12 h under N_2. The reaction mixture was diluted with water (10 mL) and extracted with EtOAC (10 mL × 2). The combined organic layers were washed with brine (15 mL × 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. Then the residue was purified by prep-TLC (SiO_2, Petroleum ether/Ethyl acetate = 5/1). Compound 8-chloro-3-cyclopropyl-isoquinoline (300 mg, 1.47 mmol, 11% yield) was obtained as a white solid.

[00900] **LC-MS:** MS (ESI^+): t_R = 0.613 min, m/z = 204.1 [M + H^+]

[00901] To a solution of 8-chloro-3-cyclopropyl-isoquinoline (300 mg, 1.47 mmol, 1.0 eq) and BPD (448 mg, 1.77 mmol, 1.2 eq) in dioxane (6 mL) was added XPhos (70 mg, 147 μmol, 0.1 eq), XPhos Pd G2 (57 mg, 73 μmol, 0.05 eq) and KOAc (433 mg, 4.42 mmol, 3.0 eq). The mixture was stirred at 110 °C for 12 h under N_2. The reaction mixture was diluted with water (50 mL) and extracted with EtOAc (50 mL × 2). The combined organic layers were washed with brine (50 mL × 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. Then the residue was purified by prep-TLC (SiO_2, Petroleum ether/Ethyl acetate = 4/1). Compound 3-cyclopropyl-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) isoquinoline (192 mg, 650 μmol, 44% yield) was obtained as a white solid.

[00902] **LC-MS:** MS (ESI^+): t_R = 0.767 min, m/z = 296.2 [M + H^+]

[00903] To a solution of 3-cyclopropyl-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) isoquinoline (142 mg, 481 μmol, 1.0 eq) and tert-butyl 4-(5-acetyl-3-iodo-6,7-dihydro-4H-pyrazolo[4,3-c] pyridin-1-yl) piperidine-1-carboxylate (228 mg, 481 μmol, 1.0 eq) in THF (8 mL) and H_2O (4 mL) was added $Pd(dppf)Cl_2$ (35 mg, 48 μmol, 0.1 eq) and Cs_2CO_3 (470 mg, 1.44 mmol, 3.0 eq). The mixture was stirred at 50 °C for 12 h. The mixture was concentrated to give a residue. Then the residue was purified by prep-TLC (SiO_2, Petroleum ether/Ethyl acetate = 4/1). Compound tert-butyl 4-[5-acetyl-3-(3-cyclopropyl-8-isoquinolyl)-6,7-dihydro-4H-pyrazolo[4,3-c] pyridin-1- yl] piperidine-1-carboxylate (210 mg, 407 μmol, 84% yield) was obtained as a yellow solid.

[00904] **LC-MS:** MS (ESI^+): t_R = 0.800 min, m/z = 516.3 [M + H^+]

[00905] To a solution of tert-butyl 4-[5-acetyl-3-(3-cyclopropyl-8-isoquinolyl)-6,7-dihydro-4H-pyrazolo[4,3-c] pyridin-1-yl] piperidine-1-carboxylate (70 mg, 135 μmol, 1.0 *eq*) in DCM (2 mL) was added TFA (1.54 g, 13.5 mmol, 1 mL, 99.2 *eq*). The mixture was stirred at 25 °C for 0.5 h. The mixture was concentrated to give a residue. Compound 1-[3-(3-cyclopropyl-8-isoquinolyl)-1-(4-piperidyl)-6,7-dihydro-4H-pyrazolo[4,3-c] pyridin-5-yl] ethanone (56 mg) was obtained as a yellow oil and directly used into the next step without further purification.

[00906] **LC-MS:** MS (ESI^+): t_R = 0.273 min, m/z = 416.3 [M + H^+]

[00907] To a solution of 1-[3-(3-cyclopropyl-8-isoquinolyl)-1-(4-piperidyl)-6,7-dihydro-4H-pyrazolo[4,3-c] pyridin-5- yl]ethanone (56 mg) and 1-[6-[[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]carbamoyl]pyridazin-3- yl]piperidine-4-carboxylic acid (69 mg, 142 μmol, 1.1 eq) in DMF (2 mL) was added DIPEA (52 mg, 404 μmol, 70 μL, 3.0 eq) and HATU (76 mg, 202 μmol, 1.5 eq).

The mixture was stirred at 25 °C for 12 h. The mixture was filtered and concentrated to give a residue, the residue was purified by prep-HPLC (column: Phenomenex luna C18 150*25mm* 10um; mobile phase: [water (FA)-ACN]; gradient: 33%-63% B over 10 min). Compound 6-[4-[4-[5-acetyl-3-(3-cyclopropyl-8-isoquinolyl)-6,7-dihydro-4H-pyrazolo[4,3-c] pyridin-1-yl] piperidine1-carbonyl]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy) cyclohexyl] pyridazine-3-carboxamide (38.44 mg, 31% yield over two steps) was obtained as a white solid.

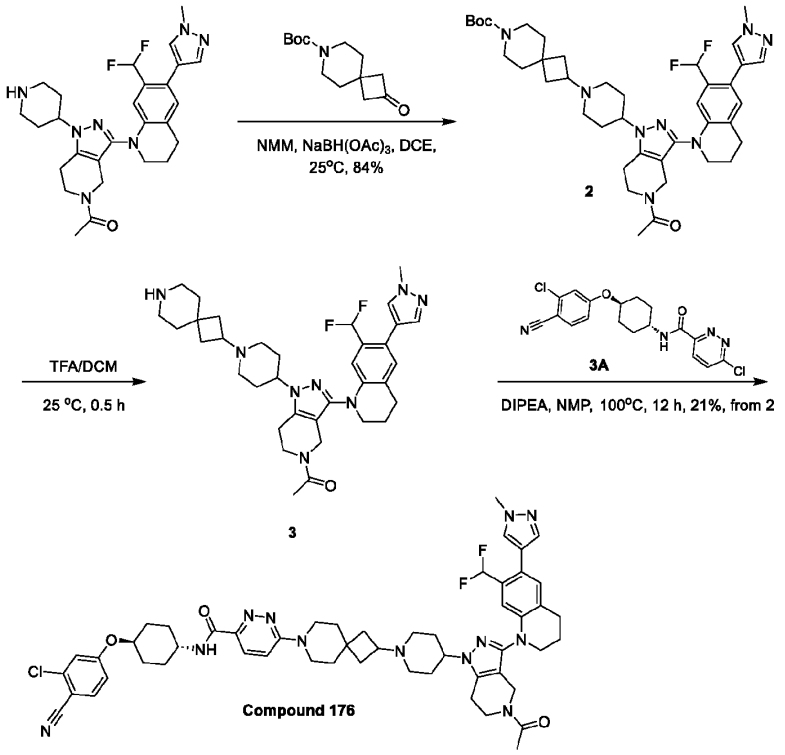
[00908] **^{1}H NMR** (400 MHz, DMSO-d_6) δ = 9.62 (s, 1H), 8.63 - 8.58 (m, 1H), 7.91 - 7.79 (m, 5H), 7.82 - 7.79 (m, 1H), 7.38 - 7.33 (m, 2H), 7.14 - 7.13 (m, 1H), 4.65 - 4.57 (m, 7H), 4.24 - 4.22 (s, 1H), 3.86 - 3.81 (m, 3H), 3.38 - 3.27 (m, 2H), 3.17 - 3.06 (m, 3H), 2.97 - 2.93 (s, 1H), 2.88 - 2.71 (m, 2H), 2.63 - 2.54 (m, 1H), 2.42 - 2.37 (m, 3H), 2.23 - 2.18 (m, 2H), 2.01 - 1.90 (s, 1H), 1.87 - 1.76 (m, 3H), 1.66 - 1.58 (m, 2H), 1.56 - 1.29 (m, 7H), 1.10 - 0.95 (m, 4H).

[00909] **LC-MS:** MS (ESI$^+$): t_R = 2.397 min, m/z = 881.4 [M + H$^+$]

[00910] The compounds below were prepared in a similar manner as described in Example 31.

Compound	Name	^{1}H NMR (DMSO-d_6)	LC-MS [M + H$^+$]
171	6-[4-[4-[5-acetyl-3-[6-cyclopropyl-7-(difluoromethyl)-1-naphthyl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]piperidine-1-carbonyl]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	δ = 8.81 - 8.70 (m, 1H), 8.65 - 8.51 (m, 1H), 7.96 - 7.89 (m, 1H), 7.88 - 7.78 (m, 2H), 7.75 - 7.69 (m, 1H), 7.67 - 7.60 (m, 1H), 7.60 - 7.28 (m, 4H), 7.18 - 7.07 (m, 1H), 4.60 - 4.40 (m, 7H), 4.31 - 4.15 (m, 1H), 3.96 - 3.74 (m, 3H), 3.32 - 3.24 (m, 1H), 3.20 - 3.07 (m, 3H), 3.01 - 2.76 (m, 3H), 2.25 - 2.17 (m, 1H), 2.15 - 1.96 (m, 8H), 1.94 - 1.82 (m, 3H), 1.81 - 1.72 (m, 2H), 1.70 - 1.45 (m, 6H), 1.09 - 0.97 (m, 2H), 0.89 - 0.79 (m, 2H).	930.4

[00911] **Example 32:** Synthesis of 6-[2-[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]-7-azaspiro[3.5]nonan-7-yl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide **(Compound 176)**



[00912] To a solution of 1-[3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-1-(4-piperidyl)-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]ethanone (100 mg, 196.24 μmol, 1.0 eq) in DCE (3 mL) was added NMM (158 mg, 1.57 mmol, 172.60 μL, 8.0 eq) and tert-butyl 2-oxo-7-azaspiro[3.5]nonane-7-carboxylate (93 mg, 392.47 μmol, 2.0 eq). The mixture was stirred at 25 °C for 0.5 h. $NaBH(OAc)_3$ (124 mg, 588.71 μmol, 3.0 eq) was added and the mixture was stirred at 25 °C for 12 h. The mixture was poured into water (30 mL). The aqueous phase was extracted with dichloromethane (15 mL × 3). The combined organic phase was washed with brine (50 mL × 3), dried with anhydrous sodium sulfate, filtered and concentrated in vacuum. The residue was purified by prep-TLC (SiO_2, Dichloromethane: Methanol = 10: 1). Compound tert-butyl 2-[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]-7-azaspiro[3.5]nonane-7-carboxylate (121 mg, 165.10 μmol, 84% yield) was obtained as a yellow solid.

[00913] **1H NMR** (400 MHz, CDCl3): δ = 7.54 (d, J = 6.0 Hz, 1H), 7.41 (d, J = 7.2 Hz, 1H), 7.06-6.98 (m, 1H), 6.85 (s, 1H), 6.69-6.36 (m, 1H), 4.09-4.25 (m, 2H), 3.97-3.88 (m, 5H), 3.77-3.65 (m, 3H), 3.37 (s, 2H), 3.32-3.24 (m, 2H), 3.01 (d, J = 11.2 Hz, 2H), 2.91-2.78 (m, 3H), 2.76-2.68 (m, 2H), 2.29-2.18 (m, 2H), 2.16 (s, 1H), 2.10-1.98 (m, 6H), 1.94-1.82 (m, 4H), 1.68-1.62 (m, 2H), 1.56 (s, 2H), 1.49 (d, J = 5.2 Hz, 2H), 1.45 (s, 9H)

[00914] **LC-MS:** MS (ESI^+): t_R = 0.486 min, m/z = 733.5 [$M + H^+$]

[00915] To a solution of tert-butyl 2-[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]-7-azaspiro[3.5]nonane-

7-carboxylate (121 mg, 165.10 μmol, 1.0 eq) in dichloromethane (3 mL) was added trifluoroacetic acid (4.61 g, 40.39 mmol, 3 mL, 244.63 eq). The mixture was stirred at 25 °C for 0.5 h. The reaction mixture was concentrated under reduced pressure to give the product. Compound 1-[1-[1-(7-azaspiro[3.5]nonan-2-yl)-4-piperidyl]-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]ethanone (104 mg) was obtained as a yellow oil and directly used in the next step without further purification.

[00916] **LC-MS:** MS (ESI^+): t_R = 0.394 min, m/z = 633.4 [M + H^+]

[00917] To a solution of 1-[1-[1-(7-azaspiro[3.5]nonan-2-yl)-4-piperidyl]-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]ethanone (104 mg) in N-methylpyrrolidone (5 mL) was added DIPEA (424 mg, 3.29 mmol, 572.53 μL, 20.0 eq) and 6-chloro-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide (64 mg, 164.35 μmol, 1.0 eq). The mixture was stirred at 100 °C for 12 h under N_2. The mixture was poured into water (50 mL). The aqueous phase was extracted with ethyl acetate (20 mL × 3). The combined organic phase was washed with brine (100 mL × 3), dried with anhydrous sodium sulfate, filtered and concentrated in vacuum. The residue was purified by prep-TLC (SiO_2, Dichloromethane: Methanol = 10: 1). The residue was purified by prep-HPLC (column: Phenomenex luna C18 150*25mm* 10um; mobile phase: [water (FA)-ACN]; gradient:28%-58% B over 10 min) to give desired compound. Then it was lyophilized. Compound 6-[2-[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]-7-azaspiro[3.5]nonan-7-yl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide (34 mg, 34.94 μmol, 21.26% yield) was obtained as a white solid.

[00918] **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.96 (d, J = 9.6 Hz, 1H), 7.87 (d, J = 8.2 Hz, 1H), 7.59-7.52 (m, 2H), 7.41 (d, J = 6.4 Hz, 1H), 7.07-6.95 (m, 3H), 6.93-6.83 (m, 2H), 6.70-6.36 (m, 1H), 4.37-4.29 (m, 1H), 4.26 (s, 1H), 4.12 (s, 1H), 4.09-4.02 (m, 1H), 3.96 (s, 3H), 3.90 (t, J = 5.6 Hz, 1H), 3.82-3.73 (m, 3H), 3.73-3.59 (m, 4H), 3.16-2.97 (m, 2H), 2.92-2.71 (m, 5H), 2.35-2.21 (m, 9H), 2.10-2.05 (m, 4H), 2.03-1.91 (m, 3H), 1.86-1.71 (m, 10H), 1.51-1.42 (m, 2H)

[00919] **LC-MS:** MS (ESI^+): t_R = 2.526 min, m/z = 987.5 [M + H^+]

[00920] The compounds below were prepared in a similar manner as described in Example 32.

Compound	Name	^{1}H NMR ($CDCl_3$)	LC-MS [M + H^+]
185	6-[7-[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]-2-azaspiro[3.5]nonan-2-yl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	δ = 7.96 (d, J = 9.2 Hz, 1 H), 7.87 (d, J = 8.0 Hz, 1 H), 7.58 - 7.50 (m, 2 H), 7.42 - 7.38 (m, 1 H), 7.06 - 6.97 (m, 2 H), 6.88 - 6.82 (m, 2 H), 6.70 - 6.31 (m, 2 H), 4.37 - 4.28 (m, 1 H), 4.23 (s, 1 H), 4.11 (s, 1 H), 4.08 - 4.00 (m, 1 H), 3.97 - 3.93 (m, 3 H), 3.92 - 3.83 (m, 6 H), 3.77 - 3.65 (m, 3 H), 3.13 - 3.03 (m, 2 H), 2.90 - 2.71 (m, 4 H), 2.40 - 2.14 (m, 10 H), 2.11 - 2.02 (m,	987.6

Compound	Name	^{1}H NMR ($CDCl_3$)	LC-MS [M + H^+]
		6 H), 1.97 - 1.84 (m, 4 H), 1.73 - 1.63 (m, 3 H), 1.53 - 1.29 (m, 5 H)	
186	rac-6-(4-(5-acetyl-3-(7-(difluoromethyl)-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroquinolin-1(2H)-yl)-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridin-1-yl)-[1,4'-bipiperidin]-1'-yl)-N-((1r,4r)-4-(3-chloro-4-cyanophenoxy)cyclohexyl)pyridazine-3-carboxamide	(DMSO-d_6): δ = 8.59 (br d, *J* = 8.4 Hz, 1H), 7.90 - 7.78 (m, 2H), 7.75 (s, 1H), 7.49 (s, 1H), 7.42 - 7.29 (m, 2H), 7.17 - 7.07 (m, 2H), 6.96 - 6.62 (m, 2H), 4.62 - 4.42 (m, 3H), 4.16 (br s, 1H), 4.11 (s, 1H), 4.05 - 3.96 (m, 1H), 3.86 (s, 3H), 3.73 (br d, *J* = 6.0 Hz, 1H), 3.69 (br d, *J* = 5.2Hz, 1H), 3.61 - 3.55 (m, 2H), 3.05 - 2.92 (m, 4H), 2.89 - 2.78 (m, 4H), 2.74 - 2.65 (m, 2H), 2.36 - 2.26 (m, 2H), 2.14 - 2.06 (m, 4H), 1.98 - 1.82 (m, 10H), 1.75 - 1.57 (m, 3H), 1.56 - 1.43 (m, 4H)	947.4
196	6-[4-[9-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-3-azaspiro[5.5]undecan-3-yl]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	δ = 8.02-7.99 (d, *J*=9.6 Hz, 1 H), 7.90-7.88 (d, *J*=8.0 Hz, 1 H), 7.59-7.54 (m, 2 H), 7.42-7.41 (d, *J*=6.8 Hz, 1 H), 7.06-6.99 (m, 3 H), 6.90-6.80 (m, 2 H), 6.55-6.41 (m, 1 H), 4.61-4.58 (m, 2 H), 4.27-4.25 (m, 1H), 4.25-4.23 (m, 2H), 4.14-4.10 (m, 1 H), 3.97 (s, 3H), 3.91-3.74 (m, 2 H), 3.72-3.71 (m, 3 H), 3.07-2.89 (m, 2H), 2.89-2.85 (m, 2 H), 2.80-2.75 (m, 1 H), 2.74-2.69 (m, 5 H), 2.25-2.20 (m, 6 H), 2.15-2.05 (m, 7 H), 1.95-1.75 (m, 8 H), 1.65-1.63 (m, 2 H), 1.62-1.41 (m, 5H), 1.27-1.25 (m, 2 H).	1015.6
197	6-[3-[9-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7- dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-3-azaspiro[5.5]undecan-3-yl]azetidin-1-yl]-N-[4-(3-chloro-4-cyanophenoxy)cyclohexyl]pyridazine-3-carboxamide	δ = 7.98 (d, J = 9.2 Hz, 1H), 7.88 (d, J = 8.4 Hz, 1H), 7.59 - 7.51 (m, 2H), 7.41 (d, J = 6.8 Hz, 1H), 7.07 - 6.97 (m, 2H), 6.93 - 6.82 (m, 2H), 6.68 - 6.36 (m, 2H), 4.40 - 4.19 (m, 4H), 4.17 - 4.00 (m, 4H), 3.95 (s, 3H), 3.92 - 3.82 (m, 2H), 3.80 - 3.64 (m, 3H), 3.54 - 3.35 (m, 1H), 2.95 - 2.84 (m, 2H), 2.83 - 2.68 (m, 2H), 2.41 (s, 4H), 2.27 - 2.14 (m, 6H), 2.14 - 1.96 (m, 6H), 1.93 - 1.75 (m, 6H), 1.56 - 1.43 (m, 4H), 1.42 -1.05 (m, 3H)	987.6
206	6-[3-[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]azetidin-1-yl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	(CD_3OD) δ = 7.93 (*d*, *J* = 9.2 Hz, 1H), 7.69 (d, *J* = 8.8 Hz, 1H), 7.65 - 7.61 (m, 1H), 7.53 - 7.48 (m, 1H), 7.20 (d, *J* = 2.4 Hz, 1H), 7.13 - 7.07 (m, 1H), 7.06 - 7.02 (m, 1H), 6.91 (d, *J* = 9.4 Hz, 1H), 6.74 (s, 1H), 6.71 - 6.40 (m, 1H), 4.66 - 4.44 (m, 2H), 4.36 - 4.27 (m, 2H), 4.26 - 4.13 (m, 3H), 4.13 - 4.04 (m, 2H), 4.01 - 3.86 (m, 5H), 3.82 (br t, *J* = 5.6 Hz, 1H), 3.72 - 3.60 (m, 2H), 3.57 - 3.45 (m, 1H), 3.16 -	919.4

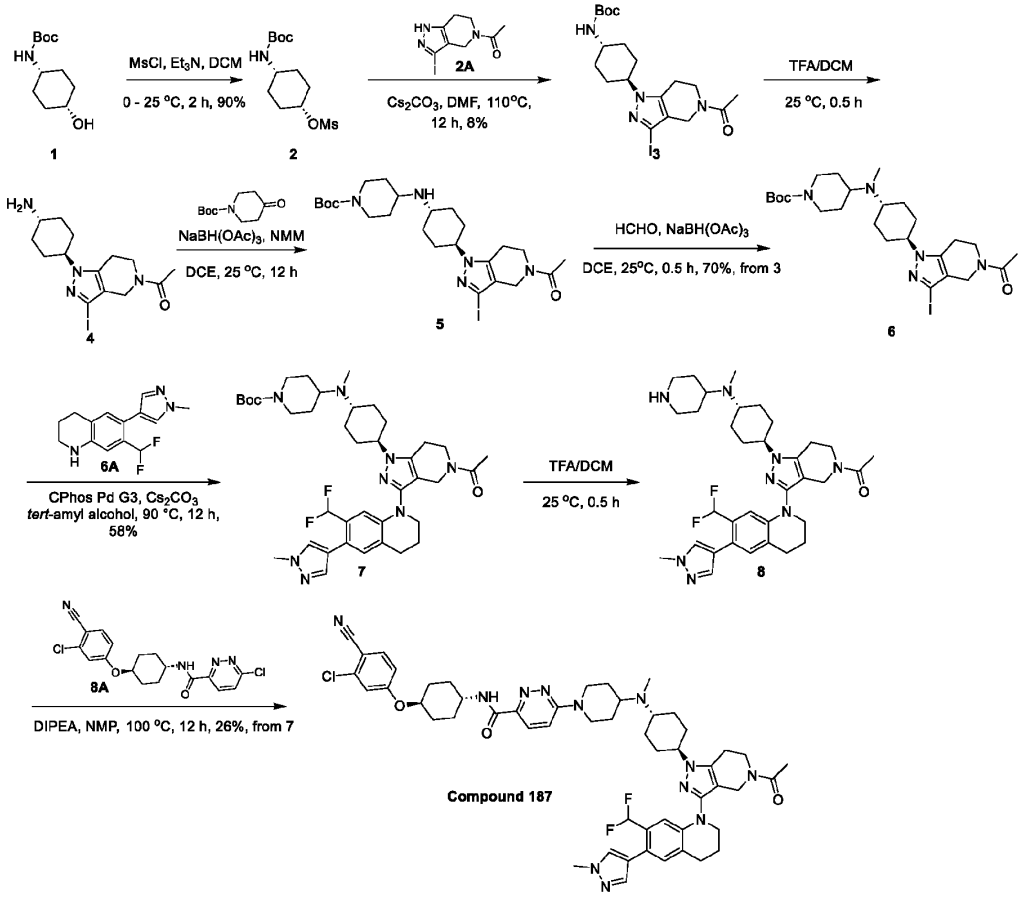
Compound	Name	^{1}H NMR ($CDCl_3$)	LC-MS [M + H^+]
		3.01 (m, 2H), 2.97 - 2.80 (m, 4H), 2.33 - 2.14 (m, 8H), 2.12 - 1.98 (m, 7H), 1.73 - 1.53 (m, 4H)	
238	6-[4-[7-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-2-azaspiro[3.5]nonan-2-yl]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	δ =8.02 - 7.94 (m, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.61 - 7.52 (m, 2H), 7.44 - 7.36 (m, 1H), 7.07 - 6.94 (m, 3H), 6.92 - 6.83 (m, 2H), 6.68 - 6.37 (m, 1H), 4.82 - 4.68 (m, 1H), 4.46 - 4.23 (m, 4H), 4.15 - 4.02 (m, 2H), 3.99 - 3.86 (m, 5H), 3.74 - 3.66 (m, 3H), 3.30 - 3.16 (m, 4H), 2.93 - 2.83 (m, 2H), 2.80 - 2.68 (m, 2H), 2.66 - 2.47 (m, 1H), 2.22 - 2.16 (m, 4H), 2.10 - 2.04 (m, 4H), 2.01 - 1.95 (m, 2H), 1.92 - 1.87 (m, 4H), 1.71 - 1.62 (m, 8H), 1.52 - 1.44 (m, 4H)	987.7
239	6-[4-[2-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-7-azaspiro[3.5]nonan-7-yl]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	δ = 8.48 (s, 1H), 7.99 (d, J = 9.6 Hz, 1H), 7.86 (d, J = 8.3 Hz, 1H), 7.67-7.49 (m, 2H), 7.41 (d, J = 6.4 Hz, 1H), 7.07-6.90 (m, 4H), 6.86 (dd, J = 8.8, 2.5 Hz, 1H), 6.69-6.35 (m, 1H), 4.70-4.48 (m, 3H), 4.43-4.30 (m, 1H), 4.25 (s, 1H), 4.13-4.03 (m, 2H), 3.95 (d, J = 2.4 Hz, 3H), 3.88 (t, J = 5.6 Hz, 1H), 3.83-3.55 (m, 3H), 3.05 (t, J = 12.0 Hz, 2H), 2.94-2.83 (m, 3H), 2.80-2.67 (m, 4H), 2.63 (s, 2H), 2.51-2.43 (m, 2H), 2.33 (t, J = 10.1 Hz, 3H), 2.15 (s, 3H), 2.12-2.04 (m, 7H), 1.86 (d, J = 4.9 Hz, 4H), 1.77-1.62 (m, 4H), 1.52-1.40 (m, 2H)	987.7
262	6-[3-[8-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-2-azaspiro[4.5]decan-2-yl]azetidin-1-yl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	(DMSO-d_6) δ = 8.56 (d, J = 8.4 Hz, 1H), 8.16 - 8.13 (m, 1H), 7.94 - 7.79 (m, 2H), 7.76 (s, 1H), 7.55 - 7.48 (m, 1H), 7.43 - 7.37 (m, 1H), 7.17 - 7.09 (m, 2H), 6.96 - 6.62 (m, 3H), 4.59 - 4.49 (m, 1H), 4.25 - 4.13 (m, 4H), 4.07 - 3.96 (m, 3H), 3.91 - 3.81 (m, 4H), 3.78 - 3.66 (m, 2H), 3.63 - 3.49 (m, 3H), 2.89 - 2.71 (m, 4H), 2.58 (br s, 2H), 2.16 - 2.06 (m, 4H), 2.02 - 1.86 (m, 6H), 1.86 - 1.70 (m, 6H), 1.69 - 1.57 (m, 4H), 1.56 - 1.45 (m, 4H)	973.6
263	6-[3-[8-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-2-azaspiro[4.5]decan-2-yl]azetidin-1-yl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	(DMSO-d_6) δ = 8.55 (d, J = 8.2 Hz, 1H), 8.15 (s, 1H), 7.90 - 7.80 (m, 2H), 7.76 (s, 1H), 7.50 (s, 1H), 7.39 (d, J = 2.4 Hz, 1H), 7.18 - 7.06 (m, 2H), 6.96 - 6.63 (m, 3H), 4.60 - 4.48 (m, 1H), 4.24 - 4.11 (m, 4H), 4.06 - 3.94 (m, 3H), 3.91 - 3.82 (m, 4H), 3.77 - 3.66 (m, 2H), 3.63 - 3.54 (m, 2H), 3.48 (br d, J = 4.8 Hz, 1H), 2.89 - 2.71 (m,	973.6

Compound	Name	^{1}H NMR ($CDCl_3$)	LC-MS [M + H^+]
		4H), 2.64 - 2.56 (m, 2H), 2.40 - 2.30 (m, 2H), 2.16 - 2.05 (m, 4H), 2.01 - 1.85 (m, 7H), 1.83 - 1.76 (m, 2H), 1.74 - 1.58 (m, 6H), 1.57 - 1.46 (m, 4H).	
264	6-[8-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-2-azaspiro[4.5]decan-2-yl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	(DMSO-d_6) δ = 8.52 - 8.43 (m, 1H), 7.86 (d, J = 8.8 Hz, 1H), 7.81 (d, J = 9.4 Hz, 1H), 7.76 (s, 1H), 7.51 (s, 1H), 7.39 (d, J = 2.4 Hz, 1H), 7.18 - 7.09 (m, 2H), 7.00 (br d, J = 9.4 Hz, 1H), 6.95 - 6.63 (m, 2H), 4.60 - 4.50 (m, 1H), 4.23 - 4.06 (m, 3H), 3.92 - 3.81 (m, 4H), 3.79 - 3.68 (m, 2H), 3.65 - 3.56 (m, 4H), 3.53 (br d, J = 5.0 Hz, 1H), 2.92 - 2.72 (m, 4H), 2.17 - 2.05 (m, 4H), 2.03 - 1.83 (m, 12H), 1.77 (br d, J = 11.0 Hz, 2H), 1.67 - 1.45 (m, 6H).	918.7
265	6-[8-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-2-azaspiro[4.5]decan-2-yl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	(DMSO-d_6) δ = 8.52 (d, J = 8.0 Hz, 1H), 7.83 (m, 2H), 7.75 (s, 1H), 7.50 (s, 1H), 7.39 (d, J = 2.4 Hz, 1H), 7.16 - 7.08 (m, 2H), 6.93 (d, J = 9.2 Hz, 1H), 6.89 - 6.60 (m, 2H), 4.59 - 4.47 (m, 1H), 4.21 - 4.03 (m, 3H), 3.87 (s, 4H), 3.77 - 3.67 (m, 2H), 3.66 - 3.55 (m, 4H), 2.89 - 2.72 (m, 4H), 2.13 - 2.06 (m, 4H), 2.04 - 1.95 (m, 7H), 1.95 - 1.81 (m, 5H), 1.80 - 1.71 (m, 2H), 1.70 - 1.59 (m, 4H), 1.57 - 1.47 (m, 2H), 1.23 (s, 1H).	918.8
267	6-[9-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-2-azaspiro[5.5]undecan-2-yl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	δ = 7.95 (d, J = 9.6 Hz, 1H), 7.85 (d, J = 8.0 Hz, 1H), 7.62 - 7.50 (m, 2H), 7.40 (d, J = 6.4 Hz, 1H), 7.05 - 6.94 (m, 3H), 6.92 - 6.83 (m, 2H), 6.69 - 6.33 (m, 1H), 4.32 (t, J = 9.6 Hz, 1H), 4.26 (s, 1H), 4.13 - 4.03 (m, 2H), 3.95 (d, J = 2.4 Hz, 3H), 3.92 - 3.85 (m, 2H), 3.78 - 3.66 (m, 5H), 3.61 (br d, J = 7.6 Hz, 2H), 2.86 (td, J = 6.0, 12.0 Hz, 2H), 2.80 - 2.68 (m, 2H), 2.25 - 2.01 (m, 12H), 1.81 - 1.62 (m, 9H), 1.50 - 1.32 (m, 4H)	932.6
268	6-[3-[9-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4Hpyrazolo[4,3-c]pyridin-1-yl]-2-azaspiro[5.5]undecan-2-yl]azetidin-1-yl]-N-[4-(3-chloro-4-cyanophenoxy)cyclohexyl]pyridazine-3-carboxamide	δ =8.52 (d, J = 8.0 Hz, 1H), 7.86 (d, J = 8.8 Hz, 1H), 7.79 - 7.77 (m, 2H), 7.53 (s, 1H), 7.39 (s, 1H), 7.15 – 7.12 (m, 2H), 6.92 – 6.80 (m, 3H), 4.55-4.53 (m, 1H), 4.25 – 4.20 (m, 4H), 4.16-4.13 (m, 1H), 3.90 – 3.87 (m, 6H), 3.74 – 3.70 (m, 2H), 3.61 – 3.60 (m, 2H), 2.86 – 2.85 (m, 4H), 2.75-2.70 (m, 1H), 2.08 – 2.00 (m, 4H), 1.90 – 1.88 (m, 4H), 1.58 – 1.57 (m,	987.3

Compound	Name	^{1}H NMR ($CDCl_3$)	LC-MS [M + H^+]
		6H), 1.55 – 1.52 (m, 10H), 1.25-1.23 (m, 5H).	
269	6-[3-[9-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4Hpyrazolo[4,3-c]pyridin-1-yl]-2-azaspiro[5.5]undecan-2-yl]azetidin-1-yl]-N-[4-(3-chloro-4-cyanophenoxy)cyclohexyl]pyridazine-3-carboxamide	δ = 8.55 (d, J = 8.0Hz, 1H), 7.92 - 7.83 (m, 2H), 7.75 (s, 1H), 7.50 (s, 1H), 7.40 (d, J = 2.4 Hz, 1H), 7.20 - 7.05 (m, 2H), 6.95 - 6.62 (m, 3H), 4.62 - 4.48 (m, 1H), 4.44 - 4.26 (m, 4H), 4.20 - 4.10 (m, 1H), 4.03 - 3.90 (m, 6H), 3.85 - 3.70 (m, 2H), 3.64 - 3.52 (m, 2H), 3.38 (s, 1H), 3.32 (s, 1H), 3.32 - 3.27 (m, 1H), 2.84 (s, 3H), 2.30 - 2.23 (m, 1H), 2.17 - 1.86 (m, 14H), 1.77 - 1.60 (m, 6H), 1.56 - 1.45 (m, 5H), 1.32 - 1.18 (m, 2H)	987.7
296	6-[7-[4-[5-acetyl-3-[7-methyl-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c] pyridin-1-yl]-1-piperidyl]-2-azaspiro [3.5] nonan-2-yl]-N-[4-(4-cyano-3-methoxy-phenoxy) cyclohexyl] pyridazine-3-carboxamide	(DMSO-d_6) δ = 8.59 - 8.46 (m, 1H), 8.27 - 8.24 (m, 1H), 7.87 (s, 1H), 7.76 (s, 1H), 7.64 - 7.58 (m, 1H), 7.52 (s, 1H), 7.03 - 6.94 (m, 1H), 6.91 - 6.78 (m, 1H), 6.77 - 6.65 (m, 2H), 6.38 - 6.25 (m, 1H), 4.58 - 4.39 (m, 1H), 4.18 - 4.05 (m, 2H), 3.96 (s, 1H), 3.92 - 3.81 (m, 9H), 3.80 - 3.67 (m, 4H), 3.57 - 3.50 (m, 2H), 2.98 - 2.89 (m, 2H), 2.86 - 2.69 (m, 4H), 2.35 - 2.25 (m, 3H), 2.17 - 2.05 (m, 7H), 2.01 - 1.82 (m, 11H), 1.74 - 1.68 (m, 2H), 1.66 - 1.46 (m, 6H), 1.41 - 1.28 (m, 2H).	947.9
298	6-[7-[4-[5-acetyl-3-[7-methyl-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]-2-azaspiro[3.5]nonan-2-yl]-N-[4-(4-cyano-3-methyl-phenoxy)cyclohexyl]pyridazine-3-carboxamide	(DMSO-d6): δ = 8.53 (d, J = 8.0 Hz, 1H), 7.82 (d, J = 9.2 Hz, 1H), 7.76 (s, 1H), 7.65 (d, J = 8.4 Hz, 1H), 7.51 (s, 1H), 7.04 (d, J = 2.0 Hz, 1H), 7.00 - 6.92 (m, 2H), 6.83 (d, J = 9.2 Hz, 1H), 6.35 - 6.28 (m, 1H), 4.49 - 4.39 (m, 1H), 4.14 - 4.05 (m, 2H), 4.00 - 3.91 (m, 1H), 3.84 (s, 6H), 3.79 - 3.67 (m, 4H), 3.56 - 3.51 (m, 2H), 2.98 - 2.90 (m, 2H), 2.85 - 2.70 (m, 4H), 2.43 (s, 3H), 2.35 - 2.26 (m, 3H), 2.18 - 2.14 (m, 3H), 2.10 (d, J = 10.0 Hz, 2H), 2.06 (s, 2H), 2.01 - 1.82 (m, 11H), 1.75 - 1.59 (m, 4H), 1.58 - 1.47 (m, 4H), 1.40 - 1.28 (m, 2H)	931.9
300	6-[7-[4-[5-acetyl-3-[7-methyl-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]-2-azaspiro[3.5]nonan-2-yl]-N-[4-(3-chloro-4-cyano-2-methyl-phenoxy)cyclohexyl]pyridazine-3-carboxamide	(DMSO-d6): δ = 8.58 - 8.49 (m, 1H), 7.84 - 7.73 (m, 3H), 7.52 (s, 1H), 7.25 (d, J = 8.8 Hz, 1H), 7.00 - 6.95 (m, 1H), 6.83 (d, J = 9.2 Hz, 1H), 6.34 - 6.29 (m, 1H), 4.56 - 4.44 (m, 1H), 4.16 - 4.02 (m, 2H), 4.01 - 3.92 (m, 1H), 3.84 (s, 6H), 3.79 - 3.68 (m, 4H), 3.56 - 3.51 (m, 2H), 2.97 - 2.90 (m, 2H), 2.86 - 2.70 (m, 4H), 2.35 - 2.27 (m, 3H), 2.24 (s, 3H), 2.15 (s, 3H),	965.7

Compound	Name	^{1}H NMR ($CDCl_3$)	LC-MS [M + H^+]
		2.11 (d, J = 10.8 Hz, 2H), 2.07 (s, 2H), 2.02 - 1.88 (m, 9H), 1.87 - 1.81 (m, 2H), 1.71 (d, J = 10.8 Hz, 2H), 1.66 - 1.48 (m, 6H), 1.41 - 1.27 (m, 2H).	

[00921] **Example 33:** Synthesis of 6-[4-[[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]cyclohexyl]-methyl-amino]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide (**Compound 187**)



[00922] Synthesis of **6A** was reported in WO2016/86200, 2016, A1.

[00923] Synthesis of **8A** was reported in WO2021/231174, 2021, A1.

[00924] To a solution of tert-butyl N-(4-hydroxycyclohexyl)carbamate (15.00 g, 69.67 mmol, 1.0 eq) in dichloromethane (150 mL) was added Et_3N (21.15 g, 209.02 mmol, 29.09 mL, 3.0 eq) and MsCl (8.94 g, 78.04 mmol, 6.04 mL, 1.12 eq) at 0 °C. The mixture was stirred at 25 °C for 2 h under N_2. The reaction

mixture was concentrated under reduced pressure to give the product. The residue was purified by column chromatography (SiO_2, Petroleum ether: Ethyl acetate = 10: 1 to 1: 1). Compound [4-(tert-butoxycarbonylamino)cyclohexyl] methanesulfonate (18.60 g, 63.40 mmol, 9% yield) was obtained as a white solid.

[00925] **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 4.90-4.82 (m, 1H), 3.51 (s, 1H), 3.00 (s, 3H), 1.85-1.78 (m, 2H), 1.77-1.69 (m, 2H), 1.68 (d, J = 3.2 Hz, 2H), 1.60-1.53 (m, 2H), 1.42 (s, 9H)

[00926] To a solution of 1-(3-iodo-1,4,6,7-tetrahydropyrazolo[4,3-c]pyridin-5-yl)ethanone (5.00 g, 17.18 mmol, 1.0 eq) in DMF (60 mL) was added Cs_2CO_3 (11.19 g, 34.35 mmol, 2.0 eq) and [4-(tert-butoxycarbonylamino)cyclohexyl] methanesulfonate (7.56 g, 25.77 mmol, 1.5 eq). The mixture was stirred at 110 °C for 12 h. The mixture was poured into water (500 mL). The aqueous phase was extracted with ethyl acetate (300 mL × 2). The combined organic phase was washed with brine (500 mL × 3), dried with anhydrous sodium sulfate, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (0% - 30% Methanol in Dichloromethane). The residue was purified by prep-HPLC (column: Welch Ultimate XB-CN 250*70*10um; mobile phase: [Heptane-EtOH (0.1%NH3H2O)]; B%:23%, isocratic elution mode) to give desired compound. Compound tert-butyl N-[4-(5-acetyl-3-iodo-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl)cyclohexyl]carbamate (685 mg, 1.40 mmol, 17% yield) was obtained as a brown solid

[00927] **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 4.47-4.36 (m, 2H), 4.24 (s, 1H), 3.87 (t, J = 5.8 Hz, 2H), 3.70 (t, J = 5.8 Hz, 1H), 3.48 (d, J = 5.3 Hz, 2H), 2.80-2.59 (m, 3H), 2.13-2.00 (m, 3H), 1.98-1.85 (m, 3H), 1.44 (s, 11H)

[00928] **LC-MS:** MS (ESI^+): t_R = 0.497 min, m/z = 489.1 [$M + H^+$]

[00929] To a solution of tert-butyl N-[4-(5-acetyl-3-iodo-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl)cyclohexyl]carbamate (685 mg, 1.40 mmol, 1.0 eq) in dichloromethane (3 mL) was added trifluoroacetic acid (4.61 g, 40.39 mmol, 3 mL, 28.79 eq). The mixture was stirred at 25 °C for 0.5 h. The reaction mixture was concentrated under reduced pressure to give the product. Compound 1-[1-(4-aminocyclohexyl)-3-iodo-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]ethanone (544 mg) was obtained as a yellow oil and directly used in the next step without further purification.

[00930] **LC-MS:** MS (ESI^+): t_R = 0.340 min, m/z = 389.0 [$M + H^+$]

[00931] To a solution of 1-[1-(4-aminocyclohexyl)-3-iodo-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]ethanone (544 mg) and NMM (1.42 g, 14.01 mmol, 1.54 mL, 10.0 eq) in DCE (8 mL) was added tert-butyl 4-oxopiperidine-1-carboxylate (558 mg, 2.80 mmol, 2.0 eq) and $NaBH(OAc)_3$ (890 mg, 4.20 mmol, 3.0 eq). The mixture was stirred at 25 °C for 12 h. The mixture was poured into water (50 mL). The aqueous phase was extracted with ethyl acetate (30 mL × 2). The combined organic phase was washed with brine (80 mL × 3), dried with anhydrous sodium sulfate, filtered and concentrated in vacuum. Compound tert-butyl 4-[[4-(5-acetyl-3-iodo-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl)cyclohexyl]amino]piperidine-1-carboxylate (800 mg) was obtained as a yellow oil and directly used in the next step.

[00932] **LC-MS:** MS (ESI^+): t_R = 0.346 min, m/z = 572.1 [$M + H^+$]

[00933] To a solution of tert-butyl 4-[[4-(5-acetyl-3-iodo-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl)cyclohexyl]amino]piperidine-1-carboxylate (800 mg) in DCE (10 mL) was added HCHO (568 mg, 7.00 mmol, 521.17 µL, 37% purity, 5.0 eq) and $NaBH(OAc)_3$ (890 mg, 4.20 mmol, 3.0 eq). The mixture was stirred at 25 °C for 0.5 h. The mixture was poured into water (50 mL). The aqueous phase was extracted with dichloromethane (30 mL × 2). The combined organic phase was washed with brine (80 mL × 3), dried with anhydrous sodium sulfate, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (0% - 10% methanol in dichloromethane). Compound tert-butyl 4-[[4-(5-acetyl-3-iodo-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl)cyclohexyl]-methyl-amino]piperidine-1-carboxylate (574 mg, 980.33 µmol, 70% yield) was obtained as a white solid.

[00934] **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 4.22-4.44 (m, 2H), 3.94-4.22 (m, 2H), 3.65-3.91 (m, 3H), 2.55-2.83 (m, 6H), 2.27 (s, 3H), 2.17-2.23 (m, 3H), 2.02-2.13 (m, 2H), 1.96 (br d, *J* = 9.3 Hz, 4H), 1.73 (br d, *J* = 11.1 Hz, 2H), 1.40-1.56 ppm (m, 13H)

[00935] **LC-MS:** MS (ESI^+): t_R = 0.436 min, m/z = 586.2 [$M + H^+$]

[00936] To a solution of 7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-1,2,3,4-tetrahydroquinoline (120 mg, 455.78 µmol, 1.0 eq), tert-butyl 4-[[4-(5-acetyl-3-iodo-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl)cyclohexyl]-methyl-amino]piperidine-1-carboxylate (293 mg, 501.36 µmol, 1.1 eq) in tert-amyl alcohol (6 mL) was added Cs_2CO_3 (445 mg, 1.37 mmol, 3.0 eq) and Cphos Pd G_3 (36 mg, 45.58 µmol, 0.1 eq). The mixture was stirred at 90 °C for 12 h under N_2. The mixture was poured into water (50 mL). The aqueous phase was extracted with ethyl acetate (30 mL × 2). The combined organic phase was washed with brine (50 mL × 3), dried with anhydrous sodium sulfate, filtered and concentrated in vacuum. The residue was purified by prep-TLC (SiO_2, Dichloromethane: Methanol = 10: 1). Compound tert-butyl 4-[[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]cyclohexyl]-methyl-amino]piperidine-1-carboxylate (193 mg, 267.72 µmol, 58% yield) was obtained as a yellow solid

[00937] **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.53 (d, *J* = 5.4 Hz, 1H), 7.40 (d, *J* = 6.3 Hz, 1H), 7.06-6.96 (m, 1H), 6.85 (d, *J* = 3.8 Hz, 1H), 6.67-6.36 (m, 1H), 4.25 (s, 1H), 4.12 (s, 1H), 3.95 (d, *J* = 2.3 Hz, 3H), 3.92-3.86 (m, 2H), 3.77-3.67 (m, 3H), 2.90-2.69 (m, 8H), 2.30 (d, *J* = 2.4 Hz, 3H), 2.16 (s, 2H), 2.11-2.00 (m, 9H), 1.89-1.83 (m, 4H), 1.46 (s, 10H), 1.34-1.23 (m, 2H)

[00938] **LC-MS:** MS (ESI^+): t_R = 0.473 min, m/z = 721.5 [$M + H^+$]

[00939] To a solution of tert-butyl 4-[[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]cyclohexyl]-methyl-amino]piperidine-1-carboxylate (97 mg, 134.56 µmol, 1.0 eq) in dichloromethane (3 mL) was added trifluoroacetic acid (4.61 g, 40.39 mmol, 3 mL, 300.1 eq). The mixture was stirred at 25 °C for 0.5 h. The reaction mixture was concentrated under reduced pressure to give the product. Compound 1-[3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-1-[4-[methyl(4-piperidyl)amino]cyclohexyl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]ethanone (83 mg) was obtained as a yellow oil and directly used in the next step without further purification.

[00940] **LC-MS:** MS (ESI^+): t_R = 0.405 min, m/z = 621.4 [M + H^+]

[00941] To a solution of 1-[3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-1-[4-[methyl(4-piperidyl)amino]cyclohexyl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]ethanone (83 mg) in NMP (3 mL) was added DIPEA (345 mg, 2.67 mmol, 465.76 µL, 20.0 eq) and 6-chloro-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide (78 mg, 200.56 µmol, 1.5 eq). The mixture was stirred at 100 °C for 12 h. The mixture was poured into water (50 mL). The aqueous phase was extracted with ethyl acetate (30 mL × 2). The combined organic phase was washed with brine (50 mL × 3), dried with anhydrous sodium sulfate, filtered and concentrated in vacuum. The residue was purified by prep-TLC (SiO_2, Dichloromethane: Methanol = 10: 1). The residue was purified by prep-HPLC (column: Unisil 3-100 C18 Ultra 150*50mm*3 um; mobile phase: [water (FA) - ACN]; gradient: 28%-58% B over 10 min) to give desired compound. Then it was lyophilized. Compound 6-[4-[[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]cyclohexyl]-methyl-amino]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide (35.64 mg, 35.85 µmol, 26% yield) was obtained as a yellow solid.

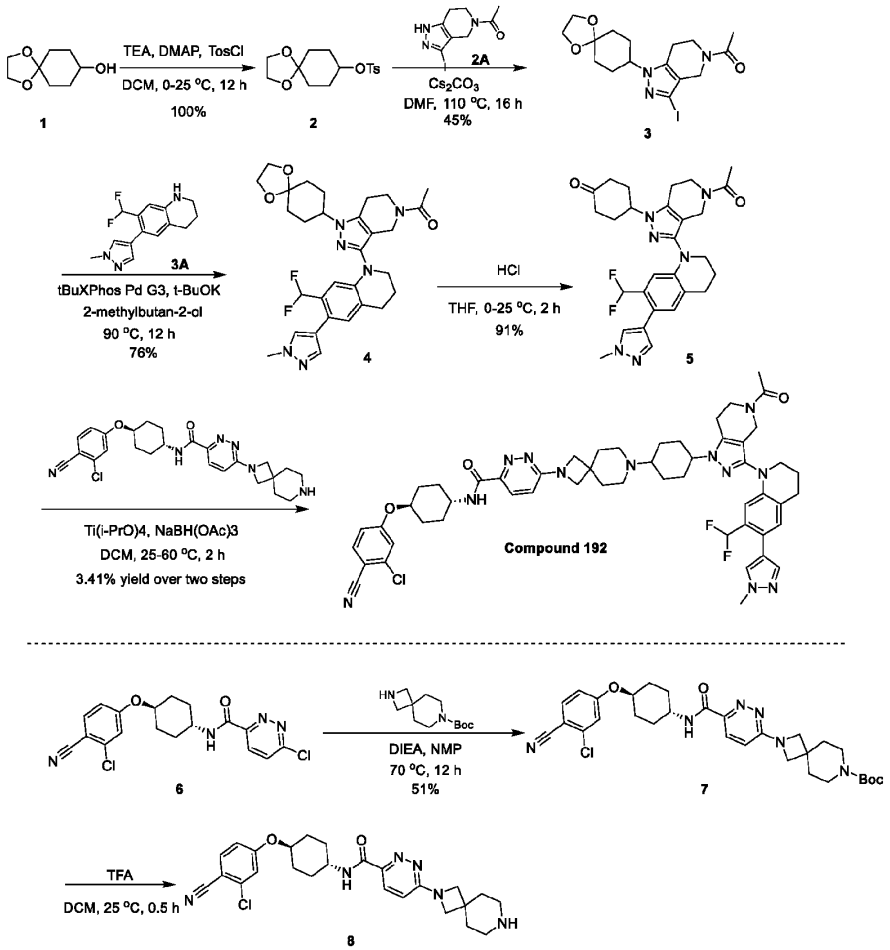
[00942] **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8.00 (dd, J = 9.5, 1.6 Hz, 1H), 7.87 (d, J = 8.3 Hz, 1H), 7.60-7.50 (m, 2H), 7.41 (d, J = 6.3 Hz, 1H), 7.07-6.97 (m, 3H), 6.90-6.82 (m, 2H), 6.69-6.35 (m, 1H), 4.55 (d, J = 12.0 Hz, 2H), 4.44-4.14 (m, 2H), 4.14-4.04 (m, 2H), 3.97-3.86 (m, 5H), 3.81-3.63 (m, 3H), 3.08 (t, J = 11.9 Hz, 2H), 3.03-2.91 (m, 1H), 2.91-2.84 (m, 2H), 2.83-2.65 (m, 3H), 2.35 (s, 3H), 2.27-2.12 (m, 6H), 2.05 (s, 6H), 2.02-1.94 (m, 4H), 1.75-1.63 (m, 5H), 1.63-1.54 (m, 2H), 1.53-1.44 (m, 2H)

[00943] **LC-MS:** MS (ESI^+): t_R = 2.545 min, m/z = 975.5 [M + H^+]

[00944] The compounds below were prepared in a similar manner as described in Example 33.

Compound	Name	^{1}H NMR ($CDCl_3$)	LC-MS [M + H^+]
189	6-[4-[[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]cyclohexyl]-methyl-amino]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	δ = 7.97 (d, J = 9.6 Hz, 1H), 7.86 (d, J = 8.4 Hz, 1H), 7.61 - 7.50 (m, 2H), 7.40 (d, J = 6.4 Hz, 1H), 7.07 - 6.95 (m, 3H), 6.92 - 6.83 (m, 2H), 6.71 - 6.35 (m, 1H), 4.57 (d, J = 12.4 Hz, 2H), 4.39 - 4.25 (m, 2H), 4.18 - 4.03 (m, 3H), 3.96 (d, J = 2.0 Hz, 3H), 3.90 (t, J = 5.6 Hz, 1H), 3.80 - 3.66 (m, 3H), 3.14 - 3.05 (m, 1H), 2.98 (t, J = 12.8 Hz, 2H), 2.92 - 2.78 (m, 4H), 2.75 (t, J = 5.6 Hz, 1H), 2.29 - 2.15 (m, 12H), 2.11 - 2.02 (m, 4H), 1.92 (d, J = 11.6 Hz, 2H), 1.82 - 1.60 (m, 8H), 1.53 - 1.40 (m, 2H)	975.6

[00945] **Example 34:** Synthesis of 6-[7-[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]cyclohexyl]-2,7-diazaspiro[3.5]nonan-2-yl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide **(Compound 192)**



[00946] Synthesis of **2A** was reported in Journal of Medicinal Chemistry, 2024, vol. 67, # 7, p. 5275 – 5304.

[00947] Synthesis of **3A** was reported in WO2016/86200, 2016, A1.

[00948] Synthesis of **6** was reported in WO2021/231174, 2021, A1.

[00949] To a solution of 1,4-dioxaspiro[4.5]decan-8-ol (10.00 g, 63 mmol, 1.0 *eq*) in DCM (100 mL) was added TEA (19.20 g, 190 mmol, 26.40 mL, 3.0 *eq*) and DMAP (772 mg, 6 mmol, 0.1 *eq*) and TosCl (24.10 g, 126 mmol, 2.0 *eq*) at 0 °C. The mixture was stirred at 25 °C for 12 h. The mixture was filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether: Ethyl acetate=50: 1 to 15: 1). Compound 1,4-dioxaspiro[4.5]decan-8-yl 4-methylbenzenesulfonate (19.70 g, 63 mmol, 100% yield) was obtained as a yellow solid.

[00950] **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.76 - 7.69 (m, 2H), 7.26 (d, J = 8.0 Hz, 2H), 4.62 - 4.53 (m, 1H), 3.90 - 3.78 (m, 4H), 2.37 (s, 3H), 1.87 - 1.67 (m, 6H), 1.53 - 1.42 (m, 2H).

[00951] A mixture of 1,4-dioxaspiro[4.5]decan-8-yl 4-methylbenzenesulfonate (8.10 g, 26 mmol, 1.5 *eq*), 1-(3-iodo-1,4,6,7-tetrahydropyrazolo[4,3-c]pyridin-5-yl)ethanone (5.00 g, 17 mmol, 1.0 *eq*), Cs_2CO_3

(16.80 g, 52 mmol, 3.0 *eq*) in DMF (50 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 110 °C for 16 h under N_2 atmosphere. The reaction mixture was diluted with water (100 mL) and the mixture was extracted with ethyl acetate (100 mL* 3). The combined organic phase was washed with brine (200 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by prep-HPLC (column: Welch Ultimate XB-NH2 250*50*10um; mobile phase: [Hexane-EtOH]; gradient: 10%-50% B over 15 min). Compound 1-[1-(1,4-dioxaspiro[4.5]decan-8-yl)-3-iodo-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]ethanone (3.30 g, 8 mmol, 45% yield) was obtained as a yellow solid.

[00952] **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 4.39 - 4.16 (m, 2H), 4.02 - 3.87 (m, 5H), 3.85 - 3.59 (m, 2H), 2.75 - 2.58 (m, 2H), 2.28 - 2.09 (m, 5H), 1.83 (d, J = 9.6 Hz, 4H), 1.66 - 1.61 (m, 1H), 1.58 (s, 1H).

[00953] **LC-MS:** MS (ESI^+): t_R = 0.523 min, m/z = 432.0 [M + H^+]

[00954] A mixture of 1-[1-(1,4-dioxaspiro[4.5]decan-8-yl)-3-iodo-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]ethanone (1.00 g, 2 mmol, 1.0 *eq*), 7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-1,2,3,4-tetrahydroquinoline (794 mg, 3 mmol, 1.3 *eq*), tBuXPhos Pd G3 (276 mg, 348 μmol, 0.15 *eq*) and t-BuOK (1 M, 4.60 mL, 2.0 *eq*) in 2-methylbutan-2-ol (20 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 90 °C for 12 h under N_2 atmosphere. The reaction mixture was diluted with water (50 mL) and the mixture was extracted with ethyl acetate (60 mL* 3). The combined organic phase was washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether: Ethyl acetate=1: 1 to 0: 1). Compound 1-[3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-1-(1,4-dioxaspiro[4.5]decan-8-yl)-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]ethanone (1.00 g, 2 mmol, 76% yield) was obtained as a white solid.

[00955] **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.46 (d, J = 5.6 Hz, 1H), 7.33 (d, J = 7.2 Hz, 1H), 6.95 (d, J = 22.4 Hz, 1H), 6.77 (s, 1H), 6.65 - 6.27 (m, 1H), 4.16 (s, 1H), 4.04 (s, 1H), 3.99 - 3.74 (m, 10H), 3.73 - 3.58 (m, 3H), 2.87 - 2.62 (m, 4H), 2.29 - 2.13 (m, 2H), 2.04 - 1.94 (m, 4H), 1.79 - 1.52 (m, 6H)

[00956] **LC-MS:** MS (ESI^+): t_R = 0.534 min, m/z = 567.3 [M + H^+]

[00957] To a solution of 1-[3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-1-(1,4-dioxaspiro[4.5]decan-8-yl)-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]ethanone (950 mg, 2 mmol, 1.0 *eq*) in THF (10 mL) was added HCl (4 M, 10 mL, 23.9 *eq*) at 0 °C. The mixture was stirred at 25 °C for 2 h. The reaction mixture was diluted with saturated $NaHCO_3$ aqueous solution (50 mL) and the mixture was extracted with DCM (30 mL* 3). The combined organic phase was washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated to give a residue. The residue was purified by prep-TLC (SiO_2, Petroleum ether: Ethyl acetate = 0: 1). Compound 4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]cyclohexanone (800 mg, 2 mmol, 91% yield) was obtained as a yellow solid.

[00958] **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.52 - 7.41 (m, 1H), 7.39 - 7.28 (m, 1H), 6.96 (d, J = 21.6 Hz, 1H), 6.81 (d, J = 3.6 Hz, 1H), 6.66 - 6.27 (m, 1H), 4.43 - 4.27 (m, 1H), 4.19 (s, 1H), 4.06 (s, 1H), 3.93 - 3.79

(m, 4H), 3.71 (t, J = 5.6 Hz, 1H), 3.67 - 3.58 (m, 2H), 2.87 - 2.55 (m, 6H), 2.50 - 2.31 (m, 4H), 2.26 - 2.13 (m, 2H), 2.06 - 2.00 (m, 1H), 1.98 (s, 1H), 1.62 (s, 3H)

[00959] **LC-MS:** MS (ESI^+): t_R = 0.509 min, m/z = 523.3 [M + H^+]

[00960] A mixture of 6-chloro-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide (200 mg, 511 μmol, 1.0 *eq*), tert-butyl 2,7-diazaspiro[3.5]nonane-7-carboxylate (139 mg, 613 μmol, 1.2 *eq*), DPIEA (198 mg, 2 mmol, 267 μL, 3.0 *eq*) in NMP (1 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 70 °C for 12 h under N_2 atmosphere. The reaction mixture was filtered and concentrated to give a residue. The crude product was triturated with ethyl acetate (6ml) at 25 °C for 60 min. Compound tert-butyl 2-[6-[[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]carbamoyl]pyridazin-3-yl]-2,7-diazaspiro[3.5]nonane-7-carboxylate (150 mg, 258 μmol, 51 % yield) was obtained as a white solid.

[00961] **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.55 (d, J = 8.0 Hz, 1H), 7.85 (t, J = 9.2 Hz, 2H), 7.38 (d, J = 1.6 Hz, 1H), 7.14 (d, J = 8.8 Hz, 1H), 6.85 (d, J = 9.2 Hz, 1H), 4.61 - 4.42 (m, 1H), 3.87 (s, 5H), 3.33 (s, 4H), 2.11 (d, J = 9.6 Hz, 2H), 1.98 - 1.83 (m, 2H), 1.78 - 1.47 (m, 8H), 1.41 (s, 9H).

[00962] **LC-MS:** MS (ESI^+): t_R = 0.600 min, m/z =581.2 [M + H^+]

[00963] To a solution of tert-butyl 2-[6-[[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]carbamoyl]pyridazin-3-yl]-2,7-diazaspiro[3.5]nonane-7-carboxylate (150 mg, 258 μmol, 1.0 *eq*) in DCM (1.5 mL) was added TFA (768 mg, 7 mmol, 0.5 mL, 26.0 *eq*). The mixture was stirred at 25 °C for 0.5 h. The reaction mixture was diluted with saturated $NaHCO_3$ aqueous solution (10 mL) and the mixture was extracted with DCM (10 mL* 5). The combined organic phase was washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. Compound N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]-6-(2,7-diazaspiro[3.5]nonan-2-yl)pyridazine-3-carboxamide (124 mg) was obtained as a yellow solid was used into the next step without further purification.

[00964] ***LC-MS:*** MS (ESI^+): t_R = 0.503 min, m/z = 481.1 [M + H^+]

[00965] To a solution of 4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]cyclohexanone (135 mg, 258 μmol, 1.0 *eq*) and N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]-6-(2,7-diazaspiro[3.5]nonan-2-yl)pyridazine-3-carboxamide (124 mg) in DCM (3.0 mL) was added $Ti(i\text{-}PrO)_4$ (147 mg, 516 μmol, 152 μL, 2.0 *eq*) at 25 °C for 1 h, $NaBH(OAc)_3$ (273 mg, 1 mmol, 5.0 *eq*) was added to the mixture. The mixture was stirred at 60 °C for 1 h. The mixture was poured into water (4 mL). The aqueous phase was extracted with dichloromethane (10 mL ×3). The combined organic phase was washed with brine (10 mL×2), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters xbridge 150*25mm 10um; mobile phase: [water(NH_4HCO_3)-ACN]; gradient: 54%-74% B over 8 min). Compound 6-[7-[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]cyclohexyl]-2,7-diazaspiro[3.5]nonan-2-yl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide (8.96 mg, 8.80 μmol, 3.41% yield over two steps) was obtained as a white solid.

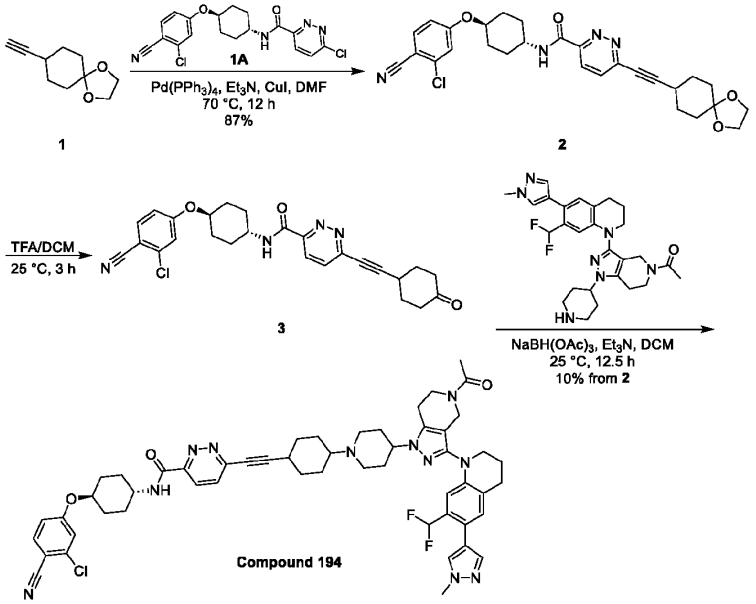
[00966] **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.90 (d, J = 9.2 Hz, 1H), 7.81 (d, J = 8.0 Hz, 1H), 7.53 - 7.43 (m, 2H), 7.37 - 7.31 (m, 1H), 7.02 - 6.91 (m, 2H), 6.87 - 6.76 (m, 2H), 6.64 - 6.29 (m, 2H), 4.36 - 4.14 (m, 2H), 4.07 (s, 2H), 4.01 - 3.95 (m, 1H), 3.88 (d, J = 2.4 Hz, 3H), 3.83 (s, 5H), 3.73 - 3.59 (m, 3H), 2.89 - 2.76 (m, 2H), 2.76 - 2.64 (m, 2H), 2.59 - 2.35 (m, 3H), 2.30 - 2.06 (m, 11H), 2.05 - 1.95 (m, 4H), 1.92 - 1.80 (m, 4H), 1.61 - 1.33 (m, 6H), 1.29 - 1.16 (m, 2H).

[00967] **LC-MS**: MS (ESI^+): t_R = 2.870 min, m/z = 987.7 [M + H^+]

[00968] The compounds below were prepared in a similar manner as described in Example 34.

Compound	Name	^{1}H NMR ($CDCl_3$)	LC-MS [M + H^+]
250	6-[4-[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]cyclohexyl]piperazin-1-yl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	δ = 7.92 (d, J = 9.6 Hz, 1H), 7.80 (d, J = 8.0 Hz, 1H), 7.53 - 7.42 (m, 2H), 7.38 - 7.29 (m, 1H), 7.01 - 6.74 (m, 5H), 6.64 - 6.24 (m, 1H), 4.34 - 4.14 (m, 2H), 4.12 - 3.94 (m, 3H), 3.92 - 3.79 (m, 4H), 3.73 (br s, 4H), 3.69 - 3.60 (m, 3H), 2.88 - 2.72 (m, 3H), 2.72 - 2.54 (m, 5H), 2.37 - 2.20 (m, 3H), 2.16 - 2.07 (m, 6H), 2.05 - 1.93 (m, 4H), 1.75 - 1.65 (m, 2H), 1.65 - 1.56 (m, 2H), 1.52 (t, J = 11.6 Hz, 2H), 1.46 - 1.32 (m, 2H), 1.31 - 1.13 (m, 1H).	947.5

[00969] **Example 35:** Synthesis of 6-[2-[4-[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]cyclohexyl]ethynyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide **(Compound 194)**



[00970] Synthesis of **1** was reported in JP5806438, 2015, B1

[00971] Synthesis of **1A** was reported in European Journal of Medicinal Chemistry, 2024, vol. 271, art. no. 116400.

[00972] To a solution of 8-ethynyl-1,4-dioxaspiro[4.5]decane (194 mg, 1.17 mmol, 3.0 eq), 6-chloro-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide (152 mg, 389 μmol, 1.0 eq), Et_3N (118 mg, 1.17 mmol, 3.0 eq), CuI (15 mg, 78 μmol, 0.2 eq) and $Pd(PPh_3)_4$ (90 mg, 78 μmol, 0.2 eq) in DMF (3 mL). The mixture was stirred at 70 °C for 12 h under N_2 atmosphere. The reaction mixture was quenched by addition water 20 mL, and then extracted with ethyl acetate (50 mL × 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~25% ethyl acetate/petroleum ethergradient @ 50 mL/min). The desired compound N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]-6-[2-(1,4-dioxaspiro[4.5]decan-8-yl)ethynyl]pyridazine-3-carboxamide (176 mg, 338 μmol, 87% yield) was obtained as brown oil.

[00973] **LC-MS: MS (ESI^+): t_R** = 1.001 min, m/z = 521.3 [$M + H^+$]

[00974] To a solution of N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]-6-[2-(1,4-dioxaspiro[4.5]decan-8-yl)ethynyl]pyridazine-3-carboxamide (236 mg, 453 μmol, 1.0 eq) in DCM (2 mL) was added TFA (1.54 g, 13.5 mmol, 29.7 eq). The mixture was stirred at 25 °C for 3 h. The reaction mixture was concentrated under reduced pressure to give a residue. Compound N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]-6-[2-(4-oxocyclohexyl)ethynyl]pyridazine-3-carboxamide (216 mg) was obtained as yellow oil and directly used in the next step without further purification.

[00975] **LC-MS:** MS (ESI^+): t_R = 0.895 min, m/z = 477.2 [$M + H^+$]

[00976] To a solution of N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]-6-[2-(4-oxocyclohexyl)ethynyl]pyridazine-3-carboxamide (216 mg), 1-[3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-1-(4-piperidyl)-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]ethanone (231 mg, 453 μmol, 1.0 eq) in DCM (5 mL) was added Et_3N (458 mg, 4.53 mmol, 10.0 eq). The mixture was stirred at 25 °C for 0.5 h. And then $NaBH(OAc)_3$ (480 mg, 2.26 mmol, 5.0 eq) was added. The mixture was stirred at 25 °C for 12 h The reaction mixture was diluted with DCM 100 mL, and then washed by water (20 mL × 2).The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (FA condition; column: Phenomenex luna C18 150 × 25mm × 10um; mobile phase: [water (FA)-ACN]; gradient:30%-60% B over 10 min). The desired compound 6-[2-[4-[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]cyclohexyl]ethynyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide (44.04 mg, 43.97 μmol, 10% yield over two steps) was obtained as yellow solid.

[00977] **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 8.56 (s, 1H), 8.21 - 8.25 (m, 1H), 8.09 (d, *J* = 8.0 Hz, 1H), 7.75 - 7.63 (m, 1H), 7.61 - 7.51 (m, 2H), 7.45 - 7.37 (m, 1H), 7.10 - 6.98 (m, 2H), 6.94 - 6.82 (m, 2H), 6.54 (s, 1H), 4.39 - 4.30 (m, 1H), 4.29 - 4.08 (m, 3H), 4.01 - 3.87 (m, 5H), 3.75 - 3.67 (m, 3H), 3.21 (d,

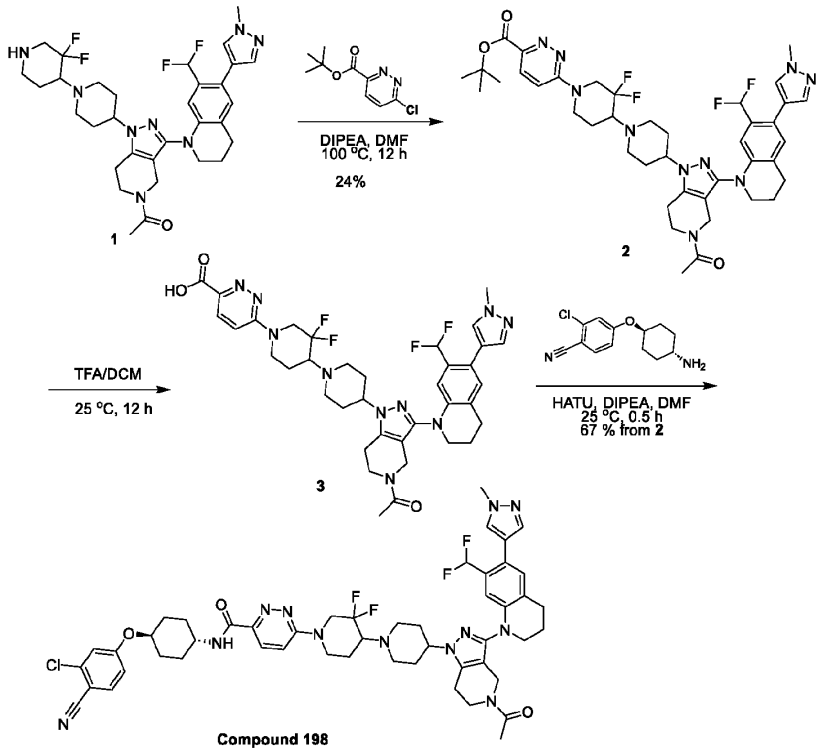
J = 3.2 Hz, 2H), 3.11 - 2.71 (m, 5H), 2.63 - 2.47 (m, 3H), 2.29 - 2.16 (m, 9H), 2.13 - 1.99 (m, 9H), 1.76 - 1.62 (m, 4H), 1.60 - 1.54 (m, 2H), 1.41 (d, J = 2.8 Hz, 1H)

[00978] **LC-MS:** MS (ESI^+): t_R = 2.317 min, m/z = 970.4 [M + H^+]

[00979] The compounds below were prepared in a similar manner as described in Example 35.

Compound	Name	^{1}H NMR ($CDCl_3$)	LC-MS [M + H^+]
195	6-[2-[3-[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]cyclobutyl]ethynyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	δ = 8.28 - 8.20 (m, 1H), 8.11 - 8.06 (m, 1H), 7.78 - 7.62 (m, 1H), 7.61 - 7.50 (m, 2H), 7.42 (d, J = 4.0 Hz, 1H), 7.13 - 6.81 (m, 4H), 6.74 - 6.34 (m, 1H), 4.53 (s, 2H), 4.25 - 4.01 (m, 2H), 3.99 - 3.88 (m, 4H), 3.81 - 3.58 (m, 3H), 3.56 - 3.24 (m, 3H), 3.14 - 3.00 (m, 1H), 2.98 - 2.83 (m, 3H), 2.81 - 2.59 (m, 5H), 2.27 - 2.12 (m, 7H), 2.11 - 1.94 (m, 5H), 1.74 - 1.60 (m, 8H)	942.4

[00980] **Example 36:** Synthesis of 6-[4-[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]-3,3-difluoro-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide (**Compound 198**)



[00981] A mixture of 1-[3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-1-[1-(3,3-difluoro-4-piperidyl)-4-piperidyl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]ethanone (80 mg, 127

μmol, 1.0 *eq*), tert-butyl 6-chloropyridazine-3-carboxylate (33 mg, 153 μmol, 1.2 *eq*), DIPEA (49 mg, 382 μmol, 66 μL, 3.0 *eq*) in DMF (2 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 100 °C for 12 h under N_2 atmosphere. The mixture was diluted with EA (50 mL), washed with brine (10 mL x 3), dried, filtered, and concentrated to give a residue. The residue was purified by *prep*-TLC (ethyl acetate : Methanol = 10 :1) to give the desired product tert-butyl 6-[4-[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]-3,3-difluoro-1-piperidyl]pyridazine-3-carboxylate (25 mg, 31 μmol, 24% yield) as a yellow solid.

[00982] **LC-MS:** MS (ESI^+): t_R = 2.000 min, m/z = 807.5 [M + H^+]

[00983] To a mixture of tert-butyl 6-[4-[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]-3,3-difluoro-1-piperidyl]pyridazine-3-carboxylate (25 mg, 30.98 μmol, 1.0 *eq*) in DCM (1 mL) was added TFA (71 mg, 620 μmol, 46 μL, 20.0 *eq*), and then the mixture was stirred at 25 °C for 12 h under N_2 atomosphere. The mixture was concentrated to give a residue. The residue 6-[4-[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]-3,3-difluoro-1-piperidyl]pyridazine-3-carboxylic acid (25 mg) as a yellow gum was used in next step directly.

[00984] LC-MS: MS (ESI+): t_R = 0.453 min, m/z = 751.4 [M + H^+]

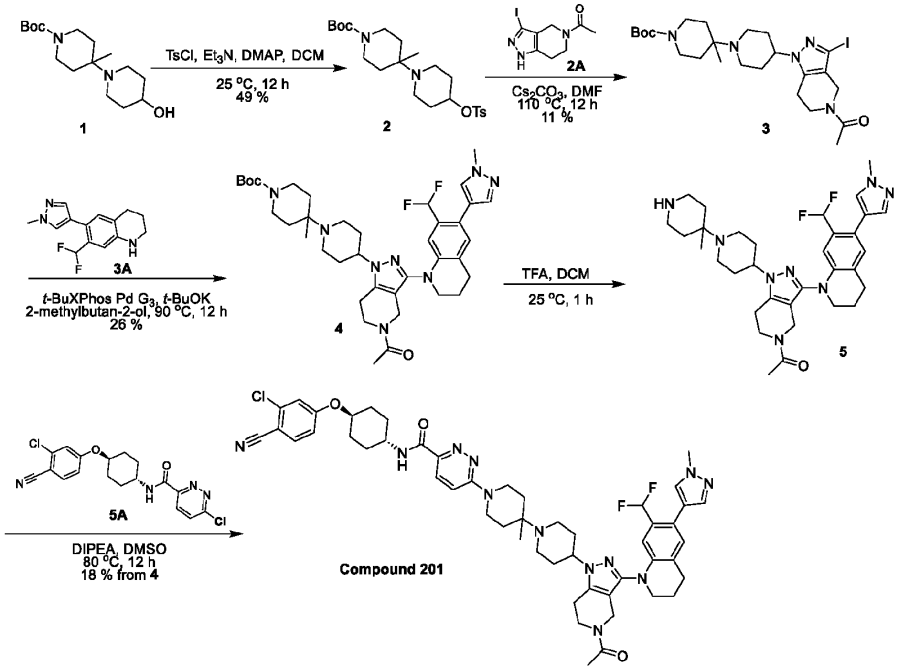
[00985] A mixture of 6-[4-[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]-3,3-difluoro-1-piperidyl]pyridazine-3-carboxylic acid (25 mg), 4-(4-aminocyclohexoxy)-2-chloro-benzonitrile (12 mg, 33 μmol, 1.0 *eq*), HATU (19 mg, 50 μmol, 1.5 *eq*), DIPEA (22 mg, 166 μmol, 29 μL, 5.0 *eq*) in DMF (1 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 25 °C for 0.5 h under N_2 atmosphere. The mixture was concentrated to give a residue. The residue was purified by *prep*-HPLC (column: Phenomenex luna C18 150*25mm* 10um;mobile phase: [water(FA)-ACN];gradient:34%-64% B over 10 min) to give the desired product 6-[4-[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]-3,3-difluoro-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide (20.38 mg, 19.80 μmol, 67% yield over two steps) as a yellow solid.

[00986] **^{1}H NMR** (400 MHz, CD_3OD) δ = 7.97 (d, *J* = 8.8 Hz, 1H), 7.70 - 7.68 (d, *J* = 8.8 Hz, 1H), 7.51 (s, 1H), 7.43 - 7.41 (d, *J* = 9.6 Hz, 1H), 7.21 - 7.20 (d, *J* = 2.4 Hz, 1H), 7.10 (m, 1H), 7.06 - 7.04 (d, *J* = 8.8 Hz, 1H), 6.73 - 6.43 (m, 2H), 4.64 (m, 1H), 4.50 (m, 1H), 4.21 (m, 3H), 3.93 (m, 5H), 3.81 (m, 1H), 3.68 - 3.67 (m, 2H), 3.35 - 3.30 (m, 6H), 3.25 - 3.15 (m, 2H), 3.10 - 2.90 (m, 6H), 2.21 - 1.95 (m, 15H), 1.67 - 1.63 (m, 3H).

[00987] **LC-MS:** MS (ESI^+): t_R = 2.568 min, m/z = 983.6 [M + H^+].

[00988] **Example 37:** Synthesis of 6-[4-[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-

dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]-4-methyl-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide (**Compound 201**)



[00989] Synthesis of **1** was reported in WO2006/77499, 2006, A1

[00990] Synthesis of **2A** was reported in **Journal of Medicinal Chemistry**, **2024**, vol. 67, # 7, p. 5275 - 5304.

[00991] Synthesis of **3A** was reported in **Journal of Medicinal Chemistry**, **2017**, vol. 60, # 22, p. 9162 - 9183

[00992] Synthesis of **5A** was reported in WO2021/231174, 2021, A1.

[00993] To a solution of tert-butyl 4-(4-hydroxy-1-piperidyl)-4-methyl-piperidine-1-carboxylate (335 mg, 1.12 mmol, 1.0 eq) in DCM (10 mL) was added Et_3N (0.34 g, 3.37 mmol, 468 μL, 3.0 eq), DMAP (14 mg, 0.11 μmol, 0.1 eq), and TsCl (428 mg, 2.25 mmol, 2.0 eq). The mixture was stirred at 25 °C for 12 h. The reaction mixture was concentrated under reduce pressure to give the crude product. The residue was purified by column chromatography (SiO_2, DCM/MeOH=50/1 to 10/1). Compound tert-butyl 4-methyl-4-[4-(p-tolylsulfonyloxy)-1-piperidyl]piperidine-1-carboxylate (250 mg, 552 μmol, 49 % yield) was obtained as a yellow solid.

[00994] **LC-MS:** MS (ESI^+): t_R =0.498 min, m/z = 453.3 [$M + H^+$]

[00995] A mixture of tert-butyl 4-methyl-4-(4-methylsulfonyloxy-1-piperidyl)piperidine-1-carboxylate (970 mg, 2.58 mmol, 1.5 eq), 1-(3-iodo-1,4,6,7-tetrahydropyrazolo[4,3-c]pyridin-5-yl)ethanone (500 mg, 1.72 mmol, 1.0 eq), Cs_2CO_3 (1.68 g, 5.15 mmol, 3 eq) in DMF (10 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 110 °C for 12 h under N_2 atmosphere. The reaction mixture was quenched by addition H_2O (20 mL) at 0 °C, and then extracted with ethyl acetate (30 mL × 3). The

combined organic layers were concentrated under reduce pressure. The residue was purified by *prep*-HPLC (column: Phenomenex luna C18 150*40mm* 15um;mobile phase: [water(FA)-ACN];gradient:10%-40% B over 10 min). Compound tert-butyl 4-[4-(5-acetyl-3-iodo-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl)-1-piperidyl]-4-methyl-piperidine-1-carboxylate (150 mg, 196 μmol, 11 % yield) was obtained as a colorless solid.

[00996] **LC-MS:** MS (ESI^+): t_R = 0.464 min, m/z = 572.3 [M + H^+]

[00997] A mixture of tert-butyl 4-[4-(5-acetyl-3-iodo-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl)-1-piperidyl]-4-methyl-piperidine-1-carboxylate (150 mg, 262 μmol, 1.0 eq), 7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-1,2,3,4-tetrahydroquinoline (69 mg, 0.26 mol, 1.0 eq), *t*-BuXPhos Pd G3 (42 mg, 52 μmol, 0.2 eq), *t*-BuOK (1 M, 787 μL, 3.0 eq) in 2-methylbutan-2-ol (2 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 90 °C for 12 h under N_2 atmosphere. The reaction was filtered and the filtrate was concentrated under reduce pressure to give the crude product. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate=20/1 to 0/1). Compound tert-butyl 4-[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]-4-methyl-piperidine-1-carboxylate (50 mg, 70 μmol, 26 % yield) was obtained as a white solid.

[00998] **LC-MS:** MS (ESI^+): t_R = 0.622 min, m/z = 707.5 [M + H^+]

[00999] To a solution of tert-butyl 4-[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]-4-methyl-piperidine-1-carboxylate (50 mg, 70 μmol, 1.0 eq) in DCM (2 mL) was added TFA (97 mg, 0.85 μmol, 63 μL, 12.0 eq). The mixture was stirred at 25 °C for 1 h. The reaction mixture was quenched by addition saturated $NaHCO_3$ (5 mL) at 0 °C, and then extracted with DCM (10 mL × 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. Compound1-[3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-1-[1-(4-methyl-4-piperidyl)-4-piperidyl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]ethanone (32 mg) was obtained as a yellow solid.

[001000] **LC-MS:** MS (ESI^+): t_R = 0.413 min, m/z = 607.5 [M + H^+]

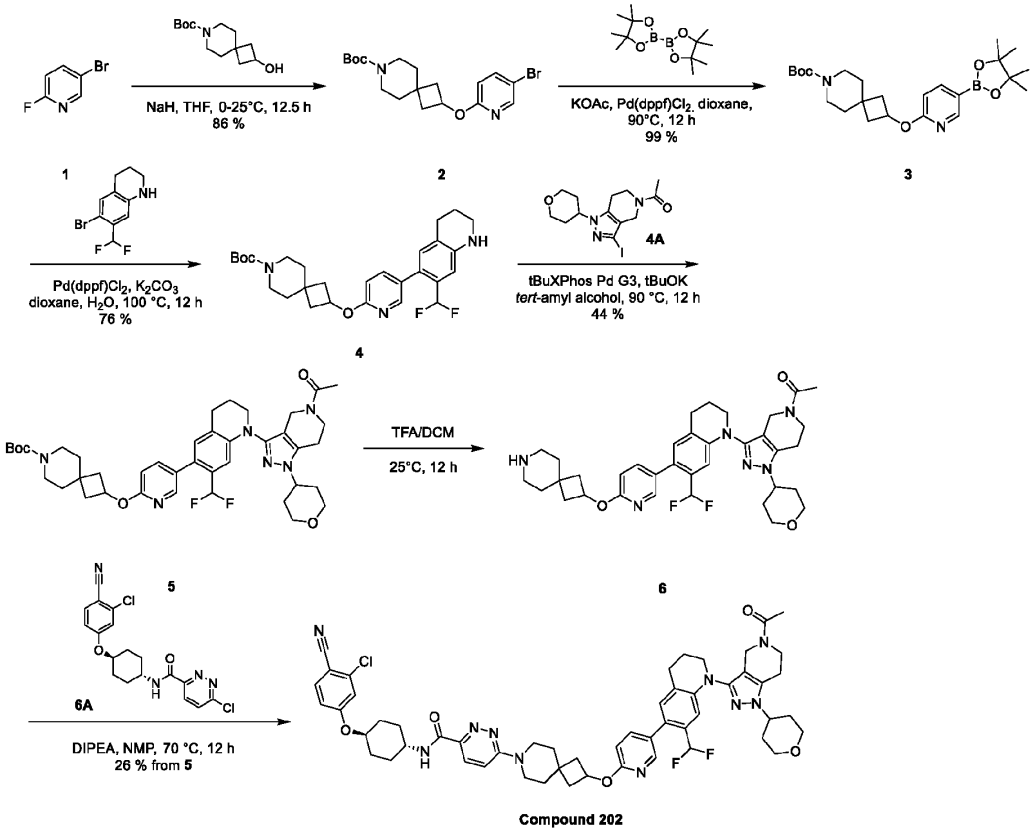
[001001] A mixture of 1-[3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-1-[1-(4-methyl-4-piperidyl)-4-piperidyl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]ethanone (32 mg), 6-chloro-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide (21 mg, 53 μmol, 1.0 eq), DIPEA (20 mg, 0.15 μmol, 28 μL, 3.0 eq) in DMSO (0.5 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 80 °C for 12 h under N_2 atmosphere. The reaction mixture was purified by *prep*-HPLC (column: Waters Xbridge 150*25mm* 5um;mobile phase: [water(FA)-ACN];gradient:27%-57% B over 10 min). Compound 6-[4-[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]-4-methyl-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide (12.02 mg, 12.00 μmol, 18 % yield over two steps) was obtained as a white solid.

[001002] **^{1}H NMR** (400 MHz, CD_3OD) δ = 7.90 (d, J = 9.5 Hz, 1H), 7.69 (d, J = 8.8 Hz, 1H), 7.62 (d, J =

2.0 Hz, 1H), 7.49 (s, 1H), 7.30 (d, J = 9.6 Hz, 1H), 7.21 (d, J = 2.4 Hz, 1H), 7.11 - 7.02 (m, 2H), 6.72 (s, 1H), 6.70 - 6.39 (m, 1H), 4.55 - 4.47 (m, 1H), 4.21 (br d, J = 5.2 Hz, 2H), 4.19 - 4.10 (m, 1H), 4.01 - 3.96 (m, 1H), 3.92 (s, 3H), 3.89 (br t, J = 5.8 Hz, 1H), 3.84 - 3.77 (m, 4H), 3.67 - 3.62 (m, 2H), 3.28 (br s, 2H), 2.94 - 2.81 (m, 4H), 2.58 - 2.41 (m, 2H), 2.24 - 2.19 (m, 3H), 2.19 (s, 3H), 2.15 - 2.04 (m, 7H), 2.03 (s, 3H), 1.75 - 1.56 (m, 7H), 1.14 (br s, 3H)

[001003] LC-MS: MS (ESI^+): t_R = 2.192 min, m/z = 961.6 [$M + H^+$]

[001004] Example 38: Synthesis of 6-[2-[[5-[1-(5-acetyl-1-tetrahydropyran-4-yl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-3-yl)-7-(difluoromethyl)-3,4-dihydro-2H-quinolin-6-yl]-2-pyridyl]oxy]-7-azaspiro[3.5]nonan-7-yl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide **(Compound 202)**



[001005] Synthesis of **4A** was reported in Journal of Medicinal Chemistry, 2023, vol. 66, # 12, p. 8178 - 8199

[001006] Synthesis of **6A** was reported in WO2021/127443, 2021, A1

[001007] To a mixture of tert-butyl 2-hydroxy-7-azaspiro[3.5]nonane-7-carboxylate (1.00 g, 4.14 mmol, 1.0 *eq*) in THF (15 mL) was added NaH (331 mg, 8.29 mmol, 60 % purity, 2.0 *eq*) at 0 °C under N_2, the mixture was stirred at 0 °C for 0.5 h, then 5-bromo-2-fluoro-pyridine (1.09 g, 6.22 mmol, 639 µL,

1.5 *eq*) was added to the reaction mixture. The mixture was stirred at 25 °C for 12 h under N_2. The mixture was quenched by addition sat. NH_4Cl, diluted with water (50 mL), extracted with EtOAc (50 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=50/1 to 5/1). Compound tert-butyl 2-[(5-bromo-2-pyridyl)oxy]-7-azaspiro[3.5]nonane-7-carboxylate (1.42 g, 3.57 mmol, 86% yield) was obtained as a white solid.

[001008] **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8.16 (d, J = 2.0 Hz, 1H), 7.67 - 7.58 (m, 1H), 6.62 (d, J = 8.8 Hz, 1H), 5.23 - 5.09 (m, 1H), 3.46 - 3.23 (m, 4H), 2.51 - 2.37 (m, 2H), 1.95 - 1.83 (m, 2H), 1.64 - 1.54 (m, 4H), 1.46 (s, 9H).

[001009] **LC-MS: MS (ESI$^+$):** t_R = 0.950 min, m/z = 341.3 [M - tBu$^+$]

[001010] To a mixture of tert-butyl 2-[(5-bromo-2-pyridyl)oxy]-7-azaspiro[3.5]nonane-7-carboxylate (1.42 g, 3.57 mmol, 1.0 *eq*) and 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (1.82 g, 7.15 mmol, 2.0 *eq*) in dioxane (20 mL) was added KOAc (1.05 g, 10.7 mmol, 3.0 *eq*) and $Pd(dppf)Cl_2$ (261 mg, 357 μmol, 0.1 *eq*) under N_2. The mixture was stirred at 90 °C for 12 h under N_2. The mixture was filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=100/1 to 5/1). Compound tert-butyl 2-[[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-pyridyl]oxy]-7-azaspiro[3.5]nonane-7-carboxylate (1.59 g, 3.58 mmol, 99% yield) was obtained as a white solid.

[001011] **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8.52 (d, J = 1.2 Hz, 1H), 7.98 - 7.87 (m, 1H), 6.67 (d, J = 8.4 Hz, 1H), 5.35 - 5.17 (m, 1H), 3.44 - 3.25 (m, 4H), 2.56 - 2.37 (m, 2H), 1.97 - 1.86 (m, 2H), 1.61 - 1.53 (m, 4H), 1.46 (s, 9H), 1.33 (s, 12H).

[001012] **LC-MS:** MS (ESI$^+$): t_R = 0.958 min, m/z = 445.5 [M + H$^+$]

[001013] To a mixture of 6-bromo-7-(difluoromethyl)-1,2,3,4-tetrahydroquinoline (850 mg, 3.24 mmol, 1.0 *eq*) and tert-butyl 2-[[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-pyridyl]oxy]-7-azaspiro[3.5]nonane-7-carboxylate (1.59 g, 3.57 mmol, 1.1 *eq*) in dioxane (15 mL) and H_2O (3 mL) was added K_2CO_3 (896 mg, 6.49 mmol, 2.0 *eq*) and $Pd(dppf)Cl_2$ (237 mg, 324 μmol, 0.1 *eq*) under N_2. The mixture was stirred at 100 °C for 12 h under N_2. The reaction mixture was diluted with water (40 mL) and extracted with EtOAc (30 mL * 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=30/1 to 3/1). Compound tert-butyl 2-[[5-[7-(difluoromethyl)-1,2,3,4-tetrahydroquinolin-6-yl]-2-pyridyl]oxy]-7-azaspiro[3.5]nonane-7-carboxylate (1.24 g, 2.48 mmol, 76% yield) was obtained as a white solid.

[001014] **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8.07 (d, J = 2.4 Hz, 1H), 7.57 - 7.46 (m, 1H), 6.87 (s, 1H), 6.82 (s, 1H), 6.73 (d, J = 8.4 Hz, 1H), 6.40 (t, J = 55.2 Hz, 1H), 5.31 - 5.16 (m, 1H), 4.24 - 3.99 (m, 1H), 3.48 - 3.25 (m, 6H), 2.90 - 2.70 (m, 2H), 2.56 - 2.41 (m, 2H), 2.02 - 1.87 (m, 4H), 1.66 - 1.58 (m, 4H), 1.46 (s, 9H).

[001015] **LC-MS:** MS (ESI$^+$): t_R = 0.940 min, m/z = 500.4 [M + H$^+$]

[001016] To a mixture of tert-butyl 2-[[5-[7-(difluoromethyl)-1,2,3,4-tetrahydroquinolin-6-yl]-2-pyridyl]oxy]-7-azaspiro[3.5]nonane-7-carboxylate (1.14 g, 2.28 mmol, 1.0 *eq*) and 1-(3-iodo-1-tetrahydropyran-4-yl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl)ethanone (856 mg, 2.28 mmol, 1.0 *eq*) in tert-amyl alcohol (20 mL) was added tBuXPhos Pd G3 (181 mg, 228 μmol, 0.1 *eq*) and tBuOK (1 M, 4.5 mL, 2.0 *eq*) under N_2. The mixture was stirred at 90 °C for 12 h under N_2. The mixture was filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO_2, Ethyl acetate/MeOH =100/1 to 10/1). Compound tert-butyl 2-[[5-[1-(5-acetyl-1-tetrahydropyran-4-yl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-3-yl)-7-(difluoromethyl)-3,4-dihydro-2H-quinolin-6-yl]-2-pyridyl]oxy]-7-azaspiro[3.5]nonane-7-carboxylate (750 mg, 1.00 mmol, 44% yield) was obtained as a white solid.

[001017] **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8.08 (d, *J* = 2.4 Hz, 1H), 7.60 - 7.49 (m, 1H), 7.03 - 6.85 (m, 2H), 6.79 - 6.70 (m, 1H), 6.58 - 6.19 (m, 1H), 5.31 - 5.18 (m, 1H), 4.18 - 4.07 (m, 5H), 4.00 - 3.68 (m, 4H), 3.60 - 3.47 (m, 2H), 3.46 - 3.27 (m, 4H), 2.95 - 2.70 (m, 4H), 2.54 - 2.43 (m, 2H), 2.39 - 2.23 (m, 2H), 2.11 - 2.04 (m, 5H), 1.99 - 1.84 (m, 4H), 1.63 - 1.57 (m, 4H), 1.46 (s, 9H).

[001018] **LC-MS:** MS (ESI^+): t_R = 0.941 min, m/z = 747.3 [$M + H^+$]

[001019] To a mixture of tert-butyl 2-[[5-[1-(5-acetyl-1-tetrahydropyran-4-yl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-3-yl)-7-(difluoromethyl)-3,4-dihydro-2H-quinolin-6-yl]-2-pyridyl]oxy]-7-azaspiro[3.5]nonane-7-carboxylate (750 mg, 1.00 mmol, 1.0 *eq*) in DCM (10 mL) was added TFA (3.07 g, 26.9 mmol, 2 mL, 26.8 *eq*). The mixture was stirred at 25 °C for 12 h. The mixture was concentrated to give a residue. The residue was diluted with DCM (20 mL), adjusted to pH about 8 by sat. $NaHCO_3$. The mixture was diluted with water (20 mL), extracted with DCM (20 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to give a crude product. Compound 1-[3-[6-[6-(7-azaspiro[3.5]nonan-2-yloxy)-3-pyridyl]-7-(difluoromethyl)-3,4-dihydro-2H-quinolin-1-yl]-1-tetrahydropyran-4-yl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]ethanone (640 mg) was obtained as a yellow solid and directly used into the next step without further purification.

[001020] **LC-MS:** MS (ESI^+): t_R = 0.717 min, m/z = 647.4 [$M + H^+$]

[001021] To a mixture of 1-[3-[6-[6-(7-azaspiro[3.5]nonan-2-yloxy)-3-pyridyl]-7-(difluoromethyl)-3,4-dihydro-2H-quinolin-1-yl]-1-tetrahydropyran-4-yl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]ethanone (100 mg) and 6-chloro-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide (60 mg, 154 μmol, 1.0 *eq*) in NMP (1.5 mL) was added DIPEA (99 mg, 773 μmol, 134 μL, 5.0 *eq*). The mixture was stirred at 70 °C for 12 h. The mixture was filtered and concentrated to give a residue. The residue was purified by prep-HPLC (column: Waters xbridge 150*25mm 10um; mobile phase: [water (NH_4HCO_3)-ACN]; gradient: 63%-83% B over 8 min). Compound 6-[2-[[5-[1-(5-acetyl-1-tetrahydropyran-4-yl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-3-yl)-7-(difluoromethyl)-3,4-dihydro-2H-quinolin-6-yl]-2-pyridyl]oxy]-7-azaspiro[3.5]nonan-7-yl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide (40.41 mg, 40.21 μmol, 26% yield over two steps) was obtained as a white solid.

[001022] **^{1}H NMR** (400 MHz, DMSO-d_6) δ = 8.65 - 8.54 (m, 1H), 8.09 - 8.01 (m, 1H), 7.91 - 7.76 (m, 2H), 7.68 - 7.59 (m, 1H), 7.45 - 7.31 (m, 2H), 7.17 - 7.10 (m, 1H), 7.02 (s, 1H), 6.93 - 6.82 (m, 2H), 6.82 - 6.50

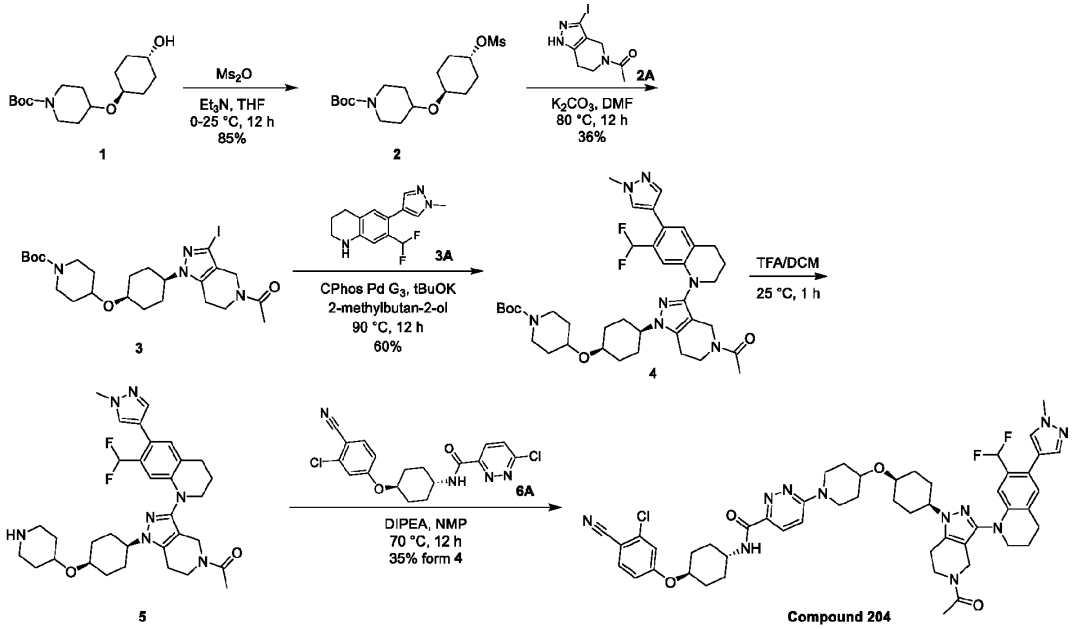
(m, 1H), 5.33 - 5.16 (m, 1H), 4.62 - 4.47 (m, 1H), 4.37 - 4.25 (m, 1H), 4.24 - 4.08 (m, 2H), 4.01 - 3.91 (m, 2H), 3.91 - 3.83 (m, 1H), 3.80 - 3.64 (m, 6H), 3.64 - 3.57 (m, 2H), 3.50 - 3.43 (m, 2H), 3.40 - 3.36 (m, 1H), 2.91 - 2.73 (m, 4H), 2.15 - 2.06 (m, 4H), 2.05 - 1.78 (m, 12H), 1.71 - 1.58 (m, 6H), 1.56 - 1.46 (m, 2H).

[001023] LC-MS: MS (ESI^+): t_R = 2.777 min, m/z = 1001.4 [M + H^+]

[001024] The compounds below were prepared in a similar manner as described in Example 38.

Compound	Name	^{1}H NMR ($CDCl_3$)	LC-MS [M + H^+]
203	6-[2-[4-[1-(5-acetyl-1-tetrahydropyran-4-yl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-3-yl)-7-(difluoromethyl)-3,4-dihydro-2H-quinolin-6-yl]phenoxy]-7-azaspiro[3.5]nonan-7-yl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	δ 8.01 – 7.96 (m, 1 H) 7.87 (m, 1 H) 7.57 (d, *J*=8.8 Hz, 1 H) 7.22 (d, *J*=8.4 Hz, 2 H) 7.05 - 7.00 (m, 2 H) 6.99 - 6.92 (m, 1 H) 6.89 - 6.82 (m, 4 H) 6.26 - 6.65 (m, 1 H) 4.78 (m, 1 H) 4.39 - 4.25 (m, 2 H) 4.20 - 4.05 (m, 5 H) 3.94 - 3.88 (m, 1 H) 3.82 - 3.68 (m, 7 H) 3.53 (m, 2 H) 2.94 - 2.81 (m, 3 H) 2.76 (m, 1 H) 2.53 (m, 2 H) 238 - 2.25 (m, 2 H) 2.25 - 2.13 (m, 6 H) 2.12 - 2.05 (m, 6 H) 1.88 (m, 2 H) 1.84 - 1.76 (m, 4 H) 1.75 - 1.67 (m, 2 H) 1.53 - 1.43 (m, 2 H)	1000.3

[001025] Example 39: Synthesis of 6-[4-[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]cyclohexoxy]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide **(Compound 204)**



[001026] Synthesis of **1** was reported in WO2012/170702, 2012, A1.

[001027] Synthesis of **2A** was reported in Journal of Medicinal Chemistry, 2024, vol. 67, # 7, p. 5275 – 5304.

[001028] Synthesis of **3A** was reported in Journal of Cell Chemical Biology, 2021, vol. 28, # 4, p. 503 - 12,514.

[001029] Synthesis of **6A** was reported in Journal of European Journal of Medicinal Chemistry, 2024, vol. 271, art. no. 116400

[001030] To a solution of tert-butyl 4-(4-hydroxycyclohexoxy)piperidine-1-carboxylate (4.60 g, 15.4 mmol, 1.0 eq) in THF (50 mL) was added Et_3N (5.44 g, 53.8 mmol, 3.5 eq) and methylsulfonyl methanesulfonate (3.21 g, 18.4 mmol, 1.2 eq). The mixture was stirred at 25 °C for 12 h under N_2. The mixture was poured into water (50 mL). The aqueous phase was extracted with ethyl acetate (60 mL × 3), dried with anhydrous sodium sulfate, concentrated under vacuum. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=5/1 to 2/1). Compound tert-butyl 4-(4-methylsulfonyloxycyclohexoxy)piperidine-1-carboxylate (4.98 g, 13.1 mmol, 85% yield) was obtained as a white solid.

[001031] LC-MS: MS (ESI^+): t_R = 0.620 min, m/z = 278.1 [M - 99]

[001032] To a solution of tert-butyl 4-(4-methylsulfonyloxycyclohexoxy)piperidine-1-carboxylate (4.98 g, 13.1 mmol, 1.2 eq) and 1-(3-iodo-1,4,6,7-tetrahydropyrazolo[4,3-c]pyridin-5-yl)ethanone (3.20 g, 11.0 mmol, 1.0 eq) in DMF (70 mL) was added Cs_2CO_3 (7.16 g, 22.0 mmol, 2.0 eq). The mixture was stirred at 80 °C for 12 h under N_2. The mixture was poured into ethyl acetate (100 mL). The aqueous phase was extracted with water 300 mL (30 mL × 3), dried with anhydrous sodium sulfate, concentrated under vacuum. The residue was purified by prep-TLC (SiO_2, DCM/MeOH = 30/1). Compound tert-butyl 4-[4-(5-acetyl-3-iodo-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl)cyclohexoxy]piperidine-1-carboxylate (2.30 g, 3.98 mmol, 36% yield) was obtained as a white solid.

[001033] LC-MS: MS (ESI^+): t_R = 0.663 min, m/z = 573.2 [$M + H^+$]

[001034] To a solution of tert-butyl 4-[4-(5-acetyl-3-iodo-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl)cyclohexoxy]piperidine-1-carboxylate (150 mg, 262 μmol, 1.0 eq), 7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-1,2,3,4-tetrahydroquinoline (83 mg, 314 μmol, 1.2 eq), [2-(2-aminophenyl)phenyl]-methylsulfonyloxy-palladium;ditert-butyl-[2-(2,4,6triisopropylphenyl)phenyl]phosphane (42 mg, 52.4 μmol, 0.2 eq) in 2-methylbutan-2-ol (3 mL) was added tBuOK (1 M, 621 μL, 2.4 eq). The mixture was stirred at 90 °C for 12 h under N_2. The mixture was poured into water (20 mL). The aqueous phase was extracted with ethyl acetate (20 mL × 3), dried with anhydrous sodium sulfate, concentrated under vacuum. The residue was purified by prep-TLC (SiO_2, DCM/MeOH = 20/1). Compound tert-butyl 4-[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2Hquinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]cyclohexoxy]piperidine-1-carboxylate (112 mg, 158 μmol, 60% yield) was obtained as yellow solid.

[001035] LC-MS: MS (ESI^+): t_R = 0.637 min, m/z = 708.6 [$M + H^+$]

[001036] To a solution of tert-butyl 4-[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]cyclohexoxy]piperidine-1-carboxylate (1.45 g, 2.05 mmol, 1.0 eq) in DCM (10 mL) was added TFA (12.3 g, 108 mmol, 52.6 eq). The

mixture was stirred at 25 °C for 1 h under N_2. The reaction mixture was concentrated. Compound 1-[3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-1-[4-(4-piperidyloxy)cyclohexyl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]ethanone (1.48 g) as a yellow solid and directly used in the next step without further purification.

[001037] LC-MS: MS (ESI^+): t_R = 0.518 min, m/z = 608.3 [M + H^+]

[001038] To a solution of 1-[3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-1-[4-(4-piperidyloxy)cyclohexyl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]ethanone (1.48 g) and 6-chloro-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide (1.04 g, 2.67 mmol, 1.3 eq) in NMP (6 mL) was added DIPEA (795 mg, 6.15 mmol, 3.0 eq) at 25 °C. The mixture was stirred at 70 °C for 12 h under N_2. The mixture was poured into water (20 mL). The aqueous phase was extracted with ethyl acetate (30 mL × 3), dried with anhydrous sodium sulfate, concentrated under vacuum. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=10/1 to 1/8) and by prep-TLC (SiO_2, DCM/MeOH = 30/1). Compound 6-[4-[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]cyclohexoxy]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide (695.90 mg, 708 μmol, 35% yield over two steps) was obtained as a off-white solid.

[001039] 1H NMR (400 MHz, CHLOROFORM-d) δ = 7.97 (d, J = 9.6 Hz, 1H), 7.87 (d, J = 8.0 Hz, 1H), 7.60 - 7.50 (m, 2H), 7.44 - 7.37 (m, 1H), 7.07 - 6.96 (m, 3H), 6.93 - 6.82 (m, 2H), 6.70 - 6.35 (m, 1H), 4.38 - 4.24 (m, 2H), 4.13 (s, 1H), 4.10 - 4.01 (m, 3H), 3.96 (d, J = 2.0 Hz, 4H), 3.90 (s, 1H), 3.80 - 3.68 (m, 5H), 3.68 - 3.59 (m, 2H), 2.93 - 2.79 (m, 3H), 2.76 (s, 1H), 2.42 - 2.27 (m, 2H), 2.23 - 2.14 (m, 5H), 2.12 - 2.01 (m, 6H), 1.98 - 1.88 (m, 2H), 1.83 - 1.64 (m, 7H), 1.56 - 1.39 (m, 3H)

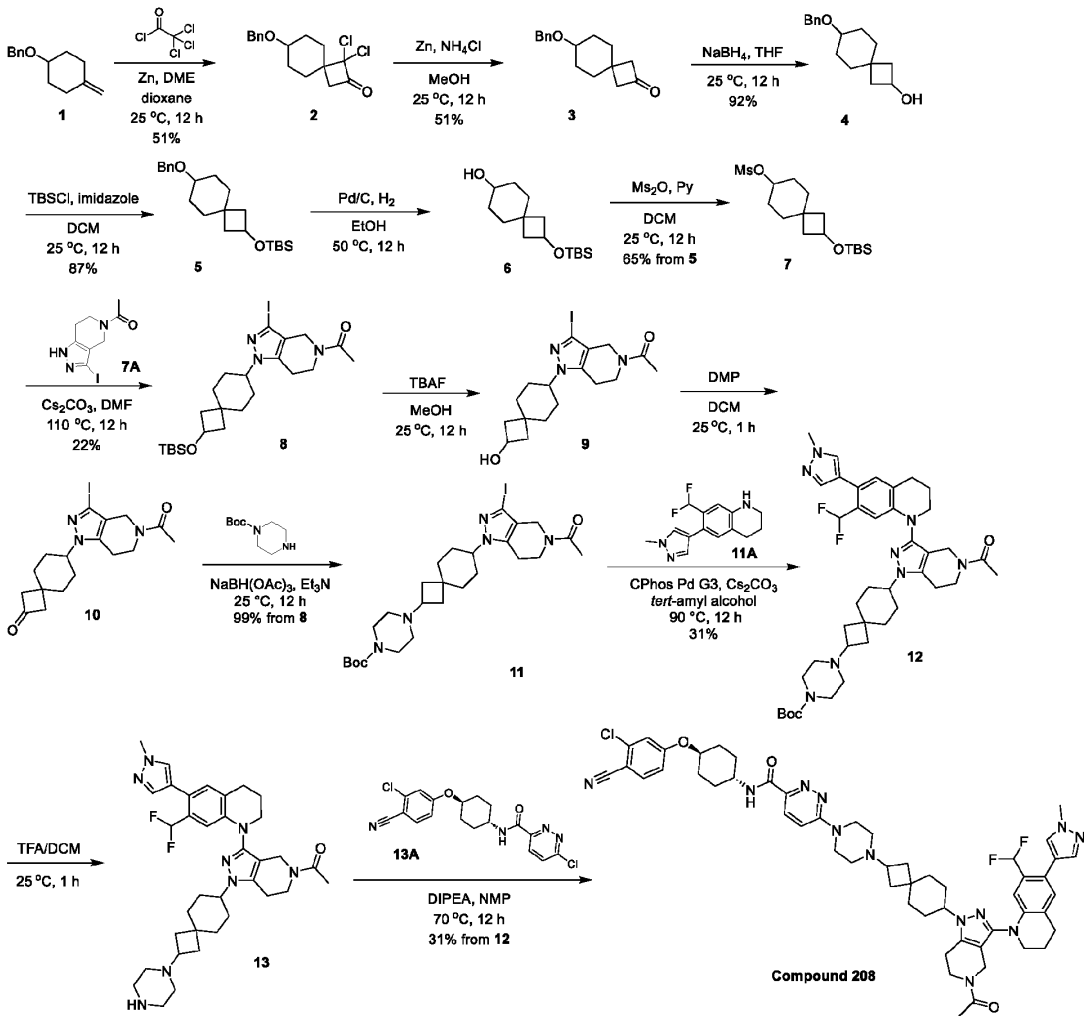
[001040] LC-MS: MS (ESI^+): t_R = 3.024 min, m/z = 962.5 [M + H^+]

[001041] The compounds below were prepared in a similar manner as described in Example 39.

Compound	Name	^{1}H NMR ($CDCl_3$)	LC-MS [M + H^+]
205	6-[4-[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]cyclohexoxy]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	δ = 8.04 - 7.95 (m, 1H), 7.91 - 7.82 (m, 1H), 7.58 - 7.51 (m, 2H), 7.44 - 7.37 (m, 1H), 7.07 - 6.98 (m, 3H), 6.90 - 6.83 (m, 2H), 6.68 - 6.38 (m, 1H), 4.38 - 4.28 (m, 1H), 4.27 - 4.23 (m, 1H), 4.15 - 4.03 (m, 4H), 3.97 - 3.95 (m, 3H), 3.93 - 3.86 (m, 2H), 3.82 - 3.66 (m, 4H), 3.58 - 3.49 (m, 3H), 2.94 - 2.85 (m, 2H), 2.84 - 2.78 (m, 1H), 2.76 - 2.71 (m, 1H), 2.21 - 2.14 (m, 6H), 2.09 - 2.01 (m, 7H), 1.98 - 1.92 (m, 2H), 1.69 (d, *J* = 10.0 Hz, 4H), 1.51 - 1.43 (m, 4H), 1.33 - 1.25 (m, 2H)	962.4
223	6-[3-[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-	δ = 7.99 (d, *J*=9.2 Hz, 1 H) 7.87 (d, *J*=8.0 Hz, 1 H) 7.57 (d, *J*=8.8 Hz, 1 H) 7.55-7.51 (m, 1 H) 7.43-	934.6

Compound	Name	^{1}H NMR ($CDCl_3$)	LC-MS [M + H^+]
	pyrazolo[4,3-c]pyridin-1-yl]cyclohexoxy]azetidin-1-yl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	7.37 (m, 1 H) 7.05-6.98 (m, 2 H) 6.91-6.88 (m, 1 H) 6.86 (dd, *J*=8.8, 2.4 Hz, 1 H) 6.62 (d, *J*=9.2 Hz, 2 H) 4.66-4.58 (m, 1 H) 4.49-4.39 (m, 2 H) 4.37-4.30 (m, 1 H) 4.26 (s, 1 H) 4.19-4.12 (m, 3 H) 4.09-4.02 (m, 1 H) 3.96 (d, *J*=1.6 Hz, 3 H) 3.92-3.89 (m, 1 H) 3.76-3.70 (m, 3 H) 2.92-2.83 (m, 2 H) 2.81 (t, *J*=6.0 Hz, 1 H) 2.75 (t, *J*=5.6 Hz, 1 H) 2.34 (d, *J*=11.6 Hz, 2 H) 2.20-2.15 (m, 4 H) 2.12-2.02 (m, 6 H) 1.80 (d, *J*=10.0 Hz, 2 H) 1.69 (d, *J*=12.4 Hz, 2 H) 1.63 (d, *J*=10.8 Hz, 4 H) 1.58 (s, 1 H) 1.52-1.45 (m, 2 H).	
224	6-[3-[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7- dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]cyclohexoxy]azetidin-1-yl]-N-[4-(3-chloro-4-cyanophenoxy)cyclohexyl]pyridazine-3-carboxamide	δ = 7.99 (d, J = 9.6 Hz, 1H), 7.88 (d, J = 8.0 Hz, 1H), 7.61 - 7.50 (m, 2H), 7.40 (d, J = 6.0 Hz, 1H), 7.08 - 6.95 (m, 2H), 6.91 - 6.81 (m, 2H), 6.68 - 6.60 (m, 1H), 6.59 - 6.34 (m, 1H), 4.71 - 4.60 (m, 1H), 4.44 (t, J = 7.6 Hz, 2H), 4.37 - 4.30 (m, 1H), 4.26 (s, 1H), 4.16 - 3.96 (m, 5H), 3.96 - 3.92 (m, 3H), 3.92 - 3.83 (m, 2H), 3.81 - 3.64 (m, 3H), 3.51 - 3.41 (m, 1H), 2.91 - 2.71 (m, 4H), 2.27 - 2.11 (m, 8H), 2.10 - 1.95 (m, 8H),1.54 - 1.42 (m, 4H)	934.6
244	methyl (7S)-2-benzyl-3-[3-[[1-[6-[[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]carbamoyl]pyridazin-3-yl]-4-piperidyl]oxy]cyclohexyl]-7-methyl-8,9-dihydro-7H-imidazo[4,5-f]quinoline-6-carboxylate	δ = 8.01 - 7.94 (m, 1H), 7.90 - 7.83 (m, 1H), 7.60 - 7.54 (m, 1H), 7.43 - 7.36 (m, 1H), 7.34 - 7.27 (m, 3H), 7.26 - 7.20 (m, 3H), 7.04 - 6.95 (m, 2H), 6.87 – 6.84 (m, 1H), 4.81 (d, *J* = 6.4 Hz, 1H), 4.56 - 4.42 (m, 1H), 4.37 - 4.21 (m, 2H), 4.13 - 4.00 (m, 3H), 3.97 - 3.88 (m, 1H), 3.79 (s, 3H), 3.55 - 3.40 (m, 3H), 3.27 (d, *J* = 9.6 Hz, 1H), 3.18 - 3.00 (m, 2H), 2.28 - 2.14 (m, 5H), 2.09 - 1.94 (m, 3H), 1.93 - 1.77 (m, 3H), 1.60 - 1.40 (m, 6H), 1.33 - 1.22 (m, 4H), 1.19 - 1.17 (m, 4H)	871.6

[001042] Example 40: Synthesis of 6-[4-[7-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]spiro[3.5]nonan-2-yl]piperazin-1-yl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide **(Compound 208)**



[001043] Synthesis of **1** was reported in Journal of Bioorganic and Medicinal Chemistry Letters, 2019, vol. 29, # 16, p. 2100 – 2106.

[001044] Synthesis of **7A** was reported in Journal of Medicinal Chemistry, 2024, vol. 67, # 7, p. 5275 – 5304.

[001045] Synthesis of **11A** was reported in Journal of Cell Chemical Biology, 2021, vol. 28, # 4, p. 503 - 12,514.

[001046] Synthesis of **13A** was reported in Journal of European Journal of Medicinal Chemistry, 2024, vol. 271, art. no. 116400

[001047] To a solution of (4-methylenecyclohexoxy)methylbenzene (23.00 g, 114 mmol, 1.0 eq), Zn (29.93 g, 458 mmol, 4.0 eq) in dioxane (230 mL) was added 1,2-dimethoxyethane (20.49 g, 227 mmol, 23.6 mL, 2.0 eq) and 2,2,2-trichloroacetyl chloride (31.01 g, 171 mmol, 19 mL, 1.5 eq) in dioxane (100 mL) under N_2 .The mixture was stirred at 25 °C for 12 h under N_2 atmosphere. The reaction mixture was adjusted with saturated aqueous $NaHCO_3$ (300 mL) solution to pH=7 and then extracted with ethyl acetate (100 mL × 3).

The combined organic layers were dried, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate=1/0 to 5/1). Compound 7-benzyloxy-3,3-dichloro-spiro[3.5]nonan-2-one (18.00 g, 57.5 mmol, 51% yield) as a light yellow gum.

[001048] A mixture of 7-benzyloxy-3,3-dichloro-spiro[3.5]nonan-2-one (18.00 g, 57.5 mmol, 1.0 eq), Zn (18.58 g, 284 mmol, 4.9 eq), NH_4Cl (18.44 g, 345 mmol, 6.0 eq) in MeOH (180 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 25 °C for 12 h under N_2 atmosphere. The reaction mixture was adjusted with saturated aqueous $NaHCO_3$ (300 mL) solution to pH=7 and then extracted with ethyl acetate (80 mL × 3). The combined organic layers were dried, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate=1/0 to 3/1). To give the product 7-benzyloxyspiro[3.5]nonan-2-one (7.20 g, 29.5 mmol, 51% yield) as a colorless oil.

[001049] **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 7.38 – 7.35 (m, 4H), 7.32 – 7.28 (m, 1H), 4.58 (s, 2H), 3.50 – 3.48 (m, 1H), 2.81 – 2.78 (m, 4H), 1.89 – 1.87 (m, 4H), 1.63 – 1.55 (m, 4H).

[001050] To a solution of 7-benzyloxyspiro[3.5]nonan-2-one (7.20 g, 29.5 mmol, 1.0 eq) in THF (75 mL) was added $NaBH_4$ (2.23 g, 58.9 mmol, 2.0 eq) at 0 °C under N_2 .The mixture was stirred at 25 °C for 12 under N_2. The mixture was quenched by addition saturated aqueous NH_4Cl, diluted with water (120 mL), extracted with ethyl acetate (60 mL × 3).The combined organic layers were dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate=50/1 to 5/1). To give the product 7-benzyloxyspiro[3.5]nonan-2-ol (6.70 g, 27.2 mmol, 92% yield) as a colourless oil.

[001051] **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ = 7.35 – 7.32 (m, 4H), 7.28 – 7.27 (m, 1H), 4.53 (s, 2H), 4.22 – 4.17 (m, 1H), 3.38 (s, 1H), 2.25 (m, 1H), 2.13 (m, 1H), 1.82 – 1.80 (m, 2H), 1.68 – 1.61 (m, 4H), 1.40 – 1.34 (m, 4H)

[001052] A mixture of 7-benzyloxyspiro[3.5]nonan-2-ol (6.70 g, 27.2 mmol, 1.0 eq) ,imidazole (5.55 g, 81.6 mmol, 3.0 eq), tert-butyl-chloro-dimethyl-silane (6.15 g, 40.8 mmol, 5.0 mL, 1.5 eq) in DCM (60 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 25 °C for 12 under N_2 atmosphere. The mixture was diluted with water (120 mL), extracted with DCM (60 mL × 3). The combined organic layers were dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO2,Petroleum ether/ethyl acetate=50/1 to 5/1).To give the product (7-benzyloxyspiro[3.5]nonan-2-yl)oxy-tert-butyl-dimethyl-silane (8.5 g, 23.57 mmol, 86.67% yield) as a light yellow oil.

[001053] To a solution of (7-benzyloxyspiro[3.5]nonan-2-yl)oxy-tert-butyl-dimethyl-silane (8.50 g, 23.6 mmol, 1.0 eq) in EtOH (100 mL) was added Pd/C (2.5 g, 10% Pd on carbon, w/w) under N_2 atmosphere. The suspension was degassed and purged with H_2 for 3 times. The mixture was stirred under H_2 at 50 °C for 12 h under H_2. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. To give the product 2-[tert-butyl(dimethyl)silyl]oxyspiro[3.5]nonan-7-ol (5.6 g) as yellow gum and directly

used in the next step without further purification.

[001054] To a solution of 2-[tert-butyl(dimethyl)silyl]oxyspiro[3.5]nonan-7-ol (5.6 g) in DCM (60 mL) was added pyridine (8.19 g, 104 mmol, 8.36 mL, 5.0 eq) and methylsulfonyl methanesulfonate (10.82 g, 62.1 mmol, 3.0 eq) in DCM (15 mL) at 0 °C under N_2 .The mixture was stirred at 25 °C for 12 under N_2. The reaction mixture was diluted with DCM (120 mL), washed with saturated brine (20 × 3 mL) dried over dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate=0/1 to 5/1). To give the product [2-[tert-butyl(dimethyl)silyl]oxyspiro[3.5]nonan-7-yl] methanesulfonate (4.70 g, 13.5 mmol, 65% yield over two steps) as a light yellow solid.

[001055] A mixture of 1-(3-iodo-1,4,6,7-tetrahydropyrazolo[4,3-c]pyridin-5-yl)ethanone (3.92 g, 13.5 mmol, 1.0 eq), [2-[tert-butyl(dimethyl)silyl]oxyspiro[3.5]nonan-7-yl] methanesulfonate (4.70 g, 13.5 mmol, 1.0 eq), Cs_2CO_3 (13.18 g, 40.5 mmol, 3.0 eq) in DMF (40 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 110 °C for 12 under N_2 atmosphere. The reaction mixture was quenched by addition iced water 400 mL, extracted with ethyl acetate (80 mL × 3). The combined organic layers were washed with brine (100 mL × 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by semi-preparative reverse phase HPLC (column: Phenomenex luna C18 (250 × 70mm, 10 um);mobile phase: [water(FA)-ACN];gradient:60%-90% B over 30 min). To give the product 1-[1-[2-[tert-butyl(dimethyl)silyl]oxyspiro[3.5]nonan-7-yl]-3-iodo-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]ethanone (1.60 g, 2.94 mmol, 22% yield) as a white solid.

[001056] LC-MS: MS (ESI^+): t_R = 0.723 min, m/z = 544.2 [M + H^+]

[001057] To a solution of 1-[1-[2-[tert-butyl(dimethyl)silyl]oxyspiro[3.5]nonan-7-yl]-3-iodo-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]ethanone (800 mg, 1.47 mmol, 1 eq) in MeOH (15 mL) was added NH_4F (545 mg, 14.7 mmol, 10.0 eq).The mixture was stirred at 25 °C for 12 h under N_2. The mixture was diluted with iced water (120 mL), extracted with DCM (60 mL × 3).The combined organic layers were dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to give a residue. To give the product 1-[1-(2-hydroxyspiro[3.5]nonan-7-yl)-3-iodo-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]ethanone (600 mg) as a white solid and directly used in the next step without further purification.

[001058] LC-MS: MS (ESI^+): t_R = 0.511 min, m/z = 430.1 [M + H^+]

[001059] To a solution of 1-[1-(2-hydroxyspiro[3.5]nonan-7-yl)-3-iodo-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]ethanone (569 mg) in DCM (10 mL) was added DMP (1.12 g, 2.65 mmol, 821 µL, 2.0 eq) at 0 °C .The mixture was stirred at 25 °C for 1 h under N_2. The mixture was quenched by addition saturated aqueous $NaHCO_3$ (40 mL) and saturated aqueous (40 mL) Na_2SO_3 at 0 °C, extracted with DCM (30 mL × 3).The combined organic layers were dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to give a residue. To give the product 7-(5-acetyl-3-iodo-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl)spiro[3.5]nonan-2-one (566 mg) as yellow gumand directly used in the next step without further purification.

[001060] LC-MS: MS (ESI^+): t_R = 0.531 min, m/z = 528.1 [M + H^+]

[001061] To a solution of 7-(5-acetyl-3-iodo-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl)spiro[3.5]nonan-2-one (566 mg, 1.32 mmol, 1.0 eq), tert-butyl piperazine-1-carboxylate (296 mg, 1.59 mmol, 1.2 eq) in DCM (10 mL) was added Et_3N (268 mg, 2.65 mmol, 369 μL, 2.0 eq) and $NaBH(OAc)_3$ (1.40 g, 6.62 mmol, 5.0 eq). The mixture was stirred at 25 °C for 12 under N_2. The mixture was quenched by addition iced water (50 mL), extracted with DCM (20 mL × 3).The combined organic layers were dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate=10/1 to Dichloromethane/Methanol =10/1). Compound tert-butyl 4-[7-(5-acetyl-3-iodo-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl)spiro[3.5]nonan-2-yl]piperazine-1-carboxylate (790 mg, 1.32 mmol, 99% yield over three steps) as a white solid.

[001062] LC-MS: MS (ESI^+): t_R = 0.515 min, m/z = 598.2 [M + H^+]

[001063] To a solution of tert-butyl 4-[7-(5-acetyl-3-iodo-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl)spiro[3.5]nonan-2-yl]piperazine-1-carboxylate (400 mg, 669 μmol, 1.0 eq) and 7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-1,2,3,4-tetrahydroquinoline (200 mg, 760 μmol, 1.1 eq) in tert-amyl alcohol (10 mL) was added XPhos Pd G4 (58 mg, 66.9 μmol, 0.1 eq) and t-BuONa (2 M, 837 μL, 2.5 eq). The mixture was stirred at 90 °C for 12 h under N_2. The mixture was poured into ice-water (50 mL). The aqueous phase was extracted with ethyl acetate (30 mL × 3). The combined organic phase was washed with brine (30 mL), dried with anhydrous sodium sulfate, filtered and concentrated under vacuum. The residue was purified by pre-TLC (DCM/MeOH = 10/1). Compound tert-butyl 4-[7-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]spiro[3.5]nonan-2-yl]piperazine-1-carboxylate (150 mg, 205 μmol, 31% yield) was obtained as a brown solid.

[001064] LC-MS: MS (ESI^+): t_R = 0.531 min, m/z = 733.4 [M + H^+]

[001065] To a solution of tert-butyl 4-[7-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]spiro[3.5]nonan-2-yl]piperazine-1-carboxylate (150 mg, 205 μmol, 1.0 eq) in DCM (5 mL) was added TFA (4.61 g, 40.4 mmol, 3 mL, 197.3 eq). The mixture was stirred at 25 °C for 1 h. The mixture was concentrated to give a residue. Compound 1-[3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-1-(2-piperazin-1-ylspiro[3.5]nonan-7-yl)-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]ethanone (150 mg,) was obtained as a brown solid and directly used in the next step without further purification.

[001066] LC-MS: MS (ESI^+): t_R = 0.772 min, m/z = 633.4 [M + H^+]

[001067] To a solution of 1-[3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-1-(2-piperazin-1-ylspiro[3.5]nonan-7-yl)-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]ethanone (150 mg) in NMP (2 mL) was added DIEA (742 mg, 5.74 mmol, 1 mL, 28.6 eq) and 6-chloro-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide (90 mg, 230 μmol, 1.2 eq). The mixture was stirred at 70 °C for 12 h. The mixture was diluted with iced water (30 mL) and the organic layer was collected. Besides, the water layer was extracted with dichloromethane (20 mL × 3). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by semi-preparative reverse phase HPLC (column: Phenomenex luna C18

150 × 25mm × 10um; mobile phase: [water (FA)-ACN]; gradient: 27%-57% B over 10 min). Compound 6-[4-[7-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]spiro[3.5]nonan-2-yl]piperazin-1-yl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide (61.68 mg, 62.12 μmol, 31% yield over two steps) was obtained as a yellow solid.

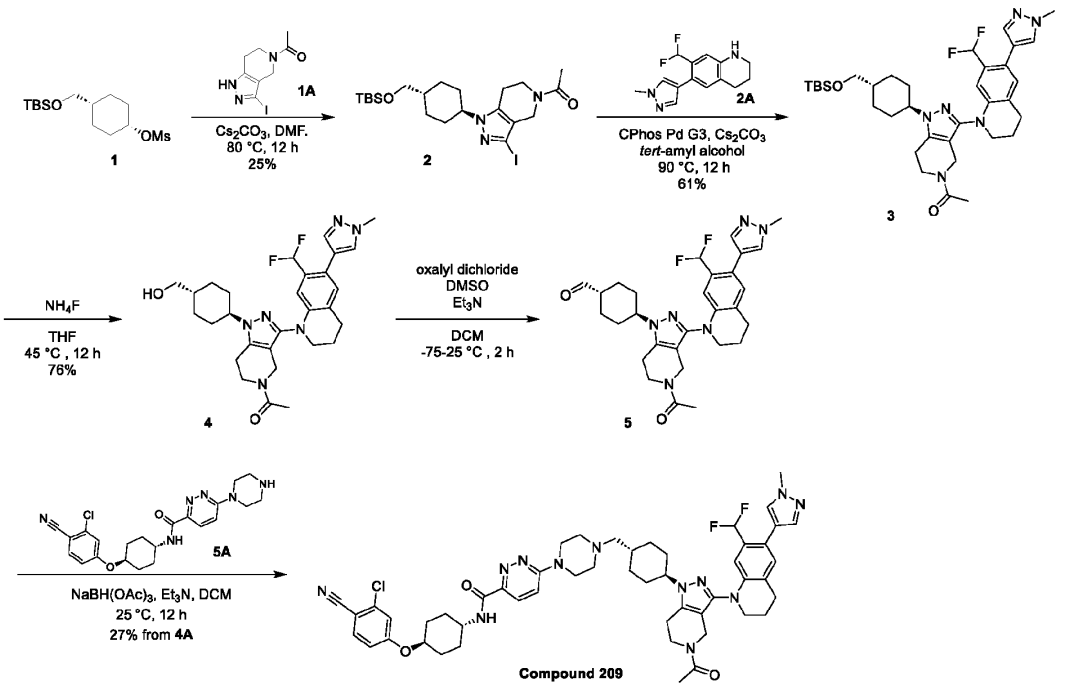
[001068] **^{1}H NMR** (400 MHz, CHLOROFORM-) δ = 8.00 (d, *J*=9.6 Hz, 1 H) 7.87 (d, *J*=8.0 Hz, 1 H) 7.51 - 7.60 (m, 2 H) 7.38 - 7.44 (m, 1 H) 6.95 - 7.08 (m, 3 H) 6.83 - 6.91 (m, 2 H) 6.35 - 6.70 (m, 1 H) 4.29 - 4.38 (m, 1 H) 4.11 - 4.28 (m, 2 H) 4.01 - 4.10 (m, 1 H) 3.96 (d, *J*=2.0 Hz, 3 H) 3.68 - 3.93 (m, 9 H) 2.87 (m, 2 H) 2.67 - 2.82 (m, 3 H) 2.47 (s, 4 H) 2.11 - 2.29 (m, 7 H) 2.00 - 2.10 (m, 5 H) 1.85 - 2.00 (m, 4 H) 1.71 - 1.84 (m, 5 H) 1.43 - 1.57 (m, 4 H).

[001069] **LC-MS:** MS (ESI$^+$): t_R = 2.987 min, m/z = 987.7 [M + H$^+$]

[001070] The compounds below were prepared in a similar manner as described in Example 40.

Compound	Name	^{1}H NMR ($CDCl_3$)	LC-MS [M + H$^+$]
241	6-[7-[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]cyclohexyl]-2-azaspiro[3.5]nonan-2-yl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	δ = 7.96 (d, J = 9.2 Hz, 1H), 7.88 (d, J = 8.4 Hz, 1H), 7.60 - 7.51 (m, 2H), 7.44 - 7.37 (m, 1H), 7.07 - 6.97 (m, 2H), 6.91 - 6.82 (m, 2H), 6.69 - 6.35 (m, 2H), 4.38 - 4.29 (m, 1H), 4.28 - 4.10 (m, 2H), 4.09 - 4.01 (m, 1H), 3.99 - 3.94 (m, 3H), 3.93 - 3.81 (m, 6H), 3.80 - 3.64 (m, 3H), 2.94 - 2.69 (m, 4H), 2.24 - 2.14 (m, 5H), 2.12 - 2.03 (m, 5H), 2.03 - 1.98 (m, 4H), 1.93 (d, J = 12.0 Hz, 3H), 1.81 - 1.72 (m, 3H), 1.61 - 1.40 (m, 5H), 1.27 - 1.06 (m, 6H)	986.7
242	6-[7-[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]cyclohexyl]-2-azaspiro[3.5]nonan-2-yl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	δ = 7.95 (d, J = 9.2 Hz, 1H), 7.88 (d, J = 8.0 Hz, 1H), 7.60 - 7.51 (m, 2H), 7.41 (d, J = 6.0 Hz, 1H), 7.07 - 6.98 (m, 2H), 6.92 (d, J = 10.4 Hz, 1H), 6.86 (dd, J = 2.4, 8.8 Hz, 1H), 6.68 - 6.36 (m, 2H), 4.37 - 4.29 (m, 1H), 4.29 - 4.11 (m, 2H), 4.10 - 3.98 (m, 2H), 3.96 (d, J = 1.6 Hz, 3H), 3.93 - 3.81 (m, 5H), 3.79 - 3.65 (m, 3H), 2.88 (td, J = 6.0, 11.6 Hz, 2H), 2.82 - 2.70 (m, 2H), 2.23 - 2.04 (m, 11H), 2.03 - 1.94 (m, 4H), 1.88 (br d, J = 11.6 Hz, 2H), 1.80 - 1.70 (m, 4H), 1.59 - 1.41 (m, 7H), 1.32 (br d, J = 2.0 Hz, 1H), 1.03 - 0.89 (m, 2H)	986.7

[001071] **Example 41:** Synthesis of 6-[4-[[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]cyclohexyl]methyl]piperazin-1-yl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide (**Compound 209**)



[001072] Synthesis of 1 was reported in WO2022/161414, 2022, A1.

[001073] Synthesis of 1A was reported in Journal of Medicinal Chemistry, 2024, vol. 67, # 7, p. 5275 – 5304.

[001074] Synthesis of 2A was reported in reported in Journal of Cell Chemical Biology, 2021, vol. 28, # 4, p. 503 - 12,514.

[001075] Synthesis of 5A was reported in EP3957633, 2022, A1

[001076] To a solution of [4-[[tert-butyl(dimethyl)silyl]oxymethyl]cyclohexyl] methanesulfonate (2.66 g, 8.24 mmol, 1.2 eq) and1-(3-iodo-1,4,6,7-tetrahydropyrazolo[4,3-c]pyridin-5-yl)ethanone (2.00 g, 6.87 mmol, 1.0 eq) in DMF (50 mL) was added Cs_2CO_3 (5.60 g, 17.2 mmol, 2.5 eq). The reaction mixture as stirred at 80 °C for 12 h under N_2. The mixture was poured into iced water (500 mL). The aqueous phase was extracted with ethyl acetate (80 mL × 3). The combined organic phase was washed with brine (100 mL × 2), dried with anhydrous sodium sulfate, filtered and concentrated under vacuum. The residue was purified by semi-preparative reverse phase HPLC (column: Phenomenex luna C18 150 × 40mm × 15um; mobile phase: [water (FA)-ACN];gradient:90%-100% B over 10 min). Compound 1-[1-[4-[[tert-butyl(dimethyl)silyl]oxymethyl]cyclohexyl]-3-iodo-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]ethanone (900 mg, 1.74 mmol, 25 % yield) was obtained as a white solid.

[001077] LC-MS: MS (ESI^+): t_R = 0.707 min, m/z = 518.2 [M + H^+]

[001078] To a solution of 1-[1-[4-[[tert-butyl(dimethyl)silyl]oxymethyl]cyclohexyl]-3-iodo-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]ethanone (800 mg, 1.55 mmol, 1.0 eq) and 7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-1,2,3,4-tetrahydroquinoline (529 mg, 2.01 mmol, 1.3 eq) in tert-amyl alcohol (15 mL) was added Cs_2CO_3 (1.26 g, 3.86 mmol, 2.5 eq) and CPhos Pd G3 (150 mg, 186 μmol, 0.12 eq). The reaction

mixture as stirred at 90 °C for 12 h under N_2. The reaction mixture was filtered and washed with DCM/MeOH (10/1; 20 mL × 2). The collected filtrate was concentrated to give a residue. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=3/1 to 1/1 to 1/3). Compound 1-[1-[4-[[tert-butyl(dimethyl)silyl]oxymethyl]cyclohexyl]-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]ethanone (620 mg, 950 μmol, 61% yield) was obtained as a light brown solid.

[001079] LC-MS: MS (ESI^+): t_R = 1.137 min, m/z = 653.4 [$M + H^+$]

[001080] To a solution of 1-[1-[4-[[tert-butyl(dimethyl)silyl]oxymethyl]cyclohexyl]-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]ethanone (620 mg, 950 μmol, 1.0 eq) in THF (8 mL) was added TBAF (1 M, 2.85 mL, 3.0 eq). The reaction mixture as stirred at 45 °C for 12 h under N_2. The mixture was poured into iced water (40 mL). The aqueous phase was extracted with ethyl acetate (25 mL × 3). The combined organic phase was washed with brine (30 mL × 2), dried with anhydrous sodium sulfate, filtered and concentrated under vacuum. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=1/1 to 3/1 to dichloromethane /methyl alcohol=30/1). Compound 1-[3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-1-[4-(hydroxymethyl)cyclohexyl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]ethanone (440 mg, 719 μmol, 76% yield) was obtained as a white solid.

[001081] LC-MS: MS (ESI^+): t_R = 0.504 min, m/z = 539.3 [$M + H^+$]

[001082] To a solution of oxalyl dichloride (319 mg, 2.51 mmol, 0.22 mL, 3.1 eq) in DCM (12 mL) was added dropwise a solution of DMSO (260 mg, 3.33 mmol, 260 μL, 4.1 eq) in DCM (3 mL) at -78 °C under nitrogen and stirred at 78 °C for 0.5 h. Then to the mixture was added dropwise a solution of 1-[3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-1-[4-(hydroxymethyl)cyclohexyl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]ethanone (440 mg, 817 μmol, 1.0 eq) in DCM (3 mL). The mixture was stirred at -78 °C for 1 h before Et_3N (800 mg, 7.90 mmol, 1.1 mL, 9.7 eq) was added dropwise at -78 °C. Then the mixture was slowly warmed to 25 °C and stirred for 0.5 h. The mixture was diluted with water (30 mL) and the organic layer was collected. Besides, the water layer was extracted with dichloromethane (20 mL × 3). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=1/1 to 4/1 to petroleum ether/tetrahydrofuran =1/1 to 1/2). Compound 4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]cyclohexanecarbaldehyde (400 mg) was obtained as a light yellow gum.

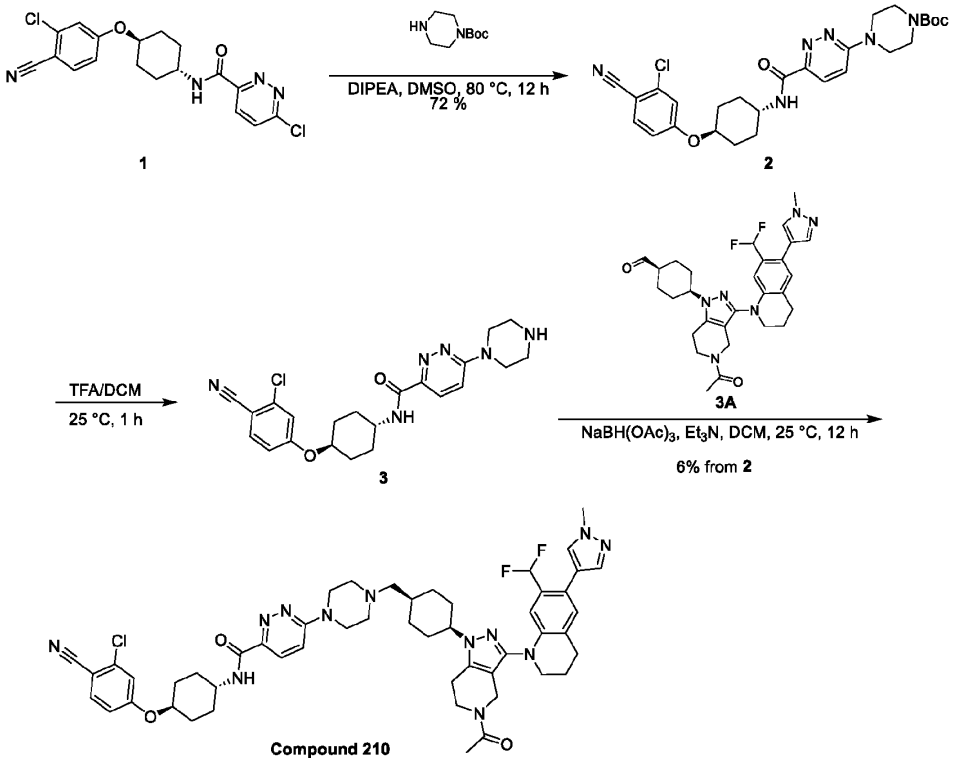
[001083] To a solution of N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]-6-piperazin-1-yl-pyridazine-3-carboxamide (310 mg) in DCM (10 mL) was added Et_3N (377 mg, 3.73 mmol, 519 μL, 10.0 eq), 4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]cyclohexanecarbaldehyde (200 mg) and $NaBH(OAc)_3$ (395 mg, 1.86 mmol, 5.0 eq). Then the mixture was stirred at 25 °C for 12 h. The mixture was diluted with water (40 mL) and the

organic layer was collected. The water layer was extracted with dichloromethane (20 mL × 2). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=0/1 to dichloromethane /methyl alcohol=30/1) and semi-preparative reverse phase HPLC (column: Unisil 3-100 C18 Ultra 150 × 50mm × 3 um; mobile phase: [water (FA)-ACN]; gradient:28%-58% B over 10 min). Compound 6-[4-[[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]cyclohexyl]methyl]piperazin-1-yl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide (99.97 mg, 100.90 μmol, 27% yield over two steps) was obtained as a off-white solid.

[001084] **^{1}H NMR** (400 MHz, CHLOROFORM-*d*) δ = 8.00 (d, *J*=9.6 Hz, 1 H) 7.88 (d, *J*=8.4 Hz, 1 H) 7.51 - 7.61 (m, 2 H) 7.37 - 7.44 (m, 1 H) 6.94 - 7.08 (m, 3 H) 6.81 - 6.90 (m, 2 H) 6.34 - 6.71 (m, 1 H) 4.29 - 4.38 (m, 1 H) 4.11 - 4.28 (m, 2 H) 4.01 - 4.11 (m, 1 H) 3.95 (d, *J*=2.0 Hz, 3 H) 3.91 (m, 2 H) 3.64 - 3.84 (m, 7 H) 2.83 - 2.93 (m, 2 H) 2.77 - 2.83 (m, 1 H) 2.75 (m, 1 H) 2.56 (s, 4 H) 2.14 - 2.26 (m, 7 H) 1.97 - 2.12 (m, 10 H) 1.61 - 1.68 (m, 3 H) 1.40 - 1.53 (m, 2 H) 1.09 (m, 2 H).

[001085] **LC-MS:** MS (ESI$^+$): t_R = 2.905 min, m/z = 961.7 [M + H$^+$]

[001086] **Example 42:** Synthesis of 6-[4-[[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]cyclohexyl]methyl]piperazin-1-yl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide (**Compound 210**)



[001087] To a solution of 6-chloro-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide (200 mg, 511 μmol, 1.0 eq), tert-butyl piperazine-1-carboxylate (95 mg, 511 μmol, 1.0 eq) in DMSO (2 mL) was added DIPEA (198 mg, 1.53 mmol, 267 μL, 3.0 eq). The mixture was stirred at 80 °C for 12 h. To the reaction mixture was added water (50 mL) and the mixture was extracted with ethyl acetate (50 mL × 3). The combined organic phase was washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduce pressure. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate=20/1 to 3/1). Compound tert-butyl 4-[6-[[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]carbamoyl]pyridazin-3-yl]piperazine-1-carboxylate (200 mg, 369 μmol, 72% yield) was obtained as a white solid.

[001088] LC-MS: MS (ESI^+): t_R = 0.628 min, m/z = 541.2 [M + H^+]

[001089] To a solution of tert-butyl 4-[6-[[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]carbamoyl]pyridazin-3-yl]piperazine-1-carboxylate (200 mg, 369 μmol, 1.0 eq) in DCM (5 mL) was added TFA (2.46 g, 21.5 mmol, 1.6 mL, 58.2 eq). The mixture was stirred at 25 °C for 1 h. The reaction mixture was concentrated under reduce pressure to give the crude product. Compound N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]-6-piperazin-1-yl-pyridazine-3-carboxamide (162 mg) was obtained as a yellow oil and directly used into next step without further purification.

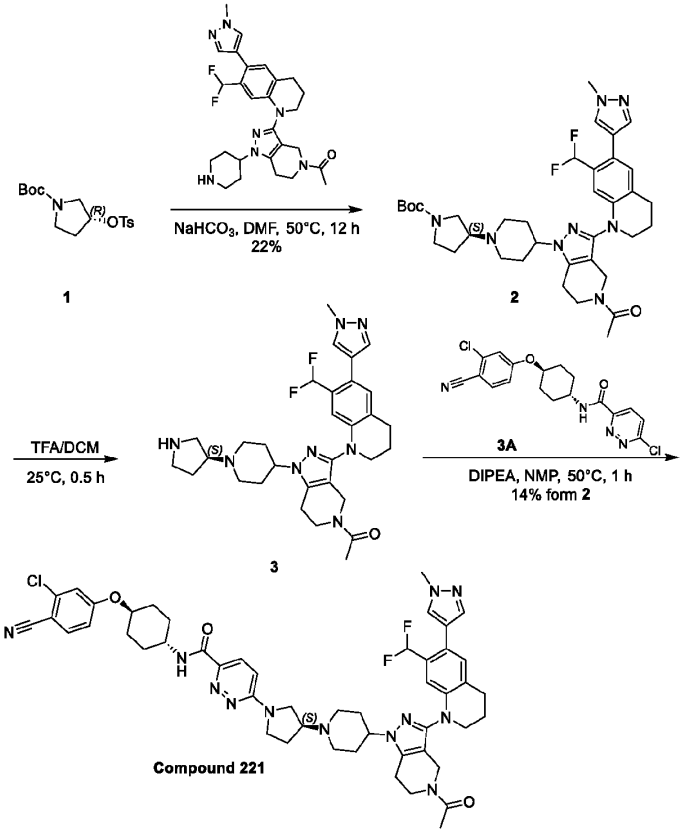
[001090] LC-MS: MS (ESI^+): t_R = 0.523 min, m/z = 441.1 [M + H^+]

[001091] To a solution of N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]-6-piperazin-1-yl-pyridazine-3-carboxamide (50 mg), 4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]cyclohexanecarbaldehyde (61 mg, 113 μmol, 1.0 eq) in DCM (3 mL) was added Et_3N (34 mg, 340 μmol, 47 μL, 3.0 eq). The mixture was stirred at 25 °C for 0.5 h, and then $NaBH(OAc)_3$ (72 mg, 340 μmol, 3.0 eq) were added. The reaction was stirred at 25 °C for 11.5 h. To the reaction mixture was added water (30 mL) and the mixture was extracted with DCM (30 mL × 3). The combined organic phase was washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduce pressure. The crude product was purified by *prep*-TLC (DCM/MeOH = 10/1) and then purified by *prep*-HPLC (column: Phenomenex Luna C18 150*25mm*10um;mobile phase: [water(FA)-ACN];gradient:28%-58% B over 10 min). Compound 6-[4-[[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]cyclohexyl]methyl]piperazin-1-yl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide (6.56 mg, 6.7 μmol, 6 % yield over two steps) was obtained as an off-white solid.

[001092] ^{1}**H NMR** (400 MHz, CD_3OD) δ = 7.92 - 7.90 (d, *J* = 9.6 Hz, 1H), 7.70 - 7.68 (d, *J* = 8.8 Hz, 1H), 7.64 (s, 1H), 7.51 (s, 1H), 7.30 - 7.28 (d, *J* = 9.6 Hz, 1H), 7.21 - 7.20 (d, *J* = 2.8 Hz, 1H), 7.09 (m, 1H), 7.06 - 7.04 (d, *J* = 8.4 Hz, 1H), 6.75 - 6.43 (m, 2H), 4.55 - 4.45 (m, 1H), 4.25 - 4.23 (m, 2H), 4.21 (m, 1H), 3.93 - 3.82 (m, 11H), 3.68 - 3.67 (m, 2H), 2.92 (m, 3H), 2.80 (m, 1H), 2.63 - 2.61 (m, 4H), 2.54 - 2.53 (m, 2H), 2.20 (m, 4H), 2.10 - 2.06 (m, 7H), 1.93 (m, 2H), 1.76 - 1.62 (m, 8H).

LC-MS: MS (ESI^+): t_R = 1.900 min, m/z = 961.6 [M + H^+]

[001093] Example 43: Synthesis of 6-[(3S)-3-[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]pyrrolidin-1-yl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide **(Compound 221)**



[001094] To a solution of 1-[3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-1-(4-piperidyl)-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]ethanone (400 mg, 385 μmol, 1.0 eq) in DMF (4 mL) was added $NaHCO_3$ (97 mg, 1.2 mmol, 3.0 eq) and tert-butyl (3R)-3-(p-tolylsulfonyloxy)pyrrolidine-1-carboxylate (657 mg, 1.9 mmol, 5.0 eq). The resulting mixture was stirred at 50 °C for 12 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150*40mm* 15um; mobile phase: [water (FA)-ACN]; gradient: 22%-52% B over 10 min). Compound tert-butyl (3S)-3-[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]pyrrolidine-1-carboxylate (80 mg, 118 μmol, 22% yield) was obtained as a yellow oil.

[001095] LC-MS: MS (ESI^+): t_R = 0.808 min, m/z = 679.5 [$M + H^+$]

[001096] To a solution of tert-butyl (3S)-3-[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]pyrrolidine-1-carboxylate (80 mg, 118 μmol, 1.0 eq) in DCM (3 mL) was added TFA (1.23 g, 10.8 mmol, 800 μL, 91.4 eq). This mixture was stirred at 25 °C for 0.5 h under N_2 and then concentrated. Compound 1-[3-[7-

(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-1-[1-[(3S)-pyrrolidin-3-yl]-4-piperidyl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]ethanone (40 mg) was obtained as a yellow oil and directly used in the next step without further purification.

[001097] LC-MS: MS (ESI^+): t_R = 0.711 min, m/z = 579.5 [M + H^+]

[001098] To a solution of 1-[3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-1-[1-[(3S)-pyrrolidin-3-yl]-4-piperidyl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]ethanone (40 mg) in NMP (1 mL) was added DIPEA (27 mg, 207 μmol, 36 μL, 3.0 eq) and 6-chloro-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide (27 mg, 69 μmol, 1.0 eq). The mixture was stirred at 50 °C for 12 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge 150*25mm* 5um; mobile phase: [water (NH_4HCO_3)-ACN]; gradient: 45%-75% B over 9 min). Compound 6-[(3S)-3-[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]pyrrolidin-1-yl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide (16.05 mg, 17 μmol, 14% yield over two steps) was obtained as an off-white solid.

[001099] ^{1}**H NMR** (400 MHz, $CDCl_3$) δ = 8.00 (d, J = 9.6 Hz, 1H), 7.89 (d, J = 8.0 Hz, 1H), 7.60 - 7.50 (m, 2H), 7.45 - 7.37 (m, 1H), 7.09 - 6.97 (m, 2H), 6.90 - 6.82 (m, 2H), 6.72 (d, *J* = 9.2 Hz, 1H), 6.69 - 6.36 (m, 1H), 4.39 - 4.29 (m, 1H), 4.25 (s, 1H), 4.12 (s, 1H), 4.10 - 4.02 (m, 1H), 4.00 - 3.88 (m, 6H), 3.78 - 3.67 (m, 3H), 3.62 - 3.50 (m, 1H), 3.50 - 3.38 (m, 1H), 3.25 - 3.16 (m, 1H), 3.15 -3.03 (m, 2H), 2.92 - 2.79 (m, 3H), 2.78 - 2.72 (m, 1H), 2.40 - 2.25 (m, 5H), 2.25 - 2.12 (m, 6H), 2.11 - 2.02 (m, 5H), 2.02 - 1.94 (m, 2H), 1.77 - 1.66 (m, 2H), 1.53 - 1.40 (m, 2H).

[001100] LC-MS: MS (ESI^+): t_R = 2.824 min, m/z = 933.6 [M + H^+]

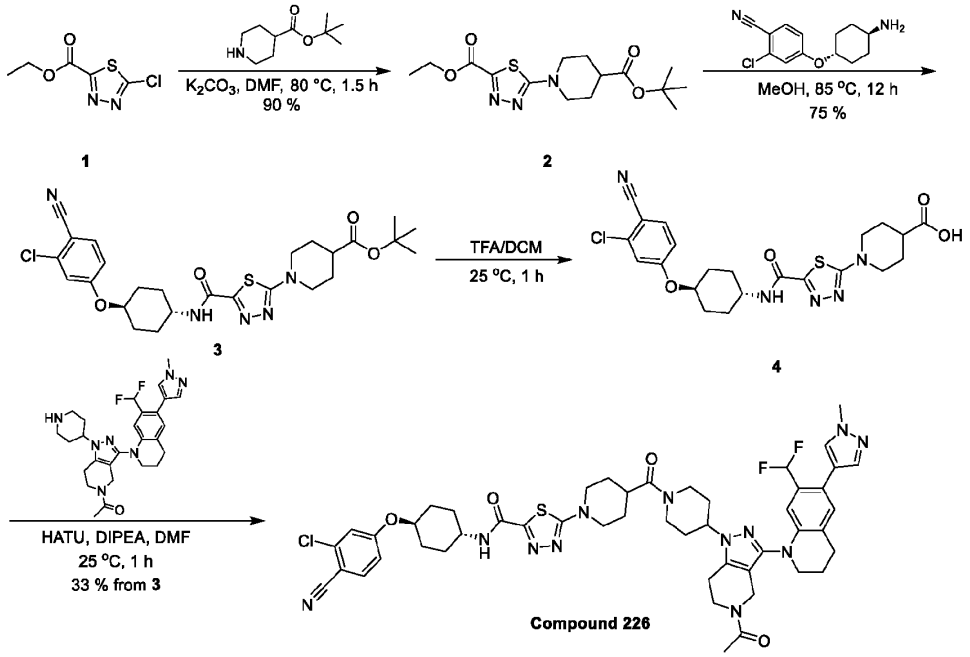
[001101] The compounds below were prepared in a similar manner as described in Example 43.

Compound	Name	^{1}H NMR (DMSO-d_6)	LC-MS [M + H^+]
222	6-[(3R)-3-[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c] pyridin-1-yl]-1-piperidyl] pyrrolidin-1-yl]-N-[4-(3-chloro-4-cyano-phenoxy) cyclohexyl] pyridazine-3-carboxamide	δ = 8.61 - 8.48 (m, 1H), 8.13 (s, 1H), 7.92 - 7.83 (m, 2H), 7.75 (s, 1H), 7.50 (s, 1H), 7.42 - 7.34 (m, 1H), 7.15 - 7.09 (m, 2H), 7.04 (s, 1H), 6.96 - 6.63 (m, 2H), 4.61 - 4.30 (m, 2H), 4.22 - 3.95 (m, 2H), 3.93 - 3.80 (m, 6H), 3.78 - 3.67 (m, 3H), 3.64 - 3.56 (m, 3H), 3.55 - 3.44 (m, 2H), 3.27 - 3.06 (m, 2H), 2.94 - 2.72 (m, 5H), 2.70 - 2.55 (m, 1H), 2.40 - 2.27 (m, 2H), 2.18 - 2.05 (m, 6H), 2.00 - 1.87 (m, 6H), 1.69 - 1.59 (m, 2H), 1.57 - 1.46 (m, 2H)	933.6
227	6-[6-[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]-2-azaspiro[3.4]octan-2-yl]-N-[4-(3-chloro-4-cyano-	($CDCl_3$) δ 8.45 - 8.30 (m, 1H), 7.98 (d, *J* = 9.2 Hz, 1H), 7.86 (d, *J* = 8.4 Hz, 1H), 7.60 - 7.50 (m, 2H), 7.41 (d, *J* = 4.4 Hz, 1H), 7.11 - 6.94 (m, 3H), 6.90 - 6.82 (m, 1H), 6.72 - 6.39 (m, 2H), 4.39 - 4.14 (m, 5H), 4.12 - 4.02 (m, 4H), 3.97 (s, 3H), 3.91 (s, 1H),	973.4

Compound	Name	^{1}H NMR (DMSO-d_6)	LC-MS [M + H$^+$]
	phenoxy)cyclohexyl]pyridazine-3-carboxamide	3.76 (t, J = 5.6 Hz, 1H), 3.72 - 3.63 (m, 2H), 3.57 - 3.39 (m, 2H), 3.30 - 3.07 (m, 2H), 2.92 - 2.86 (m, 2H), 2.81 (t, J = 5.2 Hz, 1H), 2.74 (d, J = 5.6 Hz, 1H), 2.39 - 2.33 (m, 2H), 2.20 - 2.16 (m, 5H), 2.07 (s, 3H), 1.76 - 1.64 (m, 2H), 1.54 - 1.40 (m, 2H)	
228	6-[2-[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c] pyridin-1-yl]-1-piperidyl]-6-azaspiro [3.4] octan-6-yl]-N-[4-(3-chloro-4-cyano-phenoxy) cyclohexyl] pyridazine-3-carboxamide	δ = 8.62 - 8.45 (m, 1H), 8.14 (s, 1H), 7.88 - 7.78 (m, 2H), 7.75 (s, 1H), 7.50 (s, 1H), 7.41 - 7.34 (m, 1H), 7.17 - 7.09 (m, 2H), 6.95 - 6.64 (m, 3H), 4.61 - 4.46 (m, 1H), 4.20 - 4.04 (m, 3H), 3.86 (s, 4H), 3.77 - 3.55 (m, 7H), 3.03 - 2.79 (m, 7H), 2.73 (s, 1H), 2.18 - 2.04 (m, 8H), 2.01 - 1.85 (m, 13H), 1.68 - 1.48 (m, 4H)	973.4
229	6-[6-[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c] pyridin-1-yl]-1-piperidyl]-2- azaspiro [3.3] heptan-2-yl]-N- [4-(3-chloro-4-cyano-phenoxy) cyclohexyl]pyridazine-3-carboxamide	δ = 8.54 (d, J = 8.0 Hz, 1H), 8.21 (s, 1H), 7.88 - 7.79 (m, 2H), 7.76 (s, 1H), 7.50 (s, 1H), 7.39 (d, J = 2.4 Hz, 1H), 7.17 - 7.09 (m, 2H), 6.95 - 6.65 (m, 3H), 4.60 - 4.48 (m, 1H), 4.20 - 4.10 (m, 4H), 4.04 (s, 3H), 3.87 (s, 4H), 3.76 - 3.67 (m, 2H), 3.62 - 3.57 (m, 2H), 2.94 - 2.78 (m, 6H), 2.75 - 2.65 (m, 2H), 2.41 - 2.34 (m, 2H), 2.14 - 2.03 (m, 6H), 1.99 - 1.94 (m, 4H), 1.93 - 1.84 (m, 6H), 1.70 - 1.48 (m, 4H)	959.4
258	6-[(3S)-3-[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	δ = 8.66 - 8.55 (m, 1H), 7.91 - 7.70 (m, 3H), 7.49 (s, 1H), 7.44 - 7.31 (m, 2H), 7.18 - 7.06 (m, 2H), 6.96 - 6.63 (m, 2H), 4.83 - 4.47 (m, 2H), 4.36 - 4.23 (m, 1H), 4.19 - 4.08 (m, 2H), 3.90 - 3.82 (m, 4H), 3.79 - 3.54 (m, 5H), 3.43 - 3.38 (m, 1H), 3.30 - 3.26 (m, 1H), 3.18 - 2.94 (m, 3H), 2.91 - 2.68 (m, 5H), 2.21 - 2.05 (m, 6H), 2.02 - 1.75 (m, 10H), 1.71 - 1.42 (m, 6H)	947.7
259	6-[(3R)-3-[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	($CDCl_3$) δ = 7.98 (d, J = 9.6 Hz, 1H), 7.90 - 7.82 (m, 1H), 7.60 - 7.51 (m, 2H), 7.44 - 7.37 (m, 1H), 7.08 - 6.95 (m, 3H), 6.90 - 6.82 (m, 2H), 6.70 - 6.36 (m, 1H), 7.74 - 7.61 (m, 1H), 4.40 - 4.21 (m, 3H), 4.12 (s, 1H), 4.10 - 4.00 (m, 1H), 3.98 - 3.94 (m, 3H), 3.94 - 3.86 (m, 2H), 3.79 - 3.66 (m, 3H), 3.28 - 3.11 (m, 2H), 3.10 - 2.94 (m, 2H), 2.93 - 2.70 (m, 4H), 2.60 - 2.37 (m, 3H), 2.31 - 2.13 (m, 8H), 2.13 - 2.02 (m, 5H), 2.00 - 1.88 (m, 3H), 1.64 - 1.56 (m, 3H), 1.52 - 1.40 (m, 2H)	947.7

Compound	Name	^{1}H NMR (DMSO-d_6)	LC-MS [M + H$^+$]
260	6-[(3S)-3-[4-[5-acetyl-3-[7-(difluoromethyl)-6-thiazol-4-yl-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	δ = 9.23 - 9.17 (m, 1H), 8.66 - 8.56 (m, 1H), 7.91 - 7.76 (m, 3H), 7.53 - 7.19 (m, 4H), 7.17 - 7.09 (m, 1H), 6.89 - 6.78 (m, 1H), 4.92 - 4.61 (m, 1H), 4.58 - 4.46 (m, 1H), 4.40 - 4.07 (m, 4H), 3.90 - 3.81 (m, 1H), 3.78 - 3.68 (m, 2H), 3.65 - 3.59 (m, 2H), 3.53 - 3.40 (m, 2H), 3.28 - 3.16 (m, 2H), 3.14 - 2.97 (m, 2H), 2.96 - 2.72 (m, 5H), 2.25 - 1.79 (m, 15H), 1.79 - 1.58 (m, 3H), 1.56 - 1.43 (m, 3H)	950.7
261	6-[(3R)-3-[4-[5-acetyl-3-[7-(difluoromethyl)-6-thiazol-4-yl-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	δ = 9.19 (d, *J* = 2.0 Hz, 1H), 8.60 (d, *J* = 8.4 Hz, 1H), 7.85 (d, *J* = 8.8 Hz, 1H), 7.82 - 7.76 (m, 2H), 7.53 - 7.19 (m, 4H), 7.17 - 7.10 (m, 1H), 6.86 (s, 1H), 4.64 - 4.48 (m, 2H), 4.35 - 4.26 (m, 1H), 4.22 - 4.13 (m, 2H), 4.09 - 3.96 (m, 1H), 3.92 - 3.81 (m, 1H), 3.77 - 3.67 (m, 2H), 3.66 - 3.58 (m, 2H), 3.12 - 2.95 (m, 4H), 2.92 - 2.71 (m, 4H), 2.47 - 2.34 (m, 3H), 2.15 - 2.06 (m, 4H), 2.03 - 1.76 (m, 11H), 1.70 - 1.58 (m, 3H), 1.56 - 1.38 (m, 3H)	950.6

[001102] Example 44: Synthesis of 5-[4-[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]piperidine-1-carbonyl]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy) cyclohexyl]-1,3,4-thiadiazole-2-carboxamide (**Compound 226**)



[001103] To a solution of ethyl 5-chloro-1,3,4-thiadiazole-2-carboxylate (1.00 g, 5 mmol, 1.0 eq) in DMF (10 mL) was added K_2CO_3 (2.15 g, 15 mmol, 3.0 eq) and tert-butyl piperidine-4-carboxylate (961 mg, 5 mmol, 1.0 eq). The mixture was stirred at 80 °C for 1.5 h. The reaction mixture was diluted with water (5 mL) and then extracted with ethyl acetate (5 mL x 3). The combined organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~15% Ethyl acetate/Petroleum ether gradient @ 55 mL/min). Compound ethyl 5-(4-tert-butoxycarbonyl-1-piperidyl)-1,3,4-thiadiazole-2-carboxylate (1.60 g, 4 mmol, 90 % yield) was obtained as a white solid.

[001104] LC-MS: MS (ESI^+): t_R = 0.943 min, m/z = 342.2 [M + H^+]

[001105] To a solution of ethyl 5-(4-tert-butoxycarbonyl-1-piperidyl)-1,3,4-thiadiazole-2-carboxylate (100 mg, 292 μmol, 1.0 *eq*) in MeOH (1.5 mL) was added 4-(4-aminocyclohexoxy)-2-chloro-benzonitrile (110 mg, 439 μmol, 1.5 *eq*). The mixture was stirred at 85 °C for 12 h. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, Petroleum ether: Ethyl acetate = 1: 1). Compound tert-butyl 1-[5-[[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]carbamoyl]-1,3,4-thiadiazol-2-yl]piperidine-4-carboxylate (120 mg, 219 μmol, 75 % yield) was obtained as a white solid.

[001106] LC-MS: MS (ESI^+): t_R = 0.911 min, m/z = 546.2 [M + H^+]

[001107] To a solution of tert-butyl 1-[5-[[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]carbamoyl]-1,3,4-thiadiazol-2-yl]piperidine-4-carboxylate (50 mg, 91 μmol, 1.0 eq) in DCM (0.3 mL) was added TFA (153 mg, 1 mmol, 0.1 mL, 14.7 eq). The mixture was stirred at 25 °C for 1 h. The resulting mixture was concentrated under reduced pressure to give a residue. The crude product 1-[5-[[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]carbamoyl]-1,3,4-thiadiazol-2-yl]piperidine-4-carboxylic acid (44 mg) was obtained as a white solid and directly used into the next step without further purification.

[001108] LC-MS: MS (ESI^+): t_R = 0.823 min, m/z = 490.1 [M + H^+]

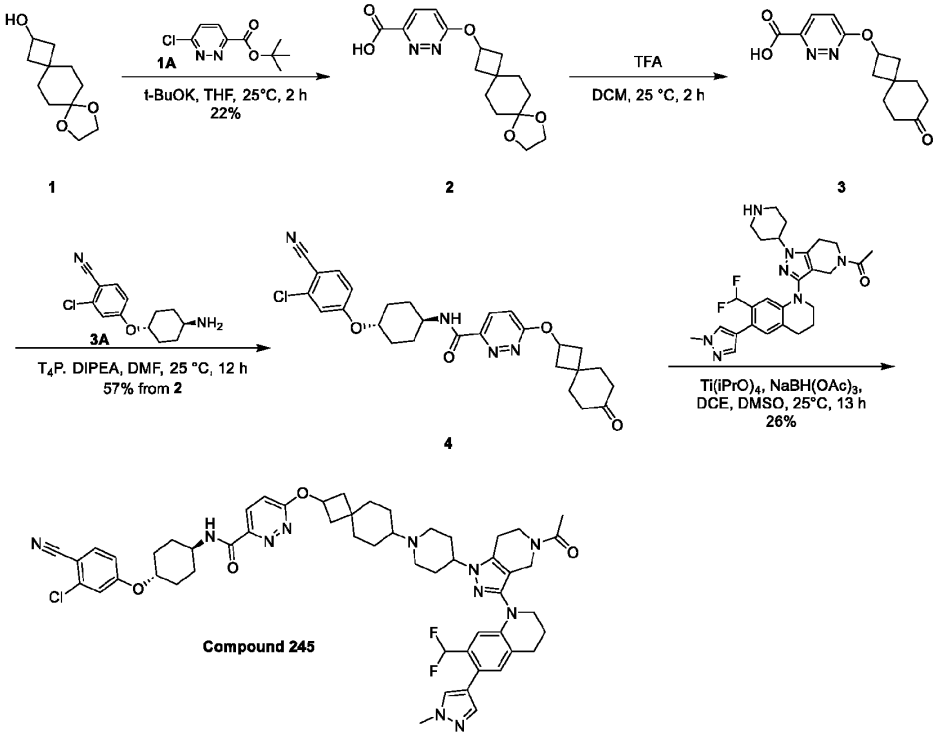
[001109] To a solution of 1-[5-[[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]carbamoyl]-1,3,4-thiadiazol-2-yl]piperidine-4-carboxylic acid (44 mg) and 1-[3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-1-(4-piperidyl)-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]ethanone (46 mg, 91 μmol, 1.0 eq) in DMF (0.5 mL) was added DIPEA (23 mg, 182 μmol, 31 μL, 2.0 eq) and HATU (45 mg, 118 μmol, 1.3 eq). The mixture was stirred at 25 °C for 1 h. The resulting mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150*25mm* 10um; mobile phase: [water (FA)-ACN]; gradient: 50%-80% B over 10 min). Compound 5-[4-[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]piperidine-1-carbonyl]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy) cyclohexyl]-1,3,4-thiadiazole-2-carboxamide (30 mg, 30.21 μmol, 33 % yield over two steps) was obtained as a white solid.

[001110] ^{1}**H NMR** (400 MHz, $CDCl_3$) δ = 7.59 - 7.51 (m, 2H), 7.44 - 7.37 (m, 1H), 7.09 - 6.95 (m, 3H), 6.92 - 6.82 (m, 2H), 6.70 - 6.36 (m, 1H), 4.80 - 4.62 (m, 1H), 4.37 - 4.20 (m, 2H), 4.17 - 4.03 (m, 5H), 3.96

(s, 4H), 3.92 - 3.63 (m, 4H), 3.34 - 3.21 (m, 3H), 2.95 - 2.69 (m, 6H), 2.25 - 1.94 (m, 15H), 1.92 - 1.82 (m, 2H), 1.48 (d, J = 12.2 Hz, 2H)

[001111] LC-MS: MS (ESI^+): t_R = 2.604 min, m/z = 981.4 [$M + H^+$]

[001112] Example 45: Synthesis of 6-[7-[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]spiro[3.5]nonan-2-yl]oxy-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide (**Compound 245**)



[001113] Synthesis of **1** was reported in WO2022/122876, 2022, A1

[001114] Synthesis of **1A** was reported in WO2023/91726, 2023, A1

[001115] Synthesis of **3A** was reported in WO2022/11205, 2022, A1

[001116] To a solution of 8,11-dioxadispiro[3.2.4^7.2^4]tridecan-2-ol (400 mg, 2.02 mmol, 1.0 *eq*) and tert-butyl 6-chloropyridazine-3-carboxylate (440 mg, 2.05 mmol, 1.0 *eq*) in THF (5 mL) was added t-BuOK (1 M, 4.00 mL, 2.0 *eq*) at 25 °C and the mixture was stirred at 25 °C for 2 h under N_2. The mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (FA condition; column: Phenomenex luna C18 150*25mm* 10um; mobile phase: [water (FA)-ACN]; gradient: 47%-77% B over 10 min) and further purified by prep-HPLC (FA condition; column: Phenomenex luna C18 150*25mm* 10um; mobile phase: [water (FA)-ACN]; gradient: 23%-53% B over 10 min). Compound tert-butyl 6-(8,11-dioxadispiro[3.2.4^7.2^4]tridecan-2-yloxy)pyridazine-3-carboxylate (180 mg, 435 μmol, 22% yield) was obtained as a white solid.

[001117] LC-MS: MS (ESI^+): t_R = 0.634 min, m/z =321.1 [M + H^+]

[001118] To a solution of tert-butyl 6-(8,11-dioxadispiro[3.2.4^7.2^4]tridecan-2-yloxy)pyridazine-3-carboxylate (180 mg, 478 μmol, 1.0 *eq*) in DCM (0.5 mL) was added TFA (0.5 mL) at 25 °C and the mixture was stirred at 25 °C for 2 h under N_2. The mixture was concentrated under reduced pressure to give a residue. The crude product 6-(7-oxospiro[3.5]nonan-2-yl)oxypyridazine-3-carboxylic acid (132 mg) was obtained as a white solid and used into the next step without further purification.

[001119] LC-MS: MS (ESI^+): t_R = 0.480 min, m/z =277.1 [M + H^+]

[001120] To a solution of 6-(7-oxospiro[3.5]nonan-2-yl)oxypyridazine-3-carboxylic acid (132 mg) and 4-(4-aminocyclohexoxy)-2-chloro-benzonitrile (150 mg, 598 μmol, 1.3 *eq*) in DMF (2 mL) was added DIPEA (445 mg, 3.44 mmol, 600 μL, 7.2 *eq*) and T4P (688 mg, 956 μmol, 50% purity, 2.0 *eq*). The mixture was stirred at 25 °C for 12 h. The reaction mixture was quenched by addition water 20 mL and extracted with Ethyl acetate (30 mL × 3), the orange phase was washed with brine 50 mL, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=10/1 to 2/1). Compound N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]-6-(7-oxospiro[3.5]nonan-2-yl)oxy-pyridazine-3-carboxamide (150 mg, 274 μmol, 57% yield over two steps) was obtained as a yellow solid.

[001121] LC-MS: MS (ESI^+): t_R = 1.010 min, m/z = 509.2 [M + H^+]

[001122] To a solution of N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]-6-(7-oxospiro[3.5]nonan-2-yl)oxy-pyridazine-3-carboxamide (70 mg) and 1-[3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-1-(4-piperidyl)-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]ethanone (70 mg, 137 μmol, 1.0 *eq*) in DCE (0.5 mL) and DMSO (0.5 mL) was added $Ti(i\text{-}PrO)_4$ (482 mg, 1.69 mmol, 0.5 mL, 12.3 *eq*) at 25 °C and the mixture was stirred at 25 °C for 12 h under N_2, Then $NaBH(OAc)_3$ (378 mg, 1.79 mmol, 13.0 *eq*) was added and the mixture was stirred at 25 °C for 1 h under N_2. The reaction mixture was quenched by addition water 20 mL and the white solid was formed, filtered and washed the cake with DCM (50 mL × 3*). The orange phase was washed with brine* (20 mL × 3*)*, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give residue. The residue was purified by prep-HPLC (FA condition; column: Phenomenex luna C18 150*25mm* 10um; mobile phase: [water (FA)-ACN]; gradient: 29%-59% B over 10 min). Compound 6-[7-[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]spiro[3.5]nonan-2-yl]oxy-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide (36.64 mg, 36 μmol, 26% yield,) was obtained as an off-white solid.

[001123] ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.81 (d, *J* = 8.0 Hz, 1H), 8.06 (d, *J* = 9.2 Hz, 1H), 7.85 (d, *J* = 8.8 Hz, 1H), 7.75 (s, 1H), 7.49 (s, 1H), 7.38 (d, *J* = 2.4 Hz, 1H), 7.32 (d, *J* = 9.2 Hz, 1H), 7.18 - 7.08 (m, 2H), 6.97 - 6.62 (m, 2H), 5.38 - 5.28 (m, 1H), 4.61 - 4.47 (m, 1H), 4.22 - 4.09 (m, 2H), 4.09 - 3.98 (m, 1H), 3.94 - 3.80 (m, 4H), 3.77 - 3.68 (m, 2H), 3.60 - 3.56 (m, 2H), 3.05 - 2.95 (m, 2H), 2.86 - 2.69 (m, 4H), 2.44 - 2.29 (m, 4H), 2.16 - 1.60 (m, 22H), 1.57 - 1.22 (m, 6H)

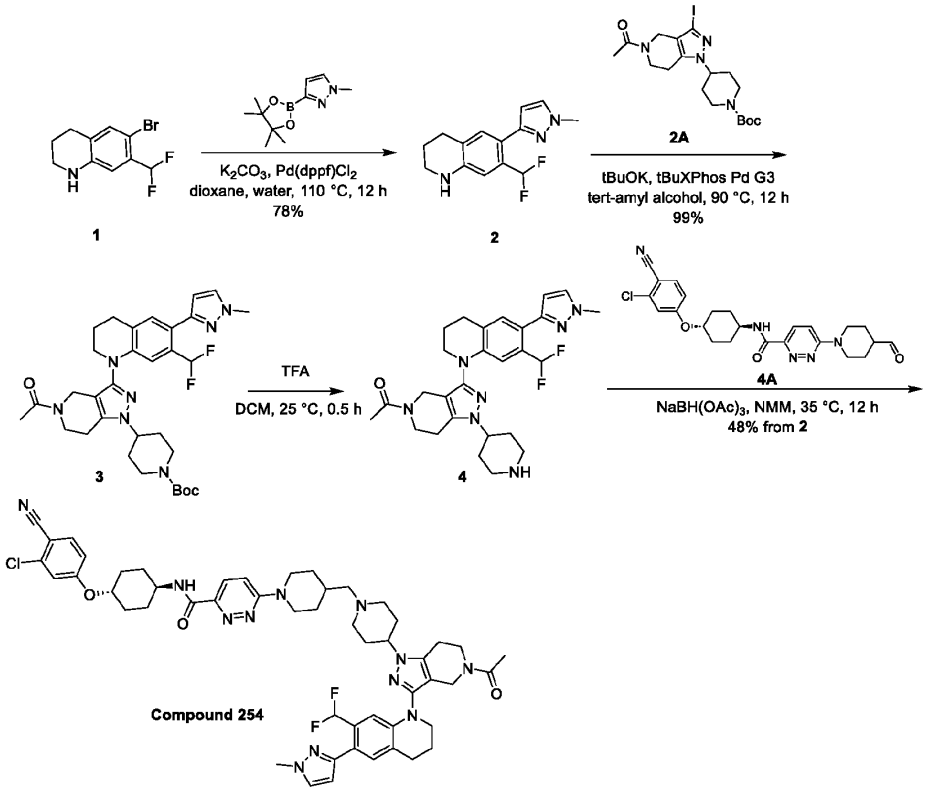
[001124] LC-MS: MS (ESI^+): t_R = 3.105 min, m/z = 1002.6 [M + H^+]

[001125] The compounds below were prepared in a similar manner as described in Example 45.

Compound	Name	^{1}H NMR ($CDCl_3$)	LC-MS [M + H$^+$]
240	6-[3-[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]cyclobutoxy]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	δ = 8.26 - 8.17 (m, 1H), 7.95 - 7.85 (m, 1H), 7.61 - 7.50 (m, 2H), 7.41 (d, J = 7.6 Hz, 1H), 7.15 - 7.00 (m, 3H), 6.98 - 6.82 (m, 2H), 6.71 - 6.35 (m, 1H), 5.61 - 5.48 (m, 1H), 4.39 - 4.28 (m, 2H), 4.15 (s, 1H), 4.12 - 4.02 (m, 1H), 3.96 (s, 3H), 3.94 - 3.86 (m, 1H), 3.80 - 3.73 (m, 1H), 3.73 - 3.62 (m, 2H), 3.53 - 3.38 (m, 1H), 3.36 - 3.23 (m, 1H), 2.93 - 2.71 (m, 6H), 2.60 - 2.46 (m, 2H), 2.33 - 2.14 (m, 9H), 2.12 - 2.01 (m, 4H), 1.81 - 1.72 (m, 4H), 1.56 - 1.41 (m, 4H).	934.6
246	6-[7-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]spiro[3.5]nonan-2-yl]oxy-N-[4-[4-cyano-3-(trifluoromethyl)phenoxy]cyclohexyl]pyridazine-3-carboxamide	(DMSO-d_6) δ = 8.84 (d, J = 8.4 Hz, 1H), 8.07 (d, J = 9.2 Hz, 2H), 7.75 (s, 1H), 7.56 - 7.44 (m, 3H), 7.34 (d, J = 9.2 Hz, 1H), 7.09 (s, 1H), 6.94 - 6.63 (m, 2H), 5.36 (br t, J = 6.8 Hz, 1H), 4.70 - 4.57 (m, 1H), 4.23 - 4.10 (m, 2H), 4.06 - 3.95 (m, 1H), 3.94 - 3.81 (m, 4H), 3.79 - 3.66 (m, 2H), 3.62 - 3.54 (m, 2H), 2.84 (s, 3H), 2.72 (s, 1H), 2.41 - 2.35 (m, 1H), 2.18 - 2.10 (m, 2H), 2.08 (s, 2H), 1.96 - 1.69 (m, 14H), 1.69 - 1.47 (m, 6H)	953.6
247	6-[6-[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]spiro[3.3]heptan-2-yl]oxy-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	(CD_3OD) δ = 8.86 - 8.84 (d, *J* = 8.4 Hz, 1H), 8.07 - 8.05 (d, *J* = 9.2 Hz, 1H), 7.86 - 7.84 (d, *J* = 8.8 Hz, 1H), 7.75 (s, 1H), 7.50 (s, 1H), 7.40 - 7.39 (d, *J* = 2.4 Hz, 1H), 7.32 - 7.30 (d, *J* = 8.8 Hz, 1H), 7.15 - 7.10 (m, 2H), 6.89 - 6.72 (m, 2H), 5.28 - 5.1 (m, 1H), 4.53 - 4.51 (m, 1H), 4.16 - 4.11 (m, 2H), 4.01 (m, 1H), 3.86 (s, 4H), 3.75 - 3.68 (m, 2H), 3.59 - 3.56 (m, 2H), 3.40 (m, 1H), 2.84 (m, 5H), 2.66 (m, 3H), 2.22 (m, 2H), 2.12 (m, 4H), 2.07 (m, 4H), 1.95 - 1.80 (m, 13H), 1.68 - 1.64 (m, 2H), 1.52 - 1.50 (m, 2H).	974.7

Compound	Name	^{1}H NMR ($CDCl_3$)	LC-MS [M + H^+]
252	6-[2-[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]spiro[3.5]nonan-7-yl]oxy-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	δ = 8.58 (s, 1H), 8.17 (d, J = 9.2 Hz, 1H), 7.91 (d, J = 8.4 Hz, 1H), 7.61 - 7.49 (m, 2H), 7.41 (d, J = 6.8 Hz, 1H), 7.08 - 6.97 (m, 3H), 6.92 - 6.82 (m, 2H), 6.71 - 6.36 (m, 1H), 5.36 - 5.25 (m, 1H), 4.39 - 4.18 (m, 2H), 4.12 (s, 1H), 4.09 - 4.02 (m, 1H), 3.96 (d, J = 2.0 Hz, 3H), 3.90 (br t, J = 5.6 Hz, 1H), 3.79 - 3.65 (m, 3H), 3.18 - 3.00 (m, 2H), 2.93 - 2.69 (m, 5H), 2.30 - 2.14 (m, 8H), 2.13 - 2.02 (m, 7H), 1.99 (br s, 4H), 1.76 - 1.59 (m, 7H), 1.59 - 1.40 (m, 4H)	1002.7

[001126] Example 46: Synthesis of 6-[4-[[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-3-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]methyl]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide **(Compound 254)**



[001127] A mixture of 6-bromo-7-(difluoromethyl)-1,2,3,4-tetrahydroquinoline (300 mg, 1.14 mmol, 1 eq),

1-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole (357 mg, 1.72 mmol, 1.5 eq), $Pd(dppf)Cl_2$ (83 mg,114 μmol, 0.1 eq), K_2CO_3 (316 mg, 2.29 mmol, 2 eq) in dioxane (5 mL) and water (1 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 110 °C for 12 h under N_2 atmosphere. To the reaction mixture was added water (20 mL) and the mixture was extracted with ethyl acetate (30 mL x 3). The combined organic phase was washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 50/1 to 5/1). Compound 7-(difluoromethyl)-6-(1-methylpyrazol-3-yl)-1,2,3,4-tetrahydroquinoline (240 mg, 893 μmol, 78%) was obtained as a yellow solid.

[001128] A mixture of tert-butyl 4-(5-acetyl-3-iodo-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl)piperidine-1-carboxylate (265 mg, 558 μmol, 1 eq), 7-(difluoromethyl)-6-(1-methylpyrazol-3-yl)-1,2,3,4-tetrahydroquinoline (218 mg, 828 μmol, 1.48eq), tBuXPhos Pd G_3 (66 mg, 83 μmol, 0.15 eq) and tBuOK (1 M, 1.68 mL, 3 eq) in 2-methylbutan-2-ol (5 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 90 °C for 12 h under N_2 atmosphere. The reaction was filtered and the filtrate was concentrated in vacuum. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 50/1 to 1/2). Compound tert-butyl 4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-3-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]piperidine-1-carboxylate (340 mg, 558 umol, 99%) was obtained as a yellow solid.

[001129] LC-MS: MS (ESI+): t_R = 0.557 min, m/z = 610.4 [M + H^+]

[001130] To a solution of tert-butyl 4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-3-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]piperidine-1-carboxylate (100 mg, 164 μmol, 1 eq) in DCM (1 mL) was added TFA (1.54 g, 13.46 mmol, 1 mL, 82.08 eq). The mixture was stirred at 25 °C for 0.5 h. The mixture was concentrated in vacuum. Compound 1-[3-[7-(difluoromethyl)-6-(1-methylpyrazol-3-yl)-3,4-dihydro-2H-quinolin-1-yl]-1-(4-piperidyl)-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]ethanone (92 mg) was obtained as a yellow oil and directly used in the next step without further purification

[001131] To a solution of 1-[3-[7-(difluoromethyl)-6-(1-methylpyrazol-3-yl)-3,4-dihydro-2H-quinolin-1-yl]-1-(4-piperidyl)-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]ethanone (92 mg) and NMM (74 mg, 737 μmol, 81 μL, 5 eq) in DCE (2 mL), stirred at 35 °C for 0.5 h. The mixture was added N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]-6-(4-formyl-1-piperidyl)pyridazine-3-carboxamide (69 mg, 147 μmol, 1 eq), stirred at 35 °C for 0.5 h. The mixture was added $NaBH(OAc)_3$ (62 mg, 295 μmol, 2 eq), stirred at 35 °C for 11 h under nitrogen atmosphere. The mixture was poured into water (100 mL) and extracted with dichloromethane (50 mL × 3). The combined organic phase was washed with brine (100 mL × 2), dried with anhydrous sodium sulfate, filtered and concentrated in vacuum. The residue was purified by prep-TLC (SiO_2, dichloromethane/methanol=20/1) and prep-HPLC(column: Phenomenex luna C18 150*25mm* 10um;mobile phase: [water(FA)-ACN];gradient:22%-52% B over 9 min). Compound 6-[4-[[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-3-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]methyl]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-

carboxamide (68.47 mg, 71 μmol, 48% yield over two steps) was obtained as a white solid.

[001132] **^{1}H NMR** (400 MHz, CHLOROFORM-*d*) δ = 7.96 (d, *J*=9.6 Hz, 1 H) 7.88 (d, *J*=8.4 Hz, 1 H) 7.57 (d, *J*=8.8 Hz, 1 H) 7.40-7.36 (m, 1 H) 7.30 (s, 1 H) 7.26-7.11 (m, 1 H) 7.01 (d, *J*=2.4 Hz, 1 H) 6.99-6.96 (m, 1 H) 6.94-6.89 (m, 1 H) 6.86 (dd, *J*=8.8, 2.4 Hz, 1 H) 6.38-6.35 (m, 1 H) 4.50 (d, *J*=13.2 Hz, 2 H) 4.39-4.30 (m, 1 H) 4.27 (s, 1 H) 4.11-4.04 (m, 2 H) 3.95 (s, 2 H) 3.94 (s, 1 H) 3.90 (t, *J*=5.6 Hz, 2 H) 3.76-3.71 (m, 2 H) 3.04 (t, *J*=11.6 Hz, 4 H) 2.92-2.87 (m, 2 H) 2.82-2.71 (m, 2 H) 2.27 (d, *J*=8.8 Hz, 4 H) 2.23-2.18 (m, 3 H) 2.16 (s, 3 H) 2.07 (d, *J*=3.2 Hz, 2 H) 2.04 (s, 2 H) 1.94 (s, 2 H) 1.71 (d, *J*=5.6 Hz, 5 H) 1.69-1.62 (m, 2 H) 1.53-1.43 (m, 2 H) 1.32-1.22 (m, 2 H).

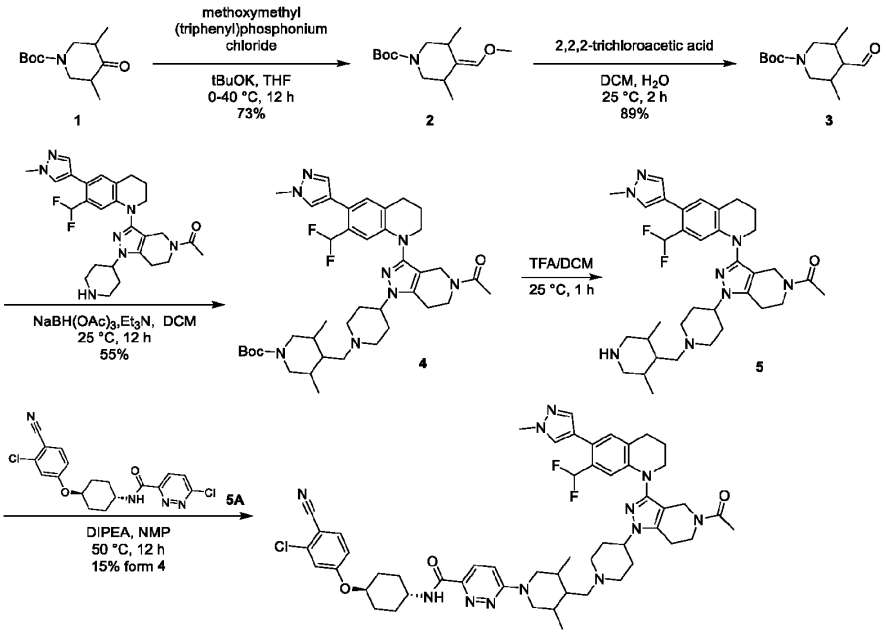
[001133] **LC-MS:** MS (ESI+): t_R = 2.867 min, m/z = 961.6 [M + H$^+$]

[001134] The compounds below were prepared in a similar manner as described in Example 46.

Compound	Name	^{1}H NMR (DMSO-d_6)	LC-MS [M + H$^+$]
253	6-[4-[[4-[5-acetyl-3-[7-(difluoromethyl)-6-thiazol-4-yl-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c] pyridin-1-yl]-1-piperidyl] methyl]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy) cyclohexyl] pyridazine-3-carboxamide	δ = 9.19 (d, J = 2.0 Hz, 1H), 8.59 (d, J = 8.4 Hz, 1H), 8.30 - 8.25 (m, 1H), 7.85 (d, J = 8.8 Hz, 1H), 7.82 - 7.76 (m, 2H), 7.51 - 7.21 (m, 4H), 7.13 (dd, J = 2.4, 8.8 Hz, 1H), 6.87 (s, 1H), 4.59 - 4.42 (m, 3H), 4.23 - 4.12 (m, 2H), 4.09 - 3.80 (m, 2H), 3.79 - 3.57 (m, 4H), 3.07 - 2.83 (m, 8H), 2.18 (m, J = 6.4 Hz, 2H), 2.11 - 1.96 (m, 11H), 1.92 - 1.79 (m, 7H), 1.67 - 1.47 (m, 4H), 1.16 - 1.05 (m, 2H)	964.6
255	6-[4-[[4-[5-acetyl-3-[7-(difluoromethyl)-6-thiazol-2-yl-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]methyl]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide	δ = 8.57 (d, J = 8.0 Hz, 1H), 7.88 (d, J = 3.2 Hz, 1H), 7.85 (d, J = 8.8 Hz, 1H), 7.82 - 7.52 (m, 3H), 7.50 (s, 1H), 7.38 (d, J = 2.4 Hz, 1H), 7.32 (d, J = 9.6 Hz, 1H), 7.13 (m, J = 2.4, 8.8 Hz, 1H), 6.98 - 6.89 (m, 1H), 4.62 - 4.39 (m, 3H), 4.28 - 4.11 (m, 2H), 4.04 (d, J = 4.0 Hz, 1H), 3.91 - 3.80 (m, 1H), 3.78 - 3.67 (m, 2H), 3.67 - 3.59 (m, 2H), 3.00 (t, J = 12.0 Hz, 2H), 2.96 - 2.85 (m, 5H), 2.85 - 2.69 (m, 1H), 2.18 (d, J = 6.4 Hz, 2H), 2.13 - 1.95 (m, 11H), 1.93 - 1.76 (m, 7H), 1.71 - 1.57 (m, 2H), 1.56 - 1.44 (m, 2H), 1.19 - 1.02 (m, 2H)	964.5
256	6-[4-[[4-[5-acetyl-3-[7-(difluoromethyl)-6-oxazol-2-yl-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c] pyridin-1-yl]-1-piperidyl] methyl]-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy) cyclohexyl] pyridazine-3-carboxamide	*δ* = 8.59 (d, J = 8.4 Hz, 1H), 8.17 (d, J = 0.6 Hz, 1H), 7.93 - 7.64 (m, 4H), 7.61 - 7.59 (m, 1H), 7.39 (d, J = 2.4 Hz, 1H), 7.36 - 6.92 (m, 4H), 4.58 - 4.43 (m, 3H), 4.25 - 4.15 (m, 2H), 4.08 - 3.82 (m, 2H), 3.77 - 3.60 (m, 4H), 3.07 - 2.81 (m, 8H), 2.18 (m, J = 5.6 Hz, 2H), 2.12 - 1.96 (m, 11H), 1.91 - 1.78 (m, 7H), 1.68 - 1.47 (m, 4H), 1.16 - 1.03 (m, 2H).	948.7

[001135] **Example 47:** Synthesis of 6-[4-[[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-

dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]methyl]-3,5-dimethyl-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide **(Compound 217)**



Compound 217

[001136] To a solution of methoxymethyl(triphenyl)phosphonium;chloride (15.08 g, 44.0 mmol, 2.0 eq) in THF (150 mL) was added tBuOK (1 M, 66 mL, 3.0 eq) at 0 °C and stirred at 0 °C for 1 h. And then tert-butyl 3,5-dimethyl-4-oxo-piperidine-1-carboxylate (5.00 g, 22.0 mmol, 1.0 eq) in THF (30 mL) was added at 0 °C. The reaction mixture was stirred at 40 °C for 11 h under N_2. The mixture was poured into ethyl acetate (300 mL). The aqueous phase was extracted with water (100 mL × 3), dried with anhydrous sodium sulfate, concentrated under vacuum. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 5/1 to 2/1). Compound tert-butyl 4-(methoxymethylene)-3,5-dimethyl-piperidine-1-carboxylate (4.15 g, 16.1 mmol, 73% yield) was obtained as a colorless oil

[001137] 1H NMR (400 MHz, CHLOROFORM-d) δ = 5.79 (s, 1H), 3.88 - 3.49 (m, 5H), 3.14 - 2.72 (m, 3H), 2.28 (d, J = 1.2 Hz, 1H), 1.46 (s, 9H), 1.12 (s, 6H)

[001138] To a solution of tert-butyl 4-(methoxymethylene)-3,5-dimethyl-piperidine-1-carboxylate (6.80 g, 26.6 mmol, 1.0 eq) in DCM (120 mL) and H_2O (40 mL) was added 2,2,2-trichloroacetic acid (26.11 g, 160 mmol, 6.0 eq). The mixture was stirred at 25 °C for 2 h under N_2. Adjust the PH to 9-10 with $NaHCO_3$ and then concentrate the system, extracted with DCM (300 mL), wash with water (100 mL × 3), dried over Na_2SO_4, concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=100/1 to 10/1). Compound tert-butyl 4-formyl-3,5-dimethyl-piperidine-1-carboxylate (5.81 g, 23.8 mmol, 89% yield) was obtained as a colorless oil.

[001139] 1H NMR (400 MHz, CHLOROFORM-d) δ = 10.11 - 9.38 (m, 1H), 4.24 - 3.76 (m, 2H), 2.86 (s 1H), 2.64 - 2.51 (m, 1H), 2.42 - 2.19 (m, 1H), 1.99 - 1.76 (m, 2H), 1.46 (s, 9H), 1.00 (d, J = 7.2 Hz, 4H),

0.86 (d, J = 6.4 Hz, 2H)

[001140] To a solution of tert-butyl 4-formyl-3,5-dimethyl-piperidine-1-carboxylate (268 mg, 1.11 mmol, 1.3 eq) and 1-[3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-1-(4-piperidyl)-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]ethanone (435 mg, 854 μmol, 1.0 eq) in DCM (8 mL) was added dropwise Et_3N (864 mg, 8.54 mmol, 10.0 eq) and $NaBH(OAc)_3$ (905 mg, 4.27 mmol, 5.0 eq) at 25 °C under N_2. The mixture was stirred at 25 °C for 12 h under N_2. The mixture was poured into water (30 mL). The aqueous phase was extracted with DCM (30 mL × 3), dried with anhydrous sodium sulfate, concentrated under vacuum. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150 × 40mm × 15um; mobile phase: [water(FA)-ACN]; gradient: 32%-62% B over 10 min). Compound tert-butyl 4-[[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]methyl]-3,5-dimethyl-piperidine-1-carboxylate (364 mg, 471 μmol, 55% yield) was obtained as a yellow solid.

[001141] LC-MS: MS (ESI^+): t_R = 0.557 min, m/z = 735.4 [$M + H^+$]

[001142] To a solution of tert-butyl 4-[[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]methyl]-3,5-dimethyl-piperidine-1-carboxylate (364 mg, 471 μmol, 1.0 eq) in DCM (4 mL) was added TFA (1.54 g, 13.5 mmol, 27.3 eq). The mixture was stirred at 25 °C for 1 h under N_2. The reaction mixture was concentrated. Compound 1-[3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-1-[1-[(3,5-dimethyl-4-piperidyl)methyl]-4-piperidyl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]ethanone (360 mg) as a yellow solid and directly used in the next step without further purification.

[001143] LC-MS: MS (ESI^+): t_R = 0.471 min, m/z = 635.6 [$M + H^+$]

[001144] To a solution of 1-[3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-1-[1-[(3,5-dimethyl-4-piperidyl)methyl]-4-piperidyl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]ethanone (100 mg) and 6-chloro-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide (63 mg, 160 μmol, 1.2 eq) in NMP (2 mL) was added DIPEA (52 mg, 400 μmol, 3.0 eq) at 25 °C. The mixture was stirred at 70 °C for 12 h under N_2. The mixture was poured into water (20 mL). The aqueous phase was extracted with ethyl acetate (30 mL × 3), dried with anhydrous sodium sulfate, concentrated under vacuum. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150 × 25mm × 10um; mobile phase: [water (FA)-ACN]; gradient: 29% - 59% B over 10 min). Compound 6-[4-[[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]methyl]-3,5-dimethyl-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy)cyclohexyl]pyridazine-3-carboxamide (20.41 mg, 20.4 μmol, 15% yield over two steps) was obtained as a yellow solid.

[001145] 1H NMR (400 MHz, CHLOROFORM-d) δ = 7.96 (d, J = 9.6 Hz, 1H), 7.87 (d, J = 8.4 Hz, 1H), 7.60 - 7.51 (m, 2H), 7.40 (d, J = 6.8 Hz, 1H), 7.07 - 6.95 (m, 3H), 6.95 - 6.83 (m, 2H), 6.70 - 6.34 (m, 1H), 4.39 - 4.23 (m, 2H), 4.10 (d, J = 3.6 Hz, 2H), 3.99 (s, 5H), 3.86 - 3.66 (m, 5H), 3.43 - 3.26 (m, 2H), 3.24 - 3.01 (m, 2H), 2.92 - 2.74 (m, 4H), 2.53 - 2.36 (m, 2H), 2.30 - 2.13 (m, 9H), 2.12 - 1.92 (m, 9H), 1.55 - 1.35

(m, 3H), 1.11 - 1.03 (m, 6H)

[001146] LC-MS: MS (ESI^+): t_R = 1.921 min, m/z = 989.6 [M + H^+]

[001147] The compounds below were prepared in a similar manner as described in Example 47.

Compound	Name	^{1}H NMR (DMSO-d_6)	LC-MS [M + H^+]
279	6-[4-[[4-[5-acetyl-3-[3-(1-methylimidazol-4-yl)-8-isoquinolyl]-6,7-dihydro-4H-pyrazolo[4,3-c] pyridin-1-yl]-1-piperidyl] methyl]-3,5-dimethyl-1-piperidyl]-N-[4-(3-chloro-4-cyano-phenoxy) cyclohexyl] pyridazine-3-carboxamide	δ = 9.81 (s, 1H), 8.58 (d, J = 8.4 Hz, 1H), 8.36 (s, 1H), 8.09 (s, 2H), 7.92 - 7.83 (m, 2H), 7.82 - 7.75 (m, 2H), 7.60 - 7.48 (m, 1H), 7.39 (d, J = 2.4 Hz, 1H), 7.35 (br d, J = 9.2 Hz, 1H), 7.17 - 7.10 (m, 1H), 4.63 - 4.49 (m, 3H), 4.27 - 4.08 (m, 1H), 3.91 (s, 3H), 3.88 - 3.71 (m, 5H), 3.43 - 3.38 (m, 2H), 3.17 - 3.04 (m, 2H), 2.97 - 2.80 (m, 2H), 2.39 - 2.29 (m, 2H), 2.18 - 1.84 (m, 16H), 1.70 - 1.58 (m, 2H), 1.57 - 1.45 (m, 2H), 0.98 (br d, J = 6.0 Hz, 6H)	935.8
287	6-[4-[[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]methyl]-3,5-dimethyl-1-piperidyl]-N-[4-(3-chloro-4-cyano-2-methyl-phenoxy)cyclohexyl]pyridazine-3-carboxamide	δ = 8.57 (d, J = 8.0 Hz, 1H), 7.80 - 7.73 (m, 3H), 7.50 (s, 1H), 7.34 (d, J = 9.6 Hz, 1H), 7.26 (d, J = 8.8 Hz, 1H), 7.10 (s, 1H), 6.95 - 6.62 (m, 2H), 4.58 - 4.44 (m, 1H), 4.21 - 4.08 (m, 2H), 4.07 - 3.95 (m, 1H), 3.91 - 3.83 (m, 4H), 3.83 - 3.65 (m, 4H), 3.63 - 3.54 (m, 2H), 3.39 - 3.34 (m, 2H), 3.09 - 2.96 (m, 2H), 2.88 - 2.69 (m, 4H), 2.32 (s, 2H), 2.24 (s, 3H), 2.15 - 2.09 (m, 2H), 2.07 (s, 2H), 2.05 - 1.80 (m, 14H), 1.69 - 1.50 (m, 4H), 0.96 (d, J = 6.4 Hz, 6H)	1003.7
289	6-[4-[[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]methyl]-3,5-dimethyl-1-piperidyl]-N-[4-(4-cyano-3-methyl-phenoxy)cyclohexyl]pyridazine-3-carboxamide	δ = 8.61 - 8.53 (m, 1H), 7.81 - 7.74 (m, 2H), 7.65 (d, J = 8.4 Hz, 1H), 7.50 (s, 1H), 7.34 (d, J = 9.6 Hz, 1H), 7.11 (s, 1H), 7.05 (d, J = 2.0 Hz, 1H), 6.97 - 6.64 (m, 3H), 4.48 - 4.31 (m, 1H), 4.22 - 4.09 (m, 2H), 4.08 - 3.96 (m, 1H), 3.93 - 3.66 (m, 8H), 3.63 - 3.56 (m, 2H), 3.33 - 3.30 (m, 2H), 3.09 - 2.92 (m, 2H), 2.85 (d, J = 6.0 Hz, 3H), 2.80 - 2.70 (m, 1H), 2.44 (s, 3H), 2.36 - 2.27 (m, 2H), 2.15 - 1.80 (m, 18H), 1.70 - 1.57 (m, 2H), 1.55 -	969.9

Compound	Name	^{1}H NMR (DMSO-d_6)	LC-MS [M + H$^+$]
		1.43 (m, 2H), 1.05 - 0.92 (m, 6H)	
290	6-[4-[[4-[5-acetyl-3-[7-(difluoromethyl)-6-(1-methylpyrazol-4-yl)-3,4-dihydro-2H-quinolin-1-yl]-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-1-yl]-1-piperidyl]methyl]-3,5-dimethyl-1-piperidyl]-N-[4-[4-cyano-3-(trifluoromethyl)phenoxy]cyclohexyl]pyridazine-3-carboxamide	($CDCl_3$) δ = 7.97 (d, *J*=9.6 Hz, 1 H) 7.90 (d, *J*=8.4 Hz, 1 H) 7.76 (d, *J*=8.8 Hz, 1 H) 7.55 (d, *J*=5.6 Hz, 1 H) 7.42 (d, *J*=6.4 Hz, 1 H) 7.27 (s, 1 H) 7.13 (m, 1 H) 7.07 (s, 1 H) 7.02 – 6.95 (m, 1 H) 6.89 - 6.87 (m, 1 H) 6.72 - 6.38 (m, 1 H) 4.41 (m, 1 H) 4.28 (m, 1 H) 4.15 (m, 1 H) 3.99 - 3.89 (m, 4 H) 3.84 (m, 1 H) 3.77 - 3.69 (m, 1 H) 3.39 - 3.22 (m, 1 H) 3.12 (m, 1 H) 3.08 (m, 1 H) 2.91 (m, 1 H) 2.84 - 2.74 (m, 2 H) 2.38 (m, 1 H) 2.27 - 2.14 (m, 7 H) 2.13 - 2.01 (m, 6 H) 1.92 (m, 1 H) 1.79 - 1.68 (m, 1 H) 1.55 - 1.45 (m, 2 H) 1.13 - 1.03 (m, 7 H)	1023.5

Example A-1: Oral Solution

[001148] To prepare a pharmaceutical composition for oral delivery, a sufficient amount of a compound of Formula (I) or (II), or a pharmaceutically acceptable salt thereof, is added to water (with optional solubilizer(s), optional buffer(s) and taste masking excipients) to provide a 20 mg/mL solution.

Example A-2: Oral Tablet

[001149] A tablet is prepared by mixing 20-50% by weight of a compound of Formula (I) or (II), or a pharmaceutically acceptable salt thereof, 20-50% by weight of microcrystalline cellulose, 1-10% by weight of low-substituted hydroxypropyl cellulose, and 1-10% by weight of magnesium stearate or other appropriate excipients. Tablets are prepared by direct compression. The total weight of the compressed tablets is maintained at 100 -500 mg.

Example A-3: Oral Capsule

[001150] To prepare a pharmaceutical composition for oral delivery, 10-500 mg of a compound of Formula (I) or (II), or a pharmaceutically acceptable salt thereof, is mixed with starch or other suitable powder blend. The mixture is incorporated into an oral dosage unit such as a hard gelatin capsule, which is suitable for oral administration.

[001151] In another embodiment, 10-500 mg of a compound of Formula (I) or (II), or a pharmaceutically acceptable salt thereof, is placed into Size 4 capsule, or size 1 capsule (hypromellose or hard gelatin) and the capsule is closed.

Example B-1: Ternary Complex Formation Assay

Preparation of mouse anti-AR antibody coated 96 well plates

[001152] Black MaxiSorp plates: coat with 50 uL of mouse 1/50 diluted AR antibody (Monoclonal Antibody (AR 441 from Thermo Fisher); diluted in phosphate buffered saline (PBS). Spin the liquid to the bottom of the wells, if necessary. Incubate overnight at 4 °C. Next day, wash 3 times with 200 uL of TBST. Block with 200 uL of blocking buffer (5% BSA in TBST) at room temperature for 2 hours (BSA: A4503 or A2153 from Sigma). Wash plates 3 times with TBST. Plates are ready for lysates

Preparation of dimerizer treated lysates

[001153] Culture cells in 96 wells at 50K VCaP cells/well for at least 3 days. Plate in 5% Omega charcoal stripped FBS in total volume of 200 uL. Treat with bifunctional for 1.5 hours by adding 1 uL of 200x stock in DMSO. Aspirate media/compound. Add and pipet-to-mix 70 uL of 1x AlphaLisa Lysis Buffer to each well (Perkin Elmer, AlphaLISA SureFire Ultra, diluted in water). Pipet up and down when adding lysis buffer to disrupt cells. Let lysis proceed for 30 min at 4 °C.

Sandwich ELISA

[001154] Transfer 50 uL of lysate to MaxiSorp plates coated with antibody and subsequently blocked with BSA. Incubate for 1 hour at room temperature. Flick out the lysates. Wash 3 times with TBST. Add 75 uL of rabbit CBP or p300 antibody to each well (diluted 1:5000 in blocking buffer (5% BSA in TBST). CBP

antibody: (D6C5) Rabbit mAb #7389; p300 antibody: (D8Z4E) Rabbit mAb #86377. Incubate overnight at 4 °C. Wash 3 times with 300uL TBST, each time on shaker for 5-10 min. Prepare goat anti-rabbit antibody conjugated to HRP (1/100K dilution in blocking buffer) Invitrogen Catalog number: 32260. Add 75 uL of HRP-conjugated goat anti-rabbit antibody. Incubate at room temperature for 1 hour. Flick out the HRP-antibody mixture. Wash 7-8 times with TBST, each time on shaker for 10 min. Later washes try to overflow the wells so that no residual HRP remains bound to the sides of the well. Prepare and add 75 uL/well of QuantaRed Enhance Chemifluorescent HRP Substrate solution. Immediately read fluorescence on BMG ClarioStar (ex: 570/em 585), and repeat the read in 5 minutes and 15 minutes.

[001155] Results of the ternary complex formation assay are shown in Table 2.

Table 2

Compound	Average Ternary Complex* (nM)	Compound	Average Ternary Complex* (nM)
1	A	**28**	A
2	A	**29**	A
3	A	**30**	A
4	A	**31**	A
5	A	**32**	A
6	A	**33**	A
8	A	**34**	B
11	A	**35**	D
12	A	**36**	C
13	A	**37**	D
14	A	**38**	D
16	A	**39**	A
17	A	**40**	B
18	A	**41**	A
19	D	**42**	B
20	A	**43**	B
21	A	**44**	A
22	A	**45**	A
23	A	**46**	A
24	A	**47**	B
25	A	**48**	A
26	A	**49**	A
27	A	**50**	A

Compound	Average Ternary Complex* (nM)
51	A
52	B
53	A
54	B
55	A
56	B
57	A
58	C
59	D
60	D
61	A
62	A
63	A
64	B
65	A
66	A
67	A
68	A
69	A
70	A
71	A
72	A
73	A
77	B
82	A
83	A
84	A
85	A
87	A
88	B
89	A
94	B

Compound	Average Ternary Complex* (nM)
100	A
101	A
102	A
103	A
104	A
105	A
106	B
107	A
108	B
109	C
110	A
112	A
113	A
118	A
119	B
120	A
121	A
122	A
123	A
126	A
127	D
130	D
135	B
138	B
139	A
140	A
141	A
142	A
144	A
145	A
147	A
148	A

Compound	Average Ternary Complex* (nM)
149	A
150	B
152	A
153	A
154	A
155	A
156	B
157	A
158	B
159	A
160	A
161	A
162	B
163	A
164	A
165	A
166	A
168	C
169	A
170	A
176	A
178	A
181	A
182	A
183	A
184	B
191	A
192	A
194	A
195	A
197	A
198	A

Compound	Average Ternary Complex* (nM)
200	A
201	A
203	A
204	A
205	A
206	A
208	A
209	A
210	A
215	A
216	A
217	A
219	A
220	A
221	D
222	A
223	A
224	A
225	A
226	A
227	A
228	A
229	A
230	A
231	A
232	B
233	A
234	A
235	A
237	A
238	A
239	A

Compound	Average Ternary Complex* (nM)
240	A
241	B
242	A
244	A
245	A
246	A
247	A
248	A
249	A
250	A
252	A
253	A
254	A
255	A
256	A
257	B
258	B
259	B
260	B
261	B
262	A
263	A
264	D
265	A
266	D
267	A

Compound	Average Ternary Complex* (nM)
268	A
269	A
270	B
275	A
279	A
280	A
281	A
282	A
283	A
285	A
286	A
287	A
288	A
289	A
290	A
291	A
292	A
293	A
294	A
295	A
296	A
297	D
298	A
299	A
300	A
301	A

*A is <1 nM; B is >1 nM and ≤10 nM; C is >10 nM and ≤100 nM; D is active and >100 nM

Example B-2: NanoBRET Cellular Assay

[001156] NanoBRET™ Histone H3.3/CBP-BD Interaction Assay Reagents and FuGENE® HD Transfection Reagents were purchased from Promega. Reference compound SGC-CBP-30 was purchased from MedChem Express. HEK293 cell line was purchased from American Type Culture Collection

(Manassas, VA). HEK293 cells were cultured in EMEM media supplemented with 10% FBS, 100 µg/ml of penicillin, and 100 µg/ml of streptomycin. Cultures were maintained at 37°C in a humidified atmosphere of 5% CO_2 and 95% air.

[001157] HEK293 cells were transfected with 2 ug of Histone H3.3-HaloTag Fusion Vector DNA plus 0.05 ug of CBP-BD-NanoLuc fusion vector. The transfected cells were treated with NanoBRET™ 618 Ligand and test compounds (starting at 1 uM, 10-dose with 3-fold dilution) or with reference compound SGC-CBP-30 (starting at 10 uM, 10-dose with 3-fold dilution) for 22 hours. Cellular Histone H3.3/CBP-BD Interaction was measured by NanoBRET assay. Curve fits were performed only when % NanoBret signal at the highest concentration of compounds was less than 55%.

[001158] Results of the NanoBRET assay are shown in Table 3.

Table 3

Compound	IC_{50} value (M)
GNE-781	1.23E-10
SGC-CBP-30	6.09E-07

Transfection for NanoBRET™ Histone H3.3/CBP-BD Interaction Assay

1. Culture HEK293 cells appropriately prior to assay.
2. Remove medium from cell flask by aspiration, trypsinize and allow cells to dissociate from the flask bottom.
3. Neutralize trypsin using cell culture medium, count cells to estimate density and resuspend to a final density of 4×10^5 cells/ml in cell culture medium.
4. Plate 2 ml of cells into each well of a six-well plate.
5. Allow the cells to attach and recover overnight at 37°C, 5% CO_2.
6. Prepare a transfection mixture consisting of the following DNA amounts:

2µg of Histone H3.3-HaloTag 0.05µg of NanoLuc-CBP-BD

7. Add 100µl of Opti-MEM® I Reduced Serum Medium, no phenol red, to the transfection mixture, and mix well.
8. Add 8µl of FuGENE® HD Transfection Reagent and incubate at room temperature for 10 minutes.
9. Add transfection mixture to wells with attached cells, and express proteins for 24 hours at 37°C, 5% CO_2.

Replating Transfected HEK293 Cells into Multiwell Plates and Adding HaloTag® NanoBRET™ 618 Ligand

1. For each well in a six-well plate, remove medium from cells, and wash with 1ml of PBS. Discard.
2. Add 0.25% trypsin-EDTA and incubate at room temperature until cells lift from well bottom.
3. Add cell culture medium to neutralize trypsin, mix to collect and resuspend cells, and transfer cell suspension to a 15ml conical tube.

4. Spin cells down at 125 × g for 5 minutes. Discard cell culture medium and resuspend in an equal volume of assay medium (Opti-MEM® I Reduced Serum Medium, no phenol red + 4% FBS).

5. Count to estimate cell density and adjust density to 2×10^5 cells/ml in assay medium.

6. Divide cells into two pools and add HaloTag® NanoBRET™ 618 Ligand or DMSO vehicle as follows: Experimental samples (+ ligand): Add 1µl of 0.1mM HaloTag® NanoBRET™ 618 Ligand per milliliter of cells (100 nM final concentration). No-acceptor controls (– ligand): Add 1µl of DMSO per milliliter of cells (0.1% DMSO final concentration). Deliver compounds to the 384-well plate with Echo 550.

7. For NanoBRET™ measurements with/without compound treatment, dispense 25µl of each pool of the cells prepared in Step 6 in duplicate to reach the requested final test concentrations (starting at 1 or 10 µM, 10-dose with 3-fold dilution).

8. Incubate plates at 37°C, 5% CO_2 22 hours.

Adding NanoBRET™ Nano-Glo® Substrate and Taking NanoBRET™ Measurements

1.Prepare a 5X solution of NanoBRET™ Nano-Glo® Substrate in Opti-MEM® I Reduced Serum Medium, no phenol red.

2. Add substrate to cells and shake plate to mix for 30 seconds.

3. Measure donor emission (460nm) and acceptor emission (600nm) within 10 minutes of substrate addition using an Envision 2104 Multilabel Reader.

NanoBRET™ Calculations

1. Divide the acceptor emission value (e.g., 600nm) by the donor emission value (e.g., 460nm) for each sample to generate raw NanoBRET™ ratio values.

2. Determine the mean NanoBRET™ ratio for each set of samples: Experimental samples with HaloTag®NanoBRET™ 618 Ligand and no-acceptor control samples.

3. The IC50 curves were plotted and IC50 values were calculated using the GraphPad Prism program based on a sigmoidal dose-response equation.

Example B-3: VCaP Growth Inhibition Assay

[001159] VCaP cells (ATCC Cat#CRL-2876) are plated at $1x10^4$ cells per well of a white plastic 96-well cluster plate (Thermo Scientific Nunc Cat#165306) in 100uL phenol red-free DMEM (Gibco Cat#21063-029) media with 5% CSS (Omega Scientific Cat#FB-04). Cluster plates are returned to the incubator (37*C/5% CO2) for 72 hours prior to treatment. Just prior to treatment, 100uL of phenol red-free DMEM/5%CSS and 60pM R1881 (Sigma Cat#R0908-10mg) was added to each well of the cluster plates (Final R1881 concentration = 30pM). Compounds (200X) were added to each well in a volume of 1uL, with serial dilutions (1:5) from 20uM to 2pM (final concentrations in well are 100nM to 10fM). Cluster plates are returned to the incubator for 9 days.

[001160] After the 9-day treatment period, media was removed from the cluster plates by inversion and 100uL room temperature CTG reagent (Promega Cat#G7573) is added to each well. The cluster plates are

placed on a shaker and incubated at room temperature for 20 minutes. Following this shaking/incubation, cluster plates are read on a luminometer (BMG ClarioStar). IC_{50} values are obtained by graphing the RLU data vs. compound concentration with nonlinear regression 4-parameter logistic curves (GraphPad Prism).

[001161] Results of the VCaP growth inhibition assay are shown in Table 4.

Table 4

Compound	IC_{50}** (M)
1	+
2	+
3	+
4	+
5	+
7	+
8	+
10	++
12	+
13	++
14	+
16	+
18	+
19	+
20	+
21	+
22	+
23	++
25	+
26	+
27	++
28	+
30	+
31	+
32	+
33	++
34	++
35	++

Compound	IC_{50}** (M)
36	+++
37	++
38	++
39	+
40	++
41	+
42	++
43	++
44	++
45	++
46	++
47	++
48	+
49	++
50	+
51	++
52	++++
53	++++
54	++
55	++++
56	++++
57	+++
58	++++
59	++++
60	++++
61	+
62	+
63	++

Compound	IC_{50}** (M)
64	++
65	+
66	++
67	++
68	+
69	+
70	++
71	++
72	++
73	+
77	++
82	++
83	++
84	++
85	+
87	+
88	++
89	+
94	++
100	++
101	+
102	++
103	++
104	+
105	++
106	++
107	+
108	++

Compound	IC_{50}** (M)
109	++
110	+
112	++
113	++
118	++
119	++
120	++
121	++
122	++
123	++
126	+
127	++++
130	++
135	++
138	+++
139	+
140	+
141	+
144	+
145	++
147	++
148	++
149	++
150	++
152	++
153	+
154	++
155	++
156	+++
157	++
158	++
159	+

Compound	IC_{50}** (M)
160	+
161	+
162	++
163	+
164	++
165	++
166	++
168	+
169	+
170	++
176	++
177	+
179	++
181	+
182	+
183	++
184	+++
185	+
187	+
189	+
191	++
192	+
194	+
195	+
197	+
198	+
200	+
201	+
202	++
204	+
205	+
206	+

Compound	IC_{50}** (M)
208	+
209	+
210	+
216	+
217	+
219	+
220	+
221	+++
222	++
223	+
224	+
229	+
230	+
231	+
232	+++
233	+
234	+
237	+
238	+
239	+
240	++
241	++
242	++
244	++
245	+
246	+++
247	+
248	++
249	+
250	+
252	+
253	+

Compound	IC_{50}** (M)
254	+
255	++
256	++
257	++
258	+++
259	+++
261	+++
262	++
263	+

Compound	IC_{50}** (M)
267	+++
268	++
270	+++
280	+
281	+
282	++
283	+
286	+
287	+

Compound	IC_{50}** (M)
288	+
289	+
291	+
292	+
293	+
298	++
299	+
300	+

** ++++ is IC_{50} active and > 1E-7; +++ is 1E-7 ≤ IC_{50} > 1E-9; ++ is 1E-9 ≤ IC_{50} > 1E-10; + is IC_{50} ≤ 1E-10

Example B-4: HEK-293 Growth Inhibition Assay

[001162] HEK-293 cells (ATCC Cat#CRL-1573) are plated at $3x10^3$ cells per well of a white plastic 96-well cluster plate (Thermo Scientific Nunc Cat#165306) in 200uL DMEM (ATCC Cat#30-2002) media with 10% FBS (Gibco Cat#26140-079). Cluster plates are returned to the incubator (37*C/5% CO2) for 24 hours prior to treatment. Compounds (200X) were added to each well in a volume of 1uL, with serial dilutions (1:5) from 2mM to 200pM (final concentrations in well are 10uM to 1pM). Cluster plates are returned to the incubator for 3 days.

[001163] After the 3-day treatment period, 100uL media was removed from each well by aspiration and 100uL room temperature CTG reagent (Promega Cat#G7573) is added back to each well. The cluster plates are placed on a shaker and incubated at room temperature for 20 minutes. Following this shaking/incubation, cluster plates are read on a luminometer (BMG ClarioStar). IC_{50} values are obtained by graphing the RLU data vs. compound concentration with nonlinear regression 4-parameter logistic curves (GraphPad Prism).

[001164] Results of the HEK-293 growth inhibition assay are shown in Table 5.

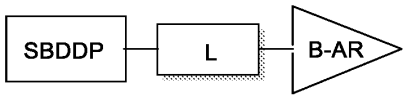
Table 5

Compound	IC_{50} (μM)
1	>10

CLAIMS

WHAT IS CLAIMED IS:

1. A heterobifunctional conditional inhibitor compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof:



wherein:

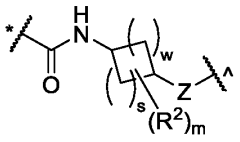
SBDDP is a silent binder of a disease-dependent protein (DDP);

L is an optional linker; wherein L is covalently attached at a position of SBDDP that is solvent exposed when SBDDP binds to the DDP;

B-AR is a binder of the androgen receptor (AR), wherein B-AR comprises:

1) a head group that occupies the ligand-binding domain (LBD) of AR and is covalently attached to a core moiety; and

2) an optional tail moiety covalently attached to the core moiety; wherein the core comprises an optionally substituted cycloalkyl having the structure of Formula (C):



, Formula (C);

the head group is covalently attached to Z at position (^);

the optional tail moiety comprises a ring D that is covalently attached to the amide (*), wherein ring D is a 5-, 6-, 8-, 9- or 10-membered aryl or a 5-, 6-, 8-, 9- or 10-membered heteroaryl that is optionally substituted with s R^3;

wherein:

s is 1, 2, or 3; w is 2 or 3;

m is 0, 1, 2, 3, or 4;

Z is -O- or -NR^5-;

each R^2 is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, -CN, -NO_2, -OH, -OR^4, $OC(=O)R^4$, -$S(=O)R^4$, -$S(=O)_2R^5$, -$S(=O)_2N(R^5)_2$, -$N(R^5)_2$, -$NR^5C(=O)NR^5$, -$NR^5C(=O)R^4$, -$C(=O)R^5$, -$C(=O)OR^5$, or -$C(=O)N(R^5)_2$; or

two R^2 on the same carbon atom are taken together with the carbon atom to which they are attached to form a substituted or unsubstituted C_3-C_8cycloalkyl or a substituted or unsubstituted monocyclic 3- to 8-membered heterocycloalkyl;

each R^3 is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, -CN, -OH, -OR^4, or

$-N(R^5)_2$.

each R^4 is independently substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted monocyclic 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted monocyclic heteroaryl;

each R^5 is independently hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted monocyclic 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted monocyclic heteroaryl;

or two R^5 on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle; and

wherein L is covalently attached to the core moiety at position (*) if the optional tail moiety is absent, or L is covalently attached to the tail moiety if present;

wherein DDP and AR are both expressed in a cell of interest (COI), and wherein the relative abundance of the AR in the COI is greater than the relative abundance of the DDP in the COI; or the COI is a diseased cell, and the AR is overexpressed, overactive, or both overexpressed and overactive, or amplified in the diseased cell as compared to when the COI is a non-diseased cell.

2. The compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof, wherein DDP is Ataxia-telangiectasia mutated (ATM), Ataxia telangiectasia and Rad3-related protein (ATR), Aurora Kinase A (AurkA), AurkB, Cell division cycle 7-related protein kinase (CDC7), Checkpoint kinase 1 (CHK1), CHK2, Cyclin-dependent kinase 1 (CDK1), CDK2, CDK4, CDK5, CDK6, CDK9, DNA methyltransferase 1 (DNMT1), Exportin 1 (XPO1), Histone deacetylase 1 (HDAC1), HDAC2, HDAC3, kinesin family member 11 (KIF11), Mitogen-activated protein kinase kinase 1 (MEK1), MEK2, Myc, neuronal precursor cell-expressed developmentally down-regulated protein 8 (NEDD8), SMARCA2/4, CREB-binding protein (CBP)/p300, WD repeat-containing protein 5 (WDR5), DDB1- and CUL4-associated factor 1 (DCAF1), phosphatidylinositol-3 kinase (PI3K), Protein arginine methyltransferase 5 (PRMT5), splicing factor 3b subunit 1 (SF3B1), WEE1, 20S proteasome subunits, Steroid Receptor Coactivator 1 (SRC1), SRC2, or SRC3.

3. The compound of claim 1 or claim 2, or a pharmaceutically acceptable salt or solvate thereof, wherein DDP is Aurora Kinase A (AurkA), Checkpoint kinase 1 (CHK1), CHK2, CDK4, CDK6, Myc, SMARCA2/4, CREB-binding protein (CBP)/p300, WD repeat-containing protein 5 (WDR5), DDB1- and CUL4-associated factor 1 (DCAF1), phosphatidylinositol-3 kinase (PI3K), or WEE1.

4. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt or solvate thereof, wherein DDP is CREB-binding protein (CBP)/p300.

5. The compound of claim 4, or a pharmaceutically acceptable salt or solvate thereof, wherein SBDDP binds in the acetyl-lysine (KAc) binding site of the bromodomain of CBP/p300.

6. The compound of claim 4, or a pharmaceutically acceptable salt or solvate thereof, wherein the SBDDP comprises an acetyl-lysine mimetic moiety that binds in the acetyl-lysine (KAc) binding site of the bromodomain of CBP/p300.
7. The compound of claim 6, or a pharmaceutically acceptable salt or solvate thereof, wherein:
the moiety comprising an acetyl-lysine mimetic makes or mimics a hydrogen bond interaction to Asn1168 in the Asn-binding pocket of the bromodomain of CBP, or makes or mimics a hydrogen bond interaction to Asn1132 in the Asn-binding pocket of the bromodomain of p300; and
the head group of B-AR forms hydrogen bonds with the side chains of Gln 711 and Arg752 of the LBD of AR.
8. The compound of any one of claims 1-7, or a pharmaceutically acceptable salt or solvate thereof, wherein: SBDDP further comprises a moiety that interacts with Arg1173 in the bromodomain of CBP or Asn1137 in the bromodomain of p300.
9. The compound of any one of claims 1-8, or a pharmaceutically acceptable salt or solvate thereof, wherein SBDDP further comprises:
    1) a moiety that occupies the lipophilic shelf (LPF) region of the bromodomain of CBP/p300; or
    2) a moiety that occupies the BC Loop region of the bromodomain of CBP/p300; or
    3) both 1) and 2).
10. The compound of any one of claims 6-9, or a pharmaceutically acceptable salt or solvate thereof, wherein the moiety comprising an acetyl-lysine mimetic comprises a moiety selected from pyrrolidonyl, phenyl, pyridinyl, pyridinonyl, triazolyl, pyrrolyl, isoxazolyl, pyrazolyl, quinolinyl, tetrahydroquinolinyl, isoquinolinyl, tetrahydroisoquinolinyl, quinazolonyl, quinazolinyl, dihydroquinazolinonyl, imidazo[4,5-c]quinolinyl fused to a dimethylisoxazolyl, triazolophthalazinyl, indolizinyl, benzoimidazolyl, isoxazole-indolizinyl, thienodiazepine-indolizinyl, benzodiazepine-indolizinyl, 5-isoxazolylbenzimidazolyl, 6-isoxazolylbenzimidazolyl, 7-isoxazolo-quinolinyl, diazobenzyl, triazolophthalazinyl, isoxazoloquinolinyl, 2-thiazolidinonyl, triazolopyrimidinyl, thienodiazepinyl, benzodiazepinyl, benzotriazepinyl, triazolobenzodiazepinyl, triazolothienodiazepinyl, triazolothienodiazepinyl, and isoxazole-azepinyl.
11. The compound of claim 9 or 10, or a pharmaceutically acceptable salt or solvate thereof, wherein L is covalently attached to SBDDP on:
    - the acetyl-lysine mimetic moiety; or
    - the moiety that occupies the lipophilic shelf (LPF) region of the bromodomain of CBP/p300, if present; or
    - the moiety that occupies the BC Loop region of the bromodomain of CBP/p300, if present;

    wherein L is covalently attached to SBDDP at a position that does not interfere with the binding of the acetyl-lysine mimetic moiety in the acetylated lysine (KAc) binding site of CBP/p300.
12. The compound of any one of claims 1-11, or a pharmaceutically acceptable salt or solvate thereof, wherein:

the head group of B-AR comprises 4-cyanophenyl; 3-fluoro-4-cyanophenyl; 3-chloro-4-cyanophenyl; 3-methoxy-4-cyanophenyl; 3-methyl-4-cyanophenyl; 3-trifluroromethyl-4-cyanophenyl; 3-trifluroromethoxy-4-cyanophenyl; 5-fluoro-6-cyanopyridin-3-yl; 5-chloro-6-cyanopyridin-3-yl; 5-methoxy-6-cyanopyridin-3-yl; 5-methyl-6-cyanopyridin-3-yl; 5-trifluroromethyl-6-cyanopyridin-3-yl; 5-trifluroromethoxy-6-cyanopyridin-3-yl; [1,2,4]triazolo[4,3-b]pyridazin-6-yl; or 3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl; and

each R^2 is $-CH_3$.

13. The compound of any one of claims 1-12, or a pharmaceutically acceptable salt or solvate thereof, wherein the acetyl-lysine mimetic moiety that binds in the acetyl-lysine (KAc) binding site of the bromodomain of CBP/p300 comprises:

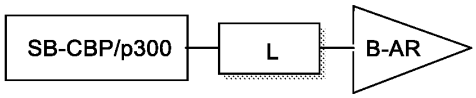
1-(1,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridin-5-yl)ethan-1-one; or N-methyl-1,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxamide; wherein the acetyl-lysine mimetic moiety optionally further comprises:

1) a moiety at the 1-position of the 1,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridin-5-yl group that occupies the lipophilic shelf (LPF) region of the bromodomain of CBP/p300; or

2) a moiety that at the 3-position of the 1,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridin-5-yl group occupies the BC Loop region of the bromodomain of CBP/p300; or

3) both 1) and 2).

14. A heterobifunctional conditional inhibitor compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof:



wherein:

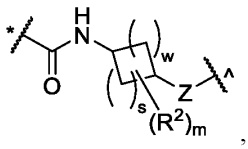
SB-CBP/p300 is a silent binder of human CREB-binding protein (CBP) or human E1A-binding protein p300 (p300) (CBP/p300);

L is an optional linker; wherein L is covalently attached at a position of SB-CBP/p300 that is solvent exposed when SB binds to CBP/p300;

B-AR is a binder of the androgen receptor (AR), wherein the B-AR comprises:

1) a head group that occupies the ligand-binding domain (LBD) of AR and is covalently attached to a core moiety; and

2) an optional tail moiety covalently attached to the core moiety; wherein the core comprises an optionally substituted cycloalkyl having the structure of Formula (C):



, Formula (C);

wherein:

s is 1, 2, or 3; w is 2 or 3;

m is 0, 1, 2, 3, or 4;

the head group is covalently attached to Z at position (^);

the optional tail moiety comprises a ring D that is covalently attached to the amide (*), wherein ring D is a 5-, 6-, 8-, 9- or 10-membered aryl or a 5-, 6-, 8-, 9- or 10-membered heteroaryl that is optionally substituted with s R^3;

Z is -O- or -NR^5-;

each R^2 is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, -CN, -NO_2, -OH, -OR^4, $OC(=O)R^4$, -$S(=O)R^4$, -$S(=O)_2R^5$, -$S(=O)_2N(R^5)_2$, -$N(R^5)_2$, -$NR^5C(=O)NR^5$, -$NR^5C(=O)R^4$, -$C(=O)R^5$, -$C(=O)OR^5$, or -$C(=O)N(R^5)_2$; or

two R^2 on the same carbon atom are taken together with the carbon atom to which they are attached to form a substituted or unsubstituted C_3-C_8cycloalkyl or a substituted or unsubstituted monocyclic 3- to 8-membered heterocycloalkyl;

each R^3 is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, -CN, -OH, -OR^4, or -$N(R^5)_2$.

each R^4 is independently substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted monocyclic 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted monocyclic heteroaryl;

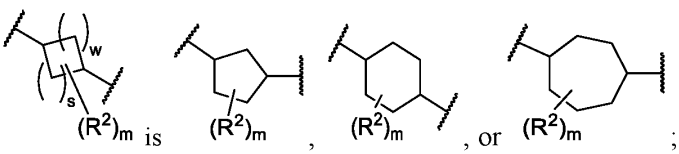
each R^5 is independently hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted monocyclic 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted monocyclic heteroaryl;

or two R^5 on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle; and

wherein L is covalently attached to the core moiety at position (*) if the optional tail moiety is absent, or L is covalently attached to the tail moiety if present.

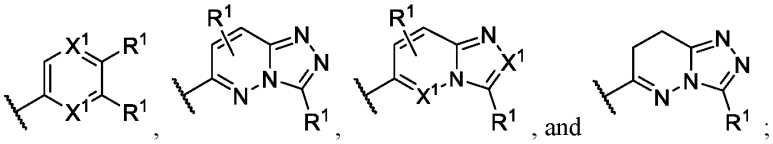
15. The compound of any one of claims 1-11 or 14, or a pharmaceutically acceptable salt or solvate thereof, wherein: the head group of B-AR forms hydrogen bonds with the side chains of Gln 711 and Arg752 of the LBD of AR.

16. The compound of any one of claims 1-11 or 14, or a pharmaceutically acceptable salt or solvate thereof, wherein:



each R^2 is independently hydrogen, $-CH_3$, $-CH_2F$, $-CHF_2$, or $-CF_3$.

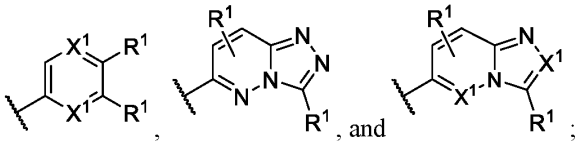
17. The compound of any one of claims 1-11 or 14, or a pharmaceutically acceptable salt or solvate thereof, wherein B-AR comprises a head group and an optional core, wherein the head group is selected from:



each X^1 is independently $-CR^1-$ or -N-;

each R^1 is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted 3- to 8-membered heterocycloalkyl, -CN, $-NO_2$, -OH, $-OR^4$, $OC(=O)R^4$, $-OC(=O)N(R^5)_2$, $-OC(=O)OR^5$, $-OC(=O)NR^5$, -SH, $-SR^4$, $-S(=O)R^4$, $-S(=O)_2R^5$, $-S(=O)_2OR^4$, $-S(=O)_2N(R^5)_2$, $-N(R^5)_2$, $-NR^5C(=O)NR^5$, $-NR^5C(=O)R^4$, $-NR^5C(=O)OR^5$, $-NR^5S(=O)_2R^5$, $-C(=O)R^5$, $-C(=O)OR^5$, or $-C(=O)N(R^5)_2$.

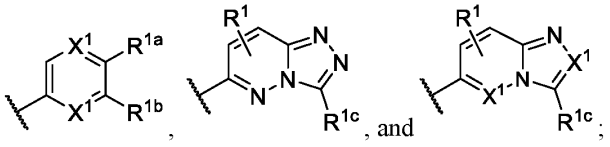
18. The compound of any one of claims 1-11 or 14, or a pharmaceutically acceptable salt or solvate thereof, wherein B-AR comprises a head group and an optional core, wherein the head group is selected from:



one X^1 is $-CR^1-$ and the other X^1 is $-CR^1-$ or -N-;

each R^1 is independently hydrogen, F, Cl, Br, I, $-CH_3$, $-CD_3$, $-CH_2CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2CH_2F$, $-CH_2CHF_2$, $-CH_2CF_3$, -OH, $-OCF_3$, $-OCH_3$, $-OCD_3$, $-OCH_2CH_3$, -CN, $-C(=O)NH_2$ - $C(=O)NH(CH_3)$or $-C(=O)NH(CD_3)$.

19. The compound of any one of claims 1-11 or 14, or a pharmaceutically acceptable salt or solvate thereof, wherein B-AR comprises a head group and an optional core, wherein the head group is selected from:



each X^1 is independently $-CR^1-$ or -N-;

R^{1a} is -CN, $-NO_2$, $-C(=O)R^5$, $-C(=O)OR^5$, or $-C(=O)N(R^5)_2$;

R^{1b} is hydrogen, halogen, C_1-C_4alkyl, C_1-C_4fluoroalkyl, -CN, -OH, $-OR^4$, or $-SR^4$;

R^{1c} is hydrogen, halogen, C_1-C_4alkyl, C_1-C_4fluoroalkyl, or -CN;

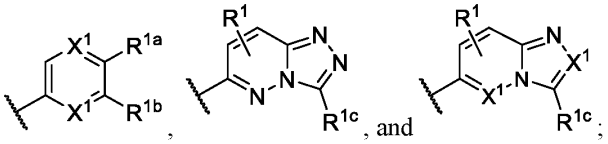
each R^1 is independently hydrogen, halogen, C_1-C_4alkyl, C_1-C_4fluoroalkyl, -CN, -OH, or $-OR^4$;

each R^4 is independently C_1-C_4alkyl, or C_1-C_4fluoroalkyl;

each R^5 is independently hydrogen, C_1-C_4alkyl, or C_1-C_4fluoroalkyl.

20. The compound of any one of claims 1-11 or 14, or a pharmaceutically acceptable salt or solvate thereof,

wherein B-AR comprises a head group and an optional core, wherein the head group is selected from:



one X^1 is $-CR^1-$ and the other X^1 is $-CR^1-$ or -N-;

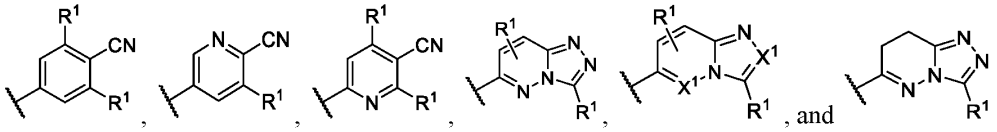
R^{1a} is -CN, $-NO_2$, $-C(=O)NH_2$ or $-C(=O)NH(CH_3)$;

R^{1b} is hydrogen, F, Cl, Br, I, $-CH_3$, $-CH_2CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, -OH, $-OCF_3$, $-OCH_3$, $-OCH_2CH_3$, or -CN;

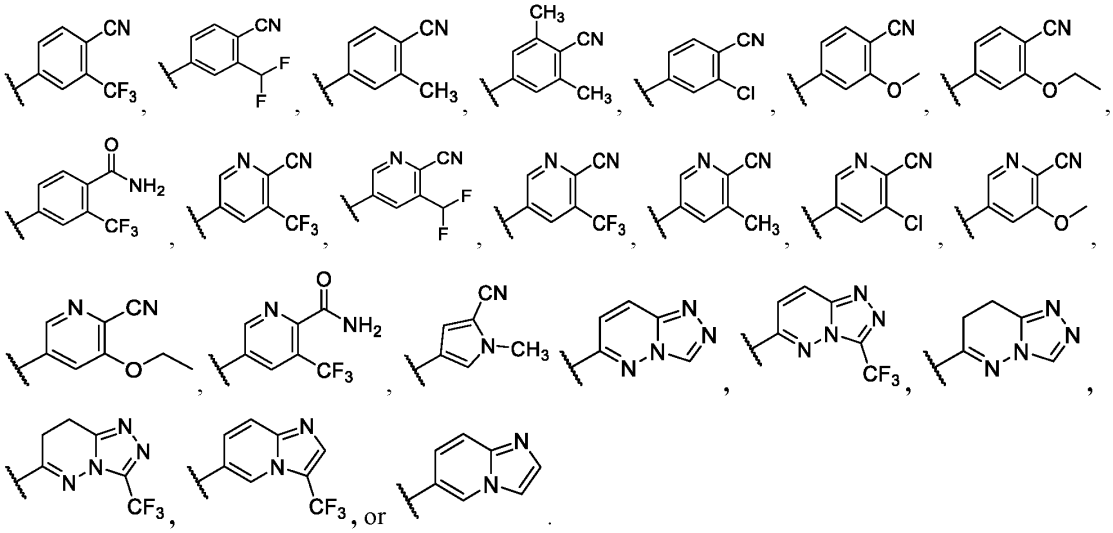
each R^{1c} is hydrogen, F, Cl, Br, $-CH_3$, $-CH_2F$, $-CHF_2$, or $-CF_3$;

each R^1 is independently hydrogen, F, Cl, Br, I, $-CH_3$, $-CH_2CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2CH_2F$, $-CH_2CHF_2$, $-CH_2CF_3$, -OH, $-OCF_3$, $-OCH_3$, or $-OCH_2CH_3$.

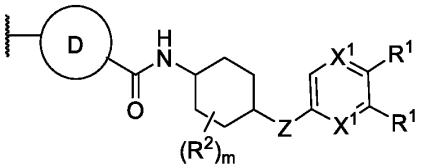
21. The compound of any one of claims 1-11, 14, or 20, or a pharmaceutically acceptable salt or solvate thereof, wherein B-AR comprises a head group and an optional core, wherein the head group is selected from:



22. The compound of any one of claims 1-11 or 14, or a pharmaceutically acceptable salt or solvate thereof, wherein B-AR comprises a head group and an optional core, wherein the head group is selected from:



23. The compound of any one of claims 1-11 or 14-20, or a pharmaceutically acceptable salt or solvate thereof, wherein B-AR has the structure of Formula (IIa), or a pharmaceutically acceptable salt or solvate thereof:



Formula (IIa)

wherein:

each X^1 is independently -CR^1- or -N-;

Z is -O- or -NR^5-;

each R^1 is independently hydrogen, F, Cl, Br, I, -CH_3, -CH_2CH_3, -CH_2F, -CHF_2, -CF_3, -CH_2CH_2F, -CH_2CHF_2, - CH_2CF_3, -OH, -OCF_3, -OCH_3, -OCH_2CH_3, -CN, -C(=O)NH_2 or -C(=O)NH(CH_3);

each R^2 is C_1-C_6alkyl;

ring D that is a 5-, 6-, 8-, 9- or 10-membered aryl or a 5-, 6-, 8-, 9- or 10-membered heteroaryl that is optionally substituted with s R^3;

each R^3 is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, -CN, -OH, -OR^4, or -$N(R^5)_2$;

m is 0, 1, 2, 3, or 4;

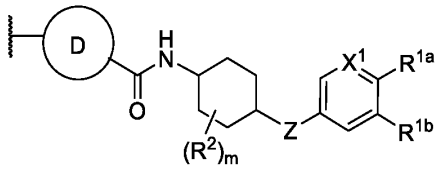
s is 1, 2, or 3.

24. The compound of claim 23, or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutically acceptable salt or solvate thereof:

one X^1 is -CR^1- and the other X^1 is -CR^1- or -N-;

each R^2 is -CH_3.

25. The compound of any one of claims 1-11 or 14-20, or a pharmaceutically acceptable salt or solvate thereof, wherein B-AR has the structure of Formula (IIIa), or a pharmaceutically acceptable salt or solvate thereof:



Formula (IIIa)

wherein:

X^1 is -CR^1- or -N-;

Z is -O- or -NR^5-;

R^{1a} is -CN, -NO_2, -C(=O)R^5, -C(=O)OR^5, or -C(=O)$N(R^5)_2$;

R^{1b} is hydrogen, halogen, C_1-C_4alkyl, C_1-C_4fluoroalkyl, -CN, -OH, or -OR^4;

R^1 is hydrogen, halogen, C_1-C_4alkyl, C_1-C_4fluoroalkyl, -CN, -OH, or -OR^4;

each R^2 is -CH_3;

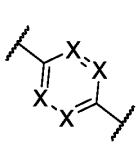
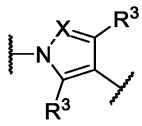
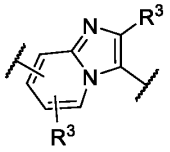
ring D that is a 5-, 6-, 8-, 9- or 10-membered aryl or a 5-, 6-, 8-, 9- or 10-membered heteroaryl that is optionally substituted with s R^3;

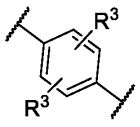
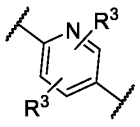
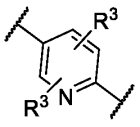
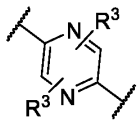
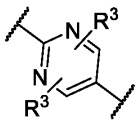
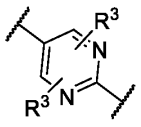
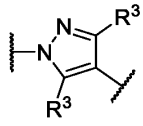
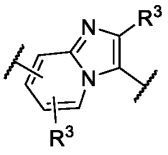
each R^3 is independently hydrogen, halogen, substituted or unsubstituted C_1-C_4alkyl, C_1-C_4fluoroalkyl, -CN, -OH, -OR^4, or -$N(R^5)_2$;

each R^4 is independently C_1-C_4alkyl, or C_1-C_4fluoroalkyl;

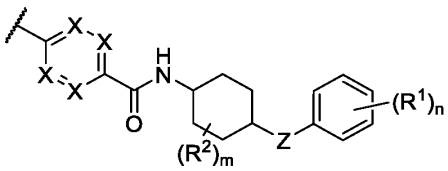
each R^5 is independently hydrogen, C_1-C_4alkyl, or C_1-C_4fluoroalkyl.

26. The compound of any one of claims 23-25, or a pharmaceutically acceptable salt or solvate thereof, wherein ring D is phenyl, naphthyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, triazinyl, pyrrolyl, thiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, imidazolyl, pyrazolyl, isothiazolyl, triazolyl, and tetrazolyl, wherein each ring D is optionally substituted with s R^3.

27. The compound of any one of claims 23-25, or a pharmaceutically acceptable salt or solvate thereof, wherein ring D is  ,  , or  ; and each X is independently -CR^3- or -N-.

28. The compound of any one of claims 23-25, or a pharmaceutically acceptable salt or solvate thereof, wherein ring D is  ,  ,  ,  ,  ,  ,  , or  .

29. The compound of any one of claims 1-11 or 14-20, or a pharmaceutically acceptable salt or solvate thereof, wherein B-AR has the structure of Formula (IVa), or a pharmaceutically acceptable salt or solvate thereof:



Formula (IVa)

wherein:

each X is independently -CR^3- or -N-;

Z is -O- or -NR^5-;

n is 2 and one R^1 is halogen, -CH_3, -OCH_3, or -CF_3, and the other R^1 is -CN;

each R^2 is -CH_3;

each R^3 is independently hydrogen, halogen, substituted or unsubstituted C_1-C_4alkyl, C_1-C_4fluoroalkyl, -CN, -OH, -OR^4, or -$N(R^5)_2$;

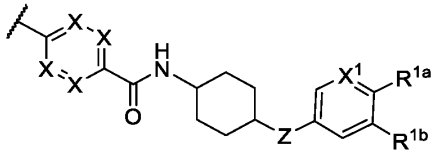
each R^4 is independently C_1-C_4alkyl, or C_1-C_4fluoroalkyl;

each R^5 is independently hydrogen, C_1-C_4alkyl, or C_1-C_4fluoroalkyl.

30. The compound of claim 20, or a pharmaceutically acceptable salt or solvate thereof, wherein:

one R^1 is -Cl, -CH_3, -OCH_3, or -CF_3, and the other R^1 is -CN.

31. The compound of any one of claims 1-11 or 14-20, or a pharmaceutically acceptable salt or solvate thereof, wherein B-AR has the structure of Formula (Va), or a pharmaceutically acceptable salt or solvate thereof:



Formula (Va)

wherein:

each X is independently -CR^3- or -N-;

Z is -O- or -NR^5-;

X^1 is -CR^1- or -N-;

R^{1a} is -CN;

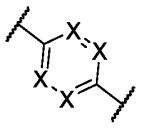
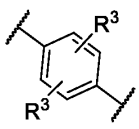
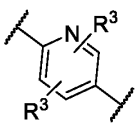
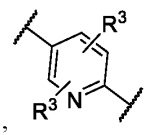
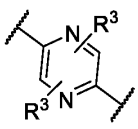
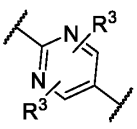
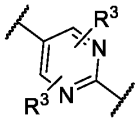
R^{1b} is hydrogen, F, Cl, Br, I, -CH_3, -CH_2CH_3, -CH_2F, -CHF_2, -CF_3, -OH, -OCF_3, -OCH_3, or -CN;

R^1 is hydrogen, F, Cl, Br, I, -CH_3, -CH_2CH_3, -CH_2F, -CHF_2, -CF_3, -CH_2CF_3, -OH, -OCF_3, -OCH_3, -OCH_2CH_3, or -OCH_2CF_3;

each R^3 is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, -CN, -OH, -OR^4, or -$N(R^5)_2$;

each R^4 is independently substituted or unsubstituted C_1-C_6alkyl, or C_1-C_6fluoroalkyl;

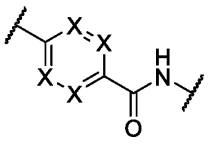
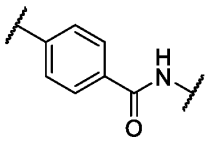
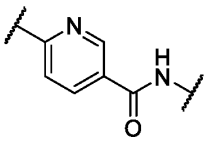
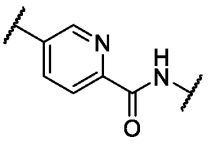
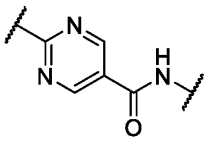
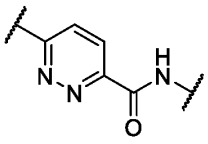
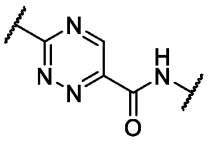
each R^5 is independently hydrogen, substituted or unsubstituted C_1-C_6alkyl, C_1-C_6fluoroalkyl.

32. The compound of any one of claims 29-31, or a pharmaceutically acceptable salt or solvate thereof, wherein  is  ,  ,  ,  ,  , or  .

33. The compound of any one of claims 1-32, or a pharmaceutically acceptable salt or solvate thereof, wherein:

each R^3 is independently hydrogen, F, Cl, Br, I, $-CH_3$, $-CH_2CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2CH_2F$, $-CH_2CHF_2$, $-CH_2CF_3$, -OH, $-OCF_3$, $-OCH_3$, $-OCH_2CH_3$, -CN, $-C(=O)NH_2$, or $-C(=O)NH(CH_3)$.

34. The compound of any one of claims 29-33, or a pharmaceutically acceptable salt or solvate thereof, wherein:


is

,

,

,

,

, or

.

35. The compound of any one of claims 1-11 or 14, or a pharmaceutically acceptable salt or solvate thereof, wherein the head group and core of B-AR is:

N-(4-(3-fluoro-4-cyanophenoxy)cyclohexyl)acetamide-*;

N-(4-(3-chloro-4-cyanophenoxy)cyclohexyl)acetamide-*;

N-(4-(3-methoxy-4-cyanophenoxy)cyclohexyl)acetamide-*;

N-(4-(3-methyl-4-cyanophenoxy)cyclohexyl)acetamide-*;

N-(4-(3-trifluroromethyl-4-cyanophenoxy)cyclohexyl)acetamide-*;

N-(4-(3-trifluroromethoxy-4-cyanophenoxy)cyclohexyl)acetamide-*;

N-(4-((5- fluoro-6-cyanopyridin-3-yl)oxy)cyclohexyl)acetamide-*;

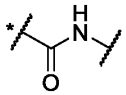
N-(4-((5-chloro-6-cyanopyridin-3-yl)oxy)cyclohexyl)acetamide-*;

N-(4-((5-methoxy -6-cyanopyridin-3-yl)oxy)cyclohexyl)acetamide-*;

N-(4-((5-methyl -6-cyanopyridin-3-yl)oxy)cyclohexyl)acetamide-*;

N-(4-((5-trifluroromethyl -6-cyanopyridin-3-yl)oxy)cyclohexyl)acetamide-*; or

N-(4-((5-trifluroromethoxy-6-cyanopyridin-3-yl)oxy)cyclohexyl)-2,2,4,4-tetramethylcyclobutyl)acetamide-*;

wherein acetamide-* is 
.

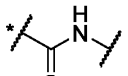
36. The compound of any one of claims 1-11 or 14, or a pharmaceutically acceptable salt or solvate thereof, wherein the head group and core of B-AR is:

N-(4-(3-chloro-4-cyanophenoxy)cyclohexyl)acetamide-*;

N-(4-(3-methoxy-4-cyanophenoxy)cyclohexyl)acetamide-*;

N-(4-(3-methyl-4-cyanophenoxy)cyclohexyl)acetamide-*; or

N-(4-(3-trifluroromethyl-4-cyanophenoxy)cyclohexyl)acetamide-*;

wherein acetamide-* is  .

37. The compound of claim 35 or 36, or a pharmaceutically acceptable salt or solvate thereof, wherein B-AR further comprises a tail moiety that is covalently attached to position (*), wherein the tail moiety is a ring D that is phenyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, triazolyl, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, indolyl, isoindolyl, indolizinyl, benzimidazolyl, napthyl, quinolyl, isoquinolyl, quinoxalinyl, quinazolinyl, indazolyl, or benzotriazolyl; wherein ring D is optionally substituted with s R^3;

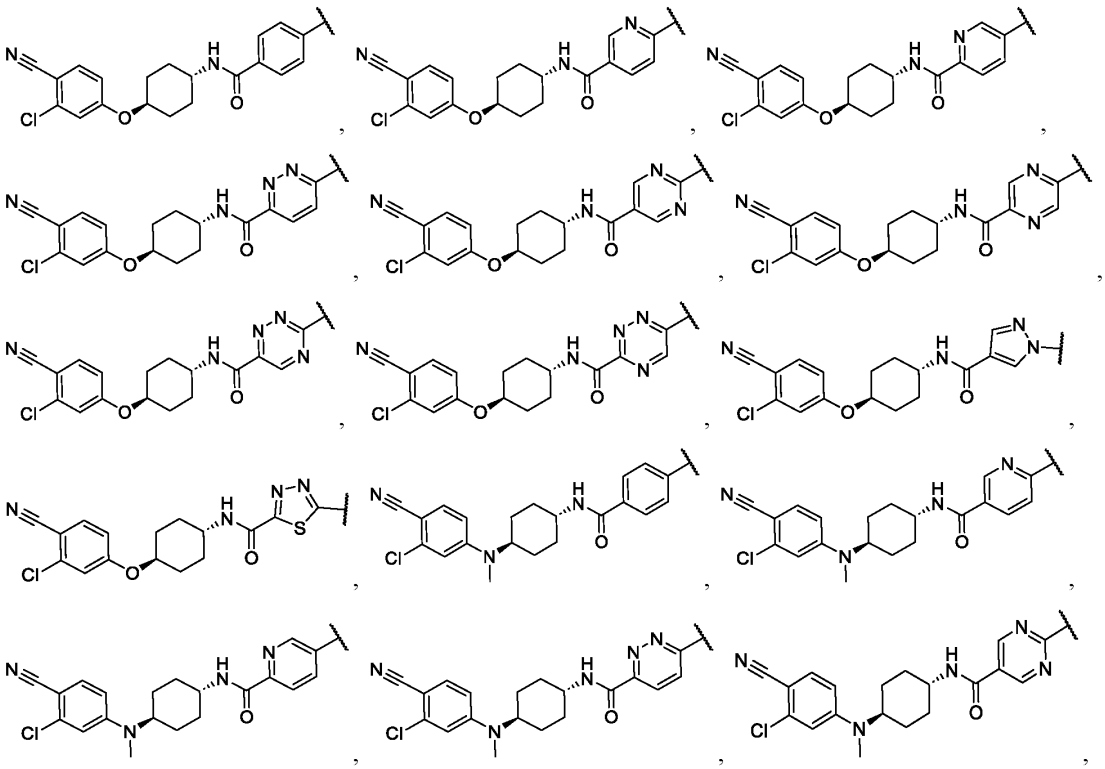
s is 1, 2, or 3;

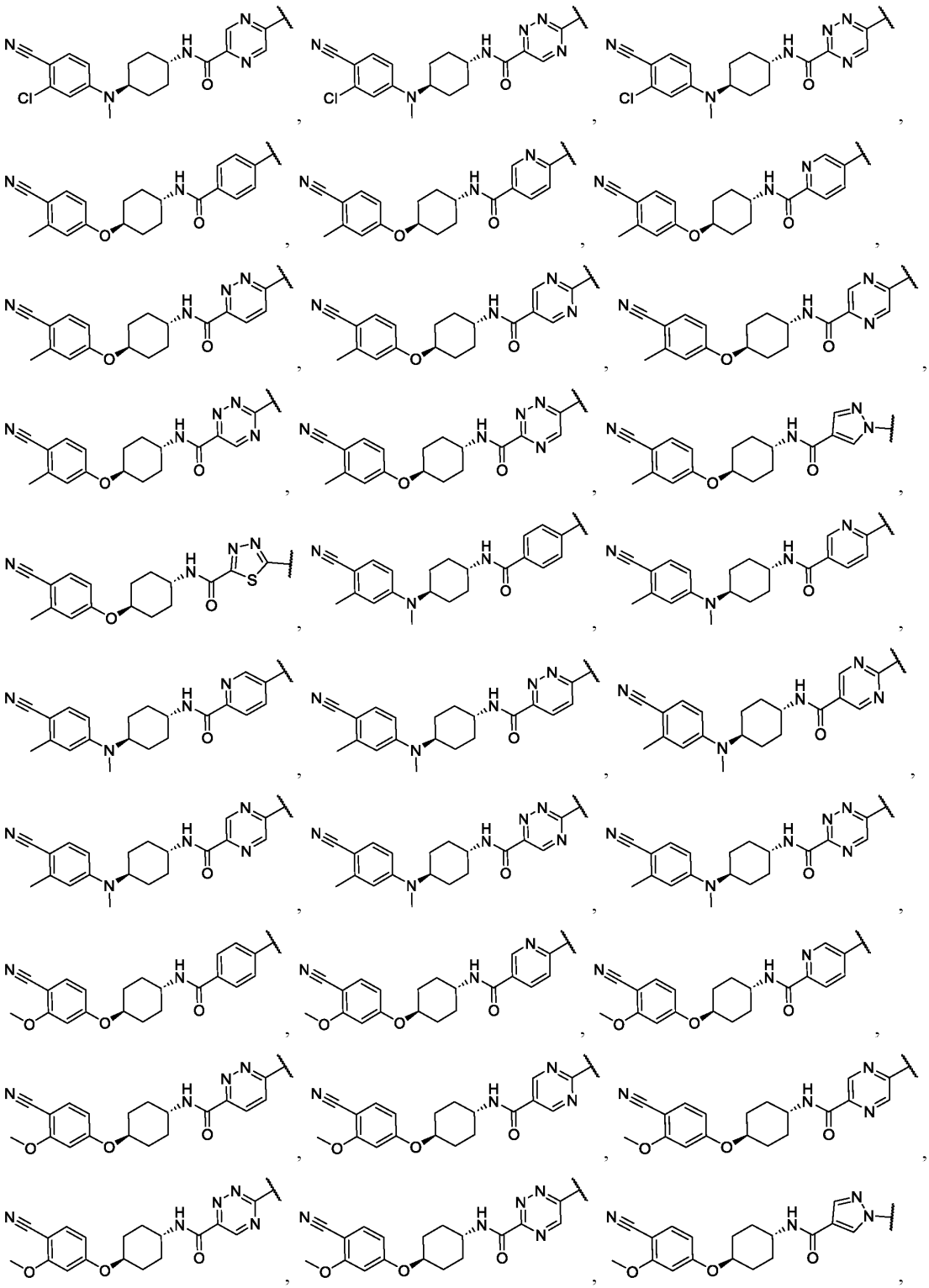
each R^3 is independently hydrogen, F, Cl, Br, I, $-CH_3$, $-CH_2CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2CH_2F$, $-CH_2CHF_2$, $-CH_2CF_3$, -OH, $-OCF_3$, $-OCH_3$, $-OCH_2CH_3$, -CN, $-C(=O)NH_2$, or $-C(=O)NH(CH_3)$.

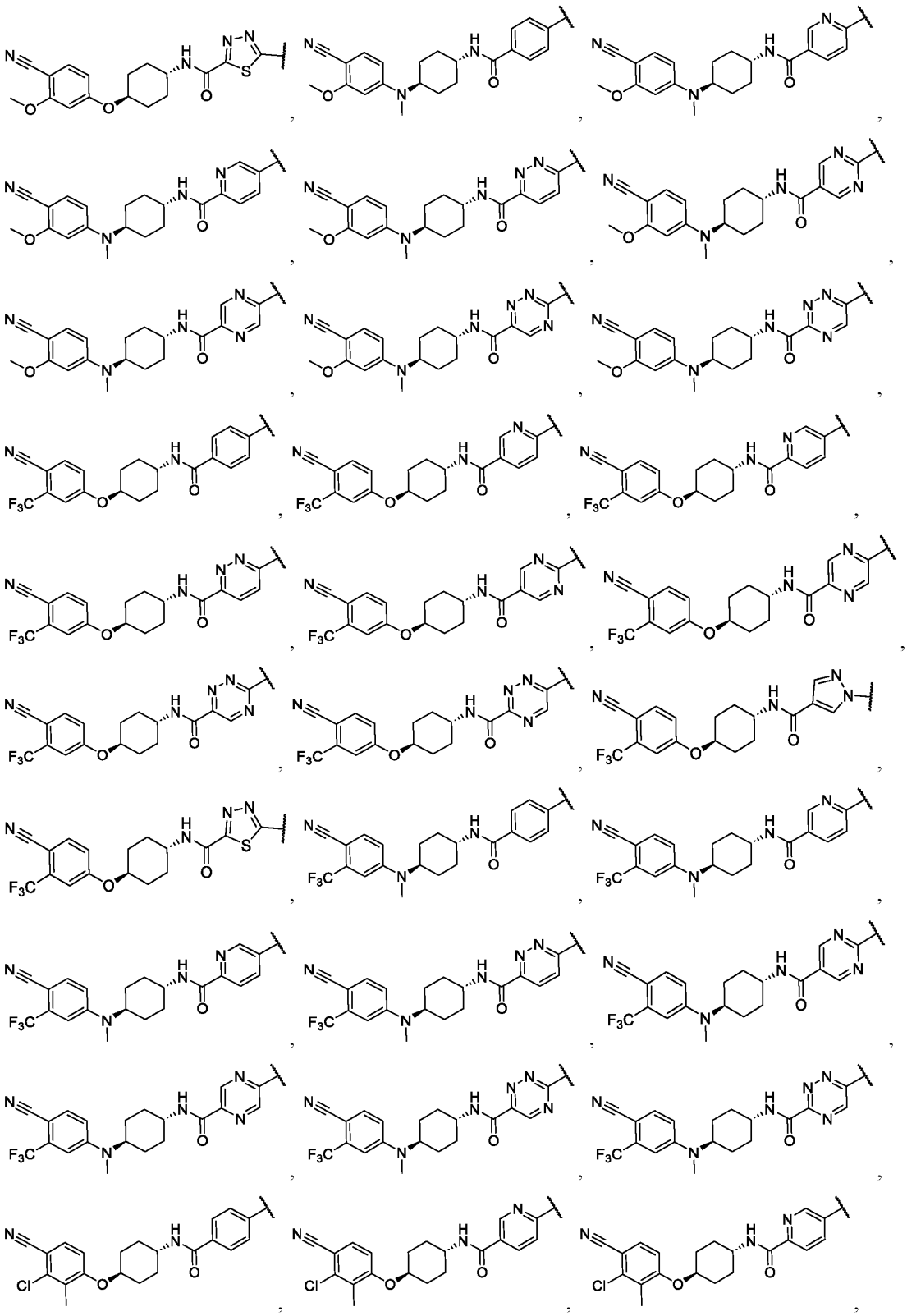
38. The compound of claim 35 or 36, or a pharmaceutically acceptable salt or solvate thereof, wherein ring D is phenyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, or triazinyl; wherein ring D is optionally substituted with s R^3; s is 1, 2, or 3;

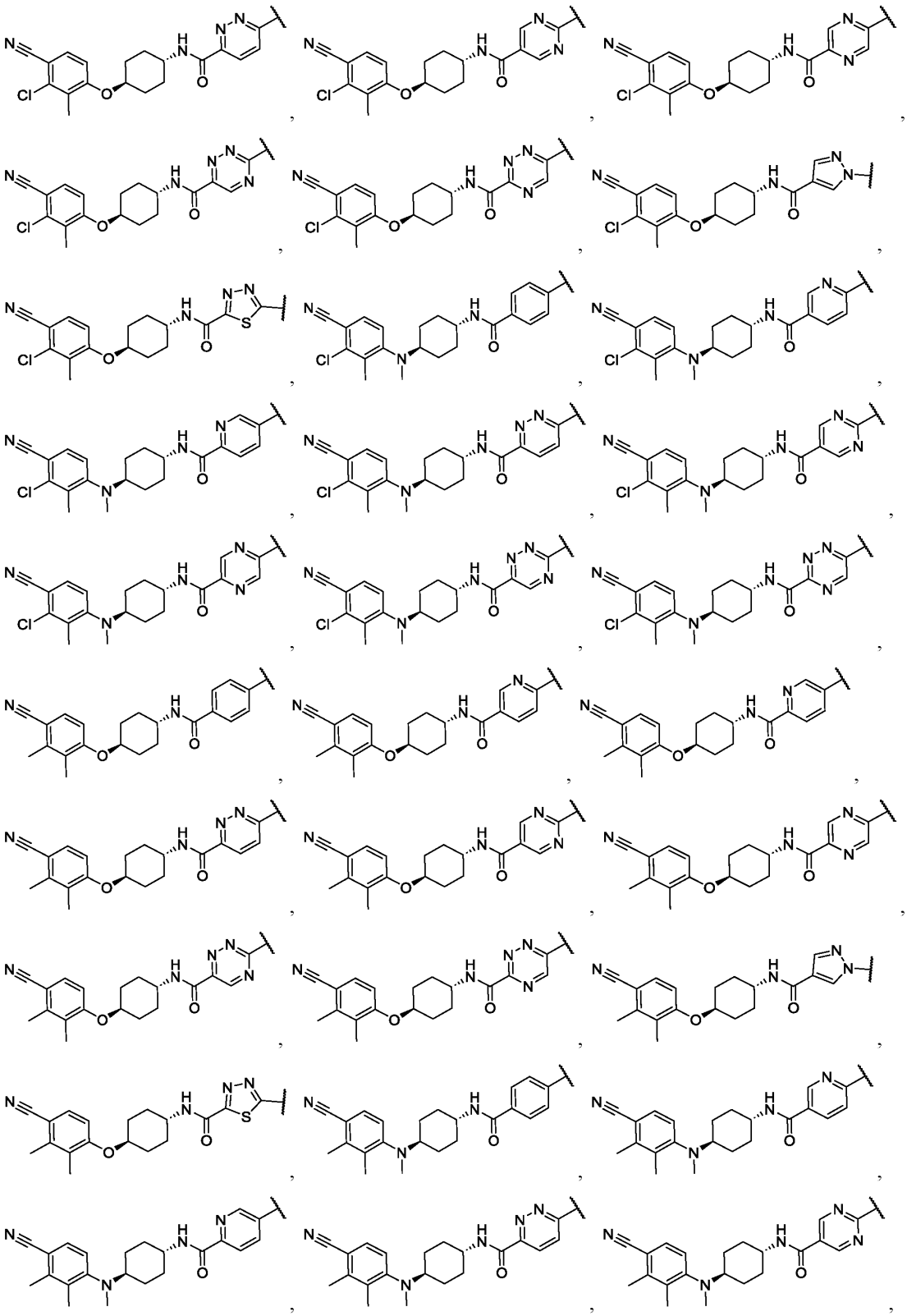
each R^3 is independently hydrogen, F, Cl, Br, I, $-CH_3$, $-CH_2CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2CH_2F$, $-CH_2CHF_2$, $-CH_2CF_3$, -OH, $-OCF_3$, $-OCH_3$, $-OCH_2CH_3$, or -CN.

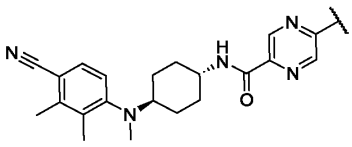
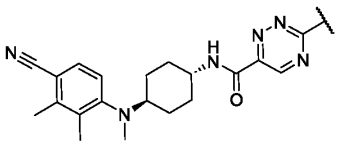
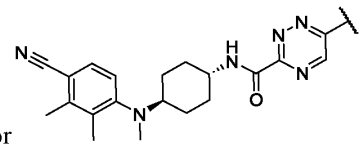
39. The compound of claim 1-11 or 14, or a pharmaceutically acceptable salt or solvate thereof, wherein B-AR has one of the following structures:









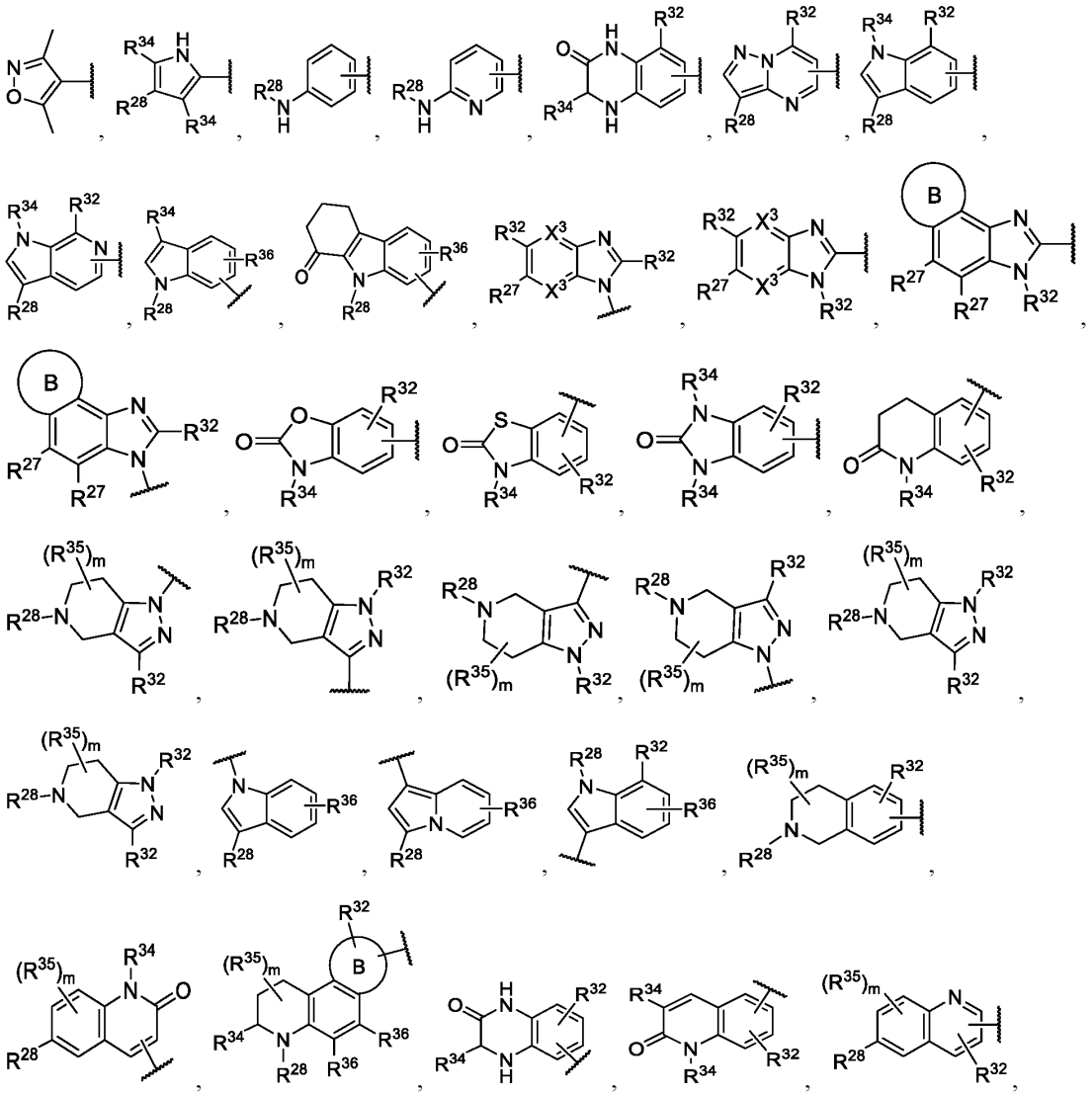

,

, or

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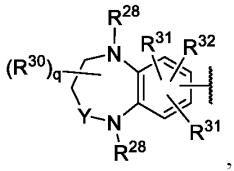
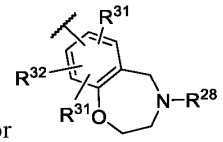
40. The compound of any one of claims 14-39, or a pharmaceutically acceptable salt or solvate thereof, wherein SB-CBP/p300 binds in the acetyl-lysine (KAc) binding site of the bromodomain of CBP/p300.
41. The compound of any one of claims 14-39, or a pharmaceutically acceptable salt or solvate thereof, wherein SB-CBP/p300 comprises an acetyl-lysine mimetic moiety that binds in the acetyl-lysine (KAc) binding site of the bromodomain of CBP/p300.
42. The compound of claim 41, or a pharmaceutically acceptable salt or solvate thereof, wherein L is covalently attached at a position of a) that is solvent exposed when a) binds the KAc binding site of the bromodomain of CBP/p300.
43. The compound of claim 41, or a pharmaceutically acceptable salt or solvate thereof, wherein the moiety comprising an acetyl-lysine mimetic makes or mimics a hydrogen bond interaction to Asn1168 in the Asn-binding pocket of the bromodomain of CBP, or makes or mimics a hydrogen bond interaction to Asn1132 in the Asn-binding pocket of the bromodomain of p300; and the head group of B-AR forms hydrogen bonds with the side chains of Gln 711 and Arg 752 of the LBD of AR.
44. The compound of any one of claims 14-43, or a pharmaceutically acceptable salt or solvate thereof, wherein SB-CBP/p300 further comprises a moiety that interacts with Arg1173 in the bromodomain of CBP or Asn1137 in the bromodomain of p300.
45. The compound of any one of claims 14-44, or a pharmaceutically acceptable salt or solvate thereof, wherein SB-CBP/p300 further comprises:
    1) a moiety that occupies the lipophilic shelf (LPF) region of the bromodomain of CBP/p300; or
    2) a moiety that occupies the BC Loop region of the bromodomain of CBP/p300; or
    3) both 1) and 2).
46. The compound of claim 41-45, or a pharmaceutically acceptable salt or solvate thereof, wherein the moiety comprising an acetyl-lysine mimetic comprises a moiety selected from pyrrolidonyl, phenyl, pyridinyl, pyridinonyl, triazolyl, pyrrolyl, isoxazolyl, pyrazolyl, quinolinyl, tetrahydroquinolinyl, isoquinolinyl, tetrahydroisoquinolinyl, quinazolonyl, quinazolinyl, dihydroquinazolinonyl, imidazo[4,5-c]quinolinyl fused to a dimethylisoxazolyl, triazolophthalazinyl, indolizinyl, benzoimidazolyl, isoxazole-indolizinyl, thienodiazepine-indolizinyl, benzodiazepine-indolizinyl, 5-isoxazolylbenzimidazolyl, 6-isoxazolylbenzimidazolyl, 7-isoxazolo-quinolinyl, diazobenzyl, triazolophthalazinyl, isoxazoloquinolinyl, 2-thiazolidinonyl, triazolopyrimidinyl, thienodiazepinyl, benzodiazepinyl, benzotriazepinyl, triazolobenzodiazepinyl, triazolothienodiazepinyl, triazolothienodiazepinyl, and isoxazole-azepinyl.
47. The compound of claim 45 or 46, or a pharmaceutically acceptable salt or solvate thereof, wherein L is covalently attached to SB-CBP/p300 on:
    - the acetyl-lysine mimetic moiety; or

- the moiety that occupies the lipophilic shelf (LPF) region of the bromodomain of CBP/p300, if present; or
- the moiety that occupies the BC Loop region of the bromodomain of CBP/p300, if present;

wherein L is covalently attached to SB-p300/CBP at a position that does not interfere with the binding of the acetyl-lysine mimetic moiety in the acetylated lysine (KAc) binding site of CBP/p300.

48. The compound of any one of claims 1-47, or a pharmaceutically acceptable salt or solvate thereof, wherein the moiety comprising an acetyl-lysine mimetic comprises a moiety selected from:




, or 
;

each R^{32} is independently an optional moiety that occupies the lipophilic shelf (LPF) region of the bromodomain of CBP/p300;

or each R^{32} is independently an optional moiety that occupies the BC Loop region of the bromodomain of CBP/p300;

—| is the point of attachment to L that covalently connects SB-CBP/p300 to B-AR;

or R^{32} comprises —| and L that covalently connects SB-CBP/p300 to B-AR is attached to R^{32};

each R^{28} is independently hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, -C(=O)R^b, or -C(=O)N(R^b)$_2$;

each R^{34} is independently hydrogen or substituted or unsubstituted C_1-C_6alkyl;

each R^{35} is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, or substituted or unsubstituted 3- to 8-membered heterocycloalkyl, -CN, -OH, -OR^a, or -N(R^b)$_2$;

m is 0, 1, 2, 3, or 4;

each R^{27} is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -CN, -NO_2, -OH, -OR^a, OC(=O)R^a, -OC(=O)N(R^b)$_2$, -OC(=O)OR^a, -OC(=O)N(R^b)$_2$, -SR^b, -S(=O)R^a, -S(=O)$_2$$R^a$, -S(=O)$_2OR^b$, -S(=O)$_2$N($R^b$)$_2$, -N($R^b$)$_2$, -N$R^b$C(=O)N($R^b$)$_2$, -N$R^b$C(=O)$R^a$, -N$R^b$C(=O)O$R^a$, -N$R^b$S(=O)$_2$$R^a$, -C(=O)$R^b$, -C(=O)O$R^b$, or -C(=O)N($R^b$)$_2$;

Y is -C(R^{30})$_2$- or C(=O);

each X^3 is independently CR^{27} or N;

each R^{30} is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, -CN, -NO_2, -OH, -OR^a, OC(=O)R^a, -OC(=O)N(R^b)$_2$, -OC(=O)OR^a, -SR^b, -S(=O)R^a, -S(=O)$_2$$R^a$, -S(=O)$_2OR^b$, -S(=O)$_2$N($R^b$)$_2$, -N($R^b$)$_2$, -N$R^b$C(=O)N($R^b$)$_2$, -N$R^b$C(=O)$R^a$, -N$R^b$C(=O)O$R^a$, -N$R^b$S(=O)$_2$$R^a$, -C(=O)$R^b$, -C(=O)O$R^b$, or -C(=O)N($R^b$)$_2$;

q is 0, 1, 2, 3, or 4;

each R^{31} is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, -CN, -NO_2, -OH, -OR^a, OC(=O)R^a, -OC(=O)N(R^b)$_2$, -OC(=O)OR^a, -

SR^b, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2OR^b$, $-S(=O)_2N(R^b)_2$, $-N(R^b)_2$, $-NR^bC(=O)NR^b$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^a$, $-NR^bS(=O)_2R^a$, $-C(=O)R^b$, $-C(=O)OR^b$, or $-C(=O)N(R^b)_2$;

each R^{36} is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, -CN, -OH, $-OR^a$, or $-N(R^b)_2$;

Ring B is a fused substituted or unsubstituted 5 or 6 membered heterocycloalkyl;

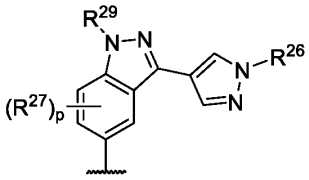
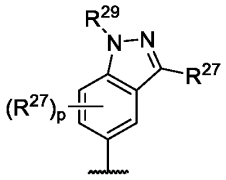
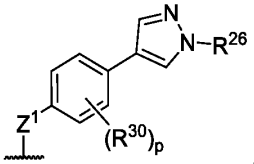
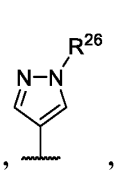
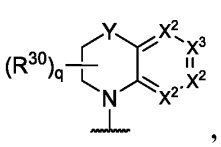
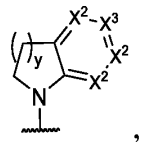
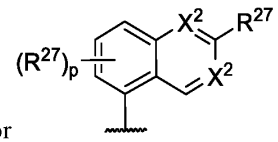
each R^a is independently substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted monocyclic 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted monocyclic heteroaryl;

each R^b is independently hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted monocyclic 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted monocyclic heteroaryl;

or two R^b on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle.

49. The compound of claim 45-48, or a pharmaceutically acceptable salt or solvate thereof, wherein the moiety that occupies the lipophilic shelf (LPF) region of the bromodomain of CBP/p300 is R^{32}, wherein:

R^{32} is hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_2-C_6alkenyl, substituted or unsubstituted C_2-C_6alkynyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{12}cycloalkyl, substituted or unsubstituted 3- to 12-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

or R^{32} is  ,  ,  ,  ,  ,  , or  ;

y is 1 or 2;

Z^1 is $-NR^e$-, -O-, or -S-;

R^e is hydrogen or substituted or unsubstituted C_1-C_6alkyl;

R^{26} is hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, or substituted or unsubstituted 3- to 8-membered heterocycloalkyl;

each X^2 is independently $-CR^{30}$- or -N-;

each X^3 is independently -CR^{27}- or -N-;

each R^{27} is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -CN, -NO_2, -OH, -OR^a, $OC(=O)R^a$, -$OC(=O)N(R^b)_2$, -$OC(=O)OR^a$, -$OC(=O)N(R^b)_2$, -SR^b, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2OR^b$, -$S(=O)_2N(R^b)_2$, -$N(R^b)_2$, -$NR^bC(=O)N(R^b)_2$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^a$, -$NR^bS(=O)_2R^a$, -$C(=O)R^b$, -$C(=O)OR^b$, or -$C(=O)N(R^b)_2$;

p is 0, 1, 2, or 3;

R^{28} is hydrogen or substituted or unsubstituted C_1-C_6alkyl;

R^{29} is hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, or substituted or unsubstituted 3- to 8-membered heterocycloalkyl;

Y is -$C(R^{30})_2$- or $N(R^{28})$-;

each R^{30} is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, -CN, -NO_2, -OH, -OR^a, $OC(=O)R^a$, -$OC(=O)N(R^b)_2$, -$OC(=O)OR^a$, -SR^b, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2OR^b$, -$S(=O)_2N(R^b)_2$, -$N(R^b)_2$, -$NR^bC(=O)N(R^b)_2$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^a$, -$NR^bS(=O)_2R^a$, -$C(=O)R^b$, -$C(=O)OR^b$, or -$C(=O)N(R^b)_2$;

q is 0, 1, 2, 3, or 4;

or R^{32} is -L-C;

L is substituted or unsubstituted C_1-C_6alkyl or substituted or unsubstituted C_1-C_6heteroalkyl;

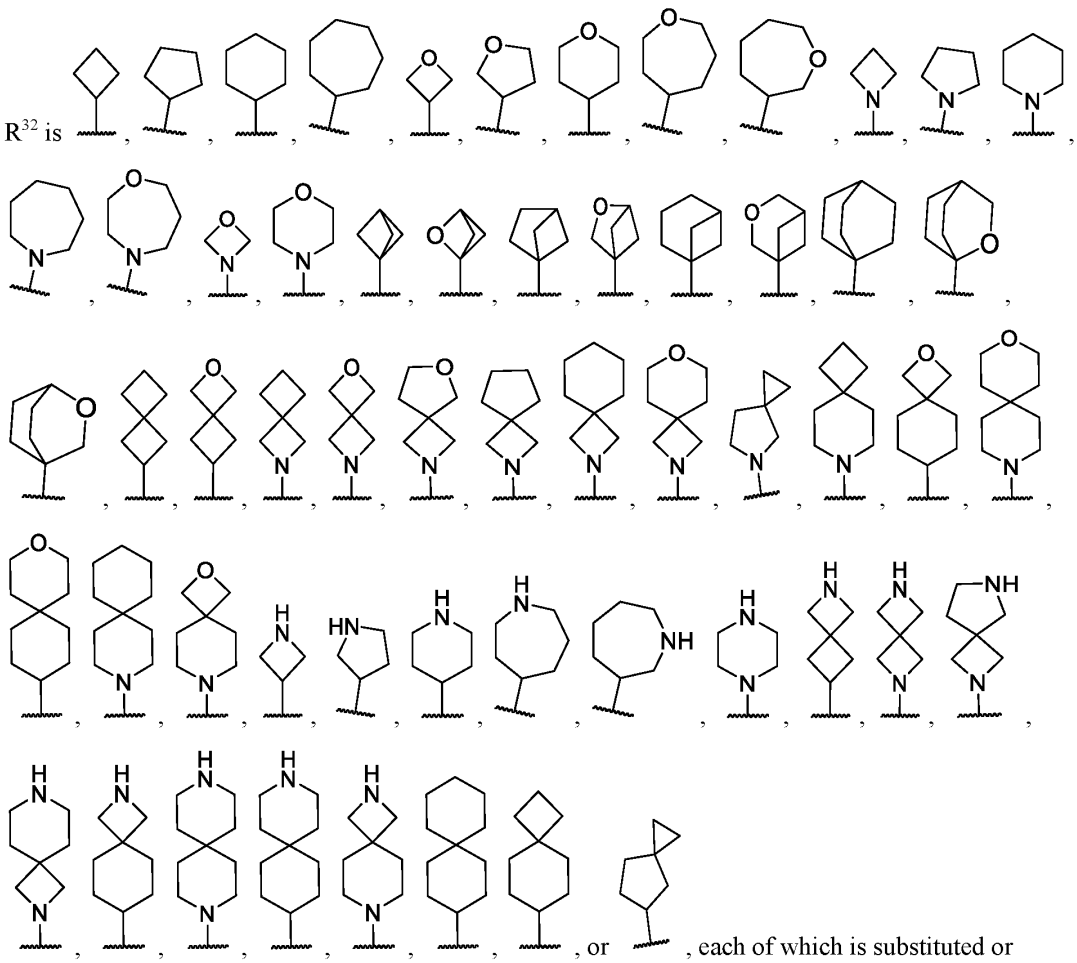
C is substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

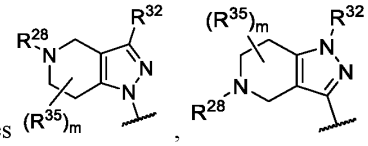
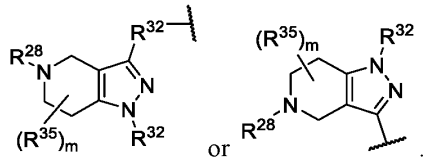
each R^a is independently substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted monocyclic 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted monocyclic heteroaryl;

each R^b is independently hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted monocyclic 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted monocyclic heteroaryl;

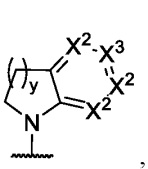
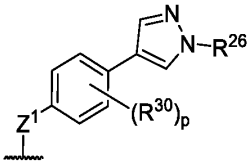
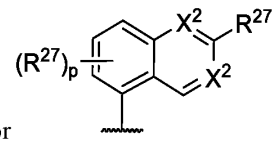
or two R^b on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle.

50. The compound of any one of claims 45-49, or a pharmaceutically acceptable salt or solvate thereof, wherein the moiety that occupies the BC Loop region of the bromodomain of CBP/p300 is R^{32}, wherein:

R^{32} is  , each of which is substituted or unsubstituted.

51. The compound of any one of claims 41-50, or a pharmaceutically acceptable salt or solvate thereof, wherein the moiety comprising an acetyl-lysine mimetic comprises  ,  or .

52. The compound of claim 51, or a pharmaceutically acceptable salt or solvate thereof, wherein:

R^{32} is  ,  , or  ;

R^{27} is hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl,

substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -CN, -OH, or -OR^a; and

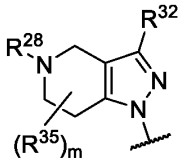
each R^{27} is independently hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, -CN, -OH, or -OR^a; and

each R^a is independently substituted or unsubstituted C_1-C_6alkyl.

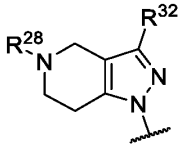
53. The compound of claim 52, or a pharmaceutically acceptable salt or solvate thereof, wherein:

each R^{27} is independently hydrogen, -CH_3, -CH_2CH_3, -F, -CHF_2, -CF_3, -CN, -OH, -OCH_3, cyclopropyl, cyclobutyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, phenyl, pyrazolyl, 1-methyl pyrazolyl, pyridinyl, or pyrimidinyl.

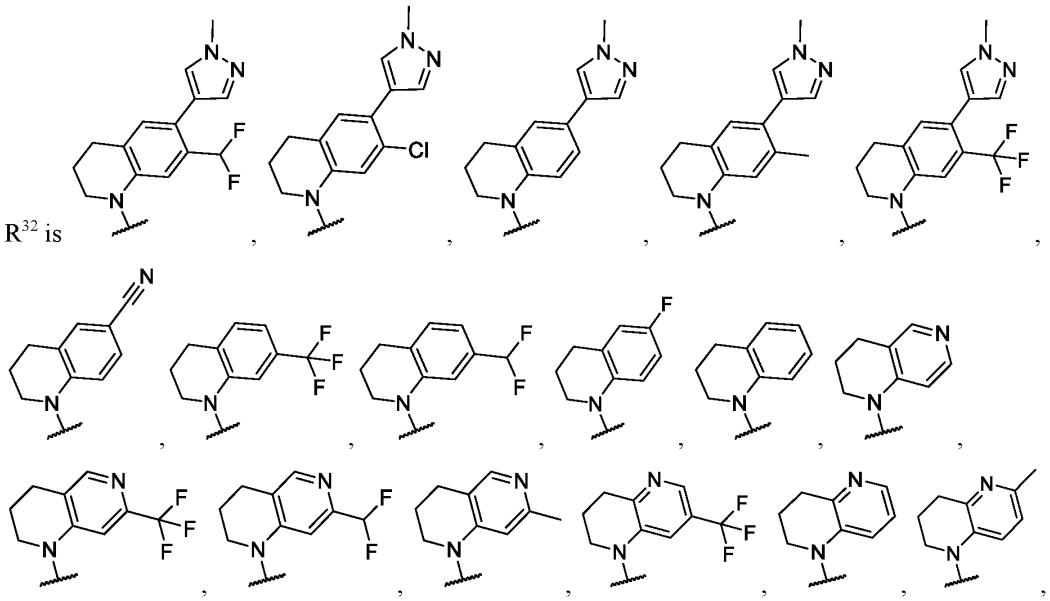
54. The compound of any one of claims 51-53, or a pharmaceutically acceptable salt or solvate thereof,

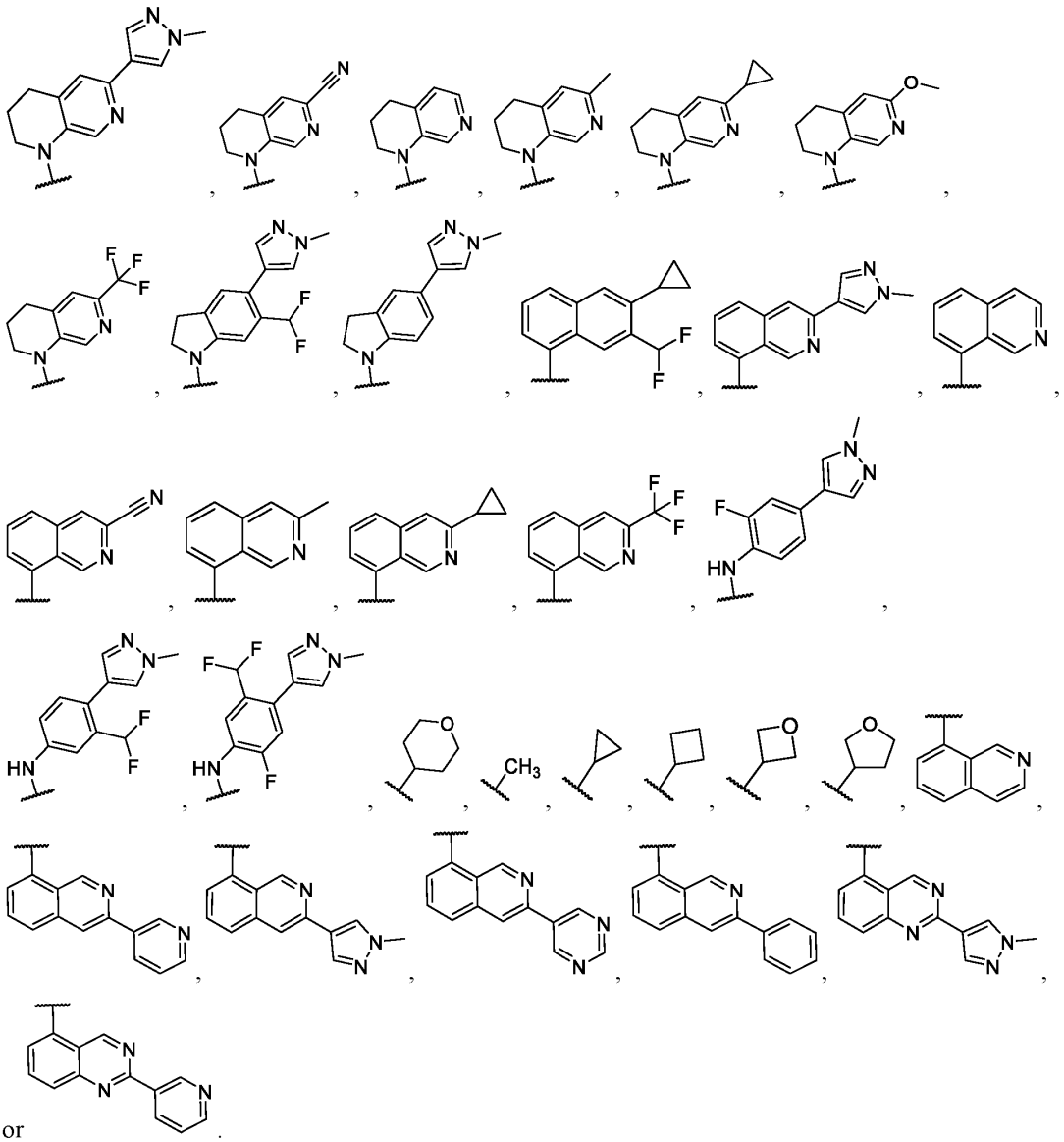
wherein the moiety comprising an acetyl-lysine mimetic comprises  .

55. The compound of any one of claims 51-53, or a pharmaceutically acceptable salt or solvate thereof,

wherein the moiety comprising an acetyl-lysine mimetic comprises  .

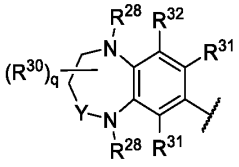
56. The compound of any one of claims 51-55, or a pharmaceutically acceptable salt or solvate thereof, wherein:

R^{32} is  .

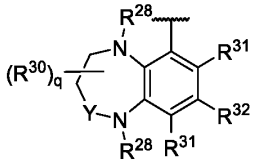


or .

57. The compound of any one of claims 41-50, or a pharmaceutically acceptable salt or solvate thereof,

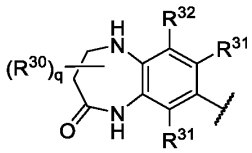
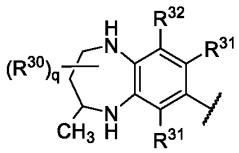
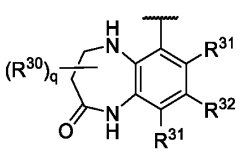
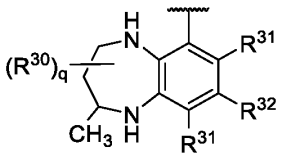


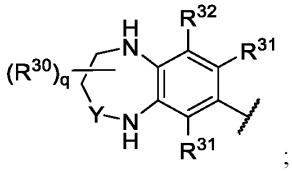
wherein the moiety comprising an acetyl-lysine mimetic comprises or



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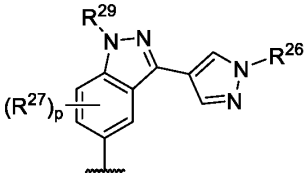
58. The compound of claim 57, or a pharmaceutically acceptable salt or solvate thereof, wherein the moiety

comprising an acetyl-lysine mimetic comprises  ,  ,  , or  .

59. The compound of claim 57, or a pharmaceutically acceptable salt or solvate thereof, wherein the moiety comprising an acetyl-lysine mimetic comprises  ;

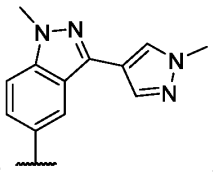
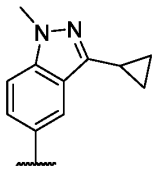
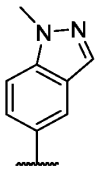
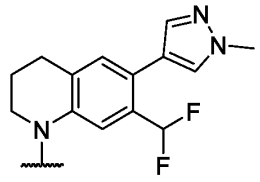
wherein:

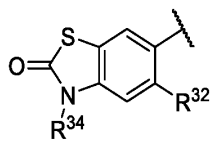
each R^{28} is independently hydrogen or substituted or unsubstituted C_1-C_6alkyl;

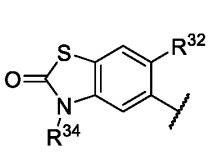
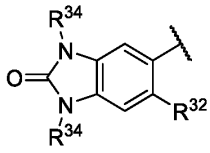
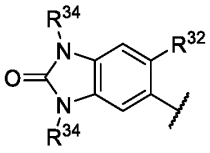
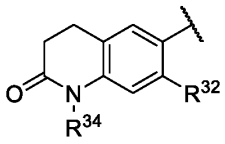
R^{32} is  ; and

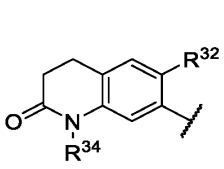
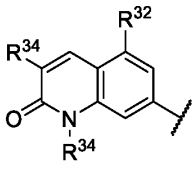
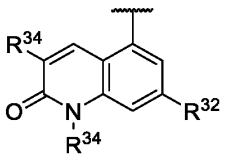
each R^{27} is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, -CN, -NO_2, -OH, -OR^a, $OC(=O)R^a$, -$OC(=O)N(R^b)_2$, -$OC(=O)OR^a$, -SR^b, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2OR^b$, -$S(=O)_2N(R^b)_2$, -$N(R^b)_2$, -$NR^bC(=O)N(R^b)_2$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^a$, -$NR^bS(=O)_2R^a$, -$C(=O)R^b$, -$C(=O)OR^b$, or -$C(=O)N(R^b)_2$.

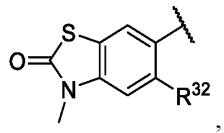
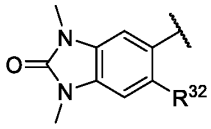
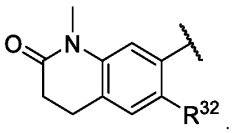
60. The compound of any one of claims 57-59, or a pharmaceutically acceptable salt or solvate thereof, wherein:

R^{32} is  ,  ,  , or  .

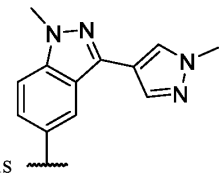
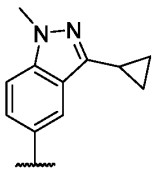
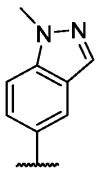
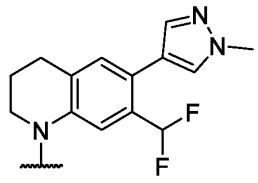
61. The compound of any one of claims 41-50, or a pharmaceutically acceptable salt or solvate thereof, wherein the moiety comprising an acetyl-lysine mimetic comprises  ,

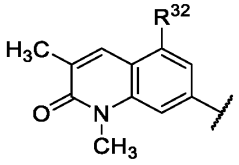
 ,  ,  ,  ,


, 
, or 
.

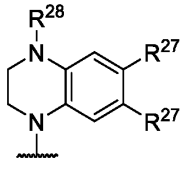
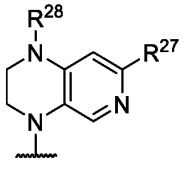
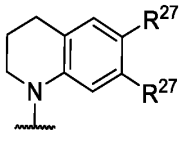
62. The compound of claim 61, or a pharmaceutically acceptable salt or solvate thereof, wherein the moiety comprising an acetyl-lysine mimetic comprises 
, 
, or 
.

63. The compound of any one of claims 61-62, or a pharmaceutically acceptable salt or solvate thereof, wherein:

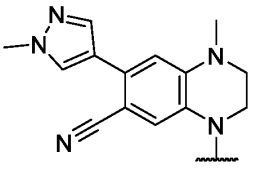
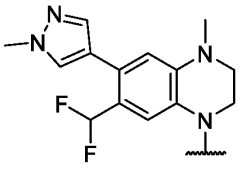
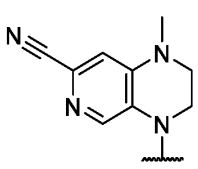
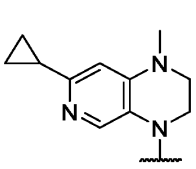
R^{32} is 
, 
, 
, or 
.

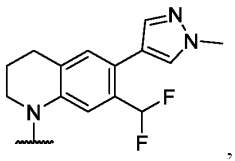
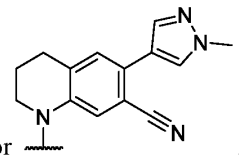
64. The compound of claim 61, or a pharmaceutically acceptable salt or solvate thereof, wherein the moiety comprising an acetyl-lysine mimetic comprises: 
.

65. The compound of claim 61 or 64, or a pharmaceutically acceptable salt or solvate thereof, wherein:

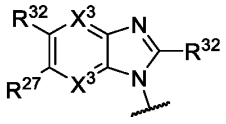
R^{32} is 
, 
, or 
.

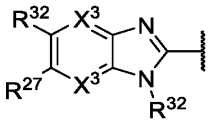
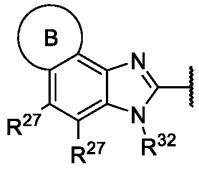
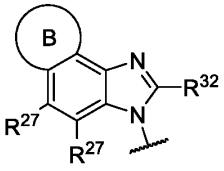
66. The compound of any one of claims 61, 62, 64, or 65, or a pharmaceutically acceptable salt or solvate thereof, wherein:

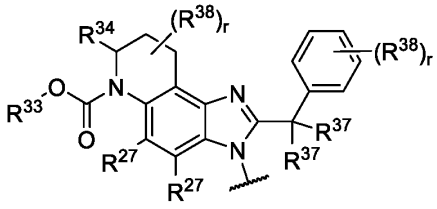
R^{32} is 
, 
, 
, 
,


, or 
.

67. The compound of any one of claims 41-50, or a pharmaceutically acceptable salt or solvate thereof,

wherein the moiety comprising an acetyl-lysine mimetic comprises 
,


, 
, or 
.

68. The compound of claim 67, or a pharmaceutically acceptable salt or solvate thereof, wherein the moiety comprising an acetyl-lysine mimetic comprises 
, wherein:

each R^{27} is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, -CN, -OH, -OR^a, or -$N(R^b)_2$;

R^{33} is hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, or substituted or unsubstituted C_1-C_6heteroalkyl;

R^{34} is hydrogen or substituted or unsubstituted C_1-C_6alkyl;

each R^{37} is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, -CN, -OH, -OR^a, or -$N(R^b)_2$;

each R^{38} is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted 3- to 8-membered heterocycloalkyl, -CN, -NO_2, -OH, -OR^a, -$OC(=O)R^a$, -$OC(=O)N(R^b)_2$, -$OC(=O)OR^a$, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2OR^b$, -$S(=O)_2N(R^b)_2$, -$N(R^b)_2$, -$NR^bC(=O)N(R^b)_2$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^a$, -$NR^bS(=O)_2R^a$, -$C(=O)R^b$, -$C(=O)OR^b$, or -$C(=O)N(R^b)_2$;

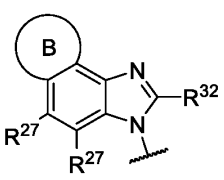
each R^a is independently substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted monocyclic 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted monocyclic heteroaryl;

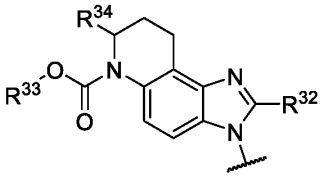
each R^b is independently hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted monocyclic 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted monocyclic heteroaryl;

or two R^b on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle;

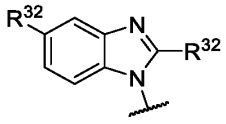
r is 0, 1, 2, 3, or 4.

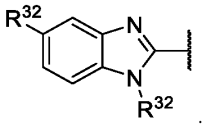
69. The compound of claim 67, or a pharmaceutically acceptable salt or solvate thereof, wherein:



is


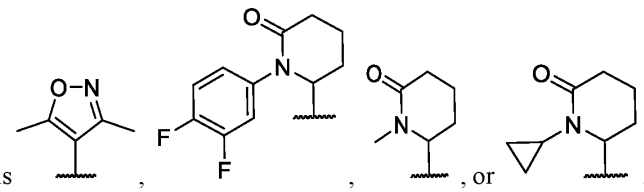
.

70. The compound of claim 67, or a pharmaceutically acceptable salt or solvate thereof, wherein the moiety comprising an acetyl-lysine mimetic comprises


or


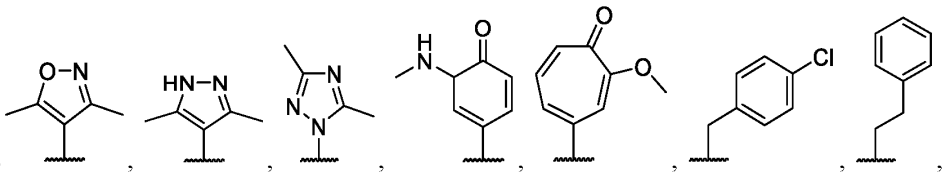
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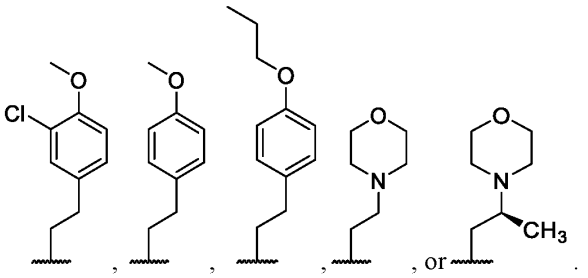
71. The compound of any one of claims 67-70, or a pharmaceutically acceptable salt or solvate thereof, wherein:

R^{32} is


, or .

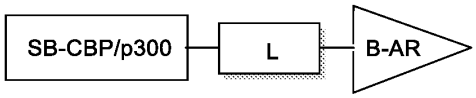
72. The compound of any one of claims 67-70, or a pharmaceutically acceptable salt or solvate thereof, wherein:

R^{32} is


,


, or .

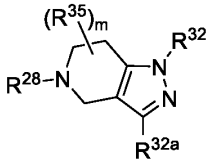
73. A heterobifunctional conditional inhibitor compound of Formula (I) or a pharmaceutically acceptable salt or solvate thereof:



wherein:

SB-CBP/p300 is a silent binder of the bromodomain of human CREB-binding protein (CBP) or human E1A-binding protein p300 (p300) (CBP/p300), wherein the binder of CBP/p300 comprises:

- an acetyl-lysine mimetic moiety that binds in the acetyl-lysine (KAc) binding site of the bromodomain of human CREB-binding protein (CBP) or human E1A-binding protein p300 (p300) (CBP/p300) and has the structure:



R^{28} is -C(=O)CH_3, -C(=O)CH_2CH_3, -C(=O)NH_2, -C(=O)NH(CH_3); or -C(=O)NH(CH_2CH_3);

R^{32} is a moiety that occupies the BC Loop region of the bromodomain of CBP/p300;

R^{32a} is a moiety that occupies the lipophilic shelf (LPF) region of the bromodomain of CBP/p300;

each R^{35} is independently hydrogen, C_1-C_4alkyl, or C_1-C_4fluoroalkyl;

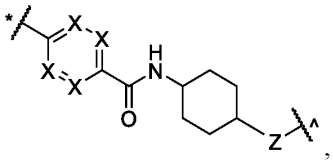
m is 0, 1, 2, 3, or 4;

L is an optional linker;

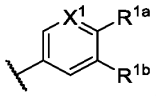
wherein L is covalently attached to the R^{32} group, or at the position occupied by R^{32}, or the R^{32a} group;

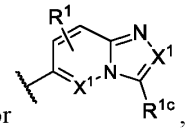
B-AR is a binder of the androgen receptor (AR), wherein the B-AR comprises:

- a head group that occupies the ligand-binding domain (LBD) of AR and is covalently attached to a core with a tail moiety covalently attached to the core moiety; wherein B-AR has the structure of Formula (D):



, Formula (D);

wherein head group is 

, or 

, and the the head group is covalently attached to Z at position (^), and L is attached at position *;

Z is -O-, -NH- or -N(C_1-C_4alkyl)-;

each X^1 is independently -CR^1- or -N-;

R^{1a} is -CN, -NO_2, -C(=O)R^5, -C(=O)OR^5, or -C(=O)$N(R^5)_2$;

R^{1b} is hydrogen, halogen, substituted or unsubstituted C_1-C_4alkyl, C_1-C_4fluoroalkyl, -CN, -OH, or -OR^4;

R^{1c} is hydrogen, halogen, C_1-C_4alkyl, C_1-C_4fluoroalkyl, or -CN;

each R^1 is independently hydrogen, halogen, substituted or unsubstituted C_1-C_4alkyl, C_1-C_4fluoroalkyl, -CN, -OH, or -OR^4;

each X is independently -CR^3- or -N-;

each R^3 is independently hydrogen, halogen, substituted or unsubstituted C_1-C_4alkyl, C_1-C_4fluoroalkyl, -CN, -OH, -OR^4, or -$N(R^5)_2$.

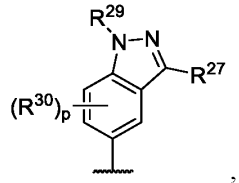
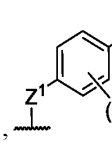
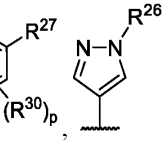
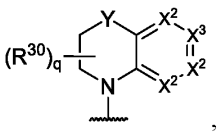
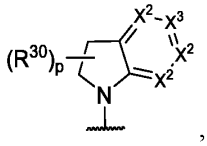
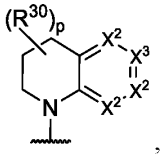
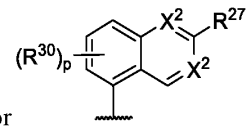
each R^4 is independently substituted or unsubstituted C_1-C_4alkyl, or C_1-C_4fluoroalkyl;

each R^5 is independently hydrogen, substituted or unsubstituted C_1-C_4alkyl, C_1-C_4fluoroalkyl; and

each s is 1, 2, or 3.

74. The compound of claim 73, or a pharmaceutically acceptable salt or solvate thereof, wherein:

R^{32} is hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_3-C_{12}cycloalkyl, or substituted or unsubstituted 3- to 12-membered heterocycloalkyl;

R^{32a} is  ,  ,  ,  ,  ,  , or  ;

at least one X^2 is -CR^{30}- and at most two X^2 are -N-;

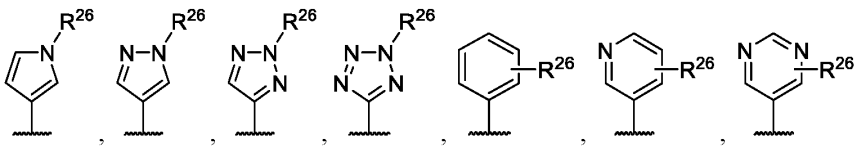
Z^1 is -NR^e- or -O-;

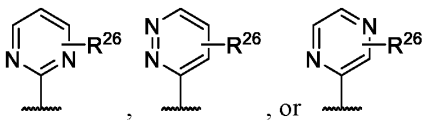
R^e is hydrogen or C_1-C_6alkyl;

R^{26} is hydrogen, substituted or unsubstituted C_1-C_4alkyl, C_1-C_4fluoroalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, or substituted or unsubstituted 3- to 8-membered heterocycloalkyl;

X^3 is -CR^{27}- or -N-;

R^{27} is hydrogen, halogen, substituted or unsubstituted C_1-C_4alkyl, C_1-C_4fluoroalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted 3- to 8-membered heterocycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted monocyclic heteroaryl, -CN, -OH, -OR^a, -$N(R^b)_2$, -$NR^bC(=O)R^a$, -$C(=O)R^b$, -$C(=O)OR^b$, or -$C(=O)N(R^b)_2$;

or R^{27} is 



p is 0, 1, 2, or 3;

R^{29} is hydrogen, substituted or unsubstituted C_1-C_4alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, or substituted or unsubstituted 3- to 8-membered heterocycloalkyl;

Y is $-C(R^{30})_2-$ or $N(R^{28})-$;

each R^{30} is independently hydrogen, halogen, C_1-C_4alkyl, C_1-C_4fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, -CN, -OH, or $-OR^a$;

q is 0, 1, 2, 3, or 4;

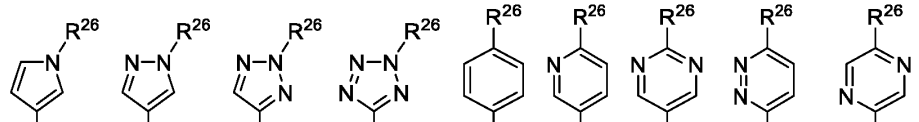
each R^a is independently C_1-C_4alkyl, C_1-C_6fluoroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted monocyclic 3- to 6-membered heterocycloalkyl, substituted or unsubstituted phenyl, or substituted or unsubstituted monocyclic heteroaryl;

each R^b is independently hydrogen, C_1-C_4alkyl, C_1-C_4fluoroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted monocyclic 3- to 6-membered heterocycloalkyl, substituted or unsubstituted phenyl, or substituted or unsubstituted monocyclic heteroaryl;

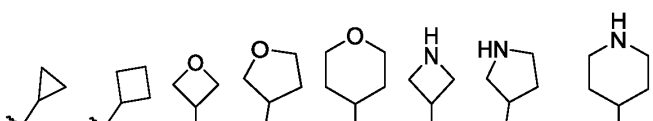
or two R^b on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle.

75. The compound of any one of claims 73-74, or a pharmaceutically acceptable salt or solvate thereof, wherein:

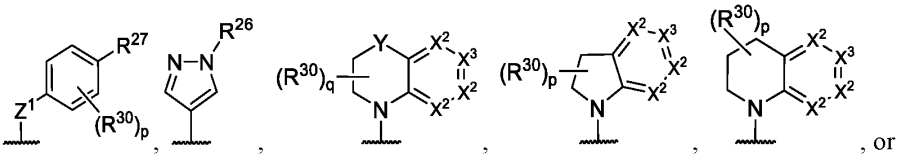
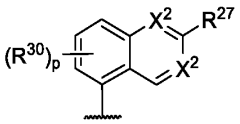
R^{27} is hydrogen, halogen, C_1-C_4alkyl, C_1-C_4fluoroalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted 3- to 8-membered heterocycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted monocyclic 5- or 6-membered heteroaryl, -CN, -OH, $-OR^a$, $-N(R^b)_2$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^a$, $-NR^bS(=O)_2R^a$, $-C(=O)R^b$, $-C(=O)OR^b$, or $-C(=O)N(R^b)_2$;

or R^{27} is 

76. The compound of any one of claims 73-75, or a pharmaceutically acceptable salt or solvate thereof, wherein:

R^{32} is  , each of which is unsubstituted or substituted with F, Cl, Br, $-CH_3$, $-CD_3$, $-CH_2CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2CH_2F$, $-CH_2CHF_2$, -

CH_2CF_3, -CN, -C(=O)CH_3, -C(=O)CH_2CH_3, -C(=O)CH_2F, -C(=O)CHF_2, -C(=O)CF_3, -C(=O)CH_2CH_2F, -C(=O)CH_2CHF_2, -C(=O)CH_2CF_3, -C(=O)CD_3, or -SO_2CH_3, -$SO_2CH_2CH_3$, -SO_2CD_3, or -$SO_2CH_2CD_3$.

R^{32a} is  , or  ;

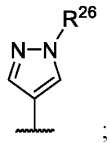
at least one X^2 is -CR^{30}- and at most two X^2 are -N-;

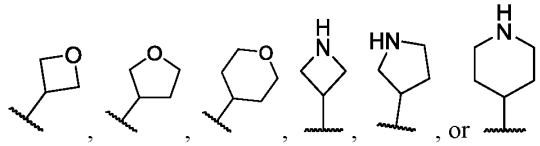
each R^{27} is independently hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -CN, -OH, or -OR^a; and

each R^a is independently substituted or unsubstituted C_1-C_6alkyl.

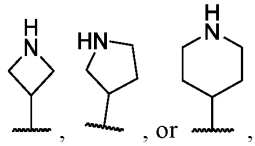
77. The compound of any one of claims 73-76, or a pharmaceutically acceptable salt or solvate thereof, wherein:

R^{27} is hydrogen, -CH_3, -CH_2CH_3, -$CH_2CH_2CH_3$, -$CH_2(CH_3)_2$, -$(CH_3)_3$, -F, -CHF_2, -CF_3, -CN, -OH, -OCH_3, cyclopropyl, cyclobutyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, unsubstituted or substituted phenyl, unsubstituted or substituted pyrazolyl, unsubstituted or substituted pyridinyl, or unsubstituted or substituted pyrimidinyl; or

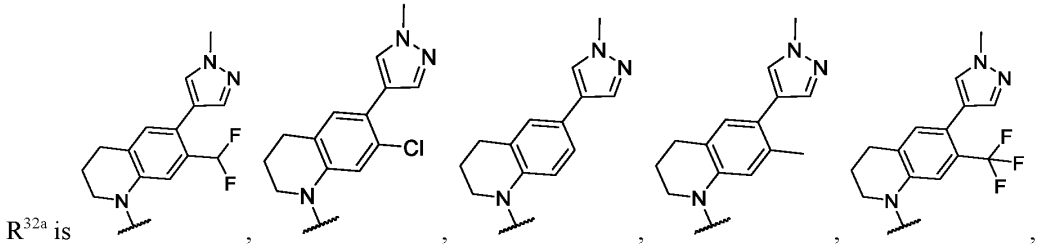
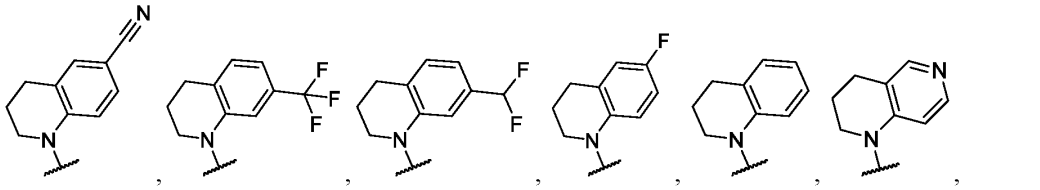
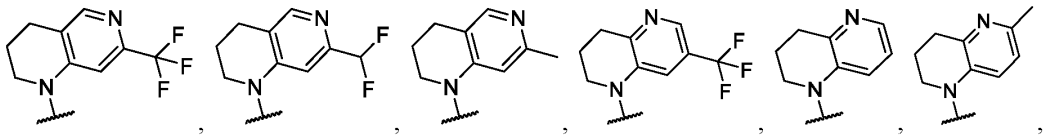
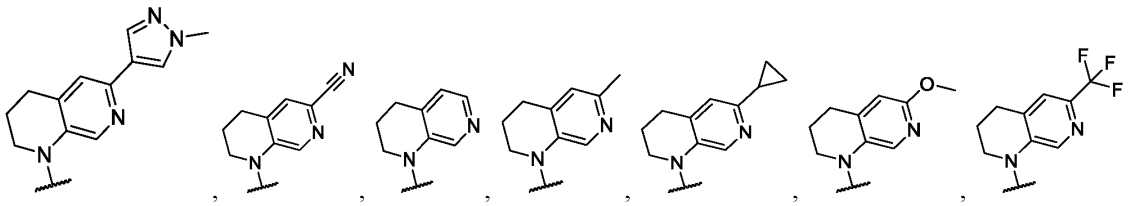
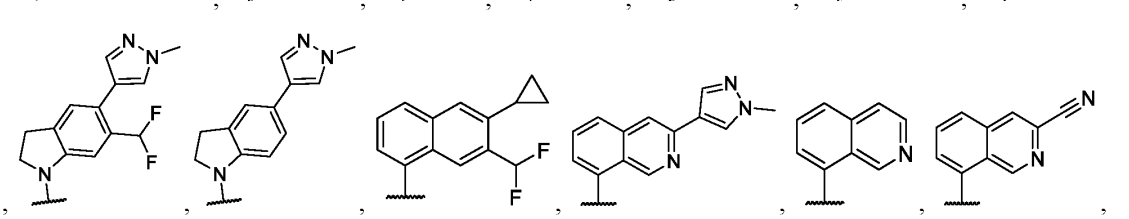
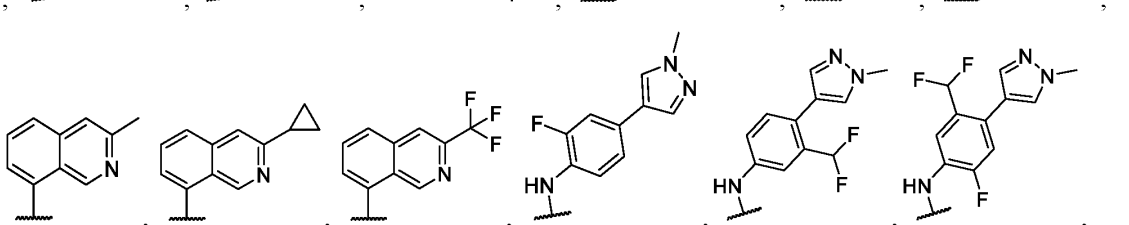
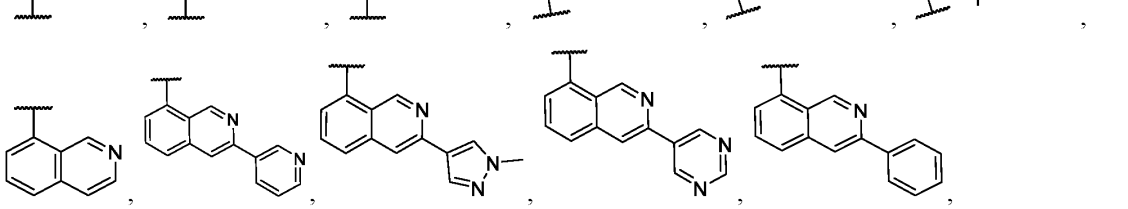
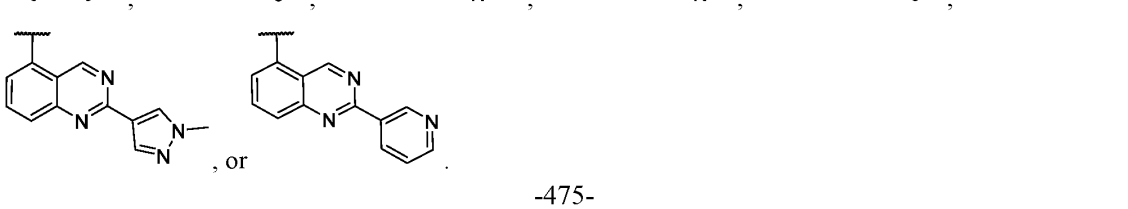
R^{27} is  ;

R^{32} is  , each of which is unsubstituted or substituted with F, Cl, Br, -CH_3, -CD_3, -CH_2CH_3, -CH_2F, -CHF_2, -CF_3, CN, -C(=O)CH_3, -C(=O)CH_2F, -C(=O)CHF_2, -C(=O)CF_3, -C(=O)CD_3.

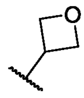
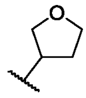
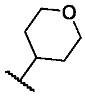
78. The compound of claim 73-77, or a pharmaceutically acceptable salt or solvate thereof, wherein:

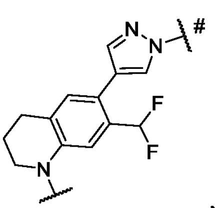
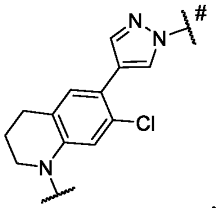
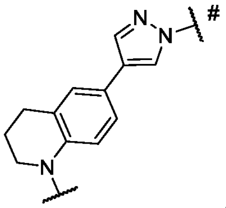
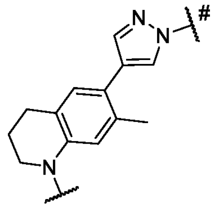
R^{32} is  , wherein the optional linker is covalently attached to the nitrogen of R^{32} group;

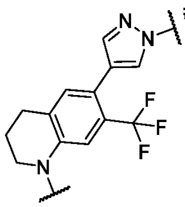
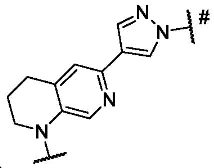
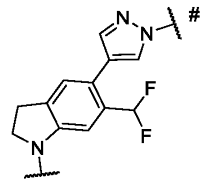
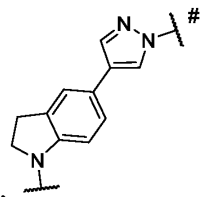
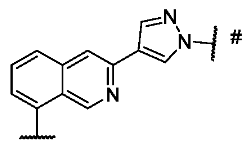
or R^{32} is absent and L is covalently attached to the acetyl-lysine mimetic moiety at the position occupied by R^{32}; and

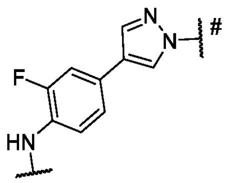
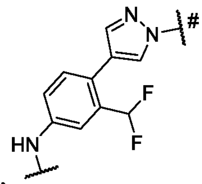
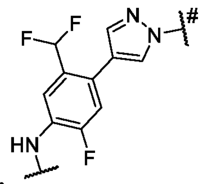
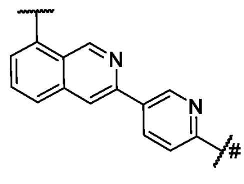
R^{32a} is  ,  ,  ,  ,  ,  ,  ,  , , or .

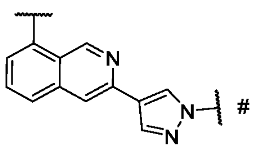
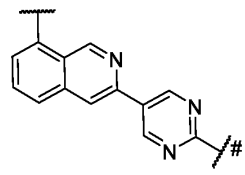
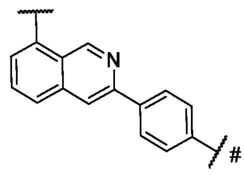
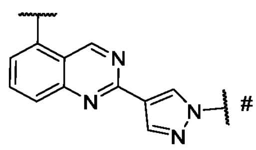
79. The compound of any one of claims 73-78, or a pharmaceutically acceptable salt or solvate thereof, wherein:

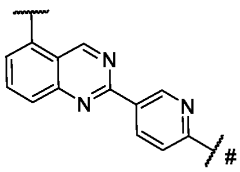
R^{32} is  ,  , or  ;

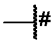
R^{32a} is  ,  ,  ,  ,

 ,  ,  ,  ,  ,

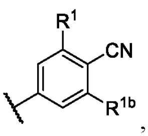
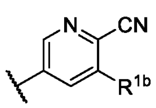
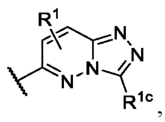
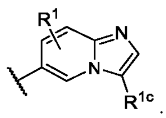
 ,  ,  ,  ,

 ,  ,  ,  , or

 , wherein

 is the point of attachment to the optional linker.

80. The compound of claim 73, or a pharmaceutically acceptable salt or solvate thereof, wherein the head group is:

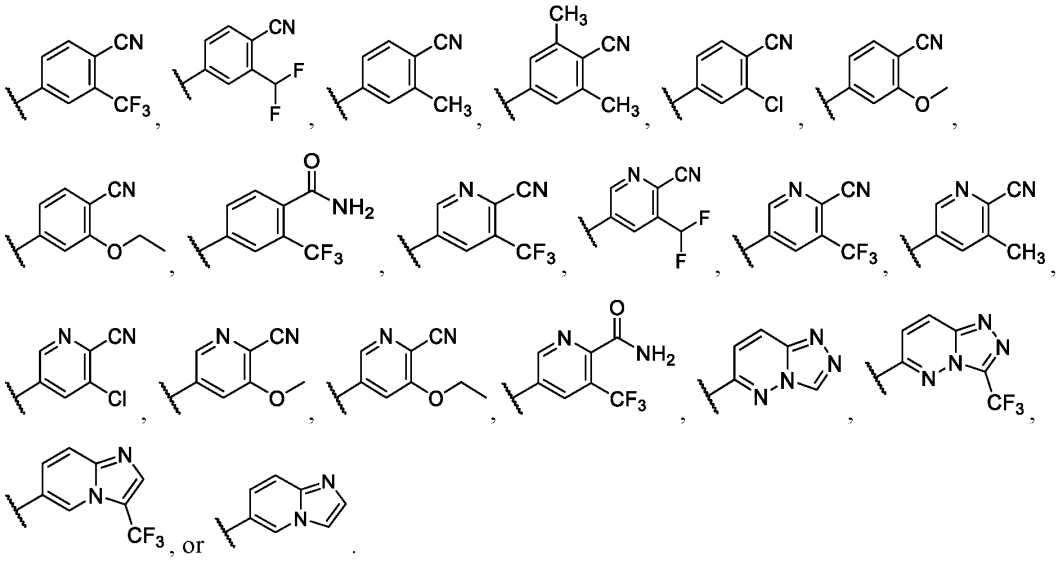
 ,  ,  , or  .

R^{1b} is hydrogen, F, Cl, Br, I, $-CH_3$, $-CD_3$, $-CH_2CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, -OH, $-OCF_3$, $-OCH_3$, -O CH_2CH_3, $-OCD_3$, $-OCH_2CD_3$, or -CN;

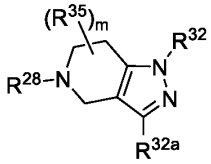
each R^{1c} is hydrogen, F, Cl, Br, $-CH_3$, $-CD_3$, $-CH_2F$, $-CHF_2$, or $-CF_3$;

each R^1 is independently hydrogen, F, Cl, Br, I, $-CH_3$, $-CD_3$, $-CH_2CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2CH_2F$, $-CH_2CHF_2$, $-CH_2CF_3$, -OH, $-OCF_3$, $-OCH_3$, $-OCD_3$, or $-OCH_2CH_3$.

81. The compound of claim 73, or a pharmaceutically acceptable salt or solvate thereof, wherein the head group is selected from:



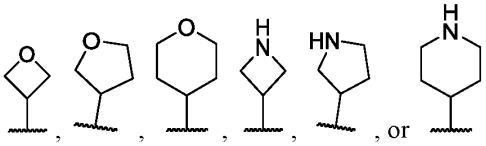
82. The compound of any one of claims 14-81, or a pharmaceutically acceptable salt or solvate thereof, wherein:

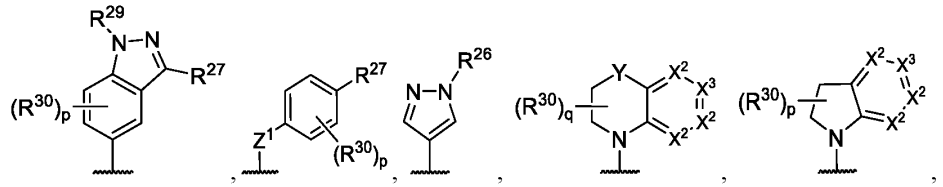
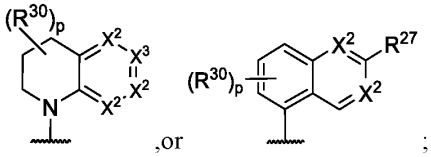
SB-CBP/p300 has the structure: 

R^{28} is $-C(=O)CH_3$ or $-C(=O)NH(CH_3)$;

each R^{35} is independently hydrogen, $-CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$;

m is 0, 1, or 2;

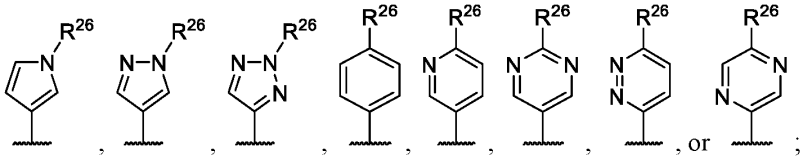
R^{32} is  , each of which is unsubstituted or substituted with F, $-CH_3$, $-CH_2F$, $-CHF_2$, or $-CF_3$;

R^{32a} is  ,or  ;

at least one X^2 is $-CR^{30}-$ and at most two X^2 are -N-;

R^{26} is hydrogen, C_1-C_4alkyl, C_1-C_4fluoroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, or substituted or unsubstituted 3- to 6-membered heterocycloalkyl;

R^{27} is hydrogen, halogen, C_1-C_4alkyl, C_1-C_4fluoroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted 3- to 6-membered heterocycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted monocyclic 5- or 6-membered heteroaryl, -CN, -OH, $-OR^a$, or $-N(R^b)_2$;

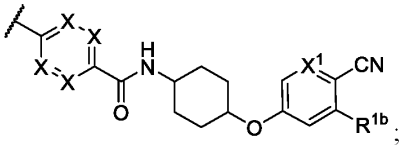
or R^{27} is  , or ;

each R^{30} is independently hydrogen, halogen, C_1-C_4alkyl, C_1-C_4fluoroalkyl, -CN, -OH, or $-OR^a$;

R^a is C_1-C_4alkyl;

each R^b is independently hydrogen or C_1-C_6alkyl;

wherein L is covalently attached to the R^{32} group, or at the position occupied by R^{26}, or at the position occupied by R^{27};

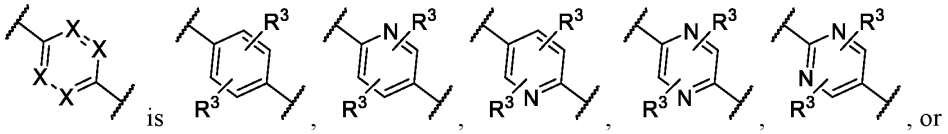
B-AR has the structure:  ;

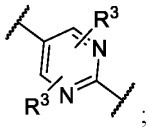
each X is independently $-CR^3-$ or -N-;

X^1 is $-CR^1-$ or -N-;

R^{1b} is hydrogen, F, Cl, $-CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, or $-OCF_3$;

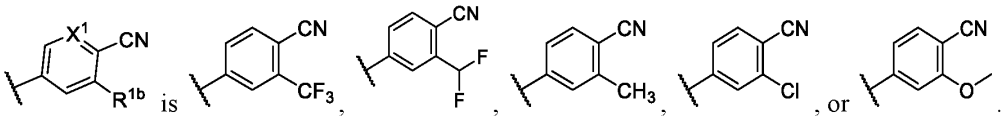
R^1 is hydrogen, F, Cl, $-CH_3$, $-CH_2F$, $-CHF_2$, or $-CF_3$;

is  , or

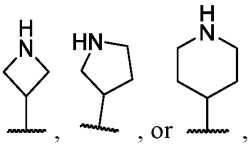

;

each R^3 is independently hydrogen, F, Cl, Br, $-CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, -OH, $-OCF_3$, $-OCH_3$, or -CN.

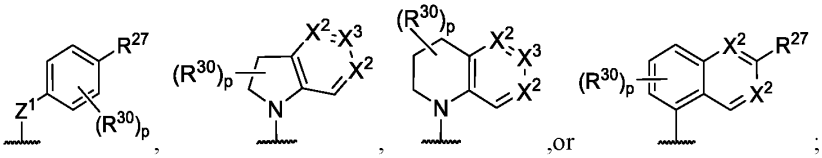
83. The compound of claim 82, or a pharmaceutically acceptable salt or solvate thereof, wherein:


is , , , , , or .

84. The compound of any one of claims 82-83, or a pharmaceutically acceptable salt or solvate thereof, wherein:

R^{32} is  , , or , wherein the optional linker is covalently attached to the nitrogen of R^{32} group;

or R^{32} is absent and the optional linker is covalently attached to the acetyl-lysine mimetic moiety at the position occupied by R^{32};

R^{32a} is 
, , , or ;

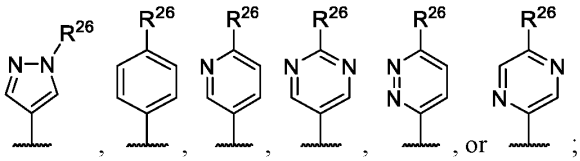
at least one X^2 is $-CR^{30}-$ and at most two X^2 are -N-;

X^3 is $-CR^{27}-$ or -N-;

Z^1 is -NH- or -O-;

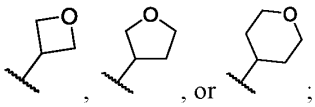
R^{26} is hydrogen, C_1-C_4alkyl, C_1-C_4fluoroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, or substituted or unsubstituted 3- to 6-membered heterocycloalkyl;

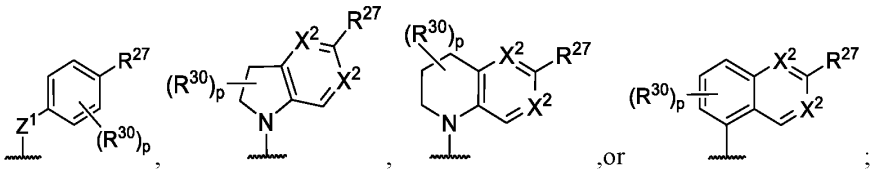
R^{27} is hydrogen, halogen, C_1-C_4alkyl, C_1-C_4fluoroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted 3- to 6-membered heterocycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted monocyclic 5- or 6-membered heteroaryl, -CN, -OH, $-OR^a$, or $-N(R^b)_2$;

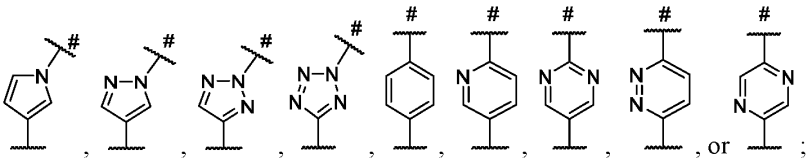
or R^{27} is 
, , , , , , or ; and

each R^{30} is independently hydrogen, halogen, C_1-C_4alkyl, C_1-C_4fluoroalkyl, -CN, -OH, or $-OR^a$.

85. The compound of any one of claims 82-84, or a pharmaceutically acceptable salt or solvate thereof, wherein:

R^{32} is  ;

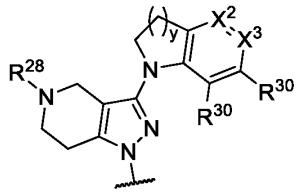
R^{32a} is  ;

R^{27} is  ;

Z^1 is -NH- or -O-;

 is the point of attachment to the optional linker.

86. The compound of any one of claims 14-81, or a pharmaceutically acceptable salt or solvate thereof, wherein SB-CBP/p300 has the structure of Formula (IIIb):



Formula (IIIb)

wherein:

X^2 is $-CR^{30}-$ or -N-;

X^3 is $-CR^{27}-$ or -N-;

each R^{27} is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -CN, $-NO_2$, -OH, $-OR^a$, $OC(=O)R^a$, $-OC(=O)N(R^b)_2$, $-OC(=O)OR^a$, $-OC(=O)N(R^b)_2$, $-SR^b$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2OR^b$, $-S(=O)_2N(R^b)_2$, $-N(R^b)_2$, $-NR^bC(=O)N(R^b)_2$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^a$, $-NR^bS(=O)_2R^a$, $-C(=O)R^b$, $-C(=O)OR^b$, or $-C(=O)N(R^b)_2$;

R^{28} is hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, $-C(=O)R^b$, or $-C(=O)N(R^b)_2$;

each R^{30} is independently hydrogen, halogen, C_1-C_4alkyl, C_1-C_4fluoroalkyl, -CN, -OH, or $-OR^a$;

y is 1 or 2;

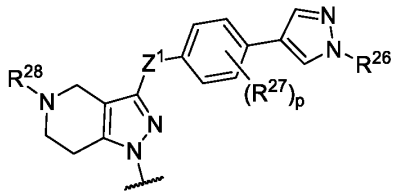
each R^a is independently substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-

C_6cycloalkyl, substituted or unsubstituted monocyclic 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted monocyclic heteroaryl;

each R^b is independently hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted monocyclic 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted monocyclic heteroaryl;

or two R^b on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle.

87. The compound of any one of claims 14-81, or a pharmaceutically acceptable salt or solvate thereof, wherein SB-CBP/p300 has the structure of Formula (IIIc):



Formula (IIIc)

wherein:

R^{26} is hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, or substituted or unsubstituted 3- to 8-membered heterocycloalkyl;

each R^{27} is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -CN, -NO_2, -OH, -OR^a, $OC(=O)R^a$, -$OC(=O)N(R^b)_2$, -$OC(=O)OR^a$, -$OC(=O)N(R^b)_2$, -SR^b, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2OR^b$, -$S(=O)_2N(R^b)_2$, -$N(R^b)_2$, -$NR^bC(=O)N(R^b)_2$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^a$, -$NR^bS(=O)_2R^a$, -$C(=O)R^b$, -$C(=O)OR^b$, or -$C(=O)N(R^b)_2$;

p is 0, 1, 2, or 3;

R^{28} is hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, -$C(=O)R^a$, or -$C(=O)N(R^b)_2$;

Z^1 is -NR^c-, -O-, or -S-;

R^c is hydrogen or substituted or unsubstituted C_1-C_6alkyl;

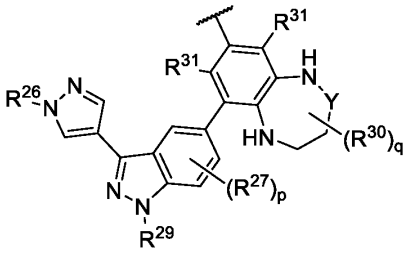
each R^a is independently substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted monocyclic 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted monocyclic heteroaryl;

each R^b is independently hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or

unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted monocyclic 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted monocyclic heteroaryl;

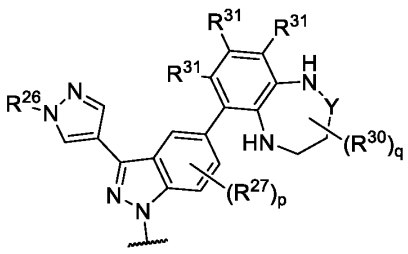
or two R^b on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle.

88. The compound of any one of claims 14-81, or a pharmaceutically acceptable salt or solvate thereof, wherein SB-CBP/p300 has the structure of Formula (IIId-1) or (IIId-2):



Formula (IIId-1)

or



Formula (IIId-2)

wherein:

R^{26} is hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, or substituted or unsubstituted 3- to 8-membered heterocycloalkyl;

each R^{27} is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -CN, -NO_2, -OH, -OR^a, $OC(=O)R^a$, -$OC(=O)N(R^b)_2$, -$OC(=O)OR^a$, -$OC(=O)N(R^b)_2$, -SR^b, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2OR^b$, -$S(=O)_2N(R^b)_2$, -$N(R^b)_2$, -$NR^bC(=O)N(R^b)_2$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^a$, -$NR^bS(=O)_2R^a$, -$C(=O)R^b$, -$C(=O)OR^b$, or -$C(=O)N(R^b)_2$;

p is 0, 1, 2, or 3;

R^{29} is hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, or substituted or unsubstituted 3- to 8-membered heterocycloalkyl;

each R^{30} is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, -CN, -NO_2, -OH, -OR^a, $OC(=O)R^a$, -$OC(=O)N(R^b)_2$, -$OC(=O)OR^a$, -SR^b, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2OR^b$, -$S(=O)_2N(R^b)_2$, -$N(R^b)_2$, -$NR^bC(=O)N(R^b)_2$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^a$, -$NR^bS(=O)_2R^a$, -$C(=O)R^b$, -$C(=O)OR^b$, or -$C(=O)N(R^b)_2$;

q is 0, 1, 2, 3, or 4;

each R^{31} is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or

unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, -CN, -NO_2, -OH, -OR^a, OC(=O)R^a, -OC(=O)N(R^b)$_2$, -OC(=O)OR^a, -SR^b, -S(=O)R^a, -$S(=O)_2R^a$, -$S(=O)_2OR^b$, -$S(=O)_2N(R^b)_2$, -$N(R^b)_2$, -$NR^bC(=O)NR^b$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^a$, -$NR^bS(=O)_2R^a$, -C(=O)R^b, -C(=O)OR^b, or -C(=O)N(R^b)$_2$;

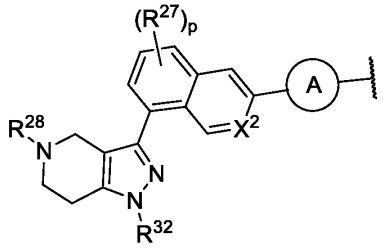
Y is -C(R^{30})$_2$- or C(=O);

each R^a is independently substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted monocyclic 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted monocyclic heteroaryl;

each R^b is independently hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted monocyclic 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted monocyclic heteroaryl;

or two R^b on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle.

89. The compound of any one of claims 14-81, or a pharmaceutically acceptable salt or solvate thereof, wherein SB-CBP/p300 has the structure of Formula (IIIe):



Formula (IIIe)

wherein:

X^2 is -CR^{27}- or -N-;

each R^{27} is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -CN, -NO_2, -OH, -OR^a, OC(=O)R^a, -OC(=O)N(R^b)$_2$, -OC(=O)OR^a, -OC(=O)N(R^b)$_2$, -SR^b, -S(=O)R^a, -$S(=O)_2R^a$, -$S(=O)_2OR^b$, -$S(=O)_2N(R^b)_2$, -$N(R^b)_2$, -$NR^bC(=O)N(R^b)_2$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^a$, -$NR^bS(=O)_2R^a$, -C(=O)R^b, -C(=O)OR^b, or -C(=O)N(R^b)$_2$;

p is 0, 1, 2, or 3;

R^{28} is hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, -C(=O)R^b, or -C(=O)N(R^b)$_2$;

R^{32} is hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, or substituted or unsubstituted 3- to 8-membered heterocycloalkyl;

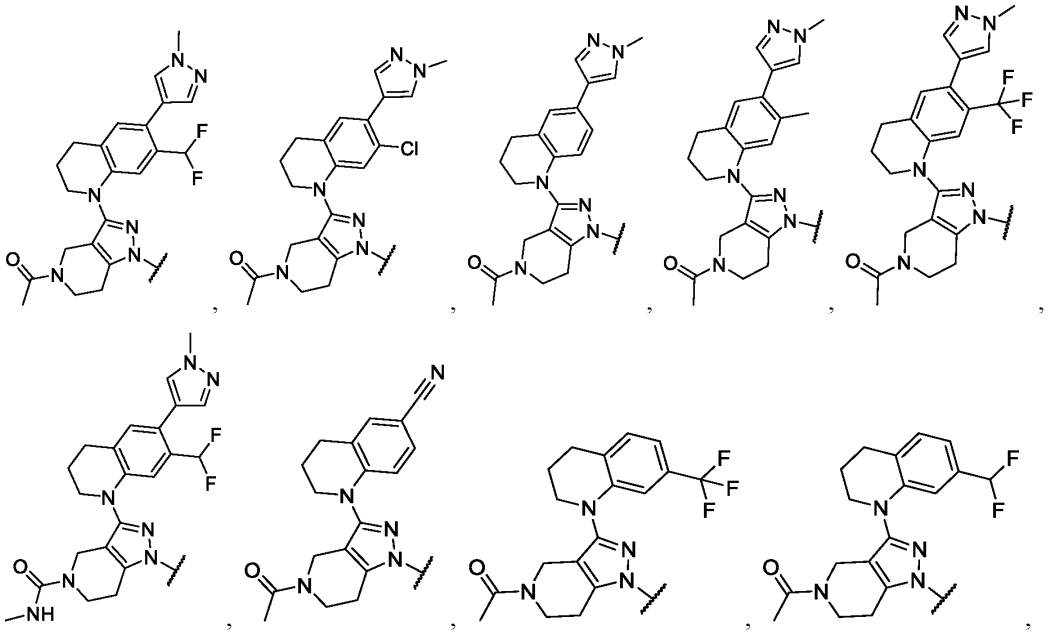
Ring A is absent or substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

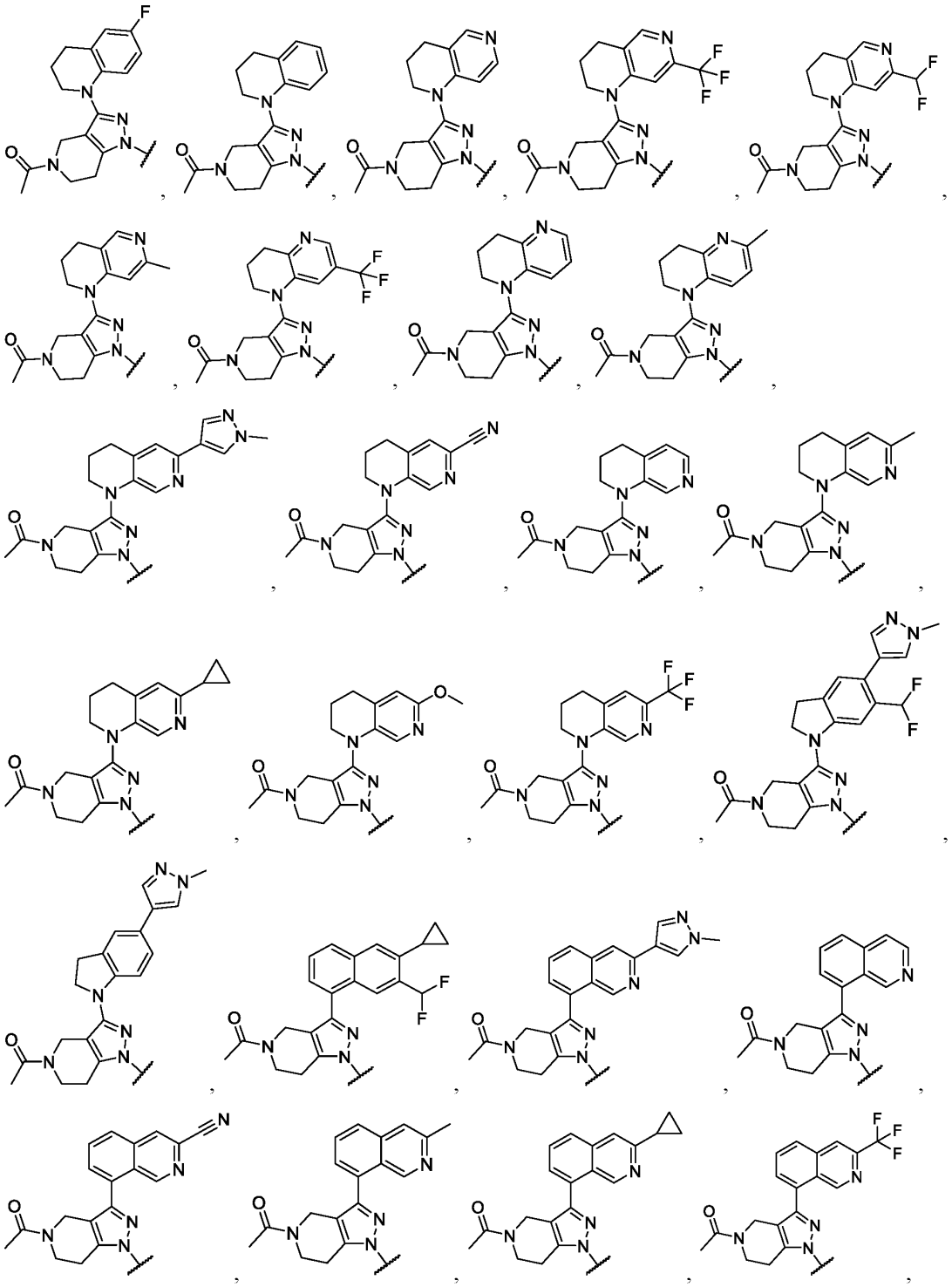
each R^a is independently substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted monocyclic 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted monocyclic heteroaryl;

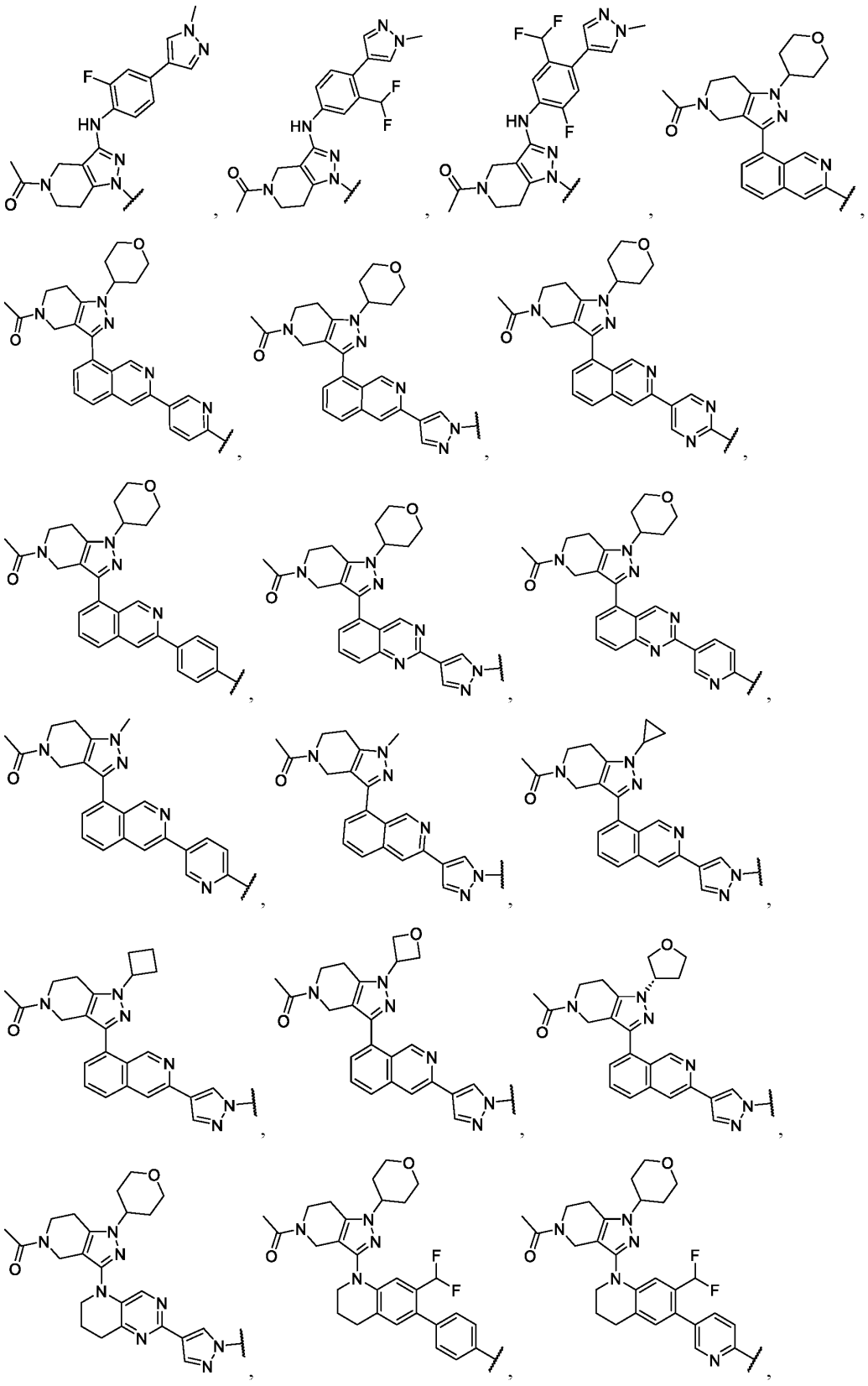
each R^b is independently hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted monocyclic 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted monocyclic heteroaryl;

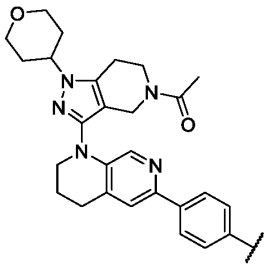
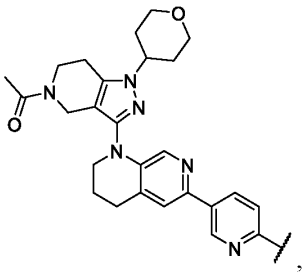
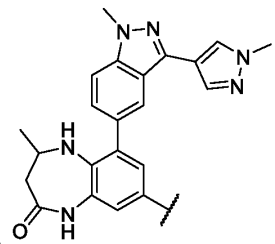
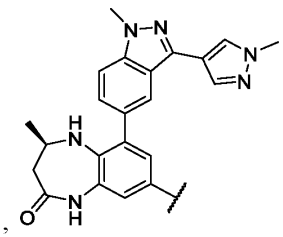
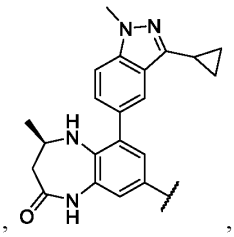
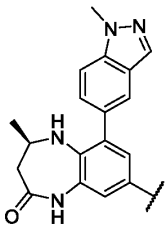
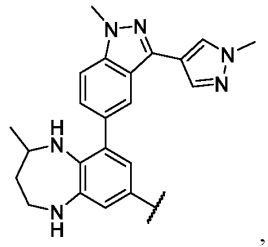
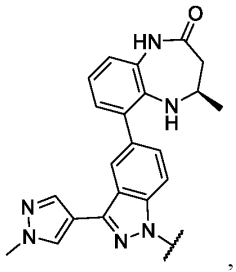
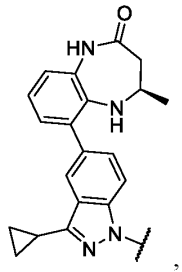
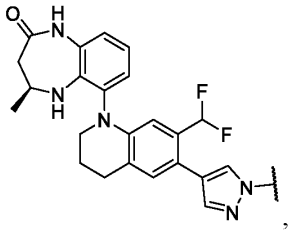
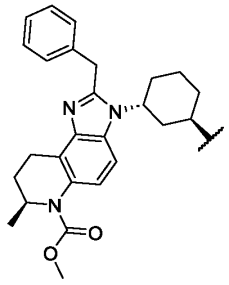
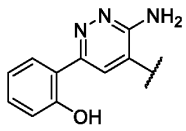
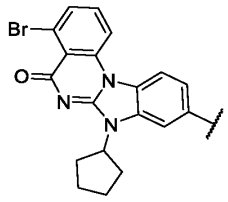
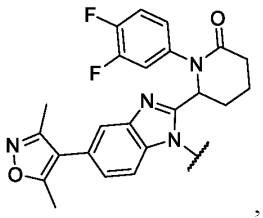
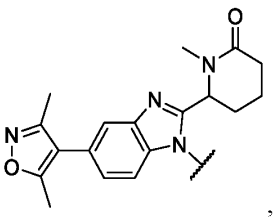
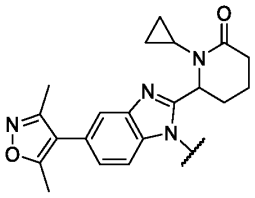
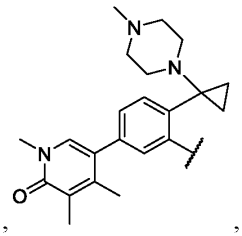
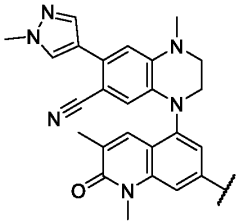
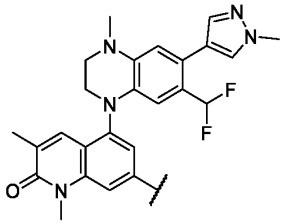
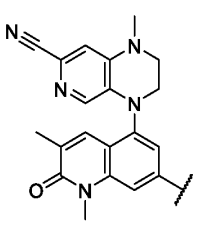
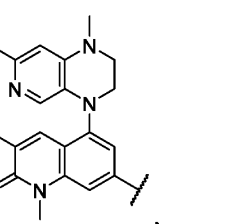
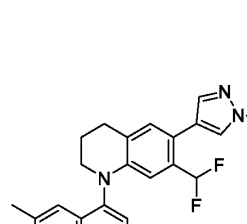
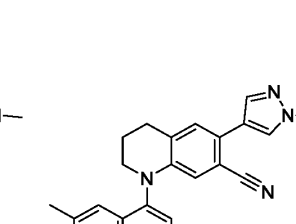
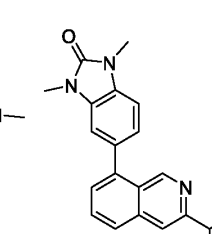
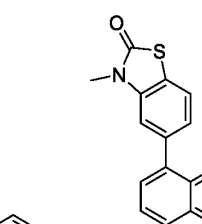
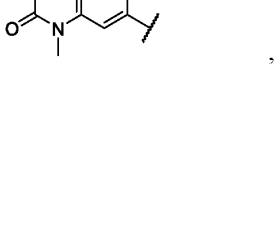
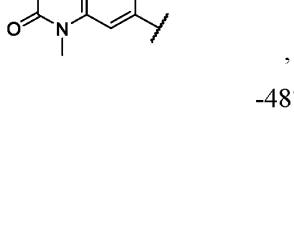
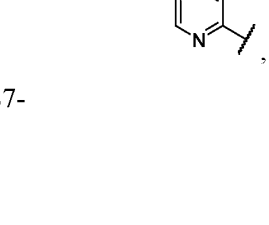
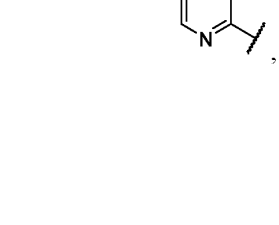
or two R^b on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle.

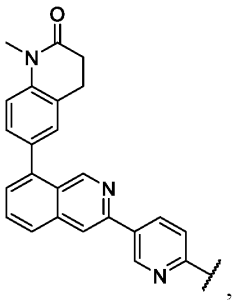
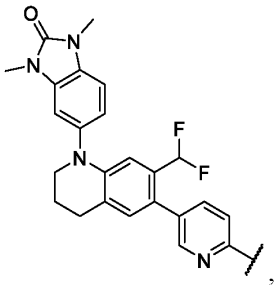
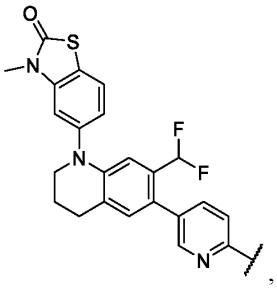
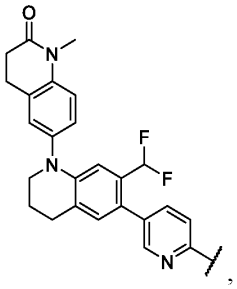
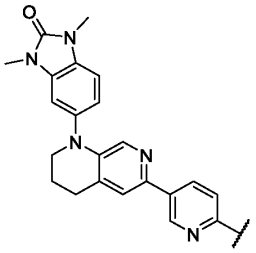
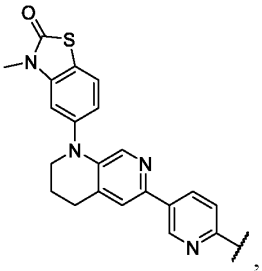
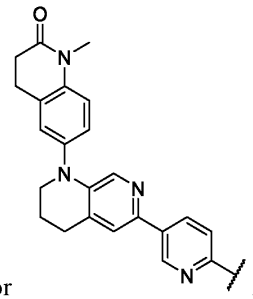
90. The compound of any one of claims 14-89, or a pharmaceutically acceptable salt or solvate thereof, wherein SB-CBP/p300 has one of the following structures:



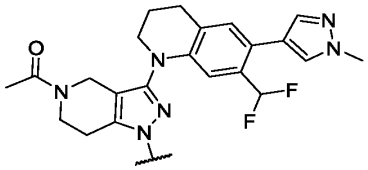
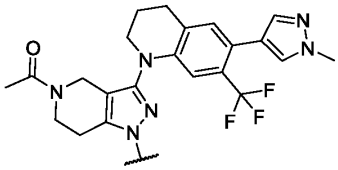
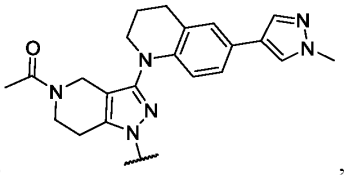
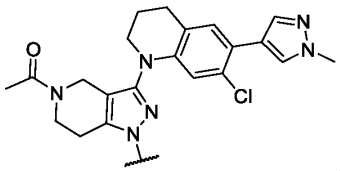
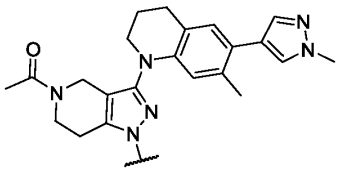
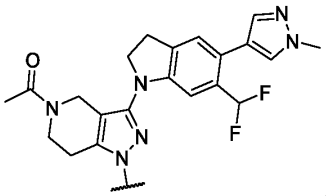
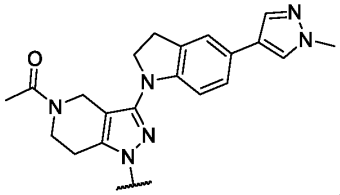
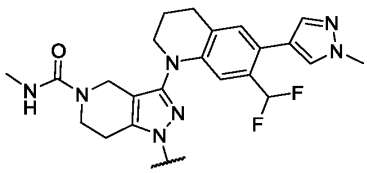
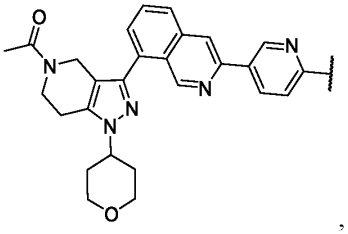
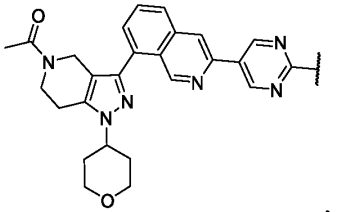
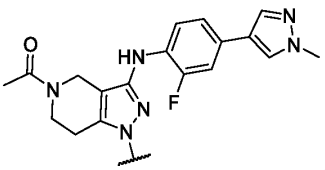
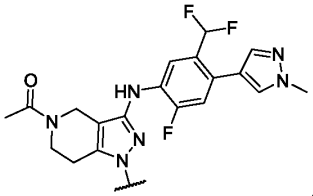


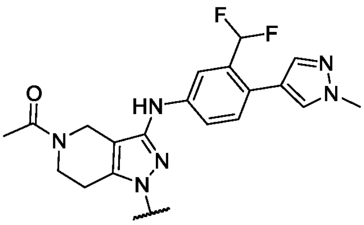
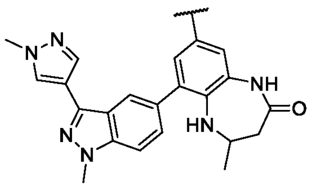
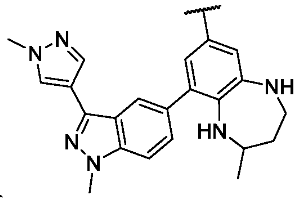
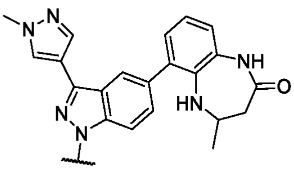
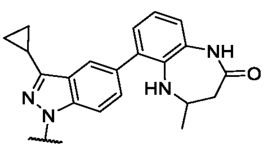
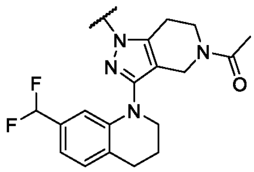
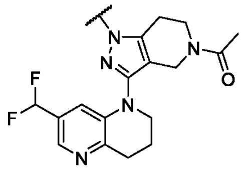
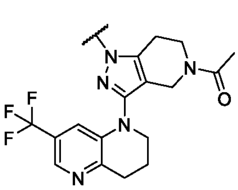
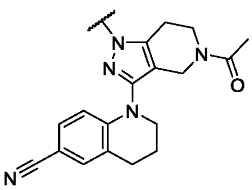
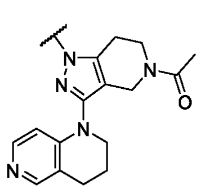
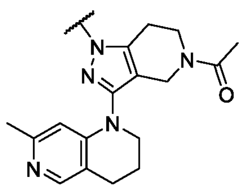
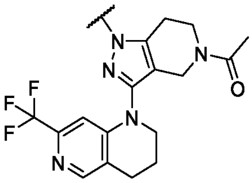
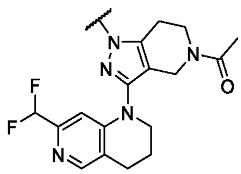
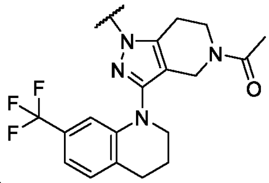
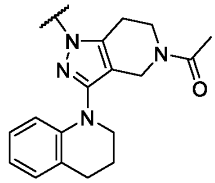
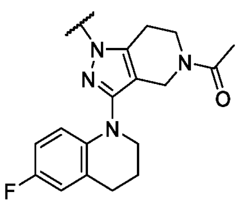
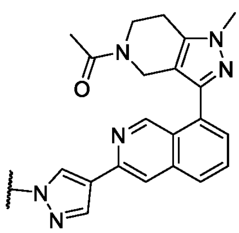
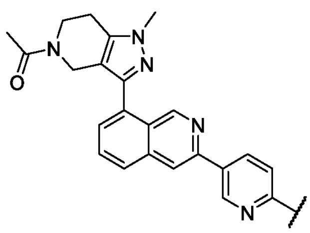
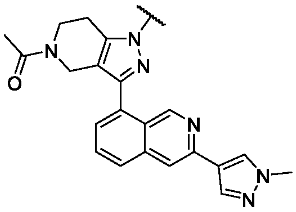
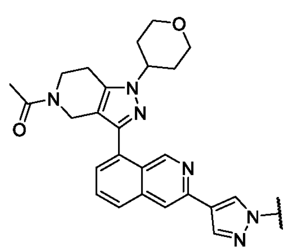
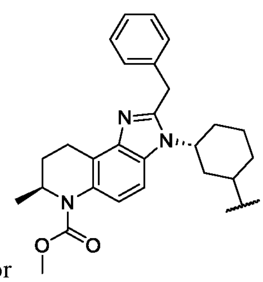



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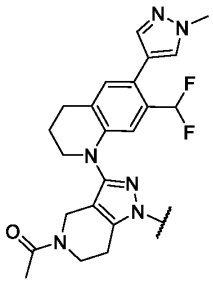
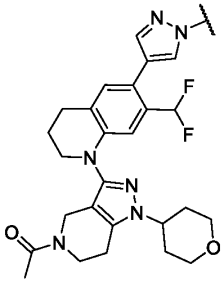
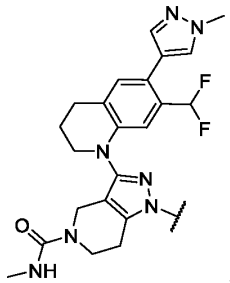
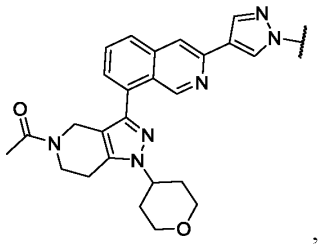
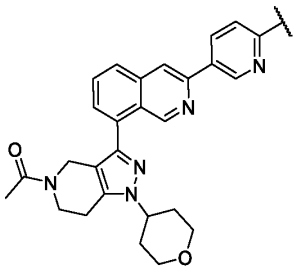
91. The compound of any one of claims 14-89, wherein SB-CBP/p300 has one of the following structures:


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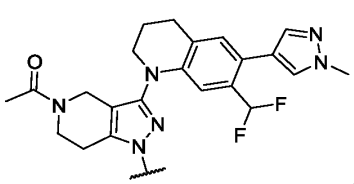
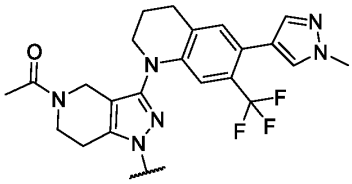
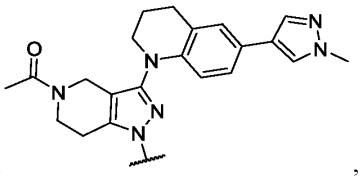
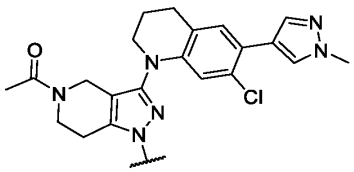
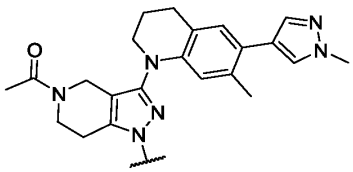
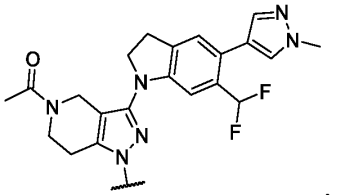
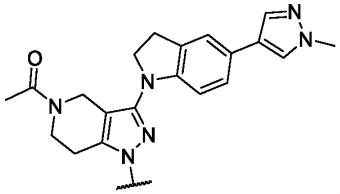
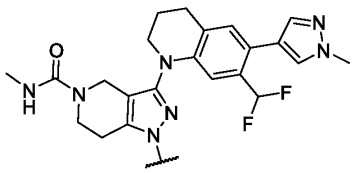
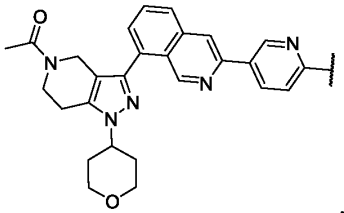
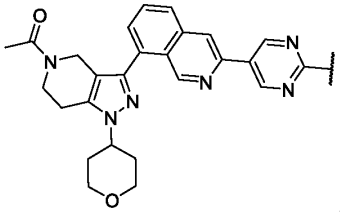
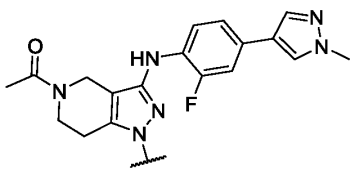
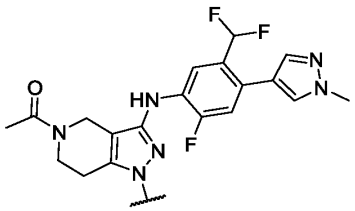
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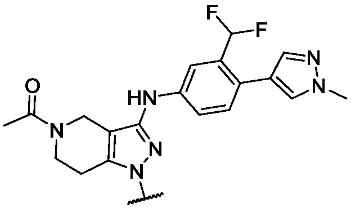
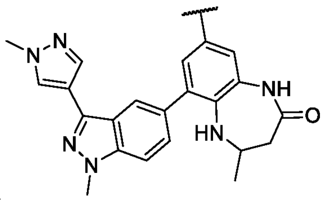
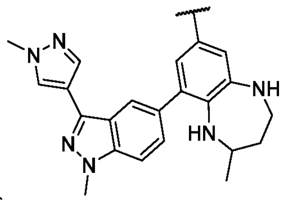
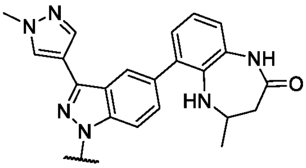
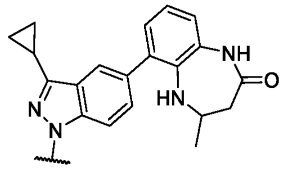
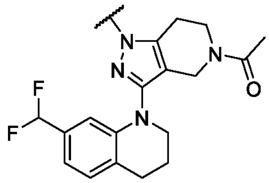
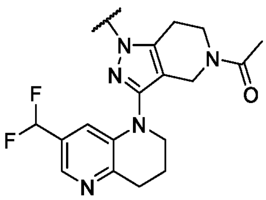
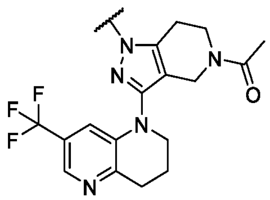
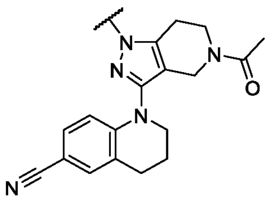
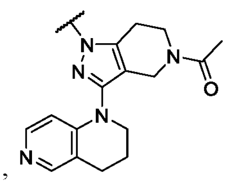
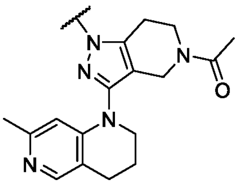
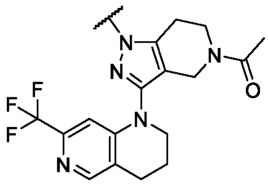
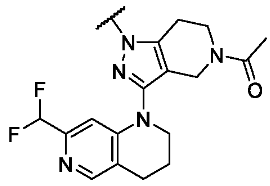
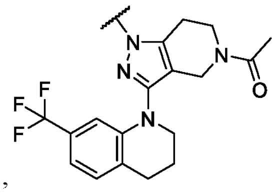
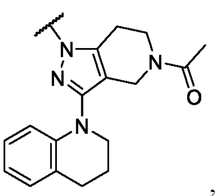
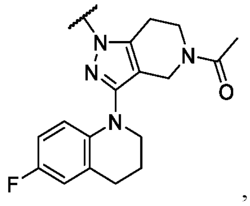
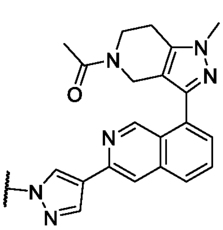
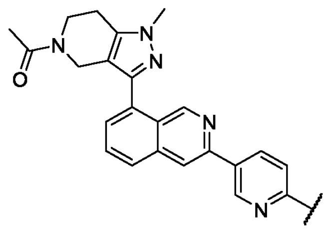
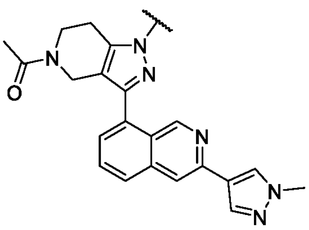
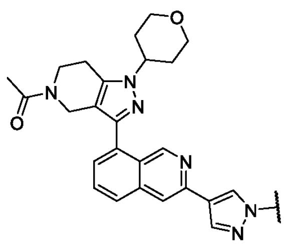
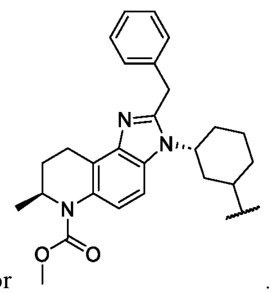
or a pharmaceutically acceptable salt or solvate thereof.

92. The compound of any one of claims 14-89, or a pharmaceutically acceptable salt or solvate thereof, wherein SB-CBP/p300 has one of the following structures:


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93. The compound of any one of claims 14-89, or a pharmaceutically acceptable salt or solvate thereof, wherein SB-CBP/p300 has one of the following structures:


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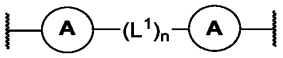
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94. The compound of any one of claims 1-93, or a pharmaceutically acceptable salt or solvate thereof, wherein L is absent.

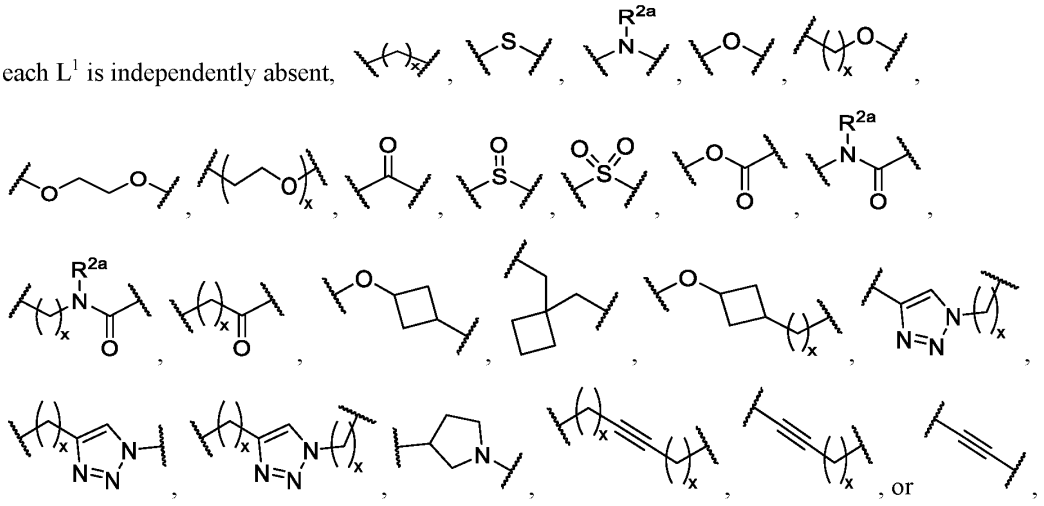
95. The compound of any one of claims 1-93, or a pharmaceutically acceptable salt or solvate thereof, wherein L comprises substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted 3- to 10-membered heterocycloalkyl, substituted or

unsubstituted aryl, substituted or unsubstituted heteroaryl, or combinations thereof.

96. The compound of any one of claims 1-93, or a pharmaceutically acceptable salt or solvate thereof,

wherein L is absent or  , wherein:

each A is independently absent, substituted or unsubstituted monocyclic C_3-C_{10}cycloalkyl, substituted or unsubstituted bridged bicyclic C_3-C_{10}cycloalkyl, substituted or unsubstituted fused bicyclic C_3-C_{10}cycloalkyl, substituted or unsubstituted spiro bicyclic C_3-C_{10}cycloalkyl, substituted or unsubstituted monocyclic 3- to 10-membered heterocycloalkyl, substituted or unsubstituted bridged bicyclic 3- to 10-membered heterocycloalkyl, substituted or unsubstituted fused bicyclic 3- to 10-membered heterocycloalkyl, substituted or unsubstituted spiro bicyclic 3- to 10-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, wherein each A is independently unsubstituted or substituted with x R^{2b};

each L^1 is independently absent,  , or ,

wherein each L^1 is independently unsubstituted or substituted with x R^{2b};

n is 1, 2, 3, 4, 5, or 6;

each x is independently 1, 2, 3, 4, 5, 6, 7, or 8;

each R^{2a} is independently hydrogen or substituted or unsubstituted C_1-C_6alkyl; and

each R^{2b} is independently hydrogen, halogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -CN, -NO_2, -OH, -OR^a, -$OC(=O)R^a$, -$OC(=O)N(R^b)_2$, -$OC(=O)OR^a$, -SR^b, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2OR^b$, -$S(=O)_2N(R^b)_2$, -$N(R^b)_2$, -$NR^bC(=O)N(R^b)_2$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^a$, -$NR^bS(=O)_2R^a$, -$C(=O)R^b$, -$C(=O)OR^b$, or -$C(=O)N(R^b)$;

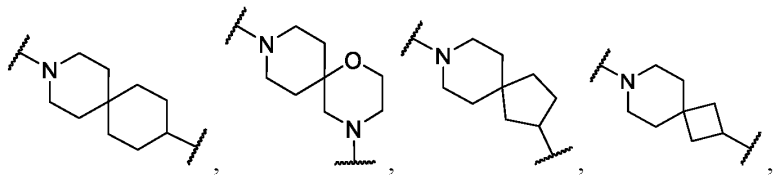
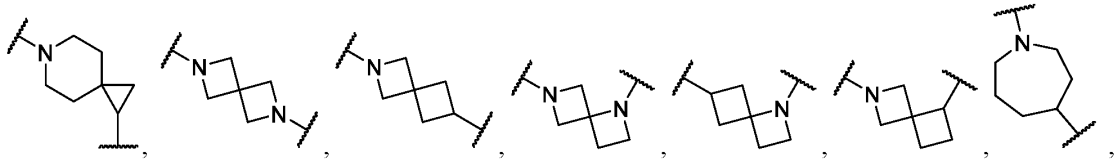
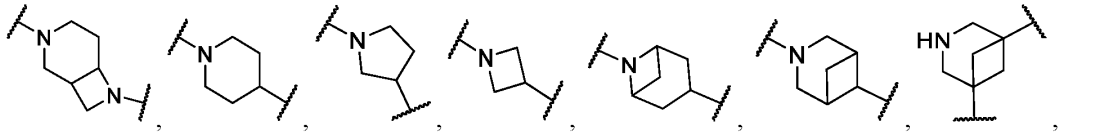
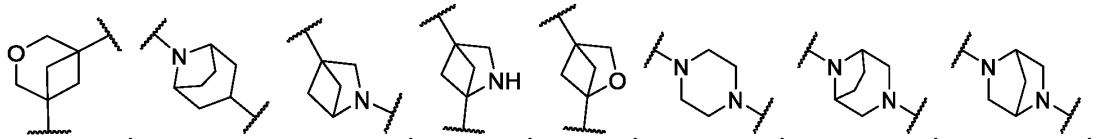
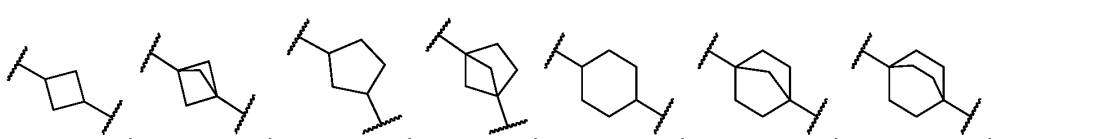
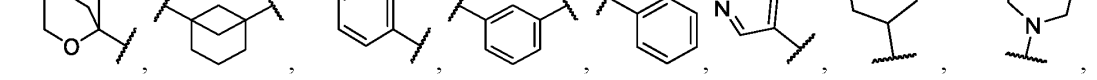
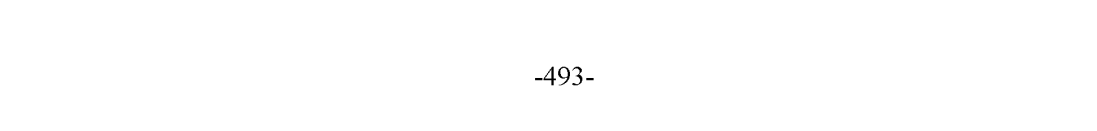
each R^a is independently substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-

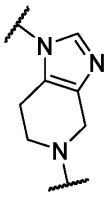
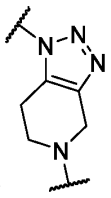
C_8cycloalkyl, substituted or unsubstituted monocyclic 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted monocyclic heteroaryl;

each R^b is independently hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_8cycloalkyl, substituted or unsubstituted monocyclic 3- to 8-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted monocyclic heteroaryl;

or two R^b on the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted N-containing heterocycle.

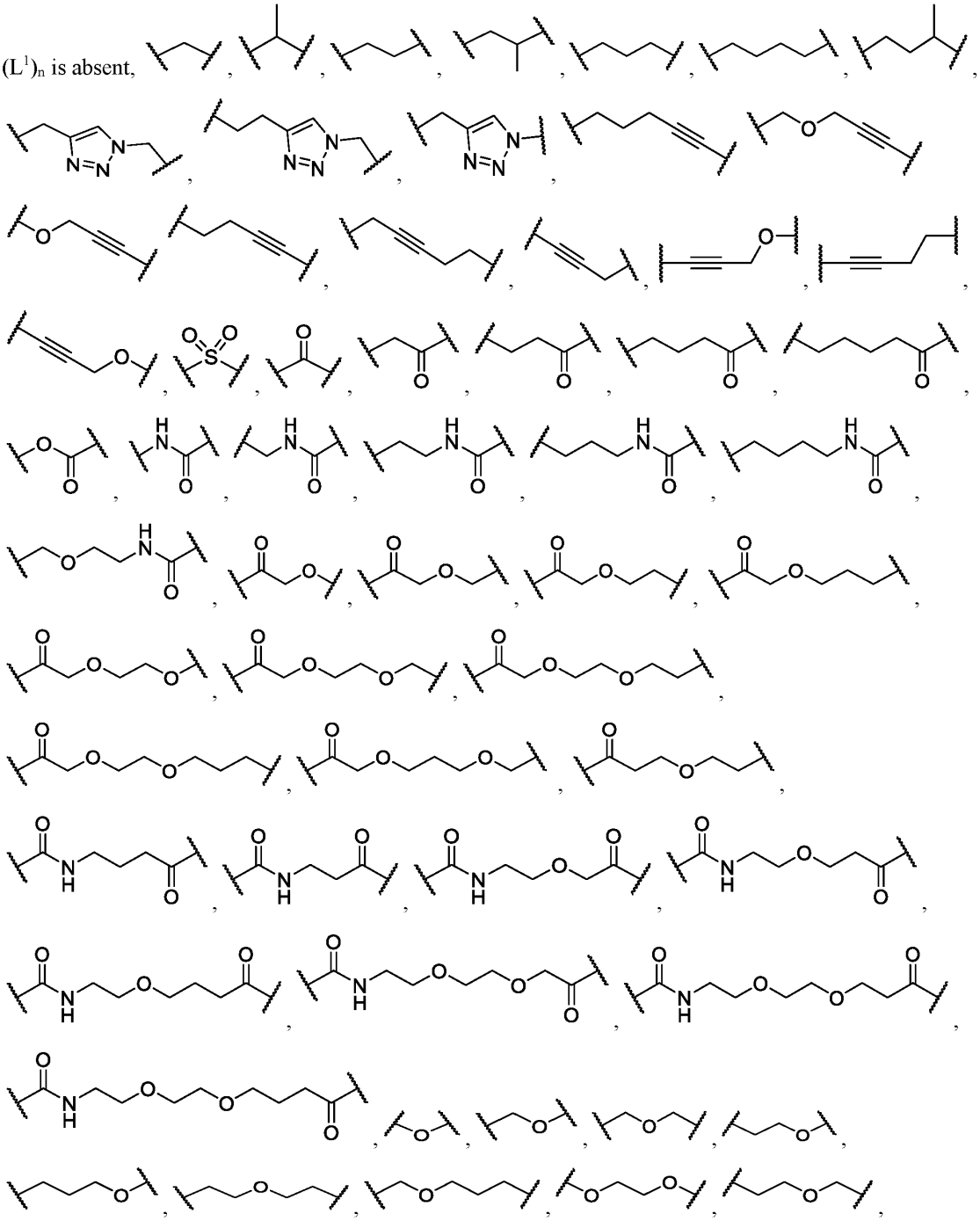
97. The compound of claim 96, or a pharmaceutically acceptable salt or solvate thereof, wherein:

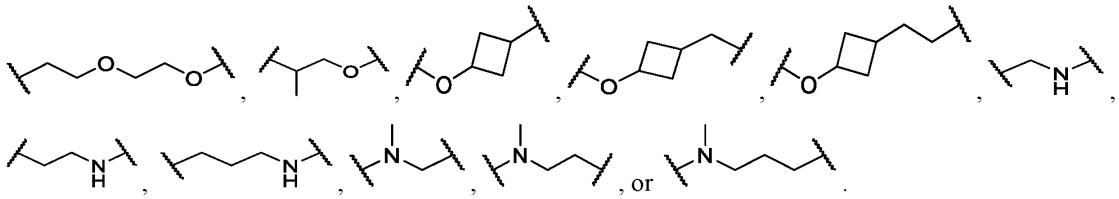
each A is independently absent,  ,  ,  ,  ,  ,  ,  , ,  ,

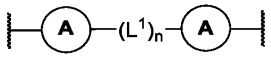
, or , wherein each A is independently unsubstituted or substituted with x R^{2b};

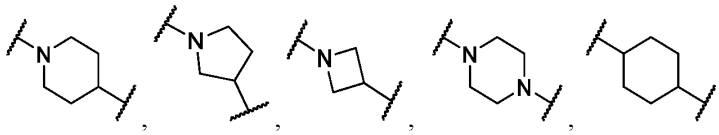
$(L^1)_n$ is absent,

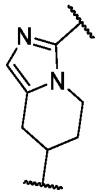


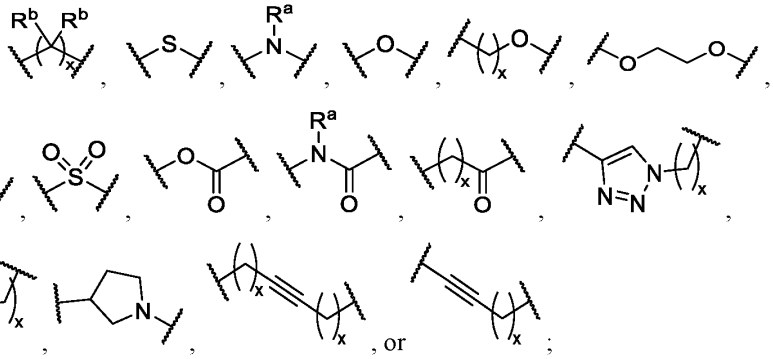


98. The compound of any one of claims 1-93, or a pharmaceutically acceptable salt or solvate thereof,

wherein L is absent or  wherein:

each A is independently absent,  , or

 ;

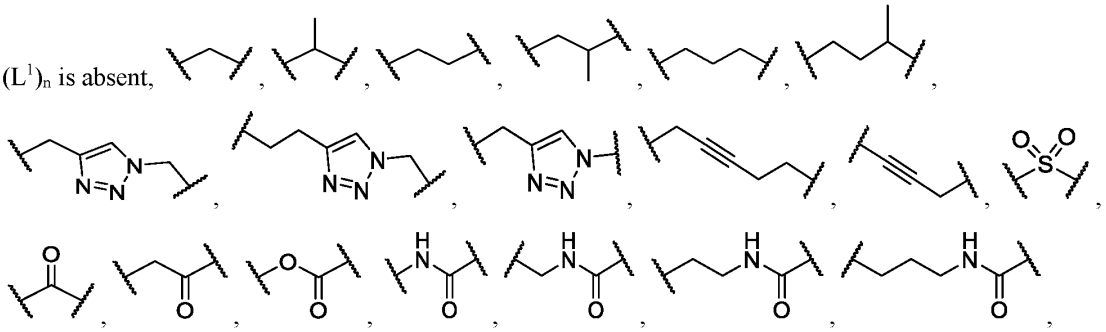
each L^1 is independently absent, 

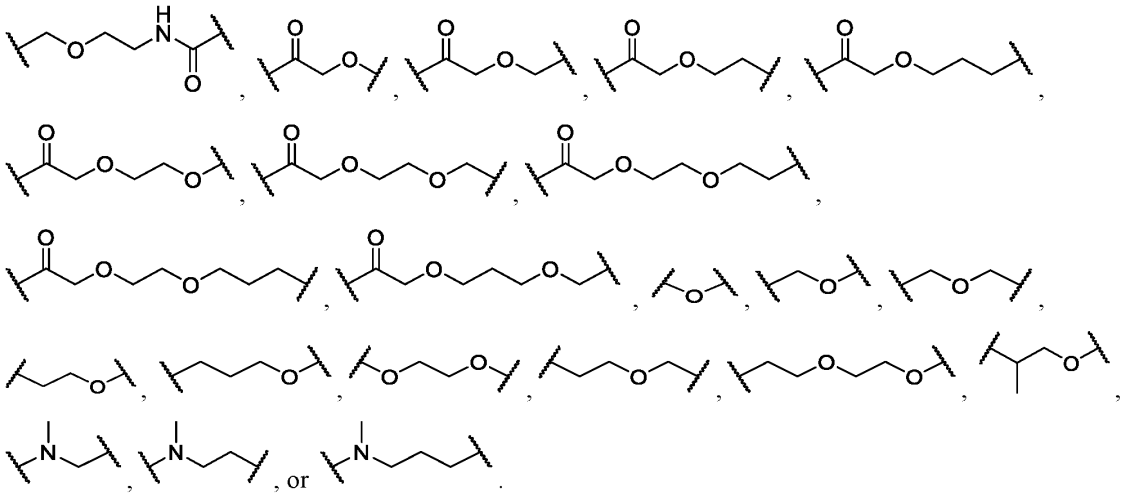
n is 1, 2, or 3; each x is independently 1, 2, 3, 4, 5, or 6;

each R^a is independently hydrogen or substituted or unsubstituted C_1-C_6alkyl; and

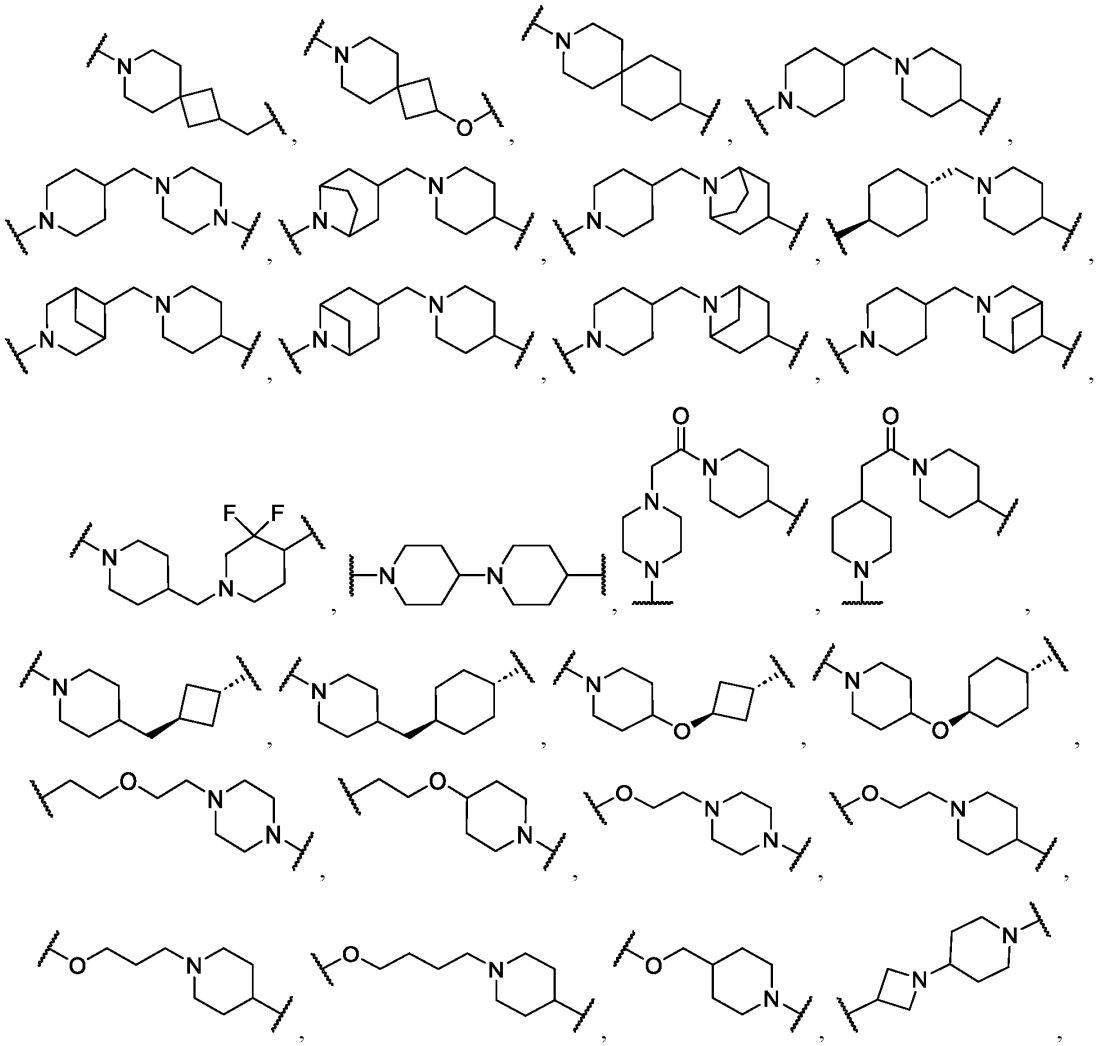
each R^b is independently hydrogen, halogen, or substituted or unsubstituted C_1-C_6alkyl.

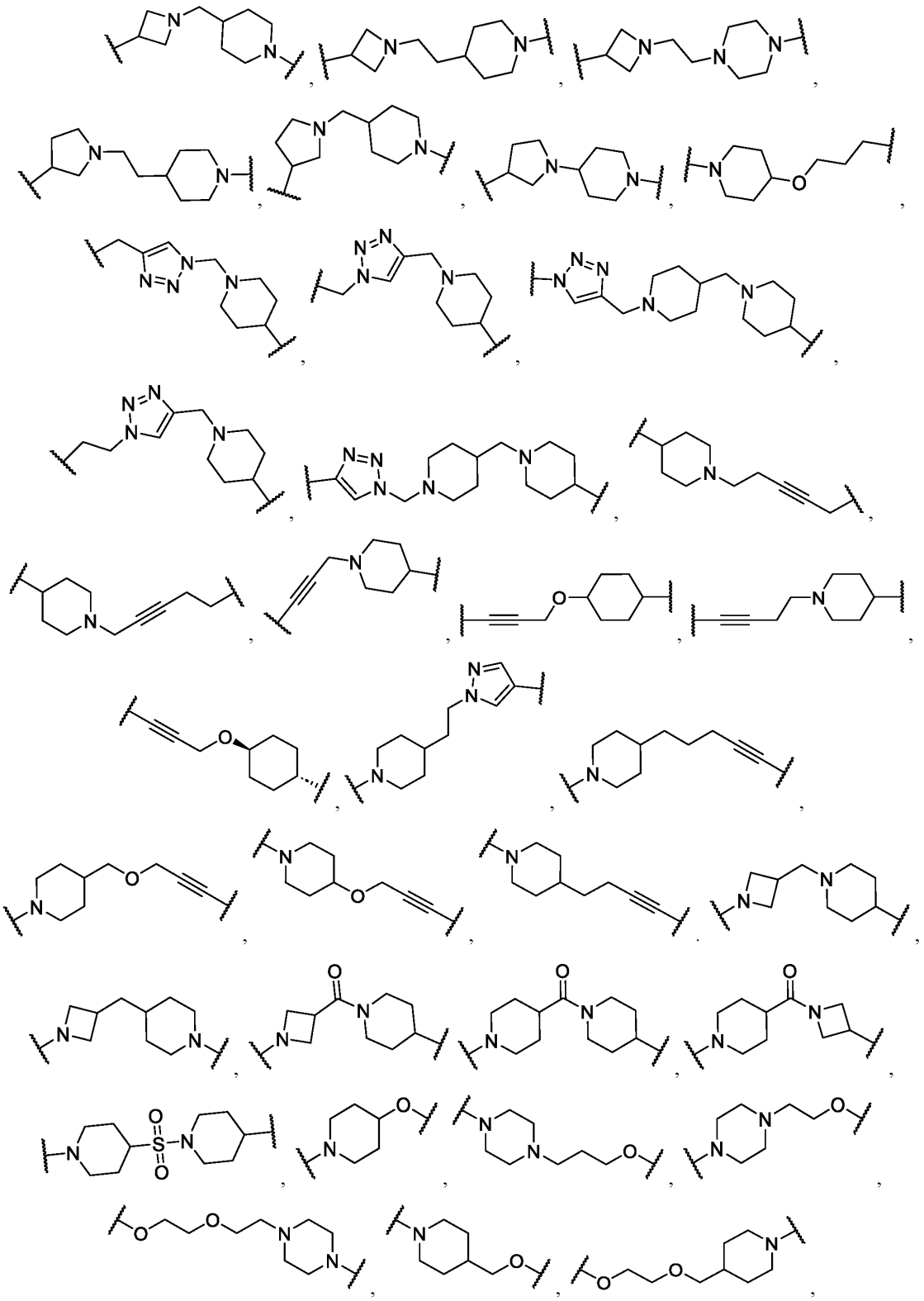
99. The compound of any one of claims 96-98, or a pharmaceutically acceptable salt or solvate thereof, wherein:

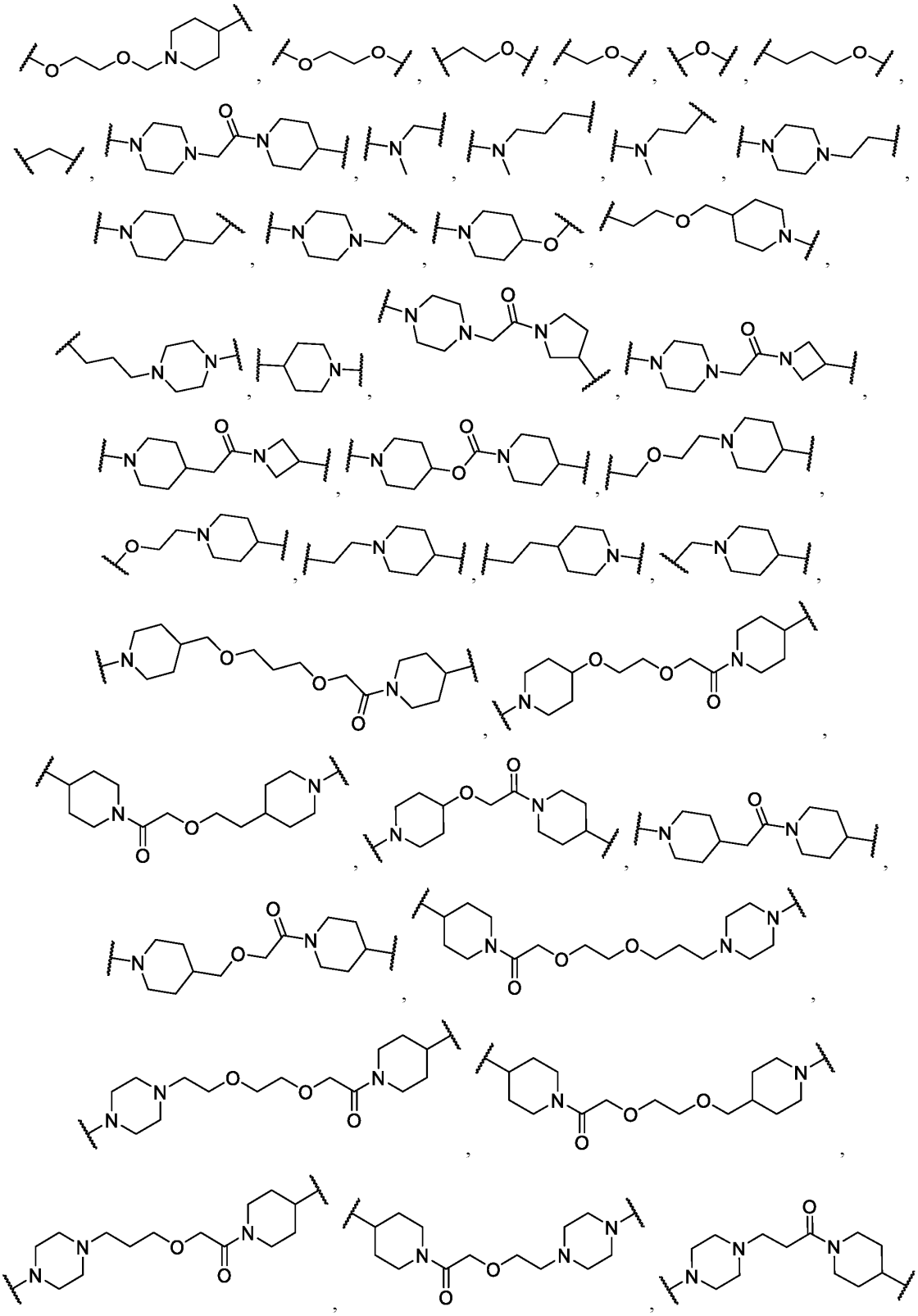
$(L^1)_n$ is absent, 

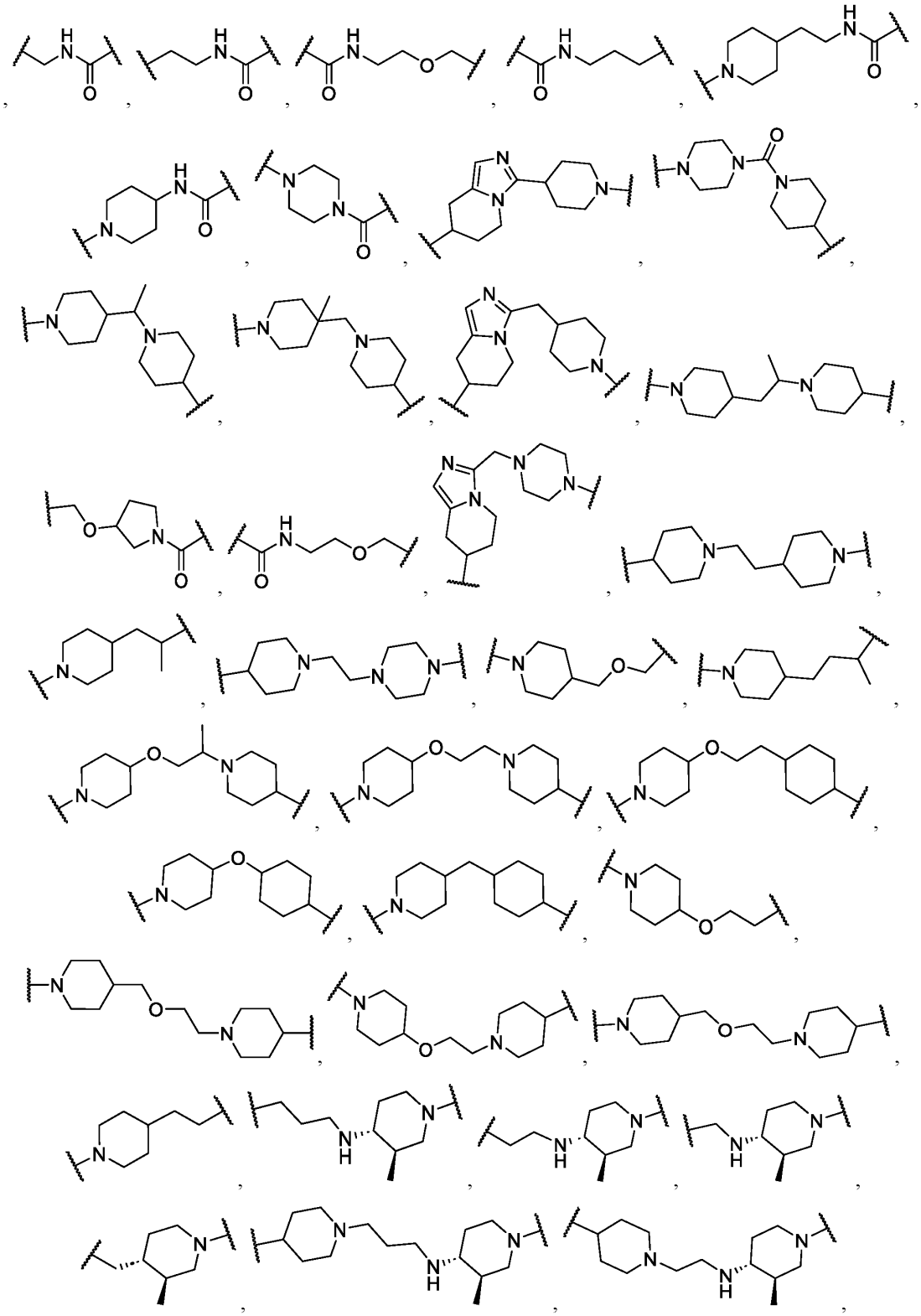


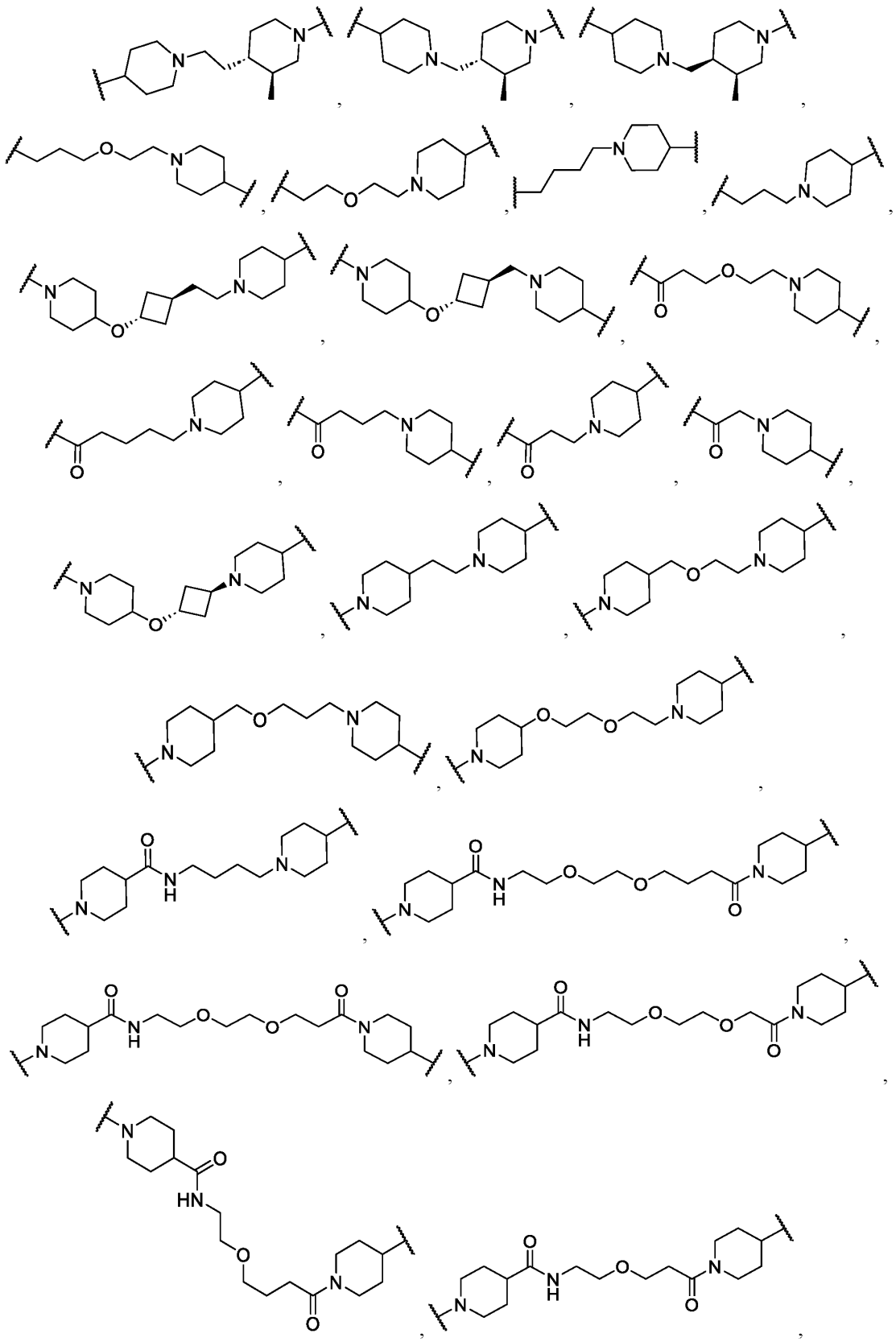
100. The compound of any one of claims 1-99, or a pharmaceutically acceptable salt or solvate thereof, wherein L has one of the following structures:

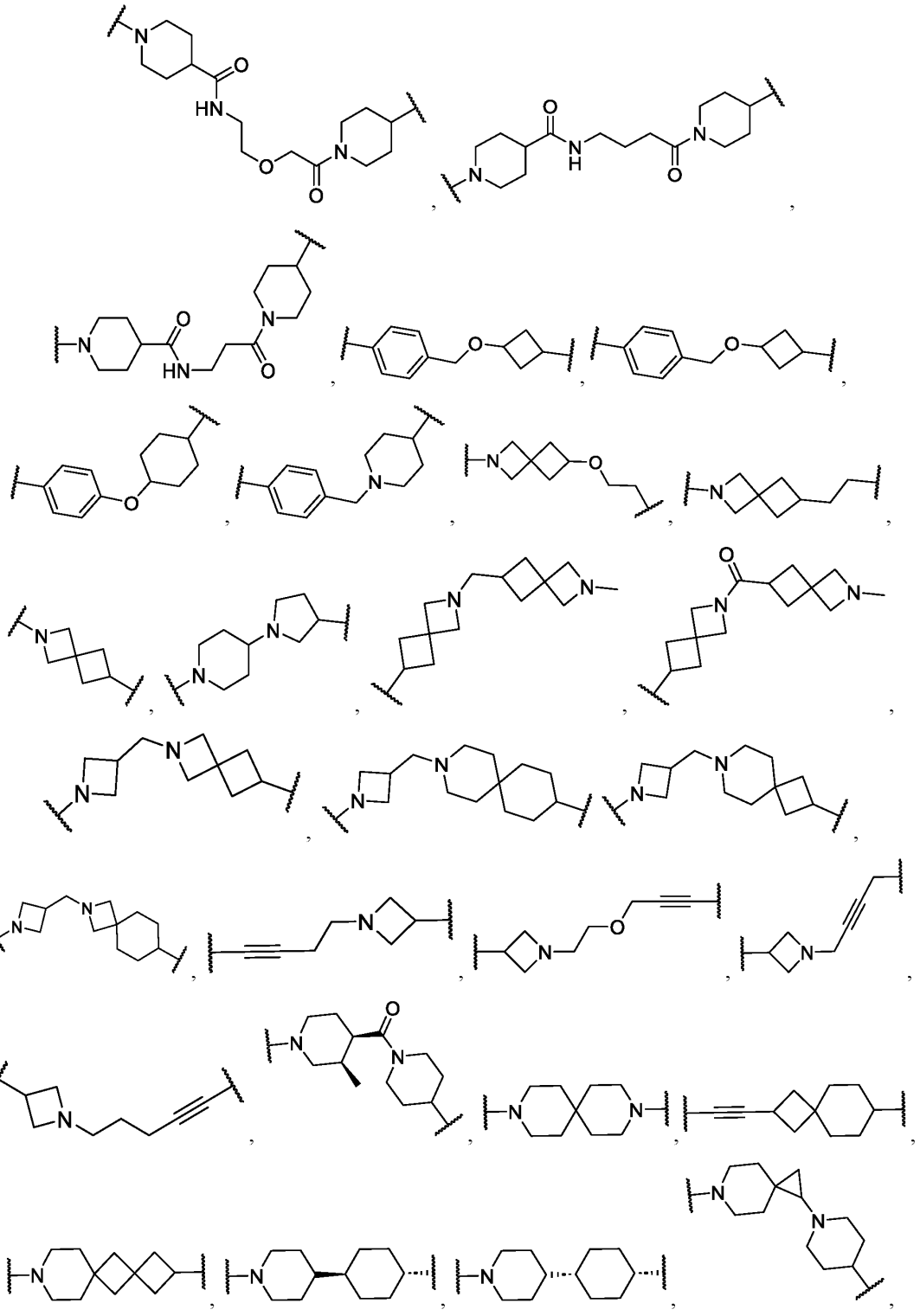


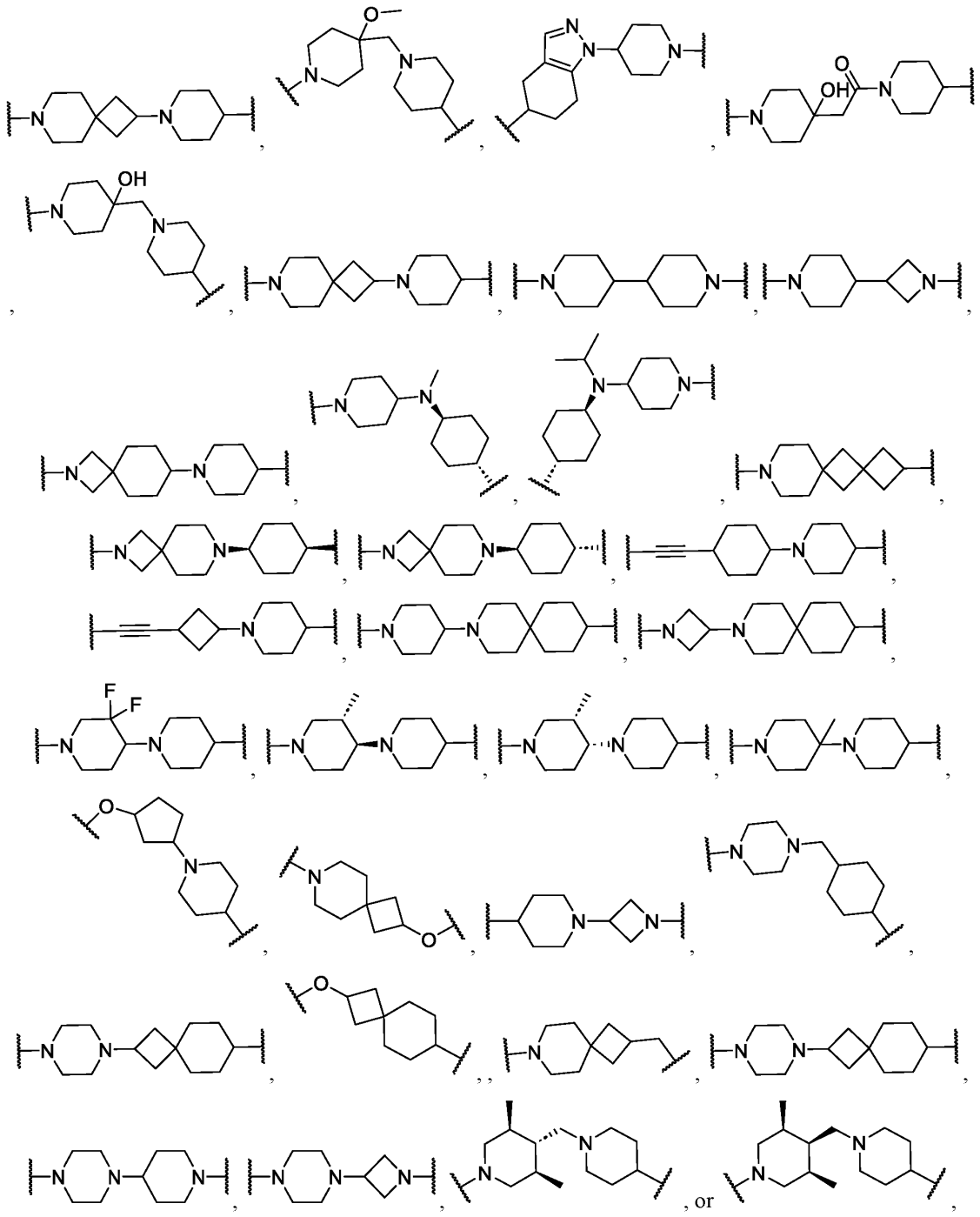






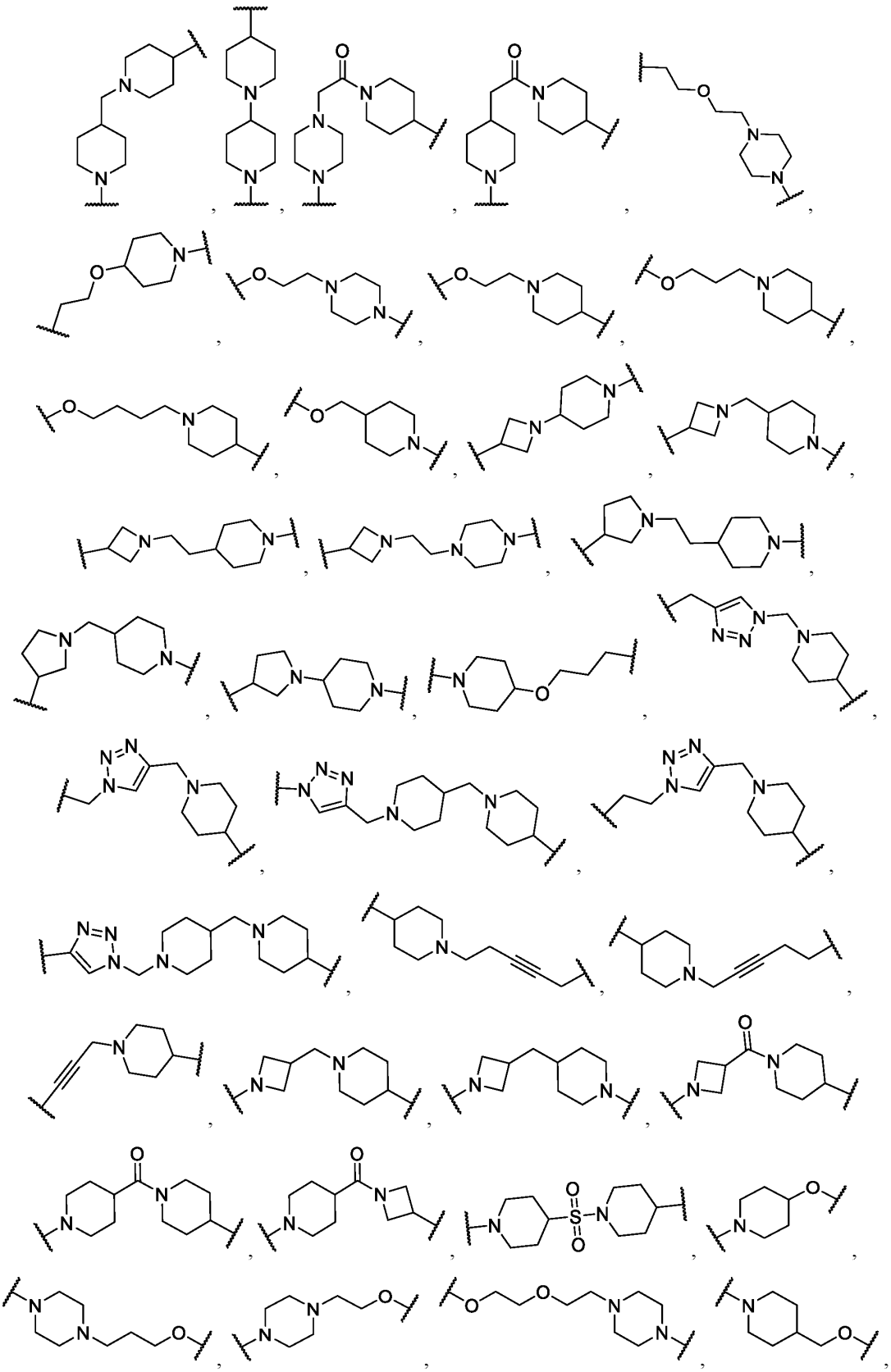


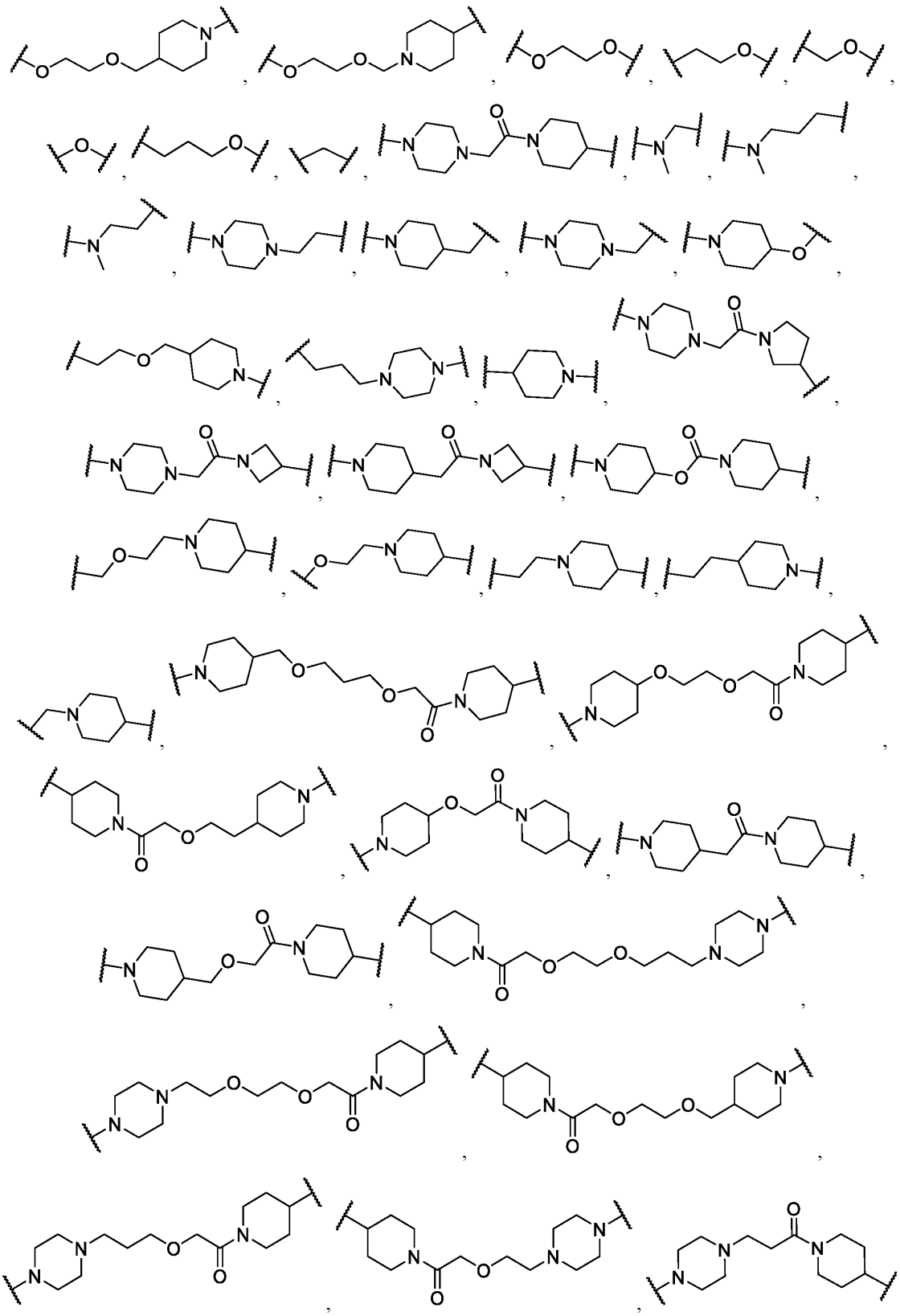


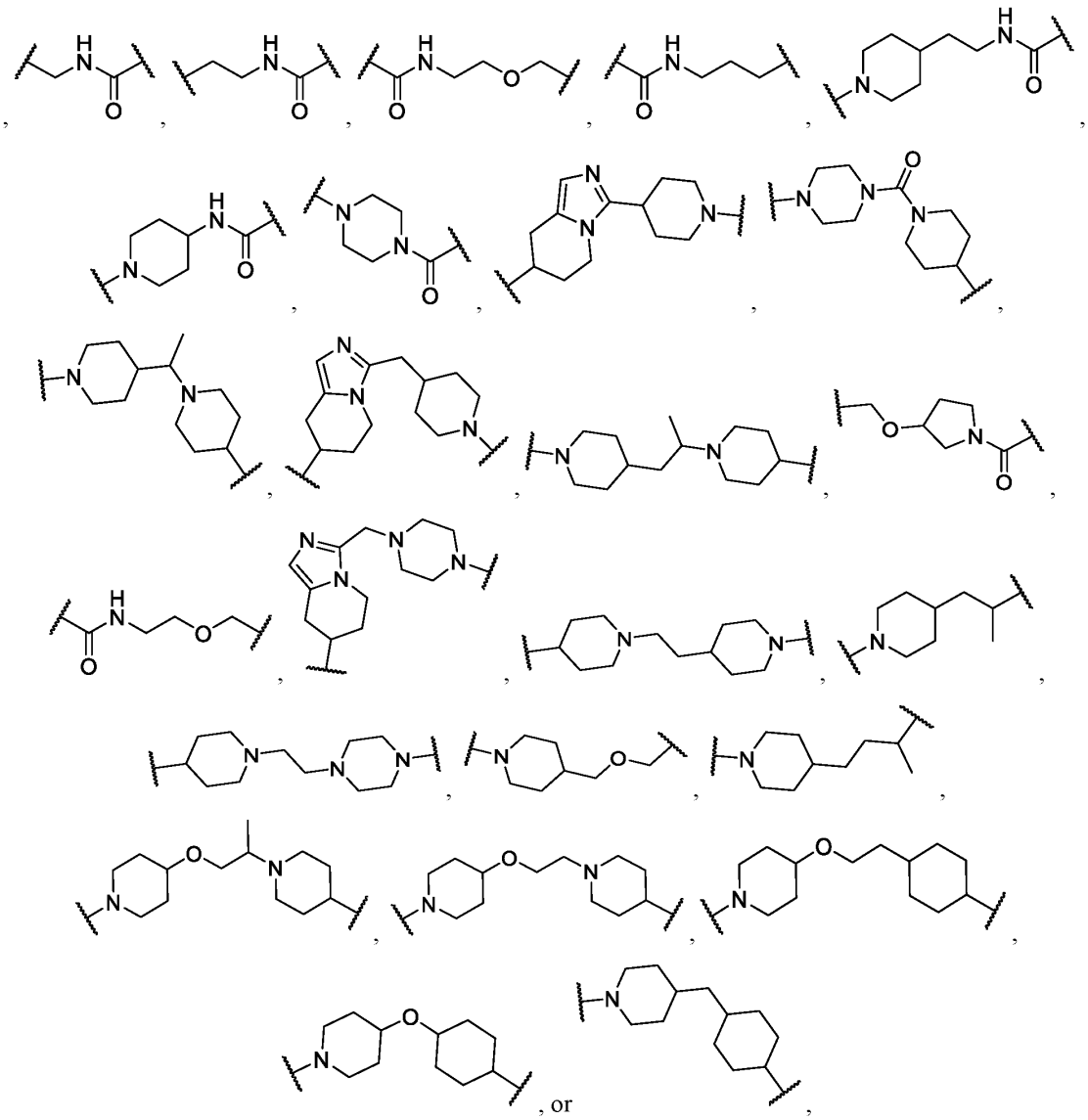


or a pharmaceutically acceptable salt or solvate thereof.

101. The compound of any one of claims 1-99, or a pharmaceutically acceptable salt or solvate thereof, wherein L has one of the following structures:







or a pharmaceutically acceptable salt or solvate thereof.

102. A compound of Table 1, or a pharmaceutically acceptable salt or solvate thereof.

103. A stable ternary complex comprising:

a. one or more disease-dependent proteins (DDPs);

b. Androgen Receptor (AR); and

c. heterobifunctional conditional inhibitor compound of any one of claims 1-102;

wherein DDP and AR are present in a cell of interest (COI) and the relative abundance of the AR in the COI is greater than the relative abundance of the DDP in the COI.

104. The stable ternary complex of claim 103, wherein DDP is Ataxia-telangiectasia mutated (ATM), Ataxia telangiectasia and Rad3-related protein (ATR), Aurora Kinase A (AurkA), AurkB, Cell division cycle 7-related protein kinase (CDC7), Checkpoint kinase 1 (CHK1), CHK2, Cyclin-

dependent kinase 1 (CDK1), CDK2, CDK4, CDK5, CDK6, CDK9, DNA methyltransferase 1 (DNMT1), Exportin 1 (XPO1), Histone deacetylase 1 (HDAC1), HDAC2, HDAC3, kinesin family member 11 (KIF11), Mitogen-activated protein kinase kinase 1 (MEK1), MEK2, Myc, neuronal precursor cell-expressed developmentally down-regulated protein 8 (NEDD8), SMARCA2/4, CREB-binding protein (CBP)/p300, WD repeat-containing protein 5 (WDR5), DDB1- and CUL4-associated factor 1 (DCAF1), phosphatidylinositol-3 kinase (PI3K), Protein arginine methyltransferase 5 (PRMT5), splicing factor 3b subunit 1 (SF3B1), WEE1, 20S proteasome subunits, Steroid Receptor Coactivator 1 (SRC1), SRC2, or SRC3.

105. The stable ternary complex of claim 103, wherein DDP is Aurora Kinase A (AurkA), Checkpoint kinase 1 (CHK1), CHK2, CDK4, CDK6, Myc, SMARCA2/4, CREB-binding protein (CBP)/p300, WD repeat-containing protein 5 (WDR5), DDB1- and CUL4-associated factor 1 (DCAF1), phosphatidylinositol-3 kinase (PI3K), or WEE1.

106. The stable ternary complex of claim 103, wherein the DDP is CREB-binding protein (CBP)/p300.

107. A stable ternary complex comprising:

a. CBP/p300;

b. Androgen receptor (AR); and

c. heterobifunctional conditional inhibitor compound of any one of claims 1-102;

wherein CBP/p300 and DP are present in a cell of interest (COI) and the relative abundance of the DP in the COI is greater than the relative abundance of CBP/p300 in the COI.

108. A method of selectively inhibiting the activity of a disease-dependent protein (DDP) in a cell of interest (COI) of a mammal comprising administering a heterobifunctional compound of any one of claims 1-102, or a pharmaceutically acceptable salt or solvate thereof, wherein the COI expresses the androgen receptor (AR).

109. The method of claim 108, wherein the heterobifunctional compound of any one of claims 1-102, or a pharmaceutically acceptable salt or solvate thereof, inhibits the activity of the DDP in the COI but does not inhibit the activity of the DDP in cells expressing the DDP and not expressing the AR.

110. The method of claim 108, wherein the AR is overexpressed, overactive or both overexpressed and overactive in the COI.

111. The method of any one of claims 108-110, wherein DDP is Ataxia-telangiectasia mutated (ATM), Ataxia telangiectasia and Rad3-related protein (ATR), Aurora Kinase A (AurkA), AurkB, Cell division cycle 7-related protein kinase (CDC7), Checkpoint kinase 1 (CHK1), CHK2, Cyclin-dependent kinase 1 (CDK1), CDK2, CDK4, CDK5, CDK6, CDK9, DNA methyltransferase 1 (DNMT1), Exportin 1 (XPO1), Histone deacetylase 1 (HDAC1), HDAC2, HDAC3, kinesin family member 11 (KIF11), Mitogen-activated protein kinase kinase 1 (MEK1), MEK2, Myc, neuronal precursor cell-expressed developmentally down-regulated protein 8 (NEDD8), SMARCA2/4, CREB-binding protein (CBP)/p300, WD repeat-containing protein 5 (WDR5), DDB1- and CUL4-associated factor 1 (DCAF1), phosphatidylinositol-3 kinase (PI3K), Protein arginine methyltransferase 5

(PRMT5), splicing factor 3b subunit 1 (SF3B1), WEE1, 20S proteasome subunits, Steroid Receptor Coactivator 1 (SRC1), SRC2, or SRC3.

112. The method of any one of claims 108-111, wherein DDP is Aurora Kinase A (AurkA), Checkpoint kinase 1 (CHK1), CHK2, CDK4, CDK6, Myc, SMARCA2/4, CREB-binding protein (CBP)/p300, WD repeat-containing protein 5 (WDR5), DDB1- and CUL4-associated factor 1 (DCAF1), phosphatidylinositol-3 kinase (PI3K), or WEE1.
113. The method of any one of claims 108-111, wherein the DDP is CREB-binding protein (CBP)/p300.
114. A method of treating cancer in a mammal comprising administering to the mammal a heterobifunctional compound of any one of claims 1-102.
115. A method of treating cancer in a mammal comprising administering to the mammal a therapeutically effective amount of a compound of any one of claims 1-102, or a pharmaceutically acceptable salt or solvate thereof.
116. The method of claim 115, wherein the cancer is a hormone dependent cancer.
117. The method of claim 115, wherein the cancer is prostate cancer.
118. A method of treating an androgen receptor dependent or androgen receptor mediated disease or condition in mammal comprising administering to the mammal a therapeutically effective amount of a compound according to any one of claims 1-102, or a pharmaceutically acceptable salt or solvate thereof.
119. The method of claim 118, wherein androgen receptor dependent or androgen receptor mediated disease or condition is selected from benign prostate hyperplasia, hirsutism, adenomas and neoplasms of the prostate, benign or malignant tumor cells containing the androgen receptor, prostate cancer, breast cancer, endometrial cancer, and uterine cancer.
120. A pharmaceutical composition comprising a compound of any one of claims 1-102, or a pharmaceutically acceptable salt or solvate thereof, and at least one pharmaceutically acceptable excipient.