

BCL-2 PROTEIN INHIBITORS

INCORPORATION BY REFERENCE TO PRIORITY APPLICATION

[0001] This application claims priority to U.S. Provisional Application Serial No. 63/016,760, filed April 28, 2020, which is hereby incorporated herein by reference in its entirety.

BACKGROUND

Field

[0002] This application relates to compounds that inhibit and/or degrade proteins in the Bcl-2 family and methods of using them to treat conditions characterized by excessive cellular proliferation, such as cancer and tumors.

Description

[0003] Proteins in the Bcl-2 family contain Bcl-2 homology (BH) domains and regulate apoptosis by modulating mitochondrial outer membrane permeabilization (MOMP). Members of the Bcl-2 family have up to four BH domains, referred to as BH1, BH2, BH3 and BH4. All four domains are conserved in the anti-apoptotic Bcl-2 family members Bcl-2, Bcl-xL, Bcl-W, Mcl-1 and A1/Bfl-1.

[0004] A number of compounds that inhibit anti-apoptotic Bcl-2 proteins have been evaluated for their ability to treat lymphomas and other types of cancer. Navitoclax, a dual Bcl-2/xL inhibitor, has been evaluated in Phase I/II clinical trials for the treatment of chronic lymphocytic leukemia (CLL). However, its efficacy in the study population was reduced by dosage limitations due to the occurrence of thrombocytopenia, a side effect of inhibiting Bcl-xL.

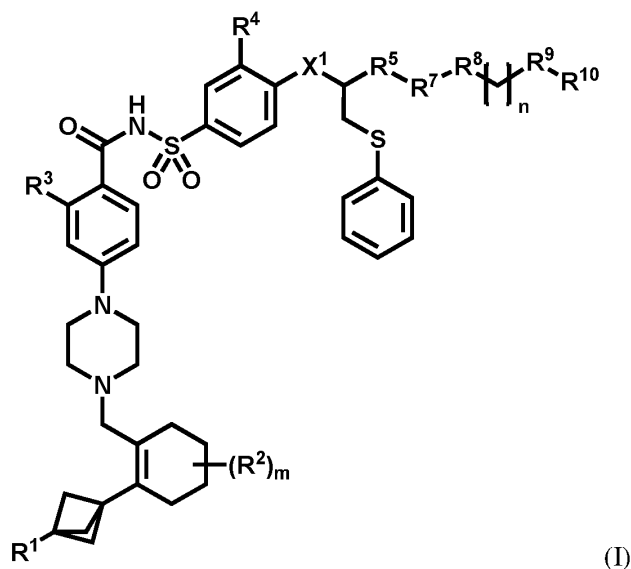
[0005] Venetoclax is the first Bcl-2 inhibitor to be approved by the FDA. It is available commercially from AbbVie Inc. under the tradename VENCLEXTA. It is currently indicated as a second line treatment for patients with CLL or small lymphocytic lymphoma (SLL).

[0006] The FDA approval of Venetoclax represents a milestone in the development of Bcl-2 protein inhibitors. However, there remains a need for improved compounds that inhibit and/or degrade proteins in the Bcl-2 family.

SUMMARY

[0007] Various embodiments provide compounds of the Formula (I) and methods of using them.

[0008] An embodiment provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof, having the structure:



[0009] wherein:

[0010] R^1 can be selected from hydrogen, halogen, a substituted or unsubstituted C_1 - C_6 alkyl, a substituted or unsubstituted C_1 - C_6 haloalkyl, a substituted or unsubstituted C_3 - C_6 cycloalkyl, a substituted or unsubstituted C_1 - C_6 alkoxy, an unsubstituted mono- C_1 - C_6 alkylamine and an unsubstituted di- C_1 - C_6 alkylamine;

[0011] each R^2 can be independently selected from halogen, a substituted or unsubstituted C_1 - C_6 alkyl, a substituted or unsubstituted C_1 - C_6 haloalkyl and a substituted or unsubstituted C_3 - C_6 cycloalkyl; or

[0012] when m is 2 or 3, each R^2 can be independently selected from halogen, a substituted or unsubstituted C_1 - C_6 alkyl, a substituted or unsubstituted C_1 - C_6 haloalkyl and a substituted or unsubstituted C_3 - C_6 cycloalkyl, or two R^2 groups taken together with the atom(s) to which they are attached form a substituted or unsubstituted C_3 - C_6 cycloalkyl or a substituted or unsubstituted 3 to 6 membered heterocyclyl;

[0013] R^3 can be hydrogen or halogen;

[0014] R^4 can be selected from NO_2 , $\text{S(O)}R^6$, SO_2R^6 , halogen, cyano and an unsubstituted $\text{C}_1\text{-C}_6$ haloalkyl;

[0015] R^5 can be a substituted or unsubstituted $\text{C}_1\text{-C}_6$ alkylene, a substituted or unsubstituted $-(\text{C}_1\text{-C}_6 \text{ alkylene})\text{-Het-}$, a substituted or unsubstituted $-(\text{C}_1\text{-C}_6 \text{ alkylene})\text{-O-}$, a substituted or unsubstituted $-(\text{C}_1\text{-C}_6 \text{ alkylene})\text{-NH-}$, a substituted or unsubstituted $-(\text{C}_1\text{-C}_6 \text{ alkylene})\text{-NH-Het-}$, a substituted or unsubstituted $-(\text{C}_1\text{-C}_6 \text{ alkylene})\text{-N}(\text{C}_1\text{-C}_6 \text{ alkyl})\text{-Het-}$, a substituted or unsubstituted $-(\text{C}_1\text{-C}_6 \text{ alkylene})\text{-Het-O-}$, a substituted or unsubstituted $-(\text{C}_1\text{-C}_6 \text{ alkylene})\text{-Het-NH-}$, a substituted or unsubstituted $-(\text{C}_1\text{-C}_6 \text{ alkylene})\text{-N}(\text{C}_1\text{-C}_6 \text{ alkyl})\text{-}$, a substituted or unsubstituted $-(\text{C}_1\text{-C}_6 \text{ alkylene})\text{-Het-N}(\text{C}_1\text{-C}_6 \text{ alkyl})\text{-}$, a substituted or unsubstituted $-(\text{C}_1\text{-C}_6 \text{ alkylene})\text{-(C=O)-O-}$, a substituted or unsubstituted $-(\text{C}_1\text{-C}_6 \text{ alkylene})\text{-Het-(C=O)-O-}$, a substituted or unsubstituted $-(\text{C}_1\text{-C}_6 \text{ alkylene})\text{-Het-(C=O)-NH-}$, a substituted or unsubstituted $-(\text{C}_1\text{-C}_6 \text{ alkylene})\text{-Het-(C=O)-N}(\text{C}_1\text{-C}_6 \text{ alkyl})\text{-}$, a substituted or unsubstituted $-(\text{C}_1\text{-C}_6 \text{ alkylene})\text{-Het-(C=O)-N}(\text{C}_3\text{-C}_6 \text{ cycloalkyl})\text{-}$, a substituted or unsubstituted $-(\text{C}_1\text{-C}_6 \text{ alkylene})\text{-N}(\text{C}_3\text{-C}_6 \text{ cycloalkyl})\text{-}$, a substituted or unsubstituted $-(\text{C}_1\text{-C}_6 \text{ alkylene})\text{-Het-N}(\text{C}_3\text{-C}_6 \text{ cycloalkyl})\text{-}$ or a substituted or unsubstituted $-(\text{C}_1\text{-C}_6 \text{ alkylene})\text{-N}(\text{C}_3\text{-C}_6 \text{ cycloalkyl})\text{-Het-}$, where Het is a substituted or unsubstituted 3 to 10 membered heterocyclyl;

[0016] R^6 can be a substituted or unsubstituted $\text{C}_1\text{-C}_6$ alkyl, a substituted or unsubstituted $\text{C}_1\text{-C}_6$ haloalkyl or a substituted or unsubstituted $\text{C}_3\text{-C}_6$ cycloalkyl;

[0017] R^7 can be absent, a substituted or unsubstituted $\text{C}_1\text{-C}_6$ alkylene, $-(\text{C=O})\text{-}$, $-(\text{C=S})\text{-}$, $-(\text{C=O})\text{-NH-}$, $-(\text{C=O})\text{-N}(\text{C}_1\text{-C}_6 \text{ alkyl})\text{-}$, $-(\text{C=O})\text{-N}(\text{C}_3\text{-C}_6 \text{ cycloalkyl})\text{-}$, $-(\text{C=O})\text{-O-}$, $-(\text{C=S})\text{-NH-}$ or a substituted or unsubstituted $(\text{C}_1\text{-C}_6 \text{ alkylene})\text{-NH-}$;

[0018] R^8 can be absent, a substituted or unsubstituted $\text{C}_1\text{-C}_6$ alkylene, a substituted or unsubstituted $-(\text{C}_1\text{-C}_6 \text{ alkylene})\text{-(C}_6\text{-C}_{12} \text{ aryl})\text{-}$, a substituted or unsubstituted $-(\text{C}_1\text{-C}_6 \text{ alkylene})\text{-(C}_3\text{-C}_{10} \text{ cycloalkyl})\text{-}$, a substituted or unsubstituted $-(\text{C}_1\text{-C}_6 \text{ alkylene})\text{-(C}_3\text{-C}_{10} \text{ heterocyclyl})\text{-}$ or a substituted or unsubstituted $-(\text{C}_1\text{-C}_6 \text{ alkylene})\text{-(5 to 10 membered heteroaryl)}\text{-}$;

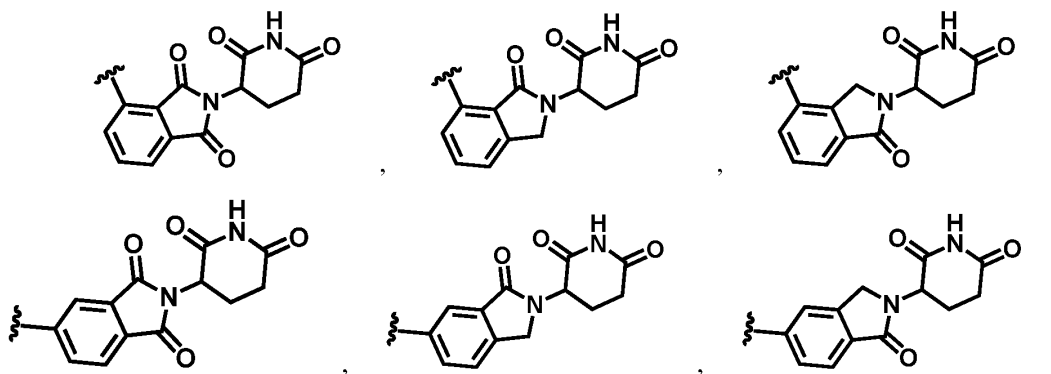
[0019] m can be 0, 1, 2 or 3;

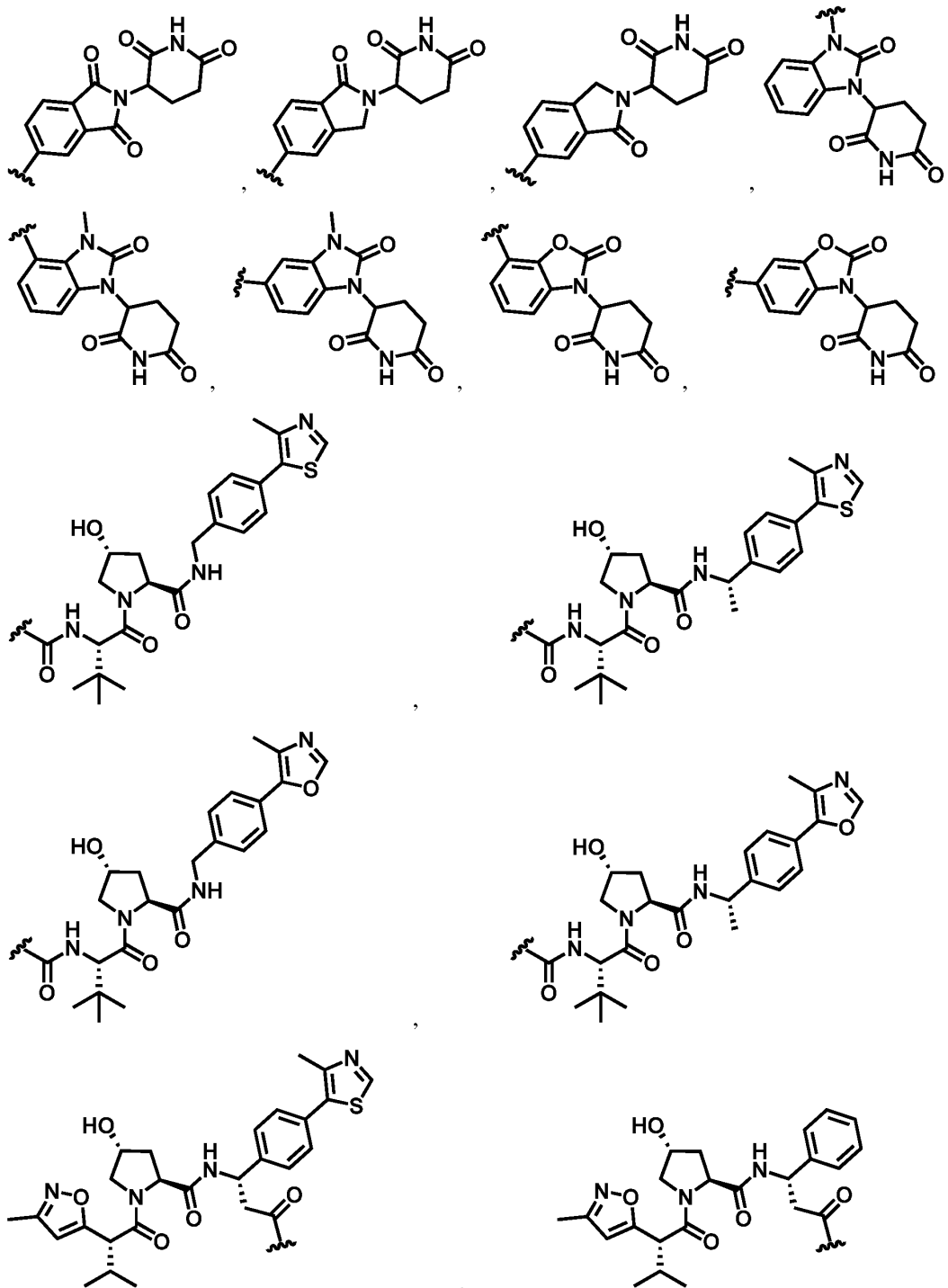
[0020] n can be 0, 1, 2, 3, 4 or 5;

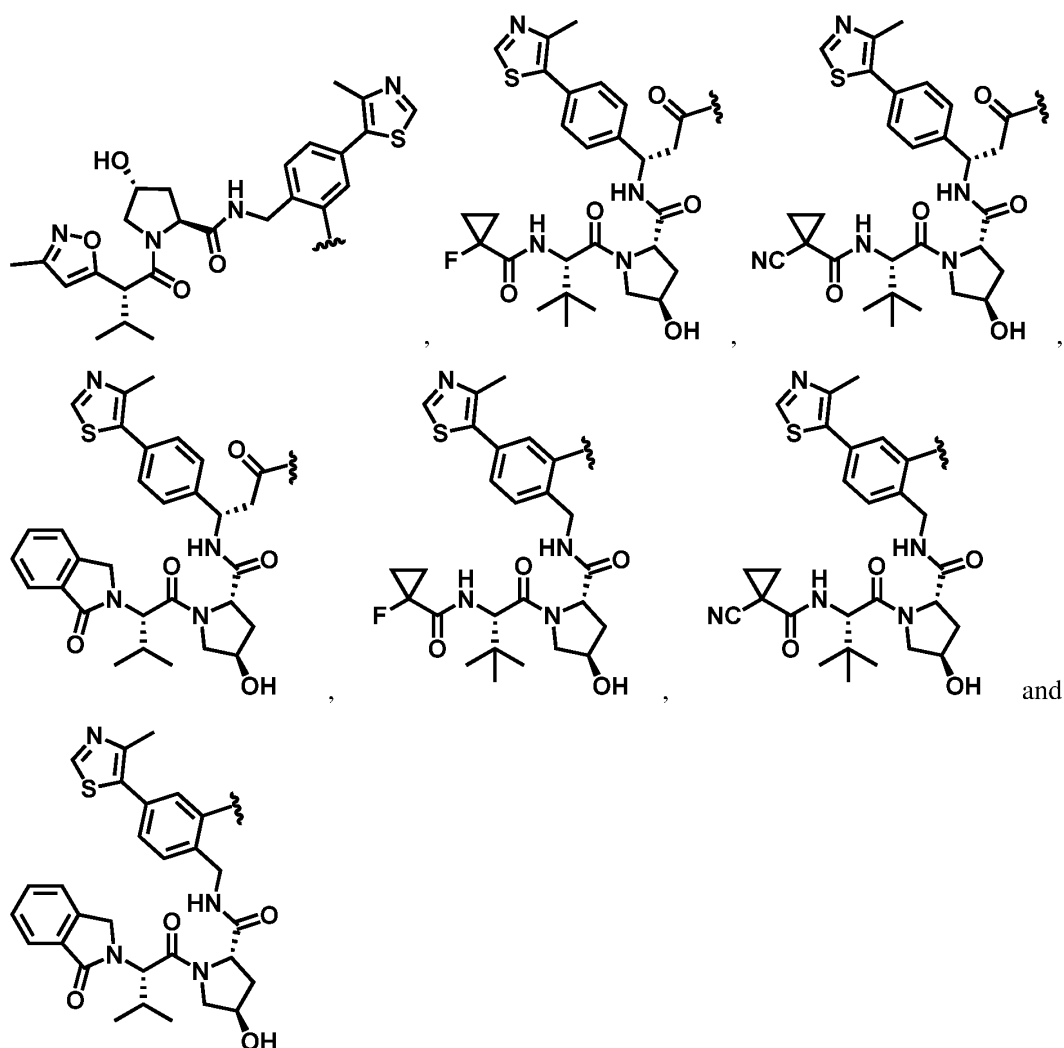
[0021] X^1 can be $-\text{O-}$ or $-\text{NH-}$;

[0022] R^9 can be a substituted or unsubstituted C_1 - C_{10} alkylene, a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-O-$, a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-NH-$, a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-NH-(C_1-C_6 \text{ alkylene})-$, a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-(C=O)NH-$, a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-NH-(C_1-C_6 \text{ alkylene})-NH-$, a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-NH-(C_1-C_6 \text{ alkylene})-O-$, a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-NH(C=O)-(C_1-C_6 \text{ alkylene})-NH-$, a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-NH(C=O)-(C_1-C_6 \text{ alkylene})-O-$, a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-NH(C=O)-(C_1-C_6 \text{ alkylene})-$, a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-NH-(C_1-C_6 \text{ alkylene})-NH(C=O)-(C_1-C_6 \text{ alkylene})-NH-$, a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-NH-(C_1-C_6 \text{ alkylene})-NH(C=O)-(C_1-C_6 \text{ alkylene})-O-$, a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-NH-(C_1-C_6 \text{ alkylene})-NH(C=O)-(C_1-C_6 \text{ alkylene})-$, a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-NH-(C_1-C_6 \text{ alkylene})-NH(C=O)-(C_1-C_6 \text{ alkylene})-O-$, a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-NH(C=O)-(C_1-C_6 \text{ alkylene})-$, a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-(C=O)NH-(C_1-C_6 \text{ alkylene})-NH-$, a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-(C=O)NH-(C_1-C_6 \text{ alkylene})-O-$, a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-NH(C=O)-(C_1-C_6 \text{ alkylene})-(C=O)NH-$, a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-NH-(C_1-C_6 \text{ alkylene})-(C=O)NH-$, a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-NH-(C_1-C_6 \text{ alkylene})-(C=O)NH-(C_1-C_6 \text{ alkylene})-$ or a substituted or an unsubstituted $-(C_1-C_6 \text{ alkylene})-C\equiv C-$;

[0023] R^{10} can be selected from:







[0024] Another embodiment provides a pharmaceutical composition comprising an effective amount of a compound of Formula (I) or any embodiment thereof described herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent, excipient or combination thereof.

[0025] Another embodiment provides a method for treating a cancer or a tumor (e.g. by inhibiting the activity of a Bcl-2 protein and/or a Bcl-xL protein) comprising administering an effective amount of a compound of Formula (I) or any embodiment thereof described herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as described herein, to a subject having the cancer or the tumor, wherein the

cancer or the tumor is selected from a bladder cancer, a brain cancer, a breast cancer, a bone marrow cancer, a cervical cancer, a colorectal cancer, an esophageal cancer, a hepatocellular cancer, a lymphoblastic leukemia, a follicular lymphoma, a lymphoid malignancy of T-cell or B-cell origin, a melanoma, a myelogenous leukemia, a Hodgkin's lymphoma, a Non-Hodgkin's lymphoma, a head and neck cancer (including oral cancer), an ovarian cancer, a non-small cell lung cancer, a chronic lymphocytic leukemia, a myeloma, a prostate cancer, a small cell lung cancer, a spleen cancer, a polycythemia vera, a thyroid cancer, an endometrial cancer, a stomach cancer, a gallbladder cancer, a bile duct cancer, a testicular cancer, a neuroblastoma, an osteosarcoma, an Ewings's tumor and a Wilm's tumor.

[0026] Another embodiment provides a method for inhibiting replication of a malignant growth or a tumor (e.g. by inhibiting the activity of a Bcl-2 protein and/or a Bcl-xL protein) comprising contacting the growth or the tumor with an effective amount of a compound of Formula (I) or any embodiment thereof described herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as described herein, wherein the malignant growth or tumor selected from an Ewings's tumor and a Wilm's tumor, or the malignant growth of tumor is due to a cancer selected from a bladder cancer, a brain cancer, a breast cancer, a bone marrow cancer, a cervical cancer, a colorectal cancer, an esophageal cancer, a hepatocellular cancer, a lymphoblastic leukemia, a follicular lymphoma, a lymphoid malignancy of T-cell or B-cell origin, a melanoma, a myelogenous leukemia, a Hodgkin's lymphoma, a Non-Hodgkin's lymphoma, a head and neck cancer (including oral cancer), an ovarian cancer, a non-small cell lung cancer, a chronic lymphocytic leukemia, a myeloma, a prostate cancer, a small cell lung cancer, a spleen cancer, a polycythemia vera, a thyroid cancer, an endometrial cancer, a stomach cancer, a gallbladder cancer, a bile duct cancer, a testicular cancer, a neuroblastoma, an osteosarcoma.

[0027] Another embodiment provides a method for treating a cancer (e.g. by inhibiting the activity of a Bcl-2 protein and/or a Bcl-xL protein) comprising contacting a malignant growth or a tumor with an effective amount of a compound of Formula (I) or any embodiment thereof described herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as described herein, wherein the malignant growth or tumor selected from an Ewings's tumor and a Wilm's tumor, or the malignant growth of tumor is due to a cancer selected from a bladder cancer, a brain cancer, a breast cancer, a bone

marrow cancer, a cervical cancer, a colorectal cancer, an esophageal cancer, a hepatocellular cancer, a lymphoblastic leukemia, a follicular lymphoma, a lymphoid malignancy of T-cell or B-cell origin, a melanoma, a myelogenous leukemia, a Hodgkin's lymphoma, a Non-Hodgkin's lymphoma, a head and neck cancer (including oral cancer), an ovarian cancer, a non-small cell lung cancer, a chronic lymphocytic leukemia, a myeloma, a prostate cancer, a small cell lung cancer, a spleen cancer, a polycythemia vera, a thyroid cancer, an endometrial cancer, a stomach cancer, a gallbladder cancer, a bile duct cancer, a testicular cancer, a neuroblastoma or an osteosarcoma.

[0028] Another embodiment provides a method for inhibiting the activity of a Bcl-2 protein and/or a Bcl-xL protein, comprising providing an effective amount of a compound of Formula (I) or any embodiment thereof described herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as described herein, to a cancer cell or a tumor, wherein the cancer cell or the tumor is from a cancer selected from a bladder cancer, a brain cancer, a breast cancer, a bone marrow cancer, a cervical cancer, a colorectal cancer, an esophageal cancer, a hepatocellular cancer, a lymphoblastic leukemia, a follicular lymphoma, a lymphoid malignancy of T-cell or B-cell origin, a melanoma, a myelogenous leukemia, a Hodgkin's lymphoma, a Non-Hodgkin's lymphoma, a head and neck cancer (including oral cancer), an ovarian cancer, a non-small cell lung cancer, a chronic lymphocytic leukemia, a myeloma, a prostate cancer, a small cell lung cancer, a spleen cancer, a polycythemia vera, a thyroid cancer, an endometrial cancer, a stomach cancer, a gallbladder cancer, a bile duct cancer, a testicular cancer, a neuroblastoma, an osteosarcoma, an Ewings's tumor and a Wilm's tumor.

[0029] Another embodiment provides a method for inhibiting the activity of a Bcl-2 protein and/or a Bcl-xL protein in a subject, comprising providing an effective amount of a compound of Formula (I) or any embodiment thereof described herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as described herein, to the subject having a cancer or a tumor, wherein the cancer or the tumor is selected from a bladder cancer, a brain cancer, a breast cancer, a bone marrow cancer, a cervical cancer, a colorectal cancer, an esophageal cancer, a hepatocellular cancer, a lymphoblastic leukemia, a follicular lymphoma, a lymphoid malignancy of T-cell or B-cell origin, a melanoma, a myelogenous leukemia, a Hodgkin's lymphoma, a Non-Hodgkin's lymphoma, a

head and neck cancer (including oral cancer), an ovarian cancer, a non-small cell lung cancer, a chronic lymphocytic leukemia, a myeloma, a prostate cancer, a small cell lung cancer, a spleen cancer, a polycythemia vera, a thyroid cancer, an endometrial cancer, a stomach cancer, a gallbladder cancer, a bile duct cancer, a testicular cancer, a neuroblastoma, an osteosarcoma, an Ewings's tumor and a Wilm's tumor.

[0030] Another embodiment provides a use of an effective amount of a compound of Formula (I) or any embodiment thereof described herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as described herein, in the manufacture of a medicament for treating a cancer or a tumor (e.g. by inhibiting the activity of a Bcl-2 protein and/or a Bcl-xL protein), wherein the cancer or the tumor is selected from a bladder cancer, a brain cancer, a breast cancer, a bone marrow cancer, a cervical cancer, a colorectal cancer, an esophageal cancer, a hepatocellular cancer, a lymphoblastic leukemia, a follicular lymphoma, a lymphoid malignancy of T-cell or B-cell origin, a melanoma, a myelogenous leukemia, a Hodgkin's lymphoma, a Non-Hodgkin's lymphoma, a head and neck cancer (including oral cancer), an ovarian cancer, a non-small cell lung cancer, a chronic lymphocytic leukemia, a myeloma, a prostate cancer, a small cell lung cancer, a spleen cancer, a polycythemia vera, a thyroid cancer, an endometrial cancer, a stomach cancer, a gallbladder cancer, a bile duct cancer, a testicular cancer, a neuroblastoma, an osteosarcoma, an Ewings's tumor and a Wilm's tumor.

[0031] Another embodiment provides a use of an effective amount of a compound of Formula (I) or any embodiment thereof described herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as described herein, in the manufacture of a medicament for treating a malignant growth or a tumor (e.g. by inhibiting the activity of a Bcl-2 protein and/or a Bcl-xL protein), wherein the malignant growth or the tumor is due to a cancer selected from a bladder cancer, a brain cancer, a breast cancer, a bone marrow cancer, a cervical cancer, a colorectal cancer, an esophageal cancer, a hepatocellular cancer, a lymphoblastic leukemia, a follicular lymphoma, a lymphoid malignancy of T-cell or B-cell origin, a melanoma, a myelogenous leukemia, a Hodgkin's lymphoma, a Non-Hodgkin's lymphoma, a head and neck cancer (including oral cancer), an ovarian cancer, a non-small cell lung cancer, a chronic lymphocytic leukemia, a myeloma, a prostate cancer, a small cell lung cancer, a spleen cancer, a polycythemia vera, a thyroid

cancer, an endometrial cancer, a stomach cancer, a gallbladder cancer, a bile duct cancer, a testicular cancer, a neuroblastoma, an osteosarcoma, an Ewings's tumor and a Wilm's tumor.

[0032] These and other embodiments are described in greater detail below.

BRIEF DESCRIPTION OF THE DRAWINGS

[0033] FIG. 1 illustrates a general synthetic scheme for preparing compounds of the Formula (I).

[0034] FIG. 2 illustrates a general synthetic scheme for preparing embodiments of compounds of the Formula (I).

[0035] FIG. 3 illustrates a general synthetic scheme for preparing embodiments of compounds of the Formula (I).

[0036] FIG. 4 illustrates a general synthetic scheme for preparing embodiments of compounds of the Formula (I).

[0037] FIG. 5 illustrates a general synthetic scheme for preparing embodiments of compounds of the Formula (I).

[0038] FIG. 6 illustrates a general synthetic scheme for preparing embodiments of compounds of the Formula (I).

[0039] FIGS. 7-10 show the results of cellular proliferation and protein degradation assays in MOLT-4 cells with several compounds of Formula (I).

DETAILED DESCRIPTION

[0040] Bcl-2 is a critical regulator of programmed cell death (apoptosis). Bcl-2 belongs to the B cell lymphoma 2 (BCL-2) family of proteins, which includes both pro-apoptotic proteins (such as Bak, Bax, Bim, Bid, tBid, Bad, Bik, PUMA, Bnip-1, Hrk, Bmf and Noxa) and anti-apoptotic proteins (such as Bcl-2, Bcl-X_L, Bcl-W, Mcl-1 and Bcl-2A1). For example, under normal conditions, Bcl-2 inhibits apoptosis in part by preventing activation of Bak and Bax. Activation of the intrinsic apoptosis pathway (e.g., by cellular stress) inhibits Bcl-2, thus activating Bak and Bax. These proteins facilitate mitochondrial outer membrane permeabilization, releasing cytochrome c and Smac. This initiates the caspase signaling pathway, ultimately resulting in cell death. Dysregulation of Bcl-2 leads to sequestration of cell-death-promoting proteins, leading to evasion of apoptosis. This process

contributes to malignancy, and facilitates cell survival under other disadvantageous conditions, such as during viral infection. Inhibition of Bcl-2 (e.g., by degrading Bcl-2 protein and/or by inhibiting binding) disrupts sequestration of pro-apoptotic proteins, restoring apoptotic signaling, and promoting damaged cells to undergo programmed cell death. Therefore, inhibition of proteins in the Bcl-2 family (e.g., by inhibition and/or degradation of Bcl-2 protein and/or Bcl-X_L protein) has the potential to ameliorate or treat cancers and tumors.

Definitions

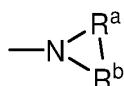
[0041] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art. All patents, applications, published applications and other publications referenced herein are incorporated by reference in their entirety unless stated otherwise. In the event that there are a plurality of definitions for a term herein, those in this section prevail unless stated otherwise.

[0042] Whenever a group is described as being “optionally substituted” that group may be unsubstituted or substituted with one or more of the indicated substituents. Likewise, when a group is described as being “unsubstituted or substituted” if substituted, the substituent(s) may be selected from one or more the indicated substituents. If no substituents are indicated, it is meant that the indicated “optionally substituted” or “substituted” group may be substituted with one or more group(s) individually and independently selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), cycloalkyl(alkyl), heteroaryl(alkyl), heterocyclyl(alkyl), hydroxy, alkoxy, acyl, cyano, halogen, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, S-sulfonamido, N-sulfonamido, C-carboxy, O-carboxy, nitro, sulfenyl, sulfinyl, sulfonyl, haloalkyl, haloalkoxy, an amino, a mono-substituted amine group, a di-substituted amine group, a mono-substituted amine(alkyl) and a di-substituted amine(alkyl).

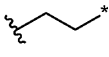
[0043] As used herein, “C_a to C_b” in which “a” and “b” are integers refer to the number of carbon atoms in a group. The indicated group can contain from “a” to “b”, inclusive, carbon atoms. Thus, for example, a “C₁ to C₄ alkyl” group refers to all alkyl groups having from 1 to 4 carbons, that is, CH₃-, CH₃CH₂-, CH₃CH₂CH₂-, (CH₃)₂CH-,

CH₃CH₂CH₂CH₂-, CH₃CH₂CH(CH₃)- and (CH₃)₃C-. If no “a” and “b” are designated, the broadest range described in these definitions is to be assumed.

[0044] If two “R” groups are described as being “taken together” the R groups and the atoms they are attached to can form a cycloalkyl, cycloalkenyl, aryl, heteroaryl or heterocycle. For example, without limitation, if R^a and R^b of an NR^aR^b group are indicated to be “taken together,” it means that they are covalently bonded to one another to form a ring:



[0045] As used herein, the term “alkyl” refers to a fully saturated aliphatic hydrocarbon group. The alkyl moiety may be branched or straight chain. Examples of branched alkyl groups include, but are not limited to, iso-propyl, sec-butyl, t-butyl and the like. Examples of straight chain alkyl groups include, but are not limited to, methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, n-heptyl and the like. The alkyl group may have 1 to 30 carbon atoms (whenever it appears herein, a numerical range such as “1 to 30” refers to each integer in the given range; *e.g.*, “1 to 30 carbon atoms” means that the alkyl group may consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, *etc.*, up to and including 30 carbon atoms, although the present definition also covers the occurrence of the term “alkyl” where no numerical range is designated). The alkyl group may also be a medium size alkyl having 1 to 12 carbon atoms. The alkyl group could also be a lower alkyl having 1 to 6 carbon atoms. An alkyl group may be substituted or unsubstituted.

[0046] As used herein, the term “alkylene” refers to a bivalent fully saturated straight chain aliphatic hydrocarbon group. Examples of alkylene groups include, but are not limited to, methylene, ethylene, propylene, butylene, pentylene, hexylene, heptylene and octylene. An alkylene group may be represented by , followed by the number of carbon atoms, followed by a “*”. For example,  to represent ethylene. The alkylene group may have 1 to 30 carbon atoms (whenever it appears herein, a numerical range such as “1 to 30” refers to each integer in the given range; *e.g.*, “1 to 30 carbon atoms” means that the alkyl group may consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, *etc.*, up to and including 30 carbon atoms, although the present definition also covers the occurrence of the term “alkylene” where no numerical range is designated). The alkylene group may also be a

medium size alkyl having 1 to 12 carbon atoms. The alkylene group could also be a lower alkyl having 1 to 4 carbon atoms. An alkylene group may be substituted or unsubstituted. For example, a lower alkylene group can be substituted by replacing one or more hydrogen of the lower alkylene group and/or by substituting both hydrogens on the same carbon with a



C₃₋₆ monocyclic cycloalkyl group (e.g., -C-).

[0047] The term “alkenyl” used herein refers to a monovalent straight or branched chain radical of from two to twenty carbon atoms containing a carbon double bond(s) including, but not limited to, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl and the like. An alkenyl group may be unsubstituted or substituted.

[0048] The term “alkynyl” used herein refers to a monovalent straight or branched chain radical of from two to twenty carbon atoms containing a carbon triple bond(s) including, but not limited to, 1-propynyl, 1-butyne, 2-butyne and the like. An alkynyl group may be unsubstituted or substituted.

[0049] As used herein, “cycloalkyl” refers to a completely saturated (no double or triple bonds) mono- or multi- cyclic (such as bicyclic) hydrocarbon ring system. When composed of two or more rings, the rings may be joined together in a fused, bridged or spiro fashion. As used herein, the term “fused” refers to two rings which have two atoms and one bond in common. As used herein, the term “bridged cycloalkyl” refers to compounds wherein the cycloalkyl contains a linkage of one or more atoms connecting non-adjacent atoms. As used herein, the term “spiro” refers to two rings which have one atom in common and the two rings are not linked by a bridge. Cycloalkyl groups can contain 3 to 30 atoms in the ring(s), 3 to 20 atoms in the ring(s), 3 to 10 atoms in the ring(s), 3 to 8 atoms in the ring(s) or 3 to 6 atoms in the ring(s). A cycloalkyl group may be unsubstituted or substituted. Examples of mono-cycloalkyl groups include, but are in no way limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl. Examples of fused cycloalkyl groups are decahydronaphthalenyl, dodecahydro-1H-phenalenyl and tetradecahydroanthracenyl; examples of bridged cycloalkyl groups are bicyclo[1.1.1]pentyl, adamantanyl and norbornanyl; and examples of spiro cycloalkyl groups include spiro[3.3]heptane and spiro[4.5]decane.

[0050] As used herein, “cycloalkenyl” refers to a mono- or multi- cyclic (such as bicyclic) hydrocarbon ring system that contains one or more double bonds in at least one ring; although, if there is more than one, the double bonds cannot form a fully delocalized pi-electron system throughout all the rings (otherwise the group would be “aryl,” as defined herein). Cycloalkenyl groups can contain 3 to 10 atoms in the ring(s), 3 to 8 atoms in the ring(s) or 3 to 6 atoms in the ring(s). When composed of two or more rings, the rings may be connected together in a fused, bridged or spiro fashion. A cycloalkenyl group may be unsubstituted or substituted.

[0051] As used herein, “aryl” refers to a carbocyclic (all carbon) monocyclic or multicyclic (such as bicyclic) aromatic ring system (including fused ring systems where two carbocyclic rings share a chemical bond) that has a fully delocalized pi-electron system throughout all the rings. The number of carbon atoms in an aryl group can vary. For example, the aryl group can be a C₆-C₁₄ aryl group, a C₆-C₁₀ aryl group or a C₆ aryl group. Examples of aryl groups include, but are not limited to, benzene, naphthalene and azulene. An aryl group may be substituted or unsubstituted.

[0052] As used herein, “heteroaryl” refers to a monocyclic or multicyclic (such as bicyclic) aromatic ring system (a ring system with fully delocalized pi-electron system) that contain(s) one or more heteroatoms (for example, 1, 2 or 3 heteroatoms), that is, an element other than carbon, including but not limited to, nitrogen, oxygen and sulfur. The number of atoms in the ring(s) of a heteroaryl group can vary. For example, the heteroaryl group can contain 4 to 14 atoms in the ring(s), 5 to 10 atoms in the ring(s) or 5 to 6 atoms in the ring(s), such as nine carbon atoms and one heteroatom; eight carbon atoms and two heteroatoms; seven carbon atoms and three heteroatoms; eight carbon atoms and one heteroatom; seven carbon atoms and two heteroatoms; six carbon atoms and three heteroatoms; five carbon atoms and four heteroatoms; five carbon atoms and one heteroatom; four carbon atoms and two heteroatoms; three carbon atoms and three heteroatoms; four carbon atoms and one heteroatom; three carbon atoms and two heteroatoms; or two carbon atoms and three heteroatoms. Furthermore, the term “heteroaryl” includes fused ring systems where two rings, such as at least one aryl ring and at least one heteroaryl ring or at least two heteroaryl rings, share at least one chemical bond. Examples of heteroaryl rings include, but are not limited to, furan, furazan, thiophene, benzothiophene, phthalazine, pyrrole, oxazole,

benzoxazole, 1,2,3-oxadiazole, 1,2,4-oxadiazole, thiazole, 1,2,3-thiadiazole, 1,2,4-thiadiazole, benzothiazole, imidazole, benzimidazole, indole, indazole, pyrazole, benzopyrazole, isoxazole, benzoisoxazole, isothiazole, triazole, benzotriazole, thiadiazole, tetrazole, pyridine, pyridazine, pyrimidine, pyrazine, purine, pteridine, quinoline, isoquinoline, quinazoline, quinoxaline, cinnoline and triazine. A heteroaryl group may be substituted or unsubstituted.

[0053] As used herein, “heterocyclyl” or “heteroalicyclyl” refers to three-, four-, five-, six-, seven-, eight-, nine-, ten-, up to 18-membered monocyclic, bicyclic and tricyclic ring system wherein carbon atoms together with from 1 to 5 heteroatoms constitute said ring system. A heterocycle may optionally contain one or more unsaturated bonds situated in such a way, however, that a fully delocalized pi-electron system does not occur throughout all the rings. The heteroatom(s) is an element other than carbon including, but not limited to, oxygen, sulfur and nitrogen. A heterocycle may further contain one or more carbonyl or thiocarbonyl functionalities, so as to make the definition include oxo-systems and thio-systems such as lactams, lactones, cyclic imides, cyclic thioimides and cyclic carbamates. When composed of two or more rings, the rings may be joined together in a fused, bridged or spiro fashion. As used herein, the term “fused” refers to two rings which have two atoms and one bond in common. As used herein, the term “bridged heterocyclyl” or “bridged heteroalicyclyl” refers to compounds wherein the heterocyclyl or heteroalicyclyl contains a linkage of one or more atoms connecting non-adjacent atoms. As used herein, the term “spiro” refers to two rings which have one atom in common and the two rings are not linked by a bridge. Heterocyclyl and heteroalicyclyl groups can contain 3 to 30 atoms in the ring(s), 3 to 20 atoms in the ring(s), 3 to 10 atoms in the ring(s), 3 to 8 atoms in the ring(s) or 3 to 6 atoms in the ring(s). For example, five carbon atoms and one heteroatom; four carbon atoms and two heteroatoms; three carbon atoms and three heteroatoms; four carbon atoms and one heteroatom; three carbon atoms and two heteroatoms; two carbon atoms and three heteroatoms; one carbon atom and four heteroatoms; three carbon atoms and one heteroatom; or two carbon atoms and one heteroatom. Additionally, any nitrogens in a heteroalicyclic may be quaternized. Heterocyclyl or heteroalicyclic groups may be unsubstituted or substituted. Examples of such “heterocyclyl” or “heteroalicyclyl” groups include but are not limited to, 1,3-dioxin, 1,3-dioxane, 1,4-dioxane, 1,2-dioxolane, 1,3-dioxolane, 1,4-dioxolane,

1,3-oxathiane, 1,4-oxathiin, 1,3-oxathiolane, 1,3-dithiole, 1,3-dithiolane, 1,4-oxathiane, tetrahydro-1,4-thiazine, 2H-1,2-oxazine, maleimide, succinimide, barbituric acid, thiobarbituric acid, dioxopiperazine, hydantoin, dihydrouracil, trioxane, hexahydro-1,3,5-triazine, imidazoline, imidazolidine, isoxazoline, isoxazolidine, oxazoline, oxazolidine, oxazolidinone, thiazoline, thiazolidine, morpholine, oxirane, piperidine N-Oxide, piperidine, piperazine, pyrrolidine, azepane, pyrrolidone, pyrrolidione, 4-piperidone, pyrazoline, pyrazolidine, 2-oxopyrrolidine, tetrahydropyran, 4H-pyran, tetrahydrothiopyran, thiamorpholine, thiamorpholine sulfoxide, thiamorpholine sulfone and their benzo-fused analogs (e.g., benzimidazolidinone, tetrahydroquinoline and/or 3,4-methylenedioxyphenyl). Examples of spiro heterocyclyl groups include 2-azaspiro[3.3]heptane, 2-oxaspiro[3.3]heptane, 2-oxa-6-azaspiro[3.3]heptane, 2,6-diazaspiro[3.3]heptane, 2-oxaspiro[3.4]octane and 2-azaspiro[3.4]octane.

[0054] As used herein, “aralkyl” and “aryl(alkyl)” refer to an aryl group connected, as a substituent, via a lower alkylene group. The lower alkylene and aryl group of an aralkyl may be substituted or unsubstituted. Examples include but are not limited to benzyl, 2-phenylalkyl, 3-phenylalkyl and naphthylalkyl.

[0055] As used herein, “heteroaralkyl” and “heteroaryl(alkyl)” refer to a heteroaryl group connected, as a substituent, via a lower alkylene group. The lower alkylene and heteroaryl group of heteroaralkyl may be substituted or unsubstituted. Examples include but are not limited to 2-thienylalkyl, 3-thienylalkyl, furylalkyl, thienylalkyl, pyrrolylalkyl, pyridylalkyl, isoxazolylalkyl and imidazolylalkyl and their benzo-fused analogs.

[0056] A “heteroalicycyl(alkyl)” and “heterocyclyl(alkyl)” refer to a heterocyclic or a heteroalicyclic group connected, as a substituent, via a lower alkylene group. The lower alkylene and heterocyclyl of a (heteroalicycyl)alkyl may be substituted or unsubstituted. Examples include but are not limited tetrahydro-2H-pyran-4-yl(methyl), piperidin-4-yl(ethyl), piperidin-4-yl(propyl), tetrahydro-2H-thiopyran-4-yl(methyl) and 1,3-thiazinan-4-yl(methyl).

[0057] As used herein, the term “hydroxy” refers to a –OH group.

[0058] As used herein, “alkoxy” refers to the Formula –OR wherein R is an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl) is defined herein. A

non-limiting list of alkoxys are methoxy, ethoxy, n-propoxy, 1-methylethoxy (isopropoxy), n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy, phenoxy and benzoxy. An alkoxy may be substituted or unsubstituted.

[0059] As used herein, “acyl” refers to a hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl) and heterocyclyl(alkyl) connected, as substituents, via a carbonyl group. Examples include formyl, acetyl, propanoyl, benzoyl and acryl. An acyl may be substituted or unsubstituted.

[0060] A “cyano” group refers to a “-CN” group.

[0061] The term “halogen atom” or “halogen” as used herein, means any one of the radio-stable atoms of column 7 of the Periodic Table of the Elements, such as, fluorine, chlorine, bromine and iodine.

[0062] A “thiocarbonyl” group refers to a “-C(=S)R” group in which R can be the same as defined with respect to O-carboxy. A thiocarbonyl may be substituted or unsubstituted.

[0063] An “O-carbamyl” group refers to a “-OC(=O)N(R_AR_B)” group in which R_A and R_B can be independently hydrogen, an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). An O-carbamyl may be substituted or unsubstituted.

[0064] An “N-carbamyl” group refers to an “ROC(=O)N(R_A)-” group in which R and R_A can be independently hydrogen, an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). An N-carbamyl may be substituted or unsubstituted.

[0065] An “O-thiocarbamyl” group refers to a “-OC(=S)-N(R_AR_B)” group in which R_A and R_B can be independently hydrogen, an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). An O-thiocarbamyl may be substituted or unsubstituted.

[0066] An “N-thiocarbamyl” group refers to an “ROC(=S)N(R_A)-” group in which R and R_A can be independently hydrogen, an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(alkyl), aryl(alkyl),

heteroaryl(alkyl) or heterocyclyl(alkyl). An N-thiocarbamyl may be substituted or unsubstituted.

[0067] A “C-amido” group refers to a “ $\text{-C(=O)N(R}_A\text{R}_B\text{)}$ ” group in which R_A and R_B can be independently hydrogen, an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). A C-amido may be substituted or unsubstituted.

[0068] An “N-amido” group refers to a “ $\text{RC(=O)N(R}_A\text{)-}$ ” group in which R and R_A can be independently hydrogen, an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). An N-amido may be substituted or unsubstituted.

[0069] An “S-sulfonamido” group refers to a “ $\text{-SO}_2\text{N(R}_A\text{R}_B\text{)}$ ” group in which R_A and R_B can be independently hydrogen, an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). An S-sulfonamido may be substituted or unsubstituted.

[0070] An “N-sulfonamido” group refers to a “ $\text{RSO}_2\text{N(R}_A\text{)-}$ ” group in which R and R_A can be independently hydrogen, an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). An N-sulfonamido may be substituted or unsubstituted.

[0071] An “O-carboxy” group refers to a “ RC(=O)O- ” group in which R can be hydrogen, an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl), as defined herein. An O-carboxy may be substituted or unsubstituted.

[0072] The terms “ester” and “C-carboxy” refer to a “ -C(=O)OR ” group in which R can be the same as defined with respect to O-carboxy. An ester and C-carboxy may be substituted or unsubstituted.

[0073] A “nitro” group refers to an “ -NO_2 ” group.

[0074] A “sulfenyl” group refers to an “ -SR ” group in which R can be hydrogen, an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). A sulfenyl may be substituted or unsubstituted.

[0075] A “sulfinyl” group refers to an “-S(=O)-R” group in which R can be the same as defined with respect to sulfenyl. A sulfinyl may be substituted or unsubstituted.

[0076] A “sulfonyl” group refers to an “-SO₂R” group in which R can be the same as defined with respect to sulfenyl. A sulfonyl may be substituted or unsubstituted.

[0077] As used herein, “haloalkyl” refers to an alkyl group in which one or more of the hydrogen atoms are replaced by a halogen (e.g., mono-haloalkyl, di-haloalkyl, tri-haloalkyl and polyhaloalkyl). Such groups include but are not limited to, chloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, 1-chloro-2-fluoromethyl, 2-fluoroisobutyl and pentafluoroethyl. A haloalkyl may be substituted or unsubstituted.

[0078] As used herein, “haloalkoxy” refers to an alkoxy group in which one or more of the hydrogen atoms are replaced by a halogen (e.g., mono-haloalkoxy, di-haloalkoxy and tri-haloalkoxy). Such groups include but are not limited to, chloromethoxy, fluoromethoxy, difluoromethoxy, trifluoromethoxy, 1-chloro-2-fluoromethoxy and 2-fluoroisobutoxy. A haloalkoxy may be substituted or unsubstituted.

[0079] The terms “amino” and “unsubstituted amino” as used herein refer to a -NH₂ group.

[0080] A “mono-substituted amine” group refers to a “-NHR_A” group in which R_A can be an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl), as defined herein. The R_A may be substituted or unsubstituted. A mono-substituted amine group can include, for example, a mono-alkylamine group, a mono-C₁-C₆ alkylamine group, a mono-arylamine group, a mono-C₆-C₁₀ arylamine group and the like. Examples of mono-substituted amine groups include, but are not limited to, -NH(methyl), -NH(phenyl) and the like.

[0081] A “di-substituted amine” group refers to a “-NR_AR_B” group in which R_A and R_B can be independently an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl), as defined herein. R_A and R_B can independently be substituted or unsubstituted. A di-substituted amine group can include, for example, a di-alkylamine group, a di-C₁-C₆ alkylamine group, a di-arylamine group, a di-C₆-C₁₀ arylamine group and the like.

Examples of di-substituted amine groups include, but are not limited to, $-N(\text{methyl})_2$, $-N(\text{phenyl})(\text{methyl})$, $-N(\text{ethyl})(\text{methyl})$ and the like.

[0082] As used herein, “mono-substituted amine(alkyl)” group refers to a mono-substituted amine as provided herein connected, as a substituent, via a lower alkylene group. A mono-substituted amine(alkyl) may be substituted or unsubstituted. A mono-substituted amine(alkyl) group can include, for example, a mono-alkylamine(alkyl) group, a mono- C_1 - C_6 alkylamine(C_1 - C_6 alkyl) group, a mono-arylamine(alkyl group), a mono- C_6 - C_{10} arylamine(C_1 - C_6 alkyl) group and the like. Examples of mono-substituted amine(alkyl) groups include, but are not limited to, $-\text{CH}_2\text{NH}(\text{methyl})$, $-\text{CH}_2\text{NH}(\text{phenyl})$, $-\text{CH}_2\text{CH}_2\text{NH}(\text{methyl})$, $-\text{CH}_2\text{CH}_2\text{NH}(\text{phenyl})$ and the like.

[0083] As used herein, “di-substituted amine(alkyl)” group refers to a di-substituted amine as provided herein connected, as a substituent, via a lower alkylene group. A di-substituted amine(alkyl) may be substituted or unsubstituted. A di-substituted amine(alkyl) group can include, for example, a dialkylamine(alkyl) group, a di- C_1 - C_6 alkylamine(C_1 - C_6 alkyl) group, a di-arylamine(alkyl) group, a di- C_6 - C_{10} arylamine(C_1 - C_6 alkyl) group and the like. Examples of di-substituted amine(alkyl) groups include, but are not limited to, $-\text{CH}_2\text{N}(\text{methyl})_2$, $-\text{CH}_2\text{N}(\text{phenyl})(\text{methyl})$, $-\text{NCH}_2(\text{ethyl})(\text{methyl})$, $-\text{CH}_2\text{CH}_2\text{N}(\text{methyl})_2$, $-\text{CH}_2\text{CH}_2\text{N}(\text{phenyl})(\text{methyl})$, $-\text{NCH}_2\text{CH}_2(\text{ethyl})(\text{methyl})$ and the like.

[0084] Where the number of substituents is not specified (e.g. haloalkyl), there may be one or more substituents present. For example, “haloalkyl” may include one or more of the same or different halogens. As another example, “ C_1 - C_3 alkoxyphenyl” may include one or more of the same or different alkoxy groups containing one, two or three atoms.

[0085] As used herein, a radical indicates species with a single, unpaired electron such that the species containing the radical can be covalently bonded to another species. Hence, in this context, a radical is not necessarily a free radical. Rather, a radical indicates a specific portion of a larger molecule. The term “radical” can be used interchangeably with the term “group.”

[0086] The term “pharmaceutically acceptable salt” refers to a salt of a compound that does not cause significant irritation to an organism to which it is administered and does not abrogate the biological activity and properties of the compound. In some embodiments, the salt is an acid addition salt of the compound. Pharmaceutical salts can be obtained by

reacting a compound with inorganic acids such as hydrohalic acid (e.g., hydrochloric acid or hydrobromic acid), a sulfuric acid, a nitric acid and a phosphoric acid (such as 2,3-dihydroxypropyl dihydrogen phosphate). Pharmaceutical salts can also be obtained by reacting a compound with an organic acid such as aliphatic or aromatic carboxylic or sulfonic acids, for example formic, acetic, succinic, lactic, malic, tartaric, citric, ascorbic, nicotinic, methanesulfonic, ethanesulfonic, p-toluensulfonic, trifluoroacetic, benzoic, salicylic, 2-oxopentanedioic or naphthalenesulfonic acid. Pharmaceutical salts can also be obtained by reacting a compound with a base to form a salt such as an ammonium salt, an alkali metal salt, such as a sodium, a potassium or a lithium salt, an alkaline earth metal salt, such as a calcium or a magnesium salt, a salt of a carbonate, a salt of a bicarbonate, a salt of organic bases such as dicyclohexylamine, N-methyl-D-glucamine, tris(hydroxymethyl)methylamine, C₁-C₇ alkylamine, cyclohexylamine, triethanolamine, ethylenediamine and salts with amino acids such as arginine and lysine. For compounds of Formula (I), those skilled in the art understand that when a salt is formed by protonation of a nitrogen-based group (for example, NH₂), the nitrogen-based group can be associated with a positive charge (for example, NH₂ can become NH₃⁺) and the positive charge can be balanced by a negatively charged counterion (such as Cl⁻).

[0087] The term “Bcl protein inhibition” and similar terms refers to inhibiting the activity or function of a Bcl protein, e.g., by degrading the Bcl protein and/or by inhibiting the binding of an anti-apoptotic Bcl protein (such as Bcl-2, Bcl-X_L, Bcl-W, Mcl-1 and Bcl-2A1) to a pro-apoptotic Bcl protein (such as Bak, Bax, Bim, Bid, tBid, Bad, Bik, PUMA, Bnip-1, Hrk, Bmf and Noxa). Similarly, the term “Bcl protein inhibitor” refers to an agent (including small molecules and proteins) that inhibits the binding of an anti-apoptotic Bcl protein (such as Bcl-2, Bcl-X_L, Bcl-W, Mcl-1 and Bcl-2A1) to a pro-apoptotic Bcl protein (such as Bak, Bax, Bim, Bid, tBid, Bad, Bik, PUMA, Bnip-1, Hrk, Bmf and Noxa). In addition to its binding inhibition function, a Bcl protein inhibitor may also have the function of degrading the Bcl protein. Such a Bcl protein inhibitor may be referred to herein as a Bcl protein degrader, particularly when degradation is the predominant mechanism of Bcl protein inhibition. See, e.g., WO 2019/144117 (disclosing Bcl protein degraders that are bivalent compounds that connect a Bcl-2 small molecule inhibitor or ligand to an E3 ligase binding moiety). Bcl protein inhibitors include, but are not limited to venetoclax, navitoclax, obatoclax, S55746,

APG-2575, ABT-737, AMG176, AZD5991 and APG-1252. Additional Bcl protein inhibitors include, but are not limited to, compounds disclosed in PCT Application Publication Nos. WO 2017/132474, WO 2014/113413 and WO 2013/110890, U.S. Patent Application Publication No. 2015/0051189 and Chinese Patent Application No. CN 106565607, which are each incorporated herein by reference for the limited purpose of disclosing additional Bcl protein inhibitors. As will be understood by those of skill in the art, there are numerous methods of evaluating protein binding interactions, including, but not limited to co-immunoprecipitation, fluorescence resonance energy transfer (FRET), surface plasmon resonance (SPR) and fluorescence polarization/anisotropy.

[0088] It is understood that, in any compound described herein having one or more chiral centers, if an absolute stereochemistry is not expressly indicated, then each center may independently be of R-configuration or S-configuration or a mixture thereof. Thus, the compounds provided herein may be enantiomerically pure, enantiomerically enriched, racemic mixture, diastereomerically pure, diastereomerically enriched or a stereoisomeric mixture. In addition, it is understood that, in any compound described herein having one or more double bond(s) generating geometrical isomers that can be defined as E or Z, each double bond may independently be E or Z a mixture thereof. Likewise, it is understood that, in any compound described, all tautomeric forms are also intended to be included.

[0089] It is to be understood that where compounds disclosed herein have unfilled valencies, then the valencies are to be filled with hydrogens or isotopes thereof, e.g., hydrogen-1 (protium) and hydrogen-2 (deuterium).

[0090] It is understood that the compounds described herein can be labeled isotopically. Substitution with isotopes such as deuterium may afford certain therapeutic advantages resulting from greater metabolic stability, such as, for example, increased *in vivo* half-life or reduced dosage requirements. Each chemical element as represented in a compound structure may include any isotope of said element. For example, in a compound structure a hydrogen atom may be explicitly disclosed or understood to be present in the compound. At any position of the compound that a hydrogen atom may be present, the hydrogen atom can be any isotope of hydrogen, including but not limited to hydrogen-1

(protium) and hydrogen-2 (deuterium). Thus, reference herein to a compound encompasses all potential isotopic forms unless the context clearly dictates otherwise.

[0091] It is understood that the methods and combinations described herein include crystalline forms (also known as polymorphs, which include the different crystal packing arrangements of the same elemental composition of a compound), amorphous phases, salts, solvates and hydrates. In some embodiments, the compounds described herein exist in solvated forms with pharmaceutically acceptable solvents such as water, ethanol or the like. In other embodiments, the compounds described herein exist in unsolvated form. Solvates contain either stoichiometric or non-stoichiometric amounts of a solvent, and may be formed during the process of crystallization with pharmaceutically acceptable solvents such as water, ethanol or the like. Hydrates are formed when the solvent is water or alcoholates are formed when the solvent is alcohol. In addition, the compounds provided herein can exist in unsolvated as well as solvated forms. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the compounds and methods provided herein.

[0092] Where a range of values is provided, it is understood that the upper and lower limit, and each intervening value between the upper and lower limit of the range is encompassed within the embodiments.

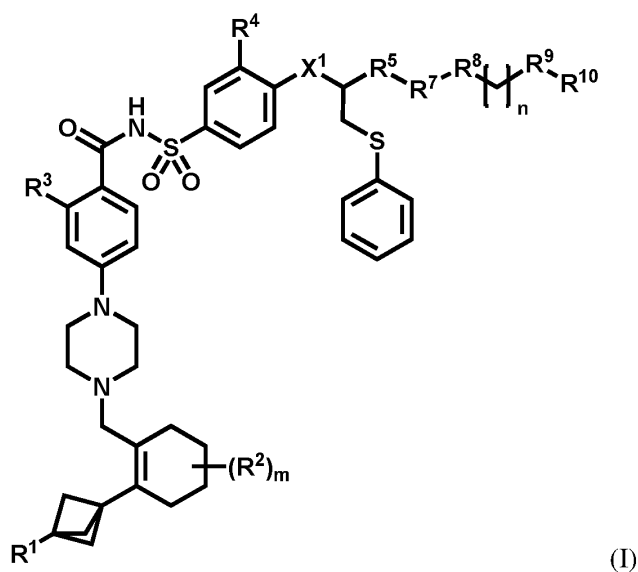
[0093] Terms and phrases used in this application, and variations thereof, especially in the appended claims, unless otherwise expressly stated, should be construed as open ended as opposed to limiting. As examples of the foregoing, the term 'including' should be read to mean 'including, without limitation,' 'including but not limited to,' or the like; the term 'comprising' as used herein is synonymous with 'including,' 'containing,' or 'characterized by,' and is inclusive or open-ended and does not exclude additional, unrecited elements or method steps; the term 'having' should be interpreted as 'having at least;' the term 'includes' should be interpreted as 'includes but is not limited to;' the term 'example' is used to provide exemplary instances of the item in discussion, not an exhaustive or limiting list thereof; and use of terms like 'preferably,' 'preferred,' 'desired,' or 'desirable,' and words of similar meaning should not be understood as implying that certain features are critical, essential, or even important to the structure or function, but instead as merely intended to highlight alternative or additional features that may or may not be utilized in a

particular embodiment. In addition, the term “comprising” is to be interpreted synonymously with the phrases “having at least” or “including at least”. When used in the context of a compound, composition or device, the term “comprising” means that the compound, composition or device includes at least the recited features or components, but may also include additional features or components.

[0094] With respect to the use of substantially any plural and/or singular terms herein, those having skill in the art can translate from the plural to the singular and/or from the singular to the plural as is appropriate to the context and/or application. The various singular/plural permutations may be expressly set forth herein for sake of clarity. The indefinite article “a” or “an” does not exclude a plurality. The mere fact that certain measures are recited in mutually different dependent claims does not indicate that a combination of these measures cannot be used to advantage. Any reference signs in the claims should not be construed as limiting the scope.

Compounds

[0095] Some embodiments disclosed herein relate to a compound of Formula (I), or a pharmaceutically acceptable salt thereof, having the structure:



[0096] In various embodiments, the variables in Formula (I) are defined as follows:

[0097] R^1 can be selected from hydrogen, halogen, a substituted or unsubstituted C_1 - C_6 alkyl, a substituted or unsubstituted C_1 - C_6 haloalkyl, a substituted or unsubstituted C_3 - C_6 cycloalkyl, a substituted or unsubstituted C_1 - C_6 alkoxy, an unsubstituted mono- C_1 - C_6 alkylamine and an unsubstituted di- C_1 - C_6 alkylamine.

[0098] Each R^2 can be independently selected from a halogen, a substituted or unsubstituted C_1 - C_6 alkyl, a substituted or unsubstituted C_1 - C_6 haloalkyl and a substituted or unsubstituted C_3 - C_6 cycloalkyl; or when m is 2 or 3, each R^2 can be independently selected from a halogen, a substituted or unsubstituted C_1 - C_6 alkyl, a substituted or unsubstituted C_1 - C_6 haloalkyl and a substituted or unsubstituted C_3 - C_6 cycloalkyl, or two R^2 groups taken together with the atom(s) to which they are attached can form a substituted or unsubstituted C_3 - C_6 cycloalkyl or a substituted or unsubstituted 3 to 6 membered heterocyclyl.

[0099] R^3 can be hydrogen or halogen.

[0100] R^4 can be selected from NO_2 , $S(O)R^6$, SO_2R^6 , halogen, cyano and an unsubstituted C_1 - C_6 haloalkyl.

[0101] R^5 can be a substituted or unsubstituted C_1 - C_6 alkylene, a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-Het-$, a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-O-$, a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-NH-$, a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-NH-Het-$, a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-N(C_1-C_6 \text{ alkyl})-Het-$, a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-Het-O-$, a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-Het-NH-$, a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-N(C_1-C_6 \text{ alkyl})-$, a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-Het-N(C_1-C_6 \text{ alkyl})-$, a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-(C=O)-O-$, a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-Het-(C=O)-O-$, a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-Het-(C=O)-NH-$, a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-Het-(C=O)-N(C_1-C_6 \text{ alkyl})-$, a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-Het-(C=O)-N(C_3-C_6 \text{ cycloalkyl})-$, a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-N(C_3-C_6 \text{ cycloalkyl})-$, a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-Het-N(C_3-C_6 \text{ cycloalkyl})-$ or a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-N(C_3-C_6 \text{ cycloalkyl})-Het-$, where Het is a substituted or unsubstituted 3 to 10 membered heterocyclyl.

[0102] R^6 can be a substituted or unsubstituted C_1 - C_6 alkyl, a substituted or unsubstituted C_1 - C_6 haloalkyl or a substituted or unsubstituted C_3 - C_6 cycloalkyl.

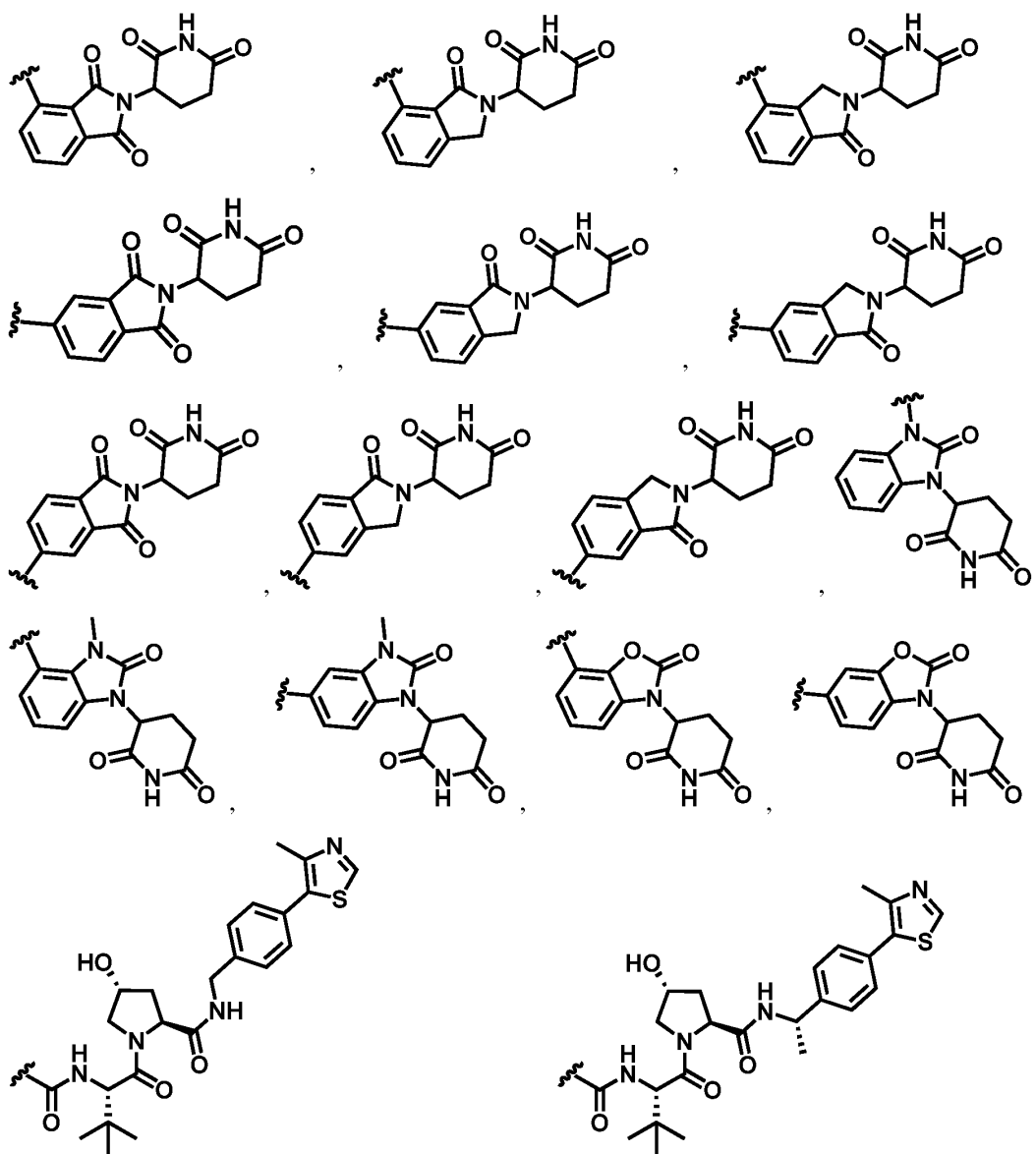
[0103] R^7 can be absent, a substituted or unsubstituted C_1 - C_6 alkylene, $-(C=O)-$, $-(C=S)-$, $-(C=O)-NH-$, $-(C=O)-N(C_1-C_6 \text{ alkyl})-$, $-(C=O)-N(C_3-C_6 \text{ cycloalkyl})-$, $-(C=O)-O-$, $-(C=S)-NH-$ or a substituted or unsubstituted $(C_1-C_6 \text{ alkylene})-NH-$.

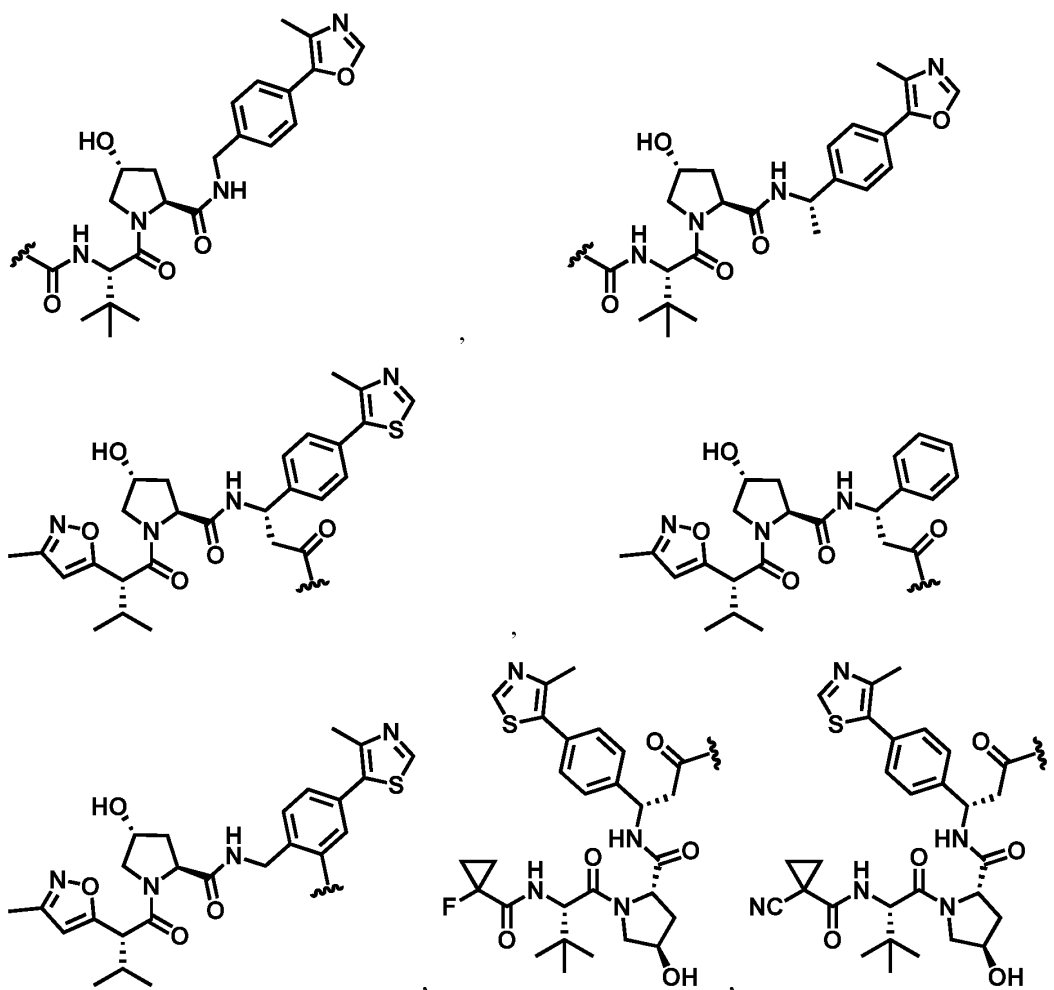
[0104] R^8 can be absent, a substituted or unsubstituted C_1 - C_6 alkylene, a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-(C_6-C_{12} \text{ aryl})-$, a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-(C_3-C_{10} \text{ cycloalkyl})-$, a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-(C_3-C_{10} \text{ heterocyclyl})-$ or a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-(5 \text{ to } 10 \text{ membered heteroaryl})-$.

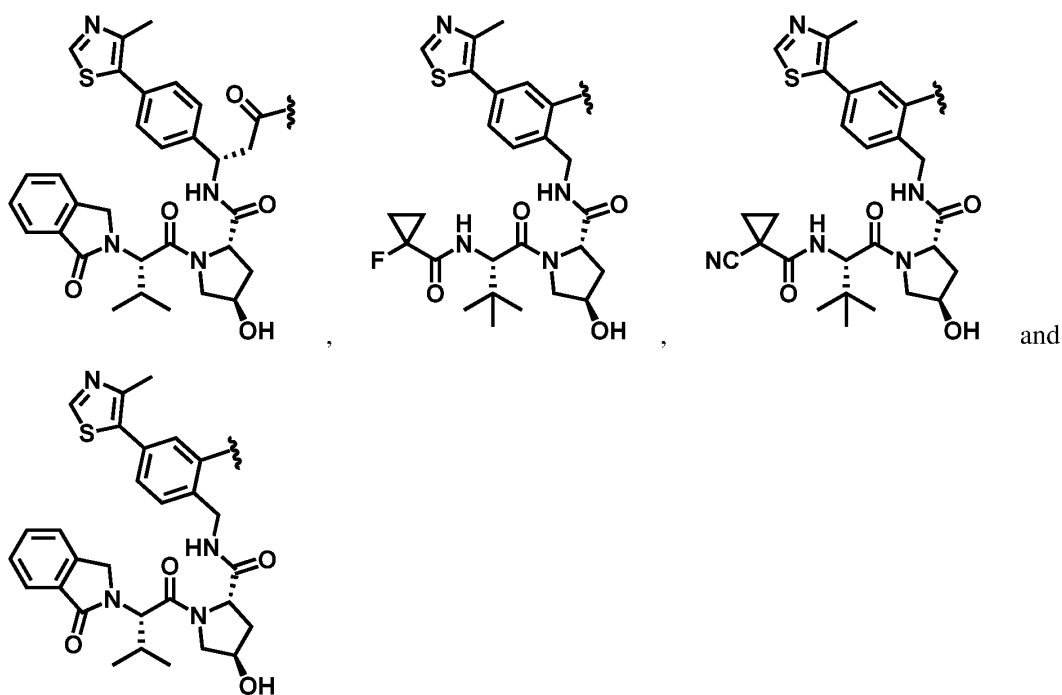
[0105] X^1 can be $-O-$ or $-NH-$; m can be 0, 1, 2 or 3; and n can be 0, 1, 2, 3, 4 or 5.

[0106] R^9 can be a substituted or unsubstituted C_1 - C_{10} alkylene, a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-O-$, a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-NH-$, a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-NH-(C_1-C_6 \text{ alkylene})-$, a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-(C=O)NH-$, a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-NH-(C_1-C_6 \text{ alkylene})-NH-$, a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-NH-(C_1-C_6 \text{ alkylene})-O-$, a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-NH(C=O)-(C_1-C_6 \text{ alkylene})-NH-$, a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-NH(C=O)-(C_1-C_6 \text{ alkylene})-O-$, a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-NH(C=O)-(C_1-C_6 \text{ alkylene})-$, a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-NH-(C_1-C_6 \text{ alkylene})-NH(C=O)-(C_1-C_6 \text{ alkylene})-NH-$, a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-NH-(C_1-C_6 \text{ alkylene})-NH(C=O)-(C_1-C_6 \text{ alkylene})-O-$, a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-NH-(C_1-C_6 \text{ alkylene})-NH(C=O)-(C_1-C_6 \text{ alkylene})-$, a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-(C=O)NH-(C_1-C_6 \text{ alkylene})-NH-$, a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-(C=O)NH-(C_1-C_6 \text{ alkylene})-O-$, a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-NH(C=O)-(C_1-C_6 \text{ alkylene})-(C=O)NH-$, a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-NH-(C_1-C_6 \text{ alkylene})-(C=O)NH-$, a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-NH-(C_1-C_6 \text{ alkylene})-(C=O)NH-(C_1-C_6 \text{ alkylene})-$ or a substituted or an unsubstituted $-(C_1-C_6 \text{ alkylene})-C\equiv C-$.

[0107] R^{10} can be selected from the following:







[0108] In some embodiments, R^1 can be halogen, for example, fluoro, chloro, bromo or iodo. In some embodiments, R^1 can be fluoro. In some embodiments, R^1 can be chloro. In some embodiments, R^1 can be hydrogen.

[0109] In some embodiments, R^1 can be a substituted or unsubstituted C_1 - C_6 alkyl. For example, in some embodiments, R^1 can be a substituted C_1 - C_6 alkyl. In other embodiments, R^1 can be an unsubstituted C_1 - C_6 alkyl. Examples of suitable C_1 - C_6 alkyl groups include, but are not limited to methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, pentyl (branched and straight-chained) and hexyl (branched and straight-chained). In some embodiments, R^1 can be an unsubstituted methyl or an unsubstituted ethyl.

[0110] In some embodiments, R^1 can be a substituted or unsubstituted C_1 - C_6 haloalkyl, for example, a substituted or unsubstituted mono-halo C_1 - C_6 alkyl, a substituted or unsubstituted di-halo C_1 - C_6 alkyl, a substituted or unsubstituted tri-halo C_1 - C_6 alkyl, a substituted or unsubstituted tetra-halo C_1 - C_6 alkyl or a substituted or unsubstituted penta-halo C_1 - C_6 alkyl. In some embodiments, R^1 can be an unsubstituted $-CHF_2$, $-CF_3$, $-CH_2CF_3$, $-CF_2CF_3$ or $-CF_2CH_3$. In some embodiments, R^1 is $-CH_2F$, $-CHF_2$ or $-CF_3$.

[0111] In some embodiments, R^1 can be a substituted or unsubstituted monocyclic or bicyclic C_3 - C_6 cycloalkyl. For example, in some embodiments, R^1 can be a

substituted monocyclic C₃-C₆ cycloalkyl. In other embodiments, R¹ can be an unsubstituted monocyclic C₃-C₆ cycloalkyl. Examples of suitable monocyclic or bicyclic C₃-C₆ cycloalkyl groups include, but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, [1.1.1]bicyclopentyl and cyclohexyl.

[0112] In some embodiments, R¹ can be a substituted or unsubstituted C₁-C₆ alkoxy. For example, in some embodiments, R¹ can be a substituted C₁-C₆ alkoxy. In other embodiments, R¹ can be an unsubstituted C₁-C₆ alkoxy. Examples of suitable C₁-C₆ alkoxy groups include, but are not limited to methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, tert-butoxy, pentoxy (branched and straight-chained) and hexoxy (branched and straight-chained). In some embodiments, R¹ can be an unsubstituted methoxy or an unsubstituted ethoxy.

[0113] In some embodiments, R¹ can be an unsubstituted mono-C₁-C₆ alkylamine, for example, methylamine, ethylamine, n-propylamine, isopropylamine, n-butylamine, isobutylamine, tert-butylamine, pentylamine (branched and straight-chained) and hexylamine (branched and straight-chained). In some embodiments, R¹ can be methylamine or ethylamine.

[0114] In some embodiments, R¹ can be an unsubstituted di-C₁-C₆ alkylamine. In some embodiments, each C₁-C₆ alkyl in the di-C₁-C₆ alkylamine is the same. In other embodiments, each C₁-C₆ alkyl in the di-C₁-C₆ alkylamine is different. Examples of suitable di-C₁-C₆ alkylamine groups include, but are not limited to di-methylamine, di-ethylamine, (methyl)(ethyl)amine, (methyl)(isopropyl)amine and (ethyl)(isopropyl)amine.

[0115] In some embodiments, m can be 0. When m is 0, those skilled in the art understand that the ring to which R² is attached is unsubstituted. In some embodiments, m can be 1. In some embodiments, m can be 2. In some embodiments, m can be 3.

[0116] In some embodiments, one R² can be an unsubstituted C₁-C₆ alkyl (for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, pentyl (branched and straight-chained) and hexyl (branched and straight-chained) and any other R², if present, can be independently selected from halogen (for example, fluoro or chloro), a substituted or unsubstituted C₁-C₆ alkyl (such as those described herein), a substituted or unsubstituted C₁-C₆ haloalkyl (such as those described herein) and a substituted or unsubstituted monocyclic or bicyclic C₃-C₆ cycloalkyl (such as those described herein). In some embodiments, each R²

can be independently selected from an unsubstituted C₁-C₆ alkyl, such as those described herein.

[0117] In some embodiments, m can be 2; and each R² can be geminal. In some embodiments, m can be 2; and each R² can be vicinal. In some embodiments, m can be 2; and each R² can be an unsubstituted methyl. In some embodiments, m can be 2; and each R² can be a geminal unsubstituted methyl.

[0118] In some embodiments, two R² groups can be taken together with the atom(s) to which they are attached to form a substituted or unsubstituted monocyclic C₃-C₆ cycloalkyl. For example, in some embodiments, two R² groups can be taken together with the atom(s) to which they are attached to form a substituted monocyclic C₃-C₆ cycloalkyl, such as those described herein. In other embodiments, two R² groups can be taken together with the atom(s) to which they are attached to form an unsubstituted monocyclic C₃-C₆ cycloalkyl, such as those described herein. In some embodiments, two R² groups can be taken together with the atom to which they are attached to form an unsubstituted cyclopropyl. In some embodiments, two R² groups can be taken together with the atom to which they are attached to form an unsubstituted cyclobutyl.

[0119] In some embodiments, two R² groups can be taken together with the atom(s) to which they are attached to form a substituted or unsubstituted monocyclic 3 to 6 membered heterocyclyl. For example, in some embodiments, two R² groups can be taken together with the atom(s) to which they are attached to form a substituted monocyclic 3 to 6 membered heterocyclyl. In other embodiments, two R² groups can be taken together with the atom(s) to which they are attached to form an unsubstituted monocyclic 3 to 6 membered monocyclic heterocyclyl. In some embodiments, the substituted monocyclic 3 to 6 membered heterocyclyl can be substituted on one or more nitrogen atoms. Examples of suitable substituted or unsubstituted monocyclic 3 to 6 membered heterocyclyl groups include, but are not limited to aziridine, oxirane, azetidine, oxetane, pyrrolidine, tetrahydrofuran, imidazoline, pyrazolidine, piperidine, tetrahydropyran, piperazine, morpholine, thiomorpholine and dioxane.

[0120] In some embodiments, R³ can be hydrogen. In some embodiments, R³ can be halogen. In some embodiments, R³ can be fluoro or chloro.

[0121] In some embodiments, R^4 can be NO_2 . In some embodiments, R^4 can be cyano. In some embodiments, R^4 can be halogen.

[0122] In some embodiments, R^4 can be an unsubstituted $\text{C}_1\text{-C}_6$ haloalkyl, such as those described herein. In some embodiments, R^4 can be $-\text{CF}_3$.

[0123] In some embodiments, R^4 can be $\text{S(O)}R^6$. In some embodiments, R^4 can be SO_2R^6 . In some embodiments, R^4 can be SO_2CF_3 .

[0124] In some embodiments, R^6 can be a substituted or unsubstituted $\text{C}_1\text{-C}_6$ alkyl. For example, in some embodiments, R^6 can be a substituted $\text{C}_1\text{-C}_6$ alkyl, such as those described herein. In other embodiments, R^6 can be an unsubstituted $\text{C}_1\text{-C}_6$ alkyl, such as those described herein.

[0125] In some embodiments, R^6 can be a substituted or unsubstituted monocyclic or bicyclic $\text{C}_3\text{-C}_6$ cycloalkyl. For example, in some embodiments, R^6 can be a substituted monocyclic or bicyclic $\text{C}_3\text{-C}_6$ cycloalkyl. In other embodiments, R^6 can be an unsubstituted monocyclic or bicyclic $\text{C}_3\text{-C}_6$ cycloalkyl. Examples of suitable monocyclic or bicyclic $\text{C}_3\text{-C}_6$ cycloalkyl groups include, but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, [1.1.1]bicyclopentyl and cyclohexyl.

[0126] In some embodiments, R^6 can be a substituted or unsubstituted $\text{C}_1\text{-C}_6$ haloalkyl, such as those described herein. In some embodiments, R^6 can be $-\text{CF}_3$.

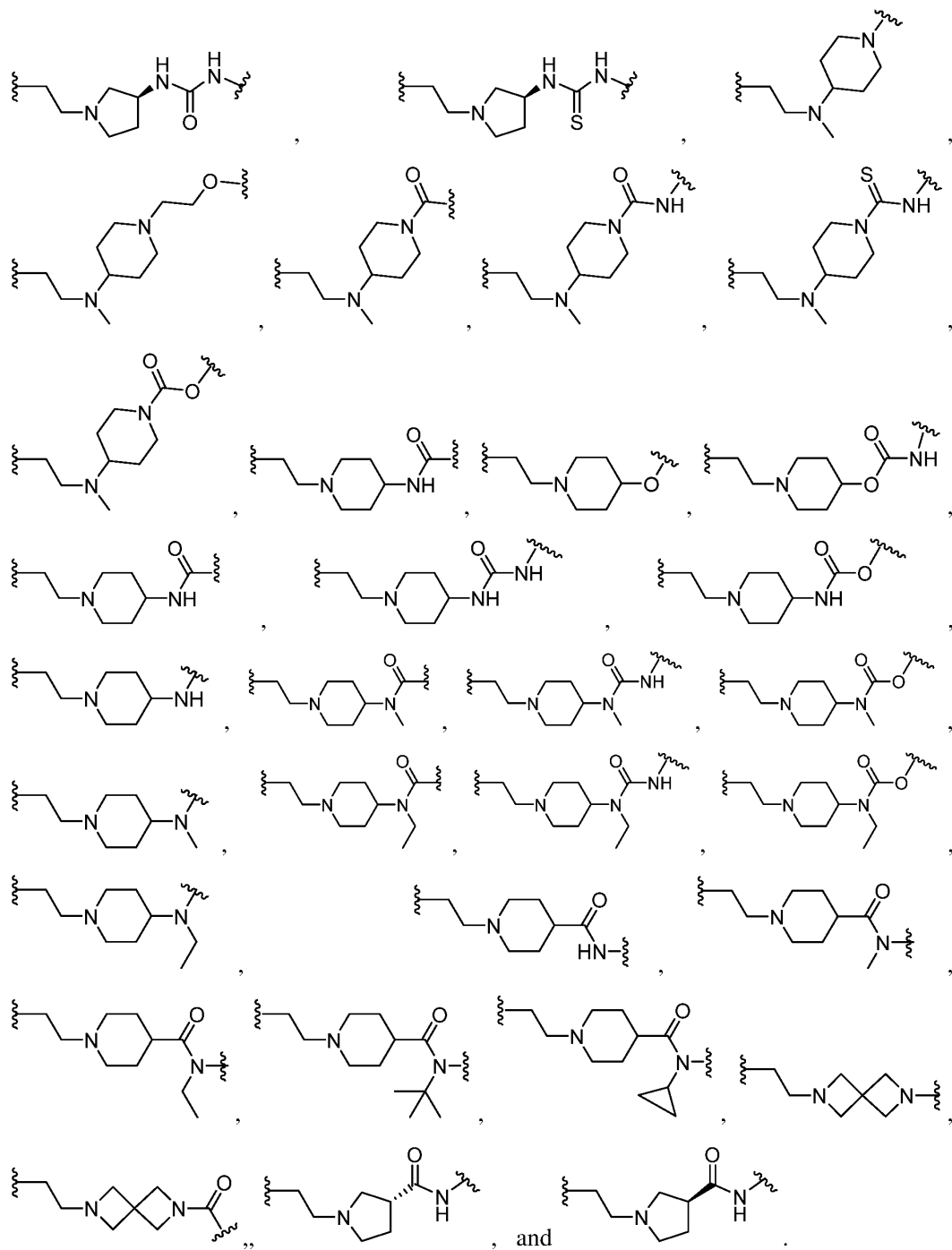
[0127] In some embodiments, R^5 can be a substituted or unsubstituted $\text{C}_1\text{-C}_6$ alkylene. For example, in some embodiments R^5 can be a $-(\text{CH}_2)_{p1}-$ group, where $p1$ is 1, 2, 3, 4, 5 or 6. In some embodiments, R^5 can be a substituted or unsubstituted $-(\text{C}_1\text{-C}_6 \text{ alkylene})\text{-Het-}$, where Het is a substituted or unsubstituted 3 to 10 membered heterocyclyl. For example, in some embodiments R^5 can be a $-(\text{CH}_2)_p\text{-Het}$ group, where p is 1, 2, 3, 4, 5 or 6. Examples of suitable Het groups include 4 to 6 membered heterocyclyl groups such as azetidiny, pyrrolidiny, piperidiny or piperazinyl. In some embodiments, R^5 can be a substituted or unsubstituted $-(\text{C}_1\text{-C}_6 \text{ alkylene})\text{-O-}$ or a substituted or unsubstituted $\text{C}_6 \text{ alkylene})\text{-Het-O-}$. For example, in some embodiments R^5 can be a $-(\text{CH}_2)_{p1}\text{-O-}$ group or a $-(\text{CH}_2)_{p1}\text{-Het-O-}$ group, where $p1$ is 1, 2, 3, 4, 5 or 6. In some embodiments, R^5 can be a substituted or unsubstituted $-(\text{C}_1\text{-C}_6 \text{ alkylene})\text{-NH-}$ or a substituted or unsubstituted $-(\text{C}_1\text{-C}_6 \text{ alkylene})\text{-Het-NH-}$. For example, in some embodiments R^5 can be a $-(\text{CH}_2)_{p1}\text{-NH-}$ group or a $-(\text{CH}_2)_{p1}\text{-Het-NH-}$ group, where $p1$ is 1, 2, 3, 4, 5 or 6. In some embodiments, R^5 can be a

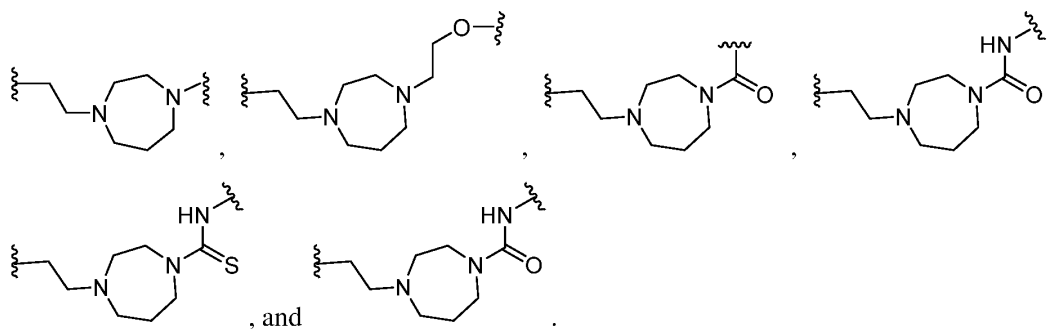
substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-NH-Het-$ or a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-N(C_1-C_6 \text{ alkyl})-Het-$. For example, in some embodiments R^5 can be a $-(CH_2)_{p1}-NH-Het-$ group or a $-(CH_2)_{p1}-N(C_1-C_6 \text{ alkyl})-Het-$ group, where $p1$ is 1, 2, 3, 4, 5 or 6. In some embodiments, R^5 can be a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-N(C_1-C_6 \text{ alkyl})-$ or a substituted or unsubstituted $(C_1-C_6 \text{ alkylene})-Het-N(C_1-C_6 \text{ alkyl})-$. For example, in some embodiments R^5 can be a $-(CH_2)_{p1}-N(C_1-C_6 \text{ alkyl})-$ group or a $-(CH_2)_{p1}-Het-N(C_1-C_6 \text{ alkyl})-$ group, where $p1$ is 1, 2, 3, 4, 5 or 6. In some embodiments, R^5 can be a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-(C=O)-O-$ or a substituted or unsubstituted $(C_1-C_6 \text{ alkylene})-Het-(C=O)-O-$. For example, in some embodiments R^5 can be a $-(CH_2)_{p1}-(C=O)-O-$ or $-(CH_2)_{p1}-Het-(C=O)-O-$ group, where $p1$ is 1, 2, 3, 4, 5 or 6. In some embodiments, R^5 can be a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-Het-(C=O)-NH-$ or a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-Het-(C=O)-N(C_1-C_6 \text{ alkyl})-$. For example, in some embodiments R^5 can be a $-(CH_2)_{p1}-Het-(C=O)-NH-$ or $-(CH_2)_{p1}-Het-(C=O)-N(C_1-C_6 \text{ alkyl})-$ group, where $p1$ is 1, 2, 3, 4, 5 or 6. In some embodiments, R^5 can be a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-Het-(C=O)-N(C_3-C_6 \text{ cycloalkyl})-$ or a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-N(C_3-C_6 \text{ cycloalkyl})-$. For example, in some embodiments R^5 can be a $-(CH_2)_{p1}-Het-(C=O)-N(C_3-C_6 \text{ cycloalkyl})-$ or $-(CH_2)_{p1}-N(C_3-C_6 \text{ cycloalkyl})-$ group, where $p1$ is 1, 2, 3, 4, 5 or 6. In some embodiments, R^5 can be a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-Het-N(C_3-C_6 \text{ cycloalkyl})-$ or a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-N(C_3-C_6 \text{ cycloalkyl})-Het-$. For example, in some embodiments R^5 can be a $-(CH_2)_{p1}-Het-N(C_3-C_6 \text{ cycloalkyl})-$ or $-(CH_2)_{p1}-N(C_3-C_6 \text{ cycloalkyl})-Het-$ group, where $p1$ is 1, 2, 3, 4, 5 or 6.

[0128] In some embodiments, R^7 can be absent, in which case R^5 can be joined directly to R^8 , or if R^8 is absent, directly to the next atom adjoining R^8 . In other embodiments, R^7 can be a substituted or unsubstituted C_1-C_6 alkylene. For example, in some embodiments R^7 can be a $-(CH_2)_{p1}-$ group, where $p1$ is 1, 2, 3, 4, 5 or 6. In other embodiments, R^7 can be $-(C=O)-$, $-(C=S)-$, $-(C=O)-NH-$, $-(C=O)-N(C_3-C_6 \text{ cycloalkyl})-$, $-(C=O)-N(C_1-C_6 \text{ alkyl})-$, $-(C=O)-O-$ or $-(C=S)-NH-$. In other embodiments, R^7 can be a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-NH-$. For example, R^7 can be $-(CH_2)_{p1}-NH-$, where $p1$ is 1, 2, 3, 4, 5 or 6.

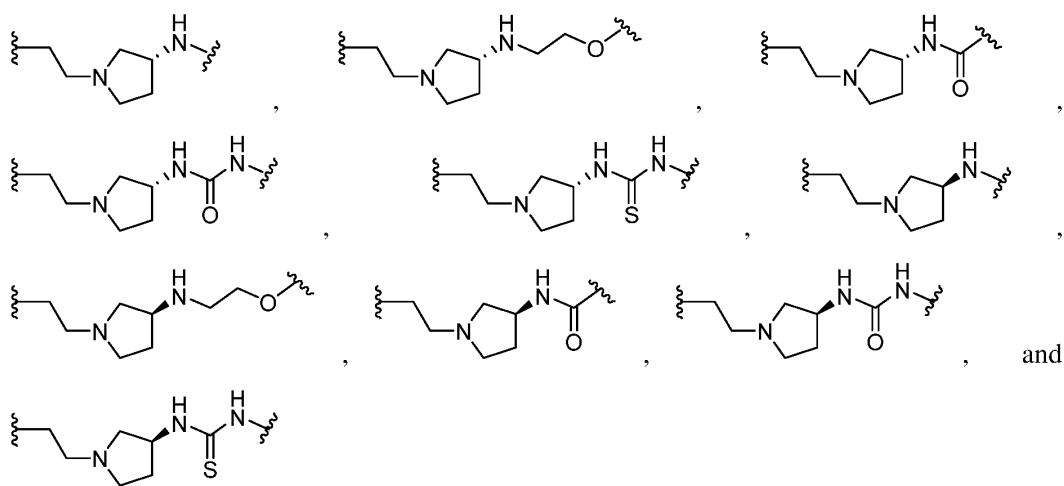
[0129] In various embodiments, R^5 and R^7 are selected together such that $-R^5-R^7-$

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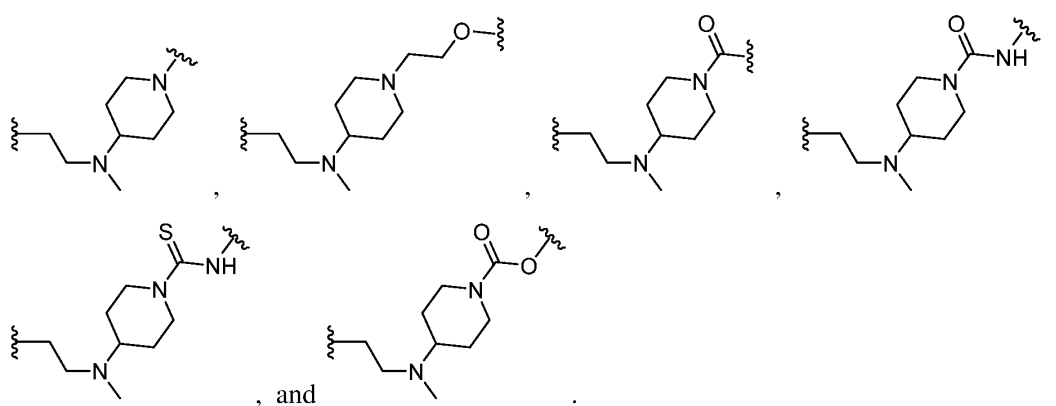




[0134] In other embodiments, R^5 and R^7 are selected together such that $-R^5-R^7-$ is selected from:



[0135] In other embodiments, R^5 and R^7 are selected together such that $-R^5-R^7-$ is selected from:



heteroaryl)–. For example, R^8 can be a substituted or unsubstituted $-(CH_2)_{p1}-(C_6-C_{12} \text{ aryl})-$, a substituted or unsubstituted $-(CH_2)_{p1}-(C_3-C_{10} \text{ cycloalkyl})-$, a substituted or unsubstituted $-(CH_2)_{p1}-(C_3-C_{10} \text{ heterocyclyl})-$ or a substituted or unsubstituted $-(CH_2)_{p1}-(5 \text{ to } 10 \text{ membered heteroaryl})-$, where $p1$ is 1, 2, 3, 4, 5 or 6.

[0139] In various embodiments, X^1 can be $-O-$. In other embodiments, X^1 can be $-NH-$.

[0140] In some embodiments, n is zero, in which case the ethyleneoxy group of the formula $-(CH_2CH_2O)_n-$ in Formula (I) is absent and the R^9 group is joined directly to the oxygen atom adjoining the ethyleneoxy group. In other embodiments, n is 1, 2, 3, 4 or 5, in which case the ethyleneoxy group of the formula $-(CH_2CH_2O)_n-$ in Formula (I) is present.

[0141] In various embodiments, R^9 can be a substituted or unsubstituted C_1-C_{10} alkylene, a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-O-$, a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-NH-$, a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-NH-(C_1-C_6 \text{ alkylene})-$, a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-(C=O)NH-$, a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-NH-(C_1-C_6 \text{ alkylene})-NH-$, a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-NH-(C_1-C_6 \text{ alkylene})-O-$, a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-NH(C=O)-(C_1-C_6 \text{ alkylene})-NH-$, a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-NH(C=O)-(C_1-C_6 \text{ alkylene})-O-$, a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-NH(C=O)-(C_1-C_6 \text{ alkylene})-NH(C=O)-(C_1-C_6 \text{ alkylene})-O-$, a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-NH(C=O)-(C_1-C_6 \text{ alkylene})-NH(C=O)-(C_1-C_6 \text{ alkylene})-$, a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-NH(C=O)-(C_1-C_6 \text{ alkylene})-O-$, a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-NH(C=O)-(C_1-C_6 \text{ alkylene})-NH(C=O)-(C_1-C_6 \text{ alkylene})-$, a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-(C=O)NH-(C_1-C_6 \text{ alkylene})-$, a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-(C=O)NH-(C_1-C_6 \text{ alkylene})-NH-$ or a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-(C=O)NH-(C_1-C_6 \text{ alkylene})-O-$, a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-NH(C=O)-(C_1-C_6 \text{ alkylene})-(C=O)NH-$, a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-NH-(C_1-C_6 \text{ alkylene})-(C=O)NH-$, a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-NH-(C_1-C_6 \text{ alkylene})-(C=O)NH-(C_1-C_6 \text{ alkylene})-$ or a substituted or an unsubstituted $-(C_1-C_6 \text{ alkylene})-C\equiv C-$.

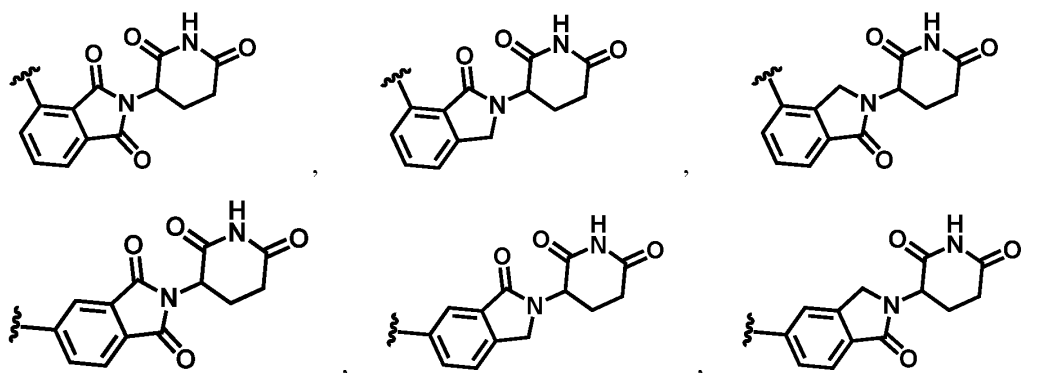
[0142] For example, in various embodiments R^9 can be a substituted or unsubstituted C_1-C_{10} alkylene, a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-O-$, a

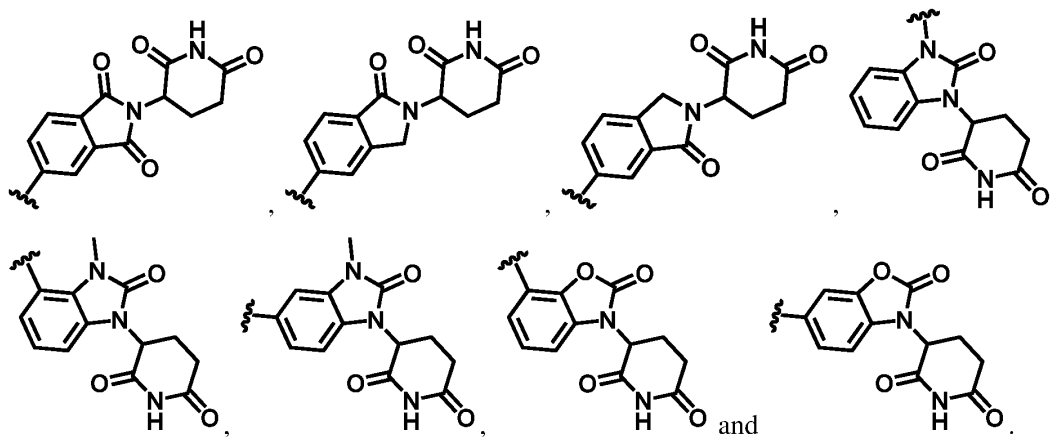
substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-NH-$, a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-NH-(C_1-C_6 \text{ alkylene})-$ or a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-(C=O)NH-$. In other embodiments R^9 can be a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-NH-(C_1-C_6 \text{ alkylene})-NH-$, a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-NH-(C_1-C_6 \text{ alkylene})-O-$, a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-NH(C=O)-(C_1-C_6 \text{ alkylene})-NH-$, a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-NH(C=O)-(C_1-C_6 \text{ alkylene})-O-$ or a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-NH(C=O)-(C_1-C_6 \text{ alkylene})-$.

[0143] In other embodiments R^9 can be a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-NH-(C_1-C_6 \text{ alkylene})-NH(C=O)-(C_1-C_6 \text{ alkylene})-NH-$, a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-NH-(C_1-C_6 \text{ alkylene})-NH(C=O)-(C_1-C_6 \text{ alkylene})-O-$, a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-NH-(C_1-C_6 \text{ alkylene})-NH(C=O)-(C_1-C_6 \text{ alkylene})-$, a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-(C=O)NH-(C_1-C_6 \text{ alkylene})-$, a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-(C=O)NH-(C_1-C_6 \text{ alkylene})-NH-$, a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-(C=O)NH-(C_1-C_6 \text{ alkylene})-O-$, a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-NH(C=O)-(C_1-C_6 \text{ alkylene})-(C=O)NH-$, a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-NH-(C_1-C_6 \text{ alkylene})-(C=O)NH-$, a substituted or unsubstituted $-(C_1-C_6 \text{ alkylene})-NH-(C_1-C_6 \text{ alkylene})-(C=O)NH-(C_1-C_6 \text{ alkylene})-$ or a substituted or an unsubstituted $-(C_1-C_6 \text{ alkylene})-C\equiv C-$.

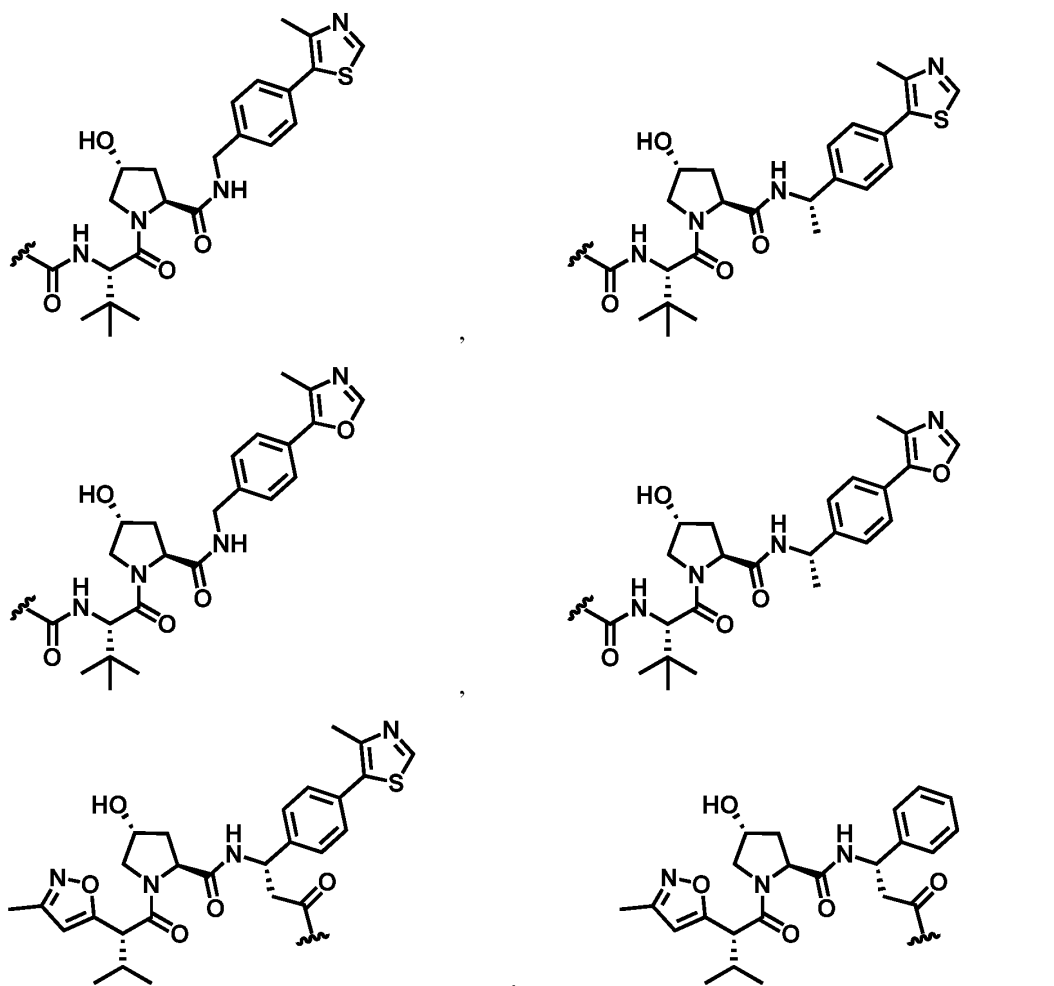
[0144] In various embodiments variables are described herein, such as R^9 , that contain a C_1-C_6 alkylene group or a group containing one or more C_1-C_6 alkylene groups. Such C_1-C_6 alkylene groups as described herein can be a $-(CH_2)_{p1}-$ group, where $p1$ is 1, 2, 3, 4, 5 or 6.

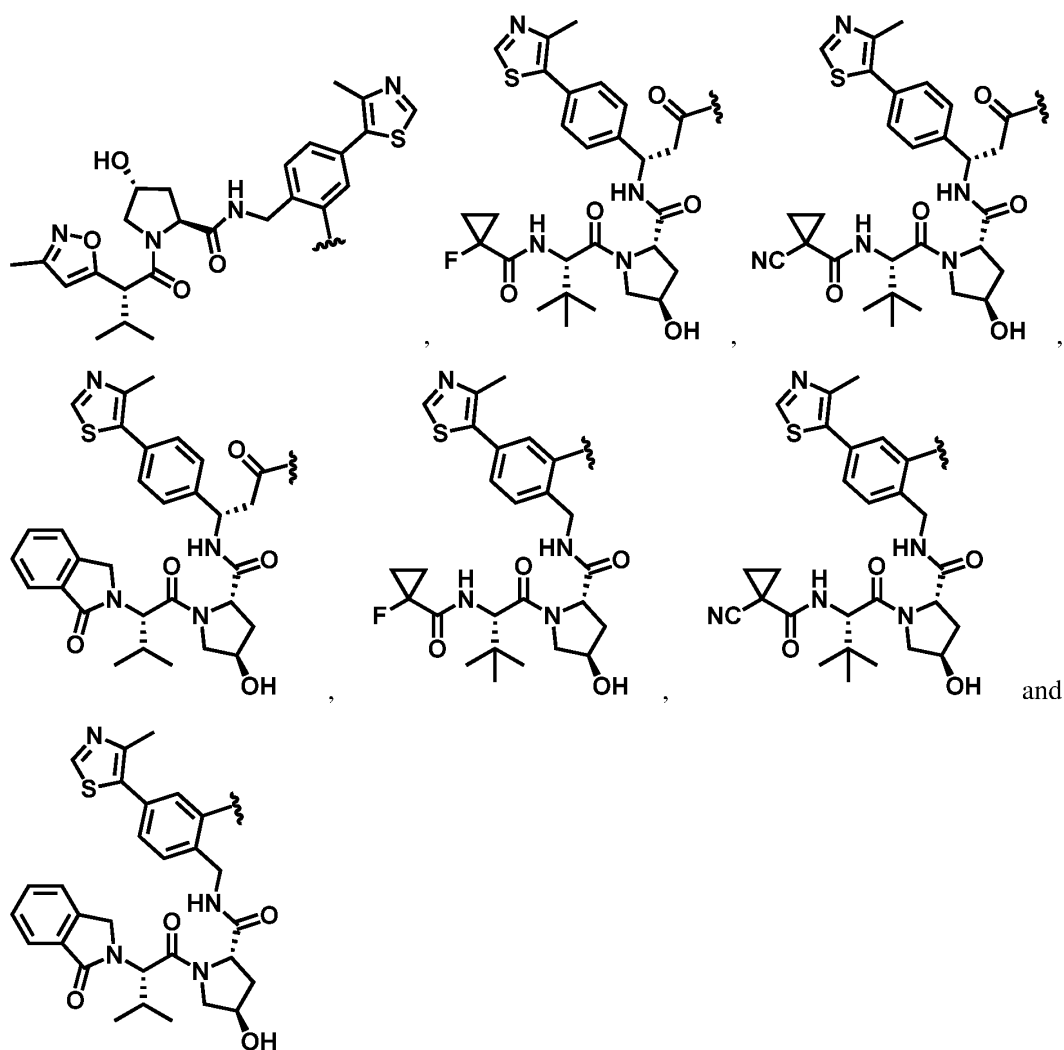
[0145] In various embodiments, R^{10} can be a group selected from





[0146] In other embodiments, R^{10} can be a group selected from





[0147] In various embodiments, compounds of the Formula (I) are selected from those described in the claims below.

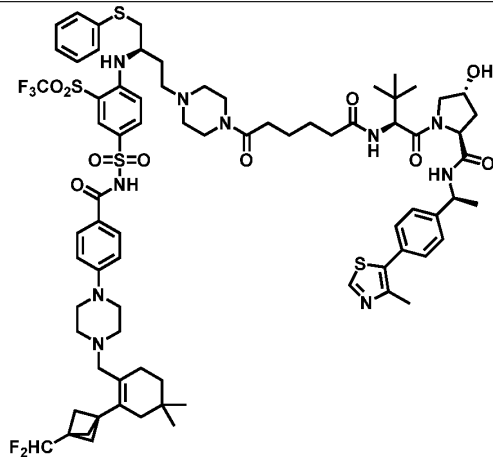
Synthesis

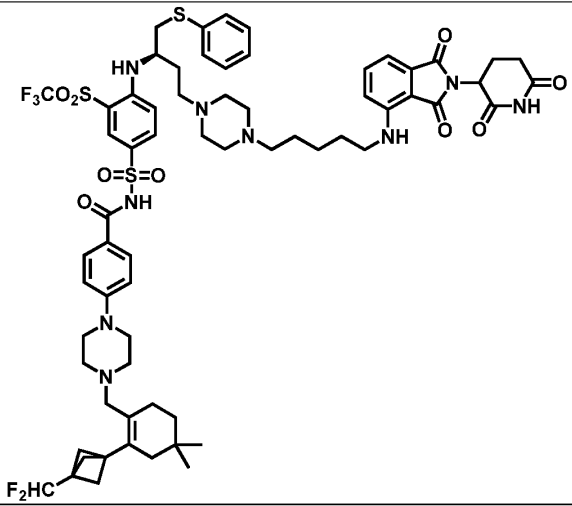
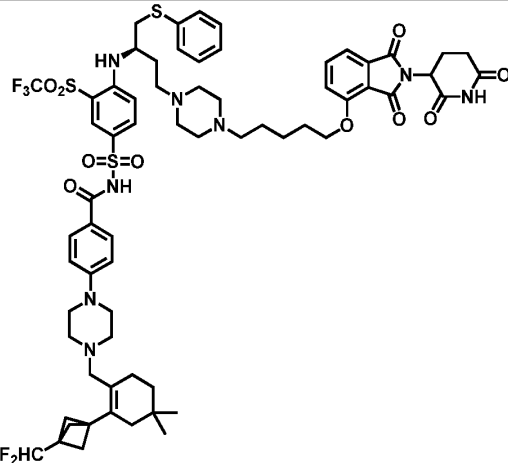
[0148] Compounds of the Formula (I), or pharmaceutically acceptable salts thereof, can be made in various ways by those skilled using known techniques as guided by the detailed teachings provided herein, including the Examples provided below. For example, in an embodiment, compounds of the Formula (I) are prepared in accordance with the general scheme illustrated in FIG 1. Embodiments of compounds of the Formula (I) can be prepared

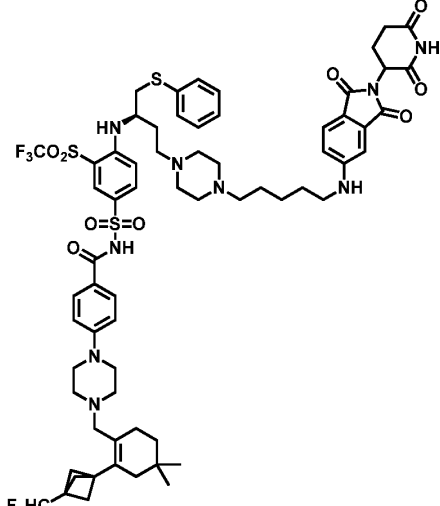
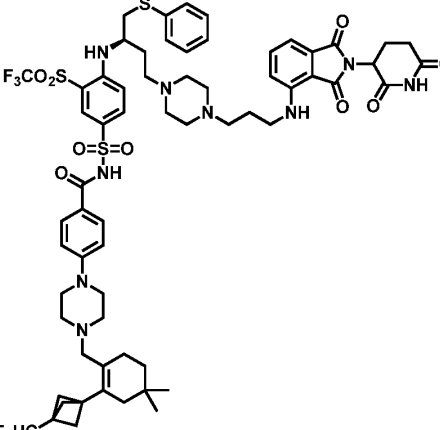
in as illustrated in FIGS. 2, 3, 4, 5 and 6. Any preliminary reaction steps required to form starting compounds or other precursors, can be carried out by those skilled in the art. In FIGS. 1-6, the variables R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , X^1 , m and n can be as described elsewhere herein, taking into consideration the synthetic conversions involved as understood by those of skill in the art. R^{5a} and R^{7a} are understood by those of skill in the art to be synthetic precursors of R^5 and R^7 , respectively, as further illustrated in the Examples below. The descriptions of the various chemical groups that can be represented by R^{5a} and R^{7a} are generally the same as for R^5 and R^7 , respectively, as described elsewhere herein.

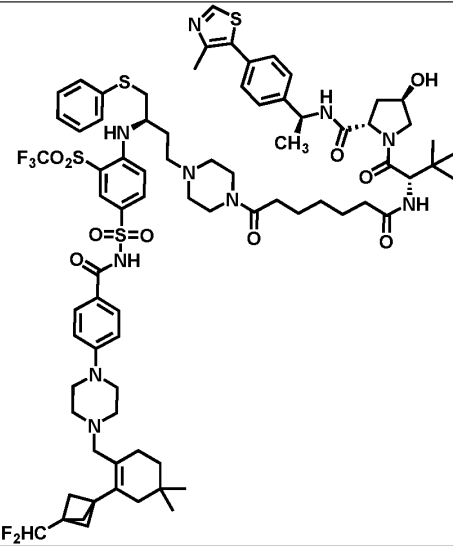
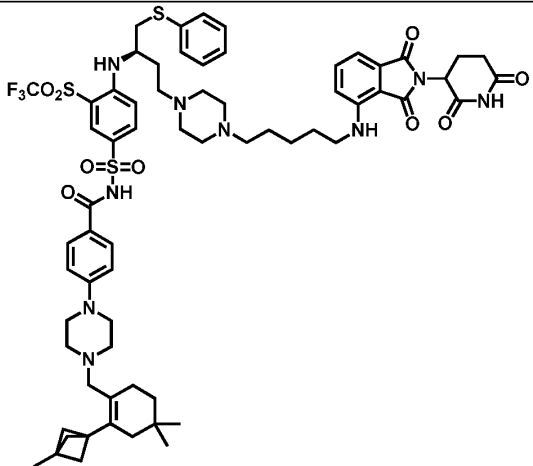
[0149] Examples of compounds of the Formula (I) are described in Table A below.

TABLE A

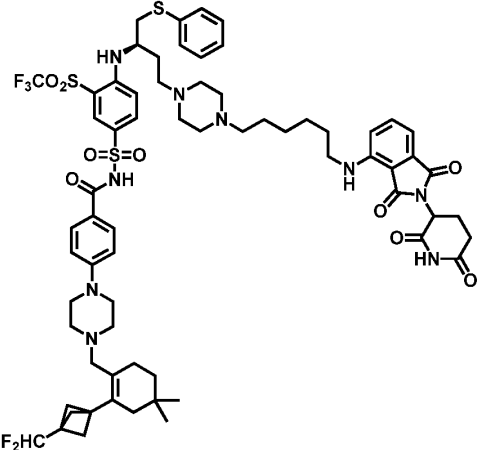
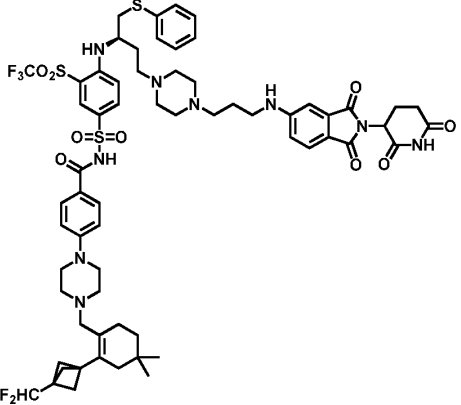
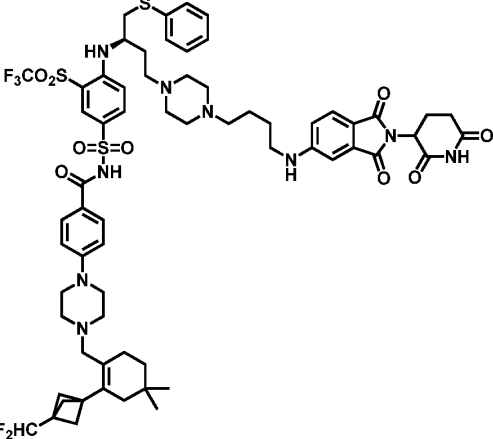
Example No.	Structure of Compound of Formula (I)
1	

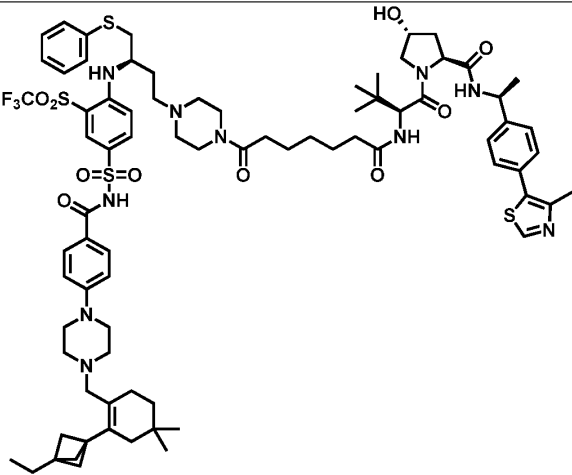
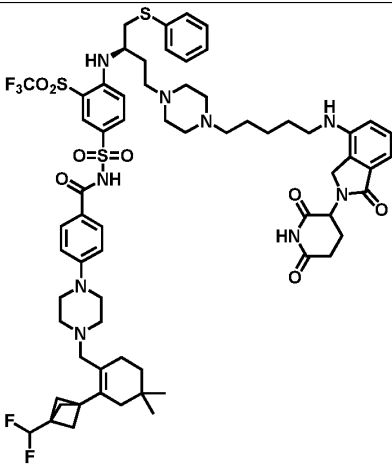
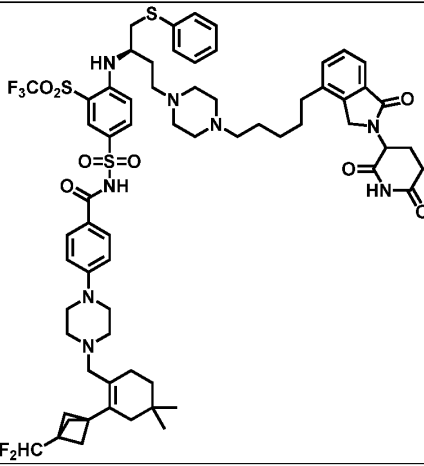
Example No.	Structure of Compound of Formula (I)
2	 Chemical structure of Compound 2: A complex molecule featuring a central piperazine ring. One nitrogen of the piperazine is connected via a 6-phenylhexyl chain to the 2-position of a benzimidazole-1-one ring. The other nitrogen of the piperazine is connected via a 2-phenylethyl chain to the nitrogen of a 4-(trifluoromethylsulfonyl)-2-((4-((2,2,6,6-tetramethyl-3-(2-(difluoromethyl)-4-methylcyclopent-1-en-1-yl)but-3-en-2-yl)phenyl)carbamoyl)benzoyl)aniline moiety.
3	 Chemical structure of Compound 3: A complex molecule featuring a central piperazine ring. One nitrogen of the piperazine is connected via a 6-phenylhexyl chain to the 2-position of a benzimidazole-1-one ring. The other nitrogen of the piperazine is connected via a 2-phenylethyl chain to the nitrogen of a 4-(trifluoromethylsulfonyl)-2-((4-((2,2,6,6-tetramethyl-3-(2-(difluoromethyl)-4-methylcyclopent-1-en-1-yl)but-3-en-2-yl)phenyl)carbamoyl)benzoyl)aniline moiety. The structure is identical to Compound 2, but the benzimidazole-1-one ring is connected to the piperazine via an ether linkage instead of an amine linkage.

Example No.	Structure of Compound of Formula (I)
4	 Chemical structure of Compound 4: A complex molecule featuring a central piperazine ring. One piperazine nitrogen is connected to a 4-(trifluoromethylsulfonyl)phenyl group via an amine linkage (-NH-). The other piperazine nitrogen is connected to a 4-((2,2,6,6-tetramethyl-3-(2-(2,2,2,2-tetrafluoroethyl)-5-norborn-2-en-2-yl)ethyl)phenyl)phenyl group via an amine linkage (-NH-). The 4-((2,2,2,2-tetrafluoroethyl)-5-norborn-2-en-2-yl)phenyl group is further substituted with a trifluoromethylsulfonyl group (-SO₂CF₃) and a sulfonamide group (-SO₂NH-). The sulfonamide group is connected to a 4-((2,2,6,6-tetramethyl-3-(2-(2,2,2,2-tetrafluoroethyl)-5-norborn-2-en-2-yl)ethyl)phenyl)phenyl group via an amine linkage (-NH-). The 4-((2,2,2,2-tetrafluoroethyl)-5-norborn-2-en-2-yl)phenyl group is further substituted with a trifluoromethylsulfonyl group (-SO₂CF₃) and a sulfonamide group (-SO₂NH-). The sulfonamide group is connected to a 4-((2,2,6,6-tetramethyl-3-(2-(2,2,2,2-tetrafluoroethyl)-5-norborn-2-en-2-yl)ethyl)phenyl)phenyl group via an amine linkage (-NH-).
5	 Chemical structure of Compound 5: A complex molecule featuring a central piperazine ring. One piperazine nitrogen is connected to a 4-(trifluoromethylsulfonyl)phenyl group via an amine linkage (-NH-). The other piperazine nitrogen is connected to a 4-((2,2,6,6-tetramethyl-3-(2-(2,2,2,2-tetrafluoroethyl)-5-norborn-2-en-2-yl)ethyl)phenyl)phenyl group via an amine linkage (-NH-). The 4-((2,2,2,2-tetrafluoroethyl)-5-norborn-2-en-2-yl)phenyl group is further substituted with a trifluoromethylsulfonyl group (-SO₂CF₃) and a sulfonamide group (-SO₂NH-). The sulfonamide group is connected to a 4-((2,2,6,6-tetramethyl-3-(2-(2,2,2,2-tetrafluoroethyl)-5-norborn-2-en-2-yl)ethyl)phenyl)phenyl group via an amine linkage (-NH-). The 4-((2,2,2,2-tetrafluoroethyl)-5-norborn-2-en-2-yl)phenyl group is further substituted with a trifluoromethylsulfonyl group (-SO₂CF₃) and a sulfonamide group (-SO₂NH-). The sulfonamide group is connected to a 4-((2,2,6,6-tetramethyl-3-(2-(2,2,2,2-tetrafluoroethyl)-5-norborn-2-en-2-yl)ethyl)phenyl)phenyl group via an amine linkage (-NH-).

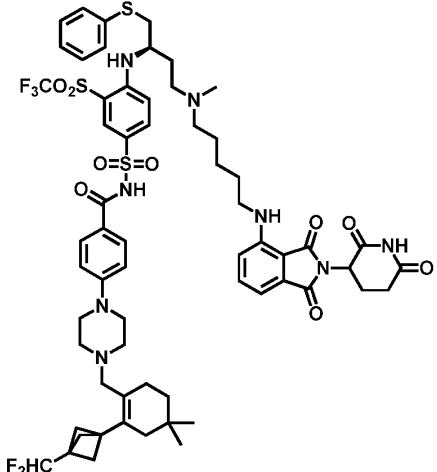
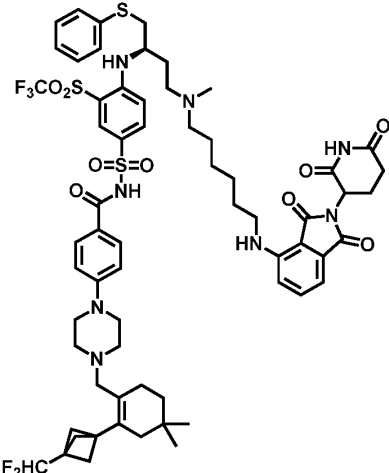
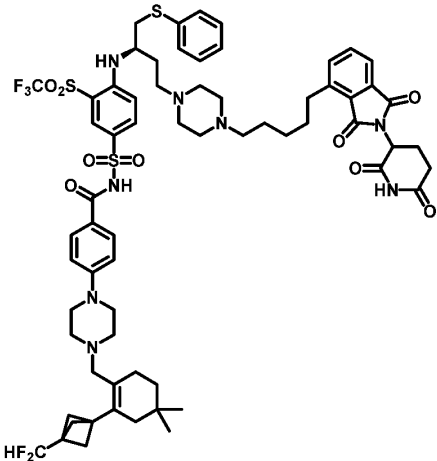
Example No.	Structure of Compound of Formula (I)
6	 Chemical structure of Compound 6: A complex molecule featuring a central piperazine ring. One nitrogen of the piperazine is connected to a 4-(trifluoromethylsulfonyl)phenyl group, which is further linked to a 4-(4-(2,2,2-trifluoroethoxy)phenyl)benzamide moiety. The other nitrogen of the piperazine is connected to a 4-(2,2,2-trifluoroethoxy)phenyl group, which is further linked to a 4-(4-(2,2,2-trifluoroethoxy)phenyl)benzamide moiety. The molecule also includes a 4-(2,2,2-trifluoroethoxy)phenyl group, a 4-(2,2,2-trifluoroethoxy)phenyl group, and a 4-(2,2,2-trifluoroethoxy)phenyl group.
7	 Chemical structure of Compound 7: A complex molecule featuring a central piperazine ring. One nitrogen of the piperazine is connected to a 4-(trifluoromethylsulfonyl)phenyl group, which is further linked to a 4-(4-(2,2,2-trifluoroethoxy)phenyl)benzamide moiety. The other nitrogen of the piperazine is connected to a 4-(2,2,2-trifluoroethoxy)phenyl group, which is further linked to a 4-(4-(2,2,2-trifluoroethoxy)phenyl)benzamide moiety. The molecule also includes a 4-(2,2,2-trifluoroethoxy)phenyl group, a 4-(2,2,2-trifluoroethoxy)phenyl group, and a 4-(2,2,2-trifluoroethoxy)phenyl group.

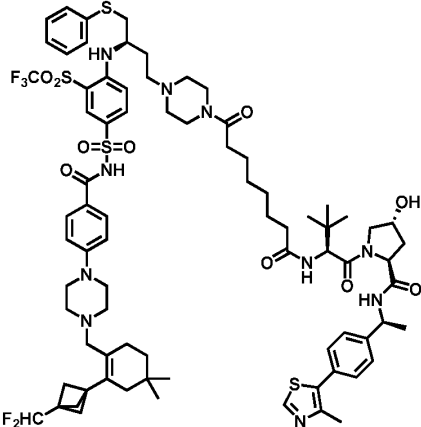
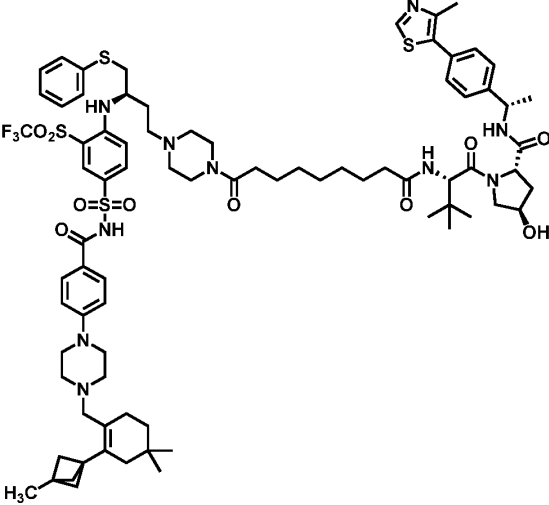
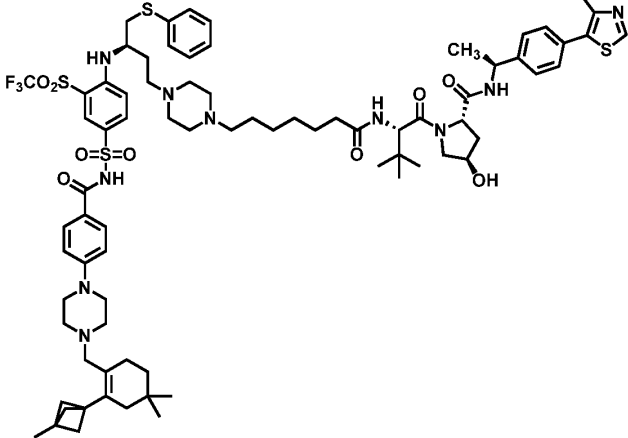
Example No.	Structure of Compound of Formula (I)
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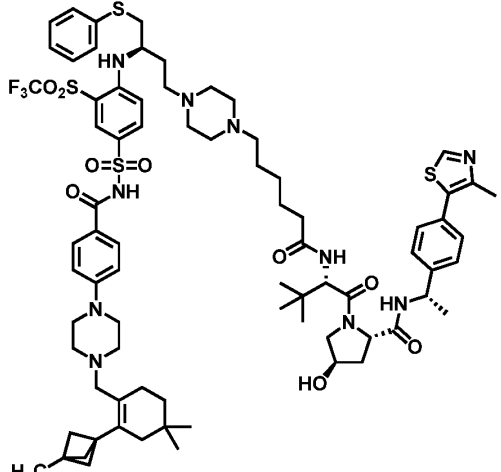
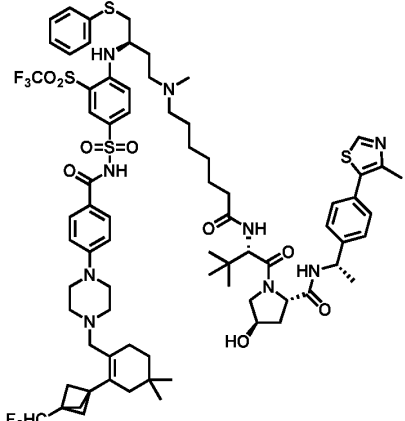
Example No.	Structure of Compound of Formula (I)
11	 Chemical structure of Compound 11: A complex molecule featuring a central piperazine ring. One nitrogen of the piperazine is connected to a 4-(trifluoromethylsulfonyl)phenyl group via an amine linkage (-NH-). The other nitrogen is connected to a 4-(2,2,2-trifluoroethoxy)phenyl group via an amine linkage (-NH-). The 4-(trifluoromethylsulfonyl)phenyl group is further substituted with a 4-(2,2,2-trifluoroethoxy)phenyl group via an amide linkage (-NH-CO-). The 4-(2,2,2-trifluoroethoxy)phenyl group is further substituted with a 4-(2,2,2-trifluoroethoxy)phenyl group via an amide linkage (-NH-CO-). The 4-(2,2,2-trifluoroethoxy)phenyl group is further substituted with a 4-(2,2,2-trifluoroethoxy)phenyl group via an amide linkage (-NH-CO-).
12	 Chemical structure of Compound 12: A complex molecule featuring a central piperazine ring. One nitrogen of the piperazine is connected to a 4-(trifluoromethylsulfonyl)phenyl group via an amine linkage (-NH-). The other nitrogen is connected to a 4-(2,2,2-trifluoroethoxy)phenyl group via an amine linkage (-NH-). The 4-(trifluoromethylsulfonyl)phenyl group is further substituted with a 4-(2,2,2-trifluoroethoxy)phenyl group via an amide linkage (-NH-CO-). The 4-(2,2,2-trifluoroethoxy)phenyl group is further substituted with a 4-(2,2,2-trifluoroethoxy)phenyl group via an amide linkage (-NH-CO-). The 4-(2,2,2-trifluoroethoxy)phenyl group is further substituted with a 4-(2,2,2-trifluoroethoxy)phenyl group via an amide linkage (-NH-CO-).
13	 Chemical structure of Compound 13: A complex molecule featuring a central piperazine ring. One nitrogen of the piperazine is connected to a 4-(trifluoromethylsulfonyl)phenyl group via an amine linkage (-NH-). The other nitrogen is connected to a 4-(2,2,2-trifluoroethoxy)phenyl group via an amine linkage (-NH-). The 4-(trifluoromethylsulfonyl)phenyl group is further substituted with a 4-(2,2,2-trifluoroethoxy)phenyl group via an amide linkage (-NH-CO-). The 4-(2,2,2-trifluoroethoxy)phenyl group is further substituted with a 4-(2,2,2-trifluoroethoxy)phenyl group via an amide linkage (-NH-CO-). The 4-(2,2,2-trifluoroethoxy)phenyl group is further substituted with a 4-(2,2,2-trifluoroethoxy)phenyl group via an amide linkage (-NH-CO-).

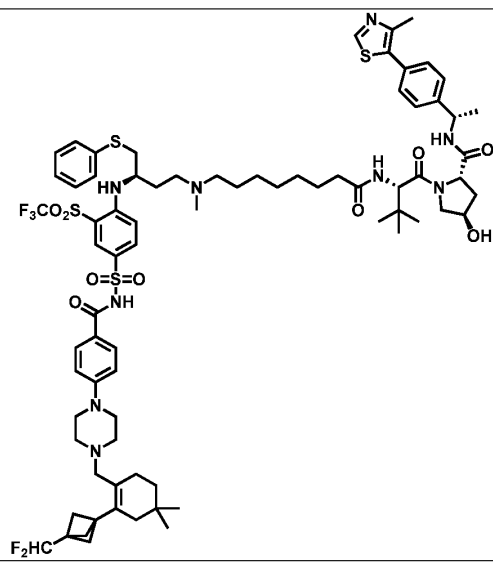
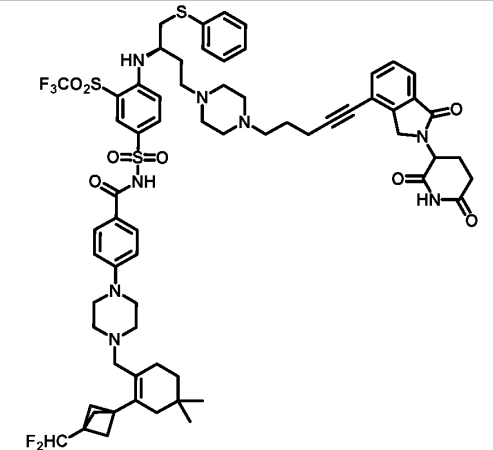
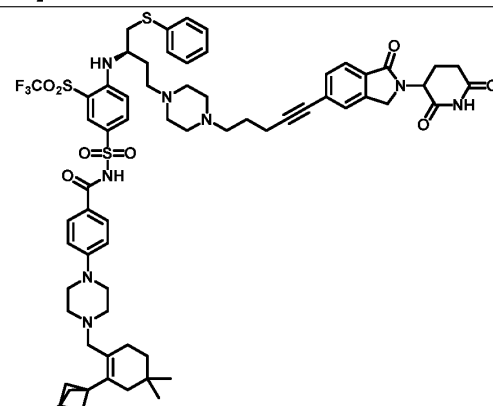
Example No.	Structure of Compound of Formula (I)
14	 Chemical structure of Compound 14: A complex molecule featuring a central piperazine ring. One nitrogen of the piperazine is substituted with a 4-(trifluoromethylsulfonyl)phenyl group and a 4-(4-(2,2,2-trimethyl-1,3-dioxane-5-yl)phenyl)phenyl group. The other nitrogen is substituted with a 4-(4-(2,2,2-trimethyl-1,3-dioxane-5-yl)phenyl)phenyl group and a 4-(4-(2,2,2-trimethyl-1,3-dioxane-5-yl)phenyl)phenyl group. The molecule also includes a 4-(4-(2,2,2-trimethyl-1,3-dioxane-5-yl)phenyl)phenyl group and a 4-(4-(2,2,2-trimethyl-1,3-dioxane-5-yl)phenyl)phenyl group.
15	 Chemical structure of Compound 15: A complex molecule featuring a central piperazine ring. One nitrogen of the piperazine is substituted with a 4-(trifluoromethylsulfonyl)phenyl group and a 4-(4-(2,2,2-trimethyl-1,3-dioxane-5-yl)phenyl)phenyl group. The other nitrogen is substituted with a 4-(4-(2,2,2-trimethyl-1,3-dioxane-5-yl)phenyl)phenyl group and a 4-(4-(2,2,2-trimethyl-1,3-dioxane-5-yl)phenyl)phenyl group. The molecule also includes a 4-(4-(2,2,2-trimethyl-1,3-dioxane-5-yl)phenyl)phenyl group and a 4-(4-(2,2,2-trimethyl-1,3-dioxane-5-yl)phenyl)phenyl group.
16	 Chemical structure of Compound 16: A complex molecule featuring a central piperazine ring. One nitrogen of the piperazine is substituted with a 4-(trifluoromethylsulfonyl)phenyl group and a 4-(4-(2,2,2-trimethyl-1,3-dioxane-5-yl)phenyl)phenyl group. The other nitrogen is substituted with a 4-(4-(2,2,2-trimethyl-1,3-dioxane-5-yl)phenyl)phenyl group and a 4-(4-(2,2,2-trimethyl-1,3-dioxane-5-yl)phenyl)phenyl group. The molecule also includes a 4-(4-(2,2,2-trimethyl-1,3-dioxane-5-yl)phenyl)phenyl group and a 4-(4-(2,2,2-trimethyl-1,3-dioxane-5-yl)phenyl)phenyl group.

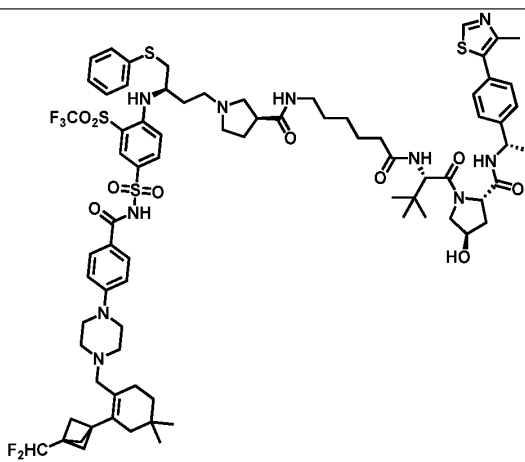
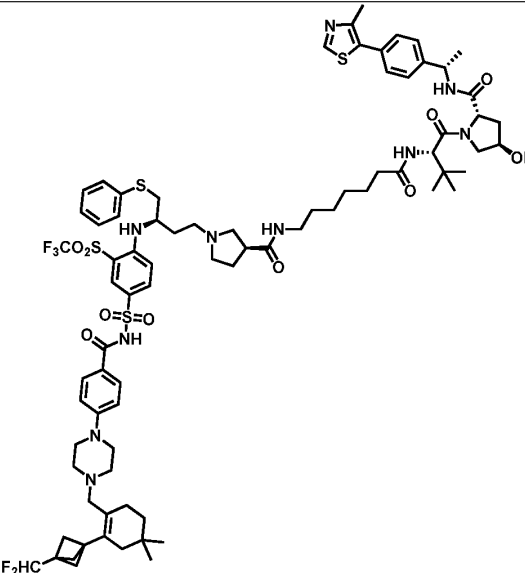
Example No.	Structure of Compound of Formula (I)
17	
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Example No.	Structure of Compound of Formula (I)
20	 Chemical structure of Compound 20: A complex molecule featuring a central piperazine ring. One nitrogen of the piperazine is connected to a 4-(trifluoromethylsulfonyl)phenyl group. The other nitrogen is connected to a 4-(2,2,2-trifluoroethoxy)phenyl group. The 2,2,2-trifluoroethoxy group is further substituted with a 4-(2,2,2-trifluoroethoxy)phenyl group. The 2,2,2-trifluoroethoxy group is also substituted with a 4-(2,2,2-trifluoroethoxy)phenyl group. The 2,2,2-trifluoroethoxy group is also substituted with a 4-(2,2,2-trifluoroethoxy)phenyl group.
21	 Chemical structure of Compound 21: A complex molecule featuring a central piperazine ring. One nitrogen of the piperazine is connected to a 4-(trifluoromethylsulfonyl)phenyl group. The other nitrogen is connected to a 4-(2,2,2-trifluoroethoxy)phenyl group. The 2,2,2-trifluoroethoxy group is further substituted with a 4-(2,2,2-trifluoroethoxy)phenyl group. The 2,2,2-trifluoroethoxy group is also substituted with a 4-(2,2,2-trifluoroethoxy)phenyl group. The 2,2,2-trifluoroethoxy group is also substituted with a 4-(2,2,2-trifluoroethoxy)phenyl group.
22	 Chemical structure of Compound 22: A complex molecule featuring a central piperazine ring. One nitrogen of the piperazine is connected to a 4-(trifluoromethylsulfonyl)phenyl group. The other nitrogen is connected to a 4-(2,2,2-trifluoroethoxy)phenyl group. The 2,2,2-trifluoroethoxy group is further substituted with a 4-(2,2,2-trifluoroethoxy)phenyl group. The 2,2,2-trifluoroethoxy group is also substituted with a 4-(2,2,2-trifluoroethoxy)phenyl group. The 2,2,2-trifluoroethoxy group is also substituted with a 4-(2,2,2-trifluoroethoxy)phenyl group.

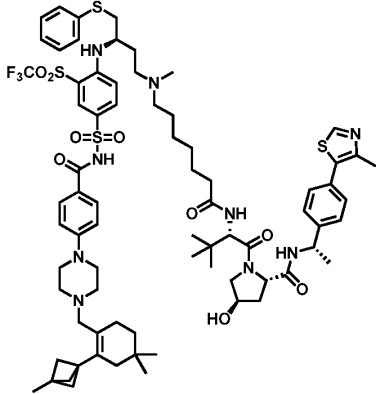
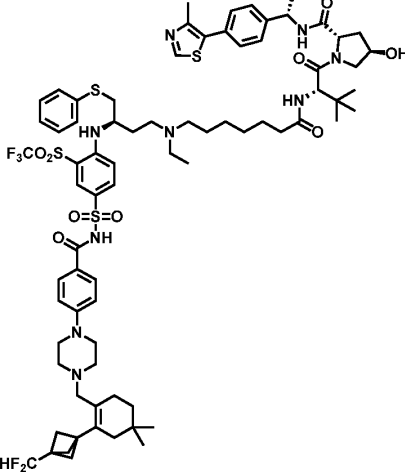
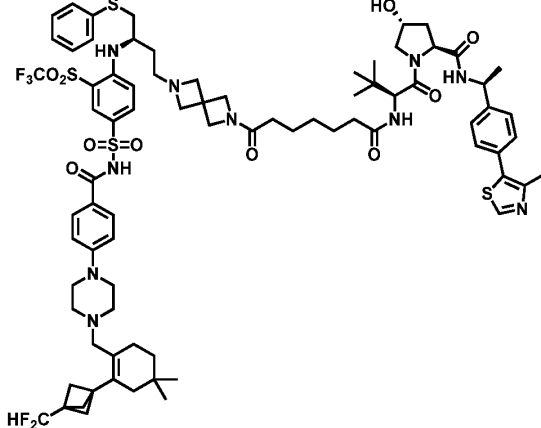
Example No.	Structure of Compound of Formula (I)
23	 Chemical structure of Compound 23: A complex molecule featuring a central piperazine ring. One nitrogen of the piperazine is connected to a 4-(trifluoromethylsulfonyl)phenyl group. The other nitrogen is connected to a 4-(4-(2,2,2-trifluoroethoxy)phenyl)phenyl group. The piperazine ring is also connected to a 4-(4-(2,2,2-trifluoroethoxy)phenyl)phenyl group. The piperazine ring is connected to a 4-(4-(2,2,2-trifluoroethoxy)phenyl)phenyl group. The piperazine ring is connected to a 4-(4-(2,2,2-trifluoroethoxy)phenyl)phenyl group.
24	 Chemical structure of Compound 24: A complex molecule featuring a central piperazine ring. One nitrogen of the piperazine is connected to a 4-(trifluoromethylsulfonyl)phenyl group. The other nitrogen is connected to a 4-(4-(2,2,2-trifluoroethoxy)phenyl)phenyl group. The piperazine ring is also connected to a 4-(4-(2,2,2-trifluoroethoxy)phenyl)phenyl group. The piperazine ring is connected to a 4-(4-(2,2,2-trifluoroethoxy)phenyl)phenyl group. The piperazine ring is connected to a 4-(4-(2,2,2-trifluoroethoxy)phenyl)phenyl group.
25	 Chemical structure of Compound 25: A complex molecule featuring a central piperazine ring. One nitrogen of the piperazine is connected to a 4-(trifluoromethylsulfonyl)phenyl group. The other nitrogen is connected to a 4-(4-(2,2,2-trifluoroethoxy)phenyl)phenyl group. The piperazine ring is also connected to a 4-(4-(2,2,2-trifluoroethoxy)phenyl)phenyl group. The piperazine ring is connected to a 4-(4-(2,2,2-trifluoroethoxy)phenyl)phenyl group. The piperazine ring is connected to a 4-(4-(2,2,2-trifluoroethoxy)phenyl)phenyl group.

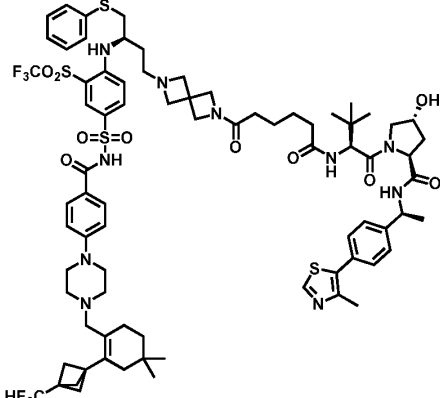
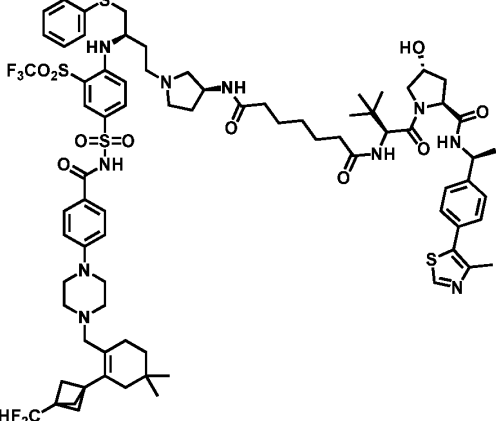
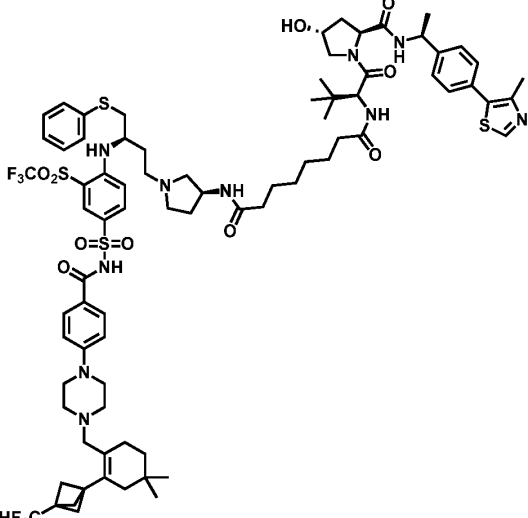
Example No.	Structure of Compound of Formula (I)
26	 Chemical structure of Compound 26. The molecule features a central piperazine ring. One nitrogen of the piperazine is substituted with a 4-(trifluoromethylsulfonyl)phenyl group and a 2-(4-(4-methyl-4,5,6,7-tetrahydrocyclopenta[b]thien-2-yl)phenyl) group. The other nitrogen is substituted with a 4-(4-(4-methyl-4,5,6,7-tetrahydrocyclopenta[b]thien-2-yl)phenyl) group and a 2-(4-(4-methyl-4,5,6,7-tetrahydrocyclopenta[b]thien-2-yl)phenyl) group. The molecule also contains a thiazole ring, a sulfonamide group, and a hydroxyl group.
27	 Chemical structure of Compound 27. The molecule is similar to Compound 26, but the trifluoromethyl group (F₃CO₂S) is replaced by a difluoromethyl group (F₂HC).

Example No.	Structure of Compound of Formula (I)
28	 Chemical structure of Compound 28: A complex molecule featuring a central piperazine ring. One nitrogen of the piperazine is connected to a 4-(trifluoromethylsulfonyl)phenyl group. The other nitrogen is connected to a 4-(2-(2,2,2-trifluoroethoxy)ethyl)phenyl group. The 2,2,2-trifluoroethoxy group is further substituted with a 4-(2-(2,2,2-trifluoroethoxy)ethyl)phenyl group. The 2,2,2-trifluoroethoxy group is also substituted with a 4-(2-(2,2,2-trifluoroethoxy)ethyl)phenyl group. The 2,2,2-trifluoroethoxy group is also substituted with a 4-(2-(2,2,2-trifluoroethoxy)ethyl)phenyl group.
29	 Chemical structure of Compound 29: A complex molecule featuring a central piperazine ring. One nitrogen of the piperazine is connected to a 4-(trifluoromethylsulfonyl)phenyl group. The other nitrogen is connected to a 4-(2-(2,2,2-trifluoroethoxy)ethyl)phenyl group. The 2,2,2-trifluoroethoxy group is further substituted with a 4-(2-(2,2,2-trifluoroethoxy)ethyl)phenyl group. The 2,2,2-trifluoroethoxy group is also substituted with a 4-(2-(2,2,2-trifluoroethoxy)ethyl)phenyl group. The 2,2,2-trifluoroethoxy group is also substituted with a 4-(2-(2,2,2-trifluoroethoxy)ethyl)phenyl group.
30	 Chemical structure of Compound 30: A complex molecule featuring a central piperazine ring. One nitrogen of the piperazine is connected to a 4-(trifluoromethylsulfonyl)phenyl group. The other nitrogen is connected to a 4-(2-(2,2,2-trifluoroethoxy)ethyl)phenyl group. The 2,2,2-trifluoroethoxy group is further substituted with a 4-(2-(2,2,2-trifluoroethoxy)ethyl)phenyl group. The 2,2,2-trifluoroethoxy group is also substituted with a 4-(2-(2,2,2-trifluoroethoxy)ethyl)phenyl group. The 2,2,2-trifluoroethoxy group is also substituted with a 4-(2-(2,2,2-trifluoroethoxy)ethyl)phenyl group.

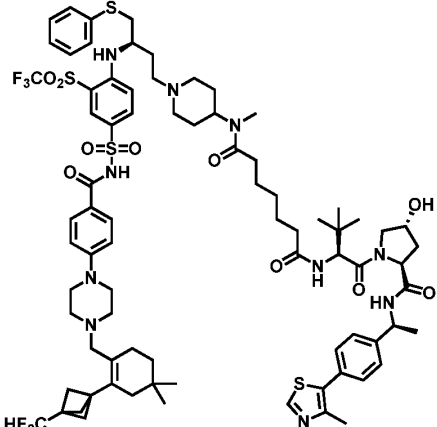
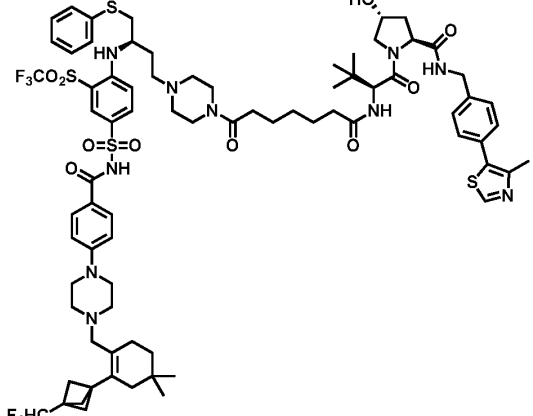
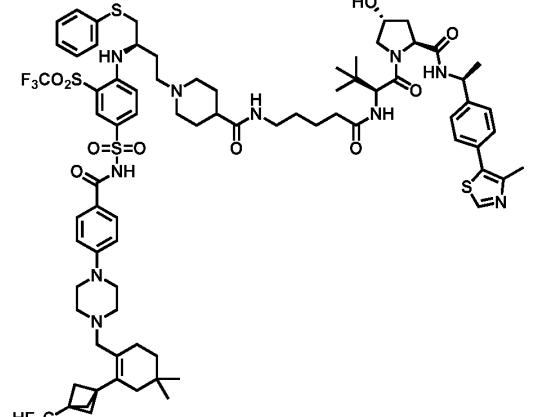
Example No.	Structure of Compound of Formula (I)
31	 Chemical structure of Compound 31. The molecule features a central piperazine ring substituted with a 4-(2,2,2-trifluoroethoxy)phenyl group and a 4-(2,2,2-trifluoroethoxy)phenyl group. The piperazine is linked via a methylene group to a 4-(2,2,2-trifluoroethoxy)phenyl group. This phenyl group is further substituted with a 2,2,2-trifluoroethoxy group and a 2,2,2-trifluoroethoxy group. The piperazine is also linked via a methylene group to a 4-(2,2,2-trifluoroethoxy)phenyl group. This phenyl group is further substituted with a 2,2,2-trifluoroethoxy group and a 2,2,2-trifluoroethoxy group. The piperazine is also linked via a methylene group to a 4-(2,2,2-trifluoroethoxy)phenyl group. This phenyl group is further substituted with a 2,2,2-trifluoroethoxy group and a 2,2,2-trifluoroethoxy group.
32	 Chemical structure of Compound 32. The molecule features a central piperazine ring substituted with a 4-(2,2,2-trifluoroethoxy)phenyl group and a 4-(2,2,2-trifluoroethoxy)phenyl group. The piperazine is linked via a methylene group to a 4-(2,2,2-trifluoroethoxy)phenyl group. This phenyl group is further substituted with a 2,2,2-trifluoroethoxy group and a 2,2,2-trifluoroethoxy group. The piperazine is also linked via a methylene group to a 4-(2,2,2-trifluoroethoxy)phenyl group. This phenyl group is further substituted with a 2,2,2-trifluoroethoxy group and a 2,2,2-trifluoroethoxy group. The piperazine is also linked via a methylene group to a 4-(2,2,2-trifluoroethoxy)phenyl group. This phenyl group is further substituted with a 2,2,2-trifluoroethoxy group and a 2,2,2-trifluoroethoxy group.

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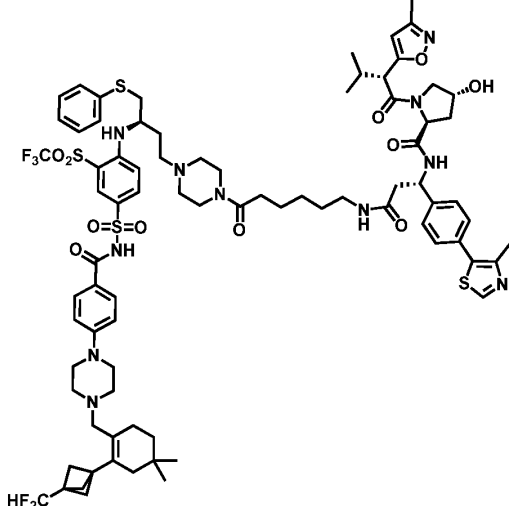
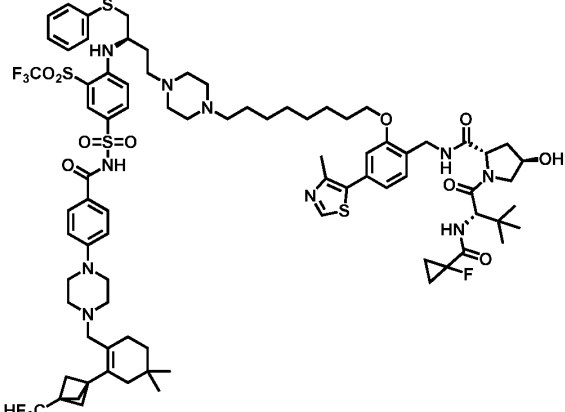
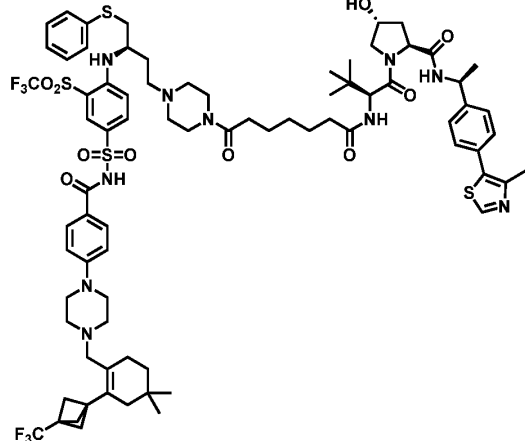
Example No.	Structure of Compound of Formula (I)
35	 Chemical structure of Compound 35: A complex molecule featuring a central piperazine ring. One nitrogen of the piperazine is connected to a 4-(trifluoromethylsulfonyl)phenyl group. The other nitrogen is connected to a 4-(hydroxymethyl)phenyl group. The hydroxymethyl group is further substituted with a 4-(methylthio)phenyl group. The central piperazine ring is also substituted with a 4-(trifluoromethylsulfonyl)phenyl group and a 4-(hydroxymethyl)phenyl group. The hydroxymethyl group is further substituted with a 4-(methylthio)phenyl group.
36	 Chemical structure of Compound 36: A complex molecule featuring a central piperazine ring. One nitrogen of the piperazine is connected to a 4-(trifluoromethylsulfonyl)phenyl group. The other nitrogen is connected to a 4-(hydroxymethyl)phenyl group. The hydroxymethyl group is further substituted with a 4-(methylthio)phenyl group. The central piperazine ring is also substituted with a 4-(trifluoromethylsulfonyl)phenyl group and a 4-(hydroxymethyl)phenyl group. The hydroxymethyl group is further substituted with a 4-(methylthio)phenyl group.
37	 Chemical structure of Compound 37: A complex molecule featuring a central piperazine ring. One nitrogen of the piperazine is connected to a 4-(trifluoromethylsulfonyl)phenyl group. The other nitrogen is connected to a 4-(hydroxymethyl)phenyl group. The hydroxymethyl group is further substituted with a 4-(methylthio)phenyl group. The central piperazine ring is also substituted with a 4-(trifluoromethylsulfonyl)phenyl group and a 4-(hydroxymethyl)phenyl group. The hydroxymethyl group is further substituted with a 4-(methylthio)phenyl group.

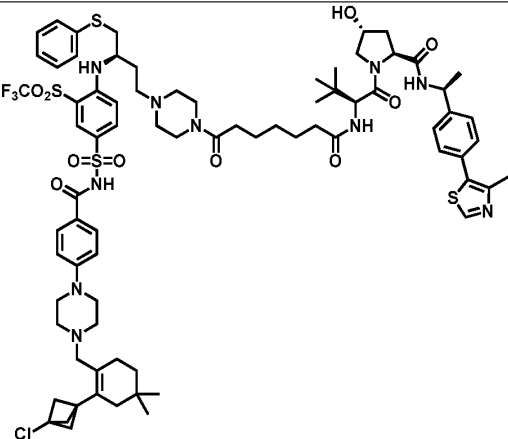
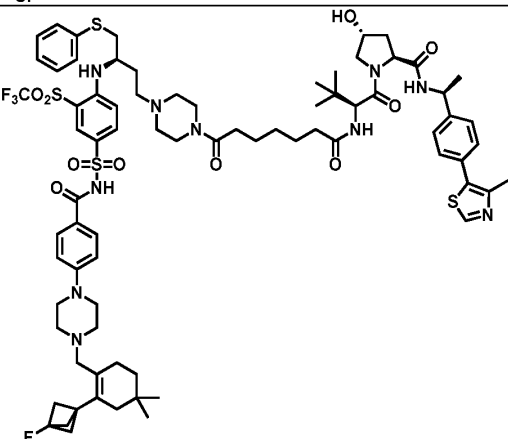
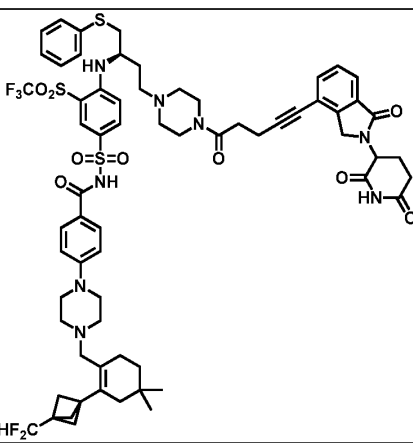
Example No.	Structure of Compound of Formula (I)
38	 Chemical structure of Compound 38. It features a central piperazine ring substituted with a 4-(trifluoromethyl)phenyl group and a 4-(4-(trifluoromethyl)phenyl)-2-thienyl group. The piperazine is also linked to a 4-(trifluoromethyl)phenyl group via a sulfonamide linkage. The structure includes a thienyl group, a sulfonamide group, and a complex side chain with multiple amide and ester linkages, including a 4-(trifluoromethyl)phenyl group and a 4-(4-(trifluoromethyl)phenyl)-2-thienyl group.
39	 Chemical structure of Compound 39. It features a central piperazine ring substituted with a 4-(trifluoromethyl)phenyl group and a 4-(4-(trifluoromethyl)phenyl)-2-thienyl group. The piperazine is also linked to a 4-(trifluoromethyl)phenyl group via a sulfonamide linkage. The structure includes a thienyl group, a sulfonamide group, and a complex side chain with multiple amide and ester linkages, including a 4-(trifluoromethyl)phenyl group and a 4-(4-(trifluoromethyl)phenyl)-2-thienyl group.
40	 Chemical structure of Compound 40. It features a central piperazine ring substituted with a 4-(trifluoromethyl)phenyl group and a 4-(4-(trifluoromethyl)phenyl)-2-thienyl group. The piperazine is also linked to a 4-(trifluoromethyl)phenyl group via a sulfonamide linkage. The structure includes a thienyl group, a sulfonamide group, and a complex side chain with multiple amide and ester linkages, including a 4-(trifluoromethyl)phenyl group and a 4-(4-(trifluoromethyl)phenyl)-2-thienyl group.

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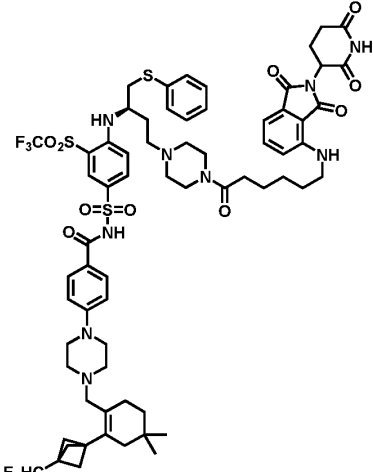
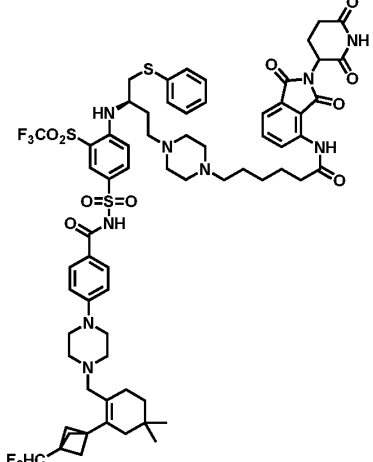
Example No.	Structure of Compound of Formula (I)
44	 Chemical structure of Compound 44. It features a central piperazine ring substituted with a 4-(trifluoromethylsulfonyl)phenyl group, a 4-(2-(2,2,6,6-tetramethyl-1,3-dioxan-5-yl)phenyl) group, and a 4-(2-(2,2,6,6-tetramethyl-1,3-dioxan-5-yl)phenyl) group. The structure also includes a 4-(2-(2,2,6,6-tetramethyl-1,3-dioxan-5-yl)phenyl) group and a 4-(2-(2,2,6,6-tetramethyl-1,3-dioxan-5-yl)phenyl) group.
45	 Chemical structure of Compound 45. It features a central piperazine ring substituted with a 4-(trifluoromethylsulfonyl)phenyl group, a 4-(2-(2,2,6,6-tetramethyl-1,3-dioxan-5-yl)phenyl) group, and a 4-(2-(2,2,6,6-tetramethyl-1,3-dioxan-5-yl)phenyl) group. The structure also includes a 4-(2-(2,2,6,6-tetramethyl-1,3-dioxan-5-yl)phenyl) group and a 4-(2-(2,2,6,6-tetramethyl-1,3-dioxan-5-yl)phenyl) group.
46	 Chemical structure of Compound 46. It features a central piperazine ring substituted with a 4-(trifluoromethylsulfonyl)phenyl group, a 4-(2-(2,2,6,6-tetramethyl-1,3-dioxan-5-yl)phenyl) group, and a 4-(2-(2,2,6,6-tetramethyl-1,3-dioxan-5-yl)phenyl) group. The structure also includes a 4-(2-(2,2,6,6-tetramethyl-1,3-dioxan-5-yl)phenyl) group and a 4-(2-(2,2,6,6-tetramethyl-1,3-dioxan-5-yl)phenyl) group.

Example No.	Structure of Compound of Formula (I)
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49	

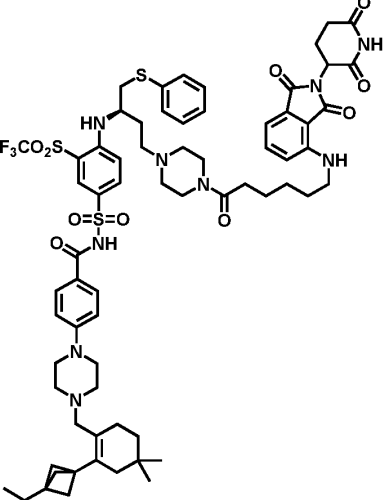
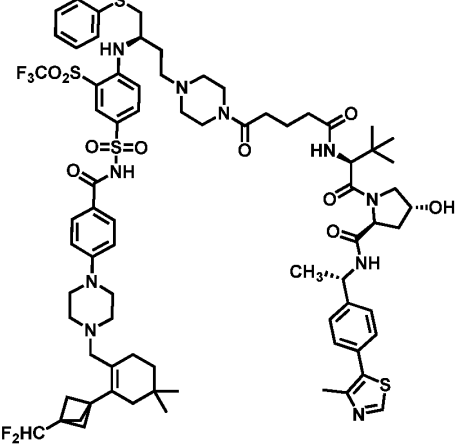
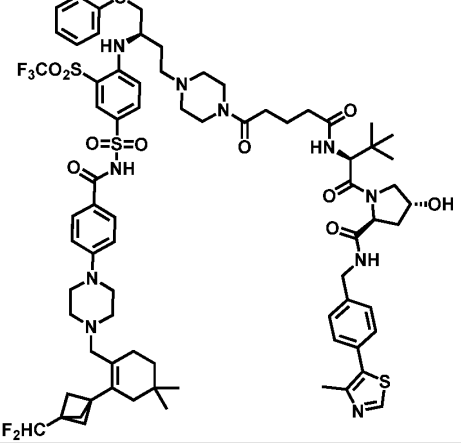
Example No.	Structure of Compound of Formula (I)
50	 Chemical structure of Compound 50: A complex molecule featuring a central piperazine ring. One nitrogen of the piperazine is connected to a 4-(trifluoromethylsulfonyl)phenyl group, which is further linked to a 4-(4-(2,2,2-trifluoroethyl)phenyl)phenyl group. The other nitrogen of the piperazine is connected to a 4-(4-(2,2,2-trifluoroethyl)phenyl)phenyl group, which is further linked to a 4-(4-(2,2,2-trifluoroethyl)phenyl)phenyl group. The molecule also includes a thiazole ring, a hydroxyl group, and a trifluoromethyl group.
51	 Chemical structure of Compound 51: A complex molecule featuring a central piperazine ring. One nitrogen of the piperazine is connected to a 4-(trifluoromethylsulfonyl)phenyl group, which is further linked to a 4-(4-(2,2,2-trifluoroethyl)phenyl)phenyl group. The other nitrogen of the piperazine is connected to a 4-(4-(2,2,2-trifluoroethyl)phenyl)phenyl group, which is further linked to a 4-(4-(2,2,2-trifluoroethyl)phenyl)phenyl group. The molecule also includes a thiazole ring, a hydroxyl group, and a trifluoromethyl group.
52	 Chemical structure of Compound 52: A complex molecule featuring a central piperazine ring. One nitrogen of the piperazine is connected to a 4-(trifluoromethylsulfonyl)phenyl group, which is further linked to a 4-(4-(2,2,2-trifluoroethyl)phenyl)phenyl group. The other nitrogen of the piperazine is connected to a 4-(4-(2,2,2-trifluoroethyl)phenyl)phenyl group, which is further linked to a 4-(4-(2,2,2-trifluoroethyl)phenyl)phenyl group. The molecule also includes a thiazole ring, a hydroxyl group, and a trifluoromethyl group.

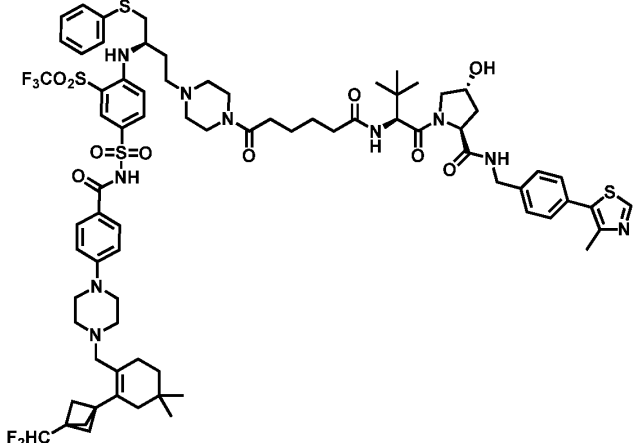
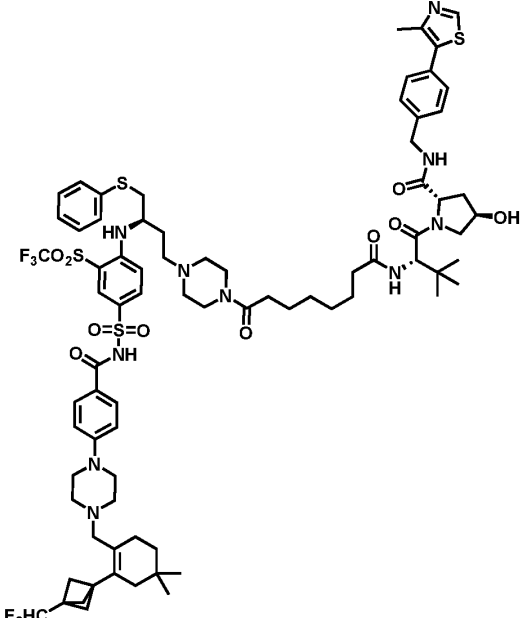
Example No.	Structure of Compound of Formula (I)
53	 Chemical structure of compound 53. It features a central piperazine ring. One nitrogen of the piperazine is connected to a 4-(trifluoromethylsulfonyl)phenyl group, which is further linked to a 4-(4-chlorocyclobutyl)phenyl group. The other nitrogen of the piperazine is connected to a 4-(4-(2-methyl-4-(methylthio)phenyl)-2-oxo-1,2,3,4-tetrahydropyridin-5-yl)butanoyl group.
54	 Chemical structure of compound 54. It is similar to compound 53, but the 4-chlorocyclobutyl group is replaced by a 4-fluorocyclobutyl group.
55	 Chemical structure of compound 55. It features a central piperazine ring. One nitrogen of the piperazine is connected to a 4-(trifluoromethylsulfonyl)phenyl group, which is further linked to a 4-(4-(2,2,2-trifluoroethoxycarbonyl)cyclobutyl)phenyl group. The other nitrogen of the piperazine is connected to a 4-(4-(2-oxo-2,3,4,5-tetrahydro-1H-benzodioxol-5-yl)butanoyl group.

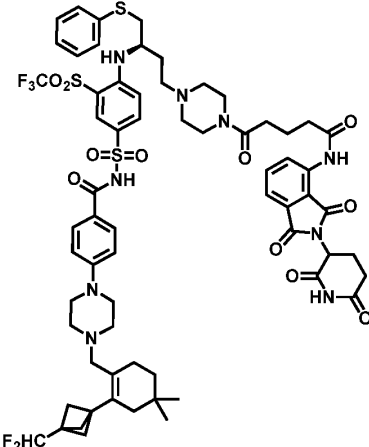
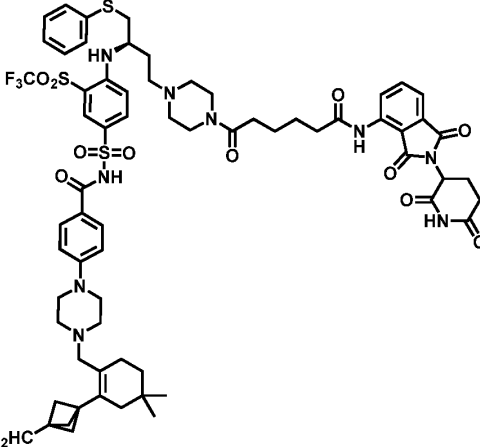
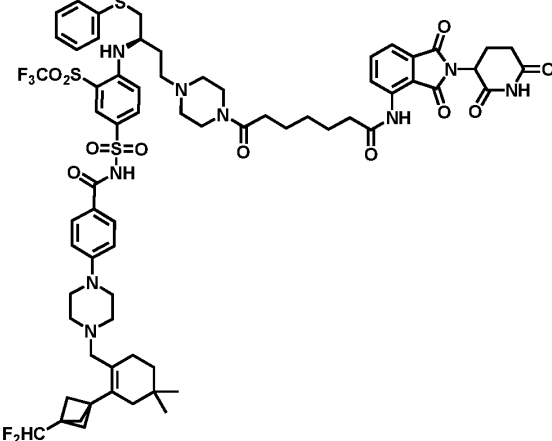
Example No.	Structure of Compound of Formula (I)
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57	

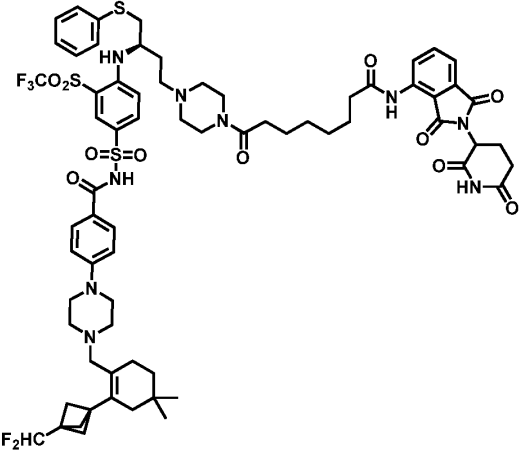
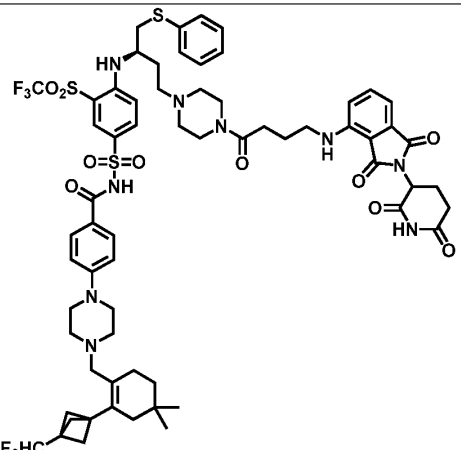
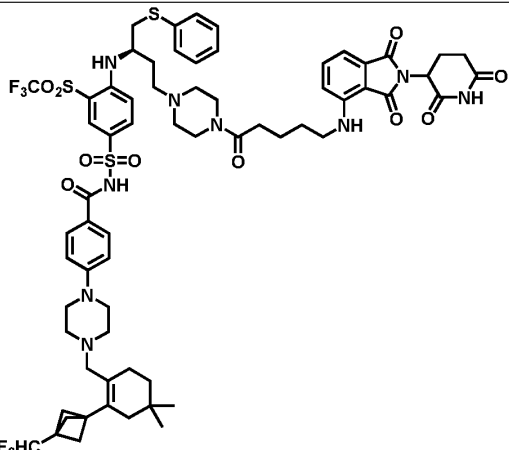
Example No.	Structure of Compound of Formula (I)
58	 Chemical structure of Compound 58. The molecule features a central piperazine ring. One nitrogen of the piperazine is connected to a 4-(trifluoromethylsulfonyl)phenyl group via a methylene linker. The other nitrogen is connected to a 4-(2-(2,2,2-trifluoroethoxy)phenyl)phenyl group via a methylene linker. The 2,2,2-trifluoroethoxy group is further substituted with a 4-(2-(2,2,2-trifluoroethoxy)phenyl)phenyl group. The 2,2,2-trifluoroethoxy group is also substituted with a 4-(2-(2,2,2-trifluoroethoxy)phenyl)phenyl group. The 2,2,2-trifluoroethoxy group is also substituted with a 4-(2-(2,2,2-trifluoroethoxy)phenyl)phenyl group.
59	 Chemical structure of Compound 59. The molecule features a central piperazine ring. One nitrogen of the piperazine is connected to a 4-(trifluoromethylsulfonyl)phenyl group via a methylene linker. The other nitrogen is connected to a 4-(2-(2,2,2-trifluoroethoxy)phenyl)phenyl group via a methylene linker. The 2,2,2-trifluoroethoxy group is further substituted with a 4-(2-(2,2,2-trifluoroethoxy)phenyl)phenyl group. The 2,2,2-trifluoroethoxy group is also substituted with a 4-(2-(2,2,2-trifluoroethoxy)phenyl)phenyl group. The 2,2,2-trifluoroethoxy group is also substituted with a 4-(2-(2,2,2-trifluoroethoxy)phenyl)phenyl group.

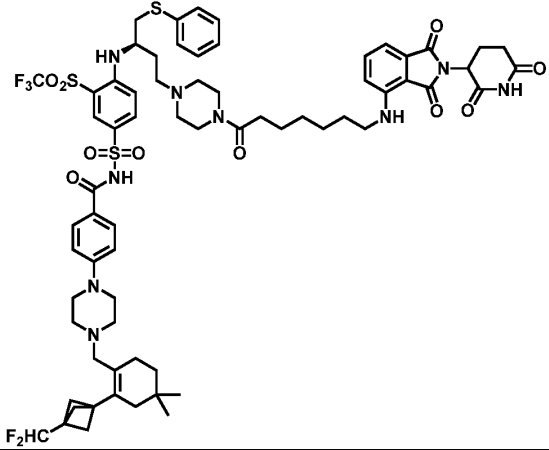
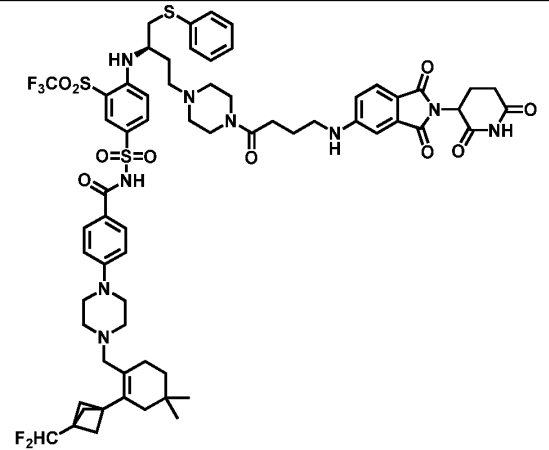
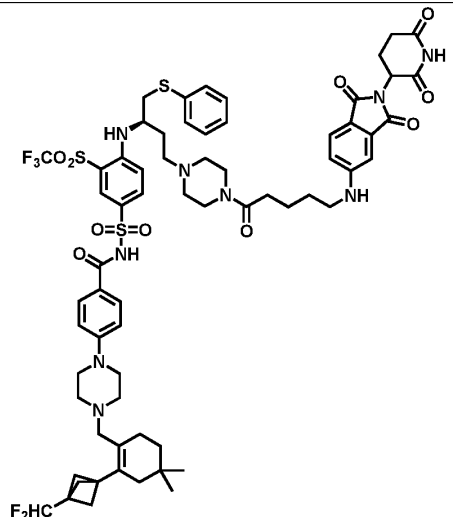
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Example No.	Structure of Compound of Formula (I)
62	 Chemical structure of Compound 62: A complex molecule featuring a central piperazine ring. One nitrogen of the piperazine is connected to a 4-(trifluoromethylsulfonyl)phenyl group. The other nitrogen is connected to a 4-(4-(2,2,2-trifluoroethoxy)phenyl)phenyl group. The 4-(2,2,2-trifluoroethoxy)phenyl group is further substituted with a 4-(4-(2,2,2-trifluoroethoxy)phenyl)phenyl group. The 4-(2,2,2-trifluoroethoxy)phenyl group is also substituted with a 4-(4-(2,2,2-trifluoroethoxy)phenyl)phenyl group. The 4-(2,2,2-trifluoroethoxy)phenyl group is also substituted with a 4-(4-(2,2,2-trifluoroethoxy)phenyl)phenyl group.
63	 Chemical structure of Compound 63: A complex molecule featuring a central piperazine ring. One nitrogen of the piperazine is connected to a 4-(trifluoromethylsulfonyl)phenyl group. The other nitrogen is connected to a 4-(4-(2,2,2-trifluoroethoxy)phenyl)phenyl group. The 4-(2,2,2-trifluoroethoxy)phenyl group is further substituted with a 4-(4-(2,2,2-trifluoroethoxy)phenyl)phenyl group. The 4-(2,2,2-trifluoroethoxy)phenyl group is also substituted with a 4-(4-(2,2,2-trifluoroethoxy)phenyl)phenyl group. The 4-(2,2,2-trifluoroethoxy)phenyl group is also substituted with a 4-(4-(2,2,2-trifluoroethoxy)phenyl)phenyl group.
64	 Chemical structure of Compound 64: A complex molecule featuring a central piperazine ring. One nitrogen of the piperazine is connected to a 4-(trifluoromethylsulfonyl)phenyl group. The other nitrogen is connected to a 4-(4-(2,2,2-trifluoroethoxy)phenyl)phenyl group. The 4-(2,2,2-trifluoroethoxy)phenyl group is further substituted with a 4-(4-(2,2,2-trifluoroethoxy)phenyl)phenyl group. The 4-(2,2,2-trifluoroethoxy)phenyl group is also substituted with a 4-(4-(2,2,2-trifluoroethoxy)phenyl)phenyl group. The 4-(2,2,2-trifluoroethoxy)phenyl group is also substituted with a 4-(4-(2,2,2-trifluoroethoxy)phenyl)phenyl group.

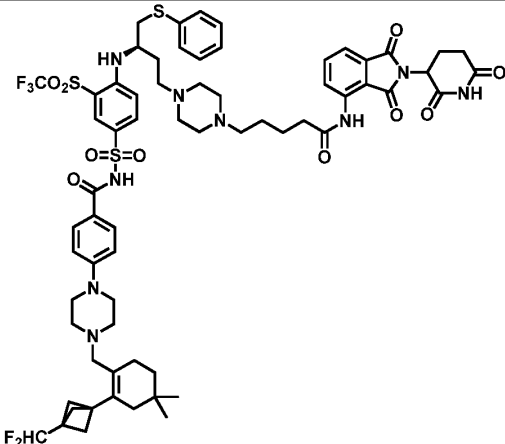
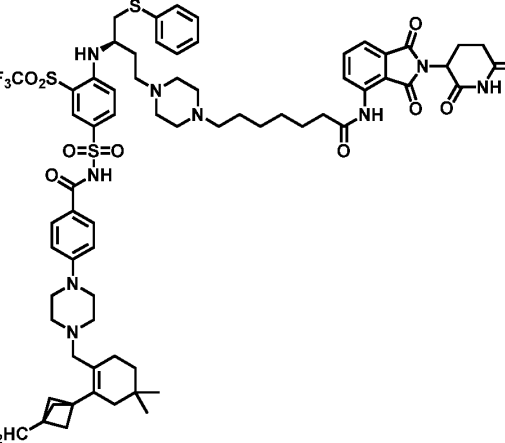
Example No.	Structure of Compound of Formula (I)
65	 Chemical structure of Compound 65. The molecule features a central piperazine ring. One nitrogen of the piperazine is connected to a 4-(trifluoromethylsulfonyl)phenyl group, which is further linked to a 4-(4-(2-(2,2,2-trifluoroethyl)-5,5-dimethyl-1,3-dioxane-1-carbonyl)phenyl)benzamide moiety. The other nitrogen of the piperazine is connected to a 4-(4-(2-(2,2,2-trifluoroethyl)-5,5-dimethyl-1,3-dioxane-1-carbonyl)phenyl)benzamide moiety. The molecule also includes a 4-(4-(2-(2,2,2-trifluoroethyl)-5,5-dimethyl-1,3-dioxane-1-carbonyl)phenyl)benzamide moiety and a 4-(4-(2-(2,2,2-trifluoroethyl)-5,5-dimethyl-1,3-dioxane-1-carbonyl)phenyl)benzamide moiety.
66	 Chemical structure of Compound 66. The molecule features a central piperazine ring. One nitrogen of the piperazine is connected to a 4-(trifluoromethylsulfonyl)phenyl group, which is further linked to a 4-(4-(2-(2,2,2-trifluoroethyl)-5,5-dimethyl-1,3-dioxane-1-carbonyl)phenyl)benzamide moiety. The other nitrogen of the piperazine is connected to a 4-(4-(2-(2,2,2-trifluoroethyl)-5,5-dimethyl-1,3-dioxane-1-carbonyl)phenyl)benzamide moiety. The molecule also includes a 4-(4-(2-(2,2,2-trifluoroethyl)-5,5-dimethyl-1,3-dioxane-1-carbonyl)phenyl)benzamide moiety and a 4-(4-(2-(2,2,2-trifluoroethyl)-5,5-dimethyl-1,3-dioxane-1-carbonyl)phenyl)benzamide moiety.

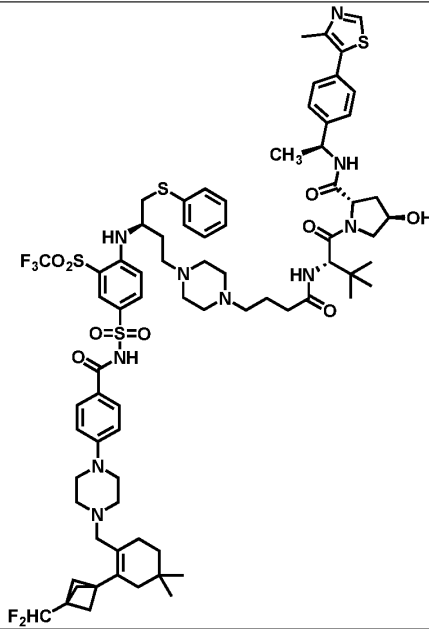
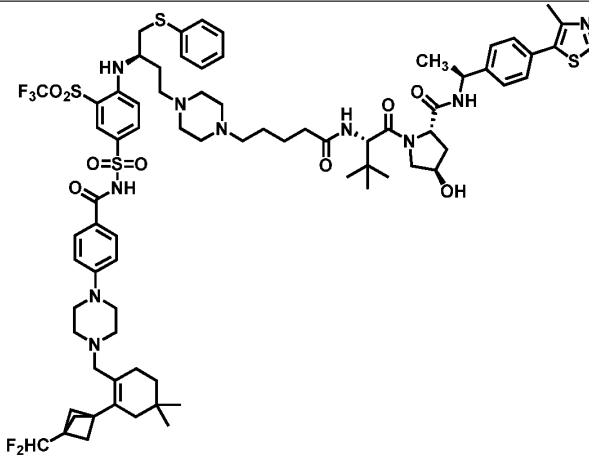
Example No.	Structure of Compound of Formula (I)
67	 Chemical structure of compound 67: A complex molecule featuring a central piperazine ring. One nitrogen of the piperazine is connected to a 4-(trifluoromethylsulfonyl)phenyl group, which is further linked to a benzothiazine moiety. The other nitrogen of the piperazine is connected to a 4-(trifluoromethylsulfonyl)phenyl group, which is further linked to a benzothiazine moiety. The molecule also includes a cyclohexene ring substituted with a difluoromethyl group and a piperazine ring.
68	 Chemical structure of compound 68: A complex molecule featuring a central piperazine ring. One nitrogen of the piperazine is connected to a 4-(trifluoromethylsulfonyl)phenyl group, which is further linked to a benzothiazine moiety. The other nitrogen of the piperazine is connected to a 4-(trifluoromethylsulfonyl)phenyl group, which is further linked to a benzothiazine moiety. The molecule also includes a cyclohexene ring substituted with a difluoromethyl group and a piperazine ring.
69	 Chemical structure of compound 69: A complex molecule featuring a central piperazine ring. One nitrogen of the piperazine is connected to a 4-(trifluoromethylsulfonyl)phenyl group, which is further linked to a benzothiazine moiety. The other nitrogen of the piperazine is connected to a 4-(trifluoromethylsulfonyl)phenyl group, which is further linked to a benzothiazine moiety. The molecule also includes a cyclohexene ring substituted with a difluoromethyl group and a piperazine ring.

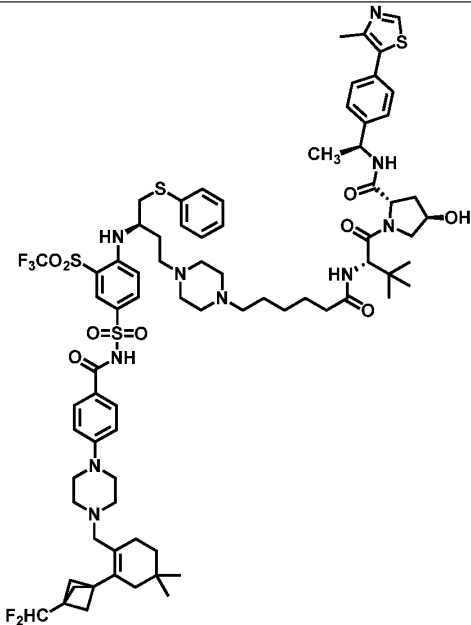
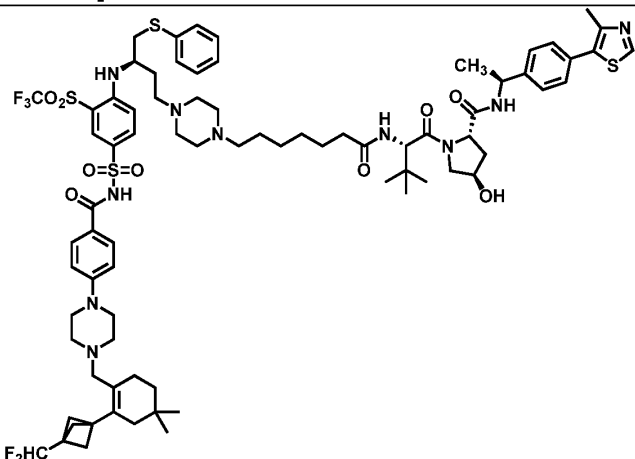
Example No.	Structure of Compound of Formula (I)
70	 Chemical structure of Compound 70: A complex molecule featuring a central piperazine ring. One nitrogen of the piperazine is connected to a 4-(trifluoromethylsulfonyl)phenyl group, which is further linked to a 4-(2,2,2-trifluoroethanesulfonyl)phenyl group. The other nitrogen of the piperazine is connected to a 4-(2,2,2-trifluoroethanesulfonyl)phenyl group, which is further linked to a 4-(2,2,2-trifluoroethanesulfonyl)phenyl group. The molecule also includes a 4-(2,2,2-trifluoroethanesulfonyl)phenyl group and a 4-(2,2,2-trifluoroethanesulfonyl)phenyl group.
71	 Chemical structure of Compound 71: A complex molecule featuring a central piperazine ring. One nitrogen of the piperazine is connected to a 4-(trifluoromethylsulfonyl)phenyl group, which is further linked to a 4-(2,2,2-trifluoroethanesulfonyl)phenyl group. The other nitrogen of the piperazine is connected to a 4-(2,2,2-trifluoroethanesulfonyl)phenyl group, which is further linked to a 4-(2,2,2-trifluoroethanesulfonyl)phenyl group. The molecule also includes a 4-(2,2,2-trifluoroethanesulfonyl)phenyl group and a 4-(2,2,2-trifluoroethanesulfonyl)phenyl group.
72	 Chemical structure of Compound 72: A complex molecule featuring a central piperazine ring. One nitrogen of the piperazine is connected to a 4-(trifluoromethylsulfonyl)phenyl group, which is further linked to a 4-(2,2,2-trifluoroethanesulfonyl)phenyl group. The other nitrogen of the piperazine is connected to a 4-(2,2,2-trifluoroethanesulfonyl)phenyl group, which is further linked to a 4-(2,2,2-trifluoroethanesulfonyl)phenyl group. The molecule also includes a 4-(2,2,2-trifluoroethanesulfonyl)phenyl group and a 4-(2,2,2-trifluoroethanesulfonyl)phenyl group.

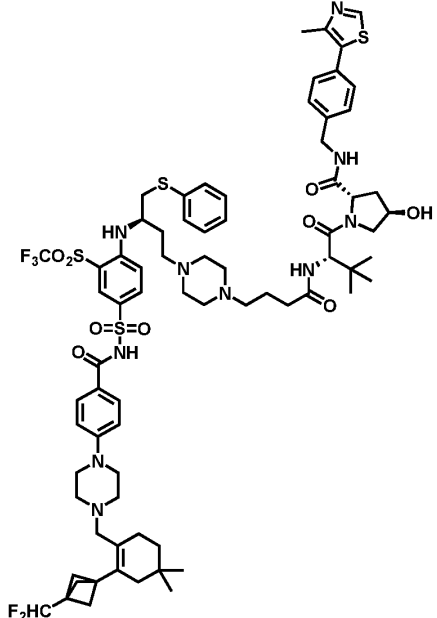
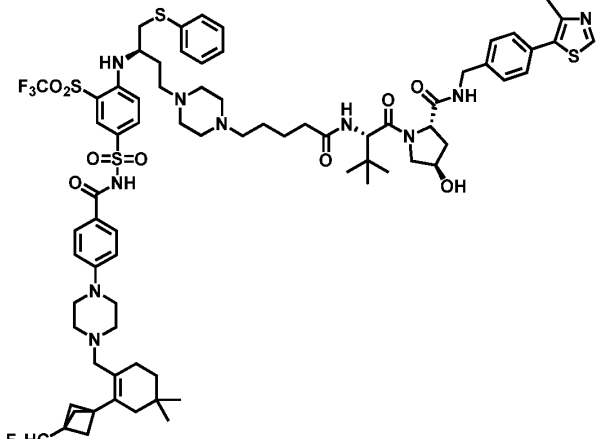
Example No.	Structure of Compound of Formula (I)
73	 Chemical structure of Compound 73: A complex molecule featuring a central piperazine ring. One nitrogen of the piperazine is substituted with a 4-(trifluoromethylsulfonyl)phenyl group and a 4-(2,2,2-trifluoroethoxy)phenyl group. The other nitrogen is substituted with a 4-(2,2,2-trifluoroethoxy)phenyl group and a 4-(2,2,2-trifluoroethoxy)phenyl group. The molecule also includes a 4-(2,2,2-trifluoroethoxy)phenyl group, a 4-(2,2,2-trifluoroethoxy)phenyl group, and a 4-(2,2,2-trifluoroethoxy)phenyl group.
74	 Chemical structure of Compound 74: A complex molecule featuring a central piperazine ring. One nitrogen of the piperazine is substituted with a 4-(trifluoromethylsulfonyl)phenyl group and a 4-(2,2,2-trifluoroethoxy)phenyl group. The other nitrogen is substituted with a 4-(2,2,2-trifluoroethoxy)phenyl group and a 4-(2,2,2-trifluoroethoxy)phenyl group. The molecule also includes a 4-(2,2,2-trifluoroethoxy)phenyl group, a 4-(2,2,2-trifluoroethoxy)phenyl group, and a 4-(2,2,2-trifluoroethoxy)phenyl group.
75	 Chemical structure of Compound 75: A complex molecule featuring a central piperazine ring. One nitrogen of the piperazine is substituted with a 4-(trifluoromethylsulfonyl)phenyl group and a 4-(2,2,2-trifluoroethoxy)phenyl group. The other nitrogen is substituted with a 4-(2,2,2-trifluoroethoxy)phenyl group and a 4-(2,2,2-trifluoroethoxy)phenyl group. The molecule also includes a 4-(2,2,2-trifluoroethoxy)phenyl group, a 4-(2,2,2-trifluoroethoxy)phenyl group, and a 4-(2,2,2-trifluoroethoxy)phenyl group.

Example No.	Structure of Compound of Formula (I)
76	
77	

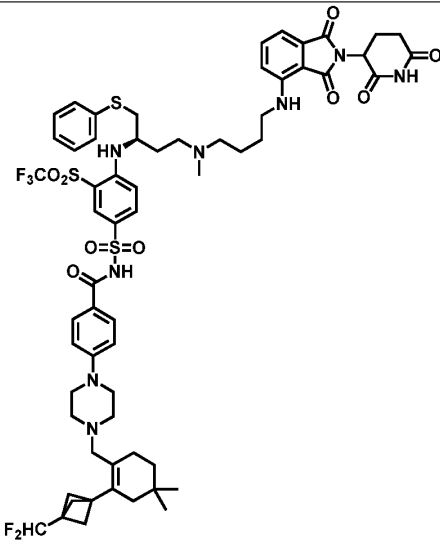
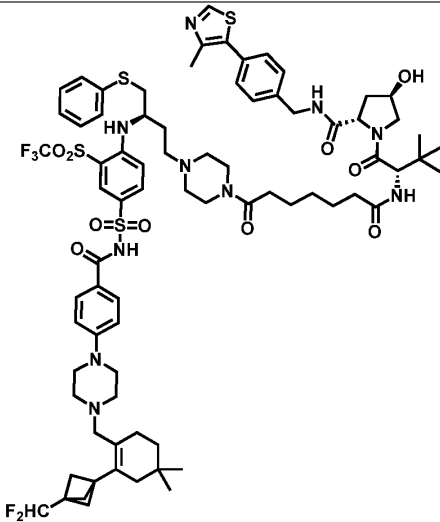
Example No.	Structure of Compound of Formula (I)
78	 Chemical structure of Compound 78: A complex molecule featuring a central piperazine ring. One nitrogen of the piperazine is substituted with a 4-(trifluoromethylsulfonyl)phenyl group and a 4-(2-(2,2,2-trifluoroethoxy)phenyl)phenyl group. The other nitrogen is substituted with a 4-(2-(2,2,2-trifluoroethoxy)phenyl)phenyl group and a 4-(2-(2,2,2-trifluoroethoxy)phenyl)phenyl group. The molecule also includes a 4-(2-(2,2,2-trifluoroethoxy)phenyl)phenyl group and a 4-(2-(2,2,2-trifluoroethoxy)phenyl)phenyl group.
79	 Chemical structure of Compound 79: A complex molecule featuring a central piperazine ring. One nitrogen of the piperazine is substituted with a 4-(trifluoromethylsulfonyl)phenyl group and a 4-(2-(2,2,2-trifluoroethoxy)phenyl)phenyl group. The other nitrogen is substituted with a 4-(2-(2,2,2-trifluoroethoxy)phenyl)phenyl group and a 4-(2-(2,2,2-trifluoroethoxy)phenyl)phenyl group. The molecule also includes a 4-(2-(2,2,2-trifluoroethoxy)phenyl)phenyl group and a 4-(2-(2,2,2-trifluoroethoxy)phenyl)phenyl group.

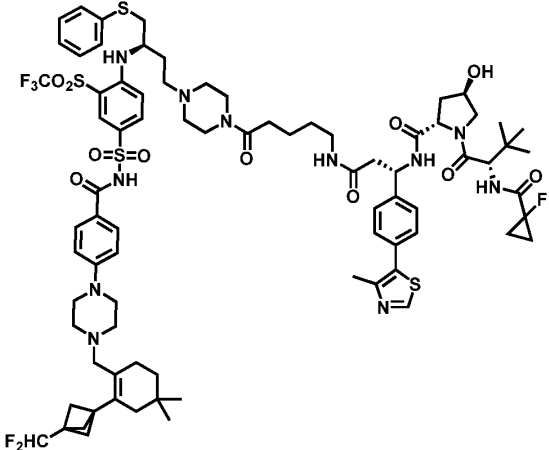
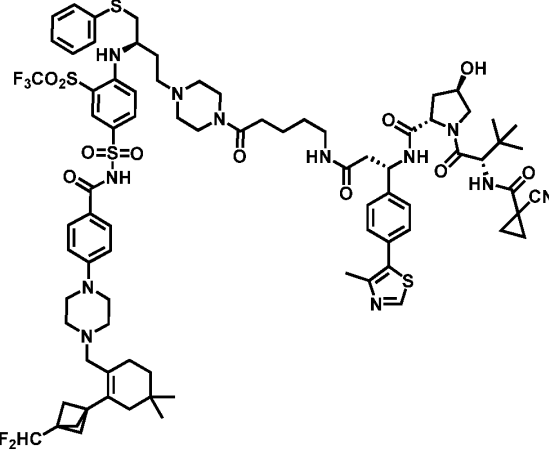
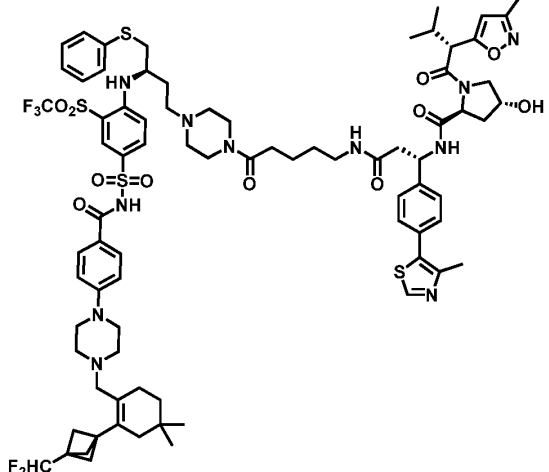
Example No.	Structure of Compound of Formula (I)
80	 Chemical structure of Compound 80: A complex molecule featuring a central piperazine ring. One nitrogen of the piperazine is substituted with a 4-(trifluoromethylsulfonyl)phenyl group. The other nitrogen is substituted with a 4-(4-(2-hydroxy-2-methyl-1H-imidazol-1-yl)-1H-imidazol-5-yl)phenyl group. The piperazine ring is also substituted with a 4-(4-(2-hydroxy-2-methyl-1H-imidazol-1-yl)-1H-imidazol-5-yl)phenyl group. The piperazine ring is further substituted with a 4-(4-(2-hydroxy-2-methyl-1H-imidazol-1-yl)-1H-imidazol-5-yl)phenyl group. The piperazine ring is also substituted with a 4-(4-(2-hydroxy-2-methyl-1H-imidazol-1-yl)-1H-imidazol-5-yl)phenyl group.
81	 Chemical structure of Compound 81: A complex molecule featuring a central piperazine ring. One nitrogen of the piperazine is substituted with a 4-(trifluoromethylsulfonyl)phenyl group. The other nitrogen is substituted with a 4-(4-(2-hydroxy-2-methyl-1H-imidazol-1-yl)-1H-imidazol-5-yl)phenyl group. The piperazine ring is also substituted with a 4-(4-(2-hydroxy-2-methyl-1H-imidazol-1-yl)-1H-imidazol-5-yl)phenyl group. The piperazine ring is further substituted with a 4-(4-(2-hydroxy-2-methyl-1H-imidazol-1-yl)-1H-imidazol-5-yl)phenyl group. The piperazine ring is also substituted with a 4-(4-(2-hydroxy-2-methyl-1H-imidazol-1-yl)-1H-imidazol-5-yl)phenyl group.

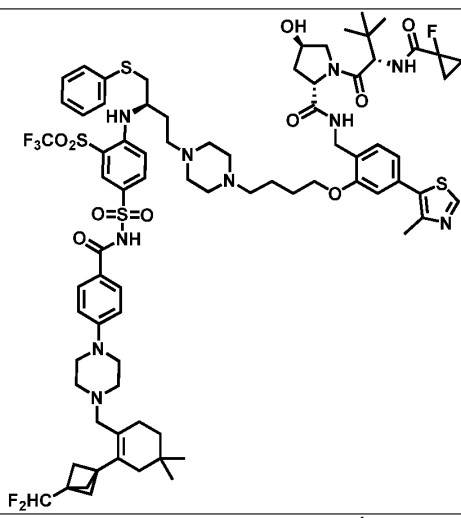
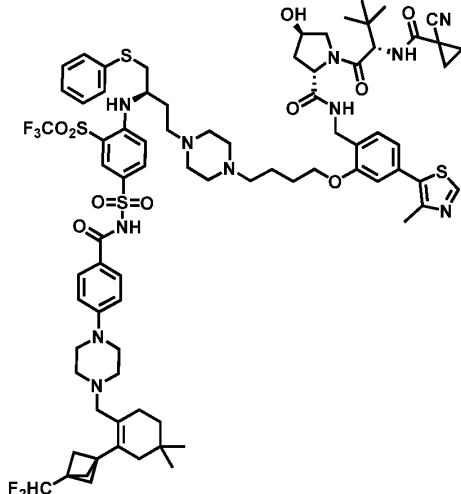
Example No.	Structure of Compound of Formula (I)
82	 Chemical structure of Compound 82: A complex molecule featuring a central piperazine ring. One piperazine nitrogen is connected to a 4-(trifluoromethylsulfonyl)phenyl group via a methylene linker. The other piperazine nitrogen is connected to a 4-(2,2,2-trimethyl-4-hydroxy-1H-pyrazol-5-yl)phenyl group via a methylene linker. The 4-(trifluoromethylsulfonyl)phenyl group is also connected to a 4-(2,2,2-trimethyl-4-hydroxy-1H-pyrazol-5-yl)phenyl group via a methylene linker. The 4-(2,2,2-trimethyl-4-hydroxy-1H-pyrazol-5-yl)phenyl group is further connected to a 4-(2,2,2-trimethyl-4-hydroxy-1H-pyrazol-5-yl)phenyl group via a methylene linker. The 4-(2,2,2-trimethyl-4-hydroxy-1H-pyrazol-5-yl)phenyl group is also connected to a 4-(2,2,2-trimethyl-4-hydroxy-1H-pyrazol-5-yl)phenyl group via a methylene linker.
83	 Chemical structure of Compound 83: A complex molecule featuring a central piperazine ring. One piperazine nitrogen is connected to a 4-(trifluoromethylsulfonyl)phenyl group via a methylene linker. The other piperazine nitrogen is connected to a 4-(2,2,2-trimethyl-4-hydroxy-1H-pyrazol-5-yl)phenyl group via a methylene linker. The 4-(trifluoromethylsulfonyl)phenyl group is also connected to a 4-(2,2,2-trimethyl-4-hydroxy-1H-pyrazol-5-yl)phenyl group via a methylene linker. The 4-(2,2,2-trimethyl-4-hydroxy-1H-pyrazol-5-yl)phenyl group is further connected to a 4-(2,2,2-trimethyl-4-hydroxy-1H-pyrazol-5-yl)phenyl group via a methylene linker. The 4-(2,2,2-trimethyl-4-hydroxy-1H-pyrazol-5-yl)phenyl group is also connected to a 4-(2,2,2-trimethyl-4-hydroxy-1H-pyrazol-5-yl)phenyl group via a methylene linker.

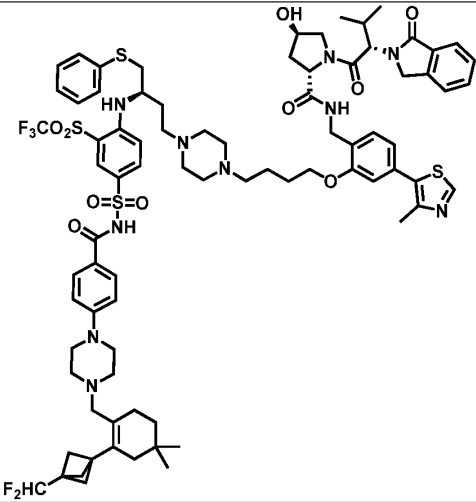
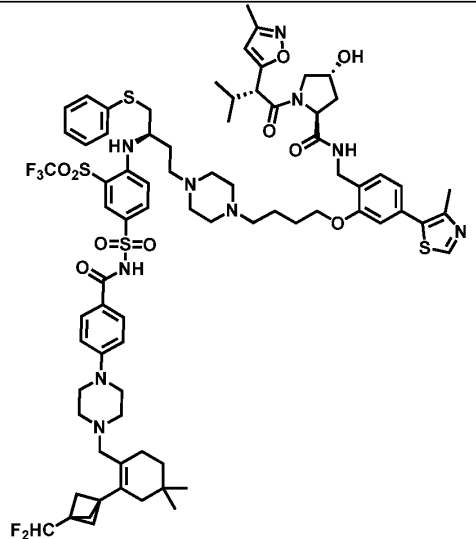
Example No.	Structure of Compound of Formula (I)
84	 Chemical structure of Compound 84. The molecule features a central piperazine ring. One nitrogen of the piperazine is substituted with a 4-(trifluoromethylsulfonyl)phenyl group. The other nitrogen is substituted with a 4-(2-(2,6-dimethyl-1,3,4-thiazol-5-yl)phenyl)phenyl group. The piperazine ring is also substituted with a 4-(2-(2,6-dimethyl-1,3,4-thiazol-5-yl)phenyl)phenyl group. The piperazine ring is also substituted with a 4-(2-(2,6-dimethyl-1,3,4-thiazol-5-yl)phenyl)phenyl group. The piperazine ring is also substituted with a 4-(2-(2,6-dimethyl-1,3,4-thiazol-5-yl)phenyl)phenyl group.
85	 Chemical structure of Compound 85. The molecule features a central piperazine ring. One nitrogen of the piperazine is substituted with a 4-(trifluoromethylsulfonyl)phenyl group. The other nitrogen is substituted with a 4-(2-(2,6-dimethyl-1,3,4-thiazol-5-yl)phenyl)phenyl group. The piperazine ring is also substituted with a 4-(2-(2,6-dimethyl-1,3,4-thiazol-5-yl)phenyl)phenyl group. The piperazine ring is also substituted with a 4-(2-(2,6-dimethyl-1,3,4-thiazol-5-yl)phenyl)phenyl group. The piperazine ring is also substituted with a 4-(2-(2,6-dimethyl-1,3,4-thiazol-5-yl)phenyl)phenyl group.

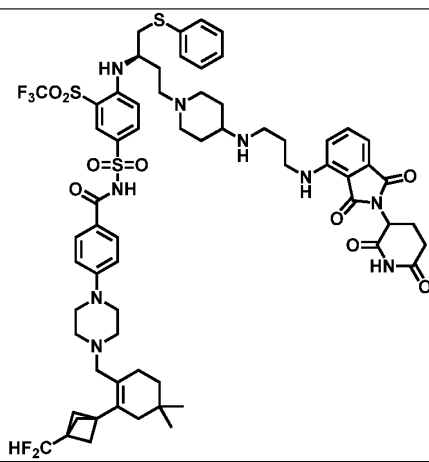
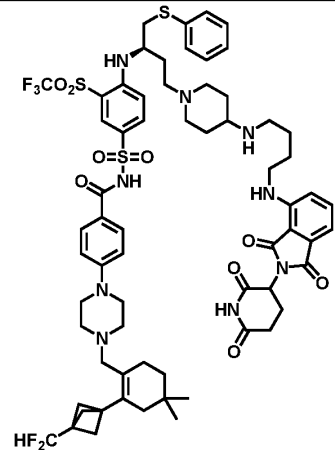
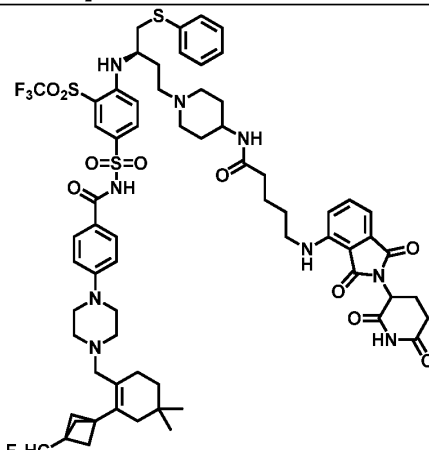
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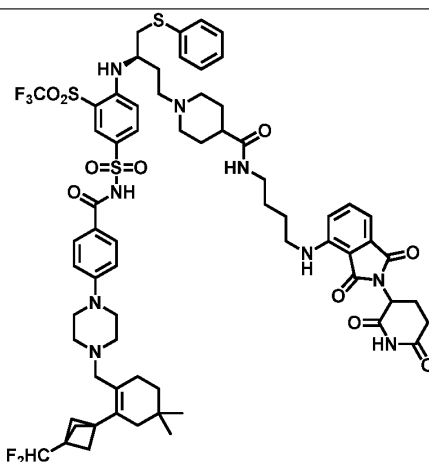
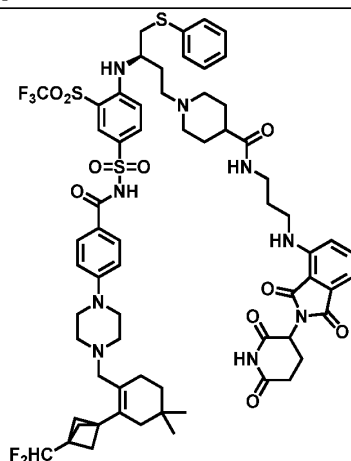
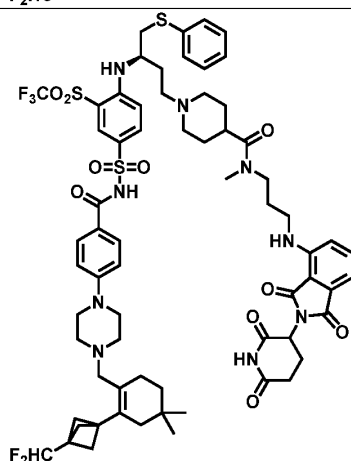
Example No.	Structure of Compound of Formula (I)
88	 Chemical structure of Compound 88: A complex molecule featuring a central piperazine ring. One nitrogen of the piperazine is connected to a 4-(trifluoromethylsulfonyl)phenyl group, which is further linked to a benzothiazine moiety. The other nitrogen of the piperazine is connected to a 4-(trifluoromethylsulfonyl)phenyl group, which is further linked to a benzothiazine moiety. The benzothiazine moiety is connected to a 4-(trifluoromethylsulfonyl)phenyl group, which is further linked to a benzothiazine moiety. The benzothiazine moiety is connected to a 4-(trifluoromethylsulfonyl)phenyl group, which is further linked to a benzothiazine moiety.
89	 Chemical structure of Compound 89: A complex molecule featuring a central piperazine ring. One nitrogen of the piperazine is connected to a 4-(trifluoromethylsulfonyl)phenyl group, which is further linked to a benzothiazine moiety. The other nitrogen of the piperazine is connected to a 4-(trifluoromethylsulfonyl)phenyl group, which is further linked to a benzothiazine moiety. The benzothiazine moiety is connected to a 4-(trifluoromethylsulfonyl)phenyl group, which is further linked to a benzothiazine moiety. The benzothiazine moiety is connected to a 4-(trifluoromethylsulfonyl)phenyl group, which is further linked to a benzothiazine moiety.

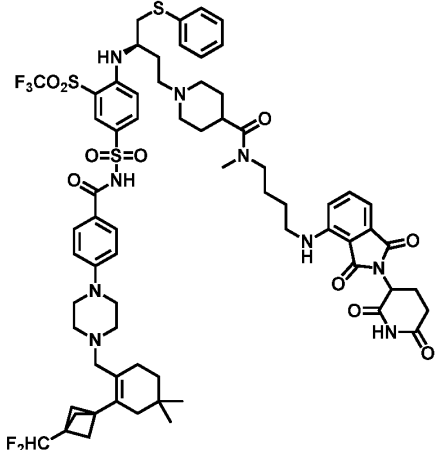
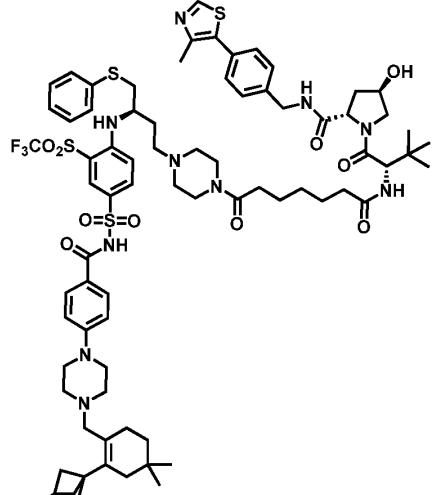
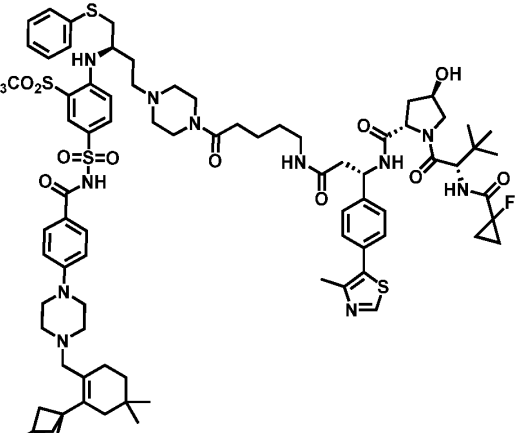
Example No.	Structure of Compound of Formula (I)
90	 Chemical structure of Compound 90: A complex molecule featuring a central piperazine ring. One nitrogen of the piperazine is substituted with a 4-(trifluoromethylsulfonyl)phenyl group. The other nitrogen is substituted with a 4-(4-(2-(2,2,2-trifluoroethyl)-1,3-dioxol-5-yl)phenyl)phenyl group. The 4-(2-(2,2,2-trifluoroethyl)-1,3-dioxol-5-yl)phenyl group is further substituted with a 4-(2-(2,2,2-trifluoroethyl)-1,3-dioxol-5-yl)phenyl group. The 4-(2-(2,2,2-trifluoroethyl)-1,3-dioxol-5-yl)phenyl group is further substituted with a 4-(2-(2,2,2-trifluoroethyl)-1,3-dioxol-5-yl)phenyl group.
91	 Chemical structure of Compound 91: A complex molecule featuring a central piperazine ring. One nitrogen of the piperazine is substituted with a 4-(trifluoromethylsulfonyl)phenyl group. The other nitrogen is substituted with a 4-(4-(2-(2,2,2-trifluoroethyl)-1,3-dioxol-5-yl)phenyl)phenyl group. The 4-(2-(2,2,2-trifluoroethyl)-1,3-dioxol-5-yl)phenyl group is further substituted with a 4-(2-(2,2,2-trifluoroethyl)-1,3-dioxol-5-yl)phenyl group. The 4-(2-(2,2,2-trifluoroethyl)-1,3-dioxol-5-yl)phenyl group is further substituted with a 4-(2-(2,2,2-trifluoroethyl)-1,3-dioxol-5-yl)phenyl group.
92	 Chemical structure of Compound 92: A complex molecule featuring a central piperazine ring. One nitrogen of the piperazine is substituted with a 4-(trifluoromethylsulfonyl)phenyl group. The other nitrogen is substituted with a 4-(4-(2-(2,2,2-trifluoroethyl)-1,3-dioxol-5-yl)phenyl)phenyl group. The 4-(2-(2,2,2-trifluoroethyl)-1,3-dioxol-5-yl)phenyl group is further substituted with a 4-(2-(2,2,2-trifluoroethyl)-1,3-dioxol-5-yl)phenyl group. The 4-(2-(2,2,2-trifluoroethyl)-1,3-dioxol-5-yl)phenyl group is further substituted with a 4-(2-(2,2,2-trifluoroethyl)-1,3-dioxol-5-yl)phenyl group.

Example No.	Structure of Compound of Formula (I)
93	 Chemical structure of Compound 93. The molecule features a central piperazine ring. One nitrogen of the piperazine is connected via a 4-oxo-4H-thiazol-2-ylmethyl group to a 4-(2,4-difluorophenyl)-2-methyl-5-oxo-1,3-dioxane-1-carboxamide moiety. The other nitrogen of the piperazine is connected via a 4-oxo-4H-thiazol-2-ylmethyl group to a 4-(2,4-difluorophenyl)-2-methyl-5-oxo-1,3-dioxane-1-carboxamide moiety. The central piperazine ring is also connected to a 4-(2,4-difluorophenyl)-2-methyl-5-oxo-1,3-dioxane-1-carboxamide moiety. The molecule includes a trifluoromethyl group (F₃CO₂S), a sulfonamide group (SO₂NH), a thiazole ring, a 2,4-difluorophenyl group, a 2-methyl-5-oxo-1,3-dioxane-1-carboxamide moiety, and a 4-oxo-4H-thiazol-2-ylmethyl group.
94	 Chemical structure of Compound 94. The molecule features a central piperazine ring. One nitrogen of the piperazine is connected via a 4-oxo-4H-thiazol-2-ylmethyl group to a 4-(2,4-difluorophenyl)-2-methyl-5-oxo-1,3-dioxane-1-carboxamide moiety. The other nitrogen of the piperazine is connected via a 4-oxo-4H-thiazol-2-ylmethyl group to a 4-(2,4-difluorophenyl)-2-methyl-5-oxo-1,3-dioxane-1-carboxamide moiety. The central piperazine ring is also connected to a 4-(2,4-difluorophenyl)-2-methyl-5-oxo-1,3-dioxane-1-carboxamide moiety. The molecule includes a trifluoromethyl group (F₃CO₂S), a sulfonamide group (SO₂NH), a thiazole ring, a 2,4-difluorophenyl group, a 2-methyl-5-oxo-1,3-dioxane-1-carboxamide moiety, and a 4-oxo-4H-thiazol-2-ylmethyl group.

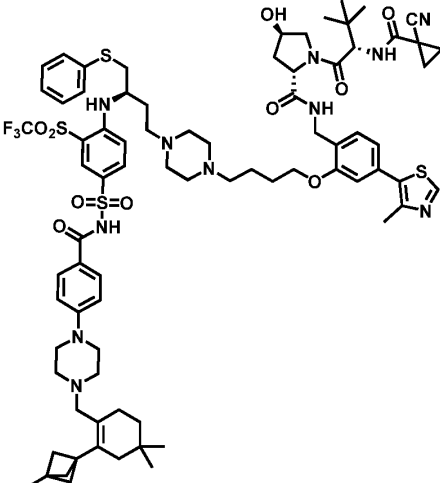
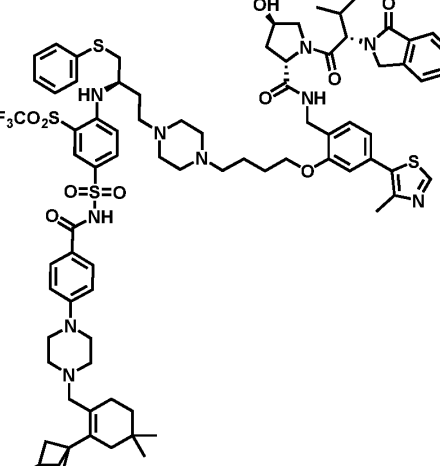
Example No.	Structure of Compound of Formula (I)
95	 Chemical structure of Compound 95. The molecule features a central piperazine ring. One nitrogen of the piperazine is connected via a methylene group to a 1-phenyl-2-(trifluoromethylsulfonyl)ethan-1-amine moiety. The other nitrogen of the piperazine is connected via a butoxy chain to a 4-(2-methyl-1,3,4-thiazol-5-yl)phenyl group. Additionally, the piperazine ring is substituted with a 4-(2-(2,2-dimethyl-4-(2,2,2-trifluoroethylidene)cyclopropyl)ethyl)piperidin-1-yl group and a 4-(2-(2,2-dimethyl-4-(2,2,2-trifluoroethylidene)cyclopropyl)ethyl)piperidin-1-yl group.
96	 Chemical structure of Compound 96. The molecule features a central piperazine ring. One nitrogen of the piperazine is connected via a methylene group to a 1-phenyl-2-(trifluoromethylsulfonyl)ethan-1-amine moiety. The other nitrogen of the piperazine is connected via a butoxy chain to a 4-(2-methyl-1,3,4-thiazol-5-yl)phenyl group. Additionally, the piperazine ring is substituted with a 4-(2-(2,2-dimethyl-4-(2,2,2-trifluoroethylidene)cyclopropyl)ethyl)piperidin-1-yl group and a 4-(2-(2,2-dimethyl-4-(2,2,2-trifluoroethylidene)cyclopropyl)ethyl)piperidin-1-yl group.

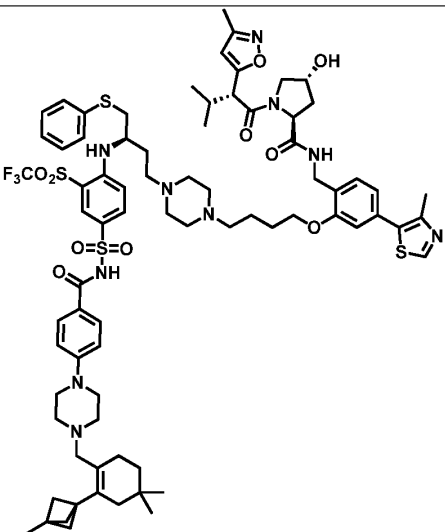
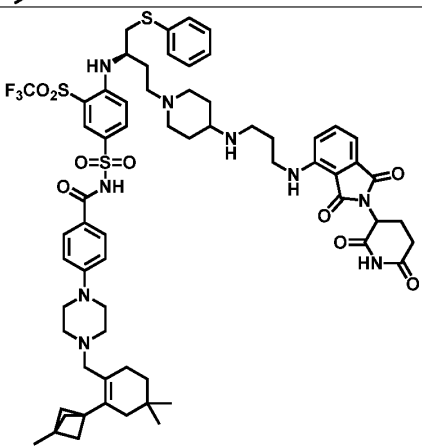
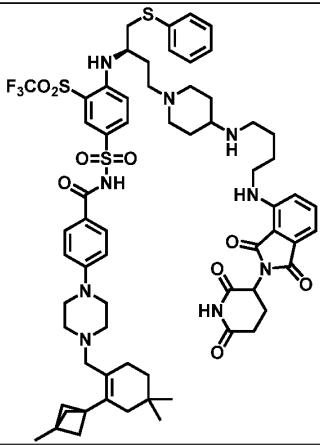
Example No.	Structure of Compound of Formula (I)
97	 Chemical structure of Compound 97: A complex molecule featuring a central piperazine ring. One nitrogen of the piperazine is connected to a 4-(trifluoromethylsulfonyl)phenyl group. The other nitrogen is connected to a 4-(2,2,2-trifluoroethyl)phenyl group. The 2,2,2-trifluoroethyl group is further substituted with a 4-(2,2,2-trifluoroethyl)phenyl group. The 2,2,2-trifluoroethyl group is also substituted with a 4-(2,2,2-trifluoroethyl)phenyl group. The 2,2,2-trifluoroethyl group is also substituted with a 4-(2,2,2-trifluoroethyl)phenyl group.
98	 Chemical structure of Compound 98: A complex molecule featuring a central piperazine ring. One nitrogen of the piperazine is connected to a 4-(trifluoromethylsulfonyl)phenyl group. The other nitrogen is connected to a 4-(2,2,2-trifluoroethyl)phenyl group. The 2,2,2-trifluoroethyl group is further substituted with a 4-(2,2,2-trifluoroethyl)phenyl group. The 2,2,2-trifluoroethyl group is also substituted with a 4-(2,2,2-trifluoroethyl)phenyl group. The 2,2,2-trifluoroethyl group is also substituted with a 4-(2,2,2-trifluoroethyl)phenyl group.
99	 Chemical structure of Compound 99: A complex molecule featuring a central piperazine ring. One nitrogen of the piperazine is connected to a 4-(trifluoromethylsulfonyl)phenyl group. The other nitrogen is connected to a 4-(2,2,2-trifluoroethyl)phenyl group. The 2,2,2-trifluoroethyl group is further substituted with a 4-(2,2,2-trifluoroethyl)phenyl group. The 2,2,2-trifluoroethyl group is also substituted with a 4-(2,2,2-trifluoroethyl)phenyl group. The 2,2,2-trifluoroethyl group is also substituted with a 4-(2,2,2-trifluoroethyl)phenyl group.

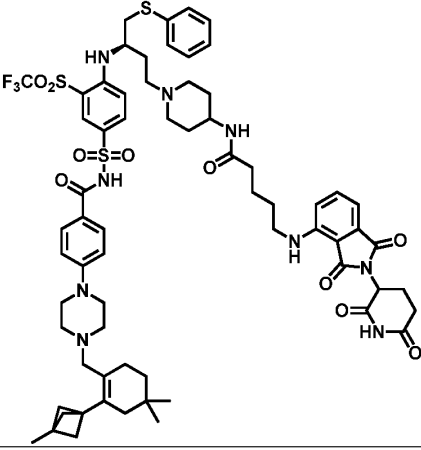
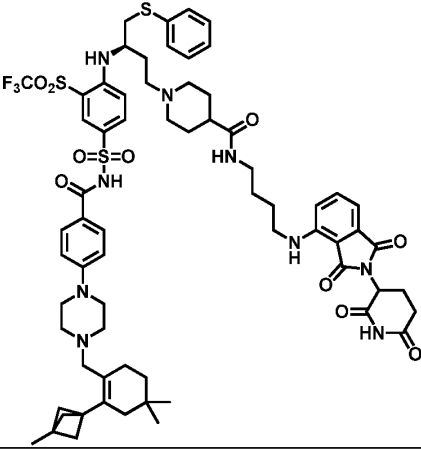
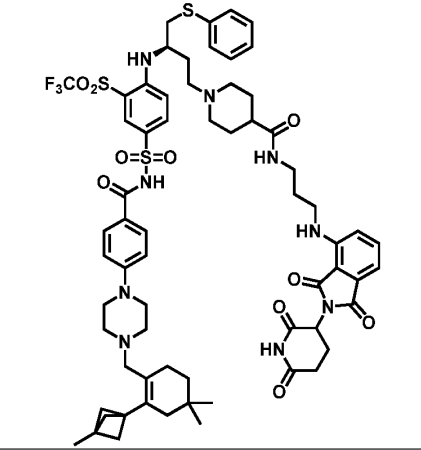
Example No.	Structure of Compound of Formula (I)
100	 Chemical structure of Compound 100. It features a central piperazine ring substituted with a 4-(trifluoromethylsulfonyl)phenyl group, a 4-(2,2,2-trifluoroethoxy)phenyl group, and a 4-(2,2,2-trifluoroethoxy)phenyl group. The piperazine is also linked to a 4-(2,2,2-trifluoroethoxy)phenyl group. The structure includes a 4-(2,2,2-trifluoroethoxy)phenyl group, a 4-(2,2,2-trifluoroethoxy)phenyl group, and a 4-(2,2,2-trifluoroethoxy)phenyl group. The structure is a complex molecule with multiple functional groups and a central piperazine ring.
101	 Chemical structure of Compound 101. It features a central piperazine ring substituted with a 4-(trifluoromethylsulfonyl)phenyl group, a 4-(2,2,2-trifluoroethoxy)phenyl group, and a 4-(2,2,2-trifluoroethoxy)phenyl group. The piperazine is also linked to a 4-(2,2,2-trifluoroethoxy)phenyl group. The structure includes a 4-(2,2,2-trifluoroethoxy)phenyl group, a 4-(2,2,2-trifluoroethoxy)phenyl group, and a 4-(2,2,2-trifluoroethoxy)phenyl group. The structure is a complex molecule with multiple functional groups and a central piperazine ring.
102	 Chemical structure of Compound 102. It features a central piperazine ring substituted with a 4-(trifluoromethylsulfonyl)phenyl group, a 4-(2,2,2-trifluoroethoxy)phenyl group, and a 4-(2,2,2-trifluoroethoxy)phenyl group. The piperazine is also linked to a 4-(2,2,2-trifluoroethoxy)phenyl group. The structure includes a 4-(2,2,2-trifluoroethoxy)phenyl group, a 4-(2,2,2-trifluoroethoxy)phenyl group, and a 4-(2,2,2-trifluoroethoxy)phenyl group. The structure is a complex molecule with multiple functional groups and a central piperazine ring.

Example No.	Structure of Compound of Formula (I)
103	 Chemical structure of Compound 103: A complex molecule featuring a central piperazine ring. One nitrogen of the piperazine is substituted with a 4-(trifluoromethylsulfonyl)phenyl group. The other nitrogen is substituted with a 4-(2-(2,2,2-trifluoroethyl)oxy)phenyl group. The piperazine ring is also substituted with a 4-(2-(2,2,2-trifluoroethyl)oxy)phenyl group. The piperazine ring is further substituted with a 4-(2-(2,2,2-trifluoroethyl)oxy)phenyl group. The piperazine ring is also substituted with a 4-(2-(2,2,2-trifluoroethyl)oxy)phenyl group.
104	 Chemical structure of Compound 104: A complex molecule featuring a central piperazine ring. One nitrogen of the piperazine is substituted with a 4-(trifluoromethylsulfonyl)phenyl group. The other nitrogen is substituted with a 4-(2-(2,2,2-trifluoroethyl)oxy)phenyl group. The piperazine ring is also substituted with a 4-(2-(2,2,2-trifluoroethyl)oxy)phenyl group. The piperazine ring is further substituted with a 4-(2-(2,2,2-trifluoroethyl)oxy)phenyl group. The piperazine ring is also substituted with a 4-(2-(2,2,2-trifluoroethyl)oxy)phenyl group.
105	 Chemical structure of Compound 105: A complex molecule featuring a central piperazine ring. One nitrogen of the piperazine is substituted with a 4-(trifluoromethylsulfonyl)phenyl group. The other nitrogen is substituted with a 4-(2-(2,2,2-trifluoroethyl)oxy)phenyl group. The piperazine ring is also substituted with a 4-(2-(2,2,2-trifluoroethyl)oxy)phenyl group. The piperazine ring is further substituted with a 4-(2-(2,2,2-trifluoroethyl)oxy)phenyl group. The piperazine ring is also substituted with a 4-(2-(2,2,2-trifluoroethyl)oxy)phenyl group.

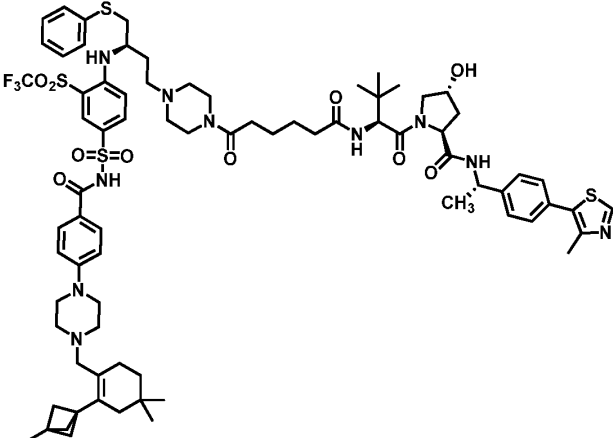
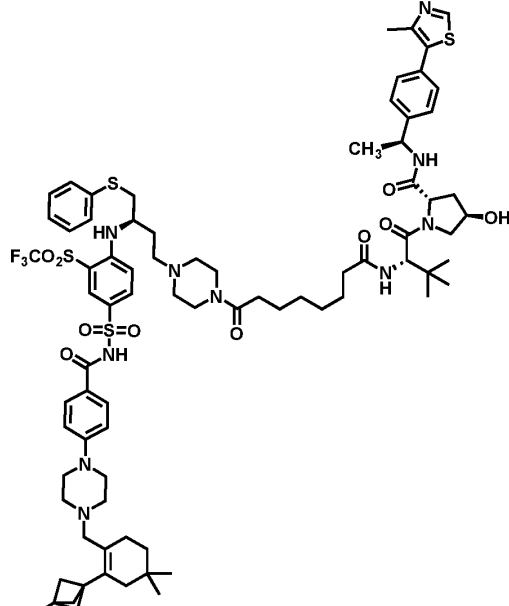
Example No.	Structure of Compound of Formula (I)
106	
107	
108	

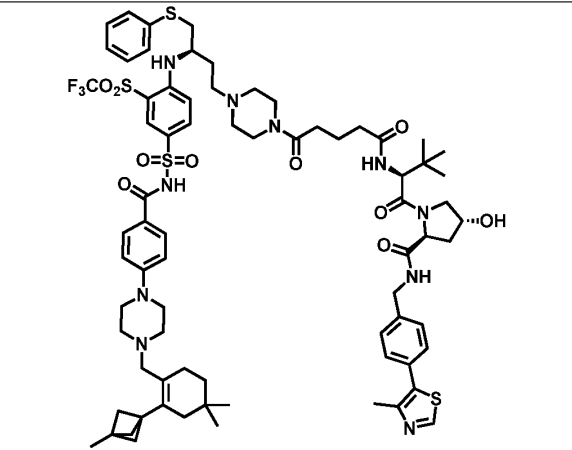
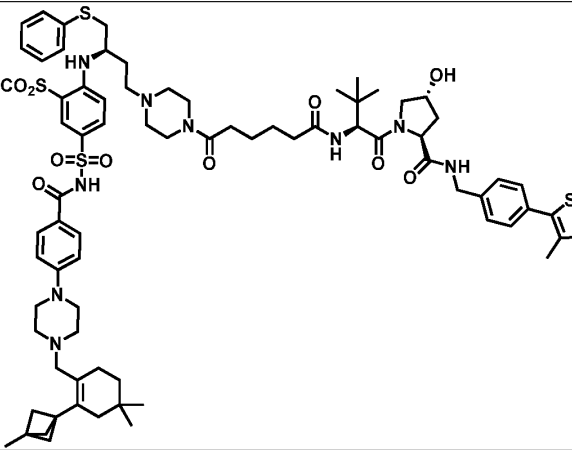
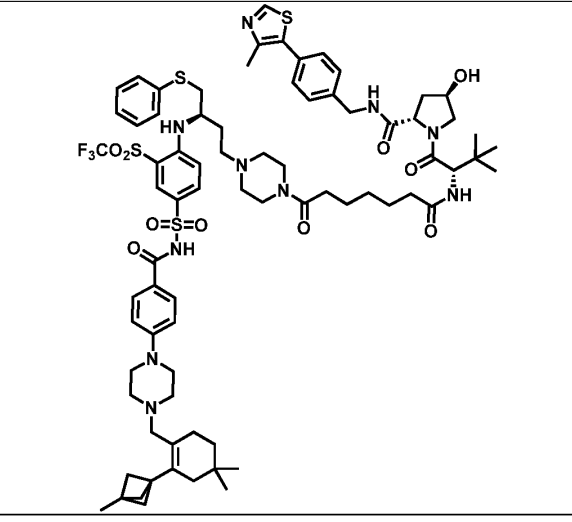
Example No.	Structure of Compound of Formula (I)
109	 Chemical structure of Compound 109. The molecule features a central piperazine ring. One nitrogen of the piperazine is connected via a methylene group to a 2-phenylthio-5-(trifluoromethylsulfonyl)phenyl group. The other nitrogen of the piperazine is connected via a 4-oxopiperidin-2-yl group to a 4-(4-methyl-1,3,4-thiazol-5-yl)phenoxy group. The 4-methyl-1,3,4-thiazol-5-yl group is further substituted with a 2-cyano-2-methyl-3-oxo-1,3-dihydro-4H-pyridin-4-yl group. The 4-oxopiperidin-2-yl group is also substituted with a 2-cyano-2-methyl-3-oxo-1,3-dihydro-4H-pyridin-4-yl group. The 2-phenylthio-5-(trifluoromethylsulfonyl)phenyl group is further substituted with a 2-((4-methyl-1,3,4-thiazol-5-yl)methyl)phenyl group. The 2-((4-methyl-1,3,4-thiazol-5-yl)methyl)phenyl group is further substituted with a 2-((4-methyl-1,3,4-thiazol-5-yl)methyl)phenyl group.
110	 Chemical structure of Compound 110. The molecule features a central piperazine ring. One nitrogen of the piperazine is connected via a methylene group to a 2-phenylthio-5-(trifluoromethylsulfonyl)phenyl group. The other nitrogen of the piperazine is connected via a 4-oxopiperidin-2-yl group to a 4-(4-methyl-1,3,4-thiazol-5-yl)phenoxy group. The 4-methyl-1,3,4-thiazol-5-yl group is further substituted with a 2-cyano-2-methyl-3-oxo-1,3-dihydro-4H-pyridin-4-yl group. The 4-oxopiperidin-2-yl group is also substituted with a 2-cyano-2-methyl-3-oxo-1,3-dihydro-4H-pyridin-4-yl group. The 2-phenylthio-5-(trifluoromethylsulfonyl)phenyl group is further substituted with a 2-((4-methyl-1,3,4-thiazol-5-yl)methyl)phenyl group. The 2-((4-methyl-1,3,4-thiazol-5-yl)methyl)phenyl group is further substituted with a 2-((4-methyl-1,3,4-thiazol-5-yl)methyl)phenyl group.

Example No.	Structure of Compound of Formula (I)
111	 Chemical structure of compound 111. It features a central piperazine ring. One nitrogen of the piperazine is connected to a 4-(trifluoromethylsulfonyl)phenyl group, which is further linked to a benzothiazine moiety. The other nitrogen of the piperazine is connected to a 4-(4-methyl-1,3,4-thiazol-5-yl)phenyl group via a propyl chain. A side chain on the benzothiazine moiety includes a hydroxyl group and a thiazole ring.
112	 Chemical structure of compound 112. It features a central piperazine ring. One nitrogen of the piperazine is connected to a 4-(trifluoromethylsulfonyl)phenyl group, which is further linked to a benzothiazine moiety. The other nitrogen of the piperazine is connected to a 4-(4-methyl-1,3,4-thiazol-5-yl)phenyl group via a propyl chain. A side chain on the benzothiazine moiety includes a hydroxyl group and a thiazole ring.
113	 Chemical structure of compound 113. It features a central piperazine ring. One nitrogen of the piperazine is connected to a 4-(trifluoromethylsulfonyl)phenyl group, which is further linked to a benzothiazine moiety. The other nitrogen of the piperazine is connected to a 4-(4-methyl-1,3,4-thiazol-5-yl)phenyl group via a propyl chain. A side chain on the benzothiazine moiety includes a hydroxyl group and a thiazole ring.

Example No.	Structure of Compound of Formula (I)
114	 Chemical structure of compound 114. It features a central piperazine ring substituted with a 4-(trifluoromethylsulfonyl)phenyl group, a 4-(2,6-dimethyl-4-(cyclopropylmethyl)-6-methylphenyl)phenyl group, and a 4-(2,6-dimethyl-4-(cyclopropylmethyl)-6-methylphenyl)phenyl group. The piperazine ring is also substituted with a 4-(2,6-dimethyl-4-(cyclopropylmethyl)-6-methylphenyl)phenyl group. The structure includes a sulfonamide group, a sulfonamide group, and a sulfonamide group.
115	 Chemical structure of compound 115. It features a central piperazine ring substituted with a 4-(trifluoromethylsulfonyl)phenyl group, a 4-(2,6-dimethyl-4-(cyclopropylmethyl)-6-methylphenyl)phenyl group, and a 4-(2,6-dimethyl-4-(cyclopropylmethyl)-6-methylphenyl)phenyl group. The piperazine ring is also substituted with a 4-(2,6-dimethyl-4-(cyclopropylmethyl)-6-methylphenyl)phenyl group. The structure includes a sulfonamide group, a sulfonamide group, and a sulfonamide group.
116	 Chemical structure of compound 116. It features a central piperazine ring substituted with a 4-(trifluoromethylsulfonyl)phenyl group, a 4-(2,6-dimethyl-4-(cyclopropylmethyl)-6-methylphenyl)phenyl group, and a 4-(2,6-dimethyl-4-(cyclopropylmethyl)-6-methylphenyl)phenyl group. The piperazine ring is also substituted with a 4-(2,6-dimethyl-4-(cyclopropylmethyl)-6-methylphenyl)phenyl group. The structure includes a sulfonamide group, a sulfonamide group, and a sulfonamide group.

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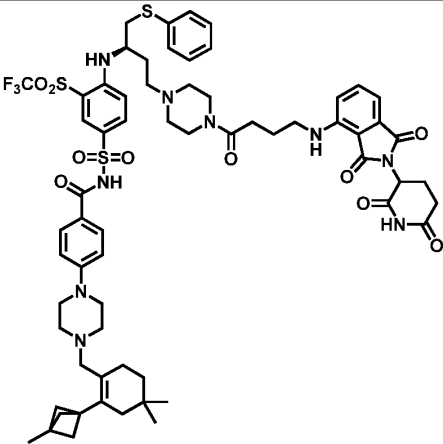
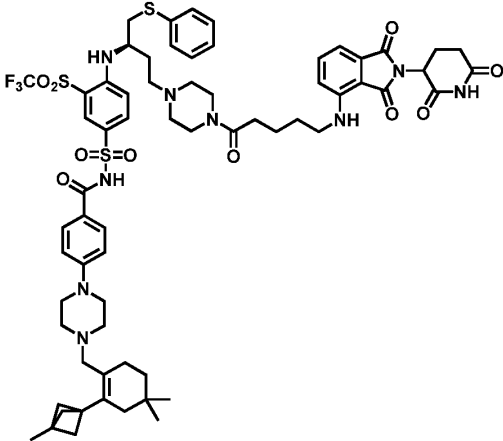
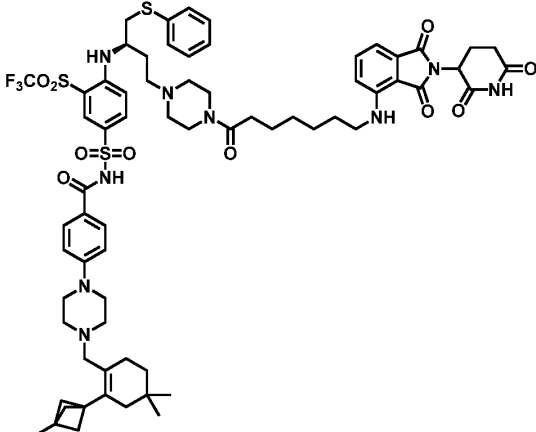
Example No.	Structure of Compound of Formula (I)
120	 Chemical structure of Compound 120. The molecule features a central piperazine ring. One nitrogen of the piperazine is connected to a 4-(trifluoromethylsulfonyl)phenyl group, which is further linked to a 4-(benzenesulfonamido)phenyl group. The other nitrogen of the piperazine is connected to a 4-(4-methyl-1,3,4-thiazol-5-yl)phenyl group. The central piperazine ring is also connected to a 4-(4-methyl-1,3,4-thiazol-5-yl)phenyl group. The molecule includes a 4-(trifluoromethylsulfonyl)phenyl group, a 4-(benzenesulfonamido)phenyl group, a 4-(4-methyl-1,3,4-thiazol-5-yl)phenyl group, and a 4-(4-methyl-1,3,4-thiazol-5-yl)phenyl group.
121	 Chemical structure of Compound 121. The molecule features a central piperazine ring. One nitrogen of the piperazine is connected to a 4-(trifluoromethylsulfonyl)phenyl group, which is further linked to a 4-(benzenesulfonamido)phenyl group. The other nitrogen of the piperazine is connected to a 4-(4-methyl-1,3,4-thiazol-5-yl)phenyl group. The central piperazine ring is also connected to a 4-(4-methyl-1,3,4-thiazol-5-yl)phenyl group. The molecule includes a 4-(trifluoromethylsulfonyl)phenyl group, a 4-(benzenesulfonamido)phenyl group, a 4-(4-methyl-1,3,4-thiazol-5-yl)phenyl group, and a 4-(4-methyl-1,3,4-thiazol-5-yl)phenyl group.

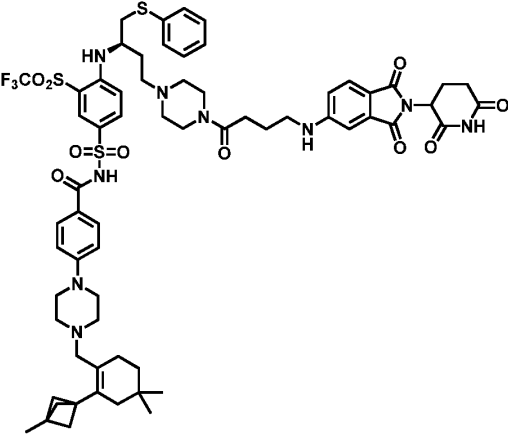
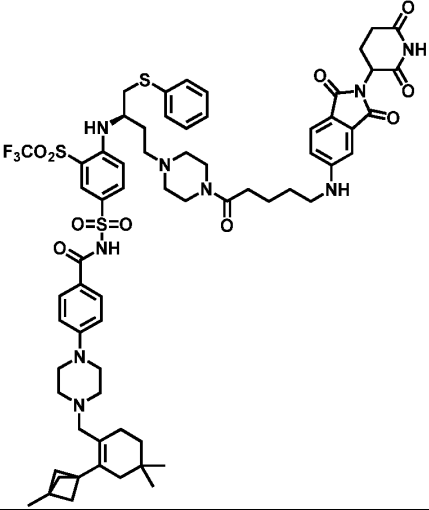
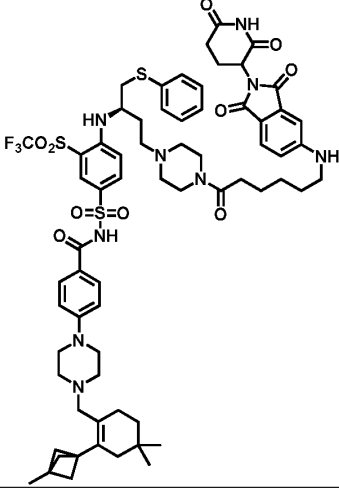
Example No.	Structure of Compound of Formula (I)
122	 Chemical structure of compound 122. It features a central piperazine ring. One nitrogen of the piperazine is connected to a 4-(trifluoromethylsulfonyl)phenyl group, which is further linked to a 4-(benzenesulfonamido)phenyl group. The other nitrogen of the piperazine is connected to a 4-(benzenesulfonamido)phenyl group, which is further linked to a 4-(benzenesulfonamido)phenyl group. The structure also includes a 4-(benzenesulfonamido)phenyl group and a 4-(benzenesulfonamido)phenyl group.
123	 Chemical structure of compound 123. It features a central piperazine ring. One nitrogen of the piperazine is connected to a 4-(trifluoromethylsulfonyl)phenyl group, which is further linked to a 4-(benzenesulfonamido)phenyl group. The other nitrogen of the piperazine is connected to a 4-(benzenesulfonamido)phenyl group, which is further linked to a 4-(benzenesulfonamido)phenyl group. The structure also includes a 4-(benzenesulfonamido)phenyl group and a 4-(benzenesulfonamido)phenyl group.
124	 Chemical structure of compound 124. It features a central piperazine ring. One nitrogen of the piperazine is connected to a 4-(trifluoromethylsulfonyl)phenyl group, which is further linked to a 4-(benzenesulfonamido)phenyl group. The other nitrogen of the piperazine is connected to a 4-(benzenesulfonamido)phenyl group, which is further linked to a 4-(benzenesulfonamido)phenyl group. The structure also includes a 4-(benzenesulfonamido)phenyl group and a 4-(benzenesulfonamido)phenyl group.

Example No.	Structure of Compound of Formula (I)
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126	

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Example No.	Structure of Compound of Formula (I)
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132	

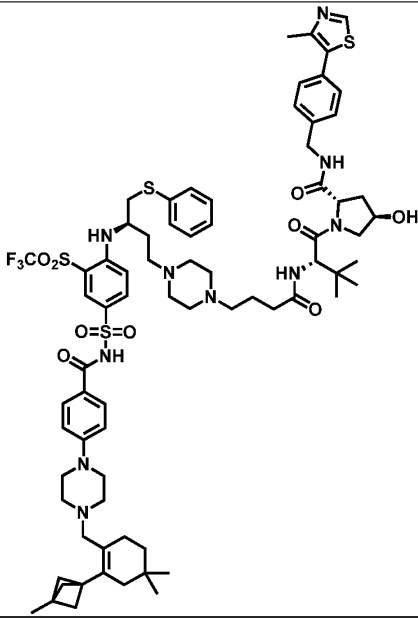
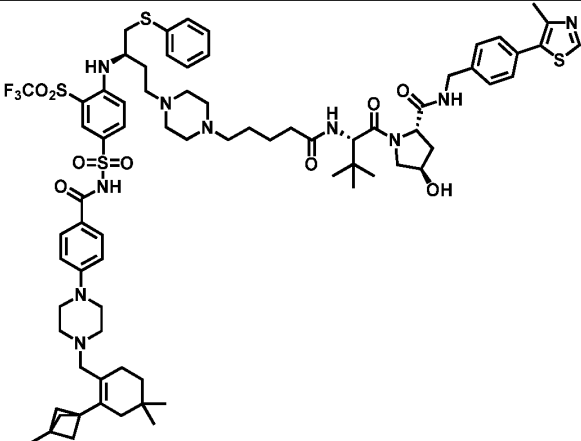
Example No.	Structure of Compound of Formula (I)
133	 Chemical structure of compound 133: A complex molecule featuring a central piperazine ring. One nitrogen of the piperazine is substituted with a 4-(trifluoromethylsulfonylamino)phenyl group. The other nitrogen is substituted with a 2-((2,2,6,6-tetramethyl-3,4-dihydrocyclohepta[1,2-b]furan-5-yl)methyl)phenyl group. The piperazine ring is also substituted with a 2-((2,2,6,6-tetramethyl-3,4-dihydrocyclohepta[1,2-b]furan-5-yl)methyl)phenyl group and a 2-((2,2,6,6-tetramethyl-3,4-dihydrocyclohepta[1,2-b]furan-5-yl)methyl)phenyl group.
134	 Chemical structure of compound 134: A complex molecule featuring a central piperazine ring. One nitrogen of the piperazine is substituted with a 4-(trifluoromethylsulfonylamino)phenyl group. The other nitrogen is substituted with a 2-((2,2,6,6-tetramethyl-3,4-dihydrocyclohepta[1,2-b]furan-5-yl)methyl)phenyl group. The piperazine ring is also substituted with a 2-((2,2,6,6-tetramethyl-3,4-dihydrocyclohepta[1,2-b]furan-5-yl)methyl)phenyl group and a 2-((2,2,6,6-tetramethyl-3,4-dihydrocyclohepta[1,2-b]furan-5-yl)methyl)phenyl group.
135	 Chemical structure of compound 135: A complex molecule featuring a central piperazine ring. One nitrogen of the piperazine is substituted with a 4-(trifluoromethylsulfonylamino)phenyl group. The other nitrogen is substituted with a 2-((2,2,6,6-tetramethyl-3,4-dihydrocyclohepta[1,2-b]furan-5-yl)methyl)phenyl group. The piperazine ring is also substituted with a 2-((2,2,6,6-tetramethyl-3,4-dihydrocyclohepta[1,2-b]furan-5-yl)methyl)phenyl group and a 2-((2,2,6,6-tetramethyl-3,4-dihydrocyclohepta[1,2-b]furan-5-yl)methyl)phenyl group.

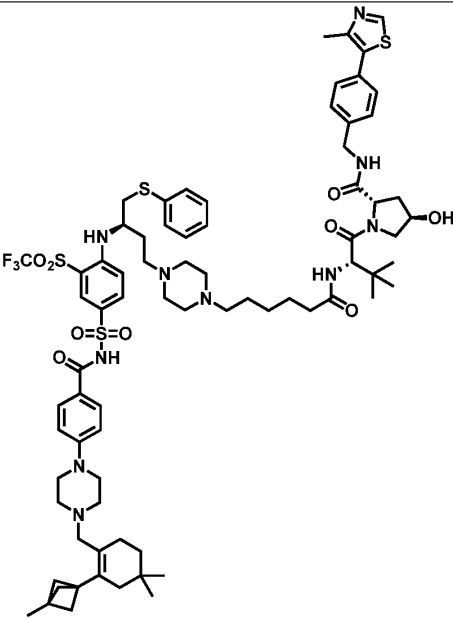
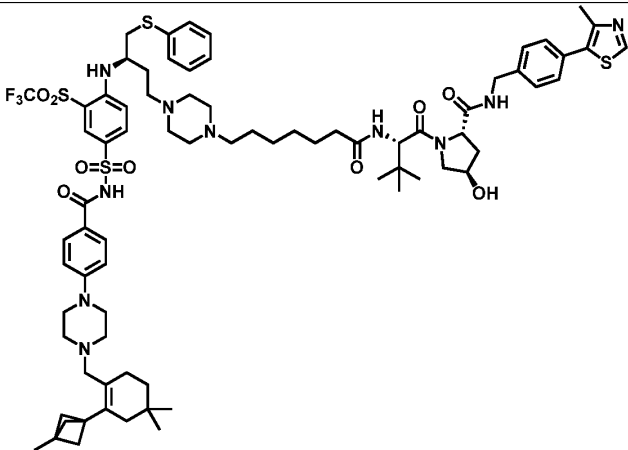
Example No.	Structure of Compound of Formula (I)
136	 Chemical structure of compound 136. It features a central piperazine ring. One nitrogen of the piperazine is substituted with a 4-(trifluoromethylsulfonyl)phenyl group and a 2-((4-methyl-2-(cyclopropylmethyl)phenyl)amino)benzamide group. The other nitrogen of the piperazine is substituted with a 2-((4-methyl-2-(cyclopropylmethyl)phenyl)amino)benzamide group and a 4-((2-((4-methyl-2-(cyclopropylmethyl)phenyl)amino)benzamide)amino)phenyl group. The 4-((2-((4-methyl-2-(cyclopropylmethyl)phenyl)amino)benzamide)amino)phenyl group is further substituted with a 2-((4-methyl-2-(cyclopropylmethyl)phenyl)amino)benzamide group.
137	 Chemical structure of compound 137. It features a central piperazine ring. One nitrogen of the piperazine is substituted with a 4-(trifluoromethylsulfonyl)phenyl group and a 2-((4-methyl-2-(cyclopropylmethyl)phenyl)amino)benzamide group. The other nitrogen of the piperazine is substituted with a 2-((4-methyl-2-(cyclopropylmethyl)phenyl)amino)benzamide group and a 4-((2-((4-methyl-2-(cyclopropylmethyl)phenyl)amino)benzamide)amino)phenyl group. The 4-((2-((4-methyl-2-(cyclopropylmethyl)phenyl)amino)benzamide)amino)phenyl group is further substituted with a 2-((4-methyl-2-(cyclopropylmethyl)phenyl)amino)benzamide group.
138	 Chemical structure of compound 138. It features a central piperazine ring. One nitrogen of the piperazine is substituted with a 4-(trifluoromethylsulfonyl)phenyl group and a 2-((4-methyl-2-(cyclopropylmethyl)phenyl)amino)benzamide group. The other nitrogen of the piperazine is substituted with a 2-((4-methyl-2-(cyclopropylmethyl)phenyl)amino)benzamide group and a 4-((2-((4-methyl-2-(cyclopropylmethyl)phenyl)amino)benzamide)amino)phenyl group. The 4-((2-((4-methyl-2-(cyclopropylmethyl)phenyl)amino)benzamide)amino)phenyl group is further substituted with a 2-((4-methyl-2-(cyclopropylmethyl)phenyl)amino)benzamide group.

Example No.	Structure of Compound of Formula (I)
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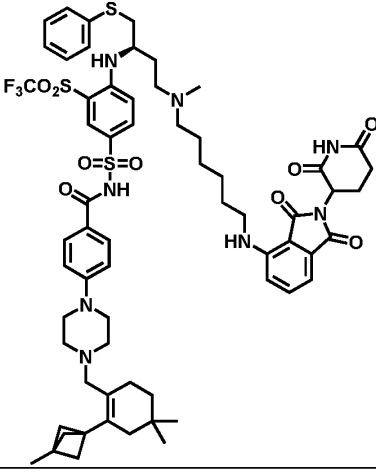
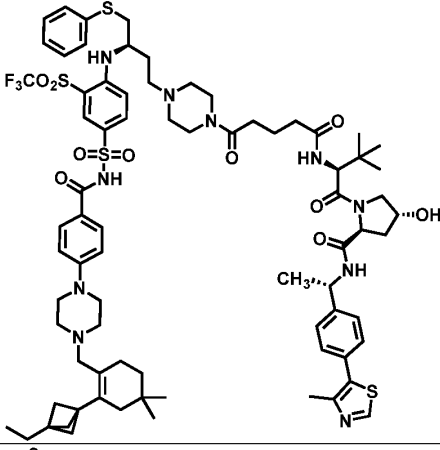
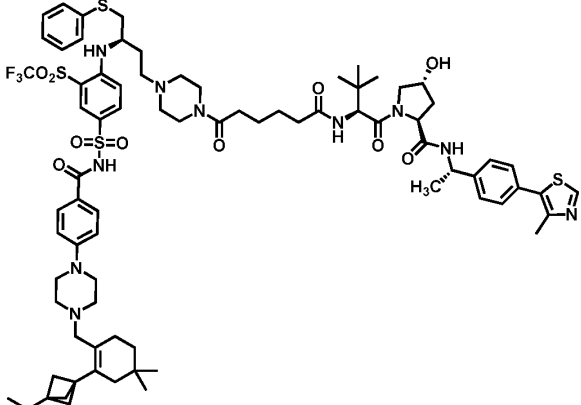
Example No.	Structure of Compound of Formula (I)
142	
143	

Example No.	Structure of Compound of Formula (I)
144	
145	

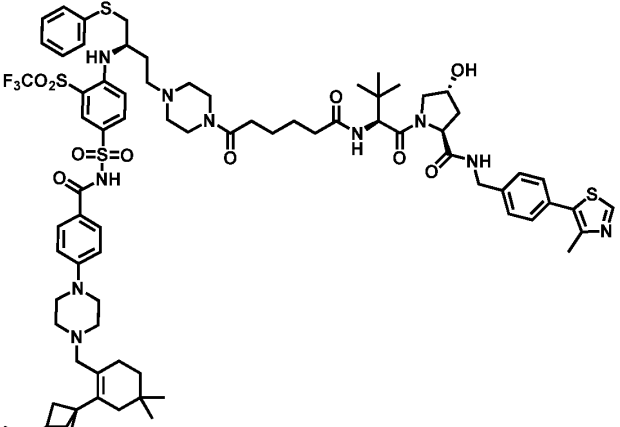
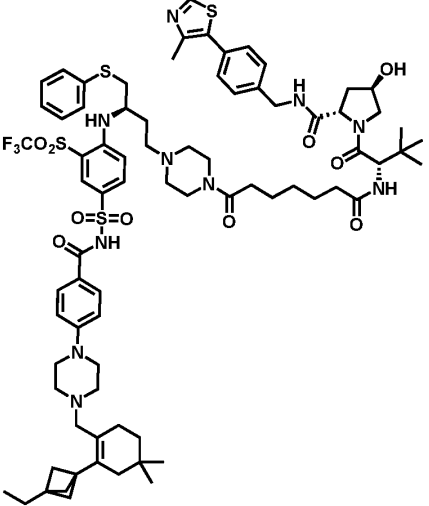
Example No.	Structure of Compound of Formula (I)
146	 Chemical structure of Compound 146. The molecule features a central piperazine ring. One nitrogen of the piperazine is substituted with a 4-(trifluoromethylsulfonylamino)phenyl group. The other nitrogen is substituted with a 4-(4-methyl-1,3-thiazol-5-yl)phenyl group. The 4-methyl-1,3-thiazol-5-yl group is further substituted with a 4-(4-(4-methyl-1,3-thiazol-5-yl)phenyl)phenyl group. The 4-methyl-1,3-thiazol-5-yl group is also substituted with a 4-(4-(4-methyl-1,3-thiazol-5-yl)phenyl)phenyl group. The 4-methyl-1,3-thiazol-5-yl group is also substituted with a 4-(4-(4-methyl-1,3-thiazol-5-yl)phenyl)phenyl group.
147	 Chemical structure of Compound 147. The molecule features a central piperazine ring. One nitrogen of the piperazine is substituted with a 4-(trifluoromethylsulfonylamino)phenyl group. The other nitrogen is substituted with a 4-(4-methyl-1,3-thiazol-5-yl)phenyl group. The 4-methyl-1,3-thiazol-5-yl group is further substituted with a 4-(4-methyl-1,3-thiazol-5-yl)phenyl group. The 4-methyl-1,3-thiazol-5-yl group is also substituted with a 4-(4-(4-methyl-1,3-thiazol-5-yl)phenyl)phenyl group. The 4-methyl-1,3-thiazol-5-yl group is also substituted with a 4-(4-(4-methyl-1,3-thiazol-5-yl)phenyl)phenyl group. The 4-methyl-1,3-thiazol-5-yl group is also substituted with a 4-(4-(4-methyl-1,3-thiazol-5-yl)phenyl)phenyl group.

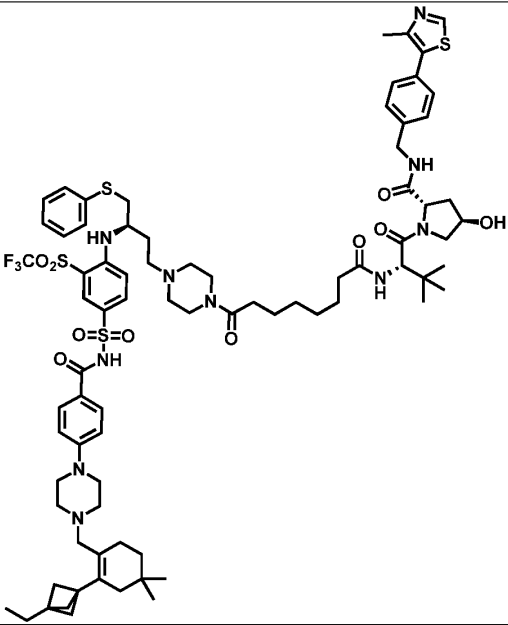
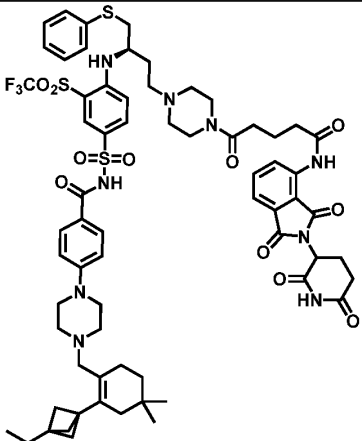
Example No.	Structure of Compound of Formula (I)
148	 Chemical structure of Compound 148. The molecule features a central piperazine ring. One nitrogen of the piperazine is substituted with a 4-(trifluoromethylsulfonyl)phenyl group. The other nitrogen is substituted with a 4-(4-(4-methyl-1,3,4-thiazol-5-yl)phenyl)phenyl group. The piperazine ring is also substituted with a 4-(4-(4-methyl-1,3,4-thiazol-5-yl)phenyl)phenyl group. The piperazine ring is also substituted with a 4-(4-(4-methyl-1,3,4-thiazol-5-yl)phenyl)phenyl group.
149	 Chemical structure of Compound 149. The molecule features a central piperazine ring. One nitrogen of the piperazine is substituted with a 4-(trifluoromethylsulfonyl)phenyl group. The other nitrogen is substituted with a 4-(4-(4-methyl-1,3,4-thiazol-5-yl)phenyl)phenyl group. The piperazine ring is also substituted with a 4-(4-(4-methyl-1,3,4-thiazol-5-yl)phenyl)phenyl group. The piperazine ring is also substituted with a 4-(4-(4-methyl-1,3,4-thiazol-5-yl)phenyl)phenyl group.

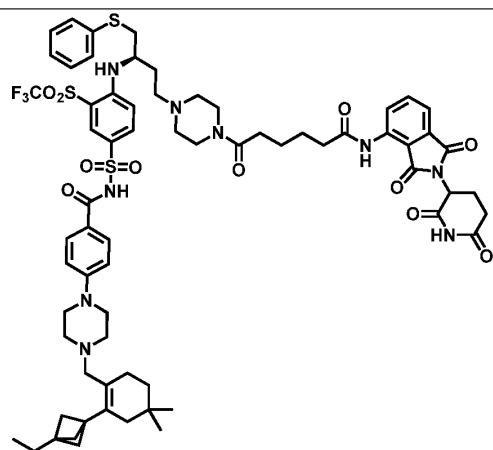
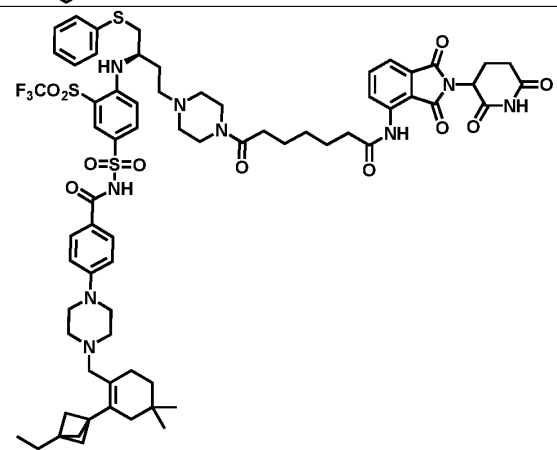
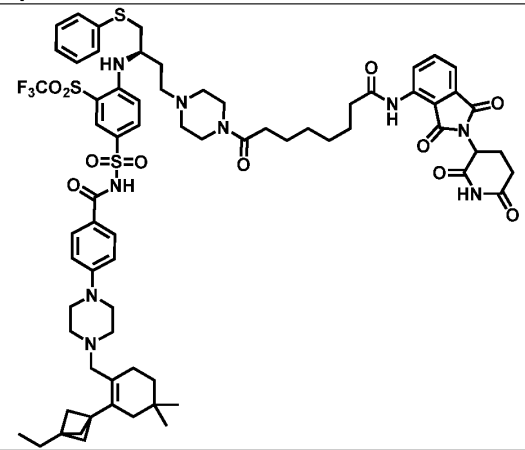
Example No.	Structure of Compound of Formula (I)
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152	

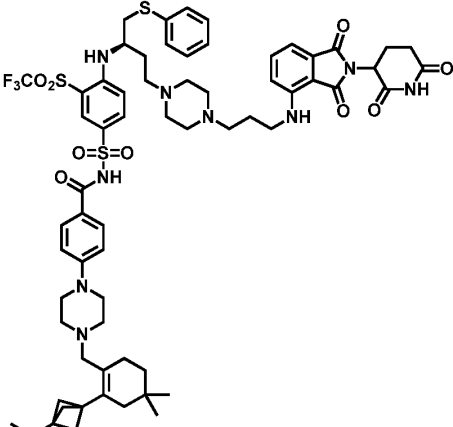
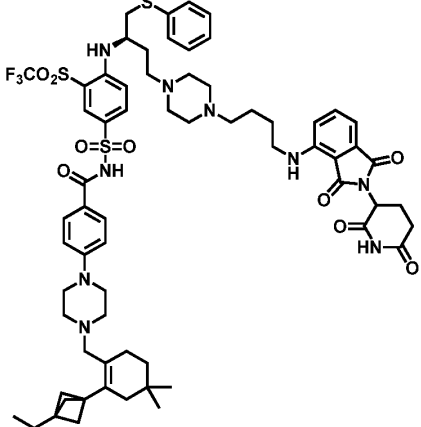
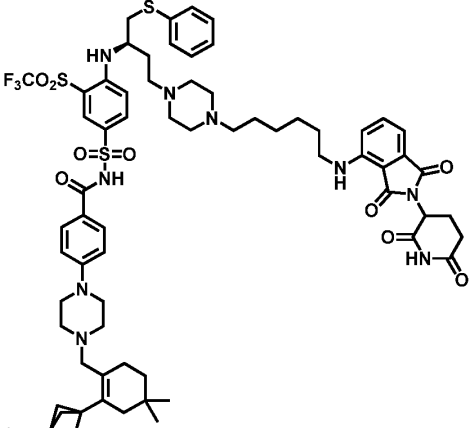
Example No.	Structure of Compound of Formula (I)
153	 Chemical structure of compound 153. It features a central piperazine ring connected to a 4-(trifluoromethylsulfonyl)phenyl group, a 4-aminophenyl group, and a 4-(2,2,6,6-tetramethyl-1,3-dioxane-5-yl)phenyl group. The 4-aminophenyl group is further substituted with a 2,6-dioxo-3,4-dihydro-1H-benzothiazine-5-yl group. The 4-(2,2,6,6-tetramethyl-1,3-dioxane-5-yl)phenyl group is substituted with a 2,2,6,6-tetramethyl-1,3-dioxane-5-yl group.
154	 Chemical structure of compound 154. It features a central piperazine ring connected to a 4-(trifluoromethylsulfonyl)phenyl group, a 4-aminophenyl group, and a 4-(2,2,6,6-tetramethyl-1,3-dioxane-5-yl)phenyl group. The 4-aminophenyl group is further substituted with a 2,6-dioxo-3,4-dihydro-1H-benzothiazine-5-yl group. The 4-(2,2,6,6-tetramethyl-1,3-dioxane-5-yl)phenyl group is substituted with a 2,2,6,6-tetramethyl-1,3-dioxane-5-yl group.
155	 Chemical structure of compound 155. It features a central piperazine ring connected to a 4-(trifluoromethylsulfonyl)phenyl group, a 4-aminophenyl group, and a 4-(2,2,6,6-tetramethyl-1,3-dioxane-5-yl)phenyl group. The 4-aminophenyl group is further substituted with a 2,6-dioxo-3,4-dihydro-1H-benzothiazine-5-yl group. The 4-(2,2,6,6-tetramethyl-1,3-dioxane-5-yl)phenyl group is substituted with a 2,2,6,6-tetramethyl-1,3-dioxane-5-yl group.

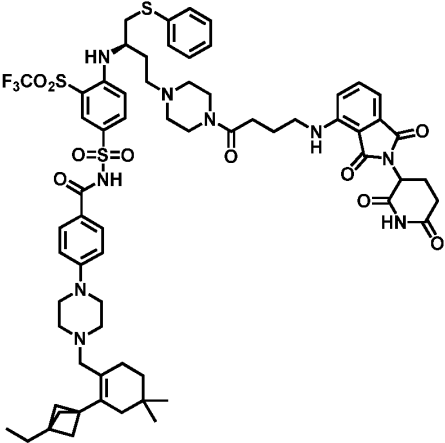
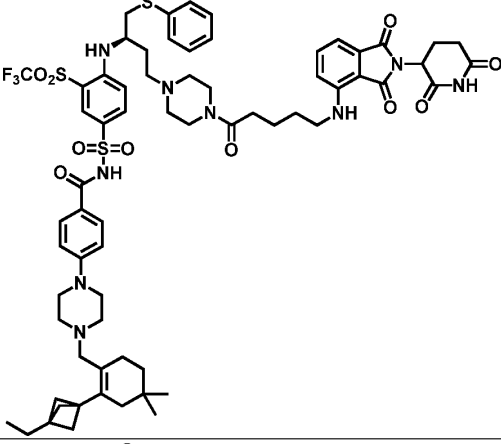
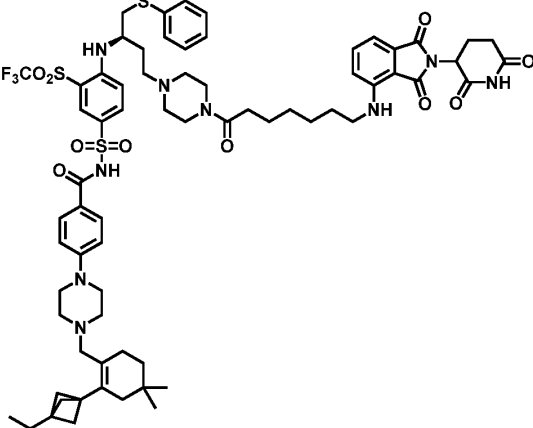
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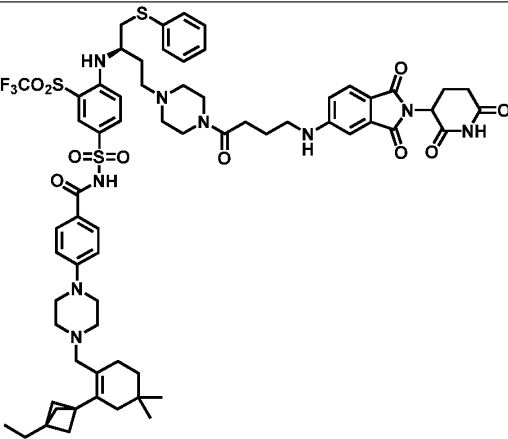
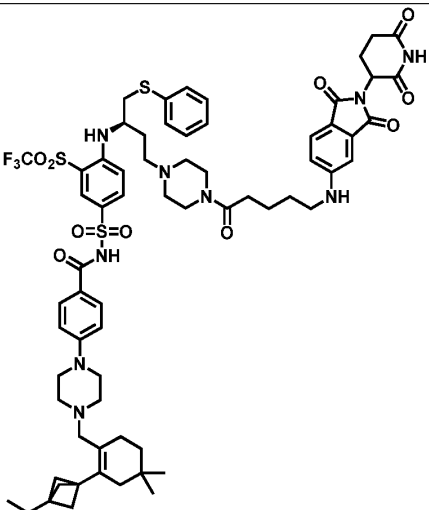
Example No.	Structure of Compound of Formula (I)
158	 Chemical structure of compound 158. It features a central piperazine ring. One nitrogen of the piperazine is connected to a 4-(trifluoromethylsulfonyl)phenyl group, which is further linked to a 4-(benzenesulfonamido)phenyl group. The other nitrogen of the piperazine is connected to a 4-(benzenesulfonamido)phenyl group, which is further linked to a 4-(benzenesulfonamido)phenyl group. The structure also includes a 4-(benzenesulfonamido)phenyl group, a 4-(benzenesulfonamido)phenyl group, and a 4-(benzenesulfonamido)phenyl group.
159	 Chemical structure of compound 159. It features a central piperazine ring. One nitrogen of the piperazine is connected to a 4-(trifluoromethylsulfonyl)phenyl group, which is further linked to a 4-(benzenesulfonamido)phenyl group. The other nitrogen of the piperazine is connected to a 4-(benzenesulfonamido)phenyl group, which is further linked to a 4-(benzenesulfonamido)phenyl group. The structure also includes a 4-(benzenesulfonamido)phenyl group, a 4-(benzenesulfonamido)phenyl group, and a 4-(benzenesulfonamido)phenyl group.

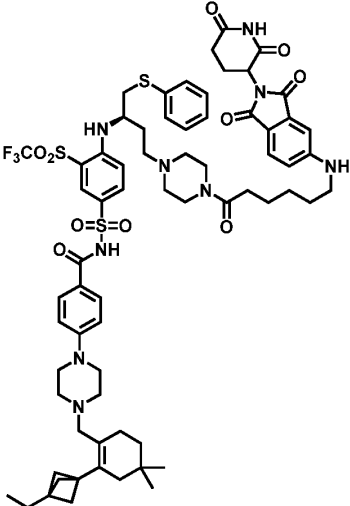
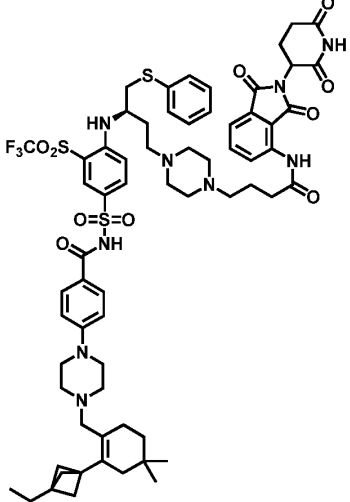
Example No.	Structure of Compound of Formula (I)
160	 Chemical structure of Compound 160. The molecule features a central piperazine ring. One nitrogen of the piperazine is connected to a 4-(trifluoromethylsulfonyl)phenyl group, which is further linked to a 4-(benzenesulfonamido)phenyl group. The other nitrogen of the piperazine is connected to a 4-(benzenesulfonamido)phenyl group, which is further linked to a 4-(benzenesulfonamido)phenyl group. The molecule also includes a 4-(benzenesulfonamido)phenyl group, a 4-(benzenesulfonamido)phenyl group, and a 4-(benzenesulfonamido)phenyl group. The molecule is a complex derivative of a piperazine core.
161	 Chemical structure of Compound 161. The molecule features a central piperazine ring. One nitrogen of the piperazine is connected to a 4-(trifluoromethylsulfonyl)phenyl group, which is further linked to a 4-(benzenesulfonamido)phenyl group. The other nitrogen of the piperazine is connected to a 4-(benzenesulfonamido)phenyl group, which is further linked to a 4-(benzenesulfonamido)phenyl group. The molecule also includes a 4-(benzenesulfonamido)phenyl group, a 4-(benzenesulfonamido)phenyl group, and a 4-(benzenesulfonamido)phenyl group. The molecule is a complex derivative of a piperazine core.

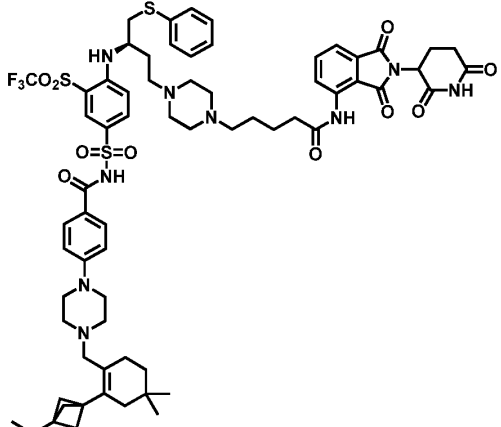
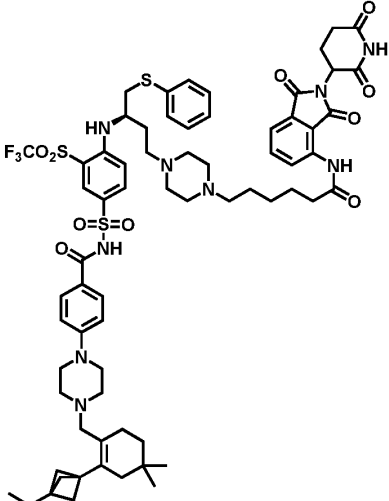
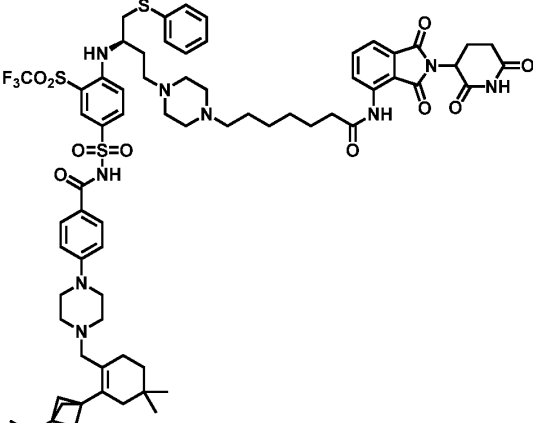
Example No.	Structure of Compound of Formula (I)
162	 Chemical structure of compound 162. It features a central piperazine ring. One nitrogen of the piperazine is connected to a 4-(trifluoromethylsulfonyl)phenyl group, which is further linked to a 4-(benzenesulfonamido)phenyl group. The other nitrogen of the piperazine is connected to a 6-oxo-1,2,3,4-tetrahydrophthalazine-5-carboxamide group. The 4-(benzenesulfonamido)phenyl group is also linked to a 4-(benzenesulfonamido)phenyl group, which is further linked to a 4-(benzenesulfonamido)phenyl group. The 4-(benzenesulfonamido)phenyl group is also linked to a 4-(benzenesulfonamido)phenyl group.
163	 Chemical structure of compound 163. It features a central piperazine ring. One nitrogen of the piperazine is connected to a 4-(trifluoromethylsulfonyl)phenyl group, which is further linked to a 4-(benzenesulfonamido)phenyl group. The other nitrogen of the piperazine is connected to a 6-oxo-1,2,3,4-tetrahydrophthalazine-5-carboxamide group. The 4-(benzenesulfonamido)phenyl group is also linked to a 4-(benzenesulfonamido)phenyl group, which is further linked to a 4-(benzenesulfonamido)phenyl group. The 4-(benzenesulfonamido)phenyl group is also linked to a 4-(benzenesulfonamido)phenyl group.
164	 Chemical structure of compound 164. It features a central piperazine ring. One nitrogen of the piperazine is connected to a 4-(trifluoromethylsulfonyl)phenyl group, which is further linked to a 4-(benzenesulfonamido)phenyl group. The other nitrogen of the piperazine is connected to a 6-oxo-1,2,3,4-tetrahydrophthalazine-5-carboxamide group. The 4-(benzenesulfonamido)phenyl group is also linked to a 4-(benzenesulfonamido)phenyl group, which is further linked to a 4-(benzenesulfonamido)phenyl group. The 4-(benzenesulfonamido)phenyl group is also linked to a 4-(benzenesulfonamido)phenyl group.

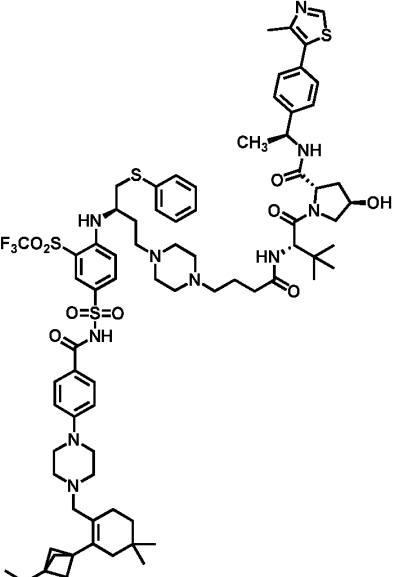
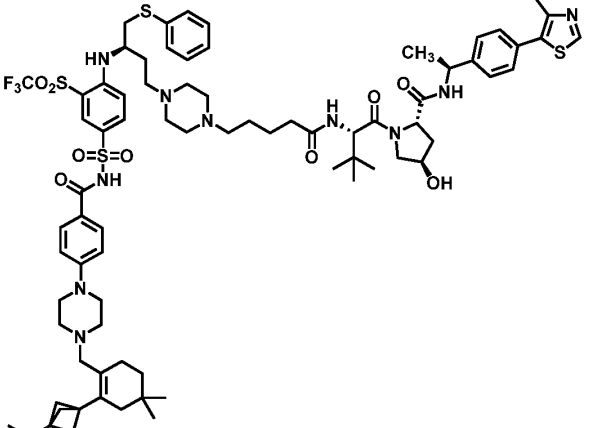
Example No.	Structure of Compound of Formula (I)
165	 Chemical structure of compound 165. It features a central piperazine ring substituted with a 4-(trifluoromethylsulfonyl)phenyl group, a 4-(4-ethylcyclopent-1-en-1-yl)phenyl group, and a 4-(benzylthio)phenyl group. The piperazine ring is also substituted with a 4-(4-ethylcyclopent-1-en-1-yl)phenyl group. The structure includes a sulfonamide group, a trifluoromethyl group, and a benzothiazine derivative.
166	 Chemical structure of compound 166. It features a central piperazine ring substituted with a 4-(trifluoromethylsulfonyl)phenyl group, a 4-(4-ethylcyclopent-1-en-1-yl)phenyl group, and a 4-(benzylthio)phenyl group. The piperazine ring is also substituted with a 4-(4-ethylcyclopent-1-en-1-yl)phenyl group. The structure includes a sulfonamide group, a trifluoromethyl group, and a benzothiazine derivative.
167	 Chemical structure of compound 167. It features a central piperazine ring substituted with a 4-(trifluoromethylsulfonyl)phenyl group, a 4-(4-ethylcyclopent-1-en-1-yl)phenyl group, and a 4-(benzylthio)phenyl group. The piperazine ring is also substituted with a 4-(4-ethylcyclopent-1-en-1-yl)phenyl group. The structure includes a sulfonamide group, a trifluoromethyl group, and a benzothiazine derivative.

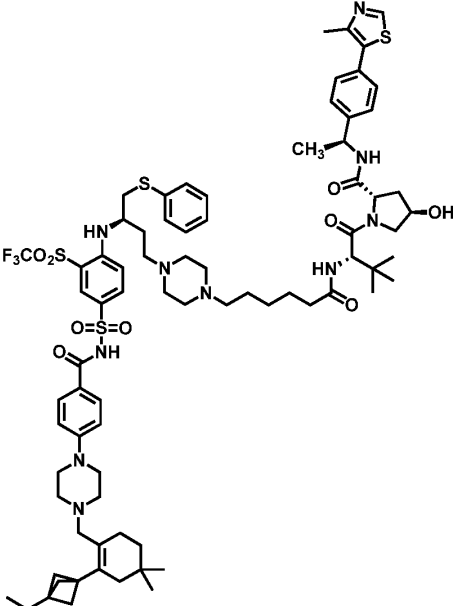
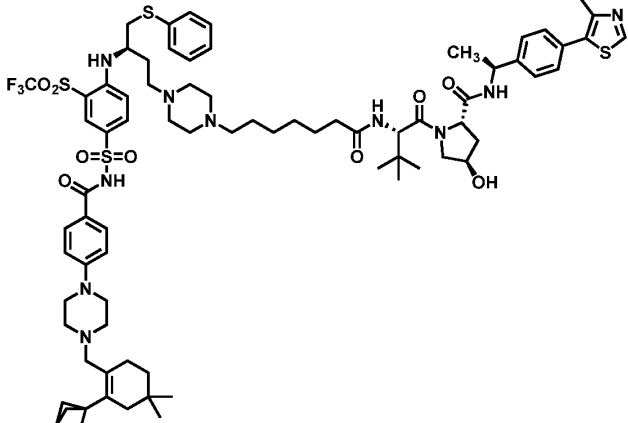
Example No.	Structure of Compound of Formula (I)
168	 Chemical structure of compound 168. It features a central piperazine ring. One nitrogen of the piperazine is substituted with a 4-(trifluoromethylsulfonylamino)phenyl group. The other nitrogen is substituted with a 4-(4-((4-ethylcyclopent-1-en-1-yl)methyl)-6-methylcyclohexyl)phenyl group. The piperazine ring is also substituted with a 4-(4-((4-ethylcyclopent-1-en-1-yl)methyl)-6-methylcyclohexyl)phenyl group and a 4-(4-((4-ethylcyclopent-1-en-1-yl)methyl)-6-methylcyclohexyl)phenyl group.
169	 Chemical structure of compound 169. It features a central piperazine ring. One nitrogen of the piperazine is substituted with a 4-(trifluoromethylsulfonylamino)phenyl group. The other nitrogen is substituted with a 4-(4-((4-ethylcyclopent-1-en-1-yl)methyl)-6-methylcyclohexyl)phenyl group. The piperazine ring is also substituted with a 4-(4-((4-ethylcyclopent-1-en-1-yl)methyl)-6-methylcyclohexyl)phenyl group and a 4-(4-((4-ethylcyclopent-1-en-1-yl)methyl)-6-methylcyclohexyl)phenyl group.
170	 Chemical structure of compound 170. It features a central piperazine ring. One nitrogen of the piperazine is substituted with a 4-(trifluoromethylsulfonylamino)phenyl group. The other nitrogen is substituted with a 4-(4-((4-ethylcyclopent-1-en-1-yl)methyl)-6-methylcyclohexyl)phenyl group. The piperazine ring is also substituted with a 4-(4-((4-ethylcyclopent-1-en-1-yl)methyl)-6-methylcyclohexyl)phenyl group and a 4-(4-((4-ethylcyclopent-1-en-1-yl)methyl)-6-methylcyclohexyl)phenyl group.

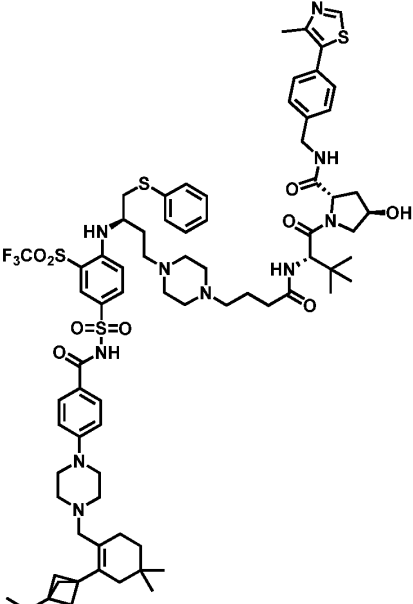
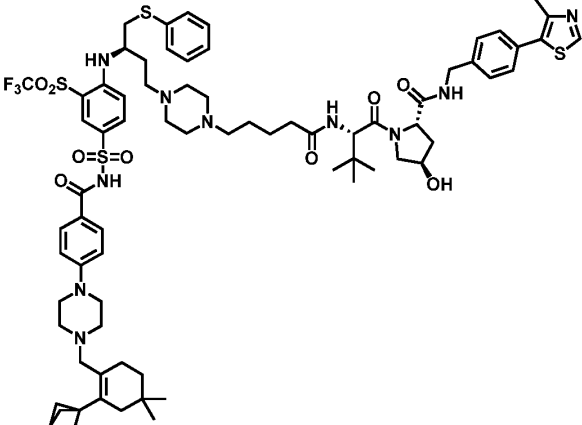
Example No.	Structure of Compound of Formula (I)
171	 Chemical structure of compound 171. The molecule features a central piperazine ring. One nitrogen of the piperazine is substituted with a 4-(trifluoromethylsulfonyl)phenyl group and a 4-(4-(2,2,6,6-tetramethyl-3-(4-ethylcyclopent-1-en-1-yl)cyclohex-1-en-1-yl)phenyl)benzamide group. The other nitrogen of the piperazine is substituted with a 2-phenyl-2-phenylthioethyl group and a 4-(2,2,6,6-tetramethyl-3-(4-ethylcyclopent-1-en-1-yl)cyclohex-1-en-1-yl)phenyl group. The 4-(2,2,6,6-tetramethyl-3-(4-ethylcyclopent-1-en-1-yl)cyclohex-1-en-1-yl)phenyl group is also substituted with a 4-(2,2,6,6-tetramethyl-3-(4-ethylcyclopent-1-en-1-yl)cyclohex-1-en-1-yl)phenyl group.
172	 Chemical structure of compound 172. The molecule features a central piperazine ring. One nitrogen of the piperazine is substituted with a 4-(trifluoromethylsulfonyl)phenyl group and a 4-(4-(2,2,6,6-tetramethyl-3-(4-ethylcyclopent-1-en-1-yl)cyclohex-1-en-1-yl)phenyl)benzamide group. The other nitrogen of the piperazine is substituted with a 2-phenyl-2-phenylthioethyl group and a 4-(2,2,6,6-tetramethyl-3-(4-ethylcyclopent-1-en-1-yl)cyclohex-1-en-1-yl)phenyl group. The 4-(2,2,6,6-tetramethyl-3-(4-ethylcyclopent-1-en-1-yl)cyclohex-1-en-1-yl)phenyl group is also substituted with a 4-(2,2,6,6-tetramethyl-3-(4-ethylcyclopent-1-en-1-yl)cyclohex-1-en-1-yl)phenyl group.

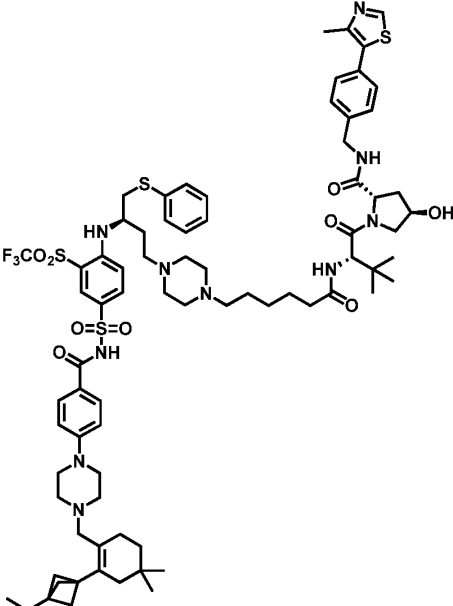
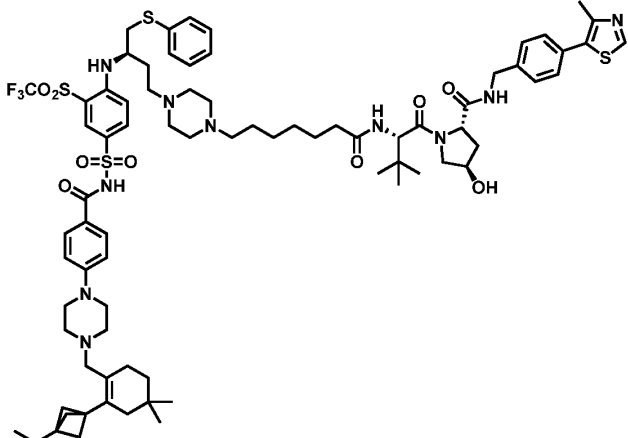
Example No.	Structure of Compound of Formula (I)
173	 Chemical structure of compound 173. The molecule features a central piperazine ring. One nitrogen of the piperazine is substituted with a 4-(trifluoromethylsulfonylamino)phenyl group, which is further linked via an amide bond to a 4-(4-ethyl-4-methylcyclopent-1-en-1-yl)phenyl group. The other nitrogen of the piperazine is substituted with a 4-(2-((2-oxo-2,3-dihydro-1H-benz[e][1,2-b]oxazol-5-yl)amino)phenyl)phenyl group. The benzoxazole moiety is further substituted with a 4-(2-((2-oxo-2,3-dihydro-1H-benz[e][1,2-b]oxazol-5-yl)amino)phenyl)phenyl group.
174	 Chemical structure of compound 174. The molecule features a central piperazine ring. One nitrogen of the piperazine is substituted with a 4-(trifluoromethylsulfonylamino)phenyl group, which is further linked via an amide bond to a 4-(4-ethyl-4-methylcyclopent-1-en-1-yl)phenyl group. The other nitrogen of the piperazine is substituted with a 4-(2-((2-oxo-2,3-dihydro-1H-benz[e][1,2-b]oxazol-5-yl)amino)phenyl)phenyl group. The benzoxazole moiety is further substituted with a 4-(2-((2-oxo-2,3-dihydro-1H-benz[e][1,2-b]oxazol-5-yl)amino)phenyl)phenyl group.

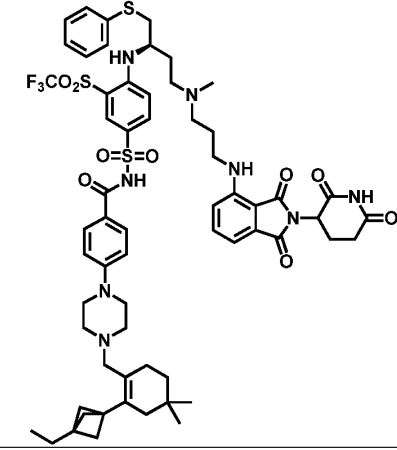
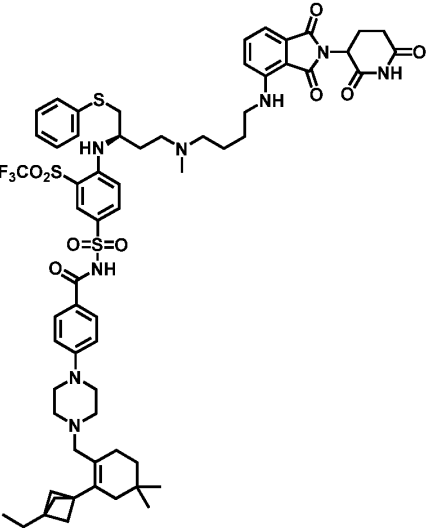
Example No.	Structure of Compound of Formula (I)
175	 Chemical structure of compound 175. It features a central piperazine ring. One nitrogen of the piperazine is substituted with a 4-(4-ethyl-4-methylcyclopent-1-en-1-yl)phenyl group. The other nitrogen is substituted with a 4-(4-(trifluoromethylsulfonyl)phenyl)phenyl group. The 4-(trifluoromethylsulfonyl)phenyl group is further substituted with a 4-(4-(4-oxo-4,5,6,7-tetrahydro-1H-benzothiazol-2-yl)butan-1-yl)phenyl group.
176	 Chemical structure of compound 176. It features a central piperazine ring. One nitrogen of the piperazine is substituted with a 4-(4-ethyl-4-methylcyclopent-1-en-1-yl)phenyl group. The other nitrogen is substituted with a 4-(4-(trifluoromethylsulfonyl)phenyl)phenyl group. The 4-(trifluoromethylsulfonyl)phenyl group is further substituted with a 4-(4-(4-oxo-4,5,6,7-tetrahydro-1H-benzothiazol-2-yl)butan-1-yl)phenyl group.
177	 Chemical structure of compound 177. It features a central piperazine ring. One nitrogen of the piperazine is substituted with a 4-(4-ethyl-4-methylcyclopent-1-en-1-yl)phenyl group. The other nitrogen is substituted with a 4-(4-(trifluoromethylsulfonyl)phenyl)phenyl group. The 4-(trifluoromethylsulfonyl)phenyl group is further substituted with a 4-(4-(4-oxo-4,5,6,7-tetrahydro-1H-benzothiazol-2-yl)butan-1-yl)phenyl group.

Example No.	Structure of Compound of Formula (I)
178	 Chemical structure of Compound 178. The molecule features a central piperazine ring. One nitrogen of the piperazine is connected to a 4-(trifluoromethylsulfonylamino)phenyl group. The other nitrogen is connected to a 4-(4-ethyl-4-methylcyclohexylmethyl)piperidin-1-yl group. A side chain on the piperazine ring includes a thioether linkage to a phenyl ring, which is further connected to a 4-(4-methyl-1,3,4-thiazol-5-yl)phenyl group. The side chain also includes a 2-hydroxy-2-methyl-3-oxo-1,3-dihydro-4H-pyrimidin-4-yl group and a 2-oxo-2-methyl-3-oxo-1,3-dihydro-4H-pyrimidin-4-yl group.
179	 Chemical structure of Compound 179. The molecule features a central piperazine ring. One nitrogen of the piperazine is connected to a 4-(trifluoromethylsulfonylamino)phenyl group. The other nitrogen is connected to a 4-(4-ethyl-4-methylcyclohexylmethyl)piperidin-1-yl group. A side chain on the piperazine ring includes a thioether linkage to a phenyl ring, which is further connected to a 4-(4-methyl-1,3,4-thiazol-5-yl)phenyl group. The side chain also includes a 2-hydroxy-2-methyl-3-oxo-1,3-dihydro-4H-pyrimidin-4-yl group and a 2-oxo-2-methyl-3-oxo-1,3-dihydro-4H-pyrimidin-4-yl group.

Example No.	Structure of Compound of Formula (I)
180	 Chemical structure of Compound 180. The molecule features a central piperazine ring. One nitrogen of the piperazine is substituted with a 4-(4-ethyl-4-methylcyclohexylmethyl)phenyl group. The other nitrogen is substituted with a 4-(4-(trifluoromethylsulfonyl)phenylamino)phenyl group. A 4-phenylthiazol-5-yl group is attached to the piperazine ring via a methylene linker. A 4-(4-(trifluoromethylsulfonyl)phenylamino)phenyl group is attached to the piperazine ring via a methylene linker. A 4-(4-(trifluoromethylsulfonyl)phenylamino)phenyl group is attached to the piperazine ring via a methylene linker. A 4-(4-(trifluoromethylsulfonyl)phenylamino)phenyl group is attached to the piperazine ring via a methylene linker.
181	 Chemical structure of Compound 181. The molecule features a central piperazine ring. One nitrogen of the piperazine is substituted with a 4-(4-ethyl-4-methylcyclohexylmethyl)phenyl group. The other nitrogen is substituted with a 4-(4-(trifluoromethylsulfonyl)phenylamino)phenyl group. A 4-phenylthiazol-5-yl group is attached to the piperazine ring via a methylene linker. A 4-(4-(trifluoromethylsulfonyl)phenylamino)phenyl group is attached to the piperazine ring via a methylene linker. A 4-(4-(trifluoromethylsulfonyl)phenylamino)phenyl group is attached to the piperazine ring via a methylene linker. A 4-(4-(trifluoromethylsulfonyl)phenylamino)phenyl group is attached to the piperazine ring via a methylene linker.

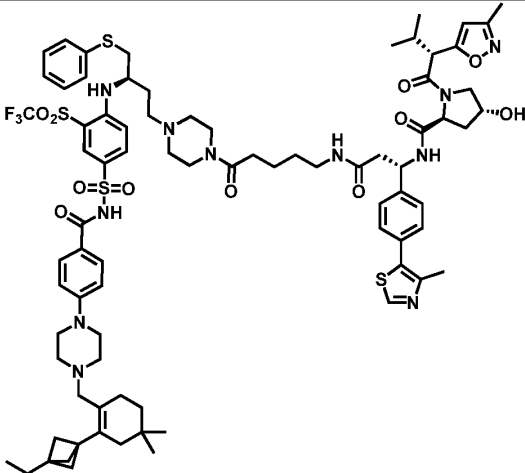
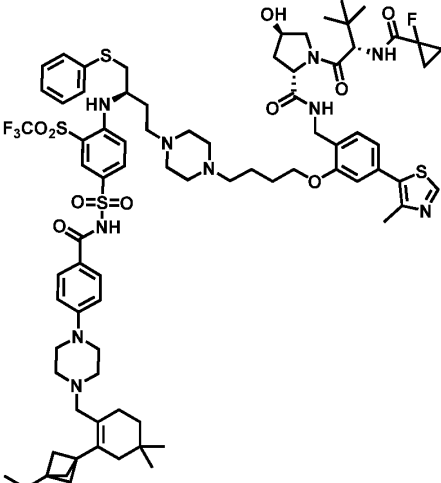
Example No.	Structure of Compound of Formula (I)
182	 Chemical structure of Compound 182. The molecule features a central piperazine ring. One nitrogen of the piperazine is substituted with a 4-(trifluoromethylsulfonylamino)phenyl group. The other nitrogen is substituted with a 4-(4-ethyl-4-methylcyclohex-1-en-1-yl)methyl group. A side chain is attached to the 4-(trifluoromethylsulfonylamino)phenyl group, consisting of a methylene group linked to a 4-(thiophen-2-yl)phenyl group. Another side chain is attached to the 4-(4-ethyl-4-methylcyclohex-1-en-1-yl)methyl group, consisting of a methylene group linked to a 4-(4-ethyl-4-methylcyclohex-1-en-1-yl)methyl group. The molecule also contains a sulfonamide group, a hydroxyl group, and a thiazole ring.
183	 Chemical structure of Compound 183. The molecule features a central piperazine ring. One nitrogen of the piperazine is substituted with a 4-(trifluoromethylsulfonylamino)phenyl group. The other nitrogen is substituted with a 4-(4-ethyl-4-methylcyclohex-1-en-1-yl)methyl group. A side chain is attached to the 4-(trifluoromethylsulfonylamino)phenyl group, consisting of a methylene group linked to a 4-(thiophen-2-yl)phenyl group. Another side chain is attached to the 4-(4-ethyl-4-methylcyclohex-1-en-1-yl)methyl group, consisting of a methylene group linked to a 4-(4-ethyl-4-methylcyclohex-1-en-1-yl)methyl group. The molecule also contains a sulfonamide group, a hydroxyl group, and a thiazole ring.

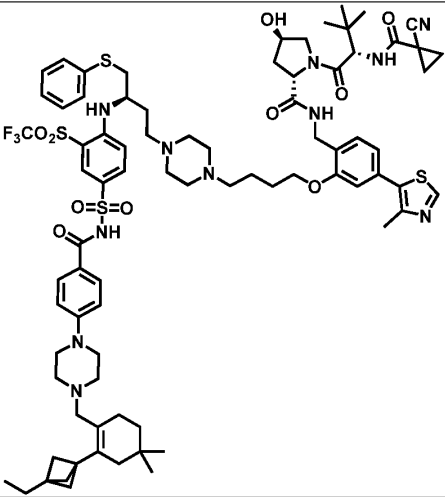
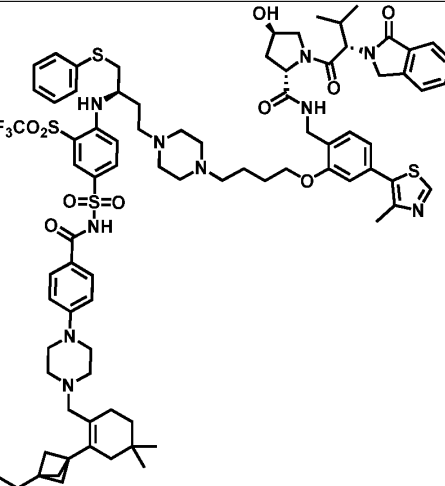
Example No.	Structure of Compound of Formula (I)
184	 Chemical structure of Compound 184. The molecule features a central piperazine ring. One nitrogen of the piperazine is substituted with a 4-(tert-butyl-1H-imidazol-2-yl)phenyl group. The other nitrogen is substituted with a 4-(trifluoromethylsulfonyl)phenyl group. A 4-(4-ethylcyclopent-1-en-1-yl)phenyl group is attached to the piperazine ring via a methylene linker. The trifluoromethylsulfonyl group is further substituted with a 4-(4-ethylcyclopent-1-en-1-yl)phenyl group via a methylene linker. The imidazole ring is substituted with a 4-(4-ethylcyclopent-1-en-1-yl)phenyl group via a methylene linker.
185	 Chemical structure of Compound 185. The molecule features a central piperazine ring. One nitrogen of the piperazine is substituted with a 4-(tert-butyl-1H-imidazol-2-yl)phenyl group. The other nitrogen is substituted with a 4-(trifluoromethylsulfonyl)phenyl group. A 4-(4-ethylcyclopent-1-en-1-yl)phenyl group is attached to the piperazine ring via a methylene linker. The trifluoromethylsulfonyl group is further substituted with a 4-(4-ethylcyclopent-1-en-1-yl)phenyl group via a methylene linker. The imidazole ring is substituted with a 4-(4-ethylcyclopent-1-en-1-yl)phenyl group via a methylene linker.

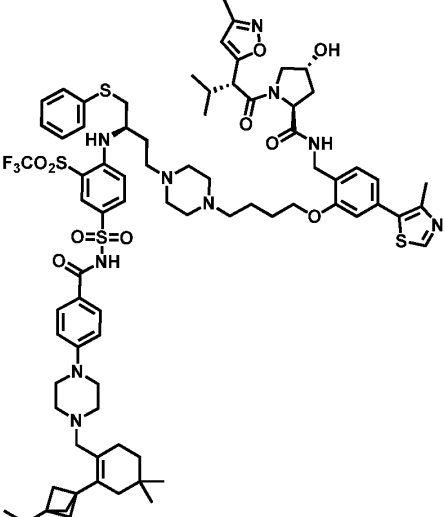
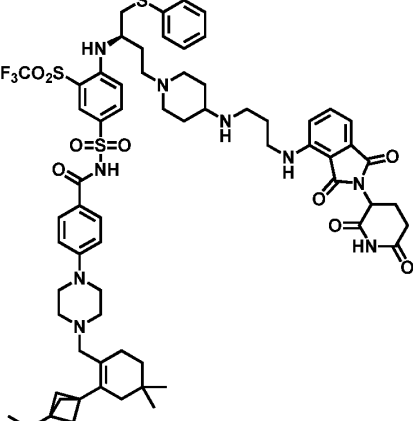
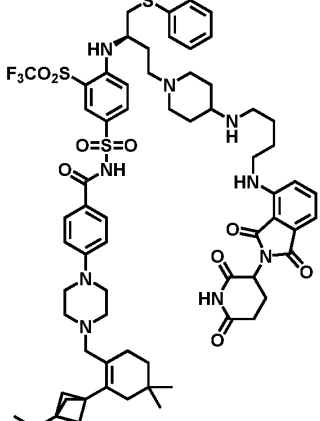
Example No.	Structure of Compound of Formula (I)
186	 Chemical structure of compound 186. It features a central p-phenylene ring substituted with a trifluoromethylsulfonyl group (F₃CO₂S-), a sulfonamide group (-SO₂NH-CO-), and a piperazine ring. The piperazine ring is further substituted with a 4-ethyl-4-methylcyclohexyl group and a 1-ethyl-2-methylcyclobutyl group. A side chain attached to the sulfonamide group includes a thiazolidine ring, a dimethylamino group, and a 1H-indole-3-carboxamide moiety.
187	 Chemical structure of compound 187. It features a central p-phenylene ring substituted with a trifluoromethylsulfonyl group (F₃CO₂S-), a sulfonamide group (-SO₂NH-CO-), and a piperazine ring. The piperazine ring is further substituted with a 4-ethyl-4-methylcyclohexyl group and a 1-ethyl-2-methylcyclobutyl group. A side chain attached to the sulfonamide group includes a thiazolidine ring, a dimethylamino group, and a 1H-indole-3-carboxamide moiety.

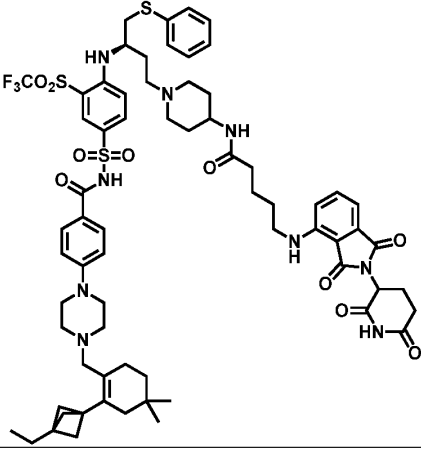
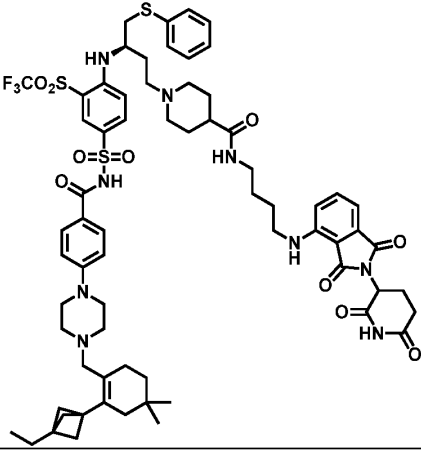
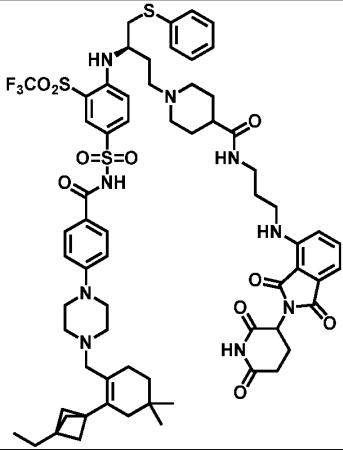
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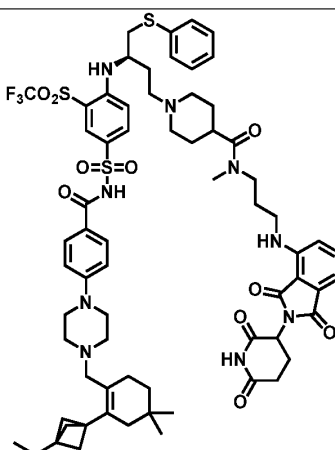
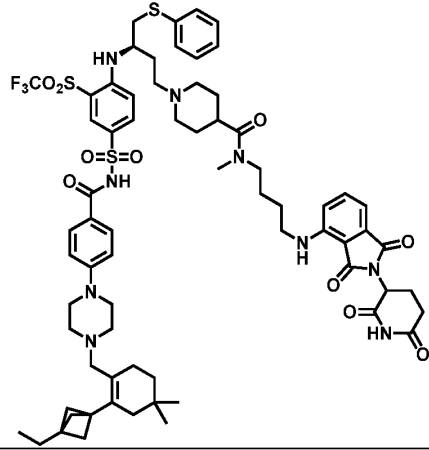
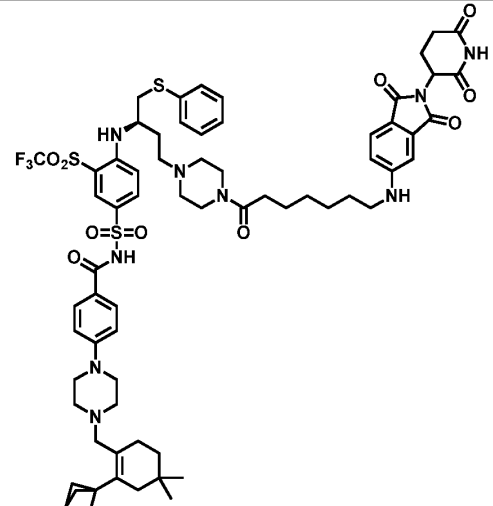
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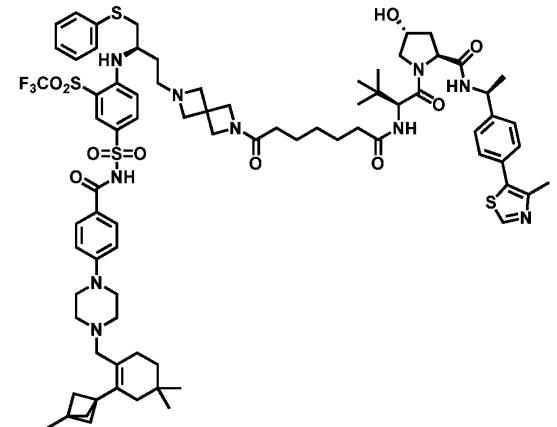
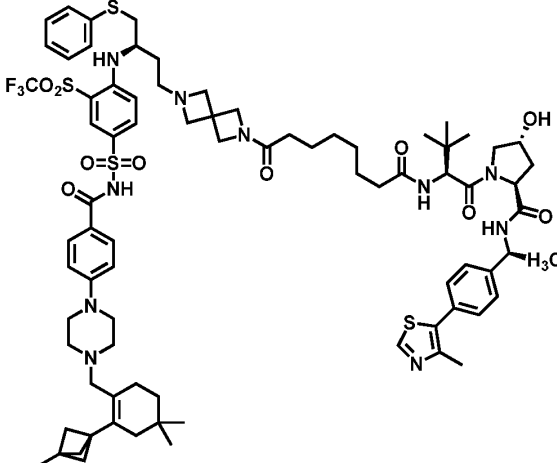
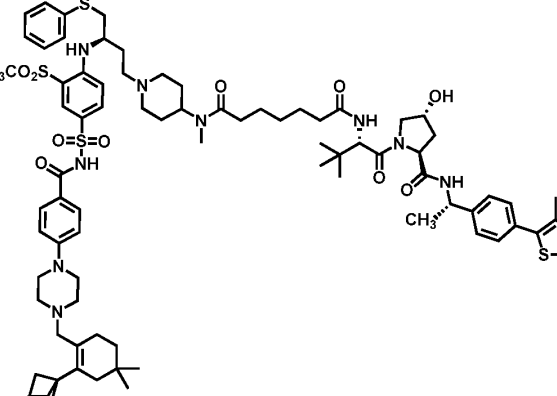
Example No.	Structure of Compound of Formula (I)
193	 Chemical structure of Compound 193: A complex molecule featuring a central piperazine ring. One nitrogen of the piperazine is connected to a 4-(trifluoromethylsulfonyl)phenyl group, which is further linked to a 4-(4-(4-ethyl-4-methylcyclopent-1-en-1-yl)piperazin-1-yl)phenyl group. The other nitrogen of the piperazine is connected to a 4-(4-(4-methyl-5-(4-methyl-1,3,4-oxadiazol-5-yl)-4,5-dihydro-1H-pyrazol-1-yl)-4-hydroxyphenyl)phenyl group. The molecule also includes a 4-(4-(4-methyl-1,3,4-oxadiazol-5-yl)-4-hydroxyphenyl)phenyl group and a 4-(4-(4-methyl-1,3,4-oxadiazol-5-yl)-4-hydroxyphenyl)phenyl group.
194	 Chemical structure of Compound 194: A complex molecule featuring a central piperazine ring. One nitrogen of the piperazine is connected to a 4-(trifluoromethylsulfonyl)phenyl group, which is further linked to a 4-(4-(4-ethyl-4-methylcyclopent-1-en-1-yl)piperazin-1-yl)phenyl group. The other nitrogen of the piperazine is connected to a 4-(4-(4-methyl-1,3,4-oxadiazol-5-yl)-4-hydroxyphenyl)phenyl group. The molecule also includes a 4-(4-(4-methyl-1,3,4-oxadiazol-5-yl)-4-hydroxyphenyl)phenyl group and a 4-(4-(4-methyl-1,3,4-oxadiazol-5-yl)-4-hydroxyphenyl)phenyl group.

Example No.	Structure of Compound of Formula (I)
195	 Chemical structure of Compound 195. The molecule features a central piperazine ring. One nitrogen of the piperazine is connected via a methylene group to a 2-phenylthio-1H-imidazole-4-carboxamide moiety. The other nitrogen of the piperazine is connected via a methylene group to a 4-(4-(tert-butyl)-1H-imidazol-2-yl)-2-(trifluoromethylsulfamoyl)phenyl group. The 4-(tert-butyl)-1H-imidazole moiety is further substituted with a 2-hydroxy-2-methyl-3-oxo-1,3-dihydro-4H-pyridin-4-ylidene group.
196	 Chemical structure of Compound 196. The molecule features a central piperazine ring. One nitrogen of the piperazine is connected via a methylene group to a 2-phenylthio-1H-imidazole-4-carboxamide moiety. The other nitrogen of the piperazine is connected via a methylene group to a 4-(4-(tert-butyl)-1H-imidazol-2-yl)-2-(trifluoromethylsulfamoyl)phenyl group. The 4-(tert-butyl)-1H-imidazole moiety is further substituted with a 2-hydroxy-2-methyl-3-oxo-1,3-dihydro-4H-pyridin-4-ylidene group.

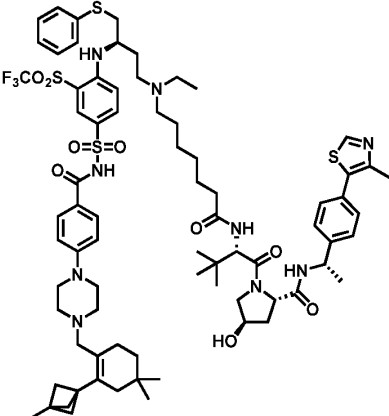
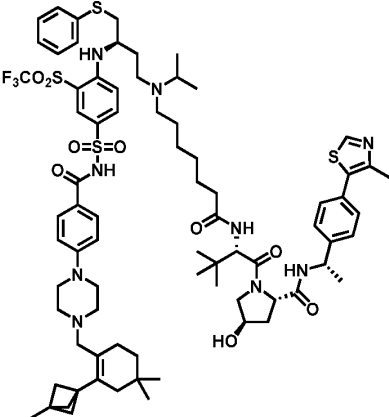
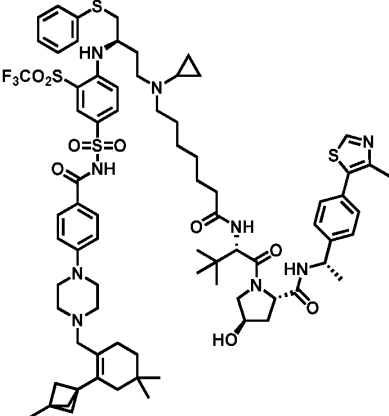
Example No.	Structure of Compound of Formula (I)
197	 Chemical structure of compound 197. It features a central piperazine ring. One nitrogen of the piperazine is connected to a 4-(trifluoromethylsulfonyl)phenyl group, which is further linked to a 4-(4-(4-ethyl-4-methylcyclopent-1-en-1-yl)phenyl)piperazine-1-carboxamide moiety. The other nitrogen of the piperazine is connected to a 4-(4-(4-ethyl-4-methylcyclopent-1-en-1-yl)phenyl)piperazine-1-carboxamide moiety. The structure also includes a 4-(4-(4-ethyl-4-methylcyclopent-1-en-1-yl)phenyl)piperazine-1-carboxamide moiety and a 4-(4-(4-ethyl-4-methylcyclopent-1-en-1-yl)phenyl)piperazine-1-carboxamide moiety.
198	 Chemical structure of compound 198. It features a central piperazine ring. One nitrogen of the piperazine is connected to a 4-(trifluoromethylsulfonyl)phenyl group, which is further linked to a 4-(4-(4-ethyl-4-methylcyclopent-1-en-1-yl)phenyl)piperazine-1-carboxamide moiety. The other nitrogen of the piperazine is connected to a 4-(4-(4-ethyl-4-methylcyclopent-1-en-1-yl)phenyl)piperazine-1-carboxamide moiety. The structure also includes a 4-(4-(4-ethyl-4-methylcyclopent-1-en-1-yl)phenyl)piperazine-1-carboxamide moiety and a 4-(4-(4-ethyl-4-methylcyclopent-1-en-1-yl)phenyl)piperazine-1-carboxamide moiety.
199	 Chemical structure of compound 199. It features a central piperazine ring. One nitrogen of the piperazine is connected to a 4-(trifluoromethylsulfonyl)phenyl group, which is further linked to a 4-(4-(4-ethyl-4-methylcyclopent-1-en-1-yl)phenyl)piperazine-1-carboxamide moiety. The other nitrogen of the piperazine is connected to a 4-(4-(4-ethyl-4-methylcyclopent-1-en-1-yl)phenyl)piperazine-1-carboxamide moiety. The structure also includes a 4-(4-(4-ethyl-4-methylcyclopent-1-en-1-yl)phenyl)piperazine-1-carboxamide moiety and a 4-(4-(4-ethyl-4-methylcyclopent-1-en-1-yl)phenyl)piperazine-1-carboxamide moiety.

Example No.	Structure of Compound of Formula (I)
200	 Chemical structure of Compound 200. It features a central piperazine ring substituted with a 4-(trifluoromethylsulfonylamino)phenyl group, a 4-(2-ethyl-5-methylcyclopropyl)phenyl group, and a 4-(2-oxo-2,3,4,5-tetrahydro-1H-benzodioxin-5-yl)phenyl group. The piperazine ring is also substituted with a 4-(2-oxo-2,3,4,5-tetrahydro-1H-benzodioxin-5-yl)phenyl group. The structure includes a trifluoromethylsulfonyl group (F₃CO₂S), a sulfonamide group (SO₂NH), and a sulfonamide group (SO₂NH).
201	 Chemical structure of Compound 201. It features a central piperazine ring substituted with a 4-(trifluoromethylsulfonylamino)phenyl group, a 4-(2-ethyl-5-methylcyclopropyl)phenyl group, and a 4-(2-oxo-2,3,4,5-tetrahydro-1H-benzodioxin-5-yl)phenyl group. The piperazine ring is also substituted with a 4-(2-oxo-2,3,4,5-tetrahydro-1H-benzodioxin-5-yl)phenyl group. The structure includes a trifluoromethylsulfonyl group (F₃CO₂S), a sulfonamide group (SO₂NH), and a sulfonamide group (SO₂NH).
202	 Chemical structure of Compound 202. It features a central piperazine ring substituted with a 4-(trifluoromethylsulfonylamino)phenyl group, a 4-(2-ethyl-5-methylcyclopropyl)phenyl group, and a 4-(2-oxo-2,3,4,5-tetrahydro-1H-benzodioxin-5-yl)phenyl group. The piperazine ring is also substituted with a 4-(2-oxo-2,3,4,5-tetrahydro-1H-benzodioxin-5-yl)phenyl group. The structure includes a trifluoromethylsulfonyl group (F₃CO₂S), a sulfonamide group (SO₂NH), and a sulfonamide group (SO₂NH).

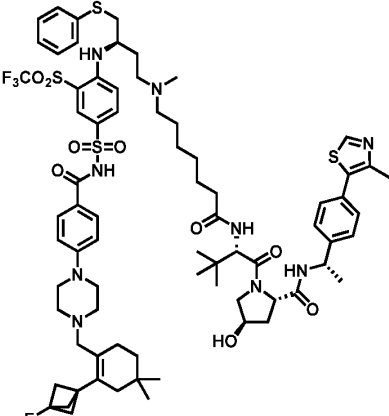
Example No.	Structure of Compound of Formula (I)
203	 Chemical structure of Compound 203: A complex molecule featuring a central piperazine ring. One nitrogen of the piperazine is substituted with a 4-(trifluoromethylsulfonyl)phenyl group and a 4-(4-ethylcyclopent-1-en-1-yl)phenyl group. The other nitrogen is substituted with a 4-(4-ethylcyclopent-1-en-1-yl)phenyl group and a 4-(4-ethylcyclopent-1-en-1-yl)phenyl group. The molecule also includes a sulfonamide group, a sulfonamide group, a sulfonamide group, and a sulfonamide group.
204	 Chemical structure of Compound 204: A complex molecule featuring a central piperazine ring. One nitrogen of the piperazine is substituted with a 4-(trifluoromethylsulfonyl)phenyl group and a 4-(4-ethylcyclopent-1-en-1-yl)phenyl group. The other nitrogen is substituted with a 4-(4-ethylcyclopent-1-en-1-yl)phenyl group and a 4-(4-ethylcyclopent-1-en-1-yl)phenyl group. The molecule also includes a sulfonamide group, a sulfonamide group, a sulfonamide group, and a sulfonamide group.
205	 Chemical structure of Compound 205: A complex molecule featuring a central piperazine ring. One nitrogen of the piperazine is substituted with a 4-(trifluoromethylsulfonyl)phenyl group and a 4-(4-ethylcyclopent-1-en-1-yl)phenyl group. The other nitrogen is substituted with a 4-(4-ethylcyclopent-1-en-1-yl)phenyl group and a 4-(4-ethylcyclopent-1-en-1-yl)phenyl group. The molecule also includes a sulfonamide group, a sulfonamide group, a sulfonamide group, and a sulfonamide group.

Example No.	Structure of Compound of Formula (I)
206	 Chemical structure of compound 206. It features a central piperazine ring substituted with a 4-(trifluoromethylsulfonyl)phenyl group, a 4-(2-methyl-5-(thiazol-2-yl)phenyl) group, and a 4-(2-methyl-5-(thiazol-2-yl)phenyl) group. The piperazine is linked via a carbonyl group to a 1,4-bis(methylamino)butane chain, which is further substituted with a 4-(trifluoromethylsulfonyl)phenyl group and a 4-(2-methyl-5-(thiazol-2-yl)phenyl) group.
207	 Chemical structure of compound 207. It features a central piperazine ring substituted with a 4-(trifluoromethylsulfonyl)phenyl group, a 4-(2-methyl-5-(thiazol-2-yl)phenyl) group, and a 4-(2-methyl-5-(thiazol-2-yl)phenyl) group. The piperazine is linked via a carbonyl group to a 1,4-bis(methylamino)butane chain, which is further substituted with a 4-(trifluoromethylsulfonyl)phenyl group and a 4-(2-methyl-5-(thiazol-2-yl)phenyl) group.
208	 Chemical structure of compound 208. It features a central piperazine ring substituted with a 4-(trifluoromethylsulfonyl)phenyl group, a 4-(2-methyl-5-(thiazol-2-yl)phenyl) group, and a 4-(2-methyl-5-(thiazol-2-yl)phenyl) group. The piperazine is linked via a carbonyl group to a 1,4-bis(methylamino)butane chain, which is further substituted with a 4-(trifluoromethylsulfonyl)phenyl group and a 4-(2-methyl-5-(thiazol-2-yl)phenyl) group.

[illegible]

Example No.	Structure of Compound of Formula (I)
212	 Chemical structure of compound 212. It features a central piperazine ring substituted with a 4-(trifluoromethylsulfonyl)phenyl group, a 4-(4-methyl-1H-thiazol-5-yl)phenyl group, and a 4-(4-methyl-1H-thiazol-5-yl)phenyl group. The piperazine is also linked to a 4-(4-methyl-1H-thiazol-5-yl)phenyl group via a carbonyl linkage. The structure includes a 4-(4-methyl-1H-thiazol-5-yl)phenyl group, a 4-(4-methyl-1H-thiazol-5-yl)phenyl group, and a 4-(4-methyl-1H-thiazol-5-yl)phenyl group.
213	 Chemical structure of compound 213. It features a central piperazine ring substituted with a 4-(trifluoromethylsulfonyl)phenyl group, a 4-(4-methyl-1H-thiazol-5-yl)phenyl group, and a 4-(4-methyl-1H-thiazol-5-yl)phenyl group. The piperazine is also linked to a 4-(4-methyl-1H-thiazol-5-yl)phenyl group via a carbonyl linkage. The structure includes a 4-(4-methyl-1H-thiazol-5-yl)phenyl group, a 4-(4-methyl-1H-thiazol-5-yl)phenyl group, and a 4-(4-methyl-1H-thiazol-5-yl)phenyl group.
214	 Chemical structure of compound 214. It features a central piperazine ring substituted with a 4-(trifluoromethylsulfonyl)phenyl group, a 4-(4-methyl-1H-thiazol-5-yl)phenyl group, and a 4-(4-methyl-1H-thiazol-5-yl)phenyl group. The piperazine is also linked to a 4-(4-methyl-1H-thiazol-5-yl)phenyl group via a carbonyl linkage. The structure includes a 4-(4-methyl-1H-thiazol-5-yl)phenyl group, a 4-(4-methyl-1H-thiazol-5-yl)phenyl group, and a 4-(4-methyl-1H-thiazol-5-yl)phenyl group.

Example No.	Structure of Compound of Formula (I)
215	
216	
217	

Example No.	Structure of Compound of Formula (I)
218	

Pharmaceutical Compositions

[0150] Some embodiments described herein relate to a pharmaceutical composition, that can include an effective amount of one or more compounds described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof) and a pharmaceutically acceptable carrier, diluent, excipient or combination thereof.

[0151] The term “pharmaceutical composition” refers to a mixture of one or more compounds and/or salts disclosed herein with other chemical components, such as diluents or carriers. The pharmaceutical composition facilitates administration of the compound to an organism. Pharmaceutical compositions can also be obtained by reacting compounds with inorganic or organic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid and salicylic acid. Pharmaceutical compositions will generally be tailored to the specific intended route of administration.

[0152] The term “physiologically acceptable” defines a carrier, diluent or excipient that does not abrogate the biological activity and properties of the compound nor cause appreciable damage or injury to an animal to which delivery of the composition is intended.

[0153] As used herein, a “carrier” refers to a compound that facilitates the incorporation of a compound into cells or tissues. For example, without limitation, dimethyl

sulfoxide (DMSO) is a commonly utilized carrier that facilitates the uptake of many organic compounds into cells or tissues of a subject.

[0154] As used herein, a “diluent” refers to an ingredient in a pharmaceutical composition that lacks appreciable pharmacological activity but may be pharmaceutically necessary or desirable. For example, a diluent may be used to increase the bulk of a potent drug whose mass is too small for manufacture and/or administration. It may also be a liquid for the dissolution of a drug to be administered by injection, ingestion or inhalation. A common form of diluent in the art is a buffered aqueous solution such as, without limitation, phosphate buffered saline that mimics the pH and isotonicity of human blood.

[0155] As used herein, an “excipient” refers to an essentially inert substance that is added to a pharmaceutical composition to provide, without limitation, bulk, consistency, stability, binding ability, lubrication, disintegrating ability etc., to the composition. For example, stabilizers such as anti-oxidants and metal-chelating agents are excipients. In an embodiment, the pharmaceutical composition comprises an anti-oxidant and/or a metal-chelating agent. A “diluent” is a type of excipient.

[0156] The pharmaceutical compositions described herein can be administered to a human patient *per se*, or in pharmaceutical compositions where they are mixed with other active ingredients, as in combination therapy, or carriers, diluents, excipients or combinations thereof. Proper formulation is dependent upon the route of administration chosen. Techniques for formulation and administration of the compounds described herein are known to those skilled in the art.

[0157] The pharmaceutical compositions disclosed herein may be manufactured in a manner that is itself known, *e.g.*, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or tableting processes. Additionally, the active ingredients are contained in an amount effective to achieve its intended purpose. Many of the compounds used in the pharmaceutical combinations disclosed herein may be provided as salts with pharmaceutically compatible counterions.

[0158] Multiple techniques of administering a compound, salt and/or composition exist in the art including, but not limited to, oral, rectal, pulmonary, topical, aerosol, injection, infusion and parenteral delivery, including intramuscular, subcutaneous,

intravenous, intramedullary injections, intrathecal, direct intraventricular, intraperitoneal, intranasal and intraocular injections. In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be administered orally.

[0159] One may also administer the compound, salt and/or composition in a local rather than systemic manner, for example, via injection or implantation of the compound directly into the affected area, often in a depot or sustained release formulation. Furthermore, one may administer the compound in a targeted drug delivery system, for example, in a liposome coated with a tissue-specific antibody. The liposomes will be targeted to and taken up selectively by the organ. For example, intranasal or pulmonary delivery to target a respiratory disease or condition may be desirable.

[0160] The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack may for example comprise metal or plastic foil, such as a blister pack. The pack or dispenser device may be accompanied by instructions for administration. The pack or dispenser may also be accompanied with a notice associated with the container in form prescribed by a governmental agency regulating the manufacture, use, or sale of pharmaceuticals, which notice is reflective of approval by the agency of the form of the drug for human or veterinary administration. Such notice, for example, may be the labeling approved by the U.S. Food and Drug Administration for prescription drugs, or the approved product insert. Compositions that can include a compound and/or salt described herein formulated in a compatible pharmaceutical carrier may also be prepared, placed in an appropriate container and labeled for treatment of an indicated condition.

Uses and Methods of Treatment

[0161] Some embodiments described herein relate to a method for treating a cancer or a tumor described herein that can include administering an effective amount of a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof) or a pharmaceutical composition that includes a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof) to a subject having a cancer described herein. Other embodiments described herein relate to the use of an effective amount of a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof) or a pharmaceutical

composition that includes a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof) in the manufacture of a medicament for treating a cancer or a tumor described herein. Still other embodiments described herein relate to an effective amount of a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof) or a pharmaceutical composition that includes a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof) for treating a cancer or a tumor described herein.

[0162] Some embodiments described herein relate to a method for inhibiting replication of a malignant growth or a tumor described herein that can include contacting the growth or the tumor with an effective amount of a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof). Other embodiments described herein relate to the use of an effective amount of a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof) in the manufacture of a medicament for inhibiting replication of a malignant growth or a tumor described herein. In some embodiments, the use can include contacting the growth or the tumor with the medicament. Still other embodiments described herein relate to an effective amount of a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof) for inhibiting replication of a malignant growth or a tumor described herein.

[0163] Some embodiments described herein relate to a method for treating a cancer described herein that can include contacting a malignant growth or a tumor described herein with an effective amount of a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof). Other embodiments described herein relate to the use of an effective amount of a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof) in the manufacture of a medicament for treating a cancer described herein. In some embodiments, the use can include contacting the malignant growth or a tumor described herein with the medicament. Still other embodiments described herein relate to an effective amount of a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable

salt thereof) for contacting a malignant growth or a tumor described herein, wherein the malignant growth or tumor is due to a cancer described herein.

[0164] Examples of suitable malignant growths, cancers and tumors include, but are not limited to: bladder cancers, brain cancers, breast cancers, bone marrow cancers, cervical cancers, colorectal cancers, esophageal cancers, hepatocellular cancers, lymphoblastic leukemias, follicular lymphomas, lymphoid malignancies of T-cell or B-cell origin, melanomas, myelogenous leukemias, Hodgkin's lymphoma, Non-Hodgkin's lymphoma, head and neck cancers (including oral cancers), ovarian cancers, non-small cell lung cancer, chronic lymphocytic leukemias, myelomas (including multiple myelomas), prostate cancer, small cell lung cancer, spleen cancers, polycythemia vera, thyroid cancers, endometrial cancer, stomach cancers, gallbladder cancer, bile duct cancers, testicular cancers, neuroblastomas, osteosarcomas, Ewings's tumor and Wilm's tumor.

[0165] As described herein, a malignant growth, cancer or tumor, can become resistant to one or more anti-proliferative agents. In some embodiments, a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof) or a pharmaceutical composition that includes a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof) can be used to treat and/or ameliorate a malignant growth, cancer or tumor, that has become resistant to one or more anti-proliferative agents (such as one or more Bcl-2 inhibitors). Examples of anti-proliferative agents that a subject may have developed resistance to include, but are not limited to, Bcl-2 inhibitors (such as venetoclax, navitoclax, obatoclax, S55746, APG-1252, APG-2575 and ABT-737). In some embodiments, the malignant growth, cancer or tumor, that has become resistant to one or more anti-proliferative agents can be a malignant growth, cancer or tumor, described herein.

[0166] Some embodiments described herein relate to a method for inhibiting the activity of Bcl-2 (such as by, for example, inhibiting the activity of a Bcl-2 protein and/or a Bcl-xL protein) that can include administering an effective amount of a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof) or a pharmaceutical composition that includes a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof) to a subject and can also include contacting a cell that expresses Bcl-2 with an effective amount

of a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof) or a pharmaceutical composition that includes a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof). Other embodiments described herein relate to the use of an effective amount of a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof) in the manufacture of a medicament for inhibiting the activity of Bcl-2 in a subject (such as by, for example, inhibiting the activity of a Bcl-2 protein and/or a Bcl-xL protein) or, in the manufacture of a medicament for inhibiting the activity of Bcl-2 (such as by, for example, inhibiting the activity of a Bcl-2 protein and/or a Bcl-xL protein), wherein the use comprises contacting with a cell that expresses Bcl-2. Still other embodiments described herein relate to an effective amount of a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof) for inhibiting the activity of Bcl-2 in a subject (such as by, for example, inhibiting the activity of a Bcl-2 protein and/or a Bcl-xL protein); or for inhibiting the activity of Bcl-2 (such as by, for example, inhibiting the activity of a Bcl-2 protein and/or a Bcl-xL protein) by contacting with a cell that expresses Bcl-2.

[0167] In some embodiments, the Bcl protein inhibitor of Formula (I) can be a selective Bcl-2 inhibitor, a selective Bcl-X_L inhibitor, a selective Bcl-W inhibitor, a selective Mcl-1 inhibitor or a selective Bcl-2A1 inhibitor. In some embodiments, the Bcl protein inhibitor of Formula (I) can inhibit more than one Bcl protein. In some embodiments, the Bcl protein inhibitor can be an inhibitor of the activity of Bcl-2 and one, two or three of Bcl-X_L, Bcl-W, Mcl-1 and Bcl-2A1. In some embodiments, the Bcl protein inhibitor can be an inhibitor of the activity of Bcl-X_L and one, two or three of Bcl-W, Mcl-1 and Bcl-2A1. In some embodiments, the Bcl protein inhibitor of Formula (I) can inhibit Bcl-2 and/or Bcl-X_L. In some embodiments, the Bcl protein inhibitor of Formula (I) can inhibit both Bcl-2 and Bcl-X_L.

[0168] Several known Bcl-2 inhibitors can cause one or more undesirable side effects in the subject being treated. Examples of undesirable side effects include, but are not limited to, thrombocytopenia, neutropenia, anemia, diarrhea, nausea and upper respiratory tract infection. In some embodiments, a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof) can decrease the

number and/or severity of one or more side effects associated with a known Bcl-2 inhibitors. In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can result in a severity of a side effect (such as one of those described herein) that is 25% less than compared to the severity of the same side effect experienced by a subject receiving a known Bcl-2 inhibitors (such as venetoclax, navitoclax, obatoclax, ABT-737, S55746, AT-101, APG-1252 and APG-2575). In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, results in a number of side effects that is 25% less than compared to the number of side effects experienced by a subject receiving a known Bcl-2 inhibitors (for example, venetoclax, navitoclax, obatoclax, ABT-737, S55746, AT-101, APG-1252 and APG-2575). In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, results in a severity of a side effect (such as one of those described herein) that is less in the range of about 10% to about 30% compared to the severity of the same side effect experienced by a subject receiving a known Bcl-2 inhibitors (for example, venetoclax, navitoclax, obatoclax, ABT-737, S55746, AT-101, APG-1252 and APG-2575). In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, results in a number of side effects that is in the range of about 10% to about 30% less than compared to the number of side effects experienced by a subject receiving a known Bcl-2 inhibitors (for example, venetoclax, navitoclax, obatoclax, ABT-737, S55746, APG-1252 and APG-2575).

[0169] The one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof, that can be used to treat, ameliorate and/or inhibit the replication of a cancer, malignant growth, or tumor wherein inhibiting the activity of Bcl-2 is beneficial is provided in any of the embodiments described above under the heading titled “Compounds.” For example, in various embodiments, the methods and uses described above in the Uses and Methods of Treatment section of this disclosure are carried out in the described manner (generally involving cancer, malignant growth, and/or tumor) using a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0170] As used herein, a “subject” refers to an animal that is the object of treatment, observation or experiment. “Animal” includes cold- and warm-blooded vertebrates and invertebrates such as fish, shellfish, reptiles and, in particular, mammals. “Mammal” includes, without limitation, mice, rats, rabbits, guinea pigs, dogs, cats, sheep, goats, cows,

horses, primates, such as monkeys, chimpanzees, and apes, and, in particular, humans. In some embodiments, the subject can be human. In some embodiments, the subject can be a child and/or an infant, for example, a child or infant with a fever. In other embodiments, the subject can be an adult.

[0171] As used herein, the terms “treat,” “treating,” “treatment,” “therapeutic,” and “therapy” do not necessarily mean total cure or abolition of the disease or condition. Any alleviation of any undesired signs or symptoms of the disease or condition, to any extent can be considered treatment and/or therapy. Furthermore, treatment may include acts that may worsen the subject’s overall feeling of well-being or appearance.

[0172] The terms “therapeutically effective amount” and “effective amount” are used to indicate an amount of an active compound, or pharmaceutical agent, that elicits the biological or medicinal response indicated. For example, a therapeutically effective amount of compound, salt or composition can be the amount needed to prevent, alleviate or ameliorate symptoms of the disease or condition, or prolong the survival of the subject being treated. This response may occur in a tissue, system, animal or human and includes alleviation of the signs or symptoms of the disease or condition being treated. Determination of an effective amount is well within the capability of those skilled in the art, in view of the disclosure provided herein. The therapeutically effective amount of the compounds disclosed herein required as a dose will depend on the route of administration, the type of animal, including human, being treated and the physical characteristics of the specific animal under consideration. The dose can be tailored to achieve a desired effect, but will depend on such factors as weight, diet, concurrent medication and other factors which those skilled in the medical arts will recognize.

[0173] For example, an effective amount of a compound is the amount that results in: (a) the reduction, alleviation or disappearance of one or more symptoms caused by the cancer, (b) the reduction of tumor size, (c) the elimination of the tumor, and/or (d) long-term disease stabilization (growth arrest) of the tumor. In the treatment of lung cancer (such as non-small cell lung cancer), a therapeutically effective amount is that amount that alleviates or eliminates cough, shortness of breath and/or pain. As another example, an effective amount, or a therapeutically effective amount of a Bcl-2 inhibitor is the amount which results in the reduction in Bcl-2 activity and/or an increase in apoptosis. Methods for measuring

reductions in Bcl-2 activity are known to those skilled in the art and can be determined by the analysis of Bcl-2 binding and/or degradation, and/or relative levels of cells undergoing apoptosis.

[0174] The amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, required for use in treatment will vary not only with the particular compound or salt selected but also with the route of administration, the nature and/or symptoms of the disease or condition being treated and the age and condition of the patient and will be ultimately at the discretion of the attendant physician or clinician. In cases of administration of a pharmaceutically acceptable salt, dosages may be calculated as the free base. As will be understood by those of skill in the art, in certain situations it may be necessary to administer the compounds disclosed herein in amounts that exceed, or even far exceed, the dosage ranges described herein in order to effectively and aggressively treat particularly aggressive diseases or conditions.

[0175] In general, however, a suitable dose will often be in the range of from about 0.05 mg/kg to about 10 mg/kg. For example, a suitable dose may be in the range from about 0.10 mg/kg to about 7.5 mg/kg of body weight per day, such as about 0.15 mg/kg to about 5.0 mg/kg of body weight of the recipient per day, about 0.2 mg/kg to 4.0 mg/kg of body weight of the recipient per day, or any amount in between. The compound may be administered in unit dosage form; for example, containing 1 to 500 mg, 10 to 100 mg, 5 to 50 mg or any amount in between, of active ingredient per unit dosage form.

[0176] The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example, as two, three, four or more sub-doses per day. The sub-dose itself may be further divided, e.g., into a number of discrete loosely spaced administrations.

[0177] As will be readily apparent to one skilled in the art, the useful *in vivo* dosage to be administered and the particular mode of administration will vary depending upon the age, weight, the severity of the affliction, the mammalian species treated, the particular compounds employed and the specific use for which these compounds are employed. The determination of effective dosage levels, that is the dosage levels necessary to achieve the desired result, can be accomplished by one skilled in the art using routine methods, for example, human clinical trials, *in vivo* studies and *in vitro* studies. For example,

useful dosages of a compound of Formula (I), or pharmaceutically acceptable salts thereof, can be determined by comparing their *in vitro* activity and *in vivo* activity in animal models. Such comparison can be done by comparison against an established drug, such as cisplatin and/or gemcitabine)

[0178] Dosage amount and interval may be adjusted individually to provide plasma levels of the active moiety which are sufficient to maintain the modulating effects, or minimal effective concentration (MEC). The MEC will vary for each compound but can be estimated from *in vivo* and/or *in vitro* data. Dosages necessary to achieve the MEC will depend on individual characteristics and route of administration. However, HPLC assays or bioassays can be used to determine plasma concentrations. Dosage intervals can also be determined using MEC value. Compositions should be administered using a regimen which maintains plasma levels above the MEC for 10-90% of the time, preferably between 30-90% and most preferably between 50-90%. In cases of local administration or selective uptake, the effective local concentration of the drug may not be related to plasma concentration.

[0179] It should be noted that the attending physician would know how to and when to terminate, interrupt or adjust administration due to toxicity or organ dysfunctions. Conversely, the attending physician would also know to adjust treatment to higher levels if the clinical response were not adequate (precluding toxicity). The magnitude of an administered dose in the management of the disorder of interest will vary with the severity of the disease or condition to be treated and to the route of administration. The severity of the disease or condition may, for example, be evaluated, in part, by standard prognostic evaluation methods. Further, the dose and perhaps dose frequency, will also vary according to the age, body weight and response of the individual patient. A program comparable to that discussed above may be used in veterinary medicine.

[0180] Compounds, salts and compositions disclosed herein can be evaluated for efficacy and toxicity using known methods. For example, the toxicology of a particular compound, or of a subset of the compounds, sharing certain chemical moieties, may be established by determining *in vitro* toxicity towards a cell line, such as a mammalian, and preferably human, cell line. The results of such studies are often predictive of toxicity in animals, such as mammals, or more specifically, humans. Alternatively, the toxicity of particular compounds in an animal model, such as mice, rats, rabbits, dogs or monkeys, may

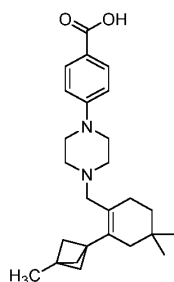
be determined using known methods. The efficacy of a particular compound may be established using several recognized methods, such as *in vitro* methods, animal models, or human clinical trials. When selecting a model to determine efficacy, the skilled artisan can be guided by the state of the art to choose an appropriate model, dose, route of administration and/or regime.

EXAMPLES

[0181] FIGS. 1-6 illustrate various synthetic schemes for making compounds of the Formula (I). Additional embodiments are disclosed in further detail in the following examples, which are not in any way intended to limit the scope of the claims.

Intermediate 1

4-(4-((4,4-Dimethyl-2-(3-methylbicyclo[1.1.1]pentan-1-yl)cyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoic acid

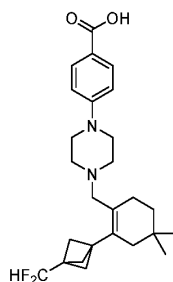


[0182] Step 1: To a stirred solution of methyl 4-(piperazin-1-yl)benzoate (1.68 g, 7.6 mmol) and 4,4-dimethyl-2-(3-methylbicyclo[1.1.1]pentan-1-yl)cyclohex-1-ene-1-carbaldehyde (2.0 g, 9.15 mmol) in THF (20 mL) was added Na(OAc)₃BH (4.8 g, 22.8 mmol) at rt. After 16 h, the reaction was put in an ice batch and quenched with sat. aq. NaHCO₃ (25 mL). The reaction mixture was extracted with EtOAc (3 x 50 mL), dried over Na₂SO₄, filtered, and concentrated. The crude product was purified by column chromatography (SiO₂, EtOAc/pet. ether) to obtain methyl 4-(4-((4,4-dimethyl-2-(3-methylbicyclo[1.1.1]pentan-1-yl)cyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoate (**Intermediate 1-1**) as a white solid (1.5 g, 46% yield). LC/MS (ESI) *m/z* 423.2[M+H]⁺.

[0183] Step 2: To a stirred solution of **Intermediate 1-1** (500 mg, 1.18 mmol) in MeOH:THF:H₂O (1:1:1) (6 mL) was added LiOH•H₂O (148 mg, 3.4 mmol) at rt. The reaction was heated to 30 °C and stirred for 16 h. The volatile solvents were then removed, and the reaction was neutralized with 1N HCl and extracted with 95:5 DCM:MeOH (3 x 25 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated to provide **Intermediate 1** (350 mg, 73% yield) as a white solid. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.25 (br s, 1H), 7.75 (d, *J*=9.0 Hz, 2H), 6.95 (d, *J*=9.0 Hz, 2H), 3.32-3.25 (m, 4H), 3.03 (s, 2H), 2.45-2.35 (m, 4H), 2.06 -2.04 (m, 2H), 1.79 (s, 6H), 1.68 (s, 2H), 1.26 (t, *J*=6.3 Hz, 2H), 1.12 (s, 3H), 0.85 (s, 6H); LC/MS (ESI) *m/z* 409.5 [M+H]⁺.

Intermediate 2

4-(4-((2-(3-(Difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoic acid

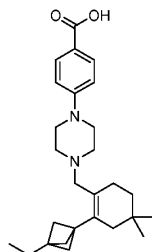


[0184] Step 1: Methyl 4-(4-((2-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoate (**Intermediate 2-1**) was prepared following the procedure described in Step 1 for **Intermediate 1** using 2-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-ene-1-carbaldehyde in place of 4,4-dimethyl-2-(3-methylbicyclo[1.1.1]pentan-1-yl)cyclohex-1-ene-1-carbaldehyde. LC/MS (ESI) *m/z* 459.6 [M+H]⁺.

[0185] Step 2: **Intermediate 2** was prepared following the procedure described in Step 2 for **Intermediate 1** using **Intermediate 2-1** in place of **Intermediate 1-1**. LC/MS (ESI) *m/z* 445.6 [M+H]⁺.

Intermediate 3

4-(4-((2-(3-ethylbicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoic acid

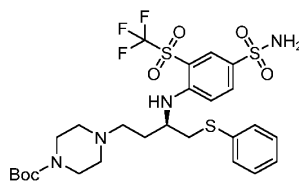


[0186] Step 1: Methyl 4-(4-((2-(3-ethylbicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoate (**Intermediate 3-1**) was prepared following the procedure described in Step 1 for **Intermediate 1** using 2-(3-ethylbicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-ene-1-carbaldehyde in place of 4,4-dimethyl-2-(3-methylbicyclo[1.1.1]pentan-1-yl)cyclohex-1-ene-1-carbaldehyde. LC/MS (ESI) m/z 437.3 $[M+H]^+$.

[0187] **Intermediate 3** was prepared following the procedure described in Step 2 for **Intermediate 1** using **Intermediate 3-1** in place of **Intermediate 1-1**. LC/MS (ESI) m/z 423.3 $[M+H]^+$.

Intermediate 4

tert-butyl (R)-4-(4-(phenylthio)-3-((4-sulfamoyl-2-((trifluoromethyl)sulfonyl)phenyl)amino)butyl)piperazine-1-carboxylate

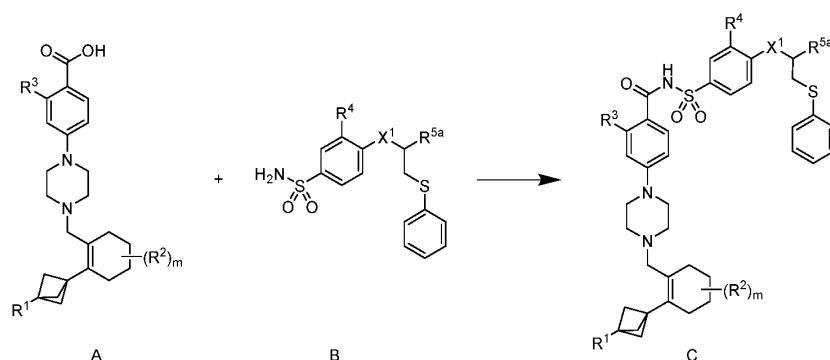


[0188] Step 1: To a stirred solution of (R)-4-(phenylthio)-3-((4-sulfamoyl-2-((trifluoromethyl)sulfonyl)phenyl)amino)butanoic acid (prepared following a procedure described in patent WO2012017251A1) (500 mg, 1.0 mmol), DMAP (122 mg, 1.0 mmol), and EDC•HCl (288 mg, 1.50 mmol) in DCM (10 mL) was added *tert*-butyl piperazine-1-carboxylate (220 mg, 1.20 mmol) and Et₃N (0.28 mL, 2.00 mmol) at rt. After 15 min, the reaction was heated to 35 °C and stirred for 16 h. The reaction mixture was then cooled to rt,

diluted with DCM (50 mL) and MeOH (5 mL) and washed with 10% CH₃CO₂H (aq.) (2 x 15 mL). The organic layer was then washed with 5% NaHCO₃ (aq.) (2 x 10 mL), 5% NaCl(aq.) (2 x 10 mL) and concentrated. The crude product was purified by column chromatography (SiO₂, DCM/MeOH) to afford (*R*)-*tert*-Butyl 4-(4-(phenylthio)-3-((4-sulfamoyl-2-((trifluoromethyl)sulfonyl)phenyl)-amino)butanoyl)piperazine-1-carboxylate (**Intermediate 4-1**) (420 mg, 62% yield). LC/MS (ESI) *m/z* 665.4 [M-H]⁻.

[0189] Step 2: To a stirred solution of **Intermediate 4-1** (300 mg, 0.45 mmol) in THF (30 mL) was added BH₃•THF (1M in THF, 2.25 mL, 2.25 mmol) at 0 °C. The resulting reaction mixture was heated to 55 °C for 16 h in a sealed tube. The reaction was then cooled to 0 °C, and treated with MeOH (4 mL) and heated to 40 °C. After 12 h, the reaction was concentrated and the crude product was purified by column chromatography (SiO₂, DCM/MeOH) to afford **Intermediate 4** (150 mg, 51% yield). LC/MS (ESI) *m/z* 653.2 [M+H]⁺.

General Procedure A: Acyl Sulfonamide Formation



[0190] To a solution of corresponding sulfonamide **B** (1.0 eq.) in DCM (0.01-0.1 M) at rt was added EDC•HCl (1.5-2.525 equiv.) and DMAP (1-2.5 equiv.). In a separate flask, the appropriate acid **A** (1-1.5 equiv.) was dissolved in DCM (0.02-0.1M) was treated with Et₃N (2-4 eq.) (Note #1). After 15 min, the acid solution was added to the sulfonamide suspension and either stirred at rt or heated to 35-40 °C. Upon completion as determined by LCMS, *N,N*-dimethylethylenediamine (2-2.5 equiv., Note #2) was added to the reaction mixture and the reaction was stirred for 90 min. The reaction mixture was then washed with 10% aq. AcOH (Note #3), 5% NaHCO₃(aq.) and then with 5% NaCl (aq.). The organic layer was concentrated, and crude product **C** was either purified by 1) column chromatography

(SiO₂), 2) HPLC (10 mM NH₄CO₃H(aq.): CH₃CN or MeOH), or 3) trituration with an organic solvent.

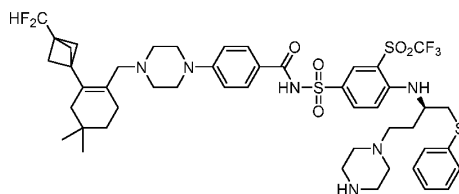
[0191] Note #1: In some instances, Et₃N was added to the flask containing sulfonamide **B**

[0192] Note #2: In some instances, *N,N*-dimethylethylenediamine was not added during the workup.

[0193] Note #3: In some instances, the organic layer was diluted with DCM and MeOH to solubilize the crude product.

Intermediate 5

(*R*)-4-(4-((2-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-*N*-((4-((1-(phenylthio)-4-(piperazin-1-yl)butan-2-yl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide



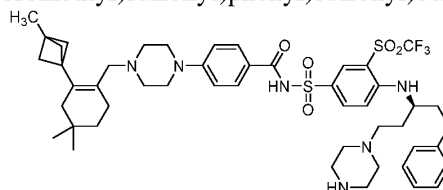
[0194] Step 1: (*R*)-*tert*-Butyl 4-(3-((4-(*N*-(4-(4-((2-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-((trifluoro-methyl)sulfonyl)phenyl)amino)-4-(phenylthio)butyl)piperazine-1-carboxylate (**Intermediate 5-1**) was prepared following General Procedure A using **Intermediate 2** and **Intermediate 4**. LC/MS (ESI) *m/z* 1079.3 [M+H]⁺

[0195] Step 2: To a stirred solution of **Intermediate 5-1** (350 mg, 0.32 mmol) in Et₂O (5 mL) at 0 °C, was added HCl (2M in Et₂O, 2.0 mL). The reaction was warmed to rt and stirred for 16 h. The reaction was concentrated, diluted with ice cold water, basified with sat. aq. NaHCO₃ (10 mL) and extracted with 10% MeOH in DCM (3 x 30 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated. The crude product was purified by HPLC (30:70 to 1:99 10 mM NH₄CO₃H(aq.)/CH₃CN) to provide **Intermediate 5** (14 mg, 4% yield) as an off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.32 (br s, 2H), 8.02 (s, 1H), 7.91 (d, *J*=8.8 Hz, 1H), 7.68 (d, *J*=8.8 Hz, 2H),

7.34-7.23 (m, 4H), 7.19-7.15 (m, 1H), 6.83-6.75 (m, 3H), 6.66 (d, $J=8.8$ Hz, 1H), 5.97 (t, $J=56.8$ Hz, 1H), 3.97 (br s, 1H), 3.26-3.23 (m, 2H), 3.15-3.10 (m, 4H), 3.02-2.90 (m, 6H), 2.52-2.50 (m, 2H), 2.40-2.23 (m, 8H), 2.10-1.83 (m, 9H), 1.67 (s, 3H), 1.23 (t, $J=6.4$ Hz, 2H), 0.82 (s, 6H); LC/MS (ESI) m/z 979.4 $[M+H]^+$.

Intermediate 6

(R)-4-(4-((4,4-dimethyl-2-(3-methylbicyclo[1.1.1]pentan-1-yl)cyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-((1-(phenylthio)-4-(piperazin-1-yl)butan-2-yl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide

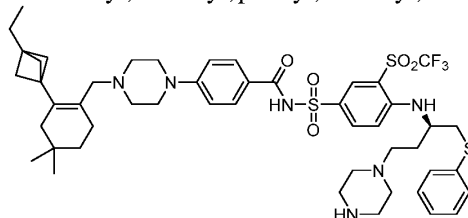


[0196] Step 1: tert-butyl (R)-4-(3-((4-(N-(4-(4-((4,4-dimethyl-2-(3-methylbicyclo[1.1.1]pentan-1-yl)cyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-((trifluoromethyl)sulfonyl)phenyl)amino)-4-(phenylthio)butyl)piperazine-1-carboxylate (**Intermediate 6-1**) was prepared following General Procedure A using **Intermediate 1** and **Intermediate 4**. LC/MS (ESI) m/z 1043.6 $[M+H]^+$.

[0197] Step 2: To a stirred solution of **Intermediate 6-1** (800 mg, 0.767 mmol) in Et₂O (8 mL) was added 2M HCl in Et₂O (8 mL) at 0 °C and the reaction was warmed to rt. After 16 h, the reaction mixture was concentrated and then dissolved in 10% MeOH in DCM (50 mL). The organic layer was washed with sat. aq. NaHCO₃ (2 x 20 mL), brine (2 x 20 mL), dried over Na₂SO₄, filtered, and concentrated to afford **Intermediate 6** (550 mg, 76% yield) as an off-white solid. ¹H NMR (400 MHz, CDCl₃) δ 8.05 (d, $J=2.0$ Hz, 1H), 7.94 (dd, $J=9.2, 7.2$ Hz, 1H), 7.72 (d, $J=8.8$ Hz, 2H), 7.37-7.35 (m, 2H), 7.31 (t, $J=5.6$ Hz, 2H), 7.22-7.20 (m, 1H), 6.85-6.79 (m, 3H), 6.69 (d, $J=9.2$ Hz, 1H), 4.00-3.99 (m, 1H), 3.31-3.23 (m, 4H), 3.15 (s, 4H), 3.01-2.97 (m, 6H), 2.49-2.33 (m, 9H), 2.03-1.99 (m, 3H), 1.79-1.67 (m, 9H), 1.26-1.23 (m, 3H), 1.11 (s, 3H), 0.84 (s, 6H); LC/MS (ESI) m/z 943.5 $[M+H]^+$.

Intermediate 7

(R)-4-(4-((2-(3-ethylbicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-((1-(phenylthio)-4-(piperazin-1-yl)butan-2-yl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide

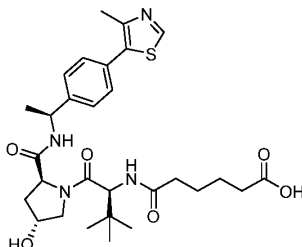


[0198] Step 1: To a stirred solution of **Intermediate 4** (1.48 g, 2.272 mmol) in DCM (30 mL) was added EDC•HCl (0.813 g, 4.26 mmol) and DMAP (0.343 g, 2.84 mmol). The resulting reaction mixture was stirred for 15 min at rt and **Intermediate 3** (1.2 g, 2.84 mmol) and TEA 0.79 mL, 5.68 mmol) were added dropwise at rt. The reaction mixture was stirred at 40 °C for 16 h and then diluted with 10% MeOH in DCM (100 mL). The organic layer was washed with 10% CH₃CO₂H(aq.) (2 x 20 mL) 5% sat. aq. NaHCO₃ (2 x 30 mL), 5% NaCl solution (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated. The crude product was purified by column chromatography (SiO₂, MeOH/DCM) to afford *tert*-butyl (R)-4-(3-((4-(N-(4-(4-((2-(3-ethylbicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-((trifluoromethyl)sulfonyl)phenyl)amino)-4-(phenylthio)butyl)piperazine-1-carboxylate (**Intermediate 7-1**) (1.85 g, 61% yield) as an off-white solid. LC/MS (ESI) *m/z* 1057.5 [M+H]⁺.

[0199] Step 2: **Intermediate 7** was prepared following the procedure described in Step 2 for **Intermediate 5** using **Intermediate 7-1** in place of **Intermediate 5-1**. LC/MS (ESI) *m/z* 957.9 [M+H]⁺.

Intermediate 8

6-(((S)-1-((2S,4R)-4-Hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-6-oxohexanoic acid

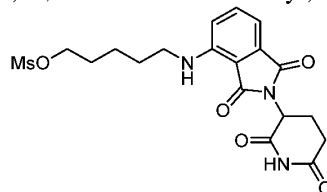


[0200] Step 1: To a solution of 6-tert-butoxy-6-oxo-hexanoic acid (118.3 mg, 584.8 μmol) and (2S,4R)-1-((S)-2-amino-3,3-dimethylbutanoyl)-4-hydroxy-N-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl) pyrrolidine-2-carboxamide (0.2 g, 449.9 μmol) in N,N-dimethylformamide (3 mL) was added HATU (205.3 mg, 539.8 μmol) and DIPEA (581.4 mg, 4.50 mmol) at 20°C. The reaction was stirred at 40 °C for 16 h, cooled to rt and then diluted with water (5 mL) and extracted with EtOAc (2 $\times$ 5 mL). The combined organic layers were washed with brine (2 $\times$ 10 mL) and dried over Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure to afford crude tert-butyl 6-(((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-6-oxohexanoate (**Intermediate 8-1**) (0.12 g) as a yellow oil. LC/MS (ESI) m/z 629.5 [M+H]⁺.

[0201] Step 2: **Intermediate 8-1** (0.12 g, 0.187 mmol) was treated with a solution of TFA (0.1 mL) in DCM (1 mL) at 0°C and stirred at rt for 12 h. The reaction was concentrated to afford the crude product which was purified by HPLC (80:20 to 50:50 H₂O (0.09% TFA)/CH₃CN) to provide **Intermediate 8** (50 mg, 27% yield) as a yellow solid. LC/MS (ESI) m/z 571.4 [M-H]⁻.

Intermediate 9

5-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)amino)pentyl methanesulfonate

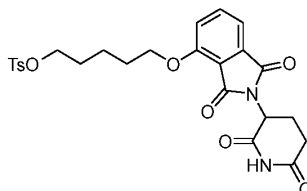


[0202] Step 1: To a solution of 2-(2,6-dioxopiperidin-3-yl)-4-fluoroisindoline-1,3-dione (1 g, 3.62 mmol) in DMSO (8 mL) was added 5-aminopentan-1-ol (0.373 g, 3.62 mmol) and DIPEA (1.3 mL, 7.25 mmol) at rt. The reaction mixture was heated to 90 °C and stirred for 12 h. The reaction mixture was cooled to rt, diluted with ice-cold water, and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with water (2 x 50 mL), brine (2 x 10 mL), dried over Na₂SO₄, filtered and concentrated. The crude product was purified by column chromatography (SiO₂, 90-100% EtOAc in pet. ether) to afford 2-(2,6-dioxopiperidin-3-yl)-4-((5-hydroxypentyl)amino)isindoline-1,3-dione (**Intermediate 9-1**) (750 mg, 57% yield) as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 7.90 (br s, 1H), 7.49 (t, *J* = 7.6 Hz, 1H), 7.09 (d, *J* = 7.2 Hz, 1H), 6.88 (d, *J* = 8.4 Hz, 1H), 6.24 (s, 1H), 4.94-4.89 (m, 1H), 3.68 (t, *J* = 6.4 Hz, 2H), 3.29 (q, *J* = 6.5 Hz, 2H), 2.92-2.76 (m, 4H), 1.76-1.70 (m, 2H), 1.65-1.59 (m, 2H), 1.56-1.51 (m, 2H); LC/MS (ESI) *m/z* 360.4 [M+H]⁺.

[0203] Step 2: To a solution of **Intermediate 9-1** (200 mg, 0.557 mmol) in DCM (10 mL) was added methanesulfonyl chloride (69 mg, 0.61 mmol) and triethylamine (225 mg, 2.23 mmol) at 0 °C. The reaction was warmed to rt, stirred for 2 h, and then quenched with ice-cold water and extracted with DCM (2 x 30 mL). The combined organic layers were washed with brine (2 x 10 mL), dried over Na₂SO₄, filtered, and concentrated to afford **Intermediate 9** (230 mg) as a yellow oil. The crude product was used in the next step without further purification. LC/MS (ESI) *m/z* 438.4 [M+H]⁺.

Intermediate 10

5-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)oxy)pentyl 4-methylbenzenesulfonate

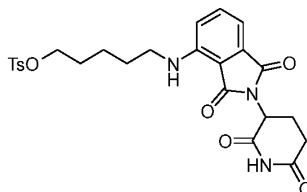


[0204] Step 1: To a solution of 2-(2,6-dioxo-3-piperidyl)-4-hydroxy-isoindoline-1,3-dione (197 mg, 718.4 μ mol) and 5-bromopentan-1-ol (200 mg, 1.2 mmol) in DMF (3 mL) was added NaHCO_3 (201.2 mg, 2.39 mmol) and KI (19.9 mg, 119.7 μ mol) at 20°C. The reaction was stirred at 80 °C for 12 h and then cooled to rt. The reaction mixture was concentrated and purified by prep-TLC to afford 2-(2,6-dioxo-3-piperidyl)-4-(5-hydroxypentoxo)isoindoline-1,3-dione (**Intermediate 10-1**) (200 mg, 46% yield) as a yellow solid. ^1H NMR (400 MHz, CDCl_3) δ 8.08-7.97 (m, 1H), 7.72-7.63 (m, 1H), 7.47-7.44 (m, 1H), 7.21 (d, J = 8.6 Hz, 1H), 5.01-4.90 (m, 1H), 4.25-4.15 (m, 4H), 3.79-3.63 (m, 4H), 3.00-2.65 (m, 2H), 2.22-2.09 (m, 1H), 2.01-1.85 (m, 2H).

[0205] Step 2: To a solution of **Intermediate 10-1** (200 mg, 555.0 μ mol) in DCM (2 mL) was added pyridine (439.0 mg, 5.55 mmol) and TsCl (1.06 g, 5.55 mmol) at 0°C. The reaction was stirred at 20°C for 12 h. The reaction mixture was then concentrated and purified by prep-TLC to afford **Intermediate 10** (100 mg, 35% yield) as a yellow oil. ^1H NMR (400 MHz, MeOH-d_4) δ 7.83-7.75 (m, 3H), 7.48-7.41 (m, 4H), 5.13 (br dd, J = 12.4, 5.4 Hz, 3H), 4.18 (t, J = 6.2 Hz, 2H), 4.14-4.07 (m, 2H), 2.92-2.84 (m, 1H), 2.82-2.78 (m, 1H), 2.78-2.72 (m, 1H), 2.43 (s, 3H), 1.85-1.72 (m, 4H), 1.59-1.50 (m, 2H); LC/MS (ESI) m/z 515.2 $[\text{M}+\text{H}]^+$.

Intermediate 11

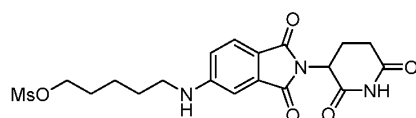
5-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)amino)pentyl 4-methylbenzenesulfonate



[0206] To a solution of 2-(2,6-dioxo-3-piperidyl)-4-(5-hydroxypentylamino)isoindoline-1,3-dione (**Intermediate 9-1**) (150 mg, 417.4 μmol) in DCM (2 mL) was added pyridine (336.9 μL , 4.17 mmol) and TsCl (67.58 mg, 667.8 μmol) at 0°C. The reaction was stirred at 20 °C for 12 h and then concentrated and purified by prep-TLC to afford **Intermediate 11** (60 mg, 28% yield) as a yellow oil. LC/MS (ESI) m/z 514.2 $[\text{M}+\text{H}]^+$.

Intermediate 12

5-[[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-5-yl] amino]pentyl methanesulfonate

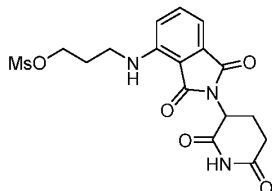


[0207] Step 1: To a solution of 2-(2,6-dioxo-3-piperidyl)-5-fluoro-isoindoline-1,3-dione (0.5 g, 1.81 mmol) and 5-aminopentan-1-ol (373.5 mg, 3.62 mmol) in NMP (5 mL) was added DIPEA (945.9 μL , 5.43 mmol) at 20°C. The reaction was stirred at 120 °C for 30 min. The reaction mixture was then concentrated and purified by HPLC (90:10 to 60:40 water (0.09% TFA)/CH₃CN) to afford 2-(2,6-dioxo-3-piperidyl)-5-(5-hydroxypentylamino)isoindoline-1,3-dione (**Intermediate 12-1**) (100 mg, 15% yield) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.04 (s, 1H), 7.55 (d, J = 8.4 Hz, 1H), 7.09 (br s, 1H), 6.93 (d, J = 1.8 Hz, 1H), 6.83 (dd, J = 8.5, 1.9 Hz, 1H), 5.01 (dd, J = 12.9, 5.4 Hz, 1H), 3.38 (br d, J = 6.4 Hz, 4H), 3.14 (br s, 2H), 2.94-2.80 (m, 1H), 2.61-2.54 (m, 1H), 2.05-1.94 (m, 1H), 1.56 (quin, J = 7.1 Hz, 2H), 1.48-1.34 (m, 4H); LC/MS (ESI) m/z 360.2 $[\text{M}+\text{H}]^+$.

[0208] Step 2: To a solution of **Intermediate 12-1** (0.06 g, 167 μmol) in DCM (1 mL) was added MsCl (15.5 μL , 200.4 μmol) and TEA (93 μL , 667.8 μmol) at 20 °C. The reaction was stirred at 20 °C for 2 h. The reaction mixture was concentrated and purified by prep-TLC to afford **Intermediate 12** (50 mg, 68% yield) as a yellow oil. LC/MS (ESI) m/z 438.2 $[\text{M}+\text{H}]^+$.

Intermediate 13

3-[[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-4-yl]amino]propyl methanesulfonate

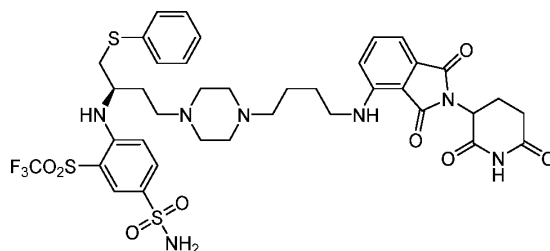


[0209] Step 1: To a solution of 2-(2,6-dioxo-3-piperidyl)-4-fluoro-isoindoline-1,3-dione (588 mg, 2.13 mmol) and 3-aminopropan-1-ol (200 mg, 2.13 mmol) in NMP (5 mL) was added DIPEA (1.31 mL, 7.99 mmol) at 20°C. The reaction was stirred at 100 °C for 12 h. The reaction mixture was cooled to rt, concentrated and purified by HPLC (90:10 to 68:32 water (0.09% TFA)/CH₃CN) to afford 2-(2,6-dioxo-3-piperidyl)-5-(3-hydroxypropylamino) isoindoline-1,3-dione (**Intermediate 13-1**) (200 mg, 23% yield) as a yellow solid. LC/MS (ESI) *m/z* 332.1 [M+H]⁺.

[0210] Step 2: **Intermediate 13** was prepared following the procedure described in Step 2 for **Intermediate 12** using **Intermediate 13-1** in place of **Intermediate 12-1**. LC/MS (ESI) *m/z* 409.9 [M+H]⁺.

Intermediate 14

4-(((2R)-4-(4-(4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)amino)butyl)piperazin-1-yl)-1-(phenylthio)butan-2-yl)amino)-3-((trifluoromethyl)sulfonyl)benzenesulfonamide



[0211] Step 1: tert-butyl 4-(4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)amino)butyl)piperazine-1-carboxylate (**Intermediate 14-1**) was prepared following the procedure described in Step 1 of **Intermediate 12** using 4-(4-aminobutyl)piperazine-1-carboxylate (559 mg, 2.17 mmol) in place of 5-aminopentan-1-ol and 2-(2,6-dioxo-3-piperidyl)-4-fluoro-isoindoline-1,3-dione (0.5 g, 1.81 mmol) in place of 2-(2,6-dioxo-3-

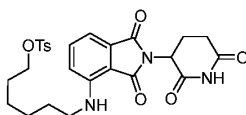
piperidyl)-5-fluoro-isoindoline-1,3-dione. ^1H NMR (400 MHz, CDCl_3 -d) δ 7.56-7.46 (m, 1H), 7.12 (d, $J = 7.1$ Hz, 1H), 6.91 (d, $J = 8.4$ Hz, 1H), 6.26 (t, $J = 5.6$ Hz, 1H), 4.96-4.88 (m, 1H), 3.66-3.40 (m, 3H), 3.40-3.28 (m, 2H), 2.95-2.68 (m, 4H), 2.61-2.30 (m, 4H), 2.17-2.11 (m, 1H), 1.86-1.51 (m, 7H), 1.47 (s, 9H); LC/MS (ESI) m/z 514.4 $[\text{M}+\text{H}]^+$.

[0212] Step 2: To a solution of **Intermediate 14-1** (0.3 g, 584.1 μmol) in dioxane (2 mL) was added HCl (4 M in dioxane, 15 mL) at 20 °C. The mixture was stirred at 20 °C for 2 h and then concentrated under reduced pressure to afford the HCl salt of 2-(2,6-dioxopiperidin-3-yl)-4-((4-(piperazin-1-yl)butyl)amino)isoindoline -1,3-dione (**Intermediate 14-2**) (0.2 g, 76% yield) as a yellow solid. The product was used for next step without purification. LC/MS (ESI) m/z 414.1 $[\text{M}+\text{H}]^+$.

[0213] Step 3: To a solution of **Intermediate 14-2** (0.2 g, 444.5 μmol) in DCM (2 mL) was added 4-[[[(1R)-3-oxo-1-(phenylsulfanylmethyl)propyl]amino]-3-(trifluoromethylsulfonyl) benzene sulfonamide (257.38 mg, 533.4 μmol) (prepared following a procedure described in WO2012017251A1), $\text{NaBH}(\text{OAc})_3$ (141.3 mg, 666.8 μmol) and TEA (134.9 mg, 1.33 mmol, 185.6 μL) at 20 °C. The mixture was stirred at 20 °C for 12 h and then diluted with water (2 mL) and extracted with EtOAc (3×2 mL). The organic layer was dried over Na_2SO_4 and filtered. The filtrate was concentrated to afford crude **Intermediate 14** (100 mg, 26% yield) as a yellow solid. The product was directly used in the next step without further purification. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 11.07 (s, 1H), 8.03-7.94 (m, 1H), 7.82 (dd, $J = 9.2, 1.9$ Hz, 1H), 7.57 (dd, $J = 8.3, 7.3$ Hz, 1H), 7.40-7.26 (m, 5H), 7.23-7.17 (m, 1H), 7.11 (d, $J = 8.6$ Hz, 1H), 7.08-6.98 (m, 2H), 6.91-6.84 (m, 1H), 6.55 (t, $J = 5.8$ Hz, 1H), 5.03 (dd, $J = 12.8, 5.4$ Hz, 1H), 4.12-4.03 (m, 1H), 3.59 (ddd, $J = 6.5, 4.1, 2.6$ Hz, 2H), 3.41-3.31 (m, 3H), 3.29-3.21 (m, 3H), 2.93-2.80 (m, 1H), 2.62-2.50 (m, 3H), 2.46-2.19 (m, 7H), 2.07-1.99 (m, 2H), 1.80-1.65 (m, 3H), 1.63-1.40 (m, 4H), 1.50-1.10 (m, 3H); LC/MS (ESI) m/z 878.3 $[\text{M}-\text{H}]^-$.

Intermediate 15

6-[[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-4-yl]amino]hexyl 4-methylbenzenesulfonate

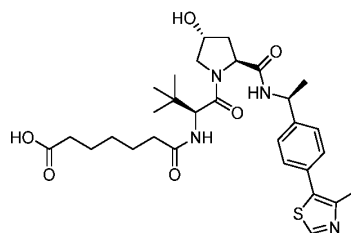


[0214] Step 1: To a solution of 2-(2,6-dioxo-3-piperidyl)-4-fluoro-isoindoline-1,3-dione (500 mg, 1.81 mmol) and 6-aminohexan-1-ol (212.1 mg, 1.81 mmol) in NMP (5 mL) was added DIPEA (1.58, 9.05 mmol) at 25 °C. The reaction was stirred at 60°C for 12 h, cooled to rt, concentrated, and purified by HPLC (90:10 to 60:40 water (0.09% TFA)/CH₃CN) to afford 2-(2,6-dioxo-3-piperidyl)-4-(6-hydroxyhexylamino) isoindoline-1,3-dione (**Intermediate 15-1**) (200 mg, 30% yield) as a yellow solid. LC/MS (ESI) *m/z* 374.2 [M+H]⁺.

[0215] Step 2: **Intermediate 15** was prepared following the procedure described in Step 2 for **Intermediate 10** using **Intermediate 15-1** in place of **Intermediate 10-1**. LC/MS (ESI) *m/z* 528.3 [M+H]⁺.

Intermediate 16

7-(((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-7-oxoheptanoic acid

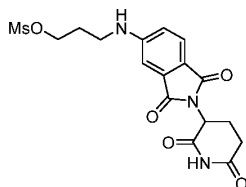


[0216] Step 1: tert-butyl 7-(((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-7-oxoheptanoate (**Intermediate 16-1**) was prepared following the procedure described in Step 1 for **Intermediate 8** using 7-(tert-butoxy)-7-oxoheptanoic acid in place of 6-tert-butoxy-6-oxo-hexanoic acid. LC/MS (ESI) *m/z* 665.5 [M+Na]⁺.

[0217] Step 2: **Intermediate 16** was prepared following the procedure described in Step 2 for **Intermediate 8** using **Intermediate 16-1** in place of **Intermediate 8-1**. ¹H NMR (400MHz, CD₃OD) δ 9.09-9.02 (m, 1H), 7.52-7.42 (m, 4H), 5.02 (q, *J* = 7.0 Hz, 1H), 4.59 (t, *J* = 8.5 Hz, 1H), 4.45 (br s, 1H), 3.91 (d, *J* = 11.6 Hz, 1H), 3.77 (dd, *J* = 10.9, 3.9 Hz, 1H), 2.52 (s, 3H), 2.38-2.26 (m, 4H), 2.25-2.18 (m, 1H), 1.97 (ddd, *J* = 13.1, 8.9, 4.6 Hz, 1H), 1.71-1.58 (m, 5H), 1.53 (d, *J* = 7.0 Hz, 3H), 1.45-1.36 (m, 2H), 1.07 (s, 9H); LC/MS (ESI) *m/z* 587.4 [M+H]⁺.

Intermediate 17

3-[[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-5-yl]amino]propyl methanesulfonate

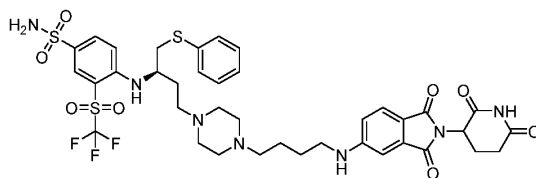


[0218] Step 1: 2-(2,6-dioxo-3-piperidyl)-5-(3-hydroxypropylamino)isoindoline-1,3-dione (**Intermediate 17-1**) was prepared following the procedure described in Step 1 for **Intermediate 12** using 3-aminopropan-1-ol in place of 5-aminopentan-1-ol. LC/MS (ESI) m/z 332.2 $[M+H]^+$.

[0219] Step 2: **Intermediate 17** was prepared following the procedure described in Step 2 for **Intermediate 12** using **Intermediate 17-1** in place of **Intermediate 12-1**. LC/MS (ESI) m/z 410.2 $[M+H]^+$.

Intermediate 18

4-[[[(1R)-3-[4-[4-[[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-5-yl]amino]butyl]piperazin-1-yl]-1-(phenylsulfonylmethyl)propyl]amino]-3-(trifluoromethylsulfonyl)benzenesulfonamide



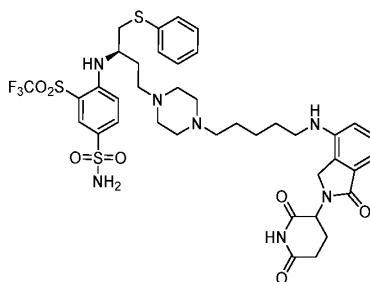
[0220] Step 1: tert-butyl 4-(4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-5-yl)amino)butyl)piperazine-1-carboxylate (**Intermediate 18-1**) was prepared following the procedure described in Step 1 of **Intermediate 12** using tert-butyl 4-(4-aminobutyl)piperazine-1-carboxylate (1 g, 3.89 mmol) (prepared following a procedure described in WO2011121055A1) in place of 5-aminopentan-1-ol. The crude product was purified by HPLC (99:1 to 60:40 water (0.09% TFA)/CH₃CN) to afford (0.3 g, 32% yield) as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 7.96 (s, 1H), 7.52 (d, J = 8.3 Hz, 1H), 6.86 (s, 1H), 6.71 (dd, J = 8.3, 1.7 Hz, 1H), 4.86 (dd, J = 12.0, 5.2 Hz, 1H), 3.53-3.41 (m, 2H), 3.24 (t, J = 6.2 Hz, 2H), 3.03-2.94 (m, 2H), 2.87-2.53 (m, 5H), 2.07-2.02 (m, 1H), 1.93-1.82 (m, 3H), 1.74-1.62 (m, 4H), 1.40 (s, 9H).

[0221] Step 2: 2-(2,6-dioxopiperidin-3-yl)-5-((4-(piperazin-1-yl)butyl)amino)isoindoline-1,3-dione (**Intermediate 18-2**) was prepared following the procedure described in Step 2 for **Intermediate 14** using **Intermediate 18-1** in place of **Intermediate 14-1**. The crude product was used for the next step without further purification.

[0222] Step 3: **Intermediate 18** was prepared following the procedure described in Step 3 for **Intermediate 14** using **Intermediate 18-2** in place of **Intermediate 14-2**. LC/MS (ESI) m/z 878.2 [M-H]⁻.

Intermediate 19

4-(((2R)-4-(4-(5-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-4-yl)amino) pentyl)piperazin-1-yl)-1-(phenylthio)butan-2-yl)amino)-3-((trifluoromethyl)sulfonyl)benzenesulfonamide



[0223] Step 1: To a solution of 3-(4-amino-1-oxo-isindolin-2-yl)piperidine-2,6-dione (1 g, 3.86 mmol) in DMF (10 mL) was added 5-bromopentan-1-ol (1.04 mL, 3.86 mmol) and DIPEA (2.02, 11.57 mmol) at 20°C. The reaction mixture was stirred at 90°C for 12 h, cooled to rt, diluted with water and then was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (30 mL), dried over Na₂SO₄ and concentrated. The crude product was purified by HPLC (90:10 to 60:40 water (0.09% TFA)/CH₃CN) to give 3-(4-((5-hydroxypentyl)amino)-1-oxoisindolin-2-yl)piperidine-2,6-dione (**Intermediate 19-1**) (0.5 g, 38% yield) as a yellow solid. LC/MS (ESI) m/z 346.1 [M+H]⁺.

[0224] Step 2: 5-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-4-yl) amino)pentyl methanesulfonate (**Intermediate 19-2**) was prepared following the procedure described in Step 2 for **Intermediate 12** using **Intermediate 19-1** in place of **Intermediate 12-1**. LC/MS (ESI) m/z 424.0 [M+H]⁺.

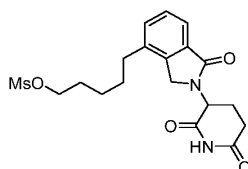
[0225] Step 3: To a solution of **Intermediate 19-2** (0.2 g, 472.3 μmol) in dioxane (3 mL) was added tert-butyl piperazine-1-carboxylate (105.6 mg, 566.7 μmol), DIPEA (164.5 μL , 944.55 μmol) and NaI (7.08 mg, 47.23 μmol) at 20°C. The reaction was stirred at 90 °C for 12 h, cooled to rt, concentrated, and purified by HPLC (75:25 to 0:100 10 mM $\text{NH}_4\text{CO}_3\text{H(aq.)}/\text{CH}_3\text{CN}$) to provide tert-butyl 4-(5-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-4-yl)amino)pentyl)piperazine-1-carboxylate (**Intermediate 19-3**) (80 mg, 33% yield) as a white solid. LC/MS (ESI) m/z 514.3 $[\text{M}+\text{H}]^+$.

[0226] Step 4: 3-(1-oxo-4-((5-(piperazin-1-yl)pentyl)amino) isoindolin-2-yl)piperidine-2,6-dione (**Intermediate 19-4**) was prepared following the procedure described in Step 2 for **Intermediate 14** using **Intermediate 19-3** in place of **Intermediate 14-1**. The crude product was used for the next step without further purification. LC/MS (ESI) m/z 414.2 $[\text{M}+\text{H}]^+$.

[0227] Step 5: **Intermediate 19** was prepared following the procedure described in Step 3 for **Intermediate 14** using **Intermediate 19-4** in place of **Intermediate 14-2**. In addition, the crude product was purified by HPLC (60:40 to 0:100 10 mM $\text{NH}_4\text{CO}_3\text{H(aq.)}/\text{CH}_3\text{CN}$) to give the final product (50 mg, 32% yield) as a white solid. LC/MS (ESI) m/z 878.5 $[\text{M}-\text{H}]^-$.

Intermediate 20

5-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-4-yl)pentyl methanesulfonate

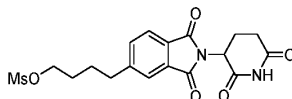


[0228] **Intermediate 20** was prepared following the procedure described in Step 2 for **Intermediate 12** using 3-(4-(5-hydroxypentyl)-1-oxoisindolin-2-yl)piperidine-2,6-dione (prepared following a procedure described in WO2017176958 A1) in place of **Intermediate 12-1**. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.99 (s, 1H), 7.57-7.54 (m, 1H), 7.48-7.43 (m, 2H), 5.14-5.11 (m, 1H), 4.46 (d, $J = 17.2$ Hz, 1H), 4.31 (d, $J = 17.2$ Hz, 1H), 4.19 (t, $J = 6.8$ Hz, 2H), 3.14 (s, 3H), 2.92-2.88 (m, 1H), 2.67-2.63 (m, 3H), 2.45-2.40 (m,

1H), 2.03-1.99 (m, 1H), 1.74-1.60 (m, 4H), 1.44-1.38 (m, 2H); LC/MS (ESI) m/z 409.3 [M+H]⁺.

Intermediate 21

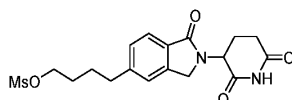
4-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-5-yl)butyl methanesulfonate



[0229] **Intermediate 21** was prepared following the procedure described in Step 2 for **Intermediate 12** using 2-(2,6-dioxopiperidin-3-yl)-5-(4-hydroxybutyl)isoindoline-1,3-dione (prepared following a procedure described in WO2018140809 A1) in place of **Intermediate 12-1**. ¹H NMR (400 MHz, CDCl₃) 8.10 (br s, 1H), δ 7.80 (d, J = 7.6 Hz, 1H), 7.70 (s, 1H), 7.57 (d, J = 7.6 Hz, 1H), 5.0-4.95 (dd, J = 13.4, 5.2 Hz, 1H), 4.38 (br s, 2H), 2.95-2.73 (m, 8H), 1.76 (m, 1H), 1.56 (m, 2H), 1.55 (s, 1H), 1.21 (s, 1H); LC/MS (ESI) m/z 409.3 [M+H]⁺.

Intermediate 22

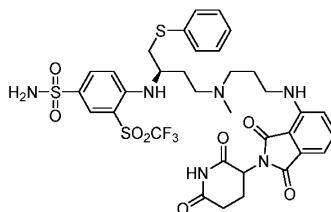
4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)butyl methanesulfonate



[0230] **Intermediate 22** was prepared following the procedure described in Step 2 for **Intermediate 12** using 3-(5-(4-hydroxybutyl)-1-oxoisindolin-2-yl)piperidine-2,6-dione (prepared following a procedure described in WO2018140809 A1 for 2-(2,6-dioxopiperidin-3-yl)-5-(4-hydroxybutyl)isoindoline-1,3-dione) in place of **Intermediate 12-1**. LC/MS (ESI) m/z 395.2 [M+H]⁺.

Intermediate 23

4-(((2R)-4-((3-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)amino)propyl)(methyl)amino)-1-(phenylthio)butan-2-yl)amino)-3-((trifluoromethyl)sulfonyl)benzenesulfonamide



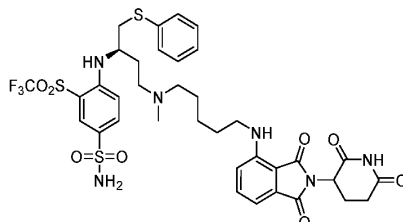
[0231] Step 1: To a solution of tert-butyl (3-aminopropyl) (methyl)carbamate (409.0 mg, 2.17 mmol) in NMP (5 mL) was added 2-(2,6-dioxo-3-piperidyl)-4- fluoroisindoline-1,3-dione (0.5 g, 1.81 mmol) and DIPEA (945.9 μ L, 5.43 mmol) at 20 °C. The mixture was stirred at 80 °C for 12 h, cooled to rt, concentrated, and purified by HPLC (80:20 to 52:48 water (0.09% TFA)/CH₃CN) to afford tert-butyl (3-((2-(2,6-dioxopiperidin-3-yl)-1,3- dioxoisindolin-4-yl)amino)propyl)(methyl)carbamate (**Intermediate 23-1**) (0.1 g, 12% yield) as a yellow solid. LC/MS (ESI) m/z 445.2 [M+H]⁺

[0232] Step 2: 2-(2,6-dioxopiperidin-3-yl)-4-((3-(methylamino)propyl)amino)isoindoline -1,3-dione (**Intermediate 23-2**) was prepared following the procedure described in Step 2 for **Intermediate 14** using **Intermediate 23-1** in place of **Intermediate 14-1**. The crude product was used for the next step without further purification. LC/MS (ESI) m/z 345.1 $[M+H]^+$.

[0233] Step 3: **Intermediate 23** was prepared following the procedure described in Step 3 for **Intermediate 14** using **Intermediate 23-2** in place of **Intermediate 14-2**. The crude product was purified by HPLC (60:40 to 0:100 10 mM NH₄CO₃H(aq.)/CH₃CN) to afford **Intermediate 23** as a yellow solid. LC/MS (ESI) *m/z* 809.3 [M-H]⁻.

Intermediate 24

4-[[[(1R)-3-[5-[[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-4-yl] amino]pentyl-methyl-amino]-1-(phenylsulfanylmethyl)propyl]amino]-3-(trifluoromethylsulfonyl)benzenesulfonamide



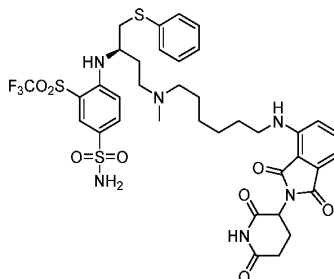
[0234] Step 1: tert-butyl(5-((2-(2,6-dioxopiperidin-3-yl)-1,3- dioxoisoindolin-4-yl)amino)pentyl) (methyl)carbamate (**Intermediate 24-1**) was prepared following the procedure described in Step 1 for **Intermediate 23** using tert-butyl (5-aminopentyl)(methyl)carbamate in place of tert-butyl (3-aminopropyl) (methyl)carbamate. The crude product was purified using HPLC (60:40 to 30:70 water (0.04% HCl)/CH₃CN) to give final product as a yellow solid. LC/MS (ESI) *m/z* 473.2 [M+H]⁺.

[0235] Step 2: 2-(2,6-dioxo-3-piperidyl)-4-[3-(methylamino)propylamino]isoindoline-1,3-dione (**Intermediate 24-2**) was prepared following the procedure described in Step 2 for **Intermediate 14** using **Intermediate 24-1** in place of **Intermediate 14-1**. The crude product was used for the next step without further purification. LC/MS (ESI) *m/z* 373.3 [M+H]⁺.

[0236] Step 3: **Intermediate 24** was prepared following the procedure described in Step 3 for **Intermediate 14** using **Intermediate 24-2** in place of **Intermediate 14-2**. The crude product was purified by HPLC (65:35 to 35:65 water (0.09% TFA)/CH₃CN) to afford **Intermediate 24** as a yellow solid. LC/MS (ESI) *m/z* 839.5 [M+H]⁺.

Intermediate 25

44-(((2R)-4-(((6-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)amino)hexyl)(methyl)amino)-1-(phenylthio)butan-2-yl)amino)-3-((trifluoromethyl)sulfonyl)benzenesulfonamide



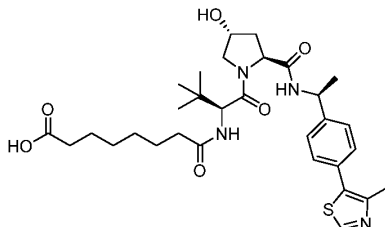
[0237] Step 1: tert-butyl (6-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)amino) hexyl)(methyl)carbamate (**Intermediate 25-1**) was prepared following the procedure described in Step 1 for **Intermediate 23** using tert-butyl (6-aminohexyl)(methyl)carbamate in place of tert-butyl (3-aminopropyl) (methyl)carbamate. The crude product was purified using HPLC (50:50 to 20:80 water (0.04% HCl)/CH₃CN) to provide **Intermediate 25-1** as a yellow solid. LC/MS (ESI) *m/z* 487.4 [M+H]⁺.

[0238] Step 2: 2-(2,6-dioxopiperidin-3-yl)-4-(((6-(methylamino)hexyl)amino)isoindoline-1,3-dione (**Intermediate 25-2**) was prepared following the procedure described in Step 2 for **Intermediate 14** using **Intermediate 25-1** in place of **Intermediate 14-1**. The crude product was used for the next step without further purification. LC/MS (ESI) *m/z* 387.3 [M+H]⁺.

[0239] Step 3: **Intermediate 25** was prepared following the procedure described in Step 3 for **Intermediate 14** using **Intermediate 25-2** in place of **Intermediate 14-2**. In addition, the crude product was purified by HPLC (65:35 to 35:65 water (0.09% TFA)/CH₃CN) to give the final product as a yellow solid. LC/MS (ESI) *m/z* 853.3[M+H]⁺.

Intermediate 26

8-(((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-8-oxooctanoic acid

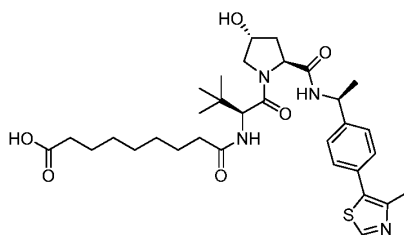


[0240] Step 1: tert-butyl 8-(((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-8-oxooctanoate (**Intermediate 26-1**) was prepared following the procedure described in Step 1 for **Intermediate 8** using 8-(tert-butoxy)-8-oxooctanoic acid in place of 6-tert-butoxy-6-oxo-hexanoic acid. LC/MS m/z 657.6 $[M+H]^+$.

[0241] Step 2: **Intermediate 16** was prepared following the procedure described in Step 2 for **Intermediate 8** using **Intermediate 26-1** in place of **Intermediate 8-1**. LC/MS (ESI) m/z 601.4 $[M+H]^+$.

Intermediate 27

9-(((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-9-oxononanoic acid

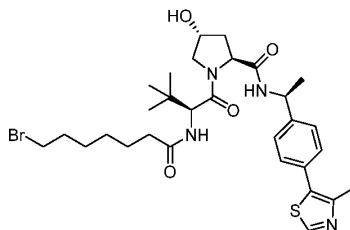


[0242] Step 1: tert-butyl 9-(((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-9-oxononanoate (**Intermediate 27-1**) was prepared following the procedure described in Step 1 for **Intermediate 8** using 9-tert-butoxy-9-oxo-nonanoic acid in place of 6-tert-butoxy-6-oxo-hexanoic acid. LC/MS m/z 693.1 $[M+Na]^+$.

[0243] Step 2: **Intermediate 16** was prepared following the procedure described in Step 2 for **Intermediate 8** using **Intermediate 27-1** in place of **Intermediate 8-1**. LC/MS (ESI) m/z 613.3 [M-H]⁻.

Intermediate 28

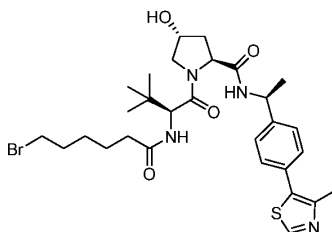
(2S,4R)-1-((S)-2-(7-bromoheptanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide



[0244] To a solution of (2S,4R)-1-((S)-2-amino-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (0.1 g, 224.9 μ mol) in DMF (1 mL) was added 7-bromoheptanoic acid (51.7 mg, 247.4 μ mol), DIPEA (156.7 μ L, 899.7 μ mol) and HATU (102.6 mg, 269.9 μ mol) at 20 °C. The reaction mixture was stirred at 20 °C for 30 min, concentrated, and purified by HPLC (60:40 to 35:65 10 mM NH₄CO₃H(aq.)/ CH₃CN) to provide **Intermediate 28** (80 mg, 56% yield) as a white solid. LC/MS (ESI) m/z 633.2 [M-H]⁻.

Intermediate 29

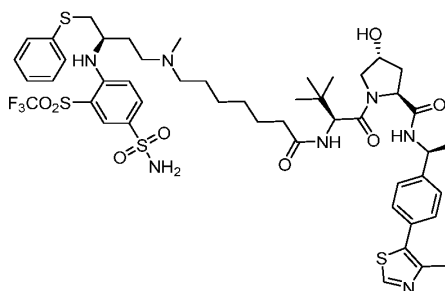
(2S,4R)-1-((S)-2-(6-bromohexanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide



[0245] **Intermediate 29** was prepared following the procedure described for **Intermediate 28** using 6-bromohexanoic acid in place of 7-bromoheptanoic acid. LC/MS (ESI) m/z 619.2 [M-H]⁻.

Intermediate 30

(2S,4R)-1-((S)-3,3-dimethyl-2-(7-(methyl((R)-4-(phenylthio)-3-((4-sulfamoyl-2-((trifluoromethyl)sulfonyl)phenyl)amino)butyl)amino)heptanamido)butanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide



[0246] Step 1: A solution of 7-[tert-butoxycarbonyl(methyl)amino]heptanoic acid (105.0 mg, 404.9 μmol in DMF (1 mL) was treated with HATU (153.9 mg, 404.9 μmol), (2S,4R)-1-((S)-2-amino-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl) pyrrolidine-2-carboxamide (0.15 g, 337.4 μmol) and DIPEA (87.21 mg, 674.8 μmol) at 25 °C. The reaction mixture was stirred at 25 °C for 12 h and then poured into water (5 mL) and extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4 , filtered and concentrated. The crude product was purified by HPLC (50:50 to 30:80 10 mM $\text{NH}_4\text{CO}_3\text{H(aq.)}$ / CH_3CN) to provide tert-butyl (7-(((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-7-oxoheptyl(methyl)carbamate (**Intermediate 30-1**) (0.18 g, 78% yield) as a white solid. LC/MS (ESI) m/z 684.4 $[\text{M-H}]^-$.

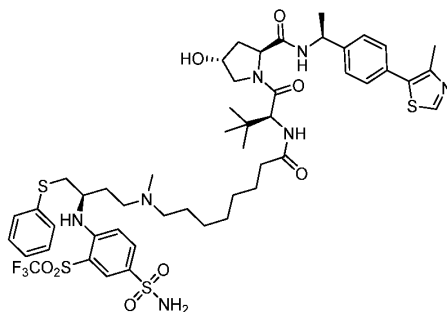
[0247] Step 2: **Intermediate 30-1** (0.18 g, 262.4 μmol) was treated with HCl (4M in EtOAc, 5 mL) and stirred at 25°C for 12 h. The reaction mixture was concentrated to afford the HCl salt of (2S,4R)-1-((S)-3,3-dimethyl-2-(7-(methylamino)heptanamido)butanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (**Intermediate 30-2**) (158 mg, 97% yield) as a yellow solid. LC/MS (ESI) m/z 584.3 $[\text{M-H}]^-$.

[0248] Step 3: To a solution of **Intermediate 30-2** (0.15 g, 241.1 μmol) in THF (2 mL) was added (R)-4-((4-oxo-1-(phenylthio)butan-2-yl)amino)-3-((trifluoromethyl)sulfonyl)benzenesulfonamide (prepared following a procedure described in

WO2012017251A1) (116.3 mg, 241.1 μmol), $\text{NaHB}(\text{OAc})_3$ (76.6 mg, 361.6 μmol) and triethylamine (73.2 mg, 723.2 μmol) at 25°C. The reaction mixture was stirred at 25 °C for 12 h, and then concentrated. The crude product was purified by HPLC (50:50 to 30:80 10 mM $\text{NH}_4\text{CO}_3\text{H}(\text{aq.})/\text{CH}_3\text{CN}$) to provide **Intermediate 30** (0.14 g, 43% yield) as a white solid. LC/MS (ESI) m/z 1050.3 $[\text{M}-\text{H}]^-$.

Intermediate 31

(2S,4R)-1-((S)-3,3-dimethyl-2-(8-(methyl((R)-4-(phenylthio)-3-((4-sulfamoyl-2-((trifluoromethyl)sulfonyl)phenyl)amino)butyl)amino)octanamido)butanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide



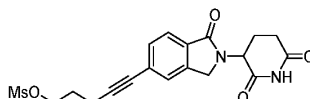
[0249] Step 1: tert-butyl (8-(((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-8-oxooctyl)(methyl)carbamate (**Intermediate 31-1**) was prepared following the procedure described in Step 1 for **Intermediate 30** using 8-[tert-butoxycarbonyl(methyl)amino]octanoic acid in place of 7-[tert-butoxycarbonyl(methyl)amino]heptanoic acid. LC/MS (ESI) m/z 700.6 $[\text{M}+\text{H}]^+$.

[0250] Step 2: (2S,4R)-1-((S)-3,3-dimethyl-2-(8-(methylamino)octanamido)butanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (**Intermediate 31-2**) was prepared following the procedure described in Step 2 for **Intermediate 30** using **Intermediate 31-1** in place of **Intermediate 30-1**. LC/MS (ESI) m/z 600.2 $[\text{M}+\text{H}]^+$.

[0251] Step 3: **Intermediate 31** was prepared following the procedure described in Step 3 for **Intermediate 30** using **Intermediate 31-2** in place of **Intermediate 30-2**. LC/MS (ESI) m/z 1064.7 $[\text{M}-\text{H}]^-$.

Intermediate 32

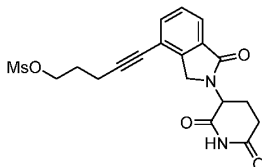
5-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)pent-4-yn-1-yl methanesulfonate



[0252] **Intermediate 32** was prepared following the procedure described in Step 2 for **Intermediate 12** using 3-(5-(5-hydroxypent-1-yn-1-yl)-1-oxoisindolin-2-yl)piperidine-2,6-dione (prepared following a procedure described in WO2018102725 A1) in place of **Intermediate 12-1**. LC/MS (ESI) m/z 405.3 $[M+H]^+$.

Intermediate 33

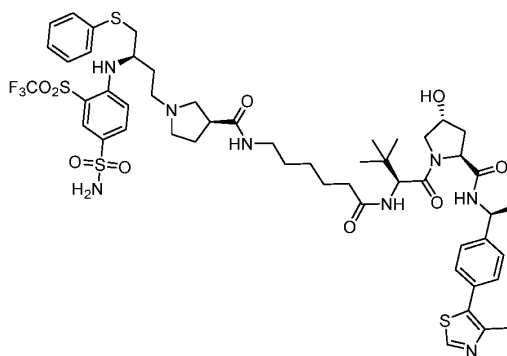
5-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-4-yl)pent-4-yn-1-yl methanesulfonate



[0253] **Intermediate 33** was prepared following the procedure described in Step 2 for **Intermediate 12** using 3-(4-(5-hydroxypent-1-yn-1-yl)-1-oxoisindolin-2-yl)piperidine-2,6-dione (prepared following a procedure described in WO2017176958 A1) in place of **Intermediate 12-1**. LC/MS (ESI) m/z 405.3 $[M+H]^+$.

Intermediate 34

(2S,4R)-1-((S)-3,3-dimethyl-2-(6-((S)-1-((R)-4-(phenylthio)-3-((4-sulfamoyl-2-((trifluoromethyl)sulfonyl)phenyl)amino)butyl)pyrrolidine-3-carboxamido)hexanamido)butanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide



[0254] Step 1: To a solution of (2S,4R)-1-((S)-2-amino-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide hydrochloride (0.5 g, 1.12 mmol) in DMF (10 mL) was added 6-(tert-butoxycarbonylamino)hexanoic acid (390.2 mg, 1.69 mmol), HATU (641.4 mg, 1.25 mmol) and DIPEA (726.8 mg, 5.62 mmol) at 20 °C. The reaction was stirred at 20 °C for 12 h and then poured into H₂O (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to afford crude tert-butyl (6-(((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-6-oxohexyl)carbamate (**Intermediate 34-1**) (0.5 g) as a yellow oil. LCMS (ESI) *m/z* 558.1 (M-C₅H₉O₂+H)⁺.

[0255] Step 2: **Intermediate 34-1** (0.5 g, 760.0 μmol) was dissolved in EtOAc and treated with HCl (4M in EtOAc, 10 mL) at rt. After 12 h, the reaction was concentrated to afford the HCl salt of (2S,4R)-1-((S)-2-(6-aminohexanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (**Intermediate 34-2**) (0.44 g) as a white solid. LCMS (ESI) *m/z* 558.1 [M+H]⁺.

[0256] Step 3: To a solution of **Intermediate 34-2** (0.4 g, 673.2 μmol) in DMF (10 mL) was added (3S)-1-tert-butoxycarbonylpyrrolidine-3-carboxylic acid (144.9 mg, 673.2 μmol), DIPEA (435 mg, 3.37 mmol), HOBT (136.4 mg, 1.01 mmol) and EDCI (156.8

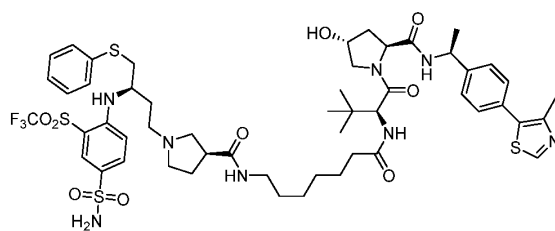
mg, 1.01 mmol) at 20°C. The mixture was stirred at 20 °C for 2 h and then poured into H₂O (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (30 mL), dried over Na₂SO₄, filtered and concentrated. The crude residue was purified by HPLC (65:35 to 45:55 10 mM NH₄HCO₃ (aq.)/CH₃CN) to afford (S)-tert-butyl-3-((6-(((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-6-oxohexyl)carbamoyl)pyrrolidine-1-carboxylate (**Intermediate 34-3**) (0.12 g, 24% yield) as a yellow solid. LCMS (ESI) *m/z* 755.4 [M+H]⁺.

[0257] Step 4: A mixture of **Intermediate 34-3** (0.12 g, 158.9 μmol) was dissolved in EtOAc and treated with HCl (4M in EtOAc, 10 mL) at rt. After 30 min, the reaction mixture was concentrated under reduced pressure to afford the HCl salt of (2S,4R)-1-((S)-3,3-dimethyl-2-(6-((S)-pyrrolidine-3-carboxamido)hexanamido)butanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (**Intermediate 34-4**) (0.1 g, 91% yield) as a yellow solid. LCMS (ESI) *m/z* 653.3 [M-H]⁻.

[0258] Step 5: **Intermediate 34** was prepared following the procedure described in Step 3 for **Intermediate 30** using **Intermediate 34-4** in place of **Intermediate 30-2**. LC/MS (ESI) *m/z* 1119.3 [M-H]⁻.

Intermediate 35

(2S,4R)-1-((S)-3,3-dimethyl-2-(7-((S)-1-((R)-4-(phenylthio)-3-((4-sulfamoyl-2-((trifluoromethyl)sulfonyl)phenyl)amino)butyl)pyrrolidine-3-carboxamido)heptanamido)butanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide



[0259] Step 1: tert-butyl (7-(((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-7-oxoheptyl)carbamate (**Intermediate 35-1**) was prepared following the procedure described in Step 1 for **Intermediate 34** using 7-(tert-

butoxycarbonylamino)heptanoic acid in place 6-(tert-butoxycarbonylamino)hexanoic acid. LC/MS (ESI) m/z 670.3 (M-H)⁻.

[0260] Step 2: (2S,4R)-1-((S)-2-(7-amino heptanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (**Intermediate 35-2**) was prepared following the procedure described in Step 2 for **Intermediate 34** using **Intermediate 35-1** in place of **Intermediate 34-1**. LC/MS (ESI) m/z 570.2 (M-H)⁻.

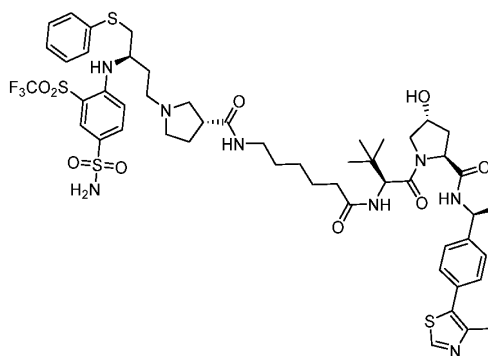
[0261] Step 3: (S)-tert-butyl 3-(((7-(((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-7-oxoheptyl)carbamoyl)pyrrolidine-1-carboxylate (**Intermediate 35-3**) was prepared following the procedure described in Step 3 for **Intermediate 34** using **Intermediate 35-2** in place of **Intermediate 34-2**. LC/MS (ESI) m/z 767.4 (M-H)⁻.

[0262] Step 4: (2S,4R)-1-((S)-3,3-dimethyl-2-(7-((S)-pyrrolidine-3-carboxamido)heptanamido)butanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (**Intermediate 35-4**) was prepared following the procedure described in Step 4 for **Intermediate 34** using **Intermediate 35-3** in place of **Intermediate 34-3**. LC/MS (ESI) m/z 667.3 (M-H)⁻.

[0263] Step 5: **Intermediate 35** was prepared following the procedure described in Step 5 for **Intermediate 34** using **Intermediate 35-4** in place of **Intermediate 34-4**. LC/MS (ESI) m/z 1133.3 (M-H)⁻.

Intermediate 36

(2S,4R)-1-((S)-3,3-dimethyl-2-(6-((R)-1-((R)-4-(phenylthio)-3-((4-sulfamoyl-2-((trifluoromethyl)sulfonyl)phenyl)amino)butyl)pyrrolidine-3-carboxamido)hexanamido)butanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide



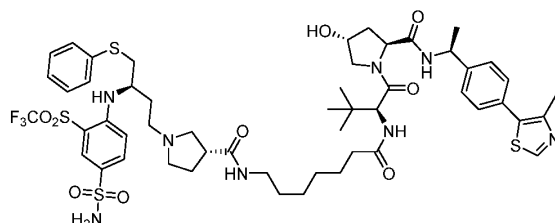
[0264] Step 1: (R)-tert-butyl 3-(((6-(((((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-6-oxohexyl)carbamoyl)pyrrolidine-1-carboxylate (**Intermediate 36-1**) was prepared following the procedure described in Step 3 for **Intermediate 34** using (3R)-1-tert-butoxycarbonylpyrrolidine-3-carboxylic acid in place of (3S)-1-tert-butoxycarbonylpyrrolidine-3-carboxylic acid LCMS (ESI) m/z 769.3 [M+H]⁺.

[0265] Step 2: (2S,4R)-1-((S)-3,3-dimethyl-2-(6-((R)-pyrrolidine-3-carboxamido)hexanamido)butanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (**Intermediate 36-2**) was prepared following the procedure described in Step 4 for **Intermediate 34** using **Intermediate 36-1** in place of **Intermediate 34-3**. LC/MS (ESI) m/z 667.3 (M-H)⁻.

[0266] Step 3: **Intermediate 36** was prepared following the procedure described in Step 5 for **Intermediate 30** using **Intermediate 36-2** in place of **Intermediate 34-4**. LC/MS (ESI) m/z 1133.3 (M-H)⁻.

Intermediate 37

(2S,4R)-1-((S)-3,3-dimethyl-2-(7-((R)-1-((R)-4-(phenylthio)-3-((4-sulfamoyl-2-((trifluoromethyl)sulfonyl)phenyl)amino)butyl)pyrrolidine-3-carboxamido)heptanamido)butanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide



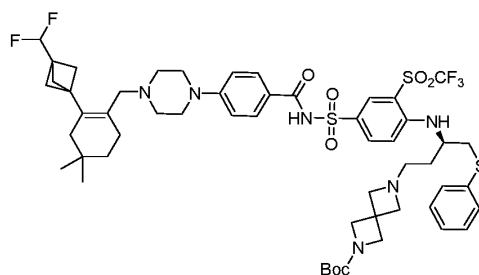
[0267] Step 1: (R)-tert-butyl 3-((7-(((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-7-oxoheptyl)carbamoyl)pyrrolidine-1-carboxylate (**Intermediate 37-1**) was prepared following the procedure described in Step 3 for **Intermediate 35** using (3R)-1-tert-butoxycarbonylpyrrolidine-3-carboxylic acid in place of (3S)-1-tert-butoxycarbonylpyrrolidine-3-carboxylic acid LC/MS (ESI) m/z 769.3 (M+H)⁺.

[0268] Step 2: (2S,4R)-1-((S)-3,3-dimethyl-2-(7-((R)-pyrrolidine-3-carboxamido)heptanamido)butanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (**Intermediate 37-2**) was prepared following the procedure described in Step 4 for **Intermediate 35** using **Intermediate 37-1** in place of **Intermediate 35-3**. LC/MS (ESI) m/z 653.3 (M-H)⁻.

[0269] Step 3: **Intermediate 36** was prepared following the procedure described in Step 5 for **Intermediate 30** using **Intermediate 37-2** in place of **Intermediate 35-4**. LC/MS (ESI) m/z 1133.4 [M-H]⁻.

Intermediate 38

tert-butyl (R)-6-(3-((4-(N-(4-(4-((2-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-((trifluoromethyl)sulfonyl)phenyl)amino)-4-(phenylthio)butyl)-2,6-diazaspiro[3.3]heptane-2-carboxylate

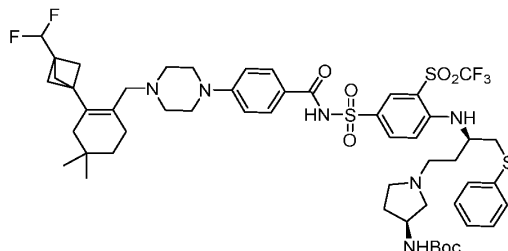


[0270] Step 1: tert-butyl (R)-6-(4-(phenylthio)-3-((4-sulfamoyl-2-((trifluoromethyl)sulfonyl)phenyl)amino)butyl)-2,6-diazaspiro[3.3]heptane-2-carboxylate (**Intermediate 38-1**) was prepared following the procedure described in Step 3 for **Intermediate 14** using tert-butyl 2,6-diazaspiro[3.3]heptane-2-carboxylate in place of **Intermediate 14-2**. LC/MS (ESI) m/z 663.1 [M-H]⁻.

[0271] Step 2: To a solution of **Intermediate 38-1** (0.6 g, 902.6 μ mol) in DCM (10 mL) was added **Intermediate 2** (441.4 mg, 992.8 μ mol), TEA (182.7 mg, 1.81 mmol), DMAP (110.3 mg, 902.6 μ mol) and EDCI (207.6 mg, 1.08 mmol) at 20°C. After 12 h, the reaction was diluted with water (15 mL) and extracted with DCM (2 $\times$ 20 mL). The combined organic layers were washed with 1N HCl (aq.) (10 mL), dried over Na₂SO₄ and concentrated to provide **Intermediate 38** (0.7 g) as a yellow solid. The crude product was used without further purification. LC/MS (ESI) m/z 1089.4 [M-H]⁻.

Intermediate 39

tert-butyl ((S)-1-((R)-3-((4-(N-(4-(4-((2-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-((trifluoromethyl)sulfonyl)phenyl)amino)-4-(phenylthio)butyl)pyrrolidin-3-yl)carbamate

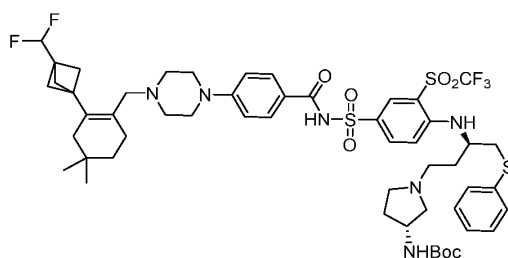


[0272] Step 1: tert-butyl ((S)-1-((R)-4-(phenylthio)-3-((4-sulfamoyl-2-((trifluoromethyl)sulfonyl)phenyl)amino)butyl)pyrrolidin-3-yl)carbamate (**Intermediate 39-1**) was prepared following the procedure described in Step 1 for **Intermediate 38** using tert-butyl N-[(3S)-pyrrolidin-3-yl]carbamate in place of tert-butyl 2,6-diazaspiro[3.3]heptane-2-carboxylate. LC/MS (ESI) m/z 651.2 [M-H]⁻.

[0273] Step 2: **Intermediate 39** was prepared following the procedure described in Step 2 for **Intermediate 38** using **Intermediate 39-1** in place of **Intermediate 38-1**. LC/MS (ESI) m/z 1077.3 [M-H]⁻.

Intermediate 40

tert-butyl ((R)-1-((R)-3-((4-(N-(4-(4-((2-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-((trifluoromethyl)sulfonyl)phenyl)amino)-4-(phenylthio)butyl)pyrrolidin-3-yl)carbamate



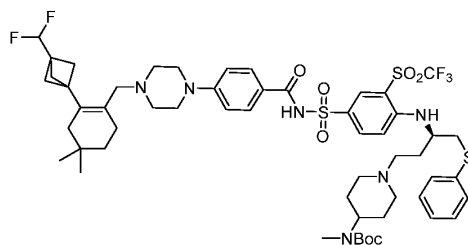
[0274] Step 1: tert-butyl ((R)-1-((R)-4-(phenylthio)-3-((4-sulfamoyl-2-((trifluoromethyl)sulfonyl)phenyl)amino)butyl)pyrrolidin-3-yl)carbamate (**Intermediate 40-1**) was prepared following the procedure described in Step 1 for **Intermediate 39** using N-

[(3R)-pyrrolidin-3-yl]carbamate in place of N-[(3S)-pyrrolidin-3-yl]carbamate. LC/MS (ESI) m/z 651.2 [M-H]⁺.

[0275] Step 2: **Intermediate 40** was prepared following the procedure described in Step 2 for **Intermediate 38** using **Intermediate 40-1** in place of **Intermediate 38-1**. LC/MS (ESI) m/z 1079.6 [M+H]⁺.

Intermediate 41

tert-butyl (R)-(1-(3-((4-(N-(4-(4-((2-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-((trifluoromethyl)sulfonyl)phenyl)amino)-4-(phenylthio)butyl)piperidin-4-yl)(methyl)carbamate

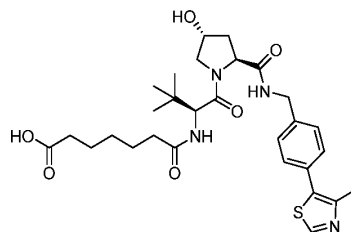


[0276] Step 1: tert-butyl (R)-methyl(1-(4-(phenylthio)-3-((4-sulfamoyl-2-((trifluoromethyl)sulfonyl)phenyl)amino)butyl)piperidin-4-yl)carbamate (**Intermediate 41-1**) was prepared following the procedure described in Step 1 for **Intermediate 38** using tert-butyl methyl(piperidin-4-yl)carbamate in place of tert-butyl 2,6-diazaspiro[3.3]heptane-2-carboxylate. LC/MS (ESI) m/z 679.3 [M-H]⁻.

[0277] Step 2: To a solution of **Intermediate 41-1** (0.7 g, 1.03 mmol) in DCM (0.1 mL) was added TEA (208.1 mg, 2.06 mmol), **Intermediate 2** (548.5 mg, 1.23 mmol), EDCI (295.7 mg, 1.54 mmol) and DMAP (125.6 mg, 1.03 mmol) at 25 °C. After 12 h, the mixture was poured into water (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over Na₂SO₄, filtered, concentrated, and purified by HPLC (40:60 to 10:90 10 mM NH₄HCO₃ (aq.)/CH₃CN) to provide **Intermediate 41** (0.4 g, 29% yield). LC/MS (ESI) *m/z* 1105.7 [M-H]⁻.

Intermediate 42

7-(((S)-1-((2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-7-oxoheptanoic acid

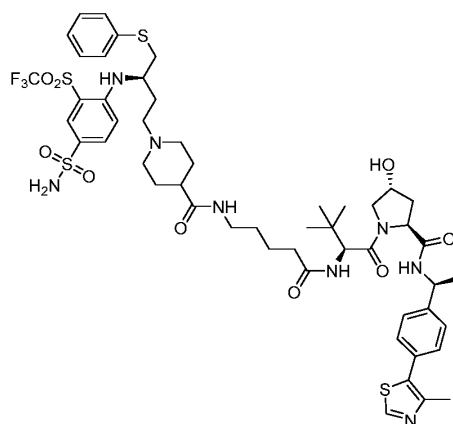


[0278] Step 1: tert-butyl 7-(((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-7-oxoheptanoate (**Intermediate 42-1**) was prepared following the procedure described in Step 1 for **Intermediate 8** using 7-(tert-butoxy)-7-oxoheptanoic acid in place of 6-tert-butoxy-6-oxo-hexanoic acid and (2S,4R)-1-((S)-2-amino-3,3-dimethylbutanoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide in place of (2S,4R)-1-((S)-2-amino-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide. LC/MS (ESI) m/z 629.5 $[M+H]^+$.

[0279] Step 2: **Intermediate 42** was prepared following the procedure described in Step 2 for **Intermediate 8** using **Intermediate 42-1** in place of **Intermediate 8-1**. LC/MS (ESI) m/z 573.5 $[M+H]^+$.

Intermediate 43

N-(5-(((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-5-oxopentyl)-1-((R)-4-(phenylthio)-3-((4-sulfamoyl-2-((trifluoromethyl)sulfonyl)phenyl)amino)butyl)piperidine-4-carboxamide



[0280] Step 1: tert-butyl (5-(((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-5-oxopentyl)carbamate (**Intermediate 43-1**) was prepared following the procedure described in Step 1 for **Intermediate 34** using 5-((tert-butoxycarbonyl)amino)pentanoic acid in place of 6-((tert-butoxycarbonyl)amino)hexanoic acid. LCMS (ESI) m/z 644.5 $[M+H]^+$.

[0281] Step 2: (2S,4R)-1-((S)-2-(5-aminopentanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide hydrochloride (**Intermediate 43-2**) was prepared following the procedure described in Step 2 for **Intermediate 34** using **Intermediate 43-1** in place of **Intermediate 34-1**. LC/MS (ESI) m/z 544.4 $[M+H]^+$.

[0282] Step 3: tert-butyl 4-(((5-(((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-5-oxopentyl)carbamoyl)piperidine-1-carboxylate (**Intermediate 43-3**) was prepared following the procedure described in Step 3 for **Intermediate 34** using **Intermediate 43-2** in place of **Intermediate 34-2**. LC/MS (ESI) m/z 755.5 $[M+H]^+$.

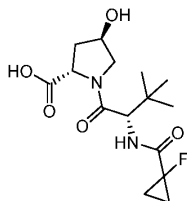
[0283] Step 4: N-(5-(((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-5-

oxopentyl)piperidine-4-carboxamide hydrochloride (**Intermediate 43-4**) was prepared following the procedure described in Step 4 for **Intermediate 34** using **Intermediate 43-3** in place of **Intermediate 34-3**. LC/MS (ESI) m/z 655.2 $[M+H]^+$.

[0284] Step 5: **Intermediate 43** was prepared following the procedure described in Step 5 for **Intermediate 34** using **Intermediate 43-4** in place of **Intermediate 34-4**. LC/MS (ESI) m/z 1119.4 $(M-H)^-$.

Intermediate 44

(2S,4R)-1-((S)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxylic acid



[0285] Step 1: A mixture of (2S, 4R)-methyl 1-((S)-2-((tert-butoxycarbonyl)amino)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxylate (8 g, 22.32 mmol) in HCl (100 mL, 4 M in dioxane) was stirred at 20°C for 12 h. The mixture was concentrated to afford (2S, 4R)-methyl 1-((S)-2-amino-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxylate hydrochloride (**Intermediate 44-1**) (6 g, 91% yield) as a white solid. LCMS m/z 259.0 $[M+H]^+$.

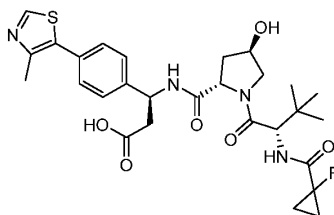
[0286] Step 2: To a solution of **Intermediate 44-1** (6 g, 20.35 mmol) in DMF (100 mL) at 20°C was added 1-fluorocyclopropanecarboxylic acid (3.18 g, 30.5 mmol), HATU (9.29 g, 24.4 mmol) and DIPEA (13.2 g, 101.8 mmol). After 12 h, the mixture was diluted with water (100 mL) and extracted with EtOAc (3 × 150 mL). The combined organic layers were washed with brine (300 mL) and dried over Na₂SO₄, filtered, and concentrated to provide (2S, 4R)-methyl 1-((S)-2-(1-fluorocyclopropanecarboxamido)-3, 3-dimethylbutanoyl)-4- hydroxypyrrolidine-2-carboxylate (**Intermediate 44-2**) (3 g, 43% yield) as a yellow oil. LCMS (ESI) m/z 345.0 $[M+H]^+$.

[0287] Step 3: To a solution of **Intermediate 44-2** (3 g, 8.71 mmol) in MeOH (60 mL) and H₂O (20 mL) was added LiOH·H₂O (1.1 g, 26.13 mmol) at 25°C. The mixture was stirred at 20°C for 12 h and then concentrated to give a residue. The residue was dissolved in

water (10 mL) and acidified to pH = 2 by the addition of conc. HCl. The resulting mixture was extracted with DCM : MeOH (5:1, 3 × 50 mL) and the combined organic layers were dried over Na₂SO₄ and filtered. The filtrate was concentrated to afford **Intermediate 44** (2.4 g, 83% yield) as a white solid. LCMS (ESI) *m/z* 331.1 [M+H]⁺,

Intermediate 45

(3S)-3-[[[(2S,4R)-1-[(2S)-2-[(1-fluorocyclopropanecarbonyl)amino]-3,3-dimethyl-butanoyl]-4-hydroxy-pyrrolidine-2-carbonyl]amino]-3-[4-(4-methylthiazol-5-yl)phenyl]propanoic acid



[0288] Step 1: To a solution of (3S)-3-(4-bromophenyl)-3-(tert-butoxycarbonylamino) propanoic acid (20.3 g, 59.0 mmol) in THF (200 mL) and MeOH (50 mL) was added TMSCH₂N₂ (2 M in hexanes, 102.33 mL) at 0°C. The mixture was stirred at 0°C for 12 h and then warmed to rt and concentrated to afford methyl (3S)-3-(4-bromophenyl)-3-(tert-butoxycarbonylamino) propanoate (**Intermediate 45-1**) (17.5 g, 83% yield) as a yellow oil. ¹H NMR (400MHz, DMSO-*d*₆) δ 7.51 (d, *J* = 8.3 Hz, 2H), 7.26 (d, *J* = 8.4 Hz, 2H), 4.93-4.82 (m, 1H), 3.55 (s, 3H), 2.80-2.64 (m, 2H), 1.34 (s, 9H); LCMS (ESI) *m/z* 301.9 (M-C₄H₉+H)⁺.

[0289] Step 2: To a solution of **Intermediate 45-1** (17 g, 47.5 mmol) in DMF (350 mL) was added 4-methylthiazole (17.3 mL, 189.8 mmol, 17.3 mL), KOAc (9.31 g, 94.9 mmol) and Pd(OAc)₂ (1.07 g, 4.75 mmol) at 20°C under N₂. The mixture was stirred at 90°C for 12 h and then cooled to rt and poured into water (400 mL). The mixture was extracted with EtOAc (3 × 650 mL) and then the combined organic layers were washed with brine (2 × 1 L), dried over Na₂SO₄, filtered and concentrated. The crude product was purified by column chromatography (SiO₂, pet. ether: EtOAc) to afford (3S)-3-(tert-butoxycarbonylamino)-3-[4-(4-methylthiazol-5-yl) phenyl]propanoate (**Intermediate 45-2**) (5.7 g, 32% yield) as a yellow oil. ¹H NMR (400MHz, DMSO-*d*₆) δ 9.00 (s, 1H), 7.59-7.52 (m, 1H), 7.47-7.44 (m, 2H), 7.42-7.39 (m, 2H), 5.01-4.92 (m, 1H), 3.57 (s, 3H), 2.78-2.73 (m, 2H), 2.45 (s, 3H), 1.36 (s, 9H); LCMS (ESI) *m/z* 377.3 [M+H]⁺.

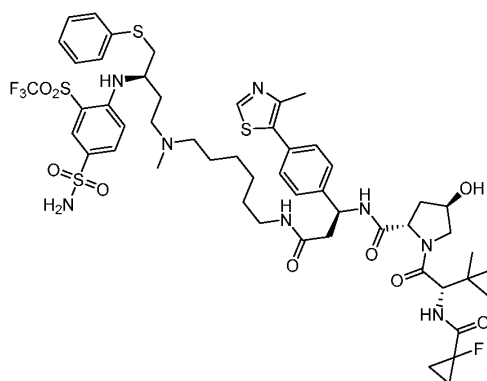
[0290] Step 3: A mixture of **Intermediate 45-2** (5.7 g, 15.14 mmol) was treated with HCl (4M in EtOAc, 57 mL) and stirred at 20°C for 12 h. The reaction was then concentrated under reduced pressure to afford methyl (3S)-3-amino-3-[4-(4-methylthiazol-5-yl)phenyl]propanoate hydrochloride (**Intermediate 45-3**) (4.55 g, 96% yield) as a yellow solid. LCMS (ESI) m/z 277.9 [M+H]⁺.

[0291] Step 4: To a solution of **Intermediate 45-3** (2 g, 6.39 mmol) in DMF (20 mL) was added DIPEA (5.28 mL, 31.97 mmol), **Intermediate 44** (2.53 g, 7.67 mmol) and HATU (2.92 g, 7.67 mmol) at 20°C. The mixture was stirred at rt for 12 h and then poured into H₂O (20 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated. The crude was purified by HPLC (88:12 to 48:52 H₂O (0.09% TFA): CH₃CN) to obtain (S)-methyl 3-((2S,4R)-1-((S)-2-(1-fluorocyclopropanecarboxamido)-3,3-dimethylbutanoyl)-4-hydroxy pyrrolidine-2-carboxamido)-3-(4-(4-methylthiazol-5-yl) phenyl)propanoate (**Intermediate 45-4**) (2.1 g, 56% yield) as a white solid. LCMS (ESI) m/z 589.4 [M+H]⁺.

[0292] Step 5: To a solution of **Intermediate 45-4** (0.4 g, 679.5 μmol) in MeOH (3 mL) and H₂O (1 mL) was added LiOH·H₂O (142.6 mg, 3.40 mmol) at 20°C. The reaction was stirred at 20°C for 12 h and then concentrated. The residue was dissolved in water (5 mL), acidified to pH = 6 using 2 N HCl(aq.), and then extracted with DCM (3 × 5 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated to afford **Intermediate 45** (0.3 g, 77% yield) as a yellow solid. LCMS (ESI) m/z 575.1 [M+H]⁺.

Intermediate 46

(2S,4R)-1-((S)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-3-((6-(methyl((R)-4-(phenylthio)-3-((4-sulfamoyl-2-((trifluoromethyl)sulfonyl)phenyl)amino)butyl)amino)hexyl)amino)-1-(4-(4-methylthiazol-5-yl)phenyl)-3-oxopropyl)pyrrolidine-2-carboxamide



[0293] Step 1: To a solution of **Intermediate 45** (500 mg, 870.1 μmol) in DMF (5 mL) was added tert-butyl N-(6-aminohexyl)-N-methyl-carbamate (220.5 mg, 957.1 μmol), DIPEA (757.8 μL , 4.35 mmol) and HATU (396.99 mg, 1.04 mmol) at 20°C. The reaction mixture was stirred at 20°C for 12 h and then poured into water (10 mL). The mixture was extracted with EtOAc (3 $\times$ 10 mL) and the combined organic layer were washed with brine (30 mL), dried over Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure to afford tert-butyl N-[6-[[[(3S)-3-[[[(2S,4R)-1-[(2S)-2-[(1-fluorocyclopropanecarbonyl)amino]-3,3-dimethyl-butanoyl]-4-hydroxy-pyrrolidine-2-carbonyl]amino]-3-[4-(4-methylthiazol-5-yl)phenyl]propanoyl]amino]hexyl]-N-methyl-carbamate (**Intermediate 46-1**) (0.6 g, 88% yield) as a yellow oil. LCMS (ESI) m/z 787.5 (M+H)⁺.

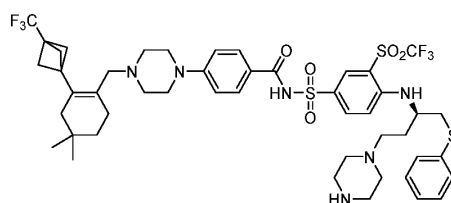
[0294] Step 2: **Intermediate 46-1** (0.6 g, 762.4 μmol) was dissolved in HCl (4M in EtOAc, 10 mL) and stirred at 20°C for 12 h. The mixture was concentrated under reduced pressure to provide the hydrochloride salt of (2S,4R)-1-[(2S)-2-[(1-fluorocyclopropanecarbonyl) amino]-3,3-dimethyl-butanoyl]-4-hydroxy-N-[(1S)-3-[6-(methylamino)hexylamino]-1-[4-(4-methylthiazol-5-yl)phenyl]-3-oxo-propyl]pyrrolidine-2-carboxamide (**Intermediate 46-2**) (0.4 g, 73% yield) as a yellow solid. **Intermediate 46-2**

was used directly in the next step without further purification. LCMS (ESI) m/z 687.5 (M+H)⁺.

[0295] Step 3: **Intermediate 46** was prepared following the procedure described in Step 3 for **Intermediate 30** using **Intermediate 46-2** in place of **Intermediate 30-2**. LCMS (ESI) m/z 1153.4 (M+H)⁺.

Intermediate 47

(R)-4-(4-((4,4-dimethyl-2-(3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)cyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-((1-(phenylthio)-4-(piperazin-1-yl)butan-2-yl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide



[0296] Step 1: To a stirred solution of 4,4-dimethyl-2-(3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)cyclohex-1-ene-1-carbaldehyde (3.5 g, 12.9 mmol) in toluene was added titanium (IV) ethoxide (3.73 g, 16.4 mmol). After 30 min, a solution of methyl 4-(piperazin-1-yl) benzoate (2.35 g, 10.71 mmol) in toluene (20 mL) was added and the resulting reaction mixture was stirred at rt for 1 h. The reaction mixture was then cooled to 0 °C, and Na(OAc)₃BH (6.9 g, 32.72 mmol) was added and the reaction was warmed to rt. After 16 h, the reaction was quenched with water (100 mL) at 0°C, and MTBE (200 mL) was added. The reaction mixture was filtered over Celite® and the collected solid was washed with DCM (2 x 100 mL). The combined organic layers were washed with sat. aq. NaHCO₃, brine, dried over Na₂SO₄, filtered and concentrated. The crude product was purified by column chromatography (SiO₂, EtOAc/pet. ether) to afford methyl 4-(4-((4,4-dimethyl-2-(3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)cyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoate (**Intermediate 47-1**) (3.2 g, 63% yield) as a white solid. LC/MS (ESI) m/z 477.3 [M+H]⁺.

[0297] Step 2: 4-(4-((4,4-dimethyl-2-(3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)cyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoic acid (**Intermediate 47-2**) was prepared

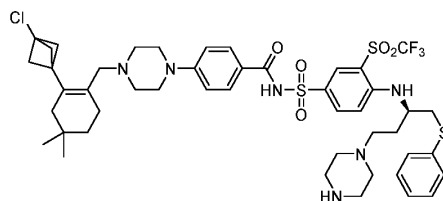
following the procedure described in Step 2 for **Intermediate 1** by using **Intermediate 47-1** in place of **Intermediate 1-1**. LC/MS (ESI) m/z 463.2 $[M+H]^+$.

[0298] Step 3: tert-Butyl (R)-4-(3-((4-(N-(4-(4-((4,4-dimethyl-2-(3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)cyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-((trifluoromethyl)sulfonyl)phenyl)amino)-4-(phenylthio)butyl)piperazine-1-carboxylate (**Intermediate 47-3**) was prepared following General Procedure A using **Intermediate 47-2** and **Intermediate 4**. LC/MS (ESI) m/z 1097.6 $[M+H]^+$

[0299] Step 4: **Intermediate 47** was prepared following the procedure described in Step 2 for **Intermediate 5** using **Intermediate 47-3** in place of **Intermediate 5-1**. LC/MS (ESI) m/z 995.6 $[M-H]^-$.

Intermediate 48

(R)-4-(4-((2-(3-Chlorobicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-((1-(phenylthio)-4-(piperazin-1-yl)butan-2-yl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide



[0300] Step 1: To a stirred solution of 2-(3-chlorobicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-ene-1-carbaldehyde (700 mg, 2.94 mmol) in toluene (15 mL) was added tert-butyl 4-(piperazin-1-yl)benzoate (773 mg, 2.94 mmol) and titanium (IV) ethoxide (1.34 g, 5.88 mmol) at rt. After 2 h, the reaction mixture was cooled to 0 °C and treated with $\text{Na}(\text{OAc})_3\text{BH}$ (1.8 g, 8.82 mmol), warmed to rt and stirred for 16 h. The reaction was then concentrated and the residue was diluted with sat. aq. NaHCO_3 (10 mL) and extracted with DCM (3 x 20 mL). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated. The crude product was purified by column chromatography (SiO_2 , EtOAc/pet. ether) to afford tert-butyl 4-(4-((2-(3-chlorobicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoate (**Intermediate 48-1**) as a white solid (540 mg, 38% yield). ^1H NMR (400 MHz, CDCl_3) δ 7.86 (d, J = 8.8 Hz, 2H), 6.84 (d, J = 9.2 Hz,

2H), 3.29-3.27 (m, 4H), 2.98 (s, 2H), 2.49-1.47 (m, 4H), 2.30 (s, 6H), 2.11-2.04 (m, 2H), 1.68 (s, 2H), 1.57 (s, 9H), 1.33-1.25 (m, 2H), 0.88 (s, 6H); LC/MS (ESI) m/z 485.4 [M+H]⁺.

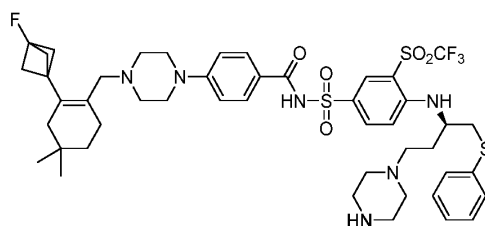
[0301] Step 2: To a stirred solution of **Intermediate 48-1** (540 mg, 1.11 mmol) in DCM (15 mL) at 0 °C was added TFA (507 mg, 4.45 mmol). The reaction mixture was warmed to rt, stirred for 3 h and then concentrated. The crude residue was diluted with sat. aq. NaHCO₃ solution (10 mL), and extracted with 10% MeOH in DCM (3 x 10 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated to afford 4-(4-((2-(3-chlorobicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoic acid (**Intermediate 48-2**) (420 mg, 88% yield) as a white solid. LC/MS (ESI) m/z 429.3 [M+H]⁺.

[0302] Step 3: tert-Butyl (R)-4-(3-((4-(N-(4-(4-((2-(3-chlorobicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-((trifluoromethyl)sulfonyl)phenyl)amino)-4-(phenylthio)butyl)piperazine-1-carboxylate (**Intermediate 48-3**) was prepared following General Procedure A using **Intermediate 48-2** and **Intermediate 4**. LC/MS (ESI) m/z 1063.6 [M+H]⁺

[0303] Step 4: **Intermediate 48** was prepared following the procedure described in Step 2 for **Intermediate 5** using **Intermediate 48-3** in place of **Intermediate 5-1**. LC/MS (ESI) m/z 963.6 [M+H]⁺.

Intermediate 49

(R)-4-(4-((4,4-dimethyl-2-(3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)cyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-((1-(phenylthio)-4-(piperazin-1-yl)butan-2-yl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide



[0304] Step 1: A stirred solution of 2-(3-fluorobicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-ene-1-carbaldehyde (1.2 g, 5.40 mmol) in toluene (15 mL) was treated with ethyl 4-(piperazin-1-yl)benzoate (1.26 g, 5.40 mmol) and titanium (IV) ethoxide (2.4 g, 10.81 mmol) at rt and stirred for 2 h. The reaction mixture was then cooled to 0 °C, and

Na(OAc)₃BH (3.4 g, 16.21 mmol) was added and the reaction was warmed to rt. After 16 h, the reaction was concentrated, diluted with sat. aq. NaHCO₃ (10 mL) and washed with DCM (3 x 25 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated. The crude product was column chromatography (SiO₂, EtOAc/pet. ether) to afford ethyl 4-(4-((2-(3-fluorobicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoate (**Intermediate 49-1**) (1.3 g, 54% yield) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.91 (d, *J* = 7.2 Hz, 2H), 6.85 (d, *J* = 7.2 Hz, 2H), 4.32 (q, *J* = 7.2 Hz, 2H), 3.31-3.29 (m, 4H), 3.00 (s, 2H), 2.50-2.47 (m, 4H), 2.21 (d, *J* = 2.4 Hz, 6H), 2.14-2.09 (m, 2H), 1.71 (s, 2H), 1.39-1.25 (m, 5H), 0.88 (s, 6H); LC/MS (ESI) *m/z* 441.7 [M+H]⁺.

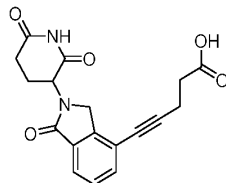
[0305] Step 2: To a stirred solution of **Intermediate 49-1** (1.3 g, 2.947 mmol) in THF:EtOH (1:1, 20 mL) was added 4N NaOH(aq.) (2 mL) at 0 °C. The reaction mixture was then heated to 50 °C and stirred for 16 h. The reaction mixture was cooled to rt, concentrated, and the resulting residue was dissolved in water (10 mL), acidified to pH ~3 using 6N HCl(aq.), and the precipitated solid was filtered. The filtered solid was washed with pentane and then dissolved in EtOAc (150 mL), washed with sat.aq NaHCO₃ (10 mL), water and brine. The organic layer was dried over Na₂SO₄, filtered and concentrated to afford 4-(4-((2-(3-fluorobicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoic acid (**Intermediate 49-2**) as a white solid (1.1 g, 90% yield) LC/MS (ESI) *m/z* 411.36 [M-H]⁻.

[0306] Step 3: tert-Butyl (R)-4-(3-((4-(N-(4-(4-((2-(3-fluorobicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-((trifluoromethyl)sulfonyl)phenyl)amino)-4-(phenylthio)butyl)piperazine-1-carboxylate (**Intermediate 48-3**) was prepared following General Procedure A using **Intermediate 48-2** and **Intermediate 4**. LC/MS (ESI) *m/z* 1047.6 [M+H]⁺

[0307] Step 4: **Intermediate 49** was prepared following the procedure described in Step 2 for **Intermediate 5** using **Intermediate 49-3** in place of **Intermediate 5-1**. LC/MS (ESI) *m/z* 947.6 [M+H]⁺

Intermediate 50

5-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-4-yl)pent-4-ynoic acid

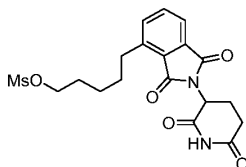


[0308] Step 1: A solution of *tert*-butyl pent-4-ynoate (1.19 g, 7.76 mmol) and 3-(4-bromo-1-oxoisindolin-2-yl)piperidine-2,6-dione in DMF (20 mL) was purged with argon for 10 min and then treated with Pd(PPh₃)₂Cl₂ (0.21 g, 0.31 mmol) and CuI (0.059 g, 0.31 mmol). After purging the reaction mixture with argon for an additional 10 min, TEA (7.79 mL, 55.9 mmol) was added and the reaction was heated to 90 °C. After 16 h, the reaction was concentrated, diluted with EtOAc (100 mL) and filtered through Celite®. The collected filtrate was washed with ice cold water (2 x 100 mL), brine (2 x 100 mL), dried over Na₂SO₄, filtered and concentrated. The crude product was purified by column chromatography (SiO₂) to afford *tert*-butyl 5-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-4-yl)pent-4-ynoate (**Intermediate 50-1**) (750 mg, 61% yield) as a brown solid. LC/MS (ESI) *m/z* 397.2 [M+H]⁺.

[0309] Step 2: To a solution of **Intermediate 50-1** (200 mg, 0.50 mmol) in 1,4-dioxane (2 mL) was added HCl (4M in 1,4-dioxane, 1 mL) at 0 °C. The reaction was warmed to rt, stirred for 16 and then concentrated. The crude product was triturated with Et₂O to afford **Intermediate 50** (150 mg, 87% yield) as a brown solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.35 (br s, 1H), 11.0 (s, 1H), 7.71 (d, *J* = 7.2 Hz, 1H), 7.62 (d, *J* = 7.2 Hz, 1H), 7.52 (t, *J* = 7.6 Hz, 1H), 5.14 (dd, *J* = 13.2, 5.2 Hz, 1H), 4.42 (d, *J* = 18.0 Hz, 1H), 4.27 (d, *J* = 18.0 Hz, 1H), 2.94-2.88 (m, 1H), 2.70-2.68 (m, 2H), 2.70-2.67 (m, 2H), 2.70-2.62 (m, 2H), 2.50-2.40 (m, 2H), 2.03-2.0 (m, 1H); LC/MS (ESI) *m/z* 341.1 [M+H]⁺.

Intermediate 51

5-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)pentyl methanesulfonate



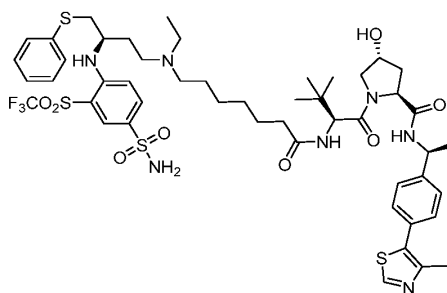
[0310] Step 1: To a stirred solution of ((pent-4-yn-1-yloxy)methyl)benzene (3 g, 13.2 mmol) in anhydrous DMF (20 mL) was added 4-bromo-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (1.23 g, 7.71 mmol) and CuI (220 mg, 1.15 mmol) at rt. The resulting reaction mixture was degassed using argon for 10 min and then TEA (32 mL, 70.8 mmol) and Pd(PPh₃)₂Cl₂ (860 mg, 1.22 mmol) were added. The reaction mixture was stirred at 80 °C for 16 h, cooled to rt, quenched with ice cold water (350 mL) and extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with brine (3 x 100 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated. The crude product was purified by column chromatography (SiO₂, EtOAc/pet. Ether) to afford 4-(5-(benzyloxy)pent-1-yn-1-yl)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (**Intermediate 51-1**) (2.1 g, 28% yield) as a brown solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.12 (s, 1H), 7.88-7.77 (m, 3H), 7.33-7.24 (m, 5H), 5.14 (dd, *J* = 12.8, 5.6 Hz, 1H), 4.50 (s, 2H), 3.63 (t, *J* = 6.4 Hz, 2H), 2.98-2.82 (m, 1H), 2.59-2.49 (m, 4H), 2.09 (m, 1H), 1.89-1.86 (m, 2H); LC/MS (ESI) *m/z* 429.4 [M-H]⁻.

[0311] Step 2: To a stirred solution of **Intermediate 51-1** (600 mg, 1.39 mmol) in MeOH (25 mL) was added Pd/C (10% w/w, 60 mg) and Pd(OH)₂ (10% w/w, 60 mg) at rt. The resulting reaction mixture was stirred at rt in a Parr Shaker apparatus under hydrogen atmosphere (75 psi) for 16 h and then filtered through a pad of Celite®. The Celite® pad was washed with MeOH (100 mL) and the combined filtrate was concentrated and the crude product was triturated with *n*-pentane to afford 2-(2,6-dioxopiperidin-3-yl)-4-(5-hydroxypentyl)isoindoline-1,3-dione (**Intermediate 51-2**) (340 mg, 70% yield) as a white solid. LC/MS (ESI) *m/z* 345.3 [M+H]⁺.

[0312] Step 3: To a stirred solution of **Intermediate 51-2** (200 mg, 0.58 mmol) in anhydrous DCM (2 mL) was added TEA (0.32 mL, 2.32 mmol) and MsCl (73 mg, 0.63 mmol) at 0 °C. The reaction mixture was warmed to rt, stirred for 2 h, diluted with water (50 mL) and extracted with DCM (3 x 50 mL). The combined organic layers were combined and dried over Na₂SO₄, filtered and concentrated. The crude product was purified by column chromatography (neutral alumina, EtOAc/pet. Ether) to afford **Intermediate 51** (220 mg, 89% yield) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.11 (s, 1H), 7.78-7.72 (m, 3H), 5.15-5.11 (m, 1H), 4.19 (t, *J* = 6.0 Hz, 2H), 3.14 (s, 3H), 3.04 (t, *J* = 7.2 Hz, 2H), 2.98-2.82 (m, 1H), 2.68-2.51 (m, 2H), 2.08-1.98 (m, 1H), 1.75-1.62 (m, 4H), 1.42-1.39 (m, 2H); LC/MS (ESI) *m/z* 423.2 [M+H]⁺.

Intermediate 52

(2S,4R)-1-((S)-2-(7-(ethyl(R)-4-(phenylthio)-3-((4-sulfamoyl-2-((trifluoromethyl)sulfonyl)phenyl)amino)butyl)amino)heptanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide



[0313] Step 1: 7-bromoheptanoic acid (0.5 g, 2.39 mmol) was dissolved in 1:1 EtOH:EtNH₂ (5 mL) at 20°C and then heated to 80°C. After 12 h, the reaction was cooled to rt and concentrated to give 7-(ethylamino)heptanoic acid (**Intermediate 52-1**) (0.4 g, 97% yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 3.07 - 2.81 (m, 5H), 2.18 (t, J = 7.0 Hz, 2H), 1.88 - 1.76 (m, 2H), 1.58 - 1.35 (m, 6H), 1.31 (t, J = 7.2 Hz, 3H).

[0314] Step 2: To a solution of Intermediate 52-1 (0.4 g, 2.31 mmol) in THF (10 mL) was added a solution of NaOH (92.4 mg, 2.31 mmol) in H₂O (2 mL) and Boc₂O (604.77 mg, 2.77 mmol) at 25°C. The reaction was stirred at 25°C for 12 h and then the pH of the reaction mixture was adjusted to pH 2-3 by the addition of 4M HCl(aq.) and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated to give the crude which was purified by prep-TLC (pet. ether: EtOAc 1:1) to provide 7-[tert-butoxycarbonyl(ethyl)amino]heptanoic acid (**Intermediate 52-2**) (0.3 g, 48% yield) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 3.24 - 3.13 (m, 4H), 2.36 (t, J = 7.5 Hz, 2H), 1.70-1.60 (m, 2H), 1.53-1.50 (m, 11H), 1.40 - 1.29 (m, 4H), 1.14-1.10 (m, 3H).

[0315] Step 3: tert-butyl ethyl(7-(((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-7-oxoheptyl)carbamate (**Intermediate 52-3**) was prepared following the procedure described in Step 1 for **Intermediate 30** using **Intermediate 52-2** in place of 7-[tert-butoxycarbonyl(methyl)amino]heptanoic acid. LC/MS (ESI) *m/z* 698.3 [M+H]⁺.

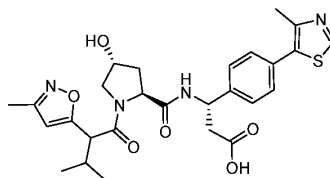
[0316] Step 4: (2S,4R)-1-((S)-2-(7-(ethylamino)heptanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-

carboxamide (**Intermediate 52-4**) was prepared following the procedure described in Step 2 for **Intermediate 30** using **Intermediate 52-3** in place of **Intermediate 30-1**. LC/MS (ESI) m/z 600.4 $[M+H]^+$.

[0317] Step 5: **Intermediate 52** was prepared following the procedure described in Step 3 for **Intermediate 30** using **Intermediate 52-4** in place of **Intermediate 30-2**. LC/MS (ESI) m/z 1064.3 $[M-H]^-$.

Intermediate 53

Methyl (3S)-3-((2S,4R)-4-hydroxy-1-(3-methyl-2-(3-methylisoxazol-5-yl)butanoyl)pyrrolidine-2-carboxamido)-3-(4-(4-methylthiazol-5-yl)phenyl)propanoate



[0318] Step 1: To a solution of 3-methyl-2-(3-methylisoxazol-5-yl)butanoic acid (5.5 g, 30.0 mmol) in DCM (200 mL) was added DIPEA (11.64 g, 15.7 mL) and HATU (13.7 g, 36.0 mmol) at 20°C. The reaction mixture was stirred at 20°C for 12 h and then diluted with water (200 mL) and extracted with DCM (3 × 200 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated to afford (2S,4R)-methyl 4-hydroxy-1-(3-methyl-2-(3-methylisoxazol-5-yl)butanoyl)pyrrolidine-2-carboxylate (**Intermediate 53-1**) (6 g, 64% yield) as a white solid and used directly in the next step without further purification. LC/MS (ESI) m/z 310.9 $[M+H]^+$.

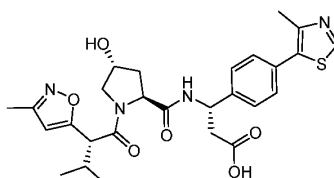
[0319] Step 2: To a solution of **Intermediate 53-1** (6 g, 19.33 mmol) in MeOH (60 mL) and H₂O (15 mL) was added LiOH monohydrate (2.43 g, 58 mmol) at 0 °C. The reaction was stirred at 20°C for 12 h and then concentrated. The resulting residue was dissolved in water (50 mL), acidified to pH = 2 using conc. HCl and then extracted with DCM (5 × 100 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated to provide (2S,4R)-4-hydroxy-1-[3-methyl-2-(3-methylisoxazol-5-yl)butanoyl]pyrrolidine-2-carboxylic acid (**Intermediate 53-2**) (5.15 g, 90% yield) as a yellow oil. The crude product was used in the next step without further purification. LC/MS (ESI) m/z 296.9 $[M+H]^+$.

[0320] Step 3: To a solution of **Intermediate 53-2** (3 g, 10.12 mmol) in DMF (60 mL) was added DIPEA (5.23 g, 40.5 mmol), methyl (3S)-3-amino-3-[4-(4-methylthiazol-5-yl)phenyl]propanoate hydrochloride (3.48 g, 11.14 mmol) and HATU (4.62 g, 12.15 mmol) at 20 °C. After 12 h, the reaction was poured into water (60 mL) and extracted with EtOAc (3 × 60 mL). The combined organic layers were washed with brine (150 mL), dried over Na₂SO₄, filtered, and concentrated. The crude residue was purified by HPLC (90:10 to 50:50 water (0.09% TFA)/CH₃CN) to provide (3S)-3-[[[(2S,4R)-4-hydroxy-1-[3-methyl-2-(3-methylisoxazol-5-yl)butanoyl]pyrrolidine-2-carbonyl]amino]-3-[4-(4-methylthiazol-5-yl)phenyl]propanoate (**Intermediate 53-3**) (1.8 g, 32% yield) as a yellow solid. LC/MS (ESI) *m/z* 555.3 [M+H]⁺.

[0321] Step 4: To a solution of **Intermediate 53-3** (1.8 g, 3.25 mmol) was added LiOH monohydrate (408.6 mg, 9.74 mmol) at 20 °C. The reaction mixture was stirred at 20 °C for 12 h and then concentrated. The crude residue was dissolved in water (20 mL), acidified to pH = 6 using conc. HCl, and extracted with DCM (5 × 30 mL). The combined organic layers was dried over Na₂SO₄, filtered and concentrated under reduced pressure to afford **Intermediate 53** (1.3 g, 74% yield) as a white solid. LC/MS *m/z* 541.1 [M+H]⁺.

Intermediate 53A

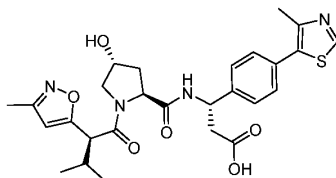
(S)-3-((2S,4R)-4-hydroxy-1-((R)-3-methyl-2-(3-methylisoxazol-5-yl)butanoyl)pyrrolidine-2-carboxamido)-3-(4-(4-methylthiazol-5-yl)phenyl)propanoic acid



[0322] **Intermediate 53** was subjected to chiral SFC separation (Chiralpak AD-3 (100 x 4.6 mm), 3 μ, 90:5 to 60:40 CO₂/EtOH (0.1% iPrOH, v/v)) to afford **Intermediate 53A** as the first eluted peak (*t_R* = 2.189 min) with 100% ee. LC/MS (ESI) *m/z* 541.1 [M+H]⁺. The absolute stereochemistry was arbitrarily assigned for the isopropyl group in **Intermediate 53A**.

Intermediate 53B

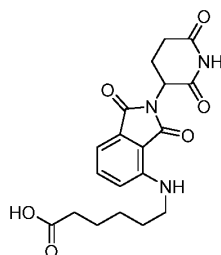
(S)-3-((2S,4R)-4-hydroxy-1-((S)-3-methyl-2-(3-methylisoxazol-5-yl)butanoyl)pyrrolidine-2-carboxamido)-3-(4-(4-methylthiazol-5-yl)phenyl)propanoic acid



[0323] **Intermediate 53** was subjected to chiral SFC separation (Chiralpak AD-3 (100 x 4.6 mm), 3 μ , 90:5 to 60:40 CO₂/EtOH (0.1% iPrOH, v/v)) to afford **Intermediate 53B** as the second eluted peak (t_R = 2.324 min) with 99.3% ee. LC/MS (ESI) m/z 541.1 [M+H]⁺. The absolute stereochemistry was arbitrarily assigned for the isopropyl group in **Intermediate 53B**.

Intermediate 54

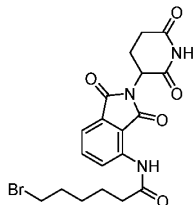
6-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)amino)hexanoic acid



[0324] A stirred solution of 2-(2,6-dioxopiperidin-3-yl)-4-fluoroisindoline-1,3-dione (1.0 eq) in DMF is treated with 6-Aminohexanoic acid (1.2 eq.) and DIPEA (2.0 eq.) at rt and heated at 80 °C. Upon completion, the crude reaction is cooled to rt, concentrated and purified by column chromatography (SiO₂) to provide **Intermediate 54**.

Intermediate 55

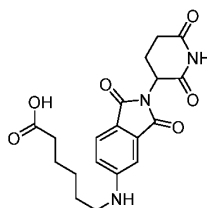
6-bromo-N-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)hexanamide



[0325] A stirred solution of 6-bromohexanoyl chloride (1.0 eq) in THF is treated with pomalidomide (1.2 eq.) and DIPEA (2.0 eq.) at rt and heated to reflux. Upon completion, the crude reaction is cooled to rt, concentrated and then diluted with DCM. The reaction mixture is washed with sat. aq. NaHCO₃, dried over Na₂SO₄, filtered and concentrated. The crude product is purified by column chromatography (SiO₂) to provide **Intermediate 55**.

Intermediate 56

6-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-5-yl)amino)hexanoic acid

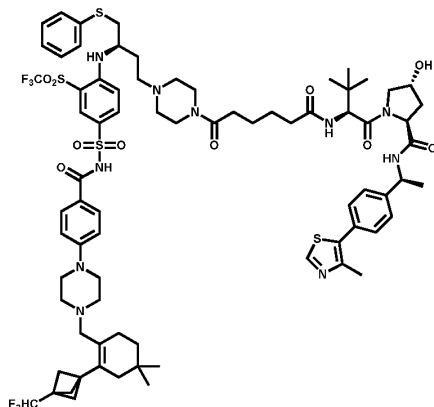


[0326] Step 1: To a solution of 2-(2,6-dioxopiperidin-3-yl)-5-fluoroisindoline-1,3-dione (1.0 eq.), and tert-butyl 6-aminohexanoate (1.2 eq.) in NMP is added DIPEA (2.0 eq.) and the reaction mixture is heated to 90 °C. Upon completion, the reaction is cooled to rt and diluted with EtOAc. The organic layer is washed with water, brine, dried over Na₂SO₄, filtered and concentrated. The crude product is purified by column chromatography (SiO₂) to provide tert-butyl 6-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-5-yl)amino)hexanoate (**Intermediate 56-1**).

[0327] Step 2: A solution of **Intermediate 56-1** in 1,4-dioxane is treated with HCl (4M in 1,3-dioxane, 20 eq.) at 0 °C and warmed to rt. Upon completion, the crude reaction is cooled to rt and concentrated to provide **Intermediate 56**. The crude product is used in the next step without further purification.

Example 1

(2S,4R)-1-((S)-2-(6-(4-((R)-3-((4-(N-(4-(4-((2-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-((trifluoromethyl)sulfonyl)phenyl)amino)-4-(phenylthio)butyl)piperazin-1-yl)-6-oxohexanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide

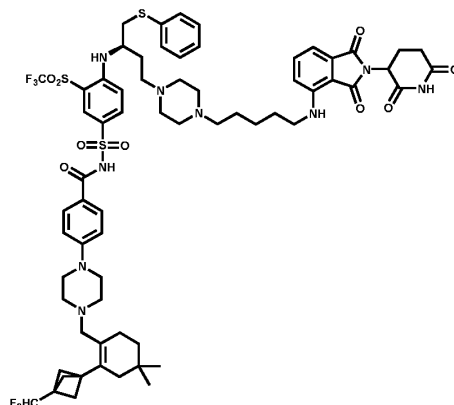


[0328] To a solution of **Intermediate 5** (0.1 g, 102.1 μ mol) and **Intermediate 8** (0.05 g, 87.30 μ mol) in DMF (1 mL) was added HATU (46.60 mg, 122.6 μ mol) and DIPEA (52.8 mg, 408.50 μ mol) at 20°C. The reaction mixture was stirred at 20°C for 2 h and then concentrated and purified by HPLC (65:35 to 25:75 10 mM $\text{NH}_4\text{CO}_3\text{H(aq.)}$ /CH₃CN) to afford **Example 1** (15 mg, 11% yield). ¹H NMR (400 MHz, CD₃OD) δ 8.89 (s, 1H), 8.30 (d, J = 2.0 Hz, 1H), 8.07-8.01 (m, 1H), 7.83 (d, J = 8.9 Hz, 2H), 7.48-7.35 (m, 6H), 7.30-7.24 (m, 2H), 7.23-7.17 (m, 1H), 6.94 (d, J = 8.9 Hz, 2H), 6.85 (d, J = 9.4 Hz, 1H), 5.79 (t, J = 56.4 Hz, 1H), 5.06-5.00 (m, 4H), 4.67-4.55 (m, 4H), 4.44 (br s, 1H), 4.10-4.08 (m, 1H), 3.89 (br d, J = 11.0 Hz, 1H), 3.76 (dd, J = 11.0, 3.9 Hz, 1H), 3.73-3.73 (m, 1H), 3.64-3.53 (m, 2H), 3.49-3.40 (m, 8H), 3.30-3.16 (m, 3H), 2.86 (br s, 3H), 2.52-2.48 (m, 3H), 2.46-2.41 (m, 2H), 2.40-2.28 (m, 6H), 2.20-2.17 (m, 2H), 2.08 (s, 6H), 2.09-1.90 (m, 1H), 1.82 (br s, 2H), 1.68-1.56 (m, 4H), 1.52 (d, J = 7.1 Hz, 3H), 1.39 (t, J = 6.4 Hz, 2H), 1.11-1.00 (m, 9H), 0.93 (s, 6H); LCMS (ESI) m/z 1531.5 [M-H]⁻.

Example 2

4-(4-((2-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-(((2R)-4-(4-(5-((2-(2,6-dioxopiperidin-3-yl)-1,3-

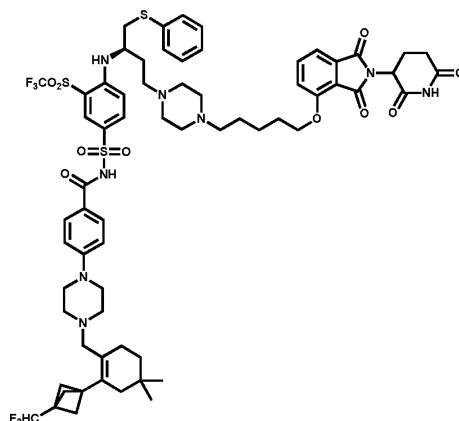
dioxoisindolin-4-yl)amino)pentyl)piperazin-1-yl)-1-(phenylthio)butan-2-yl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide



[0329] To a solution of **Intermediate 5** (100 mg, 0.10 mmol) in 1,4-dioxane (6 mL) was added **Intermediate 9** (66 mg, 0.15 mmol), DIPEA (50 μ L, 0.30 mmol) and NaI (1.53 mg, 0.01 mmol) at rt. The reaction was then heated to 90 $^{\circ}$ C and stirred for 2 days. The reaction was cooled to rt and concentrated. The crude residue was dissolved in 10% MeOH in DCM, washed with H₂O (2 x 15 mL), brine (2 x 10 mL), dried over Na₂SO₄, filtered and concentrated. The crude product was purified by HPLC (45:55 to 5:95 5 mM NH₄CO₃H(aq.)/CH₃CN) to afford **Example 2** (40 mg, 29% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.08 (s, 1H), 8.04 (d, *J* = 1.6 Hz, 1H), 7.87 (d, *J* = 9.2 Hz, 1H), 7.71 (d, *J* = 8.8 Hz, 2H), 7.57 (t, *J* = 7.6 Hz, 1H), 7.34 (d, *J* = 7.6 Hz, 2H), 7.29 (t, *J* = 7.6 Hz, 2H), 7.19 (t, *J* = 7.2 Hz, 1H), 7.09 (d, *J* = 8.4 Hz, 1H), 7.01 (d, *J* = 7.2 Hz, 1H), 6.80 (d, *J* = 8.8 Hz, 3H), 6.65 (d, *J* = 9.2 Hz, 1H), 6.53 (t, *J* = 5.6 Hz, 1H), 6.00 (t, *J* = 56.4 Hz, 1H), 5.07 -5.02 (m, 1H), 3.97 (br s, 1H), 3.30-3.15 (m, 8H), 2.98 (s, 2H), 2.91-2.84 (m, 1H), 2.60-2.50 (m, 2H), 2.48-2.15 (m, 15H), 2.07-1.96 (m, 11H), 1.70-1.53 (m, 6H), 1.50-1.39 (m, 2H), 1.33-1.27 (m, 4H), 0.85 (s, 6H); LC/MS (ESI) *m/z* 1320.7 [M+H]⁺.

Example 3

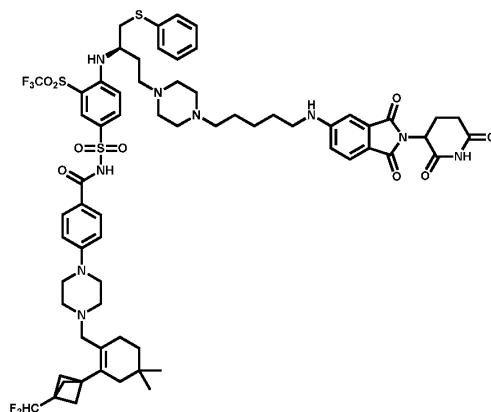
4-(4-((2-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-(((4-(((2R)-4-(4-(5-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)oxy)pentyl)piperazin-1-yl)-1-(phenylthio)butan-2-yl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide



[0330] To a solution of **Intermediate 10** (100 mg, 194.3 μ mol) and **Intermediate 5** (110.20 mg, 116.8 μ mol) in DMF (1 mL) was added DIPEA (74.78 mg, 583.0 μ mol). The reaction was then stirred at 60°C for 12 h, cooled to rt, concentrated and purified by HPLC (60:40 to 0:100 10 mM $\text{NH}_4\text{CO}_3\text{H(aq.)}$ /CH₃CN) to afford **Example 3** (17 mg, 7% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.11 (s, 1H), 8.06 (d, *J* = 1.8 Hz, 1H), 7.95 (dd, *J* = 9.1, 1.8, Hz, 1H), 7.82 (dd, *J* = 8.4, 7.3 Hz, 1H), 7.72 (d, *J* = 8.8 Hz, 2H), 7.51 (d, *J* = 8.6 Hz, 1H), 7.45 (d, *J* = 7.2 Hz, 1H), 7.36-7.25 (m, 4H), 7.22-7.16 (m, 1H), 6.89 (br d, *J* = 9.4 Hz, 1H), 6.82 (br d, *J* = 8.8 Hz, 2H), 6.70 (br d, *J* = 8.7 Hz, 1H), 6.00 (t, *J* = 56.4 Hz, 1H), 5.07 (dd, *J* = 12.8, 5.4 Hz, 1H), 4.21 (t, *J* = 6.1 Hz, 2H), 4.03-4.01 (m, 1H), 3.30-3.24 (m, 5H), 3.19 (br s, 4H), 3.02 (br s, 3H), 2.94-2.79 (m, 4H), 2.64-2.52 (m, 3H), 2.47-2.31 (m, 7H), 2.10-2.00 (m, 3H), 1.99-1.98 (m, 7H), 1.78 (qd, *J* = 13.2, 6.6 Hz, 3H), 1.70 (br s, 2H), 1.62 (br s, 2H), 1.51-1.39 (m, 2H), 1.26 (t, *J* = 5.8 Hz, 3H), 0.85 (s, 6H); LC/MS (ESI) *m/z* 1319.3 [M-H]⁻.

Example 4

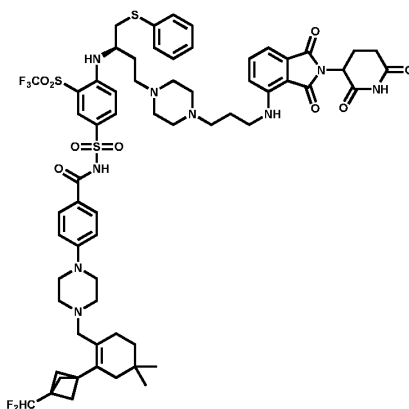
4-(4-((2-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-(((4-(((2R)-4-(4-(5-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-5-yl)amino)pentyl)piperazin-1-yl)-1-(phenylthio)butan-2-yl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide



[0331] To a solution of **Intermediate 12** (0.05 g, 114.3 μ mol) and **Intermediate 5** (100.7 mg, 102.9 μ mol) in dioxane (2 mL) was added DIPEA (39.8 μ L, 228.6 μ mol) and NaI (1.7 mg, 11.4 μ mol) at 20°C. The reaction was stirred at 90°C for 12 h, cooled to rt, concentrated, and purified by HPLC (45:55 to 0:100 10 mM $\text{NH}_4\text{CO}_3\text{H(aq.)}$ / CH_3CN) to afford **Example 4** (10 mg, 7% yield). ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 11.06 (s, 1H), 8.06 (s, 1H), 7.95 (br d, J = 8.5 Hz, 1H), 7.72 (br d, J = 8.5 Hz, 2H), 7.56 (br d, J = 8.2 Hz, 1H), 7.40-7.25 (m, 4H), 7.23-7.16 (m, 1H), 7.11 (br s, 1H), 6.94 (s, 1H), 6.92-6.77 (m, 4H), 6.69 (br d, J = 8.6 Hz, 1H), 6.00 (t, J = 56.4 Hz, 1H), 5.03 (br dd, J = 12.8, 5.3, 1H), 4.09-3.95 (m, 1H), 3.26-3.11 (m, 9H), 3.01 (br s, 3H), 2.94-2.80 (m, 3H), 2.70-2.55 (m, 4H), 2.47-2.25 (m, 9H), 2.05 (br s, 3H), 1.99-1.97 (m, 8H), 1.70 (br s, 3H), 1.59-1.50 (m, 4H), 1.42-1.21 (m, 5H), 0.85 (s, 6H); LC/MS (ESI) m/z 1318.5 $[\text{M-H}]^-$.

Example 5

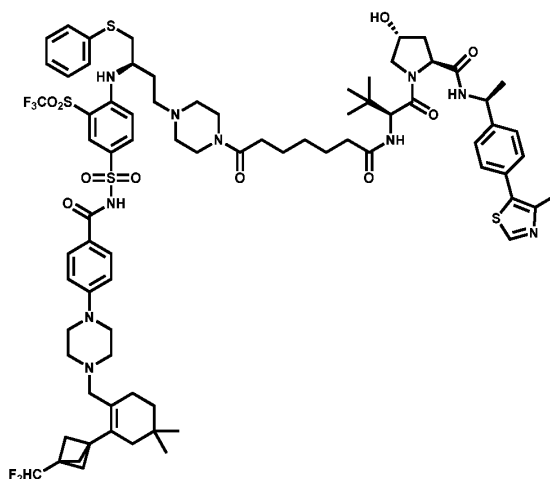
4-[4-[[2-[3-(difluoromethyl)-1-bicyclo[1.1.1]pentanyl]-4,4-dimethyl-cyclohexen-1-yl]methyl]piperazin-1-yl]-N-[4-[[[(1R)-3-[4-[3-[[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-4-yl]amino]propyl]piperazin-1-yl]-1-(phenylsulfanylmethyl)propyl]amino]-3-(trifluoromethylsulfonyl)phenyl]sulfonyl-benzamide



[0332] To a solution of **Intermediate 13** (0.1 g, 244.3 μmol) and **Intermediate 5** (263.09 mg, 268.7 μmol) in dioxane (2 mL) was added DIPEA (63.14 mg, 488.5 μmol , 85.1 μL) and NaI (1.83 mg, 12.2 μmol) at 20°C. The reaction was stirred at 90°C for 12 h, cooled to rt, concentrated, and purified by HPLC (55:45 to 25:75 10 mM $\text{NH}_4\text{CO}_3\text{H(aq.)}$ / CH_3CN) to afford **Example 5** (37 mg, 12% yield). ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 11.12 (s, 1H), 8.07 (d, $J = 1.7$ Hz, 1H), 7.95 (br d, $J = 8.9$ Hz, 1H), 7.72 (d, $J = 8.7$ Hz, 2H), 7.59 (t, $J = 7.9$ Hz, 1H), 7.37-7.31 (m, 2H), 7.31-7.25 (m, 2H), 7.21-7.15 (m, 1H), 7.12 (d, $J = 8.7$ Hz, 1H), 7.04 (d, $J = 7.0$ Hz, 1H), 6.91 (br d, $J = 9.4$ Hz, 1H), 6.83 (br d, $J = 8.8$ Hz, 2H), 6.80-6.68 (m, 2H), 6.00 (t, $J = 56.4$ Hz, 1H), 5.05 (dd, $J = 12.8, 5.4$ Hz, 1H), 4.10-4.00 (m, 1H), 3.34-3.15 (m, 13H), 3.04 (br s, 3H), 2.94-2.81 (m, 3H), 2.64-2.51 (m, 4H), 2.46 (br s, 5H), 2.08-2.00 (m, 4H), 1.98 (s, 6H), 1.96-1.89 (m, 1H), 1.85-1.68 (m, 5H), 1.35-1.15 (m, 3H), 0.85 (s, 6H); LC/MS (ESI) m/z 1290.5 $[\text{M-H}]^-$.

Example 6

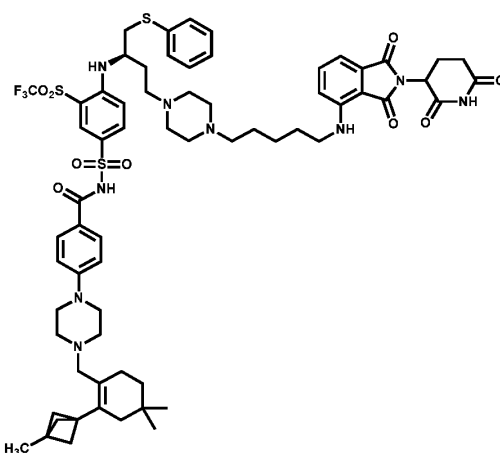
(2S,4R)-1-((S)-2-(7-(4-((R)-3-((4-(N-(4-(4-((2-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-((trifluoromethyl)sulfonyl)phenyl)amino)-4-(phenylthio)butyl)piperazin-1-yl)-7-oxoheptanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide



[0333] **Example 6** was prepared following the procedure described for **Example 1** using **Intermediate 16** in place of **Intermediate 8**. ^1H NMR (400MHz, $\text{DMSO}-d_6$) 8.98 (s, 1H), 8.36 (d, $J = 7.6$ Hz, 1H), 8.10 (s, 1H), 7.94 (d, $J = 9.2$ Hz, 1H), 7.80-7.70 (m, 3H), 7.45-7.25 (m, 8H), 7.20-7.15 (m, 1H), 6.95-6.75 (m, 4H), 6.01 (t, $J = 56.4$ Hz, 1H), 5.08 (d, $J = 3.2$ Hz, 1H), 4.95-4.85 (m 1H), 4.51 (d, $J = 9.6$ Hz, 1H), 4.42 (t, $J = 8.0$ Hz, 1H), 4.28 (br s, 1H), 4.05 (br s, 1H), 3.60 (s, 2H), 3.30-2.90 (m, 10H), 2.45 (s, 4H), 2.40-1.90 (m, 25H), 1.85-1.65 (m, 4H), 1.55-1.35 (m, 7H), 1.30-1.15 (m, 4H), 0.93 (s, 9H), 0.86 (s, 6H); LC/MS (ESI) m/z 1545.6 $[\text{M}-\text{H}]^-$.

Example 7

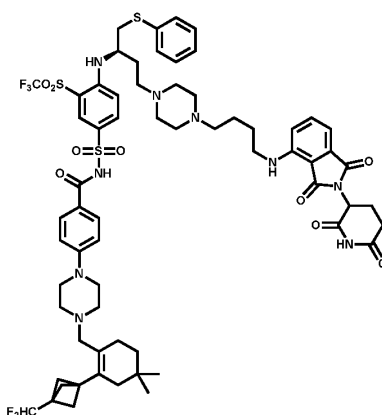
4-(4-((4,4-dimethyl-2-(3-methylbicyclo[1.1.1]pentan-1-yl)cyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-(((4-(((2R)-4-(4-(5-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)amino)pentyl)piperazin-1-yl)-1-(phenylthio)butan-2-yl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide



[0334] To a solution of **Intermediate 11** (60 mg, 116.8 μ mol) and **Intermediate 6** (110.2 mg, 116.8 μ mol) in DMF (1 mL) was added DIPEA (44.95 mg, 350.5 μ mol) at 20°C. The reaction was stirred at 40°C for 12 h, cooled to rt, concentrated, and purified by HPLC (50:50 to 0:100 10 mM $\text{NH}_4\text{CO}_3\text{H(aq.)}/\text{CH}_3\text{CN}$) to afford **Example 7** (12 mg, 8% yield). ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 11.09 (s, 1H), 8.06 (d, J = 2.0 Hz, 1H), 8.00-7.91 (m, 1H), 7.72 (d, J = 8.8 Hz, 2H), 7.62-7.56 (m, 1H), 7.36-7.32 (m, 2H), 7.31-7.26 (m, 2H), 7.22-7.16 (m, 1H), 7.10 (d, J = 8.6 Hz, 1H), 7.03 (d, J = 7.0 Hz, 1H), 6.89 (br d, J = 9.4 Hz, 1H), 6.82 (br d, J = 8.9 Hz, 2H), 6.70 (br d, J = 8.6 Hz, 1H), 6.54 (t, J = 5.9 Hz, 1H), 5.05 (dd, J = 12.7, 5.4 Hz, 1H), 4.02 (br s, 1H), 3.33-3.26 (m, 11H), 3.19 (br s, 4H), 3.06 (br s, 1H), 2.90-2.70 (m, 5H), 2.61 (br s, 1H), 2.56-2.53 (m, 3H), 2.45 (br s, 6H), 2.10-2.00 (m, 3H), 1.95-1.85 (m, 1H), 1.78 (s, 6H), 1.67 (br s, 2H), 1.63-1.51 (m, 4H), 1.39-1.25 (m, 2H), 1.24 (t, J = 5.9 Hz, 2H), 1.10 (s, 3H), 0.84 (s, 6H); LC/MS (ESI) m/z 1282.5 $[\text{M-H}]^-$.

Example 8

4-[4-[[2-[3-(difluoromethyl)-1-bicyclo[1.1.1]pentanyl]-4,4-dimethyl-cyclohexen-1-yl]methyl]piperazin-1-yl]-N-[4-[[[(1R)-3-[4-[4-[[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-4-yl]amino]butyl]piperazin-1-yl]-1-(phenylsulfanylmethyl)propyl]amino]-3-(trifluoromethylsulfonyl)phenyl]sulfonyl-benzamide

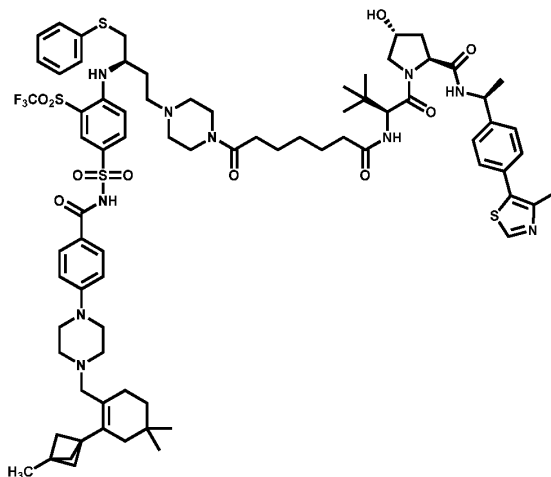


[0335] To a solution of **Intermediate 14** (100 mg, 113.6 μ mol) in DCM (2 mL) were added **Intermediate 2** (60.62 mg, 136.4 μ mol), DMAP (13.9 mg, 113.6 μ mol), TEA (31.6 μ L, 227.3 μ mol) and EDCI (32.7 mg, 170.5 μ mol) at 20°C. The reaction was stirred at 20°C for 12 h and then concentrated and purified by HPLC (45:55 to 0:100 10 mM $\text{NH}_4\text{CO}_3\text{H(aq.)}/\text{CH}_3\text{CN}$) to afford **Example 8** (30 mg, 20% yield). ^1H NMR (400MHz, $\text{DMSO}-d_6$) δ 11.10 (s, 1H), 8.08 (s, 1H), 7.96 (br d, J = 8.9 Hz, 1H), 7.74 (br d, J = 8.6 Hz, 2H), 7.58 (t, J = 7.8 Hz, 1H), 7.38-7.24 (m, 4H), 7.23-7.15 (m, 1H), 7.11 (d, J = 8.6 Hz, 1H), 7.03 (d, J = 7.0 Hz, 1H), 6.90 (br d, J = 9.4 Hz, 1H), 6.83 (br d, J = 8.8 Hz, 2H), 6.72 (br d, J = 8.7 Hz, 1H), 6.59 (t, J = 5.8 Hz, 1H), 6.00 (t, J = 56.4 Hz, 1H), 5.05 (dd, J = 12.8, 5.3 Hz, 1H), 4.02 (br d, J = 4.8 Hz, 1H), 3.34-3.24 (m, 7H), 3.19 (br s, 5H), 3.02 (br s, 3H), 2.93-2.71 (m, 5H), 2.65-2.52 (m, 3H), 2.44 (br s, 7H), 2.10-2.00 (m, 3H), 1.98 (br s, 7H), 1.80-1.68 (m, 3H), 1.58 (br s, 4H), 1.26 (t, J = 6.2 Hz, 2H), 0.85 (s, 6H); LC/MS (ESI) m/z 1304.2 $[\text{M}-\text{H}]^-$.

Example 9

(2S,4R)-1-((S)-2-(7-(4-((R)-3-((4-(N-(4-(4-((4,4-dimethyl-2-(3-methylbicyclo[1.1.1]pentan-1-yl)cyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-((trifluoromethyl)sulfonyl)phenyl)amino)-4-(phenylthio)butyl)piperazin-1-yl)-7-

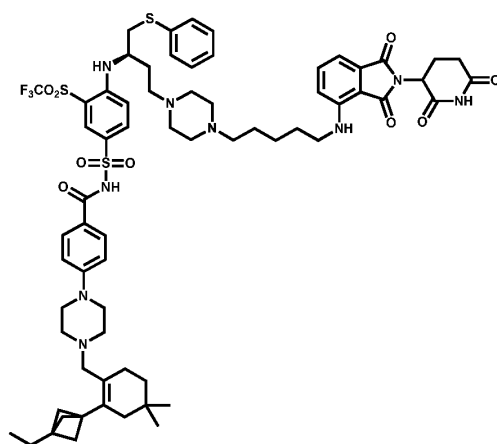
oxoheptanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide



[0336] **Example 9** was prepared following the procedure described for **Example 6** using **Intermediate 6** in place of **Intermediate 5**. ^1H NMR (400 MHz, DMSO- d_6) δ 8.97-8.92 (m, 1H), 8.37 (d, $J = 7.7$ Hz, 1H), 8.08 (s, 1H), 7.97-7.90 (m, 1H), 7.80-7.71 (m, 3H), 7.44-7.21 (m, 9H), 7.19-7.14 (m, 1H), 6.96-6.71 (m, 4H), 4.99-4.78 (m, 1H), 4.49 (d, $J = 9.3$ Hz, 1H), 4.40 (t, $J = 8.1$ Hz, 1H), 4.26 (br s, 1H), 4.04 (br s, 1H), 3.59 (br s, 3H), 3.45-3.11 (m, 12H), 2.44 (br s, 4H), 2.26-2.16 (m, 4H), 2.20-2.08 (m, 2H), 2.05-1.90 (m, 5H), 1.82-1.73 (m, 8H), 1.69 (br s, 2H), 1.52-1.39 (m, 5H), 1.36 (d, $J = 7.0$ Hz, 3H), 1.28-1.18 (m, 4H), 1.09 (s, 3H), 0.91 (s, 9H), 0.83 (s, 6H); LC/MS (ESI) m/z 1509.5 $[\text{M-H}]^-$.

Example 10

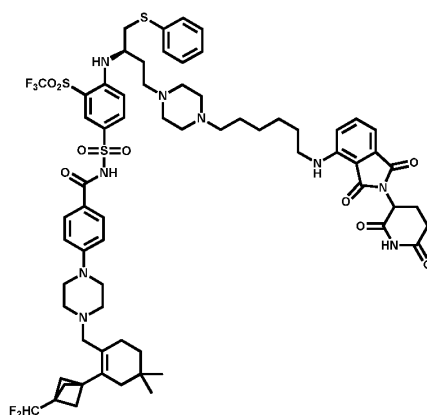
N-(((4-(((2R)-4-(4-(5-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)amino)pentyl)piperazin-1-yl)-1-(phenylthio)butan-2-yl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)-4-(4-((2-(3-ethylbicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzamide



[0337] Example 10 was prepared following the procedure described for **Example 2** using **Intermediate 7** in place of **Intermediate 5**. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.09 (s, 1H), 9.10 (br s, 1H), 8.05 (d, *J* = 1.6 Hz, 1H), 7.91 (d, *J* = 8.8 Hz, 1H), 7.72 (d, *J* = 8.8 Hz, 2H), 7.58 (t, *J* = 7.8 Hz, 1H), 7.35 (d, *J* = 7.2 Hz, 2H), 7.29 (t, *J* = 7.6 Hz, 2H), 7.19 (t, *J* = 7.2 Hz, 1H), 7.10 (d, *J* = 8.4 Hz, 1H), 7.02 (d, *J* = 6.8 Hz, 1H), 6.86-6.78 (m, 3H), 6.67 (d, *J* = 8.8 Hz, 1H), 6.54 (t, *J* = 5.8 Hz, 1H), 5.08-5.02 (m, 1H), 4.00 (s, 1H), 3.31-3.00 (m, 10H), 2.90-2.84 (m, 1H), 2.67-2.52 (m, 3H), 2.50-1.90 (m, 18H), 1.73 (s, 6H), 1.69 (s, 4H), 1.60-1.48 (m, 4H), 1.42-1.31 (m, 4H), 1.25 (t, *J* = 5.8 Hz, 2H), 0.85 (s, 6H), 0.79 (t, *J* = 7.2 Hz, 3H); LC/MS (ESI) *m/z* 1298.6 [M+H]⁺.

Example 11

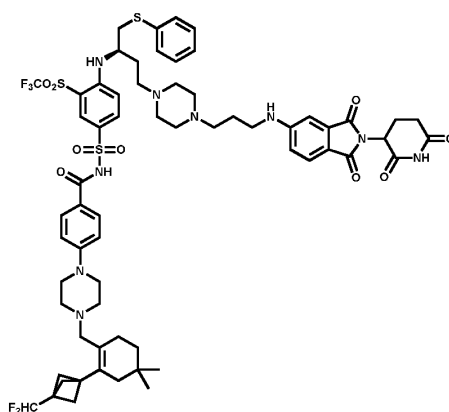
4-[4-[[2-[3-(difluoromethyl)-1-bicyclo[1.1.1]pentanyl]-4,4-dimethyl-cyclohexen-1-yl]methyl]piperazin-1-yl]-N-[4-[[[(1R)-3-[4-[6-[[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-4-yl]amino]hexyl]piperazin-1-yl]-1-(phenylsulfanylmethyl)propyl]amino]-3-(trifluoromethylsulfonyl)phenyl]sulfonyl-benzamide



[0338] To a solution of **Intermediate 15** (85 mg, 0.161 mmol) and **Intermediate 5** (78.9 mg, 0.081 mmol) in DMF (1 mL) was added DIPEA (62.5 mg, 0.483 mmol) and KI (26.7 mg, 0.161 mmol) at 25°C. The reaction was stirred at 50°C for 12 h, cooled to rt, and then concentrated and purified by HPLC (50:50 to 30:70 10 mM NH₄CO₃H(aq.)/CH₃CN) to afford **Example 11** (8 mg, 4% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.09 (s, 1H), 8.07 (s, 1H), 7.95 (br d, *J* = 9.0 Hz, 1H), 7.72 (br d, *J* = 8.8 Hz, 2H), 7.58 (t, *J* = 7.8 Hz, 1H), 7.37-7.32 (m, 2H), 7.32-7.26 (m, 2H), 7.22-7.16 (m, 1H), 7.09 (d, *J* = 8.2 Hz, 1H), 7.03 (d, *J* = 7.1 Hz, 1H), 6.88 (br d, *J* = 9.0 Hz, 1H), 6.82 (br d, *J* = 8.4 Hz, 2H), 6.69 (br d, *J* = 7.7 Hz, 1H), 6.53 (t, *J* = 5.3 Hz, 1H), 6.00 (t, *J* = 56.4 Hz, 1H), 5.05 (dd, *J* = 13.0, 5.3, Hz, 1H), 4.02 (br s, 2H), 3.29 (br s, 8H), 3.18 (br s, 3H), 3.01 (br s, 2H), 2.93-2.71 (m, 4H), 2.70-2.51 (m, 8H), 2.46-2.29 (m, 4H), 2.10-1.86 (m, 10H), 1.70 (br s, 3H), 1.67-1.42 (m, 4H), 1.42-1.21 (m, 6H), 0.85 (s, 6H); LC/MS (ESI) *m/z* 1332.5 [M-H]⁻.

Example 12

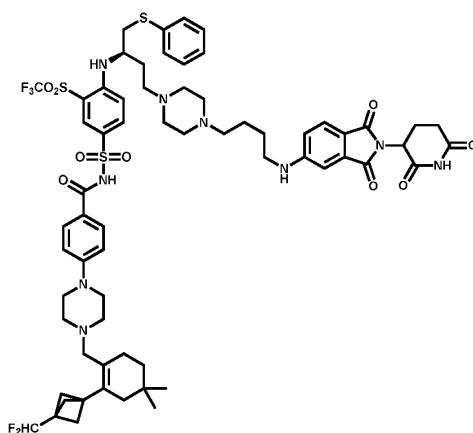
4-[4-[[2-[3-(difluoromethyl)-1-bicyclo[1.1.1]pentanyl]-4,4-dimethyl- cyclohexen-1-yl]methyl]piperazin-1-yl]-N-[4-[[[(1R)-3-[4-[3-[[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-5-yl]amino]propyl]piperazin-1-yl]-1-(phenylsulfanylmethyl)propyl]amino]-3-(trifluoromethylsulfonyl)phenyl]sulfonyl-benzamide



[0339] To a solution of **Intermediate 17** (0.025 g, 61.06 μmol) and **Intermediate 5** (65.77 mg, 67.2 μmol) in dioxane (2 mL) was added DIPEA (21.3 μL , 122.1 μmol) and NaI (915.3 μg , 6.1 μmol) at 20°C. The reaction mixture was heated to 90°C for 12 h and then cooled to rt, concentrated and purified by HPLC (60:40 to 0:100 10 mM $\text{NH}_4\text{CO}_3\text{H(aq.)}/\text{CH}_3\text{CN}$) to afford **Example 12** (25 mg, 32% yield). ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 11.06 (s, 1H), 8.08 (s, 1H), 7.96 (br d, $J = 8.8$ Hz, 1H), 7.73 (br d, $J = 8.7$ Hz, 2H), 7.58 (d, $J = 8.3$ Hz, 1H), 7.39-7.25 (m, 4H), 7.23-7.12 (m, 2H), 6.97 (s, 1H), 6.94-6.79 (m, 4H), 6.73 (br d, $J = 8.2$ Hz, 1H), 6.00 (t, $J = 56.4$ Hz, 1H), 5.03 (br dd, $J = 12.8, 5.3$ Hz, 1H), 4.03 (br d, $J = 4.2$ Hz, 1H), 3.28-3.11 (m, 10H), 3.04 (br s, 3H), 2.97-2.77 (m, 4H), 2.65-2.52 (m, 5H), 2.46 (br s, 7H), 2.05 (br s, 3H), 1.98 (s, 8H), 1.85-1.67 (m, 5H), 1.26 (t, $J = 6.0$ Hz, 2H), 0.86 (s, 6H); LC/MS (ESI) m/z 1290.5 $[\text{M-H}]^-$.

Example 13

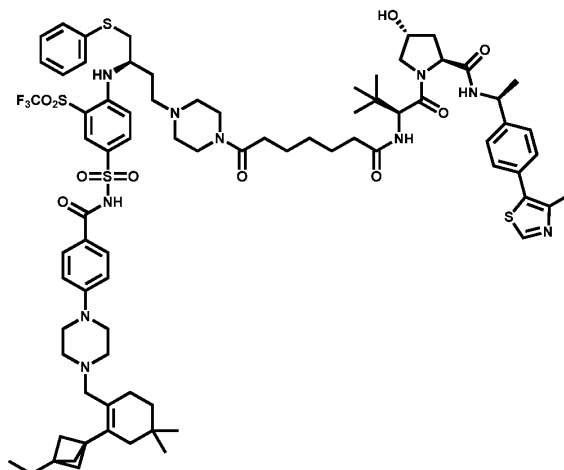
4-[4-[[2-[3-(difluoromethyl)-1-bicyclo[1.1.1]pentanyl]-4,4-dimethyl-cyclohexen-1-yl]methyl]piperazin-1-yl]-N-[4-[[[(1R)-3-[4-[4-[[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-5-yl]amino]butyl]piperazin-1-yl]-1-(phenylsulfanylmethyl)propyl]amino]-3-(trifluoromethylsulfonyl) phenyl]sulfonyl-benzamide



[0340] To a solution of **Intermediate 18** (0.1 g, 113.6 μ mol) and **Intermediate 2** (60.6 mg, 136.3 μ mol) in DCM (2 mL) were added DMAP (13.9 mg, 113.6 μ mol), EDCI (32.7 mg, 170.7 μ mol), TEA (31.6 μ L, 227.3 μ mol) at 20°C. The reaction mixture was stirred at 20°C for 12 h and then concentrated and purified by HPLC (60:40 to 0:100 10 mM $\text{NH}_4\text{CO}_3\text{H(aq.)}/\text{CH}_3\text{CN}$) to afford **Example 13** (22 mg, 15% yield). ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 11.06 (s, 1H), 8.08 (d, $J = 2.0$ Hz, 1H), 7.97 (br d, $J = 9.0$ Hz, 1H), 7.73 (d, $J = 8.8$ Hz, 2H), 7.58 (d, $J = 8.3$ Hz, 1H), 7.40-7.26 (m, 4H), 7.24-7.17 (m, 1H), 7.13 (t, $J = 5.2$ Hz, 1H), 6.96 (d, $J = 1.5$ Hz, 1H), 6.93-6.79 (m, 4H), 6.72 (br d, $J = 8.2$ Hz, 1H), 6.01 (t, $J = 56.4$ Hz, 1H), 5.04 (dd, $J = 12.8, 5.4$ Hz, 1H), 4.03 (br d, $J = 4.8$ Hz, 1H), 3.32-3.13 (m, 11H), 3.03 (br s, 3H), 2.94-2.74 (m, 4H), 2.63-2.53 (m, 4H), 2.50-2.35 (m, 7H), 2.13-1.88 (m, 11H), 1.82-1.68 (m, 3H), 1.59 (br s, 4H), 1.28-1.25 (m, 2H), 0.86 (s, 6H); LC/MS (ESI) m/z 1304.5 $[\text{M-H}]^-$.

Example 14

(2S,4R)-1-((S)-2-(7-(4-((R)-3-((4-(N-(4-(4-((2-(3-ethylbicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-((trifluoromethyl)sulfonyl)phenyl)amino)-4-(phenylthio)butyl)piperazin-1-yl)-7-oxoheptanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide



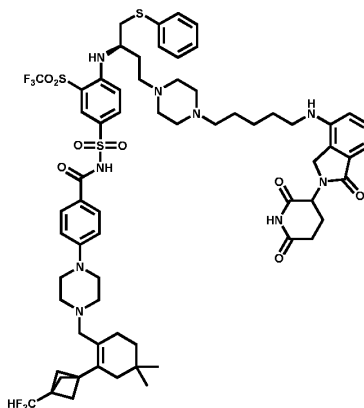
[0341] Step 1: To a stirred solution of heptanedioic acid (26 mg, 0.167 mmol) in DCM (5 mL) was added EDC•HCl (60 mg, 0.313 mmol) and DMAP (25 mg, 0.209 mmol). The resulting reaction mixture was stirred for 15 min. at rt and then **Intermediate 7** (200 mg, 0.209 mmol) and TEA 0.08 mL, 0.627 mmol) were added at rt. The reaction mixture was stirred at 40 °C for 16 h, and cooled to rt. The reaction mixture was diluted with 10% MeOH in DCM (20 mL) and washed with 10% CH₃CO₂H(aq.) (2 x 10 mL), water (2 x 10 mL), 5% NaCl solution (15 mL), dried over Na₂SO₄, filtered and concentrated. The crude product was triturated with Et₂O (10 mL) to afford (*R*)-7-(4-(3-((4-(N-(4-(4-((2-(3-ethylbicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-((trifluoromethyl)sulfonyl)phenyl)amino)-4-(phenylthio)butyl)piperazin-1-yl)-7-oxoheptanoic acid (**Example 14-1**) (190 mg) and used directly in the next step without further purification. LC/MS (ESI) *m/z* 1099.9 [M+H]⁺.

[0342] Step 2: To a stirred solution of **Example 14-1** (170 mg, 0.154 mmol) in DMF (5 mL) was added HATU (87 mg, 0.231 mmol) and DIPEA (0.13 mL, 0.77 mmol). The resulting reaction mixture was stirred for 30 min at rt and then cooled to 0 °C, and treated with (2*S*,4*R*)-1-((*S*)-2-amino-3,3-dimethylbutanoyl)-4-hydroxy-N-((*S*)-1-(4-(4-

methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide hydrochloride (74 mg, 0.154 mmol). The reaction mixture was warmed to rt and stirred for 16 h. The reaction mixture was then diluted with 10% MeOH in DCM (20 mL), washed with sat. aq. NaHCO₃ (2 x 15 mL), water (2 x 20 mL), 5% NaCl(aq.) (15 mL), dried over Na₂SO₄, filtered and concentrated. The crude product was purified by HPLC (60:40 to 40:60 10 mM NH₄CO₃H(aq.)/CH₃CN) to afford **Example 14** (40 mg, 17% yield). LC/MS (ESI) *m/z* 1525.6 [M+H]⁺.

Example 15

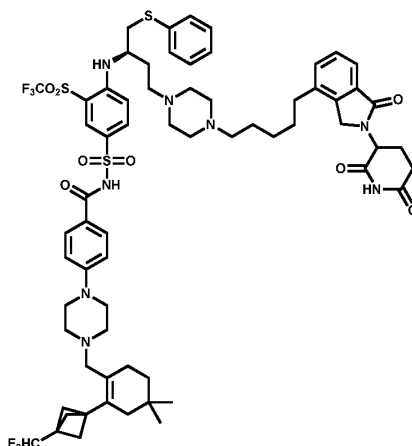
4-[4-[[2-[3-(difluoromethyl)-1-bicyclo[1.1.1] pentanyl]-4,4-dimethyl-cyclohexen-1-yl]methyl]piperazin-1-yl]-N-[4-[(1R)-3-[4-[5-[[2-(2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-4-yl]amino]pentyl]piperazin-1-yl]-1-(phenylsulfonylmethyl)propyl]amino]-3-(trifluoromethylsulfonyl)phenyl]sulfonyl-benzamide



[0343] To a solution of **Intermediate 19** (20 mg, 22.7 μ mol) in DCM (1 mL) was added **Intermediate 2** (12.1 mg, 27.3 μ mol), TEA (6.33 μ L, 45.5 μ mol), DMAP (2.78 mg, 22.73 μ mol) and EDCI (5.23 mg, 27.3 μ mol) at 20°C. The reaction was stirred at 20°C for 12 h and then concentrated and purified by HPLC (70:30 to 0:100 10 mM NH₄CO₃H(aq.)/CH₃CN) to afford **Example 15** (11 mg, 37% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.04 (s, 1H), 8.06 (d, *J* = 1.8 Hz, 1H), 8.00-7.92 (m, 1H), 7.73 (d, *J* = 8.8 Hz, 2H), 7.39-7.25 (m, 5H), 7.23-7.17 (m, 1H), 6.97-6.86 (m, 2H), 6.83 (br d, *J* = 8.8 Hz, 2H), 6.79-6.67 (m, 2H), 6.01 (t, *J* = 56.4 Hz, 1H), 5.61 (t, *J* = 5.2 Hz, 1H), 5.13 (dd, *J* = 13.1, 5.0 Hz, 1H), 4.26-4.08 (m, 2H), 4.02 (br d, *J* = 4.3 Hz, 1H), 3.33-3.25 (m, 4H), 3.22-3.09 (m, 6H), 3.04-2.88 (m, 4H), 2.64-2.60 (m, 5H), 2.43 (br s, 6H), 2.32-2.18 (m, 3H), 2.10-2.03 (m

Example 16

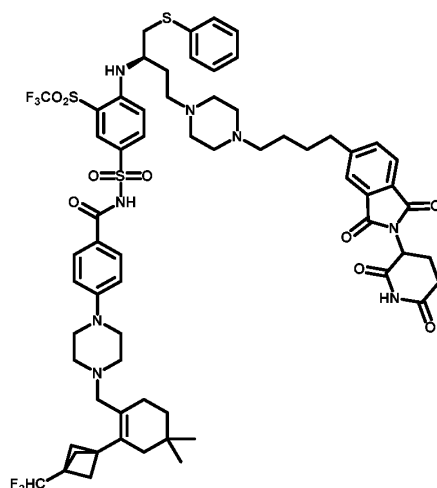
4-(4-((2-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-*N*-((4-(((2*R*)-4-(4-(5-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-4-yl)pentyl)piperazin-1-yl)-1-(phenylthio)butan-2-yl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide



-205-

Example 17

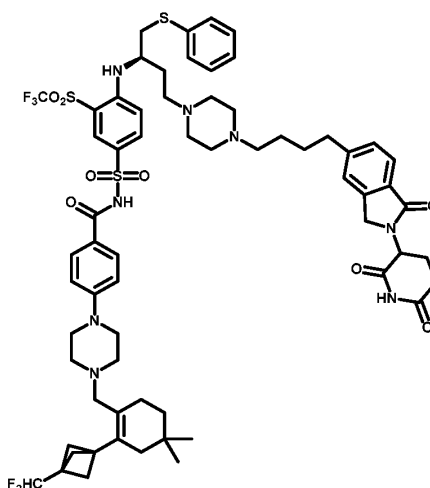
4-(4-((2-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-*N*-(((4-(((2*R*)-4-(4-(4-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)butyl)piperazin-1-yl)-1-(phenylthio)butan-2-yl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide



[0345] Example 17 was prepared following the procedure described in Example 16 using **Intermediate 21** in place of **Intermediate 20**. LC/MS (ESI) m/z 1291.4 $[M+H]^+$.

Example 18

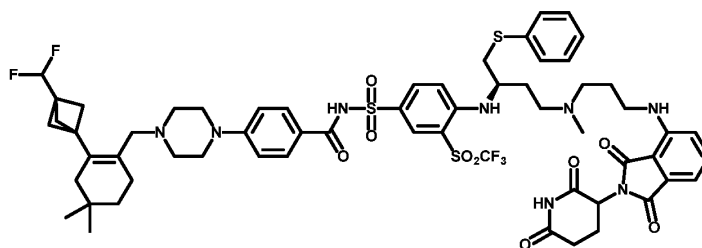
4-(4-((2-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-(((4-(((2*R*)-4-(4-(4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)butyl)piperazin-1-yl)-1-(phenylthio)butan-2-yl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide



[0346] Example 18 was prepared following the procedure described in Example 16 using **Intermediate 22** in place of **Intermediate 20**. LC/MS (ESI) m/z 1275.7 $[M-H]^-$.

Example 19

4-(4-((2-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethyl cyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-(((4-(((2*R*)-4-((3-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)amino)propyl)(methyl)amino)-1-(phenylthio)butan-2-yl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide

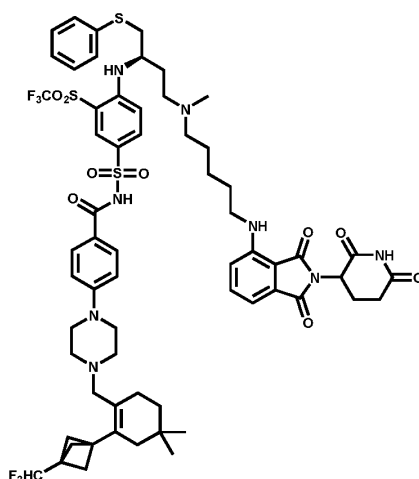


[0347] To a solution of **Intermediate 23** (30 mg, 37.0 μ mol) in DCM (1 mL) was added **Intermediate 2** (18.1 mg, 40.7 μ mol), DMAP (4.52 mg, 37.0 μ mol), TEA (10.30 μ L, 74.0 μ mol,) and EDCI (10.64 mg, 55.5 μ mol) at 20°C. The reaction was stirred at 20°C for 12 h and then concentrated and purified by HPLC (55:45 to 0:100 10 mM

$\text{NH}_4\text{CO}_3\text{H(aq.)}/\text{CH}_3\text{CN}$) to afford **Example 19** (8 mg, 18% yield). ^1H NMR (400MHz, $\text{DMSO-}d_6$) δ 11.10 (s, 1H), 8.09 (d, $J = 1.6$ Hz, 1H), 7.96 (br d, $J = 8.7$ Hz, 1H), 7.72 (d, $J = 8.7$ Hz, 2H), 7.57 (t, $J = 7.8$ Hz, 1H), 7.36-7.23 (m, 4H), 7.22-7.14 (m, 1H), 7.10-7.00 (m, 2H), 6.97-6.64 (m, 5H), 6.00 (t, $J = 56.4$ Hz, 1H), 5.05 (dd, $J = 12.8, 5.3$ Hz, 1H), 4.06-3.98 (m, 1H), 3.32-3.25 (m, 7H), 3.24-3.15 (m, 4H), 3.03 (br s, 3H), 2.89-2.80 (m, 3H), 2.56 (br s, 4H), 2.47-2.40 (m, 3H), 2.09-1.93 (m, 11H), 1.87-1.74 (m, 2H), 1.71 (br s, 2H), 1.31-1.23 (m, 2H), 1.20-1.12 (m, 1H), 0.86 (s, 6H); LC/MS (ESI) m/z 1235.4 $[\text{M-H}]^-$.

Example 20

4-(4-((2-(3-(difluoromethyl)bicyclo [1.1.1]pentan-1-yl)-4,4- dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-(((4-(((2R)-4- ((5-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)amino)pentyl)(methyl)amino)-1-(phenylthio)butan-2-yl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide

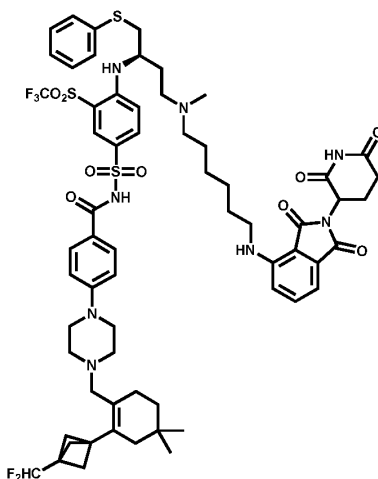


[0348] To a solution of **Intermediate 24** (80 mg, 95.4 μmol) in DCM (2 mL) were added **Intermediate 2** (46.6 mg, 104.9 μmol), EDCI (27.42 mg, 143.0 μmol), DMAP (11.65 mg, 95.4 μmol) and TEA (26.6 μL , 190.7 μmol) at 25°C. The reaction was stirred at 25°C for 12 h and then concentrated and purified by HPLC (40:60 to 0:100 10 mM $\text{NH}_4\text{CO}_3\text{H(aq.)}/\text{CH}_3\text{CN}$) to afford **Example 20** (40 mg, 33% yield). ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 11.10 (s, 1H), 8.09 (s, 1H), 7.97 (br d, $J = 8.8$ Hz, 1H), 7.72 (br d, $J = 8.7$ Hz, 2H), 7.57 (t, $J = 7.8$ Hz, 1H), 7.37-7.23 (m, 4H), 7.23-7.15 (m, 1H), 7.07 (d, $J = 8.7$ Hz, 1H), 7.02 (d, $J = 7.0$ Hz, 1H), 6.89 (br d, $J = 9.3$ Hz, 1H), 6.82 (br d, $J = 8.8$ Hz, 2H), 6.72 (br d, $J = 7.6$ Hz, 1H), 6.53 (t, $J = 5.5$ Hz, 1H), 6.00 (t, $J = 56.4$ Hz, 1H), 5.04 (dd, $J = 12.7, 5.3$ Hz,

1H), 4.01 (br d, $J = 5.0$ Hz, 1H), 3.29 (br d, $J = 8.2$ Hz, 7H), 3.18 (br s, 5H), 3.02 (br s, 3H), 2.95-2.81 (m, 3H), 2.75-2.73 (m, 1H), 2.59-2.51 (m, 3H), 2.44 (br s, 4H), 2.09-2.00 (m, 4H), 1.98 (s, 6H), 1.70 (br s, 2H), 1.57-1.53 (m, 4H), 1.35-1.21 (m, 4H), 0.86 (s, 6H); LC/MS (ESI) m/z 1263.5 [M-H]⁻.

Example 21

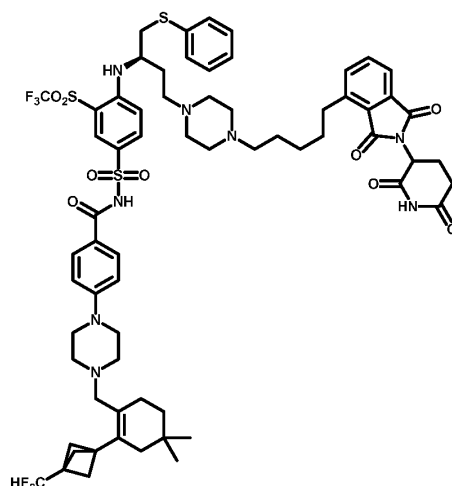
4-((4-((2-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-(((2R)-4-(((6-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)amino)hexyl)(methyl)amino)-1-(phenylthio)butan-2-yl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide



[0349] Example 21 was prepared following the procedure described in Example 20 using **Intermediate 25** in place of **Intermediate 24**. LC/MS (ESI) m/z 1277.5 [M-H]⁻.

Example 22

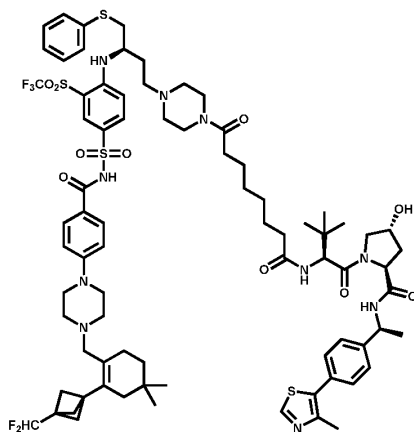
4-(4-((2-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-(((4-(((2R)-4-(4-(5-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)pentyl)piperazin-1-yl)-1-(phenylthio)butan-2-yl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide



[0350] **Example 22** was prepared following the procedure described for **Example 16** using **Intermediate 51** in place of **Intermediate 20**. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 11.11 (s, 1H), 9.00 (br s, 1H), 8.06 (s, 1H), 7.95 (d, $J = 8.0$ Hz, 1H), 7.80-7.68 (m, 5H), 7.35-7.19 (m, 5H), 6.89-6.78 (m, 3H), 6.69 (br s, 1H), 6.00 (t, $J = 56.4$ Hz, 1H), 5.12 (dd, $J = 12.8, 5.2$ Hz, 1H), 4.01 (br s, 1H), 3.21-2.84 (m, 15H), 2.69-2.51 (m, 6H), 2.49-2.33 (m, 8H), 2.08-1.98 (m, 10H), 1.82-1.49 (m, 7H), 1.33-1.24 (m, 4H), 0.85 (s, 6H); LC/MS (ESI) m/z 1305.4 $[\text{M}+\text{H}]^+$.

Example 23

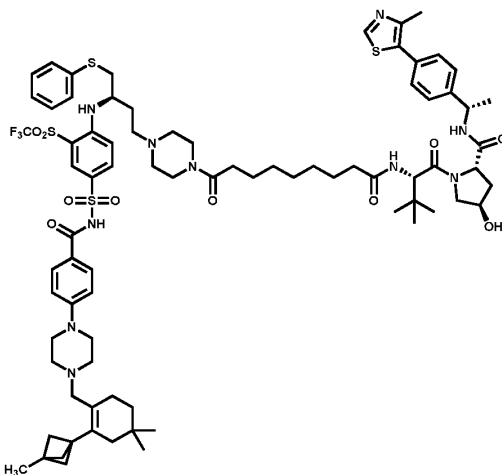
(2S,4R)-1-((S)-2-(8-(4-((R)-3-((4-(N-(4-(4-((2-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-((trifluoromethyl)sulfonyl)phenyl)amino)-4-(phenylthio)butyl)piperazin-1-yl)-8-oxooctanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide



[0351] Example 23 was prepared following the procedure described for Example 1 using Intermediate 26 in place of Intermediate 8. LC/MS (ESI) m/z 1559.5 [M-H]⁻.

Example 24

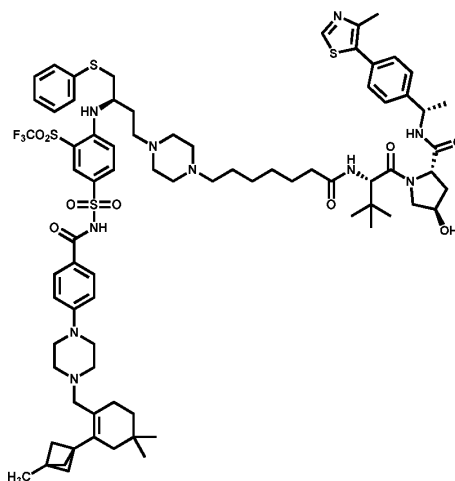
(2S,4R)-1-((S)-2-(9-(4-((R)-3-((4-(N-(4-(4-((4,4-dimethyl-2-(3-methylbicyclo[1.1.1]pentan-1-yl)cyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-((trifluoromethyl)sulfonyl)phenyl)amino)-4-(phenylthio)butyl)piperazin-1-yl)-9-oxononanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide



[0352] **Example 24** was prepared following the procedure described for **Example 9** using **Intermediate 27** in place of **Intermediate 16**. LC/MS (ESI) m/z 1537.6 [M-H]⁻.

Example 25

(2S,4R)-1-((S)-2-(7-(4-((R)-3-((4-(N-(4-(4-((4,4-dimethyl-2-(3-methylbicyclo[1.1.1]pentan-1-yl)cyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-((trifluoromethyl)sulfonyl)phenyl)amino)-4-(phenylthio)butyl)piperazin-1-yl)heptanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide

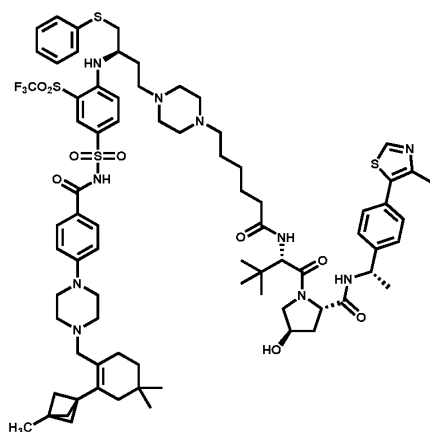


[0353] To a solution of **Intermediate 28** (60 mg, 94.4 μ mol) in dioxane (2 mL) was added **Intermediate 6** (89.0 mg, 94.4 μ mol), DIPEA (49.3 μ L, 283.2 μ mol) and NaI (1.41 mg, 9.44 μ mol) at 20 °C. The reaction mixture was heated to 100°C and stirred for 12 h and then cooled and concentrated. The crude product was purified by HPLC (60:40 to 20:80 10 mM $\text{NH}_4\text{CO}_3\text{H(aq.)}$ / CH_3CN) to afford **Example 25** (25 mg, 18% yield). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.98 (s, 1H), 8.36 (d, J = 7.6 Hz, 1H), 8.07 (s, 1H), 7.95 (br d, J = 8.6 Hz, 1H), 7.79 (br d, J = 9.5 Hz, 1H), 7.73 (d, J = 8.6 Hz, 2H), 7.45-7.40 (m, 2H), 7.40-7.32 (m, 4H), 7.29 (t, J = 7.4 Hz, 2H), 7.20 (d, J = 7.2 Hz, 1H), 6.91-6.77 (m, 3H), 6.70 (br d, J = 8.6 Hz, 1H), 5.10 (d, J = 2.9 Hz, 1H), 4.92 (s, 1H), 4.52 (d, J = 9.1 Hz, 1H), 4.42 (s, 1H), 4.28 (br s, 1H), 4.09-3.96 (m, 1H), 3.60 (br s, 2H), 3.28-3.12 (m, 7H), 3.05 (br s, 3H), 2.97-2.57 (m, 5H), 2.45 (s, 9H), 2.33-2.19 (m, 3H), 2.18-2.07 (m, 2H), 2.06-1.84 (m, 3H), 1.79 (s, 7H), 1.68 (br s, 2H), 1.56-1.43 (m, 4H), 1.37 (d, J = 7.2 Hz, 3H), 1.25 (br s, 6H), 1.11 (s, 3H), 0.94 (s, 9H), 0.84 (s, 6H); LC/MS (ESI) m/z 1495.7 $[\text{M}-\text{H}]^-$.

Example 26

(2S,4R)-1-((S)-2-(6-(4-((R)-3-((4-(N-(4-(4-((4,4-dimethyl-2-(3-methylbicyclo[1.1.1]pentan-1-yl)cyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-

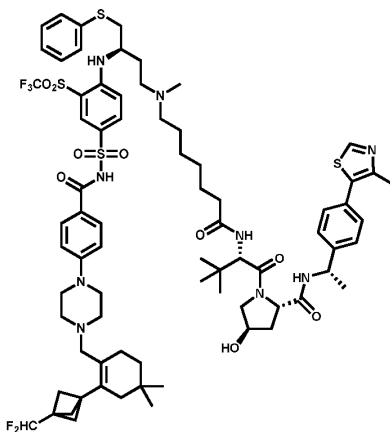
((trifluoromethyl)sulfonyl)phenyl)amino)-4-(phenylthio)butyl)piperazin-1-yl)hexanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide



[0354] **Example 26** was prepared following the procedure described for **Example 25** using **Intermediate 29** in place of **Intermediate 28**. LC/MS (ESI) m/z 1481.7 [M-H]⁻.

Example 27

(2S,4R)-1-((S)-2-(7-(((R)-3-((4-(N-(4-(4-((2-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-((trifluoromethyl)sulfonyl)phenyl)amino)-4-(phenylthio)butyl)(methyl)amino)heptanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide

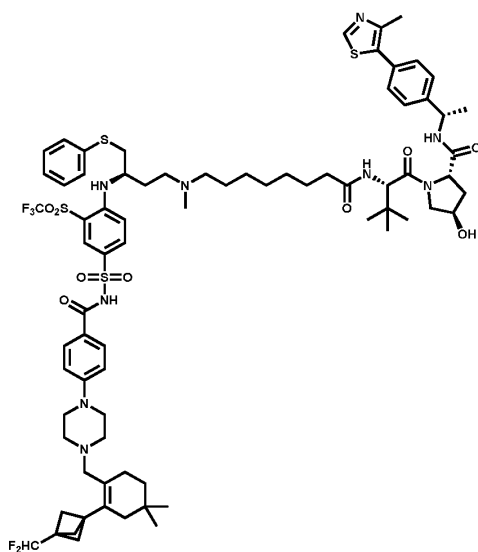


[0355] To a solution of **Intermediate 2** (35.5 mg, 79.8 μ mol) in DCM (0.5 mL) was added TEA (20.2 mg, 199.6 μ mol), **Intermediate 30** (70 mg, 66.5 μ mol), DMAP (8.13 mg, 66.5 μ mol) and EDCI (19.13 mg, 99.8 μ mol) at 25°C. The mixture was stirred at 25°C

for 12 h, concentrated and then purified by HPLC (40:60 to 10:90 10 mM $\text{NH}_4\text{CO}_3\text{H(aq.)}/\text{CH}_3\text{CN}$) to provide **Example 27** (50 mg, 51% yield). LC/MS (ESI) m/z 1476.6 $[\text{M-H}]^-$.

Example 28

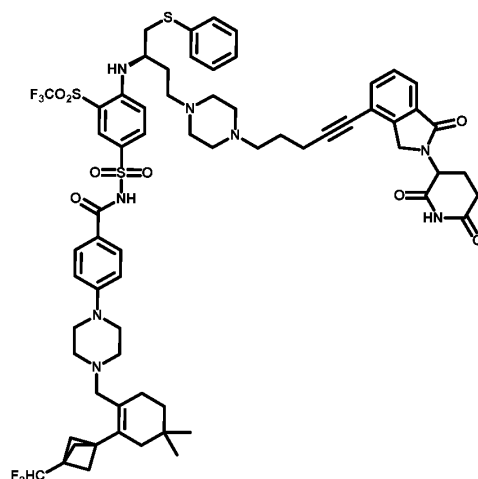
(2S,4R)-1-((S)-2-(8-(((R)-3-((4-(N-(4-(4-((2-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-((trifluoromethyl)sulfonyl)phenyl)amino)-4-(phenylthio)butyl)(methyl)amino)octanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide



[0356] Example 28 was prepared following the procedure described for **Example 27** using **Intermediate 31** in place of **Intermediate 30**. LC/MS (ESI) m/z 1490.6 [M-H]⁻.

Example 29

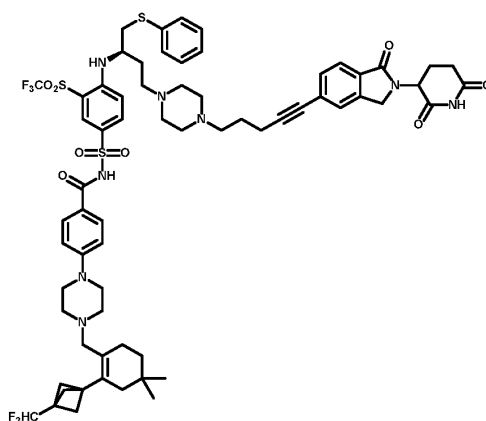
4-(4-((2-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-*N*-(((4-(((2*R*)-4-(4-(5-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-4-yl)pent-4-yn-1-yl)piperazin-1-yl)-1-(phenylthio)butan-2-yl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide



[0357] **Example 29** was prepared by following the procedure described for **Example 16** using **Intermediate 33** in place of **Intermediate 20**. LC/MS (ESI) m/z 1285.8 [M-H]⁻.

Example 30

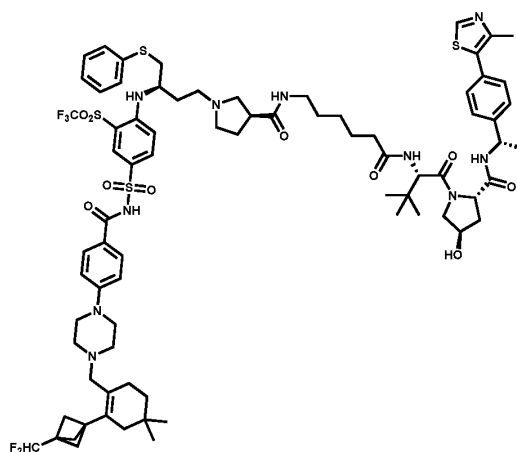
4-(4-((2-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-*N*-(((4-(((2*R*)-4-(4-(5-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)pent-4-yn-1-yl)piperazin-1-yl)-1-(phenylthio)butan-2-yl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide



[0358] **Example 30** was prepared by following the procedure described for **Example 16** using **Intermediate 32** in place of **Intermediate 20**. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.99 (s, 1H), 7.91 (d, $J = 8.0$ Hz, 1H), 7.73-7.64 (m, 4H), 7.51 (d, $J = 7.6$ Hz, 1H), 7.36-7.34 (m, 2H), 7.29 (t, $J = 8.0$ Hz, 2H), 7.19 (d, $J = 7.2$ Hz, 1H), 6.85-6.80 (m, 3H), 6.67 (d, $J = 7.2$ Hz, 1H), 6.00 (t, $J = 56.4$ Hz, 1H), 5.10 (dd, $J = 12.8, 4.8$ Hz, 1H), 4.38 (dd, $J = 17.2$ Hz, 2H), 4.00 (br s, 1H), 3.20-3.18 (m, 5H), 3.02-2.88 (m, 4H), 2.60-2.30 (m, 19H), 2.10-1.90 (m, 11H), 1.60 (br s, 5H), 1.28-1.24 (m, 3H), 0.86 (s, 6H); LC/MS (ESI) m/z 1287.97 $[\text{M}+\text{H}]^+$.

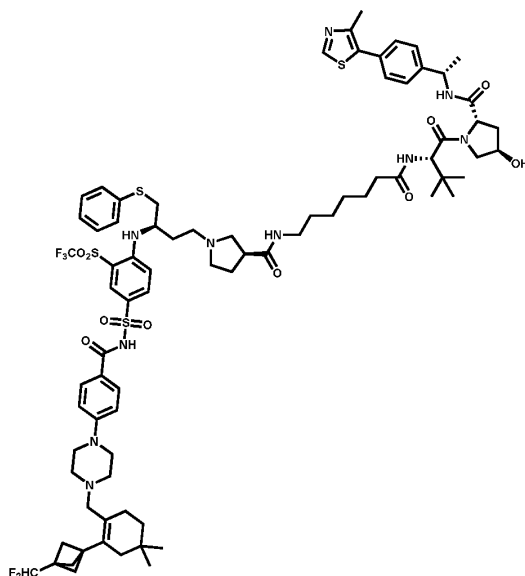
Example 31

(2S,4R)-1-((S)-2-(6-((S)-1-((R)-3-((4-(N-(4-(4-((2-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-((trifluoromethyl)sulfonyl)phenyl)amino)-4-(phenylthio)butyl)pyrrolidine-3-carboxamido)hexanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide



[0359] **Example 31** was prepared following the procedure described for **Example 19** using **Intermediate 34** in place of **Intermediate 23**. LC/MS (ESI) m/z 1545.6 $[\text{M}-\text{H}]^-$.

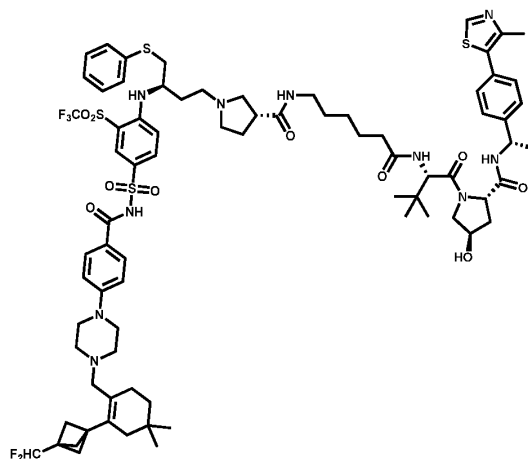
(2S,4R)-1-((S)-2-(7-((S)-1-((R)-3-((4-(N-(4-(4-((2-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-((trifluoromethyl)sulfonyl)phenyl)amino)-4-(phenylthio)butyl)pyrrolidine-3-carboxamido)heptanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide



-218-

Example 33

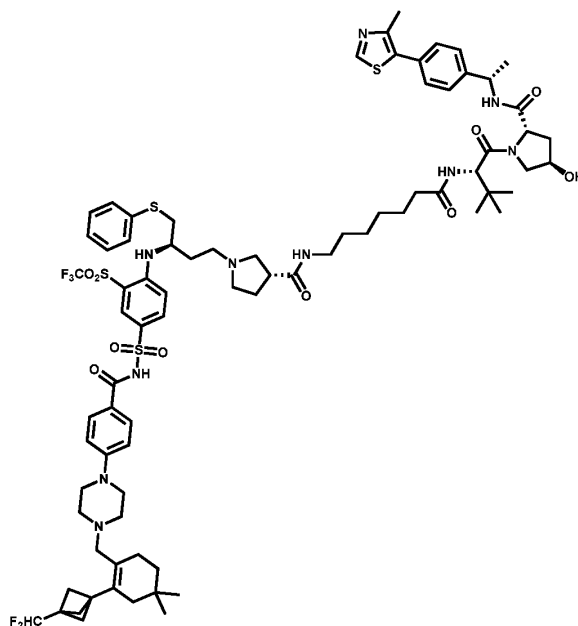
(2S,4R)-1-((S)-2-(6-((R)-1-((R)-3-((4-(N-(4-(4-((2-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-((trifluoromethyl)sulfonyl)phenyl)amino)-4-(phenylthio)butyl)pyrrolidine-3-carboxamido)hexanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide



[0361] **Example 33** was prepared following the procedure described for **Example 19** using **Intermediate 36** in place of **Intermediate 23**. LC/MS (ESI) m/z 1545.6 [M-H]⁻.

Example 34

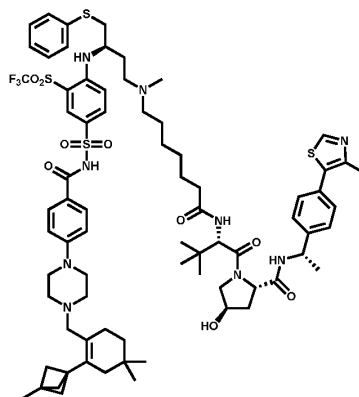
(2S,4R)-1-((S)-2-(7-((R)-1-((R)-3-((4-(N-(4-(4-((2-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-((trifluoromethyl)sulfonyl)phenyl)amino)-4-(phenylthio)butyl)pyrrolidine-3-carboxamido)heptanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide



[0362] **Example 34** was prepared following the procedure described for **Example 19** using **Intermediate 37** in place of **Intermediate 23**. LC/MS (ESI) m/z 1559.6 [M-H]⁻.

Example 35

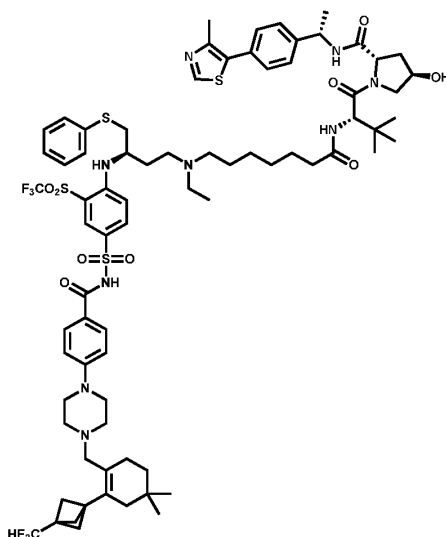
(2S,4R)-1-((S)-2-(7-(((R)-3-((4-(N-(4-(4-((4,4-dimethyl-2-(3-methylbicyclo[1.1.1]pentan-1-yl)cyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-((trifluoromethyl)sulfonyl)phenyl)amino)-4-(phenylthio)butyl)(methyl)amino)heptanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide



[0363] **Example 35** was prepared following the procedure described for **Example 27** using **Intermediate 1** in place of **Intermediate 2**. LC/MS (ESI) m/z 1440.6 [M-H]⁻.

Example 36

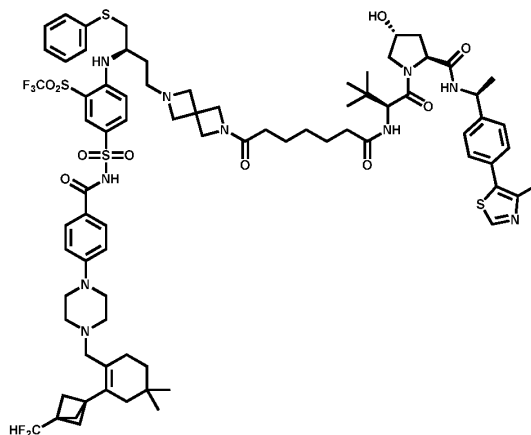
(2S,4R)-1-((S)-2-(7-(((R)-3-((4-(N-(4-(4-((2-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-((trifluoromethyl)sulfonyl)phenyl)amino)-4-(phenylthio)butyl)(ethyl)amino)heptanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide



[0364] **Example 36** was prepared following the procedure described for **Example 28** using **Intermediate 52** in place of **Intermediate 30**. LC/MS (ESI) m/z 1490.5 [M-H]⁻.

Example 37

(2S,4R)-1-((S)-2-(7-(6-((R)-3-((4-(N-(4-(4-((2-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-((trifluoromethyl)sulfonyl)phenyl)amino)-4-(phenylthio)butyl)-2,6-diazaspiro[3.3]heptan-2-yl)-7-oxoheptanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide



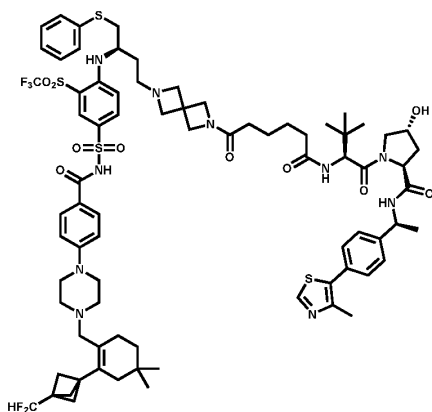
[0365] Step 1: **Intermediate 38** (0.48 g, 442.3 μmol) was dissolved in DCM/TFA (10:1, 10 mL) and stirred at rt for 12 h. The reaction mixture was then carefully poured into sat. aq. NaHCO_3 (20 mL) and extracted with DCM (2×15 mL). The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated. The crude product was purified by HPLC (80:20 to 50:50 water (0.04% HCl)/ CH_3CN) to afford the hydrochloride salt of (R)-4-(4-((2-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-((1-(phenylthio)-4-(2,6-diazaspiro[3.3]heptan-2-yl)butan-2-yl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide (**Example 37-1**) (0.38 g, 84% yield). LCMS (ESI) m/z 989.3 (M-H) $^-$.

[0366] Step 2: To a solution of **Example 37-1** (0.1 g, 97.4 μmol) in DMF (1 mL) was added **Intermediate 16** (59.2 mg, 100.9 μmol), DIPEA (65.2 mg, 504.4 μmol) and HATU (46.0 mg, 121.1 μmol) at 25°C. After 12 h, the reaction mixture was concentrated and purified by HPLC (60:40 to 10:90 10 mM $\text{NH}_4\text{CO}_3\text{H(aq.)}$ / CH_3CN) to afford **Example 37** (14.9 mg, 10% yield). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.98 (s, 1H), 8.36 (d, $J = 7.6$ Hz, 1H), 8.10 (s, 1H), 8.02-7.93 (m, 1H), 7.81-7.76 (m, 1H), 7.73 (d, $J = 8.6$ Hz, 2H), 7.46-7.41 (m, 2H), 7.40-7.32 (m, 4H), 7.32-7.26 (m, 2H), 7.20 (s, 1H), 6.86-6.82 (m, 4H), 6.01 (t, $J = 56.4$ Hz, 1H), 5.09 (d, $J = 3.3$ Hz, 1H), 4.97-4.85 (m, 1H), 4.51 (d, $J = 9.1$ Hz, 1H), 4.43-4.41

(m, 1H), 4.32-4.24 (m, 1H), 4.19 (br s, 2H), 3.98-3.92 (m, 5H), 3.62-3.60 (m, 2H), 3.31-3.14 (m, 8H), 3.11-2.91 (m, 3H), 2.49-2.46 (m, 8H), 2.25-2.24 (m, 1H), 2.14-2.02 (m, 4H), 2.02-1.93 (m, 9H), 1.85-1.75 (m, 3H), 1.71 (br s, 2H), 1.49-1.42 (m, 4H), 1.37 (d, $J = 7.2$ Hz, 3H), 1.30-1.20 (m, 4H), 0.93 (s, 9H), 0.86 (s, 6H); LCMS (ESI) m/z 1557.6 (M-H)⁻.

Example 38

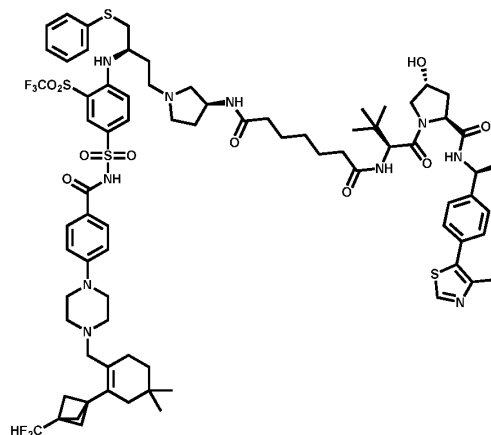
(2S,4R)-1-((S)-2-(6-(6-((R)-3-((4-(N-(4-(4-((2-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-((trifluoromethyl)sulfonyl)phenyl)amino)-4-(phenylthio)butyl)-2,6-diazaspiro[3.3]heptan-2-yl)-6-oxohexanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide



[0367] **Example 38** was prepared following the procedure described in step 2 for **Example 37** using **Intermediate 8** in place of **Intermediate 16**. LC/MS (ESI) m/z 1543.6 [M+H]⁺.

Example 39

N1-((S)-1-((R)-3-((4-(N-(4-(4-((2-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-((trifluoromethyl)sulfonyl)phenyl)amino)-4-(phenylthio)butyl)pyrrolidin-3-yl)-N7-((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)heptanediamide



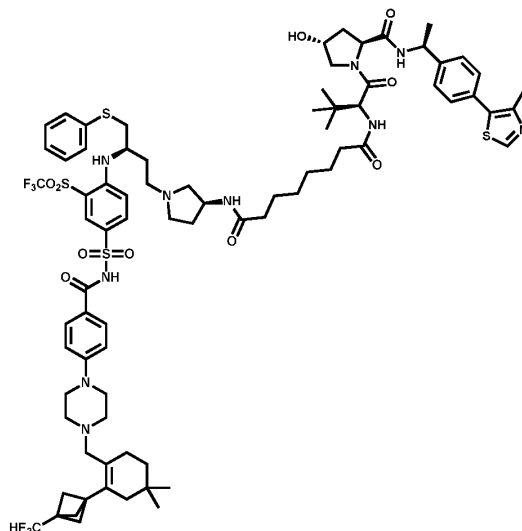
[0368] Step 1: **Intermediate 39** (0.6 g, 555.9 μ mol) was treated with HCl (4M in EtOAc, 15 mL) and stirred at rt. After the reaction was completed, the reaction was concentrated and then dissolved in water (15 mL). The pH of the aqueous layer was adjusted to pH = 8 using sat. aq. NaHCO_3 and then extracted with EtOAc (3×20 mL). The combined organic layers were dried over Na_2SO_4 and filtered. The filtrate was concentrated to afford the hydrochloride salt of N-[4-[(1R)-3-[(3S)-3-aminopyrrolidin-1-yl]-1-(phenylsulfanylmethyl)propyl]amino]-3-(trifluoromethylsulfonyl)phenyl]sulfonyl-4-[4-[2-[3-(difluoromethyl)-1-bicyclo[1.1.1]pentanyl]-4,4-dimethyl-cyclohexen-1-yl]methyl]piperazin-1-yl]benzamide (**Example 39-1**) (0.5 g, 89% yield). LCMS (ESI) m/z 977.4 (M-H)⁻,

[0369] Step 2: **Example 39** was prepared following the procedure described in step 2 for **Example 37** using **Intermediate 39-1** in place of **Intermediate 37-1**. LC/MS (ESI) m/z 1545.6 (M-H)⁻.

Example 40

N1-((S)-1-((R)-3-((4-(N-(4-(4-((2-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-((trifluoromethyl)sulfonyl)phenyl)amino)-4-(phenylthio)butyl)pyrrolidin-3-yl)-N8-((S)-1-

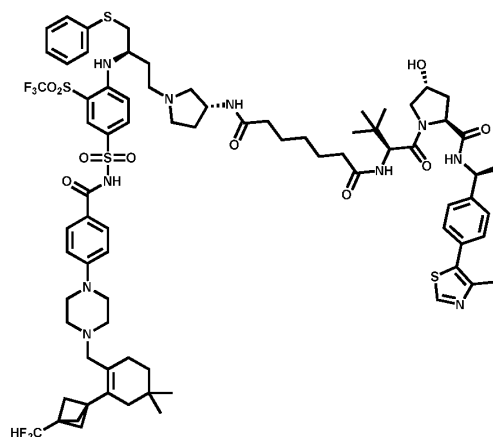
((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)octanediamide



[0370] **Example 40** was prepared following the procedure described in Step 2 for **Example 37** using **Intermediate 39-1** in place of **Intermediate 37-1** and **Intermediate 26** in place of **Intermediate 16**. LC/MS (ESI) m/z 1559.6 [M-H]⁻

Example 41

N1-((R)-1-((R)-3-((4-(N-(4-(4-((2-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-((trifluoromethyl)sulfonyl)phenyl)amino)-4-(phenylthio)butyl)pyrrolidin-3-yl)-N7-((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)heptanediamide

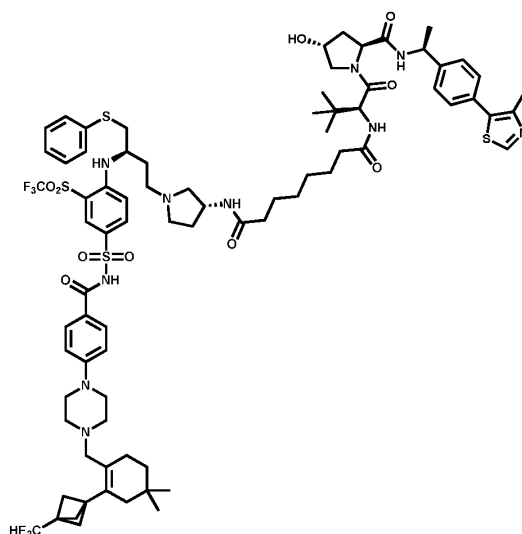


[0371] Step 1: N-[4-[[[(1R)-3-[(3S)-3-aminopyrrolidin-1-yl]-1-(phenylsulfanylmethyl)propyl]amino]-3-(trifluoromethylsulfonyl)phenyl]sulfonyl-4-[4-[[2-[3-(difluoromethyl)-1-bicyclo[1.1.1]pentanyl]-4,4-dimethyl-cyclohexen-1-yl]methyl]piperazin-1-yl]benzamide (**Example 41-1**) was prepared following the procedure described in step 1 for **Example 37** using **Intermediate 40** in place of **Intermediate 38**. LCMS (ESI) m/z 979.3 $[M+H]^+$.

[0372] Step 2: **Example 41** was prepared following the procedure described in step 2 for **Example 37** using **Intermediate 41-1** in place of **Intermediate 37-1**. LC/MS (ESI) m/z 1545.6 $(M-H)^-$.

Example 42

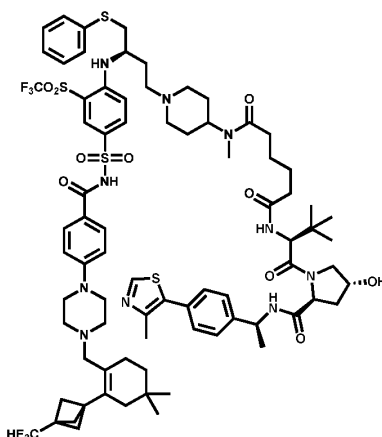
N1-((R)-1-((R)-3-((4-(N-(4-(4-((2-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-((trifluoromethyl)sulfonyl)phenyl)amino)-4-(phenylthio)butyl)pyrrolidin-3-yl)-N8-((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)octanediamide



[0373] **Example 42** was prepared following the procedure described in Step 2 for **Example 37** using **Intermediate 41-1** in place of **Intermediate 37-1** and **Intermediate 26** in place of **Intermediate 16**. LC/MS (ESI) m/z 1559.6 $[M-H]^+$.

Example 43

N1-(1-((R)-3-((4-(N-(4-(4-((2-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-((trifluoromethyl)sulfonyl)phenyl)amino)-4-(phenylthio)butyl)piperidin-4-yl)-N6-((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)-N1-methyladipamide

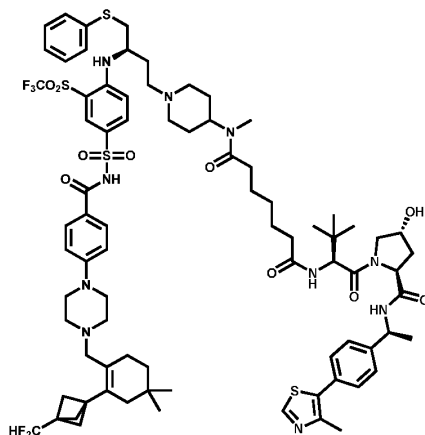


[0374] Step 1: 4-[4-[[2-[3-(difluoromethyl)-1-bicyclo[1.1.1]pentanyl]-4,4-dimethyl-cyclohexen-1-yl]methyl]piperazin-1-yl]-N-[4-[[1-(1R)-3-[4-(methylamino)-1-piperidyl]-1-(phenylsulfanylmethyl)propyl]amino]-3-(trifluoromethylsulfonyl)phenyl]sulfonyl-benzamide (**Example 43-1**) was prepared following the procedure described in Step 1 for **Example 39** using **Intermediate 40** in place of **Intermediate 39**. LCMS (ESI) m/z 1005.5 (M-H)⁺.

[0375] Step 2: **Example 43** was prepared following the procedure described in Step 2 for **Example 37** using **Example 43-1** in place of **Example 37-1**. LC/MS (ESI) m/z 1559.7 (M-H)⁺.

Example 44

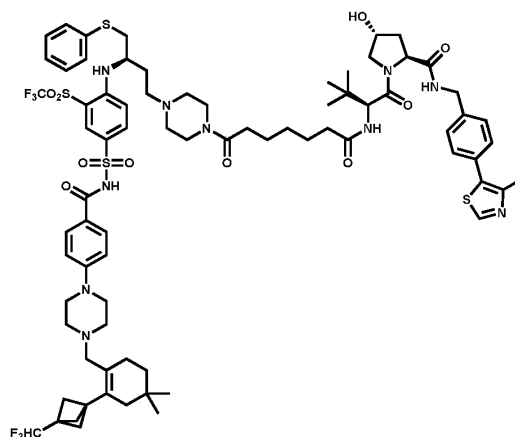
N1-(1-((R)-3-((4-(N-(4-(4-((2-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-((trifluoromethyl)sulfonyl)phenyl)amino)-4-(phenylthio)butyl)piperidin-4-yl)-N7-((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)-N1-methylheptanediamide



[0376] **Example 44** was prepared following the procedure described in Step 2 for **Example 37** using **Example 43-1** in place of **Example 37-1**. LC/MS (ESI) m/z 1573.7 [M-H]⁻.

Example 45

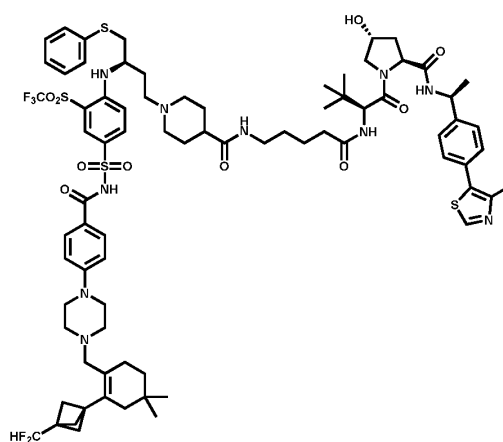
(2S,4R)-1-((S)-2-(7-(4-((R)-3-((4-(N-(4-(4-((2-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-((trifluoromethyl)sulfonyl)phenyl)amino)-4-(phenylthio)butyl)piperazin-1-yl)-7-oxoheptanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide



[0377] **Example 45** was prepared following the procedure described for **Example 1** using **Intermediate 42** in place of **Intermediate 8**. LC/MS (ESI) m/z 1531.6 $[M-H]^-$.

Example 46

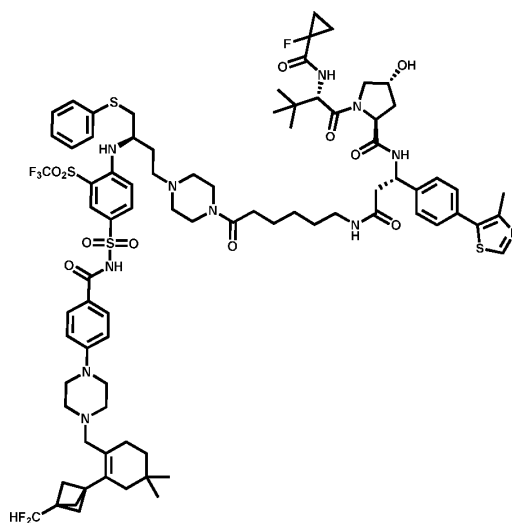
1-((R)-3-((4-(N-(4-(4-((2-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-((trifluoromethyl)sulfonyl)phenyl)amino)-4-(phenylthio)butyl)-N-(5-(((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-5-oxopentyl)piperidine-4-carboxamide



[0378] **Example 46** was prepared following the procedure described for **Example 19** using **Intermediate 43** in place of **Intermediate 23**. LC/MS (ESI) m/z 1545.6 [M-H]⁻.

Example 47

(2S,4R)-N-((S)-3-((6-(4-((R)-3-((4-(N-(4-(4-((2-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-((trifluoromethyl)sulfonyl)phenyl)amino)-4-(phenylthio)butyl)piperazin-1-yl)-6-oxohexyl)amino)-1-(4-(4-methylthiazol-5-yl)phenyl)-3-oxopropyl)-1-((S)-2-(1-fluorocyclopropanecarboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamide



[0379] Step 1: To a mixture of **Intermediate 5** (1 g, 1.02 mmol) in DMF (10 mL) was added 6-(tert-butoxycarbonylamino) hexanoic acid (472.4 mg, 2.04 mmol), DIPEA (711.5 μ L, 4.08 mmol) and HATU (466 mg, 1.23 mmol) at 20°C. After 12 h, the reaction was concentrated and purified by HPLC (45:55 to 15:85 10 mM NH₄CO₃H(aq.)/CH₃CN) to afford (R)-tert-butyl (6-(4-(3-((4-(N-(4-(4-((2-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-((trifluoromethyl)sulfonyl)phenyl)amino)-4-(phenylthio)butyl)piperazin-1-yl)-6-oxohexyl)carbamate (**Example 47-1**) (0.5 g, 41% yield). LCMS (ESI) m/z 1190.8 (M-H)⁻.

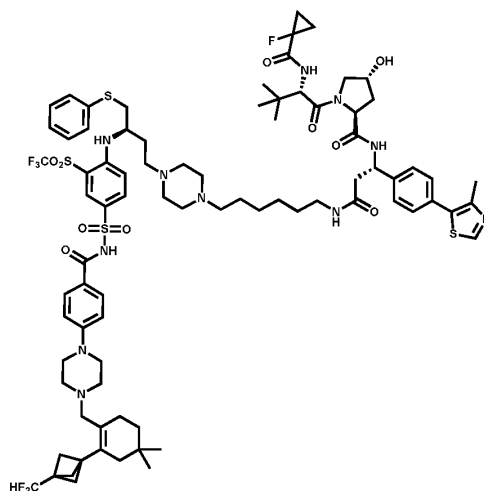
[0380] Step 2: **Example 47-1** (0.5 g, 419.3 μ mol) was treated with HCl (4M in dioxane, 10 mL) at rt and stirred for 12 h. The reaction mixture was then concentrated to provide (R)-N-((4-((4-(4-(6-aminohexanoyl)piperazin-1-yl)-1-(phenylthio)butan-2-yl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)-4-(4-((2-(3-

(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzamide hydrochloride (**Example 47-2**) (0.415 g, 88% yield). LCMS (ESI) m/z 1090.8 (M-H)⁻.

[0381] Step 3: To a solution of **Intermediate 45** (0.03 g, 52.20 μ mol) in DMF (1 mL) was added DIPEA (45.5 μ L, 261.02 μ mol), **Example 47-2** (60.00 mg, 54.93 μ mol) and HATU (23.82 mg, 62.7 μ mol) at 25°C. After 12 h, the reaction mixture was poured into water (2 mL) and extracted with EtOAc (3 $\times$ 2 mL). The combined organic layers were washed with brine (5 mL), dried over Na₂SO₄, filtered and concentrated. The crude product was purified by HPLC (55:45 to 30:70 10 mM NH₄CO₃H(aq.)/CH₃CN) to give **Example 47** (0.04 g, 47% yield). LCMS (ESI) m/z 1646.6 (M-H)⁻.

Example 48

(2S,4R)-N-[(1S)-3-[6-[4-[(3R)-3-[4-[[4-[4-[[2-[3-(difluoromethyl)-1-bicyclo[1.1.1]pentanyl]-4,4-dimethyl-cyclohexen-1-yl]methyl]piperazin-1-yl]benzoyl]sulfamoyl]-2-(trifluoromethylsulfonyl)anilino]-4-phenylsulfanyl-butyl]piperazin-1-yl]hexylamino]-1-[4-(4-methylthiazol-5-yl)phenyl]-3-oxo-propyl]-1-[(2S)-2-[(1-fluorocyclopropanecarbonyl)amino]-3,3-dimethyl-butanoyl]-4-hydroxy-pyrrolidine-2-carboxamide



[0382] Step 1: To a solution of **Intermediate 5** (1 g, 1.02 mmol) in DMF (5 mL) was added DIPEA (264 mg, 2.04 mmol) and 6-(tert-butoxycarbonylamino)hexyl 4-methylbenzenesulfonate (758.8 mg, 2.04 mmol) at 20°C. The reaction was heated to 90°C for 12 h and then cooled to rt and purified directly by HPLC (40:60 to 20:80 10 mM NH₄CO₃H(aq.)/CH₃CN) to afford tert-butyl N-[6-[4-[(3R)-3-[4-[[4-[4-[[2-[3-

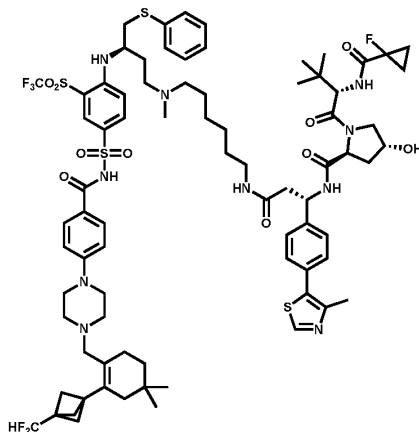
(difluoromethyl)-1-bicyclo[1.1.1]pentanyl]-4,4-dimethyl-cyclohexen-1-yl)methyl]piperazin-1-yl]benzoyl]sulfamoyl]-2-(trifluoromethylsulfonyl)anilino]-4-phenylsulfanyl-butyl]piperazin-1-yl]hexyl]carbamate (**Example 48-1**) (0.5 g, 42% yield).
LCMS (ESI) m/z 1178.2 (M+H)⁺.

[0383] Step 2: **Example 48-1** (0.5 g, 424.3 μ mol) was treated with HCl (4M in EtOAc, 10 mL) at 20°C and stirred for 2 h. The reaction was then concentrated to afford N-[4-[(1R)-3-[4-(6-aminohexyl)piperazin-1-yl]-1-(phenylsulfanylmethyl)propyl]amino]-3-(trifluoromethylsulfonyl)phenyl]sulfonyl-4-[4-[[2-[3-(difluoromethyl)-1-bicyclo[1.1.1]pentanyl]-4,4-dimethyl-cyclohexen-1-yl)methyl]piperazin-1-yl]benzamide hydrochloride (**Example 48-2**) (0.3 g, 66% yield). LCMS (ESI) m/z 1078.5 (M+H)⁺.

[0384] Step 3: **Example 48** was prepared following the procedure described in step 3 for **Example 47** using **Example 48-2** in place of **Example 47-2**. LC/MS (ESI) m/z 1632.7 (M-H)⁻.

Example 49

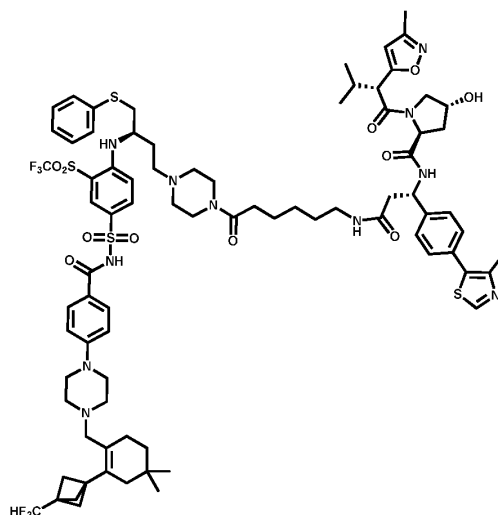
(2S,4R)-N-[(1S)-3-[6-[[[(3R)-3-[4-[[4-[4-[[2-[3-(difluoromethyl)-1-bicyclo[1.1.1]pentanyl]-4,4-dimethyl-cyclohexen-1-yl)methyl]piperazin-1-yl]benzoyl]sulfamoyl]-2-(trifluoromethylsulfonyl)anilino]-4-phenylsulfanyl-butyl]-methyl-amino]hexylamino]-1-[4-(4-methylthiazol-5-yl)phenyl]-3-oxo-propyl]-1-[(2S)-2-[(1-fluorocyclopropanecarbonyl)amino]-3,3-dimethyl-butanoyl]-4-hydroxy-pyrrolidine-2-carboxamide



[0385] **Example 49** was prepared following the procedure described for **Example 27** using **Intermediate 46** in place of **Intermediate 30**. LC/MS (ESI) m/z 1577.6 [M-H]⁻.

Example 50

(2S,4R)-N-((S)-3-((6-(4-((R)-3-((4-(N-(4-(4-((2-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-((trifluoromethyl)sulfonyl)phenyl)amino)-4-(phenylthio)butyl)piperazin-1-yl)-6-oxohexyl)amino)-1-(4-(4-methylthiazol-5-yl)phenyl)-3-oxopropyl)-4-hydroxy-1-((R)-3-methyl-2-(3-methylisoxazol-5-yl)butanoyl)pyrrolidine-2-carboxamide



[0386] Step 1: To a solution of **Intermediate 5** (1 g, 1.02 mmol) in DMF (10 mL) was added 6-(tert-butoxycarbonylamino) hexanoic acid (472.4 mg, 2.04 mmol), DIPEA (711.5 μ L, 4.08 mmol) and HATU (466.0 mg, 1.23 mmol) at 20 °C. The reaction mixture was stirred at 20 °C for 12 h, concentrated and then purified by HPLC (45:55 to 15:85, 10 mM $\text{NH}_4\text{CO}_3\text{H(aq.)}/\text{CH}_3\text{CN}$) to provide (R)-tert-butyl (6-(4-(3-((4-(N-(4-(4-((2-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-((trifluoromethyl)sulfonyl)phenyl)amino)-4-(phenylthio)butyl)piperazin-1-yl)-6-oxohexyl)carbamate (**Examples 50-1**) (0.5 g, 41% yield). LC/MS (ESI) m/z 1190.8 (M-H)⁺.

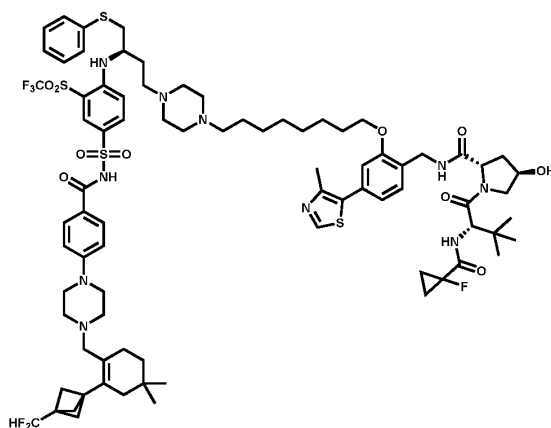
[0387] Step 2: **Example 50-1** (0.5 g, 419.3 μ mol) was treated with HCl (4M in dioxane, 10 mL) at rt and the resulting reaction mixture was stirred for 12 h. The reaction mixture was then concentrated under reduced pressure to provide (R)-N-((4-((4-(4-(6-aminohexanoyl)piperazin-1-yl)-1-(phenylthio)butan-2-yl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)-4-(4-((2-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-

yl)methyl)piperazin-1-yl)benzamide hydrochloride (**Example 50-2**) (0.415 g, 88% yield). The crude product was used in the next step without further purification. LC/MS (ESI) m/z 1090.8 (M-H)⁻.

[0388] Step 3: To a solution of **Example 50-2** (60 mg, 54.93 μ mol) in DCM (1 mL) was added **Intermediate 53A** (29.7 mg, 54.9 μ mol), DIPEA (47.8 μ L, 274.64 μ mol) and HATU (25.1 mg, 65.91 μ mol) at 20°C. The reaction mixture was stirred at 20°C for 12 h and then concentrated and purified by HPLC (55:45 to 35:65 10 mM NH₄CO₃H(aq.)/CH₃CN) to provide **Example 50** (19 mg, 22% yield). LCMS (ESI) m/z 1612.6 (M-H)⁻.

Example 51

(2S,4R)-N-(2-((8-(4-((R)-3-((4-(N-(4-(4-((2-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-((trifluoromethyl)sulfonyl)phenyl)amino)-4-(phenylthio)butyl)piperazin-1-yl)octyl)oxy)-4-(4-methylthiazol-5-yl)benzyl)-1-((S)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamide



[0389] Step 1: To a solution of 8-hydroxyoctyl 4-methylbenzenesulfonate (78.2 mg, 260.4 μ mol) in dioxane (2 mL) was added DIPEA (60.5 μ L, 347.22 μ mol), **Intermediate 5** (0.17 g, 173.61 μ mol) and NaI (2.60 mg, 17.36 μ mol) at 20°C. The reaction mixture was warmed to 90°C and stirred for 12 h at which point the reaction was cooled to rt and concentrated. The crude product was purified by HPLC (45:55 to 15:85 water (0.04% HCl)/CH₃CN) to afford 4-[4-[[2-[3-(difluoromethyl)-1-bicyclo[1.1.1]pentanyl]-4,4-dimethylcyclohexen-1-yl]methyl]piperazin-1-yl]-N-[4-[(1R)-3-[4-(8-hydroxyoctyl)piperazin-1-yl]-1-

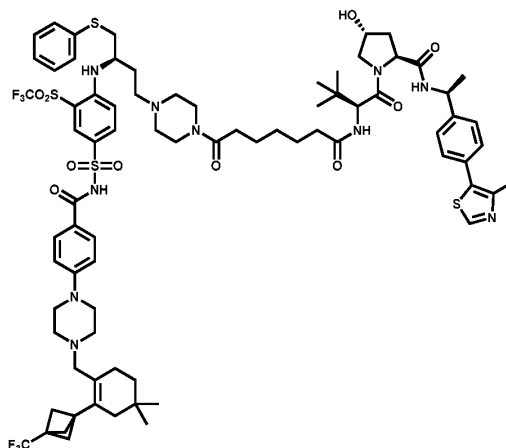
(phenylsulfanylmethyl)propyl]amino]-3-(trifluoromethylsulfonyl)phenyl]sulfonyl-benzamide (**Example 51-1**) (0.06 g, 31% yield). LCMS (ESI) m/z 1105.4 (M-H)⁻.

[0390] Step 2: To a solution of **Example 51-1** (0.06 g, 54.18 μ mol) in DCM (0.1 mL) was added MsCl (5.03 μ L, 65.02 μ mol) and TEA (15.1 μ L, 108.4 μ mol) at 0°C. The reaction was stirred at 25°C for 12 h and then concentrated. The crude product was purified by HPLC (40:60 to 10:90 10 mM NH₄CO₃H(aq.)/CH₃CN) to afford 8-[4-[(3R)-3-[4-[[4-[4-[[2-[3-(difluoromethyl)-1-bicyclo[1.1.1]pentanyl]-4,4-dimethyl-cyclohexen-1-yl]methyl]piperazin-1-yl]benzoyl]sulfamoyl]-2-(trifluoromethylsulfonyl)anilino]-4-phenylsulfanyl-butyl]piperazin-1-yl]octyl methanesulfonate (**Example 51-2**) (0.03 g, 90% purity, 43% yield). LCMS (ESI) m/z 1183.3 (M-H)⁻.

[0391] Step 3: To a solution of **Example 51-2** (0.025 g, 19.03 μ mol) in DMF (1 mL) was added K₂CO₃ (4.37 mg, 31.64 μ mol) and (2S,4R)-1-[(2S)-2-[(1-fluorocyclopropanecarbonyl) amino]-3,3-dimethyl-butanoyl]-4-hydroxy-N-[[2-hydroxy-4-(4-methylthiazol-5-yl)phenyl]methyl]pyrrolidine-2-carboxamide (0.03 g, 56.3 μ mol) and at 25°C. The reaction was stirred at 60°C for 12 h, cooled to rt, and then filtered. The filtrate was concentrated and purified by HPLC (30:70 to 10:90 10 mM NH₄CO₃H(aq.)/CH₃CN) to give **Example 51** (23 mg, 72% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.98 (s, 1H), 8.51-8.48 (m, 1H), 8.10-8.05 (m, 1H), 7.99-7.87 (m, 1H), 7.76-7.67 (m, 2H), 7.43-7.37 (m, 1H), 7.36-7.32 (m, 2H), 7.32-7.25 (m, 3H), 7.22-7.15 (m, 1H), 7.02-6.98 (m, 1H), 6.97-6.92 (m, 1H), 6.90-6.84 (m, 1H), 6.84-6.78 (m, 2H), 6.71-6.64 (m, 1H), 6.00 (t, *J* = 56.8 Hz, 1H), 5.18 (d, *J* = 3.6 Hz, 1H), 4.59 (d, *J* = 9.3 Hz, 1H), 4.52 (t, *J* = 8.2 Hz, 1H), 4.36-4.21 (m, 3H), 4.06-4.02 (m, 3H), 3.69-3.56 (m, 2H), 3.30-3.24 (m, 4H), 3.17 (br s, 5H), 3.00 (br s, 3H), 2.48-2.36 (m, 10H), 2.15-2.02 (m, 4H), 2.00-1.85 (m, 9H), 1.83-1.63 (m, 6H), 1.59-1.37 (m, 6H), 1.36-1.14 (m, 12H), 0.95 (s, 9H), 0.85 (s, 6H); LCMS (ESI) m/z 1619.7 (M-H)⁻.

Example 52

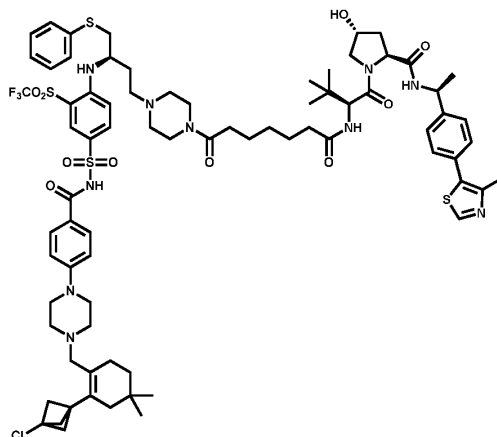
(2S,4R)-1-(2-(7-(4-((R)-3-((4-(N-(4-(4-((4,4-dimethyl-2-(3-(trifluoromethyl) bicyclo[1.1.1] pentan-1-yl)cyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-((trifluoromethyl)sulfonyl)phenyl)amino)-4-(phenylthio)butyl)piperazin-1-yl)-7-oxoheptanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide



[0392] To a stirred solution of **Intermediate 16** (88 mg, 0.15 mmol) in DCM (5 mL) was added HATU (62 mg, 0.16 mmol), **Intermediate 47** (150 mg, 0.150 mmol) and TEA (0.10 mL, 0.75 mmol) and the resulting reaction mixture was stirred for 16 h at rt. The reaction was then diluted with DCM (30 mL), washed with ice cold water (2 x 20 mL) followed by brine (2 x 20 mL), dried over Na₂SO₄, filtered and concentrated. The crude product was purified by HPLC (70:30 to 10:90 10 mM NH₄CO₃H(aq.)/CH₃CN) followed by achiral SFC separation (YMC PAK-DIOL (20x250) mm, 5 μ , 40% (CH₃CN:*i*PrOH) to afford **Example 52** (12 mg, 5% yield). ¹H NMR (400 MHz, CDCl₃) δ 8.67 (s, 1H), 8.36 (d, *J* = 2.0 Hz, 1H), 8.10 (d, *J* = 9.2, *J* = 2.0 Hz, 1H), 7.66 (d, *J* = 8.8 Hz, 2H), 7.57-7.26 (m, 10H), 7.13 (d, *J* = 8.8 Hz, 1H), 6.82 (d, *J* = 8.8 Hz, 2H), 6.62 (d, *J* = 9.2 Hz, 1H), 6.21 (d, *J* = 8.8 Hz, 1H), 5.11-5.04 (m, 1H), 4.75 (t, *J* = 8.0 Hz, 1H), 4.59 (d, *J* = 8.8 Hz, 1H), 5.00 (br s, 1H), 4.13 (d, *J* = 11.2 Hz, 1H), 3.91-3.85 (m, 1H), 3.64-3.61 (m, 1H), 3.56 (dd, *J* = 11.2, *J* = 3.2 Hz, 1H), 3.42-3.27 (m, 8H), 3.13-3.08 (m, 1H), 3.03-2.98 (m, 3H), 2.59-2.06 (m, 28H), 1.70-1.62 (m, 5H), 1.48-1.43 (m 3H), 1.33-1.25 (m, 5H), 1.04 (s, 9H), 0.88 (s, 6H); LC/MS (ESI) *m/z* 1563.7 [M-H]⁻.

Example 53

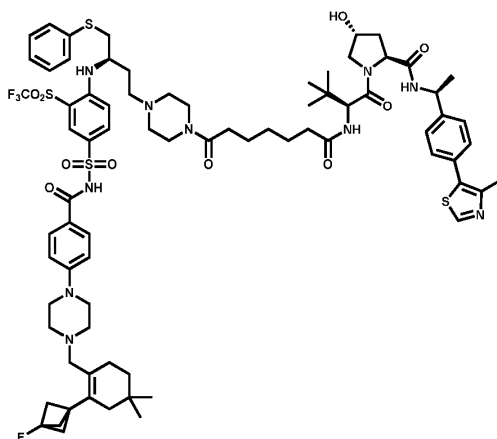
(2S,4R)-1-(2-(7-(4-((R)-3-((4-(N-(4-(4-((2-(3-chlorobicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-((trifluoromethyl)sulfonyl)phenyl)amino)-4-(phenylthio)butyl)piperazin-1-yl)-7-oxoheptanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide



[0393] **Example 53** was prepared following the procedure described for **Example 52** using **Intermediate 48** in place of **Intermediate 47**. LC/MS (ESI) *m/z* 1531.9 [M+H]⁺.

Example 54

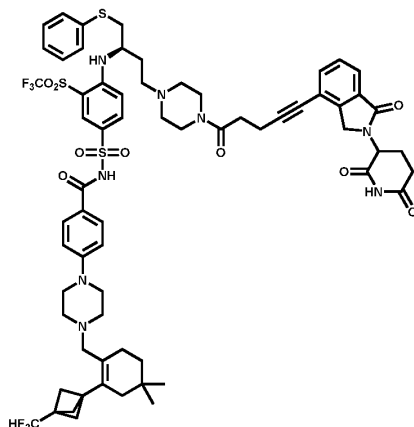
(2S,4R)-1-(2-(7-(4-((R)-3-((4-(N-(4-(4-((2-(3-fluorobicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-((trifluoromethyl)sulfonyl)phenyl)amino)-4-(phenylthio)butyl)piperazin-1-yl)-7-oxoheptanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide



[0394] **Example 54** was prepared following the procedure described for **Example 52** using **Intermediate 49** in place of **Intermediate 47**. LC/MS (ESI) m/z 1515.7 $[M+H]^+$.

Example 55

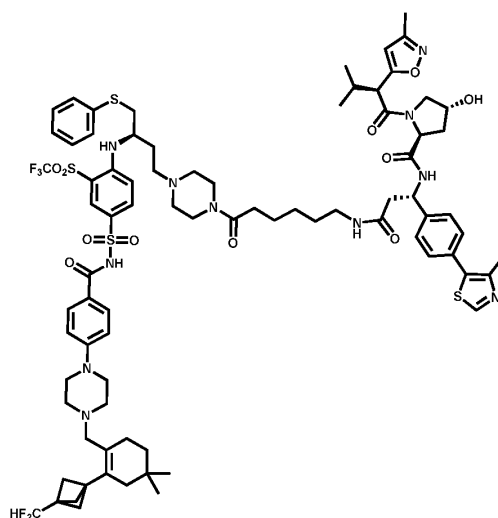
4-(4-((2-(3-(Difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-(((2R)-4-(4-(5-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-4-yl)pent-4-ynoyl)piperazin-1-yl)-1-(phenylthio)butan-2-yl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide



[0395] To a stirred solution **Intermediate 50** (69.5 mg, 0.20 mmol) in DMSO (5 mL) at 0 °C, was added EDC•HCl (62.6 mg, 0.32 mmol), HOAt (44.4 mg, 0.32 mmol), **Intermediate 5** (200 mg, 0.20 mmol) and NMM (123 mg, 1.22 mmol). The reaction mixture was warmed to rt, stirred for 16 h, and then diluted with EtOAc (30 mL), washed with ice cold water (2 x 20 mL), brine (2 x 20 mL), dried over Na₂SO₄, filtered and concentrated. The crude product was purified by HPLC (60:40 to 40:60 10 mM NH₄CO₃H(aq.)/CH₃CN) to afford **Example 54** (90 mg, 33% yield). LC/MS (ESI) *m/z* 1301.9 [M+H]⁺.

Example 56

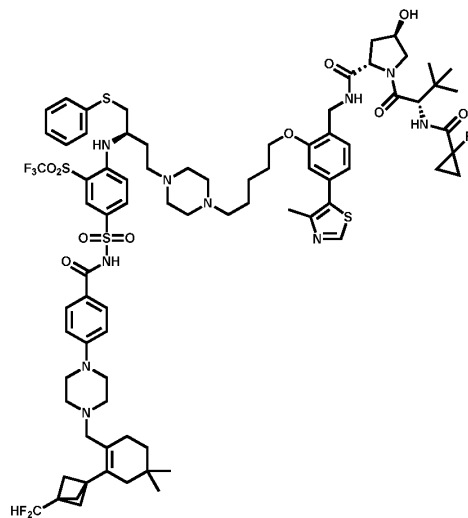
(2S,4R)-N-((S)-3-(((6-(4-((R)-3-(((4-(N-(4-(4-((2-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-((trifluoromethyl)sulfonyl)phenyl)amino)-4-(phenylthio)butyl)piperazin-1-yl)-6-oxohexyl)amino)-1-(4-(4-methylthiazol-5-yl)phenyl)-3-oxopropyl)-4-hydroxy-1-((S)-3-methyl-2-(3-methylisoxazol-5-yl)butanoyl)pyrrolidine-2-carboxamide



[0396] **Example 56** was prepared following the procedure described for **Example 50** using **Intermediate 53B** in place of **Intermediate 53A**. LC/MS (ESI) *m/z* 1612.6 [M-H]⁻.

Example 57

(2S,4R)-N-(2-((5-(4-((R)-3-((4-(N-(4-(4-((2-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-((trifluoromethyl)sulfonyl)phenyl)amino)-4-(phenylthio)butyl)piperazin-1-yl)pentyl)oxy)-4-(4-methylthiazol-5-yl)benzyl)-1-((S)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamide



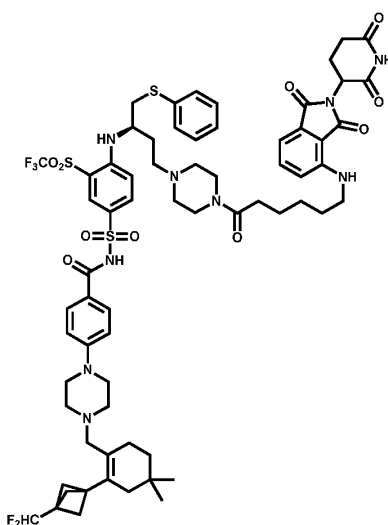
[0397] Step 1: To a solution of (2S,4R)-1-[(2S)-2-[(1-fluorocyclopropanecarbonyl)amino]-3,3-dimethyl-butanoyl]-4-hydroxy-N-[[2-hydroxy-4-(4-methylthiazol-5-yl)phenyl]methyl]pyrrolidine-2-carboxamide (0.3 g, 563.3 μ mol) in DMF (3 mL) was added 1,5-dibromopentane (194.3 mg, 844.9 μ mol) and K_2CO_3 (155.7 mg, 1.13 mmol) at rt. The reaction was warmed to 60 °C and stirred for 12 h. The reaction was then cooled to rt, and concentrated to give the crude product, which was purified by prep-TLC (10:1 EtOAc:MeOH) to give (2S,4R)-N-[[2-(5-bromopentoxo)-4-(4-methylthiazol-5-yl)phenyl]methyl]-1-[(2S)-2-[(1-fluorocyclopropanecarbonyl)amino]-3,3-dimethyl-butanoyl]-4-hydroxy-pyrrolidine-2-carboxamide (**Example 57-1**) (0.2 g, 39% yield, 75% pure by LC/MS). LC/MS (ESI) m/z 681.2 ($M+H$)⁺.

[0398] Step 2: To a solution of **Example 57-1** (0.1 g, 109.92 μ mol, 75% pure by LC/MS) in dioxane (3 mL) was added **Intermediate 5** (132.50 mg, 108.3 μ mol), DIPEA (27.98 mg, 216.50 μ mol) and NaI (1.62 mg, 10.83 μ mol) at rt. The reaction mixture was stirred at 80 °C for 12 h, cooled to rt and concentrated. The crude product was purified by

HPLC (60:40 to 40:60 10 mM $\text{NH}_4\text{CO}_3\text{H(aq.)}/\text{CH}_3\text{CN}$) to give **Example 57** (14 mg, 8% yield). LC/MS (ESI) m/z 1577.6 (M-H) $^-$.

Example 58

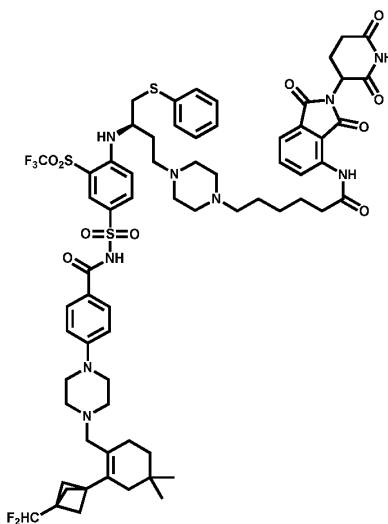
4-(4-((2-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-(((4-(((2R)-4-(4-(6-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)amino)hexanoyl)piperazin-1-yl)-1-(phenylthio)butan-2-yl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide



[0399] A solution of **Intermediate 5** (1.0 eq.), **Intermediate 54** (1.05 eq.), HATU (1.1 eq.), and DIPEA (2.1 eq.) in DCM is stirred at rt. After the reaction is deemed complete, the reaction is quenched with water and extracted with EtOAc. The combined organic layers are washed with brine, and then dried over anhydrous Na_2SO_4 , filtered and concentrated. The crude product is purified by column chromatography (SiO_2) to provide **Example 58**.

Example 59

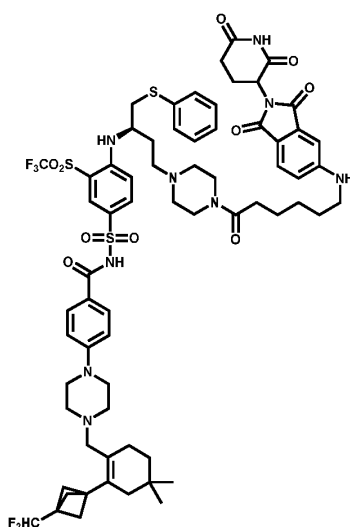
4-(4-((2-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-(((4-(((2R)-4-(4-(6-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)amino)-6-oxohexyl)piperazin-1-yl)-1-(phenylthio)butan-2-yl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide



[0400] **Example 59** is prepared following the procedure described for **Example 2** using **Intermediate 55** in place of **Intermediate 9**.

Example 60

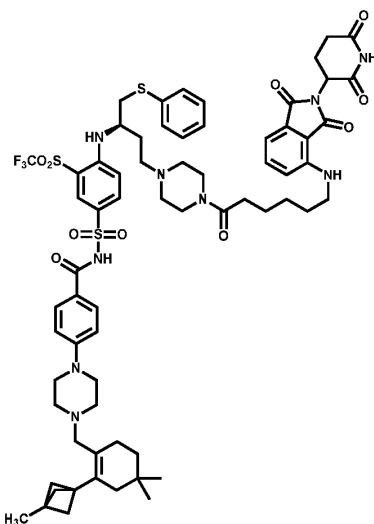
4-(4-((2-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-(((2R)-4-(4-(6-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-5-yl)amino)hexanoyl)piperazin-1-yl)-1-(phenylthio)butan-2-yl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide



[0401] Example 60 is prepared following the procedure described for Example 58 using Intermediate 56 in place of Intermediate 54.

Example 61

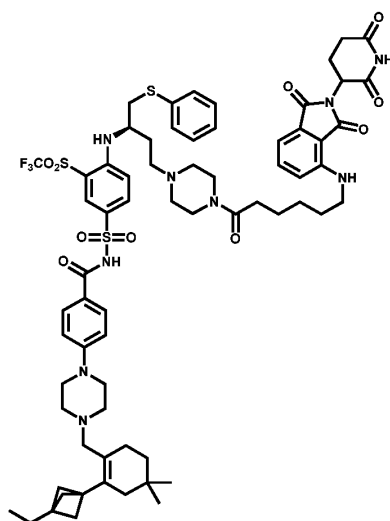
4-(4-(((4,4-dimethyl-2-(3-methylbicyclo[1.1.1]pentan-1-yl)cyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-(((4-(((2R)-4-(4-(6-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)amino)hexanoyl)piperazin-1-yl)-1-(phenylthio)butan-2-yl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide



[0402] **Example 6** is prepared following the procedure described for **Example 58** using **Intermediate 6** in place of **Intermediate 5**.

Example 62

N-(((4-(((2R)-4-(4-(6-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)amino)hexanoyl)piperazin-1-yl)-1-(phenylthio)butan-2-yl)amino)-3-((trifluoromethyl)sulfonyl)phenyl)sulfonyl)-4-(4-((2-(3-ethylbicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzamide



[0403] **Example 62** is prepared following the procedure described for **Example 58om** using **Intermediate 7** in place of **Intermediate 5**.

Example A

MOLT-4 Cell Proliferation Assay

[0404] Cell proliferation was measured using the CellTiter-Glo® Luminescent Cell Viability Assay. The assay involved the addition of a single reagent (CellTiter-Glo® Reagent) directly to cells cultured in serum-supplemented medium. MOLT-4 cells (ATCC, CRL-1582) were cultured according to ATCC recommendations and were seeded at 50,000 cells per well.

[0405] Each compound evaluated was prepared as a DMSO stock solution (10 mM). Compounds were tested in duplicate on each plate, with a 10-point serial dilution curve (1:3 dilution). The highest compound concentration was 10 μ M (final), with a 0.1% final DMSO concentration. Plates were then incubated at 37 $^{\circ}$ C, 5% CO₂ for 72 h, cell plates were equilibrated at rt for approximately 30 mins. An equi-volume amount of CellTiter-Glo[®] Reagent (100 μ L) was added to each well. Plates were mixed for 2 mins on an orbital shaker to induce cell lysis and then incubated at rt for 10 mins to stabilize the luminescent signal. Luminescence was recorded using a Envision plate reader according to CellTiter-Glo protocol. IC₅₀ of each compound was calculated using GraphPad Prism by nonlinear regression analysis. IC₅₀ values are provided in Table 1.

Table 1

Example#	MOLT-4 (nM)	Example#	MOLT-4 (nM)
1	C	21	B
2	A	22	C
3	A	23	B
4	B	24	B
5	A	25	B
6	B	26	C
7	B	28	B
8	A	29	A
9	B	30	A
10	B	43	B
11	C	44	B
12	A	45	C
13	A	47	C
14	B	48	C
15	B	49	C
17	A	50	C
18	A	56	C
19	B	ABT-263	B
20	A		

For MOLT-4 CTG IC₅₀: A = a single IC₅₀ ≤ 50 nM; B = a single IC₅₀ >50 nM and < 150 nM;
C = a single IC₅₀ ≥ 150 nM.

Example B

Protein degradation assay in MOLT-4 cells

[0406] MOLT-4 (ATCC, CRL-1582) (FIG. 7,8) were incubated with vehicle or 50 nM concentrations of the indicated compounds for 16 hours. For proteasome inhibition, MOLT-4 cells (250,000 cells/well) were pretreated with 1 μM of MG132 for 1 hour before the addition of 100 nM of the indicated compounds for 16 h. After treatment, the cells were harvested in RIPA lysis buffer supplemented with 1% Phosphatase Inhibitor and Protease Inhibitor Cocktail. An equal amount of protein (10 μg/lane) from each cell extract was resolved on a 4-12% Bis-Tris gel. Proteins were transferred using iBlot 2 Transfer Stacks. The membranes were blocked with 5% nonfat milk in TBS-T buffer (50 mM Tris-HCL, pH 7.6; 150 mM NaCl; and 0.05% Tween) and probed with primary antibodies (1:1000 dilution) overnight at 4°C. After three washes with TBS-T (10 min/wash), the membranes were

incubated with an appropriate peroxidase-conjugated secondary antibody (Cell Signaling Technology, USA) for 1 hour at rt. After three washes with TBS-T, the proteins of interest were detected with ECL Western Blotting Detection Reagents and captured with an Azure imaging system. The band intensities were determined using ImageJ software and normalized to loading control β -actin or GAPDH. The primary antibodies Bcl-xL (#2762), Bcl-2 (#2872s), and GAPDH (#5174) were purchased from Cell Signaling Technology.

[0407] Figures 7 and 8 indicate that Examples 6, 9, 24, 25, 28, 43 and 44 induce BCL-xL degradation in MOLT-4 cells at 50 nM concentrations.

[0408] Figure 9 indicates that Examples 6 and 30 can induce BCL-xL degradation in MOLT-4 cells in a dose dependent manner.

[0409] Figure 10 indicates that Bcl-xL degradation induced by Examples 6 and 30 can be inhibited by proteasome inhibitor MG132 in MOLT-4 cells.

[0410] Furthermore, although the foregoing has been described in some detail by way of illustrations and examples for purposes of clarity and understanding, it will be understood by those of skill in the art that numerous and various modifications can be made without departing from the spirit of the present disclosure. Therefore, it should be clearly understood that the forms disclosed herein are illustrative only and are not intended to limit the scope of the present disclosure, but rather to also cover all modification and alternatives coming with the true scope and spirit of the invention.