

METHODS AND COMPOSITIONS FOR TARGETING PD-L1

INCORPORATION BY REFERENCE TO ANY 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. 63/212,388, filed June 18, 2021, 63/263,427, filed November 2, 2021 and 63/363,777, filed April 28, 2022.

FIELD

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

BACKGROUND

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

SUMMARY

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

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

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

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

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

BRIEF DESCRIPTION OF THE DRAWINGS

[0009] Figures 1A and 1B show the absolute configuration structure and ORTEP crystal structure of the formate salt of Intermediate 5-1b.

DETAILED DESCRIPTION

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

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

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

[0013] HBV can be transmitted by blood, semen, and/or another body fluid. This can occur through direct blood-to-blood contact, unprotected sex, sharing of needles, and from an infected mother to her baby during the delivery process. The HBV surface antigen (HBsAg) is most frequently used to screen for the presence of this infection. Currently available medications do not cure HBV and/or HDV infection. Rather, the medications suppress replication of the virus.

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

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

[0016] Programmed cell death-ligand 1, or programmed death-ligand 1 (PD-L1), also known as B7 homolog 1 (B7-H1) is 272 amino acid long type I transmembrane protein found as a surface marker on many different cell types. PD-L1 is a major ligand of PD-1 and results in inhibition of T cell cytotoxicity and cytokine production. Cancer cells such as HCC

cells take advantage of this immune checkpoint by upregulating PD-L1 expression, resulting in dysfunctional anti-tumor immunity by proximal T cells. Viruses also have been observed to modulate the PD-1/PD-L1 pathway to inhibit immune host response. Hepatitis B virus has been shown to upregulate PD-L1 in infected hepatocytes, and PD-1 in associated T cells. PD-L1 protein (NCBI accession number NP_054862.1) is expressed from the cluster of differentiation 274 (CD274) transcript (NCBI accession number NM_014143.4). In some preferred embodiments, PD-L1 is the human PD-L1 protein, and CD274 is the human CD274 transcript or gene on chromosome 9. It should be understood that a person with ordinary skill in the art would view the terms PD-L1 and CD274 as often nominally interchangeable when considering the nucleic acid (DNA or RNA) or corresponding translated protein, or the sequences thereof.

Definitions

[0017] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art. All patents, applications, published applications and other publications referenced herein are incorporated by reference in their entirety unless stated otherwise. To the extent publications and patents or patent applications incorporated by reference contradict the disclosure contained in the specification, the specification is intended to supersede and/or take precedence over any such contradictory material. In the event that there are a plurality of definitions for a term herein, those in this section prevail unless stated otherwise.

[0018] Whenever a group is described as being “optionally substituted” that group may be unsubstituted or substituted with one or more of the indicated substituents. Likewise, when a group is described as being “unsubstituted or substituted” if substituted, the substituent(s) may be selected from one or more of the indicated substituents. If no substituents are indicated, it is meant that the indicated “optionally substituted” or “substituted” group may be substituted with one or more group(s) (such as 1, 2 or 3 groups) individually and independently selected from deuterium, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl), (heterocyclyl)alkyl, hydroxy, alkoxy, acyl, cyano, halogen, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, S-sulfonamido, N-sulfonamido,

C-carboxy, O-carboxy, isocyanato, thiocyanato, isothiocyanato, nitro, azido, silyl, sulfinyl, sulfinyl, sulfonyl, haloalkyl, haloalkoxy, trihalomethanesulfonyl, trihalomethanesulfonamido, an amino, a mono-substituted amine and a di-substituted amine.

[0019] As used herein, “C_a to C_b” 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 “C₁ to C₄ alkyl” group refers to all alkyl groups having from 1 to 4 carbons, that is, CH₃-, CH₃CH₂-, CH₃CH₂CH₂-, (CH₃)₂CH-, CH₃CH₂CH₂CH₂-, CH₃CH₂CH(CH₃)- and (CH₃)₃C-. If no “a” and “b” are designated 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 “C₁-C₄ alkyl” or similar designations. By way of example only, “C₁-C₄ 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 C₂₋₄ alkenyl, C₂₋₆ alkenyl or C₂₋₈ 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 C₂₋₄ alkynyl, C₂₋₆ alkynyl or C₂₋₈ 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 polycyclic aromatic ring system (including fused ring systems where two carbocyclic rings share a chemical bond) that has a fully delocalized pi-electron system throughout all the rings. The number of carbon atoms in an aryl group can vary. For example, the aryl group can be a C₆-C₁₄ aryl group, a C₆-C₁₀ aryl group, or a C₆ aryl group. Examples of aryl groups include, but are not limited to, benzene, naphthalene and azulene. An aryl group may be substituted or unsubstituted.

[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 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 -CH₂- 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 (-CH₂-), ethylene (-CH₂CH₂-), propylene (-CH₂CH₂CH₂-) and butylene (-CH₂CH₂CH₂CH₂-). 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, isobutoxy, sec-butoxy, tert-butoxy, phenoxy and benzoxy. In some instances, an alkoxy can be

--OR wherein R is an unsubstituted C₁₋₄ 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 C₁₋₄ 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 "SO₂R" 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 “X₃CSO₂-” group wherein each X is a halogen.

[0044] A “trihalomethanesulfonamido” group refers to an “X₃CS(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 -NH₂ 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 -N₃ 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 “-SO₂N(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 “-RSO₂N(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 “ $-\text{OC}(=\text{O})\text{N}(\text{R}_\text{A}\text{R}_\text{B})$ ” 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 “ $\text{ROC}(=\text{O})\text{N}(\text{R}_\text{A})-$ ” 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 “ $-\text{OC}(=\text{S})\text{N}(\text{R}_\text{A}\text{R}_\text{B})$ ” 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 “ $\text{ROC}(=\text{S})\text{N}(\text{R}_\text{A})-$ ” 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 “ $-\text{C}(=\text{O})\text{N}(\text{R}_\text{A}\text{R}_\text{B})$ ” 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 “ $\text{RC}(=\text{O})\text{N}(\text{R}_\text{A})-$ ” 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 “ $-\text{NHR}_\text{A}$ ” 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 $-\text{NHR}_\text{A}$, 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 “ $-\text{NR}_\text{A}\text{R}_\text{B}$ ” 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 is not specified (e.g. haloalkyl), there may be one or more substituents present. For example “haloalkyl” may include one or more of the same or different halogens. As another example, “ C_1 - C_3 alkoxyphenyl” may include one or more of the same or different alkoxy groups containing one, two or three atoms.

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

[0067] The term “pharmaceutically acceptable salt” refers to a salt of a compound that does not cause significant irritation to an organism to which it is administered and does not abrogate the biological activity and properties of the compound. In some embodiments, the salt is an acid addition salt of the compound. Pharmaceutical salts can be obtained by reacting a compound with inorganic acids such as hydrohalic acid (e.g., hydrochloric acid or hydrobromic acid), sulfuric acid, nitric acid and phosphoric acid. Pharmaceutical salts can also be obtained by reacting a compound with an organic acid such as aliphatic or aromatic carboxylic or sulfonic acids, for example formic, acetic, succinic, lactic, malic, tartaric, citric, ascorbic, nicotinic, methanesulfonic, ethanesulfonic, p-toluenesulfonic, salicylic or naphthalenesulfonic acid. Pharmaceutical salts can also be obtained by reacting a compound with a base to form a salt such as an ammonium salt (for example, ammonium or triethylammonium salt), an alkali metal salt, such as a lithium, a sodium or a potassium salt, an alkaline earth metal salt, such as a calcium or a magnesium salt, a salt of organic bases such as dicyclohexylamine, N-methyl-D-glucamine, tris(hydroxymethyl)methylamine, C_1 - C_7 alkylamine, cyclohexylamine, triethanolamine, ethylenediamine, and salts with amino acids such as arginine and lysine.

[0068] Terms and phrases used in this application, and variations thereof, especially in the appended claims, unless otherwise expressly stated, should be construed as open ended as opposed to limiting. As examples of the foregoing, the term 'including' should be read to mean 'including, without limitation,' 'including but not limited to,' or the like; the term 'comprising' as used herein is synonymous with 'including,' 'containing,' or 'characterized by,' and is inclusive or open-ended and does not exclude additional, unrecited elements or method steps; the term 'having' should be interpreted as 'having at least;' the term 'includes' should be interpreted as 'includes but is not limited to;' the term 'example' is used to provide exemplary instances of the item in discussion, not an exhaustive or limiting list thereof. In addition, the term "comprising" is to be interpreted synonymously with the phrases "having at least" or "including at least". When used in the context of a compound or composition, the term "comprising" means that the compound or composition includes at least the recited features or components, but may also include additional features or components.

[0069] With respect to the use of substantially any plural and/or singular terms herein, those having skill in the art can translate from the plural to the singular and/or from the singular to the plural as is appropriate to the context and/or application. The various singular/plural permutations may be expressly set forth herein for sake of clarity. The indefinite article "a" or "an" does not exclude a plurality.

[0070] It is understood that, in any compound described herein having one or more chiral centers, if an absolute stereochemistry is not expressly indicated, then each center may independently be of (R)-configuration or (S)-configuration or a mixture thereof. Thus, the compounds provided herein may be enantiomerically pure, enantiomerically enriched, racemic mixture, diastereomerically pure, diastereomerically enriched, or a stereoisomeric mixture. In addition it is understood that, in any compound described herein having one or more double bond(s) generating geometrical isomers that can be defined as E or Z, each double bond may independently be E or Z a mixture thereof. Likewise, it is understood that, in any compound described, all tautomeric forms are also intended to be included.

[0071] It is to be understood that where compounds disclosed herein have unfilled valencies, then the valencies are to be filled with hydrogens or isotopes thereof, e.g., hydrogen-1 (protium) and hydrogen-2 (deuterium).

[0072] It is understood that the compounds described herein can be labeled isotopically. Substitution with isotopes such as deuterium may afford certain therapeutic advantages resulting from greater metabolic stability, such as, for example, increased *in vivo* half-life or reduced dosage requirements. Each chemical element as represented in a compound structure may include any isotope of said element. For example, in a compound structure a hydrogen atom may be explicitly disclosed or understood to be present in the compound. At any position of the compound that a hydrogen atom may be present, the hydrogen atom can be any isotope of hydrogen, including but not limited to hydrogen-1 (protium) and hydrogen-2 (deuterium). Thus, reference herein to a compound encompasses all potential isotopic forms unless the context clearly dictates otherwise.

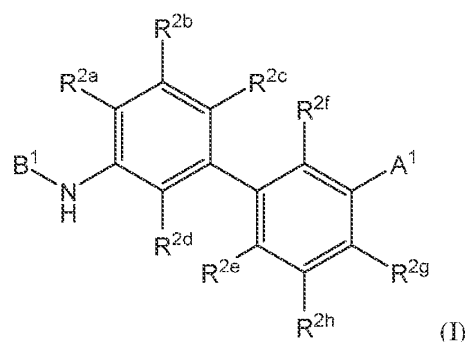
[0073] Where a range of values is provided, it is understood that the upper and lower limit, and each intervening value between the upper and lower limit of the range is encompassed within the embodiments.

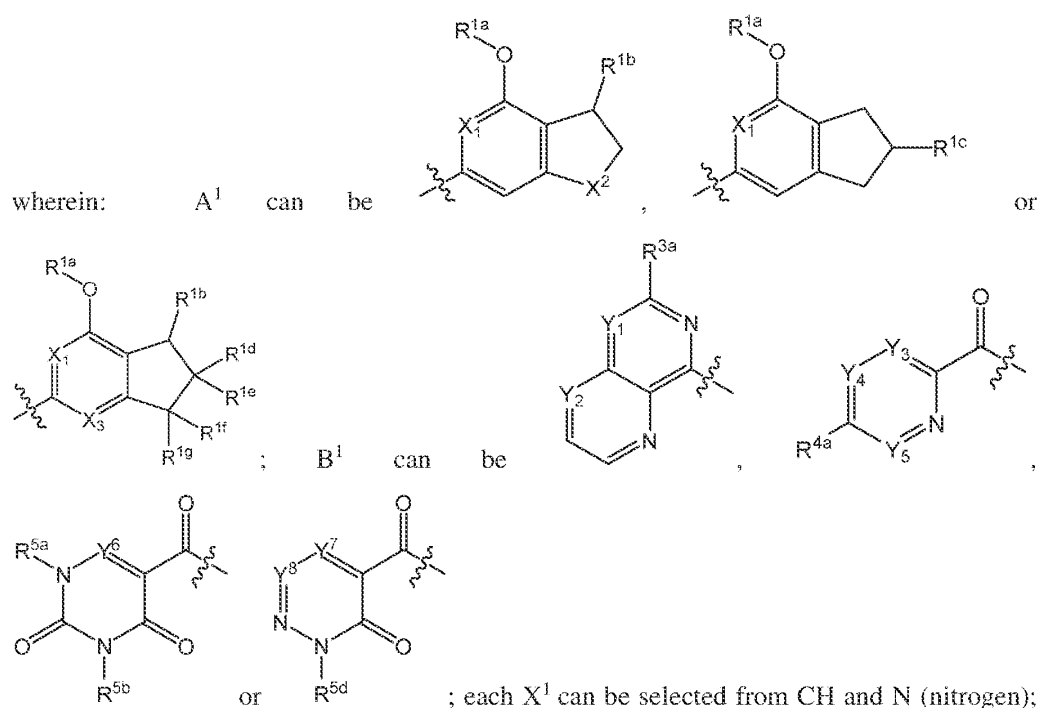
Compounds

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

Embodiment 1

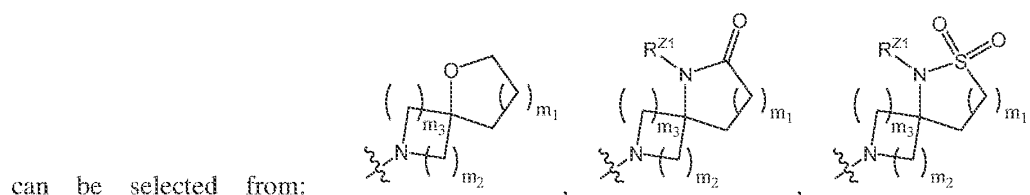
[0075] A compound of Formula (I), or a pharmaceutically acceptable salt thereof, having the structure:

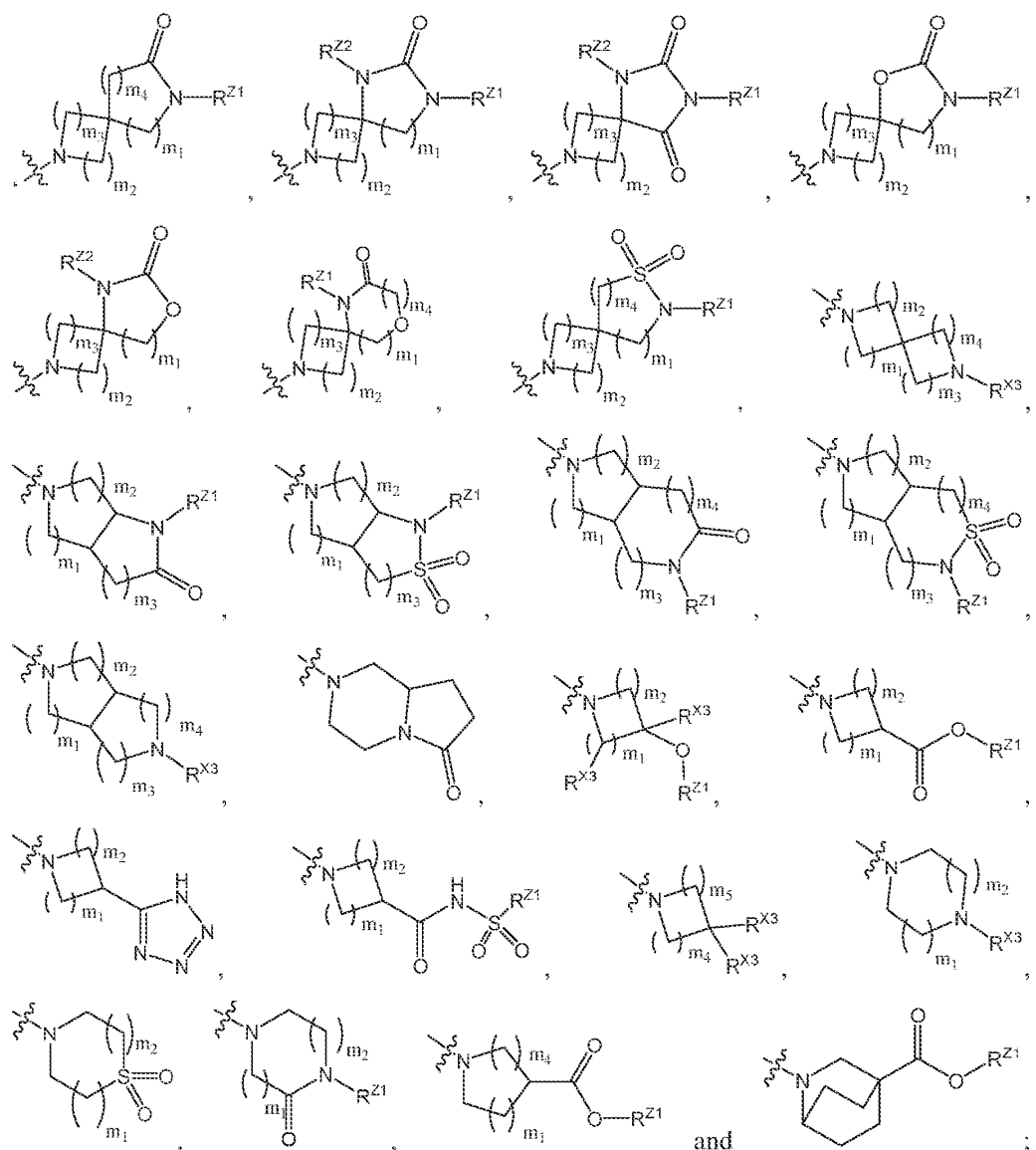


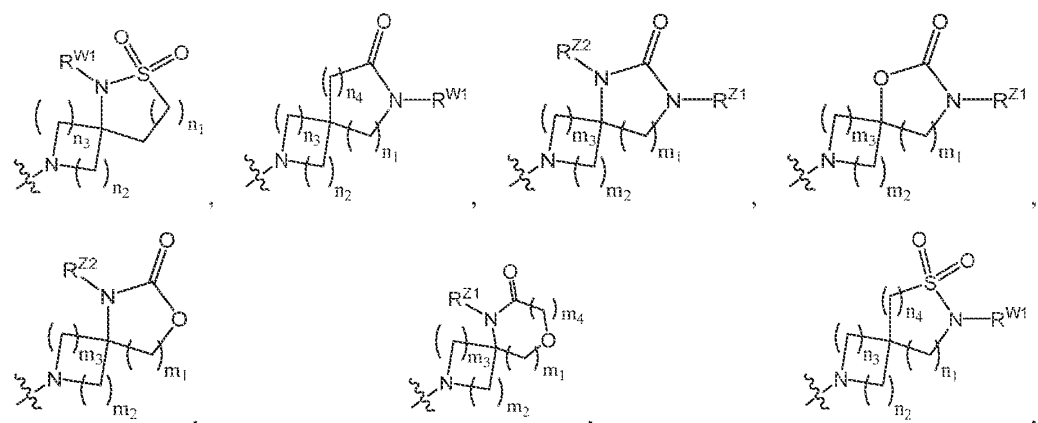
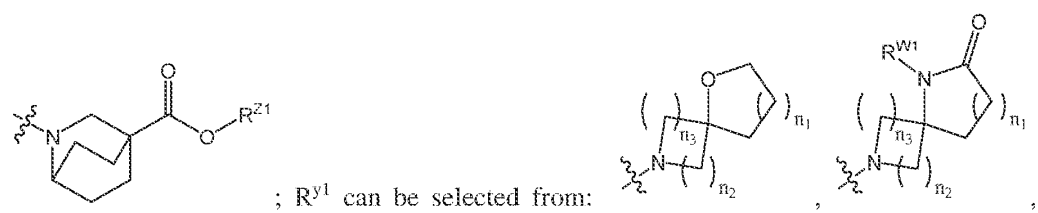
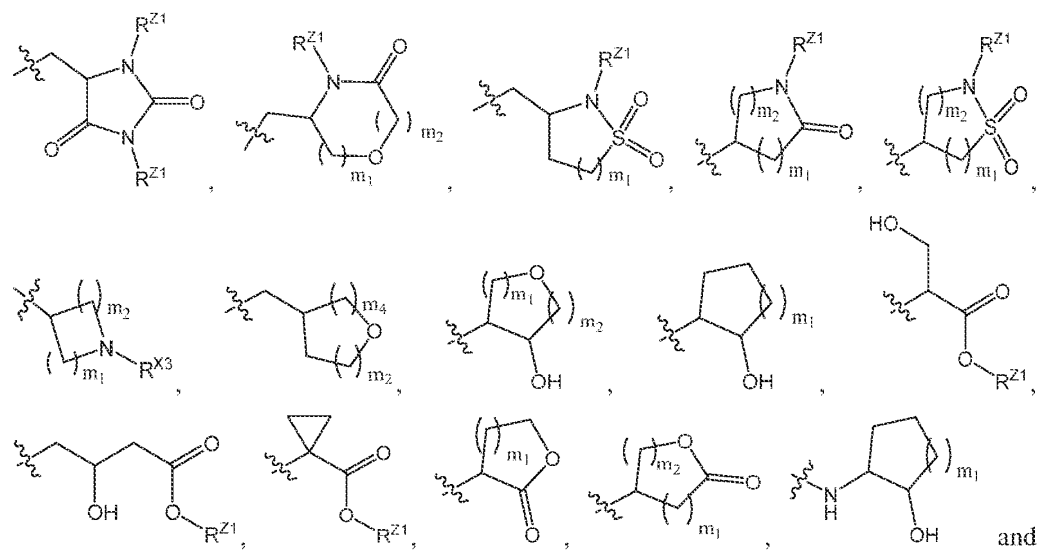
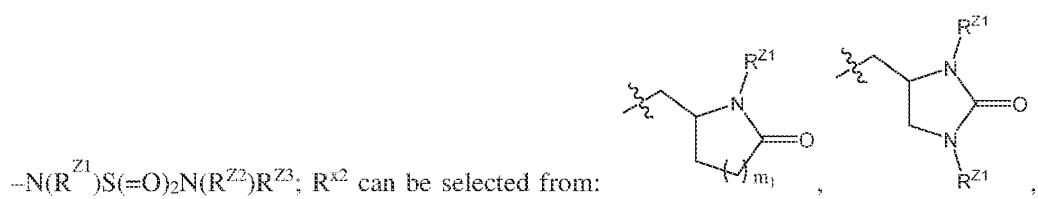


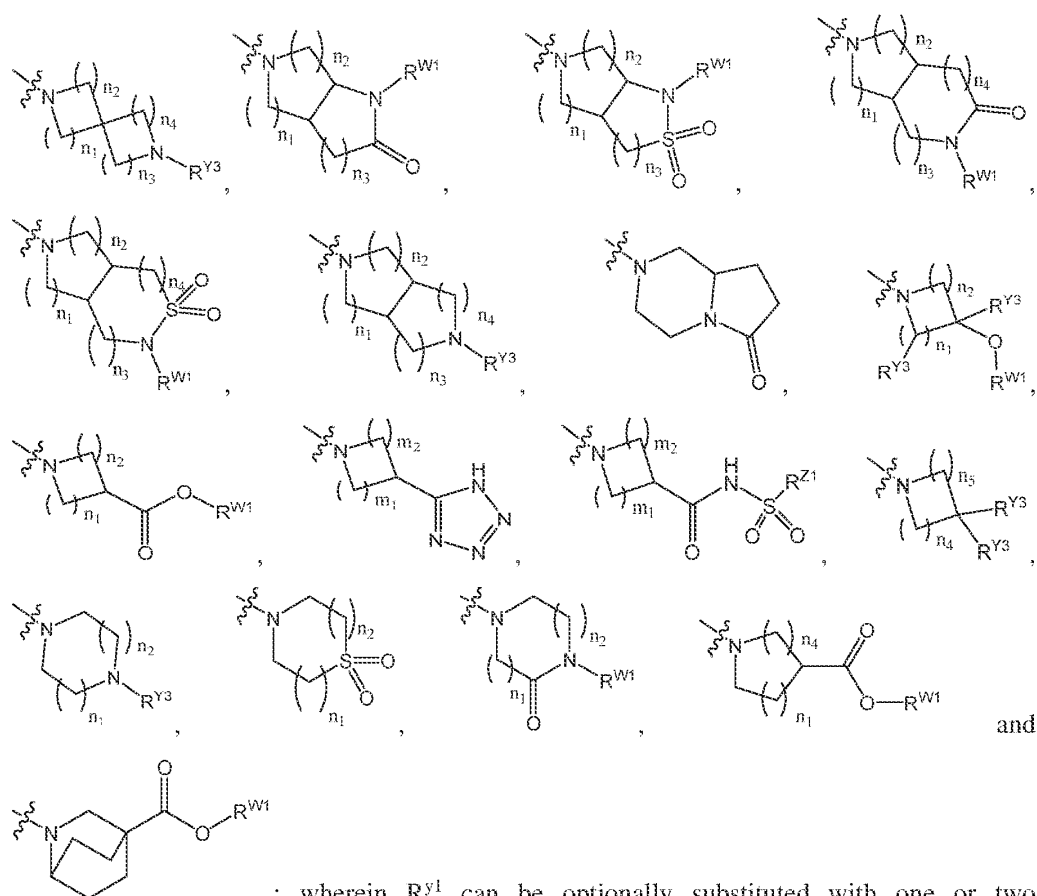
X^2 can be O (oxygen); X^3 can be selected from CH, C-halo and N; Y^1 can be selected from N (nitrogen) and CH; Y^2 can be selected from N (nitrogen) and CH; Y^3 can be selected from N (nitrogen) and CH; Y^4 can be selected from N (nitrogen) and CH; Y^5 can be selected from N (nitrogen), CH and C-OCH₃; Y^6 can be selected from N and CR^{5c}; Y^7 can be CR^{5e}; Y^8 can be CR^{5f}; each R^{1a} can be selected from -C₁₋₄ alkyl, -C₁₋₄ haloalkyl, -CH₂(C₃₋₆ monocyclic cycloalkyl), -C₂₋₄ alkyl(C₁₋₄ alkoxy), -C₂₋₄ alkyl (C₁₋₄ haloalkoxy), -CH₂(4-6 membered monocyclic heterocyclyl) and -CH₂(5-6 membered monocyclic heteroaryl); each R^{1b} can be selected from -N(R^{m1})Rⁿ¹ and -R^{x1}; R^{1c} can be selected from -N(R^{m1})Rⁿ¹ and -R^{x1}; R^{1d} can be selected from hydrogen, -CH₃, -CH₂CH₃, -OH, -OCH₃ and -F; R^{1e} can be selected from hydrogen, -CH₃, -CH₂CH₃ and -F; R^{1f} can be selected from hydrogen, -CH₃, -CH₂CH₃, -OH, -OCH₃ and -F; R^{1g} can be selected from hydrogen, -CH₃, -CH₂CH₃ and -F; 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 independently selected from hydrogen, halogen, cyano, -CH₃, -CH₂CH₃, -CH₂OH, -OCH₃ and -SCH₃; R^{3a} can be selected from H (hydrogen), -CH₃, -CF₃ and -CHF₂; R^{4a} can be selected from H (hydrogen), halogen, -C₁₋₄ alkyl, -C₁₋₄ haloalkyl, -CH₂R^{4b} and -C(CH₃)R^{4b}; R^{4b} can be selected from -N(R^{m2})Rⁿ² and -R^{y1}; R^{5a} can be selected from

hydrogen, $-\text{CH}_3$, $-\text{C}_{2-4}$ alkyl and $-\text{C}_{2-4}$ haloalkyl; R^{5b} can be selected from hydrogen, $-\text{CH}_3$, $-\text{C}_{2-4}$ alkyl and $-\text{C}_{2-4}$ haloalkyl; R^{5c} can be selected from hydrogen, $-\text{CH}_3$, $-\text{C}_{2-4}$ alkyl and $-\text{C}_{2-4}$ haloalkyl; R^{5d} can be selected from hydrogen, $-\text{CH}_3$, $-\text{C}_{2-4}$ alkyl and $-\text{C}_{2-4}$ haloalkyl; R^{5e} can be selected from hydrogen, halogen and $-\text{CH}_3$; R^{5f} can be selected from hydrogen, halogen, $-\text{OH}$, $-\text{CN}$ and $-\text{CH}_3$; R^{m1} can be selected from hydrogen, $-\text{C}_{1-4}$ alkyl, C_{3-6} monocyclic cycloalkyl, C_{5-12} bicyclic cycloalkyl, 5- or 6-membered monocyclic heteroaryl, 4-7 membered monocyclic heterocyclyl, 8-11 membered fused-heteroaryl, 8-11 membered fused-heterocyclyl and $-\text{R}^{x2}$; wherein the monocyclic heteroaryl, the bicyclic heteroaryl the monocyclic heterocyclyl and the bicyclic heterocyclyl can contain at least one atom or group of atoms independently selected from the group consisting of O (oxygen), S (sulfur), $\text{C}(=\text{O})$, $\text{S}(=\text{O})$, $\text{S}(=\text{O})_2$ and N (nitrogen); wherein the $-\text{C}_{1-4}$ alkyl can be optionally substituted with one or two or three substituents independently selected from halogen, cyano, hydroxy, $-\text{C}_{1-4}$ alkoxy, $-\text{C}_{1-4}$ haloalkyl, $-\text{C}_{1-4}$ haloalkoxy, $-\text{C}(=\text{O})\text{OR}^{Z1}$, $-\text{C}(=\text{O})\text{NHS}(=\text{O})_2\text{R}^{Z3}$, $-\text{C}(=\text{O})\text{N}(\text{R}^{Z1})\text{R}^{Z2}$, $-\text{S}(=\text{O})_2\text{R}^{Z3}$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^{Z1})\text{R}^{Z2}$, $-\text{N}(\text{R}^{Z1})\text{C}(=\text{O})\text{R}^{Z3}$, $-\text{N}(\text{R}^{Z1})\text{S}(=\text{O})\text{R}^{Z3}$, $-\text{N}(\text{R}^{Z1})\text{C}(=\text{O})\text{N}(\text{R}^{Z2})\text{R}^{Z3}$ and $-\text{N}(\text{R}^{Z1})\text{S}(=\text{O})\text{N}(\text{R}^{Z2})\text{R}^{Z3}$; wherein the C_{3-6} monocyclic cycloalkyl, the C_{5-12} bicyclic cycloalkyl, the 5- or 6-membered monocyclic heteroaryl, the 4-7 membered monocyclic heterocyclyl, the 8-11 membered fused-heteroaryl and the 8-11 membered fused-heterocyclyl can be optionally substituted with one, two, three or four substituents independently selected from halogen, cyano, $-\text{C}_{1-4}$ alkyl, hydroxy, $-\text{C}_{1-4}$ alkoxy, $-\text{C}_{1-4}$ haloalkyl, $-\text{C}_{1-4}$ haloalkoxy, $-\text{C}(=\text{O})\text{R}^{Z1}$, $-\text{C}(=\text{O})\text{OR}^{Z1}$, $-\text{C}(=\text{O})\text{NHS}(=\text{O})_2\text{R}^{Z3}$, $-\text{C}(=\text{O})\text{N}(\text{R}^{Z1})\text{R}^{Z2}$, $-\text{S}(=\text{O})_2\text{R}^{Z3}$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^{Z1})\text{R}^{Z2}$, $-\text{N}(\text{R}^{Z1})\text{C}(=\text{O})\text{R}^{Z3}$, $-\text{N}(\text{R}^{Z1})\text{S}(=\text{O})\text{R}^{Z3}$, $-\text{N}(\text{R}^{Z1})\text{C}(=\text{O})\text{N}(\text{R}^{Z2})\text{R}^{Z3}$ and $-\text{N}(\text{R}^{Z1})\text{S}(=\text{O})\text{N}(\text{R}^{Z2})\text{R}^{Z3}$; and R^{n1} can be hydrogen, $-\text{C}_{1-4}$ alkyl, $-\text{C}_{1-4}$ haloalkyl, C_{3-6} monocyclic cycloalkyl(CH_2)– or $-\text{C}(=\text{O})\text{OR}^{Z4}$; R^{m2} can be selected from $-\text{CH}_3$, $-\text{C}_{2-4}$ alkyl, $-\text{C}_{1-4}$ haloalkyl and $-\text{R}^{y2}$, wherein the $-\text{C}_{2-4}$ alkyl is optionally substituted with hydroxy; R^{n2} can be selected from H (hydrogen), $-\text{C}_{1-4}$ alkyl and $-\text{C}_{1-4}$ haloalkyl; R^{x1}





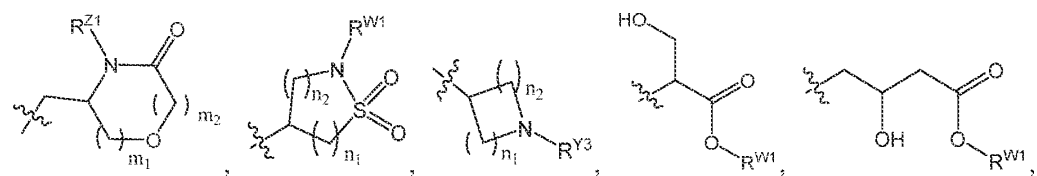


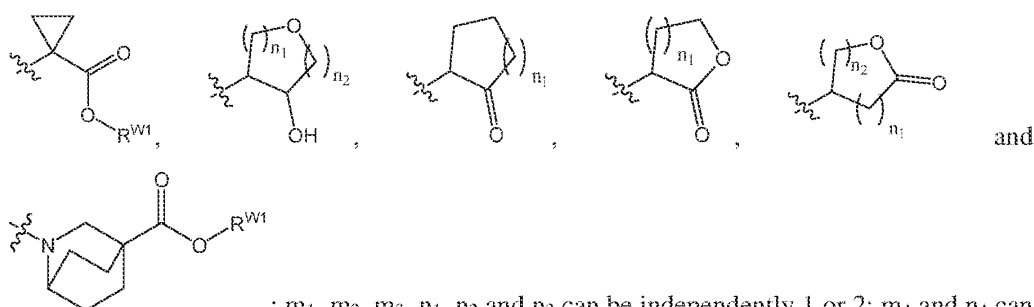


and

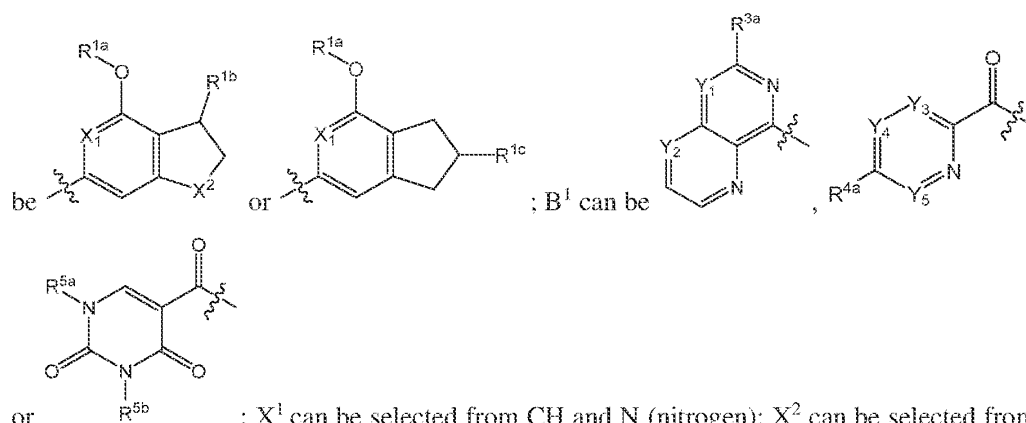
; wherein R^{Y1} can be optionally substituted with one or two substituents independently selected from halogen, cyano, $-C_{1-4}$ alkyl, hydroxy, $-C_{1-4}$ alkoxy, $-C_{1-4}$ haloalkyl, $-C_{1-4}$ haloalkoxy, $-C(=O)OR^{W1}$, $-C(=O)NHS(=O)_2R^{W3}$, $-C(=O)N(R^{W1})R^{W2}$, $-S(=O)_2R^{W3}$, $-S(=O)N(R^{W1})R^{W2}$, $-N(R^{W1})C(=O)R^{W3}$, $-N(R^{W1})S(=O)R^{W3}$, $-N(R^{W1})C(=O)N(R^{W2})R^{W3}$ and

$-N(R^{W1})S(=O)N(R^{W2})R^{W3}$; R^{Y2} can be selected from:



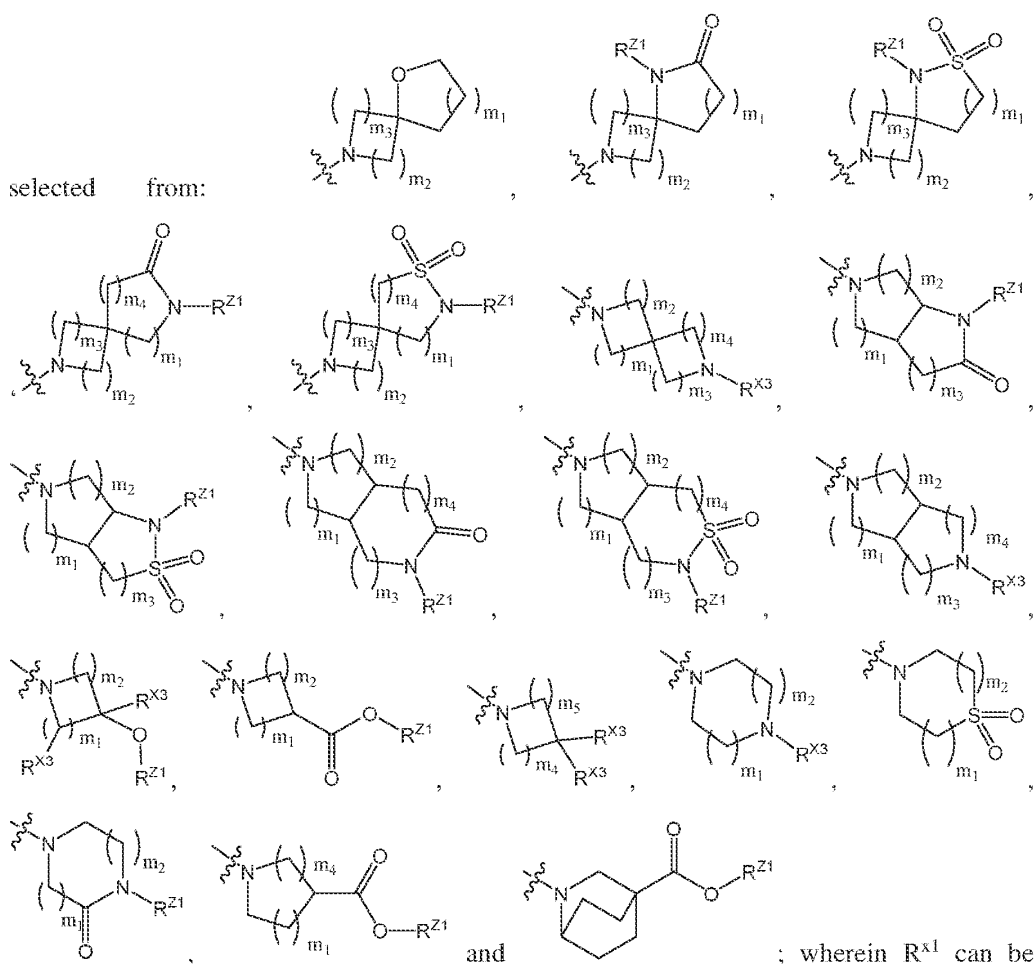


; m_1, m_2, m_3, n_1, n_2 and n_3 can be independently 1 or 2; m_4 and n_4 can be independently 0, 1 or 2; m_5 and n_5 can be independently 1, 2, 3 or 4; each R^{X3} can be independently selected from hydrogen, halogen, $-C_{1-4}$ alkyl, $-C_{1-4}$ haloalkyl, $-C(=O)R^{Z3}$, $-C(=O)OR^{Z1}$, $-S(=O)_2R^{Z1}$, $-C(=O)N(R^{Z1})R^{Z2}$ and $-S(=O)N(R^{Z1})R^{Z2}$; each R^{Y3} can be independently selected from hydrogen, halogen, $-C_{1-4}$ alkyl, $-C_{1-4}$ haloalkyl, $-C(=O)R^{W3}$, $-C(=O)OR^{W3}$, $-S(=O)_2R^{W3}$, $-C(=O)N(R^{W1})R^{W2}$ and $-S(=O)N(R^{W1})R^{W2}$; R^{Z1} and R^{Z2} can be independently selected from hydrogen, $-C_{1-4}$ alkyl, and $-C_{1-4}$ haloalkyl; or R^{Z1} and R^{Z2} can be taken together to form a monocyclic heterocyclyl when attached to the same nitrogen; R^{W1} and R^{W2} can be independently selected from hydrogen, $-C_{1-4}$ alkyl and $-C_{1-4}$ haloalkyl; R^{Z3} and R^{W3} can be independently selected from hydrogen, $-C_{1-4}$ alkyl and $-C_{1-4}$ haloalkyl; and R^{Z4} can be selected from hydrogen, $-C_{1-4}$ alkyl and 5- to 6-membered monocyclic heterocyclyl(CH₂)— optionally substituted with $-C_{1-4}$ alkyl. In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be where A^1 can

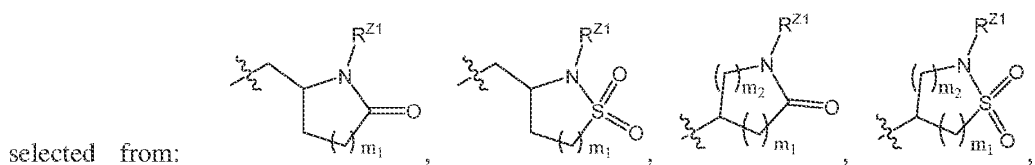


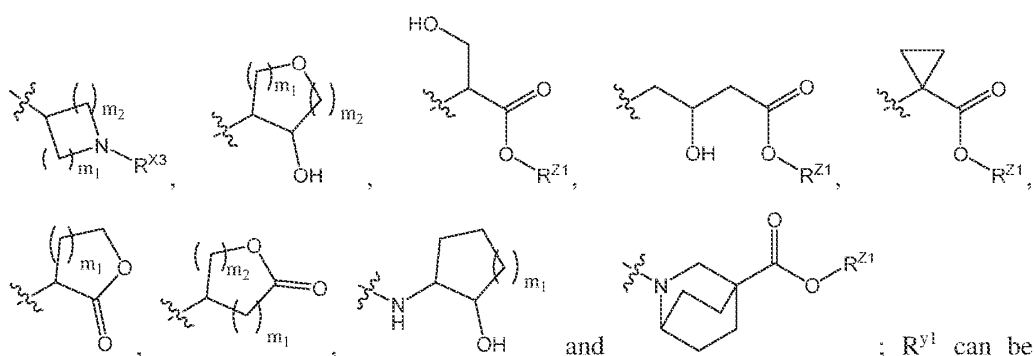
or ; X^1 can be selected from CH and N (nitrogen); X^2 can be selected from O (oxygen) and CH₂; Y^1 can be selected from N (nitrogen) and CH; Y^2 can be selected from N (nitrogen) and CH; Y^3 can be selected from N (nitrogen) and CH; Y^4 can be selected from N (nitrogen) and CH; Y^5 can be selected from N (nitrogen), CH and C—OCH₃; R^{1a} can be

selected from $-C_{1-4}$ alkyl, $-C_{1-4}$ haloalkyl, $-CH_2(C_{3-6}$ monocyclic cycloalkyl) and $-CH_2(4-6$ membered monocyclic heterocyclyl) and $-CH_2(5-6$ membered monocyclic heteroaryl); R^{1b} can be selected from $-N(R^{m1})R^{n1}$ and $-R^{x1}$; R^{1c} can be selected from $-N(R^{m1})R^{n1}$ and $-R^{x1}$; 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 independently selected from hydrogen, halogen, cyano, $-CH_3$, $-CH_2CH_3$, $-CH_2OH$, $-OCH_3$ and $-SCH_3$; R^{3a} can be selected from H (hydrogen), $-CH_3$, $-CF_3$ and $-CHF_2$; R^{4a} can be selected from H (hydrogen), halogen, $-C_{1-4}$ alkyl, $-C_{1-4}$ haloalkyl, $-CH_2R^{4b}$ and $-C(CH_3)R^{4b}$; R^{4b} can be selected from $-N(R^{m2})R^{n2}$ and $-R^{y1}$; R^{5a} can be selected from $-CH_3$, $-C_{2-4}$ alkyl and $-C_{2-4}$ haloalkyl; R^{5b} can be selected from $-CH_3$, $-C_{2-4}$ alkyl and $-C_{2-4}$ haloalkyl; R^{m1} can be selected from hydrogen, $-C_{1-4}$ alkyl, C_{3-6} monocyclic cycloalkyl, C_{5-12} bicyclic cycloalkyl, 5- or 6-membered monocyclic heteroaryl, 4-7 membered monocyclic heterocyclyl, 8-11 membered fused-heteroaryl, 8-11 membered fused-heterocyclyl and $-R^{x2}$; wherein the monocyclic heteroaryl, the bicyclic heteroaryl the monocyclic heterocyclyl and the bicyclic heterocyclyl can contain at least one atom or group of atoms independently selected from the group consisting of O (oxygen), S (sulfur), $C(=O)$, $S(=O)$, $S(=O)_2$ and N (nitrogen); wherein the $-C_{1-4}$ alkyl can be optionally substituted with one or two or three substituents independently selected from halogen, cyano, hydroxy, $-C_{1-4}$ alkoxy, $-C_{1-4}$ haloalkyl, $-C_{1-4}$ haloalkoxy, $-C(=O)OR^{Z1}$, $-C(=O)NHS(=O)_2R^{Z3}$, $-C(=O)N(R^{Z1})R^{Z2}$, $-S(=O)_2R^{Z3}$, $-S(=O)_2N(R^{Z1})R^{Z2}$, $-N(R^{Z1})C(=O)R^{Z3}$, $-N(R^{Z1})S(=O)R^{Z3}$, $-N(R^{Z1})C(=O)N(R^{Z2})R^{Z3}$ and $-N(R^{Z1})S(=O)N(R^{Z2})R^{Z3}$; wherein the C_{3-6} monocyclic cycloalkyl, the C_{5-12} bicyclic cycloalkyl, the 5- or 6-membered monocyclic heteroaryl, the 4-7 membered monocyclic heterocyclyl, the 8-11 membered fused-heteroaryl and the 8-11 membered fused-heterocyclyl can be optionally substituted with one or two or three substituents independently selected from halogen, cyano, $-C_{1-4}$ alkyl, hydroxy, $-C_{1-4}$ alkoxy, $-C_{1-4}$ haloalkyl, $-C_{1-4}$ haloalkoxy, $-C(=O)OR^{Z1}$, $-C(=O)NHS(=O)_2R^{Z3}$, $-C(=O)N(R^{Z1})R^{Z2}$, $-S(=O)_2R^{Z3}$, $-S(=O)_2N(R^{Z1})R^{Z2}$, $-N(R^{Z1})C(=O)R^{Z3}$, $-N(R^{Z1})S(=O)R^{Z3}$, $-N(R^{Z1})C(=O)N(R^{Z2})R^{Z3}$ and $-N(R^{Z1})S(=O)N(R^{Z2})R^{Z3}$; and R^{n1} can be hydrogen, $-C_{1-4}$ alkyl, $-C_{1-4}$ haloalkyl or C_{3-6} monocyclic cycloalkyl(CH_2); R^{m2} can be selected from $-CH_3$, $-C_{2-4}$ alkyl, $-C_{1-4}$ haloalkyl and $-R^{y2}$, wherein the $-C_{2-4}$ alkyl is optionally substituted with hydroxy; R^{n2} can be selected from H (hydrogen), $-C_{1-4}$ alkyl and $-C_{1-4}$ haloalkyl; R^{x1} can be

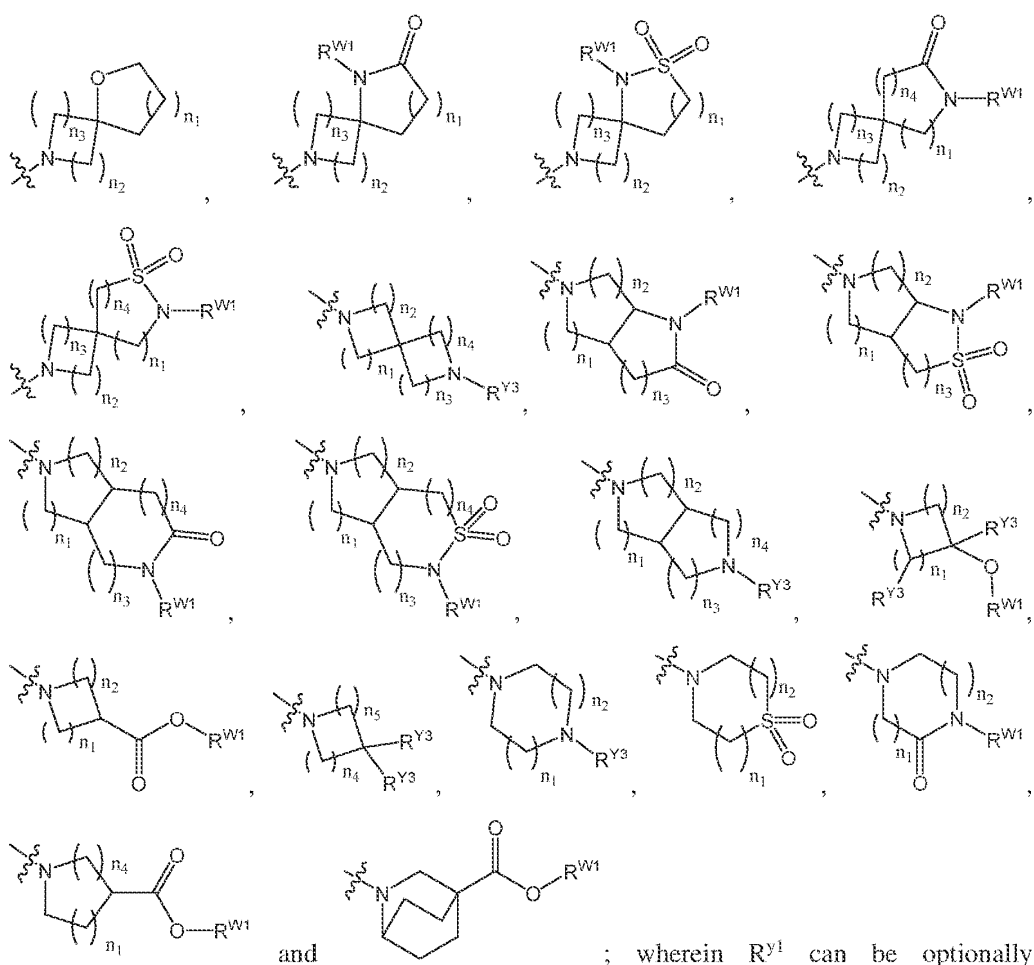


; wherein R^{X1} can be optionally substituted with one or two substituents independently selected from halogen, cyano, $-C_{1-4}$ alkyl, hydroxy, $-C_{1-4}$ alkoxy, $-C_{1-4}$ haloalkyl, $-C_{1-4}$ haloalkoxy, $-C(=O)OR^{Z1}$, $-C(=O)NHS(=O)_2R^{Z3}$, $-C(=O)N(R^{Z1})R^{Z2}$, $-S(=O)_2R^{Z3}$, $-S(=O)_2N(R^{Z1})R^{Z2}$, $-N(R^{Z1})C(=O)R^{Z3}$, $-N(R^{Z1})S(=O)_2R^{Z3}$, $-N(R^{Z1})C(=O)N(R^{Z1})R^{Z3}$ and $-N(R^{Z1})S(=O)_2N(R^{Z2})R^{Z3}$; R^{X2} can be

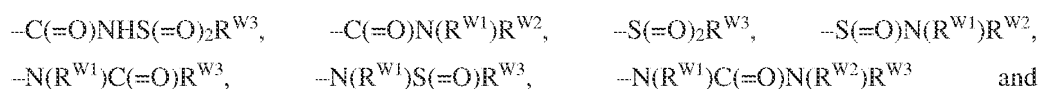




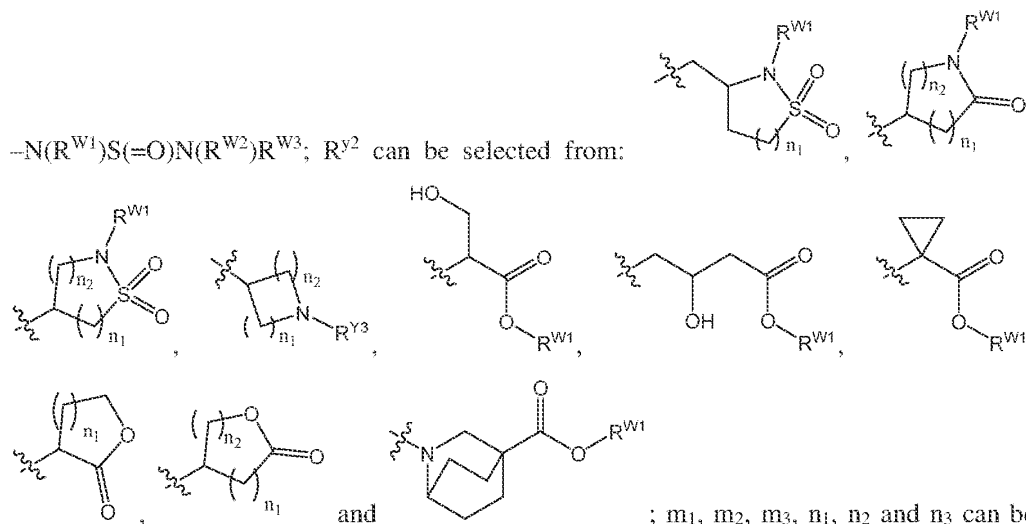
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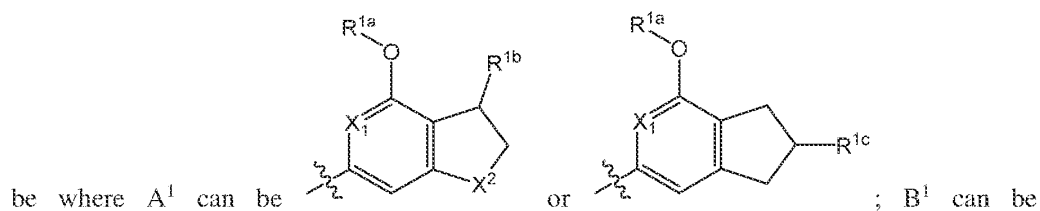
substituted with one or two substituents independently selected from halogen, cyano, $-C_{1-4}$ alkyl, hydroxy, $-C_{1-4}$ alkoxy, $-C_{1-4}$ haloalkyl, $-C_{1-4}$ haloalkoxy, $-C(=O)OR^{w1}$,

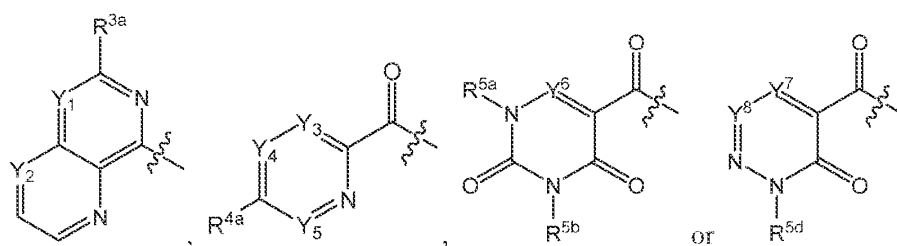


$-\text{N}(\text{R}^{\text{W}1})\text{S}(=\text{O})\text{N}(\text{R}^{\text{W}2})\text{R}^{\text{W}3}$; $\text{R}^{\text{Y}2}$ can be selected from:



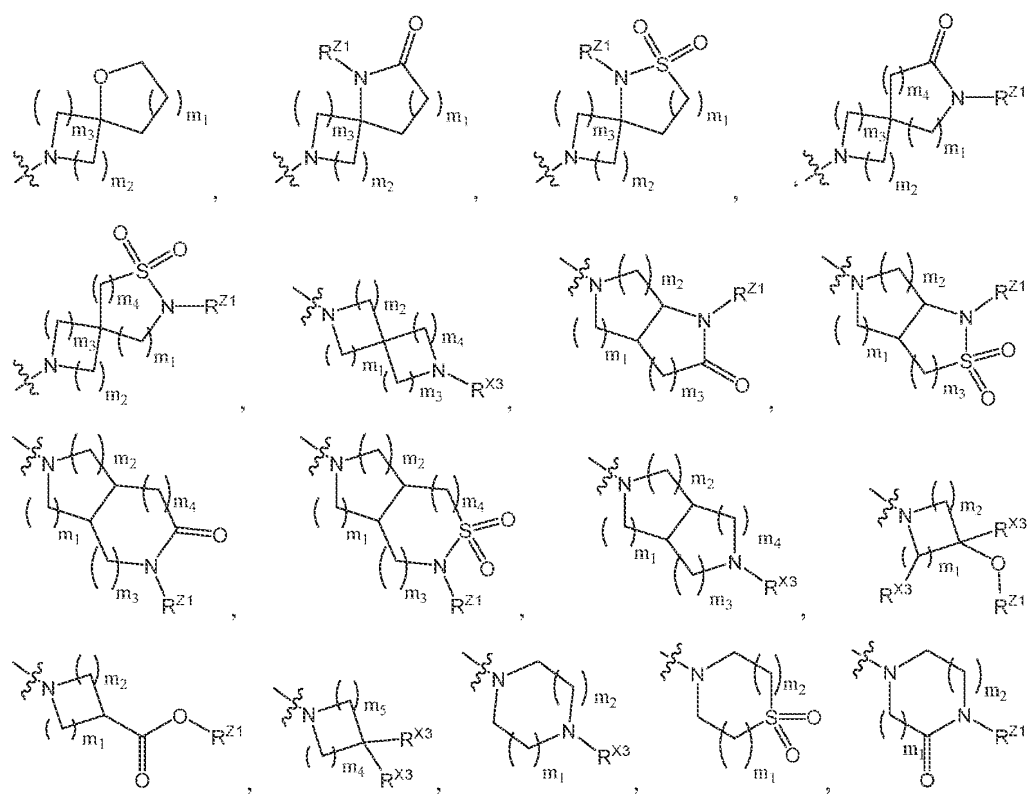
; m_1, m_2, m_3, n_1, n_2 and n_3 can be independently 1 or 2; m_4 and n_4 can be independently 0, 1 or 2; m_5 and n_5 can be independently 1, 2, 3 or 4; each $\text{R}^{\text{X}3}$ can be independently selected from hydrogen, halogen, $-\text{C}_{1-4}$ alkyl, $-\text{C}_{1-4}$ haloalkyl, $-\text{C}(=\text{O})\text{R}^{\text{Z}3}$, $-\text{C}(=\text{O})\text{OR}^{\text{Z}1}$, $-\text{S}(=\text{O})_2\text{R}^{\text{Z}1}$, $-\text{C}(=\text{O})\text{N}(\text{R}^{\text{Z}1})\text{R}^{\text{Z}2}$ and $-\text{S}(=\text{O})\text{N}(\text{R}^{\text{Z}1})\text{R}^{\text{Z}2}$; each $\text{R}^{\text{Y}3}$ can be independently selected from hydrogen, halogen, $-\text{C}_{1-4}$ alkyl, $-\text{C}_{1-4}$ haloalkyl, $-\text{C}(=\text{O})\text{R}^{\text{W}3}$, $-\text{C}(=\text{O})\text{OR}^{\text{W}3}$, $-\text{S}(=\text{O})_2\text{R}^{\text{W}3}$, $-\text{C}(=\text{O})\text{N}(\text{R}^{\text{W}1})\text{R}^{\text{W}2}$ and $-\text{S}(=\text{O})\text{N}(\text{R}^{\text{W}1})\text{R}^{\text{W}2}$; $\text{R}^{\text{Z}1}$, $\text{R}^{\text{Z}2}$, $\text{R}^{\text{W}1}$ and $\text{R}^{\text{W}2}$ can be independently selected from hydrogen, $-\text{C}_{1-4}$ alkyl, and $-\text{C}_{1-4}$ haloalkyl; and $\text{R}^{\text{Z}3}$ and $\text{R}^{\text{W}3}$ can be independently selected from hydrogen, $-\text{C}_{1-4}$ alkyl and $-\text{C}_{1-4}$ haloalkyl. In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can

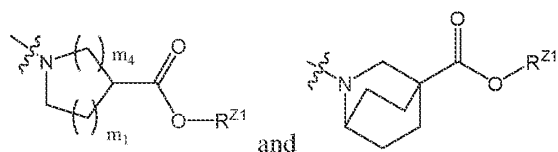




; X¹ can be selected from CH and N (nitrogen); X² can be selected from O (oxygen) and CH₂; Y¹ can be selected from N (nitrogen) and CH; Y² can be selected from N (nitrogen) and CH; Y³ can be selected from N (nitrogen) and CH; Y⁴ can be selected from N (nitrogen) and CH; Y⁵ can be selected from N (nitrogen), CH and C-OCH₃; Y⁶ can be selected from N and CR^{5c}; Y⁷ can be CR^{5c}; Y⁸ can be CR^{5f}; R^{1a} can be selected from -C₁₋₄ alkyl, -C₁₋₄ haloalkyl, -CH₂(C₃₋₆ monocyclic cycloalkyl), -CH₂(4-6 membered monocyclic heterocyclyl) and -CH₂(5-6 membered monocyclic heteroaryl); R^{1b} can be selected from -N(R^{m1})Rⁿ¹ and -R^{x1}; R^{1c} can be selected from -N(R^{m1})Rⁿ¹ and -R^{x1}; 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 independently selected from hydrogen, halogen, cyano, -CH₃, -CH₂CH₃, -CH₂OH, -OCH₃ and -SCH₃; R^{3a} can be selected from H (hydrogen), -CH₃, -CF₃ and -CHF₂; R^{4a} can be selected from H (hydrogen), halogen, -C₁₋₄ alkyl, -C₁₋₄ haloalkyl, -CH₂R^{4b} and -C(CH₃)R^{4b}; R^{4b} can be selected from -N(R^{m2})Rⁿ² and -R^{y1}; R^{5a} can be selected from hydrogen, -CH₃, -C₂₋₄ alkyl and -C₂₋₄ haloalkyl; R^{5b} can be selected from hydrogen, -CH₃, -C₂₋₄ alkyl and -C₂₋₄ haloalkyl; R^{5c} can be selected from hydrogen, -CH₃, -C₂₋₄ alkyl and -C₂₋₄ haloalkyl; R^{5d} can be selected from hydrogen, -CH₃, -C₂₋₄ alkyl and -C₂₋₄ haloalkyl; R^{5e} can be selected from hydrogen, halogen and -CH₃; R^{5f} can be selected from hydrogen, halogen, -OH, CN and -CH₃; R^{m1} can be selected from hydrogen, -C₁₋₄ alkyl, C₃₋₆ monocyclic cycloalkyl, C₅₋₁₂ bicyclic cycloalkyl, 5- or 6-membered monocyclic heteroaryl, 4-7 membered monocyclic heterocyclyl, 8-11 membered fused-heteroaryl, 8-11 membered fused-heterocyclyl and -R^{x2}; wherein the monocyclic heteroaryl, the bicyclic heteroaryl the monocyclic heterocyclyl and the bicyclic heterocyclyl can contain at least one atom or group of atoms independently selected from the group consisting of O (oxygen), S (sulfur), C(=O), S(=O), S(=O)₂ and N (nitrogen); wherein the -C₁₋₄ alkyl can be optionally substituted with one or two or three substituents independently selected from halogen, cyano, hydroxy, -C₁₋₄ alkoxy, -C₁₋₄ haloalkyl, -C₁₋₄ haloalkoxy, -C(=O)OR^{Z1}, -C(=O)NHS(=O)₂R^{Z3}, -C(=O)N(R^{Z1})R^{Z2}, -S(=O)₂R^{Z3},

$-\text{S}(=\text{O})_2\text{N}(\text{R}^{\text{Z1}})\text{R}^{\text{Z2}}$, $-\text{N}(\text{R}^{\text{Z1}})\text{C}(=\text{O})\text{R}^{\text{Z3}}$, $-\text{N}(\text{R}^{\text{Z1}})\text{S}(=\text{O})\text{R}^{\text{Z3}}$, $-\text{N}(\text{R}^{\text{Z1}})\text{C}(=\text{O})\text{N}(\text{R}^{\text{Z2}})\text{R}^{\text{Z3}}$ and $-\text{N}(\text{R}^{\text{Z1}})\text{S}(=\text{O})\text{N}(\text{R}^{\text{Z2}})\text{R}^{\text{Z3}}$; wherein the C_{3-6} monocyclic cycloalkyl, the C_{5-12} bicyclic cycloalkyl, the 5- or 6-membered monocyclic heteroaryl, the 4-7 membered monocyclic heterocyclyl, the 8-11 membered fused-heteroaryl and the 8-11 membered fused-heterocyclyl can be optionally substituted with one or two or three substituents independently selected from halogen, cyano, $-\text{C}_{1-4}$ alkyl, hydroxy, $-\text{C}_{1-4}$ alkoxy, $-\text{C}_{1-4}$ haloalkyl, $-\text{C}_{1-4}$ haloalkoxy, $-\text{C}(=\text{O})\text{OR}^{\text{Z1}}$, $-\text{C}(=\text{O})\text{NHS}(=\text{O})_2\text{R}^{\text{Z3}}$, $-\text{C}(=\text{O})\text{N}(\text{R}^{\text{Z1}})\text{R}^{\text{Z2}}$, $-\text{S}(=\text{O})_2\text{R}^{\text{Z3}}$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^{\text{Z1}})\text{R}^{\text{Z2}}$, $-\text{N}(\text{R}^{\text{Z1}})\text{C}(=\text{O})\text{R}^{\text{Z3}}$, $-\text{N}(\text{R}^{\text{Z1}})\text{S}(=\text{O})\text{R}^{\text{Z3}}$, $-\text{N}(\text{R}^{\text{Z1}})\text{C}(=\text{O})\text{N}(\text{R}^{\text{Z2}})\text{R}^{\text{Z3}}$ and $-\text{N}(\text{R}^{\text{Z1}})\text{S}(=\text{O})\text{N}(\text{R}^{\text{Z2}})\text{R}^{\text{Z3}}$; and R^{n1} can be hydrogen, $-\text{C}_{1-4}$ alkyl, $-\text{C}_{1-4}$ haloalkyl, C_{3-6} monocyclic cycloalkyl(CH_2)– or $-\text{C}(=\text{O})\text{OR}^{\text{Z4}}$, R^{m2} can be selected from $-\text{CH}_3$, $-\text{C}_{2-4}$ alkyl, $-\text{C}_{1-4}$ haloalkyl and $-\text{R}^{\text{y2}}$, wherein the $-\text{C}_{2-4}$ alkyl is optionally substituted with hydroxy; R^{n2} can be selected from H (hydrogen), $-\text{C}_{1-4}$ alkyl and $-\text{C}_{1-4}$ haloalkyl; R^{x1} can be selected from:



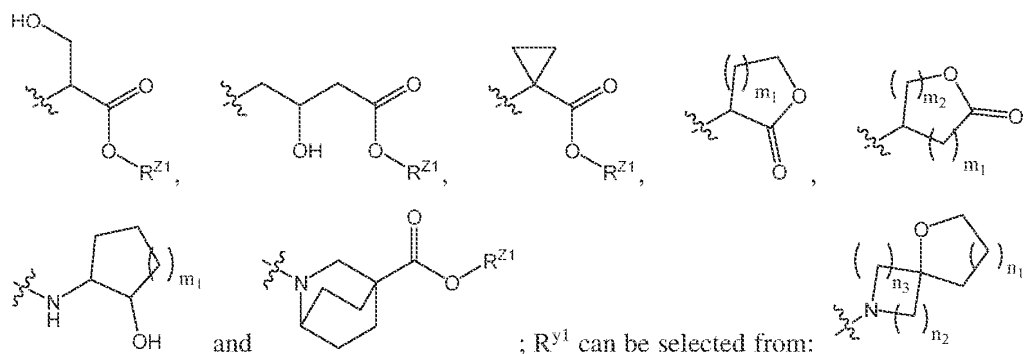
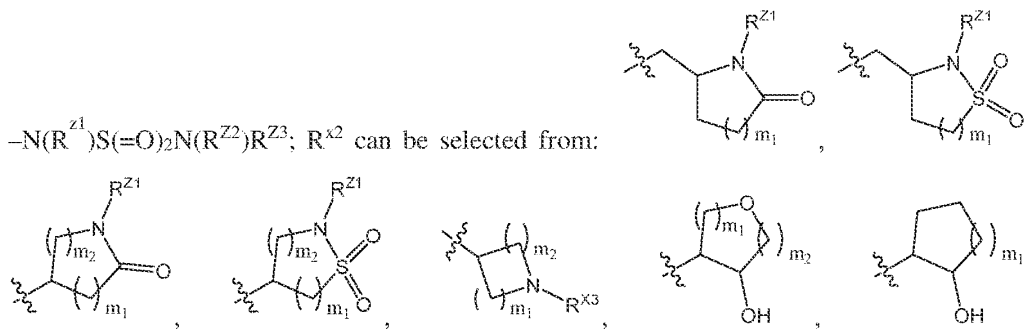
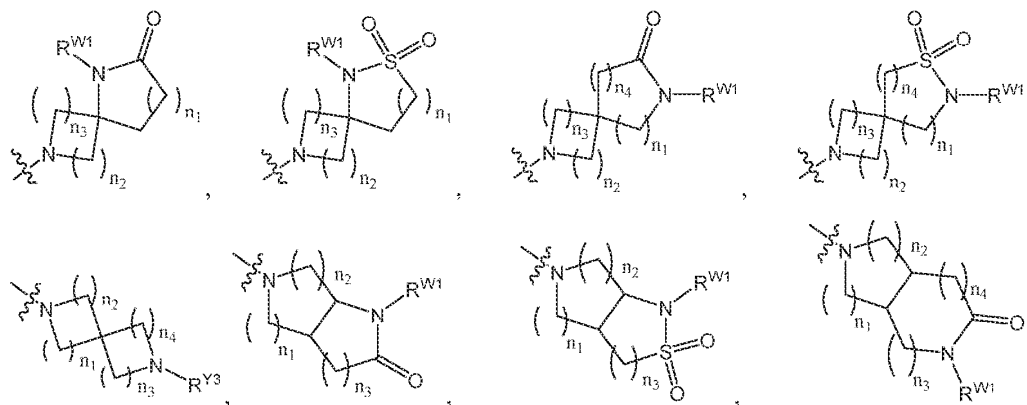


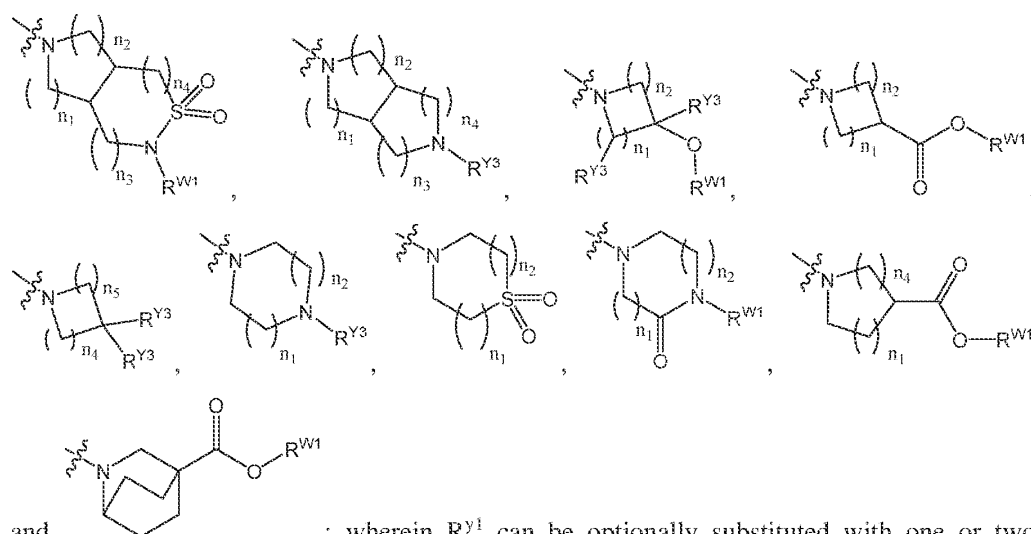
and

; wherein R^{x1} can be optionally substituted

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

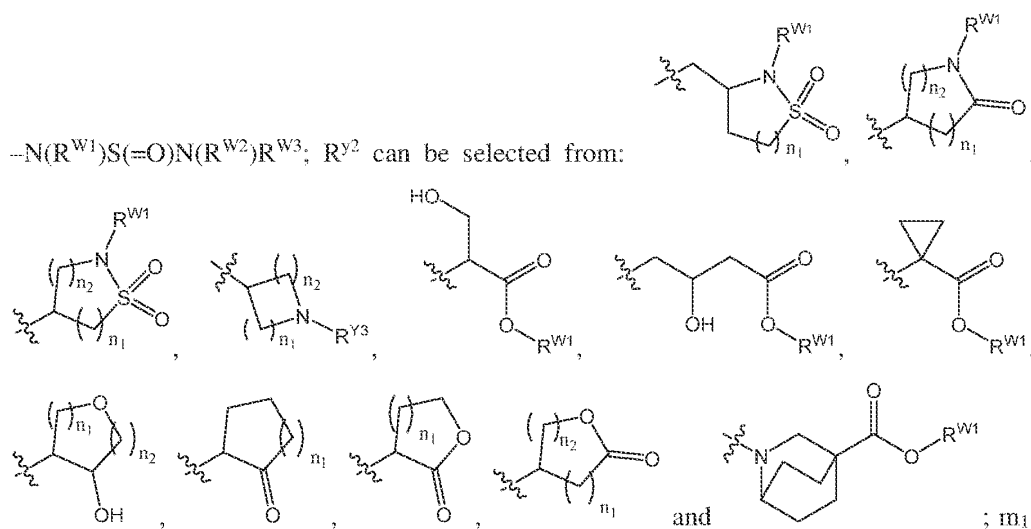
$-N(R^{Z1})S(=O)_2N(R^{Z2})R^{Z3}$; R^{x2} can be selected from:

; R^{y1} can be selected from:



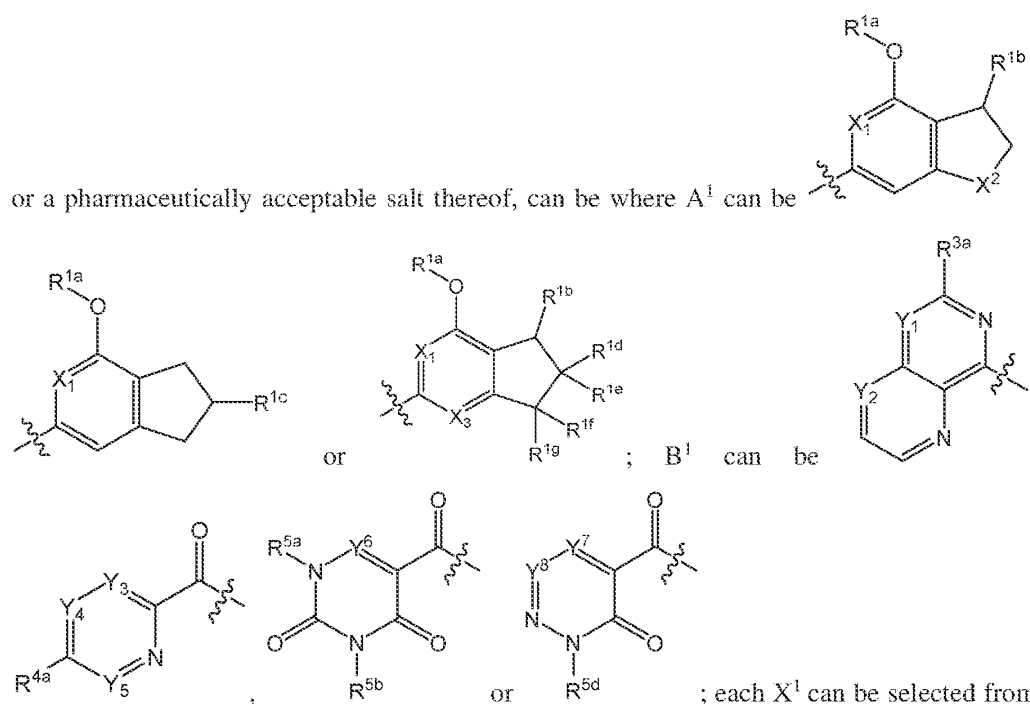
and ; wherein R^{Y1} can be optionally substituted with one or two substituents independently selected from halogen, cyano, $-C_{1-4}$ alkyl, hydroxy, $-C_{1-4}$ alkoxy, $-C_{1-4}$ haloalkyl, $-C_{1-4}$ haloalkoxy, $-C(=O)OR^{W1}$, $-C(=O)NHS(=O)_2R^{W3}$, $-C(=O)N(R^{W1})R^{W2}$, $-S(=O)_2R^{W3}$, $-S(=O)N(R^{W1})R^{W2}$, $-N(R^{W1})C(=O)R^{W3}$, $-N(R^{W1})S(=O)R^{W3}$, $-N(R^{W1})C(=O)N(R^{W2})R^{W3}$ and

$-N(R^{W1})S(=O)N(R^{W2})R^{W3}$; R^{Y2} can be selected from:



m_2 , m_3 , n_1 , n_2 and n_3 can be independently 1 or 2; m_4 and n_4 can be independently 0, 1 or 2; m_5 and n_5 can be independently 1, 2, 3 or 4; each R^{X3} can be independently selected from hydrogen, halogen, $-C_{1-4}$ alkyl, $-C_{1-4}$ haloalkyl, $-C(=O)R^{Z3}$, $-C(=O)OR^{Z1}$, $-S(=O)_2R^{Z1}$, $-C(=O)N(R^{Z1})R^{Z2}$ and $-S(=O)N(R^{Z1})R^{Z2}$; each R^{Y3} can be independently selected from

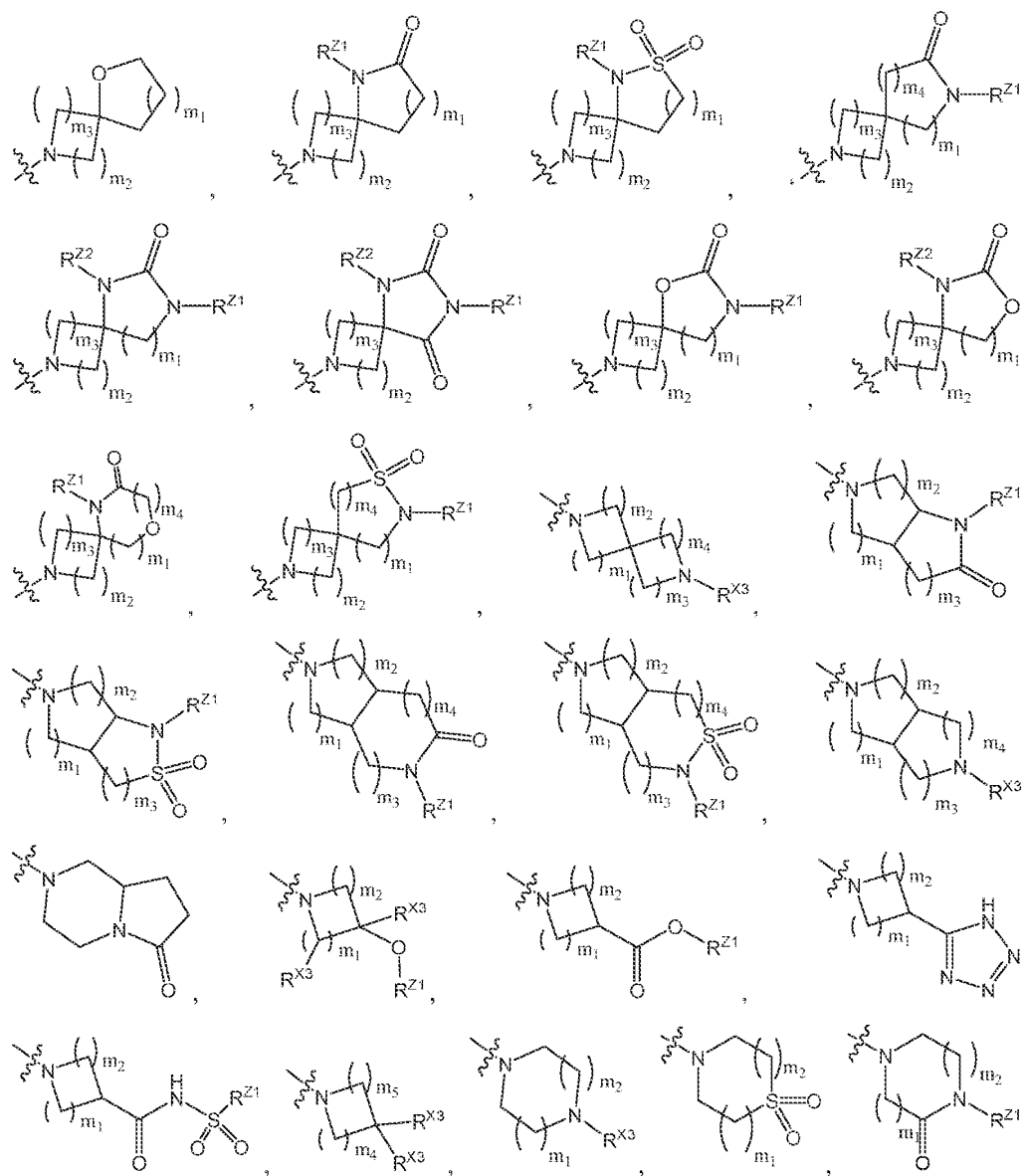
hydrogen, halogen, $-C_{1-4}$ alkyl, $-C_{1-4}$ haloalkyl, $-C(=O)R^{W3}$, $-C(=O)OR^{W3}$, $-S(=O)_2R^{W3}$, $-C(=O)N(R^{W1})R^{W2}$ and $-S(=O)N(R^{W1})R^{W2}$; R^{Z1} and R^{Z2} can be independently selected from hydrogen, $-C_{1-4}$ alkyl, and $-C_{1-4}$ haloalkyl; or R^{Z1} and R^{Z2} can be taken together to form a monocyclic heterocyclyl when attached to the same nitrogen; R^{W1} and R^{W2} can be independently selected from hydrogen, $-C_{1-4}$ alkyl and $-C_{1-4}$ haloalkyl; R^{Z3} and R^{W3} can be independently selected from hydrogen, $-C_{1-4}$ alkyl and $-C_{1-4}$ haloalkyl; and R^{Z4} can be selected from hydrogen, $-C_{1-4}$ alkyl and 5- to 6-membered monocyclic heterocyclyl(CH_2)-optionally substituted with $-C_{1-4}$ alkyl. In some embodiments, a compound of Formula (I),

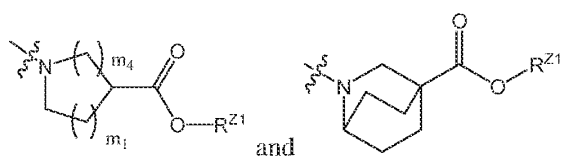


CH and N (nitrogen); X^2 can be O (oxygen); X^3 can be selected from CH, C-halo and N; Y^1 can be selected from N (nitrogen) and CH; Y^2 can be selected from N (nitrogen) and CH; Y^3 can be selected from N (nitrogen) and CH; Y^4 can be selected from N (nitrogen) and CH; Y^5 can be selected from N (nitrogen), CH and $C-OCH_3$; Y^6 can be selected from N and CR^{5c} ; Y^7 can be CR^{5c} ; Y^8 can be CR^{5f} ; each 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(C_{1-4} alkoxy), $-C_{2-4}$ alkyl (C_{1-4} haloalkoxy), $-CH_2(4-6$ membered monocyclic heterocyclyl) and $-CH_2(5-6$ membered monocyclic heteroaryl); each R^{1b} can be selected from $-N(R^{m1})R^{n1}$ and $-R^{x1}$; R^{1c} can be selected from

$-N(R^{m1})R^{n1}$ and $-R^{x1}$; R^{1d} can be selected from hydrogen, $-CH_3$, $-CH_2CH_3$, $-OH$, $-OCH_3$ and $-F$; R^{1e} can be selected from hydrogen, $-CH_3$, $-CH_2CH_3$ and $-F$; R^{1f} can be selected from hydrogen, $-CH_3$, $-CH_2CH_3$, $-OH$, $-OCH_3$ and $-F$; R^{1g} can be selected from hydrogen, $-CH_3$, $-CH_2CH_3$ and $-F$; 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 independently selected from hydrogen, halogen, cyano, $-CH_3$, $-CH_2CH_3$, $-CH_2OH$, $-OCH_3$ and $-SCH_3$; R^{3a} can be selected from H (hydrogen), $-CH_3$, $-CF_3$ and $-CHF_2$; R^{4a} can be selected from H (hydrogen), halogen, $-C_{1-4}$ alkyl, $-C_{1-4}$ haloalkyl, $-CH_2R^{4b}$ and $-C(CH_3)R^{4b}$; R^{4b} can be selected from $-N(R^{m2})R^{n2}$ and $-R^{y1}$; R^{5a} can be selected from hydrogen, $-CH_3$, $-C_{2-4}$ alkyl and $-C_{2-4}$ haloalkyl; R^{5b} can be selected from hydrogen, $-CH_3$, $-C_{2-4}$ alkyl and $-C_{2-4}$ haloalkyl; R^{5c} can be selected from hydrogen, $-CH_3$, $-C_{2-4}$ alkyl and $-C_{2-4}$ haloalkyl; R^{5d} can be selected from hydrogen, $-CH_3$, $-C_{2-4}$ alkyl and $-C_{2-4}$ haloalkyl; R^{5e} can be selected from hydrogen, halogen and $-CH_3$; R^{5f} can be selected from hydrogen, halogen, $-OH$, $-CN$ and $-CH_3$; R^{m1} can be selected from hydrogen, $-C_{1-4}$ alkyl, C_{3-6} monocyclic cycloalkyl, C_{5-12} bicyclic cycloalkyl, 5- or 6-membered monocyclic heteroaryl, 4-7 membered monocyclic heterocyclyl, 8-11 membered fused-heteroaryl, 8-11 membered fused-heterocyclyl and $-R^{x2}$; wherein the monocyclic heteroaryl, the bicyclic heteroaryl the monocyclic heterocyclyl and the bicyclic heterocyclyl can contain at least one atom or group of atoms independently selected from the group consisting of O (oxygen), S (sulfur), $C(=O)$, $S(=O)$, $S(=O)_2$ and N (nitrogen); wherein the $-C_{1-4}$ alkyl can be optionally substituted with one or two or three substituents independently selected from halogen, cyano, hydroxy, $-C_{1-4}$ alkoxy, $-C_{1-4}$ haloalkyl, $-C_{1-4}$ haloalkoxy, $-C(=O)OR^{Z1}$, $-C(=O)NHS(=O)_2R^{Z3}$, $-C(=O)N(R^{Z1})R^{Z2}$, $-S(=O)_2R^{Z3}$, $-S(=O)_2N(R^{Z1})R^{Z2}$, $-N(R^{Z1})C(=O)R^{Z3}$, $-N(R^{Z1})S(=O)R^{Z3}$, $-N(R^{Z1})C(=O)N(R^{Z2})R^{Z3}$ and $-N(R^{Z1})S(=O)N(R^{Z2})R^{Z3}$; wherein the C_{3-6} monocyclic cycloalkyl, the C_{5-12} bicyclic cycloalkyl, the 5- or 6-membered monocyclic heteroaryl, the 4-7 membered monocyclic heterocyclyl, the 8-11 membered fused-heteroaryl and the 8-11 membered fused-heterocyclyl can be optionally substituted with one or two or three substituents independently selected from halogen, cyano, $-C_{1-4}$ alkyl, hydroxy, $-C_{1-4}$ alkoxy, $-C_{1-4}$ haloalkyl, $-C_{1-4}$ haloalkoxy, $-C(=O)OR^{Z1}$, $-C(=O)NHS(=O)_2R^{Z3}$, $-C(=O)N(R^{Z1})R^{Z2}$, $-S(=O)_2R^{Z3}$, $-S(=O)_2N(R^{Z1})R^{Z2}$, $-N(R^{Z1})C(=O)R^{Z3}$, $-N(R^{Z1})S(=O)R^{Z3}$, $-N(R^{Z1})C(=O)N(R^{Z2})R^{Z3}$ and $-N(R^{Z1})S(=O)N(R^{Z2})R^{Z3}$; and R^{n1} can be hydrogen, $-C_{1-4}$ alkyl, $-C_{1-4}$ haloalkyl, C_{3-6}

monocyclic cycloalkyl(CH₂)_n or -C(=O)OR^{Z4}; R^{m2} can be selected from -CH₃, -C₂₋₄ alkyl, -C₁₋₄ haloalkyl and -R^{y2}, wherein the -C₂₋₄ alkyl is optionally substituted with hydroxy; Rⁿ² can be selected from H (hydrogen), -C₁₋₄ alkyl and -C₁₋₄ haloalkyl; R^{x1} can be selected from:



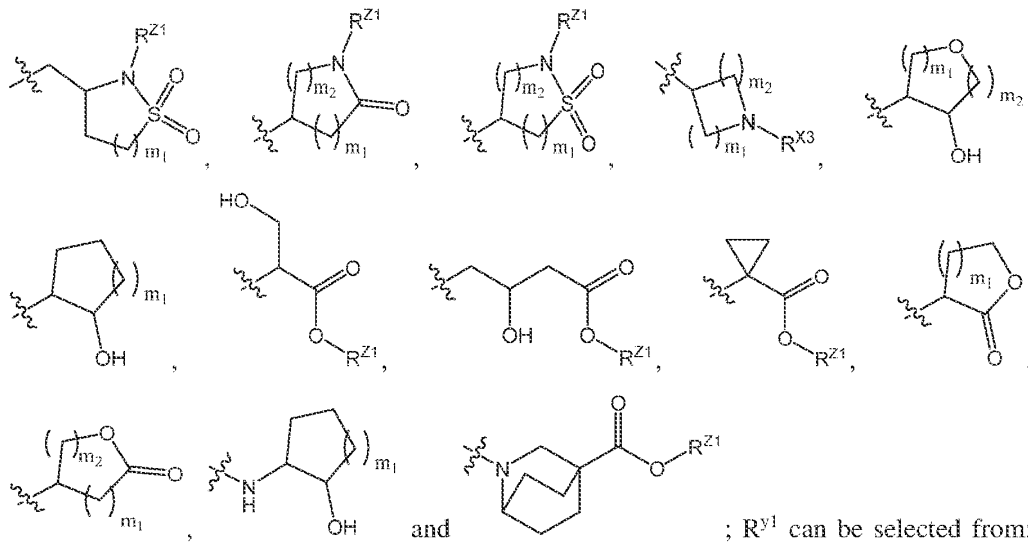


and

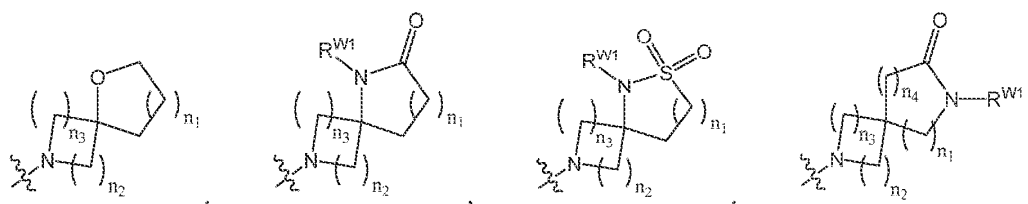
; wherein R^{x1} can be optionally substituted

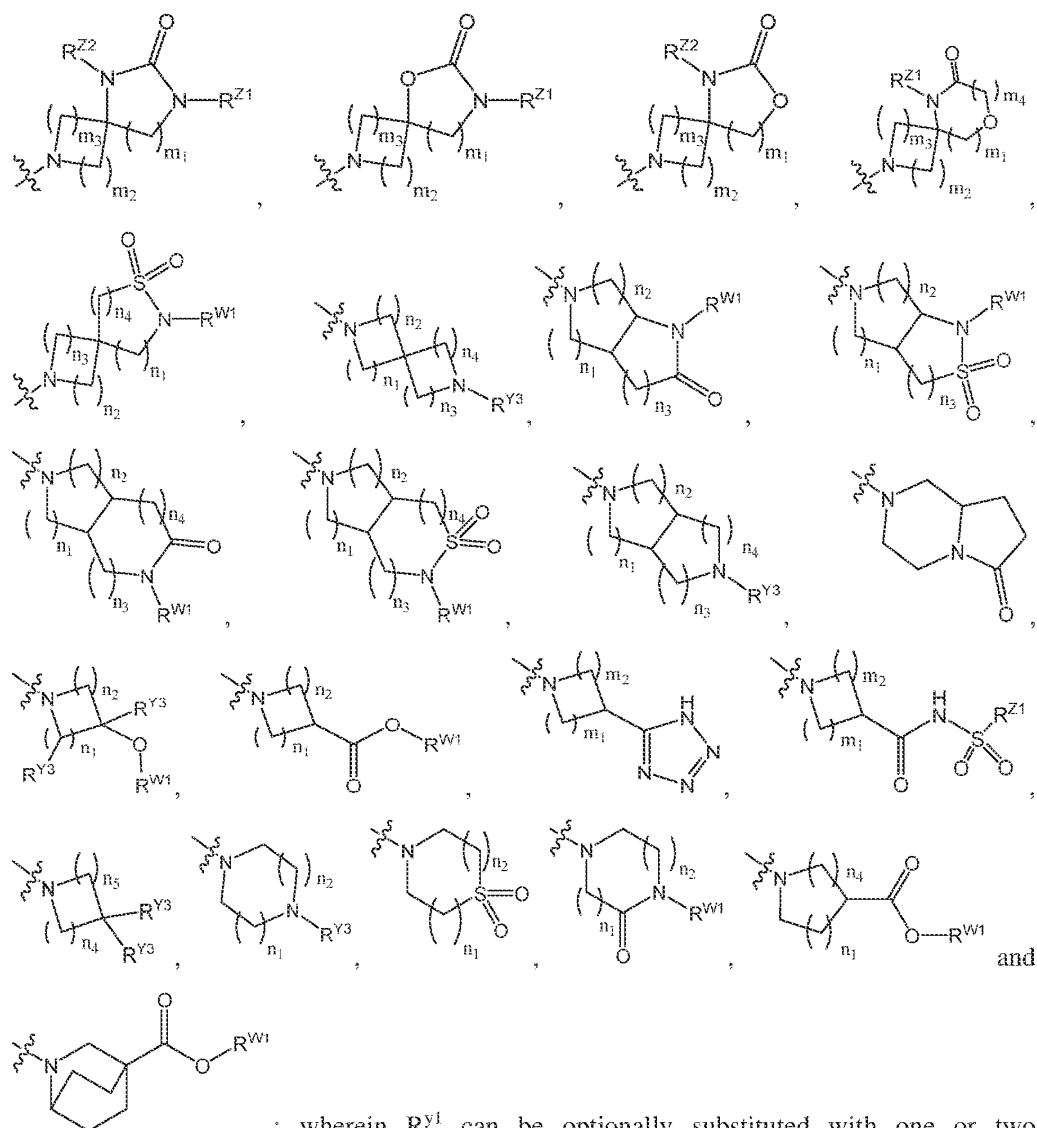
with one or two substituents independently selected from halogen, cyano, $-C_{1-4}$ alkyl, hydroxy, $-C_{1-4}$ alkoxy, $-C_{1-4}$ haloalkyl, $-C_{1-4}$ haloalkoxy, $-C(=O)OR^{Z1}$, $-C(=O)NHS(=O)_2R^{Z3}$, $-C(=O)N(R^{Z1})R^{Z2}$, $-S(=O)_2R^{Z3}$, $-S(=O)_2N(R^{Z1})R^{Z2}$, $-N(R^{Z1})C(=O)R^{Z3}$,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

$-N(R^{Z1})S(=O)_2N(R^{Z2})R^{Z3}$; R^{x2} can be selected from:

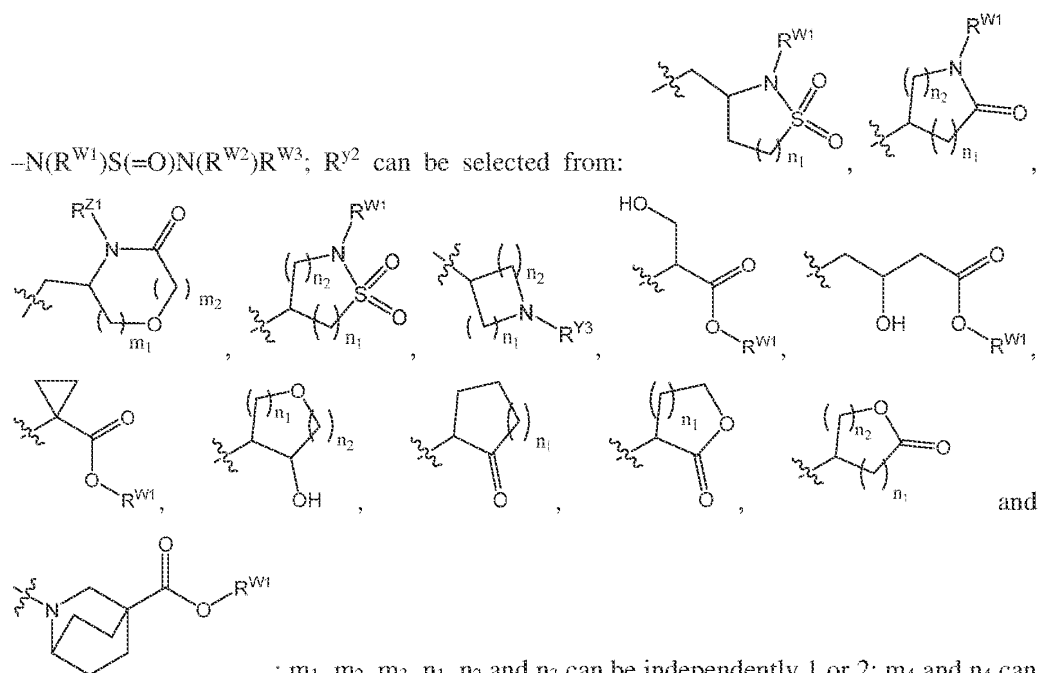


and

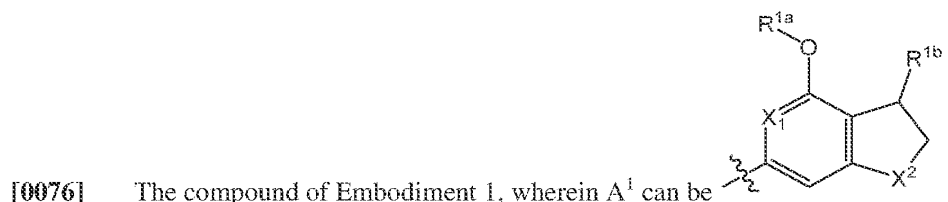
; R^{y1} can be selected from:



; wherein R^{Y1} can be optionally substituted with one or two substituents independently selected from halogen, cyano, $-C_{1-4}$ alkyl, hydroxy, $-C_{1-4}$ alkoxy, $-C_{1-4}$ haloalkyl, $-C_{1-4}$ haloalkoxy, $-C(=O)OR^{W1}$, $-C(=O)NHS(=O)_2R^{W3}$, $-C(=O)N(R^{W1})R^{W2}$, $-S(=O)_2R^{W3}$, $-S(=O)N(R^{W1})R^{W2}$, $-N(R^{W1})C(=O)R^{W3}$, $-N(R^{W1})S(=O)R^{W3}$, $-N(R^{W1})C(=O)N(R^{W2})R^{W3}$ and



Embodiment 2



Embodiment 3

[0077] The compound of Embodiment 2, wherein X^1 can be CH.

Embodiment 4

[0078] The compound of Embodiment 2, wherein X^1 can be N (nitrogen).

[0078] [0079] Embodiment 5

[0079] The compound of any one of Embodiments 2-4, 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 6

[0080] The compound of any one of Embodiments 2-4, wherein R^{1a} can be $-C_{1-4}$ haloalkyl, such as $-CF_3$, $-CHF_2$, $-CH_2F$, $-CCl_3$, $-CHCl_2$, $-CH_2Cl$, $-CH_2CF_3$ and $-CH_2CHF_2$.

Embodiment 7

[0081] The compound of any one of Embodiments 2-4, wherein R^{1a} can be $-C_{2-4}$ alkyl(C_{1-4} alkoxy) or $-C_{2-4}$ alkyl (C_{1-4} haloalkoxy).

Embodiment 8

[0082] The compound of any one of Embodiments 2-4, wherein R^{1a} can be selected from $-CH_2(C_{3-6}$ monocyclic cycloalkyl), $-CH_2(4-6$ membered monocyclic heterocyclyl) and $-CH_2(5-6$ membered monocyclic heteroaryl). Exemplary monocyclic cycloalkyls include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. In some embodiments, the 4-6 membered monocyclic heterocyclyl of the $-CH_2(4-6$ membered monocyclic heterocyclyl) and/or the 5-6 membered monocyclic heteroaryl of the $-CH_2(5-6$ membered monocyclic heteroaryl) can include one or more ring atoms (such as 1, 2 or 3) selected from N (nitrogen), O (oxygen) and S (sulfur).

Embodiment 9

[0083] The compound of any one of Embodiments 2-8, wherein R^{1b} can be $-N(R^{m1})R^{n1}$.

Embodiment 10

[0084] The compound of Embodiment 9, wherein R^{n1} can be hydrogen, such that R^{1b} can be $-NH(R^{m1})$.

Embodiment 11

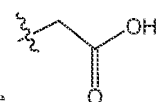
[0085] The compound of any one of Embodiments 2-8, wherein R^{n1} can be $-C(=O)OR^{Z4}$. In some embodiments, R^{Z4} can be a C_{1-4} alkyl. In other embodiments, R^{Z4} can be 5- to 6-membered monocyclic heterocyclyl(CH_2)-- optionally substituted with $-C_{1-4}$ alkyl.

Embodiment 12

[0086] The compound of any one of Embodiments 9-11, wherein R^{m1} can be $-C_{1-4}$ alkyl optionally substituted with $-C(=O)OR^{Z1}$ or 4-7 membered monocyclic heterocyclyl optionally substituted with hydroxy. Examples of C_{1-4} alkyls include methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl and tert-butyl. In some embodiments, the 4-7 membered monocyclic heterocyclyl optionally substituted with hydroxy can include one or more ring atoms (such as 1, 2 or 3) selected from N (nitrogen), O (oxygen) and S (sulfur).

Embodiment 13

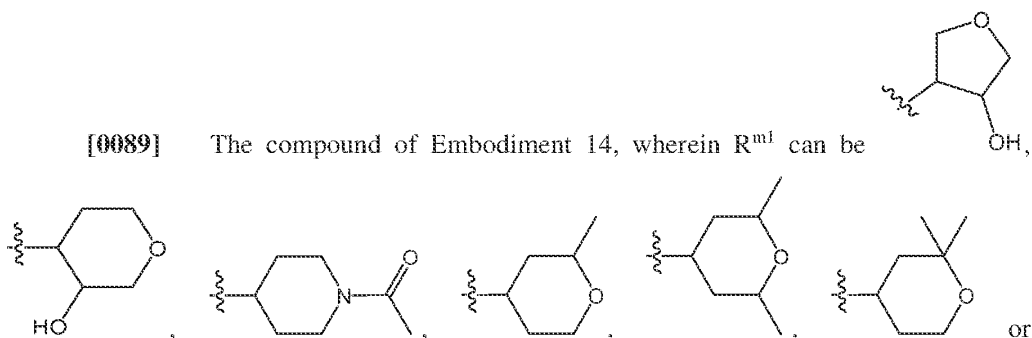
[0087] The compound of Embodiment 12, wherein R^{m1} can be

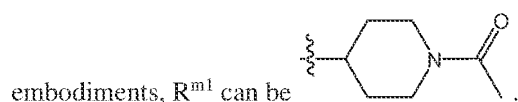
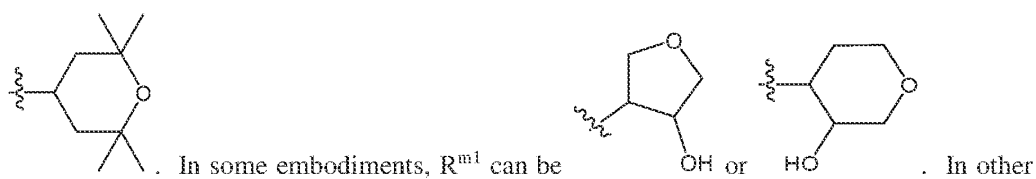
Embodiment 14

[0088] The compound of Embodiment 12, wherein R^{m1} can be tetrahydrofuran or tetrahydro-2H-pyran, each optionally substituted with hydroxy.

Embodiment 15

[0089] The compound of Embodiment 14, wherein R^{m1} can be



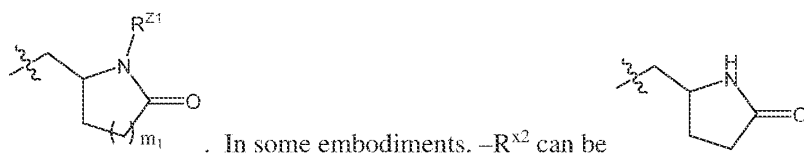


Embodiment 16

[0090] The compound of any one of Embodiments 9-11, wherein R^{m1} can be $-R^{x2}$.

Embodiment 17

[0091] The compound of Embodiment 16, wherein $-R^{x2}$ can be

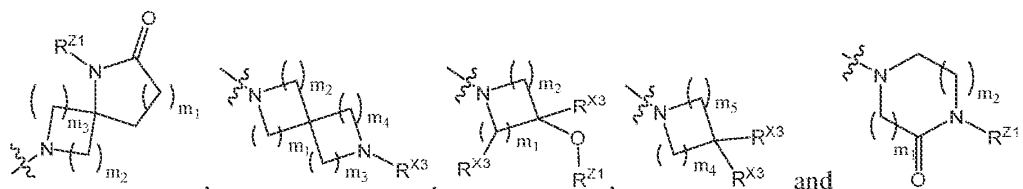


Embodiment 18

[0092] The compound of any one of Embodiments 2-8, wherein R^{1b} can be $-R^{x1}$.

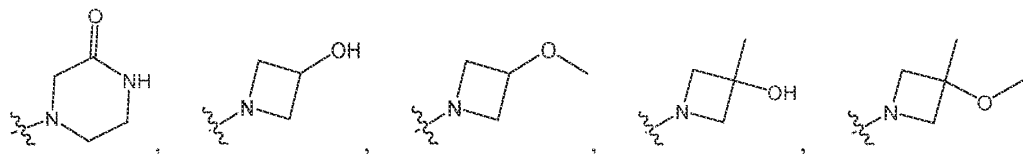
Embodiment 19

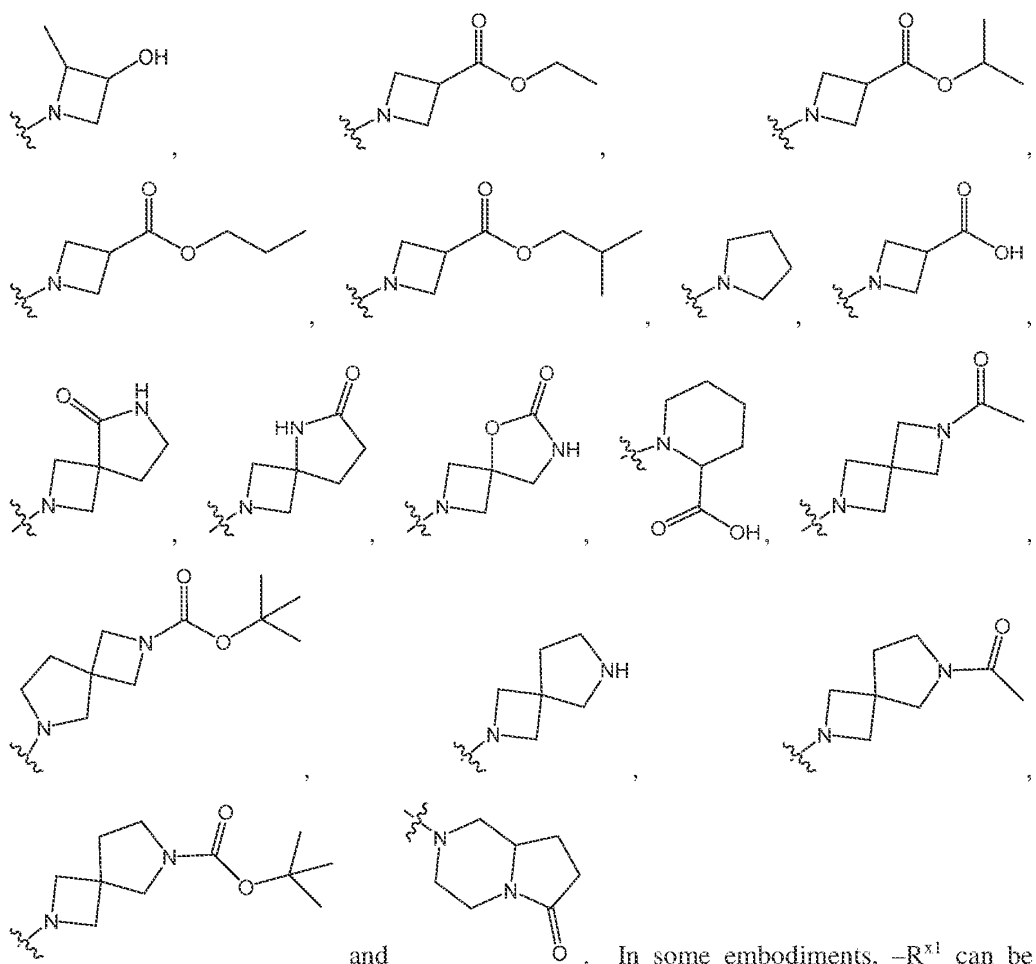
[0093] The compound of Embodiment 18, wherein $-R^{x1}$ can be selected from:



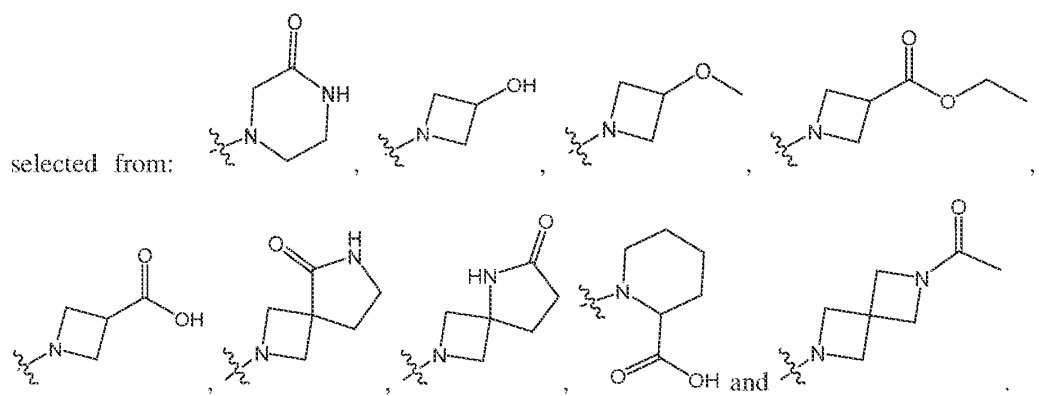
Embodiment 20

[0094] The compound of Embodiment 19, wherein $-R^{x1}$ can be selected from:



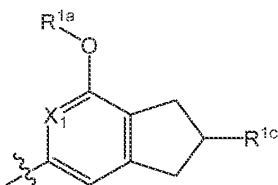


In some embodiments, $-R^{X1}$ can be



Embodiment 21

[0095] The compound of Embodiment 1, wherein A¹ can be

Embodiment 22

[0096] The compound of Embodiment 21, wherein X¹ can be CH.

Embodiment 23

[0097] The compound of Embodiment 21, wherein X¹ can be N (nitrogen).

Embodiment 24

[0098] The compound of any one of Embodiments 21-23, wherein R^{1a} can be -C₁₋₄ alkyl, such as methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl and tert-butyl.

Embodiment 25

[0099] The compound of any one of Embodiments 21-23, wherein R^{1a} can be -C₁₋₄ haloalkyl. Examples of suitable C₁₋₄ haloalkyls include, but are not limited to, -CF₃, -CHF₂, -CH₂F, -CCl₃, -CHCl₂, -CH₂Cl, -CH₂CF₃ and -CH₂CHF₂.

Embodiment 26

[0100] The compound of any one of Embodiments 21-23, wherein R^{1a} can be selected from -CH₂(C₃₋₆ monocyclic cycloalkyl), -CH₂(4-6 membered monocyclic heterocyclyl) and -CH₂(5-6 membered monocyclic heteroaryl). Examples of monocyclic cycloalkyls include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. In some embodiments, the 4-6 membered monocyclic heterocyclyl of the -CH₂(4-6 membered monocyclic heterocyclyl) and/or the 5-6 membered monocyclic heteroaryl of the -CH₂(5-6 membered monocyclic heteroaryl) can include one or more ring atoms (such as 1, 2 or 3) selected from N (nitrogen), O (oxygen) and S (sulfur).

Embodiment 27

[0101] The compound of any one of Embodiments 21-26, wherein R^{1c} can be -N(R^{m1})Rⁿ¹.

Embodiment 28

[0102] The compound of Embodiment 27, wherein R^{n1} can be hydrogen.

Embodiment 29

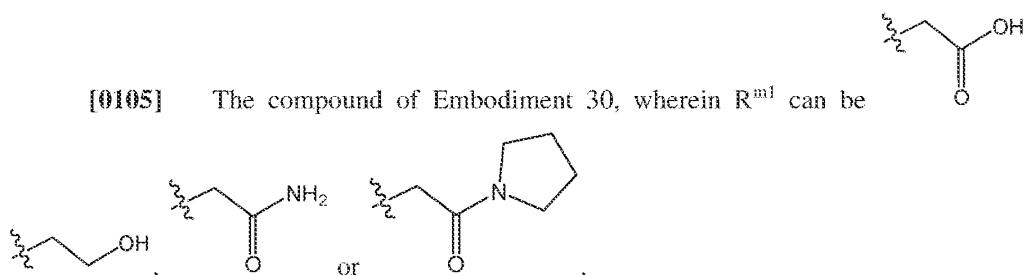
[0103] The compound of Embodiment 27, wherein R^{n1} can be $-C(=O)OR^{Z4}$. In some embodiments, R^{Z4} can be a C_{1-4} alkyl. In other embodiments, R^{Z4} can be 5- to 6-membered monocyclic heterocyclyl(CH₂)– optionally substituted with $-C_{1-4}$ alkyl.

Embodiment 30

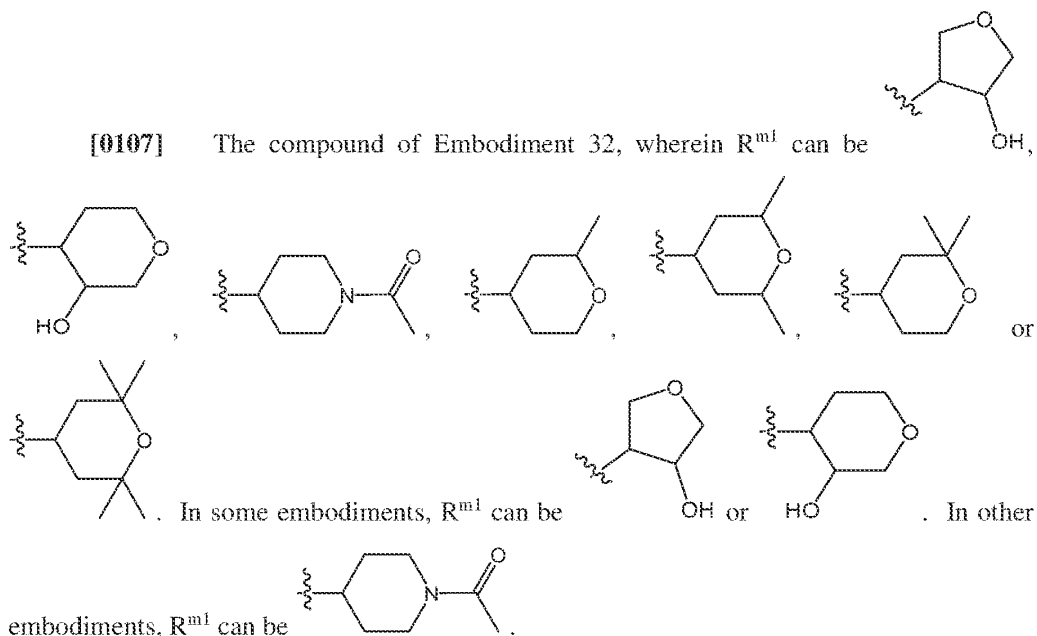
[0104] The compound of any one of Embodiments 27-29, wherein R^{m1} can be C_{3-6} monocyclic cycloalkyl, $-C_{1-4}$ alkyl optionally substituted with $-C(=O)OR^{Z1}$ or 4-7 membered monocyclic heterocyclyl optionally substituted with hydroxy. Exemplary C_{1-4} alkyls include methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl and tert-butyl. In some embodiments, the 4-7 membered monocyclic heterocyclyl optionally substituted with hydroxy can include one or more ring atoms (such as 1, 2 or 3) selected from N (nitrogen), O (oxygen) and S (sulfur).

Embodiment 31

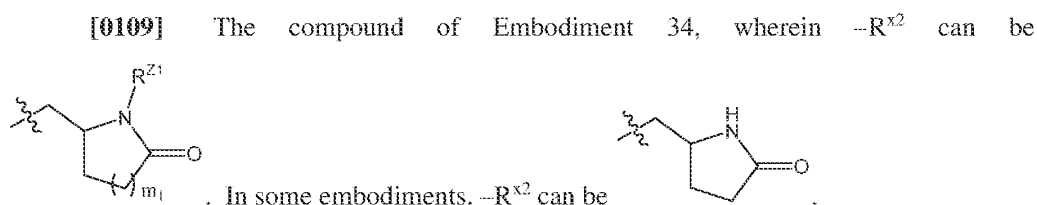
[0105] The compound of Embodiment 30, wherein R^{m1} can be

Embodiment 32

[0106] The compound of Embodiment 30, wherein R^{m1} can be oxetane, tetrahydrofuran or tetrahydro-2H-pyran, each optionally substituted with hydroxy.

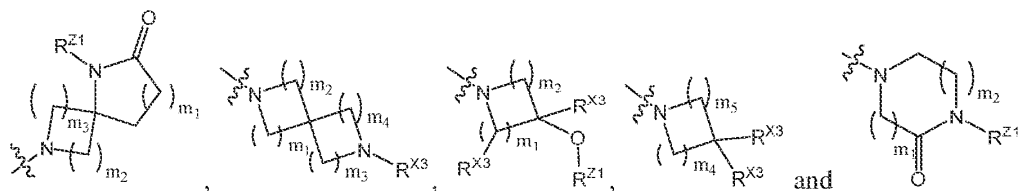
Embodiment 33Embodiment 34

[0108] The compound of any one of Embodiments 27-29, wherein R^{m1} can be $-R^{x2}$.

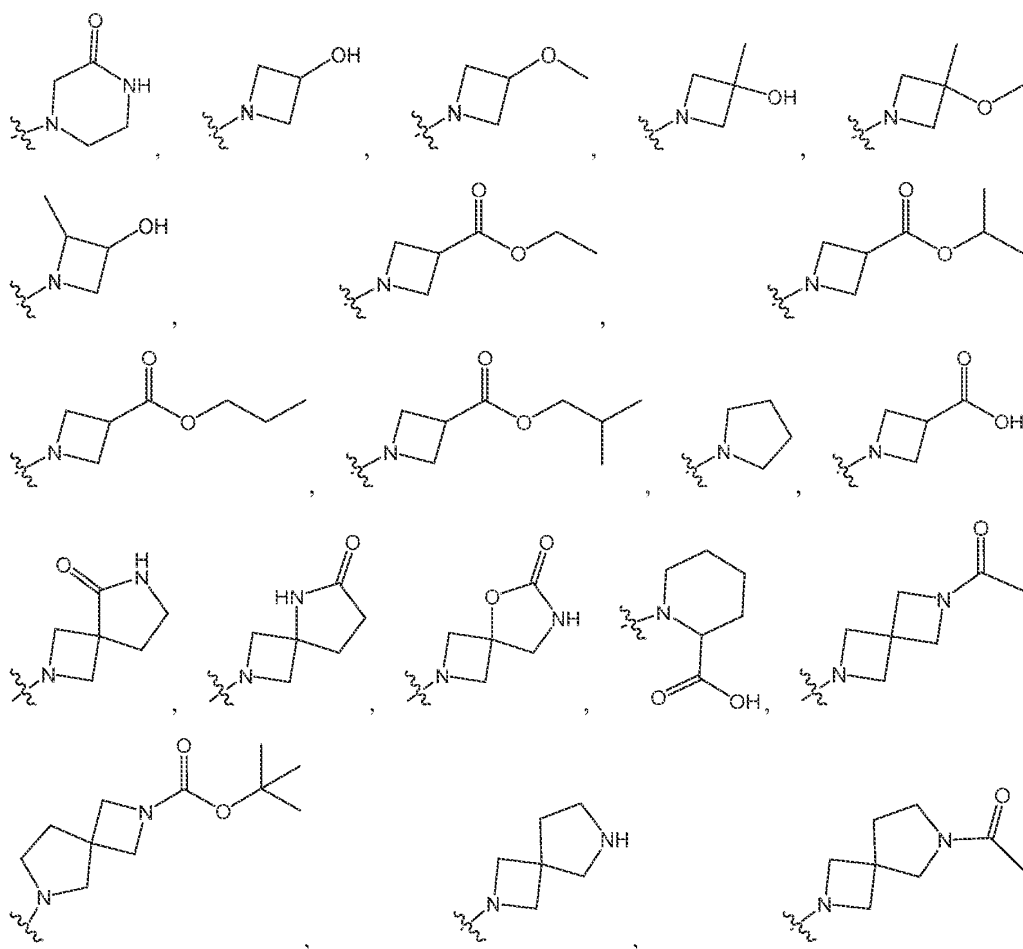
Embodiment 35

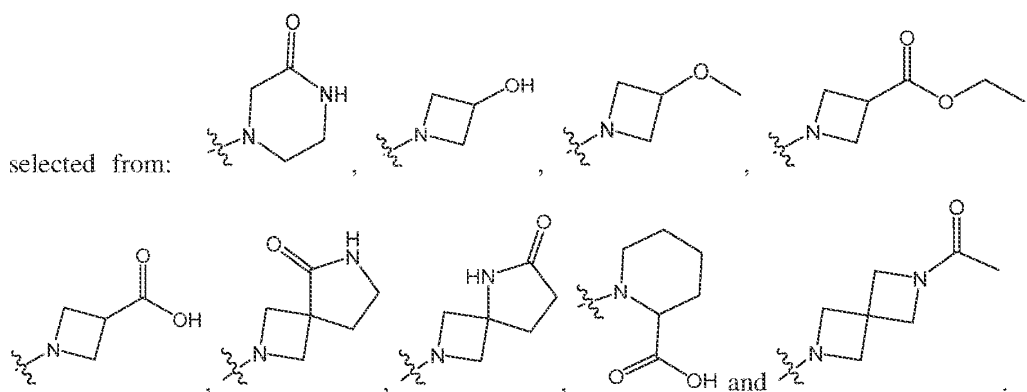
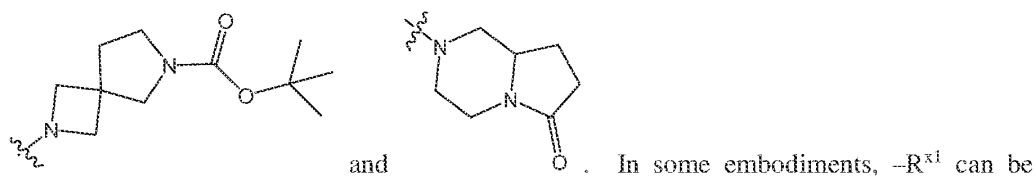
Embodiment 37

[0111] The compound of Embodiment 36, wherein $-R^{x1}$ can be selected from:

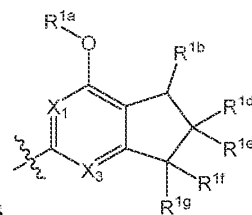
Embodiment 38

[0112] The compound of Embodiment 37, wherein $-R^{x1}$ can be selected from:





Embodiment 39



[0113] The compound of Claim 1, wherein A^1 is

Embodiment 40

[0114] The compound of Embodiment 39, wherein X^1 is CH.

Embodiment 41

[0115] The compound of Embodiment 39, wherein X^1 is N.

Embodiment 42

[0116] The compound of any one of Embodiments 39-41, wherein X^3 is CH.

Embodiment 43

[0117] The compound of any one of Embodiments 39-41, wherein X^3 is C-halo.

Embodiment 44

[0118] The compound of any one of Embodiments 39-41, wherein X^3 is N.

Embodiment 45

[0119] The compound of any one of Embodiments 39-44, wherein R^{1a} is $-C_{1-4}$ alkyl. As an example, R^{1a} can be $-CH_3$.

Embodiment 46

[0120] The compound of any one of Embodiments 39-44, wherein R^{1a} is $-C_{1-4}$ haloalkyl.

Embodiment 47

[0121] The compound of any one of Embodiments 39-44, wherein R^{1a} is selected from the group consisting of $-CH_2(C_{3-6}$ monocyclic cycloalkyl), $-CH_2(4-6$ membered monocyclic heterocyclyl) and $-CH_2(5-6$ membered monocyclic heteroaryl).

Embodiment 48

[0122] The compound of any one of Embodiments 39-47, wherein R^{1b} is $-N(R^{m1})R^{n1}$.

Embodiment 49

[0123] The compound of any one of Embodiments 39-47, wherein R^{n1} is hydrogen.

Embodiment 50

[0124] The compound of any one of Embodiments 39-47, wherein R^{n1} is $-C(=O)OR^{Z4}$.

Embodiment 51

[0125] The compound of any one of Embodiments 39-50, wherein R^{m1} is hydrogen.

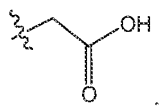
Embodiment 52

[0126] The compound of any one of Embodiments 39-50, wherein R^{m1} is $-C_{1-4}$ alkyl optionally substituted with $-C(=O)OR^{Z1}$ or 4-7 membered monocyclic heterocyclyl optionally substituted with hydroxy.

Embodiment 53

[0127] The compound of any one of Embodiments 39-50, wherein R^{m1} is C_5 monocyclic cycloalkyl or C_6 monocyclic cycloalkyl.

Embodiment 54

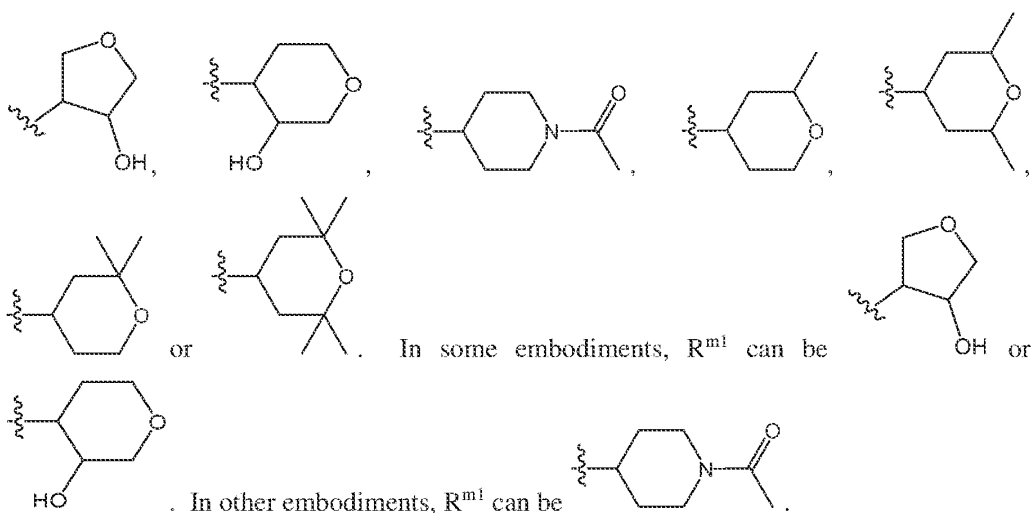
[0128] The compound of Embodiment 52, wherein R^{m1} is .

Embodiment 55

[0129] The compound of Embodiment 52, wherein R^{m1} is tetrahydrofuran or tetrahydro-2H-pyran, each optionally substituted with hydroxy, or piperidine optionally substituted with $-C(=O)R^{Z1}$.

Embodiment 56

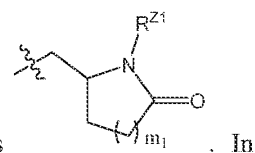
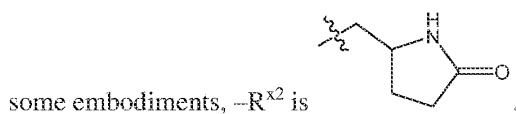
[0130] The compound of Embodiment 55, wherein R^{m1} is wherein R^{m1} can be

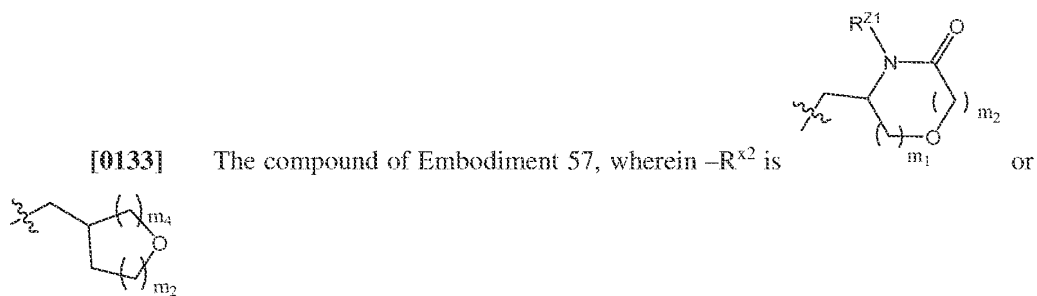
Embodiment 57

[0131] The compound of any one of Embodiments 39-50, wherein R^{m1} is $-R^{x2}$.

Embodiment 58

[0132] The compound of Embodiment 57, wherein $-R^{x2}$ is

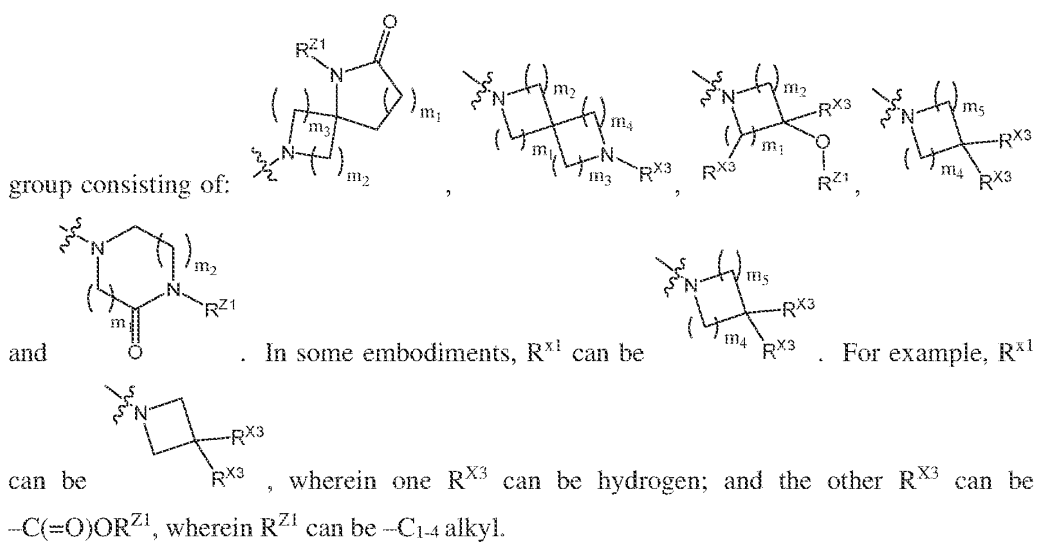


Embodiment 59Embodiment 60

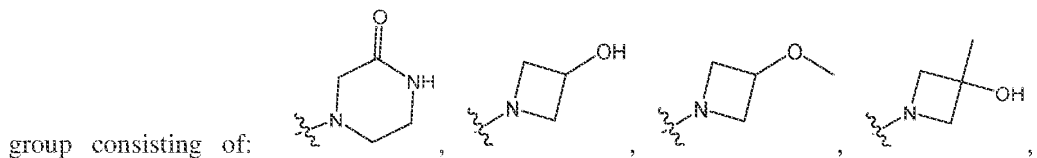
[0134] The compound of any one of Embodiments 39-47, wherein R^{1b} is $-R^{x1}$.

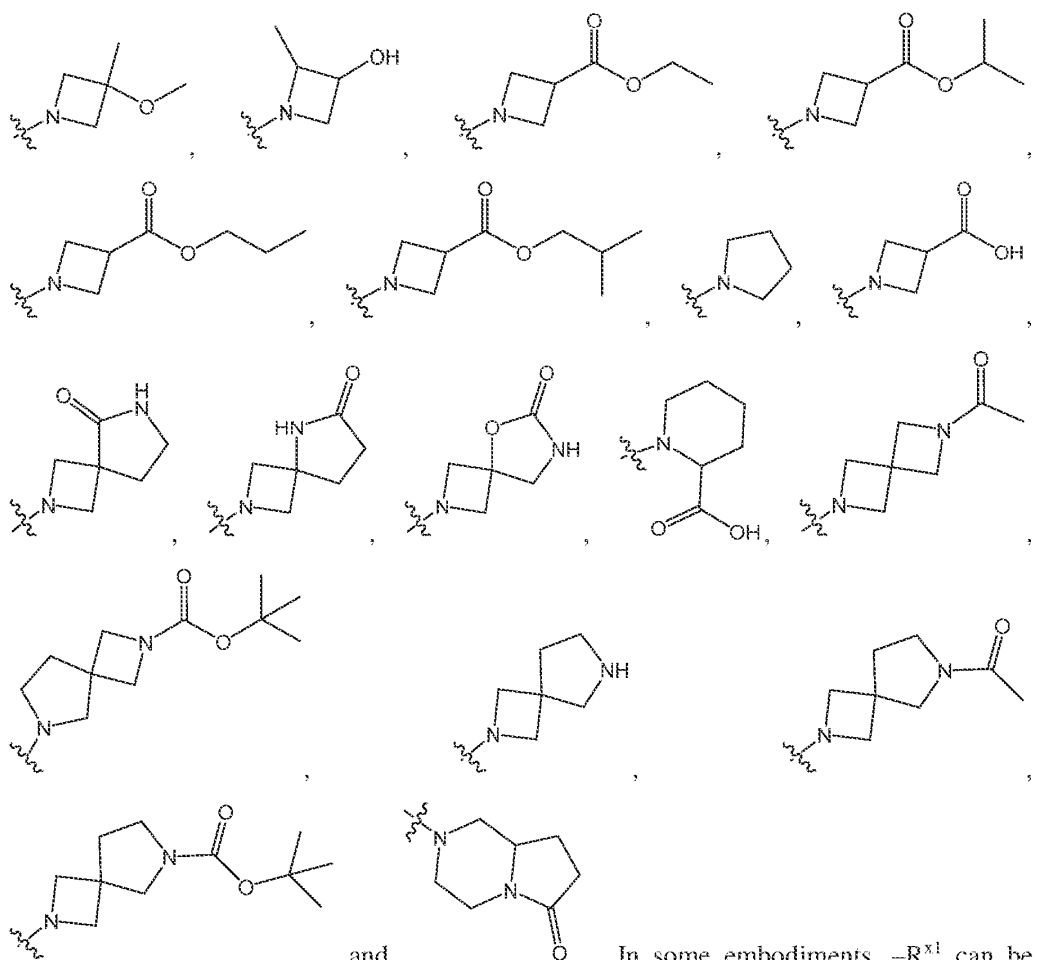
Embodiment 61

[0135] The compound of Embodiment 60, wherein $-R^{x1}$ is selected from the

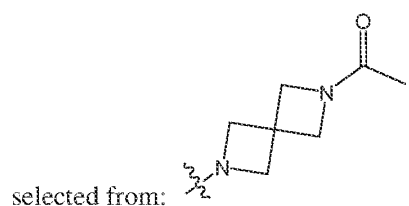
Embodiment 62

[0136] The compound of Embodiment 61, wherein $-R^{x1}$ is selected from the





In some embodiments, $-R^{x1}$ can be



Embodiment 63

[0137] The compound of any one of Embodiments 39-62, wherein R^{1d} is hydrogen.

Embodiment 64

[0138] The compound of any one of Embodiments 39-62, wherein R^{1d} is $-OH$.

Embodiment 65

[0139] The compound of any one of Embodiments 39-62, wherein R^{1d} is $-\text{CH}_3$.

Embodiment 66

[0140] The compound of any one of Embodiments 39-62, wherein R^{1d} is $-\text{F}$.

Embodiment 67

[0141] The compound of any one of Embodiments 63-66, wherein R^{1e} is hydrogen.

Embodiment 68

[0142] The compound of any one of Embodiments 63-66, wherein R^{1e} is $-\text{CH}_3$.

Embodiment 69

[0143] The compound of any one of Embodiments 63-68, wherein R^{1f} is hydrogen.

Embodiment 70

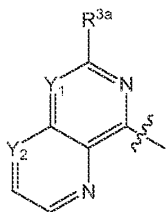
[0144] The compound of any one of Embodiments 63-68, wherein R^{1f} is $-\text{CH}_3$.

Embodiment 71

[0145] The compound of any one of Embodiments 63-70, wherein R^{1g} is hydrogen.

Embodiment 72

[0146] The compound of any one of Embodiments 1-71, wherein B^1 can be

Embodiment 73

[0147] The compound of Embodiment 72, wherein Y^1 can be N (nitrogen).

Embodiment 74

[0148] The compound of Embodiment 72, wherein Y^1 can be CH.

Embodiment 75

[0149] The compound of any one of Embodiments 72-74, wherein Y^2 can be N (nitrogen).

Embodiment 76

[0150] The compound of any one of Embodiments 72-74, wherein Y^2 is CH.

Embodiment 77

[0151] The compound of any one of Embodiments 72-76, wherein R^{3a} can be H (hydrogen).

Embodiment 78

[0152] The compound of any one of Embodiments 72-76, wherein R^{3a} can be $-CH_3$.

Embodiment 79

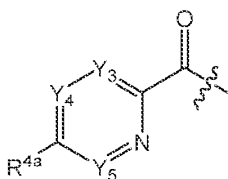
[0153] The compound of any one of Embodiments 72-76, wherein R^{3a} can be $-CF_3$.

Embodiment 80

[0154] The compound of any one of Embodiments 72-76, wherein R^{3a} can be $-CHF_2$.

Embodiment 81

[0155] The compound of any one of Embodiments 1-71, wherein B^1 can be

Embodiment 82

[0156] The compound of Embodiment 81, wherein Y^3 can be N (nitrogen).

Embodiment 83

[0157] The compound of Embodiment 81, wherein Y^3 can be CH.

Embodiment 84

[0158] The compound of any one of Embodiments 81-83, wherein Y^4 can be N (nitrogen).

Embodiment 84

[0159] The compound of any one of Embodiments 81-83, wherein Y^4 can be CH.

Embodiment 86

[0160] The compound of any one of Embodiments 81-85, wherein Y^5 can be N (nitrogen).

Embodiment 87

[0161] The compound of any one of Embodiments 81-85, wherein Y^5 can be CH.

Embodiment 88

[0162] The compound of any one of Embodiments 81-85, wherein Y^5 can be C-OCH₃.

Embodiment 89

[0163] The compound of any one of Embodiments 81-88, wherein R^{4a} can be H (hydrogen).

Embodiment 90

[0164] The compound of any one of Embodiments 81-88, wherein R^{4a} can be halogen. In some embodiments, R^{4a} can be fluoro. In other embodiments, R^{4a} can be chloro.

Embodiment 91

[0165] The compound of any one of Embodiments 81-88, wherein R^{4a} can be -C₁₋₄ alkyl, such as methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl and tert-butyl.

Embodiment 92

[0166] The compound of any one of Embodiments 81-88, wherein R^{4a} can be -C₁₋₄ haloalkyl. For example, R^{4a} can be selected from -CF₃, -CHF₂, -CH₂F, -CCl₃, -CHCl₂, -CH₂Cl, -CH₂CF₃ or -CH₂CHF₂.

Embodiment 93

[0167] The compound of any one of Embodiments 81-88, wherein R^{4a} can be -CH₂R^{4b}.

Embodiment 94

[0168] The compound of any one of Embodiments 81-88, wherein R^{4a} can be -C(CH₃)R^{4b}.

Embodiment 95

[0169] The compound of Embodiment 93 or 94, wherein R^{4b} can be -N(R^{m2})Rⁿ².

Embodiment 96

[0170] The compound of Embodiment 95, wherein R^{m2} can be $-CH_3$.

Embodiment 97

[0171] The compound of Embodiment 95, wherein R^{m2} can be $-C_{2-4}$ alkyl, such as ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl and tert-butyl.

Embodiment 98

[0172] The compound of Embodiment 95, wherein R^{m2} can be $-C_{1-4}$ haloalkyl. In some embodiments, R^{m2} can be selected from $-CF_3$, $-CHF_2$, $-CH_2F$, $-CCl_3$, $-CHCl_2$, $-CH_2Cl$, $-CH_2CF_3$ and $-CH_2CHF_2$.

Embodiment 99

[0173] The compound of Embodiment 95, wherein R^{m2} can be $-C_{2-4}$ alkyl substituted with hydroxy. Examples of suitable C_{2-4} alkyls include ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl and tert-butyl.

Embodiment 100

[0174] The compound of any one of Embodiments 95-99, wherein R^{n2} can be H (hydrogen).

Embodiment 101

[0175] The compound of any one of Embodiments 95-99, wherein R^{n2} can be $-C_{1-4}$ alkyl. For example, R^{n2} can be methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl or tert-butyl.

Embodiment 102

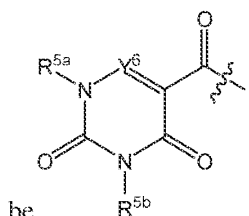
[0176] The compound of any one of Embodiments 95-99, wherein R^{n2} can be $-C_{1-4}$ haloalkyl. For example, R^{n2} can be $-CF_3$, $-CHF_2$, $-CH_2F$, $-CCl_3$, $-CHCl_2$, $-CH_2Cl$, $-CH_2CF_3$ or $-CH_2CHF_2$.

Embodiment 103

[0177] The compound of Embodiment 93 or 94, wherein R^{4b} can be $-R^{y1}$.

Embodiment 104

[0178] The compound of any one of Embodiments 1-71, wherein B¹ can

Embodiment 105

[0179] The compound of Embodiment 104, R^{5a} can be hydrogen.

Embodiment 106

[0180] The compound of Embodiment 104, R^{5a} can be -CH₃.

Embodiment 107

[0181] The compound of Embodiment 104, R^{5a} can be -C₂₋₄ alkyl. Exemplary C₂₋₄ alkyls include ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl and tert-butyl.

Embodiment 108

[0182] The compound of Embodiment 104, R^{5a} can be -C₂₋₄ haloalkyl. Suitable C₂₋₄ haloalkyls include, but are not limited to, -CH₂CF₃, -CH₂CHF₂, -CH₂CH₂CF₃, -CH₂CH₂CHF₂, -CH₂CH₂CH₂CF₃ and -CH₂CH₂CH₂CHF₂.

Embodiment 109

[0183] The compound of any one of Embodiments 104-108, wherein R^{5b} is hydrogen.

Embodiment 110

[0184] The compound of any one of Embodiments 104-108, wherein R^{5b} can be -CH₃.

Embodiment 111

[0185] The compound of any one of Embodiments 104-108, wherein R^{5b} can be -C₂₋₄ alkyl, such as ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl and tert-butyl.

Embodiment 112

[0186] The compound of any one of Embodiments 104-108, wherein R^{5b} can be -C₂₋₄ haloalkyl. Exemplary C₂₋₄ haloalkyls include, but are not limited to, -CH₂CF₃, -CH₂CHF₂, -CH₂CH₂CF₃, -CH₂CH₂CHF₂, -CH₂CH₂CH₂CF₃ and -CH₂CH₂CH₂CHF₂.

Embodiment 113

[0187] The compound of any one of Embodiments 104-112, wherein Y^6 can be N (nitrogen).

Embodiment 114

[0188] The compound of any one of Embodiments 104-112, wherein Y^6 can be CR^{5c} .

Embodiment 115

[0189] The compound of Embodiment 114, wherein R^{5c} can be hydrogen.

Embodiment 116

[0190] The compound of Embodiment 114, wherein R^{5c} can be $-CH_3$.

Embodiment 117

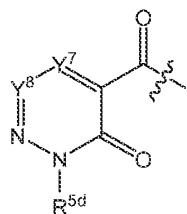
[0191] The compound of Embodiment 114, wherein R^{5c} can be $-C_{2-4}$ alkyl, for example, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl and tert-butyl. .

Embodiment 118

[0192] The compound of Embodiment 114, wherein R^{5c} can be $-C_{2-4}$ haloalkyl. A non-limiting list of C_{2-4} haloalkyls include, but are not limited to, $-CH_2CF_3$, $-CH_2CHF_2$, $-CH_2CH_2CF_3$, $-CH_2CH_2CHF_2$, $-CH_2CH_2CH_2CF_3$ and $-CH_2CH_2CH_2CHF_2$.

Embodiment 119

[0193] The compound of any one of Embodiments 1-71, wherein B^1 can be

Embodiment 120

[0194] The compound of Embodiment 119, wherein R^{5d} can be hydrogen.

Embodiment 121

[0195] The compound of Embodiment 119, wherein R^{5d} can be $-CH_3$.

Embodiment 122

[0196] The compound of Embodiment 119, wherein R^{5d} can be $-C_{2-4}$ alkyl.

Embodiment 123

[0197] The compound of Embodiment 119, wherein R^{5d} can be $-C_{2-4}$ haloalkyl.

Embodiment 124

[0198] The compound of any one of Embodiments 119-123, wherein Y^7 can be CR^{5e} , wherein R^{5e} is hydrogen.

Embodiment 125

[0199] The compound of any one of Embodiments 119-123, wherein Y^7 can be CR^{5e} , wherein R^{5e} is halogen, such as fluoro or chloro.

Embodiment 126

[0200] The compound of any one of Embodiments 119-123, wherein Y^7 can be CR^{5e} , wherein R^{5e} is $-CH_3$.

Embodiment 127

[0201] The compound of any one of Embodiments 119-126, wherein Y^8 can be CR^{5f} , wherein R^{5f} can be hydrogen.

Embodiment 128

[0202] The compound of any one of Embodiments 119-126, wherein Y^8 can be CR^{5f} , wherein R^{5f} can be halogen, such as F, Cl or Br.

Embodiment 129

[0203] The compound of any one of Embodiments 119-126, wherein Y^8 can be CR^{5f} , wherein R^{5f} can be $-OH$.

Embodiment 130

[0204] The compound of any one of Embodiments 119-126, wherein Y^8 can be CR^{5f} , wherein R^{5f} can be CN .

Embodiment 131

[0205] The compound of any one of Embodiments 119-126, wherein Y^8 can be CR^{5f} , wherein R^{5f} can be $-CH_3$.

Embodiment 132

[0206] The compound of any one of Embodiments 1-131, wherein R^{2a} , R^{2b} , R^{2c} , R^{2e} , R^{2g} and R^{2g} can be each hydrogen.

Embodiment 133

[0207] The compound of any one of Embodiments 1-131, wherein R^{2a} , R^{2c} , R^{2e} , R^{2g} and R^{2h} are each hydrogen; and R^{2b} is halogen.

Embodiment 134

[0208] The compound of any one of Embodiments 1-131, wherein R^{2b} , R^{2c} , R^{2e} , R^{2g} and R^{2h} are each hydrogen; and R^{2a} is halogen.

Embodiment 135

[0209] The compound of any one of Embodiments 1-134, wherein R^{2d} and R^{2f} can be each halogen. In some embodiments, R^{2d} and R^{2f} can be each fluoro. In other embodiments, R^{2d} and R^{2f} can be each chloro.

Embodiment 136

[0210] The compound of any one of Embodiments 1-134, wherein R^{2d} and R^{2f} can be each $-\text{CH}_3$.

Embodiment 137

[0211] The compound of any one of Embodiments 1-134, wherein R^{2d} can be halogen; and R^{2f} can be $-\text{CH}_3$.

Embodiment 138

[0212] The compound of any one of Embodiments 1-134, wherein R^{2d} is $-\text{CH}_3$; and R^{2f} is halogen.

Embodiment 139

[0213] The compound of any one of Embodiments 1-134, wherein R^{2d} is cyano; and R^{2f} is halogen.

Embodiment 140

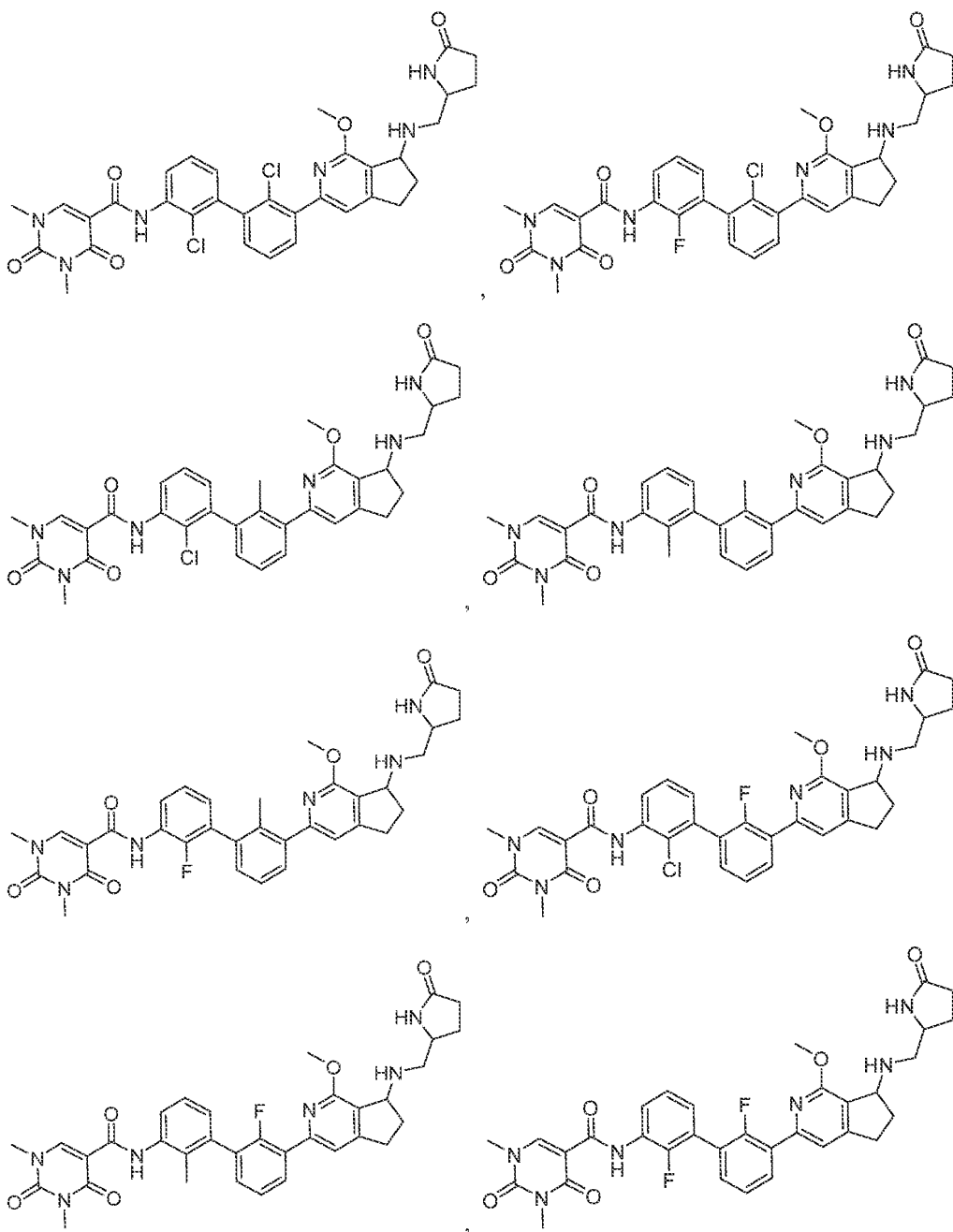
[0214] The compound of any one of Embodiments 1-134, wherein R^{2d} is $-\text{OCH}_3$; and R^{2f} is halogen.

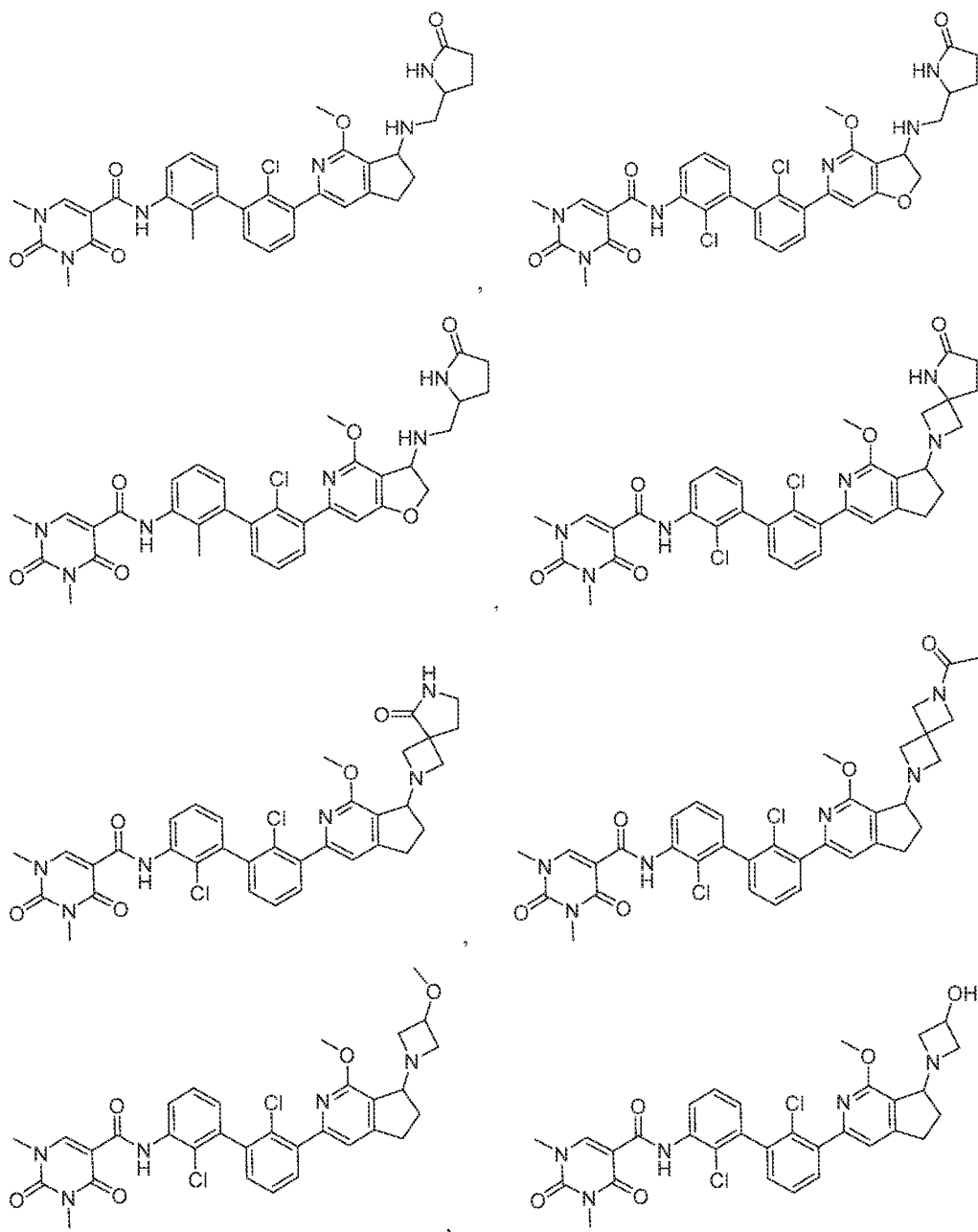
Embodiment 141

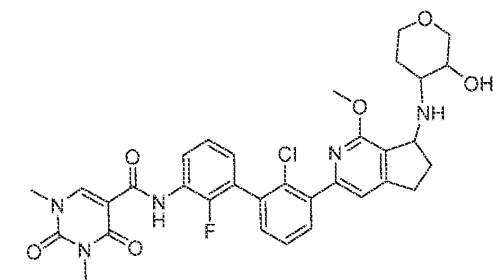
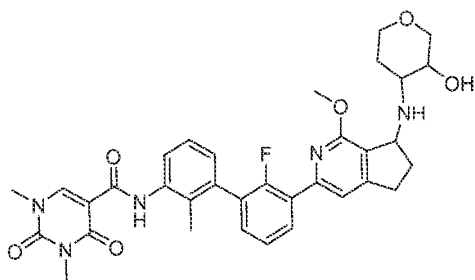
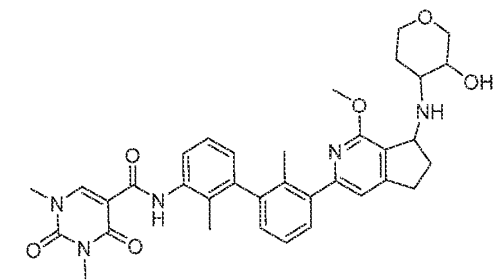
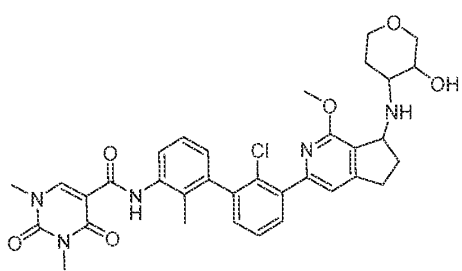
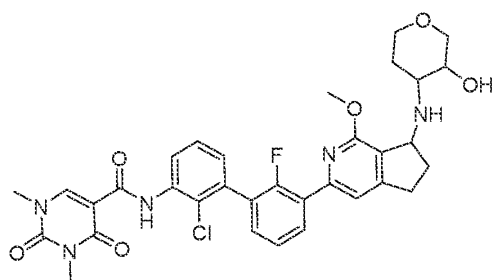
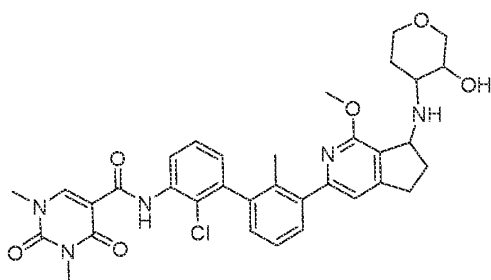
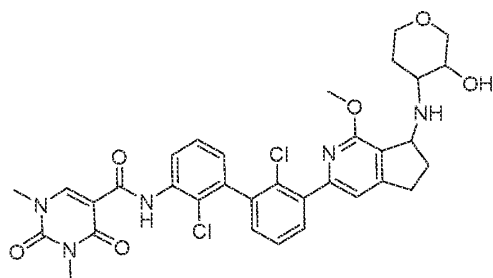
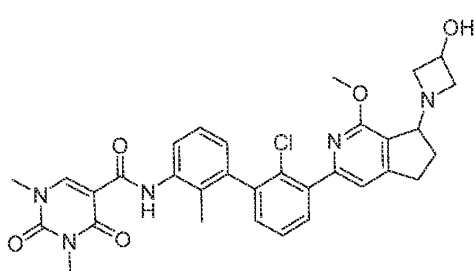
[0215] The compound of any one of Embodiments 133-135 or 137-140, wherein the halogen can be chloro or fluoro.

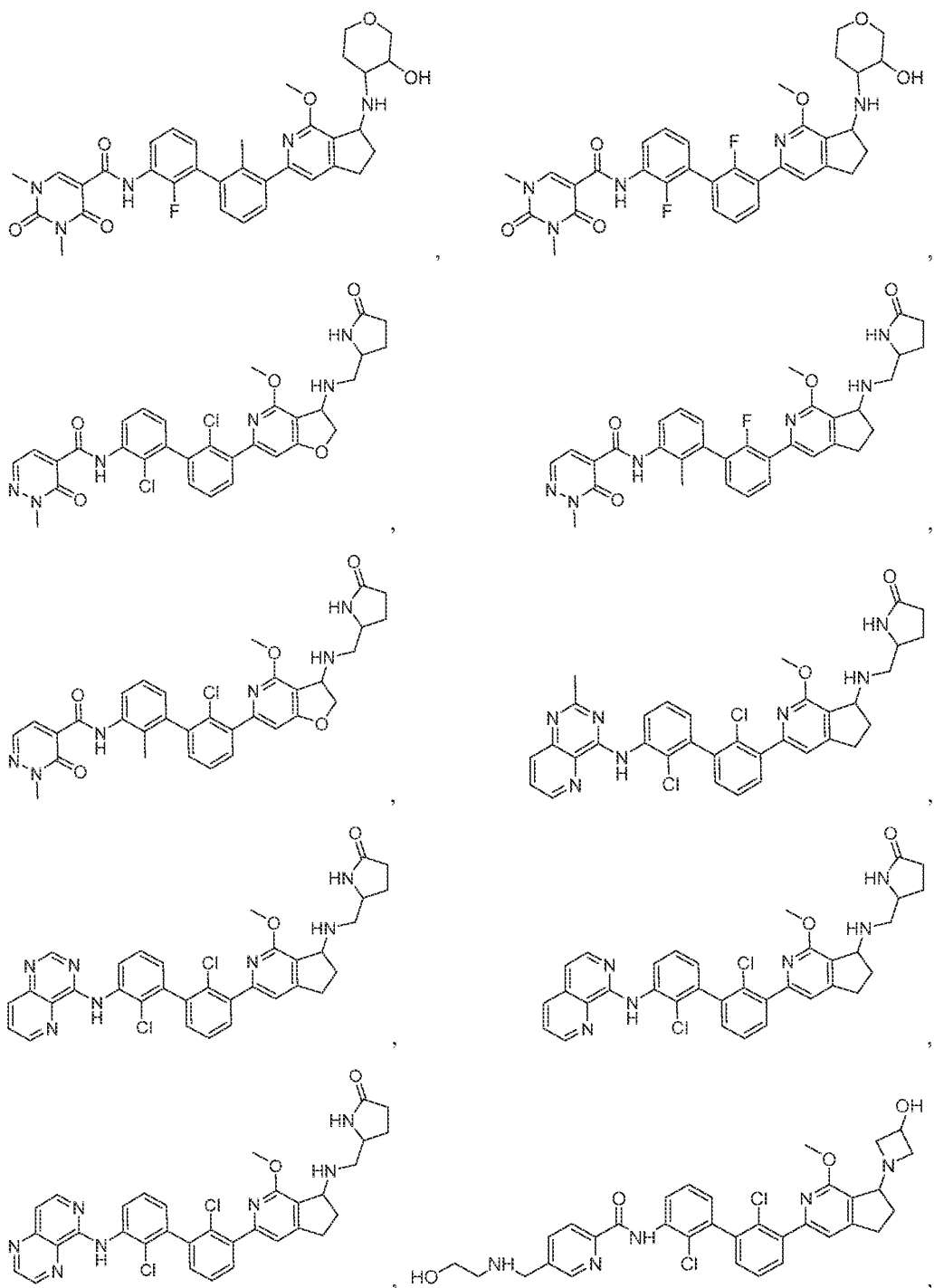
Embodiment 142

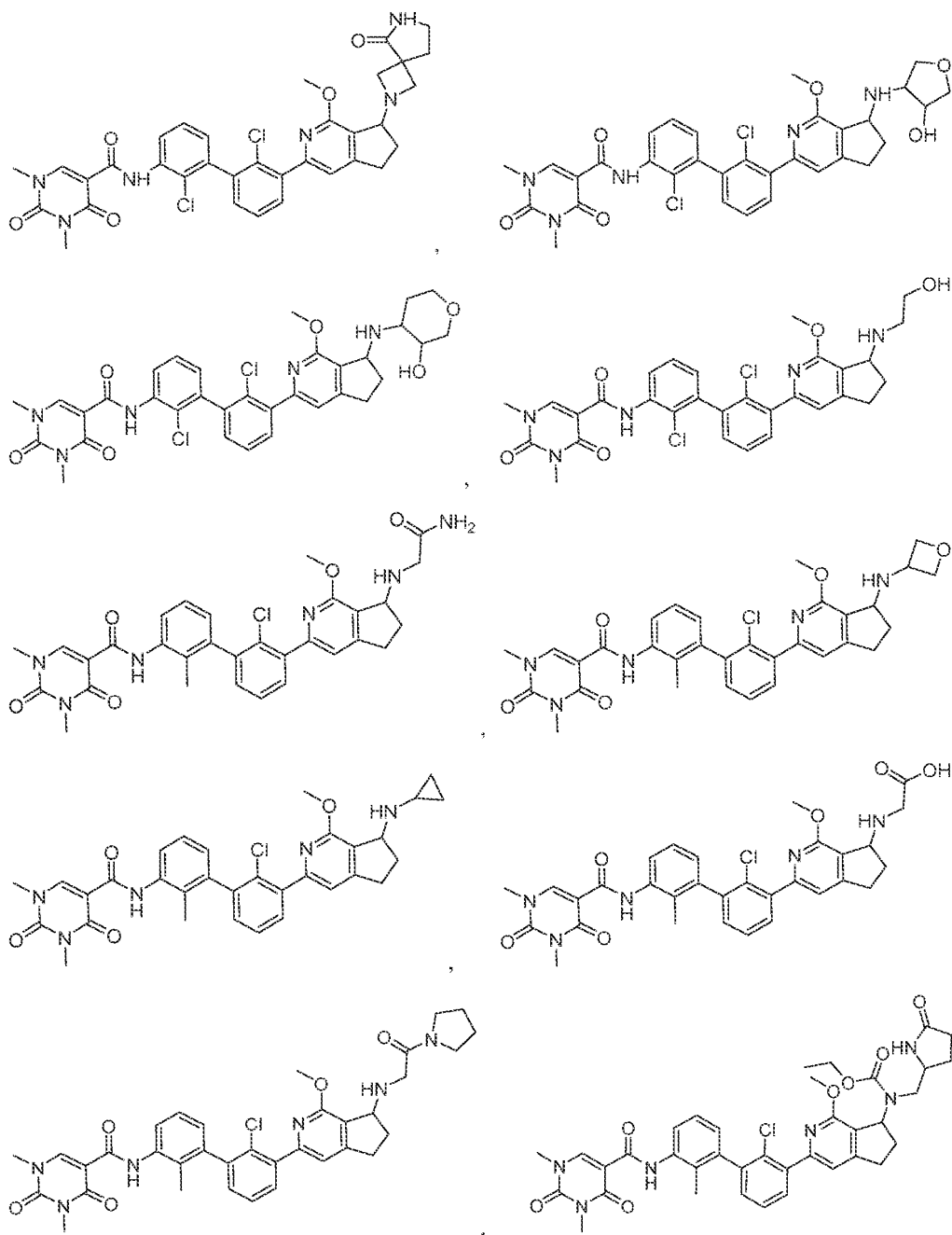
[0216] The compound of Embodiment 1 selected from:

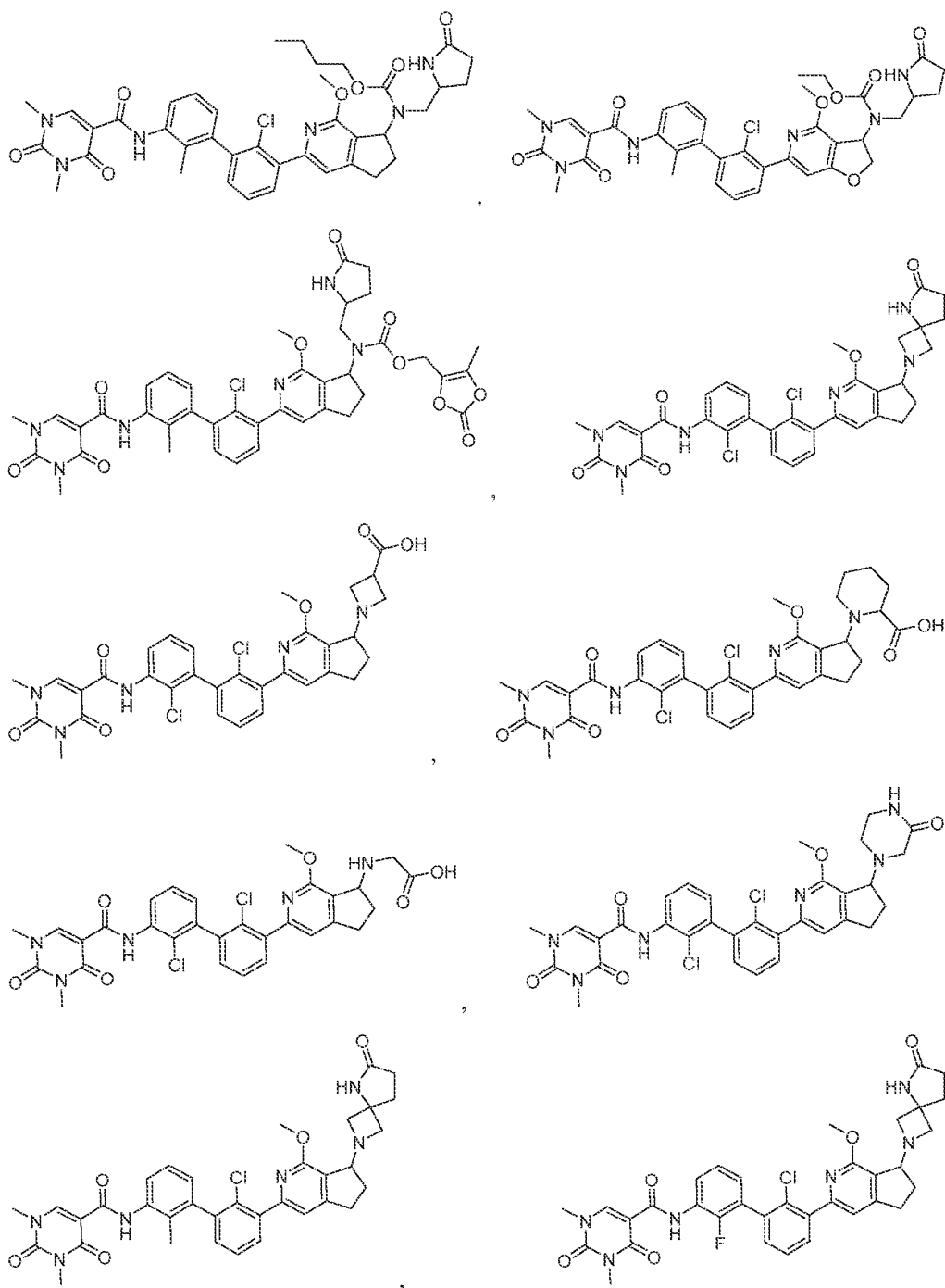


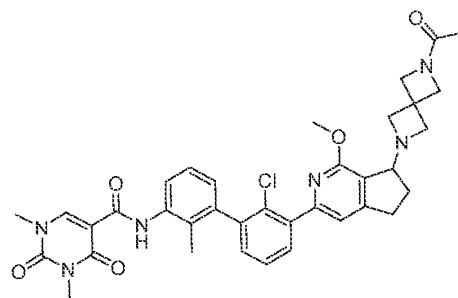
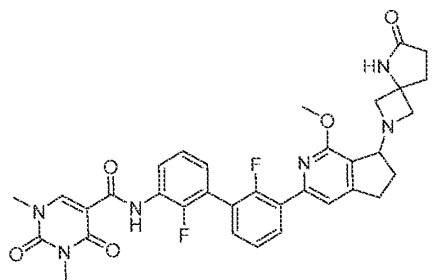
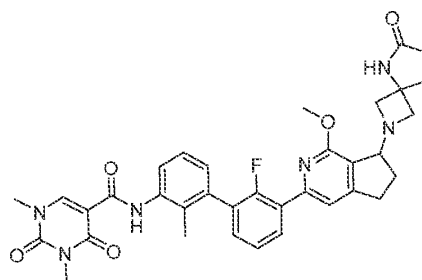
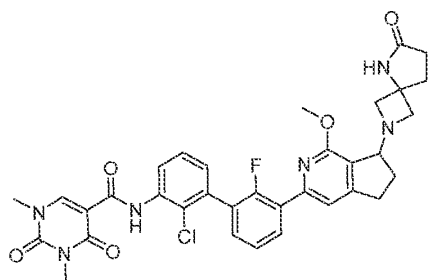
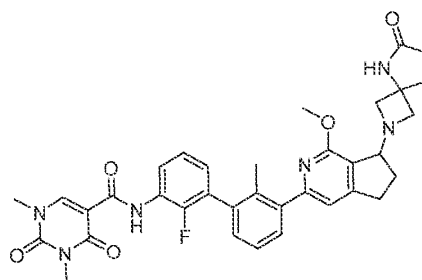
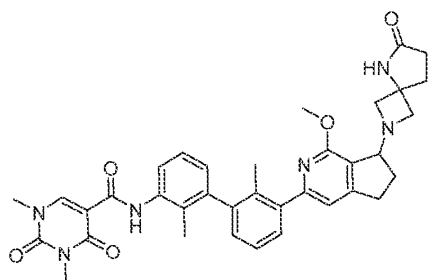
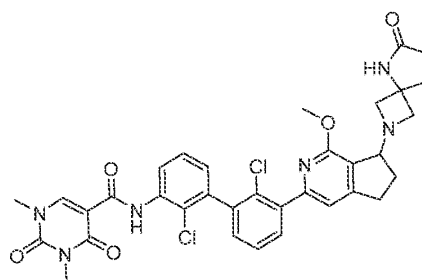
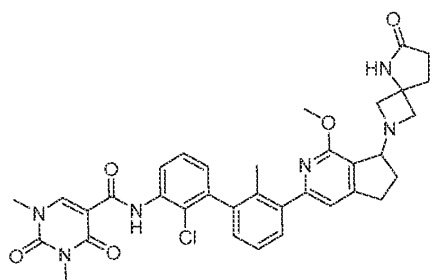


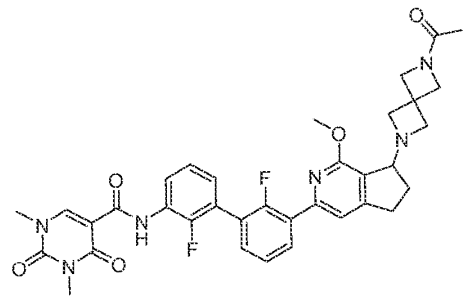
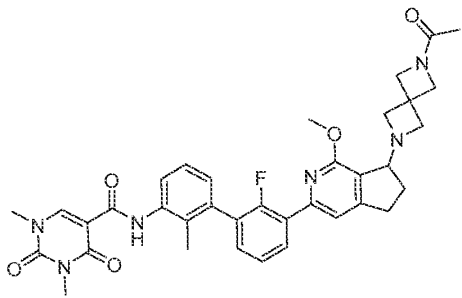
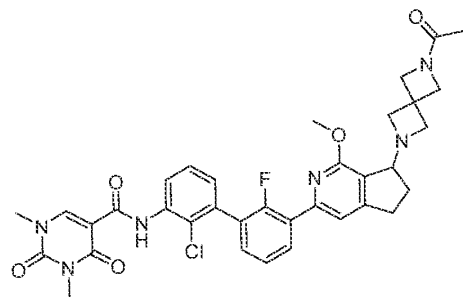
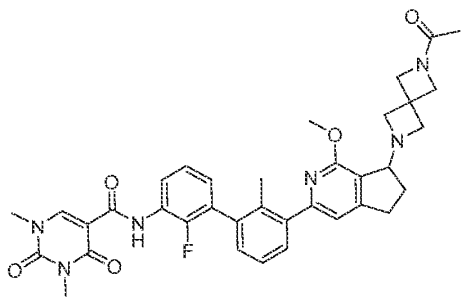
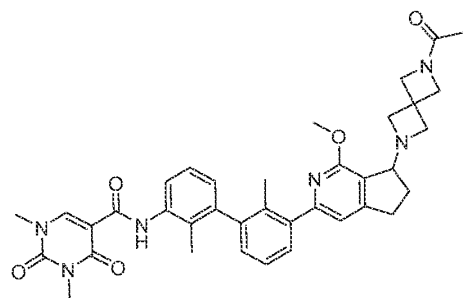
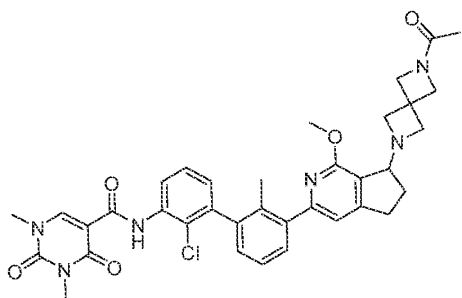
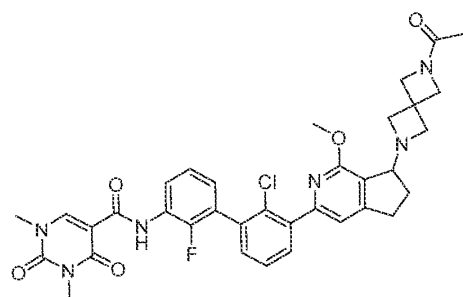
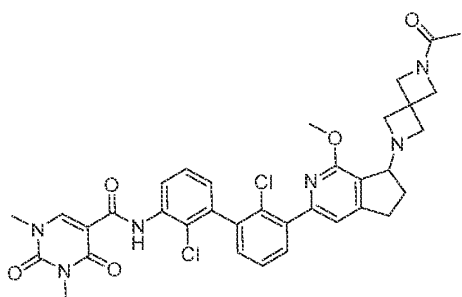


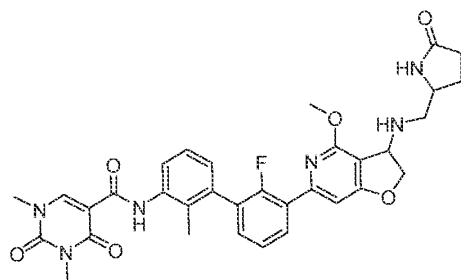
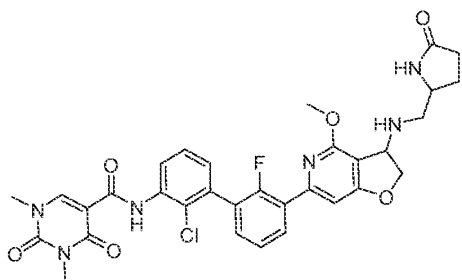
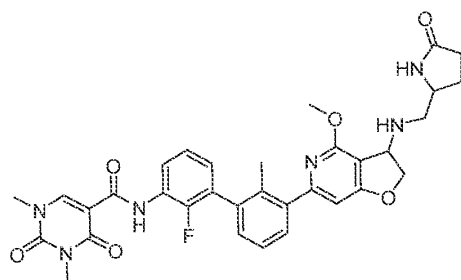
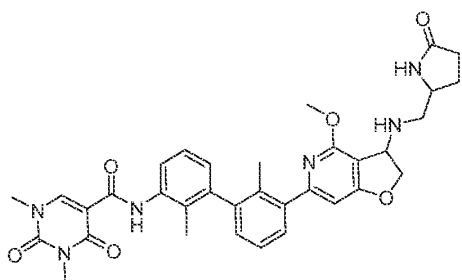
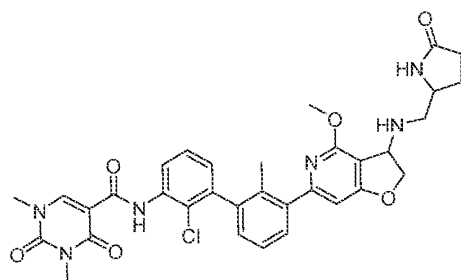
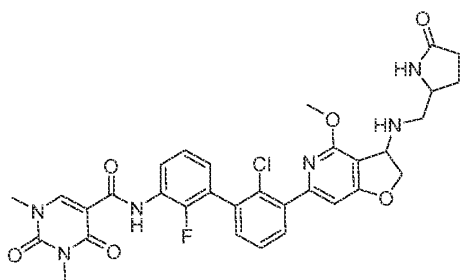
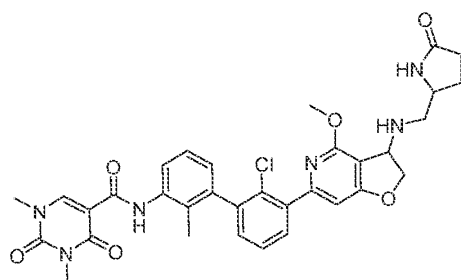
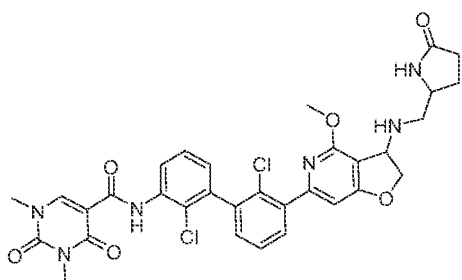


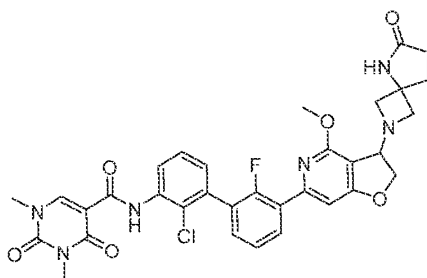
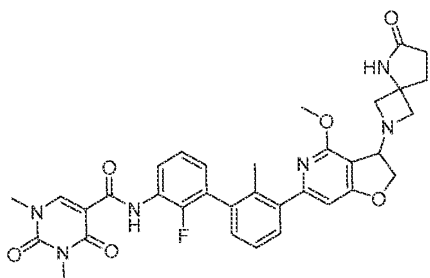
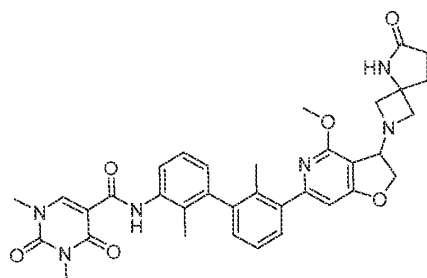
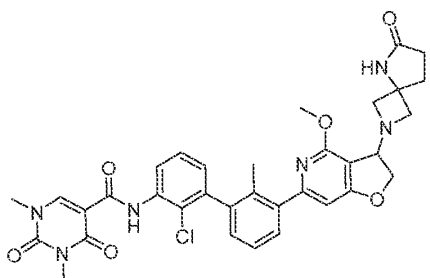
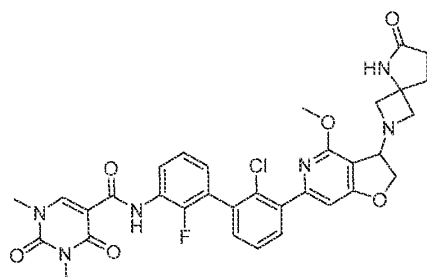
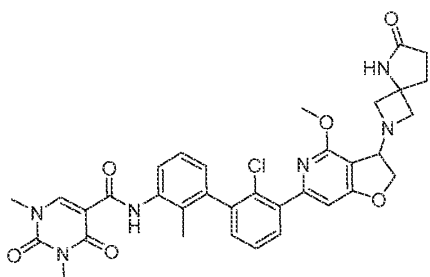
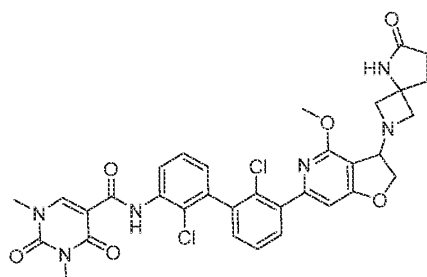
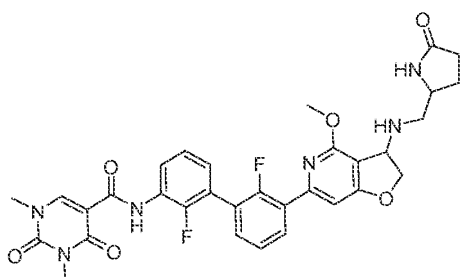


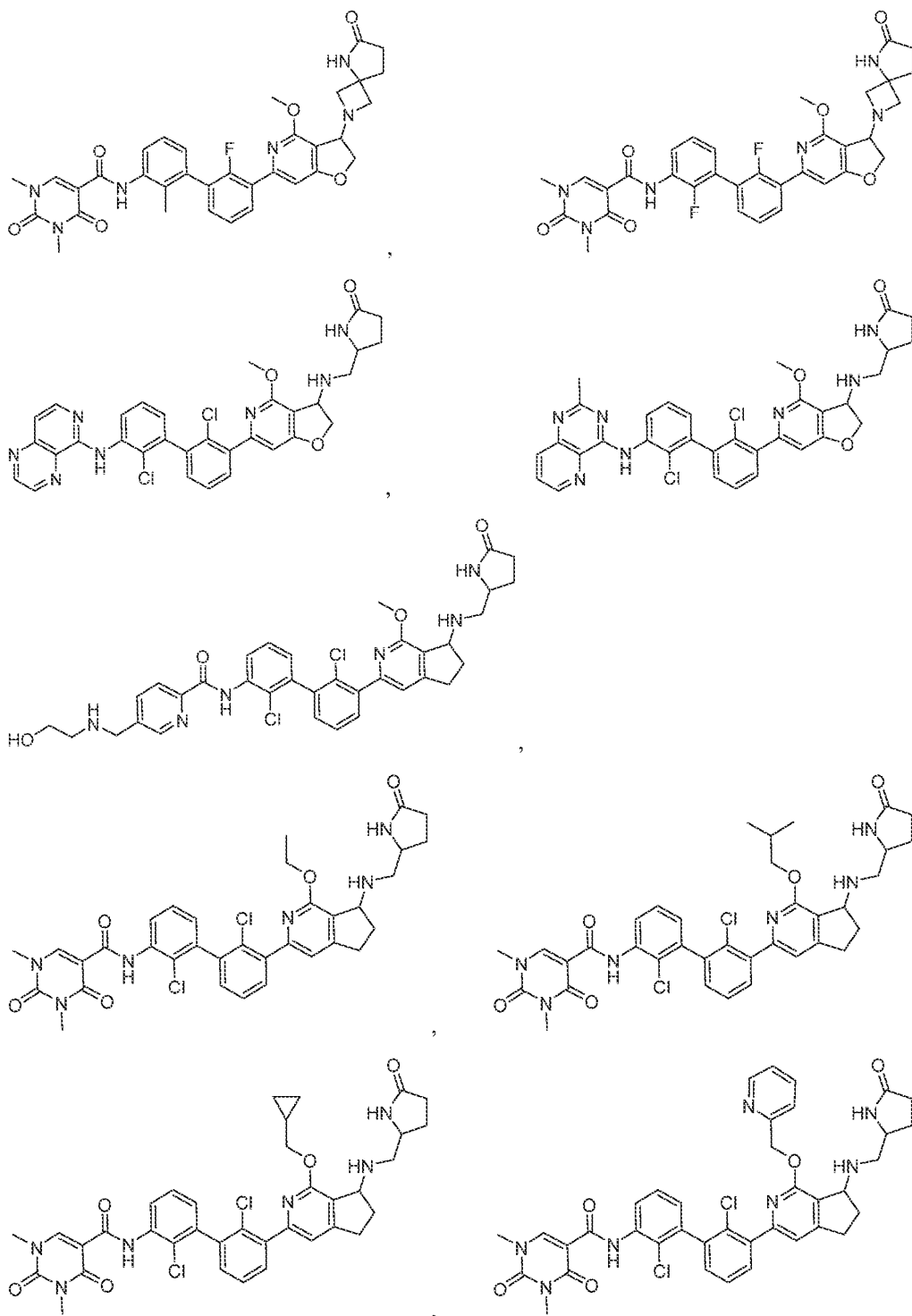


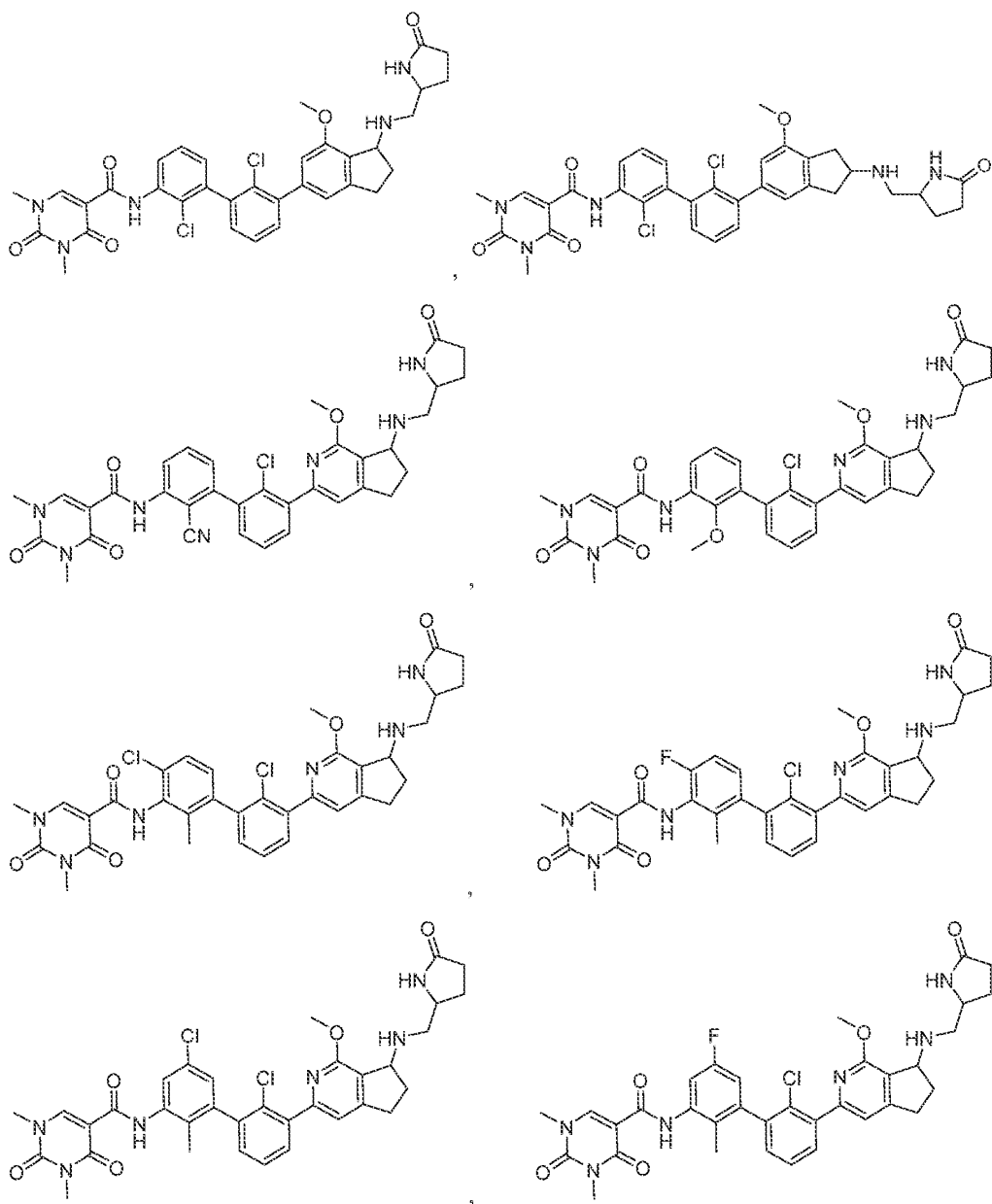


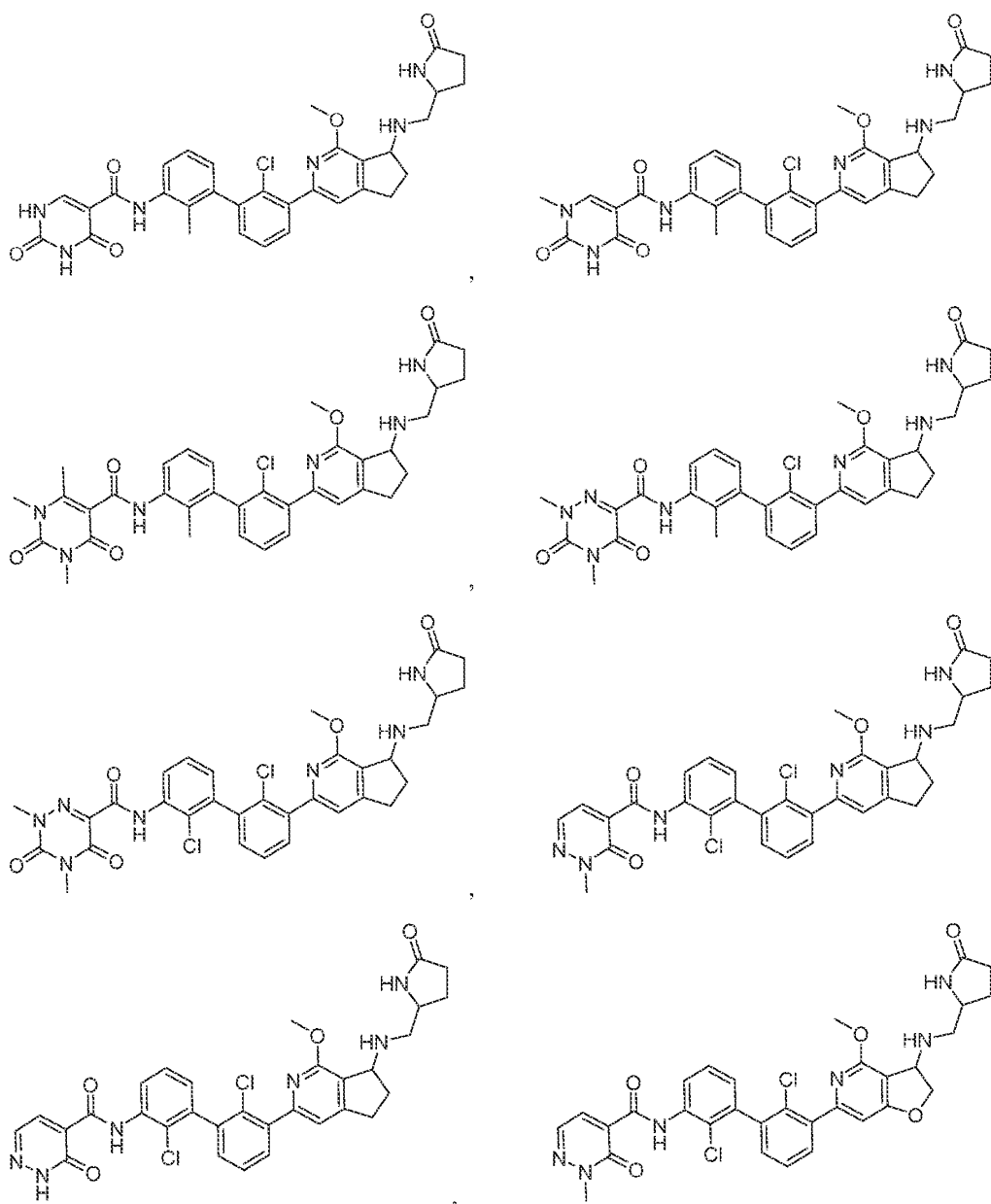


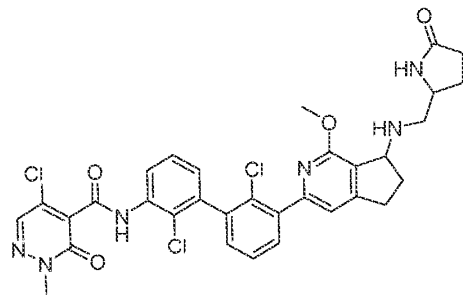
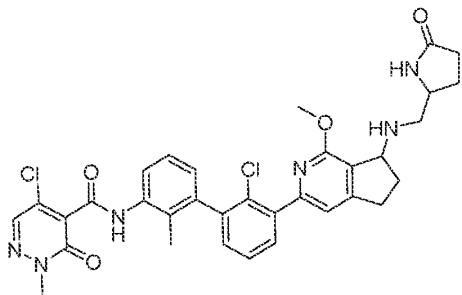
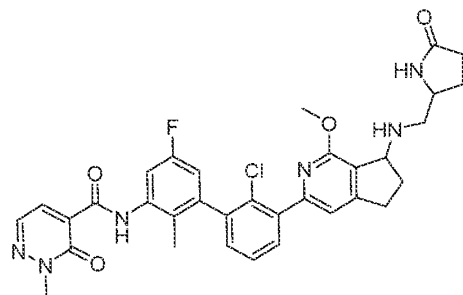
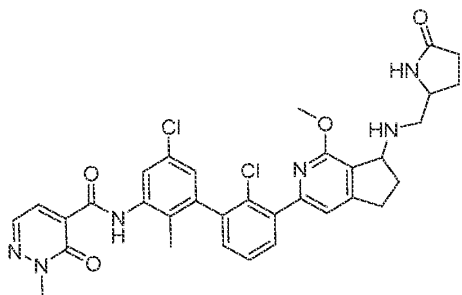
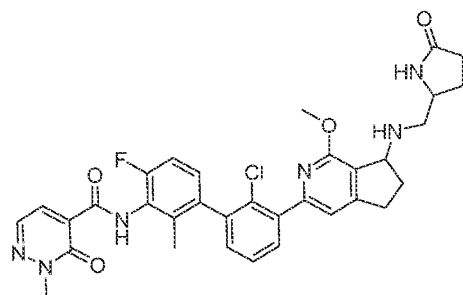
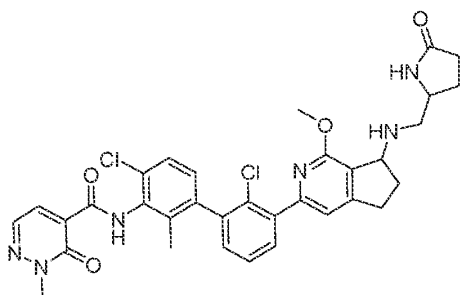
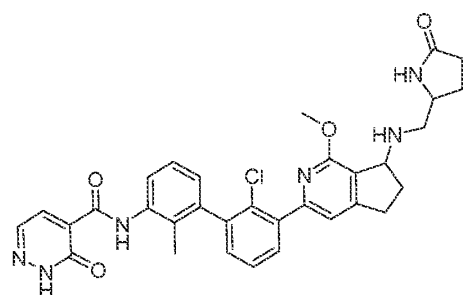
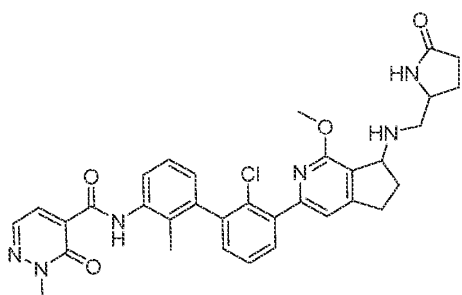


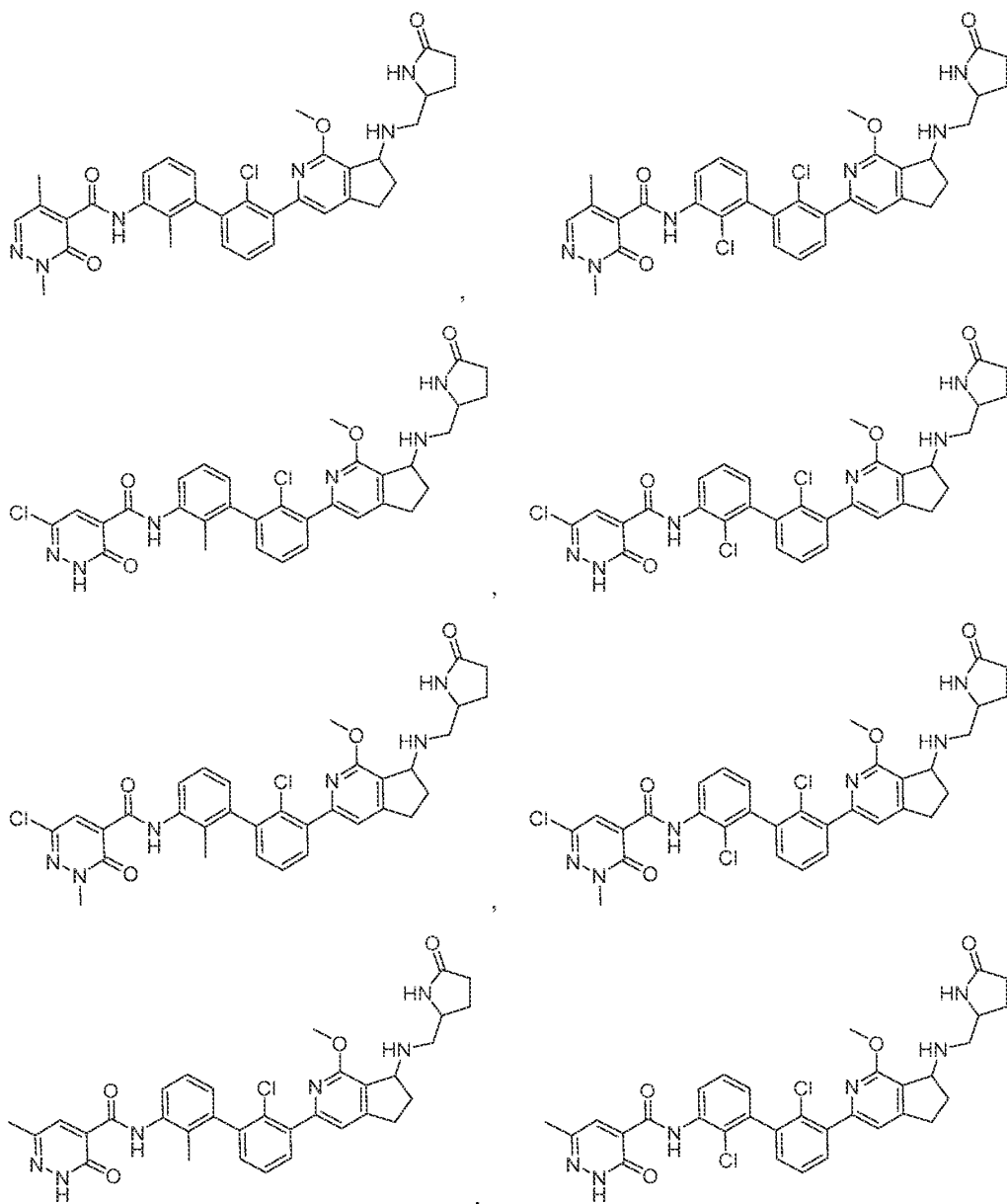


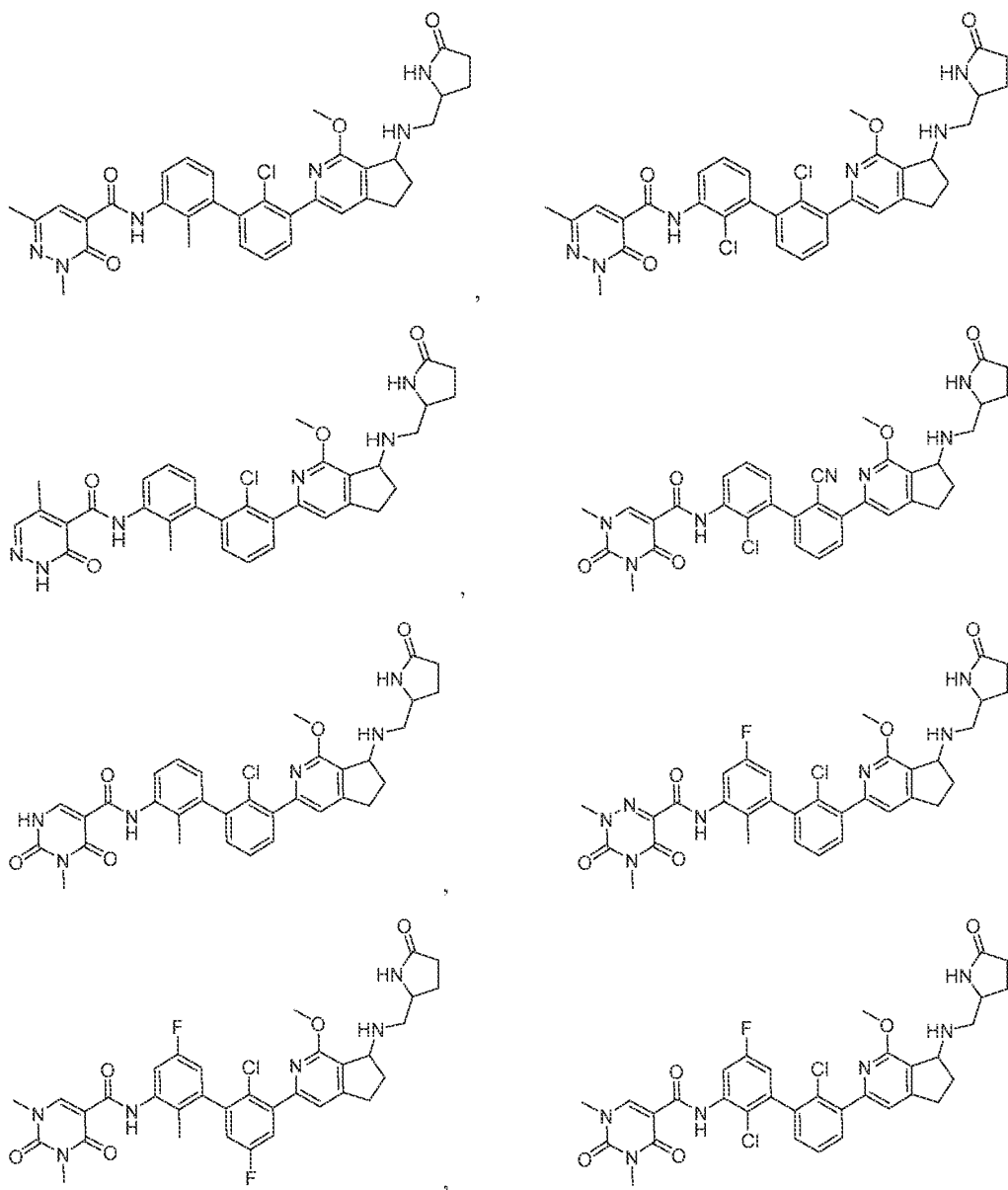


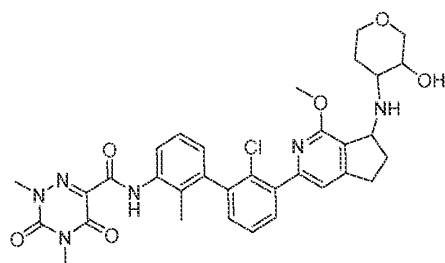
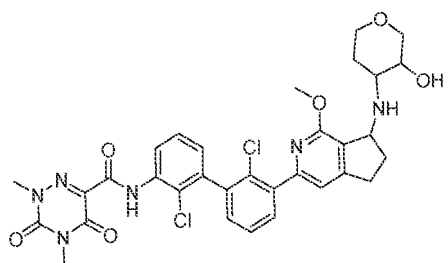
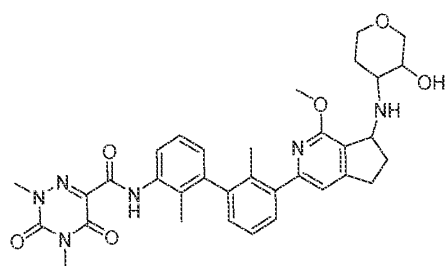
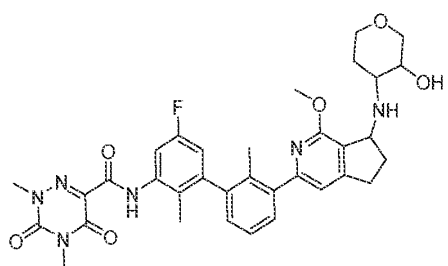
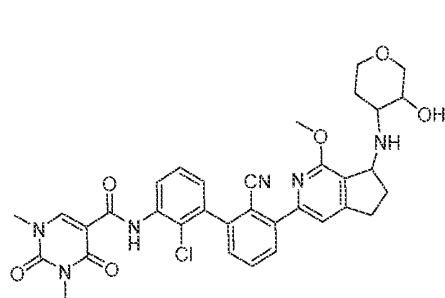
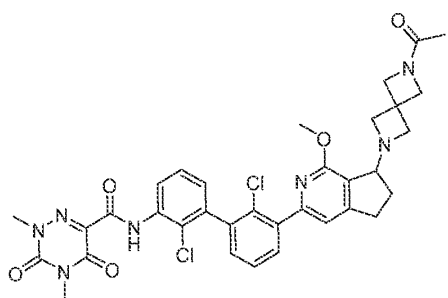
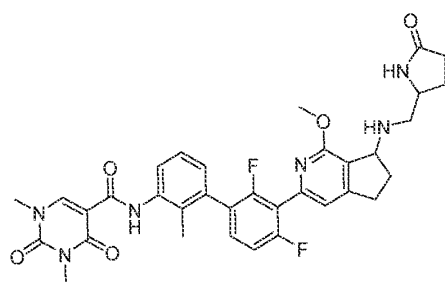
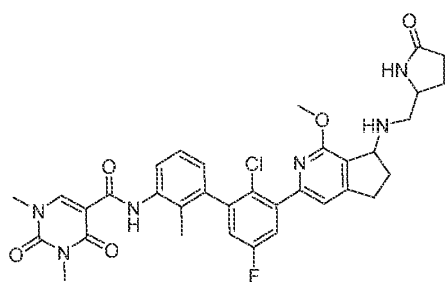
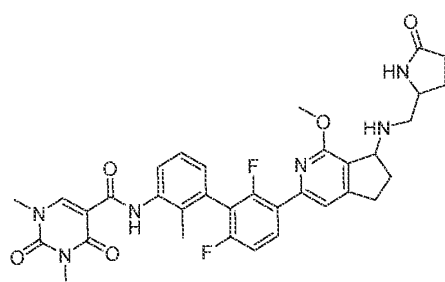
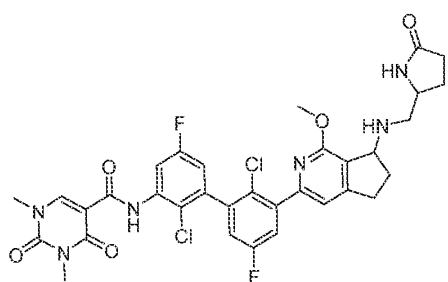


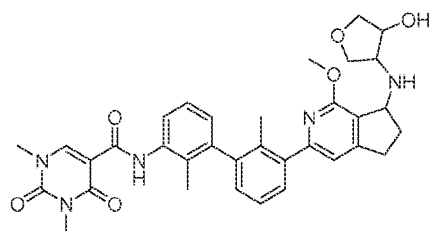
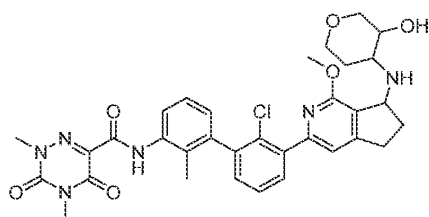
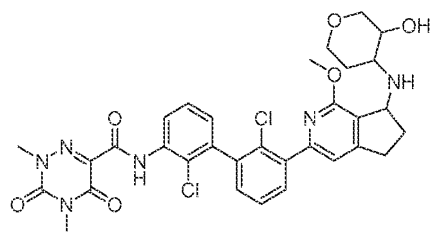
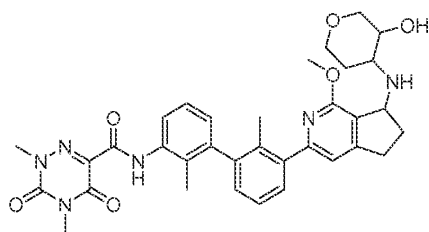
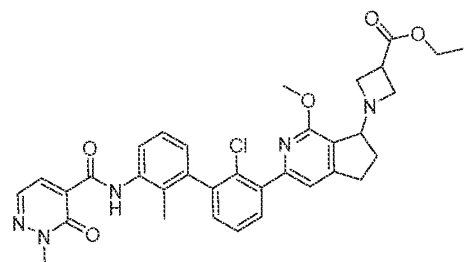
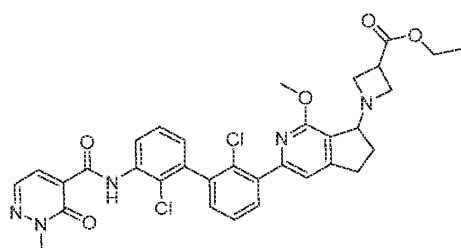
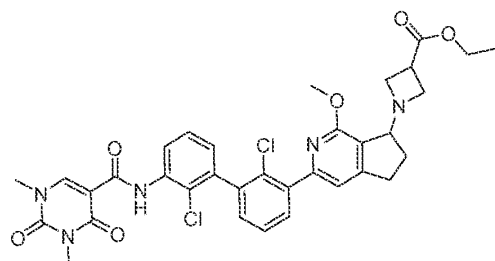
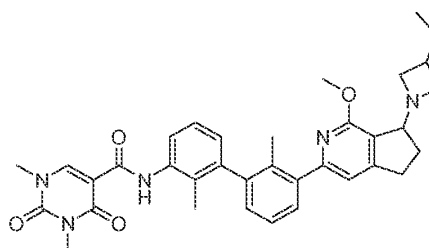
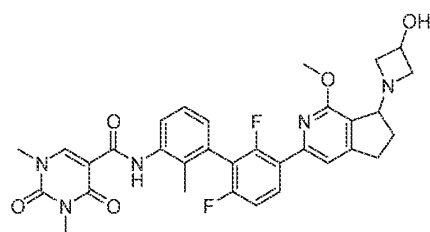
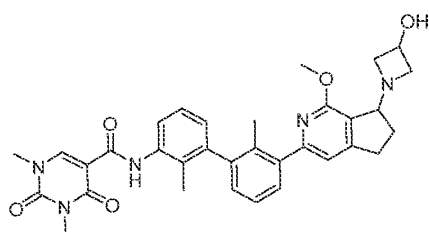


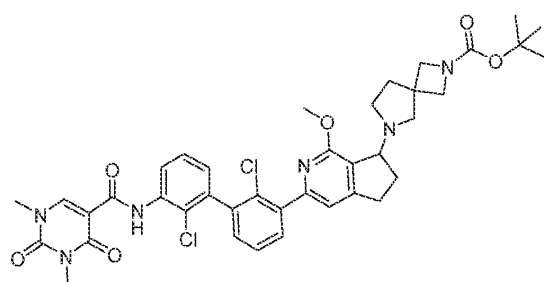
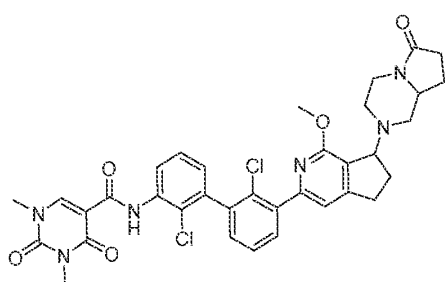
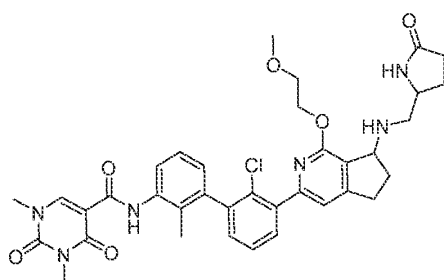
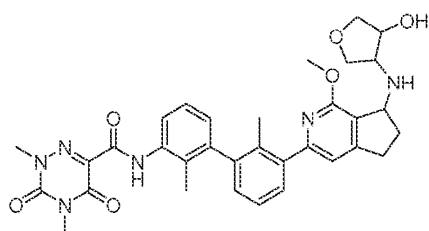
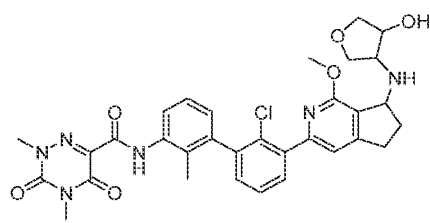
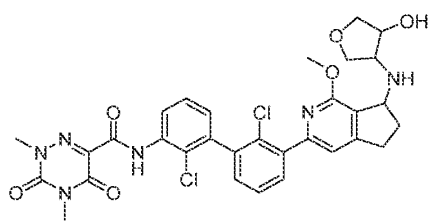
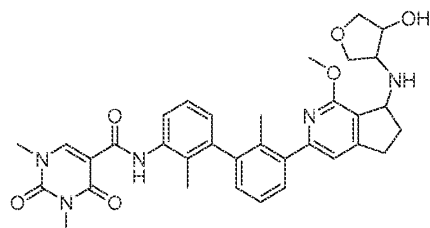
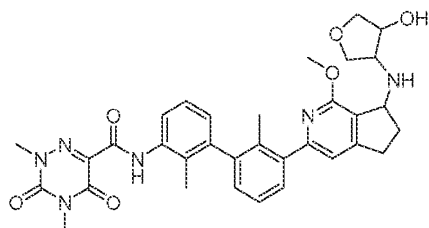
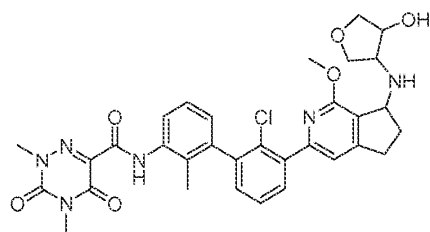
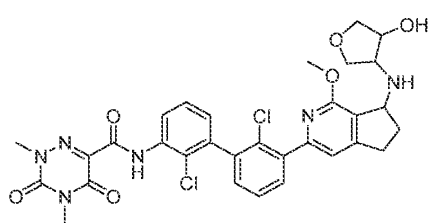


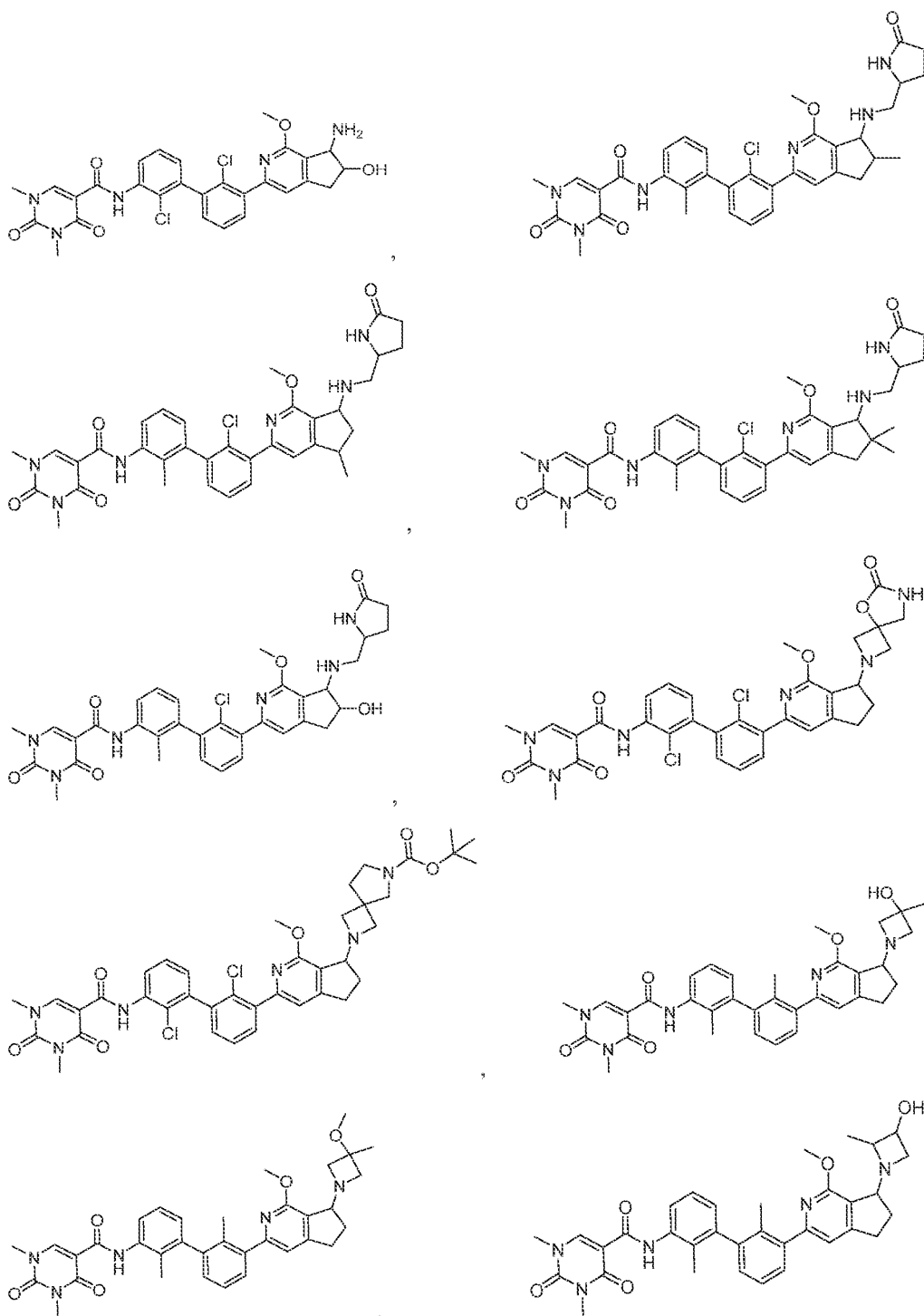


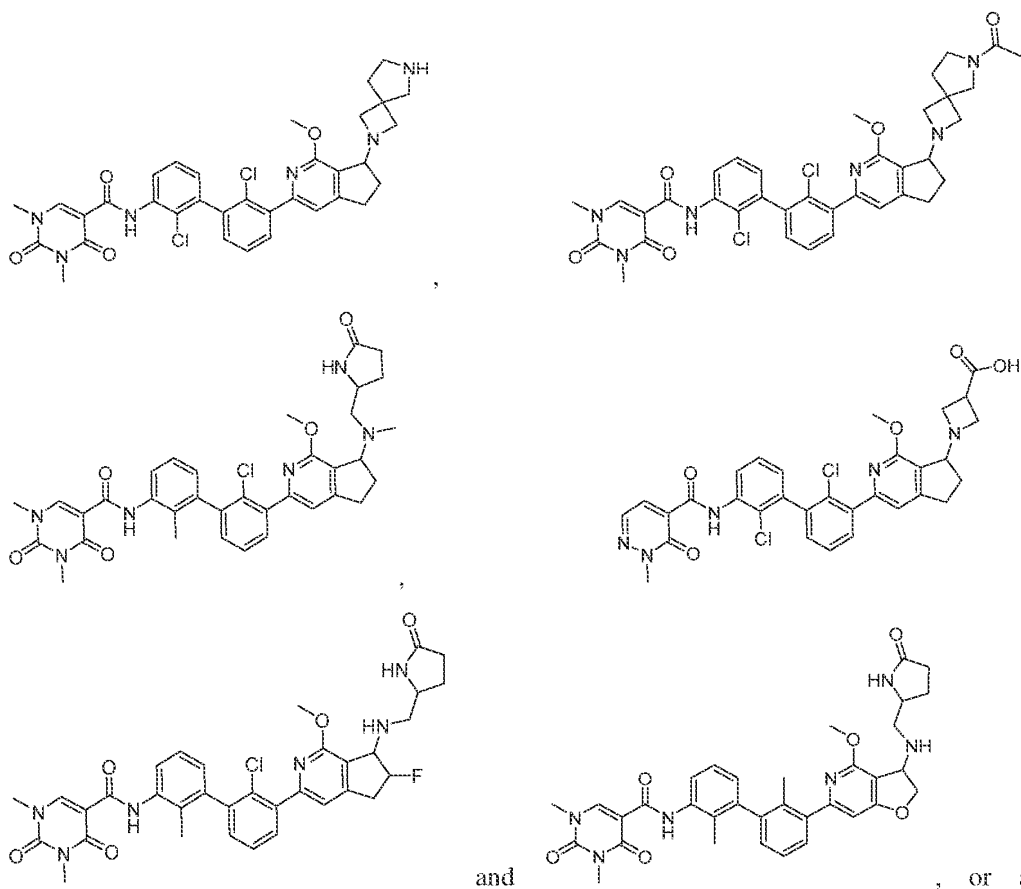








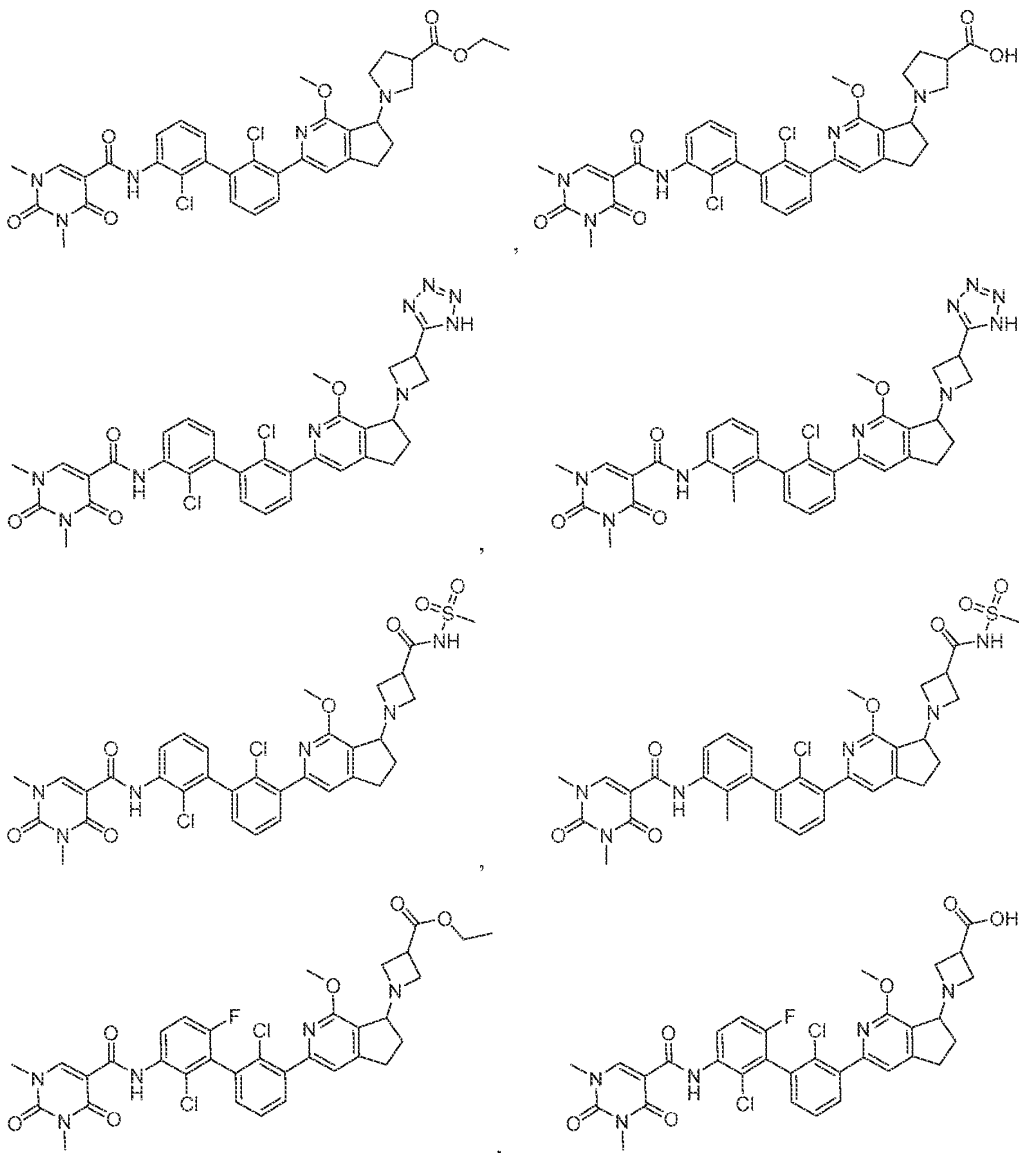


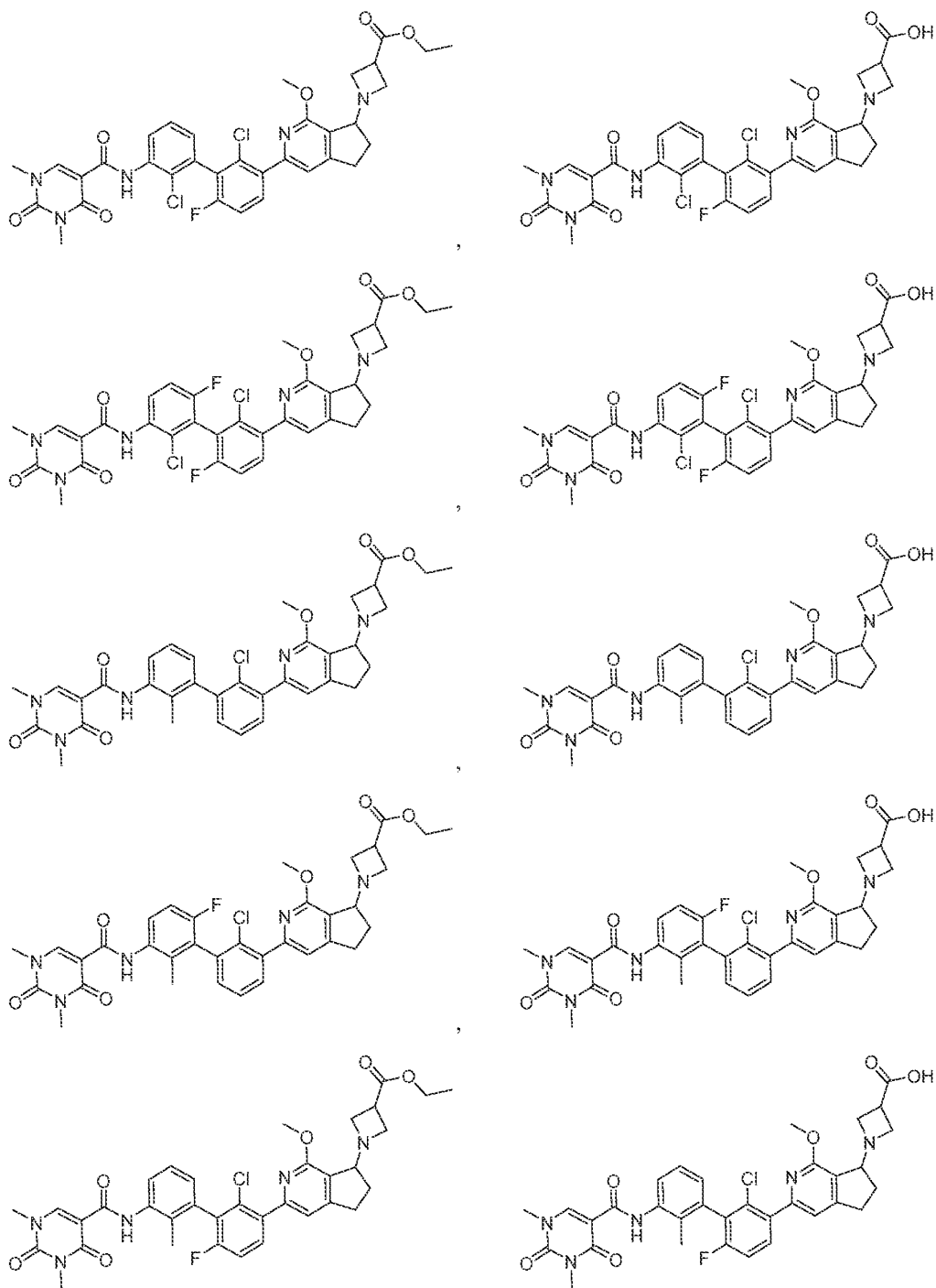


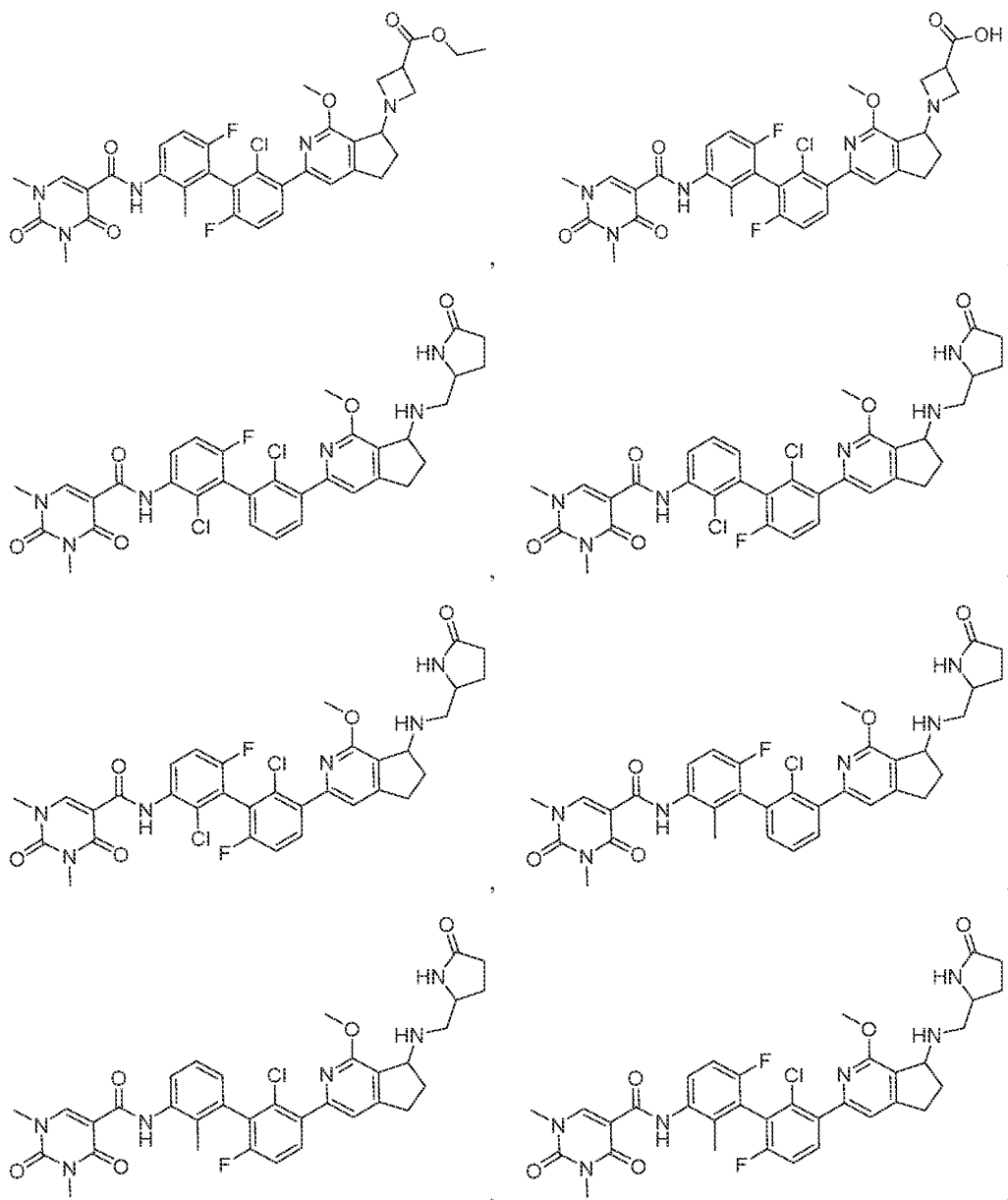
pharmaceutically acceptable salt of any of the foregoing.

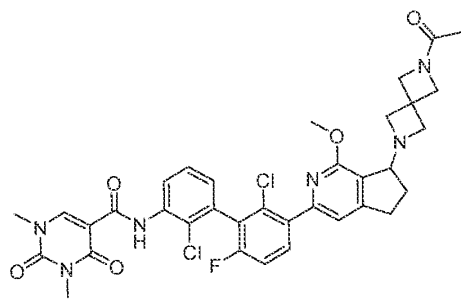
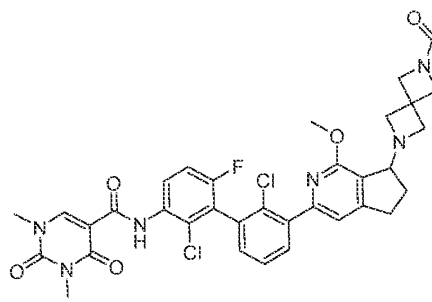
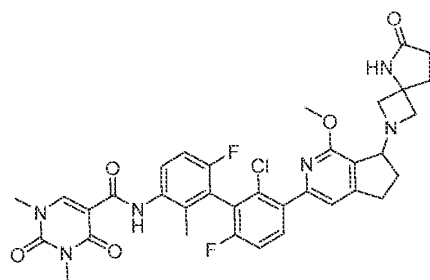
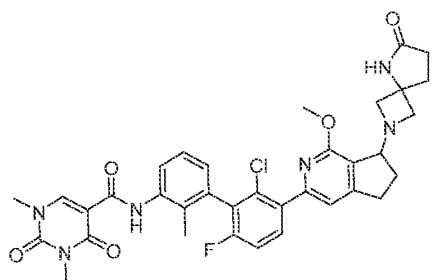
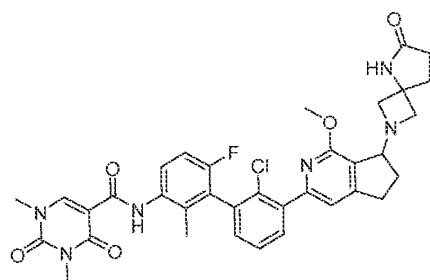
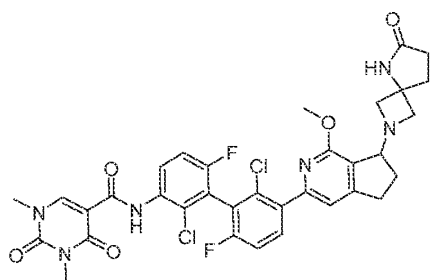
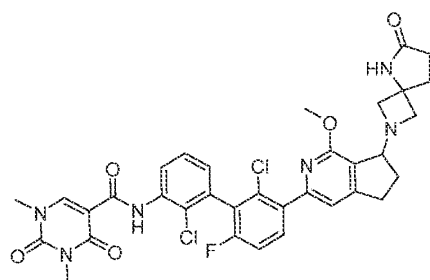
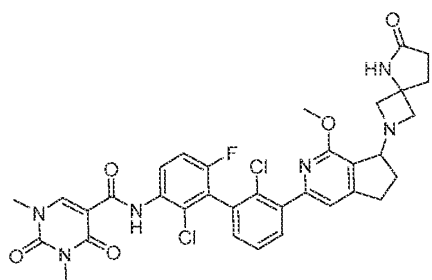
Embodiment 143

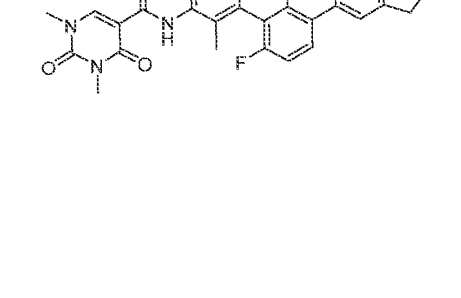
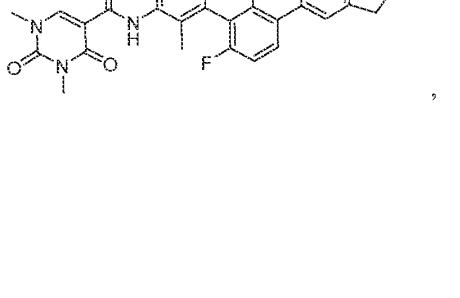
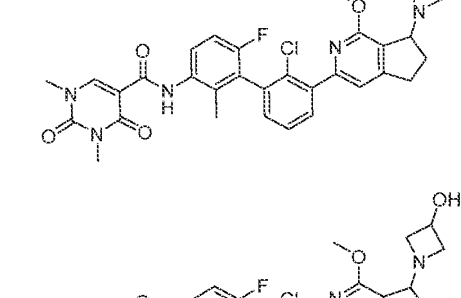
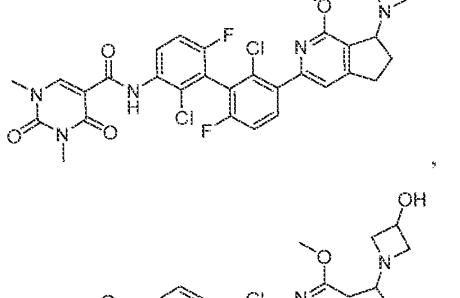
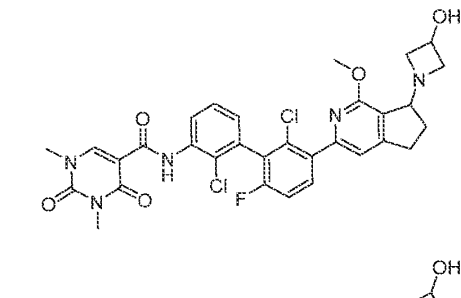
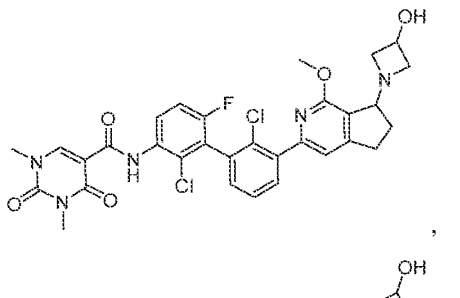
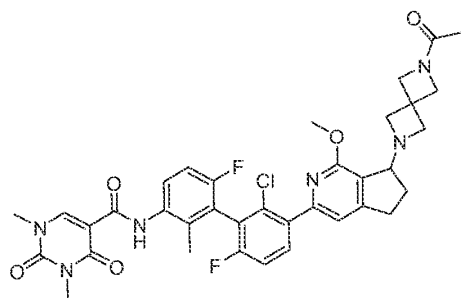
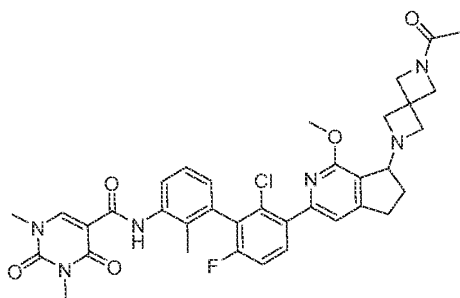
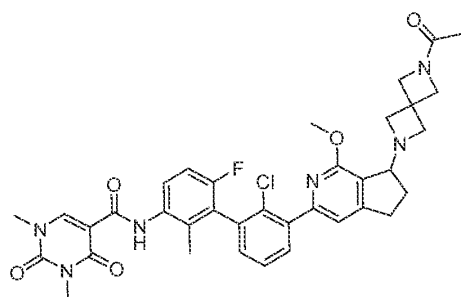
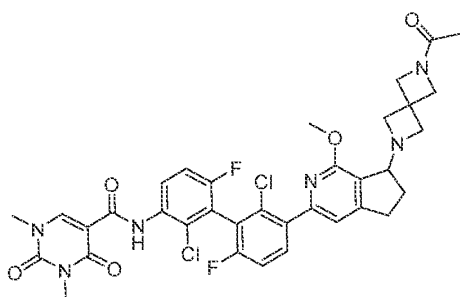
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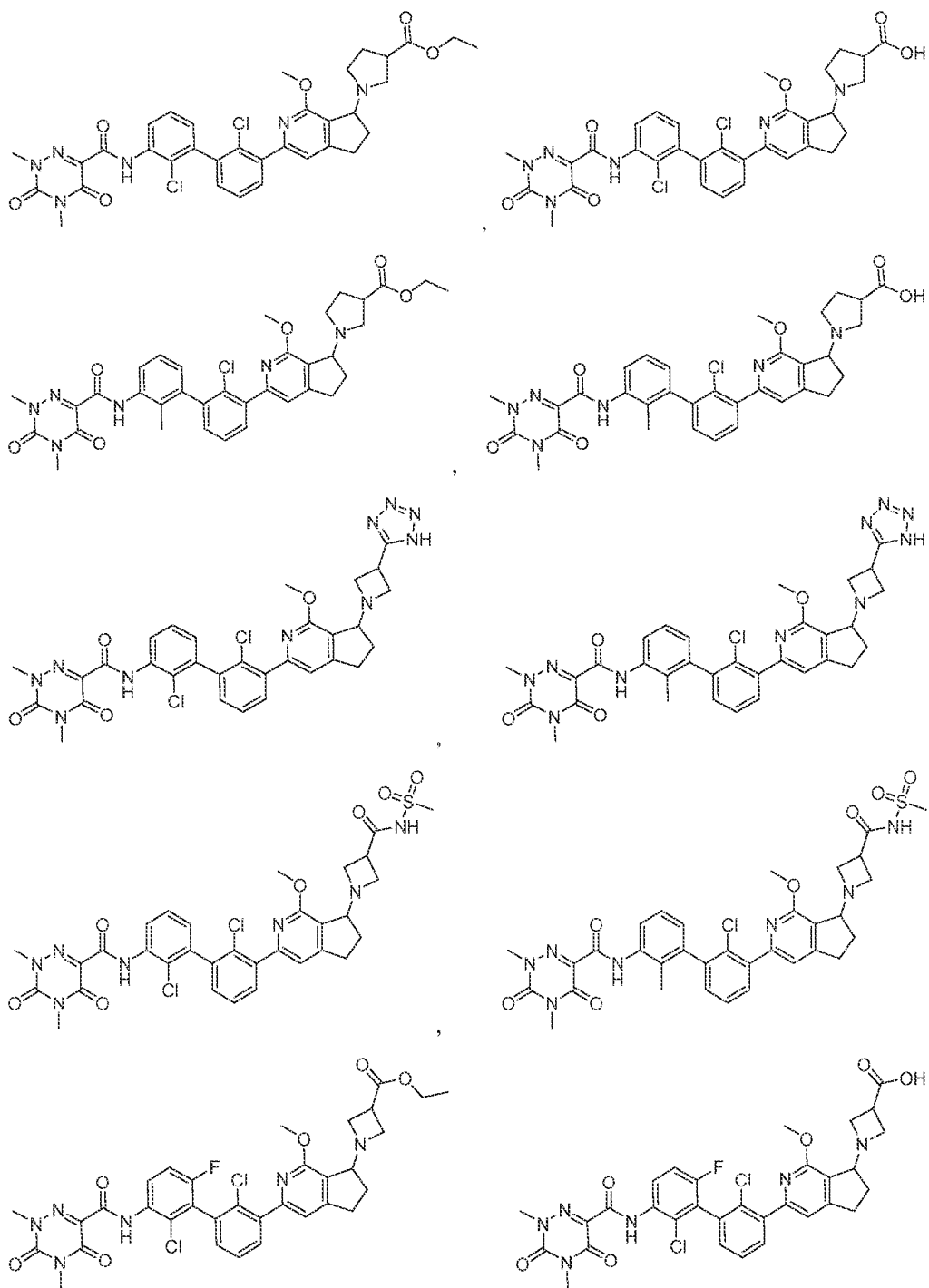


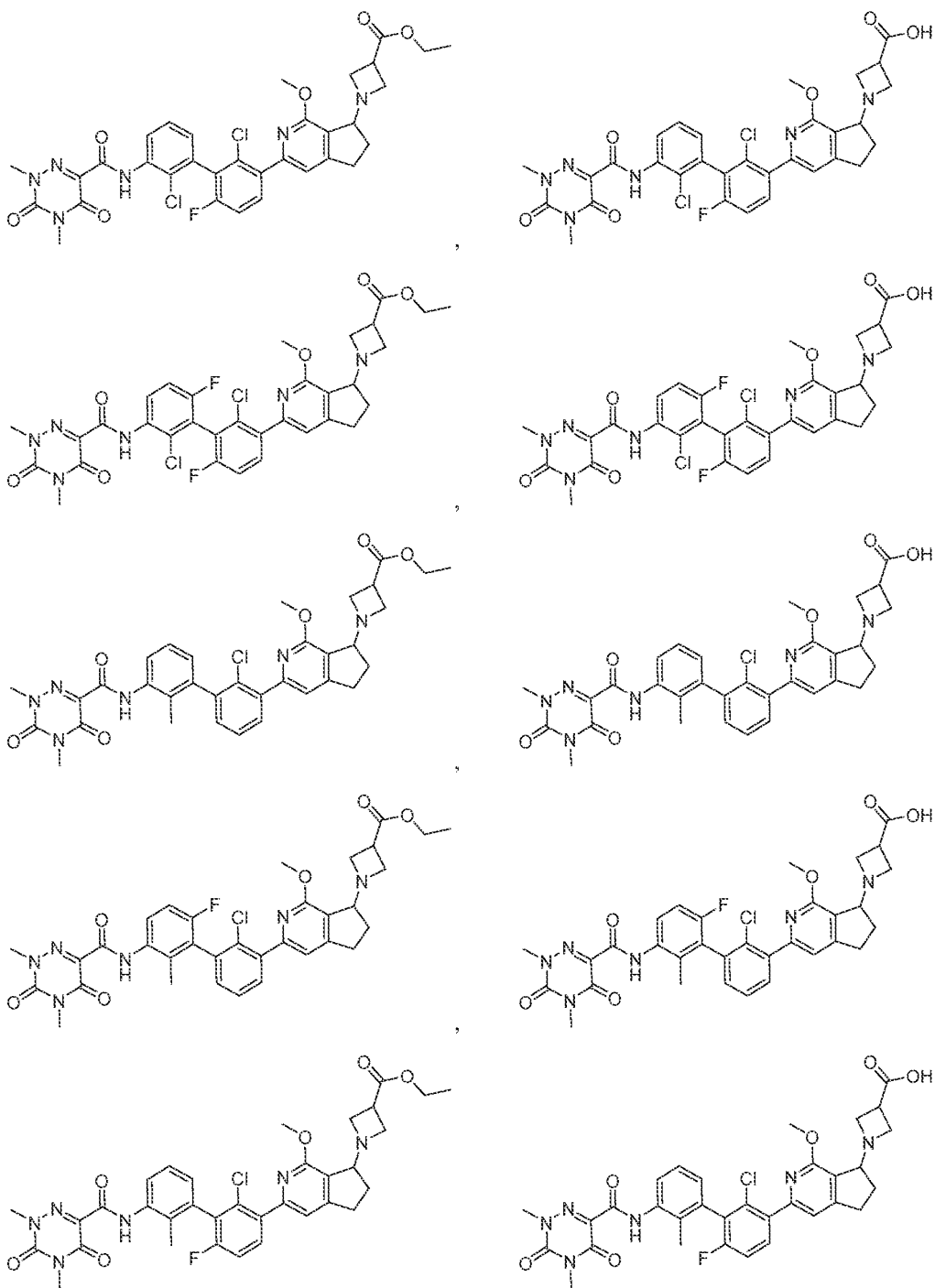


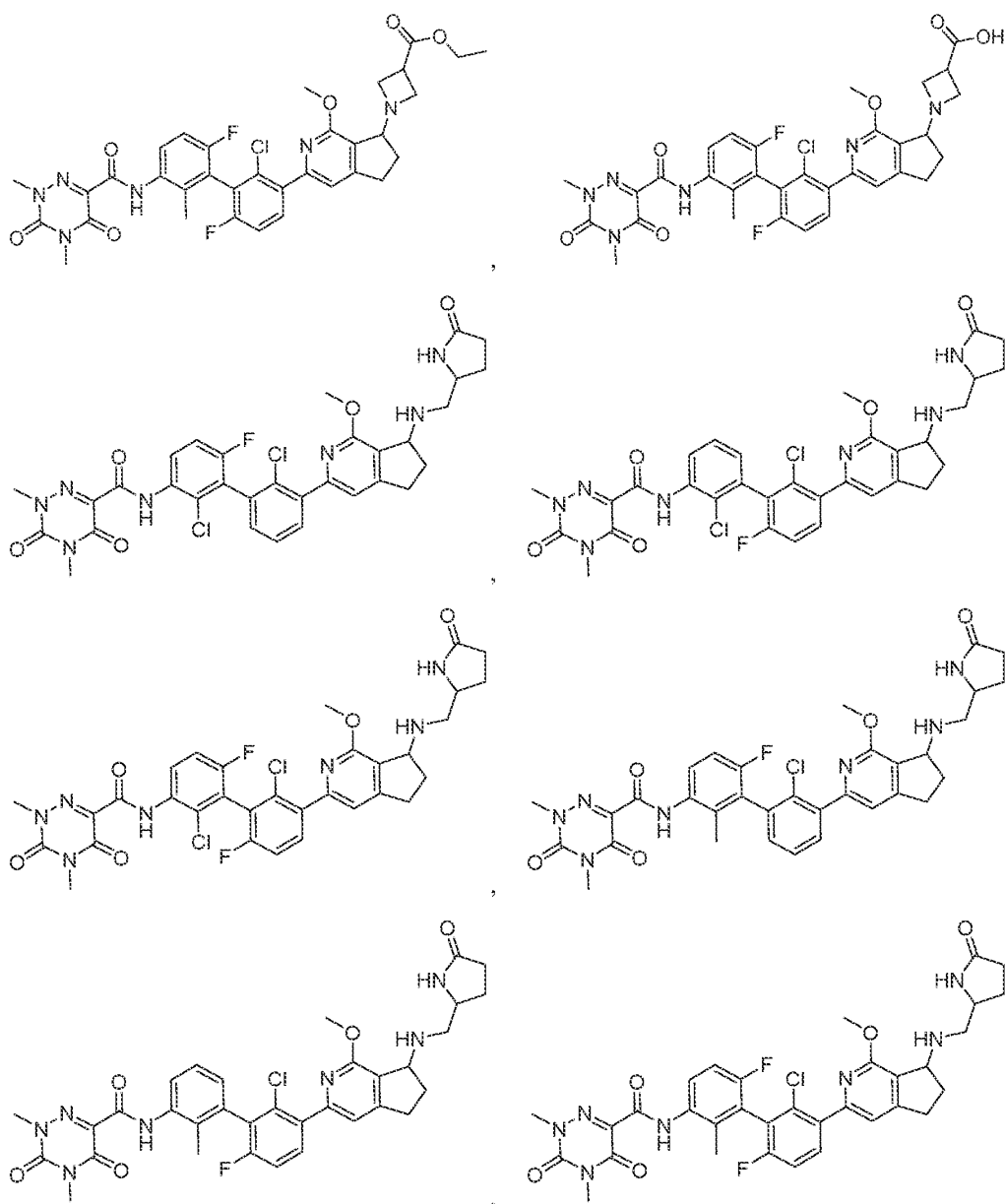


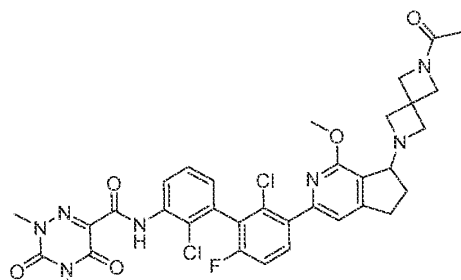
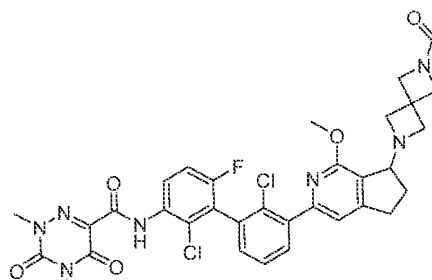
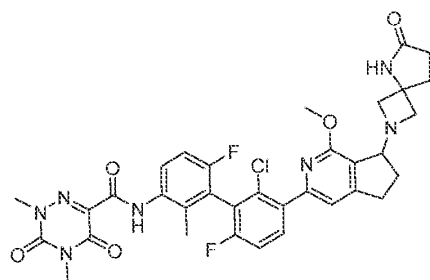
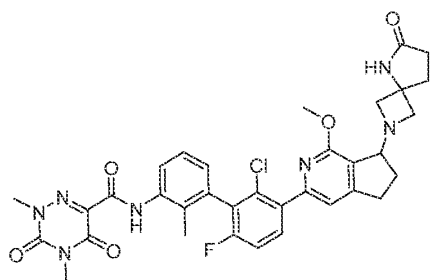
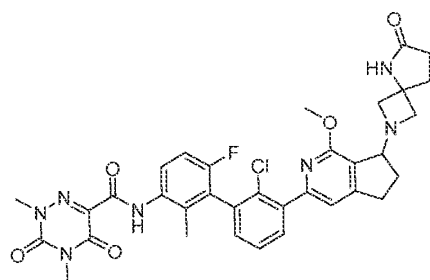
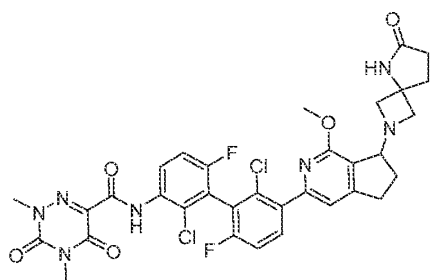
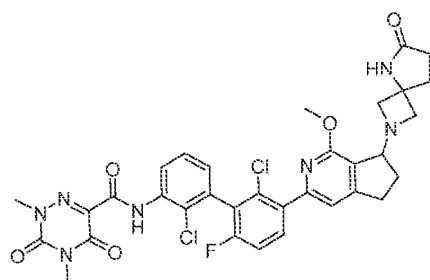
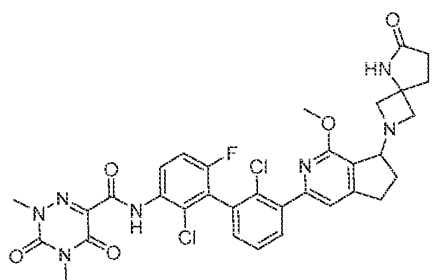


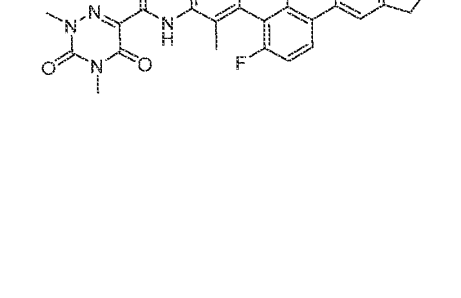
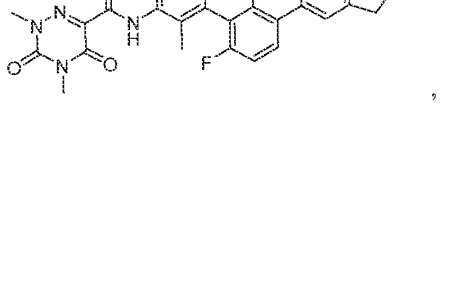
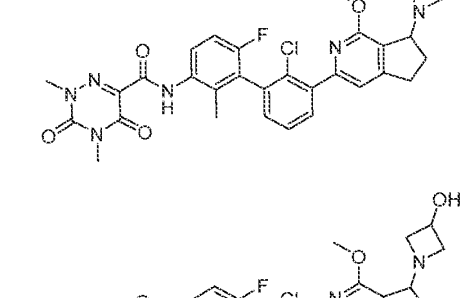
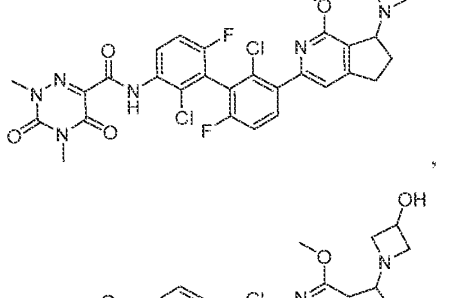
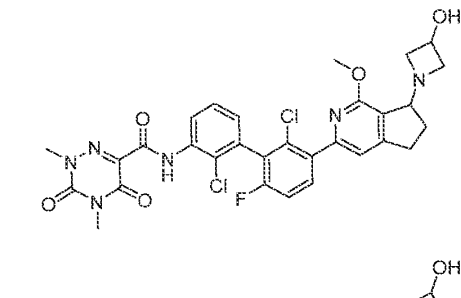
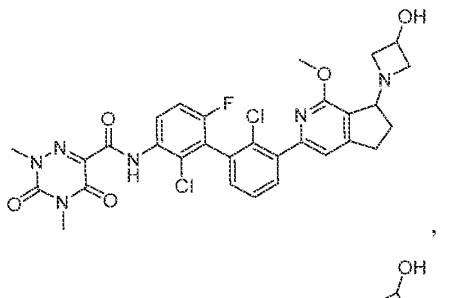
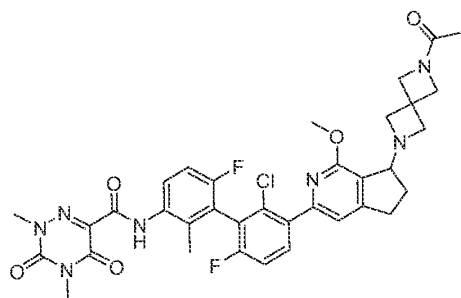
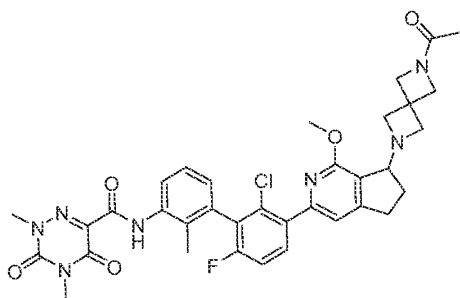
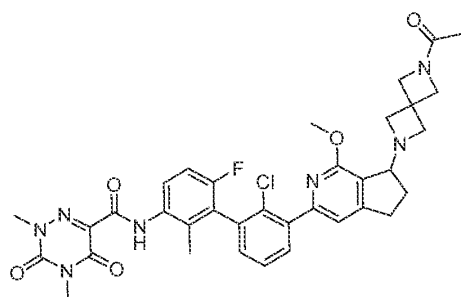
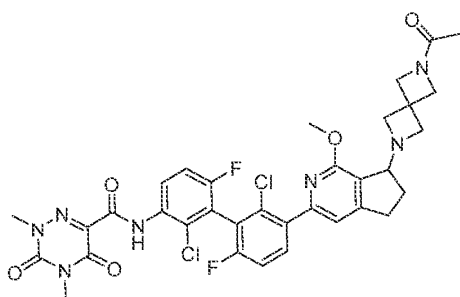


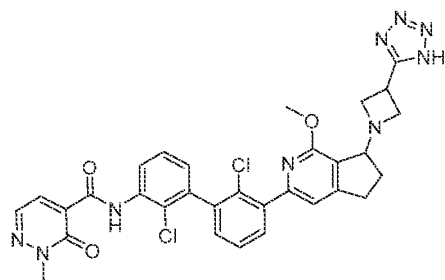
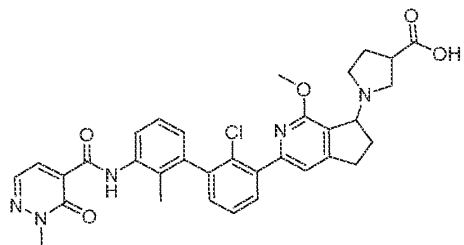
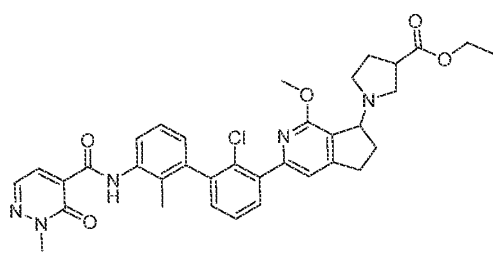
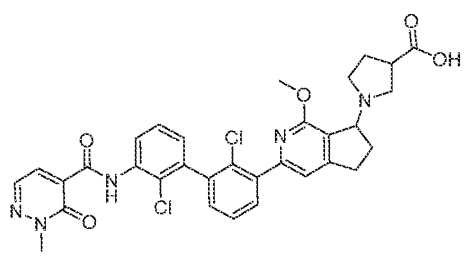
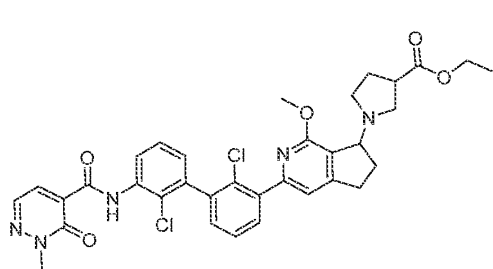
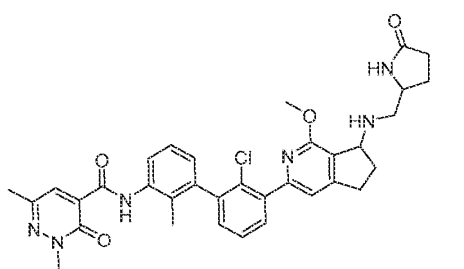
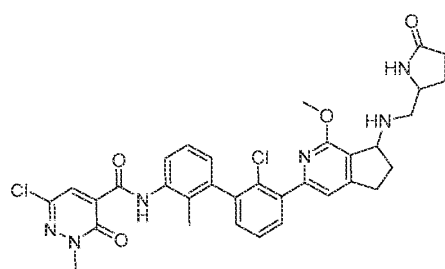
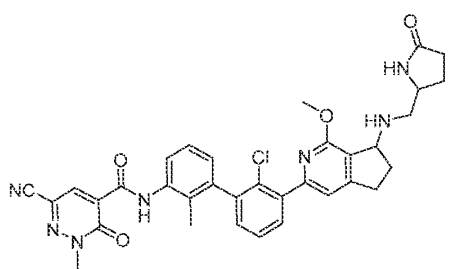
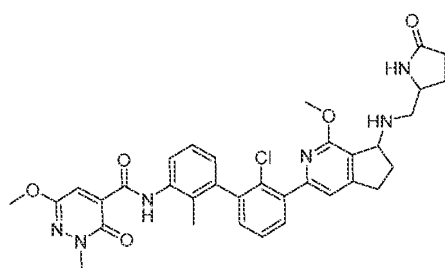
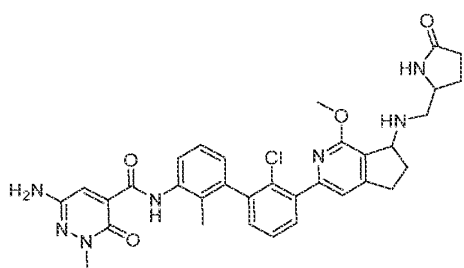


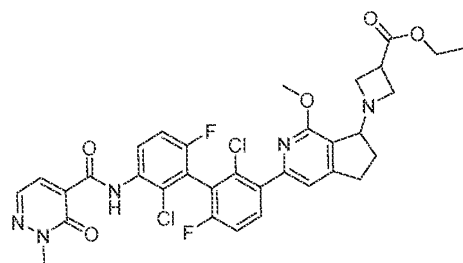
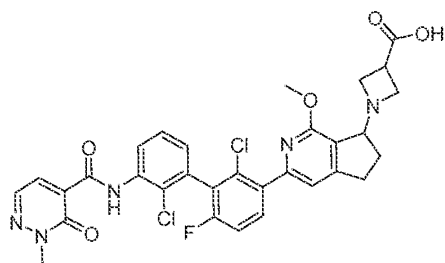
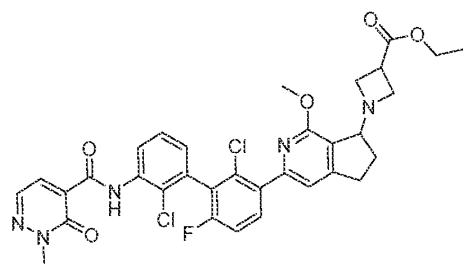
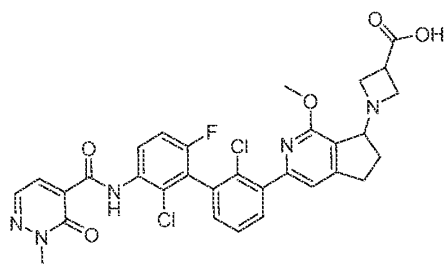
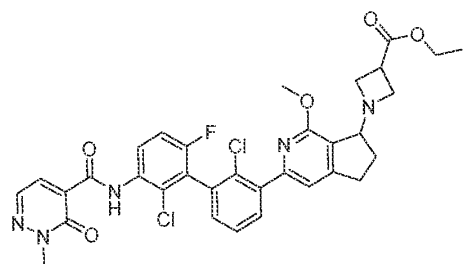
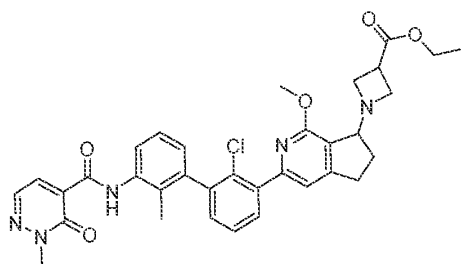
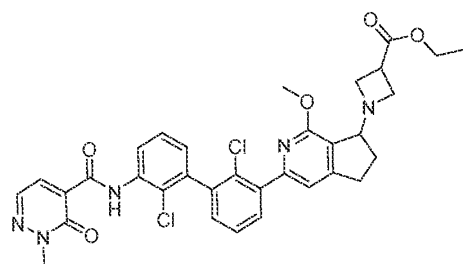
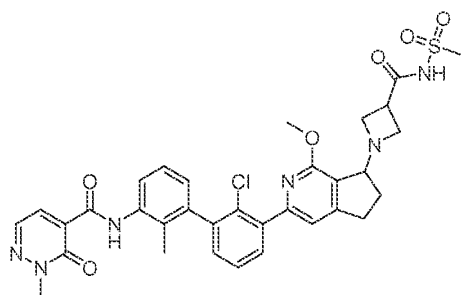
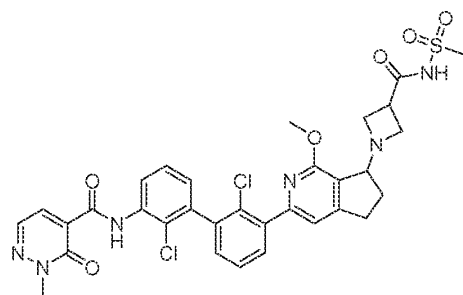
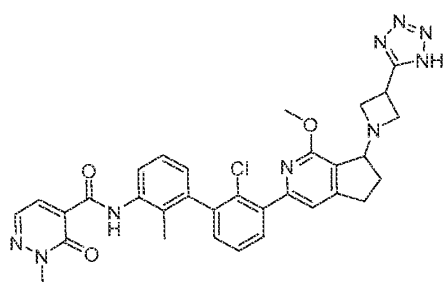


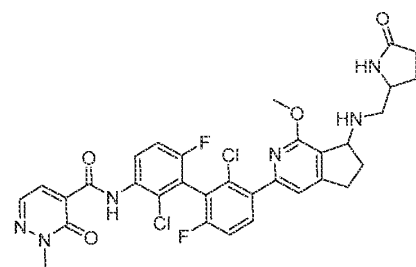
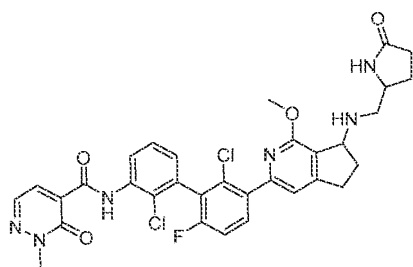
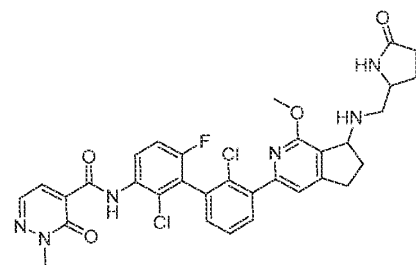
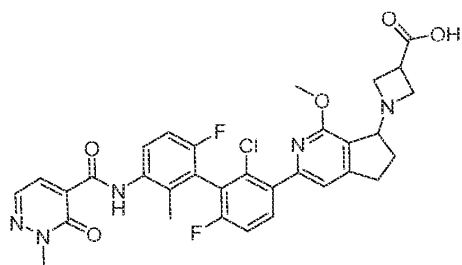
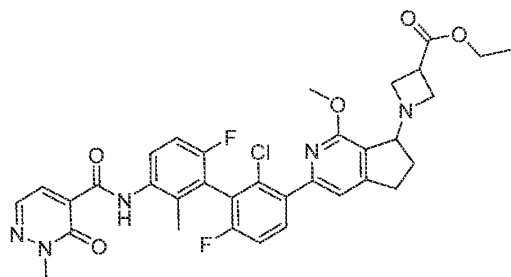
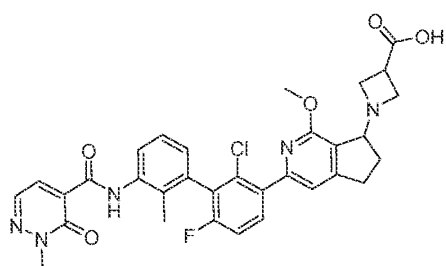
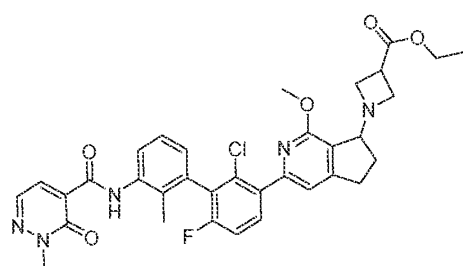
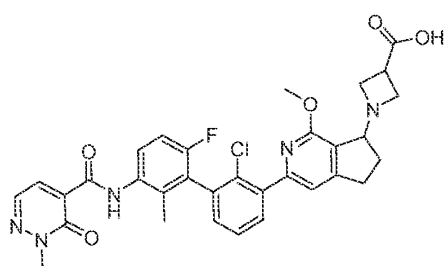
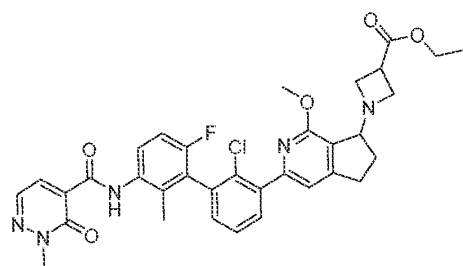
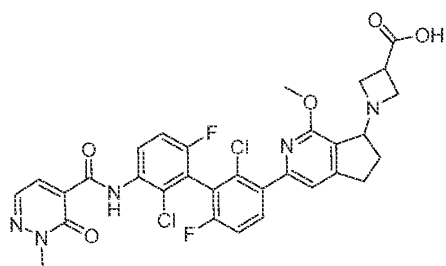


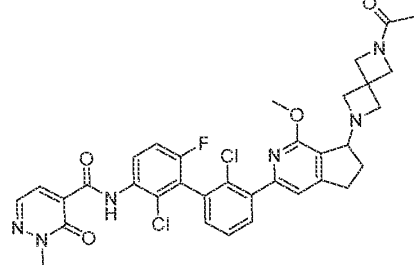
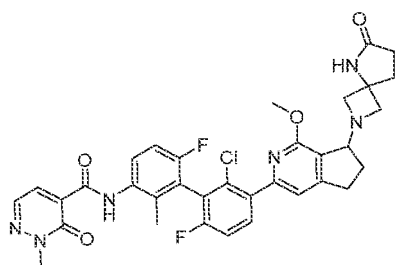
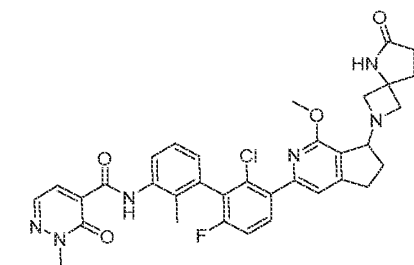
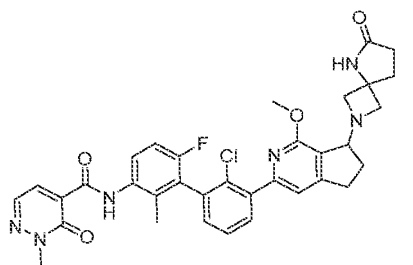
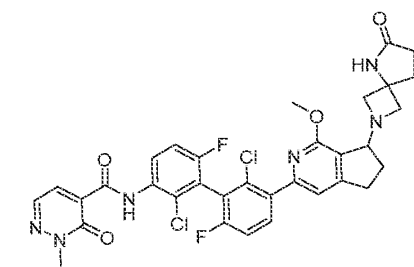
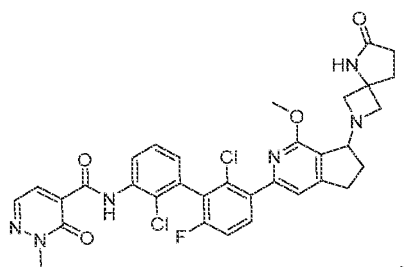
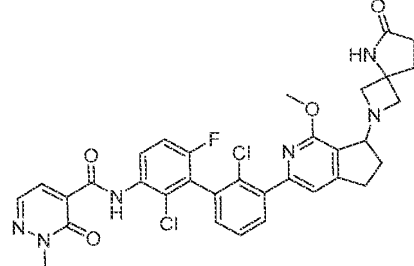
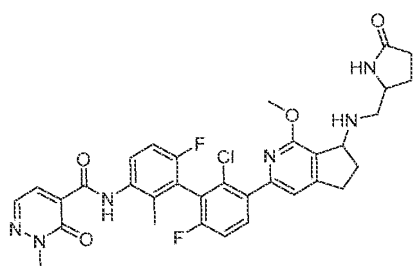
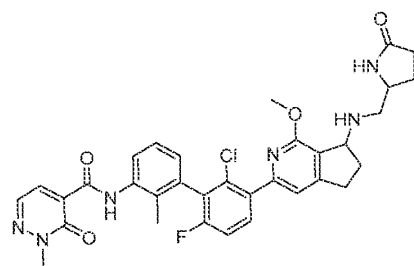
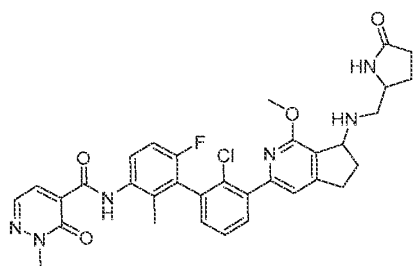


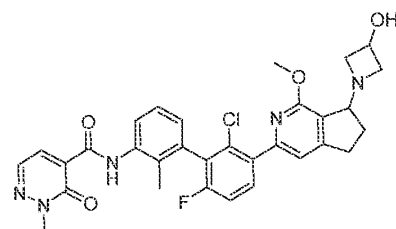
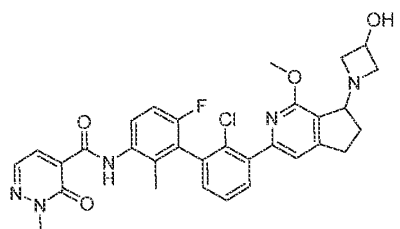
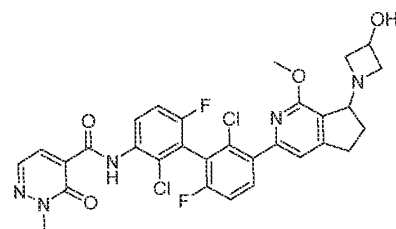
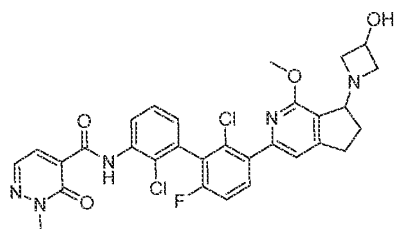
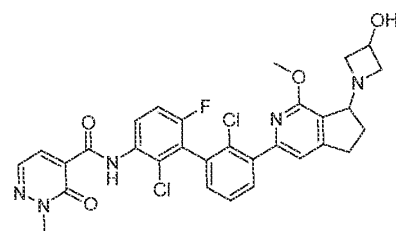
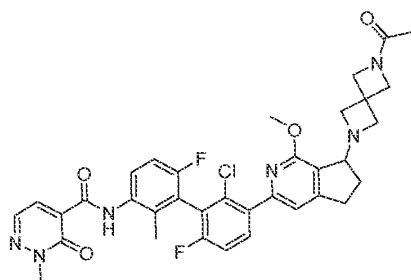
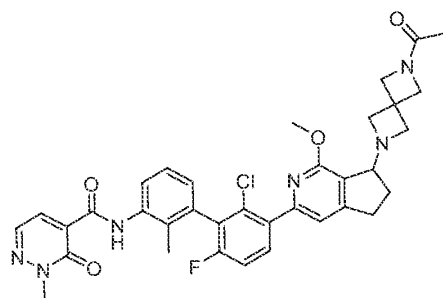
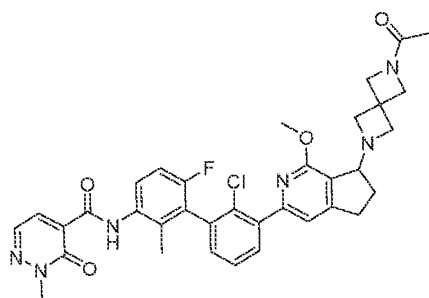
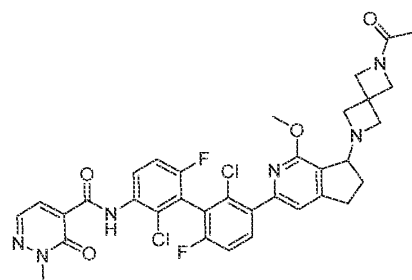
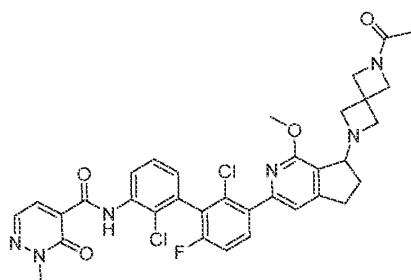


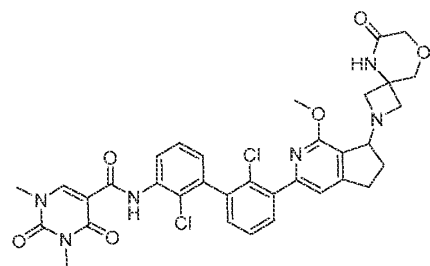
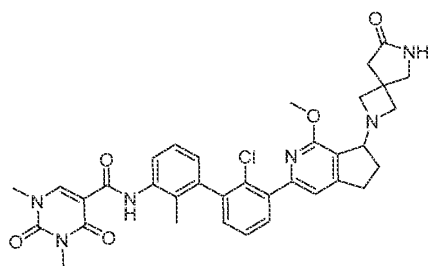
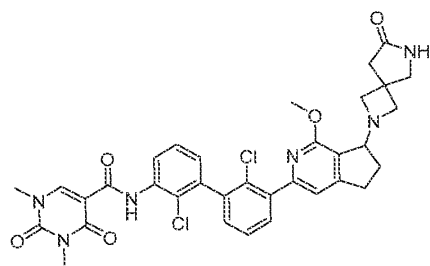
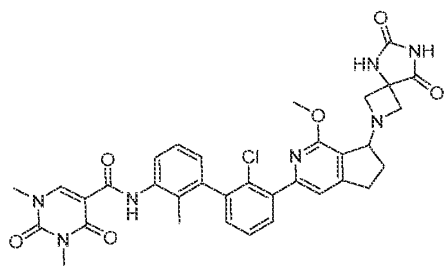
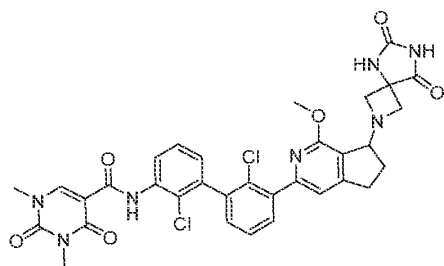
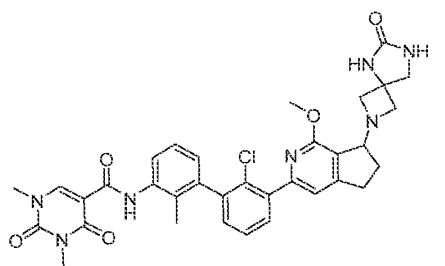
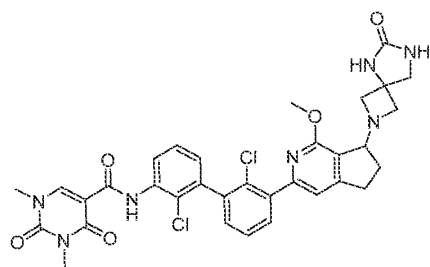
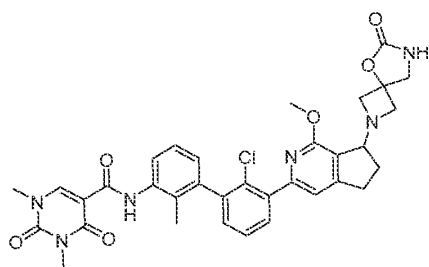
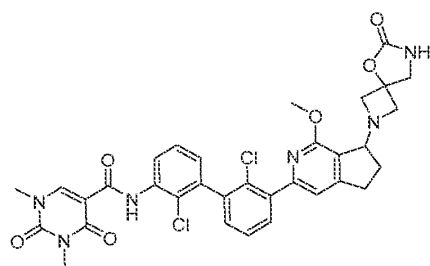
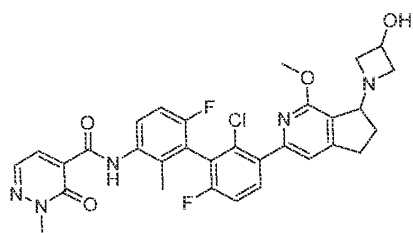


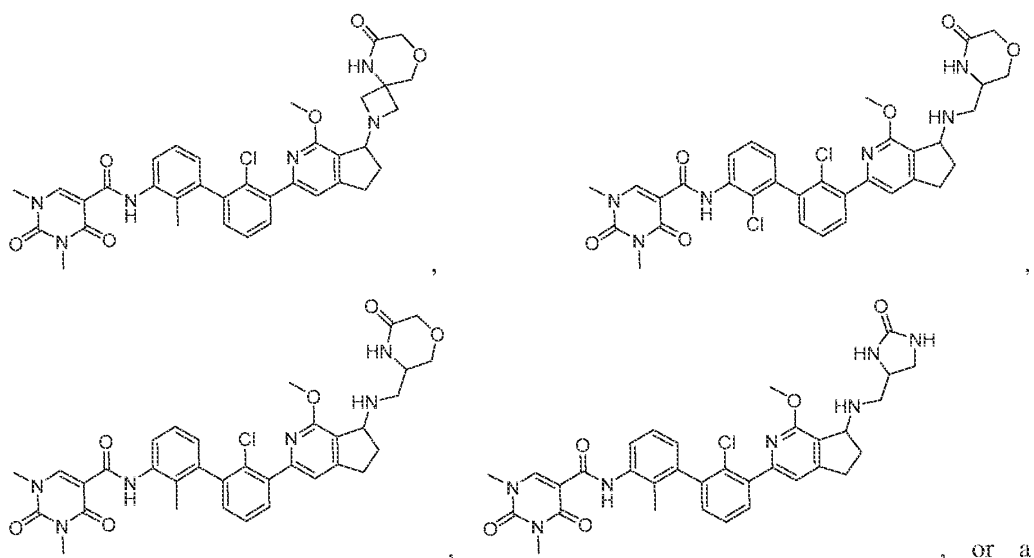








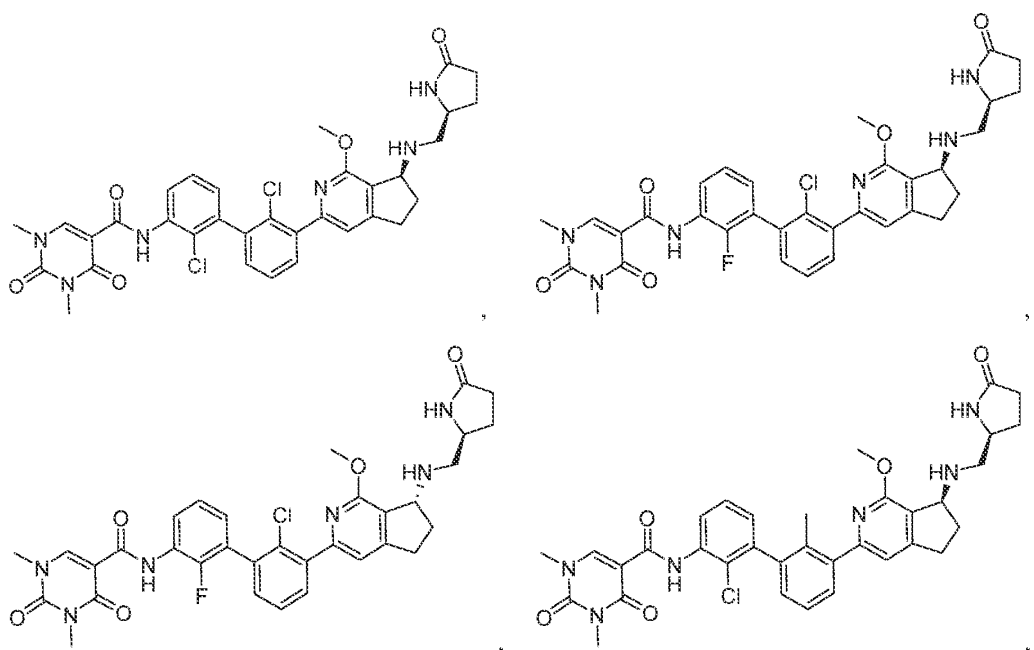


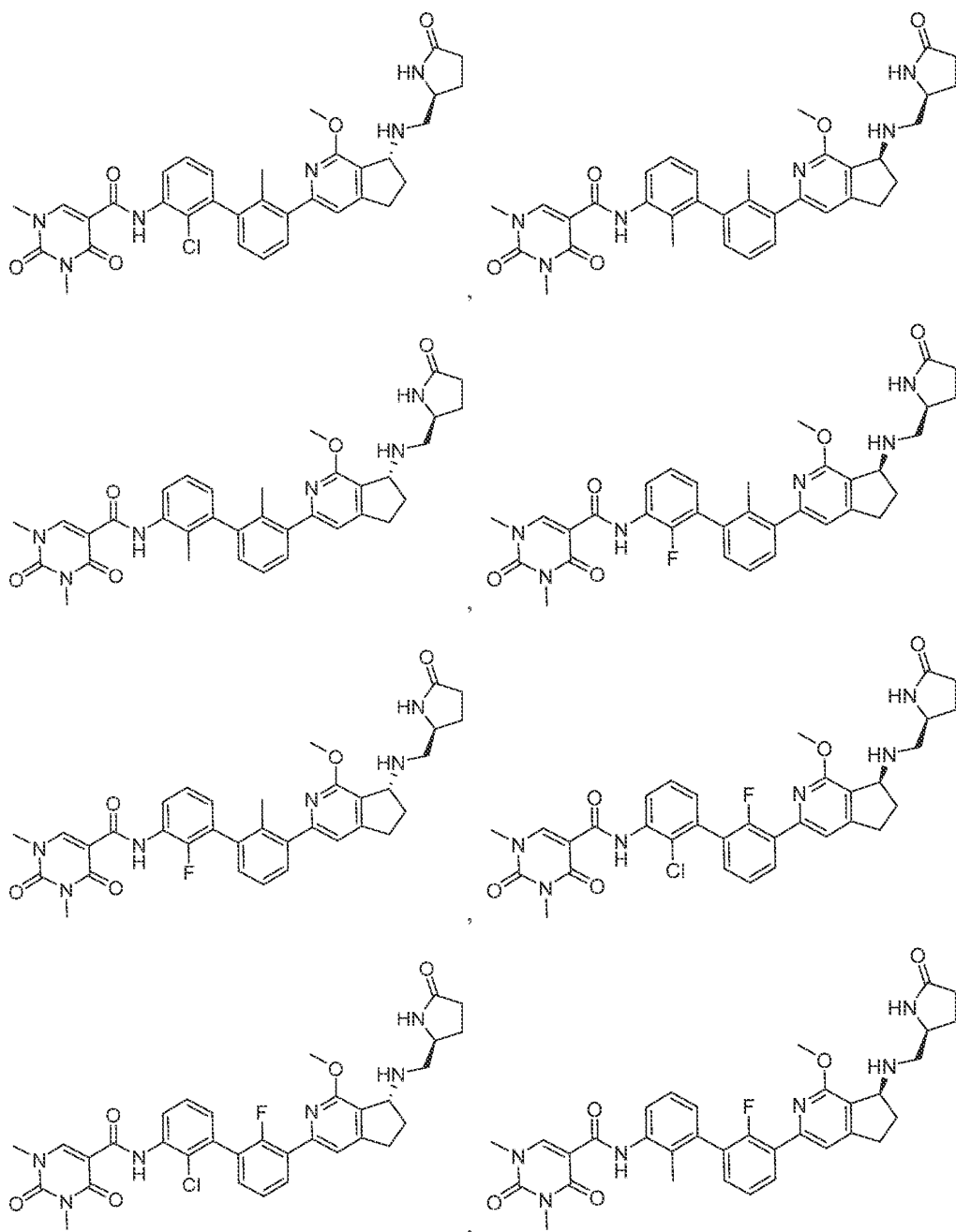


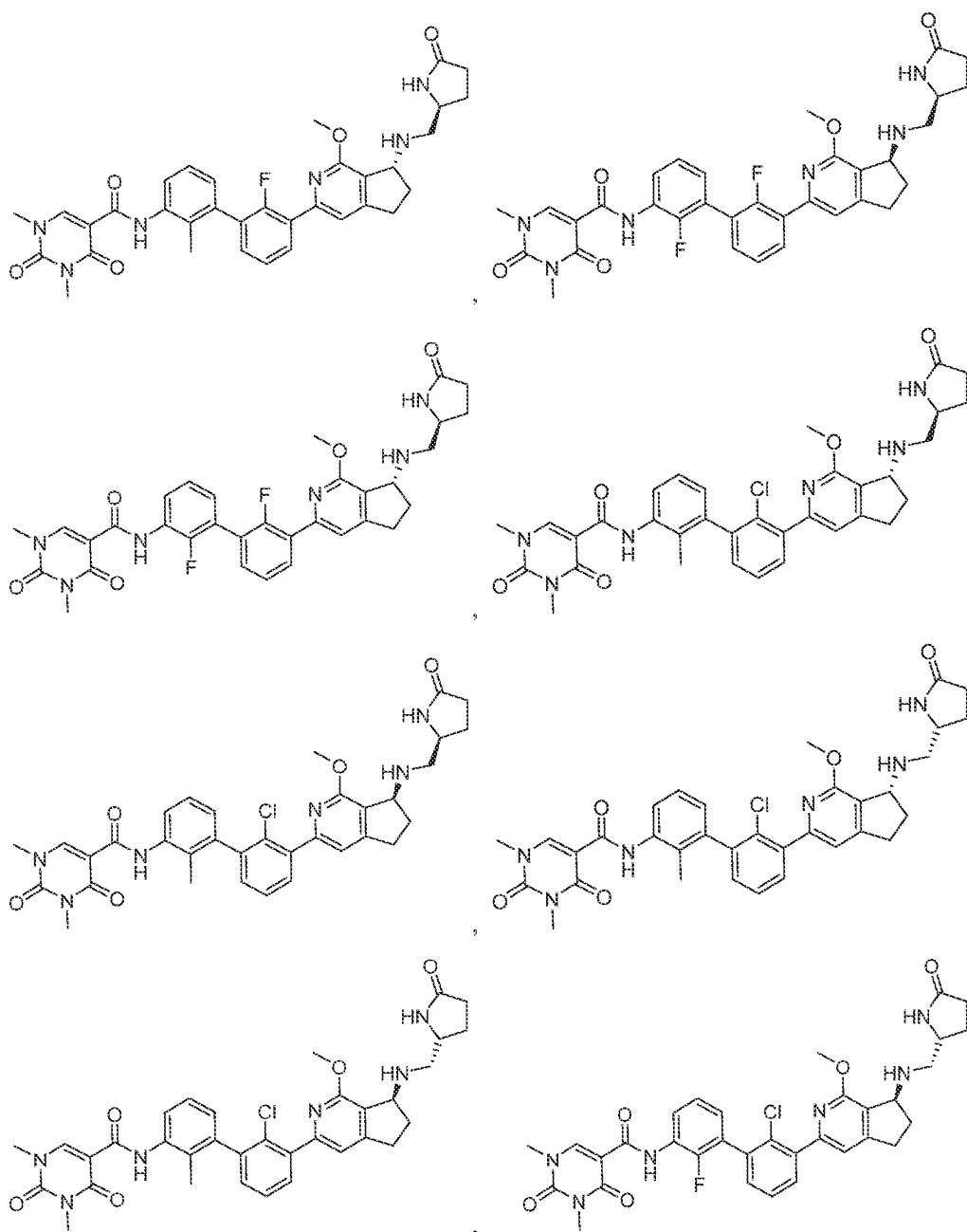
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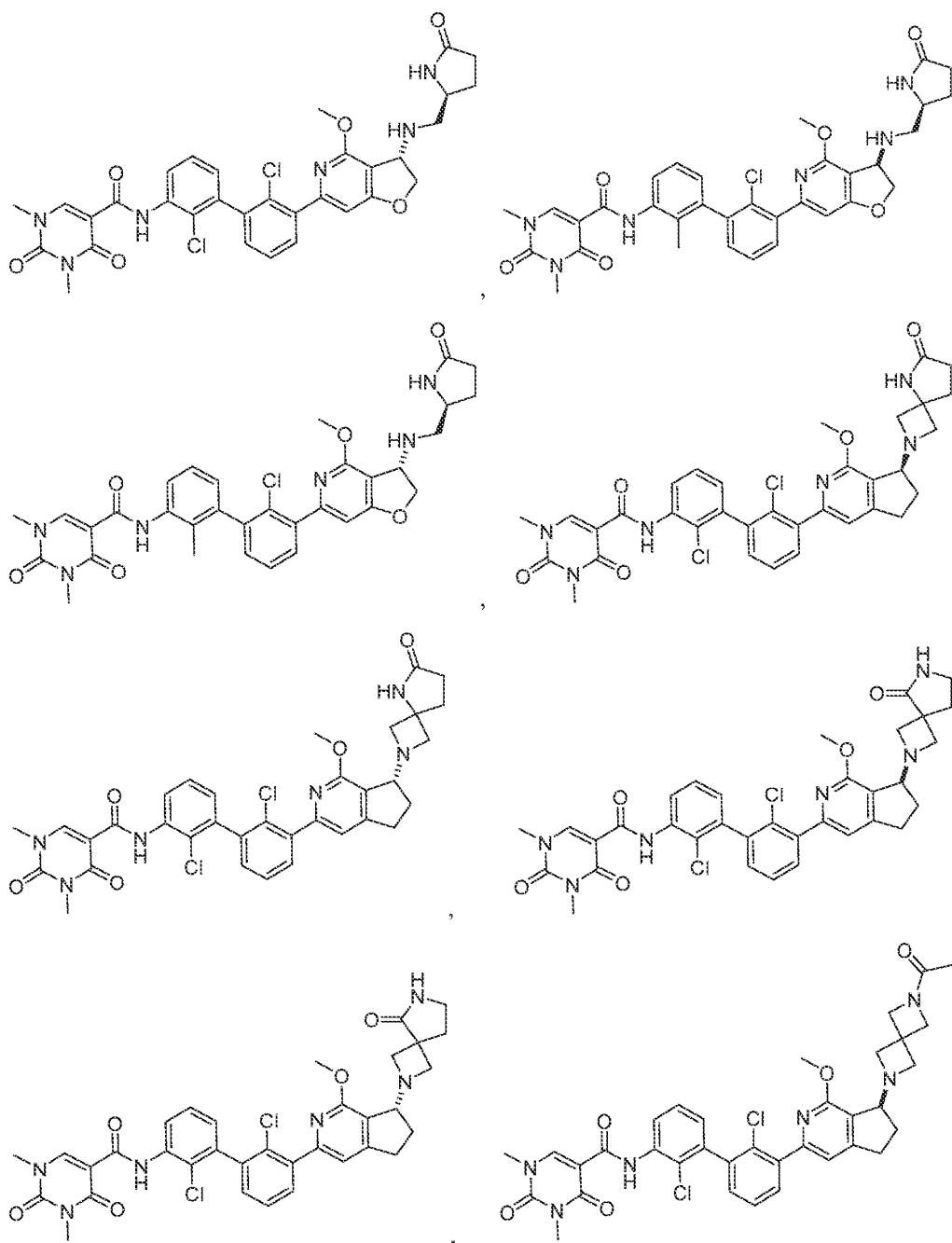
Embodiment 144

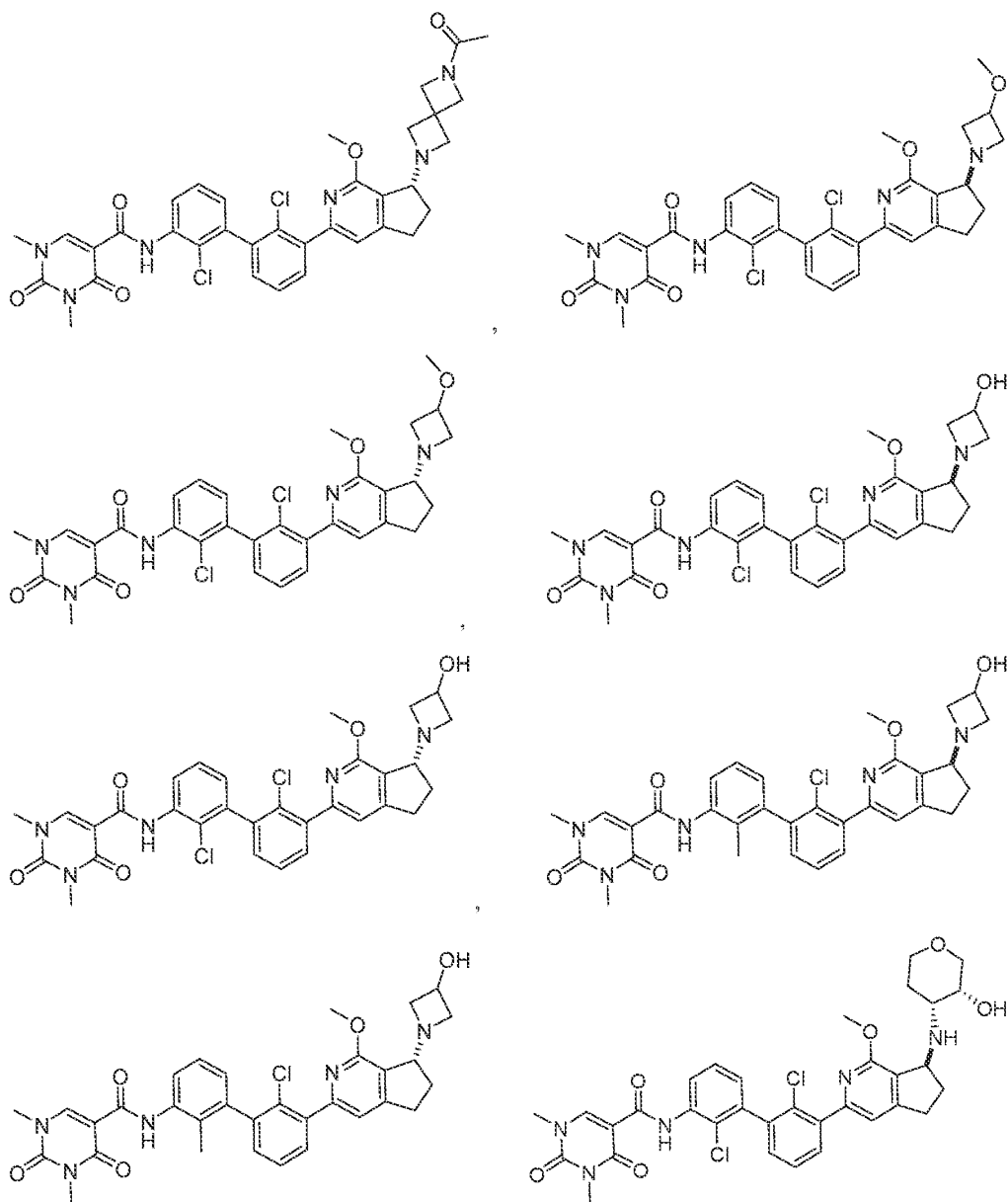
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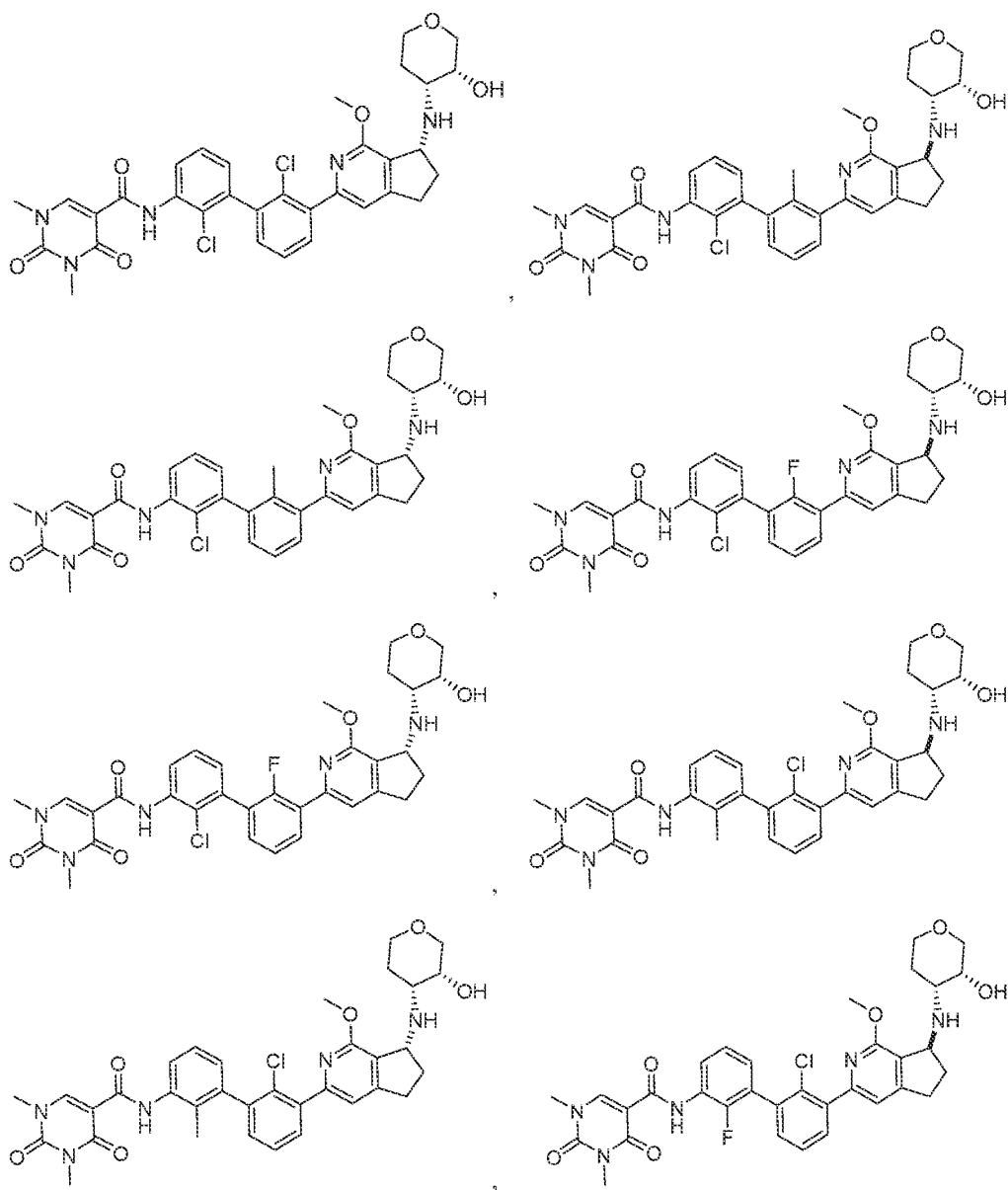


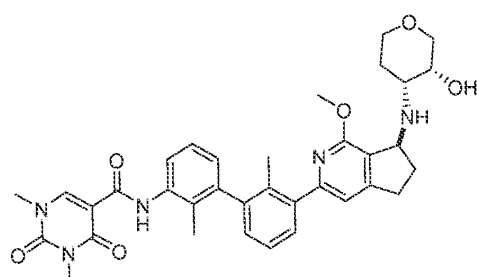
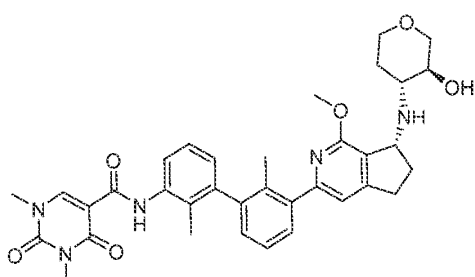
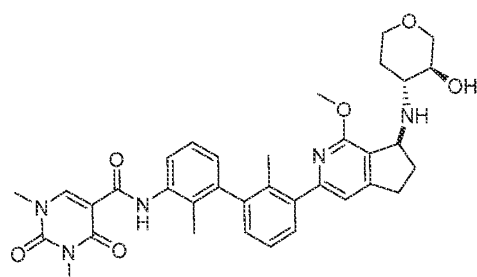
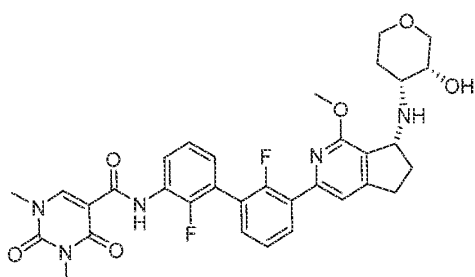
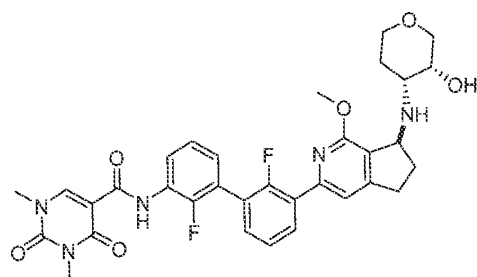
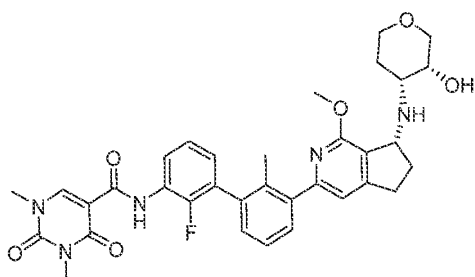
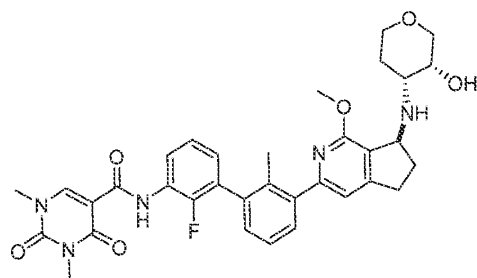
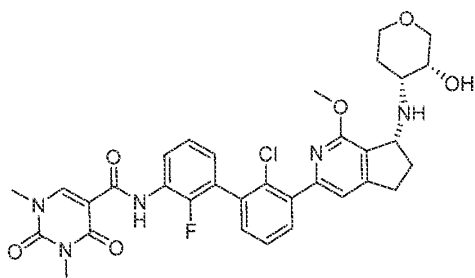


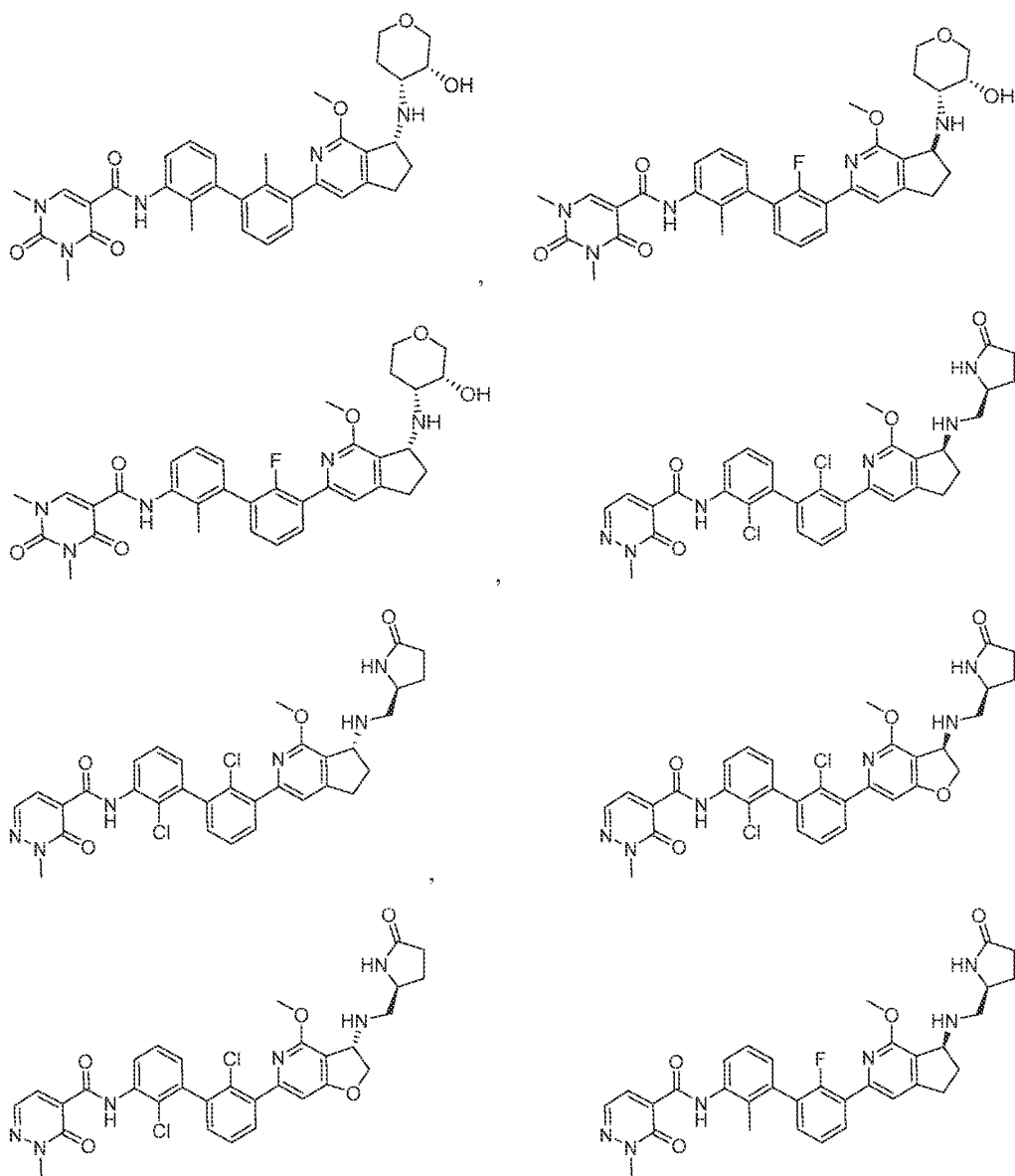


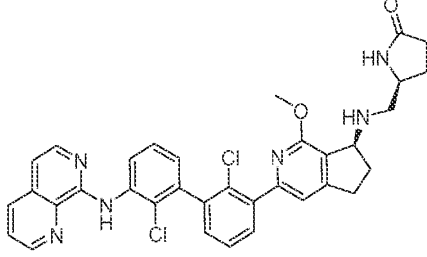
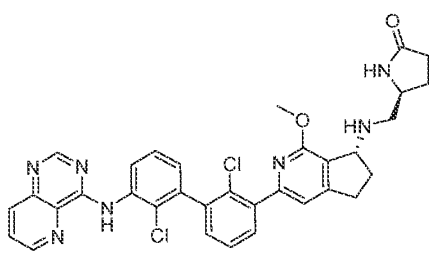
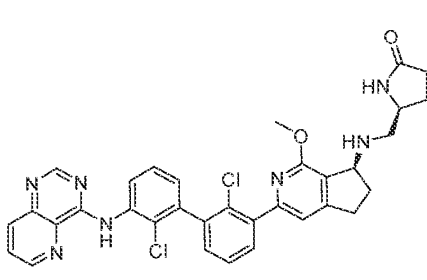
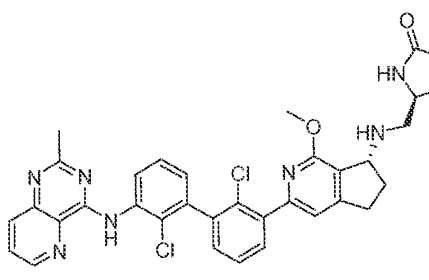
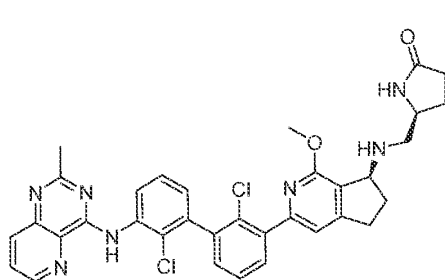
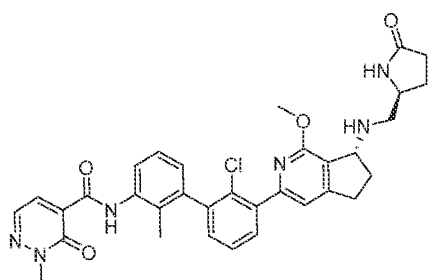
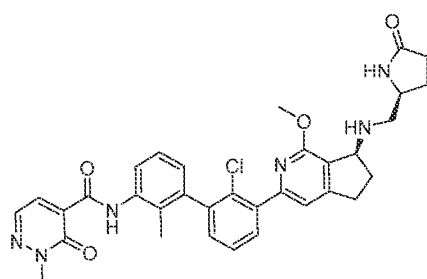
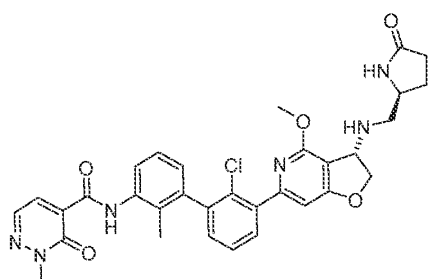
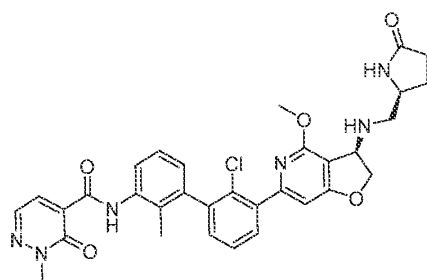
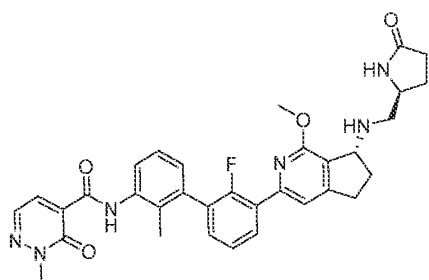


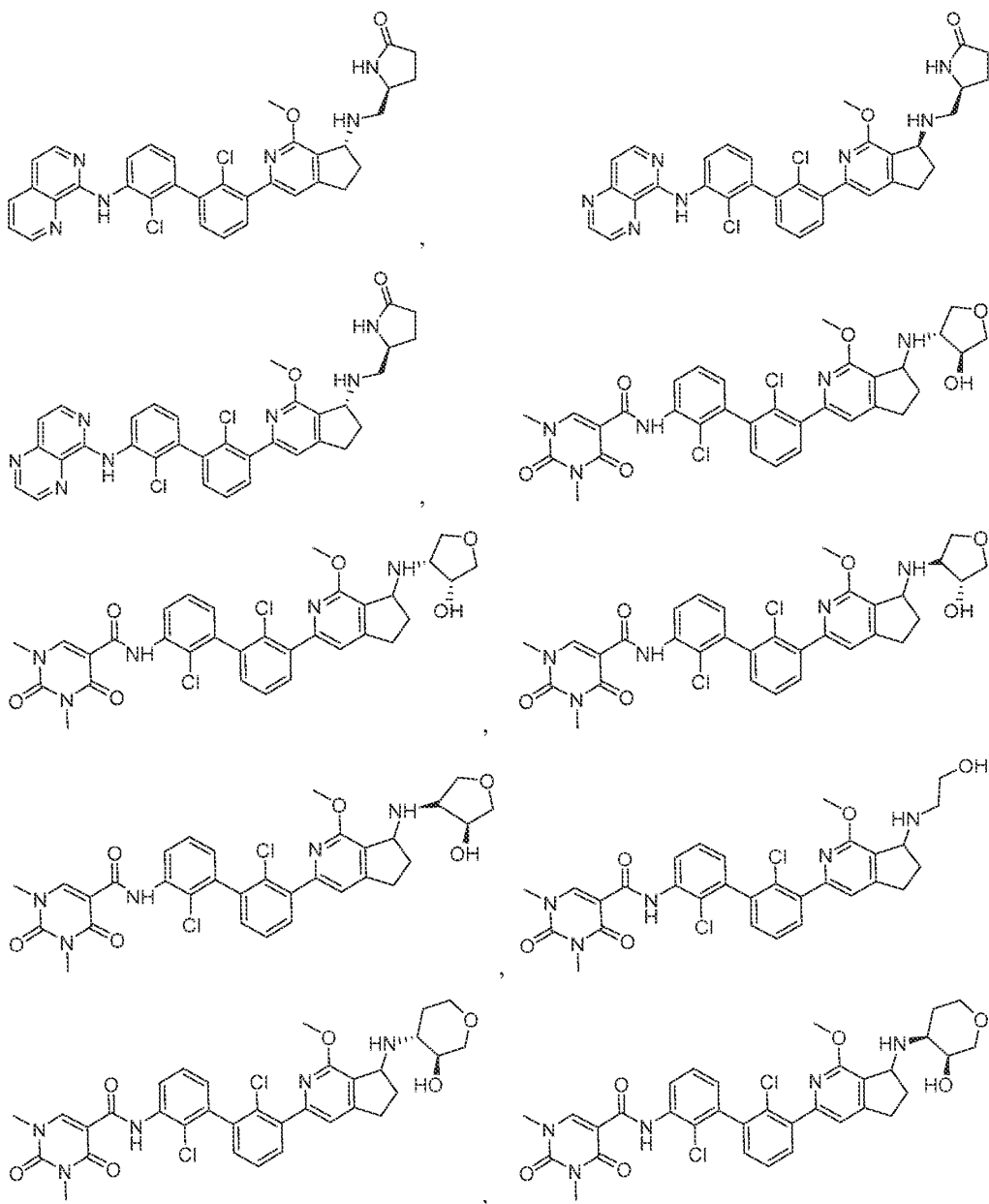


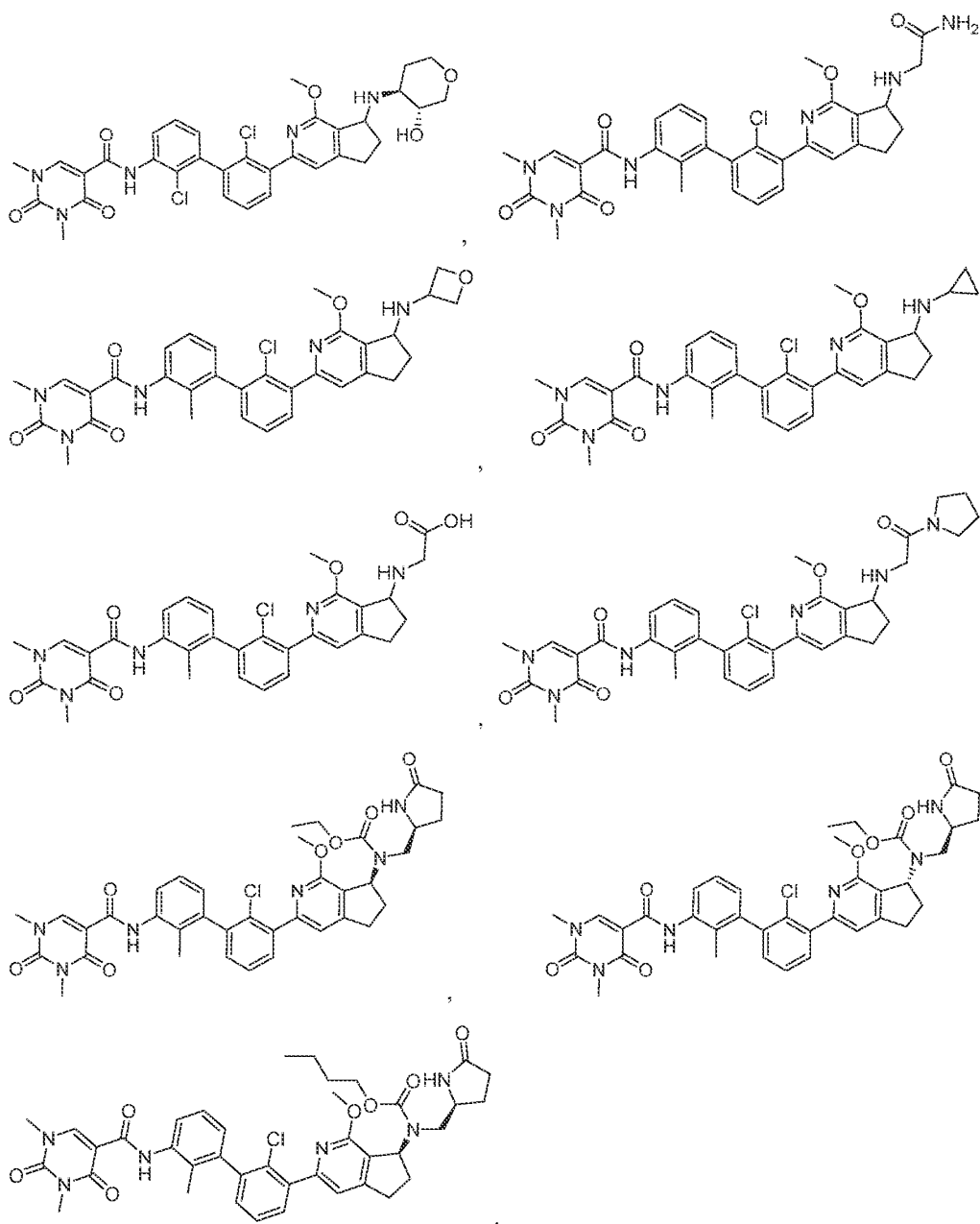


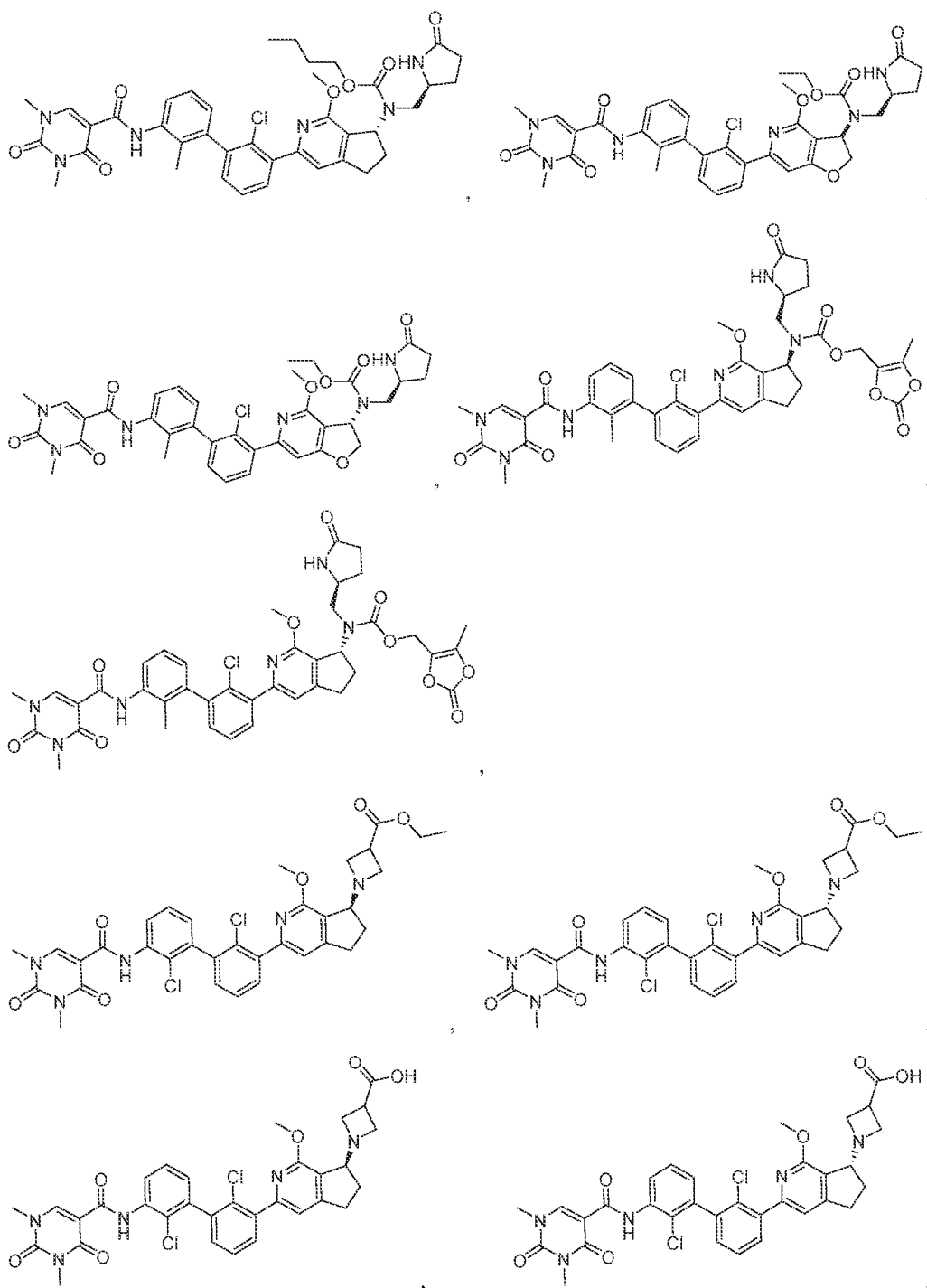


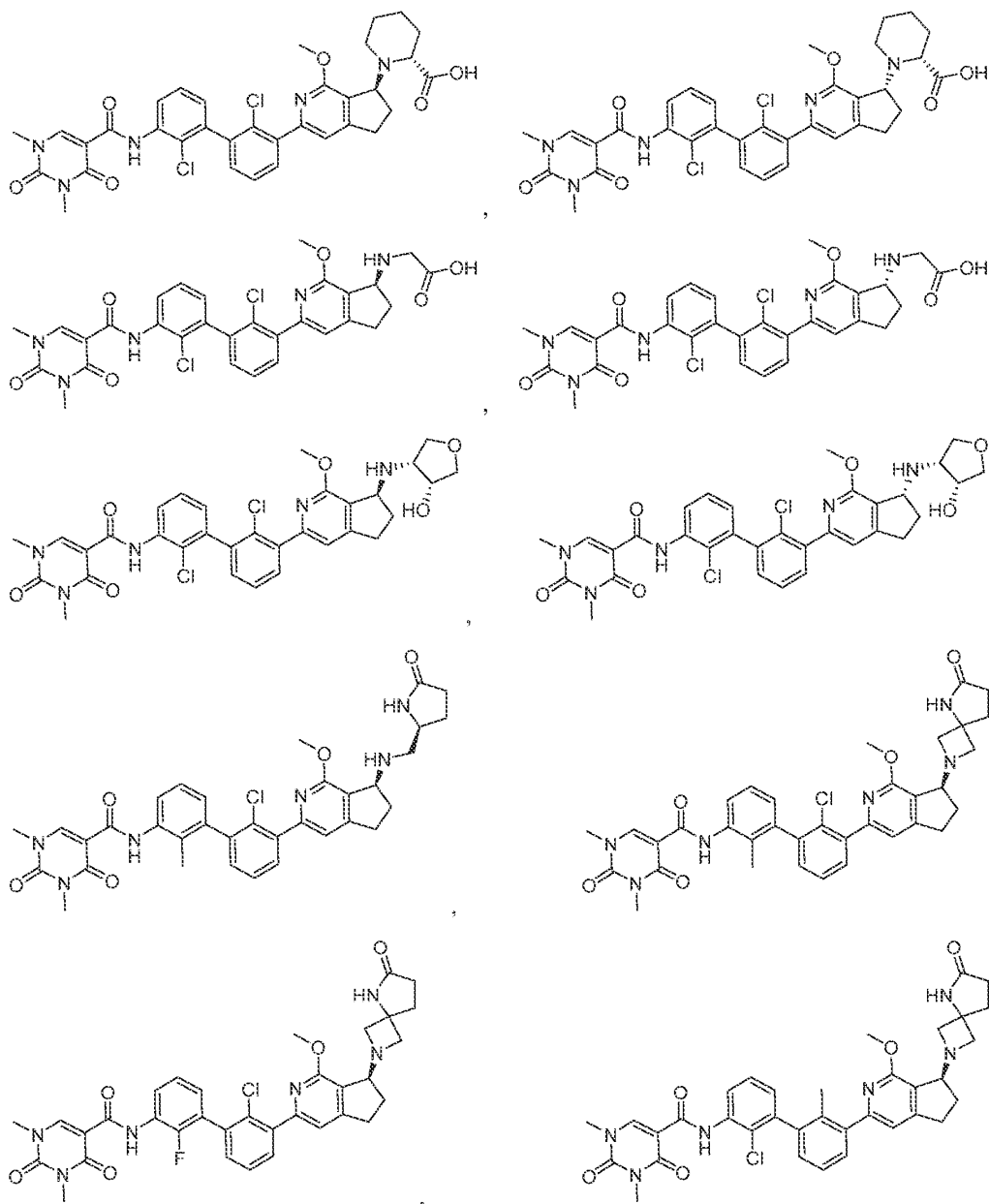


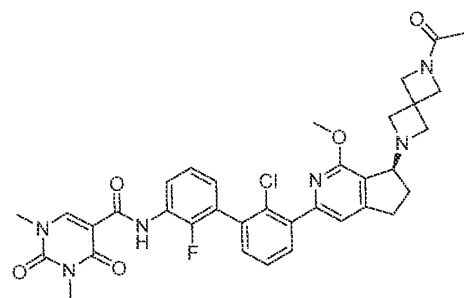
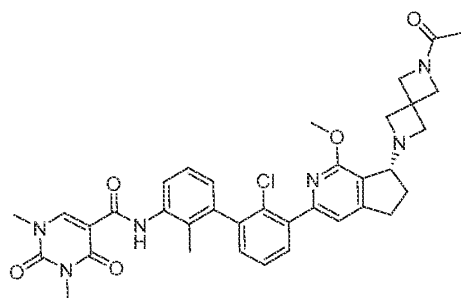
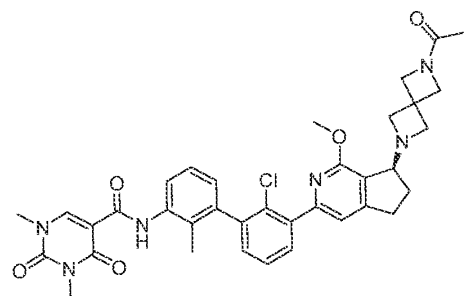
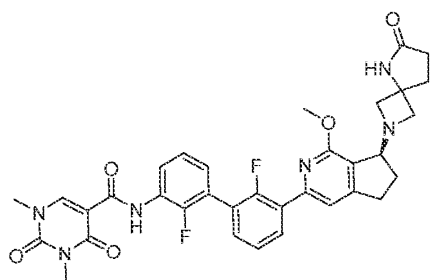
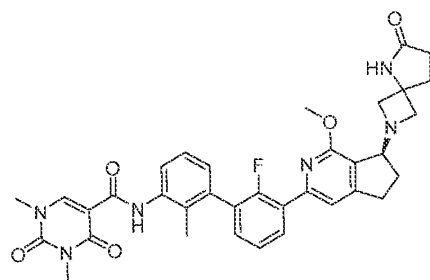
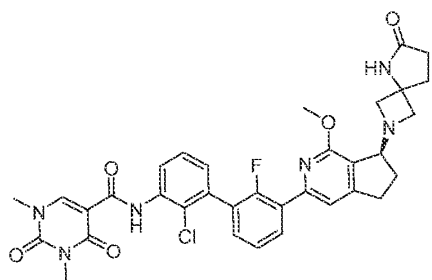
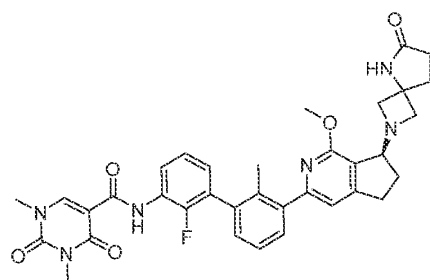
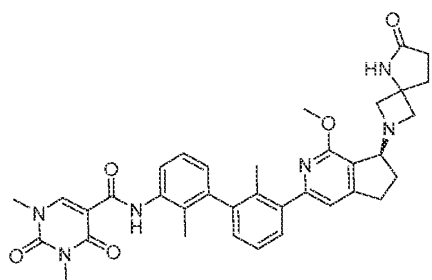


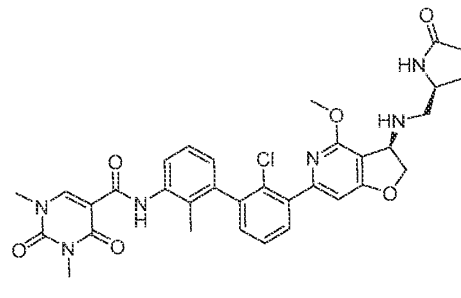
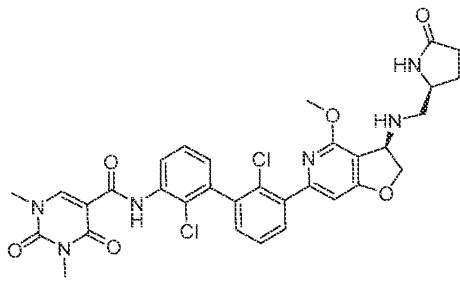
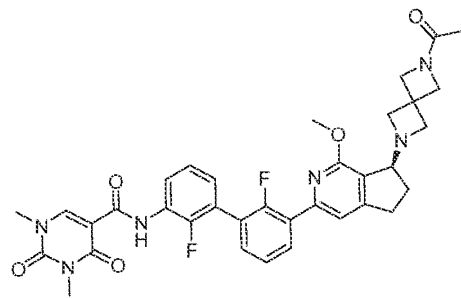
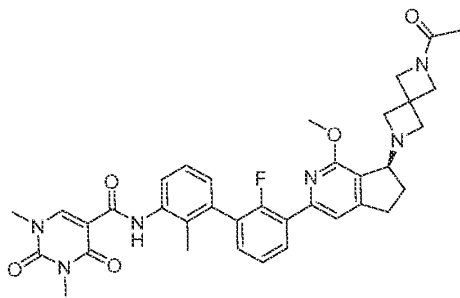
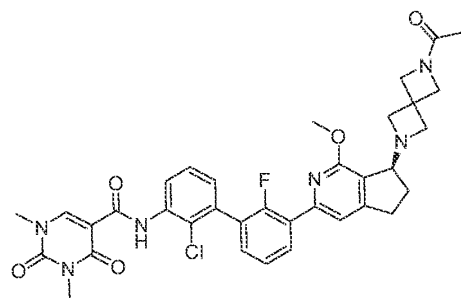
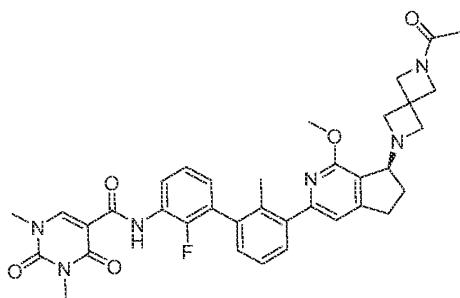
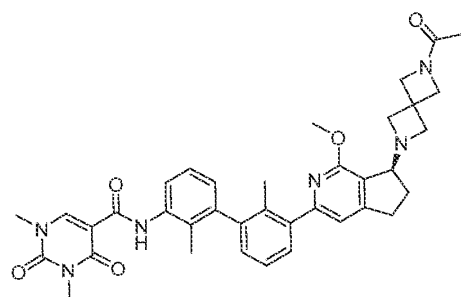
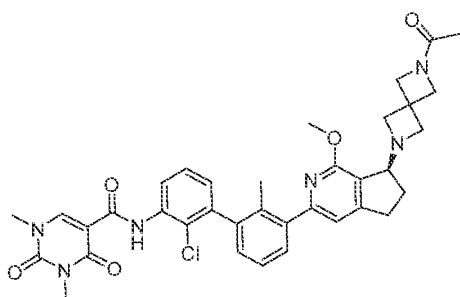


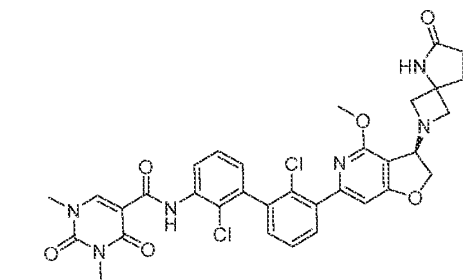
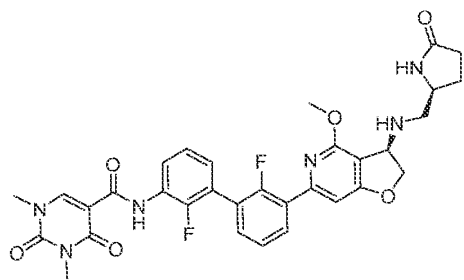
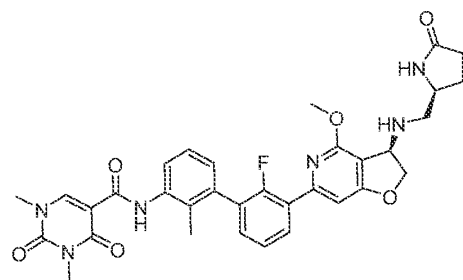
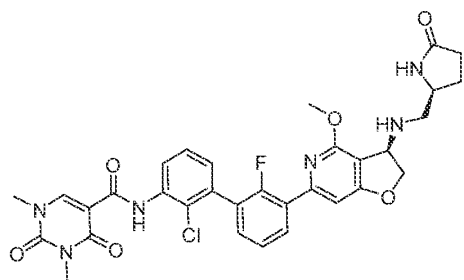
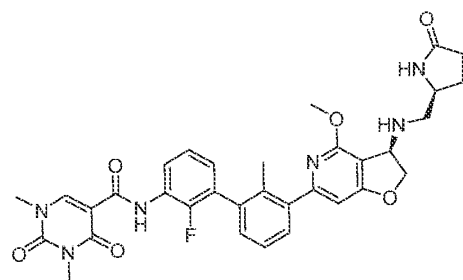
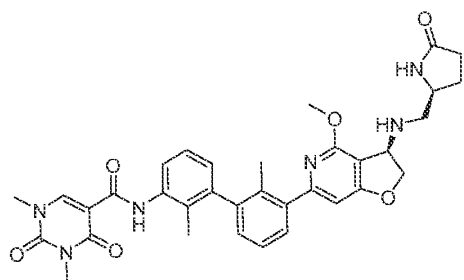
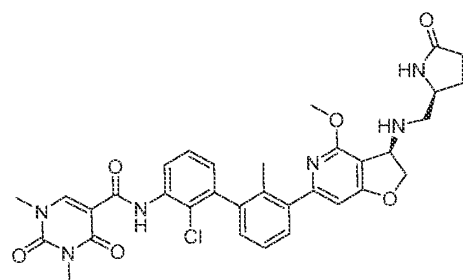
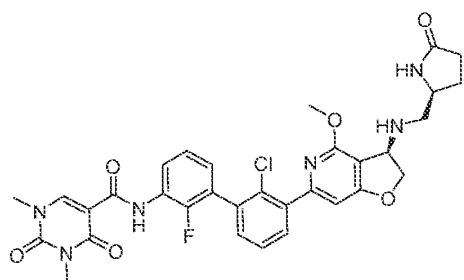


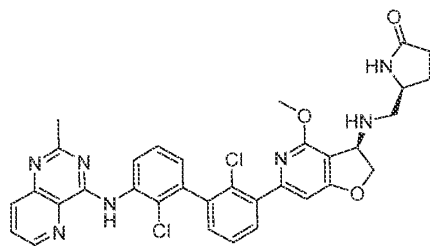
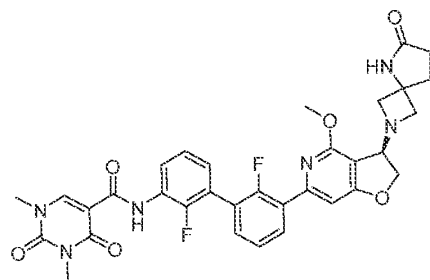
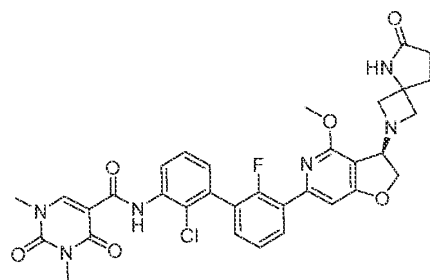
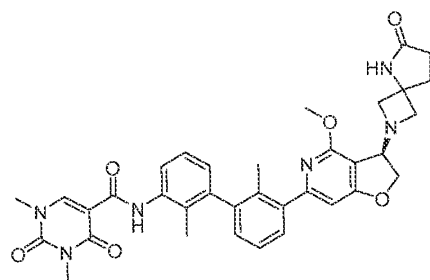
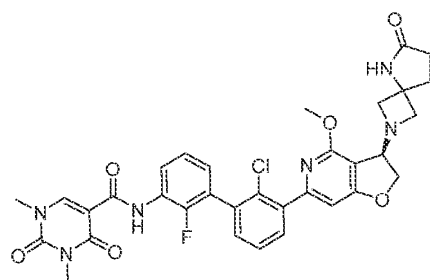


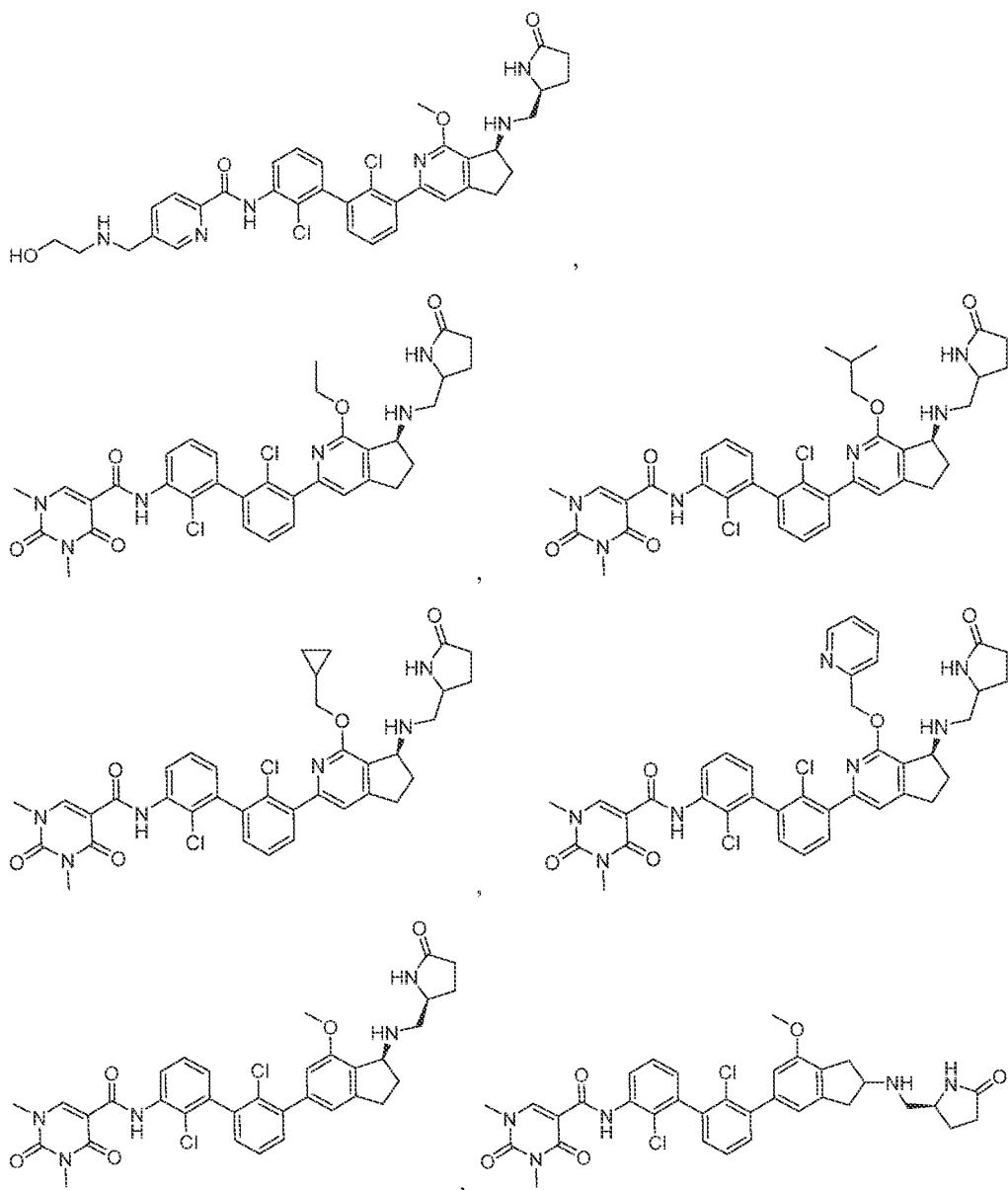


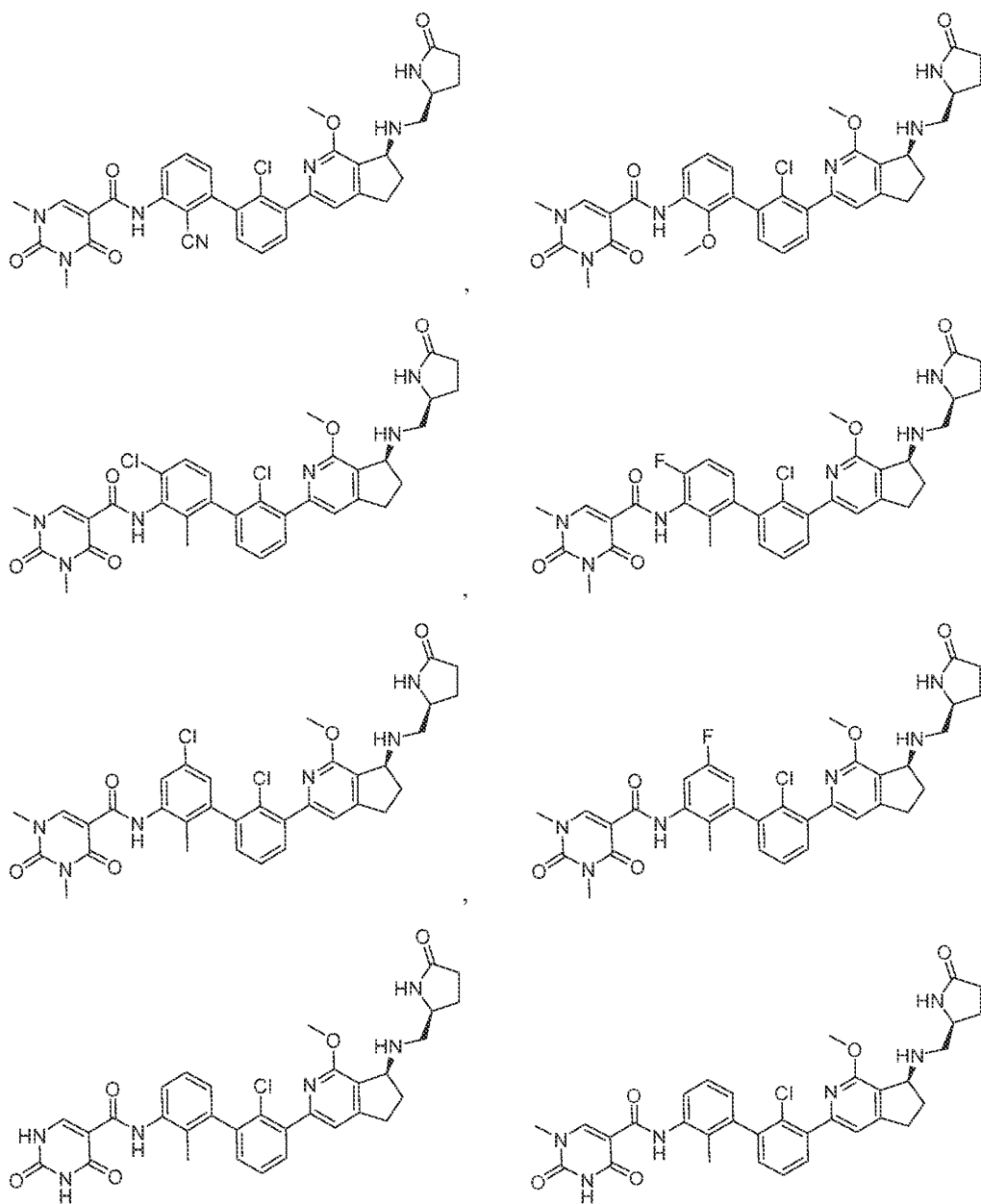


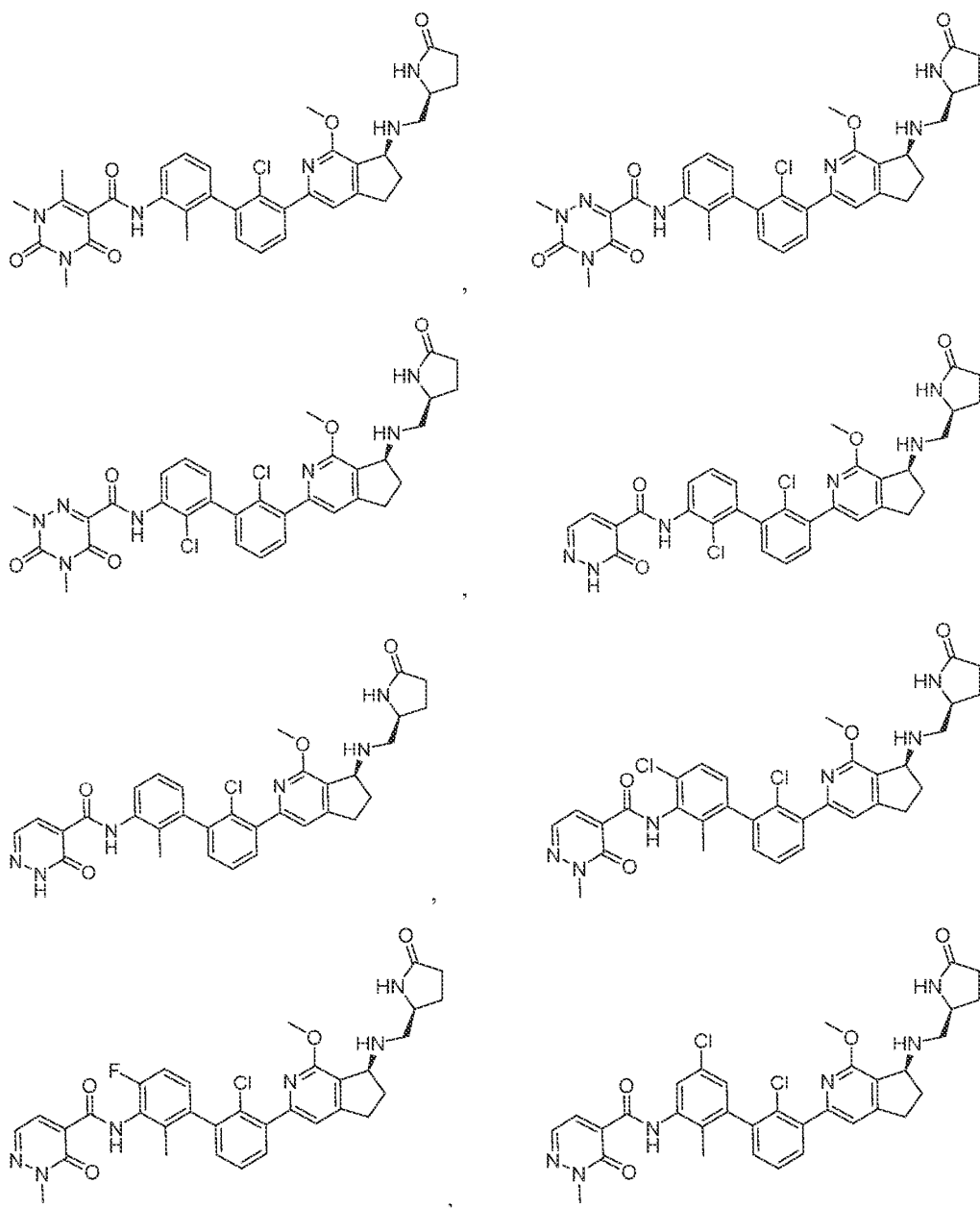


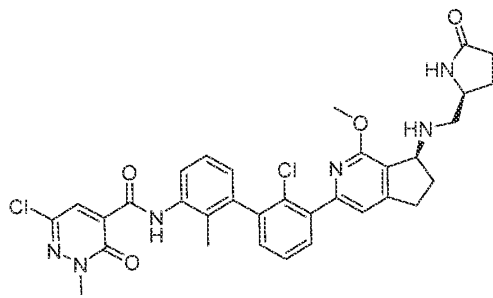
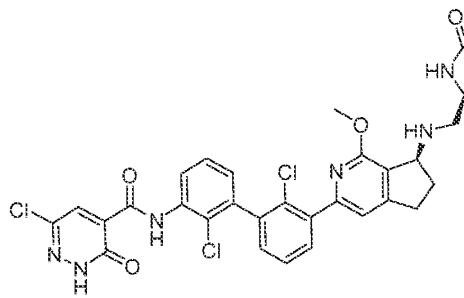
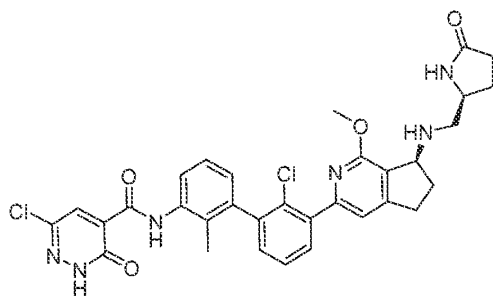
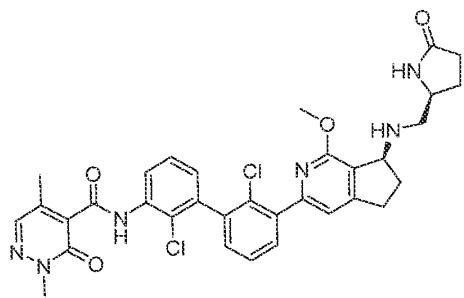
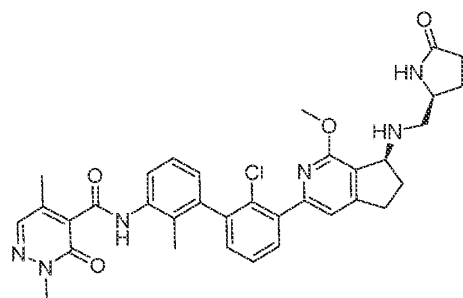
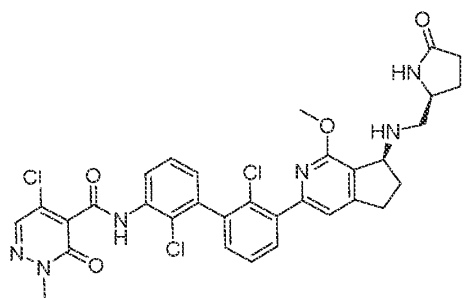
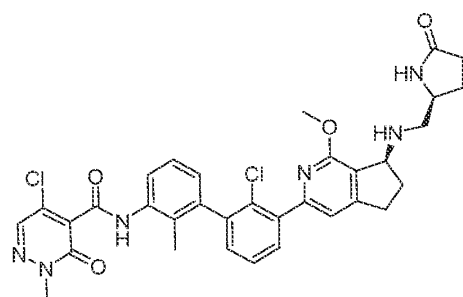
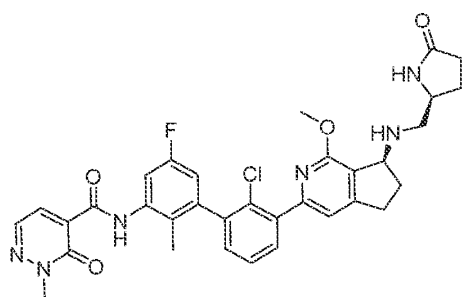


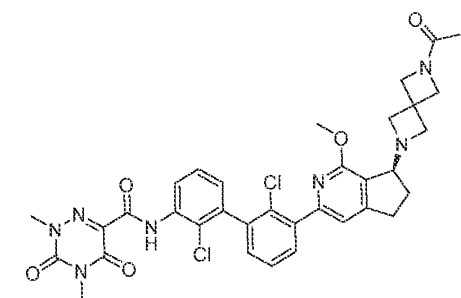
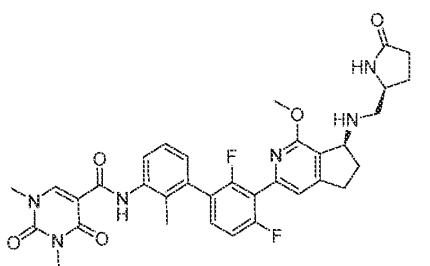
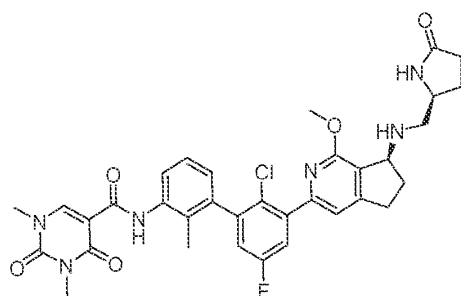
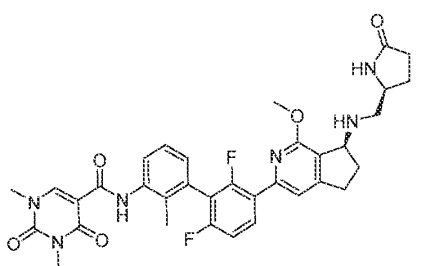
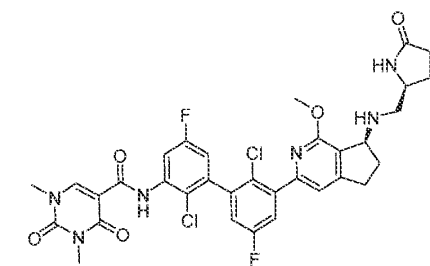
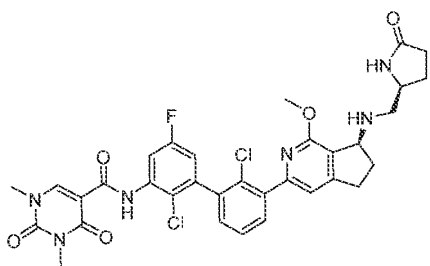
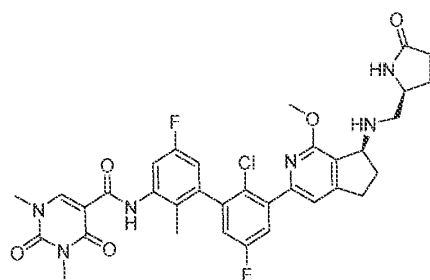
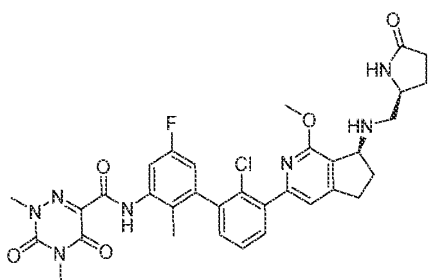


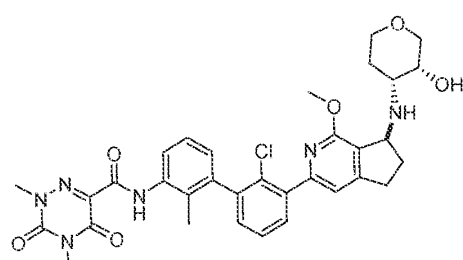
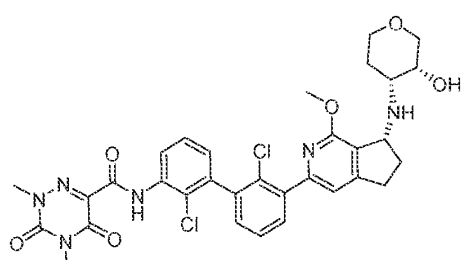
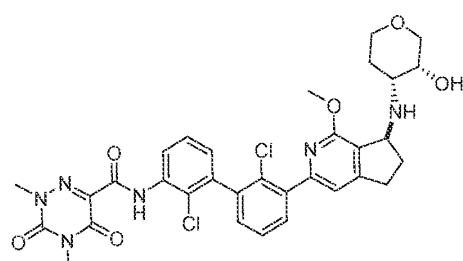
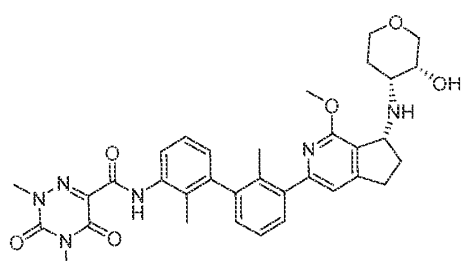
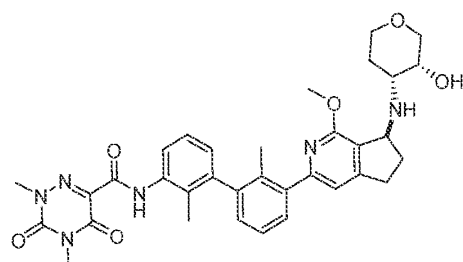
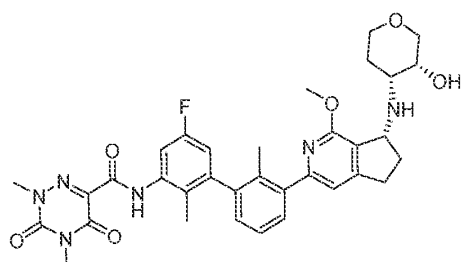
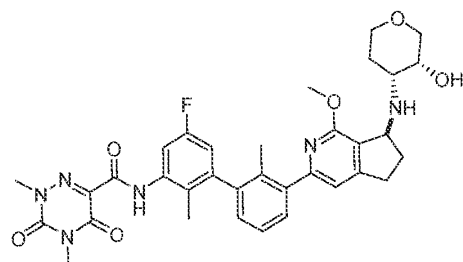
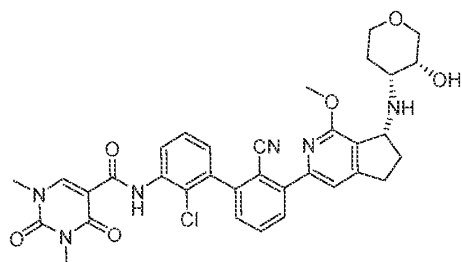
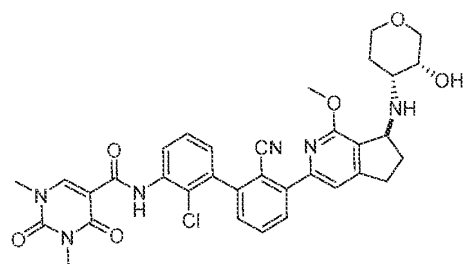
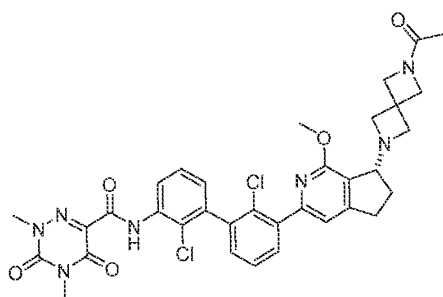


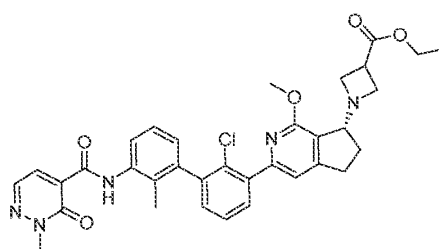
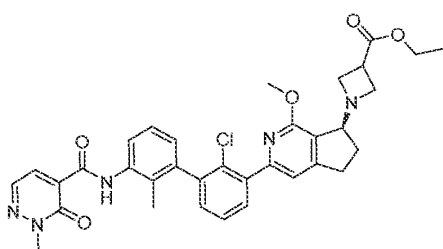
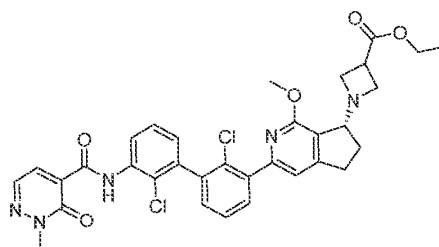
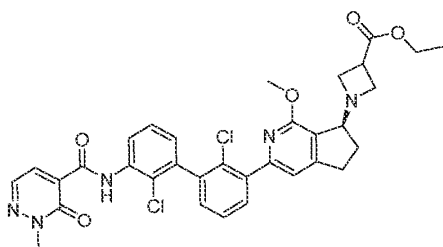
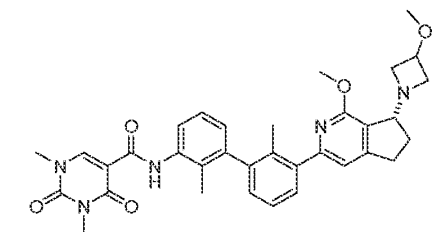
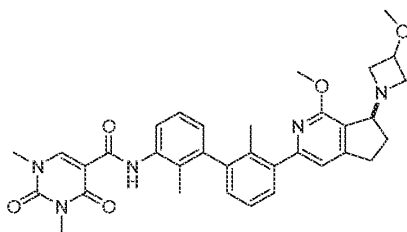
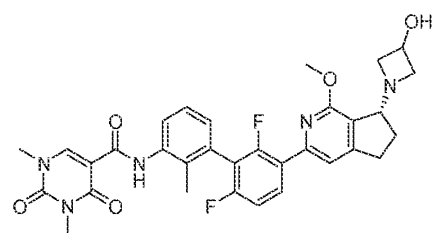
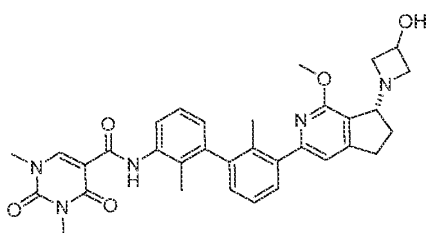
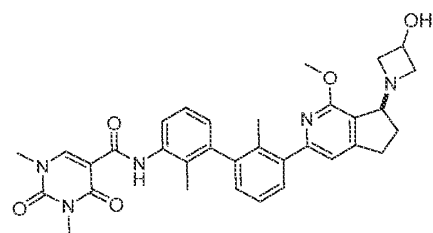
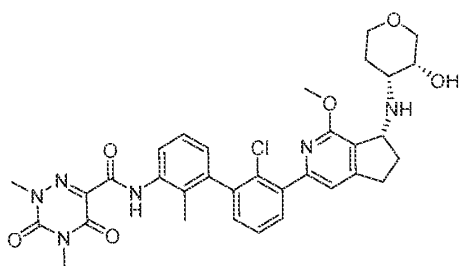


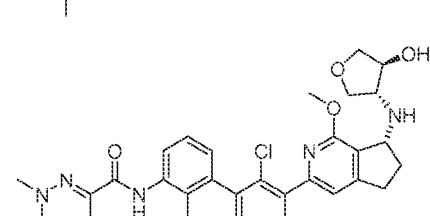
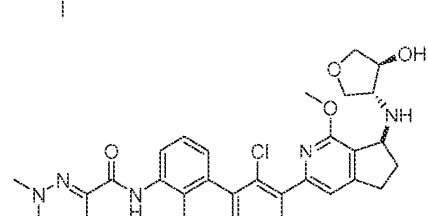
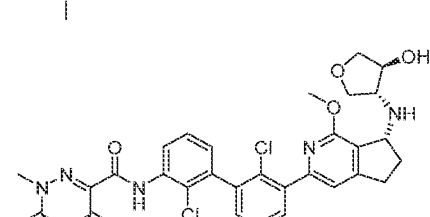
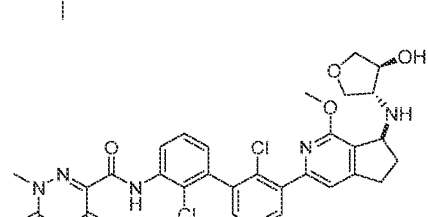
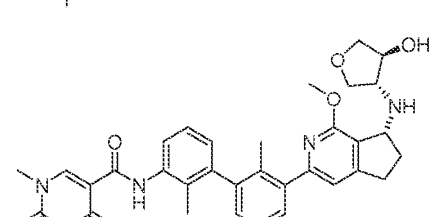
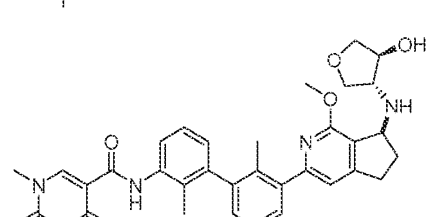
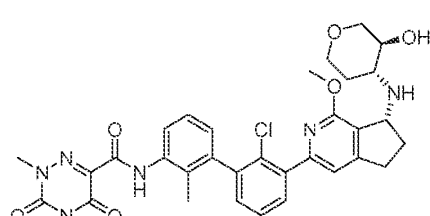
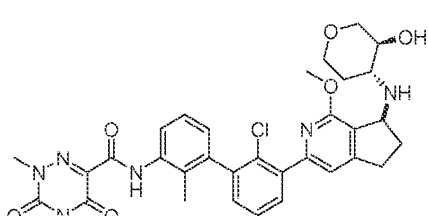
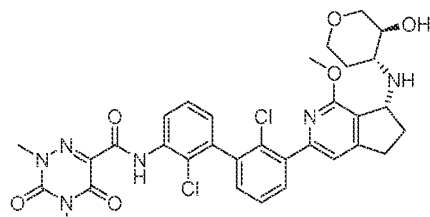
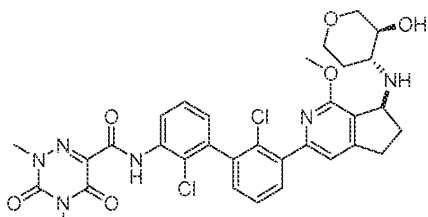
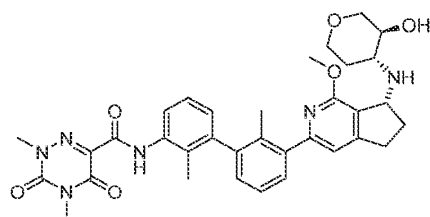
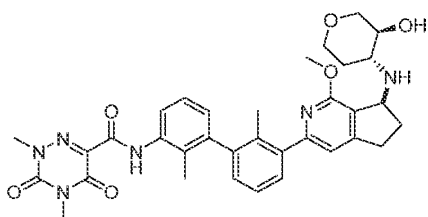


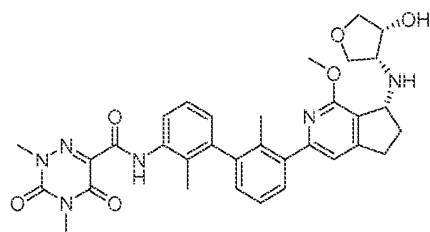
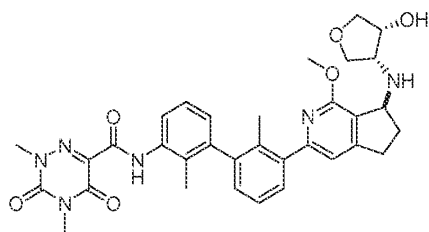
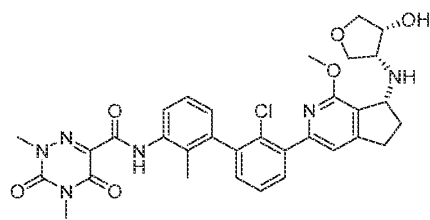
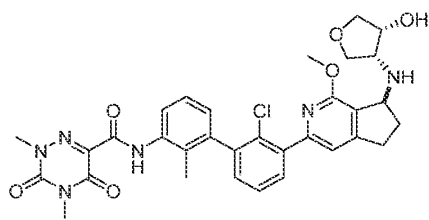
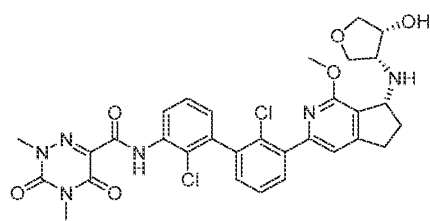
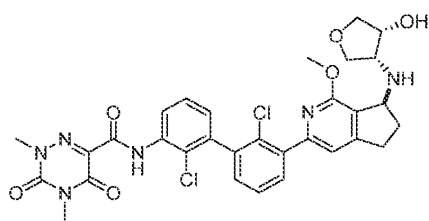
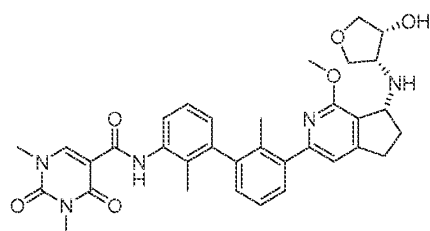
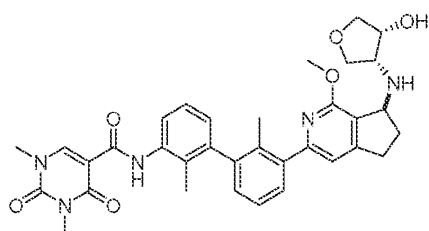
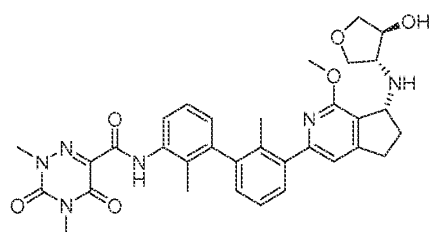
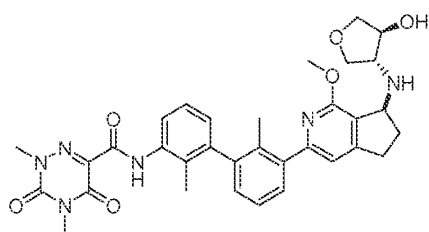


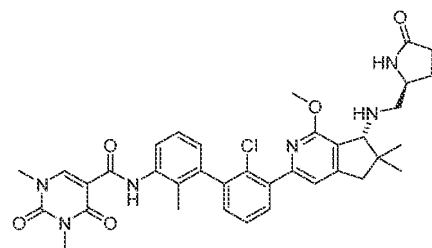
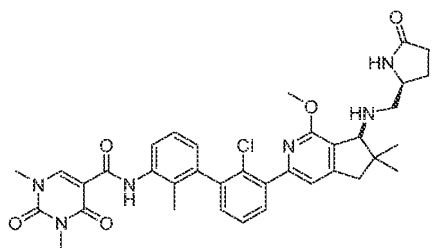
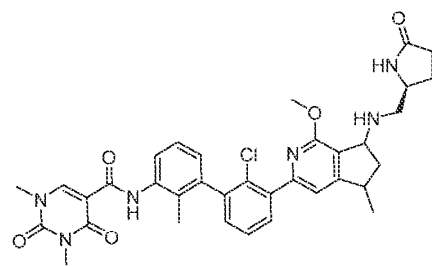
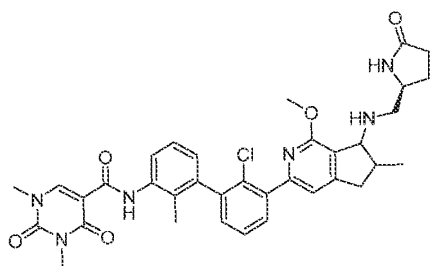
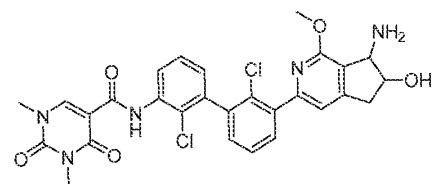
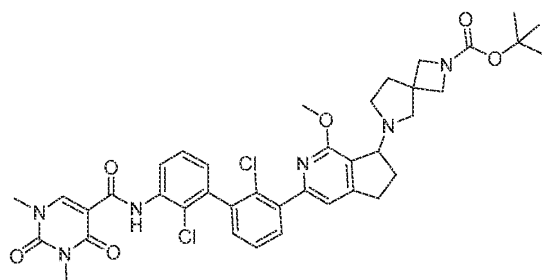
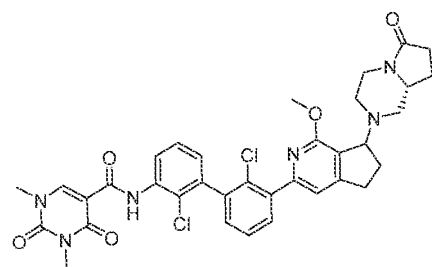
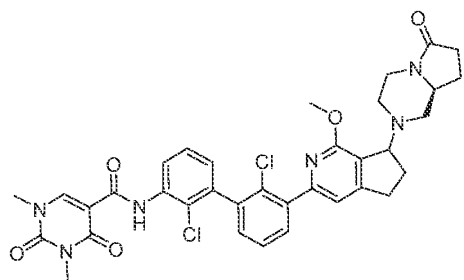
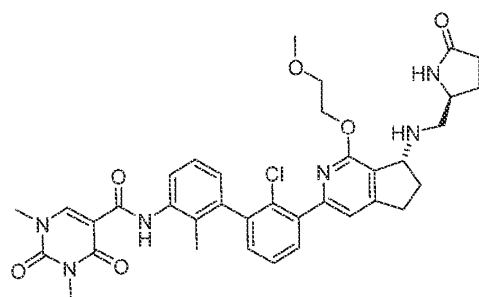
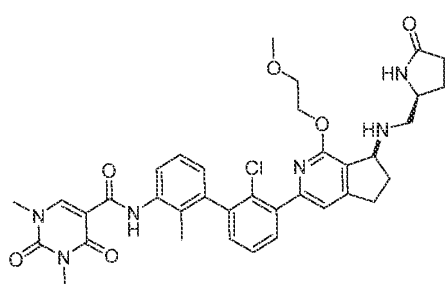


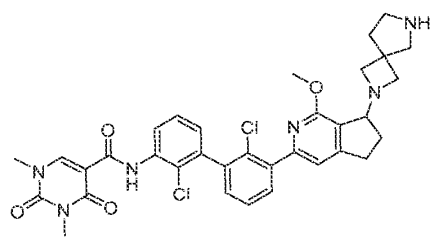
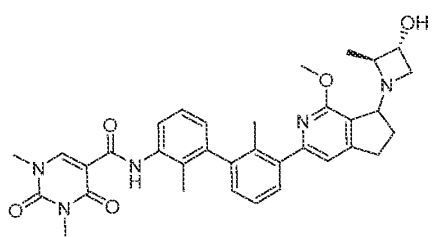
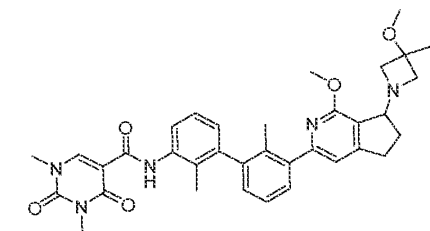
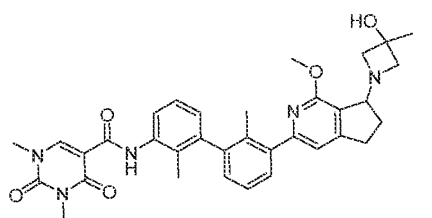
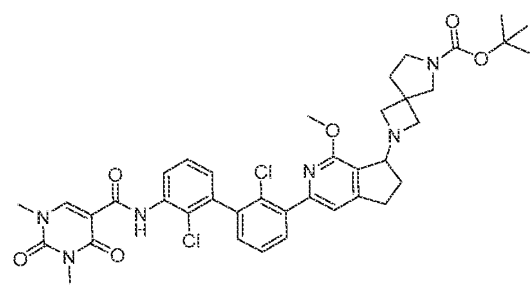
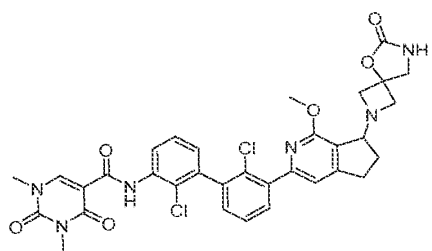
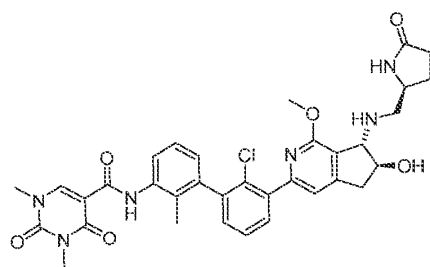
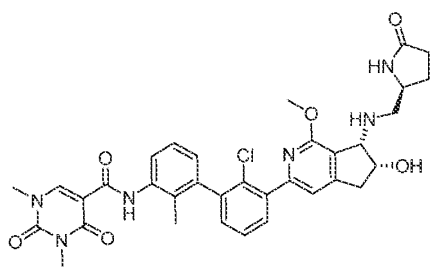
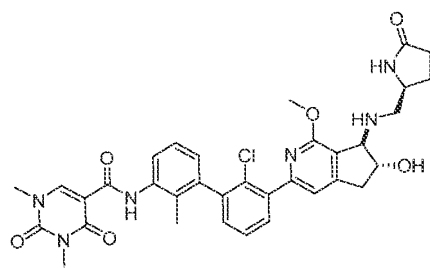
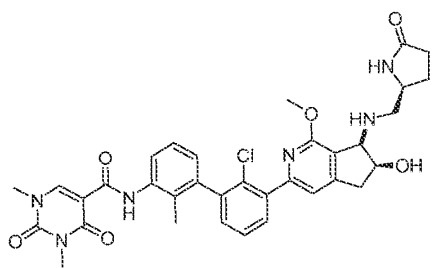


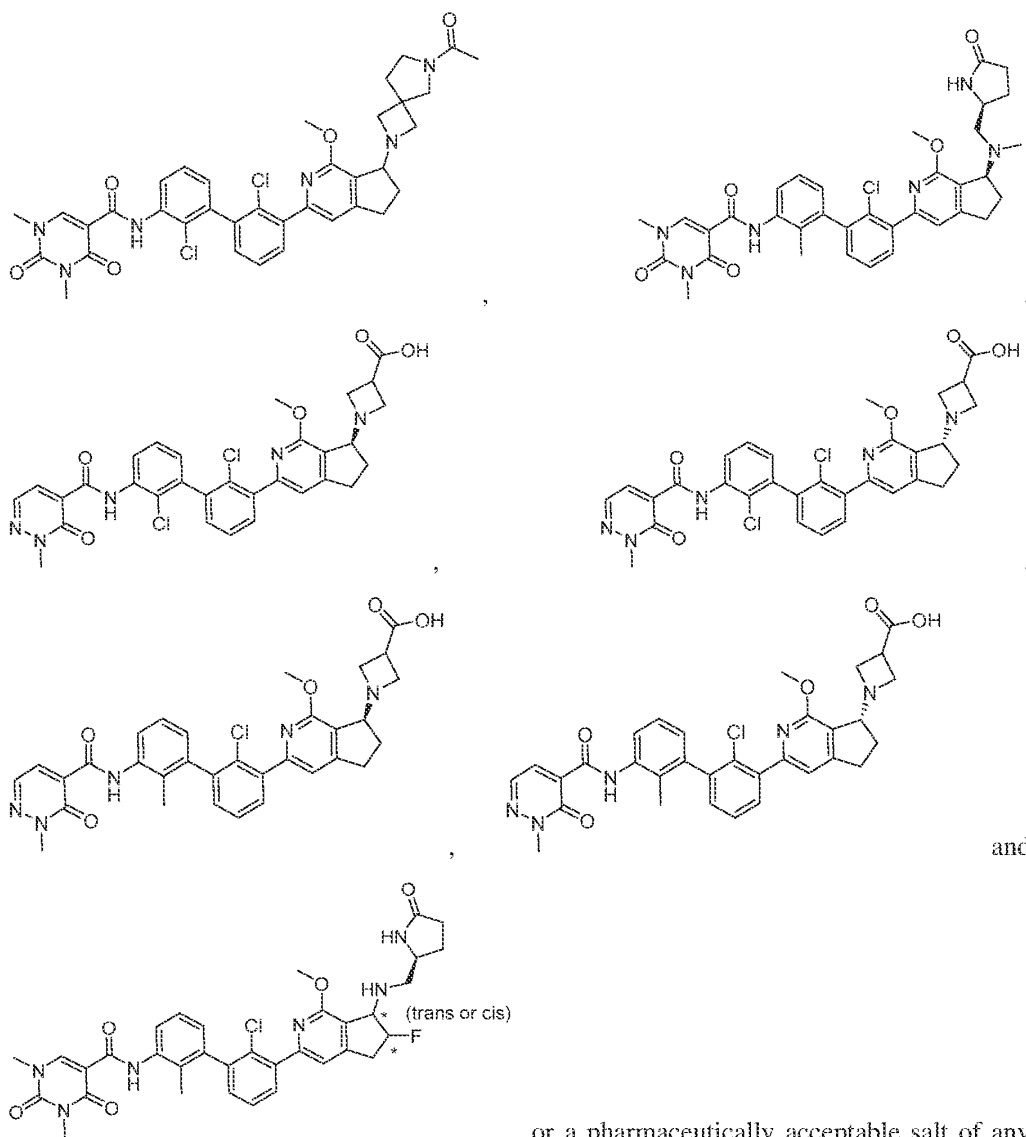








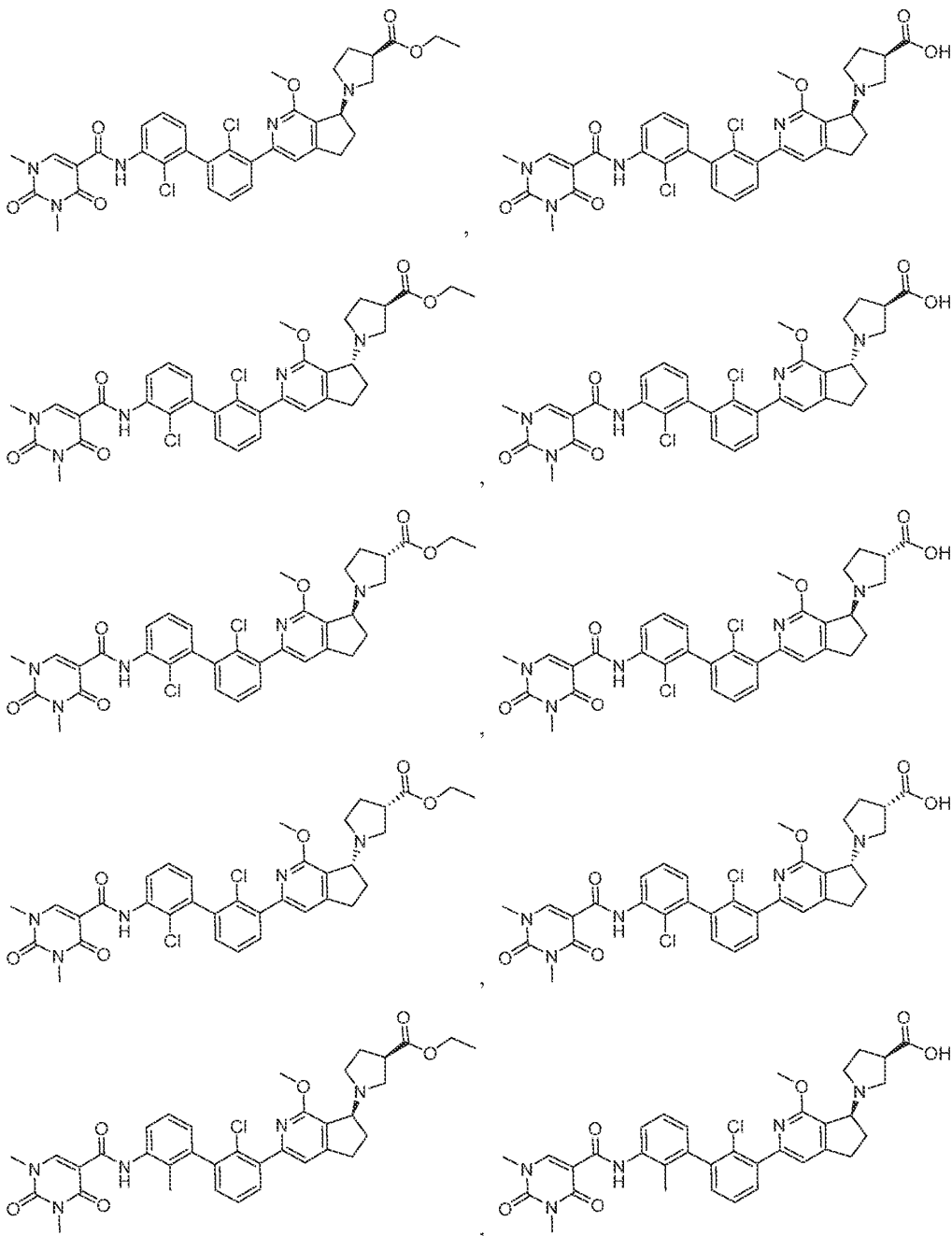


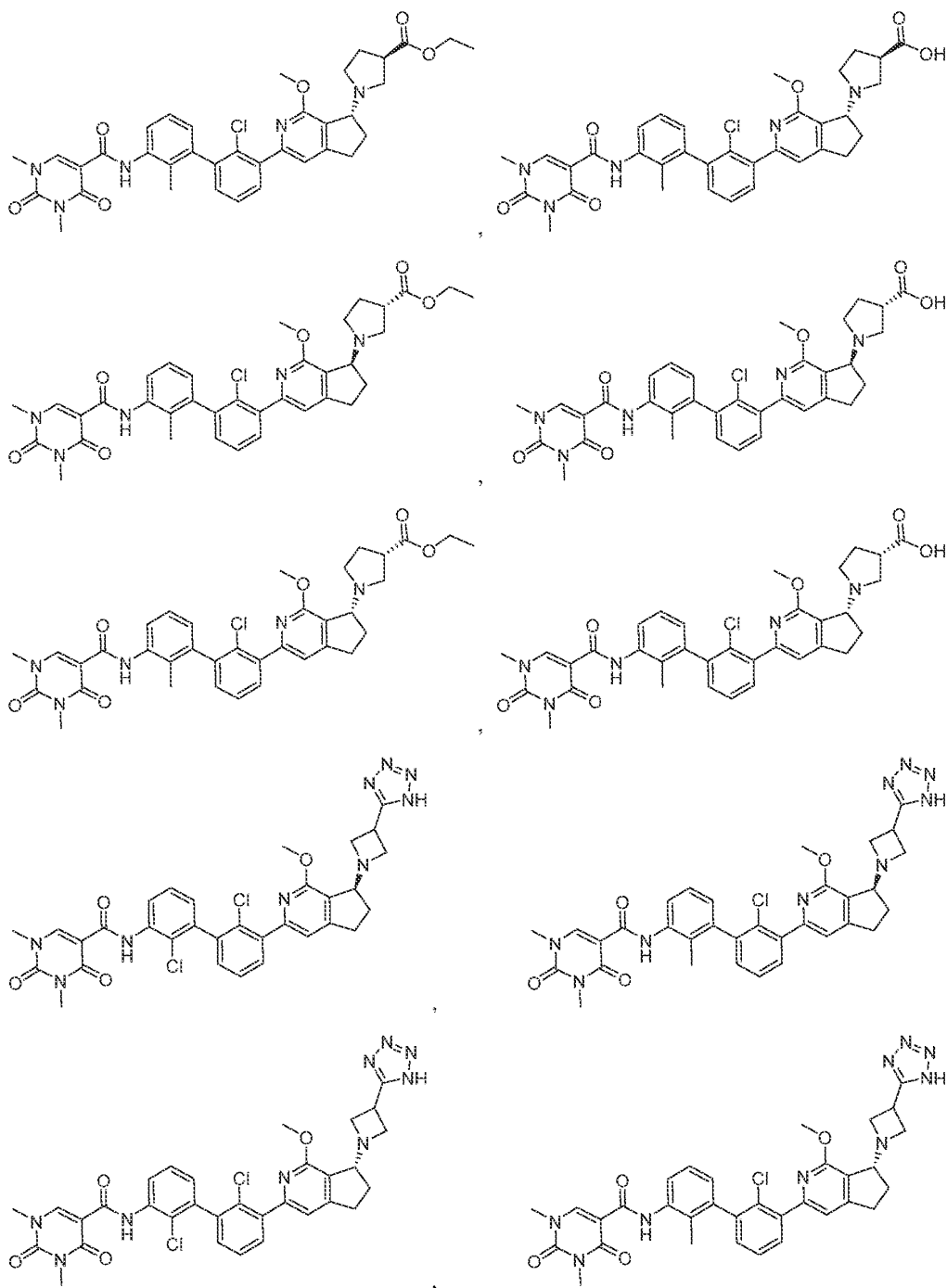


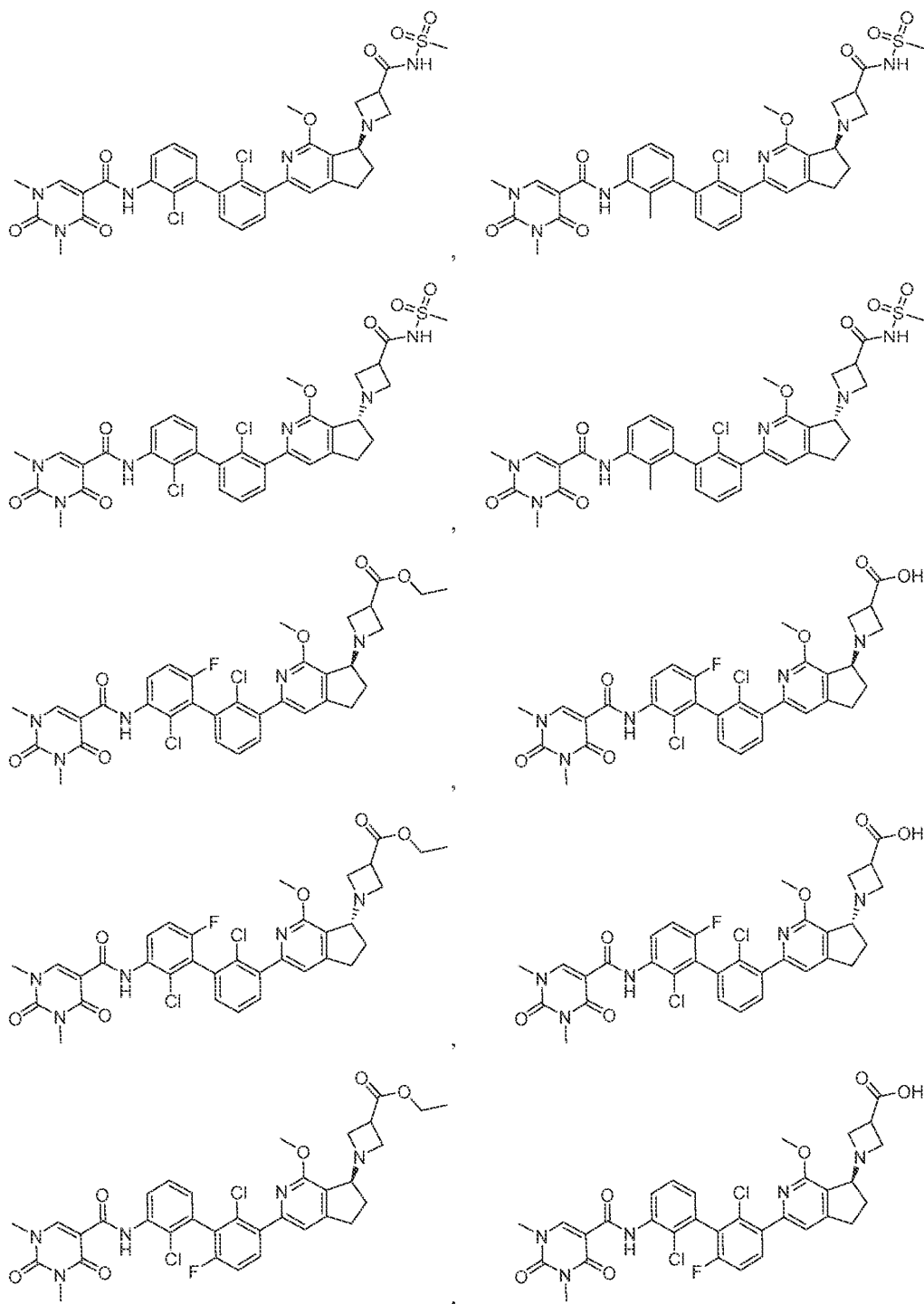
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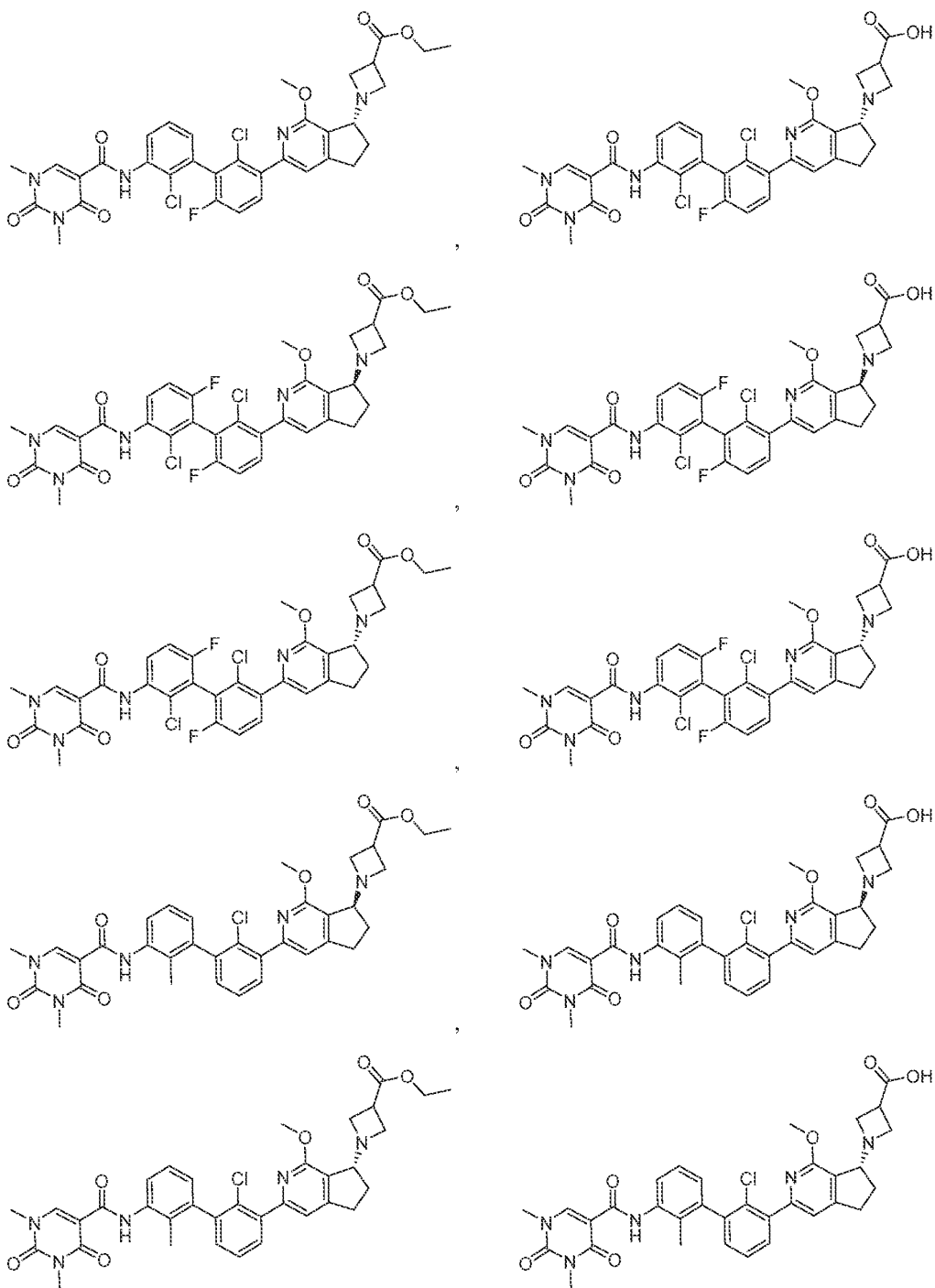
Embodiment 145

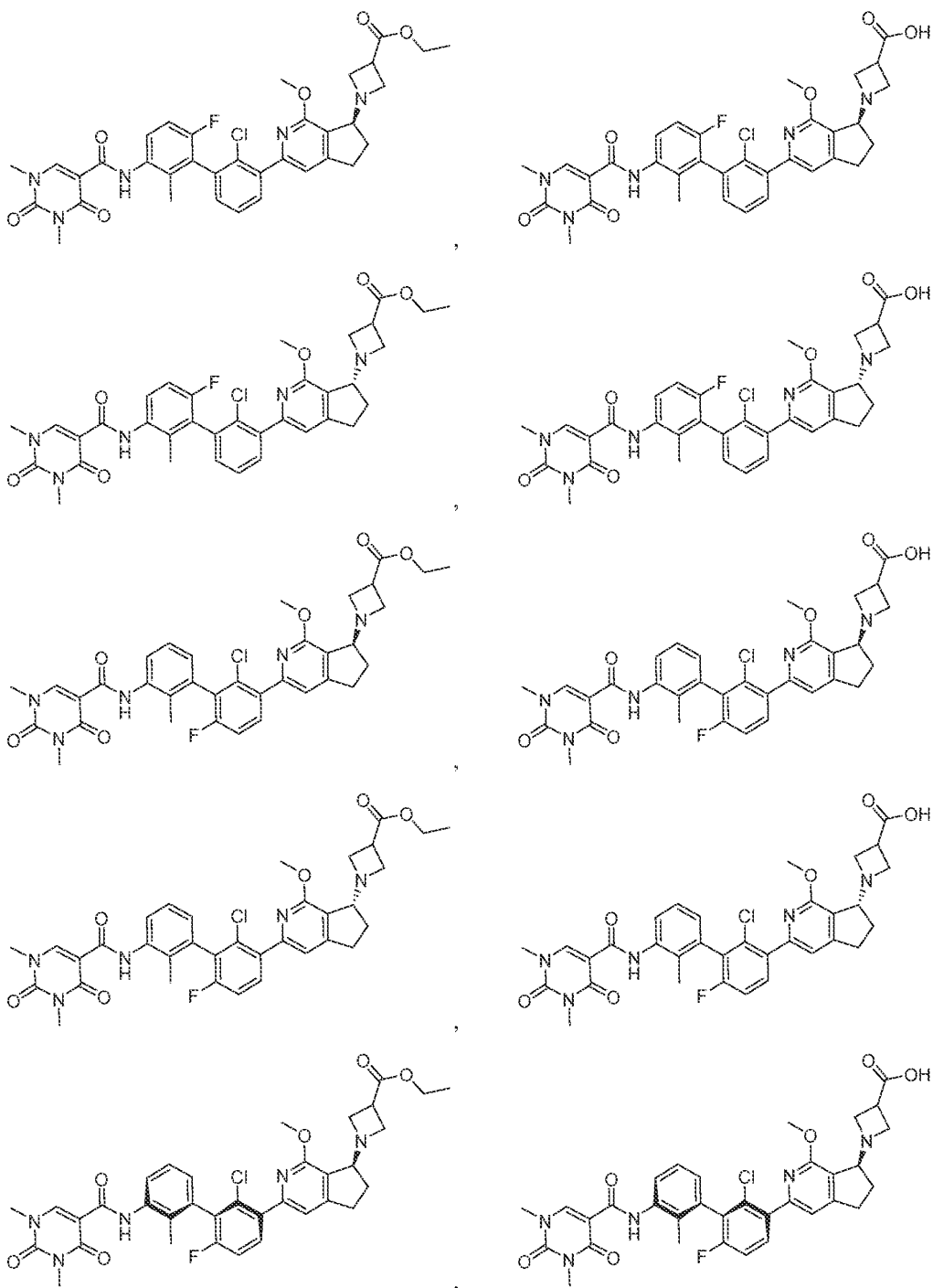
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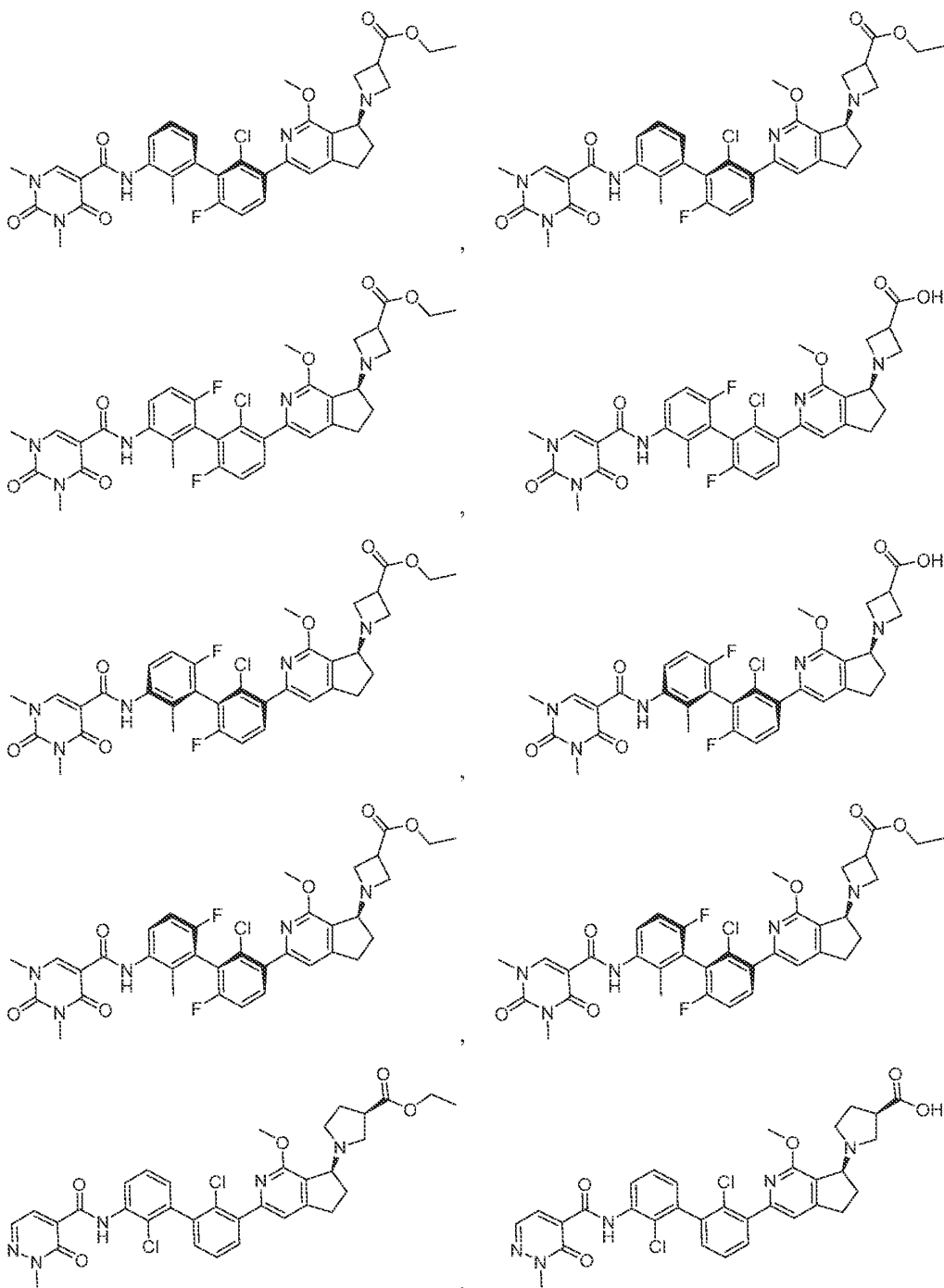


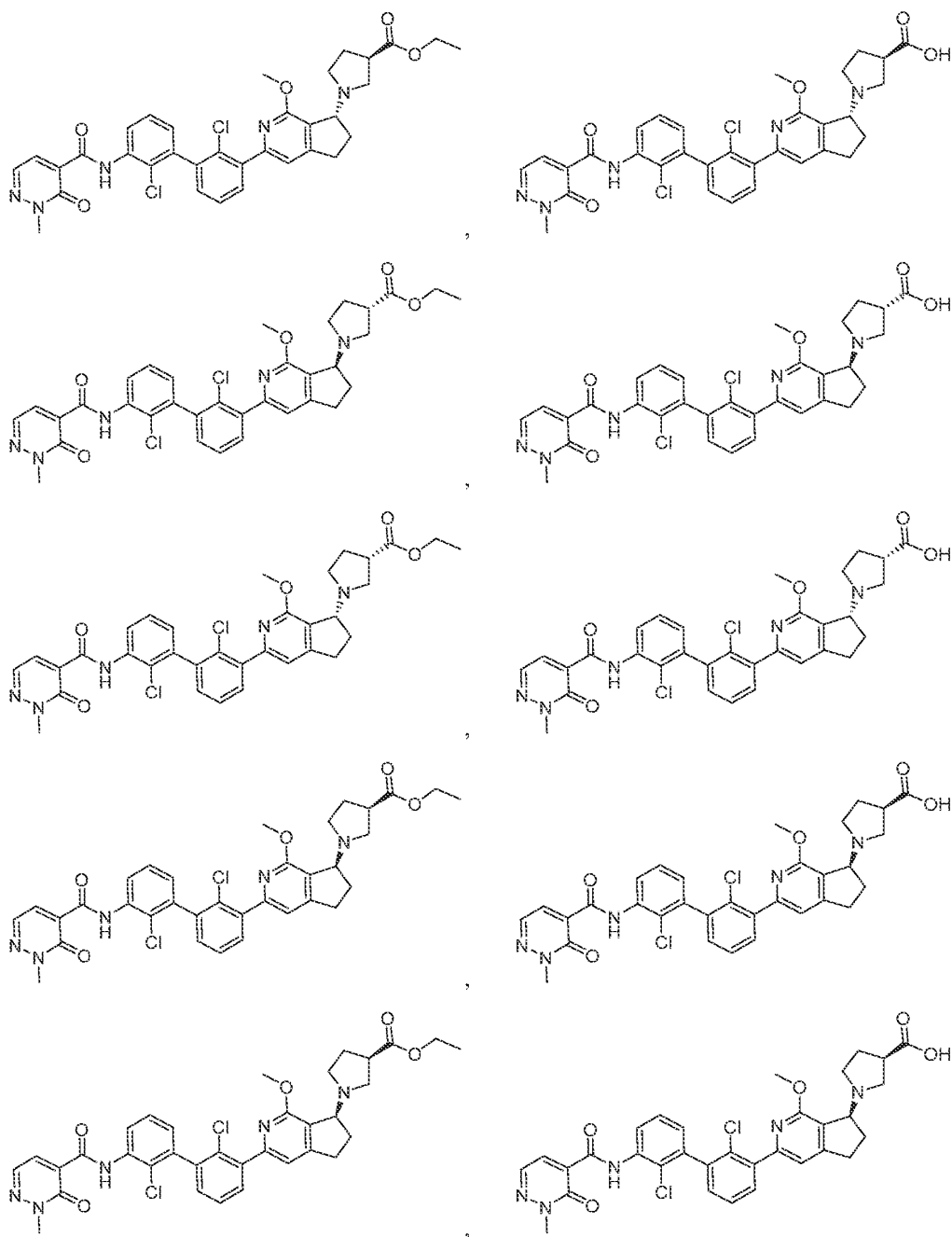


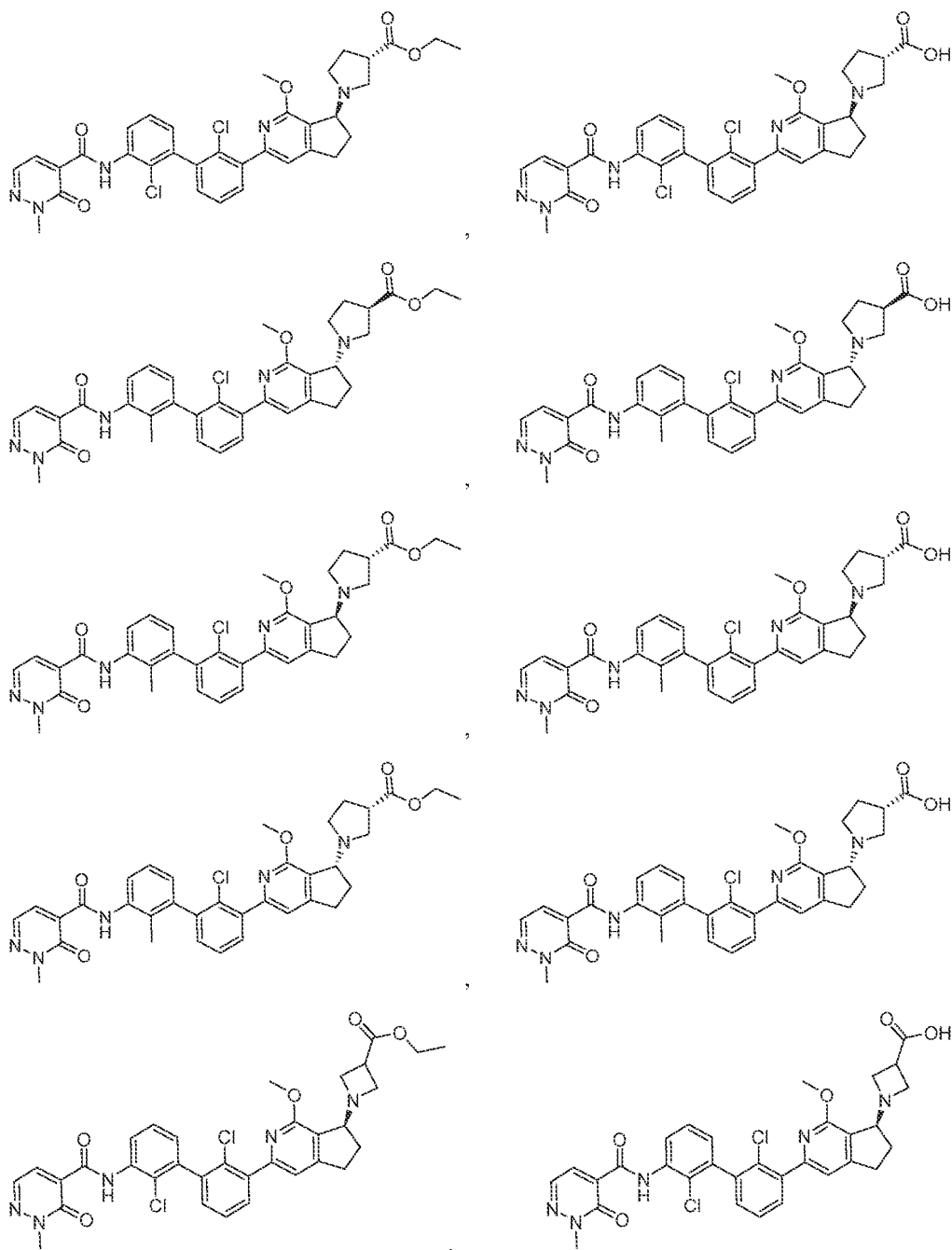


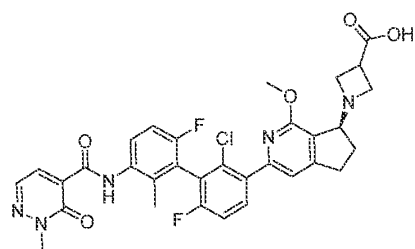
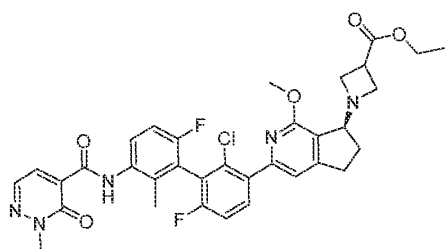
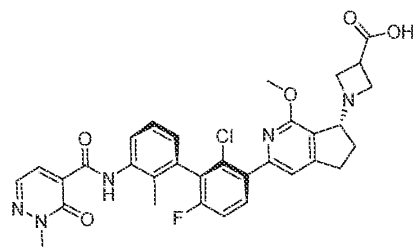
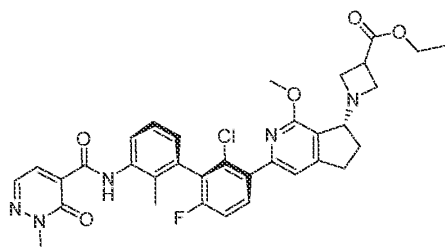
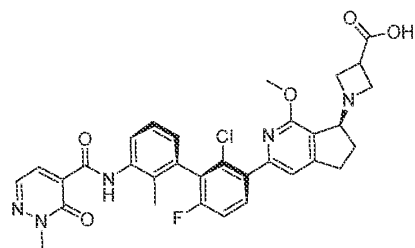
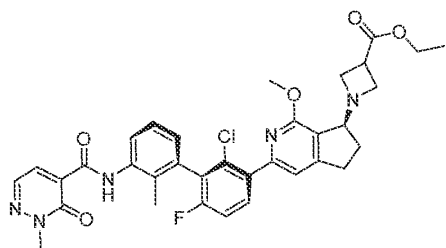
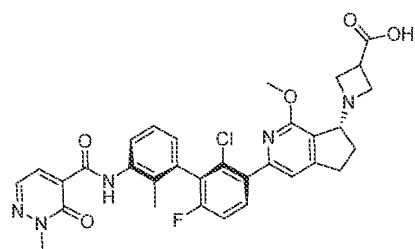
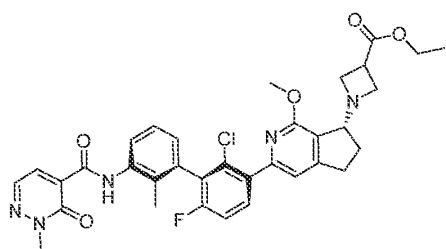
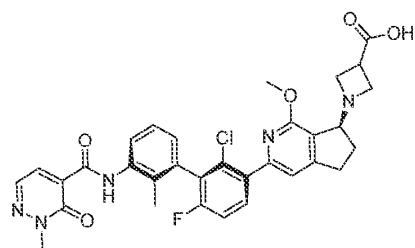
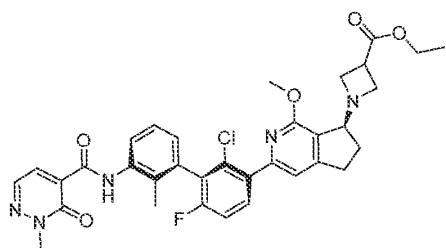


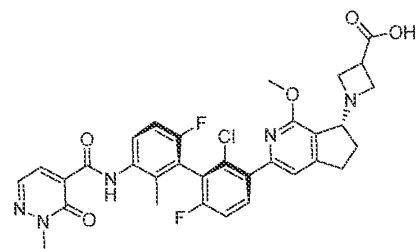
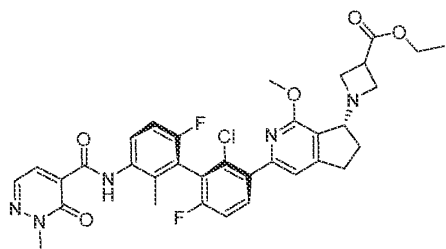
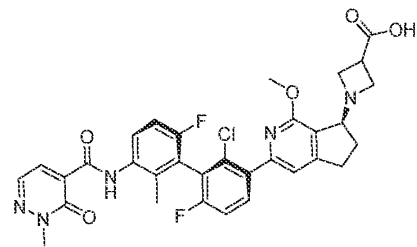
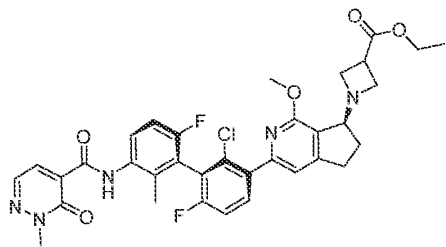
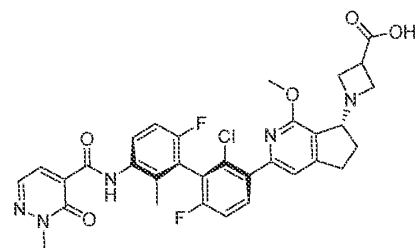
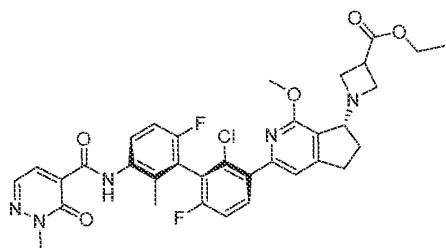
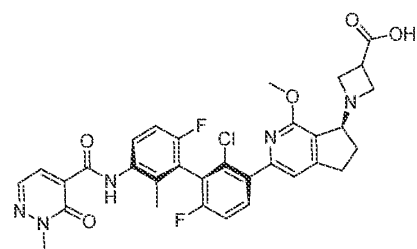
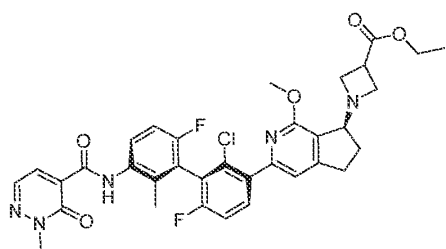
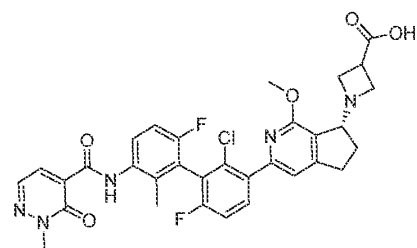
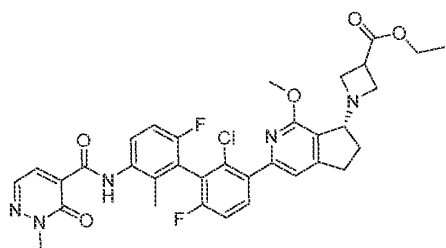


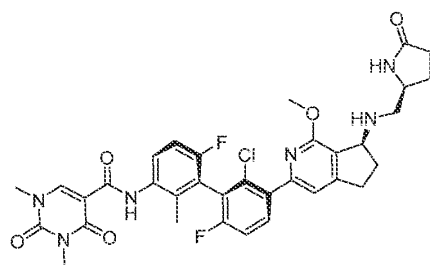
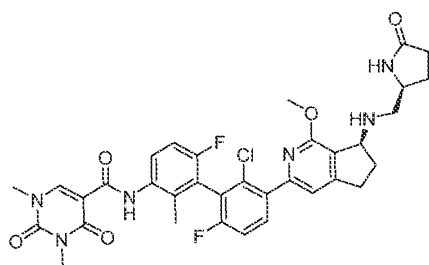
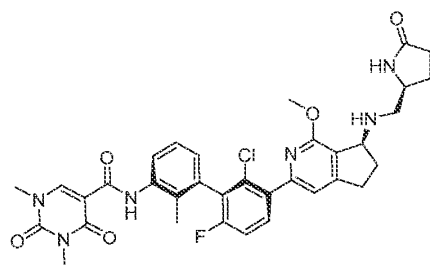
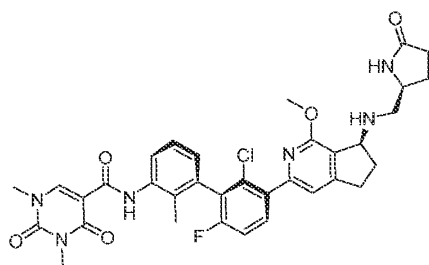
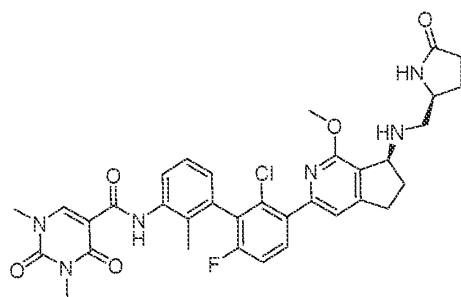
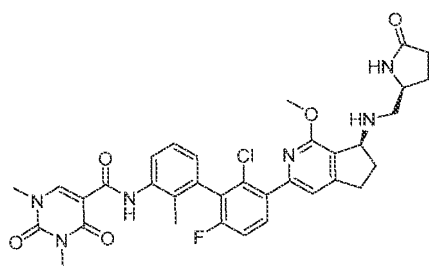
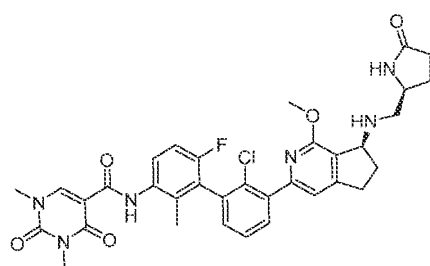
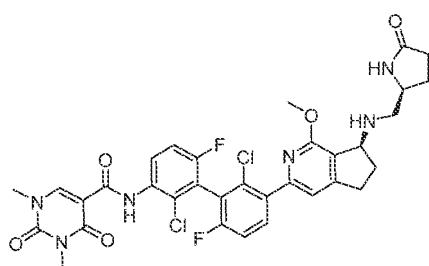
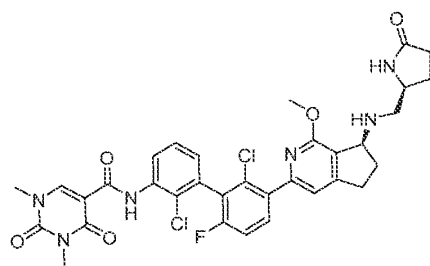
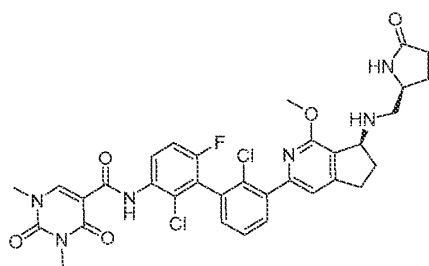


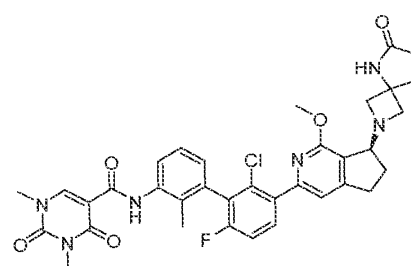
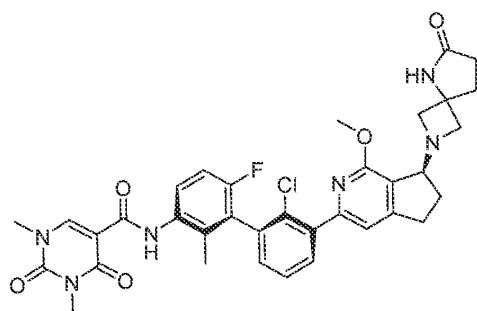
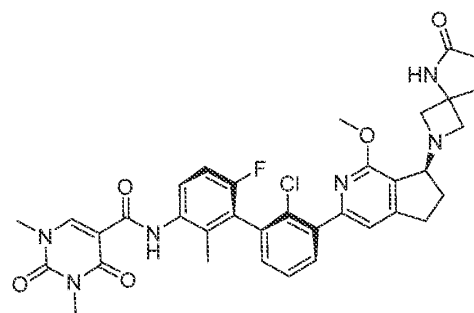
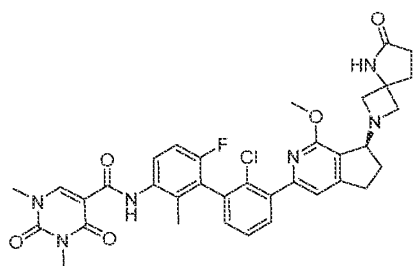
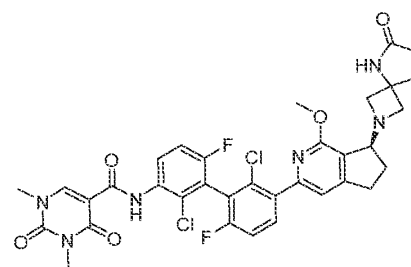
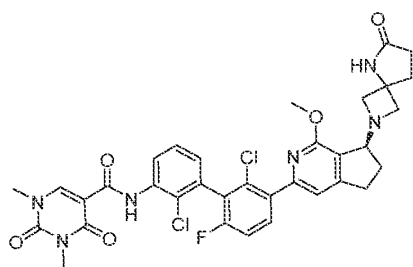
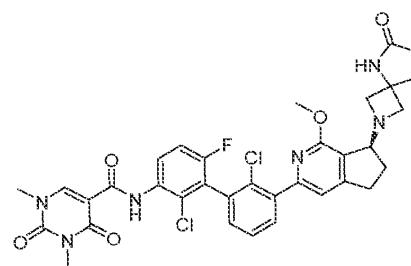
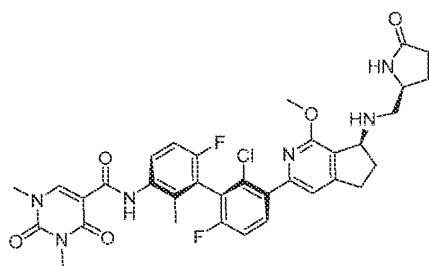


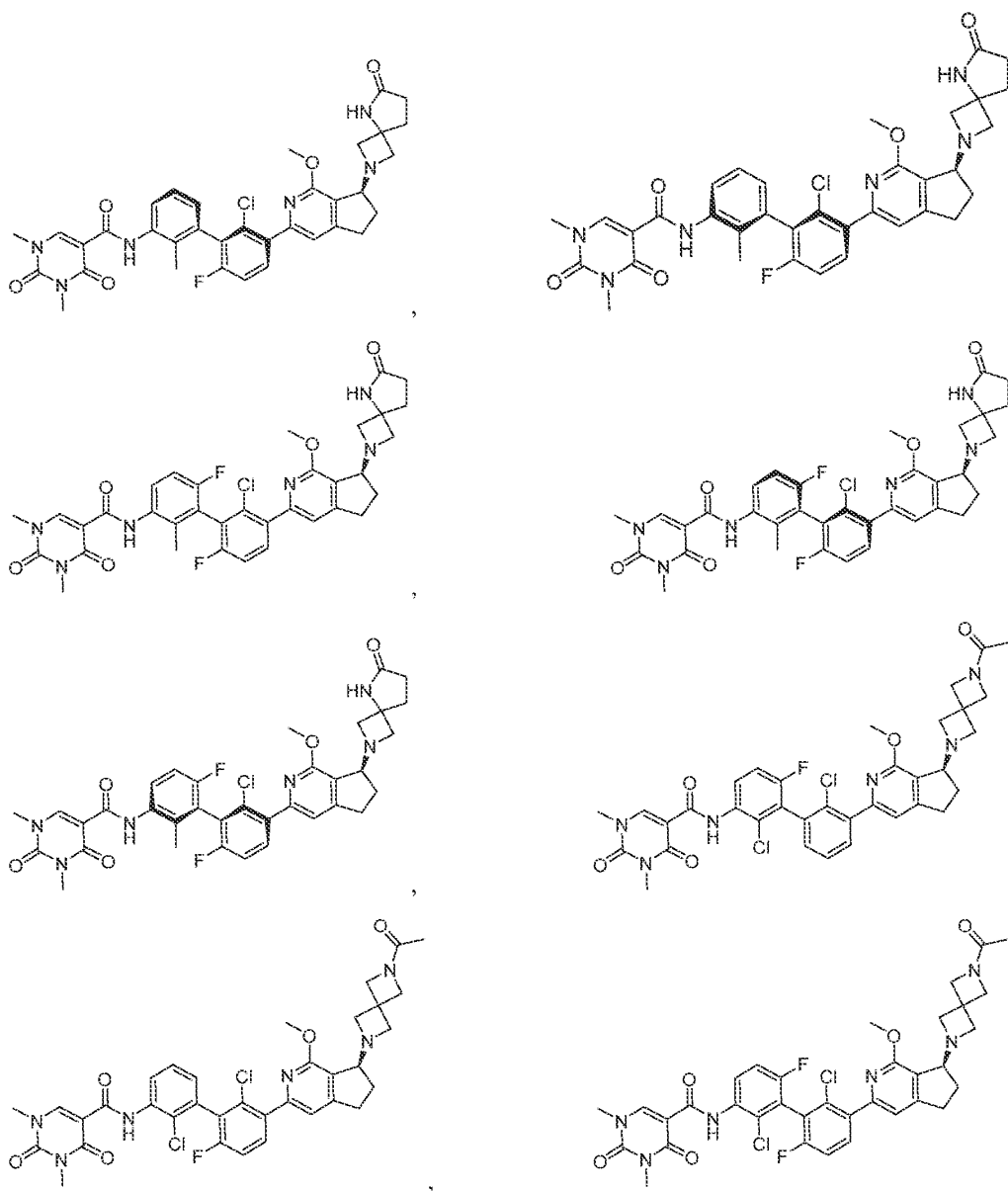


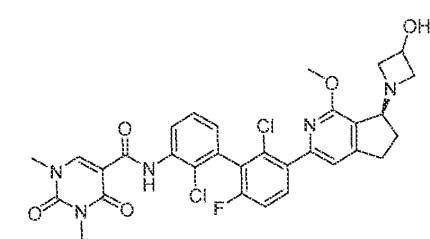
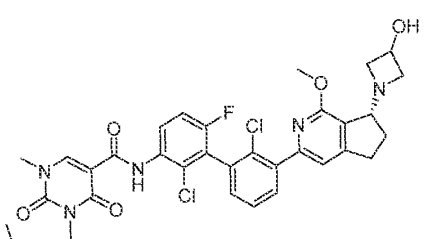
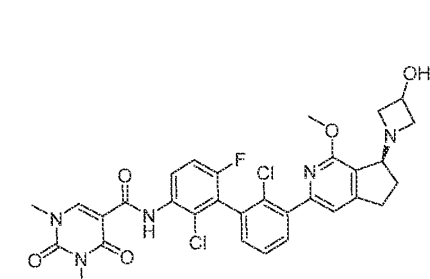
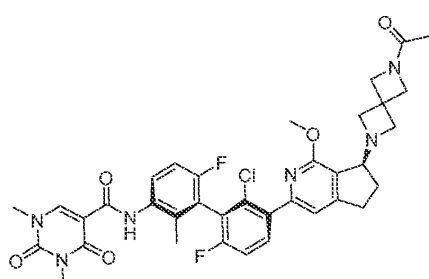
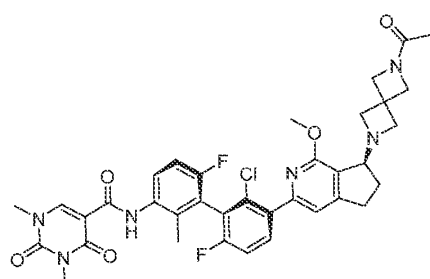
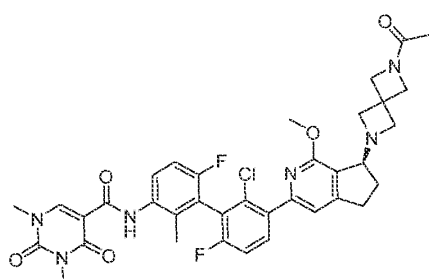
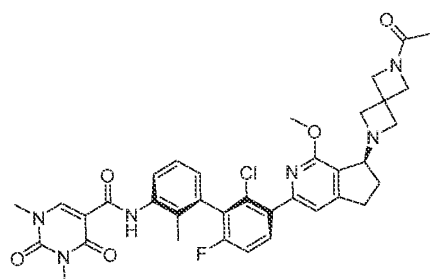
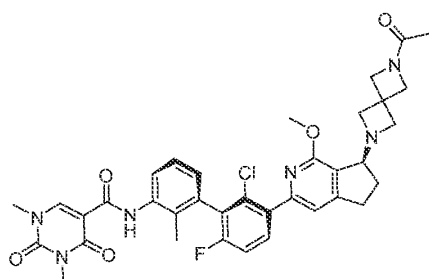
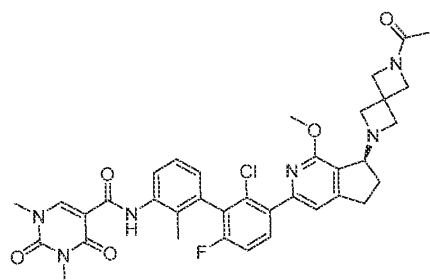
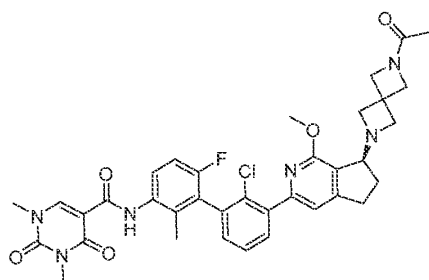


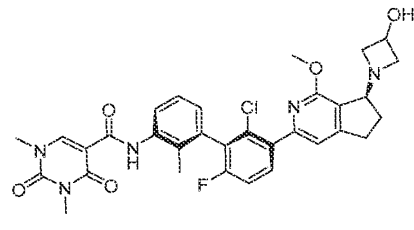
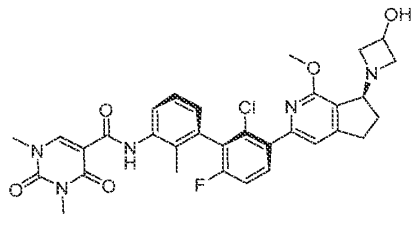
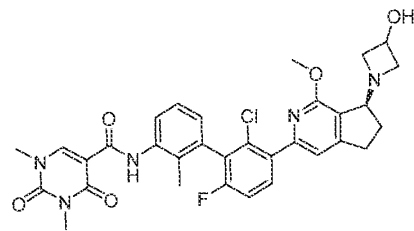
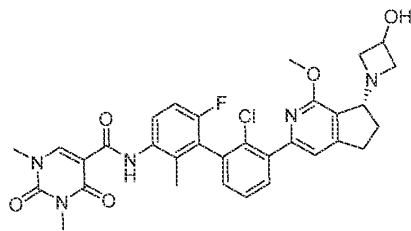
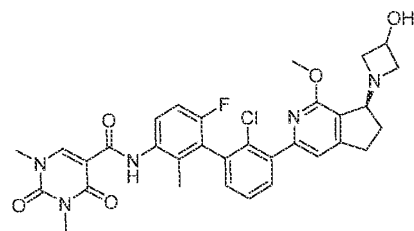
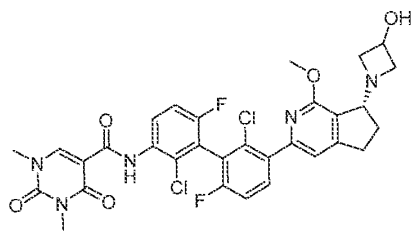
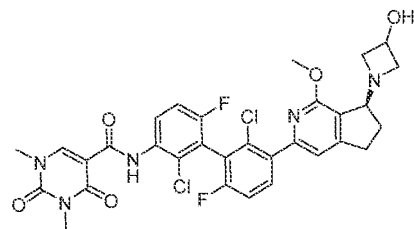
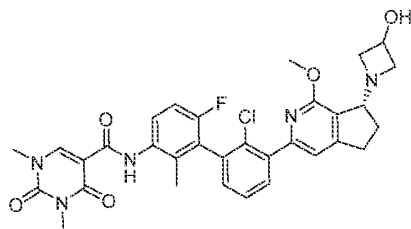
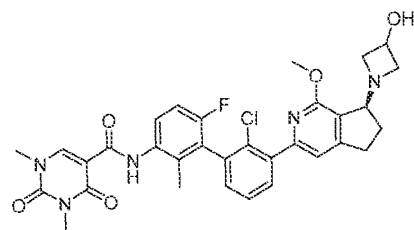
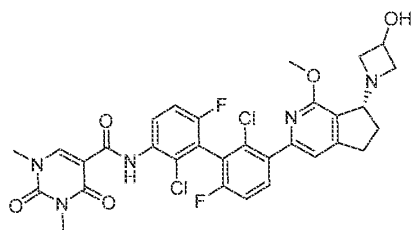
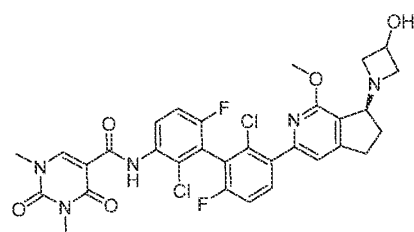
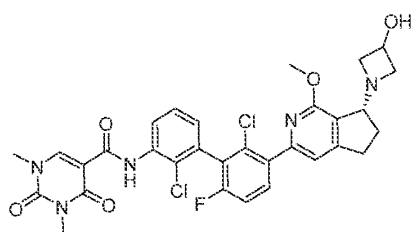


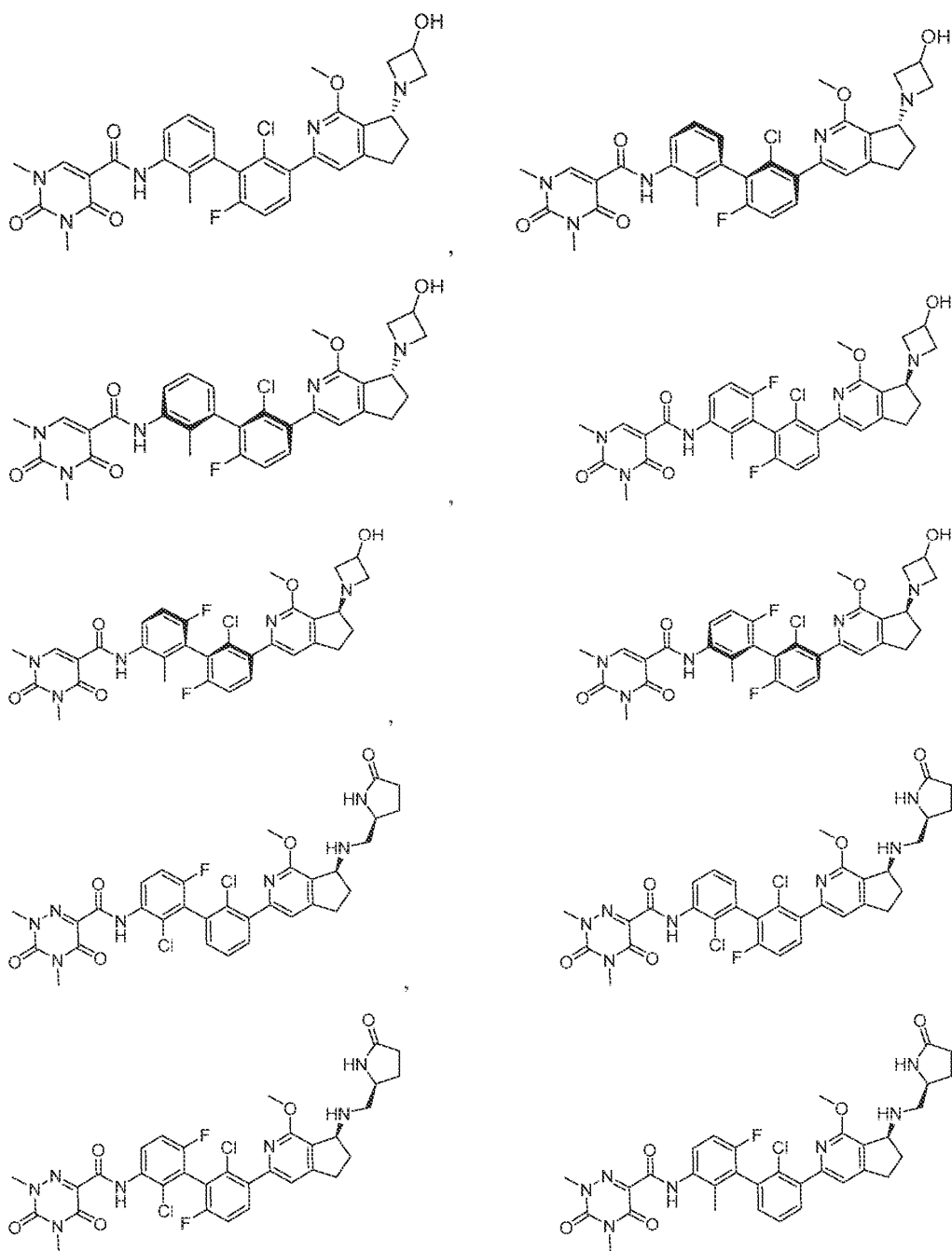


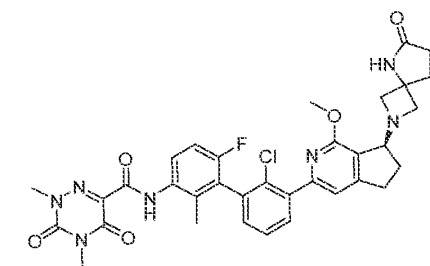
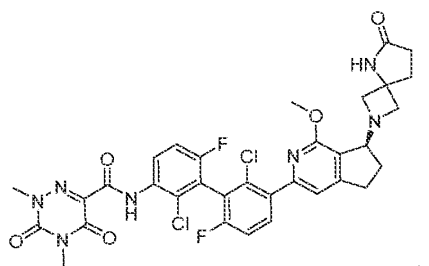
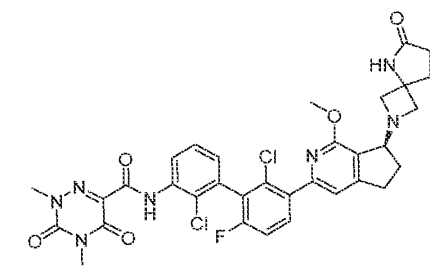
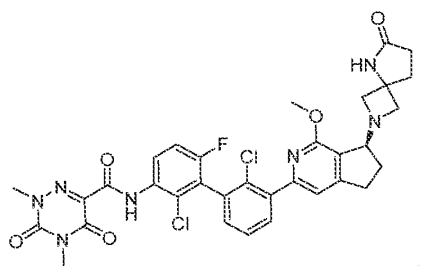
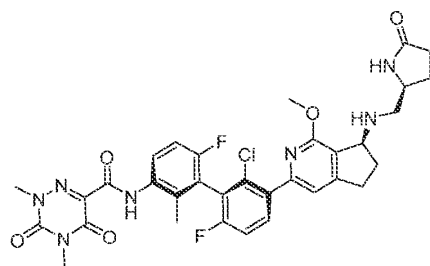
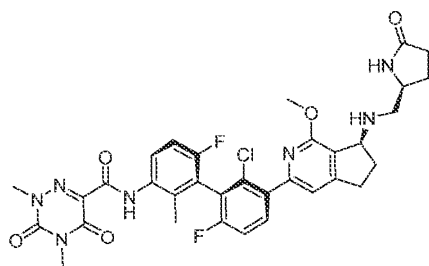
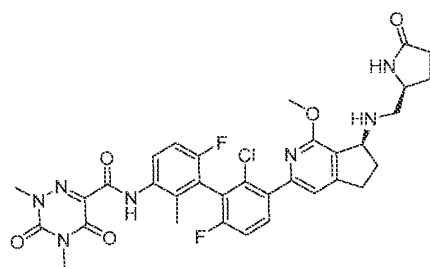
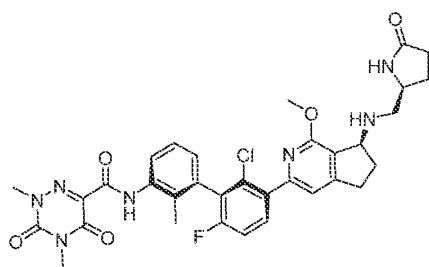
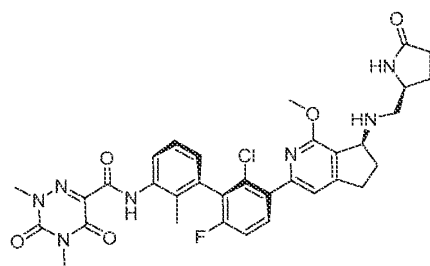
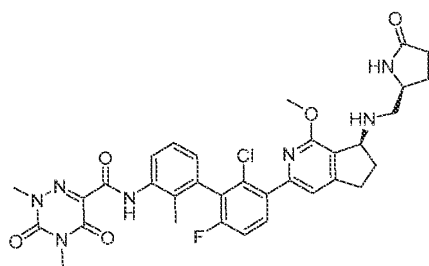


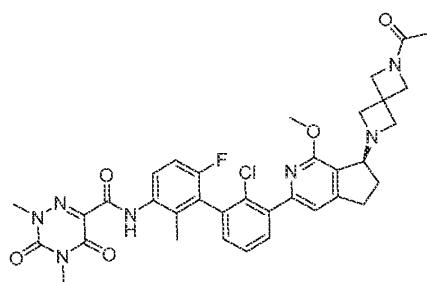
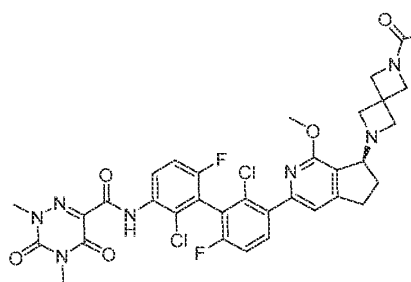
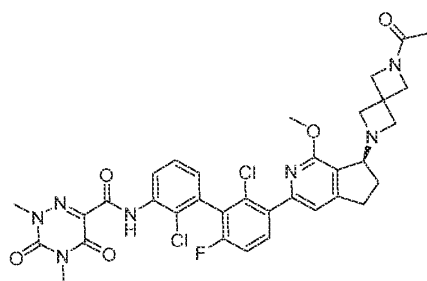
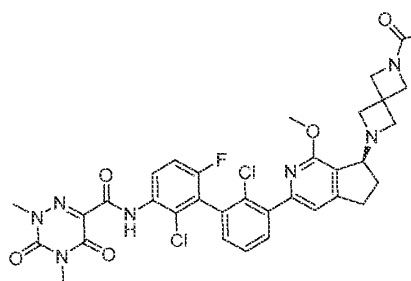
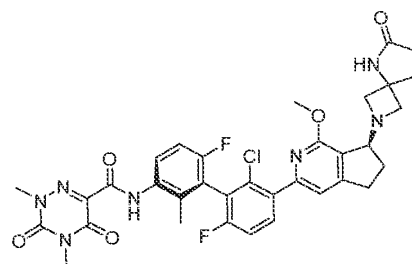
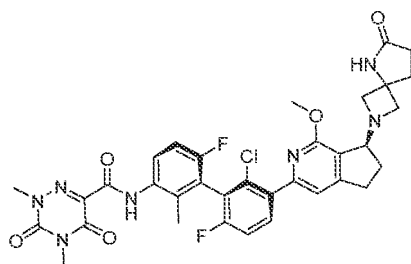
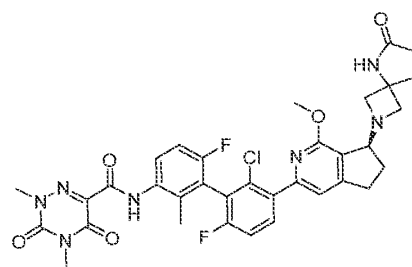
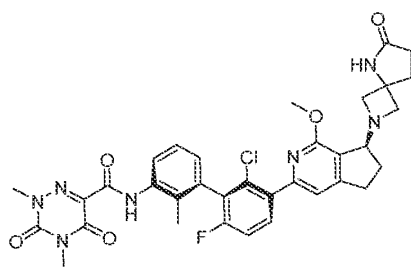
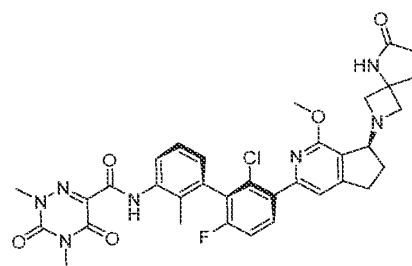
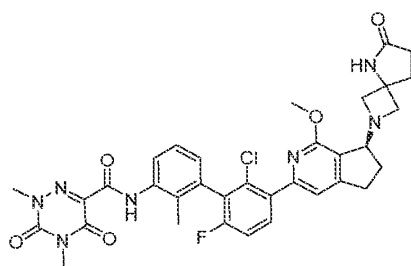


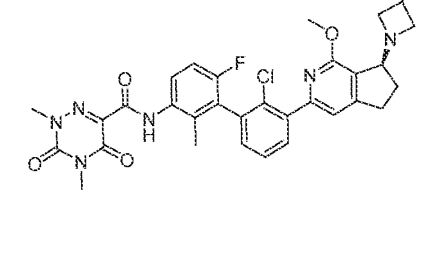
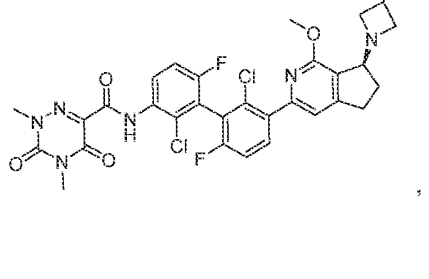
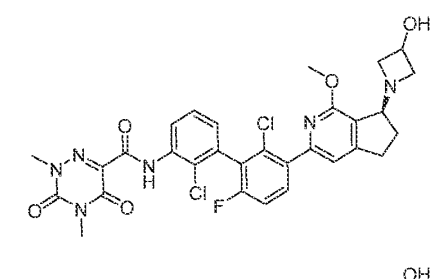
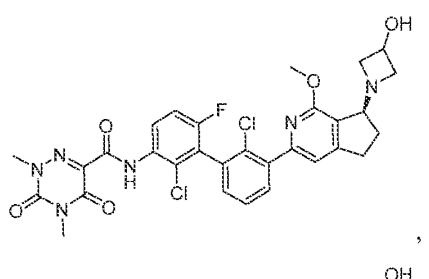
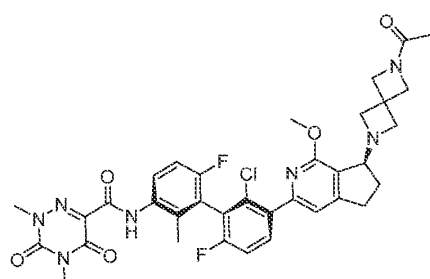
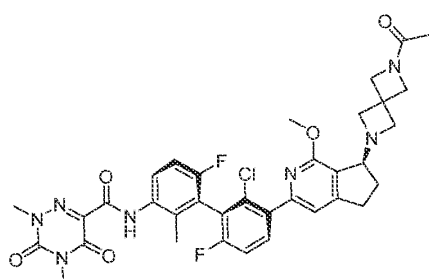
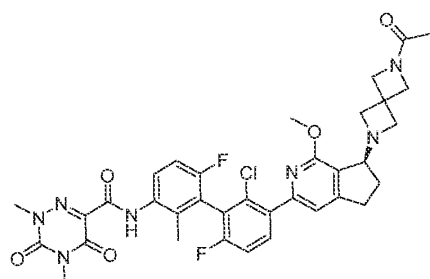
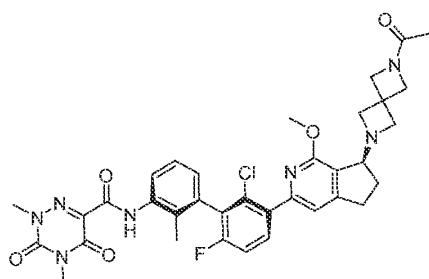
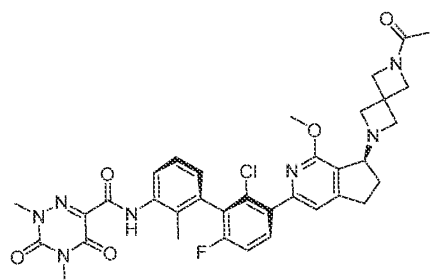
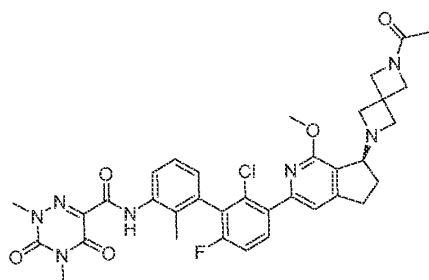


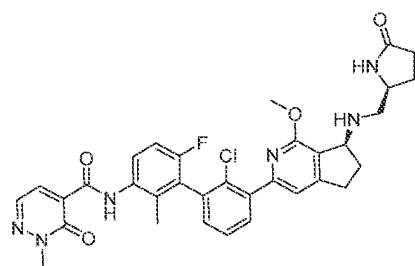
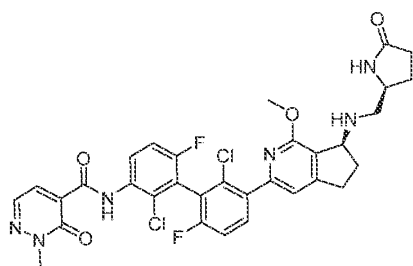
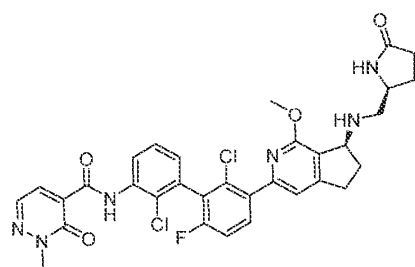
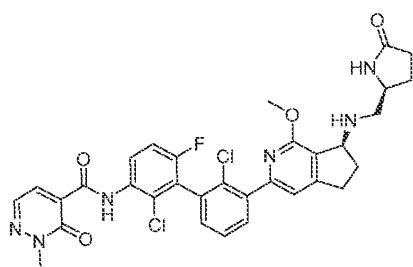
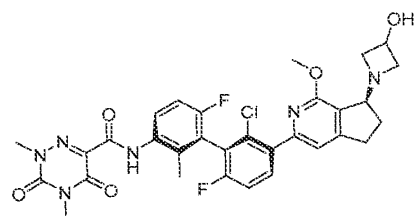
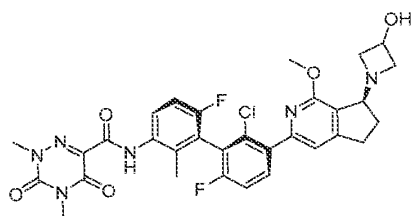
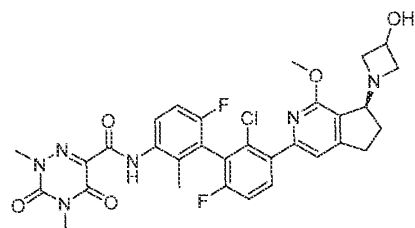
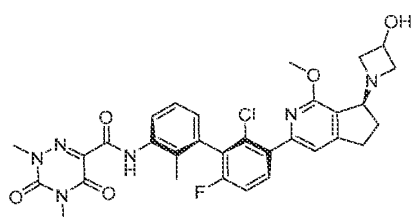
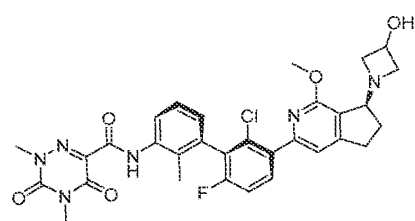
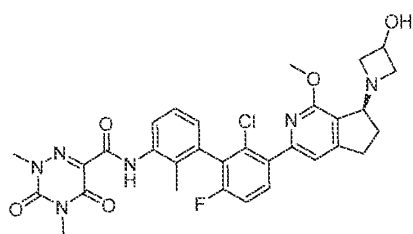


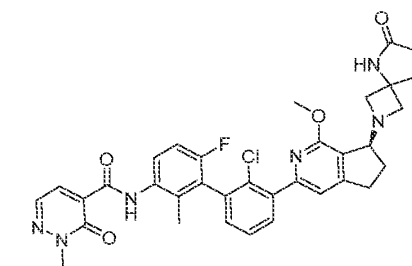
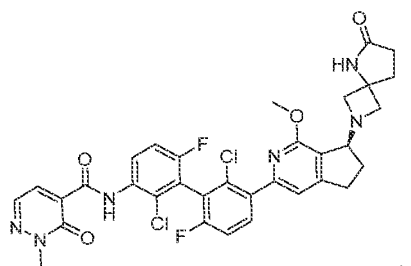
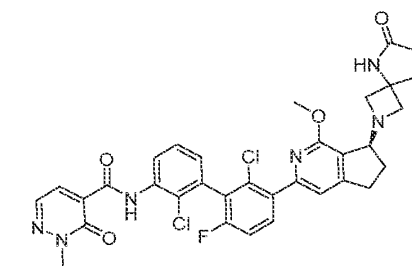
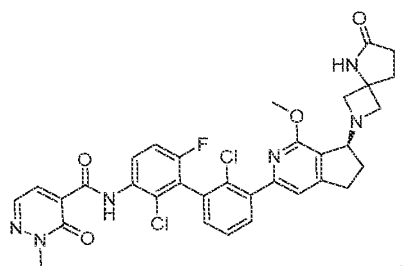
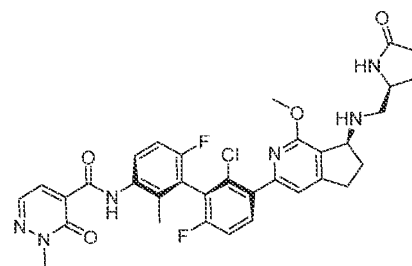
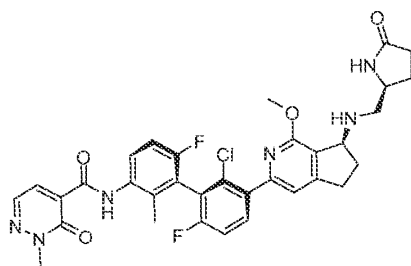
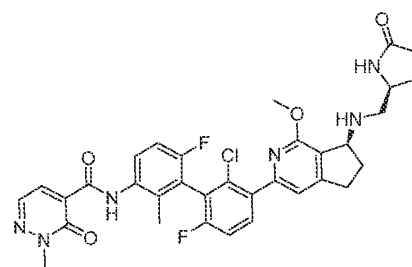
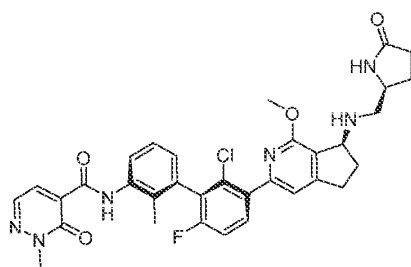
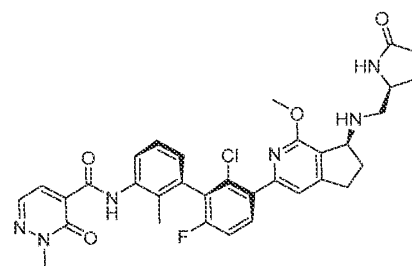
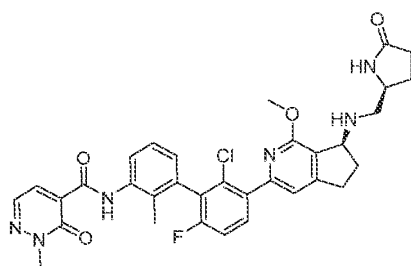


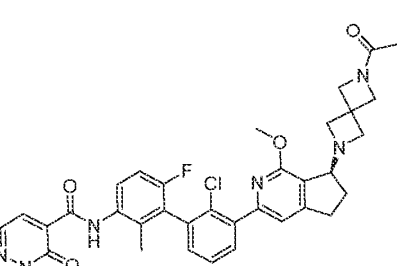
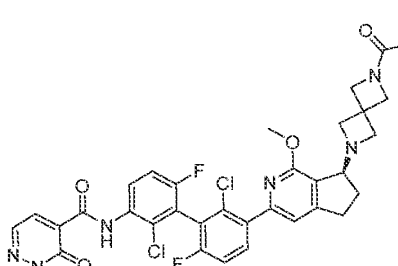
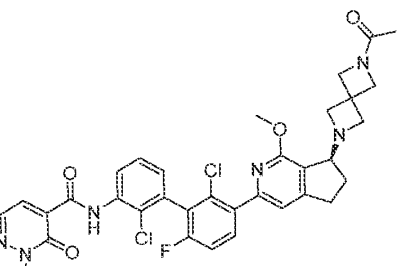
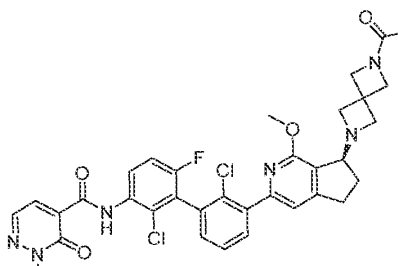
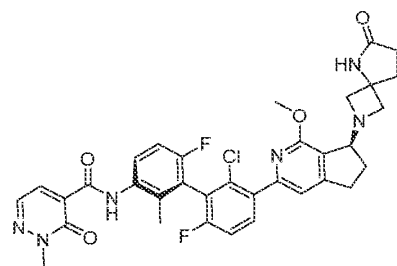
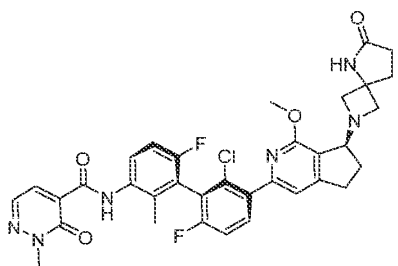
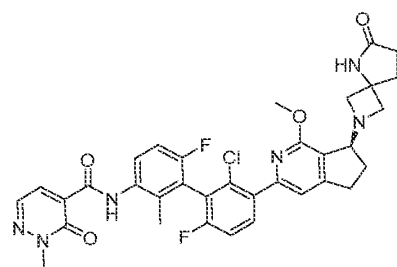
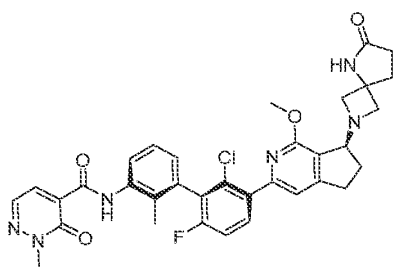
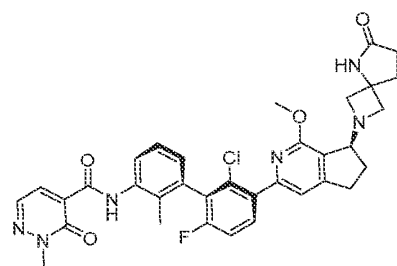
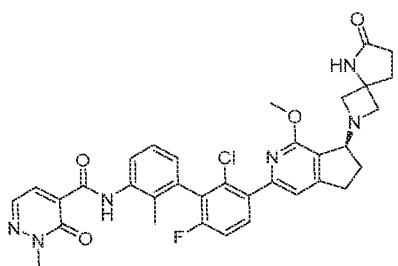


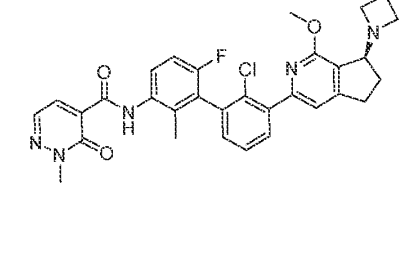
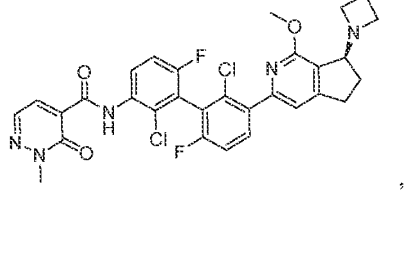
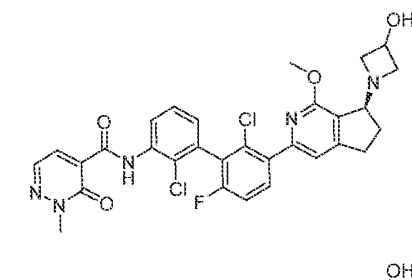
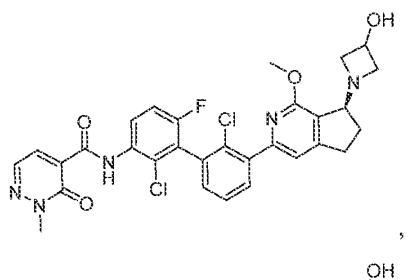
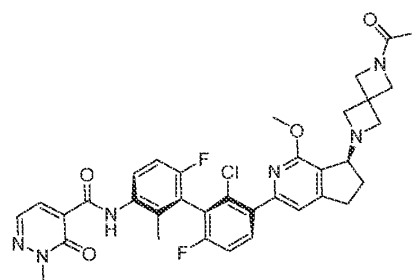
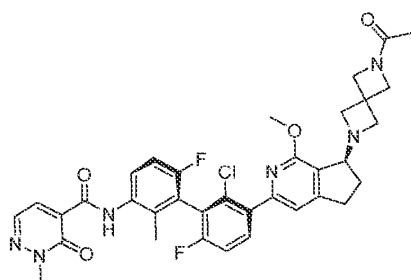
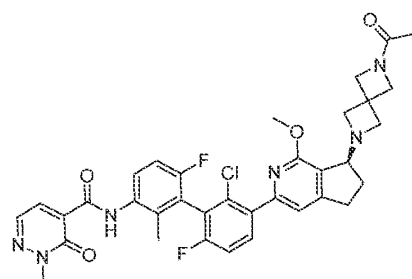
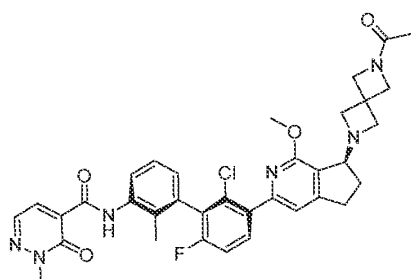
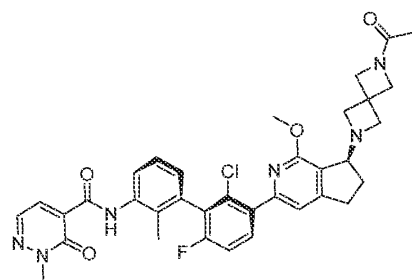
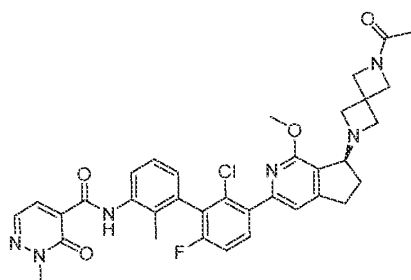


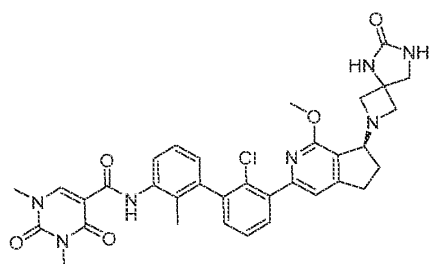
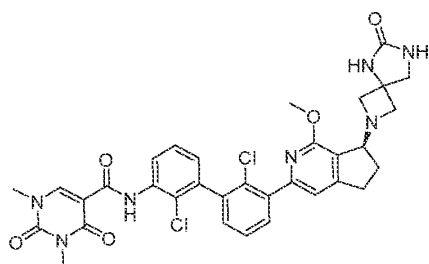
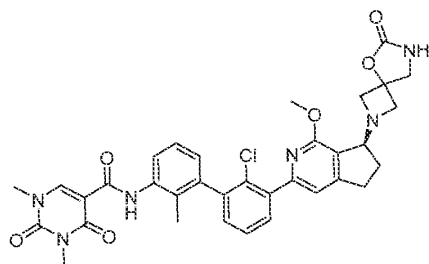
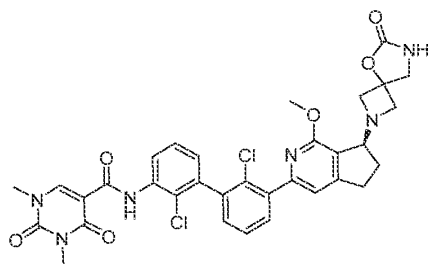
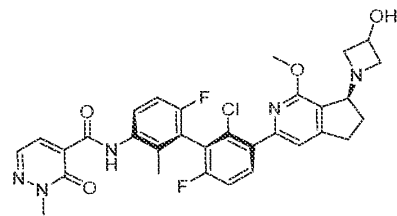
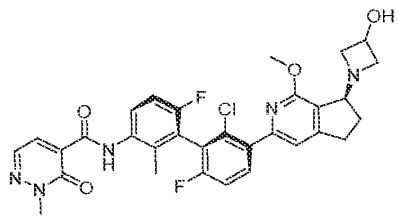
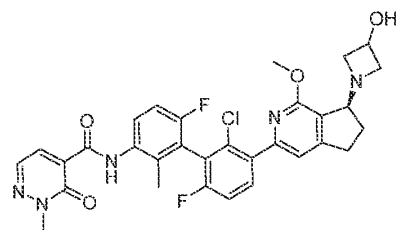
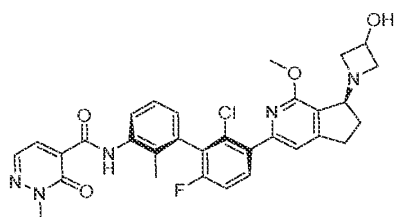
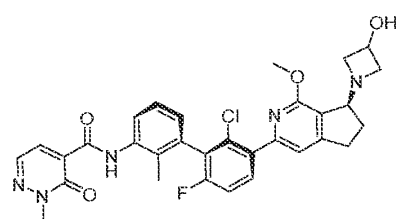
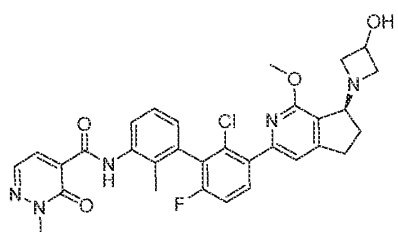


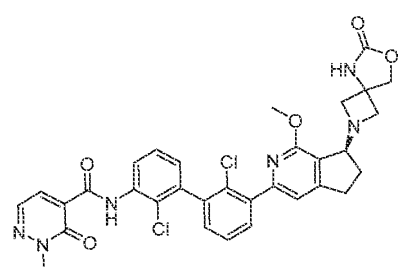
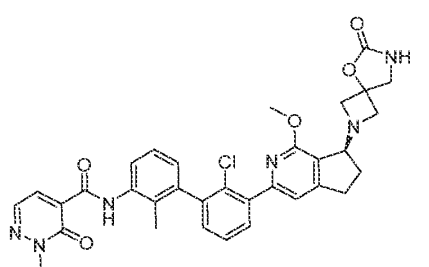
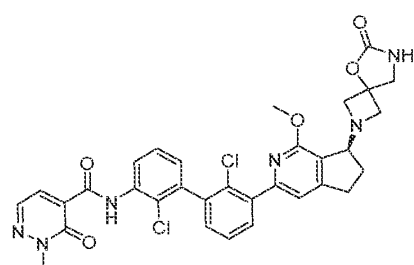
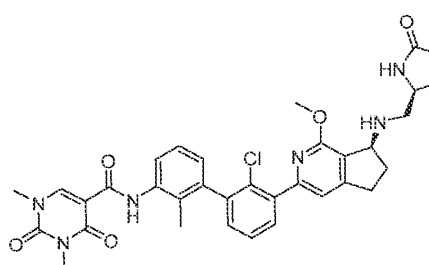
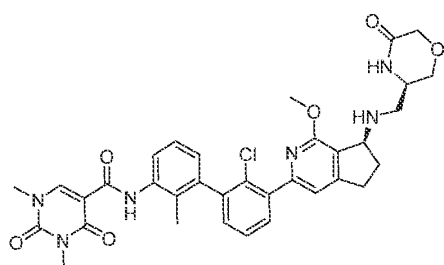
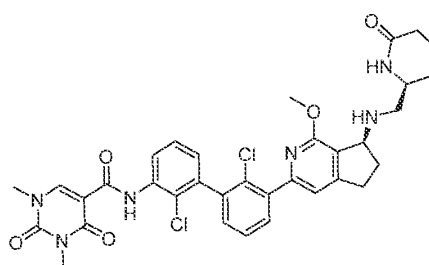
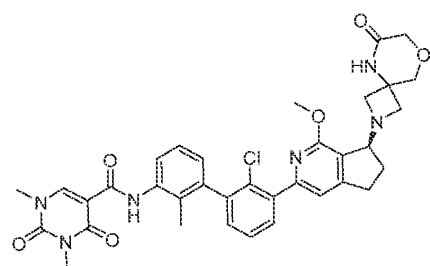
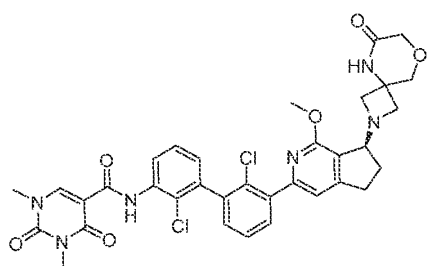
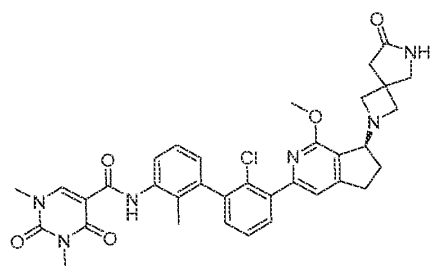
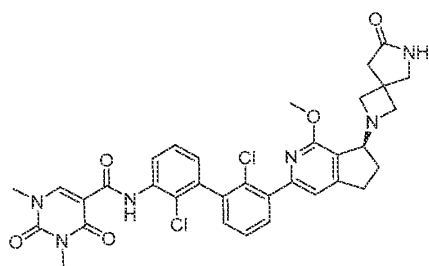


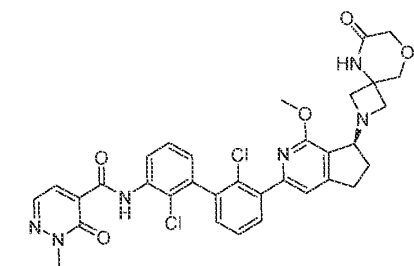
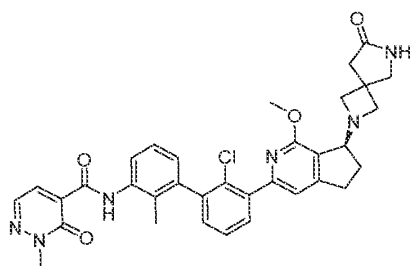
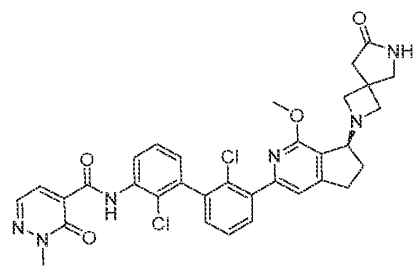
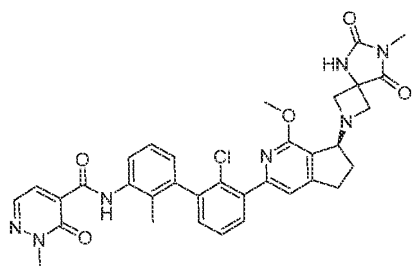
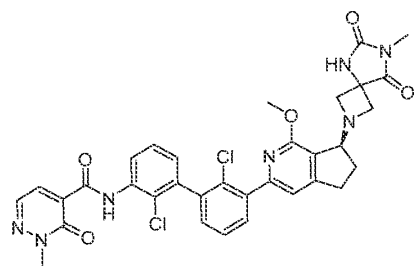
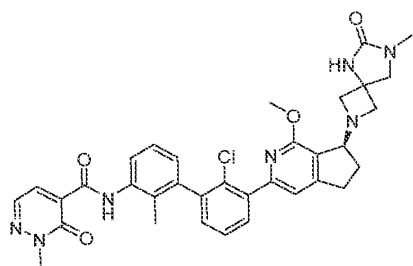
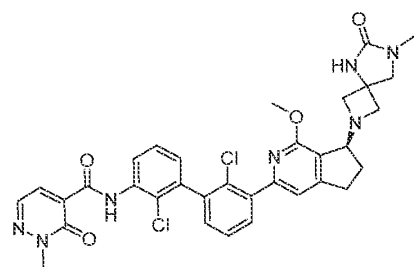
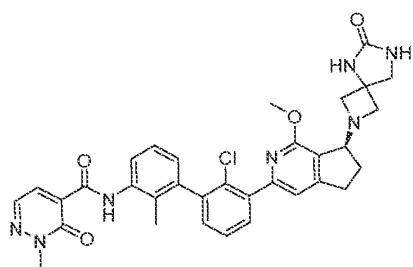
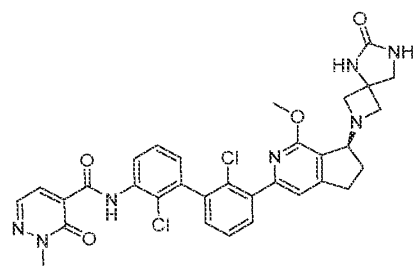
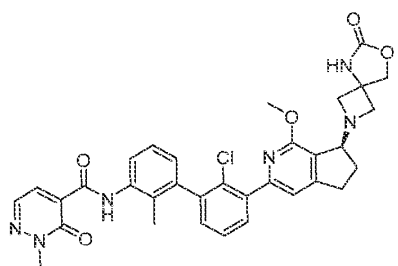


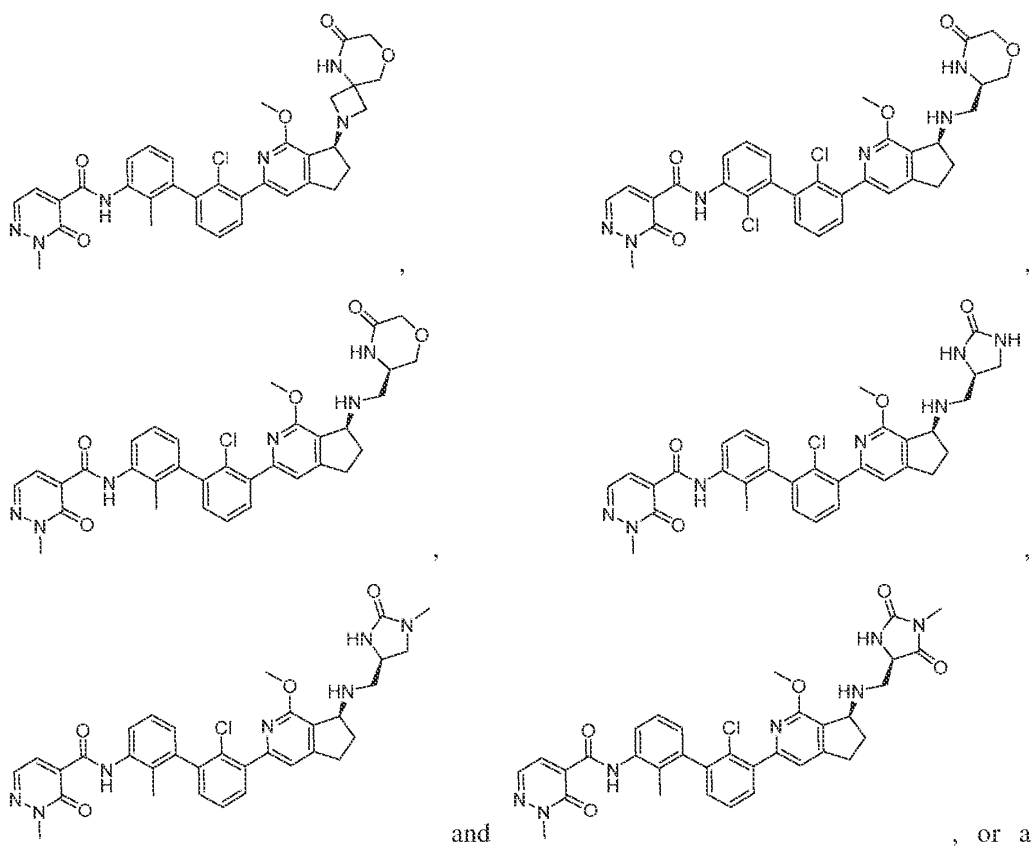








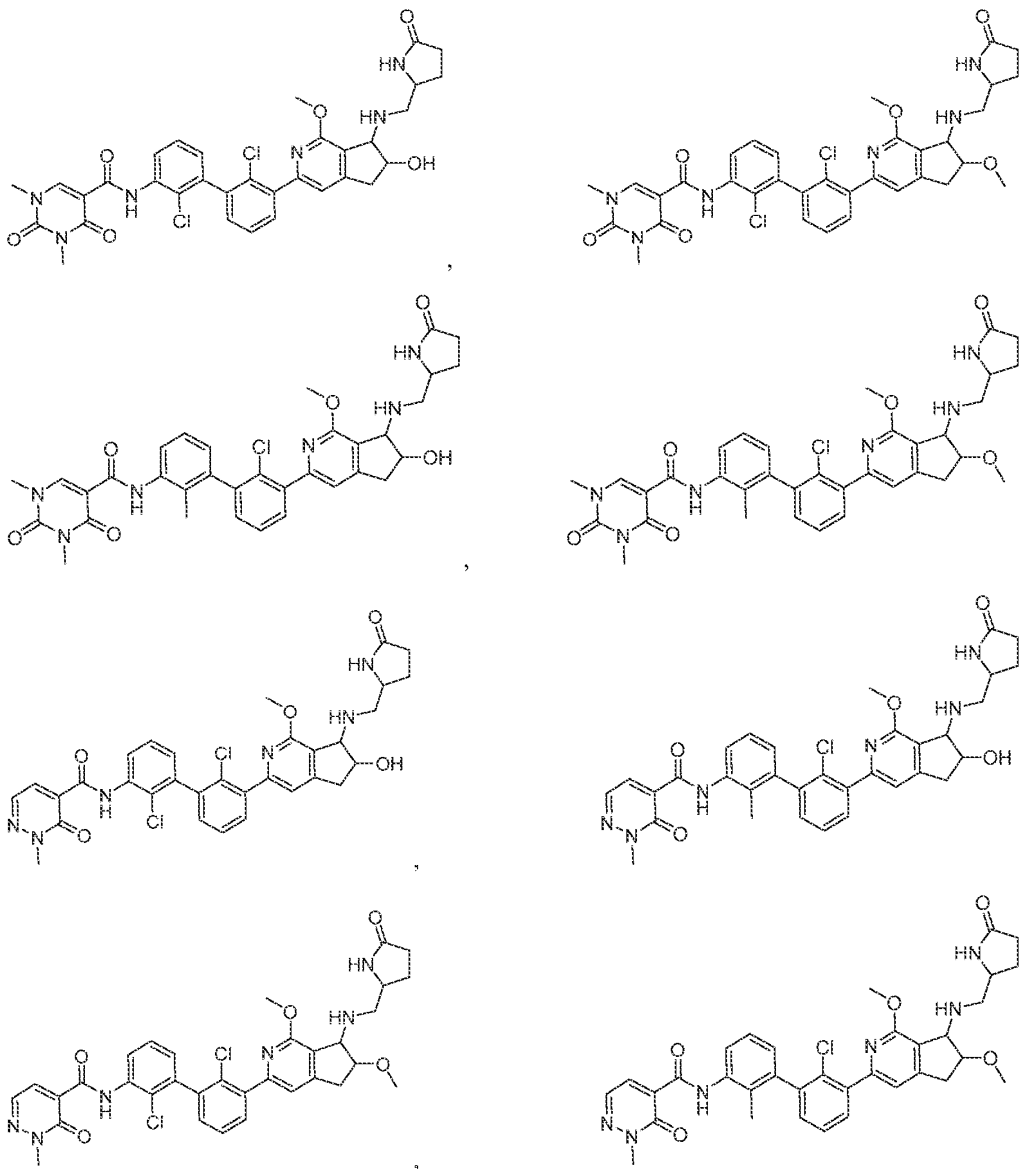


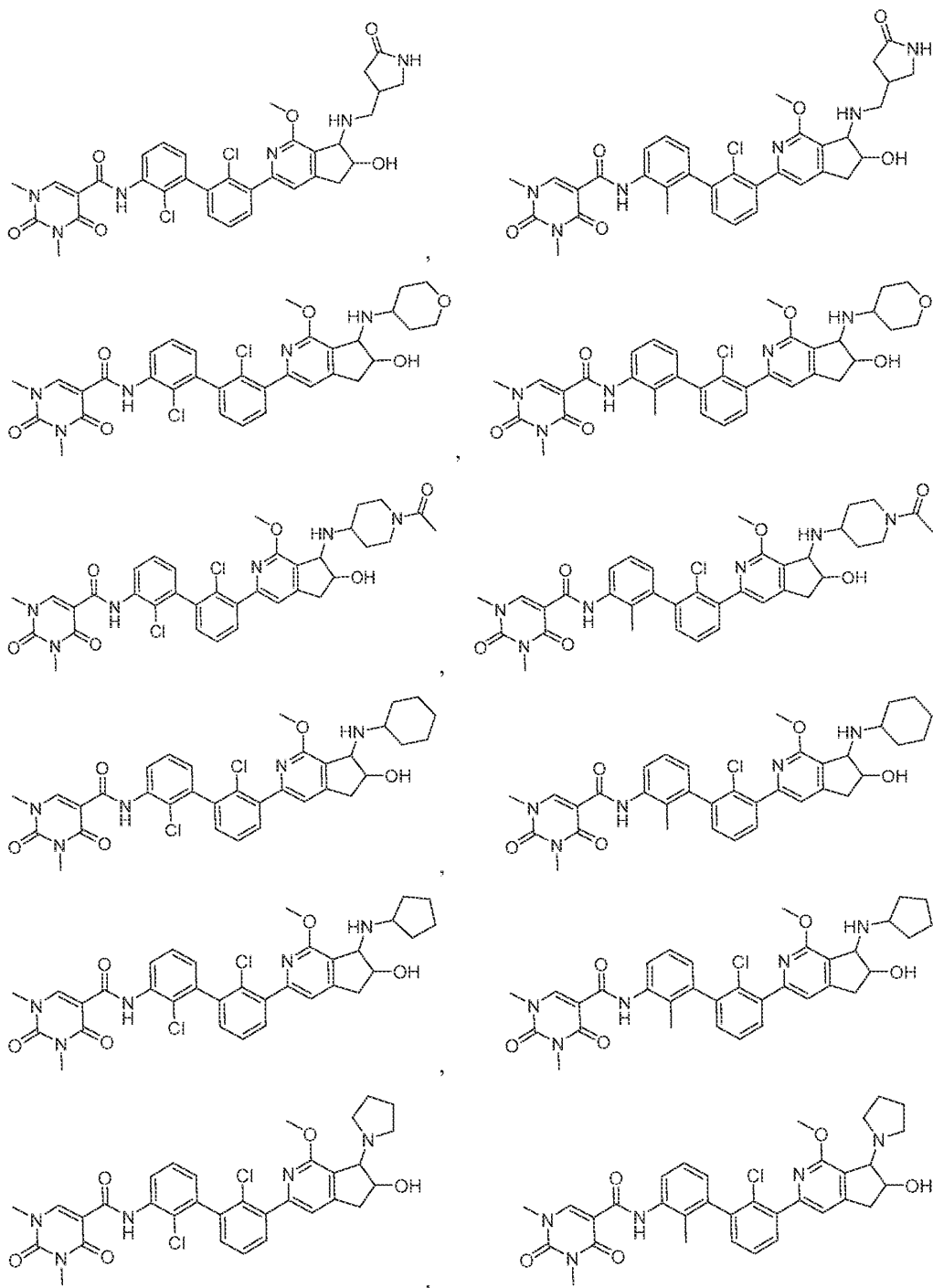


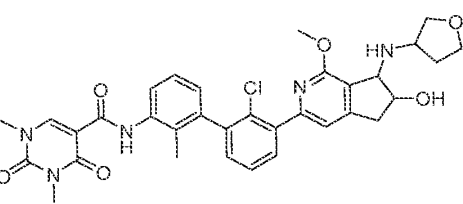
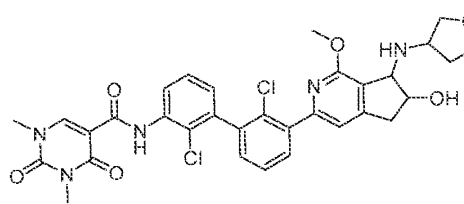
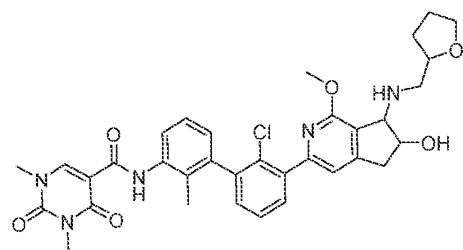
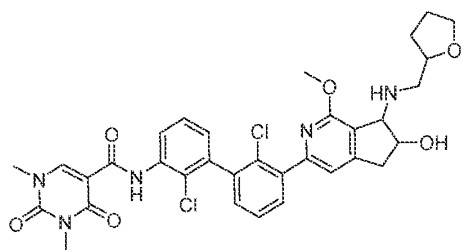
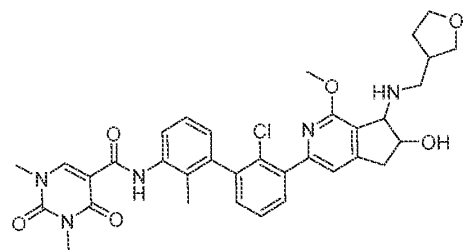
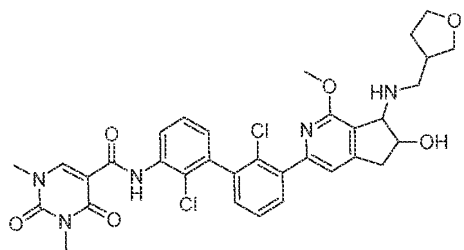
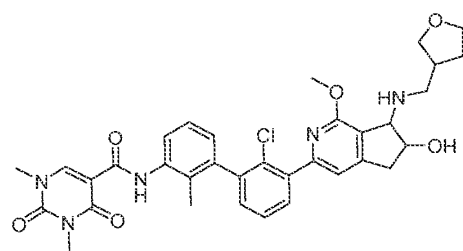
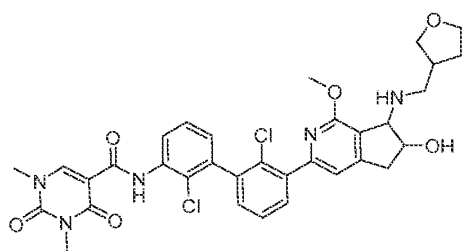
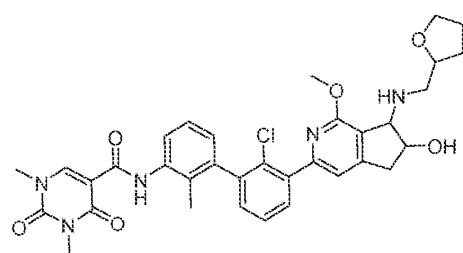
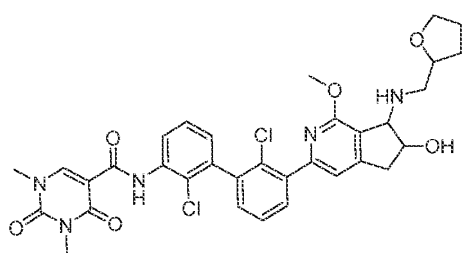
pharmaceutically acceptable salt of any of the foregoing.

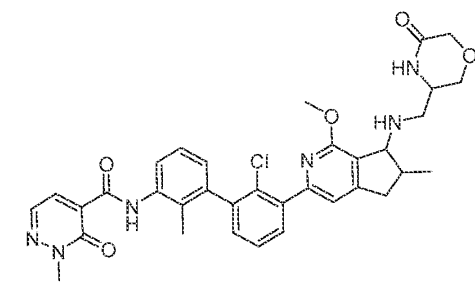
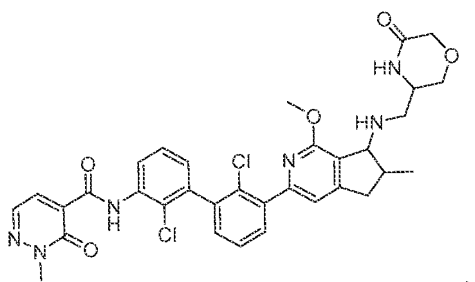
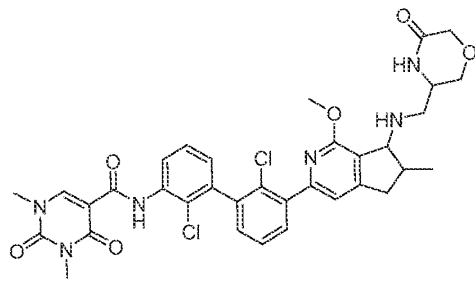
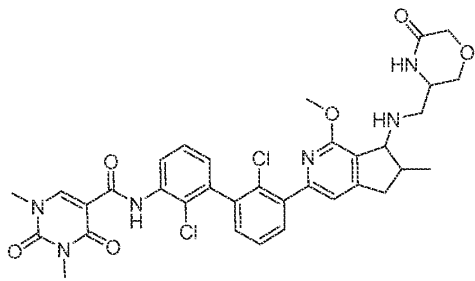
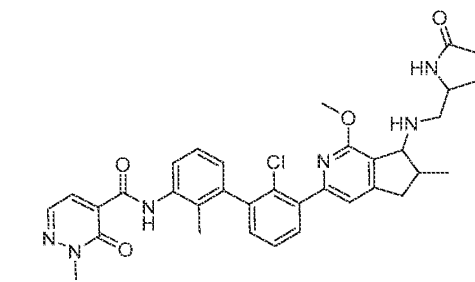
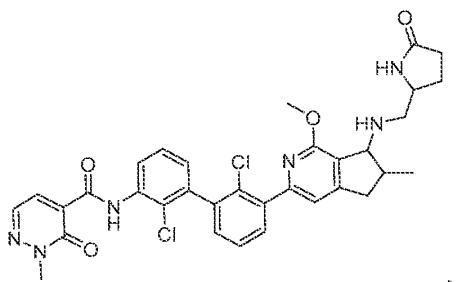
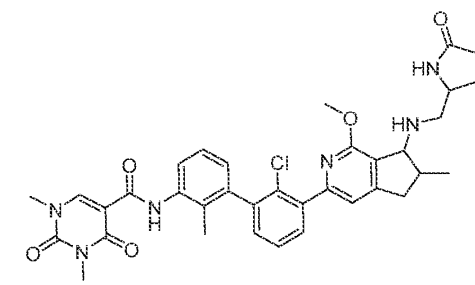
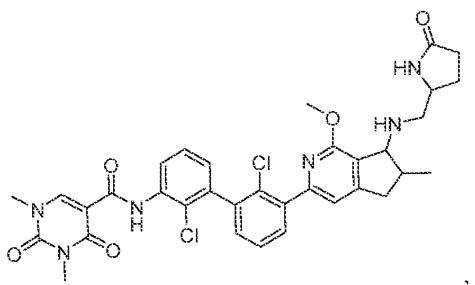
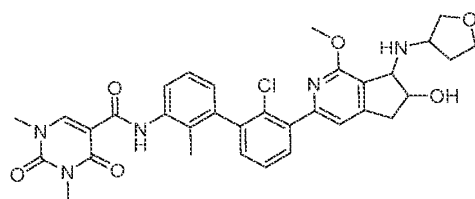
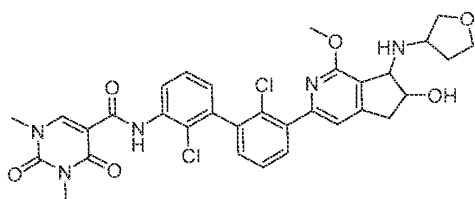
Embodiment 146

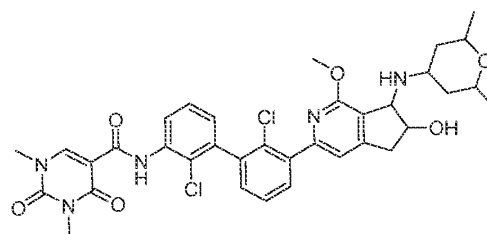
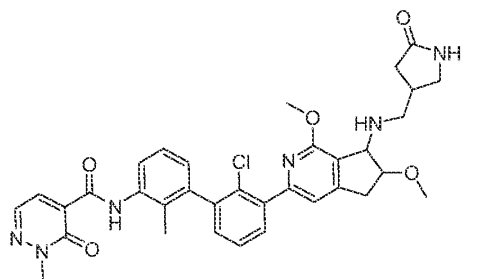
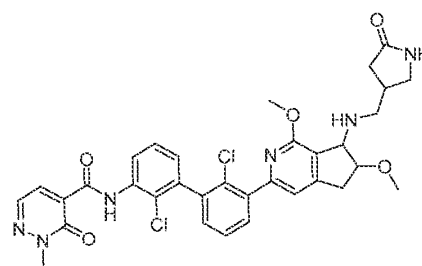
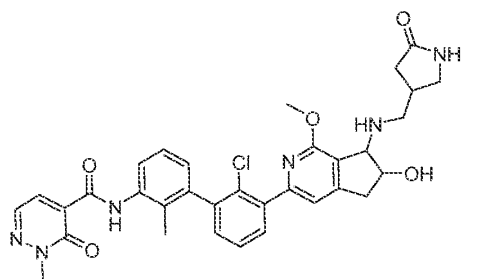
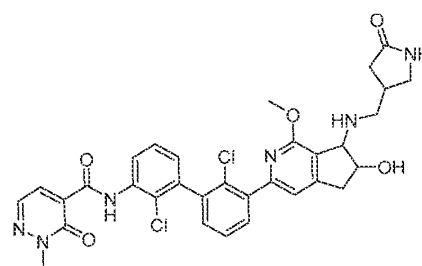
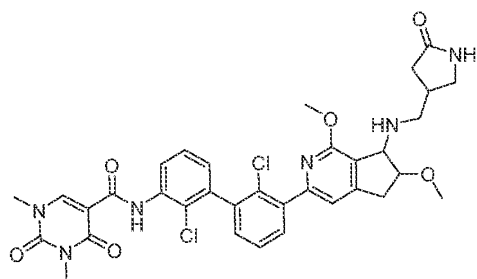
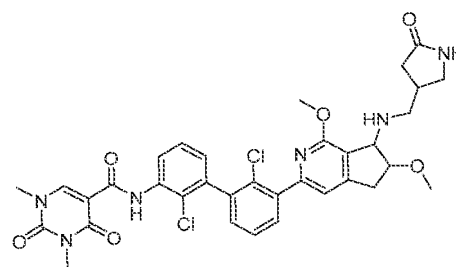
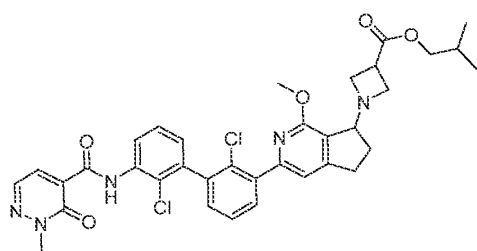
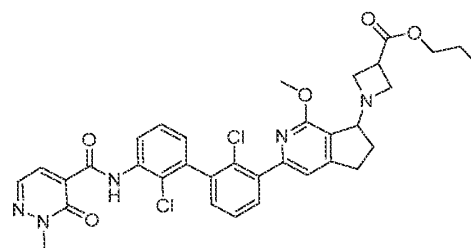
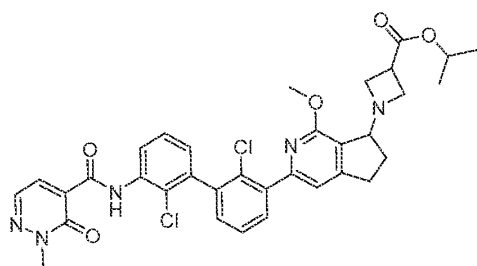
[0220] The compound of Embodiment 1 selected from:

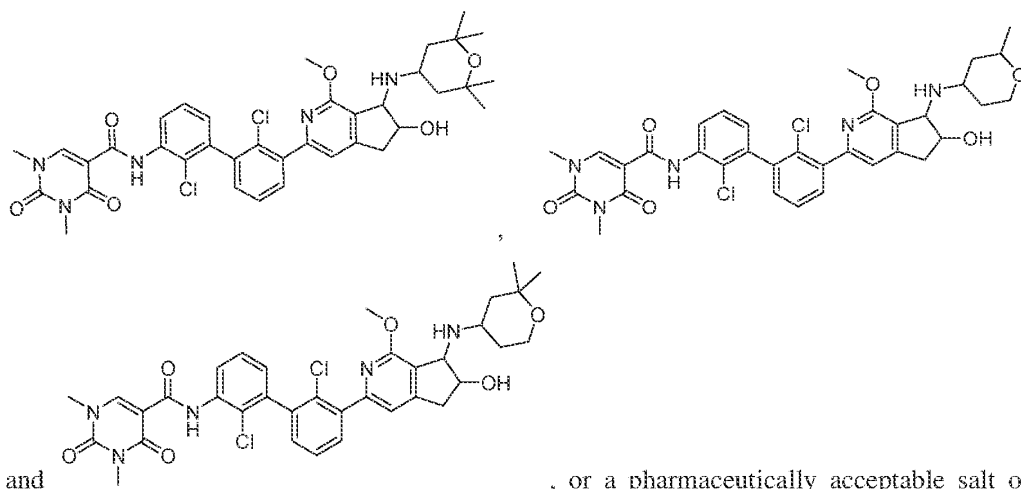








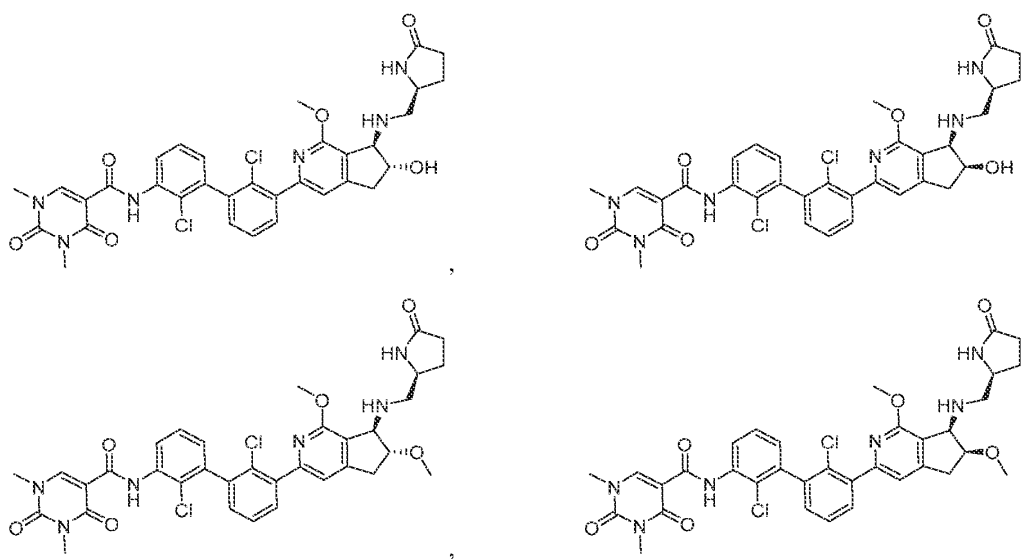


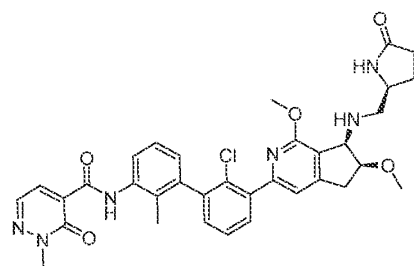
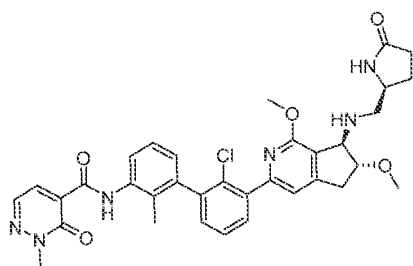
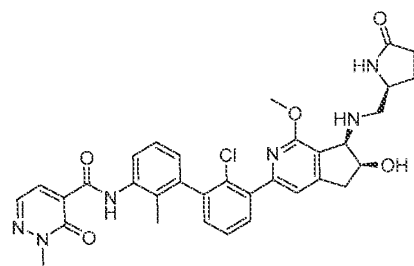
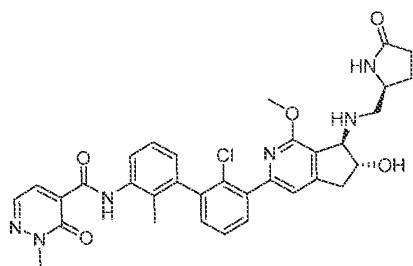
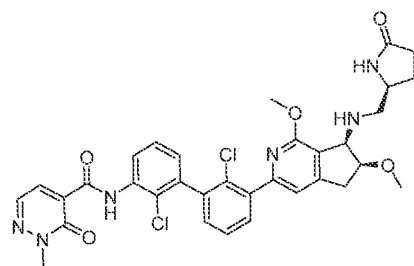
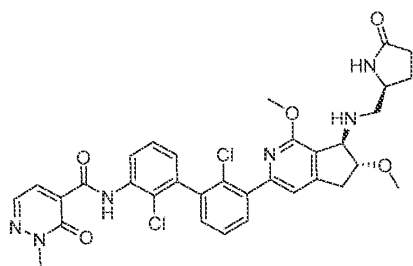
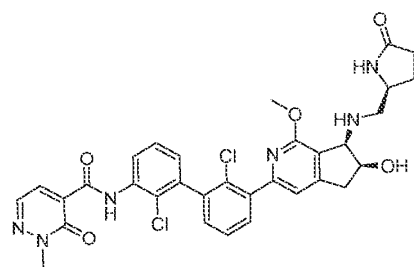
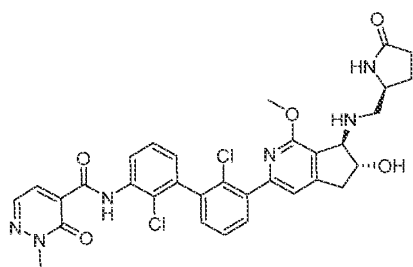
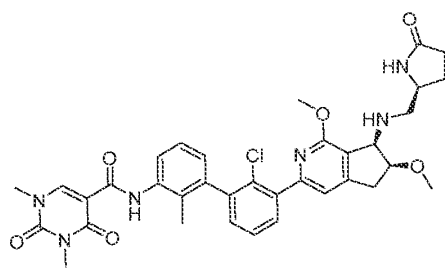
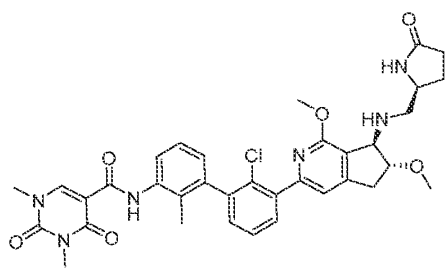


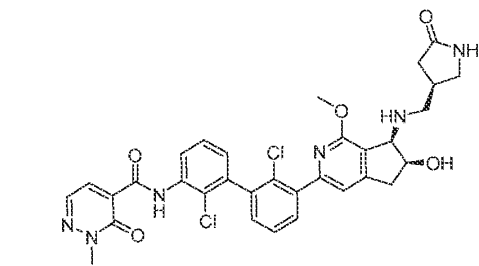
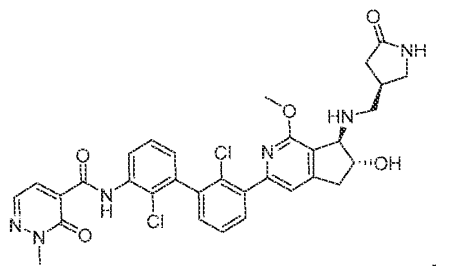
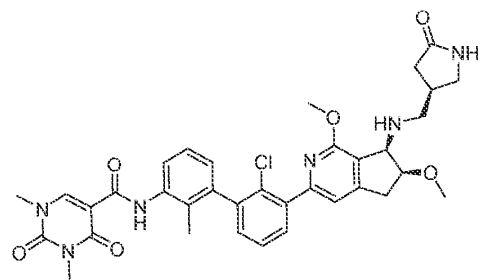
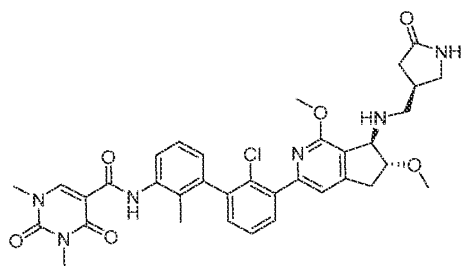
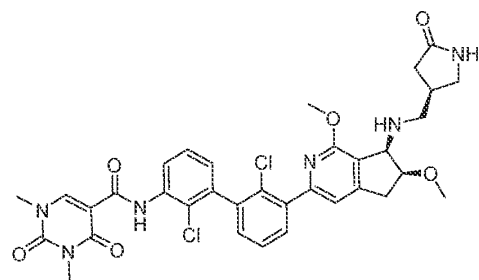
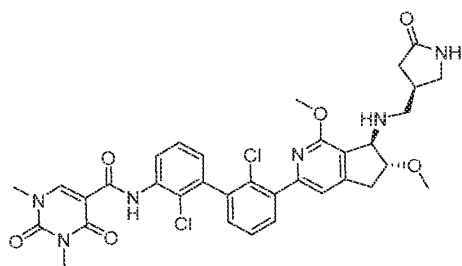
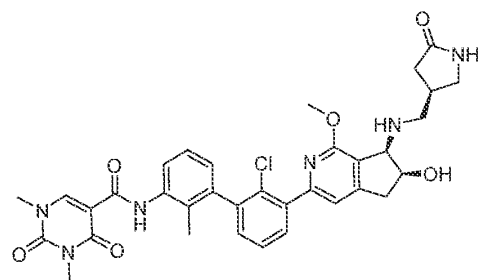
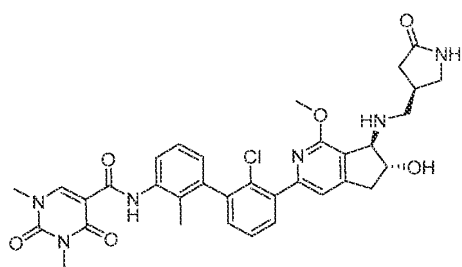
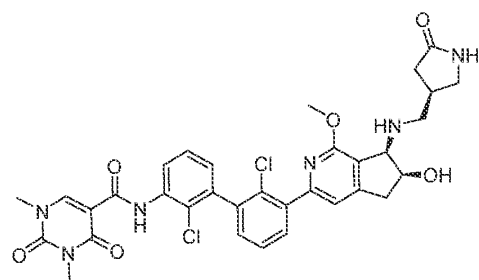
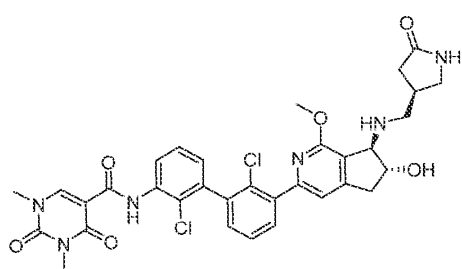
and
any of the foregoing.

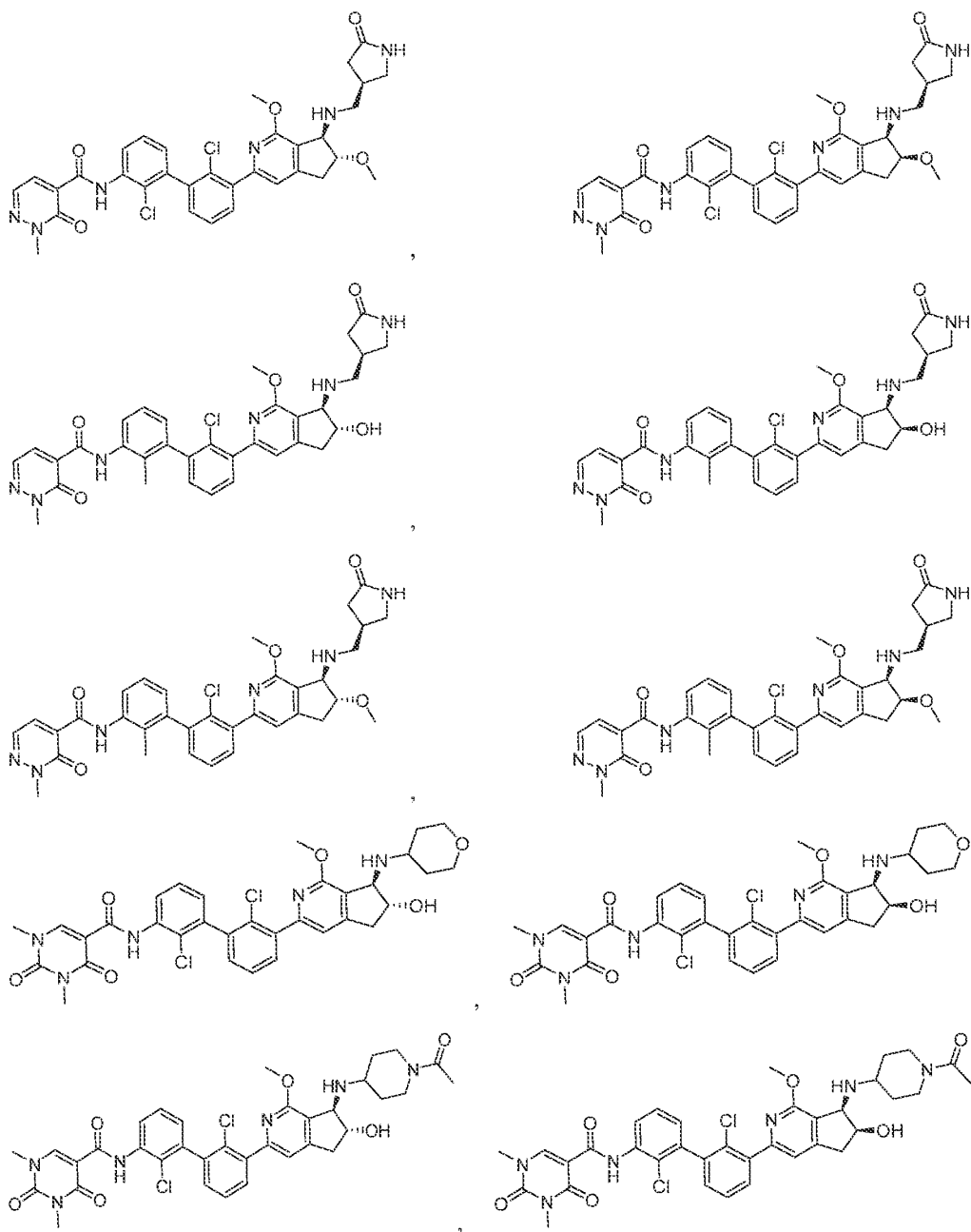
Embodiment 147

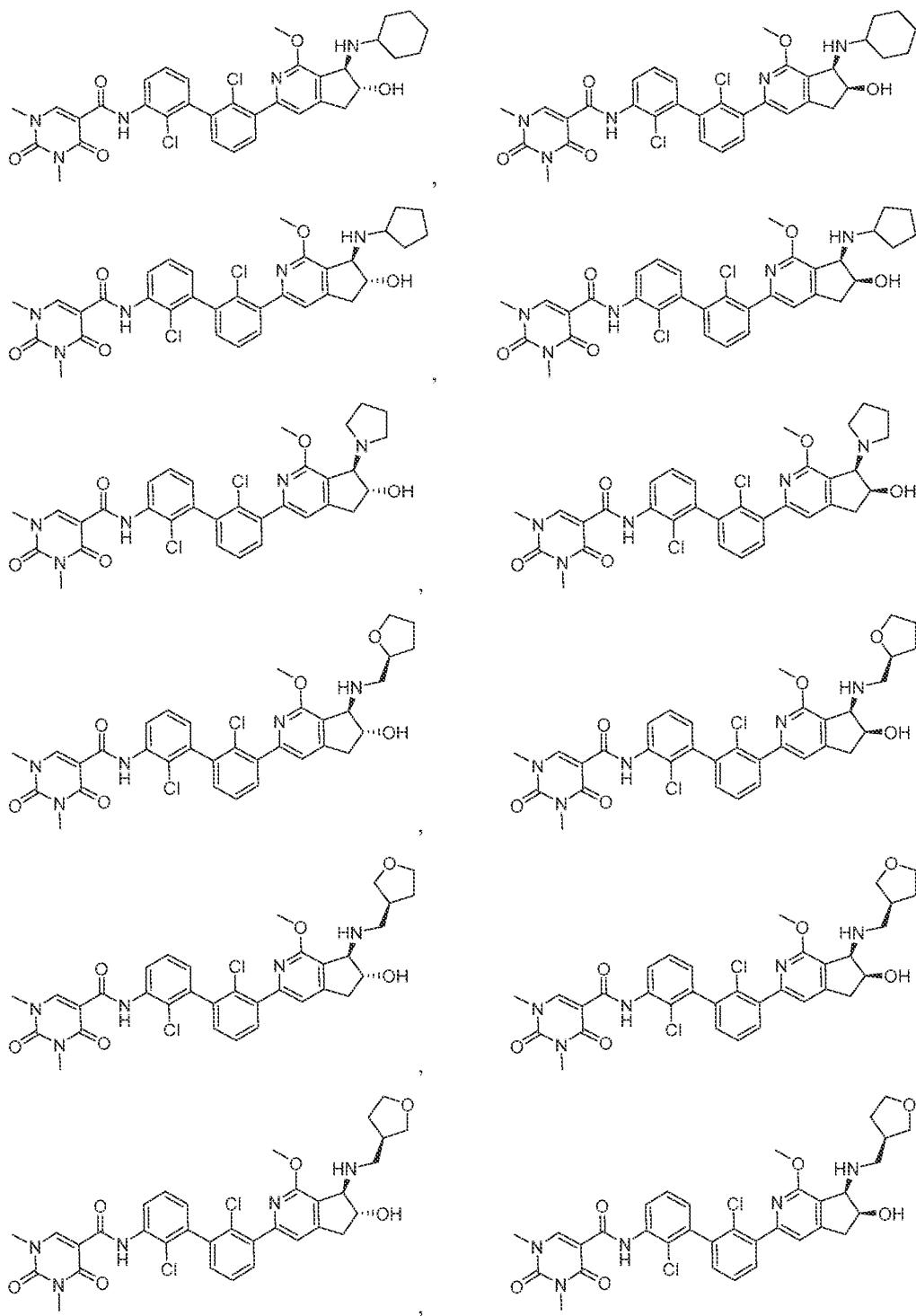
[0221] The compound of Embodiment 1 selected from:

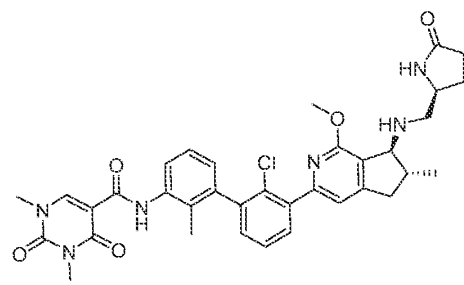
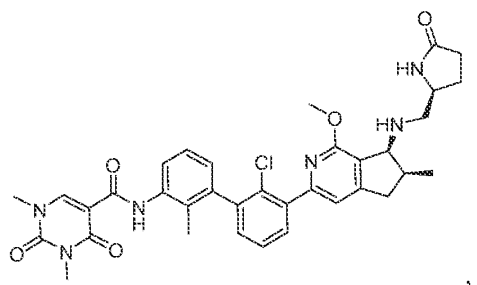
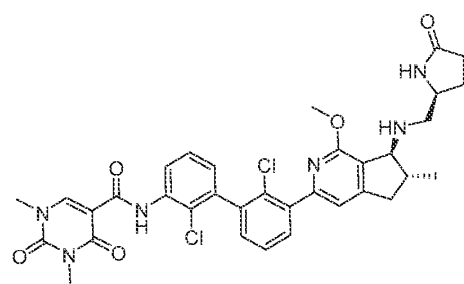
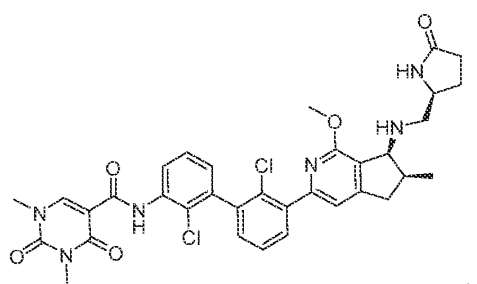
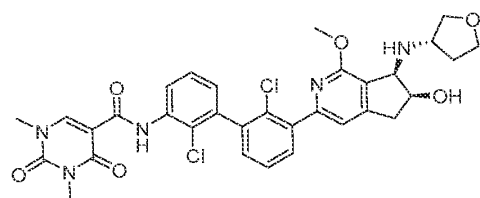
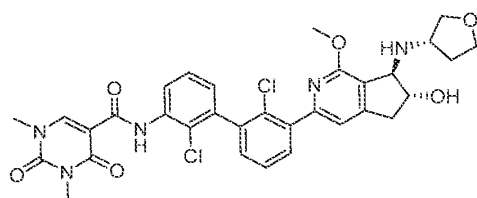
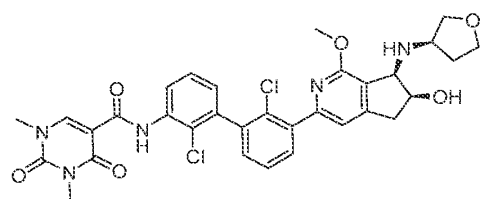
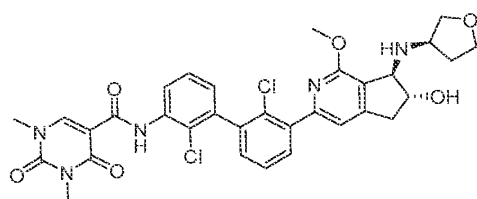
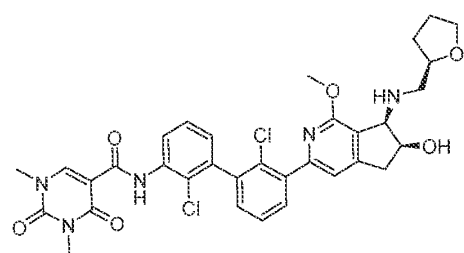
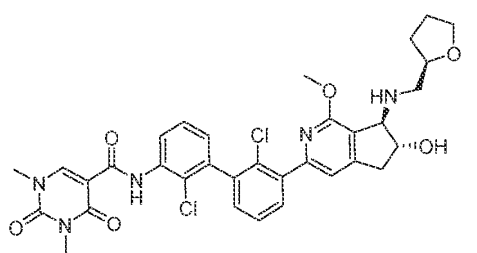


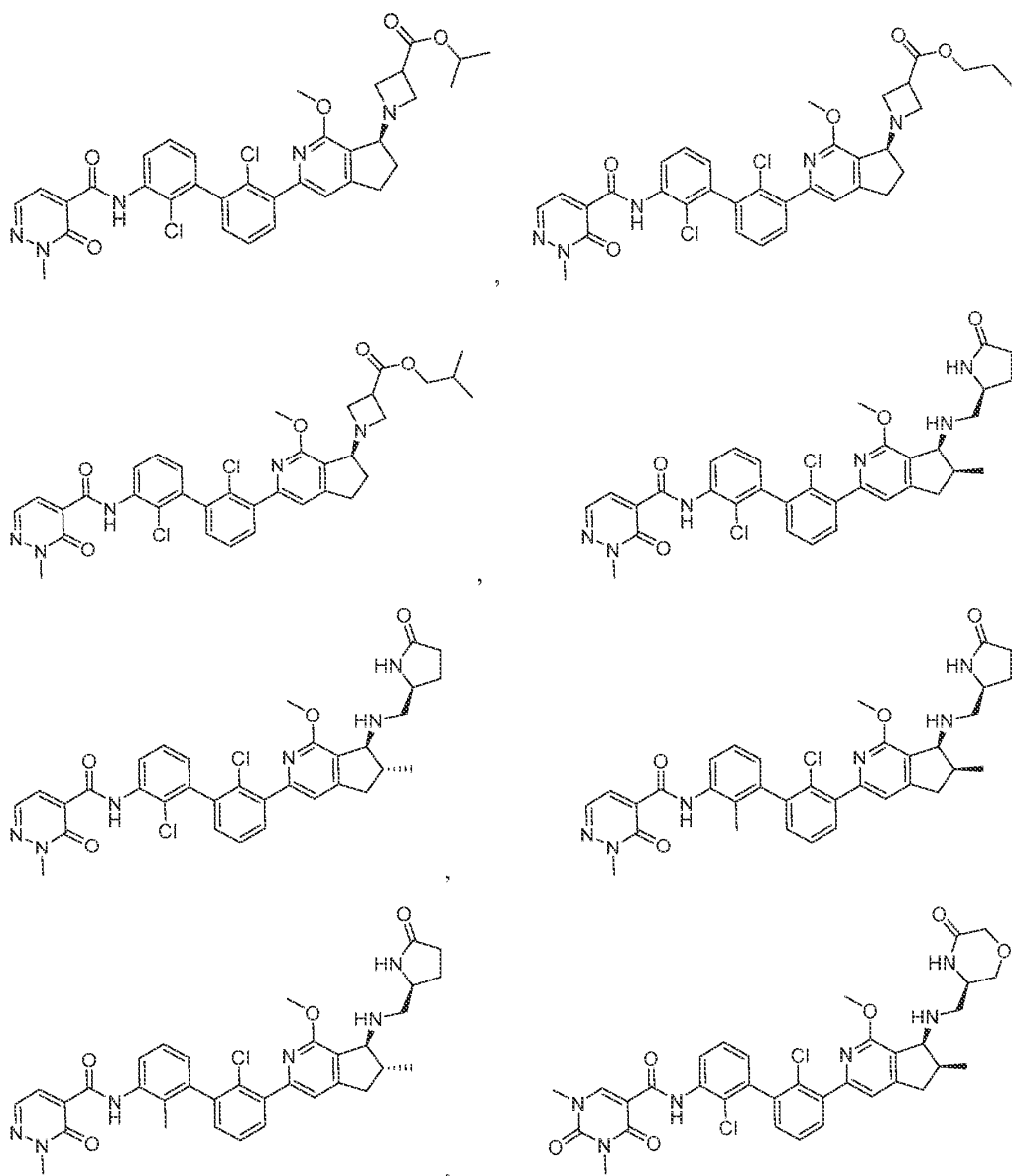


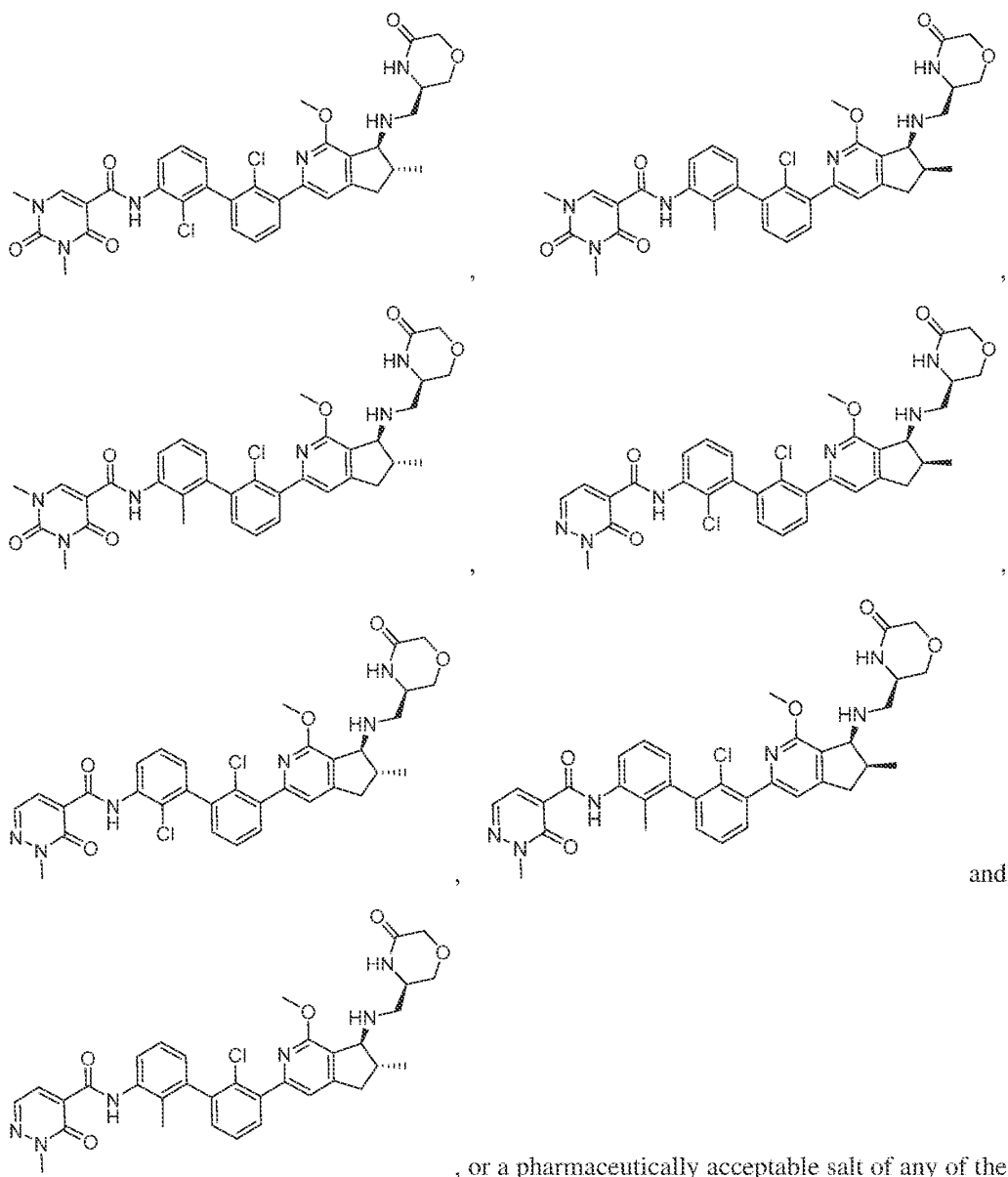












foregoing.

Embodiment 148

[0222] The compound of Embodiment 1 selected from: A-1 to A-139, B-1, B-2, B-3, B-4, C-1, D-1, D-2, D-3, D-4, D-5, D-6, D-7, D-8a, D-8b, D-10, D-11, D-12, D-13, D-14, D-15, D-16, D-17, D-18, D-19, E-1, E-2, E-3, F-1, G-1, H-1, I-1, J-1, J-2, J-3, J-4, K-1a,

K-1b, L-1a, L-1b, M-1a, M-1b, M-2a, M-2b, M-3a and M-3b, or a pharmaceutically acceptable salt of any of the foregoing.

Embodiment 149

[0223] A pharmaceutical composition that can include an effective amount of a compound of any one of Embodiments 1-148, or a pharmaceutically acceptable salt thereof, and excipient.

Embodiment 150

[0224] 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 1-148, or a pharmaceutically acceptable salt thereof.

Embodiment 151

[0225] 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 1-148, or a pharmaceutically acceptable salt thereof.

Embodiment 152

[0226] The method of any one of Embodiments 150-151, that can further include administering surgery, radiation therapy, chemotherapy, targeted therapy, immunotherapy, hormonal therapy, or antiviral therapy.

Embodiment 153

[0227] A compound of any one of Embodiments 1-148, or a pharmaceutically acceptable salt thereof, for use in treating hepatitis B.

Embodiment 154

[0228] A compound of any one of Embodiments 1-148, or a pharmaceutically acceptable salt thereof, for use in treating hepatocellular carcinoma (HCC).

Embodiment 155

[0229] The compound of any one of Embodiments 153-154, that can further include administering surgery, radiation therapy, chemotherapy, targeted therapy, immunotherapy, hormonal therapy, or antiviral therapy.

Embodiment 156

[0230] Use of a compound of any one of Embodiments 1-148, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for use in treating hepatitis B.

Embodiment 157

[0231] Use of a compound of any one of Embodiments 1-148, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for use in treating hepatocellular carcinoma (HCC).

Embodiment 158

[0232] The use of any one of Embodiments 156-157, that can further include administering surgery, radiation therapy, chemotherapy, targeted therapy, immunotherapy, hormonal therapy, or antiviral therapy.

Methods for the Preparation

[0233] In this section, as in all other sections unless the context indicates otherwise, references to Formula (I), along with pharmaceutical acceptable salts thereof, include all other sub-groups and examples thereof as provided herein. The general preparations of some representative examples of compounds of Formula (I) are described herein, and are generally prepared from starting materials which are either commercially available or prepared by standard synthetic processes used by those skilled in the art.

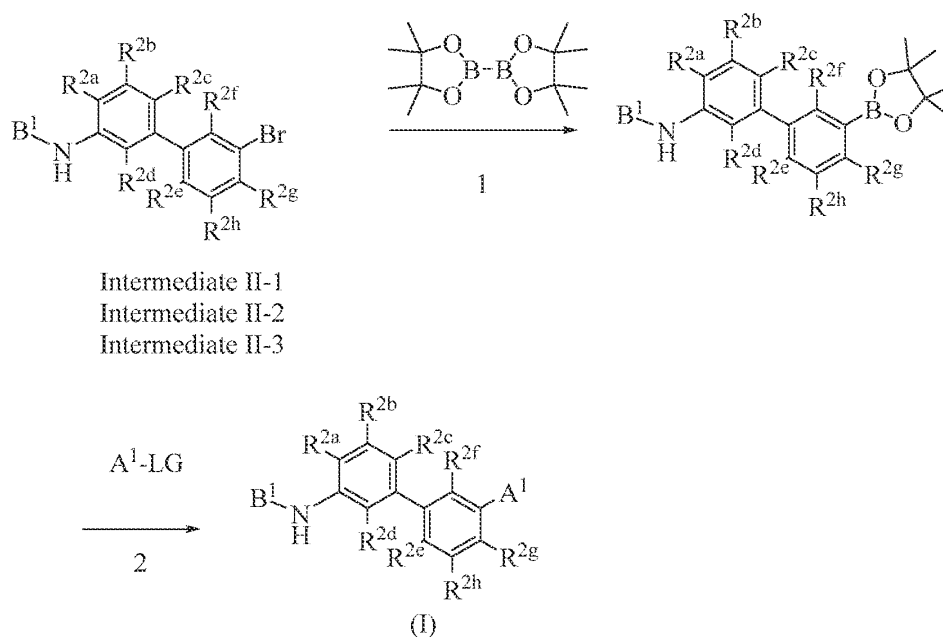
[0234] In this section, as in all other sections unless the context indicates otherwise, references to Formula (I), Formula (II), Formula (III) and Formula (IV), along with pharmaceutical acceptable salts thereof, include all other sub-groups and examples thereof as provided herein. The general preparations of some representative examples of compounds of Formula (I), Formula (II), Formula (III), and Formula (IV) are described herein, and are generally prepared from starting materials which are either commercially available or prepared by standard synthetic processes used by those skilled in the art.

[0235] The following schemes a represent example preparations compounds of Formula (I), Formula (II), Formula (III) and Formula (IV), along with pharmaceutically acceptable salts thereof. Compounds of Formula (I), Formula (II), Formula (III) and Formula (IV), along with pharmaceutically acceptable salts thereof may also be prepared by

analogous reaction protocols as described in the general schemes below, combined with standard synthetic processes used by those skilled in the art.

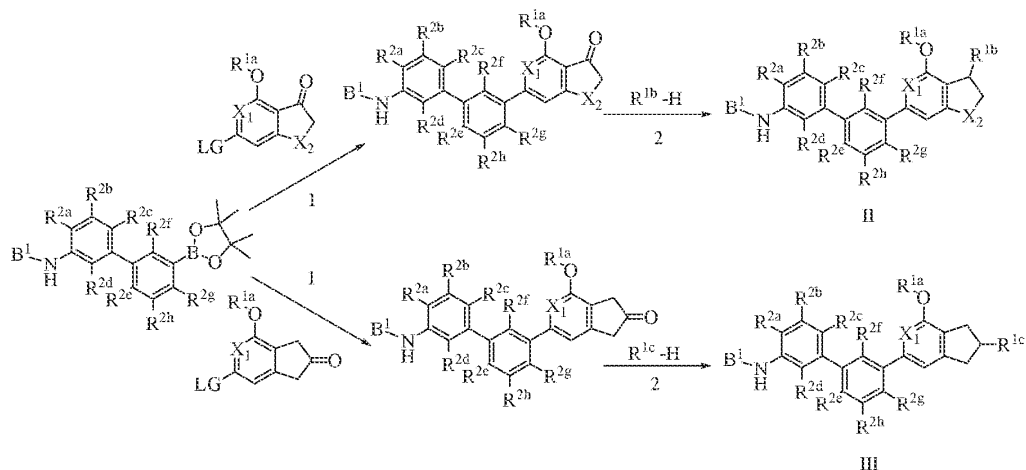
[0236] All variables shown in the schemes are defined as mentioned herein, unless otherwise is indicated or is clear from the context.

General Scheme 1



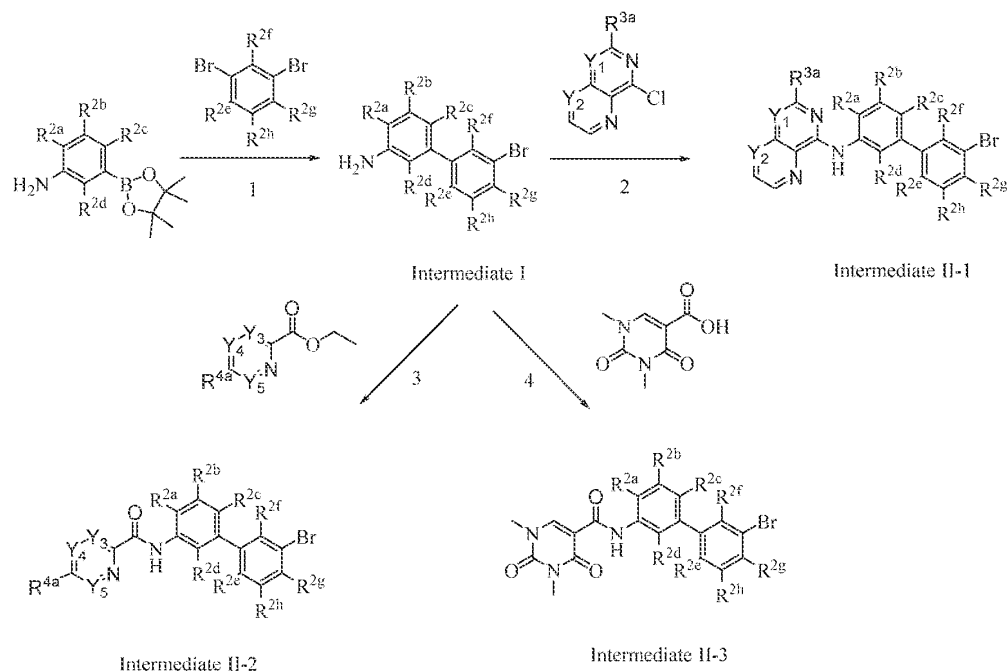
[0237] In general, compounds of Formula (I) can be prepared according to Scheme 1. In Scheme 1, LG is defined as Br or Cl. All other variables in Scheme 1 are defined according to descriptions provided herein. In Scheme 1, the following reaction conditions apply: (1) In the presence of suitable catalyst (for example, bis(triphenylphosphine)palladium(II) dichloride) in a suitable solvent, such as 1,4-dioxane, with a suitable base (for example, KOAc) at a suitable temperature (for example, 90 °C); (2) In the presence of suitable catalyst (for example bis(triphenylphosphine)palladium(II) dichloride) in a suitable solvent, such as 1,4-dioxane, with a suitable base, such as K₂CO₃ at a suitable temperature (for example 90 °C).

General Scheme 2



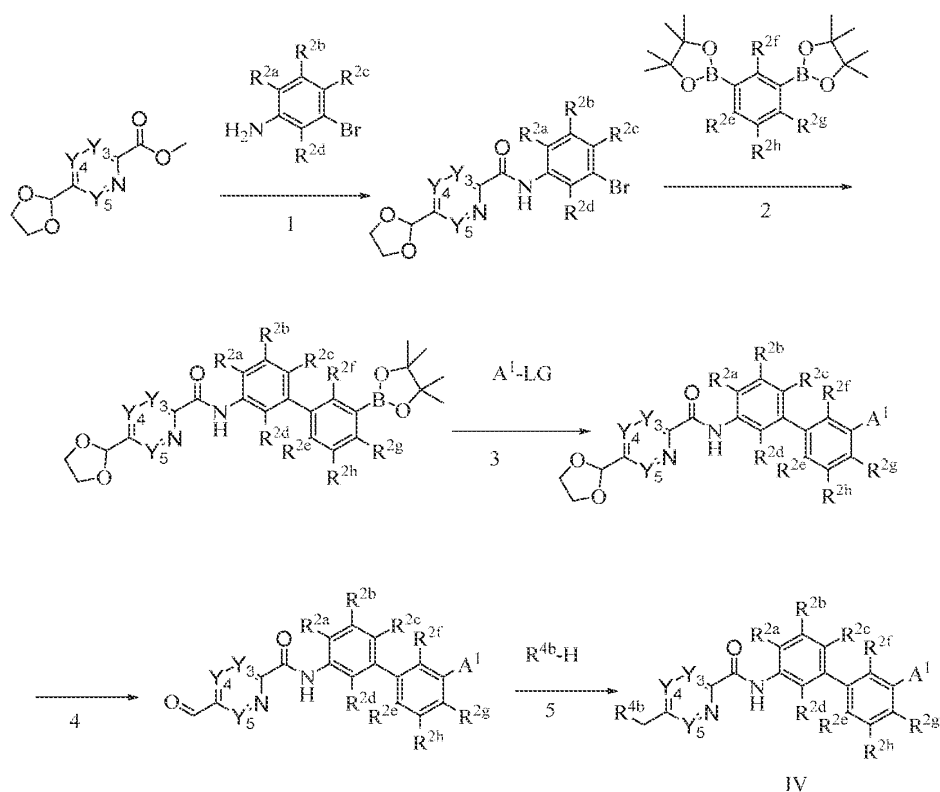
[0238] In general, compound with Formulae (II) and (III) can be prepared according to Scheme 2. In Scheme 2, the following reaction conditions apply: (1) In the presence of suitable catalyst (for example, bis(triphenylphosphine)palladium(II) dichloride) in a suitable solvent, such as 1,4-dioxane, with a suitable base (for example, K₂CO₃) at a suitable temperature (for example, 90 °C); (2) In the presence of an appropriate reductive reagent, such as sodium cyanoborohydride or sodium triacetoxyborohydride, in a suitable solvent (for example, DCM or MeOH) at a suitable temperature, such as approximately 20 °C.

General Scheme 3



[0239] In general, Intermediates for preparing compounds with Formulae (I), (II) and (III) can be prepared according to Scheme 3 with suitable protection group. In Scheme 3, the following reaction conditions apply: (1) In the presence of suitable catalyst (for example, bis(triphenylphosphine)palladium(II) dichloride) in a suitable solvent, such as 1,4-dioxane, with a suitable base (for example, K_2CO_3) at a suitable temperature (for example, 90 °C); (2) In the presence of suitable acid (for example, HCL in 1,4-dioxane) in a suitable solvent (for example, t-BuOH) at a suitable temperature (for example, 100 °C); (3) In the presence of suitable base (for example, potassium tert-butoxide) in a suitable solvent, such as THF, at a suitable temperature (for example, 20 °C); (4) In the presence of suitable coupling reagents (for example, N,N,N',N'-tetramethylchloroformamidinium hexafluorophosphate and N-methylimidazole) in a suitable solvent (for example, acetonitrile) at a suitable temperature (for example, 50 °C).

General Scheme 4



[0240] In general, compounds with Formula (IV) be also prepared according to Scheme 4. In Scheme 4, the following reaction conditions apply: (1) In the presence of suitable base (for example, potassium tert-butoxide) in a suitable solvent, such as THF, at a suitable temperature (for example, 20 °C); (2) In the presence of suitable catalyst (for example, bis(triphenylphosphine)palladium(II) dichloride) in a suitable solvent, such as 1,4-dioxane, with a suitable base (for example, K₂CO₃) at a suitable temperature (for example, 90 °C); (3) In the presence of suitable catalyst (for example, bis(triphenylphosphine)palladium(II) dichloride) in a suitable solvent, such as 1,4-dioxane, with a suitable base (for example, K₂CO₃) at a suitable temperature (for example, 90 °C); (4) In the presence of a suitable acid, such as concentric HCl acid, in a suitable solvent (for example the mixture of H₂O and THF), at a suitable temperature (for example approximately 20 °C); (5) In the presence of an appropriate reductive reagent, such as sodium

cyanoborohydride or sodium triacetoxymborohydride, in a suitable solvent (for example, DCM or MeOH) at a suitable temperature, such as approximately 20 °C.

Pharmaceutical Compositions

[0241] Some embodiments described herein relate to pharmaceutical compositions that comprise, consist essentially of, or consist of an effective amount of a compound described herein (such as a compound of Formula (I), or a pharmaceutically acceptable salt thereof) and a pharmaceutically acceptable carrier, excipient, or combination thereof. A pharmaceutical composition described herein is suitable for human and/or veterinary applications.

[0242] The terms “function” and “functional” as used herein refer to a biological, enzymatic, or therapeutic function.

[0243] The terms “effective amount” or “effective dose” is used to indicate an amount of an active compound, or pharmaceutical agent, that elicits the biological or medicinal response indicated. For example, an effective amount of compound can be the amount needed to alleviate or ameliorate symptoms of disease or prolong the survival of the subject being treated. This response may occur in a tissue, system, animal or human and includes alleviation of the signs or symptoms of the disease being treated. Determination of an effective amount is well within the capability of those skilled in the art, in view of the disclosure provided herein. The effective amount of the compounds disclosed herein required as a dose will depend on the route of administration, the type of animal, including human, being treated, and the physical characteristics of the specific animal under consideration. The dose can be tailored to achieve a desired effect, but will depend on such factors as weight, diet, concurrent medication and other factors which those skilled in the medical arts will recognize.

[0244] The term “pharmaceutically acceptable salts” includes relatively non-toxic, inorganic and organic acid, or base addition salts of compositions, including without limitation, analgesic agents, therapeutic agents, other materials, and the like. Examples of pharmaceutically acceptable salts include those derived from mineral acids, such as hydrochloric acid and sulfuric acid, and those derived from organic acids, such as ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, and the like. Examples of

suitable inorganic bases for the formation of salts include the hydroxides, carbonates, and bicarbonates of ammonia, sodium, lithium, potassium, calcium, magnesium, aluminum, zinc, and the like. Salts may also be formed with suitable organic bases, including those that are non-toxic and strong enough to form such salts. For example, the class of such organic bases may include but are not limited to mono-, di-, and trialkylamines, including methylamine, dimethylamine, and triethylamine; mono-, di-, or trihydroxyalkylamines including mono-, di-, and triethanolamine; amino acids, including glycine, arginine and lysine; guanidine; N-methylglucosamine; N-methylglucamine; L-glutamine; N-methylpiperazine; morpholine; ethylenediamine; N-benzylphenethylamine; trihydroxymethyl aminoethane.

[0245] “Formulation”, “pharmaceutical composition”, and “composition” as used interchangeably herein are equivalent terms referring to a composition of matter for administration to a subject.

[0246] The term “pharmaceutically acceptable” means compatible with the treatment of a subject, and in particular, a human.

[0247] 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.

[0248] 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.

[0249] 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.

[0250] 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.

[0251] 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.

[0252] 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.

[0253] 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.

[0254] 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.

[0255] 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.

[0256] 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

[0257] Some embodiments disclosed herein related to selecting a subject or patient in need. In some embodiments, a patient is selected who is in need of treatment, inhibition, amelioration, prevention or slowing of diseases or conditions associated with PD-L1 dysregulation. In some embodiments, such diseases or conditions associated with PD-L1 dysregulation may include, for example, cancer, HCC, viral infections, 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.

[0258] 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).

[0259] 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.

[0260] 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.

[0261] 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.

[0262] 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.

[0263] Some embodiments described herein relate to a method of inducing apoptosis of a cell (for example, a cancer cell or cell infected with a virus) that can include contacting the cell with an effective amount of a compound, or a pharmaceutically acceptable salt thereof, described herein, or a pharmaceutical composition that includes an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as described herein. Other embodiments described herein relate to using an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, described herein in the manufacture of a medicament for inducing apoptosis of a cell, such as a cancer cell or cell infected with a virus. Still other embodiments described herein relate to the use of an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein or a pharmaceutical composition that includes an effective amount of a compound, or a

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

[0264] 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.

[0265] 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.

[0266] 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.

[0267] 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.

[0268] 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.

[0269] 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, or vinorelbine, or any combination thereof.

[0270] 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 is a small molecule, compound, polysaccharide, lipid, peptide, polypeptide, protein, antibody, nucleoside, nucleoside analog, nucleotide, nucleotide analog, nucleic acid, or oligonucleotide. In some embodiments, 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, or vemurafenib, or any combination thereof.

[0271] 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 is a small molecule, compound, polysaccharide, lipid, peptide, polypeptide, protein, antibody, nucleoside, nucleoside analog, nucleotide, nucleotide analog, nucleic acid, or oligonucleotide. In some embodiments, the immune checkpoint is the PD-1/PD-L1 checkpoint. In some embodiments, the PD-1 checkpoint includes but is not limited to nivolumab, pembrolizumab, spartalizumab, cemiplimab, camrelizumab, sintilimab, tislelizumab, toripalimab, AMP-224 or AMP-514, or any combination thereof. In some embodiments, the PD-L1 checkpoint inhibitor includes but is not limited to atezolizumab, avelumab, durvalumab, KN035, AUNP12, CA-170, or BMS-986189, or any combination thereof. In some embodiments, the immune checkpoint is the CTLA-4 checkpoint. In some embodiments, the CTLA-4 checkpoint inhibitor includes but is not limited to ipilimumab or tremilimumab, or any combination thereof.

[0272] 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 is a small molecule, compound, polysaccharide, lipid, peptide, polypeptide, protein, antibody, nucleoside, nucleoside analog, nucleotide, nucleotide analog, nucleic acid, or oligonucleotide. In some embodiments, the 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, or vandetanib, or any combination thereof.

[0273] As used herein, the term “antiviral medication” refers to a pharmaceutical composition administered to treat a viral infection. In some embodiments, the viral infection is 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, varicella zoster virus.

[0274] In some embodiments, the antiviral medication is a small molecule, compound, polysaccharide, lipid, peptide, polypeptide, protein, antibody, nucleoside, nucleoside analog, nucleotide, nucleotide analog, nucleic acid, or oligonucleotide. In some embodiments, the antiviral medication is an interferon, a capsid assembly modulator, a sequence specific oligonucleotide, an entry inhibitor, or a small molecule immunomodulatory. In some embodiments, the antiviral medication includes 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, radialbuvir, ravidasvir, remdesivir, REP 2139, REP 2165, resiquimod, R07049389 (RG7907), ribavirin, rifampicin, rimantadine, ruzasvir, samatasvir,

setrobuvir, simeprevir, sofosbuvir, sorivudine, sovalprevir, taribavirin, telaprevir, telbivudine, tenofovir, tenofovir disoproxil, tenofovir alafenamide, triazavirin, trifluridine, tromantadine, umifenovir, uprifosbuvir, valaciclovir, valganciclovir, 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 Mycludex 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 (BRIL-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, lenveximab, 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, ALG-125755 or any combination thereof.

[0275] 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

[0276] 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.

[0277] Hereinafter, the term “rt”, “r.t.” or “RT” means room temperature; “h” means hours; “Me” means methyl; “MeOH” means methanol; “Et” means ethyl; “EtOH” means ethanol; “NaH” means sodium hydride; “NaBH(AcO)₃” or “NaBH(OAc)₃” means sodium triacetoxyborohydride; “EtOAc” means ethyl acetate; “TEA” or “Et₃N” means triethylamine; “DCM” means dichloromethane; “MeCN” or “ACN” means acetonitrile;

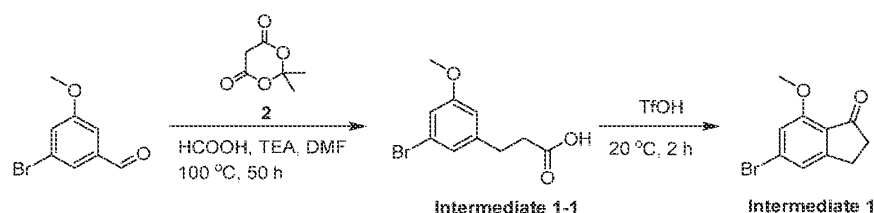
“DMF” means -dimethyl formamide; “DMA” means dimethylacetamide; “Pd(dppf)Cl₂” means [1,1'-Bis(diphenylphosphino)ferrocene]-dichloropalladium(II); “THF” means tetrahydrofuran; “i-PrOH” or “iPrOH” means 2-propanol; “LC” means liquid chromatography; “LCMS” means Liquid Chromatography/Mass spectrometry; “HPLC” means high-performance liquid chromatography; “prep-HPLC” means preparative high-performance liquid chromatography; “TFA” means trifluoroacetic acid; “RP” means reversed phase; “min” means minute(s); “h” means hour(s); “PE” means petroleum ether; “v/v” means volume per volume; “Celite ®” means diatomaceous earth; “DMSO” means dimethyl sulfoxide; “SFC” means Supercritical Fluid Chromatography; “DIPE” means diisopropyl ether; “DIPEA” or “DIEA” means N,N-diisopropylethylamine; “Pd₂(dba)₃” means Tris(dibenzylideneacetone)-dipalladium; “Pd(OAc)₂” means palladium(II) acetate; “AcOH” means acetic acid; “DMAP” means 4-(dimethylamino)pyridine; “t-BuOK”, “BuO” or “KOtBu” means potassium tert-butoxide; “TLC” means thin layer chromatography; “prep-TLC” means preparative TLC; “KOAc” means potassium acetate.

[0278] 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.

[0279] 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

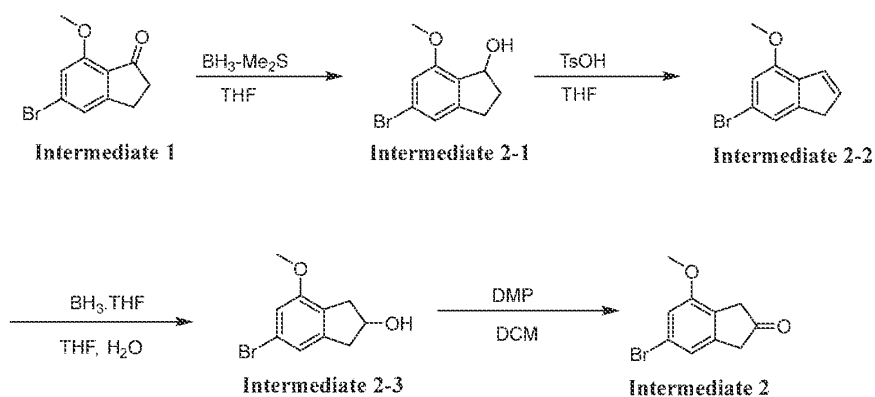
Example A1 Preparation of Intermediate 1



[0280] To HCOOH (16.5 mL, 419 mmol) at 0 °C was added TEA (23.3 mL, 167.41 mmol) dropwise at 0 °C. The mixture was stirred at 0 °C for 30 min. To the mixture were added 3-Bromo-5-methoxybenzaldehyde (30 g, 140 mmol) and isopropylidene malonate (20.1 g, 140 mmol) in DMF (180 mL) dropwise at 25 °C. The mixture was stirred at 100 °C for 50 h. Once the mixture was cooled to 0 °C, the reaction was quenched with conc. HCl (120 mL) and diluted with water (800 mL). The mixture was extracted with DCM (2 x 400 mL). The combined organic layers were washed with NaOH (1N, 2 x 800 mL). The combined aqueous phases were acidified to pH ~2 with conc. HCl, and then extracted with EtOAc (2 x 300 mL). The combined organic layers were washed with brine (2 x 300 mL), dried over Na₂SO₄, filtered and concentrated to give **Intermediate 1-1** (70 g) as a pink solid, which was used into the next step without further purification. ¹H NMR (400 MHz, CDCl₃) δ 6.96 (s, 1H), 6.91 (t, J = 1.9 Hz, 1H), 6.69 (s, 1H), 3.78 (s, 3H), 2.95-2.88 (m, 2H), 2.70-2.62 (m, 2H).

[0281] A solution of **Intermediate 1-1** (70 g, 270 mmol) in TFOH (150 mL) was stirred at 25 °C for 2 h. The reaction was quenched by the addition of ice water (1500 mL) at 0 °C, extracted with DCM (3 x 600 mL). The combined organic layers were washed with NaHCO₃ (2 x 800 mL), dried over anhydrous Na₂SO₄ and concentrated to give a residue, which was purified by flash silica gel chromatography to give **Intermediate 1** (12.6 g) as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 7.19 (d, J = 0.9 Hz, 1H), 6.93 (s, 1H), 3.94 (s, 3H), 3.11-2.97 (m, 2H), 2.73-2.59 (m, 2H).

Example A2
Preparation of Intermediate 2



[0282] To a solution of compound **Intermediate 1** (3.7 g, 15.4 mmol) in THF (120 mL) was added $\text{BH}_3\text{-Me}_2\text{S}$ (10 M, 2.61 mL) at $-10\text{ }^\circ\text{C}$. The mixture was stirred at $25\text{ }^\circ\text{C}$ for 2 h. The reaction was quenched by the addition of ice water (200 mL) at $0\text{ }^\circ\text{C}$, and then extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with NaHCO_3 (2 x 150 mL), dried over anhydrous Na_2SO_4 and concentrated to give a residue, which was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, 0~10% EtOAc:PE) to give **Intermediate 2-1** (3.68 g) as a white solid. ^1H NMR (400 MHz, CDCl_3) δ 7.02 (s, 1H), 6.85 (s, 1H), 5.41 (dd, $J = 4.4, 7.1\text{ Hz}$, 1H), 3.86 (s, 3H), 3.17-2.98 (m, 1H), 2.93-2.72 (m, 1H), 2.56 - 2.35 (m, 2H), 2.15-1.93 (m, 1H).

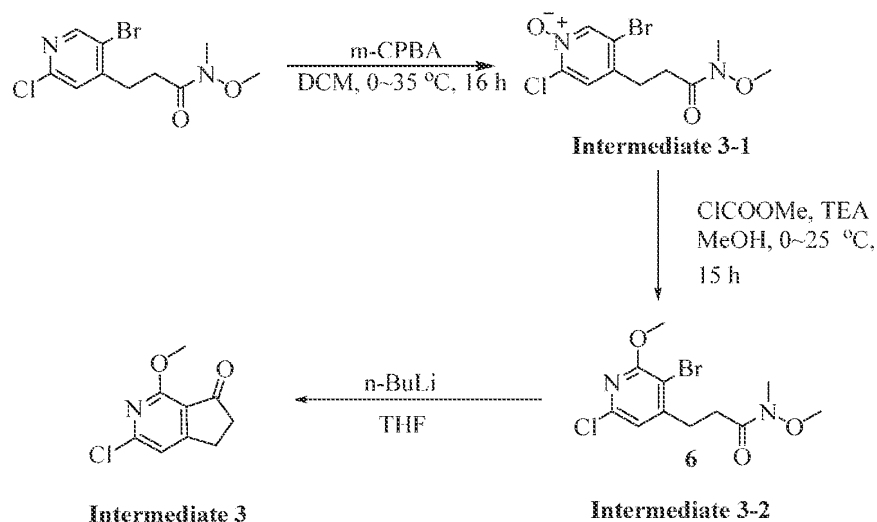
[0283] To a solution of **Intermediate 2-1** (3.68 g, 15.1 mmol) in THF (350 mL) was added TsOH (782 mg, 4.54 mmol) at $25\text{ }^\circ\text{C}$. The mixture was stirred at $60\text{ }^\circ\text{C}$ for 16 h. The mixture was diluted with H_2O (200 mL) and then extracted with EtOAc (3 x 150 mL). The combined organic layers were washed with brine (200 mL), dried over Na_2SO_4 , filtered and concentrated to give a residue, which was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, 0~5% EtOAc:PE) to give **Intermediate 2-2** (3.16 g) as a white solid. ^1H NMR (400 MHz, CDCl_3) δ 7.26 (s, 1H), 7.01 - 6.90 (m, 2H), 6.45 (td, $J = 1.9, 5.6\text{ Hz}$, 1H), 3.88 (s, 3H), 3.40 (s, 2H);

[0284] To a solution of **Intermediate 2-2** (3.16 g, 14.0 mmol) in THF (60 mL) was added $\text{BH}_3\cdot\text{THF}$ (1 M, 42.12 mL) at $0\text{ }^\circ\text{C}$. The mixture was stirred at $25\text{ }^\circ\text{C}$ for 2 h. The reaction was quenched by the addition of ice water (100 mL) at $0\text{ }^\circ\text{C}$ and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with NaHCO_3 (2 x 80 mL), dried over anhydrous Na_2SO_4 and concentrated to give a residue, which was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, 0~10% EtOAc:PE) to give **Intermediate 2-3** (2.86 g) as a yellow oil.

[0285] To a solution of **Intermediate 2-3** (2.86 g) in DCM (40 mL) was added Dess-Martin periodinane (7.48 g, 17.7 mmol) at $25\text{ }^\circ\text{C}$. The mixture was stirred at $25\text{ }^\circ\text{C}$ for 1 h. The mixture was diluted with Na_2SO_3 (100 mL) and extracted with DCM (3 x 80 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4 , filtered and concentrated to give a residue, which was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, 0~10% EtOAc:PE) to give

Intermediate 2 (1.4 g) as a white solid. ^1H NMR (400 MHz, CDCl_3) δ 7.08 (s, 1H), 6.93 (s, 1H), 3.85 (s, 3H), 3.53 (s, 2H), 3.40 (s, 2H).

Example A3
Preparation of Intermediate 3



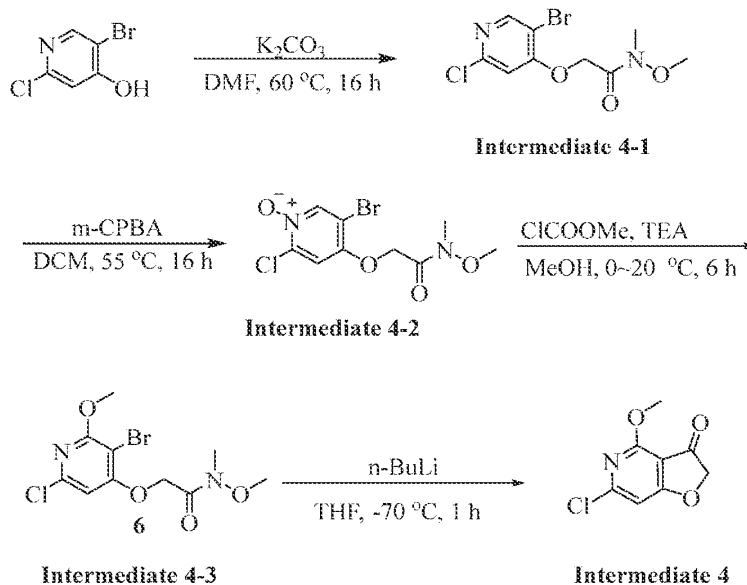
[0286] To a solution of 3-(5-bromo-2-chloro-4-pyridyl)-N-methoxy-N-methylpropanamide (27.5 g, 89.4 mmol) in DCM (400 mL) was added m-CPBA (46.3 g, 268 mmol) at 0 °C. The mixture was stirred at 35 °C for 16 h. The reaction was quenched with sat. aq. $\text{Na}_2\text{S}_2\text{O}_4$ (300 mL) and then extracted with DCM (2 x 100 mL). The combined organic layers were concentrated in vacuo. The residue was purified by flash silica gel chromatography to provide **Intermediate 3-1** as a yellow solid. ^1H NMR (400 MHz, CDCl_3) δ 8.50 (s, 1H), 7.48 (s, 1H), 3.67 (s, 3H), 3.18 (s, 3H), 3.06-2.99 (m, 2H), 2.81-2.75 (m, 2H).

[0287] To a solution of **Intermediate 3-1** (26.8 g, 82.8 mmol) and methyl carbonochloridate (26.9 g, 285 mmol) in MeOH (150 mL) was added dropwise TEA (41.9 g, 414 mmol) at 0 °C, and the mixture was stirred at 0 °C for 1.5 h. Additional methyl carbonochloridate (26.9 g, 285 mmol) was added, followed by the dropwise addition of TEA (41.9 g, 414 mmol) at 0 °C. The mixture was stirred at 30 °C for 15 h, and then concentrated under reduced pressure. The mixture was diluted with 1M aq. NaOH (300 mL) and extracted with EtOAc (2 x 200 mL). The combined organic layers were washed with brine (2 x 100 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give

a residue. The residue was purified by flash silica gel chromatography to provide **Intermediate 3-2** as a white solid (17 g, 61% yield). ^1H NMR (400 MHz, CDCl_3) δ 6.87 (s, 1H), 4.00 (s, 3H), 3.66 (s, 3H), 3.19 (s, 3H), 3.06-3.01 (m, 2H), 2.74 (br t, 2H).

[0288] To a solution of **Intermediate 3-2** (3.4 g, 10.1 mmol) in THF (40 mL) was added $n\text{-BuLi}$ (2.5 M, 6.04 mL) at -70°C . The mixture was stirred at -70°C for 0.5 h. The mixture was poured into sat. aq. NH_4Cl (80 mL) and then extracted with EtOAc (2 x 100 mL). The combined organic layers were washed with brine (2 x 80 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to provide **Intermediate 3** as a white solid (1.45 g, 73% yield). ^1H NMR (400 MHz, CDCl_3) δ 7.03 (s, 1H), 4.11 (s, 3H), 3.20-2.97 (m, 2H), 2.79-2.52 (m, 2H).

Example A4
Preparation of Intermediate 4



[0289] A mixture of 5-Bromo-2-chloro-pyridin-4-ol (3 g, 14.4 mmol), 2-bromo-N-methoxy-N-methyl-acetamide (3.93 g, 21.6 mmol) and K_2CO_3 (5.97 g, 43.2 mmol) in DMF (30 mL) was stirred at 60°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

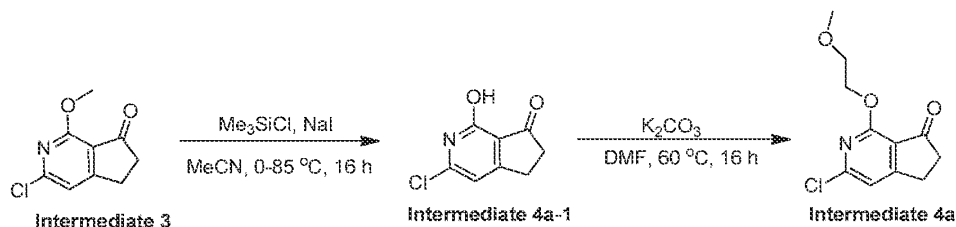
give **Intermediate 4-1** (3.5 g) as a white solid. ^1H NMR (400 MHz, CDCl_3) δ 8.38 (s, 1H), 6.73 (s, 1H), 4.99 (s, 2H), 3.80 (s, 3H), 3.26 (s, 3H).

[0290] A mixture of **Intermediate 4-1** (2 g, 6.46 mmol), m-CPBA (6.69 g, 38.8 mmol) in DCM (50 mL) was stirred at 55 °C for 16 h. The crude mixture was poured into sat. aq. $\text{Na}_2\text{S}_2\text{O}_3$ (100 mL) and then extracted with DCM (2 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography to give **Intermediate 4-2** (1 g, 48% yield). ^1H NMR (400 MHz, CDCl_3) δ 8.50 (s, 1H), 6.93 (s, 1H), 4.99 (s, 2H), 3.80 (s, 3H), 3.25 (s, 3H).

[0291] To a solution of **Intermediate 4-2** (1.7 g, 5.22 mmol) and methyl carbonochloridate (1.21 mL, 15.67 mmol) in MeOH (20 mL) was added dropwise TEA (1.59 g, 15.7 mmol, 2.18 mL) at 0 °C. After addition, the mixture was stirred at 20 °C for 1 h. Additional methyl carbonochloridate (1.21 mL, 15.67 mmol) was added at 20 °C, and then TEA (2.18 mL, 15.67 mmol) was added dropwise at 0 °C. The mixture was stirred at 20 °C for 3 h and then concentrated under reduced pressure. The residue was diluted with H_2O (40 mL) and then extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with brine (30 mL x 2), dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography to give **Intermediate 4-3** (1.3 g, 73% yield) as a white solid. ^1H NMR (400 MHz, CDCl_3) δ 6.44 (s, 1H), 4.96 (s, 2H), 4.01 (s, 3H), 3.79 (s, 3H), 3.25 (s, 3H).

[0292] To a solution of **Intermediate 4-3** (1.3 g, 3.83 mmol) in THF (15 mL) was added n-BuLi (2.5 M, 2.30 mL) at -70 °C under N_2 . The mixture was stirred at -70 °C for 1 h. The reaction was quenched by addition sat. aq. NH_4Cl (10 mL) at 0 °C and then extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous 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** (534 mg, 70% yield) as a yellow solid. ^1H NMR (400 MHz, CDCl_3) δ 6.75 (s, 1H), 4.72 (s, 2H), 4.12 (s, 3H).

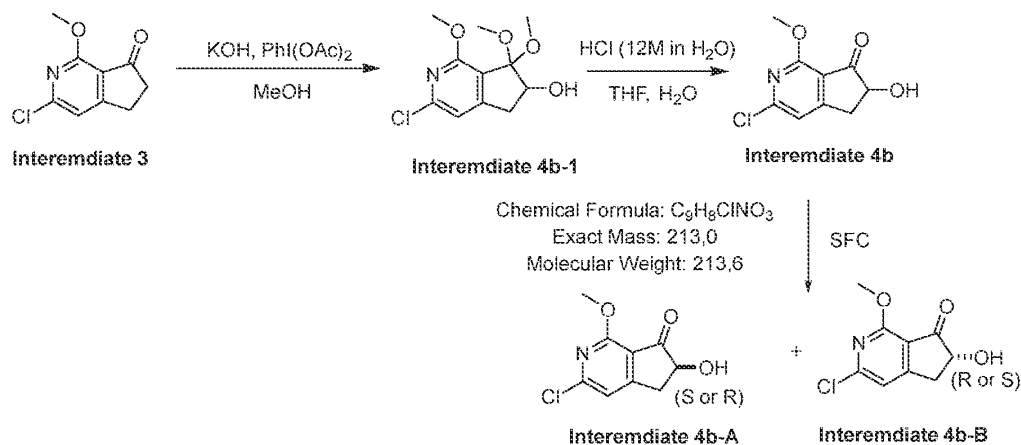
Example A4a
Preparation of Intermediate 4a



[0293] To a mixture of **Intermediate 3** (500 mg, 2.53 mmol) and NaI (1.14 g, 7.59 mmol) in MeCN (20 mL) was added dropwise chloro-trimethyl-silane (963 μ L, 7.59 mmol) at 0 °C. The mixture was stirred at 85 °C for 16 hours. The reaction mixture was filtered and concentrated under reduced pressure to give **Intermediate 4a-1** (460 mg) as a yellow solid. MS: ES m/z calculated for $C_8H_7ClNO_2$ $[M+H]^+$ 184.0 found 184.2.

[0294] To a solution of **Intermediate 4a-1** (460 mg, 2.51 mmol) and 1-bromo-2-methoxy-ethane (471 μ L, 5.01 mmol) in DMF (15 mL) was added K_2CO_3 (693 mg, 5.01 mmol). The mixture was stirred at 50 °C for 16 hours. The reaction mixture was filtered and concentrated under reduced pressure to give a residue, which was purified by prep-HPLC to give **Intermediate 4a** (150 mg) as a brown oil. MS: ES m/z calculated for $C_{11}H_{13}ClNO_3$ $[M+H]^+$ 242.1 found 242.0; ^1H NMR (400 MHz, Chloroform- d) δ = 7.02 (s, 1H), 4.71 - 4.55 (m, 2H), 3.87 - 3.73 (m, 2H), 3.46 (s, 3H), 3.17 - 3.03 (m, 2H), 2.80 - 2.64 (m, 2H).

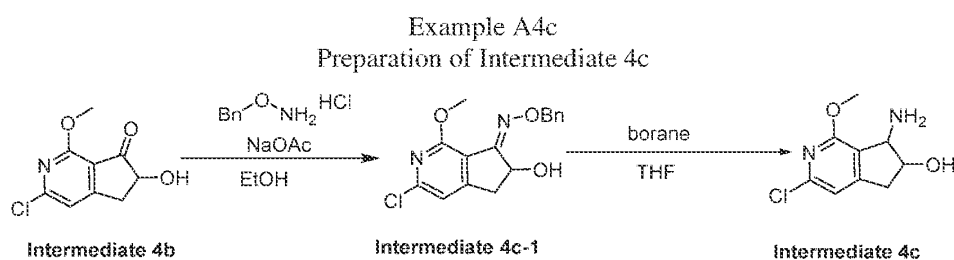
Example A4b
Preparation of Intermediate 4b, 4b-A and 4b-B



[0295] A solution of **Intermediate 3** (250 mg, 1.27 mmol) and KOH (781 mg, 13.9 mmol) in MeOH (10 mL) was stirred for 30 minutes at 0 °C. To the reaction mixture was added [acetox(phenyl)-λ³-iodanyl] acetate (488.97 mg, 1.52 mmol, 1.2 eq). The resulting solution was stirred at 0 °C for 1 hour, followed by stirring at 25 °C for 16 hours. The reaction mixture was concentrated under reduced pressure to give crude **Intermediate 4b-1** (1.3 g) as a black solid. MS: ES *m/z* calculated for C₁₁H₁₄ClNO₄ [M+H]⁺ 260.1 found 260.0;

[0296] To a solution of crude **Intermediate 4b-1** (1.3 g) in THF (10 mL) and H₂O (8 mL) was added Hydrochloric acid (12 M in H₂O, 417 μL). The mixture was stirred at 20 °C for 2 hours. The reaction mixture was diluted with Ethyl acetate (20 mL). The organic layer was washed with aq. NaHCO₃ (20 mL x 3) and brine (20 mL), dried with anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue, which was purified by prep-HPLC to give **Intermediate 4b** (350 mg) as a brown solid. MS: ES *m/z* calculated for C₉H₉ClNO₃ [M+H]⁺ 214.0 found 213.9; ¹H NMR (400 MHz, CHLOROFORM-*d*) δ = 7.04 (s, 1H), 4.49 (dd, *J* = 4.9, 7.8 Hz, 1H), 4.12 (s, 3H), 3.49 (dd, *J* = 7.8, 17.6 Hz, 1H), 2.96 (ddd, *J* = 0.7, 5.0, 17.6 Hz, 1H)

[0297] **Intermediate 4b** (350 mg) was separated by SFC (Column: Instrument: SFC-80; Column: DAICEL CHIRALCEL OX (250mm*30mm, 10μm); Condition: 0.1%NH₃H₂O ETOH; Begin B: 25; End B: 25; FlowRate(ml/min): 70; Injections:60) to give **Intermediate 4b-A** (130 mg, 99.6%ee) MS: ES *m/z* calculated for C₉H₉ClNO₃ [M+H]⁺ 214.0 found 213.9 and **Intermediate 4b-B** (145 mg, 98.9%ee) as brown solid. MS: ES *m/z* calculated for C₉H₉ClNO₃ [M+H]⁺ 214.0 found 213.9.

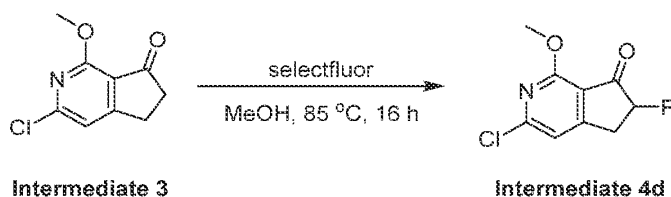


[0298] A mixture of **Intermediate 4b** (100 mg, 468 μmol), O-benzylhydroxylamine hydrochloride salt (112 mg, 702 μmol) and NaOAc (115 mg, 1.40

mmol) in EtOH (3 mL) was stirred at 45 °C for 12 hours. The reaction mixture was filtered and concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography to give **Intermediate 4c-1** (100 mg) as a yellow liquid.

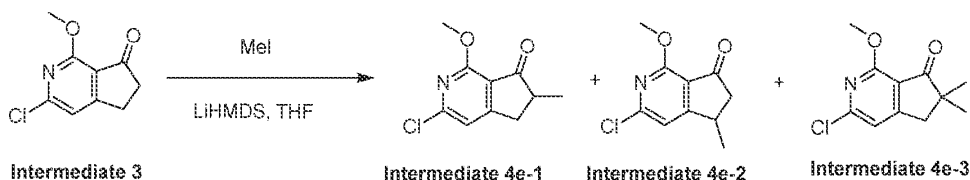
[0299] To a solution of **Intermediate 4c-1** (88 mg) in THF (2 mL) was added borane (1 M in THF 828 μ L) at 10 °C. Then the reaction mixture was stirred at 50 °C for 16 hours. The reaction mixture was quenched by addition 1N NaOH, and then extracted with ethyl acetate (2 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give **Intermediate 4c** (32 mg) as a brown solid. MS: ES m/z calculated for C₉H₁₂ClN₂O₂ [M+H]⁺ 215.1 found 214.9.

Example A4d
Preparation of Intermediate 4d



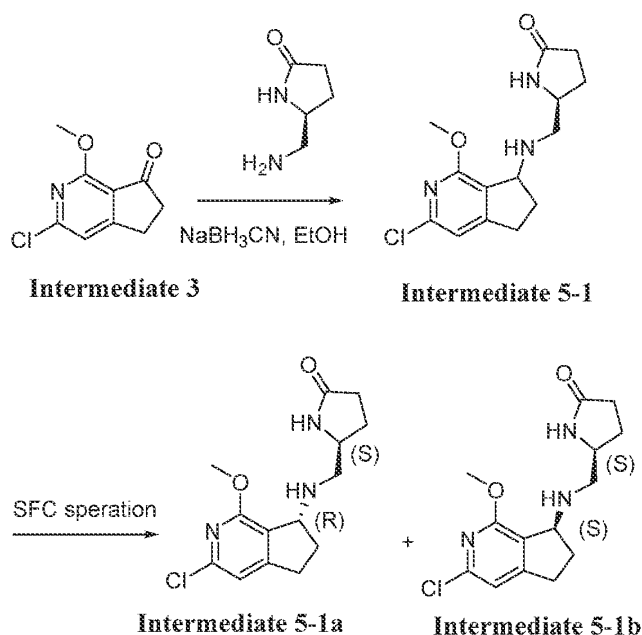
[0300] To a solution of **Intermediate 3** (300 mg, 1.52 mmol) in MeOH (3 mL) was added 1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane ditetrafluoroborate (1.61 g, 4.55 mmol). The resulting mixture was stirred at 85 °C for 16 hours. The reaction mixture was filtered and concentrated under reduced pressure to give crude **Intermediate 4d** (310 mg) as a yellow solid. MS: ES m/z calculated for C₉H₈ClFNO₂ [M+H]⁺ 216.1 found 216.0.

Example A4e
Preparation of Intermediate 4e



[0301] To a solution of **Intermediate 3** (2 g, 10.12 mmol) and MeI (7.18 g, 50.60 mmol, 3.15 mL, 5 eq) in THF (20 mL) was added slowly LiHMDS (1 M, 20.24 mL, 2 eq) at -20°C. The mixture was stirred at -15°C for 1 h, then the reaction was warmed up to 15 °C and stirred for 2 h. The reaction mixture was quenched by addition sat.NH₄Cl (20 mL) at 0 °C, then diluted with H₂O (50 mL) and extracted with EtOAc (3 x 60 mL). The combined organic layers were washed with brine (1 x 100 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography to give **Intermediate 4e-1** (70 mg) as a yellow oil, MS: ES *m/z* calculated for C₁₀H₁₁ClNO₂ [M+H]⁺ 212.0 found 211.9; **Intermediate 4e-2** (300 mg) as a yellow oil, MS: ES *m/z* calculated for C₁₀H₁₁ClNO₂ [M+H]⁺ 212.0 found 211.9; and **Intermediate 4e-3** (1.05 g) as a yellow oil, MS: ES *m/z* calculated for C₁₁H₁₃ClNO₂ [M+H]⁺ 226.1 found 226.0.

Example A5
Preparation of Intermediates 5-1a and 5-1b



[0302] The mixture of **Intermediate 3** (1.45 g, 7.34 mmol) and (5S)-5-(aminomethyl)pyrrolidin-2-one HCl salt (2.21 g, 14.7 mmol) in EtOH (20 mL) was stirred at 20–45 °C for 1 h. NaBH₃CN (1.38 g, 22 mmol) was added into the mixture at 20 °C. The

mixture was stirred at 20~45 °C for 15 h, filtered and concentrated under reduced pressure to give a residue. The residue was diluted with H₂O (80 mL) and extracted with EtOAc (2 x 100 mL). The combined organic layers were washed with brine (2 x 80 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography to give **Intermediate 5-1** (2.2 g, 92% purity) as a yellow oil.

[0303] **Intermediate 5-1** was further separated by SFC (Column: DAICEL CHIRALPAK IC (250mm*50mm, 10um), Mobile phase: A: CO₂; B: IPA (0.1% NH₃•H₂O); Gradient: 55% B; Flow Rate (mL/min): 140; Injections: 300 min (3 mL per injection, Cycle time: ~6.8 min); Column temperature: 40 °C) to give pure enantiomers **Intermediate 5-1a** and **Intermediate 5-1b**. The absolute chiral centers of the intermediates are assigned based on a single crystal structure of **Intermediate 5-1b**.

[0304] **Intermediate 5-1a** (800 mg) was obtained as a yellow oil with SFC. Rt = 3.44 minutes (SFC analytical Instrument: CAS-QD-ANA-SFC-SD (Agilent 1260 with DAD detector); Method: Column: Chiralpak IC-3 100x4.6mm I.D., 3μm; Mobile phase: 40% of IPA (0.05%) in CO₂; Flow rate: 2.8mL/min Column temperature: 40 °C). ¹H NMR (400 MHz, CD₃OD) δ 6.96 (s, 1H), 4.51 (dd, *J* = 3.9, 7.7 Hz, 1H), 3.98 (s, 3H), 3.91-3.80 (m, 1H), 3.61 (q, *J* = 7.1 Hz, 1H), 3.18-3.02 (m, 1H), 2.95-2.74 (m, 3H), 2.52-2.40 (m, 1H), 2.39 - 2.25 (m, 3H), 2.08 (tdd, *J* = 4.4, 8.9, 13.4 Hz, 1H), 1.92-1.76 (m, 1H).

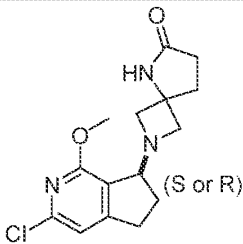
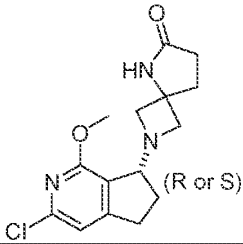
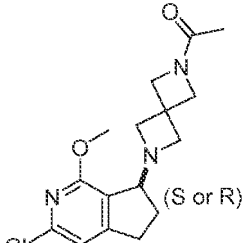
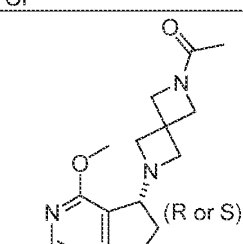
[0305] **Intermediate 5-1b** (1.14 g) was obtained as a yellow solid with SFC. Rt = 4.74 minutes (SFC analytical Instrument: CAS-QD-ANA-SFC-SD (Agilent 1260 with DAD detector) Method: Column: Chiralpak IC-3 100x4.6mm I.D., 3μm Mobile phase: 40% of IPA (0.05%) in CO₂; Flow rate: 2.8mL/min Column temperature: 40 °C). ¹H NMR (400 MHz, CD₃OD) δ 6.91 (s, 1H), 4.37 (dd, *J* = 4.8, 7.5 Hz, 1H), 3.96 (s, 3H), 3.86-3.74 (m, 1H), 3.05 (ddd, *J* = 5.9, 8.8, 17.1 Hz, 1H), 2.89-2.68 (m, 2H), 2.59 (dd, *J* = 7.1, 11.9 Hz, 1H), 2.46-2.19 (m, 4H), 1.97 (tdd, *J* = 5.3, 8.4, 13.5 Hz, 1H), 1.89-1.72 (m, 1H).

[0306] The single crystal of **Intermediate 5-1b's formate salt** was obtained. The crystal was a colorless needle with the following dimensions: 0.30 × 0.04 × 0.04 mm³. The symmetry of the crystal structure was assigned the monoclinic space group P2₁ with the following parameters: *a* = 20.8793(7) Å, *b* = 5.8084(2) Å, *c* = 28.1836(9) Å, *α* = 90°, *β* = 102.238(3)°, *γ* = 90°, *V* = 3340.3(2) Å³, *Z* = 8, *D_c* = 1.359 g/cm³, *F*(000) = 1440.0, *μ*(CuKα)

= 2.236 mm⁻¹, and T = 149.99(10) K. Figures 1A and 1B show the absolute configuration structure and ORTEP crystal structure of the formate salt of **Intermediate 5-1b**.

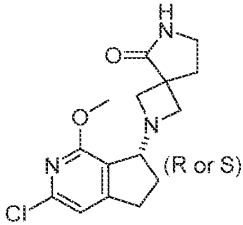
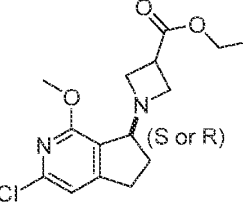
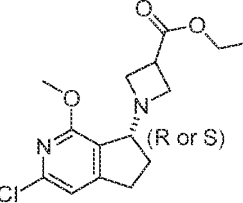
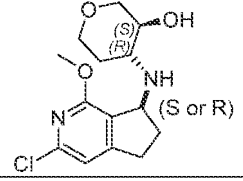
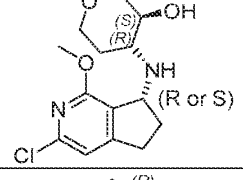
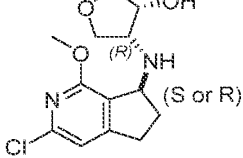
[0307] The intermediates in Table A-1 were prepared using similar methodologies are described for preparing Intermediate 5-1a and 5-1b.

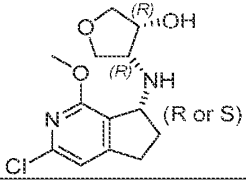
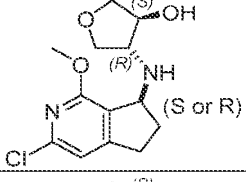
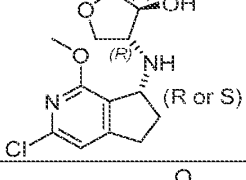
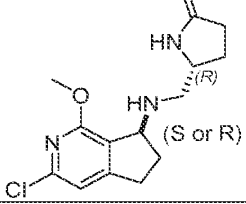
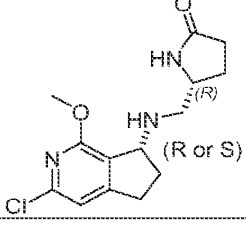
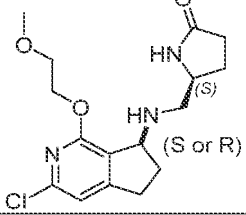
Table A-1

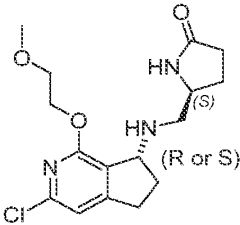
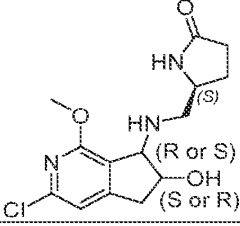
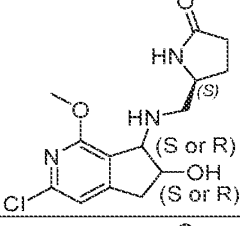
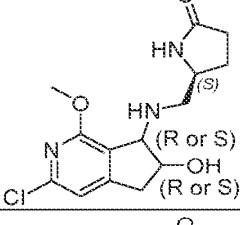
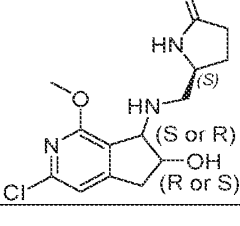
Intermediate No.	Structure	SFC Method	Retention time (minute)	Starting Materials
5-2a		E	3.33	Intermediate 3 2,5-Diazaspiro[3.4] octan-6-one hydrochloride
5-2b		E	4.00	Intermediate 3 2,5-Diazaspiro[3.4] octan-6-one hydrochloride
5-3a		F	1.19	Intermediate 3 1-(2,6- diazaspiro[3.3] heptan-2-yl)ethan-1- one
5-3b		F	1.34	Intermediate 3 1-(2,6- diazaspiro[3.3] heptan-2-yl)ethan-1- one

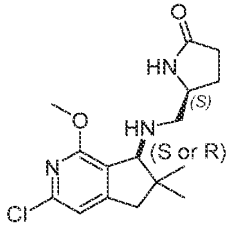
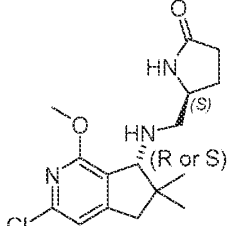
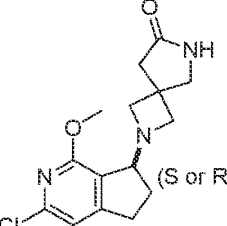
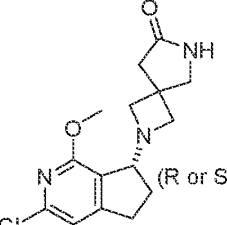
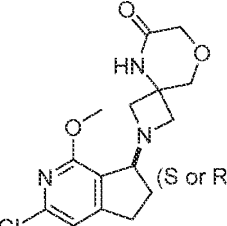
Intermediate No.	Structure	SFC Method	Retention time (minute)	Starting Materials
6-1a		I	1.36	Intermediate 4 (5S)-5-(aminomethyl)pyrrolidin-2-one HCl
6-1b		I	1.67	Intermediate 4 (5S)-5-(aminomethyl)pyrrolidin-2-one HCl
6-2a		G	1.51	Intermediate 4 2,5-Diazaspiro[3.4]octan-6-one hydrochloride
6-2b		G	2.10	Intermediate 4 2,5-Diazaspiro[3.4]octan-6-one hydrochloride
5-4a		J	1.98	Intermediate 3 (3R,4R)-4-Aminooxan-3-ol hydrochloride

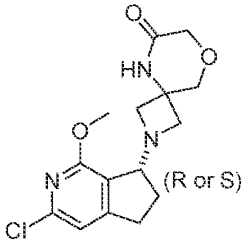
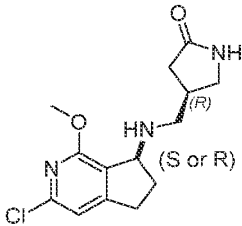
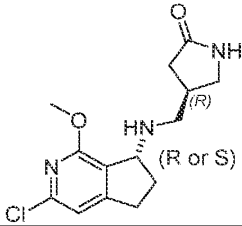
Intermediate No.	Structure	SFC Method	Retention time (minute)	Starting Materials
5-4b		J	1.83	Intermediate 3 (3R,4R)-4-Aminooxan-3-ol hydrochloride
5-5a		L	3.28	Intermediate 3 3-Hydroxyazetidine Hydrochloride
5-5b		L	3.58	Intermediate 3 3-Hydroxyazetidine Hydrochloride
5-6a		L	1.96	Intermediate 3 3-methoxyazetidine hydrochloride
5-6b		L	2.14	Intermediate 3 3-methoxyazetidine hydrochloride
5-7a		K	1.69	Intermediate 3 2,6-Diazaspiro[3.4]octan-5-one hydrochloride

Intermediate No.	Structure	SFC Method	Retention time (minute)	Starting Materials
5-7b		K	1.80	Intermediate 3 2,6-Diazaspiro[3.4]octan-5-one hydrochloride
5-8a		J	0.76	Intermediate 3 Ethyl Azetidine-3-carboxylate Hydrochloride
5-8b		J	0.96	Intermediate 3 Ethyl Azetidine-3-carboxylate Hydrochloride
5-9a		J	1.02	Intermediate 3 (3S,4R)-4-aminotetrahydro-2H-pyran-3-ol hydrochloride
5-9b		J	1.31	Intermediate 3 (3S,4R)-4-aminotetrahydro-2H-pyran-3-ol hydrochloride
5-10a		N	1.62	Intermediate 3 (3R,4R)-4-aminotetrahydrofuran-3-ol hydrochloride

Intermediate No.	Structure	SFC Method	Retention time (minute)	Starting Materials
5-10b		N	1.81	Intermediate 3 (3R,4R)-4-aminotetrahydrofuran-3-ol hydrochloride
5-11a		M	1.64	Intermediate 3 (3S,4R)-4-Aminotetrahydro-3-furanol
5-11b		M	1.78	Intermediate 3 (3S,4R)-4-Aminotetrahydro-3-furanol
5-12a		O	2.10	Intermediate 3 (5R)-5-(aminomethyl)pyrrolidin-2-one HCl
5-12b		O	2.33	Intermediate 3 (5R)-5-(aminomethyl)pyrrolidin-2-one HCl
5-13a		J	1.48	Intermediate 4a (5S)-5-(aminomethyl)pyrrolidin-2-one HCl

Intermediate No.	Structure	SFC Method	Retention time (minute)	Starting Materials
5-13b		J	1.89	Intermediate 4a (5S)-5-(aminomethyl)pyrrolidin-2-one HCl
5-14a		G	1.69	Intermediate 4b-A (5S)-5-(aminomethyl)pyrrolidin-2-one HCl
5-14b		G	2.37	Intermediate 4b-A (5S)-5-(aminomethyl)pyrrolidin-2-one HCl
5-15a		P	1.99	Intermediate 4b-B (5S)-5-(aminomethyl)pyrrolidin-2-one HCl
5-15b		P	2.72	Intermediate 4b-B (5S)-5-(aminomethyl)pyrrolidin-2-one HCl

Intermediate No.	Structure	SFC Method	Retention time (minute)	Starting Materials
5-16a		P	1.61	Intermediate 4e-3 (5S)-5-(aminomethyl)pyrrolidin-2-one HCl
5-16b		P	1.85	Intermediate 4e-3 (5S)-5-(aminomethyl)pyrrolidin-2-one HCl
5-17a		M	2.47	Intermediate 3 2,6-diazaspiro[3.4]octan-7-one hydrochloride
5-17b		M	2.67	Intermediate 3 2,6-diazaspiro[3.4]octan-7-one hydrochloride
5-18a		G	1.411	Intermediate 3 8-oxa-2,5-diazaspiro[3.5]nonan-6-one hydrochloride

Intermediate No.	Structure	SFC Method	Retention time (minute)	Starting Materials
5-18b		G	1.675	Intermediate 3 8-oxa-2,5-diazaspiro[3.5]nonan-6-one hydrochloride
5-19a		Q	1.97	Intermediate 3 (R)-4-(aminomethyl)pyrrolidin-2-one hydrochloride
5-19b		Q	2.16	Intermediate 3 (R)-4-(aminomethyl)pyrrolidin-2-one hydrochloride

[0308] SFC Method E: Column: UniChiral ND 100×4.6mm I.D., 5 μm; Mobile phase: A: CO₂; B: iso-propanol (0.05% DEA); Gradient: from 5% to 40% of B in 4.5min and hold 40% for 0.5 min, then 5% of B for 1 min; Flow rate: 2.8mL/min; Column temperature: 40 °C.

[0309] SFC Method F: Column: Chiralpak AD-3 100×4.6mm I.D., 3 μm; Mobile phase: A: CO₂, B: Ethanol (0.05% DEA); Gradient: from 5% to 40% of B in 4.5min and hold 40% for 2.5 min, then 5% of B for 1 min; Flow rate: 2.8mL/min; Column temperature: 40°C.

[0310] SFC Method G: Column: Chiralpak AD-3 50×4.6mm I.D., 3 μm; Mobile phase: A: CO₂, B: Ethanol (0.05% DEA); Gradient: from 5% to 40% of B in 2.5min and hold 40% for 0.5 min, then 5% of B for 1 min; Flow rate: 4mL/min; Column temperature: 35°C.

[0311] SFC Method H: Column: Lux Cellulose-2 100×4.6mm I.D., 3 μm; Mobile phase: A: CO₂; B: IPA (0.05% DEA); Gradient: from 5% to 40% of B in 4.5min and hold

40% for 2.5 min, then 5% of B for 1 min; Flow rate: 2.5mL/min; Column temperature: 40 °C.

[0312] SFC Method I: Column: Chiralpak AY-3 50×4.6mm I.D., 3 µm; Mobile phase: A: CO₂; B: IPA (0.05% DEA); Gradient: from 5% to 40% of B in 2.5min and hold 40% for 0.5 min, then 5% of B for 1 min; Flow rate: 4mL/min; Column temperature: 35 °C.

[0313] SFC Method J: Column: Chiralpak AY-3 50×4.6mm I.D., 3 µm; Mobile phase: A: CO₂; B: Ethanol (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 mL/min; Column temperature: 35 °C.

[0314] SFC Method K: Column: (S,S)-Whelk-0-1.8 50×4.6mm I.D., 1.8 µm; Mobile phase: A: CO₂; B: methanol (0.05% DEA); Gradient: from 10% to 40% of B in 2 min and hold 40% for 1 min, then 5% of B for 1 min; Flow rate: 2.8 mL/min; Column temperature: 35 °C.

[0315] SFC Method L: Column: Lux Cellulose-2 100×4.6mm I.D., 3 µm; Mobile phase: A: CO₂; B: IPA (0.05% DEA); Gradient: from 5% to 40% of B in 4.5 min, then 5% of B for 2.5 min, then 5% of B for 1 min; Flow rate: 2.5 mL/min; Column temperature: 40 °C.

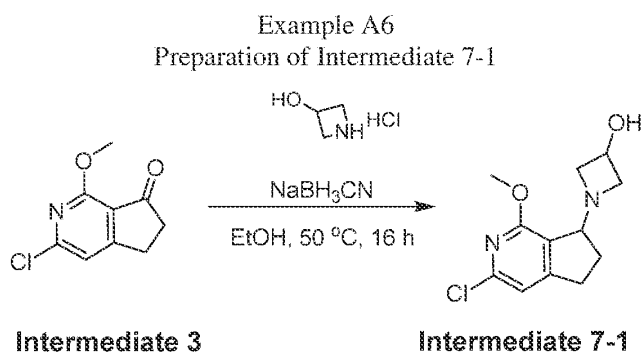
[0316] SFC Method M: Column: MChiral NS-3 100×4.6mm I.D., 3 µm Mobile phase: A: CO₂ B:IPA (0.05% DEA) Gradient: from 5% to 40% of B in 2 min and hold 40% for 1 min, then 5% of B for 1 min Flow rate: 2.8mL/min; Column temp.: 35 °C.

[0317] SFC Method N: Column: Chiralcel OJ-3 100×4.6mm I.D., 3 µm Mobile phase: A: CO₂ 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.

[0318] SFC Method O: Column: Chiralpak AS-3 50×4.6mm I.D., 3 µm; Mobile phase: A: CO₂; B: Ethanol (0.05% DEA); Gradient: from 5% to 40% of B in 2.5 min, then 40% of B for 0.5 min, then 5% of B for 1 min; Flow rate: 4 mL/min; Column temperature: 35 °C.

[0319] SFC Method P: Column: Chiralpak IG 50×4.6mm I.D., 3 µm; Mobile phase: A: CO₂; B: Ethanol (0.05% DEA); Gradient: from 5% to 40% of B in 2.5 min, then 40% of B for 0.5 min, then 5% of B for 1 min; Flow rate: 4 mL/min; Column temperature: 35 °C.

[0320] SFC Method Q: Column: Chiralpak IC-3 50×4.6mm I.D., 3 μ m; Mobile phase: A: CO₂ B: Methanol (0.05% DEA); Gradient: from 20% to 40% of B in 2.5 min and hold 40% of 0.5 min, then 20% of B for 1 min; Flow rate: mL/min ;Column temp.:35 °C.

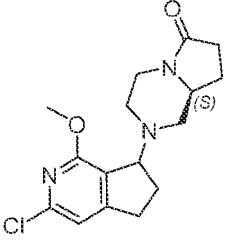
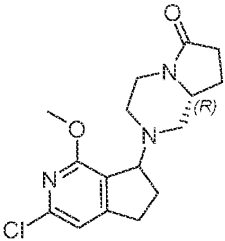
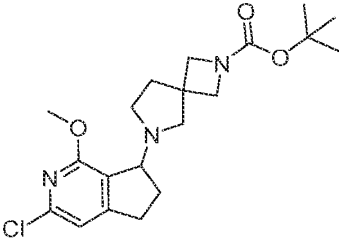
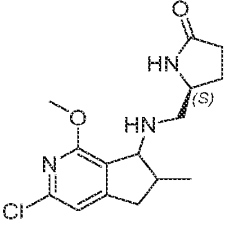
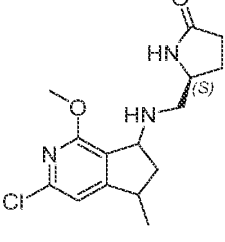


[0321] To a solution of **Intermediate 3** (500 mg, 2.53 mmol) in EtOH (6 mL) was added 3-Hydroxyazetidine hydrochloride (416 mg, 3.80 mmol). The mixture was stirred at 50 °C for 1 h. After adding NaBH₃CN (477 mg, 7.59 mmol) at 25 °C into the mixture, the resulting mixture was stirred at 50 °C for 15 h to give a yellow mixture. The reaction was quenched with H₂O (30 mL) and then extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue, which was purified by prep-HPLC to give **Intermediate 7-1** (280 mg, 39% yield, 90% purity) as a yellow solid. MS: ES *m/z* calculated for C₁₂H₁₆ClN₂O₂ [M+H]⁺ 255.1 found 255.0.

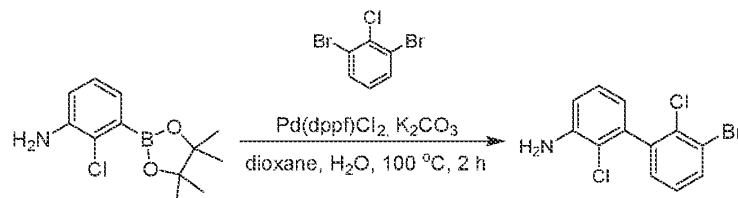
[0322] The intermediates shown in Table A-2 were prepared by an analogous reaction protocol as was used for the preparation of **Intermediate 7-1** using the appropriate starting materials.

Table A-2

Intermediate No.	Structure	Starting Materials
7-2		(5S)-5-(aminomethyl)pyrrolidin-2-one HCl salt Intermediate 2

7-3		(8aS)- Hexahydropyrrolo[1,2- a]pyrazin-6(2H)-one hydrochloride Intermediate 3
7-4		(8aR)- Hexahydropyrrolo[1,2- a]pyrazin-6(2H)-one hydrochloride Intermediate 3
7-5		tert-butyl 2,6- diazaspiro[3.4]octane-2- carboxylate Intermediate 3
7-6		(5S)-5- (aminomethyl)pyrrolidin- 2-one HCl salt Intermediate 4e-1
7-7		(5S)-5- (aminomethyl)pyrrolidin- 2-one HCl salt Intermediate 4e-2

Example 7
Preparation Intermediate 8-1



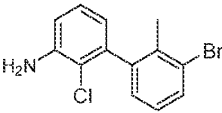
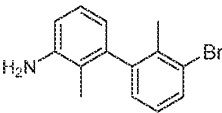
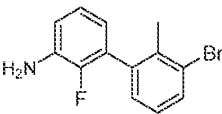
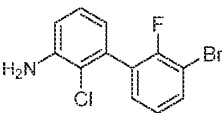
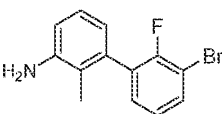
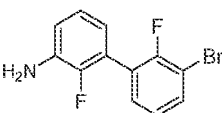
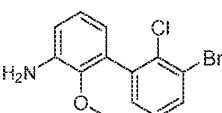
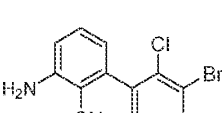
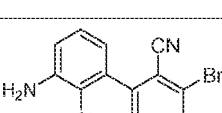
Intermediate 8-1

[0323] 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)Cl₂ (606 mg, 828 μmol) and K₂CO₃ (3.43 g, 24.9 mmol) in dioxane (25 mL) and H₂O (2.5 mL) was degassed and purged with N₂ (3x). After stirring the mixture at 100 °C for 2 h under N₂ atmosphere, the reaction was quenched with H₂O (30 mL) and then extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography to give **Intermediate 8-1** (1.4 g) as a yellow solid. MS: ES *m/z* calculated for C₁₂H₉BrCl₂N [M+H]⁺ 315.9, found 316.0.

[0324] The intermediates shown in Table A-3 were prepared by an analogous reaction protocol as was used for the preparation of **Intermediate 8-1** using the appropriate starting materials.

Table A-3

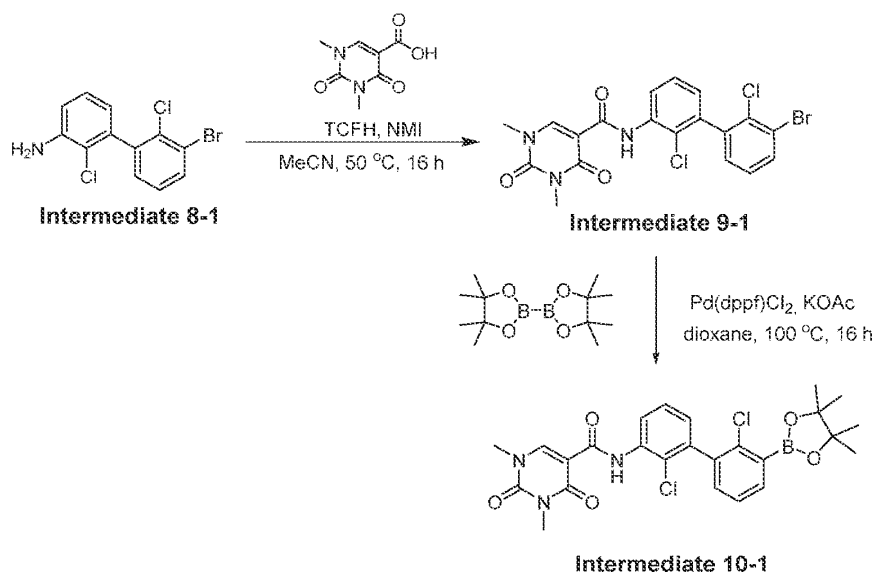
Intermediate No.	Structure	Starting Materials
8-2		2-Methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline 1,3-Dibromo-2-chlorobenzene
8-3		2-Fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline 1,3-Dibromo-2-chlorobenzene

Intermediate No.	Structure	Starting Materials
8-4		2-Chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline 1,3-Dibromo-2-methylbenzene
8-5		2-Methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline 1,3-Dibromo-2-methylbenzene
8-6		2-Fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline 1,3-Dibromo-2-methylbenzene
8-7		2-Chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline 1,3-Dibromo-2-fluorobenzene
8-8		2-Methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline 1,3-Dibromo-2-fluorobenzene
8-9		2-Fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline 1,3-Dibromo-2-fluorobenzene
8-10		2-Methoxy-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline 1,3-Dibromo-2-chlorobenzene
8-11		2-amino-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile 1,3-Dibromo-2-chlorobenzene
8-12		2-Chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline 2,6-dibromobenzonitrile

Intermediate No.	Structure	Starting Materials
8-14		5-chloro-2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline 1,3-Dibromo-2-chlorobenzene
8-15		5-fluoro-2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylamine 1,3-Dibromo-2-chlorobenzene
8-15a		5-fluoro-2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylamine 1,3-dibromo-2-methylbenzene
8-16		2-Chloro-5-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline 1,3-Dibromo-2-chlorobenzene
8-18		6-fluoro-2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline 1,3-Dibromo-2-chlorobenzene
8-20		2-Methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline 1,3-dibromo-2-chloro-5-fluorobenzene
8-21		5-fluoro-2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylamine 1,3-dibromo-2-chloro-5-fluorobenzene

Intermediate No.	Structure	Starting Materials
8-22		2-chloro-5-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline 1,3-dibromo-2-chloro-5-fluorobenzene
8-23		2-Methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline 2-bromo-4-chloro-1,3-difluorobenzene
8-24		2-Methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline 1-bromo-3-chloro-2,4-difluorobenzene

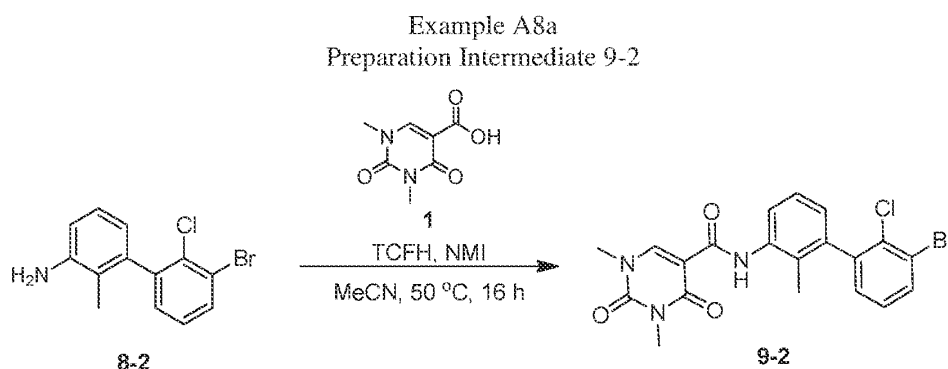
Example A8
Preparation Intermediate 10-1



[0325] To a solution of compound **Intermediate 8-1** (300 mg, 946 μ mol) and 1,3-dimethyl-2,4-dioxypyrimidine-5-carboxylic acid (145 mg, 789 μ mol) in MeCN (4 mL) were added *N,N,N',N'*-tetramethylchloroformamidinium hexafluorophosphate (TCFH, 443 mg, 1.58 mmol) and *N*-methylimidazole (NMI, 157.16 μ L, 1.97 mmol). The

mixture was stirred at 50 °C for 16 h. The reaction was quenched with H₂O (20 mL) and then extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography to give **Intermediate 9-1** (420 mg, crude) as a yellow solid. MS: ES *m/z* calculated for C₁₉H₁₄BrCl₂N₃O₃Na[M+Na]⁺ 504.0 found 504.0.

[0326] A mixture of crude **Intermediate 9-1** (420 mg), Bis(pinacolato)diboron (132 mg, 521 μmol), KOAc (128 mg, 1.30 mmol) and Pd(dppf)Cl₂ (31.8 mg, 43.5 μmol) in dioxane (3 mL) was degassed and purged with N₂ (3x). The mixture was stirred at 100 °C for 16 h under N₂ atmosphere, filtered and concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, 0–50% EtOAc:PE) to give **Intermediate 10-1** (330 mg) as a yellow solid. MS: ES *m/z* calculated for C₂₅H₂₇BCl₂N₃O₅ [M+H]⁺ 530.1 found 530.1



[0327] To a solution of **Intermediate 8-2** (850 mg, 2.87 mmol) and 1,3-dimethyl-2,4-dioxypyrimidine-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 reaction mixture was stirred at 50 °C for 16 hours. The reaction 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 9-2** (1 g) as a white solid.

[0328] The intermediates shown in Table A-4 were prepared by an analogous reaction protocol as was used for the preparation of Intermediate 9-2 using the appropriate starting materials.

Table A-4

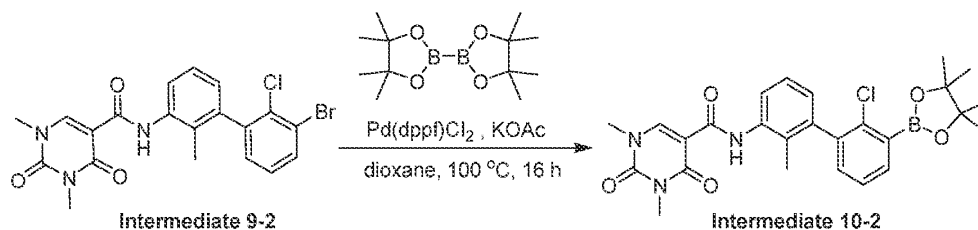
Intermediate No.	Structure	Starting Materials
9-3		1,3-dimethyl-2,4-dioxypyrimidine-5-carboxylic acid Intermediate 8-3
9-4		1,3-dimethyl-2,4-dioxypyrimidine-5-carboxylic acid Intermediate 8-4
9-5		1,3-dimethyl-2,4-dioxypyrimidine-5-carboxylic acid Intermediate 8-5
9-6		1,3-dimethyl-2,4-dioxypyrimidine-5-carboxylic acid Intermediate 8-6
9-7		1,3-dimethyl-2,4-dioxypyrimidine-5-carboxylic acid Intermediate 8-7
9-8		1,3-dimethyl-2,4-dioxypyrimidine-5-carboxylic acid Intermediate 8-8
9-9		1,3-dimethyl-2,4-dioxypyrimidine-5-carboxylic acid Intermediate 8-9
9-10		2-Methyl-3-oxo-2,3-dihydropyridazine-4-carboxylic acid Intermediate 8-1

Intermediate No.	Structure	Starting Materials
9-11		2-Methyl-3-oxo-2,3-dihydropyridazine-4-carboxylic acid Intermediate 8-2
9-12		2-Methyl-3-oxo-2,3-dihydropyridazine-4-carboxylic acid Intermediate 8-8
9-13		1,3-dimethyl-2,4-dioxypyrimidine-5-carboxylic acid Intermediate 8-10
9-14		1,3-dimethyl-2,4-dioxypyrimidine-5-carboxylic acid Intermediate 8-11
9-15		1,3-dimethyl-2,4-dioxypyrimidine-5-carboxylic acid Intermediate 8-12
9-17		1,3-dimethyl-2,4-dioxypyrimidine-5-carboxylic acid Intermediate 8-14
9-18		1,3-dimethyl-2,4-dioxypyrimidine-5-carboxylic acid Intermediate 8-15
9-19		1,3-dimethyl-2,4-dioxypyrimidine-5-carboxylic acid Intermediate 8-16
9-21		1,3-dimethyl-2,4-dioxypyrimidine-5-carboxylic acid Intermediate 8-18

Intermediate No.	Structure	Starting Materials
9-23		1,3-dimethyl-2,4-dioxypyrimidine-5-carboxylic acid Intermediate 8-20
9-24		1,3-dimethyl-2,4-dioxypyrimidine-5-carboxylic acid Intermediate 8-21
9-25		1,3-dimethyl-2,4-dioxypyrimidine-5-carboxylic acid Intermediate 8-22
9-26		1,3-dimethyl-2,4-dioxypyrimidine-5-carboxylic acid Intermediate 8-23
9-27		1,3-dimethyl-2,4-dioxypyrimidine-5-carboxylic acid Intermediate 8-24
9-28a		1,2,3,6-Tetrahydro-1-methyl-2,6-dioxo-5-pyrimidinecarboxylic acid Intermediate 8-2
9-28b		1,2,3,4-Tetrahydro-1-methyl-2,4-dioxo-5-pyrimidinecarboxylic acid Intermediate 8-2
9-29		1,2,3,4-Tetrahydro-2,4-dioxo-5-pyrimidinecarboxylic acid Intermediate 8-2
9-30		2,3,4,5-Tetrahydro-2,4-dimethyl-3,5-dioxo-1,2,4-triazine-6-carboxylic acid Intermediate 8-1

Intermediate No.	Structure	Starting Materials
9-31		2,3,4,5-Tetrahydro-2,4-dimethyl-3,5-dioxo-1,2,4-triazine-6-carboxylic acid Intermediate 8-2
9-32		2,3,4,5-Tetrahydro-2,4-dimethyl-3,5-dioxo-1,2,4-triazine-6-carboxylic acid Intermediate 8-5
9-33		2,3,4,5-Tetrahydro-2,4-dimethyl-3,5-dioxo-1,2,4-triazine-6-carboxylic acid Intermediate 8-15
9-33a		2,3,4,5-Tetrahydro-2,4-dimethyl-3,5-dioxo-1,2,4-triazine-6-carboxylic acid Intermediate 8-15a
9-34		3-hydroxy-4-pyridazinecarboxylic acid Intermediate 8-1
9-35		3-hydroxy-4-pyridazinecarboxylic acid Intermediate 8-2
9-36		2-Methyl-3-oxo-2,3-dihydropyridazine-4-carboxylic acid Intermediate 8-15

Example A8b
Preparation Intermediate 10-2

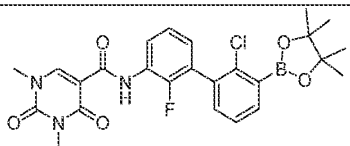
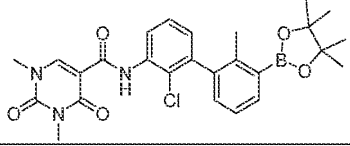
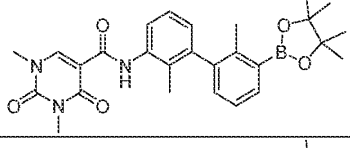
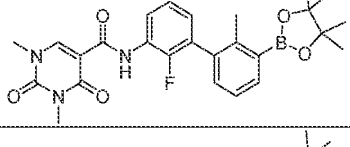
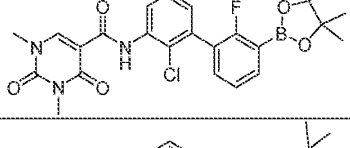
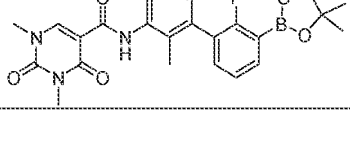


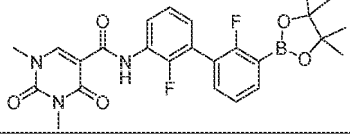
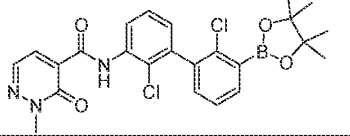
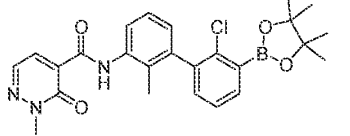
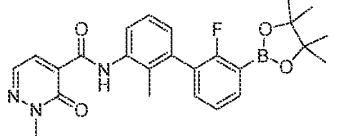
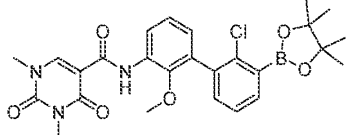
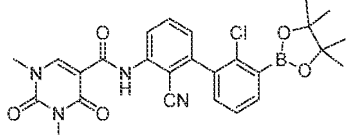
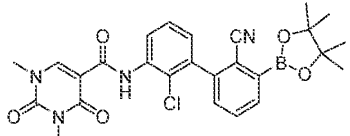
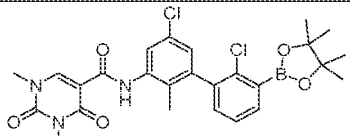
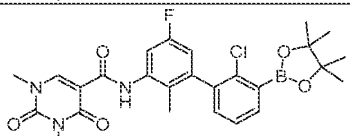
[0329] A mixture of **Intermediate 9-2** (1.0 g), Bis(pinacolato)diboron (823 mg, 3.24 mmol), KOAc (636 mg, 6.48 mmol) and Pd(dppf)Cl₂ (158 mg, 216 μmol) in dioxane (10 mL) was degassed and purged with N₂ (3x). The mixture was stirred at 100 °C for 16 h

under N₂ 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 10-2** (780 mg) as a white solid. MS: ES *m/z* calculated for C₂₆H₃₀BClN₃O₅ [M+H]⁺ 510.2 found 510.0

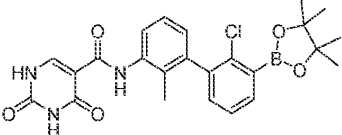
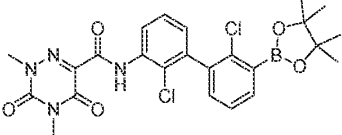
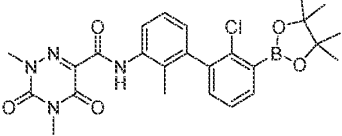
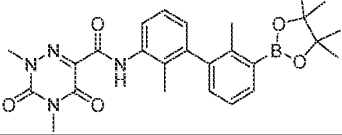
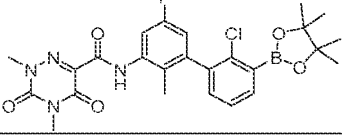
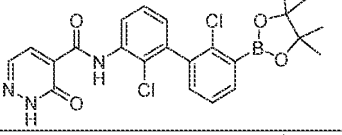
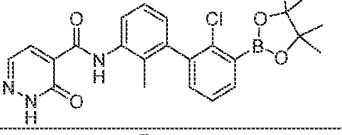
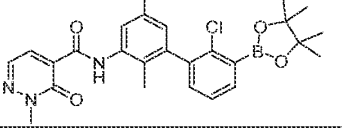
[0330] The intermediates shown in Table A-5 were prepared by an analogous reaction protocol as was used for the preparation of **Intermediate 10-2** using the appropriate starting materials.

Table A-5

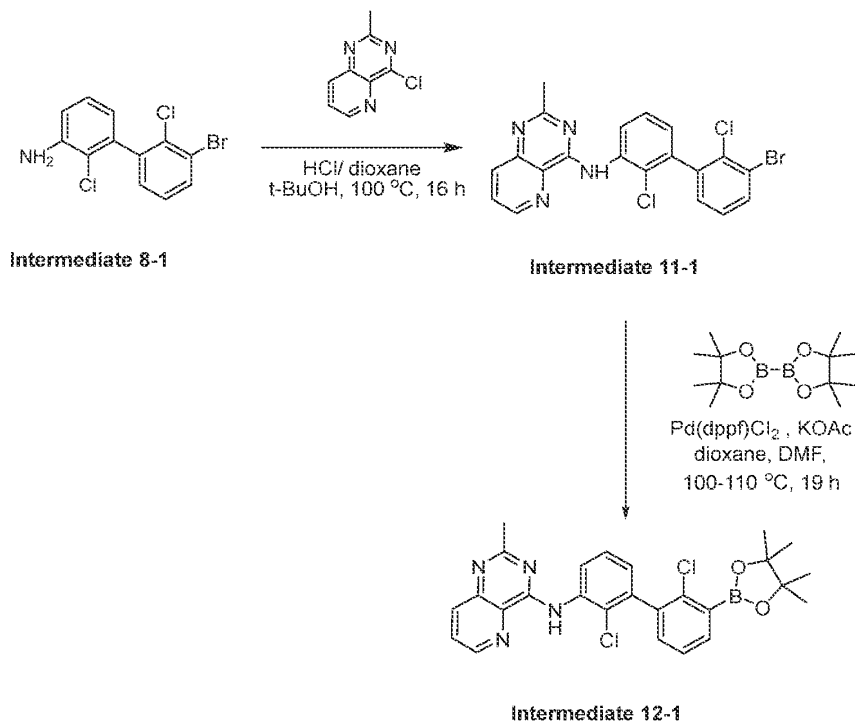
Intermediate No.	Structure	Starting Materials
10-3		Bis(pinacolato)diboron Intermediate 9-3
10-4		Bis(pinacolato)diboron Intermediate 9-4
10-5		Bis(pinacolato)diboron Intermediate 9-5
10-6		Bis(pinacolato)diboron Intermediate 9-6
10-7		Bis(pinacolato)diboron Intermediate 9-7
10-8		Bis(pinacolato)diboron Intermediate 9-8

Intermediate No.	Structure	Starting Materials
10-9		Bis(pinacolato)diboron Intermediate 9-9
10-10		Bis(pinacolato)diboron Intermediate 9-10
10-11		Bis(pinacolato)diboron Intermediate 9-11
10-12		Bis(pinacolato)diboron Intermediate 9-12
10-13		Bis(pinacolato)diboron Intermediate 9-13
10-14		Bis(pinacolato)diboron Intermediate 9-14
10-15		Bis(pinacolato)diboron Intermediate 9-15
10-17		Bis(pinacolato)diboron Intermediate 9-17
10-18		Bis(pinacolato)diboron Intermediate 9-18

Intermediate No.	Structure	Starting Materials
10-19		Bis(pinacolato)diboron Intermediate 9-19
10-21		Bis(pinacolato)diboron Intermediate 9-21
10-23		Bis(pinacolato)diboron Intermediate 9-23
10-24		Bis(pinacolato)diboron Intermediate 9-24
10-25		Bis(pinacolato)diboron Intermediate 9-25
10-26		Bis(pinacolato)diboron Intermediate 9-26
10-27		Bis(pinacolato)diboron Intermediate 9-27
10-28a		Bis(pinacolato)diboron Intermediate 9-28a
10-28b		Bis(pinacolato)diboron Intermediate 9-28b

Intermediate No.	Structure	Starting Materials
10-29		Bis(pinacolato)diboron Intermediate 9-29
10-30		Bis(pinacolato)diboron Intermediate 9-30
10-31		Bis(pinacolato)diboron Intermediate 9-31
10-32		Bis(pinacolato)diboron Intermediate 9-32
10-33		Bis(pinacolato)diboron Intermediate 9-33
10-34		Bis(pinacolato)diboron Intermediate 9-34
10-35		Bis(pinacolato)diboron Intermediate 9-35
10-36		Bis(pinacolato)diboron Intermediate 9-36

Example A9
Preparation Intermediate 12-1



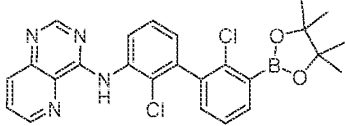
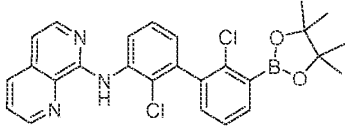
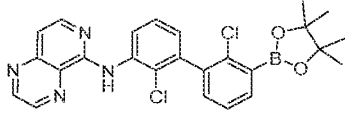
[0331] A mixture of **Intermediate 8-1** (200 mg, 631 μmol), 4-chloro-2-methylpyrido[3,2-d]pyrimidine (113 mg, 631 μmol) and HCl/dioxane (4 M, 156 μL) in t-BuOH (3.5 mL) was stirred at 100 °C for 16 h. The mixture was concentrated under reduced pressure to give a residue, which was triturated with EtOAc (20 mL) to give **Intermediate 11-1** (211 mg, crude) as an off-white solid. MS: ES m/z calculated for $\text{C}_{20}\text{H}_{14}\text{BrCl}_2\text{N}_4$ $[\text{M}+\text{H}]^+$ 459.0, found 458.9.

[0332] A mixture of **Intermediate 11-1** (100 mg, 217 μmol), Bis(pinacolato)diboron (166 mg, 652 μmol), KOAc (597 mg, 6.08 mmol) and Pd(dppf) Cl_2 (15.9 mg, 21.7 μmol) in dioxane (2.5 mL) was degassed and stirred at 100 °C for 16 h under N_2 atmosphere. After adding DMF (1 mL) into the mixture, the resulting mixture was stirred at 110 °C for 3 h under N_2 atmosphere. The mixture was partitioned between EtOAc (50 mL) and H_2O (50 mL). The organic layer was separated, washed with brine (50 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue, which was

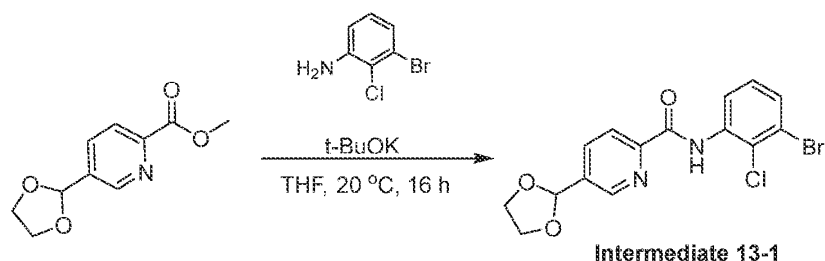
purified by flash silica gel chromatography to give **Intermediate 12-1** (244 mg, crude) as a brown solid. MS: ES m/z calculated for $C_{26}H_{26}BCl_2N_4O_2$ $[M+H]^+$ 507.1, found 507.1.

[0333] The intermediates shown in Table A-6 were prepared by an analogous reaction protocol as was used for the preparation of **Intermediate 12-1** using the appropriate starting materials.

Table A-6

Intermediate No.	Structure	Starting Materials
12-2		4-Chloropyrido[3,2-d]pyrimidine Intermediate 8-1
12-3		8-Chloro-1,7-naphthyridine Intermediate 8-1
12-4		5-chloropyrido[4,3-b]pyrazine Intermediate 8-1

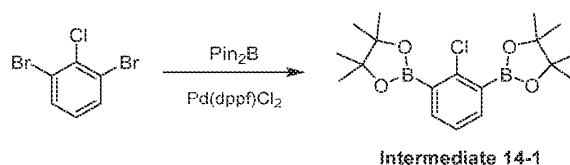
Example A10
Preparation Intermediate 13-1



[0334] To a solution of methyl 5-(1,3-dioxolan-2-yl)pyridine-2-carboxylate (800 mg, 3.82 mmol) and 3-Bromo-2-chloroaniline (790 mg, 3.82 mmol) in THF (6 mL) was added t-BuOK (644 mg, 5.74 mmol). The mixture was stirred at 20 °C for 16 h to give a yellow solution. After the mixture's pH was adjusted to be ~7 with aq. NH_4Cl , the mixture

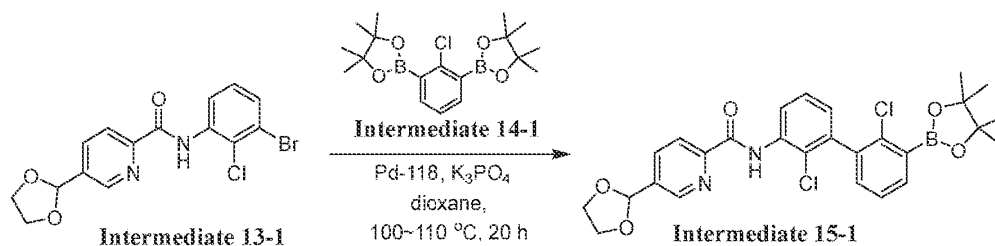
was diluted with H₂O (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography to give **Intermediate 13-1** (950 mg) as a yellow solid. MS: ES *m/z* calculated for C₁₅H₁₃BrClN₂O₃ [M+H]⁺ 383.0, found 382.9.

Example A11
Preparation of Intermediate 14-1



[0335] To a mixture of 1,3-dibromo-2-chloro-benzene (50 g, 185 mmol) and 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (93.9 g, 370 mmol) in dioxane (400 mL) were added KOAc (90.76 g, 924.73 mmol, 5 eq.) and Pd(dppf)Cl₂ (13.53 g, 18.49 mmol, 0.1 eq.) at 25°C under N₂. The mixture was stirred at 110 °C for 12 h. The mixture was evaporated and diluted with water (500 mL). The mixture was extracted with MTBE (2 x 500 mL). The combined organic layers were evaporated to give the crude product. The crude product was triturated with MeOH (150 mL) to give **Intermediate 14-1** (41.3 g, 61% yield) as white solid. ¹H NMR: (400MHz, CDCl₃) δ 7.59 (d, *J* = 7.2 Hz, 2H), 7.13 (t, *J* = 7.2 Hz, 1H), 1.29 (s, 24H).

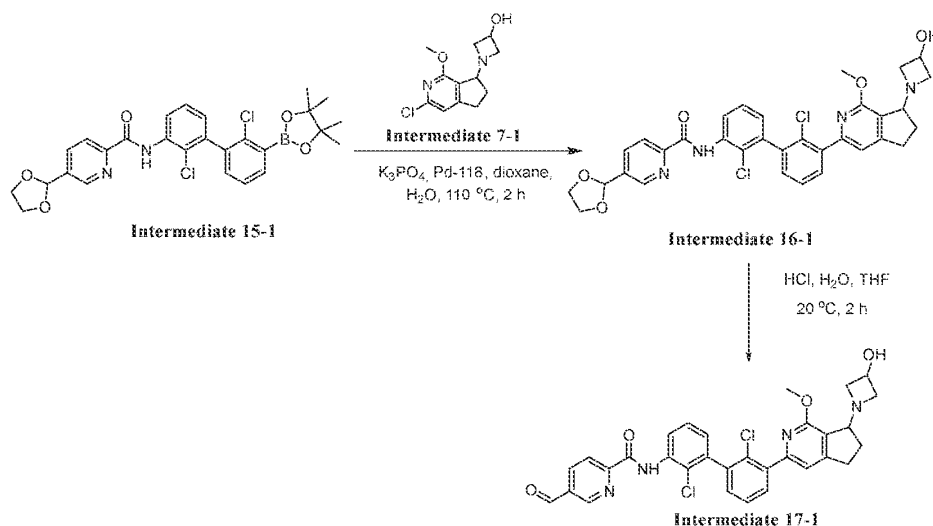
Example A12
Preparation Intermediate 15-1



[0336] A mixture of **Intermediate 13-1** (950 mg, 2.35 mmol), **Intermediate 14-1** (2.57 g, 7.05 mmol) and Pd-118 (153 mg, 235 μmol), K₃PO₄ (1.50 g, 7.05 mmol) in dioxane (10 mL) was degassed and purged with N₂ (3x). The mixture was stirred at 100 °C for 16

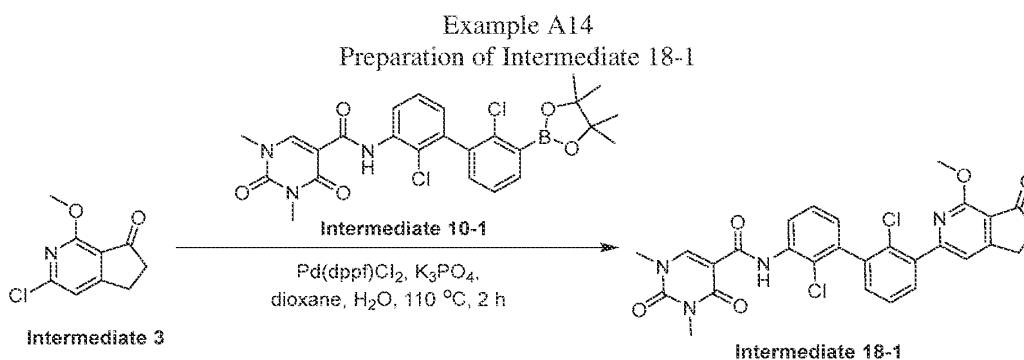
h under N₂ atmosphere to give a black mixture. LC-MS showed **Intermediate 13-1** was not consumed completely. To the mixture were added additional **Intermediate 14-1** (2.57 g, 7.05 mmol), Pd-118 (153 mg, 235 μ mol), K₃PO₄ (1.50 g, 7.05 mmol) and dioxane (10 mL). The mixture was degassed and purged with N₂ (3x), and then the mixture was stirred at 110 °C for 4 h under N₂. The reaction was quenched with H₂O (30 mL) and then extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography to give **Intermediate 15-1** (550 mg) as a yellow solid. MS: ES *m/z* calculated for C₂₇H₂₈BCl₂N₂O₅ [M+H]⁺ 541.1, found 541.1.

Example A13
Preparation Intermediate 17-1



[0337] A mixture of **Intermediate 15-1** (127 mg, 236 μ mol), **Intermediate 7-1** (50 mg, 196 μ mol), Pd-118 (12.8 mg, 19.6 μ mol) and K₃PO₄ (125 mg, 589 μ mol) in dioxane (3 mL) and H₂O (0.3 mL) was degassed and purged with N₂ (3x). The mixture was stirred at 110 °C for 2 h under N₂ atmosphere to give a black mixture. The reaction was quenched with H₂O (30 mL) and then extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue, which was purified by prep-HPLC to give **Intermediate 16-1** (35 mg) as a yellow solid. MS: ES *m/z* calculated for C₃₃H₃₁Cl₂N₄O₅ [M+H]⁺ 633.2, found 633.1.

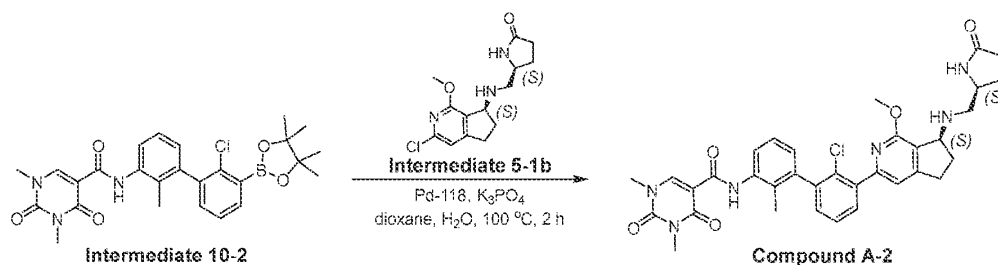
[0338] A mixture of **Intermediate 16-1** (20 mg) in THF (0.7 mL) was added H₂O (0.6 mL) and aq. HCl (12 M, 0.2 mL), and then the mixture was stirred at 20 °C for 2 h to give a yellow solution. The mixture was diluted with THF (30 mL), and then concentrated to give **Intermediate 17-1** (15 mg, crude) as a yellow solid. MS: ES *m/z* calculated for C₃₁H₂₇Cl₂N₄O₄ [M+H]⁺ 589.1, found 589.1.



[0339] To the solvent mixture of dioxane (3 mL) and H₂O (0.3 mL) were added **Intermediate 10-1** (150 mg, 283 μmol), **Intermediate 3** (56 mg, 283 μmol), K₃PO₄ (180 mg, 849 μmol) and Pd(dppf)Cl₂ (21 mg, 29 μmol). The reaction mixture was degassed and purged with N₂ for 3 times. Then the reaction mixture was stirred at 110 °C for 2 hours under N₂ atmosphere. The reaction mixture was concentrated under reduced pressure to give a residue, which was purified by prep-HPLC to give **Intermediate 18-1** (27 mg) as a white solid. MS: ES *m/z* calculated for C₂₈H₂₃Cl₂N₄O₅ [M+H]⁺ 565.1, found 565.3; ¹H NMR (400 MHz, CHLOROFORM-*d*) δ = 11.50 (s, 1H), 8.58 (d, *J* = 8.3 Hz, 1H), 8.53 (s, 1H), 7.68 (dd, *J* = 1.3, 7.6 Hz, 1H), 7.46 (t, *J* = 7.6 Hz, 1H), 7.42 - 7.32 (m, 3H), 7.12 - 7.06 (m, 1H), 4.16 (s, 3H), 3.59 (s, 3H), 3.46 (s, 3H), 3.20 - 3.12 (m, 2H), 2.79 - 2.70 (m, 2H).

[0340] The intermediate shown in Table A-7 was prepared by an analogous reaction protocol as was used for the preparation of **Intermediate 18-1** using the appropriate starting materials.

Example 1a
Preparation of Compound A-2

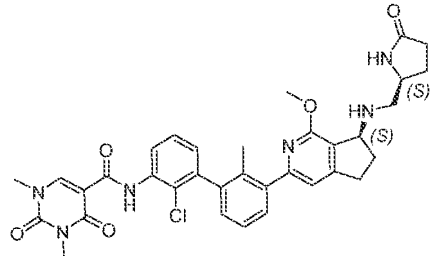
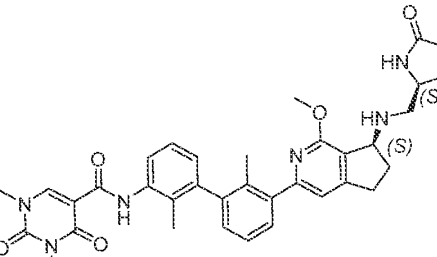
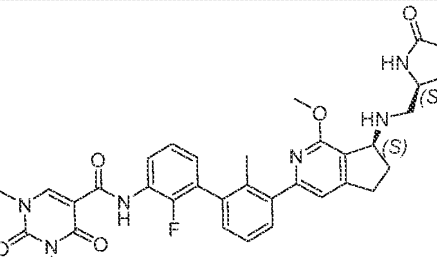
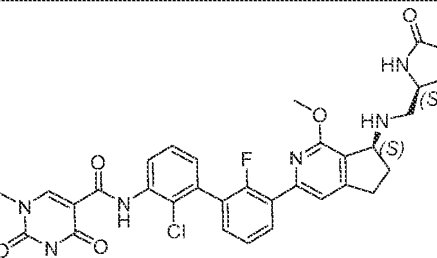
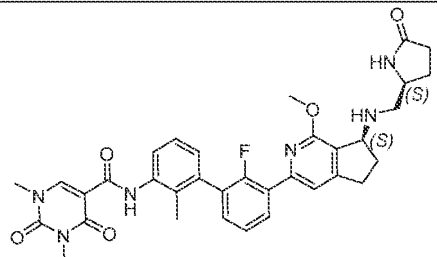


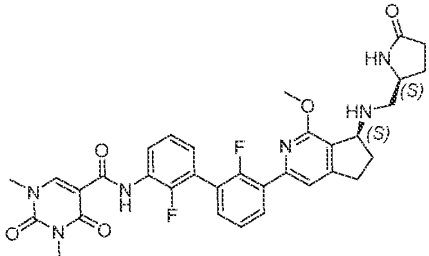
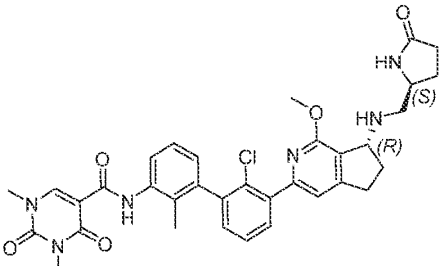
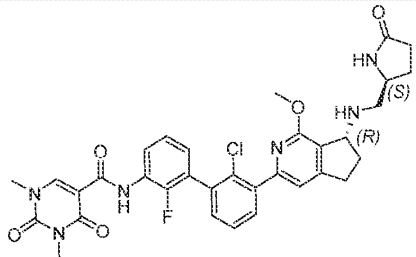
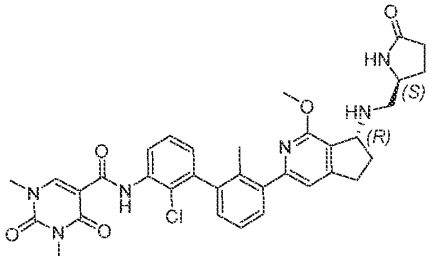
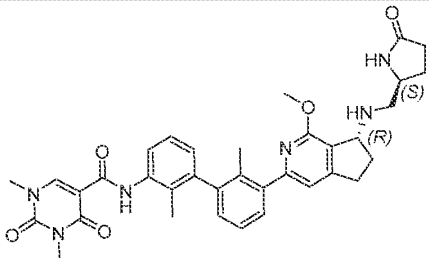
[0342] A mixture of compound **Intermediate 10-2** (240 mg), **Intermediate 5-1b** (107 mg, 363 μmol), ditert-butyl(cyclopentyl)phosphane;dichloropalladium;iron (Pd-118, 22 mg, 33 μmol) and K_3PO_4 (210 mg, 989 μmol) in dioxane (2.5 mL) and H_2O (0.25 mL) was degassed and purged with N_2 (3x). The mixture was stirred at 100 $^\circ\text{C}$ for 2 h under N_2 atmosphere. The mixture was filtered and concentrated under reduced pressure to give a residue, which was purified by prep-HPLC to give **Compound A-2** (56 mg) as an off-white solid.

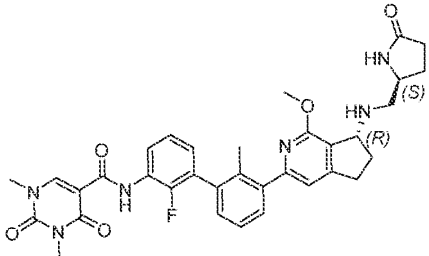
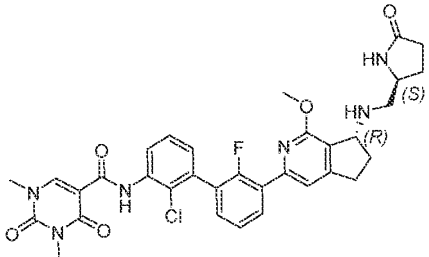
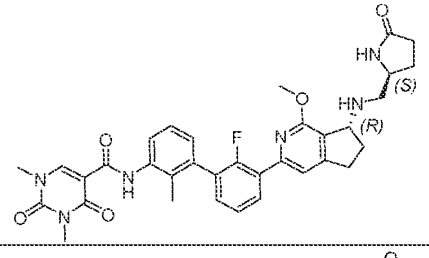
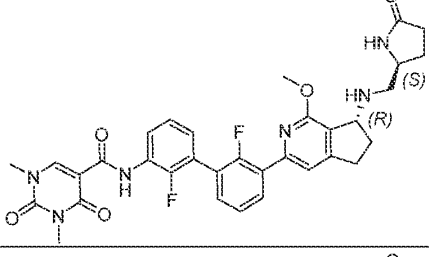
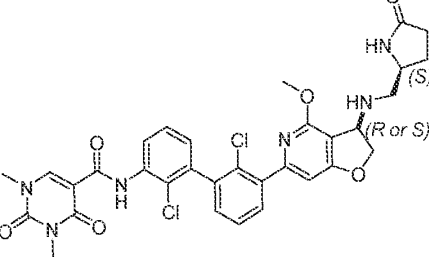
[0343] The compounds shown below in Table 1 were prepared by an analogous reaction protocol as was used for the preparation of **Compound A-2** using the appropriate starting materials.

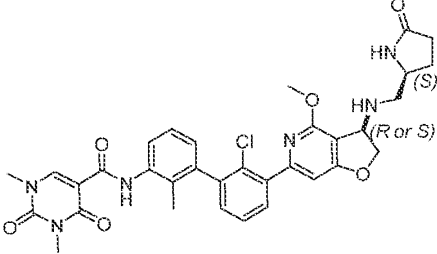
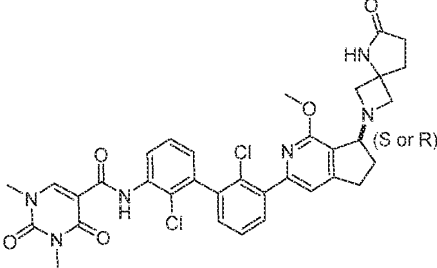
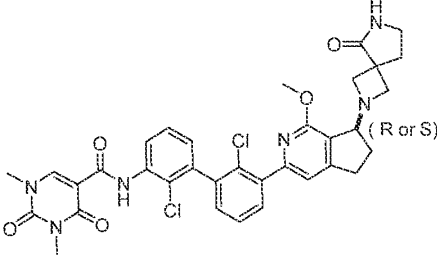
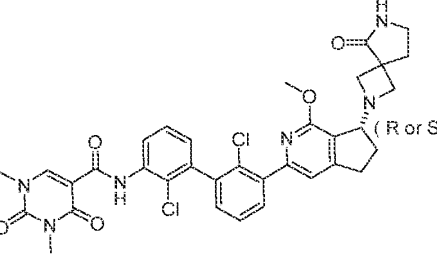
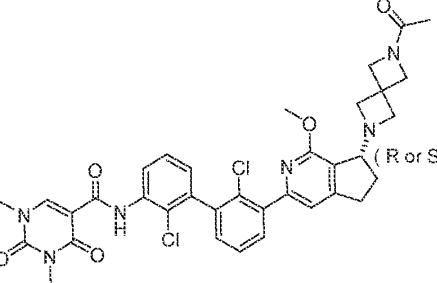
Table 1

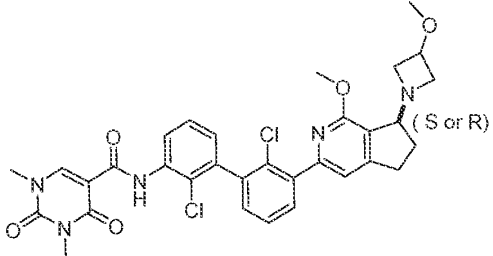
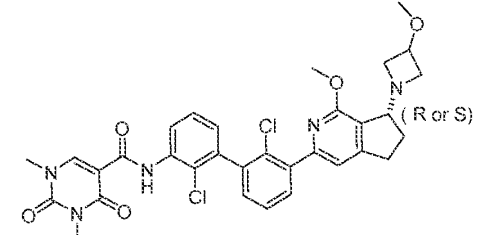
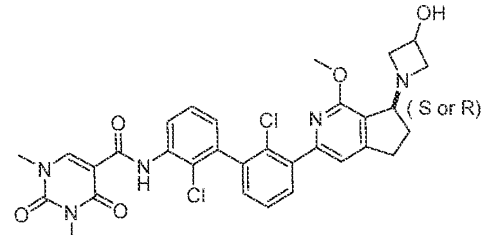
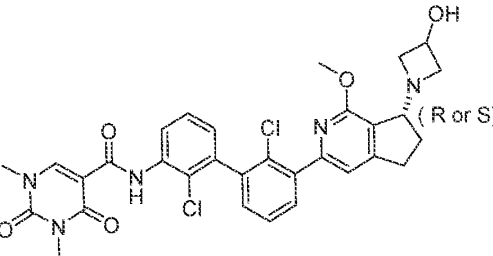
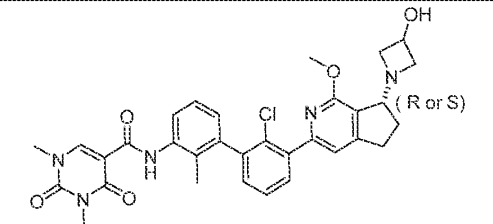
Cmpd No.	Structure	Starting materials
A-3		Intermediate 10-3 Intermediate 5-1b

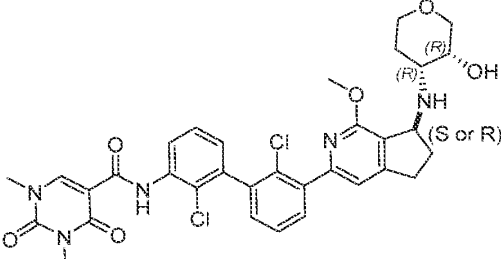
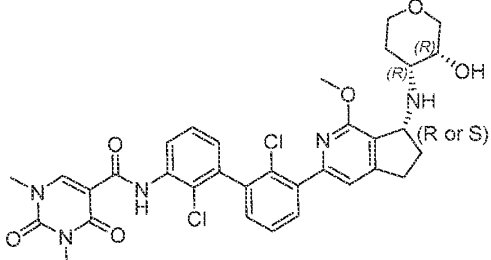
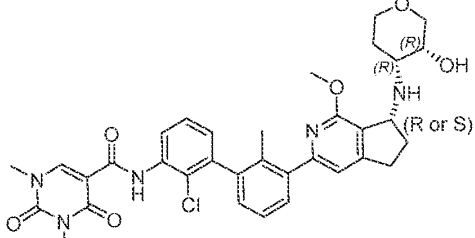
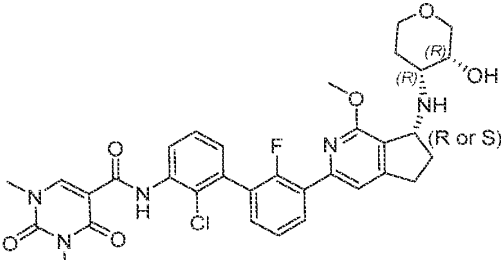
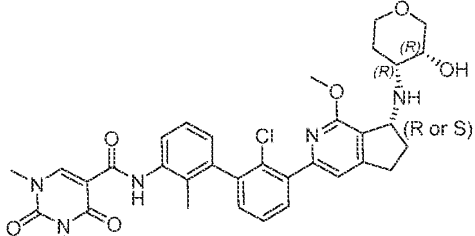
Cmpd No.	Structure	Starting materials
A-4		Intermediate 10-4 Intermediate 5-1b
A-5		Intermediate 10-5 Intermediate 5-1b
A-6		Intermediate 10-6 Intermediate 5-1b
A-7		Intermediate 10-7 Intermediate 5-1b
A-8		Intermediate 10-8 Intermediate 5-1b

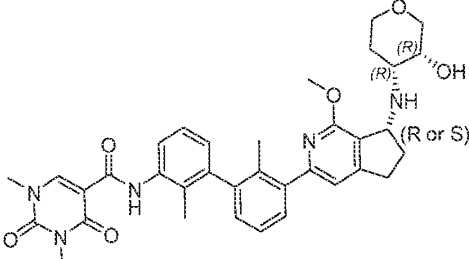
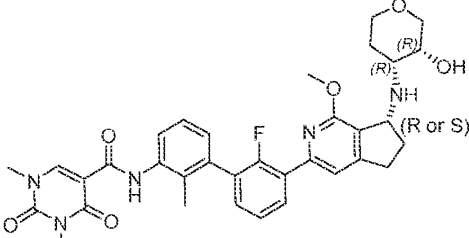
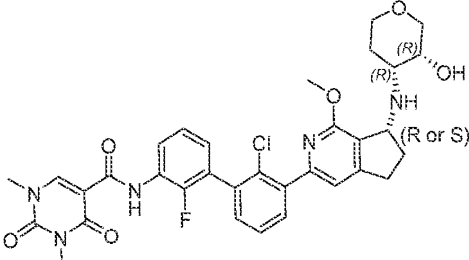
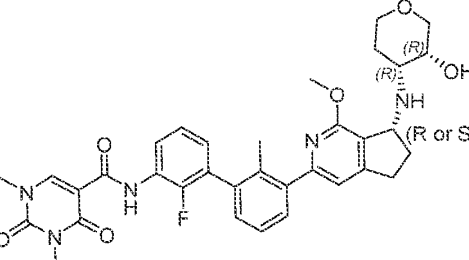
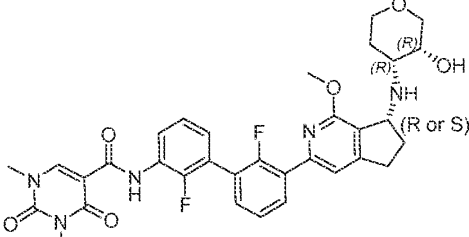
Cmpd No.	Structure	Starting materials
A-9		Intermediate 10-9 Intermediate 5-1b
A-10		Intermediate 10-2 Intermediate 5-1a
A-11		Intermediate 10-3 Intermediate 5-1a
A-12		Intermediate 10-4 Intermediate 5-1a
A-13		Intermediate 10-5 Intermediate 5-1a

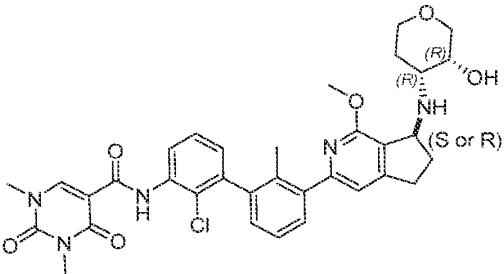
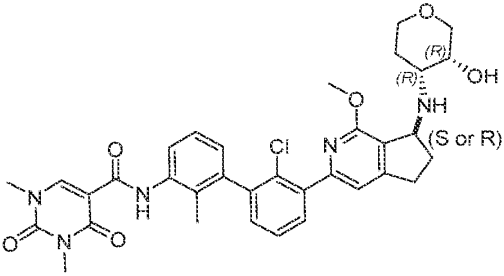
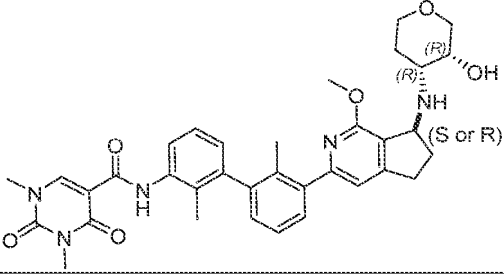
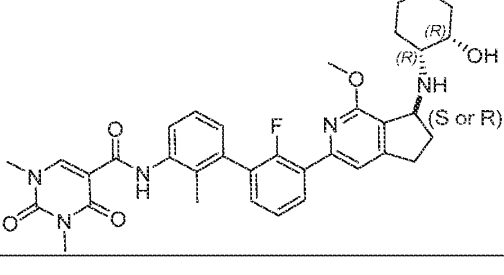
Cmpd No.	Structure	Starting materials
A-14		Intermediate 10-6 Intermediate 5-1a
A-15		Intermediate 10-7 Intermediate 5-1a
A-16		Intermediate 10-8 Intermediate 5-1a
A-17		Intermediate 10-9 Intermediate 5-1a
A-18		Intermediate 10-1 Intermediate 6-1a

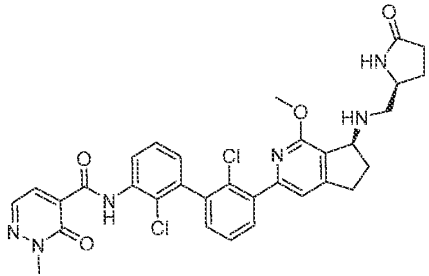
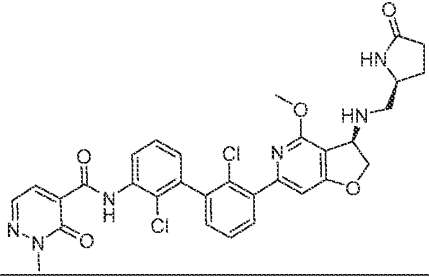
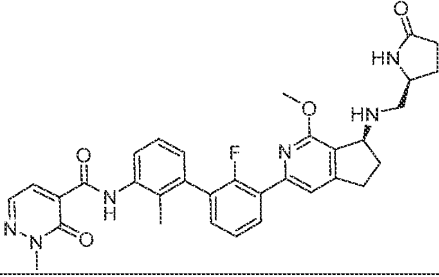
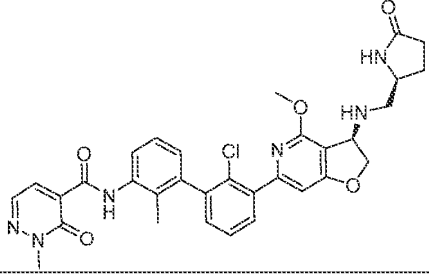
Cmpd No.	Structure	Starting materials
A-19		Intermediate 10-2 Intermediate 6-1a
A-20		Intermediate 10-1 Intermediate 5-2a
A-21		Intermediate 10-1 Intermediate 5-7a
A-22		Intermediate 10-1 Intermediate 5-7b
A-23		Intermediate 10-1 Intermediate 5-3b

Cmpd No.	Structure	Starting materials
A-24		Intermediate 10-1 Intermediate 5-6a
A-25		Intermediate 10-1 Intermediate 5-6b
A-26		Intermediate 10-1 Intermediate 5-5a
A-27		Intermediate 10-1 Intermediate 5-5b
A-28		Intermediate 10-1 Intermediate 5-5b

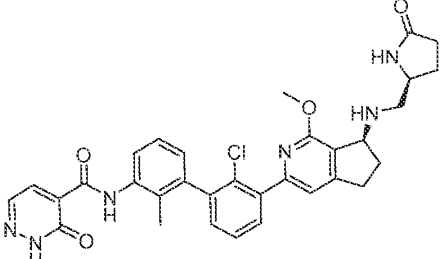
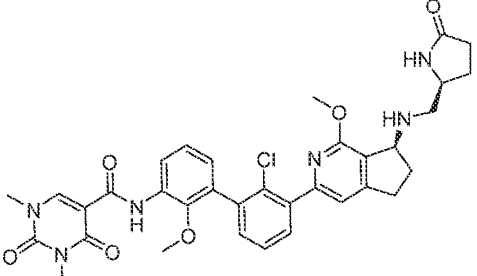
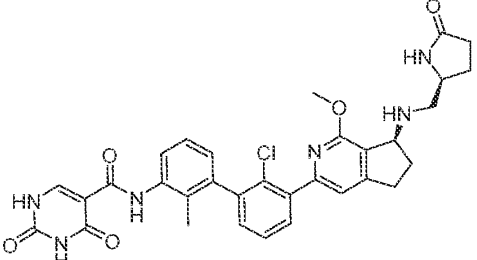
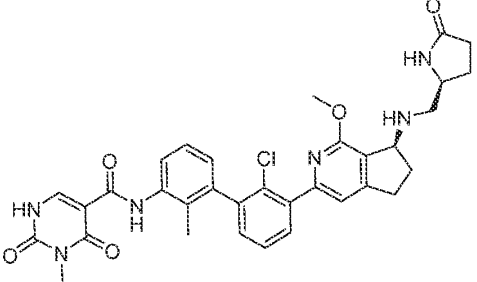
Cmpd No.	Structure	Starting materials
A-29		Intermediate 10-1 Intermediate 5-4a
A-30		Intermediate 10-1 Intermediate 5-4b
A-31		Intermediate 10-4 Intermediate 5-4b
A-32		Intermediate 10-7 Intermediate 5-4b
A-33		Intermediate 10-2 Intermediate 5-4b

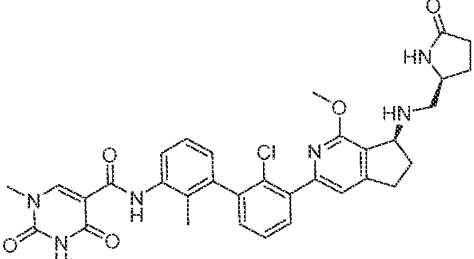
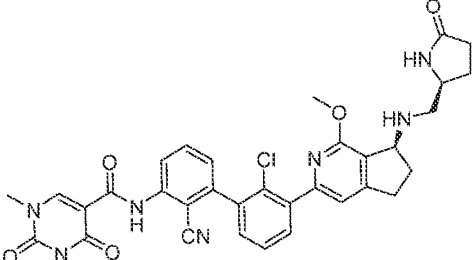
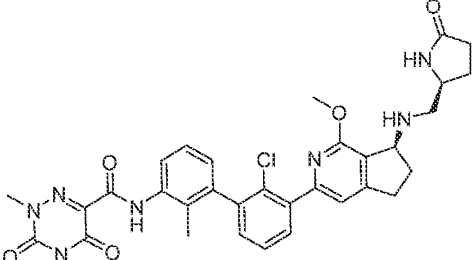
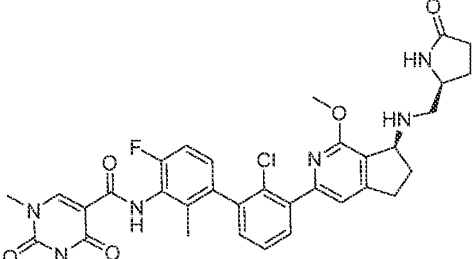
Cmpd No.	Structure	Starting materials
A-34		Intermediate 10-5 Intermediate 5-4b
A-35		Intermediate 10-8 Intermediate 5-4b
A-36		Intermediate 10-3 Intermediate 5-4b
A-37		Intermediate 10-6 Intermediate 5-4b
A-38		Intermediate 10-9 Intermediate 5-4b

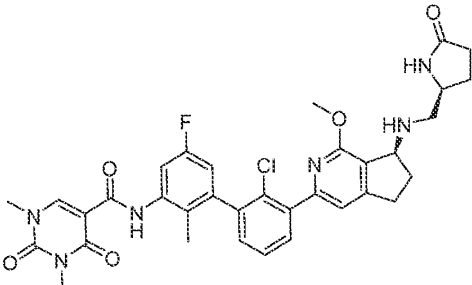
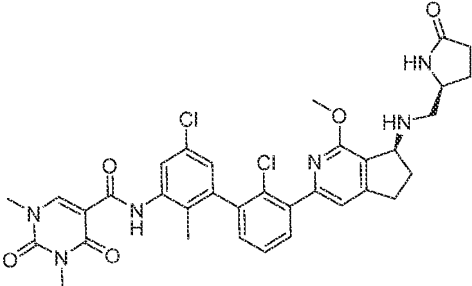
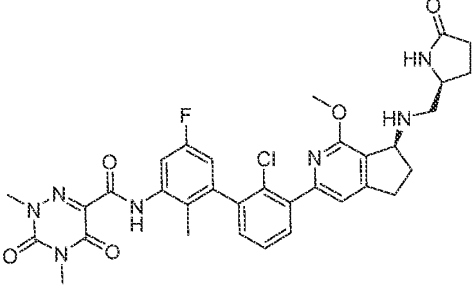
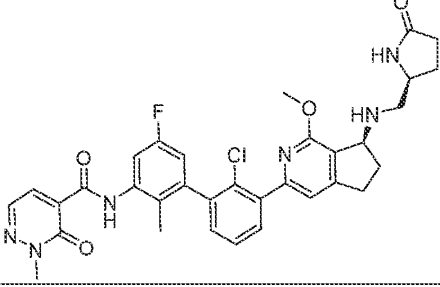
Cmpd No.	Structure	Starting materials
A-39		Intermediate 10-4 Intermediate 5-4a
A-40		Intermediate 10-2 Intermediate 5-4a
A-41		Intermediate 10-5 Intermediate 5-4a
A-42		Intermediate 10-8 Intermediate 5-4a

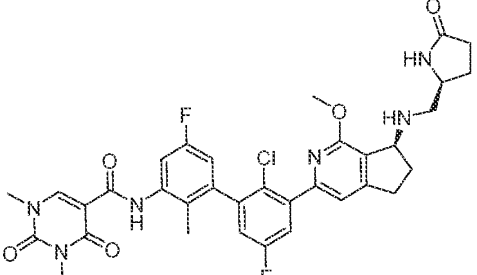
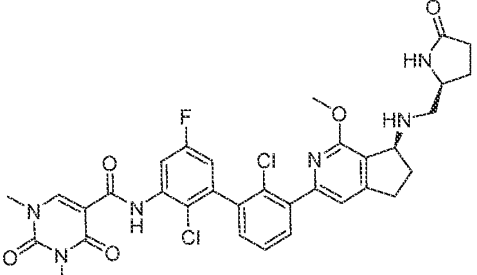
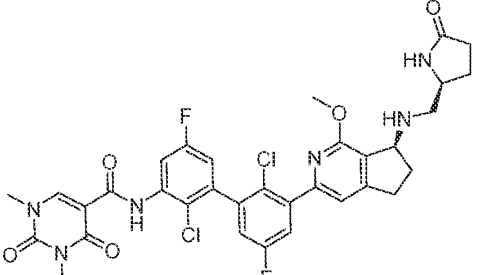
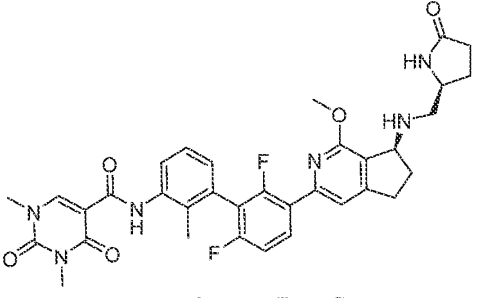
Cmpd No.	Structure	Starting materials
A-43		Intermediate 10-10 Intermediate 5-1b
A-44		Intermediate 10-10 Intermediate 6-1a
A-45		Intermediate 10-12 Intermediate 5-1b
A-46		Intermediate 10-11 Intermediate 6-1a

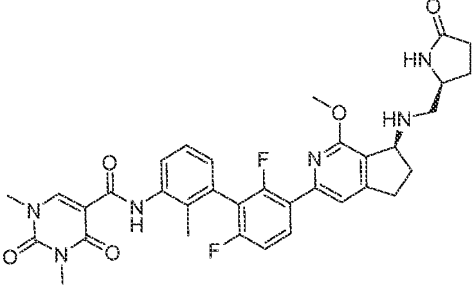
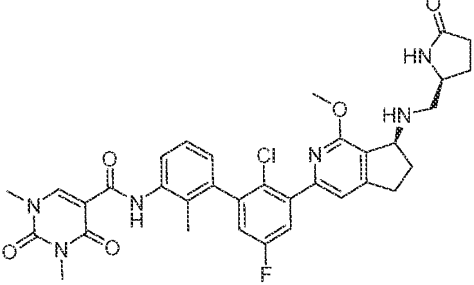
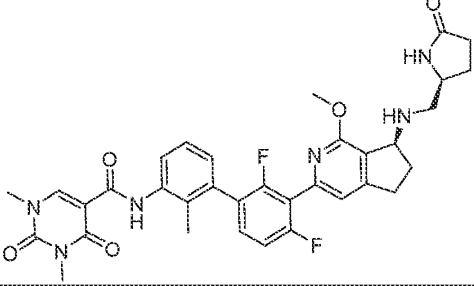
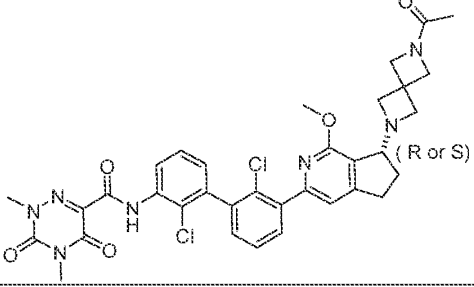
Cmpd No.	Structure	Starting materials
A-47		Intermediate 10-11 Intermediate 5-1b
A-48		Intermediate 10-1 Intermediate 7-2
A-49		Intermediate 10-5 Intermediate 6-1a
A-50		Intermediate 10-15 Intermediate 5-1b
A-51		Intermediate 10-34 Intermediate 5-1b

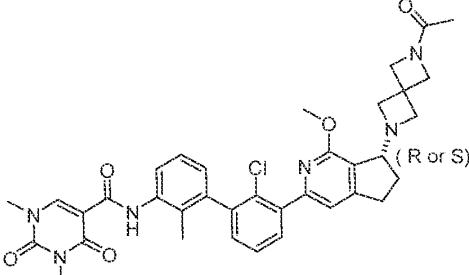
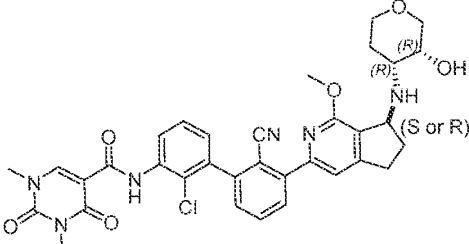
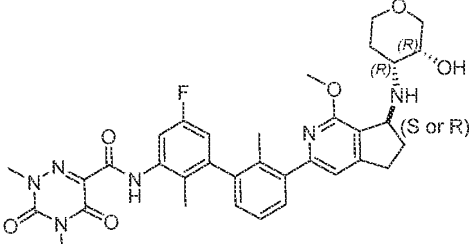
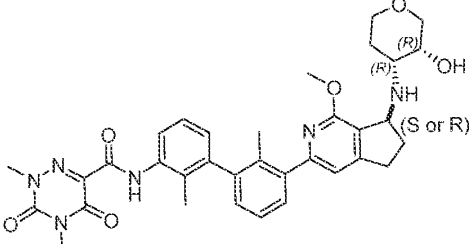
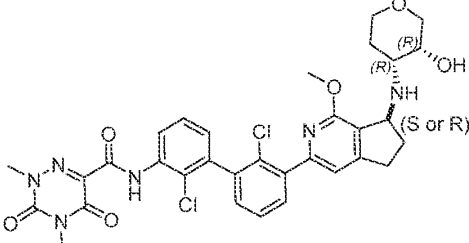
Cmpd No.	Structure	Starting materials
A-52		Intermediate 10-35 Intermediate 5-1b
A-53		Intermediate 10-13 Intermediate 5-1b
A-54		Intermediate 10-29 Intermediate 5-1b
A-55		Intermediate 10-28a Intermediate 5-1b

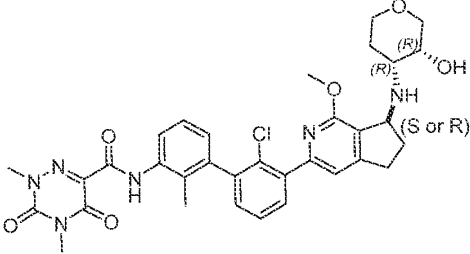
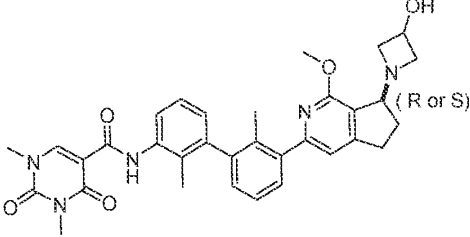
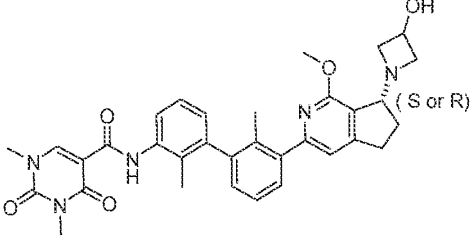
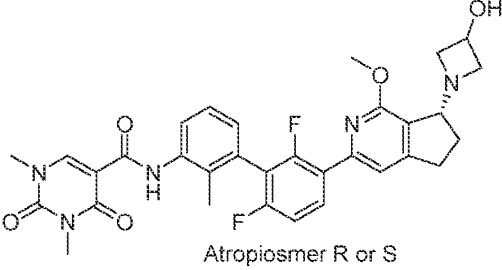
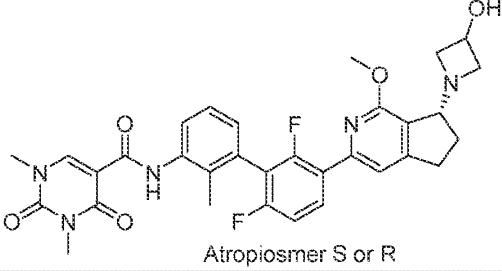
Cmpd No.	Structure	Starting materials
A-56		Intermediate 10-28b Intermediate 5-1b
A-57		Intermediate 10-14 Intermediate 5-1b
A-58		Intermediate 10-31 Intermediate 5-1b
A-59		Intermediate 10-21 Intermediate 5-1b

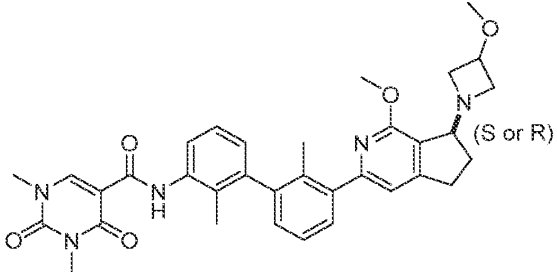
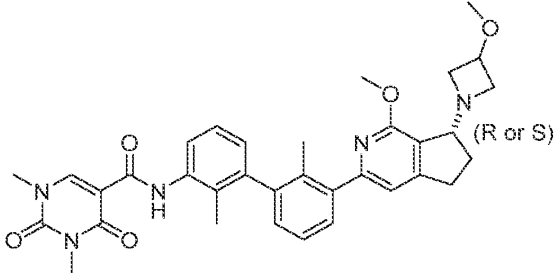
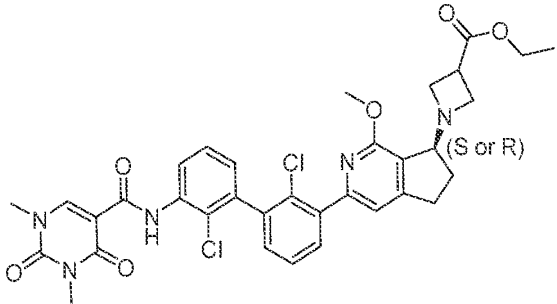
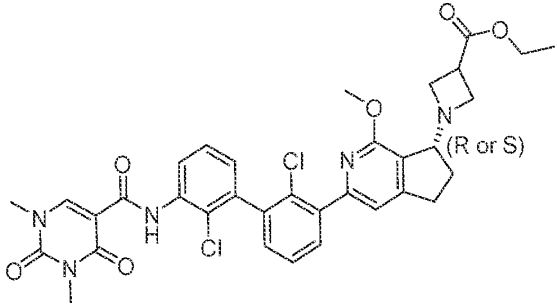
Cmpd No.	Structure	Starting materials
A-60		Intermediate 10-18 Intermediate 5-1b
A-61		Intermediate 10-17 Intermediate 5-1b
A-62		Intermediate 10-33 Intermediate 5-1b
A-63		Intermediate 10-36 Intermediate 5-1b

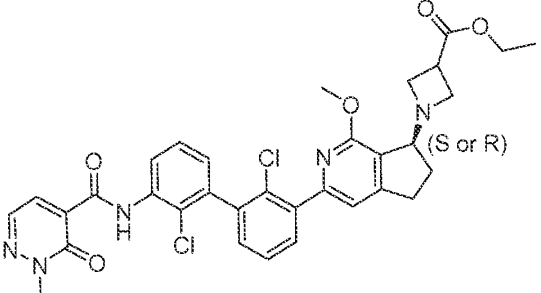
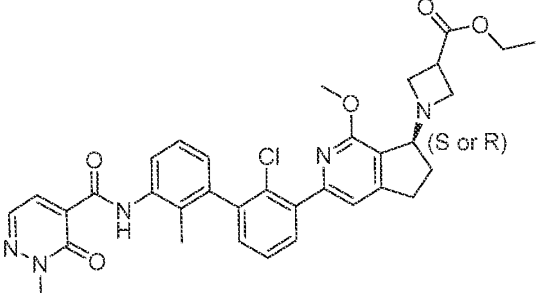
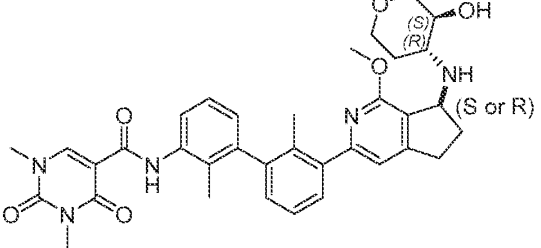
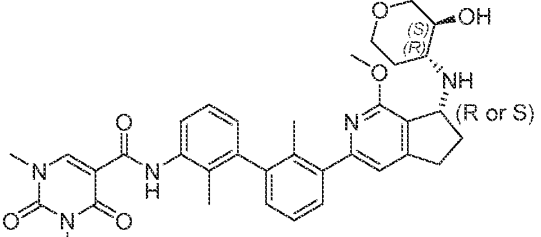
Cmpd No.	Structure	Starting materials
A-64		Intermediate 10-24 Intermediate 5-1b
A-65		Intermediate 10-19 Intermediate 5-1b
A-66		Intermediate 10-25 Intermediate 5-1b
A-67	 atropoisomer R or S	Intermediate 10-26 Intermediate 5-1b

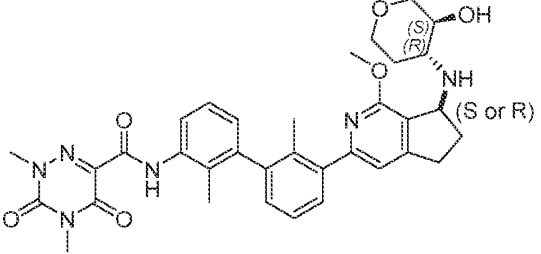
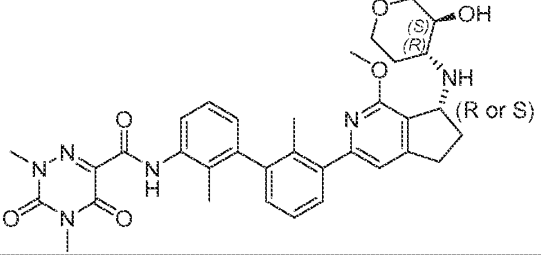
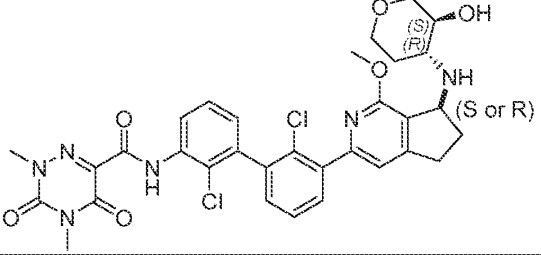
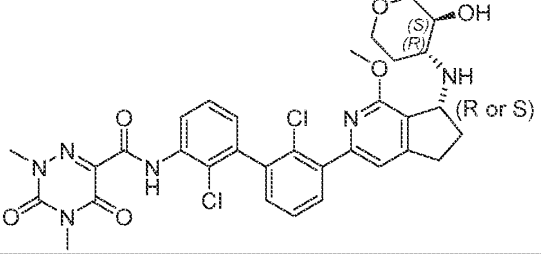
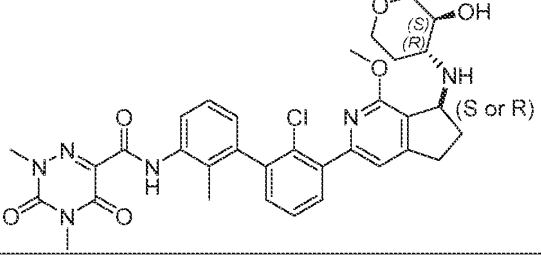
Cmpd No.	Structure	Starting materials
A-68	 atropoisomer S or R	Intermediate 10-26 Intermediate 5-1b
A-69		Intermediate 10-23 Intermediate 5-1b
A-70		Intermediate 10-27 Intermediate 5-1b
A-71	 (R or S)	Intermediate 10-30 Intermediate 5-3b

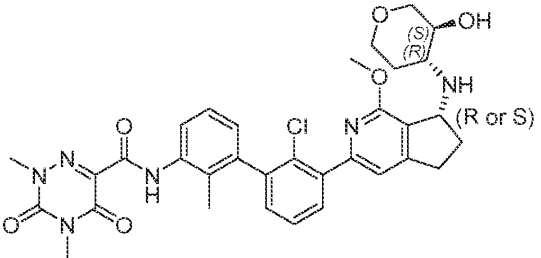
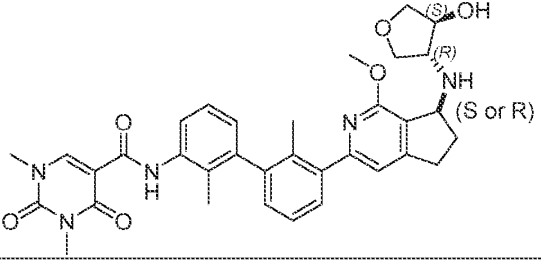
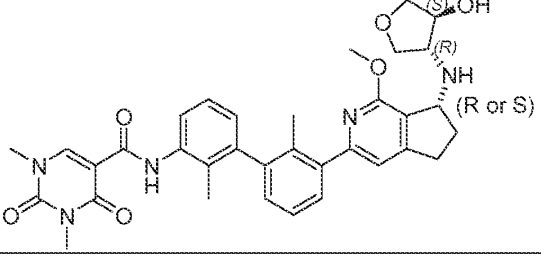
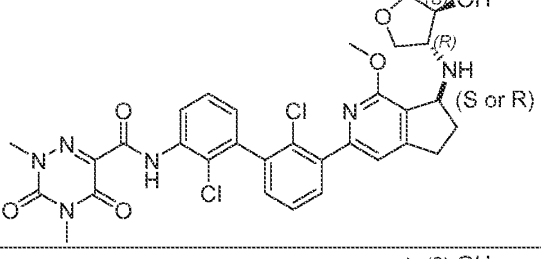
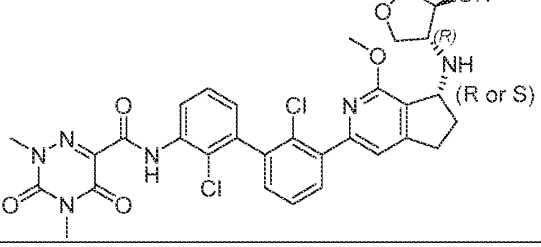
Cmpd No.	Structure	Starting materials
A-72		Intermediate 10-2 Intermediate 5-3b
A-73		Intermediate 10-15 Intermediate 5-4a
A-74		Intermediate 10-33a Intermediate 5-4a
A-75		Intermediate 10-32 Intermediate 5-4a
A-76		Intermediate 10-30 Intermediate 5-4a

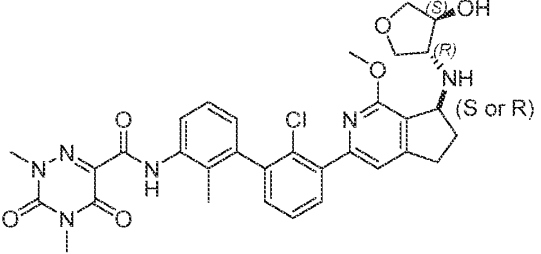
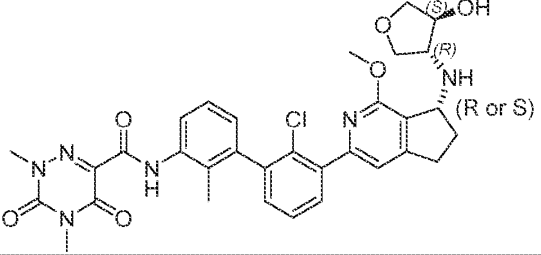
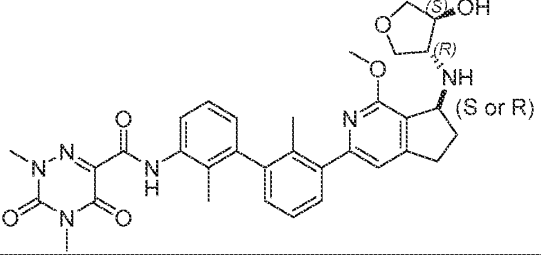
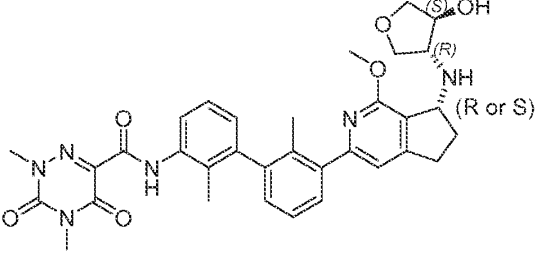
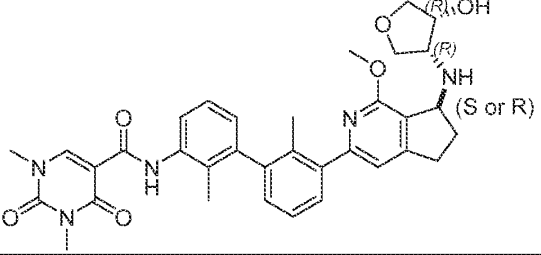
Cmpd No.	Structure	Starting materials
A-77		Intermediate 10-31 Intermediate 5-4a
A-79		Intermediate 10-5 Intermediate 5-5a
A-80		Intermediate 10-5 Intermediate 5-5b
A-81	 Atropiosmer R or S	Intermediate 10-26 Intermediate 5-5b
A-82	 Atropiosmer S or R	Intermediate 10-26 Intermediate 5-5b

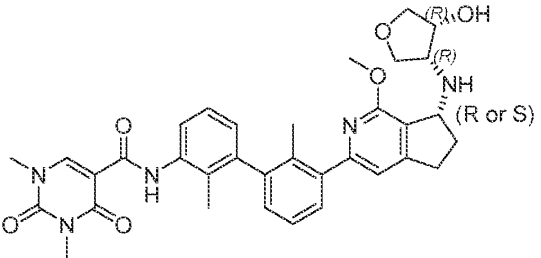
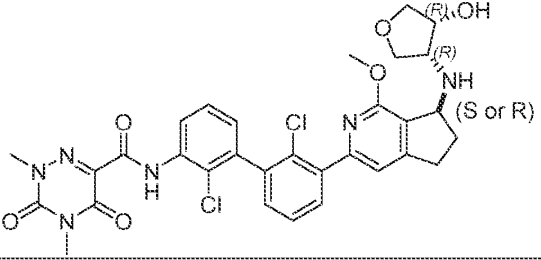
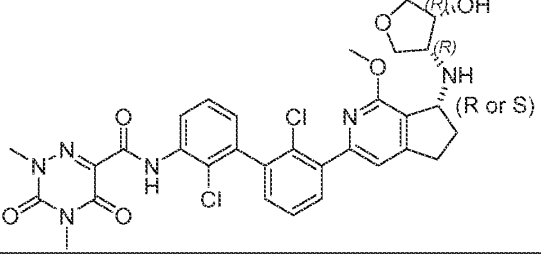
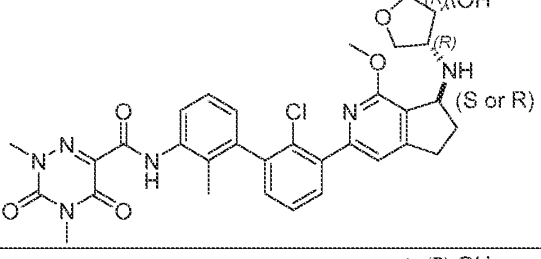
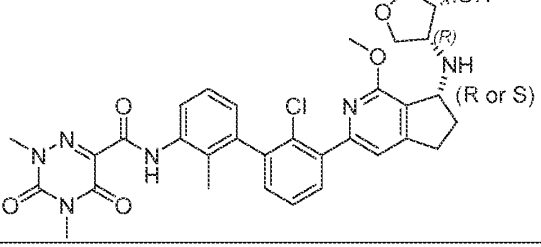
Cmpd No.	Structure	Starting materials
A-83		Intermediate 10-5 Intermediate 5-6a
A-84		Intermediate 10-5 Intermediate 5-6b
A-85		Intermediate 10-1 Intermediate 5-8a
A-86		Intermediate 10-1 Intermediate 5-8b

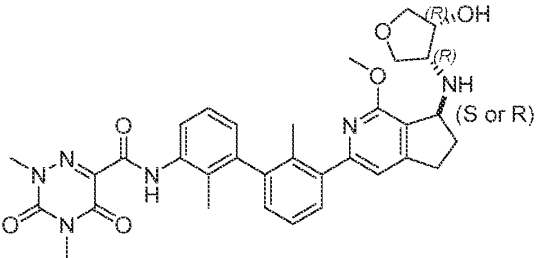
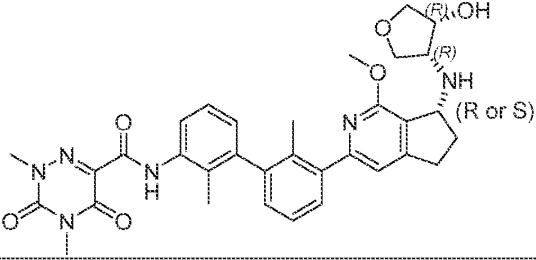
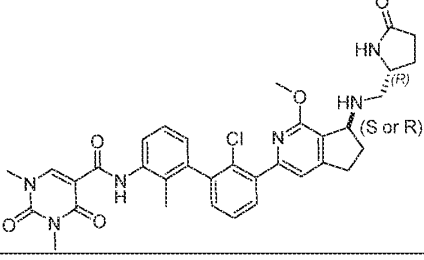
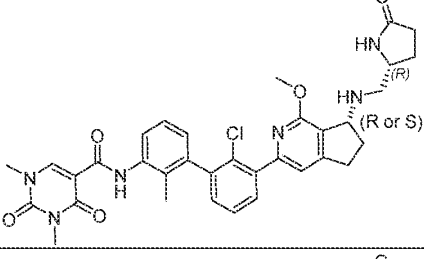
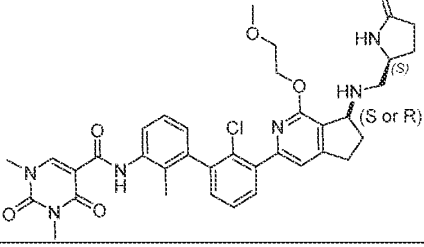
Cmpd No.	Structure	Starting materials
A-87		Intermediate 10-10 Intermediate 5-8a
A-88		Intermediate 10-11 Intermediate 5-8a
A-89		Intermediate 10-5 Intermediate 5-9a
A-90		Intermediate 10-5 Intermediate 5-9b

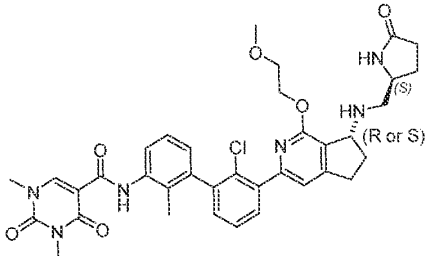
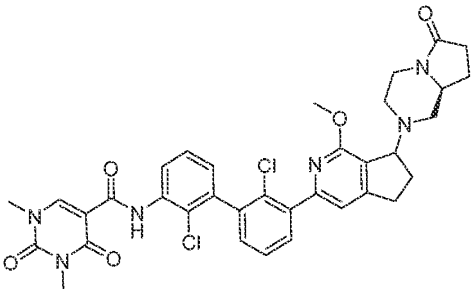
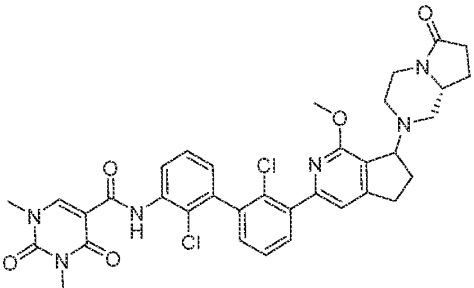
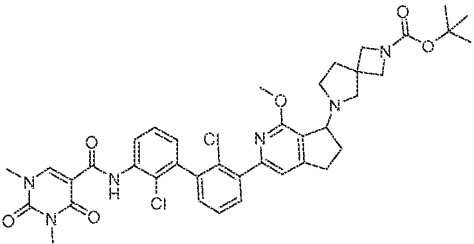
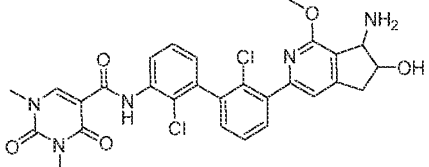
Cmpd No.	Structure	Starting materials
A-91		Intermediate 10-32 Intermediate 5-9a
A-92		Intermediate 10-32 Intermediate 5-9b
A-93		Intermediate 10-30 Intermediate 5-9a
A-94		Intermediate 10-30 Intermediate 5-9b
A-95		Intermediate 10-31 Intermediate 5-9a

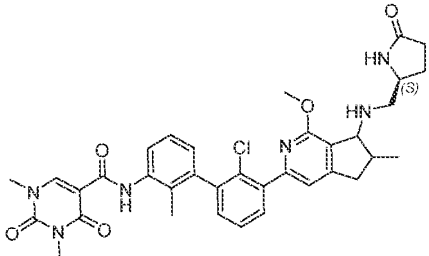
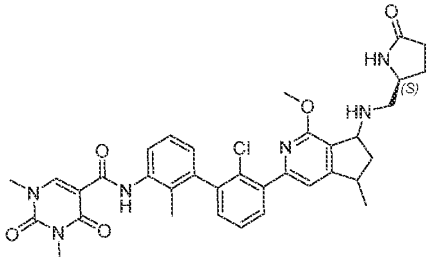
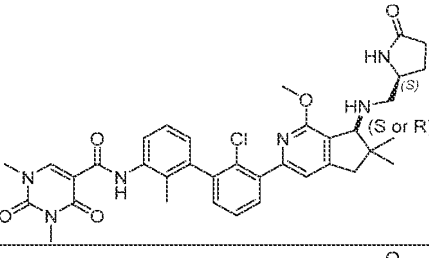
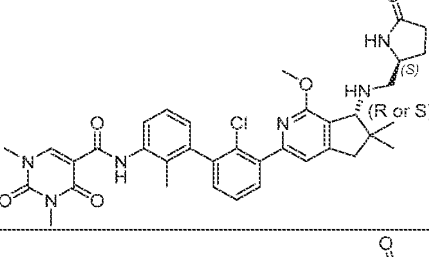
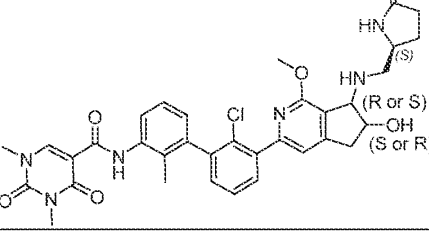
Cmpd No.	Structure	Starting materials
A-96		Intermediate 10-31 Intermediate 5-9b
A-97		Intermediate 10-5 Intermediate 5-11a
A-98		Intermediate 10-5 Intermediate 5-11b
A-99		Intermediate 10-30 Intermediate 5-11a
A-100		Intermediate 10-30 Intermediate 5-11b

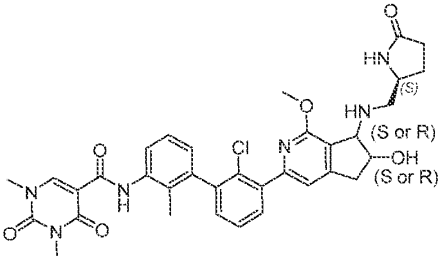
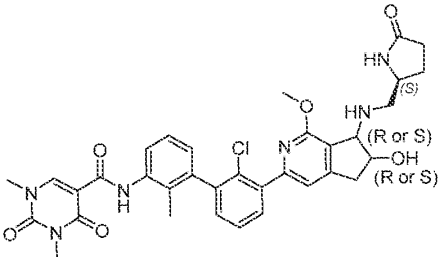
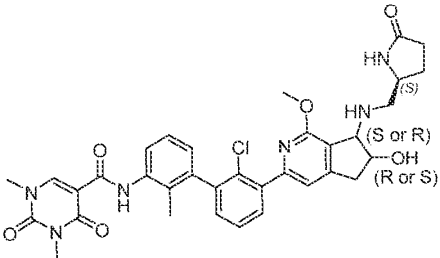
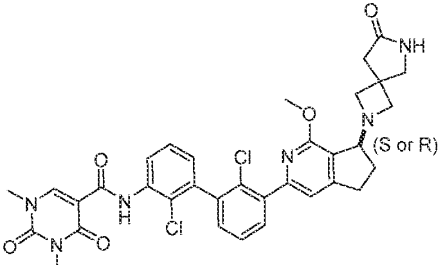
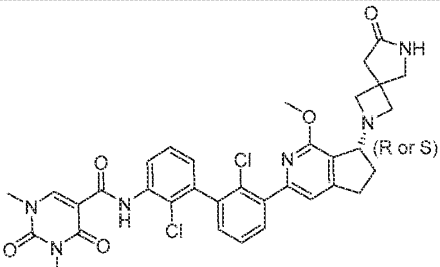
Cmpd No.	Structure	Starting materials
A-101		Intermediate 10-31 Intermediate 5-11a
A-102		Intermediate 10-31 Intermediate 5-11b
A-103		Intermediate 10-32 Intermediate 5-11a
A-104		Intermediate 10-32 Intermediate 5-11b
A-105		Intermediate 10-5 Intermediate 5-10a

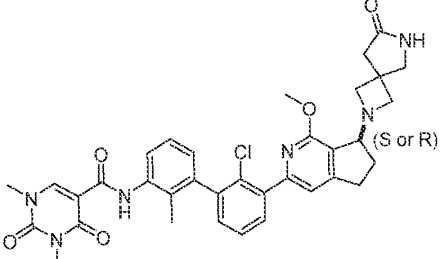
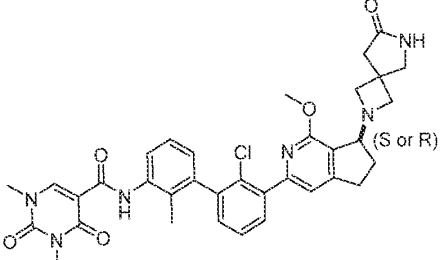
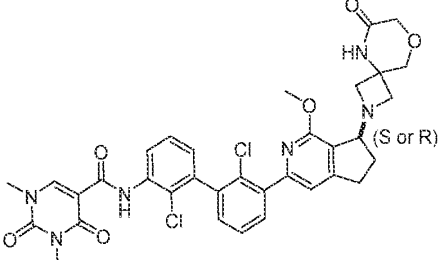
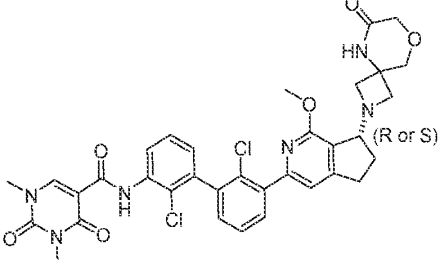
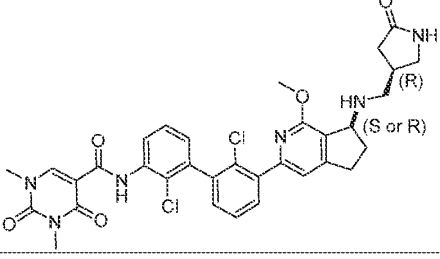
Cmpd No.	Structure	Starting materials
A-106		Intermediate 10-5 Intermediate 5-10b
A-107		Intermediate 10-30 Intermediate 5-10a
A-108		Intermediate 10-30 Intermediate 5-10b
A-109		Intermediate 10-31 Intermediate 5-10a
A-110		Intermediate 10-31 Intermediate 5-10b

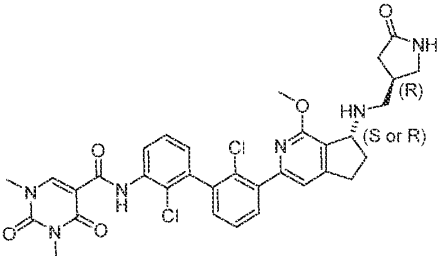
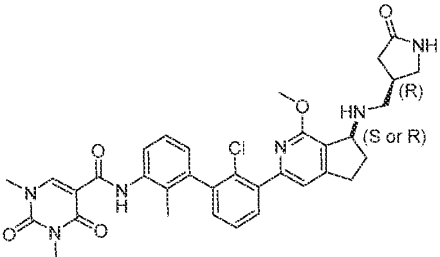
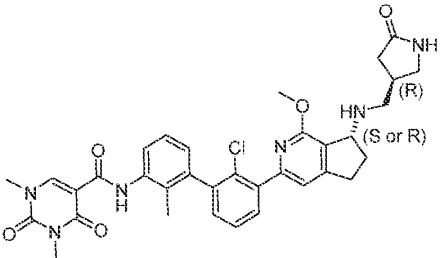
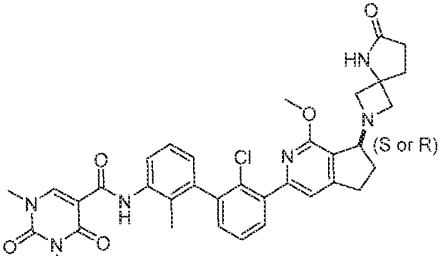
Cmpd No.	Structure	Starting materials
A-111		Intermediate 10-32 Intermediate 5-10a
A-112		Intermediate 10-32 Intermediate 5-10b
A-113		Intermediate 10-2 Intermediate 5-12a
A-114		Intermediate 10-2 Intermediate 5-12b
A-115		Intermediate 10-2 Intermediate 5-13a

Cmpd No.	Structure	Starting materials
A-116		Intermediate 10-2 Intermediate 5-13b
A-117		Intermediate 10-1 Intermediate 7-3
A-118		Intermediate 10-1 Intermediate 7-4
A-119		Intermediate 10-1 Intermediate 7-5
A-120		Intermediate 10-1 Intermediate 4c

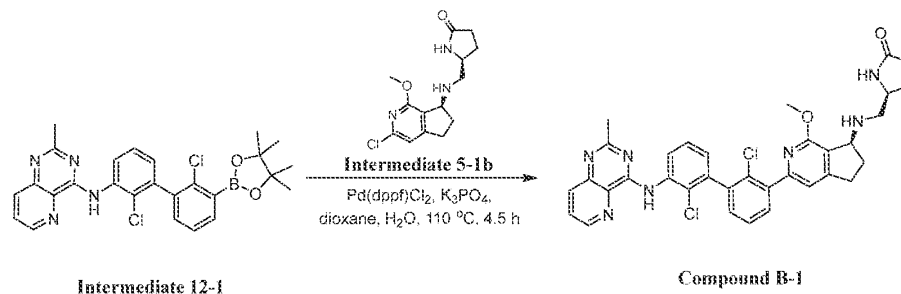
Cmpd No.	Structure	Starting materials
A-121		Intermediate 10-2 Intermediate 7-6
A-122		Intermediate 10-2 Intermediate 7-7
A-123		Intermediate 10-2 Intermediate 5-16a
A-124		Intermediate 10-2 Intermediate 5-16b
A-125		Intermediate 10-2 Intermediate 5-14a

Cmpd No.	Structure	Starting materials
A-126		Intermediate 10-2 Intermediate 5-14b
A-127		Intermediate 10-2 Intermediate 5-15a
A-128		Intermediate 10-2 Intermediate 5-15b
A-129		Intermediate 10-1 Intermediate 5-17a
A-130		Intermediate 10-1 Intermediate 5-17b

Cmpd No.	Structure	Starting materials
A-131		Intermediate 10-2 Intermediate 5-17a
A-132		Intermediate 10-2 Intermediate 5-17b
A-133		Intermediate 10-1 Intermediate 5-18a
A-134		Intermediate 10-1 Intermediate 5-18b
A-135		Intermediate 10-1 Intermediate 5-19a

Cmpd No.	Structure	Starting materials
A-136		Intermediate 10-1 Intermediate 5-19b
A-137		Intermediate 10-2 Intermediate 5-19a
A-138		Intermediate 10-2 Intermediate 5-19b
A-139		Intermediate 10-2 Intermediate 5-2a

Example 2
Preparation of Compound B-1

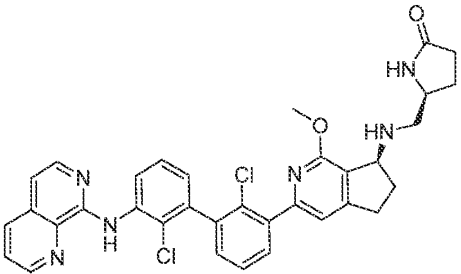
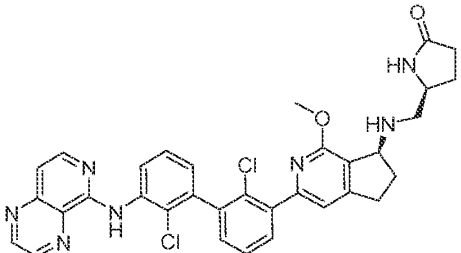


[0344] A mixture of **Intermediate 12-1** (64 mg, 126 μmol), **Intermediate 5-1b** (18 mg, 63 μmol), Pd(dppf)Cl₂ (4.62 mg, 6.31 μmol) and K₃PO₄ (40 mg, 189 μmol) in dioxane (1 mL) and H₂O (0.1 mL) was degassed and purged with N₂ (3x). After the mixture was stirred at 110 °C for 4.5 h under N₂ atmosphere, the mixture was filtered and concentrated to give a residue, which was purified by prep-HPLC to give **Compound B-1** (8.8 mg) as a yellow solid.

[0345] The compounds shown below in Table 2 were prepared by an analogous reaction protocol as was used for the preparation of **Compound B-1** using the appropriate starting materials.

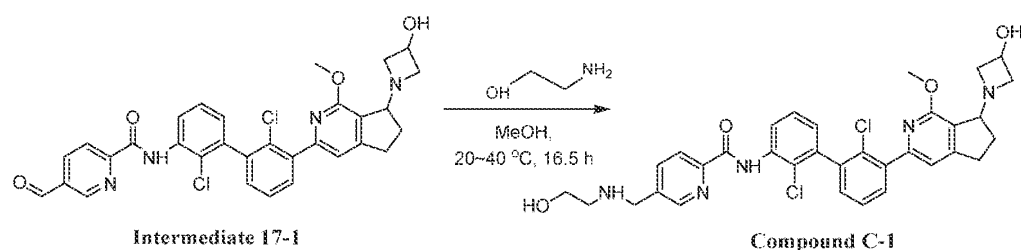
Table 2

Cmpd No.	Structure	Starting Materials
B-2		Intermediate 12-2 Intermediate 5-1b

Cmpd No.	Structure	Starting Materials
B-3		Intermediate 12-3 Intermediate 5-1b
B-4		Intermediate 12-4 Intermediate 5-1b

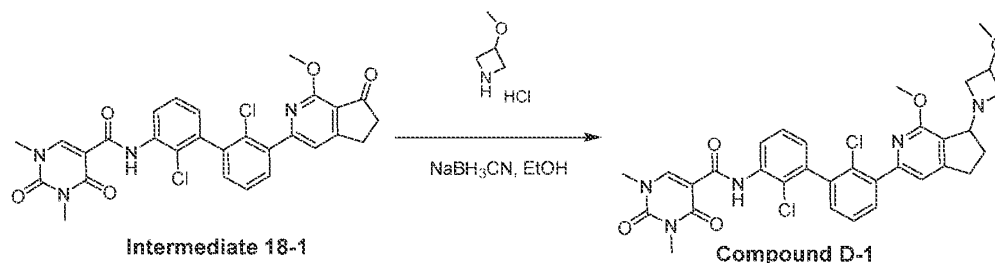
Example 3

Preparation of Compound C-1



[0346] The mixture of **Intermediate 17-1** (37 mg, 62.8 μ mol) and 2-aminoethanol (5.7 μ L, 94.2 μ mol) in MeOH (2 mL) was stirred at 20 $^{\circ}$ C for 0.5 h. After adding NaBH₃CN (11.8 mg, 188 μ mol) into the mixture, the reaction mixture was stirred at 40 $^{\circ}$ C for 16 hours. The reaction mixture was concentrated under reduced pressure, diluted with H₂O (20 mL) and extracted with EtOAc (20 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue, which was purified by prep-HPLC to give **Compound C-1** (11 mg) as a yellow solid.

Example 3a
Preparation of Compound D-1

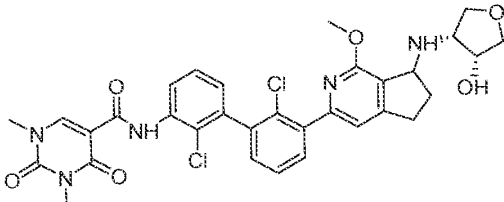
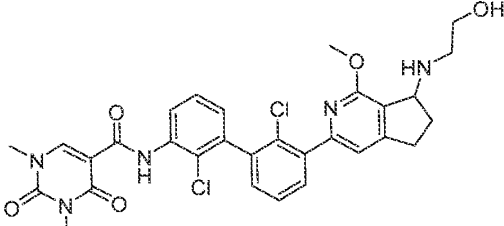
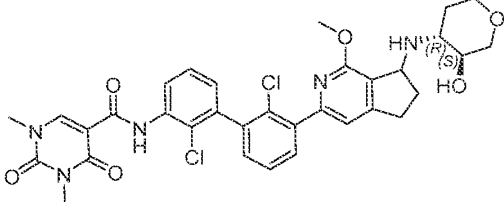
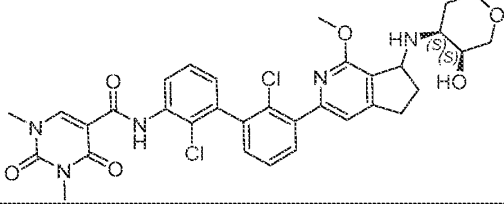
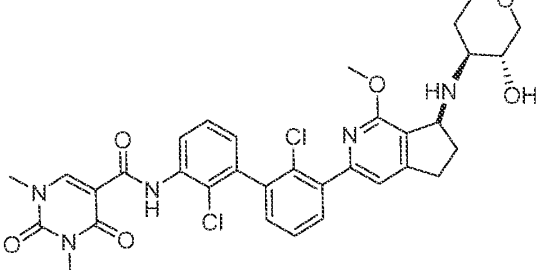


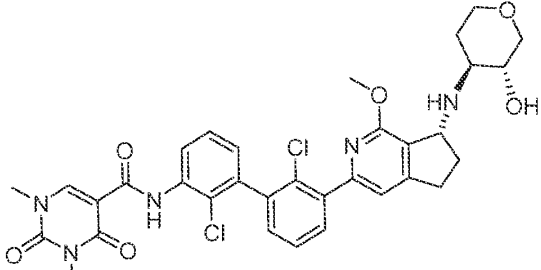
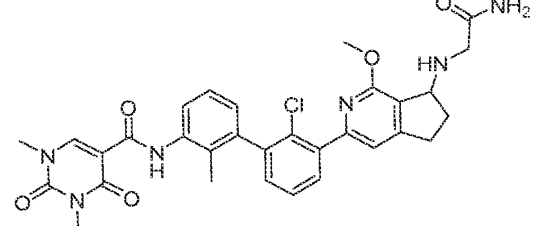
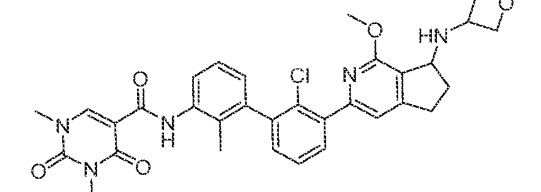
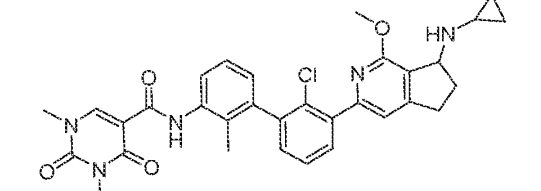
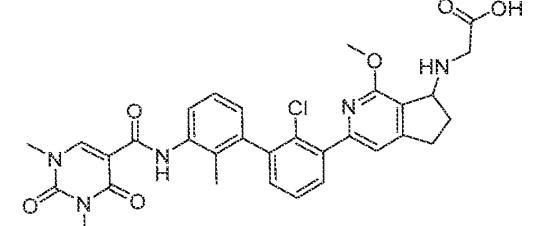
[0347] A mixture of **Intermediate 18-1** (100 mg, 177 μmol), 3-methoxyazetidine hydrochloride (44 mg, 354 μmol) and NaBH_3CN (33 mg, 531 μmol) in EtOH (2 mL) was stirred at 50 $^\circ\text{C}$ for 16 h. The mixture was filtered and concentrated under reduced pressure to give a residue, which was purified by prep-HPLC to give **compound D-1** (23 mg) as an off-white solid.

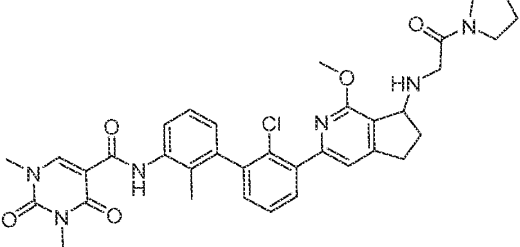
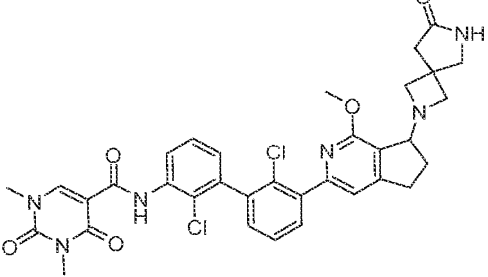
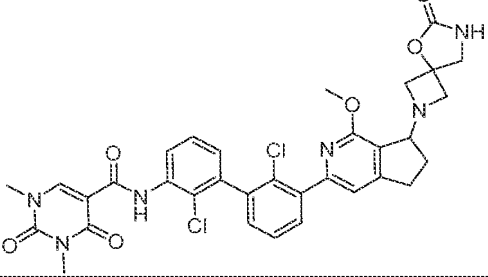
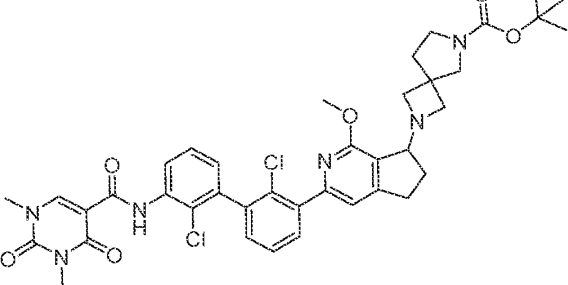
[0348] The compounds shown below in Table 3 were prepared by an analogous reaction protocol as was used for the preparation of **Compound D-1** using the appropriate starting materials.

Table 3

Cmpd No.	Structure	Starting Materials
D-2		3-Hydroxyazetidine Hydrochloride Intermediate 18-1
D-3		2,6-Diazaspiro[3.4]octan-5-one hydrochloride Intermediate 18-1

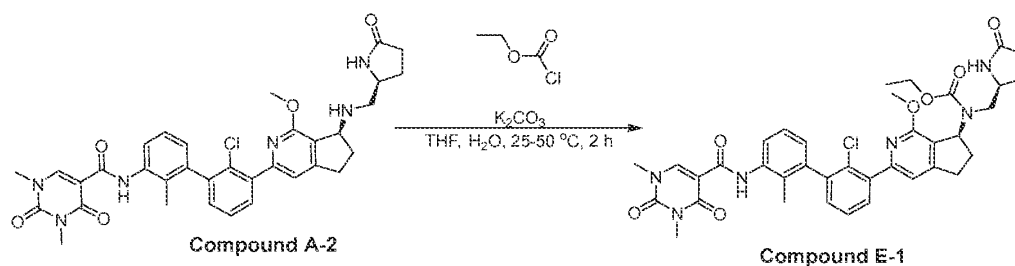
Cmpd No.	Structure	Starting Materials
D-4		(3R,4R)-4-aminooxolan-3-ol Intermediate 18-1
D-5		Ethanolamine Intermediate 18-1
D-6		(3S,4R)-4-aminooxan-3-ol hydrochloride Intermediate 18-1
D-7		(3S,4S)-4-aminooxan-3-ol hydrochloride Intermediate 18-1
D-8a		(3R,4S)-4-aminooxan-3-ol hydrochloride Intermediate 18-1

Cmpd No.	Structure	Starting Materials
D-8b		(3R,4S)-4-aminooxan-3-ol hydrochloride Intermediate 18-1
D-9		Glycinamide hydrochloride Intermediate 18-2
D-10		Oxetan-3-amine Intermediate 18-2
D-11		Cyclopropylamine Intermediate 18-2
D-12		Glycine Intermediate 18-2

Cmpd No.	Structure	Starting Materials
D-13		2-Amino-1-(pyrrolidin-1-yl)ethanone hydrochloride Intermediate 18-2
D-14		2,6-Diazaspiro[3.4]octan-7-one Intermediate 18-1
D-15		5-oxa-2,7-diazaspiro[3.4]octan-6-one Intermediate 18-1
D-16		tert-butyl 2,6-diazaspiro[3.4]octane-6-carboxylate Intermediate 18-1

Cmpd No.	Structure	Starting Materials
D-17		3-Hydroxy-3-methylazetidine hydrochloride Intermediate 18-3
D-18		3-methoxy-3-methylazetidine hydrochloride Intermediate 18-3
D-19		(2S,3R)-2-Methyl-3-azetidinol Intermediate 18-3

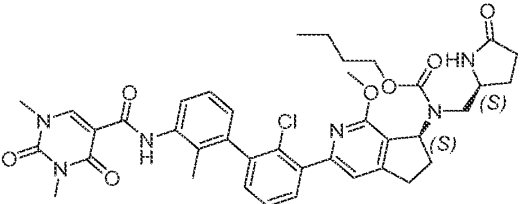
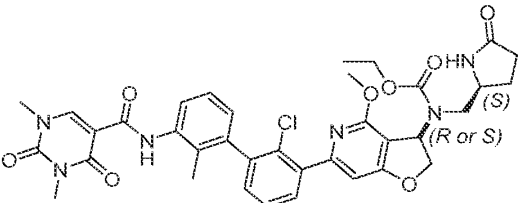
Example 3b
Preparation of Compound E-1



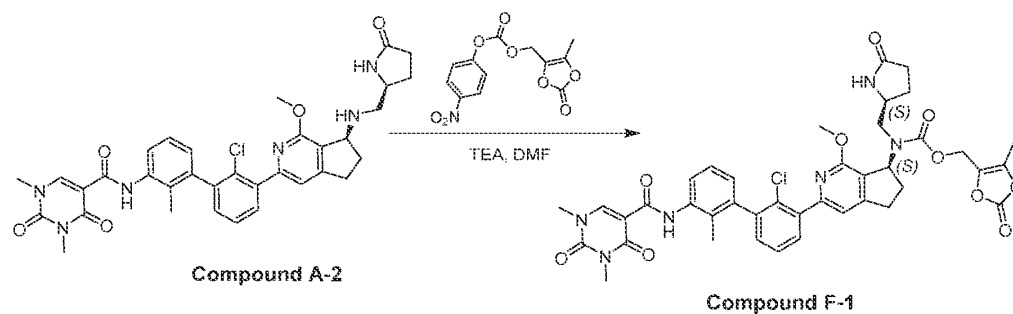
[0349] To a solution of **Compound A-2** (120 mg) in THF (3 mL) were added K_2CO_3 (46 mg, 336 μmol) and ethyl chloroformate (40 μL , 420 μmol). The mixture was stirred at 25 $^\circ\text{C}$ for 2 h. The mixture was filtered and concentrated under reduced pressure to give a residue, which was purified by prep-HPLC to give **Compound E-1** (17 mg, 99% purity) as a yellow solid.

[0350] The compounds shown below in Table 4 were prepared by an analogous reaction protocol as was used for the preparation of **Compound E-1** using the appropriate starting materials.

Table 4

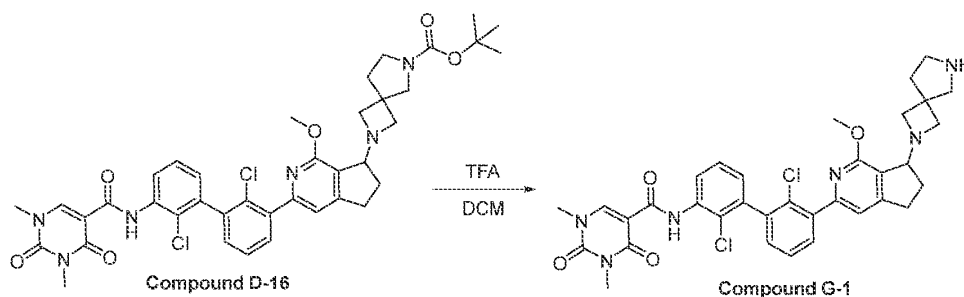
Cmpd No.	Structure	Starting Materials
E-2		A-2 n-Butyl Chloroformate
E-3		A-19 Ethyl chloroformate

Example 3c
Preparation of Compound F-1



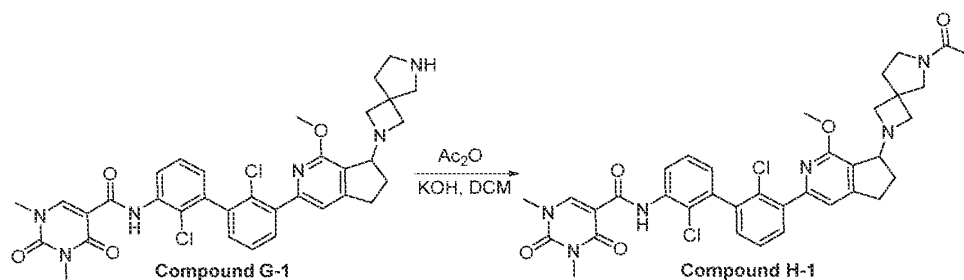
[0351] To a solution of **Compound A-2** (75 mg, 117 μ mol) and (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl 4-nitrophenyl carbonate (69 mg, 233 μ mol) in DMF (1 mL) was added TEA (49 μ L, 350 μ mol). The mixture was stirred at 60 °C for 48 h. The mixture was concentrated under reduced pressure to give a residue, which was purified by prep-HPLC twice to give **Compound F-1** (3.0 mg, 96% purity) as a white solid.

Example 3d
Preparation of Compound G-1



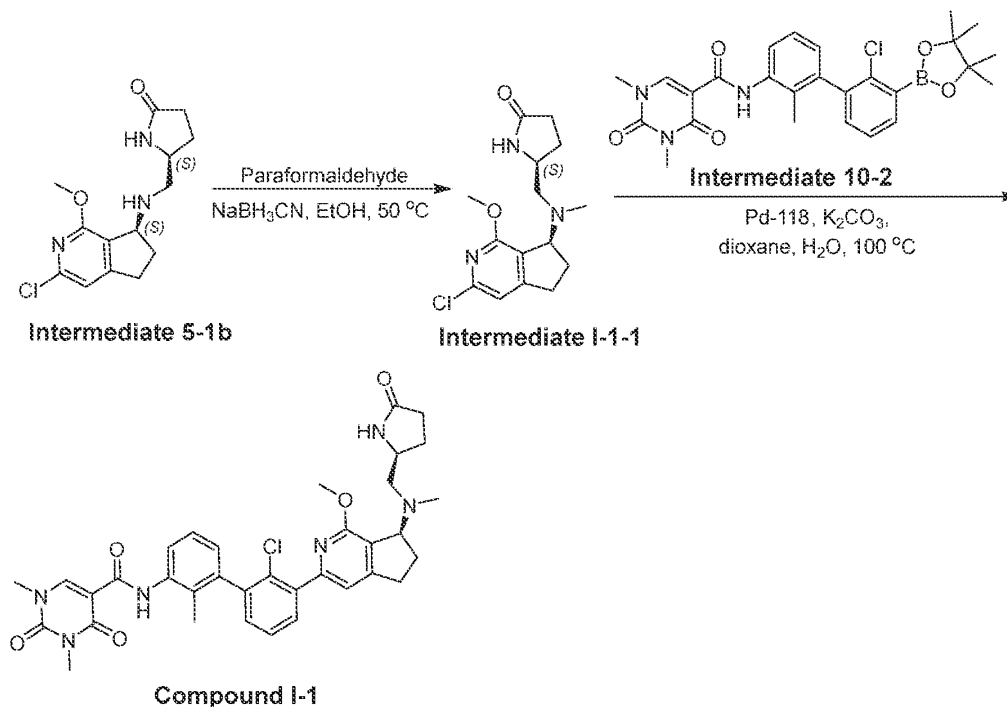
[0352] To a solution of **Compound D-16** (80 mg, 105 μmol) in DCM (2 mL) was added TFA (2 mL). The mixture was stirred at 20 °C for 0.5 h to give a colorless solution. The mixture was concentrated under reduced pressure to give a residue, which was purified by prep-HPLC to give **Compound G-1** (6.27 mg, 97% purity) as a white solid.

Example 3e
Preparation of Compound H-1



[0353] To a solution of **Compound G-1** (40 mg, 61 μmol) in DCM (2 mL) were added KOH (10 mg, 181 μmol) and acetic anhydride (6.0 μL , 60 μmol). The mixture was stirred at 20 °C for 2 h to give a yellow solution. The mixture was concentrated under reduced pressure to give a residue, which was purified by prep-HPLC to give **Compound H-1** (9.48 mg) as a white solid.

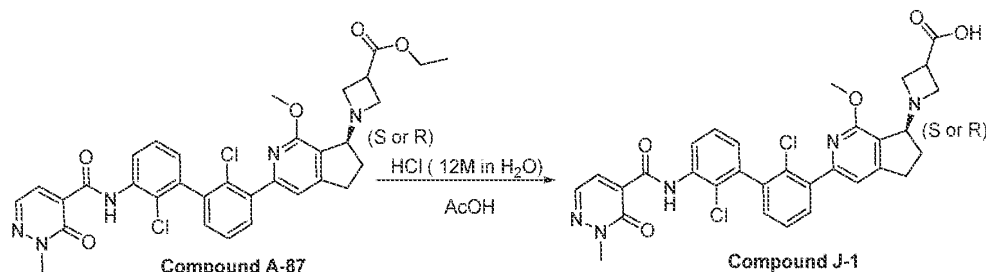
Example 3f
Preparation of Compound I-1



[0354] A mixture of **Intermediate 5-1b** (50 mg, 169 μmol) and paraformaldehyde (15 mg, 507 μmol) in EtOH (1 mL) was stirred at $50\text{ }^\circ\text{C}$ for 15 h. After adding NaBH_3CN (53 mg, 845 μmol), the mixture was stirred at $50\text{ }^\circ\text{C}$ for 1 h. The mixture was filtered and concentrated under reduced pressure to give a residue, which was purified by prep-TLC to give **Intermediate I-1-1** (30 mg) as a liquid. MS: ES m/z calculated for $\text{C}_{15}\text{H}_{21}\text{ClN}_3\text{O}_2$ $[\text{M}+\text{H}]^+$ 310.1, found 310.1.

[0355] A mixture of **Intermediate I-1-1** (30 mg), **Intermediate 10-2** (54 mg, 107 μmol), $[1,1'\text{-Bis}(\text{di-tert-butylphosphino})\text{ferrocene}]\text{dichloropalladium(II)}$ (6.3 mg, 9.68 μmol), K_2CO_3 (40 mg, 291 μmol) in dioxane (2 mL) and H_2O (0.2 mL) was degassed and then purged with N_2 (3x). The mixture was stirred at $100\text{ }^\circ\text{C}$ for 16 h under N_2 atmosphere. The mixture was filtered and concentrated under reduced pressure to give a residue, which was purified by prep-HPLC to give **Compound I-1** (2.4 mg) as an off-white solid.

Example 3g
Preparation of Compound J-1

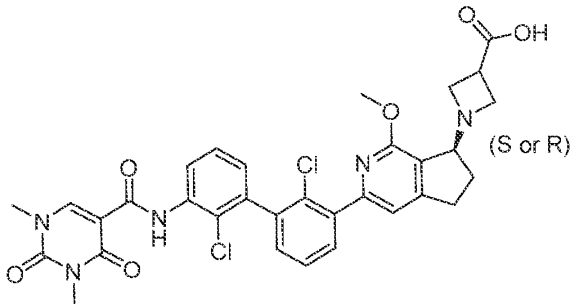
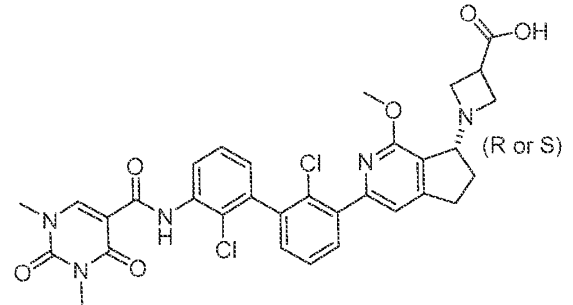


[0356] A mixture of **Compound A-87** (90 mg, 139 μ mol) with HCl acid (12 M in H₂O, 1 mL) and AcOH (1 mL) was stirred at 20 °C for 16 h. The mixture was filtered and concentrated under reduced pressure to give a residue, which was purified by prep-HPLC to give **Compound J-1** (12 mg) as an off-white solid.

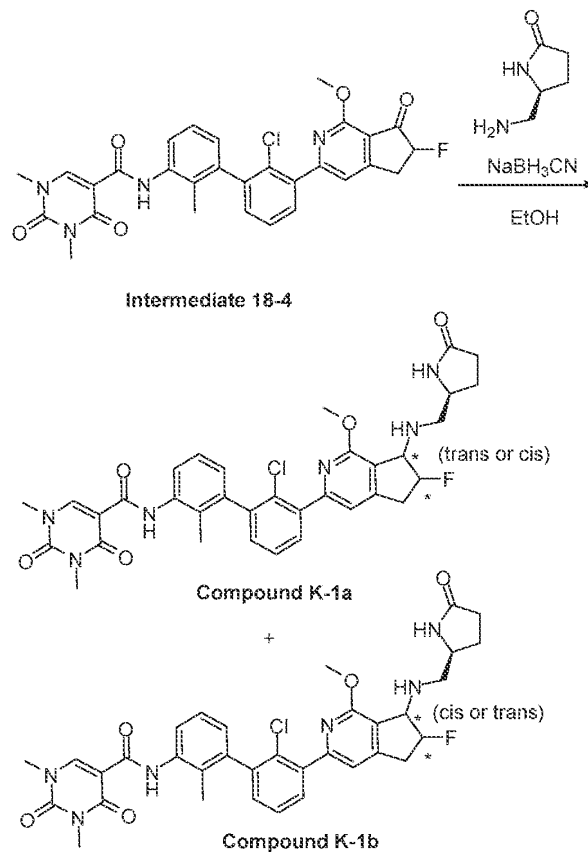
[0357] The compounds shown below in Table 5 were prepared by an analogous reaction protocol as used for the preparation of **Compound J-1** using the appropriate starting materials.

Table 5

Cmpd No.	Structure	Starting Materials
J-2		Compound A-88

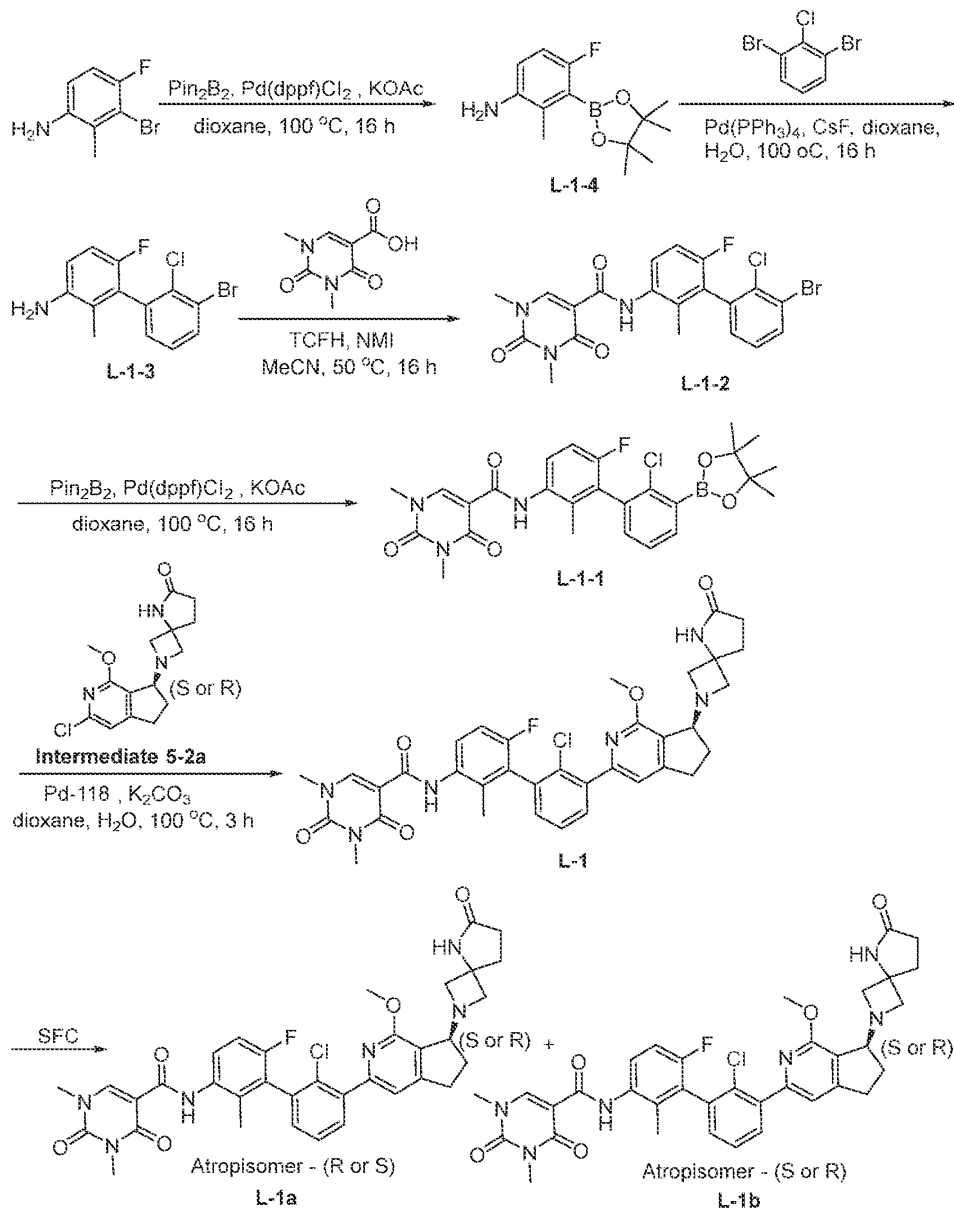
J-3	 Chemical structure of Compound A-85: A 1,3,5-trimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-6-ylidenehydrazide group is attached via its hydrazide nitrogen to a 2,4-dichlorophenyl ring. This ring is further attached to a 3-chlorophenyl ring, which is connected to a 6-methoxy-1,2,3,4-tetrahydroquinoline-5-yl group. The tetrahydroquinoline ring is substituted with a 2-methyl-2-oxoazetidine-1-carboxylic acid group at the 3-position. The stereochemistry at the chiral center is indicated as (S or R).	Compound A-85
J-4	 Chemical structure of Compound A-86: This structure is identical to Compound A-85, but the stereochemistry at the chiral center is indicated as (R or S).	Compound A-86

Example 3h
Preparation of Compound K-1a & K-1b



[0358] To a solution of **Intermediate 18-4** (50 mg, 88.81 μmol) in MeOH (1 mL) was added (5S)-5-(aminomethyl) pyrrolidin-2-one HCl salt (20 mg, 133 μmol). The mixture was stirred at 50 °C for 13 h. To the mixture was added NaBH_3CN (17 mg, 266 μmol) at 20 °C. The mixture was stirred at 50 °C for 3 h. The mixture was filtered to give a filtrate, which was purified by prep-HPLC to give **Compound K-1a** (3.3 mg) as a white solid and **Compound K-1b** (3.81 mg) as white solid.

Example 3i
Preparation of Compound L-1a & L-1b



[0359] A mixture of 3-Bromo-4-fluoro-2-methylaniline (390 mg, 1.91 mmol), Bis(pinacolato)diboron (1.21 g, 4.78 mmol), $\text{Pd}(\text{dppf})\text{Cl}_2$ (140 mg, 191 μmol) and AcOK (563 mg, 5.73 mmol) 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 chromatography to give **Intermediate L-1-4** (390 mg). MS: ES m/z calculated for $C_{13}H_{20}BFNO_2$ $[M+H]^+$ 252.1, found 252.3.

[0360] A mixture of **Intermediate L-1-4** (390 mg), 1,3-dibromo-2-chlorobenzene (840 mg, 3.11 mmol), $Pd(PPh_3)_4$ (180 mg, 155 μ mol) and CsF (708 mg, 4.66 mmol) in dioxane (5 mL) and H_2O (0.5 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 chromatography to give **Intermediate L-1-3** (190 mg) as a yellow liquid. MS: ES m/z calculated for $C_{13}H_{11}BrClFN_2$ $[M+H]^+$ 314.0, found 314.0.

[0361] To a solution of **Intermediate L-1-3** (190 mg) and 1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylic acid (167 mg, 906 μ mol) in MeCN (3 mL) was added chloro- N,N,N',N' -tetramethylformamidinium hexafluorophosphate (TCFH, 339 mg, 1.21 mmol) and N -methyl imidazole (NMI, 124 mg, 1.51 mmol). The mixture was stirred at 50 °C for 16 h to give a yellow mixture. The mixture was filtered and concentrated under reduced pressure to give a residue, which was triturated with ethyl acetate at 25 °C for 1 h to give **Intermediate L-1-2** (130 mg) as a white solid. MS: ES m/z calculated for $C_{20}H_{17}BrClFN_3O_3$ $[M+H]^+$ 480.0, found 480.0.

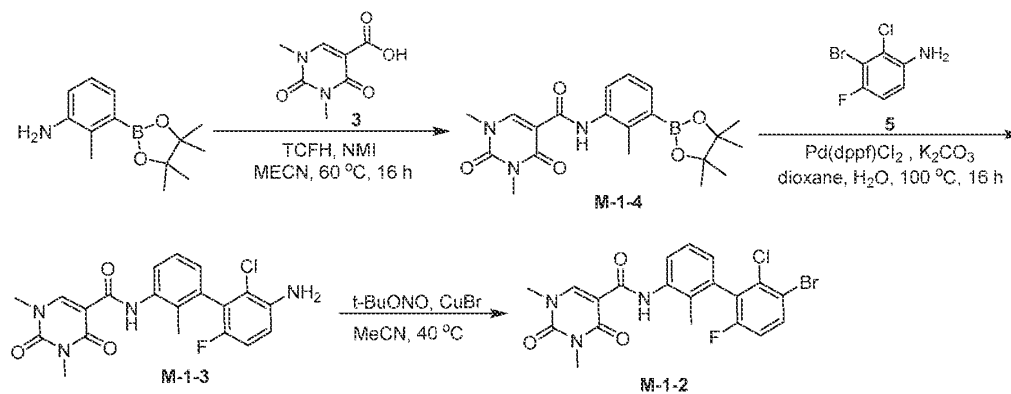
[0362] A mixture of **Intermediate L-1-2** (130 mg, 270 μ mol), bis(pinacolato)diboron (172 mg, 676 μ mol), $Pd(dppf)Cl_2$ (20 mg, 27 μ mol) and KOAc (80 mg, 811 μ mol) in dioxane (5 mL) was degassed and purged with N_2 (3x). The mixture was stirred at 100 °C for 16 h under N_2 atmosphere. The mixture was filtered and concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography to give **Intermediate L-1-1** (230 mg) as a yellow liquid. MS: ES m/z calculated for $C_{26}H_{29}BClFN_3O_5$ $[M+H]^+$ 528.2, found 528.3.

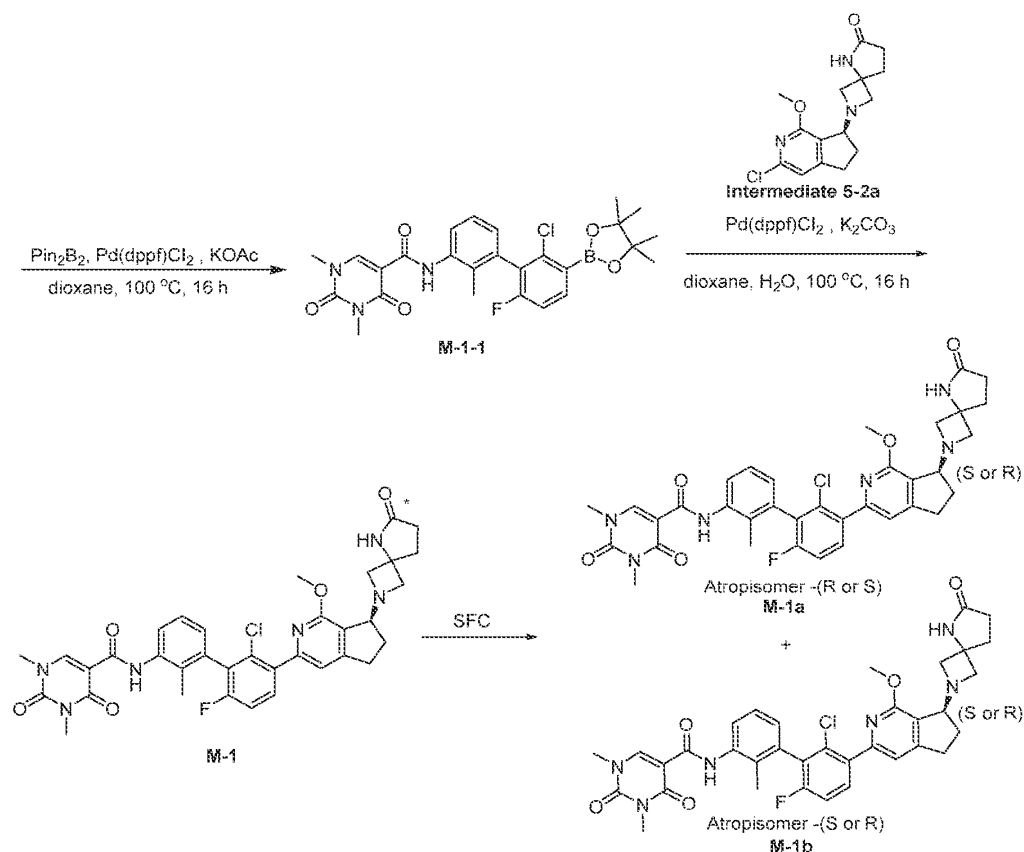
[0363] A mixture of **Intermediate L-1-1** (76 mg, 144 μ mol), **Intermediate 5-2a** (37 mg, 120 μ mol), K_2CO_3 (50 mg, 360 μ mol) and Pd-118 (7.8 mg, 12 μ mol) in dioxane (1.5 mL) and H_2O (0.15 mL) was degassed and purged with N_2 (3x). The mixture was stirred at 100 °C for 3 h under N_2 atmosphere. The mixture was filtered and concentrated under reduced pressure to give a residue, which was purified by prep-HPLC to give **Compound L-**

1 (34 mg, 99 % purity) as a yellow solid. MS: ES m/z calculated for $C_{35}H_{34}ClFN_6O_5$ $[M+H]^+$ 673.23, found 673.6.

[0364] **Compound L-1** (10 mg) was separated by SFC (Instrument: SFC-80; Column: DAICEL CHIRALPAK AS (250mm*30mm,10um); Condition: A:CO₂; B: 0.1% NH₃H₂O ETOH; Begin B: 60; End B: 60; Flow Rate (mL/min): 80; Injections:90) to give **Compound L-1a** (2.46 mg, 98% purity, 96% ee) and **Compound L-1b** (2.95 mg, 98% purity, 100% ee) as white solid.

Example 3j-1
Preparation of Compound M-1a & M-1b





[0365] To a solution of 2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (3.80 g, 16.3 mmol) and 1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylic acid (3 g, 16.29 mmol) in MeCN (30 mL) was added chloro-N,N,N',N'-tetramethylformamidium hexafluorophosphate (TCFH, 9.14 g, 32.6 mmol) and N-methyl imidazole (NMI, 3.34 g, 40.73 mmol, 3.25 mL). The mixture was stirred at 60°C for 16 h. The mixture was filtered and concentrated under reduced pressure to give a residue, which was triturated with EtOAc (30 mL) at 25°C for 10 min to give **Intermediate M-1-4** (4.5 g) as a white solid.

[0366] A mixture of **Intermediate M-1-4** (3.5 g, 8.77 mmol), 3-bromo-2-chloro-4-fluorobenzenamine (1.97 g, 8.77 mmol), K_2CO_3 (3.63 g, 26.3 mmol) and $\text{Pd}(\text{dppf})\text{Cl}_2$ (641 mg, 877 μmol) in dioxane (35 mL) and H_2O (3.5 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 chromatography to give **Intermediate M-1-3** (2.2 g) as a yellow solid. MS: ES m/z calculated for $C_{20}H_{19}ClFN_4O_3 [M+H]^+$ 417.0, found 417.1.

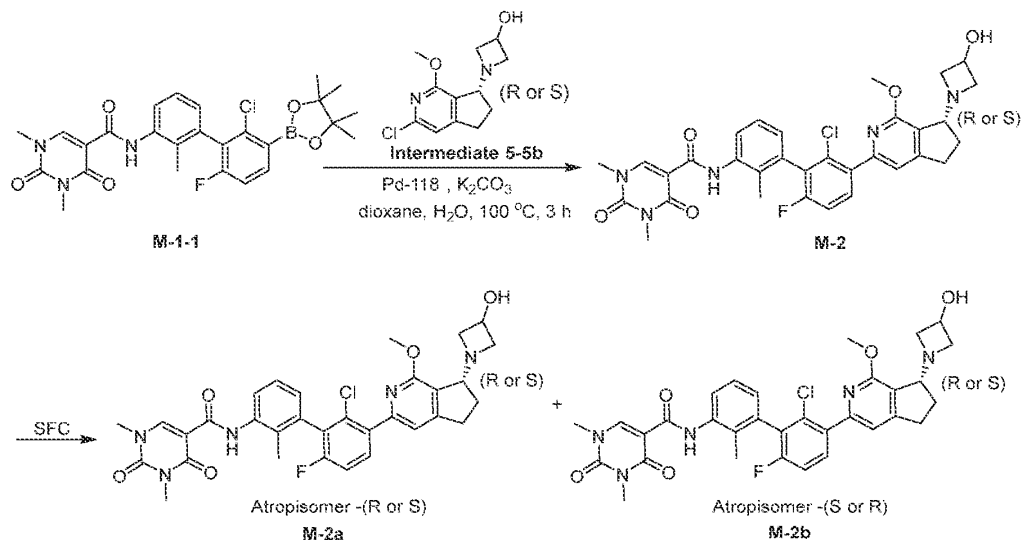
[0367] To a solution of **Intermediate M-1-3** (1.7 g, 4.08 mmol) in MeCN (15 mL) was added CuBr (878 mg, 6.12 mmol) and isopentyl nitrite (956 mg, 8.16 mmol). The mixture was stirred at 40 °C for 16 h. The mixture was filtered and concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography to give **Intermediate M-1-2** (1.2 g) as a yellow solid.

[0368] A mixture of **Intermediate M-1-2** (1.49 g, 3.10 mmol), bis(pinacolato)diboron (866 mg, 3.41 mmol), KOAc (913 mg, 9.30 mmol) and Pd(dppf)Cl₂ (227 mg, 310 μmol, 0.1 eq.) in dioxane (15 mL) was degassed and purged with N₂ (3x). The mixture was stirred at 100 °C for 16 h under N₂ atmosphere. The mixture was filtered and concentrated to give a residue, which was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0–50% ethyl acetate/petroleum ether gradient @ 60 mL/min) to give **Intermediate M-1-1** (1.1 g, 43.99% yield, 70% purity) as a yellow solid. MS: ES m/z calculated for $C_{26}H_{29}BClFN_3O_5 [M+H]^+$ 528.2, found 528.1.

[0369] A mixture of **Intermediate M-1-1** (211 mg), **Intermediate 5-2a** (80 mg, 260 μmol), K₂CO₃ (108 mg, 780 μmol) and Pd-118 (16.9 mg, 26 μmol) in dioxane (2 mL) and H₂O (0.2 mL) was degassed and purged with N₂ (3x). The mixture was stirred at 100 °C for 16 h under N₂ atmosphere. The mixture was filtered and concentrated under reduced pressure to give a residue, which was purified by prep-HPLC to give **Compound M-1** (45 mg) as a white solid. MS: ES m/z calculated for $C_{35}H_{35}ClFN_6O_5 [M+H]^+$ 673.2, found 673.5.

[0370] **Compound M-1** (45 mg) was separated by SFC (Instrument: SFC-80; Column: DAICEL CHIRALPAK AD (250mm*30mm,10um); Condition: A:CO₂; B: 0.1% NH₃H₂O EtOH; Begin B: 60; End B: 60; Flow Rate (mL/min): 80; Injections:90). The separated peaks were purified by prep-HPLC, Column: Xtimate C18 100*30mm*10um; Condition: water (0.225%FA)-ACN; Begin B:25; End B:55; Gradient Time(min):10; 100%B Hold Time(min):2; Injections:1) to give **Compound M-1a** (4.77 mg, 100% ee, >99% purity) and **Compound M-1b** (5.01 mg, 99 % ee, >99% purity) as a white solid.

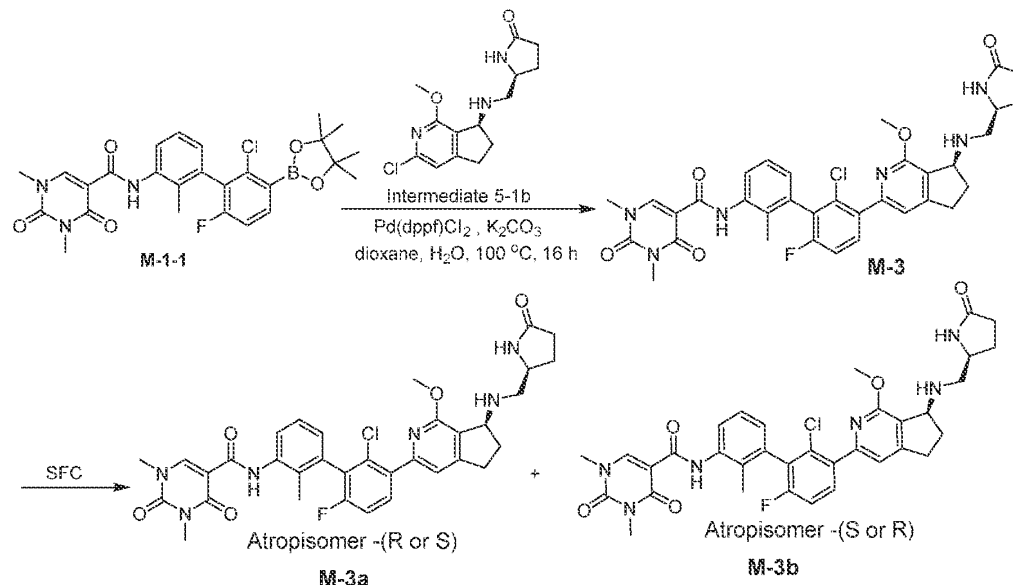
Example 3j-2
Preparation of Compound M-2a & M-2b



[0371] A solution of **Intermediate M-1-1** (150 mg, 284 μ mol), **Intermediate 5-5b** (60 mg, 237 μ mol), K₂CO₃ (98 mg, 711 μ mol) and Pd-118 (15 mg, 24 μ mol) in dioxane (2 mL) and H₂O (0.2 mL) was degassed and purged with N₂ (3x). The mixture was stirred at 100 °C for 3 h under N₂ atmosphere. The mixture filtered and concentrated under reduced pressure to give a residue, which was purified by prep-HPLC to give **Compound M-2** (32 mg) as an off-white solid. MS: ES m/z calculated for C₃₂H₃₁ClFN₅O₅ [M+H]⁺ 621.2, found 620.5.

[0372] **Compound M-2** (32 mg) was separated by SFC (Instrument: SFC-80; Column: DAICEL CHIRALPAK AS (250mm*30mm,10um); Condition: A:CO₂; B: 0.1% NH₃H₂O EtOH; Begin B: 30; End B: 30; Flow Rate (mL/min): 70; Injections:90) to give **Compound M-2a** (7.5 mg, 94.5% ee, 96 % purity) as a white solid and **Compound M-2b** (6.6 mg, 97.3 % ee, 96 % purity) as a white solid.

Example 3j-3
Preparation of Compound M-3a & M-3b

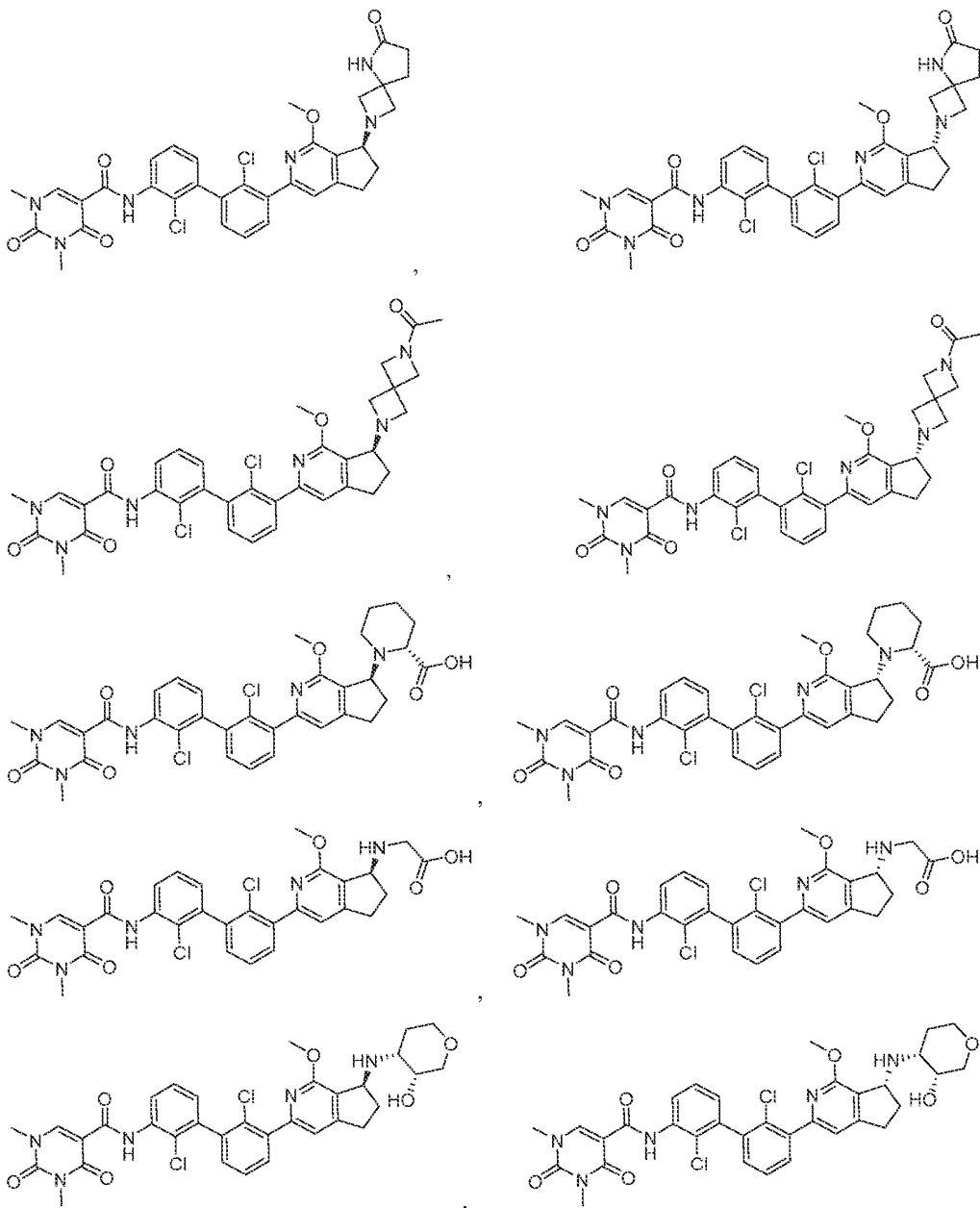


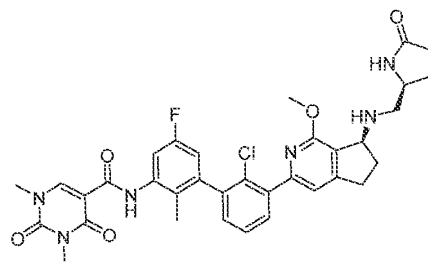
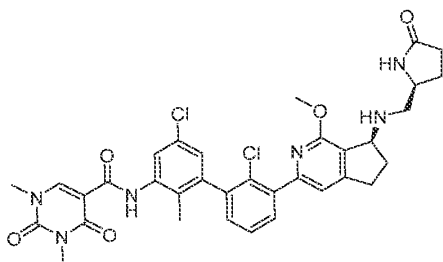
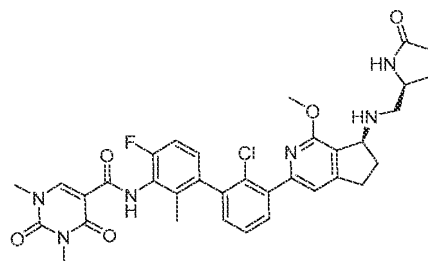
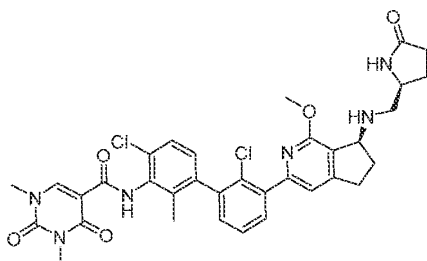
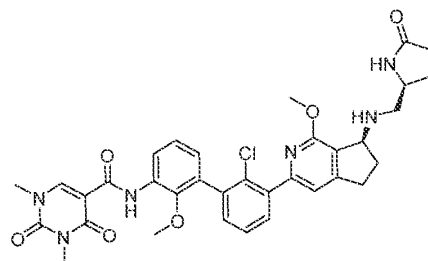
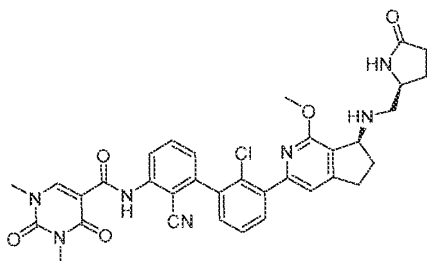
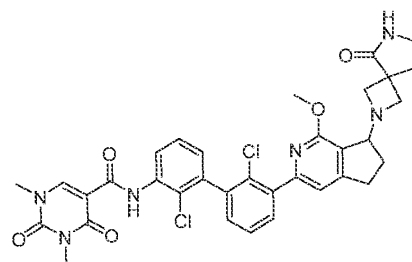
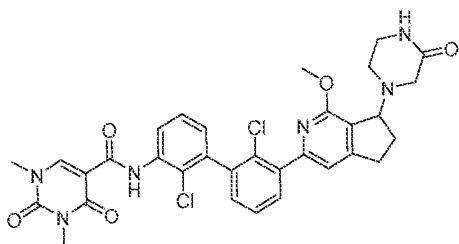
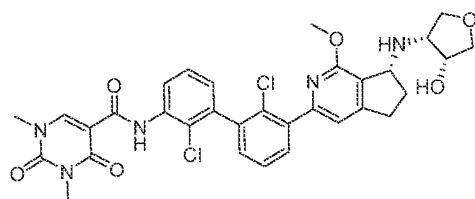
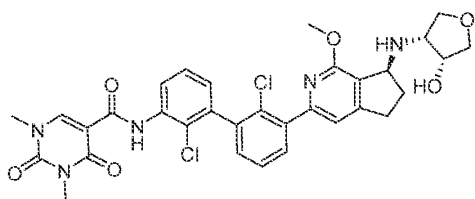
[0373] A mixture of **Intermediate M-1-1** (151 mg), **Intermediate 5-1b** (55 mg, 186 μ mol), K₂CO₃ (77 mg, 558 μ mol) and Pd-118 (12 mg, 18.6 μ mol) in dioxane (2 mL) and H₂O (0.2 mL) was degassed and purged with N₂ (3x). The mixture was stirred at 100 °C for 16 h under N₂ atmosphere. The mixture was filtered and concentrated under reduced pressure to give a residue, which was purified by prep-HPLC to give **Compound M-3** (80 mg) as a brown solid. MS: ES m/z calculated for C₃₄H₃₅ClFN₆O₅ [M+H]⁺ 661.2, found 661.2.

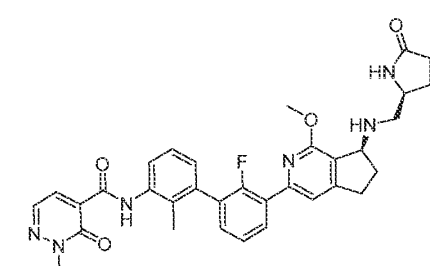
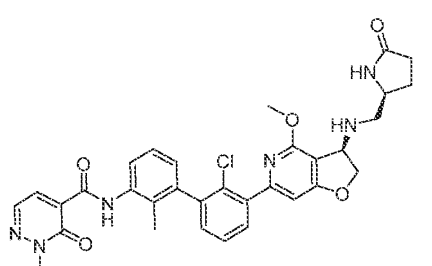
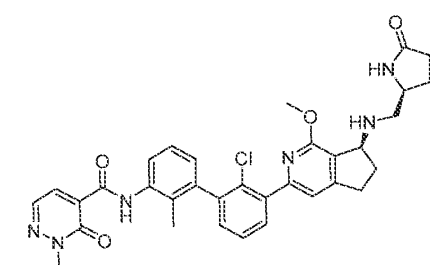
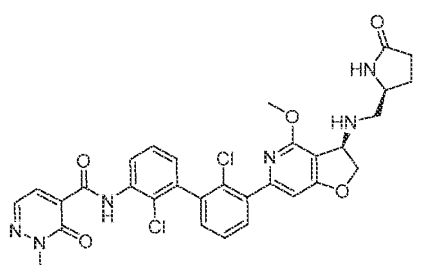
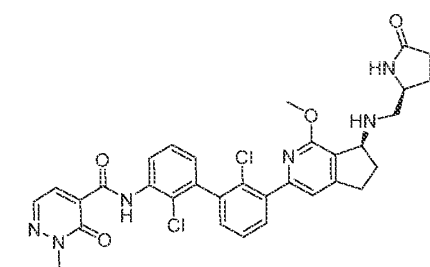
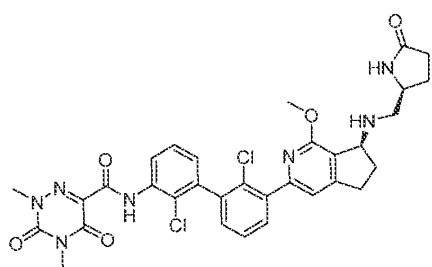
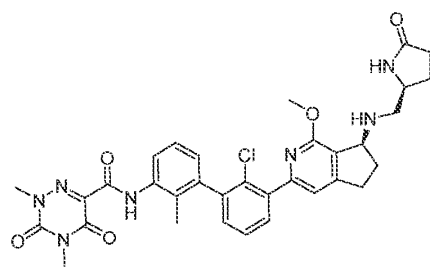
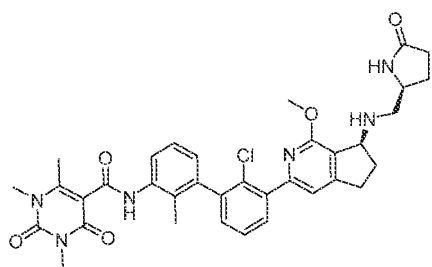
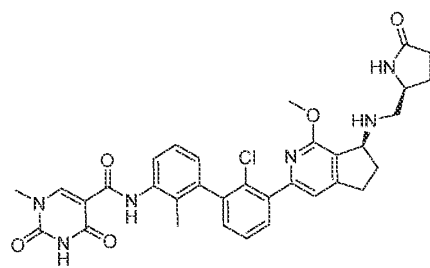
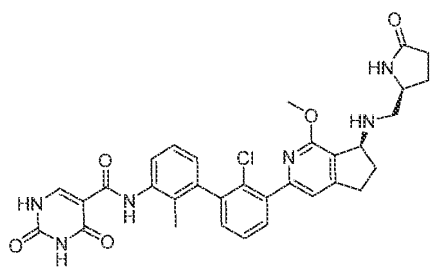
[0374] **Compound M-3** (80 mg) was separated by SFC (Instrument: SFC-80; Column: Column:DAICEL CHIRALPAK OD (250mm*30mm, 10 μ m); Condition: A:CO₂; B: 0.1% NH₃H₂O MeOH; Begin B: 60; End B: 60; Flow Rate (mL/min): 80; Injections:150). The two separate peaks were re-purified by prep-HPLC to give **Compound M-3a** (16.5 mg, 96.38% ee, 99.76% purity) and **Compound M-3b** (6.5 mg, 96.98% ee, 99.71% purity) as a white solid.

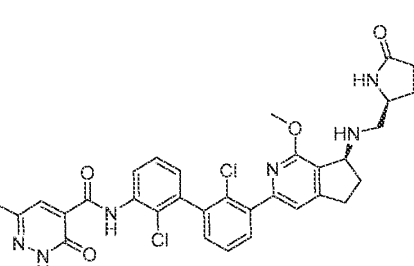
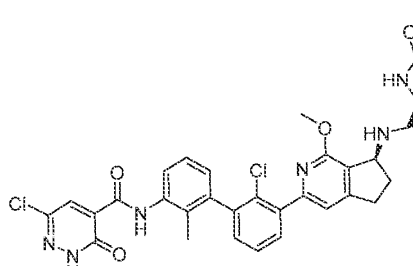
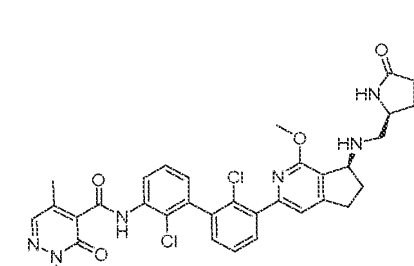
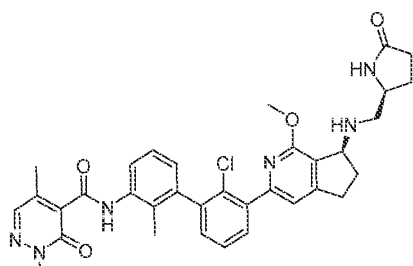
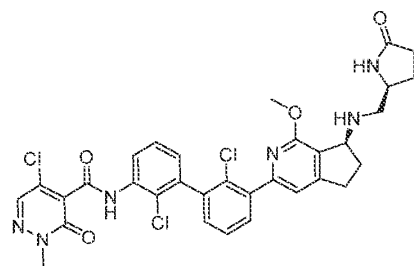
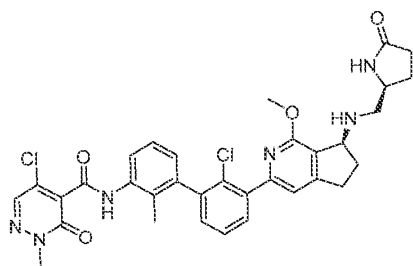
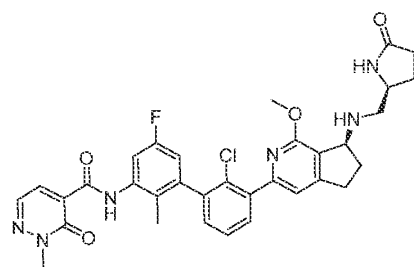
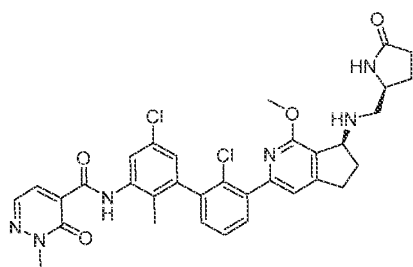
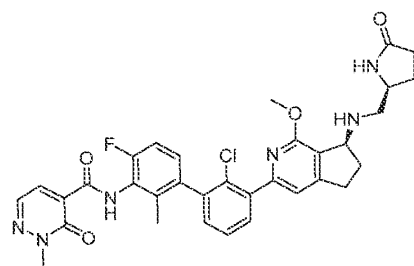
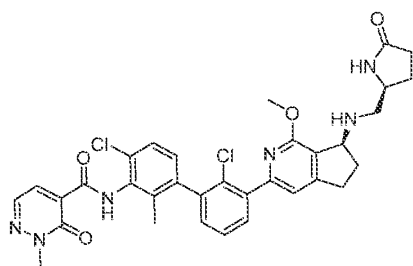
Example 4
Additional Compounds

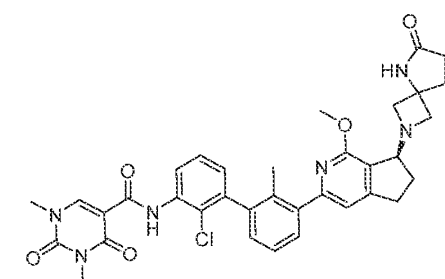
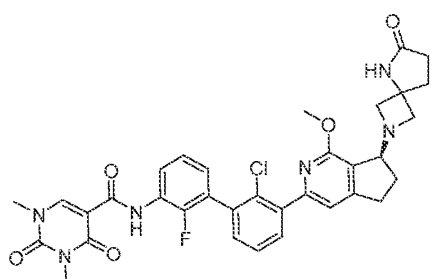
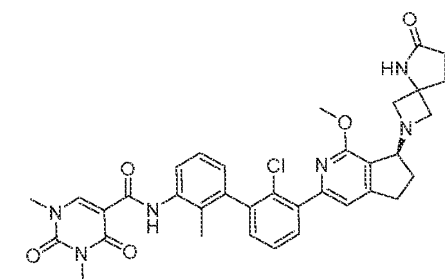
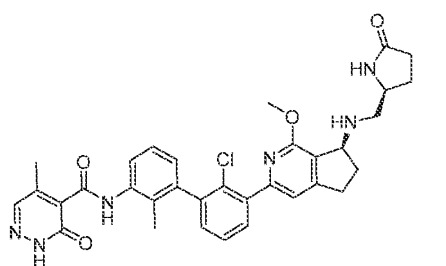
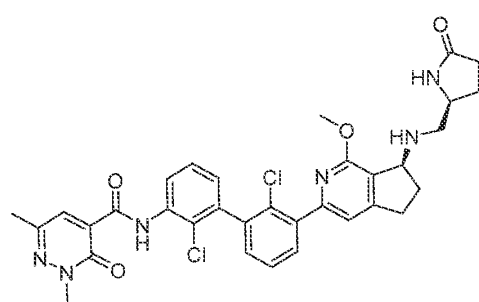
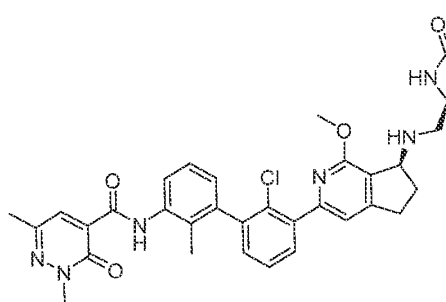
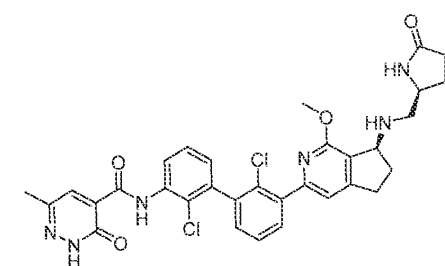
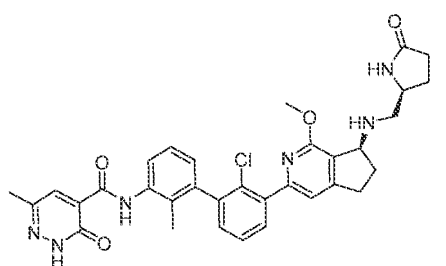
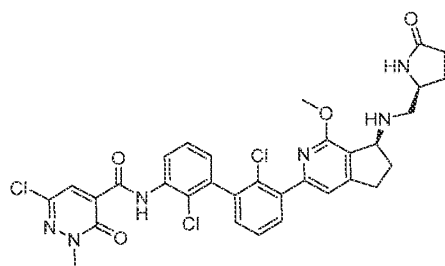
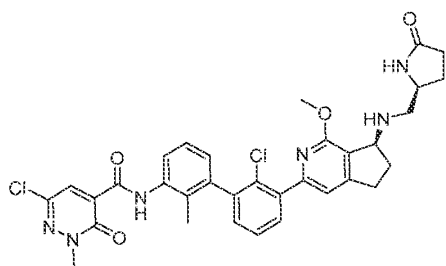
[0375] Other compounds, including those provided in Embodiments 145-147 and below, can be prepared applying similar procedures as those described herein.

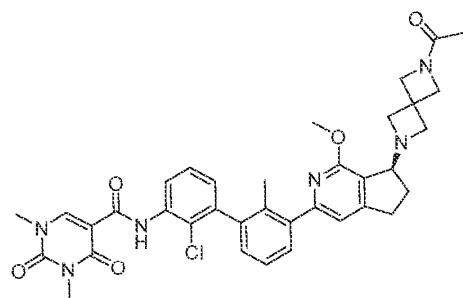
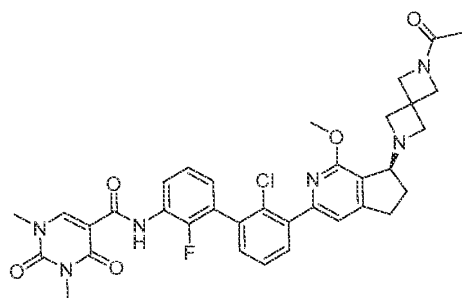
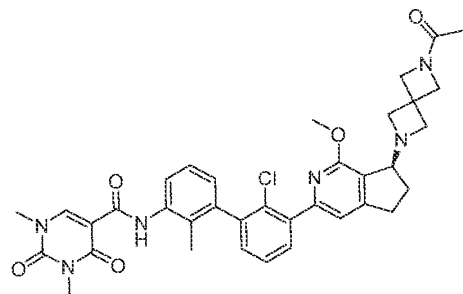
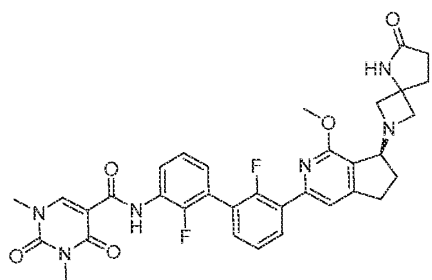
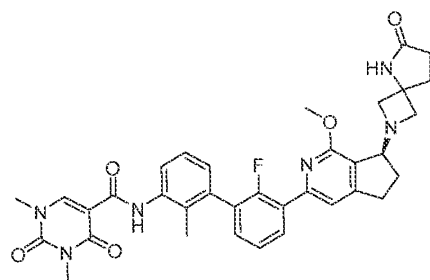
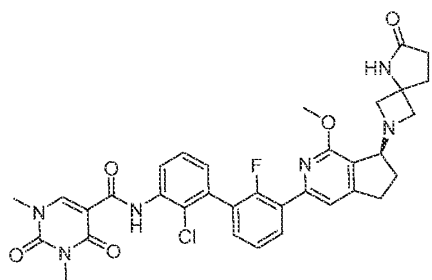
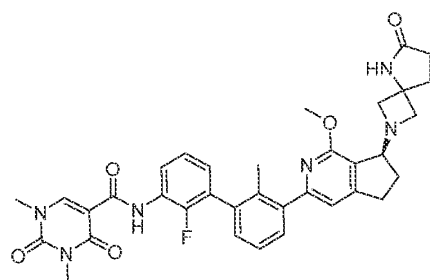
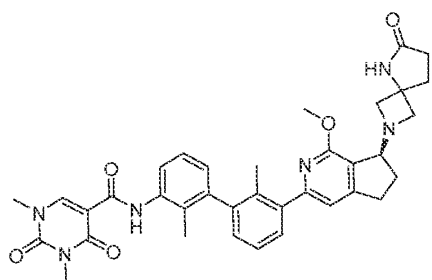


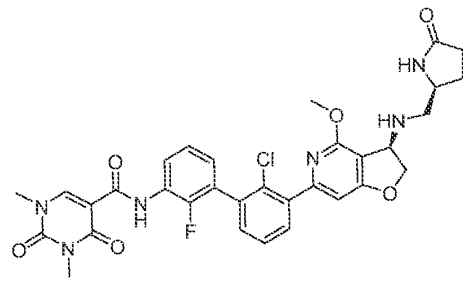
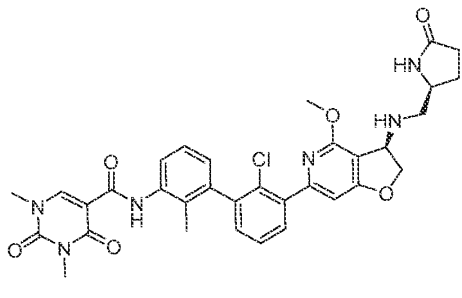
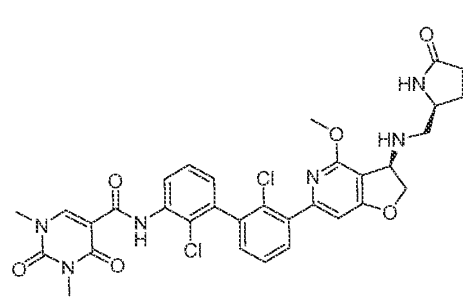
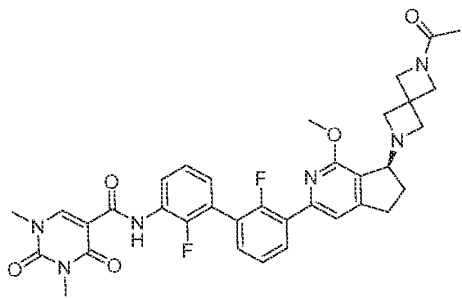
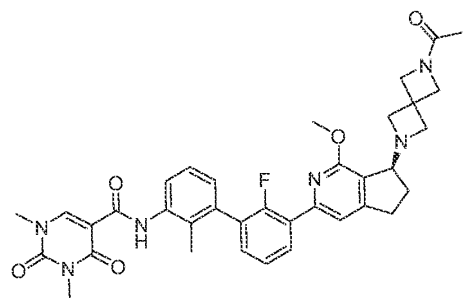
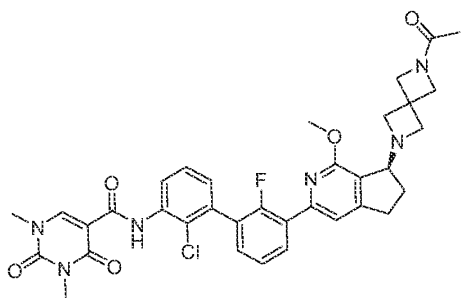
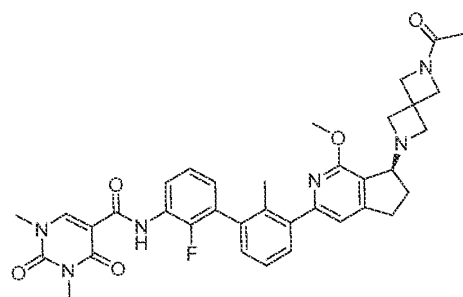
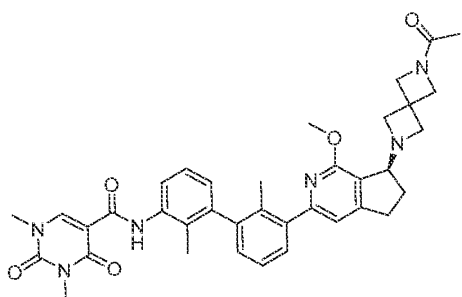


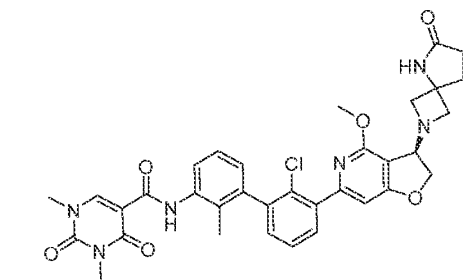
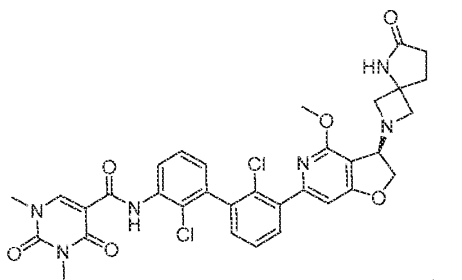
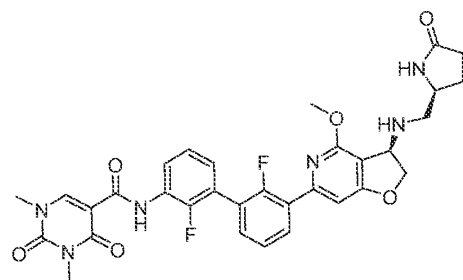
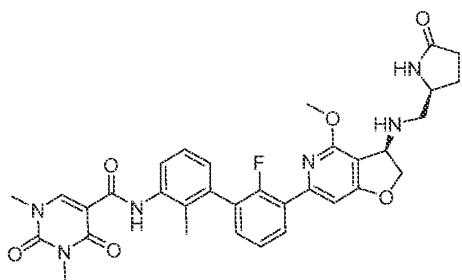
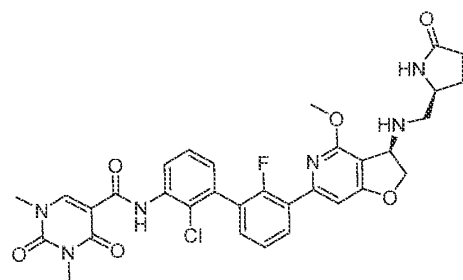
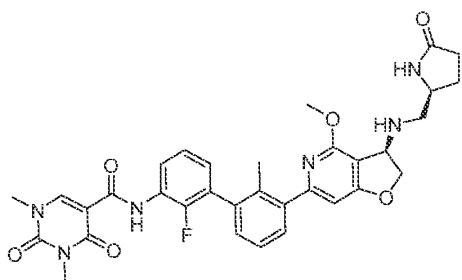
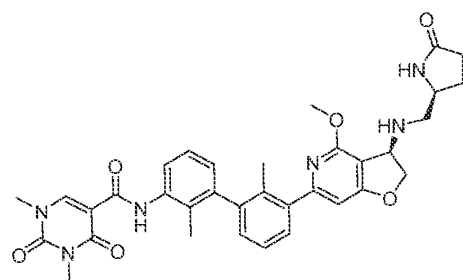
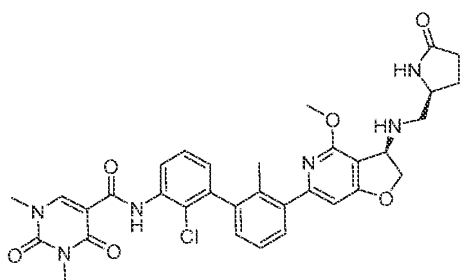


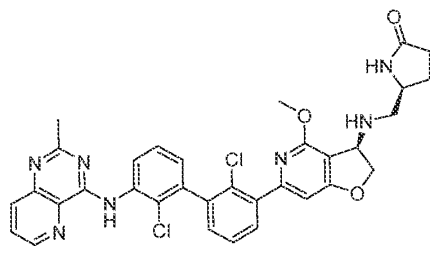
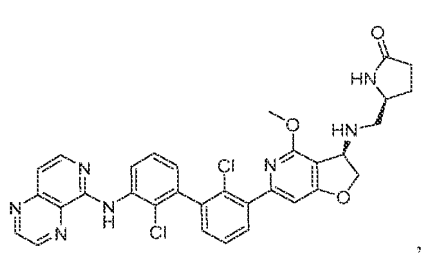
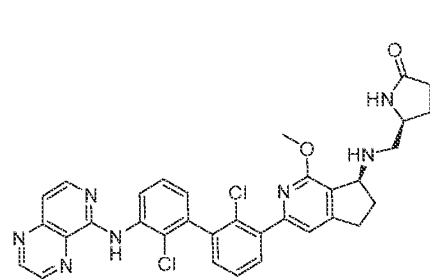
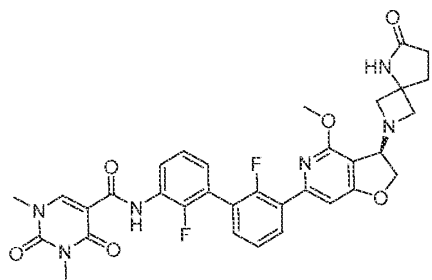
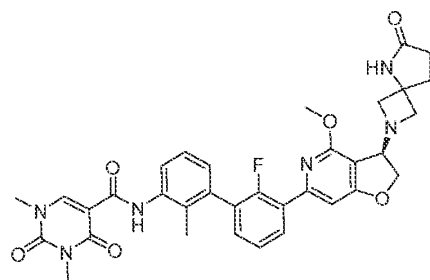
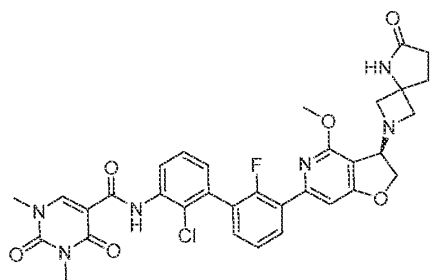
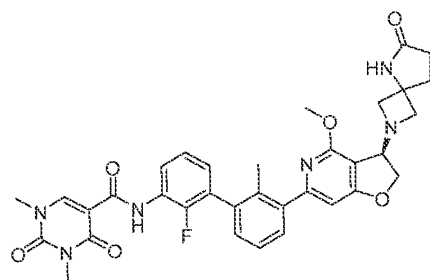
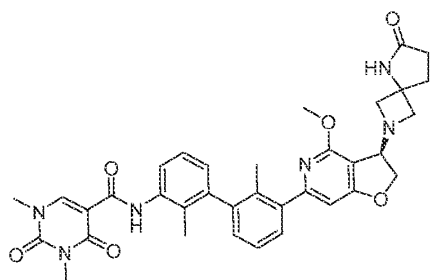
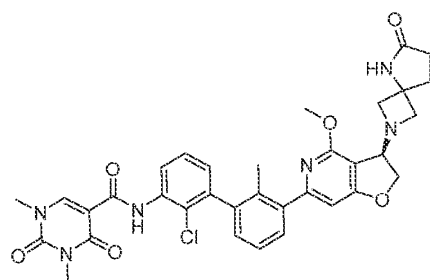
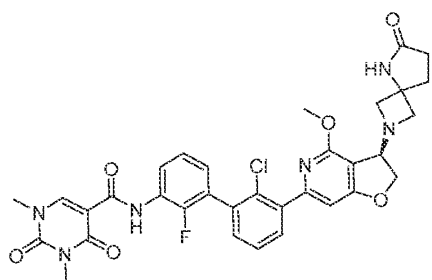


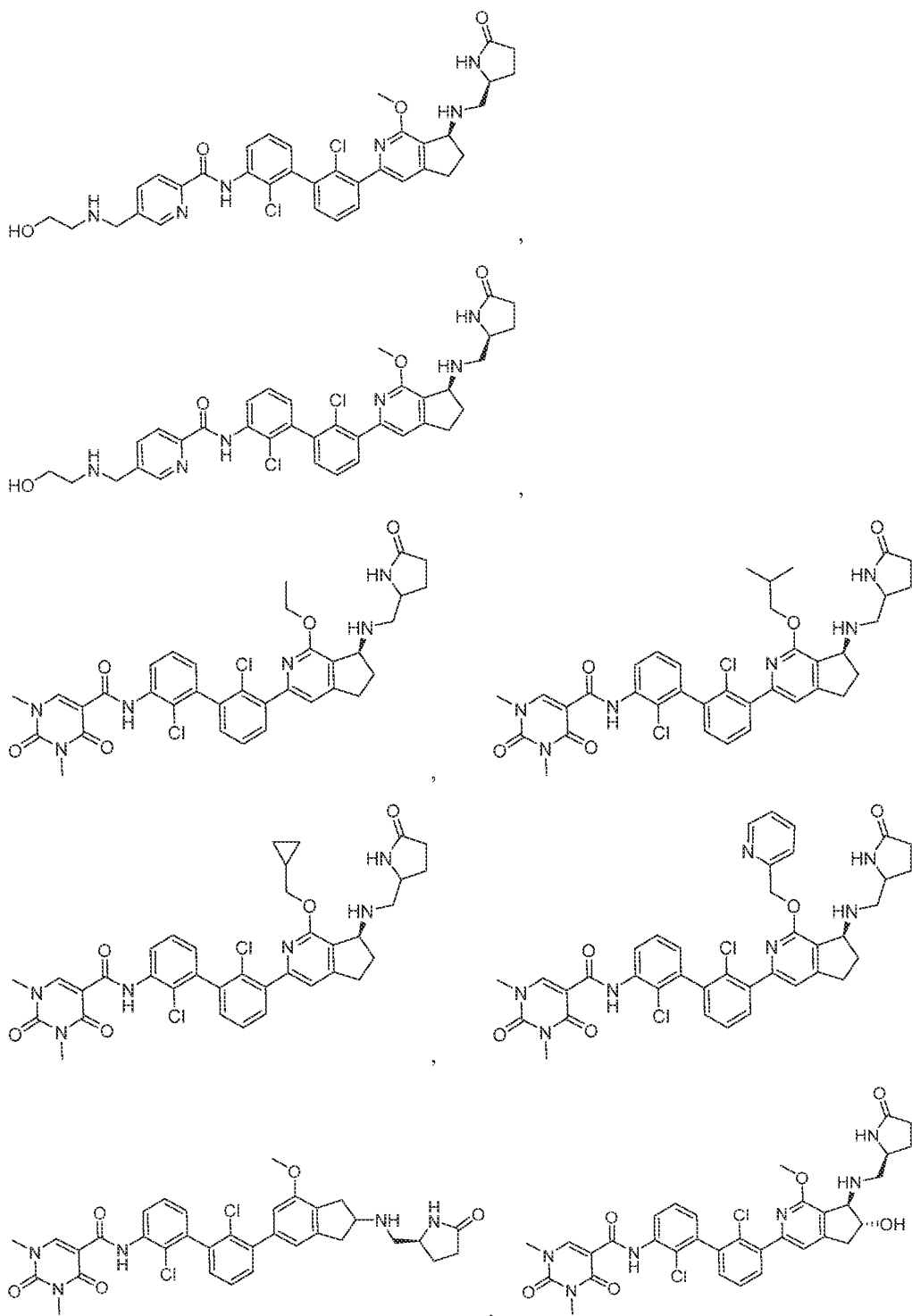


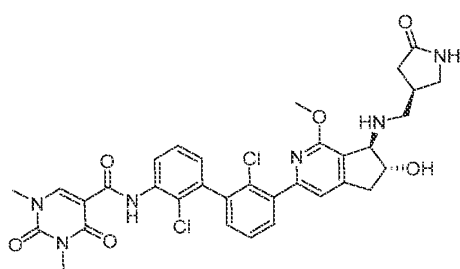
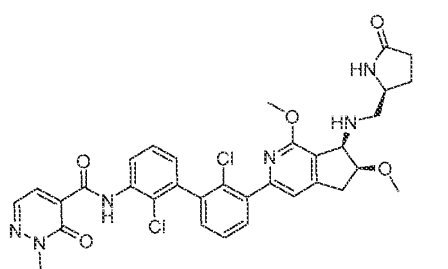
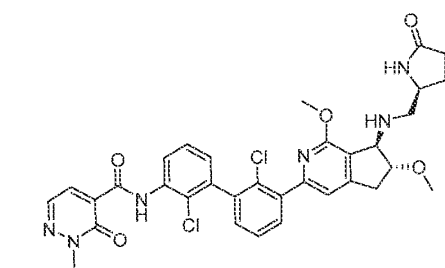
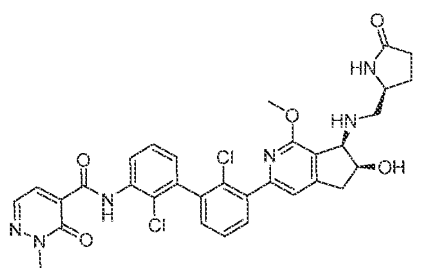
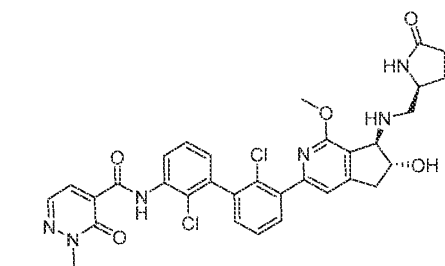
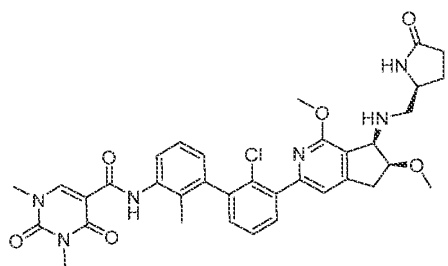
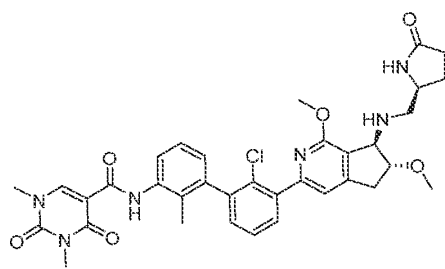
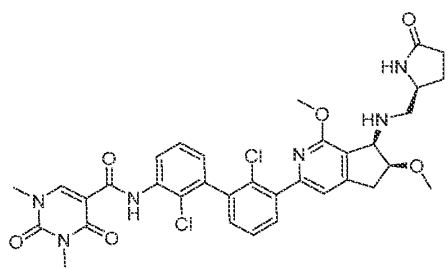
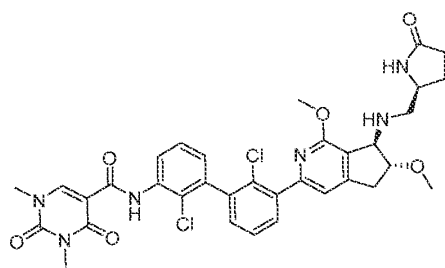
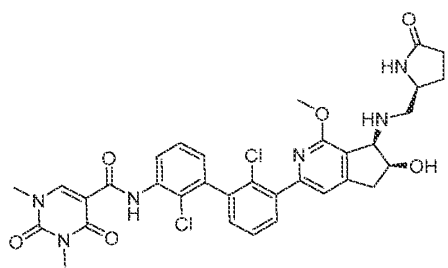


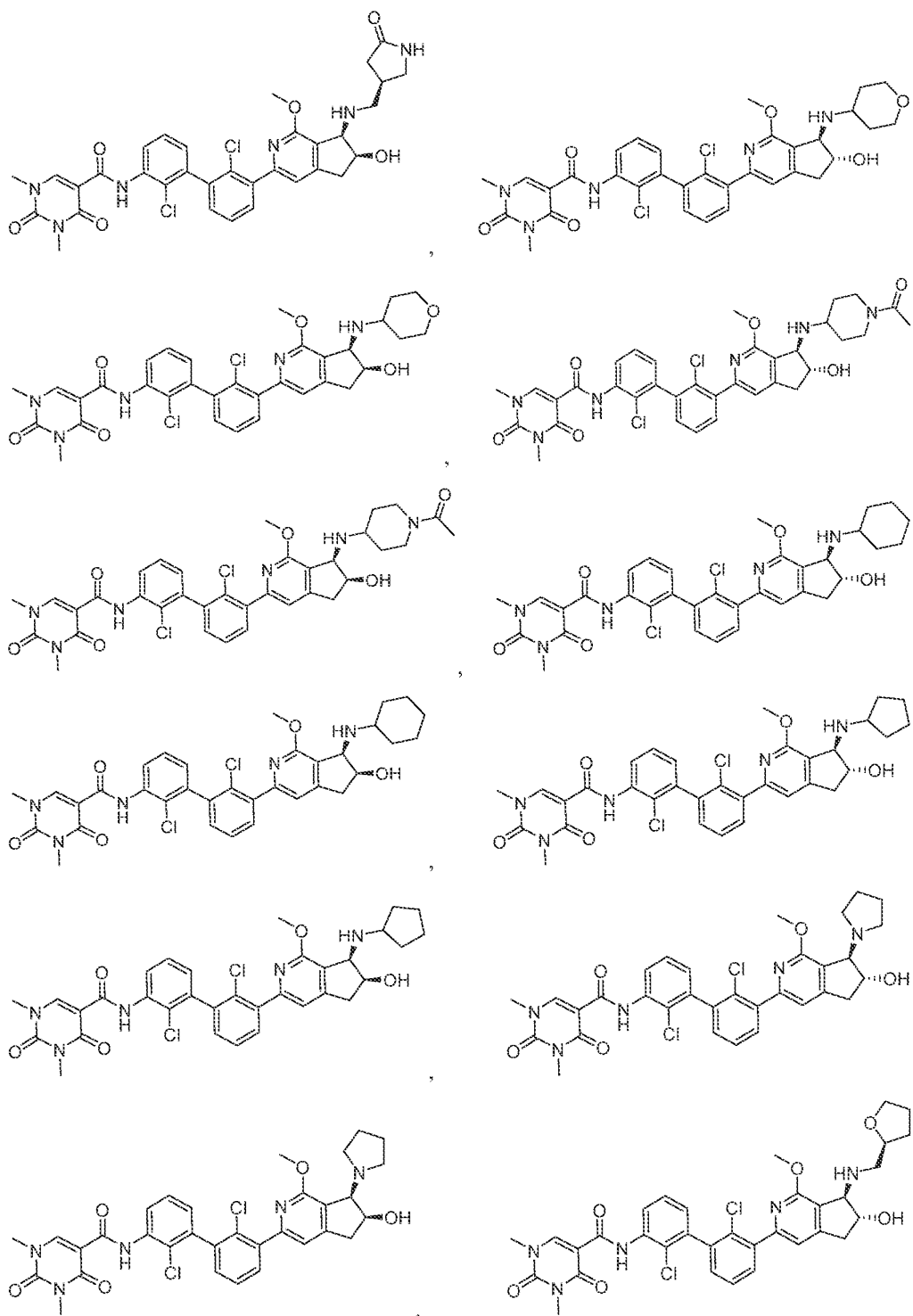


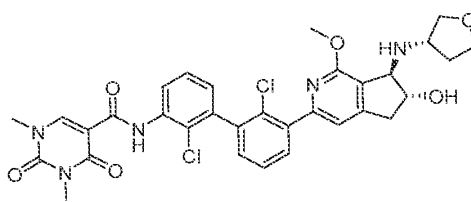
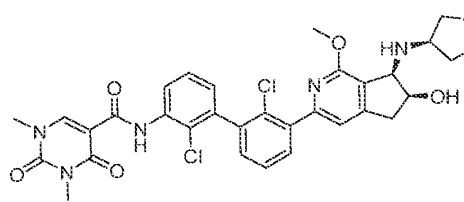
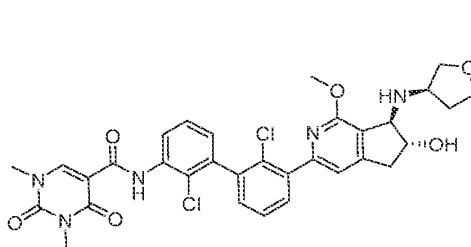
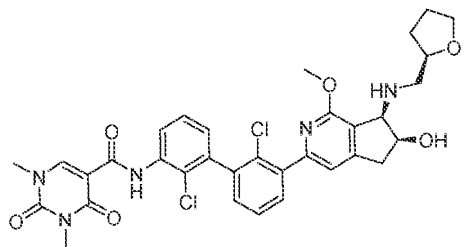
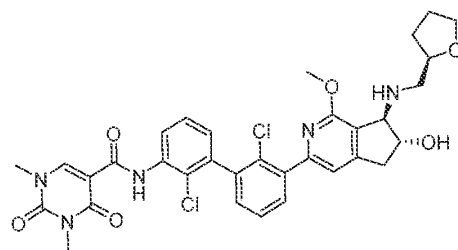
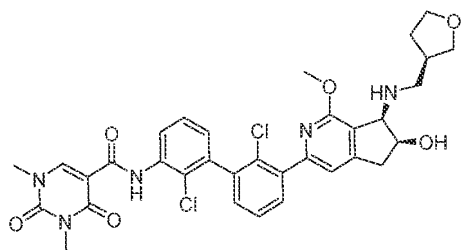
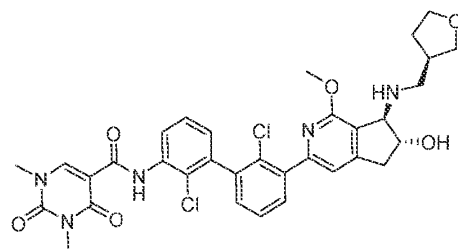
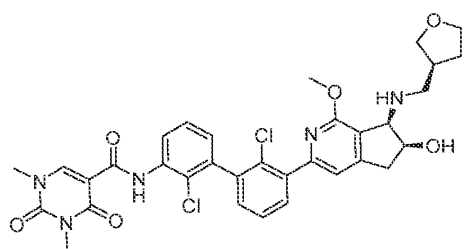
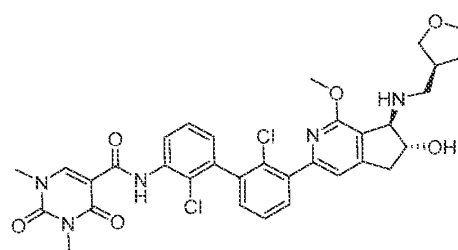
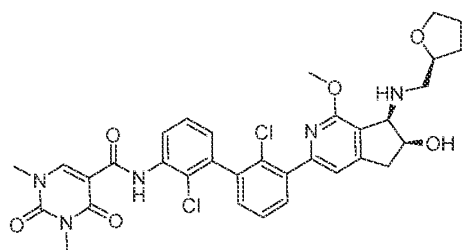


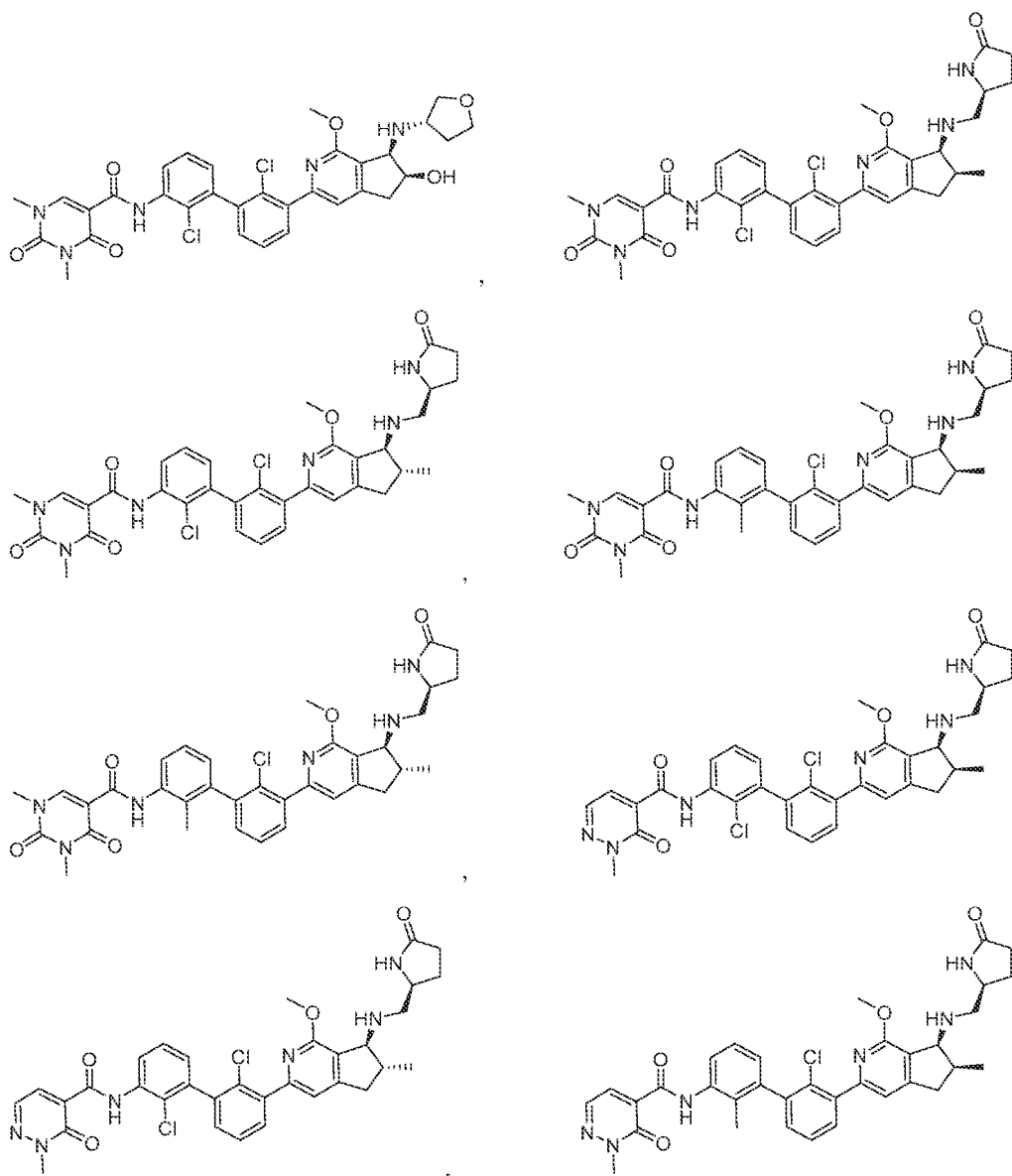


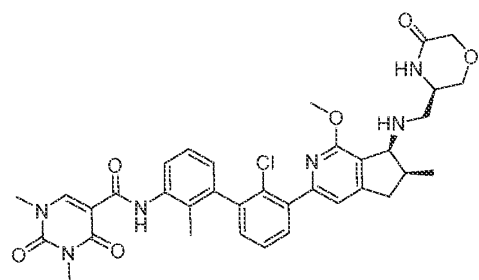
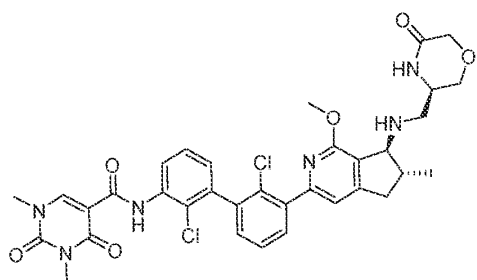
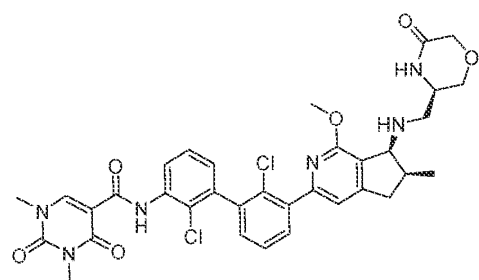
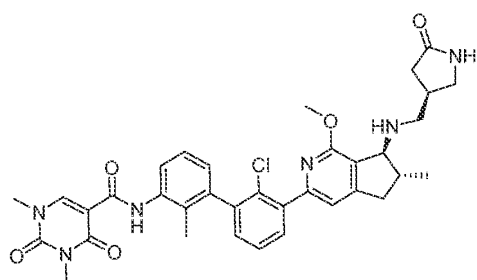
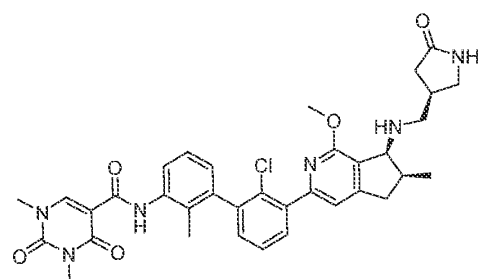
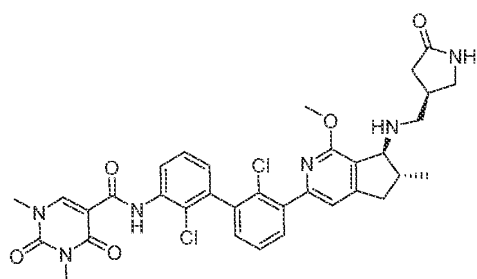
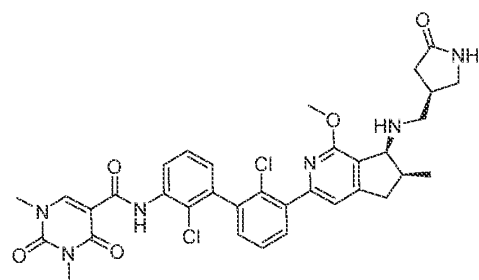
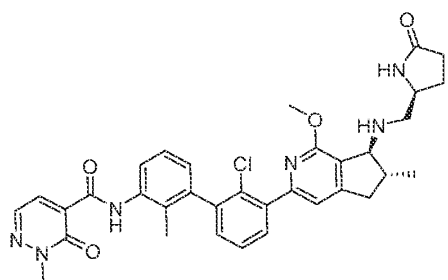


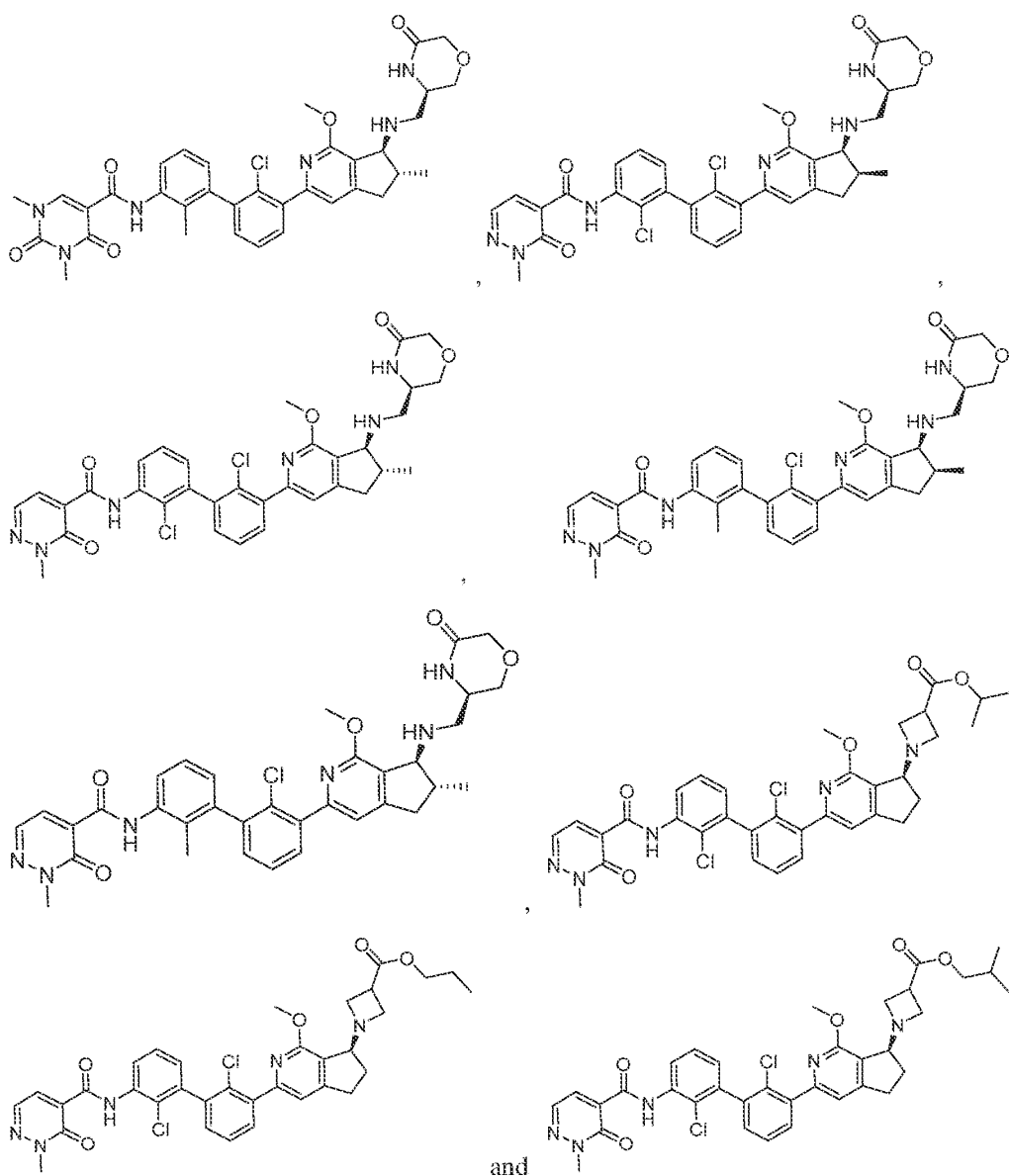












(including pharmaceutically acceptable salts thereof).

Example A LCMS (Liquid chromatography/Mass spectrometry)

[0376] 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, Cl), 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-of-flight mass spectrometers, "CLND", ChemiLuminescent Nitrogen Detector, "ELSD" Evaporative Light Scanning Detector.

Table A: LCMS Method Codes

Method code	Instrument	Column	Mobile phase	Gradient	Flow T	Run Time
1	Shimadzu LCMS2020	Xtimate C18 2.1*30mm, 3um	A:water(4L)+TFA(1.5mL) B:acetonitrile (4L)+TFA (0.75mL)	From 90% A to 20% A in 3 minutes and holding at 20% for 0.5 minutes, to 90% A in 0.01 min held for 0.49 min	1.0 50	4.0
2	Shimadzu LCMS2020	Chromolith® Flash RP-18e 25-3 mm	A:water(4L)+TFA(1.5mL) B:acetonitrile (4L)+TFA (0.75mL)	from 95% A to 5% A in 0.7 minutes and holding at 5% for 0.4 minutes, to 95% A in 0.01 min held for 0.49 min	1.5 50	1.5

Method code	Instrument	Column	Mobile phase	Gradient	Flow T	Run Time
3	Shimadzu LC20-MS2020	Agilent Pursit 5 C18 20*2.0mm	A:water(4L)+TFA(1.5mL) B:acetonitrile (4L)+TFA (0.75mL)	from 95% A to 5% A in 0.7 minutes and holding at 5% for 0.4 minutes, to 95% A in 0.01 min held for 0.39 min	1.5 50	1.5
4	Shimadzu LCMS2020	Xbrige Shield RP-18,5um,2.1*50mm	A:water(4L)+NH ₃ H ₂ O (0.8mL) B:acetonitrile (4L)	from 90% A to 20% A in 3 minutes and holding at 20% for 0.5 minutes, to 90% A in 0.01 min held for 0.49 min	1.0 50	4.0
5	Shimadzu LCMS2020	Xtimate® C18 2.1*30mm, 3um	A:water(4L)+TFA(1.5mL) B:acetonitrile (4L)+TFA (0.75mL)	from 95% A to 5% A in 3 minutes and holding at 5% for 0.5 minutes, to 95% A in 0.01 min held for 0.49 min	1.0 50	4.0
6	Shimadzu LCMS2020	Xtimate® C18 2.1*30mm, 3um	A:water(4L)+TFA(1.5mL) B:acetonitrile (4L)+TFA (0.75mL)	from 95% A to 5% A in 3 minutes and holding at 5% for 0.5 minutes, to 95% A in 0.01 min held for 0.49 min	1.2 50	4.0
7	Shimadzu LCMS2020	Xtimate C18 2.1*30mm, 3um	A:water(4L)+TFA(1.5mL) B:acetonitrile (4L)+TFA (0.75mL)	From 90% A to 20% A in 3 minutes and holding at 20% for 0.5 minutes, to 90% A in 0.01 min held for 0.49 min	1.0 50	4.0
8	Shimadzu LCMS2020	Xtimate® C18 2.1*30mm, 3um	A:water(4L)+TFA(1.5mL) B:acetonitrile (4L)+TFA (0.75mL)	From 90% A to 20% A in 3 minutes and holding at 20% for 0.5 minutes, to 90% A in 0.01 min held for 0.49 min	1.2 50	4.0
9	Shimadzu LCMS2020	Xtimate C18 2.1*30mm, 3um	A:water(4L)+TFA(1.5mL) B:acetonitrile (4L)+TFA (0.75mL)	From 100% A to 40% A in 3 minutes, to 10% A in 0.01 min and holding at 10% for 0.5 minutes, to 0% A in 0.01 min held for 0.49 min	1.2 50	4.0

Method code	Instrument	Column	Mobile phase	Gradient	Flow T	Run Time
10	Shimadzu LCMS2020	Xtimate C18 2.1*30mm, 3um	A:water(4L)+TFA(1.5mL) B:acetonitrile (4L)+TFA (0.75mL)	From 100% A to 40% A in 3 minutes, to 10% A in 0.01 min and holding at 10% for 0.5 minutes, to 0% A in 0.01 min held for 0.49 min	1.0 50	4.0
11	Shimadzu LCMS2020	Xtimate C18 2.1*30mm, 3um	A:water(4L)+TFA(1.5mL) B:acetonitrile (4L)+TFA (0.75mL)	From 100% A to 40% A in 6 minutes, to 10% A in 0.01 min and holding at 10% for 0.5 minutes, to 0% A in 0.01 min held for 0.49 min	1.0 50	7.0

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

Table B: LCMS

Cmpd No.	R _t	LC/MS	LCMS Method
A-1	1.35	640.4	1
B-1	1.28	634.4	1
C-1	1.61	663.4	1
A-2	1.54	643.5	7
A-3	1.53	647.4	7
A-4	1.60	643.5	7
A-5	1.59	623.5	7
A-6	1.57	627.5	7
A-7	1.60	647.5	7
A-8	1.56	627.5	7
A-9	1.55	631.4	7
A-10	1.55	643.5	7
A-11	2.19	647.2	4
A-12	2.28	643.2	4
A-13	1.58	623.5	7
A-14	1.56	627.5	7
A-15	2.23	647.3	4
A-16	1.56	627.5	7
A-17	1.59	631.5	7
A-18	1.56	665.4	7
A-19	1.65	645.4	7
A-20	1.62	675.4	7
A-21	1.61	675.4	7

Cmpd No.	R _t	LC/MS	LCMS Method
A-22	1.62	675.4	7
A-23	1.62/1.65	689.5/689.4	7
A-24	1.87	636.4	7
A-25	1.74	636.4	7
A-26	1.63	622.4	7
A-27	1.62	622.4	7
A-28	1.80	602.4	7
A-29	1.69	666.2	5
A-30	1.62	666.4	7
A-31	1.64	646.4	7
A-32	1.66	650.4	7
A-33	1.59	646.5	7
A-34	1.64	626.5	7
A-35	1.61	630.5	7
A-36	1.58	650.4	7
A-37	1.61	630.5	7
A-38	1.63	634.5	7
A-39	1.86	646.5	7
A-40	1.67	646.5	7
A-41	1.77	626.5	7
A-42	1.84	630.6	7
A-43	1.80	633.4	7
A-44	1.77	635.4	7
A-45	1.74	597.5	7
A-46	1.72	615.4	7
A-47	1.72	613.5	7
A-48	1.64	662.4	7
A-49	1.68	625.5	7
A-50	1.44	654.5	7
A-51	1.57	619.4	7
A-52	1.50	599.4	7
A-53	1.60	659.5	7
A-54	1.36	615.5	7
A-55	1.51	629.5	7
A-56	3.42	629.2	11
A-57	1.51	654.5	7
A-58	1.49	644.6	7
A-59	1.57	661.5	7
A-60	1.71	661.5	7
A-61	1.82	677.5	7
A-62	1.70	662.6	7
A-63	1.88	631.5	7
A-64	1.76	679.3	8
A-65	1.80	681.4	7

Cmpd No.	R _t	LC/MS	LCMS Method
A-66	1.84	699.5	7
A-67	1.64	645.5	7
A-68	1.66	645.5	7
A-69	1.72	661.5	7
A-70	1.65	645.5	7
A-71	1.63	690.2	5
A-72	1.66	669.3	5
A-73	1.43	657.5	5
A-74	1.66	645.3	5
A-75	1.58	627.3	5
A-76	1.67	667.5	7
A-77	1.59	647.5	7
A-79	1.71	582.5	7
A-80	1.72	582.5	7
A-81	1.57	604.5	7
A-82	1.61	604.4	7
A-83	1.76	596.5	7
A-84	1.78	596.5	7
A-85	1.90	678.5	7
A-86	1.90	678.5	7
A-87	1.83	648.4	7
A-88	1.77	628.5	7
A-89	1.75	626.5	7
A-90	1.74	626.5	7
A-91	1.62	627.5	8
A-92	1.62	627.3	8
A-93	1.65	667.4	7
A-94	1.67	667.4	7
A-95	1.58	647.3	7
A-96	1.61	647.5	7
A-97	1.64	612.5	5
A-98	1.62	612.5	5
A-99	1.59	653.2	5
A-100	1.58	653.3	5
A-101	1.51	633.5	5
A-102	1.52	633.6	5
A-103	1.55	613.5	5
A-104	1.55	613.6	5
A-105	1.64	612.5	5
A-106	1.66	612.5	5
A-107	1.59	653.2	5
A-108	1.60	653.2	5
A-109	1.51	633.5	5
A-110	1.54	633.5	5

Cmpd No.	R _t	LC/MS	LCMS Method
A-111	1.54	613.6	5
A-112	1.60	613.3	5
A-113	1.62	643.5	7
A-114	1.63	643.5	7
A-115	1.56	687.6	7
A-116	1.56	687.6	7
A-117	1.61	689.5	7
A-118	1.60	689.4	7
A-119	1.91	761.5	7
A-120	1.66	582.3	7
A-121	1.81	657.5	7
A-122	1.80	657.6	7
A-123	1.48	671.5	5
A-124	1.47	671.5	5
A-125	1.36	659.5	7
A-126	1.39	659.5	7
A-127	1.35	659.6	7
A-128	1.38	659.5	7
A-129	1.48	675.5	7
A-130	1.49	675.5	7
A-131	1.44	655.5	7
A-132	1.43	655.5	7
A-133	1.44	691.5	7
A-134	1.46	691.5	7
A-135	1.45	663.5	7
A-136	1.45	663.5	7
A-137	1.40	643.5	7
A-138	1.42	643.5	7
A-139	2.03	655.5	10
B-2	1.74	626.4	7
B-3	1.56	625.4	7
B-4	1.50	626.4	7
D-1	2.32	636.4	10
D-2	1.64	622.4	7
D-3	1.62	675.4	7
D-4	1.61	652.4	7
D-5	1.59	610.4	7
D-6	1.64	666.4	7
D-7	1.62	666.4	7
D-8a	1.651	666.5	7
D-8b	1.650	666.5	7
D-9	1.70	603.5	7
D-10	1.73	602.5	7
D-11	1.83	586.5	7

Cmpd No.	R _t	LC/MS	LCMS Method
D-12	1.24	604.2	4
D-13	2.29	657.3	4
D-14	1.76	675.5	7
D-15	2.19	677.4	10
D-16	1.91	761.5	5
D-17	1.76	596.6	7
D-18	1.84	610.6	7
D-19	1.78	596.6	7
E-1	2.35	715.5	7
E-2	2.54	743.5	7
E-3	2.27	717.5	7
F-1	2.23	799.5	7
G-1	1.58	661.5	5
H-1	1.71	703.5	5
I-1	1.61	657.5	7
J-1	1.67	620.4	7
J-2	1.64	600.5	7
J-3	1.77	650.4	7
J-4	1.77	650.5	7
K-1a	1.46	661.6	7
K-1b	1.55	661.6	7
L-1a	1.42	673.5	7
L-1b	1.43	673.5	7
M-1a	1.44	673.5	7
M-1b	1.44	673.5	7
M-2a	1.45	620.1	7
M-2b	1.45	620.1	7
M-3a	1.40	661.5	7
M-3b	1.42	661.5	7

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

Example B

Nuclear magnetic resonance spectroscopy

[0377] For a number of compounds, ¹H NMR spectra were recorded on a Bruker DPX-360 operating a 360 MHz, on a Bruker Avance 600 operating at 600 z, on a Bruker Avance 400 operating at 400 MHz, or on a Varian 400MR spectrometer operating at 400MHz. As solvents CHLOROFORM-*d*₃ (deuterated chloroform, CDC1₃) and/or DMSO-*d*₆ (deuterated DMSO, dimethyl-*d*₆ sulfoxide) were used. Chemical shifts (δ) are reported in parts per million (ppm) relative to tetramethylsilane (TMS), which was used as internal standard.

[0378] **Compound A-1:** $^1\text{H-NMR}$ (400 MHz, CHCl_3) δ = 11.48 (s, 1H), 8.57 (dd, J = 1.4, 8.3 Hz, 1H), 8.53 (s, 1H), 7.63 (d, J = 7.9 Hz, 1H), 7.39 (td, J = 7.8, 15.4 Hz, 2H), 7.29 (br d, J = 1.6 Hz, 1H), 7.21 (br s, 1H), 7.09 (dd, J = 1.3, 7.6 Hz, 1H), 4.62-4.31 (m, 1H), 4.05 (s, 3H), 3.90 (br dd, J = 3.6, 6.8 Hz, 1H), 3.59 (s, 3H), 3.46 (s, 3H), 3.31-3.12 (m, 1H), 3.07-2.96 (m, 1H), 2.94-2.83 (m, 1H), 2.77-2.60 (m, 1H), 2.38 (br t, J = 8.1 Hz, 3H), 2.33-2.25 (m, 1H), 2.15-2.01 (m, 1H), 1.85-1.73 (m, 2H).

[0379] **Compound A-2:** $^1\text{H-NMR}$ (400 MHz, CHCl_3) δ = 10.92 (br d, J = 4.6 Hz, 1H), 8.61-8.51 (m, 1H), 8.22 (br d, J = 8.0 Hz, 1H), 7.59 (ddd, J = 1.5, 4.4, 7.5 Hz, 1H), 7.40 (br t, J = 7.3 Hz, 1H), 7.36-7.27 (m, 2H), 7.21 (d, J = 7.6 Hz, 1H), 7.03 (d, J = 7.5 Hz, 1H), 6.98-6.64 (m, 1H), 5.33-4.38 (m, 1H), 4.13-3.93 (m, 4H), 3.64-3.58 (m, 3H), 3.45 (s, 3H), 3.28-3.19 (m, 1H), 3.03 (br d, J = 12.8 Hz, 1H), 2.94-2.86 (m, 1H), 2.76-2.66 (m, 1H), 2.44 (br d, J = 6.6 Hz, 1H), 2.39-2.34 (m, 2H), 2.30 (br dd, J = 6.4, 13.8 Hz, 2H), 2.22-2.17 (m, 4H), 1.78-1.73 (m, 1H).

[0380] **Compound A-71:** $^1\text{H-NMR}$ (400 MHz, CHCl_3) δ = 11.43 (s, 1H), 8.66 (d, J = 8.3 Hz, 1H), 8.00 (s, 1H), 7.63 (br d, J = 8.1 Hz, 1H), 7.49-7.39 (m, 2H), 7.37-7.29 (m, 2H), 7.14 (d, J = 7.5 Hz, 1H), 4.72-4.48 (m, 2H), 4.40-4.03 (m, 9H), 3.94-3.62 (m, 5H), 3.49 (s, 3H), 3.02-2.92 (m, 1H), 2.63-2.29 (m, 2H), 1.92-1.85 (m, 3H).

[0381] **Compound A-87:** $^1\text{H-NMR}$ (400 MHz, CHCl_3) δ = 12.24 (s, 1H), 8.64 (dd, J = 1.4, 8.3 Hz, 1H), 8.33 (d, J = 4.1 Hz, 1H), 8.06 (d, J = 4.3 Hz, 1H), 7.63 (ddd, J = 1.7, 6.1, 7.7 Hz, 1H), 7.43-7.40 (m, 1H), 7.39-7.37 (m, 1H), 7.31-7.28 (m, 1H), 7.19 (d, J = 5.1 Hz, 1H), 7.14-7.10 (m, 1H), 4.18 (dq, J = 0.8, 7.1 Hz, 2H), 4.05 (br d, J = 6.0 Hz, 1H), 4.01 (d, J = 1.4 Hz, 3H), 3.97 (s, 3H), 3.68 (br dd, J = 7.3, 14.9 Hz, 2H), 3.58 (br t, J = 6.9 Hz, 1H), 3.46 (br t, J = 7.2 Hz, 1H), 3.34-3.27 (m, 1H), 3.17-3.09 (m, 1H), 2.84-2.76 (m, 1H), 2.14-2.06 (m, 1H), 2.02-1.95 (m, 1H), 1.29 (dt, J = 0.9, 7.1 Hz, 3H).

[0382] **Compound A-126:** $^1\text{H-NMR}$ (400 MHz, CHCl_3) δ = 10.91 (s, 1H), 8.54 (s, 1H), 8.22 (d, J = 8.0 Hz, 1H), 7.56 (br d, J = 7.4 Hz, 1H), 7.39 (t, J = 7.6 Hz, 1H), 7.34-7.28 (m, 2H), 7.19 (s, 1H), 7.03 (br d, J = 7.5 Hz, 1H), 6.34 (br s, 1H), 4.49-4.42 (m, 1H), 4.25 (br d, J = 3.9 Hz, 1H), 4.06 (s, 3H), 3.94 (br d, J = 4.0 Hz, 1H), 3.59 (s, 3H), 3.45 (s, 3H), 3.09-3.03 (m, 3H), 2.75 (br dd, J = 7.9, 12.2 Hz, 1H), 2.44-2.39 (m, 2H), 2.37-2.30 (m, 2H), 2.19 (s, 3H), 1.91-1.85 (m, 1H).

[0383] **Compound A-129:** $^1\text{H-NMR}$ (400 MHz, CHCl_3) δ = 11.48 (s, 1H), 8.59-8.52 (m, 2H), 8.26 (s, 1H), 7.67-7.61 (m, 1H), 7.45-7.35 (m, 2H), 7.32-7.28 (m, 1H), 7.22 (s, 1H), 7.11-7.06 (m, 1H), 5.87 (br s, 1H), 4.25 (br d, J = 7.0 Hz, 1H), 4.02 (d, J = 1.4 Hz, 3H), 3.88 (br t, J = 7.8 Hz, 1H), 3.81-3.75 (m, 1H), 3.67-3.58 (m, 7H), 3.45 (s, 3H), 3.19 (br d, J = 8.5 Hz, 1H), 2.86-2.79 (m, 1H), 2.55 (d, J = 2.6 Hz, 2H), 2.28-2.18 (m, 1H), 2.11 (br d, J = 7.4 Hz, 1H).

[0384] **Compound A-130:** $^1\text{H-NMR}$ (400 MHz, CHCl_3) δ = 11.48 (s, 1H), 8.60-8.47 (m, 2H), 8.26 (s, 1H), 7.63 (ddd, J = 1.6, 3.3, 7.7 Hz, 1H), 7.40 (td, J = 7.9, 17.0 Hz, 2H), 7.30 (d, J = 1.5 Hz, 1H), 7.22 (s, 1H), 7.09 (ddd, J = 1.4, 3.0, 7.5 Hz, 1H), 5.72 (br s, 1H), 4.20 (br d, J = 6.9 Hz, 1H), 4.02 (d, J = 1.3 Hz, 3H), 3.81 (br t, J = 6.4 Hz, 1H), 3.77-3.71 (m, 1H), 3.66-3.53 (m, 6H), 3.46 (s, 3H), 3.26-3.15 (m, 1H), 2.86-2.78 (m, 1H), 2.55 (d, J = 1.5 Hz, 2H), 2.20-2.17 (m, 1H), 2.10-2.05 (m, 1H).

[0385] **Compound A-131:** $^1\text{H-NMR}$ (400 MHz, CHCl_3) δ = 10.91 (s, 1H), 8.54 (s, 1H), 8.22 (d, J = 8.0 Hz, 1H), 7.59 (td, J = 2.0, 7.6 Hz, 1H), 7.40 (t, J = 7.6 Hz, 1H), 7.34-7.28 (m, 2H), 7.21 (d, J = 3.8 Hz, 1H), 7.03 (br d, J = 7.6 Hz, 1H), 5.72 (s, 1H), 4.27 (br d, J = 5.6 Hz, 1H), 4.03 (s, 3H), 3.91 (br d, J = 6.6 Hz, 1H), 3.85-3.77 (m, 1H), 3.71-3.56 (m, 7H), 3.45 (s, 3H), 3.29-3.18 (m, 1H), 2.97 (s, 1H), 2.89 (s, 1H), 2.88-2.81 (m, 1H), 2.56 (s, 2H), 2.23-2.18 (m, 4H).

[0386] **Compound A-132:** $^1\text{H-NMR}$ (400 MHz, CHCl_3) δ = 10.91 (s, 1H), 8.55 (s, 1H), 8.22 (d, J = 8.0 Hz, 1H), 7.59 (td, J = 1.9, 7.6 Hz, 1H), 7.43-7.36 (m, 1H), 7.34-7.29 (m, 1H), 7.26-7.24 (m, 1H), 7.21 (d, J = 3.4 Hz, 1H), 7.05-7.00 (m, 1H), 5.88 (s, 1H), 4.24 (br d, J = 7.0 Hz, 1H), 4.02 (s, 3H), 3.87 (br t, J = 6.8 Hz, 1H), 3.78 (br dd, J = 4.6, 8.3 Hz, 1H), 3.67-3.57 (m, 7H), 3.45 (s, 3H), 3.23-3.17 (m, 1H), 2.86-2.78 (m, 1H), 2.55 (s, 2H), 2.19 (d, J = 3.1 Hz, 4H), 2.14-2.05 (m, 1H).

[0387] **Compound A-135:** $^1\text{H-NMR}$ (400 MHz, CHCl_3) δ = 11.49 (s, 1H), 8.61-8.49 (m, 2H), 7.63 (br d, J = 7.6 Hz, 1H), 7.44-7.34 (m, 2H), 7.32-7.29 (m, 1H), 7.24 (br s, 1H), 7.08 (br d, J = 7.5 Hz, 1H), 6.03 (br s, 1H), 4.65 (br d, J = 2.3 Hz, 1H), 4.08-3.99 (m, 3H), 3.71-3.63 (m, 1H), 3.59 (s, 3H), 3.45 (s, 3H), 3.36-3.25 (m, 2H), 3.03-2.88 (m, 4H), 2.62-2.47 (m, 3H), 2.19-2.13 (m, 2H).

[0388] **Compound A-136:** $^1\text{H-NMR}$ (400 MHz, CHCl_3) δ = 11.49 (s, 1H), 8.81-8.38 (m, 2H), 7.63 (br d, J = 7.5 Hz, 1H), 7.40 (td, J = 7.8, 19.1 Hz, 2H), 7.31

(br s, 1H), 7.24 (br s, 1H), 7.09 (br d, $J = 7.6$ Hz, 1H), 6.06 (br s, 1H), 4.74 (br d, $J = 3.8$ Hz, 1H), 4.11-3.99 (m, 3H), 3.71-3.57 (m, 4H), 3.46 (s, 3H), 3.42-3.28 (m, 2H), 3.11-2.99 (m, 2H), 2.99-2.88 (m, 2H), 2.65-2.47 (m, 3H), 2.24-2.18 (m, 2H).

[0389] **Compound A-137:** $^1\text{H-NMR}$ (400 MHz, CHCl_3) $\delta = 10.91$ (s, 1H), 8.55 (s, 1H), 8.22 (br d, $J = 8.1$ Hz, 1H), 7.59 (br d, $J = 6.9$ Hz, 1H), 7.40 (t, $J = 7.6$ Hz, 1H), 7.34-7.30 (m, 1H), 7.26-7.24 (m, 1H), 7.22 (s, 1H), 7.06-7.00 (m, 1H), 5.96 (br s, 1H), 4.63 (br d, $J = 1.1$ Hz, 1H), 4.10-3.98 (m, 3H), 3.70-3.56 (m, 4H), 3.45 (s, 3H), 3.35-3.20 (m, 2H), 3.02-2.83 (m, 4H), 2.67-2.43 (m, 3H), 2.19 (br d, $J = 1.9$ Hz, 5H).

[0390] **Compound A-138:** $^1\text{H-NMR}$ (400 MHz, CHCl_3) $\delta = 10.91$ (s, 1H), 8.55 (s, 1H), 8.22 (br d, $J = 8.1$ Hz, 1H), 7.59 (br d, $J = 7.1$ Hz, 1H), 7.40 (br t, $J = 7.3$ Hz, 1H), 7.34-7.29 (m, 2H), 7.24 (br s, 1H), 7.06-7.00 (m, 1H), 6.03 (br s, 1H), 4.70 (br d, $J = 2.3$ Hz, 1H), 4.11-3.98 (m, 3H), 3.71-3.55 (m, 4H), 3.45 (s, 3H), 3.40-3.25 (m, 2H), 3.08-2.85 (m, 4H), 2.65-2.45 (m, 3H), 2.19 (br d, $J = 2.8$ Hz, 5H).

[0391] **Compound 139:** $^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$) $\delta = 11.06$ (d, $J = 2.9$ Hz, 1H), 8.75 (s, 1H), 8.25 (d, $J = 8.3$ Hz, 1H), 8.13 (s, 1H), 8.10 (s, 1H), 7.62-7.57 (m, 1H), 7.51 (t, $J = 7.6$ Hz, 1H), 7.37-7.29 (m, 2H), 7.19 (s, 1H), 6.98 (dd, $J = 3.4, 7.3$ Hz, 1H), 3.90 (s, 4H), 3.50 (s, 4H), 3.27 (s, 3H), 3.25 (br s, 2H), 3.19-3.16 (m, 1H), 3.03-2.96 (m, 1H), 2.77 (br dd, $J = 7.8, 17.2$ Hz, 1H), 2.19-2.11 (m, 4H), 2.09 (d, $J = 6.4$ Hz, 3H), 2.02 (br dd, $J = 7.8, 13.9$ Hz, 1H), 1.91-1.85 (m, 1H).

[0392] **Compound J-1:** $^1\text{H-NMR}$ (400 MHz, CHCl_3) $\delta = 12.23$ (d, $J = 4.0$ Hz, 1H), 8.64 (dd, $J = 1.4, 8.3$ Hz, 1H), 8.33 (d, $J = 4.3$ Hz, 1H), 8.06 (d, $J = 4.1$ Hz, 1H), 7.65 (dd, $J = 1.7, 7.7$ Hz, 1H), 7.44-7.37 (m, 2H), 7.35-7.27 (m, 2H), 7.25 (d, $J = 2.4$ Hz, 1H), 7.11 (td, $J = 1.3, 7.6$ Hz, 1H), 4.57 (br d, $J = 7.5$ Hz, 2H), 4.28 (br s, 1H), 4.25-4.19 (m, 1H), 4.11 (br t, $J = 9.4$ Hz, 1H), 4.02 (d, $J = 3.4$ Hz, 3H), 3.97 (s, 3H), 3.48 (br dd, $J = 8.7, 16.1$ Hz, 1H), 3.17 (br s, 1H), 2.93-2.85 (m, 1H), 2.62-2.51 (m, 1H), 2.37-2.27 (m, 1H).

[0393] **Compound H-1:** $^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$) $\delta = 11.62$ (d, $J = 2.9$ Hz, 1H), 8.79 (s, 1H), 8.57 (dd, $J = 1.3, 8.3$ Hz, 1H), 8.17 (s, 1H), 7.64 (d, $J = 7.6$ Hz, 1H), 7.55-7.45 (m, 2H), 7.40 (dd, $J = 1.5, 7.5$ Hz, 1H), 7.19 (s, 1H), 7.14 (ddd, $J = 1.4, 3.4, 7.6$ Hz, 1H), 3.95-3.87 (m, 4H), 3.50 (br s, 1H), 3.51 (s, 4H), 3.34-3.32 (m, 2H), 3.27 (s, 3H), 3.25-3.23 (m, 1H), 3.18-3.06 (m, 3H), 3.02-2.95 (m, 1H), 2.76 (br dd, $J = 8.6, 16.8$ Hz, 1H), 2.05-1.95 (m, 2H), 1.93-1.86 (m, 5H).

[0394] **Compound L-1a:** ^1H -NMR (400 MHz, $\text{DMSO-}d_6$) δ = 10.99 (s, 1H), 8.75 (s, 1H), 8.20 (dd, J = 5.4, 9.0 Hz, 1H), 8.11 (s, 1H), 7.66 (br d, J = 7.5 Hz, 1H), 7.55 (t, J = 7.6 Hz, 1H), 7.39 (br d, J = 7.4 Hz, 1H), 7.25-7.18 (m, 2H), 3.90 (s, 3H), 3.87 (br d, J = 6.5 Hz, 1H), 3.50 (s, 3H), 3.27 (br s, 4H), 3.21-3.20 (m, 1H), 3.14 (br d, J = 6.8 Hz, 1H), 3.09-2.94 (m, 2H), 2.77 (br dd, J = 8.1, 16.8 Hz, 1H), 2.15 (br dd, J = 5.4, 10.9 Hz, 4H), 2.04 (s, 3H), 1.99 (br s, 1H), 1.91-1.85 (m, 1H).

[0395] **Compound L-1b:** ^1H -NMR (400 MHz, $\text{DMSO-}d_6$) δ = 11.00 (s, 1H), 8.75 (s, 1H), 8.20 (dd, J = 5.6, 8.8 Hz, 1H), 8.11 (s, 1H), 7.65 (br d, J = 7.3 Hz, 1H), 7.55 (t, J = 7.6 Hz, 1H), 7.42-7.35 (m, 1H), 7.24-7.19 (m, 2H), 3.90 (s, 3H), 3.86 (br d, J = 6.5 Hz, 1H), 3.50 (s, 3H), 3.27 (br s, 4H), 3.21 (br s, 1H), 3.14 (br d, J = 6.9 Hz, 1H), 2.98 (br d, J = 8.8 Hz, 2H), 2.77 (br dd, J = 8.9, 16.2 Hz, 1H), 2.19-2.11 (m, 4H), 2.06 (s, 3H), 1.99 (br d, J = 6.4 Hz, 1H), 1.89 (br d, J = 7.3 Hz, 1H).

[0396] **Compound M-2a:** ^1H -NMR (400 MHz, $\text{CHLOROFORM-}d_3$) δ = 10.94 (s, 1H), 8.54 (s, 1H), 8.29 (br d, J = 8.1 Hz, 1H), 7.62 (dd, J = 6.1, 8.5 Hz, 1H), 7.38-7.37 (m, 1H), 7.38-7.33 (m, 1H), 7.22-7.17 (m, 2H), 7.04 (br d, J = 7.5 Hz, 1H), 4.42 (br s, 1H), 4.27 (br s, 1H), 4.30-4.21 (m, 1H), 4.08-3.97 (m, 4H), 3.91-3.79 (m, 1H), 3.71-3.63 (m, 1H), 3.59 (s, 3H), 3.45 (s, 4H), 3.33-3.25 (m, 1H), 2.85 (br dd, J = 8.5, 16.9 Hz, 1H), 2.28-2.21 (m, 1H), 2.19 (s, 3H), 2.14-2.04 (m, 2H).

[0397] **Compound M-2b:** ^1H -NMR (400 MHz, $\text{CHLOROFORM-}d_3$) δ = 10.94 (s, 1H), 8.54 (s, 1H), 8.30 (d, J = 7.9 Hz, 1H), 7.62 (dd, J = 6.1, 8.6 Hz, 1H), 7.35 (br t, J = 8.0 Hz, 2H), 7.21 (br s, 1H), 7.05-7.00 (m, 1H), 4.76-4.54 (m, 2H), 4.53-4.40 (m, 1H), 4.29-4.15 (m, 2H), 4.13-3.99 (m, 4H), 3.98-3.87 (m, 1H), 3.59 (s, 3H), 3.46 (s, 3H), 2.94 (br dd, J = 8.3, 17.0 Hz, 1H), 2.48-2.24 (m, 3H), 2.19 (s, 3H).

[0398] **Compound M-3a:** ^1H -NMR (400 MHz, $\text{CHLOROFORM-}d_3$) δ = 10.95 (s, 1H), 8.63-8.51 (m, 1H), 8.29 (br d, J = 7.6 Hz, 1H), 7.61 (dd, J = 6.1, 8.5 Hz, 1H), 7.36 (t, J = 7.8 Hz, 1H), 7.21-7.14 (m, 2H), 7.07-7.00 (m, 1H), 6.69 (br s, 1H), 4.47 (br dd, J = 4.1, 7.3 Hz, 1H), 4.03 (s, 3H), 3.95 (br d, J = 6.9 Hz, 1H), 3.60 (s, 3H), 3.45 (s, 3H), 3.17 (td, J = 7.8, 15.8 Hz, 1H), 2.99 (br dd, J = 3.1, 12.1 Hz, 1H), 2.94-2.82 (m, 1H), 2.65 (br dd, J = 9.3, 11.9 Hz, 1H), 2.46-2.25 (m, 6H), 2.19 (s, 3H), 1.82-1.72 (m, 1H).

[0399] **Compound M-3b:** ^1H -NMR (400 MHz, $\text{CHLOROFORM-}d_3$) δ = 10.94 (s, 1H), 9.84-9.55 (m, 1H), 8.55 (s, 1H), 8.29 (br d, J = 8.1 Hz, 1H), 8.14-7.95 (m, 1H), 7.77-

7.57 (m, 1H), 7.34 (t, J = 7.9 Hz, 1H), 7.26-7.11 (m, 2H), 7.07-6.99 (m, 1H), 4.96-4.74 (m, 1H), 4.46-3.88 (m, 4H), 3.59 (s, 4H), 3.45 (d, J = 3.6 Hz, 3H), 3.30-2.89 (m, 3H), 2.78-2.12 (m, 7H), 2.10-1.80 (m, 1H).

Example C PDL1/PD1 Binding Assay

[0400] 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 room temperature. 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 room temperature, Anti-6xHis Acceptor beads (final concentration 20 ug/ml) were added to the wells, and the incubation continued for 1 h. Streptavidin Donor beads (final concentration 20 ug/mL) were added at reduced light. The plates were sealed with foil and incubated in the dark for additional 1 h or overnight before reading on an Envision reader. The IC₅₀ values were determined by fitting the curves using a four-parameter equation in Graphpad Prism 8.

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

[0401] 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.

[0402] 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 hrs 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.

[0403] Compounds described herein, as exemplified in the Examples, showed EC₅₀ or IC₅₀ values in the following ranges: A: IC₅₀ or EC₅₀ ≤ 10 nM; B: 10 nM < IC₅₀ or EC₅₀ ≤ 100 nM; C: 100 nM < IC₅₀ or EC₅₀ ≤ 1000 nM; D: 1000 nM < IC₅₀ or EC₅₀ ≤ 10000 nM; E: IC₅₀ or EC₅₀ > 10000 nM; F: IC₅₀ or EC₅₀ > 5000 nM; n.d. = not determined; n.r. = EC₅₀ not reached in the range of tested concentrations starting from 1 nM to 10000 nM.

Table C:

Cmpd No.	PD-1/PD-L1 PPI IC ₅₀	Jurkat NFAT EC ₅₀	Cmpd No.	PD-1/PD-L1 PPI IC ₅₀	Jurkat NFAT EC ₅₀
A-1	A	A	A-28	A	A
B-1	A	B	A-29	A	A
C-1	A	B	A-30	A	C
A-2	A	A	A-31	A	D
A-3	A	A	A-32	A	n.r.
A-4	A	A	A-33	A	A
A-5	A	A	A-34	A	n.r.
A-6	A	B	A-35	A	n.r.
A-7	A	A	A-36	A	n.r.
A-8	A	A	A-37	A	n.r.
A-9		B	A-38	A	n.r.
A-10	A	n.r.	A-39	A	A
A-11	A	n.r.	A-40	A	A
A-12	A	n.r.	A-41	A	A
A-13	A	n.r.	A-42	A	B
A-14	A	n.r.	A-43	A	A
A-15	A	n.r.	A-44	A	B
A-16	A	n.r.	A-45	A	B
A-17	A	C	A-46	A	A
A-18	A	A	A-47	A	A
A-19	A	B	A-48		C
A-20	A	B	A-49	A	B
A-21	A	C	A-50		B
A-22	A	A	A-51	A	A
A-23	A	A	A-52	A	B
A-24	A	n.r.	A-53	A	C
A-25	A	A	A-54	A	B
A-26	A	n.r.	A-55	A	A
A-27	A	A	A-56	A	B

Cmpd No.	PD-1/PD-L1 PPI IC ₅₀	Jurkat NFAT EC ₅₀	Cmpd No.	PD-1/PD-L1 PPI IC ₅₀	Jurkat NFAT EC ₅₀
A-57	A	A	A-97	B	D
A-58	A	A	A-98	A	C
A-59	A	B	A-99	A	C
A-60	A	A	A-100	A	A
A-61	A	B	A-101	A	F
A-62	A	A	A-102	A	A
A-63	A	A	A-103	B	F
A-64	A	A	A-104	A	B
A-65	A	A	A-105	B	B
A-66	A	B	A-106	A	C
A-67	A	A	A-107	A	A
A-68	A	B	A-108	A	C
A-69	A	A	A-109	A	A
A-70	A	B	A-110	A	C
A-71		A	A-111	A	B
A-72	A	B	A-112	A	D
A-73		B	A-113	B	D
A-74	A	B	A-114	A	A
A-75	A	B	A-115	A	B
A-76		A	A-116	A	D
A-77		A	A-117	A	B
A-79	B	F	A-118	A	B
A-80	A	B	A-119	A	C
A-81		B	A-120	A	B
A-82		B	A-121	A	B
A-83	A	B	A-122	A	C
A-84	B	F	A-123		F
A-85	A	B	A-124		D
A-86	C	F	A-125	A	F
A-87	A	B	A-126	A	B
A-88	A	B	A-127	A	C
A-89	B	D	A-128	A	C
A-90	A	B	A-129	A	A
A-91	A	D	A-130	A	B
A-92	A	B	A-131	A	A
A-93	A	C	A-132	A	C
A-94	A	A	A-133	B	C
A-95	A	C	A-134	A	A
A-96	A	A	A-135	A	C

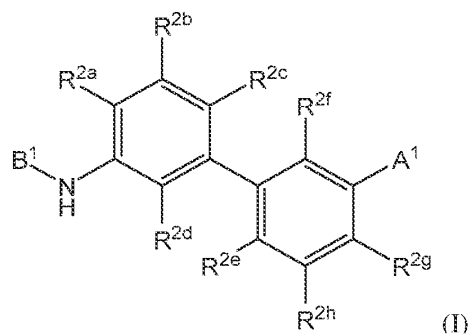
Cmpd No.	PD-1/PD-L1 PPI IC ₅₀	Jurkat NFAT EC ₅₀
A-136	A	A
A-137	A	D
A-138		A
A-139		A
B-2	A	B
B-3	A	C
B-4	A	B
D-1	A	A
D-2	A	A
D-3	A	A
D-4	A	B
D-5	A	B
D-6	A	B
D-7	A	B
D-8a		B
D-8b		B
D-9	A	B
D-10	A	B
D-11	A	B
D-12		B
D-13		B
D-14		A
D-15	A	B
D-16	B	C

Cmpd No.	PD-1/PD-L1 PPI IC ₅₀	Jurkat NFAT EC ₅₀
D-17	A	B
D-18	A	B
D-19	A	C
E-1	A	n.r
E-2	A	E
E-3	A	E
F-1	A	
G-1	A	B
H-1	A	A
I-1		A
J-1	A	A
J-2	A	A
J-3	A	A
J-4	A	C
K-1a	A	B
K-1b	A	C
L-1a		C
L-1b		A
M-1a		C
M-1b		A
M-2a		C
M-2b		A
M-3a		A

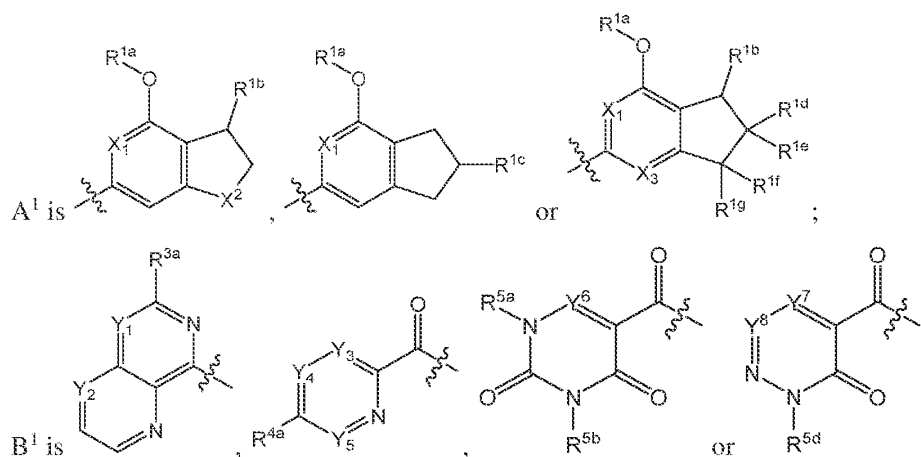
[0404] Although the foregoing has been described in some detail by way of illustrations and examples for purposes of clarity and understanding, it will be understood by those of skill in the art that numerous and various modifications can be made without departing from the spirit of the present disclosure. 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:



wherein:



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

X^2 is O;

X^3 is selected from the group consisting of CH, C-halo and N;

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

Y^2 is selected from the group consisting of N and CH;

Y^3 is selected from the group consisting of N and CH;

Y^4 is selected from the group consisting of N and CH;

Y^5 is selected from the group consisting of N, CH and C-OCH₃;

Y^6 is selected from the group consisting of N and CR^{5c};

Y^7 is CR^{5c};

Y^8 is CR^{5f} ;

each 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(C_{1-4} alkoxy), $-C_{2-4}$ alkyl (C_{1-4} haloalkoxy), $-CH_2(4-6$ membered monocyclic heterocyclyl) and $-CH_2(5-6$ membered monocyclic heteroaryl);

each R^{1b} is selected from the group consisting of $-N(R^{m1})R^{n1}$ and $-R^{x1}$;

R^{1d} is selected from the group consisting of hydrogen, $-CH_3$, $-CH_2CH_3$, $-OH$, $-OCH_3$ and $-F$;

R^{1e} is selected from the group consisting of hydrogen, $-CH_3$, $-CH_2CH_3$ and $-F$;

R^{1f} is selected from the group consisting of hydrogen, $-CH_3$, $-CH_2CH_3$, $-OH$, $-OCH_3$ and $-F$;

R^{1g} is selected from the group consisting of hydrogen, $-CH_3$, $-CH_2CH_3$ and $-F$;

R^{1c} is selected from the group consisting of $-N(R^{m1})R^{n1}$ and $-R^{x1}$;

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 H, $-CH_3$, $-CF_3$ and $-CHF_2$;

R^{4a} is selected from the group consisting of H, halogen, $-C_{1-4}$ alkyl, $-C_{1-4}$ haloalkyl, $-CH_2R^{4b}$ and $-C(CH_3)R^{4b}$;

R^{4b} is selected from the group consisting of $-N(R^{m2})R^{n2}$ and $-R^{y1}$;

R^{5a} is selected from the group consisting of hydrogen, $-CH_3$, $-C_{2-4}$ alkyl and $-C_{2-4}$ haloalkyl;

R^{5b} is selected from the group consisting of hydrogen, $-CH_3$, $-C_{2-4}$ alkyl and $-C_{2-4}$ haloalkyl;

R^{5c} is selected from the group consisting of hydrogen, $-CH_3$, $-C_{2-4}$ alkyl and $-C_{2-4}$ haloalkyl;

R^{5d} is selected from the group consisting of hydrogen, $-CH_3$, $-C_{2-4}$ alkyl and $-C_{2-4}$ haloalkyl;

R^{5e} is selected from the group consisting of hydrogen, halogen and $-CH_3$;

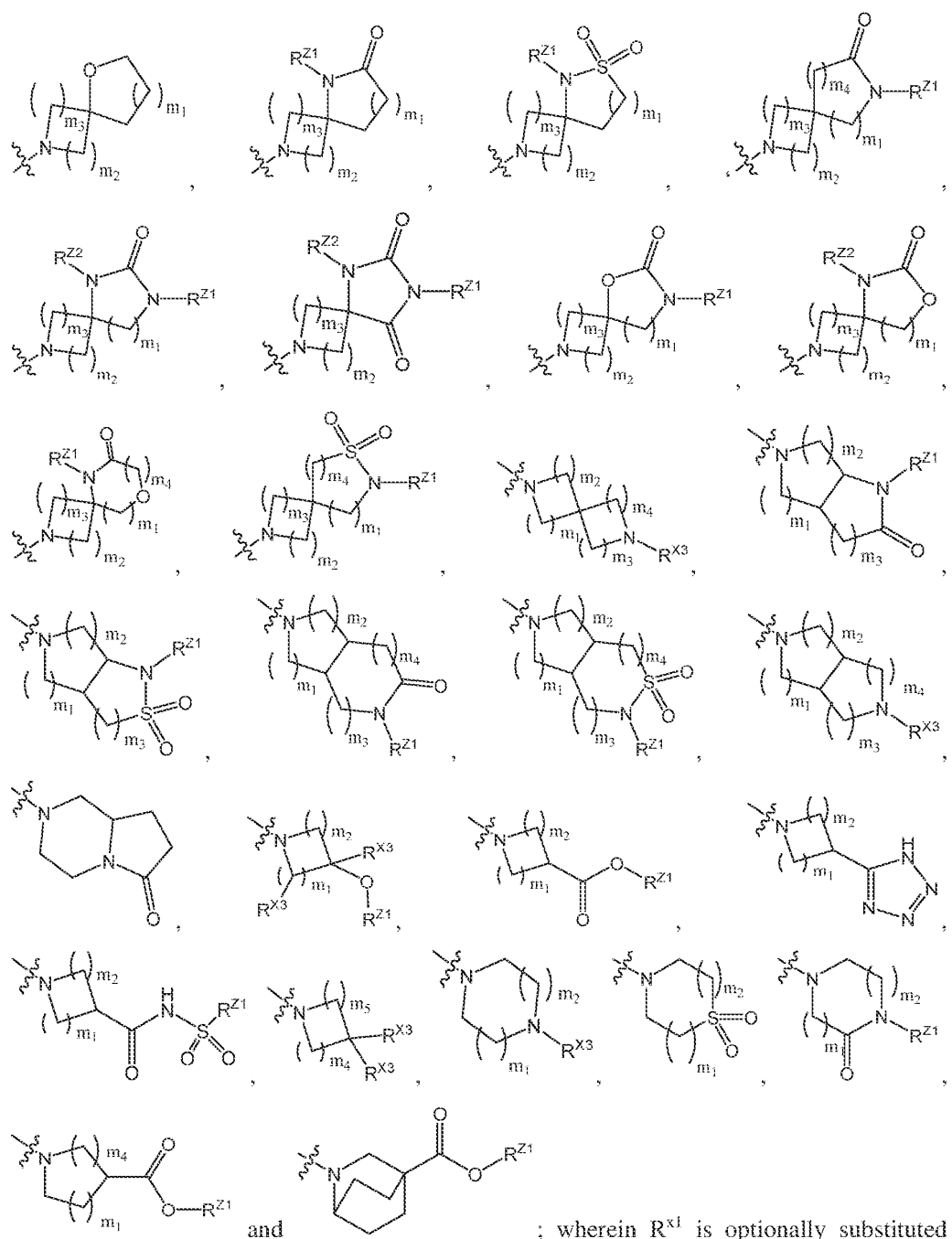
R^{5f} is selected from the group consisting of hydrogen, halogen, $-OH$, $-CN$ and $-CH_3$;

R^{m1} is selected from the group consisting of hydrogen, $-C_{1-4}$ alkyl, C_{3-6} monocyclic cycloalkyl, C_{5-12} bicyclic cycloalkyl, 5- or 6-membered monocyclic heteroaryl, 4-7 membered monocyclic heterocyclyl, 8-11 membered fused-heteroaryl, 8-11 membered fused-heterocyclyl and $-R^{x2}$; wherein the monocyclic heteroaryl, the bicyclic heteroaryl, the monocyclic heterocyclyl and the bicyclic heterocyclyl contain at least one atom or group of atoms independently selected from the group consisting of O (oxygen), S (sulfur), C(=O), S(=O), S(=O)₂ and N (nitrogen); wherein the $-C_{1-4}$ alkyl is optionally substituted with one or two or three substituents independently selected from halogen, cyano, hydroxy, $-C_{1-4}$ alkoxy, $-C_{1-4}$ haloalkyl, $-C_{1-4}$ haloalkoxy, $-C(=O)OR^{Z1}$, $-C(=O)NHS(=O)_2R^{Z3}$, $-C(=O)N(R^{Z1})R^{Z2}$, $-S(=O)_2R^{Z3}$, $-S(=O)_2N(R^{Z1})R^{Z2}$, $-N(R^{Z1})C(=O)R^{Z3}$, $-N(R^{Z1})S(=O)R^{Z3}$, $-N(R^{Z1})C(=O)N(R^{Z2})R^{Z3}$ and $-N(R^{Z1})S(=O)N(R^{Z2})R^{Z3}$; wherein the C_{3-6} monocyclic cycloalkyl, the C_{5-12} bicyclic cycloalkyl, the 5- or 6-membered monocyclic heteroaryl, the 4-7 membered monocyclic heterocyclyl, the 8-11 membered fused-heteroaryl and the 8-11 membered fused-heterocyclyl are optionally substituted with one, two, three or four substituents independently selected from halogen, cyano, $-C_{1-4}$ alkyl, hydroxy, $-C_{1-4}$ alkoxy, $-C_{1-4}$ haloalkyl, $-C_{1-4}$ haloalkoxy, $-C(=O)R^{Z1}$, $-C(=O)OR^{Z1}$, $-C(=O)NHS(=O)_2R^{Z3}$, $-C(=O)N(R^{Z1})R^{Z2}$, $-S(=O)_2R^{Z3}$, $-S(=O)_2N(R^{Z1})R^{Z2}$, $-N(R^{Z1})C(=O)R^{Z3}$, $-N(R^{Z1})S(=O)R^{Z3}$, $-N(R^{Z1})C(=O)N(R^{Z2})R^{Z3}$ and $-N(R^{Z1})S(=O)N(R^{Z2})R^{Z3}$; and R^{n1} is hydrogen, $-C_{1-4}$ alkyl, $-C_{1-4}$ haloalkyl, C_{3-6} monocyclic cycloalkyl(CH₂)– or $-C(=O)OR^{Z4}$;

R^{m2} is selected from the group consisting of $-CH_3$, $-C_{2-4}$ alkyl, $-C_{1-4}$ haloalkyl and $-R^{y2}$, wherein the $-C_{2-4}$ alkyl is optionally substituted with hydroxy;

R^{n2} is selected from the group consisting of H, $-C_{1-4}$ alkyl and $-C_{1-4}$ haloalkyl;

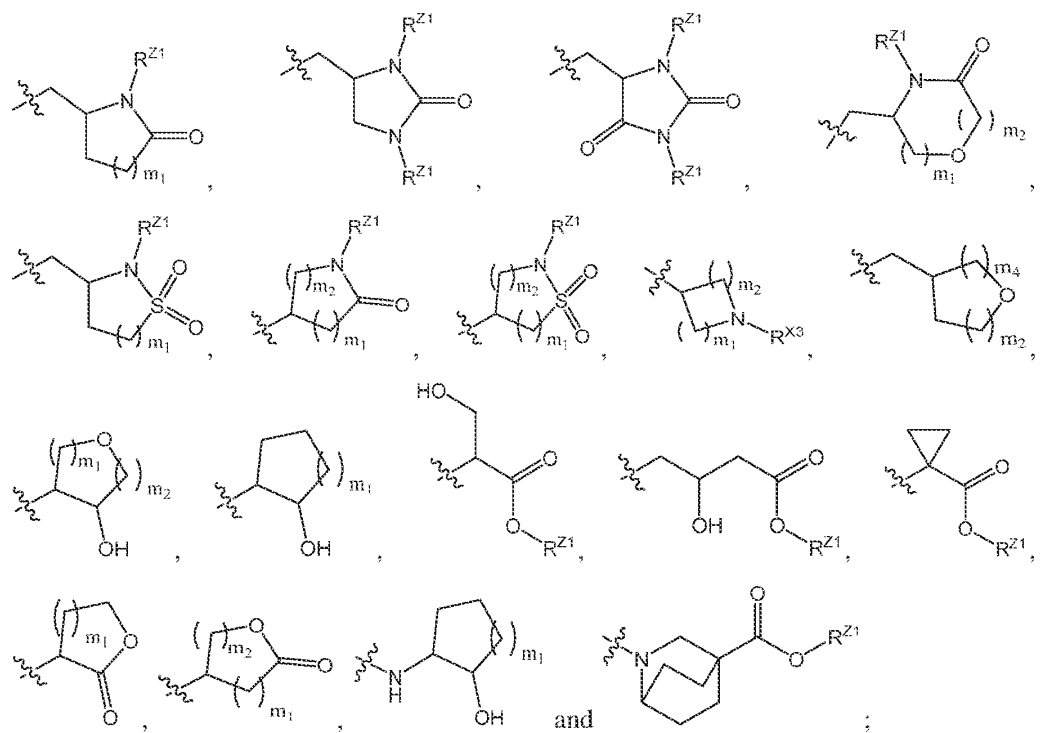
R^{x1} is selected from the group consisting of:



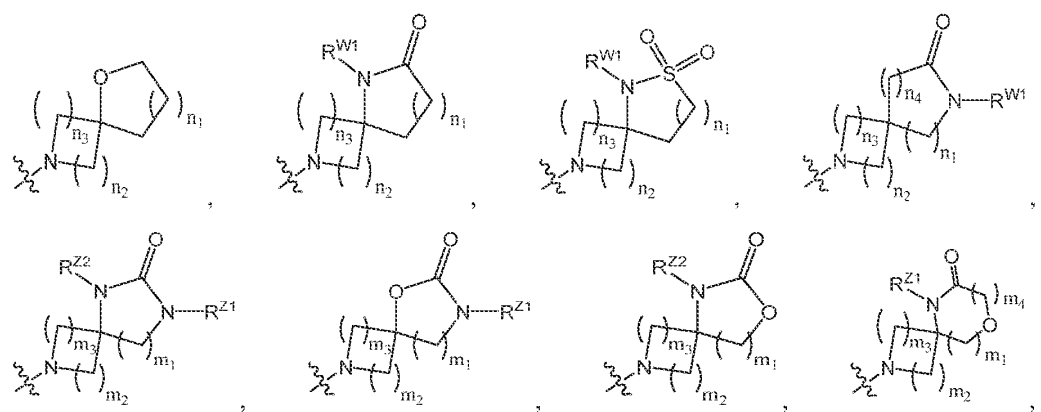
with one or two substituents independently selected from halogen, cyano, $-C_{1-4}$ alkyl, hydroxy, $-C_{1-4}$ alkoxy, $-C_{1-4}$ haloalkyl, $-C_{1-4}$ haloalkoxy, $-C(=O)OR^{Z1}$,

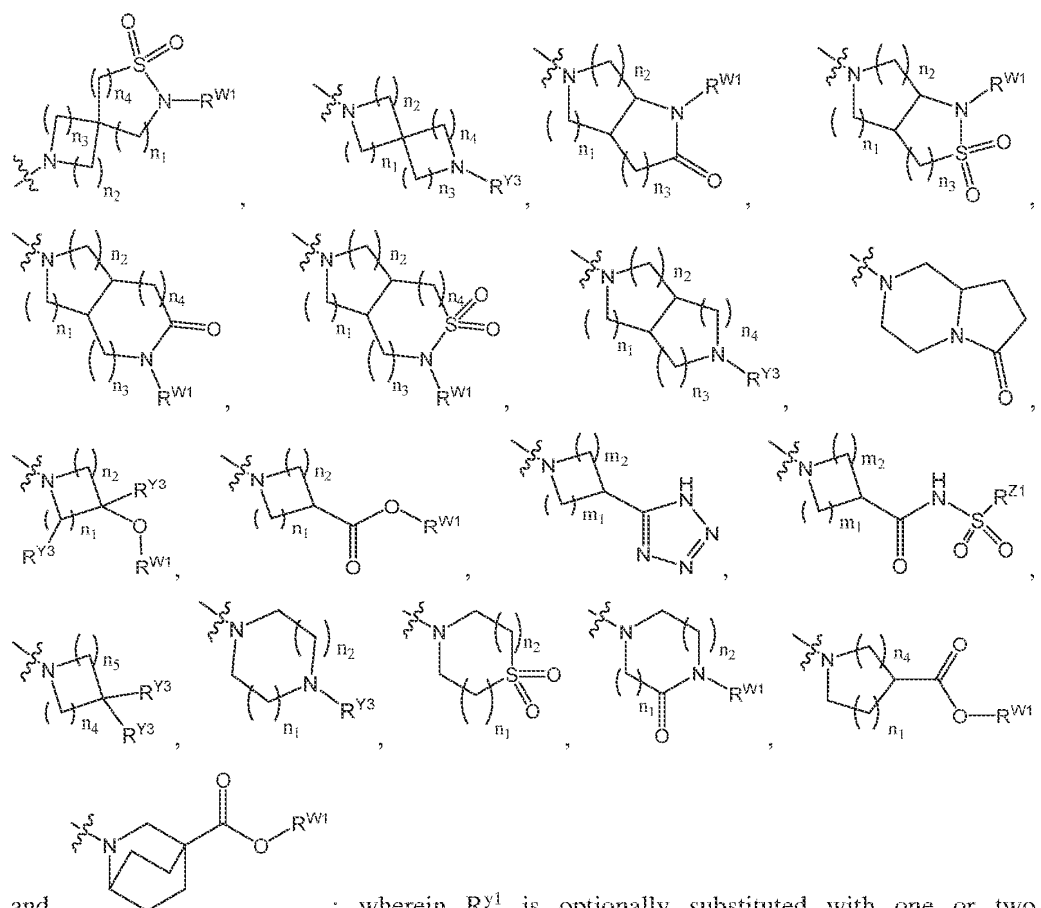
$-\text{C}(=\text{O})\text{NHS}(=\text{O})_2\text{R}^{\text{Z3}}$, $-\text{C}(=\text{O})\text{N}(\text{R}^{\text{Z1}})\text{R}^{\text{Z2}}$, $-\text{S}(=\text{O})_2\text{R}^{\text{Z3}}$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^{\text{Z1}})\text{R}^{\text{Z2}}$,
 $-\text{N}(\text{R}^{\text{Z1}})\text{C}(=\text{O})\text{R}^{\text{Z3}}$, $-\text{N}(\text{R}^{\text{Z1}})\text{S}(=\text{O})\text{R}^{\text{Z3}}$, $-\text{N}(\text{R}^{\text{Z1}})\text{C}(=\text{O})\text{N}(\text{R}^{\text{Z1}})\text{R}^{\text{Z3}}$ and
 $-\text{N}(\text{R}^{\text{Z1}})\text{S}(=\text{O})_2\text{N}(\text{R}^{\text{Z2}})\text{R}^{\text{Z3}}$;

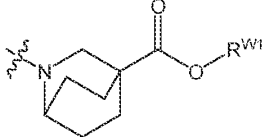
R^{Z2} is selected from the group consisting of:



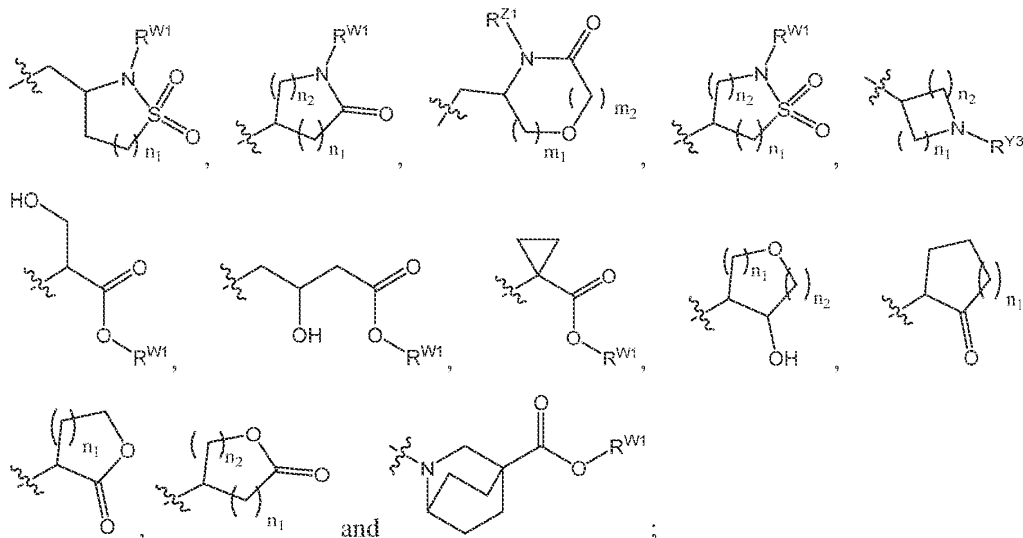
R^{Y1} is selected from the group consisting of:





and  ; wherein R^{Y1} is optionally substituted with one or two substituents independently selected from halogen, cyano, $-C_{1-4}$ alkyl, hydroxy, $-C_{1-4}$ alkoxy, $-C_{1-4}$ haloalkyl, $-C_{1-4}$ haloalkoxy, $-C(=O)OR^{W1}$, $-C(=O)NHS(=O)_2R^{W3}$, $-C(=O)N(R^{W1})R^{W2}$, $-S(=O)_2R^{W3}$, $-S(=O)N(R^{W1})R^{W2}$, $-N(R^{W1})C(=O)R^{W3}$, $-N(R^{W1})S(=O)R^{W3}$, $-N(R^{W1})C(=O)N(R^{W2})R^{W3}$ and $-N(R^{W1})S(=O)N(R^{W2})R^{W3}$;

R^{Y2} is selected from the group consisting of:



m_1, m_2, m_3, n_1, n_2 and n_3 are independently 1 or 2;

m_4 and n_4 are independently 0, 1 or 2;

m_5 and n_5 are independently 1, 2, 3 or 4;

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

each R^{Y3} is independently selected from the group consisting of hydrogen, halogen, $-C_{1-4}$ alkyl, $-C_{1-4}$ haloalkyl, $-C(=O)R^{W3}$, $-C(=O)OR^{W3}$, $-S(=O)_2R^{W3}$, $-C(=O)N(R^{W1})R^{W2}$ and $-S(=O)N(R^{W1})R^{W2}$;

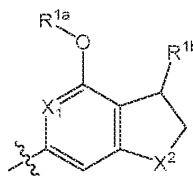
R^{Z1} and R^{Z2} are independently selected from the group consisting of hydrogen, $-C_{1-4}$ alkyl and $-C_{1-4}$ haloalkyl; or

R^{Z1} and R^{Z2} are taken together to form a monocyclic heterocyclyl when attached to the same nitrogen;

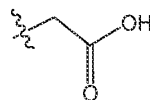
R^{W1} and R^{W2} are independently selected from the group consisting of hydrogen, $-C_{1-4}$ alkyl and $-C_{1-4}$ haloalkyl;

R^{Z3} and R^{W3} are independently selected from the group consisting of hydrogen, $-C_{1-4}$ alkyl and $-C_{1-4}$ haloalkyl; and

R^{Z4} is selected from the group consisting of hydrogen, $-C_{1-4}$ alkyl and 5- to 6-membered monocyclic heterocyclyl(CH_2)-- optionally substituted with $-C_{1-4}$ alkyl.

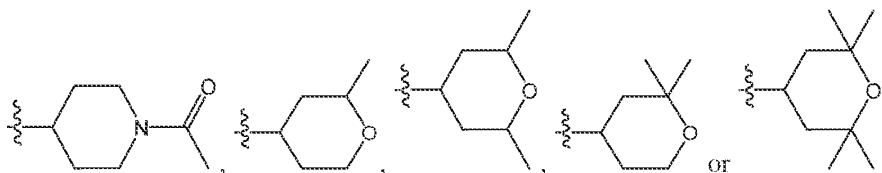
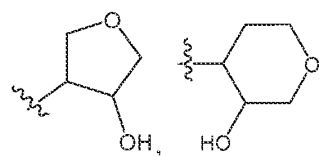


2. The compound of Claim 1, wherein A^1 is
3. The compound of Claim 2, wherein X^1 is CH.
4. The compound of Claim 2, wherein X^1 is N.
5. The compound of any one of Claims 2-4, wherein R^{1a} is $-C_{1-4}$ alkyl.
6. The compound of any one of Claims 2-4, wherein R^{1a} is $-C_{1-4}$ haloalkyl.
7. The compound of any one of Claims 2-4, wherein R^{1a} is $-C_{2-4}$ alkyl(C_{1-4} alkoxy) or $-C_{2-4}$ alkyl (C_{1-4} haloalkoxy).
8. The compound of any one of Claims 2-4, wherein R^{1a} is selected from the group consisting of $-CH_2(C_{3-6}$ monocyclic cycloalkyl), $-CH_2(4-6$ membered monocyclic heterocyclyl) and $-CH_2(5-6$ membered monocyclic heteroaryl).
9. The compound of any one of Claims 2-8, wherein R^{1b} is $-N(R^{m1})R^{n1}$.
10. The compound of Claim 9, wherein R^{n1} is hydrogen.
11. The compound of Claim 9, wherein R^{n1} is $-C(=O)OR^{Z4}$.
12. The compound of any one of Claims 9-11, wherein R^{m1} is $-C_{1-4}$ alkyl optionally substituted with $-C(=O)OR^{Z1}$ or 4-7 membered monocyclic heterocyclyl optionally substituted with hydroxy.

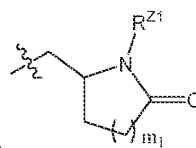


13. The compound of Claim 12, wherein R^{m1} is
14. The compound of Claim 12, wherein R^{m1} is tetrahydrofuran or tetrahydro-2H-pyran, each optionally substituted with hydroxy or C_{1-4} alkyl.

15. The compound of Claim 14, wherein R^{m1} is



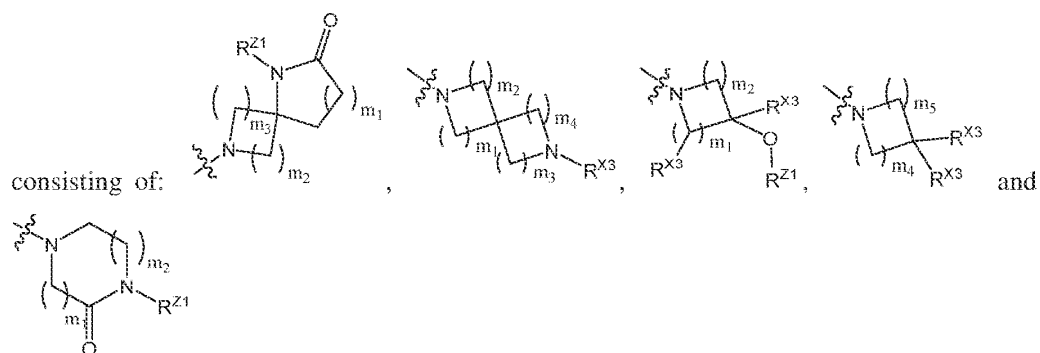
16. The compound of any one of Claims 9-11, wherein R^{m1} is $-R^{x2}$.



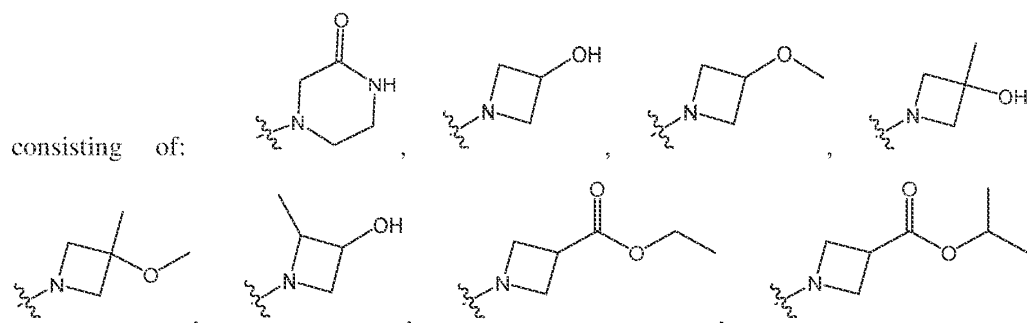
17. The compound of Claim 16, wherein $-R^{x2}$ is

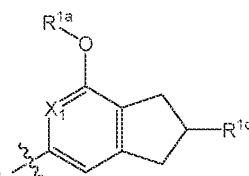
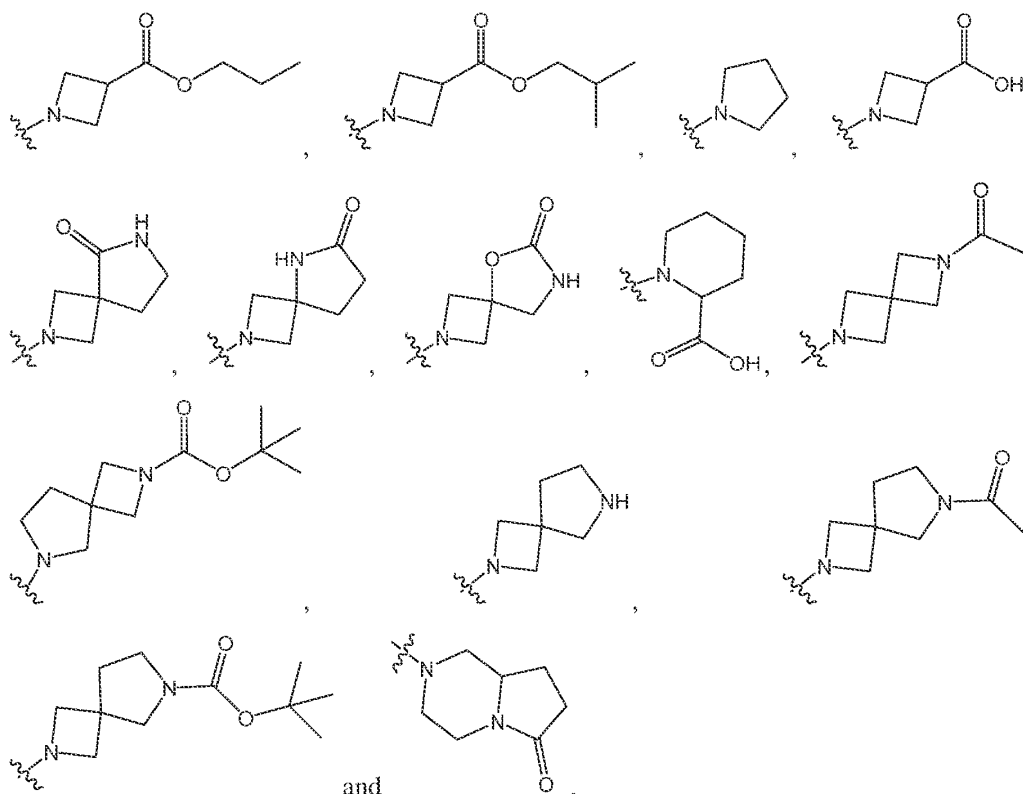
18. The compound of any one of Claims 2-8, wherein R^{1b} is $-R^{x1}$.

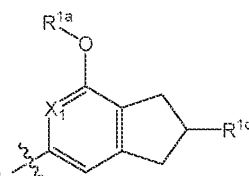
19. The compound of Claim 18, wherein $-R^{x1}$ is selected from the group



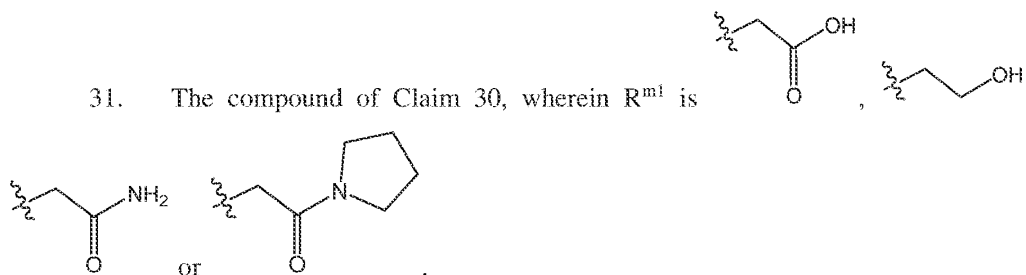
20. The compound of Claim 19, wherein $-R^{x1}$ is selected from the group



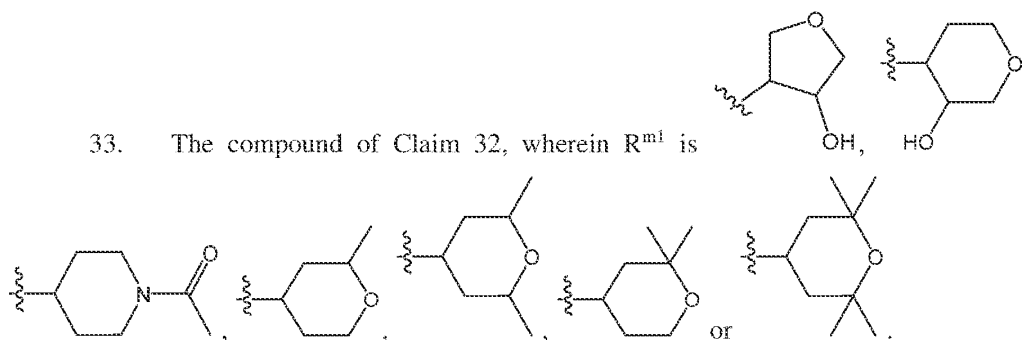


21. The compound of Claim 1, wherein A^1 is .
22. The compound of Claim 21, wherein X^1 is CH.
23. The compound of Claim 21, wherein X^1 is N.
24. The compound of any one of Claims 21-23, wherein R^{1a} is $-C_{1-4}$ alkyl.
25. The compound of any one of Claims 21-23, wherein R^{1a} is $-C_{1-4}$ haloalkyl.
26. The compound of any one of Claims 21-23, wherein R^{1a} is selected from the group consisting of $-CH_2(C_{3-6}$ monocyclic cycloalkyl), $-CH_2(4-6$ membered monocyclic heterocyclyl) and $-CH_2(5-6$ membered monocyclic heteroaryl).
27. The compound of any one of Claims 21-26, wherein R^{1c} is $-N(R^{n1})R^{n1}$.
28. The compound of Claim 27, wherein R^{n1} is hydrogen.
29. The compound of Claim 27, wherein R^{n1} is $-C(=O)OR^{Z4}$.

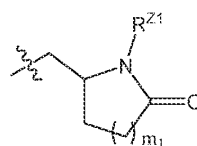
30. The compound of any one of Claims 27-29, wherein R^{m1} is C_{3-6} monocyclic cycloalkyl, $-C_{1-4}$ alkyl optionally substituted with $-C(=O)OR^{Z1}$ or 4-7 membered monocyclic heterocyclyl optionally substituted with hydroxy.



32. The compound of Claim 30, wherein R^{m1} is tetrahydrofuran or tetrahydro-2H-pyran, each optionally substituted with hydroxy.



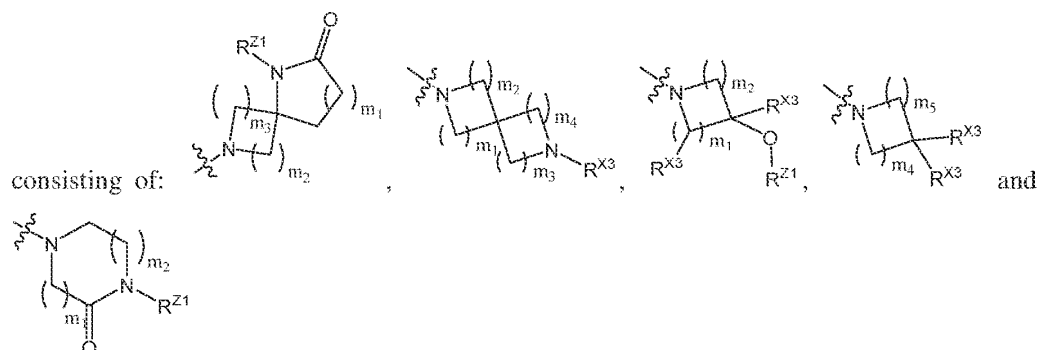
34. The compound of any one of Claims 27-29, wherein R^{m1} is $-R^{x2}$.



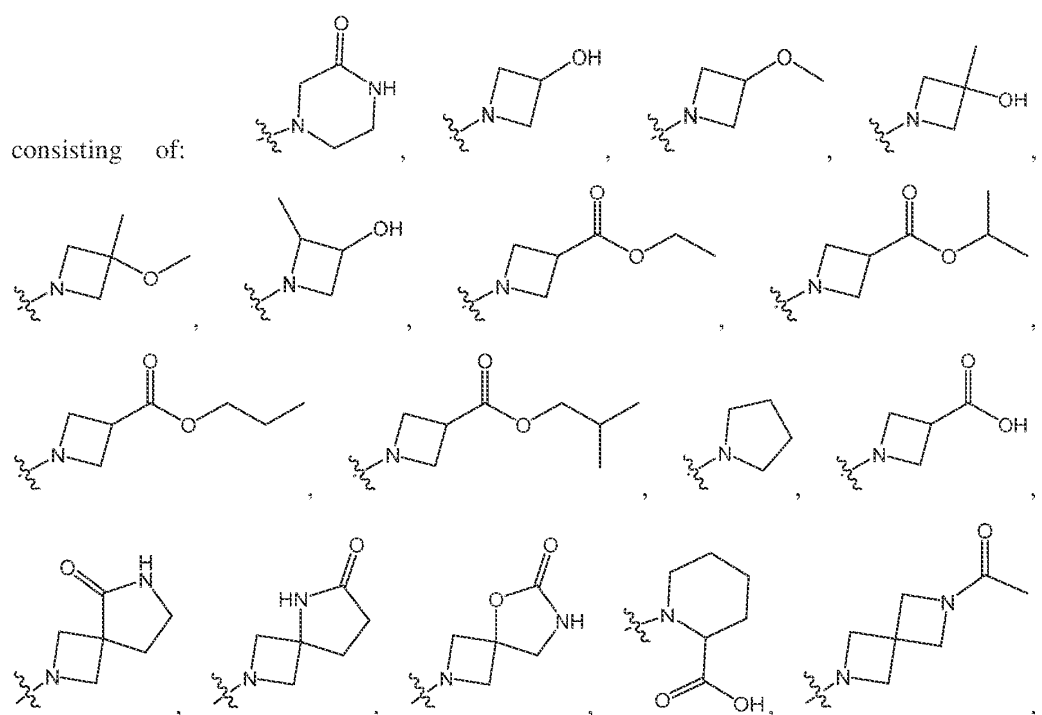
35. The compound of Claim 34, wherein $-R^{x2}$ is

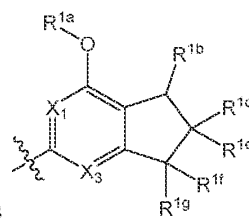
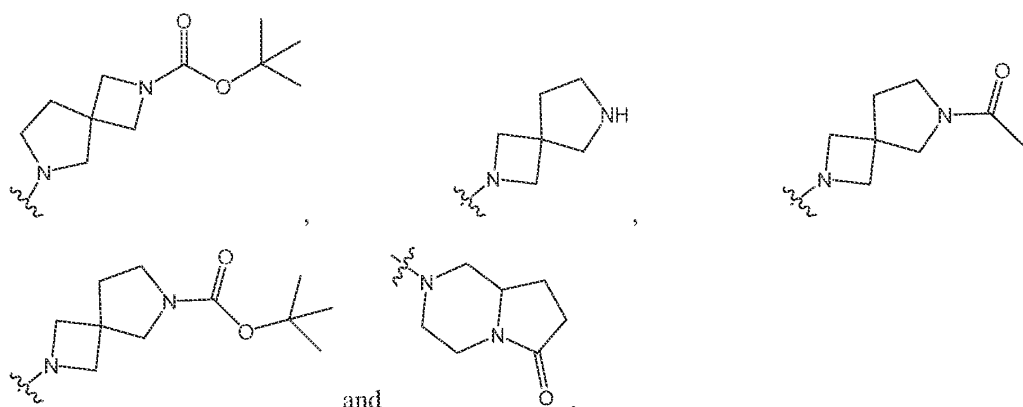
36. The compound of any one of Claims 21-26, wherein R^{1c} is $-R^{x1}$.

37. The compound of Claim 36, wherein $-R^{x1}$ is selected from the group



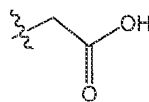
38. The compound of Claim 37, wherein $-R^{x1}$ is selected from the group





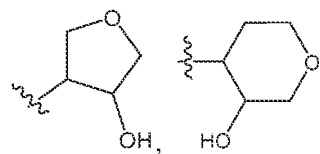
39. The compound of Claim 1, wherein A¹ is
40. The compound of Claim 39, wherein X¹ is CH.
41. The compound of Claim 39, wherein X¹ is N.
42. The compound of any one of Claims 39-41, wherein X³ is CH.
43. The compound of any one of Claims 39-41, wherein X³ is C-halo.
44. The compound of any one of Claims 39-41, wherein X³ is N.
45. The compound of any one of Claims 39-44, wherein R^{1a} is -C₁₋₄ alkyl.
46. The compound of any one of Claims 39-44, wherein R^{1a} is -C₁₋₄ haloalkyl.
47. The compound of any one of Claims 39-44, wherein R^{1a} is selected from the group consisting of -CH₂(C₃₋₆ monocyclic cycloalkyl), -CH₂(4-6 membered monocyclic heterocyclyl) and -CH₂(5-6 membered monocyclic heteroaryl).
48. The compound of any one of Claims 39-47, wherein R^{1b} is -N(R^{m1})Rⁿ¹.
49. The compound of any one of Claims 39-47, wherein Rⁿ¹ is hydrogen.
50. The compound of any one of Claims 39-47, wherein Rⁿ¹ is -C(=O)OR^{z1}.
51. The compound of any one of Claims 39-50, wherein R^{m1} is hydrogen.
52. The compound of any one of Claims 39-50, wherein R^{m1} is -C₁₋₄ alkyl optionally substituted with -C(=O)OR^{z1} or 4-7 membered monocyclic heterocyclyl optionally substituted with hydroxy.

53. The compound of any one of Claims 39-50, wherein R^{m1} is C_5 monocyclic cycloalkyl or C_6 monocyclic cycloalkyl.

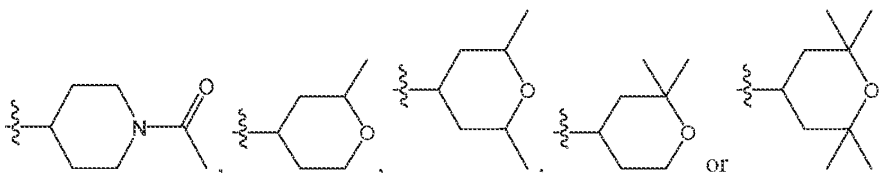


54. The compound of Claim 52, wherein R^{m1} is

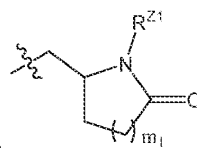
55. The compound of Claim 52, wherein R^{m1} is tetrahydrofuran or tetrahydro-2H-pyran, each optionally substituted with hydroxy, or piperidine optionally substituted with $-C(=O)R^{Z1}$.



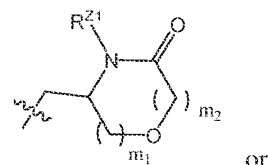
56. The compound of Claim 55, wherein R^{m1} is



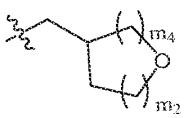
57. The compound of any one of Claims 39-50, wherein R^{m1} is $-R^{x2}$.



58. The compound of Claim 57, wherein $-R^{x2}$ is

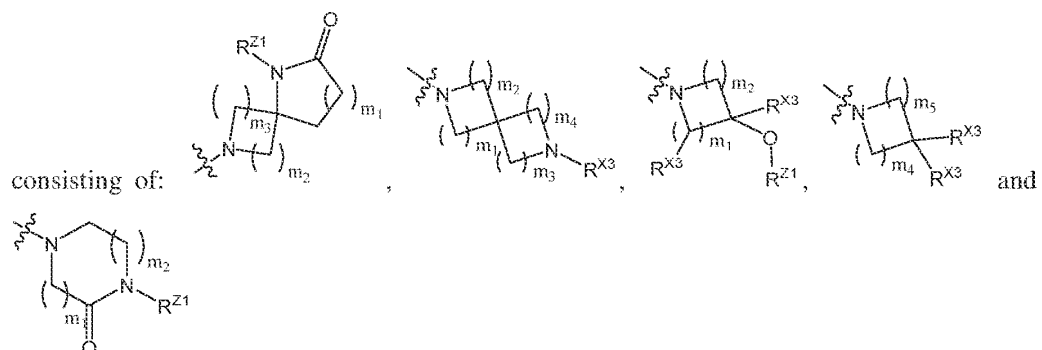


59. The compound of Claim 57, wherein $-R^{x2}$ is

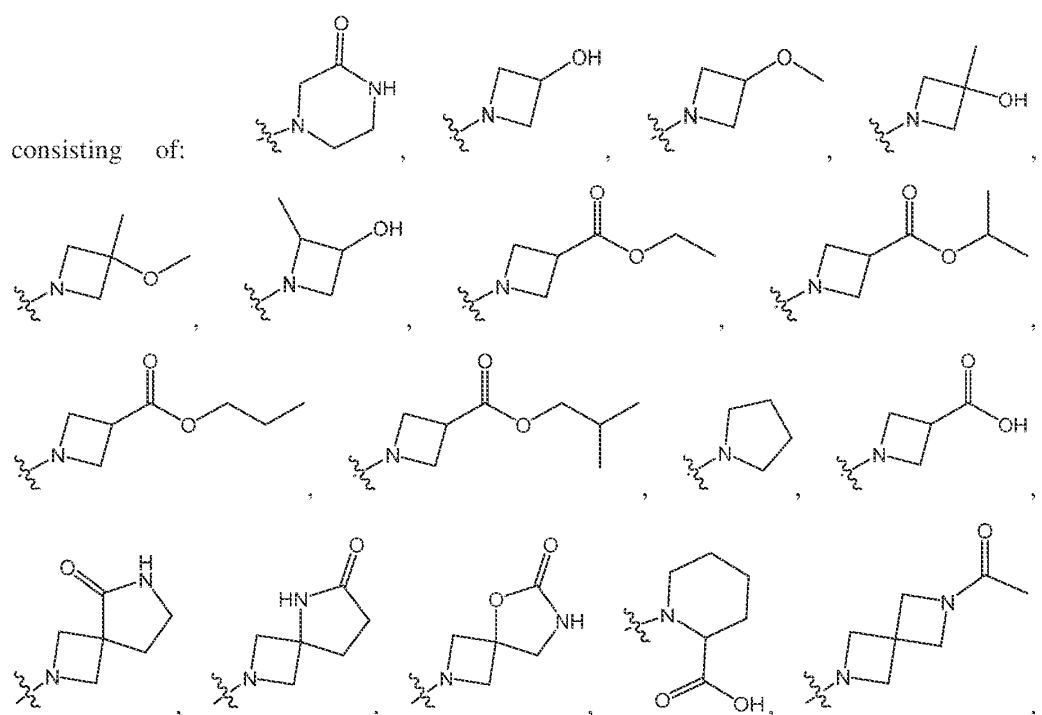


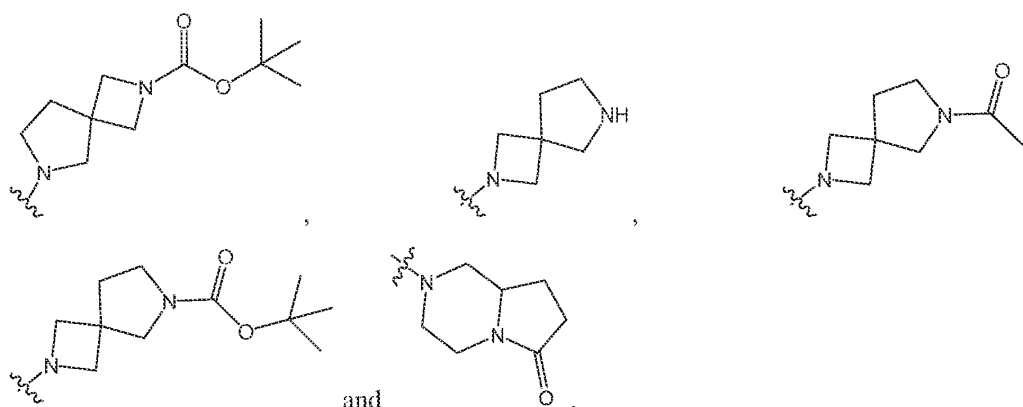
60. The compound of any one of Claims 39-47, wherein R^{1b} is $-R^{x1}$.

61. The compound of Claim 60, wherein $-R^{x1}$ is selected from the group

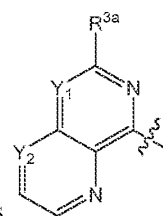


62. The compound of Claim 61, wherein $-R^{x1}$ is selected from the group

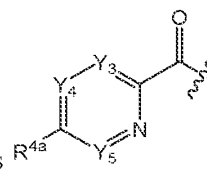




63. The compound of any one of Claims 39-62, wherein R^{1d} is hydrogen.
64. The compound of any one of Claims 39-62, wherein R^{1d} is $-OH$.
65. The compound of any one of Claims 39-62, wherein R^{1d} is $-CH_3$.
66. The compound of any one of Claims 39-62, wherein R^{1d} is $-F$.
67. The compound of any one of Claims 63-66, wherein R^{1e} is hydrogen.
68. The compound of any one of Claims 63-66, wherein R^{1e} is $-CH_3$.
69. The compound of any one of Claims 63-68, wherein R^{1f} is hydrogen.
70. The compound of any one of Claims 63-68, wherein R^{1f} is $-CH_3$.
71. The compound of any one of Claims 63-70, wherein R^{1g} is hydrogen.

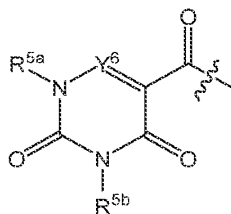


72. The compound of any one of Claims 1-71, wherein B^1 is
73. The compound of Claim 72, wherein Y^1 is N.
74. The compound of Claim 72, wherein Y^1 is CH.
75. The compound of any one of Claims 72-74, wherein Y^2 is N.
76. The compound of any one of Claims 72-74, wherein Y^2 is CH.
77. The compound of any one of Claims 72-76, wherein R^{3a} is H.
78. The compound of any one of Claims 72-76, wherein R^{3a} is $-CH_3$.
79. The compound of any one of Claims 72-76, wherein R^{3a} is $-CF_3$.
80. The compound of any one of Claims 72-76, wherein R^{3a} is $-CHF_2$.

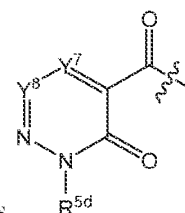


81. The compound of any one of Claims 1-71, wherein B¹ is R^{4a}.
82. The compound of Claim 81, wherein Y³ is N.
83. The compound of Claim 81, wherein Y³ is CH.
84. The compound of any one of Claims 81-83, wherein Y⁴ is N.
85. The compound of any one of Claims 81-83, wherein Y⁴ is CH.
86. The compound of any one of Claims 81-85, wherein Y⁵ is N.
87. The compound of any one of Claims 81-85, wherein Y⁵ is CH.
88. The compound of any one of Claims 81-85, wherein Y⁵ is C-OCH₃.
89. The compound of any one of Claims 81-88, wherein R^{4a} is H.
90. The compound of any one of Claims 81-88, wherein R^{4a} is halogen.
91. The compound of any one of Claims 81-88, wherein R^{4a} is -C₁₋₄ alkyl.
92. The compound of any one of Claims 81-88, wherein R^{4a} is -C₁₋₄ haloalkyl.
93. The compound of any one of Claims 81-88, wherein R^{4a} is -CH₂R^{4b}.
94. The compound of any one of Claims 81-88, wherein R^{4a} is -C(CH₃)R^{4b}.
95. The compound of Claim 93 or 94, wherein R^{4b} is -N(R^{m2})Rⁿ².
96. The compound of Claim 95, wherein R^{m2} is -CH₃.
97. The compound of Claim 95, wherein R^{m2} is -C₂₋₄ alkyl.
98. The compound of Claim 95, wherein R^{m2} is -C₁₋₄ haloalkyl.
99. The compound of Claim 95, wherein R^{m2} is -C₂₋₄ alkyl substituted with hydroxy.
100. The compound of any one of Claims 95-99, wherein Rⁿ² is H.
101. The compound of any one of Claims 95-99, wherein Rⁿ² is -C₁₋₄ alkyl.
102. The compound of any one of Claims 95-99, wherein Rⁿ² is -C₁₋₄ haloalkyl.
103. The compound of Claim 93 or 94, wherein R^{4b} is -R^{y1}.

104. The compound of any one of Claims 1-71, wherein B¹ is



- 105. The compound of Claim 104, R^{5a} is hydrogen.
- 106. The compound of Claim 104, R^{5a} is -CH₃.
- 107. The compound of Claim 104, R^{5a} is -C₂₋₄ alkyl.
- 108. The compound of Claim 104, R^{5a} is -C₂₋₄ haloalkyl.
- 109. The compound of any one of Claims 104-108, wherein R^{5b} is hydrogen.
- 110. The compound of any one of Claims 104-108, wherein R^{5b} is -CH₃.
- 111. The compound of any one of Claims 104-108, wherein R^{5b} is -C₂₋₄ alkyl.
- 112. The compound of any one of Claims 104-108, wherein R^{5b} is -C₂₋₄ haloalkyl.
- 113. The compound of any one of Claims 104-112, wherein Y⁶ is N.
- 114. The compound of any one of Claims 104-112, wherein Y⁶ is CR^{5c}.
- 115. The compound of Claim 114, wherein R^{5c} is hydrogen.
- 116. The compound of Claim 114, wherein R^{5c} is -CH₃.
- 117. The compound of Claim 114, wherein R^{5c} is -C₂₋₄ alkyl.
- 118. The compound of Claim 114, wherein R^{5c} is -C₂₋₄ haloalkyl.



- 119. The compound of any one of Claims 1-71, wherein B¹ is
- 120. The compound of Claim 119, wherein R^{5d} is hydrogen.
- 121. The compound of Claim 119, wherein R^{5d} is -CH₃.
- 122. The compound of Claim 119, wherein R^{5d} is -C₂₋₄ alkyl.
- 123. The compound of Claim 119, wherein R^{5d} is -C₂₋₄ haloalkyl.
- 124. The compound of any one of Claims 119-123, wherein Y⁷ is CR^{5e}, wherein

R^{5e} is hydrogen.

125. The compound of any one of Claims 119-123, wherein Y^7 is CR^{5e} , wherein R^{5e} is halogen.

126. The compound of any one of Claims 119-123, wherein Y^7 is CR^{5e} , wherein R^{5e} is $-CH_3$.

127. The compound of any one of Claims 119-126, wherein Y^8 is CR^{5f} , wherein R^{5f} is hydrogen.

128. The compound of any one of Claims 119-126, wherein Y^8 is CR^{5f} , wherein R^{5f} is halogen.

129. The compound of any one of Claims 119-126, wherein Y^8 is CR^{5f} , wherein R^{5f} is $-OH$.

130. The compound of any one of Claims 119-126, wherein Y^8 is CR^{5f} , wherein R^{5f} is CN .

131. The compound of any one of Claims 119-126, wherein Y^8 is CR^{5f} , wherein R^{5f} is $-CH_3$.

132. The compound of any one of Claims 1-131, wherein R^{2a} , R^{2b} , R^{2c} , R^{2e} , R^{2g} and R^{2h} are each hydrogen.

133. The compound of any one of Claims 1-131, wherein R^{2a} , R^{2c} , R^{2e} , R^{2g} and R^{2h} are each hydrogen; and R^{2b} halogen.

134. The compound of any one of Claims 1-131, wherein R^{2b} , R^{2c} , R^{2e} , R^{2g} and R^{2h} are each hydrogen; and R^{2a} halogen.

135. The compound of any one of Claims 1-134, wherein R^{2d} and R^{2f} are each halogen.

136. The compound of any one of Claims 1-134, wherein R^{2d} and R^{2f} are each $-CH_3$.

137. The compound of any one of Claims 1-134, wherein R^{2d} is halogen; and R^{2f} is $-CH_3$.

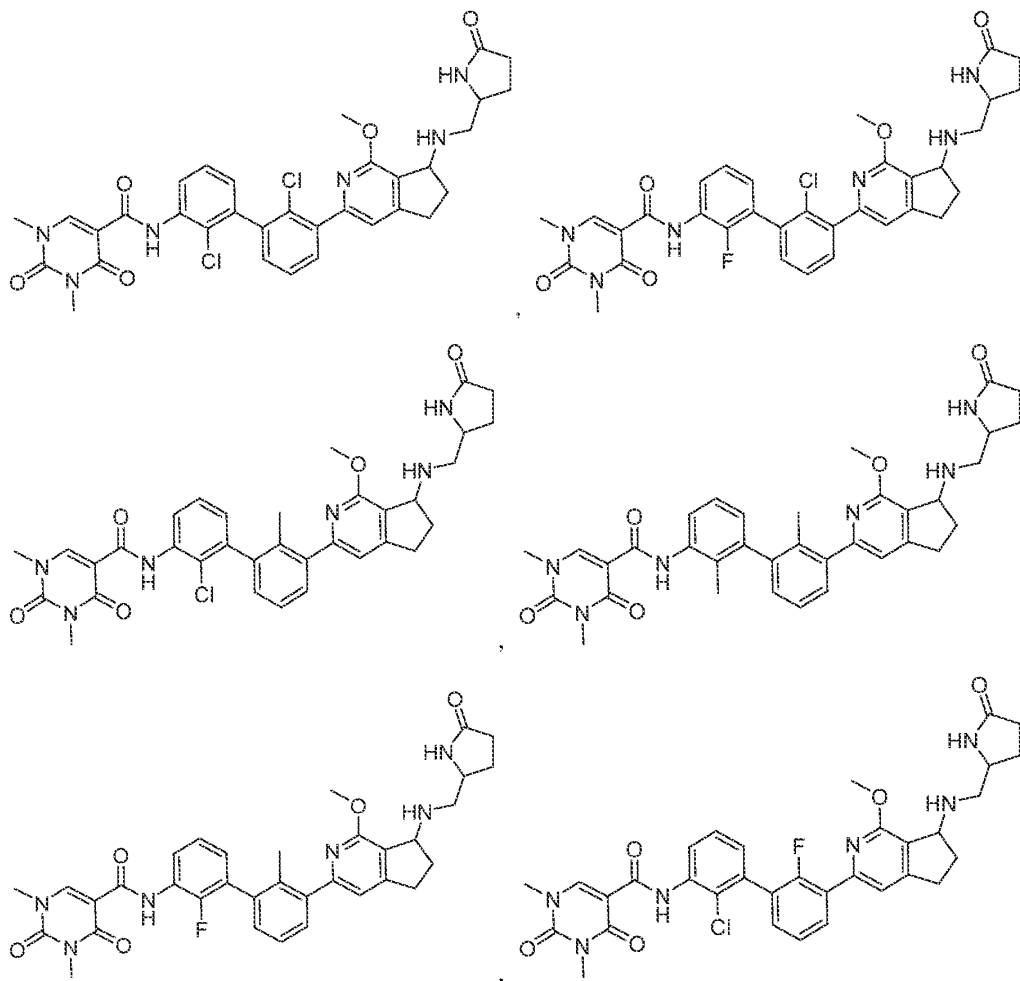
138. The compound of any one of Claims 1-134, wherein R^{2d} is $-CH_3$; and R^{2f} is halogen.

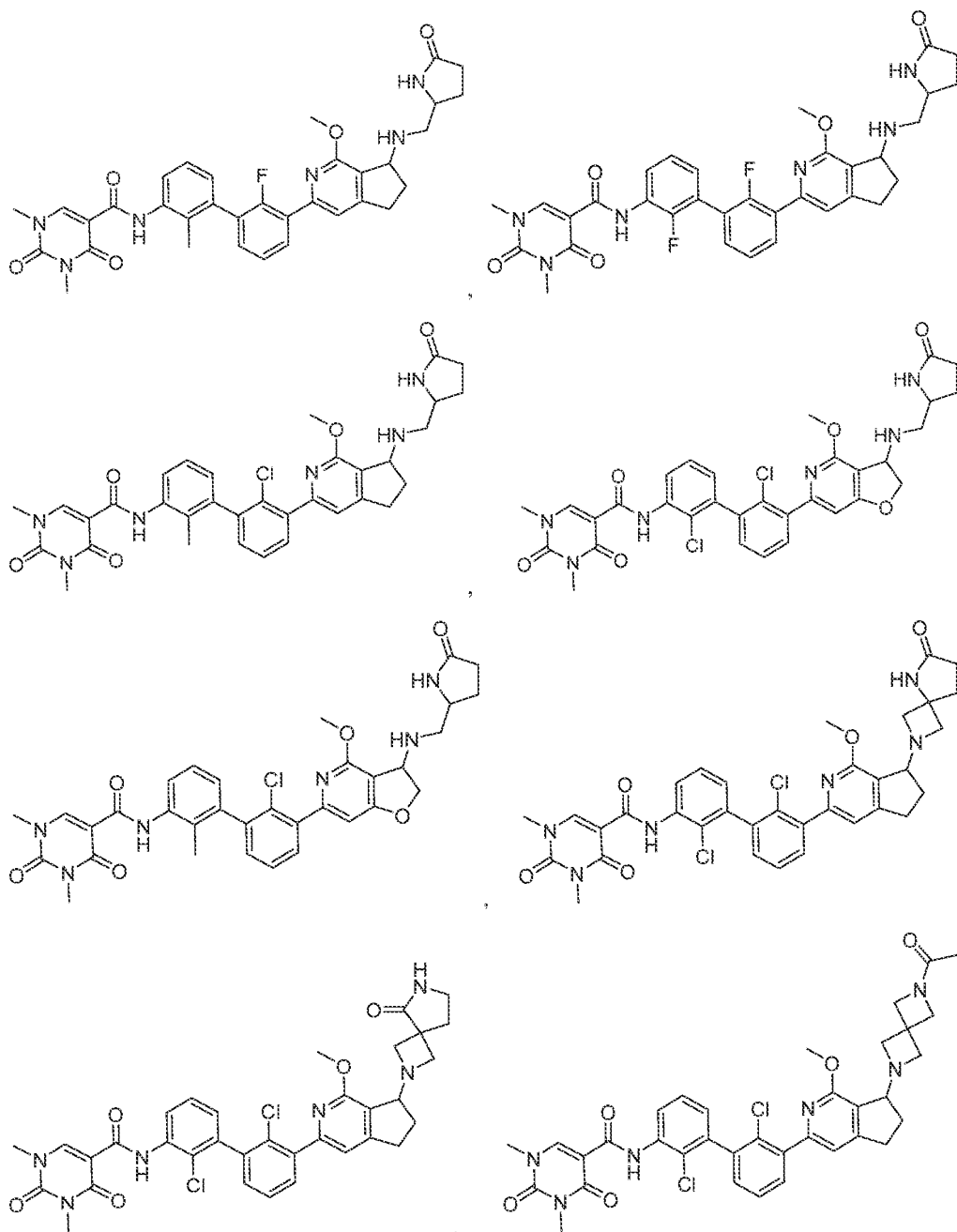
139. The compound of any one of Claims 1-134, wherein R^{2d} is cyano; and R^{2f} is halogen.

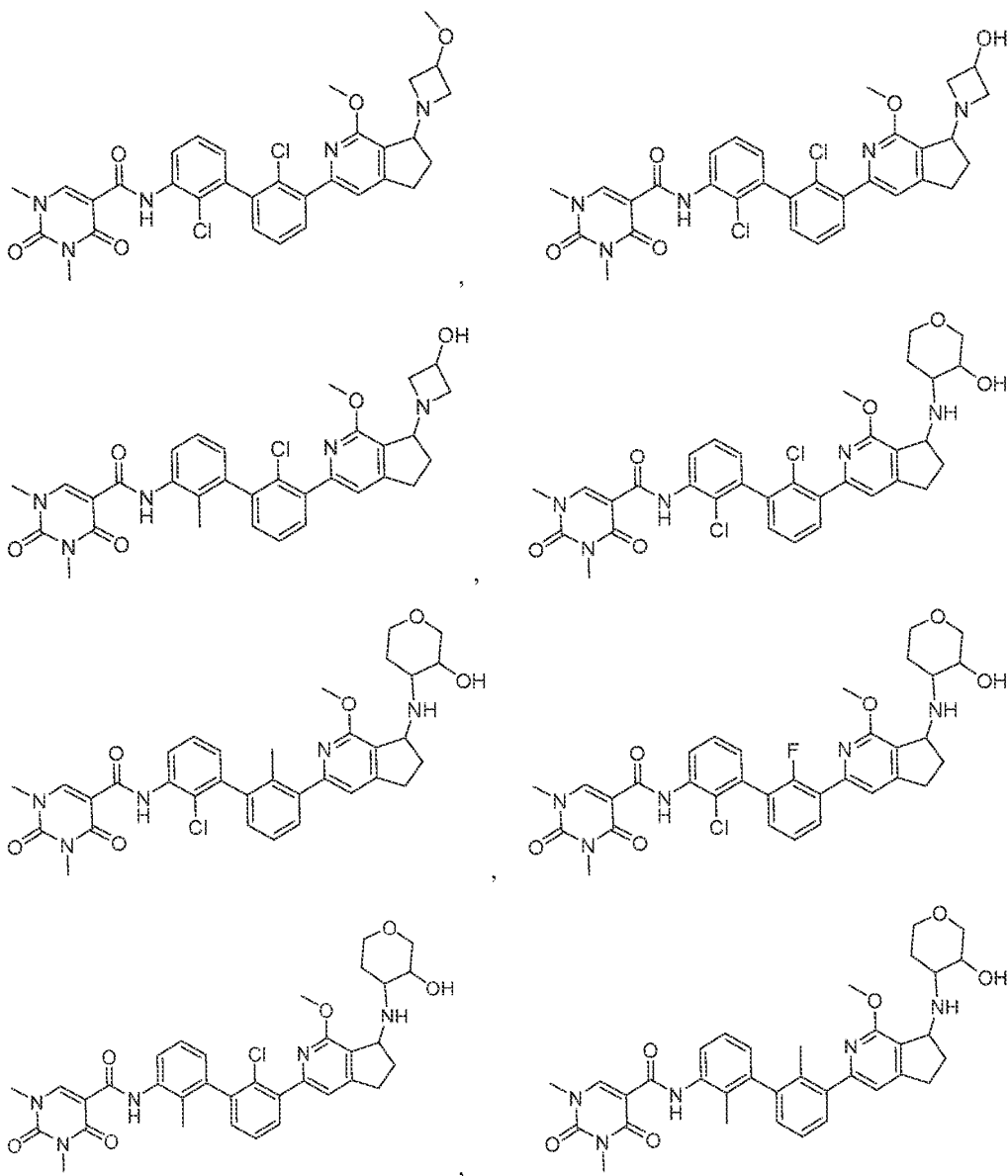
140. The compound of any one of Claims 1-134, wherein R^{2d} is $-OCH_3$; and R^{2f} is halogen.

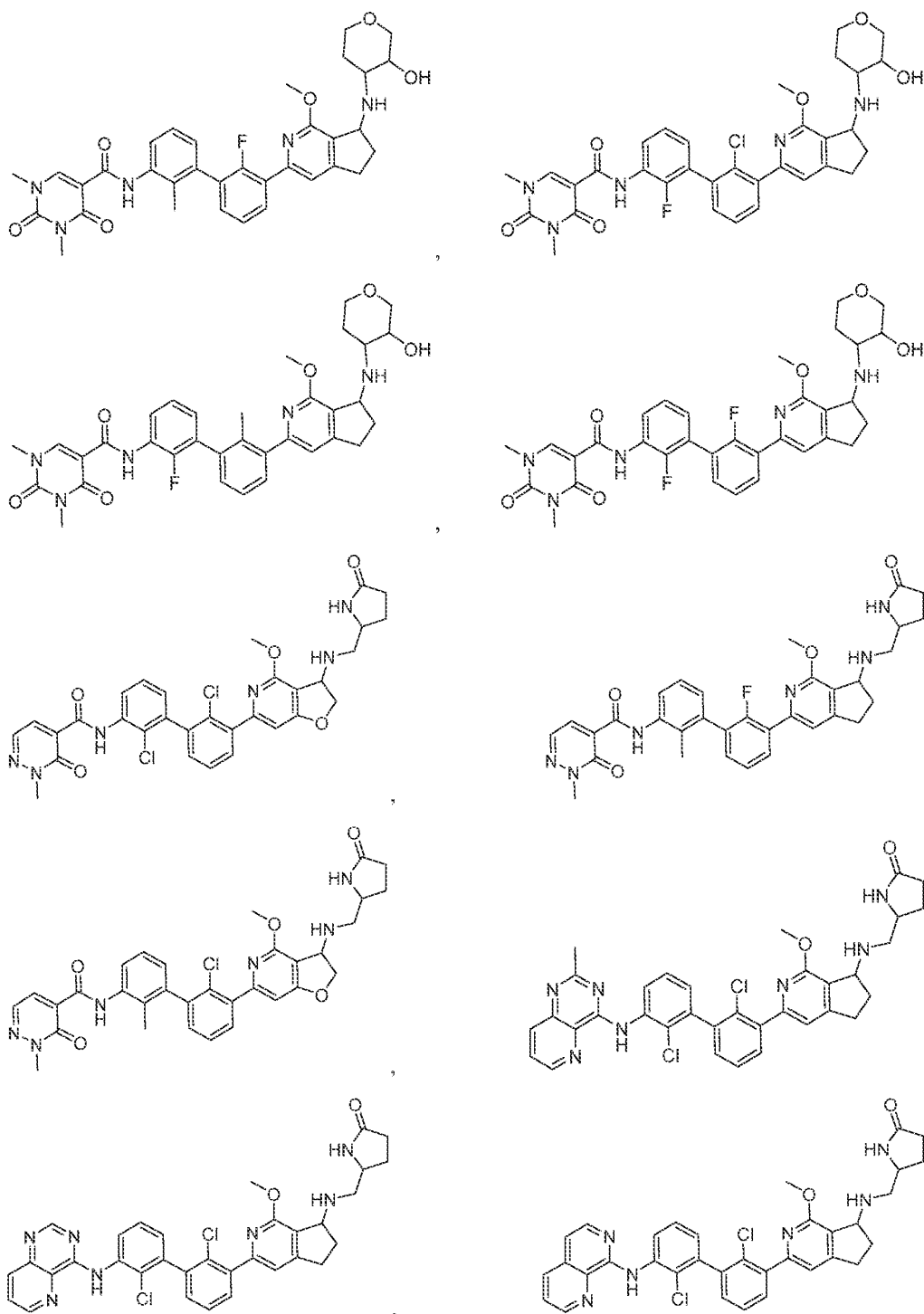
141. The compound of any one of Claims 133-135 or 137-140, wherein the halogen is chloro or fluoro.

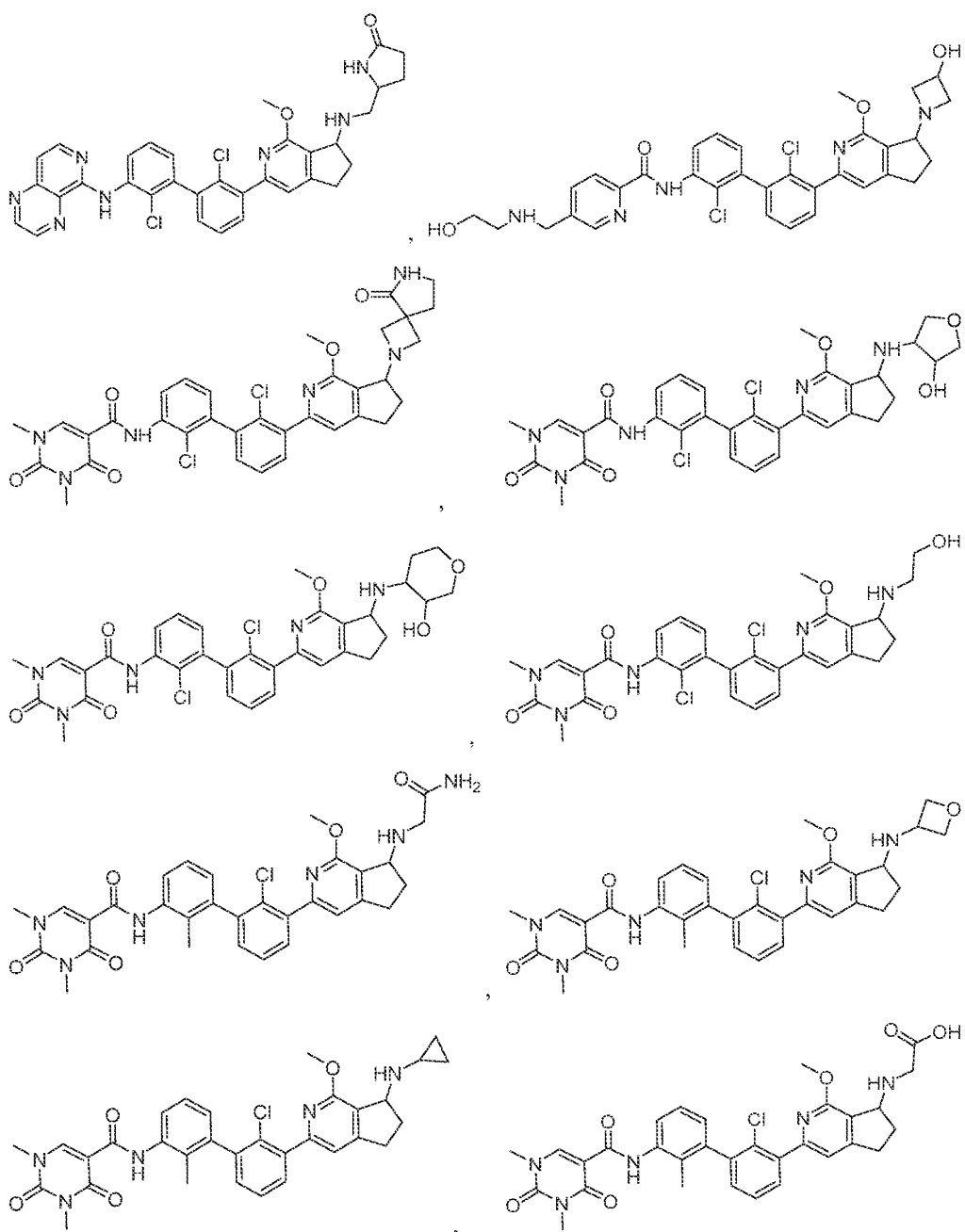
142. The compound of Claim 1 selected from the group consisting of:

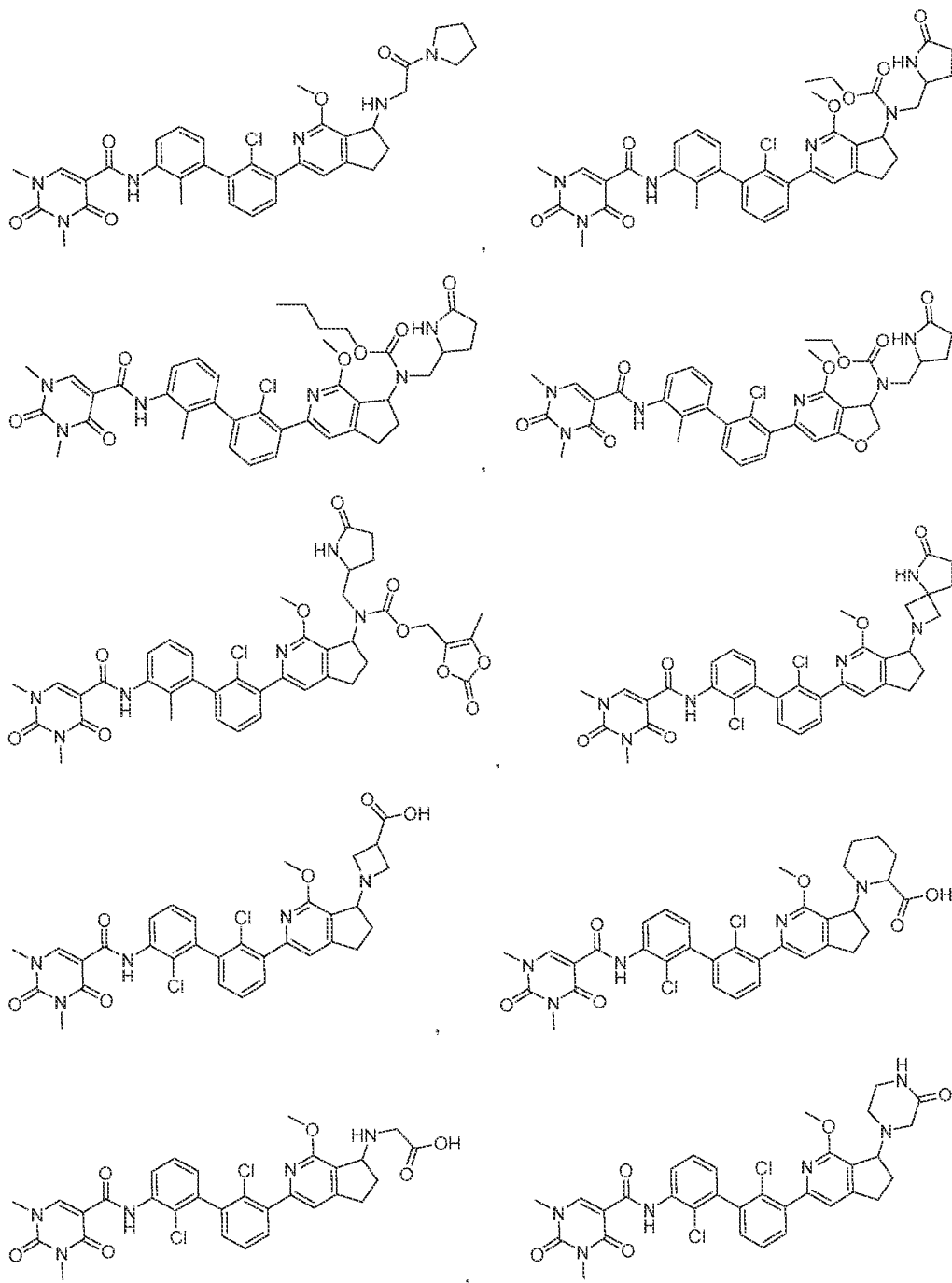


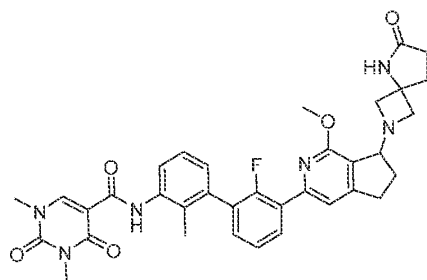
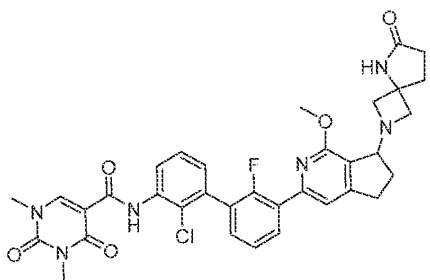
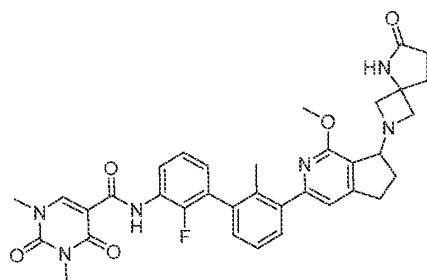
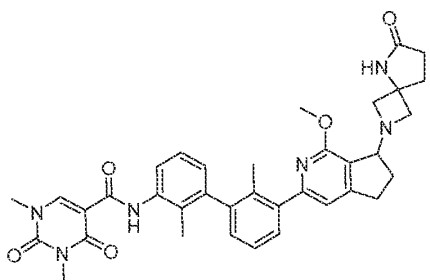
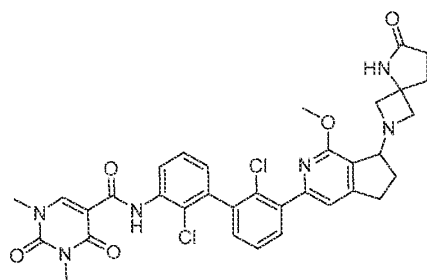
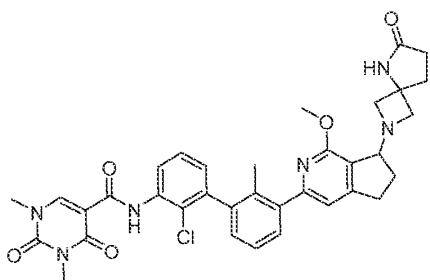
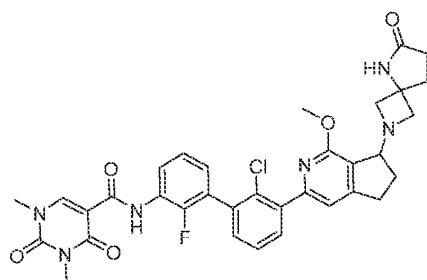
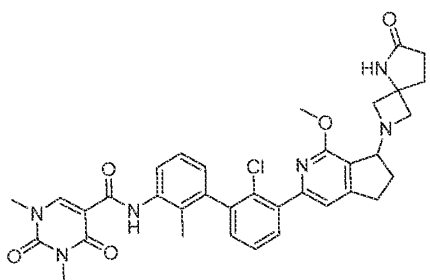


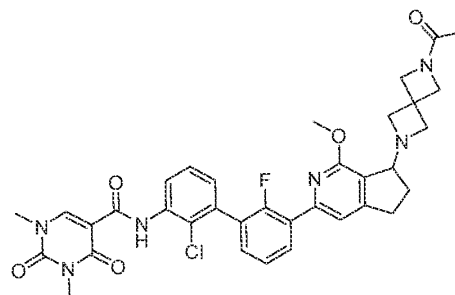
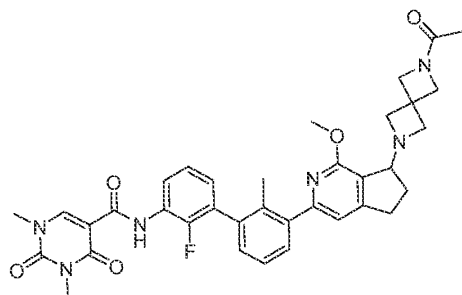
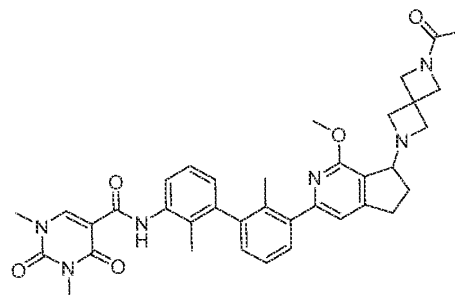
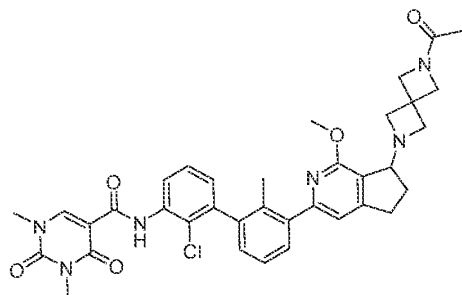
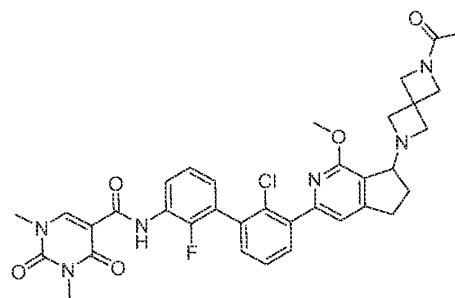
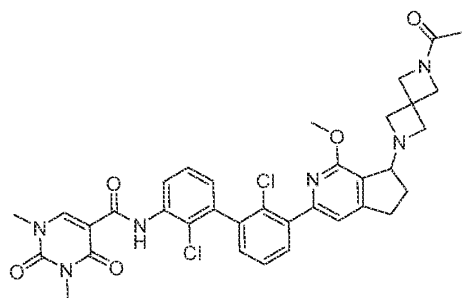
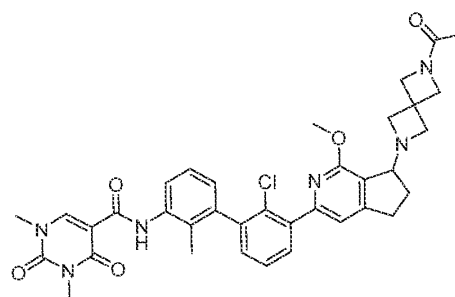
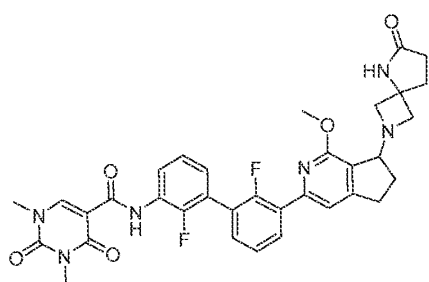


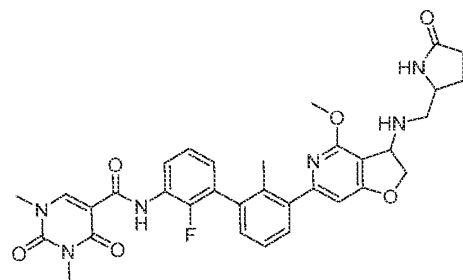
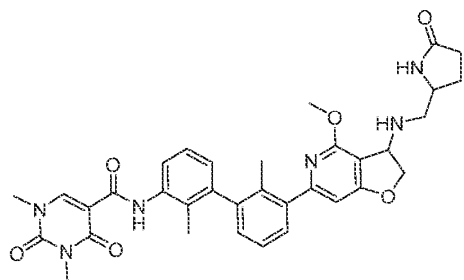
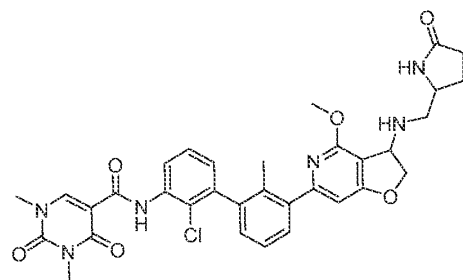
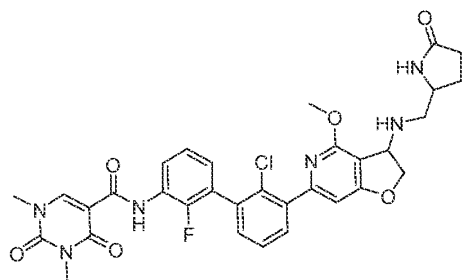
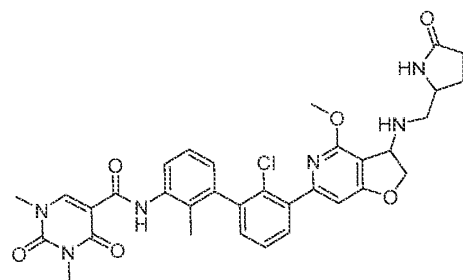
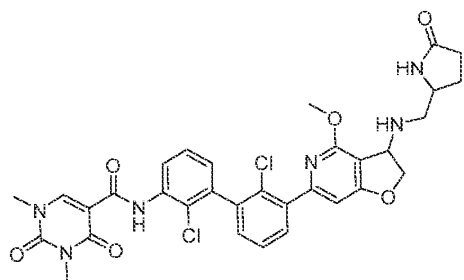
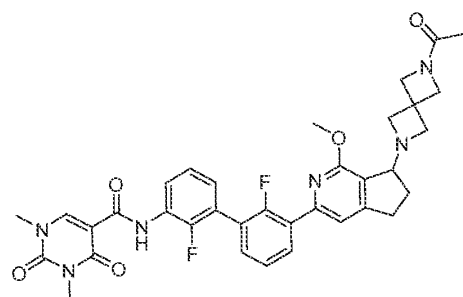
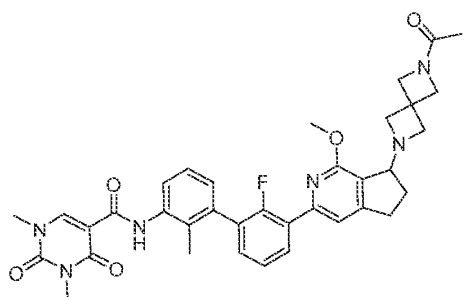


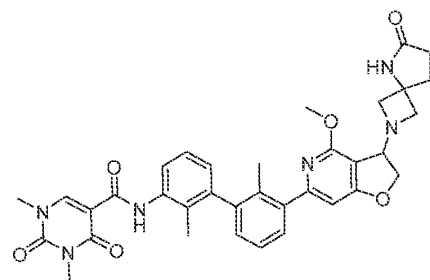
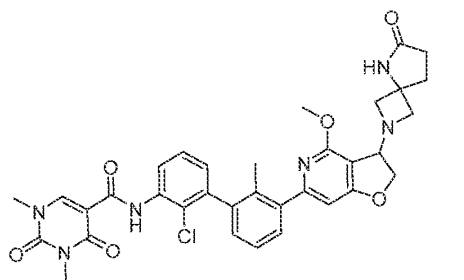
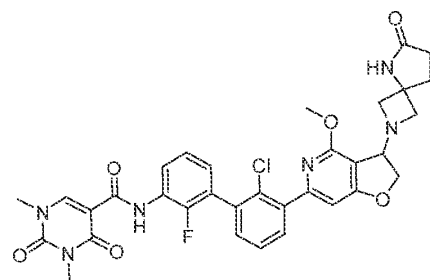
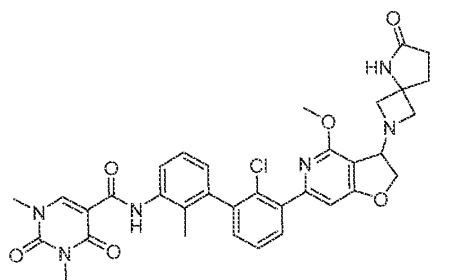
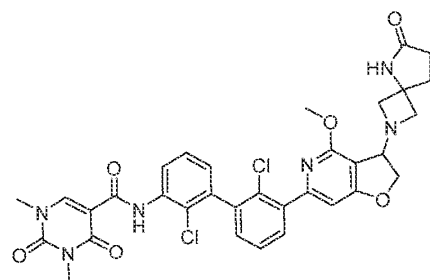
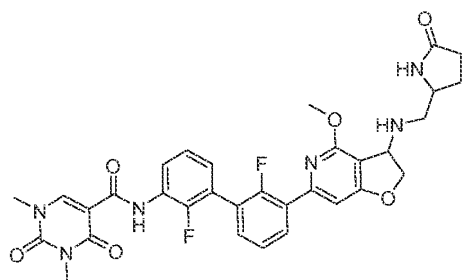
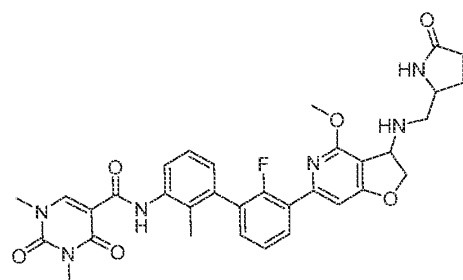
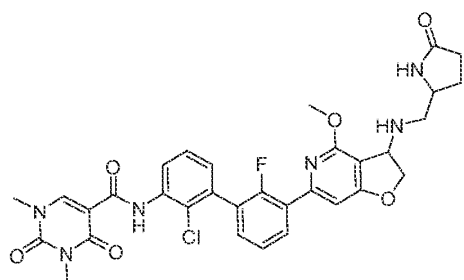


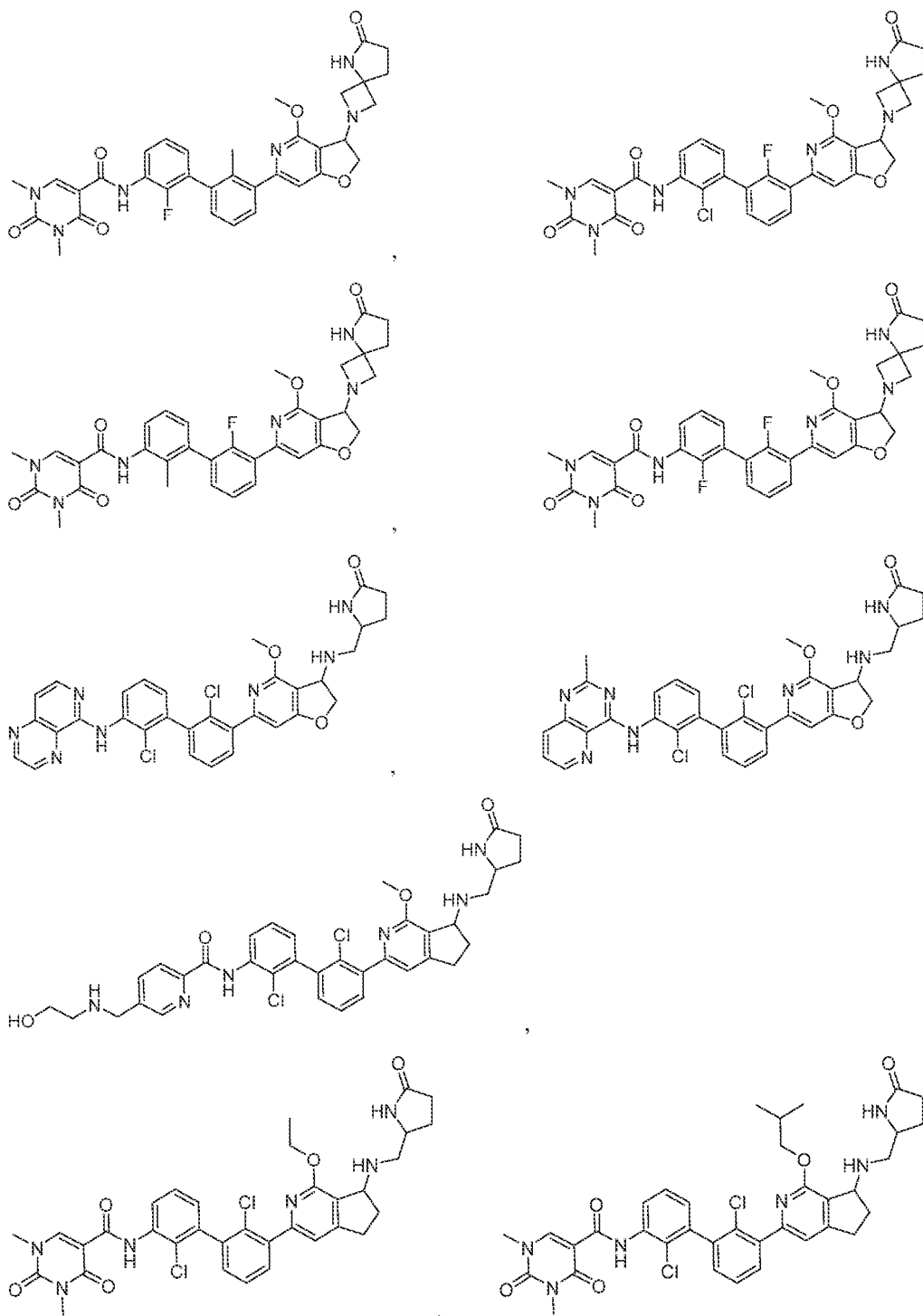


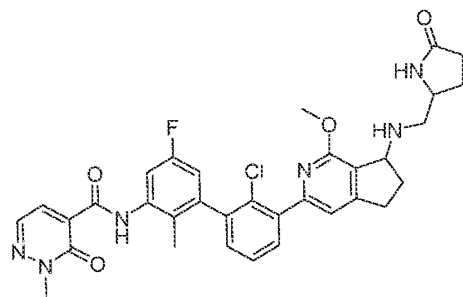
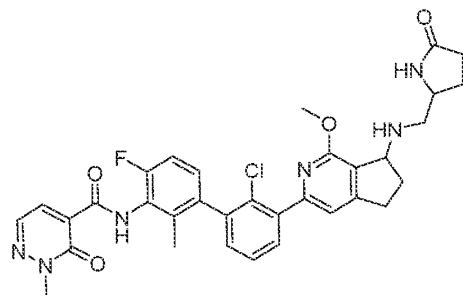
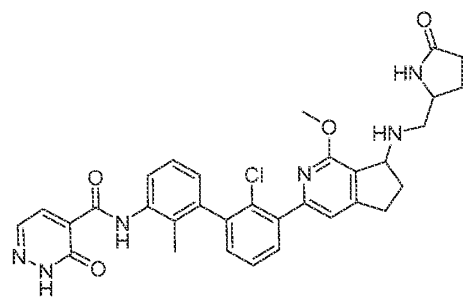
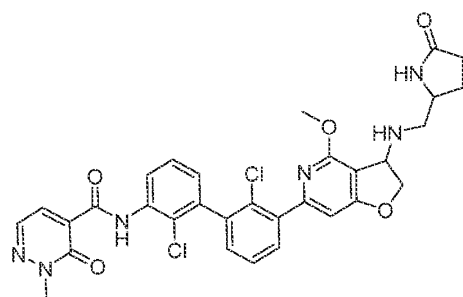


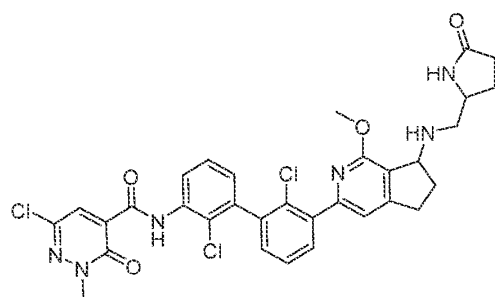
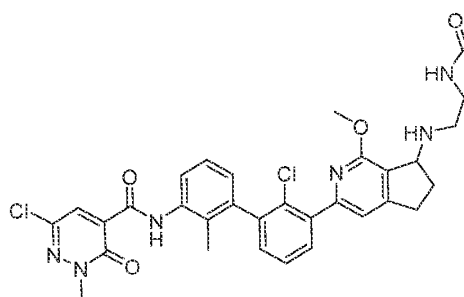
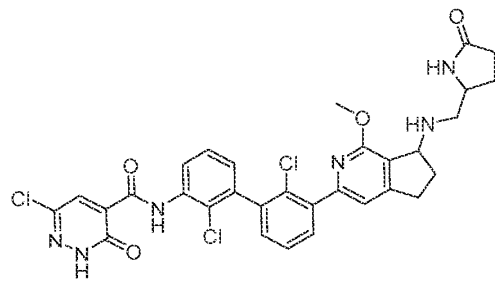
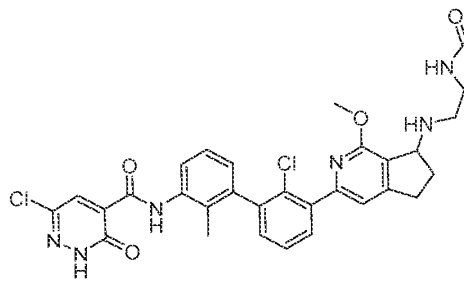
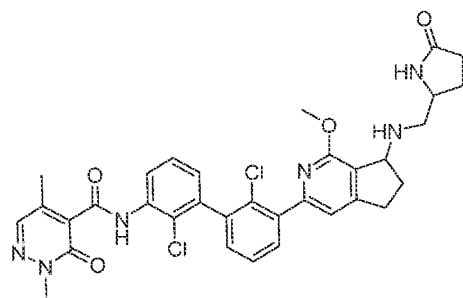
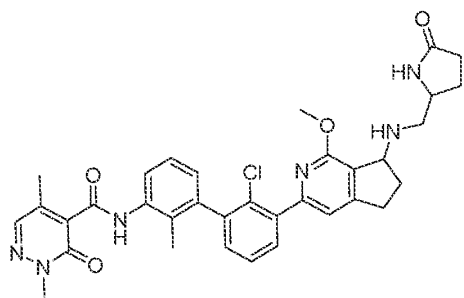
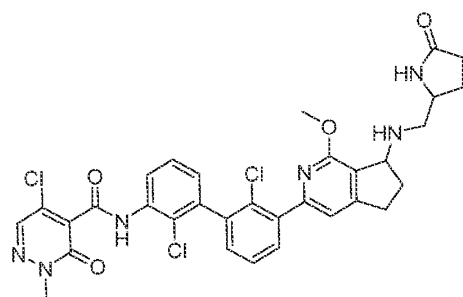
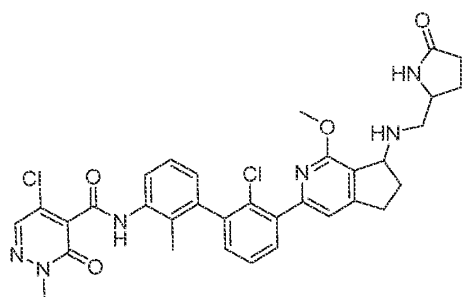


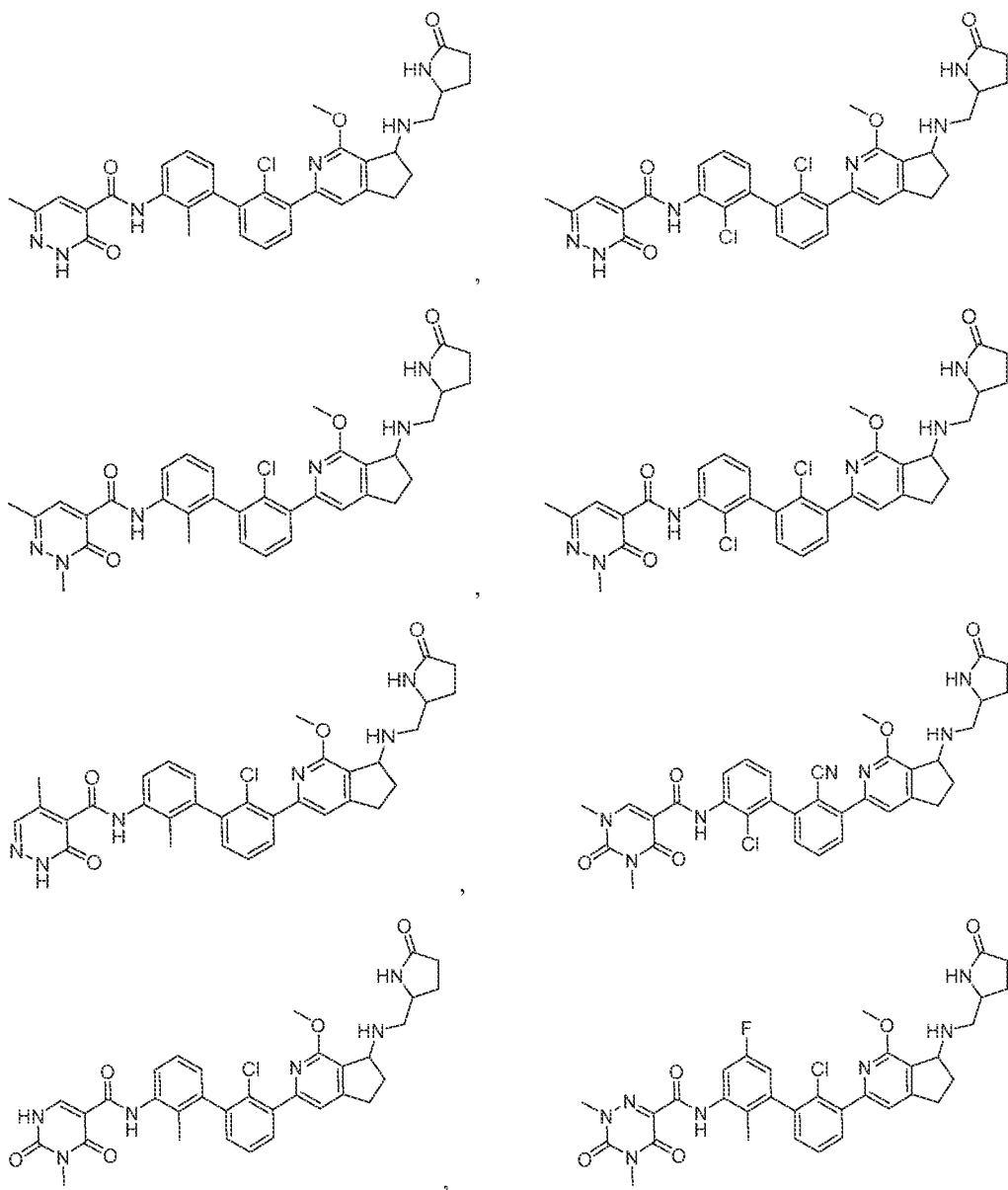


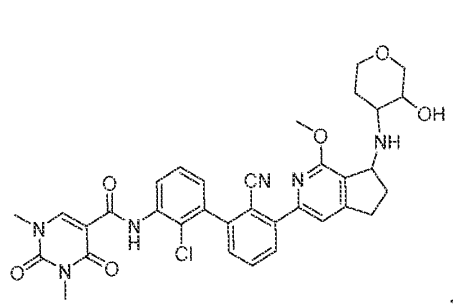
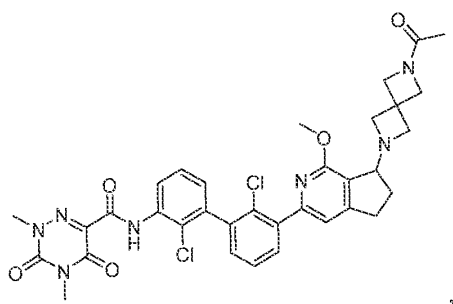
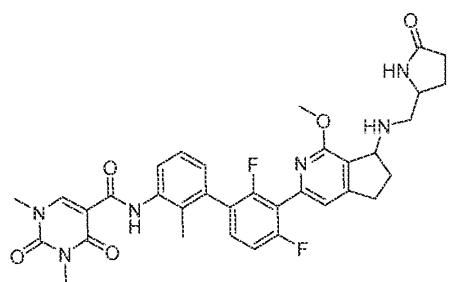
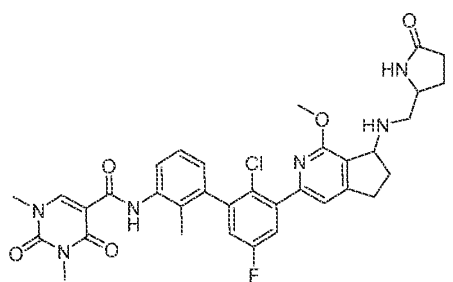
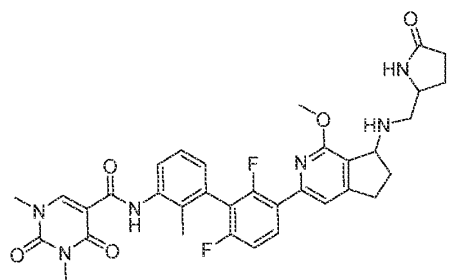
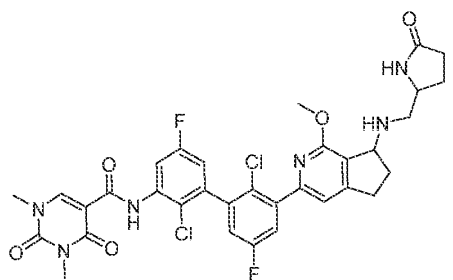
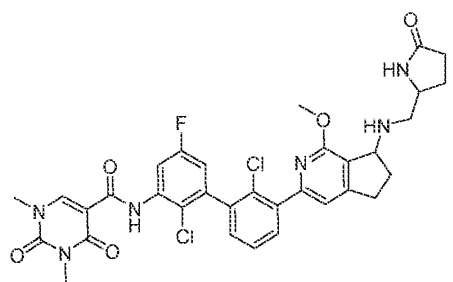
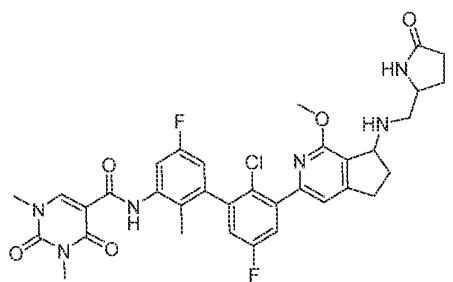


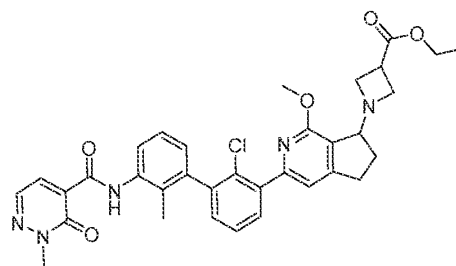
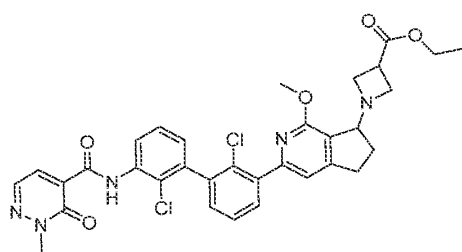
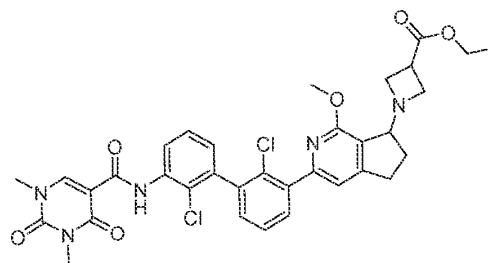
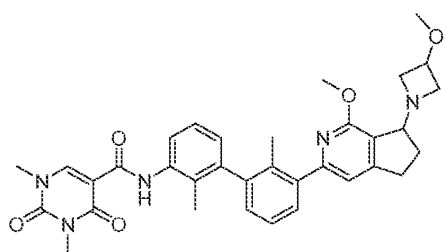
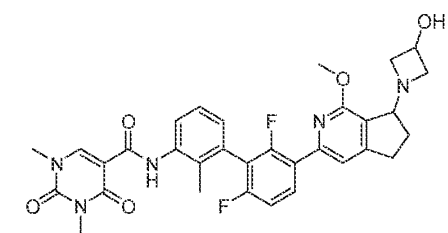
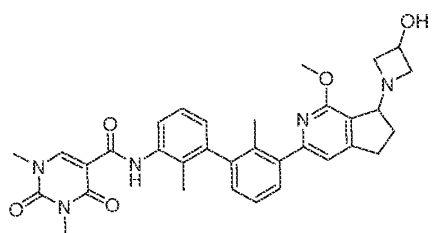
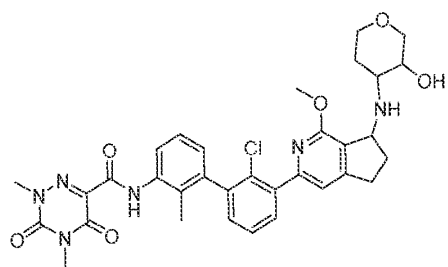
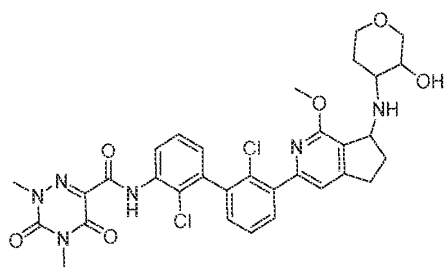
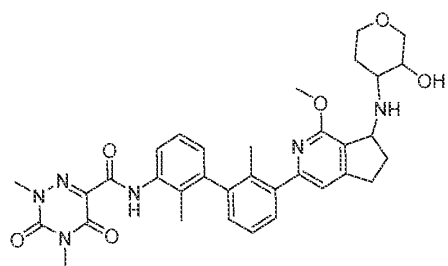
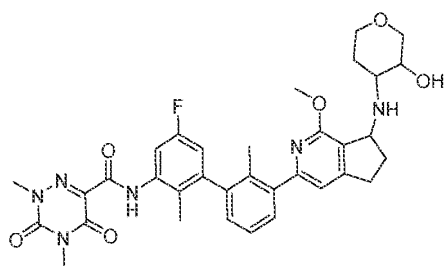


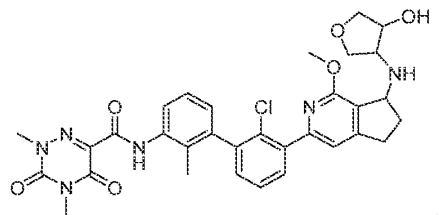
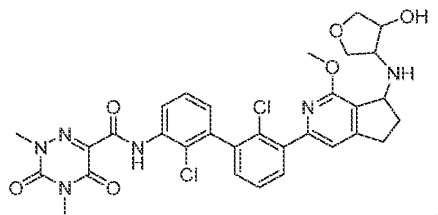
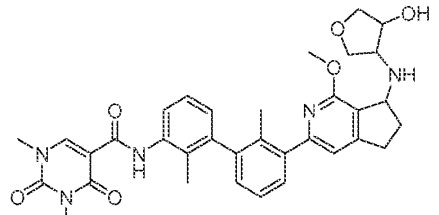
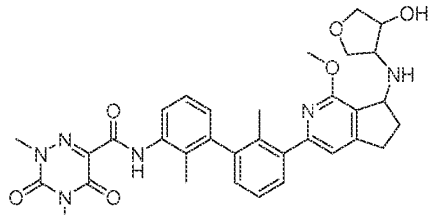
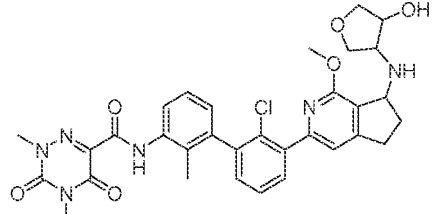
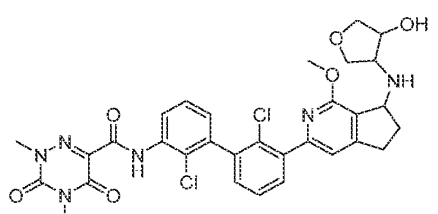
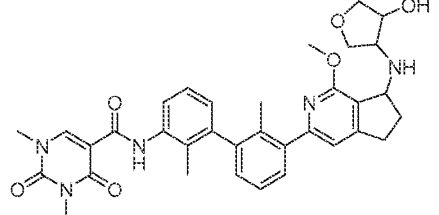
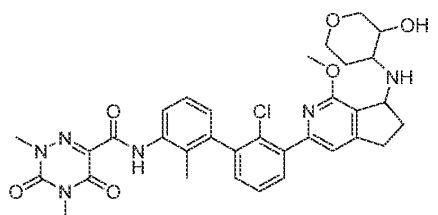
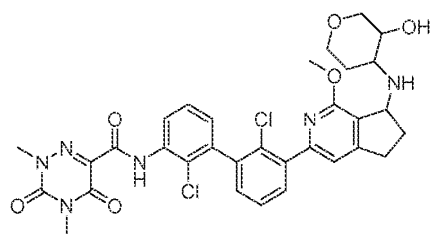
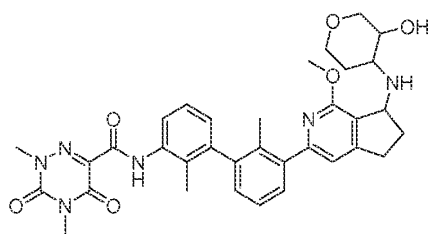


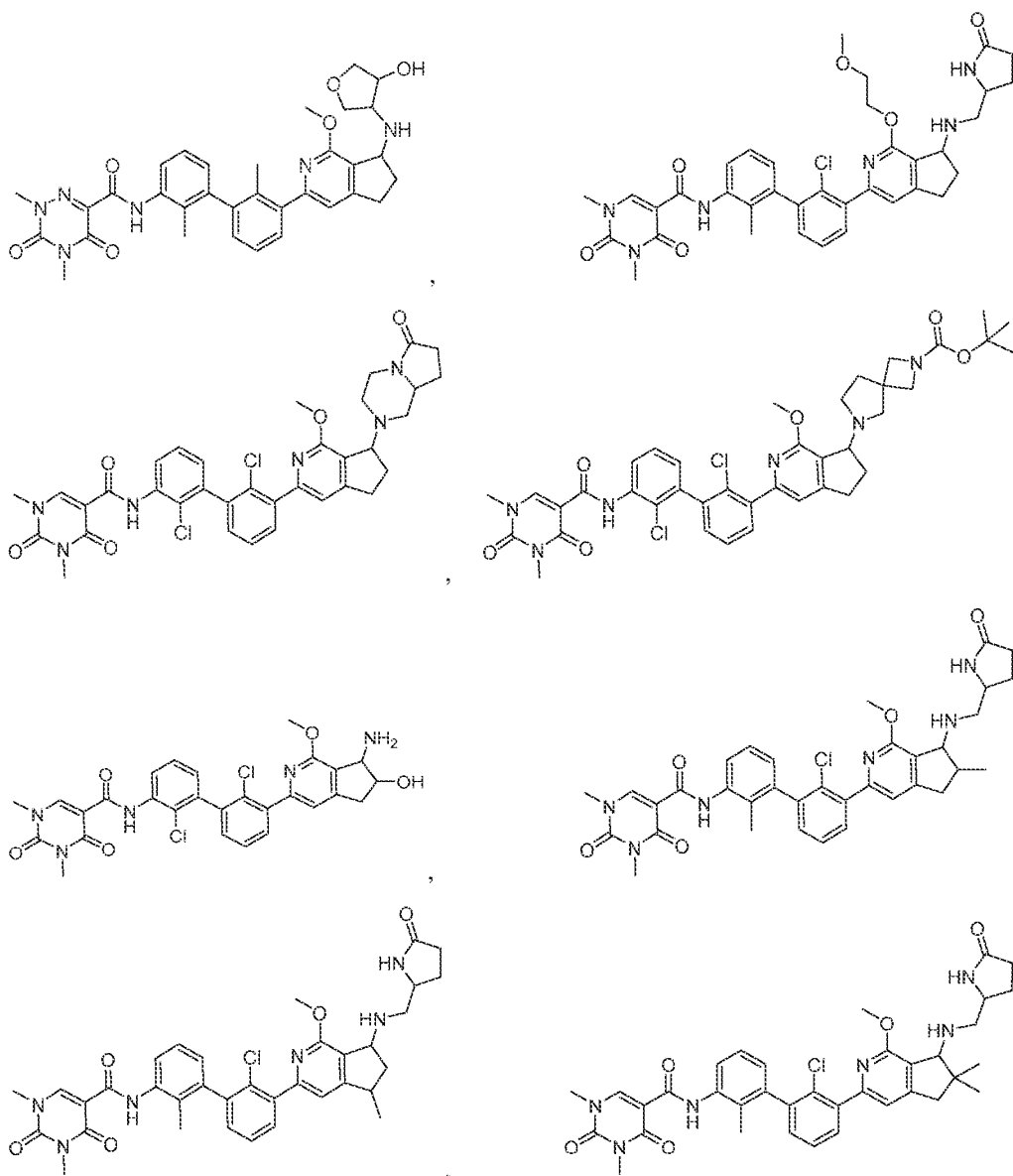


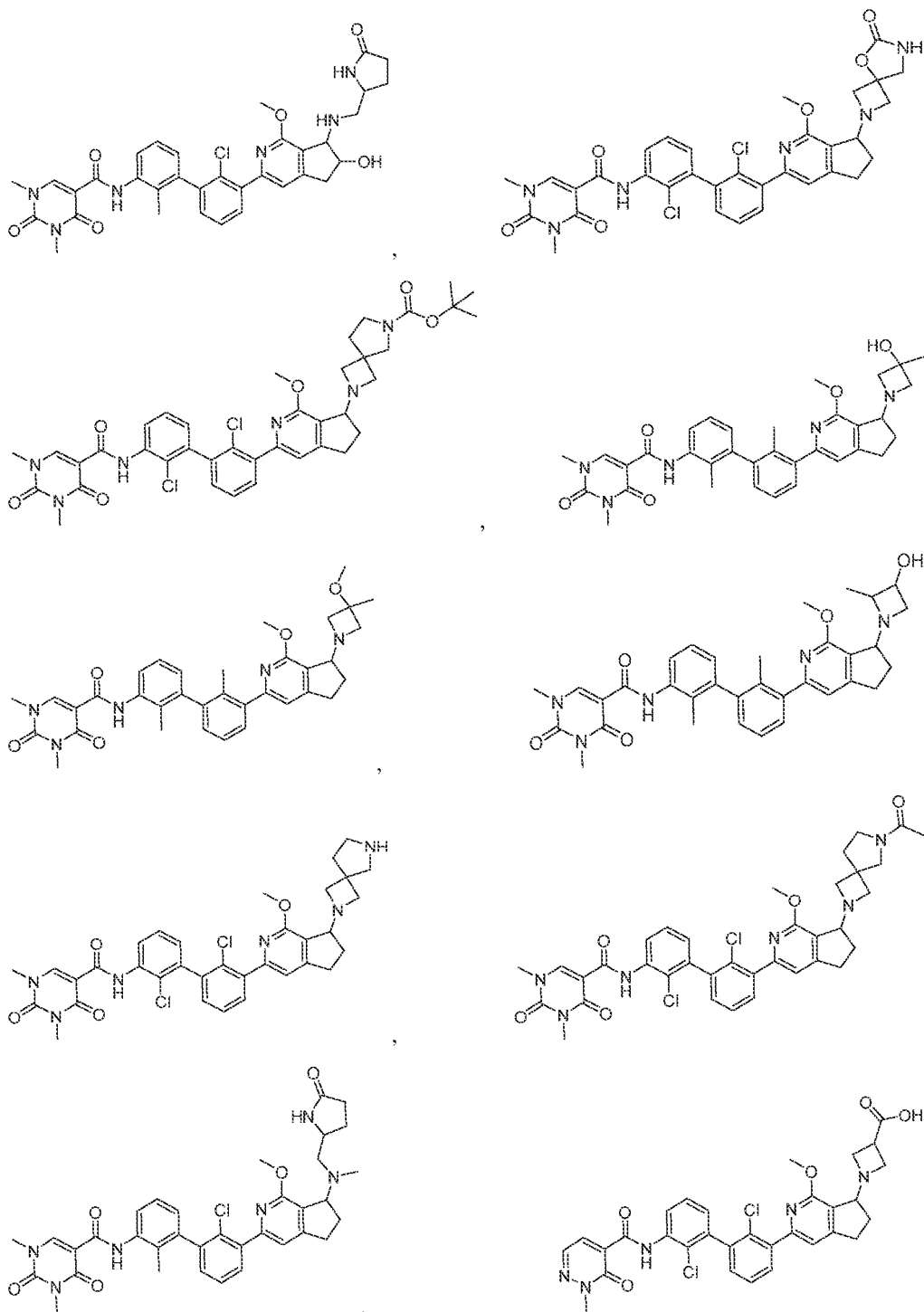


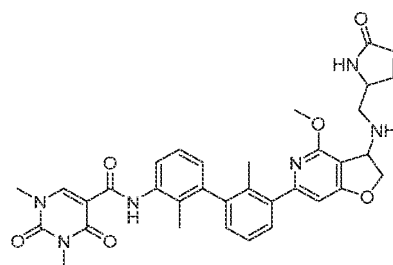
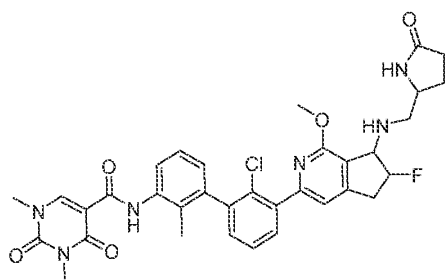










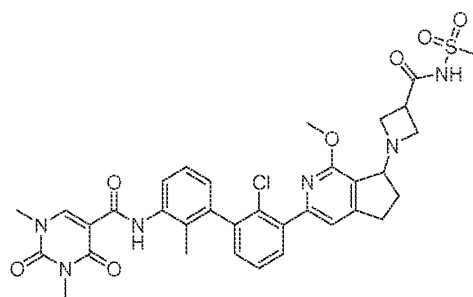
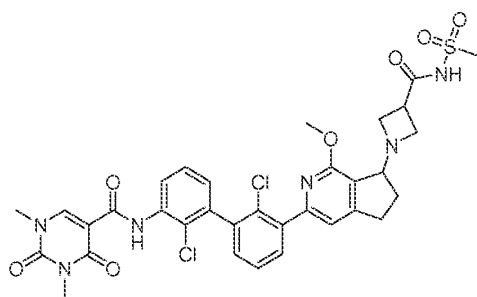
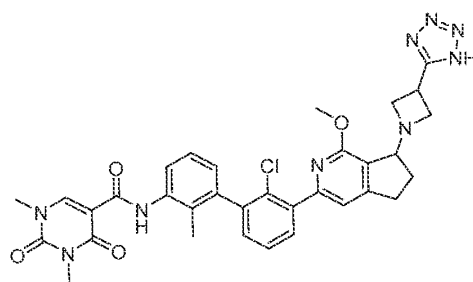
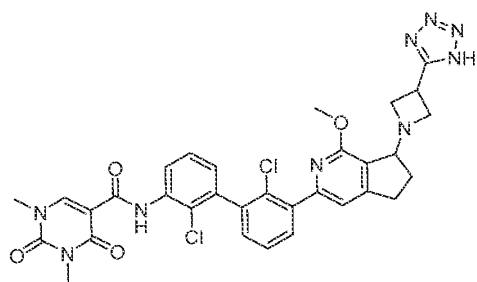
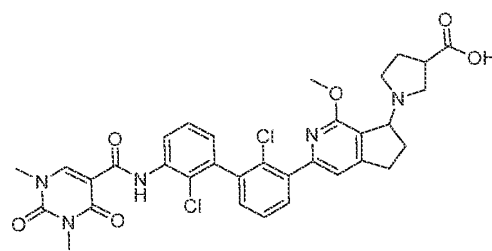
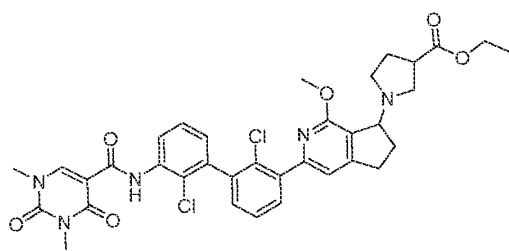


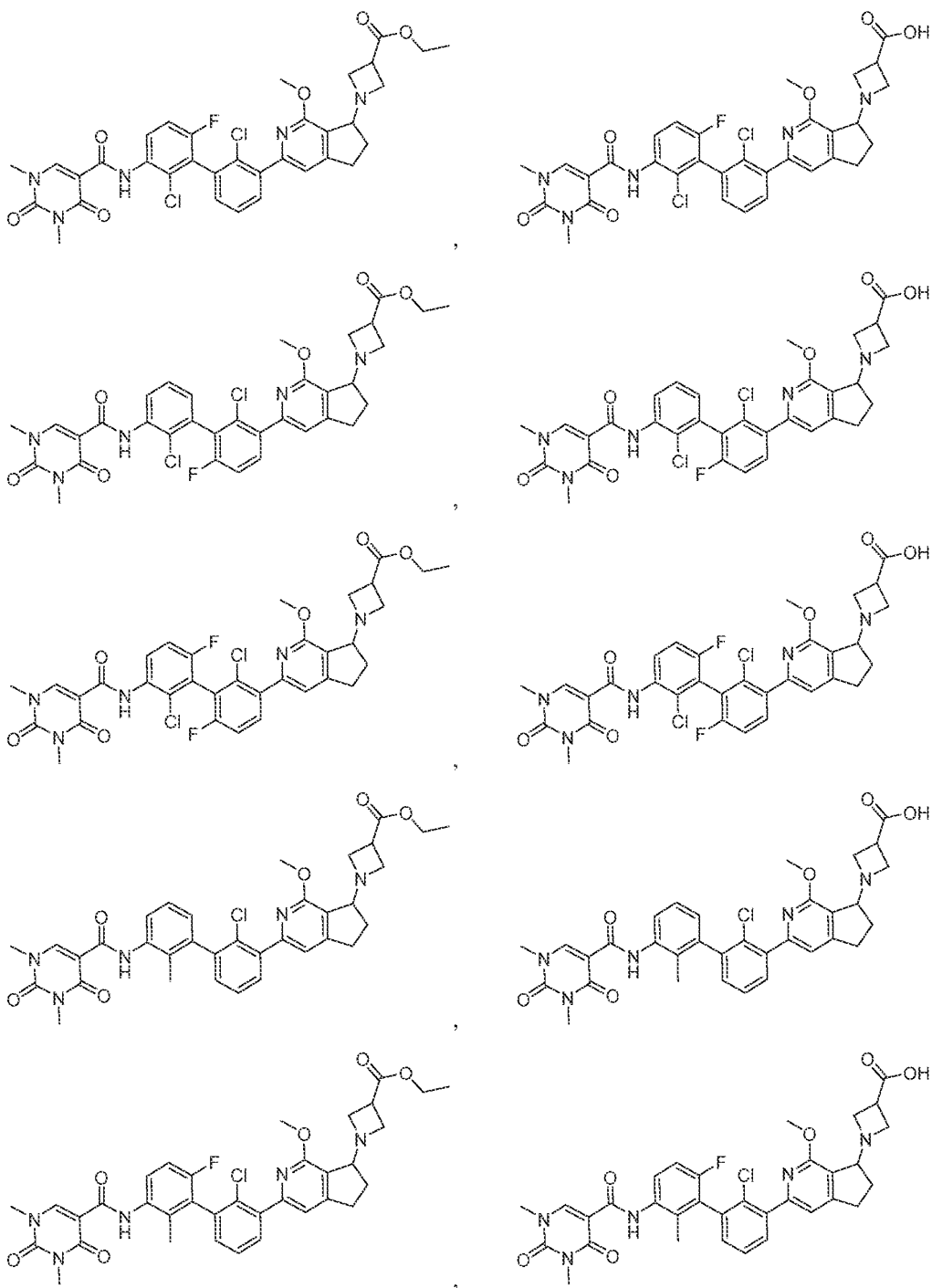
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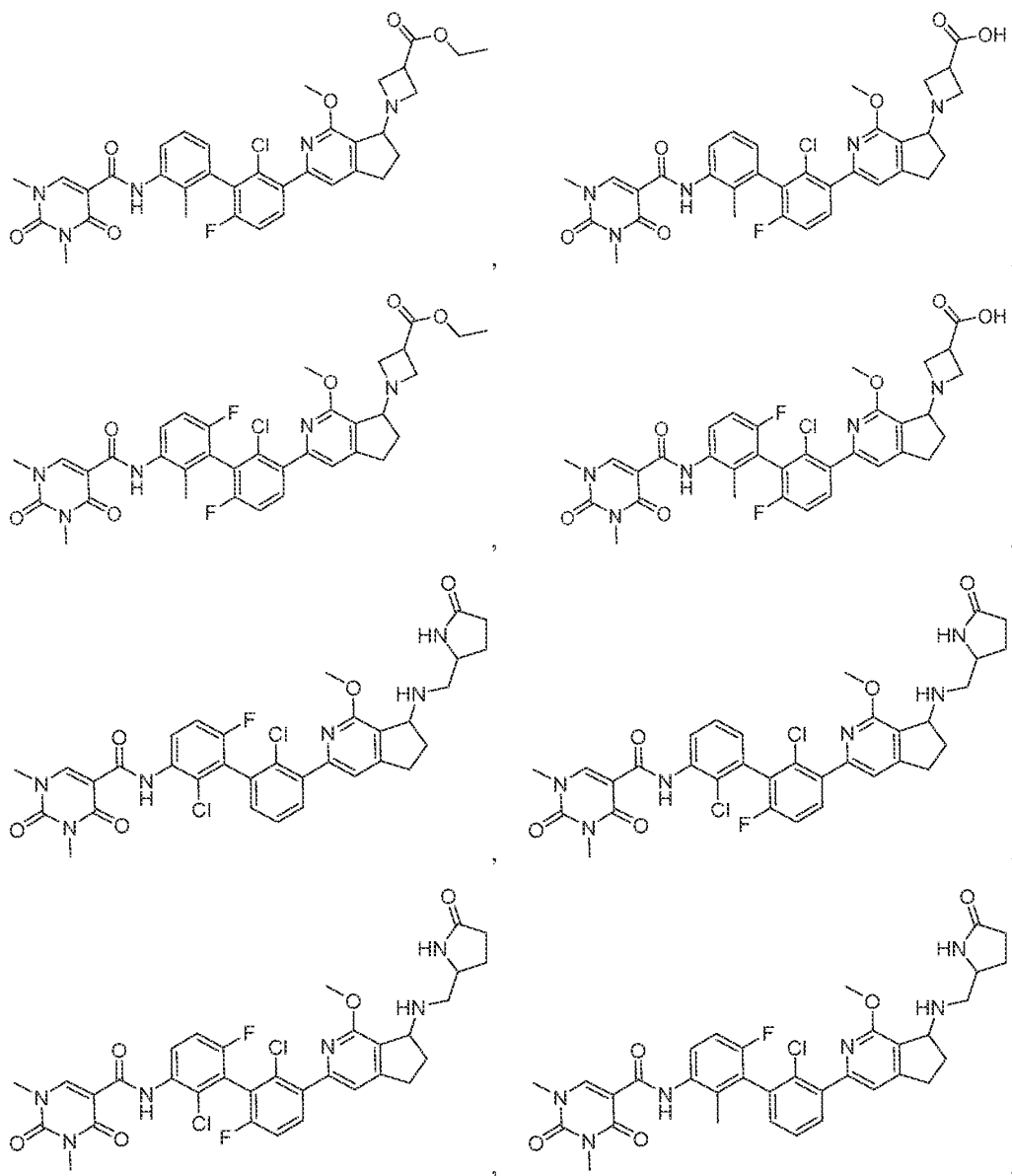
, or a

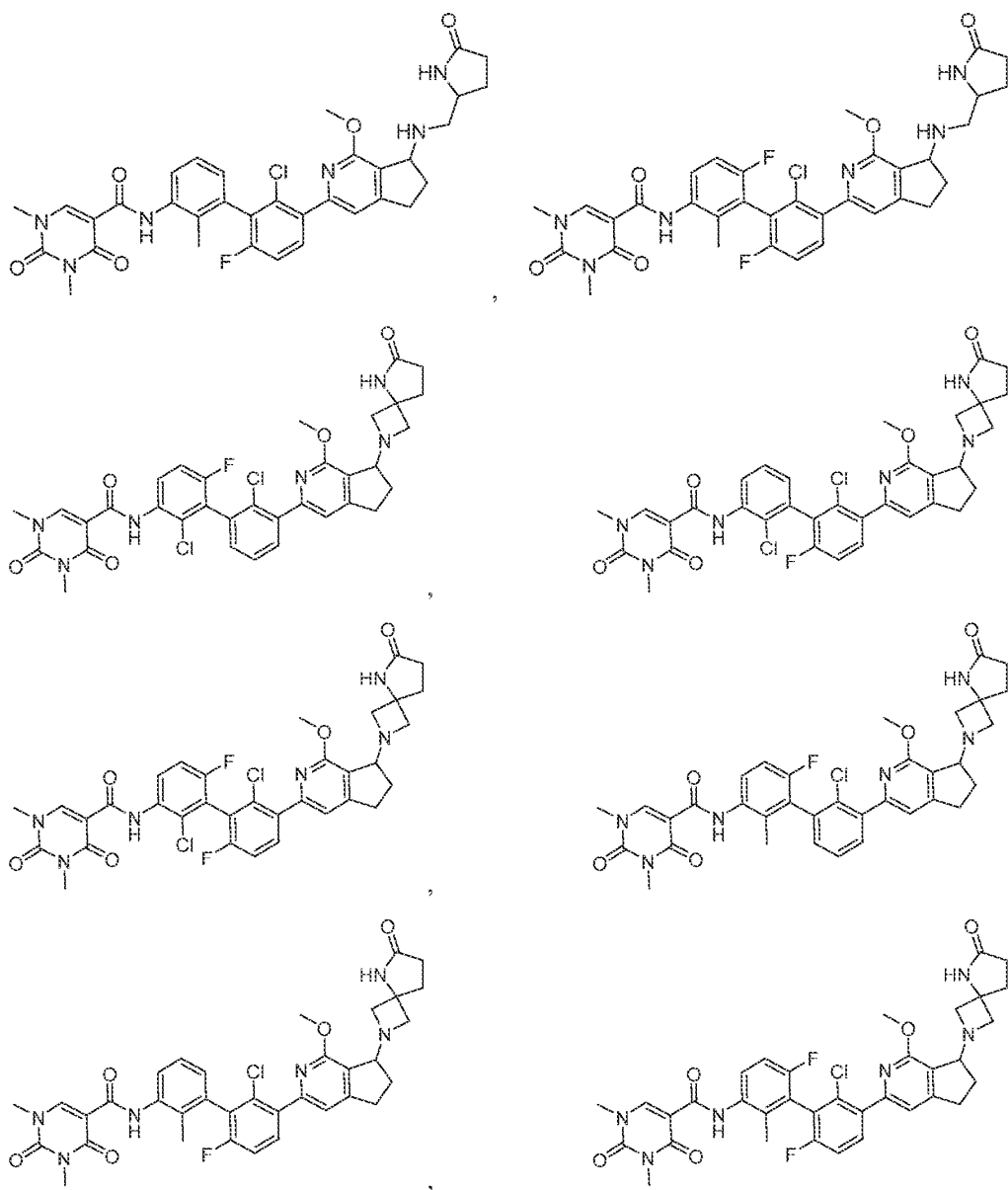
pharmaceutically acceptable salt of any of the foregoing.

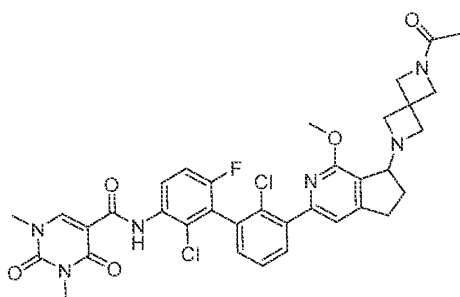
143. The compound of Claim 1 selected from the group consisting of:

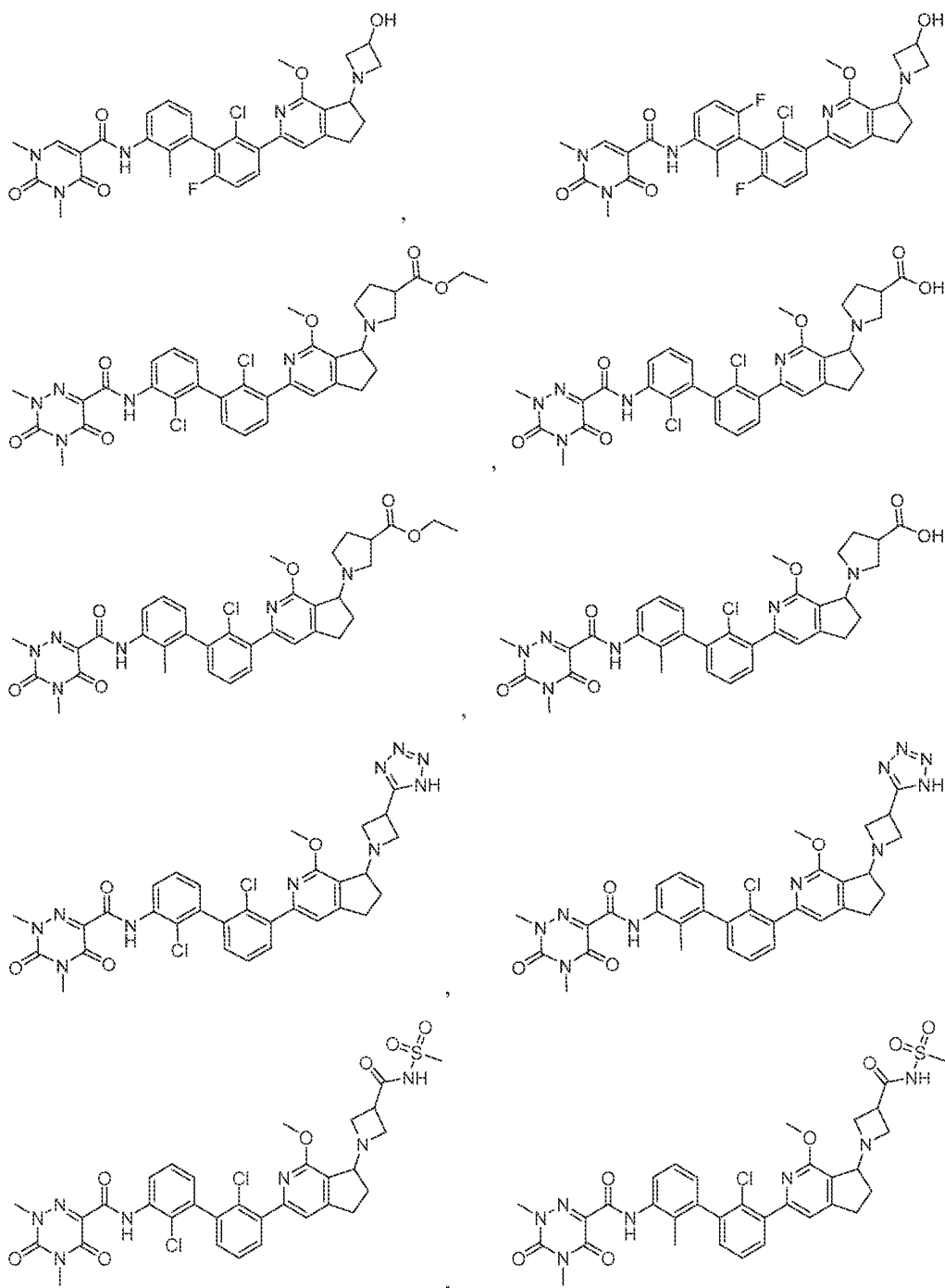


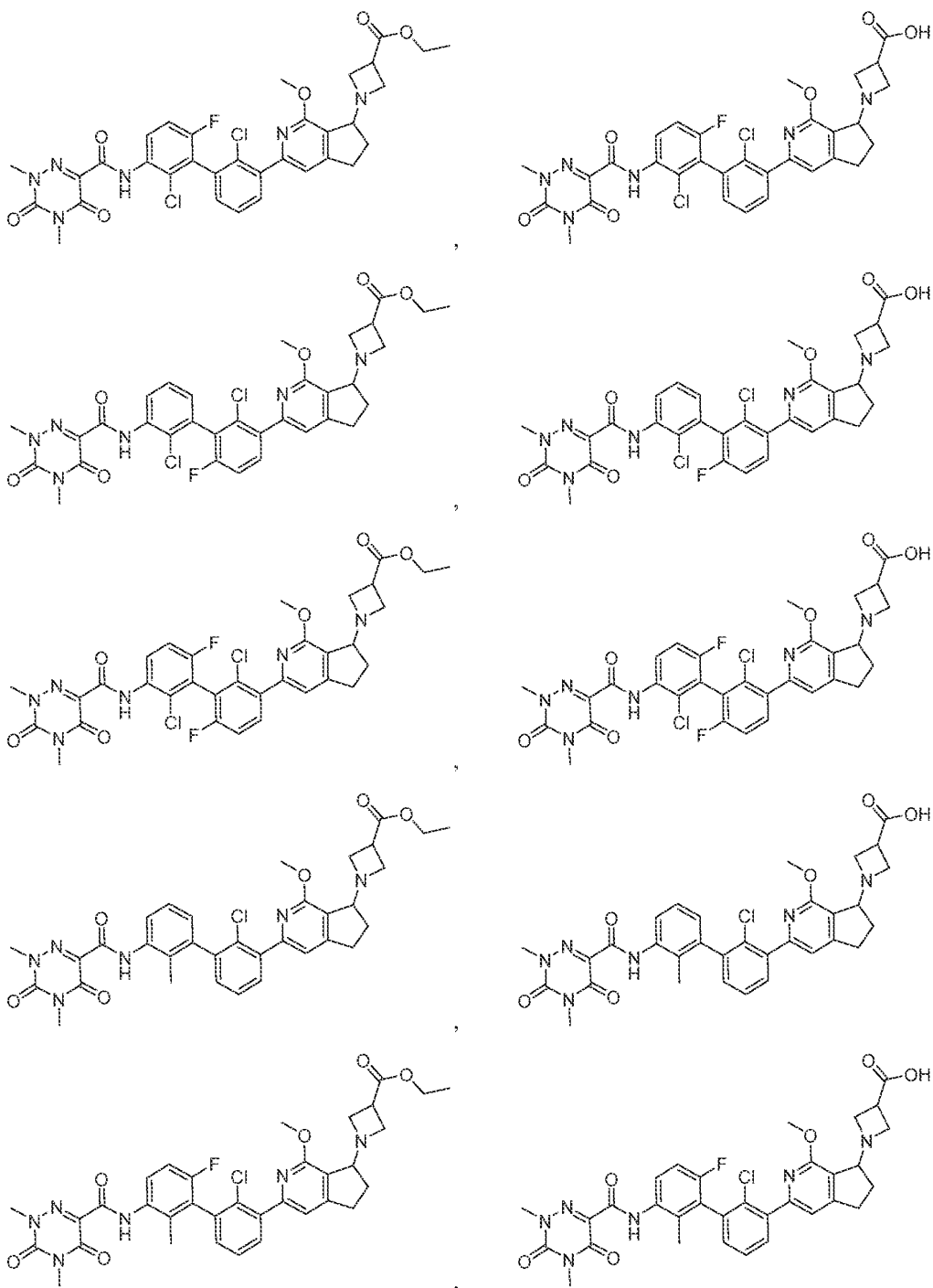


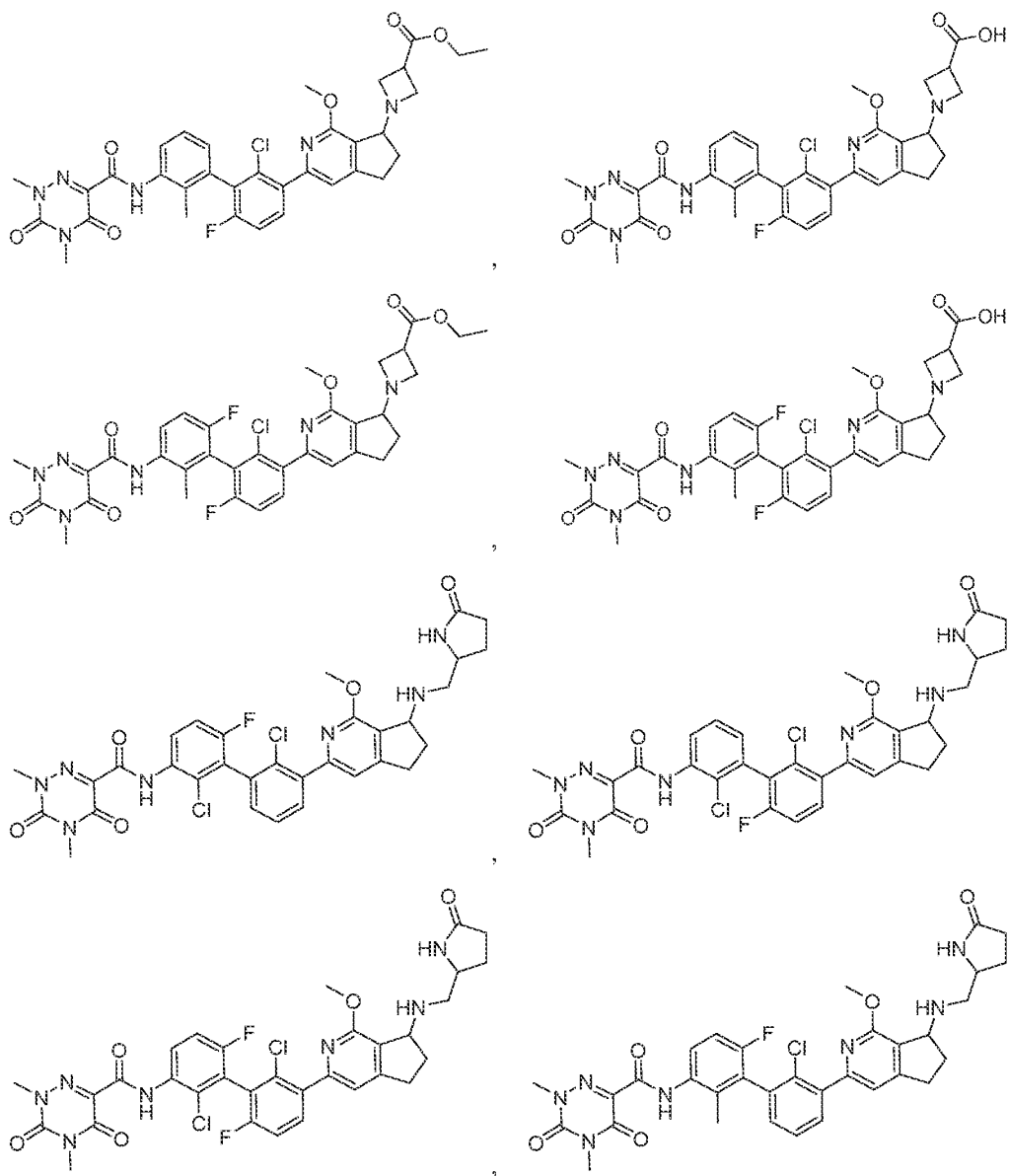


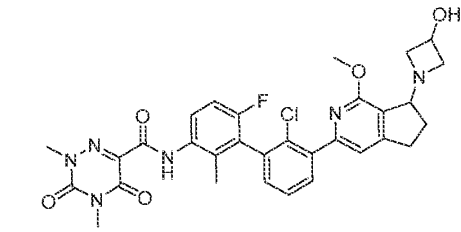
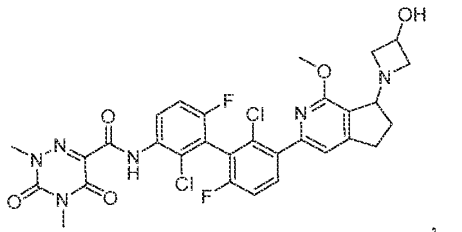
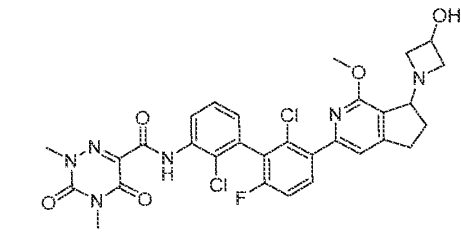
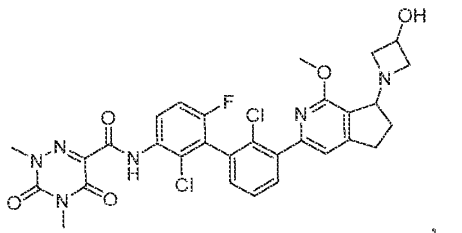
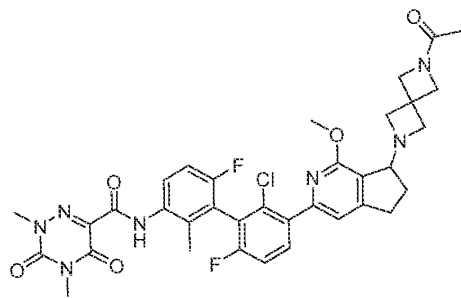
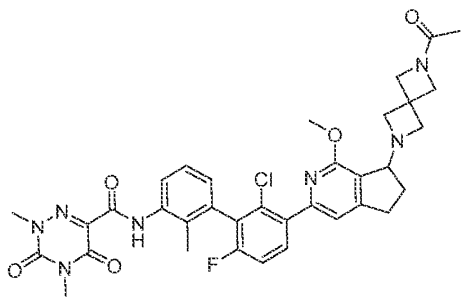
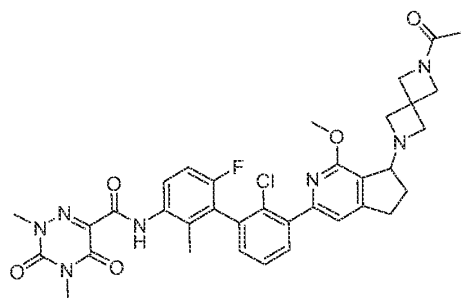
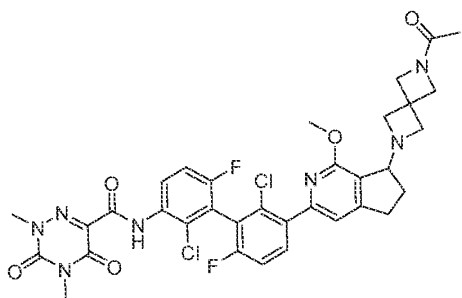
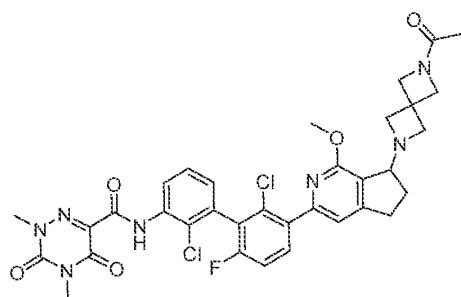
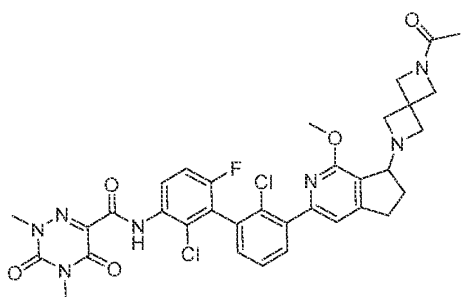


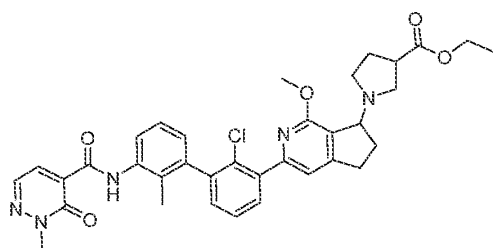
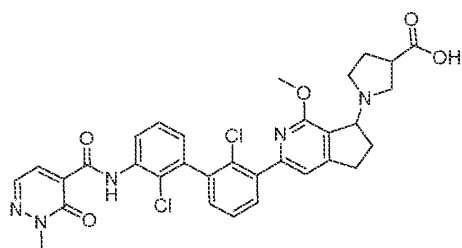
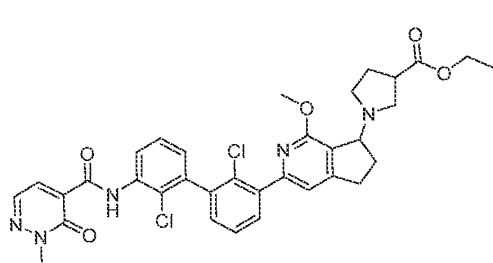
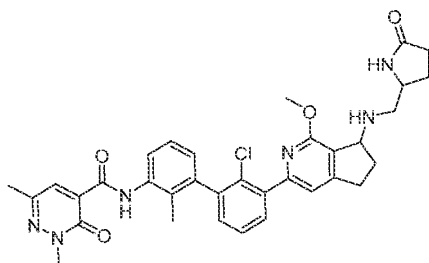
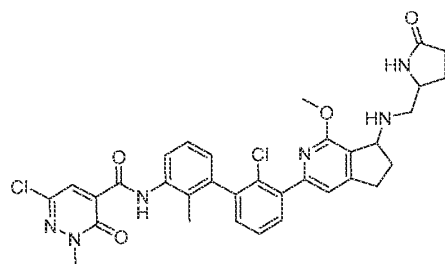
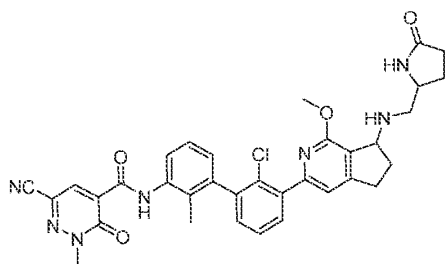
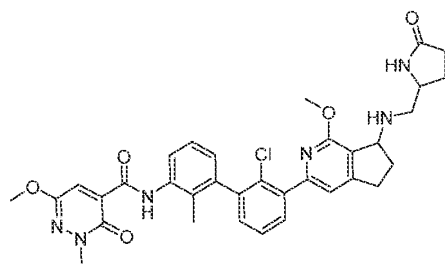
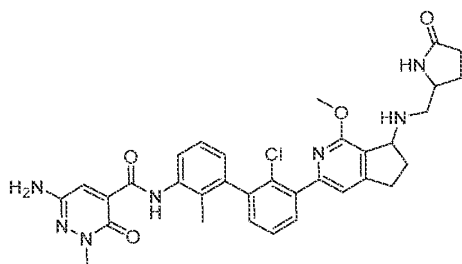
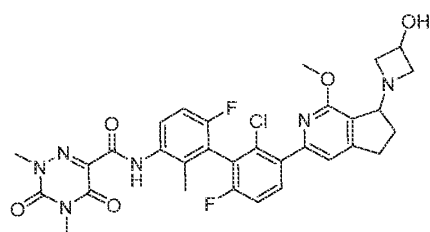
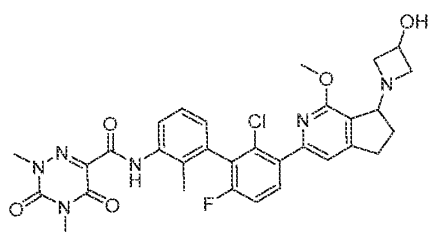


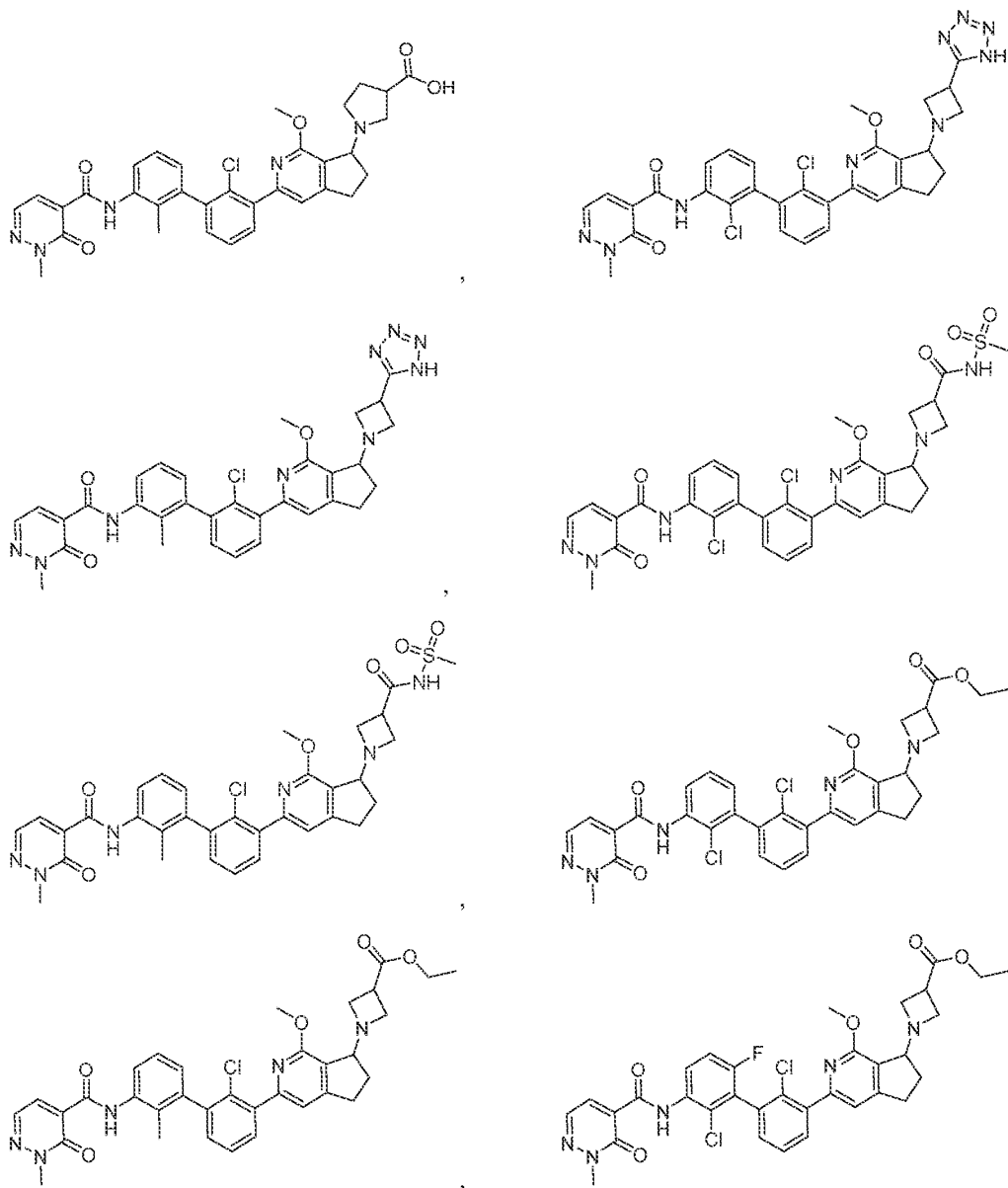


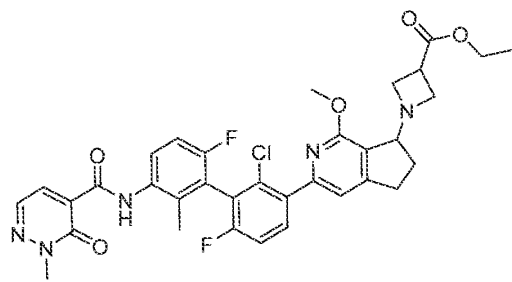
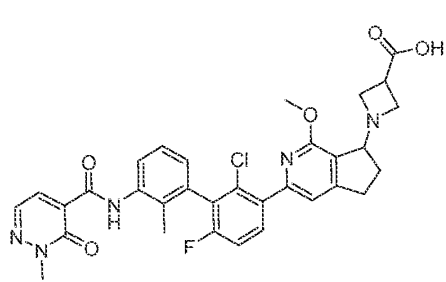
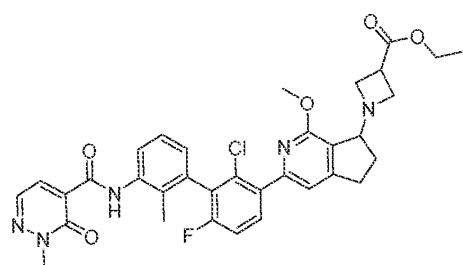
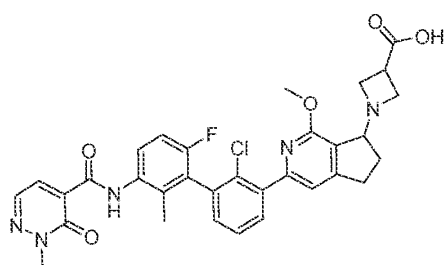
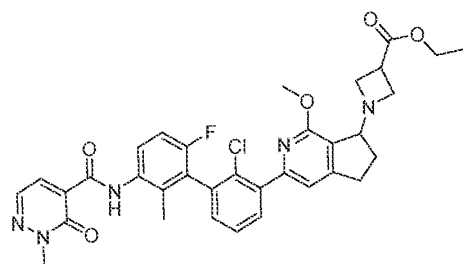
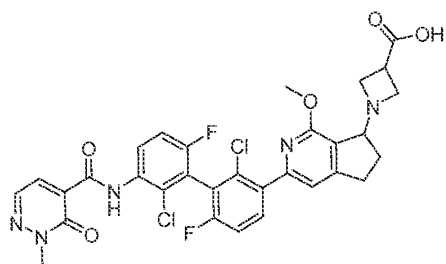
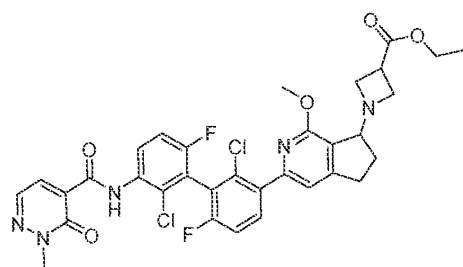
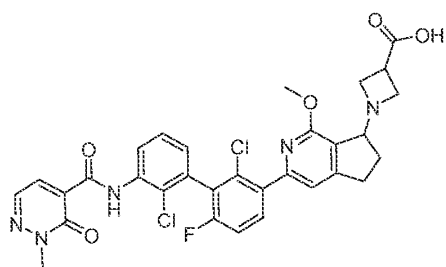
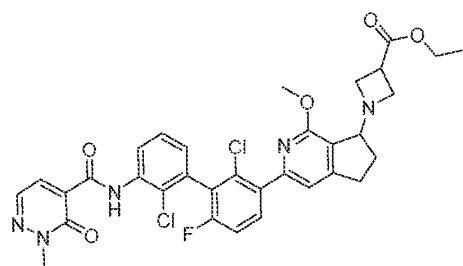
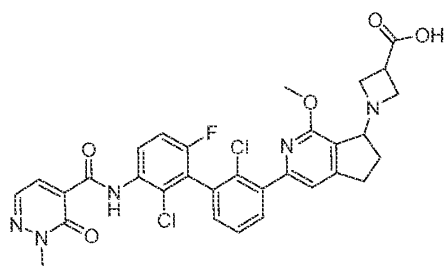


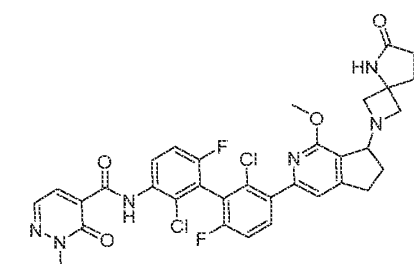
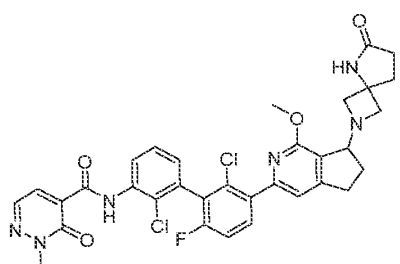
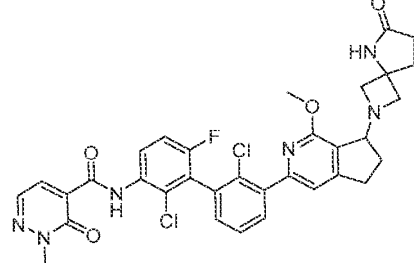
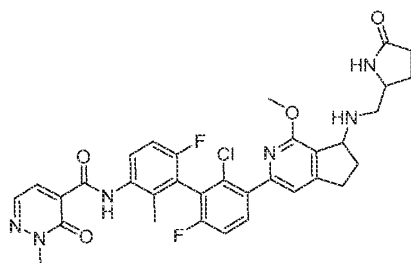
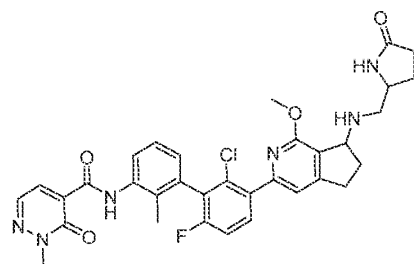
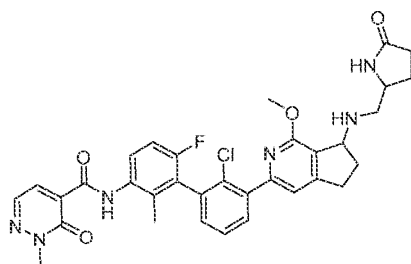
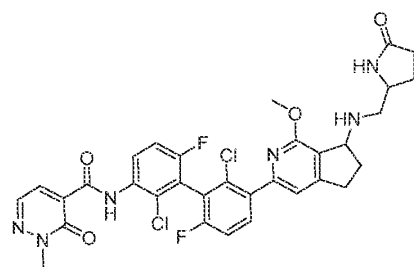
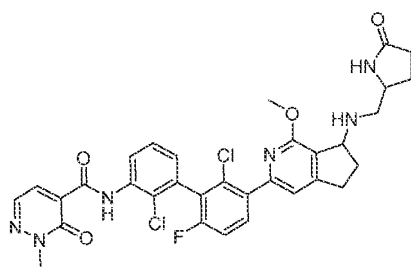
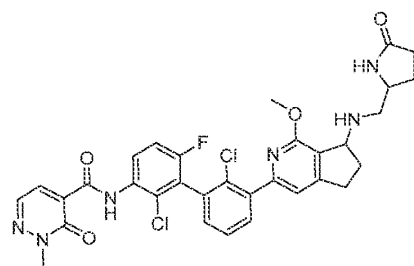
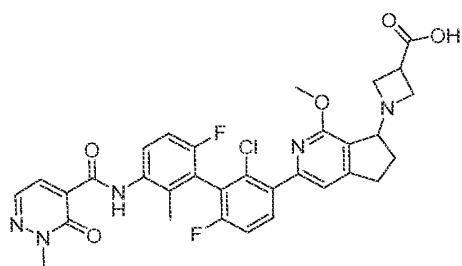


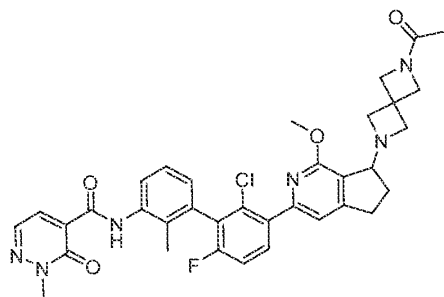
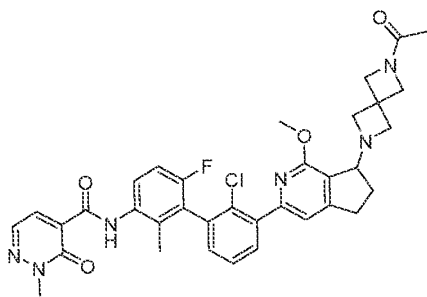
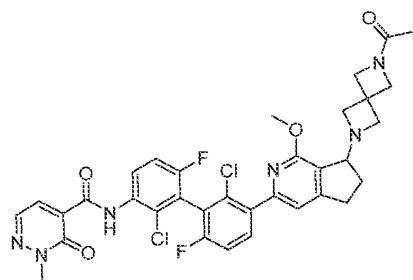
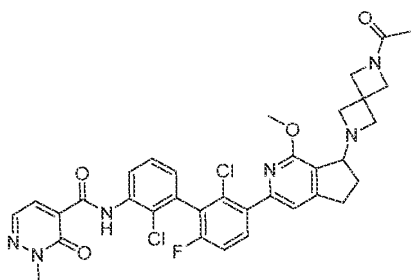
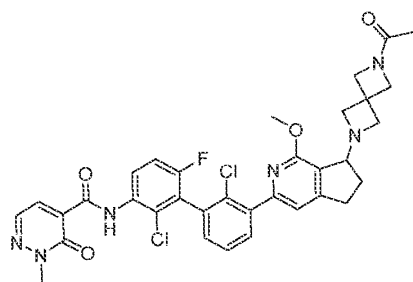
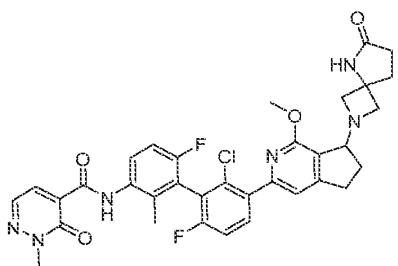
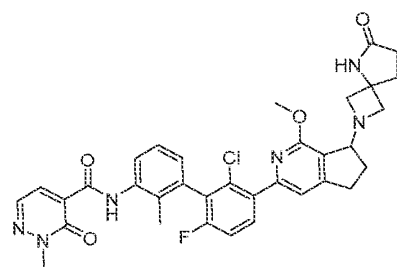
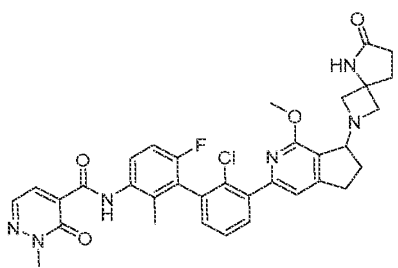


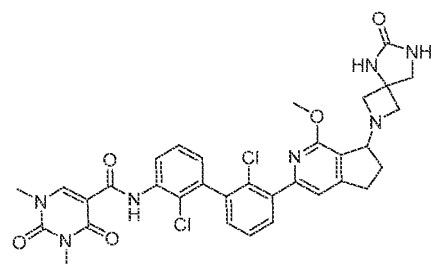
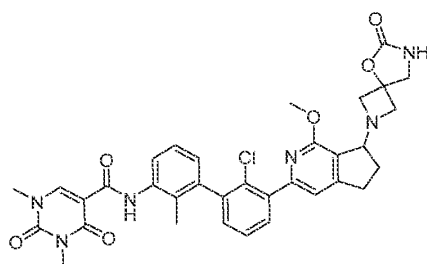
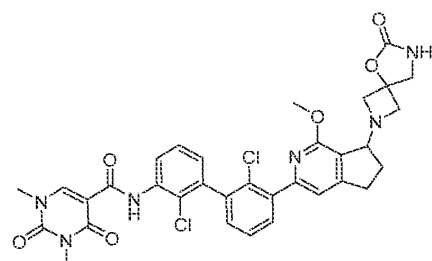
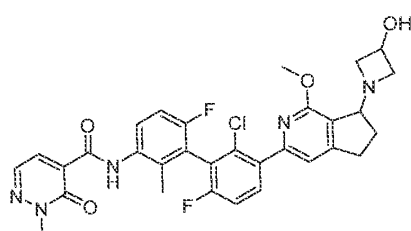
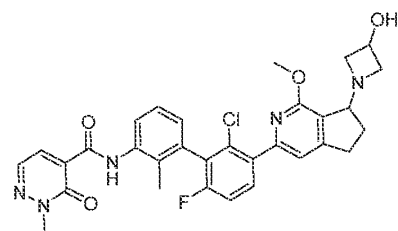
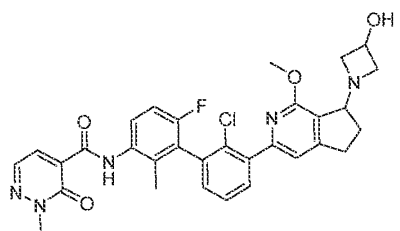
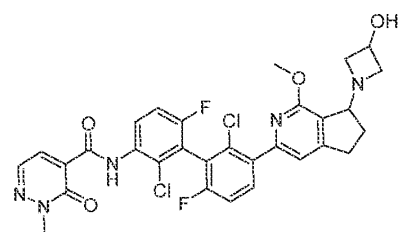
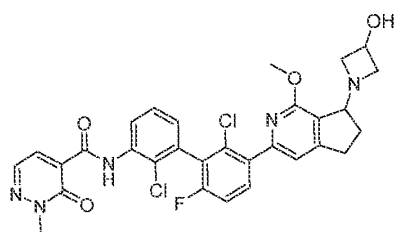
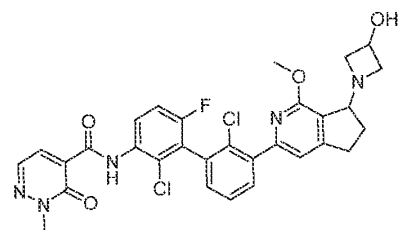
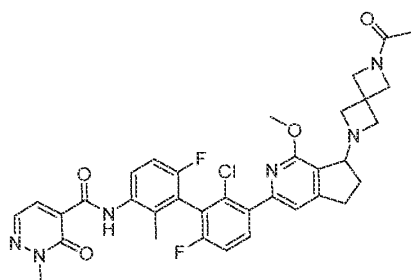


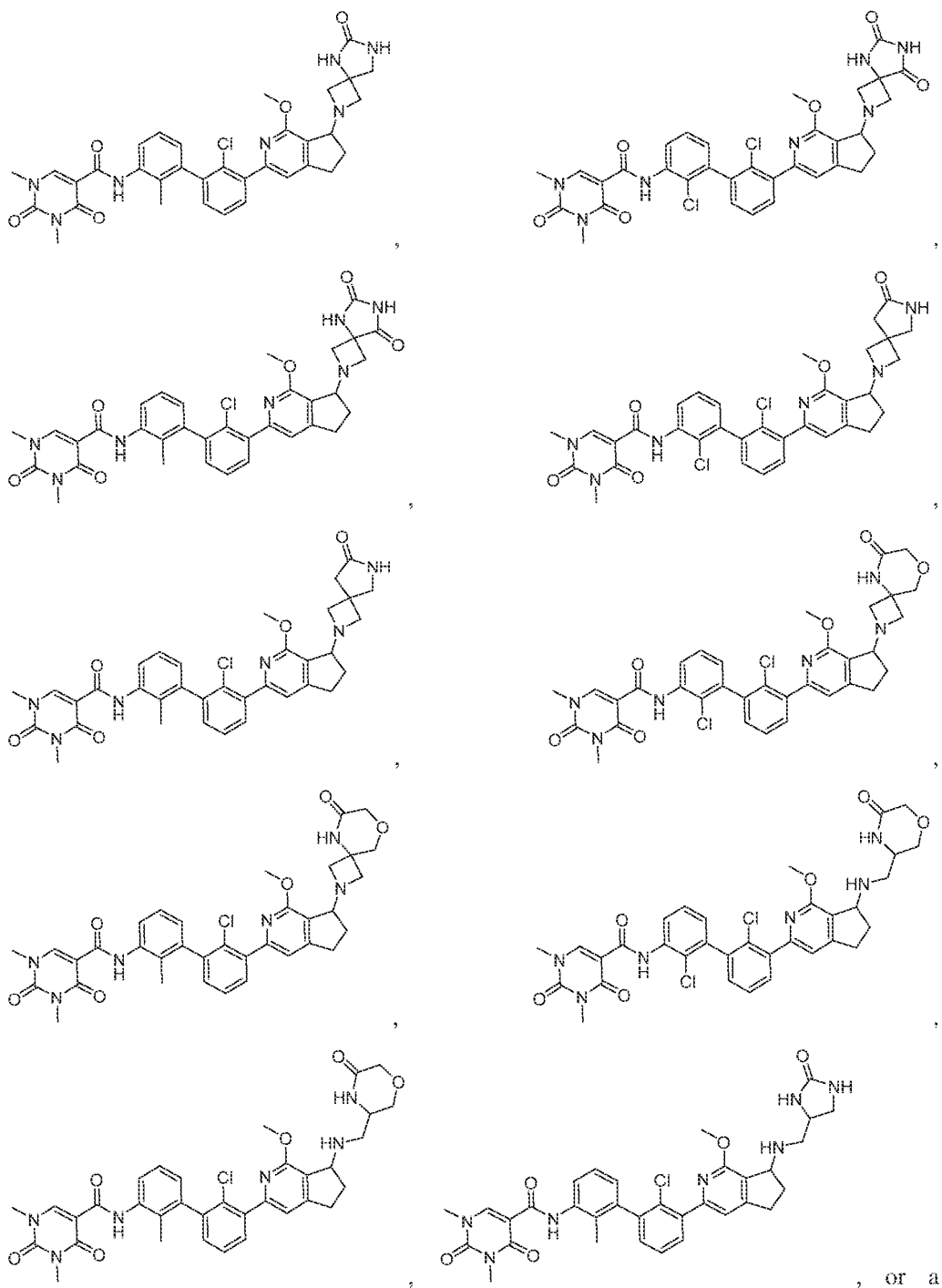






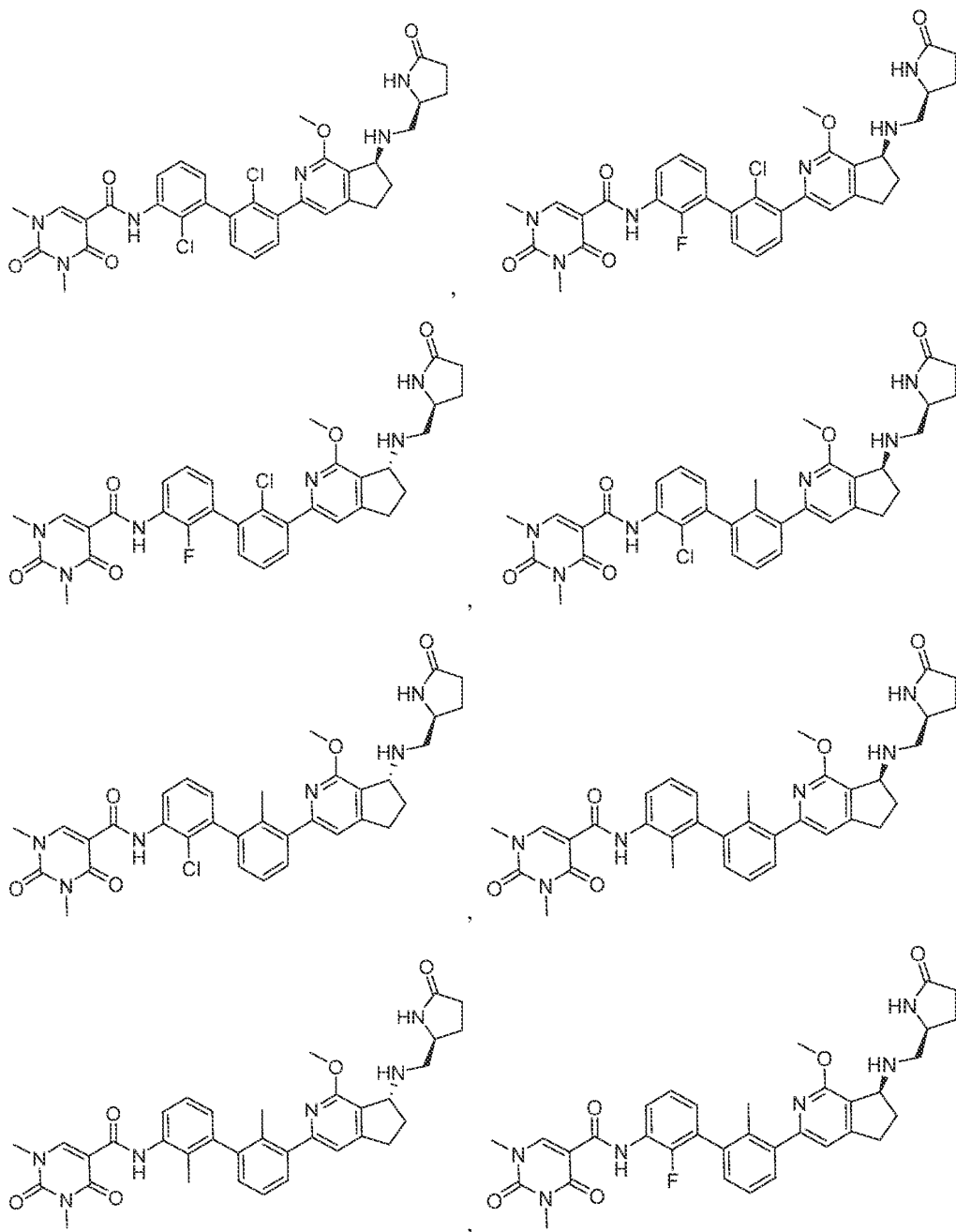


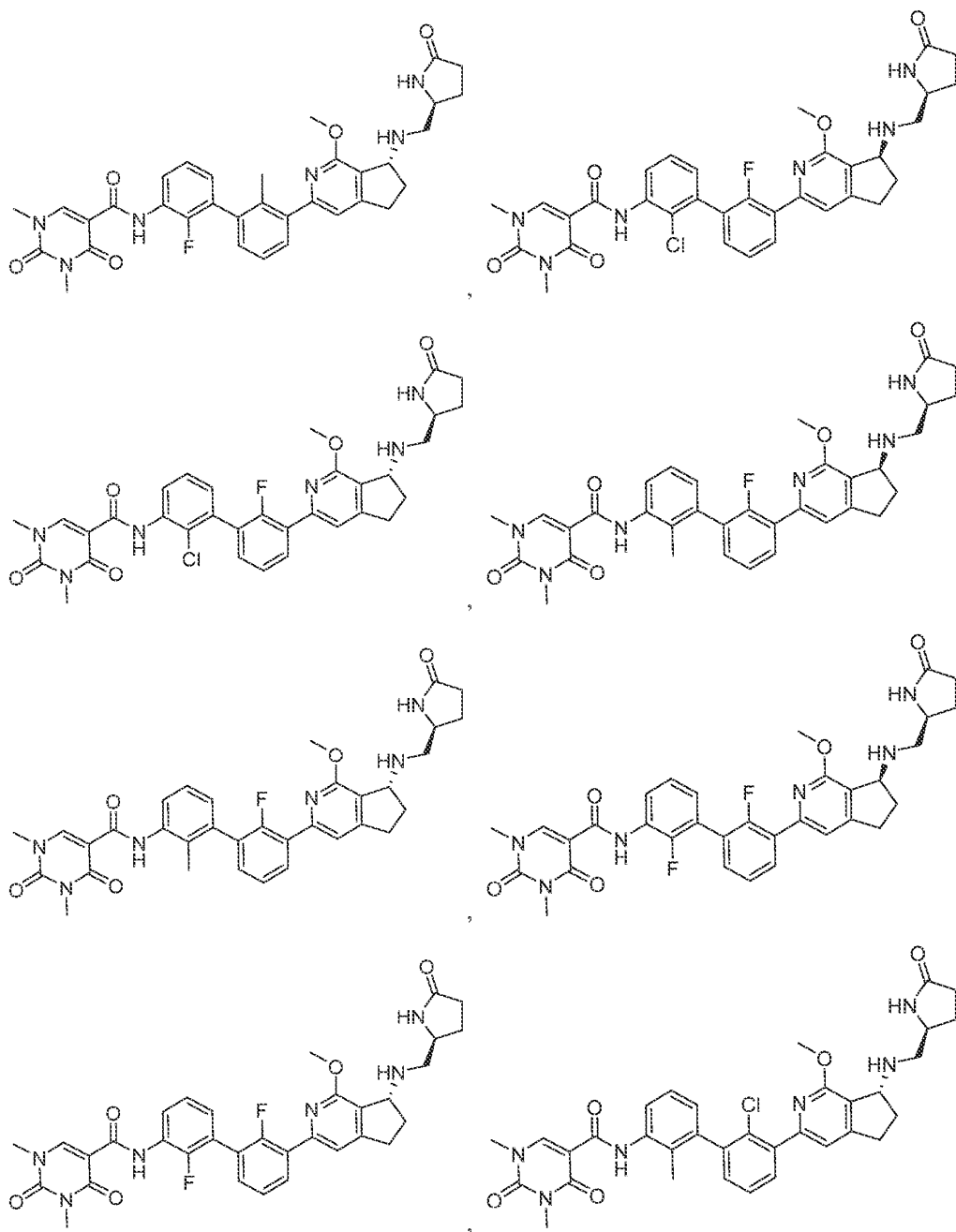


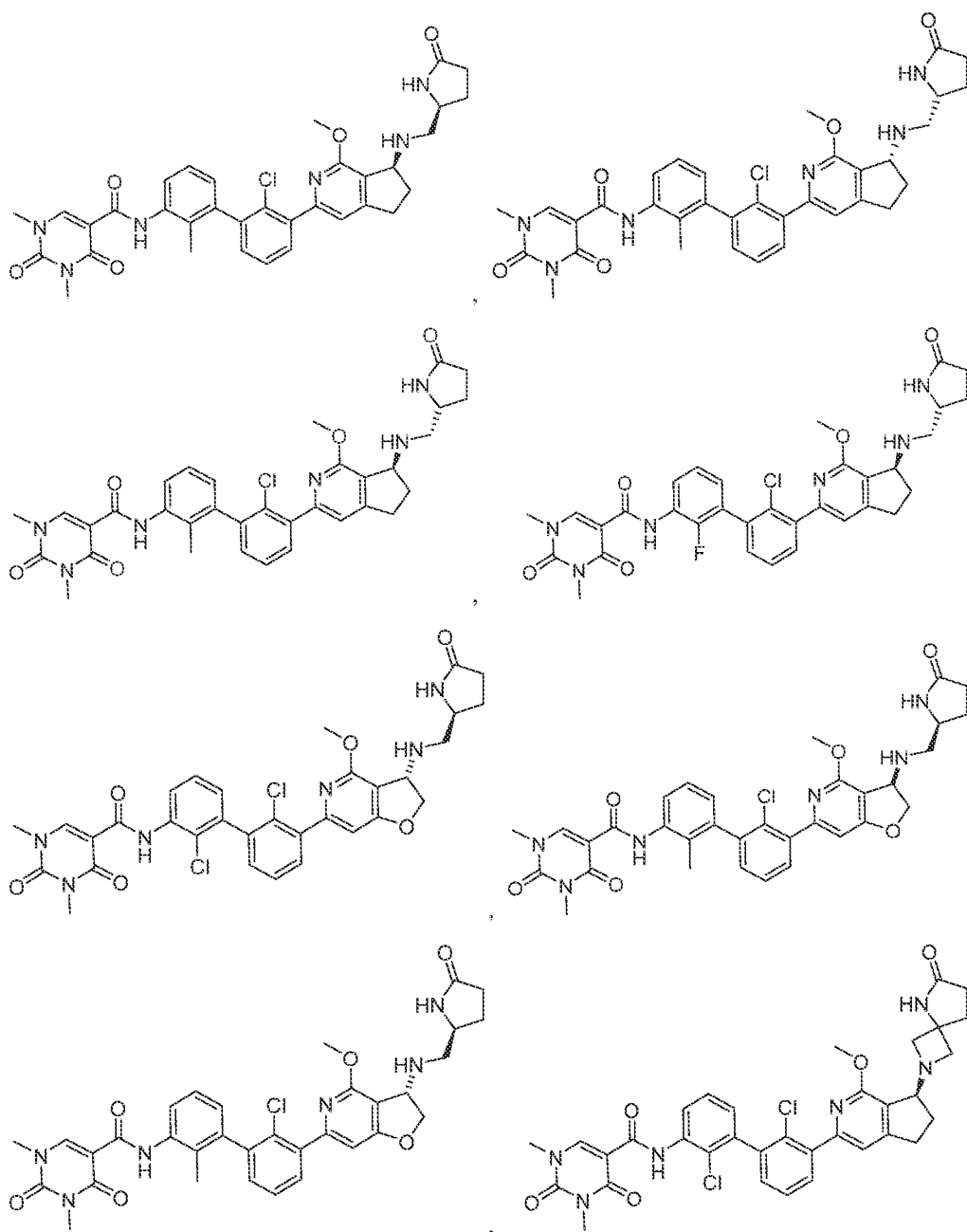


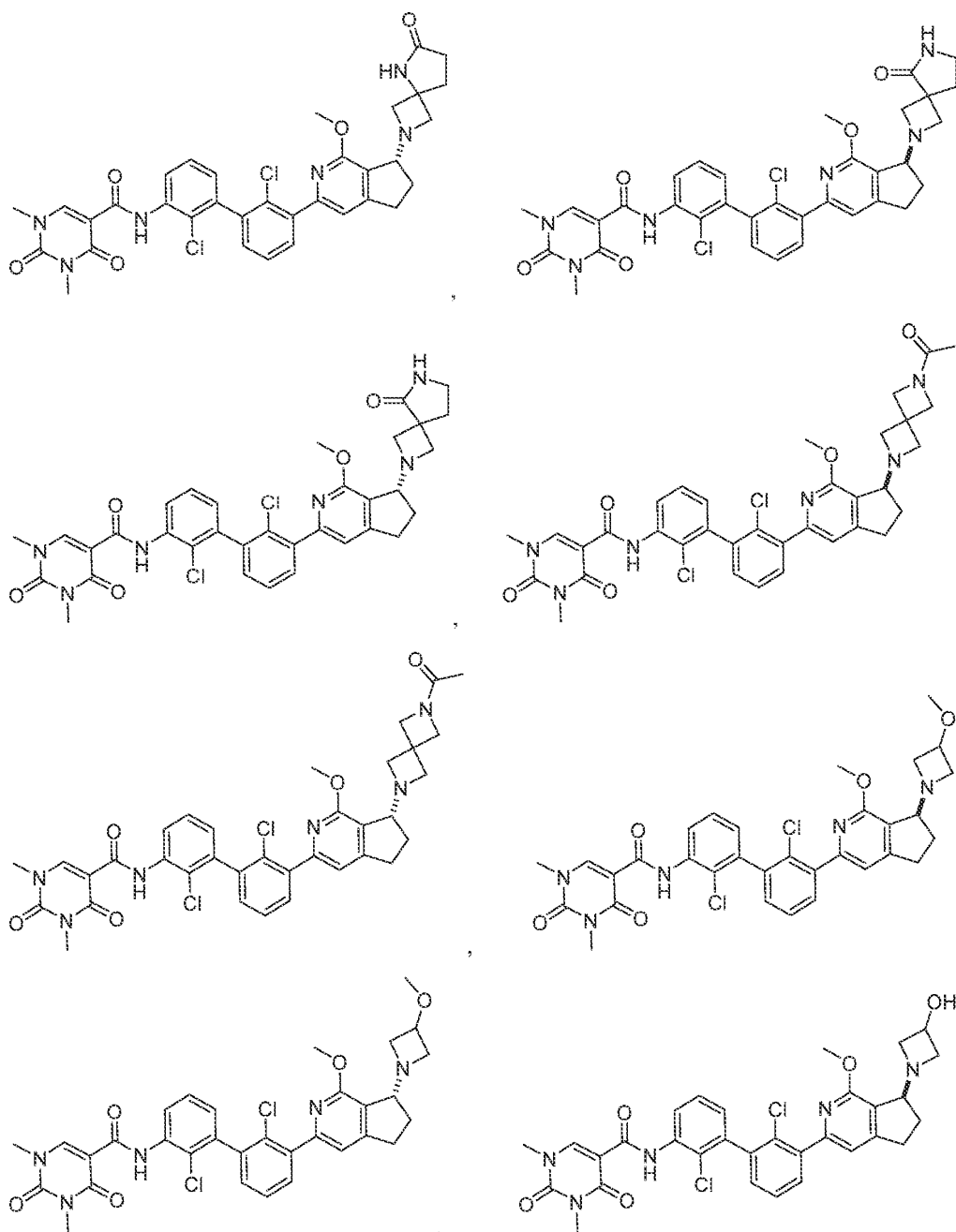
pharmaceutically acceptable salt of any of the foregoing.

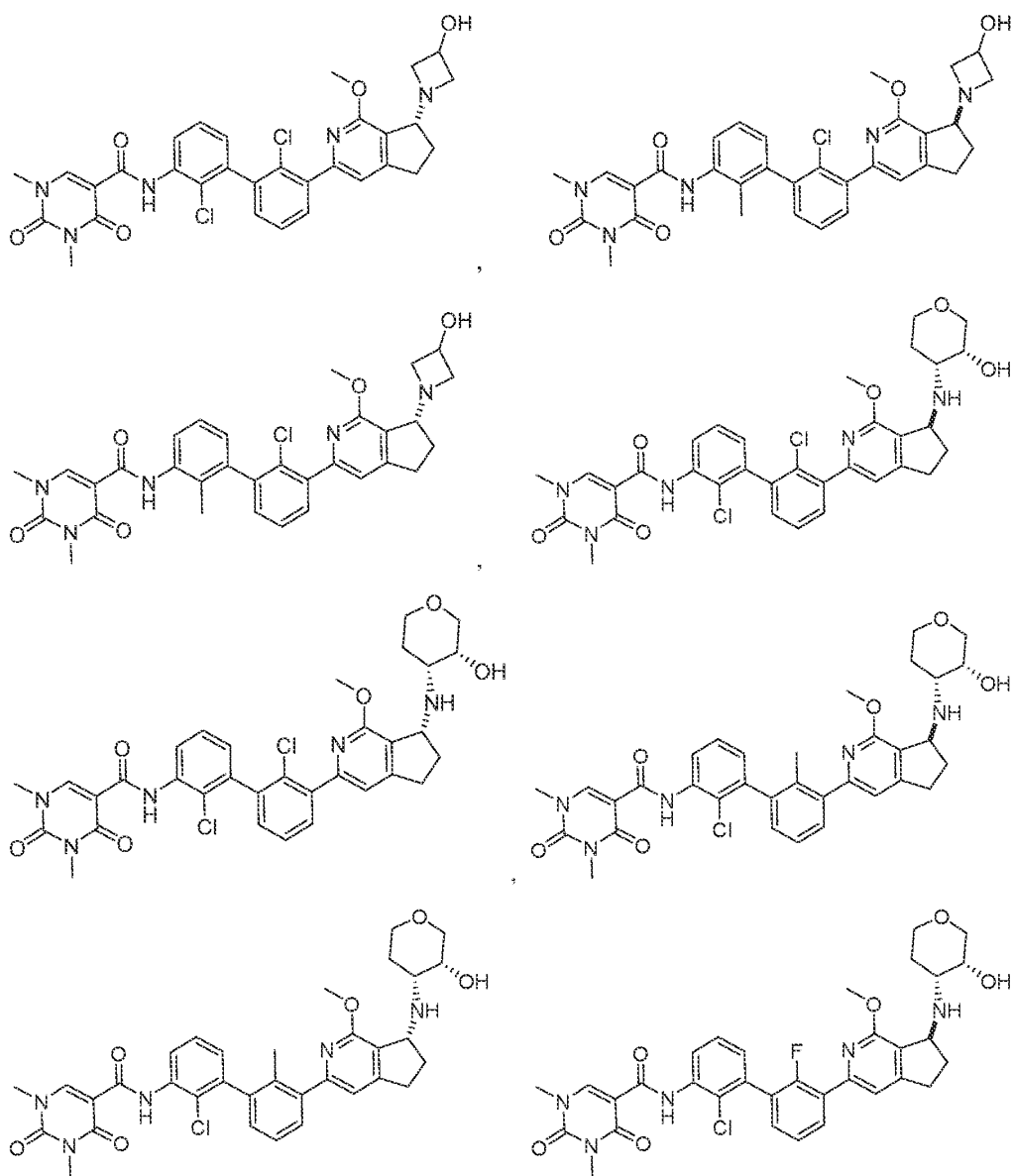
144. The compound of Claim 1 selected from the group consisting of:

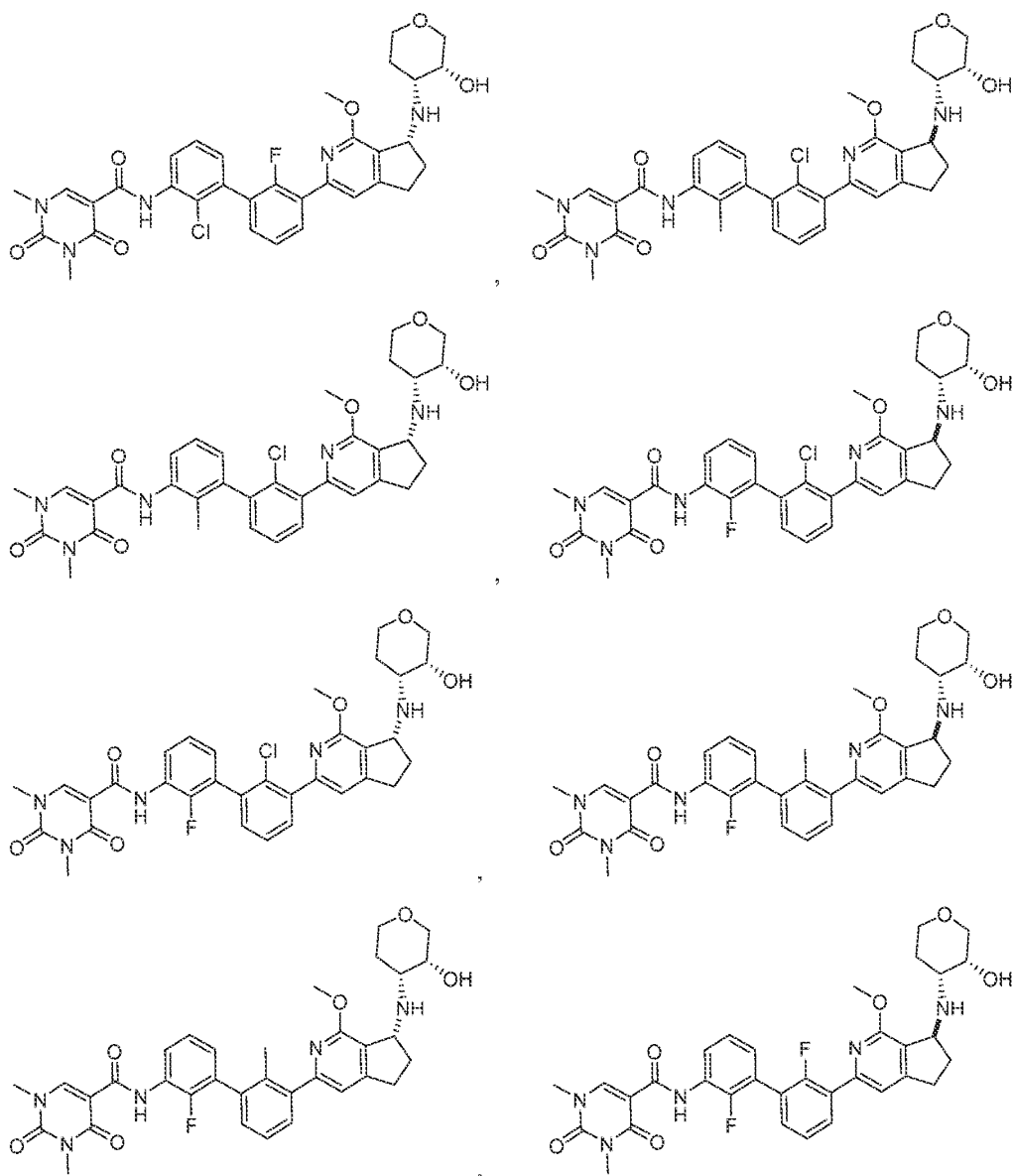


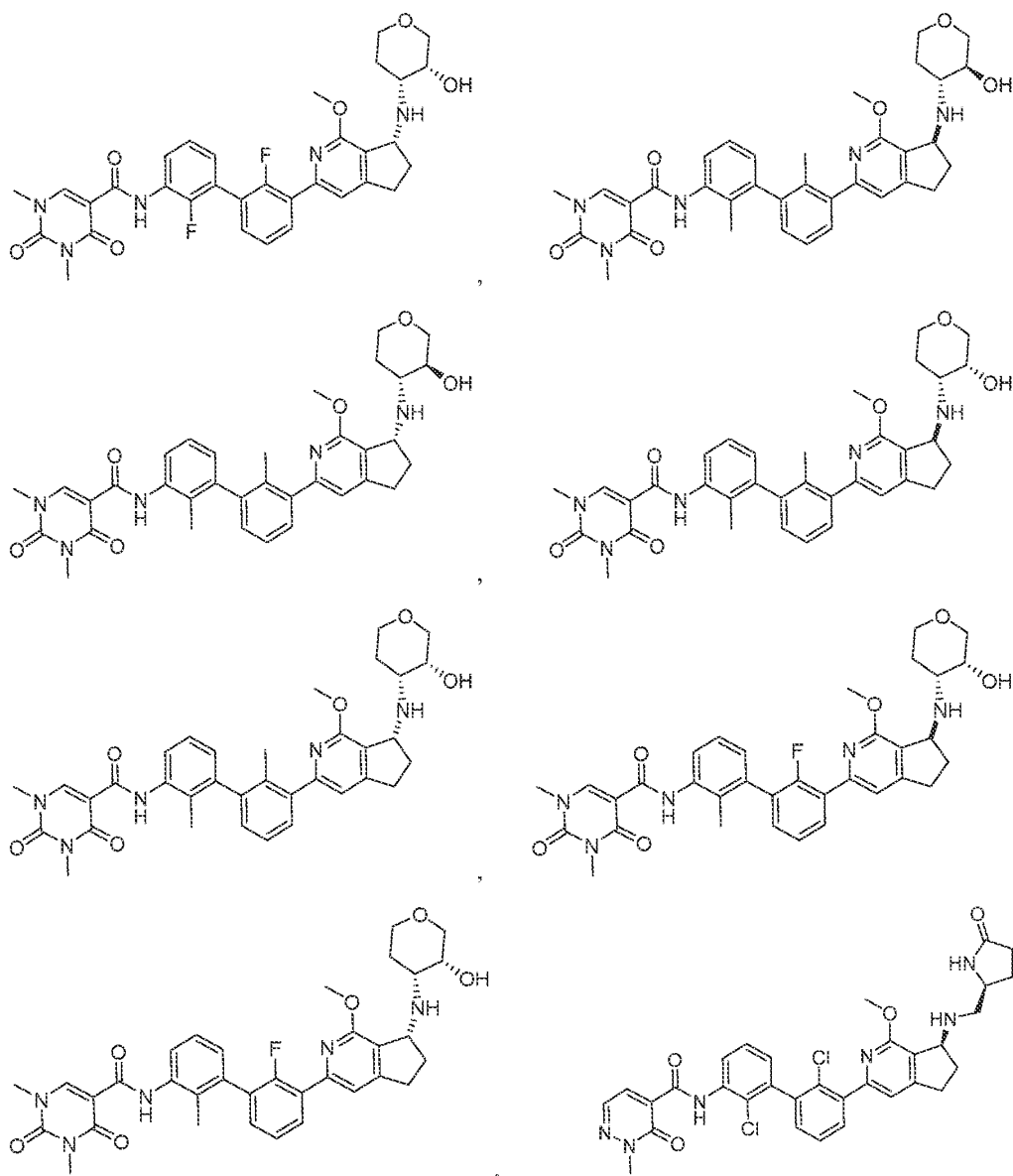


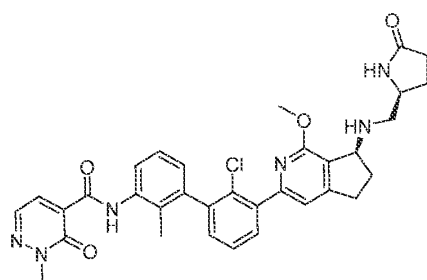
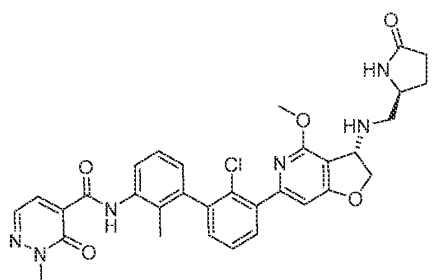
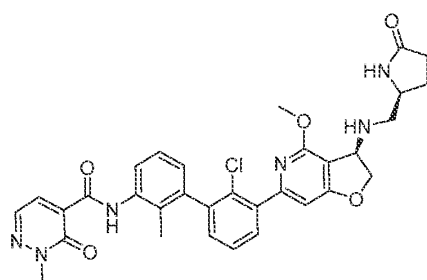
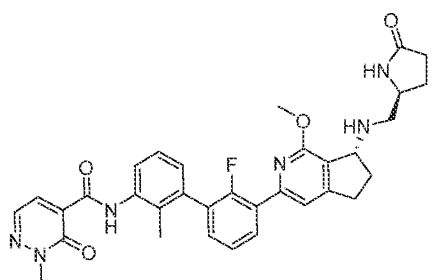
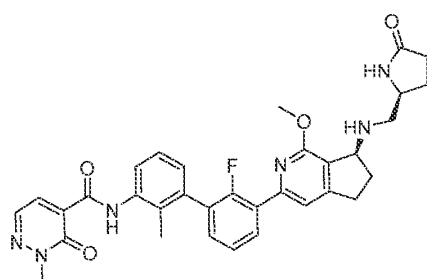
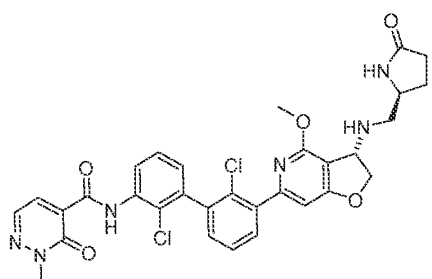
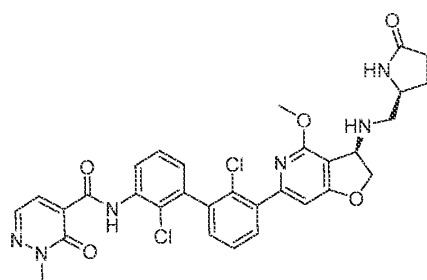
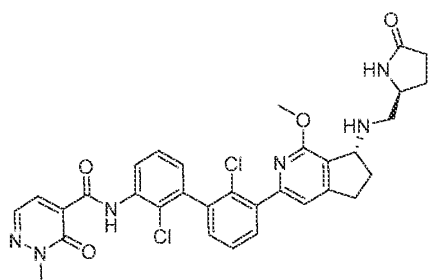


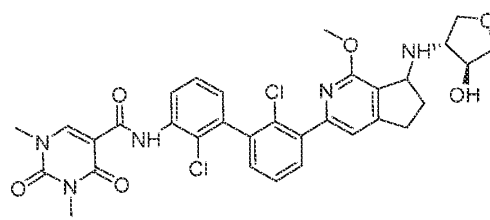
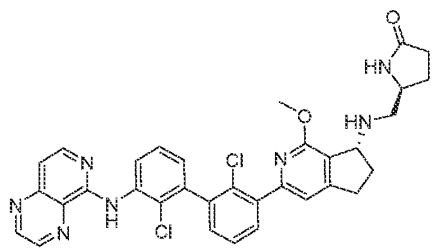
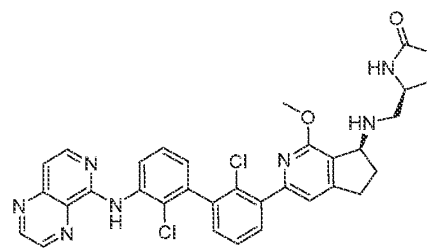
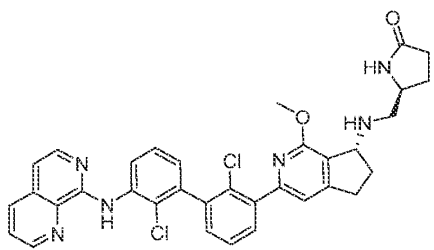
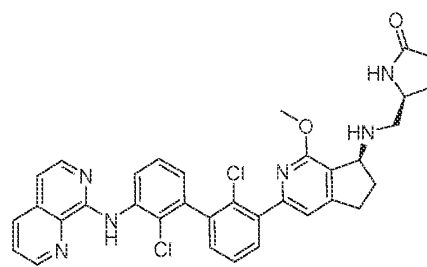
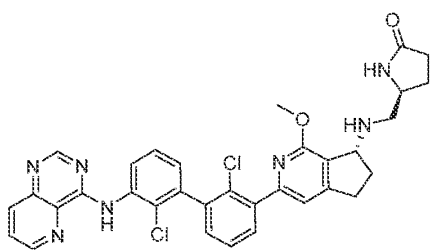
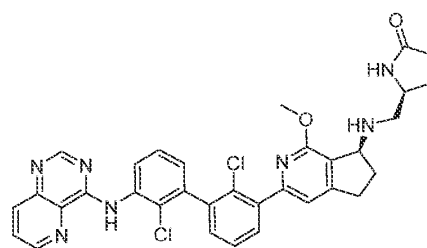
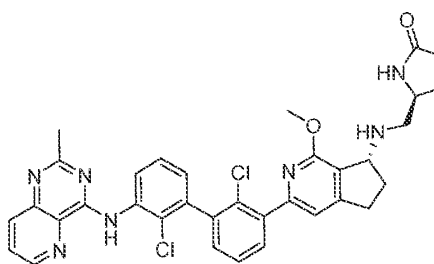
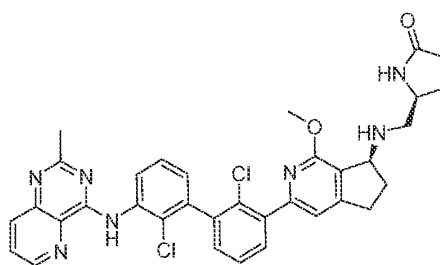
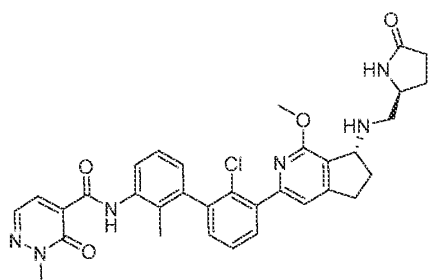


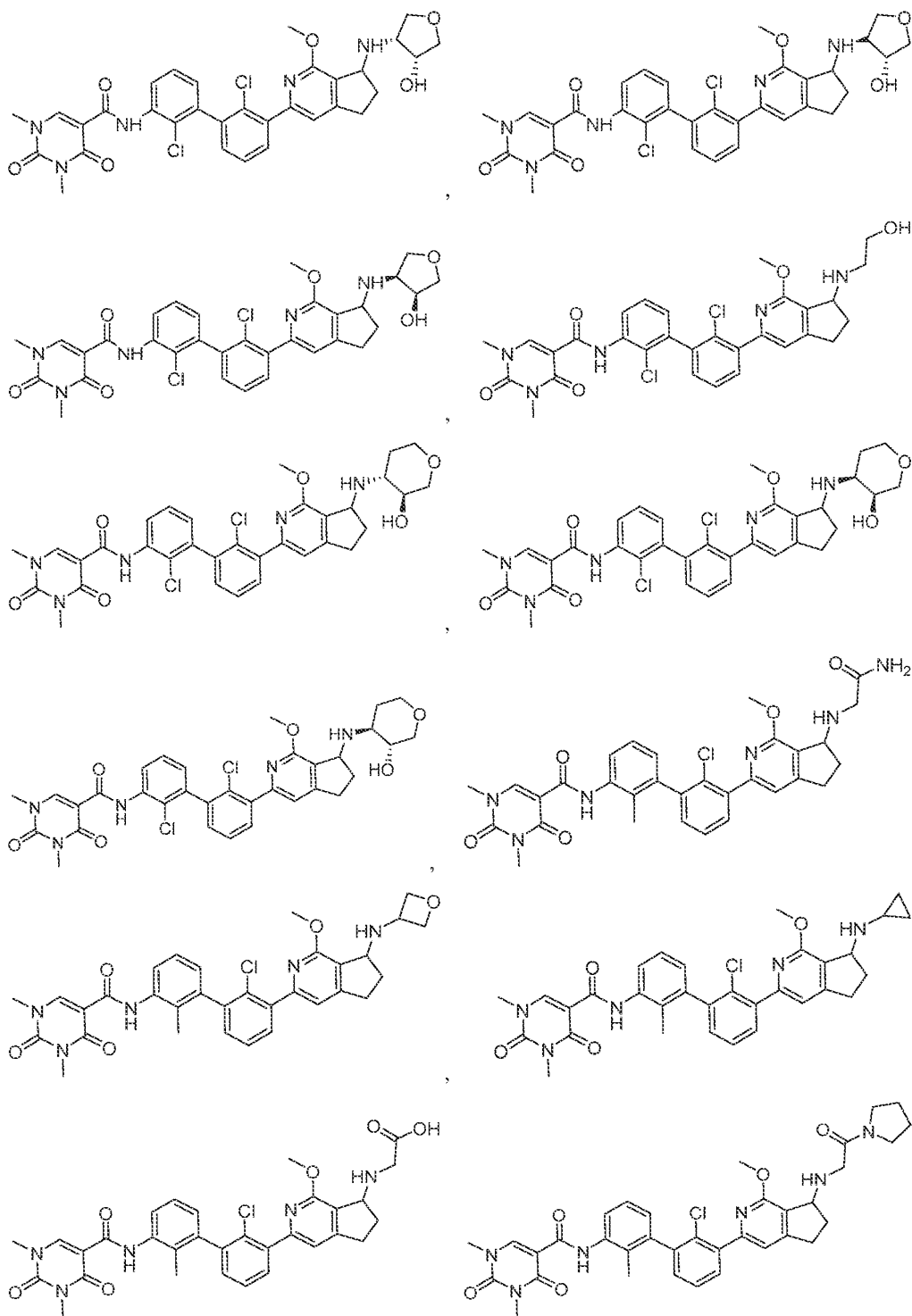


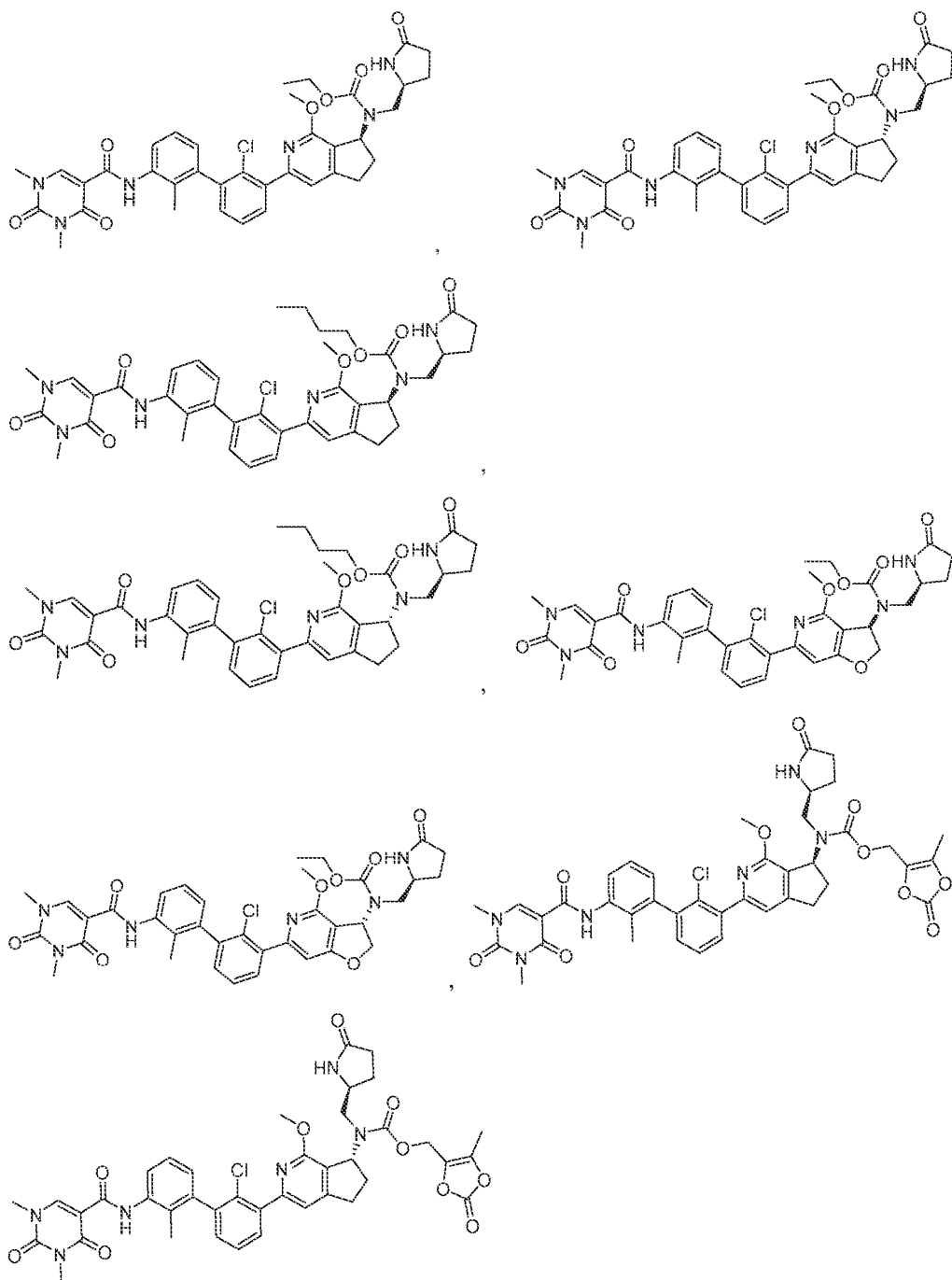


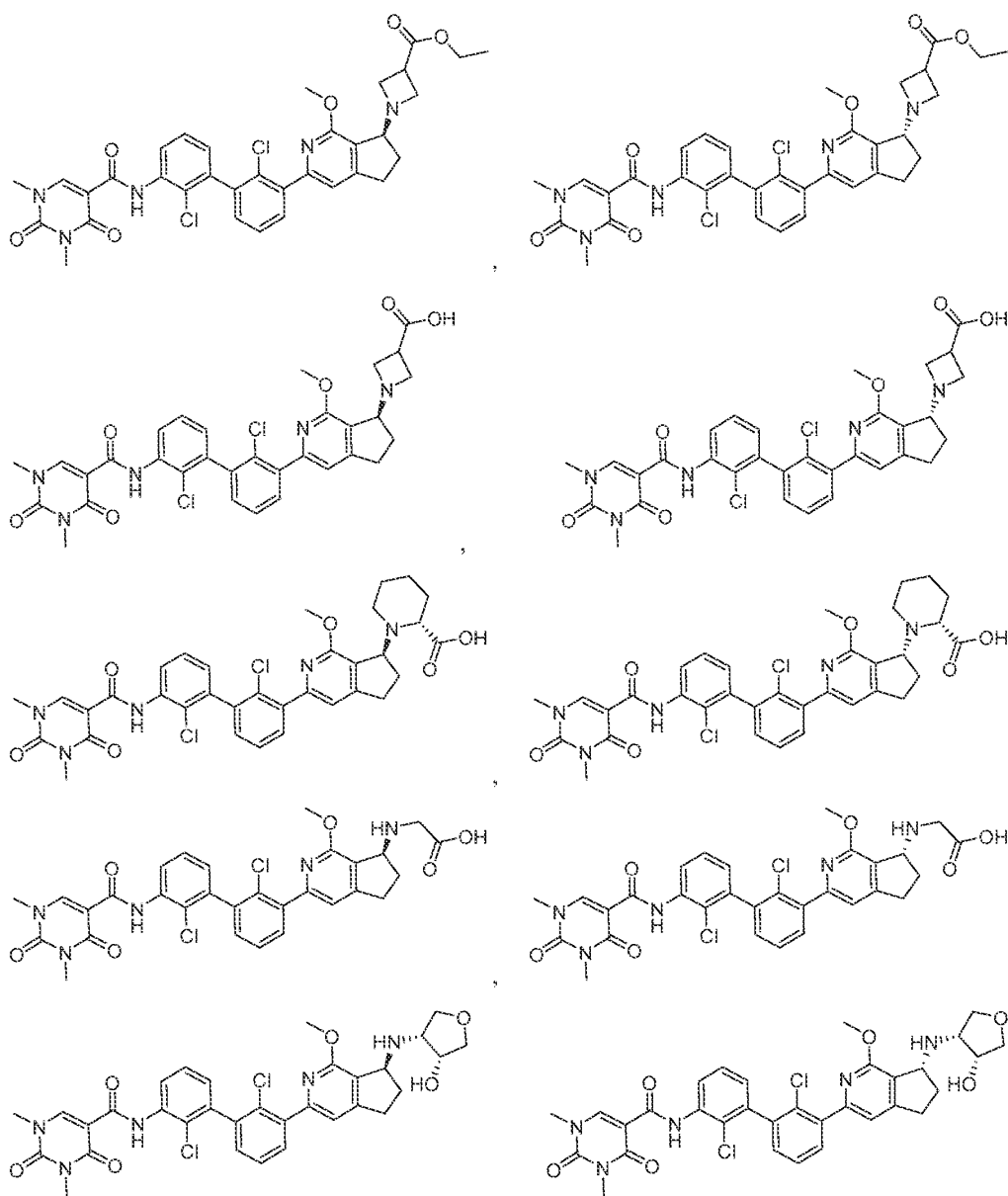


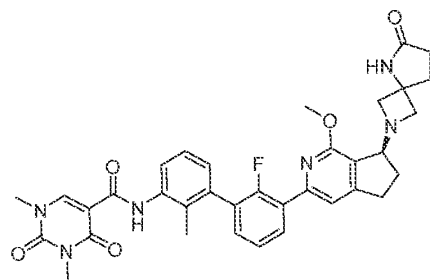
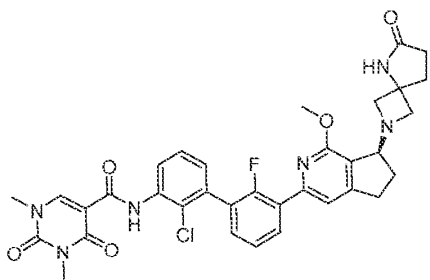
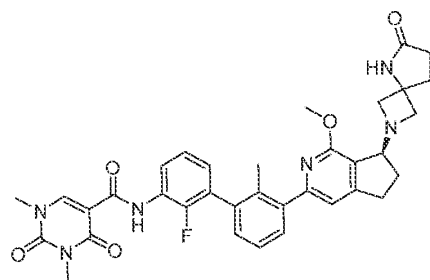
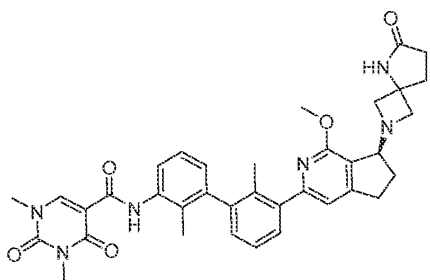
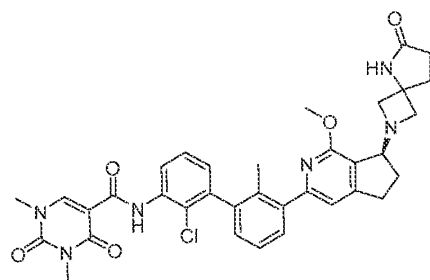
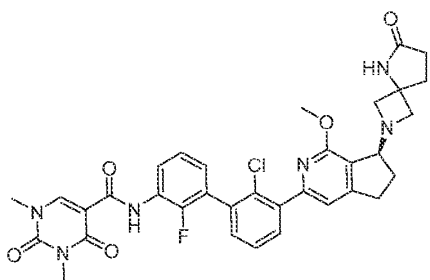
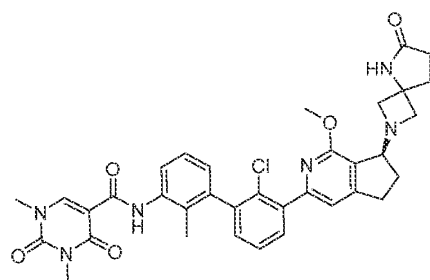
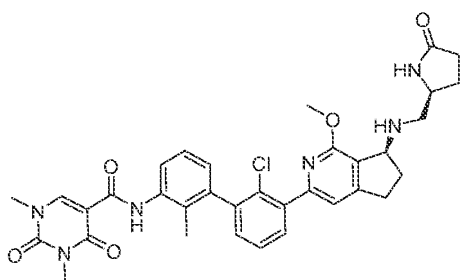


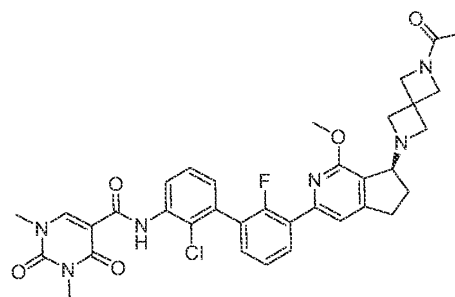
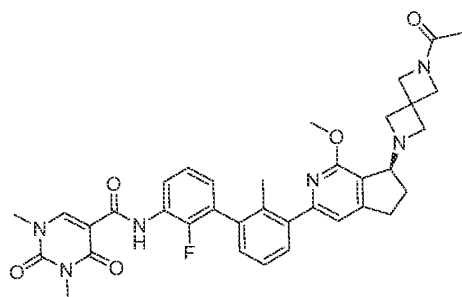
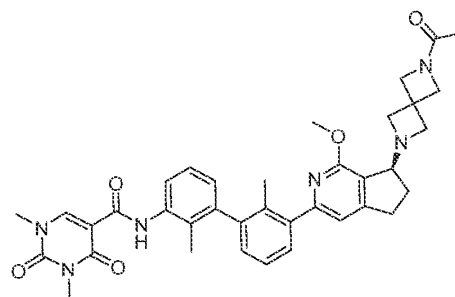
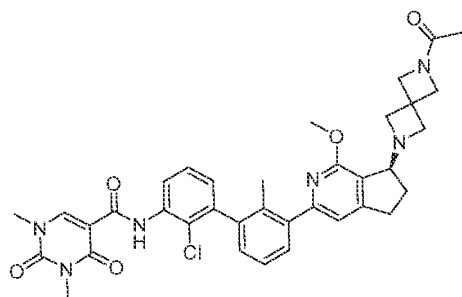
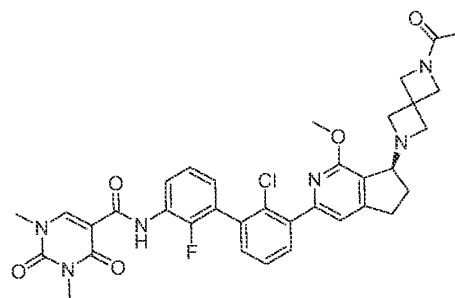
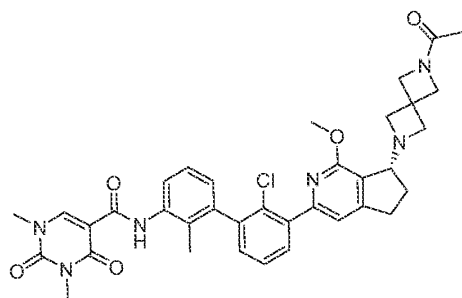
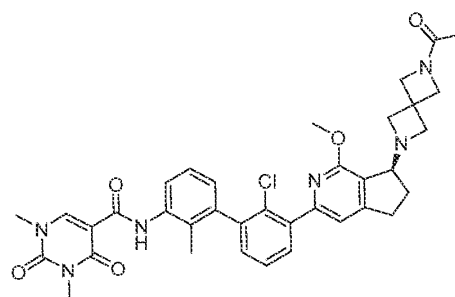
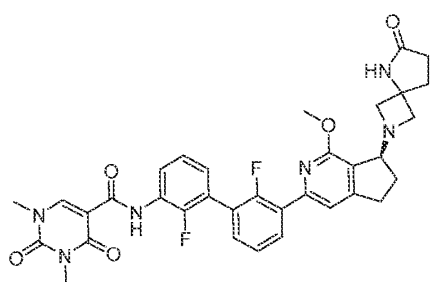


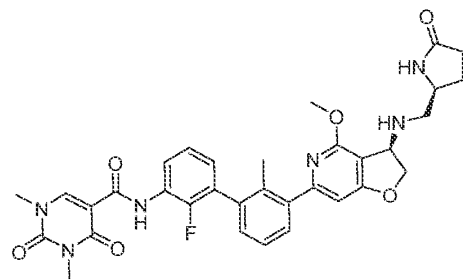
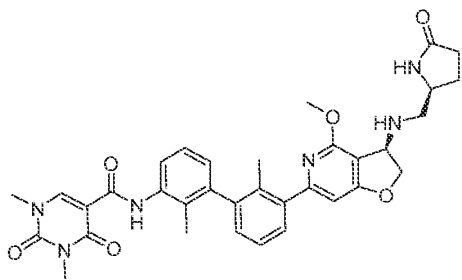
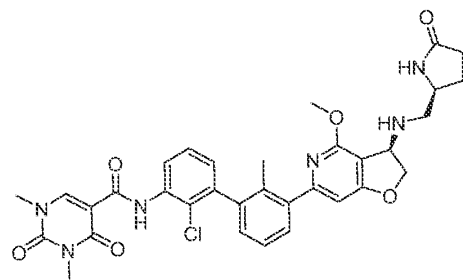
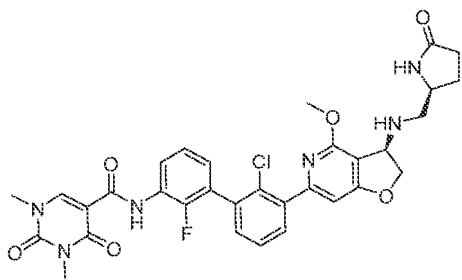
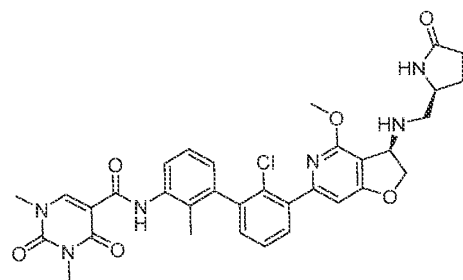
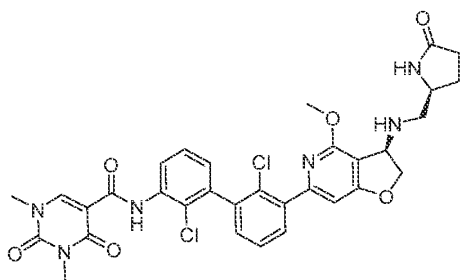
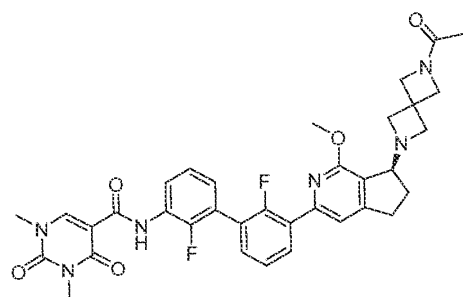
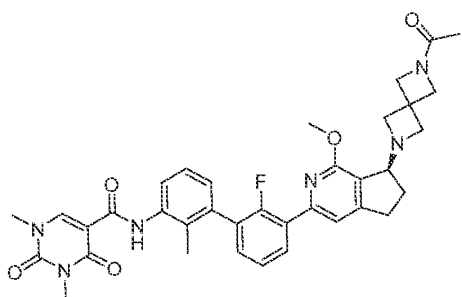


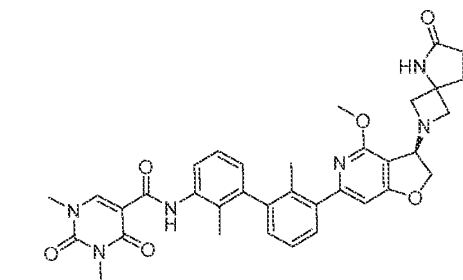
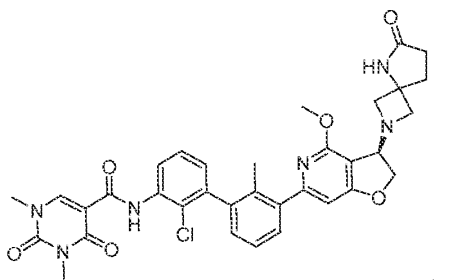
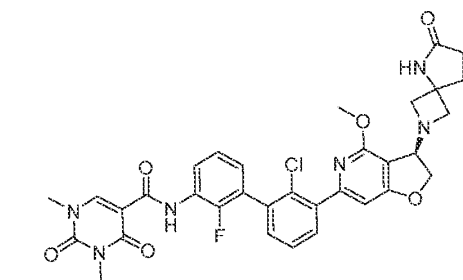
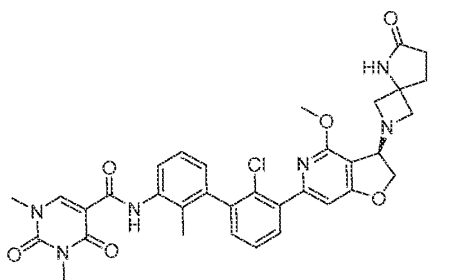
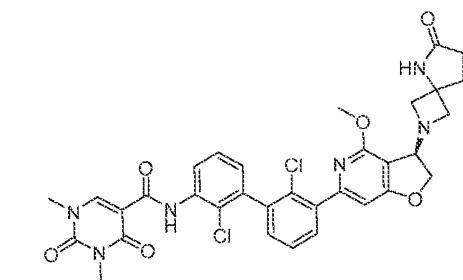
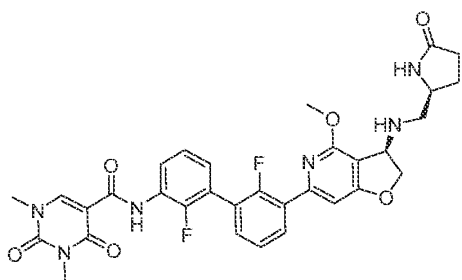
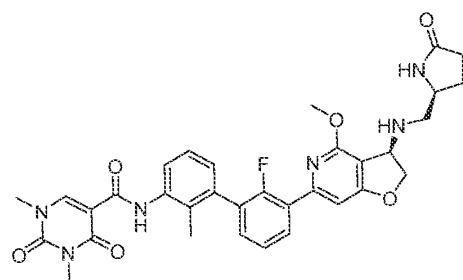
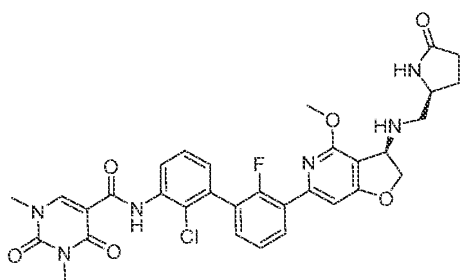


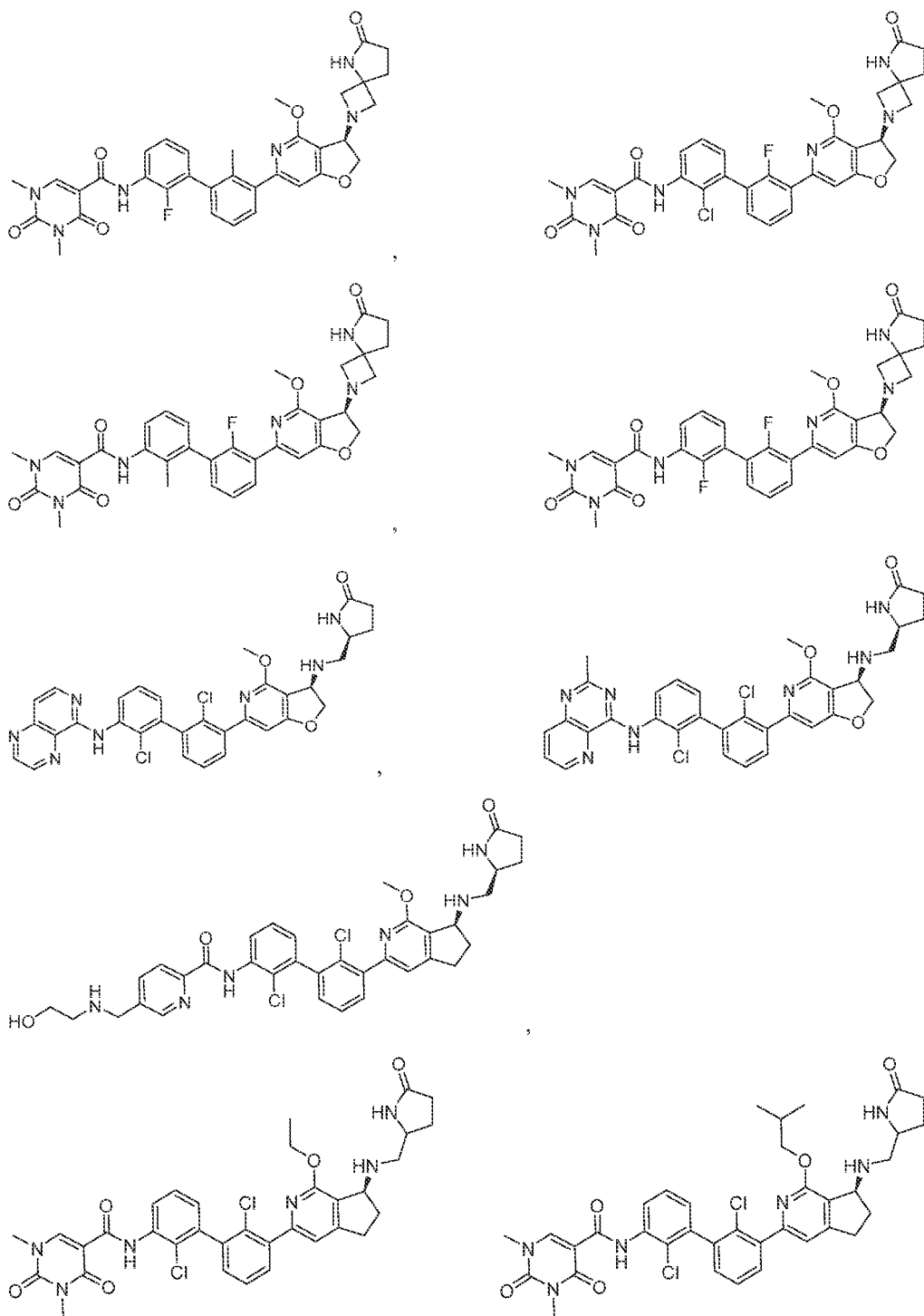


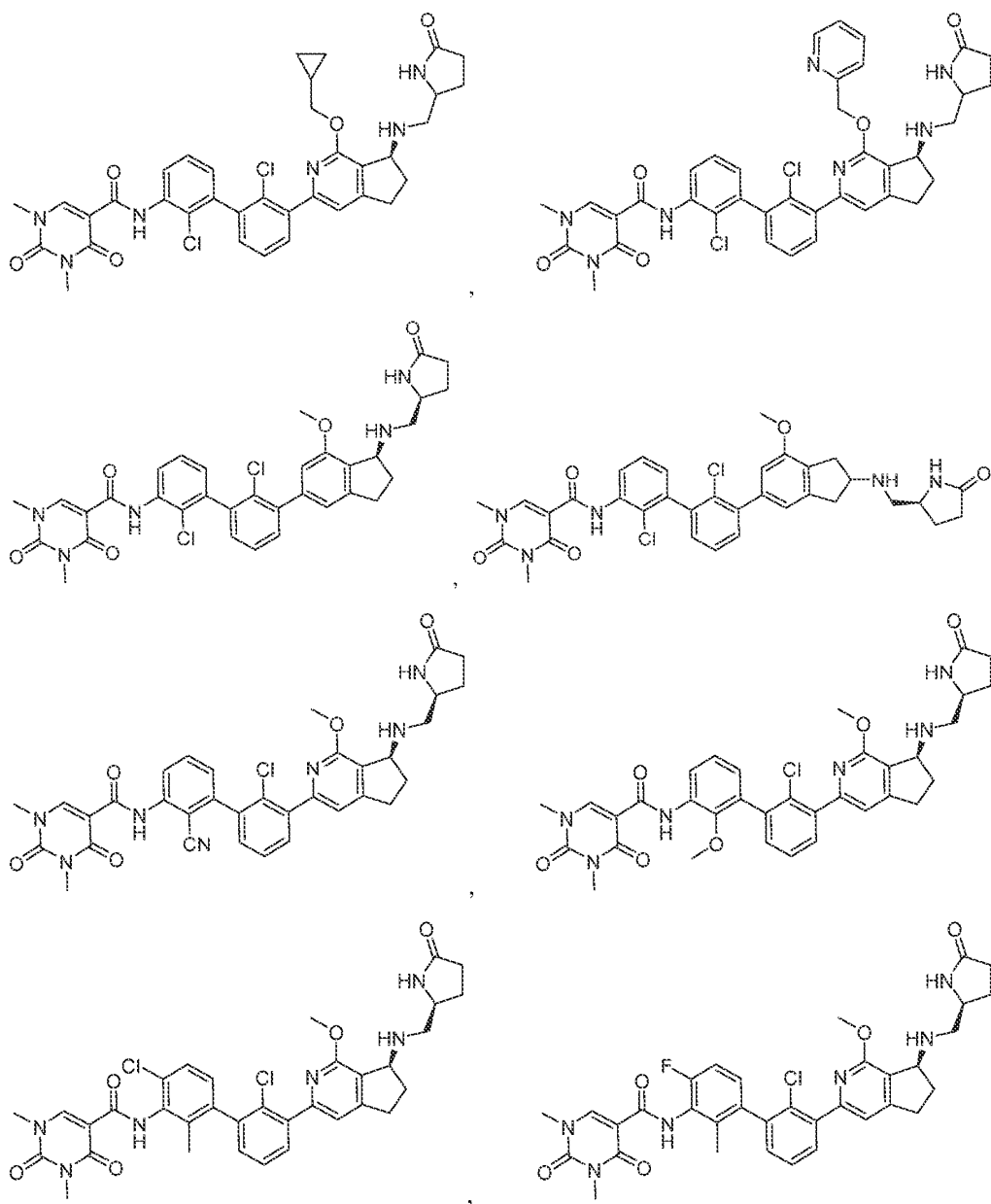


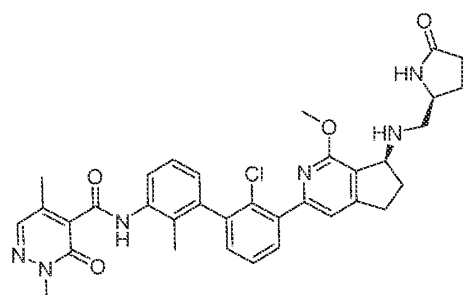
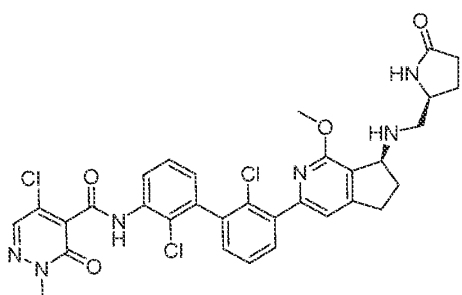
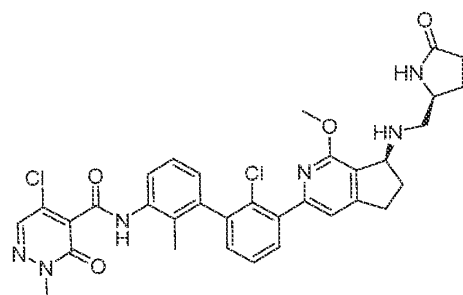
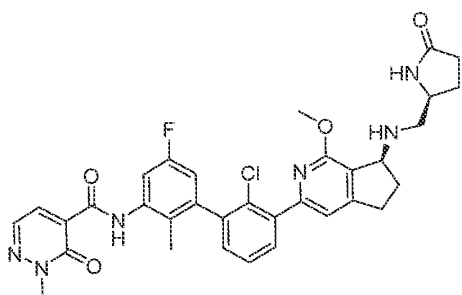
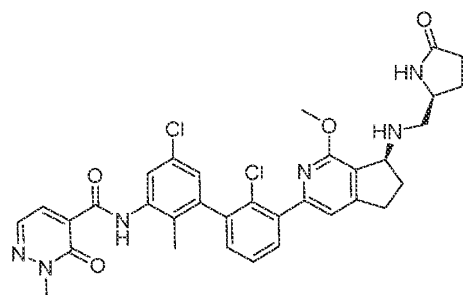
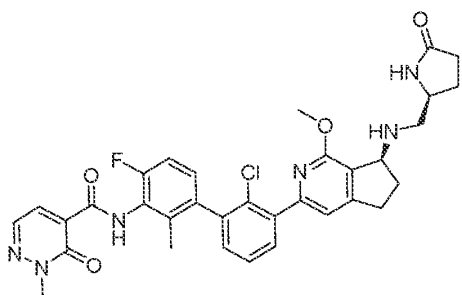
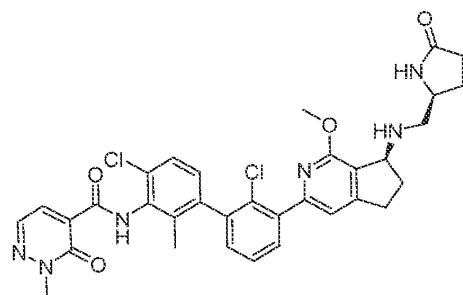
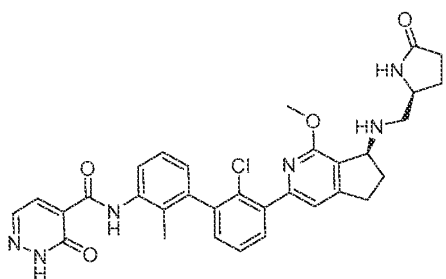


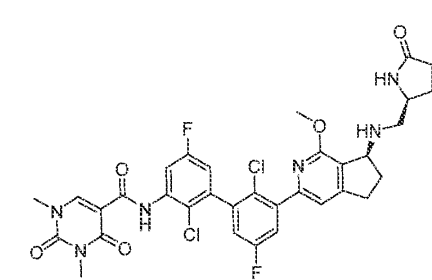
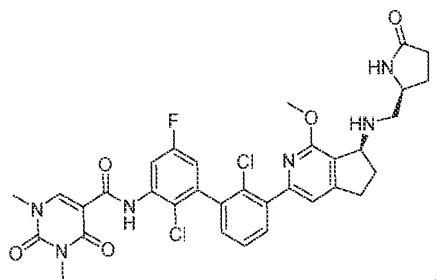
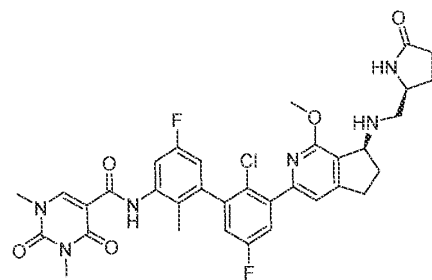
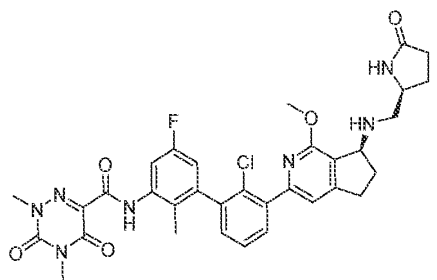
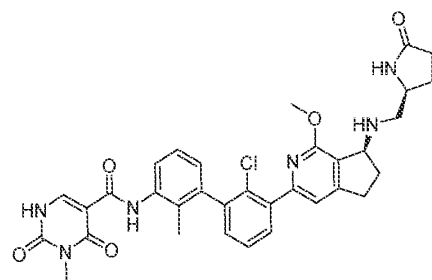
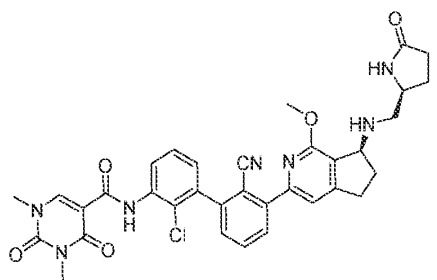
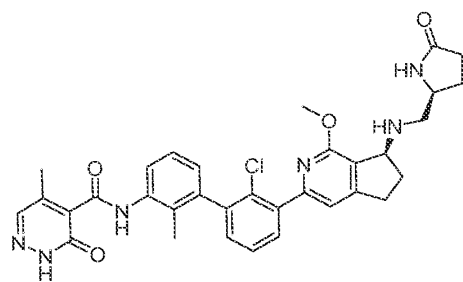
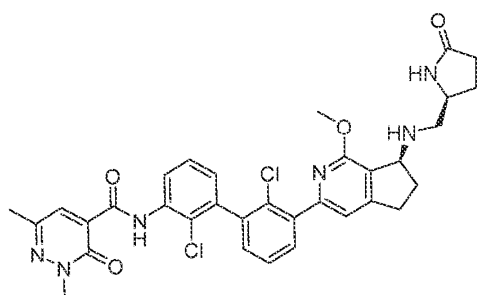


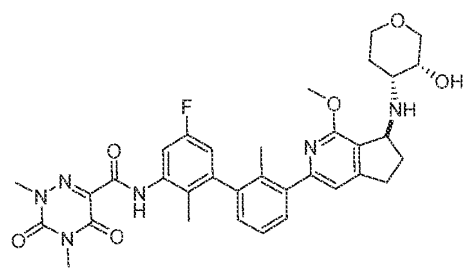
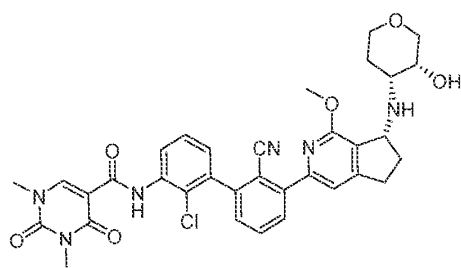
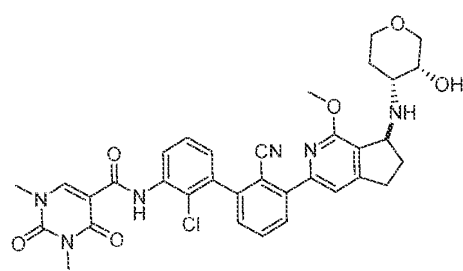
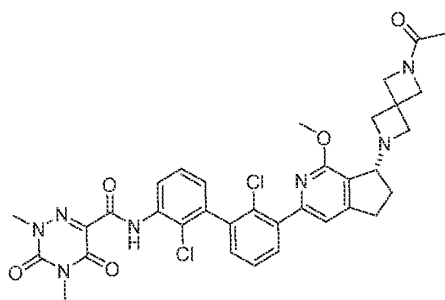
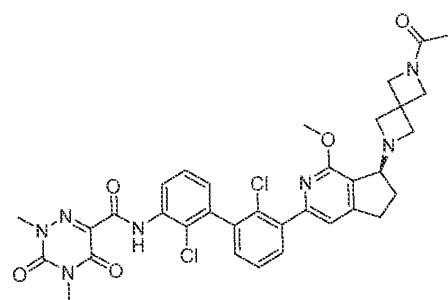
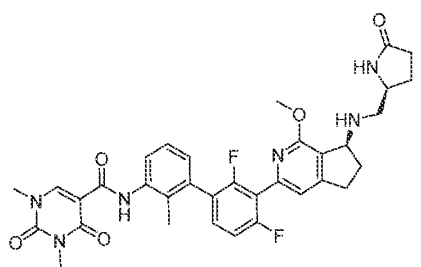
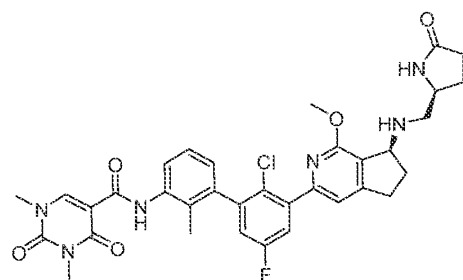
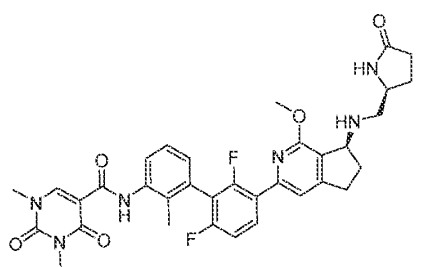


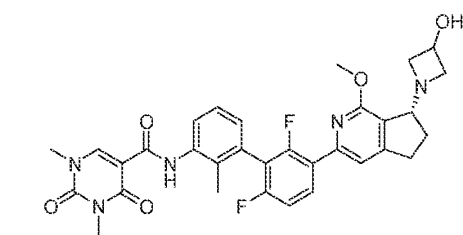
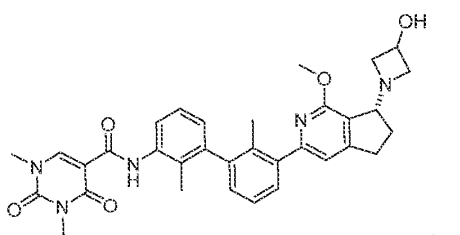
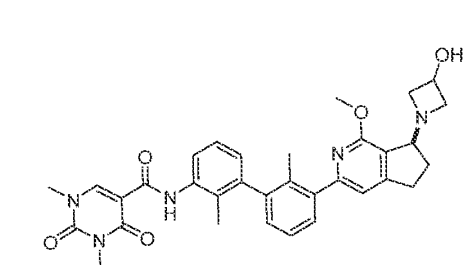
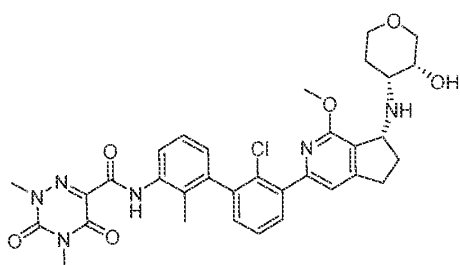
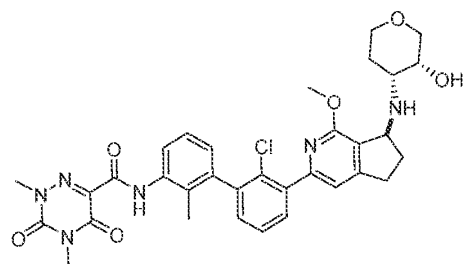
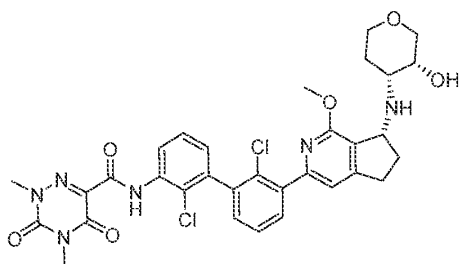
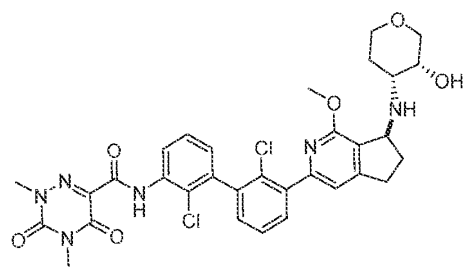
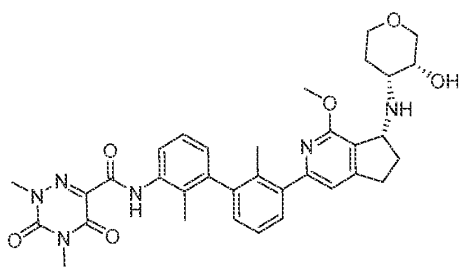
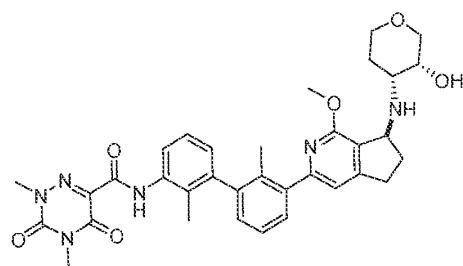
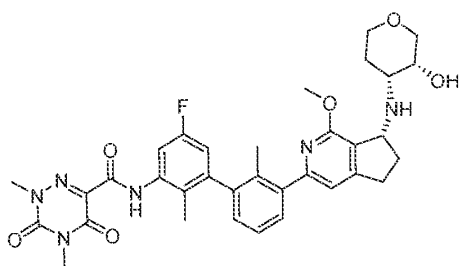


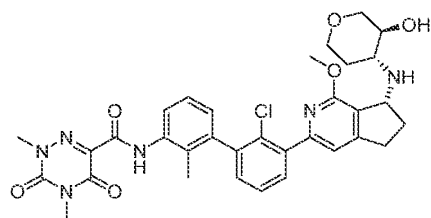
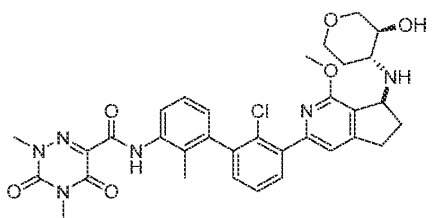
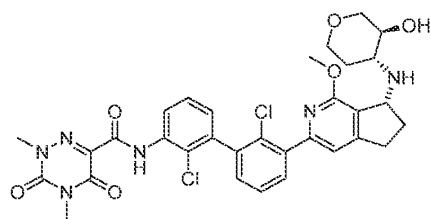
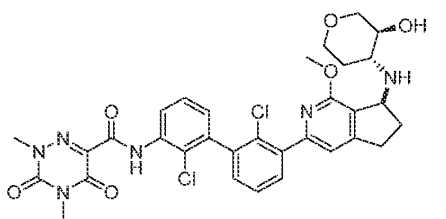
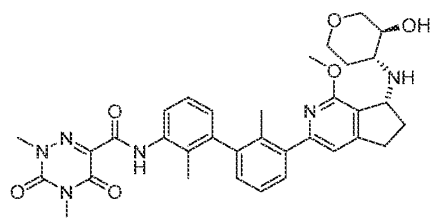
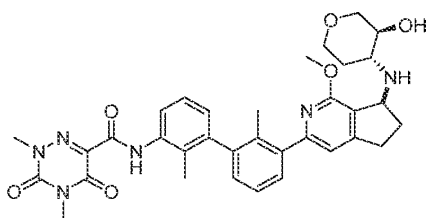
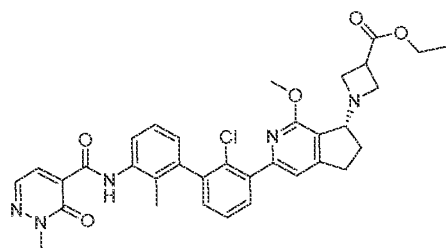
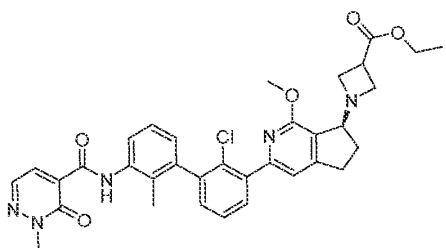
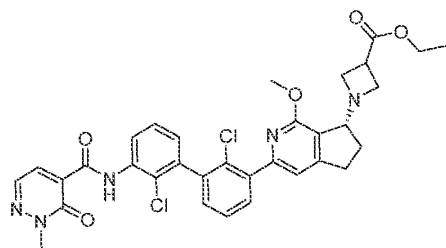
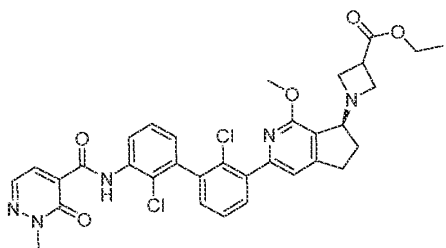
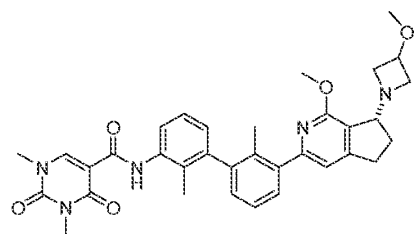
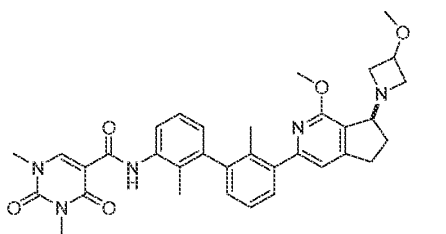


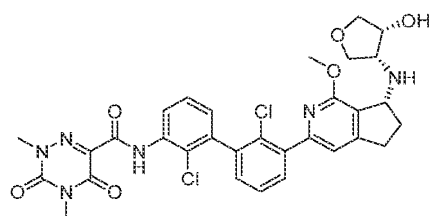
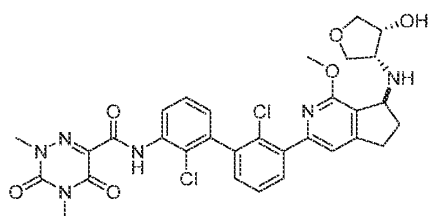
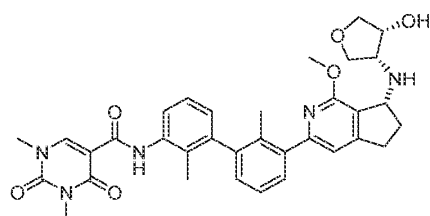
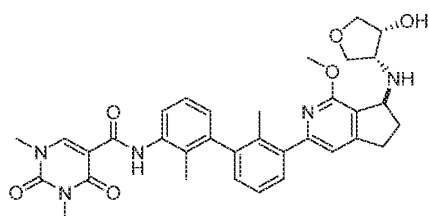
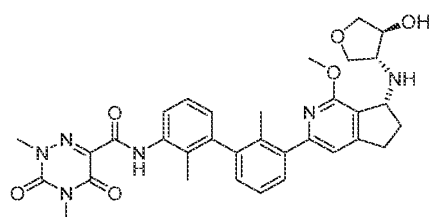
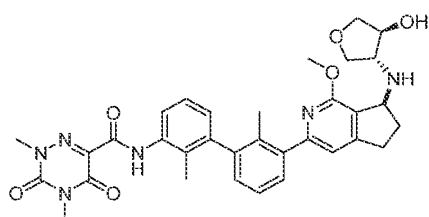
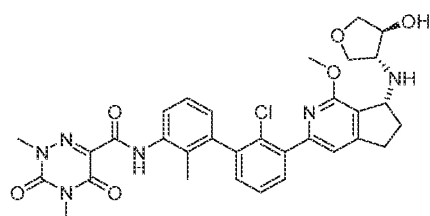
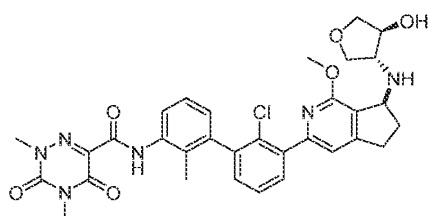
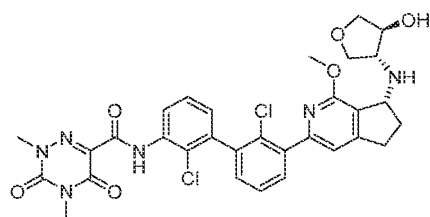
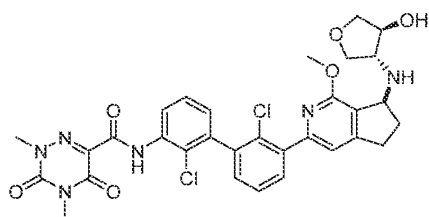
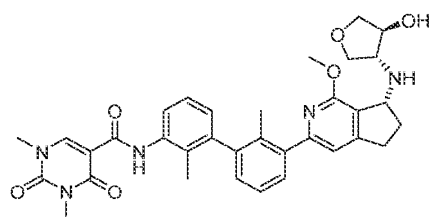
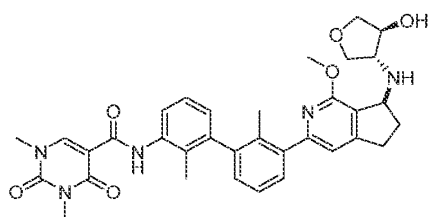


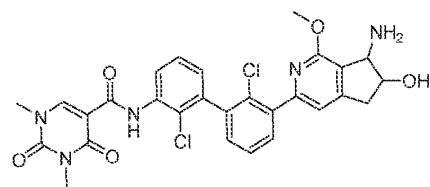
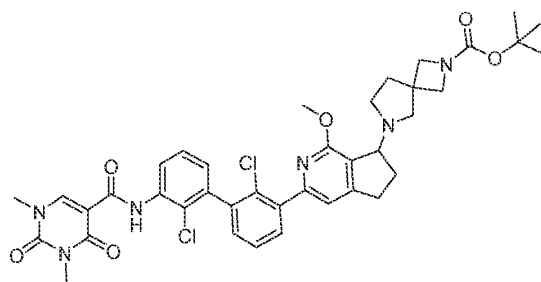
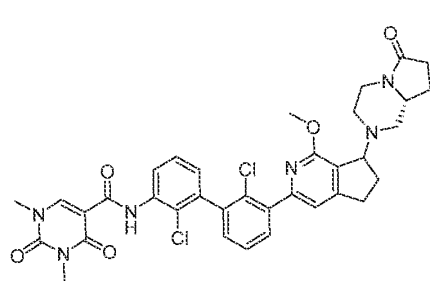
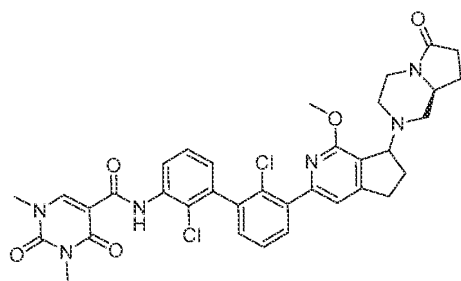
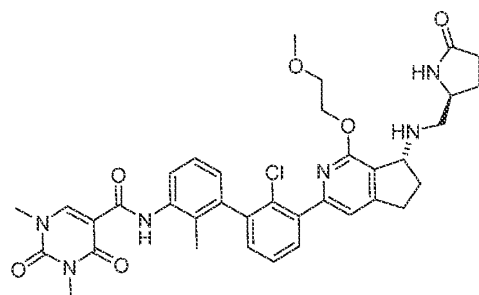
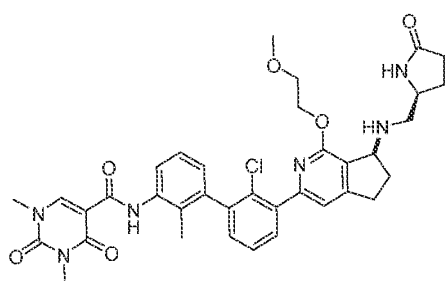
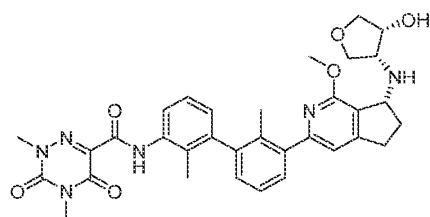
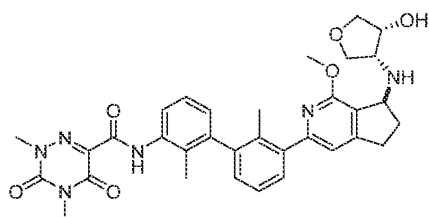
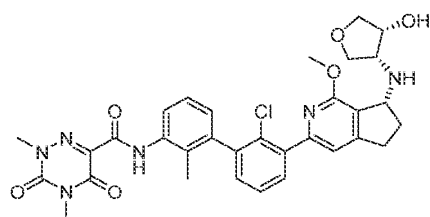
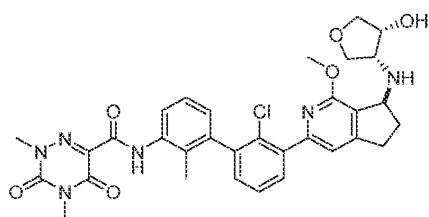


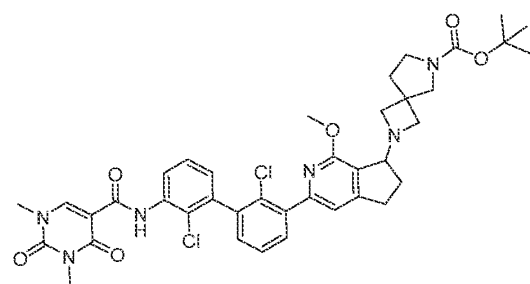
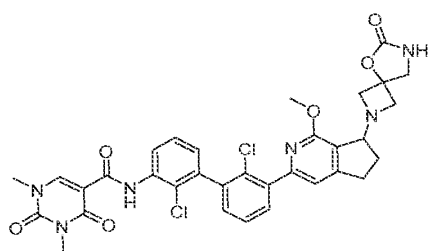
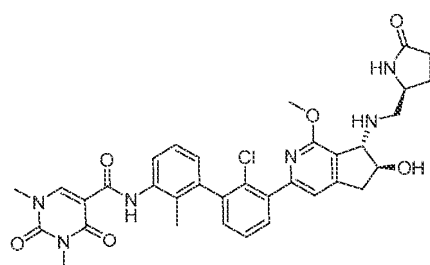
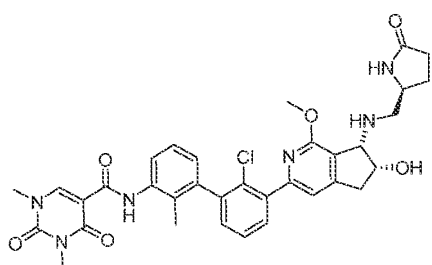
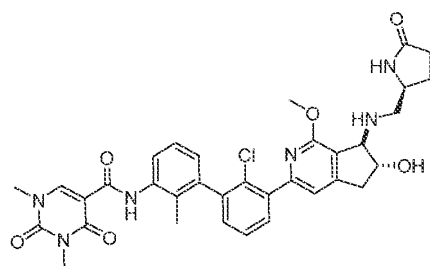
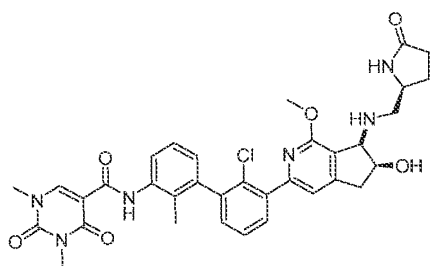
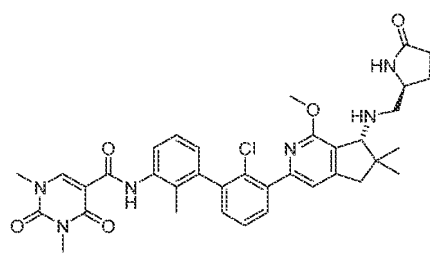
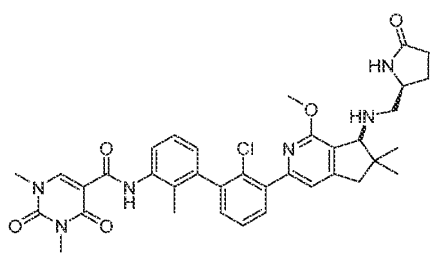
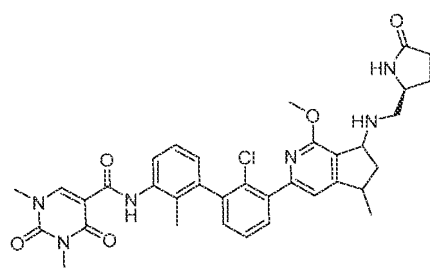
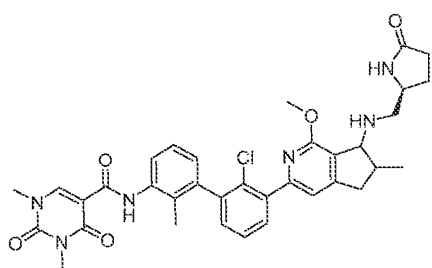


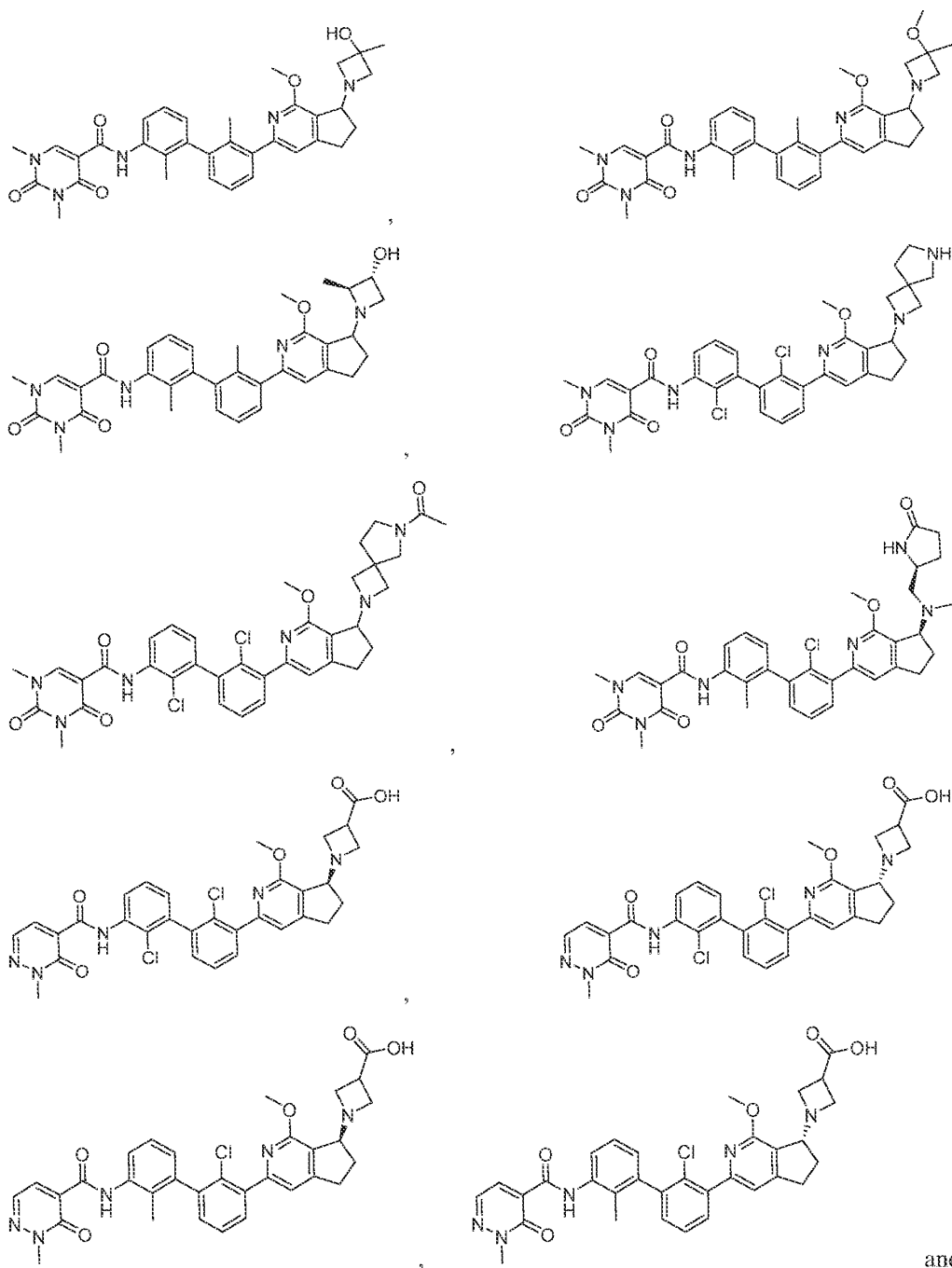


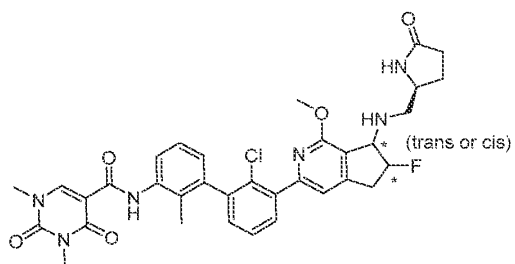






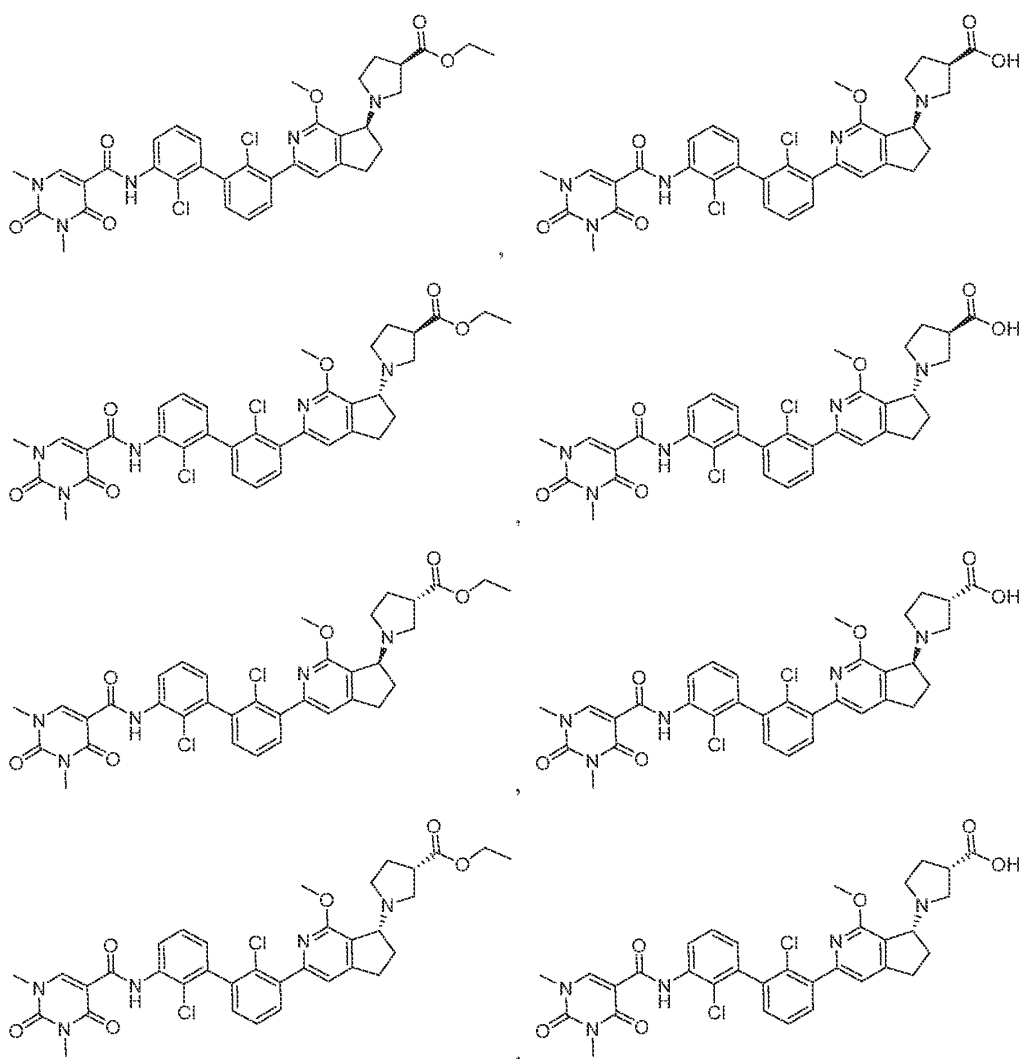


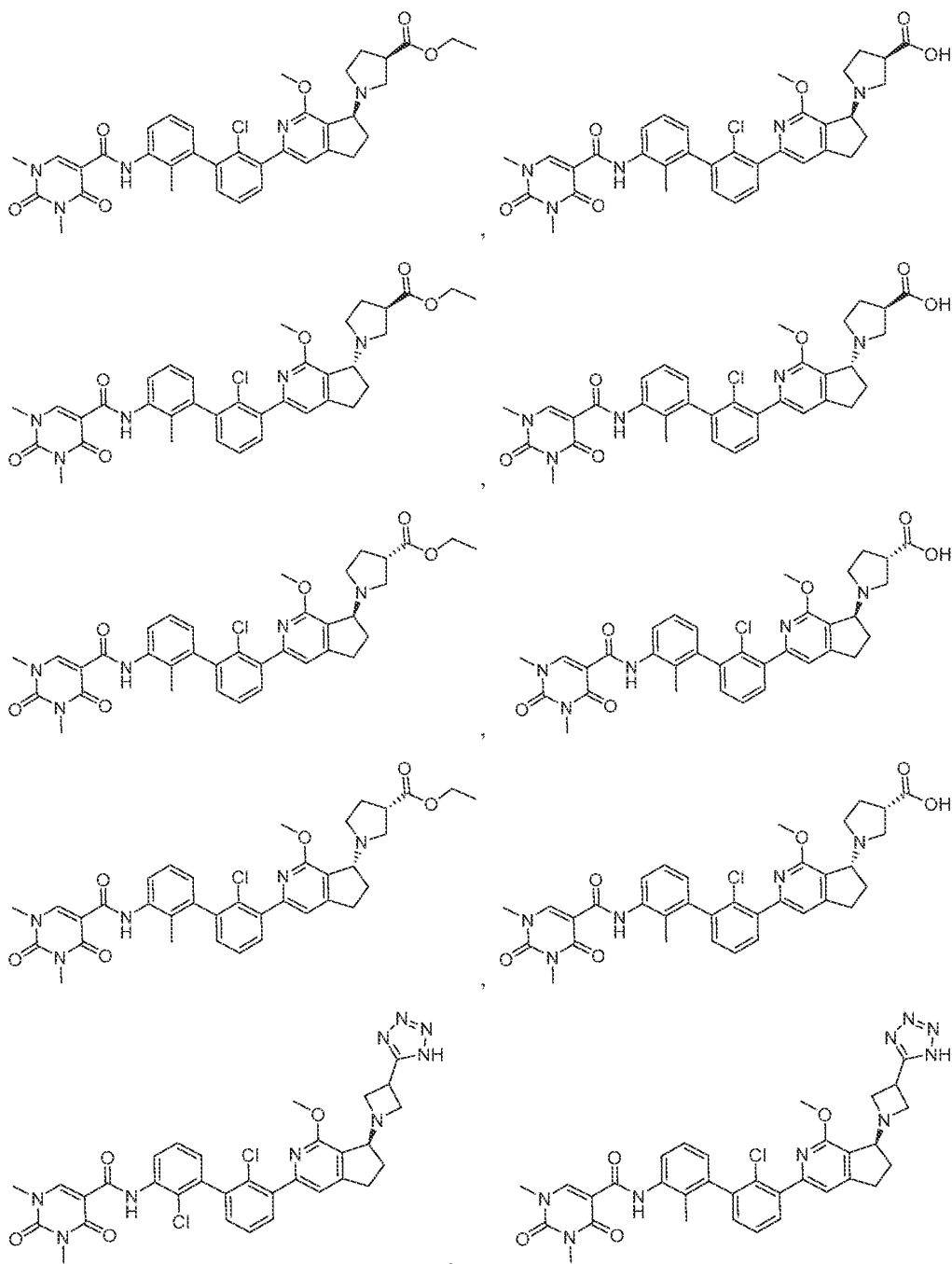


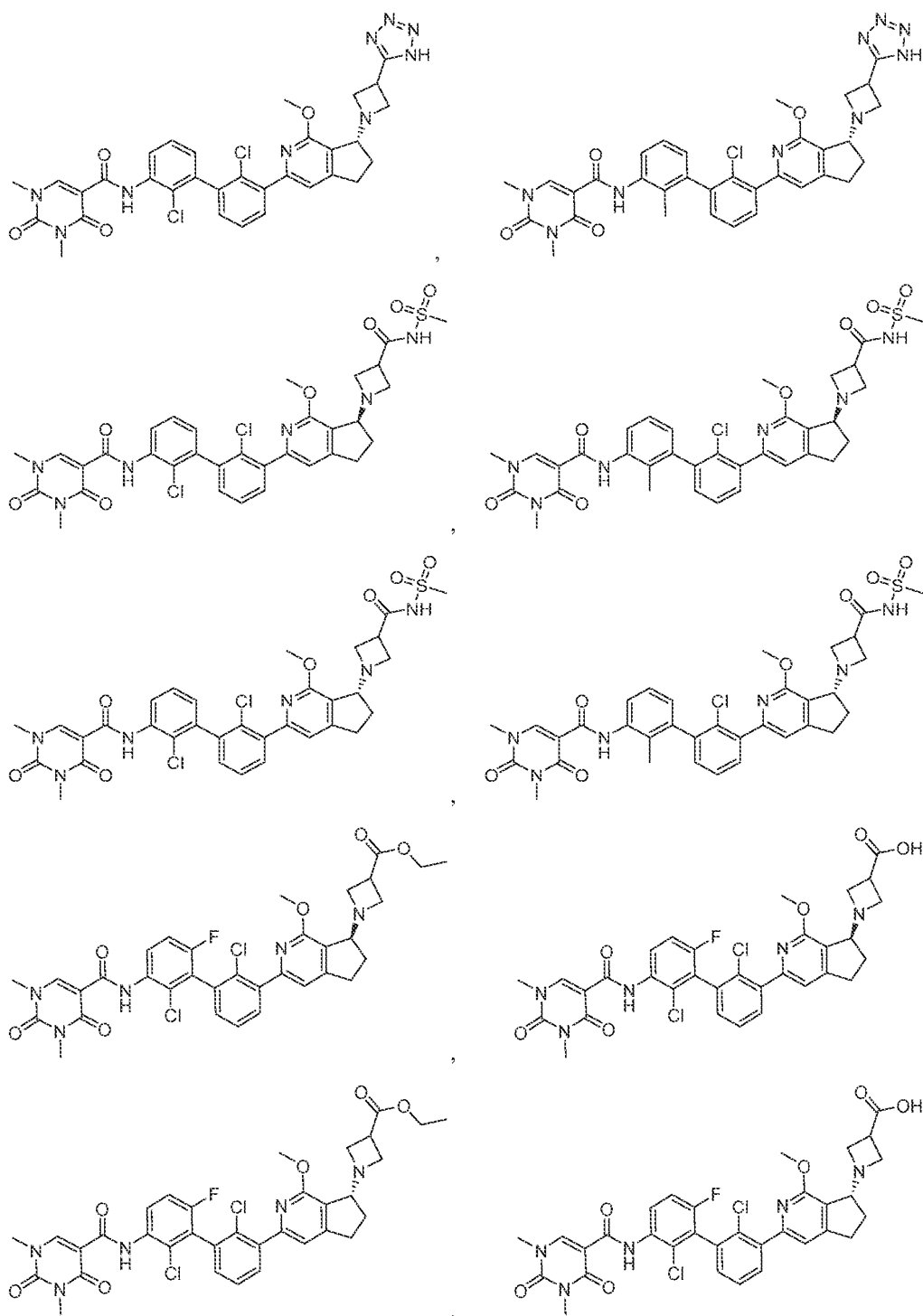


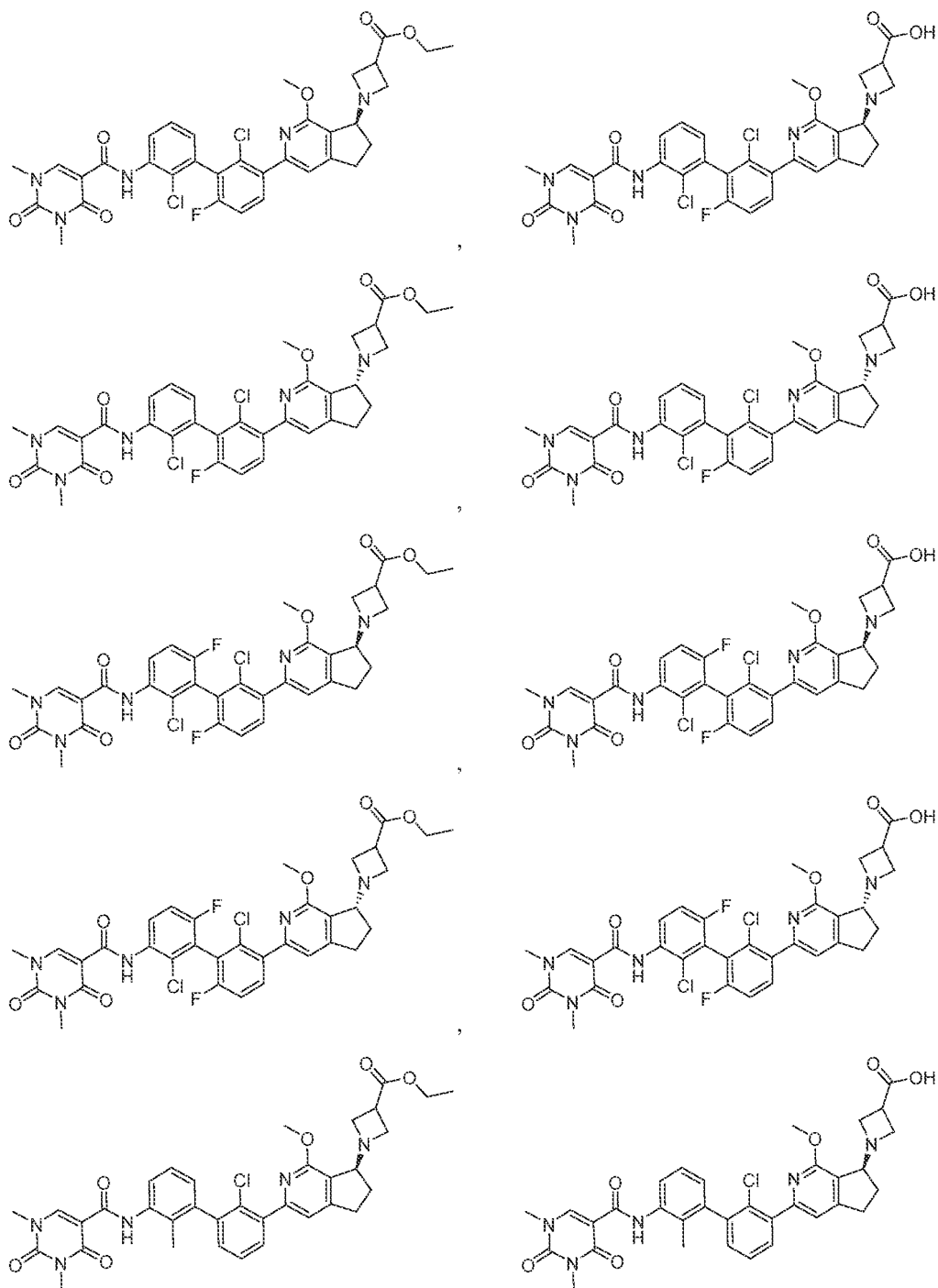
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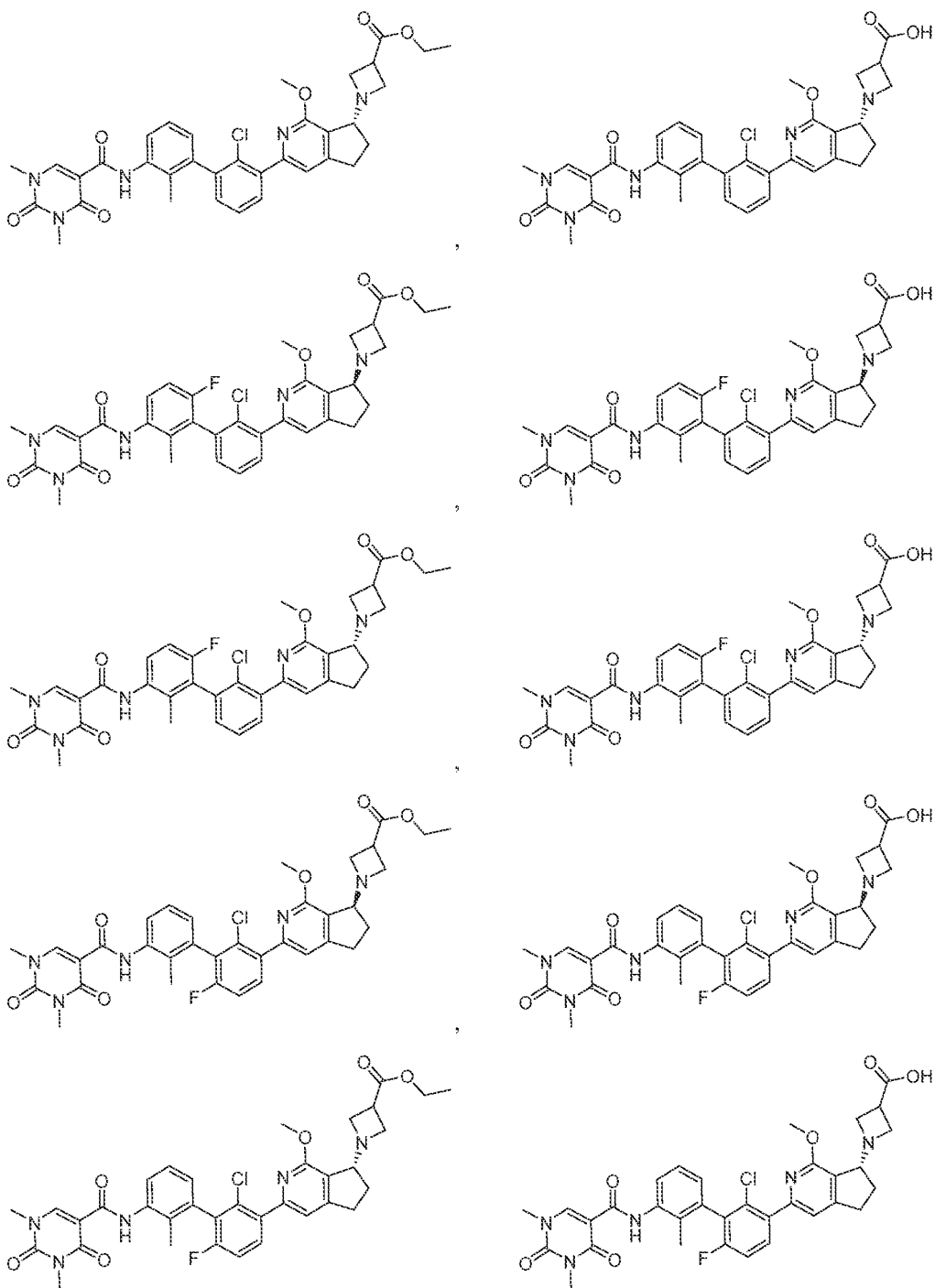
145. The compound of Claim 1 selected from the group consisting of:

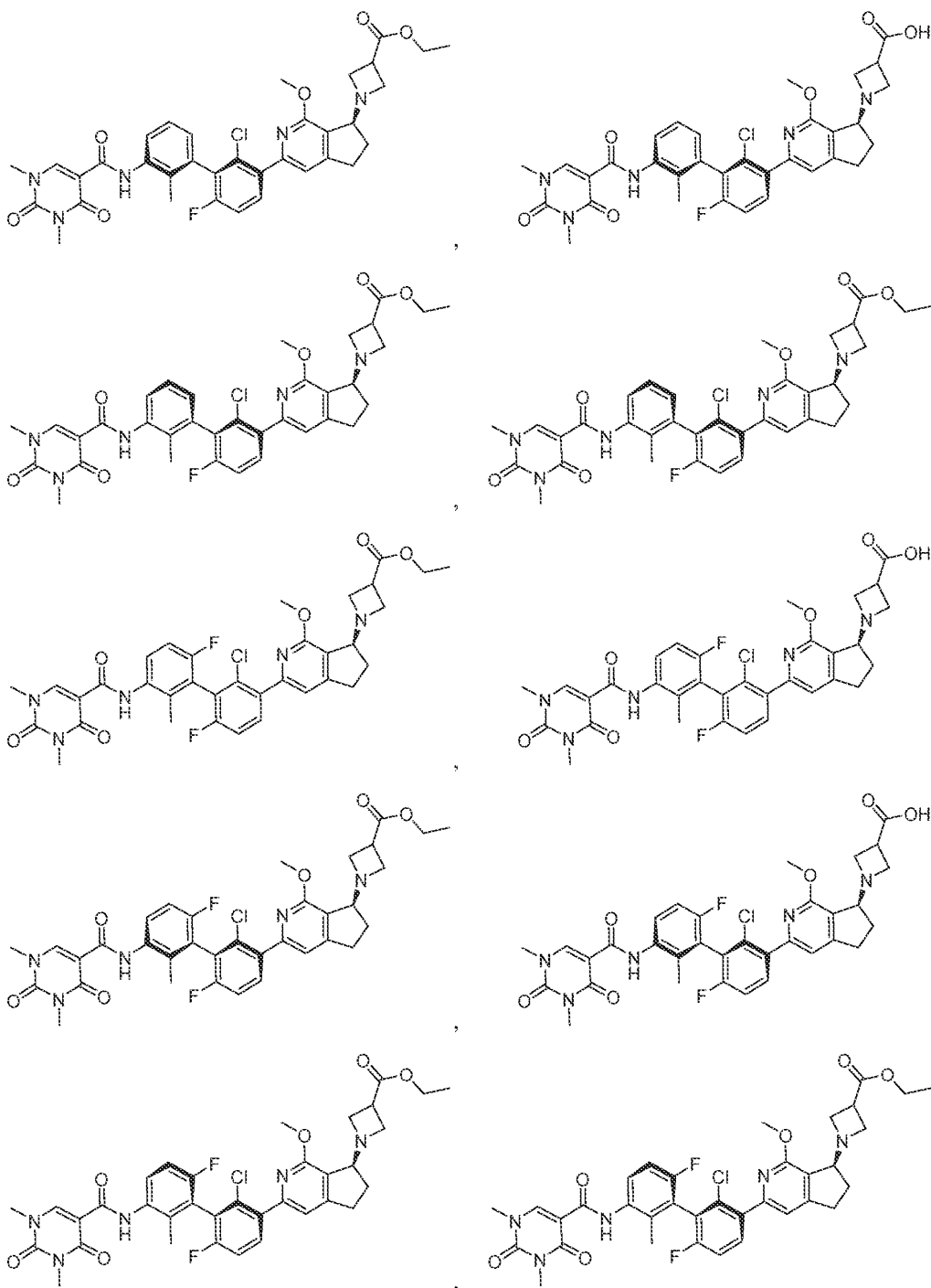


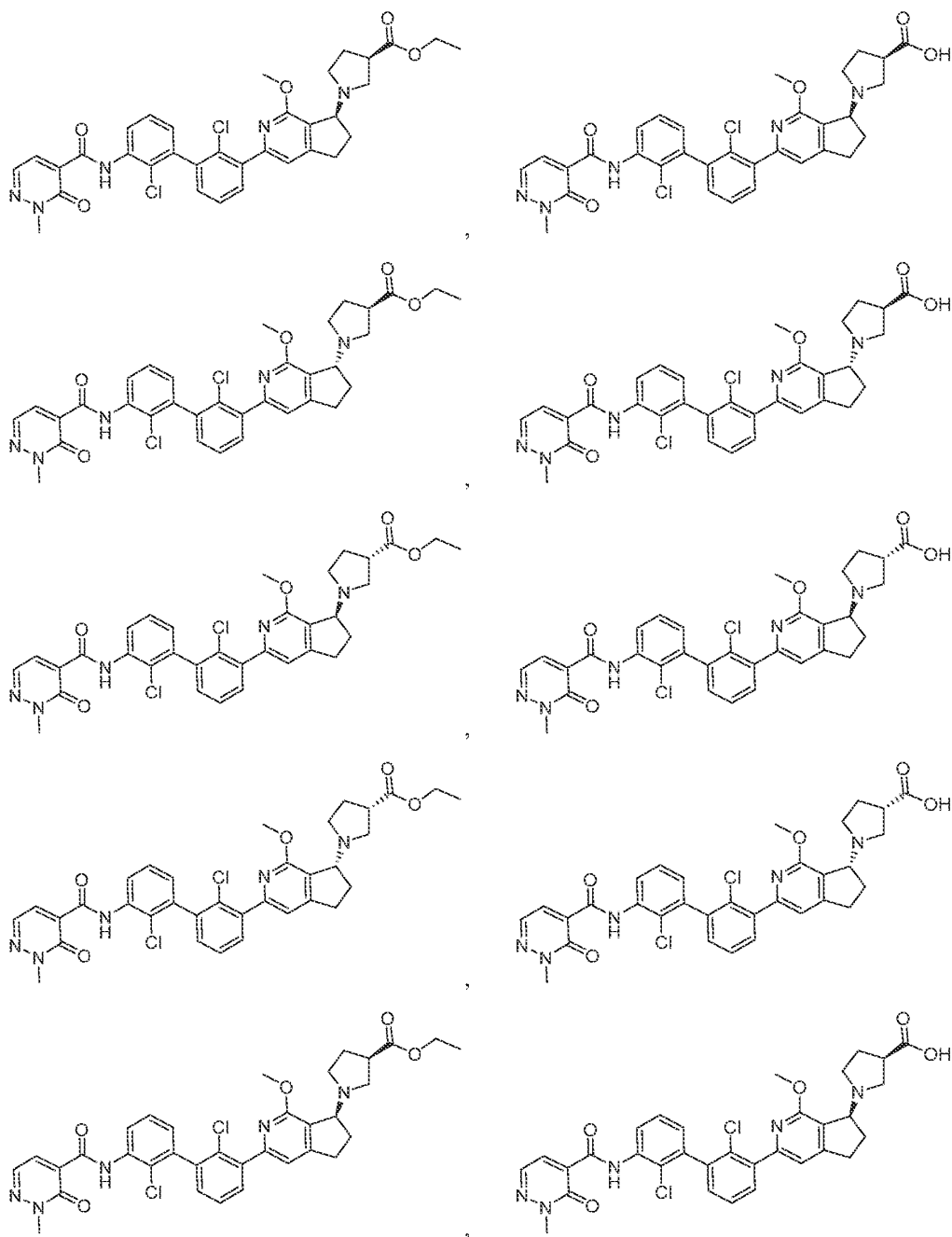


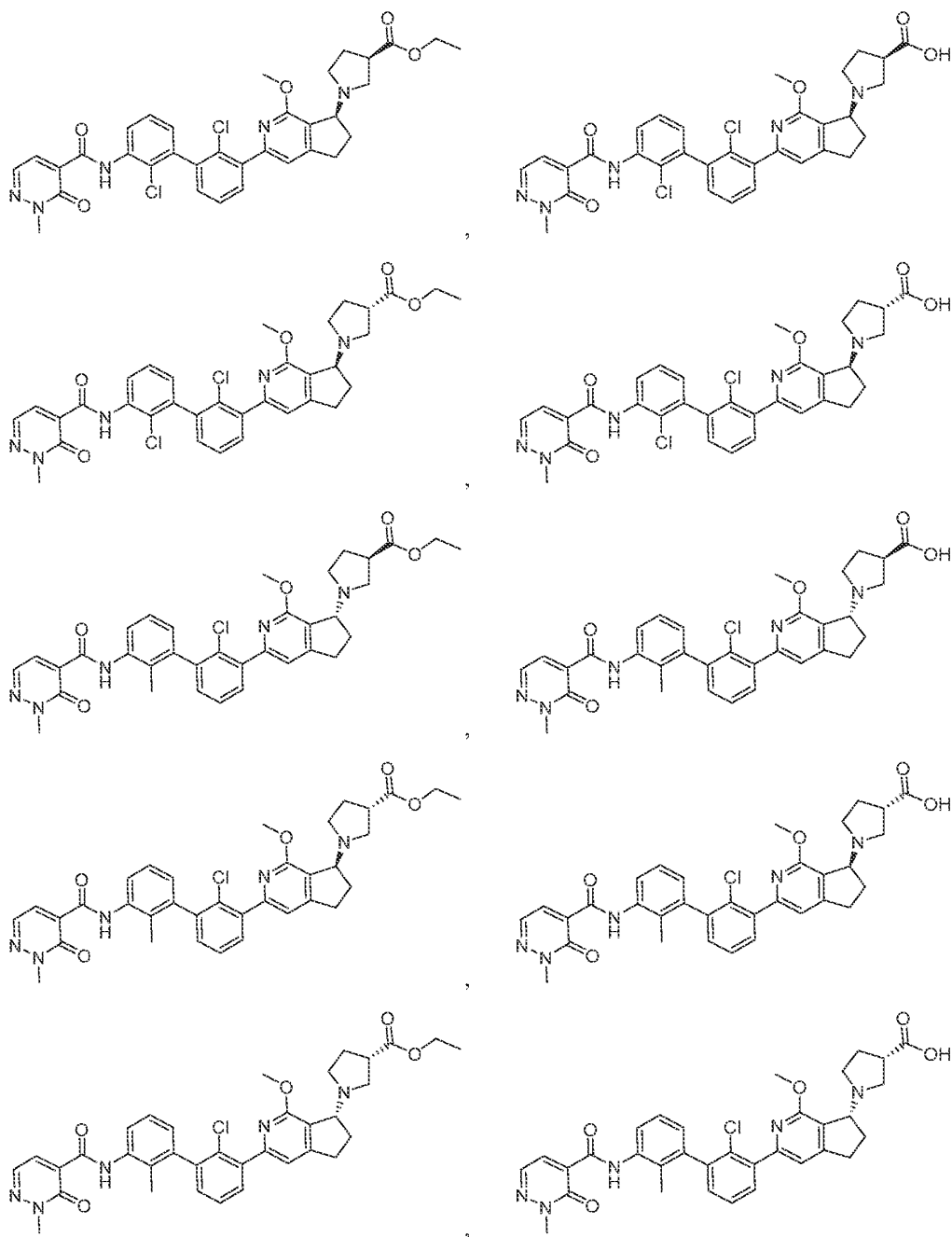


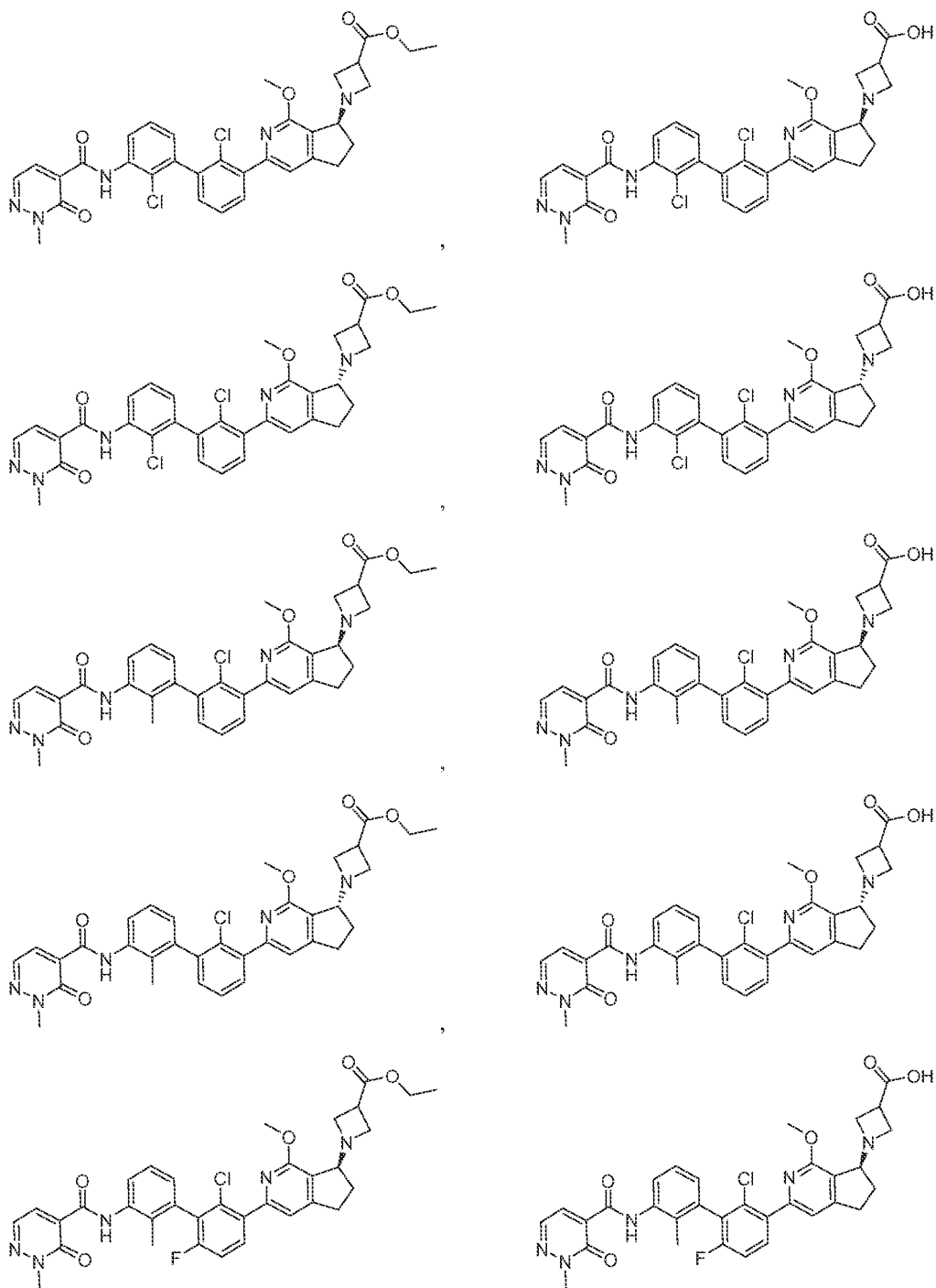


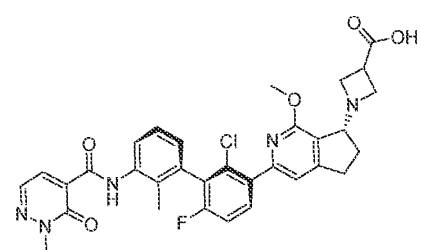
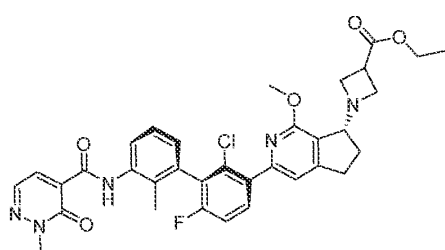
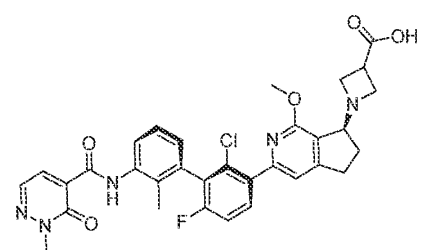
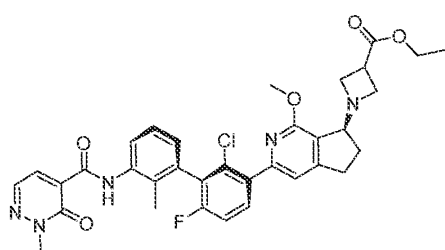
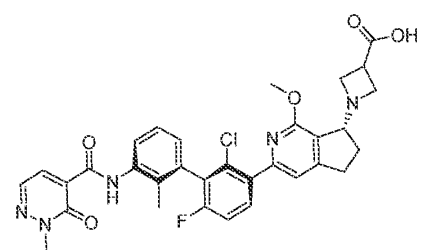
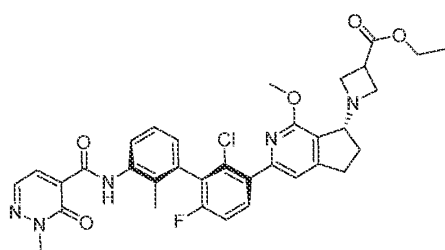
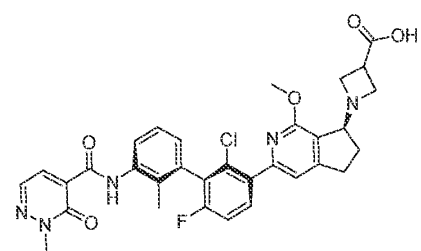
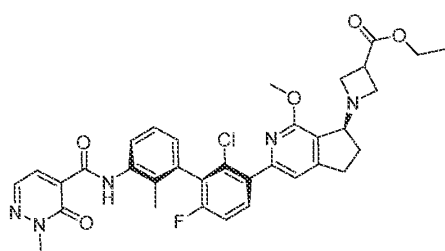
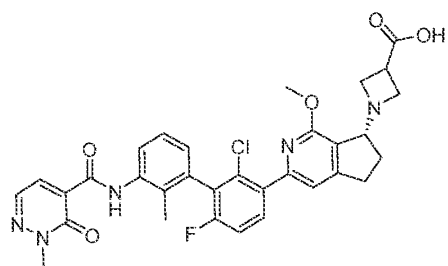
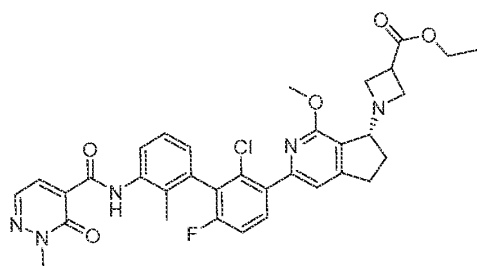


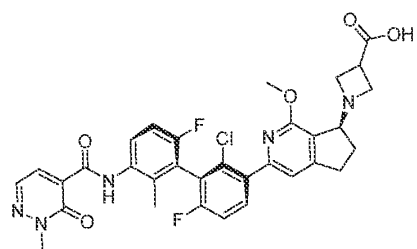
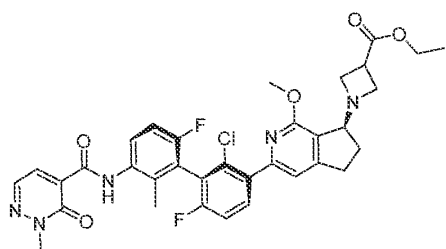
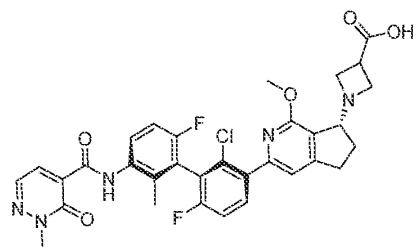
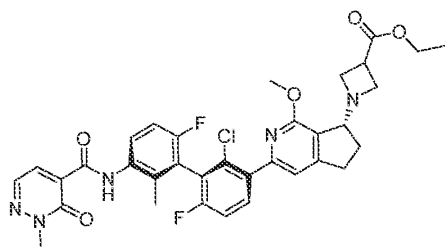
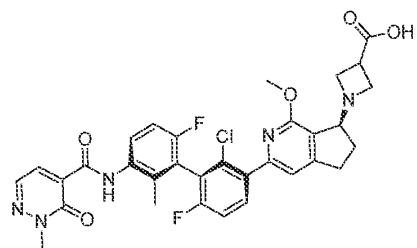
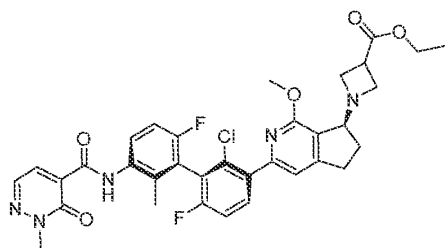
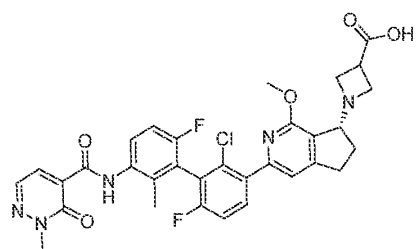
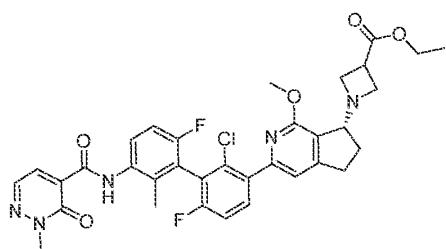
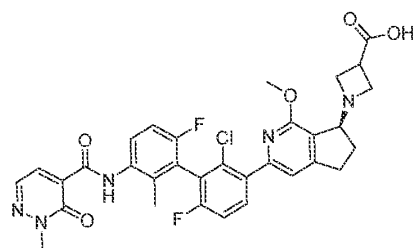
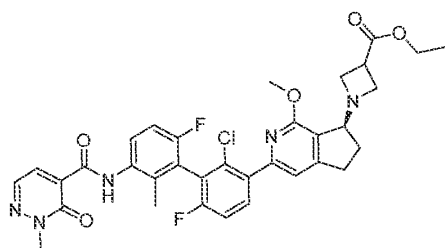


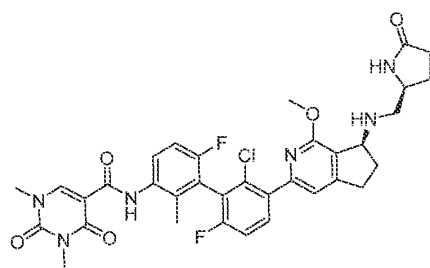
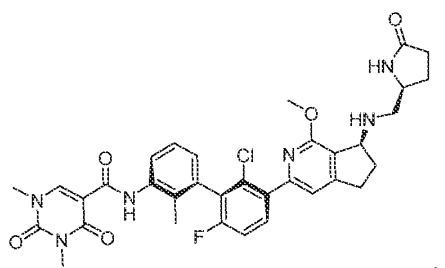
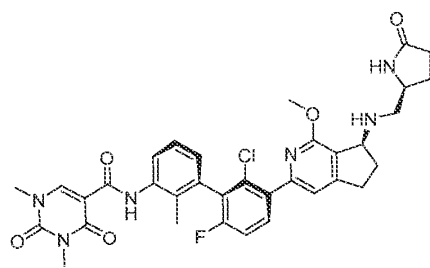
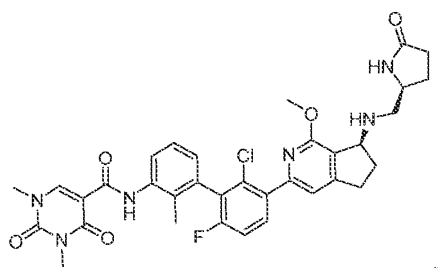
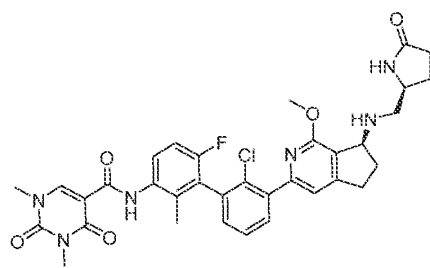
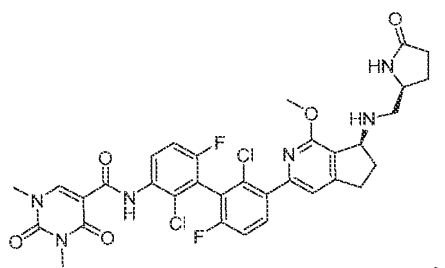
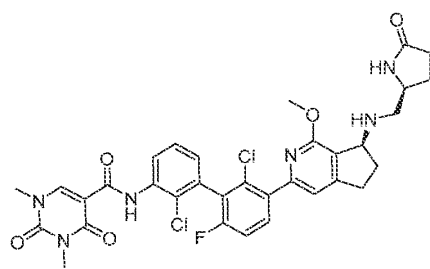
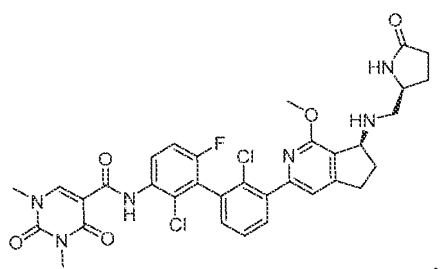
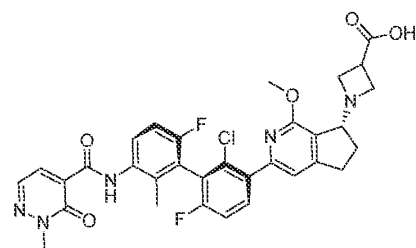
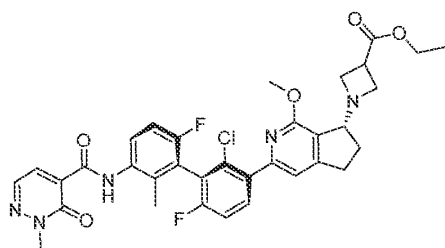


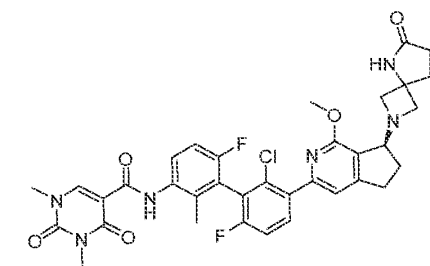
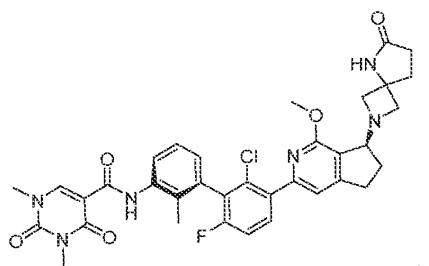
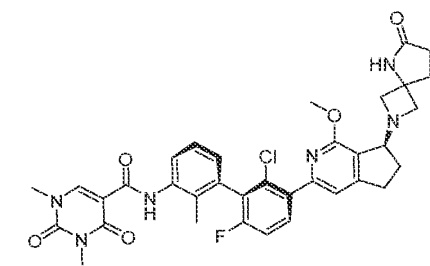
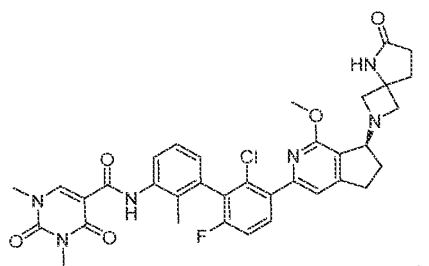
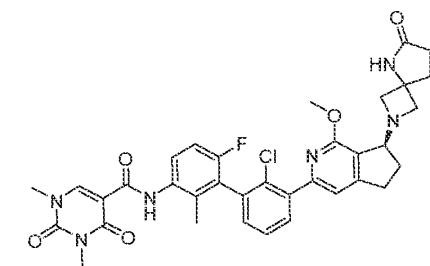
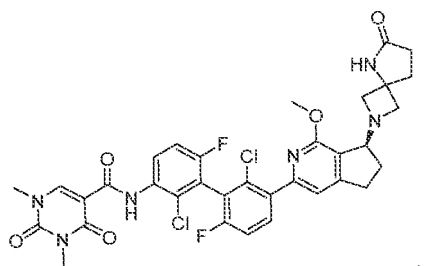
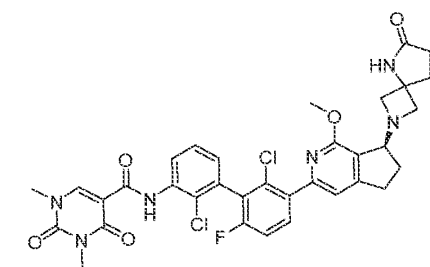
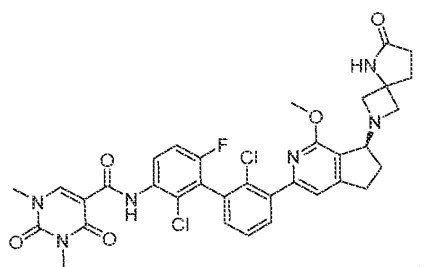
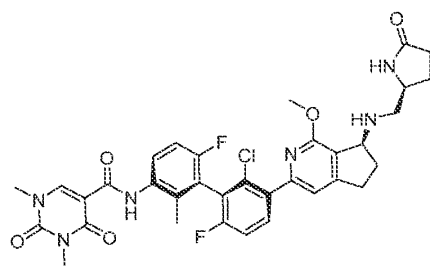
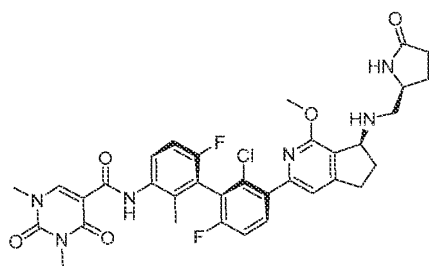


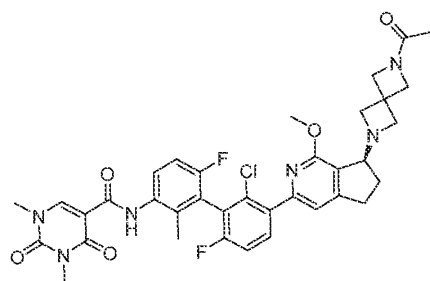
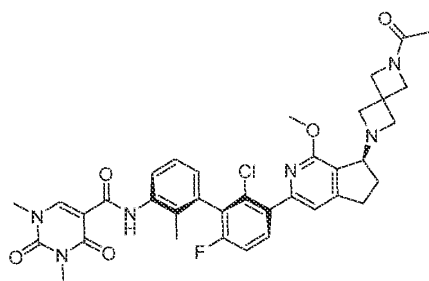
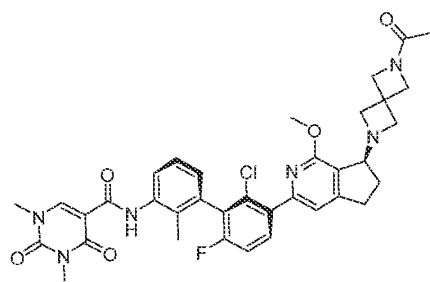
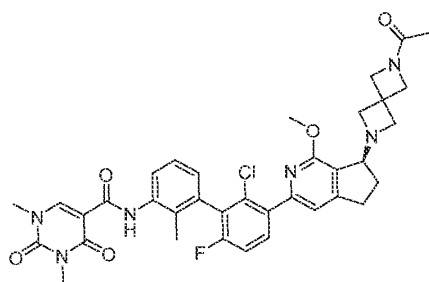
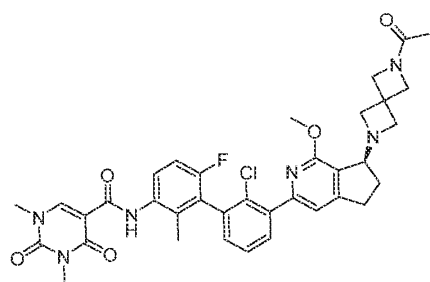
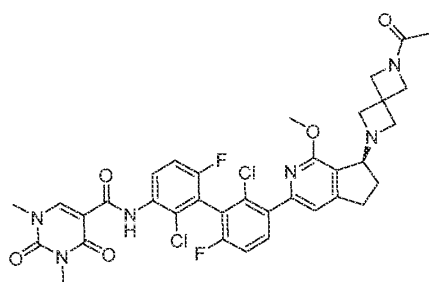
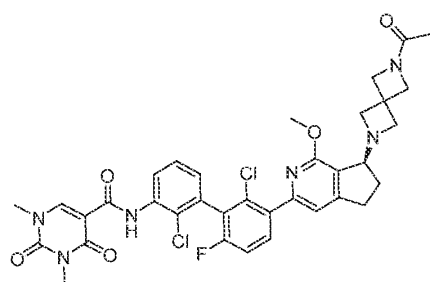
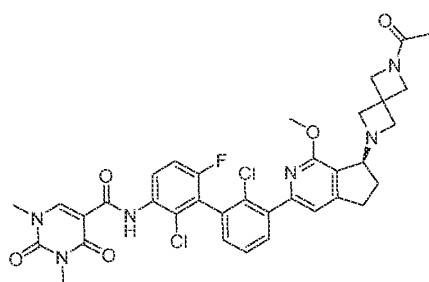
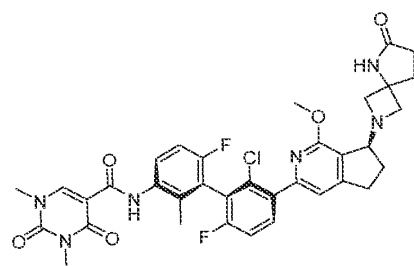
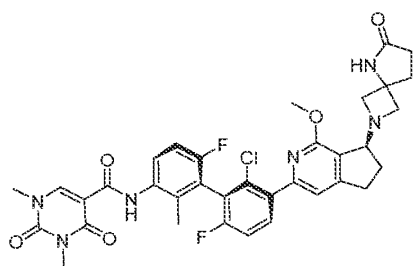


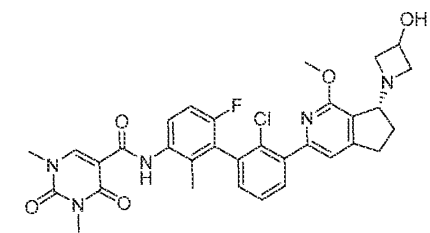
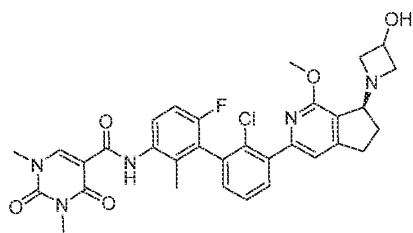
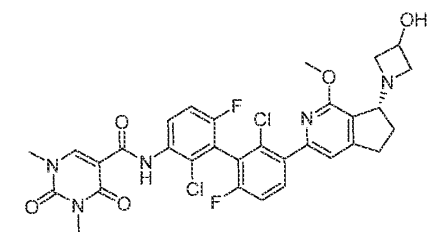
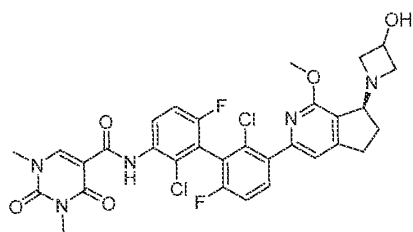
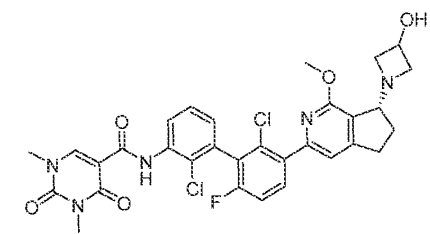
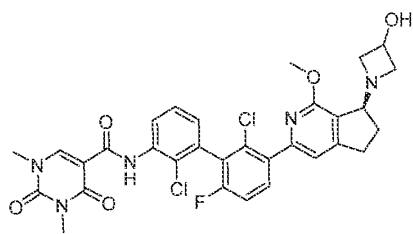
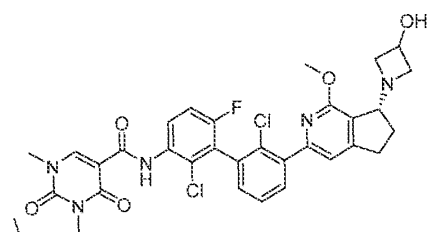
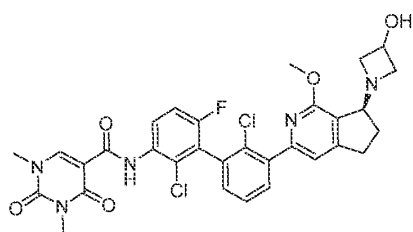
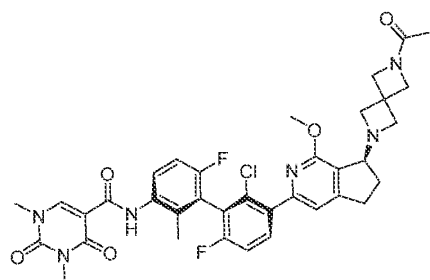
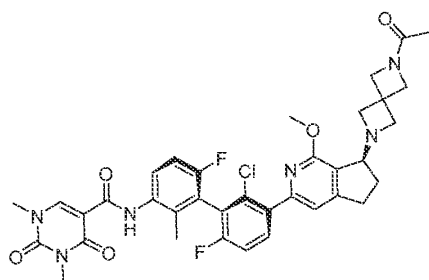


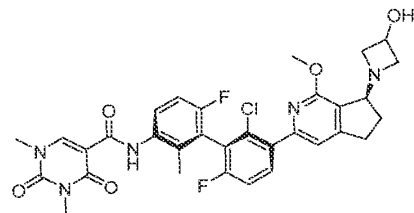
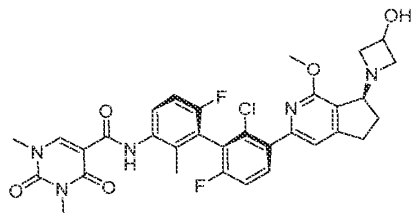
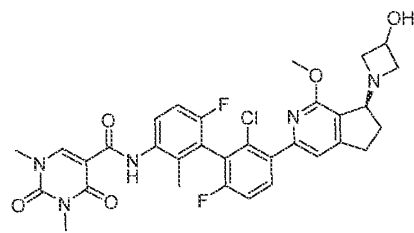
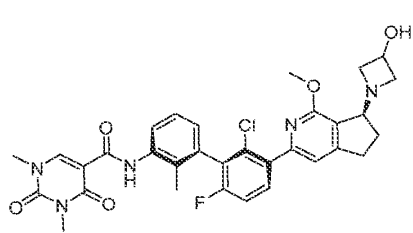
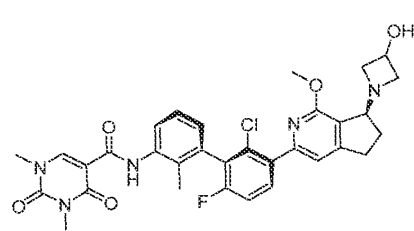
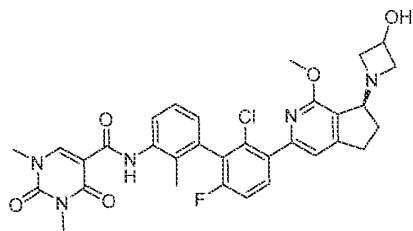
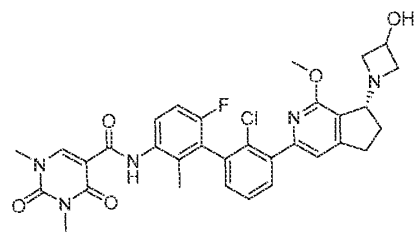
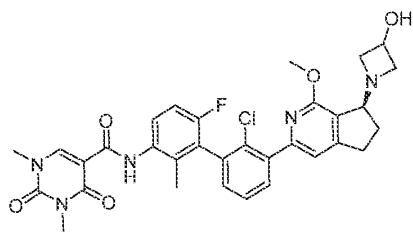
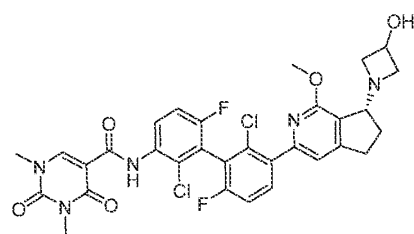
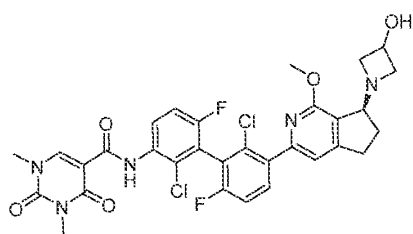


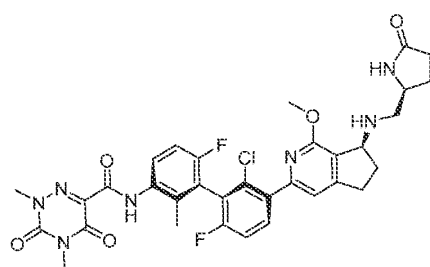
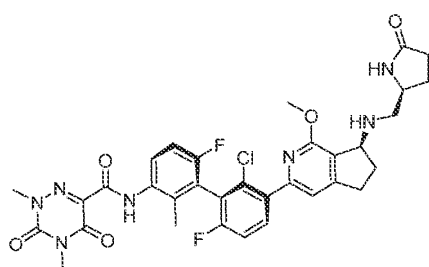
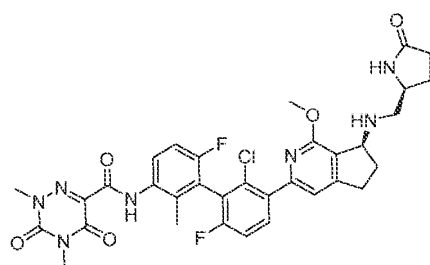
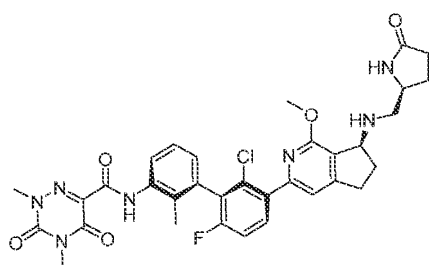
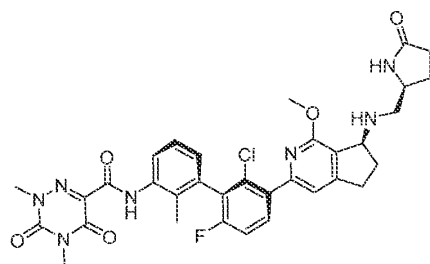
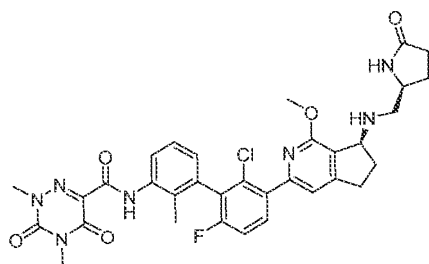
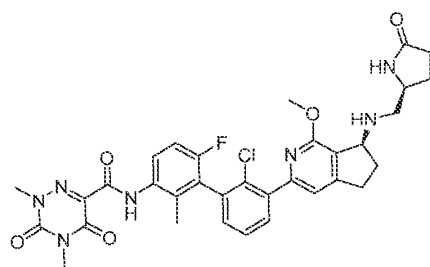
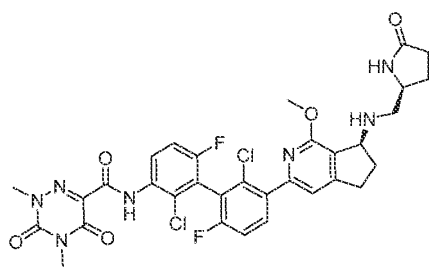
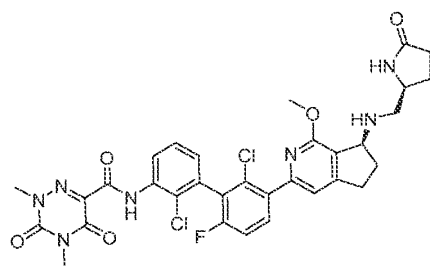
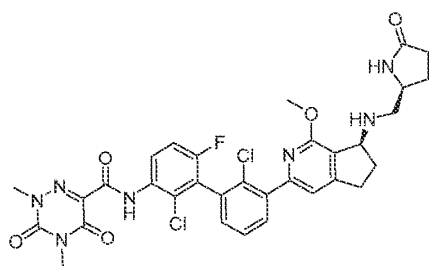


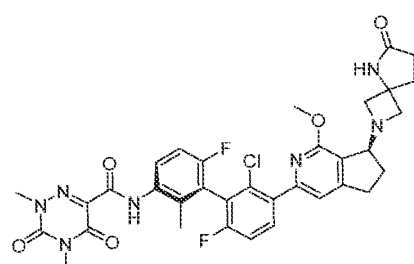
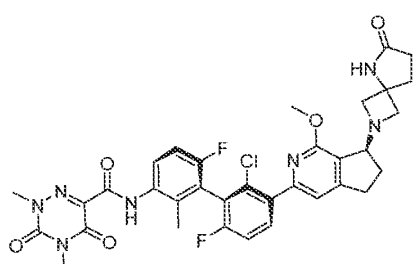
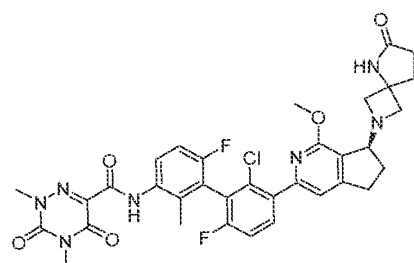
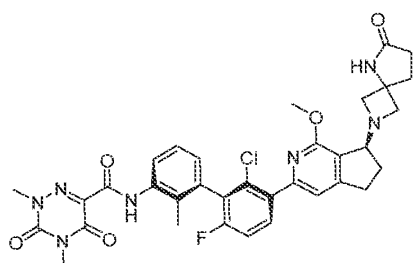
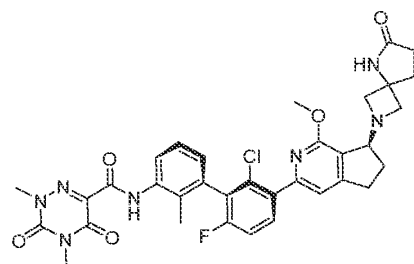
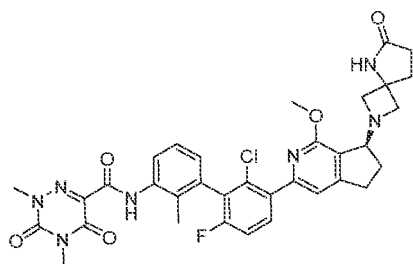
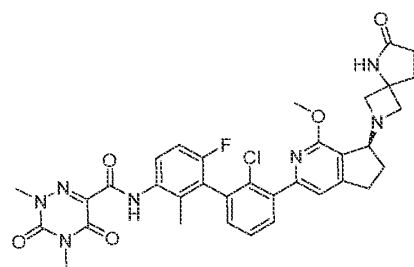
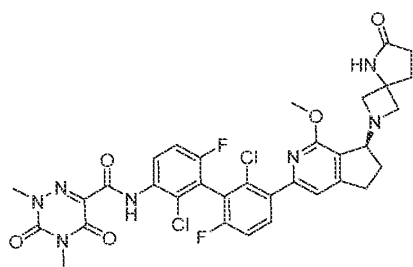
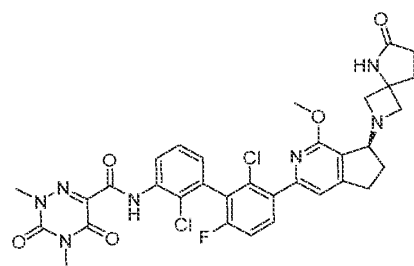
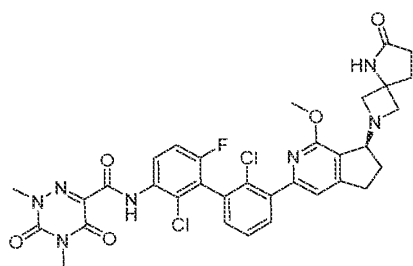


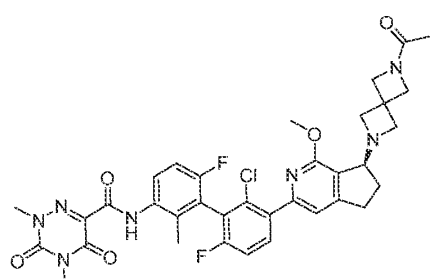
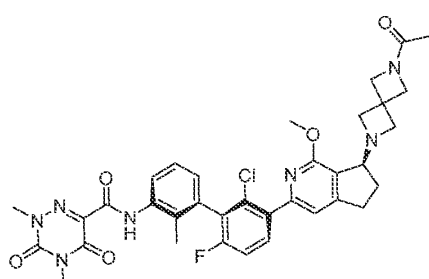
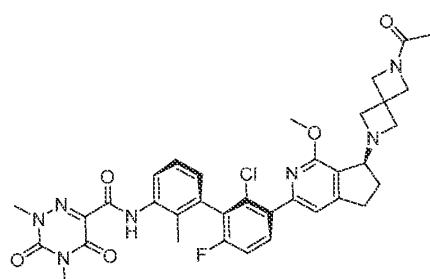
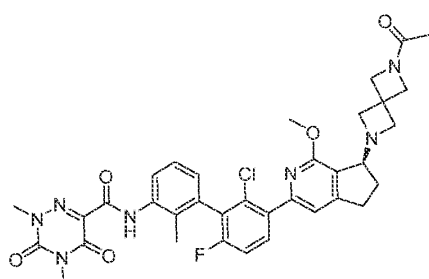
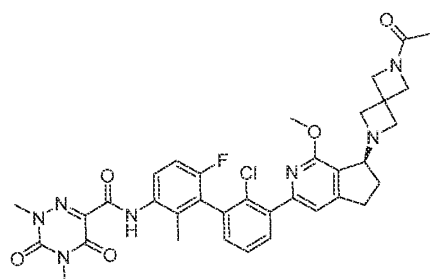
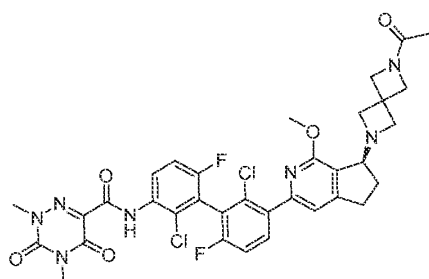
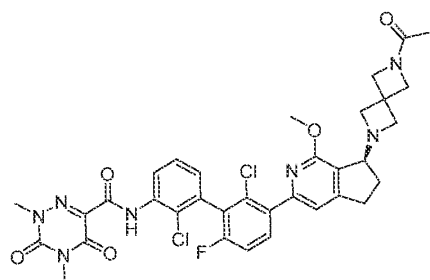
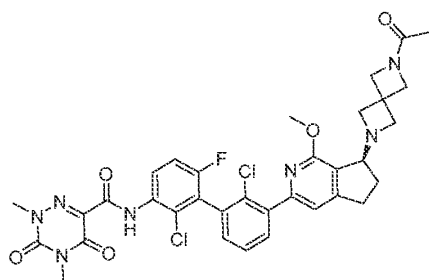


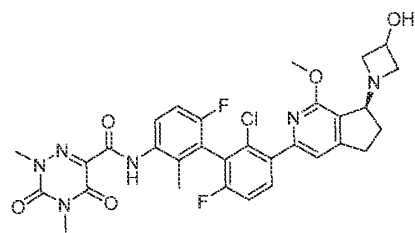
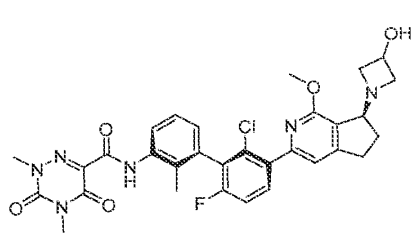
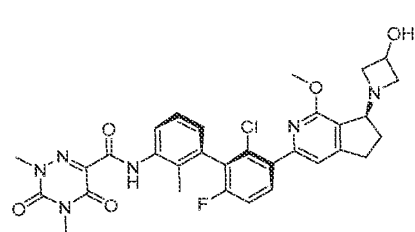
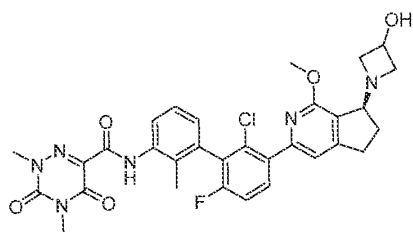
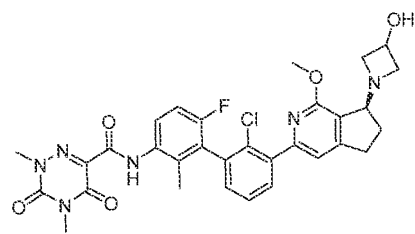
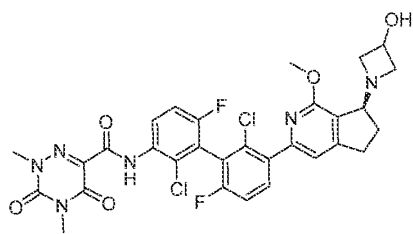
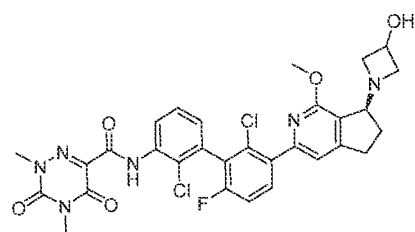
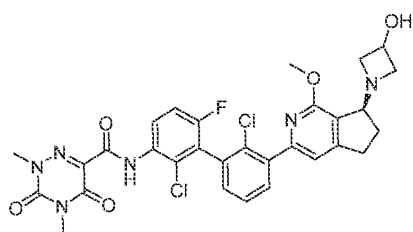
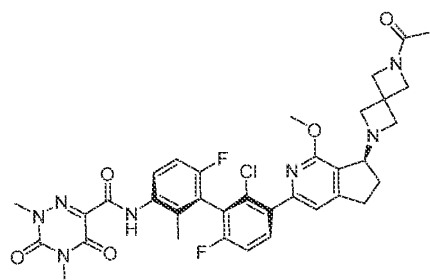
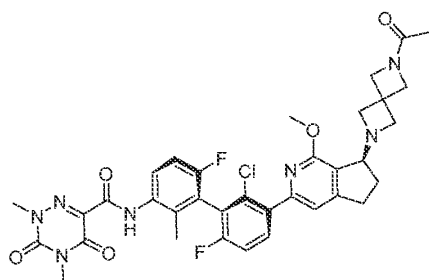


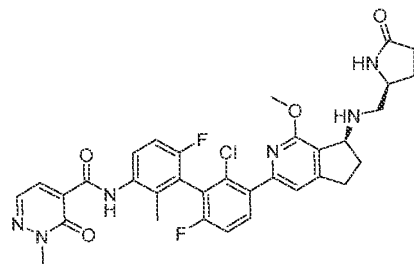
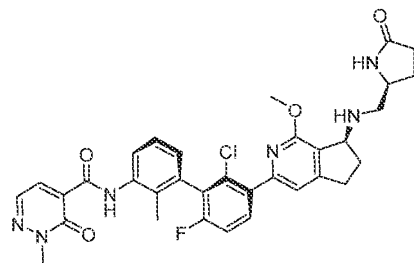
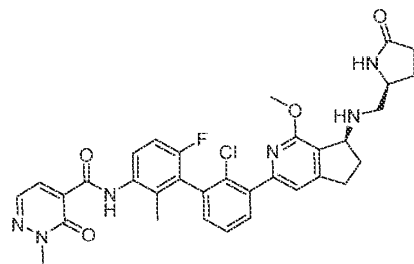
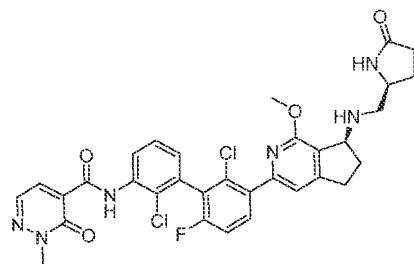
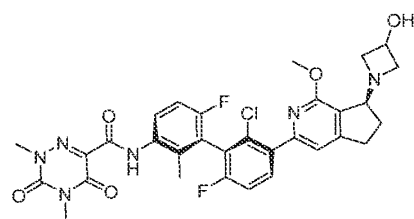


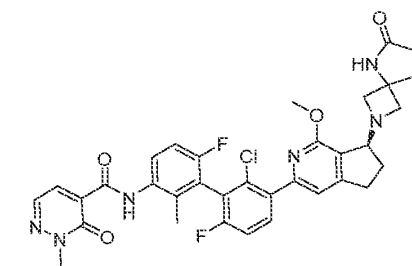
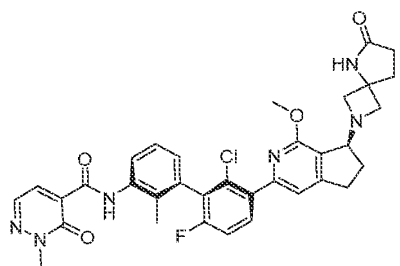
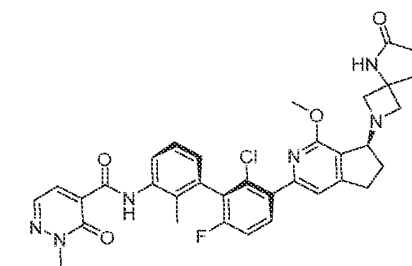
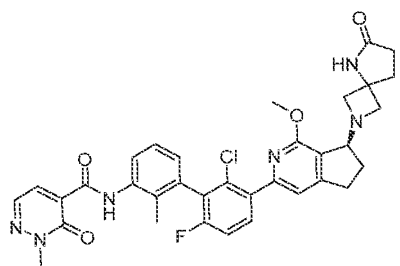
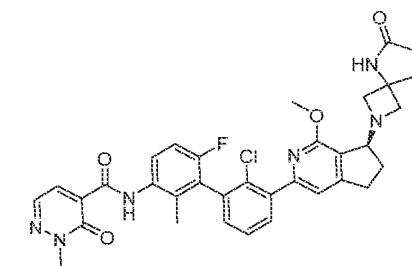
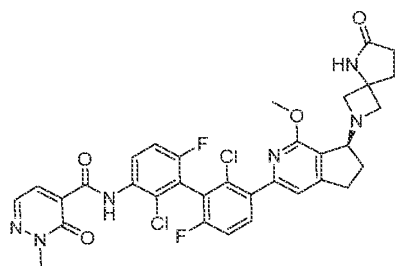
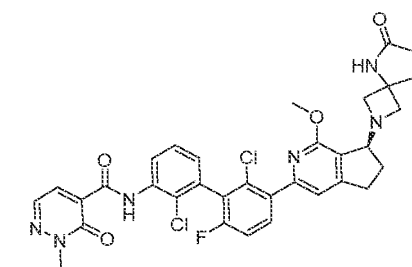
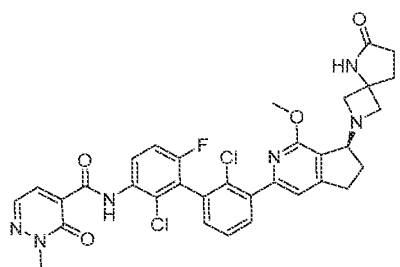
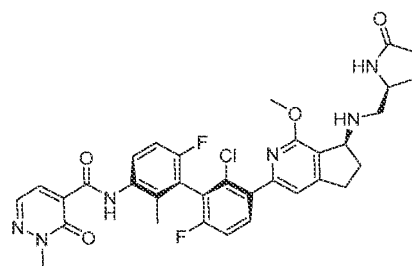
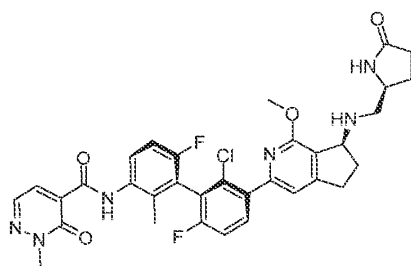


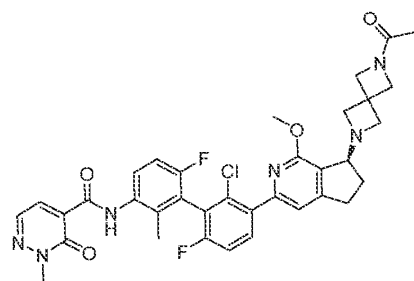
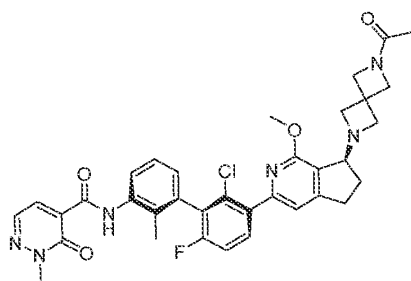
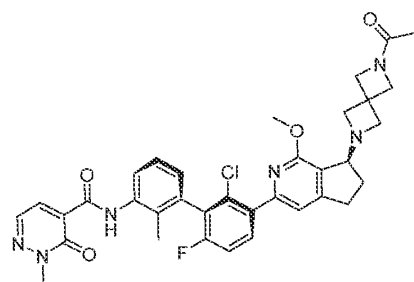
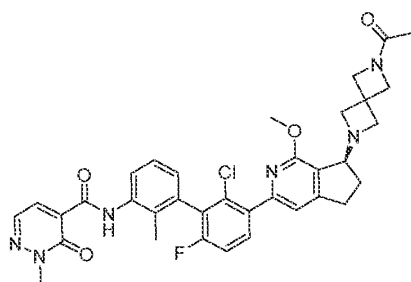
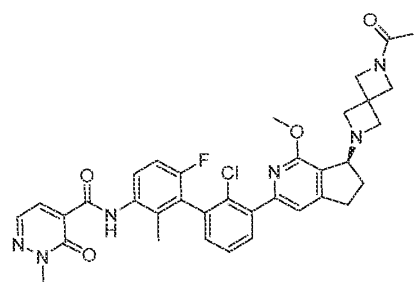
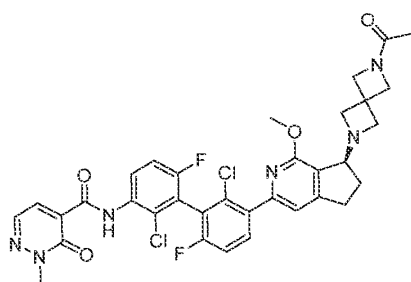
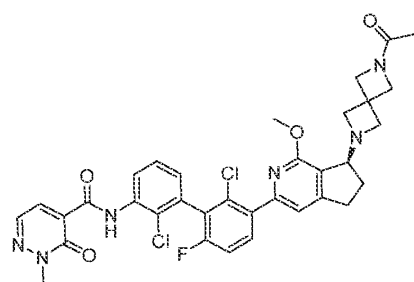
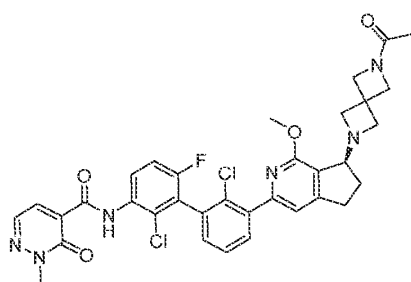
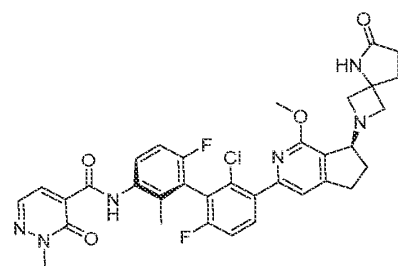
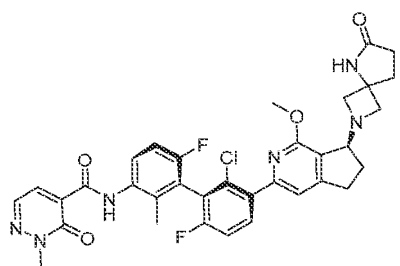


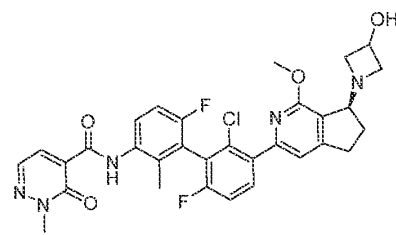
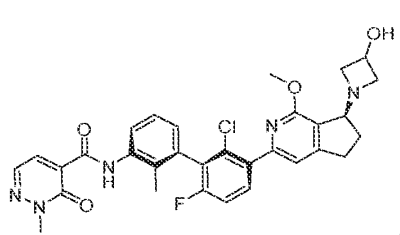
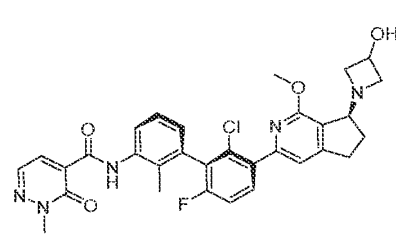
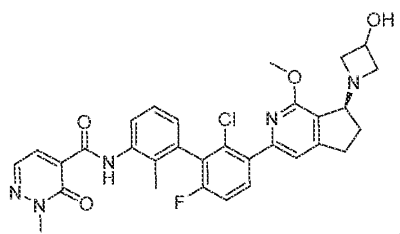
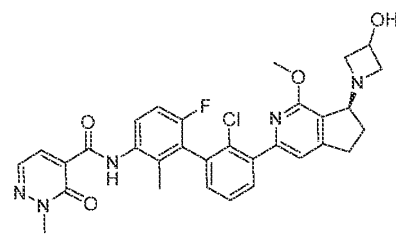
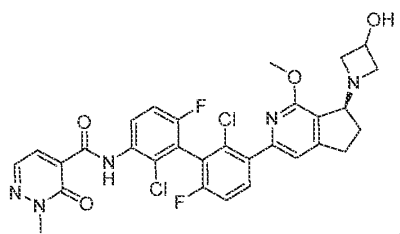
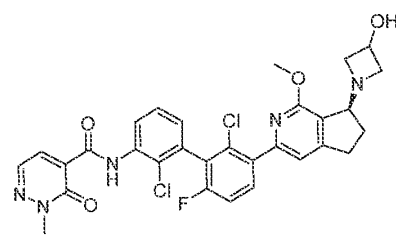
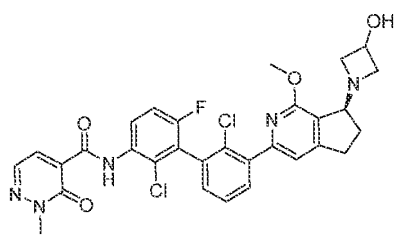
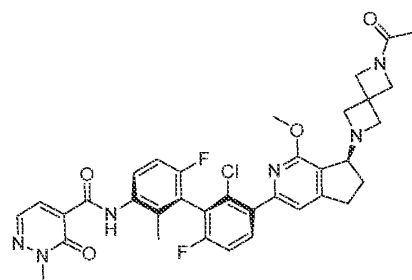
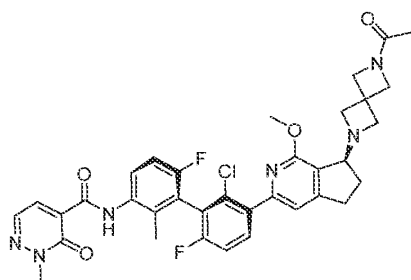


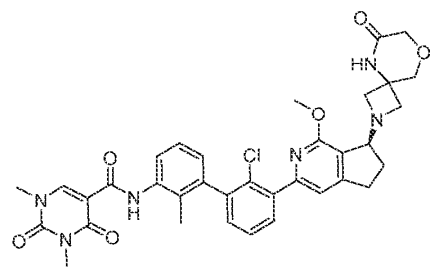
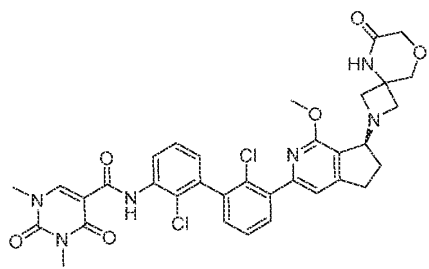
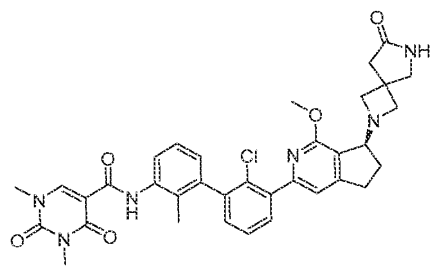
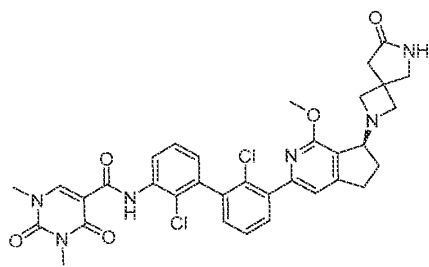
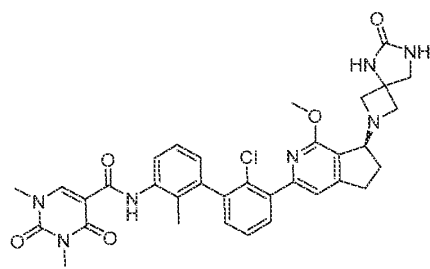
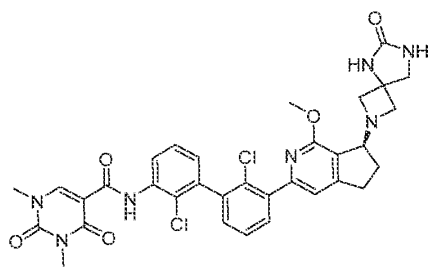
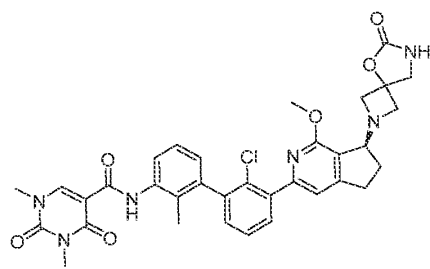
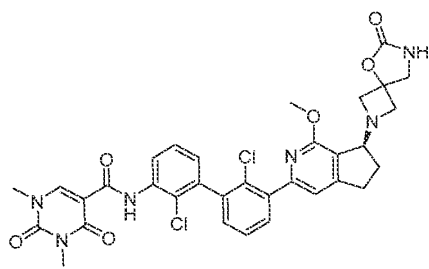
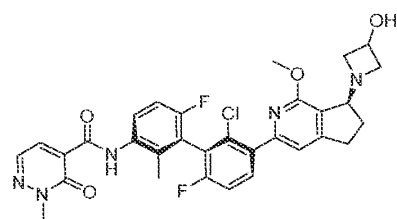
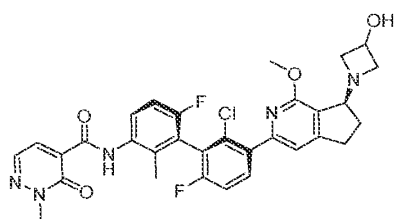


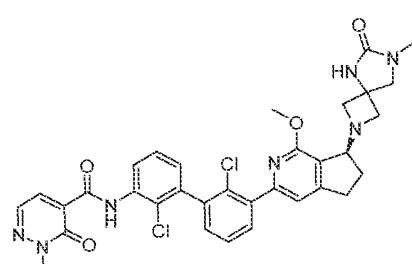
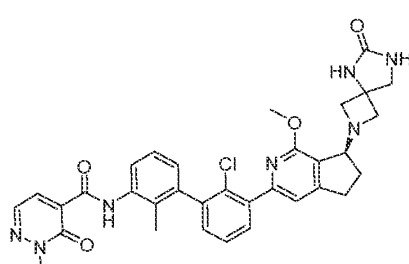
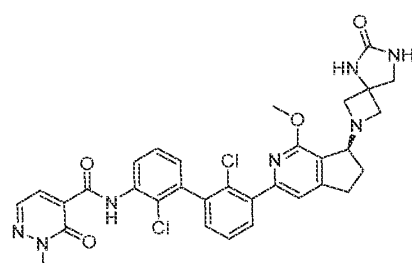
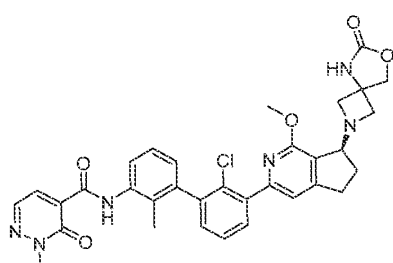
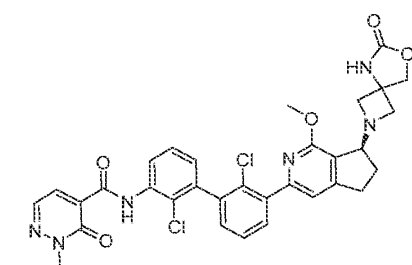
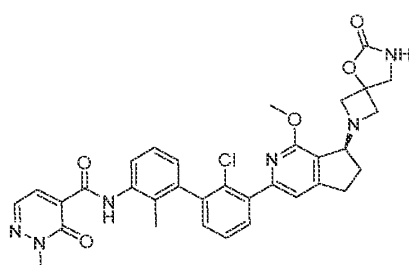
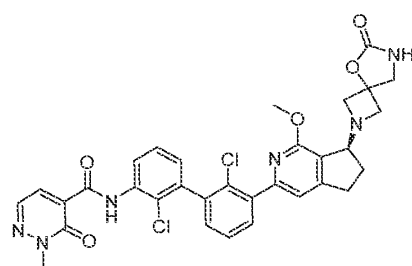
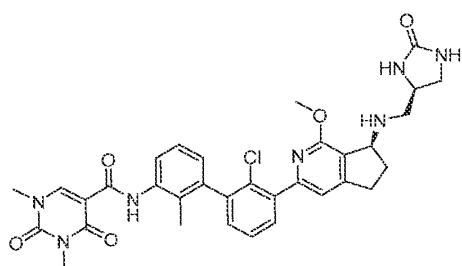
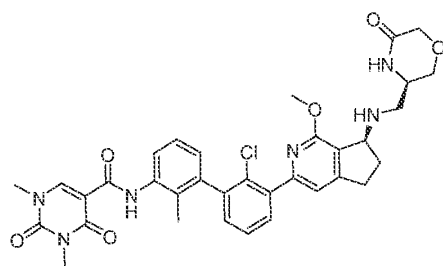
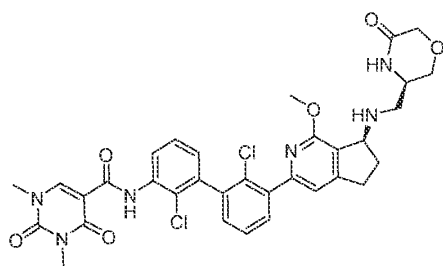


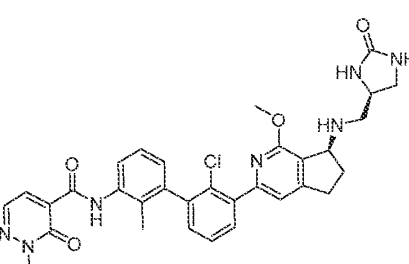
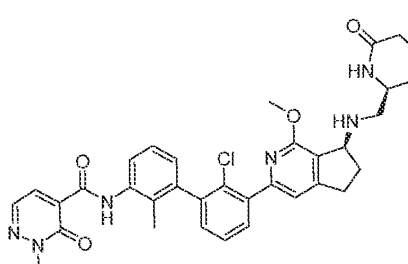
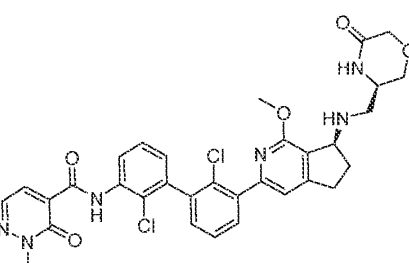
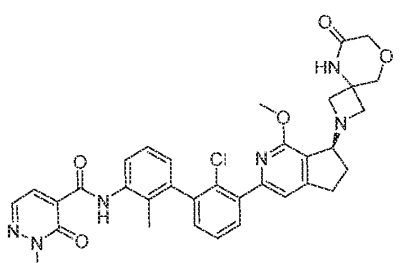
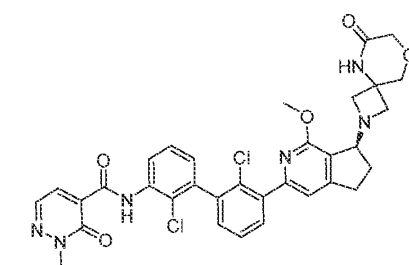
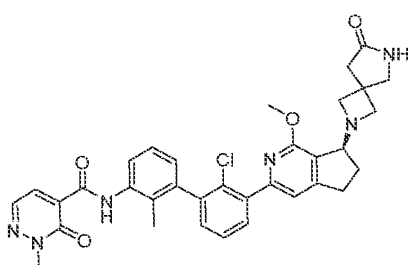
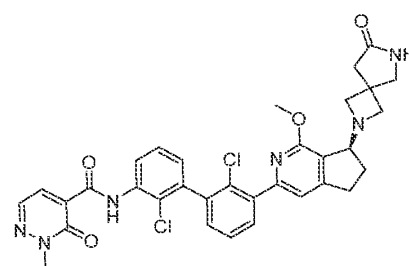
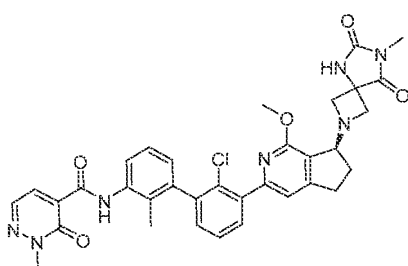
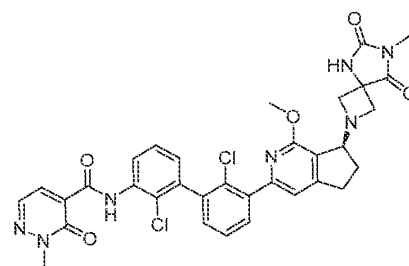
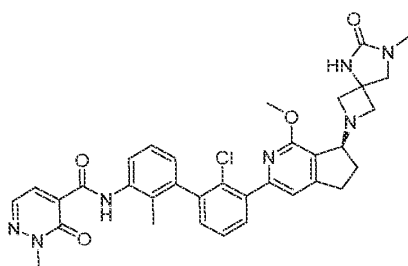


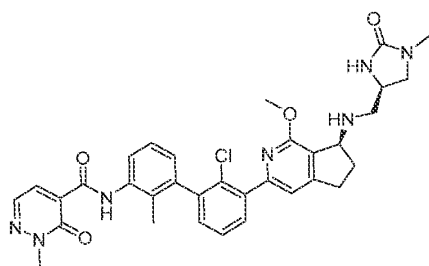




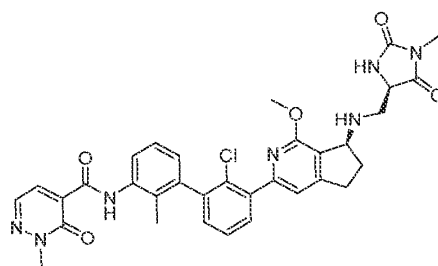








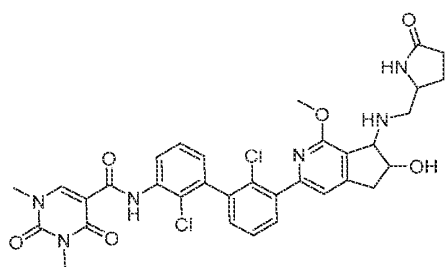
and



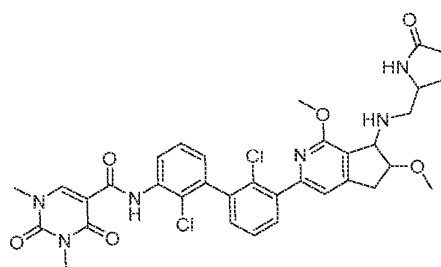
, or a

pharmaceutically acceptable salt of any of the foregoing.

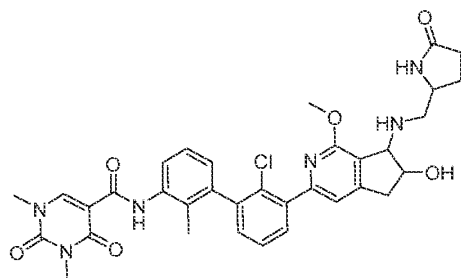
146. The compound of Claim 1 selected from the group consisting of:



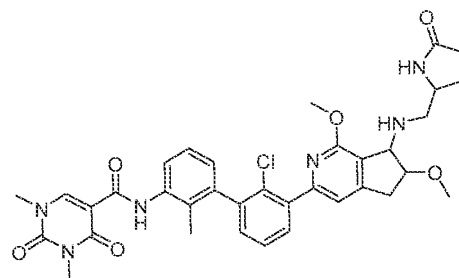
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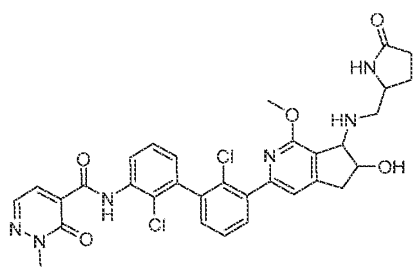
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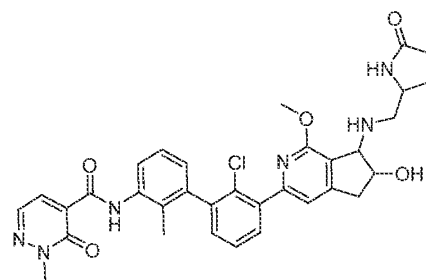
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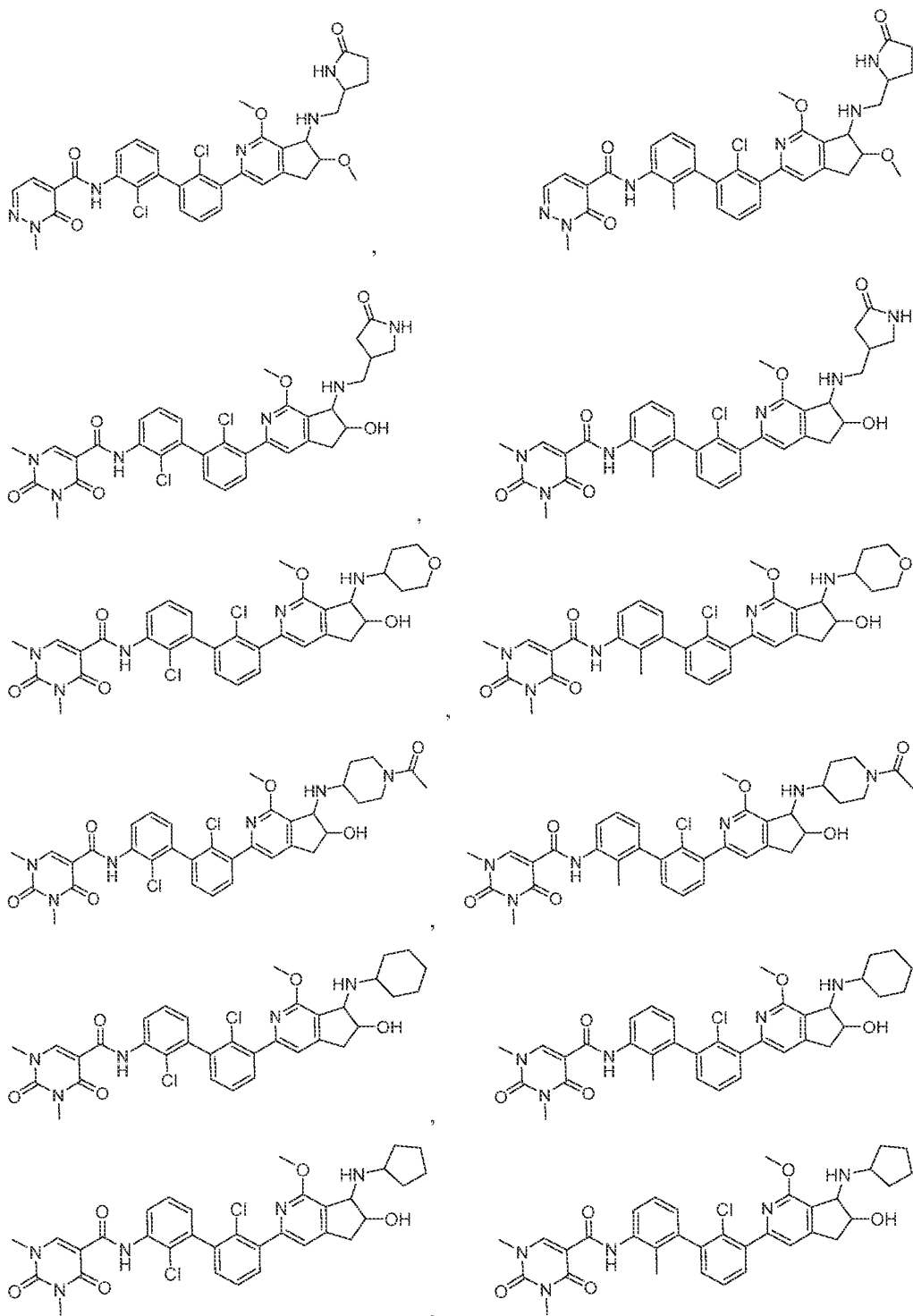
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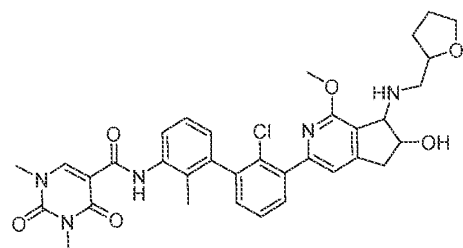
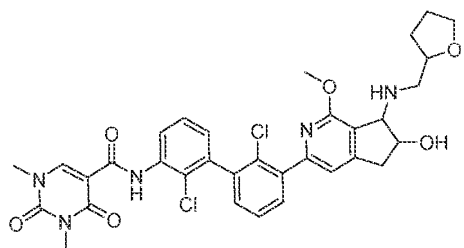
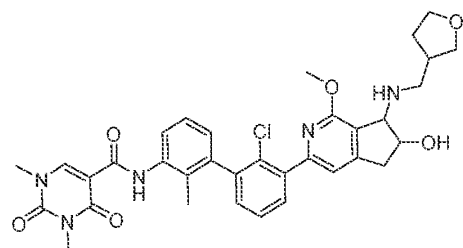
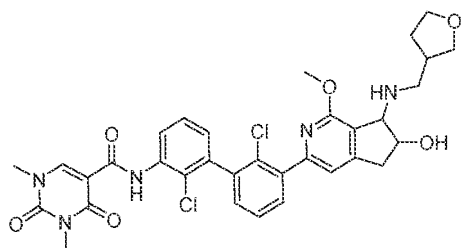
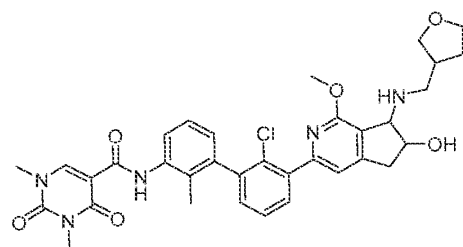
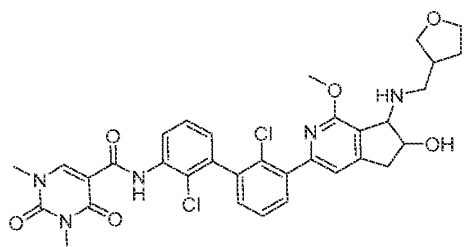
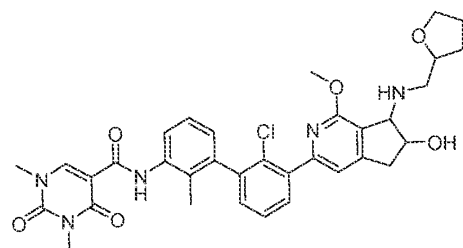
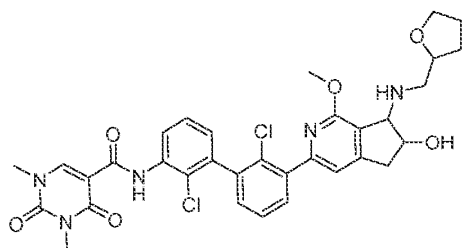
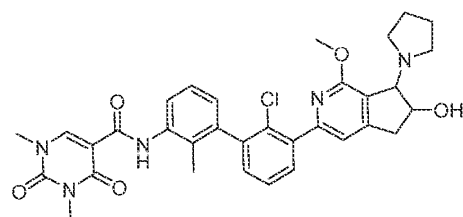
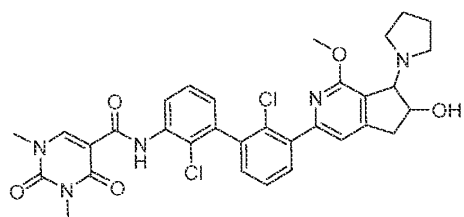


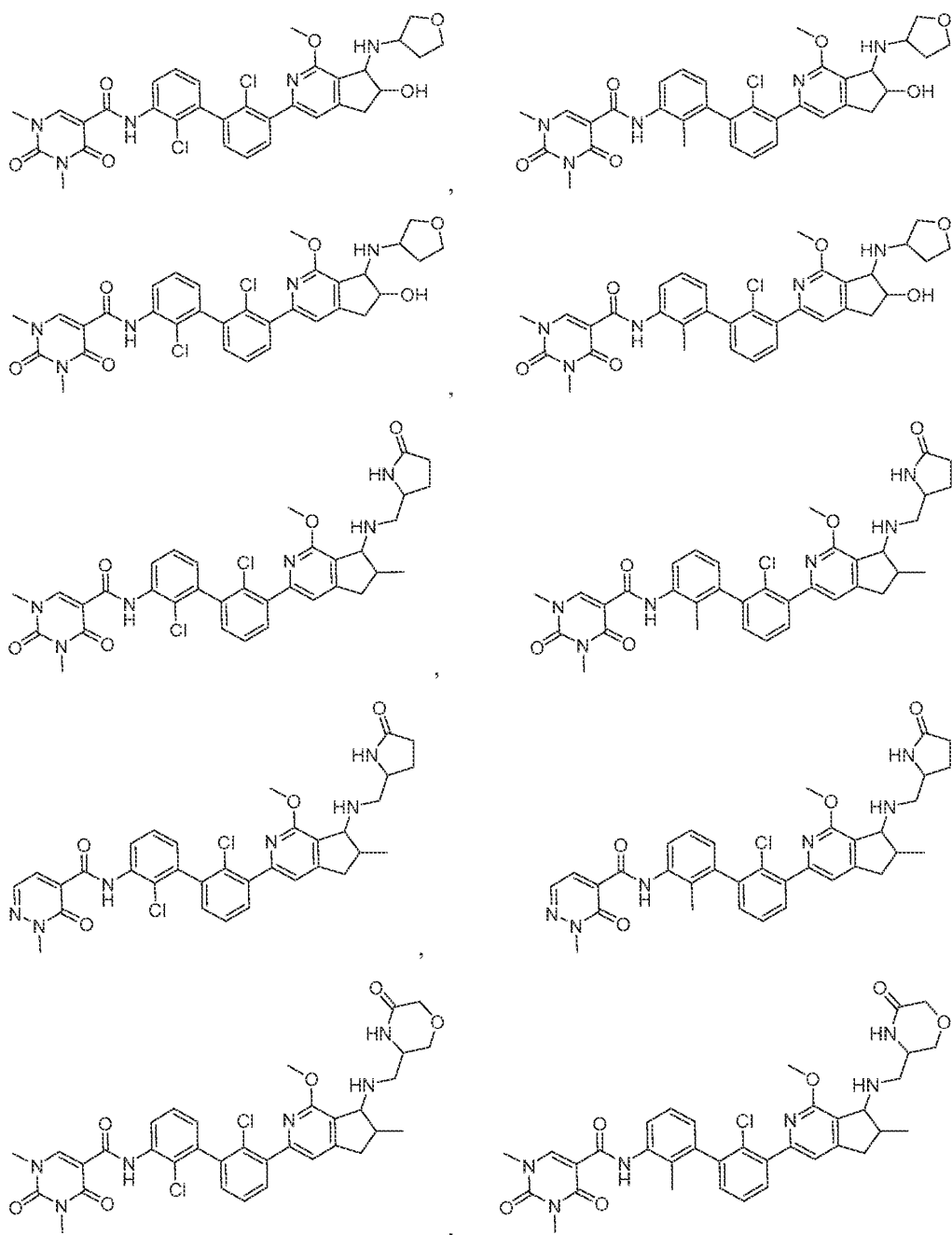
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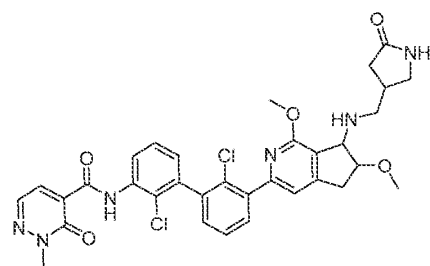
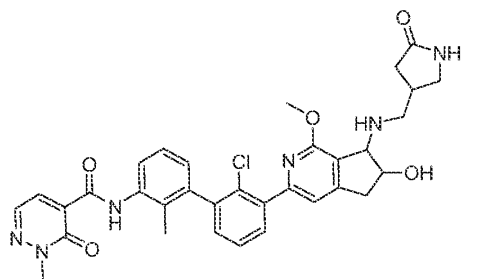
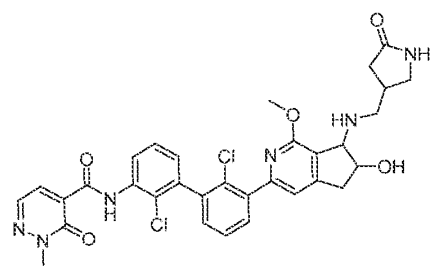
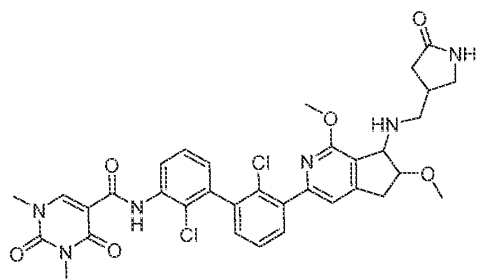
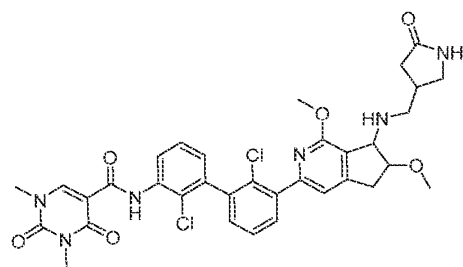
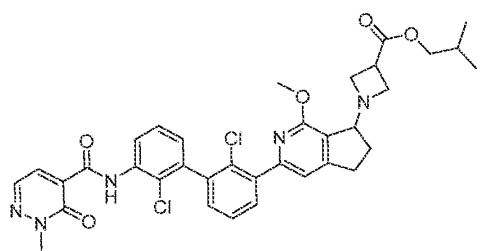
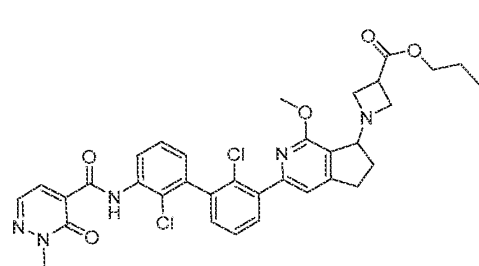
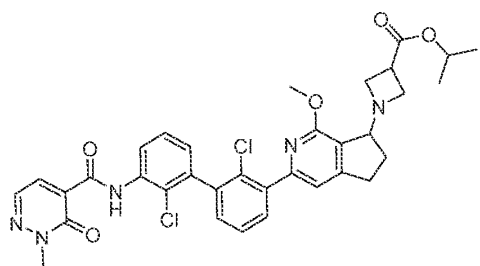
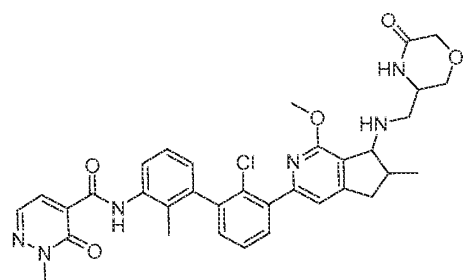
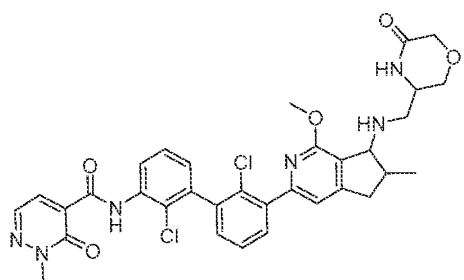


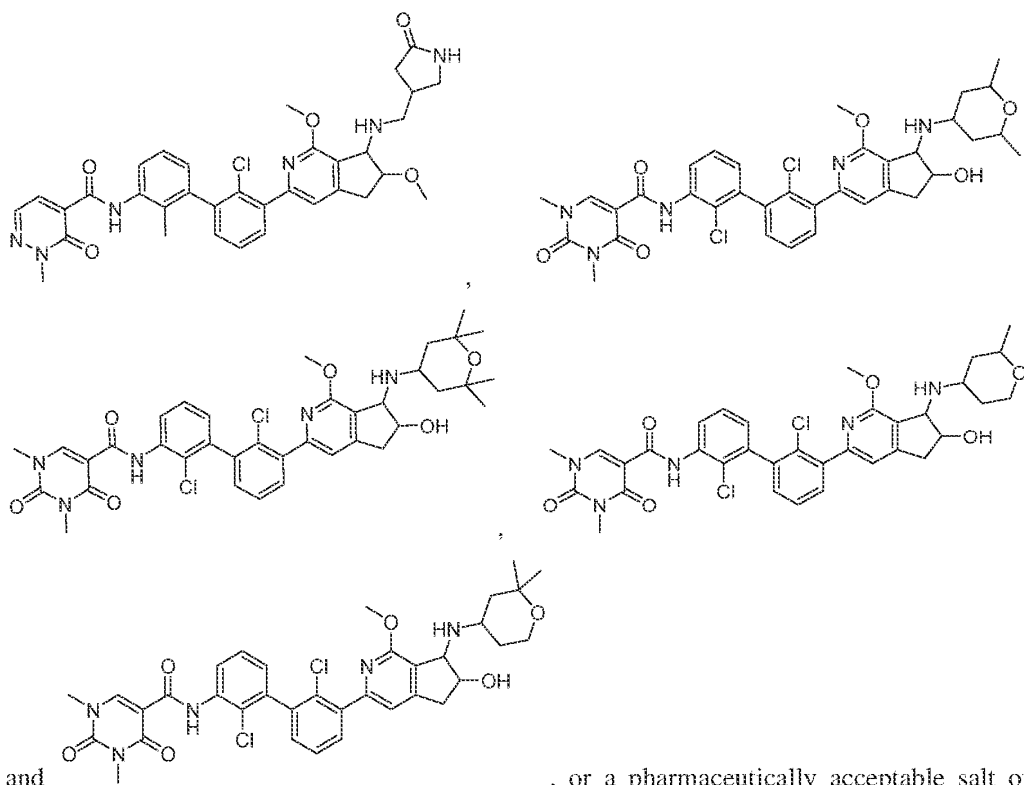
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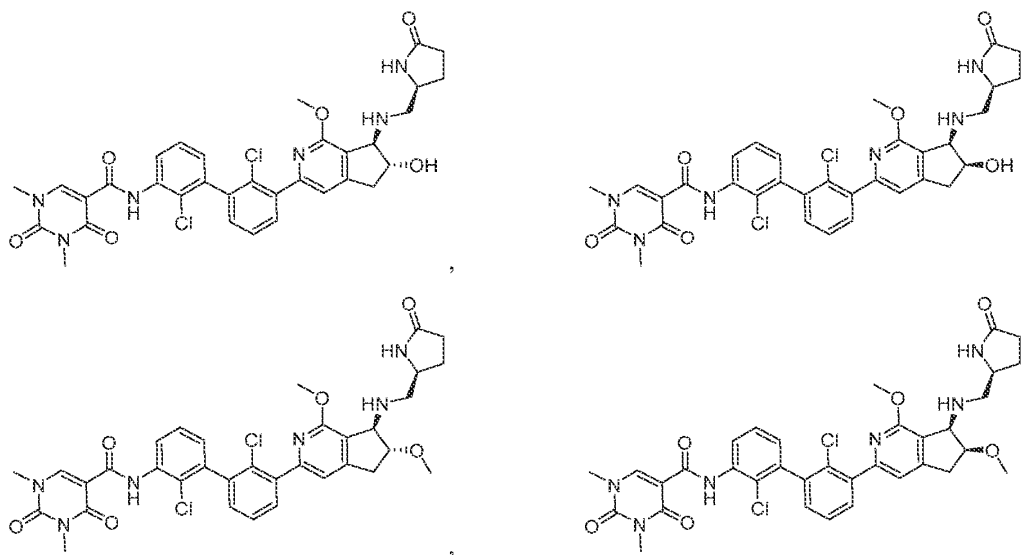


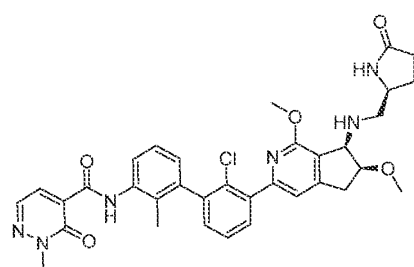
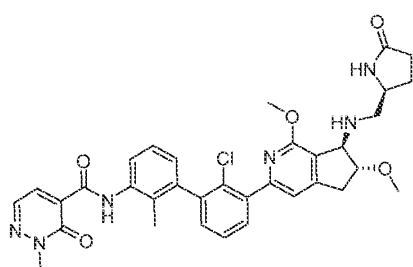
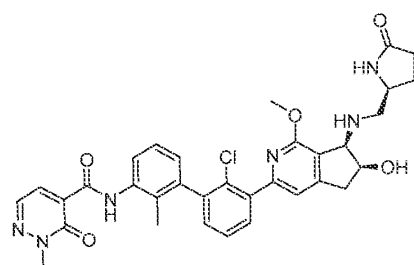
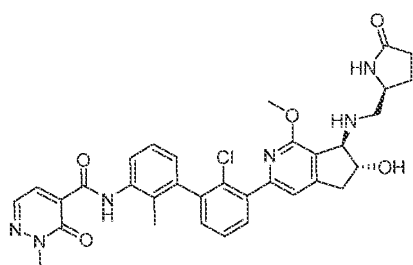
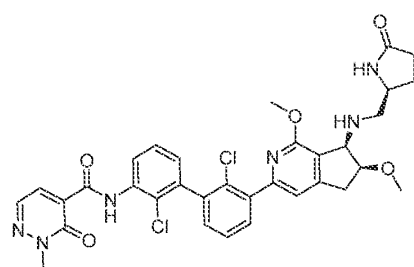
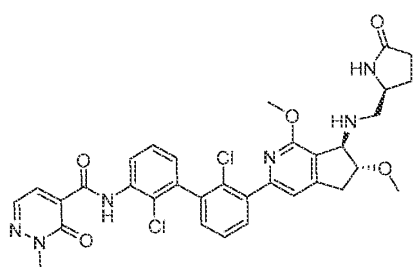
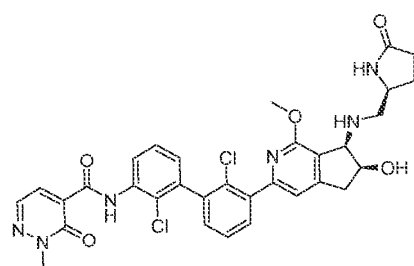
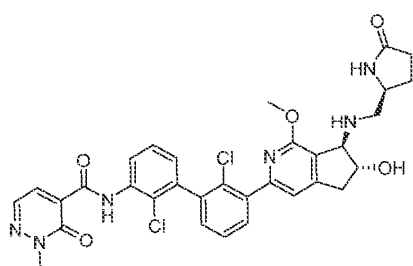
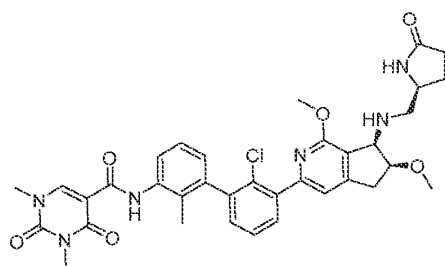
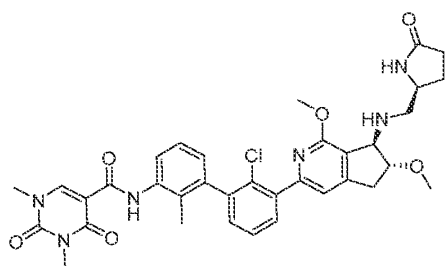


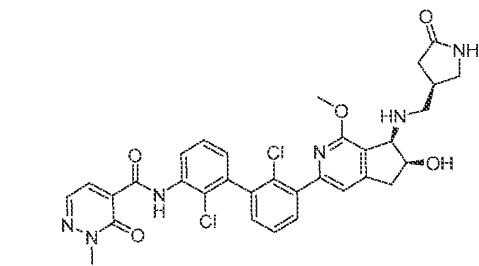
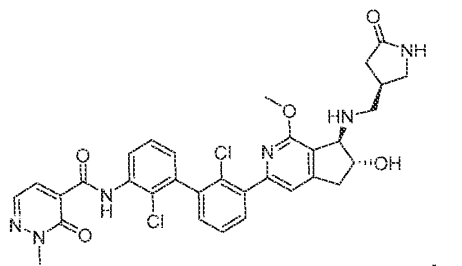
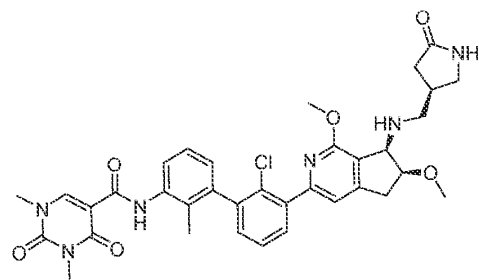
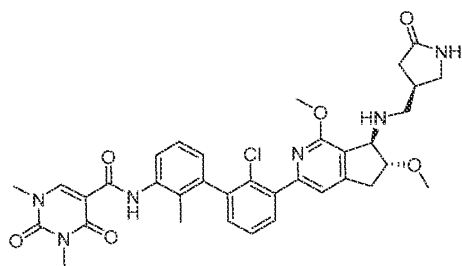
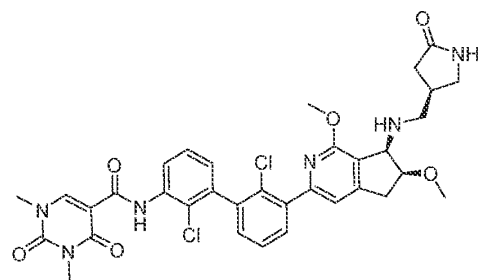
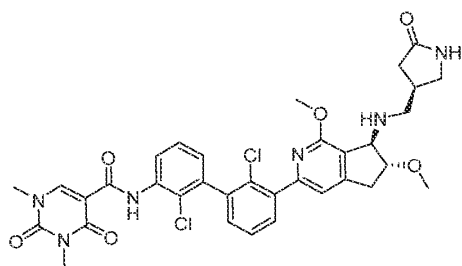
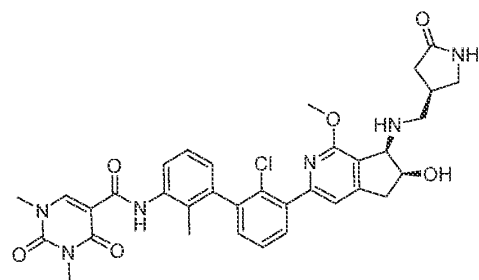
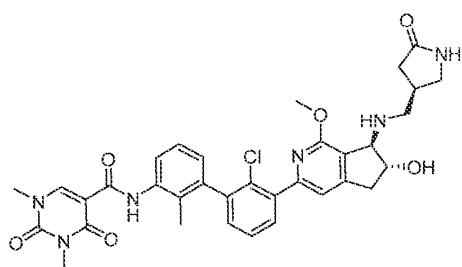
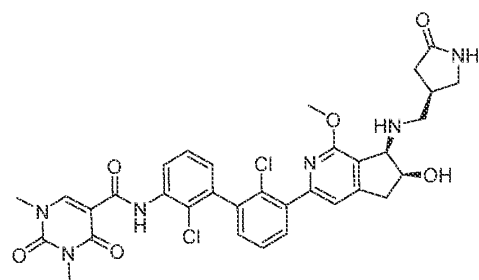
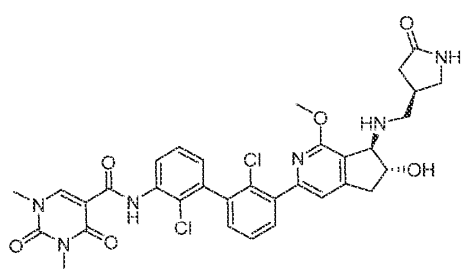


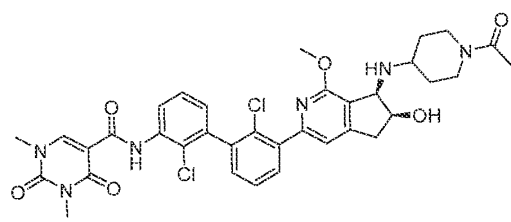
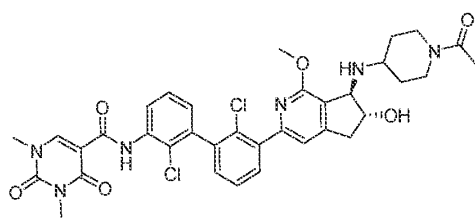
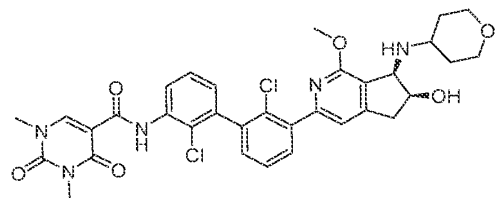
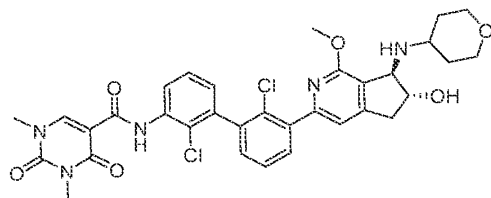
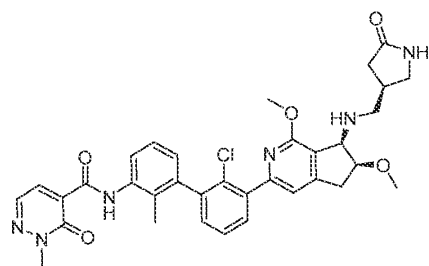
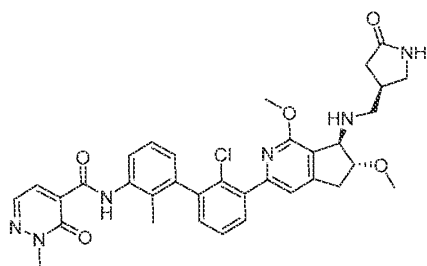
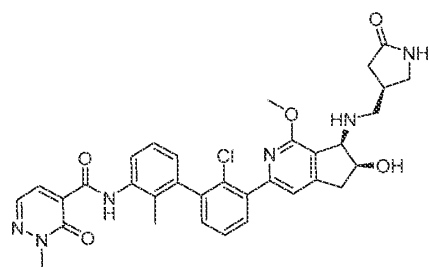
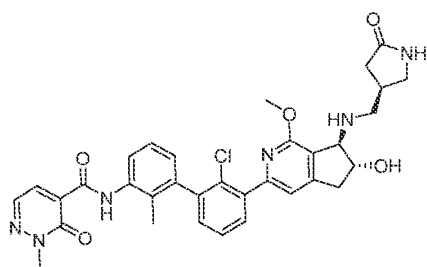
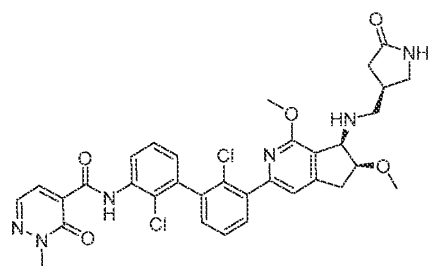
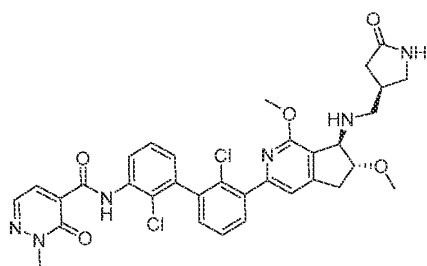
any of the foregoing.

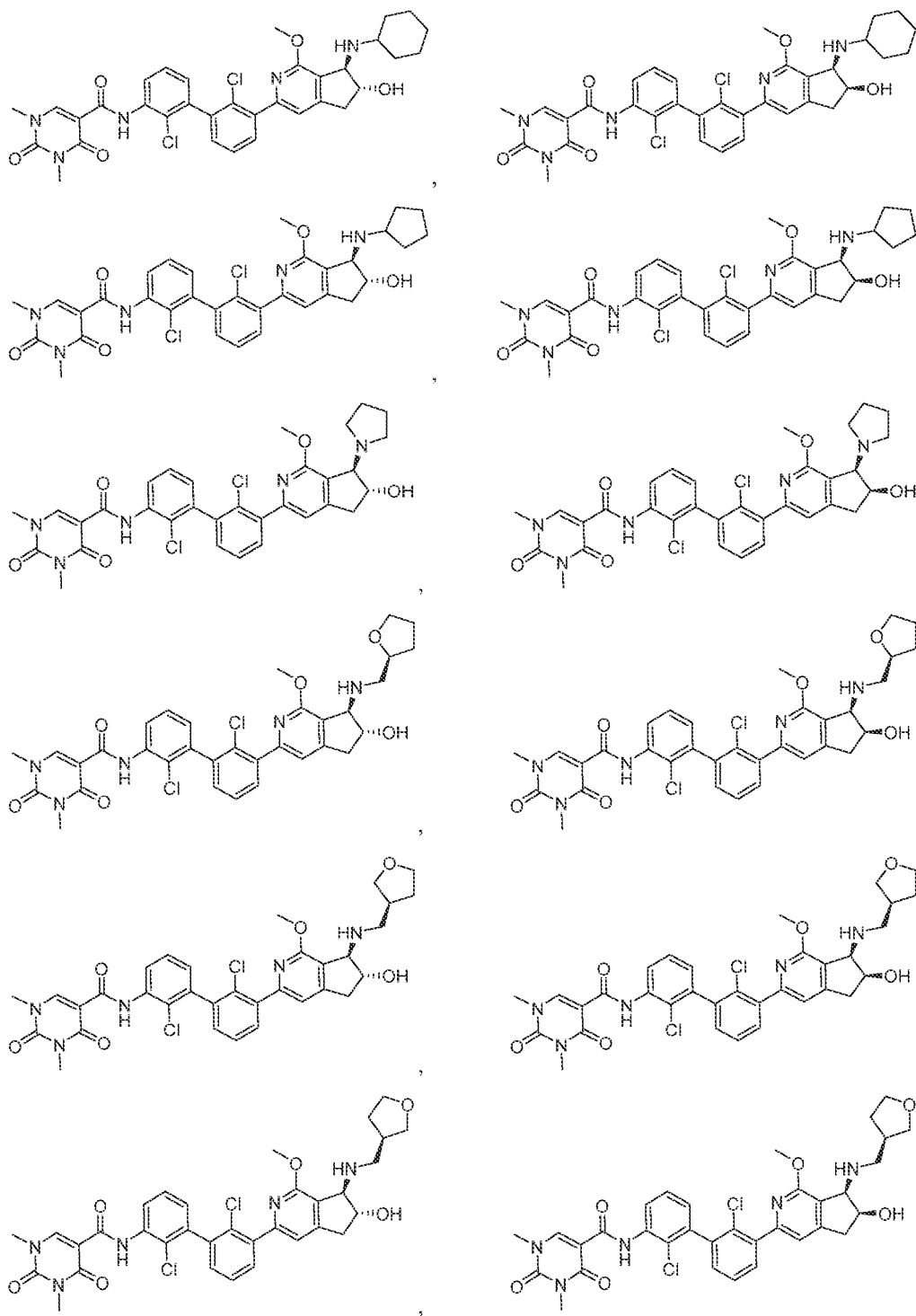
147. The compound of Claim 1 selected from the group consisting of:

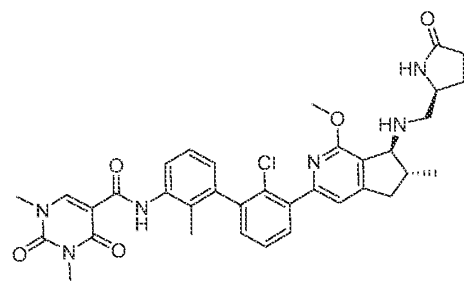
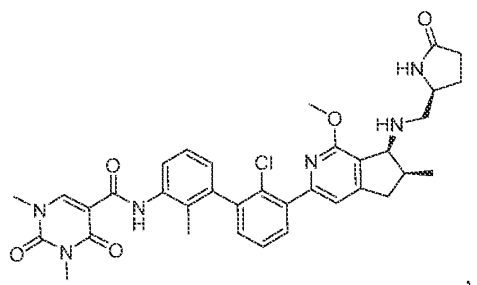
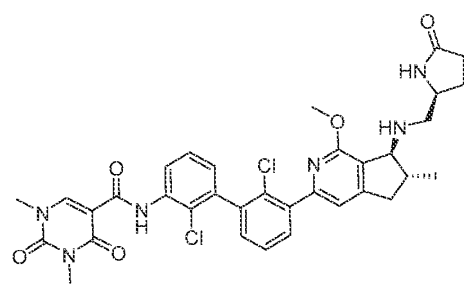
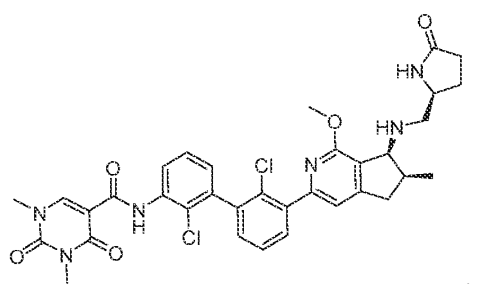
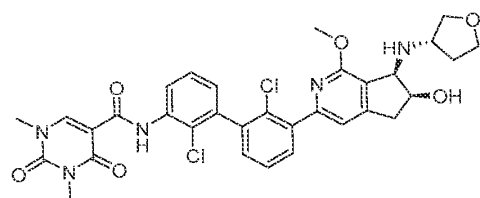
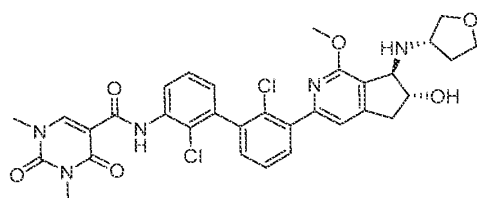
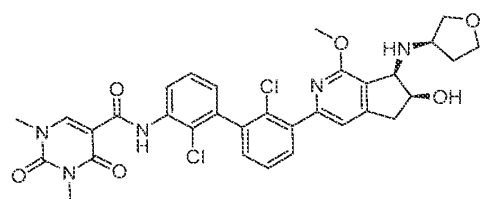
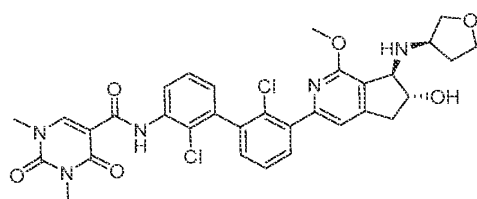
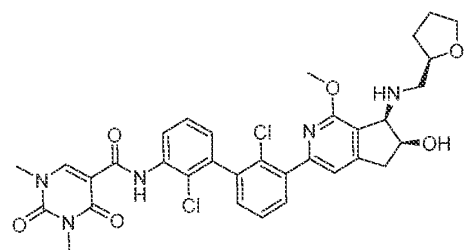
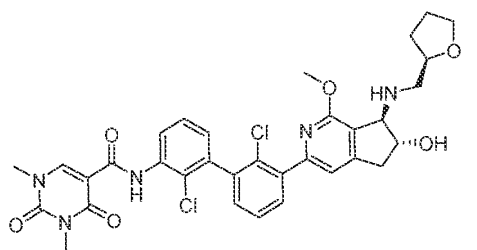


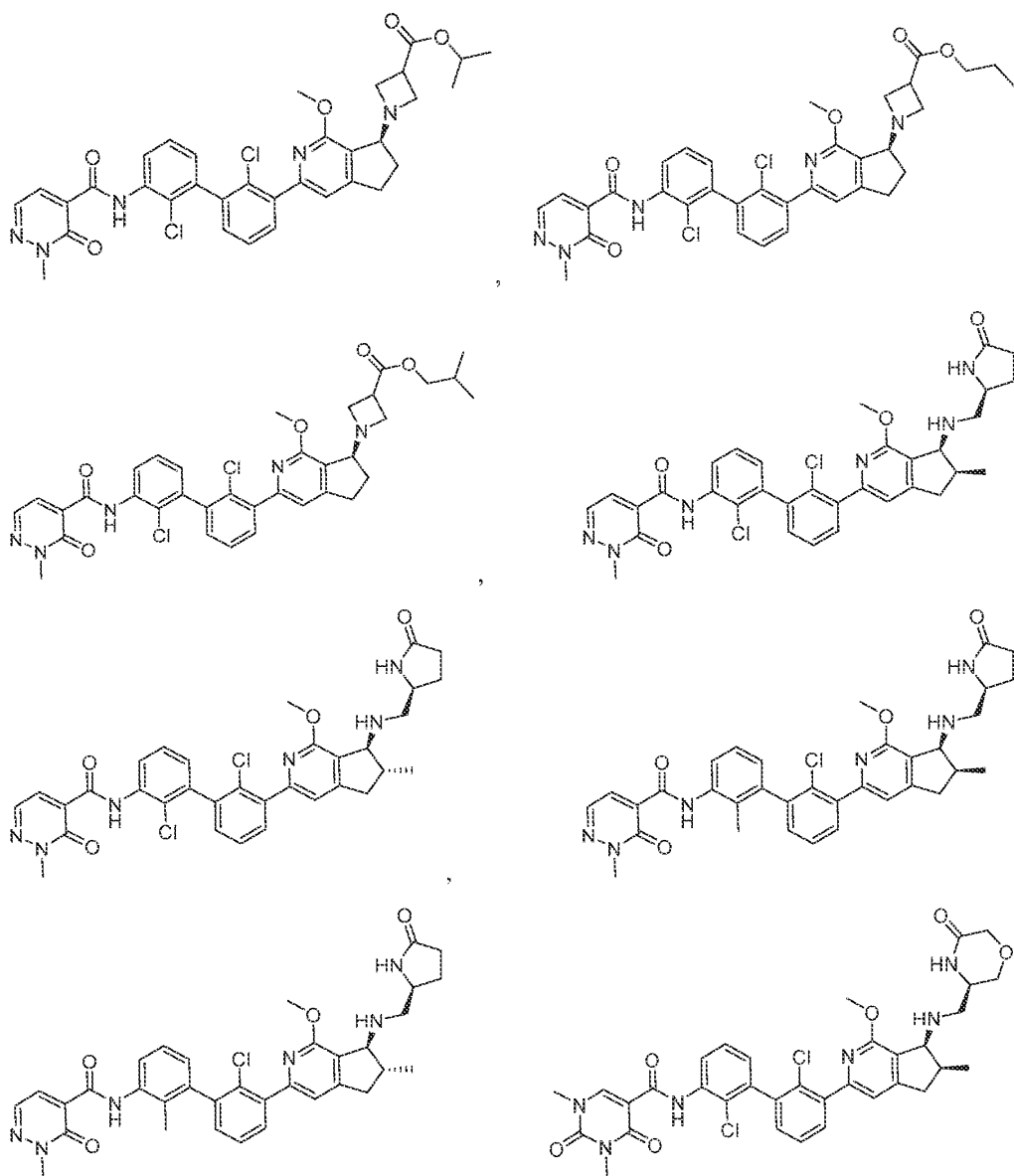


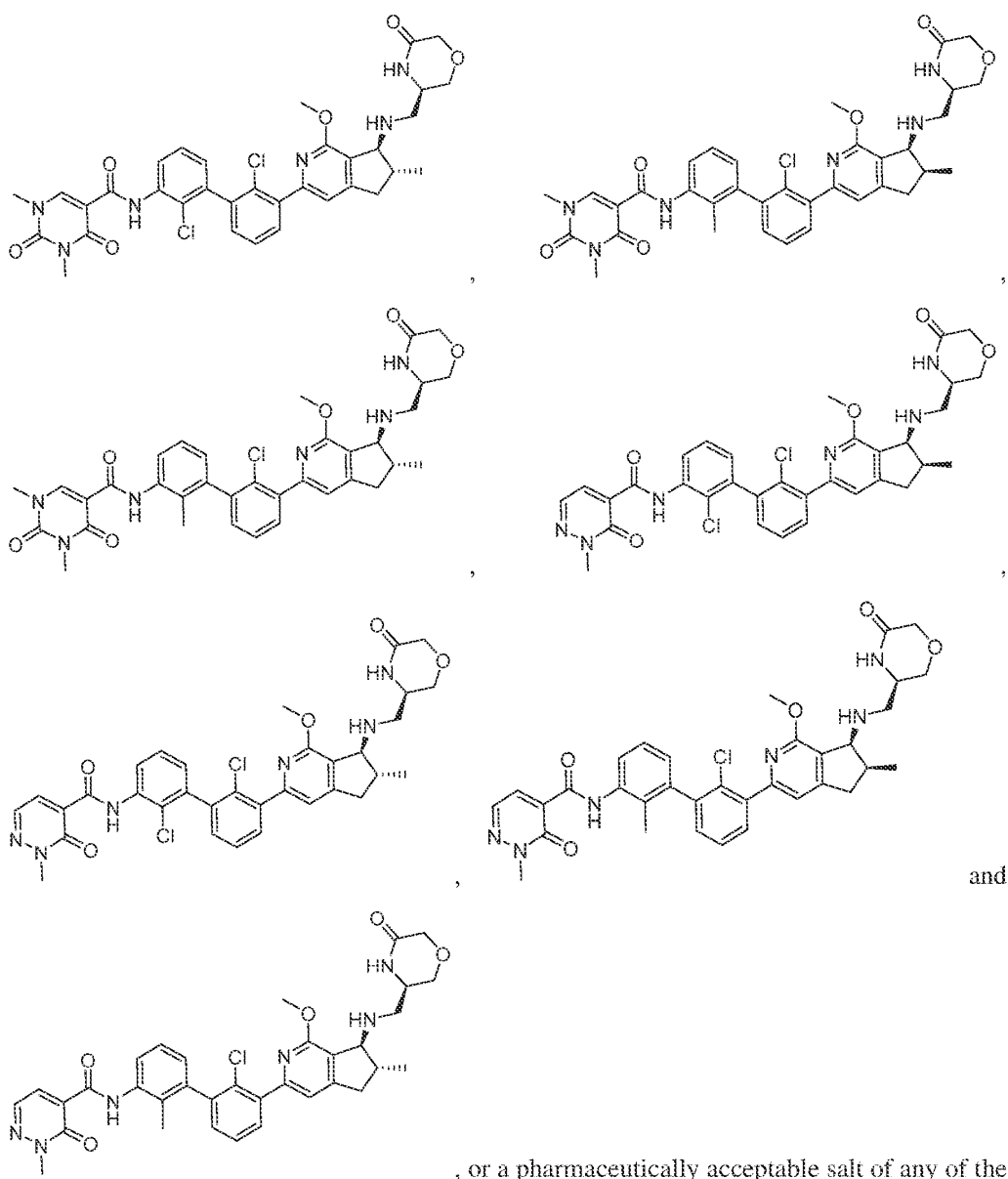












foregoing.

148. The compound of Claim 11 selected from the group consisting of: A-1 to A-139, B-1, B-2, B-3, B-4, C-1, D-1, D-2, D-3, D-4, D-5, D-6, D-7, D-8a, D-8b, D-10, D-11, D-12, D-13, D-14, D-15, D-16, D-17, D-18, D-19, E-1, E-2, E-3, F-1, G-1, H-1, I-1, J-1, J-2,

J-3, J-4, K-1a, K-1b, L-1a, L-1b, M-1a, M-1b, M-2a, M-2b, M-3a and M-3b, or a pharmaceutically acceptable salt of any of the foregoing.

149. A pharmaceutical composition comprising an effective amount of a compound of any one of Claims 1-148, or a pharmaceutically acceptable salt thereof, and excipient.

150. A method for treating hepatitis B in a subject comprising administering to the subject in need thereof an effective amount of a compound of any one of Claims 1-148, or a pharmaceutically acceptable salt thereof.

151. A method for treating hepatocellular carcinoma (HCC) in a subject comprising administering to the subject in need thereof an effective amount of a compound of any one of Claims 1-148, or a pharmaceutically acceptable salt thereof.

152. The method of any one of Claims 150-151, further comprising administering surgery, radiation therapy, chemotherapy, targeted therapy, immunotherapy, hormonal therapy, or antiviral therapy.

153. A compound of any one of Claims 1-148, or a pharmaceutically acceptable salt thereof, for use in treating hepatitis B.

154. A compound of any one of Claims 1-148, or a pharmaceutically acceptable salt thereof, for use in treating hepatocellular carcinoma (HCC).

155. The compound of any one of Claims 153-154, further comprising administering surgery, radiation therapy, chemotherapy, targeted therapy, immunotherapy, hormonal therapy, or antiviral therapy.

156. Use of a compound of any one of Claims 1-148, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for use in treating hepatitis B.

157. Use of a compound of any one of Claims 1-148, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for use in treating hepatocellular carcinoma (HCC).

158. The use of any one of Claims 156-157, further comprising administering surgery, radiation therapy, chemotherapy, targeted therapy, immunotherapy, hormonal therapy, or antiviral therapy.