PD-L1 COMPOUNDS WITH A BICYCLIC GROUP

INCORPORATION BY REFERENCE TO PRIORITY APPLICATIONS

[0001] Any and all applications for which a foreign or domestic priority claim is identified, for example, in the Application Data Sheet or Request as filed with the present application, are hereby incorporated by reference under 37 CFR 1.57, and Rules 4.18 and 20.6, including U.S. Provisional Application Nos. 63/550,953, filed February 7, 2024 and 63/670,541, filed July 12, 2024, each of which is hereby expressly incorporated herein by reference in their entireties.

FIELD

[0002] The present application relates to the fields of chemistry, biochemistry, molecular biology and medicine. The present disclosure related to compounds that can be useful as inhibitors of PD-1, PD-Ll or the PD-1/PD-Ll interaction. Also disclosed herein are pharmaceutical compositions of compounds described herein and uses of or methods of using the compounds for the treatment of PD-L1 related diseases including but not limited to liver diseases, cancer, hepatocellular carcinoma, viral diseases, or hepatitis B.

BACKGROUND

[0003] The programmed cell death 1 (PD-1) immune checkpoint expressed on the surface of activated $CD4^+$ and $CD8^+$ T cells controls an inhibitory mechanism to prevent autoimmunity. Engagement of PD-1 by programmed death-ligand 1 (PD-L1) expressed on the multitude of cell types, including macrophages, dendritic cells, mast cells as well as cancer cells induces T cell exhaustion resulting in reduction or loss of effector cytokine production (e.g. IL-2, TNF-α, IFN-γ) and upregulation of other inhibitory receptors and immune checkpoints (e.g. CTLA-4, LAG-3, and BTLA) or T cell apoptosis. High expression of PD-L1 is exhibited by many types of cancers to escape tumor immune surveillance and has been associated with poorer prognosis. PD-1-mediated immunosuppression is also linked to some viral infections, such as hepatitis B. There is an ongoing need for PD-1/PD-L1 therapies and improvements thereof for the treatment of disease.

SUMMARY

[0004] Some embodiments disclosed herein relate to a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0005] Some embodiments disclosed herein relate to a pharmaceutical composition that can contain an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0006] Some embodiments described herein relate to a method of treating a HBV and/or HDV infection that can include administering to a subject identified as suffering from the HBV and/or HDV infection an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein. Other embodiments described herein relate to a compound, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein for the use of treating a HBV and/or HDV infection.

[0007] Some embodiments disclosed herein relate to a method of inhibiting replication of HBV and/or HDV that can include contacting a cell infected with the HBV and/or HDV with an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein. Other embodiments described herein relate to a compound, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein for the use of inhibiting the replication HBV and/or HDV.

[0008] These and other embodiments are described in greater detail below.

BRIEF DESCRIPTION OF THE DRAWINGS

[0009] Figures 1A and 1B show the absolute configuration structure and ORTEP crystal structure of the chloride salt of Intermediate 10B-1.

DETAILED DESCRIPTION

[0010] Hepatocellular carcinoma (HCC) is the most common form of liver cancer. HCC can be caused by a variety of conditions, such as alcohol consumption, cirrhosis, and viral infections that cause hepatitis, such as hepatitis B virus, hepatitis C virus, and hepatitis D virus. The inflammation, fibrosis, and cirrhosis linked with these conditions can induce malignancies in affected liver cells. HCC has relatively poor prognosis, with a five-year survival rate of about 30%, depending on if full surgical resection of the tumor is possible.

[0011] For early disease, surgical resection is used. However, most HCC are identified at later stages because of difficulties in diagnosing. Upon late-stage diagnosis, the tumors are unresectable and most patients are given systemic therapies. The current standard of care in front line are multi-kinase inhibitors (including, for example, sorafenib and/or lenvatinib). Most patients are refractory or relapse from these treatments, and undergo second line therapies that have anti-angiogenic agents (including, for example, Regorafinib, Cabozantinib, and/or Ramicirumab) or immune checkpoint inhibitors (including, for example, nivolumab and/or pembrolizumab). However, most patients do not respond to first and second therapies, and the clinical benefit is poor, with overall survival not exceeding one year. In addition, biomarker driven therapies are lacking. Thus, there is a need to develop more tolerable and efficacious therapies for the treatment of HCC and related liver disorders.

[0012] HBV is a partially double-stranded circular DNA of about 3.2 kilobase (kb) pairs, and is classified into eight genotypes, A to H. The HBV replication pathway has been studied in great detail. One part of replication includes the formation of the covalently closed circular DNA (cccDNA) form. The presence of the cccDNA gives rise to the risk of viral reemergence throughout the life of the host organism. HBV carriers can transmit the disease for many years. An estimated 300 million people are living with hepatitis B virus infection, and it is estimated that over 750,000 people worldwide die of hepatitis B each year. In addition, immunosuppressed individuals or individuals undergoing chemotherapy are especially at risk for reactivation of an HBV infection. HBV can be acute and/or chronic. Acute HBV infection can be either asymptomatic or present with symptomatic acute hepatitis.

[0013] HBV can be transmitted by blood, semen, and/or another body fluid. This can occur through direct blood-to-blood contact, unprotected sex, sharing of needles, and from an infected mother to her baby during the delivery process. The HBV surface antigen (HBsAg) is most frequently used to screen for the presence of this infection. Currently available

medications do not cure HBV and/or HDV infection. Rather, the medications suppress replication of the virus.

[0014] The hepatitis D virus (HDV) is a DNA virus, also in the Hepadnaviridae family of viruses. HDV can propagate only in the presence of HBV. The routes of transmission of HDV are similar to those for HBV. Transmission of HDV can occur either via simultaneous infection with HBV (coinfection) or in addition to chronic hepatitis B or hepatitis B carrier state (superinfection). Both superinfection and coinfection with HDV results in more severe complications compared to infection with HBV alone. These complications include a greater likelihood of experiencing liver failure in acute infections and a rapid progression to liver cirrhosis, with an increased risk of developing liver cancer in chronic infections. In combination with hepatitis B, hepatitis D has the highest fatality rate of all the hepatitis infections, at 20%. There is currently no cure or vaccine for hepatitis D.

[0015] Programmed cell death 1, or programmed death 1 (PD-1) is a 268 amino acid long type I transmembrane protein found as a surface marker on T cells and other immune cells. As an immune checkpoint, PD-1 serves to negatively regulate immune responses to prevent autoimmune disorder. PD-1 protein (NCBI accession number NP_005009.2) is expressed from the cluster of differentiation 279 (CD279) gene (NCBI accession number NG_012110.1) or mRNA transcript (NCBI accession number NM_005018.3). In some preferred embodiments, PD-1 is the human PD-1 protein, and CD279 is the human CD279 transcript or gene on chromosome 2. It should be understood that a person with ordinary skill in the art would view the terms PD-1 and CD279 as often nominally interchangeable when considering the nucleic acid (DNA or RNA) or corresponding translated protein, or the sequences thereof.

[0016] Programmed cell death-ligand 1, or programmed death-ligand 1 (PD-L1), also known as B7 homolog 1 (B7-H1) is 272 amino acid long type I transmembrane protein found as a surface marker on many different cell types. PD-L1 is a major ligand of PD-1 and results in inhibition of T cell cytotoxicity and cytokine production. Cancer cells such as HCC cells take advantage of this immune checkpoint by upregulating PD-L1 expression, resulting in dysfunctional anti-tumor immunity by proximal T cells. Viruses also have been observed to modulate the PD-1/PD-L1 pathway to inhibit immune host response. Hepatitis B virus has been shown to upregulate PD-L1 in infected hepatocytes, and PD-1 in associated T cells. PD-

L1 protein (NCBI accession number NP_054862.1) is expressed from the cluster of differentiation 274 (CD274) transcript (NCBI accession number NM_014143.4). In some preferred embodiments, PD-L1 is the human PD-L1 protein, and CD274 is the human CD274 transcript or gene on chromosome 9. It should be understood that a person with ordinary skill in the art would view the terms PD-L1 and CD274 as often nominally interchangeable when considering the nucleic acid (DNA or RNA) or corresponding translated protein, or the sequences thereof.

Definitions

[0017] 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. To the extent publications and patents or patent applications incorporated by reference contradict the disclosure contained in the specification, the specification is intended to supersede and/or take precedence over any such contradictory material. In the event that there are a plurality of definitions for a term herein, those in this section prevail unless stated otherwise.

[0018] 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 of 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) (such as 1, 2 or 3 groups) individually and independently selected from deuterium, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aryl(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, isocyanato, thiocyanato, isothiocyanato, nitro, azido, silyl, sulfenyl, sulfinyl, sulfonyl, haloalkyl, haloalkoxy, trihalomethanesulfonyl, trihalomethanesulfonamido, an amino, a mono-substituted amine and a di-substituted amine.

[0019] As used herein, "C_a to C_b", "C_a-C_b" or "C_{a-b}" in which "a" and "b" are integers refer to the number of carbon atoms in an alkyl, alkenyl or alkynyl group, or the

number of carbon atoms in the ring of a cycloalkyl, cycloalkenyl, aryl, heteroaryl or heterocyclyl group. That is, the alkyl, alkenyl, alkynyl, ring of the cycloalkyl, ring of the cycloalkenyl, ring of the aryl, ring of the heteroaryl or ring of the heterocyclyl can contain from "a" to "b", inclusive, carbon atoms. Thus, for example, a "C_1 to C_4 alkyl" group refers to all alkyl groups having from 1 to 4 carbons, that is, CH_3-, CH_3CH_2-, $CH_3CH_2CH_2$-, $(CH_3)_2CH$-, $CH_3CH_2CH_2CH_2$-, $CH_3CH_2CH(CH_3)$- and $(CH_3)_3C$-. If no "a" and "b" are designated with regard to an alkyl, alkenyl, alkynyl, cycloalkyl cycloalkenyl, aryl, heteroaryl or heterocyclyl group, the broadest range described in these definitions is to be assumed.

[0020] As used herein, "alkyl" refers to a straight or branched hydrocarbon chain that comprises a fully saturated (no double or triple bonds) hydrocarbon group. The alkyl group may have 1 to 20 carbon atoms (whenever it appears herein, a numerical range such as "1 to 20" refers to each integer in the given range; *e.g.*, "1 to 20 carbon atoms" means that the alkyl group may consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, *etc.*, up to and including 20 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 10 carbon atoms. The alkyl group could also be a lower alkyl having 1 to 6 carbon atoms. The alkyl group of the compounds may be designated as "C_1-C_4 alkyl" or similar designations. By way of example only, "C_1-C_4 alkyl" indicates that there are one to four carbon atoms in the alkyl chain, i.e., the alkyl chain is selected from methyl, ethyl, propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl and t-butyl. Typical alkyl groups include, but are in no way limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tertiary butyl, pentyl and hexyl. The alkyl group may be substituted or unsubstituted.

[0021] As used herein, "alkenyl" refers to an alkyl group that contains in the straight or branched hydrocarbon chain one or more double bonds. The length of an alkenyl can vary. For example, the alkenyl can be a C_{2-4} alkenyl, C_{2-6} alkenyl or C_{2-8} alkenyl. Examples of alkenyl groups include allenyl, vinylmethyl and ethenyl. An alkenyl group may be unsubstituted or substituted.

[0022] As used herein, "alkynyl" refers to an alkyl group that contains in the straight or branched hydrocarbon chain one or more triple bonds. The length of an alkynyl can vary. For example, the alkynyl can be a C_{2-4} alkynyl, C_{2-6} alkynyl or C_{2-8} alkynyl. Examples

of alkynyls include ethynyl and propynyl. An alkynyl group may be unsubstituted or substituted.

[0023] As used herein, "cycloalkyl" refers to a completely saturated (no double or triple bonds) mono- or multi- cyclic hydrocarbon ring system. When composed of two or more rings, the rings may be joined together in a fused fashion. Cycloalkyl 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). A cycloalkyl group may be unsubstituted or substituted. Typical cycloalkyl groups include, but are in no way limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

[0024] As used herein, "cycloalkenyl" refers to a mono- or multi- cyclic 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). When composed of two or more rings, the rings may be connected together in a fused fashion. A cycloalkenyl can contain 3 to 10 atoms in the ring(s) or 3 to 8 atoms in the ring(s). A cycloalkenyl group may be unsubstituted or substituted.

[0025] As used herein, "aryl" refers to a carbocyclic (all carbon) monocyclic or multicyclic 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 C_6-C_{14} aryl group, a C_6-C_{10} aryl group, or a C_6 aryl group. Examples of aryl groups include, but are not limited to, benzene, naphthalene and azulene. An aryl group may be substituted or unsubstituted.

[0026] As used herein, "heteroaryl" refers to a monocyclic, bicyclic and tricyclic aromatic ring system (a ring system with fully delocalized pi-electron system) that contain(s) one or more heteroatoms (for example, 1 to 5 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). 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.

[0027] As used herein, "heterocyclyl" refers to a 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 number of atoms in the ring(s) of a heterocyclyl group can vary. For example, the heterocyclyl 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). 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 fashion. Additionally, any nitrogens in a heterocyclyl may be quaternized. Heterocyclyl groups may be unsubstituted or substituted. Examples of such "heterocyclyl 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, pyrrolidone, pyrrolidione, 4-piperidone, pyrazoline, pyrazolidine, 2-oxopyrrolidine, tetrahydropyran, 4H-pyran, tetrahydrothiopyran, thiamorpholine, thiamorpholine sulfoxide, thiamorpholine sulfone and their benzo-fused analogs (e.g., tetrahydroquinoline and 3,4-methylenedioxyphenyl).

[0028] As used herein, "aryl(alkyl)" refers to an aryl group connected, as a substituent, via a lower alkylene group. The lower alkylene and aryl group of an aryl(alkyl)

may be substituted or unsubstituted. Examples include but are not limited to benzyl, 2-phenyl(alkyl), 3-phenyl(alkyl), and naphthyl(alkyl).

[0029] As used herein, "heteroaryl(alkyl)" refers to a heteroaryl group connected, as a substituent, via a lower alkylene group. The lower alkylene and heteroaryl group of heteroaryl(alkyl) may be substituted or unsubstituted. Examples include but are not limited to 2-thienyl(alkyl), 3-thienyl(alkyl), furyl(alkyl), thienyl(alkyl), pyrrolyl(alkyl), pyridyl(alkyl), isoxazolyl(alkyl), imidazolyl(alkyl) and their benzo-fused analogs.

[0030] A "(heterocyclyl)alkyl" refers to a heterocyclic group connected, as a substituent, via a lower alkylene group. The lower alkylene and heterocyclyl of a heterocyclyl(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).

[0031] "Lower alkylene groups" are straight-chained -CH_2- tethering groups, forming bonds to connect molecular fragments via their terminal carbon atoms. In some embodiments, a lower alkylene can include 1, 2, 3, 4, 5 or 6 carbons. Examples include but are not limited to methylene (-CH_2-), ethylene (-CH_2CH_2-), propylene (-$CH_2CH_2CH_2$-) and butylene (-$CH_2CH_2CH_2CH_2$-). A lower alkylene group can be substituted by replacing one or more hydrogen of the lower alkylene group with a substituent(s) listed under the definition of "substituted."

[0032] 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, 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. In some instances, an alkoxy can be –OR wherein R is an unsubstituted C_{1-4} alkyl. An alkoxy may be substituted or unsubstituted.

[0033] As used herein, "acyl" refers to a hydrogen an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl) connected, as substituents, via a carbonyl group. Examples include formyl, acetyl, propanoyl, benzoyl and acryl. An acyl may be substituted or unsubstituted.

[0034] As used herein, "hydroxyalkyl" refers to an alkyl group in which one or more of the hydrogen atoms are replaced by a hydroxy group. Exemplary hydroxyalkyl groups

include but are not limited to, 2-hydroxyethyl, 3-hydroxypropyl, 2-hydroxypropyl and 2,2-dihydroxyethyl. A hydroxyalkyl may be substituted or unsubstituted.

[0035] 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 and tri-haloalkyl). Such groups include but are not limited to, chloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, 1-chloro-2-fluoromethyl and 2-fluoroisobutyl. A haloalkyl may be substituted or unsubstituted.

[0036] As used herein, "haloalkoxy" refers to a O-alkyl 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. In some instances, a haloalkoxy can be –OR, wherein R is a C_{1-4} alkyl substituted by 1, 2 or 3 halogens. A haloalkoxy may be substituted or unsubstituted.

[0037] A "sulfenyl" group refers to an "-SR" group in which R can be hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). A sulfenyl may be substituted or unsubstituted.

[0038] 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.

[0039] A "sulfonyl" group refers to an "SO_2R" group in which R can be the same as defined with respect to sulfenyl. A sulfonyl may be substituted or unsubstituted.

[0040] An "O-carboxy" group refers to a "RC(=O)O-" group in which R can be hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl), as defined herein. An O-carboxy may be substituted or unsubstituted.

[0041] 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.

[0042] 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.

[0043] A "trihalomethanesulfonyl" group refers to an "X_3CSO_2-" group wherein each X is a halogen.

[0044] A "trihalomethanesulfonamido" group refers to an "$X_3CS(O)_2N(R_A)$-" group wherein each X is a halogen, and R_A is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl).

[0045] The term "amino" as used herein refers to a $–NH_2$ group.

[0046] As used herein, the term "hydroxy" refers to a –OH group.

[0047] A "cyano" group refers to a "-CN" group.

[0048] The term "azido" as used herein refers to a $–N_3$ group.

[0049] An "isocyanato" group refers to a "–NCO" group.

[0050] A "thiocyanato" group refers to a "–SCN" group.

[0051] An "isothiocyanato" group refers to an " –NCS" group.

[0052] A "mercapto" group refers to an "–SH" group.

[0053] A "carbonyl" group refers to a –C(=O)– group.

[0054] An "S-sulfonamido" group refers to a "$–SO_2N(R_AR_B)$" group in which R_A and R_B can be independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). An S-sulfonamido may be substituted or unsubstituted.

[0055] An "N-sulfonamido" group refers to a "$RSO_2N(R_A)–$" group in which R and R_A can be independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). An N-sulfonamido may be substituted or unsubstituted.

[0056] 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, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). An O-carbamyl may be substituted or unsubstituted.

[0057] An "N-carbamyl" group refers to an "$ROC(=O)N(R_A)–$" group in which R and R_A can be independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). An N-carbamyl may be substituted or unsubstituted.

[0058] 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, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). An O-thiocarbamyl may be substituted or unsubstituted.

[0059] An "N-thiocarbamyl" group refers to an "ROC(=S)N(R_A)–" group in which R and R_A can be independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). An N-thiocarbamyl may be substituted or unsubstituted.

[0060] A "C-amido" group refers to a "–C(=O)N(R_AR_B)" group in which R_A and R_B can be independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). A C-amido may be substituted or unsubstituted.

[0061] An "N-amido" group refers to a "RC(=O)N(R_A)–" group in which R and R_A can be independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). An N-amido may be substituted or unsubstituted.

[0062] A "mono-substituted amine" refers to a "–NHR_A" in which R_A can be independently alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). A mono-substituted amine may be substituted or unsubstituted. In some instances, a mono-substituted amine can be –NHR_A, wherein R_A can be an unsubstituted $C_{1\text{-}6}$ alkyl or an unsubstituted or a substituted benzyl.

[0063] A "di-substituted amine" refers to a "–NR_AR_B" in which R_A and R_B can be independently can be independently alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). A mono-substituted amine may be substituted or unsubstituted. In some instances, a mono-substituted amine can be –NR_AR_B, wherein R_A and R_B can be independently an unsubstituted $C_{1\text{-}6}$ alkyl or an unsubstituted or a substituted benzyl.

[0064] 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.

[0065] 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.

[0066] As used herein, the abbreviations for any protective groups, amino acids and other compounds, are, unless indicated otherwise, in accord with their common usage, recognized abbreviations, or the IUPAC-IUB Commission on Biochemical Nomenclature (See, Biochem. 11:942-944 (1972)).

[0067] 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), sulfuric acid, nitric acid and phosphoric acid. 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-toluenesulfonic, salicylic 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 (for example, ammonium or triethylammonium salt), an alkali metal salt, such as a lithium, a sodium or a potassium salt, an alkaline earth metal salt, such as a calcium or a magnesium salt, a salt of organic bases such as dicyclohexylamine, N-methyl-D-glucamine, tris(hydroxymethyl)methylamine, C_1-C_7 alkylamine, cyclohexylamine, triethanolamine, ethylenediamine, and salts with amino acids such as arginine and lysine.

[0068] 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. 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 or composition, the term "comprising" means that the compound or composition includes at least the recited features or components, but may also include additional features or components.

[0069] 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.

[0070] 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.

[0071] 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).

[0072] 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.

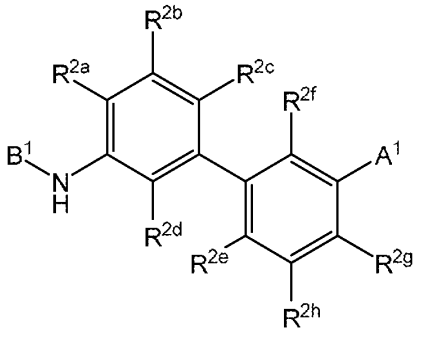
[0073] Where a range of values is provided, it is understood that the upper and lower limit, and each intervening value between the upper and lower limit of the range is encompassed within the embodiments.

Compounds

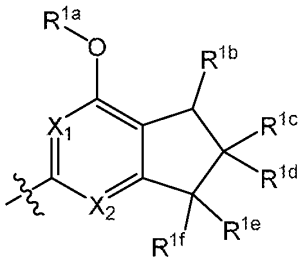
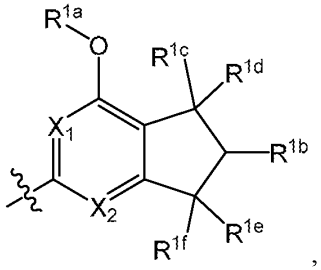
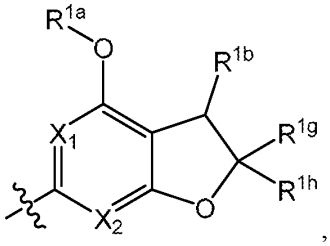
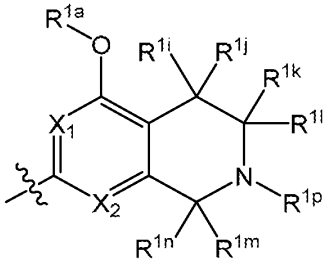
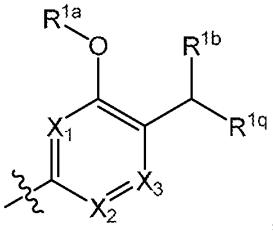
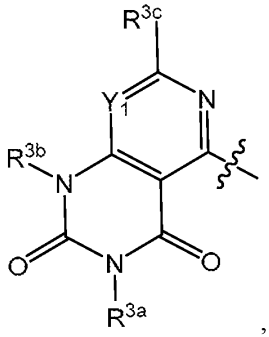
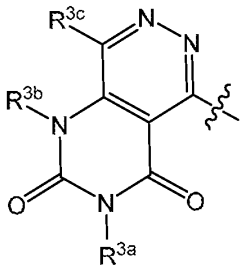
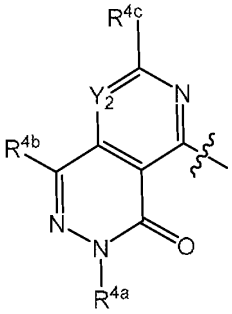
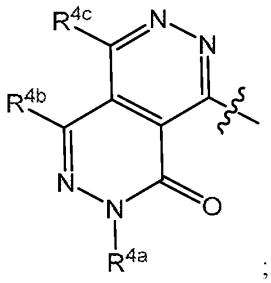
[0074] Examples of embodiments of the present application include the following:

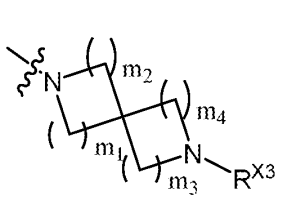
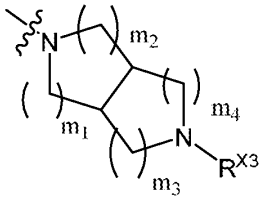
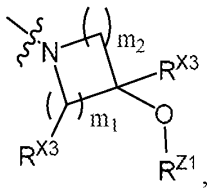
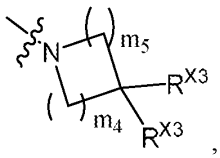
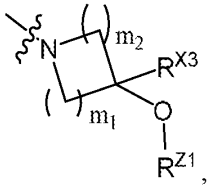
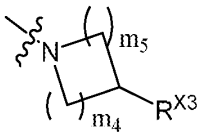
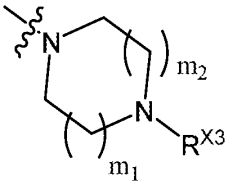
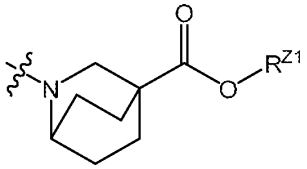
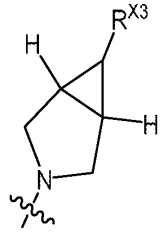
Embodiment 1

[0075] A compound of Formula (I), or a pharmaceutically acceptable salt thereof, having the structure:

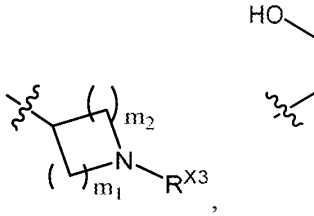


(I)

wherein: A^1 can be , , , , or ; B^1 can be , , , or ; X^1 can be selected from CH, C-halo and N (nitrogen); X^2 can be selected from CH, C-halo and N (nitrogen); X^3 can be selected from CH, C-halo, N (nitrogen) and C-OR^{Z1}; Y^1 can be selected from CH, C-halo and N(nitrogen); Y^2 can be selected from CH, C-halo and N(nitrogen); R^{1a} can be selected from $-C_{1-4}$ alkyl, $-C_{1-4}$ haloalkyl, $-CH_2$(C_{3-6} monocyclic cycloalkyl), $-CH_2$(4-6 membered monocyclic heterocyclyl) and $-CH_2$(5-6 membered monocyclic heteroaryl); R^{1b} can be selected from $-R^{x1}$ and $-N(R^{m1})R^{n1}$; R^{x1} can be

selected from , , , , , , ,  and  ; wherein R^{x1} can be optionally substituted with one or two substituents independently selected from halogen, cyano, $-C_{1-4}$ alkyl, hydroxy, $-C_{1-4}$ alkoxy, $-C_{1-4}$ haloalkyl, $-C_{1-4}$ haloalkoxy, $-C(=O)OR^{Z1}$, $-C(=O)NHS(=O)_2R^{Z3}$, $-C(=O)N(R^{Z1})R^{Z2}$, $-S(=O)_2R^{Z3}$, $-S(=O)_2N(R^{Z1})R^{Z2}$, $-N(R^{Z1})C(=O)R^{Z3}$, $-N(R^{Z1})S(=O)R^{Z3}$, $-N(R^{Z1})C(=O)N(R^{Z1})R^{Z3}$ and $-N(R^{Z1})S(=O)_2N(R^{Z2})R^{Z3}$; R^{m1} can be selected from $-C_{1-4}$ alkyl, C_{3-6} monocyclic cycloalkyl, C_{5-12} bicyclic cycloalkyl, 4-7 membered monocyclic heterocyclyl, 8-11 membered fused-heterocyclyl and $-R^{x2}$; wherein the 4-7 membered monocyclic heterocyclyl and the 8-11 membered fused-heterocyclyl contain at least one atom or group of atoms independently selected from O (oxygen), S (sulfur), C(=O), S(=O), $S(=O)_2$ and N (nitrogen); wherein the $-C_{1-4}$ alkyl is substituted by $-C(=O)OR^{Z1}$, and the $-C_{1-4}$ alkyl can be optionally substituted with one or two or three substituents independently selected from halogen, cyano, hydroxy, $-C_{1-4}$ alkoxy, $-C_{1-4}$ haloalkyl, $-C_{1-4}$ haloalkoxy, $-C(=O)NHS(=O)_2R^{Z3}$, $-C(=O)N(R^{Z1})R^{Z2}$, $-S(=O)_2R^{Z3}$, $-S(=O)_2N(R^{Z1})R^{Z2}$, $-N(R^{Z1})C(=O)R^{Z3}$, $-N(R^{Z1})S(=O)R^{Z3}$, $-N(R^{Z1})C(=O)N(R^{Z2})R^{Z3}$ and $-N(R^{Z1})S(=O)N(R^{Z2})R^{Z3}$; wherein the C_{3-6} monocyclic cycloalkyl, the C_{5-12} bicyclic cycloalkyl, the 4-7 membered monocyclic heterocyclyl, and the 8-11 membered fused-heterocyclyl is substituted by $-C(=O)OR^{Z1}$, and the C_{3-6} monocyclic cycloalkyl, the C_{5-12}

bicyclic cycloalkyl, the 4-7 membered monocyclic heterocyclyl, and the 8-11 membered fused-heterocyclyl can be optionally substituted with one or two or three substituents independently selected from halogen, cyano, $-C_{1-4}$ alkyl, hydroxy, $-C_{1-4}$ alkoxy, $-C_{1-4}$ haloalkyl, $-C_{1-4}$ haloalkoxy, $-C(=O)NHS(=O)_2R^{Z3}$, $-C(=O)N(R^{Z1})R^{Z2}$, $-S(=O)_2R^{Z3}$, $-S(=O)_2N(R^{Z1})R^{Z2}$, $-N(R^{Z1})C(=O)R^{Z3}$, $-N(R^{Z1})S(=O)R^{Z3}$, $-N(R^{z1})C(=O)N(R^{Z2})R^{Z3}$ and $-N(R^{Z1})S(=O)N(R^{Z2})R^{Z3}$; R^{x2} can be selected from



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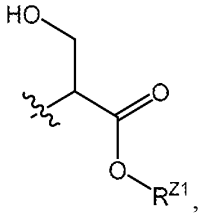

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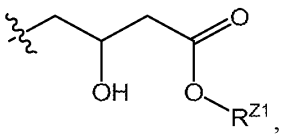

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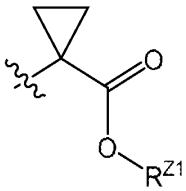

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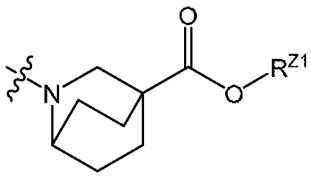
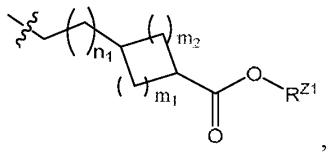
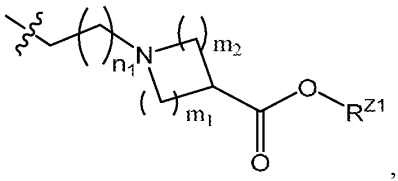
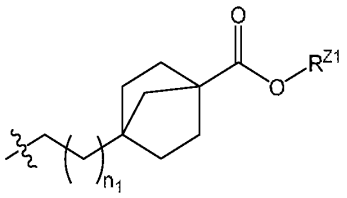
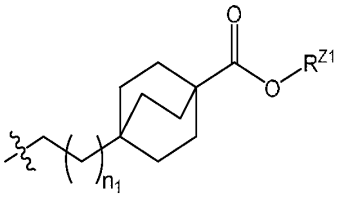
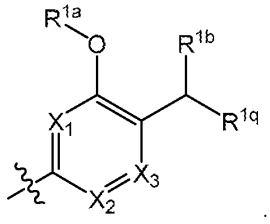


; each R^{X3} can be $-C(=O)OR^{Z1}$; R^{n1} can be selected from hydrogen, $-C_{1-4}$ alkyl, $-C_{1-4}$ haloalkyl, $-CH_2(C_{3-6}$ monocyclic cycloalkyl) and $-C(=O)OR^{Z4}$; R^{1c} can be selected from hydrogen, halogen, -OH, –CN, $-CH_3$, $-C_{2-4}$ alkyl and $-C_{2-4}$ haloalkyl; R^{1d} can be selected from hydrogen, $-C_{1-2}$ alkyl and $-C_{1-2}$ haloalkyl; R^{1e} can be selected from hydrogen, $-C_{1-2}$ alkyl and $-C_{1-2}$ haloalkyl; R^{1f} can be selected from hydrogen, $-C_{1-2}$ alkyl and $-C_{1-2}$ haloalkyl; R^{1g} can be selected from hydrogen, $-C_{1-2}$ alkyl and $-C_{1-2}$ haloalkyl; R^{1h} can be selected from hydrogen, $-C_{1-2}$ alkyl and $-C_{1-2}$ haloalkyl; R^{1i}, R^{1j}, R^{1k}, R^{1l}, R^{1m} and R^{1n} each can be independently selected from hydrogen, $-C_{1-2}$ alkyl and $-C_{1-2}$ haloalkyl; R^{1p} can be selected from $-CH_3$, $-C_{2-4}$ alkyl and $-R^{1p1}$, wherein when R^{1p} is $-CH_3$ or $-C_{2-4}$ alkyl, the $-CH_3$ and the $-C_{2-4}$ alkyl is substituted by $-C(=O)OR^{Z1}$ and the$-CH_3$ and the $-C_{2-4}$ alkyl can be optionally substituted with one or two substituents independently selected from halogen, cyano, $-C_{1-4}$ alkyl, hydroxy, $-C_{1-4}$ alkoxy, $-C_{1-4}$ haloalkyl, $-C_{1-4}$ haloalkoxy, $-C(=O)NHS(=O)_2R^{Z3}$, $-C(=O)N(R^{Z1})R^{Z2}$, $-S(=O)_2R^{Z3}$, $-S(=O)_2N(R^{Z1})R^{Z2}$, $-N(R^{Z1})R^{Z2}$, $-N(R^{Z1})C(=O)R^{Z3}$, $-N(R^{Z1})S(=O)R^{Z3}$, $-N(R^{Z1})C(=O)N(R^{Z2})R^{Z3}$ and

$-N(R^{Z1})S(=O)_2N(R^{Z2})R^{Z3}$; R^{1p1} can be selected from , ,  and ; R^{1q} can be independently selected from hydrogen, $-C_{1-4}$ alkyl and $-C_{1-4}$ haloalkyl; R^{2a}, R^{2b}, R^{2c}, R^{2e}, R^{2g} and R^{2h} each can be independently selected from hydrogen and halogen; R^{2d} and R^{2f} each can be independently selected from hydrogen, halogen, cyano, $-CH_3$, $-CH_2CH_3$, $-CH_2OH$, $-OCH_3$ and $-SCH_3$; R^{3a} can be selected from hydrogen, $-CH_3$, $-C_{2-4}$ alkyl and $-C_{2-4}$ haloalkyl; R^{3b} can be selected from hydrogen, $-CH_3$, $-C_{2-4}$ alkyl, $-C_{2-4}$ haloalkyl and $-C_{1-4}$ alkoxy; wherein R^{3b} can be optionally substituted with one or two substituents independently selected from halogen, -OH, –CN, $-CH_3$, $-C_{2-4}$ alkyl, $-C_{2-4}$ haloalkyl, $-CH_2CH_2OH$ and $-CH_2CH_2OC_{1-4}$ haloalkyl; R^{3c} can be selected from hydrogen, halogen, $-C_{1-2}$ alkyl and $-C_{1-2}$ haloalkyl; R^{4a} can be selected from hydrogen, $-CH_3$, $-C_{2-4}$ alkyl and $-C_{2-4}$ haloalkyl; R^{4b} can be selected from hydrogen, halogen, $-C_{1-4}$ alkyl, $-C_{1-4}$ haloalkyl, –OH, $-NH_2$, $-OC_{1-4}$ alkyl and $-OC_{1-4}$ haloalkyl, wherein R^{4b} can be optionally substituted with one or two substituents independently selected from halogen, -OH, –CN, $-CH_3$, $-C_{2-4}$ alkyl, $-C_{2-4}$ haloalkyl, $-CH_2CH_2OH$ and $-CH_2CH_2O-C_{1-4}$ haloalkyl; R^{4c} can be selected from hydrogen, halogen, $-C_{1-2}$ alkyl and $-C_{1-2}$ haloalkyl; m_1, m_2 and m_3 each can be independently 1 or 2; m_4 can be 0, 1 or 2; m_5 can be 1, 2, 3 or 4; n_1 independently can be 0, 1 or 2; and R^{Z1}, R^{Z2}, R^{Z3} and R^{Z4} each independently can be selected from hydrogen, $-C_{1-4}$ alkyl and $-C_{1-4}$ haloalkyl.

Embodiment 2

[0076] The compound of Embodiment 1, or a pharmaceutically acceptable salt thereof, wherein A^1 can be 

.

Embodiment 3

[0077] The compound of Embodiment 1 or 2, or a pharmaceutically acceptable salt thereof, wherein X^1 can be N (nitrogen).

Embodiment 4

[0078] The compound of any one of Embodiments 1-3, or a pharmaceutically acceptable salt thereof, wherein X^2 can be CH.

Embodiment 5

[0079] The compound of any one of Embodiments 1-4, or a pharmaceutically acceptable salt thereof, wherein X^3 can be CH.

Embodiment 6

[0080] The compound of any one of Embodiments 1-4, or a pharmaceutically acceptable salt thereof, wherein X^3 can be N.

Embodiment 7

[0081] The compound of any one of Embodiments 1-6, or a pharmaceutically acceptable salt thereof, wherein R^{1a} can be $-C_{1-4}$ alkyl. Examples of C_{1-4} alkyls include methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl and tert-butyl.

Embodiment 8

[0082] The compound of Embodiment 7, or a pharmaceutically acceptable salt thereof, wherein R^{1a} can be $-CH_3$.

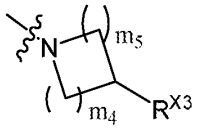
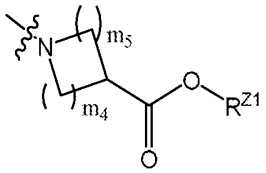
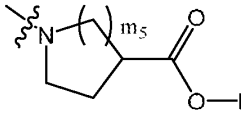
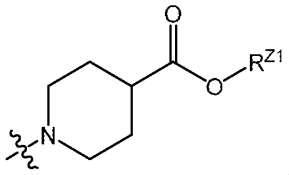
Embodiment 9

[0083] The compound of any one of Embodiments 1-8, or a pharmaceutically acceptable salt thereof, wherein R^{1q} can be hydrogen.

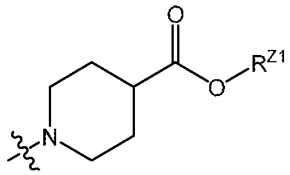
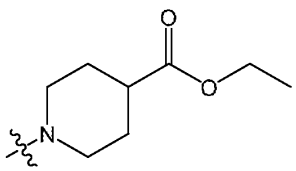
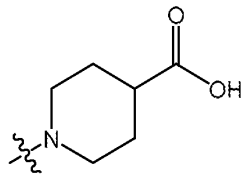
Embodiment 10

[0084] The compound of any one of Embodiments 1-9, or a pharmaceutically acceptable salt thereof, wherein R^{1b} can be $-R^{x1}$.

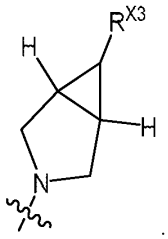
Embodiment 11

[0085] The compound of Embodiment 10, or a pharmaceutically acceptable salt thereof, wherein $-R^{x1}$ can be . In some embodiments, R^{X3} can be $-C(=O)OR^{Z1}$, such that $-R^{x1}$ can be . In other embodiments, m_4 can be 2, R^{X3} can be $-C(=O)OR^{Z1}$, such that $-R^{x1}$ can be . In still other embodiments, m_4 and m_5 can each be 2, R^{X3} can be $-C(=O)OR^{Z1}$, such that $-R^{x1}$ can be .

Embodiment 12

[0086] The compound of Embodiment 11, or a pharmaceutically acceptable salt thereof, wherein R^{Z1} can be $-C_{1-4}$ alkyl or hydrogen. Examples of  when $-R^{Z1}$ is C_{1-4} alkyl or hydrogen are  or .

Embodiment 13

[0087] The compound of Embodiment 10, or a pharmaceutically acceptable salt thereof, wherein $-R^{x1}$ can be . In some embodiments, R^{X3} can be $-C(=O)OH$. In other embodiments, R^{X3} can be $-C(=O)OCH_3$. In still other embodiments, R^{X3} can be $-C(=O)OCH_2CH_3$.

Embodiment 14

[0088] The compound of any one of Embodiments 1-9, or a pharmaceutically acceptable salt thereof, wherein R^{1b} can be $-N(R^{m1})R^{n1}$.

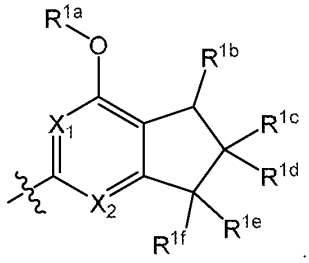
Embodiment 15

[0089] The compound of Embodiment 14, or a pharmaceutically acceptable salt thereof, wherein R^{n1} can be hydrogen, such that R^{1b} can be $-NH(R^{m1})$.

Embodiment 16

[0090] The compound of Embodiment 14 or 15, or a pharmaceutically acceptable salt thereof, wherein R^{m1} can be $-R^{x2}$.

Embodiment 17

[0091] The compound of Embodiment 1, or a pharmaceutically acceptable salt thereof, wherein A^1 can be .

Embodiment 18

[0092] The compound of Embodiment 17, or a pharmaceutically acceptable salt thereof, wherein X^1 can be N (nitrogen).

Embodiment 19

[0093] The compound of Embodiment 17 or 18, or a pharmaceutically acceptable salt thereof, wherein X^2 can be CH.

Embodiment 20

[0094] The compound of any one of Embodiments 17-19, or a pharmaceutically acceptable salt thereof, wherein R^{1a} can be $-C_{1-4}$ alkyl. Exemplary C_{1-4} alkyls include methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl and tert-butyl.

Embodiment 21

[0095] The compound of Embodiment 20, or a pharmaceutically acceptable salt thereof, wherein R^{1a} can be $-CH_3$.

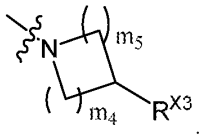
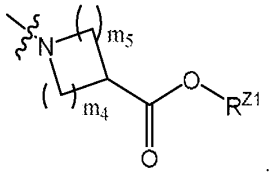
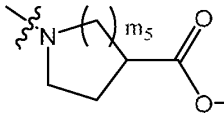
Embodiment 22

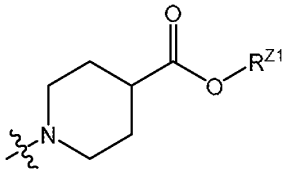
[0096] The compound of any one of Embodiments 17-21, or a pharmaceutically acceptable salt thereof, wherein R^{1c}, R^{1d}, R^{1e} and R^{1f} can be each hydrogen.

Embodiment 23

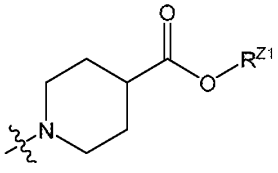
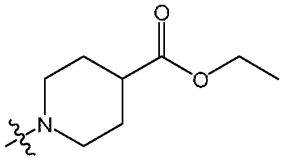
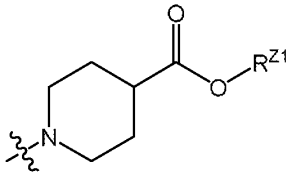
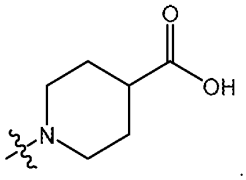
[0097] The compound of any one of Embodiments 17-22, or a pharmaceutically acceptable salt thereof, wherein R^{1b} can be $-R^{x1}$.

Embodiment 24

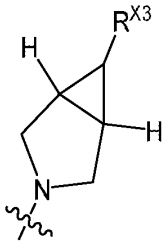
[0098] The compound of Embodiment 23, or a pharmaceutically acceptable salt thereof, wherein $-R^{x1}$ can be . In some embodiments, R^{X3} can be $-C(=O)OR^{Z1}$, such that $-R^{x1}$ can be . In other embodiments m_4 can be 2, R^{X3} can be $-C(=O)OR^{Z1}$, such that $-R^{x1}$ can be . In still other

embodiments, m_4 and m_5 can each be 2, R^{X3} can be $-C(=O)OR^{Z1}$, such that $-R^{x1}$ can be .

Embodiment 25

[0099] The compound of Embodiment 24, or a pharmaceutically acceptable salt thereof, wherein R^{Z1} can be $-C_{1-4}$ alkyl or hydrogen. An example of  wherein R^{Z1} can be $-C_{1-4}$ alkyl is . When R^{Z1} is hydrogen,  can be .

Embodiment 26

[0100] The compound of Embodiment 23, or a pharmaceutically acceptable salt thereof, wherein $-R^{x1}$ can be . In some embodiments, R^{X3} can be $-C(=O)OH$. In other embodiments, R^{X3} can be $-C(=O)OCH_3$. In other embodiments, R^{X3} can be $-C(=O)OCH_2CH_3$.

Embodiment 27

[0101] The compound of any one of Embodiments 17-22, or a pharmaceutically acceptable salt thereof, wherein R^{1b} can be $-N(R^{m1})R^{n1}$.

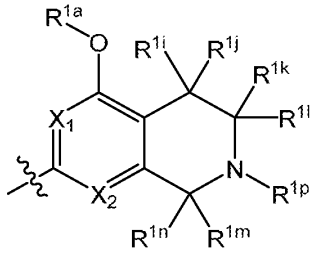
Embodiment 28

[0102] The compound of Embodiment 27, or a pharmaceutically acceptable salt thereof, wherein R^{n1} can be hydrogen.

Embodiment 29

[0103] The compound of Embodiment 27 or 28, or a pharmaceutically acceptable salt thereof, wherein R^{m1} can be $-R^{x2}$.

Embodiment 30

[0104] The compound of Embodiment 1, or a pharmaceutically acceptable salt thereof, wherein A^1 can be 

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Embodiment 31

[0105] The compound of Embodiment 30, or a pharmaceutically acceptable salt thereof, wherein X^1 can be N (nitrogen).

Embodiment 32

[0106] The compound of Embodiment 30 or 30, or a pharmaceutically acceptable salt thereof, wherein X^2 can be CH.

Embodiment 33

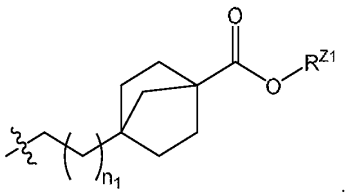
[0107] The compound of any one of Embodiments 30-32, wherein R^{1i}, R^{1j}, R^{1k}, R^{1l}, R^{1m} and R^{1n} can be each hydrogen.

Embodiment 34

[0108] The compound of any one of Embodiments 30-33, wherein R^{1p} can be $-R^{1p1}$.

Embodiment 35

[0109] The compound of Embodiment 34, wherein $-R^{1p1}$ can be



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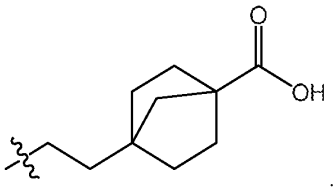
Embodiment 36

[0110] The compound of Embodiment 35, wherein n_1 can be 1 and R^{Z1} can be H, such that $-R^{1p1}$ can be



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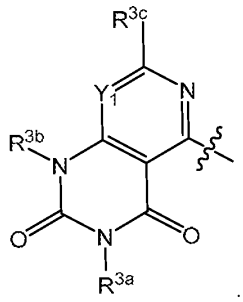
Embodiment 37

[0111] The compound of any one of Embodiments 1-36, or a pharmaceutically acceptable salt thereof, wherein B^1 can be



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Embodiment 38

[0112] The compound of Embodiment 37, or a pharmaceutically acceptable salt thereof, wherein Y_1 can be CH.

Embodiment 39

[0113] The compound of Embodiment 37, or a pharmaceutically acceptable salt thereof, wherein Y^1 can be N (nitrogen).

Embodiment 40

[0114] The compound of any one of Embodiments 37-39, or a pharmaceutically acceptable salt thereof, wherein R^{3a} and R^{3b} can be each $-CH_3$.

Embodiment 41

[0115] The compound of any one of Embodiments 37-40, or a pharmaceutically acceptable salt thereof, wherein R^{3c} can be hydrogen.

Embodiment 42

[0116] The compound of any one of Embodiments 37-40, or a pharmaceutically acceptable salt thereof, wherein R^{3c} can be $-CH_3$.

Embodiment 43

[0117] The compound of any one of Embodiments 37-40, or a pharmaceutically acceptable salt thereof, wherein R^{3c} can be $-C_{1\text{-}2}$ haloalkyl, such as $-CF_3$, $-CHF_2$, $-CH_2F$,$-CCl_3$, $-CHCl_2$, $-CH_2Cl$, $-CH_2CF_3$ or $-CH_2CHF_2$.

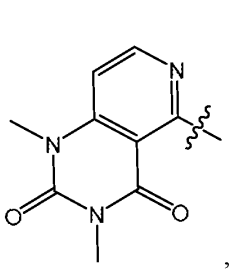
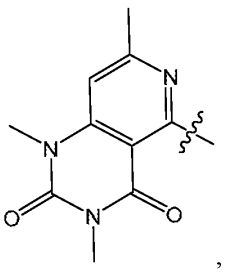
Embodiment 44

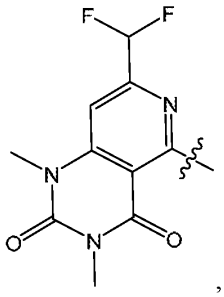
[0118] The compound of Embodiment 43, or a pharmaceutically acceptable salt thereof, wherein R^{3c} can be $-CF_3$.

Embodiment 45

[0119] The compound of Embodiment 43, or a pharmaceutically acceptable salt thereof, wherein R^{3c} can be $-CHF_2$.

Embodiment 46

[0120] The compound of Embodiment 37, or a pharmaceutically acceptable salt thereof, wherein B^1 can be selected from , ,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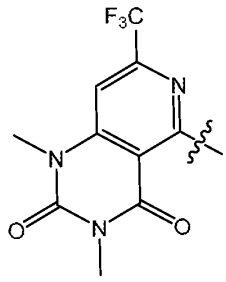
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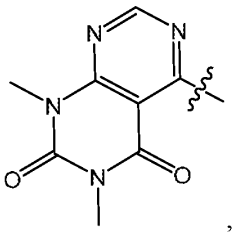
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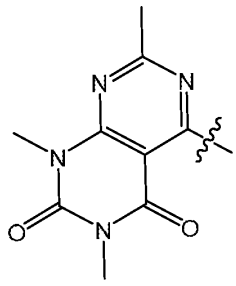
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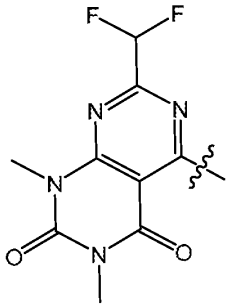
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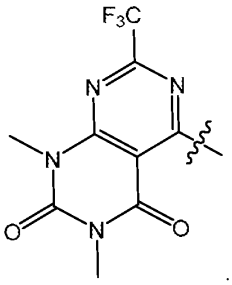
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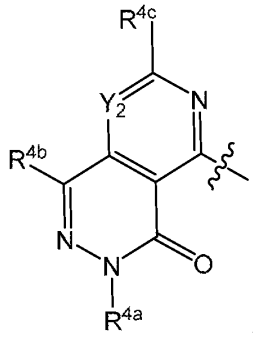
Embodiment 47

[0121] The compound of any one of Embodiments 1-36, or a pharmaceutically acceptable salt thereof, wherein B^1 can be 
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Embodiment 48

[0122] The compound of Embodiment 47, or a pharmaceutically acceptable salt thereof, wherein Y_2 can be CH.

Embodiment 49

[0123] The compound of Embodiment 47 or 48, or a pharmaceutically acceptable salt thereof, wherein R^{4a} can be $-CH_3$.

Embodiment 50

[0124] The compound of any one of Embodiments 47-49, or a pharmaceutically acceptable salt thereof, wherein R^{4b} can be hydrogen.

Embodiment 51

[0125] The compound of any one of Embodiments 47-50, or a pharmaceutically acceptable salt thereof, wherein R^{4c} can be hydrogen.

Embodiment 52

[0126] The compound of any one of Embodiments 47-50, or a pharmaceutically acceptable salt thereof, wherein R^{4c} can be $-CH_3$.

Embodiment 53

[0127] The compound of any one of Embodiments 47-50, or a pharmaceutically acceptable salt thereof, wherein R^{4c} can be $-C_{1\text{-}2}$ haloalkyl, such as $-CF_3$, $-CHF_2$, $-CH_2F$,$-CCl_3$, $-CHCl_2$, $-CH_2Cl$, $-CH_2CF_3$ or $-CH_2CHF_2$.

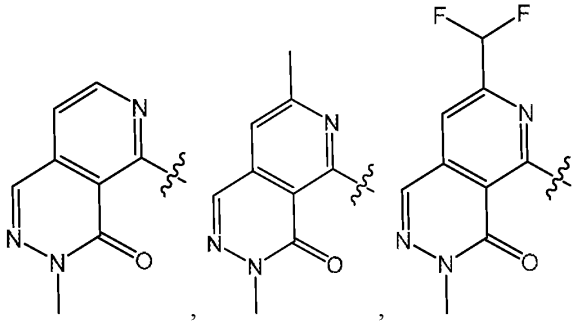
Embodiment 54

[0128] The compound of Embodiment 53, or a pharmaceutically acceptable salt thereof, wherein R^{4c} can be $-CF_3$.

Embodiment 55

[0129] The compound of Embodiment 53, or a pharmaceutically acceptable salt thereof, wherein R^{4c} can be $-CHF_2$.

Embodiment 56

[0130] The compound of Embodiment 47, or a pharmaceutically acceptable salt thereof, wherein B^1 can be selected from 

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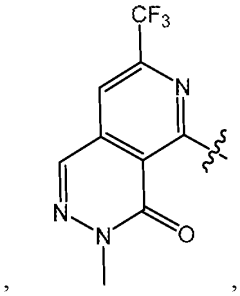
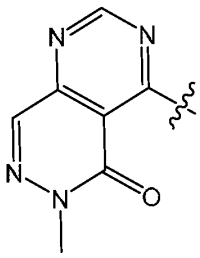
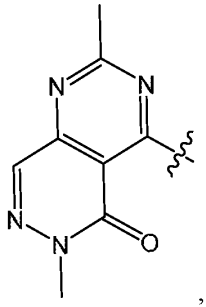
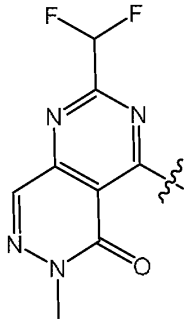
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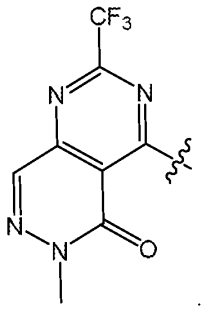


Embodiment 57

[0131] The compound of any one of Embodiments 1-56, or a pharmaceutically acceptable salt thereof, wherein R^{2a}, R^{2b}, R^{2c}, R^{2e}, R^{2g} and R^{2h} can be each hydrogen.

Embodiment 58

[0132] The compound of any one of Embodiments 1-57, or a pharmaceutically acceptable salt thereof, wherein R^{2d} and R^{2f} can be each halogen.

Embodiment 59

[0133] The compound of any one of Embodiments 1-57, or a pharmaceutically acceptable salt thereof, wherein R^{2d} can be halogen; and R^{2f} can be $-CH_3$.

Embodiment 60

[0134] The compound of any one of Embodiments 1-57, or a pharmaceutically acceptable salt thereof, wherein R^{2d} can be $-CH_3$; and R^{2f} can be halogen.

Embodiment 61

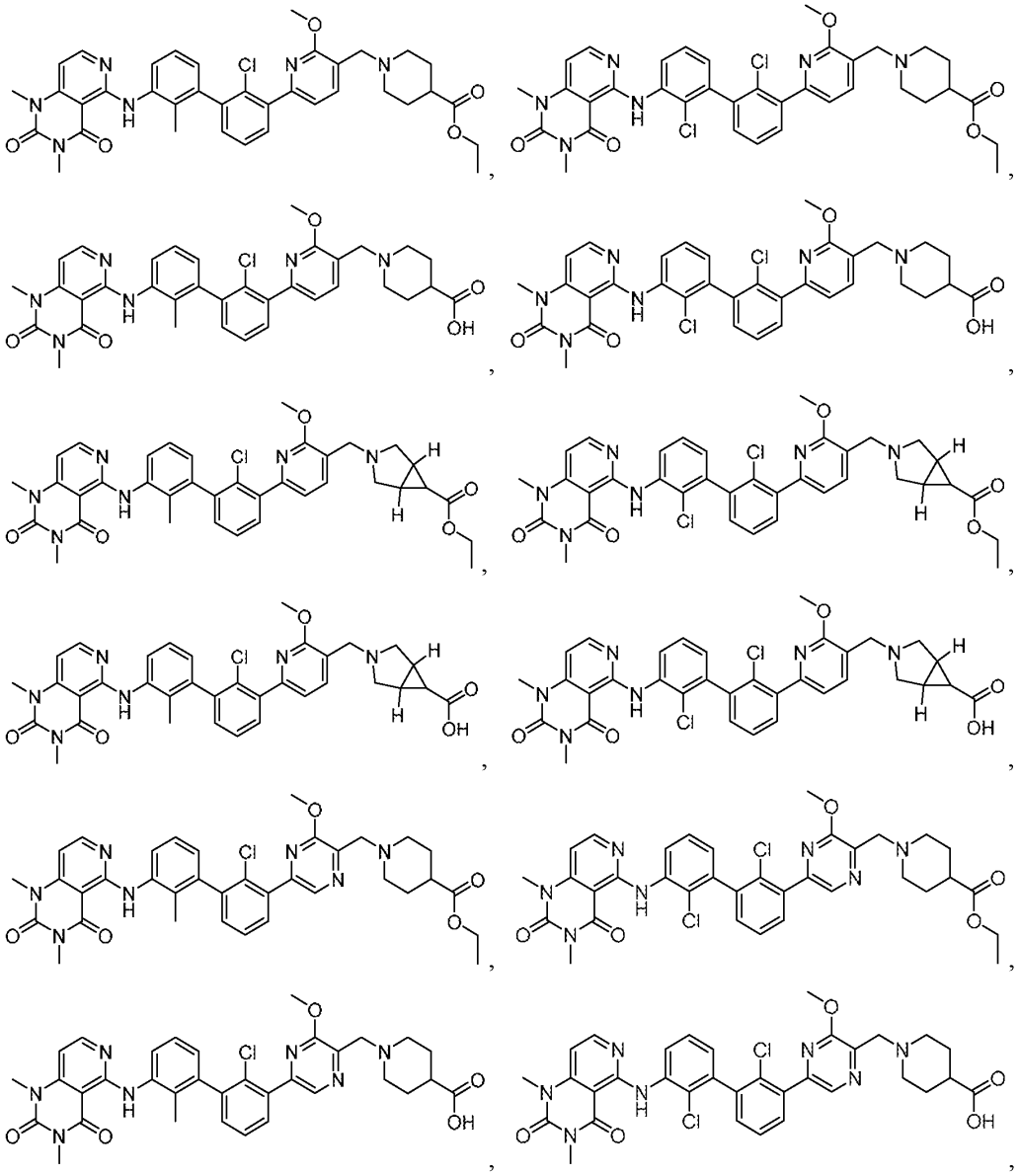
[0135] The compound of any one of Embodiments 58-60, or a pharmaceutically acceptable salt thereof, wherein the halogen can be chloro.

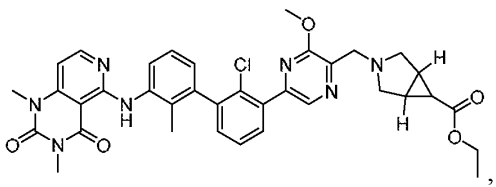
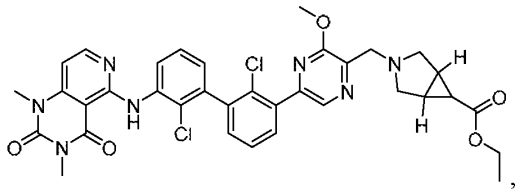
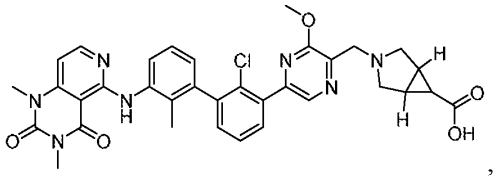
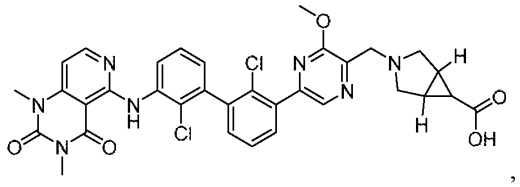
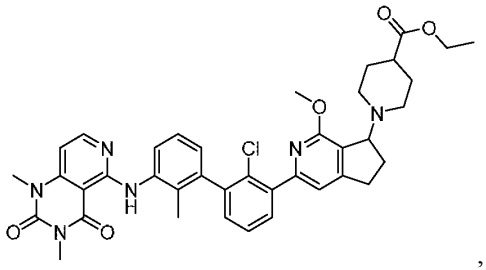
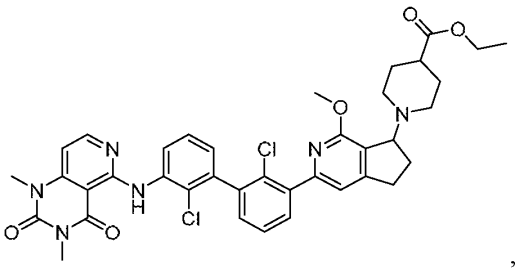
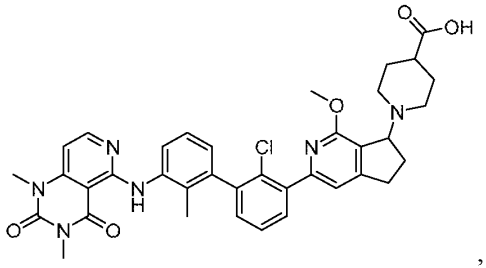
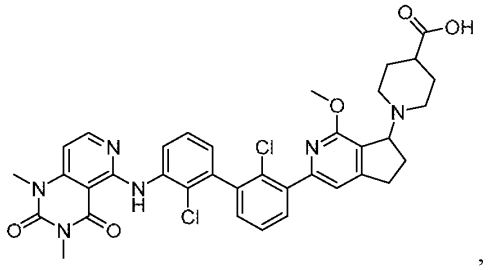
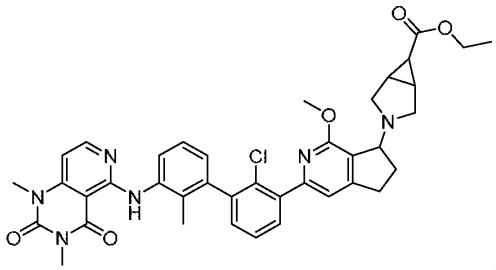
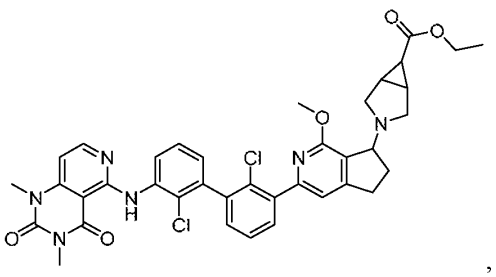
Embodiment 62

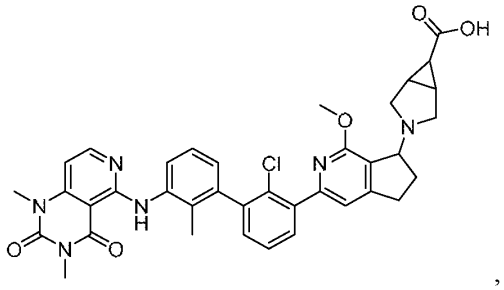
[0136] The compound of any one of Claims 1-57, or a pharmaceutically acceptable salt thereof, wherein R^{2d} and R^{2f} can be each $-CH_3$.

Embodiment 63

[0137] The compound of Embodiment 1, or a pharmaceutically acceptable salt thereof, selected from:



,
,
,
,
,
,
,
,
,
,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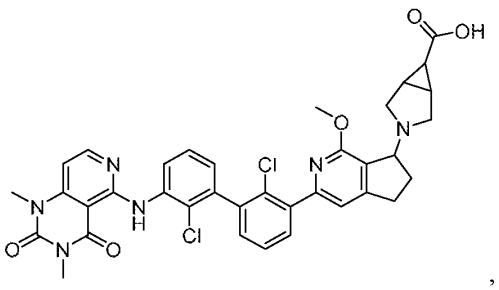
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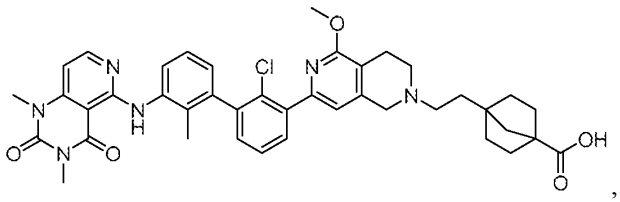
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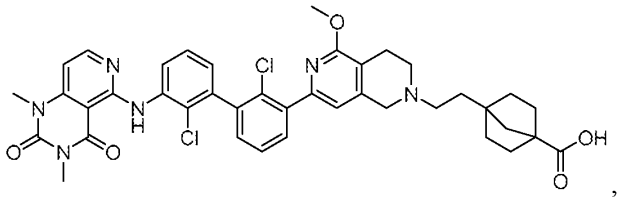
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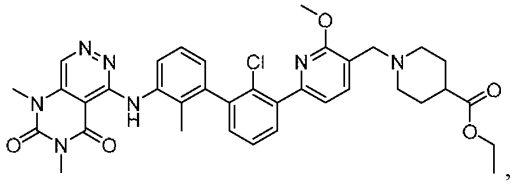
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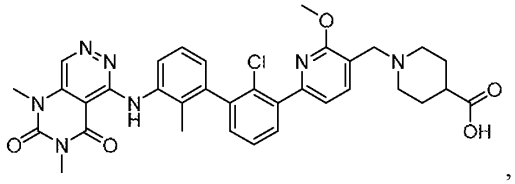
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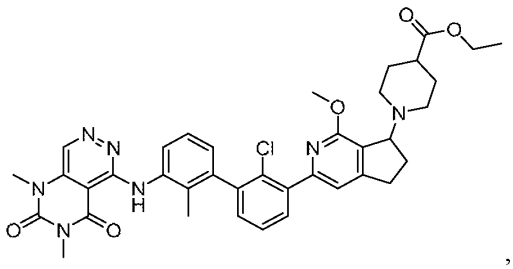
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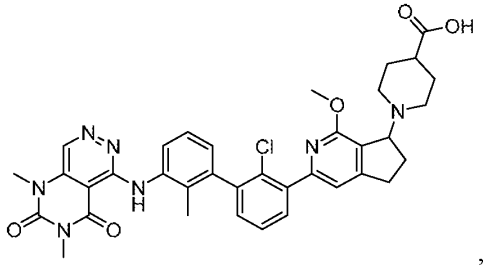
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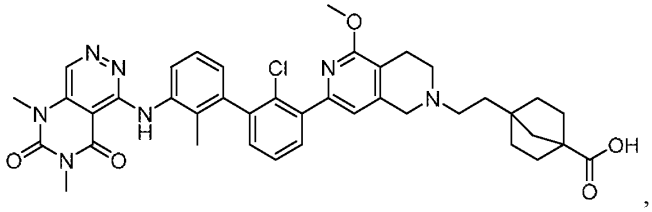
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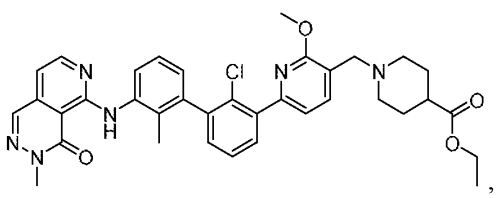
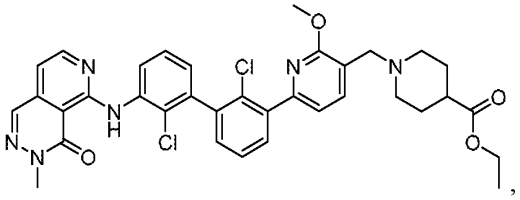
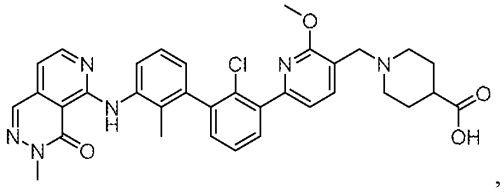
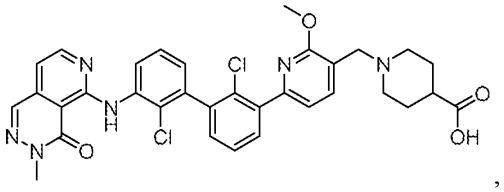
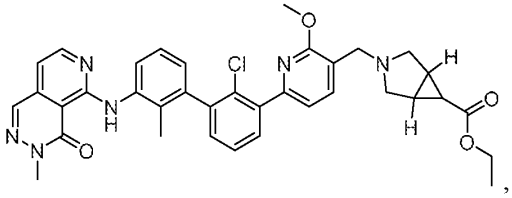
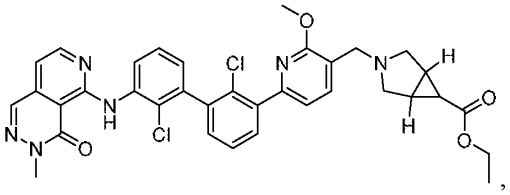
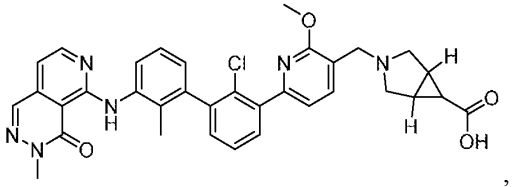
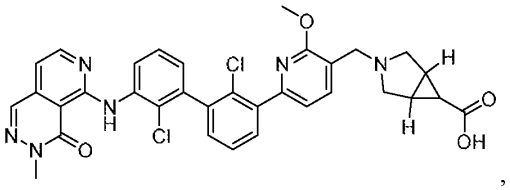
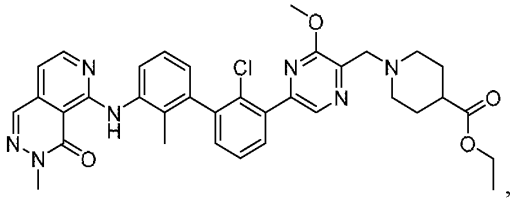
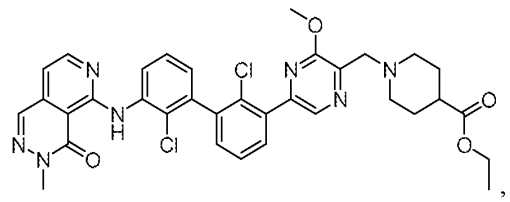
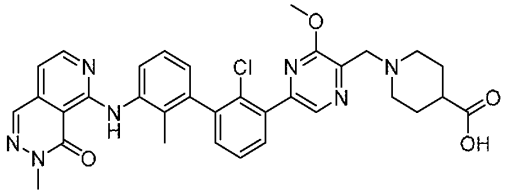
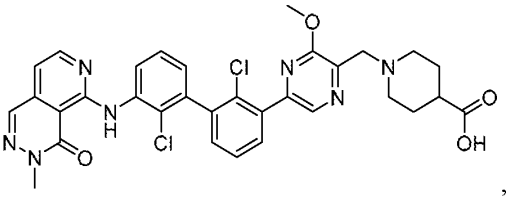
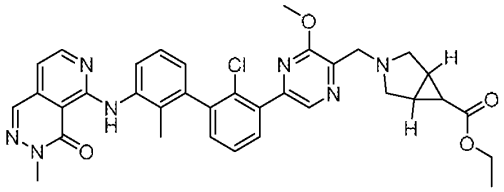
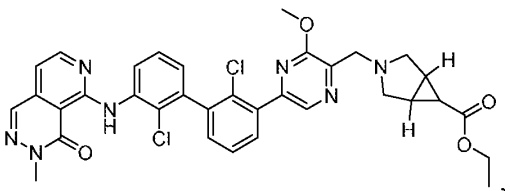
,
,
,
,
,
,
,
,
,
,
,
,
,
,
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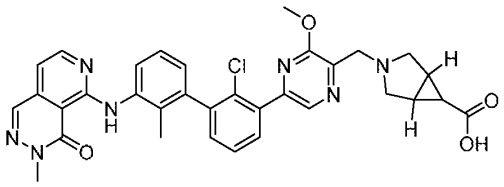
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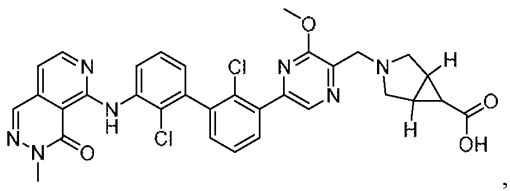
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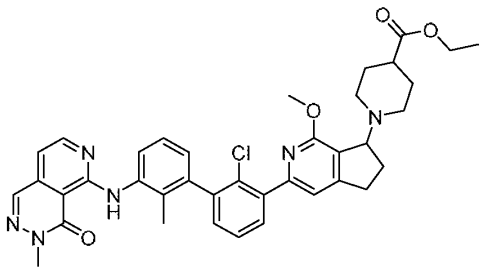
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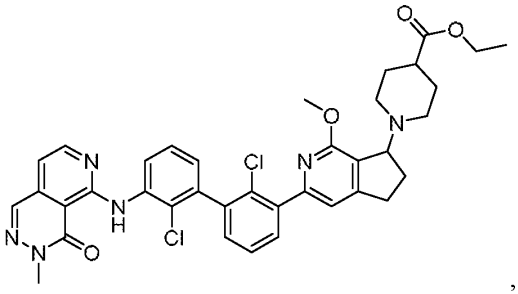
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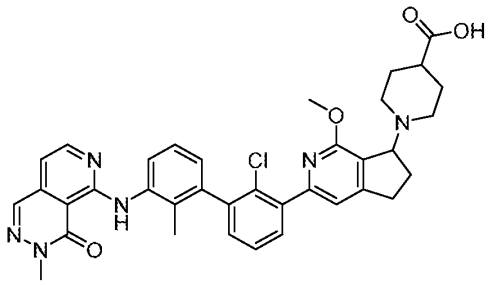
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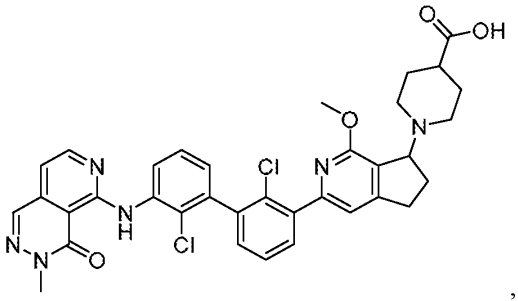
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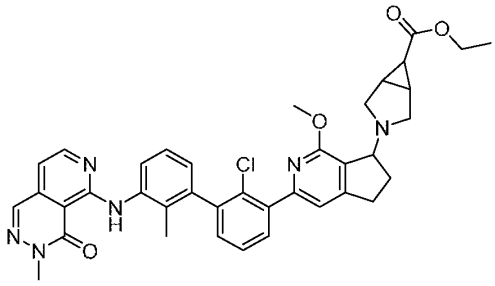
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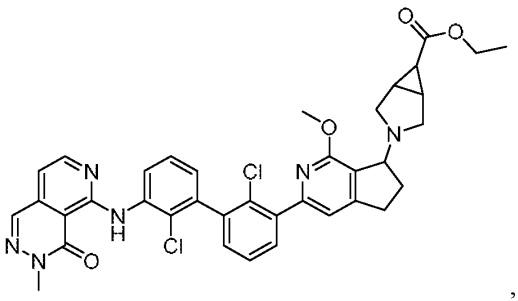
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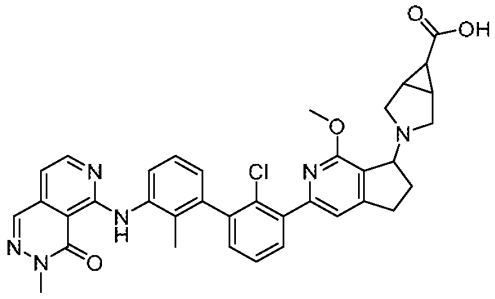
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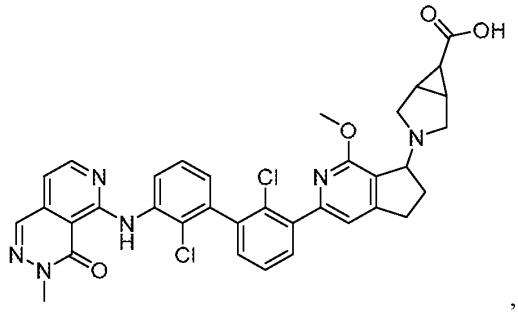
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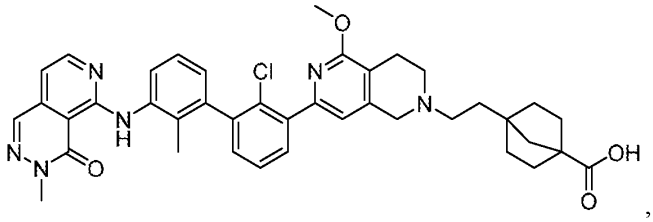

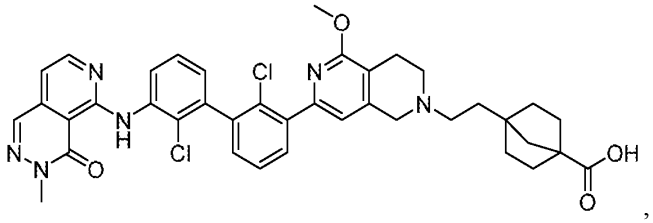

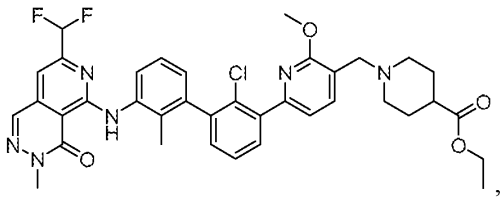

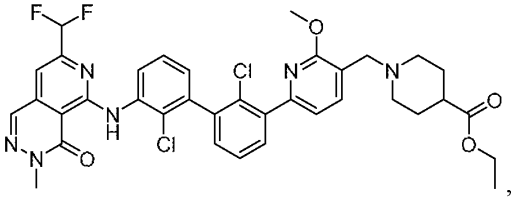

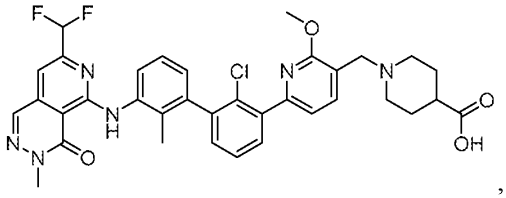

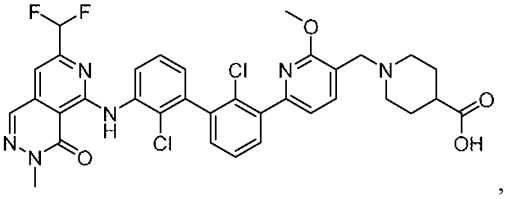

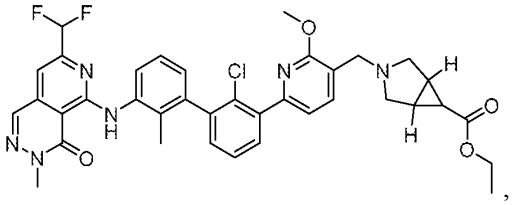

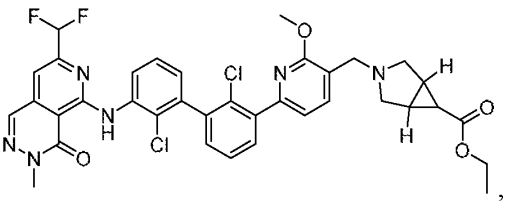

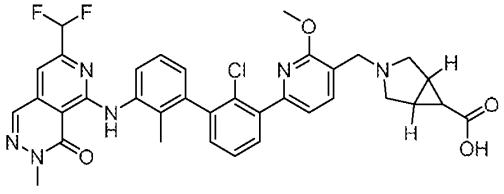

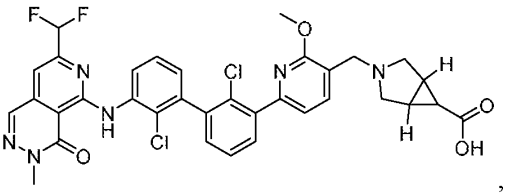

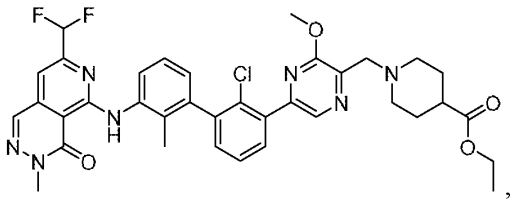
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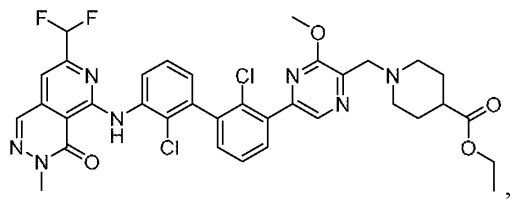
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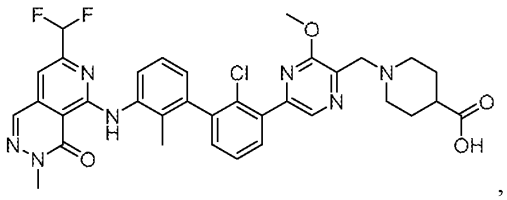
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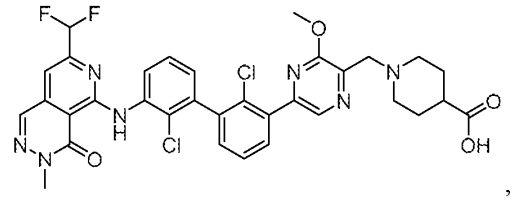
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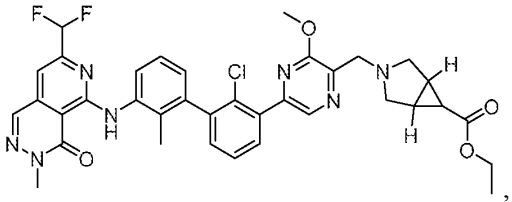
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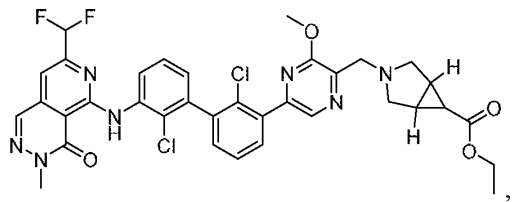
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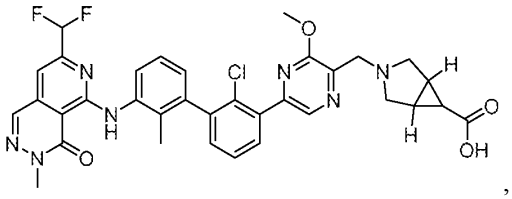
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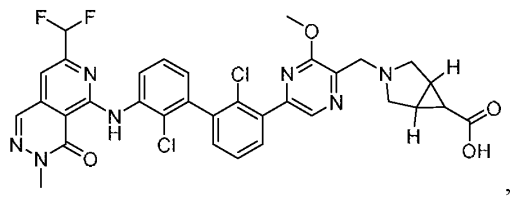
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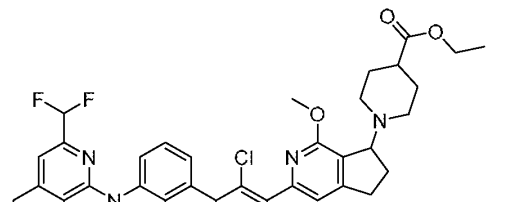
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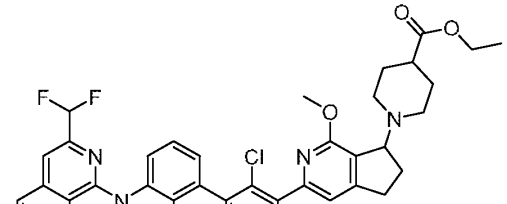
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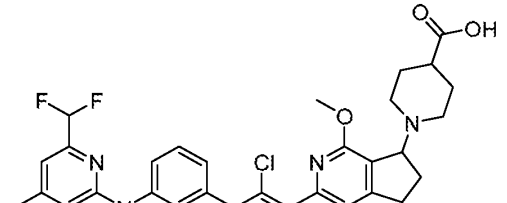
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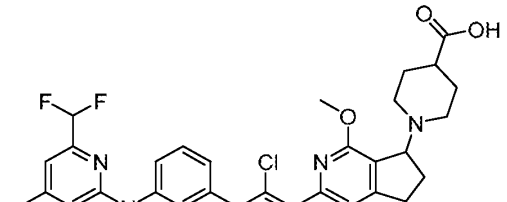
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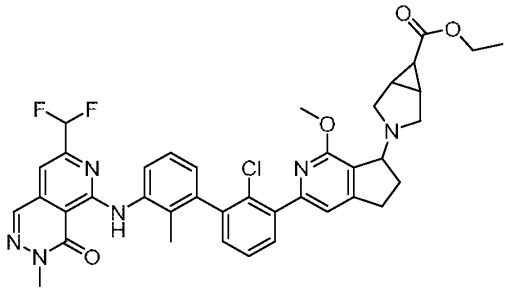
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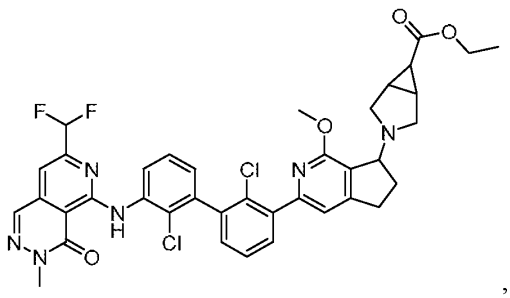
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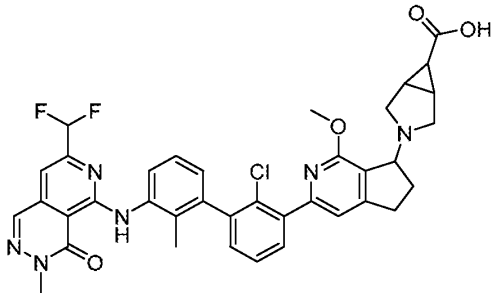
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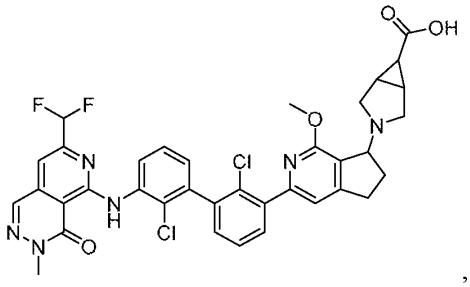
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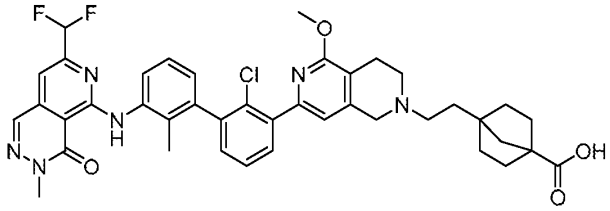
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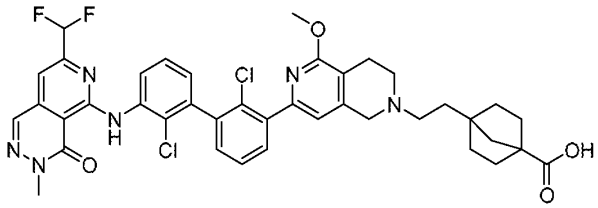
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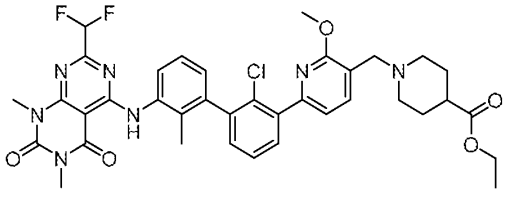
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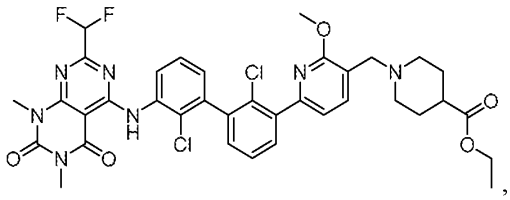
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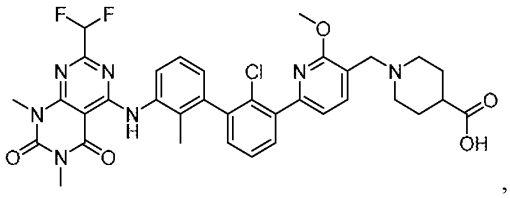
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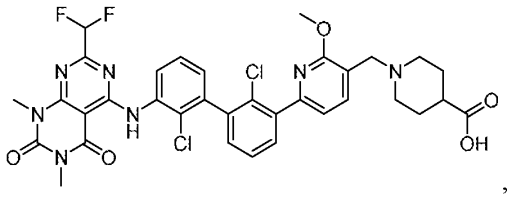
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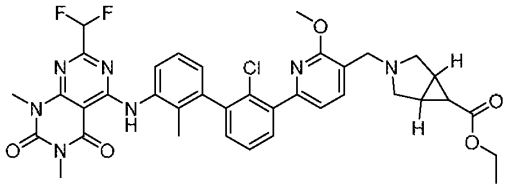
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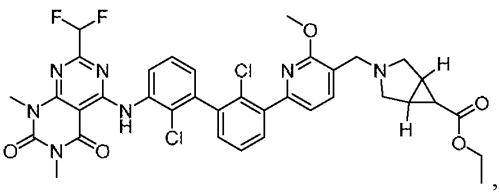
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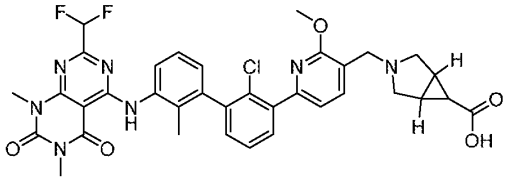
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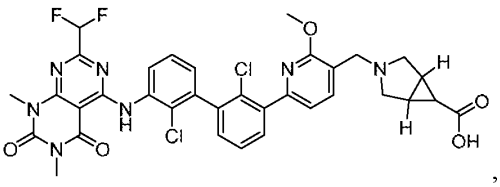
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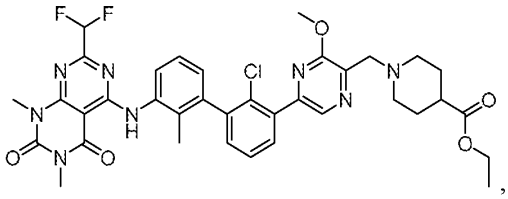
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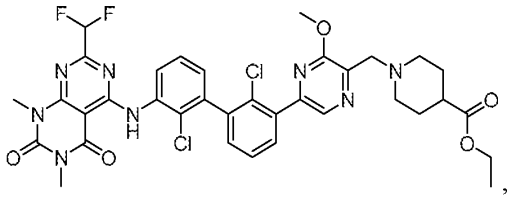
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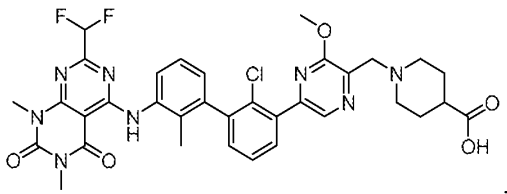
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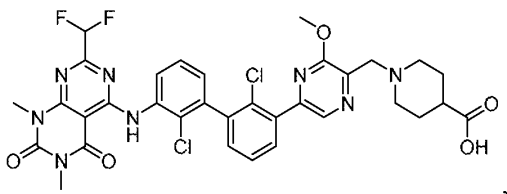
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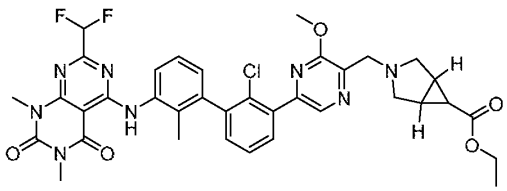
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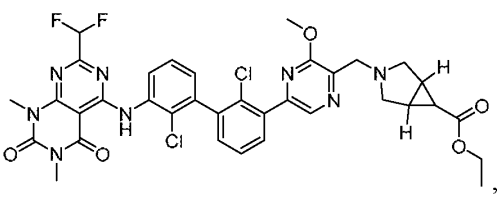
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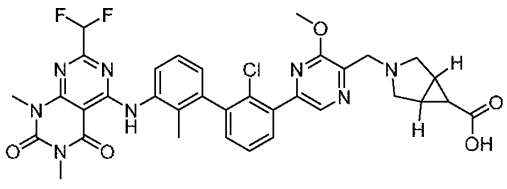
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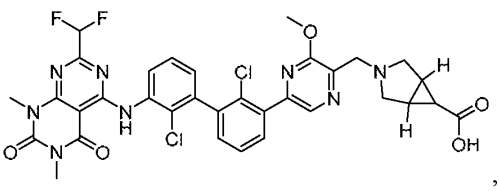
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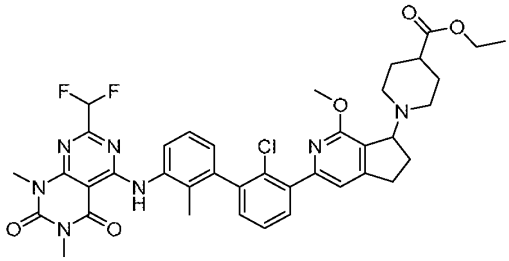
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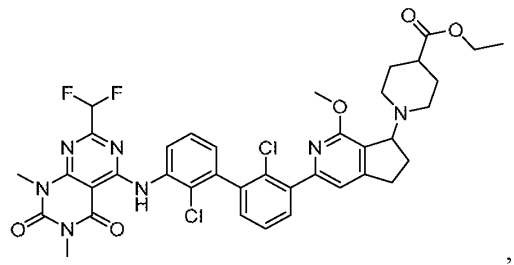
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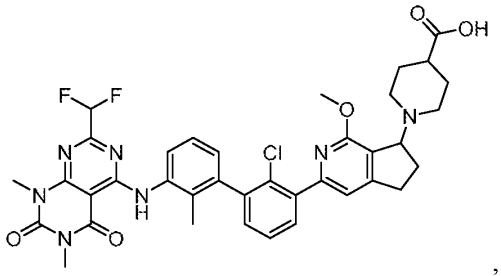
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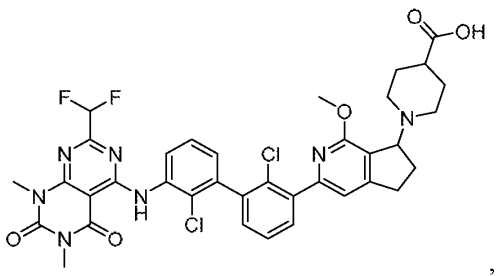
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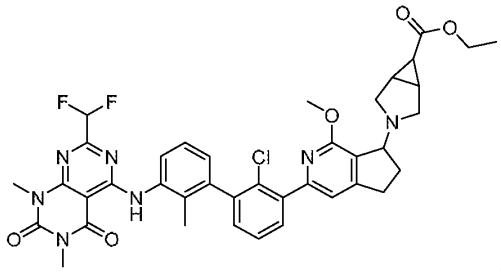
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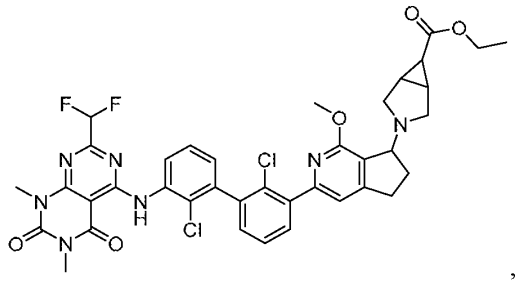
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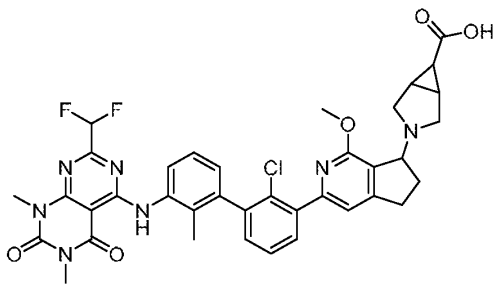
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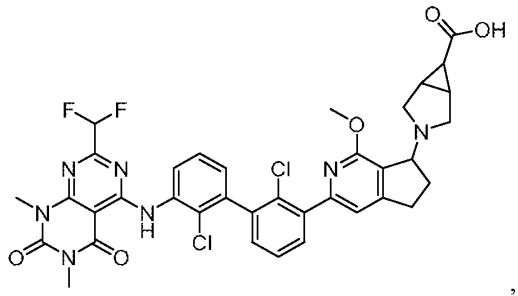
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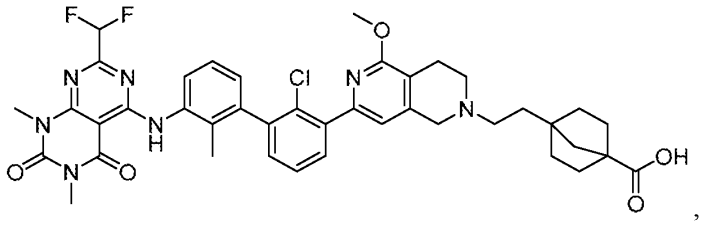
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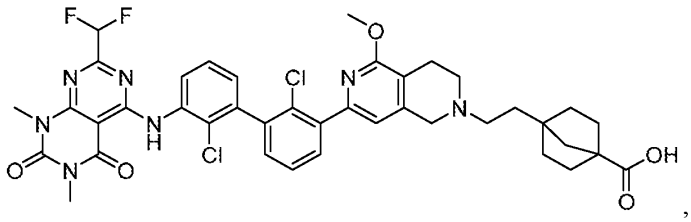

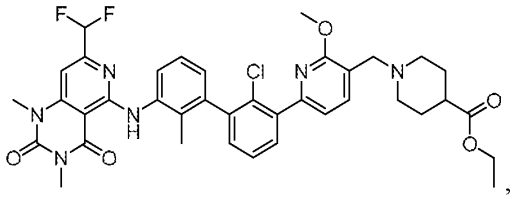

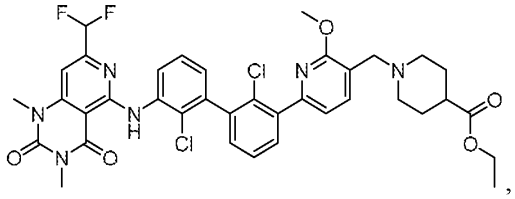

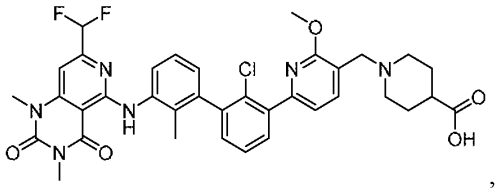

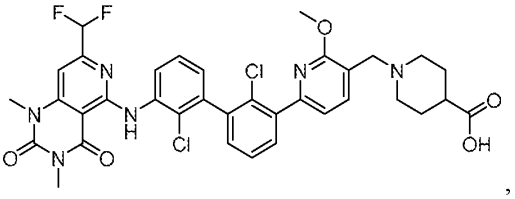

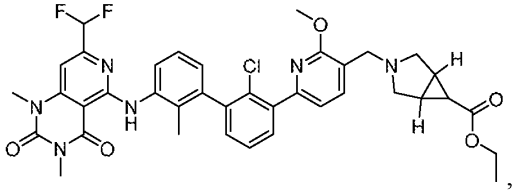

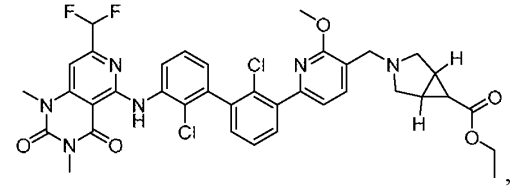

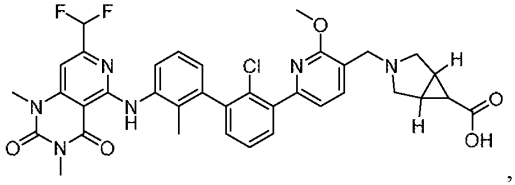

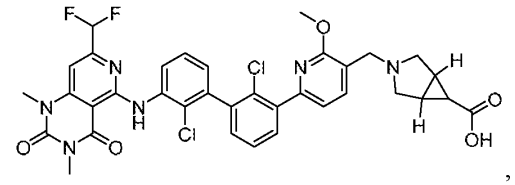

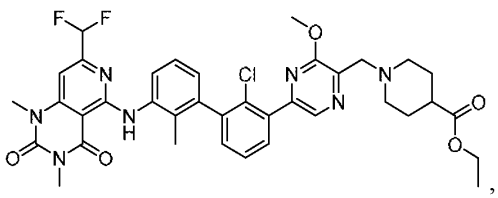

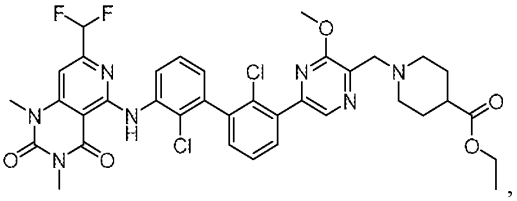

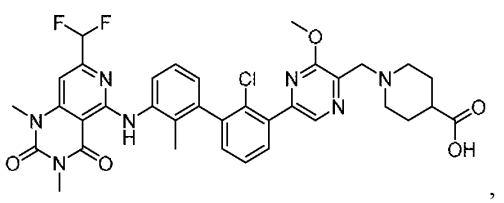
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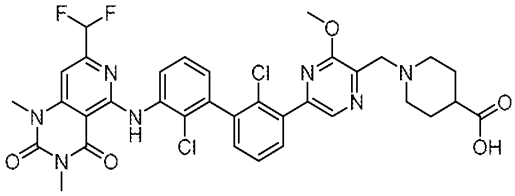
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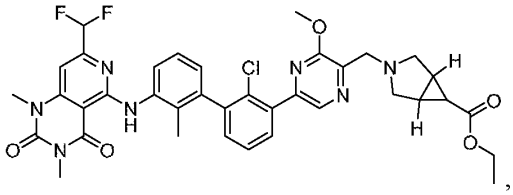
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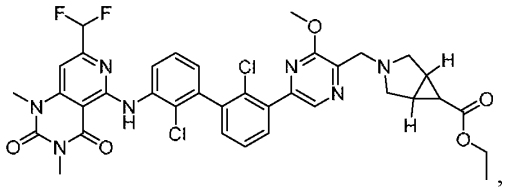
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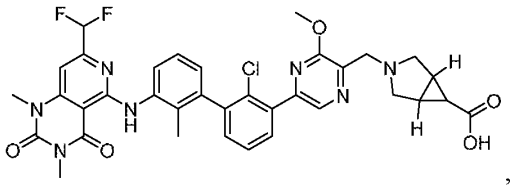
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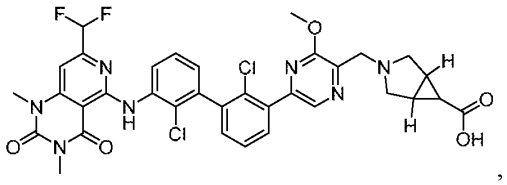
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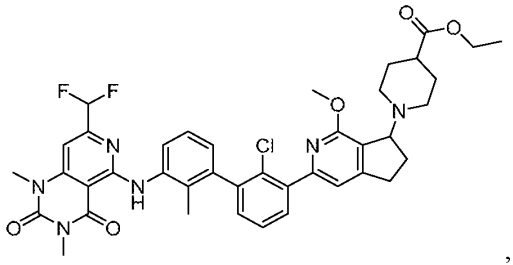
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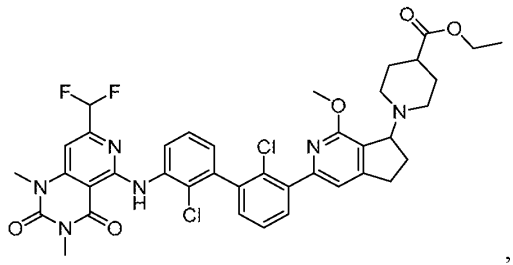
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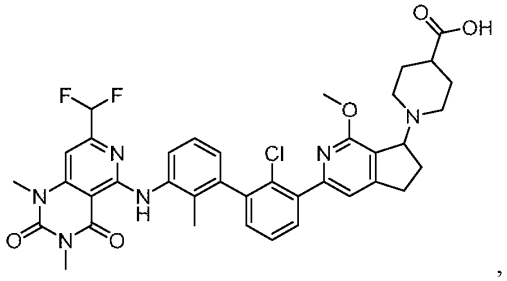
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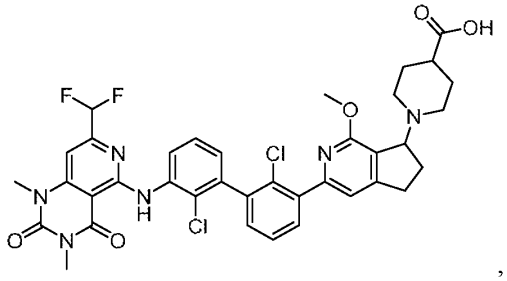
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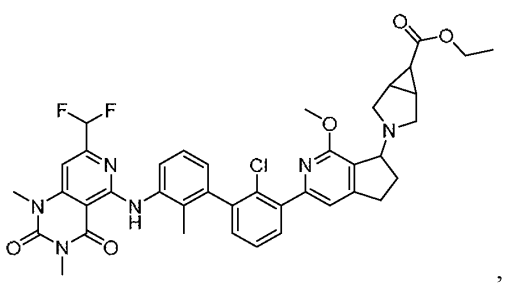
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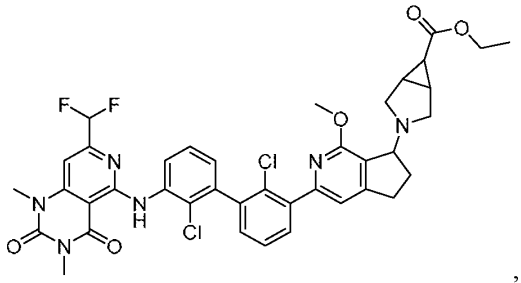
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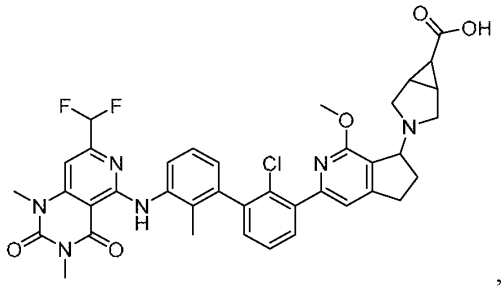
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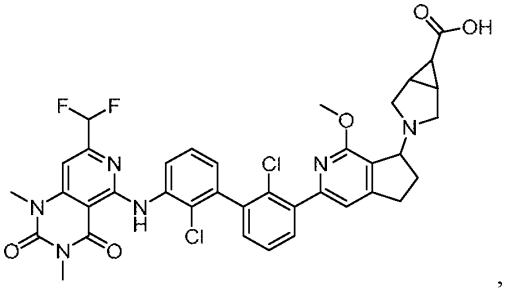
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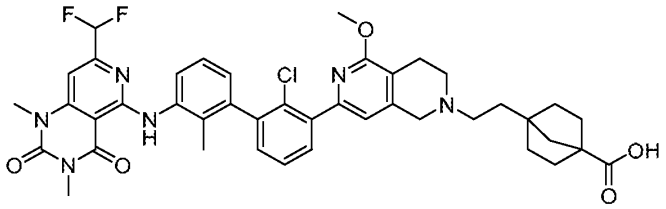
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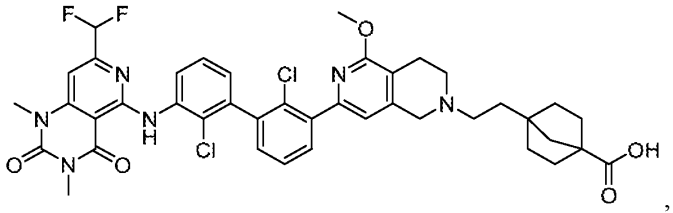
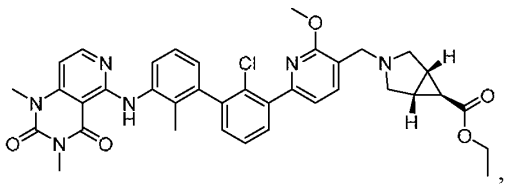

, or a pharmaceutically acceptable salt of any of the foregoing.

Embodiment 64

[0138] The compound of Embodiment 1, or a pharmaceutically acceptable salt thereof, selected from: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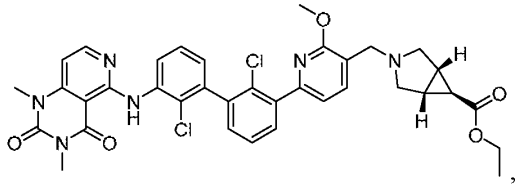
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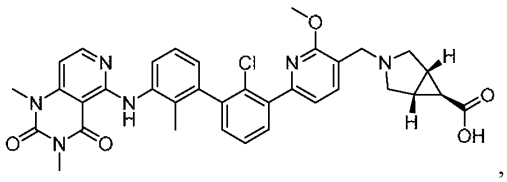
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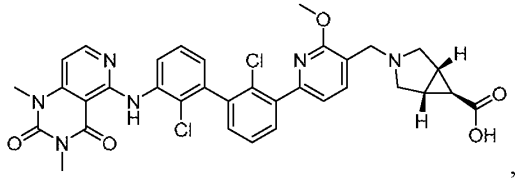
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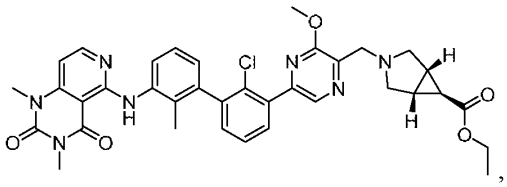
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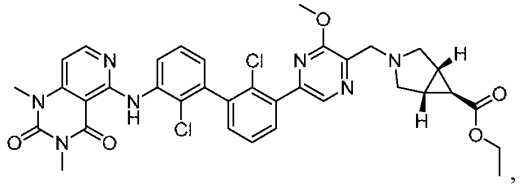
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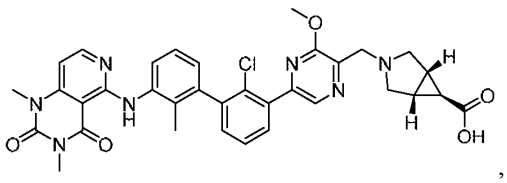
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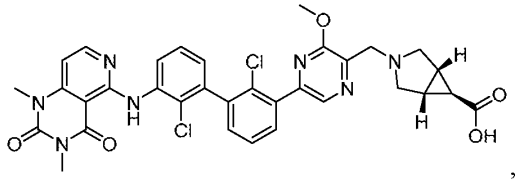
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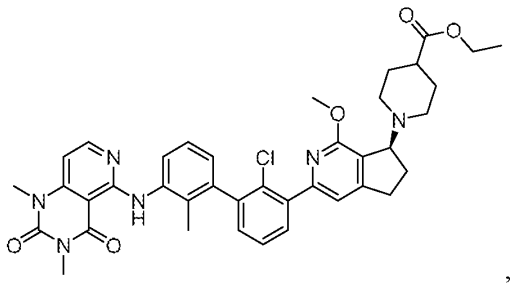
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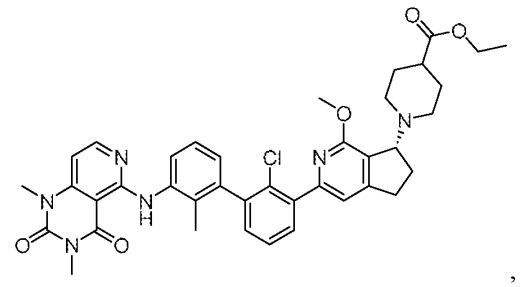
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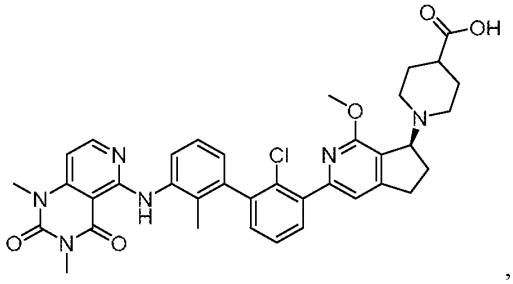
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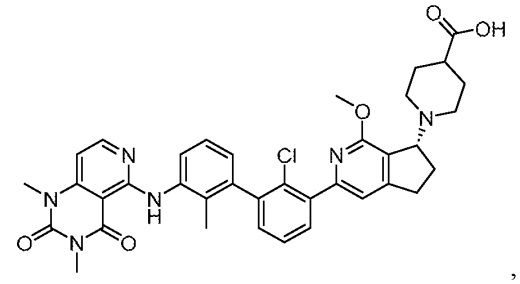
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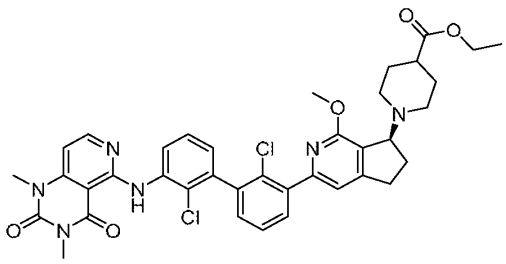
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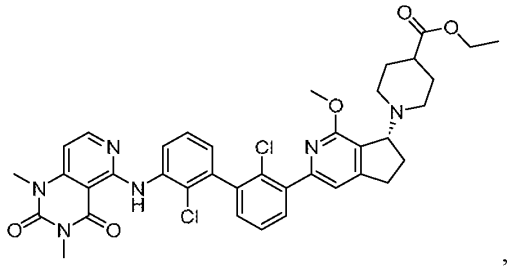
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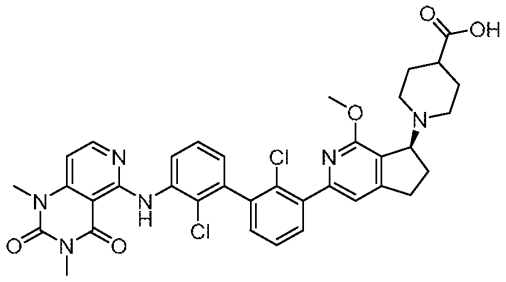
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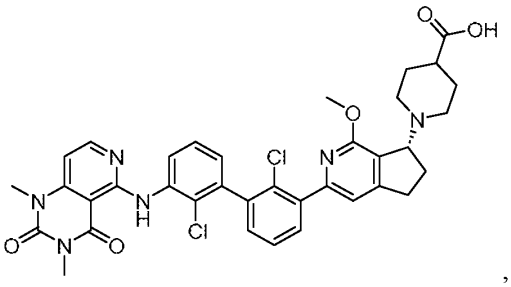
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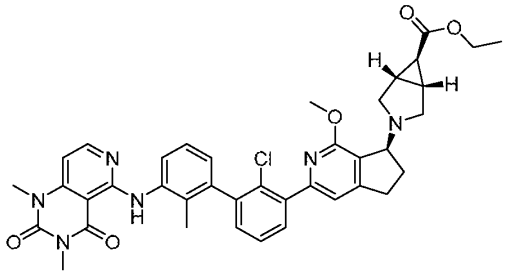
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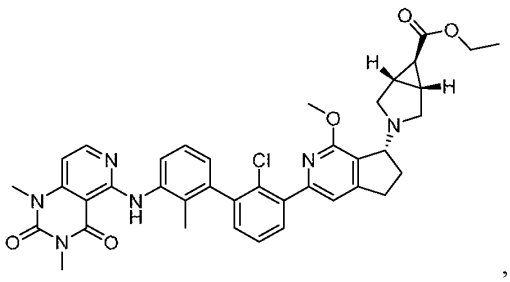
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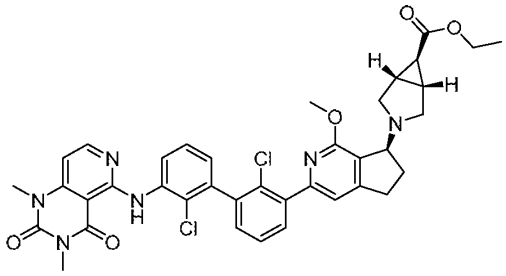
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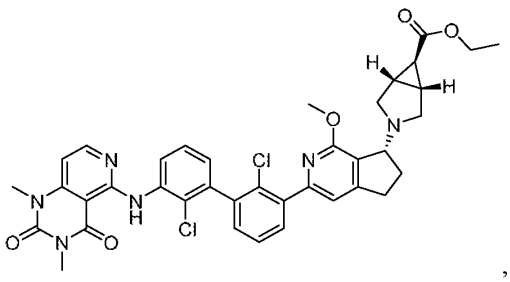
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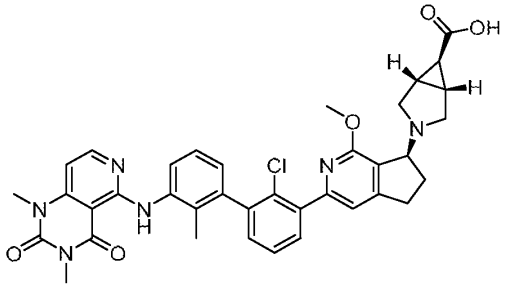
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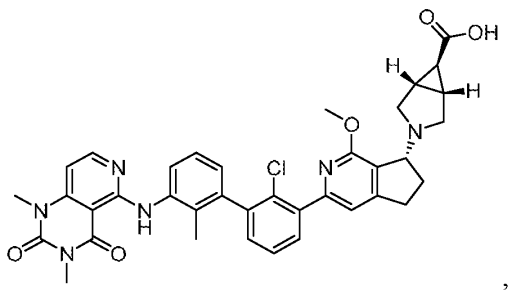
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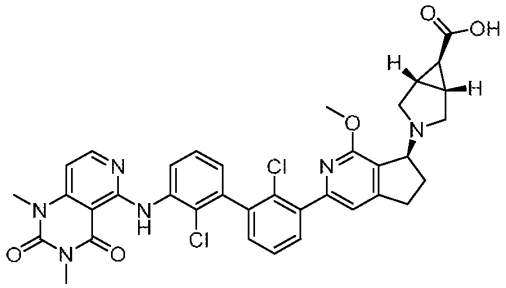
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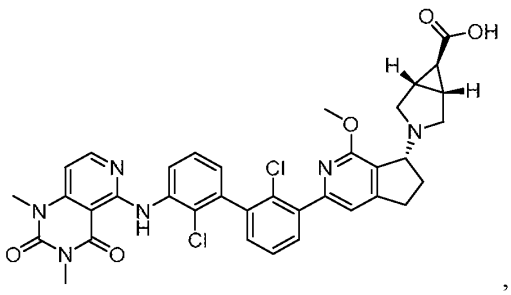
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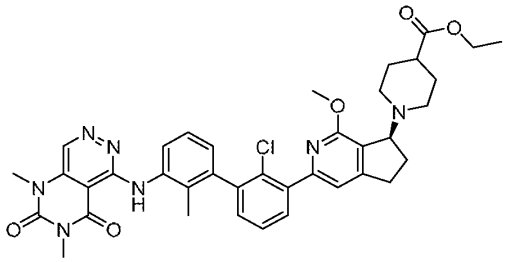
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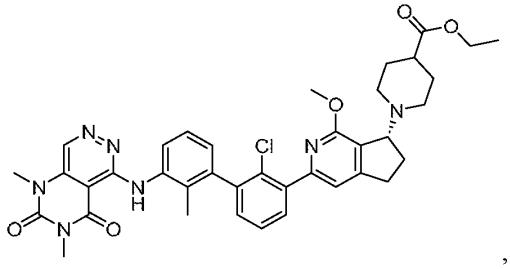
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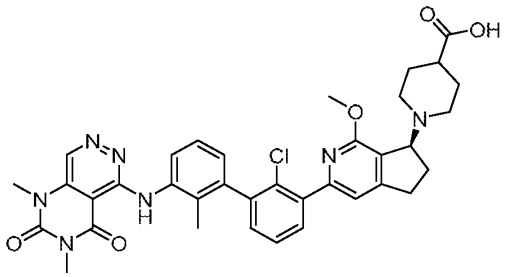
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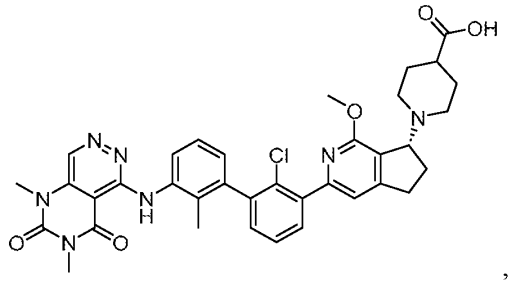
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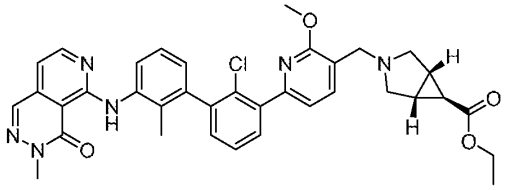
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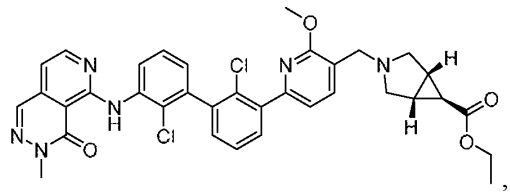
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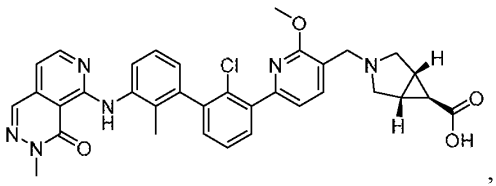
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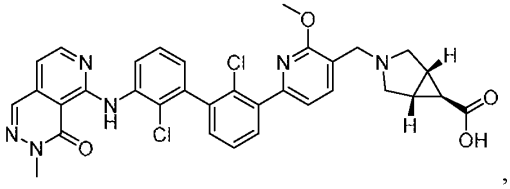
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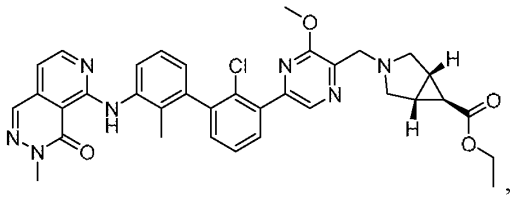
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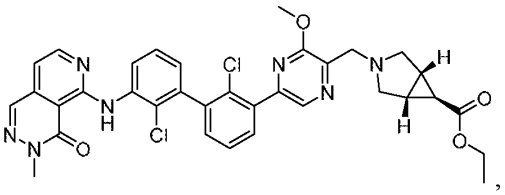
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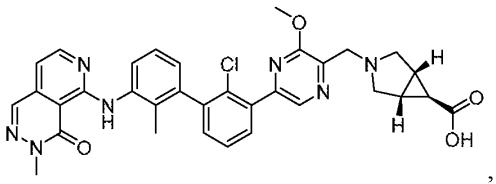
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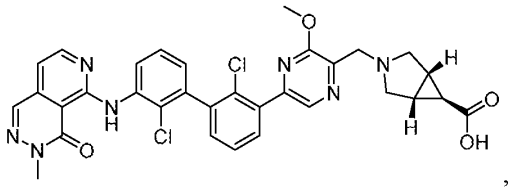
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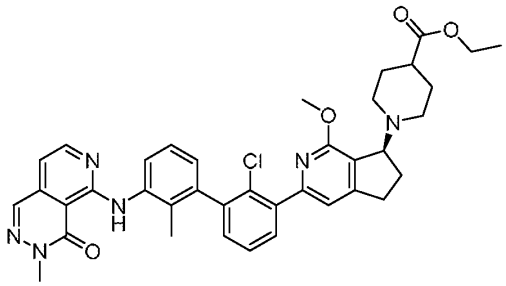
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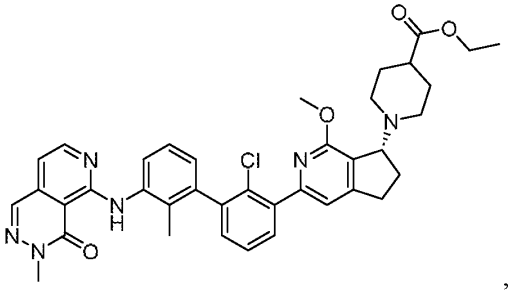
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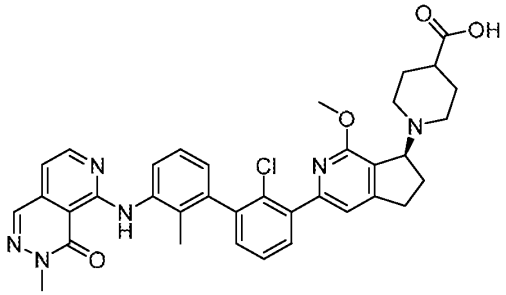
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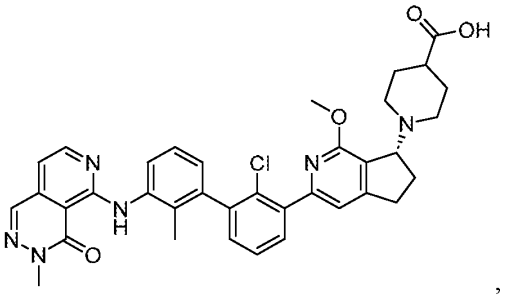
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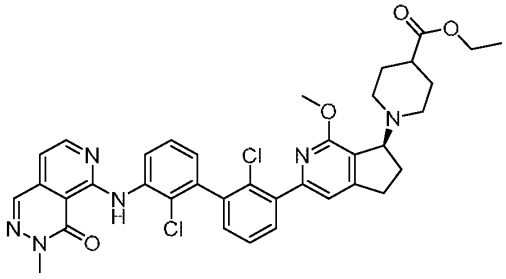
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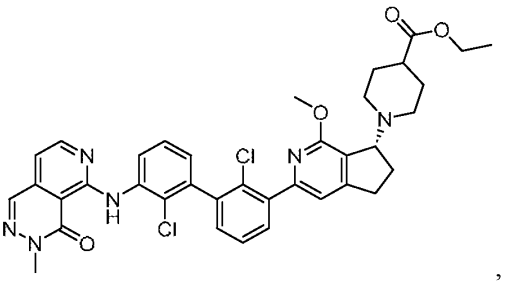
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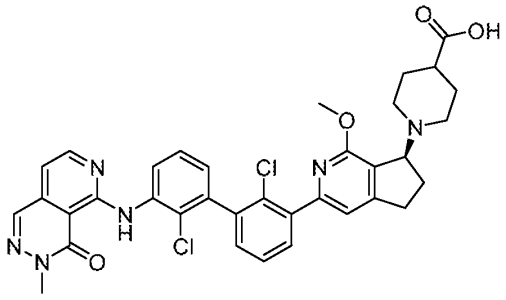
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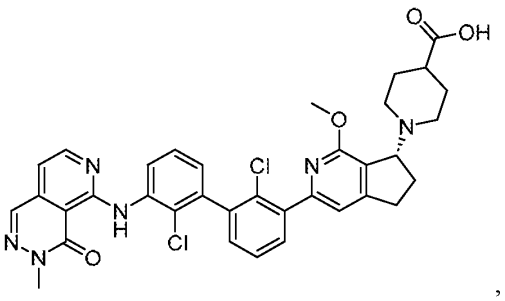
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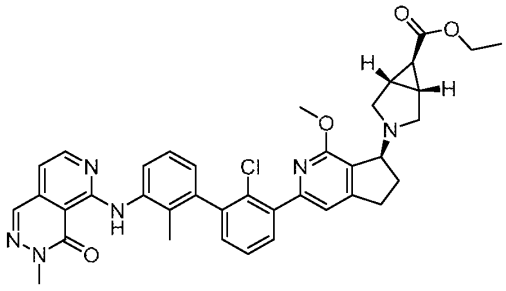
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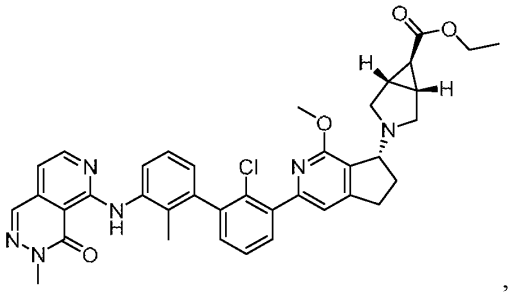
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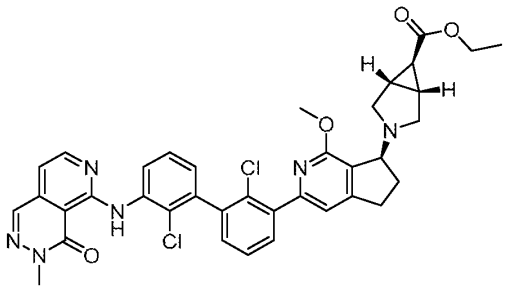
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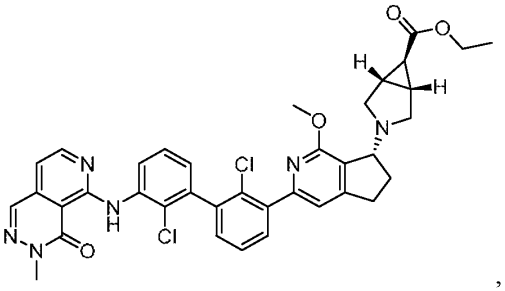
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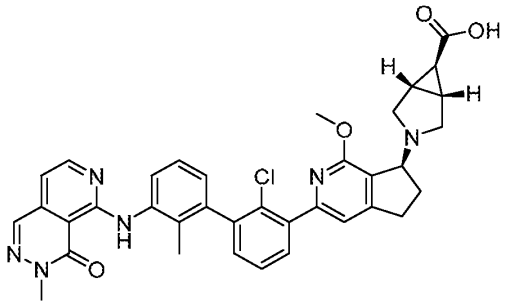
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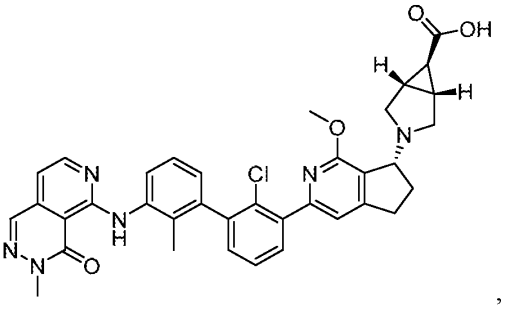
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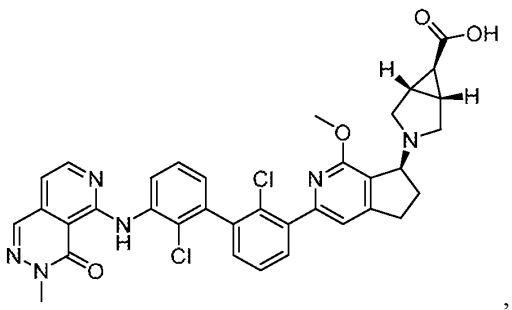
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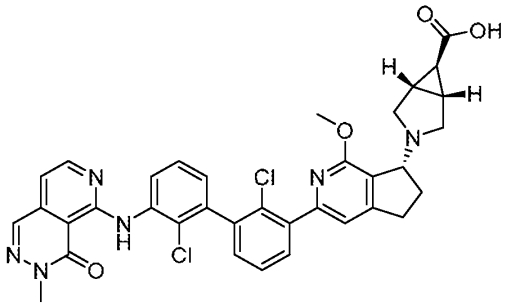
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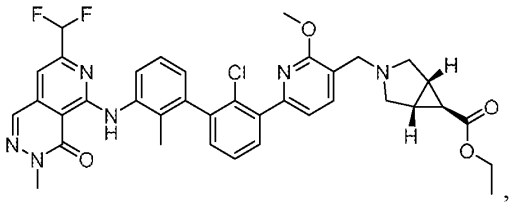
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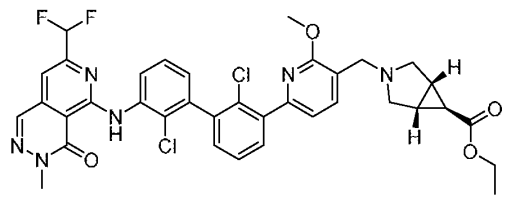
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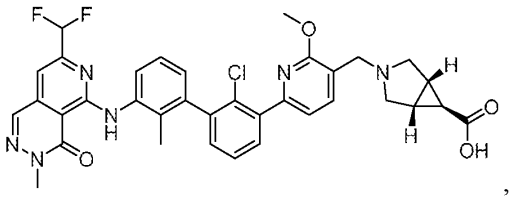
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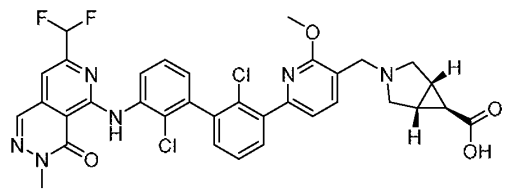
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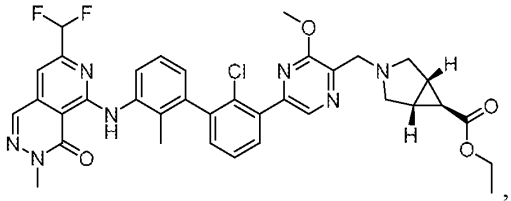
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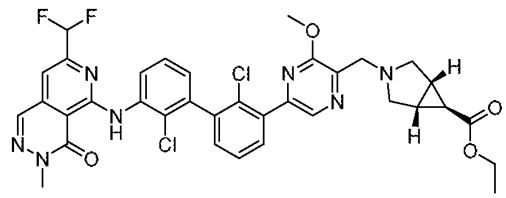
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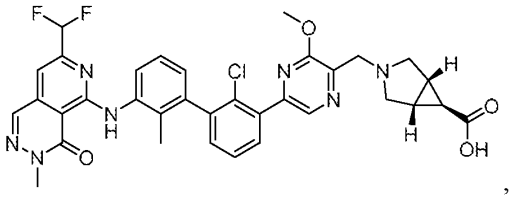
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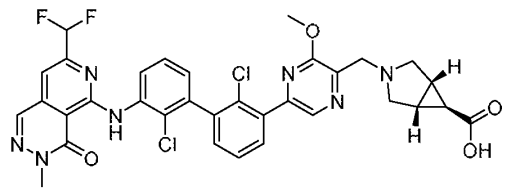
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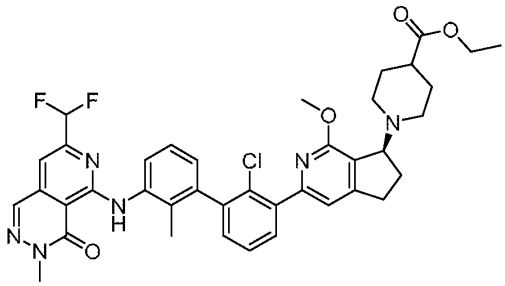
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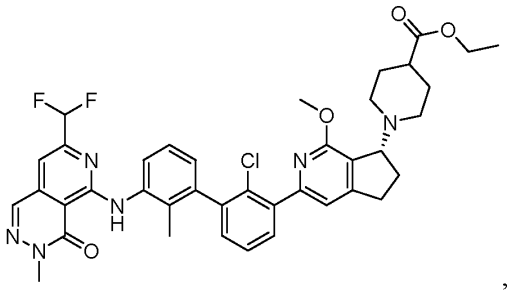
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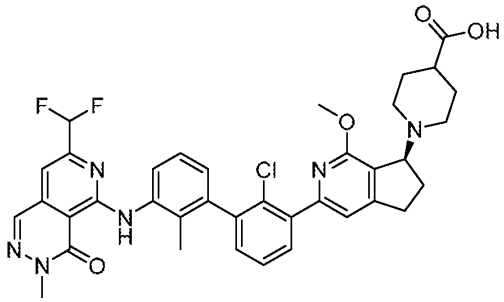
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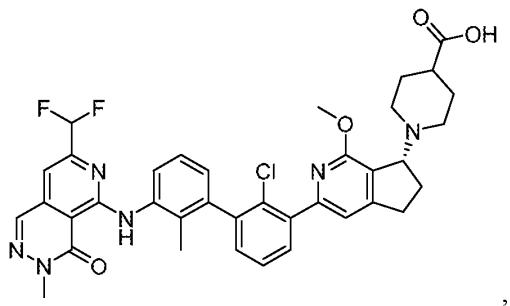
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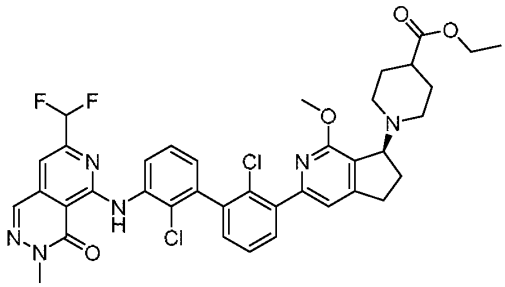
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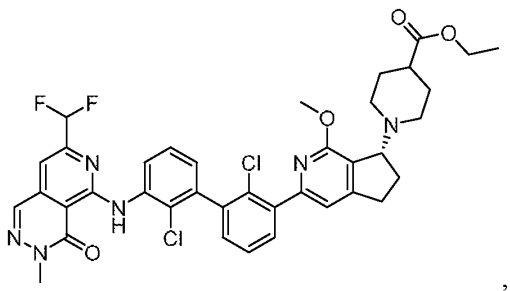
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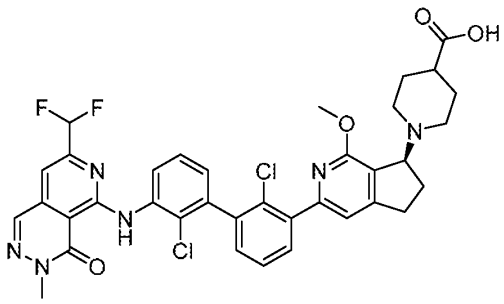
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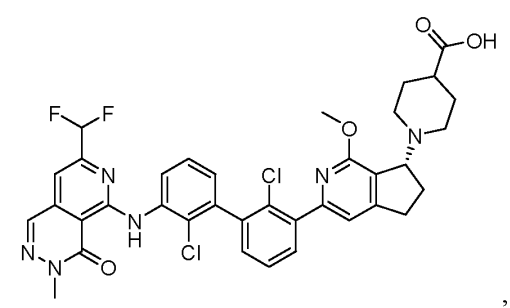
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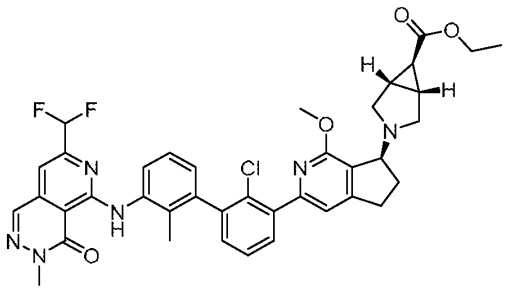
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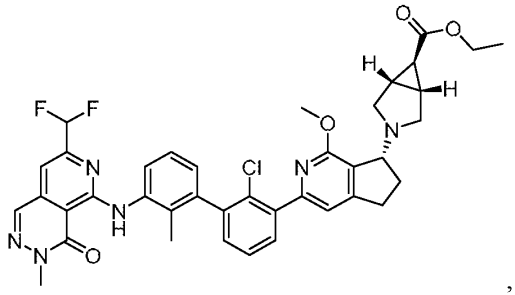
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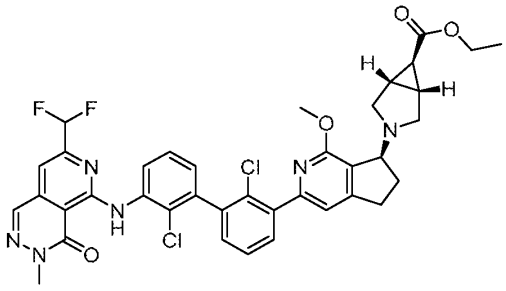
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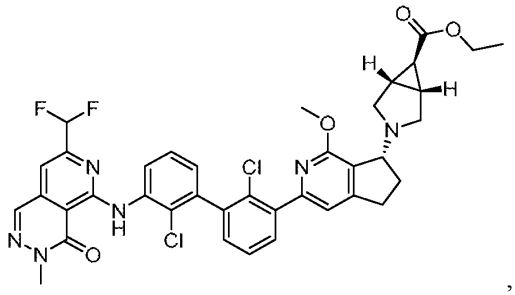
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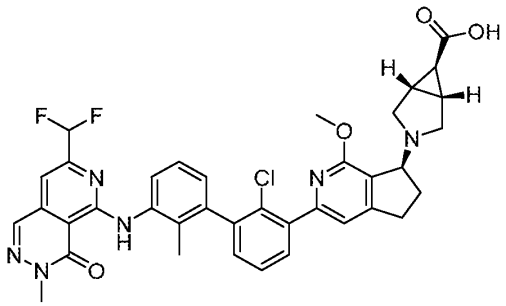
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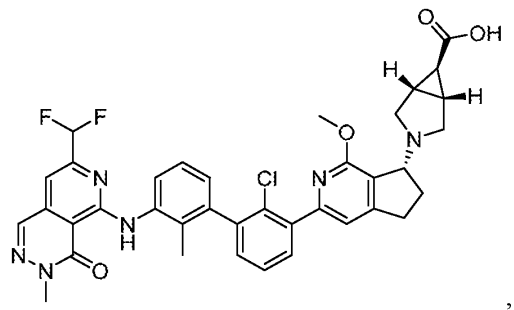
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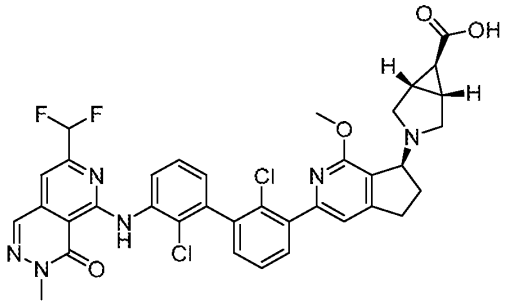
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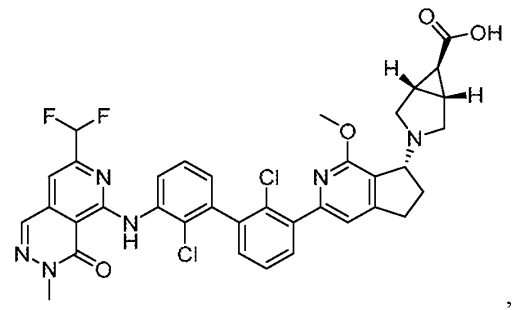
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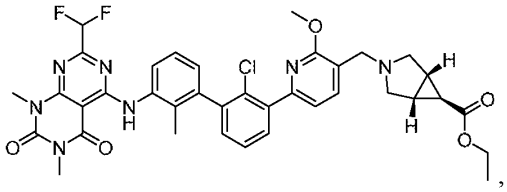
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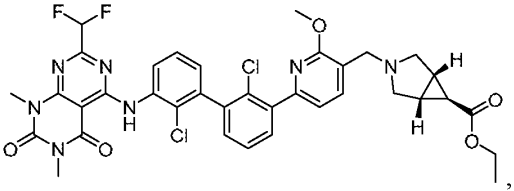
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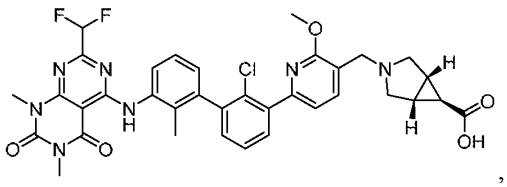
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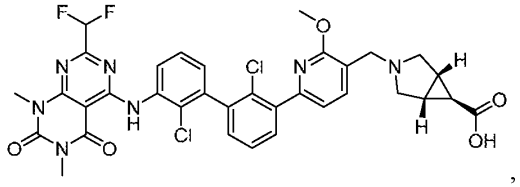
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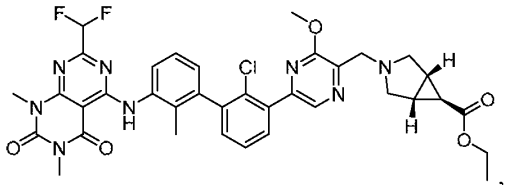
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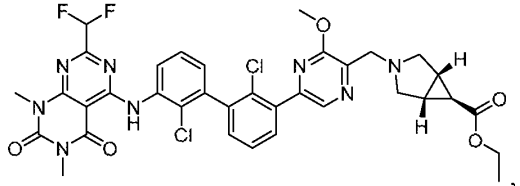
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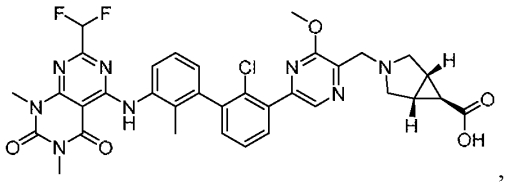
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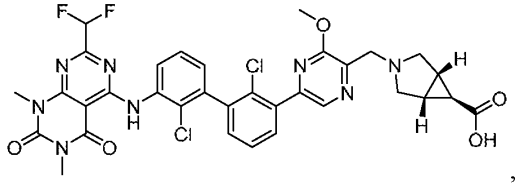
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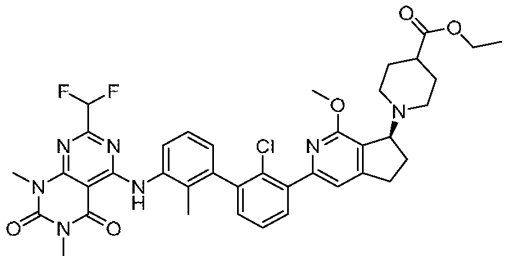
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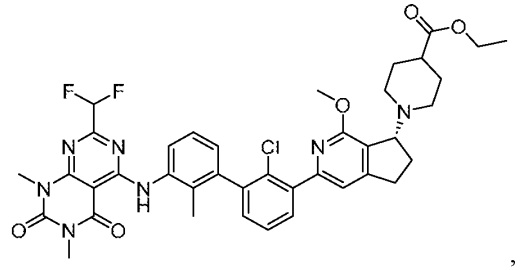
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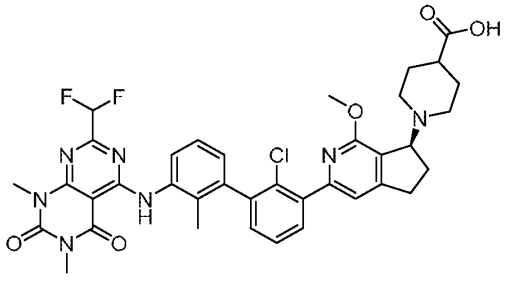
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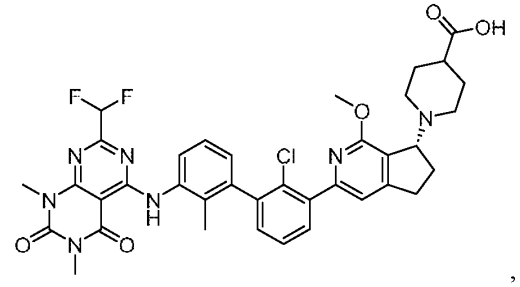
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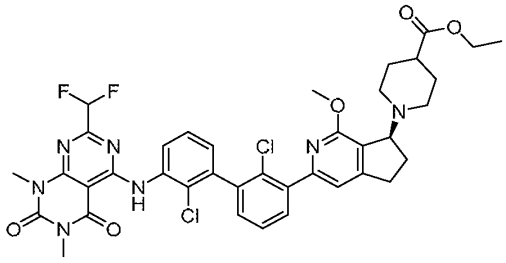
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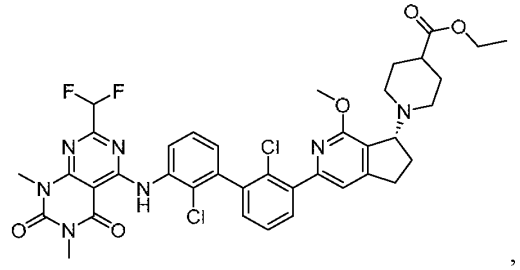
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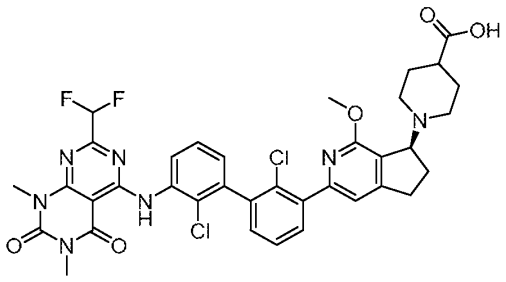
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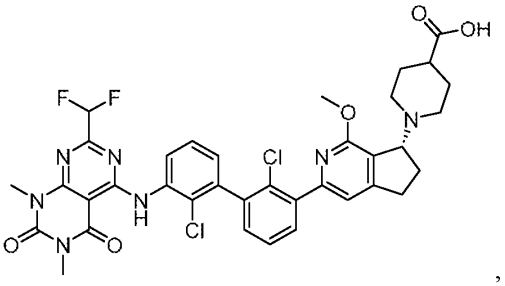
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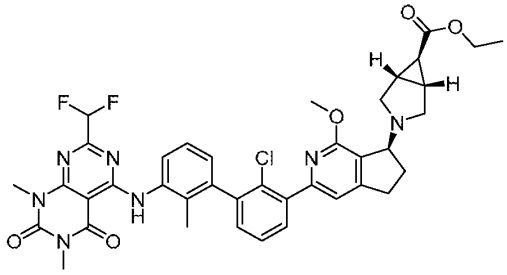
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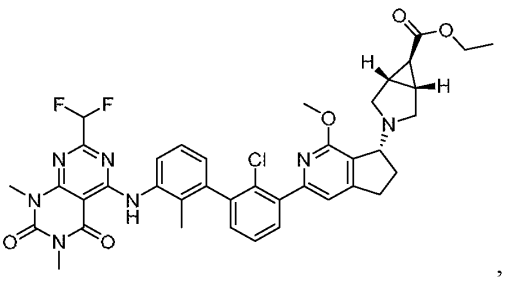
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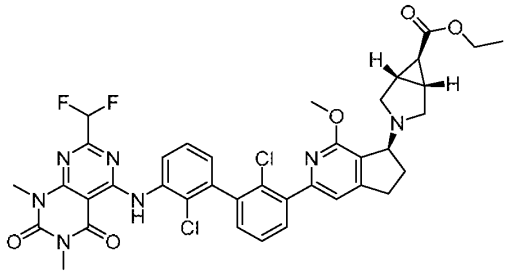
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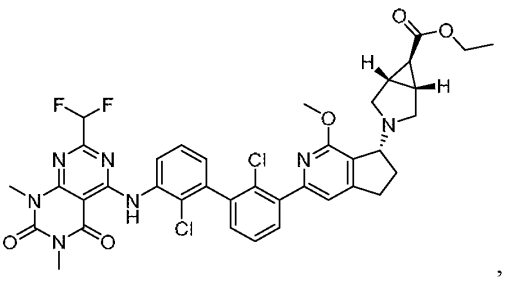
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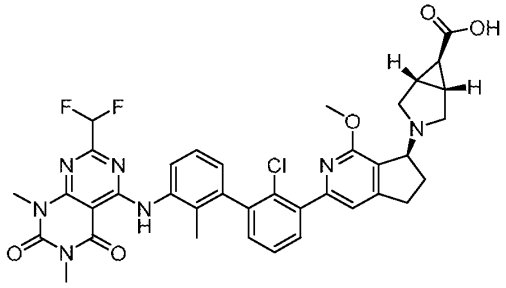
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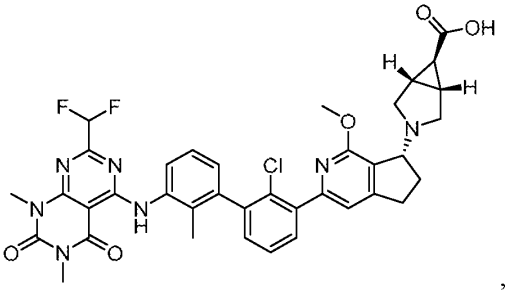
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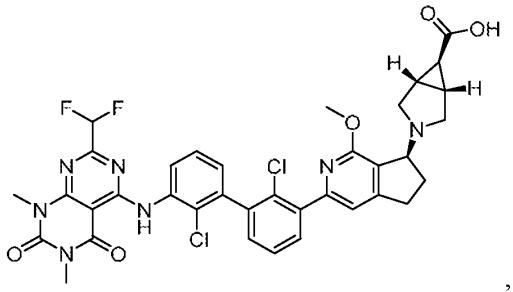
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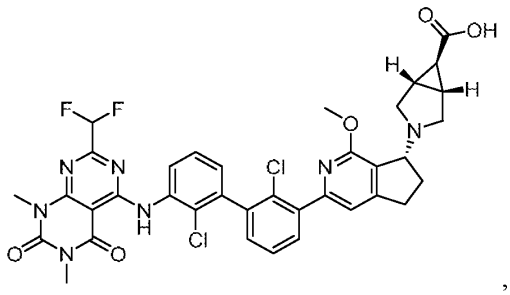
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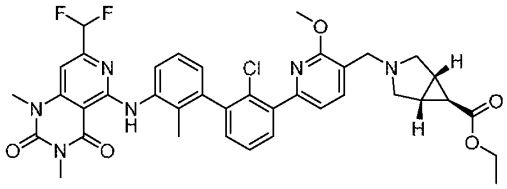
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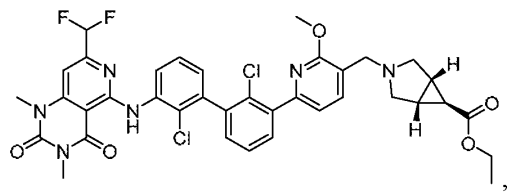
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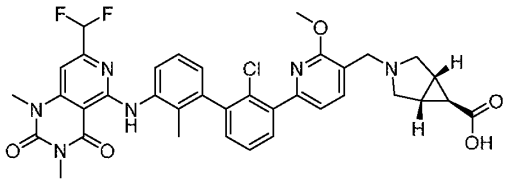
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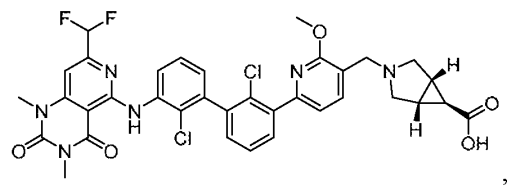
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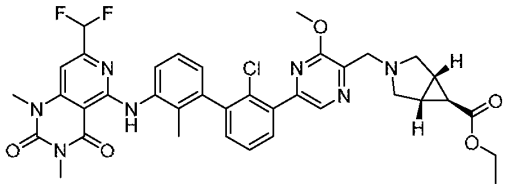
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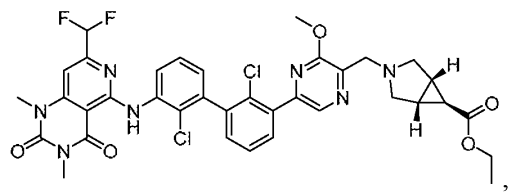
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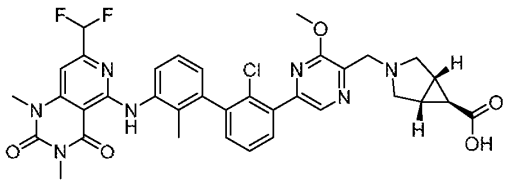
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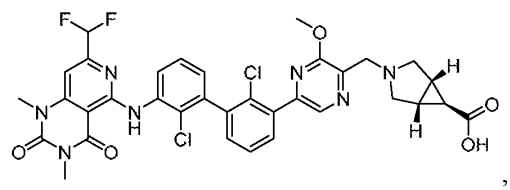
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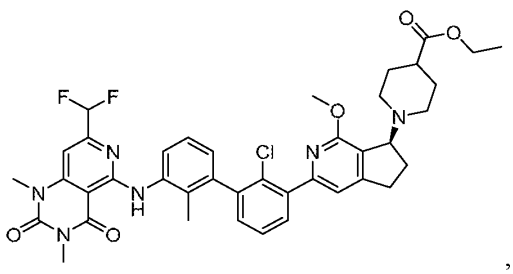
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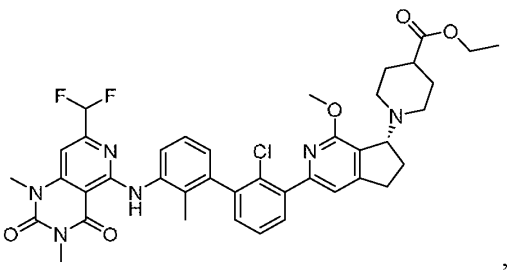
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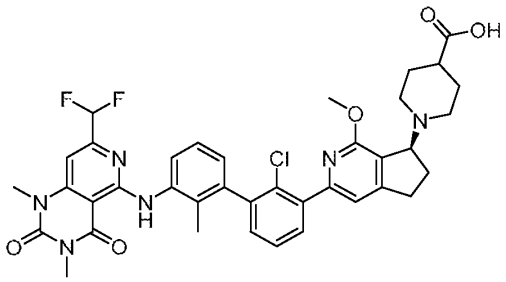
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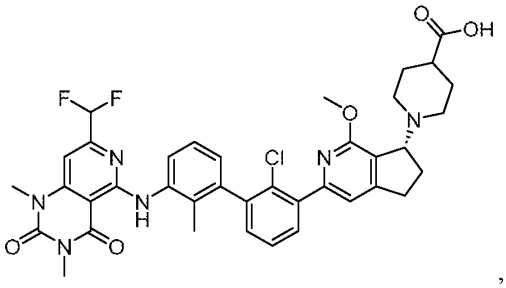
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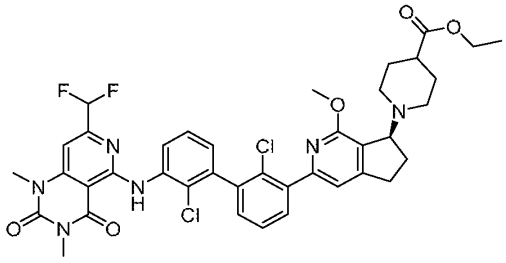
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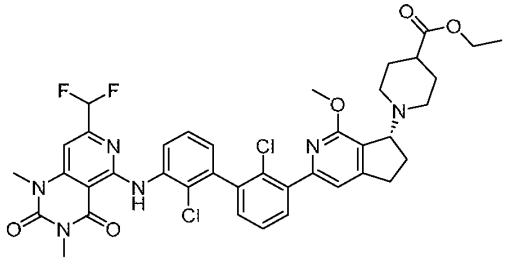
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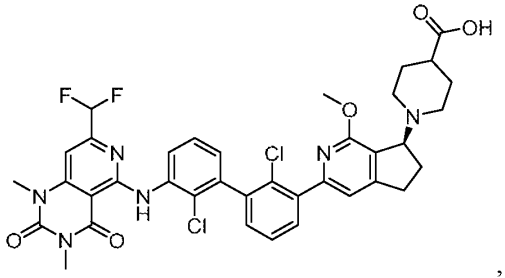
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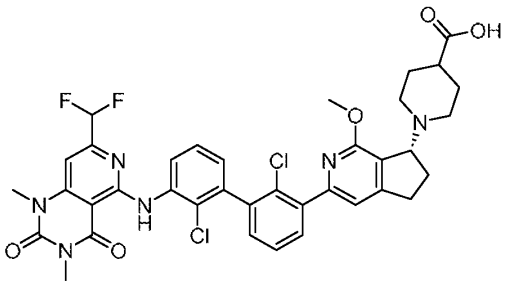
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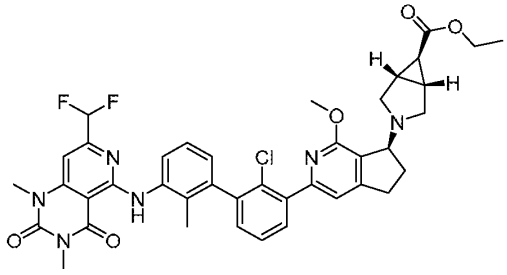
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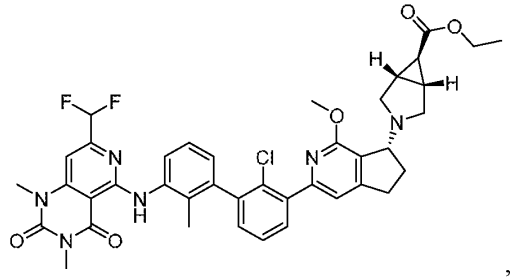
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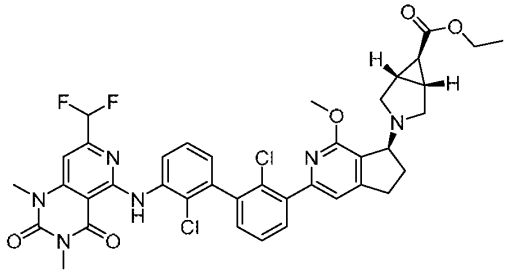
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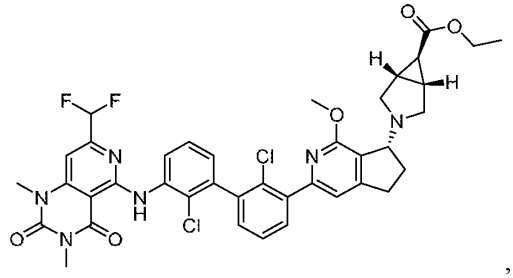
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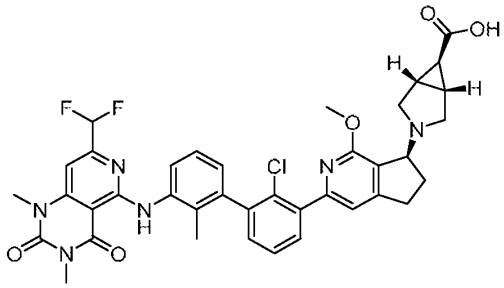
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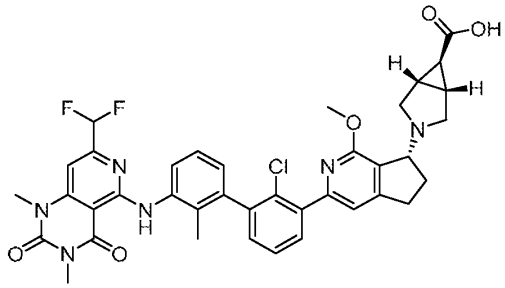
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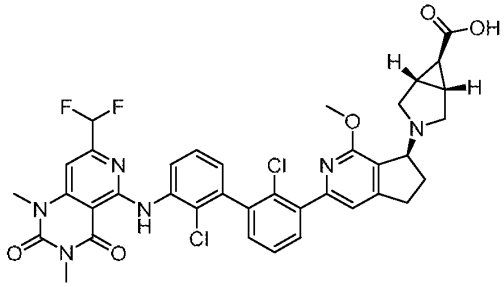
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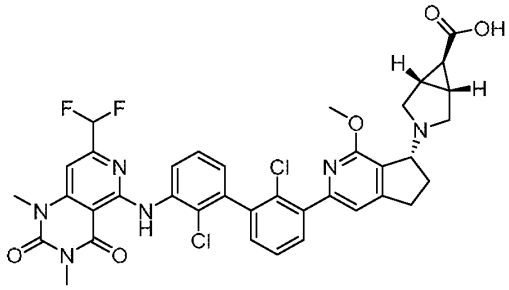

, or a pharmaceutically acceptable salt of any of the foregoing.

Embodiment 65

[0139] A pharmaceutical composition that can include an effective amount of a compound of any one of Embodiments 1-64, or a pharmaceutically acceptable salt thereof, and excipient.

Embodiment 66

[0140] A method for treating hepatitis B in a subject that can include administering to the subject in need thereof an effective amount of a compound of any one of Embodiments 1-64, or a pharmaceutically acceptable salt thereof.

Embodiment 67

[0141] A method for treating hepatocellular carcinoma (HCC) in a subject that can include administering to the subject in need thereof an effective amount of a compound of any one of Embodiments 1-64, or a pharmaceutically acceptable salt thereof.

Embodiment 68

[0142] The method of any one of Embodiments 66-67, that can further include administering surgery, radiation therapy, chemotherapy, targeted therapy, immunotherapy, hormonal therapy and/or antiviral therapy.

Embodiment 69

[0143] A compound of any one of Embodiments 1-64, or a pharmaceutically acceptable salt thereof, for use in treating hepatitis B.

Embodiment 70

[0144] A compound of any one of Embodiments 1-64, or a pharmaceutically acceptable salt thereof, for use in treating hepatocellular carcinoma (HCC).

Embodiment 71

[0145] The compound of any one of Embodiments 69-70, or a pharmaceutically acceptable salt thereof, wherein the use can further include administering surgery, radiation therapy, chemotherapy, targeted therapy, immunotherapy, hormonal therapy and/or antiviral therapy.

Embodiment 72

[0146] Use of a compound of any one of Embodiments 1-64, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for use in treating hepatitis B.

Embodiment 73

[0147] Use of a compound of any one of Embodiments 1-64, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for use in treating hepatocellular carcinoma (HCC).

Embodiment 74

[0148] The use of any one of Embodiments 72-73, wherein the medicament can be for use in combination with surgery, radiation therapy, chemotherapy, targeted therapy, immunotherapy, hormonal therapy and/or antiviral therapy.

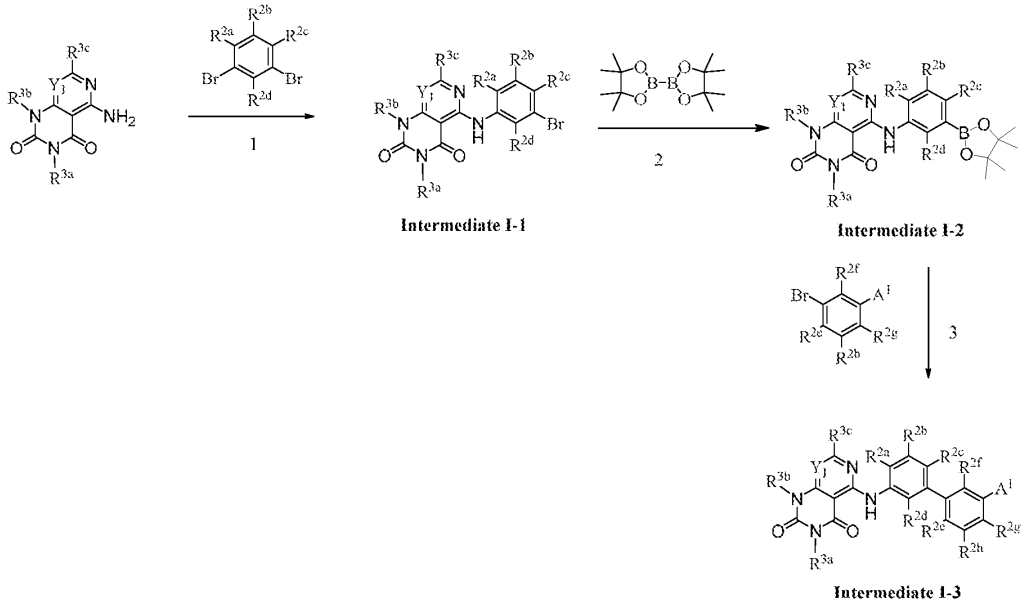
[0149] In some embodiments, including any of Embodiments 1-74, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, Y^1 cannot be C-halo, such as C-F. In some embodiments, including any of Embodiments 1-74, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, Y^1 cannot be C-halo, such as C-F. In some embodiments, including any of Embodiments 1-74, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, Y^2 cannot be C-halo, such as C-F. In some embodiments, including any of Embodiments 1-74, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, Y^2 cannot be C-halo, such as C-F.

Methods for the Preparation

[0150] In this section, as in all other sections unless the context indicates otherwise, references to Formula (I), along with pharmaceutical acceptable salts thereof, include all other sub-groups and examples thereof as provided herein. The general preparations of some representative examples of compounds of Formula (I) are described herein, and are generally prepared from starting materials which are either commercially available or prepared by standard synthetic processes used by those skilled in the art.

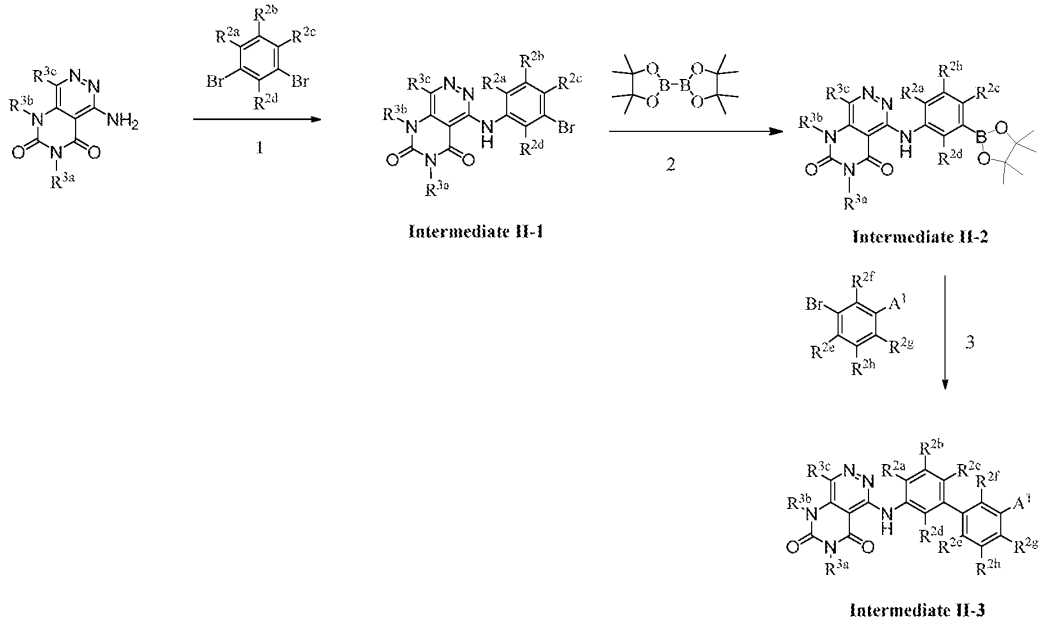
[0151] The following schemes a represent example preparations compounds of Formula (I), along with pharmaceutically acceptable salts thereof. Compounds of Formula (I), along with pharmaceutically acceptable salts thereof may also be prepared by analogous reaction protocols as described in the general schemes below, combined with standard synthetic processes used by those skilled in the art.

General Scheme 1



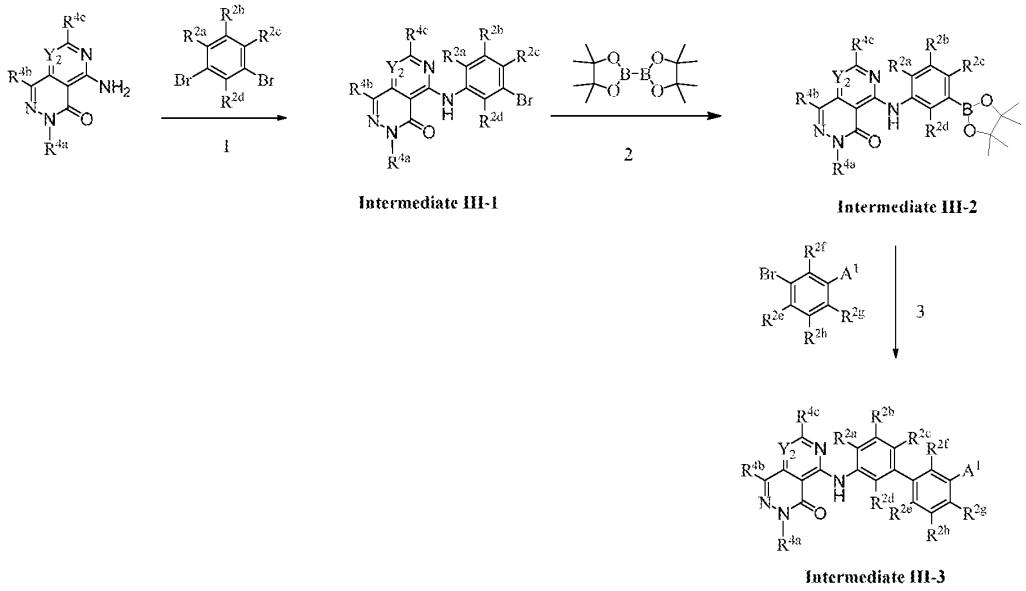
[0152] In general, compounds having the structure of Intermediate I-3 can be prepared according to Scheme 1. All variables in Scheme 1 are defined according to descriptions provided herein. In Scheme 1, the following reaction conditions apply: (1) In the presence of suitable catalyst (for example, bis(triphenylphosphine)palladium(II) dichloride) with a suitable ligand (for example, 2,2′-Bis(diphenylphosphino)-1,1′-binaphthalene) in a suitable solvent, such as 1,4-dioxane, with a suitable base (for example, t-BuONa) at a suitable temperature (for example, 100 °C); (2) In the presence of suitable catalyst (for example, bis(triphenylphosphine)palladium(II) dichloride) in a suitable solvent, such as 1,4-dioxane, with a suitable base (for example, KOAc) at a suitable temperature (for example, 85 °C) (3) In the presence of a suitable catalyst (for example, [1,1′-Bis(di-tert-butylphosphino)ferrocene]-dichloropalladium(II) in a suitable solvent, such as 1,4-dioxane, with a suitable base (for example, K_2CO_3) at a suitable temperature (for example, 100 °C).

General Scheme 2



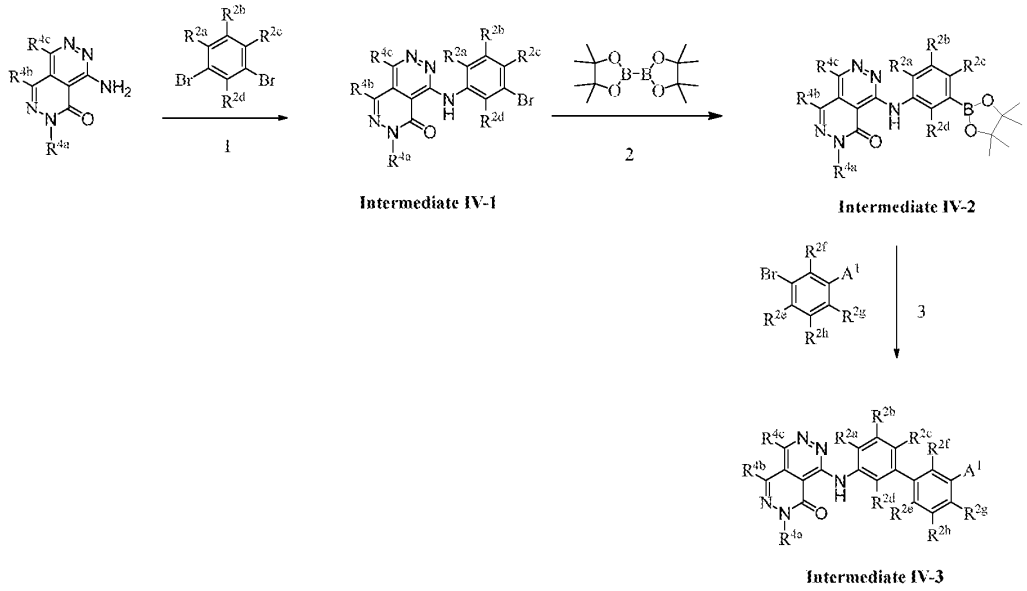
[0153] In general, compounds having the structure of Intermediate II-3 can be prepared according to Scheme 2. All variables in Scheme 2 are defined according to descriptions provided herein. In Scheme 2, the following reaction conditions apply: (1) In the presence of a suitable catalyst (for example, bis(triphenylphosphine)palladium(II) dichloride) with a suitable ligand (for example, 2,2′-Bis(diphenylphosphino)-1,1′-binaphthalene) in a suitable solvent, such as 1,4-dioxane, with a suitable base (for example, t-BuONa) at a suitable temperature (for example, 100 °C); (2) In the presence of a suitable catalyst (for example, bis(triphenylphosphine)palladium(II) dichloride) in a suitable solvent, such as 1,4-dioxane, with a suitable base (for example, KOAc) at a suitable temperature (for example, 85 °C); (3) In the presence of a suitable catalyst (for example, [1,1′-Bis(di-tert-butylphosphino)ferrocene]-dichloropalladium(II) in a suitable solvent, such as 1,4-dioxane, with a suitable base (for example, K_2CO_3) at a suitable temperature (for example, 100 °C).

General Scheme 3



[0154] In general, compounds having the structure of Intermediate III-3 can be prepared according to Scheme 3. All variables in Scheme 3 are defined according to descriptions provided herein. In Scheme 3, the following reaction conditions apply: (1) In the presence of a suitable catalyst (for example, bis(triphenylphosphine)palladium(II) dichloride) with a suitable ligand (for example, 2,2′-Bis(diphenylphosphino)-1,1′-binaphthalene) in a suitable solvent, such as 1,4-dioxane, with a suitable base (for example, t-BuONa) at a suitable temperature (for example, 100 °C); (2) In the presence of a suitable catalyst (for example, bis(triphenylphosphine)palladium(II) dichloride) in a suitable solvent, such as 1,4-dioxane, with a suitable base (for example, KOAc) at a suitable temperature (for example, 85 °C); (3) In the presence of a suitable catalyst (for example, [1,1′-Bis(di-tert-butylphosphino)ferrocene]-dichloropalladium(II) in a suitable solvent, such as 1,4-dioxane, with a suitable base (for example, K_2CO_3) at a suitable temperature (for example, 100 °C).

General Scheme 4



[0155] In general, compounds having the structure of Intermediate IV-3 can be prepared according to Scheme 4. All variables in Scheme 4 are defined according to descriptions provided herein. In Scheme 4, the following reaction conditions apply: (1) In the presence of a suitable catalyst (for example, bis(triphenylphosphine)palladium(II) dichloride) with a suitable ligand (for example, 2,2′-Bis(diphenylphosphino)-1,1′-binaphthalene) in a suitable solvent, such as 1,4-dioxane, with a suitable base (for example, t-BuONa) at a suitable temperature (for example, 100 °C); (2) In the presence of a suitable catalyst (for example, bis(triphenylphosphine)palladium(II) dichloride) in a suitable solvent, such as 1,4-dioxane, with a suitable base (for example, KOAc) at a suitable temperature (for example, 85 °C); (3) In the presence of suitable catalyst (for example, [1,1′-Bis(di-tert-butylphosphino)ferrocene]-dichloropalladium(II) in a suitable solvent, such as 1,4-dioxane, with a suitable base (for example, K_2CO_3) at a suitable temperature (for example, 100 °C)

Pharmaceutical Compositions

[0156] Some embodiments described herein relate to pharmaceutical compositions that comprise, consist essentially of, or consist of an effective amount of a compound described herein (such as a compound of Formula (I), or a pharmaceutically acceptable salt thereof) and

a pharmaceutically acceptable carrier, excipient, or combination thereof. A pharmaceutical composition described herein is suitable for human and/or veterinary applications.

[0157] The terms "function" and "functional" as used herein refer to a biological, enzymatic or therapeutic function.

[0158] The terms "effective amount" or "effective dose" is used to indicate an amount of an active compound, or pharmaceutical agent, that elicits the biological or medicinal response indicated. For example, an effective amount of compound can be the amount needed to alleviate or ameliorate symptoms of disease 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 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 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.

[0159] The term "pharmaceutically acceptable salts" includes relatively non-toxic, inorganic and organic acid, or base addition salts of compositions, including without limitation, analgesic agents, therapeutic agents, other materials, and the like. Examples of pharmaceutically acceptable salts include those derived from mineral acids, such as hydrochloric acid and sulfuric acid, and those derived from organic acids, such as ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, and the like. Examples of suitable inorganic bases for the formation of salts include the hydroxides, carbonates, and bicarbonates of ammonia, sodium, lithium, potassium, calcium, magnesium, aluminum, zinc, and the like. Salts may also be formed with suitable organic bases, including those that are non-toxic and strong enough to form such salts. For example, the class of such organic bases may include but are not limited to mono-, di-, and trialkylamines, including methylamine, dimethylamine, and triethylamine; mono-, di- or trihydroxyalkylamines including mono-, di-, and triethanolamine; amino acids, including glycine, arginine and lysine; guanidine; N-methylglucosamine; N-methylglucamine; L-glutamine; N-methylpiperazine; morpholine; ethylenediamine; N-benzylphenethylamine; trihydroxymethyl aminoethane.

[0160] "Formulation", "pharmaceutical composition", and "composition" as used interchangeably herein are equivalent terms referring to a composition of matter for administration to a subject.

[0161] The term "pharmaceutically acceptable" means compatible with the treatment of a subject, and in particular, a human.

[0162] The terms "agent" refers to an active agent that has biological activity and may be used in a therapy. Also, an "agent" can be synonymous with "at least one agent," "compound," or "at least one compound," and can refer to any form of the agent, such as a derivative, analog, salt or a prodrug thereof. The agent can be present in various forms, components of molecular complexes, and pharmaceutically acceptable salts (e.g., hydrochlorides, hydrobromides, sulfates, phosphates, nitrates, borates, acetates, maleates, tartrates, and salicylates). The term "agent" can also refer to any pharmaceutical molecules or compounds, therapeutic molecules or compounds, matrix forming molecules or compounds, polymers, synthetic molecules and compounds, natural molecules and compounds, and any combination thereof.

[0163] The term "subject" as used herein has its ordinary meaning as understood in light of the specification and refers to an animal that is the object of treatment, inhibition, or amelioration, observation or experiment. "Animal" has its ordinary meaning as understood in light of the specification and includes cold- and warm-blooded vertebrates and/or invertebrates such as fish, shellfish or reptiles and, in particular, mammals. "Mammal" has its ordinary meaning as understood in light of the specification, and includes but is not limited to mice, rats, rabbits, guinea pigs, dogs, cats, sheep, goats, cows, horses, primates, such as humans, monkeys, chimpanzees or apes. In some embodiments, the subject is human.

[0164] 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. Multiple techniques of administering a compound exist in the art including, but not limited to, enteral, oral, rectal, topical, sublingual, buccal, intraaural, epidural, epicutaneous, aerosol, parenteral delivery, including intramuscular, subcutaneous, intra-arterial, intravenous, intraportal, intra-articular, intradermal, peritoneal, intramedullary injections, intrathecal, direct intraventricular, intraperitoneal, intranasal or intraocular injections. Pharmaceutical compositions will generally be tailored to the specific intended

route of administration. Pharmaceutical compositions can also be administered to isolated cells from a patient or individual, such as T cells, Natural Killer cells, B cells, macrophages, lymphocytes, stem cells, bone marrow cells or hematopoietic stem cells.

[0165] The pharmaceutical compound can also be administered in a local rather than systemic manner, for example, via injection of the compound directly into an organ, tissue, cancer, tumor or infected 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 may be targeted to and taken up selectively by the organ, tissue, cancer, tumor or infected area.

[0166] 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. As described herein, compounds used in a pharmaceutical composition may be provided as salts with pharmaceutically compatible counterions.

[0167] As used herein, a "carrier" refers to a compound, particle, solid, semi-solid, liquid or diluent that facilitates the passage, delivery and/or incorporation of a compound to cells, tissues and/or bodily organs. For example, without limitation, a lipid nanoparticle (LNP) is a type of carrier that can encapsulate a compound, or a pharmaceutically acceptable salt thereof, as described herein to thereby protect the compound, or a pharmaceutically acceptable salt thereof, as described herein from degradation during passage through the bloodstream and/or to facilitate delivery to a desired organ, such as to the liver.

[0168] As used herein, a "diluent" refers to an ingredient in a pharmaceutical composition that lacks 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 composition of human blood.

[0169] The term "excipient" has its ordinary meaning as understood in light of the specification, and refers to inert substances, compounds or materials added to a pharmaceutical composition to provide, without limitation, bulk, consistency, stability, binding ability,

lubrication, disintegrating ability etc., to the composition. Excipients with desirable properties include but are not limited to preservatives, adjuvants, stabilizers, solvents, buffers, diluents, solubilizing agents, detergents, surfactants, chelating agents, antioxidants, alcohols, ketones, aldehydes, ethylenediaminetetraacetic acid (EDTA), citric acid, salts, sodium chloride, sodium bicarbonate, sodium phosphate, sodium borate, sodium citrate, potassium chloride, potassium phosphate, magnesium sulfate sugars, dextrose, fructose, mannose, lactose, galactose, sucrose, sorbitol, cellulose, serum, amino acids, polysorbate 20, polysorbate 80, sodium deoxycholate, sodium taurodeoxycholate, magnesium stearate, octylphenol ethoxylate, benzethonium chloride, thimerosal, gelatin, esters, ethers, 2-phenoxyethanol, urea or vitamins, or any combination thereof. The amount of the excipient may be found in a pharmaceutical composition at a percentage of 0%, 0.1%, 0.2%, 0.3%, 0.4%, 0.5%, 0.6%, 0.7%, 0.8%, 0.9%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, 100% w/w or any percentage by weight in a range defined by any two of the aforementioned numbers.

[0170] The term "adjuvant" as used herein refers to a substance, compound or material that stimulates the immune response and increase the efficacy of protective immunity and is administered in conjunction with an immunogenic antigen, epitope or composition. Adjuvants serve to improve immune responses by enabling a continual release of antigen, up-regulation of cytokines and chemokines, cellular recruitment at the site of administration, increased antigen uptake and presentation in antigen presenting cells, or activation of antigen presenting cells and inflammasomes. Commonly used adjuvants include but are not limited to alum, aluminum salts, aluminum sulfate, aluminum hydroxide, aluminum phosphate, calcium phosphate hydroxide, potassium aluminum sulfate, oils, mineral oil, paraffin oil, oil-in-water emulsions, detergents, MF59®, squalene, AS03, α-tocopherol, polysorbate 80, AS04, monophosphoryl lipid A, virosomes, nucleic acids, polyinosinic:polycytidylic acid, saponins, QS-21, proteins, flagellin, cytokines, chemokines, IL-1, IL-2, IL-12, IL-15, IL-21, imidazoquinolines, CpG oligonucleotides, lipids, phospholipids, dioleoyl phosphatidylcholine (DOPC), trehalose dimycolate, peptidoglycans, bacterial extracts, lipopolysaccharides or Freund's Adjuvant, or any combination thereof.

[0171] The term "purity" of any given substance, compound or material as used herein refers to the actual abundance of the substance, compound or material relative to the

expected abundance. For example, the substance, compound or material may be at least 80, 85, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99 or 100% pure, including all decimals in between. Purity may be affected by unwanted impurities, including but not limited to side products, isomers, enantiomers, degradation products, solvent, carrier, vehicle or contaminants, or any combination thereof. Purity can be measured technologies including but not limited to chromatography, liquid chromatography, gas chromatography, spectroscopy, UV-visible spectrometry, infrared spectrometry, mass spectrometry, nuclear magnetic resonance, gravimetry or titration, or any combination thereof.

Methods of Use

[0172] Some embodiments disclosed herein related to selecting a subject or patient in need. In some embodiments, a patient is selected who is in need of treatment, inhibition, amelioration, prevention or slowing of diseases or conditions associated with PD-L1 dysregulation. In some embodiments, such diseases or conditions associated with PD-L1 dysregulation may include, for example, cancer, HCC, viral infections and/or HBV. In some embodiments, a subject can be selected who has previously been treated for the disease or disorder described herein. In some embodiments, a subject can be selected who has previously been treated for being at risk for the disease or disorder described herein. In some embodiments, a subject can be selected who has developed a recurrence of the disease or disorder described herein. In some embodiments, a subject can be selected who has developed resistance to therapies for the disease or disorder described herein. In some embodiments, a subject can be selected who may have any combination of the aforementioned selection criteria.

[0173] Compounds, and pharmaceutically acceptable salts thereof, disclosed herein can be evaluated for efficacy and toxicity using known methods. A non-limiting list of potential advantages of a compound, or a pharmaceutically acceptable salt thereof, described herein include improved stability, increased safety profile, increased efficacy, increased binding to the target, increased specificity for the target (for example, a cancer cell or virally infected cell).

[0174] The terms “treating,” “treatment,” “therapeutic,” or “therapy” as used herein has its ordinary meaning as understood in light of the specification, and do not

necessarily mean total cure or abolition of the disease or condition. The term "treating" or "treatment" as used herein (and as well understood in the art) also means an approach for obtaining beneficial or desired results in a subject's condition, including clinical results. Beneficial or desired clinical results can include, but are not limited to, alleviation or amelioration of one or more symptoms or conditions, diminishment of the extent of a disease, stabilizing (i.e., not worsening) the state of disease, prevention of a disease's transmission or spread, delaying or slowing of disease progression, amelioration or palliation of the disease state, diminishment of the reoccurrence of disease, and remission, whether partial or total and whether detectable or undetectable. "Treating" and "treatment" as used herein also include prophylactic treatment. Treatment methods comprise administering to a subject a therapeutically effective amount of an active agent. The administering step may consist of a single administration or may comprise a series of administrations. The compositions are administered to the subject in an amount and for a duration sufficient to treat the subject. The length of the treatment period depends on a variety of factors, such as the severity of the condition, the age and genetic profile of the subject, the concentration of active agent, the activity of the compositions used in the treatment, or a combination thereof. It will also be appreciated that the effective dosage of an agent used for the treatment or prophylaxis may increase or decrease over the course of a particular treatment or prophylaxis regime. Changes in dosage may result and become apparent by standard diagnostic assays known in the art. In some instances, chronic administration may be required.

[0175] Some embodiments described herein relate to a method of treating, inhibiting, ameliorating, preventing or slowing the disease or disorder described herein. In some embodiments, the methods include administering to a subject identified as suffering from the disease or disorder described herein an effective amount of a compound, or a pharmaceutically acceptable salt thereof, described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein. Other embodiments described herein relate to using a compound, or a pharmaceutically acceptable salt thereof, as described herein in the manufacture of a medicament for treating, inhibiting ameliorating, preventing, or slowing the disease or disorder described herein. Still other embodiments described herein relate to the use of a compound, or a pharmaceutically acceptable salt thereof, as described herein or a pharmaceutical

composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein for treating, inhibiting ameliorating, preventing, or slowing the disease or disorder described herein.

[0176] Some embodiments described herein relate to a method for inhibiting replication of a cancer cell or a virus that can include contacting the cell or virus or administering to a subject identified as suffering from a cancer or a viral infection with an effective amount of a compound, or a pharmaceutically acceptable salt thereof, described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, described herein. Other embodiments described herein relate to the use of an effective amount of a compound, or a pharmaceutically acceptable salt thereof, described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, described herein in the manufacture of a medicament for inhibiting replication of a cancer cell or virus. Still other embodiments described herein relate to an effective amount of a compound, or a pharmaceutically acceptable salt thereof, described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, described herein for inhibiting replication of a cancer cell or virus. In some embodiments, the cancer cell is an HCC cell. In some embodiments, the virus is hepatitis B.

[0177] Some embodiments described herein relate to a method for inhibiting cell proliferation, such as inhibiting cell proliferation of a cancer cell or cell infected with a virus, that can include administering to a subject identified as suffering from a disease wherein inhibiting cell proliferation is desirable with an effective amount of a compound, or a pharmaceutically acceptable salt thereof, described herein, or a pharmaceutical composition that includes effective amount of a compound, or a pharmaceutically acceptable salt thereof, described herein. Other embodiments described herein relate to the use of an effective amount of a compound, or a pharmaceutically acceptable salt thereof, described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, described herein in the manufacture of a medicament for inhibiting cell proliferation, such as inhibiting cell proliferation of a cancer cell or cell infected with a virus. Still other embodiments described herein relate to an effective amount of a compound, or a pharmaceutically acceptable salt thereof, described herein, or a

pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, described herein for inhibiting cell proliferation, such as inhibiting cell proliferation of a cancer cell or cell infected with a virus. In some embodiments, the cancer cell is an HCC cell. In some embodiments, the cell infected with a virus is infected with hepatitis B virus.

[0178] Some embodiments described herein relate to a method of inducing apoptosis of a cell (for example, a cancer cell or cell infected with a virus) that can include contacting the cell with an effective amount of a compound, or a pharmaceutically acceptable salt thereof, described herein, or a pharmaceutical composition that includes an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as described herein. Other embodiments described herein relate to using an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, described herein in the manufacture of a medicament for inducing apoptosis of a cell, such as a cancer cell or cell infected with a virus. Still other embodiments described herein relate to the use of an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein for inducing apoptosis of a cell, such as a cancer cell or cell infected with a virus. In some embodiments, the cancer cell is an HCC cell. In some embodiments, the cell infected with a virus is infected with hepatitis B virus.

[0179] Some embodiments described herein relate to a method of decreasing the viability of a cell (for example, a cancer cell or cell infected with a virus) that can include contacting the cell with an effective amount of a compound, or a pharmaceutically acceptable salt thereof, described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein. Other embodiments described herein relate to using a compound, or a pharmaceutically acceptable salt thereof, as described herein in the manufacture of a medicament for decreasing the viability of a cell, such as a cancer cell or cell infected with a virus. Still other embodiments described herein relate to the use of an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein or a pharmaceutical composition that includes an

effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein for decreasing the viability of a cell, such as a cancer cell or cell infected with a virus. In some embodiments, the cancer cell is an HCC cell. In some embodiments, the cell infected with a virus is infected with hepatitis B virus.

[0180] Those of skill in the treatment of such diseases could determine the effective therapeutic daily amount from test results. An effective therapeutic daily amount would be from about 0.005 mg /kg to 50 mg/kg. in particular 0.01 mg/kg to 50 mg/kg body weight, more in particular from 0.01 mg/kg to 25 mg/kg body weight, preferably from about 0.01 mg/kg to about 15 mg/kg, more preferably from about 0.01 mg/kg to about 10 mg/kg, even more preferably from about 0.01 mg/kg to about 1 mg/kg, most preferably from about 0.05 mg/kg to about 1 mg/kg body weight.

[0181] In some embodiments, the effective amount of a compound, or a pharmaceutically acceptable salt thereof, described herein is dosed more than one time. In some embodiments, the compound, or a pharmaceutically acceptable salt thereof, described herein can be administered every 1, 2, 3, 4, 5, 6, 7 days, or 1, 2, 3, 4 weeks, or 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 months, or 1, 2, 3, 4, 5 years, or any period or combination thereof within the range defined by any two aforementioned times. In some embodiments, at least one loading dose and at least one maintenance dose is administered to the subject, where the at least one loading dose is a higher dose of a compound, or a pharmaceutically acceptable salt thereof, described herein than the at least one maintenance dose.

[0182] As used herein, the term “combination therapy” is intended to define therapies which comprise the use of a combination of two or more pharmaceutical compounds/agents or therapies. Thus, references to “combination therapy”, “combinations” and the use of compounds/agents “in combination” in this application may refer to compounds/agents that are administered as part of the same overall treatment regimen. As such, the dosage or timing of each of the two or more compounds/agents may differ: each may be administered at the same time or at different times. Accordingly, the compounds/agents of the combination may be administered sequentially (e.g. before or after) or simultaneously, either in the same pharmaceutical formulation (i.e. together), or in different pharmaceutical formulations (i.e. separately). Each of the two or more compounds/agents in a combination therapy may also differ with respect to the route of administration.

[0183] The term "inhibitor", as used herein, refers to an enzyme inhibitor or receptor inhibitor which is a molecule that binds to an enzyme or receptor, and decreases and/or blocks its activity. The term may relate to a reversible or an irreversible inhibitor.

[0184] Cancer may be treated with surgery, radiation therapy, chemotherapy, targeted therapies, immunotherapy or hormonal therapies. Any of these mentioned therapies may be used in conjunction with another therapy as a combination therapy. Chemotherapeutic compounds include, but are not limited to, alemtuzumab, altretamine, azacitidine, bendamustine, bleomycin, bortezomib, busulfan, cabazitaxel, capecitabine, carboplatin, carmofur, carmustine, chlorambucil, chlormethine, cisplatin, cladribine, clofarabine, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, daunorubicin, decitabine, denosumab, docetaxel, doxorubicin, epirubicin, estramustine, etoposide, everolimus, floxuridine, fludarabine, fluorouracil, fotemustine, gemcitabine, gemtuzumab, hydroxycarbamide, ibritumomab, idarubicin, ifosfamide, irinotecan, ixabepilone, lomustine, melphalan, mercaptopurine, methotrexate, mitomycin, mitoxantrone, nedaplatin, nelarabine, ofatumumab, oxaliplatin, paclitaxel, pemetrexed, pentostatin, pertuzumab, procarbazine, raltitrexed, streptozotocin, tegafur, temozolomide, temsirolimus, teniposide, tioguanine, topotecan, tositumomab, valrubicin, vinblastine, vincristine, vindesine, vinflunine and vinorelbine, or any combination thereof (including pharmaceutically acceptable salts of any of the foregoing).

[0185] As used herein, the term "protein kinase inhibitor" refers to inhibitors of protein kinases, serine/threonine kinases, tyrosine kinases, or dual-specificity kinases for the treatment of cancer or other illness. In some embodiments, the protein kinase inhibitor can be a small molecule, compound, polysaccharide, lipid, peptide, polypeptide, protein, antibody, nucleoside, nucleoside analog, nucleotide, nucleotide analog, nucleic acid or oligonucleotide (along with pharmaceutically acceptable salts of any of the foregoing). A non-limiting list of the protein kinase inhibitor includes, but is not limited to, acalabrutinib, adavosertib, afatinib, alectinib, axitinib, binimetinib, bosutinib, brigatinib, cediranib, ceritinib, cetuximab, cobimetinib, crizotinib, cabozantinib, dacomitinib, dasatinib, entrectinib, erdafitinib, erlotinib, fostamatinib, gefitinib, ibrutinib, imatinib, lapatinib, lenvatinib, lestaurtinib, lortatinib, masitinib, momelotinib, mubritinib, neratinib, nilotinib, nintedanib, olmutinib, osimertinib, pacritinib, panitumumab, pazopanib, pegaptanib, ponatinib, radotinib, regorafenib, rociletinib,

ruxolitinib, selumetinib, semaxanib, sorafenib, sunitinib, SU6656, tivozanib, toceranib, trametinib, trastuzumab, vandetanib and vemurafenib, or any combination thereof (including pharmaceutically acceptable salts of any of the foregoing).

[0186] As used herein, the term "checkpoint inhibitor" refers to an immunotherapy that targets immune checkpoints to stimulate immune function. In some embodiments, the checkpoint inhibitor can be a small molecule, compound, polysaccharide, lipid, peptide, polypeptide, protein, antibody, nucleoside, nucleoside analog, nucleotide, nucleotide analog, nucleic acid or oligonucleotide (along with pharmaceutically acceptable salts of any of the foregoing). In some embodiments, the immune checkpoint can be the PD-1/PD-L1 checkpoint. Examples of PD-1 checkpoint inhibitors includes, but is not limited to, nivolumab, pembrolizumab, spartalizumab, cemiplimab, camrelizumab, sintilimab, tislelizumab, toripalimab, AMP-224 and AMP-514, or any combination thereof (including pharmaceutically acceptable salts of any of the foregoing). Additional examples of PD-L1 checkpoint inhibitor includes, but is not limited to, atezolizumab, avelumab, durvalumab, KN035, AUNP12, CA-170 and BMS-986189, or any combination thereof (including pharmaceutically acceptable salts of any of the foregoing). In some embodiments, the immune checkpoint can be the CTLA-4 checkpoint. A non-limiting list of CTLA-4 checkpoint inhibitors includes, but is not limited to, ipilimumab and tremilimumab, or any combination thereof (including pharmaceutically acceptable salts of any of the foregoing).

[0187] As used herein, the term "VEGF inhibitor" refers to inhibitors of vascular endothelial growth factor (VEGF) or a VEGF receptor (VEGFR). In some embodiments, the VEGF inhibitor can be a small molecule, compound, polysaccharide, lipid, peptide, polypeptide, protein, antibody, nucleoside, nucleoside analog, nucleotide, nucleotide analog, nucleic acid or oligonucleotide (along with pharmaceutically acceptable salts of any of the foregoing). Examples of VEGF inhibitor includes, but is not limited to, aflibercept, axitinib, bevacizumab, brivanib, cabozantinib, cediranib, lenvatinib, linifinib, nintedanib, pazopanib, ponatinib, ramucirumab, regorafenib, semaxanib, sorafenib, sunitinib, tivozanib, toceranib and vandetanib, or any combination thereof (including pharmaceutically acceptable salts of any of the foregoing).

[0188] As used herein, the term "antiviral medication" refers to a pharmaceutical composition administered to treat a viral infection. In some embodiments, the viral infection

can be caused by adenovirus, Ebola virus, coronavirus, Epstein-Barr virus (EBV), Friend virus, hantavirus, hepatitis B virus (HBV), hepatitis C virus (HCV), herpes simplex virus, human immunodeficiency virus (HIV), human metapneumovirus, human papillomavirus (HPV), influenza virus, Japanese encephalitis virus, Kaposi's sarcoma-associated herpesvirus, lymphocytic choriomeningitis virus, parainfluenza virus, rabies virus, respiratory syncytial virus, rhinovirus and/or varicella zoster virus.

[0189] In some embodiments, the antiviral medication can be a small molecule, compound, polysaccharide, lipid, peptide, polypeptide, protein, antibody, nucleoside, nucleoside analog, nucleotide, nucleotide analog, nucleic acid or oligonucleotide (along with pharmaceutically acceptable salts of any of the foregoing). In some embodiments, the antiviral medication can be an interferon, a capsid assembly modulator, a sequence specific oligonucleotide, an entry inhibitor or a small molecule immunomodulatory. A non-limiting list of antiviral medications include, but is not limited to, AB-423, AB-506, ABI-H2158, vebicorvir (ABI-HO731), acyclovir, adapromine, adefovir, adefovir dipivoxil, alafenamide, amantadine, asunaprevir, baloxavir marboxil, beclabuvir, boceprevir, brivudine, cidofovir, ciluprevir, clevudine, cytarabine, daclatasvir, danoprevir, dasabuvir, deleobuvir, dipivoxil, edoxudine, elbasvir, entecavir, faldaprevir, famciclovir, favipiravir, filibuvir, fomivirsen, foscarnet, galidesivir, ganciclovir, glecaprevir, GLS4, grazoprevir, idoxuridine, imiquimod, IFN-α, interferon alfa 2b, JNJ-440, JNJ-6379 (JNJ-56136379), lamivudine, laninamivir, ledipasvir, mericitabine, methisazone, MK-608, moroxydine, narlaprevir, NITD008, NZ-4, odalasvir, ombitasvir, oseltamivir, paritaprevir, peginterferon alfa-2a, penciclovir, peramivir, pibrentasvir, pimodivir, pleconaril, podophyllotoxin, presatovir, radalbuvir, ravidasvir, remdesivir, REP 2139, REP 2165, resiquimod, R07049389 (RG7907), ribavirin, rifampicin, rimantadine, ruzasvir, samatasvir, setrobuvir, simeprevir, sofosbuvir, sorivudine, sovaprevir, taribavirin, telaprevir, telbivudine, tenofovir, tenofovir disoproxil, tenofovir alfenamide, triazavirin, trifluridine, tromantadine, umifenovir, uprifosbuvir, valaciclovir, valgancicovir, vaniprevir, vedroprevir, velpatasvir, vidarabine, voxilaprevir, zanamivir, cledvudine, ANA-380/LB80380, thymalfasin (Zadaxin), ATI-2173, VIR-2218, RG6346, JNJ-73763989 (JNJ-3989), AB-729, BB-103, Hepcludex (Bulevirtide formerly Myrcludex B), hzVSF, morphothiadin, JNJ-56136379, EDP-514, QL- 007, ABI-H3733, ZM-H1505R, B-836, VNRX-9945, GLP-26, ABI-4334, IONIS-HBVRx (GSK 3228836), EBT107, NASVAC, GS-

4774, HepTcell, VBI-2601 (BRII-179), VVX001, VTP-300, CVI-HBV-002, AIC-649, HB-110, JNJ-64300535, CARG-201, PRGN-2013, SA104, VRON-0200, selgantolimod, RG7854, SBT-8230, YS-HBV-002, lenvervimab, Vir-3434, IMC-I109V, LTCR-H2-1, APG-1387, ASC42, EYP001, EDP-721, ENOB-HB-01, GV1001, CP101, DF-006, ALG-000184, ALG-010133, ALG-125097, ALG-020572 and ALG-125755, or any combination thereof (including pharmaceutically acceptable salts of any of the foregoing).

[0190] The term "% w/w" or "% wt/wt" as used herein has its ordinary meaning as understood in light of the specification and refers to a percentage expressed in terms of the weight of the ingredient or agent over the total weight of the composition multiplied by 100. The term "% v/v" or "% vol/vol" as used herein has its ordinary meaning as understood in the light of the specification and refers to a percentage expressed in terms of the liquid volume of the compound, substance, ingredient or agent over the total liquid volume of the composition multiplied by 100.

EXAMPLES

[0191] Some aspects of the embodiments discussed above are disclosed in further detail in the following examples, which are not in any way intended to limit the scope of the present disclosure. Those in the art will appreciate that many other embodiments also fall within the scope of the present disclosure, as it is described herein above and in the claims.

[0192] Hereinafter, the term "rt", "r.t." or "RT" means room temperature; "Me" means methyl; "MeOH" means methanol; "Et" means ethyl; "EtOH" means ethanol; "NaH" means sodium hydride; "$NaBH(AcO)_3$" or "$NaBH(Oac)_3$" means sodium triacetoxyborohydride; "NBS" means N-bromosuccinimide; "AIBN" means azobisisobutyronitrile; "EtOAc" means ethyl acetate; "TEA" or "Et_3N" means triethylamine; "DCM" means dichloromethane; "$MeNHNH_2$" means methylhydrazine; "$MeNH_2HCl$" means methylamine hydrochloride; "MeCN" or "ACN" means acetonitrile; "DMF" means dimethyl formamide; "DMA" means dimethy1acetamide; "$Pd(dppf)Cl_2$." Means [1,1'-Bis(diphenylphosphino)ferrocene]-dichloropalladium(II); "$PdCl_2(dtbpf)$" or "PD-118" means [1,1'-Bis(di-tert-butylphosphino)ferrocene]-dichlropalladium(II); "THF" means tetrahydrofuran; "HATU" means hexafluorophosphate azabenzotriazole tetramethyl uronium; "LDA" means lithium diisopropylamide; "DABCO" means 1,4-diazabicyclo[2.2.2]octane;

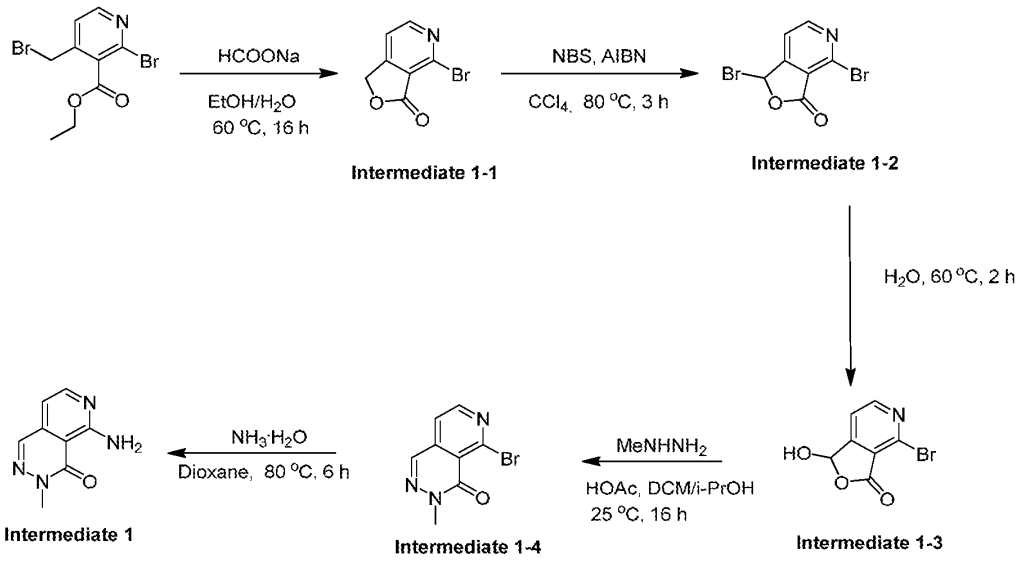
"$(Boc)_2O$" means di-tert-buty-dicarbonate "i-PrOH" or "iPrOH" means 2-propanol; "triphosgene" means bis(trichloromethyl) carbonate; "TMT" means 2,4,6-trimercapto-s-triazine; "LC" means liquid chromatography; "LCMS" means Liquid Chromatography/Mass spectrometry; "HPLC" means high-performance liquid chromatography; "prep-HPLC" means preparative high-performance liquid chromatography; "SFC" means supercritical fluid chromatography; "TFA" means trifluoroacetic acid; "RP" means reversed phase; "min" means minute(s); "h" means hour(s); "PE" means petroleum ether; "v/v" means volume per volume; "Celite ®" means diatomaceous earth; "DMSO" means dimethyl sulfoxide; "SFC" means Supercritical Fluid Chromatography; "DIPE" means diisopropyl ether; "DIPEA" or "DIEA" means N,N-diisopropylethylamine; "BINAP" means (2,2'-bis(diphenylphosphino)-1,1'-binaphthyl); "$Pd_2(dba)_3$" means Tris(dibenzylideneacetone)-dipalladium; "$Pd(Oac)_2$" means palladium(II) acetate; "$Pd(PPh_3)_4$ means tetrakis(triphenylphosphine)palladium(0); "AcOH" means acetic acid; "DMAP" means 4-(dimethylamino)pyridine; "t-BuOK", "BuO" or "KotBu" means potassium tert-butoxide; "t-BuONa" means "sodium tert-butoxide"; "TLC" means thin layer chromatography; "prep-TLC" means preparative TLC; "KOAc" or "AcOK" means potassium acetate; "NaOAc" means sodium acetate; "Pin_2B_2" means bis(pinacolato)diboron.

[0193] For intermediates that were used in a next reaction step as a crude or as a partially purified intermediate, estimated mol amounts (in some cases indicated by ~) are indicated in the reaction protocols described below, or alternatively theoretical mol amounts are indicated.

[0194] The meanings of the abbreviations in the nuclear magnetic resonance spectra are provided as follows: s = singlet, d = doublet, dd = double doublet, dt = double triplet, ddd = doublet of doublets of doublets, Sept = septet, t = triplet, m = multiplet, br = broad, brs = broad singlet, q = quartet.

Preparation of Intermediates

Example A1
Preparation of Intermediate 1



[0195] To a solution of ethyl 2-bromo-4-(bromomethyl) pyridine-3-carboxylate (1.1 g, 3.4 mmol) in EtOH (10 mL) and H_2O (2 mL) was added $HCOONa \cdot 2H_2O$ (1.06 g, 10.2 mmol). The mixture was stirred at 60 °C for 16 h. The mixture was concentrated under reduced pressure to remove solvent. The residue was purified by flash silica gel chromatography to give **Intermediate 1-1** (500 mg) as a white solid. MS: ES m/z calculated for $C_7H_5BrNO_2$ $[M+H]^+$ 212.9, found 213.8.

[0196] To a mixture of **Intermediate 1-1** (500 mg, 2.34 mmol) in CCl_4 (15 mL) was added N-bromosuccinimide (NBS, 499 mg, 2.80 mmol) and azobisisobutyronitrile (AIBN, 38.4 mg, 234 μmol) in one portion at 25 °C under N_2. The mixture was stirred at 80 °C for 3 h. The mixture was concentrated under reduced pressure to remove the solvent. The residue was purified by flash silica gel chromatography to give **Intermediate 1-2** (380 mg) as a white solid. MS: ES m/z calculated for $C_7H_4Br_2NO_2$ $[M+H]^+$ 293.9, found 293.8; ^1H NMR (400 MHz, Chloroform-d) δ = 8.76-8.69 (m, 1H), 7.60-7.53 (m, 1H), 7.34-7.30 (m, 1H).

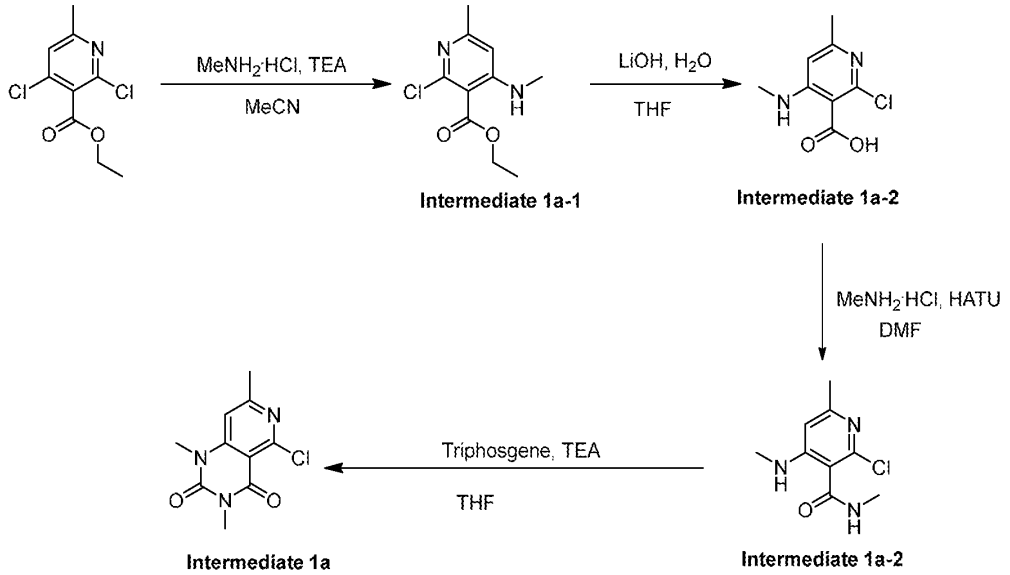
[0197] A mixture of **Intermediate 1-2** (380 mg, 1.30 mmol) in H_2O (10 mL) was stirred at 60 °C for 2 h. The mixture was poured into water (10 mL). The aqueous phase was extracted with ethyl acetate (3 x 20 mL). The combined organic phase was dried with

anhydrous Na_2SO_4, filtered and concentrated in vacuum to give crude **Intermediate 1-3** (300 mg) as a white solid. MS: ES m/z calculated for $C_7H_5BrNO_3$ $[M+H]^+$ 229.9, found 229.8.

[0198] To a mixture of **Intermediate 1-3** (300 mg) in i-PrOH (10 mL) and DCM (10 mL) were added HOAc (299 µL, 5.22 mmol) and methylhydrazine (263 µL, 2.00 mmol) in one portion at 25 °C. The mixture was stirred at 25 °C for 16 h. The mixture was poured into water (20 mL). The aqueous phase was extracted with ethyl acetate (3 x 20 mL). The combined organic phase was dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography to afford **Intermediate 1-4** (160 mg) as a yellow solid. MS: ES m/z calculated for $C_8H_7BrN_3O$ $[M+H]^+$ 234.0, found 239.8.

[0199] To a mixture of **Intermediate 1-4** (160 mg, 667 µmol) in dioxane (5 mL) was added $NH_3 \cdot H_2O$ (1.71 mL, 30% purity, 13.3 mmol) in one portion at 25 °C in a sealed tube. The mixture was stirred at 80 °C for 6 h at 15 psi. The mixture was concentrated in vacuum. The residue was purified by silica gel chromatography (Petroleum ether:Ethyl acetate=100:1, 1:1) to afford **Intermediate 1** (140 mg) as a yellow solid. MS: ES m/z calculated for $C_8H_9N_4O$ $[M+H]^+$ 177.1, found 177.2.

Example A1-a
Preparation of Intermediate 1a



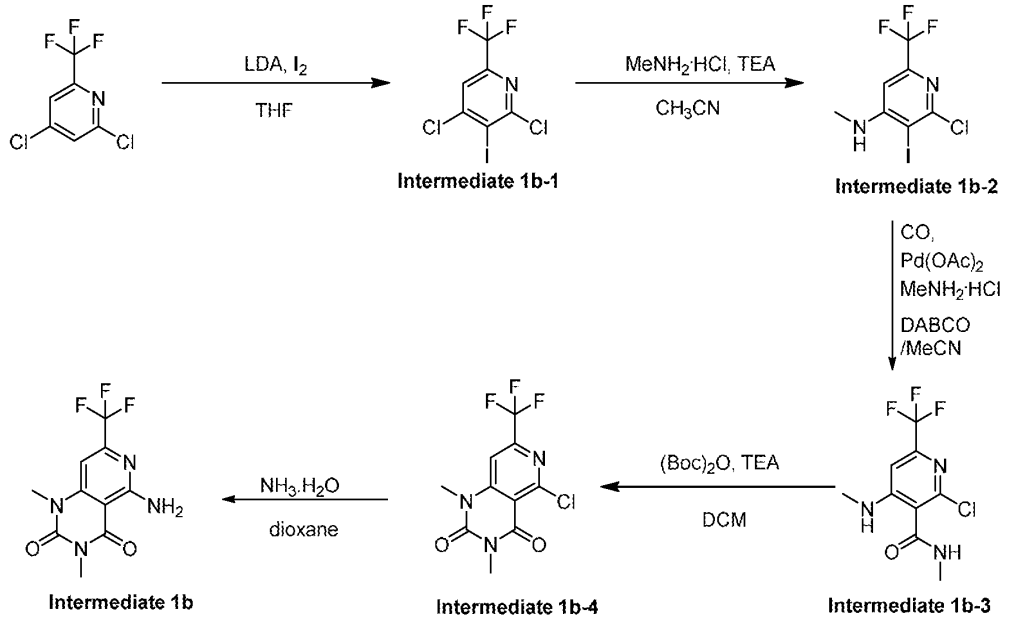
[0200] To a solution of methylamine hydrochloride (5.77 g, 85.4 mmol) and ethyl-2,4-dichloro-6-methylpyridine-3-carboxylate (10 g, 42.7 mmol) in CH_3CN (150 mL) was added TEA (17.8 mL, 128.16 mmol). The mixture was stirred at 80 °C for 12 h. The mixture was concentrated under reduced pressure to remove solvent. The residue was purified by flash silica gel chromatography to give **Intermediate 1a-1** (3.6 g, 95% purity) as a white solid. MS: ES m/z calculated for $C_{10}H_{14}ClN_2O_2$ $[M+H]^+$ 229.1, found 228.9; ^1H NMR (400 MHz, Chloroform-d) δ = 7.15 (br s, 1H), 6.32 (s, 1H), 4.38 (q, J = 7.2 Hz, 2H), 2.88 (d, J = 5.0 Hz, 3H), 2.41 (s, 3H), 1.40 (t, J = 7.1 Hz, 3H).

[0201] To a solution of **Intermediate 1a-1** (3.6 g, 15.7 mmol) in a mixture of THF (20 mL) and H_2O (4 mL) was added $LiOH•H_2O$ (1.98 g, 47.2 mmol). The mixture was stirred at 60 °C for 12 h. The mixture was lyophilized. Crude **Intermediate 1a-2** (3.4 g, crude) was obtained as a white solid. ES m/z calculated for $C_8H_{10}ClN_2O_2$ $[M+H]^+$ 201.0, found 201.2.

[0202] To a solution of crude **Intermediate 1a-2** (4.0 g, 19.94 mmol) and methylamine hydrochloride (2.69 g, 39.88 mmol) in DMF (20 mL) were added hexafluorophosphate azabenzotriazole tetramethyl uronium (HATU, 9.10 g, 23.93 mmol) and DIEA (7.73 g, 59.81 mmol, 10.42 mL, 3 eq.). The mixture was diluted with H_2O (50 mL) and extracted with EA (2 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give **Intermediate 1a-3** (3.8 g) as a white solid. ES m/z calculated for $C_9H_{13}ClN_3O$ $[M+H]^+$ 214.1, found 214.1.

[0203] To a solution of **Intermediate 1a-3** (1.1 g) in THF (20 mL) at 25 °C under nitrogen was added bis(trichloromethyl) carbonate (triphosgene, 1.25 g, 4.21 mmol), and the resulting mixture was stirred at 25 °C for 1 h. After adding TEA (2.15 mL, 15.44 mmol) into the mixture, the resulting mixture was stirred at 25 °C for 12 h. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (20 mL). The aqueous layer was extracted with EtOAc (50 mL). The EtOAc layer was collected and dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash silica gel chromatography to give **Intermediate 1a** (154 mg) as a yellow solid. ES m/z calculated for $C_{10}H_{11}ClN_3O_2$ $[M+H]^+$ 240.1, found 240.0.

Example A1-b
Preparation of Intermediate 1b



[0204] To a solution of 2,4-dichloro-6-(trifluoromethyl)pyridine (7 g, 32.41 mmol) in THF (150 mL) was added dropwise lithium diisopropylamide (LDA, 2 M, 17.83 mL) at -78 °C. After addition of LDA, the mixture was stirred at -78 °C for 30 min. Then the solution of I_2 (9.05 g, 35.65 mmol, 7.18 mL, 1.1 eq.) in THF (2 mL) was added dropwise into the mixture at -78 °C. The resulting mixture was stirred at -78 °C for 1 h. After the mixture's temperature changed to rt, ethyl acetate (100 mL)was added. The reaction was further quenched with saturated ammonium chloride aqueous solution (60 mL) and saturated $Na_2S_2O_3$ aqueous solution (60 mL). The organic layer was washed with saturated sodium bicarbonate solution, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography to give **Intermediate 1b-1** (6.77 g) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ =8.21 (s, 1H)

[0205] A mixture of **Intermediate 1b-1** (6.77 g, 19.8 mmol), methylamine hydrochloride (2.67 g, 39.6 mmol), TEA (8.27 mL, 59.4 mmol) in CH_3CN (50 mL) was stirred at 80 °C for 16 h under N_2 atmosphere. The mixture was concentrated under reduced pressure to remove the solvent. The residue was purified by flash silica gel chromatography to give **Intermediate 1b-2** (4.4 g, 93% purity) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ =

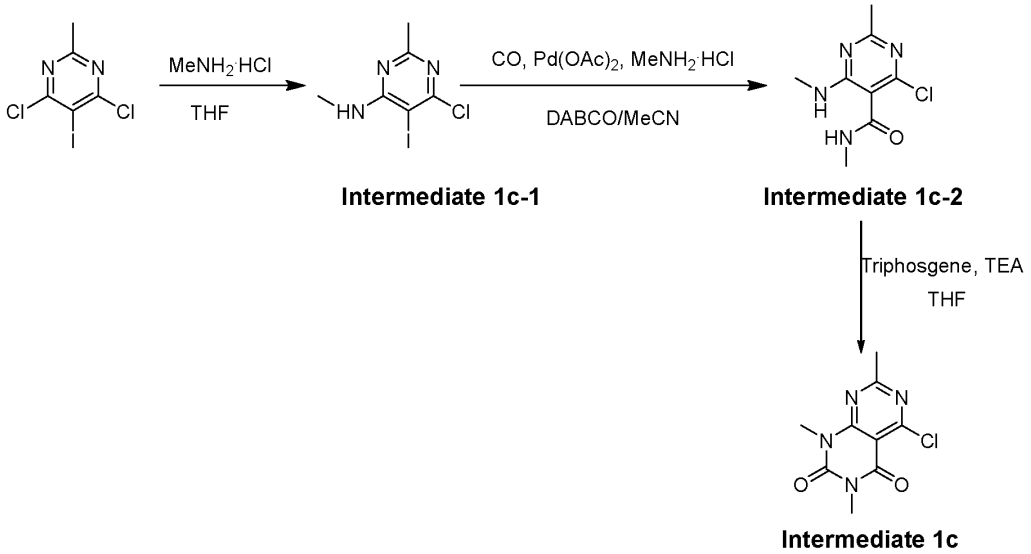
6.80 (br d, J = 4.5 Hz, 1H), 6.74 (s,1H), 2.90 (d, J = 4.8 Hz,3H); ES m/z calculated for $C_7H_6ClF_3IN_2$ $[M+H]^+$ 336.9, found 336.7.

[0206] To a solution of **Intermediate 1b-2** (2 g, 5.94 mmol) in CH_3CN (30 mL) were added methylamine hydrochloride (602 mg, 8.92 mmol), $Pd(OAc)_2$ (107 mg, 476 μmol), Na_2CO_3 (1.57 g, 14.9 mmol) and 1,4-diazabicyclo[2.2.2]octane(DABCO, 105 μL, 951 μmol). The mixture was degassed and purged with N_2 3 times. The mixture was stirred at 80 °C for 16 h under CO atmosphere. The reaction was quenched by the addition of H_2O (50 mL). The aqueous layer was extracted by DCM (3 x 10 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4 and concentrated in vacuo to give a residue. The residue was purified by flash silica gel chromatography to give **Intermediate 1b-3** (310 mg) as a yellow solid. ES m/z calculated for $C_9H_{10}ClF_3N_3O$ $[M+H]^+$ 268.0, found 267.9.

[0207] To a solution of **Intermediate 1b-3** (310 mg, 1.16 mmol) in DCM (5 mL) was added $(Boc)_2O$ (266 μL, 1.16 mmol), DMAP (7.1 mg, 58 μmol, 0.05 eq.) and TEA (484 μL, 3.47 mmol). The mixture was stirred at 25 °C for 16 h under N_2 atmosphere. The mixture was concentrated under reduced pressure to remove solvent. The residue was purified by flash silica gel chromatography to give **Intermediate 1b-4** (260 mg) as a yellow solid. ES m/z calculated for $C_{10}H_8ClF_3N_3O_2$ $[M+H]^+$ 294.0. found 293.9.

[0208] A mixture of **Intermediate 1b-4** (400 mg, 1.36 mmol, 1 eq.), $NH_3{\cdot}H_2O$ (795.69 mg, 6.81 mmol, 874.39 μL, 30% purity, 5 eq.) in dioxane (4 mL) was stirred at 80 °C for 12 h. The mixture was concentrated under reduced pressure to remove solvent. The crude product was triturated twice with EA:PE=1:1 (10 mL) at 15 °C. **Intermediate 1b** (370 mg) was obtained as a white solid. ^1H NMR (400 MHz, DMSO-d_6) δ = 8.39 (br s, 1H), 7.95 (br s, 1H), 6.88 (s, 1H), 3.48 (s, 3H), 3.28 (s, 3H); ES m/z calculated for $C_{10}H_{10}F_3N_4O_2$ $[M+H]^+$ 275.1, found 274.9.

Example A1-c
Preparation of Intermediate 1c



Intermediate 1c-1 **Intermediate 1c-2**

Intermediate 1c

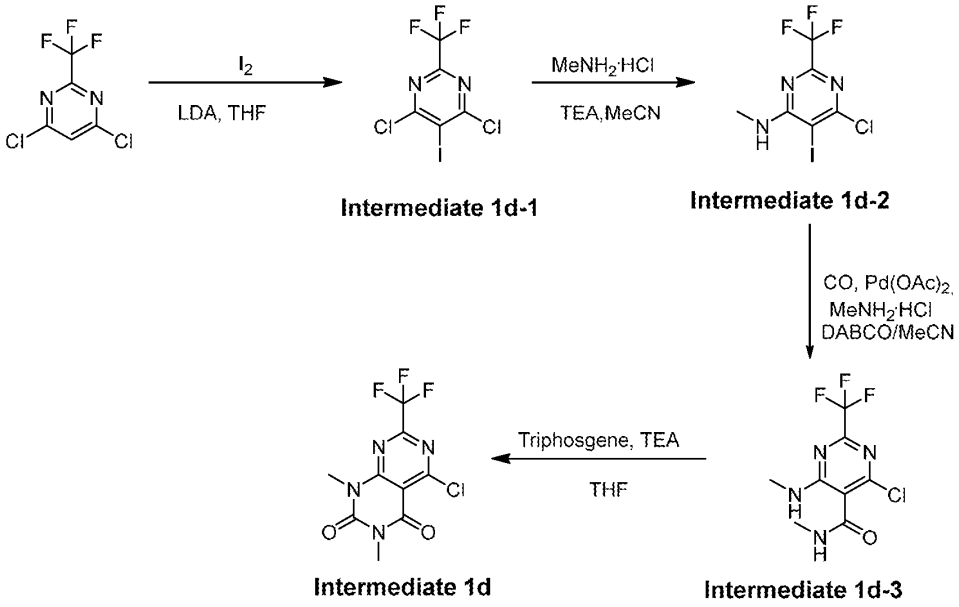
[0209] To a solution of 4,6-dichloro-5-iodo-2-methylpyrimidine (2.0 g, 6.92 mmol) in THF (20 mL) was added TEA (2.89 mL, 20.8 mmol) and methylamine hydrochloride (701 mg, 10.4 mmol). The mixture was stirred at 25 °C for 16 h. The mixture was concentrated under reduced pressure to remove solvent. The residue was purified by flash silica gel chromatography to give **Intermediate 1c-1** (2.0 g) as a white solid. ES m/z calculated for $C_6H_8ClIN_3$ $[M+H]^+$ 283.9, found 283.

[0210] A mixture of **Intermediate 1c-1** (2.4 g, 8.47 mmol), methylamine hydrochloride (1.43 g, 21.16 mmol), Na_2CO_3 (3.59 g, 33.86 mmol), DABCO (93 μL, 847 μmol) and $Pd(OAc)_2$ (190 mg, 847 μmol) in CH_3CN (30 mL) was degassed and purged with N_2 3 times at 20 °C. Then the mixture was stirred at 80 °C for 16 h under CO (50 psi) atmosphere. The mixture was filtered to remove solids, and the filtrate was concentrated under reduced pressure to remove solvent. The residue was purified by flash silica gel to give **Intermediate 1c-2** (0.45 g) as a white solid. ES m/z calculated for $C_8H_{12}ClN_4O$ $[M+H]^+$ 215.1, found 215.0.

[0211] To a solution of **Intermediate 1c-2** (455 mg) in THF (8.0 mL) was added bis(trichloromethyl) carbonate (triphosgene, 510 mg, 1.72 mmol) at 20 °C under nitrogen atmosphere. The mixture was stirred at 20 °C for 1 h. After adding TEA (442 μL, 3.18 mmol)

into the mixture, the resulting mixture was further stirred at 20 °C for 12 h. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (20 mL). The mixture was extracted with EtOAc (30 mL). The EtOAc layer was collected and dried Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash silica gel chromatography to give **Intermediate 1c** (130 mg) as a white solid. ES m/z calculated for $C_9H_{10}ClN_4O_2$ $[M+H]^+$ 241.0, found 241.1.

Example A1-d
Preparation of Intermediate 1d



[0212] To a solution of 4,6-dichloro-2-(trifluoromethyl)pyrimidine (4.5 g, 20.7 mmol) in THF (50 mL) was added dropwise LDA (2 M, 15.55 mL) at -78 °C over 5 min. After addition of LDA, the mixture was stirred at -78 °C for 30 min. Then the solution of I_2 (5.79 g, 22.81 mmol) in THF (3 mL) was added dropwise into the mixture at -78 °C. The mixture was stirred at -78 °C for 1 h. After the mixture's temperature was slowly warmed to rt, ethyl acetate (100 mL) was added. The reaction was further quenched with saturated ammonium chloride aqueous solution (100 mL) and saturated $Na_2S_2O_3$ aqueous solution (100 mL). The organic layer was washed with saturated sodium bicarbonate solution, dried over anhydrous sodium

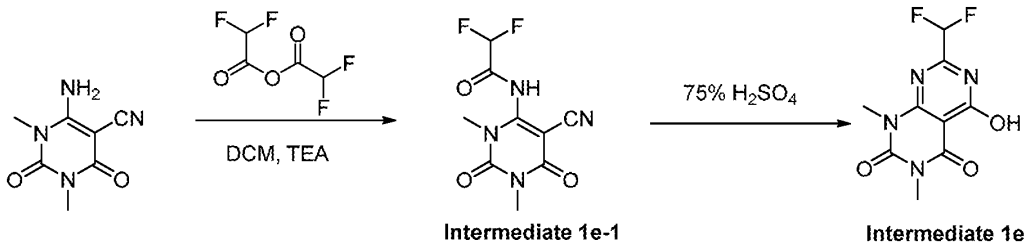
sulfate and concentrated under reduced pressure. The residue was purified by column chromatography to give **Intermediate 1d-1** (8 g) as a colorless oil.

[0213] To a solution of **Intermediate 1d-1** (8 g) and methylamine hydrochloride (3.15 g, 46.66 mmol) in MeCN (100 mL) was added TEA (9.74 mL, 70.00 mmol). The mixture was stirred at 25 °C for 16 h. The reaction was quenched by addition of H_2O (50 mL). The aqueous layer was extracted with DCM (3 x 30 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4 and concentrated in vacuo to give a residue. The residue was purified by column chromatography to give **Intermediate 1d-2** (6 g, 17.07 mmol, 73.15% yield, 96% purity) as a yellow solid. ES m/z calculated for $C_6H_5ClF_3IN_3$ $[M+H]^+$ 337.9, found 337.8.

[0214] A mixture of **Intermediate 1d-2** (3.0 g, 8.89 mmol), methanamine;hydrochloride (00.60 g, 8.89 mmol), $Pd(OAc)_2$ (200 mg, 889 µmol), Na_2CO_3 (2.36 g, 22.22 mmol) and DABCO (196 µL, 1.78 mmol) in MeCN (200 mL) was degassed and purged with N_2 three times. The mixture was stirred at 50 °C for 16 h under CO (50 psi) atmosphere. After cooling the mixture to rt, the reaction was quenched by addition of H_2O (100 mL). The aqueous layer was extracted by DCM (3 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4 and concentrated in vacuo to give a residue. The residue was purified by silica gel chromatography to give **Intermediate 1d-3** (0.65 g) as a yellow oil. ES m/z calculated for $C_8H_8ClF_3N_4O$ $[M+H]^+$ 269.0, found 269.0.

[0215] To a solution of **Intermediate1d-3** (1.3 g, 4.84 mmol) in THF (10 mL) was added bis(trichloromethyl) carbonate (1.15 g, 3.87 mmol, 0.8 eq.) at 25 °C under nitrogen atmosphere. After the mixture was stirred at 25 °C for 1 h, TEA (2.94 g, 29.04 mmol, 4.04 mL, 6 eq.) was added. The mixture was further stirred at 25 °C for 16 h. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (20 mL). The aqueous layer was extracted with EtOAc (30 mL). The organic layer was collected and dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by silica column chromatograph to give **Intermediate 1d** (500 mg) as a yellow oil. ES m/z calculated for $C_9H_7ClF_3N_4O_2$ $[M+H]^+$ 295.0, found 294.9.

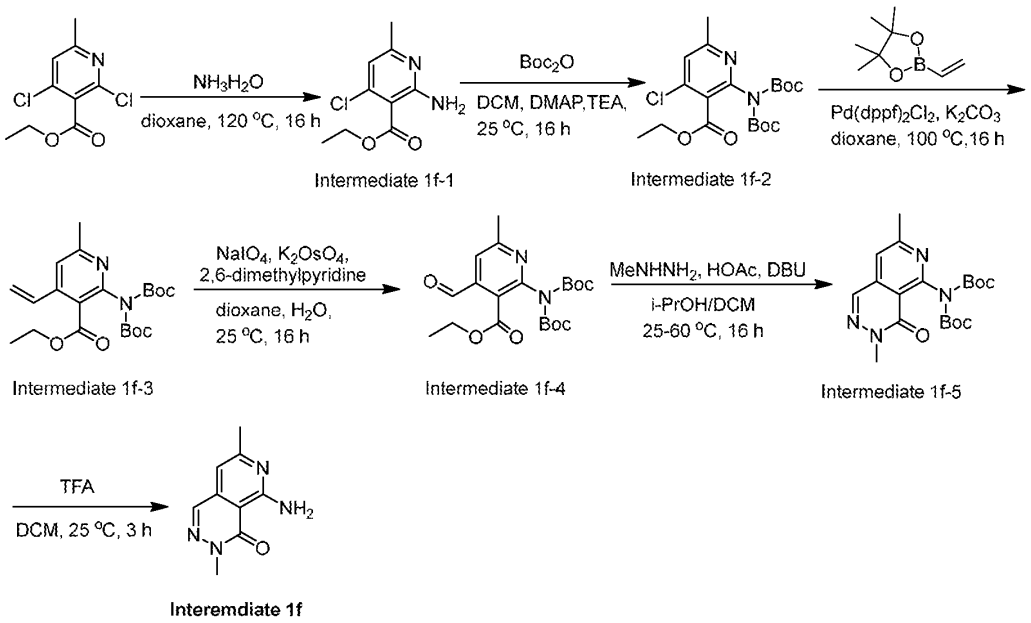
Example A1-e
Preparation of Intermediate 1e



[0216] To a solution of 6-amino-5-cyano-1,3-dimethyluracil (480 mg, 2.66 mmol), 2,2-difluoroacetyl) 2,2-difluoroacetate (696 mg, 4.00 mmol) in DCM (5 mL) were added DMAP (33 mg, 266 μmol) and TEA (1.11 mL, 7.99 mmol). The resulting mixture was stirred at 25 °C for 16 h. The reaction was quenched by addition of H_2O (20 mL). The aqueous layer was extracted by DCM (3 x 20 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4 and concentrated in vacuo to give a residue. The residue was purified by silica column chromatography to give **Intermediate 1e-1** (250 mg) as a yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.92 (br s, 1H), 5.94 (t, J =56.0 Hz, 1H), 3.20 (s, 3H), 3.12 (s, 3H).

[0217] A solution of **Intermediate 1e-1** (250 mg, 968 μmol) in sulfuric acid (75% H_2SO_4 aqueous solution, 4 mL) was stirred at 90 °C for 1 h. The reaction was quenched by addition of H_2O (20 mL). The aqueous layer was extracted with DCM (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 and concentrated in vacuo to give a residue. The residue was purified by flash silica gel chromatography to give **Intermediate 1e** (110 mg,) as a yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 6.60 (t, J = 53.7 Hz, 1H), 3.40 (s, 3H), 3.14 (s, 3H).

Example A1-f
Preparation of Intermediate 1f



[0218] A solution of Ethyl 2,4-dichloro-6-methyl-3-pyridinecarboxylate (5.0 g, 21.4 mmol) in the mixture of 1,4-dioxane (20 mL) and $NH_3 \cdot H_2O$ (30% NH_3 basis, 27.4 mL) was stirred at 120 °C for 16 hours in a sealed tube (100 mL). The reaction was quenched by the addition of H_2O (50 mL) and extracted with DCM (60 mL x 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 and concentrated in vacuo to give a residue. The residue was purified by silica column chromatography to give **Intermediate 1f-1** (2.4 g) as a white solid. ^1H NMR (400 MHz, CHLOROFORM-d) δ = 6.56 (s, 1H), 6.14 (s, 2H), 4.39 (q, J = 7.2 Hz, 2H), 2.33 (s, 3H), 1.40 (t, J = 7.2 Hz, 3H).

[0219] To the reaction mixture of **Intermediate 1f-1** (2.4 g, 11.2 mmol) and Boc anhydride (10.3 mL, 44.7 mmol) in DCM (20 mL) were added DMAP (273.20 mg, 2.24 mmol) and TEA (9.34 mL, 67.09 mmol) at 25 °C. The mixture was stirred at 25 °C for 16 hours. The reaction was quenched by addition of H_2O (30 mL) and extracted by DCM (30 mL x 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4 and concentrated in vacuo to give a residue. The residue was purified by silica column chromatography to give **Intermediate 1f-2** (4.2 g) as a white solid. ^1H NMR (400 MHz,

DMSO-d_6) δ = 7.65 (s, 1H), 4.30 (d, J = 7.2 Hz, 2H), 2.53-2.51 (m, 3H), 1.34 (s, 18H), 1.27 (t, J = 7.2 Hz, 3H).

[0220] To a solution of **Intermediate 1f-2** (4.2 g, 10.1 mmol) and 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (2.58 mL, 15.2 mmol) in the mixture of 1,4-dioxane (40 mL) and H_2O (4 mL) were added Pd(dppf)Cl_2 (740 mg, 1.0 mmol) and K_2CO_3 (2.80 g, 20.3 mmol). The mixture was stirred at 100 °C for 16 hours under N_2 atmosphere. The mixture was concentrated in vacuo to give a residue. The residue was purified by silica column chromatography to give **Intermediate 1f-3** (2.4 g) as a white solid. ^{1}H NMR (400 MHz, DMSO-d6) δ = 7.64 (s, 1H), 6.85 (dd, J = 11.2, 17.2 Hz, 1H), 6.12 (d, J = 17.6 Hz, 1H), 5.61 (d, J = 11.2 Hz, 1H), 4.27 (q, J = 7.2 Hz, 2H), 2.53-2.50 (m, 3H), 1.33 (s, 18H), 1.26 (t, J = 7.2 Hz, 3H).

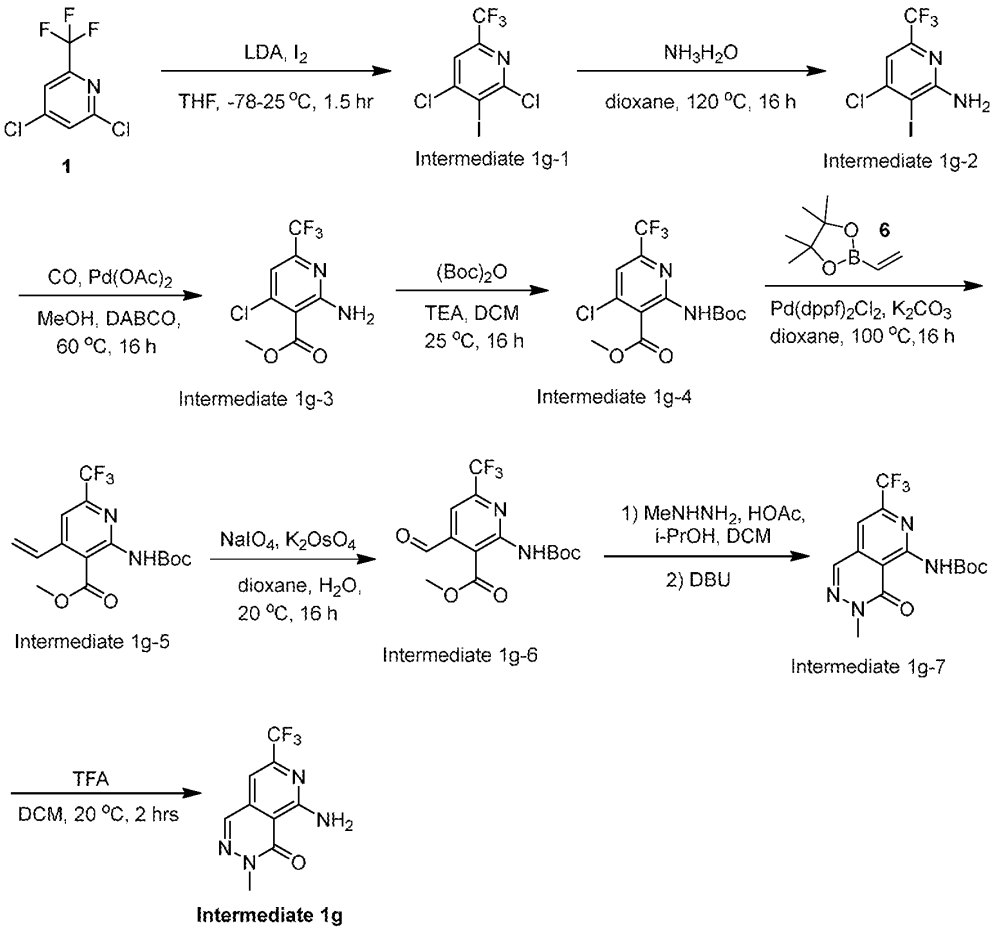
[0221] To a solution of **Intermediate 1f-3** (2.4 g, 5.9 mmol) in the mixture of dioxane (30 mL) and H_2O (4 mL) were added $NaIO_4$ (3.16 g, 14.76 mmol), 2,6-dimethylpyridine (1.38 mL, 11.8 mmol) and dipotassium;dioxido(dioxo)osmium;dihydrate (43.5 mg, 118 μmol) in one portion at 25 °C. The mixture was stirred at 25 °C for 16 hours. The mixture was poured into water (30 mL). The aqueous phase was extracted with ethyl acetate (50 mL x 3). The combined organic phase was dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash silica gel chromatography to give **Intermediate 1f-4** (2.7 g, 4.69 mmol, 79.49% yield, 71% purity) as a yellow oil. MS: ES m/z calculated for MS: ES m/z calculated for $C_{20}H_{29}N_2O_7$ $[M+H]^+$ 409.2, found 409.0.

[0222] To a mixture of **Intermediate 1f-4** (2.7 g, 6.61 mmol), HOAc (1.89 mL, 33.1 mmol) and $MgSO_4$ (3.98 g, 33.05 mmol) in i-PrOH (15 mL) and DCM (15 mL) was added methylhydrazine (1.91 mL, 14.50 mmol) in one portion at 25 °C. The mixture was stirred at 25 °C for 14 hours. After adding DBU (9.96 mL, 66.1 mmol) at 25 °C, the mixture was warmed to 60 °C and then stirred at 60 °C for 2 hours. The reaction was quenched by addition of water (30 mL), and then extracted with DCM (30 mL x 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 and concentrated in vacuo to give a residue. The residue was purified by silica column chromatography to give **Intermediate 1f-5** (1.87 g) as a white solid.

[0223] To a solution of **Intermediate 1f-5** (220 mg, 563.48 μmol) in DCM (3 mL) was added dropwise TFA (2.20 mL, 3.38 g) at 25 °C. The mixture was stirred at 25 °C for 3

hours. The reaction was quenched by addition of H_2O (20 mL), and then extracted with DCM (10 mL x 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4 and concentrated in vacuo to give a residue. The residue was purified by silica column chromatography to give **Intermediate 1f** (100 mg,) as a white solid. MS: ES m/z calculated for MS: ES m/z calculated for $C_9H_{11}N_4O$ $[M+H]^+$ 190.09, found 191.0.

Example A1-g
Preparation of Intermediate 1g



[0224] To a solution of 2,4-Dichloro-6-(trifluoromethyl)pyridine (5.0 g, 23.2 mmol) was added dropwise LDA (2 M, 12.73 mL) at -78 °C over 5 min. After the mixture was stirred at this temperature for 30 min, I_2 (5.13 mL, 25.5 mmol) in THF (100 mL) was added dropwise to at -78 °C. The mixture was stirred at -78 °C for 1 hour. After the mixture

was slowly warmed to rt, EtOAc (100 mL), ammonium chloride (60 mL) and saturated $Na_2S_2O_3$ solution (60 mL) were added into the mixture. The organic layer of the mixture was separated, washed with saturated sodium bicarbonate solution, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography to give **Intermediate 1g-1** (10.4 g) as a white solid. MS: ES m/z calculated for MS: ES m/z calculated for $C_6H_2Cl_2F_3IN$ $[M+H]^+$ 341.9, found 341.7.

[0225] A solution of **Intermediate 1g-1** (10 g, 29.2 mmol) in the mixture of 1,4-dioxane (60 mL) and $NH_3{\cdot}H_2O$ (30% NH_3 basis, 37.6 mL) was stirred at 120 °C for 16 hours in a sealed tube (100 mL). After cooling down the mixture to rt, the reaction was quenched by addition of H_2O (100 mL), and then extracted by DCM (100 mL x 3). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4 and concentrated in vacuo to give a residue, which was purified by flash silica gel chromatography to give **Intermediate 1g-2** (3.47 g) as a white solid. MS: ES m/z calculated for MS: ES m/z calculated for $C_6H_4ClF_3IN_2$ $[M+H]^+$ 322.9, found 322.8.

[0226] A mixture of **Intermediate 1g-2** (3.47 g, 10.76 mmol), Na_2CO_3 (2.85 g, 26.9 mmol), DABCO (237 μL, 2.15 mmol) and $Pd(OAc)_2$ (241.60 mg, 1.08 mmol) in MeOH (100 mL) was degassed and purged with N_2 (3x). Then the mixture was stirred at 60 °C for 16 hours under CO (50 PSi) atmosphere. The mixture was cooled into 25 °C and purged with Ar (3x). The reaction was quenched by addition of H_2O (60 mL) and extracted with DCM (60 mL x 3). The combined organic layers were washed with brine (60 mL), dried over Na_2SO_4 and concentrated in vacuo to give a residue, which was purified by flash silica gel chromatography to give **Intermediate 1g-3** (2.45 g) as a white solid. MS: ES m/z calculated for MS: ES m/z calculated for $C_8H_7ClF_3N_2O_2$ $[M+H]^+$ 255.0, found 255.0.

[0227] To a solution of **Intermediate 1g-3** (2.45 g, 9.62 mmol) and TEA (8.04 mL, 57.7 mmol) in DCM (35 mL) was added Boc anhydride (8.84 mL, 38.49 mmol) and DMAP (117 mg, 962μmol). The mixture was stirred at 25 °C for 16 hours. The mixture was concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography to give **Intermediate 1g-4** (3.6 g) as a colorless oil.

[0228] To a solution of **Intermediate 1g-4** (3 g, 6.60 mmol) and 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (3.36 mL, 19.8 mmol) in dioxane (30 mL) and H_2O (3 mL) were added K_2CO_3 (1.82 g, 13.2 mmol) and $Pd(dppf)Cl_2$ (483 mg, 660 μmol) at rt.

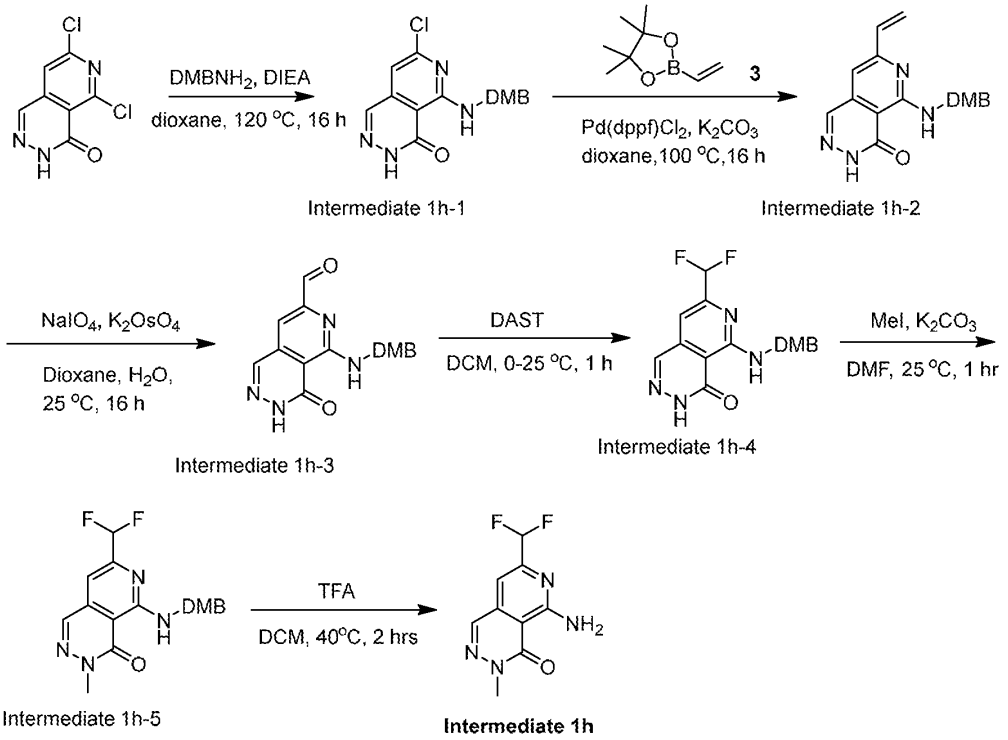
After the mixture was degassed and purged with N_2 (3x), the mixture was warmed to 100 °C and then stirred at 100 °C for 16 hours under N_2 atmosphere. The mixture was filtered and concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography to give **Intermediate 1g-5** (2.57 g) as a yellow oil. MS: ES m/z calculated for MS: ES m/z calculated for $C_{15}H_{18}F_3N_2O_4$ [M+H]+ 347.1, found 347.0.

[0229] To a solution of **Intermediate 1g-5** (2.07 g, 4.64 mmol) in dioxane (40 mL) and H_2O (8 mL) were added $NaIO_4$ (2.48 g, 11.6 mmol), 2, 6-dimethylpyridine (1.08 mL, 9.27 mmol) and dipotassium;dioxido(dioxo)osmium;dihydrate (34.2 mg, 92.7 μmol,) at 20 °C. The mixture was stirred at 20 °C for 16 hours. The mixture was poured into water (30 mL) and extracted with ethyl acetate (50 mL x 3). The combined organic phase was dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum, which was purified by flash silica gel chromatography to give **Intermediate 1g-6** (1.29 g) as a yellow oil

[0230] To a solution of **Intermediate 1g-6** (1.49 g, 3.32 mmol) in i-PrOH (20 mL) and DCM (20 mL) were added AcOH (951 μL, 16.62 mmol), $MgSO_4$ (2.00 g, 16.6 mmol) and methylhydrazine (1.09 mL, 8.25 mmol) at 20 °C. The mixture was stirred at 20 °C for 2 hours. After adding DBU (10.0 mL, 66.5 mmol), the mixture was further stirred at 20 °C for 2 hours. The reaction was quenched by addition of H_2O (50 mL) and extracted with DCM (50 mL x 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 and concentrated in vacuo to give a residue, which was purified by flash silica gel chromatography to give **Intermediate 1g-7** (783 mg,) as a yellow solid. MS: ES m/z calculated for MS: ES m/z calculated for $C_{14}H_{16}F_3N_4O_3$ $[M+H]^+$ 345.1, found 345.1.

[0231] A mixture of **Intermediate 1g-7** (783 mg, 1.76 mmol) in TFA (5 mL) and DCM (20 mL) was stirred at 20 °C for 2 hours. The mixture was concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography to give **Intermediate 1g** (430 mg) as a white solid. MS: ES m/z calculated for MS: ES m/z calculated for $C_9H_8F_3N_4O$ $[M+H]^+$ 245.1, found 244.9.

Example A1-h
Preparation of Intermediate 1h



[0232] To a solution of 5,7-dichloro-3H-pyrido[3,4-d]pyridazin-4-one (387mg, 2.31 mmol) and 2,4-Dimethoxybenzylamine (348 µL, 2.31 mmol) in dioxane (60 mL) was added DIEA (2.42 mL, 13.9 mmol) at rt. The mixture warmed to 120 °C and then stirred at 120 °C for 16 hours. The mixture was concentrated in vacuo to give a residue. The residue was purified by silica column chromatography to give **Intermediate 1h-1** (710 mg) as a white solid. MS: ES m/z calculated for MS: ES m/z calculated for $C_{16}H_{16}ClN_4O_3$ $[M+H]^+$ 347.1, found 347.0.

[0233] To a solution of **Intermediate 1h-1** (710 mg, 2.05 mmol) and 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (695 µL, 4.09 mmol) in dioxane (10 mL) and H_2O (1 mL) were added $Pd(dppf)Cl_2$ (150mg, 205 µmol) and K_2CO_3 (566 mg, 4.09 mmol) at rt. The mixture was warmed to 100 °C and then stirred at 100 °C for 16 hours under N_2 atmosphere. The mixture was concentrated in vacuo to give a residue. The residue was purified by silica column chromatography to give **Intermediate 1h-2** (560 mg) as a white solid. MS: ES m/z calculated for $C_{18}H_{19}N_4O_3$ $[M+H]^+$ 339.1, found 339.1.

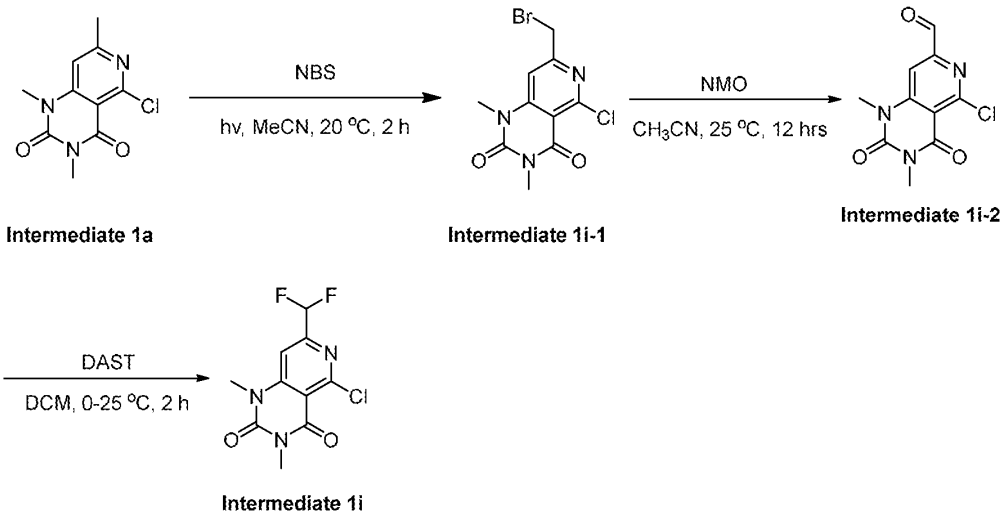
[0234] To a solution of Intermediate **1h-2** (400 mg, 1.18 mmol) in dioxane (10 mL) and H_2O (2 mL) were added $NaIO_4$ (632 mg, 2.96 mmol), 2,6-dimethylpyridine (275 μL, 2.36 mmol) and dipotassium;dioxido(dioxo)osmium;dihydrate (8.71 mg, 23.64 μmol) in one portion at 25 °C. The mixture was stirred at 25 °C for 16 hours. The mixture was poured into water (10 mL) and extracted with ethyl acetate (20 mL x 3). The combined organic layers were dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash silica gel chromatography to give **Intermediate 1h-3** (280 mg) as a yellow solid. MS: ES m/z calculated for $C_{17}H_{17}N_4O_4$ $[M+H]^+$ 341.12, found 341.0.

[0235] To a solution of **Intermediate 1h-3** (280 mg, 823μmol) in DCM (10 mL) was added DAST (217 μL, 1.65 mmol) in one portion at 0 °C. The mixture was stirred at 25 °C for 1 hour. The mixture was poured into water (20 mL) and extracted with DCM (10 mL x 3). The combined organic layers were dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residues were purified by flash silica gel chromatography to give **Intermediate 1h-4** (230 mg) as a white solid. MS: ES m/z calculated for $C_{17}H_{17}F_2N_4O_3$ $[M+H]^+$ 363.1, found 363.2.

[0236] To a mixture of **Intermediate 1h-4** (230 mg, 635 μmol) and K_2CO_3 (263 mg, 1.90 mmol) in DMF (3 mL) was added MeI (59 μL 952 μmol) in one portion at 25 °C. The mixture was stirred at 25 °C for 1 hour. The mixture was poured into water (2 mL) and extracted with EtOAc (5 mL x 3). The combined organic layer was dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash silica gel chromatography to give **Intermediate 1h-5** (170 mg) as a white solid. ^1H NMR (400 MHz, CHLOROFORM-d) δ = 9.50-9.37 (m, 1H), 7.92 (s, 1H), 7.29-7.26 (m, 1H), 6.80 (s, 1H), 6.61-6.31 (m, 3H), 4.68 (d, J = 5.6 Hz, 2H), 3.86 (s, 3H), 3.77 (s, 3H), 3.76 (s, 3H).

[0237] To a solution of **Intermediate 1h-5** (170 mg, 452 μmol) in DCM (2 mL) was added dropwise TFA (2 mL) at rt. The mixture was stirred at 40 °C for 2 hours. The pH of the mixture was adjusted to 7~8 by adding sat. aq. $NaHCO_3$. The aqueous phase was extracted with DCM (5 mL x 3). The combined organic layer was dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash silica gel chromatography to give **Intermediate 1h** (60 mg) as a white solid. ^1H NMR (400 MHz, DMSO-d_6) δ = 8.43 (s, 1H), 8.30 (s, 1H), 7.89 (s, 1H), 7.08 (s, 1H), 6.79 (t, J = 56.0 Hz, 1H), 3.68 (s, 3H).

Example A1-i
Preparation of Intermediate 1i



Intermediate 1a

Intermediate 1i-1

Intermediate 1i-2

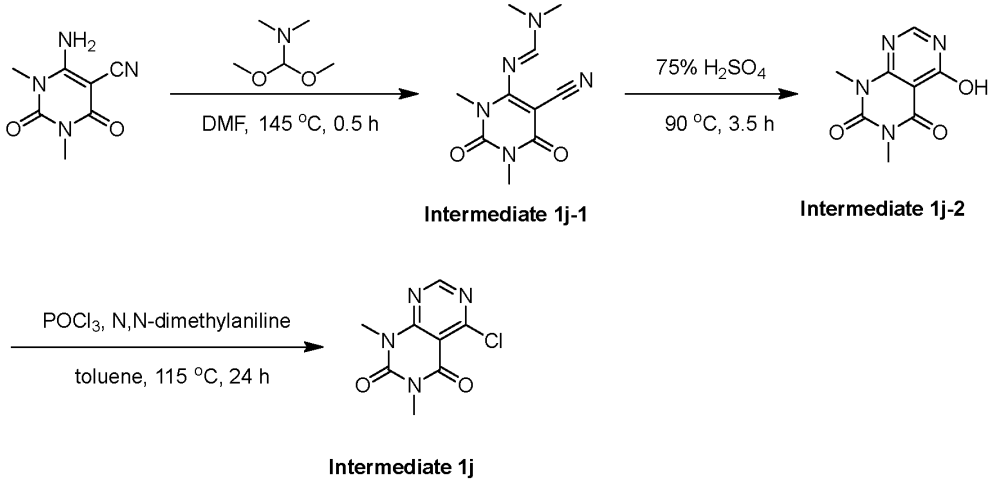
Intermediate 1i

[0238] To a solution of **Intermediate 1a** (200 mg, 835 μmol) in CH_3CN (50 mL) was added NBS (297 mg, 1.67 mmol). The mixture was stirred at 20 °C for 2 hours under blue light. The mixture was concentrated under reduced pressure to remove solvent**.** The residue was purified by prep-HPLC to give **Intermediate 1i-1** (130 mg) as a white solid. MS: ES m/z calculated for MS: ES m/z calculated for $C_{10}H_{10}BrClN_3O_2$ $[M+H]^+$ 318.0, found 318.1.

[0239] To a solution of **Intermediate 1i-1** (120 mg, 377 μmol) in CH_3CN (3.0 mL) was added NMO (88 mg, 753 μmol) at 25 °C. The mixture was stirred at 25 °C for 12 hours. The mixture was concentrated under reduced pressure to remove the solvent. The residue was purified by flash silica gel chromatography to give **Intermediate 1i-2** (50 mg) as a white solid.

[0240] To a solution of **Intermediate 1i-2** (30 mg, 118 μmol) in DCM (5.0 mL) was added DAST (47 μL, 354.83 μmol) at 0 °C. The mixture was stirred at 25 °C for 2 hours. The reaction was quenched by adding saturated aqueous $NaHCO_3$ (5 mL). The aqueous layer was extracted with DCM 10 mL (5 mL x 2). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give **Intermediate 1i** (30 mg) as a white solid. MS: ES m/z calculated for $C_{10}H_9ClF_2N_3O_2$ $[M+H]^+$ 276.0, found 276.0.

Example A1-j
Preparation of Intermediate 1j



Intermediate 1j-1

Intermediate 1j-2

Intermediate 1j

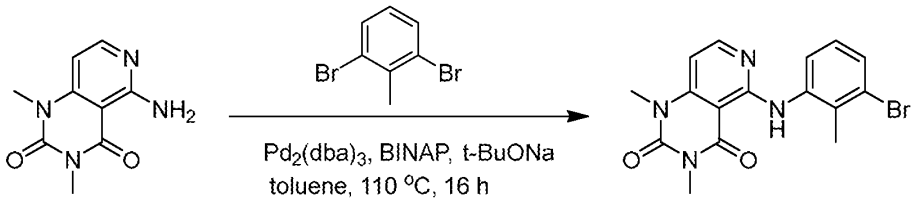
[0241] The mixture of 6-amino-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (1.5 g, 8.33 mmol) and 1,1-dimethoxy-N,N-dimethyl-methanamine (3.97 g, 33.30 mmol, 4.42 mL, 4 eq) in DMF (40 mL) was degassed and purged with N_2 (3x) at rt. The mixture was stirred at 145 °C for 0.5 hour under N_2 atmosphere. The mixture was concentrated under reduced pressure to remove the solvent. The residue was purified by flash silica gel chromatography to give **Intermediate 1j-1** (1.22 g) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.26 (s, 1H), 3.27 (s, 3H), 3.19 (s, 3H), 3.15 (s, 3H), 3.07 (s, 3H).

[0242] The mixture of **Intermediate 1j-1** (1.22 g, 5.19 mmol) in H_2SO_4 (75% v/v aq. soln., 12 mL) was degassed and purged with N_2 (3x) at rt. The mixture was stirred at 90 °C for 3.5 hours under N_2 atmosphere. The mixture was cooled to rt, diluted with ice cold water (30 mL). The mixture was filtered, and the filter cake was dried directly to give **Intermediate 1j-2** (0.83 g) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 12.74 (br s, 1H), 8.32 (s, 1H), 3.40 (s, 3H), 3.11 (s, 3H).

[0243] To a solution of **Intermediate 1j-2** (0.96 g, 4.61 mmol) in toluene (20 mL) were added $POCl_3$ (516 µL, 5.53 mmol) and N, N-dimethylaniline (585 µL, 4.61 mmol) at rt. The mixture was stirred at 115 °C for 24 hours. The reaction was quenched by addition H_2O (30 mL) and $NaHCO_3$ (50 mL). The mixture was extracted with DCM (40 mL x 3). The combined organic layers were washed with H_2O (40 mL x 2), dried Na_2SO_4, filtered and

concentrated in vacuum. The residues were purified by silica column chromatography to give **Intermediate 1j** (0.25 g) as a white solid. MS: ES m/z calculated for MS: ES m/z calculated for $C_8H_8ClN_4O_2$ $[M+H]^+$ 227.0, found 226.9.

Example A2
Preparation of Intermediate 2-1

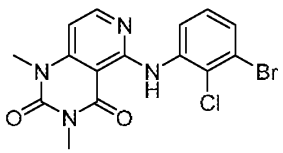


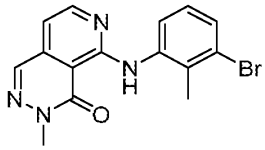
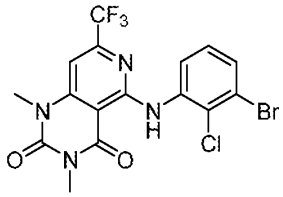
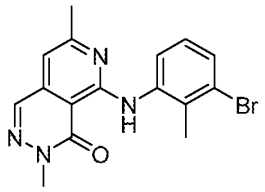
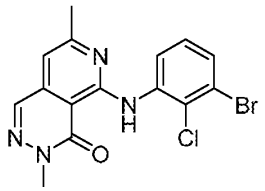
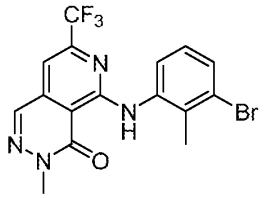
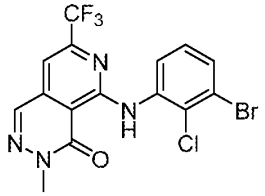
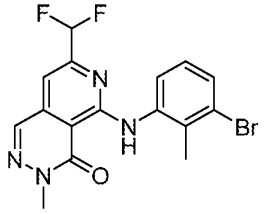
Intermediate 2-1

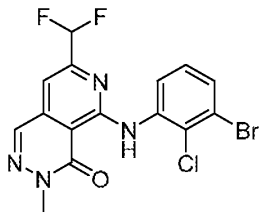
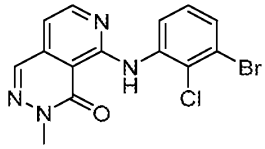
[0244] A mixture of 5-amino-1,3-dimethylpyrido[3,4-e]pyrimidine-2,4-dione (200 mg, 970 μmol), 1,3-dibromo-2-methylbenzene (291 mg, 1.16 mmol), NaOtBu (280 mg, 2.91 mmol), $Pd_2(dba)_3$ (44 mg, 49 μmol) and BINAP (36 mg, 58 μmol) in toluene (6 mL) was degassed and purged with N_2 for 3 times, then the mixture was stirred at 110 °C for 16 h under N_2 atmosphere. Upon completion, the mixture was concentrated under reduced pressure to remove the solvent. The crude product was triturated with EtOAc at 15 °C three times, to give **Intermediate 2-1** (300 mg, crude) as a white solid. MS: ES m/z calculated for $C_{16}H_{16}BrN_4O_2$ $[M+H]^+$ 375.0, found 374.9.

[0245] The intermediates shown in Table A-1 were prepared by an analogous reaction protocol as was used for the preparation of Intermediate 2-1 using the appropriate starting materials.

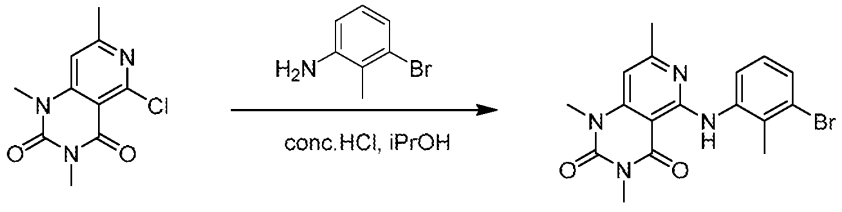
Table A-1

Intermediate No.	Structure	Starting Materials
2-2		5-amino-1,3-dimethyl-1H,2H,3H,4H-pyrido[4,3-d]pyrimidine-2,4-dione 1,3-dibromo-2-chlorobenzene

Intermediate No.	Structure	Starting Materials
2-3		Intermediate 1 1,3-dibromo-2-methylbenzene
2-4		Intermediate 1b 1,3-dibromo-2-chlorobenzene
2-5		Intermediate 1f 1,3-dibromo-2-methylbenzene
2-6		Intermediate 1f 1,3-dibromo-2-chlorobenzene
2-7		Intermediate 1g 1,3-dibromo-2-methylbenzene
2-8		Intermediate 1g 1,3-dibromo-2-chlorobenzene
2-9		Intermediate 1h 1,3-dibromo-2-methylbenzene

Intermediate No.	Structure	Starting Materials
2-10		Intermediate 1h 1,3-dibromo-2-chlorobenzene
2-11		Intermediate 1 1,3-dibromo-2-chlorobenzene

Example A2-a
Preparation of Intermediate 2a-1

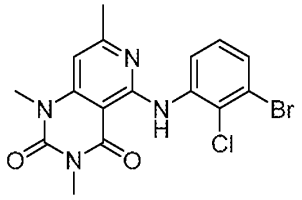
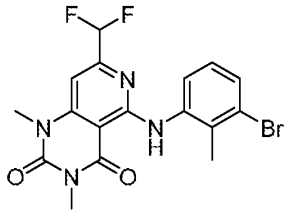
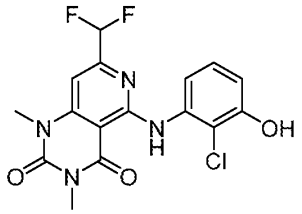
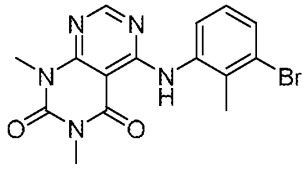
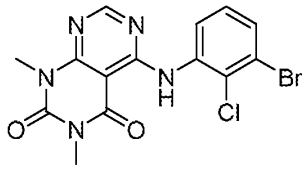


Intermediate 1a **Intermediate 2a-1**

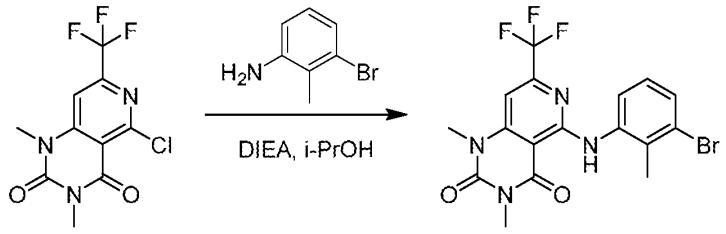
[0246] To a solution of **Intermediate 1a** (60 mg, 250 μmol) and 3-bromo-2-methylaniline (62 μL, 501 μmol) in isopropyl alcohol (iPrOH, 0.5 mL) was added hydrochloric acid (12 M, 2.1 μL). The mixture was stirred at 90 °C for 12 h. The mixture was concentrated under reduced pressure to remove the solvent. The residue was purified by flash silica gel chromatography to give **Intermediate 2a-1** (65 mg) as a white solid. MS: ES m/z calculated for $C_{17}H_{18}BrN_4O_2$ $[M+H]^+$ 389.1, found 389.0.

[0247] The intermediates shown in Table A-1a were prepared by an analogous reaction protocol as was used for the preparation of Intermediate 2a-1 using the appropriate starting materials.

Table A-1a

Intermediate No.	Structure	Starting Materials
2a-2		Intermediate 1a 3-bromo-2-chloroaniline
2a-3		Intermediate 1i 3-bromo-2-methylaniline
2a-4		Intermediate 1i 3-Amino-2-chlorophenol
2a-5		Intermediate 1j 3-bromo-2-methylaniline
2a-6		Intermediate 1j 3-bromo-2-chloroaniline

Example A2-b
Preparation of Intermediate 2b-1

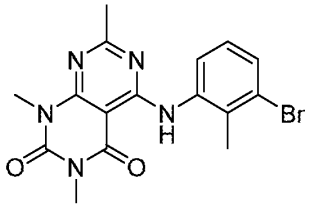
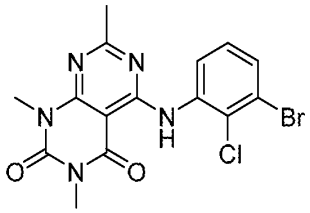


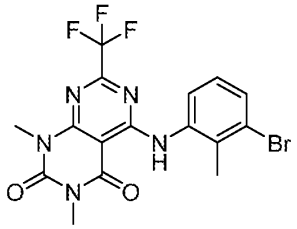
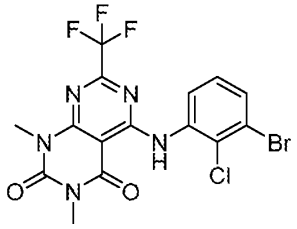
Intermediate 1b-4 **Intermediate 2b-1**

[0248] A mixture of **Intermediate 1b-4** (260 mg, 885.47 μmol, 1 eq.), 3-bromo-2-methylaniline (197.69 mg, 1.06 mmol, 130.92 μL, 1.2 eq.) and DIEA (572.20 mg, 4.43 mmol, 771.16 μL, 5 eq.) in i-PrOH (3 mL) was stirred at 90 °C for 48 h under N_2 atmosphere. The mixture was concentrated under reduced pressure to remove the solvent. The residue was purified by flash silica gel chromatography. The crude product was triturated twice with MeOH at 25 °C. **Intermediate 2b-1** (140 mg) was obtained as a white solid. MS: ES m/z calculated for $C_{17}H_{15}BrF_3N_4O_2$ $[M+H]^+$ 443.0, found 442.9.

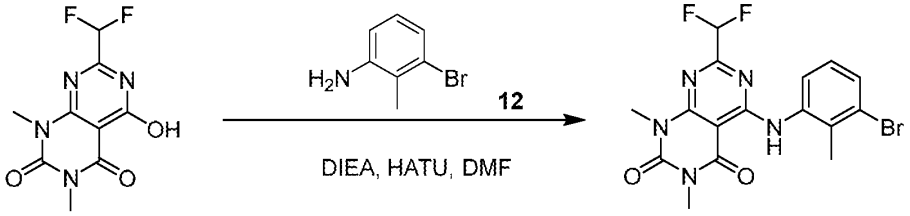
[0249] The intermediates shown in Table A-1b were prepared by an analogous reaction protocol as was used for the preparation of Intermediate 2b-1 using the appropriate starting materials.

Table A-1b

Intermediate No.	Structure	Starting Materials
2b-2		Intermediate 1c 3-bromo-2-methylaniline
2b-3		Intermediate 1c 3-bromo-2-chloroaniline

Intermediate No.	Structure	Starting Materials
2b-4		Intermediate 1d 3-bromo-2-methylaniline
2b-5		Intermediate 1d 3-bromo-2-chloroaniline

Example A2-c
Preparation of Intermediate 2c-1

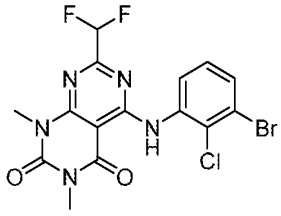


Intermediate 1e **Intermediate 2c-1**

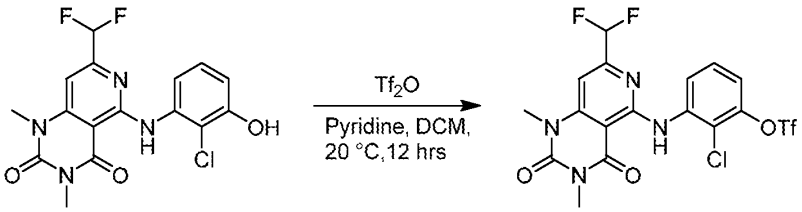
[0250] To a solution of **Intermediate 1e** (110 mg, 426 μmol), 3-bromo-2-methylaniline (63 μL, 511 μmol) and DIEA (148 μL, 852 μmol) in DMF (1 mL) was added HATU (243mg, 639 μmol). The mixture was stirred at 25 °C for 16 h. The reaction was quenched by addition of H_2O (10 mL). The aqueous layer was extracted by DCM (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 and concentrated in vacuo to give a residue. The residue was purified by silica column chromatography to give **Intermediate 2c-1** (70 mg) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.13 (s, 1H), 7.87 (d, J = 8.0 Hz, 1H), 7.52 (d, J = 8.0 Hz, 1H), 7.22 (t, J = 8.0 Hz, 1H), 6.70 (t, J = 54.0 Hz, 1H), 3.52 (s, 3H), 3.31 (s, 3H), 2.36 (s, 3H).

[0251] The intermediates shown in Table A-1c were prepared by an analogous reaction protocol as was used for the preparation of Intermediate 2c-1 using the appropriate starting materials.

Table A-1c

Intermediate No.	Structure	Starting Materials
2c-2		Intermediate 1e 3-bromo-2-chloroaniline

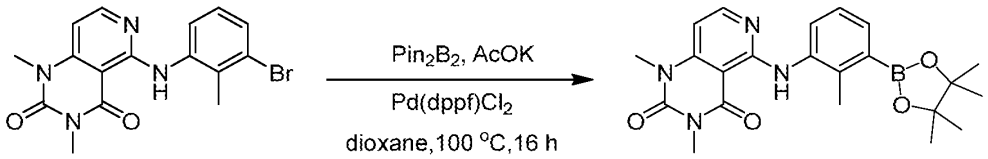
Example A2-d
Preparation of Intermediate 2a-4a



Intermediate 2a-4 **Intermediate 2a-4a**

[0252] To a solution of **Intermediate 2a-4** (0.45 g, 1.18 mmol) in DCM (5.0 mL) were added pyridine (285 μL, 3.53 mmol) and Tf_2O (291 μL, 1.76 mmol) at 0 °C. The mixture was stirred at 20 °C for 12 hours. The mixture was concentrated under reduced pressure to remove the solvent. The residue was purified by flash silica gel chromatography to give **Intermediate 2a-4a** as a yellow solid. ^1H NMR (400 MHz, DMSO-d_6) δ = 11.94 (s, 1H), 8.89 (d, J = 8.4 Hz, 1H), 7.58 (t, J = 8.4 Hz, 1H), 7.34 (d, J = 8.4 Hz, 1H), 7.19 (s, 1H), 6.96 (t, J = 54.4 Hz, 1H), 3.55 (s, 3H), 3.35 (s, 3H).

Example A3
Preparation of Intermediate 3-1

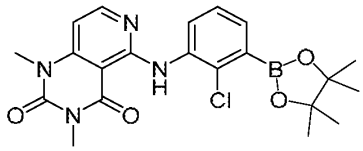
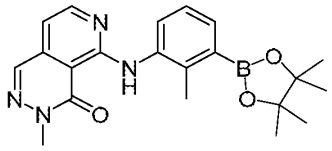
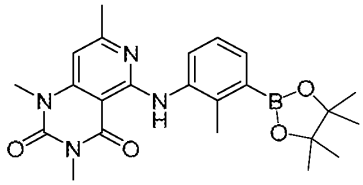
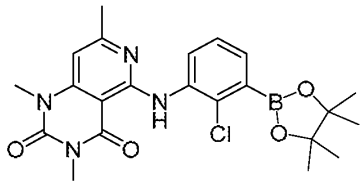


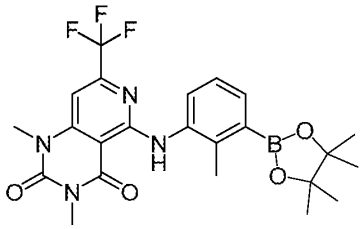
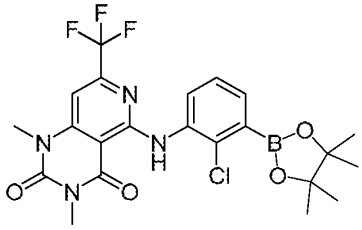
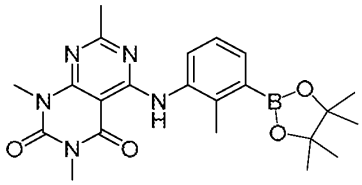
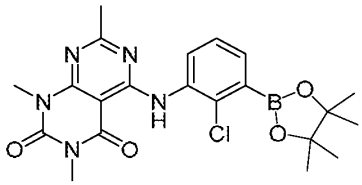
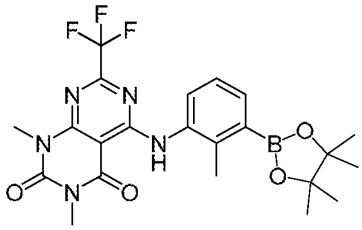
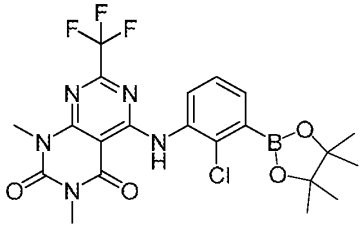
Intermediate 2-1 **Intermediate 3-1**

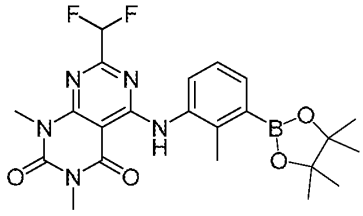
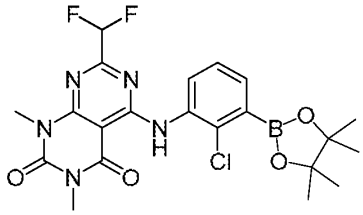
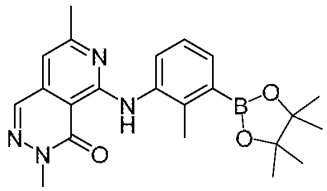
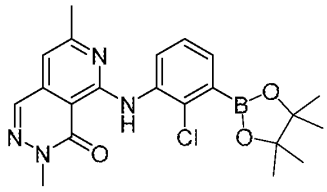
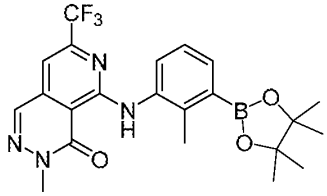
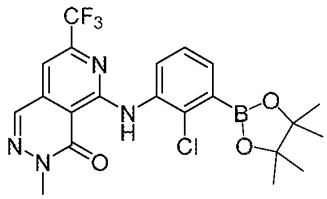
[0253] A mixture of **Intermediate 2-1** (150 mg, crude), Pin_2B_2 (203mg, 800 μmol), KOAc (118 mg, 1.20 mmol), $Pd(dppf)Cl_2$ (23 mg, 32 μmol) in dioxane (2 mL) was degassed and purged with N_2 three times, and then the mixture was stirred at 100 °C for 16 h under N_2 atmosphere. The mixture was filtered. The filtrate was concentrated directly. The residue was purified by flash silica gel chromatography to give **Intermediate 3-1** (168 mg) as a white solid. MS: ES m/z calculated for $C_{22}H_{28}BN_4O_4$ $[M+H]^+$ 423.2, found 423.1.

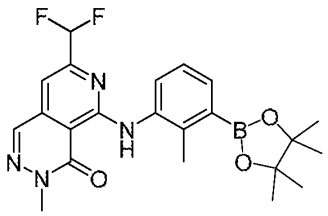
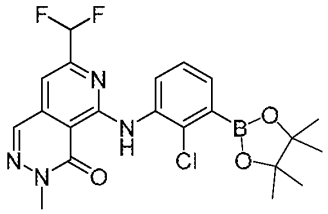
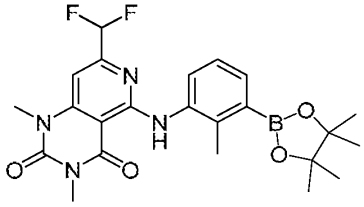
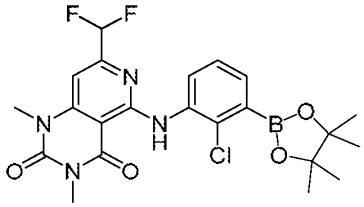
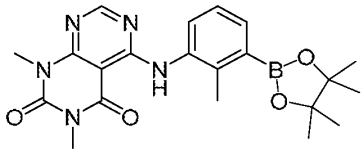
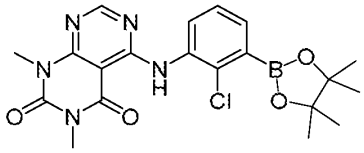
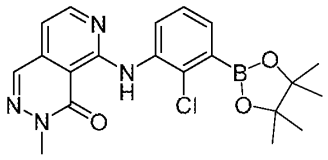
[0254] The intermediates shown in Table A-2 were prepared by an analogous reaction protocol as was used for the preparation of Intermediate 3-1 using the appropriate starting materials.

Table A-2:

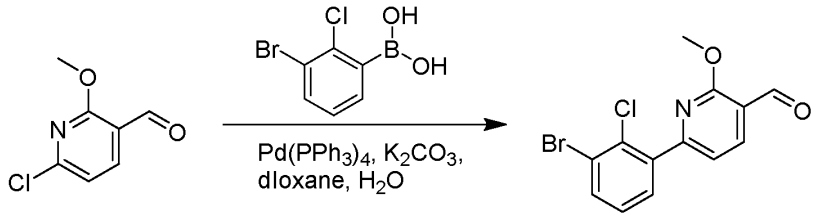
Intermediate No.	Structure	Starting Materials
3-2		Intermediate 2-2
3-3		Intermediate 2-3
3-4		Intermediate 2a-1
3-5		Intermediate 2a-2

Intermediate No.	Structure	Starting Materials
3-6		Intermediate 2b-1
3-7		Intermediate 2-4
3-8		Intermediate 2b-2
3-9		Intermediate 2b-3
3-10		Intermediate 2b-4
3-11		Intermediate 2b-5

Intermediate No.	Structure	Starting Materials
3-12		Intermediate 2c-1
3-13		Intermediate 2c-2
3-14		Intermediate 2-5
3-15		Intermediate 2-6
3-16		Intermediate 2-7
3-17		Intermediate 2-8

Intermediate No.	Structure	Starting Materials
3-18		Intermediate 2-9
3-19		Intermediate 2-10
3-20		Intermediate 2a-3
3-21		Intermediate 2a-4a
3-22		Intermediate 2a-5
3-23		Intermediate 2a-6
3-24		Intermediate 2-11

Example A4
Preparation of Intermediate 4

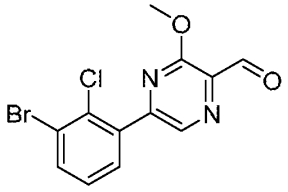


Intermediate 4

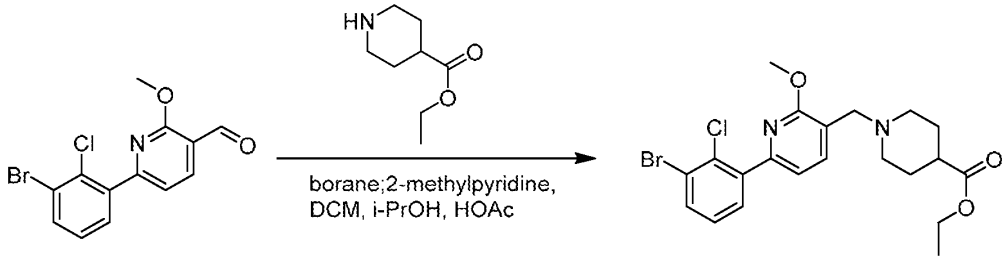
[0255] A mixture of 6-Chloro-2-methoxynicotinaldehyde (1.5 g, 8.74 mmol), (3-Bromo-2-chlorophenyl)boronic acid (2.06 g, 8.74 mmol), K_2CO_3 (3.62 g, 26.23 mmol), $Pd(PPh_3)_4$ (1.01 g, 874 μmol) in dioxane (30 mL) and H_2O (3 mL) was degassed and purged with N_2 three times, and then the mixture was stirred at 95 °C for 3 h under N_2 atmosphere. The mixture was filtered and concentrated under reduced pressure to give a residue, which was purified by flash silica gel to give **Intermediate 4** (2.24 g) as a white solid. MS: ES m/z calculated for MS: ES m/z calculated for $C_{13}H_{10}BrClNO_2$ $[M+H]^+$ 326.0, found 325.7.

[0256] The intermediate shown in Table A-2a were prepared by an analogous reaction protocol as was used for the preparation of **Intermediate 4-1** using the appropriate starting materials.

Table A-2a

Intermediate No.	Structure	Starting Materials
4-1		5-chloro-3-methoxypyrazine-2-carbaldehyde

Example A5
Preparation of Intermediate 5-1

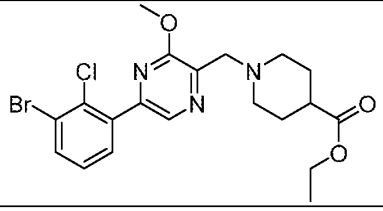


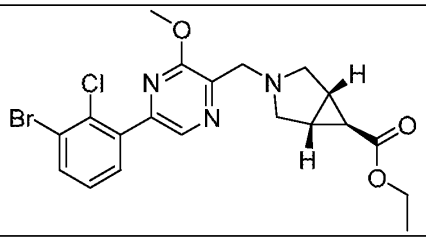
Intermediate 4 **Intermediate 5-1**

[0257] To a solution of **Intermediate 4** (263 mg, 805.33 μmol, 1 eq.) and ethyl piperidine-4-carboxylate (379.82 mg, 2.42 mmol, 372.37 μL, 3 eq.) in DCM (3 mL) and i-PrOH (3 mL) were added AcOH (193.45 mg, 3.22 mmol, 184.41 μL, 4 eq.) and borane;2-methylpyridine (344.56 mg, 3.22 mmol, 4 eq.). The mixture was stirred at 25 °C for 3 h. LCMS showed **Intermediate 4** was consumed completely and 50% of mass was detected. The mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~37% EA/PE gradient @ 50 mL/min). **Intermediate 5-1** (311 mg, 418.85 μmol, 52.01% yield, 63% purity) was obtained as a yellow oil. MS: ES m/z calculated for $C_{21}H_{24}BrClN_2O_3$ $[M+H]^+$ 467.07 found 467.0.

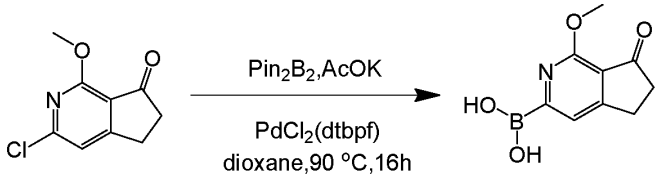
[0258] The intermediates shown in Table A-3 were prepared by an analogous reaction protocol as was used for the preparation of **Intermediate 5-1** using the appropriate starting materials.

Table A-3

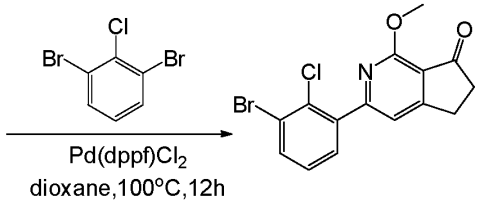
Intermediate No.	Structure	Starting Materials
5-2		Intermediate 4-1 ethyl piperidine-4-carboxylate

Intermediate No.	Structure	Starting Materials
5-3		Intermediate 4-1 (1R,5S,6R)-rel-ethyl 3-azabicyclo[3.1.0]hexane-6-carboxylate hydrochloride

Example A6
Preparation of Intermediate 6



Intermediate 6-1



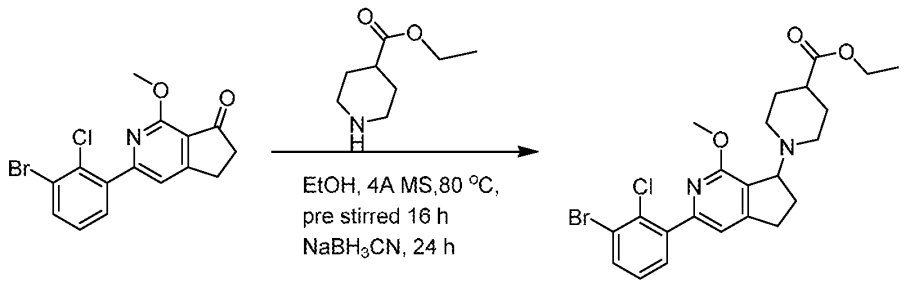
Intermediate 6

[0259] A mixture 3-chloro-1-methoxy-5,6-dihydro-7*H*-cyclopenta[c]yridin-7-one (7.0 g, 35 mmol), Pin_2B_2 (18 g, 71 mmol), AcOK (10.4 g, 106 mmol) and $PdCl_2$(dtbpf) (1.15 g, 1.77 mmol) in dioxane (70 mL) was degassed and purged with N_2 three times, and the mixture was stirred at 90 °C for 16 h under N_2 atmosphere. The mixture was filtered and concentrated under reduced pressure to give a residue, which was triturated with a mixture of methyl-tert-butyl ether and ethyl acetate(MTBE:EA = 3:1) at 15 °C for 16 h to give **Intermediate 6-1** (15 g, crude) as a black oil, which was used for next step reaction without further purification.

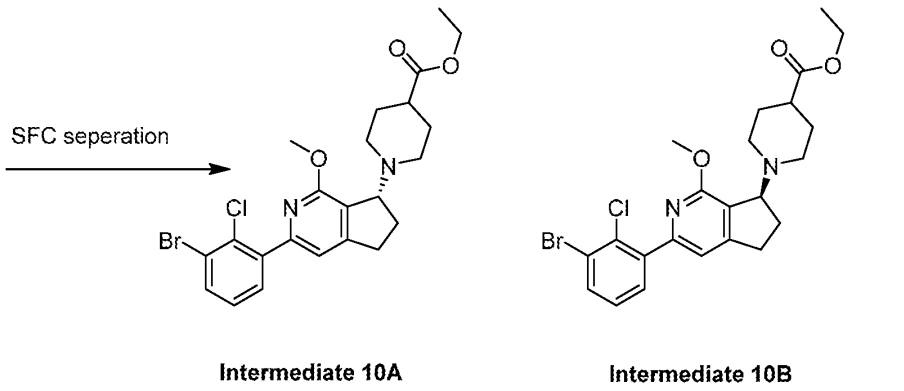
[0260] A mixture of **Intermediate 6-1** (15.00 g), 1,3-dibromo-2-chloro-benzene (23.5 g, 87.0 mmol), K_2CO_3 (18.0 g, 130 mmol), Pd(dppf)Cl_2 (3.18 g, 4.35 mmol) in dioxane (150 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 100 °C for 12 h under N_2 atmosphere. The mixture was filtered and concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography to

give **Intermediate 6** (5 g) as a brown solid. MS: ES m/z calculated for $C_{15}H_{12}BrClNO_2$ $[M+H]^+$ 352.0, found 352.0.

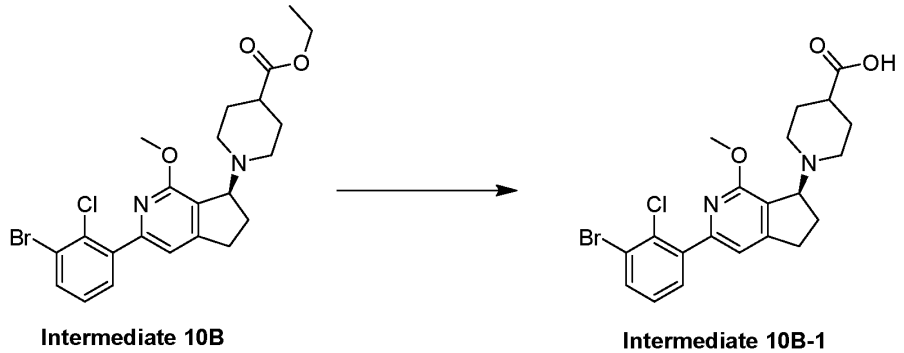
Example A7
Preparation of Intermediate 10B-1



Intermediate 6 **Intermediate 10**



Intermediate 10A **Intermediate 10B**



Intermediate 10B **Intermediate 10B-1**

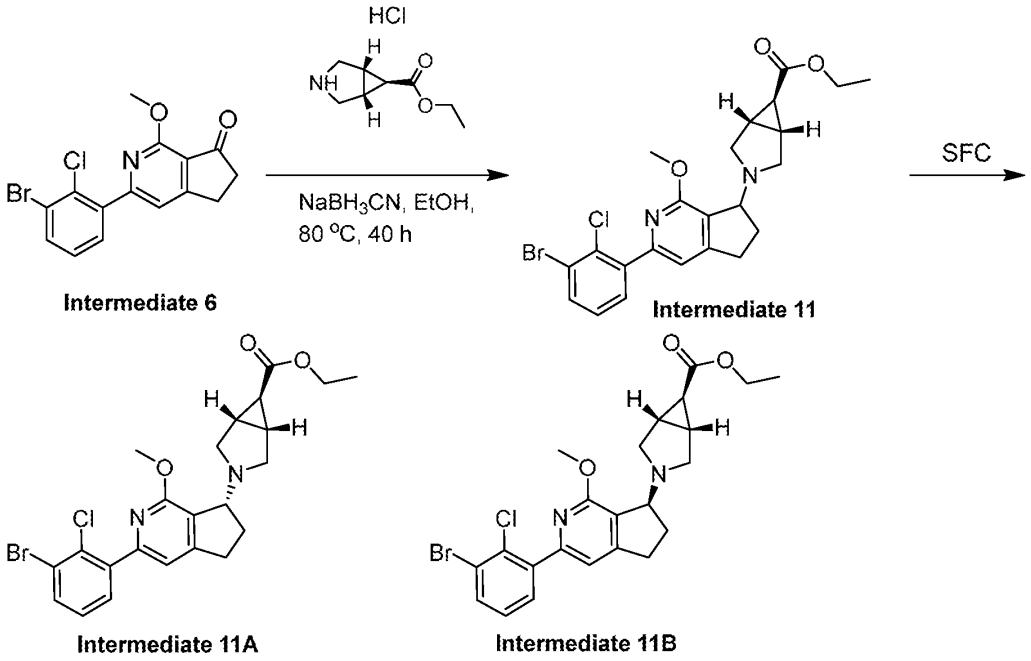
[0261] A mixture of **Intermediate 6** (3 g, 8.52 mmol), ethyl piperidine-4-carboxylate (6.54 mL, 42.54 mmol) and 4A Molecular Sieve (3 g) in EtOH (60 mL) was

adjusted to pH 5~6 and stirred at 80 °C for 16 h. Then $NaBH_3CN$ (1.60 g, 25.50 mmol, 3 eq.) was added into the mixture and stirred at 80 °C for 24 h. The mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (2 x 50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, which was purified by prep-HPLC to give **Intermediate 10** (1.7 g, 96% purity) as a yellow oil. MS: ES m/z calculated for $C_{23}H_{27}BrClN_2O_3$ $[M+H]^+$ 493.1, found 493.1.

[0262] A mixture of **Intermediate 10** (1.7 g, 3.44 mmol) was separated by SFC to give **Intermediate 10A** (790 mg, 99% purity) as a yellow oil and **Intermediate 10B** (750 mg, yield, 99% purity) as a yellow oil. With analytic SFC conditions (Column: Chiral NS-3 100 x 4.6mm I.D., 3 μm; mobile phase: A: CO_2 B: ethanol (0.05% DEA); Gradient: from 5% to 40% of B in 2 min and hold 40% for 1 min, then 5% of B for 1 min Flow rate: 2.8mL/min; Column temp.: 35 °C; ABPR: 1500 psi), **Intermediate 10A**'s retention time is 2.33 min, and **Intermediate 10B**'s retention time 2.57 min.

[0263] **Intermediate 10B** (6 mg) and 15 μL of HCl (1 mol/L in water) were dissolved in 400 μL of methanol and kept in a 4 mL vial. The solution evaporates slowly at rt. Crystals of **Intermediate 10B-1** were observed on the second day. The crystal of **Intermediate 10B-1**'s HCl salt was a colorless plate with the following dimensions: $0.20 \times 0.15 \times 0.02$ mm^3. The symmetry of the crystal structure was assigned the orthorhombic space group P212121 with the following parameters: a = 7.5631(2) Å, b = 7.7926(2) Å, c = 35.4625(8) Å, α = 90°, β = 90°, γ = 90°, V = 2090.03(9) $Å^3$, Z = 4, Dc = 1.596 g/cm^3, F(000) = 1024.0, μ(CuKα) = 5.252 mm^{-1}, and T = 149.99(10) K. Figure 1A shows the absolute configuration structure and Figure 1B shows the ORTEP crystal structure of the chloride salt of **Intermediate 10B-1**.

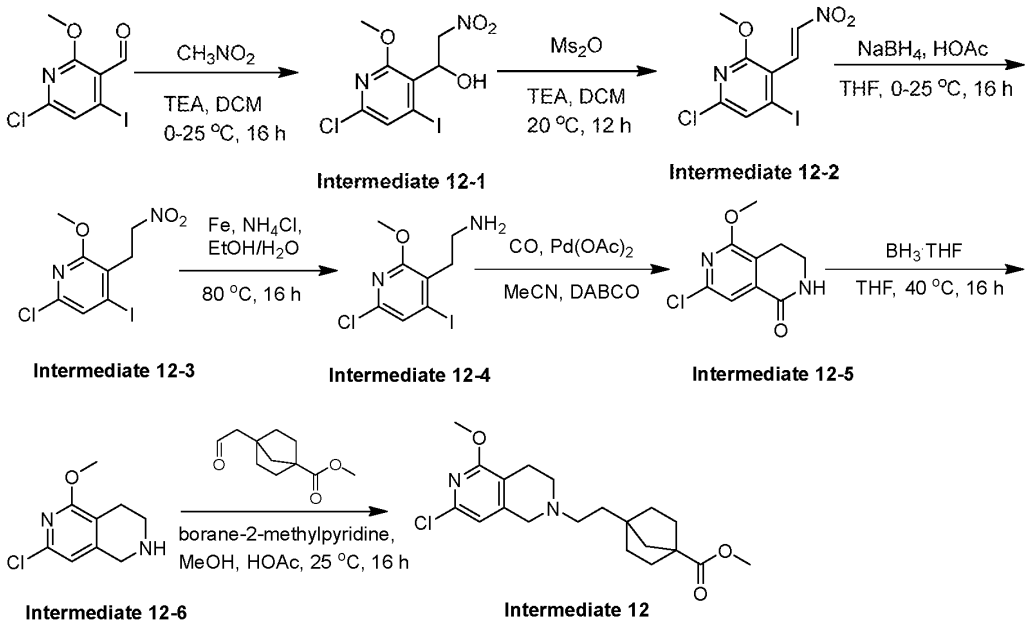
Example A8
Preparation of Intermediates 11A and 11B



[0264] To a solution of **Intermediate 6** (2 g, 5.67 mmol) and (1R,5S,6R)-rel-ethyl 3-azabicyclo[3.1.0]hexane-6-carboxylate hydrochloride (1.76 g, 11.34 mmol) in EtOH (22 mL) was stirred at 85 °C for 16 h. Once the mixture was cooled to 25 °C, $NaBH_3CN$ (1.07 g, 17.02 mmol) was added. The mixture was warmed to 85 °C and stirred for 32 h. The mixture was concentrated under reduced pressure to remove solvent. The residue was purified by column chromatography **Intermediate 11** (2.2 g) was obtained as a colorless oil. MS: ES m/z calculated for $C_{23}H_{25}BrClN_2O_3$ $[M+H]^+$ 491.1, found 490.9.

[0265] **Intermediate 11** was purified by SFC to give **Intermediate 11A** (980 mg) as a colorless oil and **Intermediate 11B** (970 mg) as a colorless oil. Under analytic SFC conditions (Column: Chiralpak OJ-3 50 x 4.6 mm I.D., 3 μm; Mobile phase: A: CO_2 B: isopropanol (0.05% DEA); Gradient: from 5% to 40% of B in 2.5 min and hold 40% for 0.5 min, then 5% of B for 1 min; Flow rate: 4.0 mL/min; Column temp.: 35 °C; ABPR: 1500 psi), **Intermediate 11A**'s retention time is 1.24 min, and **Intermediate 11B**'s retention time is 1.55 min.

Example A9
Preparation of Intermediates 12



[0266] To a solution of 6-chloro-4-iodo-2-methoxynicotinaldehyde (9.20 g, 30.9 mmol) and TEA (12.9 mL, 92.8 mmol) in DCM (180 mL) was added CH_3NO_2 (2.54 mL, 46.9 mmol) at 0 °C. The mixture was stirred at 25 °C for 16 hours. The reaction was quenched by addition of H_2O (150 mL) and then extracted by DCM (50 mL x 3). The combined organic layers were washed with brine (150 mL), dried over Na_2SO_4 and concentrated in vacuo to give a residue. The residue was purified by flash silica gel chromatography to give **Intermediate 12-1** (5.17 g) as a white solid. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.49 (s, 1H), 5.74 (dd, J = 3.6, 10.8 Hz, 1H), 4.89-4.77 (m, 2H), 4.51 (dd, J = 3.6, 12.4 Hz, 1H), 4.07 (s, 3H).

[0267] To a solution of **Intermediate 12-1** (5.17 g, 14.42 mmol) and TEA (6.02 mL, 43.3 mmol) in DCM (120 mL) was added methylsulfonyl methanesulfonate (3.77 g, 21.63 mmol) at 0 °C. After the mixture was degassed and purged with N_2 (3x), the mixture was stirred at 20 °C for 12 hours under N_2 atmosphere. The mixture was concentrated under reduced pressure to remove solvent. The residue was purified by silica column chromatography to give **Intermediate 12-2** (2.5 g) as a yellow solid. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 8.25 (dd, J = 2.0, 13.6 Hz, 1H), 8.00 (dd, J =1.6, 13.2 Hz, 1H), 7.60 (d, J = 2.0 Hz, 1H), 4.12 (d, J = 2.0 Hz, 3H).

[0268] To a solution of **Intermediate 12-2** (4.2 g, 12.3 mmol) in THF (110 mL) were added HOAc (7.06 mL, 123.35 mmol) and $NaBH_4$ (1.22 g, 32.3 mmol) at 0 °C. The resulting suspension was stirred at 25 °C for 16 hours. The reaction was quenched by the addition of water (100 mL). The aqueous phase was extracted with ethyl acetate (100 mL x 3). The combined organic layers were washed with brine dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography to give **Intermediate 12-3** (4.0 g) as a yellow solid. MS: ES m/z calculated for MS: ES m/z calculated for $C_8H_9ClIN_2O_3$ $[M+H]^+$ 342.9, found 342.8; ^1H NMR (400 MHz, CHLOROFORM-d) δ = 7.32 (s, 1H), 4.47-4.40 (m, 2H), 3.89 (s, 3H), 3.43-3.37 (m, 2H).

[0269] To a solution of **Intermediate 12-3** (4.0 g, 11.7 mmol) in MeOH (100 mL) and H_2O (60 mL) were added Fe (3.26 g, 58.4 mmol) and NH_4Cl (3.12 g, 58.4 mmol) at rt. The mixture was stirred at 80 °C for 16 hours under N_2 atmosphere. The mixture was filtered. The filtrate was concentrated under reduced pressure. The residues were purified by flash silica gel chromatography to give **Intermediate 12-4** (2.5 g) as a white solid. MS: ES m/z calculated for MS: ES m/z calculated for $C_8H_{11}ClIN_2O$ $[M+H]^+$ 313.0, found 312.8; ^1H NMR (400 MHz, DMSO-d_6) δ = 8.43-7.72 (m, 1H), 7.59 (s, 1H), 7.45-6.38 (m, 1H), 3.87 (s, 3H), 3.01-2.96 (m, 2H), 2.86-2.81 (m, 2H).

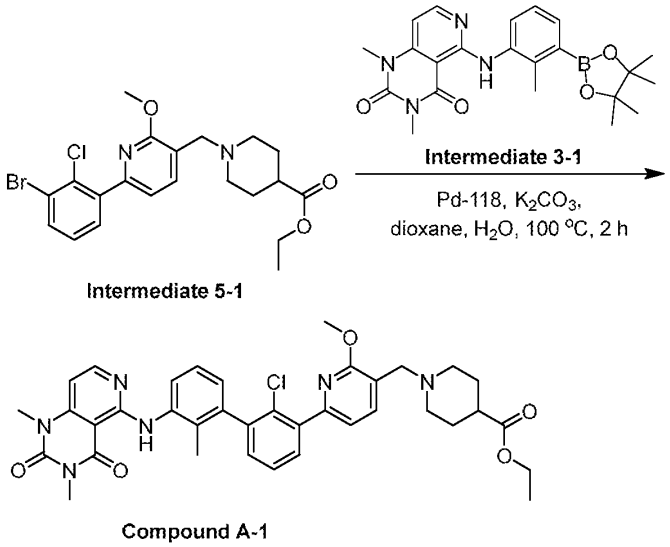
[0270] A mixture of **Intermediate 12-4** (2.5 g, 8.00 mmol), $Pd(OAc)_2$ (180 mg, 800 μmol), Na_2CO_3 (2.12 g, 20.0 mmol) and DABCO (176 μL,.60 mmol) in CH_3CN (150 mL) was degassed and purged with N_2 (3x) at rt. The mixture was stirred at 60 °C for 16 hours under CO (50 PSI) atmosphere. The mixture was filtered and concentrated under reduced pressure. The residues were purified by flash silica gel chromatography to give **Intermediate 12-5** (1.1 g,) as a yellow solid. MS: ES m/z calculated for MS: ES m/z calculated for $C_9H_{10}ClN_2O_2$ $[M+H]^+$ 213.04, found 212.9; ^1H NMR (400 MHz, DMSO-d_6) δ = 8.32 (s, 1H), 7.31 (s, 1H), 3.92 (s, 3H), 3.38 (dt, *J* = 2.8, 6.8 Hz, 2H), 2.76 (t, *J* = 6.8 Hz, 2H).

[0271] To a solution of **Intermediate 12-5** (1.1 g, 5.17 mmol) in THF (40 mL) was added BH_3-Me_2S (10 M, 1.03 mL) at rt. The mixture was stirred at 40 °C for 16 hours. The reaction was quenched by addition MeOH 10 mL at 25 °C, and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give **Intermediate 12-6** (100 mg) as a white solid. MS: ES m/z calculated for $C_9H_{12}ClN_2O$ $[M+H]^+$ 199.06, found 199.0.

[0272] To a solution of **Intermediate 12-6** (100 mg, 503 μmol), methyl 4-(2-oxoethyl) norbornane-1-carboxylate (99 mg, 503 μmol) and AcOH (1 mL, 17.5 mmol) in MeOH (10 mL) was added borane 2-methylpyridine (162 mg, 1.51 mmol) at 25 °C. The mixture was stirred at 25 °C for 16 hours. The reaction was quenched by addition of H_2O (50 mL), and extracted by DCM (50 mL x 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 and concentrated in vacuo to give a residue. The residue was purified by silica column chromatography to give **Intermediate 12** (200 mg) as a yellow oil. MS: ES m/z calculated for $C_{20}H_{28}ClN_2O_3$ $[M+H]^+$ 379.2, found 379.1.

Preparation of Compounds

Example 1
Preparation of Compound A-1

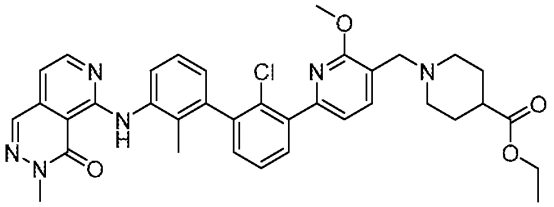
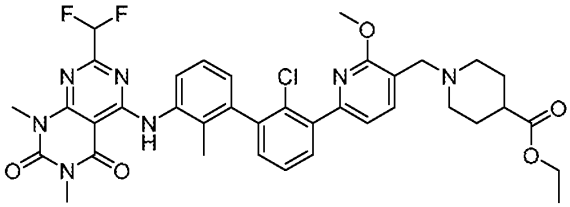
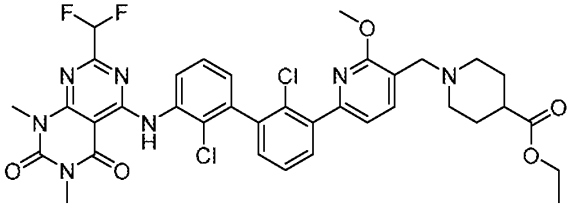
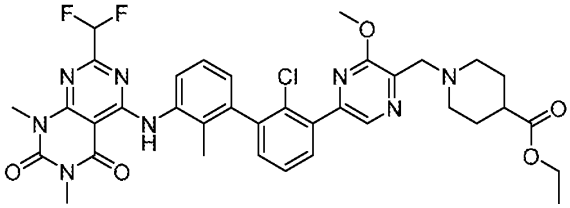


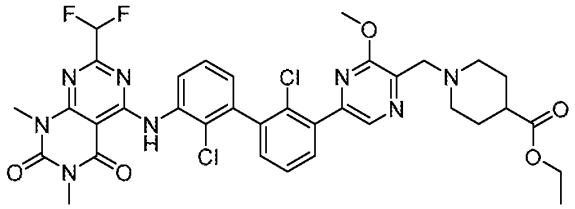
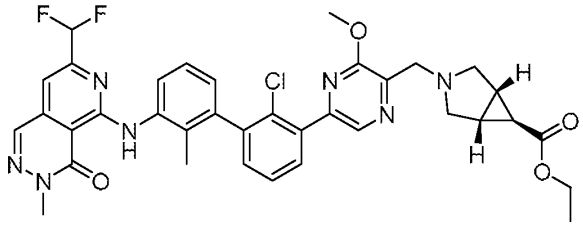
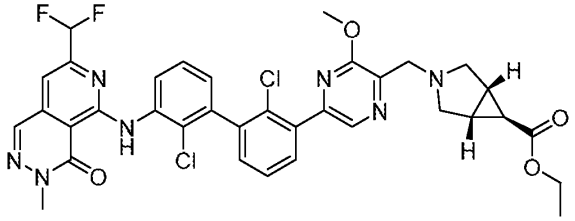
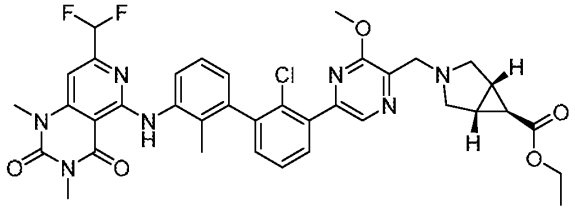
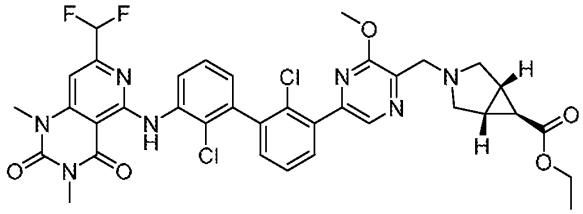
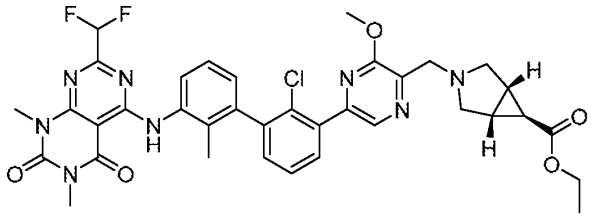
[0273] A mixture of **Intermediate 3-1** (115.00 mg, 245.84 μmol, 1 eq.), **Intermediate 5-1** (103.81 mg, 245.84 μmol, 1 eq.), K_2CO_3 (101.93 mg, 737.52 μmol, 3 eq.) and ditert-butyl(cyclopentyl)phosphane;dichloropalladium;iron (16.02 mg, 24.58 μmol, 0.1 eq.) in dioxane (2 mL) and H_2O (0.2 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 100 °C for 2 h under N_2 atmosphere. LCMS showed 62% of mass was detected. The mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~27% EA/PE gradient @ 50 mL/min).

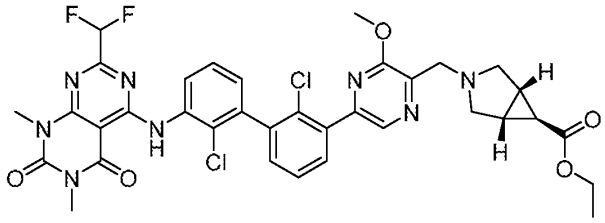
Compound A-1 (180 mg, 213.41 μmol, 86.81% yield, 81% purity) was obtained as a yellow solid. MS: ES m/z calculated for $C_{37}H_{39}ClN_6O_5$ $[M+H]^+$ 683.27 found 683.4.

[0274] The compounds shown below in Table 1 were prepared by an analogous reaction protocol as was used for the preparation of Compound A-1 using the appropriate starting materials.

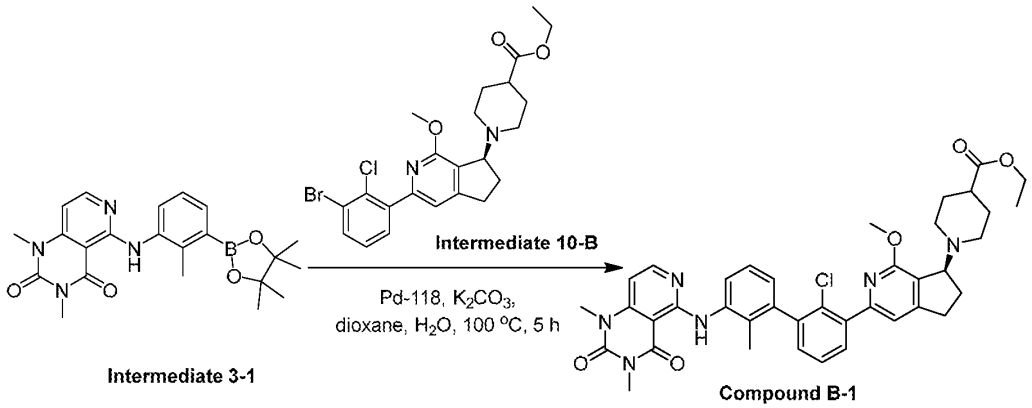
Table 1

Cmpd No.	**Structure**	**Starting Materials**
A-2		Intermediate 3-3 Intermediate 5-1
A-3		Intermediate 3-12 Intermediate 5-1
A-4		Intermediate 3-13 Intermediate 5-1
A-5		Intermediate 3-12 Intermediate 5-2

Cmpd No.	Structure	Starting Materials
A-6		Intermediate 3-13 Intermediate 5-2
A-7		Intermediate 3-18 Intermediate 5-3
A-8		Intermediate 3-19 Intermediate 5-3
A-9		Intermediate 3-20 Intermediate 5-3
A-10		Intermediate 3-21 Intermediate 5-3
A-11		Intermediate 3-12 Intermediate 5-3

Cmpd No.	Structure	Starting Materials
A-12		Intermediate 3-13 Intermediate 5-3

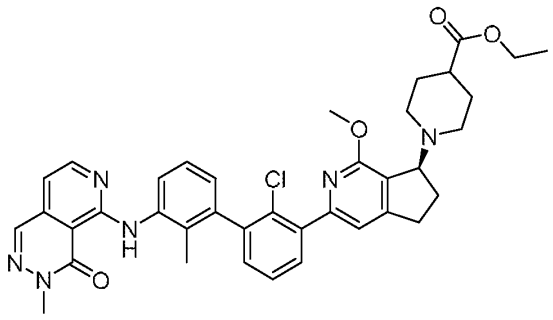
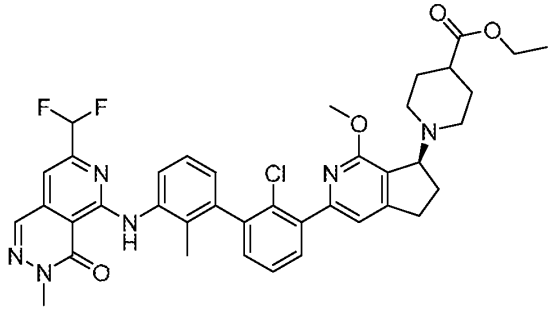
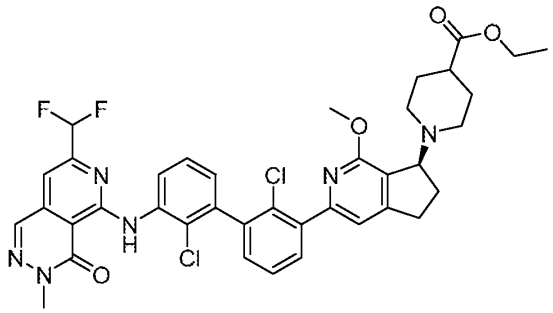
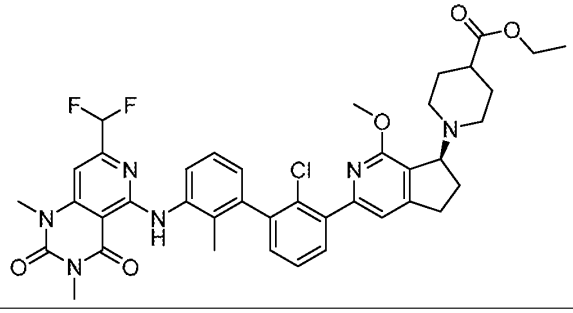
Example 2
Preparation of Compound B-1

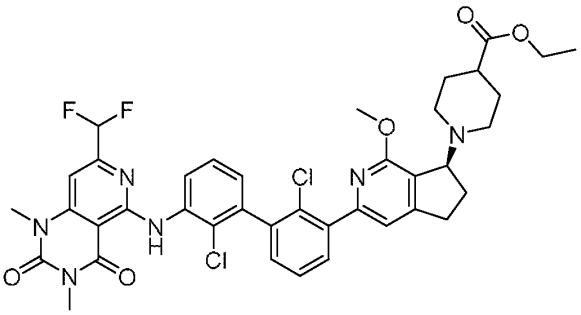
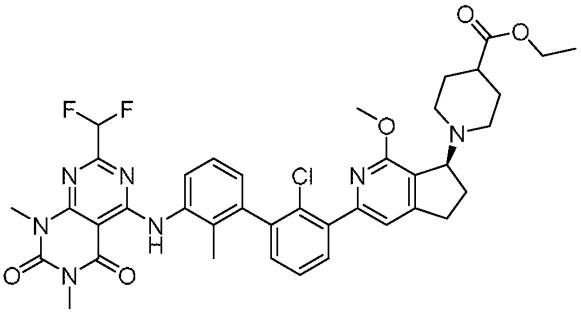
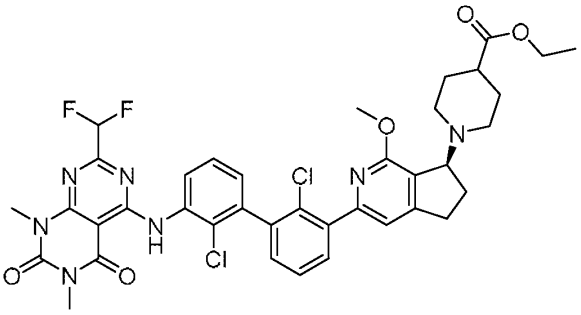
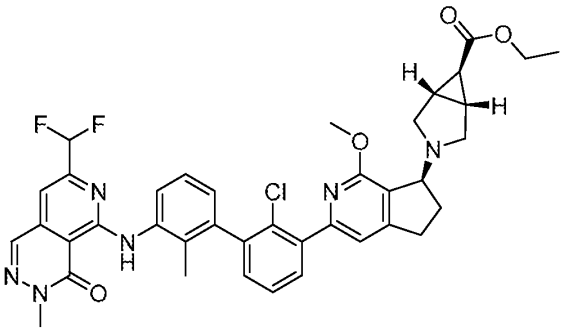


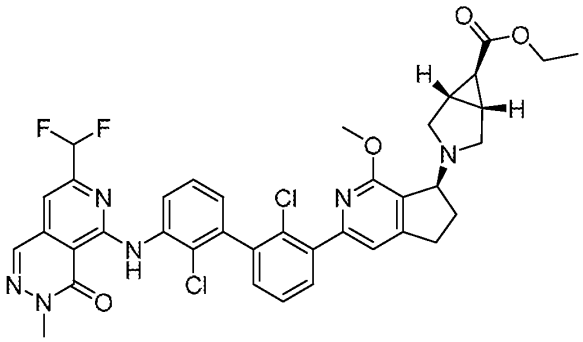
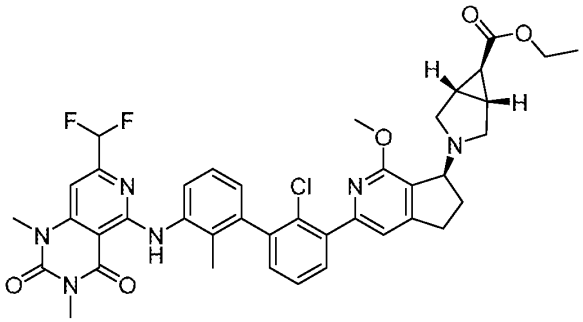
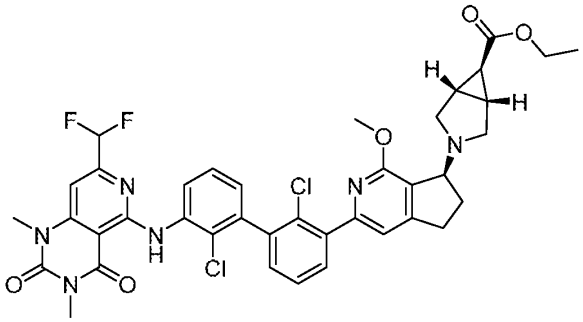
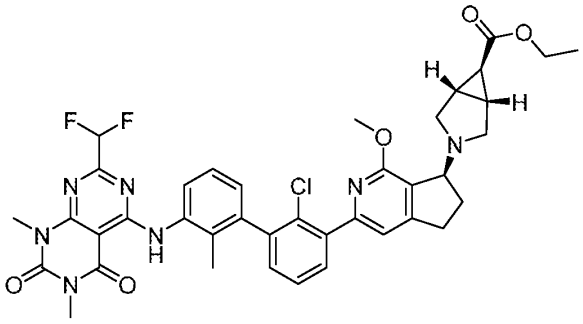
[0275] A mixture of **Intermediate 3-1** (97.49 mg, 230.85 μmol, 1.2 eq.), **Intermediate 10-B** (95.00 mg, 192.38 μmol, 1 eq.), K_2CO_3 (79.76 mg, 577.13 μmol, 3 eq.) and ditert-butyl(cyclopentyl)phosphane;dichloropalladium;iron (12.54 mg, 19.24 μmol, 0.1 eq.) in dioxane (3 mL) and H_2O (0.3 mL) was degassed and purged with N_2 (3x). The mixture was stirred at 100 °C for 5 h under N_2 atmosphere. LCMS showed ~90% of desired compound was detected. The mixture was filtered. The filtrate was concentrated directly. The residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~100% EA/PE gradient @ 40 mL/min). **Compound B-1** (110 mg, 136.49 μmol, 70.95% yield, 88% purity) was obtained as a brown oil. MS: ES m/z calculated for $C_{39}H_{41}ClN_6O_5$ $[M+H]^+$ 709.28 found 709.4.

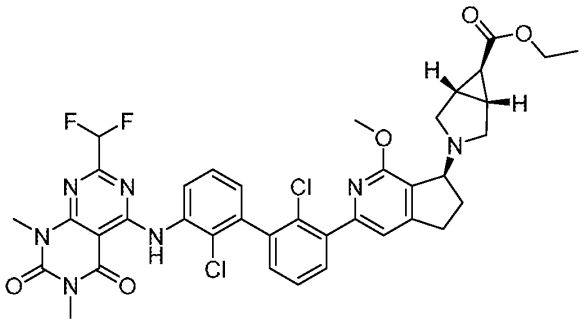
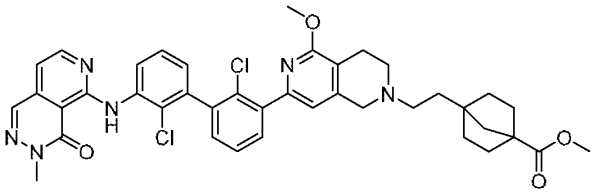
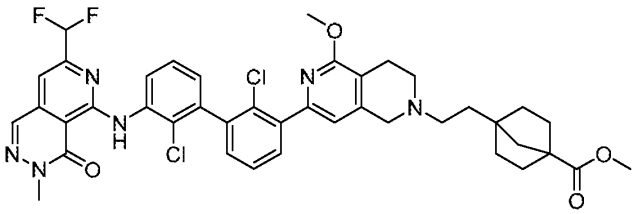
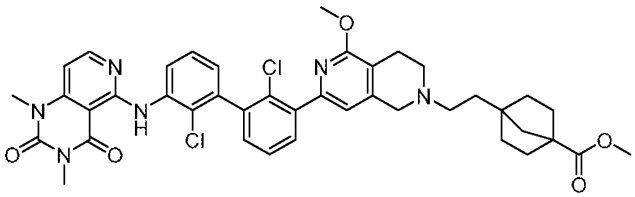
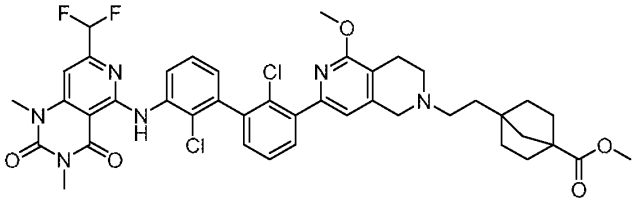
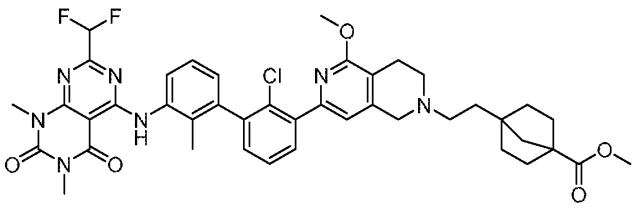
[0276] The compounds shown below in Table 2 were prepared by an analogous reaction protocol as was used for the preparation of Compound B-1 using the appropriate starting materials.

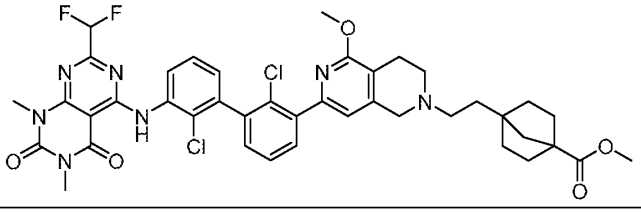
Table 2

Cmpd No.	Structure	Starting Materials
B-2		Intermediate 3-3 Intermediate 10B
B-3		Intermediate 3-18 Intermediate 10B
B-4		Intermediate 3-19 Intermediate 10B
B-5		Intermediate 3-20 Intermediate 10B

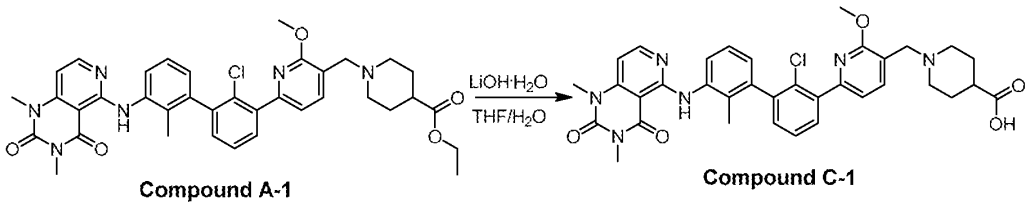
Cmpd No.	Structure	Starting Materials
B-6		Intermediate 3-21 Intermediate 10B
B-7		Intermediate 3-12 Intermediate 10B
B-8		Intermediate 3-13 Intermediate 10B
B-9		Intermediate 3-18 Intermediate 11B

Cmpd No.	Structure	Starting Materials
B-10		Intermediate 3-19 Intermediate 11B
B-11		Intermediate 3-20 Intermediate 11B
B-12		Intermediate 3-21 Intermediate 11B
B-13		Intermediate 3-12 Intermediate 11B

Cmpd No.	Structure	Starting Materials
B-14		Intermediate 3-13 Intermediate 11B
B-15		Intermediate 3-24 Intermediate 12
B-16		Intermediate 3-19 Intermediate 12
B-17		Intermediate 3-2 Intermediate 12
B-18		Intermediate 3-21 Intermediate 12
B-19		Intermediate 3-12 Intermediate 12

Cmpd No.	Structure	Starting Materials
B-20		Intermediate 3-13 Intermediate 12

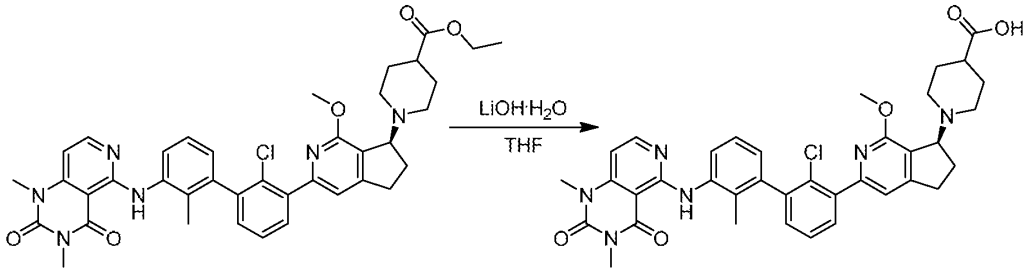
Example 3
Preparation of Compound C-1



Compound A-1 Compound C-1

[0277] A mixture of **Compound A-1** (160 mg, 234 μmol), LiOH•H_2O (49 mg, 1.2 mmol) in THF (8 mL) and H_2O (4 mL) was stirred at 45 °C for 3 h. The mixture was concentrated under reduced pressure to give a residue, which was purified by prep-HPLC to give **Compound C-1** (37 mg, 99.95% purity) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.12 (s, 1H), 8.38-8.26 (m, 2H), 7.76 (br d, J = 7.5 Hz, 1H), 7.69-7.61 (m, 1H), 7.51 (br t, J = 7.6 Hz, 1H), 7.40-7.25 (m, 3H), 6.95 (br d, J = 7.1 Hz, 1H), 6.82-6.70 (m, 1H), 3.90 (s, 3H), 3.47 (s, 6H), 2.87-2.61 (m, 4H), 2.35-2.23 (m, 1H), 2.16-2.05 (m, 5H), 1.80 (br d, J = 10.1 Hz, 2H), 1.66-1.53 (m, 2H); MS: ES m/z calculated for $C_{35}H_{36}ClN_6O_5$ $[M+H]^+$ 655.2, found 655.2.

Example 4
Preparation of Compound C-2

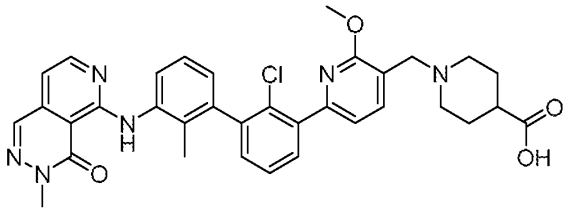
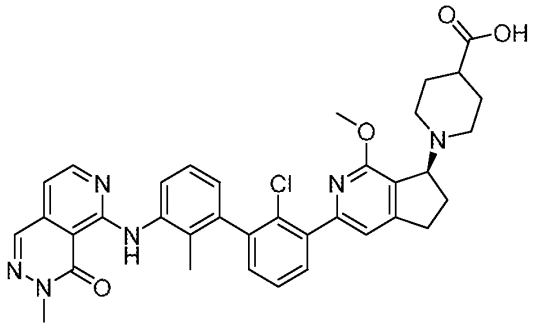


Compound B-1 Compound C-2

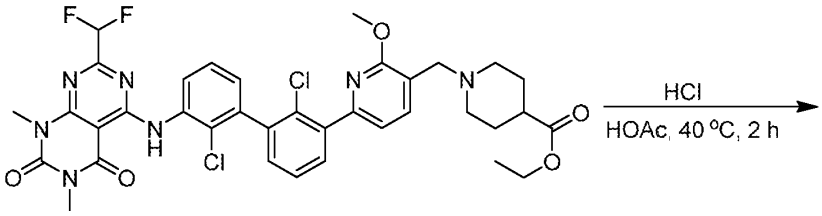
[0278] A mixture of **Compound B-1** (100 mg, 141 μmol), LiOH•H_2O (30 mg, 705 μmol) in THF (5 mL) and H_2O (1 mL) was degassed and purged with N_2 for 3 times, then the mixture was stirred at 45 °C for 2 h under N_2 atmosphere. The mixture was concentrated under reduced pressure to remove solvent. The residue was purified by prep- to give **Compound C-2** (46 mg, 100% purity) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.12 (s, 1H), 8.35-8.26 (m, 2H), 7.66-7.60 (m, 1H), 7.50 (t, J = 7.6 Hz, 1H), 7.38-7.27 (m, 2H), 7.19 (s, 1H), 6.98-6.92 (m, 1H), 6.78 (d, J = 6.0 Hz, 1H), 4.27 (br d, J = 6.0 Hz, 1H), 3.90 (s, 3H), 3.48 (s, 3H), 3.28-3.25 (m, 3H), 3.01-2.93 (m, 1H), 2.82-2.71 (m, 2H), 2.66-2.60 (m, 1H), 2.32 (br t, J = 10.5 Hz, 1H), 2.23-2.12 (m, 3H), 2.10 (br d, J = 6.9 Hz, 3H), 2.07-1.99 (m, 1H), 1.81-1.69 (m, 2H), 1.59-1.39 (m, 2H); MS: ES m/z calculated for $C_{37}H_{38}ClN_6O_5$ $[M+H]^+$ 681.3, found 681.3.

[0279] The compounds shown below in Table 3 were prepared by an analogous reaction protocol as was used for the preparation of Compound C-2 using the appropriate starting materials.

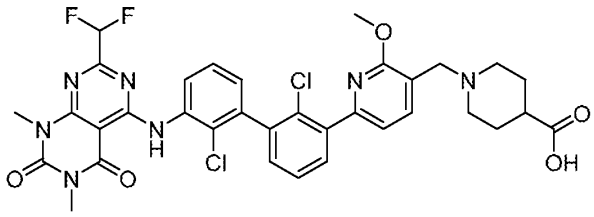
Table 3

Cmpd No.	Structure	Starting Materials
C-3		Compound A-2
C-4		Compound B-2

Example 5
Preparation of Compound D-1



Compound A-4



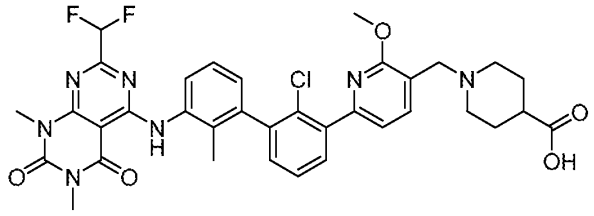
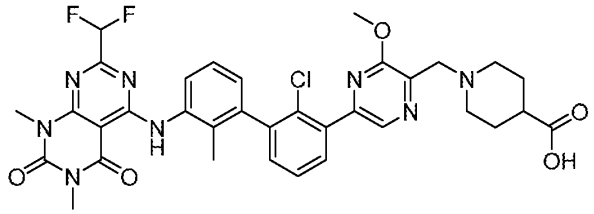
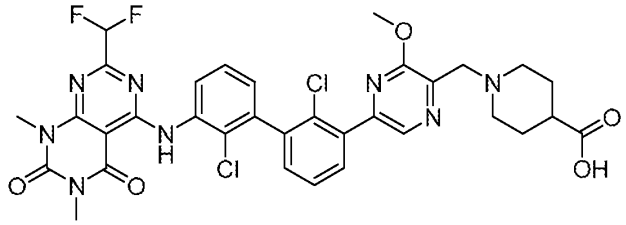
Compound D-1

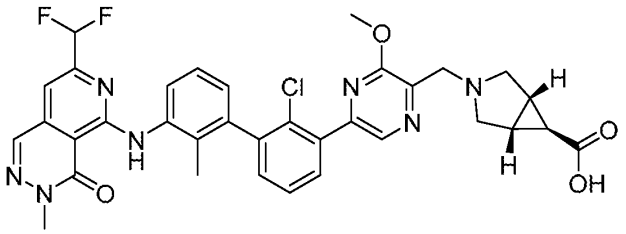
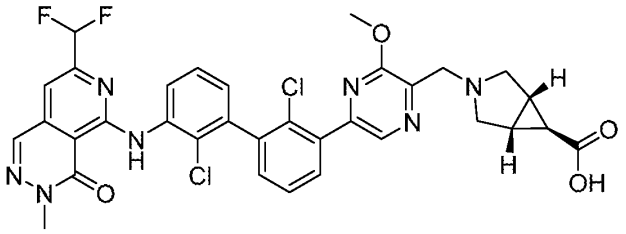
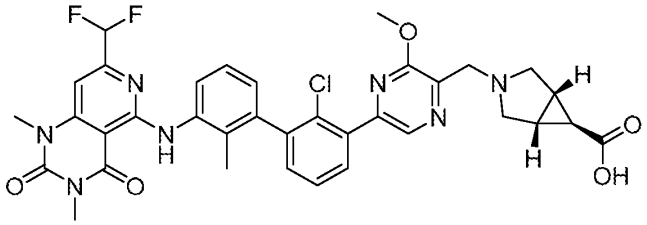
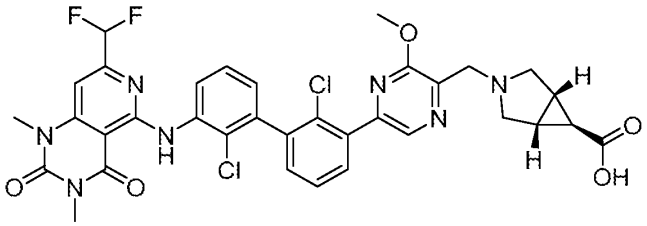
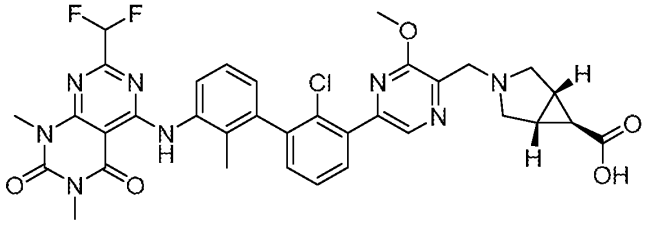
[0280] The mixture of **Compound A-4** (40 mg, 53 μmol) in HCl (1 mL) and HOAc (1 mL) was stirred at 40 °C for 2 hours. The mixture was concentrated under

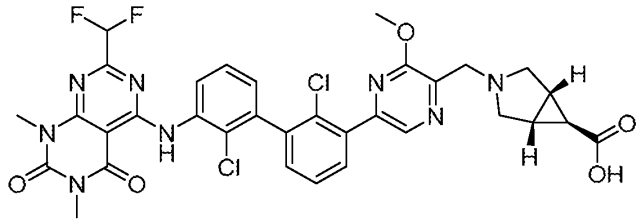
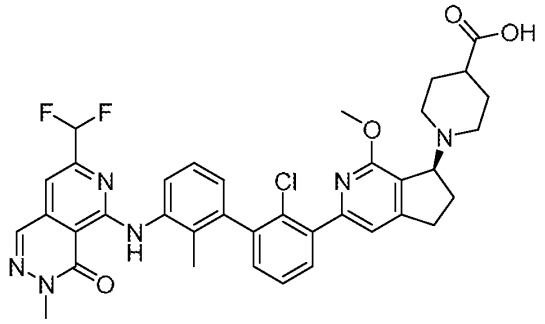
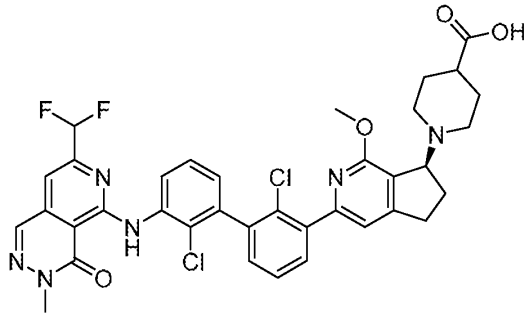
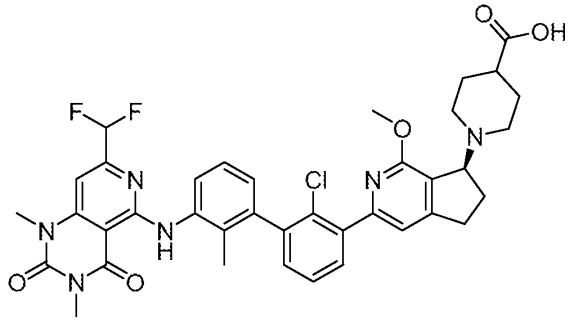
reduced pressure to give a residue. The residue was purified by prep-HPLC to give **Compound D-1** (25 mg) as a white solid. MS: ES m/z calculated for $C_{34}H_{32}Cl_2F_2N_7O_5$ $[M+H]^+$ 726.2, found 726.1; ^{1}H NMR (400 MHz, DMSO-d_6) 1H NMR (400 MHz, DMSO-d6) δ = 11.77 (s, 1H), 8.60 (d, J = 8.4 Hz, 1H), 7.78 (d, J = 7.2 Hz, 1H), 7.70 (dd, J = 1.2, 7.6 Hz, 1H), 7.55 (dt, J = 3.6, 8.0 Hz, 2H), 7.46-7.40 (m, 1H), 7.27 (dd, J = 7.6, 17.6 Hz, 2H), 6.86 (t, J = 52.0 Hz, 1H), 3.91 (s, 3H), 3.54 (s, 3H), 3.47 (s, 2H), 3.36-3.35 (m, 3H), 2.80 (br d, J = 11.2 Hz, 2H), 2.27-2.16 (m, 1H), 2.08 (br t, J = 10.8 Hz, 2H), 1.84-1.75 (m, 2H), 1.64-1.53 (m, 2H).

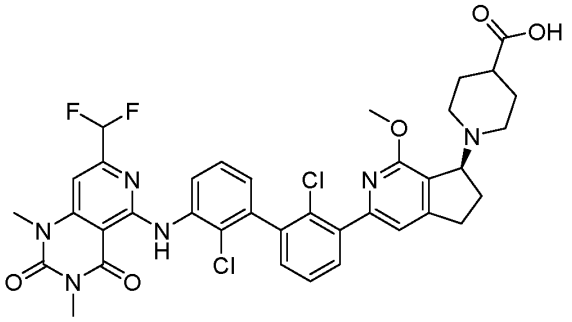
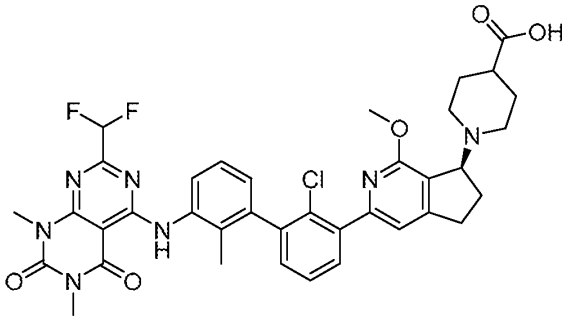
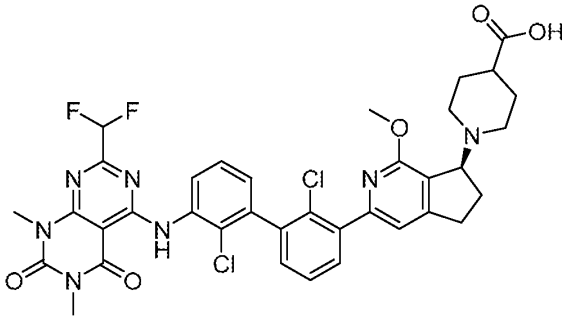
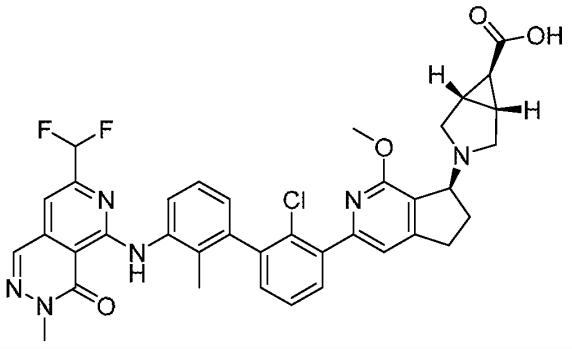
[0281] The compounds shown below in Table 4 were prepared by an analogous reaction protocol as was used for the preparation of Compound D-1 using the appropriate starting materials.

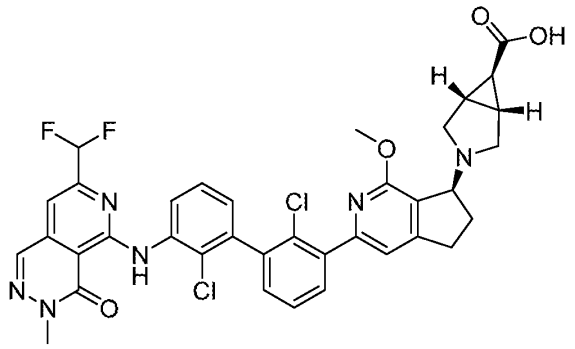
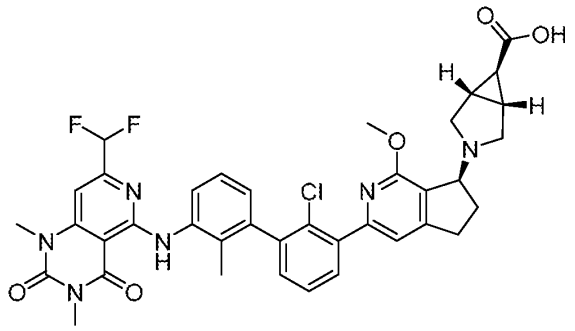
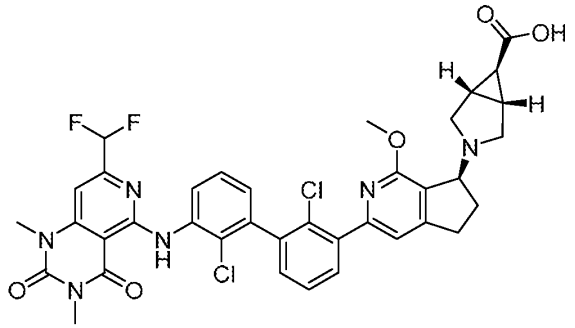
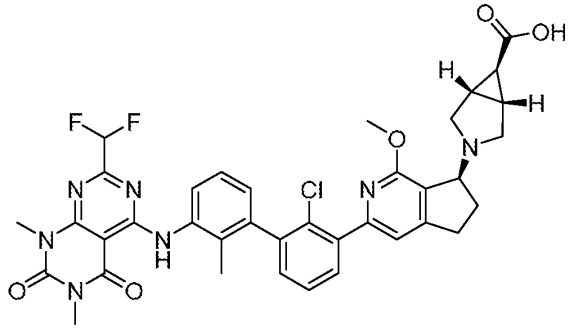
Table 4

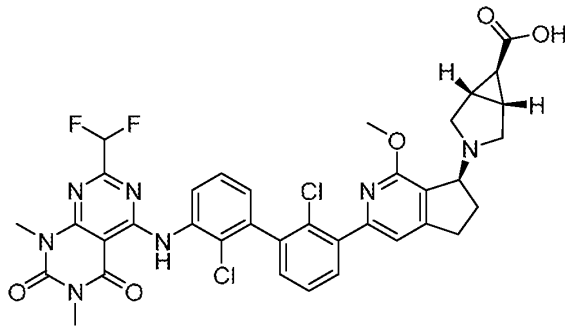
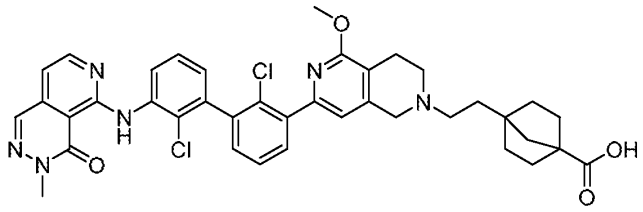
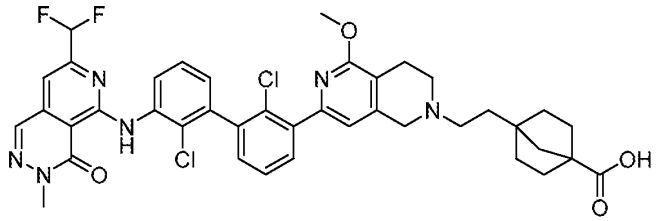
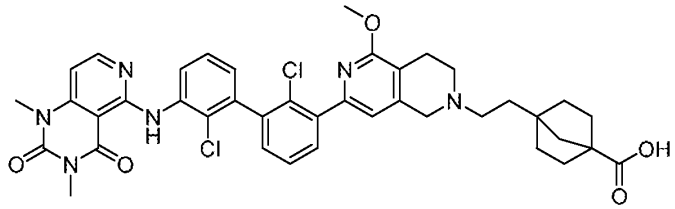
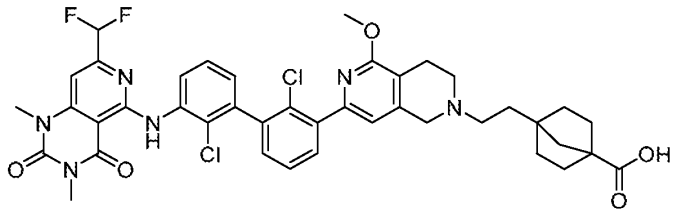
Cmpd No.	**Structure**	**Starting Materials**
D-2		**A-3**
D-3		**A-5**
D-4		**A-6**

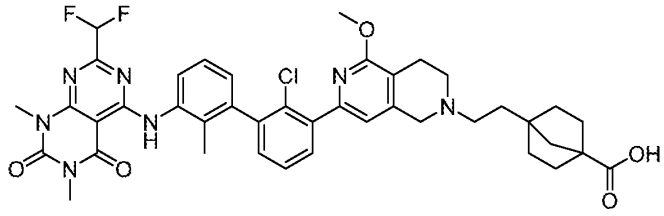
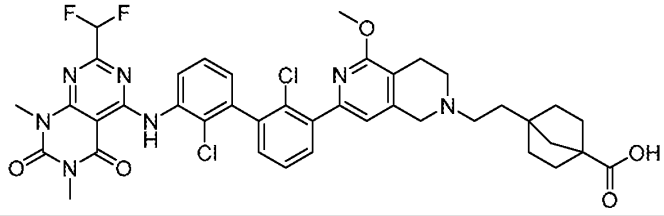
Cmpd No.	Structure	Starting Materials
D-5		A-7
D-6		A-8
D-7		A-9
D-8		A-10
D-9		A-11

Cmpd No.	Structure	Starting Materials
D-10		A-12
D-11		B-3
D-12		B-4
D-13		B-5

Cmpd No.	Structure	Starting Materials
D-14		B-6
D-15		B-7
D-16		B-8
D-17		B-9

Cmpd No.	Structure	Starting Materials
D-18		B-10
D-19		B-11
D-20		B-12
D-21		B-13

Cmpd No.	Structure	Starting Materials
D-22		B-14
D-23		B-15
D-24		B-16
D-25		B-17
D-26		B-18

Cmpd No.	Structure	Starting Materials
D-27		B-19
D-28		B-20

Example A
LCMS (Liquid chromatography/Mass spectrometry)

[0282] The High Performance Liquid Chromatography (HPLC) measurement was performed using a LC pump, a diode-array (DAD) or a UV detector and a column as specified in the respective methods. If necessary, additional detectors were included (see table of methods below). Flow from the column was brought to the Mass Spectrometer (MS) which was configured with an atmospheric pressure ion source. It is within the knowledge of the skilled person to set the tune parameters (e.g. scanning range, dwell time) in order to obtain ions allowing the identification of the compound's nominal monoisotopic molecular weight (MW). Data acquisition was performed with appropriate software. Compounds are described by their experimental retention times (Rt) and ions. If not specified differently in the table of data, the reported molecular ion corresponds to the $[M+H]^+$ (protonated molecule) and/or $[M-H]^-$(deprotonated molecule). In case the compound was not directly ionizable the type of adduct is specified (i.e. $[M+NH_4]^+$, $[M+Na]^+$, $[M+HCOO]^-$, etc.). For molecules with multiple isotopic patterns (Br, CI), the reported value is the one obtained for the lowest isotope mass. All results were obtained with experimental uncertainties that are commonly associated with the method used. Hereinafter, "SQD" means Single Quadrupole Detector, "MSD" Mass Selective Detector, "RT" room temperature, "BEH" bridged ethylsiloxane/silica hybrid, "DAD" Diode Array Detector, "HSS" High Strength silica., "Q-Tof Quadrupole Time-off light

mass spectrometers, "CLND", ChemiLuminescent Nitrogen Detector, "ELSD" Evaporative Light Scanning Detector.

Table A: LCMS Method Codes

Method code	Instrument	Column	Mobile Phase	Gradient	Flow T	Run Time
1	SHIMADZU LC-20AD; LCMS-2020	Agilent PoroShell 120 EC-C18 2.7 µm 3.0*50 mm	A: Water (3.8L) + ACN (0.2L) + TFA (1.5mL) B: ACN (4L) + TFA (0.75mL)	From 10% to 80% (solvent B) over 3 min and holding at 80% for 0.5 min at a flow rate of 1.0 mL/min, return back to 10% acetonitrile (solvent B) in water and hold for 0.5 min;	1.0 50	4.0
2	Shimadzu LC-20AD; LCMS-2020	Welch Boltimate ® Core-Shell	A: Water (3.8L) + ACN (0.2L) + TFA (1.5mL) B: ACN (4L) + TFA (0.75mL)	From 5% to 95% (solvent B) over 0.4 min and holding at 95% for 0.3 min at a flow rate of 1.5 mL/min, then return back to 5% ACN in water and hold for 0.3 min;	1.5 50	1.0

Method code	Instrument	Column	Mobile Phase	Gradient	Flow T	Run Time
3	SHIMADZU LC-20AD; LCMS-2020	Welch Boltimate ® Core-Shell	A: Water (3.8L) + ACN (0.2L) + TFA (1.5mL) B: ACN (4L) + TFA (0.75mL)	From 5% to 100% (solvent B) over 0.6 min and holding at 100% for 0.3 min at a flow rate of 1.5 mL/min, return back to 5% (solvent B) in water and hold for 0.1 min;	1.5 45	1.0
4	SHIMADZU LC-20AD; LCMS-2020	Agilent PoroShell 120 EC-C18 2.7 µm 3.0*50mm	A: Water (3.8L) + ACN (0.2L)+ TFA (1.5mL) B: ACN (4L) + TFA (0.75mL)	From 5% to 95% (solvent B) over 3 min and holding at 95% for 0.5 min at a flow rate of 1.0 mL/min, return back to 5% acetonitrile (solvent B) in water and hold for 0.5 min;	1.0 50	4.0
5	SHIMADZU LC-20AD; LCMS-2020	Agilent PoroShell 120 EC-C18 2.7 µm 3.0*50 mm	A: Water (3.8L) + ACN (0.2L) + TFA (1.5mL) B: ACN (4L) + TFA (0.75mL)	From 10%-80% (solvent B) over 6 min and holding at 80% for 0.5 min at a flow rate of 0.8 mL/min, return back to 10% acetonitrile (solvent B) in water and hold for 0.5 min;	0.8 50	7.0

Flow expressed in mL/min; column temperature (T) in °C; Run time in min.

Table B: LCMS

Cmpd No.	R_t	LC/MS	LCMS Method
A-1	0.60	683.4	2
B-1	0.65	709.4	3
B-2	0.67	679.3	3
C-1	1.81	655.2	1
C-2	1.86	681.3	1
C-3	2.17	625.1	1
C-4	2.31	651.2	1
D-1	2.44	726.1	1
D-2	2.42	706.2	1
D-3	2.34	707.2	1
D-4	2.37	727.2/729.2	1
D-5	2.57	674.2	6
D-6	2.65	694.2	6
D-7	2.79	704.2	7
D-8	2.79	724.2	7
D-9	2.73	705.3	7
D-10	2.79	725.2	7
D-11	2.59	701.2	1

Cmpd No.	R_t	LC/MS	LCMS Method
D-12	2.35	721.2	4
D-13	2.52	731.3	1
D-14	2.27	751.2	4
D-15	2.47	732.3	1
D-16	2.51	752.2	1
D-17	2.67	699.3	6
D-18	2.69	719.2	6
D-19	2.91	729.3	7
D-20	3.07	749.2	7
D-21	2.89	730.3	7
D-22	2.93	750.2	7
D-23	2.65	725.3	1
D-24	2.51	775.2	4
D-25	2.51	755.2	1
D-26	2.47	805.3	4
D-27	2.57	786.3	1
D-28	2.63	806.2	1

Example A-1
NMR (Nuclear Magnetic Resonance)

[0283] Proton (^{1}H) NMR spectra were recorded on a Bruker spectrometer operating at 400 MHz using $CDCL_3$ (deuterated chloroform) or DMSO-d_6 (deuterated DMSO, dimethyl-d_6-sulfoxide) as solvents. Chemical shifts (d) are reported in parts per million (ppm) relative to tetramethylsilane (TMS), which was used as an internal standard.

[0284] **Compound D-4:** ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.77 (s, 1H), 8.60 (d, J = 8.0 Hz, 1H), 8.50 (s, 1H), 7.77 (br d, J = 7.2 Hz, 1H), 7.62 (t, J = 7.6 Hz, 1H), 7.58-7.51 (m, 2H), 7.26 (d, J = 6.8 Hz, 1H), 6.85 (t, J = 54.0 Hz, 1H), 3.99 (s, 3H), 3.83-3.80 (m, 2H), 3.54 (s, 3H), 3.32 (s, 3H), 2.98-2.96 (m, 2H), 2.35-2.01 (m, 3H), 1.85-1.82 (m, 2H), 1.71-1.53 (m, 2H).

[0285] **Compound D-12:** ^{1}H NMR (400 MHz, DMSO-d_6) δ = 12.09 (d, J = 2.4 Hz, 1H), 8.89 (dd, J = 1.6, 8.4 Hz, 1H), 8.53 (s, 1H), 7.68 (td, J = 2.0, 8.0 Hz, 1H), 7.56-7.47 (m, 3H), 7.42 (dd, J = 1.6, 7.6 Hz, 1H), 7.21-6.89 (m, 3H), 4.30-4.21 (m, 1H), 3.91 (s, 3H), 3.78

(s, 3H), 3.01-2.92 (m, 1H), 2.84-2.71 (m, 2H), 2.61-2.63 (m, 1H), 2.34-2.27 (m, 1H), 2.22-2.09 (m, 3H), 2.08-1.99 (m, 1H), 1.81-1.72 (m, 2H), 1.57-1.40 (m, 2H).

[0286] **Compound D-14:** ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.83 (d, J = 2.0 Hz, 1H), 8.79 (dd, J = 1.2, 8.4 Hz, 1H), 7.68 (td, J = 2.0, 7.6 Hz, 1H), 7.54 (t, J = 7.6 Hz, 1H), 7.48 (t, J = 8.0 Hz, 1H), 7.41 (dd, J = 1.6, 7.6 Hz, 1H), 7.20 (s, 1H), 7.14-6.82 (m, 3H), 4.29-4.26 (m, 1H), 3.91 (s, 3H), 3.55 (s, 3H), 3.41 (s, 3H), 3.02-2.93 (m, 1H), 2.80-2.62 (m, 3H), 2.35-2.29 (m, 1H), 2.21-2.02 (m, 4H), 1.78-1.75 (m, 2H), 1.55-1.41 (m, 2H).

[0287] **Compound D-20:** ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.82 (d, J = 1.6 Hz, 1H), 8.78 (dd, J = 1.2, 8.4 Hz, 1H), 7.66 (td, J = 1.6, 7.6 Hz, 1H), 7.53 (t, J = 7.6 Hz, 1H), 7.47 (t, J = 8.0 Hz, 1H), 7.41 (dd, J = 1.6, 7.6 Hz, 1H), 7.20 (s, 1H), 7.13-6.80 (m, 3H), 4.27 (t, J = 4.8 Hz, 1H), 3.91 (s, 3H), 3.54 (s, 3H), 3.33 (s, 3H), 3.00-2.98 (m, 1H), 2.89-2.87 (m, 1H), 2.80-2.71 (m, 3H), 2.56-2.52 (m, 1H), 2.08-2.00 (m, 2H), 1.84-1.78 (m, 2H), 1.74-1.70 (m, 1H).

Example B
PDL1/PD1 Binding Assay

[0288] Compounds to be tested were serially diluted in DMSO, and further diluted in assay buffer (25 mM Hepes pH 7.4, 150 mM NaCl, 0.005% Tween 20, BSA 0.01%). Diluted compounds were added to the wells with final concentration of DMSO at 1%. PDL1-6xHis protein was added to the wells, mixed well with compound. The plates were incubated for 30 min at rt. PD1-Fc-Avi-Biotin protein was added to the wells. Final concentration of PDL1 and PD1 protein is 0.3 nM and 2.5 nM, respectively. After a binding time of 30 min at rt, Anti-6xHis Acceptor beads (final concentration 20 ug/mL) were added to the wells, and the incubation continued for 1 h. Streptavidin Donor beads (final concentration 20 ug/mL) were added at reduced light. The plates were sealed with foil and incubated in the dark for additional 1 h or overnight before reading on an Envision reader. The IC_{50} values were determined by fitting the curves using a four-parameter equation in GraphPad Prism 8.

Example C
PD-1/PD-L1 NFAT Reporter Assay

[0289] Cellular activity of the compounds was assessed using a co-culture reporter assay in which TCR-mediated NFAT activity of Jurkat T cells is constitutively inhibited by

the engagement of PD-1 by PD-L1 expressing CHO cells. Blocking the PD-1/ PD-L1 interaction will release the inhibitory signal and results in TCR signaling and NFAT-mediated luciferase activity.

[0290] CHO cells expressing surface-bound anti-CD3 antibodies and PD-L1 were first seeded overnight and treated with the compounds. Jurkat cells overexpressing PD-1 and a luciferase construct under NFAT promoter were then immediately seeded on the monolayer of CHO cells. The co-culture was then incubated for 6 h at 37 °C. Luciferase activity was assessed by adding the ONE-Glo reagent and measuring luminescence with a plate reader. EC_{50} values were determined from the fit of the dose-response curves.

[0291] Compounds described herein, as exemplified in the Examples, showed EC_{50} or IC_{50} values in the following ranges: A: IC_{50} or $EC_{50} \leq 10$ nM; B: 10 nM < IC_{50} or $EC_{50} \leq 100$ nM; C: 100 nM < IC_{50} or $EC_{50} \leq 1000$ nM; D : 1000 nM < IC_{50} or $EC_{50} \leq 10000$ nM; E : IC_{50} or EC_{50} > 10000 nM; n.d. = not determined; n.r. = EC_{50} not reached in the range of tested concentrations starting from 1 nM to 5000 nM.

Table C

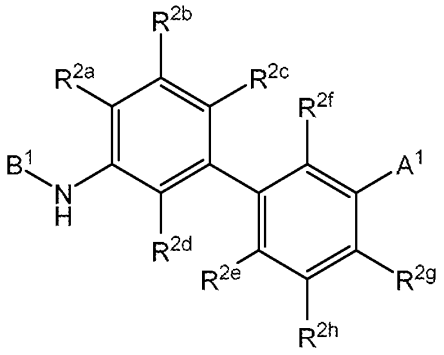
Cmpd No.	**PD-1/PD-L1 PPI IC50**	**Jurkat NFAT EC_{50}**
C-1	A	B
C-2	A	B
C-3	A	B
C-4	A	A
D-1	A	A
D-2	A	A
D-3		A
D-4	A	A
D-5	A	B
D-6	A	B
D-7	A	B
D-8	A	B
D-9	A	B
D-10	A	B
D-11	A	A
D-12	A	A

Cmpd No.	**PD-1/PD-L1 PPI IC50**	**Jurkat NFAT EC_{50}**
D-13	A	A
D-14	A	A
D-15	A	A
D-16	A	A
D-17	A	A
D-18	A	A
D-19	A	A
D-20	A	A
D-21	A	A
D-22	A	A
D-23	A	B
D-24	A	B
D-25	A	B
D-26	A	B
D-27	A	B
D-28	A	A

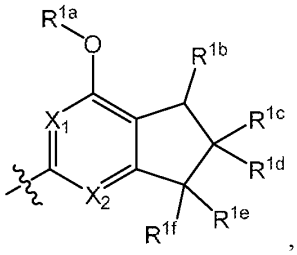
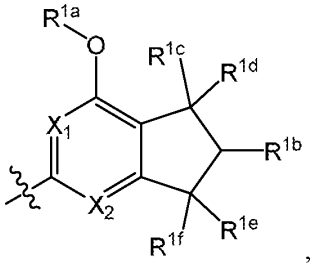
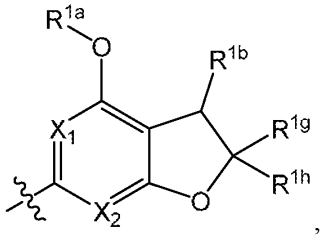
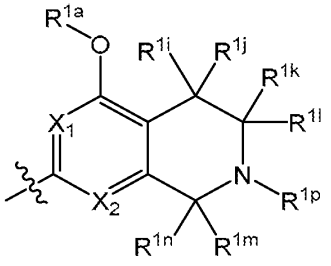
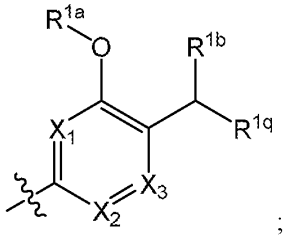
[0292] Although the foregoing has been described in some detail by way of illustrations and examples for purposes of clarity and understanding, it will be understood by those of skill in the art that numerous and various modifications can be made without departing from the spirit of the present disclosure. 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 present disclosure.

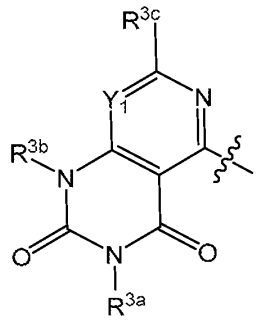
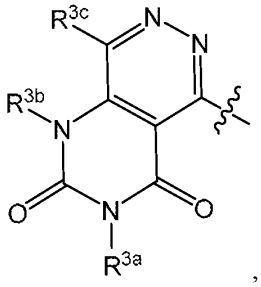
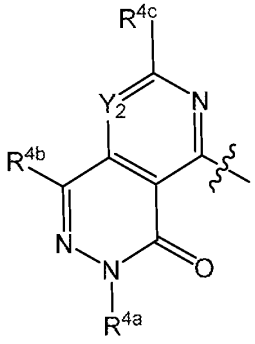
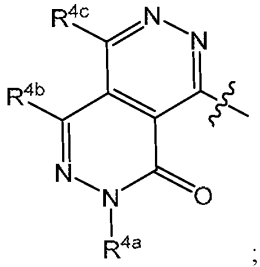
WHAT IS CLAIMED IS:

1. A compound of Formula (I), or a pharmaceutically acceptable salt thereof, having the structure:



(I)

wherein: A^1 is , , , , or ;

B^1 is  ,  ,  or  ;

X^1 is selected from CH, C-halo and N;

X^2 is selected from CH, C-halo and N;

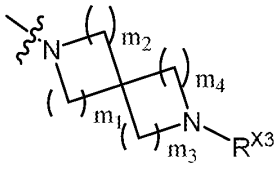
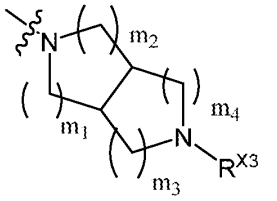
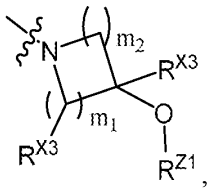
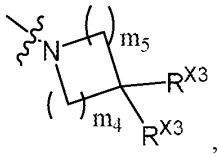
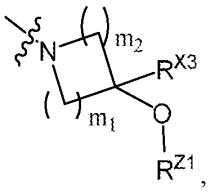
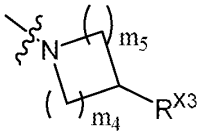
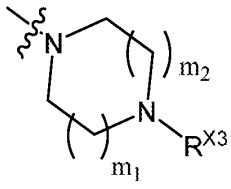
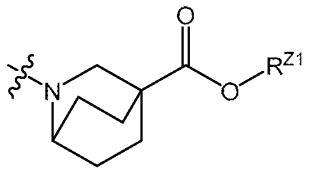
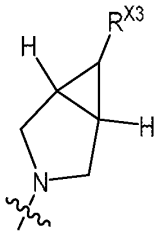
X^3 is selected from CH, C-halo, N and C-OR^{Z1};

Y^1 is selected from CH, C-halo and N;

Y^2 is selected from CH, C-halo and N;

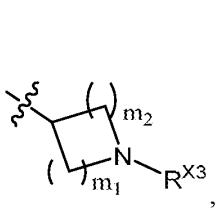
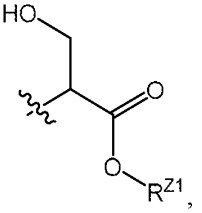
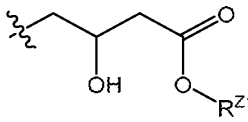
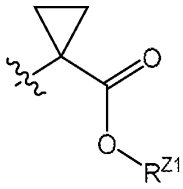
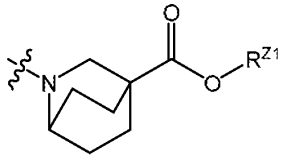
R^{1a} is selected from $-C_{1-4}$ alkyl, $-C_{1-4}$ haloalkyl, $-CH_2$(C_{3-6} monocyclic cycloalkyl), $-CH_2$(4-6 membered monocyclic heterocyclyl) and $-CH_2$(5-6 membered monocyclic heteroaryl);

R^{1b} is selected from $-R^{x1}$ and $-N(R^{m1})R^{n1}$;

R^{x1} is selected from , , , , , , , , and ; wherein R^{x1} is optionally substituted with one or two substituents independently selected from halogen, cyano, $-C_{1-4}$ alkyl, hydroxy, $-C_{1-4}$ alkoxy, $-C_{1-4}$ haloalkyl, $-C_{1-4}$ haloalkoxy, $-C(=O)OR^{Z1}$, $-C(=O)NHS(=O)_2R^{Z3}$, $-C(=O)N(R^{Z1})R^{Z2}$, $-S(=O)_2R^{Z3}$, $-S(=O)_2N(R^{Z1})R^{Z2}$, $-N(R^{Z1})C(=O)R^{Z3}$, $-N(R^{Z1})S(=O)R^{Z3}$, $-N(R^{Z1})C(=O)N(R^{Z1})R^{Z3}$ and $-N(R^{Z1})S(=O)_2N(R^{Z2})R^{Z3}$;

R^{m1} is selected from $-C_{1-4}$ alkyl, C_{3-6} monocyclic cycloalkyl, C_{5-12} bicyclic cycloalkyl, 4-7 membered monocyclic heterocyclyl, 8-11 membered fused-heterocyclyl and $-R^{x2}$; wherein the 4-7 membered monocyclic heterocyclyl and the 8-11 membered fused-heterocyclyl contain at least one atom or group of atoms independently selected from O (oxygen), S (sulfur), C(=O), S(=O), $S(=O)_2$ and N (nitrogen); wherein the $-C_{1-4}$ alkyl is substituted by $-C(=O)OR^{Z1}$, and the $-C_{1-4}$ alkyl is optionally substituted optionally substituted with one or two or three substituents independently selected from halogen, cyano, hydroxy, $-C_{1-4}$ alkoxy, $-C_{1-4}$ haloalkyl, $-C_{1-4}$ haloalkoxy, $-C(=O)NHS(=O)_2R^{Z3}$, $-C(=O)N(R^{Z1})R^{Z2}$, $-S(=O)_2R^{Z3}$, $-S(=O)_2N(R^{Z1})R^{Z2}$, $-N(R^{Z1})C(=O)R^{Z3}$, $-N(R^{Z1})S(=O)R^{Z3}$, $-N(R^{Z1})C(=O)N(R^{Z2})R^{Z3}$ and $-N(R^{Z1})S(=O)N(R^{Z2})R^{Z3}$; wherein the C_{3-6} monocyclic cycloalkyl, the C_{5-12}

bicyclic cycloalkyl, the 4-7 membered monocyclic heterocyclyl, and the 8-11 membered fused-heterocyclyl is substituted by $–C(=O)OR^{Z1}$, and the C_{3-6} monocyclic cycloalkyl, the C_{5-12} bicyclic cycloalkyl, the 4-7 membered monocyclic heterocyclyl, and the 8-11 membered fused-heterocyclyl is optionally substituted with one or two or three substituents independently selected from halogen, cyano, $–C_{1-4}$ alkyl, hydroxy, $–C_{1-4}$ alkoxy, $–C_{1-4}$ haloalkyl, $–C_{1-4}$ haloalkoxy, $–C(=O)NHS(=O)_2R^{Z3}$, $–C(=O)N(R^{Z1})R^{Z2}$, $–S(=O)_2R^{Z3}$, $–S(=O)_2N(R^{Z1})R^{Z2}$, $–N(R^{Z1})C(=O)R^{Z3}$, $–N(R^{Z1})S(=O)R^{Z3}$, $–N(R^{z1})C(=O)N(R^{Z2})R^{Z3}$ and $–N(R^{Z1})S(=O)N(R^{Z2})R^{Z3}$;

R^{x2} is selected from , , ,  and ;

each R^{X3} is $–C(=O)OR^{Z1}$;

R^{n1} is selected from hydrogen, $–C_{1-4}$ alkyl, $–C_{1-4}$ haloalkyl, $–CH_2(C_{3-6}$ monocyclic cycloalkyl) and $–C(=O)OR^{Z4}$;

R^{1c} is selected from hydrogen, halogen, -OH, –CN, $–CH_3$, $–C_{2-4}$ alkyl and $–C_{2-4}$ haloalkyl;

R^{1d} is selected from hydrogen, $–C_{1-2}$ alkyl and $–C_{1-2}$ haloalkyl;

R^{1e} is selected from hydrogen, $–C_{1-2}$ alkyl and $–C_{1-2}$ haloalkyl;

R^{1f} is selected from hydrogen, $–C_{1-2}$ alkyl and $–C_{1-2}$ haloalkyl;

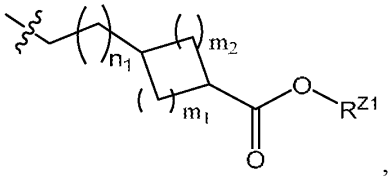
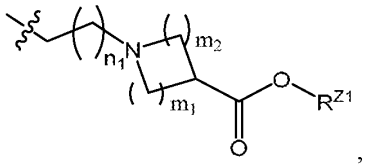
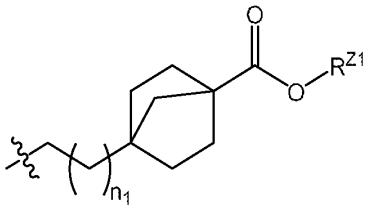
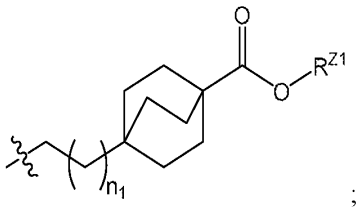
R^{1g} is selected from hydrogen, $–C_{1-2}$ alkyl and $–C_{1-2}$ haloalkyl;

R^{1h} is selected from hydrogen, $–C_{1-2}$ alkyl and $–C_{1-2}$ haloalkyl;

R^{1i}, R^{1j}, R^{1k}, R^{1l}, R^{1m} and R^{1n} are each independently selected from hydrogen, $–C_{1-2}$ alkyl and $–C_{1-2}$ haloalkyl;

R^{1p} is selected from $–CH_3$, $–C_{2-4}$ alkyl and $–R^{1p1}$, wherein when R^{1p} is $–CH_3$ or $–C_{2-4}$ alkyl, the $–CH_3$ and the $–C_{2-4}$ alkyl is substituted by $–C(=O)OR^{Z1}$ and the $–CH_3$

and the –C_{2-4} alkyl is optionally substituted with one or two substituents independently selected from halogen, cyano, –C_{1-4} alkyl, hydroxy, –C_{1-4} alkoxy, –C_{1-4} haloalkyl, –C_{1-4} haloalkoxy, –C(=O)NHS(=O)$_2R^{Z3}$, –C(=O)N(R^{Z1})R^{Z2}, –S(=O)$_2R^{Z3}$, –S(=O)$_2$N(R^{Z1})R^{Z2}, –N(R^{Z1})R^{Z2}, –N(R^{Z1})C(=O)R^{Z3}, –N(R^{Z1})S(=O)R^{Z3}, –N(R^{Z1})C(=O)N(R^{Z2})R^{Z3} and –N(R^{Z1})S(=O)$_2$N(R^{Z2})R^{Z3};

R^{1p1} is selected from , ,  and ;

R^{1q} is independently selected from hydrogen, –C_{1-4} alkyl and –C_{1-4} haloalkyl;

R^{2a}, R^{2b}, R^{2c}, R^{2e}, R^{2g} and R^{2h} are each independently selected from hydrogen and halogen;

R^{2d} and R^{2f} are each independently selected from hydrogen, halogen, cyano, –CH_3, –CH_2CH_3, –CH_2OH, –OCH_3 and –SCH_3;

R^{3a} is selected from hydrogen, –CH_3, –C_{2-4} alkyl and –C_{2-4} haloalkyl;

R^{3b} is selected from hydrogen, –CH_3, –C_{2-4} alkyl, –C_{2-4} haloalkyl and –C_{1-4} alkoxy; wherein R^{3b} is optionally substituted with one or two substituents independently selected from halogen, -OH, –CN, –CH_3, –C_{2-4} alkyl, –C_{2-4} haloalkyl, –CH_2CH_2OH and –$CH_2CH_2OC_{1-4}$ haloalkyl;

R^{3c} is selected from hydrogen, halogen, –C_{1-2} alkyl and –C_{1-2} haloalkyl;

R^{4a} is selected from hydrogen, –CH_3, –C_{2-4} alkyl and –C_{2-4} haloalkyl;

R^{4b} is selected from hydrogen, halogen, $–C_{1-4}$ alkyl, $–C_{1-4}$ haloalkyl, –OH, $–NH_2$, $–OC_{1-4}$ alkyl and $–OC_{1-4}$ haloalkyl, wherein R^{4b} is optionally substituted with one or two substituents independently selected from halogen, -OH, –CN, $–CH_3$, $–C_{2-4}$ alkyl, $–C_{2-4}$ haloalkyl, $-CH_2CH_2OH$ and $-CH_2CH_2O–C_{1-4}$ haloalkyl;

R^{4c} is selected from hydrogen, halogen, $–C_{1-2}$ alkyl and $–C_{1-2}$ haloalkyl;

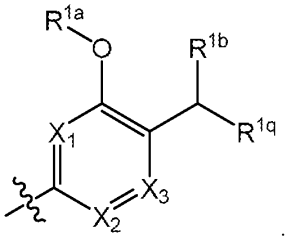
m_1, m_2 and m_3 are each independently 1 or 2;

m_4 is 0, 1 or 2;

m_5 is 1, 2, 3 or 4;

n_1 is independently 0, 1 or 2; and

R^{Z1}, R^{Z2}, R^{Z3} and R^{Z4} are each independently selected from hydrogen, $–C_{1-4}$ alkyl and $–C_{1-4}$ haloalkyl.

2. The compound of Claim 1, or a pharmaceutically acceptable salt thereof, wherein A^1 is 

.

3. The compound of Claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein X^1 is N.

4. The compound of any one of Claims 1-3, or a pharmaceutically acceptable salt thereof, wherein X^2 is CH.

5. The compound of any one of Claims 1-4, or a pharmaceutically acceptable salt thereof, wherein X^3 is CH.

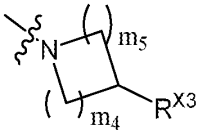
6. The compound of any one of Claims 1-4, or a pharmaceutically acceptable salt thereof, wherein X^3 is N.

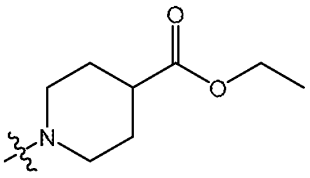
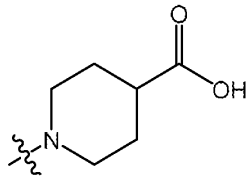
7. The compound of any one of Claims 1-6, or a pharmaceutically acceptable salt thereof, wherein R^{1a} is $–C_{1-4}$ alkyl.

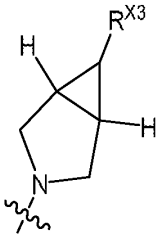
8. The compound of Claim 7, or a pharmaceutically acceptable salt thereof, wherein R^{1a} is $–CH_3$.

9. The compound of any one of Claims 1-8, or a pharmaceutically acceptable salt thereof, wherein R^{1q} is hydrogen.

10. The compound of any one of Claims 1-9, or a pharmaceutically acceptable salt thereof, wherein R^{1b} is $-R^{x1}$.

11. The compound of Claim 10, or a pharmaceutically acceptable salt thereof, wherein $-R^{x1}$ is .

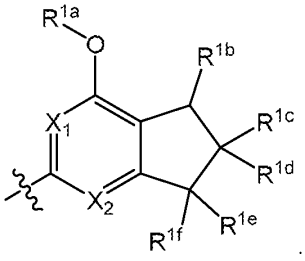
12. The compound of Claim 11, or a pharmaceutically acceptable salt thereof, wherein $-R^{x1}$ is  or .

13. The compound of Claim 10, or a pharmaceutically acceptable salt thereof, wherein $-R^{x1}$ is .

14. The compound of any one of Claims 1-9, or a pharmaceutically acceptable salt thereof, wherein R^{1b} is $-N(R^{m1})R^{n1}$.

15. The compound of Claim 13, or a pharmaceutically acceptable salt thereof, wherein R^{n1} is hydrogen.

16. The compound of Claim 13 or 14, or a pharmaceutically acceptable salt thereof, wherein R^{m1} is $-R^{x2}$.

17. The compound of Claim 1, or a pharmaceutically acceptable salt thereof, wherein A^1 is .

18. The compound of Claim 16, or a pharmaceutically acceptable salt thereof, wherein X^1 is N.

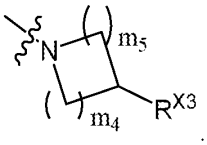
19. The compound of Claim 16 or 17, or a pharmaceutically acceptable salt thereof, wherein X^2 is CH.

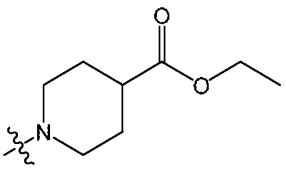
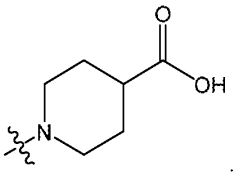
20. The compound of any one of Claims 16-18, or a pharmaceutically acceptable salt thereof, wherein R^{1a} is $-C_{1-4}$ alkyl.

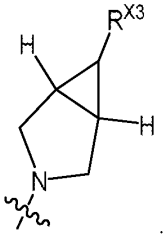
21. The compound of Claim 19, or a pharmaceutically acceptable salt thereof, wherein R^{1a} is $-CH_3$.

22. The compound of any one of Claims 16-20, or a pharmaceutically acceptable salt thereof, wherein R^{1c}, R^{1d}, R^{1e} and R^{1f} are each hydrogen.

23. The compound of any one of Claims 16-21, or a pharmaceutically acceptable salt thereof, wherein R^{1b} is $-R^{x1}$.

24. The compound of Claim 23, or a pharmaceutically acceptable salt thereof, wherein $-R^{x1}$ is .

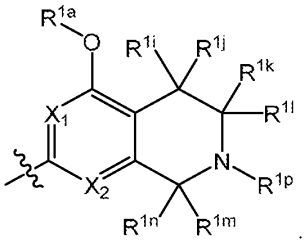
25. The compound of Claim 24, or a pharmaceutically acceptable salt thereof, wherein $-R^{x1}$ is  or .

26. The compound of Claim 23, or a pharmaceutically acceptable salt thereof, wherein $-R^{x1}$ is .

27. The compound of any one of Claims 16-21, or a pharmaceutically acceptable salt thereof, wherein R^{1b} is $-N(R^{m1})R^{n1}$.

28. The compound of Claim 27, or a pharmaceutically acceptable salt thereof, wherein R^{n1} is hydrogen.

29. The compound of Claim 27 or 28, or a pharmaceutically acceptable salt thereof, wherein R^{m1} is $-R^{x2}$.

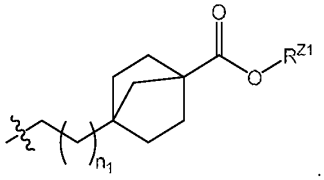
30. The compound of Claim 1, or a pharmaceutically acceptable salt thereof, wherein A^1 is .

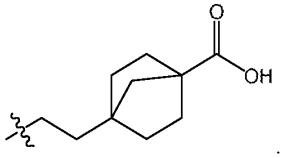
31. The compound of Claim 30, or a pharmaceutically acceptable salt thereof, wherein X^1 is N.

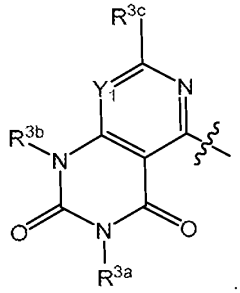
32. The compound of Claim 30 or 31, or a pharmaceutically acceptable salt thereof, wherein X^2 is CH.

33. The compound of any one of Claims 30-32, wherein R^{1i}, R^{1j}, R^{1k}, R^{1l}, R^{1m} and R^{1n} are each hydrogen.

34. The compound of any one of Claims 30-33, wherein R^{1p} is $-R^{1p1}$.

35. The compound of Claim 34, wherein $-R^{1p1}$ is .

36. The compound of Claim 35, wherein $-R^{1p1}$ is .

37. The compound of any one of Claims 1-36, or a pharmaceutically acceptable salt thereof, wherein B^1 is .

38. The compound of Claim 37, or a pharmaceutically acceptable salt thereof, wherein Y_1 is CH.

39. The compound of Claim 37, or a pharmaceutically acceptable salt thereof, wherein Y_1 is N.

40. The compound of any one of Claims 37-39, or a pharmaceutically acceptable salt thereof, wherein R^{3a} and R^{3b} are each $-CH_3$.

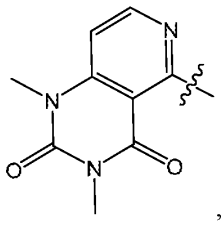
41. The compound of any one of Claims 37-40, or a pharmaceutically acceptable salt thereof, wherein R^{3c} is hydrogen.

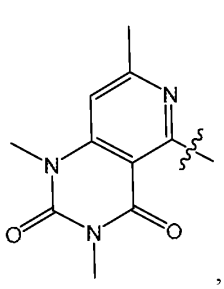
42. The compound of any one of Claims 37-40, or a pharmaceutically acceptable salt thereof, wherein R^{3c} is $-CH_3$.

43. The compound of any one of Claims 37-40, or a pharmaceutically acceptable salt thereof, wherein R^{3c} is $-C_{1-2}$ haloalkyl.

44. The compound of Claim 43, or a pharmaceutically acceptable salt thereof, wherein R^{3c} is $-CF_3$.

45. The compound of Claim 43, or a pharmaceutically acceptable salt thereof, wherein R^{3c} is $-CHF_2$.

46. The compound of Embodiment 37, or a pharmaceutically acceptable salt thereof, wherein B^1 is selected from the group consisting of ,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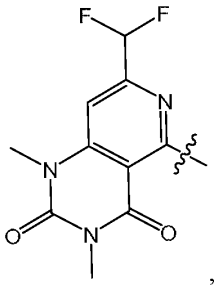
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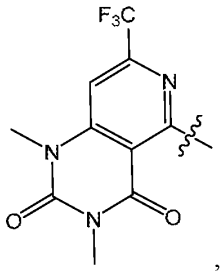
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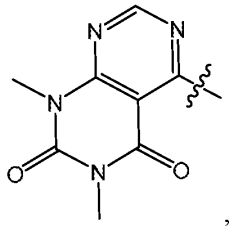
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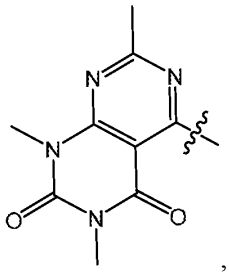
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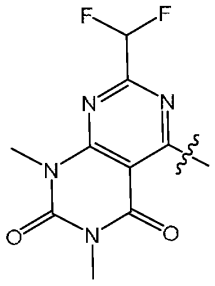
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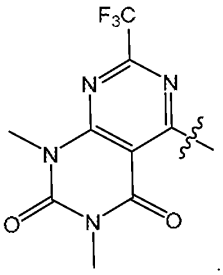
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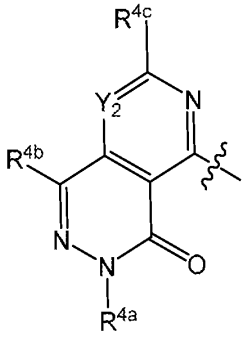
47. The compound of any one of Claims 1-36, or a pharmaceutically acceptable salt thereof, wherein B^1 is 
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48. The compound of Claim 47, or a pharmaceutically acceptable salt thereof, wherein Y_2 is CH.

49. The compound of Claim 47 or 48, or a pharmaceutically acceptable salt thereof, wherein R^{4a} is $-CH_3$.

50. The compound of any one of Claims 47-49, or a pharmaceutically acceptable salt thereof, wherein R^{4b} is hydrogen.

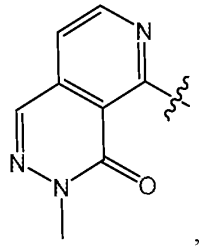
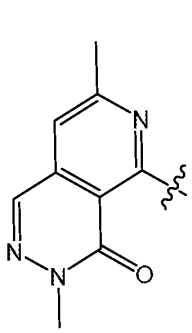
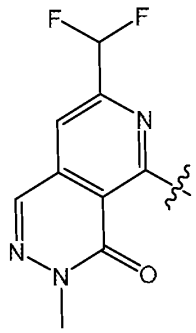
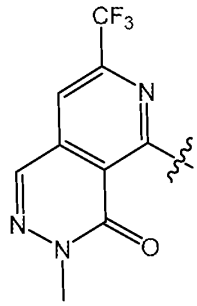
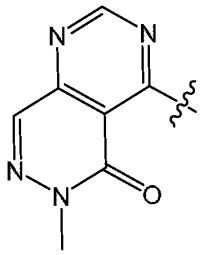
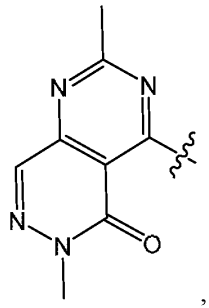
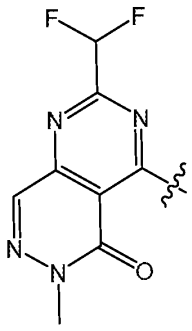
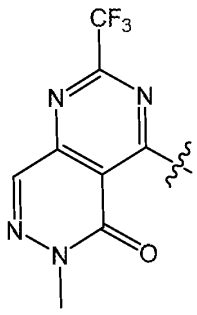
51. The compound of any one of Claims 47-50, or a pharmaceutically acceptable salt thereof, wherein R^{4c} is hydrogen.

52. The compound of any one of Claims 47-50, or a pharmaceutically acceptable salt thereof, wherein R^{4c} is $-CH_3$.

53. The compound of any one of Claims 47-50, or a pharmaceutically acceptable salt thereof, wherein R^{4c} is $-C_{1-2}$ haloalkyl.

54. The compound of Claim 53, or a pharmaceutically acceptable salt thereof, wherein R^{4c} is $-CF_3$.

55. The compound of Claim 53, or a pharmaceutically acceptable salt thereof, wherein R^{4c} is $-CHF_2$.

56. The compound of Embodiment 47, or a pharmaceutically acceptable salt thereof, wherein B^1 is selected from the group consisting of , , , , , ,  and .

57. The compound of any one of Claims 1-56, or a pharmaceutically acceptable salt thereof, wherein R^{2a}, R^{2b}, R^{2c}, R^{2e}, R^{2g} and R^{2h} are each hydrogen.

58. The compound of any one of Claims 1-57, or a pharmaceutically acceptable salt thereof, wherein R^{2d} and R^{2f} are each halogen.

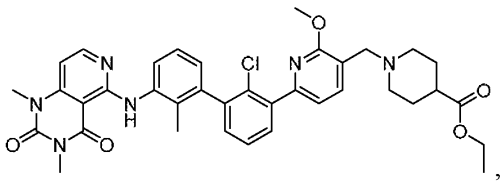
59. The compound of any one of Claims 1-57, or a pharmaceutically acceptable salt thereof, wherein R^{2d} is halogen; and R^{2f} is $–CH_3$.

60. The compound of any one of Claims 1-57, or a pharmaceutically acceptable salt thereof, wherein R^{2d} is $–CH_3$; and R^{2f} is halogen.

61. The compound of any one of Claims 58-60, or a pharmaceutically acceptable salt thereof, wherein the halogen is chloro.

62. The compound of any one of Claims 1-57, or a pharmaceutically acceptable salt thereof, wherein R^{2d} and R^{2f} are each $–CH_3$.

63. The compound of Claim 1, or a pharmaceutically acceptable salt thereof, selected from the group consisting of: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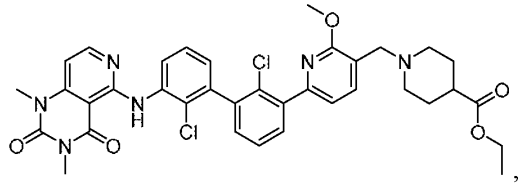
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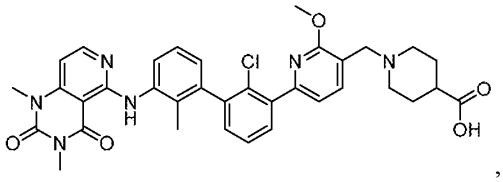
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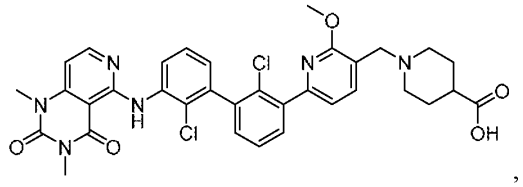
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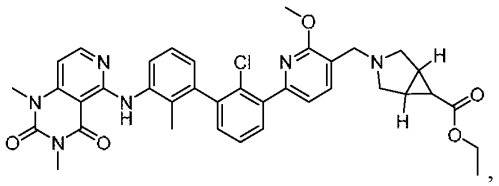
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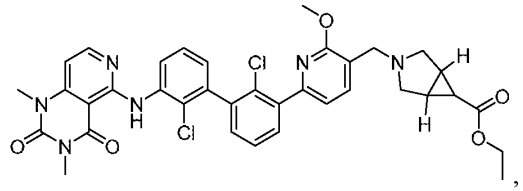
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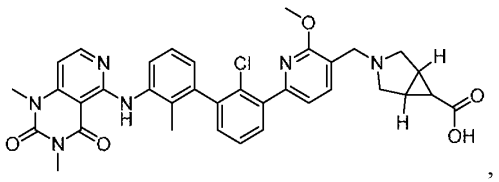
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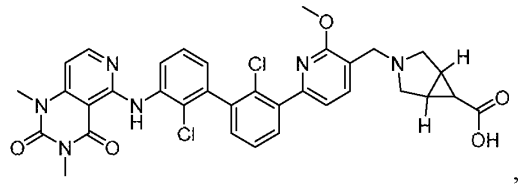
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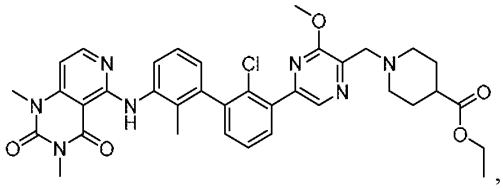
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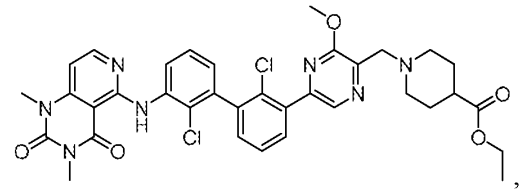
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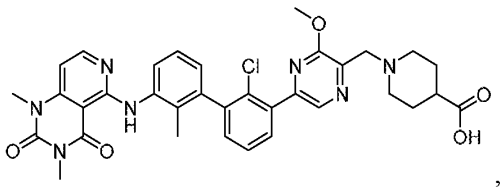
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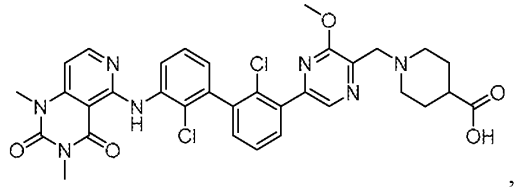
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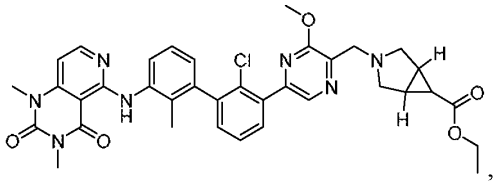
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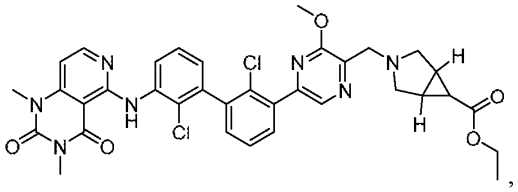
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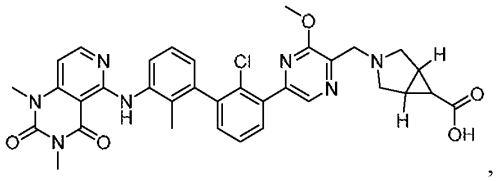
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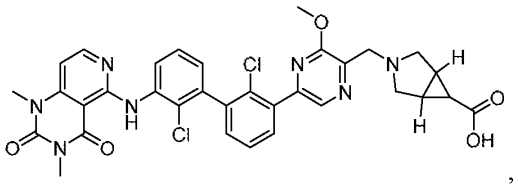
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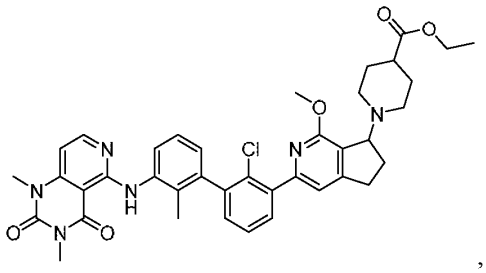
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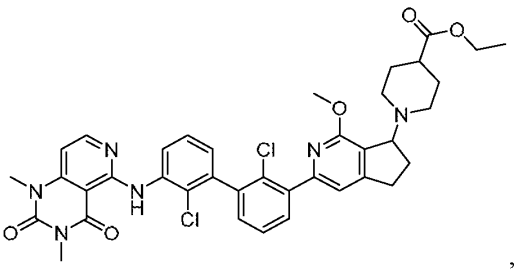
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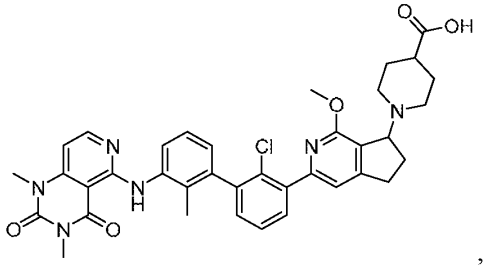
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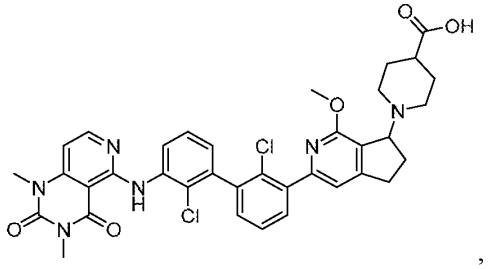
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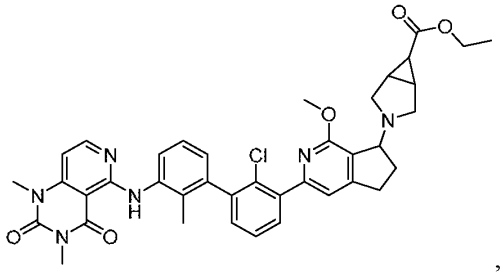
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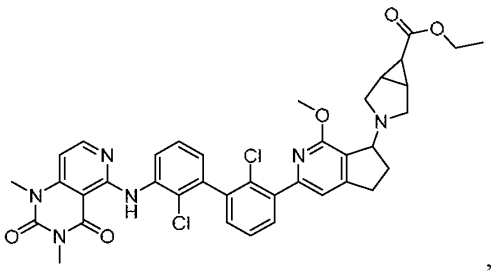
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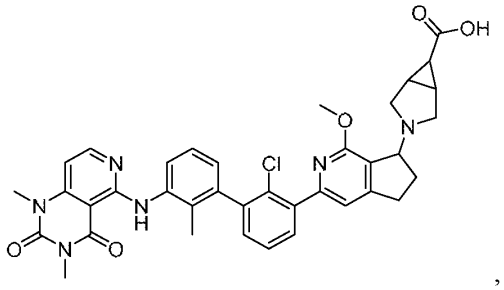
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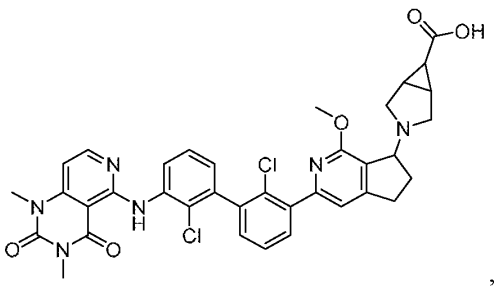
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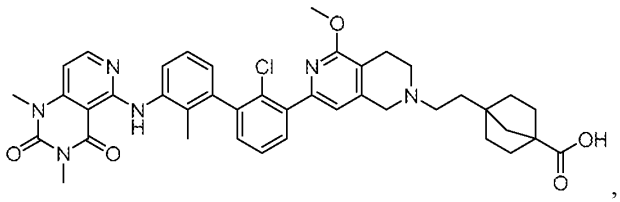
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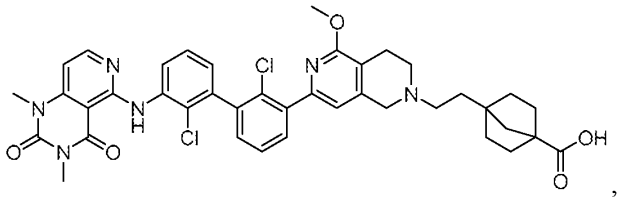
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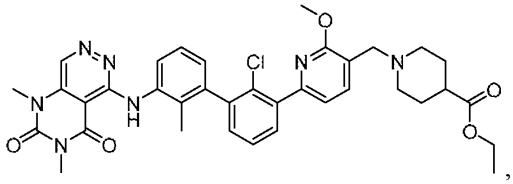
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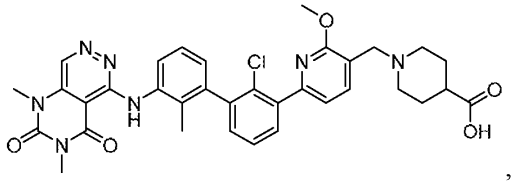
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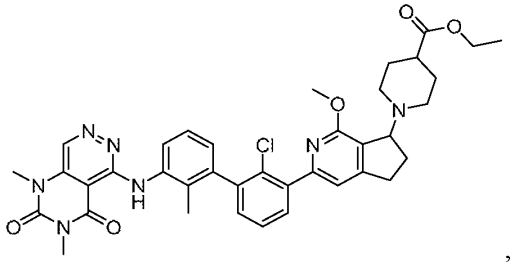
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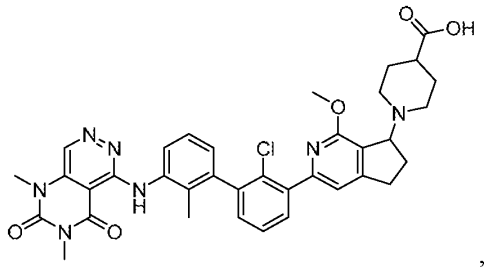
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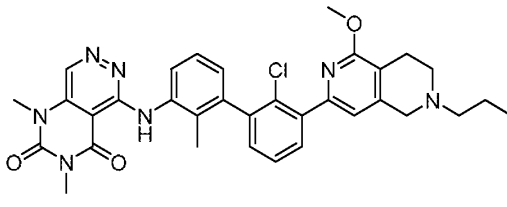
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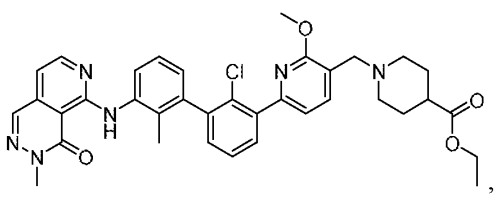
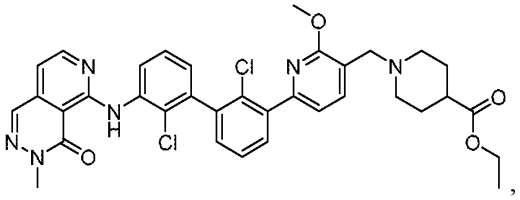
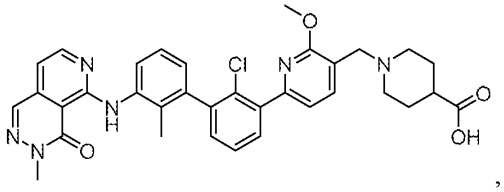
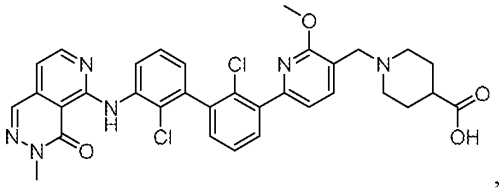
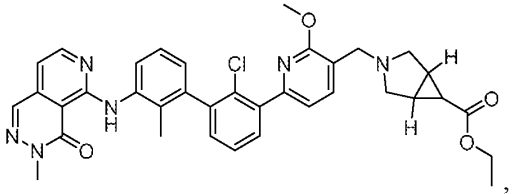
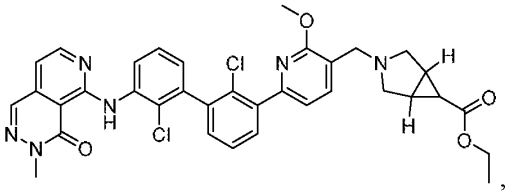
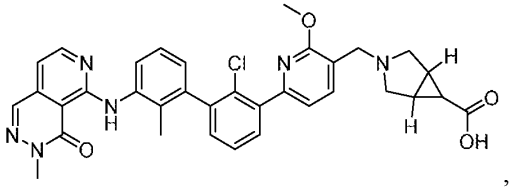
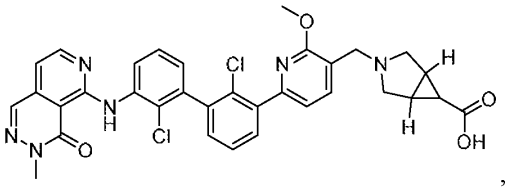
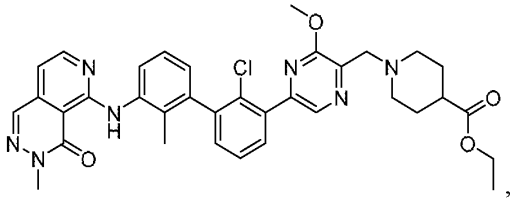
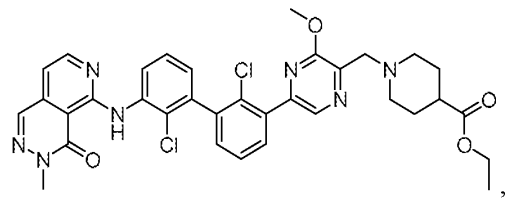
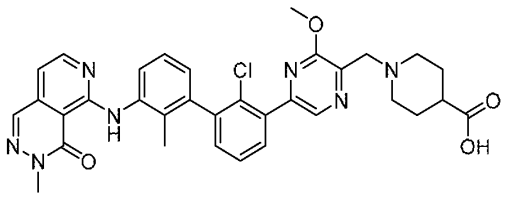
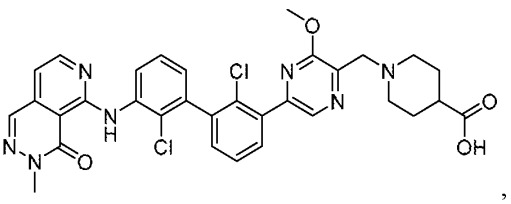
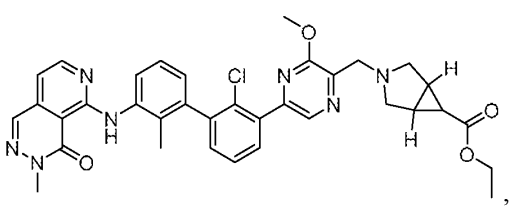
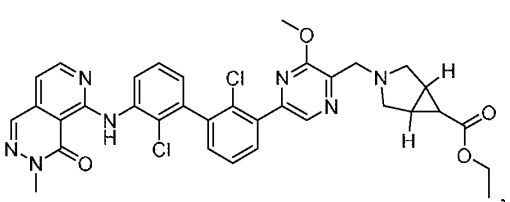
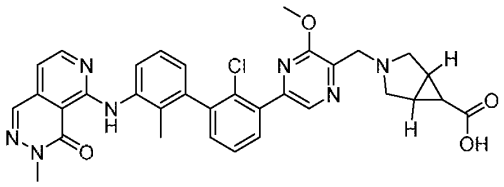
,
,
,
,
,
,
,
,
,
,
,
,
,
,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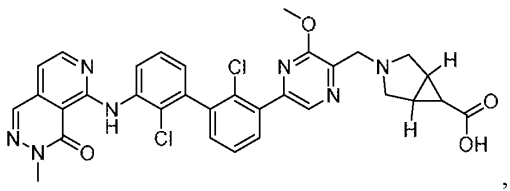
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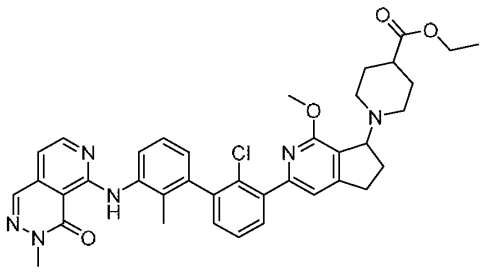
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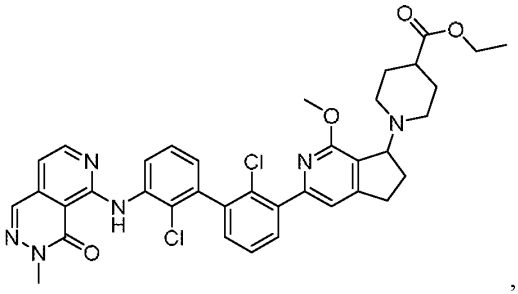
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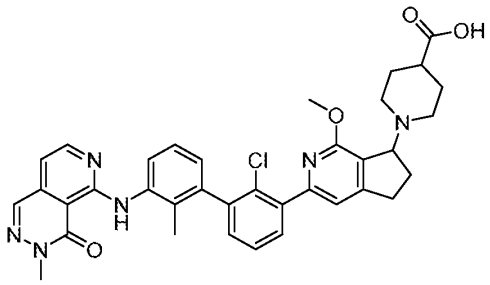
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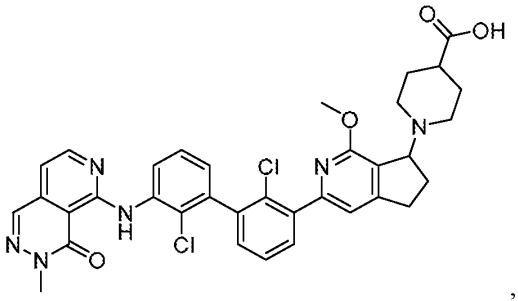
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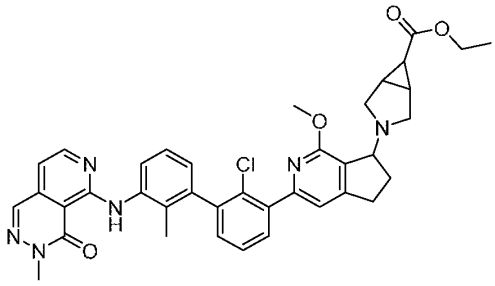
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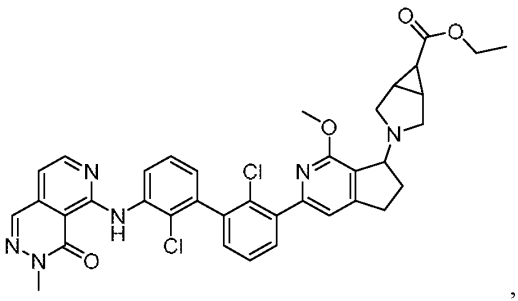
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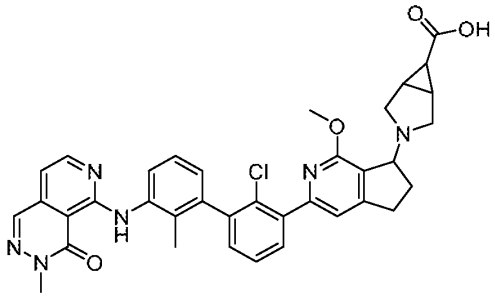
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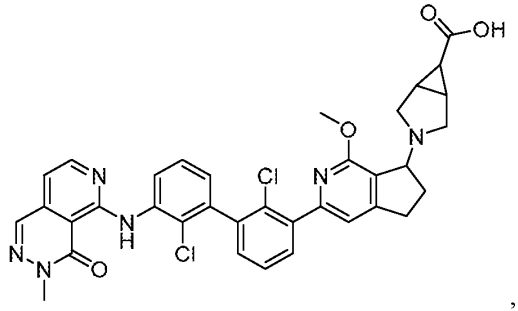
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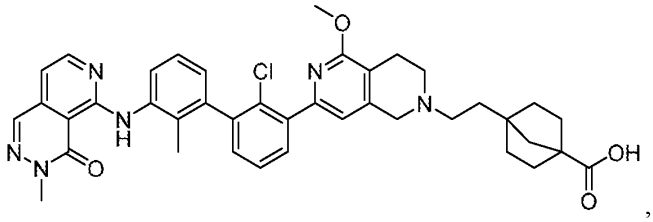
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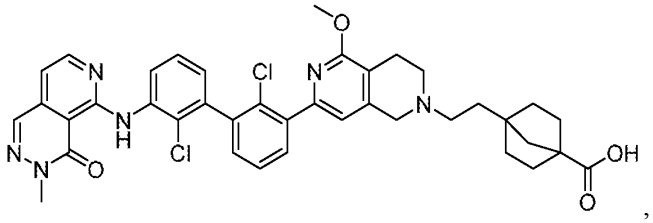
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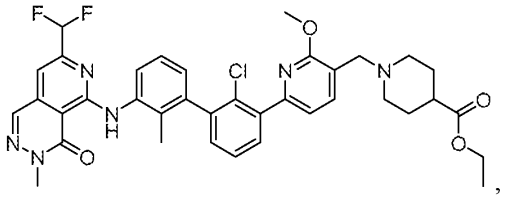
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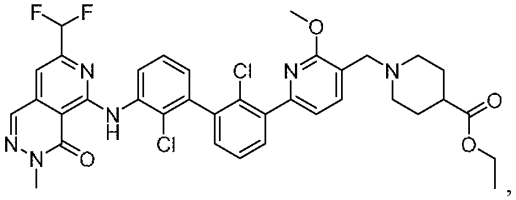
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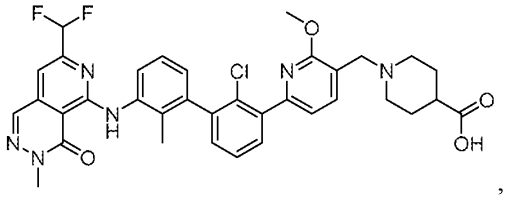
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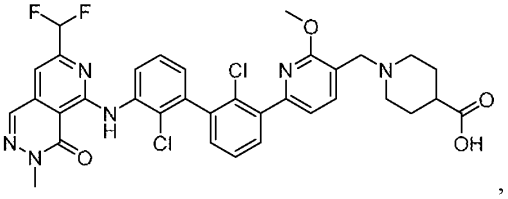
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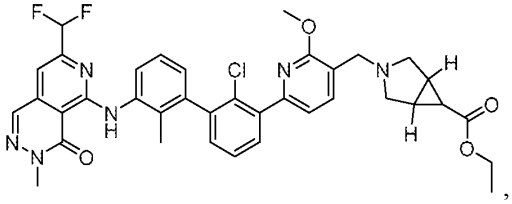
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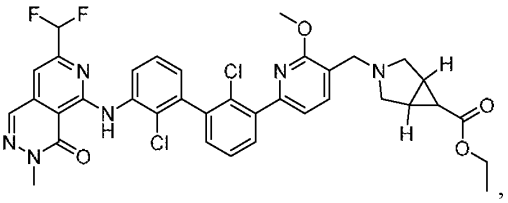
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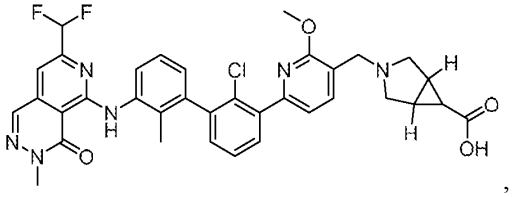
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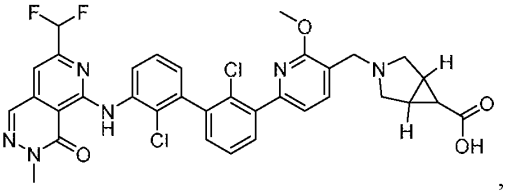
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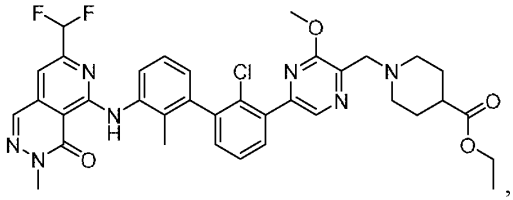
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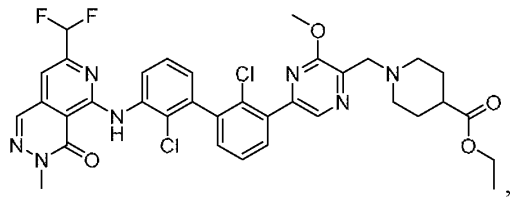
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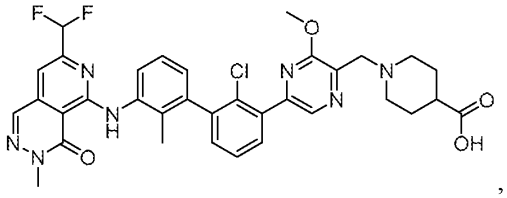
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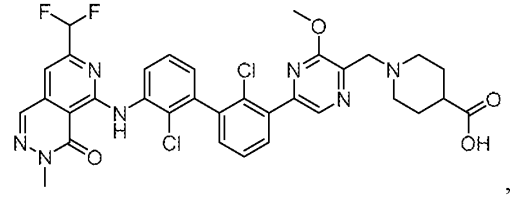
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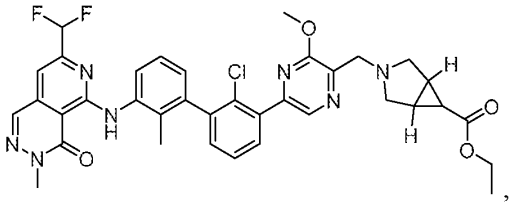
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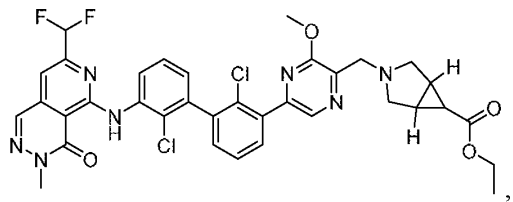
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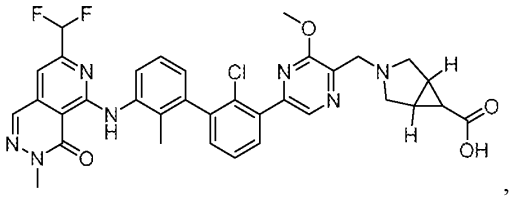
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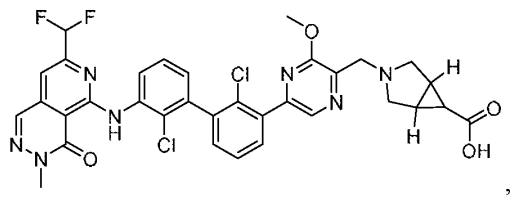
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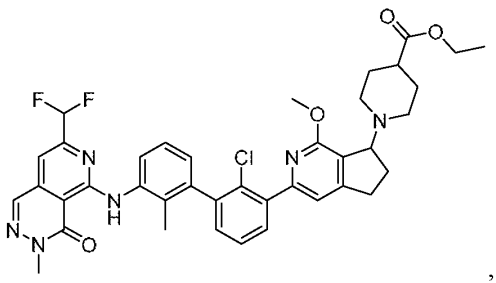
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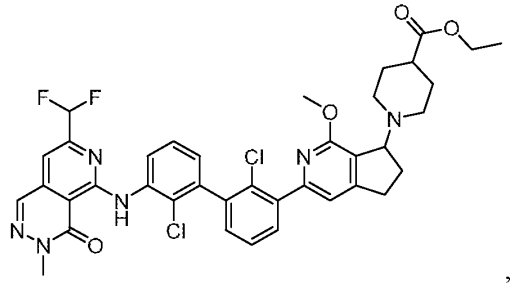
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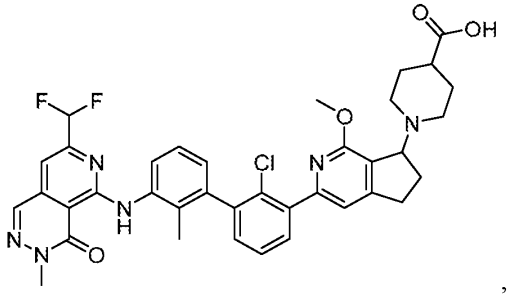
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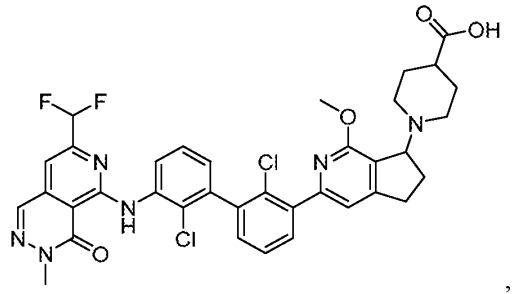
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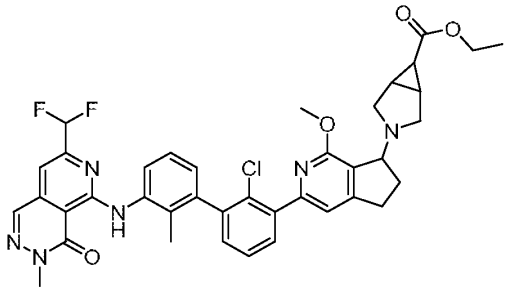
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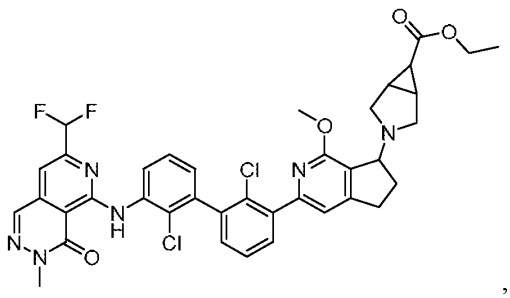
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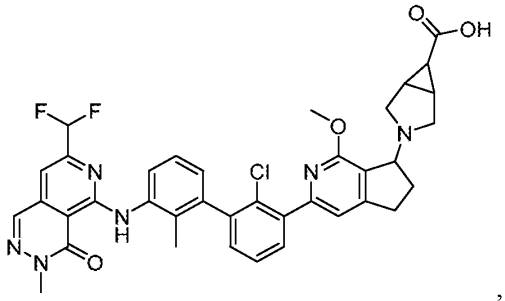
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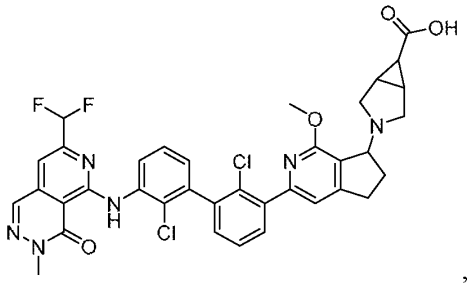
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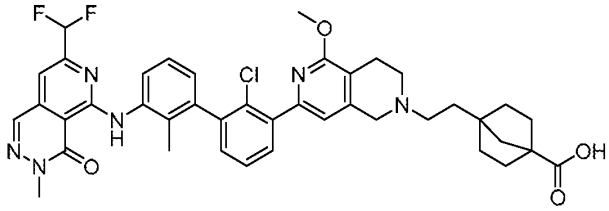
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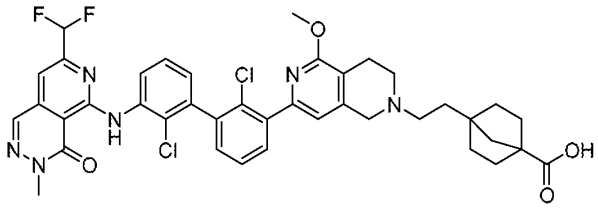
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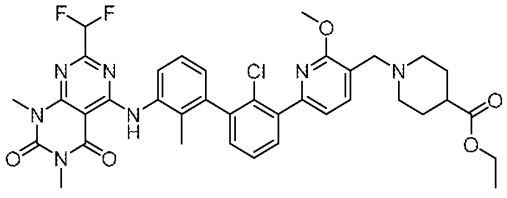
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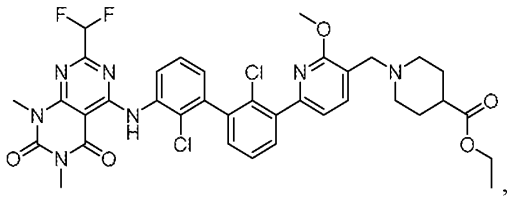
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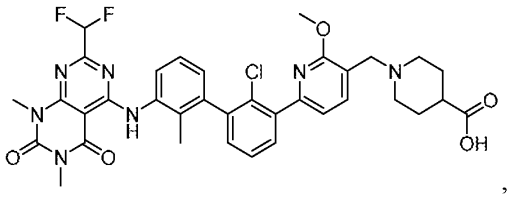
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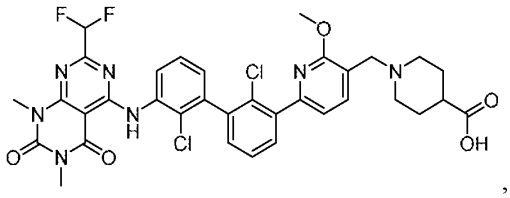
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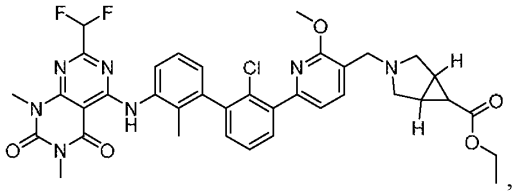
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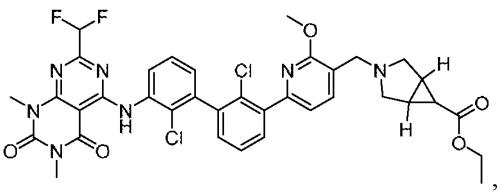
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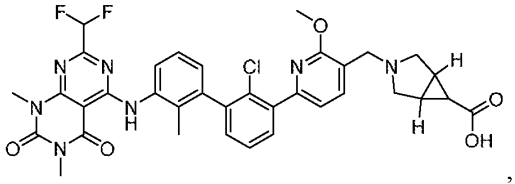
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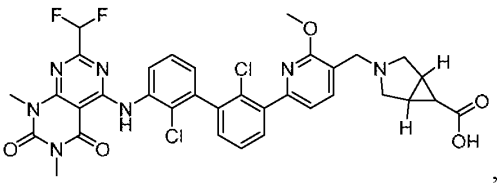
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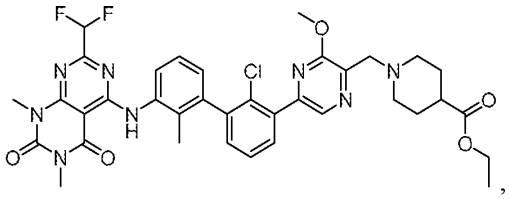
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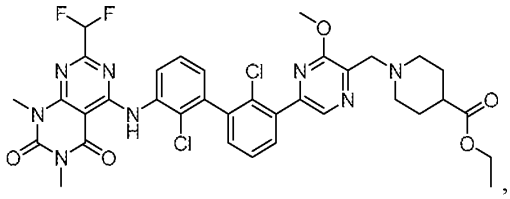
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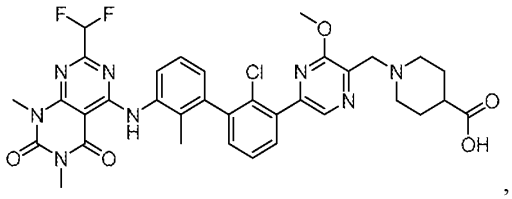
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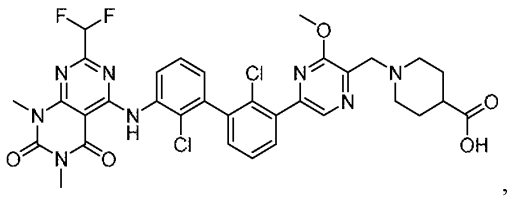
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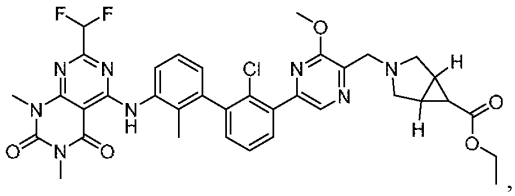
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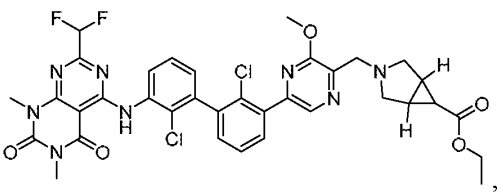
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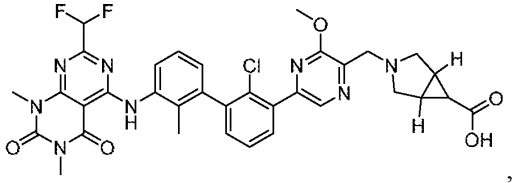
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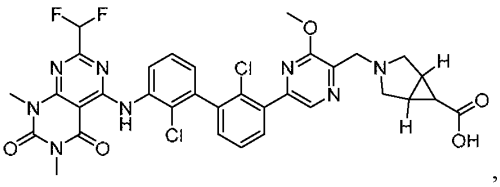
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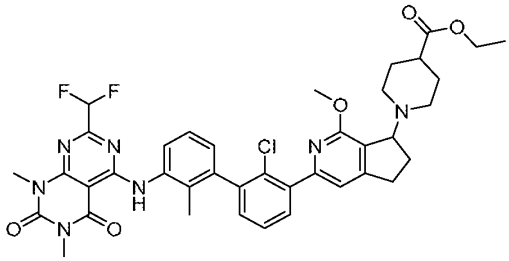
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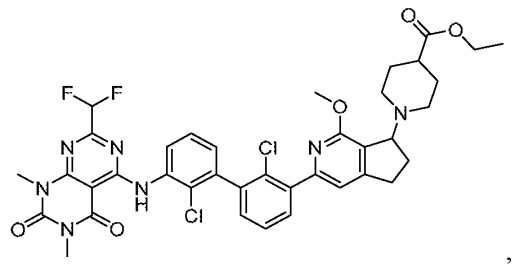
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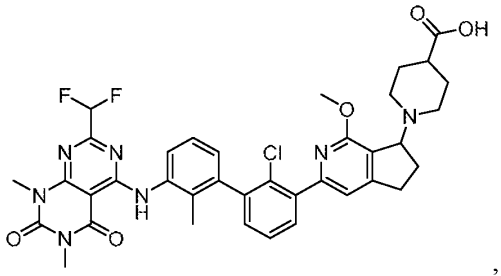
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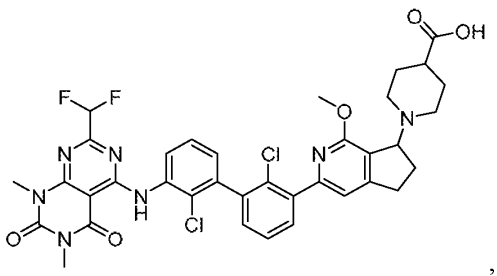
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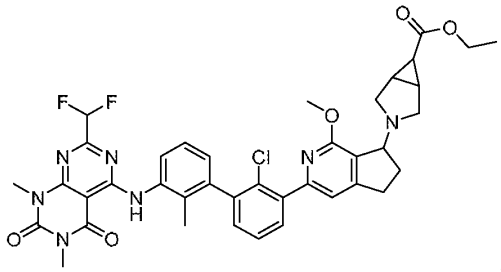
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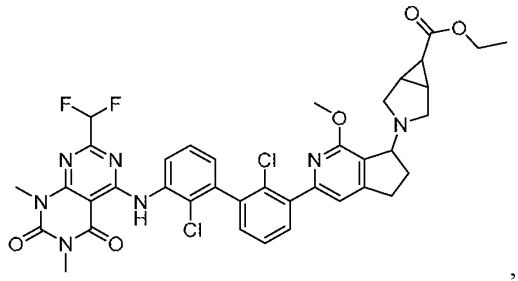
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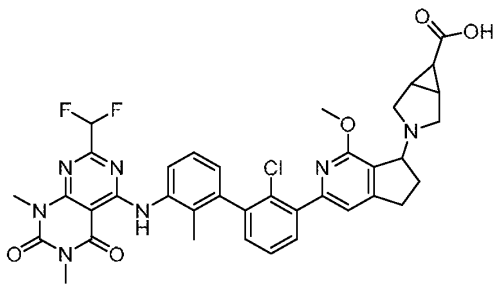
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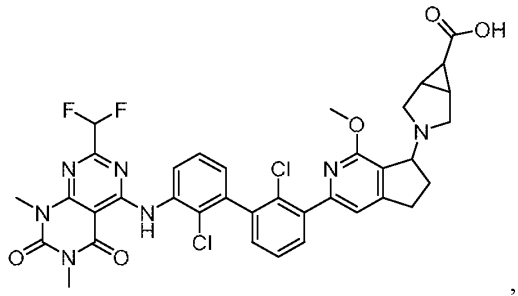
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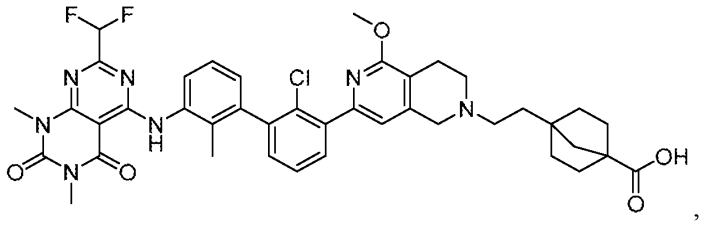
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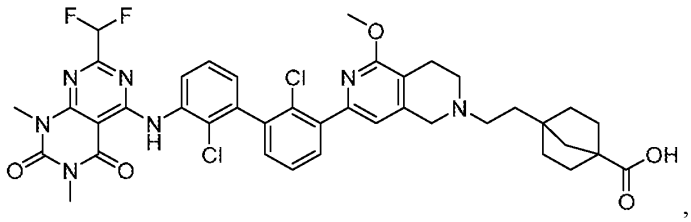

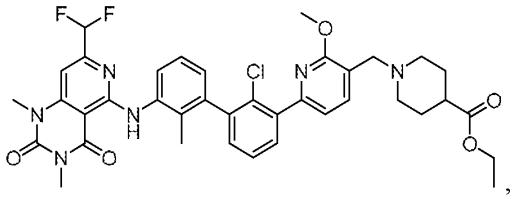

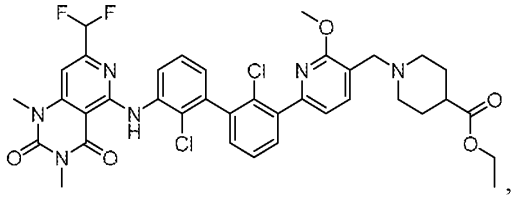

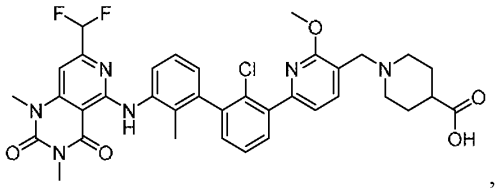

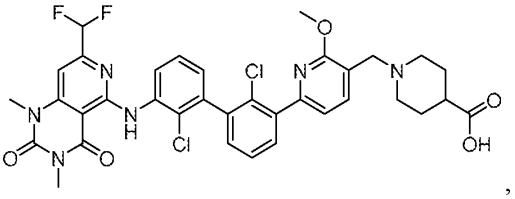

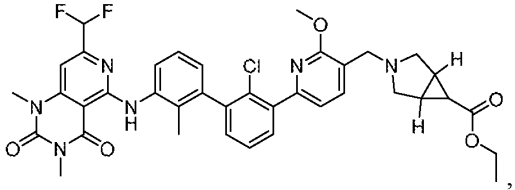

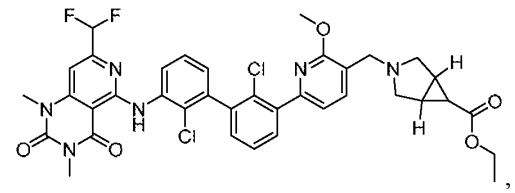

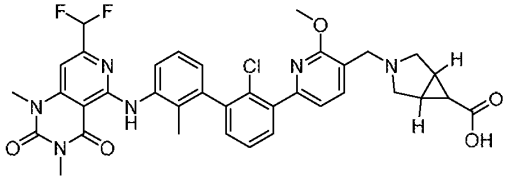

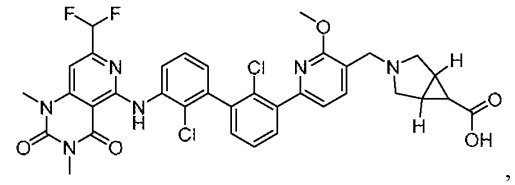

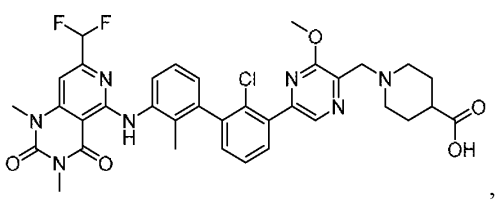
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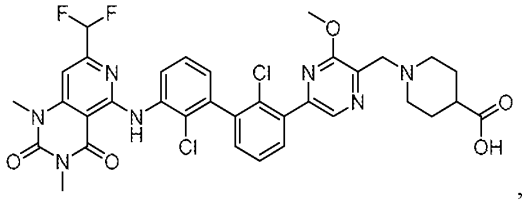
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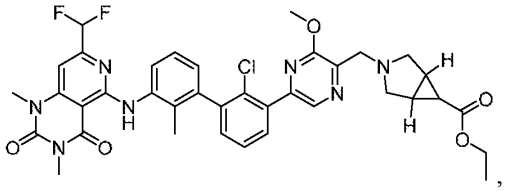
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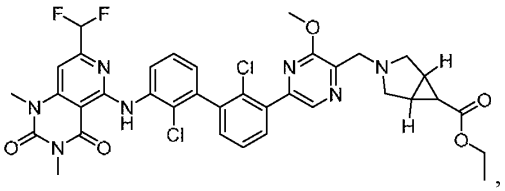
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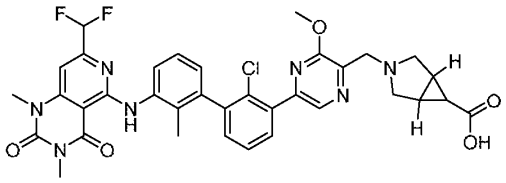
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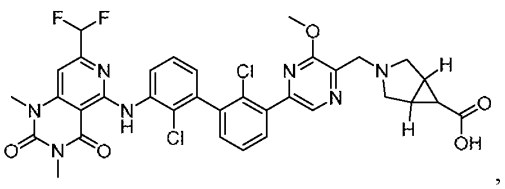
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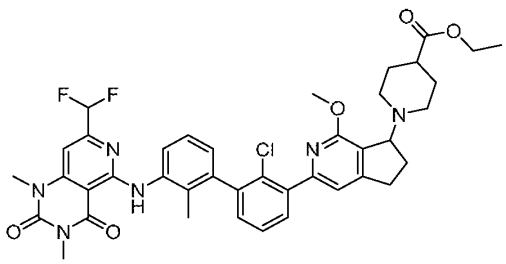
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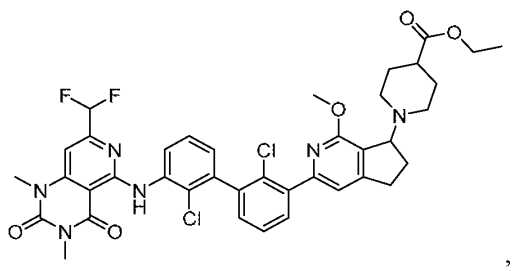
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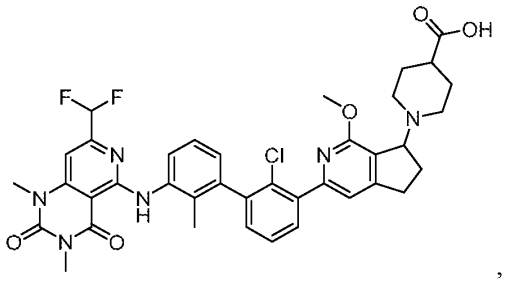
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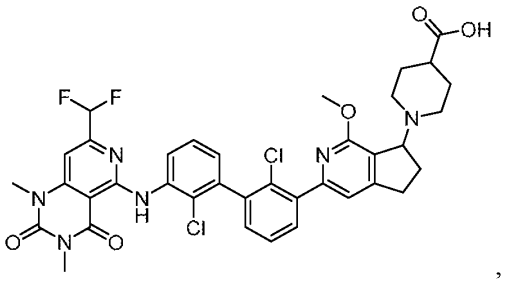
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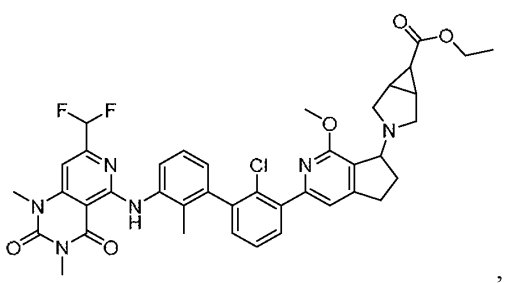
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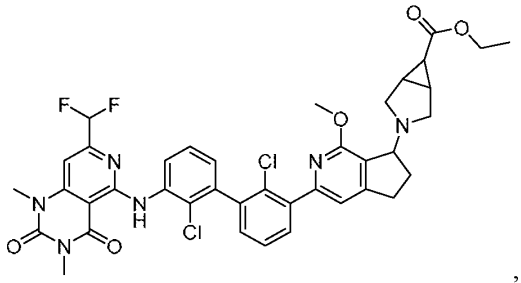
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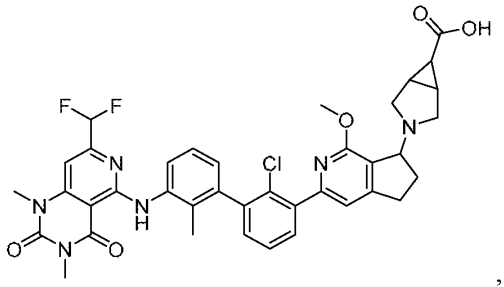
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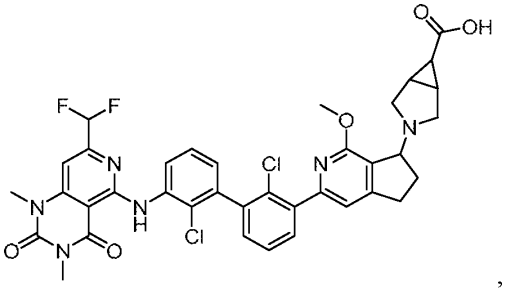
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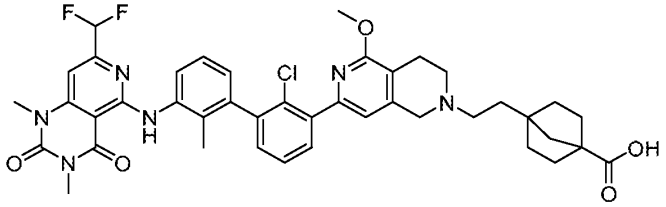
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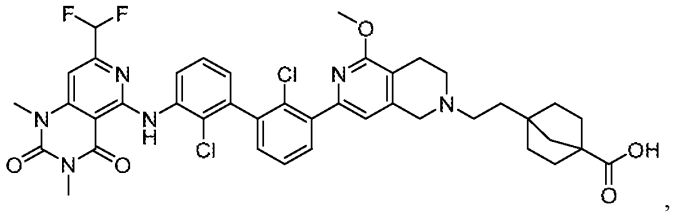
, or a pharmaceutically acceptable salt of any of the foregoing.

64. A pharmaceutical composition comprising an effective amount of a compound of any one of Claims 1-63, or a pharmaceutically acceptable salt thereof, and an excipient.

65. A method for treating hepatitis B in a subject comprising administering to the subject in need thereof an effective amount of a compound of any one of Claims 1-63, or a pharmaceutically acceptable salt thereof.

66. A method for treating hepatocellular carcinoma (HCC) in a subject comprising administering to the subject in need thereof an effective amount of a compound of any one of Claims 1-63, or a pharmaceutically acceptable salt thereof.

67. The method of any one of Claims 65-66, further comprising administering surgery, radiation therapy, chemotherapy, targeted therapy, immunotherapy, hormonal therapy or antiviral therapy.

68. A compound of any one of Claims 1-63, or a pharmaceutically acceptable salt thereof, for use in treating hepatitis B.

69. A compound of any one of Claims 1-63, or a pharmaceutically acceptable salt thereof, for use in treating hepatocellular carcinoma (HCC).

70. The compound any one of Claims 68-69, or pharmaceutically acceptable salt thereof, wherein the use further comprises administering surgery, radiation therapy, chemotherapy, targeted therapy, immunotherapy, hormonal therapy or antiviral therapy.

71. Use of a compound of any one of Claims 1-63, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for use in treating hepatitis B.

72. Use of a compound of any one of Claims 1-63, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for use in treating hepatocellular carcinoma (HCC).

73. The use of any one of Claims 71-72, wherein the medicament is for use in combination with administering surgery, radiation therapy, chemotherapy, targeted therapy, immunotherapy, hormonal therapy or antiviral therapy.