METHODS AND COMPOSITIONS FOR TARGETING PD-L1

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. 63/568,984, filed March 22, 2024 and 63/670,574, 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 relates to compounds that can be useful as inhibitors of PD-1, PD-Ll and/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 as described herein, 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 disclosed herein, or a pharmaceutically acceptable salt thereof.

[0006] Some embodiments described herein relate to a method of treating an 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 an 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 of HBV and/or HDV.

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

BRIEF DESCRIPTION OF THE DRAWINGS

[0009] Figure 1A shows the absolute configuration structure and Figure 1B shows the ORTEP crystal structure of Intermediate 9B.

[0010] Figure 2A shows the absolute configuration structure and Figure 2B shows the ORTEP crystal structure of the chloride salt of Intermediate 12B.

DETAILED DESCRIPTION

[0011] 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.

[0012] 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.

[0013] 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.

[0014] 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.

[0015] 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.

[0016] 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.

[0017] 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

[0018] 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.

[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., benzimidazolidinone, tetrahydroquinoline and 3,4-methylenedioxyphenyl).

[0028] As used herein, "aryl(alkyl)" refer 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)" refer 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" refer 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

to, 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 "–$OC(=S)\text{-}N(R_AR_B)$" 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_{1-6} 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_{1-6} 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 numbers of substituents are 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.

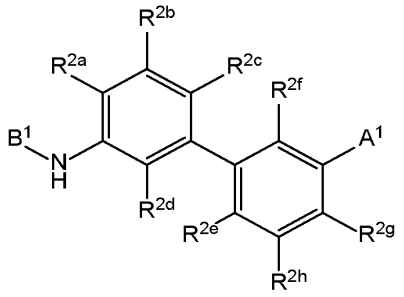
[0073] Where a range of values is provided, it is understood that the upper and lower limit, and each intervening value between the upper and lower limit of the range is encompassed within the embodiments.

Compounds

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

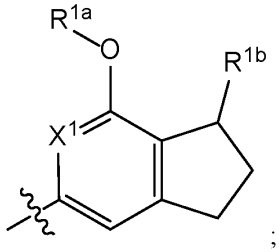
Embodiment 1

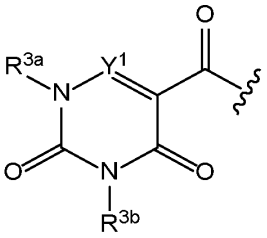
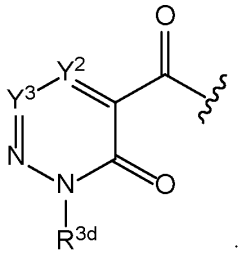
[0075] A compound of Formula (I), or a pharmaceutically acceptable salt thereof, having the structure:



(I)

wherein:

A^1 can be  ;

B^1 can be  or  ;

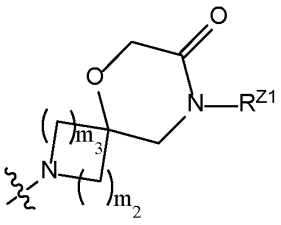
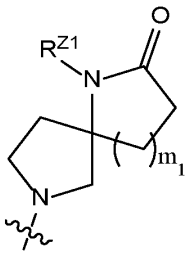
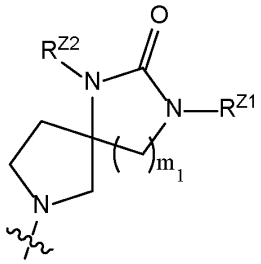
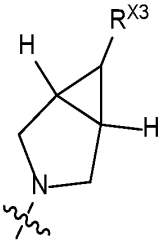
X^1 can be selected from CH and N;

Y^1 can be selected from N and CR^{3c};

Y^2 can be CR^{3e};

Y^3 can be CR^{3f};

R^{1a} can be selected from $–C_{1-4}$ alkyl, $–C_{1-4}$ haloalkyl, $–CH_2$(C_{3-6} monocyclic cycloalkyl), $–C_{2-4}$ alkyl(O-C_{1-4} alkyl), $–C_{2-4}$ alkyl(OC_{1-4} haloalkyl), $–CH_2$(4-6 membered monocyclic heterocyclyl) and $–CH_2$(5-6 membered monocyclic heteroaryl);

R^{1b} can be selected from , ,   and ;

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

R^{2d} and R^{2f} can be 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, wherein the $–C_{2-4}$ alkyl can be optionally substituted with one or two or three substituents independently selected from hydroxy and $–OR^{3a1}$;

R^{3a1} can be $–C_{1-4}$ alkyl;

R^{3b} can be selected from hydrogen, $–CH_3$, $–C_{2-4}$ alkyl and $–C_{2-4}$ haloalkyl;

R^{3c} can be selected from hydrogen, $–CH_3$, $–C_{2-4}$ alkyl and $–C_{2-4}$ haloalkyl;

R^{3d} can be selected from hydrogen, $–CH_3$, $–C_{2-4}$ alkyl and $–C_{2-4}$ haloalkyl;

R^{3e} can be selected from hydrogen, halogen and $–CH_3$;

R^{3f} can be selected from hydrogen, halogen, -OH, –CN and $–CH_3$;

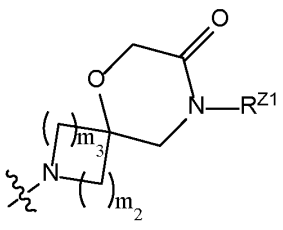
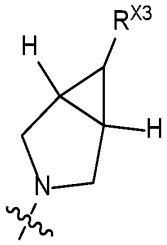
m_1, m_2, and m_3 can be independently 1 or 2;

R^{Z1} and R^{Z2} can be independently selected from hydrogen, $–C_{1-4}$ alkyl and $–C_{1-4}$ haloalkyl, wherein the $–C_{1-4}$ alkyl can be optionally substituted with one or two or three substituents independently selected from hydroxy and $–OR^{Z3}$;

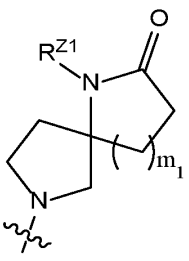
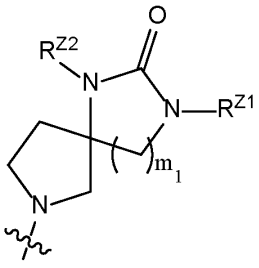
R^{Z3} can be $–C_{1-4}$ alkyl; and

R^{X3} can be selected from hydrogen, halogen, $–C_{1-4}$ alkyl, $–C_{1-4}$ haloalkyl, $–C(=O)R^{Z3}$, $–S(=O)_2R^{Z1}$, $–C(=O)N(R^{Z1})R^{Z2}$ and $–S(=O)_2N(R^{Z1})R^{Z2}$.

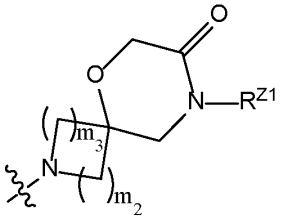
Embodiment 2

[0076] The compound of Embodiment 1, or a pharmaceutically acceptable salt thereof, wherein R^{1b} can be  or . In some embodiments, m_2 and m_3 can each be 1. In other embodiments, m_2 and m_3 can each be 2. In still other embodiments, m_2 can be 1; and m_3 can be 2. In yet still other embodiments, m_2 can be 2; and m_3 can be 1.

Embodiment 3

[0077] The compound of Embodiment 1, or a pharmaceutically acceptable salt thereof, wherein R^{1b} can be  or . In some embodiments, m_1 can be 1. In other embodiments, m_1 can be 2.

Embodiment 4

[0078] The compound of Embodiment 1 or 2, or a pharmaceutically acceptable salt thereof, wherein R^{1b} can be .

Embodiment 5

[0079] The compound of Embodiment 4, or a pharmaceutically acceptable salt thereof, wherein R^{Z1} can be hydrogen.

Embodiment 6

[0080] The compound of Embodiment 4, or a pharmaceutically acceptable salt thereof, wherein R^{Z1} can be $-C_{1-4}$ alkyl.

Embodiment 7

[0081] The compound of Embodiment 4, or a pharmaceutically acceptable salt thereof, wherein R^{Z1} can be $-C_{1-4}$ alkyl, wherein the $-C_{1-4}$ alkyl can be optionally substituted with one or two or three substituents independently selected from hydroxy and $-OR^{Z3}$.

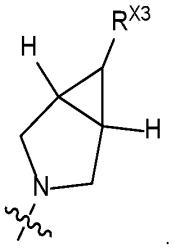
Embodiment 8

[0082] The compound of Embodiment 4, or a pharmaceutically acceptable salt thereof, wherein R^{Z1} can be $-C_{1-4}$ haloalkyl.

Embodiment 9

[0083] The compound of any one of Embodiments 4-8, or a pharmaceutically acceptable salt thereof, wherein m_2 and m_3 can be each 1.

Embodiment 10

[0084] The compound of Embodiment 1 or 2, or a pharmaceutically acceptable salt thereof, wherein R^{1b} can be 

.

Embodiment 11

[0085] The compound of Embodiment 10, or a pharmaceutically acceptable salt thereof, wherein R^{X3} can be hydrogen.

Embodiment 12

[0086] The compound of Embodiment 10, or a pharmaceutically acceptable salt thereof, wherein R^{X3} can be $-C_{1-4}$ alkyl or $-C_{1-4}$ haloalkyl.

Embodiment 13

[0087] The compound of Embodiment 10, or a pharmaceutically acceptable salt thereof, wherein R^{X3} can be $-C(=O)R^{Z3}$.

Embodiment 14

[0088] The compound of Embodiment 10, or a pharmaceutically acceptable salt thereof, wherein R^{X3} can be $-S(=O)_2R^{Z1}$.

Embodiment 15

[0089] The compound of Embodiment 10, or a pharmaceutically acceptable salt thereof, wherein R^{X3} can be $-C(=O)N(R^{Z1})R^{Z2}$.

Embodiment 16

[0090] The compound of Embodiment 10, or a pharmaceutically acceptable salt thereof, wherein R^{X3} can be $-S(=O)_2N(R^{Z1})R^{Z2}$.

Embodiment 17

[0091] The compound of any one of Embodiments 14-16, or a pharmaceutically acceptable salt thereof, wherein R^{Z1} can be hydrogen.

Embodiment 18

[0092] The compound of any one of Embodiments 14-16, or a pharmaceutically acceptable salt thereof, wherein R^{Z1} 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 19

[0093] The compound of any one of Embodiments 14-16, or a pharmaceutically acceptable salt thereof, wherein R^{Z1} can be $-C_{1-4}$ haloalkyl.

Embodiment 20

[0094] The compound of any one of Embodiments 15-19, or a pharmaceutically acceptable salt thereof, wherein R^{Z2} can be hydrogen.

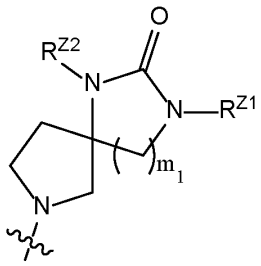
Embodiment 21

[0095] The compound of any one of Embodiments 15-19, or a pharmaceutically acceptable salt thereof, wherein R^{Z2} 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 22

[0096] The compound of any one of Embodiments 15-19, or a pharmaceutically acceptable salt thereof, wherein R^{Z2} can be $-C_{1-4}$ haloalkyl.

Embodiment 23

[0097] The compound of Embodiment 1 or 3, or a pharmaceutically acceptable salt thereof, wherein R^{1b} can be . In some embodiments, m_1 can be 1. In other embodiments, m_1 can be 2.

Embodiment 24

[0098] The compound of Embodiment 23, or a pharmaceutically acceptable salt thereof, wherein R^{Z1} can be hydrogen.

Embodiment 25

[0099] The compound of Embodiment 23, or a pharmaceutically acceptable salt thereof, wherein R^{Z1} 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 26

[0100] The compound of Embodiment 23, or a pharmaceutically acceptable salt thereof, wherein R^{Z1} can be $-C_{1-4}$ alkyl, wherein the $-C_{1-4}$ alkyl can be optionally substituted with one or two or three substituents independently selected from hydroxy and $-OR^{Z3}$. In some embodiments, R^{Z1} can be a substituted ethyl.

Embodiment 27

[0101] The compound of Embodiment 26, wherein R^{Z1} can be substituted with hydroxy.

Embodiment 28

[0102] The compound of Embodiment 26, wherein R^{Z1} can be substituted with $-OR^{Z3}$.

Embodiment 29

[0103] The compound of Embodiment 28, wherein R^{Z3} can be methyl.

Embodiment 30

[0104] The compound of Embodiment 23, or a pharmaceutically acceptable salt thereof, wherein R^{Z1} can be $-C_{1-4}$ haloalkyl.

Embodiment 31

[0105] The compound of any one of Embodiments 23-30, or a pharmaceutically acceptable salt thereof, wherein R^{Z2} can be hydrogen.

Embodiment 32

[0106] The compound of any one of Embodiments 23-30, or a pharmaceutically acceptable salt thereof, wherein R^{Z2} 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.

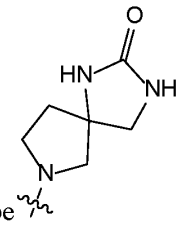
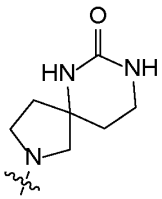
Embodiment 33

[0107] The compound of any one of Embodiments 23-30, or a pharmaceutically acceptable salt thereof, wherein R^{Z2} can be $-C_{1-4}$ alkyl, wherein the $-C_{1-4}$ alkyl can be optionally substituted with one or two or three substituents independently selected from hydroxy and $-OR^{Z3}$.

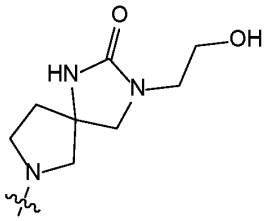
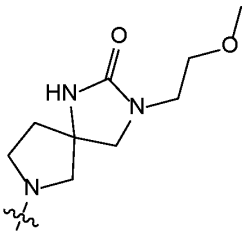
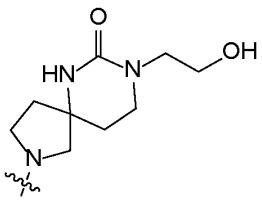
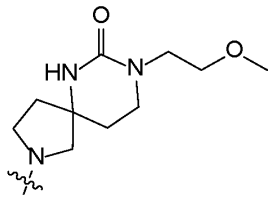
Embodiment 34

[0108] The compound of any one of Embodiments 23-30, or a pharmaceutically acceptable salt thereof, wherein R^{Z2} can be $-C_{1-4}$ haloalkyl.

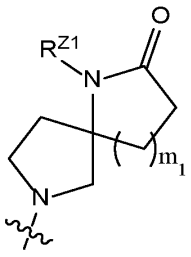
Embodiment 35

[0109] The compound of Embodiment 23, or a pharmaceutically acceptable salt thereof, wherein R^{1b} can be  or .

Embodiment 36

[0110] The compound of Embodiment 23, wherein R^{1b} can be  ,  ,  or  .

Embodiment 37

[0111] The compound of Embodiment 1 or 3, or a pharmaceutically acceptable salt thereof, wherein R^{1b} can be  . In some embodiments, m_1 can be 1. In other embodiments, m_1 can be 2.

Embodiment 38

[0112] The compound of Embodiment 37, or a pharmaceutically acceptable salt thereof, wherein R^{Z1} can be hydrogen.

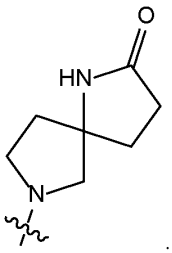
Embodiment 39

[0113] The compound of Embodiment 37, or a pharmaceutically acceptable salt thereof, wherein R^{Z1} 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 40

[0114] The compound of Embodiment 37, or a pharmaceutically acceptable salt thereof, wherein R^{Z1} can be $-C_{1-4}$ haloalkyl.

Embodiment 41

[0115] The compound of Embodiment 37, or a pharmaceutically acceptable salt thereof, wherein R^{1b} can be 

.

Embodiment 42

[0116] The compound of any one of Embodiments 1-41, or a pharmaceutically acceptable salt thereof, wherein X^1 can be N (nitrogen).

Embodiment 43

[0117] The compound of any one of Embodiments 1-42, 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 44

[0118] The compound of Embodiment 43, or a pharmaceutically acceptable salt thereof, wherein R^{1a} can be $-CH_3$.

Embodiment 45

[0119] The compound of any one of Embodiments 1-42, or a pharmaceutically acceptable salt thereof, wherein R^{1a} can be $-C_{1-4}$ haloalkyl.

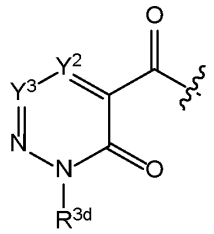
Embodiment 46

[0120] The compound of any one of Embodiments 1-42, or a pharmaceutically acceptable salt thereof, wherein R^{1a} can be $-CH_2$(C_{3-6} monocyclic cycloalkyl),$-CH_2$(4-6 membered monocyclic heterocyclyl) or $-CH_2$(5-6 membered monocyclic heteroaryl).

Embodiment 47

[0121] The compound of any one of Embodiments 1-42, or a pharmaceutically acceptable salt thereof, wherein R^{1a} can be $-C_{2-4}$ alkyl(OC_{1-4} alkyl) or $-C_{2-4}$ alkyl(OC_{1-4} haloalkyl).

Embodiment 48

[0122] The compound of any one of Embodiments 1-47, or a pharmaceutically acceptable salt thereof, wherein B^1 can be .

Embodiment 49

[0123] The compound of Embodiment 48, or a pharmaceutically acceptable salt thereof, wherein R^{3d} can be hydrogen.

Embodiment 50

[0124] The compound of Embodiment 48, or a pharmaceutically acceptable salt thereof, wherein R^{3d} can be $-CH_3$.

Embodiment 51

[0125] The compound of Embodiment 48, or a pharmaceutically acceptable salt thereof, wherein R^{3d} can be $-C_{2\text{-}4}$ alkyl.

Embodiment 52

[0126] The compound of Embodiment 48, or a pharmaceutically acceptable salt thereof, wherein R^{3d} can be $-C_{2\text{-}4}$ haloalkyl.

Embodiment 53

[0127] The compound of any one of Embodiments 48-52, or a pharmaceutically acceptable salt thereof, wherein Y^2 can be CR^{3e}, wherein R^{3e} can be hydrogen.

Embodiment 54

[0128] The compound of any one of Embodiments 48-52, or a pharmaceutically acceptable salt thereof, wherein Y^2 can be CR^{3e}, wherein R^{3e} can be halogen.

Embodiment 55

[0129] The compound of any one of Embodiments 48-52, or a pharmaceutically acceptable salt thereof, wherein Y^2 can be CR^{3e}, wherein R^{3e} can be $-CH_3$.

Embodiment 56

[0130] The compound of any one of Embodiments 48-55, or a pharmaceutically acceptable salt thereof, wherein Y^3 can be CR^{3f}, wherein R^{3f} can be hydrogen.

Embodiment 57

[0131] The compound of any one of Embodiments 48-55, or a pharmaceutically acceptable salt thereof, wherein Y^3 can be CR^{3f}, wherein R^{3f} can be halogen.

Embodiment 58

[0132] The compound of any one of Embodiments 48-55, or a pharmaceutically acceptable salt thereof, wherein Y^3 can be CR^{3f}, wherein R^{3f} can be –OH.

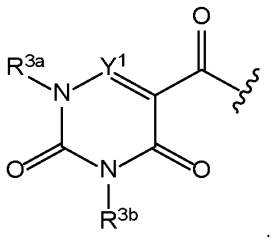
Embodiment 59

[0133] The compound of any one of Embodiments 48-55, or a pharmaceutically acceptable salt thereof, wherein Y^3 can be CR^{3f}, wherein R^{3f} can be –CN.

Embodiment 60

[0134] The compound of any one of Embodiments 48-55, or a pharmaceutically acceptable salt thereof, wherein Y^3 can be CR^{3f}, wherein R^{3f} can be $–CH_3$.

Embodiment 61

[0135] The compound of any one of Embodiments 1-47, or a pharmaceutically acceptable salt thereof, wherein B^1 can be 

.

Embodiment 62

[0136] The compound of Embodiment 61, or a pharmaceutically acceptable salt thereof, wherein Y^1 can be CR^{3c}, wherein R^{3c} can be hydrogen.

Embodiment 63

[0137] The compound of Embodiment 61, or a pharmaceutically acceptable salt thereof, wherein Y^1 can be CR^{3c}, wherein R^{3c} can be $–CH_3$.

Embodiment 64

[0138] The compound of Embodiment 61, or a pharmaceutically acceptable salt thereof, wherein Y^1 can be CR^{3c}, wherein R^{3c} can be $–C_{2\text{-}4}$ alkyl.

Embodiment 65

[0139] The compound of Embodiment 61, or a pharmaceutically acceptable salt thereof, wherein Y^1 can be CR^{3c}, wherein R^{3c} can be $–C_{2\text{-}4}$ haloalkyl.

Embodiment 66

[0140] The compound of any one of Embodiments 61-65, or a pharmaceutically acceptable salt thereof, wherein R^{3b} can be hydrogen.

Embodiment 67

[0141] The compound of any one of Embodiments 61-65, or a pharmaceutically acceptable salt thereof, wherein R^{3b} can be $-CH_3$.

Embodiment 68

[0142] The compound of any one of Embodiments 61-65, or a pharmaceutically acceptable salt thereof, wherein R^{3b} can be $-C_{2-4}$ alkyl.

Embodiment 69

[0143] The compound of any one of Embodiments 61-65, or a pharmaceutically acceptable salt thereof, wherein R^{3b} can be $-C_{2-4}$ haloalkyl.

Embodiment 70

[0144] The compound of any one of Embodiments 61-69, or a pharmaceutically acceptable salt thereof, wherein R^{3a} can be hydrogen.

Embodiment 71

[0145] The compound of any one of Embodiments 61-69, or a pharmaceutically acceptable salt thereof, wherein R^{3a} can be $-CH_3$.

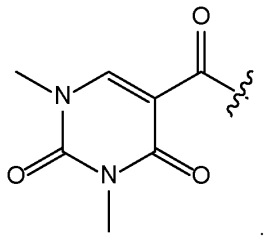
Embodiment 72

[0146] The compound of any one of Embodiments 61-69, or a pharmaceutically acceptable salt thereof, wherein R^{3a} can be–C_{2-4} alkyl optionally substituted with one or two or three substituents independently selected from hydroxy and $-OR^{3a1}$. Examples of C_{2-4} alkyls include ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl and tert-butyl. In some embodiments, R^{3a} can be $-C_{2-4}$ alkyl substituted with hydroxy. In other embodiments, R^{3a} can be $-C_{2-4}$ alkyl substituted with $-OR^{3a1}$. For example, R^{3a} can be $-C_{2-4}$ alkyl substituted with $-OCH_3$.

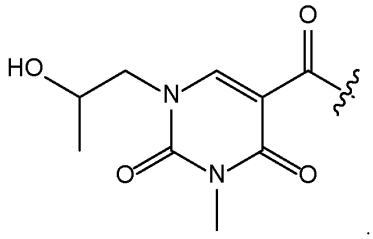
Embodiment 73

[0147] The compound of any one of Embodiments 61-69, or a pharmaceutically acceptable salt thereof, wherein R^{3a} can be $-C_{2-4}$ haloalkyl.

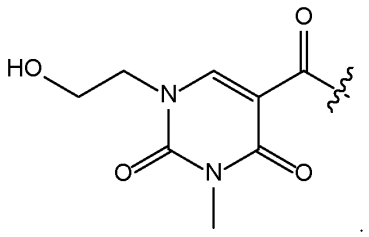
Embodiment 74

[0148] The compound of Embodiments 61, or a pharmaceutically acceptable salt thereof, wherein B^1 can be .

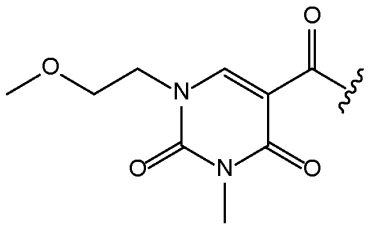
Embodiment 75

[0149] The compound of Embodiment 61, or a pharmaceutically acceptable salt thereof, wherein B^1 can be .

Embodiment 76

[0150] The compound of Embodiment 61, or a pharmaceutically acceptable salt thereof, wherein B^1 can be .

Embodiment 77

[0151] The compound of Embodiment 61, or a pharmaceutically acceptable salt thereof, wherein B^1 can be .

Embodiment 78

[0152] The compound of any one of Embodiments 1-77, or a pharmaceutically acceptable salt thereof, wherein R^{2a}, R^{2b}, R^{2g} and R^{2h} each can be hydrogen.

Embodiment 79

[0153] The compound of any one of Embodiments 1-78, or a pharmaceutically acceptable salt thereof, wherein R^{2d} and R^{2f} each can be halogen.

Embodiment 80

[0154] The compound of any one of Embodiments 1-78, or a pharmaceutically acceptable salt thereof, wherein R^{2d} can be $-CH_3$ and R^{2f} can be halogen.

Embodiment 81

[0155] The compound of Embodiment 79 or 80, or a pharmaceutically acceptable salt thereof, wherein the halogen can be chloro.

Embodiment 82

[0156] The compound of any one of Embodiments 1-81, or a pharmaceutically acceptable salt thereof, wherein R^{2c} and R^{2e} each can be hydrogen.

Embodiment 83

[0157] The compound of any one of Embodiments 1-81, or a pharmaceutically acceptable salt thereof, wherein R^{2c} can be halogen and R^{2e} can be hydrogen.

Embodiment 84

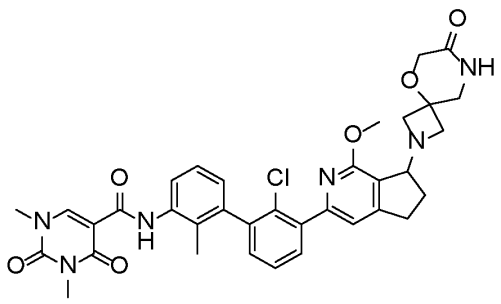
[0158] The compound of any one of Embodiments 1-81, or a pharmaceutically acceptable salt thereof, wherein R^{2e} can be halogen and R^{2c} can be hydrogen.

Embodiment 85

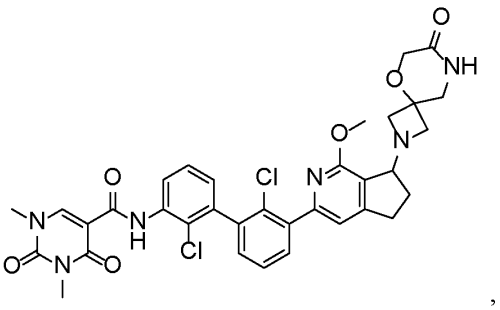
[0159] The compound of Embodiment 83 or 84, or a pharmaceutically acceptable salt thereof, wherein the halogen can be fluoro.

Embodiment 86

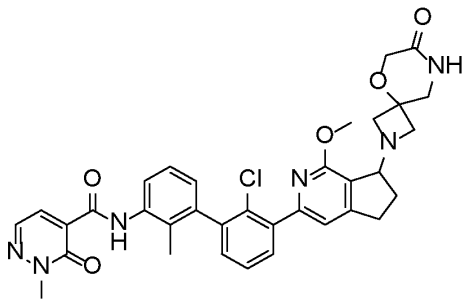
[0160] The compound of Embodiment 2, wherein the compound can be selected from:



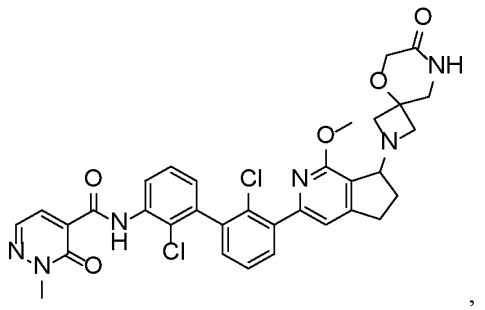
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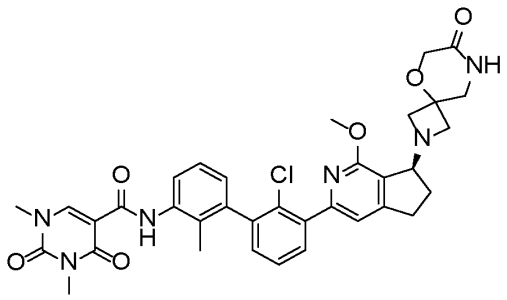
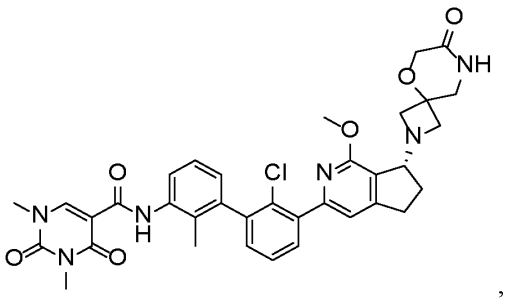
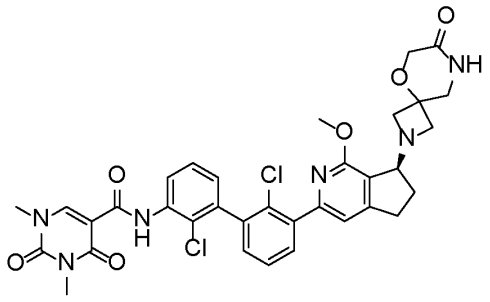
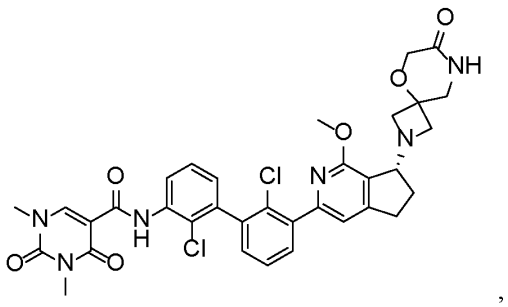
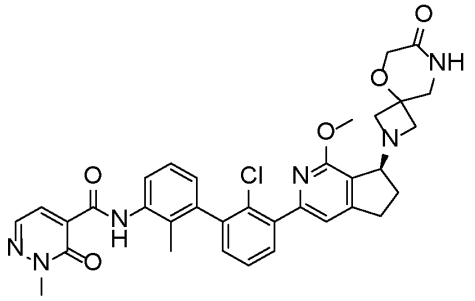
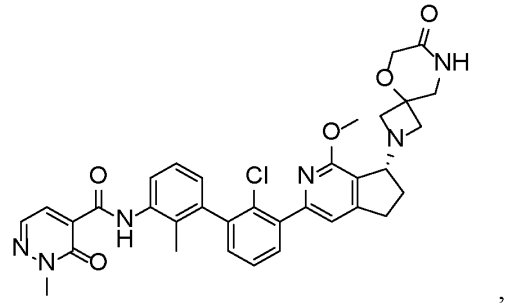
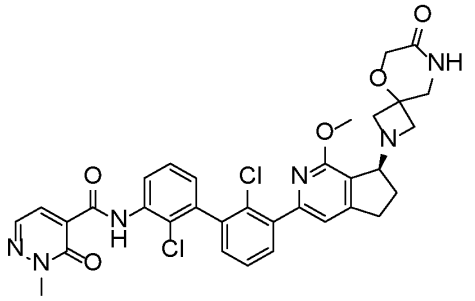
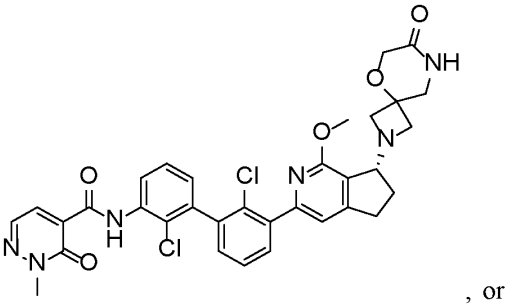
and



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

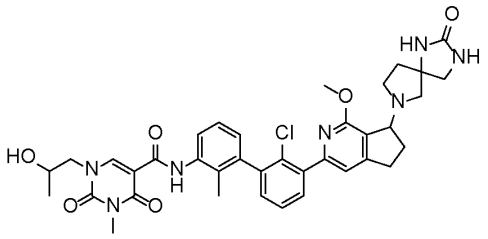
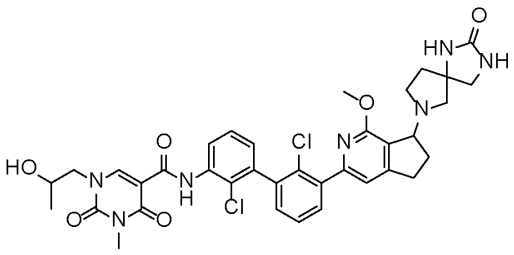
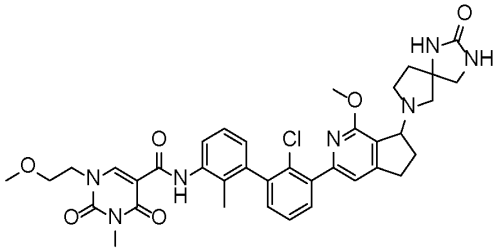
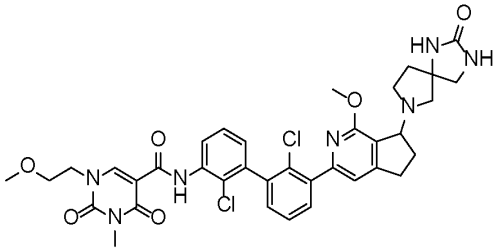
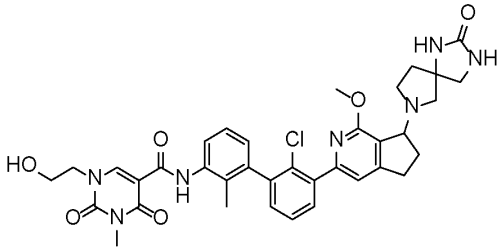
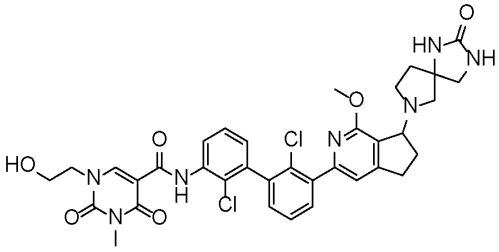
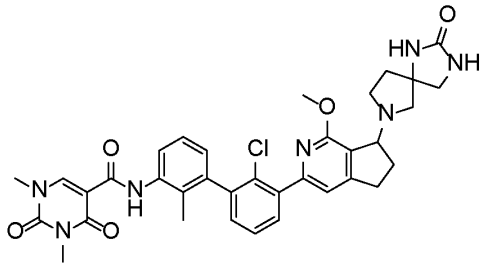
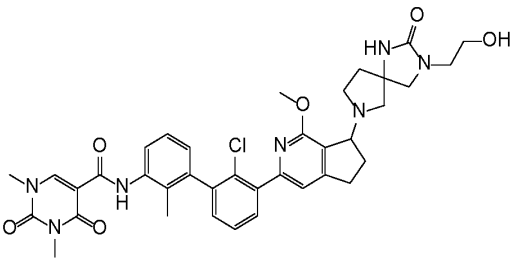
Embodiment 87

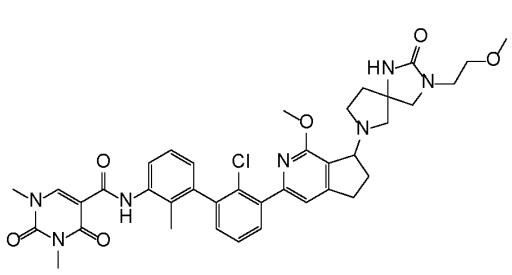
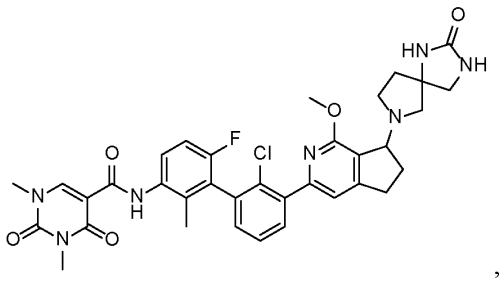
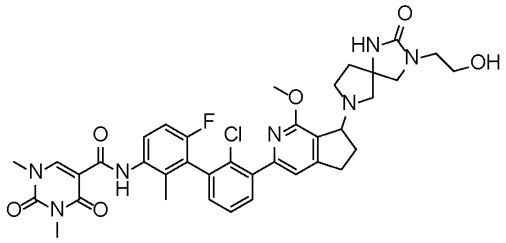
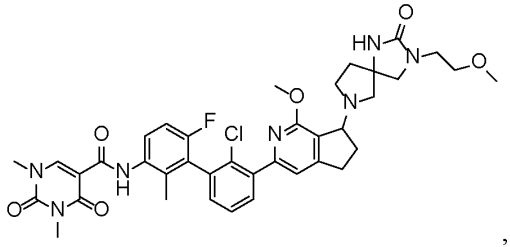
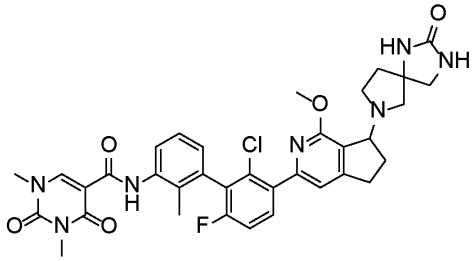
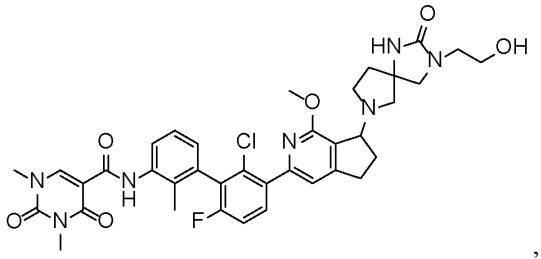
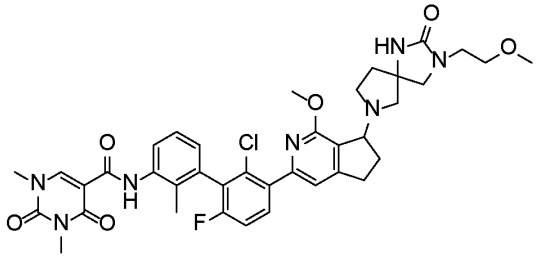
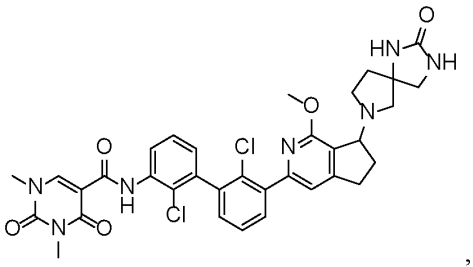
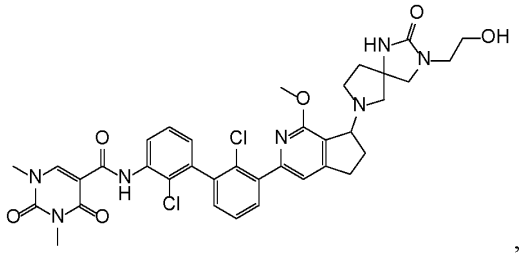
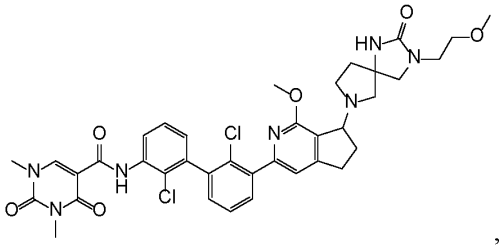
[0161] The compound of Embodiment 2, wherein the compound can be selected from:

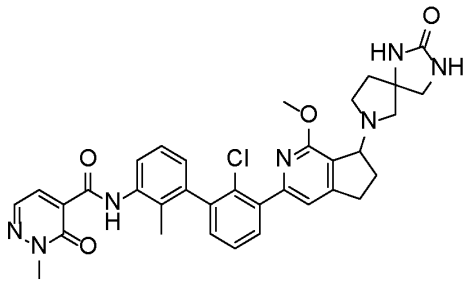
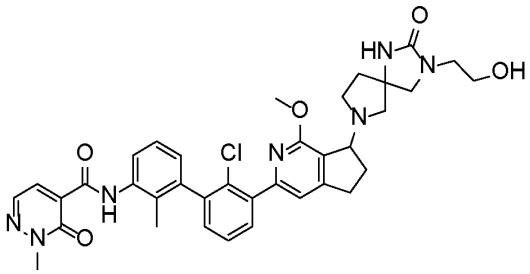
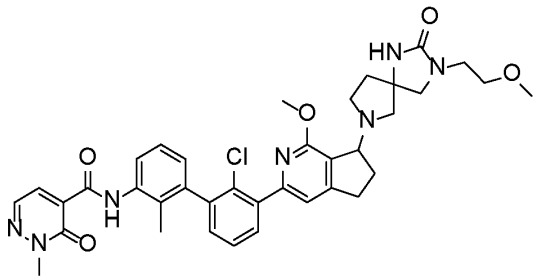
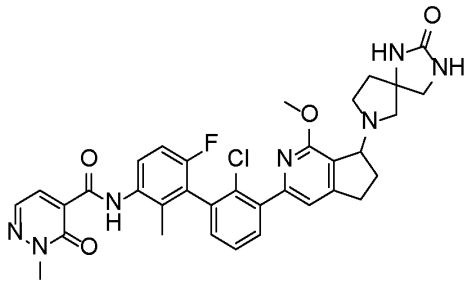
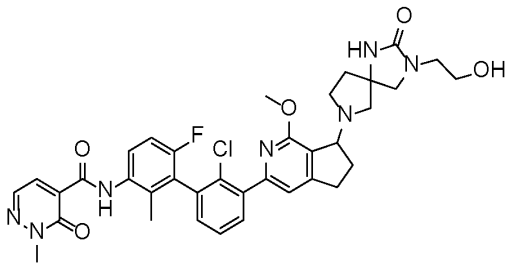
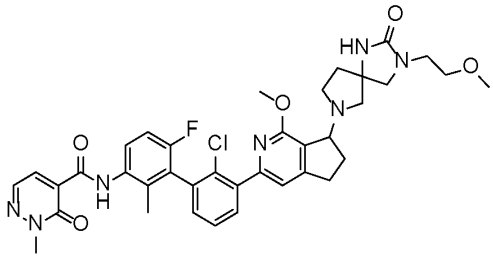
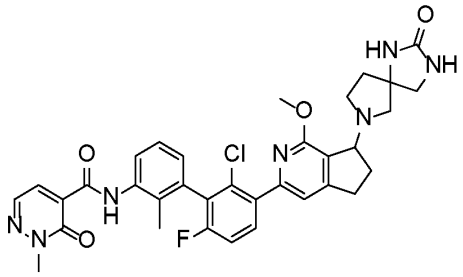
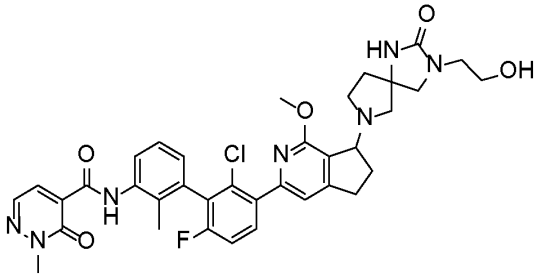
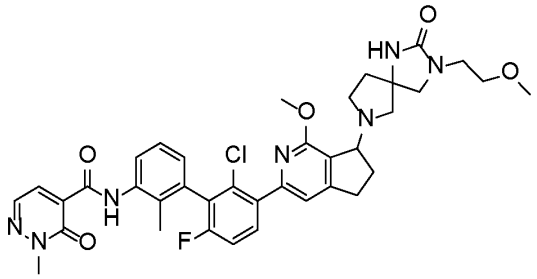
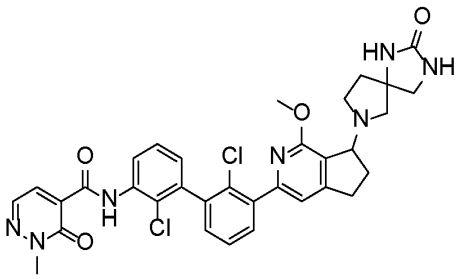

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, or a pharmaceutically acceptable salt of any of the foregoing.

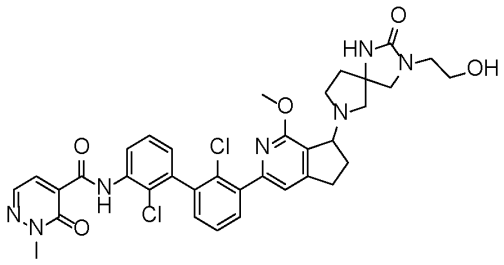
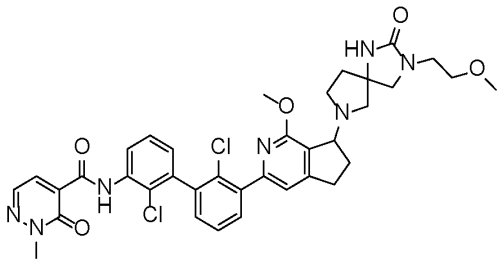
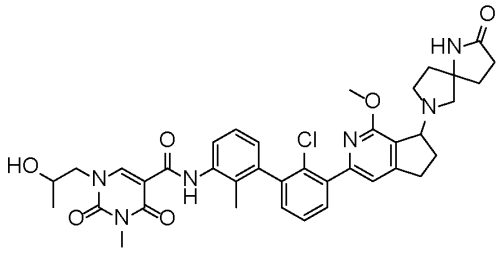
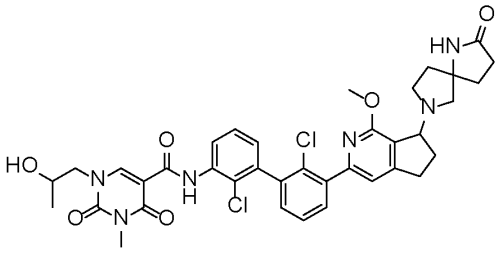
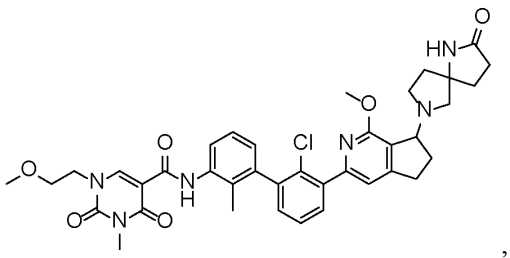
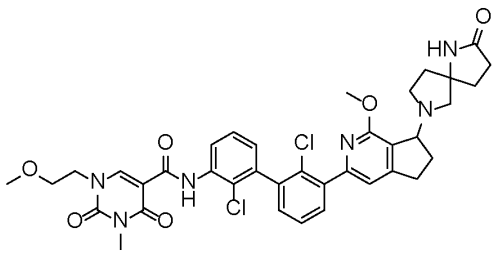
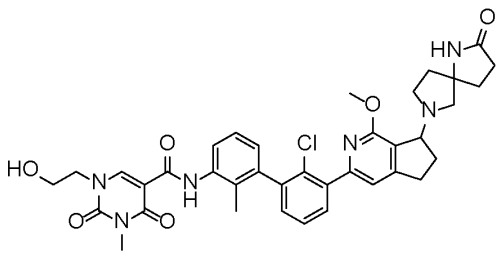
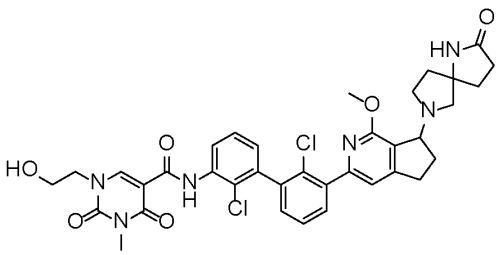
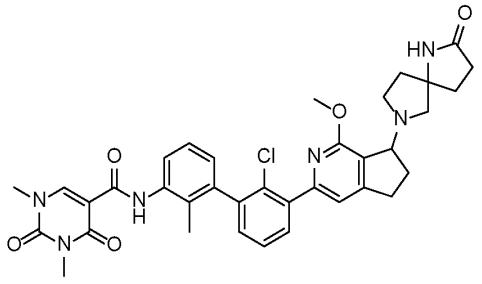
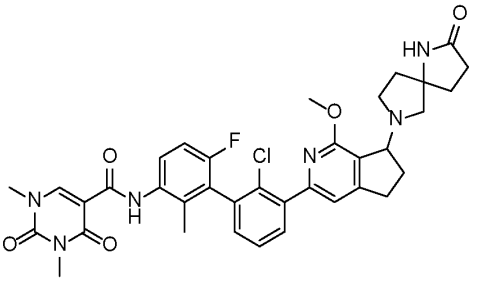
Embodiment 88

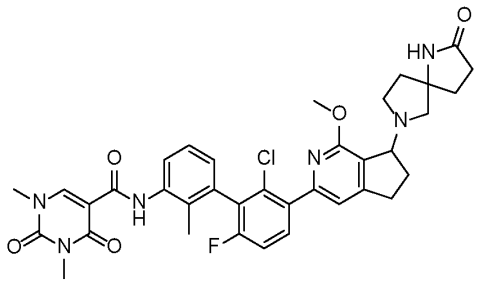
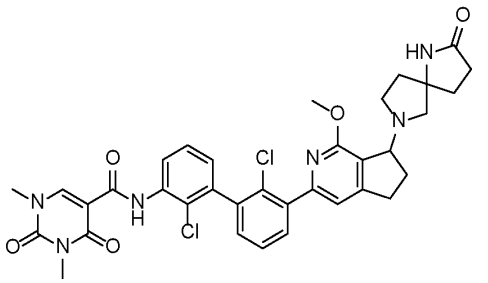
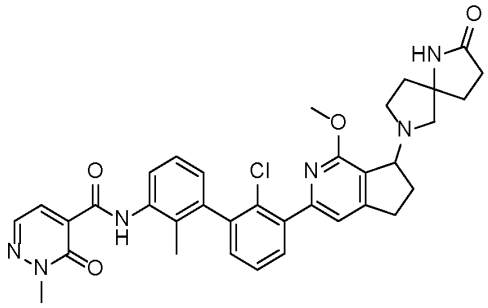
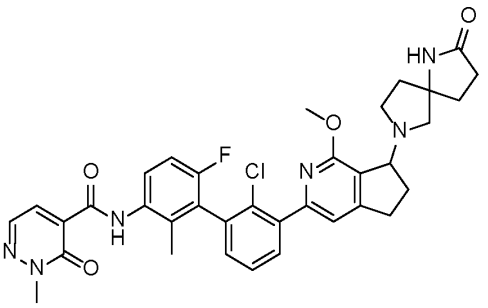
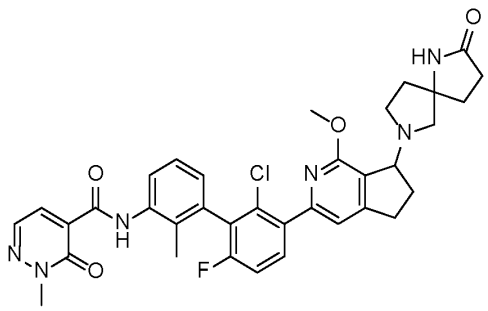
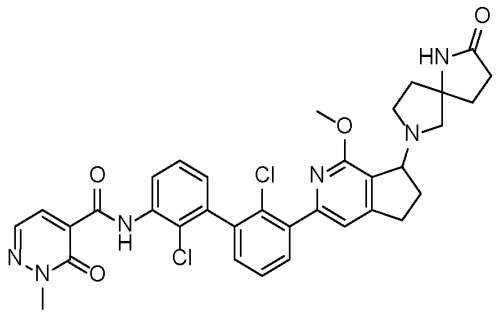
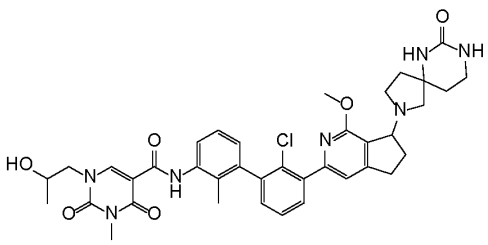
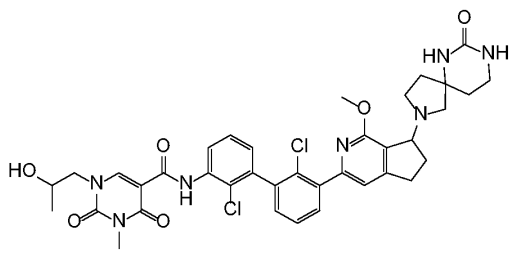
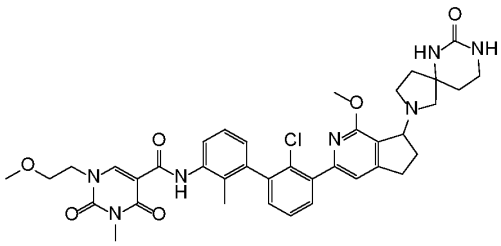
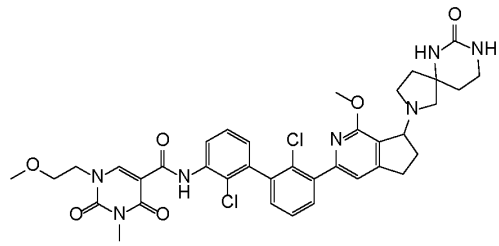
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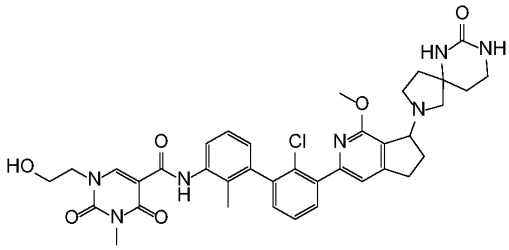
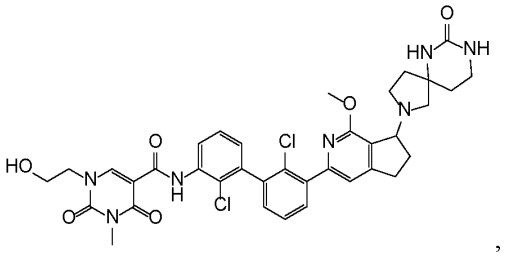
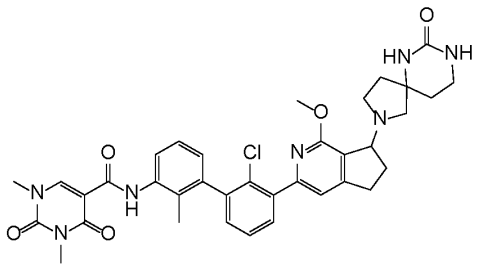
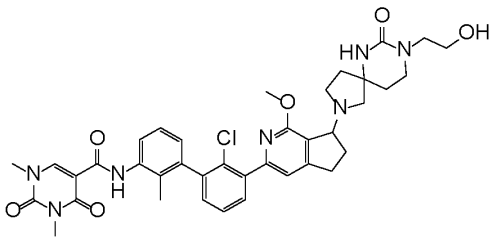
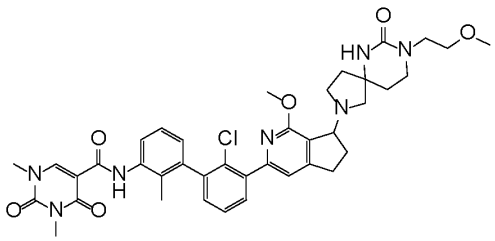
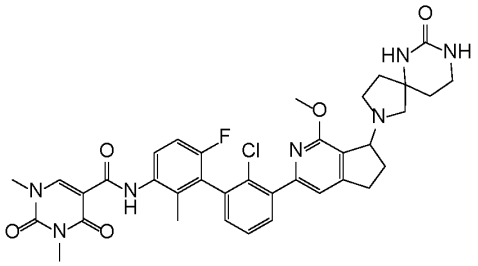
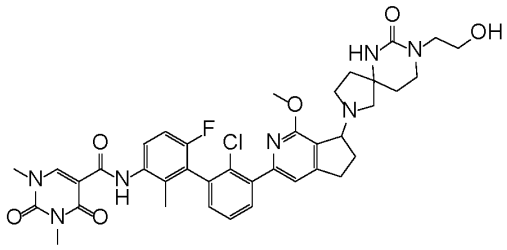
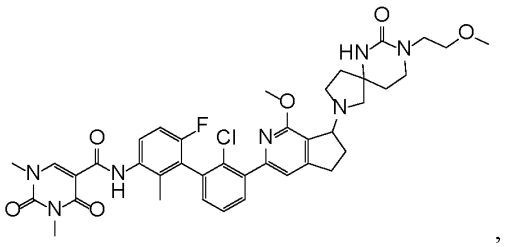
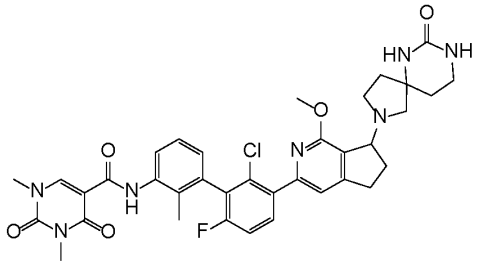
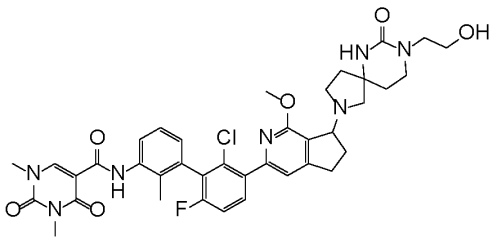

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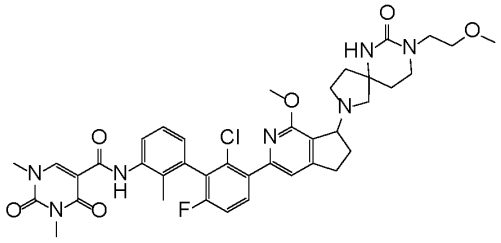
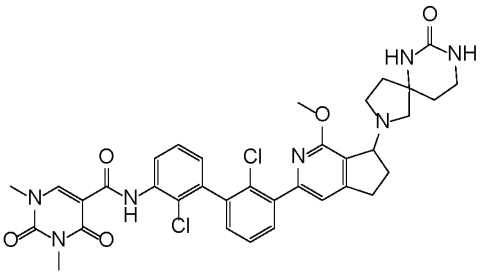
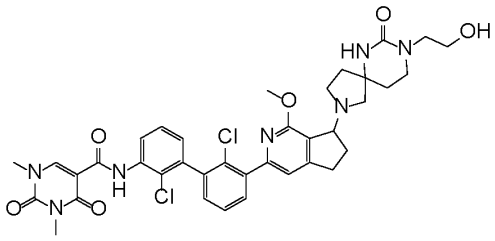
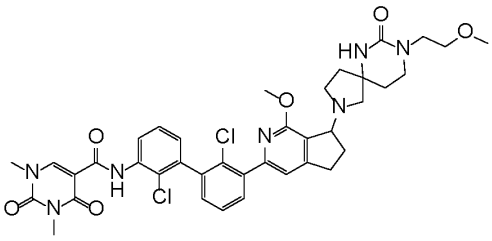
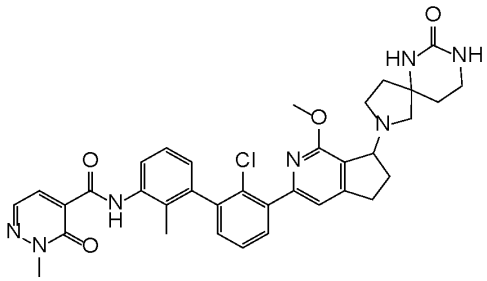
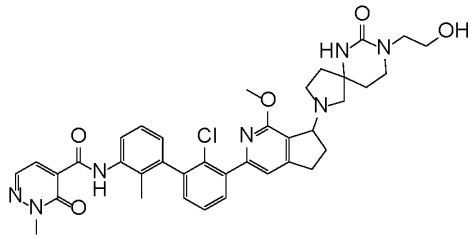
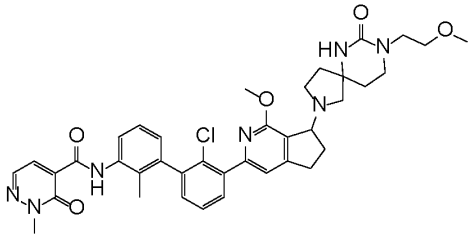
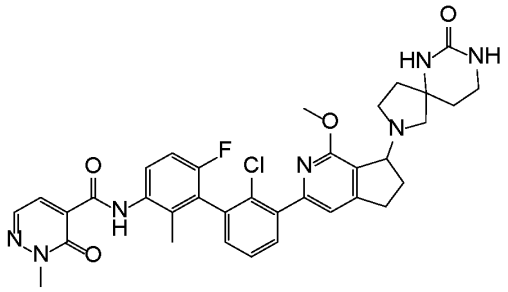
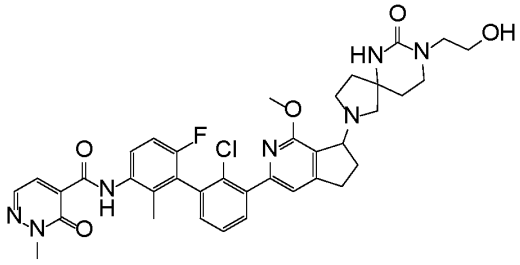
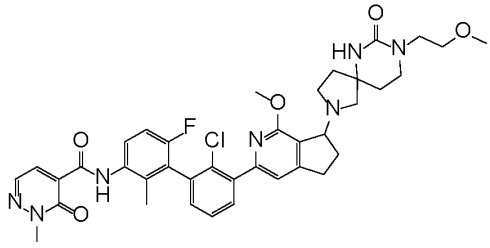

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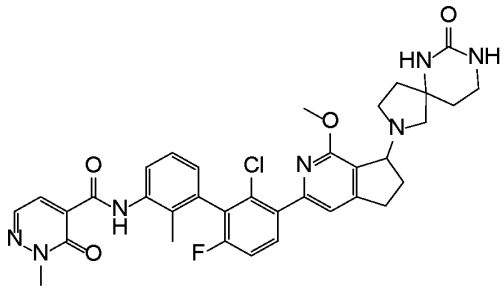
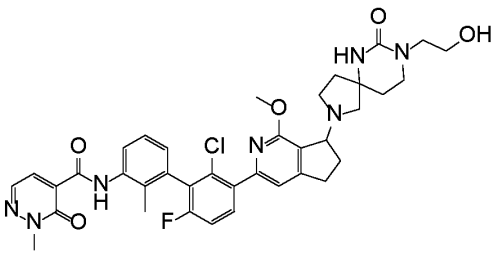
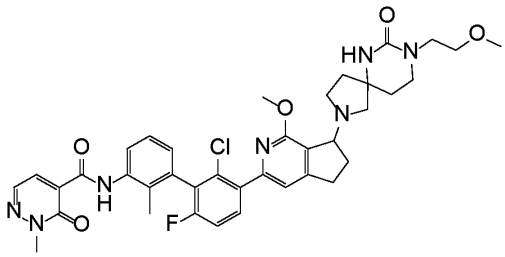
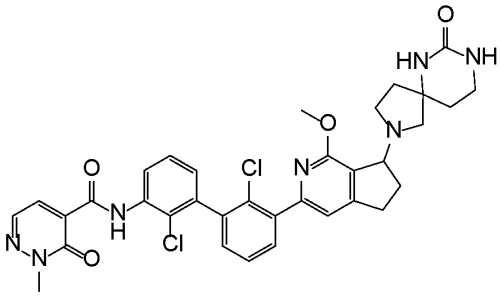
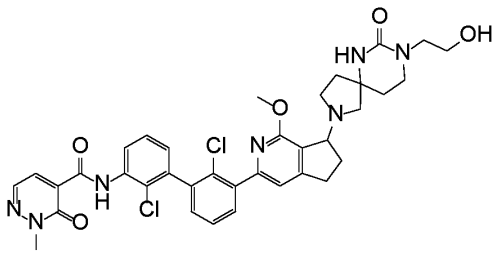
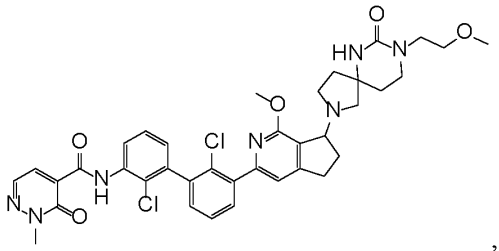

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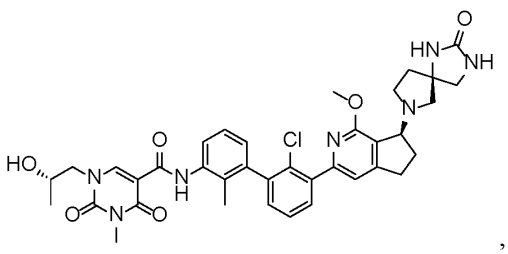
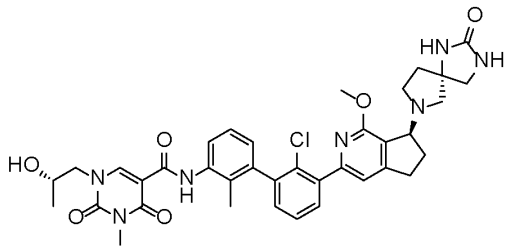
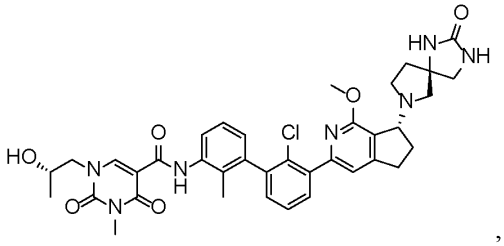
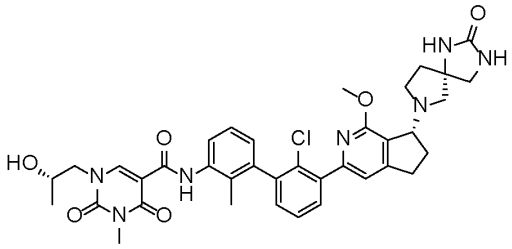
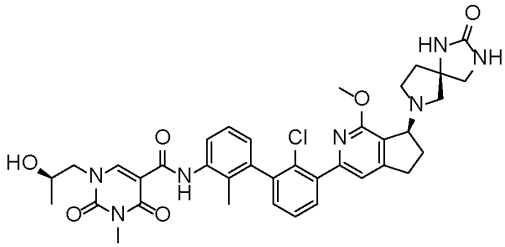
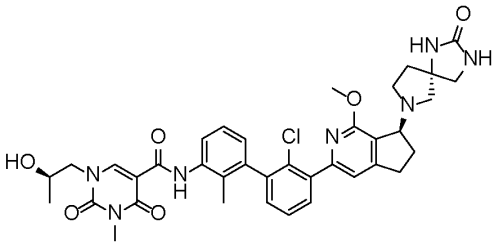
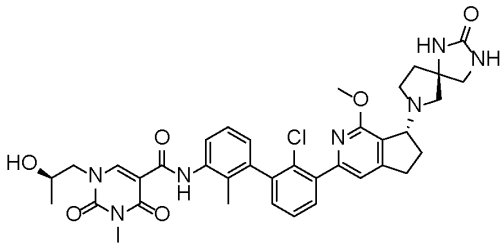
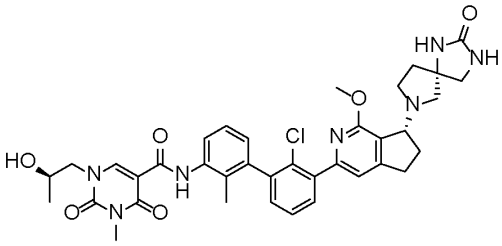
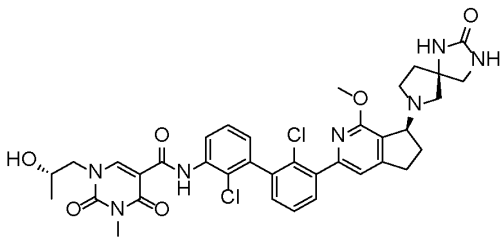
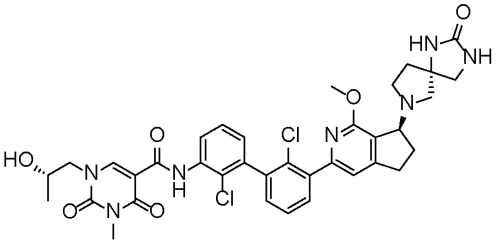

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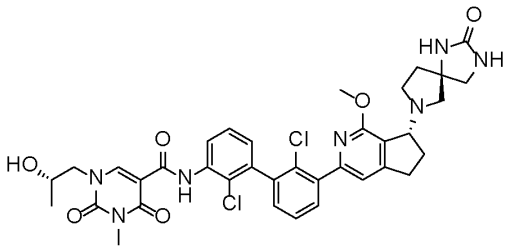
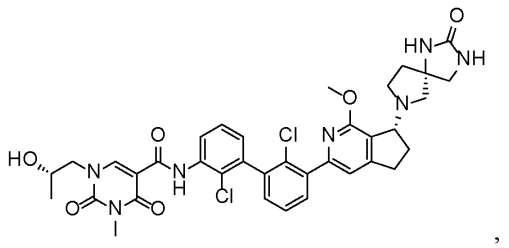
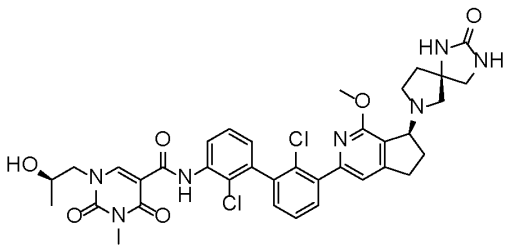
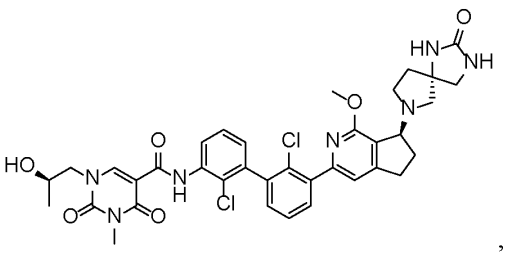
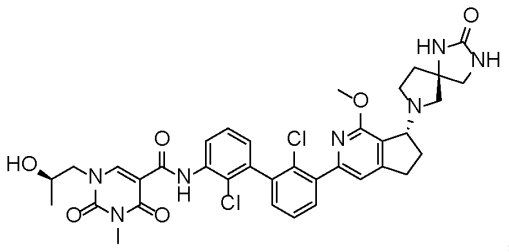
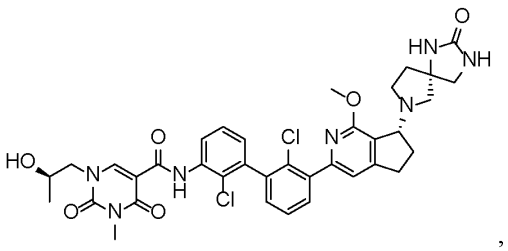
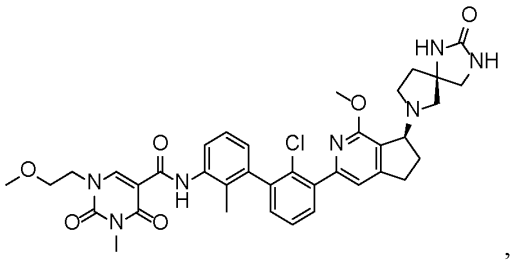
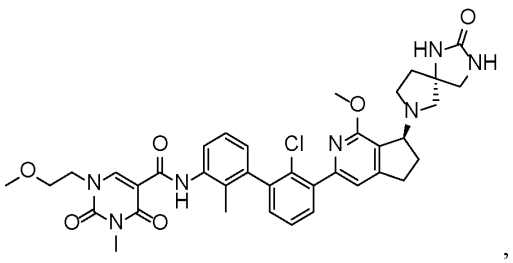
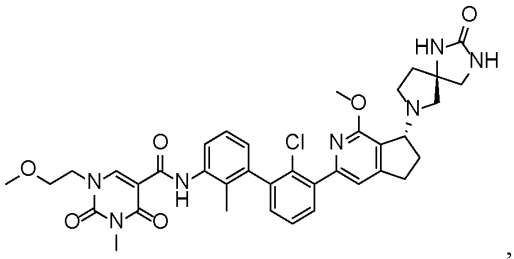
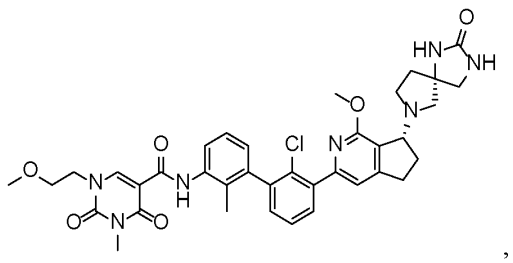

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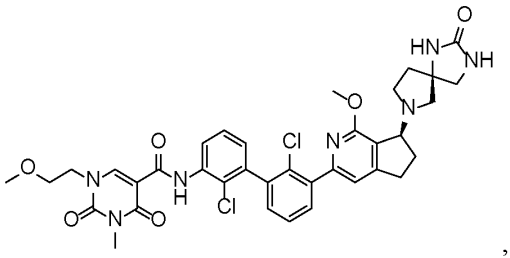
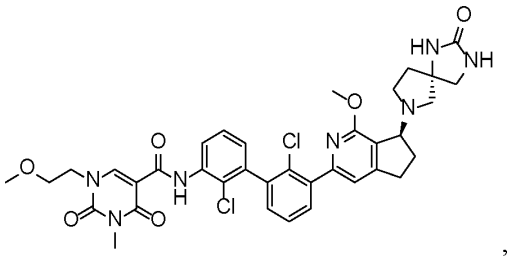
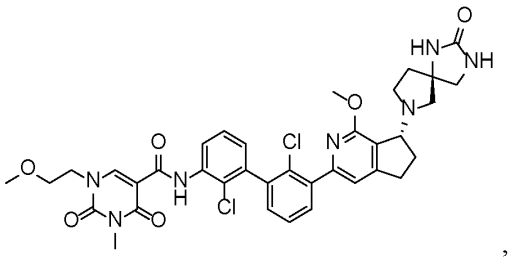
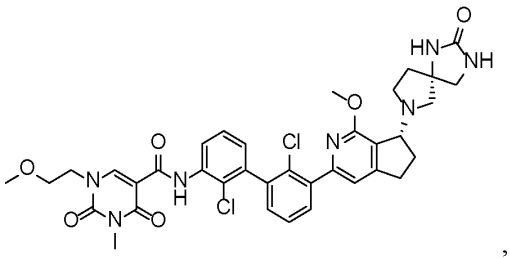
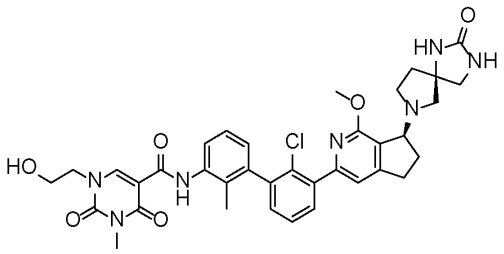
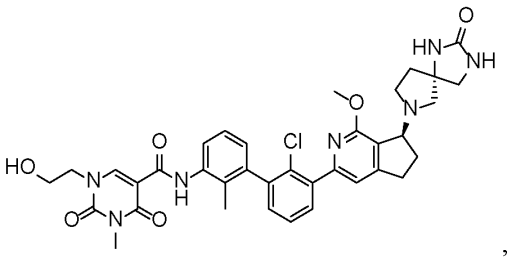
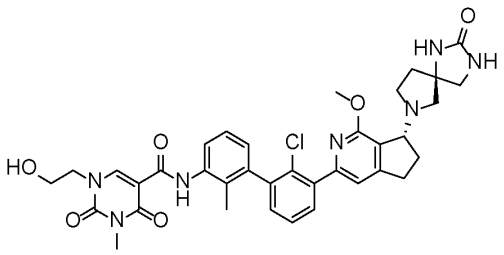
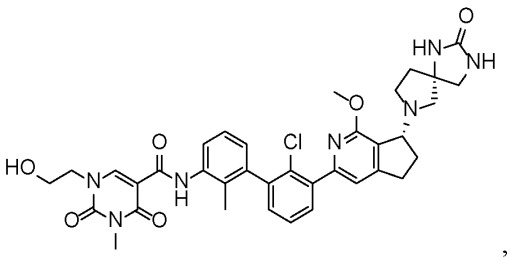
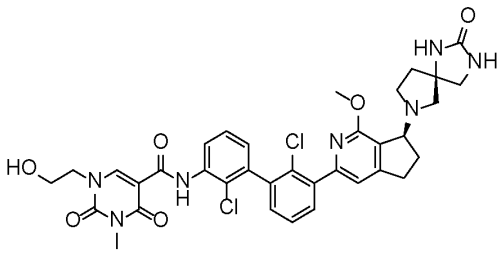
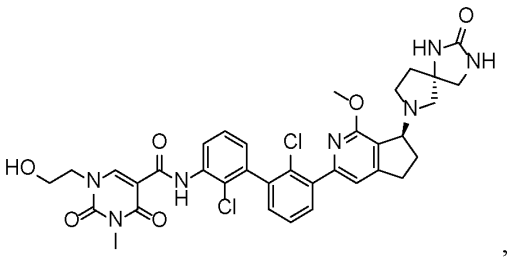

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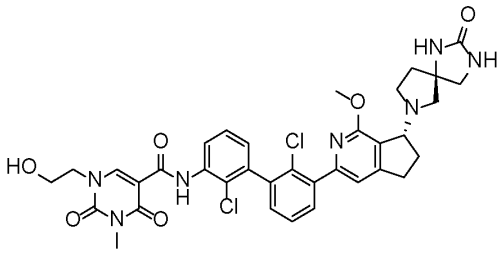
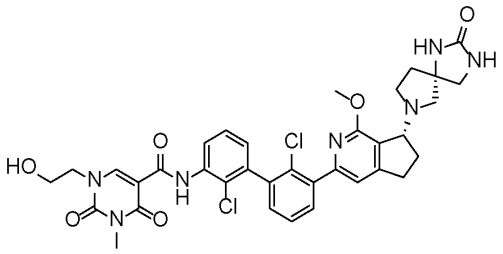
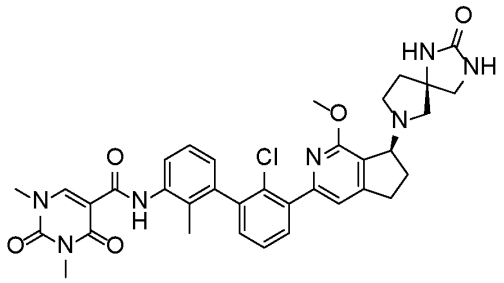
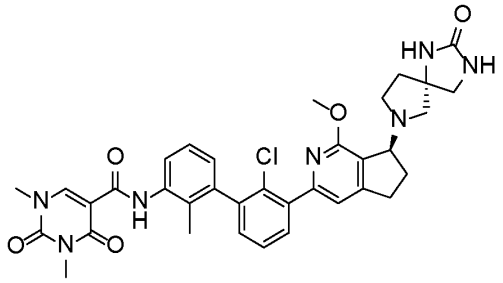
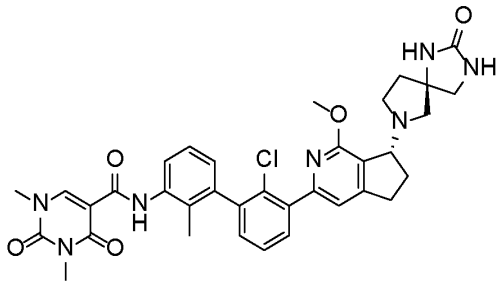
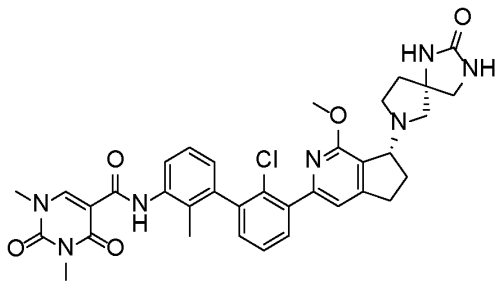
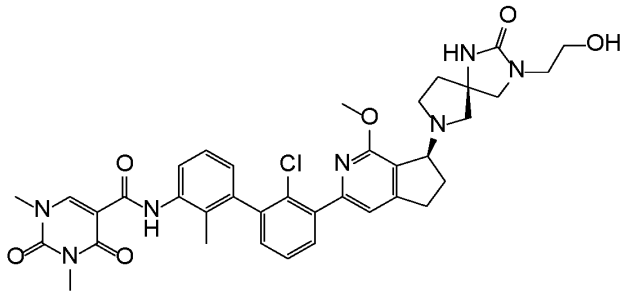
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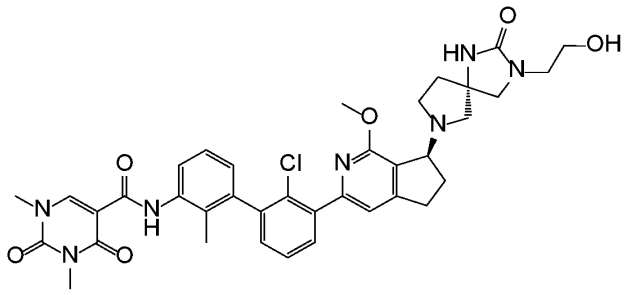
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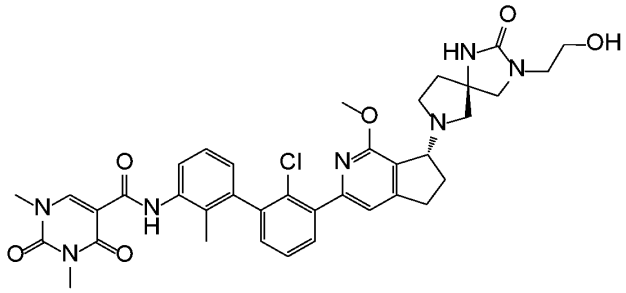

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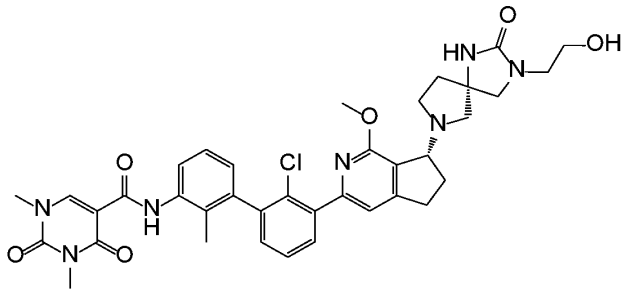

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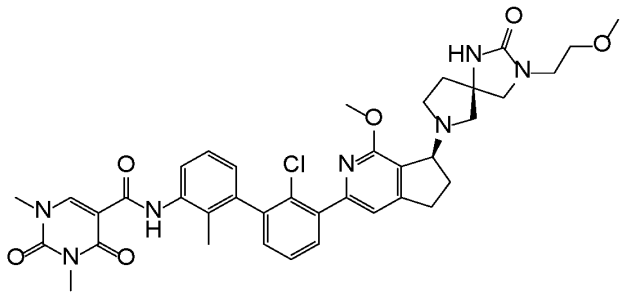
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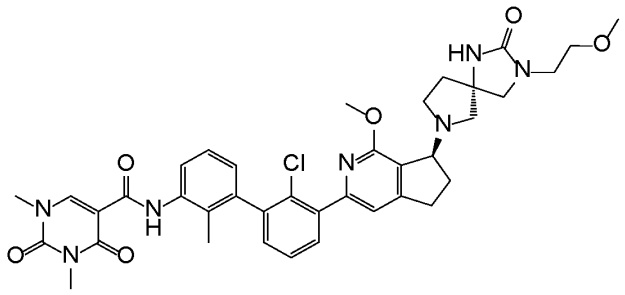
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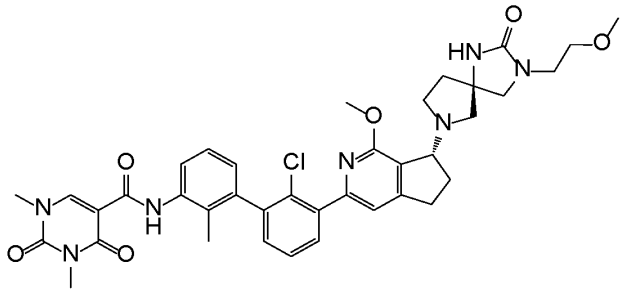
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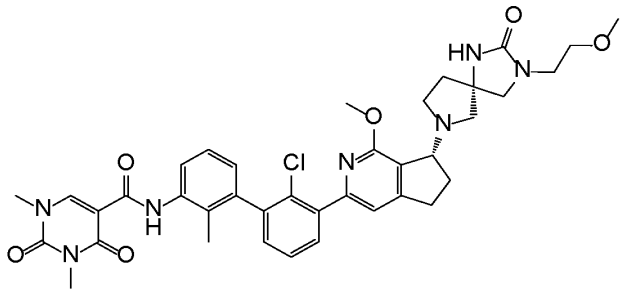
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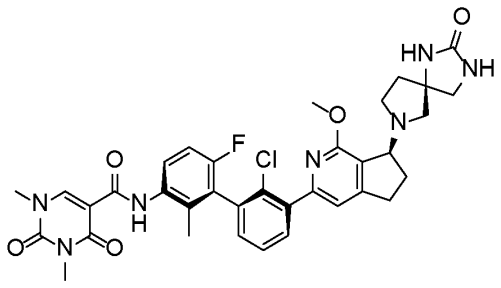
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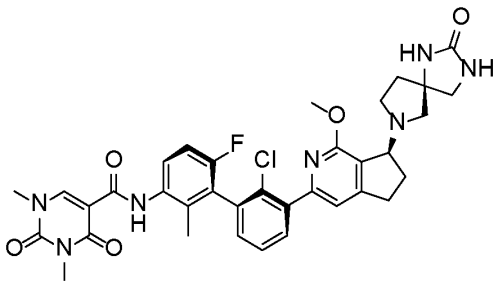
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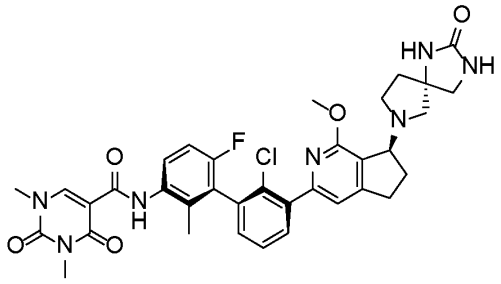
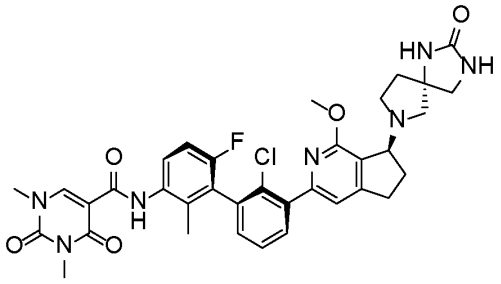
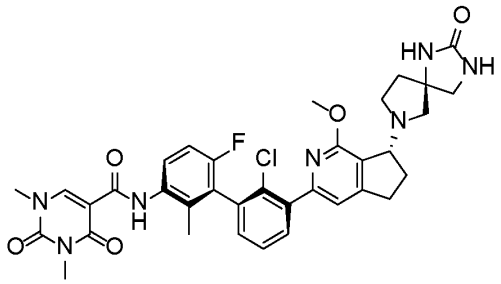
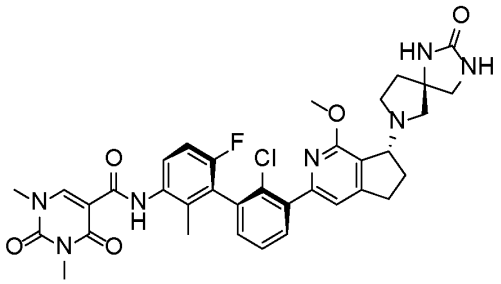
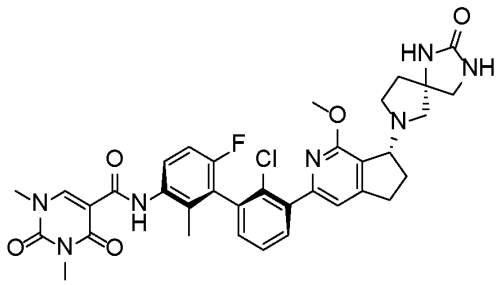
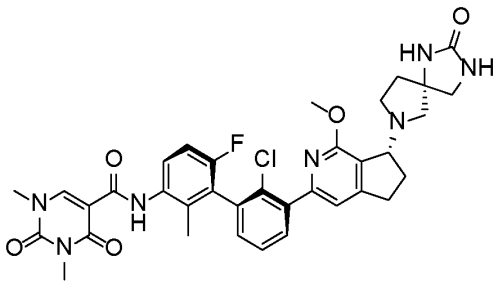
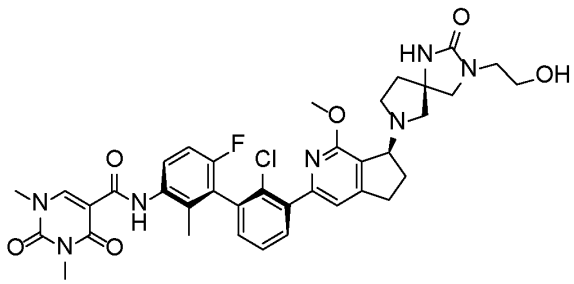
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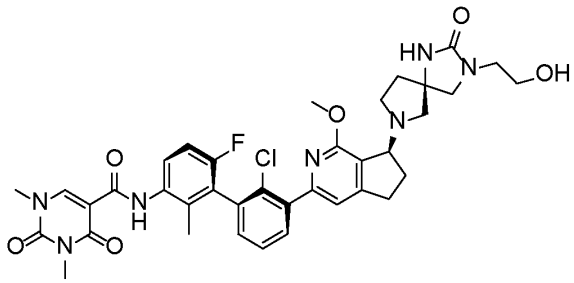


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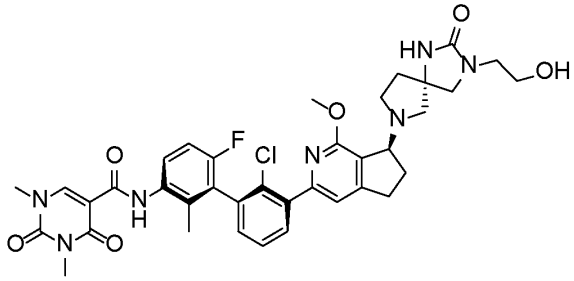


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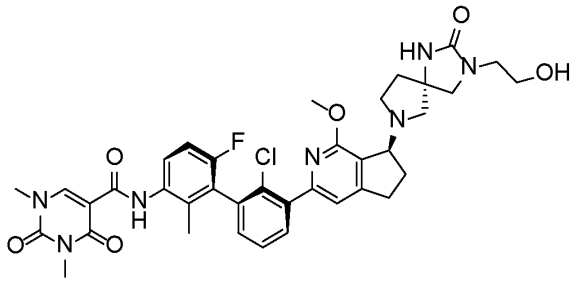

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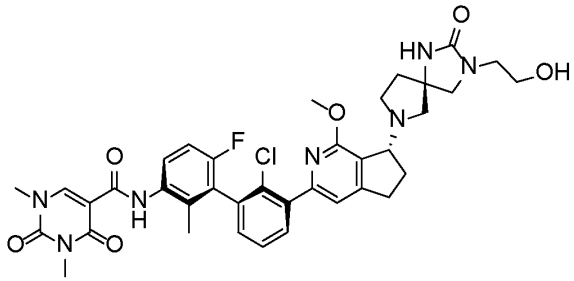
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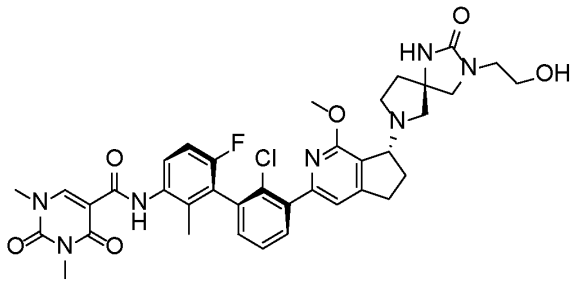
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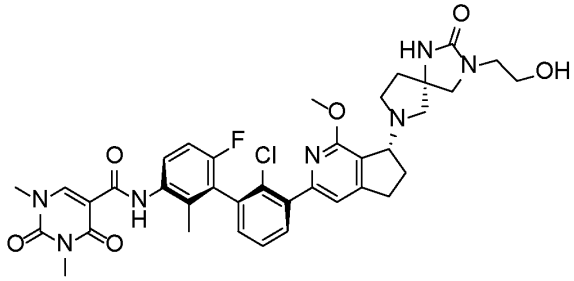
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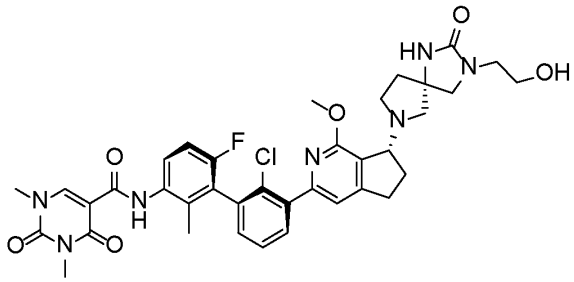
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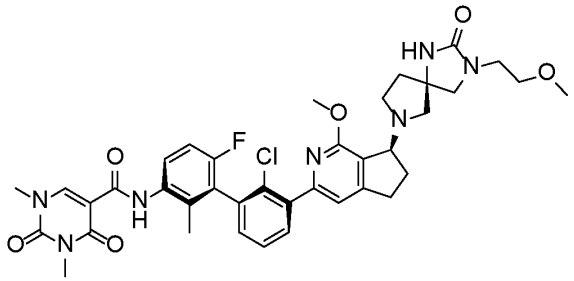
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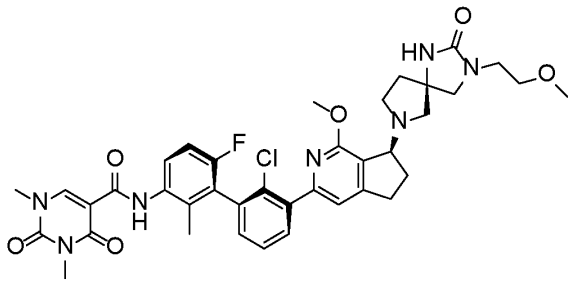
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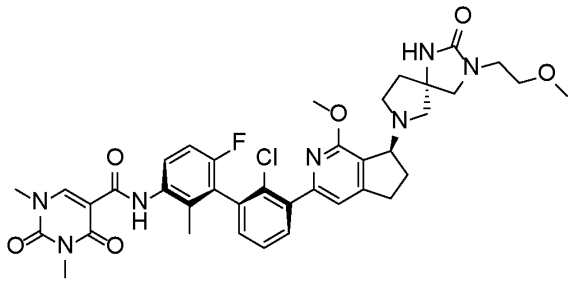
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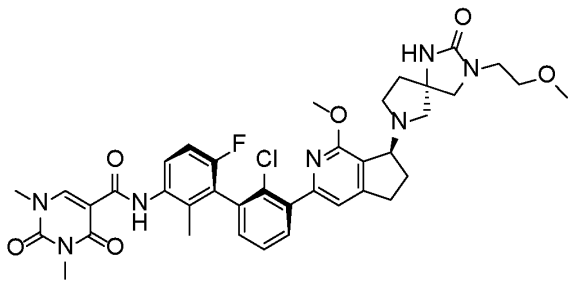
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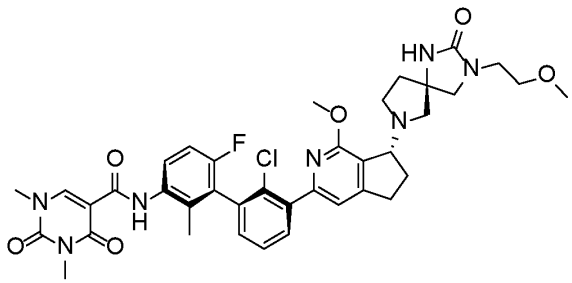
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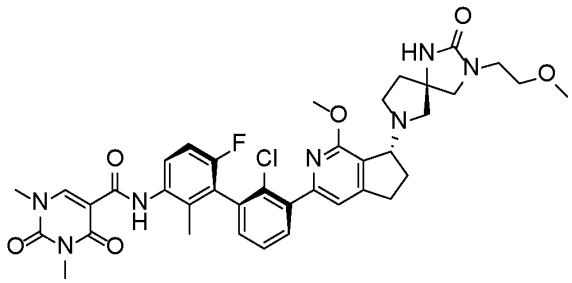
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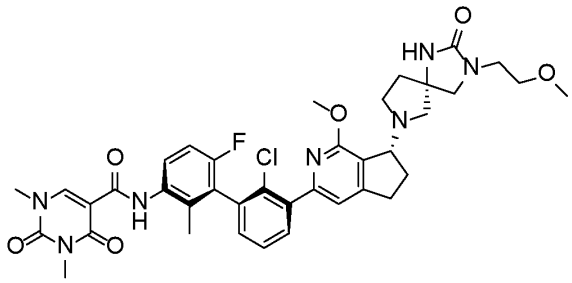


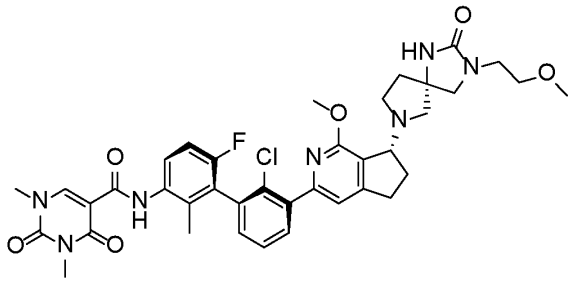
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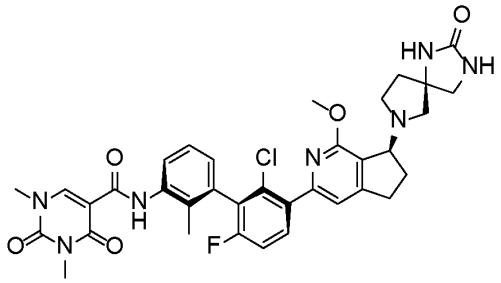


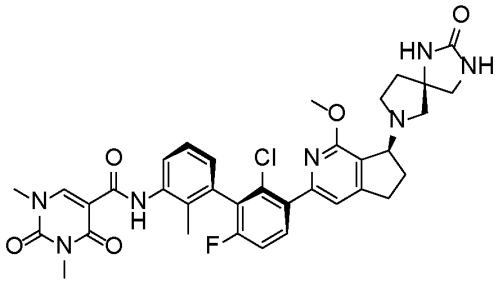
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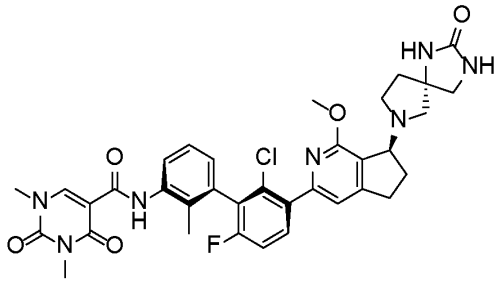
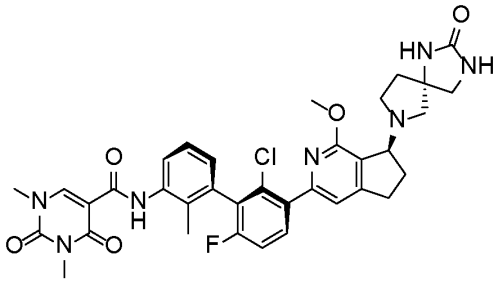
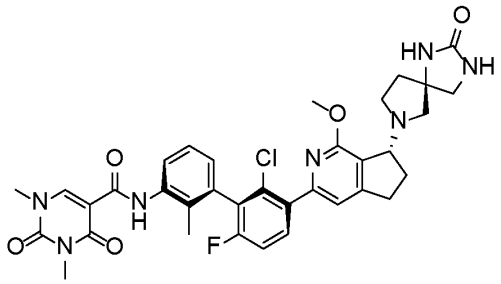
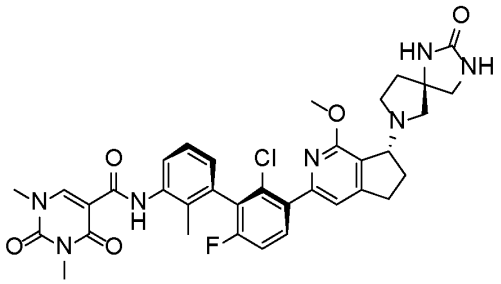
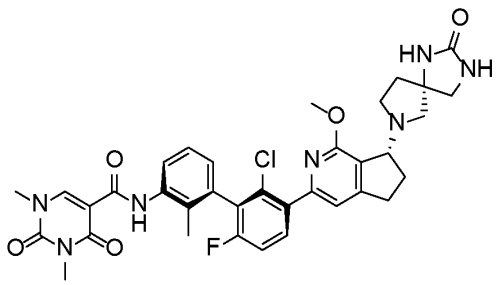
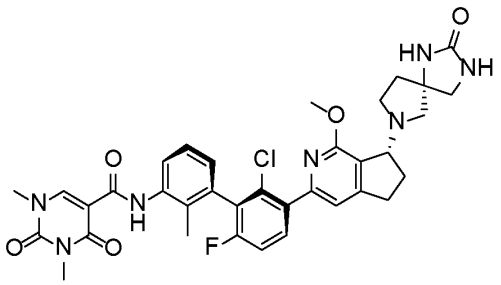
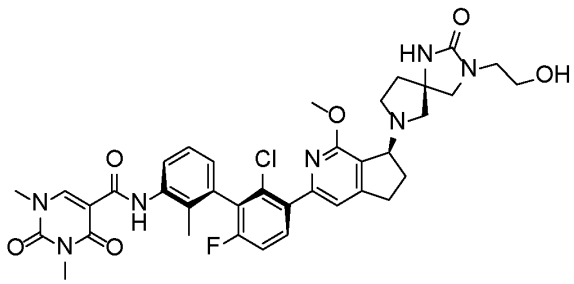

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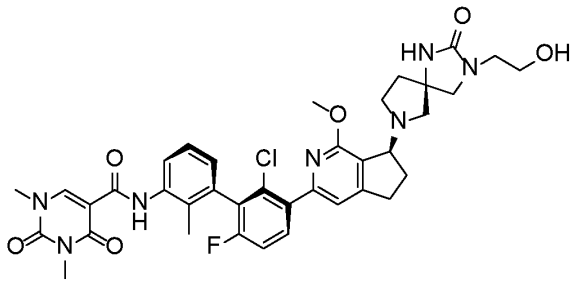

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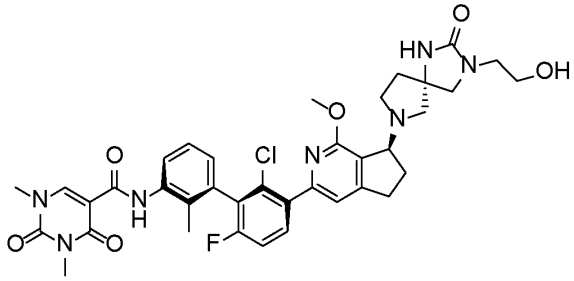

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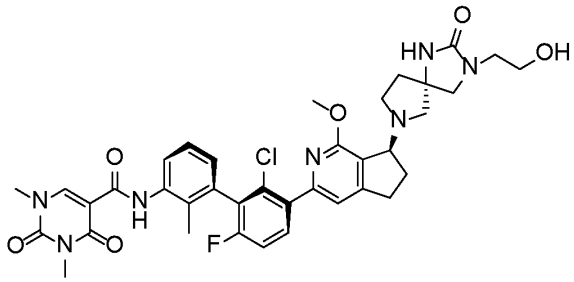

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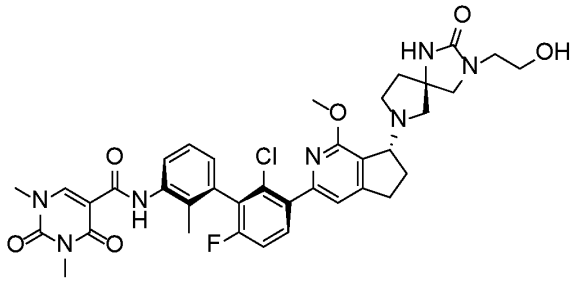
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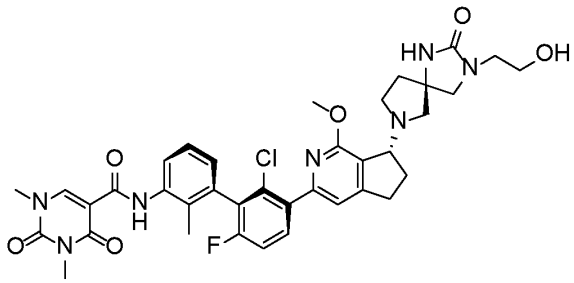
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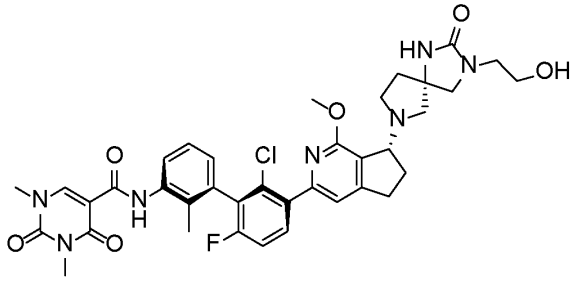
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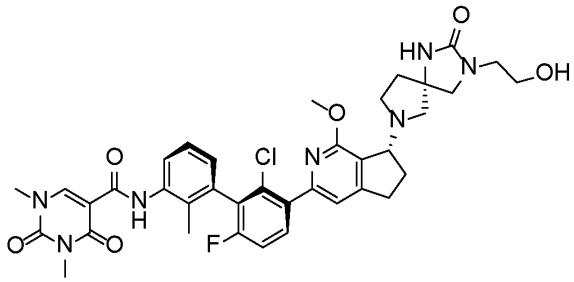
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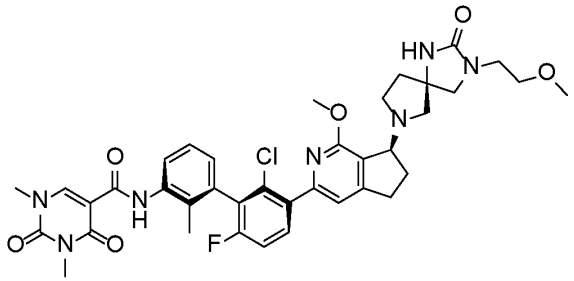
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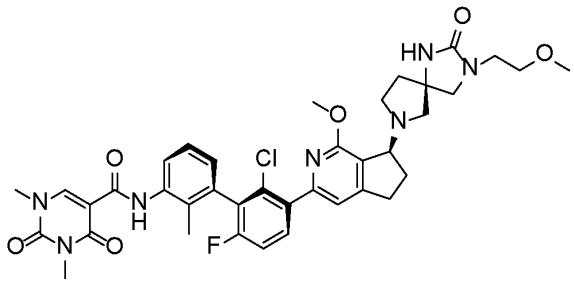
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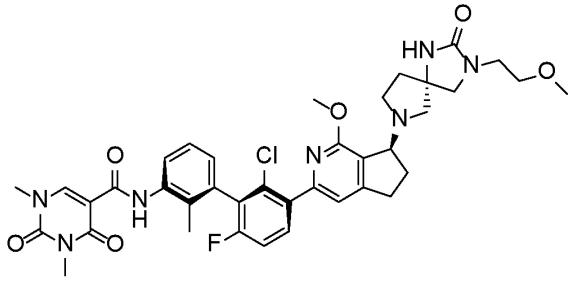
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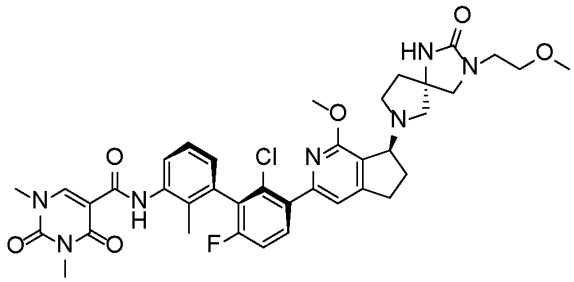
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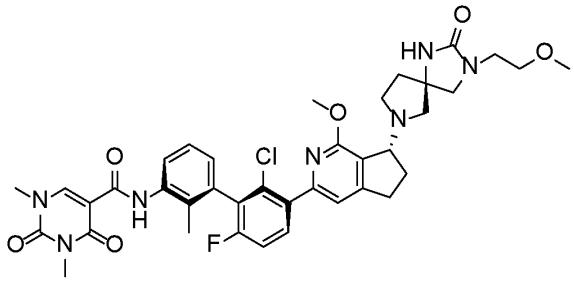
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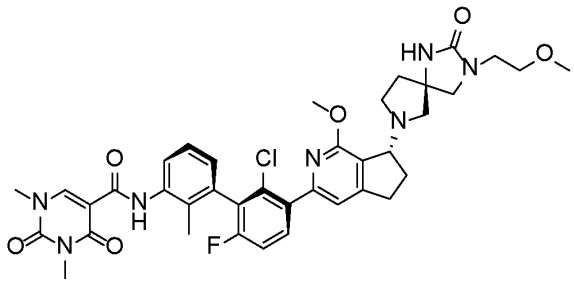
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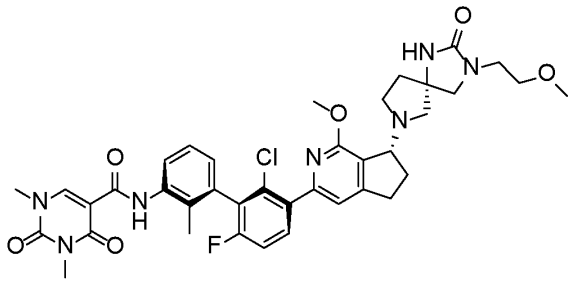
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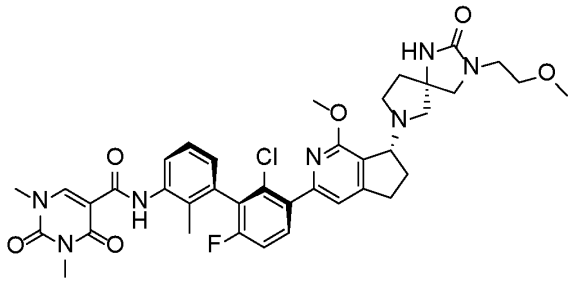
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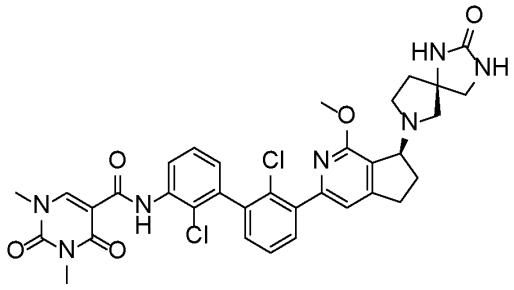
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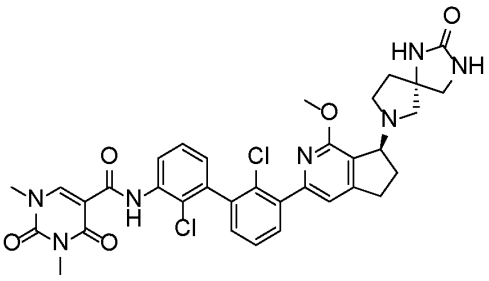
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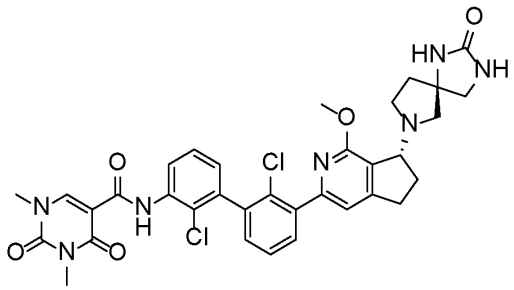
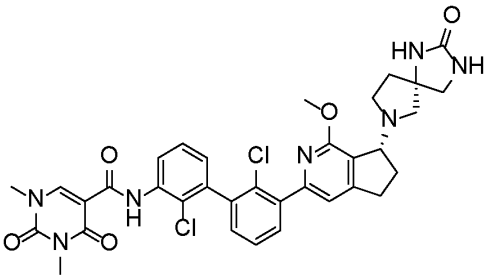
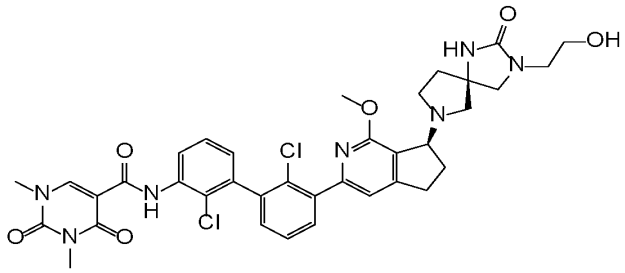
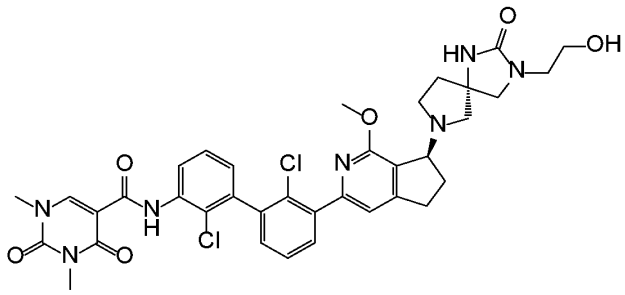
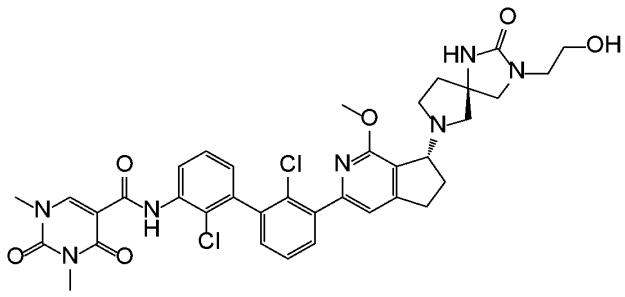
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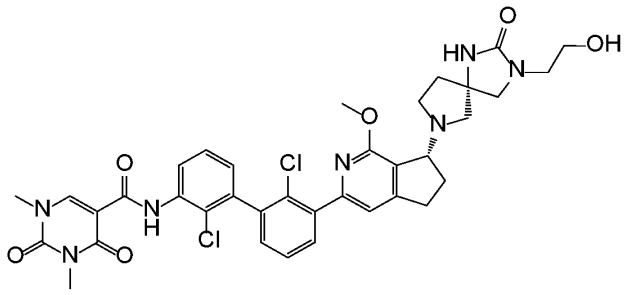


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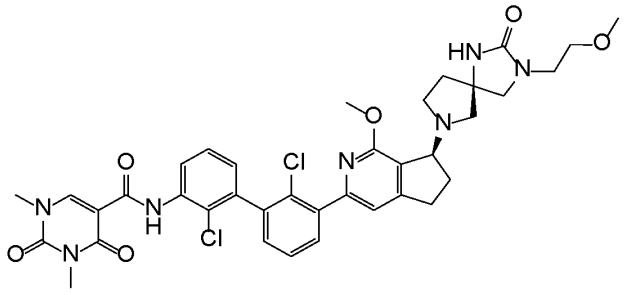


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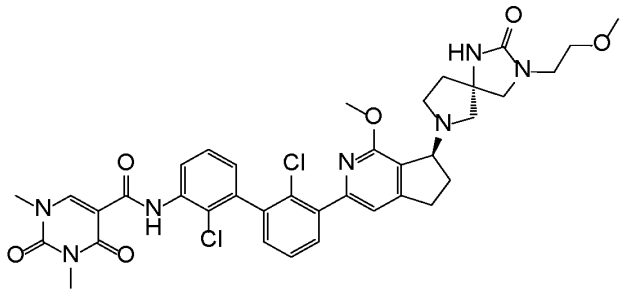

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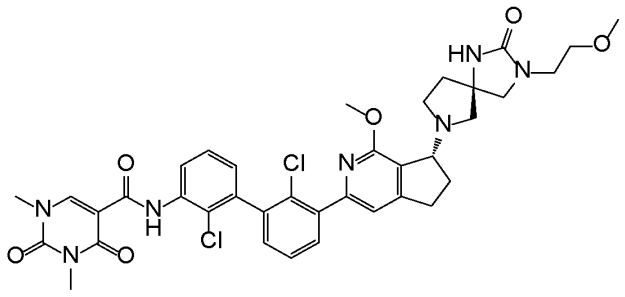
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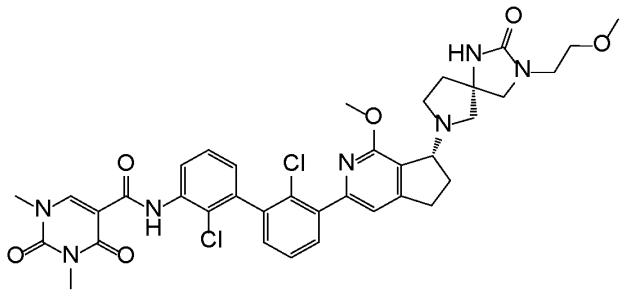
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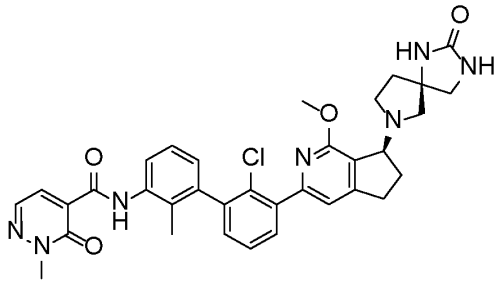
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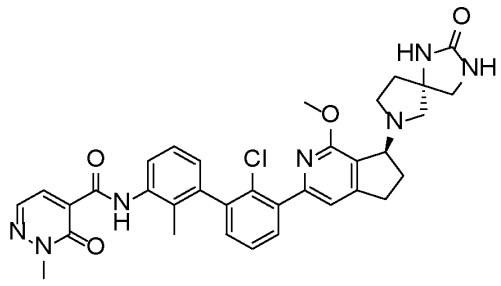
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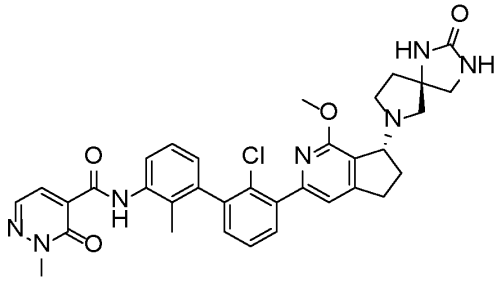
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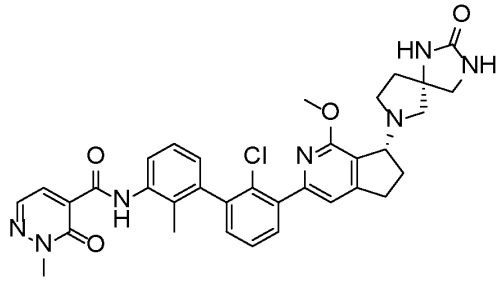
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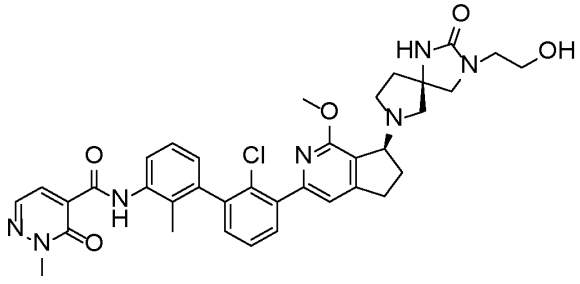
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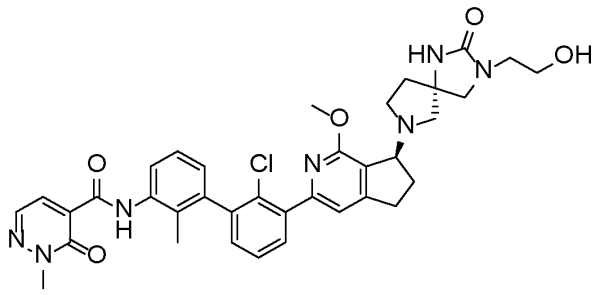
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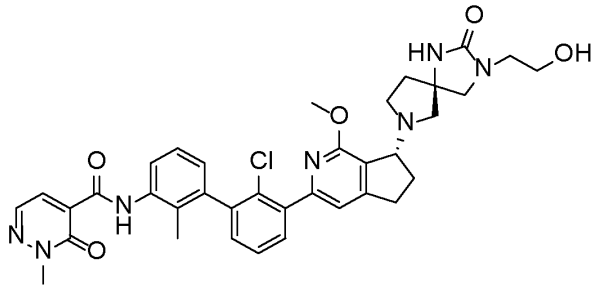
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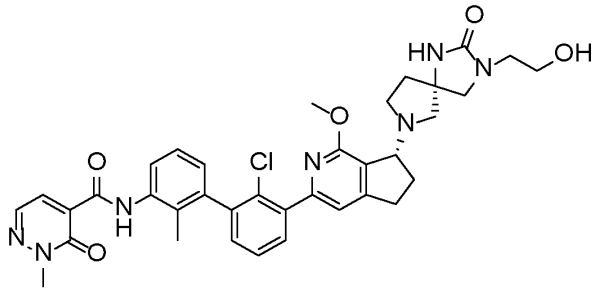
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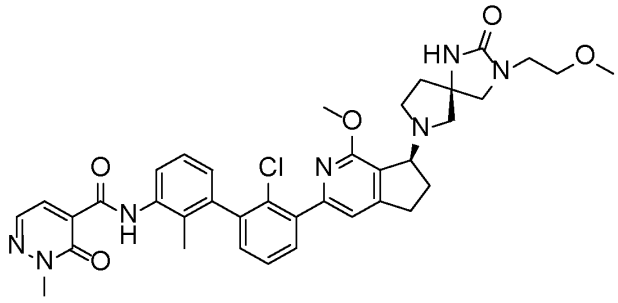
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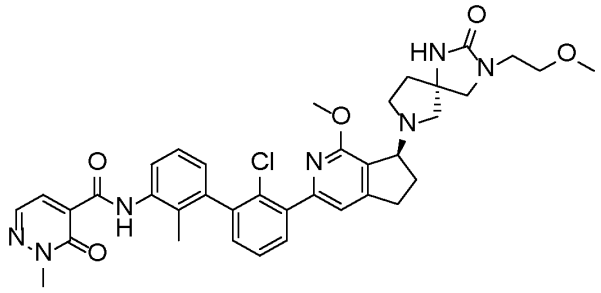
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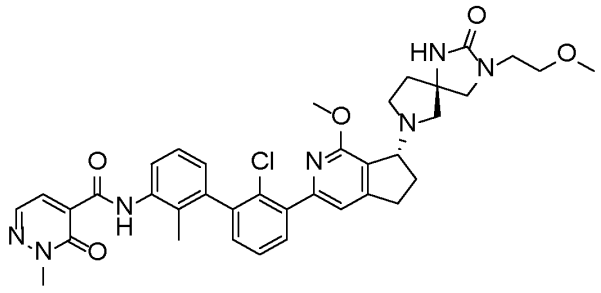
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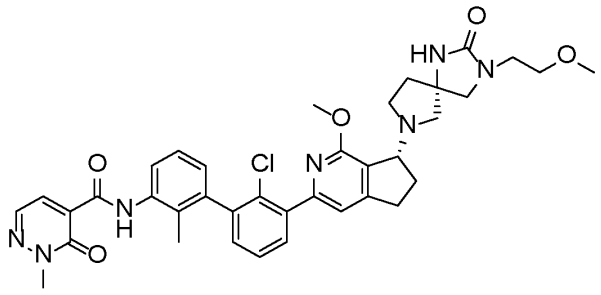
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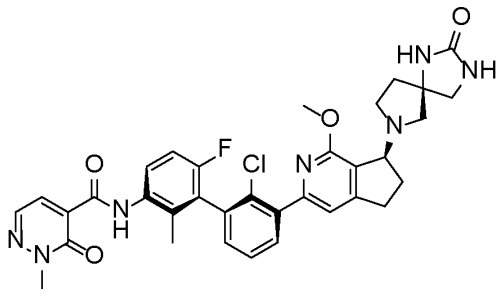
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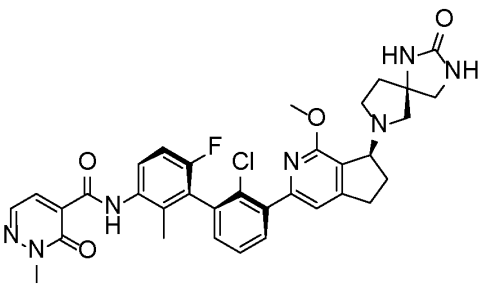
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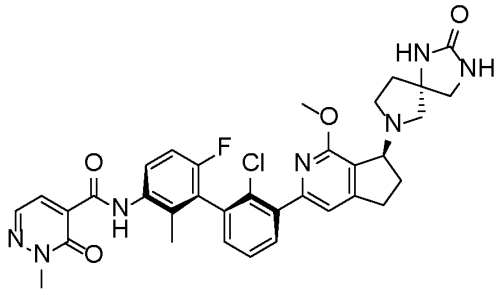
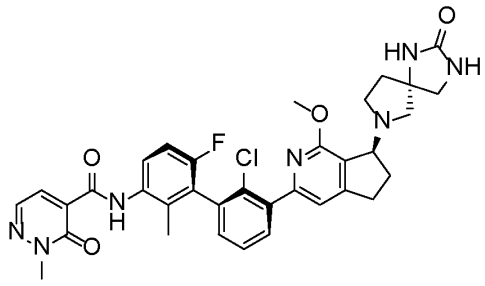
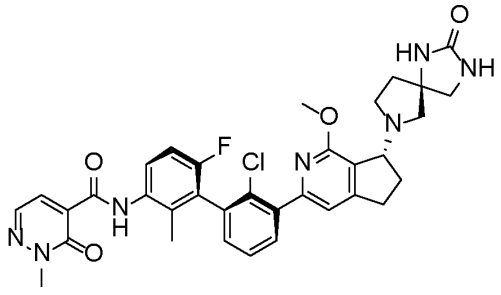
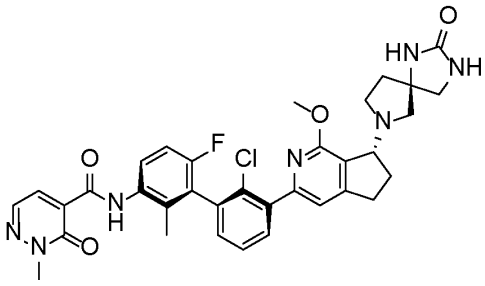
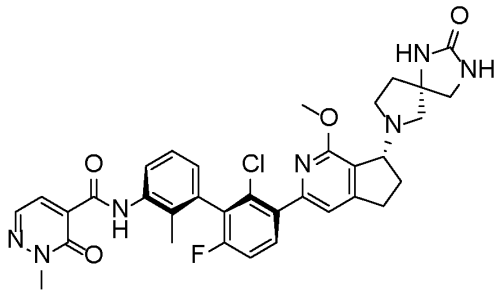
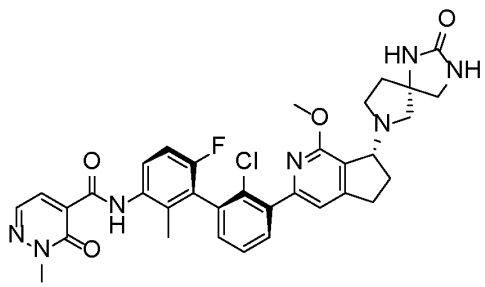
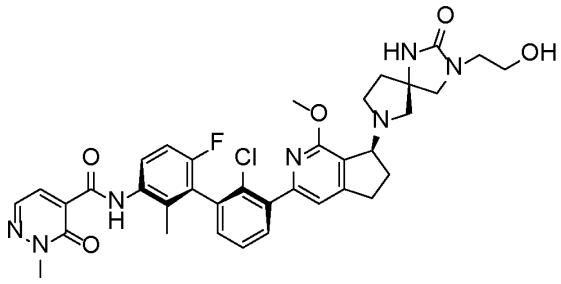
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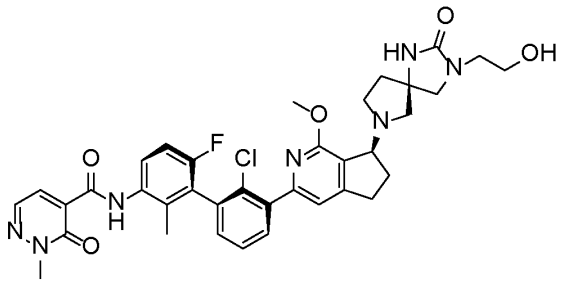


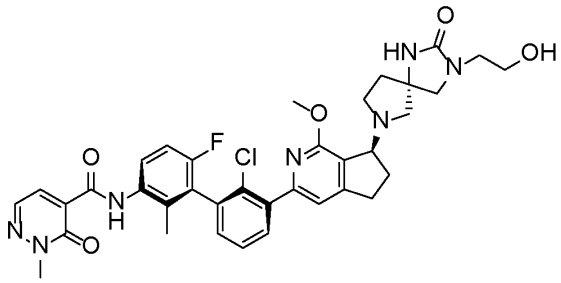
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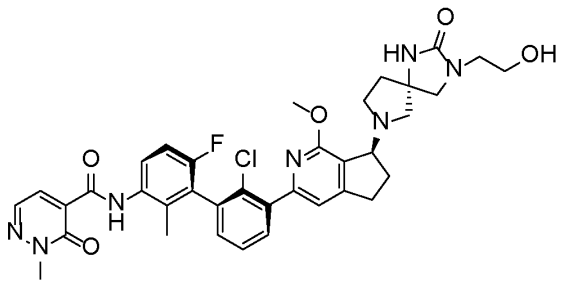


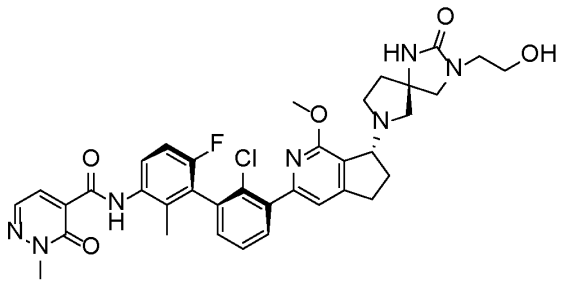
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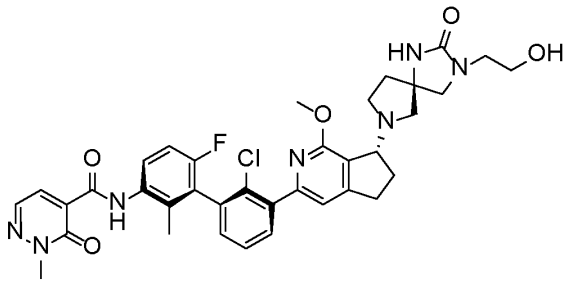

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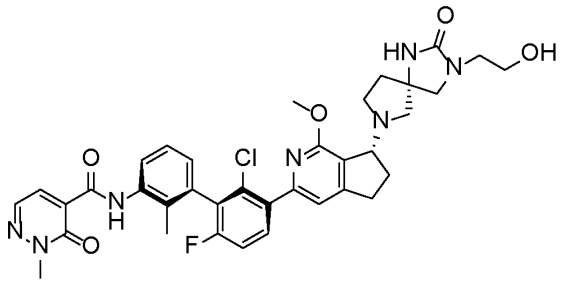

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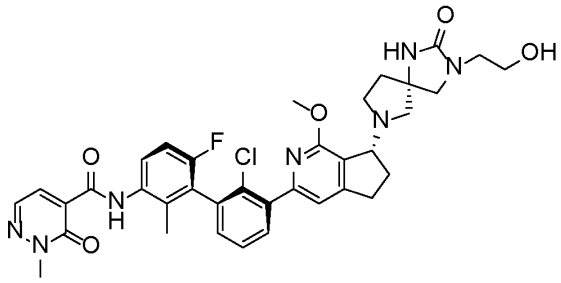

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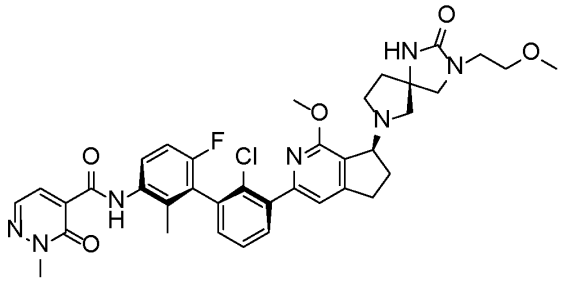
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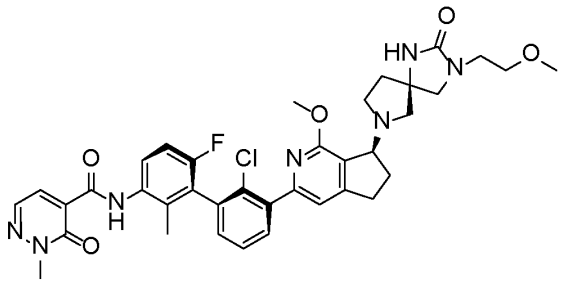
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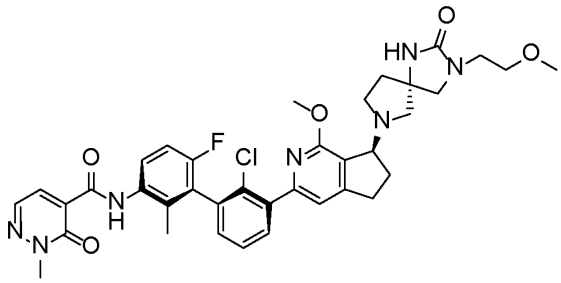
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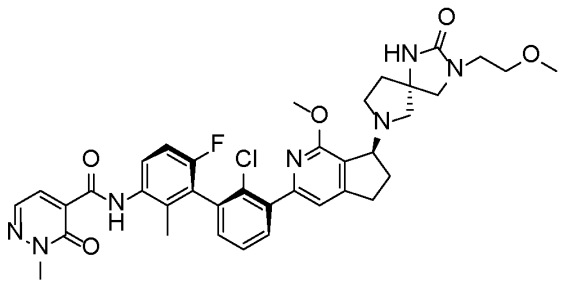
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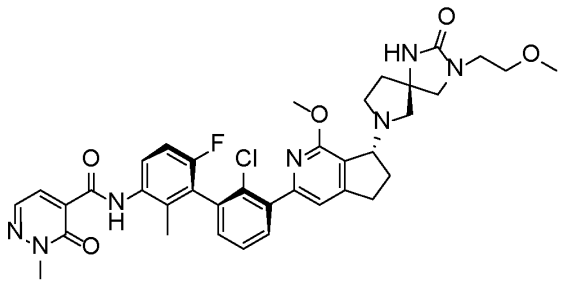
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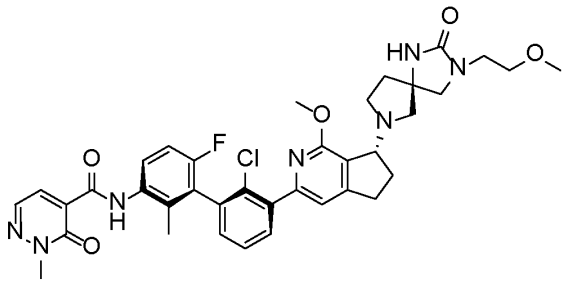
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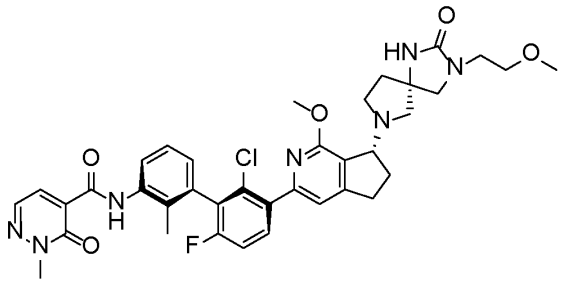


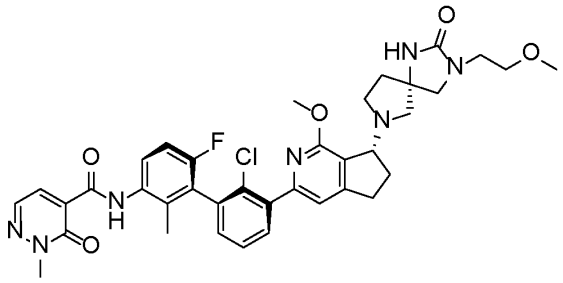
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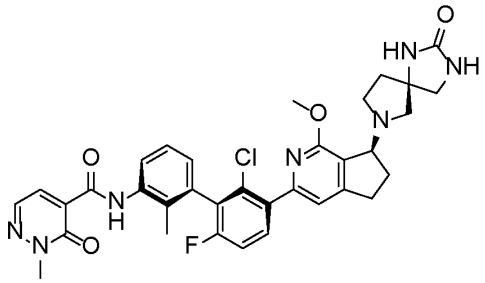


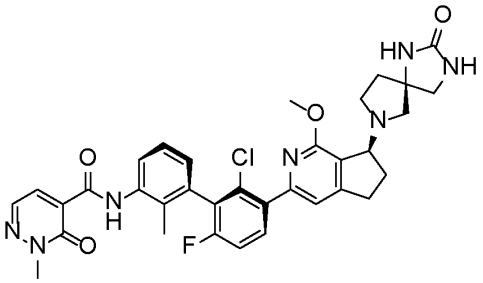
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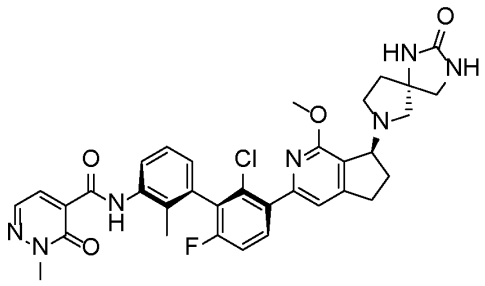
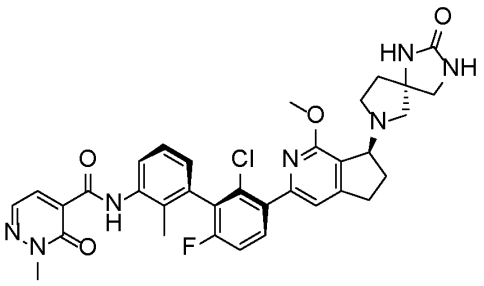
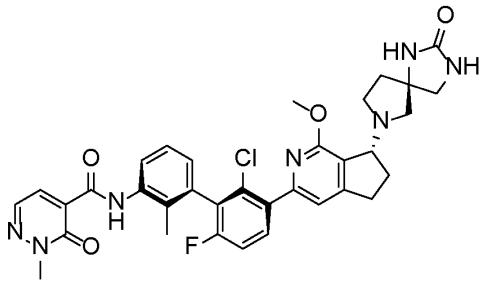
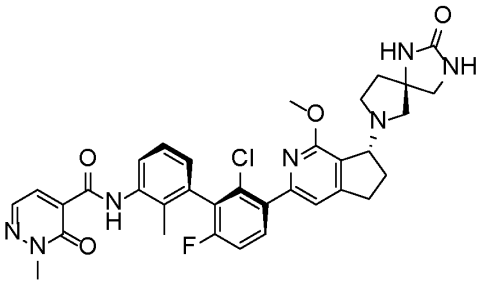
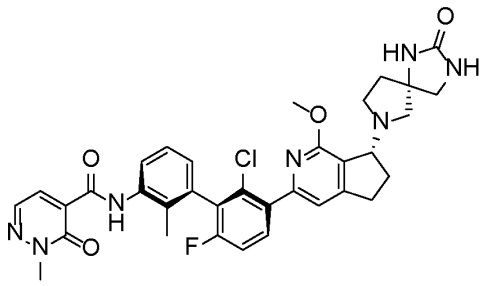
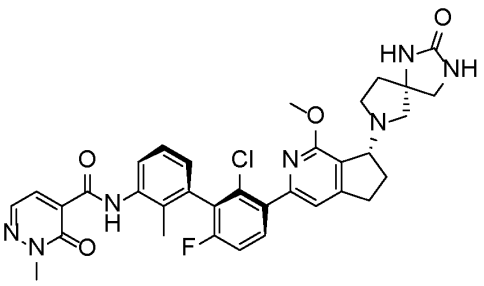
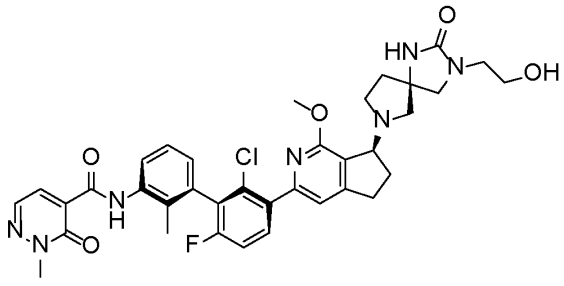

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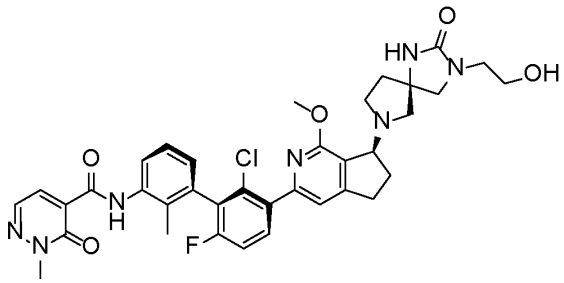

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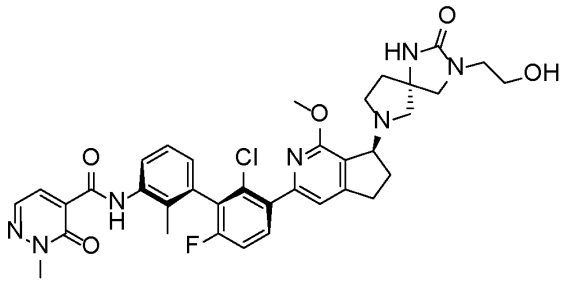

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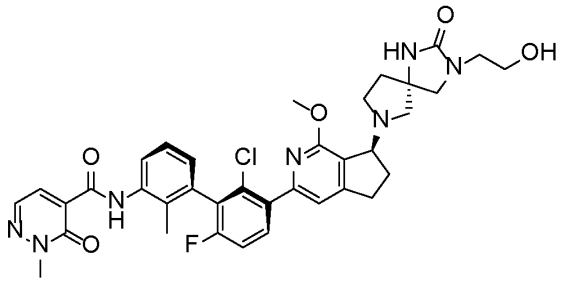

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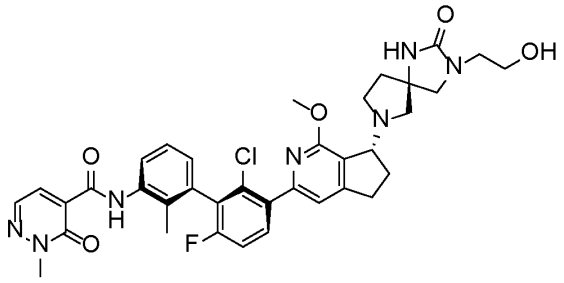
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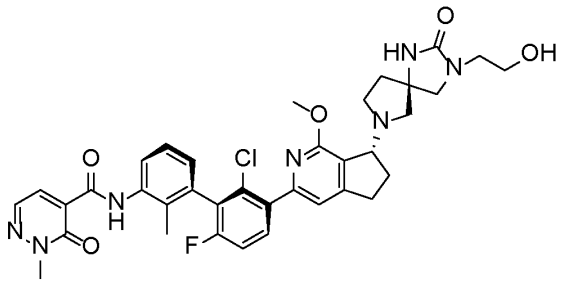
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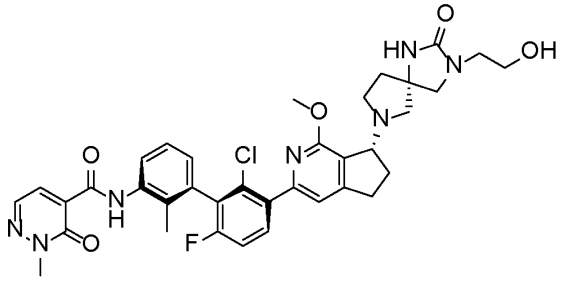
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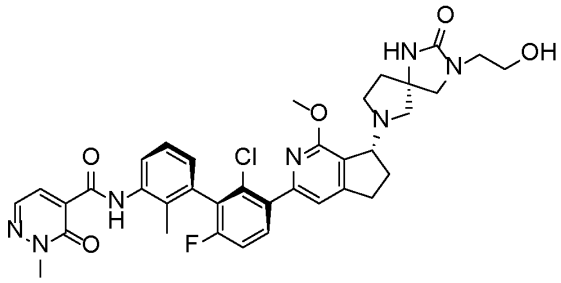
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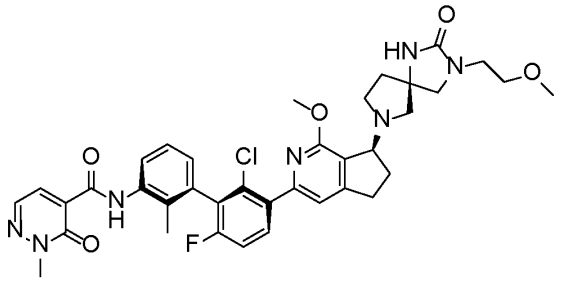
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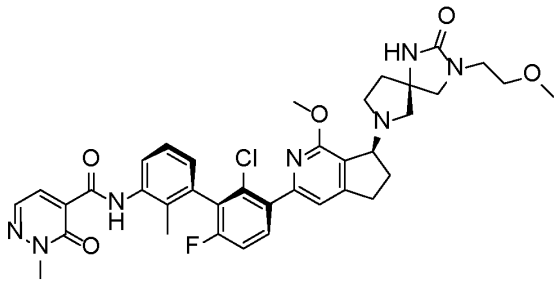
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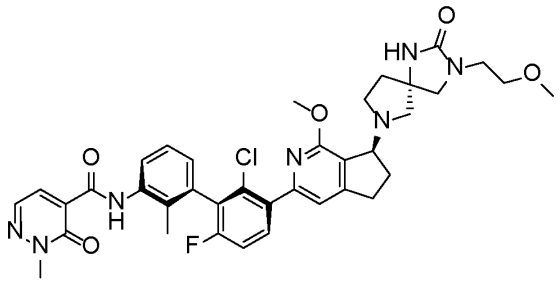


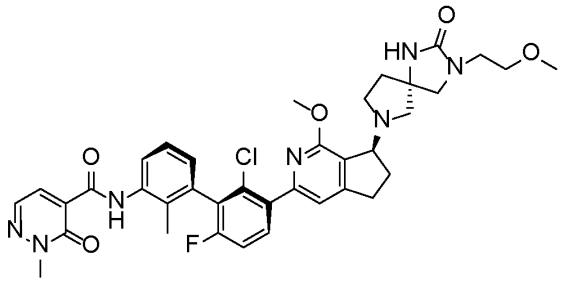
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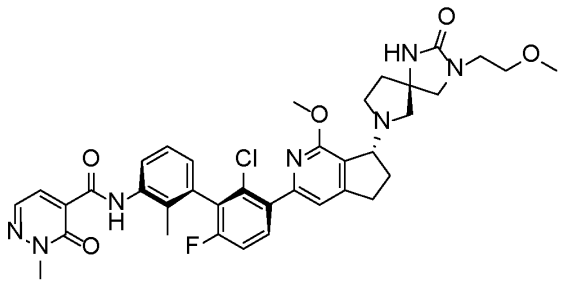


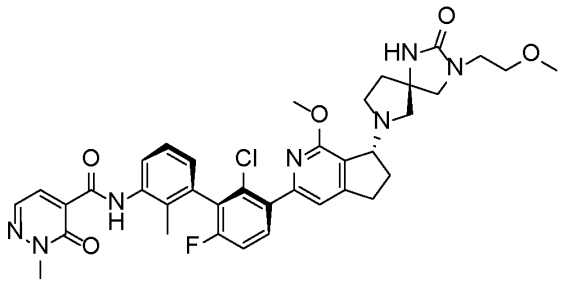
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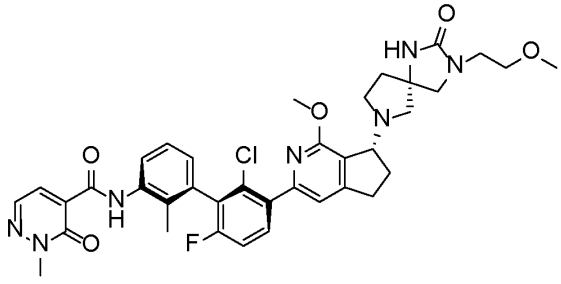

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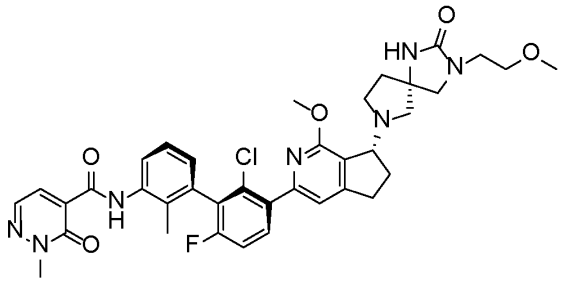

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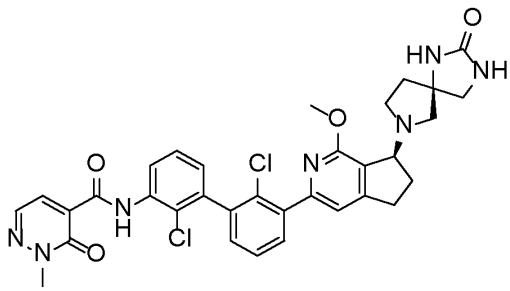
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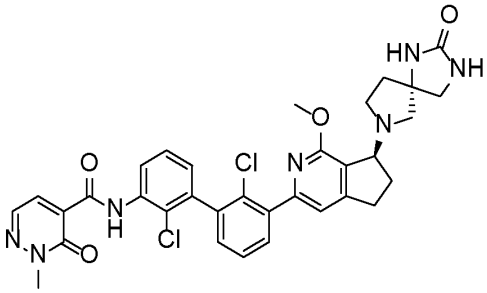
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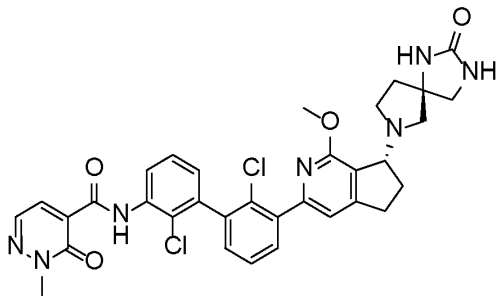
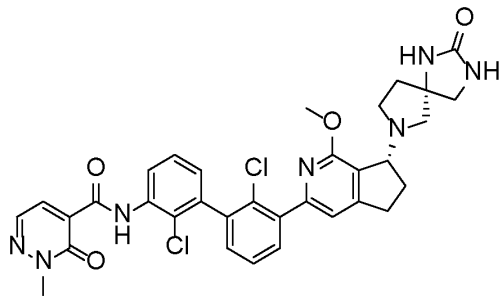
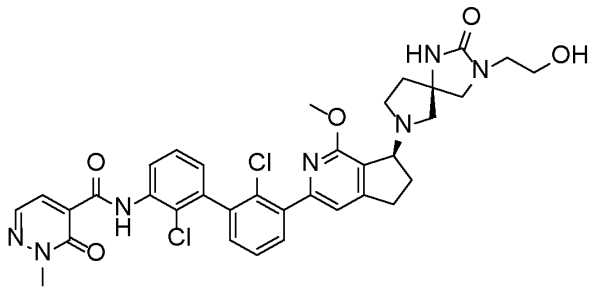
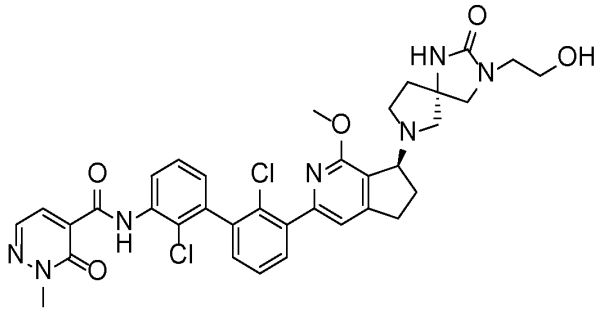
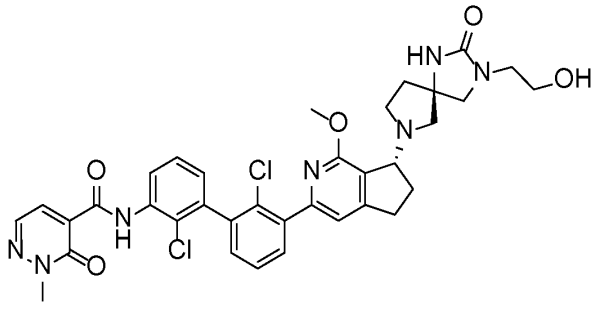
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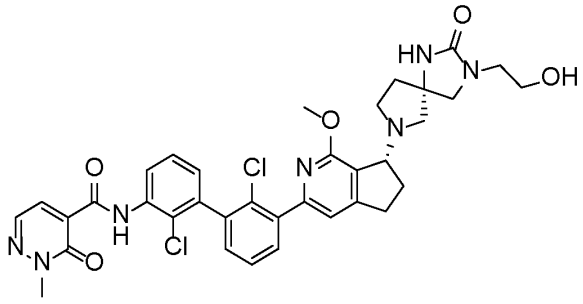


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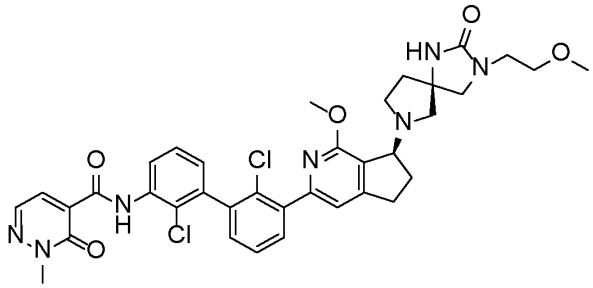


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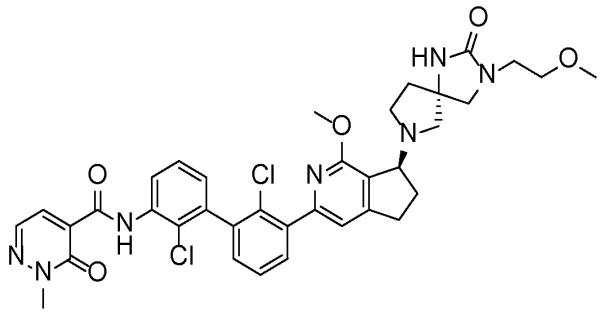

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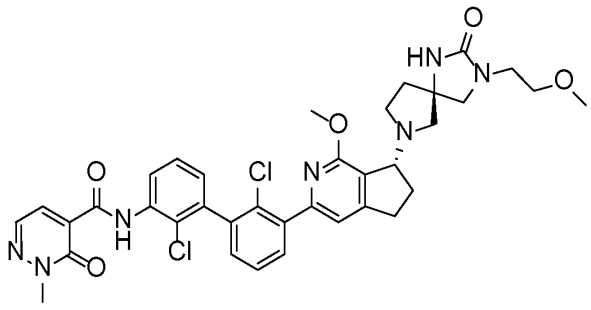
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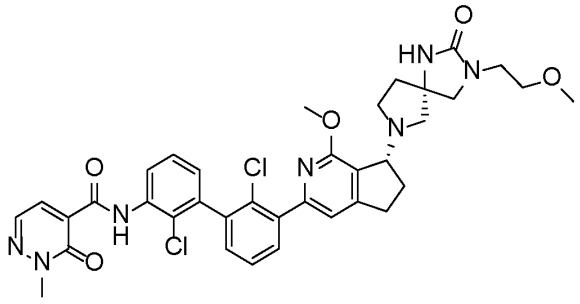
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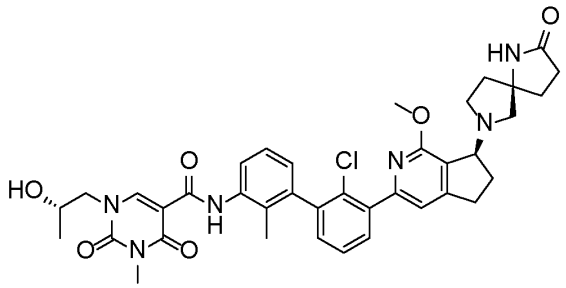
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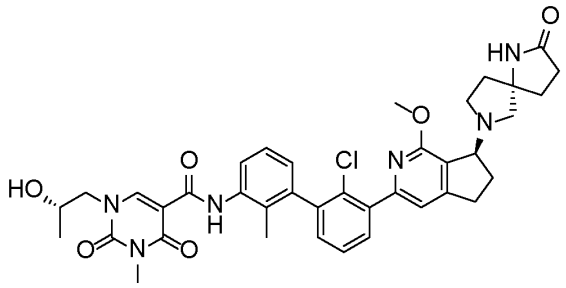
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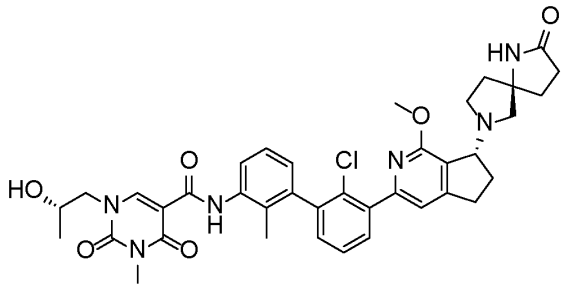
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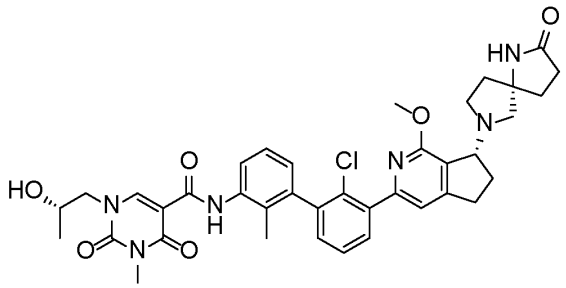
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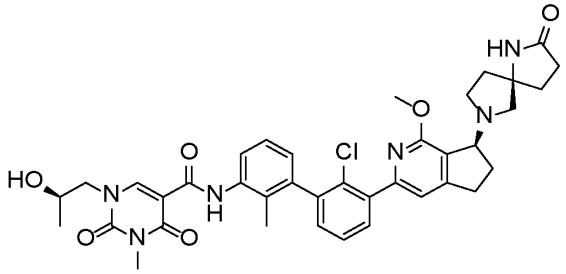
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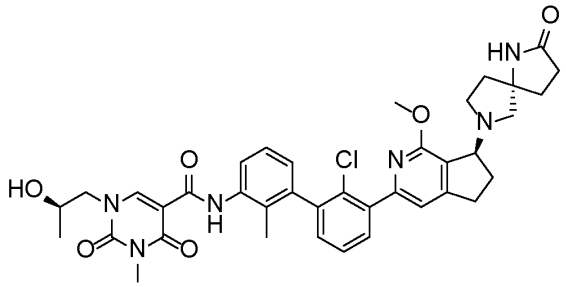
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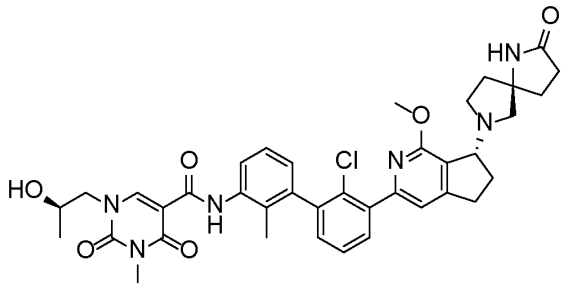
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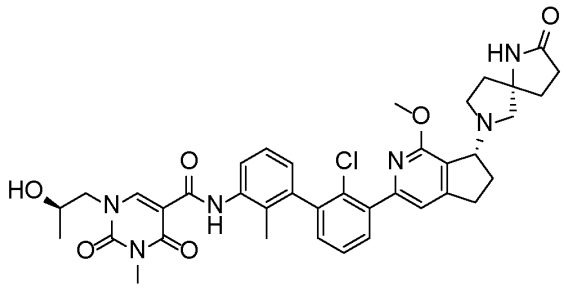
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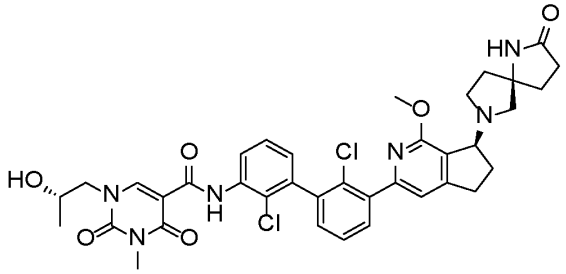
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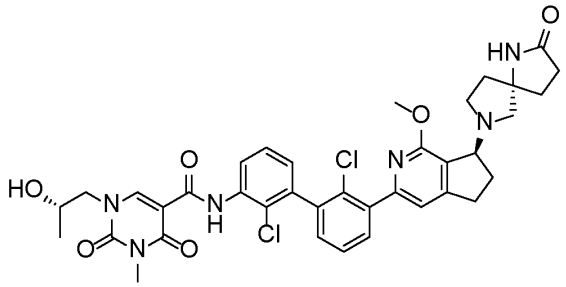
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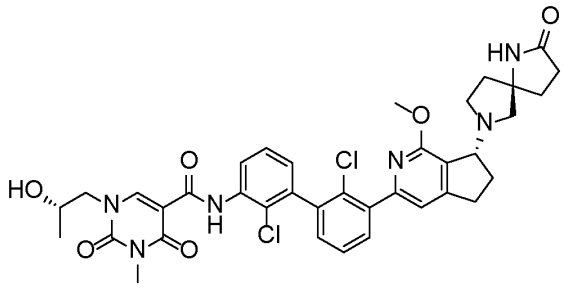
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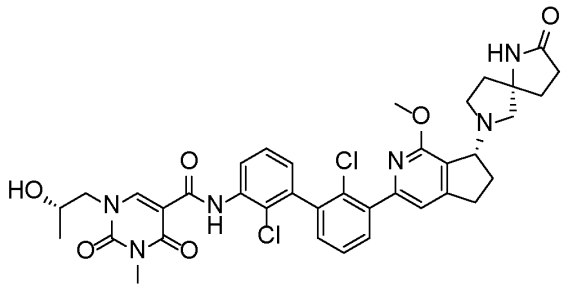
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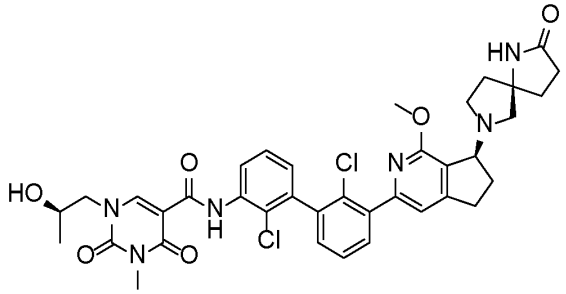
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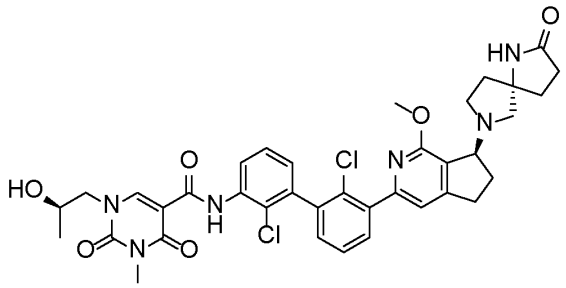
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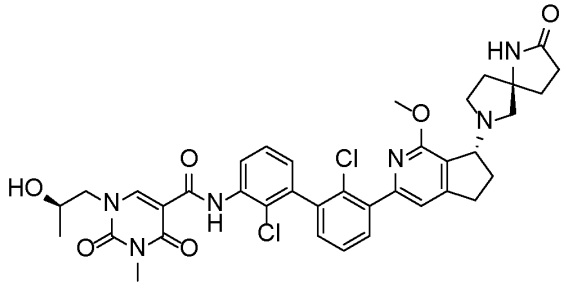
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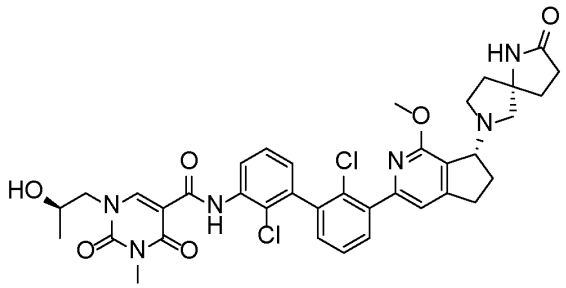
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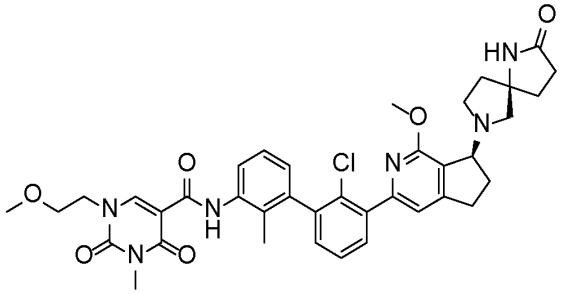
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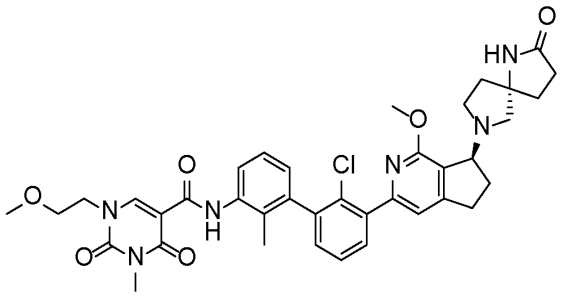
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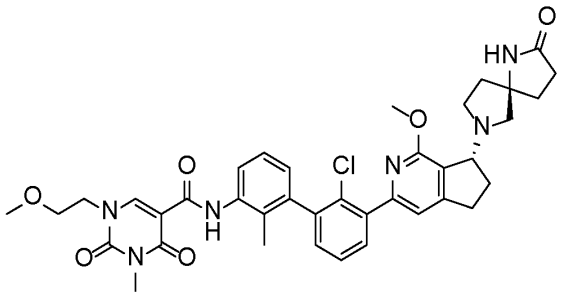
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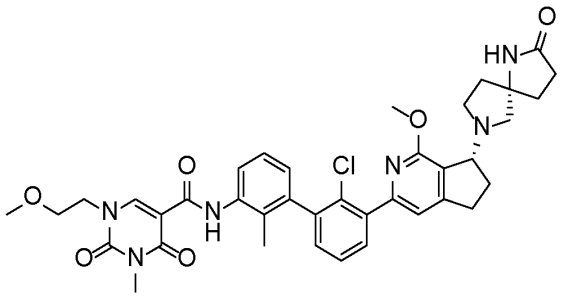
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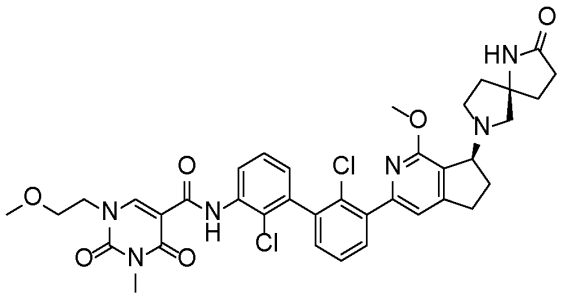
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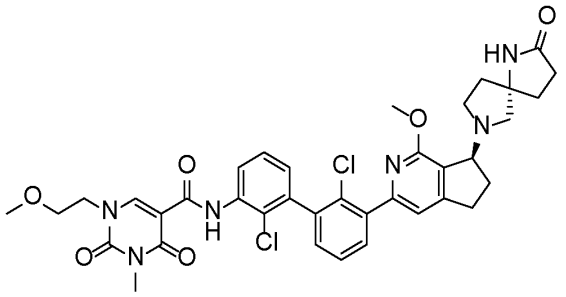
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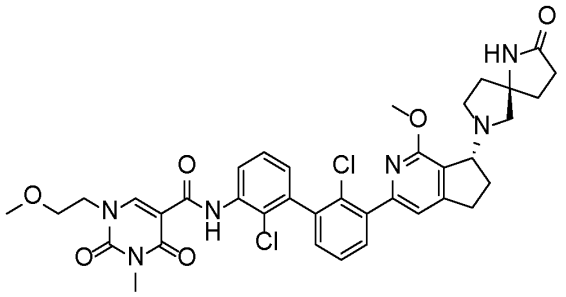
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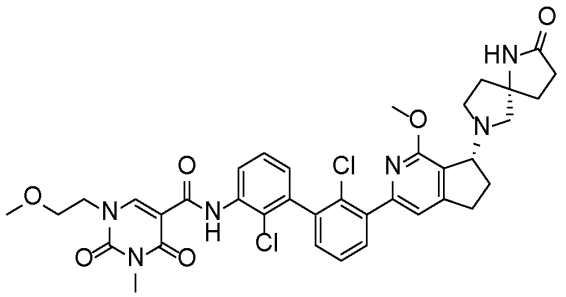
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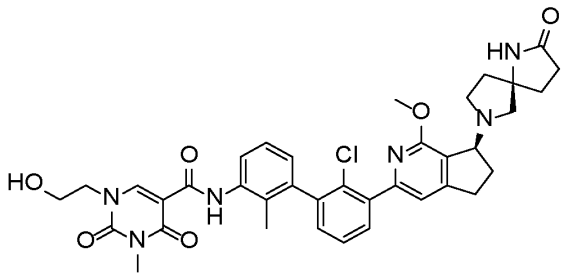
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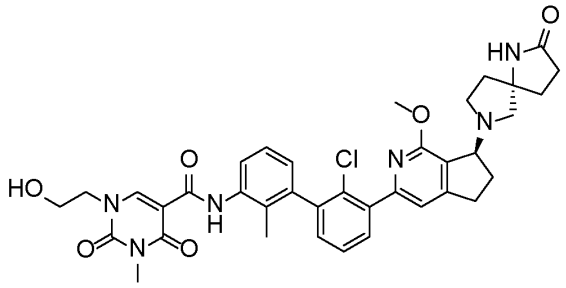
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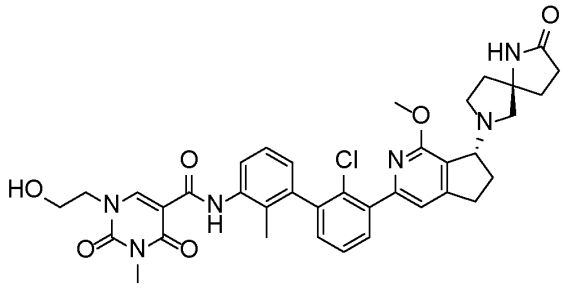
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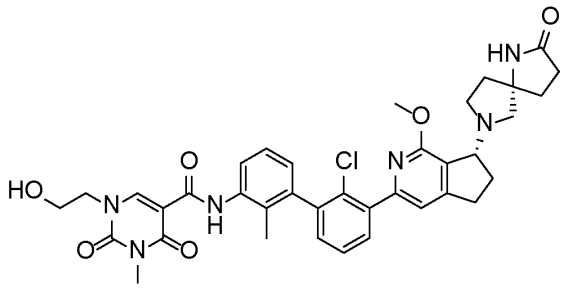
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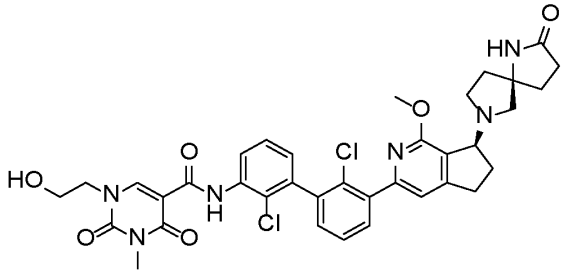
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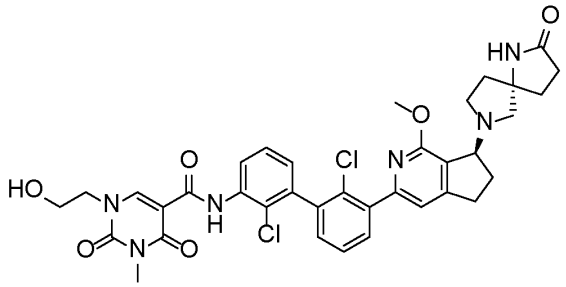
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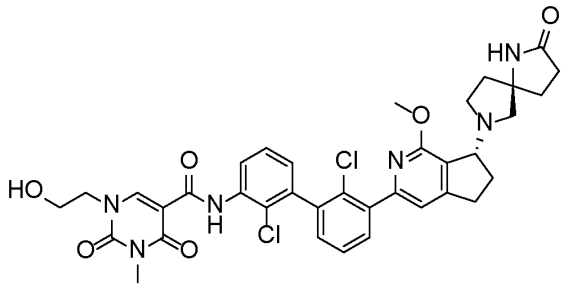
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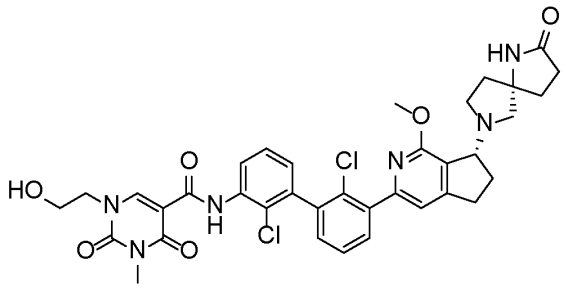
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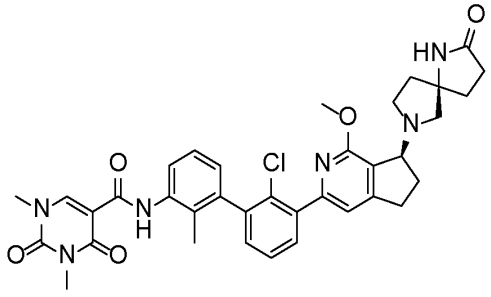
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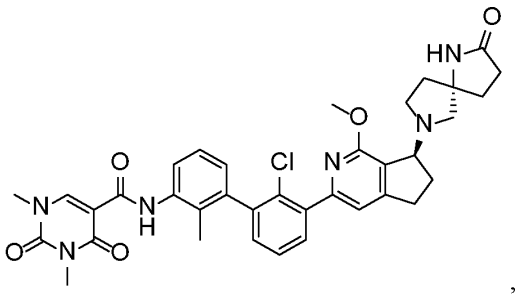
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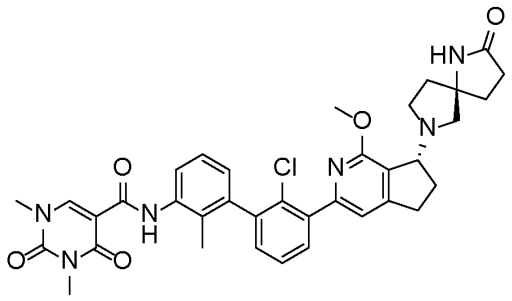
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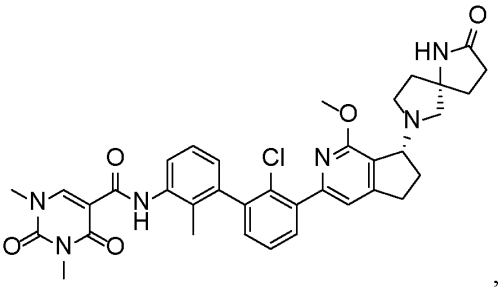
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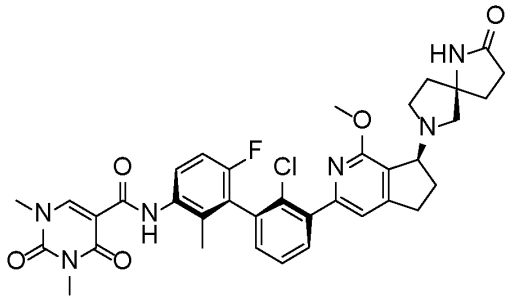
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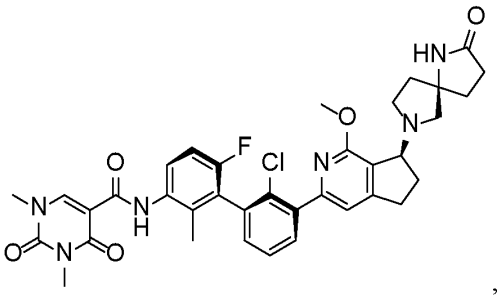
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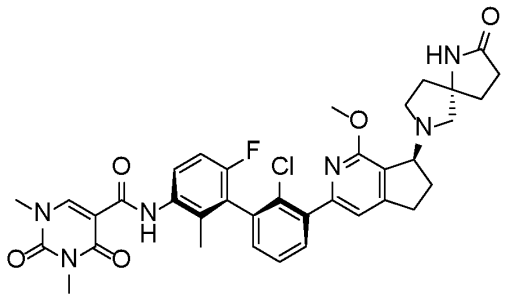
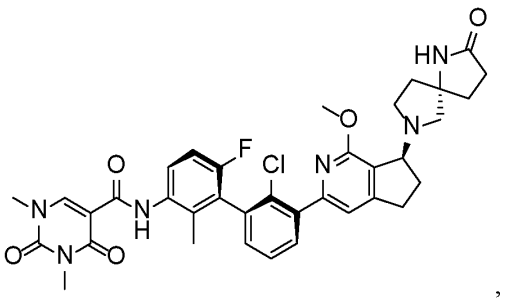
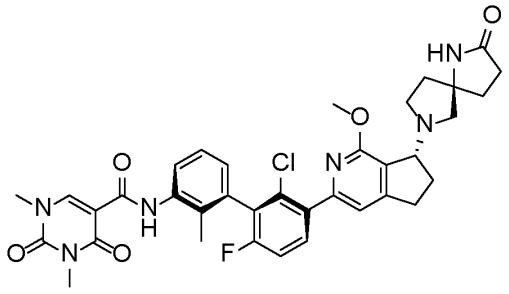
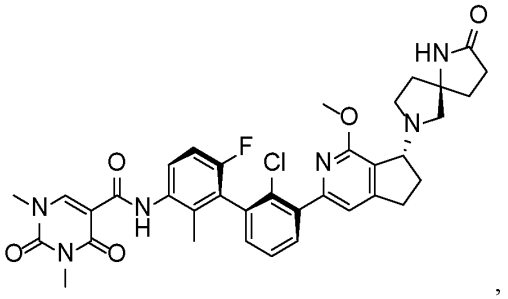
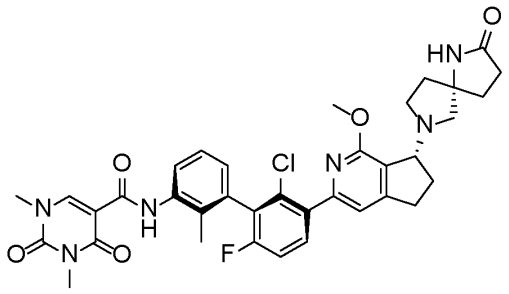
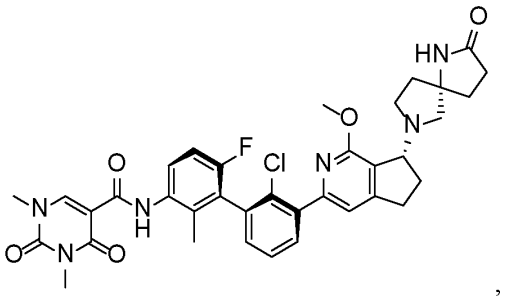
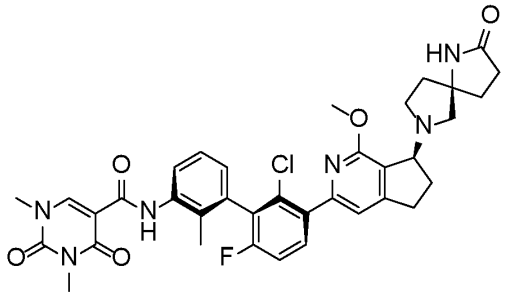
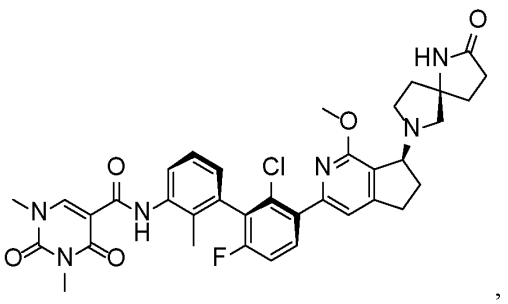
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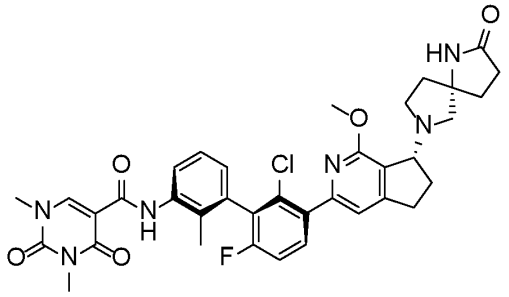
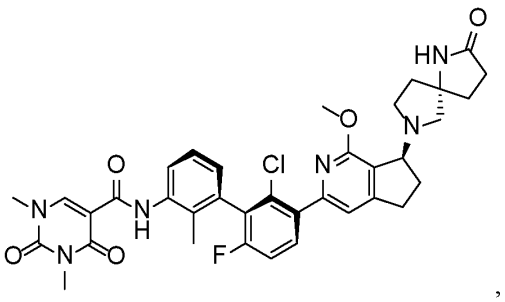
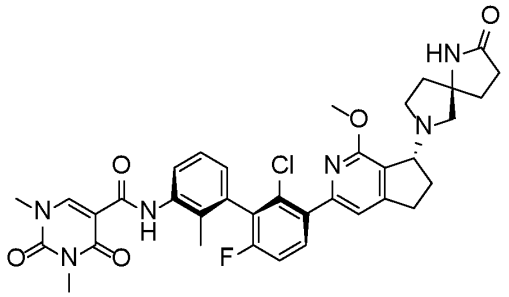
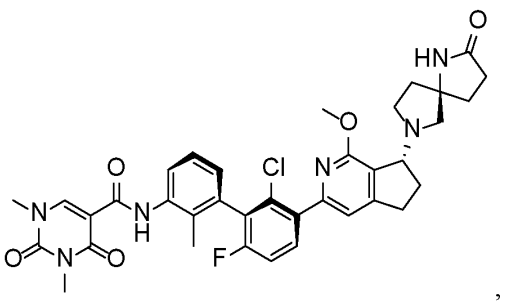
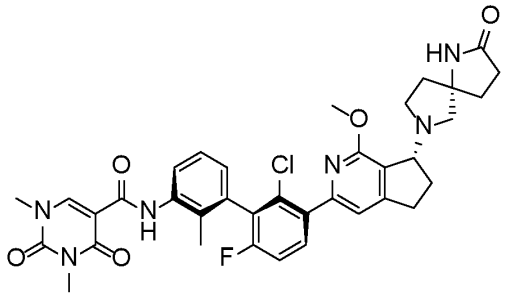
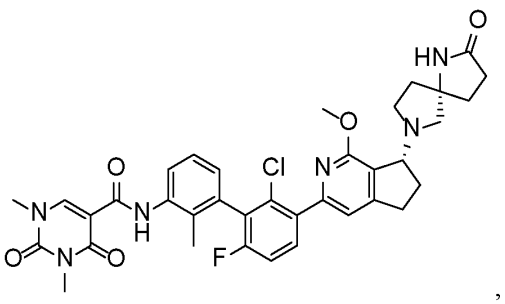
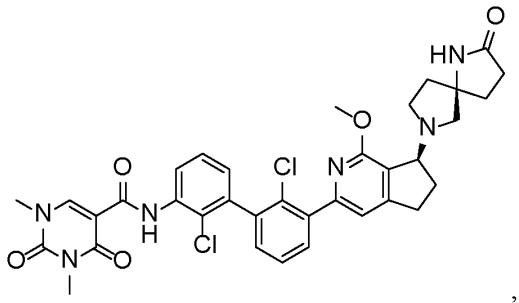
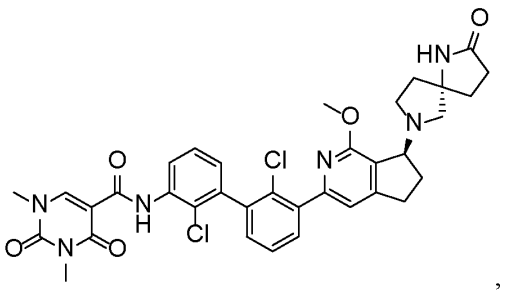


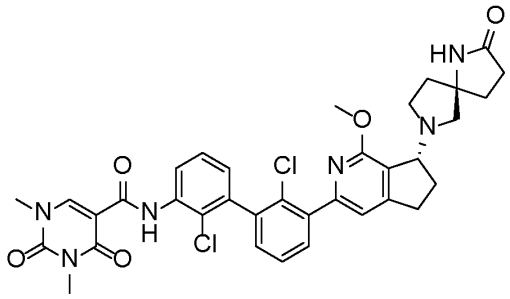
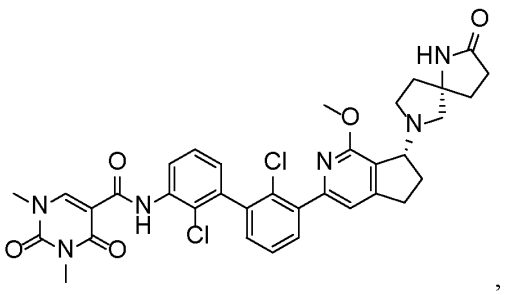
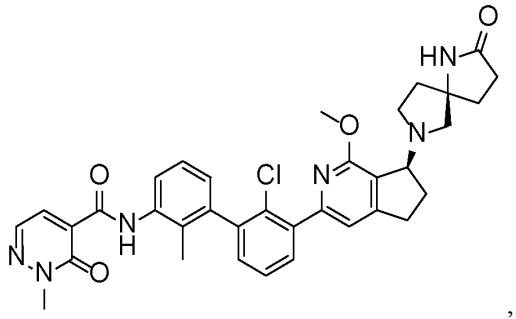
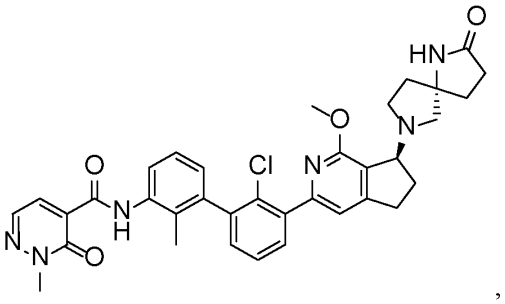
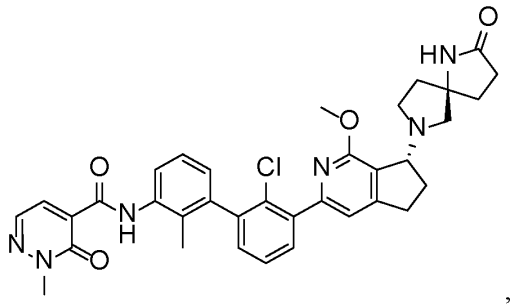
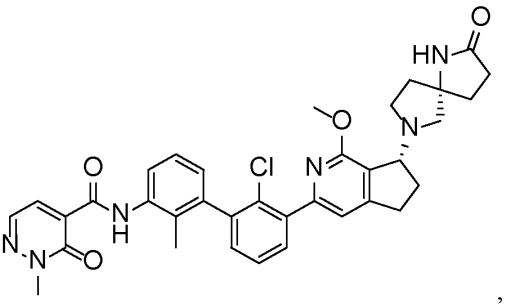
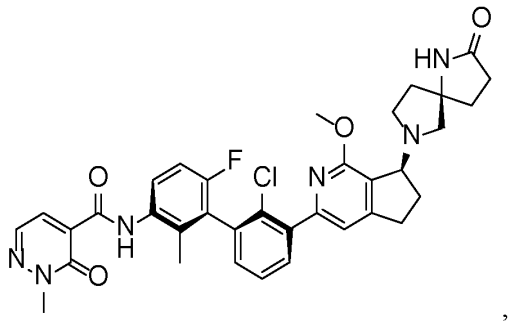
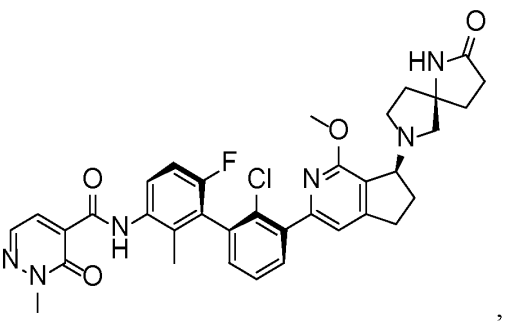
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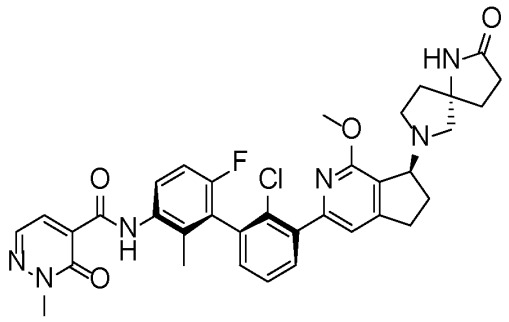
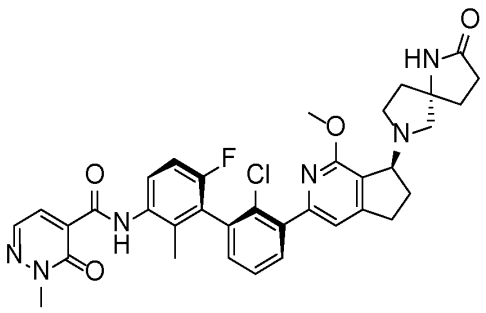
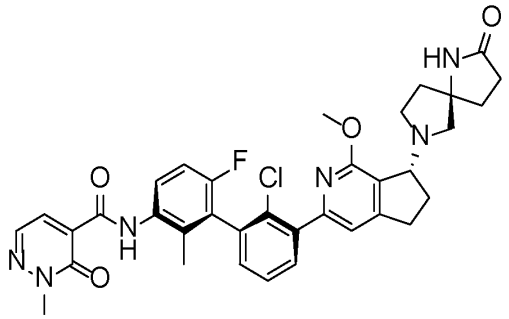
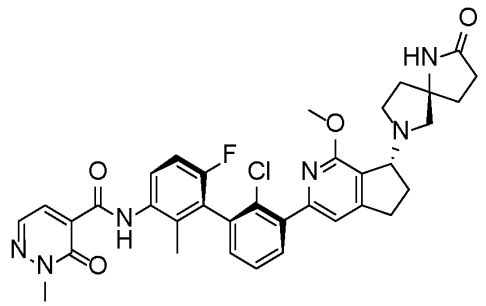
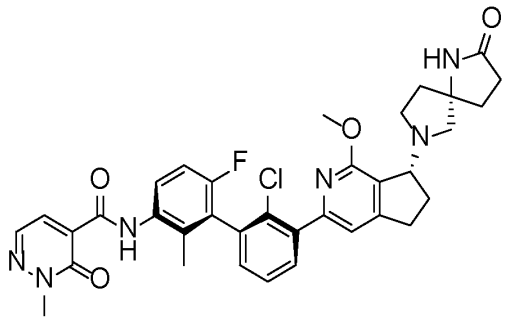
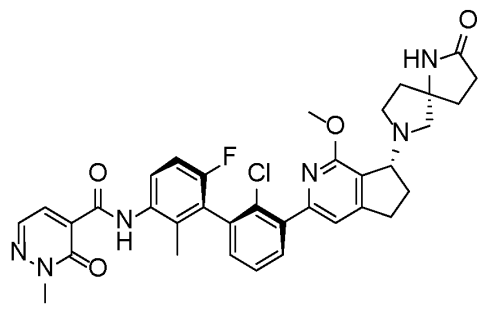
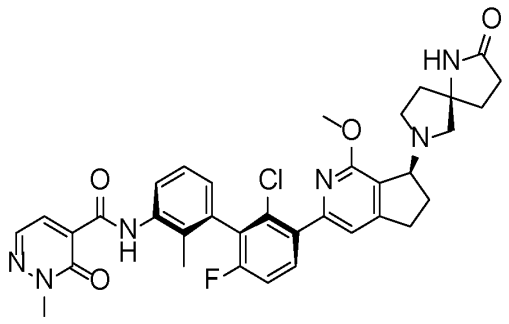
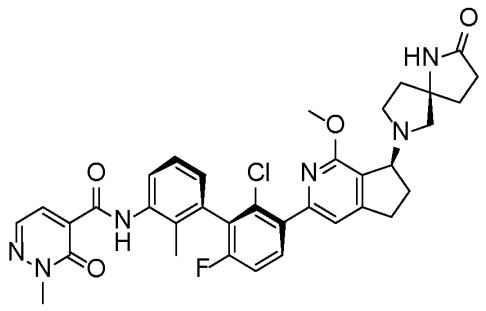


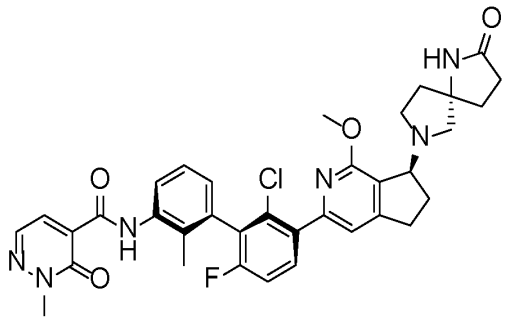
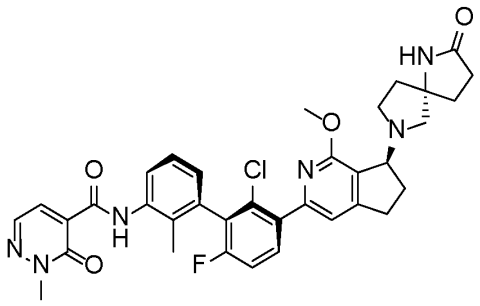
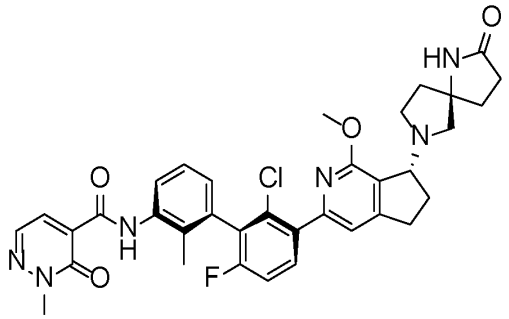
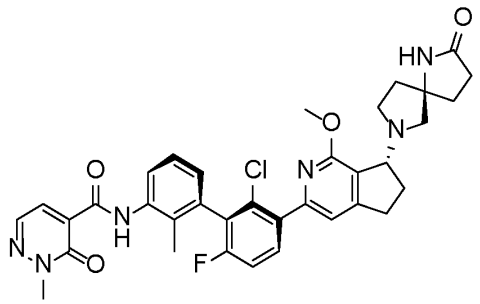
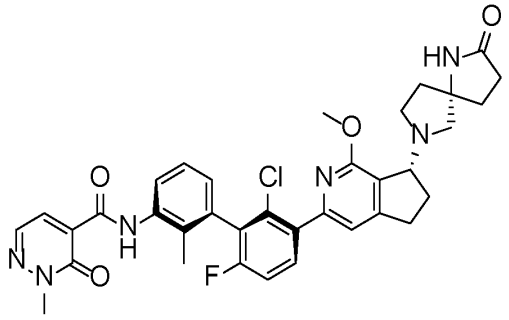
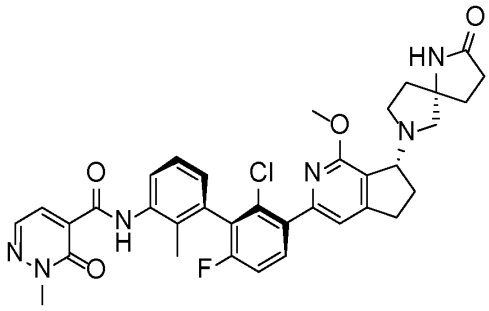
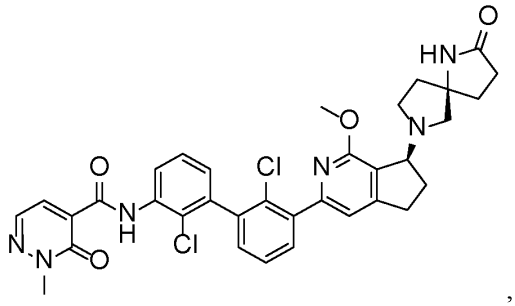
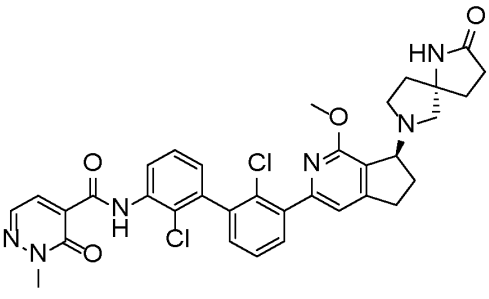
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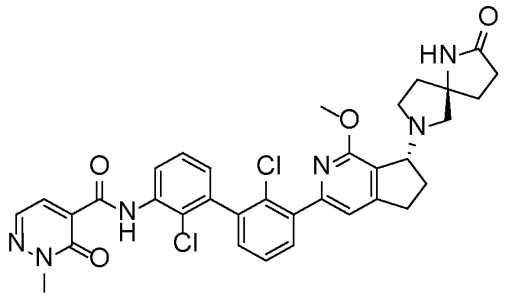
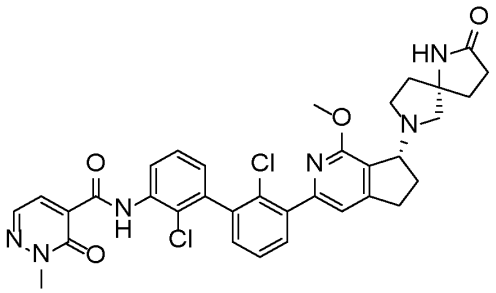
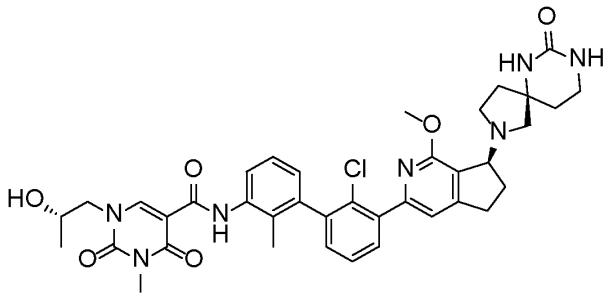
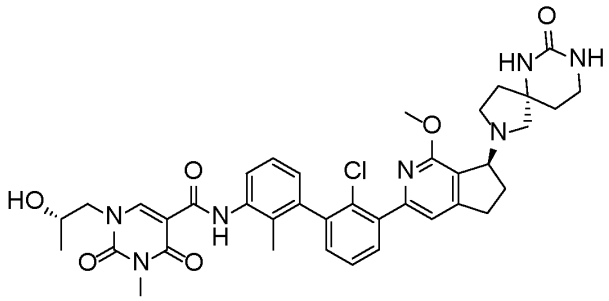
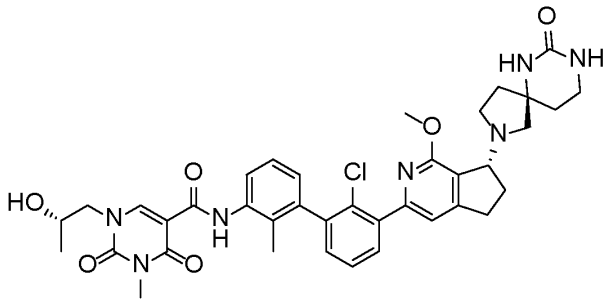

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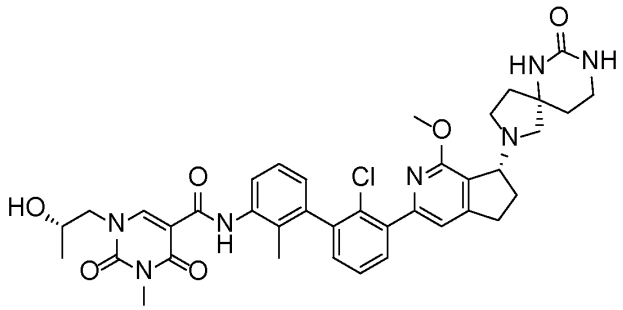

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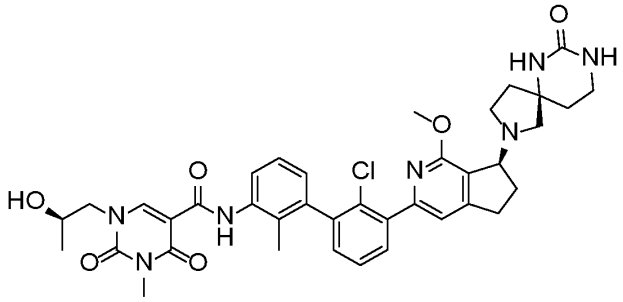

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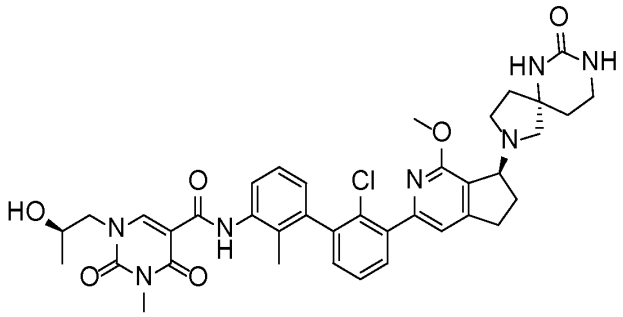

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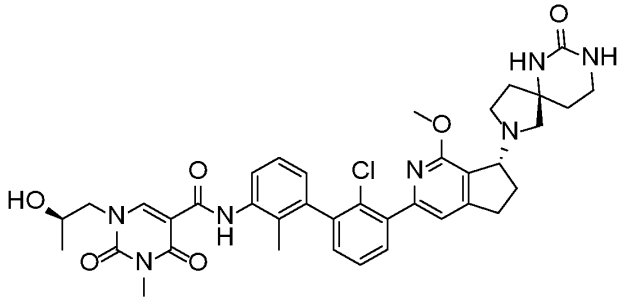
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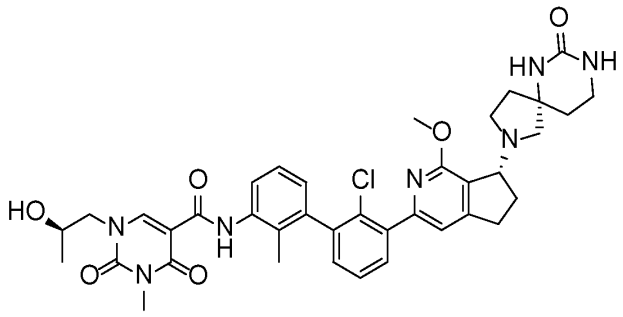
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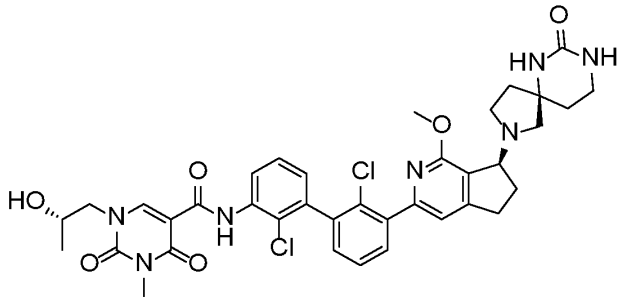
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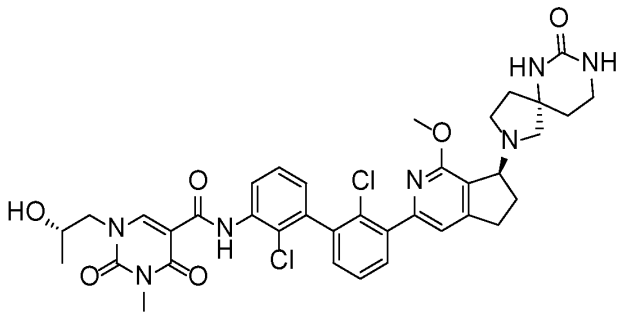
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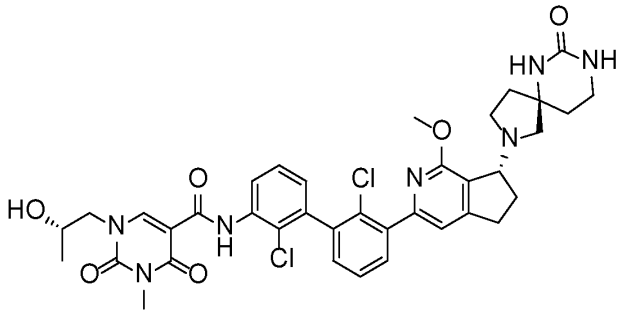
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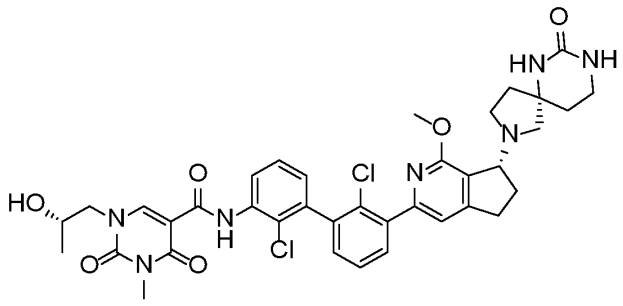
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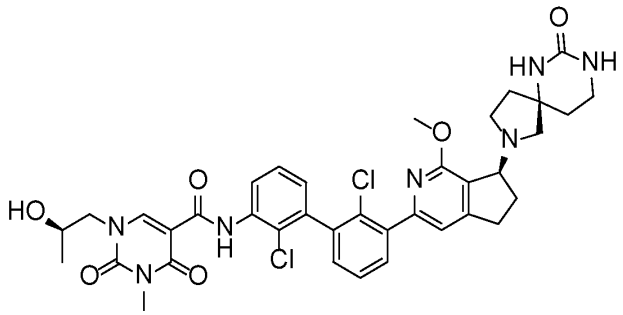
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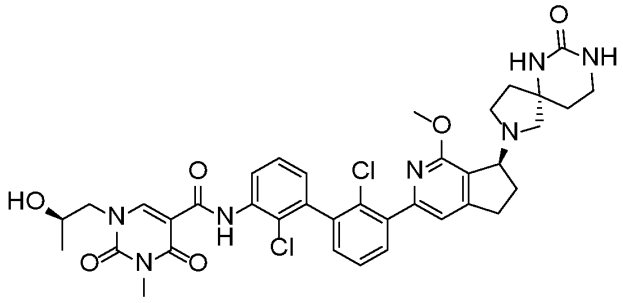
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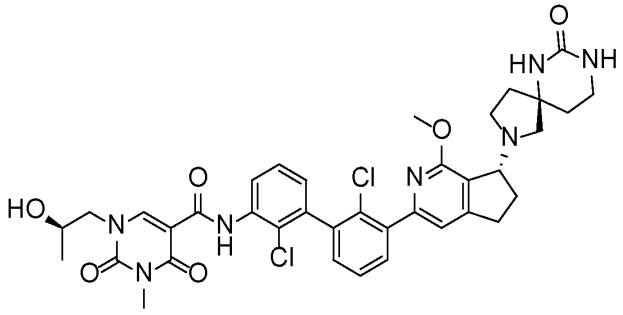
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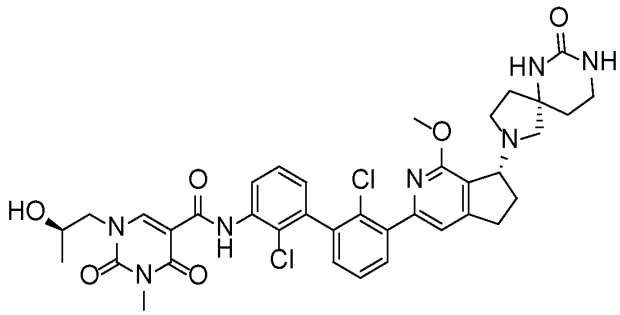
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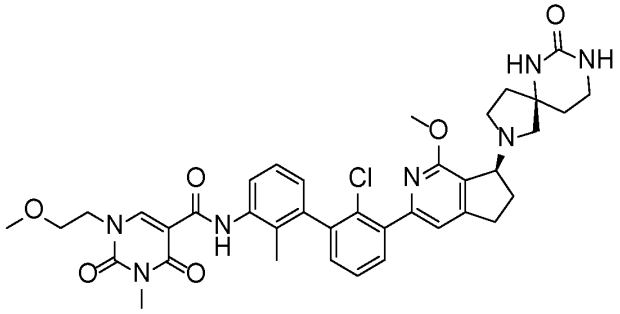
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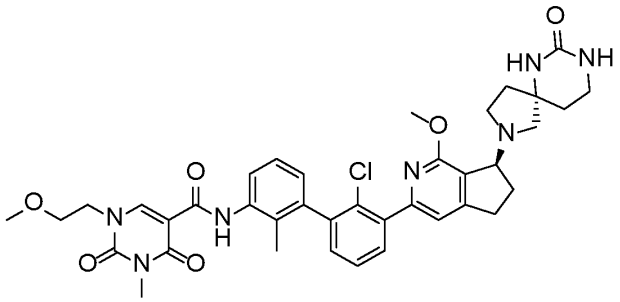
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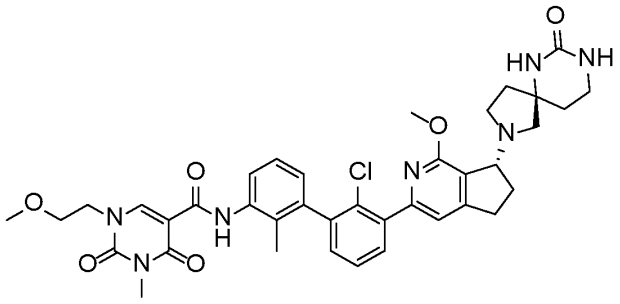
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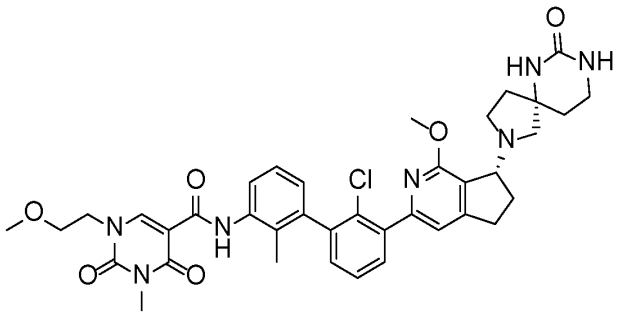
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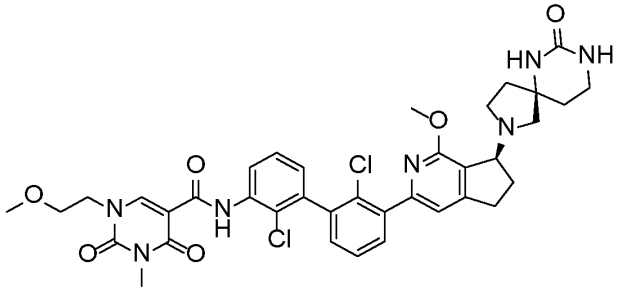
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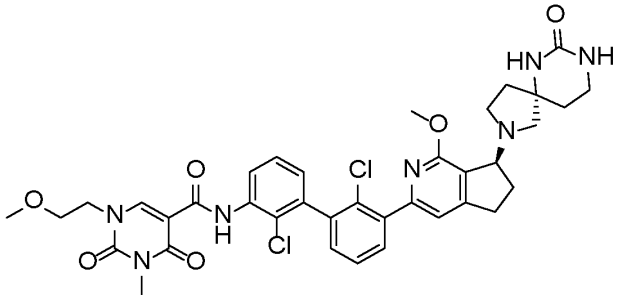
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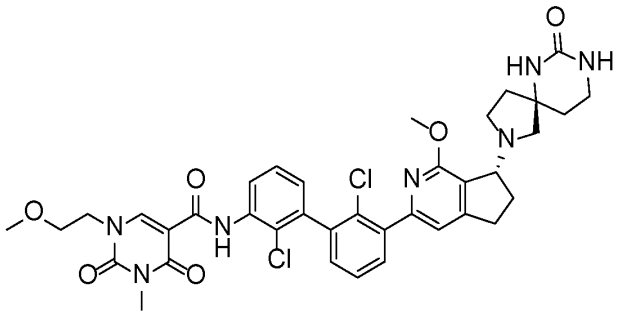
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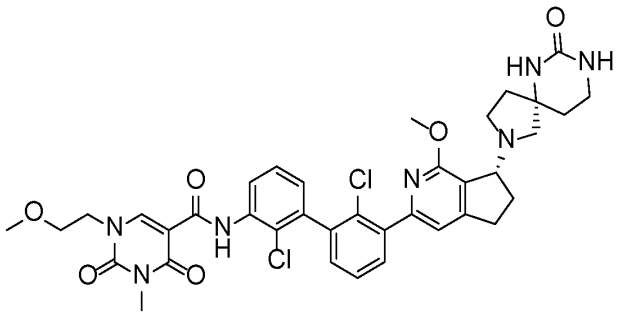
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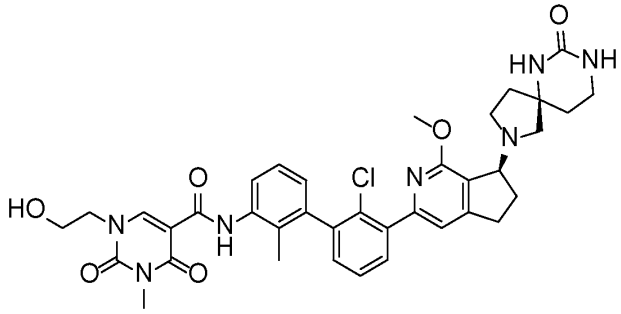
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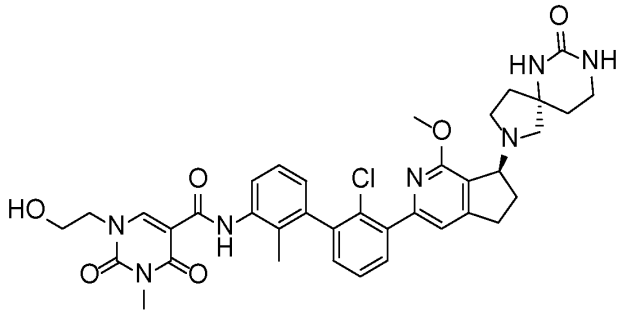
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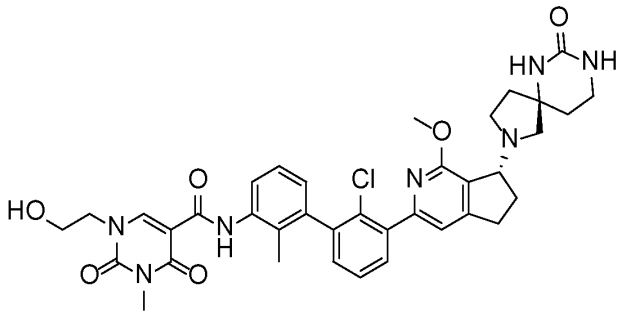
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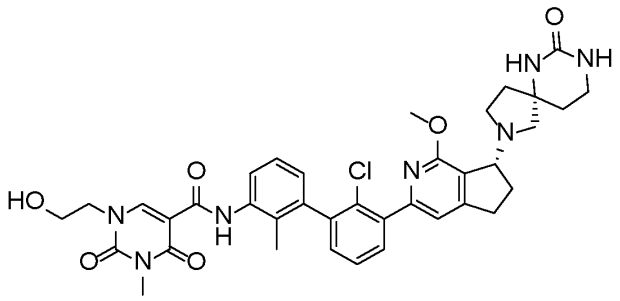
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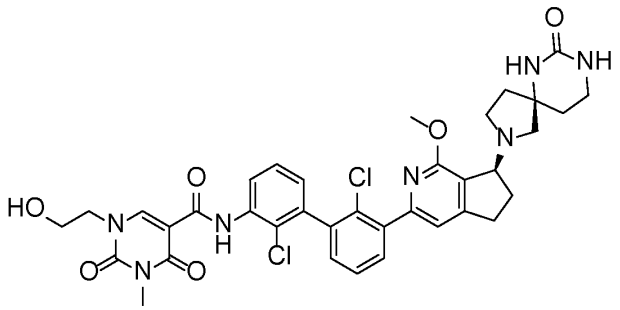
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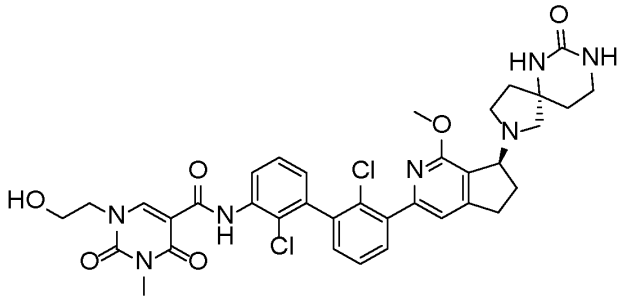
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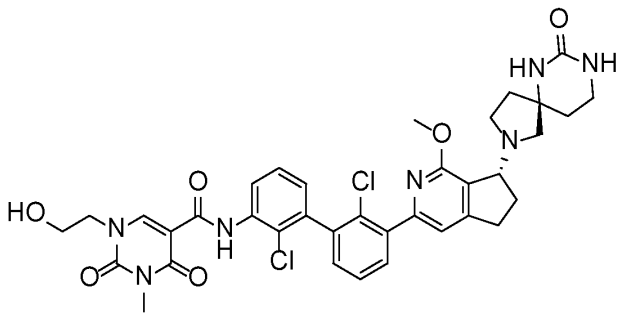
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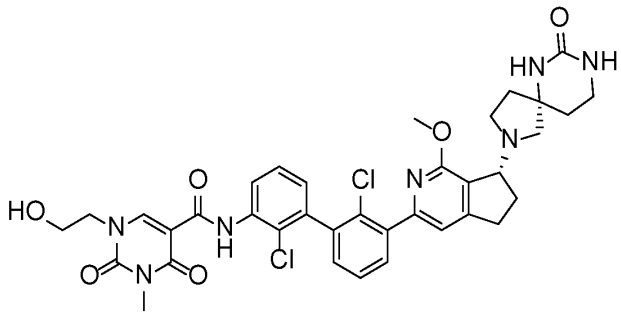
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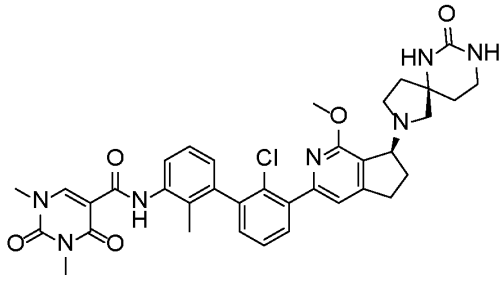
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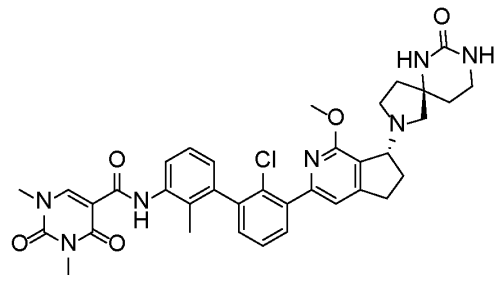
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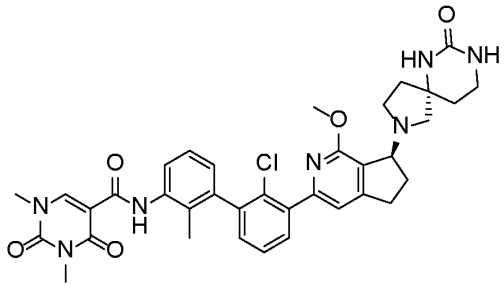
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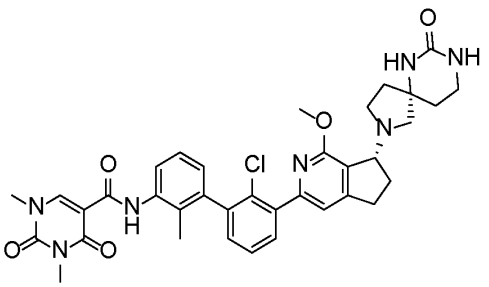
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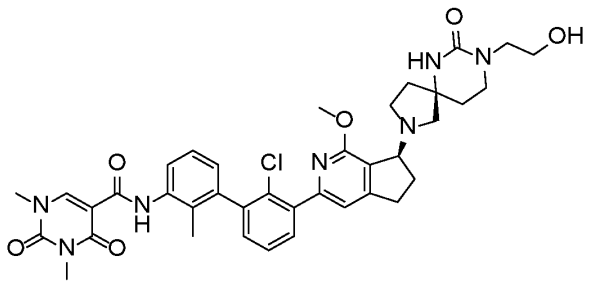
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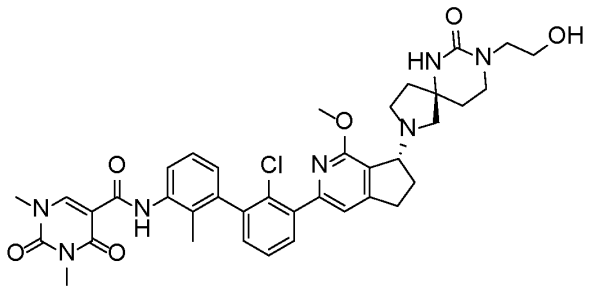
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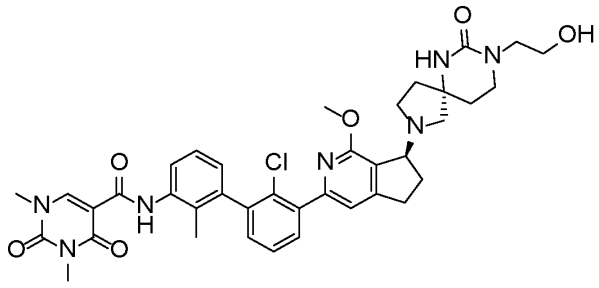
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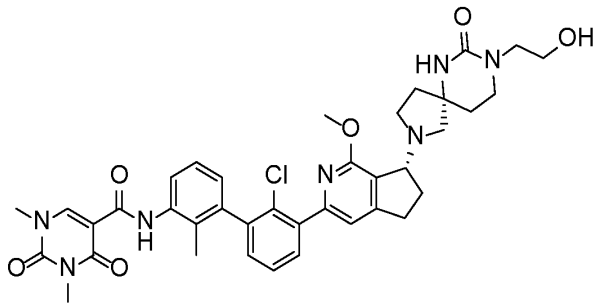
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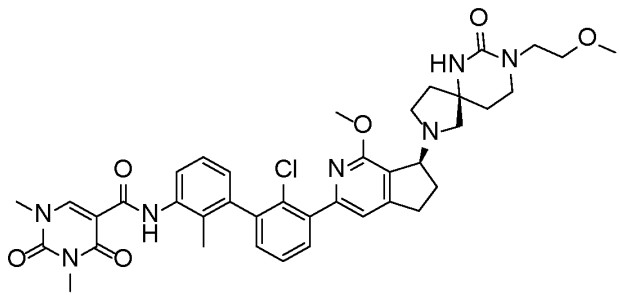
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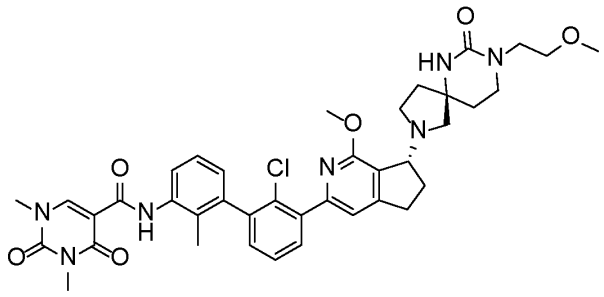
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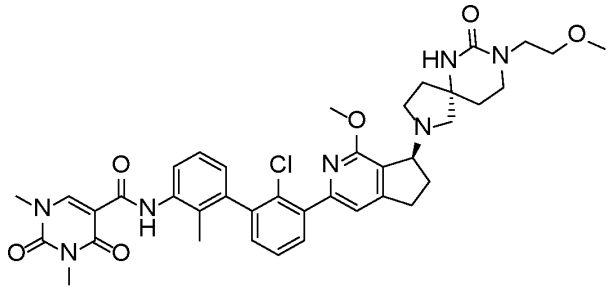
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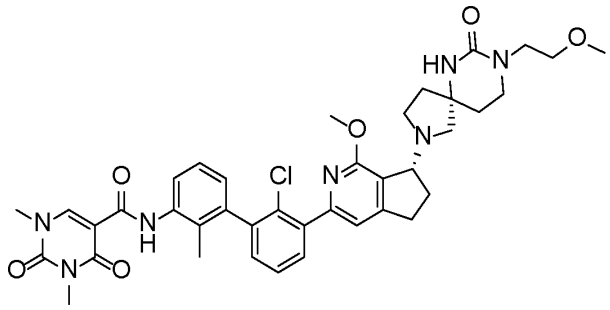
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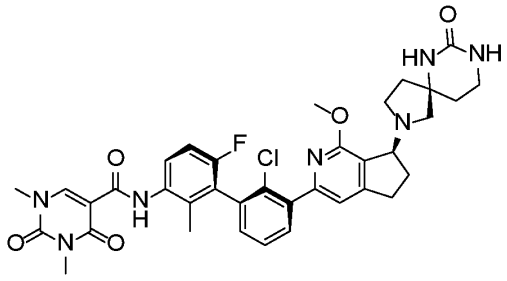
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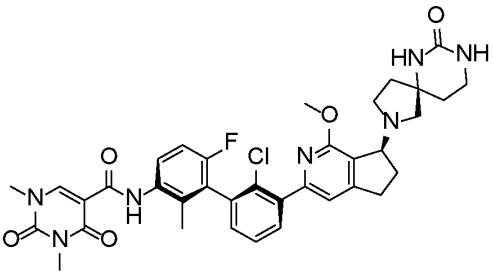
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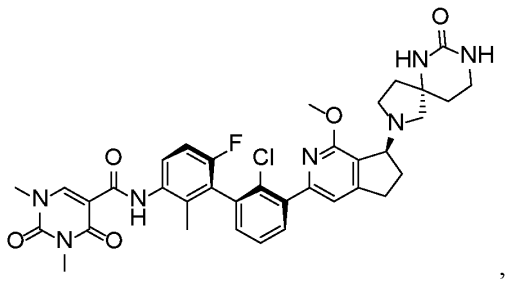
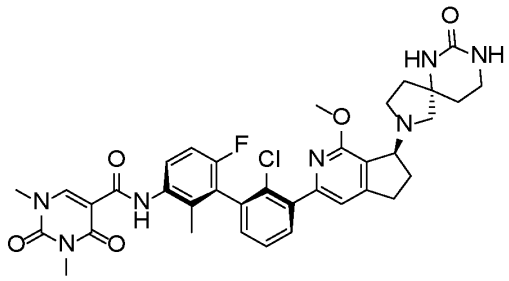
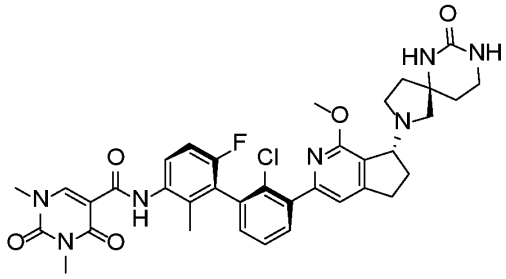
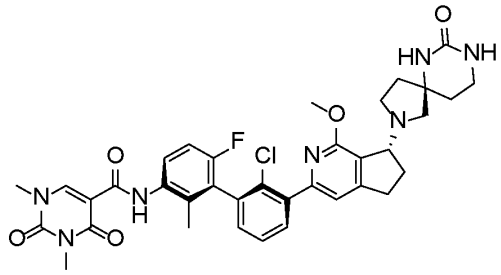
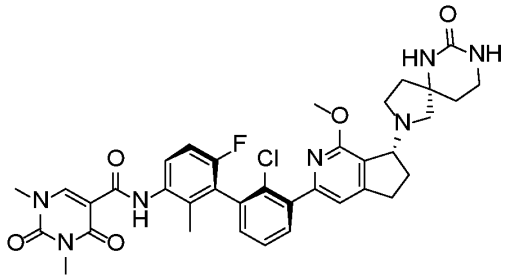
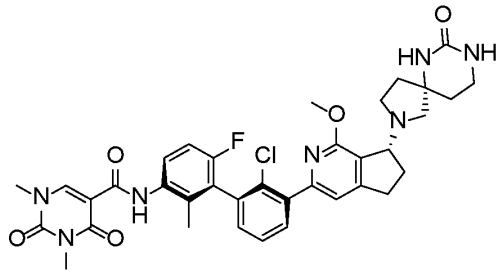
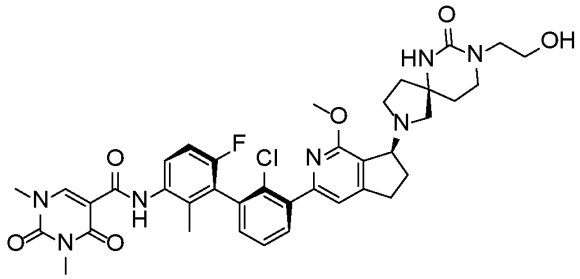
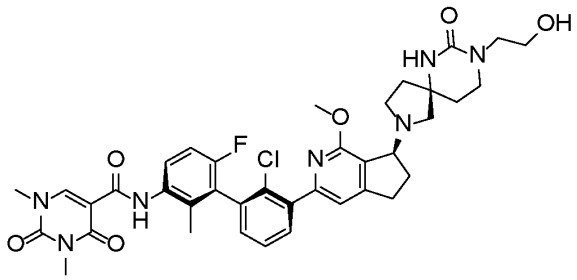
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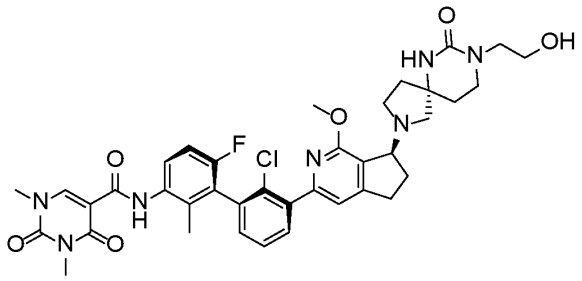


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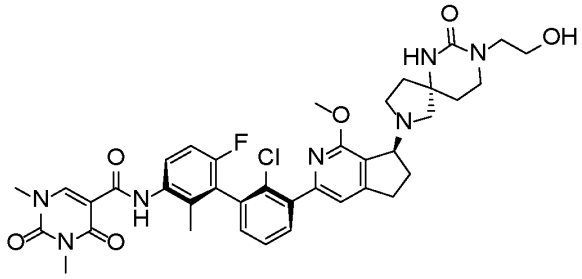


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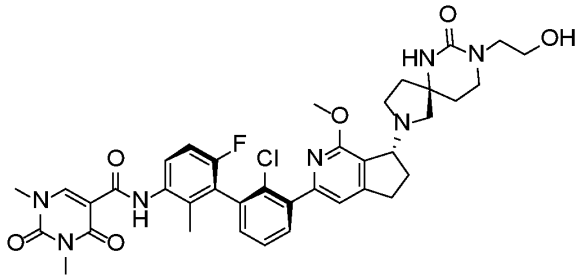

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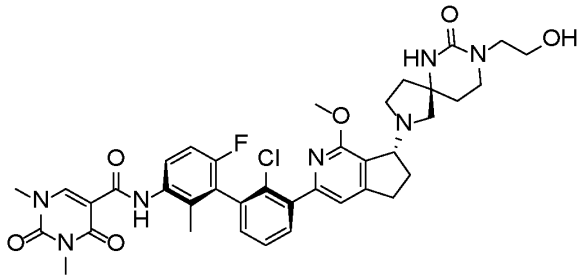
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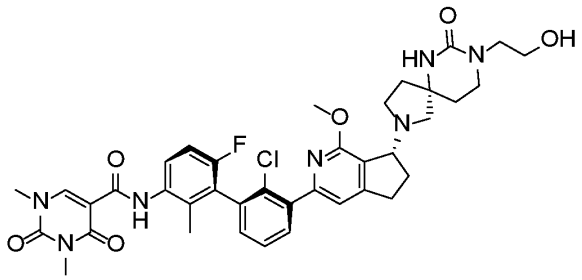
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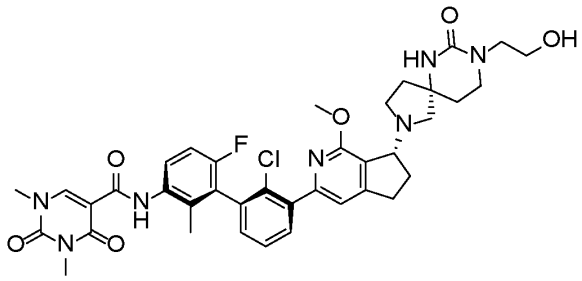
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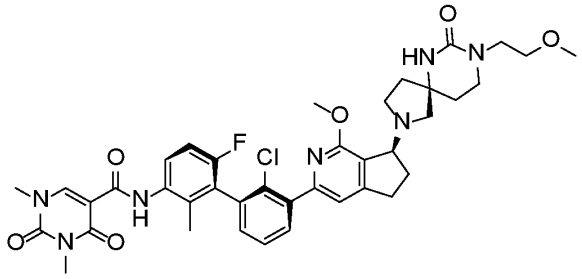
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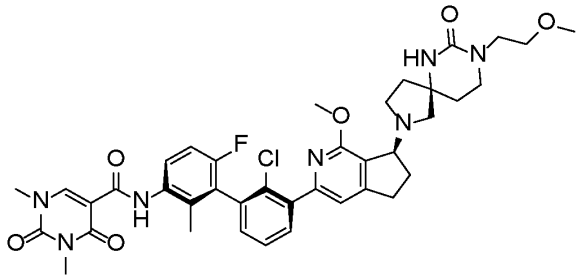
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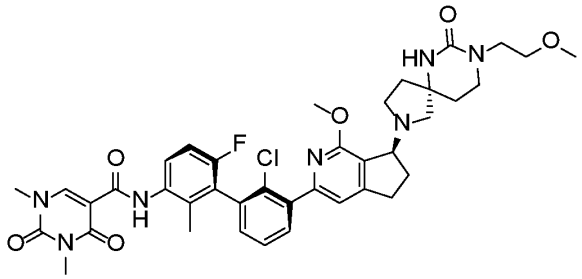
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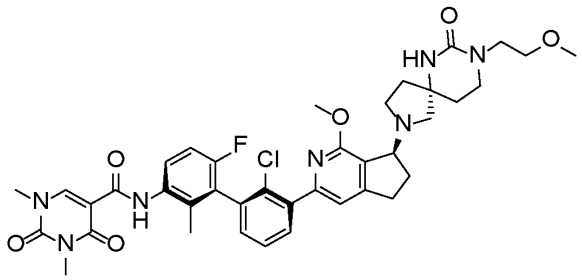
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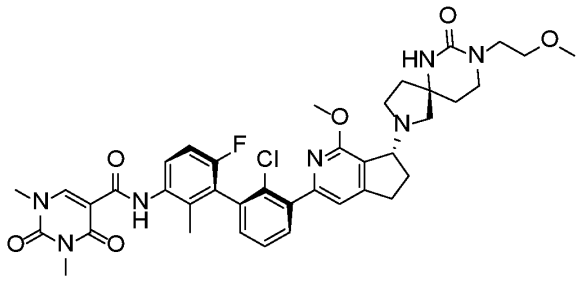
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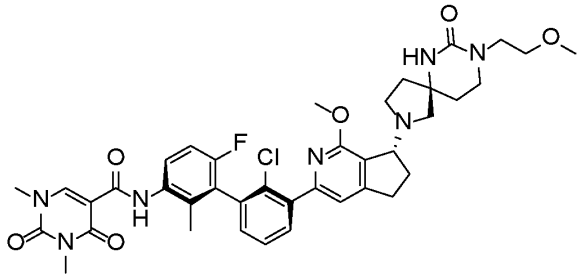


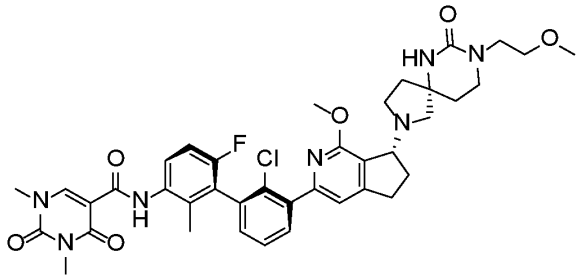
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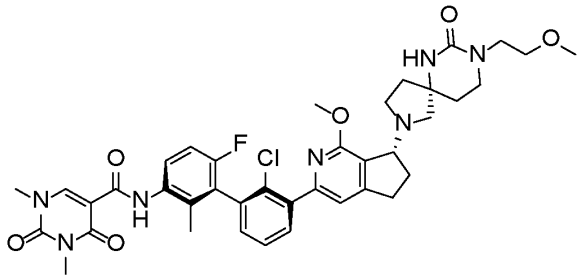


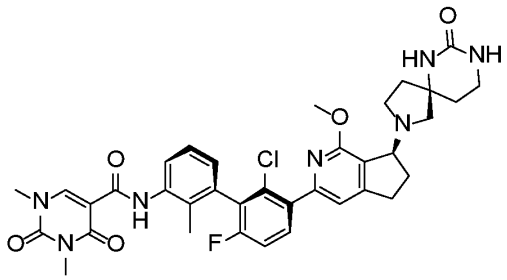
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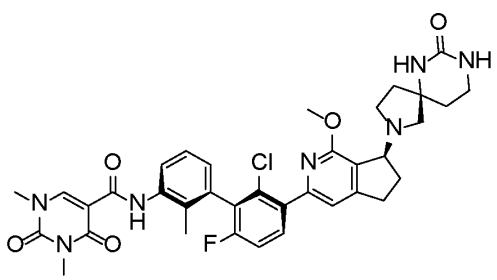

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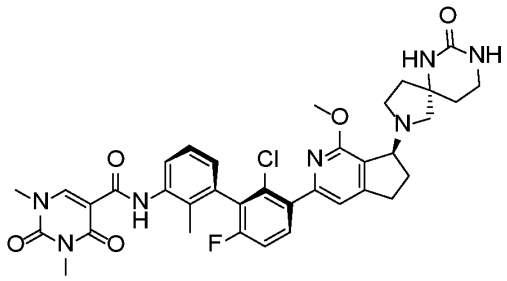
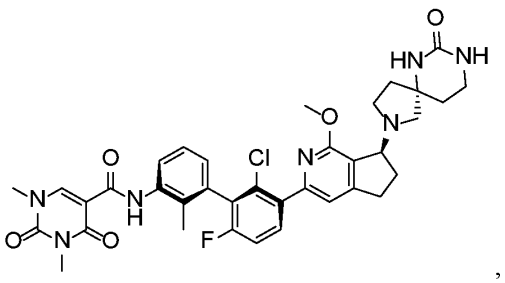
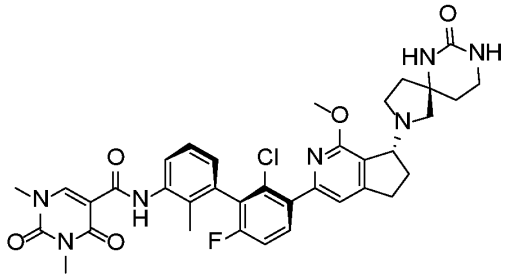
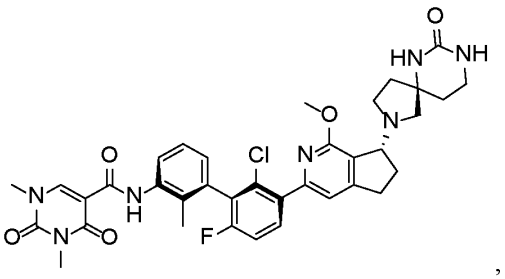
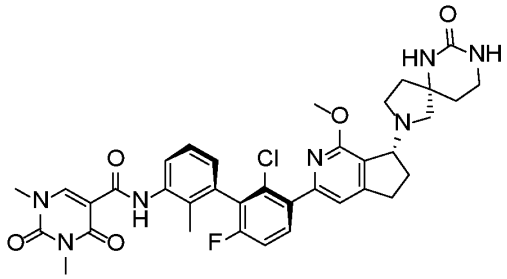
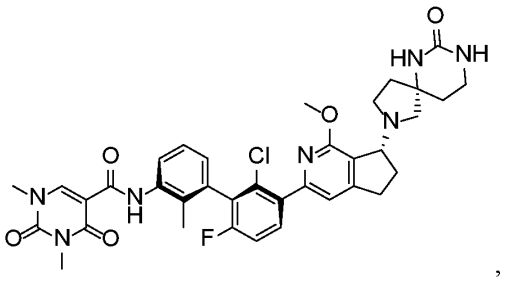
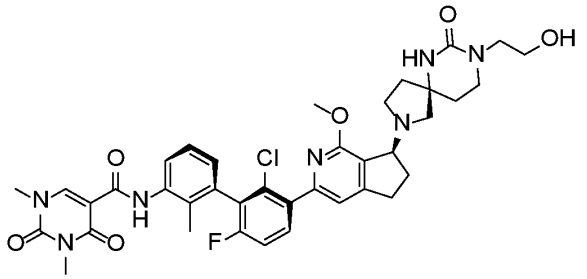
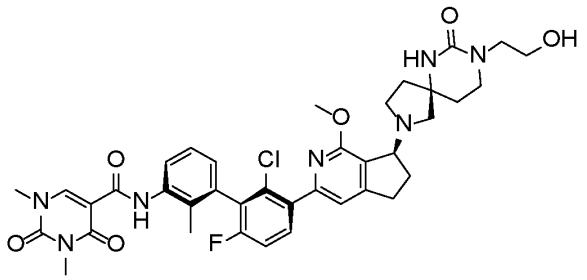

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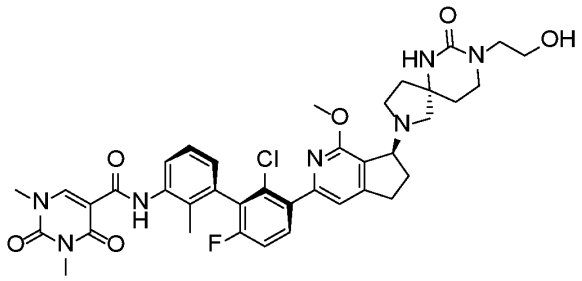

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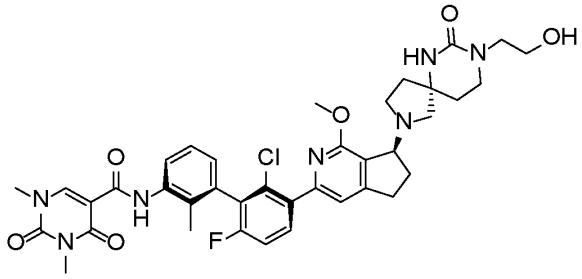

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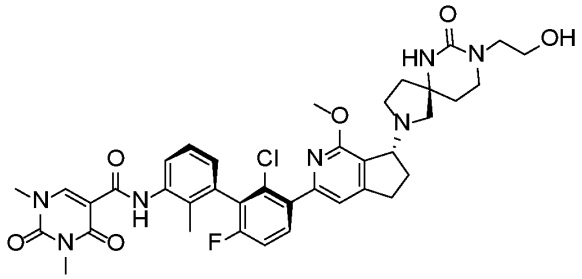

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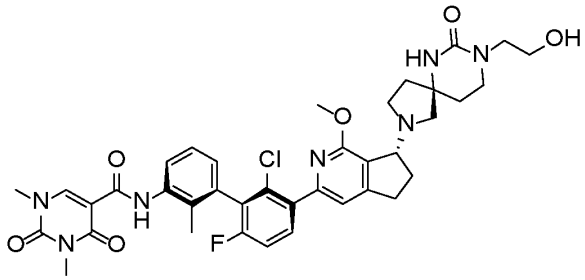
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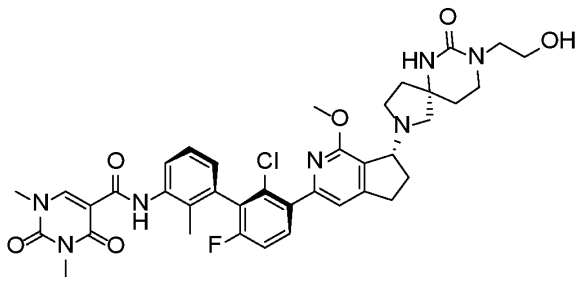
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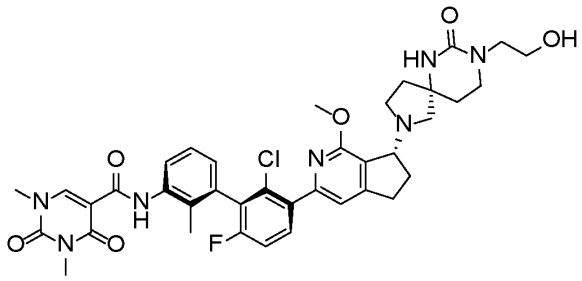
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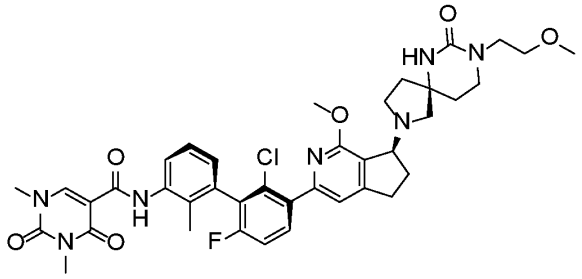
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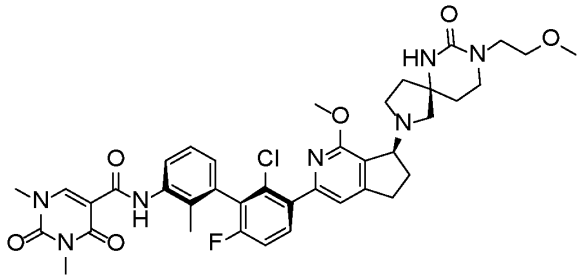
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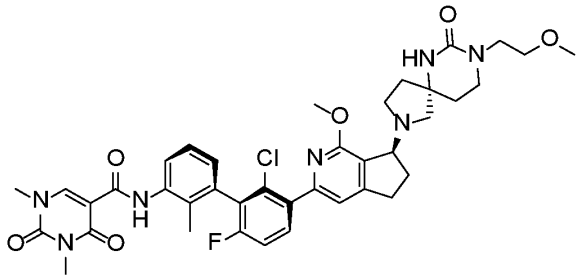
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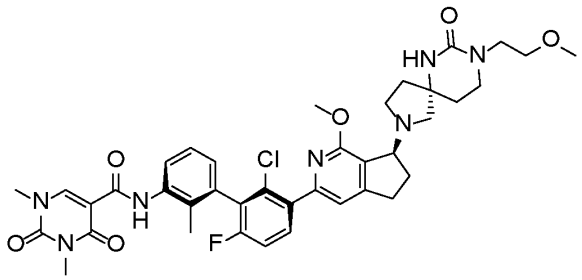
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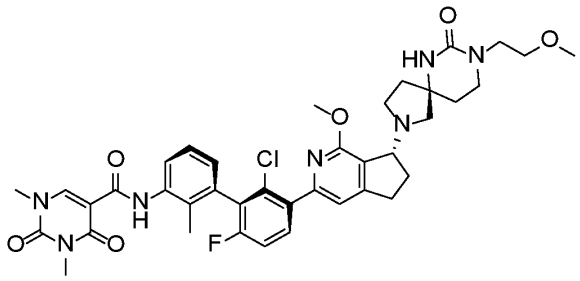
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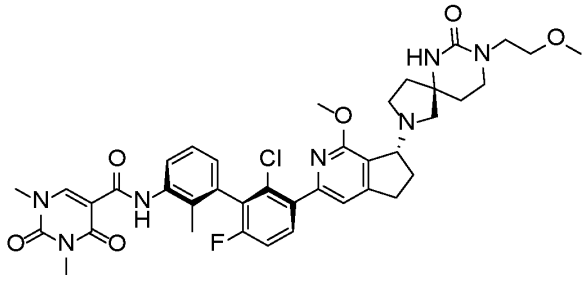


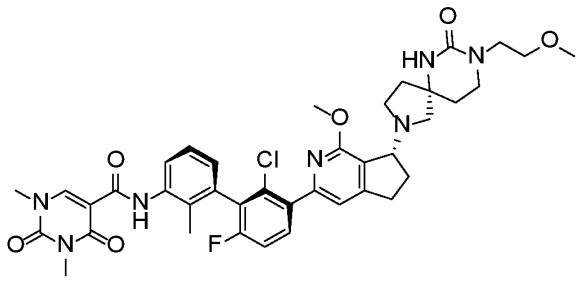
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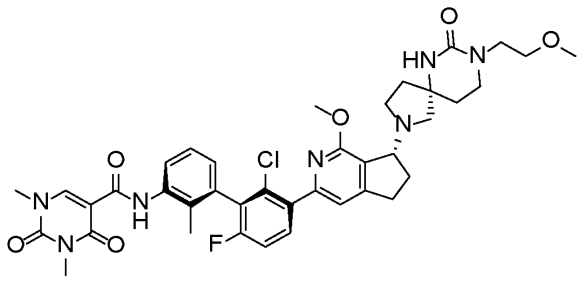


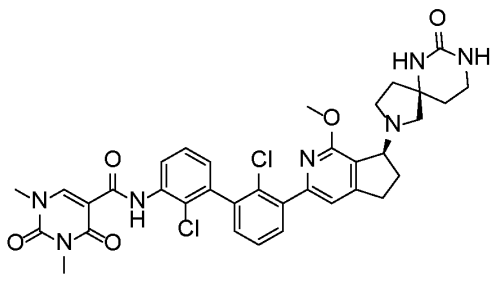
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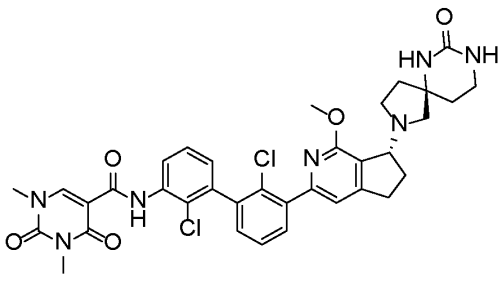

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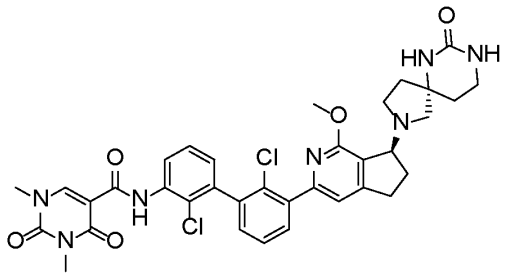
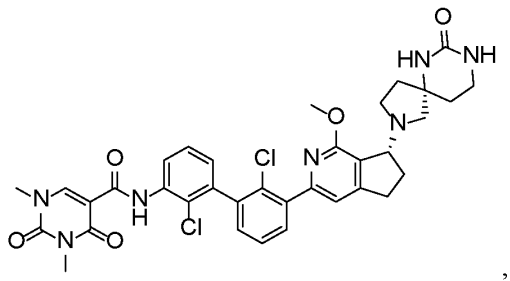
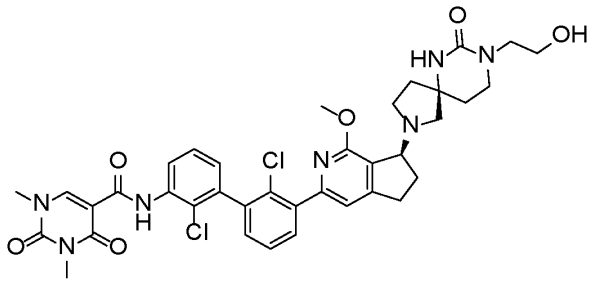
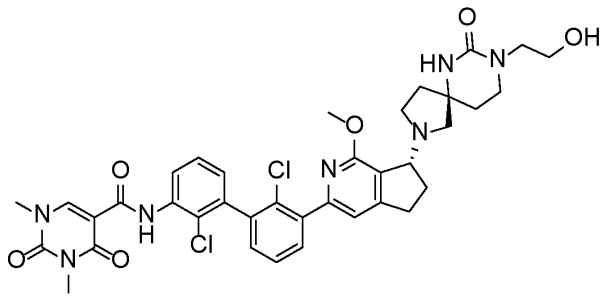
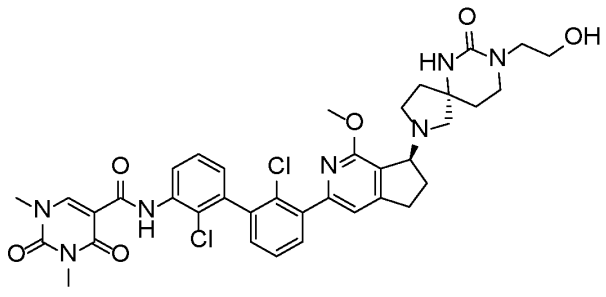

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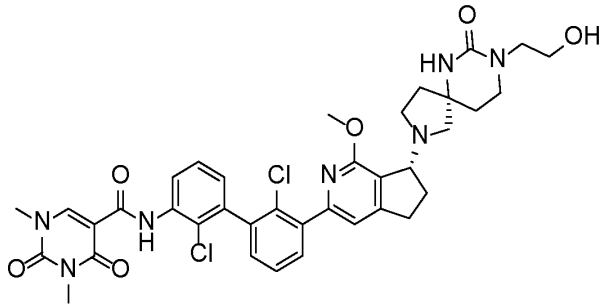

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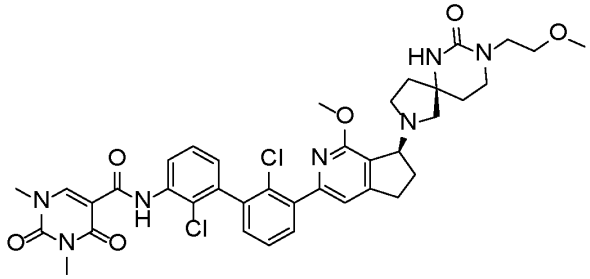

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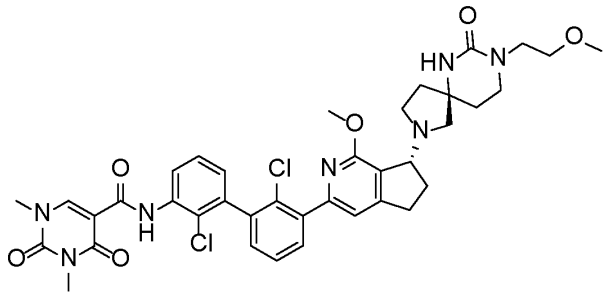

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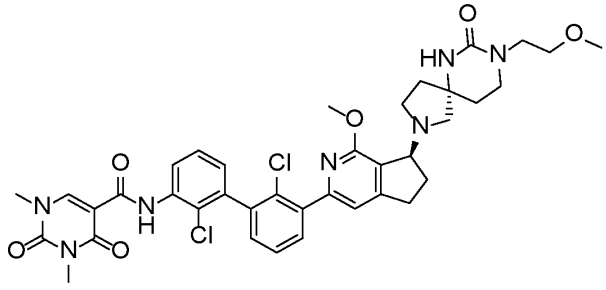
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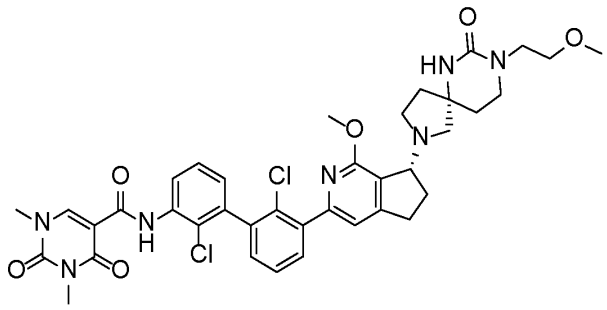
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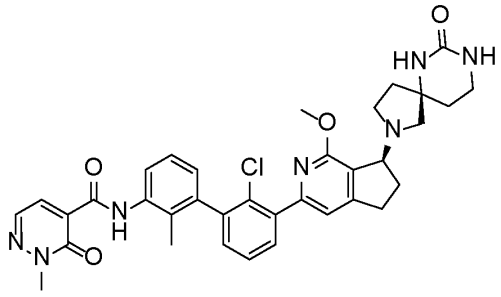
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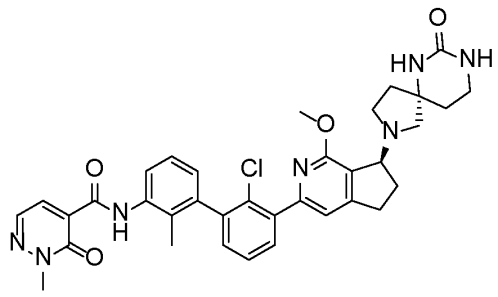
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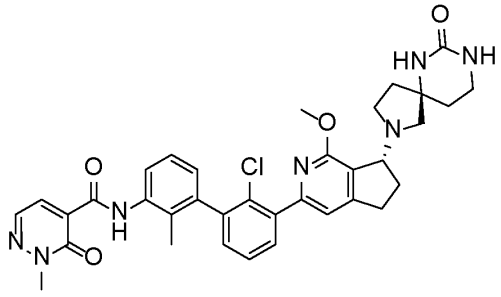
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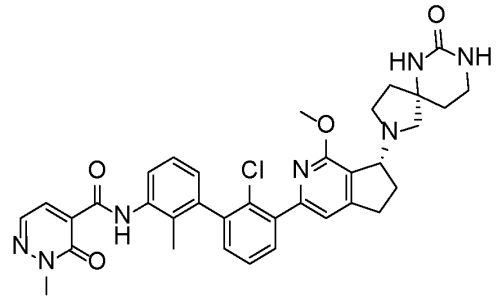
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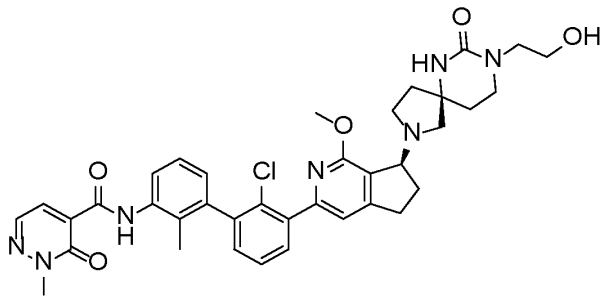
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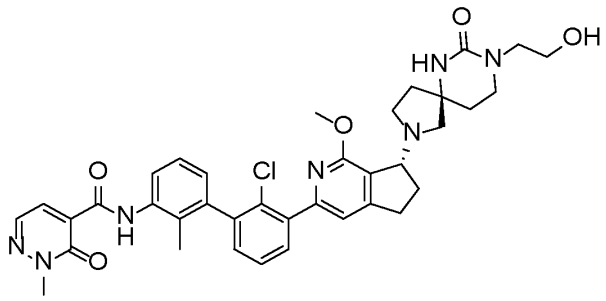
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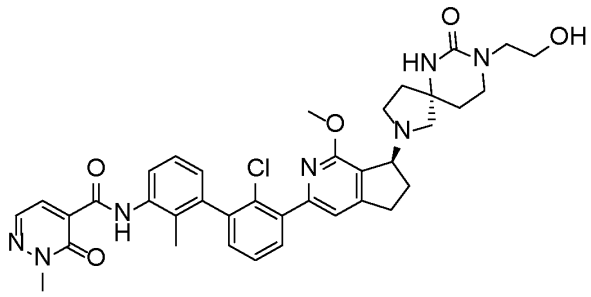
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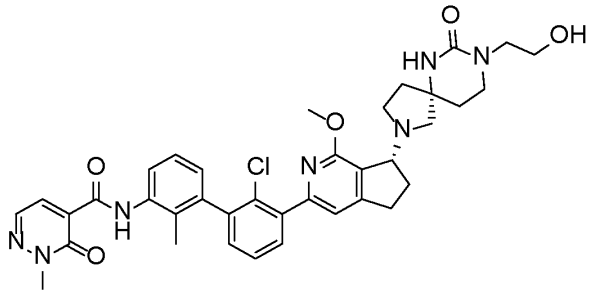
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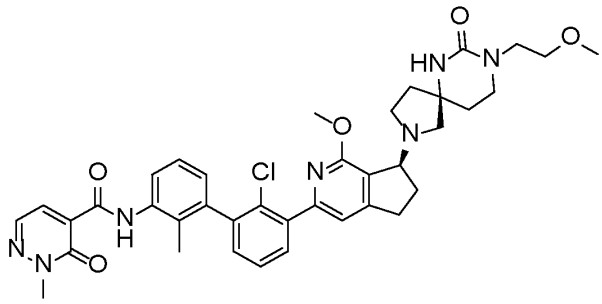
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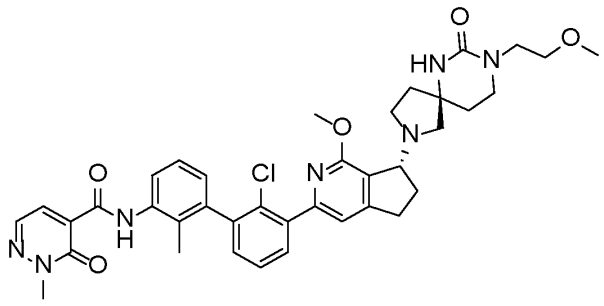
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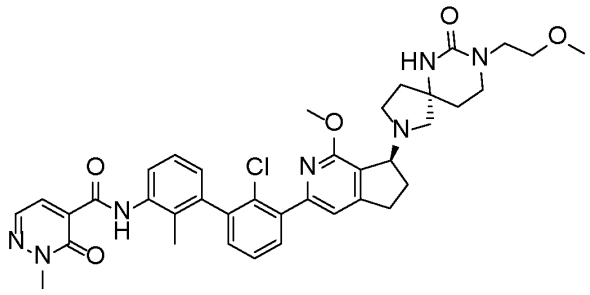
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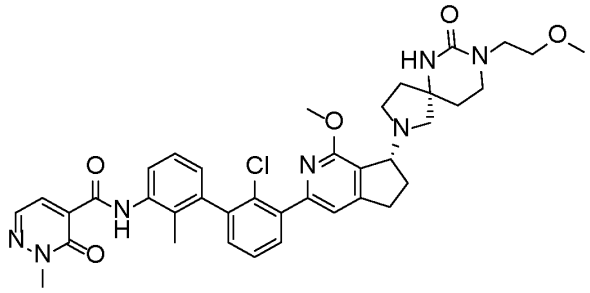
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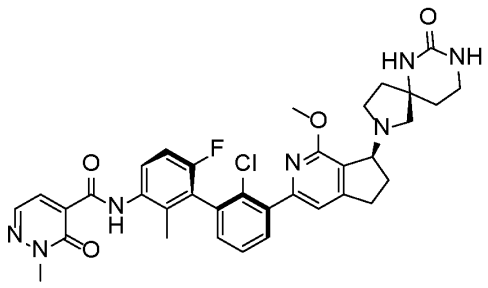
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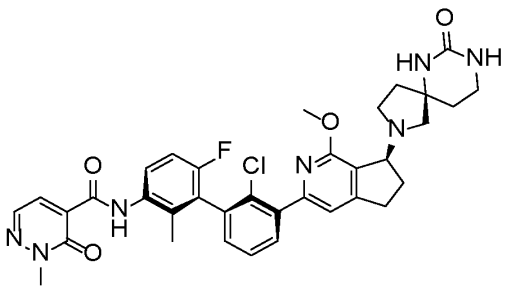
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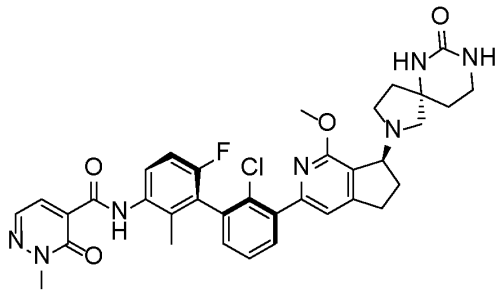
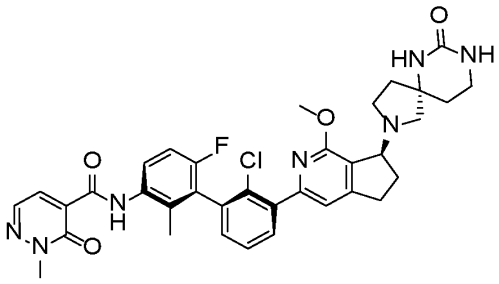
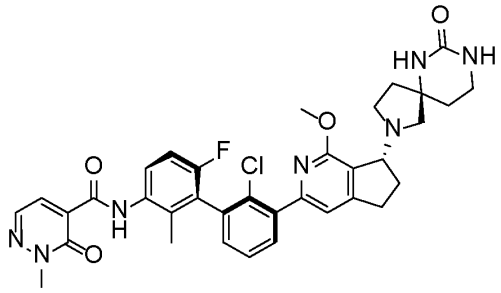
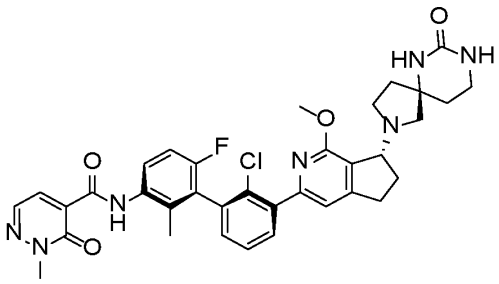
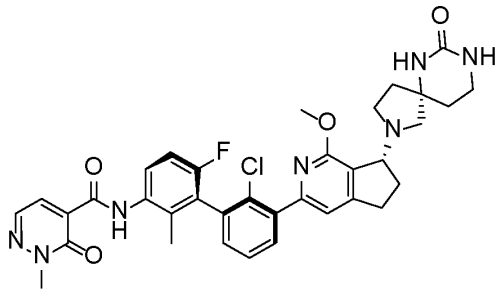
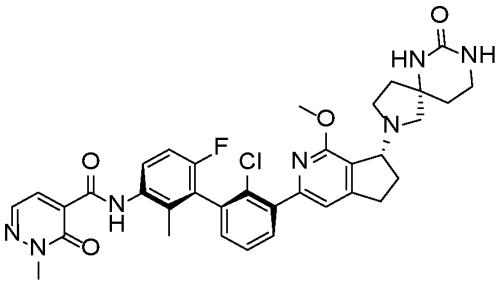
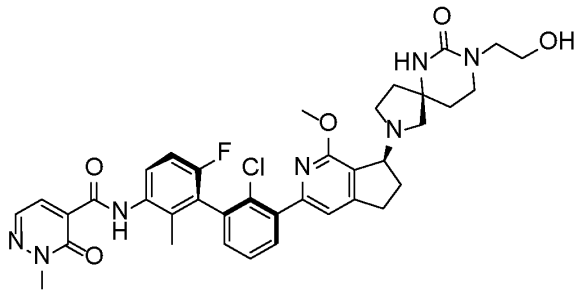
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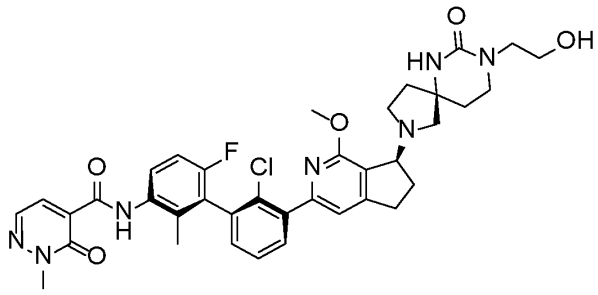


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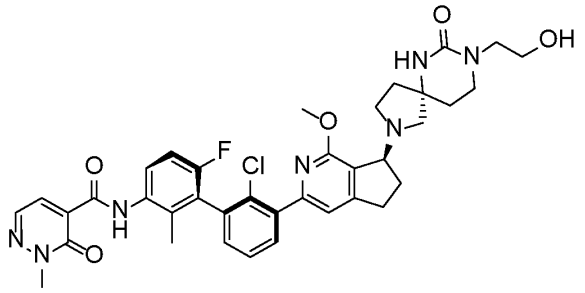


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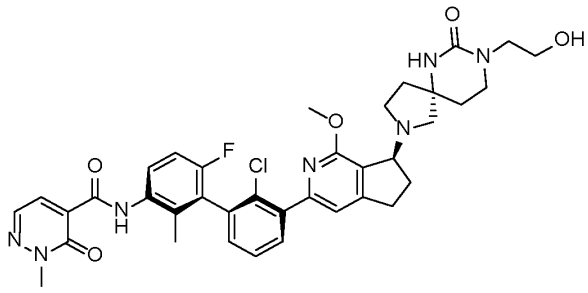

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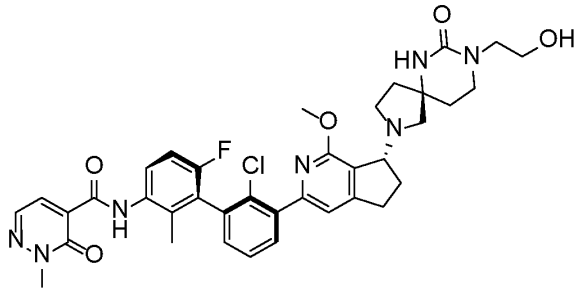
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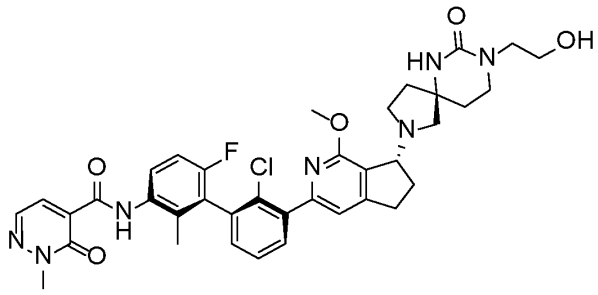
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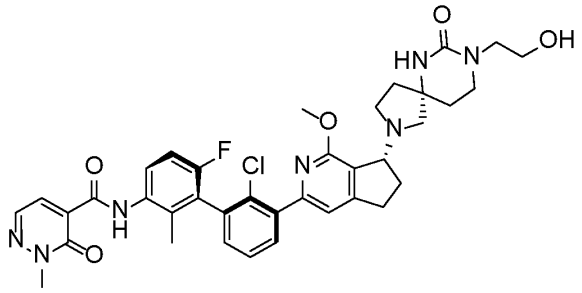
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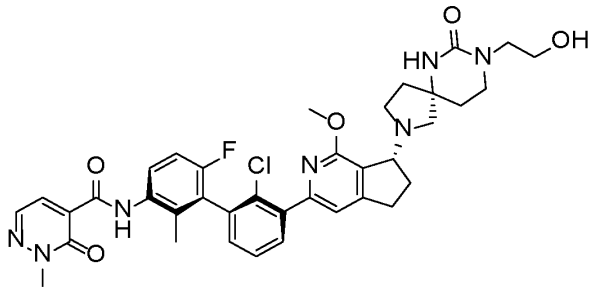
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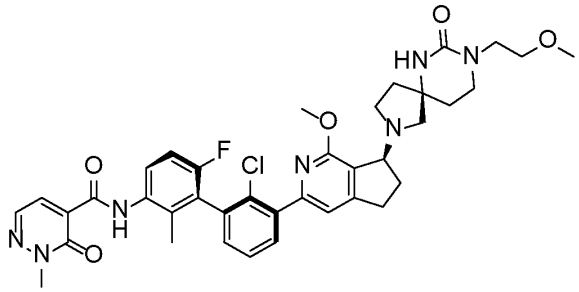
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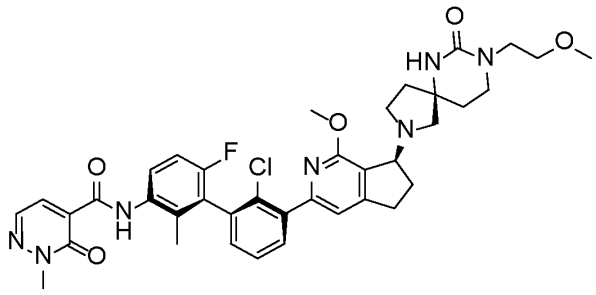
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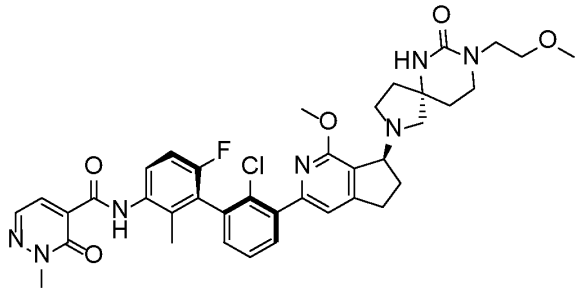
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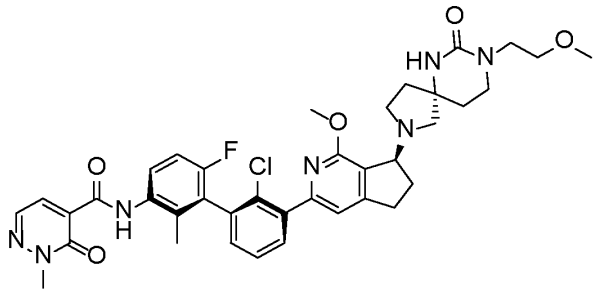
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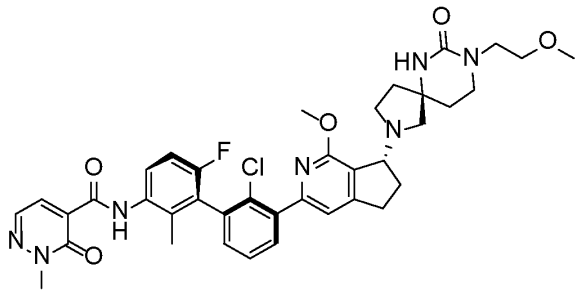
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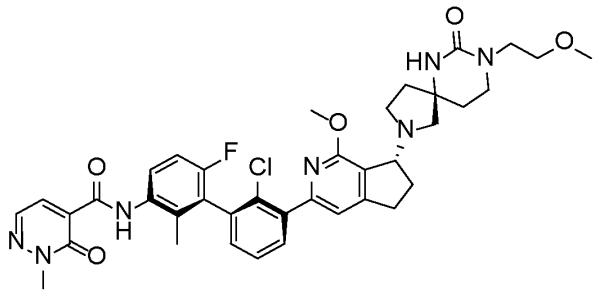
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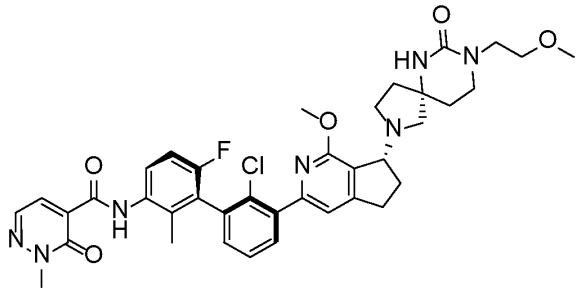
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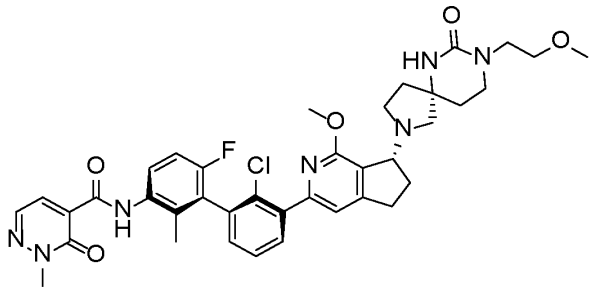
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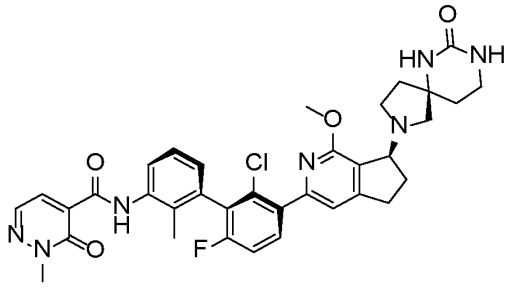
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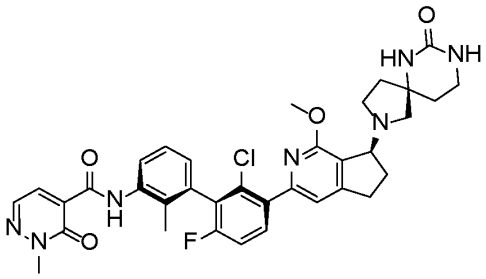
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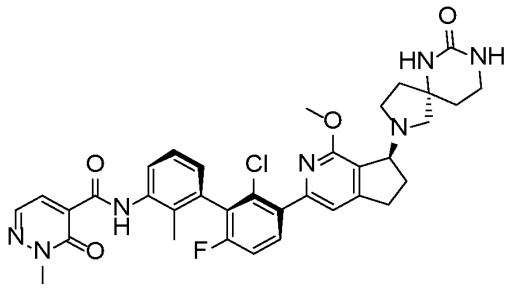
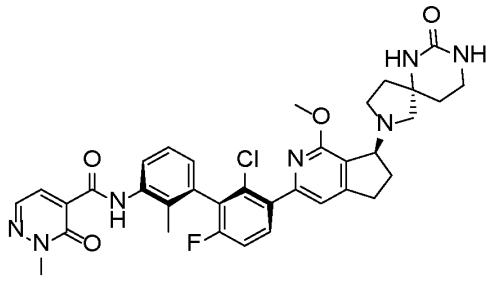
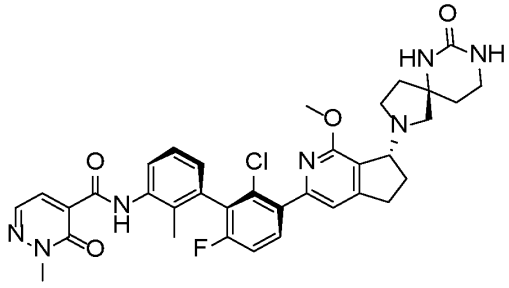
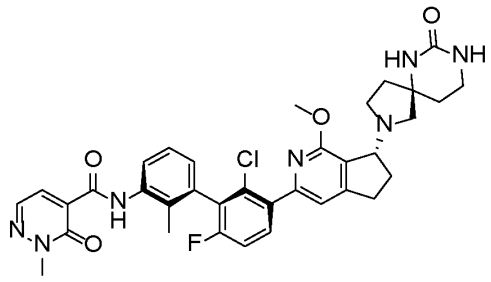
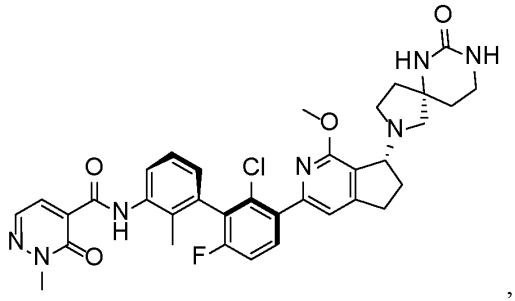
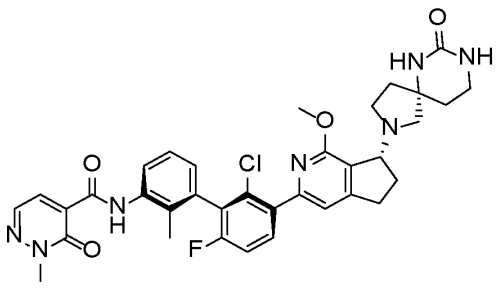
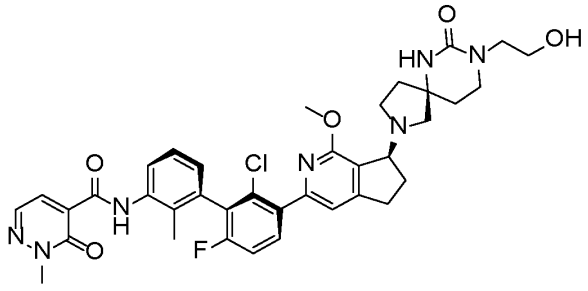
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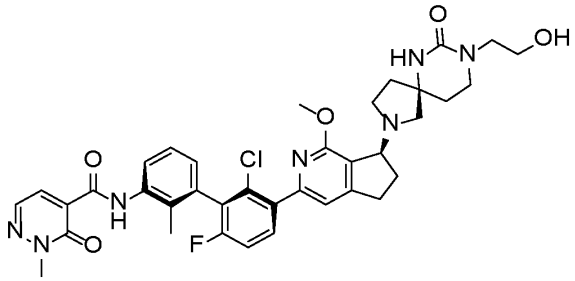


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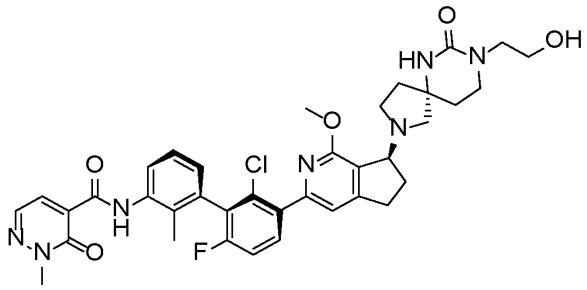


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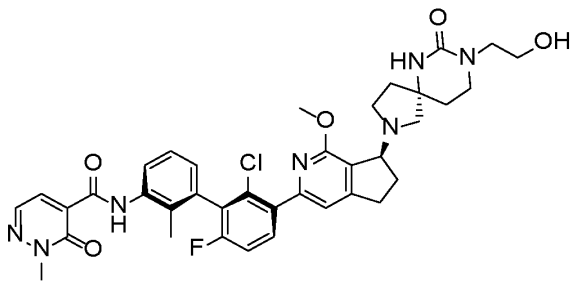

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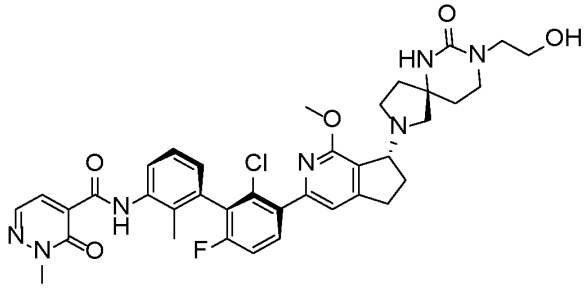
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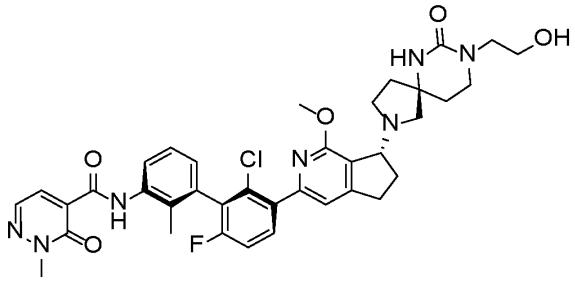
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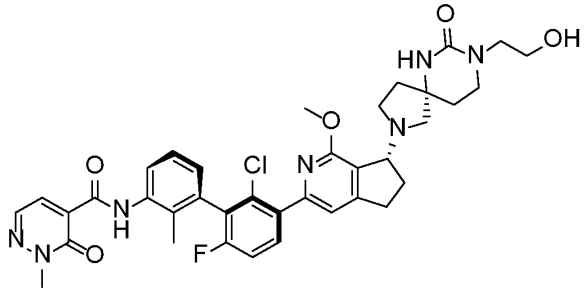
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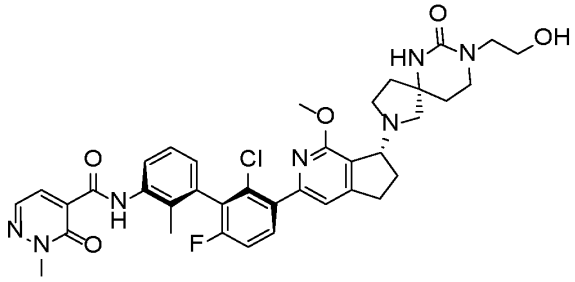
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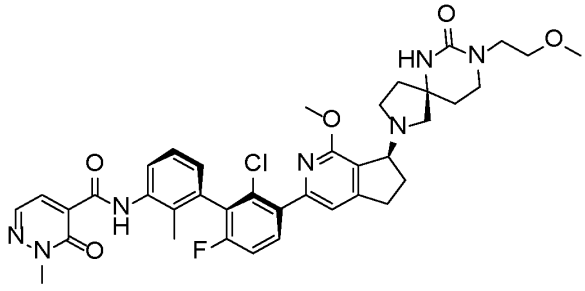
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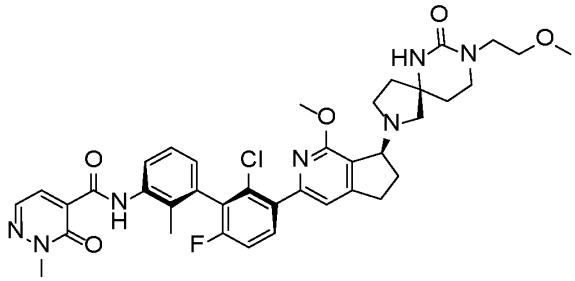
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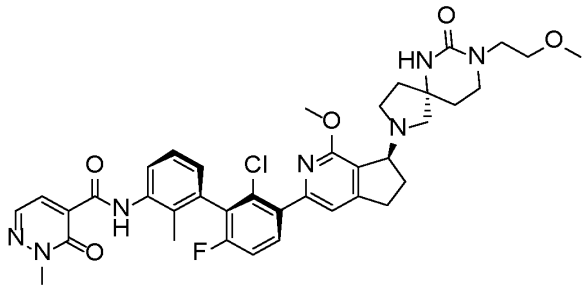


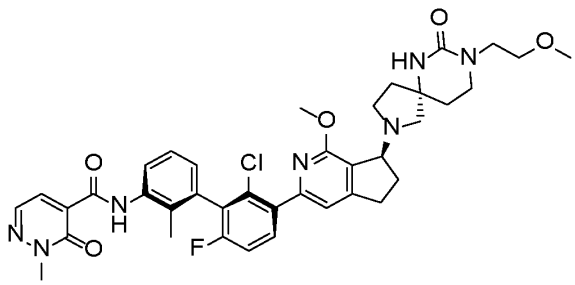
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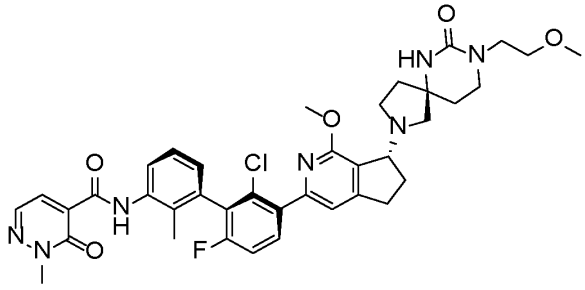


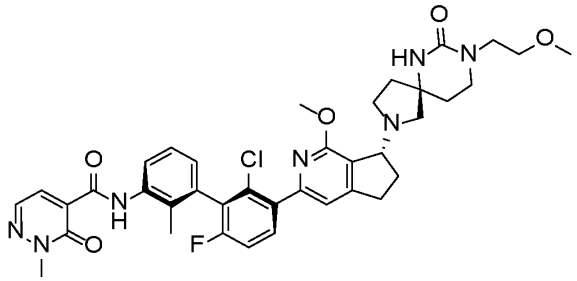
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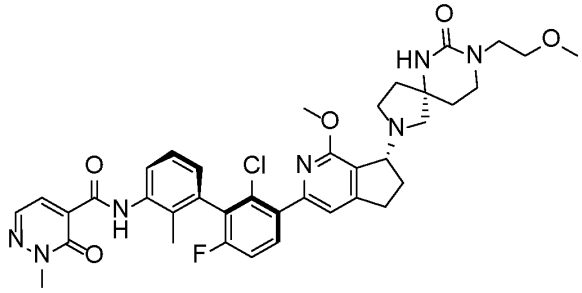

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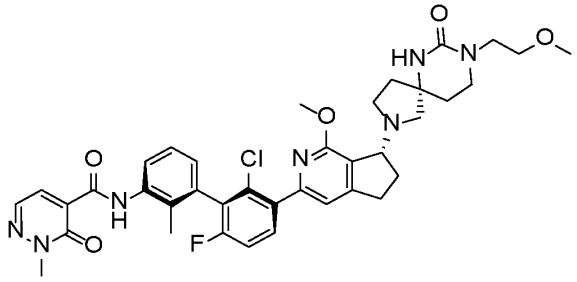

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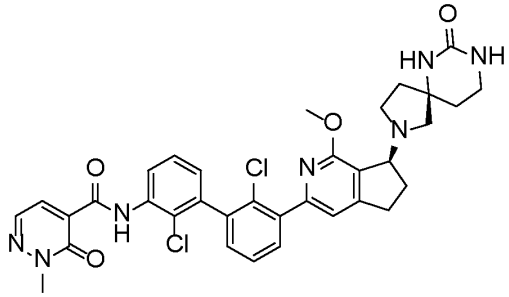
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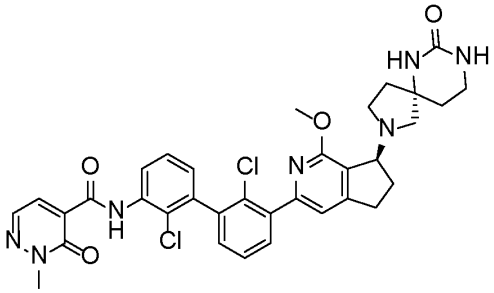
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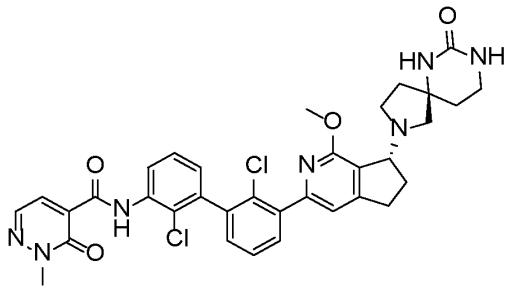
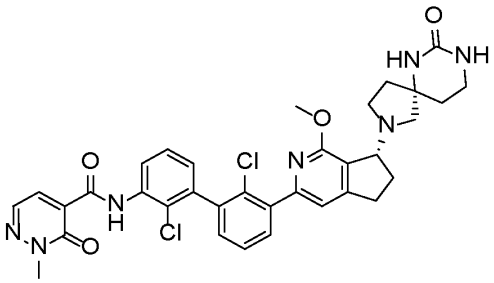
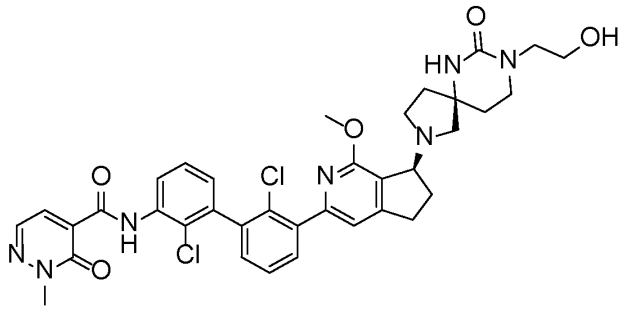
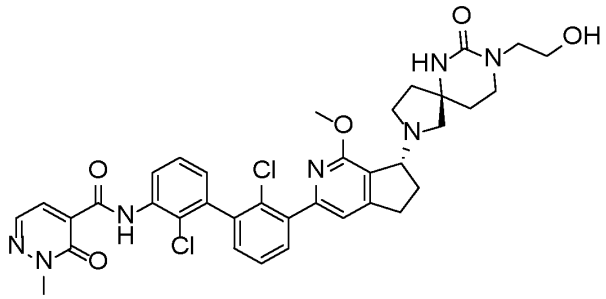
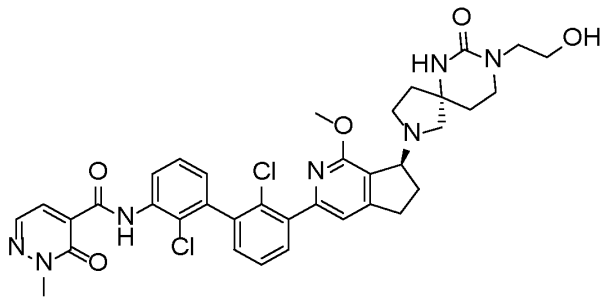
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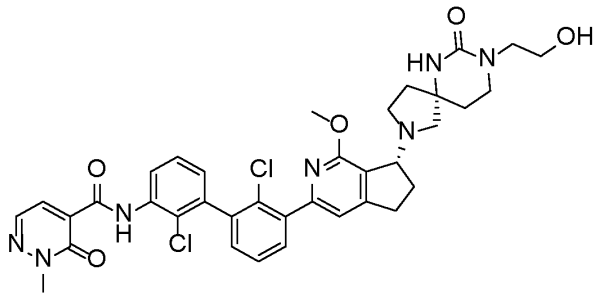


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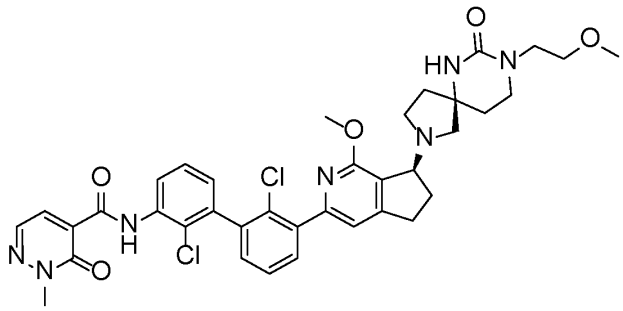


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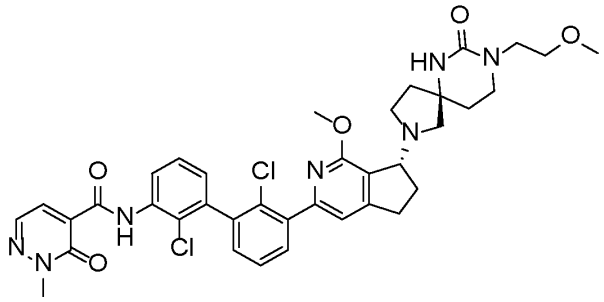

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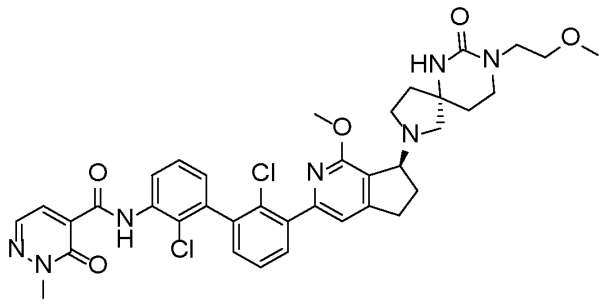
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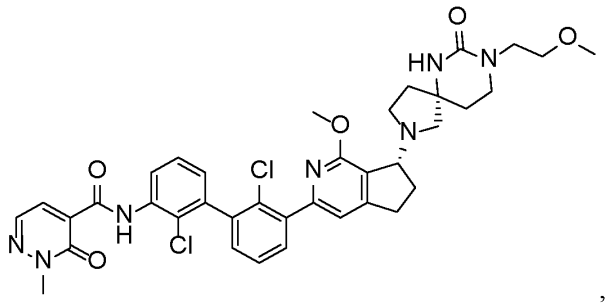
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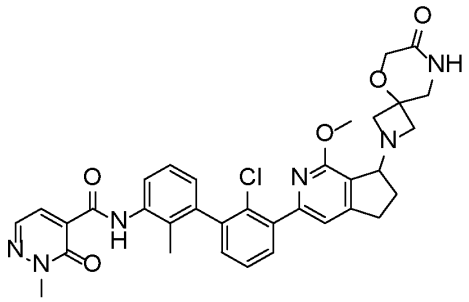
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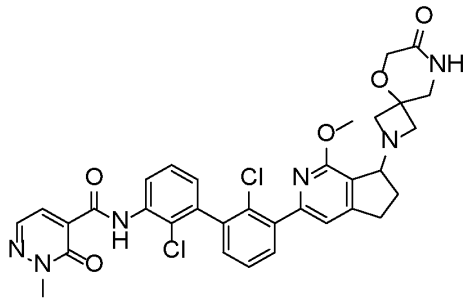
, or a pharmaceutically acceptable salt of any of the foregoing.

Embodiment 90

[0164] The compound of Embodiment 1 or 2, wherein the compound can be



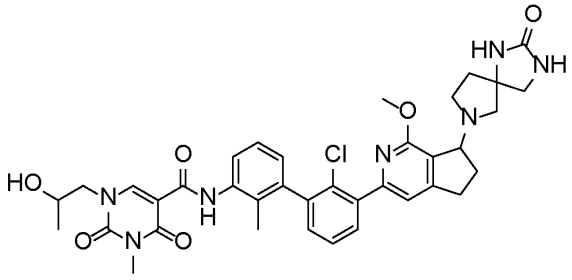
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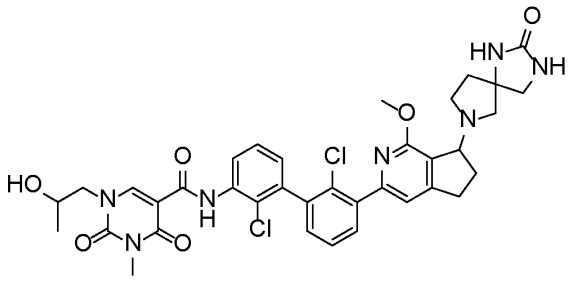
, or a pharmaceutically acceptable salt any of the foregoing.

Embodiment 91

[0165] The compound of Embodiment 1 or 3, wherein the compound can be



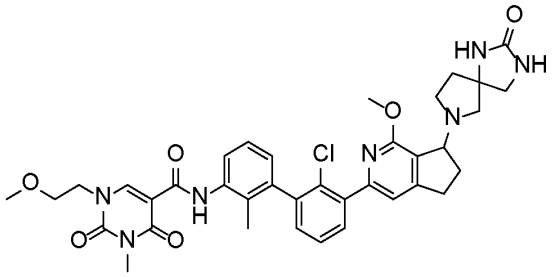
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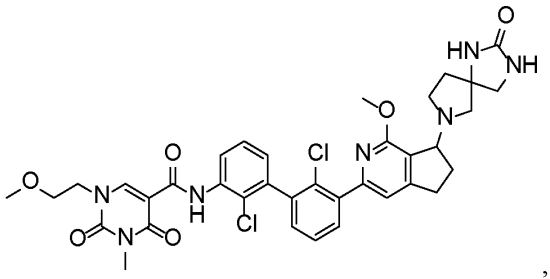
, or a pharmaceutically acceptable salt any of the foregoing.

Embodiment 92

[0166] The compound of Embodiment 1 or 3, wherein the compound can be



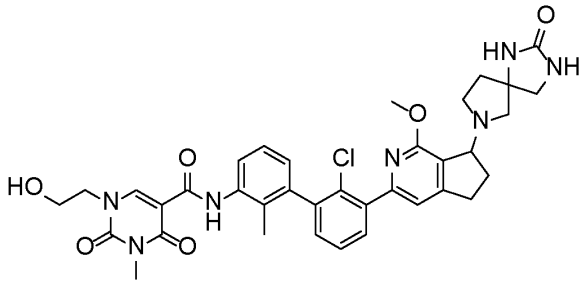
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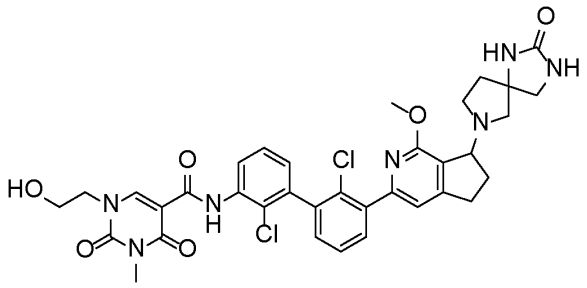
, or a pharmaceutically acceptable salt any of the foregoing.

Embodiment 93

[0167] The compound of Embodiment 1 or 3, wherein the compound can be



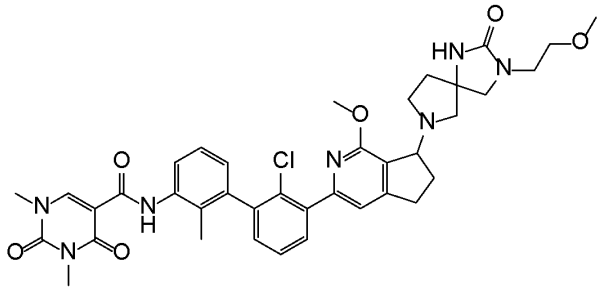
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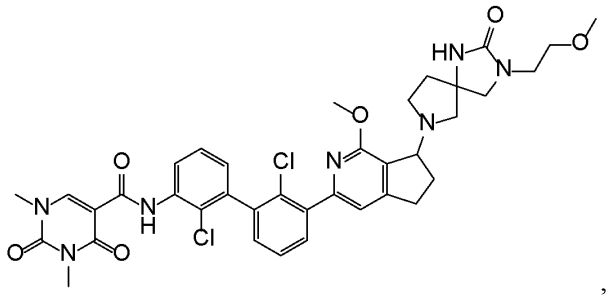
, or a pharmaceutically acceptable salt any of the foregoing.

Embodiment 94

[0168] The compound of Embodiment 1 or 3, wherein the compound can be



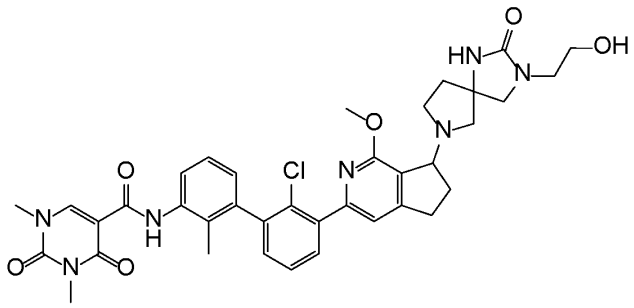
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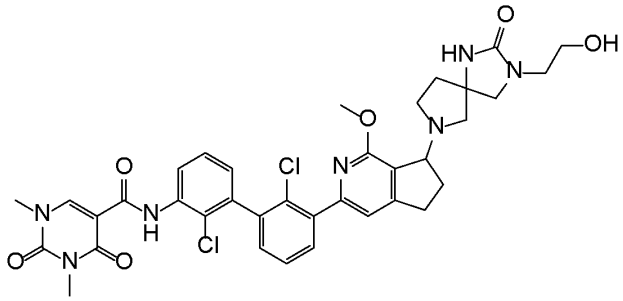
, or a pharmaceutically acceptable salt any of the foregoing.

Embodiment 95

[0169] The compound of Embodiment 1 or 3, wherein the compound can be



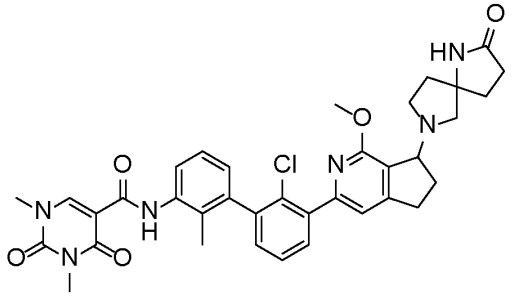
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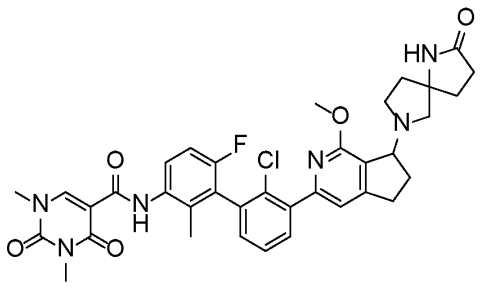
, or a pharmaceutically acceptable salt any of the foregoing.

Embodiment 96

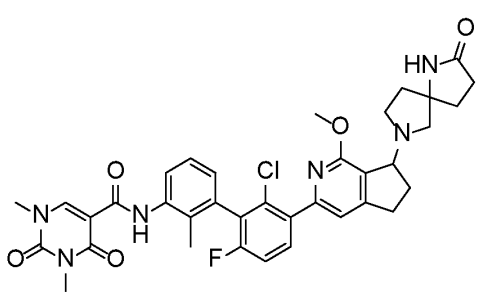
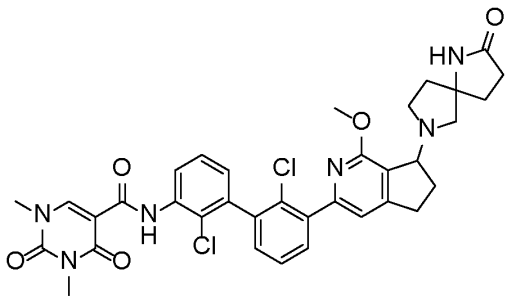
[0170] The compound of Embodiment 1 or 3, wherein the compound can be,



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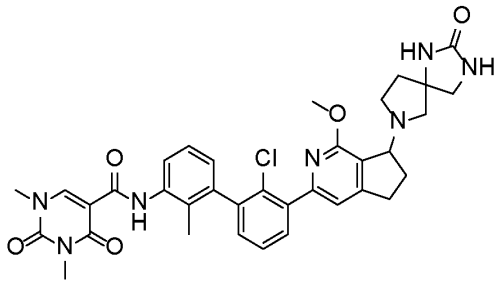
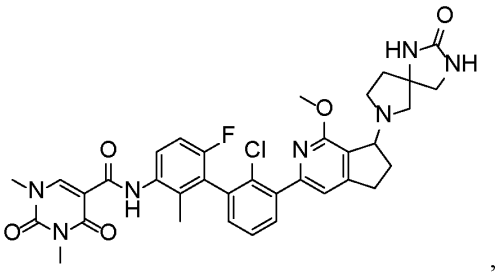
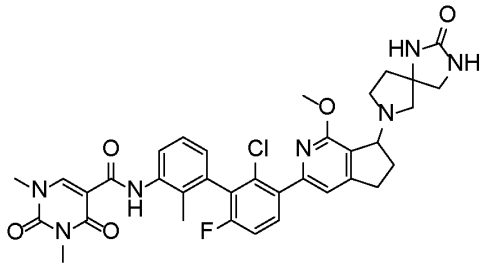
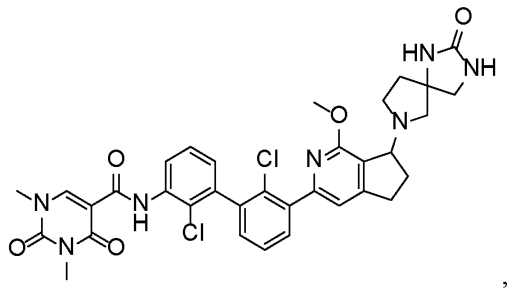
,


or


, or a pharmaceutically acceptable salt any of the foregoing.

Embodiment 97

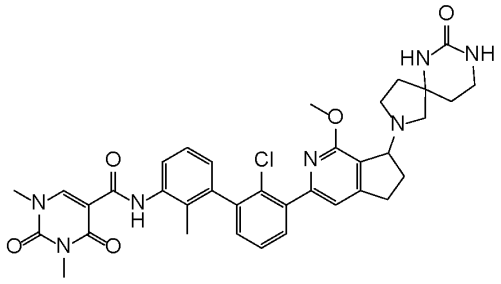
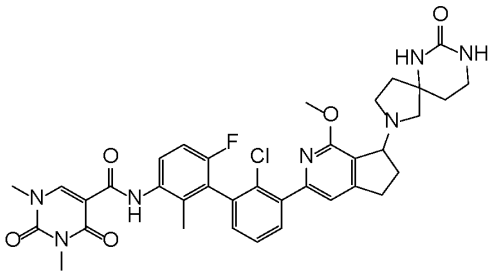
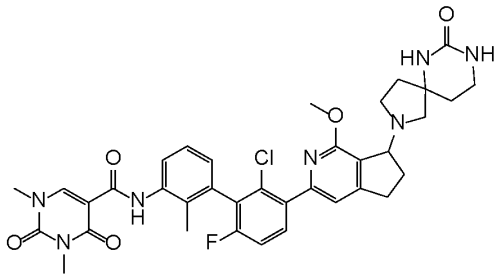
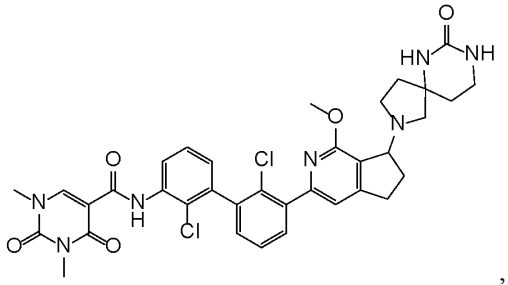
[0171] The compound of Embodiment 1 or 3, wherein the compound can be,


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or

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or a pharmaceutically acceptable salt any of the foregoing.

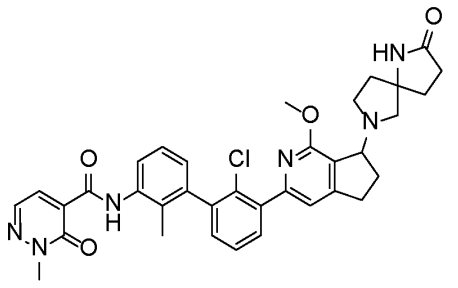
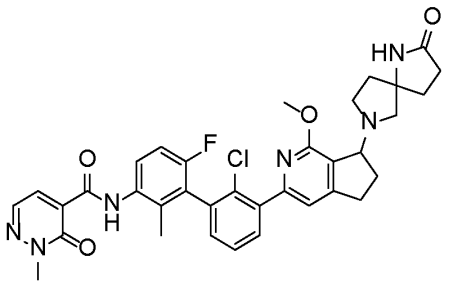
Embodiment 98

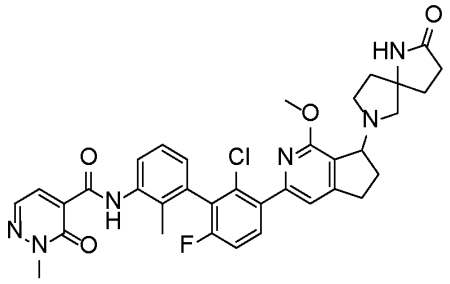
[0172] The compound of Embodiment 1 or 3, wherein the compound can be,


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or

, or a pharmaceutically acceptable salt any of the foregoing.

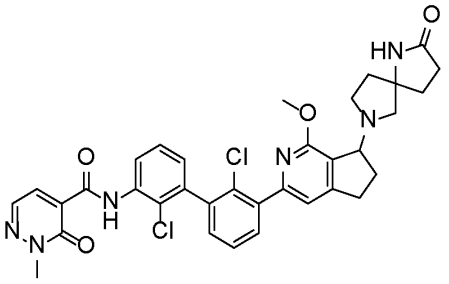
Embodiment 99

[0173] The compound of Embodiment 1 or 3, wherein the compound can be


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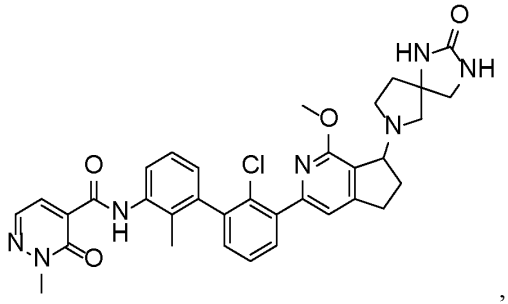
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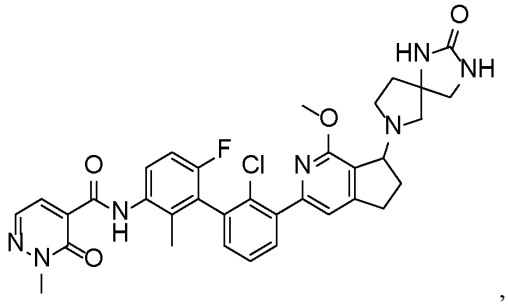
, or a pharmaceutically acceptable salt of any of the foregoing.

Embodiment 100

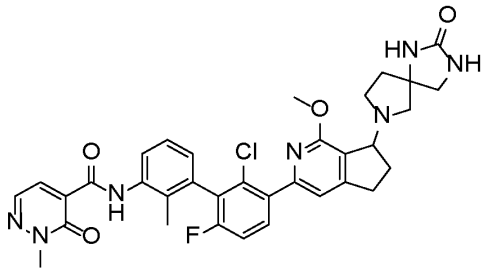
[0174] The compound of Embodiment 1 or 3, wherein the compound can be



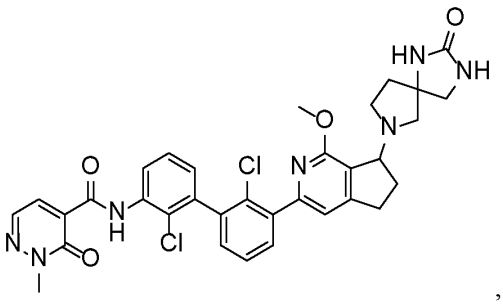
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or

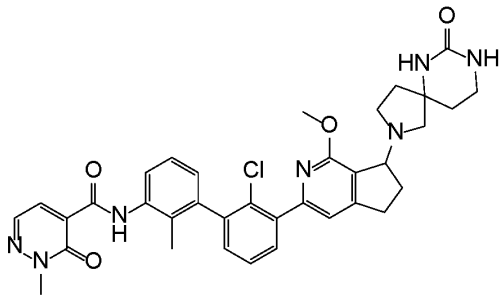
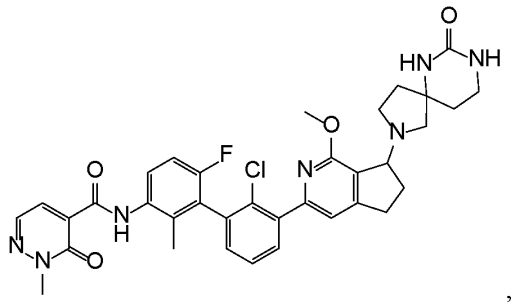
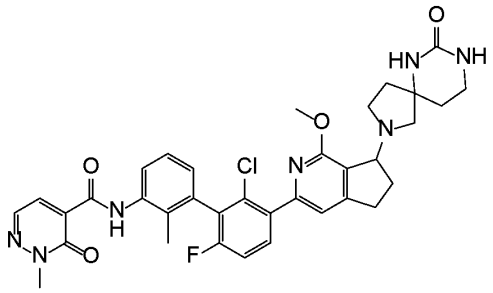
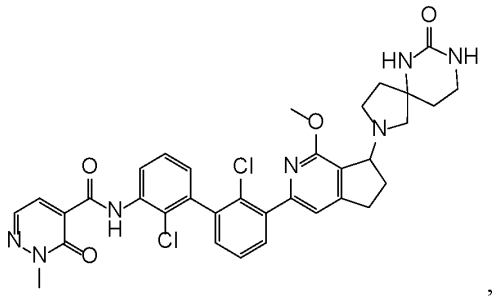


,

or a pharmaceutically acceptable salt of any of the foregoing.

Embodiment 101

[0175] The compound of Embodiment 1 or 3, wherein the compound can be


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or

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or a pharmaceutically acceptable salt of any of the foregoing.

Embodiment 102

[0176] A pharmaceutical composition that can include an effective amount of a compound of any one of Embodiments 1-101, or a pharmaceutically acceptable salt thereof, and an excipient.

Embodiment 103

[0177] 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 1-101, or a pharmaceutically acceptable salt thereof.

Embodiment 104

[0178] 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 1-101, or a pharmaceutically acceptable salt thereof.

Embodiment 105

[0179] The method of any one of Embodiments 103-104, that can further include administering surgery, radiation therapy, chemotherapy, targeted therapy, immunotherapy, hormonal therapy, or antiviral therapy.

Embodiment 106

[0180] A compound of any one of Embodiments 1-101, or a pharmaceutically acceptable salt thereof, for use in treating hepatitis B.

Embodiment 107

[0181] A compound of any one of Embodiments 1-101, or a pharmaceutically acceptable salt thereof, for use in treating hepatocellular carcinoma (HCC).

Embodiment 108

[0182] The compound of any one of Embodiments 106-107, or a pharmaceutically acceptable salt thereof, wherein the use can further include administering surgery, radiation therapy, chemotherapy, targeted therapy, immunotherapy, hormonal therapy, or antiviral therapy.

Embodiment 109

[0183] Use of a compound of any one of Embodiments 1-101, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for use in treating hepatitis B.

Embodiment 110

[0184] Use of a compound of any one of Embodiments 1-101, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for use in treating hepatocellular carcinoma (HCC).

Embodiment 111

[0185] The use of any one of Embodiments 109-110, wherein the medicament can be for use in combination with surgery, radiation therapy, chemotherapy, targeted therapy, immunotherapy, hormonal therapy, or antiviral therapy.

Methods of Preparation

[0186] The compounds described herein, along with pharmaceutically acceptable salts thereof, can be prepared according to the Examples 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.

Pharmaceutical Compositions

[0187] Some embodiments described herein relate to pharmaceutical compositions that comprise, consist essentially of, or consist of an effective amount of a compound described herein, 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.

[0188] The terms "function" and "functional" as used herein refer to a biological, enzymatic, or therapeutic function.

[0189] The terms "effective amount" or "effective dose" is used to indicate an amount of an active compound, or pharmaceutical agent, which 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.

[0190] "Formulation", "pharmaceutical composition", and "composition" as used interchangeably herein are equivalent terms referring to a composition of matter for administration to a subject.

[0191] The term "pharmaceutically acceptable" means compatible with the treatment of a subject, and in particular, a human.

[0192] 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.

[0193] 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.

[0194] 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.

[0195] 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.

[0196] 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.

[0197] 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.

[0198] 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.

[0199] 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.

[0200] 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.

[0201] 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

[0202] Some embodiments disclosed herein relate 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, 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.

[0203] 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).

[0204] 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.

[0205] 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.

[0206] 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.

[0207] 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.

[0208] 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 described herein, or a pharmaceutically acceptable salt thereof. 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.

[0209] 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.

[0210] 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.

[0211] 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.

[0212] A potential advantage of utilizing a compound as described herein, or a pharmaceutically acceptable salt thereof, may include effective inhibition of PD-1/PD-L1 interactions and/or inhibition of the PD-1/PD-L1 pathway.

[0213] Additional advantages of utilizing a compound as described herein, or a pharmaceutically acceptable salt thereof, may include low toxicity and reduced drug-drug interactions. Further advantages of utilizing a compound as described herein, or a pharmaceutically acceptable salt thereof, may include increased levels of plasma exposure at lower dosages compared to INCB086550 and higher oral bioavailability in comparison to INCB086550. Even further advantages of utilizing a compound as described herein, or a pharmaceutically acceptable salt thereof, may include prolonged half-lives and/or liver-tropic tissue distributions.

[0214] 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.

[0215] 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.

[0216] 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).

[0217] 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).

[0218] 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).

[0219] 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).

[0220] 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.

[0221] 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).

[0222] 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

[0223] 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.

[0224] Hereinafter, the term "rt", "r.t." or "RT" means room temperature; "EtOAc" or "EA" means ethyl acetate; "MeCN" or "ACN" means acetonitrile; "Pd(dppf)Cl_2." means [1.1'-Bis(diphenylphosphino)ferrocene]-dichloropalladium(II); "$PdCl_2$(dtbpf)" or "Pd-118" means bis(di-tert-butylphosphino)ferrocene]-dichloropalladium(II); "$Zn(OAc)_2$" means zinc(II) acetate; "TCFH" means N,N,N′,N′-tetramethylchloroformamidinium

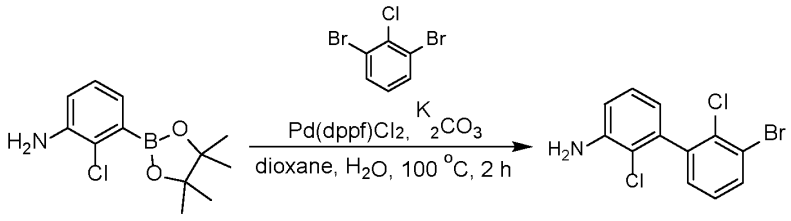
hexafluorophosphate; "DBU" means 1,8-diazabicyclo[5.4.0]undec-7-ene; "NMI" means N-methylimidazole; "PE" means petroleum ether; "AcOK" or "KOAc" means potassium acetate; "HOAc" means acetic acid; "EtOH" means ethanol; "t-BuOH" means tert-butoxide; "DCM" means dichloromethane; "DMF" means dimethylformamide; "TBDPS" or "TBS" means tert-butyldiphenylsilyl; "EDCI" means 1-ethyl-3-(3-dimehtylaminopropyl)carbodiimide; "Pin_2B_2" means bis(pinacolato)diboron; "DIEA" means *N,N,*-diisopropylethylamine; "DMAP" means 4-dimehtylaminopyridine; "TEA" means triethylamine; "$(Boc)_2O$" means di-tert-butyl-dicarbonate; "HATU" means hexafluorophosphate azabenzotriazole tetramethyl uronium; "LC" means liquid chromatography; "LCMS" means Liquid Chromatography/Mass spectrometry; "HPLC" means high-performance liquid chromatography; "SFC" means supercritical fluid chromatography; "TFA" means trifluoroacetic acid; "min" means minute(s); "h" means hour(s); "v/v" means volume per volume.

[0225] 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.

[0226] 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 1-1

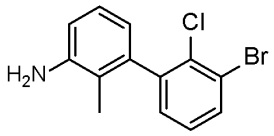


Intermediate 1-1

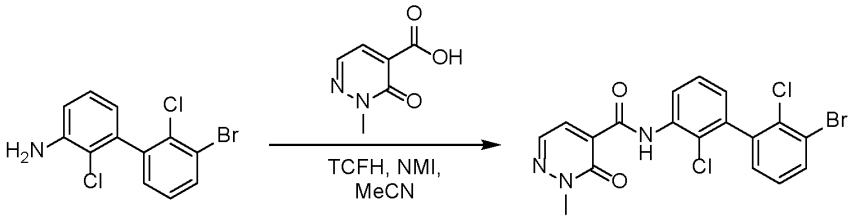
[0227] A mixture of 2-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (2.1 g, 8.28 mmol), 1,3-dibromo-2-chlorobenzene (4.48 g, 16.6 mmol), $Pd(dppf)Cl_2$ (606 mg, 828 μmol) and K_2CO_3 (3.43 g, 24.9 mmol) in dioxane (25 mL) and H_2O (2.5 mL) was degassed and purged with N_2 (3x). After stirring the mixture at 100 °C for 2 h under N_2 atmosphere, the reaction was quenched with H_2O (30 mL) and then extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography to give **Intermediate 1-1** (1.4 g) as a yellow solid. MS: ES m/z calculated for $C_{12}H_9BrCl_2N$ $[M+H]^+$ 315.9, found 316.0.

[0228] The intermediates shown in Table 1 were prepared by an analogous reaction protocol as was used for the preparation of Intermediate 1-1 using the appropriate starting materials.

Table 1

Intermediate No.	Structure	Starting Materials
1-2		2-Methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline 1,3-Dibromo-2-chlorobenzene

Example A2
Preparation of Intermediate 2-1

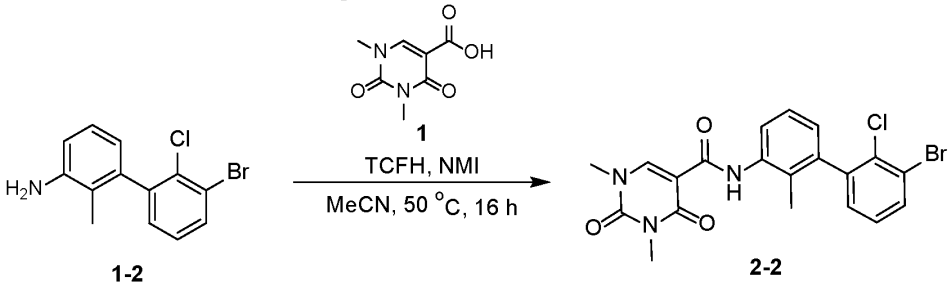


Intermediate 1-1 **Intermediate 2-1**

[0229] A mixture of **Intermediate 1-1** (52.5 g, 149 mmol), 2-methyl-3-oxo-2,3-dihydropyridazine-4-carboxylic acid (23 g, 149 mmol), N,N,N′,N′-tetramethylchloroformamidinium hexafluorophosphate (TCFH, 83.7 g, 299 mmol) and N-methylimidazole (NMI, 29.7 mL, 373 mmol) in MeCN (500 mL) was purged with N_2 three

times. The mixture was stirred at 60 °C for 16 h under N_2 atmosphere. The mixture was concentrated under reduced pressure to remove the solvent. The crude product was triturated with EtOAc at 25 °C for 30 min. **Intermediate 2-1** (48 g, 95% purity) was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.35 (s, 1H), 8.61 (dd, J = 1.4, 8.3 Hz, 1H), 8.32-8.20 (m, 2H), 7.87 (t, J = 4.8 Hz, 1H), 7.50 (t, J = 8.0 Hz, 1H), 7.44-7.37 (m, 2H), 7.16 (dd, J = 1.5, 7.6 Hz, 1H), 3.85 (s, 3H).

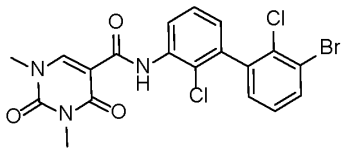
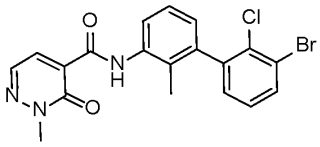
Example A3
Preparation of Intermediate 2-2



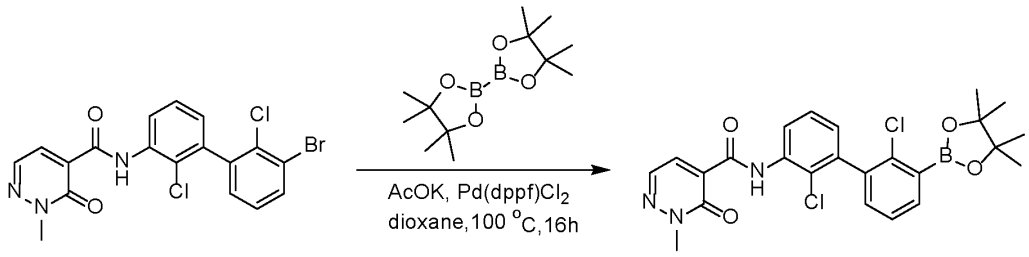
[0230] To a solution of **Intermediate 1-2** (850 mg, 2.87 mmol) and 1,3-dimethyl-2,4-dioxopyrimidine-5-carboxylic acid (580 mg, 3.15 mmol) in MeCN (8 mL) were added N,N,N',N'-tetramethylchloroformamidinium hexafluorophosphate (TCFH) (1.61 g, 5.73 mmol) and N-methylimidazole (NMI) (571 µL 7.16 mmol). The mixture was stirred at 50 °C for 16 h. The mixture was filtered, and the crude product was triturated with EtOAc (30 mL) at 25 °C for 10 min. The solid residue was filtered and dried to give **Intermediate 2-2** (1 g) as a white solid.

[0231] The intermediates shown in Table 2 were prepared by an analogous reaction protocol as was used for the preparation of **Intermediate 2-1** and **Intermediate 2-2** using the appropriate starting materials.

Table 2

Intermediate No.	Structure	Starting Materials
2-3		1,3-dimethyl-2,4-dioxopyrimidine-5-carboxylic acid Intermediate 1-1
2-4		2-methyl-3-oxo-2,3-dihydropyridazine-4-carboxylic acid Intermediate 1-2

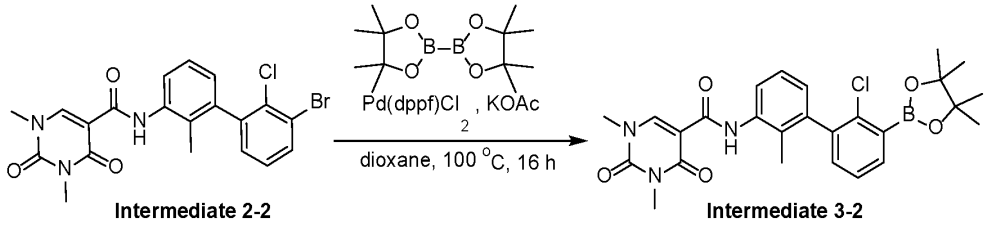
Example A4
Preparation of Intermediate 3-1



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

[0232] A mixture of Intermediate 2-1 (48 g,101 mmol), Bis(pinacolato)diboron (76.7 g, 302 mmol), AcOK (29.6 g, 302 mmol), $Pd(dppf)Cl_2$ (5.89 g, 8.05 mmol) in dioxane (500 mL) was purged with N_2 (3x), and the mixture was stirred at 100 °C for 16 h under N_2 atmosphere. The mixture was concentrated under reduced pressure to remove the solvent. The residue was purified by column chromatography (SiO_2, PE:EA = 100:1 to 3:2). Compound **3-1** (60 g) was obtained as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 12.21 (s, 1H), 8.61 (dd, J = 1.4, 8.3 Hz, 1H), 8.32 (d, J = 4.1 Hz, 1H), 8.05 (d, J = 4.1 Hz, 1H), 7.70 (dd, J = 2.9, 6.4 Hz, 1H), 7.38-7.30 (m, 3H), 7.07-7.02 (m, 1H), 3.97-3.95 (m, 3H), 1.39 (s, 12H).

Example A5
Preparation of Intermediate 3-2

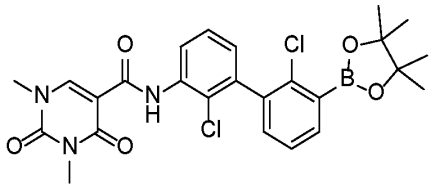
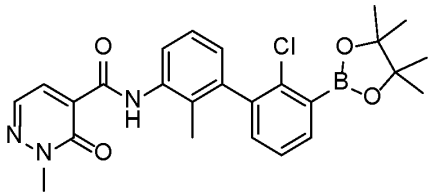


Intermediate 2-2 Intermediate 3-2

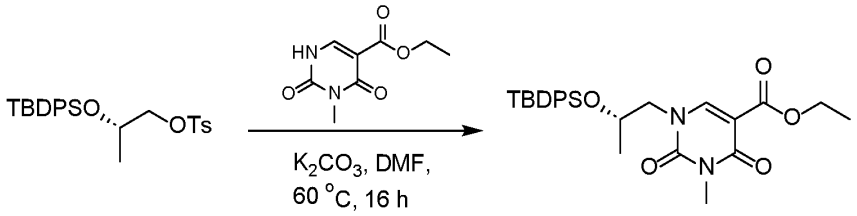
[0233] A mixture of **Intermediate 2-2** (1.0 g), Bis(pinacolato)diboron (823 mg, 3.24 mmol), KOAc (636 mg, 6.48 mmol) and $Pd(dppf)Cl_2$ (158 mg, 216 μmol) in dioxane (10 mL) was degassed and purged with N_2 (3x). The mixture was stirred at 100 °C for 16 h under N_2 atmosphere. The mixture was filtered and concentrated under reduced pressure to give a residue, which was purified by flash silica gel column to give **Intermediate 3-2** (780 mg) as a white solid. MS: ES *m/z* calculated for $C_{26}H_{30}BClN_3O_5$ $[M+H]^+$ 510.2, found 510.0.

[0234] The intermediates shown in Table 3 were prepared by an analogous reaction protocol as was used for the preparation of **Intermediate 3-**1 and **Intermediate 3-2** using the appropriate starting materials.

Table 3

Intermediate No.	Structure	Starting Materials
3-3		Bis(pinacolato)diboron Intermediate 2-3
3-4		Bis(pinacolato)diboron Intermediate 2-4

Example A6
Preparation of Intermediate 4-1

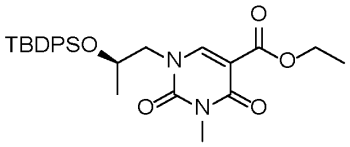
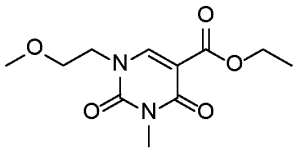
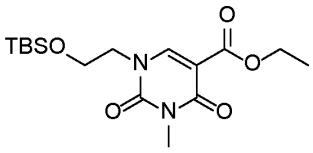


Intermediate 4-1-1 **Intermediate 4-1**

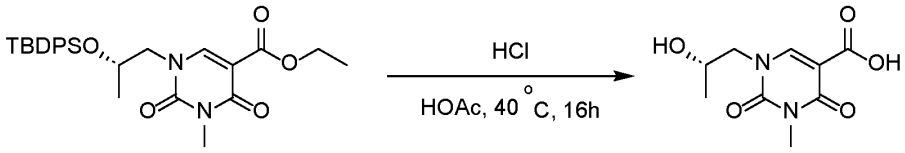
[0235] To a solution of **Intermediate 4-1-1** (3 g, 6.40 mmol) and ethyl 3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (1 g, 5.05 mmol) in DMF (15 mL) were added K_2CO_3 (2.09 g, 15.14 mmol) and KI (2.51 g, 15.14 mmol). The mixture was stirred at 70 °C for 40 h. The mixture was diluted with EtOAc (30 mL) and washed with brine (2 x 30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography to give **Intermediate 4-1** (2.1 g) as a colorless oil. MS: ES m/z calculated for $C_{27}H_{35}N_2O_5Si$ $[M+H]^+$ 495.2, found 495.2.

[0236] The intermediates shown in Table 4 were prepared by an analogous reaction protocol as was used for the preparation of **Intermediate 4-1** using the appropriate starting materials.

Table 4

Intermediate No.	Structure	Starting Materials
4-2		Ethyl 3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate 4-Methylbenzenesulfonic acid (2R)-2-[(tert-butyldiphenylsilyl)oxy]propyl ester
4-3		Ethyl 3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate 1-Bromo-2-Methoxyethane
4-4		Ethyl 3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (2-Bromoethoxy)(tert-butyl)dimethylsilane

Example A7
Preparation of Intermediate 5-1

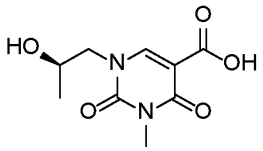
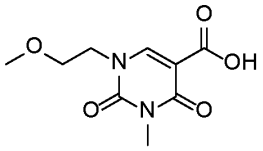
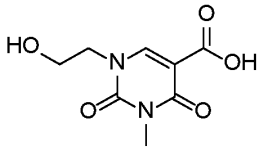


Intermediate 4-1 **Intermediate 5-1**

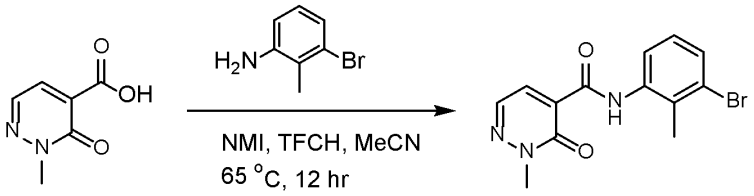
[0237] To a solution of Intermediate 4-1 (2.1 g, 4.25 mmol) in aqueous HCl (12M, 10 mL) and HOAc (10 mL). The mixture was stirred at 40 °C for 16 h. The mixture was concentrated under reduced pressure to give a residue and then adjusted to pH~6 and lyophilized, the crude product Intermediate 5-1 (1.7 g, crude) was obtained as a yellow solid and used into the next step without further purification. MS: ES m/z calculated for $C_9H_{13}N_2O_5$ $[M+H]^+$ 229.1, found 228.9.

[0238] The intermediates shown in Table 5 were prepared by an analogous reaction protocol as was used for the preparation of **Intermediate 5-1** using the appropriate starting materials.

Table 5

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

Example A8
Preparation of Intermediate 6-1

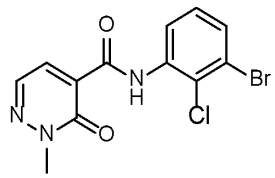
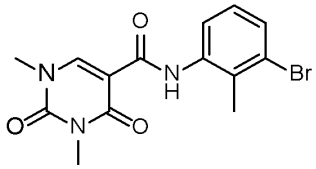
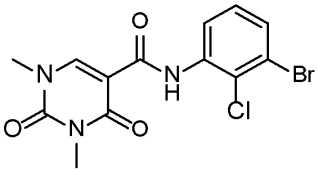
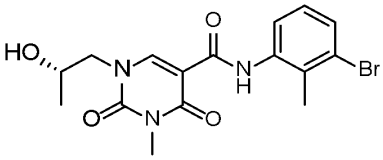
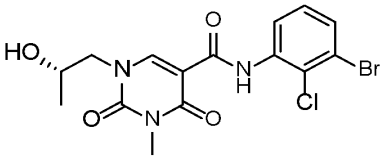
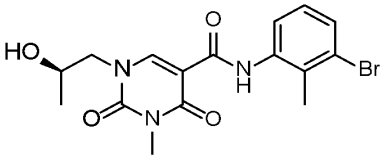


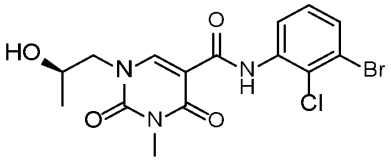
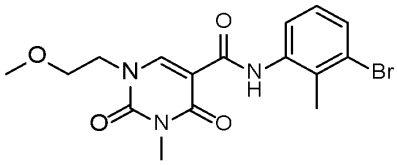
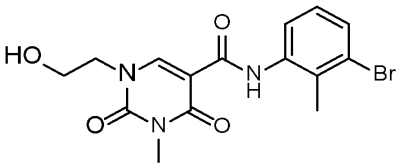
Intermediate 6-1

[0239] A mixture of 2-methyl-3-oxo-2,3-dihydropyridazine-4-carboxylic acid (26.6 g, 173 mmol), 3-bromo-2-methylaniline (32.8 g, 176 mmol), N-methylimidazole (NMI, 28.3 g, 345 mmol) and N,N,N′,N′-tetramethylchloroformamidinium hexafluorophosphate (TCFH, 121 g, 431 mmol) in MeCN (500 mL) was stirred at 65 °C for 12 h. The mixture was filtered and concentrated under reduced pressure to give a crude residue. The crude product was triturated with EtOAc (2 x 50 mL) to get **Intermediate 6-1** (52.2 g) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.82 (s, 1H), 8.25 (d, J =4.4 Hz, 1H), 8.23 (d, J =4.0 Hz, 1H), 8.19 (d, J = 8.0 Hz, 1H), 7.45 (d, J = 7.6 Hz, 1H), 7.20 (t, J = 8.0 Hz, 1H), 3.86 (s, 3H), 3.30 (s, 3H).

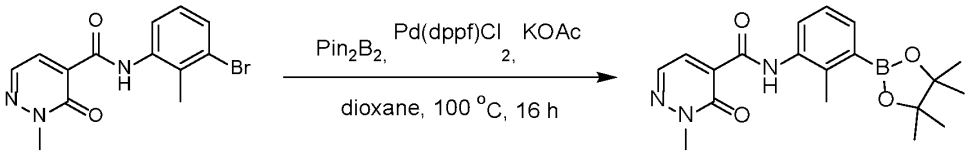
[0240] The intermediates shown in Table 6 were prepared by an analogous reaction protocol as was used for the preparation of **Intermediate 6-1** using the appropriate starting materials.

Table 6

Intermediate No.	Structure	Starting Materials
6-2		2-methyl-3-oxo-2,3-dihydropyridazine-4-carboxylic acid 3-bromo-2-chloroaniline
6-3		1,3-dimethyl-2,4-dioxopyrimidine-5-carboxylic acid 3-bromo-2-methylaniline
6-4		1,3-dimethyl-2,4-dioxopyrimidine-5-carboxylic acid 3-bromo-2-chloroaniline
6-5		Intermediate 5-1 3-bromo-2-methylaniline
6-6		Intermediate 5-1 3-bromo-2-chloroaniline
6-7		Intermediate 5-2 3-bromo-2-methylaniline

Intermediate No.	Structure	Starting Materials
6-8		Intermediate 5-2 3-bromo-2-chloroaniline
6-9		Intermediate 5-3 3-bromo-2-methylaniline
6-10		Intermediate 5-4 3-bromo-2-methylaniline

Example A9
Preparation of Intermediate 7-1

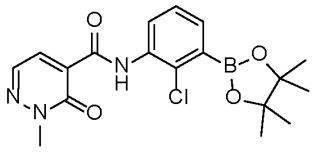
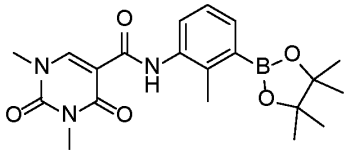
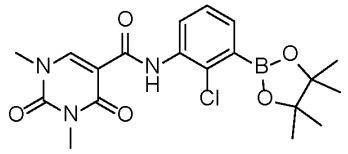
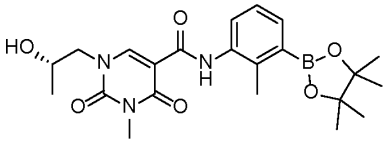
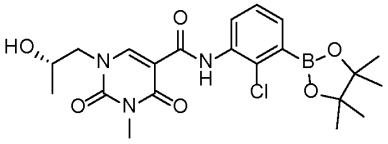
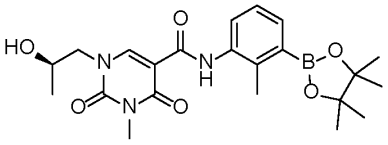
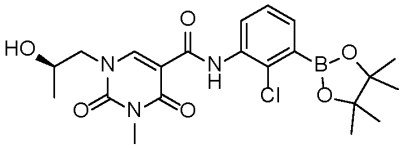
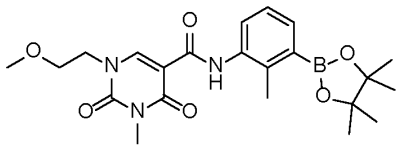


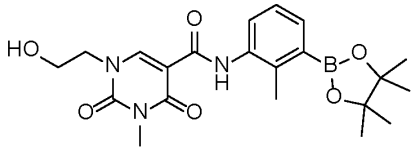
Intermediate 6-1 **Intermediate 7-1**

[0241] A mixture of **Intermediate 6-1** (49.09 g, 153 mmol), Pin_2B_2 (77.39 g, 304 mmol), $Pd(dppf)Cl_2$ (5.57 g, 7.62 mmol) and KOAc (44.86 g, 457mmol) in dioxane (500 mL) was degassed and purged with N_2 (3x), and then the mixture was stirred at 100 °C for 16 h under N_2 atmosphere. The mixture was filtered and concentrated under reduced pressure to give a residue. The crude product was triturated with MTBE:hexane=1:1 (160 mL). The crude product was triturated with hexane (70 mL) to give **Intermediate 7-1** (60.79 g, 97.25% yield, 90% purity) as a black-brown solid. ^1H NMR (400 MHz, Chloroform-d_4) δ 11.62 (br s,1H), 8.40 - 8.24 (m, 2H), 8.04 (d, J= 4.1 Hz, 1H), 7.61 (d, J = 7.4 Hz,1H), 7.26 - 7.22 (m, 1H), 3.97 (s, 3H), 2.64 (s, 3H), 1.37 (s, 12H).

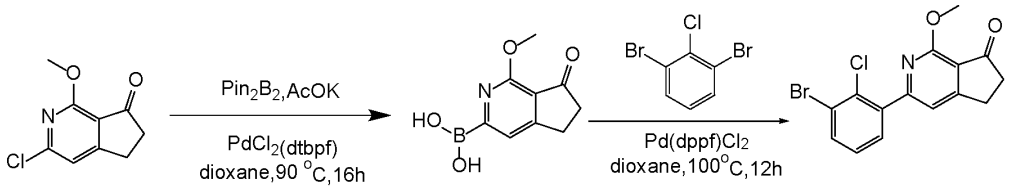
[0242] The intermediates shown in Table 7 were prepared by an analogous reaction protocol as was used for the preparation of Intermediate 7-1 using the appropriate starting materials.

Table 7

Intermediate No.	Structure	Starting Materials
7-2		Bis(pinacolato)diboron Intermediate 6-2
7-3		Bis(pinacolato)diboron Intermediate 6-3
7-4		Bis(pinacolato)diboron Intermediate 6-4
7-5		Bis(pinacolato)diboron Intermediate 6-5
7-6		Bis(pinacolato)diboron Intermediate 6-6
7-7		Bis(pinacolato)diboron Intermediate 6-7
7-8		Bis(pinacolato)diboron Intermediate 6-8
7-9		Bis(pinacolato)diboron Intermediate 6-9

Intermediate No.	Structure	Starting Materials
7-10		Bis(pinacolato)diboron Intermediate 6-10

Example A10
Preparation of Intermediate 8

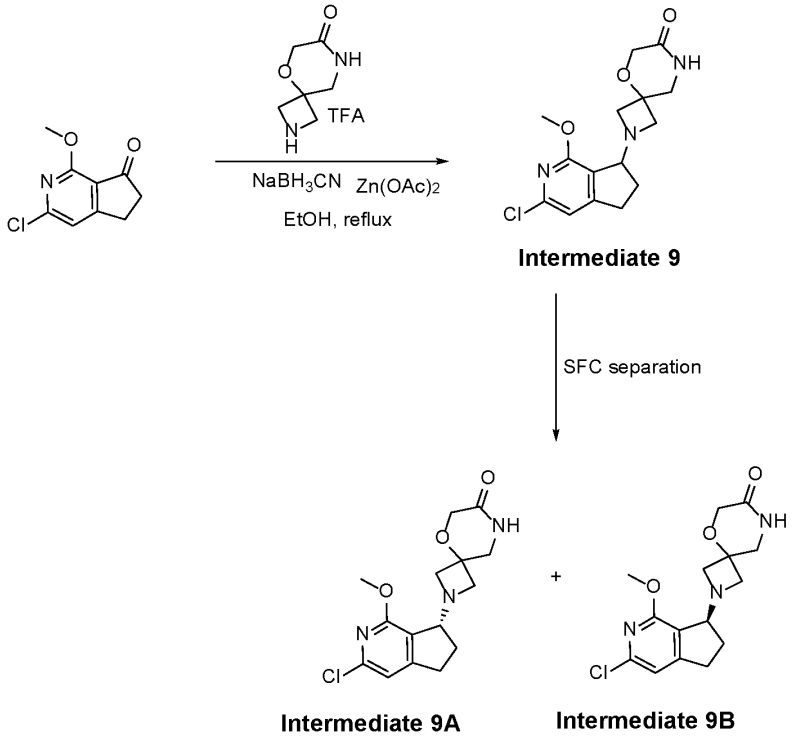


Intermediate 8-1 **Intermediate 8**

[0243] A mixture of compound 3-chloro-1-methoxy-5,6-dihydrocyclopenta[c]pyridin-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 (3x). 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 the mixture of methyl-tert-butyl ether and ethyl acetate(MTBE:EA = 3:1) at 15 °C for 16 h to give **Intermediate 8-1** (15 g, crude) as a black oil, which was used for next step reaction without further purification.

[0244] A mixture of **Intermediate 8-1** (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(3x), 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 8** (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 A11
Preparation of Intermediate 9B



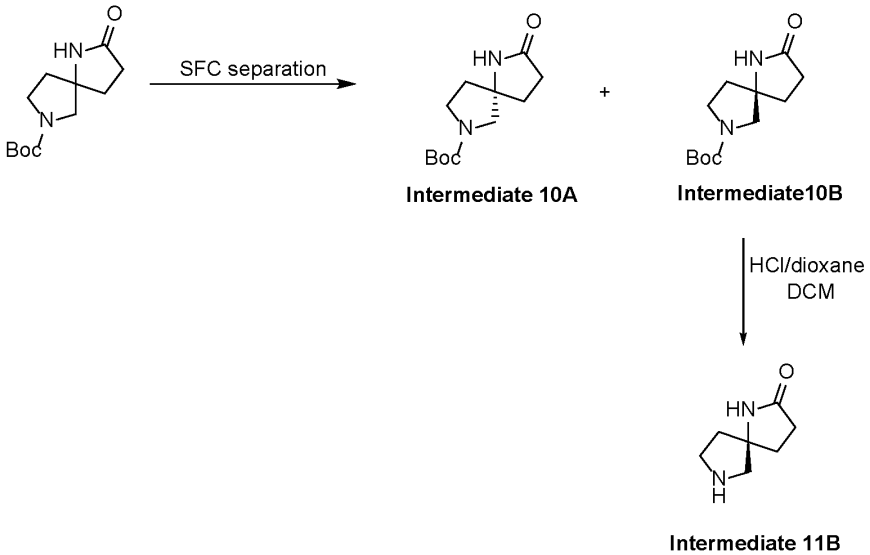
[0245] To a stirred solution of 3-chloro-1-methoxy-5,6-dihydrocyclopenta[c]pyridin-7-one (563 mg, 2.2 mmol) and 5-oxa-2,8-diazaspiro[3.5]nonan-7-one's TFA salt (394 mg, 2 mmol) in anhydrous ethanol (10 ml) were added zinc acetate (917 mg, 5 mmol) and sodium cyanoborohydride (252 mg, 4 mmol). The mixture was heated to 70°C and stirred for 4 h. After the mixture was cooled to rt, the mixture was quenched by the addition of aqueous saturated ammonium chloride solution (20 mL) and ammonium hydroxide (3 mL). The mixture was stirred at RT until the solids dissolved and extracted with dichloromethane. The organic layer was washed with water, dried over sodium sulfate, and concentrated to dryness. The residue was crystallized from ethyl acetate (3 mL) and hexane (3 mL). **Intermediate 9** (640 mg) was isolated by filtration and dried under vacuum. MS: ES m/z calculated for $C_{15}H_{18}ClN_3O_3$ $[M+H]^+$ 324.1, found 324.1.

[0246] A mixture of **Intermediate 9** (5.28 g, 16.1 mmol) was separated by SFC to give compound **Intermediate 9A** (2.6 g) as a yellow oil and **Intermediate 97B** (2.35 g) as a

yellow oil. With analytic SFC conditions (Column: Chiralpak AD 100 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 9A**'s retention time is 1.24xx min, and **Intermediate 9B**'s retention time is 1.37 min.

[0247] The absolute configuration of **Intermediate 9B** was identified by X-ray. The crystal of **Intermediate 9B** was a colorless block with the following dimensions: 0.40 × 0.30 × 0.30 mm^3. The symmetry of the crystal structure was assigned the orthorhombic space group $P2_12_12_1$ with the following parameters: a = 8.25580(10) Å, b = 10.21280(10) Å, c = 17.70530(10) Å, α = 90°, β = 90°, γ = 90°, V = 1492.82(2) $Å^3$, Z = 4, Dc = 1.441 g/cm^3, F(000) = 680.0, μ(CuKα) = 2.420 mm^{-1}, and T = 150.01(10) K. Figure 1A shows the absolute configuration structure and Figure 1B shows the ORTEP crystal structure of **Intermediate 9B**.

Example A12
Preparation of Intermediate 11B

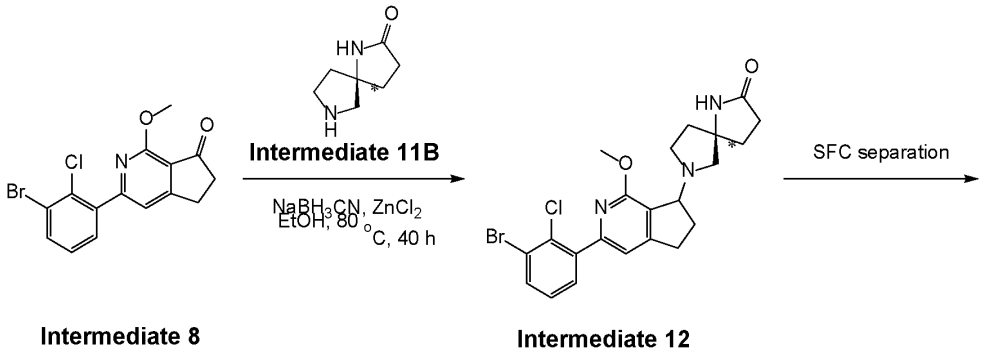


[0248] A mixture of tert-butyl 2-oxo-1,7-diazaspiro[4.4]nonane-7-carboxylate (10.5 g, 43.70 mmol) was separated by supercritical fluid chromatography (SFC) to give **Intermediate 10A** (5.18 g, 96% purity) and **Intermediate 10B** (5.24 g, 98% purity) as white solids. With analytic SFC conditions (Column: Chiral NS-3 100 x 4.6mm I.D., 3um; Mobile

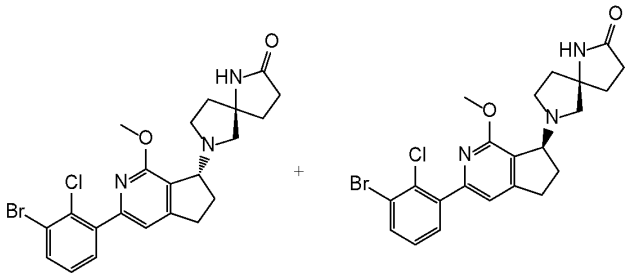
phase: A: CO_2 B: ethanol (0.05% DEA); Gradient: from 5% to 40% of B in 2 min and hold 40% for 1 min, then 5% of B for 1 min Flow rate: 2.8mL/min; Column temp.: 35 °C; ABPR: 1500 psi), **Intermediate 10A**'s retention time is 1.69 min, and **Intermediate 10B**'s retention time is 1.98 min.

[0249] A mixture of **Intermediate 10B** (5.19 g, 21.60 mmol) in HCl/dioxane (50 mL) and DCM (50 mL) was stirred at 25 °C for 1 h. The mixture was concentrated under reduced pressure to give **Intermediate 11B** (4.1 g) as a white solid HCl salt. ^{1}H NMR (400 MHz, methanol-d_4) δ 3.57 - 3.37 (m, 3H), 3.34 (s, 1H), 2.55 - 2.45 (m, 2H), 2.38 - 2.15 (m, 4H).

Example A13
Preparation of Intermediates 12A & 12B



Intermediate 8 **Intermediate 12**



Intermediate 12A **Intermediate 12B**

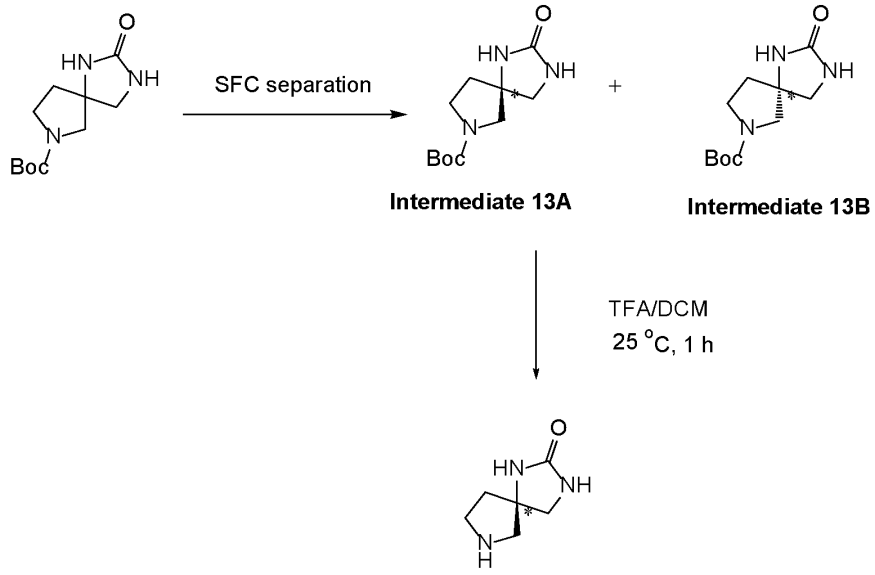
[0250] A mixture of **Intermediate 8** (3.74 g, 10.7 mmol) and **Intermediate 11B**'s HCl salt (3.75 g) and $ZnCl_2$ (2.92 g, 21.4 mmol) in EtOH (80 mL) was stirred at 80 °C for 12 h. Then $NaBH_3CN$ (2.00 g, 31.9 mmol) was added into the mixture and stirred at 80 °C for 28

h. The mixture was quenched by adding water (100 mL). The mixture was extracted with DCM (3 x 100 mL). The combined organic layers were washed with brine (2 x 100 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 12** (2.46 g, 98% purity) as a yellow oil. MS: ES m/z calculated for $C_{22}H_{24}BrClN_3O_2$ $[M+H]^+$ 476.1, found 476.1.

[0251] A mixture of **Intermediate 12** (2.46 g, 5.16 mmol) was separated by SFC to give **Intermediate 12A** (1.1 g, 96% purity) as a brown oil and **Intermediate 12B** (1.2 g, 96% purity) as a brown oil. With analytic SFC conditions (Column: Chiral NS-3 100 x 4.6mm I.D., 3μm; 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 12A**'s retention time is 2.14 min, and **Intermediate 12B**'s retention time 2.51 min.

[0252] The absolute configuration of **Intermediate 12B** was identified by X-ray. The crystal of **Intermediate 12B**'s HCl salt was a colorless block with the following dimensions: 0.40 × 0.15 × 0.05 mm^3. The symmetry of the crystal structure was assigned the monoclinic space group P21 with the following parameters: a = 7.9600(2) Å, b = 7.16290(10) Å, c = 19.9493(3) Å, α = 90°, β = 100.938(2)°, γ = 90°, V = 1116.78(4) $Å^3$, Z = 2, Dc = 1.526 g/cm3, F(000) = 524.0, μ(CuKα) = 4.907 mm^{-1}, and T = 293(2) K. Figure 2A shows the absolute configuration structure and Figure 2B shows the ORTEP crystal structure of the chloride salt of **Intermediate 12B**.

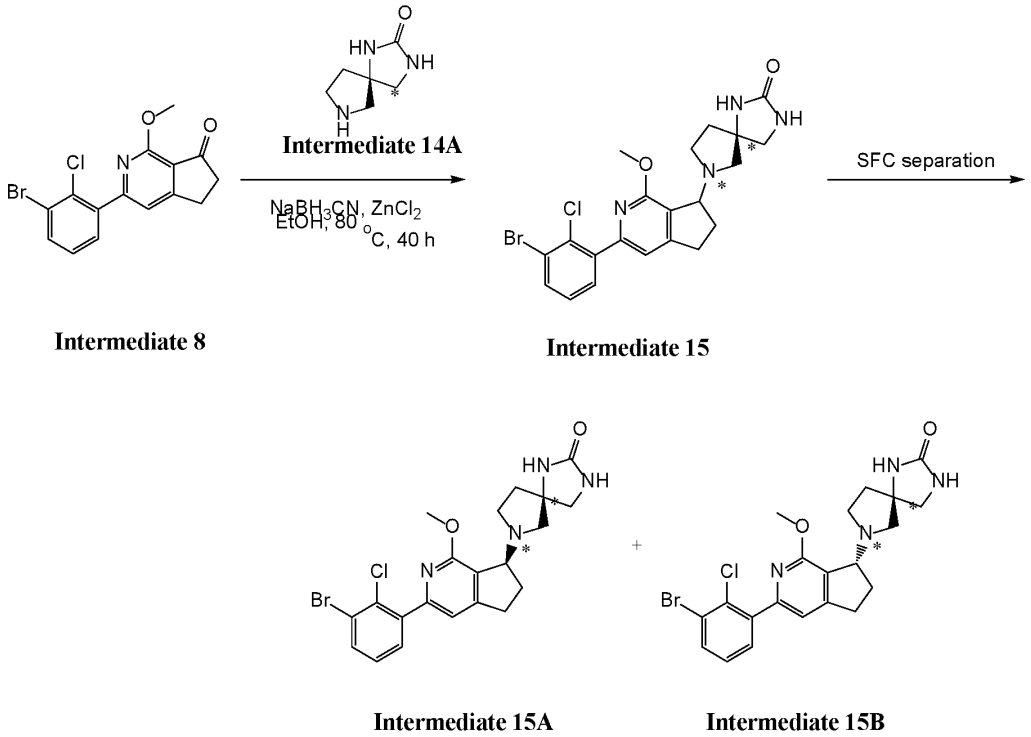
Example A14
Preparation of Intermediate 14A



[0253] Tert-butyl 7-oxo-2,6,8-triazaspiro[4.4]nonane-2-carboxylate (6.62 g, 25.52 mmol) was separated by SFC to give compound **Intermediate 13A** (3.16 g) as an off-white solid and **Intermediate 13B** (3.03 g) as an off-white solid. With analytic SFC conditions (Column: Chiralpak IC-3 50×4.6mm I.D., 3 μm Mobile phase: A: CO_2 B: Ethanol (0.05% DEA) Gradient: from 5% to 40% of B in 1.5 min and hold 40% of 1 min, then 5% of B for 0.5 min; Flow rate: 4 mL/min, Column temp.: 35 °C, ABPR: 1500 psi), **Intermediate 13A**'s retention time is 1.46 min, and **Intermediate 13B**'s retention time is 2.15 min. The chiral centers in **Intermediate 13A** and **Intermediate 13B** marked with asterisks are indicated as (*S*) and (*R*), respectively, but represent relative configurations.

[0254] To a solution of **Intermediate13A** (3.16 g, 13.10 mmol) in DCM (32 mL) was added TFA (8 mL). The mixture was stirred at 25 °C for 16 h. The mixture was concentrated under reduced pressure to give **Intermediate 14A** (6.26 g, TFA salt) as a brown oil.

Example A15
Preparation of Intermediates 15A and 15B

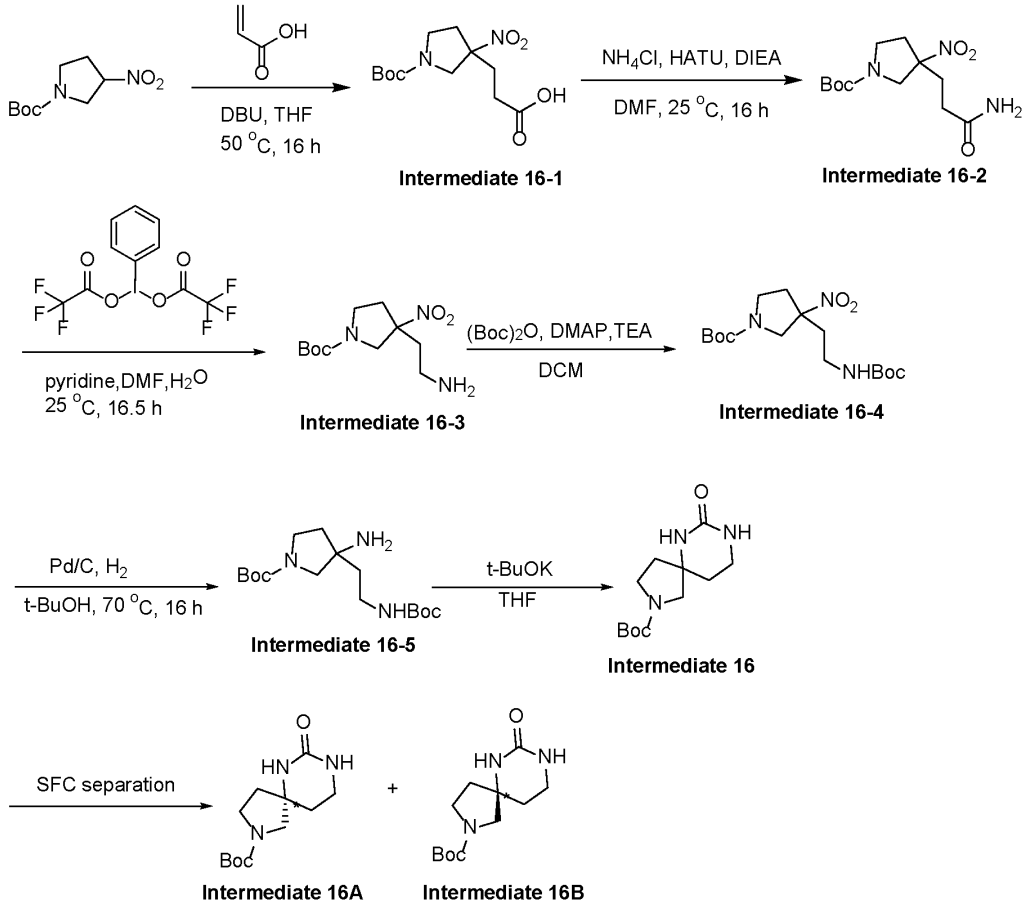


[0255] To a solution of **Intermediate 8** (2.33 g, 6.62 mmol) in EtOH (100 mL) was added **Intermediate 14A** (4.8 g) and $ZnCl_2$ (621 µL, 13.2 mmol). The mixture was stirred at 80 °C for 16 h. Then $NaBH_3CN$ (1.25 g, 19.87 mmol) was added into the mixture, and the mixture was stirred at 80 °C for a further 24 h. The mixture was cooled to rt and diluted with water (100 mL). The aqueous phase was extracted with DCM (3 x 50 mL). The combined organic extracts were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to afford a residue. The residue was purified by flash silica gel chromatography to give **Intermediate 15** (1.9 g) as a yellow solid. MS: ES m/z calculated for $C_{21}H_{23}BrClN_4O_2$ $[M+Na]^+$ 499.1, found 499.0.

[0256] **Intermediate 15** (1.9 g, 3.98 mmol) was separated by SFC to afford **Intermediate 15A** (890 mg) as an off-white solid and **Intermediate 15B** (810 mg) as an off-white solid. With analytic SFC condition (Column: Chiralpak IC-3 50×4.6mm I.D., 3 µm Mobile phase: A: CO_2 B: Ethanol (0.05% DEA) Gradient: from 5% to 40% of B in 1.5 min

and hold 40% of 1 min, then 5% of B for 0.5 min Flow rate: 4 mL/min, Column temp.: 35 °C, ABPR: 1500 psi), **Intermediate 15A**'s retention time is 1.55 min, and **Intermediate 15B**'s retention time is 1.64 min. The chiral centers of **Intermediate 15A** marked with asterisks are assigned as (*S*,*S*), but are relative configurations, and could be assigned as (*R*,*S*), (*R*,*R*) or (*S*,*R*) once the absolute configuration is determined. The chiral centers of **Intermediate 15B** marked with asterisks are assigned as (*R*,*S*), but are relative configurations, and could be assigned as (*S*,*S*), (*R*,*R*) or (*S*,*R*) once the absolute configuration is determined.

Example A16
Preparation of Intermediates 16A and 16B



[0257] To a solution of tert-butyl 3-nitropyrrolidine-1-carboxylate (2 g, 9.25 mmol) in THF (30 mL) were added DBU (2.09 mL, 13.87 mmol) and acrylic acid (761 μL, 11.1 mmol)

at 25 °C. The mixture was stirred at 80 °C for 4 h. The mixture was concentrated under reduced pressure to remove solvent. The crude product was purified by prep-HPLC to give **Intermediate 16-1** (2.1 g) as a white solid.

[0258] To a solution of **Intermediate 16-1** (1.9 g, 6.59 mmol), DIEA (1.70 g, 13.18 mmol, 2.30 mL) and NH_4Cl (705.06 mg, 13.18 mmol) in DMF (20 mL) was added HATU (3.01 g, 7.91 mmol). The mixture was stirred at 25 °C for 16 h. The mixture was concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography and re-purified by prep-HPLC to give **Intermediate 16-2** (957 mg) as a colorless oil. MS: ES m/z calculated for $C_{12}H_{21}N_3NaO_5$ $[M+Na]^+$ 310.1, found 310.0.

[0259] A mixture of **Intermediate 16-2** (850 mg, 2.96 mmol), pyridine (478 μL, 5.92 mmol) in DMF (8 mL) and H_2O (8 mL) was stirred at 25 °C for 0.5 h. (Bis(trifluoroacetoxy)iodo)benzene (1.91 g, 4.44 mmol) was added into the mixture at 25 °C for 16 h. The mixture was concentrated under reduced pressure to give a residue, which was purified by prep-HPLC to give **Intermediate 16-3** (784 mg) as a white solid. MS: ES m/z calculated for $C_{11}H_{21}N_3NaO_4$ $[M+Na]^+$ 282.2, found 282.0.

[0260] To a solution of **Intermediate 16-3** (784 mg, 3.02 mmol) and TEA (1.26 mL, 9.07 mmol) in DCM (20 mL) were added $(Boc)_2O$ (1.39 mL, 6.05 mmol) and DMAP (37 mg, 302 μmol). The mixture was stirred at 25 °C for 16 h. The mixture was concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography to give **Intermediate 16-4** (639 mg) as a yellow oil. MS: ES m/z calculated for $C_{16}H_{29}N_3NaO_6$$[M+Na]^+$ 382.2, found 382.1.

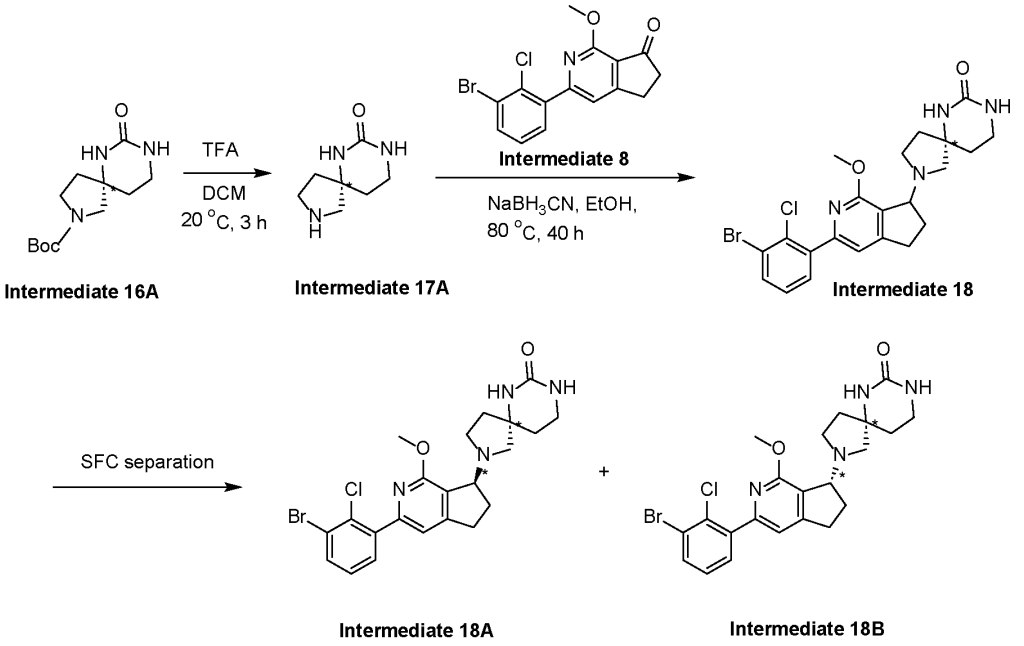
[0261] To a flask with Pd/C (189 mg, 10% purity) was added t-BuOH (20 mL) and **Intermediate 16-4** (639 mg, 1.78 mmol) under Ar. The suspension was degassed under vacuum and purged with H_2 several times. The mixture was stirred under H_2 (50 psi) at 70 °C for 16 h. The mixture was filtered and concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography to give **Intermediate 16-5** (465 mg) as a colorless oil. ^1H NMR (400 MHz, chloroform-*d*) δ 5.28 (s, 1H), 3.47 (dd, J = 8.8, 18.8 Hz, 2H), 3.36 - 3.11 (m, 4H), 1.93-1.68 (m, 4H), 1.50 (s, 18H).

[0262] To a solution of **Intermediate 16-5** (360 mg, 1.09 mmol) in THF (10 mL) was added t-BuOK (1 M, 1.64 mL). The mixture was stirred at 25 °C for 16 h. The mixture was adjusted to pH~7 by addition of FA, then concentrated under reduced pressure to give a

residue, which was purified by flash silica gel chromatography to give **Intermediate 16** (220 mg) as a white solid.

[0263] A mixture of **Intermediate 16** (200 mg) was separated by SFC to give **Intermediate 16A** (70 mg) as a white solid and **Intermediate 16B** (80 mg) as a white solid. The chiral centers in **Intermediate 16A** and **Intermediate 16B** marked with asterisks are indicated as (S) and (R), respectively, but represent relative configurations. **Intermediate 16A**: ^{1}H NMR (400 MHz, chloroform-*d*) δ 5.60 - 5.15 (m, 2H), 3.63-3.20 (m, 6H), 1.99-1.76 (m, 4H), 1.57-1.36 (m, 9H). **Intermediate 16B**: MS: ES m/z calculated for $C_{12}H_{21}N_3NaO_3[M+Na]^+$ 278.2, found 278.3.

Example A17
Preparation of Intermediates 18A and 18B



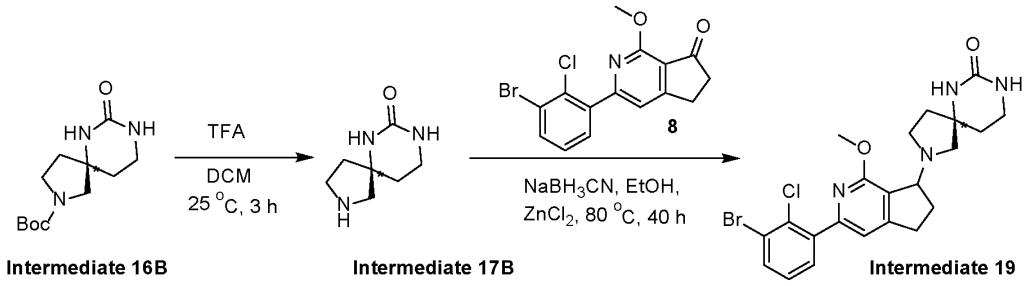
[0264] A mixture of **Intermediate 16A** (70 mg, 274.17 μmol) in TFA (1 mL) and DCM (1 mL) was stirred at 20 °C for 3 h. The mixture was concentrated under reduced pressure to give **Intermediate 17A** (crude, 42 mg) as a colorless oil, which was directly used in the next step without further purification.

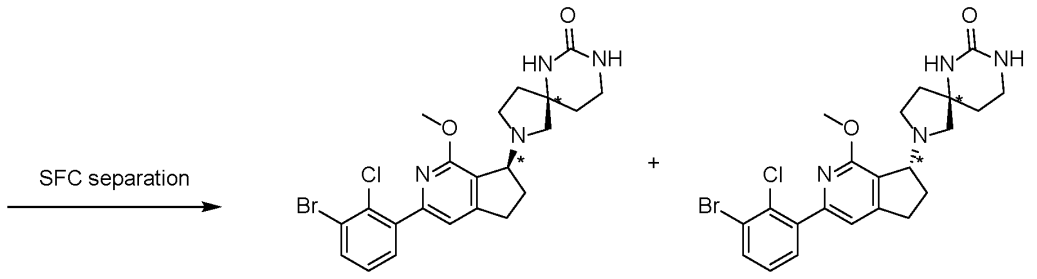
[0265] To a solution of crude **Intermediate 17A** (95 mg), **Intermediate 8** (42 mg, 270.62 μmol) and $ZnCl_2$ (73.77 mg, 541.25 μmol, 25.38 μL) in EtOH (1 mL) was stirred at 80 °C for 12 h. $NaBH_3CN$ (51.02 mg, 811.87 μmol) was added and the mixture was stirred at 80 °C for 28 h. The mixture was extracted with DCM (3 x 5 mL). The combined organic layers were washed with brine (2 x 5 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography to give **Intermediate 18** (65 mg, 47.37% yield) as a yellow solid. MS: ES m/z calculated for $C_{22}H_{25}BrClN_4O_2$ $[M+H]^+$ 491.1, found 491.2.

[0266] A mixture of **Intermediate 18** (65 mg) was separated by SFC to offer compound **18A** (31 mg) as a colorless oil and compound **18B** (31 mg) as a colorless oil. With analytic SFC condition (Column: Chiralpak AD-3 50 x 4.6 mm I.D.,3 μm Mobile phase: A: CO_2 B: Ethanol with 0.05% DEA; Gradient: from 5% to 40% of B in 1.5 min and hold 40% of 1 min, then 5% of B for 0.5 min Flow rate: 4mL/min Column temp.:35 ABPR: 1500 psi).

[0267] **Intermediate 18A**'s retention time is 1.54 min, and **Intermediate 18B**'s retention time is 1.72 min. The chiral centers of **Intermediate 18A** marked with asterisks are assigned as (*S*,*S*), but are relative configurations, and could be assigned as (*R*,*S*), (*R*,*R*) or (*S*,*R*) once the absolute configuration is determined. The chiral centers of **Intermediate 18B** marked with asterisks are assigned as (*R*,*S*), but are relative configurations, and could be assigned as (*S*,*S*), (*R*,*R*) or (*S*,*R*) once the absolute configuration is determined.

Example A18
Preparation of Intermediates 19A and 19B





Intermediate 19A Intermediate 19B

[0268] To a mixture of **Intermediate 16B** (80mg) in DCM (4 mL) was added TFA (1 mL) in one portion at 25 °C. The mixture was stirred at 25 °C for 3 h. The mixture was concentrated in vacuum to afford **Intermediate 17B** (crude, 50 mg) as a yellow solid TFA salt.

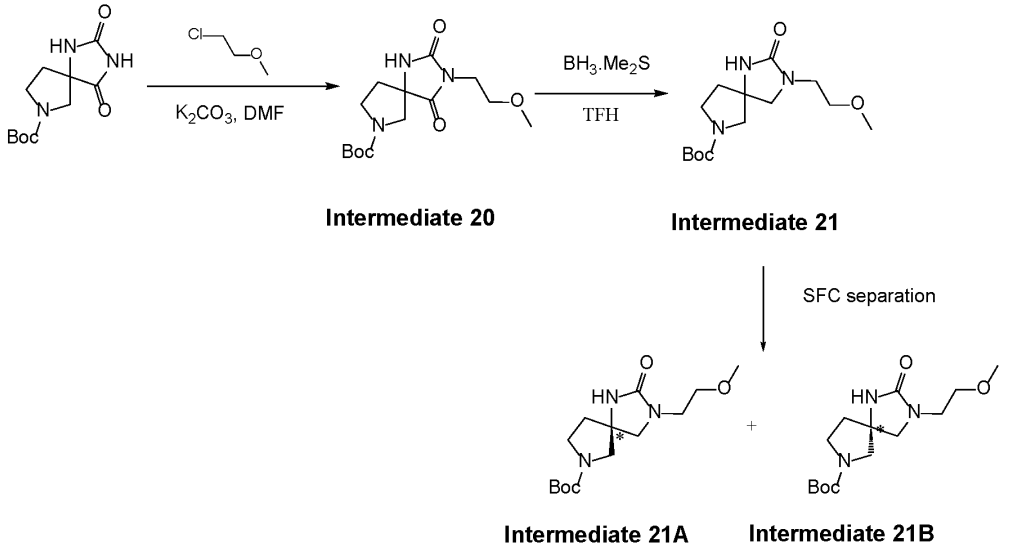
[0269] To a solution of **Intermediate 8** (100 mg, 283.60 μmol), **Intermediate 17B** (50 mg) and $ZnCl_2$ (26.59 μL, 567 μmol) in EtOH (10 mL) were added and the mixture was stirred at 80 °C for 12 h. To the mixture was added $NaBH_3CN$ (35.64 mg, 567 μmol), and the mixture was stirred at 80 °C for 28 h. The mixture was poured in water (10 mL) and extracted with DCM (3 x 10 mL). The combined organic layers were washed with brine (2 x 5 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give **Intermediate 19** (120 mg) as a yellow solid. MS: ES m/z calculated for $C_{22}H_{25}BrClN_4O_2$ $[M+H]^+$ 491.1, found 490.9.

[0270] **Intermediate 19** (120 mg) was separated by SFC to offer **Intermediate 19A** (35 mg) as a white solid and **Intermediate 19B** (35 mg) as a white solid.

[0271] Under analytic SFC conditions (Column: Chiralpak AD-3 50 x 4.6 mm I.D.,3 μm Mobile phase: A: CO2 B: Ethanol with 0.05% DEA; Gradient: from 5% to 40% of B in 1.5 min and hold 40% of 1 min, then 5% of B for 0.5 min; Flow rate: 4mL/min; Column temp.:35 °C, ABPR: 1500psi). Intermediate 19A's retention time is 1.67 min, and Intermediate 19B's retention time is 1.72 min.

[0272] The chiral centers of **Intermediate 19A** marked with asterisks are assigned as (*S,R*), but are relative configurations, and could be assigned as (*R,R*), (*S,S*) or (*R,S*) once the absolute configuration is determined. The chiral centers of **Intermediate 19B** marked with asterisks are assigned as (*R,R*), but are relative configurations, and could be assigned as (*S,R*), (*R,S*) or (*S,S*) once the absolute configuration is determined.

Example A19
Preparation of Intermediates 21A and 21B



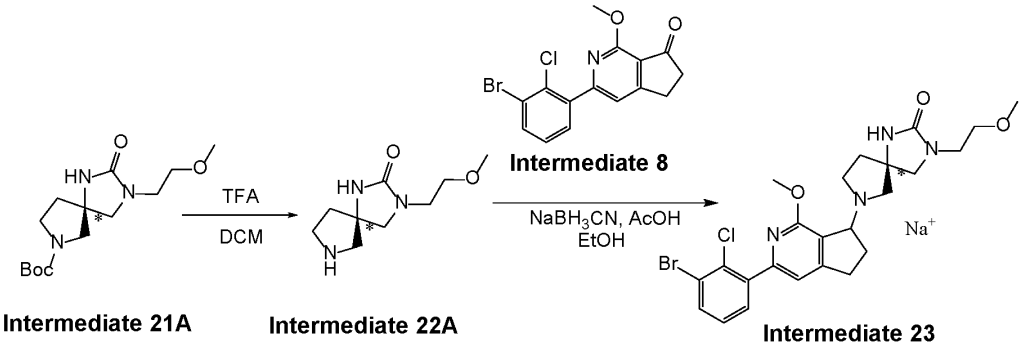
[0273] To a solution of tert-Butyl 6,8-dioxo-3,7,9-triazaspiro[4.4]nonane-3-carboxylate (2 g, 7.83 mmol) in DMF (20 mL) were added 1-chloro-2-methoxy-ethane (2.14 mL, 23.50 mmol), K_2CO_3 (2.71 g, 19.6 mmol) and KI (2.60 g, 15.67 mmol). The mixture was stirred at 40 °C for 20 h. The mixture was cooled to RT and filtered. The filtrate was diluted with EtOAc (30 mL) and washed with water (150 mL). The organic layers were separated. The aqueous phase was extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with brine (150 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to afford a residue. The residue was purified by flash silica gel chromatography and prep-HPLC to give **Intermediate 20** (1.85 g) as a colorless oil. MS: ES m/z calculated for $C_{14}H_{23}N_3NaO_5$ $[M+Na]^+$ 336.2, found 336.0.

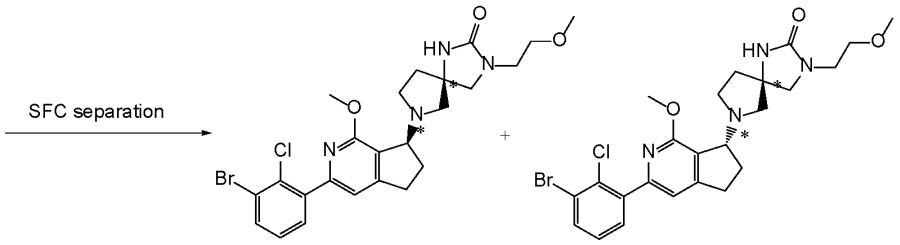
[0274] To a solution of **Intermediate 20** (1 g, 3.19 mmol) in THF (50 mL) was added BH_3-Me_2S (10 M, 2.07 mL, 20.7 mmol) at 0 °C. The mixture was stirred at 65 °C for 4.5 h. To the mixture was added MeOH (5 mL) slowly at 0 °C. The mixture was concentrated in vacuum. The residue was purified by HPLC to give **Intermediate 21** (300 mg). MS: ES m/z calculated for $C_{14}H_{26}N_3O_4$ $[M+H]^+$ 300.2, found 300.0.

[0275] **Intermediate 21** (300 mg) was purified by SFC to give **Intermediate 21A** (100 mg) as a yellow oil and **Intermediate 21B** (120 mg) as a yellow oil. Under analytic SFC

conditions (Column: Chiralpak IG 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 21A**'s retention time is 1.20 min. **Intermediate 21B's** retention time is 1.28 min. The chiral centers in **Intermediate 21A** and **Intermediate 21B** marked with asterisks are indicated as (*R*) and (*S*), respectively, but represent relative configurations.

Example A20
Preparation of Intermediates 23A and 23B





[0276] To a mixture of **Intermediate 21A** (100 mg) in DCM (4 mL) was added TFA (1 mL) in one portion at 25 °C. The mixture was stirred at 25 °C for 16 h. The mixture was concentrated in vacuum to afford **Intermediate 22A's** TFA salt (100 mg) as a yellow solid. **Intermediate 22A**'s TFA salt was directly used in the next step without further purification.

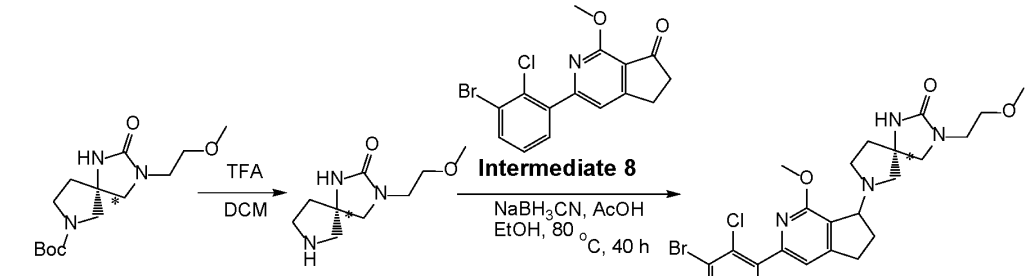
[0277] To a mixture of **Intermediate 22A**'s TFA salt (100 mg) and **Intermediate 8** (113 mg, 319 μmol) in EtOH (10 mL) was added $ZnCl_2$ (30 μL, 638 μmol) in one portion at 25 °C under N_2. The mixture was stirred at 80 °C for 16 h. Once the mixture was cooled to

25 °C, $NaBH_3CN$ (40 mg, 638 μmol) was added. The mixture was then warmed to 80 °C and stirred at 80 °C for 24 h. The mixture was poured into water (50 mL). The aqueous phase was extracted with EA (3 x 50 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 23** (100 mg) as a yellow solid. MS: ES m/z calculated for $C_{24}H_{28}BrClN_4NaO_3$ $[M+Na]^+$ 557.1, found 556.9.

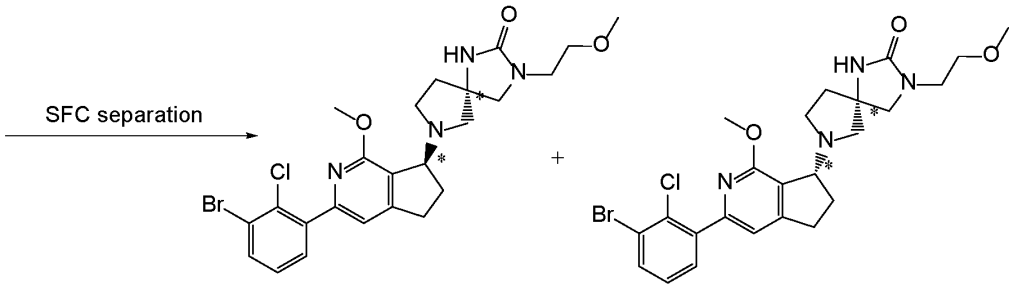
[0278] **Intermediate 23** was separated by SFC to give **Intermediate 23A** (22 mg) as a colorless oil and **Intermediate 23B** (24 mg) as a colorless oil. Under analytic SFC conditions (Column: Chiralpak AS-3 50 x 4.6 mm I.D., 3 μm; Mobile phase: A: CO_2 B: isopropanol (0.05% DEA); Gradient: from 5% 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), **Compound 23A**'s retention time is 1.61 min, and **Compound 23B**'s retention time 2.19 min.

[0279] The chiral centers of **Intermediate 23A** marked with asterisks are assigned as (*S*,*R*), but are relative configurations, and could be assigned as (*S*,*S*), (*R*,*R*) or (*R*,*S*) once the absolute configuration is determined. The chiral centers of **Intermediate 23B** marked with asterisks are assigned as (*R*,*R*), but are relative configurations, and could be assigned as (*S*,*R*), (*R*,*S*) or (*S*,*S*) once the absolute configuration is determined.

Example A21
Preparation of Intermediates 24A and 24B



Intermediate 21B **Intermediate 22B** **Intermediate 24**



Intermediate 24A **Intermediate 24B**

[0280] To a solution of **Intermediate 21B** (120 mg, 401 μmol) in DCM (4 mL) was added TFA (1.54 g, 13.46 mmol, 1 mL). The mixture was stirred at 25 °C for 12 h. The mixture was concentrated under reduced pressure to give crude **Intermediate 22B's** TFA salt (120 mg) as a white solid. Crude **Intermediate 22B** was used in the next step reaction directly without further purification.

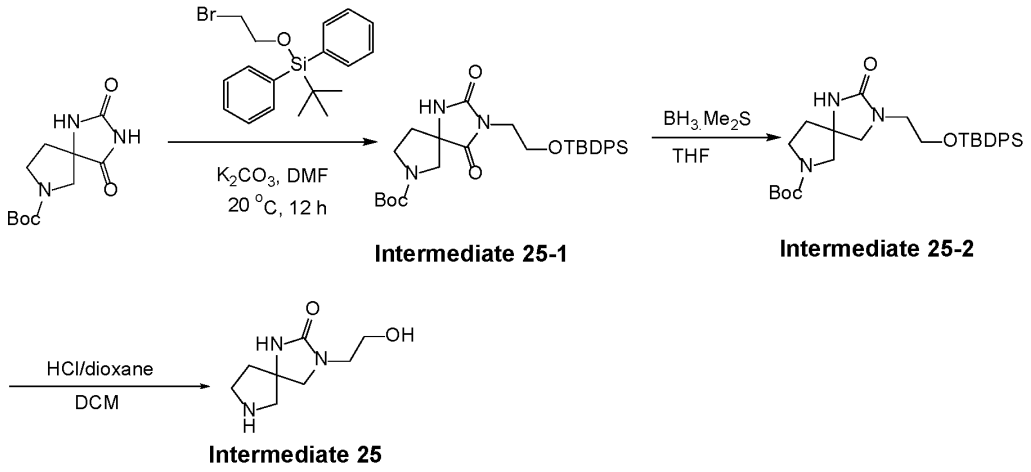
[0281] To a solution of crude **Intermediate 22B** (120.00 mg) and **Intermediate 8** (212 mg, 602.26 μmol) in EtOH (10 mL) was added $ZnCl_2$ (56 μL, 1.20 mmol) in one portion at 25 °C under N_2. The mixture was stirred at 80 °C for 16 h. Once the mixture was cooled to 25 °C, $NaBH_3CN$ (75.69 mg, 1.20 mmol) was added. The mixture was warmed to 80 °C and stirred at 80 °C for 24 h. The mixture was concentrated in vacuum to give a residue. The crude product was purified by column chromatography on silica gel to give **Intermediate 24** (0.17 g) as a white solid. MS: ES m/z calculated for $C_{24}H_{29}BrClN_4O_3$ $[M+H]^+$ 535.1, found 534.9.

[0282] **Intermediate 24** (0.17 g) was purified by SFC to give **Intermediate 24A** (0.06 g) as a white solid and **Intermediate 24B** (0.04 g) as a white solid. Under analytic SFC conditions (Column: Chiralpak IG 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 24A**'s retention time is 1.57 min, and **Intermediate 24B**'s retention time is 1.77 is min.

[0283] The chiral centers of **Intermediate 24A** marked with asterisks are assigned as (*S*,*S*), but are relative configurations, and could be assigned as (*R*,*S*), (*S*,*R*) or (*R*,*R*) once the absolute configuration is determined. The chiral centers of **Intermediate 24B** marked with

asterisks are assigned as (*R*,*S*), but are relative configurations, and could be assigned as (*S*,*S*), (*R*,*R*) or (*S*,*R*) once the absolute configuration is determined.

Example A22
Preparation of Intermediate 25



Intermediate 25-1

Intermediate 25-2

Intermediate 25

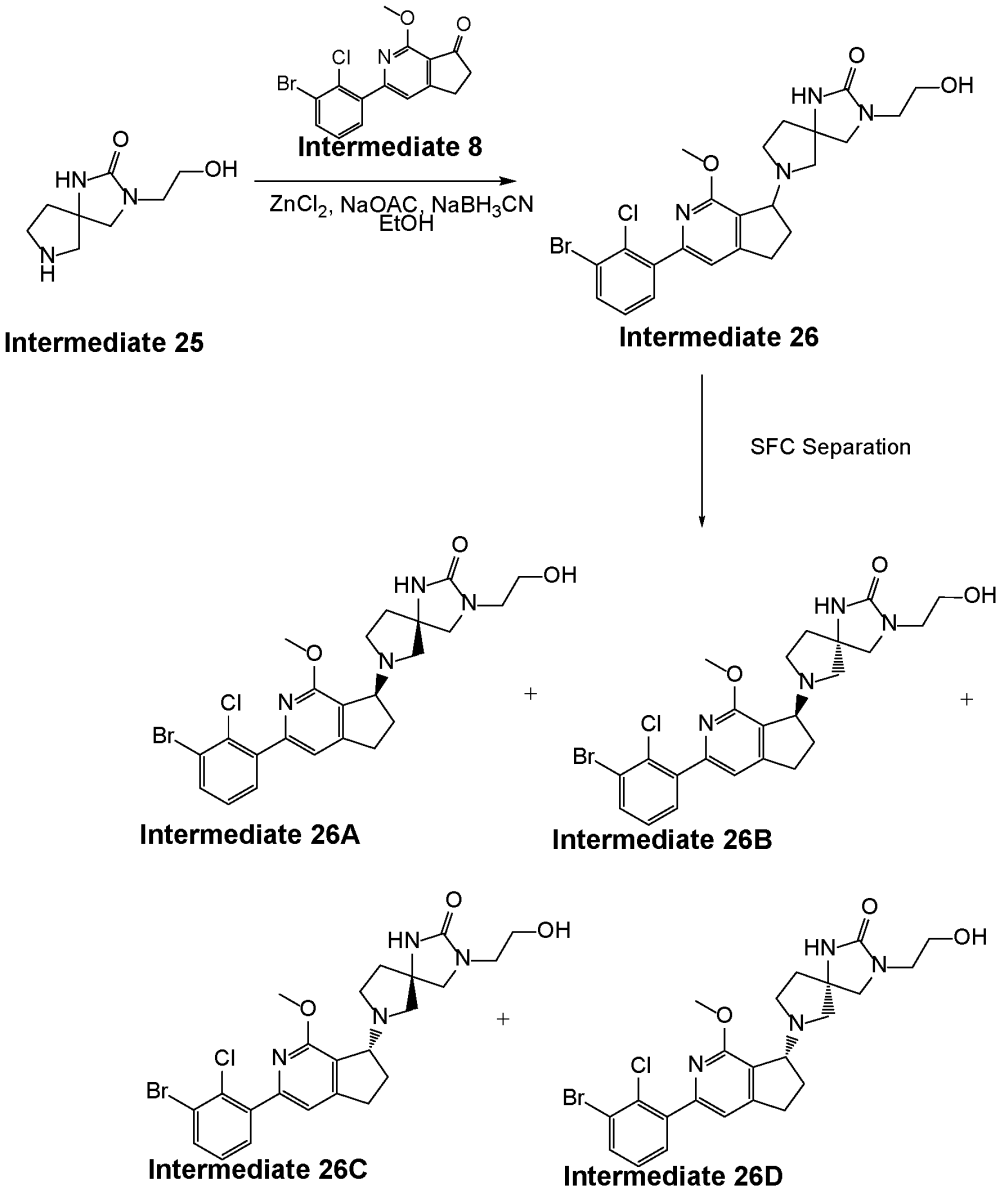
[0284] To a solution of (2-bromoethoxy)(tert-butyl)diphenylsilane (5.81 g, 15.98 mmol) and tert-Butyl 6,8-dioxo-3,7,9-triazaspiro[4.4]nonane-3-carboxylate (4 g, 15.67 mmol) in DMF (40 mL) was added K_2CO_3 (4.33 g, 31.34 mmol). The mixture was stirred at 20 °C for 16 h. The mixture was diluted with EtOAc (60 mL). The organic layer was washed with brine (2 x 60 mL), dried over Na_2SO_4 and concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography to give **Intermediate 25-1** (3.6 g) as a white solid. MS: ES m/z calculated for $C_{29}H_{39}N_3NaO_5Si$ $[M+H]^+$ 560.3, found 560.4.

[0285] To a solution of **Intermediate 25-1** (1 g, 1.86 mmol) in THF (20 mL) was added BH_3-Me_2S (10 M, 929 µL, 9.29 mmol). The mixture was stirred at 65 °C for 3 h. The mixture was quenched by addition of MeOH (20 mL) at 25 °C. The mixture was concentrated under reduced pressure to give a residue, which was purified by prep-HPLC to give **Intermediate 25-2** (300 mg) as a yellow solid. MS: ES m/z calculated for $C_{29}H_{42}N_3O_4Si$ $[M+H]^+$ 524.3, found 524.3.

[0286] To a solution of **Intermediate 25-2** (65 mg, 124 µmol) in DCM (1 mL) was added HCl/dioxane (2 M, 1 mL). The mixture was stirred at 25 °C for 16 h. The mixture was

concentrated under reduced pressure to give crude **Intermediate 25** (50 mg, crude) as a yellow solid and directly used into the next step without further purification.

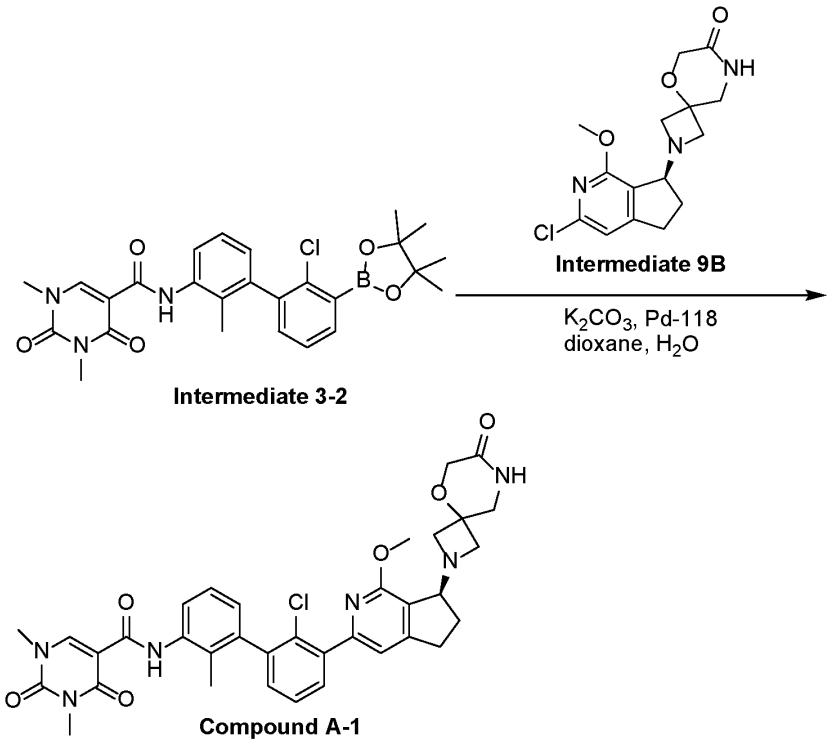
Example A23
Preparation of Intermediates 26A, 26B, 26C, 26D



[0287] To a solution of crude **Intermediate 25** (25 mg) and **Intermediate 8** (30 mg, 85 μmol) in EtOH (3 mL) was added $ZnCl_2$ (7.98 μL, 170 μmol) and NaOAc (14 mg, 170 μmol). The mixture was stirred at 80 °C for 16 h. $NaBH_3CN$ (16 mg, 255 μmol) was added in the mixture and stirred at 80 °C for 16 h. The mixture was quenched by addition of H_2O (5 mL) at 20 °C, and then extracted with EtOAc (2 x 10 mL). The combined organic layers were washed with brine (2 x 10 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 26** (15 mg, 8.91 μmol, 10.47% yield, 93% purity) as a white solid. MS: ES m/z calculated for $C_{23}H_{27}BrClN_4O_3$ $[M+H]^+$ 521.1, found 521.2. **Intermediate 26** was separated by SFC to give **Intermediate 26A**, **Intermediate 26B**, **Intermediate 26C** and **Intermediate 26D.**

Preparation of Compounds

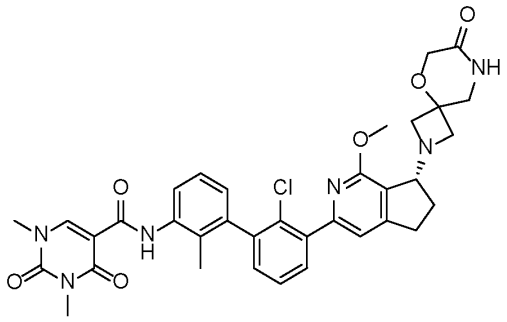
Example 1
Preparation of Compound A-1

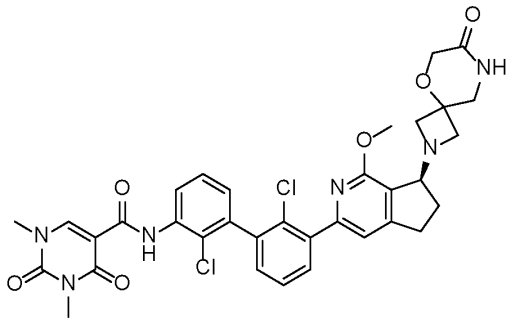
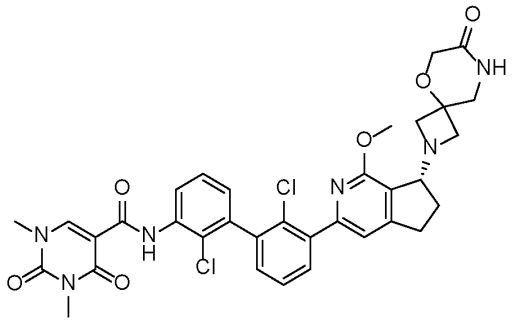
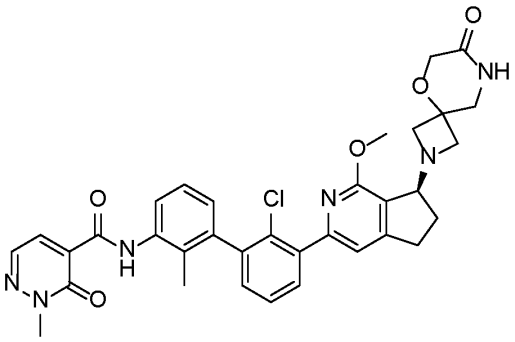


[0288] A mixture of **Intermediate 9B** (1.15 g, 3.55 mmol), **Intermediate 3-2** (2.17 g, 4.26 mmol,) , K_2CO_3 (1.47 g, 10.66 mmol) and di-tert-butyl(cyclopentyl)phosphane;dichloro-palladium;iron (231.49 mg, 355 μmol) in dioxane (45 mL) and H_2O (4.5 mL) was degassed and purged with N_2 (3x), and then the mixture was stirred at 100 °C for 2 h under N_2 atmosphere. The mixture was concentrated under reduced pressure to give a residue, which was purified by prep-HPLC to give **Compound A-1** (1.01 g) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.91 (s,1H), 8.56 (s, 1H), 8.20 (br d, J = 7.3Hz, 2H), 7.59 (br d, J = 7.6 Hz, 1H), 7.39 (br t, J = 7.6 Hz, 1H), 7.33 -7.29 (m, 1H), 7.21 (br d, J = 3.0 Hz, 1H), 7.02 (br d, J = 7.3 Hz, 1H), 6.86 - 6.68 (m, 1H), 4.36 (br d, J = 6.6 Hz, 1H), 4.23 (br s, 2H), 4.02 (s, 3H), 3.93 (br s, 1H), 3.80 - 3.77 (m, 1H), 3.73 (br s, 1H), 3.65 (br s, 2H), 3.57 (s, 4H), 3.44 (s, 3H), 3.23 -3.15 (m, 1H), 2.84 (br dd, J = 8.6, 16.6 Hz, 1H), 2.30 - 2.23 (m, 1H), 2.19 (br s, 3H), 2.12 (br d, J = 7.8 Hz, 1H).

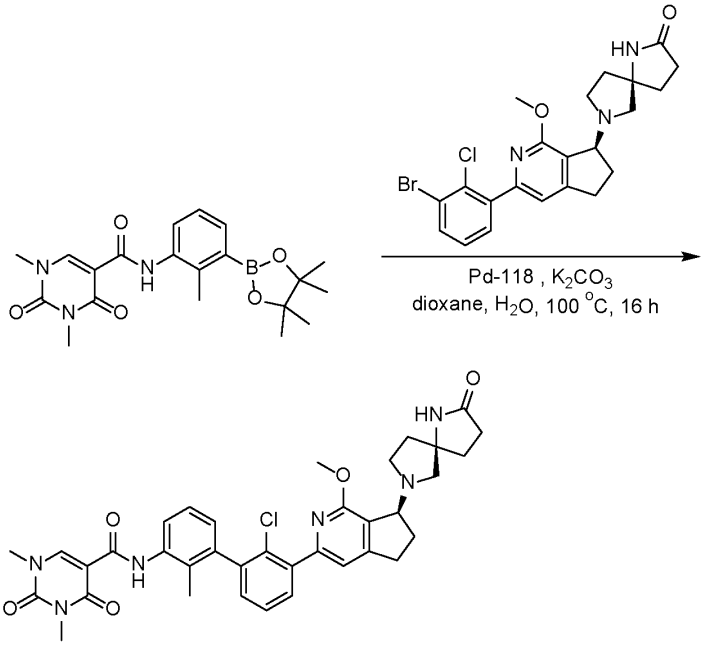
[0289] The compounds shown in Table A-1 were prepared by an analogous reaction protocol as was used for the preparation of Compound A-1 using the appropriate starting materials.

Table A-1

Compound No.	Structure	Starting Materials
A-2		Intermediate 3-2 Intermediate 9A

Compound No.	Structure	Starting Materials
A-3		Intermediate 3-3 Intermediate 9B
A-4		Intermediate 3-3 Intermediate 9A
A-5		Intermediate 3-4 Intermediate 9B

Example 2
Preparation of Compound B-1

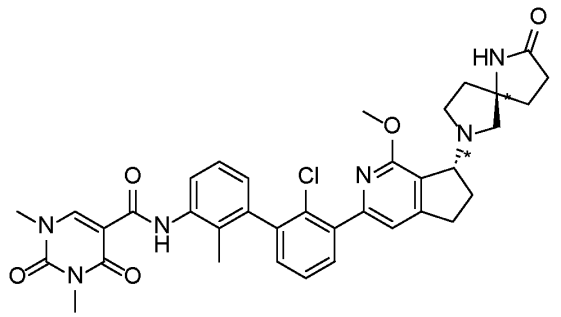
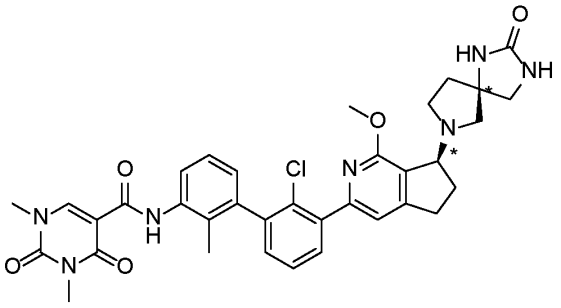
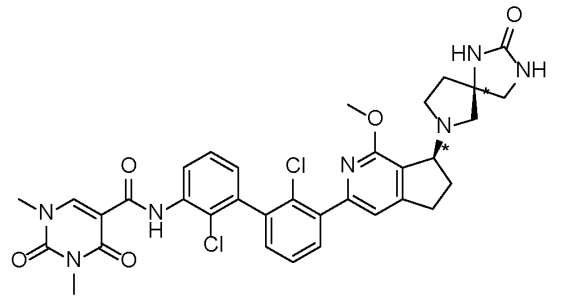
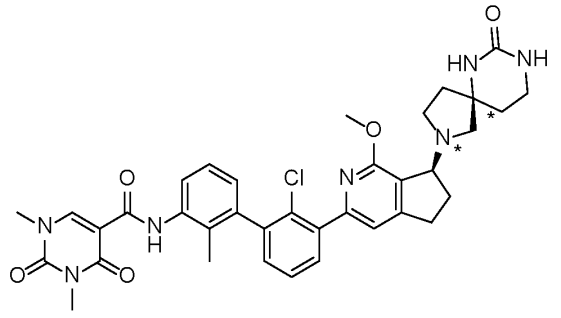


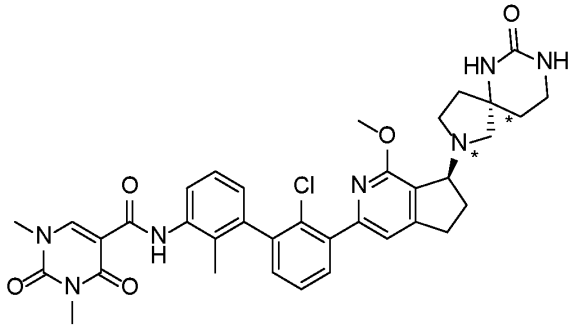
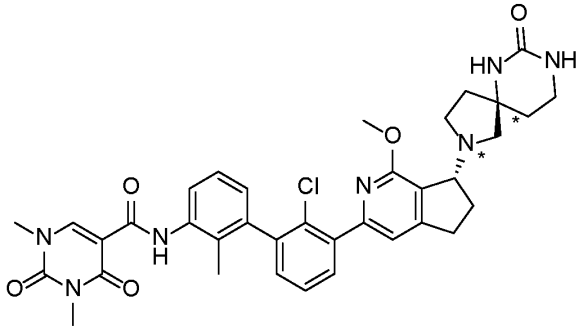
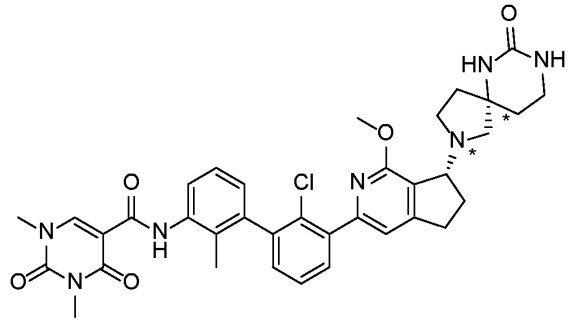
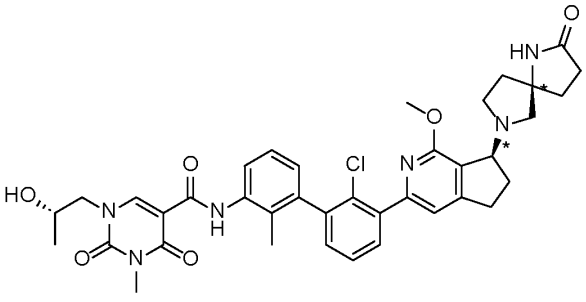
Compound B-1

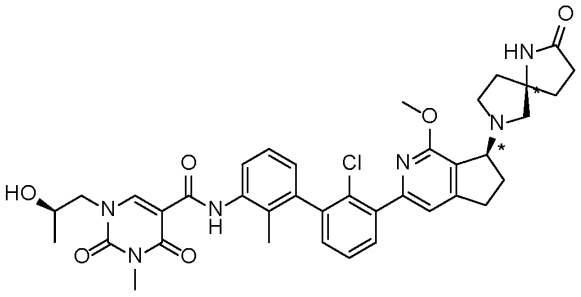
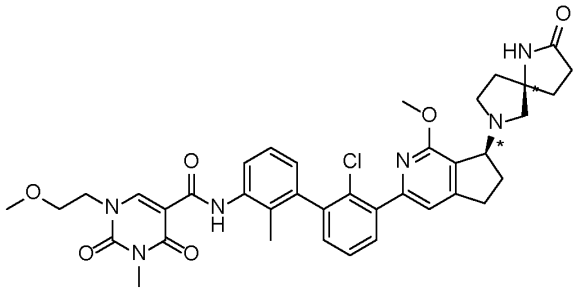
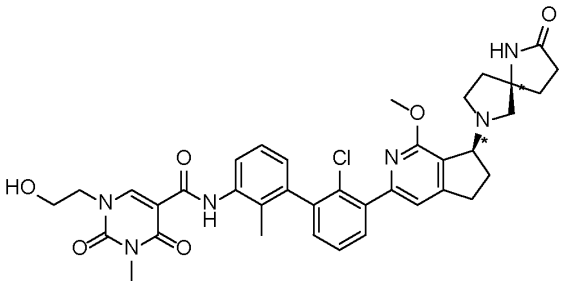
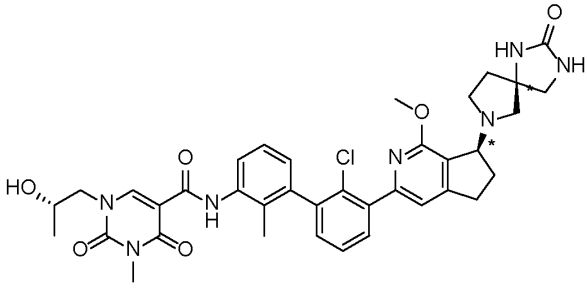
[0290] To a solution of **Intermediate 12B** (186 mg, 390 μmol) and **Intermediate 7-3** (231 mg, 429 μmol) in dioxane (3 mL) and H_2O (0.3 mL) were added ditert-butyl(cyclopentyl)phosphane;dichloropalladium;iron (51mg, 78 μmol) and K_2CO_3 (162 mg, 1.17 mmol) with N_2. The mixture was stirred at 100 °C for 2 h. The mixture was filtered and concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography and re-purified by prep-HPLC to give **Compound B-1** (92 mg) as an off-white solid. MS: ES m/z calculated for $C_{36}H_{38}ClN_6O_5$ $[M+H]^+$ 669.3 found 669.3; 1H NMR (400 MHz, Chloroform-*d*) δ 10.91 (s, 1H), 8.54 (s, 1H), 8.23 (d, J = 8.0Hz, 1H), 7.63 (ddd, J = 1.8, 3.7, 5.6 Hz, 1H), 7.40 (t, J = 7.6 Hz, 1H), 7.32 (t, J = 7.9 Hz, 1H), 7.27 - 7.25 (m, 1H), 7.21 (br s, 1H), 7.04 (t, J = 6.3 Hz, 1H), 6.02 - 5.82 (m, 1H), 4.39 - 4.23 (m, 1H), 4.02 (s, 3H), 3.59 (s, 3H), 3.46 (d, J = 0.8 Hz, 3H), 3.19 - 2.88 (m, 2H), 2.86 - 2.50 (m, 4H), 2.44 - 2.34 (m, 2H), 2.26 - 2.08 (m, 7H), 1.97 (br d, J = 7.9 Hz, 2H).

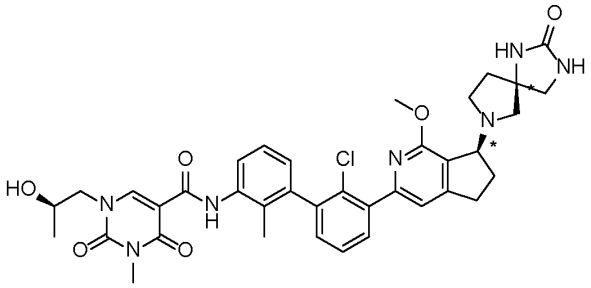
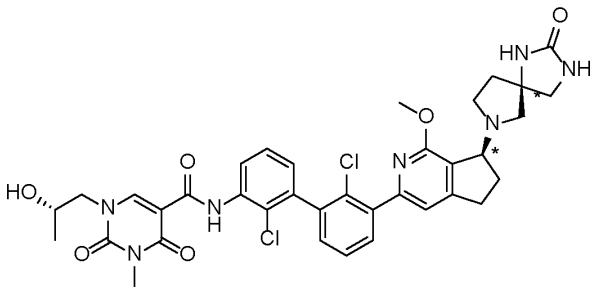
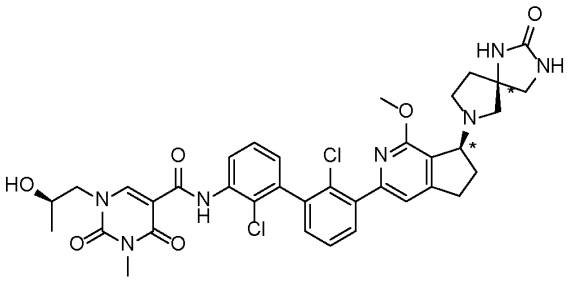
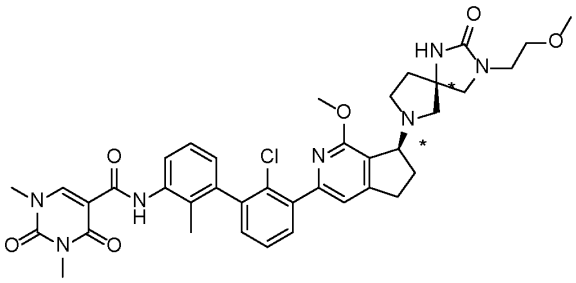
[0291] The compounds shown in Table A-2 were prepared by an analogous reaction protocol as was used for the preparation of Compound B-1 using the appropriate starting materials.

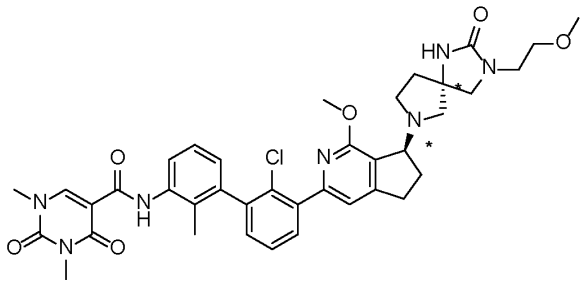
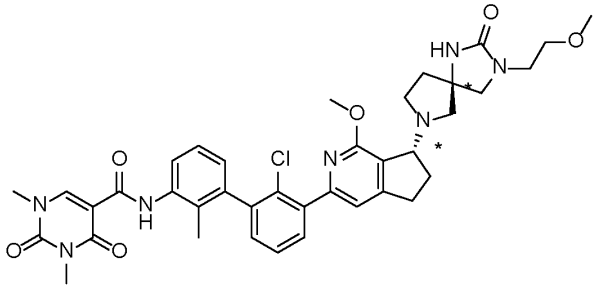
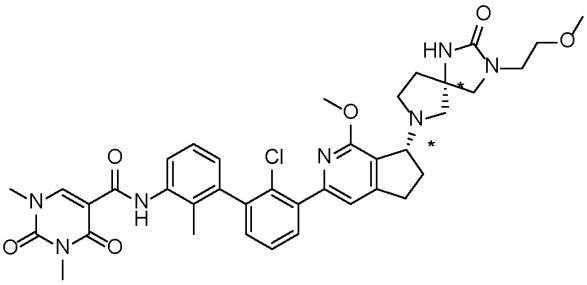
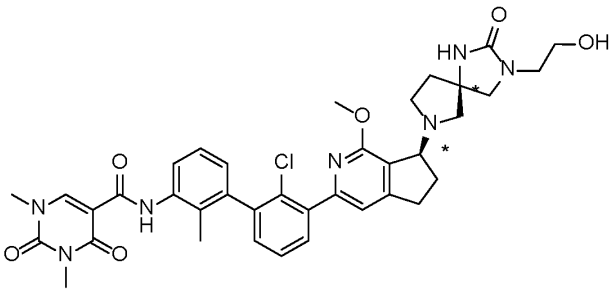
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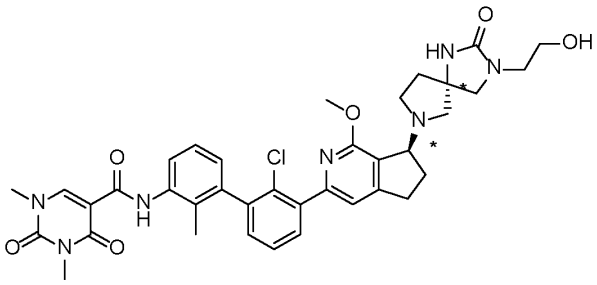
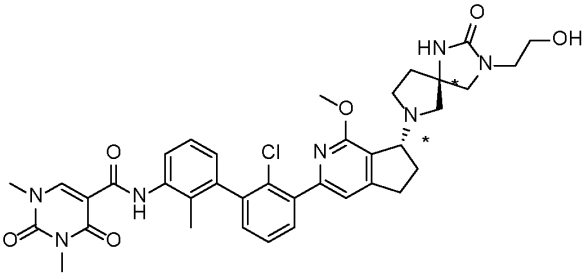
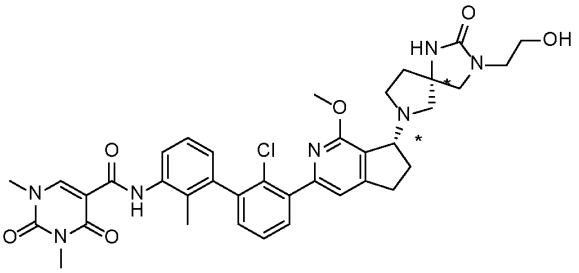
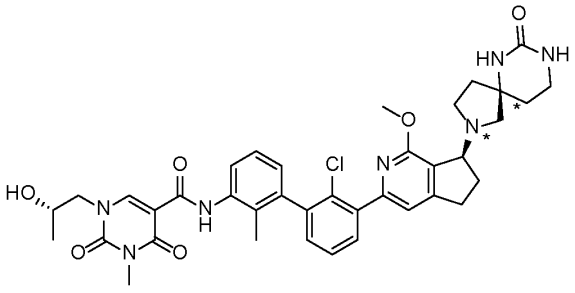
Compound No.	Structure	Starting Materials
B-2		Intermediate 7-3 Intermediate 12A
B-3		Intermediate 7-3 Intermediate 15A
B-4		Intermediate 7-4 Intermediate 15A
B-5		Intermediate 7-3 Intermediate 19A

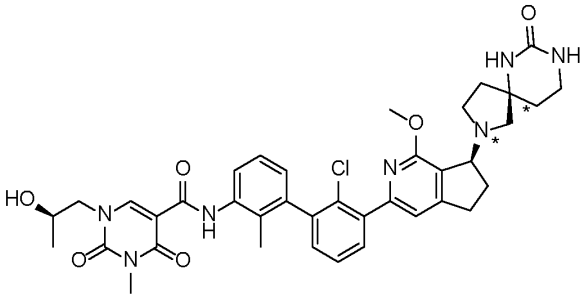
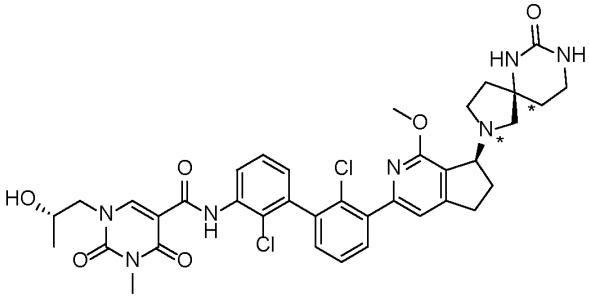
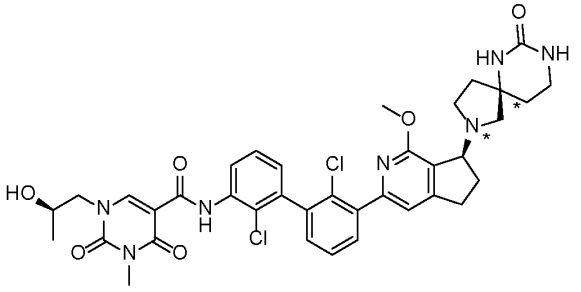
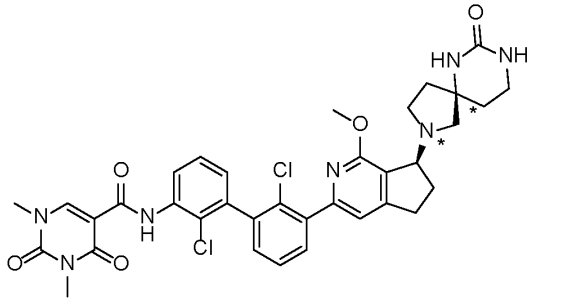
Compound No.	Structure	Starting Materials
B-6		Intermediate 7-3 Intermediate 18A
B-7		Intermediate 7-3 Intermediate 19B
B-8		Intermediate 7-3 Intermediate 18B
B-9		Intermediate 7-5 Intermediate 12B

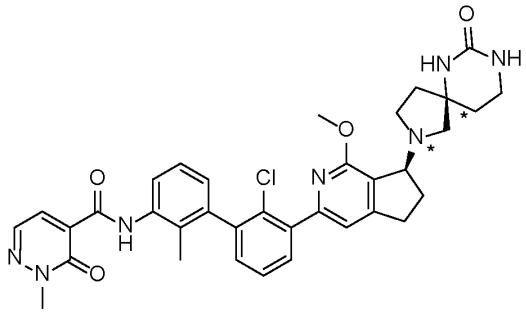
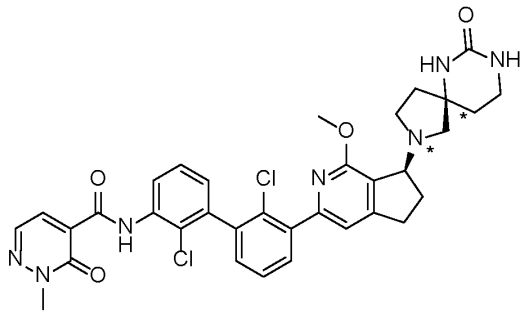
Compound No.	Structure	Starting Materials
B-10		Intermediate 7-7 Intermediate 12B
B-11		Intermediate 7-9 Intermediate 12B
B-12		Intermediate 7-10 Intermediate 12B
B-13		Intermediate 7-5 Intermediate 15A

Compound No.	Structure	Starting Materials
B-14		Intermediate 7-7 Intermediate 15A
B-15		Intermediate 7-6 Intermediate 15A
B-16		Intermediate 7-8 Intermediate 15A
B-17		Intermediate 7-3 Intermediate 23A

Compound No.	Structure	Starting Materials
B-18		Intermediate 7-3 Intermediate 24A
B-19		Intermediate 7-3 Intermediate 23B
B-20		Intermediate 7-3 Intermediate 24B
B-21		Intermediate 7-3 Intermediate 26A

Compound No.	Structure	Starting Materials
B-22		Intermediate 7-3 Intermediate 26B
B-23		Intermediate 7-3 Intermediate 26C
B-24		Intermediate 7-3 Intermediate 26D
B-25		Intermediate 7-5 Intermediate 19A

Compound No.	Structure	Starting Materials
B-26		Intermediate 7-7 Intermediate 19A
B-27		Intermediate 7-6 Intermediate 19A
B-28		Intermediate 7-8 Intermediate 19A
B-29		Intermediate 7-4 Intermediate 19A

Compound No.	Structure	Starting Materials
B-30		Intermediate 7-1 Intermediate 19A
B-31		Intermediate 7-2 Intermediate 19A

Example A
LCMS (Liquid chromatography/Mass spectrometry)

[0292] 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 8: LCMS Method Codes

Method code	**Instrument**	**Column**	**Mobile phase**	**Gradient**	**Flow** **T**	**Run Time**
1	Shimadzu LCMS2020	Agilent PoroShell 120EC-C18 3.0*50mm, 2.7μm	A: water (3.8L) + ACN(0.2L) TFA (1.5mL) B: ACN (4L) + TFA (0.75mL)	10% B increase to 80% B within 3 min; hold at 80% B for 0.5 min; then back to 10% B at 3.51 min and hold for 0.49 min.	1.0 45	4.0
2	Shimadzu LCMS2020	Xtimate C18 2.1*30mm, 3μm	A: water (3.8L) + ACN(0.2L) TFA (1.5mL) B: ACN (4L) + TFA (0.75mL)	Using the elution gradient 5%-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 45	1.0
3	Shimadzu LCMS2020	Xtimate C18 2.1*30 mm, 3μm	A: water (3.8L) + ACN (0.2L) + TFA (1.5mL) B: acetonitrile (4L)+ TFA (0.75mL)	Using the elution gradient 5%-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

Method code	Instrument	Column	Mobile phase	Gradient	Flow T	Run Time
4	Shimadzu LCMS2020	Agilent PoroShell 120 EC-C18 2.7 µm, 3.0*50 mm	A: water (3.8L) + acetonitrile (0.2L) + TFA (1.5mL) B: acetonitrile (4L) + TFA (0.75mL)	Using the elution gradient 10%-80% (solvent B) over 1.5 min and holding at 95% for 0.5 min at a flow rate of 1.2 mL/min, return back to 10% acetonitrile (solvent B) in water and hold for 0.5 min.	1.2 45	2.5

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

Table 9: LCMS Results

Cmpd No.	R_t	LC/MS	LCMS Method
A-1	1.78	671.2	1
A-2	2.76	671.3	1
A-3	2.04	691.2	1
A-4	1.95	691.4	1
A-5	1.84	641.2	1
B-1	1.16	669.3	2
B-2	2.49	669.3	1
B-3	1.74	670.2	1
B-4	1.83	690.2	1
B-5	1.80	684.2	1
B-6	1.78	684.2	1
B-7	1.79	684.3	1
B-8	1.79	684.3	1
B-9	1.75 and 1.79	713.3	1
B-10	1.77 and 1.82	713.4	1
B-11	1.95	713.3	1
B-12	1.64	700.2	1
B-13	1.74 and 1.79	714.3	1
B-14	1.73 and 1.78	714.3	1
B-15	1.76 and 1.81	734.2	1
B-16	1.76 and 1.82	734.2	1
B-17	1.93	728.3	1
B-18	1.90	728.3	1
B-19	2.61	728.3	3

Cmpd No.	R_t	LC/MS	LCMS Method
B-20	1.28	728.3	4
B-21	1.80	714.3	1
B-22	1.78	714.3	1
B-23	1.78	714.2	1
B-24	1.78	714.3	1
B-25	1.73/ 1.78	728.3	1
B-26	1.73/ 1.78	728.3	1
B-27	1.75/ 1.80	748.3	1
B-28	1.74/ 1.80	748.2	1
B-29	1.83	704.2	1
B-30	1.88	654.2	1
B-31	1.95	674.2	1

Retention time (R_t,) in min; LC/MS: without indication the mass is corresponding to $[M+H]^+$.

Example B
PDL1/PD1 Binding Assay

[0293] 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 µg/ml) were added to the wells, and the incubation continued for 1 h. Streptavidin Donor beads (final concentration 20 µg/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

[0294] 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.

[0295] 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. EC50 values were determined from the fit of the dose-response curves.

[0296] 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. As shown by the data in Table 10, the compounds described herein are active for controlling expression of PD-L1.

Table 10

Cmpd No.	PD-1/PD-L1 PPI IC_{50}	Jurkat NFAT EC_{50}
A-1	A	A
A-2	A	C
A-3	A	A
A-4	B	C
A-5		A
B-1	A	A
B-2	A	D
B-3		A
B-4		A
B-5	A	A
B-6	A	A
B-7	A	C
B-8	A	C
B-9	A	A
B-10	A	A
B-11	A	A
B-12	A	A
B-13	A	A

Cmpd No.	PD-1/PD-L1 PPI IC_{50}	Jurkat NFAT EC_{50}
B-14	A	A
B-15	A	A
B-16	A	A
B-17	A	A
B-18	A	B
B-19	A	n.r.
B-20		n.r.
B-21	A	A
B-22	A	n.r.
B-23	A	A
B-24	A	D
B-25	A	A
B-26	A	A
B-27	A	A
B-28	A	A
B-29	A	A
B-30	A	A
B-31	A	A

Example D
ADME Studies

Table 11

	Compound A-1	**Compound B-1**
Caco-2-Papp (10^{-6} cm/s) A → B/B → A (ER)	0.6 / 1.6 (2.7)	0.32 / 1.4 (4.2)
Liver Microsomal Stability $T_{1/2}$ (min) m/r/d/c/h*	>60 / >60 / 35 / 9 / >60	28 / 19/ 35 / 9.8 / 15
Hepatocyte Stability $T_{1/2}$ (min) m/r/d/c/h*	>120 / >120 / >120 / 68 / >120	43 / 46 / 103 / 48 / 75
CYP inhibition @ 10 µM	All < 40%	All < 40%
CYP3A4-T TDI ± NADPH IC_{50} Shift	NA (+NADPH IC_{50} > 50 µM)	>4.4 (+NADPH IC_{50} > 50 µM)
CYP3A4 PXR Activation up to 10 µM	No activation	No activation
GSH Conjugation	No adduct	No adduct
PPB (% bound) m/r/d/c/h*	99.64 / 99.71 / 99.54 / 99.40 / 99.36	99.77 / 99.71 / 99.65 / 99.35 / 99.73

*m/r/d/c/h mouse/rat/dog/monkey/human
[a] CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4-M/T

[0297] As shown in Table 11, Compound A-1 demonstrated no *in vitro* drug-drug interactions, cytochrome P450 time-dependent inhibition or reactive metabolite alerts. Compound B-1 demonstrated no *in vitro* drug-drug interaction or reactive metabolite alerts.

Example E
Toxicology Assays

Table 12

	Compound A-1	**Compound B-1**
hERG/NaV/CaV IC_{50} (µM)	All > 10	hERG 9.6 NaV/CaV > 10
MNT: TK6 ± S9	Negative	

	Compound A-1	Compound B-1
AMES – 5 Strains ± S9 (TA98, TA100, TA1535, TA97a, WP2 uvrA/pKM101)	Negative	Negative
CEREP safety functional panel* (78 targets dosed up to 10 µM)	No significant activity	
CEREP 58 Kinases @ 10 µM	No significant inhibition	No significant inhibition

*Significant response designated as greater than 50% max response up to 10 µM.

[0298] Compounds A-1 and B-1 demonstrated low *in vitro* toxicity based on hERG/NaV/CaV, MNT: TK6, AMES and CEREP testing as shown in Table 12.

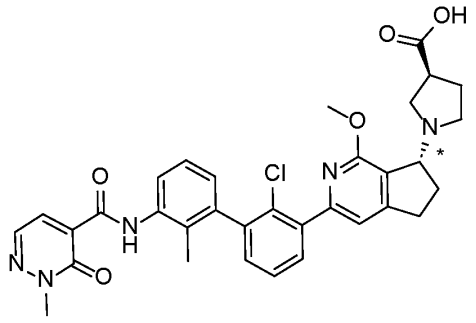
Example F
Mouse PO Pharmacokinetics

Table 13

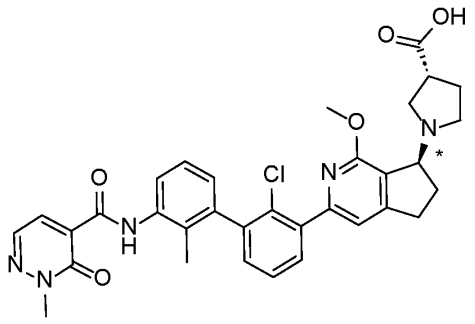
Mouse PO PK Parameter	Compound A-1	Compound B-1	INCB086550	Compound 1	Compound 2
PO	50 mg/kg	50 mg/kg	100 mg/kg	50 mg/kg	50 mg/kg
$T_{1/2}$ (h)	2.38*	2.76	3.2	ND	ND
C_{max} (ng/mL)	9,553	5,098	2,694	2,127	3,730
C_{12h} (ng/mL)	6,940	1,900	ND	37	27
AUC (ng·h/mL)	0-12 h 97,012	0-12h 38,466	0-24 h 23,351	0-12 h 5,756	0-12 h 8,380

*15 mg/kg

[0299] Pharmacokinetic properties of Compound A-1 were compared to known PD-1/PD-L1 inhibitor, INCB086550, along with Compound 1, having the structure:



and Compound 2, having the structure:



. As shown in Table 13, Compound A-1 has significantly improved oral exposure compared to Compounds 1 and 2. Oral dosages of 50 mg/kg for Compound A-1 and B-1 have higher plasma exposure than 100 mg/kg INCB086550.

Example G
Tissue Distribution in Mice

Table 14

Ratios to Plasma	Compound A-1	Compound B-1
Liver/Plasma	6.15	5.09
Brain/Plasma	0.06	0.06

Table 15

Liver Ratio to Other Tissues	Compound A-1	Compound B-1
Liver/Lung	2.09	1.78
Liver/Kidney	1.31	1.46
Liver/Skin	30	21

[0300] As shown in Tables 14 and 15, Compounds A-1 and B-1 demonstrated a higher distribution in liver, kidney and lung and relative to plasma and a lower distribution in brain and skin relative to plasma.

Example H
Rat Pharmacokinetics

Table 16

Rat IV – Plasma	INCB086550	Compound A-1	Compound B-1
Dosage	0.5 mg/kg	2 mg/kg	2 mg/kg
Clearance (mL/min/kg)	11	9.3	9.5
Vd_{ss} (L/kg)	2.7	2.8	2.2
$t_{1/2}$ (h)	3.7	3.6	3.0

Table 17

Rat PO – Plasma	INCB086550	Compound A-1	Compound B-1
Dosage	3 mg/kg	15 mg/kg	15 mg/kg
C_{max} (ng/mL)	–	1,803	1,193
$AUC_{0\text{-}inf}$ (ng·h/mL)	444	23,847	11,239
Oral bioavailability	F = 10%	F = 89%	F = 40%

[0301] As shown in Tables 16 and 17, Compounds A-1 and B-1 showed similar clearance, Vd_{ss} and $t_{1/2}$ in comparison to INCB086550, demonstrated moderate to high rat oral bioavailability, and higher bioavailability compared to INCB086550.

Example I
Monkey Pharmacokinetics

Table 18

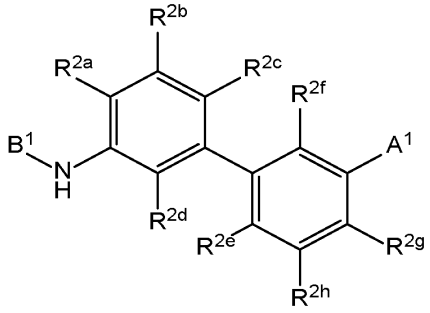
IV PK Parameter	INCB086550	Compound A-1	Compound B-1
Dosage	0.5 mg/kg	1 mg/kg	
Clearance (mL/min/kg)	10	5.3	8.9
Vd_{ss} (L/kg)	1.44	1.9	2.2
$t_{1/2}$ (h)	5.7	4.6	4.3
$AUC_{0\text{-}last}$ (ng·h/mL)		3,237	1,865

[0302] Compounds A-1 and B-1 demonstrated low clearance and low-to-moderate volume of distribution in monkey as shown in Table 18.

[0303] 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.

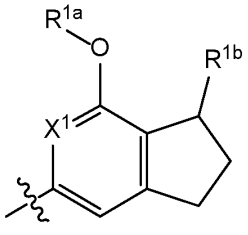
WHAT IS CLAIMED IS:

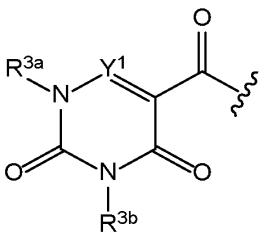
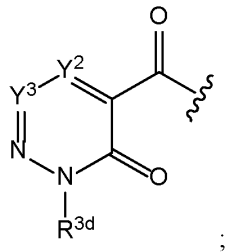
1. A compound of Formula (I), or a pharmaceutically acceptable salt thereof, having the structure:



(I)

wherein:

A^1 is  ;

B^1 is  or  ;

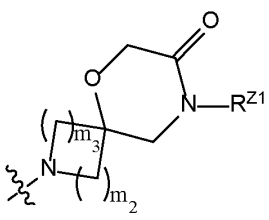
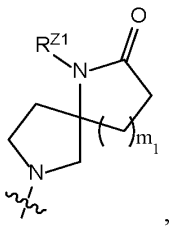
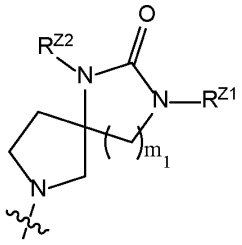
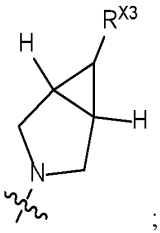
X^1 is selected from the group consisting of CH and N;

Y^1 is selected from the group consisting of N and CR^{3e};

Y^2 is CR^{3e};

Y^3 is CR^{3f};

R^{1a} is selected from the group consisting of $-C_{1-4}$ alkyl, $-C_{1-4}$ haloalkyl, $-CH_2$(C_{3-6} monocyclic cycloalkyl), $-C_{2-4}$ alkyl(O-C_{1-4} alkyl), $-C_{2-4}$ alkyl(OC_{1-4} haloalkyl), $-CH_2$(4-6 membered monocyclic heterocyclyl) and $-CH_2$(5-6 membered monocyclic heteroaryl);

R^{1b} is selected from the group consisting of , ,  and ;

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

R^{2d} and R^{2f} are independently selected from the group consisting of hydrogen, halogen, cyano, $–CH_3$, $–CH_2CH_3$, $–CH_2OH$, $–OCH_3$ and $–SCH_3$;

R^{3a} is selected from the group consisting of hydrogen, $–CH_3$, $–C_{2-4}$ alkyl and $–C_{2-4}$ haloalkyl, wherein the $–C_{2-4}$ alkyl is optionally substituted with one or two or three substituents independently selected from hydroxy, and $–OR^{3a1}$;

R^{3a1} is $–C_{1-4}$ alkyl;

R^{3b} is selected from the group consisting of hydrogen, $–CH_3$, $–C_{2-4}$ alkyl and $–C_{2-4}$ haloalkyl;

R^{3c} is selected from the group consisting of hydrogen, $–CH_3$, $–C_{2-4}$ alkyl and $–C_{2-4}$ haloalkyl;

R^{3d} is selected from the group consisting of hydrogen, $–CH_3$, $–C_{2-4}$ alkyl and $–C_{2-4}$ haloalkyl;

R^{3e} is selected from the group consisting of hydrogen, halogen and $–CH_3$;

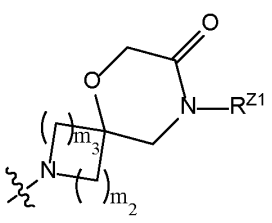
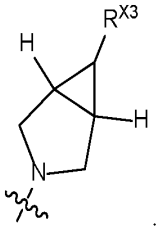
R^{3f} is selected from the group consisting of hydrogen, halogen, -OH, –CN and $–CH_3$;

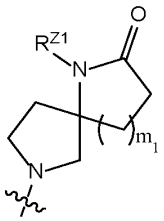
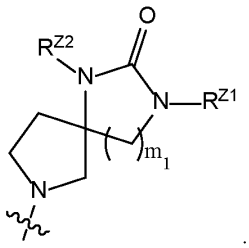
m_1, m_2, and m_3 are independently 1 or 2;

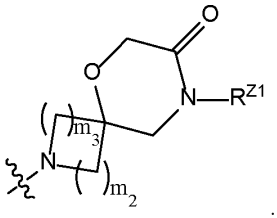
R^{Z1} and R^{Z2} are independently selected from the group consisting of hydrogen, $–C_{1-4}$ alkyl and $–C_{1-4}$ haloalkyl, wherein the $–C_{1-4}$ alkyl is optionally substituted with one or two or three substituents independently selected from hydroxy, and $–OR^{Z3}$;

R^{Z3} is $–C_{1-4}$ alkyl; and

R^{X3} is selected from the group consisting of hydrogen, halogen, –C_{1-4} alkyl, –C_{1-4} haloalkyl, –$C(=O)R^{Z3}$, –$S(=O)_2R^{Z1}$, –$C(=O)N(R^{Z1})R^{Z2}$ and –$S(=O)_2N(R^{Z1})R^{Z2}$.

2. The compound of Claim 1, or a pharmaceutically acceptable salt thereof, wherein R^{1b} is  or .

3. The compound of Claim 1, or a pharmaceutically acceptable salt thereof, wherein R^{1b} is  or .

4. The compound of Claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein R^{1b} is .

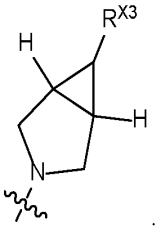
5. The compound of Claim 4, or a pharmaceutically acceptable salt thereof, wherein R^{Z1} is hydrogen.

6. The compound of Claim 4, or a pharmaceutically acceptable salt thereof, wherein R^{Z1} is –C_{1-4} alkyl.

7. The compound of Claim 4, or a pharmaceutically acceptable salt thereof, wherein R^{Z1} is –C_{1-4} alkyl, wherein the –C_{1-4} alkyl is optionally substituted with one or two or three substituents independently selected from hydroxy and –OR^{Z3}.

8. The compound of Embodiment 4, or a pharmaceutically acceptable salt thereof, wherein R^{Z1} is –C_{1-4} haloalkyl.

9. The compound of any one of Claims 4-8, or a pharmaceutically acceptable salt thereof, wherein m_2 and m_3 are each 1.

10. The compound of Claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein R^{1b} is 

.

11. The compound of Claim 10, or a pharmaceutically acceptable salt thereof, wherein R^{X3} is hydrogen.

12. The compound of Claim 10, or a pharmaceutically acceptable salt thereof, wherein R^{X3} is $-C_{1-4}$ alkyl or $-C_{1-4}$ haloalkyl.

13. The compound of Claim 10, or a pharmaceutically acceptable salt thereof, wherein R^{X3} is $-C(=O)R^{Z3}$.

14. The compound of Claim 10, or a pharmaceutically acceptable salt thereof, wherein R^{X3} is $-S(=O)_2R^{Z1}$.

15. The compound of Claim 10, or a pharmaceutically acceptable salt thereof, wherein R^{X3} is $-C(=O)N(R^{Z1})R^{Z2}$.

16. The compound of Claim 10, or a pharmaceutically acceptable salt thereof, wherein R^{X3} is $-S(=O)_2N(R^{Z1})R^{Z2}$.

17. The compound of any one of Claims 13-16, or a pharmaceutically acceptable salt thereof, wherein R^{Z1} is hydrogen.

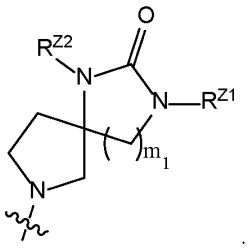
18. The compound of any one of Claims 13-16, or a pharmaceutically acceptable salt thereof, wherein R^{Z1} is $-C_{1-4}$ alkyl.

19. The compound of any one of Claims 13-16, or a pharmaceutically acceptable salt thereof, wherein R^{Z1} is $-C_{1-4}$ haloalkyl.

20. The compound of any one of Claims 15-19, or a pharmaceutically acceptable salt thereof, wherein R^{Z2} is hydrogen.

21. The compound of any one of Claims 15-19, or a pharmaceutically acceptable salt thereof, wherein R^{Z2} is $-C_{1-4}$ alkyl.

22. The compound of any one of Claims 15-19, or a pharmaceutically acceptable salt thereof, wherein R^{Z2} is $-C_{1-4}$ haloalkyl.

23. The compound of Claim 1 or 3, or a pharmaceutically acceptable salt thereof, wherein R^{1b} is .

24. The compound of Claim 23, or a pharmaceutically acceptable salt thereof, wherein R^{Z1} is hydrogen.

25. The compound of Claim 23, or a pharmaceutically acceptable salt thereof, wherein R^{Z1} is $-C_{1-4}$ alkyl.

26. The compound of Claim 23, or a pharmaceutically acceptable salt thereof, wherein R^{Z1} is $-C_{1-4}$ alkyl, wherein the $-C_{1-4}$ alkyl is optionally substituted with one or two or three substituents independently selected from hydroxy and $-OR^{Z3}$.

27. The compound of Claim 26, wherein R^{Z1} is substituted with hydroxy.

28. The compound of Claim 26, wherein R^{Z1} is substituted with $-OR^{Z3}$.

29. The compound of Claim 28, wherein R^{Z3} is methyl.

30. The compound of Claim 23, or a pharmaceutically acceptable salt thereof, wherein R^{Z1} is $-C_{1-4}$ haloalkyl.

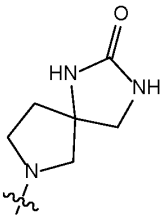
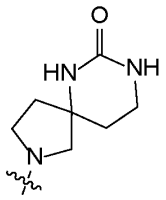
31. The compound of any one of Claims 23-30, or a pharmaceutically acceptable salt thereof, wherein R^{Z2} is hydrogen.

32. The compound of any one of Claims 23-30, or a pharmaceutically acceptable salt thereof, wherein R^{Z2} is $-C_{1-4}$ alkyl.

33. The compound of any one of Claims 23-30, or a pharmaceutically acceptable salt thereof, wherein R^{Z2} is $-C_{1-4}$ alkyl, wherein the $-C_{1-4}$ alkyl is optionally substituted with one or two or three substituents independently selected from hydroxy and $-OR^{Z3}$.

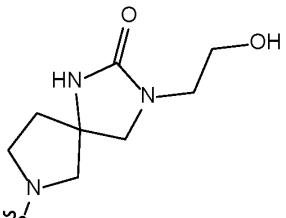
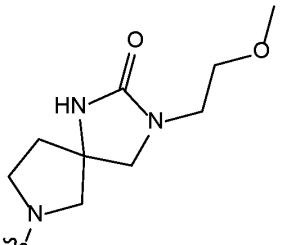
34. The compound of any one of Claims 23-30, or a pharmaceutically acceptable salt thereof, wherein R^{Z2} is $-C_{1-4}$ haloalkyl.

35. The compound of Claim 23, or a pharmaceutically acceptable salt thereof,

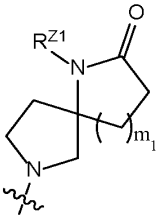
wherein R^{1b} is or .

36. The compound of Claim 23, or a pharmaceutically acceptable salt thereof,

wherein R^{1b} is or .

37. The compound of Claim 1 or 3, or a pharmaceutically acceptable salt thereof,

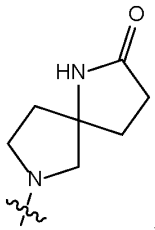


wherein R^{1b} is .

38. The compound of Claim 37, or a pharmaceutically acceptable salt thereof, wherein R^{Z1} is hydrogen.

39. The compound of Claim 37, or a pharmaceutically acceptable salt thereof, wherein R^{Z1} is $-C_{1-4}$ alkyl.

40. The compound of Claim 37, or a pharmaceutically acceptable salt thereof, wherein R^{Z1} is $-C_{1-4}$ haloalkyl.

41. The compound of Claim 37, wherein R^{1b} is .

42. The compound of any one of Claims 1-41, or a pharmaceutically acceptable salt thereof, wherein X^1 is N.

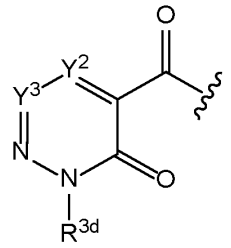
43. The compound of any one of Claims 1-42, or a pharmaceutically acceptable salt thereof, wherein R^{1a} is $-C_{1-4}$ alkyl.

44. The compound of Claim 43, or a pharmaceutically acceptable salt thereof, wherein R^{1a} is $-CH_3$.

45. The compound of any one of Claims 1-42, or a pharmaceutically acceptable salt thereof, wherein R^{1a} is $-C_{1-4}$ haloalkyl.

46. The compound of any one of Claims 1-42, or a pharmaceutically acceptable salt thereof, wherein R^{1a} is $-CH_2$(C_{3-6} monocyclic cycloalkyl),$-CH_2$(4-6 membered monocyclic heterocyclyl) or $-CH_2$(5-6 membered monocyclic heteroaryl).

47. The compound of any one of Claims 1-42, or a pharmaceutically acceptable salt thereof, wherein R^{1a} is $-C_{2-4}$ alkyl(OC_{1-4} alkyl) or $-C_{2-4}$ alkyl(OC_{1-4} haloalkyl).

48. The compound of any one of Claims 1-47, or a pharmaceutically acceptable salt thereof, wherein B^1 is 

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49. The compound of Claim 48, or a pharmaceutically acceptable salt thereof, wherein R^{3d} is hydrogen.

50. The compound of Claim 48, or a pharmaceutically acceptable salt thereof, wherein R^{3d} is $-CH_3$.

51. The compound of Claim 48, or a pharmaceutically acceptable salt thereof, wherein R^{3d} is $-C_{2-4}$ alkyl.

52. The compound of Claim 48, or a pharmaceutically acceptable salt thereof, wherein R^{3d} is $-C_{1-4}$ haloalkyl.

53. The compound of any one of Claims 48-52, or a pharmaceutically acceptable salt thereof, wherein Y^2 is CR^{3e}, wherein R^{3e} is hydrogen.

54. The compound of any one of Claims 48-52, or a pharmaceutically acceptable salt thereof, wherein Y^2 is CR^{3e}, wherein R^{3e} is halogen.

55. The compound of any one of Claims 48-52, or a pharmaceutically acceptable salt thereof, wherein Y^2 is CR^{3e}, wherein R^{3e} is $–CH_3$.

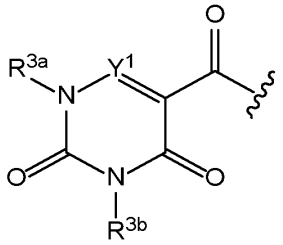
56. The compound of any one of Claims 48-55, or a pharmaceutically acceptable salt thereof, wherein Y^3 is CR^{3f}, wherein R^{3f} is hydrogen.

57. The compound of any one of Claims 48-55, or a pharmaceutically acceptable salt thereof, wherein Y^3 is CR^{3f}, wherein R^{3f} is halogen.

58. The compound of any one of Claims 48-55, or a pharmaceutically acceptable salt thereof, wherein Y^3 is CR^{3f}, wherein R^{3f} is –OH.

59. The compound of any one of Claims 48-55, or a pharmaceutically acceptable salt thereof, wherein Y^3 is CR^{3f}, wherein R^{3f} is –CN.

60. The compound of any one of Claims 48-55, or a pharmaceutically acceptable salt thereof, wherein Y^3 is CR^{3f}, wherein R^{3f} is $–CH_3$.

61. The compound of any one of Claims 1-47, or a pharmaceutically acceptable salt thereof, wherein B^1 is 

.

62. The compound of Claim 61, or a pharmaceutically acceptable salt thereof, wherein Y^1 is CR^{3c}, wherein R^{3c} is hydrogen.

63. The compound of Claim 61, or a pharmaceutically acceptable salt thereof, wherein Y^1 is CR^{3c}, wherein R^{3c} is $–CH_3$.

64. The compound of Claim 61, or a pharmaceutically acceptable salt thereof, wherein Y^1 is CR^{3c}, wherein R^{3c} is $–C_{2\text{-}4}$ alkyl.

65. The compound of Claim 61, or a pharmaceutically acceptable salt thereof, wherein Y^1 is CR^{3c}, wherein R^{3c} is $–C_{2\text{-}4}$ haloalkyl.

66. The compound of any one of Claims 61-65, or a pharmaceutically acceptable salt thereof, wherein R^{3b} is hydrogen.

67. The compound of any one of Claims 61-65, or a pharmaceutically acceptable salt thereof, wherein R^{3b} is $–CH_3$.

68. The compound of any one of Claims 61-65, or a pharmaceutically acceptable salt thereof, wherein R^{3b} is $–C_{2-4}$ alkyl.

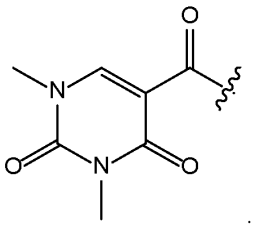
69. The compound of any one of Claims 61-65, or a pharmaceutically acceptable salt thereof, wherein R^{3b} is $–C_{2-4}$ haloalkyl.

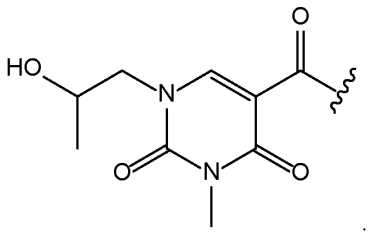
70. The compound of any one of Claims 61-69, or a pharmaceutically acceptable salt thereof, wherein R^{3a} is hydrogen.

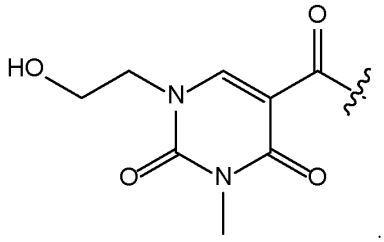
71. The compound of any one of Claims 61-69, or a pharmaceutically acceptable salt thereof, wherein R^{3a} is $–CH_3$.

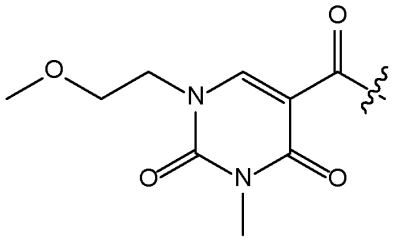
72. The compound of any one of Claims 61-69, or a pharmaceutically acceptable salt thereof, wherein R^{3a} is$–C_{2-4}$ alkyl optionally substituted with one or two or three substituents independently selected from hydroxy and $–OR^{3a1}$.

73. The compound of any one of Claims 61-69, or a pharmaceutically acceptable salt thereof, wherein R^{3a} is $–C_{2-4}$ haloalkyl.

74. The compound of Claim 61, or a pharmaceutically acceptable salt thereof, wherein B^1 is .

75. The compound of Claim 61, or a pharmaceutically acceptable salt thereof, wherein B^1 is .

76. The compound of Claim 61, or a pharmaceutically acceptable salt thereof, wherein B^1 is .

77. The compound of Claim 61, or a pharmaceutically acceptable salt thereof, wherein B^1 is .

78. The compound of any one of Claims 1-77, or a pharmaceutically acceptable salt thereof, wherein R^{2a}, R^{2b}, R^{2g} and R^{2h} are each hydrogen.

79. The compound of any one of Claims 1-78, or a pharmaceutically acceptable salt thereof, wherein R^{2d} and R^{2f} are each halogen.

80. The compound of any one of Claims 1-78, or a pharmaceutically acceptable salt thereof, wherein R^{2d} is $-CH_3$; and R^{2f} is halogen.

81. The compound of Claim 79 or 80, or a pharmaceutically acceptable salt thereof, wherein the halogen is chloro.

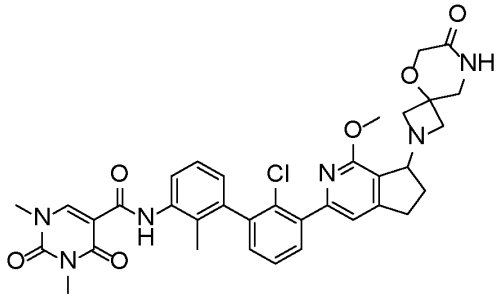
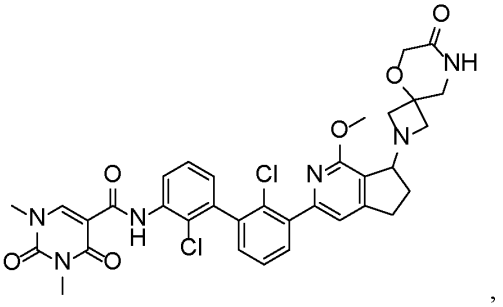
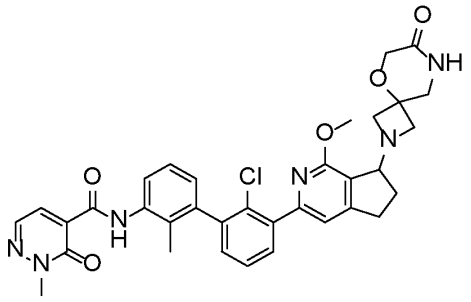
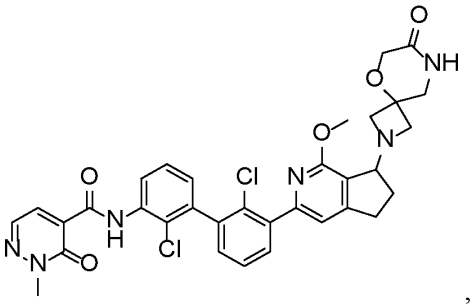
82. The compound of any one of Claims 1-81, or a pharmaceutically acceptable salt thereof, wherein R^{2c} and R^{2e} are each hydrogen.

83. The compound of any one of Claims 1-81, or a pharmaceutically acceptable salt thereof, wherein R^{2c} is halogen and R^{2e} is hydrogen.

84. The compound of any one of Claims 1-81, or a pharmaceutically acceptable salt thereof, wherein R^{2e} is halogen and R^{2c} is hydrogen.

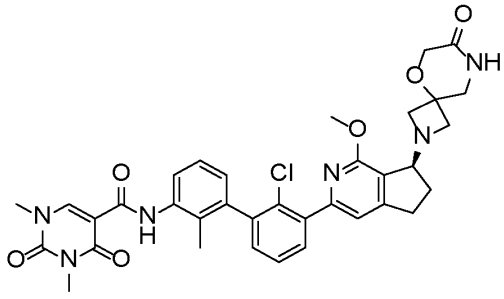
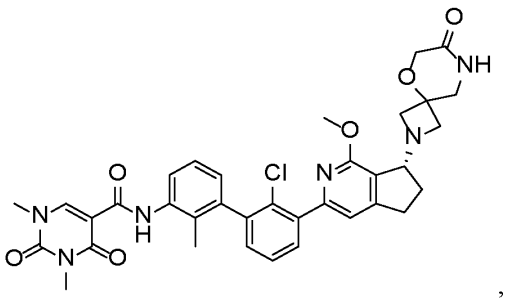
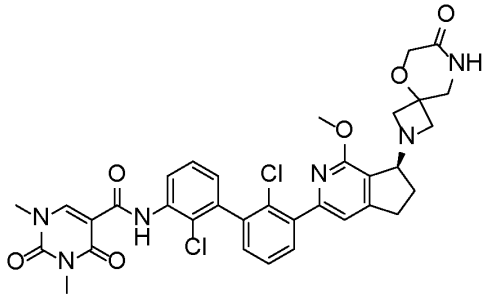
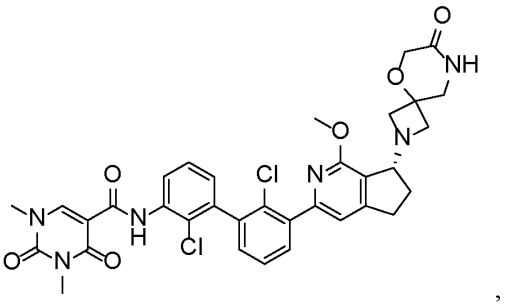
85. The compound of Claim 83 or 84, or a pharmaceutically acceptable salt thereof, wherein the halogen is fluoro.

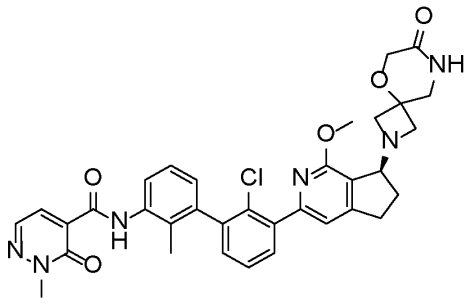
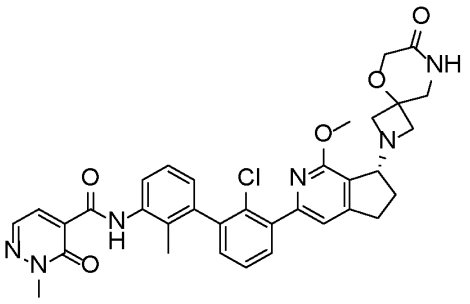
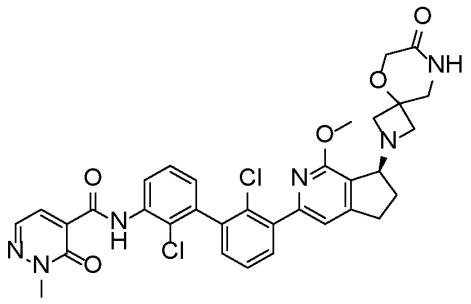
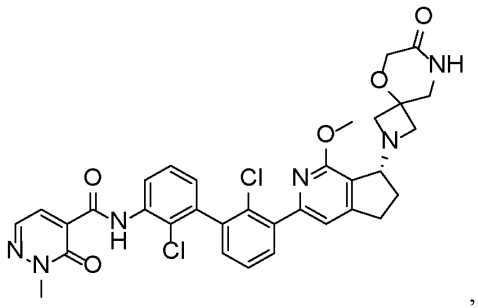
86. The compound of Claim 1, wherein the compound is selected from:


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and

, or

a pharmaceutically acceptable salt of any of the foregoing.

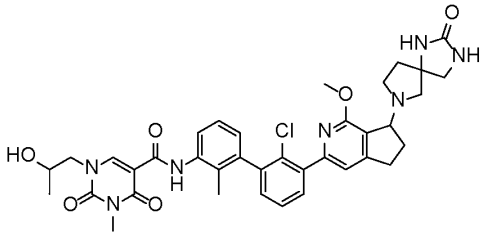
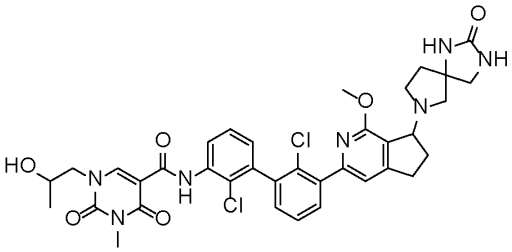
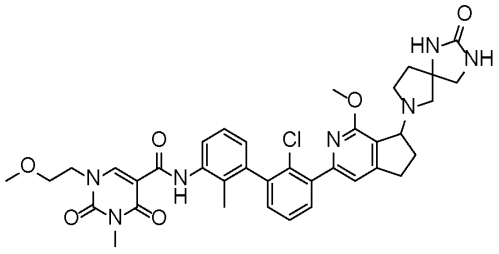
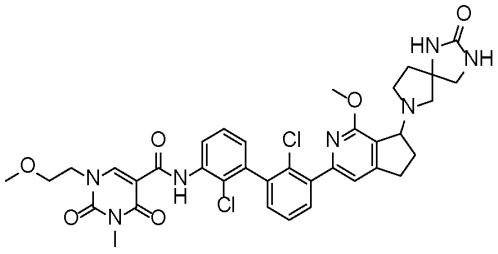
87. The compound of Claim 1, wherein the compound is selected from:

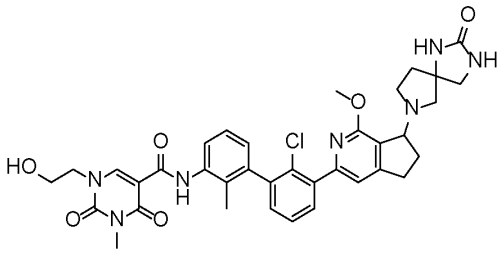
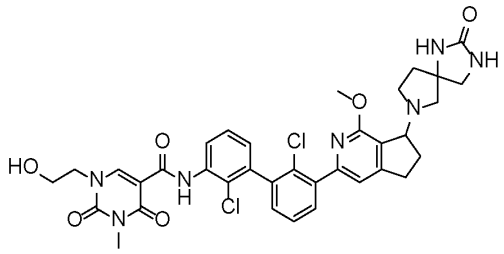
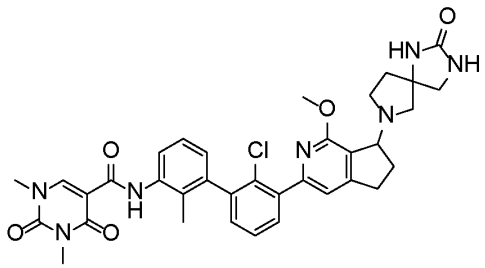
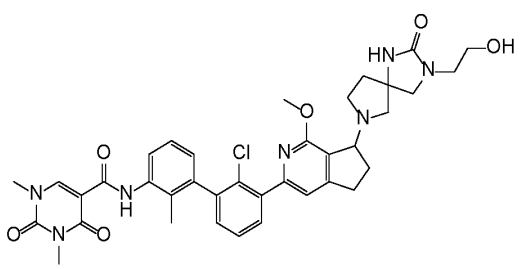
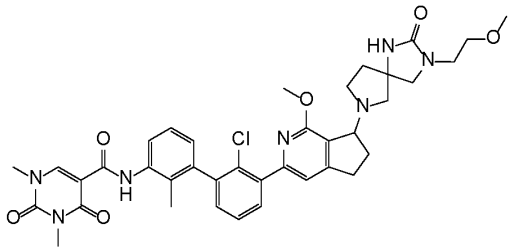
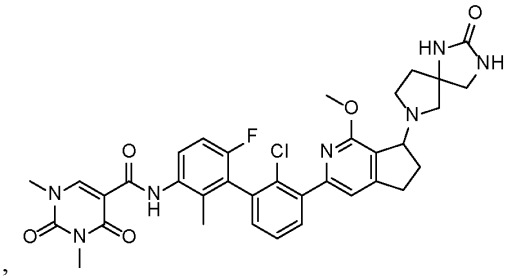
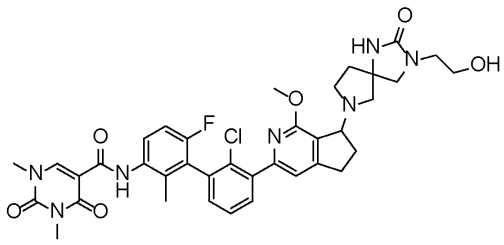
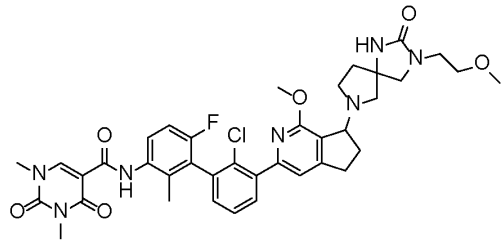
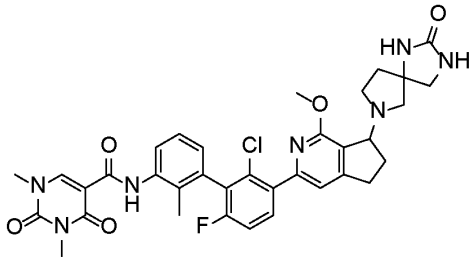
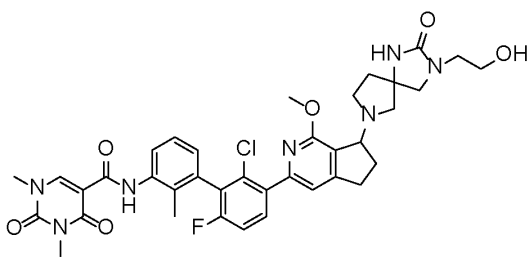

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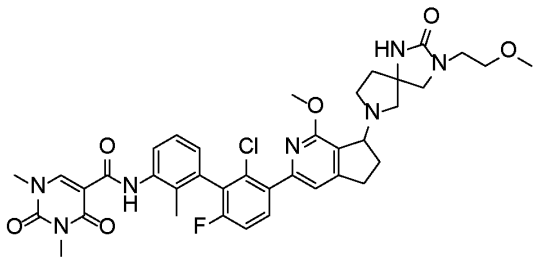
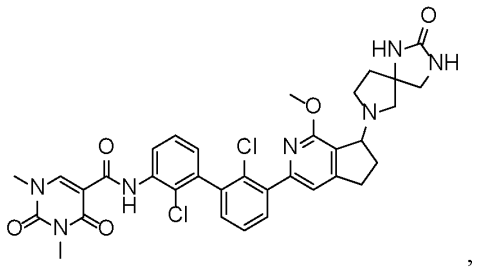
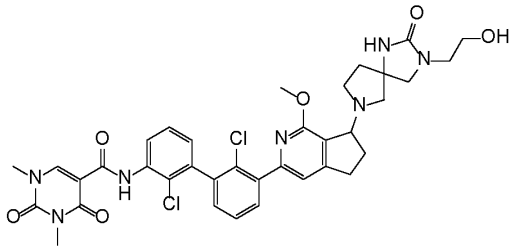
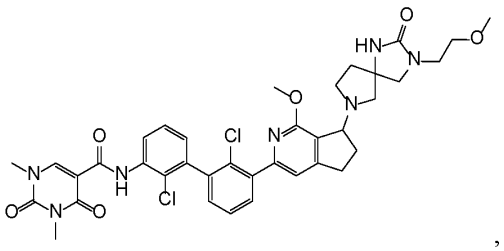
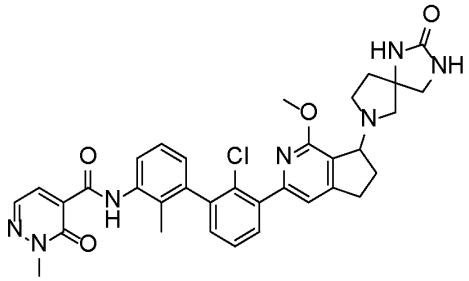
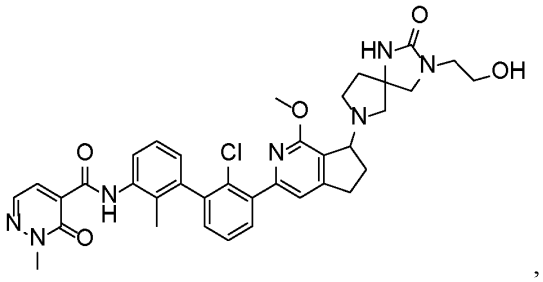
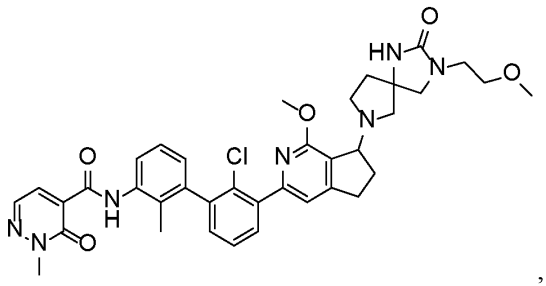
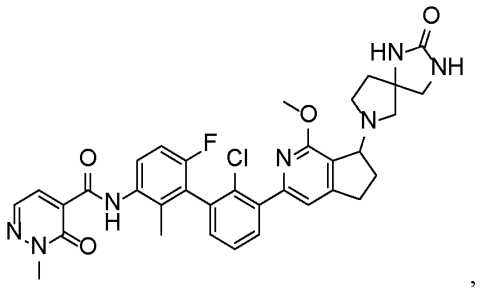
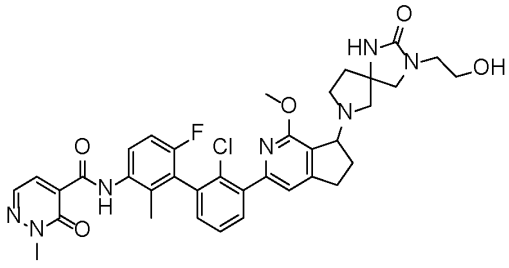
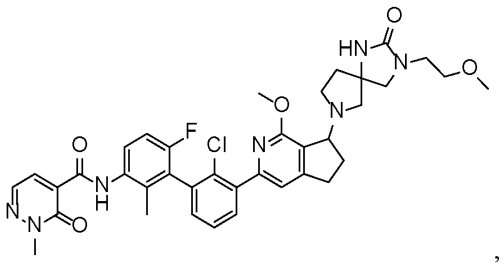

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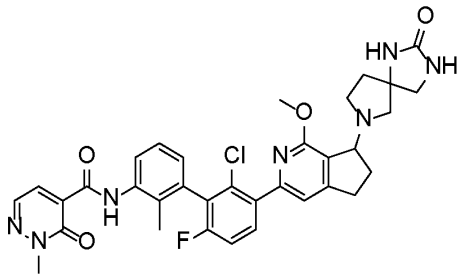
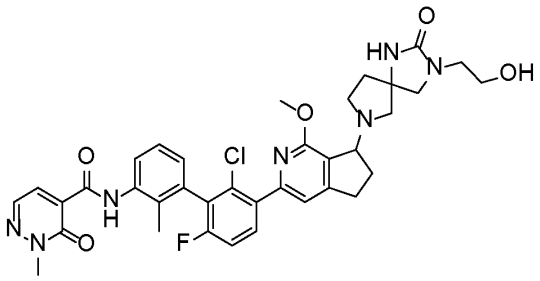
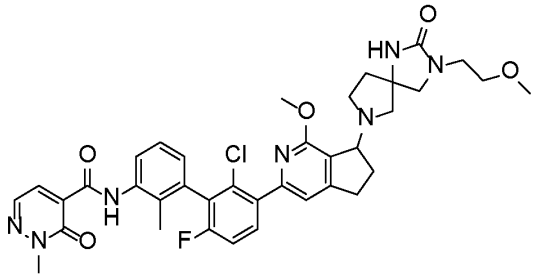
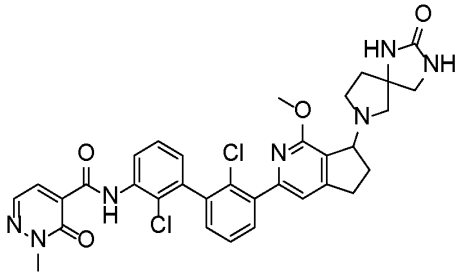
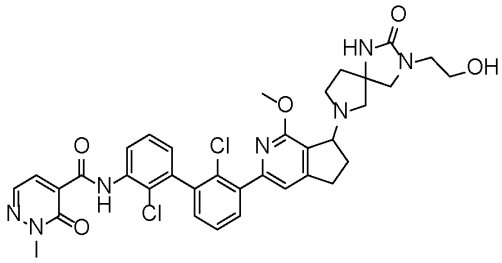
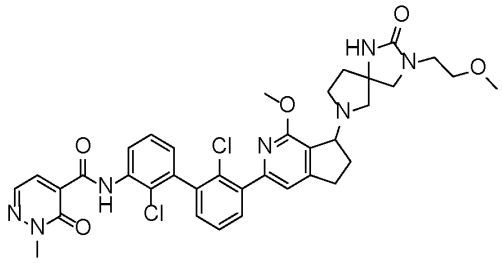
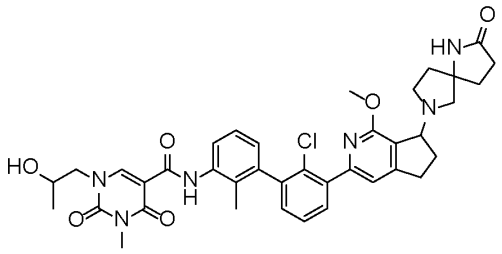
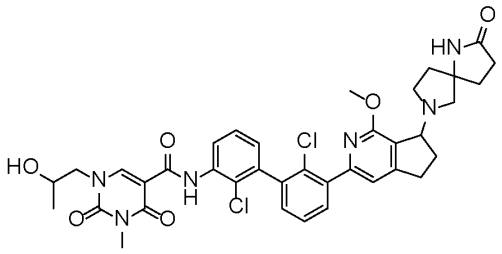
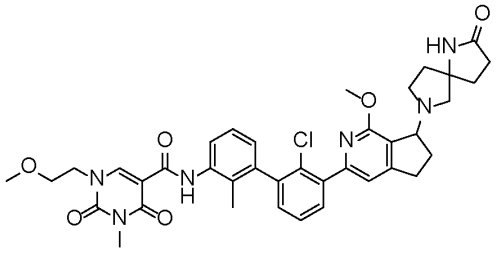
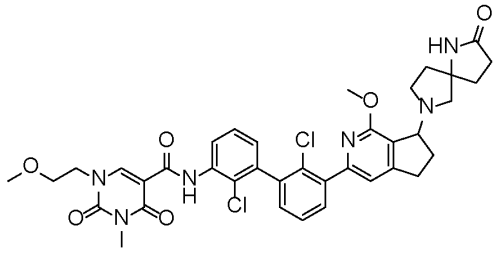
a pharmaceutically acceptable salt of any of the foregoing.

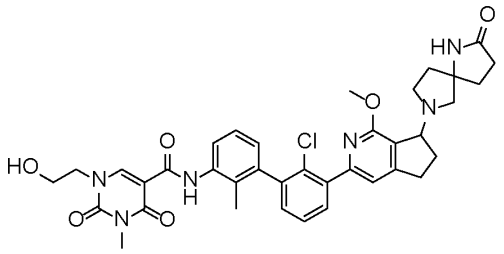
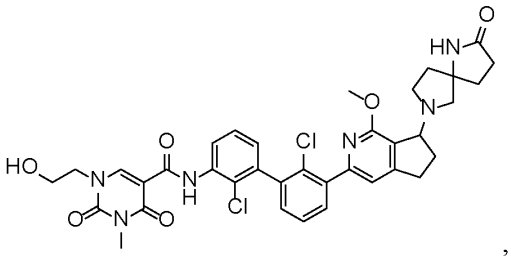
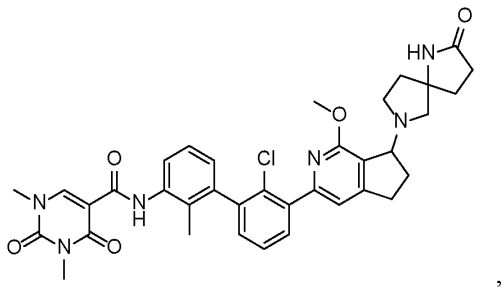
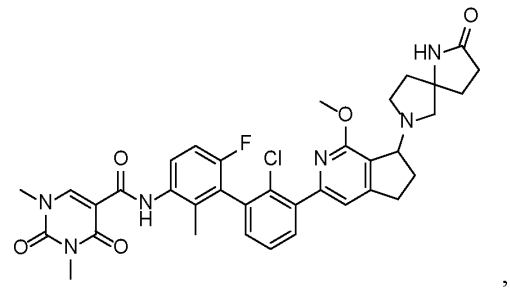
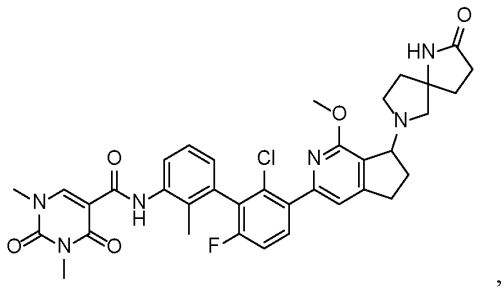
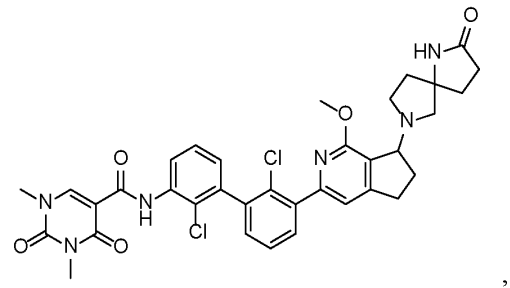
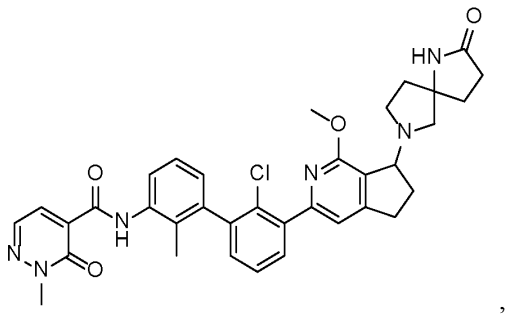
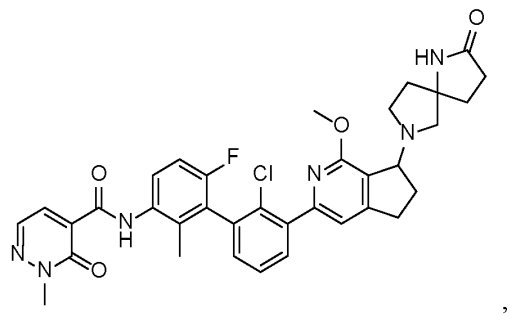
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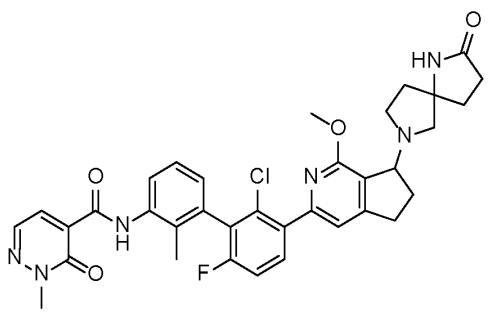
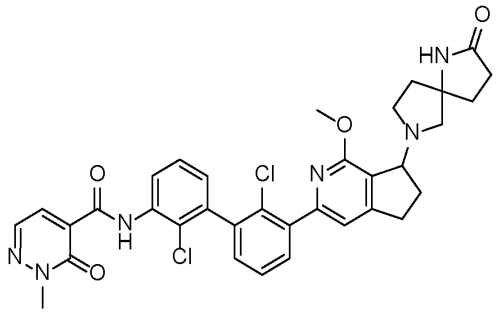
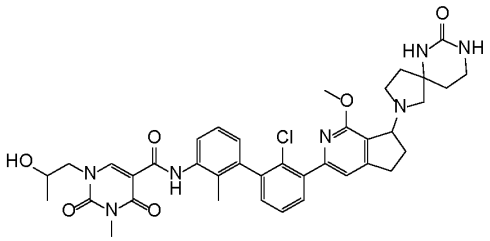
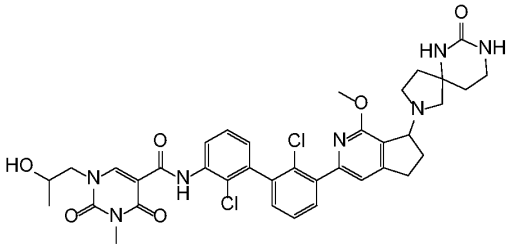
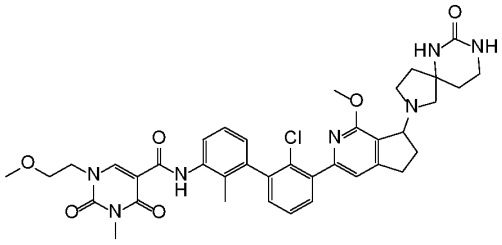
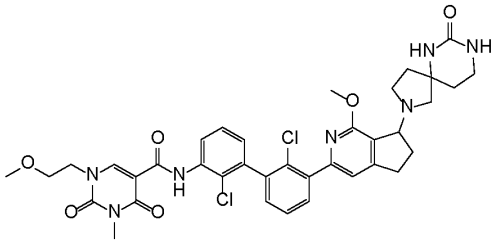
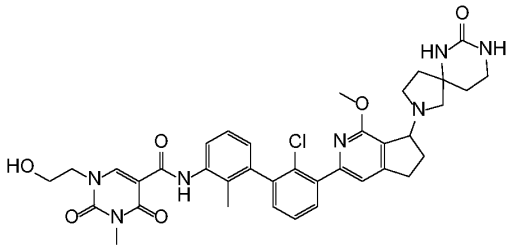
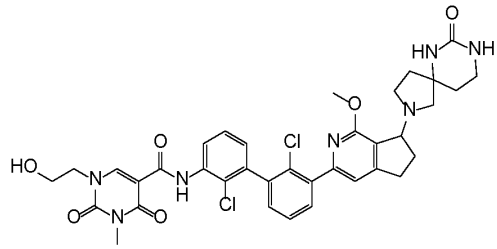
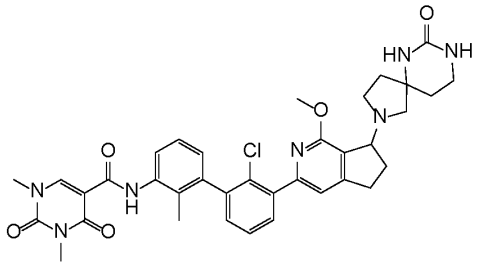
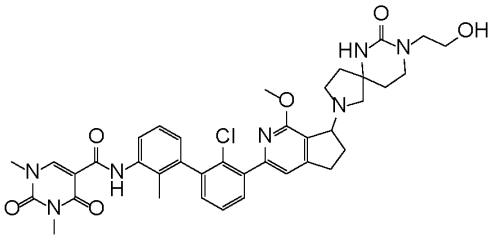

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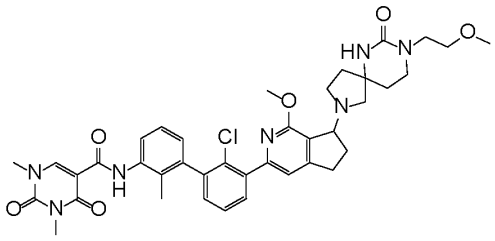
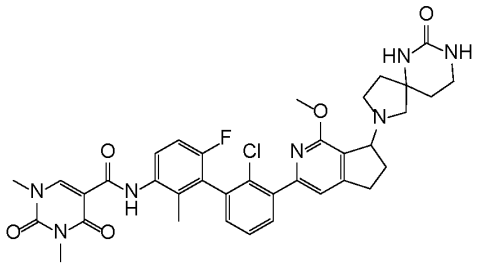
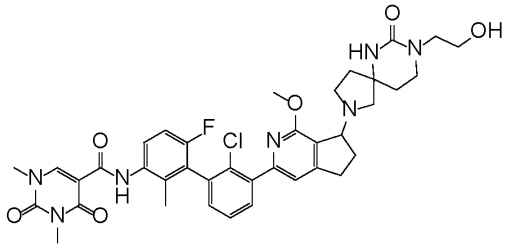
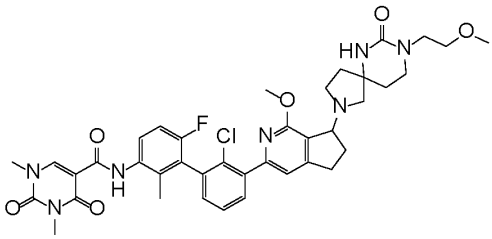
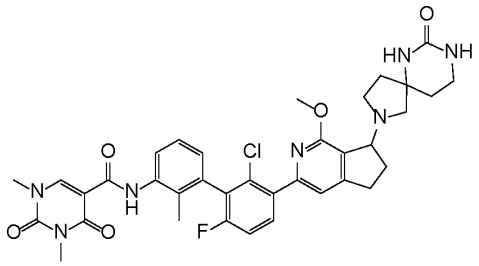
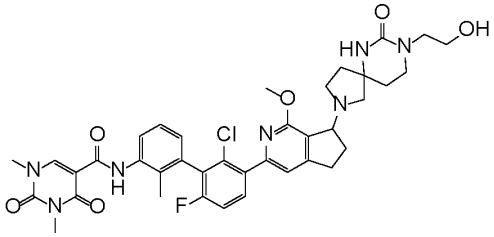
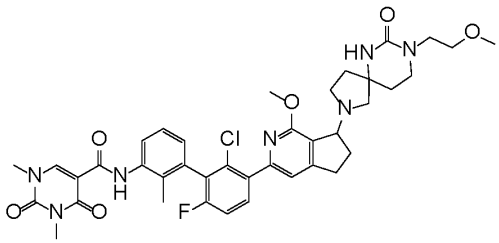
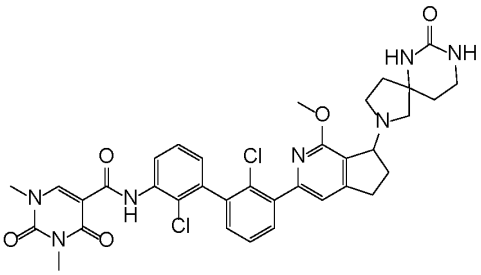
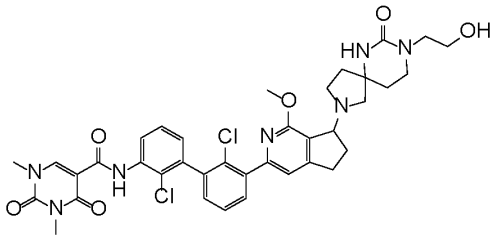
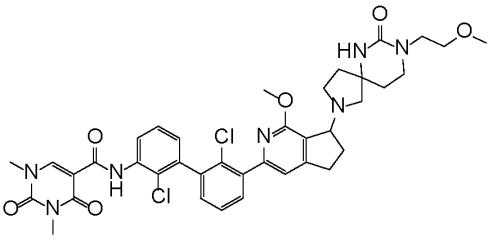

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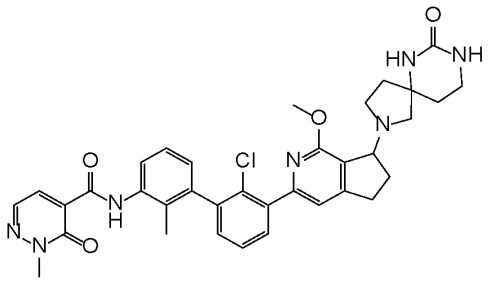
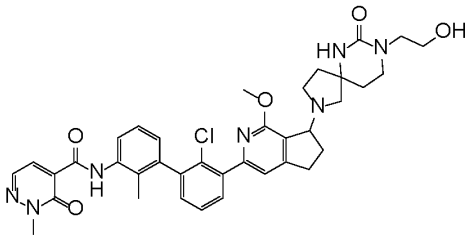
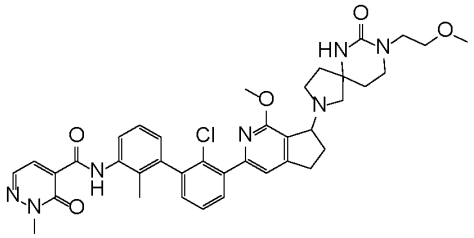
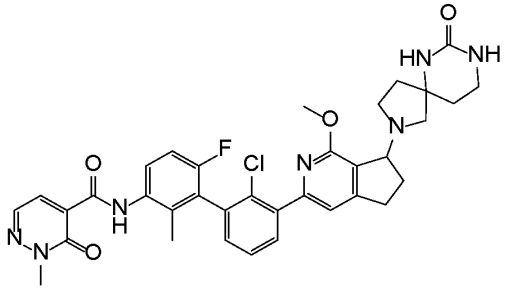
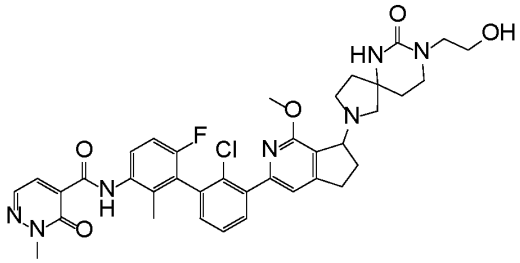
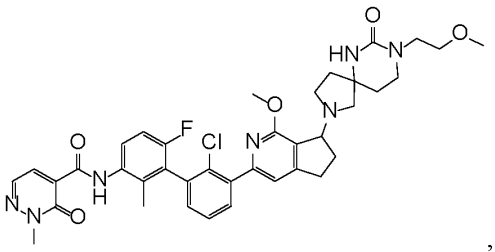
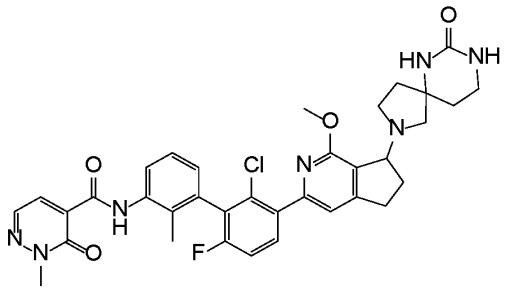
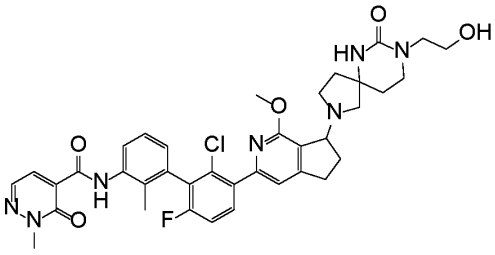

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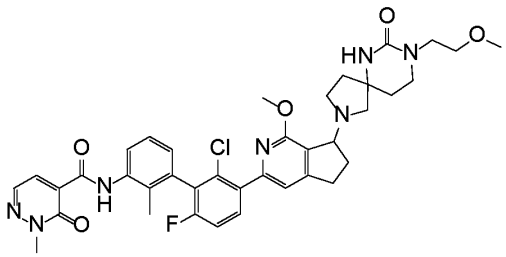
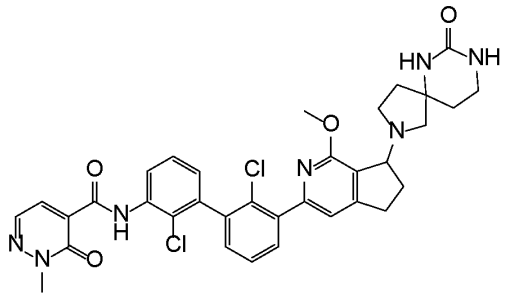
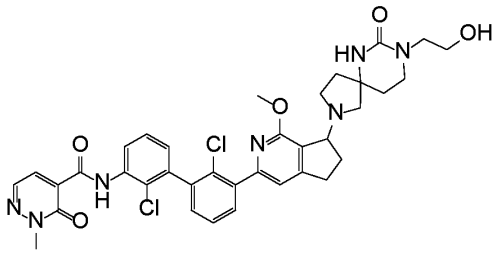
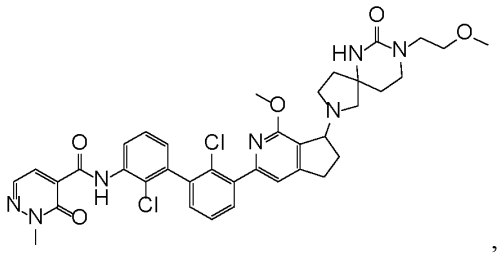

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and

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

89. A pharmaceutical composition comprising an effective amount of a compound of any one of Claims 1-88, or a pharmaceutically acceptable salt thereof, and an excipient.

90. A method for treating hepatitis B in a subject comprising administering to the subject in need thereof an effective amount of a compound of Claims 1-88, or a pharmaceutically acceptable salt thereof.

91. 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 Claims 1-88, or a pharmaceutically acceptable salt thereof.

92. The method of any one of Claims 90-91, further comprising administering surgery, radiation therapy, chemotherapy, targeted therapy, immunotherapy, hormonal therapy, or antiviral therapy.

93. A compound of any one of Claims 1-88, or a pharmaceutically acceptable salt thereof, for use in treating hepatitis B.

94. A compound of any one of Claims 1-88, or a pharmaceutically acceptable salt thereof, for use in treating hepatocellular carcinoma (HCC).

95. The compound of any one of Claims 93-94, or a pharmaceutically acceptable salt thereof, wherein the use further comprises administering surgery, radiation therapy, chemotherapy, targeted therapy, immunotherapy, hormonal therapy, or antiviral therapy.

96. Use of a compound of any one of Claims 1-88, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for use in treating hepatitis B.

97. Use of a compound of any one of Claims 1-88, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for use in treating hepatocellular carcinoma (HCC).

98. The use of any one of Claims 96-97, further comprising administering surgery, radiation therapy, chemotherapy, targeted therapy, immunotherapy, hormonal therapy, or antiviral therapy.