QUINOLIZINONES AS PI3K INHIBITORS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional No. 63/571,644, filed March 29, 2024, and U.S. Provisional No. 63/749,421, filed January 24, 2025, the disclosures of which are incorporated by reference in their entireties for all purposes.

BACKGROUND OF THE INVENTION

[0002] Phosphatidylinositol lipids (PIs) and their various phosphorylated subspecies are second messengers involved in a wide array of cellular vesicle trafficking and signal transduction processes. Phosphoinositide 3' kinases (PI3Ks) are a family of enzymes responsible for phosphorylation of the 3' hydroxyl position of the inositol ring of PIs. PI3Ks are subdivided into 3 classes according to their structure and substrates. Class II PI3Ks (PI3K-C2α, PI3K-C2β, PI3K-C2γ) and Class III PI3Ks (vps34) are monomeric enzymes primarily associated with endocytosis and autophagy (Posor *et al.*, Biochim Biophys Acta **2015**, 1851, 794; Backer, Biochem J. **2016**, 473, 2251). The Class I PI3Ks are heterodimeric, consisting of a catalytic kinase subunit (p110α, β, γ, δ) and one of several regulatory subunits that determine binding partners and subcellular localization. Class I PI3Ks are activated upon interaction with receptor tyrosine kinases (RTKs), Ras-related GTPases, G-protein coupled receptors, and/or related adaptor proteins, and in their active form convert phosphatidylinositol 4,5-diphosphate (PIP2) to phosphatidyl 3,4,5-triphosphate (PIP3) (Fruman *et al.*, Cell **2017**, 170, 605).

[0003] High local concentrations of PIP3 promote the recruitment and activation of downstream signaling partners, including AKT and mTOR. Activation of the AKT/mTOR pathways are implicated in several growth-related roles and pathologies including glucose regulation, cell survival, angiogenesis, and proliferation (Porta *et al.*, Front Oncol. **2014**, 4, 1), indicating a role for Class I PI3Ks as a critical upstream regulator of these functions.

[0004] Class I PI3Ks are further subdivided into 4 isoforms (α, β, γ, and δ) based on the identity of their catalytic (p110α, p110β, p110γ, or p110δ) and regulatory (p85α or its various splice variants, p85β, p55γ, or p101) subunits, giving rise to distinct roles in cellular physiology (Vanhaesebroeck *et al.*, J Mol Med (Berl). **2016**, 94, 5). PI3Kγ and PI3Kδ are mostly expressed in leukocytes and play an important role in pro-inflammatory pathways (Hawkins *et. al.,* Biochimica et Biophysica Acta **2015**, 1851, 882; Okkenhaug *et al.*, Science **2002**, 297, 1031; Ali *et al.*, Nature

2004, 431, 1007). PI3Kα and β are more ubiquitously expressed and share similar but not identical roles. For example, PI3Kα has a nonredundant role in angiogenesis (Soler *et al.*, J Exp Med. **2013**, 210, 1937), while PI3Kβ is known to serve a specific function in platelet aggregation (Liu *et. al.,* Nat Rev Drug Discov. **2009**, 8, 627; Jackson *et al.*, Nat Med. **2005**, 11, 507).

[0005] Elevation or constitutive activation of the PI3K pathway is one of the most frequent events in human cancers. The PI3K pathway is overactivated through a variety of mechanisms, including activating mutation of PI3K isoforms, up-regulation of PI3K isoforms, loss or inactivation of the tumor suppressor PTEN, or hyperactivation of tyrosine kinase growth factor receptors or other upstream signaling partners (Yang *et al.*, *Mol Cancer* **2019**, 18, 1). Mutations in the gene coding for PI3Kα or mutations which lead to upregulation of PI3Kα have been found to occur in many human cancers such as lung, stomach, endometrial, ovarian, bladder, breast, colon, brain, prostate, and skin cancers (Goncalves *et al.*, N Eng J Med. **2018**, 379,2052). In particular, PIK3CA, the gene encoding the p110α subunit of PI3Kα, is frequently mutated or amplified in a variety of tumor types. Missense mutations occur in all domains of p110α, but cluster in two 'hot spots', the most common being E542K and E545K in the helical domain, and H1047R in the kinase domain. Helical domain mutations reduce inhibition of p110α by p85 or facilitate direct interaction of p110α with insulin receptor substrate 1 (IRS1)37, whereas kinase domain mutations increase interaction of p110α with lipid membranes, concomitantly upregulating signaling events. (Thorpe *et al.*, Nat Rev Cancer **2015**, 15, 7).

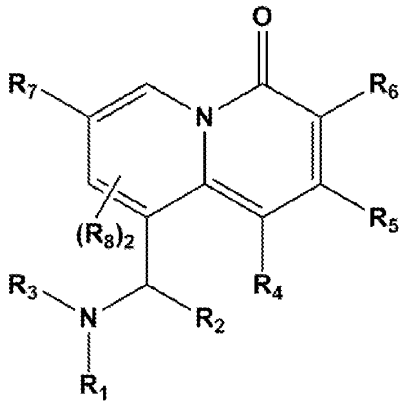
[0006] The development of inhibitors for the PI3K pathway has been challenging due to the inability to achieve dosing sufficient for tumor suppression without adverse events. To date PI3K inhibitors in the clinic (alpelisib, buparlisib, copanlisib, duvelisib, idelalisib, pictilisib, taselisib, and others) have caused dose-dependent adverse events such as hyperglycemia, rash, fatigue, diarrhea, etc. (Jiang *et al.*, Mol Biol Rep. **2020**, 47, 4587) which are known on-target toxicities. Hyperglycemia is a result of the body not producing enough insulin or aberrant utilization. The pancreas regulates insulin release in response to changes in blood glucose levels, resulting in either glucose uptake by muscle and fat cells when insulin levels are high or gluconeogenesis by the liver when insulin levels are low. Tissue cellular response to insulin requires PI3K signaling through the ubiquitously expressed p110α sub-unit. As a result, pan-PI3K inhibition of the target disrupts glucose metabolism in tissues, leading to insulin resistance (Hopkins *et al.*, Nature **2018**, 560, 499). To mitigate adverse events, selective PI3K isoform inhibitors were developed. The

severity of the adverse event is dependent on the select isoform, for example PI3Kα inhibitors are associated with hyperglycemia and rash due to the p110α sub-unit role in insulin response (Rugo *et al.*, The Breast **2022**, 61, 156). Similarly, use of a selective PI3Kδ inhibitor (idelalisib), where the p110δ sub-unit is highly expressed in immune cells, causes severe diarrhea and colitis. Inhibition with a dual inhibitor (taselisib), a potent PI3Kδ inhibitor possessing modest PI3Kα inhibition led to gastrointestinal (GI) side effects, but a highly selective and potent PI3Kδ inhibitor (umbralisib) reported no GI related adverse events (Gadkar *et al.*, CPT Pharmacometrics Syst Pharmacol. **2021**, 11, 616). Such amelioration of adverse events with highly isoform selective and potent inhibitors demonstrates that a strategy to mitigate toxicity by developing mutant selective isoform inhibitors is promising for decreasing the severity of toxicity. Furthermore, selective inhibition of the mutant PI3Kα isoform over wild type may suppress cancer signaling while having minimal effect on PI3K signaling in healthy cells bearing just wild type PI3Kα, leading to a reduction in the toxicities associated with nonselective PI3K inhibition (Castel *et al.*, Nat Cancer **2021** 2, 587).

[0007] There is currently an interest in developing PI3K inhibitors for cancer therapy (WO 2023/081209, WO 2023/078401, WO 2023/060262, WO 2023/056407, WO 2021/202964). However, there is a continued need for novel potent and selective PI3K inhibitors, either as single agents or as combination therapies, in the treatment of cancer.

SUMMARY OF THE INVENTION

[0008] An aspect of the invention is a compound of Formula (1)



(1)

or a solvate, enantiomer, diastereomer, tautomer, polymorph or isotope-labeled compound thereof, or a pharmaceutically acceptable salt thereof,

wherein:

R_1 is aryl, heteroaryl or heterocyclyl, where each of the aryl, heteroaryl and heterocyclyl is unsubstituted or substituted, with the proviso that when R_1 is aryl or heteroaryl, a carboxylic acid or ester thereof is not a substituent at a position ortho to the point of attachment of the aryl or heteroaryl ring to the nitrogen atom of N-R_3;

R_2 is H, C_1-C_4 alkyl, C_3-C_7 cycloalkyl, CF_3, CFH_2 or CF_2H, where the C_1-C_4 alkyl and C_3-C_7 cycloalkyl is unsubstituted or substituted, and where R_2 is not H, the carbon atom attached to R_2 is a chiral center and exists as a (R)- and (S)-racemic mixture or as either the (R)- or (S)- enantiomer;

R_3 is H or C_1-C_4 alkyl, where the C_1-C_4 alkyl is unsubstituted or substituted;

R_4 is H, F, Cl, C_1-C_4 alkyl, C_3-C_7 cycloalkyl, CN, CF_3, OCF_3, CFH_2 or CF_2H, where the C_1-C_4 alkyl and C_3-C_7 cycloalkyl is unsubstituted or substituted;

R_6 is H, F, Cl, C_1-C_4 alkyl, C_3-C_7 cycloalkyl, heteroaryl, CF_3, CFH_2 or CF_2H, where each of the C_1-C_4 alkyl, C_3-C_7 cycloalkyl and heteroaryl is unsubstituted or substituted;

R_7 is H, F, Cl, C_1-C_4 alkyl, C_3-C_7 cycloalkyl, CN, CF_3, OCF_3, CFH_2 or CF_2H, where the C_1-C_4 alkyl and C_3-C_7 cycloalkyl is unsubstituted or substituted;

each R_8 is independently H, F, Cl, C_1-C_4 alkyl, C_3-C_7 cycloalkyl, CN, CF_3, OCF_3, CFH_2 or CF_2H, where the C_1-C_4 alkyl and C_3-C_7 cycloalkyl is unsubstituted or substituted;

R_5 is

halogen;

-O-L_1-L_2-L_3-L_4-L_5-L_6-L_7-R_9;

-S-L_1-L_2-L_3-L_4-L_5-L_6-L_7-R_9;

-S(O)-L_1-L_2-L_3-L_5-L_6-L_7-R_9;

-$S(O)_2$-L_1-L_2-L_3-L_5-L_6-L_7-R_9;

-(NR_{10})-L_1-L_2-L_3-L_4-L_5-L_6-L_7-R_9; or

-L_8-L_9-L_{10}-L_{11}-L_{12}-R_{14},

wherein:

each of L_1, L_2, L_3, L_6 and L_7 is independently (CHR_{11}), (CHR_{11}-O), (CHR_{11}-S), (C_3-C_7 cycloalkyl), $(CH_2)_{1\text{-}4}$ or a bond;

L_4 is C=O, C=S or a bond;

L_5 is NR_{10}, S, O or a bond;

R_9 is H, C(=O)R_{12}, C(=O)$NR_{12}R_{13}$, $NR_{12}R_{13}$, C(=O)OR_{12}, C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl, where each of the C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl is unsubstituted or substituted; or alternatively when NR_{10} is present, R_9 and R_{10} together with the attached nitrogen atom may form a substituted or unsubstituted ring. In an exemplary embodiment, the ring is 4- to 7- membered substituted or unsubstituted non-aromatic heterocyclic ring containing (in addition to the nitrogen atom) 0, 1 or 2 heteroatoms which may be N, O, S or Si, with the proviso that if the ring size is 4 or 5, the number of additional heteroatoms will be 0 or 1 and if the ring size is from 6 to 7, the number of additional heteroatoms will be 0, 1 or 2, where if the ring is substituted, the substituents include, but are not limited to, one or more of CH_3, F, Cl, CF_3, CF_2H, CH_2F, OCH_3, cyclopropyl,

CH_2CF_3, an oxetane ring, or COR_a where R_a is C_1-C_4 alkyl, O-C_1-C_4 alkyl, or NR_bR_c where R_b and R_c are independently H or C_1-C_4 alkyl;

each of R_{10} and R_{11} is independently H or C_1-C_4 alkyl (such as CH_3, CH_2CH_3 or $CH(CH_3)_2$), where the C_1-C_4 alkyl is unsubstituted or substituted;

each of R_{12} and R_{13} is independently H, C_1-C_6 alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl, where each of the C_1-C_6 alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl is unsubstituted or substituted; or alternatively, R_{12} and R_{13} together with the attached nitrogen atom may form a substituted or unsubstituted ring. In an exemplary embodiment, the ring is 4- to 7- membered substituted or unsubstituted non-aromatic heterocyclic ring containing (in addition to the nitrogen atom) 0, 1 or 2 heteroatoms which may be N, O, S or Si, with the proviso that if the ring size is 4 or 5, the number of additional heteroatoms will be 0 or 1 and if the ring size is from 6 to 7, the number of additional heteroatoms will be 0, 1 or 2, where if the ring is substituted, the substituents include, but are not limited to, one or more of CH_3, F, Cl, CF_3, CF_2H, CH_2F, OCH_3, cyclopropyl, CH_2CF_3, an oxetane ring, or COR_a where R_a is C_1-C_4 alkyl, O-C_1-C_4 alkyl, or NR_bR_c where R_b and R_c are independently H or C_1-C_4 alkyl;

L_8 is (CHR_{15}), (CHR_{15}-O), (CHR_{15}-S), (CHR_{15}-NR_{16}), C=O, C=S or a bond;

L_9 is C_3-C_7 cycloalkyl that is optionally part of a bridged, fused or spiro ring system, $C(R_{15})$=$C(R_{15})$, C≡C or a bond;

L_{10} is independently (CHR_{15}), O, S, (NCR_{15}), N(C=O) or a bond;

L_{11} is (CHR_{15}), C=O, C=S or a bond;

L_{12} is H, (C_3-C_7 cycloalkyl), heterocyclyl, aryl, heteroaryl or a bond, where each of the C_3-C_7 cycloalkyl, heterocyclyl, aryl or heteroaryl is unsubstituted or substituted, and the C_3-C_7 cycloalkyl and/or heterocyclyl is optionally part of a bridged, fused or spiro ring system;

R_{14} is H, $CR_{15}R_{16}R_{17}$, OR_{17}, SR_{17}, $NR_{16}R_{17}$, C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl, where each of the C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl is unsubstituted or substituted,

each of R_{15} and R_{16} is independently H or C_1-C_3 alkyl; and

each R_{17} is independently H, C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl, where each of the C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, cycloalkyl, heterocyclyl, aryl or

heteroaryl is unsubstituted or substituted; or alternatively, R_{16} and R_{17} together with the attached nitrogen atom may form a substituted or unsubstituted ring. In an exemplary embodiment, the ring is 4- to 7- membered substituted or unsubstituted non-aromatic heterocyclic ring containing (in addition to the nitrogen atom) 0, 1 or 2 heteroatoms which may be N, O or S, with the proviso that if the ring size is 4 or 5, the number of additional heteroatoms will be 0 or 1 and if the ring size is from 6 to 7, the number of additional heteroatoms will be 0, 1 or 2, where if the ring is substituted, the substituents include, but are not limited to, one or more of Me, F, Cl, CF_3, CF_2H, CH_2F, OCH_3, cyclopropyl, CH_2CF_3, an oxetane ring, or COR_a where R_a is C_1-C_4 alkyl, O-C_1-C_4 alkyl, or NR_bR_c where R_b and R_c are independently H or C_1-C_4 alkyl;

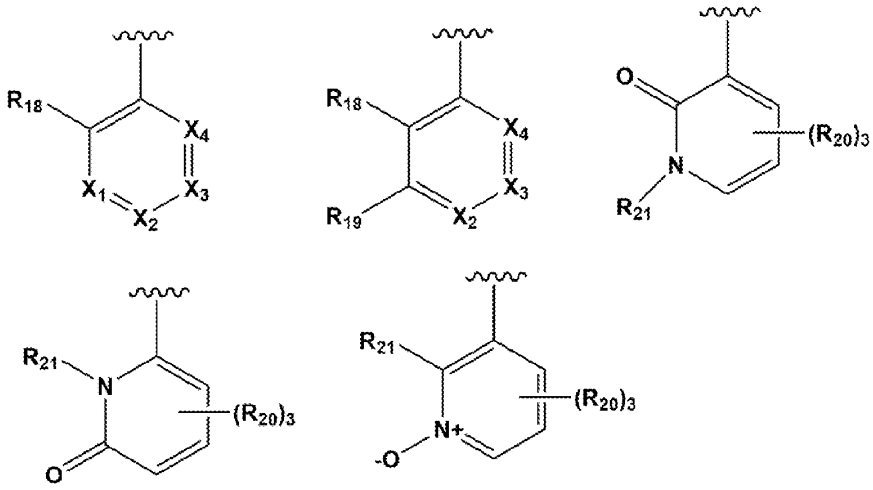
with the proviso that when R_5 is -L_8-L_9-L_{10}-L_{11}-L_{12}-R_{14}, at least one of L_8, L_9, L_{10}, L_{11}, L_{12} and R_{14} is a carbon-containing moiety and R_5 is directly attached to the core structure by a carbon atom;

or R_5 is

a non-aromatic N-linked heterocyclic ring 

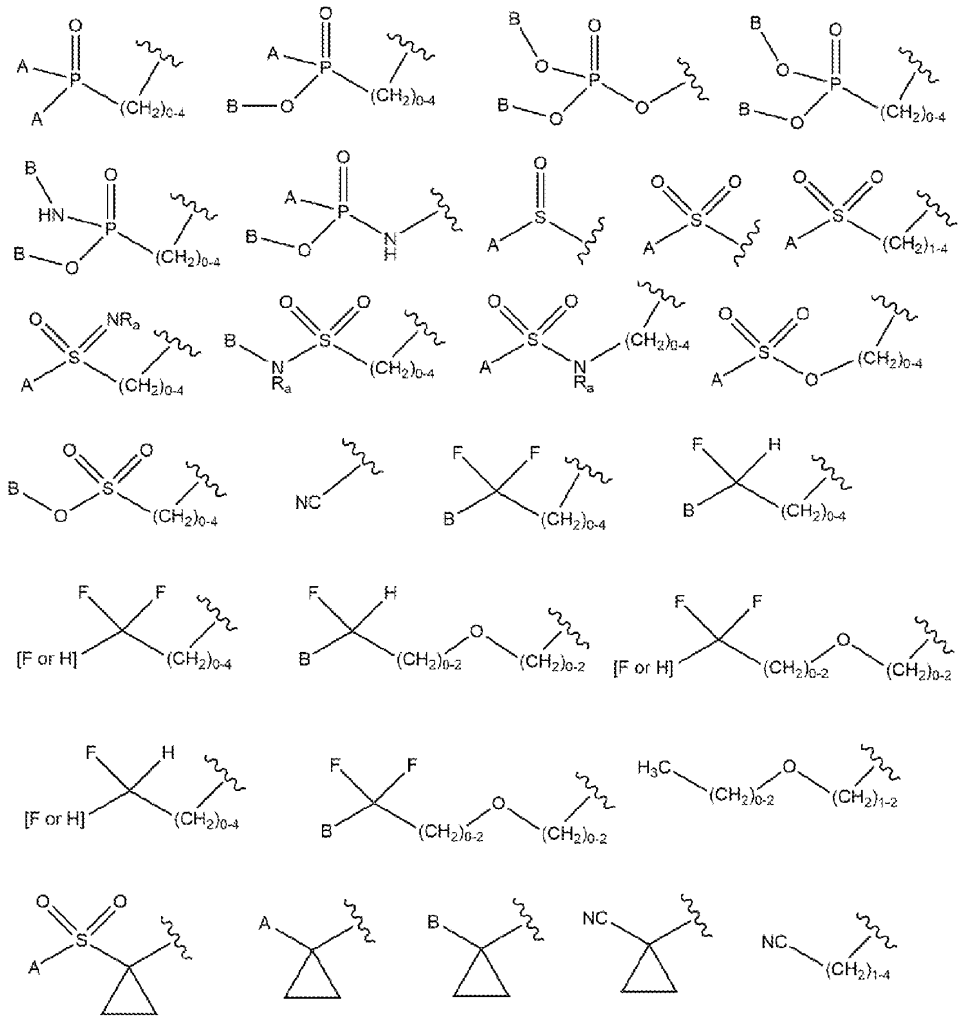
, where the heterocyclic ring is substituted or unsubstituted, optionally contains one or more additional ring atoms selected from N, O, Si and S, and is optionally part of a bridged, fused or spiro ring system. In particular embodiments, the N-linked heterocyclyl ring is a substituted or unsubstituted azetidine, pyrrolidine, imidazoline, imidazolidine, piperazine, morpholine, thiomorpholine, piperidine, indoline, tetrahydroquinoline, decahydroquinoline, 2-oxa-7-azaspiro[3.5]nonane, 1, 4-dioxa-7-azaspiro[4.4]nonane or 2-azaadamantane.

[0009] In an exemplary embodiment, R_1 is selected from the following:



wherein:

R_{18} is a substituted or unsubstituted 5- or 6-membered nitrogen-containing heteroaryl ring or R_{18} is selected from the following:



,

where each A is independently C_1-C_4 alkyl, fluoroalkyl, C_3-C_7 cycloalkyl, $N(R_a)_2$, $(CH_2)_{0-5}$-NR_a-C(O)-C_3-C_7 cycloalkyl, $(CH_2)_{1-5}$-O-C_1-C_3 cycloalkyl, $(CH_2)_{1-5}$-O-$(CH_2)_{1-5}$-C_1-C_3 fluoroalkyl, $(CH_2)_{0-5}$-aryl, $(CH_2)_{0-5}$-heteroaryl, $(CH_2)_{0-5}$-heterocyclyl, $(CH_2)_{0-5}$-NR_a-$(CH_2)_{0-5}$-heteroaryl or $(CH_2)_{0-5}$-NR_a-$(CH_2)_{1-5}$-N-heterocyclyl, where the alkyl, fluoroalkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl are substituted or unsubstituted, or alternatively, A and A together with the attached -P(=O)- moiety may form a substituted or unsubstituted heterocyclyl ring;

each B is independently H, C_1-C_4 alkyl, C_3-C_7 cycloalkyl, $(CH_2)_{1-5}$-NR_a-C(O)-C_3-C_7 cycloalkyl, $(CH_2)_{0-5}$-aryl, $(CH_2)_{0-5}$-heteroaryl, $(CH_2)_{0-5}$-heterocyclyl, $(CH_2)_{1-5}$-NR_a-$(CH_2)_{0-5}$-heteroaryl or $(CH_2)_{1-5}$-NR_a-$(CH_2)_{2-5}$-N-heterocyclyl, O-C_{1-5}-alkyl, O-C_{0-5}-cycloalkyl, O-C_{0-5}-heterocyclyl, where the alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl are substituted or unsubstituted, or alternatively, B and B together with the attached -[O or NH]-P(=O)-O- moiety may form a substituted or unsubstituted heterocyclyl ring, or alternatively, A and B together with the attached -P(=O)-O- moiety may form a substituted or unsubstituted heterocyclyl ring;

each R_a is independently H, C_1-C_4 alkyl, C(O)C_1-C_3 alkyl or C(O)-$(CH_2)_{1-5}$-O-C_1-C_3 alkyl, where the alkyl is substituted or unsubstituted, or alternatively, R_a and A together with the attached -$S(=O)_2$- moiety may form a substituted or unsubstituted heterocyclic ring, or

R_{18} and R_{19} together form a substituted or unsubstituted heterocyclic ring (such as a 5- or 6-membered heterocyclic ring) containing one or more sulfur atoms (which includes the sulfoxide (SO) and sulfone (SO_2) forms), nitrogen atoms (which includes the oxidized forms) and oxygen atoms;

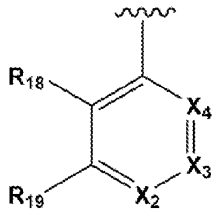
R_{19} is H, C_1-C_4 alkyl, C_3-C_7 cycloalkyl, halogen, CN, CF_3, OCF_3, CFH_2 or CF_2H, where the alkyl and cycloalkyl is substituted or unsubstituted, or R_{19} and R_{18} together form a heterocyclic ring as described herein;

each R_{20} is independently H, C_1-C_4 alkyl, C_3-C_7 cycloalkyl, halogen, CN, CF_3, OCF_3, CFH_2 or CF_2H, where the alkyl and cycloalkyl is substituted or unsubstituted;

R_{21} is H, C_1-C_4 alkyl, C_3-C_7 cycloalkyl, CF_3, CFH_2 or CF_2H, where the alkyl and cycloalkyl is substituted or unsubstituted; and

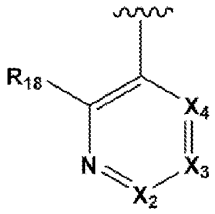
each X_1, X_2, X_3 and X_4 is independently CH, N or substituted C.

[00010] In an exemplary embodiment, R_1 is



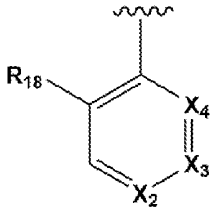
wherein R_{18}, R_{19}, X_2, X_3 and X_4 are defined as described herein.

[00011] In an exemplary embodiment, R_1 is



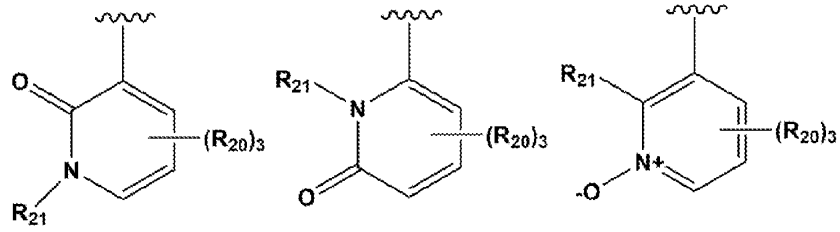
wherein R_{18}, X_2, X_3 and X_4 are defined as described herein.

[00012] In an exemplary embodiment, R_1 is



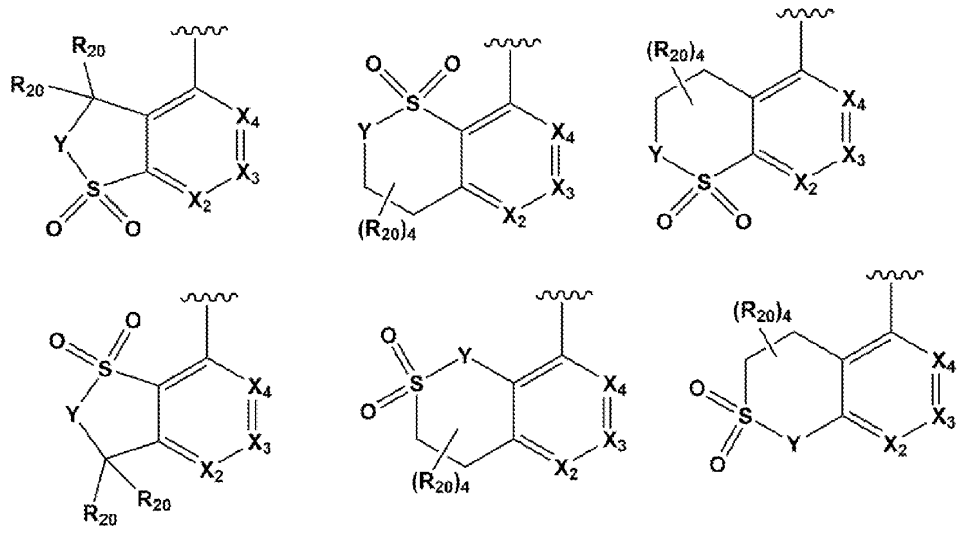
wherein R_{18}, X_2, X_3 and X_4 are defined as described herein.

[00013] In an exemplary embodiment, R_1 is selected from the following:



wherein R_{20} and R_{21} are defined as described herein.

[00014] In an exemplary embodiment, R_1 is selected from the following:



wherein:

X_2, X_3 and X_4 are defined as described herein;

Y is O, NR_{21} or $C(R_4)_2$; and

each R_4, R_{20} and R_{21} is independently defined as described herein.

[00015] In an exemplary embodiment, R_5 is $-(NR_{10})-L_1-L_2-L_3-L_4-L_5-L_6-L_7-R_9$, where L_1 to L_7, R_9 and R_{10} are as defined.

[00016] In an exemplary embodiment, R_5 is $-O-L_1-L_2-L_3-L_4-L_5-L_6-L_7-R_9$, where L_1 to L_7 and R_9 are as defined.

[00017] In an exemplary embodiment, R_5 is $-S-L_1-L_2-L_3-L_4-L_5-L_6-L_7-R_9$; $-S(O)-L_1-L_2-L_3-L_5-L_6-L_7-R_9$; or $-S(O)_2-L_1-L_2-L_3-L_5-L_6-L_7-R_9$, where L_1 to L_7 and R_9 are as defined.

[00018] In an exemplary embodiment, R_9 is a 6-membered aryl ring; or is a 5- to 6- membered heteroaryl ring containing from 1-3 nitrogen atoms; or is a non-aromatic 3- to 7- membered carbocycle; or is a non-aromatic 4- to 7- membered heterocycle containing from 1 to 3 heteroatoms selected from N, O, S and Si with the proviso that if the ring size is 4 or 5 then the number of heteroatoms will be 1 or 2 and if the ring size is 6 or 7 the number heteroatoms will be 1, 2 or 3; or is a C_1-C_6 alkyl group, where the aryl ring, the heteroaryl ring, the carbocycle, the heterocycle and the C_1-C_6 alkyl group are unsubstituted or substituted with one or more of CH_3,

F, Cl, CF_3, CF_2H, CH_2F, OCH_3, $-CH_2CF_3$, cyclopropyl, -CN, $N(CH_3)_2$, an oxetane ring, a phenyl or phenoxy group optionally substituted with from 1 to 3 halogens (F, Cl or Br) or CH_3 groups, or COR_a where R_a is C_1-C_4alkyl, O-C_1-C_4 alkyl or NR_bR_c, where R_b and R_c are independently H or C_1-C_4 alkyl.

[00019] In an exemplary embodiment of R_5, each of L_8, L_{10} and L_{11} is a bond and L_9 is not a bond.

[00020] In an exemplary embodiment of R_5, each of L_8, L_{10} and L_{11} is a bond and L_9 is cycloalkyl that is optionally part of a bridged, fused or spiro ring system.

[00021] In an exemplary embodiment of R_5, each of L_8, L_{10} and L_{11} is a bond and L_9 is cycloalkyl that is part of a bridged ring system.

[00022] In an exemplary embodiment of R_5, each of L_8, L_{10} and L_{11} is a bond and L_9 is cycloalkyl that is part of a fused ring system.

[00023] In an exemplary embodiment of R_5, each of L_8, L_{10} and L_{11} is a bond and L_9 is cycloalkyl that is part of a spiro ring system.

[00024] In an exemplary embodiment of R_5, each of L_8, L_{10} and L_{11} is a bond and L_9 is $C(R_{15})=C(R_{15})$.

[00025] In an exemplary embodiment of R_5, each of L_8, L_{10} and L_{11} is a bond and L_9 is C≡C.

[00026] In an exemplary embodiment of R_5, each of L_8, L_9, L_{10} and L_{11} is a bond and L_{12} is cycloalkyl, heterocyclyl, aryl or heteroaryl, where each of the cycloalkyl, heterocyclyl, aryl or heteroaryl is unsubstituted or substituted.

[00027] In an exemplary embodiment of R_5, each of L_8, L_9, L_{10} and L_{11} is a bond and L_{12} is cycloalkyl, heterocyclyl, aryl or heteroaryl, where each of the cycloalkyl, heterocyclyl, aryl or heteroaryl is unsubstituted or substituted, and R_{14} is H.

[00028] In an exemplary embodiment of R_5, each of L_8, L_9, L_{10} and L_{11} is a bond and L_{12} is cycloalkyl, heterocyclyl, aryl or heteroaryl, where each of the cycloalkyl, heterocyclyl, aryl or heteroaryl is unsubstituted or substituted, and R_{14} is cycloalkyl, heterocyclyl, aryl or heteroaryl, where each of the C_1-C_6 alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl is unsubstituted or substituted.

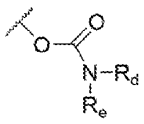
[00029] In an exemplary embodiment of R_5, each of L_8, L_9, L_{10} and L_{11} is a bond and L_{12} is cycloalkyl, heterocyclyl, aryl or heteroaryl, where each of the cycloalkyl, heterocyclyl, aryl or heteroaryl is unsubstituted or substituted, and R_{14} is $-CR_{14}R_{15}R_{16}$.

[00030] In an exemplary embodiment of R_5, each of L_8, L_9, L_{10} and L_{11} is a bond and L_{12} is cycloalkyl, heterocyclyl, aryl or heteroaryl, where each of the cycloalkyl, heterocyclyl, aryl or heteroaryl is unsubstituted or substituted, and R_{14} is $-OR_{16}$ or $-OR_{17}$.

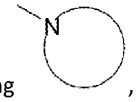
[00031] In an exemplary embodiment of R_5, each of L_8, L_9, L_{10} and L_{11} is a bond and L_{12} is cycloalkyl, heterocyclyl, aryl or heteroaryl, where each of the cycloalkyl, heterocyclyl, aryl or heteroaryl is unsubstituted or substituted, and R_{14} is $-SR_{17}$.

[00032] In an exemplary embodiment of R_5, each of L_8, L_9, L_{10} and L_{11} is a bond and L_{12} is cycloalkyl, heterocyclyl, aryl or heteroaryl, where each of the cycloalkyl, heterocyclyl, aryl or heteroaryl is unsubstituted or substituted, and R_{14} is $-NR_{16}R_{17}$.

[00033] In an exemplary embodiment, R_5 is



[00034] where R_d is H or CH_3 and R_e is CH_3, C_3-C_6 cycloalkyl, a six-membered aromatic or heteroaromatic ring containing from 0, 1 or 2 nitrogen atoms which may be optionally substituted with CH_3, F, Cl, CF_3, CF_2H, CH_2F, OCH_3, cyclopropyl, CN or $N(CH_3)_2$, or R_d and R_e together with the attached nitrogen atom may form a 4- to 7- membered non-aromatic heterocycle containing from 1 to 2 heteroatoms which may be either N or O, with the proviso that if the ring size is 4 or 5 the number of heteroatoms will be 1 and if the ring size is from 6 to 7, the number of heteroatoms will be 1 or 2, where the ring is unsubstituted or is substituted with one or more that includes, but is not limited to, CH_3, F, Cl, CF_3, CF_2H, CH_2F, OCH_3, cyclopropyl, CH_2CF_3, an oxetane ring, or COR_a where R_a is C_1-C_4 alkyl, O-C_1-C_4 alkyl, or NR_bR_c where R_b and R_c are independently H or C_1-C_4 alkyl.

[00035] In an exemplary embodiment, R_5 is a N-linked non-aromatic heterocyclyl ring , where the heterocyclyl ring is substituted or unsubstituted, optionally contains one or more additional atoms selected from N, O, Si and S, and is optionally part of a bridged, fused or spiro ring system. In particular embodiments, the N-linked heterocyclyl ring is azetidine, pyrrolidine, imidazoline, imidazolidine, piperazine, morpholine, thiomorpholine, piperidine, indoline,

tetrahydroquinoline, decahydroquinoline, 2-oxa-7-azaspiro[3.5]nonane, 1,3,8-triazaspiro[4.5]-decan-4-one, 1, 4-dioxa-7-azaspiro[4.4]nonane.

[00036] In an exemplary embodiment, the N-linked non-aromatic heterocyclyl ring is substituted or unsubstituted, optionally contains one or more additional atoms selected from N, O, Si and S, and is not part of a bridged, fused or spiro ring system.

[00037] In an exemplary embodiment, the N-linked non-aromatic heterocyclyl ring is substituted or unsubstituted, optionally contains one or more additional atoms selected from N, O, Si and S, and is part of a bridged, fused or spiro ring system.

[00038] In an exemplary embodiment, the N-linked non-aromatic heterocyclyl ring is substituted or unsubstituted, does not contain additional atoms selected from N, O, Si and S, and is not part of a bridged, fused or spiro ring system.

[00039] In an exemplary embodiment, the N-linked non-aromatic heterocyclyl ring is substituted or unsubstituted, does not contain additional atoms selected from N, O, Si and S, and is part of a bridged, fused or spiro ring system.

[00040] In an exemplary embodiment, the N-linked non-aromatic heterocyclyl ring is substituted or unsubstituted, contains at least one sulfur ring atom, and is not part of a bridged, fused or spiro ring system.

[00041] In an exemplary embodiment, the N-linked non-aromatic heterocyclyl ring is substituted or unsubstituted, contains at least one sulfur ring atom, and is part of a bridged, fused or spiro ring system.

[00042] In an exemplary embodiment, the N-linked non-aromatic heterocyclyl ring is substituted or unsubstituted, contains at least one oxygen ring atom, and is not part of a bridged, fused or spiro ring system.

[00043] In an exemplary embodiment, the N-linked non-aromatic heterocyclyl ring is substituted or unsubstituted, contains at least one oxygen ring atom, and is part of a bridged, fused or spiro ring system.

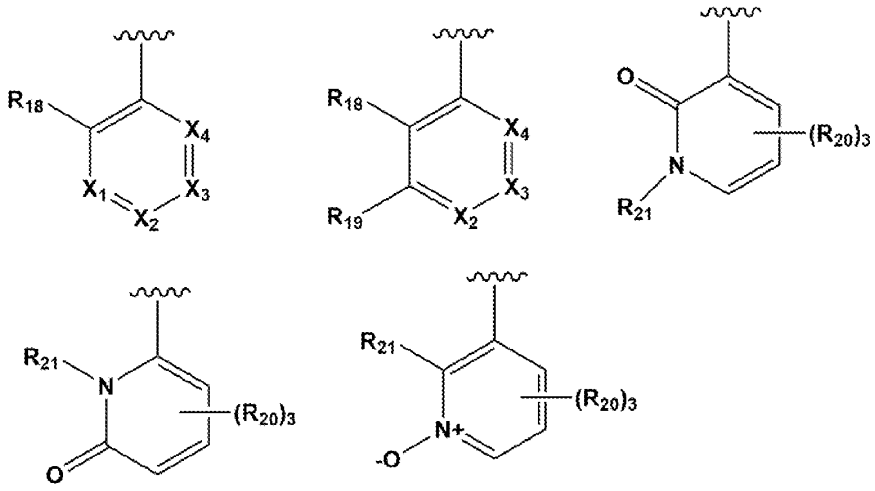
[00044] In an exemplary embodiment, the N-linked non-aromatic heterocyclyl ring is substituted or unsubstituted, contains at least one additional nitrogen ring atom, and is not part of a bridged, fused or spiro ring system.

[00045] In an exemplary embodiment, the N-linked non-aromatic heterocyclyl ring is substituted or unsubstituted, contains at least one additional nitrogen ring atom, and is part of a bridged, fused or spiro ring system.

[00046] In an exemplary embodiment of Formula (1), the C_1-C_4 alkyl is preferably methyl.

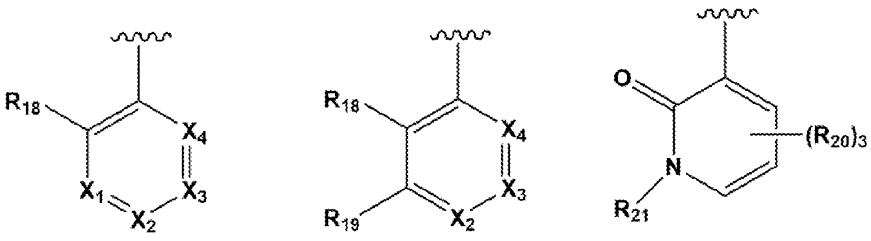
[00047] In an exemplary embodiment of Formula (1), halogen is preferably F.

[00048] In an exemplary embodiment of the compound of Formula (1), R_1 is selected from



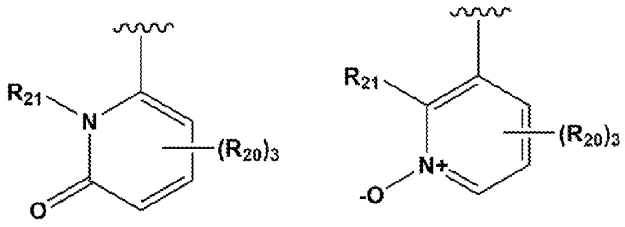
where R_{18}, R_{19}, R_{20}, R_{21}, X_1, X_2, X_3 and X_4 are defined as described herein.

[00049] In an exemplary embodiment of the compound of Formula (1), R_1 is selected from



where R_{18}, R_{19}, R_{20}, R_{21}, X_1, X_2, X_3 and X_4 are as defined herein.

[00050] In an exemplary embodiment of the compound of Formula (1), R_1 is selected from



where R_{20} and R_{21} are defined as described herein.

[00051] In an exemplary embodiment of the compound of Formula (1), R_2 is CH_3.

[00052] In an exemplary embodiment of the compound of Formula (1), R_2 is CH_2F.

[00053] In an exemplary embodiment of the compound of Formula (1), R_3 is H.

[00054] In an exemplary embodiment of the compound of Formula (1), R_4 is H or F.

[00055] In an exemplary embodiment of the compound of Formula (1), R_6 is CH_3 or F.

[00056] In an exemplary embodiment of the compound of Formula (1), R_7 is CH_3 or F.

[00057] In an exemplary embodiment of R_1, X_1, X_2, X_3 and X_4 are independently CH or CF.

[00058] In an exemplary embodiment of R_1, X_2 is N, and X_1, X_3 and X_4 are independently CH or CF.

[00059] In an exemplary embodiment of R_1, X_1 is N, and X_2, X_3 and X_4 are independently CH or CF.

[00060] In an exemplary embodiment of R_1, X_4 is N and X_1, X_2 and X_3 are independently CH or CF.

[00061] In an exemplary embodiment of R_1, X_3 is N and X_1, X_2 and X_4 are independently CH or CF.

[00062] In an exemplary embodiment of R_1, X_1 and X_3 are N, and X_2 and X_4 are independently CH or CF.

[00063] In an exemplary embodiment of R_1, X_1 and X_2 are N, and X_3 and X_4 are independently CH or CF.

[00064] In an exemplary embodiment of R_1, X_2 and X_3 are N, and X_1 and X_4 are independently CH or CF.

[00065] In an exemplary embodiment of R_1, X_2 and X_4 are N, and X_2 and X_3 are independently CH or CF.

[00066] In an exemplary embodiment of R_1, X_1, X_2 and X_3 are N, and X_4 is CH or CF.

[00067] In an exemplary embodiment of R_1, X_1, X_2 and X_4 are N, and X_3 is CH or CF.

[00068] In an exemplary embodiment of R_1, X_2, X_3 and X_4 are N, and X_1 is CH or CF.

[00069] In an exemplary embodiment of R_1, X_1, X_3 and X_4 are N, and X_2 is CH or CF.

[00070] In an exemplary embodiment of R_1, X_1, X_2, X_3 and X_4 are N.

[00071] In an exemplary embodiment of the compound of Formula (1), R_5 is $-O-L_1-L_2-L_3-L_4-L_5-L_6-L_7-R_9$.

[00072] In an exemplary embodiment of the compound of Formula (1), R_5 is $-S-L_1-L_2-L_3-L_4-L_5-L_6-L_7-R_9$.

[00073] In an exemplary embodiment of the compound of Formula (1), R_5 is $-S(O)-L_1-L_2-L_3-L_5-L_6-L_7-R_9$.

[00074] In an exemplary embodiment of the compound of Formula (1), R_5 is $-S(O)_2-L_1-L_2-L_3-L_5-L_6-L_7-R_9$.

[00075] In an exemplary embodiment of the compound of Formula (1), R_5 is $-(NR_{10})-L_1-L_2-L_3-L_4-L_5-L_6-L_7-R_9$.

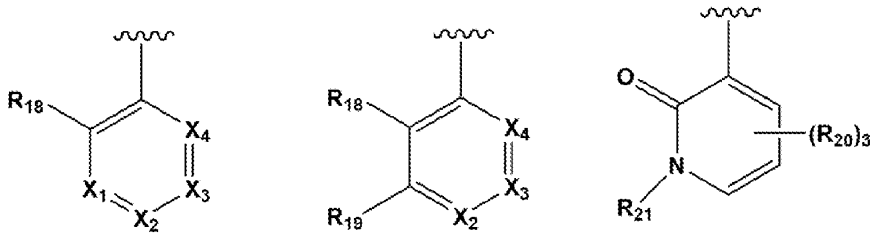
[00076] In an exemplary embodiment of the compound of Formula (1), R_5 is $-L_8-L_9-L_{10}-L_{11}-L_{12}-R_{14}$.

[00077] In an exemplary embodiment of the compound of Formula (1), R_6 is CH_3.

[00078] In an exemplary embodiment of the compound of Formula (1), R_7 is CH_3.

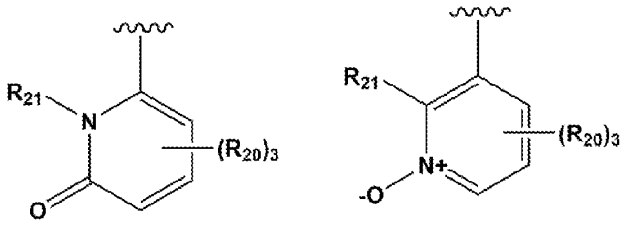
[00079] In an exemplary embodiment of the compound of Formula (1), each R_8 is independently H or F.

[00080] In an exemplary embodiment of the compound of Formula (1), R_2 is CH_3 or CH_2F, R_3 is H, and R_1 is selected from



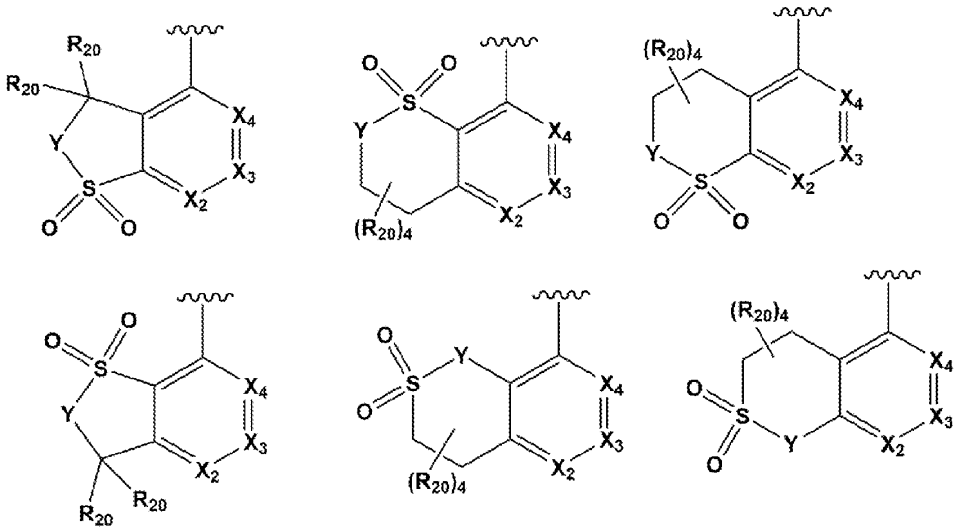
where R_{18}, R_{19}, R_{20}, R_{21}, X_1, X_2, X_3 and X_4 are defined as described herein.

[00081] In an exemplary embodiment of the compound of Formula (1), R_2 is CH_3 or CH_2F, R_3 is H, and R_1 is selected from



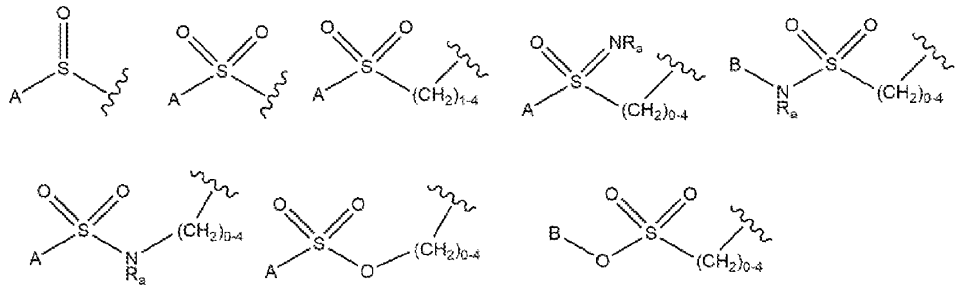
where R_{20} and R_{21} are defined as described herein.

[00082] In an exemplary embodiment of the compound of Formula (1), R_2 is CH_3 or CH_2F, R_3 is H, R_1 is selected from



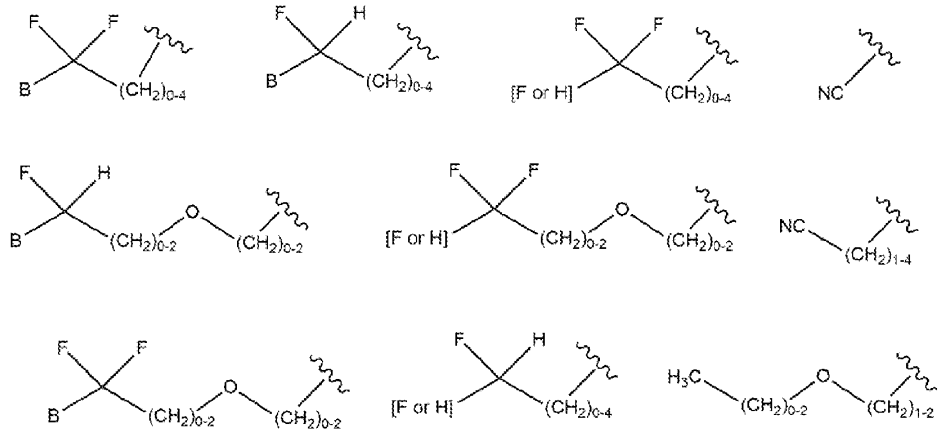
wherein R_{20}, Y, X_2, X_3 and X_4 are defined as described herein, and R_5 is a N-linked heterocyclyl ring selected from azetidine, pyrrolidine, imidazoline, imidazolidine, piperazine, morpholine, thiomorpholine and piperidine, where each of these rings is unsubstituted or substituted.

[00083] In an exemplary embodiment of the compound of Formula (1), R_2 is CH_3 or CH_2F, R_3 is H, R_{18} is selected from



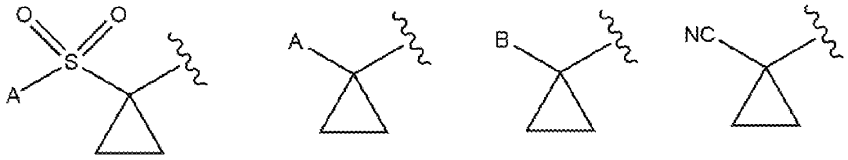
where A, B and R_a are defined as described herein, and R_5 is a N-linked heterocyclyl ring selected from azetidine, pyrrolidine, imidazoline, imidazolidine, piperazine, morpholine, thiomorpholine and piperidine, where each of these rings is unsubstituted or substituted.

[00084] In an exemplary embodiment of the compound of Formula (1), R_2 is CH_3 or CH_2F, R_3 is H, R_{18} is selected from



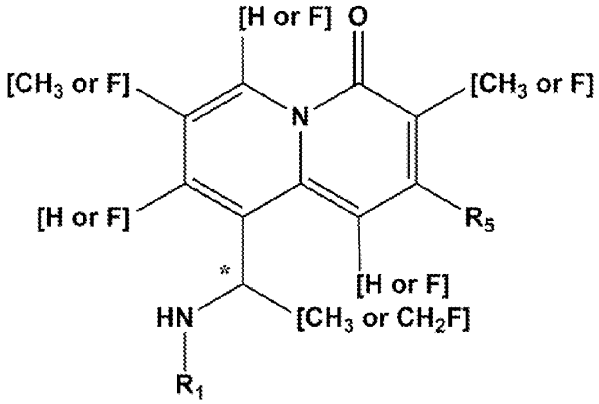
where B is defined as described herein, and R_5 is a N-linked heterocyclyl ring selected from azetidine, pyrrolidine, imidazoline, imidazolidine, piperazine, morpholine, thiomorpholine and piperidine, where each of these rings is unsubstituted or substituted.

[00085] In an exemplary embodiment of the compound of Formula (1), R_2 is CH_3 or CH_2F, R_3 is H, R_{18} is selected from



where A and B are defined as described herein, and R_5 is a N-linked heterocyclyl ring selected from azetidine, pyrrolidine, imidazoline, imidazolidine, piperazine, morpholine, thiomorpholine and piperidine, where each of these rings is unsubstituted or substituted.

[00086] In an exemplary embodiment, the compound of Formula (1) is a compound of Formula (2)



(2)

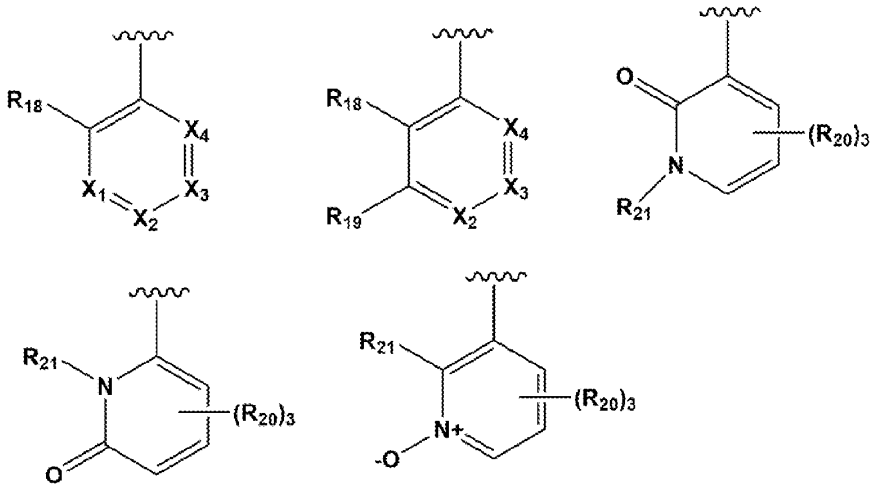
or a solvate, enantiomer, diastereomer, tautomer, polymorph or isotope-labeled compound, or a pharmaceutically acceptable salt thereof,

wherein:

R_1 and R_5 are defined as described herein for the compound of Formula (1), and

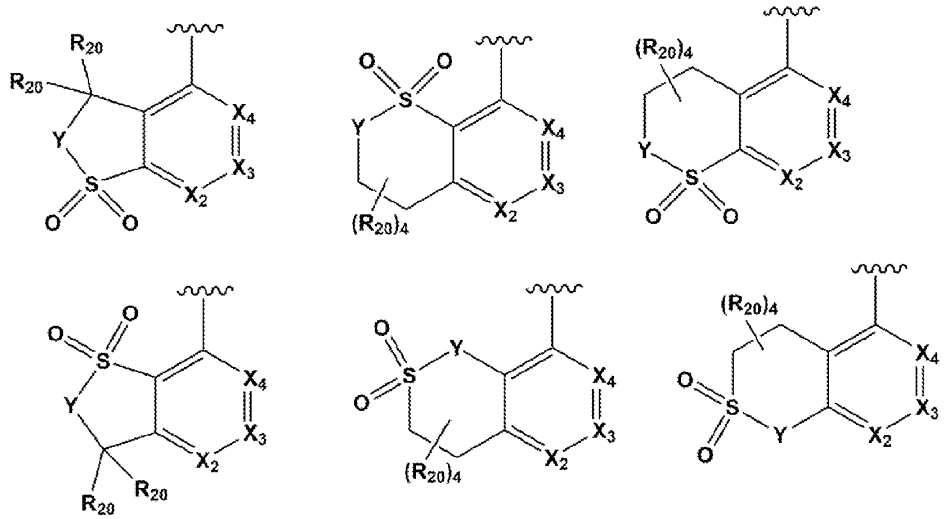
the carbon marked with * is a chiral center and exists as a (R)- and (S)-racemic mixture or as either the (R)- or (S)- enantiomer.

[00087] In an exemplary embodiment of the compound of Formula (2), R_1 is selected from



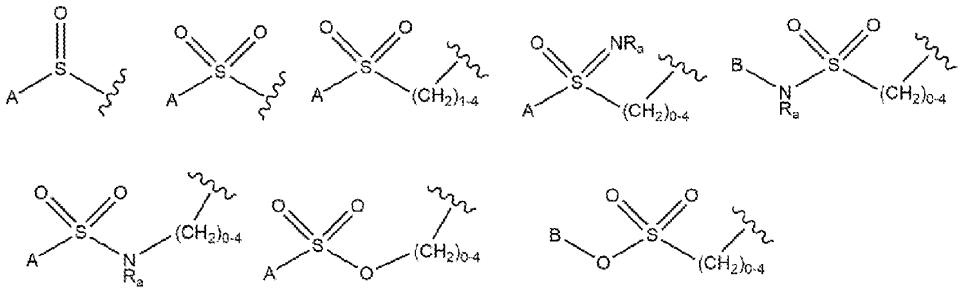
where R_{18}, R_{19}, R_{20}, R_{21}, X_1, X_2, X_3 and X_4 are defined as described herein.

[00088] In an exemplary embodiment of the compound of Formula (2), R_1 is selected from



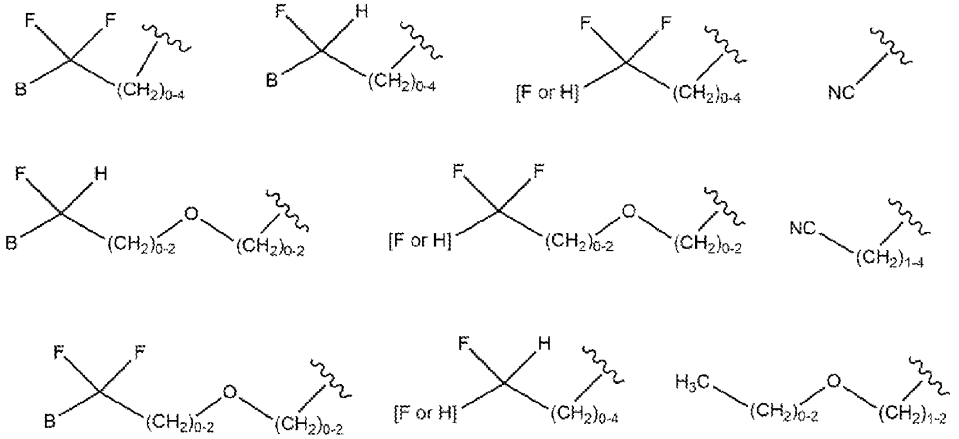
where R_{20}, Y, X_2, X_3 and X_4 are defined as described herein.

[00089] In an exemplary embodiment of the compound of Formula (2), R_{18} is selected from



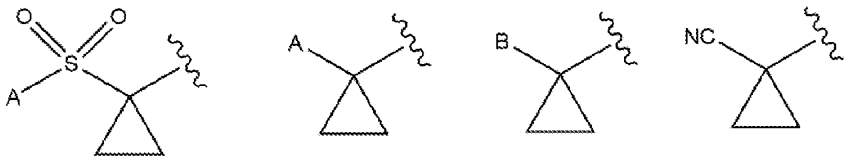
where A, B and R_a are defined as described herein.

[00090] In an exemplary embodiment of the compound of Formula (2), R_{18} is selected from



where B is as defined herein.

[00091] In an exemplary embodiment of the compound of Formula (2), R_{18} is selected from



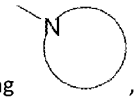
where A and B are defined as described herein.

[00092] In an exemplary embodiment of the compound of Formula (2), R_5 is $-O-L_1-L_2-L_3-L_4-L_5-L_6-L_7-R_9$ where $-O-L_1-L_2-L_3-L_4-L_5-L_6-L_7-R_9$ is defined as in the compound of Formula (1).

[00093] In an exemplary embodiment of the compound of Formula (2), R_5 is -S-L_1-L_2-L_3-L_4-L_5-L_6-L_7-R_9 where -S-L_1-L_2-L_3-L_4-L_5-L_6-L_7-R_9 is defined as in the compound of Formula (1).

[00094] In an exemplary embodiment of the compound of Formula (2), R_5 is -(NR_{10})-L_1-L_2-L_3-L_4-L_5-L_6-L_7-R_9 where -(NR_{10})-L_1-L_2-L_3-L_4-L_5-L_6-L_7-R_9 is defined as in the compound of Formula (1).

[00095] In an exemplary embodiment of the compound of Formula (2), R_5 is -L_8-L_9-L_{10}-L_{11}-L_{12}-R_{14} where -L_8-L_9-L_{10}-L_{11}-L_{12}-R_{14} is defined as in the compound of Formula (1).

[00096] In an exemplary embodiment of the compound of Formula (2), R_5 is a N-linked non-aromatic heterocyclyl ring , where  is defined as in the compound of Formula (1).

[00097] In an exemplary embodiment of R_1 of Formula (2), X_1, X_2, X_3 and X_4 are independently CH or CF.

[00098] In an exemplary embodiment of R_1 of Formula (2), X_2 is N, and X_1, X_3 and X_4 are independently CH or CF.

[00099] In an exemplary embodiment of R_1 of Formula (2), X_1 is N, and X_2, X_3 and X_4 are independently CH or CF.

[000100] In an exemplary embodiment of R_1 of Formula (2), X_4 is N and X_1, X_2 and X_3 are independently CH or CF.

[000101] In an exemplary embodiment of R_1 of Formula (2), X_3 is N and X_1, X_2 and X_4 are independently CH or CF.

[000102] In an exemplary embodiment of R_1 of Formula (2), X_1 and X_3 are N, and X_2 and X_4 are independently CH or CF.

[000103] In an exemplary embodiment of R_1 of Formula (2), X_1 and X_2 are N, and X_3 and X_4 are independently CH or CF.

[000104] In an exemplary embodiment of R_1 of Formula (2), X_2 and X_3 are N, and X_1 and X_4 are independently CH or CF.

[000105] In an exemplary embodiment of R_1 of Formula (2), X_2 and X_4 are N, and X_2 and X_3 are independently CH or CF.

[000106] In an exemplary embodiment of R_1 of Formula (2), X_1, X_2 and X_3 are N, and X_4 is CH or CF.

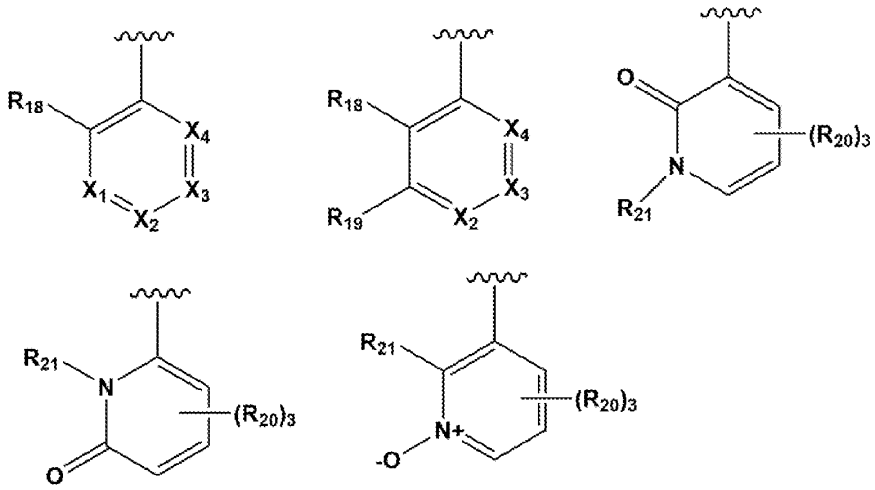
[000107] In an exemplary embodiment of R_1 of Formula (2), X_1, X_2 and X_4 are N, and X_3 is CH or CF.

[000108] In an exemplary embodiment of R_1 of Formula (2), X_2, X_3 and X_4 are N, and X_1 is CH or CF.

[000109] In an exemplary embodiment of R_1 of Formula (2), X_1, X_3 and X_4 are N, and X_2 is CH or CF.

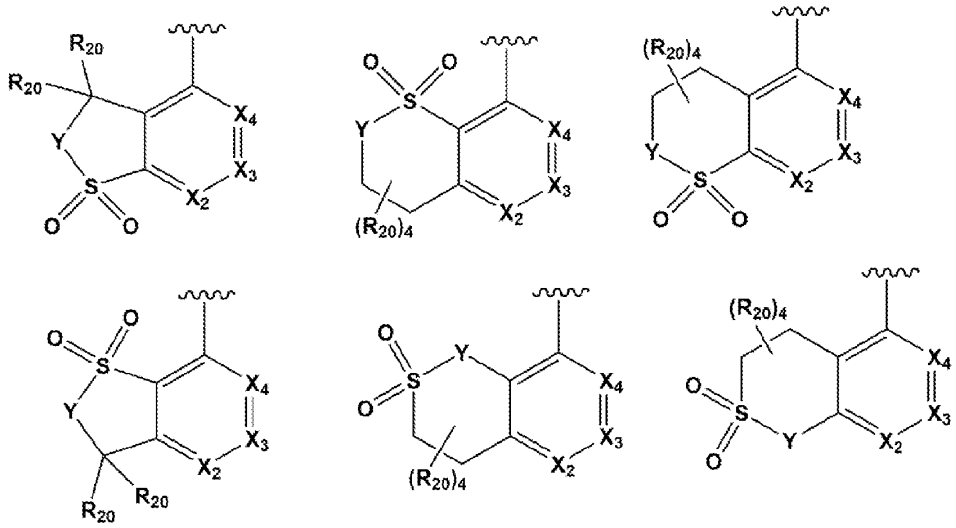
[000110] In an exemplary embodiment of R_1 of Formula (2), X_1, X_2, X_3 and X_4 are N.

[000111] In an exemplary embodiment of the compound of Formula (2), R_1 is selected from



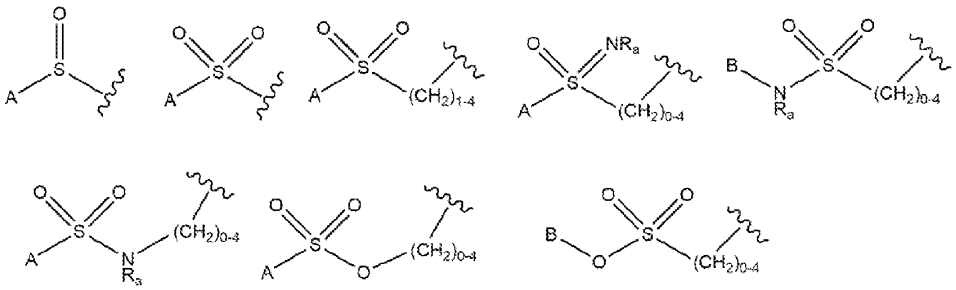
where R_{18}, R_{19}, R_{20}, R_{21}, X_1, X_2, X_3 and X_4 are defined as described herein, and R_5 is a N-linked heterocyclyl ring selected from azetidine, pyrrolidine, imidazoline, imidazolidine, piperazine, morpholine, thiomorpholine and piperidine, where each of these rings is unsubstituted or substituted.

[000112] In an exemplary embodiment of the compound of Formula (2), R_1 is selected from



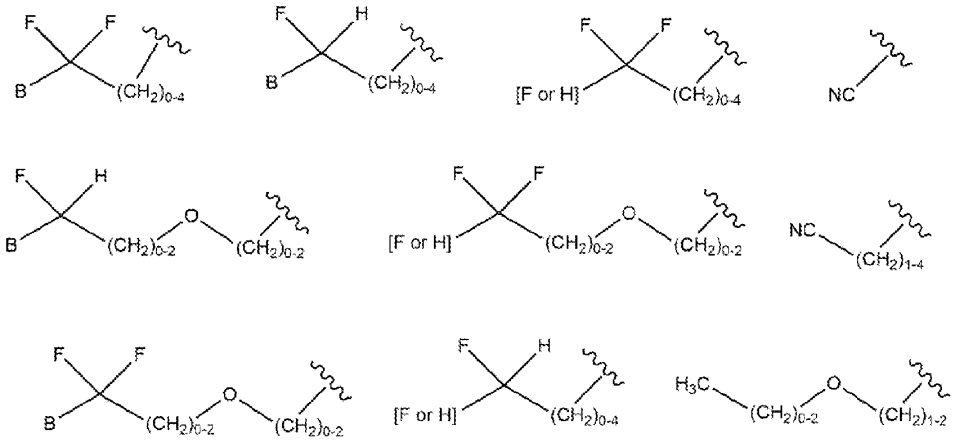
where R_{20}, Y, X_2, X_3 and X_4 are defined as described herein and R_5 is a N-linked heterocyclyl ring selected from azetidine, pyrrolidine, imidazoline, imidazolidine, piperazine, morpholine, thiomorpholine and piperidine, where each of these rings is unsubstituted or substituted.

[000113] In an exemplary embodiment of the compound of Formula (2), R_{18} is selected from



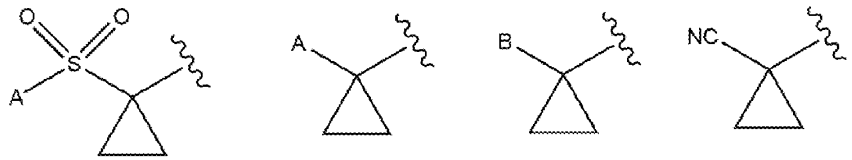
where A, B and R_a are defined as described herein, and R_5 is a N-linked heterocyclyl ring selected from azetidine, pyrrolidine, imidazoline, imidazolidine, piperazine, morpholine, thiomorpholine and piperidine, where each of these rings is unsubstituted or substituted.

[000114] In an exemplary embodiment of the compound of Formula (2), R_{18} is selected from



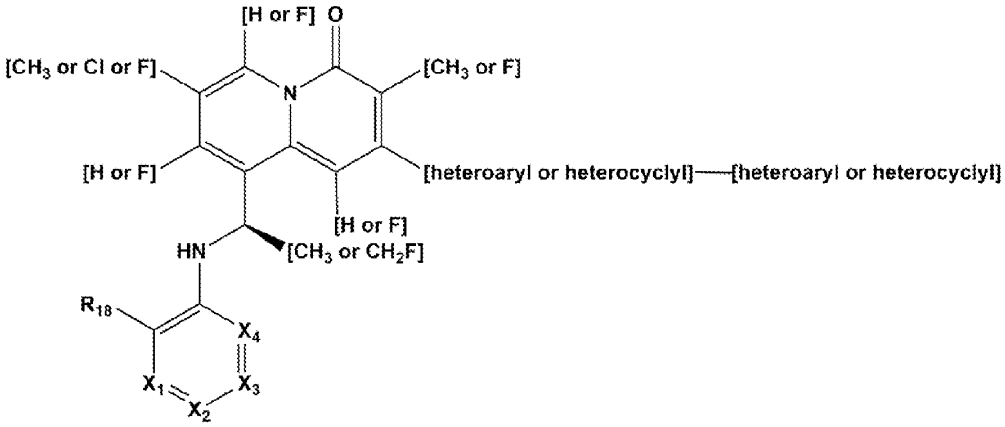
where B is as defined herein, and R_5 is a N-linked heterocyclyl ring selected from azetidine, pyrrolidine, imidazoline, imidazolidine, piperazine, morpholine, thiomorpholine and piperidine, where each of these rings is unsubstituted or substituted.

[000115] In an exemplary embodiment of the compound of Formula (2), R_{18} is selected from



where A and B are defined as described herein, and R_5 is a N-linked heterocyclyl ring selected from azetidine, pyrrolidine, imidazoline, imidazolidine, piperazine, morpholine, thiomorpholine and piperidine, where each of these rings is unsubstituted or substituted.

[000116] In an exemplary embodiment, the compound of Formula (1) is a compound of Formula (3)



(3)

or a solvate, enantiomer, diastereomer, tautomer, polymorph or isotope-labeled compound, or a pharmaceutically acceptable salt thereof,

wherein:

R_{18}, X_1, X_2, X_3, X_4, heteroaryl and heterocyclyl are defined as described herein and the heteroaryl and heterocyclyl rings may be further substituted.

[000117] In an exemplary embodiment of R_1 of Formula (3), X_1, X_2, X_3 and X_4 are independently CH, CCl or CF.

[000118] In an exemplary embodiment of R_1 of Formula (3), X_2 is N, and X_1, X_3 and X_4 are independently CH, CCl or CF.

[000119] In an exemplary embodiment of R_1 of Formula (3), X_1 is N, and X_2, X_3 and X_4 are independently CH, CCl or CF.

[000120] In an exemplary embodiment of R_1 of Formula (3), X_4 is N and X_1, X_2 and X_3 are independently CH, CCl or CF.

[000121] In an exemplary embodiment of R_1 of Formula (3), X_3 is N and X_1, X_2 and X_4 are independently CH, CCl or CF.

[000122] In an exemplary embodiment of R_1 of Formula (3), X_1 and X_3 are N, and X_2 and X_4 are independently CH, CCl or CF.

[000123] In an exemplary embodiment of R_1 of Formula (3), X_1 and X_2 are N, and X_3 and X_4 are independently CH, CCl or CF.

[000124] In an exemplary embodiment of R_1 of Formula (3), X_2 and X_3 are N, and X_1 and X_4 are independently CH, CCl or CF.

[000125] In an exemplary embodiment of R_1 of Formula (3), X_2 and X_4 are N, and X_2 and X_3 are independently CH, CCl or CF.

[000126] In an exemplary embodiment of R_1 of Formula (3), X_1, X_2 and X_3 are N, and X_4 is CH, CCl or CF.

[000127] In an exemplary embodiment of R_1 of Formula (3), X_1, X_2 and X_4 are N, and X_3 is CH, CCl or CF.

[000128] In an exemplary embodiment of R_1 of Formula (3), X_2, X_3 and X_4 are N, and X_1 is CH, CCl or CF.

[000129] In an exemplary embodiment of R_1 of Formula (3), X_1, X_3 and X_4 are N, and X_2 is CH, CCl or CF.

[000130] In an exemplary embodiment of R_1 of Formula (3), X_1, X_2, X_3 and X_4 are N.

[000131] In an exemplary embodiment of Formula (3), each heteroaryl is independently a 5- to 6- membered ring containing from 1-3 nitrogen atoms. In a further embodiment, the 5-membered heteroaryl ring additionally contains a sulfur atom or an oxygen atom. In every case, the 5- to 6- membered heteroaryl ring may be further substituted.

[000132] In an exemplary embodiment of Formula (3), each heterocyclyl is independently a non-aromatic 4- to 7- membered ring containing from 1 to 3 nitrogen atoms. In a further embodiment, the 4- to 7- membered heterocyclic ring additionally contains from 1 to 2 oxygen or sulfur atoms, with the proviso that if the ring size is 4 or 5, the total number of ring heteroatoms is 1, 2 or 3, and if the ring size is 6 or 7, the total number of ring heteroatoms is 1, 2, 3 or 4. In every case, the 4- to 7- membered heterocyclic ring may be further substituted.

[000133] In an exemplary embodiment of Formula (3), the heteroaryl is a pyridine, pyridone, oxazole, isoxazole, thiazole, isothiazole, 1,2,4-triazole, 1,2,3-triazole, tetrazole, 1,2,5-oxadiazole, 1,2,3-oxadiazole, 1,3,4-thiadiazole, pyridazine, pyrimidine, pyrazine, 1,2,4-triazine or 1,3,5-triazine, where the heteroaryl ring may be further substituted.

[000134] In an exemplary embodiment of Formula (3), the heterocyclyl is an azetidine, morpholine, thiomorpholine, pyrrolidinone, pyrrolidinine, 2-pyrroline, 3-pyrroline, pyrazolidine, 2-pyrazoline, 2-imidazoline, imidazolidine, piperidine or piperazine, where the heterocyclyl ring may be further substituted.

[000135] In an exemplary embodiment of Formula (3), R^{18} is $(CH_3)_2SO_2$-, CF_3-, CF_2H-, -CN, CF_3O-, CF_2HO-, a N-linked pyrazole, a C-linked pyrazole or a pyridine.

[000136] An aspect of the invention is a pharmaceutical composition comprising any compound of the invention as described herein (such as Formula (1), Formula (2) or Formula (3)) or a solvate, enantiomer, diastereomer, tautomer, polymorph or isotope-labeled compound thereof, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

[000137] In an exemplary embodiment, the pharmaceutical composition comprising any compound of the invention as described herein (such as Formula (1), Formula (2) or Formula (3)) or a solvate, enantiomer, diastereomer, tautomer, polymorph or isotope-labeled compound thereof, or a pharmaceutically acceptable salt thereof further comprises one or more anti-cancer agents.

[000138] Another aspect of the invention is a method of treating a disease in which PI3K activity is implicated in a subject in need of such treatment, the method comprising administering to the subject a therapeutically effective amount of any compound of the invention as described herein (such as Formula (1), Formula (2) or Formula (3)) or a solvate, enantiomer, diastereomer, tautomer, polymorph or isotope-labeled compound thereof, or a pharmaceutically acceptable salt thereof.

[000139] In an exemplary embodiment, the disease to be treated is cancer. In particular embodiments, the disease is a cancer bearing a PI3Kα H1047 mutation (such as H1047R, H1047L, or H1047Y), a PI3Kα E545 mutation (such as E545K), or a PI3Kα E542 mutation (such as E542K).

DETAILED DESCRIPTION OF THE INVENTION

[000140] The term "at risk for" as used herein, refers to a medical condition or set of medical conditions exhibited by a patient which may predispose the patient to a particular disease or affliction. For example, these conditions may result from influences that include, but are not limited to, behavioral, emotional, chemical, biochemical, or environmental influences.

[000141] The term "effective amount" as used herein, refers to a particular amount of a pharmaceutical composition comprising a therapeutic agent that achieves a clinically beneficial result (*i.e.*, for example, a reduction of symptoms). Toxicity and therapeutic efficacy of such compositions can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, *e.g.*, for determining the LD_{50} (the dose lethal to 50% of the population)

and the ED_{50} (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index, which can be expressed as the ratio LD_{50}/ ED_{50}. Compounds that exhibit large therapeutic indices are preferred. The data obtained from these cell culture assays and additional animal studies can be used in formulating a range of dosages for human use. The dosages of such compounds lie preferably within a range of circulating concentrations that include the ED_{50} with little or no toxicity. The dosage varies within this range depending upon the dosage form employed, the sensitivity of the patient, and the route of administration.

[000142] The term "symptom" as used herein, refers to any subjective or objective evidence of disease or physical disturbance observed by the patient. For example, subjective evidence is usually based upon patient self-reporting and may include, but is not limited to, pain, headache, visual disturbances, nausea and/or vomiting. Alternatively, objective evidence is usually a result of medical testing including, but not limited to, body temperature, complete blood count, lipid panels, thyroid panels, blood pressure, heart rate, electrocardiogram, tissue body imaging scans and other medical testing results.

[000143] The term "disease" as used herein, refers to any impairment of the normal state of the living animal or one of its parts that interrupts or modifies the performance of the vital functions. Typically manifested by distinguishing signs and symptoms, a disease is usually a response to i) environmental factors (such as malnutrition, industrial hazards, or climate); ii) specific infective agents (such as worms, bacteria, or viruses); iii) inherent defects of the organism (such as genetic anomalies); and/or iv) combinations of these factors.

[000144] The terms "reduce", "inhibit", "diminish", "suppress", "decrease", "prevent" and grammatical equivalents thereof (including "lower", "smaller", *etc.*) when used in reference to the expression of any symptom in an untreated subject relative to a treated subject, indicate that the quantity and/or magnitude of the symptoms in the treated subject is lower than in the untreated subject by any amount that is recognized as clinically relevant by any medically trained personnel. In one embodiment, the quantity and/or magnitude of the symptoms in the treated subject is at least 10% lower than, at least 25% lower than, at least 50% lower than, at least 75% lower than, and/or at least 90% lower than the quantity and/or magnitude of the symptoms in the untreated subject.

[000145] The term "inhibitory compound" as used herein, refers to any compound capable of interacting with (*i.e.*, for example, attaching, binding, *etc.*) to a binding partner under conditions such that the binding partner becomes unresponsive to its natural ligands. Inhibitory compounds may include, but are not limited to, small organic molecules, antibodies, and proteins/peptides.

[000146] The term "attached" as used herein, refers to any interaction between a medium (or carrier) and a drug. Attachment may be reversible or irreversible. Such attachment includes, but is not limited to, covalent bonding, ionic bonding, Van der Waals forces or friction, and the like. A drug is attached to a medium (or carrier) if it is impregnated, incorporated, coated, in suspension with, in solution with, mixed with, *etc.*

[000147] The term "drug" or "compound" as used herein, refers to any pharmacologically active substance capable of being administered which achieves a desired effect. Drugs or compounds can be synthetic or naturally occurring, non-peptide, proteins or peptides, oligonucleotides or nucleotides, polysaccharides, or sugars.

[000148] The term "administered" or "administering" as used herein, refers to any method of providing a composition to a patient such that the composition has its intended effect on the patient. An exemplary method of administering is by a direct mechanism such as, local tissue administration (*i.e.*, for example, extravascular administration, such as subcutaneous, intramuscular, or intraperitoneal), intravenous, oral ingestion, transdermal patch, topical, inhalation, suppository, etc.

[000149] The term "patient" as used herein, is a human or animal and needs not be hospitalized. For example, out-patients and persons in nursing homes are "patients." A patient may be a human or non-human animal of any age and therefore includes both adults and juveniles (*i.e.*, children). It is not intended that the term "patient" connote a need for medical treatment. Therefore, a patient may voluntarily be subject to experimentation, whether clinical or in support of basic science studies.

[000150] The term “subject” as used herein, refers to, but is not limited to, humans (e.g., a male or female of any age group, e.g., a pediatric subject (e.g., infant, child, adolescent) or adult subject (e.g., young adult, middle-aged adult or senior adult)) and/or other primates (e.g., monkeys); non-human mammals, such as cows, pigs, horses, sheep, mice, goats, cats, dogs; and/or birds, such as chickens, ducks and/or geese.

[000151] The term "affinity" as used herein, refers to any attractive force between substances or particles that causes them to enter into and remain in chemical combination. For example, an inhibitor compound that has a high affinity for a receptor will provide greater efficacy in preventing the receptor from interacting with its natural ligands, than an inhibitor with a low affinity.

[000152] The term "derived from" as used herein, refers to the source of a compound or sequence. In one respect, a compound or sequence may be derived from an organism or particular species. In another respect, a compound or sequence may be derived from a larger complex or sequence.

[000153] The term "test compound" as used herein, refers to any compound or molecule considered a candidate as an inhibitory compound.

[000154] The term "combination therapy" as used herein refers to refers to a dosing regimen of two or more different therapeutically active agents during a period of time, wherein the therapeutically active agents are administered together or separately. In one embodiment the combination therapy is a non-fixed combination.

[000155] The term "non-fixed combination" as used herein refers to two or more different therapeutic agents that are formulated as separate compositions or dosages such that they may be administered separately to a subject in need thereof either simultaneously or sequentially with variable intervening time limits.

[000156] The term "synergy" or "synergistic" as used herein refers to the phenomenon where the combination of two therapeutic agents of a combination therapy is greater in terms of measured results than the sum of the effect of each agent when administered alone.

[000157] The term "*in vivo*" as used herein refers to an event that takes place in a subject's body.

[000158] The term "*in vitro*" as used herein refers to an event that takes places outside of a subject's body.

[000159] The term "protein" as used herein, refers to any of numerous naturally occurring extremely complex substances (such as an enzyme or antibody) that contain amino acid residues joined by peptide bonds, and which include carbon, hydrogen, nitrogen, oxygen, and typically

sulfur. In general, a protein comprises amino acids having an order of magnitude within the hundreds.

[000160] The term "peptide" as used herein, refers to any of various amides that are derived from two or more amino acids by combination of the amino group of one acid with the carboxyl group of another and are usually obtained by partial hydrolysis of proteins. In general, a peptide comprises amino acids having an order of magnitude with the tens.

[000161] The term "pharmaceutically acceptable" or "pharmacologically acceptable" as used herein, refers to molecular entities and compositions that do not produce adverse, allergic, or other untoward reactions when administered to an animal or a human.

[000162] The term, "pharmaceutically acceptable carrier" as used herein, includes any and all solvents, or a dispersion medium including, but not limited to, water, ethanol, a polyol (such as, for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, vegetable oils, coatings, isotonic and absorption delaying agents, liposome, commercially available cleansers, and the like. Supplementary bioactive ingredients also can be incorporated into such carriers.

[000163] The term "pharmaceutically acceptable salt" as used herein, refers to a salt that does not adversely impact the biological activity and properties of the compound and is suitable for use in contact with the tissues of subjects without undue toxicity, irritation and/or allergic response and the like. Pharmaceutically acceptable salts include those derived from suitable inorganic acids, organic acids and bases, and include hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, nitric acid, acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid, malonic acid, ascorbic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, benzoic acid, naphthalene sulfonic acid, lactic acid, succinic acid, oxalic acid, stearic acid, and the like. In some instances, pharmaceutically acceptable salts are obtained by reacting a compound having acidic group described herein with a base to form a salt such as an ammonium salt, an alkali metal salt (*e.g.*, a sodium or a potassium salt), an alkaline earth metal salt (*e.g.*, a calcium or a magnesium salt), a salt formed from an organic base, and an amino acid salt. Pharmaceutically acceptable salts derived from appropriate bases include alkali metals, alkaline earth metals, and ammonium and quaternary ammonium compounds. Specific metals include, but are not limited to, sodium, lithium,

potassium, calcium, magnesium, iron, zinc, copper, manganese, aluminum, and the like. Organic bases from which salts may be prepared include, for example, primary, secondary, and tertiary amines.

[000164] The term "prodrug" as used herein, refers to a compound that is transformed *in vivo* to yield a disclosed compound or a pharmaceutically acceptable form of the compound. A prodrug may be inactive when administered to a subject, but is converted *in vivo* to an active compound. In various instances, a prodrug has improved physicochemical properties (such as bioavailability) and/or delivery properties over the parent compound. Prodrugs are typically designed to enhance pharmaceutically and/or pharmacokinetically based properties associated with the parent compound. The prodrug compound often offers advantages of solubility, tissue compatibility or delayed release in subject. Prodrugs include compounds wherein a hydroxy, amino, or mercapto group is bonded to any group that, when the prodrug is administered to a subject, cleaves to form a free hydroxy, free amino, or free mercapto group, respectively. Prodrugs are well known to be prepared from carboxylic acids in the form of, for example, carboxylate esters or thioesters.

[000165] The term, "purified" or "isolated" as used herein, may refer to a composition (such as, for example, a peptide composition) that has been subjected to treatment (*e.g.*, fractionation) to remove various other components, and which composition substantially retains its expressed biological activity.

[000166] The term "sample" as used herein, includes, for example, environmental and biological samples. Environmental samples include material from the environment such as soil and water. Biological samples include animal (*e.g.*, human), fluids (*e.g.*, blood, plasma, and serum), solids (*e.g.*, stool), tissue, liquid foods (*e.g.*, milk), and solid foods (*e.g.*, vegetables). For example, a pulmonary sample may be collected by bronchoalveolar lavage (BAL) which comprises fluid and cells derived from lung tissues. A biological sample may comprise a cell, tissue extract, body fluid, chromosomes or extrachromosomal elements isolated from a cell, genomic DNA (in solution or bound to a solid support such as for Southern blot analysis), RNA (in solution or bound to a solid support such as for Northern blot analysis), cDNA (in solution or bound to a solid support) and the like.

[000167] The term "biologically active" as used herein, refers to any molecule having structural, regulatory or biochemical functions. For example, biological activity may be determined, for example, by restoration of wild-type growth in cells lacking protein activity. Cells lacking protein activity may be produced by many methods (i.e., for example, point mutation and frame-shift mutation). Complementation is achieved by transfecting cells which lack protein activity with an expression vector which expresses the protein, a derivative thereof, or a portion thereof.

[000168] The term "label" or "detectable label" as used herein, refers to any composition detectable by spectroscopic, photochemical, biochemical, immunochemical, electrical, optical or chemical means. Such labels include biotin for staining with labeled streptavidin conjugate, magnetic beads (*e.g.*, Dynabeads®), fluorescent dyes (*e.g.*, fluorescein, Texas Red®, rhodamine, green fluorescent protein, and the like), radiolabels (*e.g.*, ^{3}H, ^{125}I, ^{35}S, ^{14}C, or ^{32}P), enzymes (*e.g.*, horse radish peroxidase, alkaline phosphatase and others commonly used in an ELISA), and calorimetric labels such as colloidal gold or colored glass or plastic (*e.g.*, polystyrene, polypropylene, latex, etc.) beads. Patents teaching the use of such labels include, but are not limited to, U.S. Patent Nos. 3,817,837; 3,850,752; 3,939,350; 3,996,345; 4,277,437; 4,275,149; and 4,366,241 (all herein incorporated by reference in their entireties). The labels contemplated in the present invention may be detected by conventional methods. For example, radiolabels may be detected using photographic film or scintillation counters, fluorescent markers may be detected using a photodetector to detect emitted light. Enzymatic labels are typically detected by providing the enzyme with a substrate and detecting, the reaction product produced by the action of the enzyme on the substrate, and calorimetric labels are detected by simply visualizing the colored label.

[000169] The term "conjugate" as used herein, refers to any compound that has been formed by the joining of two or more moieties.

[000170] A "moiety" or "group" as used herein, is any type of molecular arrangement designated by formula, chemical name, or structure. Within the context of certain embodiments, a conjugate comprises one or more moieties or chemical groups. This means that the formula of the moiety is substituted at some position in order to be joined and be a part of the molecular arrangement of the conjugate. Although moieties may be directly covalently joined, it is not intended that the joining of two or more moieties must be directly to each other. A linking

group, a crosslinking group, or a joining group refers to any molecular arrangement that will connect moieties by covalent bonds such as, but not limited to, one or more amide group(s). Additionally, although the conjugate may be unsubstituted, the conjugate may have a variety of additional substituents connected to the linking groups and/or connected to the moieties.

[000171] A "polymer" or "polymer group" as used herein, refers to a chemical species or group composed of repeatedly linked moieties. Within certain embodiments, it is preferred that the number of repeating moieties is 3 or more or greater than 10. The linked moieties may be identical in structure or may vary in their moiety structures. A "monomeric polymer" or "homopolymer" is a polymer that contains the same repeating, asymmetric subunit. A "copolymer" is a polymer derived from two or more types of monomeric species (*i.e.*, two or more different chemical asymmetric subunits). "Block copolymers" are polymers comprised of two or more species of polymer subunits linked by covalent bonds.

[000172] The term "substituted" as used herein, refers to at least one hydrogen atom of a molecular arrangement that is replaced with a substituent. The number of substituents present depends on the number of hydrogen atoms available for replacement and includes replacement of more than one hydrogen atom bound to a single atom (such as in the case of a carbon atom or a silicon atom which may be available for mono-, di- or tri-substitution or in the case of a nitrogen atom which may be available for mono-, di- or tri-substitution or in the case of an oxygen atom or a sulfur atom which may be available for mono-substitution). In the case of an oxo substituent ("=O"), two hydrogen atoms are replaced (which provides, for example, -(CH_2)-C(=O)-CH_3 as a substituent when the two hydrogen atoms of the middle carbon atom of -CH_2-CH_2-CH_3 are replaced). When substituted, one or more of the groups below are "substituents." Substituents include, but are not limited to, halogen (*e.g.*, F, Cl, Br, I), hydroxy (OH), hydroxyalkyl (*e.g.*, CH_2-OH, $CH(CH_3)OH$, $C(CH_3)_2OH$), oxo, cyano (CN), cyanoalkyl (*e.g.*, CH_2-CN, $CH(CH_3)CN$, $C(CH_3)_2CN$), nitro (NO_2), amino, alkylamino, dialkylamino, branched or unbranched alkyl (*e.g.*, methyl, ethyl, propyl, isopropyl, sec-butyl, *etc.*), cycloalkyl (*e.g.*, cyclopropyl), fluoroalkyl (*e.g.*, CF_3, CF_2H, CH_2F, CH_2CF_3, CH_2CF_2H, $CHFCHF_2$, CF_2CH_2F, CF_2CF_3, CF_2CH_3, $CF(CH_3)_2$, $CH_2CH_2CF_3$, $CF_2CH_2CF_3$, $CF_2CF_2CF_3$, *etc.*) or more generally, haloalkyl (*e.g.*, CH_2Cl, $CH(CH_3)Br$, *etc.*), O-alkyl (alkoxy) (*e.g.*, OCH_3, OCH_2CH_3, $OCH(CH_3)_2$, *etc.*), O-cycloalkyl (*e.g.*, O-cyclopropyl), O-haloalkyl (*e.g.*, OCF_2H, $OCFH_2$, OCF_3, OCH_2CF_3, OCH_2CF_2H, $OCHFCHF_2$, OCF_2CH_2F, OCF_2CF_3, OCF_2CH_3, $OCF(CH_3)_2$, $OCH_2CH_2CF_3$, $OCF_2CH_2CF_3$, $OCF_2CF_2CF_3$ or OCH_2Cl), O-aryl (e.g., O-phenyl), O-

heteroaryl, O-heterocyclyl, $(CH_2)_{1-3}$-cycloalkyl, $(CH_2)_{1-3}$-haloalkyl, $(CH_2)_{1-3}$-heterocyclyl, $(CH_2)_{1-3}$-aryl, $(CH_2)_{1-3}$-heteroaryl, thioalkyl (*e.g.*, S-CH_3), hydroxyalkyl (*e.g.*, CH_2OH), alkyl ether (*e.g.*, CH_2OCH_3), alkynyl (e.g., -C≡CR_f), alkenyl (e.g., -CR_f=CR_fR_g), aryl (*e.g.*, phenyl), arylalkyl (*e.g.*, CH_2Ph), heteroaryl (*e.g.*, pyridyl or any 5- or 6- membered heteroaryl ring), heteroarylalkyl (*e.g.*, CH_2-pyridine), heterocyclyl, heterocycloalkyl and as well as -NR_fR_g, -$NR_fC(=O)R_g$, -$NR_fC(=O)NR_fNR_g$, -$NR_fC(=O)OR_fSO_2R_g$, -$C(=O)R_f$, -$C(=O)OR_f$, -$C(=O)(CH_2)_{1-3}R_f$, -$C(=O)O(CH_2)_{1-3}R_f$, -$C(=O)(CH(CH_3))(CH_2)_{0-3}R_f$, -$C(=O)O(CH(CH_3))(CH_2)_{0-3}R_f$, -$C(=O)(C(CH_3)_2)(CH_2)_{0-3}R_f$, -$C(=O)O(C(CH_3)_2)(CH_2)_{0-3}R_f$, -$OR_f$, -$C(=O)NR_fR_g$, -$OC(=O)NR_fR_g$, -$SR_f$, -$SOR_f$, -$S(=O)_2R_f$, -$OS(=O)_2R_f$, -$S(=O)OR_f$, and $P(O)R_fR_g$, where each R_f and R_g may be the same or different and are independently, hydrogen, alkyl (*e.g.*, CH_3), substituted alkyl, cycloalkyl, substituted cycloalkyl, haloalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heterocyclyl, substituted heterocyclyl, heterocycloalkyl, substituted heterocycloalkyl, heteroaryl or substituted heteroaryl. In addition, the above substituents may be further substituted with one or more of the above substituents, such that the substituent may constitute, for example, a substituted alkyl, a substituted aryl, a substituted heteroaryl, a substituted arylalkyl, a substituted heterocyclyl, or a substituted heterocycloalkyl.

[000173] The term "unsubstituted" as used herein, refers to any compound that does not contain extra substituents attached to the compound. An unsubstituted compound refers to the chemical makeup of the compound without extra substituents (*e.g.*, no non-hydrogen substituents). For example, unsubstituted proline is a proline amino acid even though the amino group of proline may be considered as disubstituted with alkyl groups.

[000174] The term “bond” as used herein in describing a substituent with atoms on both sides, refers to the absence of that substituent. For example, in the 4-atom sequence A-B-C-D, when B and C are both listed as being bonds, the result is the 2-atom sequence A-D. If only B is listed as being a bond, the result is the 3-atom sequence A-C-D.

[000175] The term "alkyl" as used herein, refers to any straight chain or branched, non-cyclic or cyclic, unsaturated or saturated aliphatic hydrocarbon containing from 1 to 10 carbon atoms, while the term "lower alkyl" has the same meaning as alkyl but contains from 1 to 3 carbon atoms. The term "higher alkyl" has the same meaning as alkyl but contains from 4 to 10 carbon atoms. Representative saturated straight chain alkyls include, but are not limited to, methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, n-nonyl, and the like, while

saturated branched alkyls include, but are not limited to, isopropyl, sec-butyl, isobutyl, tert-butyl, isopentyl, and the like. As used herein, a methyl substituent may be depicted as "CH_3" or "Me" or as a terminal bond with no indication of specific atoms.

[000176] The term "cycloalkyl" as used herein, refers to saturated and unsaturated cyclic alkyls. Representative saturated cyclic alkyls include, but are not limited to, C_3-C_{14} (such as C_3-C_7) cycloalkyls, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclododecyl, and the like; while unsaturated cyclic alkyls include, but are not limited to, cyclobutenyl, cyclopentenyl and cyclohexenyl, cyclohexadiene, and the like. Cyclic alkyls are also referred to herein as "homocycles" or "homocyclic rings".

[000177] The term "bicyclic compounds" as used herein, encompasses "bridged" compounds, "fused" compounds and "spiro" compounds as described.

[000178] The term "spiro" or "spirocyclic" as used herein, refers to chemical structures having at least two rings sharing one common atom. The rings may be cycloalkyl, heterocyclyl or a combination thereof, and may include one or more aryl or heteroaryl rings. Exemplary embodiments include 1,4-dioxaspiro[4.5]decane, spirocyclic azetidines and spirocyclic pyrrolidines and spirocyclic piperidines, where the other ring is cycloalkyl (*e.g.*, cyclobutane, cyclopentane or cyclohexane) or heterocyclyl (*e.g.*, piperidine, tetrahydropyran, tetrahydrofuran, azetidine or pyrrolidine).

[000179] The term "bridged" as used herein, refers to a compound containing two nonadjacent atoms common to two rings. Exemplary embodiments include, but are not limited to, norbornane, bicyclo[1.1.1]pentane, bicyclo[2.2.1]heptane, 1,4-diazabicyclo[2.2.2]octane, other bridged piperazines and bridged piperidines.

[000180] The term "fused" as used herein, refers to polycyclic ring systems in which any two adjacent rings have two, and only two, adjacent atoms in common (ortho-fused) and polycyclic ring systems in which a ring contains two, and only two, adjacent atoms in common with each of two or more rings of a contiguous series of ortho-fused rings (ortho- and peri-fused). An exemplary embodiment is pentalene and dibenzoxepine (ortho-fused) and pyrene (ortho- and peri-fused). Ortho-fused systems have "n" common sides and "2n" common atoms while peri-fused systems have "n" common sides and less than "2n" atoms in common. Other exemplary fused systems include fused cyclopropyl rings, fused aziridines and fused azetidines, such as

when these rings are fused to a pyrrolidine ring. Other examples include two fused pyrrolidine rings (octahydropyrrolo[3,4-c]pyrrole), fused pyridine rings, such as a pyridine ring fused with a cycloalkyl (*e.g.*, cyclopentane) or with a heterocyclyl (*e.g.*, tetrahydrofuran or tetrahydropyran).

[000181] The term "aromatic" or "aryl" as used herein, refers to any aromatic carbocyclic (*i.e.*, all of the ring atoms are carbon) substituent such as, but not limited to, phenyl (from benzene), tolyl (from toluene), xylyl (from xylene) or multi-ring systems (e.g., naphthyl (from naphthalene) and anthracenyl (from anthracene).

[000182] The term "arylalkyl" or "aralkyl" as used herein, refers to any alkyl having at least one alkyl hydrogen atom replaced with an aryl moiety such as, but not limited to, benzyl, -$(CH_2)_2$phenyl, -$(CH_2)_3$phenyl, -$CH(phenyl)_2$, and the like.

[000183] The term "halogen" as used herein, refers to any fluoro, chloro, bromo, or iodo moiety.

[000184] The term "haloalkyl" as used herein, refers to any alkyl where at least one hydrogen atom (and including all hydrogen atoms) has been replaced with a halogen atom, such as, for example, trifluoromethyl, dichloromethyl, difluoromethyl, monofluoromethyl, monobromomethyl, 1,1,1-trifluoroethyl and the like.

[000185] The term "aminoalkyl" as used herein, refers to any alkyl where at least one hydrogen atom has been replaced with a nitrogen atom, such as, for example, -$(CH_2)_{1\text{-}5}$-NH_2, -$(CH_2)_{1\text{-}5}$-$NHCH_3$, -$(CH_2)_{1\text{-}5}$-$N(CH_3)_2$, -$(CH_2)_{1\text{-}5}$-NH-$(CH_2)_{1\text{-}5}$-$N(CH_3)_2$, and the like.

[000186] The term "heteroaromatic" or "heteroaryl" as used herein, refers to any aromatic heterocyclic ring of 5 to 10 or more members and having at least one heteroatom selected from nitrogen, oxygen or sulfur, and containing at least 1 carbon atom, including, but not limited to, both mono- and bicyclic- ring systems, and where the nitrogen atom may be in an oxidized state. The heteroaryl ring may be attached as a substituent via a ring heteroatom or a carbon atom. Representative heteroaromatics include, but are not limited to, furan, benzofuran, thiophene, benzothiophene, pyrrole, indole, isoindole, indazole, 7-azaindole, 4-azaindole, 5-azaindole, 6-azaindole, 7-azaindazole, pyridine, pyridone (*e.g.*, 2-pyridone, 3-pyridone or 4-pyridone), pyrimidinone, oxopyrazine, pyridine oxide, quinoline, isoquinoline, oxazole, isoxazole, benzoxazole, pyrazole, imidazole, imidazopyrimidine, benzimidazole, thiazole, benzothiazole, isothiazole, 1,2,4-triazole, 1,2,3-triazole, tetrazole, oxadiazole (*e.g.*, 1,2,3-oxadiazole, 1,2,4-

oxadiazole, 1,2,5-oxadiazole, 1,3,4-oxadiazole), thiadiazole (*e.g.*, 1,2,3-thiadiazole, 1,2,4-thiadiazole, 1,2,5-thiadiazole, 1,3,4-thiadiazole), pyridazine, pyrimidine, pyrazine, 1,2,4-triazine, 1,3,5-triazine, triazolopyrazine, cinnoline, phthalazine, quinazoline, 1,8-naphthylpyridine, pyrido[3,2-d]pyrimidine, pyrido[4,3-d]pyrimidine, pyrido[3,4-b]pyrazine, pyrido[2,3-b]pyrazine, pteridine, triazolopyridines (*e.g.*, [1,2,4]triazolo[4,3-a]pyridine) and the like.

[000187] The term "heteroarylalkyl" as used herein, means any alkyl having at least one alkyl hydrogen atom replaced with a heteroaryl moiety, such as -CH_2pyridinyl, -CH_2pyrimidinyl, and the like.

[000188] The term "heterocycle" or “heterocyclyl” or "heterocyclic ring" as used herein, refers to a nonaromatic ring which is either saturated or unsaturated and which contains 1 or more heteroatoms independently selected from nitrogen, oxygen, sulfur, phosphorus and silicon, wherein each of the nitrogen, phosphorus and sulfur heteroatoms may be in an oxidized state, and each of the nitrogen and silicon heteroatoms is substituted or unsubstituted and the nitrogen heteroatoms may be optionally quaternized, and includes bicyclic rings in which any of the above heterocycles are fused to an aryl or heteroaryl ring. The heterocyclic ring may be attached as a substituent via a ring heteroatom or a carbon atom. In various embodiments, heterocycles may contain 3 to 14 or more ring atoms (such as 3- to 7-membered monocyclic rings or 7- to 10-membered bicyclic rings) and include, but are not limited to, 2H-azirine, azetidine, 2,3-dihydroazete, 1,3-diazetidine, 2H-oxete, thietane, 2H-thiete, azetidin-2-one, morpholine, thiomorpholine, pyrrolidinone, pyrrolidinine, 2-pyrroline, 3-pyrroline, pyrazolidine, 2-pyrazoline, pyridazinone, pyrazinone, oxazolidin-2-one, 2-imidazoline, imidazolidine, piperidine, oxopiperidine, tetrahydropyrimidinone, piperazine, oxopiperazine, diazepane, ethylene oxide (oxirane), ethylene imine (aziridine), 1,1-dioxoisothiazolidine, ethylene sulfide (thiirane), oxetane, propylene oxide, 1,3-dioxolane, 1,2-oxathiolane, 1,3-oxathiolane, sulfolane, 2,4-thiazolidinedione, succinimide, 4-methyl-1,4-azaphosphinane 4-oxide, oxadiazolone, dioxane (e.g. 1,4-dioxane and 1,3-dioxane), hydantoin, valerolactam, tetrahydrofuran, tetrahydropyran, 2H-pyran, 4H-pyran, thiane, 2H-thiopyran, 1,3-dithiane, 1,4-dithiane, 1,3,5-trithiane, pyrrolizidine, 1,4,5,6-tetrahydrocyclopenta[b]pyrrole, tetrahydropyridine, tetrahydropyrimidine, dihydropyridazine, 6-oxo-1,6-dihydropyridazine, 6-oxo-1,4-dihydropyridazine, 6-oxo-1,6-dihydropyrazine, 6-oxo-1,4-dihydropyrazine, tetrahydrothiophene, tetrahydrothiopyran, tetrahydrotriazolopyrazine, tetrahydropyrazolopyridine, dihydrotriazolopyrazine,

dihydropyrazolopyrazine, dihydroimidazopyrazine, indoline, isoindoline, decahydroisoquinoline, decahydroquinoline, 1,2,3,4-tetrahydroquinoline, 1,2-dihydroquinoline, 2H-benzo[e][1,3]oxazine, 2H-benzo[b][1,4]oxazine, quinolin-2(1H)-one, isoquinolin-1(2H)-one, quinuclidine, triethylenediamine, 1-azaadamantane, 2-azaadamantane, 2,3-dihydroazepine, 2,5-dihydroazepine, oxepane, azonane, spiro[cyclobutane-1,3'-indole], 1-oxaspiro[4,5]decane, 1,6-dioxaspiro[3,4]octane, 2-oxa-7-azaspiro[3,5]nonane, 1,4-dioxa-7-azaspiro[4,4]nonane, 1,3-diazaspiro[4,4]non-2-en-4-one, 2,9-diazaspiro[5,5]undecan-1-one, oxa-diazabicyclo[3.3.1]nonane, 8-azaspiro[4,5]decane-7,9-dione, 1,4-dithia-7-azaspiro[4,4]nonane, and the like.

[000189] The term "heterocycloalkyl" as used herein, refers to any alkyl having at least one alkyl hydrogen atom replaced with a heterocycle, such as -CH_2morpholinyl, and the like.

[000190] The term "alkylamino" as used herein, means at least one alkyl moiety attached through a nitrogen bridge (*i.e.*, -N-$(alkyl)_n$, where n = 1 or 2, such as alkylamino or dialkylamino) including, but not limited to, methylamino, ethylamino, dimethylamino, diethylamino, and the like.

[000191] The term "alkyloxy" or "alkoxy", as used herein, means any alkyl moiety attached through an oxygen bridge (*i.e.*, -O-alkyl) such as, but not limited to, methoxy, ethoxy, and the like.

[000192] The term "thioalkyl" as used herein, means any alkyl moiety attached through a sulfur bridge (*i.e.*, -S-alkyl) such as, but not limited to, methylthio, ethylthio, and the like.

[000193] The term "alkenyl" as used herein, refers to an unbranched or branched hydrocarbon chain having one or more carbon-carbon double bonds therein and may also be referred to as an "unsaturated alkyl". The double bond of an alkenyl group can be unconjugated or conjugated to another unsaturated group. Suitable alkenyl groups include, but are not limited to vinyl, allyl, butenyl, pentenyl, hexenyl, butadienyl, pentadienyl, hexadienyl, 2-ethylhexenyl, 2-propyl-2-butenyl, 4-(2-methyl-3-butene)-pentenyl. An alkenyl group can be unsubstituted or substituted with one or two suitable substituents.

[000194] The term "alkynyl" as used herein, refers to unbranched or branched hydrocarbon chain having one or more carbon-carbon triple bonds therein and may also be referred to as an "unsaturated alkyl". The triple bond of an alkynyl group can be unconjugated or conjugated to

another unsaturated group. Suitable alkynyl groups include, but are not limited to ethynyl, propynyl, butynyl, pentynyl, hexynyl, methylpropynyl, 4-methyl-1-butynyl, 4-propyl-2-pentynyl-, and 4-butyl-2-hexynyl. An alkynyl group can be unsubstituted or substituted with one or two suitable substituents.

[000195] As used herein, "reactive groups" refer to nucleophiles, electrophiles, or radically active groups, *i.e.*, groups that react in the presence of radicals. A nucleophile is a moiety that forms a chemical bond to its reaction partner (the electrophile) by donating both bonding electrons. Electrophiles accept these electrons. Nucleophiles may take part in nucleophilic substitution, whereby a nucleophile becomes attracted to a full or partial positive charge on an element and displaces the group it is bonded to. Alternatively, nucleophiles may take part in substitution of carbonyl group. Carboxylic acids are often made electrophilic by creating succinyl esters and reacting these esters with aminoalkyls to form amides. Other common nucleophilic groups are thiolalkyls, hydroxylalkyls, primary and secondary amines, and carbon nucleophiles such as enols and alkyl metal complexes. Other preferred methods of ligating proteins, oligosaccharides and cells using reactive groups are disclosed (Lemieux *et al.*, Trends in Biotechnology **1998**, 16, 506, incorporated herein by reference in its entirety). In yet another preferred method, one provides reactive groups for the Staudinger ligation, *i.e.*, "click chemistry" with an azide comprising moiety and alkynyl reactive groups to form triazoles. Michael additions of a carbon nucleophile enolate with an electrophilic carbonyl, or the Schiff base formation of a nucleophilic primary or secondary amine with an aldehyde or ketone may also be utilized. Other methods of bioconjugation are provided (Hang *et al.* Accounts of Chemical Research **2001**, 34, 727, and Kiick *et al.* Proc Natl Acad Sci US.A. **2002**, 99, 19, both of which are incorporated by reference in its entirety).

[000196] The term "biocompatible" as used herein, refers to any material that does not illicit a substantial detrimental response in the host. There is always concern when a foreign object is introduced into a living body that the object will induce an immune reaction, such as an inflammatory response that will have negative effects on the host. In the context of this invention, biocompatibility is evaluated according to the application for which it was designed: for example, a bandage is regarded as biocompatible with the skin, whereas an implanted medical device is regarded as biocompatible with the internal tissues of the body. Preferably, biocompatible materials include, but are not limited to, biodegradable and biostable materials. A

substantial detrimental response has not occurred if an implant comprising the material is in close association to its implant site within the host animal and the response is better than a tissue response recognized and established as suitable from materials provided in an ASTM. ASTM subcommittee F04.16 on Biocompatibility Test Methods has developed biocompatibility standards for medical and surgical materials and devices which includes E1262-88, F612-20, F719-20e1, F720-17, F748-16, F749-20, F750-20, F756-17; F763-04, F813-20, F895-11, F981-04, F1027-86, F1408-20a, F1439-03, F1877-16, F1903-18, F1904-14, F1983-14, F1984-99, F2147-01, F2148-18, F2382-18, F2808-17, F1288-19 and F2909-19, each of which is incorporated herein by reference. For example, materials that are to be used in contact with the blood stream must be composed of materials that meet hemocompatibility standards. One of these tests is for damage to red blood cells, which can result in hemolysis that is, rupturing of the cells, as described in F756-17 Standard Practice for Assessment of Hemolytic Properties of Materials.

[000197] As used herein, a "bioactive substance" refers to any of a variety of chemical moieties and that binds with a biomolecule such as, but not limited to, peptides, proteins, enzymes, receptors, substrates, lipids, antibodies, antigens, and nucleic acids. In certain preferred embodiments, the bioactive substance is a biomolecule but it is not intended that the bioactive substance be limited to biomolecules. In other preferred embodiments, the bioactive substances provide hydrophobic, hydrophilic, or electrostatic interactions, such as polycarboxylic acids that are anionic at physiological pH. In other preferred embodiment, the alkaline growth factors (with isoelectric point above 7) are retained via favorable electrostatic interactions by the polycarboxylates, and subsequently released in a controlled and sustained manner.

[000198] “Cancer” is a term used for a physiological condition in mammals that is typically characterized by unregulated cell growth. Examples of cancer include, but are not limited to, carcinoma, lymphoma, leukemia, blastoma, and sarcoma. More particular examples of such cancers include squamous cell carcinoma, small cell lung cancer, non-small cell lung cancer (NSCLC), glioma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, acute myeloid leukemia (AML), multiple myeloma, gastrointestinal cancer, renal cell carcinoma, renal cancer (*e.g.*, advanced renal cell carcinoma), ovarian cancer, liver cancer, lymphoblastic leukemia, lymphocytic leukemia, colorectal cancer, endometrial cancer, kidney cancer, prostate cancer, thyroid cancer, melanoma, chondrosarcoma, neuroblastoma, pancreatic cancer, glioblastoma multiforme, cervical cancer, brain cancer, stomach cancer, urothelial carcinoma (including local

advanced or metastatic urothelial carcinoma), bladder cancer, hepatoma, breast cancer and head and neck cancer.

[000199] The term "stereoisomer" refers to compounds that have the same atomic connectivity but different atomic arrangement in space. Stereoisomers include cis-trans isomers, E and Z isomers, enantiomers, diastereomers and atropisomers. In the context of the present invention, the term "enantiomerically pure" is understood to mean that the compound in question with respect to the absolute configuration of the chiral center is present in an enantiomeric excess of more than 95%, preferably more than 97%.

[000200] The present disclosure contemplates all such compounds, including cis and trans isomers, (-)- and (+)-enantiomers, (R)- and (S)-enantiomers, diastereomers isomers, (D)-isomers, (L)-isomers, atropisomers, tautomers and racemic and other mixtures thereof, such as enantiomers or diastereomeric enriched mixtures, all of which are within the scope of the present disclosure. Insofar as compounds of the invention as defined herein may exist in optically active or racemic forms by virtue of one or more asymmetric carbon atoms, the invention includes in its definition any such optically active or racemic form. The synthesis of optically active compounds may be carried out by standard techniques of organic chemistry well known in the art such as, for example, by synthesis from optically active starting materials or by resolution of a racemic compound. Similarly, the enantiomeric or diastereomeric purity of a compound may be evaluated using standard laboratory techniques.

[000201] In experimental procedures described herein where mixtures of stereoisomers (including but not limited to diastereomers, enantiomers, and geometric isomers) were generated during synthesis, their separation into stereochemically-enriched components was achieved by conventional techniques, such as chiral SFC, prep-HPLC, or other appropriate methods. Where appropriate, the absolute stereochemistry of the separated components was assigned by comparing the observed biological activity of the target compounds or appropriate intermediates thereof to similar components of known absolute stereochemistry and biological activity described in the literature. An exemplary publication used for reference in this manner includes, but is not limited to, Ketcham et al., J Med Chem (2024), 67, 4936-4949.

[000202] The pharmaceutical compositions of the invention can take any suitable form for the desired route of administration. Where the composition is to be administered orally, any

suitable orally deliverable dosage form can be used, including without limitation water, glycols, oils, alcohols, and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs, emulsions, and solutions; or solid carriers such as starches, sugars, kaolin, diluents, lubricants, binders, disintegrating agents, and the like in the case of powders, pills, capsules, and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit forms. Injectable compositions or intravenous infusions are also provided in the form of solutions, suspensions, and emulsions. For parenteral compositions, the carrier usually comprises sterile water and possibly other ingredients to aid solubility. Injectable solutions may be prepared in which the carrier comprises a saline solution, a glucose solution, or a mixture of a saline and a glucose solution. Suitable oils include, for example, peanut oil, sesame oil, cottonseed oil, corn oil, soybean oil, synthetic glycerol esters of long chain fatty acids, and mixtures of these and other oils. In compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wetting agent, optionally combined with suitable additives as needed, where the additives may facilitate administration of the composition to the skin and/or may facilitate preparation of the compositions to be delivered. These compositions may be administered in various ways, e.g., as a transdermal patch or as an ointment. Acid or base addition salts of the compounds of the invention are typically more suitable in the preparation of aqueous compositions due to their increased water solubility over the corresponding neutral form of the compounds.

[000203] The pharmaceutical compositions of the invention may comprise one or more of a filler, diluent, adjuvant, vehicle, or other excipient to facilitate storage and/or administration of the active ingredients contained therein.

[000204] In an exemplary embodiment, a pharmaceutical composition according to the present invention may contain one or more additional therapeutic agents, for example, to increase efficacy or to decrease undesired side effects. In a particular embodiment, the pharmaceutical composition further contains one or more additional therapeutic agents useful to treat or inhibit a disease mediated directly or indirectly by PI3K. Examples of such agents include, without limitation, agents to treat or inhibit cancer, Huntington's disease, cystic fibrosis, liver fibrosis, renal fibrosis, pulmonary fibrosis, skin fibrosis, rheumatoid arthritis, diabetes, or heart failure.

[000205] In a specific embodiment, the additional therapeutic agent to be included is an anti-cancer agent. Examples of an anti-cancer agent include, but are not limited to, DNA-damaging cytotoxic drugs, alkylating agents such as cyclophosphamide, dacarbazine, and cisplatin; anti-metabolites such as methotrexate, mercaptopurine, thioguanine, fluorouracil, and cytarabine; plant alkaloids such as vinblastine and paclitaxel; antitumor antibiotics such as doxorubicin, bleomycin and mitomycin; hormones/antihormones such as prednisone, tamoxifen, and flutamide; other types of anticancer agents such as asparaginase, rituximab, trastuzumab, imatinib, retinoic acid, and derivatives, colony stimulating factors, amifostine, camptothecin, topotecan, thalidomide analogs such as lenalidomide, and proteasome inhibitors such as Velcade.

[000206] In another embodiment, the present invention provides a method of inhibiting or treating diseases arising from abnormal cell proliferation and/or differentiation in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of one or more compounds according to the present invention. In one embodiment, the method of inhibiting or treating disease comprises administering to a subject in need thereof, a composition comprising an effective amount of one or more compounds of the invention and a pharmaceutically acceptable carrier. The composition to be administered may further contain a therapeutic agent such as an anti-cancer agent.

[000207] The compounds of the invention are defined herein by their chemical structures and/or chemical names and are generally listed according to the IUPAC or CAS nomenclature system. Abbreviations that are well known to one of ordinary skill in the art may be used. When a compound is referred to by both a chemical structure and a chemical name, and the chemical structure and chemical name conflict, the chemical structure is intended to be determinative of the compound's identity, except in cases where the legibility of the chemical structures in the original application is adversely affected by publication of the application.

[000208] The present invention includes compounds labeled with various radioactive or nonradioactive isotopes. Examples of atomic isotopes may include, but are not limited to, deuterium (^{2}H), tritium (^{3}H), iodine-125 (^{125}I), carbon-14 (^{14}C), nitrogen-15 (^{15}N), sulfur-35 (^{35}S) and chlorine-36 (^{36}Cl). In an exemplary embodiment, one or more hydrogen atoms in a compound of the invention can be replaced by deuterium. In various embodiments, a compound of the invention includes at least one deuterium atom, or two or more deuterium

atoms, or three or more deuterium atoms, *etc*. As described herein, compounds of the invention may also be radiolabeled with a radioactive isotope such as tritium (^{3}H), iodine-125 (^{125}I), and carbon-14 (^{14}C). A radiolabeled compound is useful as a therapeutic or prophylactic agent, provides a reagent for research such as for an assay, and/or provides a diagnostic agent for techniques such as *in vivo* imaging. Synthetic methods for incorporating isotopes into organic compounds are well known in the art.

[000209] In an embodiment of the invention, a compound of the invention as defined herein (such as a compound of Formula (1), Formula (2) or Formula (3)) or a pharmaceutically-acceptable salt thereof, exists as a single enantiomer being in an enantiomeric excess (% ee) of ≥ 95%, such as ≥ 98%, such as ≥ 99%.

[000210] In an embodiment of the invention, a pharmaceutical composition comprises a compound of the invention as defined herein (such as a compound of Formula (1), Formula (2) or Formula (3)) or a pharmaceutically-acceptable salt thereof, where the compound exists as a single enantiomer being in an enantiomeric excess (% ee) of ≥ 95%, such as ≥ 98%, such as ≥ 99%.

[000211] In an exemplary embodiment of the invention, the disease or disorder to be treated by the compounds of the invention is selected from congenital lipomatous overgrowth, vascular malformations, epidermal naevi, scoliosis/skeletal and spinal syndrome (CLOVES), mosaic tissue overgrowth syndromes, venous malformations and brain malformations associated with severe epilepsy or PIK3CA-related overgrowth syndrome (PROS) (Keppler-Noreuil *et al.*, Am J Med Genet A. **2015**, 167A, 287; Kurek *et al.* Am. J. Hum. Genet. **2012**, 90, 1108).

[000212] In an exemplary embodiment of the invention, the cancer to be treated is a cancer bearing a PI3K H1047 mutation (such as H1047R) (Thorpe *et al*., Nat Rev Cancer **2015**, 15, 7).

[000213] The compounds of the invention (such as defined by Formula (1), Formula (2), or Formula (3)) are typically PI3Kα mutant-selective inhibitors that exhibit greater selectivity for any of the H1047R, H1047L, H1047Y, E542K, or E545K mutations over the wild-type. As such, the compounds may decrease the amount of phosphorylated AKT (pAKT) and decrease proliferation selectively in PI3Kα mutant cell lines, across several tumor types.

[000214] A PI3Kα mutant selective inhibitor of the invention (such as defined by Formula (1), Formula (2) or Formula (3)) dosed in combination with an aromatase inhibitor (AI) such as, but not limited to letrozole or anastrozole, a selective estrogen receptor modulator (SERM) such as,

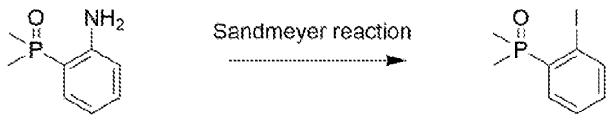
but not limited to tamoxifen, or a selective estrogen receptor degrader (SERD) such as, but not limited to, fulvestrant, elacestrant, or camizestrant may exhibit a combination benefit leading to tumor regression in ER+/PI3Kα mutant tumors such as, but not limited to, the breast cancer xenograft model T47D, the breast cancer xenograft model MCF7, or the breast cancer xenograft model BT483, at doses where little or no regression would be observed with either single agent. Similarly, triple combinations of a PI3Kα mutant selective inhibitor of the invention (such as defined by Formula (1), Formula (2) or Formula (3)) dosed in combination with an aromatase inhibitor (AI), selective estrogen receptor modulator (SERM), or selective estrogen receptor degrader (SERD) in addition to a CDK4 or CDK4/6 inhibitor such as, but not limited to atirmociclib, ribociclib, abemaciclib, or palbociclib, may exhibit a combination benefit leading to tumor regression in ER+/PI3Kα mutant tumors such as, but not limited to, the breast cancer xenograft model T47D, the breast cancer xenograft model MCF7, or the breast cancer xenograft model BT483, at doses where little or no regression would be observed with either single agent and greater regressions that would be observed with doublet combinations.

[000215] A PI3K H1047R mutant selective inhibitor of the invention (such as defined by Formula (1), Formula (2) or Formula (3)) dosed in combination with a HER2 inhibitor such as, but not limited to, tucatinib or trastuzumab may exhibit a combination benefit leading to tumor regression in ER-/HER2+/PI3K H1047R mutant tumors such as, but not limited to, the breast cancer xenograft model HCC1954, at doses where little or no regression would be observed with either single agent.

[000216] Compounds of Formula (1), Formula (2) and Formula (3) of the present invention may be generally prepared according to the synthetic routes identified in Schemes 1-20.

[000217] Substituted (hetero)aryl inputs necessary for the synthesis of compounds of Formula (1) are either commercially available or readily prepared via the use of known synthetic chemistry methods. For example, commercially available aminophenylphosphine oxide **1** may be used as a nucleophilic reactant in the subsequently described synthetic Schemes, or it can be transformed into the corresponding iodide **2** for use in transition metal-mediated couplings via a Sandmeyer reaction under standard reaction conditions, Scheme 1.

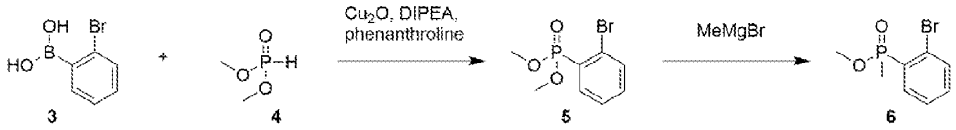
Scheme 1



1 2

[000218] The preparation of (hetero)aryl phosphate esters (e.g., dimethyl (2-bromophenyl)phosphonate **5**) may be accomplished by copper-oxide-mediate couplings of (hetero)aryl boronic acids (e.g., **3**) with dimethylphophonate to provide suitable coupling partners in transition metal-mediated couplings, Scheme 2. Such phosphate esters may be transformed by reaction with Grignard reagents into alkyl phosphinates (e.g., **6**) that are also suitable for use as coupling partners.

Scheme 2

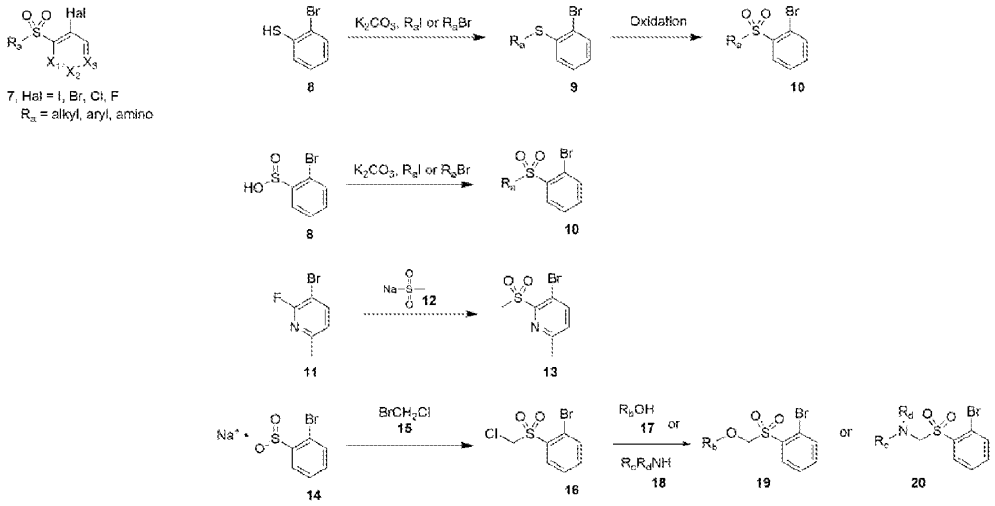


3 4 5 6

[000219] Halogen-substituted (hetero)aryl sulfones and sulfonamides are either readily available from commercial sources (e.g., **7** where $R_a = CH_3$ or NH_2, respectively) or can be prepared via known synthetic chemistry methods, Scheme 3. For example, benzene thiols such as **8** may be alkylated with alkyl halides (e.g., iodoethane) under basic conditions to provide thioethers such as **9**. Subsequently, the thioether functionality may be oxidized by any of a number of reagents (for example, such as meta-chloroperoxybenzoic acid) to afford aryl sulfones like **10**. Alternatively, aryl sulfones **10** can be prepared from the corresponding aryl sulfinic acids **8** via S_N2 alkylations with alkyl bromides or alkyl iodides in the presence of an appropriate base (e.g., potassium carbonate). Heteroarylsulfones (for example, pyridyl sulfone **13**) may be prepared by reacting sodium methylsulfinate with 2-fluoro- or 2-chloropyridines (such as **11**). The preparation of alkyl aryl sulfones (such as **19** or **20**) containing oxygen- or nitrogen-linked chains may be achieved from an appropriate halogen methyl-substituted sulfone (e.g., but not limited to, 1-bromo-2-((chloromethyl)sulfonyl)benzene **16**). The synthesis of **16** may be

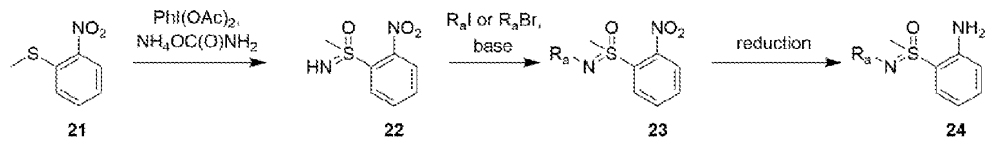
achieved by alkylating aryl sulfinate **14** with bromochloromethane. Oxygen- or nitrogen- linked species inputs, **19** or **20**, respectively, can be synthesized from **16** via alkylations of alcohols **17** or amines **18** in the presence of an appropriate base (e.g., but not limited to, sodium hydride or potassium carbonate).

Scheme 3



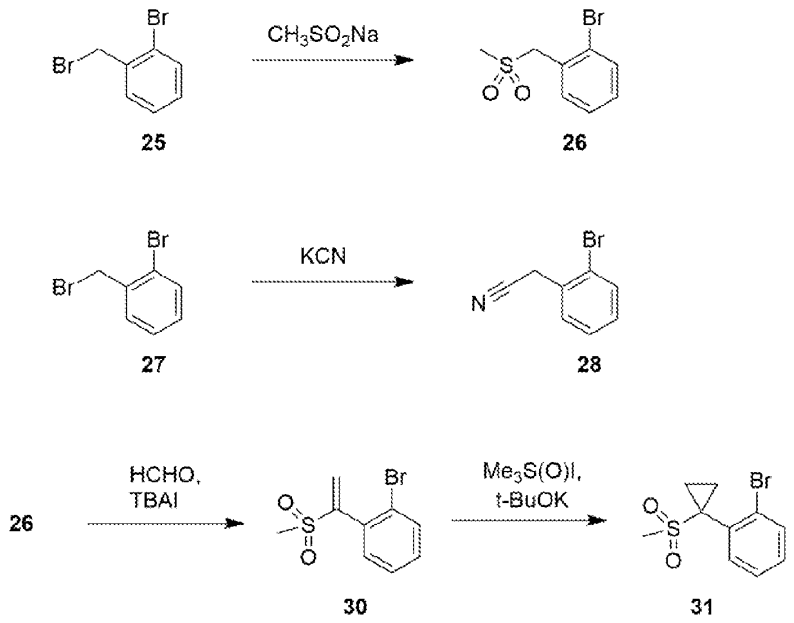
[000220] Sulfoximine-containing inputs may be prepared from thioethers, Scheme 4. Thioether-containing nitrobenzenes (for example, but not limited to, **21**) may be reacted with ammonium carbamate in the presence of phenyliodonium reagents to yield sulfoximine-containing intermediates like **22**. The sulfoximine may optionally be further functionalized via an alkylation step to yield species such as **23**. Reduction of the nitro group of **23** (e.g., by iron in the presence of ammonium chloride) can yield anilino sulfoximines **24**.

Scheme 4



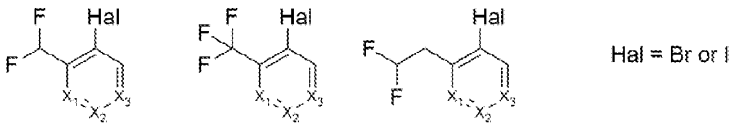
[000221] Halogen-substituted (hetero)aryl methylsulfones may be readily prepared from the appropriate substituted benzyl halides, Scheme 5. Displacement of the benzyl halide group of aryls such as **25** by alkali alkylsulfonates (such as sodium methanesulfinate) can yield the requisite sulfones **26**. Halogen-substituted (hetero)aryl methylnitriles analogous to sulfones **26** may be prepared via similar S_N2 displacements of benzyl halides by using potassium cyanide instead of sodium methanesulfinate to yield **28**. Corresponding (methylsulfonyl)cyclopropyl (hetero)aryl halide inputs such as **31** may be prepared from **26** via a condensation/addition-cyclization sequence.

Scheme 5



[000222] Various halogen-substituted (hetero)aryl difluoromethyls, methyldifluoromethyls, and trifluoromethyls (**32**, **33**, and **34**) are commercially available inputs, Scheme 6.

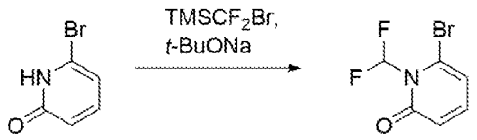
Scheme 6



32 **33** **34**

[000223] Pyridone inputs are either readily available from commercially available sources or may be prepared via known synthetic chemistry methods, Scheme 7. Bromopyridones such as **35** can be alkylated at the nitrogen position using standard alkylation conditions to yield substituted pyridones like **36**.

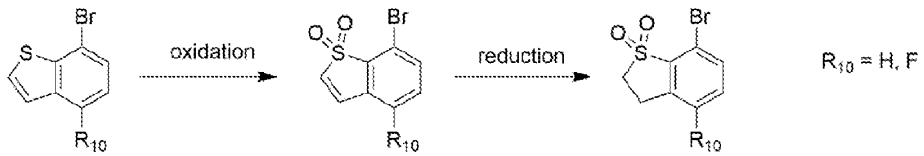
Scheme 7



35 **36**

[000224] Dihydrobenzothiophene dioxide inputs may be readily prepared from commercially available benzothiophenes, Scheme 8. Oxidation of benzothiophenes **37** can be accomplished via a number of oxidizing reagents (e.g., *m*-CPBA) to give rise to benzothiophene dioxides **38**. Subsequent partial reduction of compounds **38** (e.g., with $NaBH_4$) can yield the requisite dihydrobenzothiophene dioxides **39**.

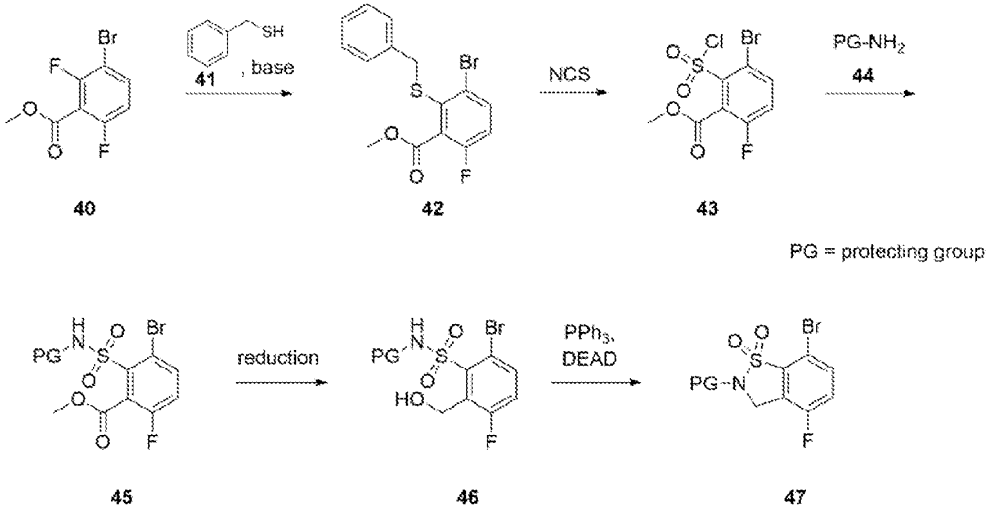
Scheme 8



37 **38** **39**

[000225] Dihydrobenzoisothiazole dioxide inputs may be readily prepared from commercially available 2-fluorobenzoate esters, Scheme 9. Nucleophilic displacement of the appropriate fluoride of **40** with phenylmethanethiol (**41**) after treatment with base (e.g., NaH) can yield thioethers **42**. Oxidation of thioether moiety of **42** (e.g., with NCS) can give rise to sulfonyl chlorides **43**. After reacting sulfonyl chlorides **43** with amines **44** (e.g., but not limited to, PG = benzyl or dimethoxylbenzyl) to furnish sulfonamides **45**, the ester functionality within compounds **45** can be reduced (e.g, with di-isobutylaluminum hydride) to give rise to primary alcohols **46**. Such sulfonamide-alcohol-containing species may then be cyclized (e.g., via standard Mitsunobu reaction conditions) to afford the requisite dihydrobenzoisothiazole dioxide inputs **47**.

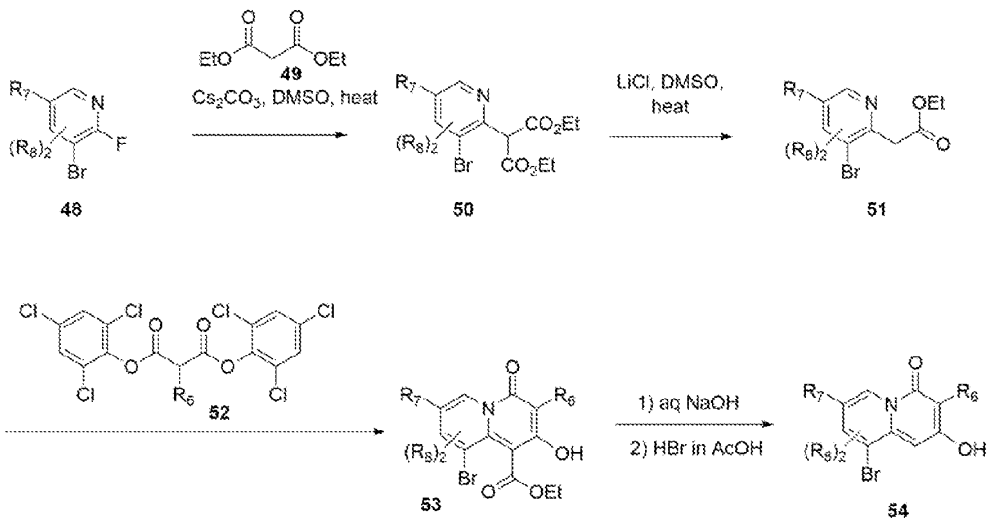
Scheme 9



[000226] The bicyclic cores of the present invention may be synthesized by cyclization methodologies, Scheme 10. The synthesis of pyridopyrimidinone core intermediates may begin with appropriately substituted 2-fluoropyridines **48**. In the case of **48**, where R_7 is methyl, this is commercially available. In other cases, the starting material may be prepared via established methods known to those skilled in the art. The addition of malonate functionality to **48** can be accomplished via base-mediated S_NAr reactions under standard conditions (e.g., Cs_2CO_3 and

heat). Subsequent decarboxylation of **50** to yield heteroarylacetic esters **51** can be accomplished under thermal conditions (e.g., LiCl at 100 °C). Esters **51** may then be condensed with aryl malonates **52** to give rise to carboxylate-substituted pyridopyrimidinone intermediates **53** (for a similar transformation, see Kappe, T., *et al.,* **1983**, 114, 349). Decarboxylations of **53** via acidic or basic conditions can yield hydroxyl-substituted pyridopyrimidinone intermediates **54**.

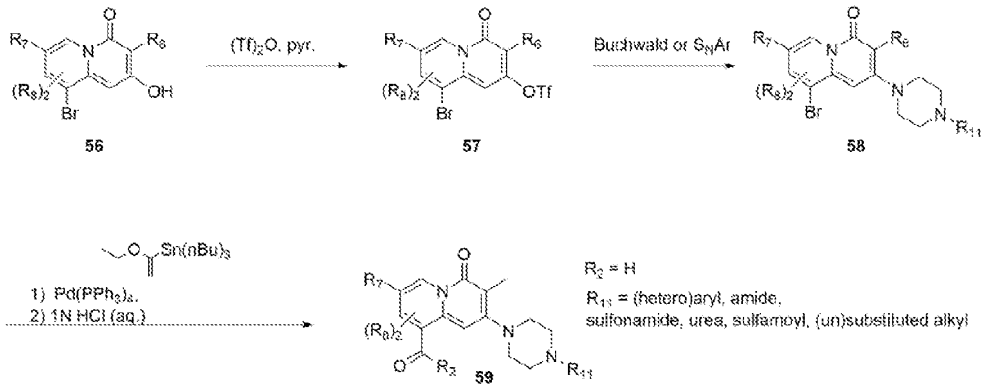
Scheme 10



[000227] Pyridopyridinones **56** can be functionalized in a number of ways to give rise to intermediates that enable the preparation of the compounds of the present invention; one such sequence is depicted in Scheme 11. The hydroxyl group of intermediates **56** may be converted to triflates **56**. Alternatively, the hydroxyl group of intermediates **56** can be converted to the corresponding halides (e.g., Cl) via treatment with the appropriate phosphoryl oxyhalide (e.g., phosphoryl oxychloride), resulting in intermediates that could be elaborated further as described for the analogous triflates **57**. Then, standard transition-metal-mediated couplings can be employed to selectively introduce side chains at the triflate position (e.g., Buchwald couplings with piperazine inputs) to yield **58**. To convert the bromide within compounds **58** to the ketones **59**, a Stille coupling reaction may be employed using an appropriate tin reagent such as (α-ethoxyvinyl)-tributyl tin followed by acid hydrolysis (Sugiyama, *et al.*, Bull. Chem. Soc. Jpn. **1987**, 60(2), 767-768). Alternatively, conversion of **58** to **59** may be accomplished by other established

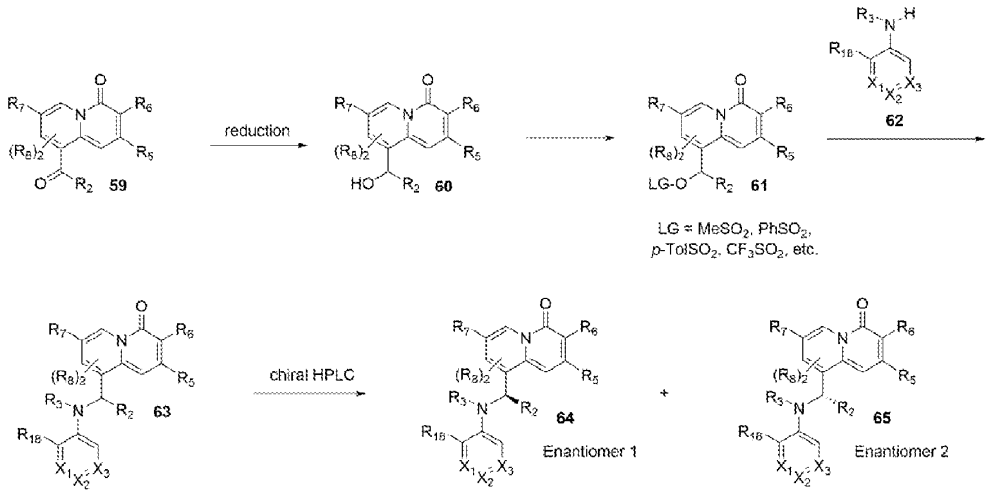
methods, for example using a Heck coupling reaction with an appropriate enol-ether followed by acid hydrolysis (Mingcui, L. *et al.*, Org. Biomol. Chem., **2010**, 8, 2012–2015). It should be understood that apart from the methodology described in Scheme 11, there are other reported methods that can be utilized to prepare pyridopyrimidinones (for example, see the following reports and references cited therein: Schwartz, A., *et al.,* J. Heterocyclic Chem. **1987**, 24, 645; Newkome, G., *et al.,* Heterocycles, **1988**, 2, 385; Kudak, S., *et al.,* J. Med. Chem. **2011**, 54, 4773; Zhao, D. *et al.*, Angew. Chem. Int. Ed. **2015**, 54, 4508; Zhou, X., *et al.*, Org. Lett. **2019**, 21, 9114).

Scheme 11



[000228] Ketone-substituted pyridopyridones like **59** may be transformed into the compounds of the present invention in any of a number of ways; one such way is depicted in Scheme 12. Reduction of the ketones **59** to alcohols **60** may then be accomplished by use of an appropriate hydride reducing agent (such as sodium borohydride). Subsequently, the alcohol group within compounds **60** can be activated for further functionalization via its conversion to a leaving group such as a mesylate (compounds **61**). Then, via S_N2 displacements with nucleophilic amines **62** under basic conditions can convert **61** to the corresponding benzyl amines **63**. Alternatively, should the nucleophilic amines be suitably activated via appropriate substitution patterns, such amines could be coupled directly with benzylic alcohols **60** to give the desired benzyl amines **63** (e.g., under Mitsunobu conditions). The individual stereoisomers of such amines **63** can be isolated after their separation via chiral chromatography methods (e.g., chiral HPLC).

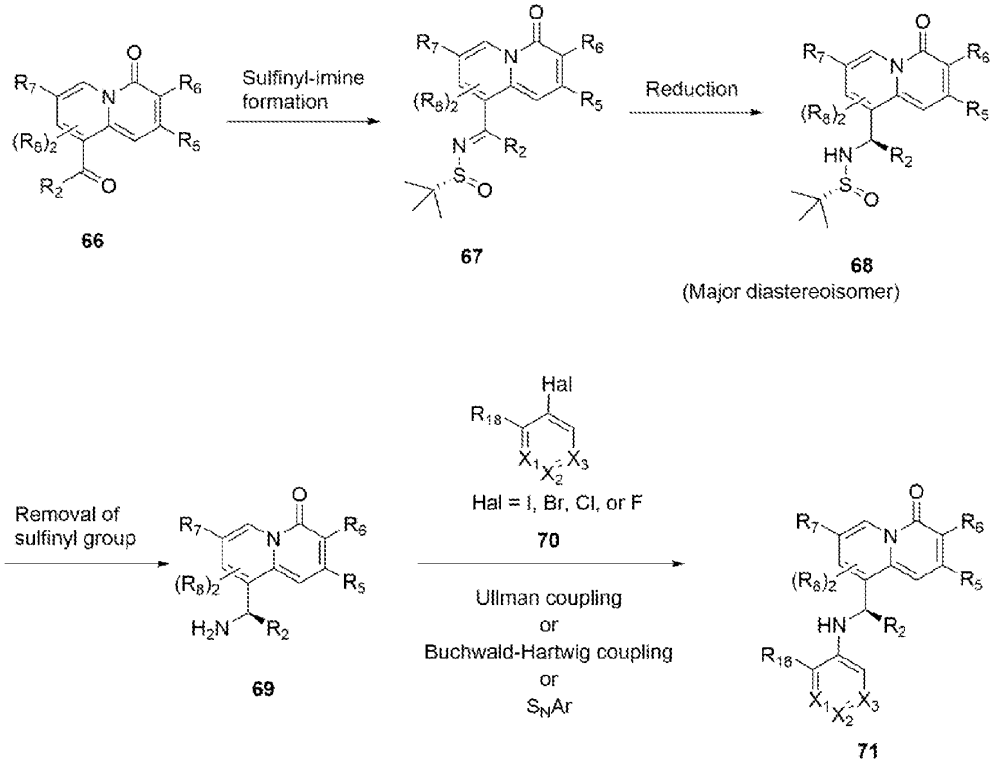
Scheme 12



[000229] A synthesis leading to a single enantiomer intermediate such as **71** is depicted in Scheme 13. This reaction sequence utilizes the formation of a chiral sulfinyl imine to control the stereochemistry. Such methods have been extensively reported. Ketones **66** may be converted to chiral sulfinyl-imines **67** via known procedures, which may then in turn be reduced to the sulfinyl-amines **68** in a stereo-controlled fashion using a suitable reducing agent (Datta and Ellman, J. Org. Chem. **2010**, 75, 6283–6285; Ellman *et al.*, Acc. Chem. Res. **2002**, 35, 984-995; Ellman *et al.*, J. Org. Chem. **2007**, 72, 626-629; Colyer *et al.*, Journal of Organic Chemistry **2006**, 71(18), 6859-6862). With use of the R isomer of the sulfinyl group, generally, resulting a predominantly the R, R – isomer of the product when (for example) the reducing agent used is a mixture of sodium borohydride and cerium chloride-heptahydrate. The use of this particular reducing system has been shown to be effective at reducing imines and may often give enhanced stereo-control in similar reductions (Hua *et al*, **Synthesis** 1991, (11), 970-4; Zhu *et al*, Journal of Chemical Research **2015**, 39(7), 390-393). The major isomer may be separated from the other minor isomer via standard chromatographic means. As has been demonstrated in the preceding literature references a judicious choice of the antipode of the sulfinyl-imine and the reducing agent may give access to either antipode of the sulfinyl-amine. The sulfinyl-amine can be cleaved to the single enantiomer of the chiral amine **69** using standard conditions (such as hydrogen chloride in dioxane). A standard coupling reaction of amine **69** with the (hetero)aryl halide **70** (such as an Ullman coupling or Buchwald-Hartwig coupling for **70**, Hal = I or Br) may

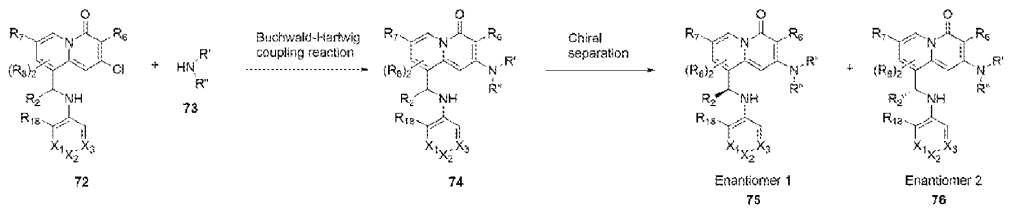
then give the resulting (hetero)aryl amine derivative **71** (Yang *et al*, Organic Process Research & Development **2022**, 26(6), 1690-1750; Surry and Buchwald, Chemical Science **2011**, 2(1), 27-50). Alternatively, S_NAr reactions with amines **69** with (hetero)aryl halides **70** may also give rise to intermediates **71** should the inputs **70** be reactive enough (e.g., Hal = F or Cl and R_1 be an electron-withdrawing functionality).

Scheme 13



[000230] Certain final compounds **74-76** may be prepared as outlined in Scheme 14. Intermediates **72** may be reacted under suitable Buchwald-Hartwig coupling conditions with an amine **73**, wherein R' and R" may be either alkyl or aryl or one of R' and R" may be hydrogen. R' and R" may also be joined to form a ring. In some cases, the R' and/or R" groups may be further elaborated prior to subsequent steps. The racemic compounds **74** may then be separated into individual enantiomers (**75** and **76**) utilizing chiral chromatography (HPLC or SFC).

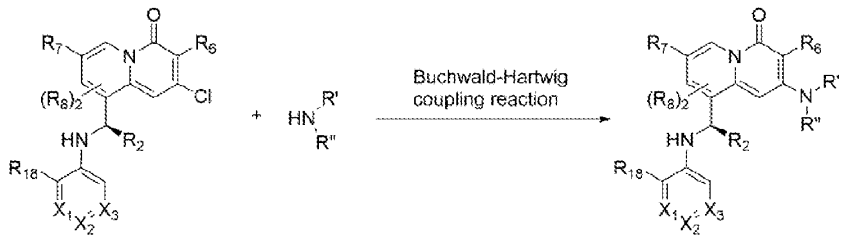
Scheme 14



72 73 74 75 76

[000231] Single enantiomers **78** may be prepared directly as shown in Scheme 15 from the enantiomerically pure intermediates **77** using chemistry analogous to that shown in Scheme 15.

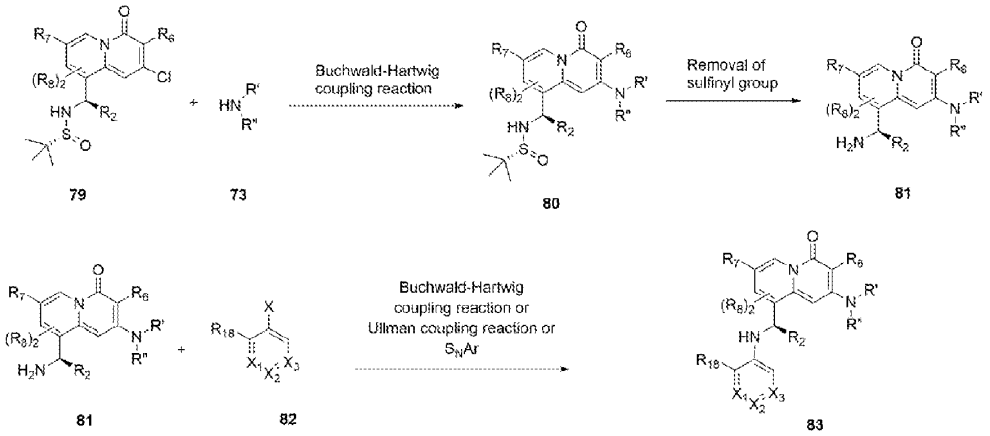
Scheme 15



77 73 78

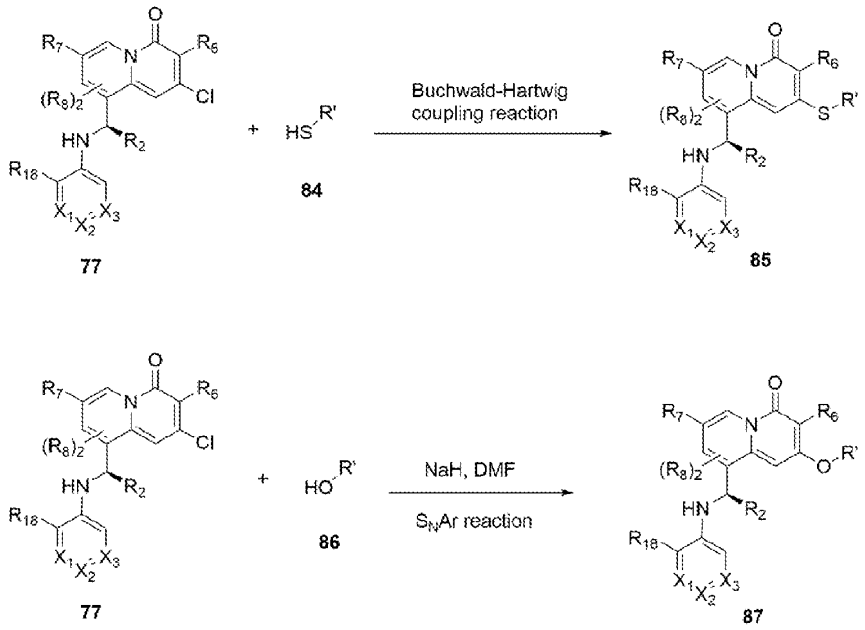
[000232] In some cases, the order of reactions may be adjusted as shown in Scheme 16. In this case a Buchwald-Hartwig coupling with the intermediates **79** and appropriately substituted amines **73** can give **80**. Removal of the sulfinyl group to give **81** may then be followed by a Buchwald-Hartwig coupling with (hetero)arylhalides **82** (e.g., X = I or Br) to give compounds such as **83**. Alternatively, intermediate **81** may undergo an S_NAr reaction with suitably reactive (hetero)arylhalides **82** (e.g., X = F or Cl with R_1 being an electron-withdrawing group) to give compounds **83**.

Scheme 16



[000233] Compounds where there is an oxygen- or sulfur-linked substitution from the 2-position of the pyridopyrimidinone ring may be prepared as shown in Scheme 17. The intermediate **77** may undergo a Buchwald-Hartwig coupling with an appropriate sulfhydryl compound to give **85**. Alternatively intermediate **77** may undergo an S_NAr reaction with an appropriate alcohol (this reaction may be mediated by a base, for example, sodium hydride) to give compounds such as **87**.

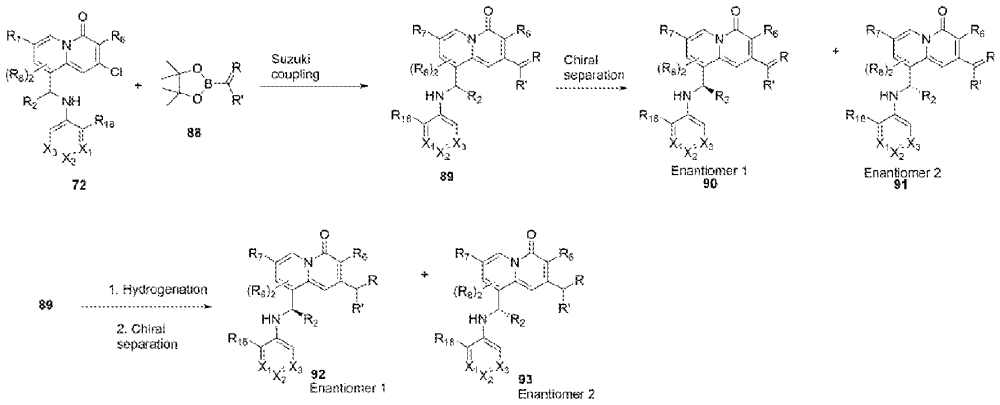
Scheme 17



77 84 85 77 86 87

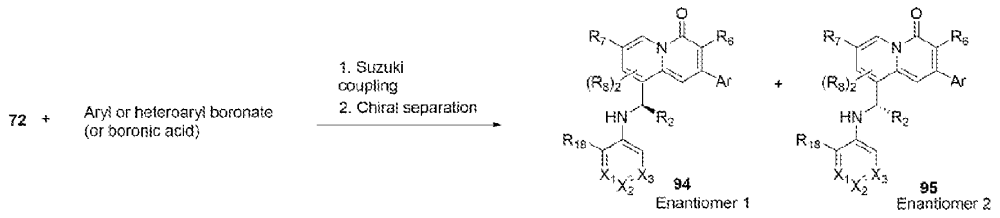
[000234] In the cases where the substitution from the 2-position of the pyridopyrimidinone ring system is either an alkyl or an alkenyl group, these compounds may be prepared as shown in Scheme 18. The intermediate **72** may undergo a Suzuki coupling reaction (Stanforth, S.P. Tetrahedron **1998**, 54(3/4), 263-303) with suitable alkenyl-boronates **88** (or, alternatively, corresponding boronic acids) to give **89**. The racemate **89** may then be subjected to chiral chromatographic separation to give the enantiomers **90** and **91**. Alternatively the double bond of **89** may be reduced under standard hydrogenation conditions (e.g., hydrogen with a palladium catalyst). Following chiral chromatographic separation this may give the enantiomers **92** and **93**. In the case where R and R' do not form a symmetrical arrangement, further isomers may result which may also be separated chromatographically.

Scheme 18



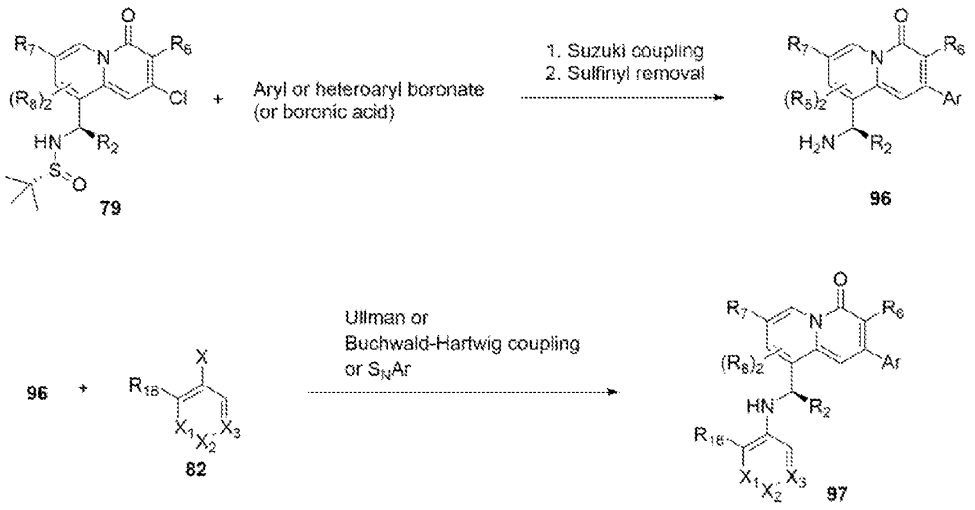
[000235] In the case where the substitution from the 2-position of the pyridopyrimidinone group is an aryl or heteroaryl group, these types of compounds may be prepared in an analogous method to that shown in Scheme 18. As depicted in Scheme 19, a Suzuki coupling reaction between **72** and an appropriate aryl (or heteroaryl) bononate (or boronic acid) may give, following chiral separation, the enantiomers **94** and **95**.

Scheme 19



[000236] An alternative mode of synthesis of aryl- or heteroaryl-substituted pyridopyrimidinones is depicted in Scheme 20. A Suzuki coupling reaction between intermediates **79** and appropriate aryl or heteroaryl boronates (or boronic acids) followed by removal of the sulfinyl group can yield intermediates **96**. An Ullman or Buchwald-Hartwig coupling between amines **95** and (hetero)arylhalides **82** may give compounds such as **97**. Alternatively, amines **96** may undergo an S_NAr reactions with suitably substituted (hetero)arylhalides **82** (e.g., where X = F or Cl and R_1 is an electron-withdrawing group) to also give compounds **97**.

Scheme 20



[000237] The chemistries depicted in Schemes 1 to 20 demonstrate various modes of synthesis of the compounds described. It should be understood that other variations on these modes may be employed and that the precise protecting groups, the order of the listed reactions or the particular transition metals used in the catalyzed coupling reaction may be replaced with suitable alternatives that would be known to those skilled in the art.

Experimental

[000238] All commercially available solvents and reagents were used as received. All ^{1}H NMR spectra were recorded using a Bruker Avance III HD 300 MHz or Bruker Avance III HD 400 MHz. MS samples were analyzed on a Shimadzu LCMS-2020 mass spectrometer with electrospray ionization operating in positive and negative ion mode. Samples were introduced into the mass spectrometer using chromatography. All final products had a purity of ≥ 90 %, unless specified otherwise in the experimental details. HPLC purity was measured on a Shimadzu Acquity HPLC system.

[000239] The following represents acronyms used in the experimental section for well-known chemical solvents, reagents, parameters and techniques:

^{1}H NMR: proton nuclear magnetic resonance spectroscopy

Ac_2O: acetic anhydride

ACN: acetonitrile

AcOH: acetic acid

BINAP: 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl

c-Bu: cyclobutyl

c-Pr: cyclopropyl

CDI: carbonyl diimidazole

$CeCl_3$: cerium (III) chloride

CH_2Cl_2: dichloromethane

CH_3I: iodomethane

$CHCl_3$: chloroform

CH_3CN: acetonitrile

CO_2: carbon dioxide

Cs_2CO_3: cesium carbonate

CsF: cesium fluoride

CuI: copper iodide

Cu_2O: copper oxide

DBAD: di-*tert*-butyl azodicarboxylate

DBU: 1,8-Diazabicyclo[5.4.0]undec-7-ene

DCM: dichloromethane

DIBAL: diisobutylaluminum hydride

DIEA: *N,N*-diisopropylethylamine

DIPEA: *N,N*-diisopropylethylamine

DMA: *N,N*-dimethylacetamide

DMF: *N,N*-dimethylformamide

DMSO: dimethyl sulfoxide

DTAD: di-tert-butyl azodicarboxylate

EA: ethyl acetate

ee: enantiomeric excess

Et_2O: diethyl ether

Et_3N: triethylamine

Et_3SiH: triethylsilane

EtOAc: ethyl acetate

EtOH: ethanol

FA: formic acid

h: hours

H_2O: water

HATU: 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate

HBr: hydrobromic acid

HCl: hydrochloric acid

Hex: hexanes

HPLC: high-performance liquid chromatography

IPA: isopropanol

K_2CO_3: potassium carbonate

K_3PO_4: potassium triphosphate

KOAc: potassium acetate

LCMS: liquid chromatography mass spectrometry

LiCl: lithium chloride

LiOH: lithium hydroxide

*m*CPBA: *meta*-chloroperoxybenzoic acid

Me: methyl

MeCN: acetonitrile

MeOH: methanol

mg: milligram

$MgSO_4$: magnesium sulfate

min: minutes

mL: milliliter

MsCl: methanesulfonyl chloride

Ms_2O: methanesulfonic anhydride

$NaBH_4$: sodium borohydride

N_2: nitrogen

NaCl: sodium chloride

Na_2CO_3: sodium carbonate

NaH: sodium hydride

NaI: sodium iodide

NaOH: sodium hydroxide

$NaHCO_3$: sodium bicarbonate

NaH_2PO_4: monosodium phosphate

Na_2SO_3: sodium sulfite

Na_2SO_4: sodium sulfate

NH_3: ammonia

NH_4Cl: ammonium chloride

NH_4HCO_3: ammonium bicarbonate

NH_4OH: ammonium hydroxide

$(NH_4)_2CO_3$: ammonium carbonate

NMP: *N*-methylpyrrolidone

Oxetane: 4-membered ring containing 3 carbon ring atoms and 1 oxygen ring atom.

PBr_3: phosphorous tribromide

PCl_5: phosphorous pentachloride

Pd/C: palladium on carbon

Pd-PEPPSI-IHeptCl 3-chloropyridine: dichloro[1,3-bis(2,6-di-4-heptylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium(II)

$Pd(dppf)Cl_2$: (1,1'-bis(diphenylphosphino)ferrocene)palladium(II) dichloride

$Pd(PPh_3)_4$: tetrakis(triphenylphosphine)palladium(0)

$Pd_2(dba)_3$: tris(dibenzylideneacetone)dipalladium(0)

$PdCl_2(PPh_3)_2$: bis(triphenylphosphine)palladium(II) dichloride

PE: petroleum ether

$POCl_3$: phosphorus oxychloride

PPh_3: triphenylphosphine

Prep: preparative

PyBOP: benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate

RuPhos: 2-dicyclohexylphosphino-2',6'-diisopropoxybiphenyl

RuPhos-Pd-G3: methanesulfonato(2-dicyclohexylphosphino-2',6'-di-isopropoxy-1,1'-biphenyl)(2'-amino-1,1'-biphenyl-2-yl)palladium(II)

SEM-Cl: 2-(trimethylsilyl)ethoxymethyl chloride

SiO_2: silica

TBAF: tetrabutylammonium fluoride

TBAI: tetrabutylammonium iodide (See scheme 5)

TBSCl: tert-butyldimethylsilyl chloride

TEA: triethylamine

TFA: trifluoroacetic acid

THF: tetrahydrofuran

$Ti(OEt)_4$: titanium (IV) ethoxide

$Ti(Oi\text{-}Pr)_4$: titanium(IV) isopropoxide

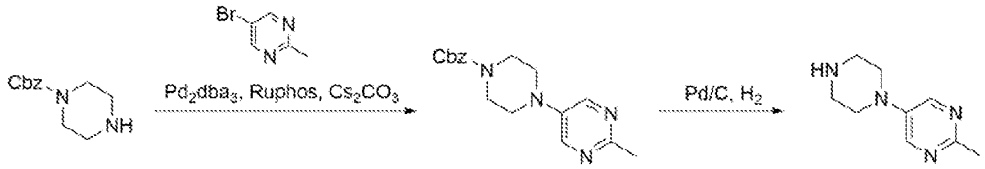
TLC: thin-layer chromatography

Xantphos: 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene

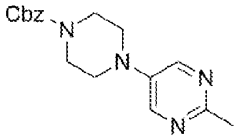
Xphos-Pd-G4: (SP-4-3)-[Dicyclohexyl[2',4',6'-tris(1-methylethyl)[1,1'-biphenyl]-2-yl]phosphine](methanesulfonato-κO)[2'-(methylamino-κN)[1,1'-biphenyl]-2-yl-κC]palladium

$Zn(CN)_2$: zinc cyanide

[000240] **Intermediate 1:** 2-methyl-5-(piperazin-1-yl)pyrimidine



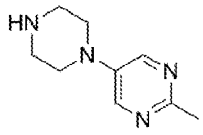
Step 1: Preparation of benzyl 4-(2-methylpyrimidin-5-yl)piperazine-1-carboxylate



[000241] To a stirred mixture of 5-bromo-2-methylpyrimidine (2.0 g, 11.5 mmol) and benzyl piperazine-1-carboxylate (2.0 g, 8.9 mmol) in toluene (30.0 mL) were added Cs_2CO_3 (5.8 g, 17.8 mmol), tris(dibenzylideneacetone)dipalladium(0) (1.6 g, 1.8 mmol) and RuPhos (0.8 g, 1.8 mmol) at room temperature. The resulting mixture was stirred for overnight at 100 °C under a nitrogen atmosphere. The reaction was diluted with water (40 mL) at room temperature and the resulting mixture was extracted with EtOAc (2 × 40 mL). The combined organic phases were washed with

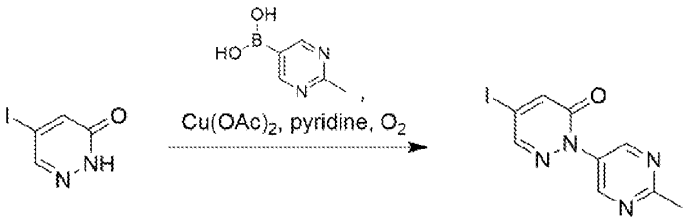
brine and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2:MeOH, to afford benzyl 4-(2-methylpyrimidin-5-yl)piperazine-1-carboxylate (2.0 g, 72 % yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.40 (s, 2H), 7.38 (d, J = 4.3 Hz, 4H), 7.37 – 7.28 (m, 1H), 5.11 (s, 2H), 3.59 – 3.51 (m, 4H), 3.24 – 3.16 (m, 4H), 2.49 (s, 3H).

Step 2: Preparation of 2-methyl-5-(piperazin-1-yl)pyrimidine

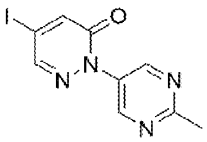


[000242] To a stirred mixture of benzyl 4-(2-methylpyrimidin-5-yl)piperazine-1-carboxylate (2.0 g, 6.4 mmol) in MeOH (30 mL) was added 10% Pd/C (500 mg, 4.7 mmol) at room temperature. The resulting mixture was stirred for 2 h at room temperature under a hydrogen atmosphere. The resulting mixture was filtered, the filter cake was washed with MeOH (3 x 10 mL). The filtrate was concentrated under reduced pressure to afford 2-methyl-5-(piperazin-1-yl)pyrimidine (900 mg, 79% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.35 (s, 2H), 3.11 – 3.04 (m, 4H), 2.87 – 2.78 (m, 4H), 2.48 (s, 3H).

[000243] **Intermediate 2:** 5-iodo-2-(2-methylpyrimidin-5-yl)pyridazin-3(2H)-one

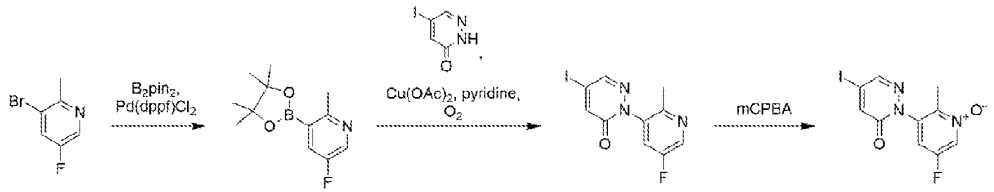


Step 1: Preparation of 5-iodo-2-(2-methylpyrimidin-5-yl)pyridazin-3(2H)-one

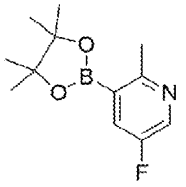


[000244] In two batches run in parallel, mixtures of 4-iodo-1H-pyridazin-6-one (2.5 g, 11.3 mmol), (2-methylpyrimidin-5-yl) boronic acid (4.66 g, 33.8 mmol), $Cu(OAc)_2$ (20.5 g, 113 mmol), and pyridine (8.91 g, 113 mmol, 9.1 mL) in DCE (300 mL) were degassed and purged with nitrogen three times. The two mixtures were then stirred at 60 °C for 12 h under an oxygen (15 psi) atmosphere. The reaction mixtures were then filtered, combined, and concentrated under reduced pressure to give a residue. The residue was diluted with DCM (200 mL) and washed with 10% aqueous ammonium hydroxide (5 x 30 mL). The organic phase was then dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a crude product. The crude product was triturated with PE:EA = 1:1 (30 mL) at 25 °C for 10 min to afford 5-iodo-2-(2-methylpyrimidin-5-yl)pyridazin-3(2H)-one (5.04 g, 59% yield) as an off-white solid. LCMS: (ESI^+) m/z = 314.8 (M+H).

[000245] **Intermediate 3:** 5-fluoro-3-(4-iodo-6-oxopyridazin-1(6H)-yl)-2-methylpyridine 1-oxide



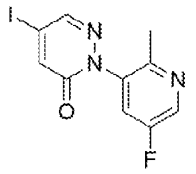
Step 1: Preparation of 5-fluoro-2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine



[000246] To a solution of 3-bromo-5-fluoro-2-methyl-pyridine (4.5 g, 23.7 mmol) and bis(pinacolato)diboron (6.62 g, 26.1 mmol) in dioxane (50 mL) was added KOAc (6.97 g, 71.1 mmol) and $Pd(dppf)Cl_2$ (3.47 g, 4.74 mmol). The mixture was stirred at 70 °C for 16 h under a nitrogen atmosphere. The resulting mixture was then partitioned between EA (500 mL) and water (500 mL). The organic phase was separated, washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The

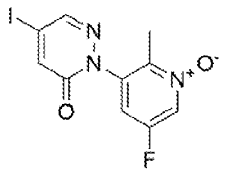
residue was purified by column chromatography (PE: EA = 50:1 to 15:1) to afford 5-fluoro-2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (5.2 g, 92% yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.48 – 8.26 (m, 1H), 7.85 – 7.61 (m, 1H), 2.72 (s, 3H), 1.36 (s, 12H).

Step 2: Preparation of 2-(5-fluoro-2-methyl-3-pyridyl)-5-iodo-pyridazin-3-one



[000247] A mixture of 5-fluoro-2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (5.0 g, 21.1 mmol), 4-iodo-1H-pyridazin-6-one (4.26 g, 19.2 mmol), $Cu(OAc)_2$ (6.96 g, 38.4 mmol), isoquinolin-6-ol (0.56 g, 3.83 mmol), TEA (19.4 g, 192 mmol, 26.7 mL), Na_2SO_4 (27.2 g, 192 mmol) and boric acid (5.93 g, 95.9 mmol) in DCE (50 mL) was degassed and purged with oxygen three times. The mixture was then stirred at 50 °C for 5 h, then filtered and the filtrate was partitioned between DCM (500 mL) and saturated aqueous $NaHCO_3$ (500 mL). The organic phase was separated, washed with brine (500 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (PE:EA = 50:1 to 8:1) to afford 2-(5-fluoro-2-methyl-3-pyridyl)-5-iodo-pyridazin-3-one (2.4 g, 37% yield) as a yellow solid. LCMS: (ESI^+) m/z = 332.0 (M+H).

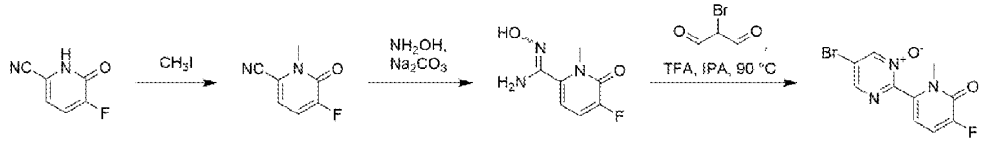
Step 3: Preparation of 5-fluoro-3-(4-iodo-6-oxopyridazin-1(6H)-yl)-2-methylpyridine 1-oxide



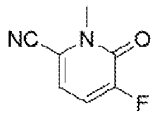
[000248] In two batches run in parallel, m-CPBA (85% purity, 2.02 g, 9.95 mmol) was added to a 0 °C mixture of 2-(5-fluoro-2-methyl-3-pyridyl)-5-iodo-pyridazin-3-one (1.9 g, 5.74 mmol) in DCM (30 mL) in portions. The mixture was then stirred at 25 °C for 12 h. To the mixture was then added saturated aqueous $NaHSO_3$ (50 mL) and the resulting mixture was stirred for 10 min. The mixture was then partitioned between DCM (200 mL) and water (200 mL). The organic phase

was separated, washed with brine (200 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was suspended in DMF (10 mL) and the precipitate was filtered off. The filtrate was then purified by prep-HPLC (column: Phenomenex luna C18 (250 x 70 mm, 10 μm); mobile phase: [H_2O (0.225% FA)-ACN]; gradient: 1%-30% B over 26 min) to afford 5-fluoro-3-(4-iodo-6-oxopyridazin-1(6H)-yl)-2-methylpyridine 1-oxide (1.53 g, 38% yield) as a yellow solid. LCMS: (ESI^+) m/z = 347.8 (M+H).

[000249] **Intermediate 4:** 5-bromo-2-(5-fluoro-1-methyl-6-oxo-1,6-dihydropyridin-2-yl)pyrimidine 1-oxide

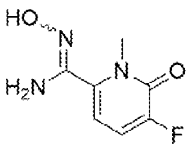


Step 1: Preparation of 5-fluoro-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile



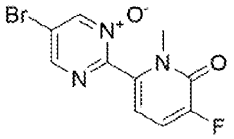
[000250] To a mixture of 5-fluoro-6-oxo-1H-pyridine-2-carbonitrile (10 g, 72.4 mmol) and K_2CO_3 (20.0 g, 145 mmol) in ACN (100 mL) was added iodomethane (15.4 g, 109 mmol). The mixture was stirred at 25 °C for 12 h and then the mixture was poured into ice water (100 mL) and stirred for 3 min. The mixture was then extracted three times with ethyl acetate (50 mL each). The organics were combined and washed with brine (30 mL x 2), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (PE:EA = 100:1 to 3:1) to afford 5-fluoro-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile (7.5 g, 68% yield) as a white solid. LCMS: (ESI^+) m/z = 153.1 (M+H).

Step 2: Preparation of 5-fluoro-N'-hydroxy-1-methyl-6-oxo-1,6-dihydropyridine-2-carboximidamide



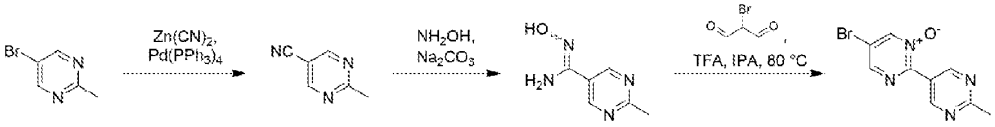
[000251] To a solution of 5-fluoro-1-methyl-6-oxo-pyridine-2-carbonitrile (7.5 g, 49.3 mmol) in ethanol (75 mL) was added TEA (24.9 g, 247 mmol) and hydroxylamine hydrochloride (10.3 g, 148 mmol). The mixture was stirred at 80 °C for 0.5 h and then concentrated under reduced pressure. The residue was suspended in water (20 mL) and the resulting precipitate was collected by filtration to afford 5-fluoro-N'-hydroxy-1-methyl-6-oxo-1,6-dihydropyridine-2-carboximidamide (7.2 g, 78% yield) as a white solid. LCMS: (ESI$^+$) m/z = 186.0 (M+H).

Step 3: Preparation of 5-bromo-2-(5-fluoro-1-methyl-6-oxo-1,6-dihydropyridin-2-yl)pyrimidine 1-oxide

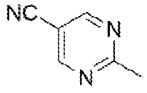


[000252] In fourteen batches run in parallel, trifluoroacetic acid (369 mg, 3.24 mmol, 0.24 mL) was added to a mixture of 5-fluoro-N'-hydroxy-1-methyl-6-oxo-1,6-dihydropyridine-2-carboximidamide (500 mg, 2.70 mmol) and 2-bromopropanedial (611 mg, 4.05 mmol) in IPA (15 mL). The resulting mixture was stirred at 90 °C for 2 h and then concentrated under reduced pressure. The residue was purified by silica gel chromatography (PE:EA = 3:1 to 0:1) to afford 5-bromo-2-(5-fluoro-1-methyl-6-oxo-1,6-dihydropyridin-2-yl)pyrimidine 1-oxide (6.2 g, 55% yield) as a white solid. LCMS: (ESI$^+$) m/z = 300.0 (M+H).

[000253] **Intermediate 5:** 5-bromo-2'-methyl-[2,5'-bipyrimidine] 1-oxide



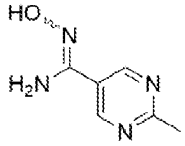
Step 1: Preparation of 2-methylpyrimidine-5-carbonitrile



[000254] In two batches run in parallel, a mixture of 5-bromo-2-methyl-pyrimidine (25.0 g, 145 mmol), $Zn(CN)_2$ (23.9 g, 204 mmol), and $Pd(PPh_3)_4$ (16.7 g, 14.5 mmol) in DMF (150 mL) was stirred under a nitrogen atmosphere at 110 °C for 12 h and then was partitioned between

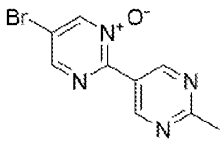
saturated aqueous $NaHCO_3$ (200 mL) and DCM (100 mL). The aqueous phase was then further extracted with DCM (100 mL x 2). The combined organics were washed with brine (50 mL x 2), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by silica gel chromatography (PE:EA = 10:1 to 5:1) to afford 2-methylpyrimidine-5-carbonitrile (21.7 g, 62% yield) as a white solid. LCMS: (ESI^+) m/z = 120.1 (M+H).

Step 2: Preparation of N'-hydroxy-2-methylpyrimidine-5-carboximidamide



[000255] To a mixture of 2-methylpyrimidine-5-carbonitrile (21.7 g, 182 mmol) and TEA (92.2 g, 911 mmol, 127 mL) in EtOH (200 mL) was added hydroxylamine hydrochloride (38.0 g, 547 mmol) at 25 °C. The resulting mixture was then stirred at 80 °C for 2 h and then concentrated under reduced pressure to give a residue. The residue was triturated with water (20 mL) at 100 °C for 10 min and the resulting precipitate was collected by filtration and dried to afford N'-hydroxy-2-methylpyrimidine-5-carboximidamide (18.2 g, 66% yield) as white solid. LCMS: (ESI^+) m/z = 153.0 (M+H).

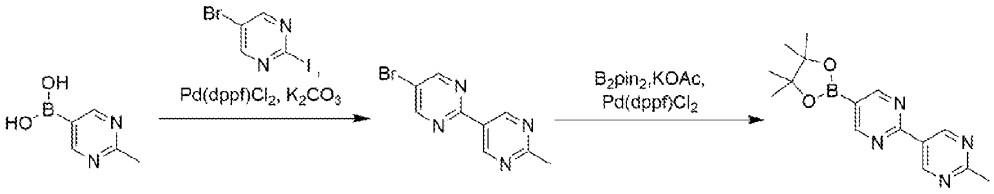
Step 3: Preparation of 5-bromo-2'-methyl-[2,5'-bipyrimidine] 1-oxide



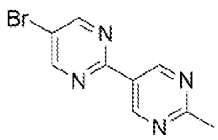
[000256] In twenty-four batches run in parallel, 2-bromopropanedial (595 mg, 3.94 mmol) was added to a mixture of N'-hydroxy-2-methylpyrimidine-5-carboximidamide (0.5 g, 3.29 mmol) and TFA (674 mg, 5.92 mmol, 0.44 mL) in IPA (15 mL) at 25 °C. The resulting mixtures were heated to 80 °C for 2 h, then cooled to room temperature and quenched with saturated aqueous $NaHCO_3$ (20 mL) and extracted with DCM (20 mL x 3). The combined organics were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residues were triturated with EtOAc (20 mL) at 25 °C for 10 min and the

precipitates were collected by filtration, combined, and dried to afford 5-bromo-2'-methyl-[2,5'-bipyrimidine] 1-oxide (9.3 g, 41% yield) as a yellow solid. LCMS: (ESI$^+$) m/z = 268.9 (M+H).

[000257] **Intermediate 6:** 2'-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,5'-bipyrimidine

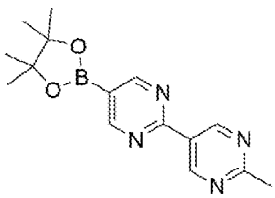


Step 1: Preparation of 5-bromo-2'-methyl-2,5'-bipyrimidine



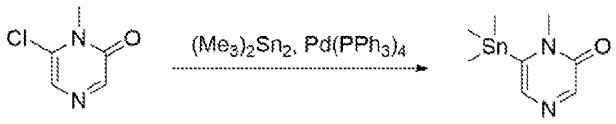
[000258] To a stirred mixture of 2-methylpyrimidin-5-ylboronic acid (1 g, 7.25 mmol) and 5-bromo-2-iodopyrimidine (2.07 g, 7.25 mmol) in dioxane (15 mL) and H_2O (3 mL) were added $Pd(dppf)Cl_2$ (0.53 g, 0.73 mmol) and K_2CO_3 (3.01 g, 21.8 mmol) in portions at room temperature under a nitrogen atmosphere. The resulting mixture was stirred for 2 h at 80 °C and then was filtered and the filter cake was washed with ethyl acetate (3 x 10 mL). The filtrate was concentrated under reduced pressure and the resulting residue was purified by silica gel chromatography (eluted with PE:EA = 1:1) to afford 5-bromo-2'-methyl-2,5'-bipyrimidine (1.2 g, 67% yield) as a brown solid. LCMS: (ESI$^+$) m/z = 251.0 (M+H).

Step 2: Preparation of 2'-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,5'-bipyrimidine

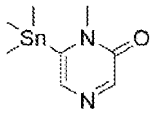


[000259] To a stirred mixture of 5-bromo-2'-methyl-2,5'-bipyrimidine (400 mg, 1.59 mmol) and bis(pinacolato)diboron (607 mg, 2.39 mmol) in dioxane (10 mL) were added $Pd(dppf)Cl_2$ (117 mg, 0.16 mmol) and KOAc (469 mg, 4.78 mmol) in portions at room temperature under a nitrogen atmosphere. The resulting mixture was stirred for 2 h at 100 °C. The resulting mixture was then filtered and the filter cake was washed with CH_2Cl_2 (3 x 20 mL). The filtrate was concentrated under reduced pressure to afford 2'-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,5'-bipyrimidine (400 mg, 84% crude yield) which was used directly in the next step without further purification. LCMS: (ESI^+) m/z = 299.1 (M+H).

[000260] **Intermediate 7:** 1-methyl-6-(trimethylstannyl)pyrazin-2(1H)-one

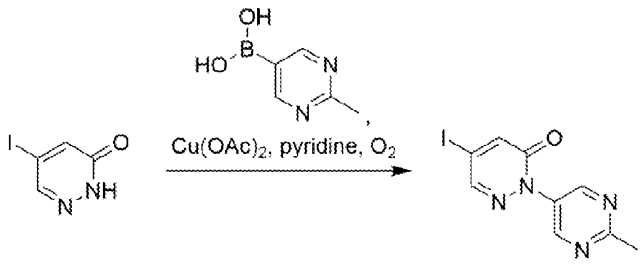


Step 1: Preparation of 1-methyl-6-(trimethylstannyl)pyrazin-2(1H)-one



[000261] A solution of 6-chloro-1-methylpyrazin-2-one (500 mg, 3.46 mmol) in dioxane (5 mL) was treated with $Pd(PPh_3)_4$ (799 mg, 0.69 mmol) at room temperature under a nitrogen atmosphere, followed by the dropwise addition of hexamethylditin (3.40 g, 10.4 mmol). The resulting mixture was stirred at 100 °C overnight and then concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography (C18 silica gel; mobile phase of MeCN in water, 0% to 70% gradient over 30 min) to afford 1-methyl-6-(trimethylstannyl)pyrazin-2-one (300 mg, 32% yield) as a light yellow oil. LCMS: (ESI^+) m/z = 275.0 (M+H).

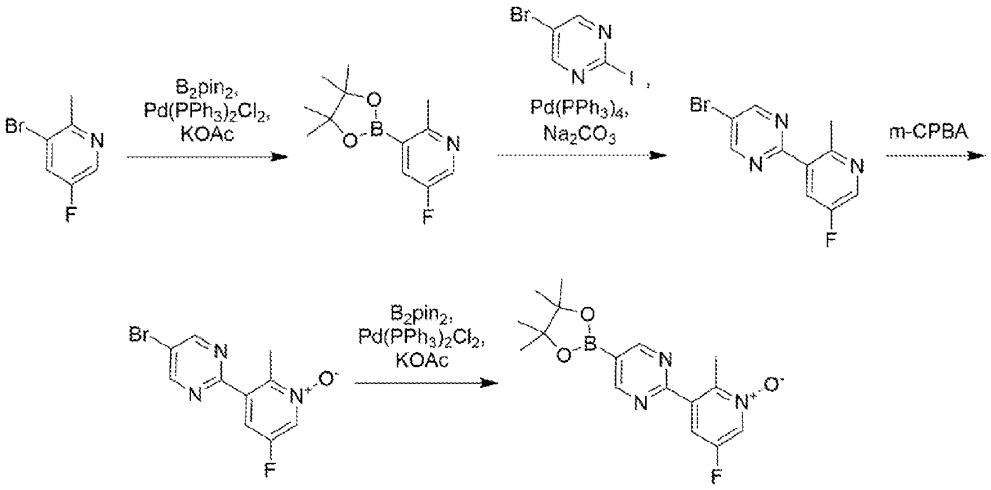
[000262] **Intermediate 8:** 5-iodo-2-(2-methylpyrimidin-5-yl)pyridazin-3(2H)-one



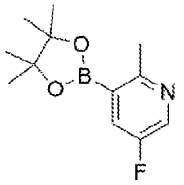
Step 1: Preparation of 5-iodo-2-(2-methylpyrimidin-5-yl)pyridazin-3(2H)-one

[000263] Copper(II) acetate (4.50 g, 24.8 mmol) and pyridine (1.96 g, 24.8 mmol) was added to a room temperature mixture of 2-methylpyrimidin-5-ylboronic acid (1.03 g, 7.43 mmol) and 5-iodo-2H-pyridazin-3-one (550 mg, 2.48 mmol) in DCM (10 mL). The resulting mixture was stirred at 60 °C for 12 h under an oxygen atmosphere, and then was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography (C18 silica gel; mobile phase of MeCN in water (10 mmol/L NH_4HCO_3), 10% to 50% gradient over 10 min) to afford 5-iodo-2-(2-methylpyrimidin-5-yl)pyridazin-3(2H)-one (250 mg, 32% yield) as a light yellow solid. LCMS: (ESI^+) m/z = 315.4 (M+H).

[000264] **Intermediate 9:** 5-fluoro-2-methyl-3-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidin-2-yl)pyridine 1-oxide

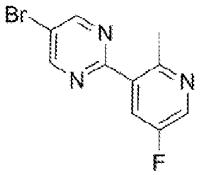


Step 1: Preparation of 5-fluoro-2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine



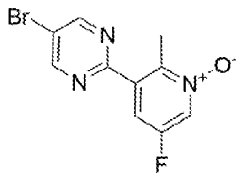
[000265] A mixture of 3-bromo-5-fluoro-2-methylpyridine (200 mg, 1.05 mmol) in dioxane (6 mL) at room temperature under a nitrogen atmosphere was treated with bis(pinacolato)diboron (400 mg, 1.58 mmol), followed by the addition of KOAc (155 mg, 1.58 mmol) and $Pd(dppf)Cl_2$ (86 mg, 0.11 mmol). The resulting mixture was stirred at 100 °C for 0.5 h and then cooled to room temperature and filtered. The filtrate was concentrated under reduced pressure to afford 5-fluoro-2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (200 mg crude yield) which was used directly in the next step without further purification. LCMS: (ESI^+) m/z = 238.0 (M+H).

Step 2: Preparation of 5-bromo-2-(5-fluoro-2-methylpyridin-3-yl)pyrimidine



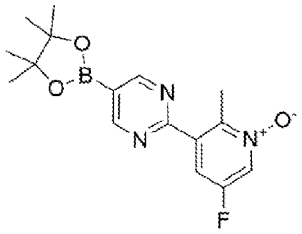
[000266] A mixture of 5-fluoro-2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (200 mg, 0.84 mmol) in dioxane (6 mL) and H_2O (1.2 mL)) at room temperature under a nitrogen atmosphere was treated with 5-bromo-2-iodopyrimidine (240 mg, 0.84 mmol), Na_2CO_3 (179 mg, 1.68 mmol), and $Pd(PPh_3)_4$ (97 mg, 0.08 mmol). The resulting mixture was stirred at 100 °C for 3 h, then filtered and the filter cake was washed with EtOAc (3 x 10 mL). The filtrate was concentrated under reduced pressure and the residue was purified by prep-TLC (100% EA) to afford 5-bromo-2-(5-fluoro-2-methylpyridin-3-yl)pyrimidine (150 mg, 69% yield) as an off-white solid. LCMS: (ESI^+) m/z = 269.9 (M+H).

Step 3: Preparation of 3-(5-bromopyrimidin-2-yl)-5-fluoro-2-methylpyridine 1-oxide



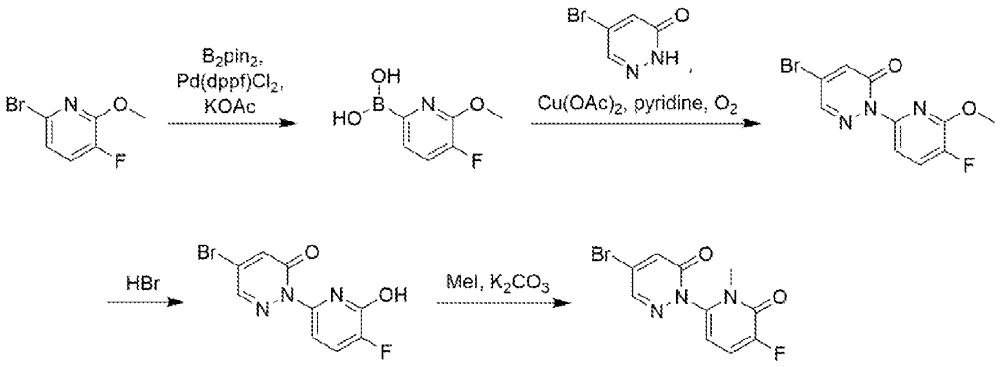
[000267] A mixture of 5-bromo-2-(5-fluoro-2-methylpyridin-3-yl)pyrimidine (110 mg, 0.41 mmol) in DCM (2 mL) was treated with m-CPBA (106 mg, 0.61 mmol) at 0 °C. The resulting mixture was stirred overnight at room temperature and then concentrated under reduced pressure. The residue was purified by prep-TLC (100% EA) to afford 3-(5-bromopyrimidin-2-yl)-5-fluoro-2-methylpyridine 1-oxide (70 mg, 60% yield) as an off-white solid. LCMS: (ESI$^+$) m/z = 284.0 (M+H).

Step 4: Preparation of 5-fluoro-2-methyl-3-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidin-2-yl)pyridine 1-oxide

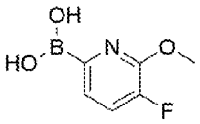


[000268] A mixture of 3-(5-bromopyrimidin-2-yl)-5-fluoro-2-methylpyridine 1-oxide (200 mg, 0.70 mmol) in dioxane (6 mL) at room temperature under a nitrogen atmosphere was treated with bis(pinacolato)diboron (268 mg, 1.06 mmol), KOAc (138 mg, 1.41 mmol) and Pd(dppf)Cl_2 (52 mg, 0.070 mmol). The resulting mixture was stirred at 100 °C for 1 h and then filtered and concentrated under reduced pressure to afford 5-fluoro-2-methyl-3-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidin-2-yl)pyridine 1-oxide (~200 mg crude yield) which was used directly in the next step without further purification. LCMS: (ESI$^+$) m/z = 332.2 (M+H).

[000269] **Intermediate 10:** 5-bromo-2-(5-fluoro-1-methyl-6-oxo-1,6-dihydropyridin-2-yl)pyridazin-3(2H)-one

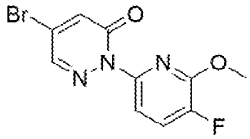


Step 1: Preparation of (5-fluoro-6-methoxypyridin-2-yl)boronic acid



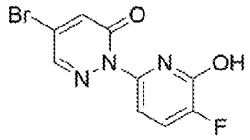
[000270] This intermediate was prepared using methods similar to those described in Intermediate 3, Step 1 using 6-bromo-3-fluoro-2-methoxypyridine in place of 3-bromo-5-fluoro-2-methyl-pyridine. LCMS: (ESI$^+$) m/z = 172.1 (M+H).

Step 2: Preparation of 5-bromo-2-(5-fluoro-6-methoxypyridin-2-yl)pyridazin-3(2H)-one



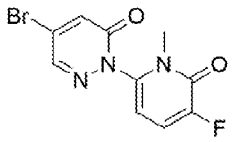
[000271] This intermediate was prepared using methods similar to those described in Intermediate 3, Step 2 using (5-fluoro-6-methoxypyridin-2-yl)boronic acid and 4-bromo-1H-pyridazin-6-one in place of 5-fluoro-2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine and 4-iodo-1H-pyridazin-6-one, respectively. LCMS: (ESI$^+$) m/z = 300.1 (M+H).

Step 3: Preparation of 5-bromo-2-(5-fluoro-6-hydroxypyridin-2-yl)pyridazin-3(2H)-one



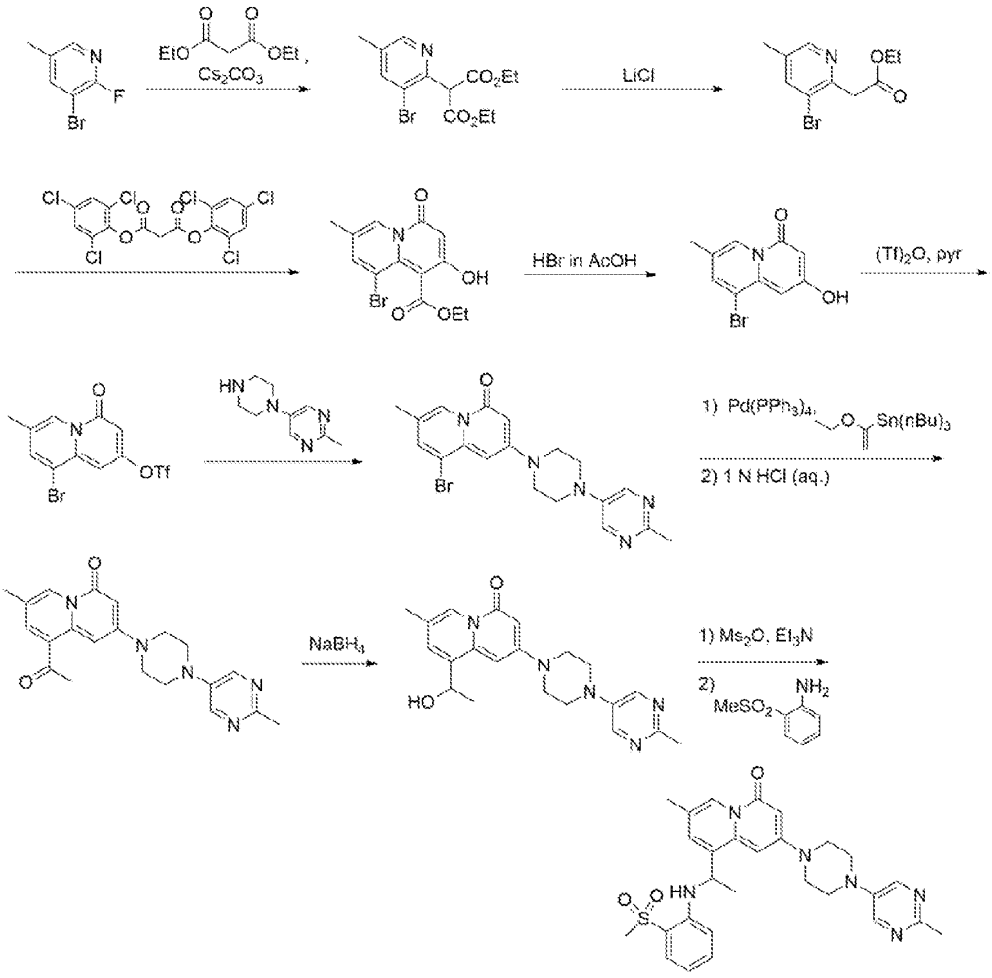
[000272] A mixture of 5-bromo-2-(5-fluoro-6-methoxypyridin-2-yl)pyridazin-3(2H)-one (1.0 g, 3.33 mmol) in hydrobromic acid (33 wt % in acetic acid, 10 mL) was stirred at 80°C for 2 h. The resulting mixture was concentrated under reduced pressure to afford 5-bromo-2-(5-fluoro-6-hydroxypyridin-2-yl)pyridazin-3(2H)-one (930 mg crude yield) as a yellow solid which was used as is in the next step without further purification. LCMS: (ESI$^+$) m/z = 286.1 (M+H).

Step 4: Preparation of 5-bromo-2-(5-fluoro-1-methyl-6-oxo-1,6-dihydropyridin-2-yl)pyridazin-3(2H)-one

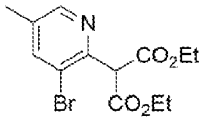


[000273] To a stirred mixture of 5-bromo-2-(5-fluoro-6-hydroxypyridin-2-yl)pyridazin-3(2H)-one (300 mg, 1.05 mmol) and K_2CO_3 (290 mg, 2.10 mmol) in DMF (5 mL) was added MeI (298 mg, 2.10 mmol) dropwise at 0 °C under a nitrogen atmosphere. The resulting mixture was stirred at room temperature for 2 h and then diluted with H_2O (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organics were washed with brine (2 x 10 mL), dried over anhydrous Na_2SO_4, filtered, and then concentrated under reduced pressure. The residue was purified by prep-TLC (PE:EA = 1:2) to afford 5-bromo-2-(5-fluoro-1-methyl-6-oxo-1,6-dihydropyridin-2-yl)pyridazin-3(2H)-one (92 mg, 29% yield) as an off-white solid. LCMS: (ESI$^+$) m/z = 299.9 (M+H).

[000274] **Example 1:** 7-methyl-2-(4-(2-methylpyrimidin-5-yl)piperazin-1-yl)-9-(1-((2-(methylsulfonyl)phenyl)amino)ethyl)-4H-quinolizin-4-one



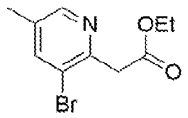
Step 1: Preparation of 1,3-diethyl 2-(3-bromo-5-methylpyridin-2-yl)propanedioate



[000275] To a stirred solution of 3-bromo-2-fluoro-5-methylpyridine (15 g, 78.9 mmol) and diethyl malonate (25.3 g, 158 mmol) in DMSO (150 mL) was added Cs_2CO_3 (51.4 g, 158 mmol) at room temperature under an argon atmosphere. The resulting mixture was stirred for 6 h at

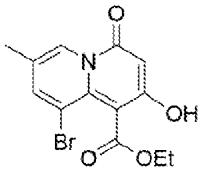
100 °C. The mixture was diluted with ice water (500 mL) at room temperature and then extracted with EtOAc (3 x 500 mL). The combined organic phases were washed with brine and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE:EA = 4:1, to afford 1,3-diethyl 2-(3-bromo-5-methylpyridin-2-yl) propanedioate (6.8 g, 26% yield) as a colorless oil. ^{1}H NMR (400 MHz, chloroform-*d*): δ 8.38 – 8.33 (m, 1H), 7.73 – 7.68 (m, 1H), 5.20 (s, 1H), 4.32 – 4.21 (m, 4H), 2.33 (s, 3H), 1.30 – 1.27 (m, 6H).

Step 2: Preparation of ethyl 2-(3-bromo-5-methylpyridin-2-yl)acetate



[000276] To a stirred solution of 1,3-diethyl 2-(3-bromo-5-methylpyridin-2-yl)propanedioate (3.9 g, 11.8 mmol) and H_2O (0.53 mL, 29.5 mmol) in DMSO (40 mL, 563 mmol) was added LiCl (1.25 g, 29.5 mmol) at room temperature. The resulting mixture was stirred at 100°C for 1 day under an argon atmosphere. The mixture was diluted with ice water (200 mL) at room temperature and the resulting mixture was extracted with EtOAc (3 x 200 mL). The combined organic phases were washed with brine and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography (10% to 70% CH_3CN in H_2O gradient over 30 min) to afford ethyl 2-(3-bromo-5-methylpyridin-2-yl)acetate (2 g, 66% yield) as a colorless oil. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.38 – 8.34 (m, 1H), 8.00 – 7.93 (m, 1H), 4.14 – 4.07 (m, 2H), 3.93 (s, 2H), 2.30 (s, 3H), 1.22 – 1.16 (m, 3H).

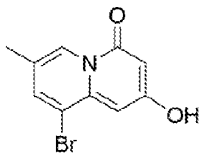
Step 3: Preparation of ethyl 9-bromo-2-hydroxy-7-methyl-4-oxoquinolizine-1-carboxylate



[000277] Into a vial were added ethyl 2-(3-bromo-5-methylpyridin-2-yl)acetate (2 g, 7.75 mmol) and bis(2,4,6-trichlorophenyl) propanedioate (7.17 g, 15.5 mmol) in diphenyl ether (100

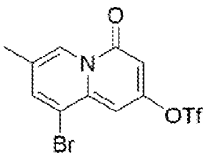
mL) at room temperature. The mixture was then irradiated with microwave radiation for 30 min at 200 °C. The mixture was diluted with ice water (100 mL) at room temperature and the resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic phases were washed with brine and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography (10% to 70% CH_3CN in H_2O gradient over 30 min) to afford ethyl 9-bromo-2-hydroxy-7-methyl-4-oxoquinolizine-1-carboxylate (700 mg, 28% yield) as a yellow oil. ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.38 (s, 1H), 8.85 – 8.82 (m, 1H), 7.92 (d, J = 1.7 Hz, 1H), 5.93 (s, 1H), 4.40 – 4.22 (m, 2H), 2.27 (d, J = 1.2 Hz, 3H), 1.30 – 1.24 (m, 3H).

Step 4: Preparation of 9-bromo-2-hydroxy-7-methylquinolizin-4-one



[000278] A solution of ethyl 9-bromo-2-hydroxy-7-methyl-4-oxoquinolizine-1-carboxylate (700 mg, 2.15 mmol) in HBr in aqueous AcOH (40%, 1 mL) was stirred for 30 min at 100 °C under an argon atmosphere. The mixture was diluted with ice water (50 mL) and the resulting mixture was extracted with EtOAc (3 x 50 mL). The combined organic phases were washed with brine and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The crude product was re-crystallized from EtOAc (10 mL) to afford 9-bromo-2-hydroxy-7-methylquinolizin-4-one (70 mg, 13% yield) as an orange solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.98 (s, 1H), 8.65 – 8.61 (m, 1H), 7.79 (d, J = 1.6 Hz, 1H), 6.52 (d, J = 2.5 Hz, 1H), 5.82 (d, J = 2.4 Hz, 1H), 2.26 (d, J = 1.3 Hz, 3H).

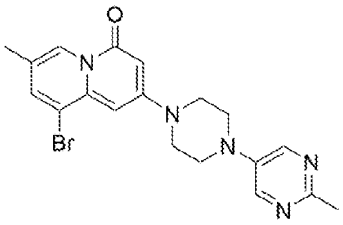
Step 5: Preparation of 9-bromo-7-methyl-4-oxo-4H-quinolizin-2-yl trifluoromethanesulfonate



[000279] To a stirred solution of 9-bromo-2-hydroxy-7-methylquinolizin-4-one (60 mg, 0.24 mmol) in pyridine (1 mL) was added triflic anhydride (0.08 mL, 0.47 mmol) dropwise at 0 °C under

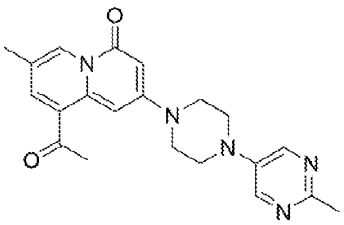
an argon atmosphere. The resulting mixture was stirred at 0 °C for 30 min. The reaction was then quenched with saturated aqueous $NaHCO_3$ (20 mL) at 0 °C. The resulting mixture was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic phases were washed with brine and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The crude product was used in the next step directly without further purification. LCMS: (ESI^+) m/z = 385.8.

Step 6: Preparation of 9-bromo-7-methyl-2-(4-(2-methylpyrimidin-5-yl)piperazin-1-yl)-4H-quinolizin-4-one



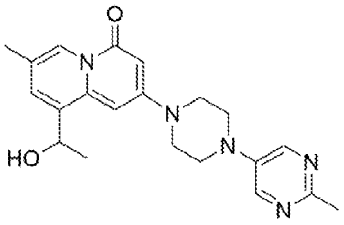
[000280] To a stirred solution of 9-bromo-7-methyl-4-oxoquinolizin-2-yl trifluoromethanesulfonate (60 mg, 0.16 mmol) and 2-methyl-5-(piperazin-1-yl)pyrimidine (Intermediate 1, 55 mg, 0.31 mmol) in DMA was added DIPEA (0.08 mL, 0.47 mmol) dropwise at room temperature under an argon atmosphere. The resulting mixture was stirred at 80 °C for 1 h. The mixture was diluted with ice water (10 mL) at room temperature. The resulting precipitated solids were collected by filtration and dried by lyophilization to afford 9-bromo-7-methyl-2-(4-(2-methylpyrimidin-5-yl) piperazin-1-yl)-4H-quinolizin-4-one (50 mg, 78% yield) as a yellow solid. ^1H NMR (400 MHz, DMSO-d_6): δ 8.58 (s, 1H), 8.43 (s, 2H), 7.73 (d, J = 1.6 Hz, 1H), 6.53 (d, J = 2.6 Hz, 1H), 5.94 (d, J = 2.6 Hz, 1H), 3.60 – 3.57 (m, 4H), 3.36 (m, 4H), 2.23 (d, J = 1.2 Hz, 3H).

Step 7: Preparation of 9-acetyl-7-methyl-2-(4-(2-methylpyrimidin-5-yl)piperazin-1-yl)-4H-quinolizin-4-one



[000281] To a stirred mixture of 9-bromo-7-methyl-2-(4-(2-methylpyrimidin-5-yl)piperazin-1-yl)-4H-quinolizin-4-one (80 mg, 0.19 mmol) and tributyl(1-ethoxyvinyl)tin (84 mg, 0.23 mmol) in dioxane (1 mL) was added $Pd(PPh_3)_4$ (22 mg, 0.019 mmol) at room temperature under an argon atmosphere. The resulting mixture was stirred at 100 °C for 2 h. To the resulting mixture was added aqueous HCl (1 M, 1.0 mL) dropwise at 0 °C. The resulting mixture was stirred at 0 °C for an additional 30 min. The mixture was diluted with ice water (30 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 30 mL). The combined organic phases were washed with brine and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The crude product was used in the next step directly without further purification. LCMS: (ESI^+) m/z = 378.2 (M+H).

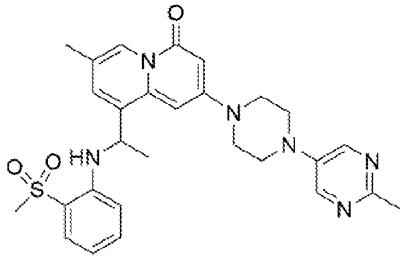
Step 8: Preparation of 9-(1-hydroxyethyl)-7-methyl-2-(4-(2-methylpyrimidin-5-yl)piperazin-1-yl)-4H-quinolizin-4-one



[000282] To a stirred solution of 9-acetyl-7-methyl-2-(4-(2-methylpyrimidin-5-yl)piperazin-1-yl)-4H-quinolizin-4-one (50 mg, 0.13 mmol) in MeOH (1 mL) was added $NaBH_4$ (10 mg, 0.26 mmol) at room temperature under an argon atmosphere. The resulting mixture was stirred at room temperature for 1 h. The reaction was then quenched with water (20 mL) at room temperature and the resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic phases were washed with brine and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions (5% to 70% CH_3CN in H_2O over a 30 min

gradient) to afford 9-(1-hydroxyethyl)-7-methyl-2-(4-(2-methylpyrimidin-5-yl)piperazin-1-yl)-4H-quinolizin-4-one (30 mg, 60% yield) as a light yellow solid. LCMS: (ESI$^+$) m/z = 380.1 (M+H).

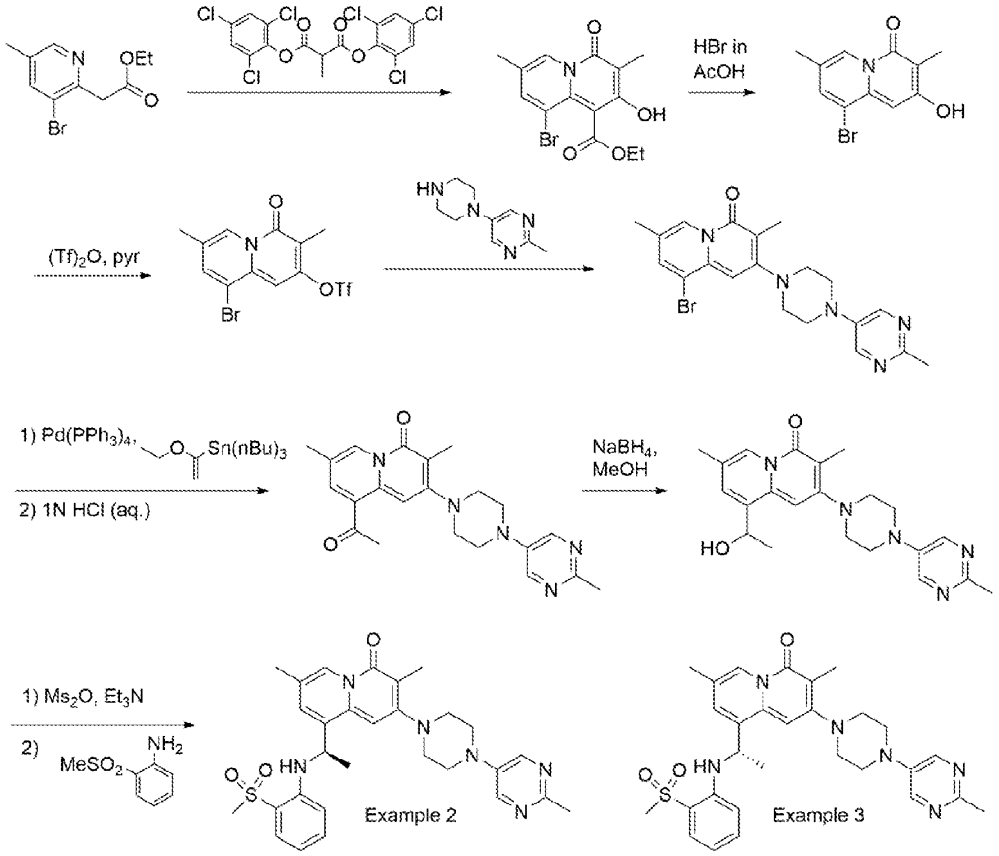
Step 9: Preparation of 7-methyl-2-(4-(2-methylpyrimidin-5-yl)piperazin-1-yl)-9-(1-((2-(methylsulfonyl)phenyl)amino)ethyl)-4H-quinolizin-4-one (Example 1)



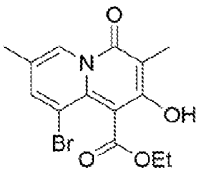
[000283] To a stirred mixture of 9-(1-hydroxyethyl)-7-methyl-2-(4-(2-methylpyrimidin-5-yl)piperazin-1-yl)-4H-quinolizin-4-one (30 mg, 0.079 mmol) and TEA (48 mg, 0.47 mmol) in DCM (3 mL) was added methanesulfonyl methanesulfonate (41 mg, 0.24 mmol) at 0 °C under an argon atmosphere. The resulting mixture was stirred at room temperature for 30 min. To the resulting mixture was added 2-methanesulfonylaniline (27 mg, 0.16 mmol) at room temperature. The mixture was then stirred at room temperature overnight. The reaction was quenched with saturated aqueous $NaHCO_3$ (10 mL) at 0 °C and the resulting mixture was extracted with EtOAc (3 x 15 mL). The combined organic phases were washed with brine and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The crude product (20 mg) was purified by prep-HPLC to afford 7-methyl-2-(4-(2-methylpyrimidin-5-yl)piperazin-1-yl)-9-(1-((2-(methylsulfonyl)phenyl)amino)ethyl)-4H-quinolizin-4-one (3.6 mg, 8.4% yield) as a light yellow solid. LCMS: (ESI$^+$) m/z = 533.2 (M+H); ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.54 (s, 1H), 8.45 (d, J = 1.3 Hz, 2H), 7.70 – 7.63 (m, 1H), 7.41 – 7.37 (m, 1H), 7.24 (s, 1H), 6.80 – 6.76 (m, 1H), 6.59 (d, J = 5.5 Hz, 1H), 6.54 (s, 1H), 6.45 (d, J = 8.5 Hz, 1H), 5.93 (s, 1H), 5.15 (d, J = 6.5 Hz, 1H), 3.60 (m, 4H), 3.30 (m, 4H), 3.26 (d, J = 1.1 Hz, 3H), 2.17 (s, 3H), 1.57 (d, J = 6.4 Hz, 3H), 1.24 (s, 3H).

[000284] **Example 2:** (R)-3,7-dimethyl-2-(4-(2-methylpyrimidin-5-yl)piperazin-1-yl)-9-(1-((2-(methylsulfonyl)phenyl)amino)ethyl)-4H-quinolizin-4-one, and

[000285] **Example 3:** (S)-3,7-dimethyl-2-(4-(2-methylpyrimidin-5-yl)piperazin-1-yl)-9-(1-((2-(methylsulfonyl)phenyl)amino)ethyl)-4H-quinolizin-4-one



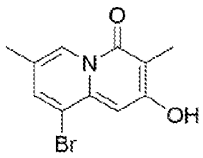
Step 1: Preparation of ethyl 9-bromo-2-hydroxy-3,7-dimethyl-4-oxo-4H-quinolizine-1-carboxylate



[000286] To a stirred mixture of ethyl 2-(3-bromo-5-methylpyridin-2-yl)acetate (1 g, 3.87 mmol) in diphenyl ether (10 mL) was added bis(2,4,6-trichlorophenyl) 2-methylpropanedioate (3.7 g, 7.75 mmol) in portions at room temperature under an argon atmosphere. The mixture

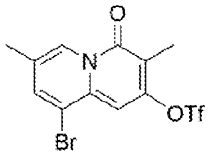
was irradiated with microwave radiation at 200 °C for 30 min. The mixture was diluted with ice water (60 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 60 mL), and the combined organic phases were washed with brine and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography (30% to 80% of CH_3CN in H_2O over a 25 min gradient) to afford ethyl 9-bromo-2-hydroxy-3,7-dimethyl-4-oxo-4H-quinolizine-1-carboxylate (900 mg, 62% yield) as an off-white oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.33 (s, 1H), 8.87 – 8.81 (m, 1H), 7.85 (d, J = 1.7 Hz, 1H), 4.33 – 4.24 (m, 2H), 2.27 (d, J = 1.3 Hz, 3H), 2.10 (s, 3H), 1.32 – 1.27 (m, 3H).

Step 2: Preparation of 9-bromo-2-hydroxy-3,7-dimethyl-4H-quinolizin-4-one



[000287] A solution of ethyl 9-bromo-2-hydroxy-3,7-dimethyl-4-oxo-4H-quinolizine-1-carboxylate (600 mg, 1.76 mmol) in a solution of hydrobromic acid in acetic acid (6 mL) was stirred for 1 h at 100 °C under an argon atmosphere. The reaction was quenched by the addition of ice water (30 mL) at room temperature. The precipitated solids were collected by filtration and washed with water (3 x 30 mL). The resulting mixture was concentrated under reduced pressure to afford in 9-bromo-2-hydroxy-3,7-dimethyl-4H-quinolizin-4-one (200 mg, 40% yield) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.81 (s, 1H), 8.73 – 8.60 (m, 1H), 7.69 (d, J = 1.6 Hz, 1H), 6.71 (s, 1H), 2.26 (d, J = 1.3 Hz, 3H), 2.02 (s, 3H).

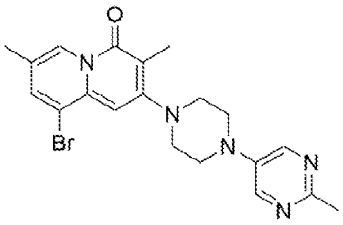
Step 3: Preparation of 9-bromo-3,7-dimethyl-4-oxo-4H-quinolizin-2-yl trifluoromethanesulfonate



[000288] Into a 50 mL round-bottom flask were added 9-bromo-2-hydroxy-3,7-dimethyl-4H-quinolizin-4-one (350 mg, 1.31 mmol) and pyridine (5 mL) at room temperature. To this mixture was added triflic anhydride (958 mg, 3.39 mmol) in DCM in portions at 0 °C. The resulting

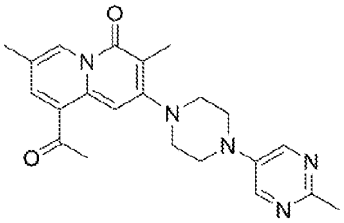
mixture was stirred for 1 h at 0 °C. The reaction was quenched by the addition of saturated aqueous sodium bicarbonate (30 mL) at 0 °C. The resulting mixture was extracted with EtOAc (3 x 30 mL). The combined organic phases were washed with brine and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford 9-bromo-3,7-dimethyl-4-oxo-4H-quinolizin-2-yl trifluoromethanesulfonate (260 mg, 50% yield) as a brown solid. The crude product was used in the next step directly without further purification. LCMS: (ESI^+) m/z = 399.8.

Step 4: Preparation of 9-bromo-3,7-dimethyl-2-(4-(2-methylpyrimidin-5-yl)piperazin-1-yl)-4H-quinolizin-4-one



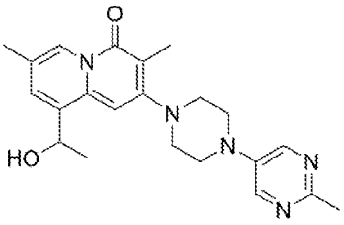
[000289] To a stirred mixture of 9-bromo-3,7-dimethyl-4-oxo-4H-quinolizin-2-yl trifluoromethanesulfonate (200 mg, 0.50 mmol) and 2-methyl-5-(piperazin-1-yl)pyrimidine (Intermediate 1, 107 mg, 0.60 mmol) in DMA (3.3 mL, 36 mmol) was added DIEA (194 mg, 1.5 mmol) dropwise at 0 °C under a nitrogen atmosphere. The resulting mixture was stirred for overnight at 80 °C. The reaction was quenched by the addition of ice water (30 mL) at 0 °C. The resulting mixture was extracted with EtOAc (3 x 30 mL). The combined organic phases were washed with brine and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE:EA = 5:1, to afford 9-bromo-3,7-dimethyl-2-(4-(2-methylpyrimidin-5-yl)piperazin-1-yl)-4H-quinolizin-4-one (70 mg, 33% yield) as a white solid. LCMS: (ESI^+) m/z = 428.1.

Step 5: Preparation of 9-acetyl-3,7-dimethyl-2-(4-(2-methylpyrimidin-5-yl)piperazin-1-yl)-4H-quinolizin-4-one



[000290] Into a 50 mL 2-necked round-bottom flask were added 9-bromo-3,7-dimethyl-2-(4-(2-methylpyrimidin-5-yl)piperazin-1-yl)-4H-quinolizin-4-one (100 mg, 0.23 mmol) in dioxane (3 mL) at room temperature. To the above mixture was added $Pd(PPh_3)_4$ (54 mg, 0.047 mmol) and tributyl(1-ethoxyethenyl)stannane (110 mg, 0.30 mmol) in portions at room temperature. The resulting mixture was stirred at 60 °C overnight. The reaction was quenched by the addition of ice water (20 mL) at 0 °C. The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic phases were washed with brine and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography (30% to 80% CH_3CN in H_2O over a 30 min gradient) to afford 9-acetyl-3,7-dimethyl-2-(4-(2-methylpyrimidin-5-yl)piperazin-1-yl)-4H-quinolizin-4-one (50 mg, 53% yield) as a yellow solid. LCMS: (ESI^+) m/z = 392.2 (M+H).

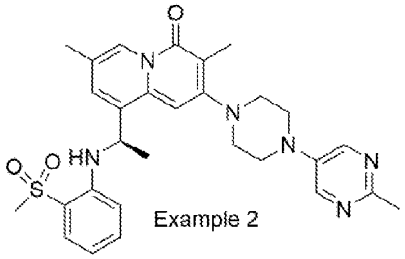
Step 6: Preparation of 9-(1-hydroxyethyl)-3,7-dimethyl-2-(4-(2-methylpyrimidin-5-yl)piperazin-1-yl)-4H-quinolizin-4-one



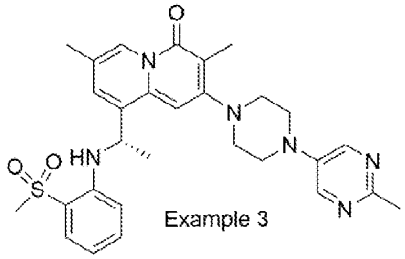
[000291] To a stirred mixture of 9-acetyl-3,7-dimethyl-2-(4-(2-methylpyrimidin-5-yl)piperazin-1-yl)-4H-quinolizin-4-one (40 mg, 0.10 mmol) in MeOH (1.2 mL) was added $NaBH_4$ (7.7 mg, 0.20 mmol) at 0 °C under an argon atmosphere. The resulting mixture was stirred at room temperature for 3 h. The reaction was then quenched by the addition of ice water (20 mL) at 0 °C. The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic phases were washed with brine and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford crude 9-(1-hydroxyethyl)-3,7-dimethyl-2-(4-(2-

methylpyrimidin-5-yl)piperazin-1-yl)-4H-quinolizin-4-one which was used in the next step immediately without further purification. LCMS: (ESI^+) m/z = 394.3 (M+H).

Step 7: Preparation (R)-3,7-dimethyl-2-(4-(2-methylpyrimidin-5-yl)piperazin-1-yl)-9-(1-((2-(methylsulfonyl)phenyl)amino)ethyl)-4H-quinolizin-4-one (Example 2) and (S)-3,7-dimethyl-2-(4-(2-methylpyrimidin-5-yl)piperazin-1-yl)-9-(1-((2-(methylsulfonyl)phenyl)amino)ethyl)-4H-quinolizin-4-one (Example 3)



Example 2



Example 3

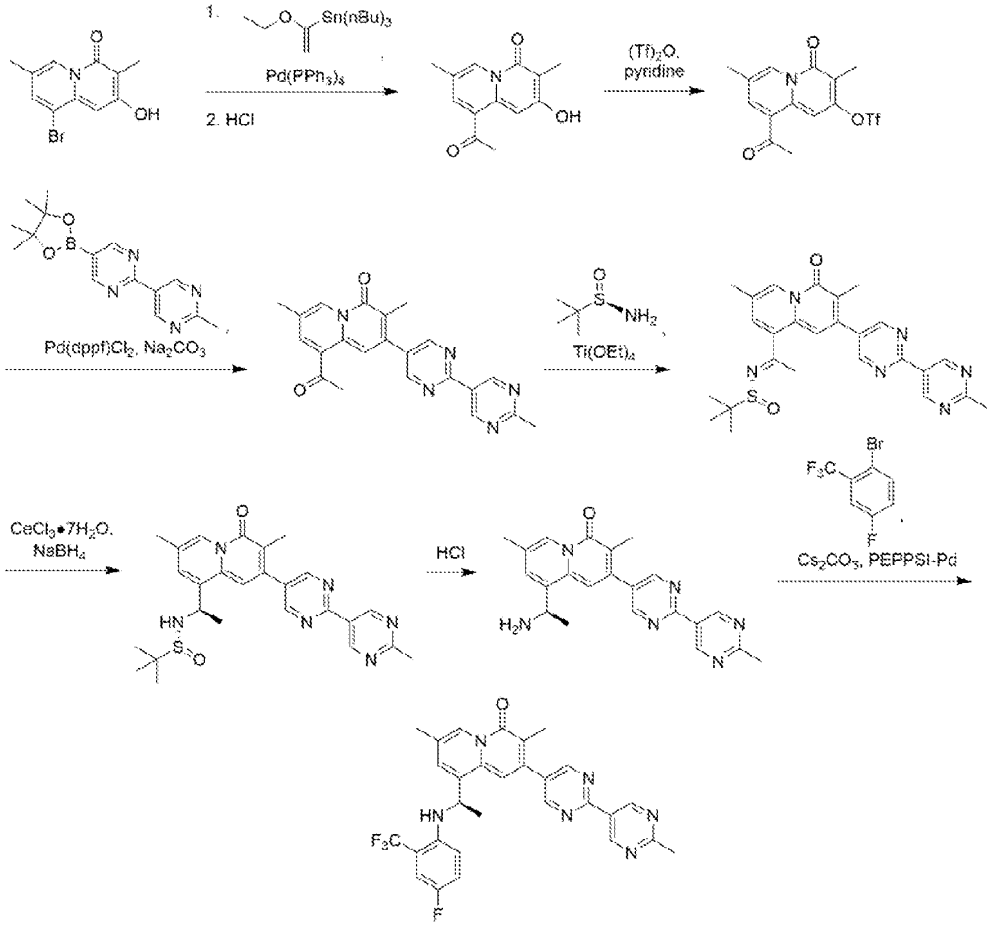
[000292] A mixture of 9-(1-hydroxyethyl)-3,7-dimethyl-2-(4-(2-methylpyrimidin-5-yl)piperazin-1-yl)-4H-quinolizin-4-one (60 mg, 0.15 mmol) and Et_3N (93 mg, 0.91 mmol) in DCM (1 mL) was stirred at 0 °C for 30 min under an argon atmosphere. To this mixture was added methanesulfonyl methanesulfonate (705 mg, 0.76 mmol) in portions at 0 °C. The resulting mixture was stirred at room temperature overnight. The reaction was quenched by the addition of ice water (30 mL) at 0 °C. The resulting mixture was extracted with DCM (3 x 30 mL). The combined organic phases were washed with brine and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography (20% to 50% CH_3CN in water over a gradient of 20 min). The resulting product (32 mg) was purified further by prep-chiral-HPLC to afford (R)-3,7-dimethyl-2-(4-(2-methylpyrimidin-5-yl)piperazin-1-yl)-9-(1-((2-(methylsulfonyl)phenyl)amino)ethyl)-4H-quinolizin-4-one and (S)-3,7-dimethyl-2-(4-(2-methylpyrimidin-5-yl)piperazin-1-yl)-9-(1-((2-(methylsulfonyl)phenyl)amino)ethyl)-4H-quinolizin-4-one (7.4 mg, 9% yield) and (S)-3,7-dimethyl-2-(4-(2-methylpyrimidin-5-yl)piperazin-1-yl)-9-(1-((2-(methylsulfonyl)phenyl)amino)ethyl)-4H-quinolizin-4-one (9.6 mg, 11% yield) each as a white solid:

[000293] (R)-3,7-dimethyl-2-(4-(2-methylpyrimidin-5-yl)piperazin-1-yl)-9-(1-((2-(methylsulfonyl)phenyl)amino)ethyl)-4H-quinolizin-4-one: ^1H NMR (400 MHz, DMSO-d_6): δ 8.77 –

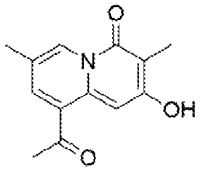
8.64 (m, 1H), 8.46 (s, 2H), 7.70 – 7.61 (m, 1H), 7.43 – 7.35 (m, 1H), 7.31 (d, *J* = 1.8 Hz, 1H), 6.84 – 6.75 (m, 1H), 6.64 (s, 1H), 6.59 (d, *J* = 5.8 Hz, 1H), 6.51 (d, *J* = 8.4 Hz, 1H), 5.24 – 5.09 (m, 1H), 3.40 – 3.37 (m, 3H), 3.32 – 3.21 (m, 8H), 2.51 (s, 3H), 2.25 (d, *J* = 1.3 Hz, 3H), 2.18 (s, 3H), 1.62 (d, *J* = 6.5 Hz, 3H); LCMS: (ESI$^+$) m/z = 547.3 (M+H).

[000294] (S)-3,7-dimethyl-2-(4-(2-methylpyrimidin-5-yl)piperazin-1-yl)-9-(1-((2-(methylsulfonyl)phenyl)amino)ethyl)-4H-quinolizin-4-one: ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.78 – 8.66 (m, 1H), 8.46 (s, 2H), 7.70 – 7.62 (m, 1H), 7.44 – 7.35 (m, 1H), 7.31 (d, *J* = 1.7 Hz, 1H), 6.84 – 6.75 (m, 1H), 6.64 (s, 1H), 6.59 (d, *J* = 5.8 Hz, 1H), 6.51 (d, *J* = 8.4 Hz, 1H), 5.26 – 5.11 (m, 1H), 3.40 – 3.37 (m, 3H), 3.32 – 3.22 (m, 8H), 2.51 (s, 3H), 2.25 (d, *J* = 1.2 Hz, 3H), 2.17 (s, 3H), 1.62 (d, *J* = 6.5 Hz, 3H); LCMS: (ESI$^+$) m/z = 547.3 (M+H).

[000295] **Example 21:** (R)-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3,7-dimethyl-2-(2'-methyl-[2,5'-bipyrimidin]-5-yl)-4H-quinolizin-4-one



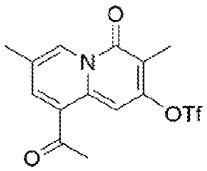
Step 1: Preparation of 9-acetyl-2-hydroxy-3,7-dimethyl-4H-quinolizin-4-one



[000296] To a stirred mixture of 9-bromo-2-hydroxy-3,7-dimethylquinolizin-4-one (Examples 2 and 3, Step 2) (10 g, 37.3 mmol) in dioxane (100 mL) at room temperature under an argon atmosphere were added tributyl(1-ethoxyethenyl)stannane (20.2 g, 56.0 mmol) and $Pd(PPh_3)_4$ (4.3 g, 3.73 mmol). The resulting mixture was stirred at 100 °C overnight and then allowed to

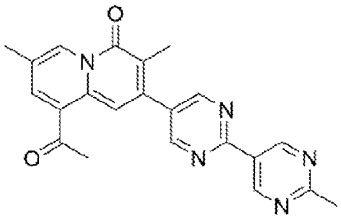
cool to room temperature. Aqueous 1 M HCl (110 mL) was added over 1 min at room temperature and the resulting mixture was stirred for 1 h. The mixture was then diluted with ice water (100 mL) and then extracted with CH_2Cl_2 (3 x 100 mL). The combined organics were washed with brine (1 x 100 mL), dried over anhydrous Na_2SO_4, filtrated, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluted with CH_2Cl_2:MeOH = 10:1) to afford 9-acetyl-2-hydroxy-3,7-dimethylquinolizin-4-one (7.5 g, 87% yield) as a light red solid. LCMS: (ESI^+) m/z = 232.0 (M+H).

Step 2: Preparation of 9-acetyl-3,7-dimethyl-4-oxo-4H-quinolizin-2-yl trifluoromethanesulfonate



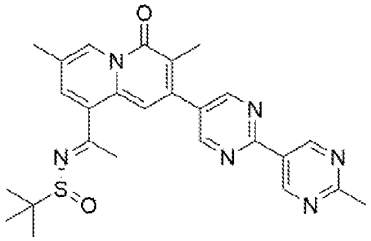
[000297] To a stirred mixture of 9-acetyl-2-hydroxy-3,7-dimethyl-4H-quinolizin-4-one (7.5 g, 32.4 mmol) in pyridine (100 mL) under an argon atmosphere was added trifluoromethanesulfonic anhydride (18.3 g, 64.9 mmol) dropwise at -10 °C. The resulting mixture was stirred at -10 °C for 30 min and then was poured into saturated aqueous $NaHCO_3$ and then extracted with EtOAc (3 x 50 mL). The combined organics were washed with brine (2 x 50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford 9-acetyl-3,7-dimethyl-4-oxo-4H-quinolizin-2-yl trifluoromethanesulfonate (8.0 g, 68% crude yield) as a yellow solid which was used directly in the next step without further purification. LCMS: (ESI^+) m/z = 364.1 (M+H).

Step 3: Preparation of 9-acetyl-3,7-dimethyl-2-(2'-methyl-[2,5'-bipyrimidin]-5-yl)-4H-quinolizin-4-one



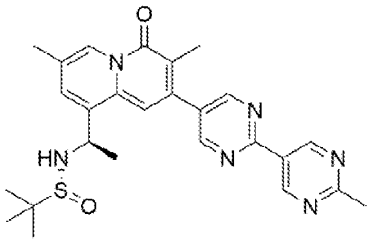
[000298] To a stirred mixture of 9-acetyl-3,7-dimethyl-4-oxo-4H-quinolizin-2-yl trifluoromethanesulfonate (8.0 g, 22.0 mmol) and 2'-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,5'-bipyrimidine (Intermediate 6) (9.85 g, 33.0 mmol) in dioxane (100 mL) and H_2O (10 mL) at room temperature under a nitrogen atmosphere were added $Pd(dppf)Cl_2$ (1.80 g, 2.20 mmol) and Na_2CO_3 (7.0 g, 66.1 mmol) in portions. The resulting mixture was stirred at 90 °C for 2 h, cooled to room temperature, and then diluted with H_2O (100 mL). The mixture was then extracted with EtOAc (3 x 100 mL). The combined organics were washed with brine (1 x 200 mL), dried over anhydrous Na_2SO_4, filtered, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluted with CH_2Cl_2:MeOH = 8:1) to afford 9-acetyl-3,7-dimethyl-2-(2'-methyl-[2,5'-bipyrimidin]-5-yl)-4H-quinolizin-4-one (4.0 g, 47% yield) as a light yellow oil. LCMS: (ESI^+) m/z = 386.1 (M+H).

Step 4: Preparation of (R,E)-N-(1-(3,7-dimethyl-2-(2'-methyl-[2,5'-bipyrimidin]-5-yl)-4-oxo-4H-quinolizin-9-yl)ethylidene)-2-methylpropane-2-sulfinamide



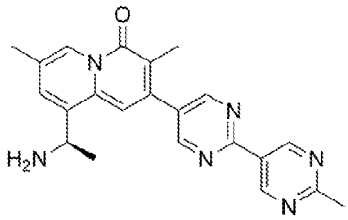
[000299] To a stirred mixture of 9-acetyl-3,7-dimethyl-2-(2'-methyl-[2,5'-bipyrimidin]-5-yl)-4H-quinolizin-4-one (4.0 g, 10.4 mmol) and (R)-2-methylpropane-2-sulfinamide (2.52 g, 20.8 mmol) in toluene (80 mL) at room temperature under an argon atmosphere was added titanium ethoxide (5.90 g, 20.8 mmol) dropwise. The resulting mixture was stirred at 80 °C overnight, then cooled to room temperature and then poured into water (100 mL). The resulting mixture was filtered and the filter cake was washed with EtOAc (2 x 50 mL). The filtrate phases were separated, and the aqueous phase was extracted further with EtOAc (3 x 200 mL). The combined organics were washed with brine (2 x 100 mL), dried over anhydrous Na_2SO_4, filtered, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluted with CH_2Cl_2:MeOH = 15:1) to afford (R,E)-N-(1-(3,7-dimethyl-2-(2'-methyl-[2,5'-bipyrimidin]-5-yl)-4-oxo-4H-quinolizin-9-yl)ethylidene)-2-methylpropane-2-sulfinamide (4.0 g, 79% yield) as a light yellow solid. LCMS: (ESI^+) m/z = 489.3 (M+H).

Step 5: Preparation of (R)-N-((R)-1-(3,7-dimethyl-2-(2'-methyl-[2,5'-bipyrimidin]-5-yl)-4-oxo-4H-quinolizin-9-yl)ethyl)-2-methylpropane-2-sulfinamide



[000300] To a stirred mixture of (R,E)-N-(1-(3,7-dimethyl-2-(2'-methyl-[2,5'-bipyrimidin]-5-yl)-4-oxo-4H-quinolizin-9-yl)ethylidene)-2-methylpropane-2-sulfinamide (3.0 g, 6.14 mmol) in MeOH (25 mL) was added cerium(III) chloride heptahydrate (4.57 g, 12.3 mmol) at 0 °C under an argon atmosphere. The mixture was then cooled to -40 °C and $NaBH_4$ (465 mg, 12.3 mmol) was added in portions over 5 min. The resulting mixture was stirred at -40°C for 2 h and then diluted with ice water (100 mL). The mixture was then extracted with EtOAc (3 x 100 mL). The combined organics were washed with brine (1 x 200 mL), dried over anhydrous Na_2SO_4, filtered, and then concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography (C18 silica gel; mobile phase of MeCN in water (10 mmol/L NH_4HCO_3), 5% to 100% gradient over 30 min) to afford (R)-N-((R)-1-(3,7-dimethyl-2-(2'-methyl-[2,5'-bipyrimidin]-5-yl)-4-oxo-4H-quinolizin-9-yl)ethyl)-2-methylpropane-2-sulfinamide (1.26 g, 42% yield) as a light yellow solid. LCMS: (ESI^+) m/z = 491.3 (M+H).

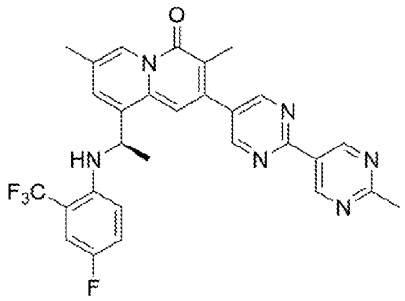
Step 6: Preparation of (R)-9-(1-aminoethyl)-3,7-dimethyl-2-(2'-methyl-[2,5'-bipyrimidin]-5-yl)-4H-quinolizin-4-one



[000301] To a stirred mixture of (R)-N-((R)-1-(3,7-dimethyl-2-(2'-methyl-[2,5'-bipyrimidin]-5-yl)-4-oxo-4H-quinolizin-9-yl)ethyl)-2-methylpropane-2-sulfinamide (600 mg, 1.22 mmol) in MeOH (12 mL) was added hydrogen chloride (4.0 M in ethyl acetate, 0.61 mL, 2.44

mmol) dropwise at 0 °C under a nitrogen atmosphere. The resulting mixture was stirred at room temperature for 1 h, diluted with MeOH (50 mL), and then adjusted to pH 8 via the addition of saturated aqueous $NaHCO_3$. The mixture was then extracted with DCM (3 x 50 mL). The combined organics were washed with brine (1 x 100 mL), dried over anhydrous Na_2SO_4, filtered, and then concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography (C18 silica gel; mobile phase of MeCN in water (10 mmol/L NH_4HCO_3), 5% to 50% gradient over 30 min) to afford (R)-9-(1-aminoethyl)-3,7-dimethyl-2-(2'-methyl-[2,5'-bipyrimidin]-5-yl)-4H-quinolizin-4-one (440 mg, 93% yield) as a light yellow solid. LCMS: (ESI^+) m/z = 387.1 (M+H).

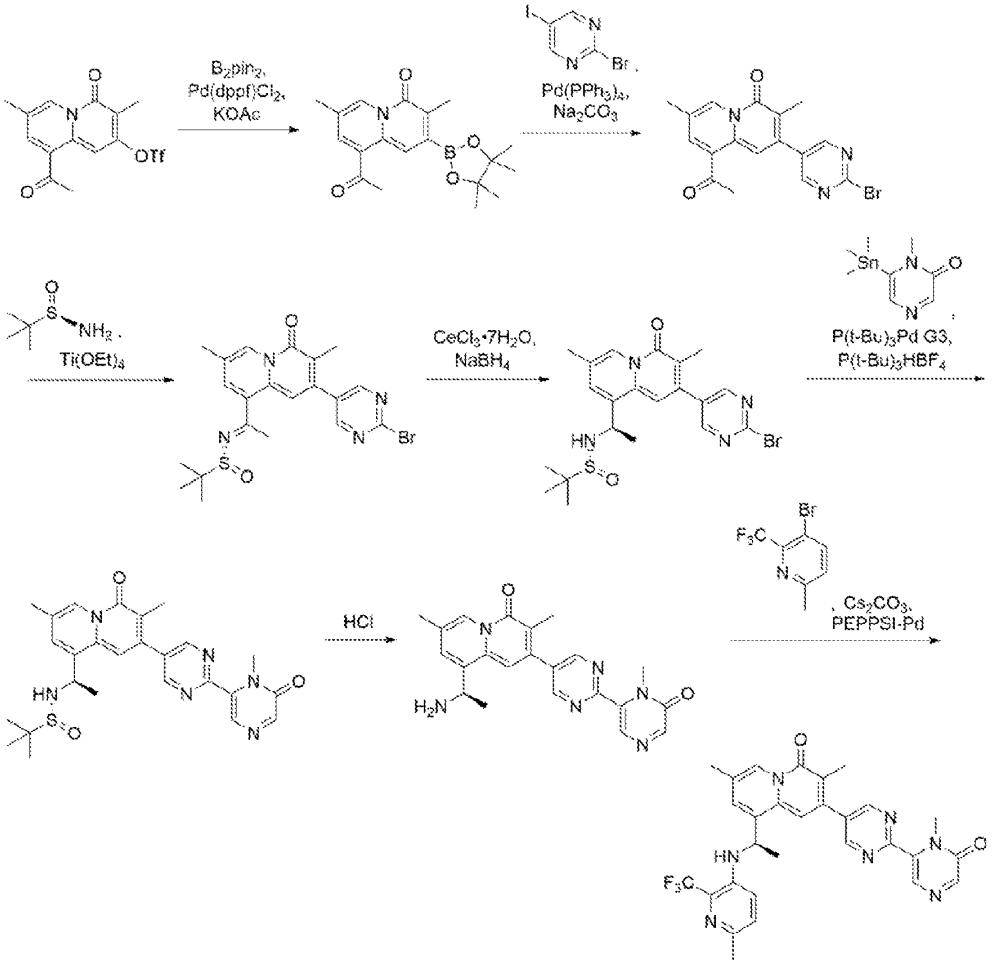
Step 7: Preparation of (R)-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3,7-dimethyl-2-(2'-methyl-[2,5'-bipyrimidin]-5-yl)-4H-quinolizin-4-one (Example 21)



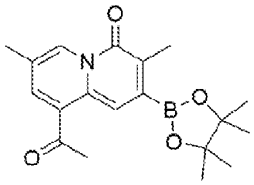
[000302] To a stirred solution of (R)-9-(1-aminoethyl)-3,7-dimethyl-2-(2'-methyl-[2,5'-bipyrimidin]-5-yl)-4H-quinolizin-4-one (50 mg, 0.13 mmol) and 1-bromo-4-fluoro-2-(trifluoromethyl)benzene (47 mg, 0.19 mmol) in dioxane (2 mL) were added Cs_2CO_3 (126 mg, 0.39 mmol) and [1,3-bis[2,6-bis(1-ethylpropyl)phenyl]-4,5-dichloro-imidazol-2-ylidene]-dichloro-(2-methylpyridin-1-ium-1-yl)palladium (11 mg, 0.013 mmol) in portions at room temperature under an argon atmosphere. The resulting mixture was stirred at 80 °C overnight, and then was cooled to room temperature and diluted with water (10 mL). The resulting mixture was extracted with EtOAc (2 x 20 mL). The combined organics were washed with brine (2 x 20 mL), dried over anhydrous Na_2SO_4, filtered, and then concentrated under reduced pressure. The crude product was purified by prep-HPLC and then purified further by prep-chiral-HPLC (column: CHIRALPAK AD-3; mobile phase of hexanes(0.1% FA):EtOH = 95:5) to afford (R)-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3,7-dimethyl-2-(2'-methyl-[2,5'-bipyrimidin]-5-yl)-4H-

quinolizin-4-one (17.3 mg, 24 % yield, >99% ee) as a light yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.60 (s, 2H), 9.19 (s, 2H), 8.83 (s, 1H), 7.41 (d, J = 1.7 Hz, 1H), 7.38 – 7.31 (m, 1H), 7.23 (d, J = 5.1 Hz, 1H), 7.22 – 7.14 (m, 1H), 6.50 – 6.42 (m, 1H), 5.49 (d, J = 6.3 Hz, 1H), 5.27 – 5.19 (m, 1H), 2.75 (s, 3H), 2.30 (d, J = 1.3 Hz, 3H), 2.25 (s, 3H), 1.59 (d, J = 6.6 Hz, 3H); LCMS: (ESI$^+$) m/z = 549.2 (M+H).

[000303] **Example 22:** (R)-3,7-dimethyl-9-(1-((6-methyl-2-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-2-(2-(1-methyl-6-oxo-1,6-dihydropyrazin-2-yl)pyrimidin-5-yl)-4H-quinolizin-4-one

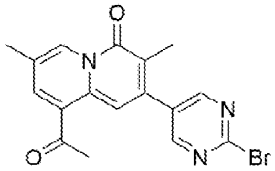


Step 1: Preparation of 9-acetyl-3,7-dimethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4H-quinolizin-4-one



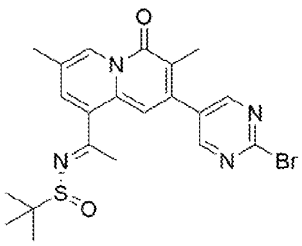
[000304] A mixture of 9-acetyl-3,7-dimethyl-4-oxo-4H-quinolizin-2-yl trifluoromethanesulfonate (Example 21, Step 2) (6 g, 16.5 mmol), bis(pinacolato)diboron (8.39 g, 33.0 mmol), potassium acetate (3.24 g, 33.0 mmol) and $Pd(dppf)Cl_2$ (1.21 g, 1.65 mmol) in dioxane (100 mL) was stirred at 100 °C overnight under an argon atmosphere. The mixture was then filtered, and the filter cake was washed with dioxane. The filtrate was concentrated under reduced pressure to afford 9-acetyl-3,7-dimethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4H-quinolizin-4-one (6 g, crude yield) which was used in the next step directly without further purification. LCMS: (ESI^+) m/z = 342.1 (M+H).

Step 2: Preparation of 9-acetyl-2-(2-bromopyrimidin-5-yl)-3,7-dimethyl-4H-quinolizin-4-one



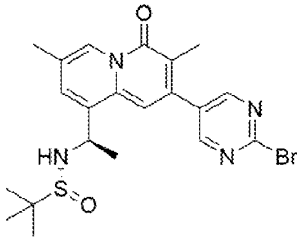
[000305] A mixture of 9-acetyl-3,7-dimethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4H-quinolizin-4-one (6 g, 17.6 mmol), 2-bromo-5-iodopyrimidine (6.01 g, 21.1 mmol), Na_2CO_3 (3.73 g, 35.2 mmol) and $Pd(dppf)Cl_2$ (1.29 g, 1.76 mmol) in dioxane (100 mL) and H_2O (10 mL) was stirred at 100 °C overnight under an argon atmosphere. The mixture was then cooled to room temperature and diluted with H_2O (100 mL). The resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organics were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluted with EA) to afford 9-acetyl-2-(2-bromopyrimidin-5-yl)-3,7-dimethyl-4H-quinolizin-4-one (2.24 g, 34 % yield) as a brown solid. LCMS: (ESI^+) m/z = 371.9 (M+H).

Step 3: Preparation of (R,E)-N-(1-(2-(2-bromopyrimidin-5-yl)-3,7-dimethyl-4-oxo-4H-quinolizin-9-yl)ethylidene)-2-methylpropane-2-sulfinamide



[000306] To a stirred mixture of 9-acetyl-2-(2-bromopyrimidin-5-yl)-3,7-dimethyl-4H-quinolizin-4-one (2.25 g, 6.03 mmol) and (R)-2-methylpropane-2-sulfinamide (3.6 g, 30.5 mmol) in toluene (45 mL) under an argon atmosphere at room temperature was added titanium ethoxide (4.12 g, 18.0 mmol). The resulting mixture was stirred at 80 °C overnight and then cooled to room temperature. The mixture was poured into water (100 mL) and then filtered. The filter cake was washed with EtOAc (2 x 50 mL). The filtrate mixture was extracted with EtOAc (3 x 100 mL). The combined organics were washed with brine (2 x 100 mL), dried over anhydrous Na_2SO_4, filtered, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluted with CH_2Cl_2:MeOH = 10:1) to afford (R,E)-N-(1-(2-(2-bromopyrimidin-5-yl)-3,7-dimethyl-4-oxo-4H-quinolizin-9-yl)ethylidene)-2-methylpropane-2-sulfinamide (2.24 g, 78% yield) as a brown solid. LCMS: (ESI^+) m/z = 475.1 (M+H).

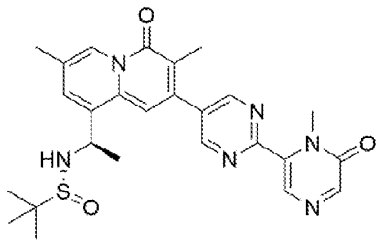
Step 4: Preparation of (R)-N-((R)-1-(2-(2-bromopyrimidin-5-yl)-3,7-dimethyl-4-oxo-4H-quinolizin-9-yl)ethyl)-2-methylpropane-2-sulfinamide



[000307] To a stirred mixture of (R,E)-N-(1-(2-(2-bromopyrimidin-5-yl)-3,7-dimethyl-4-oxo-4H-quinolizin-9-yl)ethylidene)-2-methylpropane-2-sulfinamide (1.2 g, 2.52 mmol) and cerium(III) chloride heptahydrate (940 mg, 2.52 mmol) in MeOH (20 mL) and DCM (4 mL) was added $NaBH_4$ (191 mg, 5.05 mmol) in portions at -40 °C under an argon atmosphere. The resulting mixture was stirred at -40 °C for 2 h and then quenched with H_2O (100 mL). The resulting mixture was

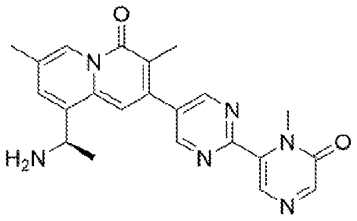
extracted with EtOAc (3 x 100 mL). The combined organics were washed with brine (1 x 100 mL), dried over anhydrous Na_2SO_4, filtered, and then concentrated under reduced pressure. The crude product was purified by prep-HPLC (C18 silica gel; mobile phase of MeCN in water (5 mmol/L FA), 5% to 70% gradient over 30 min) to afford (R)-N-((R)-1-(2-(2-bromopyrimidin-5-yl)-3,7-dimethyl-4-oxo-4H-quinolizin-9-yl)ethyl)-2-methylpropane-2-sulfinamide (765 mg, 63% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.89 (s, 2H), 8.84 (s, 1H), 7.60 – 7.55 (m, 1H), 7.04 (s, 1H), 5.88 (d, J = 6.8 Hz, 1H), 4.93 – 4.86 (m, 1H), 2.39 (d, J = 1.3 Hz, 3H), 2.16 (s, 3H), 1.49 (d, J = 6.6 Hz, 3H), 1.10 (s, 9H).

Step 5: Preparation of (R)-N-((R)-1-(3,7-dimethyl-2-(2-(1-methyl-6-oxo-1,6-dihydropyrazin-2-yl)pyrimidin-5-yl)-4-oxo-4H-quinolizin-9-yl)ethyl)-2-methylpropane-2-sulfinamide



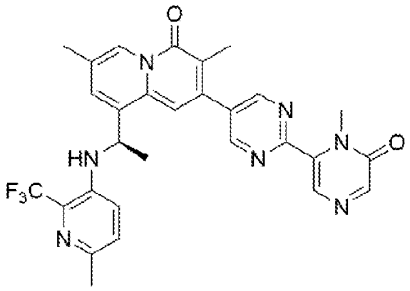
[000308] A mixture of (R)-N-((R)-1-(2-(2-bromopyrimidin-5-yl)-3,7-dimethyl-4-oxo-4H-quinolizin-9-yl)ethyl)-2-methylpropane-2-sulfinamide (250 mg, 0.49 mmol), 1-methyl-6-(trimethylstannyl)pyrazin-2-one (Intermediate 7) (275 mg, 1.01 mmol), mesyl[(tri-t-butylphosphine)-2-(2-aminobiphenyl)]palladium(II) (40 mg, 0.067 mmol), and t-Bu_3P•HBF_4 (19.5 mg, 0.067 mmol) in DMF (10 mL) was stirred at 80 °C overnight under an argon atmosphere. The mixture was then poured into water (70 mL) and then extracted with EtOAc (2 x 70 mL). The combined organics were washed with brine (1 x 70 mL), dried over anhydrous Na_2SO_4, filtered, and then concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography (C18 silica gel; mobile phase of MeCN in water (10 mmol/L NH_4HCO_3), 10% to 95% gradient over 20 min) to afford (R)-N-((R)-1-(3,7-dimethyl-2-(2-(1-methyl-6-oxo-1,6-dihydropyrazin-2-yl)pyrimidin-5-yl)-4-oxo-4H-quinolizin-9-yl)ethyl)-2-methylpropane-2-sulfinamide (200 mg, 74% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.20 (d, J = 0.9 Hz, 2H), 8.87 (s, 1H), 8.22 – 8.20 (m, 1H), 7.79 – 7.85 (m. 1H), 7.65 – 7.53 (m, 1H), 7.08 (s, 1H), 5.92 (d, J = 6.8 Hz, 1H), 4.97 – 4.80 (m, 1H), 3.61 (s, 3H), 2.40 (d, J = 1.3 Hz, 3H), 2.23 (s, 3H), 1.51 (d, J = 6.6 Hz, 3H), 1.11 (s, 9H).

Step 6: Preparation of (R)-9-(1-aminoethyl)-3,7-dimethyl-2-(2-(1-methyl-6-oxo-1,6-dihydropyrazin-2-yl)pyrimidin-5-yl)-4H-quinolizin-4-one



[000309] To a stirred solution of (R)-N-((R)-1-(3,7-dimethyl-2-(2-(1-methyl-6-oxo-1,6-dihydropyrazin-2-yl)pyrimidin-5-yl)-4-oxo-4H-quinolizin-9-yl)ethyl)-2-methylpropane-2-sulfinamide (200 mg, 0.40 mol) in MeOH (5 mL) was added HCl in 1,4-dioxane (4.0 M, 0.2 mL, 0.80 mol) dropwise at 0 °C under an argon atmosphere. The resulting mixture was stirred at room temperature for 1 h and then adjusted to pH 8 via the addition of saturated aqueous $NaHCO_3$. The resulting mixture was concentrated under reduced pressure and the residue was purified by reversed-phase flash chromatography (C18 silica gel; mobile phase of MeCN in water (10 mmol/L NH_4HCO_3), 5% to 50% gradient over 30 min) to afford (R)-9-(1-aminoethyl)-3,7-dimethyl-2-(2-(1-methyl-6-oxo-1,6-dihydropyrazin-2-yl)pyrimidin-5-yl)-4H-quinolizin-4-one (155 mg, 98% yield) as a yellow solid. LCMS: (ESI^+) m/z = 403.3 (M+H).

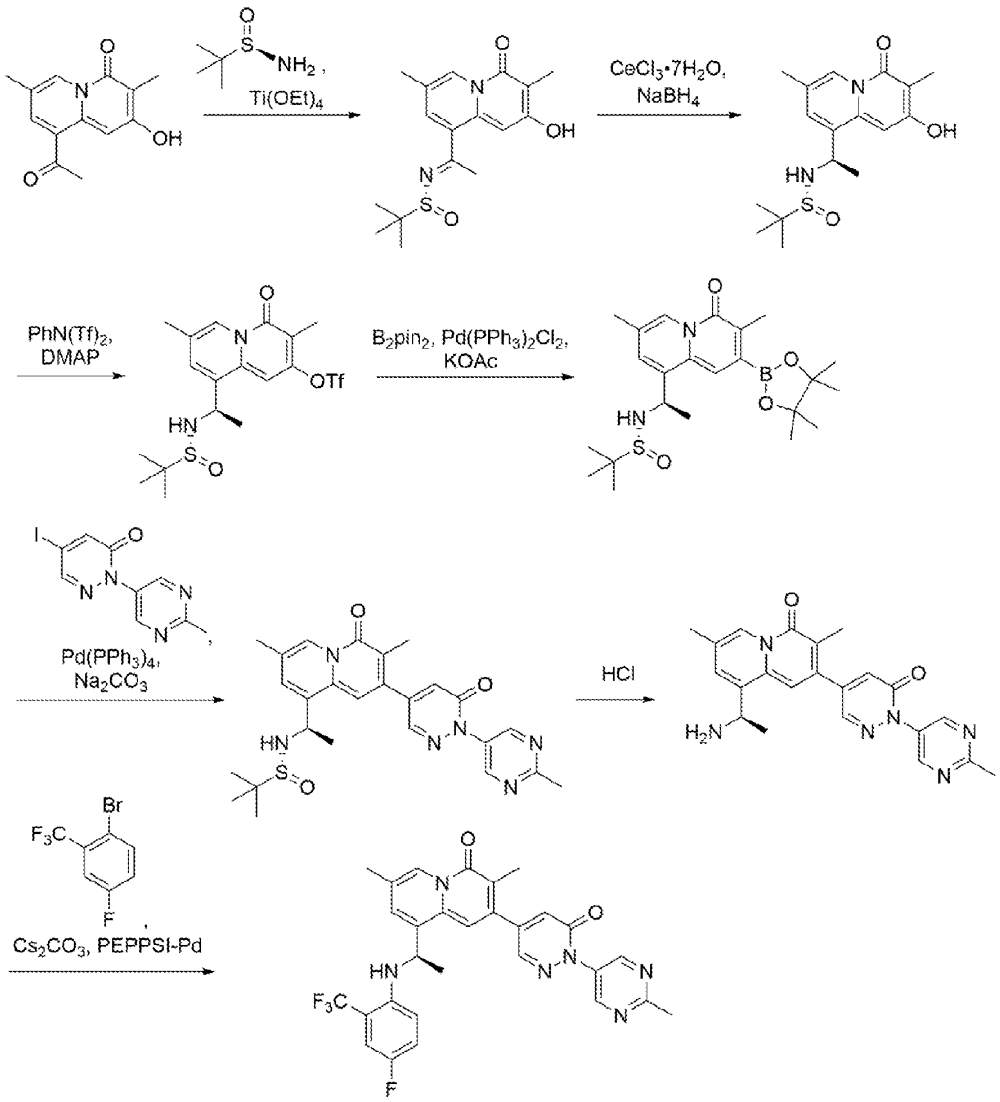
Step 7: Preparation of (R)-3,7-dimethyl-9-(1-((6-methyl-2-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-2-(2-(1-methyl-6-oxo-1,6-dihydropyrazin-2-yl)pyrimidin-5-yl)-4H-quinolizin-4-one (Example 22)



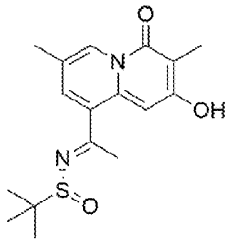
[000310] A mixture of (R)-9-(1-aminoethyl)-3,7-dimethyl-2-(2-(1-methyl-6-oxo-1,6-dihydropyrazin-2-yl)pyrimidin-5-yl)-4H-quinolizin-4-one (38 mg, 0.09 mmol), 3-bromo-6-methyl-2-(trifluoromethyl)pyridine (27 mg, 0.11 mmol), Cs_2CO_3 (92 mg, 0.28 mmol), and [1,3-bis[2,6-bis(1-ethylpropyl)phenyl]-4,5-dichloro-imidazol-2-ylidene]-dichloro-(2-methylpyridin-1-ium-1-

yl)palladium (7.9 mg, 0.01 mmol) in dioxane (2 mL) was stirred at 100 °C for 2 h under an argon atmosphere. The mixture was then poured into water (10 mL) and extracted with EtOAc (2 x 20 mL). The combined organics were washed with brine, dried over anhydrous Na_2SO_4, filtered, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluted with CH_2Cl_2:MeOH = 10:1) and then purified further by prep-HPLC (XBridge Prep OBD C18 column 30 x 150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 5% B to 5% B in 1 min, 5% B to 30% B in 2 min, 30% to 48% B in 11 min) to afford (R)-3,7-dimethyl-9-(1-((6-methyl-2-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-2-(2-(1-methyl-6-oxo-1,6-dihydropyrazin-2-yl)pyrimidin-5-yl)-4H-quinolizin-4-one (28.5 mg, 54% yield, >99% ee) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.25 (s, 2H), 8.83 (s, 1H), 8.21 (s, 1H), 7.79 (s, 1H), 7.41 (s, 1H), 7.22 (s, 1H), 7.17 (d, J = 8.6 Hz, 1H), 6.84 (d, J = 8.8 Hz, 1H), 5.71 (d, J = 6.6 Hz, 1H), 5.28 – 5.20 (m, 1H), 3.62 (s, 3H), 2.32 – 2.28 (m, 6H), 2.25 (s, 3H), 1.60 (d, J = 6.5 Hz, 3H); LCMS: (ESI$^+$) m/z = 562.3 (M+H).

[000311] **Example 23:** (R)-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3,7-dimethyl-2-(1-(2-methylpyrimidin-5-yl)-6-oxo-1,6-dihydropyridazin-4-yl)-4H-quinolizin-4-one

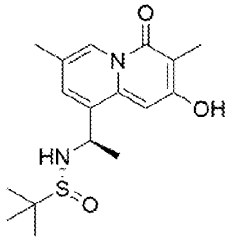


Step 1: Preparation of (R,E)-N-(1-(2-hydroxy-3,7-dimethyl-4-oxo-4H-quinolizin-9-yl)ethylidene)-2-methylpropane-2-sulfinamide



[000312] A mixture of 9-acetyl-2-hydroxy-3,7-dimethyl-4H-quinolizin-4-one (Example 21, Step 1) (10 g, 43.2 mmol) in toluene (40 mL) under a nitrogen atmosphere was treated with (R)-2-methylpropane-2-sulfinamide (15.7 g, 130 mmol) followed by the dropwise addition of titanium ethoxide (29.5 g, 130 mmol). The resulting mixture was stirred at 80 °C overnight, and then was poured into H_2O (100 mL) at room temperature. The resulting mixture was filtered, and the filter cake was washed with EtOAc (2 x 50 mL). The filtrate mixture was extracted with EtOAc (3 x 100 mL). The combined organics were washed with brine (2 x 100 mL), dried over anhydrous Na_2SO_4, filtered, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluted with CH_2Cl_2:MeOH = 10:1) to afford (R,E)-N-(1-(2-hydroxy-3,7-dimethyl-4-oxo-4H-quinolizin-9-yl)ethylidene)-2-methylpropane-2-sulfinamide (12.2 g, 84% yield) as a brown solid. LCMS: (ESI^+) m/z = 335.1 (M+H).

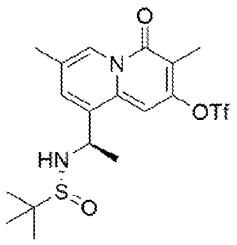
Step 2: Preparation of (R)-N-((R)-1-(2-hydroxy-3,7-dimethyl-4-oxo-4H-quinolizin-9-yl)ethyl)-2-methylpropane-2-sulfinamide



[000313] A mixture of (R,E)-N-(1-(2-hydroxy-3,7-dimethyl-4-oxo-4H-quinolizin-9-yl)ethylidene)-2-methylpropane-2-sulfinamide (12.2 g, 36.5 mmol) in MeOH (30 mL) under a nitrogen atmosphere was treated with $CeCl_3 \cdot 7H_2O$ (18.0 g, 72.9 mmol) at room temperature followed by the addition of $NaBH_4$ (2.76 g, 73.0 mmol) in portions at -40 °C. The resulting mixture was then stirred at -40 °C for 2 h, and then was quenched by the addition of water (100 mL) at

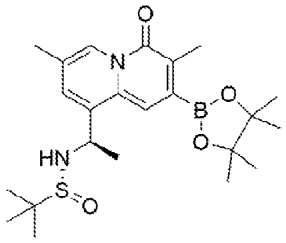
0 °C. The resulting mixture was extracted with EtOAc (3 x 200 mL). The combined organics were washed with brine (2 x 200 mL), dried over anhydrous Na_2SO_4, filtered, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluted with CH_2Cl_2:MeOH = 10:1) to afford (R)-N-((R)-1-(2-hydroxy-3,7-dimethyl-4-oxo-4H-quinolizin-9-yl)ethyl)-2-methylpropane-2-sulfinamide (8.5 g, 69% yield) as a light yellow solid. LCMS: (ESI^+) m/z = 337.2 (M+H).

Step 3: Preparation of 9-((R)-1-(((R)-tert-butylsulfinyl)amino)ethyl)-3,7-dimethyl-4-oxo-4H-quinolizin-2-yl trifluoromethanesulfonate



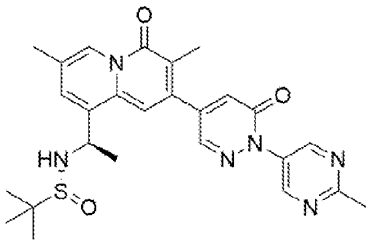
[000314] To a stirred mixture of (R)-N-((R)-1-(2-hydroxy-3,7-dimethyl-4-oxo-4H-quinolizin-9-yl)ethyl)-2-methylpropane-2-sulfinamide (2.0 g, 5.9 mmol) and DMAP (1.4 g, 11.8 mmol) in DCM (20 mL) was added 1,1,1-trifluoro-N-phenyl-N-(trifluoromethane)sulfonylmethanesulfonamide (2.5 g, 7.1 mmol) in portions at 0 °C under an argon atmosphere. The resulting mixture was stirred at room temperature for 2 h and then was diluted with ice water (50 mL) at 0°C. The resulting mixture was extracted with CH_2Cl_2 (3 x 80 mL), dried over anhydrous Na_2SO_4, filtered, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluted with PE:EA = 1:1) to afford 9-((R)-1-(((R)-tert-butylsulfinyl)amino)ethyl)-3,7-dimethyl-4-oxo-4H-quinolizin-2-yl trifluoromethanesulfonate (2.1 g, 75% yield) as a light yellow oil. LCMS: (ESI^+) m/z = 469.1 (M+H).

Step 4: Preparation of (R)-N-((R)-1-(3,7-dimethyl-4-oxo-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4H-quinolizin-9-yl)ethyl)-2-methylpropane-2-sulfinamide



[000315] To a stirred mixture of 9-((R)-1-(((R)-tert-butylsulfinyl)amino)ethyl)-3,7-dimethyl-4-oxo-4H-quinolizin-2-yl trifluoromethanesulfonate (1.3 g, 2.7 mmol) and bis(pinacolato)diboron (1.1 g, 4.1 mmol) in dioxane (15.0 mL) were added potassium acetate (545 mg, 5.5 mmol) and $Pd(PPh_3)_2Cl_2$ (195 mg, 0.3 mmol) in portions at room temperature under an argon atmosphere. The resulting mixture was stirred at 80 °C for 2 h and then was cooled to room temperature. The resulting mixture was filtered, and the filter cake was washed with CH_2Cl_2 (3 x 20 mL). The filtrate was concentrated under reduced pressure to afford (R)-N-((R)-1-(3,7-dimethyl-4-oxo-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4H-quinolizin-9-yl)ethyl)-2-methylpropane-2-sulfinamide (1.0 g, crude yield) which was used directly in the next step without further purification. LCMS: (ESI^+) m/z = 447.1 (M+H).

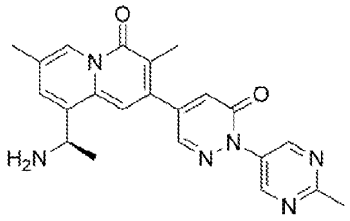
Step 5: Preparation of (R)-N-((R)-1-(3,7-dimethyl-2-(1-(2-methylpyrimidin-5-yl)-6-oxo-1,6-dihydropyridazin-4-yl)-4-oxo-4H-quinolizin-9-yl)ethyl)-2-methylpropane-2-sulfinamide



[000316] To a stirred mixture of (R)-N-((R)-1-(3,7-dimethyl-4-oxo-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4H-quinolizin-9-yl)ethyl)-2-methylpropane-2-sulfinamide (500 mg, 1.1 mmol) and 5-iodo-2-(2-methylpyrimidin-5-yl)pyridazin-3-one (Intermediate 2) (528 mg, 1.7 mmol) in dioxane (5 mL) and H_2O (0.5 mL) under an argon atmosphere were added Na_2CO_3 (237 mg, 2.2 mmol) and $Pd(PPh_3)_4$ (129 mg, 0.1 mmol) in portions at room temperature. The resulting mixture was stirred at 100 °C for 2 h, then cooled to 0 °C and diluted with ice water (40 mL). The resulting mixture was extracted with CH_2Cl_2 (3 x 80 mL). The combined organics were washed

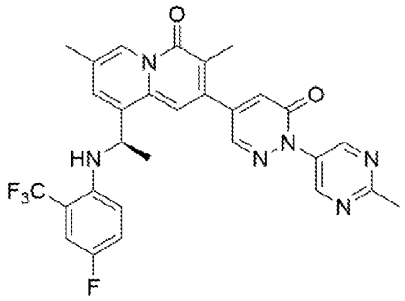
with brine (2 x 200 mL), dried over anhydrous Na_2SO_4, filtered, and then concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography (C18 silica gel; mobile phase of MeCN in water (10 mmol/L NH_4HCO_3), 5% to 70% gradient over 40 min) to afford (R)-N-((R)-1-(3,7-dimethyl-2-(1-(2-methylpyrimidin-5-yl)-6-oxo-1,6-dihydropyridazin-4-yl)-4-oxo-4H-quinolizin-9-yl)ethyl)-2-methylpropane-2-sulfinamide (200 mg, 35% yield) as a light yellow solid. LCMS: (ESI^+) m/z = 507.2 (M+H).

Step 6: Preparation of (R)-9-(1-aminoethyl)-3,7-dimethyl-2-(1-(2-methylpyrimidin-5-yl)-6-oxo-1,6-dihydropyridazin-4-yl)-4H-quinolizin-4-one



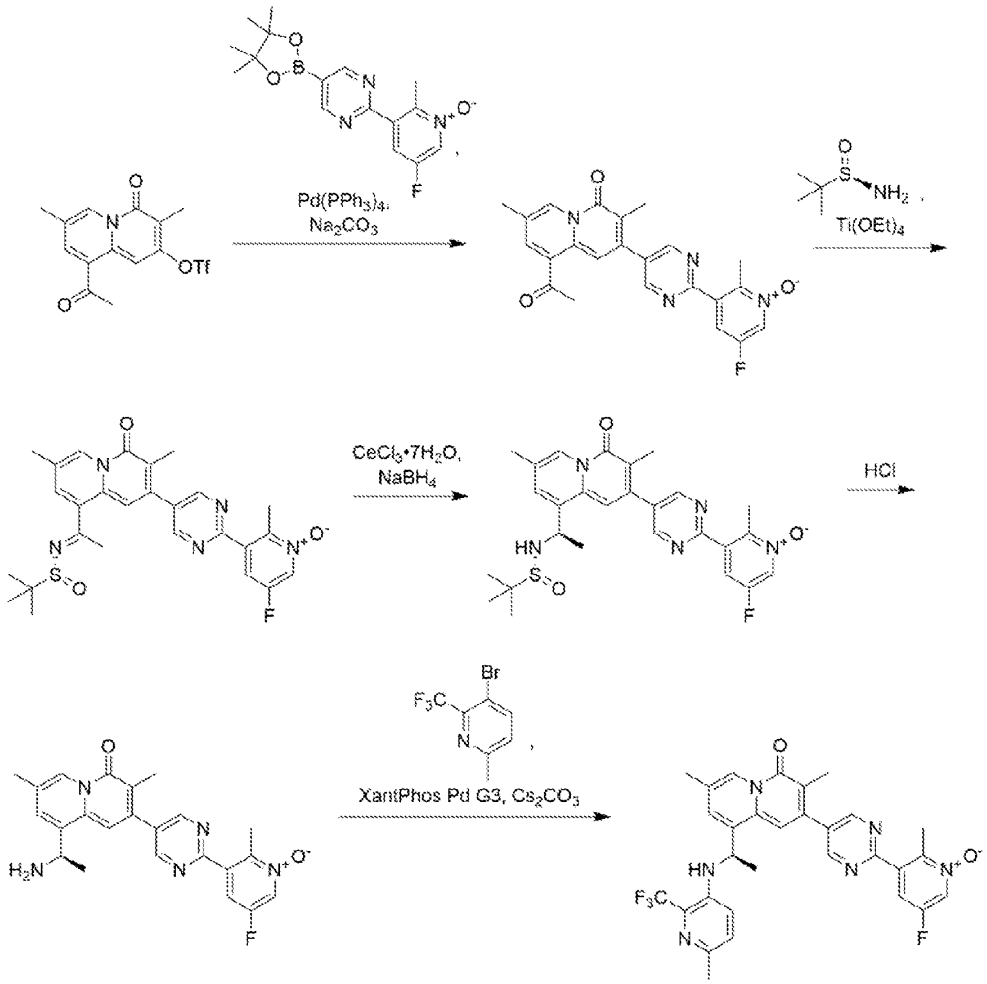
[000317] To a stirred solution of (R)-N-((R)-1-(3,7-dimethyl-2-(1-(2-methylpyrimidin-5-yl)-6-oxo-1,6-dihydropyridazin-4-yl)-4-oxo-4H-quinolizin-9-yl)ethyl)-2-methylpropane-2-sulfinamide (200 mg, 0.4 mmol) in methanol (5 mL) was added HCl (4 M in EtOAc, 0.2 mL) dropwise at 0 °C under an argon atmosphere. The resulting mixture was stirred at room temperature for 1 h and then adjusted to pH 8 via the addition of saturated aqueous $NaHCO_3$. The resulting mixture was concentrated under reduced pressure and the residue was purified by reversed-phase flash chromatography (C18 silica gel; mobile phase of MeCN in water (10 mmol/L NH_4HCO_3), 5% to 50% gradient over 30 min) to afford (R)-9-(1-aminoethyl)-3,7-dimethyl-2-(1-(2-methylpyrimidin-5-yl)-6-oxo-1,6-dihydropyridazin-4-yl)-4H-quinolizin-4-one (140 mg, 88% yield) as a yellow solid. LCMS: (ESI^+) m/z = 403.0 (M+H).

Step 7: Preparation of (R)-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3,7-dimethyl-2-(1-(2-methylpyrimidin-5-yl)-6-oxo-1,6-dihydropyridazin-4-yl)-4H-quinolizin-4-one (Example 23)

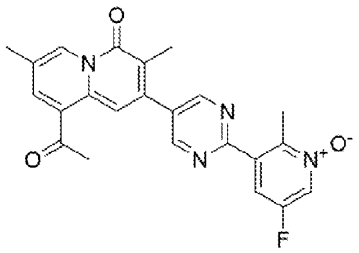


[000318] To a stirred mixture of (R)-9-(1-aminoethyl)-3,7-dimethyl-2-(1-(2-methylpyrimidin-5-yl)-6-oxo-1,6-dihydropyridazin-4-yl)-4H-quinolizin-4-one (4.0 g, 9.94 mmol) and 1-bromo-4-fluoro-2-(trifluoromethyl)benzene (3.13 g, 12.9 mmol) in dioxane (20 mL) under an argon atmosphere were added Cs_2CO_3 (9.71 g, 29.8 mmol) and [1,3-bis[2,6-bis(1-ethylpropyl)phenyl]-4,5-dichloro-imidazol-2-ylidene]-dichloro-(2-methylpyridin-1-ium-1-yl)palladium (0.84 g, 0.99 mmol) in portions at room temperature. The resulting mixture was stirred at 100 °C, and then was cooled to 0 °C and diluted with ice water (30 mL). The mixture was extracted with EtOAc (3 x 60 mL). dried over anhydrous Na_2SO_4, filtered, and then concentrated under reduced pressure. The crude product was purified by prep-HPLC (Column: Xbridge Phenyl OBD column, 30 x 150 mm, 5 µm; Mobile Phase A: water (0.1% FA), Mobile Phase B: ACN; flow rate: 60 mL/min; Gradient (B%): 42% B to 57% B over 10 min) to afford (R)-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3,7-dimethyl-2-(1-(2-methylpyrimidin-5-yl)-6-oxo-1,6-dihydropyridazin-4-yl)-4H-quinolizin-4-one (2.53 g, 45% yield, >99% ee) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.08 (s, 2H), 8.82 (s, 1H), 8.39 (d, J = 2.0 Hz, 1H), 7.43 – 7.32 (m, 3H), 7.21 – 7.14 (m, 2H), 6.49 – 6.42 (m, 1H), 5.50 (d, J = 6.3 Hz, 1H), 5.26 – 5.19 (m, 1H), 2.72 (s, 3H), 2.32 – 2.25 (m, 6H), 1.59 (d, J = 6.5 Hz, 3H); LCMS: (ESI$^+$) m/z = 565.2 (M+H).

[000319] **Example 24:** (R)-3-(5-(3,7-dimethyl-9-(1-((6-methyl-2-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-4-oxo-4H-quinolizin-2-yl)pyrimidin-2-yl)-5-fluoro-2-methylpyridine 1-oxide (Example 24)

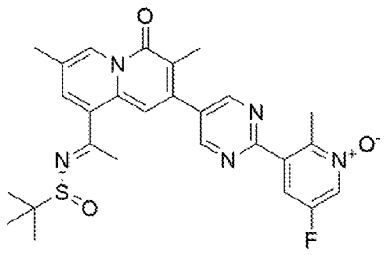


Step 1: Preparation of 3-(5-(9-acetyl-3,7-dimethyl-4-oxo-4H-quinolizin-2-yl)pyrimidin-2-yl)-5-fluoro-2-methylpyridine 1-oxide



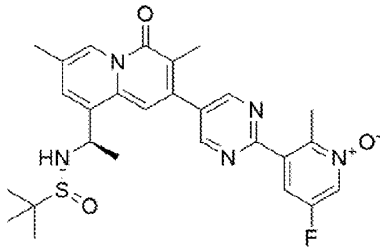
[000320] To a stirred mixture of 9-acetyl-3,7-dimethyl-4-oxo-4H-quinolizin-2-yl trifluoromethanesulfonate (Example 21, Step 2) (500 mg, 1.38 mmol) in 1,4-dioxane (10 mL) and H_2O (2 mL) at room temperature and under a nitrogen atmosphere was added 5-fluoro-2-methyl-3-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidin-2-yl)pyridine 1-oxide (Intermediate 9) (501 mg, 1.52 mmol), Na_2CO_3 (292 mg, 2.75 mmol), and $Pd(PPh_3)_4$ (159 mg, 0.14 mmol). The resulting mixture was stirred at 90 °C for 2 h. The mixture was then filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by prep-TLC (CH_2Cl_2:MeOH = 20:1) to afford 3-(5-(9-acetyl-3,7-dimethyl-4-oxo-4H-quinolizin-2-yl)pyrimidin-2-yl)-5-fluoro-2-methylpyridine 1-oxide (125 mg, 21% yield) as a light yellow solid. LCMS: (ESI^+) m/z = 419.2 (M+H).

Step 2: Preparation of (R,E)-3-(5-(9-(1-((tert-butylsulfinyl)imino)ethyl)-3,7-dimethyl-4-oxo-4H-quinolizin-2-yl)pyrimidin-2-yl)-5-fluoro-2-methylpyridine 1-oxide



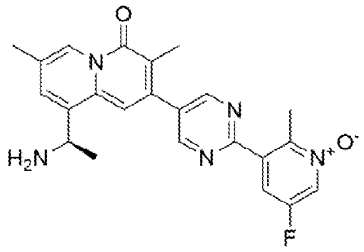
[000321] To a stirred mixture of 3-(5-(9-acetyl-3,7-dimethyl-4-oxo-4H-quinolizin-2-yl)pyrimidin-2-yl)-5-fluoro-2-methylpyridine 1-oxide (100 mg, 0.24 mmol) in THF (5 mL) was added (R)-2-methylpropane-2-sulfinamide (145 mg, 1.19 mmol) and titanium ethoxide (273 mg, 1.19 mmo) at room temperature. The resulting mixture was then stirred at 80 °C for 5 h, then concentrated under reduced pressure. The residue was purified by prep-TLC (CH_2Cl_2:MeOH = 10:1) to afford (R,E)-3-(5-(9-(1-((tert-butylsulfinyl)imino)ethyl)-3,7-dimethyl-4-oxo-4H-quinolizin-2-yl)pyrimidin-2-yl)-5-fluoro-2-methylpyridine 1-oxide (75 mg, 60% yield) as a light yellow solid. LCMS: (ESI^+) m/z = 522.3 (M+H).

Step 3: Preparation of 3-(5-(9-((R)-1-(((R)-tert-butylsulfinyl)amino)ethyl)-3,7-dimethyl-4-oxo-4H-quinolizin-2-yl)pyrimidin-2-yl)-5-fluoro-2-methylpyridine 1-oxide



[000322] To a stirred mixture of (R,E)-3-(5-(9-(1-((tert-butylsulfinyl)imino)ethyl)-3,7-dimethyl-4-oxo-4H-quinolizin-2-yl)pyrimidin-2-yl)-5-fluoro-2-methylpyridine 1-oxide (120 mg, 0.23 mmol) in MeOH (1.5 mL) and DCM (1.5 mL) was added cerium(III) chloride heptahydrate (214 mg, 0.58 mmol). The mixture was then cooled to -40 °C and $NaBH_4$ (23 mg, 0.60 mmol) was added in portions. The resulting mixture was stirred at -40 °C for 2 h and then diluted with water (10 mL). The resulting mixture was extracted with DCM (3 x 10 mL) and the combined organics were washed with brine (3 x 10 mL), dried over anhydrous Na_2SO_4, filtered, and then concentrated under reduced pressure. The residue was purified by prep-TLC (CH_2Cl_2:MeOH = 10:1) to afford 3-(5-(9-((R)-1-(((R)-tert-butylsulfinyl)amino)ethyl)-3,7-dimethyl-4-oxo-4H-quinolizin-2-yl)pyrimidin-2-yl)-5-fluoro-2-methylpyridine 1-oxide (100 mg, 83% yield) as a light yellow solid. LCMS: (ESI^+) m/z = 524.3 (M+H).

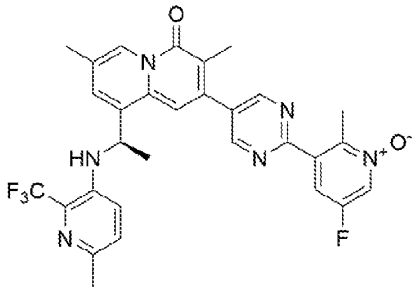
Step 4: Preparation of (R)-3-(5-(9-(1-aminoethyl)-3,7-dimethyl-4-oxo-4H-quinolizin-2-yl)pyrimidin-2-yl)-5-fluoro-2-methylpyridine 1-oxide



[000323] A stirred mixture of 3-(5-(9-((R)-1-(((R)-tert-butylsulfinyl)amino)ethyl)-3,7-dimethyl-4-oxo-4H-quinolizin-2-yl)pyrimidin-2-yl)-5-fluoro-2-methylpyridine 1-oxide (100 mg, 0.19 mmol) in MeOH (2 mL) was treated with HCl (4 M in EtOAc, 0.1 mL) at room temperature. The resulting mixture was stirred for 2 h and then adjusted to pH 8 via the addition of aqueous Na_2CO_3. The resulting mixture was filtered and the filter cake was washed with MeOH (2 mL). The filtrate was

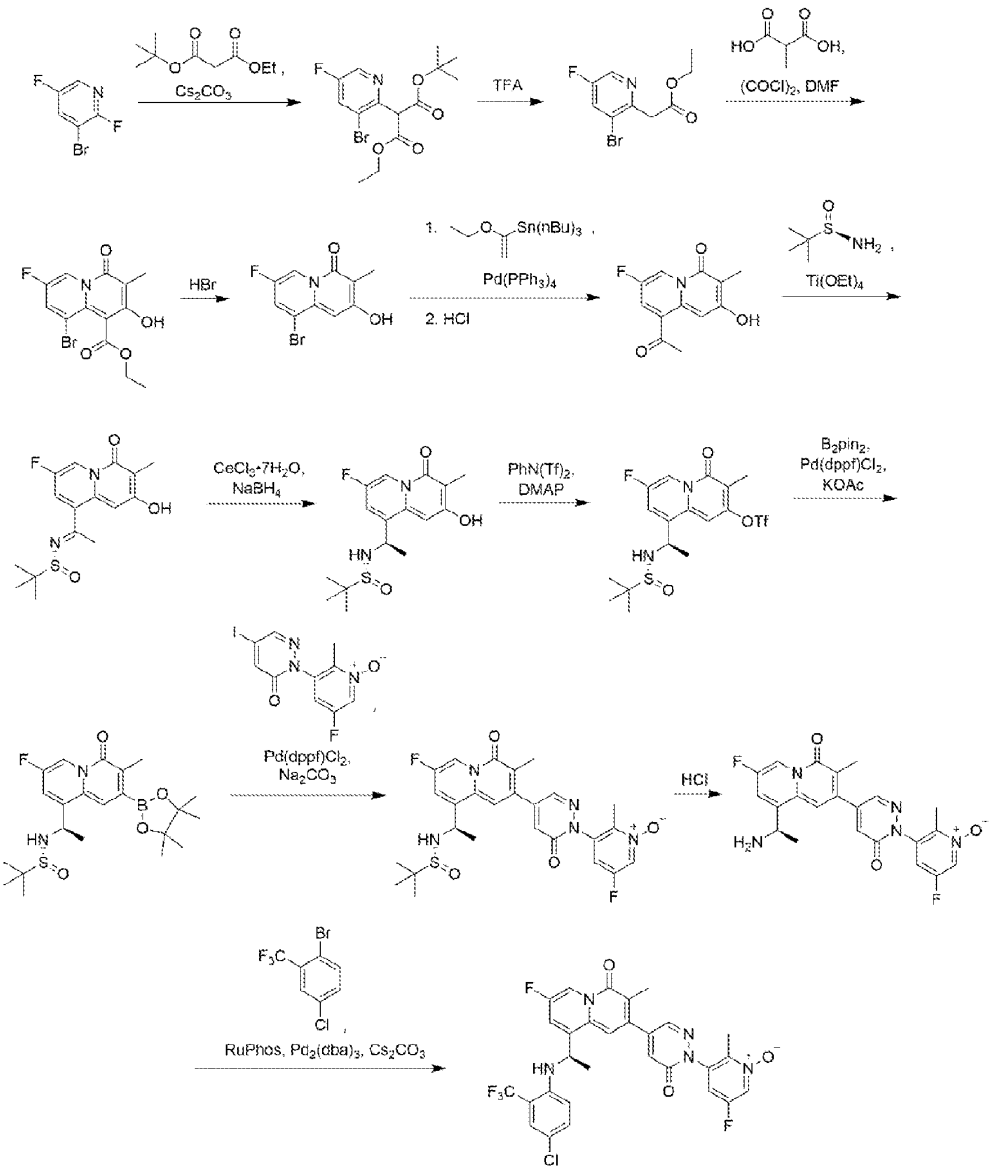
concentrated under reduced pressure and the residue was purified by reversed-phase flash chromatography (C18 silica gel; mobile phase of ACN in H_2O (5 mmol/L NH_4HCO_3), 10% to 50% gradient over 10 min) to afford (R)-3-(5-(9-(1-aminoethyl)-3,7-dimethyl-4-oxo-4H-quinolizin-2-yl)pyrimidin-2-yl)-5-fluoro-2-methylpyridine 1-oxide (70 mg, 87% yield) as a yellow solid. LCMS: (ESI^+) m/z = 420.2 (M+H).

Step 5: Preparation of (R)-3-(5-(3,7-dimethyl-9-(1-((6-methyl-2-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-4-oxo-4H-quinolizin-2-yl)pyrimidin-2-yl)-5-fluoro-2-methylpyridine 1-oxide

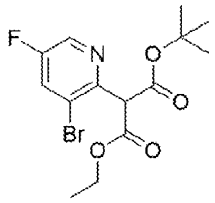


[000324] To a mixture of (R)-3-(5-(9-(1-aminoethyl)-3,7-dimethyl-4-oxo-4H-quinolizin-2-yl)pyrimidin-2-yl)-5-fluoro-2-methylpyridine 1-oxide (55 mg, 0.13 mmol) in dioxane (5 mL) were added 3-bromo-6-methyl-2-(trifluoromethyl)pyridine (63 mg, 0.2 mmol), Cs_2CO_3 (85.4 mg, 0.26 mol) and [(4,5-bis(diphenylphosphino)-9,9-dimethylxanthene)-2-(2'-amino-1,1'-biphenyl)]palladium(II) methanesulfonate (12.4 mg, 0.01 mmol) under a nitrogen atmosphere. After stirring for 5 h at 100 °C, the mixture was filtered and the filter cake was washed with DCM (3 x 5 mL). The filtrate was concentrated under reduced pressure and the crude product was purified by prep-HPLC (Column: XBridge Prep OBD C18 column, 30 x 150 mm, 5 μm; Mobile Phase A: water (10mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 30% B to 60% B in 8 min) and then purified further by prep-chiral-HPLC (Column: $CHIRALPAKIH_3$; Mobile Phase A: Hex:(MeOH:DCM = 1:1) = 75:25) to afford (R)-3-(5-(3,7-dimethyl-9-(1-((6-methyl-2-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-4-oxo-4H-quinolizin-2-yl)pyrimidin-2-yl)-5-fluoro-2-methylpyridine 1-oxide (8.2 mg, 11% yield, >99% ee) as a light yellow solid. ^1H NMR (400 MHz, MeOD): δ 9.15 (s, 2H), 8.96 (s, 1H), 8.68 – 8.63 (m, 1H), 8.08 – 7.99 (m, 1H), 7.52 (d, *J* = 1.7 Hz, 1H), 7.26 (s, 1H), 7.12 (d, *J* = 8.6 Hz, 1H), 6.82 (d, *J* = 8.6 Hz, 1H), 5.25 – 5.14 (m, 1H), 2.80 (d, *J* = 1.1 Hz, 3H), 2.45 – 2.30 (m, 9H), 1.71 (d, *J* = 6.6 Hz, 3H); LCMS: (ESI^+) m/z = 579.3 (M+H).

[000325] **Example 25:** (R)-3-(4-(9-(1-((4-chloro-2-(trifluoromethyl)phenyl)amino)ethyl)-7-fluoro-3-methyl-4-oxo-4H-quinolizin-2-yl)-6-oxopyridazin-1(6H)-yl)-5-fluoro-2-methylpyridine 1-oxide

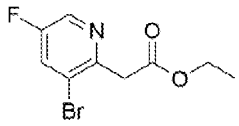


Step 1: Preparation of 1-(tert-butyl) 3-ethyl 2-(3-bromo-5-fluoropyridin-2-yl)malonate



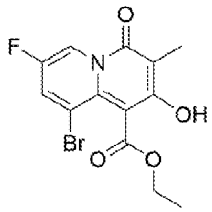
[000326] To a stirred mixture of 3-bromo-2,5-difluoropyridine (5.0 g, 25.8 mmol) and 1-tert-butyl 3-ethyl propanedioate (9.70 g, 51.6 mmol) in DMSO (40 mL) under a nitrogen atmosphere at room temperature was added Cs_2CO_3 (16.8 g, 51.6 mmol). The resulting mixture was stirred at 100 °C for 16 h and then cooled to room temperature. The resulting mixture was diluted with H_2O (50 mL) and extracted with PE (3 x 60 mL). The combined organics were washed with brine (2 x 50 mL) and then were concentrated under reduced pressure to half volume. The resulting mixture was stirred for 0.5 h at 0 °C, then filtered and the filter cake was washed with cold PE (2 x 10 mL) to afford 1-(tert-butyl) 3-ethyl 2-(3-bromo-5-fluoropyridin-2-yl)malonate (5.1 g, 54% yield) was obtained as an off-white solid. LCMS: (ESI^+) m/z = 362.0 (M+H).

Step 2: Preparation of ethyl 2-(3-bromo-5-fluoropyridin-2-yl)acetate



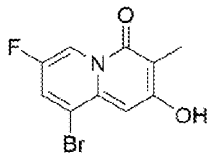
[000327] A mixture of 1-(tert-butyl) 3-ethyl 2-(3-bromo-5-fluoropyridin-2-yl)malonate (50 g, 138 mmol) in DCM (200 mL) and trifluoroacetic acid (200 mL) was stirred at room temperature for 16 h under a nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure and the resulting residue was suspended in DCM (300 mL). The mixture was then neutralized to pH 8 via the addition of aqueous Na_2CO_3 and then extracted with DCM (3 x 200 mL). The combined organics were washed with brine (3 x 100 mL), dried over anhydrous Na_2SO_4, filtered, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluted with PE:EA = 3:1) to afford ethyl 2-(3-bromo-5-fluoropyridin-2-yl)acetate (30 g, 83% yield) as a light yellow solid. LCMS: (ESI^+) m/z = 262.0 (M+H).

Step 3: Preparation of ethyl 9-bromo-7-fluoro-2-hydroxy-3-methyl-4-oxo-4H-quinolizine-1-carboxylate



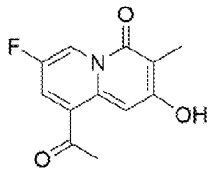
[000328] To a 0 °C mixture of methylmalonic acid (1.0 g, 8.47 mmol) and DMF (0.12 g, 1.70 mmol) in xylene (10 mL) under a nitrogen atmosphere was added oxalyl chloride (2.36 g, 18.6 mmol) dropwise. The resulting mixture was stirred at room temperature for 1 h until a clear solution was obtained. Ethyl 2-(3-bromo-5-fluoropyridin-2-yl)acetate (1.48 g, 5.64 mmol) was then added in portions and the resulting mixture was stirred at 130 °C for 3 h. The mixture was then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluted with DCM:MeOH = 10:1) to afford ethyl 9-bromo-7-fluoro-2-hydroxy-3-methyl-4-oxo-4H-quinolizine-1-carboxylate (0.8 g, 43% yield) as a yellow solid. LCMS: (ESI$^+$) m/z = 344.1 (M+H).

Step 4: Preparation of 9-bromo-7-fluoro-2-hydroxy-3-methyl-4H-quinolizin-4-one



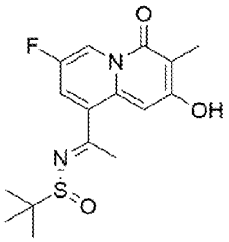
[000329] A mixture of ethyl 9-bromo-7-fluoro-2-hydroxy-3-methyl-4-oxo-4H-quinolizine-1-carboxylate (4.0 g, 11.6 mmol) and hydrobromic acid (33 wt % in HOAc, 20 mL) was stirred at 100 °C for 16 h under a nitrogen atmosphere and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluted with CH_2Cl_2:MeOH = 20:1) to afford 9-bromo-7-fluoro-2-hydroxy-3-methyl-4H-quinolizin-4-one (2.78 g, 85% yield) as a yellow solid. LCMS: (ESI$^+$) m/z = 272.0 (M+H).

Step 5: Preparation of 9-acetyl-7-fluoro-2-hydroxy-3-methyl-4H-quinolizin-4-one



[000330] A mixture of 9-bromo-7-fluoro-2-hydroxy-3-methyl-4H-quinolizin-4-one (70 g, 257 mmol), tributyl(1-ethoxyethenyl)stannane (112 g, 309 mmol) and $Pd(PPh_3)_4$ (29.7 g, 25.7 mmol) in dioxane (200 mL) was stirred at 100 °C for 16 h under a nitrogen atmosphere. Aqueous 1 M HCl (300 mL) was then added dropwise at room temperature and the resulting mixture was stirred for 0.5 h. The mixture was extracted with EtOAc (3 x 100 mL). The combined organics were washed with brine (3 x 100 mL), dried over anhydrous Na_2SO_4, filtered, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (CH_2Cl_2:MeOH = 10:1) to afford 9-acetyl-7-fluoro-2-hydroxy-3-methyl-4H-quinolizin-4-one (53 g, 88% yield) as a red solid. LCMS: (ESI^+) m/z = 236.1 (M+H).

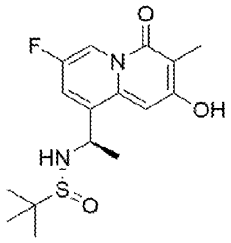
Step 6: Preparation of (R,E)-N-(1-(7-fluoro-2-hydroxy-3-methyl-4-oxo-4H-quinolizin-9-yl)ethylidene)-2-methylpropane-2-sulfinamide



[000331] To a stirred mixture of 9-acetyl-7-fluoro-2-hydroxy-3-methyl-4H-quinolizin-4-one (3.0 g, 12.8 mmol) and (R)-2-methylpropane-2-sulfinamide (7.73 g, 63.8 mmol) in toluene (30 mL) at room temperature was added titanium ethoxide (14.6 g, 63.8 mmol) in dropwise fashion. The resulting mixture was stirred at 80 °C for 16 h and then was cooled to room temperature and diluted with H_2O (50 mL). The mixture was filtered, and the filter cake was washed with EtOAc (2 x 50 mL). The phases were separated, and the aqueous phase was extracted with EtOAc (3 x 200 mL). The combined organics were washed with brine (2 x 100 mL), dried over anhydrous Na_2SO_4, filtered, and then concentrated under reduced pressure. The residue

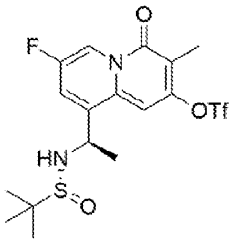
was purified by silica gel column chromatography (eluted with CH_2Cl_2:MeOH = 10:1) to afford (R,E)-N-(1-(7-fluoro-2-hydroxy-3-methyl-4-oxo-4H-quinolizin-9-yl)ethylidene)-2-methylpropane-2-sulfinamide (3.6 g, 83% yield) as a brown solid. LCMS: (ESI^+) m/z = 339.1 (M+H).

Step 7: Preparation of (R)-N-((R)-1-(7-fluoro-2-hydroxy-3-methyl-4-oxo-4H-quinolizin-9-yl)ethyl)-2-methylpropane-2-sulfinamide



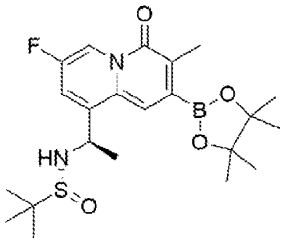
[000332] This intermediate was prepared using methods similar to those described in Example 23, Step 2 using (R,E)-N-(1-(7-fluoro-2-hydroxy-3-methyl-4-oxo-4H-quinolizin-9-yl)ethylidene)-2-methylpropane-2-sulfinamide in place of (R,E)-N-(1-(2-hydroxy-3,7-dimethyl-4-oxo-4H-quinolizin-9-yl)ethylidene)-2-methylpropane-2-sulfinamide. LCMS: (ESI^+) m/z = 341.2 (M+H).

Step 8: Preparation of 9-((R)-1-(((R)-tert-butylsulfinyl)amino)ethyl)-7-fluoro-3-methyl-4-oxo-4H-quinolizin-2-yl trifluoromethanesulfonate



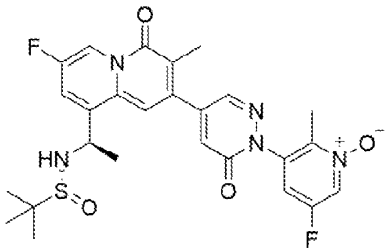
[000333] This intermediate was prepared using methods similar to those described in Example 23, Step 3 using (R)-N-((R)-1-(7-fluoro-2-hydroxy-3-methyl-4-oxo-4H-quinolizin-9-yl)ethyl)-2-methylpropane-2-sulfinamide in place of (R)-N-((R)-1-(2-hydroxy-3,7-dimethyl-4-oxo-4H-quinolizin-9-yl)ethyl)-2-methylpropane-2-sulfinamide. LCMS: (ESI^+) m/z = 473.0 (M+H).

Step 9: Preparation of (R)-N-((R)-1-(7-fluoro-3-methyl-4-oxo-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4H-quinolizin-9-yl)ethyl)-2-methylpropane-2-sulfinamide



[000334] This intermediate was prepared using methods similar to those described in Example 23, Step 4 using 9-((R)-1-(((R)-tert-butylsulfinyl)amino)ethyl)-7-fluoro-3-methyl-4-oxo-4H-quinolizin-2-yl trifluoromethanesulfonate in place of 9-((R)-1-(((R)-tert-butylsulfinyl)amino)ethyl)-3,7-dimethyl-4-oxo-4H-quinolizin-2-yl trifluoromethanesulfonate. LCMS: (ESI^+) m/z = 451.2 (M+H).

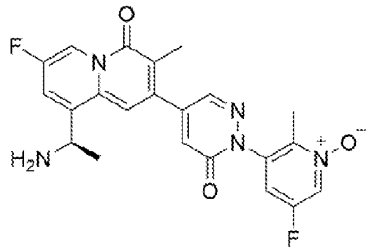
Step 10: Preparation of 3-(4-(9-((R)-1-(((R)-tert-butylsulfinyl)amino)ethyl)-7-fluoro-3-methyl-4-oxo-4H-quinolizin-2-yl)-6-oxopyridazin-1(6H)-yl)-5-fluoro-2-methylpyridine 1-oxide



[000335] A mixture of (R)-N-((R)-1-(7-fluoro-3-methyl-4-oxo-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4H-quinolizin-9-yl)ethyl)-2-methylpropane-2-sulfinamide (260 mg, 0.58 mmol), 5-fluoro-3-(4-iodo-6-oxopyridazin-1(6H)-yl)-2-methylpyridine 1-oxide (Intermediate 3) (100 mg, 0.29 mmol), $Pd(dppf)Cl_2$ (23.5 mg, 0.03 mmol), and Na_2CO_3 (61 mg, 0.58 mmol) in dioxane (4 mL) and H_2O (0.4 mL) under a nitrogen atmosphere was stirred at 90 °C for 40 minutes. The mixture was cooled to room temperature and diluted with water (20 mL). The resulting mixture was extracted with EtOAc (5 x 20 mL). The combined organics were washed with brine (2 x 20 mL), dried over anhydrous Na_2SO_4, filtered, and then concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography (C_{18} silica

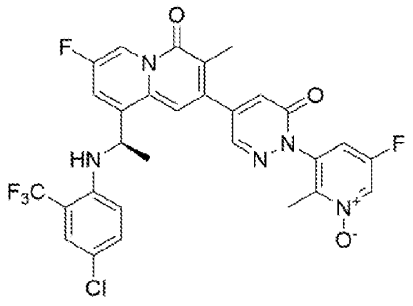
gel; mobile phase of MeCN in water, 10% to 50% gradient over 10 min) to afford 3-(4-(9-((R)-1-(((R)-tert-butylsulfinyl)amino)ethyl)-7-fluoro-3-methyl-4-oxo-4H-quinolizin-2-yl)-6-oxopyridazin-1(6H)-yl)-5-fluoro-2-methylpyridine 1-oxide (70 mg, 45% yield) as a yellow solid. LCMS: (ESI$^+$) m/z = 544.3 (M+H).

Step 11: Preparation of (R)-3-(4-(9-(1-aminoethyl)-7-fluoro-3-methyl-4-oxo-4H-quinolizin-2-yl)-6-oxopyridazin-1(6H)-yl)-5-fluoro-2-methylpyridine 1-oxide



[000336] This intermediate was prepared using methods similar to those described in Example 23, Step 6 using 3-(4-(9-((R)-1-(((R)-tert-butylsulfinyl)amino)ethyl)-7-fluoro-3-methyl-4-oxo-4H-quinolizin-2-yl)-6-oxopyridazin-1(6H)-yl)-5-fluoro-2-methylpyridine 1-oxide in place of (R)-N-((R)-1-(3,7-dimethyl-2-(1-(2-methylpyrimidin-5-yl)-6-oxo-1,6-dihydropyridazin-4-yl)-4-oxo-4H-quinolizin-9-yl)ethyl)-2-methylpropane-2-sulfinamide. LCMS: (ESI$^+$) m/z = 440.1 (M+H).

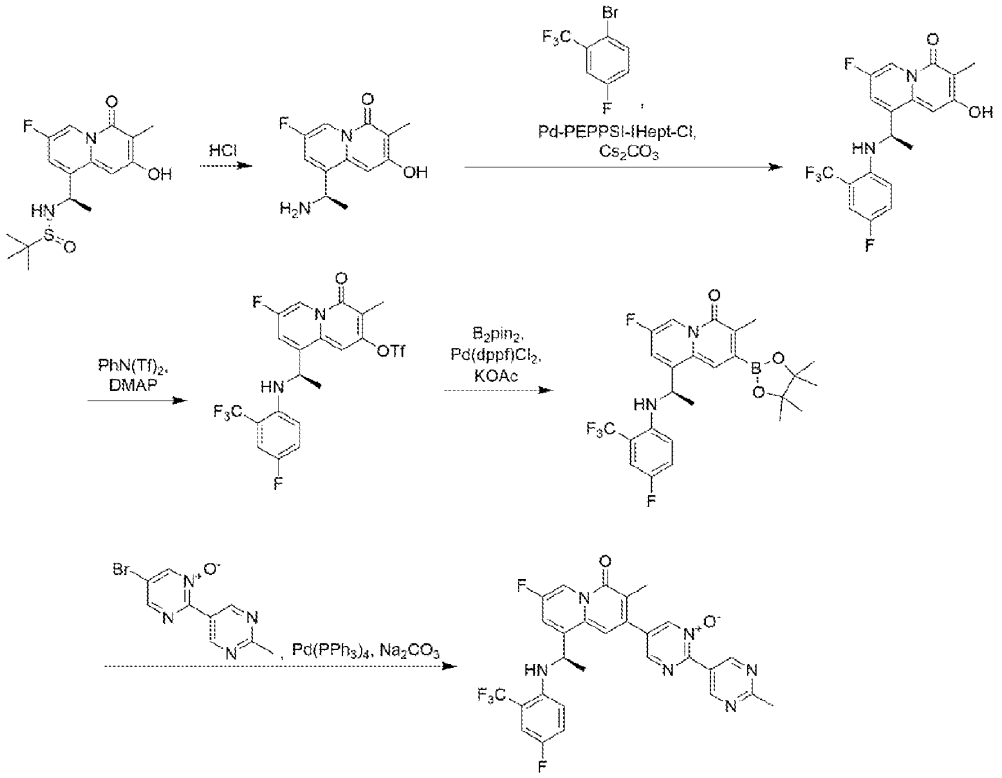
Step 12: Preparation of (R)-3-(4-(9-(1-((4-chloro-2-(trifluoromethyl)phenyl)amino)ethyl)-7-fluoro-3-methyl-4-oxo-4H-quinolizin-2-yl)-6-oxopyridazin-1(6H)-yl)-5-fluoro-2-methylpyridine 1-oxide (Example 25)



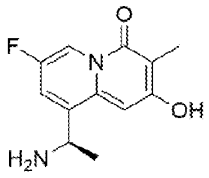
[000337] A mixture of (R)-3-(4-(9-(1-aminoethyl)-7-fluoro-3-methyl-4-oxo-4H-quinolizin-2-yl)-6-oxopyridazin-1(6H)-yl)-5-fluoro-2-methylpyridine 1-oxide (45 mg, 0.10 mmol), RuPhos (9.6 mg, 0.02 mmol), $Pd_2(dba)_3$ (9.4 mg, 0.01 mmol), Cs_2CO_3 (66.7 mg, 0.2 mmol), and 1-bromo-4-chloro-

2-(trifluoromethyl)benzene (133 mg, 0.51 mmol) in dioxane (3 mL) under a nitrogen atmosphere was stirred at 90 °C for 16 h. The resulting mixture was cooled to room temperature, filtered, and the filter cake was washed with CH_2Cl_2 (5x10 mL). The combined filtrates were concentrated under reduced pressure and the residue was purified by prep-TLC (CH_2Cl_2:MeOH = 8:1) and then purified further by prep-achiral SFC (Column: GreenSep Basic 3 x 15 cm, 5 µm; Mobile Phase A: CO_2, Mobile Phase B: MeOH (0.3% 7 M NH_3 in MeOH); Flow rate: 70 mL/min; Gradient (B%): isocratic 16% B; Column Temperature (°C): 35; Back Pressure (bar): 100; Wavelength: 220 nm) to afford (R)-3-(4-(9-(1-((4-chloro-2-(trifluoromethyl)phenyl)amino)ethyl)-7-fluoro-3-methyl-4-oxo-4H-quinolizin-2-yl)-6-oxopyridazin-1(6H)-yl)-5-fluoro-2-methylpyridine 1-oxide (12.0 mg, 19% yield, >99% ee) as a yellow solid. ^{1}H NMR (400 MHz, Methanol-d_4): δ 9.14 – 8.87 (m, 1H), 8.73 – 8.58 (m, 1H), 8.29 (d, J = 2.0 Hz, 1H), 7.89 – 7.68 (m, 1H), 7.62 – 7.52 (m, 1H), 7.50 (d, J = 2.4 Hz, 1H), 7.33 (s, 1H), 7.30 (s, 1H), 7.29 – 7.20 (m, 1H), 6.45 (d, J = 8.8 Hz, 1H), 5.30 – 5.14 (m, 1H), 2.40 (s, 3H), 2.38 (s, 3H), 1.73 (d, J = 6.8 Hz, 3H); LCMS: (ESI$^+$) m/z = 618.0 (M+H).

[000338] **Example 26:** (R)-5-(7-fluoro-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3-methyl-4-oxo-4H-quinolizin-2-yl)-2'-methyl-[2,5'-bipyrimidine] 1-oxide

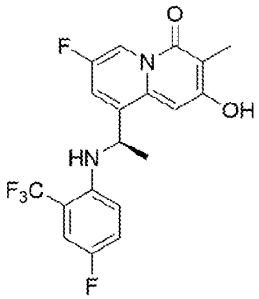


Step 1: Preparation of (R)-9-(1-aminoethyl)-7-fluoro-2-hydroxy-3-methyl-4H-quinolizin-4-one



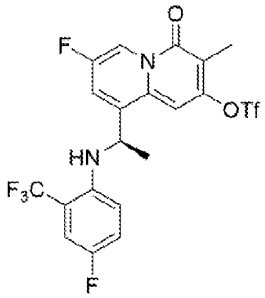
[000339] This intermediate was prepared using methods similar to those described in Example 23, Step 6 using (R)-N-((R)-1-(7-fluoro-2-hydroxy-3-methyl-4-oxo-4H-quinolizin-9-yl)ethyl)-2-methylpropane-2-sulfinamide (Example 25, Step 7) in place of (R)-N-((R)-1-(3,7-dimethyl-2-(1-(2-methylpyrimidin-5-yl)-6-oxo-1,6-dihydropyridazin-4-yl)-4-oxo-4H-quinolizin-9-yl)ethyl)-2-methylpropane-2-sulfinamide. LCMS: (ESI^+) m/z = 237.1 (M+H).

Step 2: Preparation of (R)-7-fluoro-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-2-hydroxy-3-methyl-4H-quinolizin-4-one



[000340] A mixture of (R)-9-(1-aminoethyl)-7-fluoro-2-hydroxy-3-methyl-4H-quinolizin-4-one (0.30 g, 1.27 mmol), 1-bromo-4-fluoro-2-(trifluoromethyl)benzene (1.54 g, 6.35 mmol), palladium(2+) 1,3-bis[2,6-bis(heptan-4-yl)phenyl]-4,5-dichloro-1,2-didehydro-1λ^5-imidazole 3-chloropyridine dichloride (124 mg, 0.13 mmol), and Cs_2CO_3 (1.24 g, 3.81 mmol) in 1,4-dioxane (3 mL) was stirred at 100 °C for 2 h. The resulting mixture was cooled to room temperature, filtered, and the filter cake was washed with DCM (3 x 10 mL). The combined filtrates were concentrated under reduced pressure and the residue was purified by prep-TLC (PE:EA = 1:1) to afford (R)-7-fluoro-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-2-hydroxy-3-methyl-4H-quinolizin-4-one (160 mg, 32% yield) as a yellow solid. LCMS: (ESI$^+$) m/z = 399.4 (M+H).

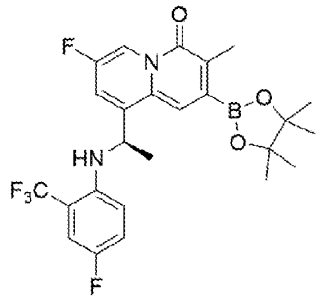
Step 3: Preparation of (R)-7-fluoro-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3-methyl-4-oxo-4H-quinolizin-2-yl trifluoromethanesulfonate



[000341] This intermediate was prepared using methods similar to those described in Example 23, Step 3 using (R)-7-fluoro-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-2-hydroxy-3-methyl-4H-quinolizin-4-one in place of (R)-N-((R)-1-(2-hydroxy-3,7-dimethyl-4-oxo-

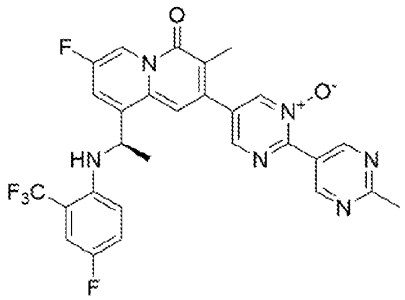
4H-quinolizin-9-yl)ethyl)-2-methylpropane-2-sulfinamide. LCMS: (ESI$^+$) m/z = 531.4 (M+H).

Step 4: Preparation of (R)-7-fluoro-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4H-quinolizin-4-one



[000342] This intermediate was prepared using methods similar to those described in Example 23, Step 4 using (R)-7-fluoro-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3-methyl-4-oxo-4H-quinolizin-2-yl trifluoromethanesulfonate in place of 9-((R)-1-(((R)-tert-butylsulfinyl)amino)ethyl)-3,7-dimethyl-4-oxo-4H-quinolizin-2-yl trifluoromethanesulfonate. LCMS: (ESI$^+$) m/z = 509.2 (M+H).

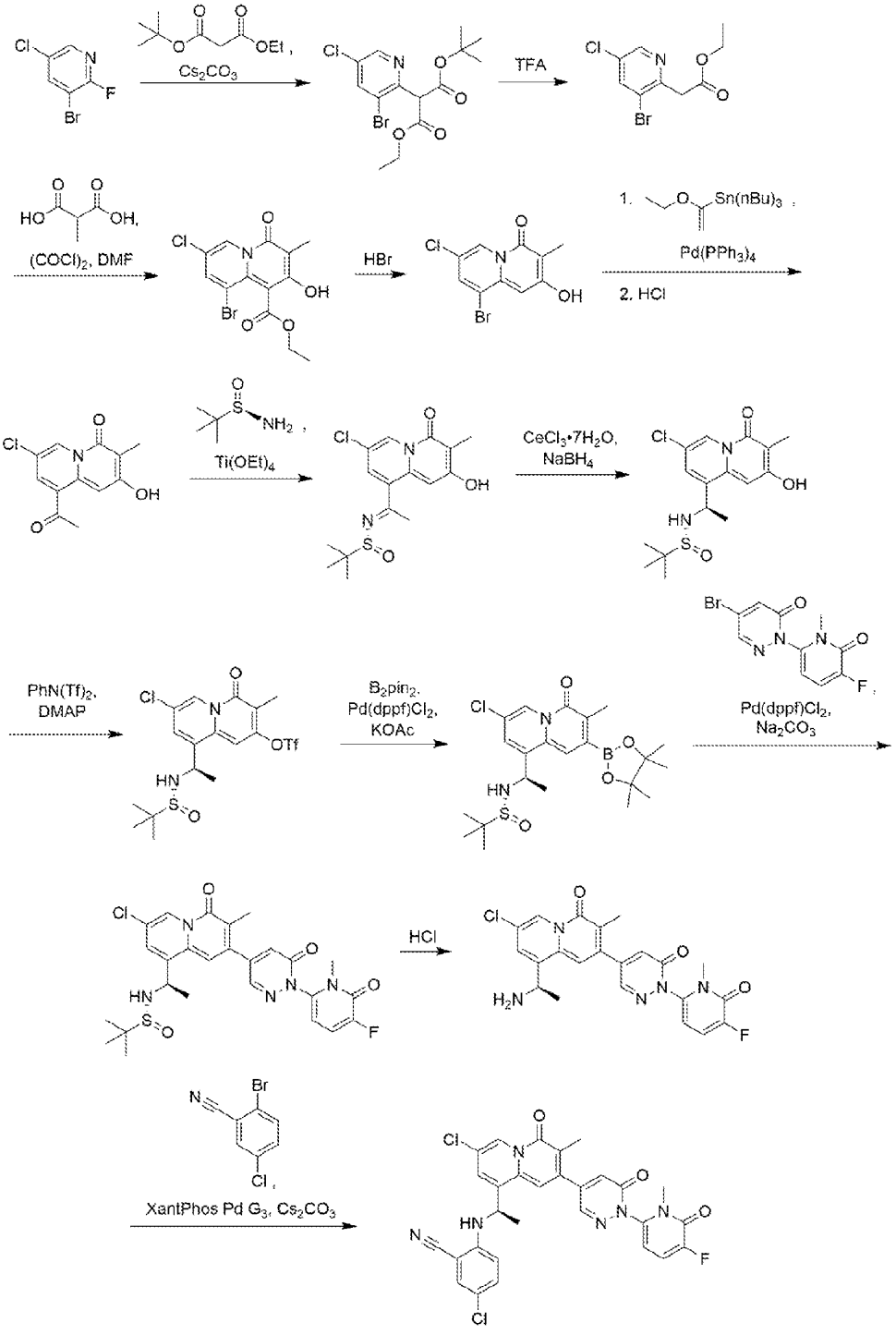
Step 5: Preparation of (R)-5-(7-fluoro-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3-methyl-4-oxo-4H-quinolizin-2-yl)-2'-methyl-[2,5'-bipyrimidine] 1-oxide (Example 26)



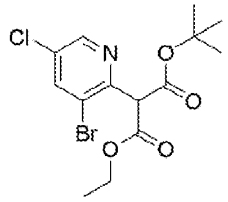
[000343] A mixture of (R)-7-fluoro-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4H-quinolizin-4-one (100 mg, 0.20 mmol), 5-bromo-2'-methyl-[2,5'-bipyrimidine] 1-oxide (Intermediate 5) (63 mg, 0.24 mmol), $Pd(PPh_3)_4$ (24 mg, 0.02 mmol) and Na_2CO_3 (42 mg, 0.39 mmol) in 1,4-dioxane (4 mL) and H_2O (0.8 mL) was stirred at 90 °C for 1 h under a nitrogen atmosphere. The resulting mixture cooled to

room temperature, filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by prep-HPLC (Column: XBridge Prep OBD C18 Column, 30 x 150 mm, 5 μm; Mobile Phase A: water (10mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient (B%): 37% B to 67% B in 8 min) and then purified further by prep-chiral-HPLC (Column: CHIRALPAK IA3; Mobile Phase A: Hex (0.1% DEA):(EtOH:DCM = 1:1) = 70:30) to afford (R)-5-(7-fluoro-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3-methyl-4-oxo-4H-quinolizin-2-yl)-2'-methyl-[2,5'-bipyrimidine] 1-oxide (25.2 mg, 23% yield, >99.0% ee) as a yellow solid. ^{1}H NMR (400 MHz, DMSO): δ 9.76 (s, 2H), 9.10 (d, *J* = 2.0 Hz, 1H), 8.94 – 8.92 (m, 1H), 8.72 (d, *J* = 1.9 Hz, 1H), 7.56 – 7.50 (m, 1H), 7.41 – 7.35 (m, 2H), 7.23 – 7.19 (m, 1H), 6.50 – 6.46 (m, 1H), 5.64 (d, *J* = 6.4 Hz, 1H), 5.32 – 5.24 (m, 1H), 2.76 (s, 3H), 2.31 (s, 3H), 1.62 (d, *J* = 6.5 Hz, 3H); LCMS: (ESI$^+$) m/z = 569.2 (M+H).

[000344] **Example 27:** (R)-5-chloro-2-((1-(7-chloro-2-(1-(5-fluoro-1-methyl-6-oxo-1,6-dihydropyridin-2-yl)-6-oxo-1,6-dihydropyridazin-4-yl)-3-methyl-4-oxo-4H-quinolizin-9-yl)ethyl)amino)benzonitrile

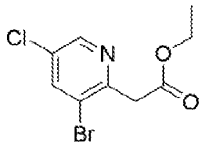

Cs2CO3
TFA
(COCl)2, DMF
HBr
1. Sn(nBu)3
Pd(PPh3)4
2. HCl
Ti(OEt)4
CeCl3•7H2O, NaBH4
PhN(Tf)2, DMAP
B2pin2, Pd(dppf)Cl2, KOAc
Pd(dppf)Cl2, Na2CO3
HCl
XantPhos Pd G3, Cs2CO3

Step 1: Preparation of 1-tert-butyl 3-ethyl 2-(3-bromo-5-chloropyridin-2-yl)propanedioate



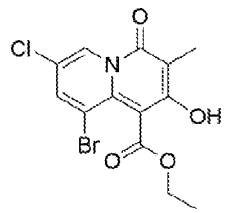
[000345] This intermediate was prepared using methods similar to those described in Example 25, Step 1 using 3-bromo-5-chloro-2-fluoropyridine in place of 3-bromo-2,5-difluoropyridine. LCMS: (ESI$^+$) m/z = 378.0 (M+H).

Step 2: Preparation of ethyl 2-(3-bromo-5-chloropyridin-2-yl)acetate



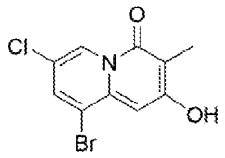
[000346] This intermediate was prepared using methods similar to those described in Example 25, Step 2 using 1-tert-butyl 3-ethyl 2-(3-bromo-5-chloropyridin-2-yl)propanedioate in place of 1-(tert-butyl) 3-ethyl 2-(3-bromo-5-fluoropyridin-2-yl)malonate. LCMS: (ESI$^+$) m/z = 278.0 (M+H).

Step 3: Preparation of ethyl 9-bromo-7-chloro-2-hydroxy-3-methyl-4-oxo-4H-quinolizine-1-carboxylate



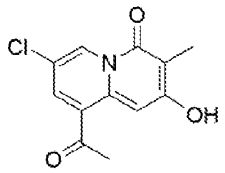
[000347] This intermediate was prepared using methods similar to those described in Example 25, Step 3 using ethyl 2-(3-bromo-5-chloropyridin-2-yl)acetate in place of ethyl 2-(3-bromo-5-fluoropyridin-2-yl)acetate. LCMS: (ESI$^+$) m/z = 360.1 (M+H).

Step 4: Preparation of 9-bromo-7-chloro-2-hydroxy-3-methyl-4H-quinolizin-4-one



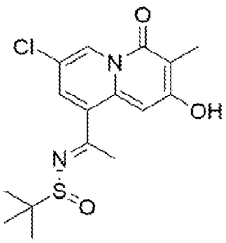
[000348] This intermediate was prepared using methods similar to those described in Example 25, Step 4 using ethyl 9-bromo-7-chloro-2-hydroxy-3-methyl-4-oxo-4H-quinolizine-1-carboxylate in place of ethyl 9-bromo-7-fluoro-2-hydroxy-3-methyl-4-oxo-4H-quinolizine-1-carboxylate. LCMS: (ESI$^+$) m/z = 289.9 (M+H).

Step 5: Preparation of 9-acetyl-7-chloro-2-hydroxy-3-methyl-4H-quinolizin-4-one



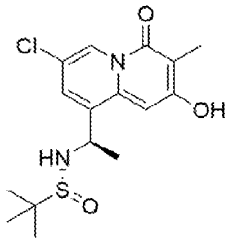
[000349] This intermediate was prepared using methods similar to those described in Example 25, Step 5 using 9-bromo-7-chloro-2-hydroxy-3-methyl-4H-quinolizin-4-one in place of 9-bromo-7-fluoro-2-hydroxy-3-methyl-4H-quinolizin-4-one. LCMS: (ESI$^+$) m/z = 252.0 (M+H).

Step 6: Preparation of (R,E)-N-(1-(7-chloro-2-hydroxy-3-methyl-4-oxo-4H-quinolizin-9-yl)ethylidene)-2-methylpropane-2-sulfinamide



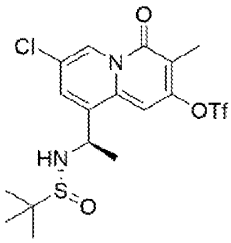
[000350] This intermediate was prepared using methods similar to those described in Example 25, Step 6 using 9-acetyl-7-chloro-2-hydroxy-3-methyl-4H-quinolizin-4-one in place of 9-acetyl-7-fluoro-2-hydroxy-3-methyl-4H-quinolizin-4-one. LCMS: (ESI$^+$) m/z = 355.1 (M+H).

Step 7: Preparation of (R)-N-((R)-1-(7-chloro-2-hydroxy-3-methyl-4-oxo-4H-quinolizin-9-yl)ethyl)-2-methylpropane-2-sulfinamide



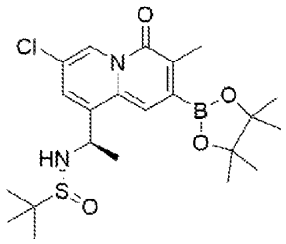
[000351] This intermediate was prepared using methods similar to those described in Example 25, Step 7 using (R,E)-N-(1-(7-chloro-2-hydroxy-3-methyl-4-oxo-4H-quinolizin-9-yl)ethylidene)-2-methylpropane-2-sulfinamide in place of (R,E)-N-(1-(7-fluoro-2-hydroxy-3-methyl-4-oxo-4H-quinolizin-9-yl)ethylidene)-2-methylpropane-2-sulfinamide. LCMS: (ESI^+) m/z = 357.1 (M+H).

Step 8: Preparation of 9-((R)-1-(((R)-tert-butylsulfinyl)amino)ethyl)-7-chloro-3-methyl-4-oxo-4H-quinolizin-2-yl trifluoromethanesulfonate



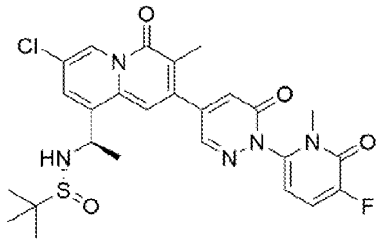
[000352] This intermediate was prepared using methods similar to those described in Example 25, Step 8 using (R)-N-((R)-1-(7-chloro-2-hydroxy-3-methyl-4-oxo-4H-quinolizin-9-yl)ethyl)-2-methylpropane-2-sulfinamide in place of (R)-N-((R)-1-(7-fluoro-2-hydroxy-3-methyl-4-oxo-4H-quinolizin-9-yl)ethyl)-2-methylpropane-2-sulfinamide. LCMS: (ESI^+) m/z = 489.1 (M+H).

Step 9: Preparation of (R)-N-((R)-1-(7-chloro-3-methyl-4-oxo-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4H-quinolizin-9-yl)ethyl)-2-methylpropane-2-sulfinamide



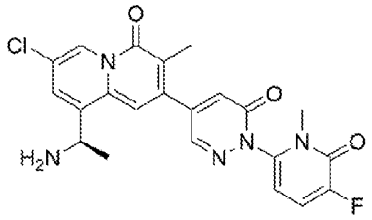
[000353] This intermediate was prepared using methods similar to those described in Example 25, Step 9 using 9-((R)-1-(((R)-tert-butylsulfinyl)amino)ethyl)-7-chloro-3-methyl-4-oxo-4H-quinolizin-2-yl trifluoromethanesulfonate in place of 9-((R)-1-(((R)-tert-butylsulfinyl)amino)ethyl)-7-fluoro-3-methyl-4-oxo-4H-quinolizin-2-yl trifluoromethanesulfonate. LCMS: (ESI$^+$) m/z = 467.2 (M+H).

Step 10: Preparation of (R)-N-((R)-1-(7-chloro-2-(1-(5-fluoro-1-methyl-6-oxo-1,6-dihydropyridin-2-yl)-6-oxo-1,6-dihydropyridazin-4-yl)-3-methyl-4-oxo-4H-quinolizin-9-yl)ethyl)-2-methylpropane-2-sulfinamide



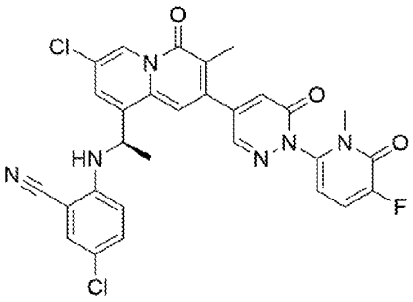
[000354] This intermediate was prepared using methods similar to those described in Example 25, Step 10 using (R)-N-((R)-1-(7-chloro-3-methyl-4-oxo-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4H-quinolizin-9-yl)ethyl)-2-methylpropane-2-sulfinamide and 5-bromo-2-(5-fluoro-1-methyl-6-oxo-1,6-dihydropyridin-2-yl)pyridazin-3(2H)-one (Intermediate 10) in place of (R)-N-((R)-1-(7-fluoro-3-methyl-4-oxo-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4H-quinolizin-9-yl)ethyl)-2-methylpropane-2-sulfinamide and 5-fluoro-3-(4-iodo-6-oxopyridazin-1(6H)-yl)-2-methylpyridine 1-oxide. LCMS: (ESI$^+$) m/z = 560.0 (M+H).

Step 11: Preparation of (R)-9-(1-aminoethyl)-7-chloro-2-(1-(5-fluoro-1-methyl-6-oxo-1,6-dihydropyridin-2-yl)-6-oxo-1,6-dihydropyridazin-4-yl)-3-methyl-4H-quinolizin-4-one



[000355] This intermediate was prepared using methods similar to those described in Example 23, Step 6 using (R)-N-((R)-1-(7-chloro-2-(1-(5-fluoro-1-methyl-6-oxo-1,6-dihydropyridin-2-yl)-6-oxo-1,6-dihydropyridazin-4-yl)-3-methyl-4-oxo-4H-quinolizin-9-yl)ethyl)-2-methylpropane-2-sulfinamide in place of (R)-N-((R)-1-(3,7-dimethyl-2-(1-(2-methylpyrimidin-5-yl)-6-oxo-1,6-dihydropyridazin-4-yl)-4-oxo-4H-quinolizin-9-yl)ethyl)-2-methylpropane-2-sulfinamide. LCMS: (ESI$^+$) m/z = 456.0 (M+H).

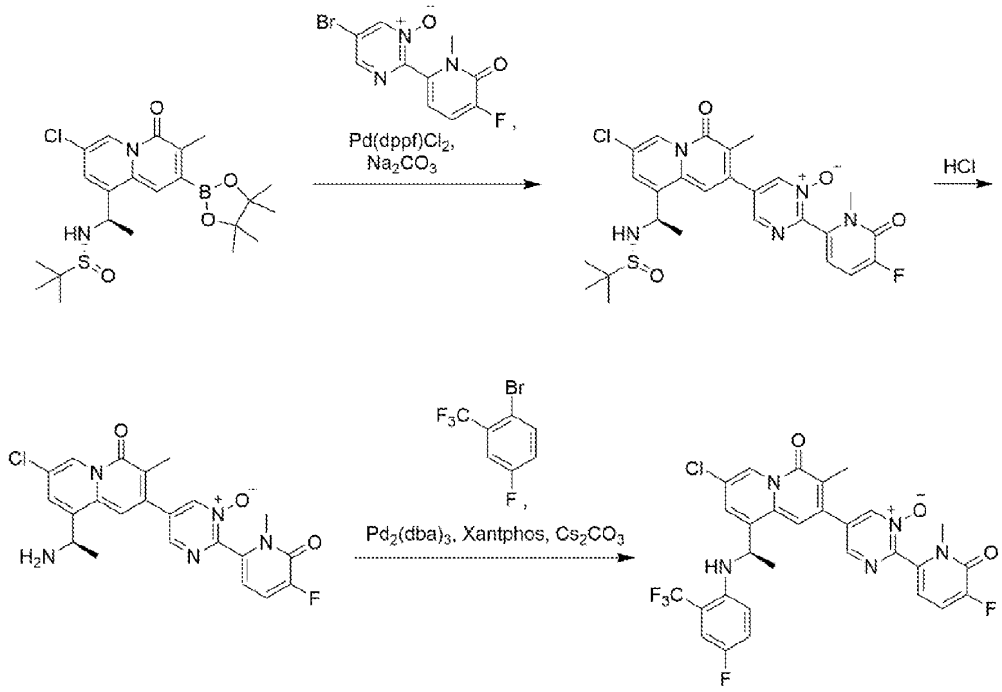
Step 12: Preparation of (R)-5-chloro-2-((1-(7-chloro-2-(1-(5-fluoro-1-methyl-6-oxo-1,6-dihydropyridin-2-yl)-6-oxo-1,6-dihydropyridazin-4-yl)-3-methyl-4-oxo-4H-quinolizin-9-yl)ethyl)amino)benzonitrile (Example 27)



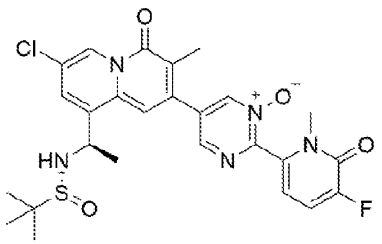
[000356] To a mixture of (R)-9-(1-aminoethyl)-7-chloro-2-(1-(5-fluoro-1-methyl-6-oxo-1,6-dihydropyridin-2-yl)-6-oxo-1,6-dihydropyridazin-4-yl)-3-methyl-4H-quinolizin-4-one (90 mg, 0.19 mmol) and 2-bromo-5-chlorobenzonitrile (83 mg, 0.38 mmol) in dioxane (5 mL) under a nitrogen atmosphere were added [(4,5-bis(diphenylphosphino)-9,9-dimethylxanthene)-2-(2'-amino-1,1'-biphenyl)]palladium(II) methanesulfonate (18 mg, 0.02 mmol) and Cs_2CO_3 (186 mg, 0.57 mmol). The resulting mixture was stirred at 100 °C for 1 h and then was diluted with water (10 mL) and extracted with EtOAc (3 x 20 mL). The combined organics were washed with brine (2 x 10 mL), dried over anhydrous Na_2SO_4, filtered, and then concentrated under reduced pressure. The residue was purified by prep-TLC (PE:EA = 10:1) and then purified further by prep-HPLC (XBridge

Prep OBD C_{18} Column, 30 x 150 mm, 5 µm; Mobile Phase A: water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient (B%): 37% B to 67 % B in 10 min) to afford (R)-5-chloro-2-((1-(7-chloro-2-(1-(5-fluoro-1-methyl-6-oxo-1,6-dihydropyridin-2-yl)-6-oxo-1,6-dihydropyridazin-4-yl)-3-methyl-4-oxo-4H-quinolizin-9-yl)ethyl)amino)benzonitrile (49.6 mg, 42 % yield, >99.0% ee) as a yellow solid. ^{1}H NMR (Methanol-d_4, 400 MHz): δ 9.13 (d, J = 1.6 Hz, 1H), 8.29 (d, J = 2.0 Hz, 1H), 7.65 – 7.42 (m, 3H), 7.41 – 7.20 (m, 3H), 6.76 – 6.58 (m, 1H), 6.44 (d, J = 7.2 Hz, 1H), 5.29 – 5.13 (m, 1H), 3.49 (s, 3H), 2.39 (s, 3H), 1.73 (d, J = 6.8 Hz, 3H); LCMS: (ESI$^+$) m/z = 591.1 (M+H).

[000357] **Example 28:** (R)-5-(7-chloro-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3-methyl-4-oxo-4H-quinolizin-2-yl)-2-(5-fluoro-1-methyl-6-oxo-1,6-dihydropyridin-2-yl)pyrimidine 1-oxide

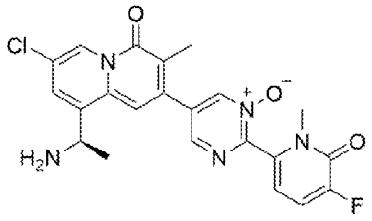


Step 1: Preparation of 5-(9-((R)-1-(((R)-tert-butylsulfinyl)amino)ethyl)-7-chloro-3-methyl-4-oxo-4H-quinolizin-2-yl)-2-(5-fluoro-1-methyl-6-oxo-1,6-dihydropyridin-2-yl)pyrimidine 1-oxide



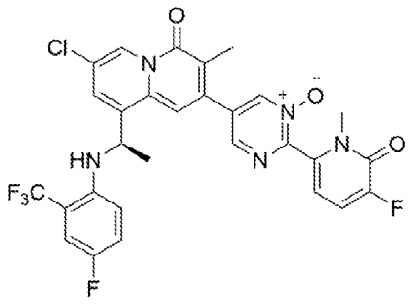
[000358] This intermediate was prepared using methods similar to those described in Example 25, Step 10 using (R)-N-((R)-1-(7-chloro-3-methyl-4-oxo-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4H-quinolizin-9-yl)ethyl)-2-methylpropane-2-sulfinamide (Example 27, Step 9) and 5-bromo-2-(5-fluoro-1-methyl-6-oxo-1,6-dihydropyridin-2-yl)pyrimidine 1-oxide (Intermediate 4) in place of (R)-N-((R)-1-(7-fluoro-3-methyl-4-oxo-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4H-quinolizin-9-yl)ethyl)-2-methylpropane-2-sulfinamide and 5-fluoro-3-(4-iodo-6-oxopyridazin-1(6H)-yl)-2-methylpyridine 1-oxide. LCMS: (ESI$^+$) m/z = 560.2 (M+H).

Step 2: Preparation of (R)-5-(9-(1-aminoethyl)-7-chloro-3-methyl-4-oxo-4H-quinolizin-2-yl)-2-(5-fluoro-1-methyl-6-oxo-1,6-dihydropyridin-2-yl)pyrimidine 1-oxide



[000359] This intermediate was prepared using methods similar to those described in Example 23, Step 6 using 5-(9-((R)-1-(((R)-tert-butylsulfinyl)amino)ethyl)-7-chloro-3-methyl-4-oxo-4H-quinolizin-2-yl)-2-(5-fluoro-1-methyl-6-oxo-1,6-dihydropyridin-2-yl)pyrimidine 1-oxide in place of (R)-N-((R)-1-(3,7-dimethyl-2-(1-(2-methylpyrimidin-5-yl)-6-oxo-1,6-dihydropyridazin-4-yl)-4-oxo-4H-quinolizin-9-yl)ethyl)-2-methylpropane-2-sulfinamide. LCMS: (ESI$^+$) m/z = 456.1 (M+H).

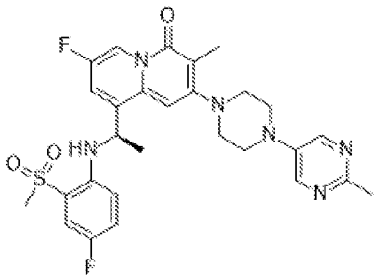
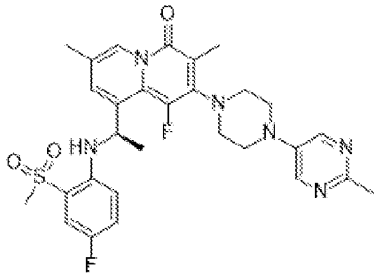
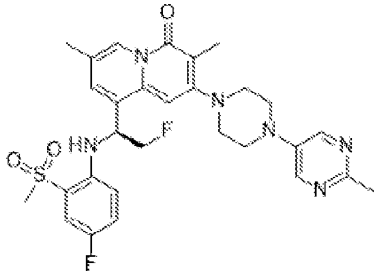
Step 3: Preparation of (R)-5-(7-chloro-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3-methyl-4-oxo-4H-quinolizin-2-yl)-2-(5-fluoro-1-methyl-6-oxo-1,6-dihydropyridin-2-yl)pyrimidine 1-oxide (Example 28)

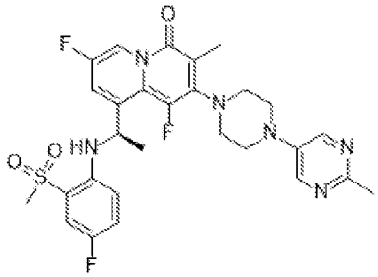
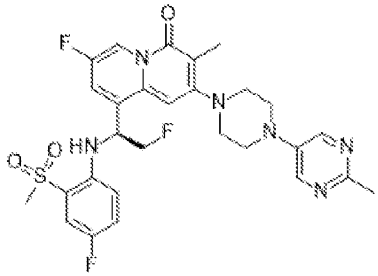
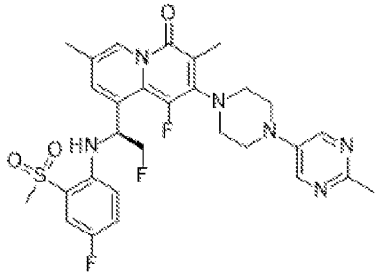


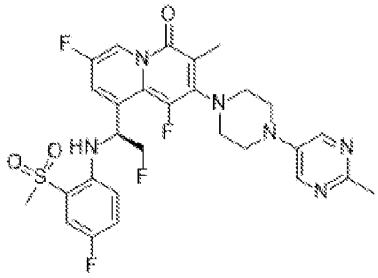
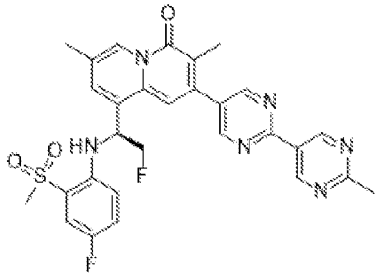
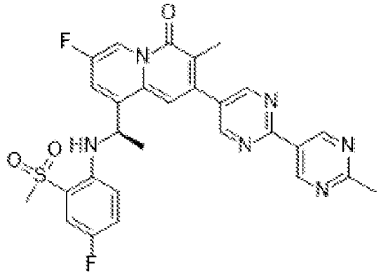
[000360] A mixture of (R)-5-(9-(1-aminoethyl)-7-chloro-3-methyl-4-oxo-4H-quinolizin-2-yl)-2-(5-fluoro-1-methyl-6-oxo-1,6-dihydropyridin-2-yl)pyrimidine 1-oxide (90 mg, 0.20 mmol), 1-bromo-4-fluoro-2-(trifluoromethyl)benzene (96 mg, 0.40 mmol), $Pd_2(dba)_3$ (18 mg, 0.02 mmol), Xantphos (23 mg, 0.04 mmol), and Cs_2CO_3 (193 mg, 0.60 mmol) in dioxane (5 mL) under a nitrogen atmosphere was stirred at 100 °C for 4 h. The resulting mixture cooled to room temperature, diluted with water (20 mL), and extracted with EtOAc (2 x 20 mL). The combined organics were washed with brine (2 x 10 mL), dried over anhydrous Na_2SO_4, filtered, and then concentrated under reduced pressure. The residue was purified by prep-TLC (CH_2Cl_2:MeOH = 15:1). The crude product was purified by prep-HPLC (XBridge Prep Phenyl OBD C18 column, 30 x 150 mm, 5 μm; Mobile Phase A: water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 43% B to 58% B over 10 min) to afford (R)-5-(7-chloro-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3-methyl-4-oxo-4H-quinolizin-2-yl)-2-(5-fluoro-1-methyl-6-oxo-1,6-dihydropyridin-2-yl)pyrimidine 1-oxide (14 mg, 12% yield, >99.0% ee) as a yellow solid. ^{1}H NMR (CD_3OD, 400 MHz): δ 9.13 (d, J = 1.6 Hz, 1H), 8.99 (d, J = 1.6 Hz, 1H), 8.71 (d, J = 2.0 Hz, 1H), 7.62 – 7.42 (m, 2H), 7.40 – 7.19 (m, 2H), 7.12 – 7.01 (m, 1H), 6.80 – 6.59 (m, 1H), 6.50 – 6.33 (m, 1H), 5.27 – 5.11 (m, 2H), 3.58 (s, 3H), 2.40 (s, 3H), 1.71 (d, J = 6.0 Hz, 3H); LCMS: (ESI^+) m/z = 618.0 (M+H).

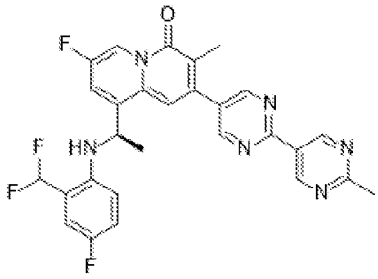
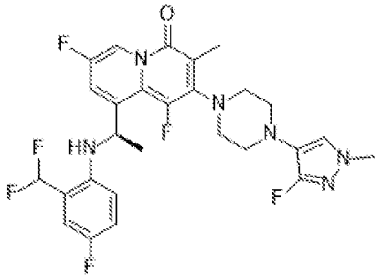
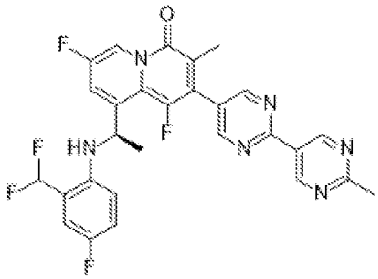
[000361] Examples 4-20 in Table 1 can be prepared either in a manner similar to that described for Examples 1 to 3 or via the general methods depicted in Schemes 1 to 20 as well as via the references described in the accompanying text.

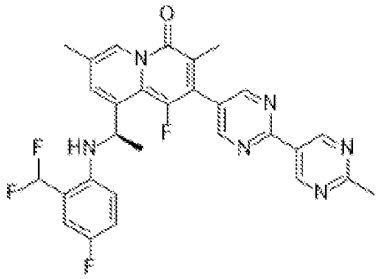
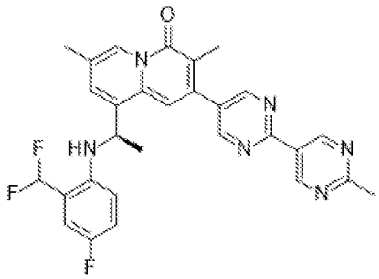
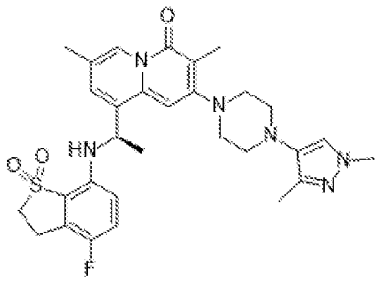
Table 1. Examples 4 to 20 and Examples 29 to 395

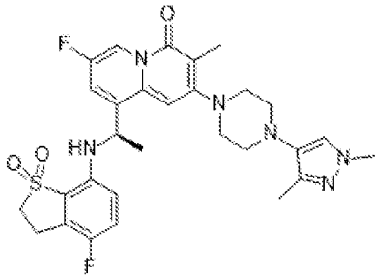
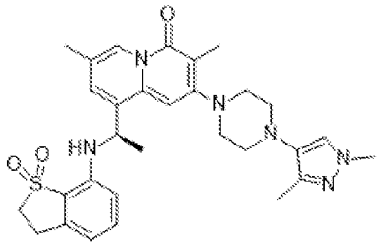
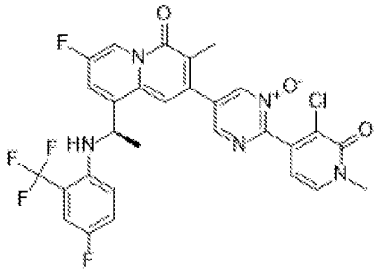
Structure	Example	IUPAC Name
 $C_{28}H_{30}F_2N_6O_3S$	4	(R)-7-fluoro-9-(1-((4-fluoro-2-(methylsulfonyl)phenyl)amino)ethyl)-3-methyl-2-(4-(2-methylpyrimidin-5-yl)piperazin-1-yl)-4H-quinolizin-4-one
 $C_{29}H_{32}F_2N_6O_3S$	5	(R)-1-fluoro-9-(1-((4-fluoro-2-(methylsulfonyl)phenyl)amino)ethyl)-3,7-dimethyl-2-(4-(2-methylpyrimidin-5-yl)piperazin-1-yl)-4H-quinolizin-4-one
 $C_{29}H_{32}F_2N_6O_3S$	6	(S)-9-(2-fluoro-1-((4-fluoro-2-(methylsulfonyl)phenyl)amino)ethyl)-3,7-dimethyl-2-(4-(2-methylpyrimidin-5-yl)piperazin-1-yl)-4H-quinolizin-4-one

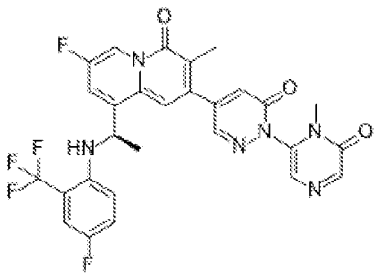
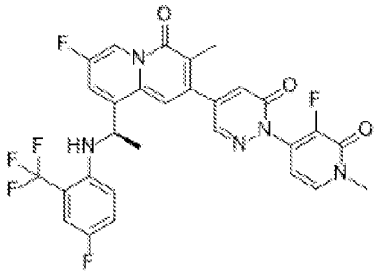
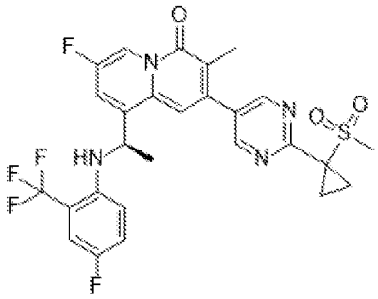
 $C_{28}H_{29}F_3N_6O_3S$	7	(R)-1,7-difluoro-9-(1-((4-fluoro-2-(methylsulfonyl)phenyl)amino)ethyl)-3-methyl-2-(4-(2-methylpyrimidin-5-yl)piperazin-1-yl)-4H-quinolizin-4-one
 $C_{28}H_{29}F_3N_6O_3S$	8	(S)-7-fluoro-9-(2-fluoro-1-((4-fluoro-2-(methylsulfonyl)phenyl)amino)ethyl)-3-methyl-2-(4-(2-methylpyrimidin-5-yl)piperazin-1-yl)-4H-quinolizin-4-one
 $C_{29}H_{31}F_3N_6O_3S$	9	(S)-1-fluoro-9-(2-fluoro-1-((4-fluoro-2-(methylsulfonyl)phenyl)amino)ethyl)-3,7-dimethyl-2-(4-(2-methylpyrimidin-5-yl)piperazin-1-yl)-4H-quinolizin-4-one

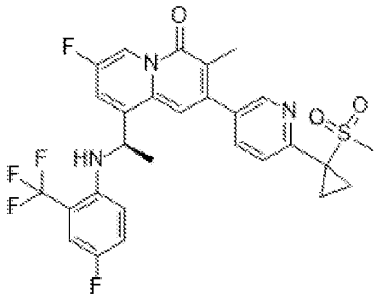
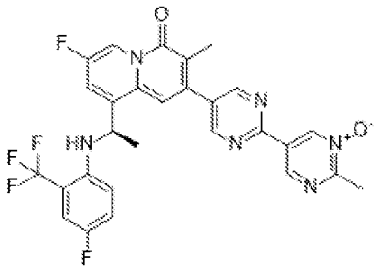
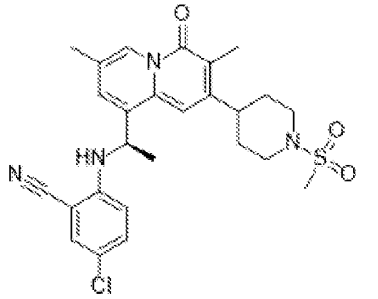
 $C_{28}H_{28}F_4N_6O_3S$	10	(S)-1,7-difluoro-9-(2-fluoro-1-((4-fluoro-2-(methylsulfonyl)phenyl)amino)ethyl)-3-methyl-2-(4-(2-methylpyrimidin-5-yl)piperazin-1-yl)-4H-quinolizin-4-one
 $C_{29}H_{26}F_2N_6O_3S$	11	(S)-9-(2-fluoro-1-((4-fluoro-2-(methylsulfonyl)phenyl)amino)ethyl)-3,7-dimethyl-2-(2'-methyl-[2,5'-bipyrimidin]-5-yl)-4H-quinolizin-4-one
 $C_{28}H_{24}F_2N_6O_3S$	12	(R)-7-fluoro-9-(1-((4-fluoro-2-(methylsulfonyl)phenyl)amino)ethyl)-3-methyl-2-(2'-methyl-[2,5'-bipyrimidin]-5-yl)-4H-quinolizin-4-one

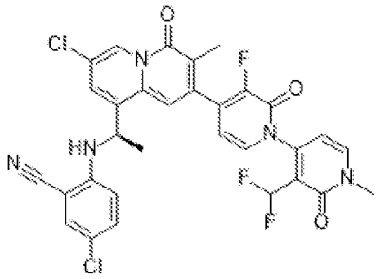
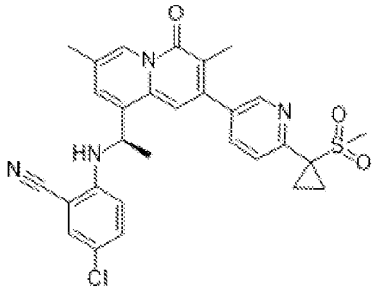
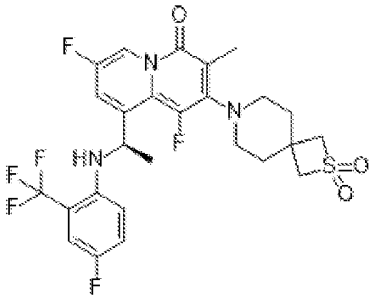
 $C_{28}H_{22}F_4N_6O$	13	(R)-9-(1-((2-(difluoromethyl)-4-fluorophenyl)amino)ethyl)-7-fluoro-3-methyl-2-(2'-methyl-[2,5'-bipyrimidin]-5-yl)-4H-quinolizin-4-one
 $C_{27}H_{26}F_6N_6O$	14	(R)-9-(1-((2-(difluoromethyl)-4-fluorophenyl)amino)ethyl)-1,7-difluoro-2-(4-(3-fluoro-1-methyl-1H-pyrazol-4-yl)piperazin-1-yl)-3-methyl-4H-quinolizin-4-one
 $C_{28}H_{21}F_5N_6O$	15	(R)-9-(1-((2-(difluoromethyl)-4-fluorophenyl)amino)ethyl)-1,7-difluoro-3-methyl-2-(2'-methyl-[2,5'-bipyrimidin]-5-yl)-4H-quinolizin-4-one

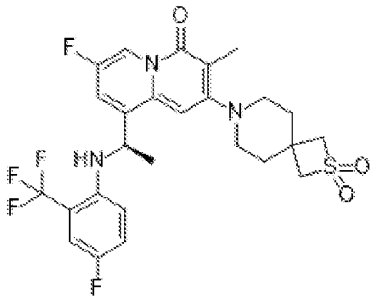
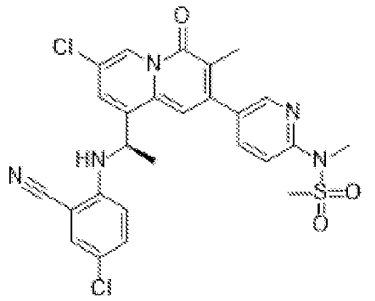
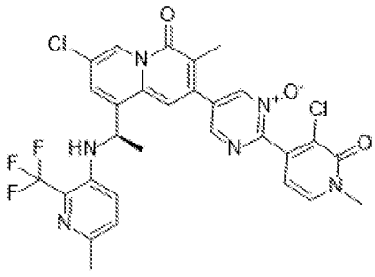
 $C_{29}H_{24}F_4N_6O$	16	(R)-9-(1-((2-(difluoromethyl)-4-fluorophenyl)amino)ethyl)-1-fluoro-3,7-dimethyl-2-(2'-methyl-[2,5'-bipyrimidin]-5-yl)-4H-quinolizin-4-one
 $C_{29}H_{25}F_3N_6O$	17	(R)-9-(1-((2-(difluoromethyl)-4-fluorophenyl)amino)ethyl)-3,7-dimethyl-2-(2'-methyl-[2,5'-bipyrimidin]-5-yl)-4H-quinolizin-4-one
 $C_{30}H_{35}FN_6O_3S$	18	(R)-2-(4-(1,3-dimethyl-1H-pyrazol-4-yl)piperazin-1-yl)-9-(1-((4-fluoro-1,1-dioxido-2,3-dihydrobenzo[b]thiophen-7-yl)amino)ethyl)-3,7-dimethyl-4H-quinolizin-4-one

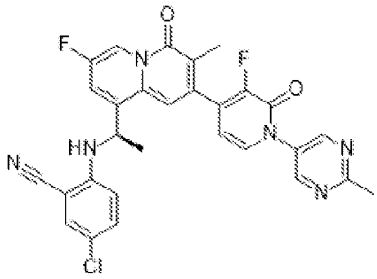
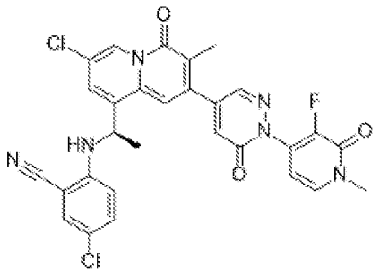
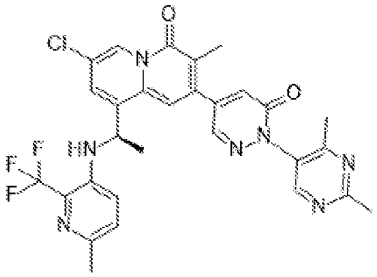
 $C_{29}H_{32}F_2N_6O_3S$	19	(R)-2-(4-(1,3-dimethyl-1H-pyrazol-4-yl)piperazin-1-yl)-7-fluoro-9-(1-((4-fluoro-1,1-dioxido-2,3-dihydrobenzo[b]thiophen-7-yl)amino)ethyl)-3-methyl-4H-quinolizin-4-one
 $C_{30}H_{36}N_6O_3S$	20	(R)-2-(4-(1,3-dimethyl-1H-pyrazol-4-yl)piperazin-1-yl)-9-(1-((1,1-dioxido-2,3-dihydrobenzo[b]thiophen-7-yl)amino)ethyl)-3,7-dimethyl-4H-quinolizin-4-one
 $C_{29}H_{21}ClF_5N_5O_3$	29	(R)-2-(3-chloro-1-methyl-2-oxo-1,2-dihydropyridin-4-yl)-5-(7-fluoro-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3-methyl-4-oxo-4H-quinolizin-2-yl)pyrimidine 1-oxide

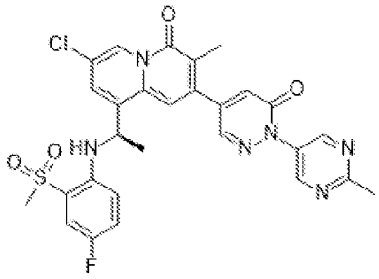
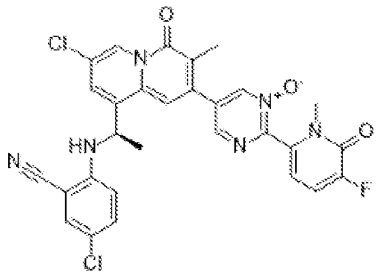
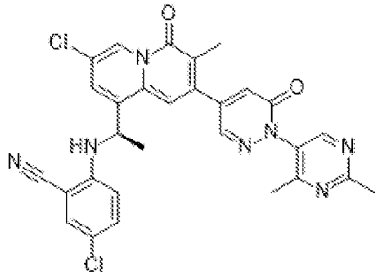
 $C_{28}H_{21}F_5N_6O_3$	30	(R)-7-fluoro-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3-methyl-2-(1-(1-methyl-6-oxo-1,6-dihydropyrazin-2-yl)-6-oxo-1,6-dihydropyridazin-4-yl)-4H-quinolizin-4-one
 $C_{29}H_{21}F_6N_5O_3$	31	(R)-7-fluoro-2-(1-(3-fluoro-1-methyl-2-oxo-1,2-dihydropyridin-4-yl)-6-oxo-1,6-dihydropyridazin-4-yl)-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3-methyl-4H-quinolizin-4-one
 $C_{27}H_{23}F_5N_4O_3S$	32	(R)-7-fluoro-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3-methyl-2-(2-(1-(methylsulfonyl)cyclopropyl)pyrimidin-5-yl)-4H-quinolizin-4-one

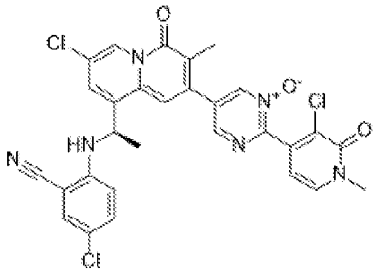
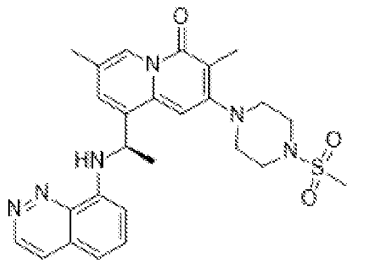
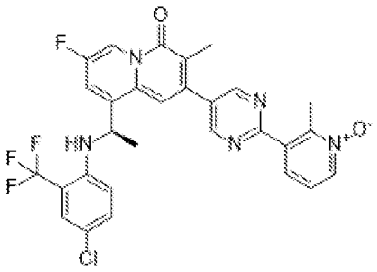
 $C_{28}H_{24}F_5N_3O_3S$	33	(R)-7-fluoro-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3-methyl-2-(6-(1-(methylsulfonyl)cyclopropyl)pyridin-3-yl)-4H-quinolizin-4-one
 $C_{28}H_{21}F_5N_6O_2$	34	(R)-5-(7-fluoro-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3-methyl-4-oxo-4H-quinolizin-2-yl)-2'-methyl-[2,5'-bipyrimidine] 1'-oxide
 $C_{26}H_{29}ClN_4O_3S$	35	(R)-5-chloro-2-((1-(3,7-dimethyl-2-(1-(methylsulfonyl)piperidin-4-yl)-4-oxo-4H-quinolizin-9-yl)ethyl)amino)benzonitrile

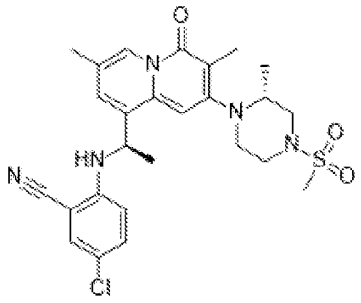
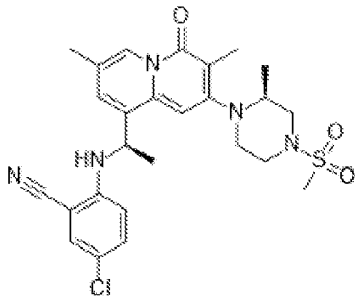
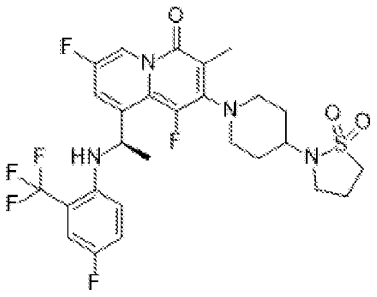
 $C_{31}H_{22}Cl_2F_3N_5O_3$	36	(R)-5-chloro-2-((1-(7-chloro-2-(3'-(difluoromethyl)-3-fluoro-1'-methyl-2,2'-dioxo-1',2'-dihydro-2H-[1,4'-bipyridin]-4-yl)-3-methyl-4-oxo-4H-quinolizin-9-yl)ethyl)amino)benzonitrile
 $C_{29}H_{27}ClN_4O_3S$	37	(R)-5-chloro-2-((1-(3,7-dimethyl-2-(6-(1-(methylsulfonyl)cyclopropyl)pyridin-3-yl)-4-oxo-4H-quinolizin-9-yl)ethyl)amino)benzonitrile
 $C_{26}H_{25}F_6N_3O_3S$	38	(R)-2-(2,2-dioxido-2-thia-7-azaspiro[3.5]nonan-7-yl)-1,7-difluoro-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3-methyl-4H-quinolizin-4-one

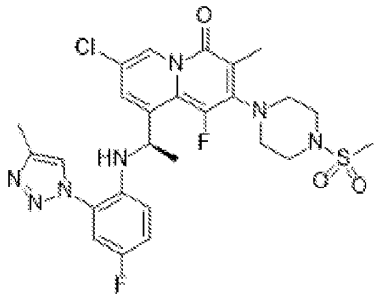
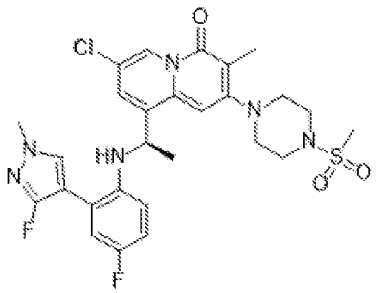
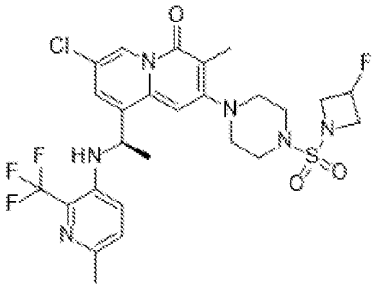
 $C_{26}H_{26}F_5N_3O_3S$	39	(R)-2-(2,2-dioxido-2-thia-7-azaspiro[3.5]nonan-7-yl)-7-fluoro-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3-methyl-4H-quinolizin-4-one
 $C_{26}H_{23}Cl_2N_5O_3S$	40	(R)-N-(5-(7-chloro-9-(1-((4-chloro-2-cyanophenyl)amino)ethyl)-3-methyl-4-oxo-4H-quinolizin-2-yl)pyridin-2-yl)-N-methylmethanesulfonamide
 $C_{29}H_{23}Cl_2F_3N_6O_3$	41	(R)-2-(3-chloro-1-methyl-2-oxo-1,2-dihydropyridin-4-yl)-5-(7-chloro-3-methyl-9-(1-((6-methyl-2-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-4-oxo-4H-quinolizin-2-yl)pyrimidine 1-oxide

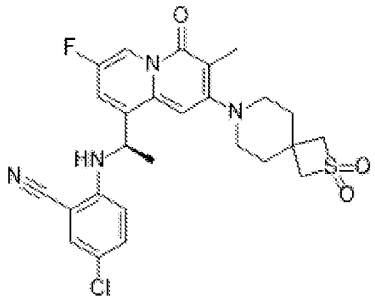
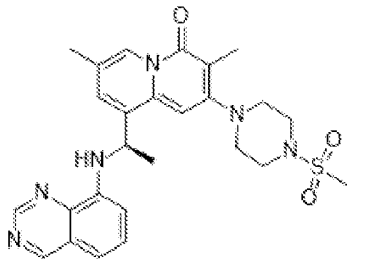
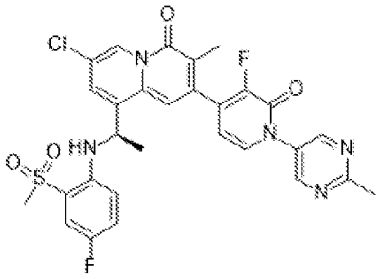
 $C_{29}H_{21}ClF_2N_6O_2$	42	(R)-5-chloro-2-((1-(7-fluoro-2-(3-fluoro-1-(2-methylpyrimidin-5-yl)-2-oxo-1,2-dihydropyridin-4-yl)-3-methyl-4-oxo-4H-quinolizin-9-yl)ethyl)amino)benzonitrile
 $C_{29}H_{21}Cl_2FN_6O_3$	43	(R)-5-chloro-2-((1-(7-chloro-2-(1-(3-fluoro-1-methyl-2-oxo-1,2-dihydropyridin-4-yl)-6-oxo-1,6-dihydropyridazin-4-yl)-3-methyl-4-oxo-4H-quinolizin-9-yl)ethyl)amino)benzonitrile
 $C_{29}H_{25}ClF_3N_7O_2$	44	(R)-7-chloro-2-(1-(2,4-dimethylpyrimidin-5-yl)-6-oxo-1,6-dihydropyridazin-4-yl)-3-methyl-9-(1-((6-methyl-2-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-4H-quinolizin-4-one

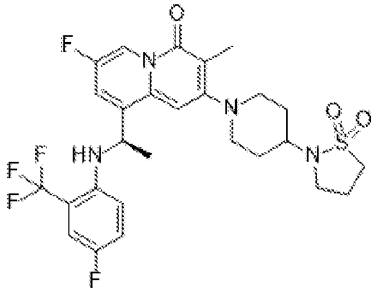
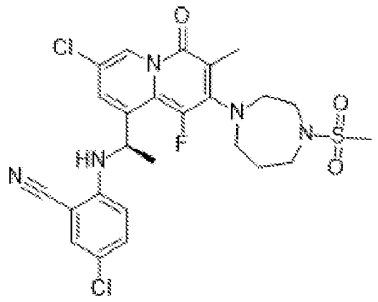
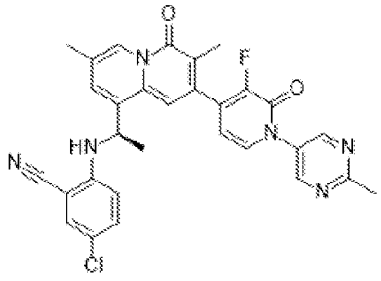
 $C_{28}H_{24}ClFN_6O_4S$	45	(R)-7-chloro-9-(1-((4-fluoro-2-(methylsulfonyl)phenyl)amino)ethyl)-3-methyl-2-(1-(2-methylpyrimidin-5-yl)-6-oxo-1,6-dihydropyridazin-4-yl)-4H-quinolizin-4-one
 $C_{29}H_{21}Cl_2FN_6O_3$	46	(R)-5-(7-chloro-9-(1-((4-chloro-2-cyanophenyl)amino)ethyl)-3-methyl-4-oxo-4H-quinolizin-2-yl)-2-(5-fluoro-1-methyl-6-oxo-1,6-dihydropyridin-2-yl)pyrimidine 1-oxide
 $C_{29}H_{23}Cl_2N_7O_2$	47	(R)-5-chloro-2-((1-(7-chloro-2-(1-(2,4-dimethylpyrimidin-5-yl)-6-oxo-1,6-dihydropyridazin-4-yl)-3-methyl-4-oxo-4H-quinolizin-9-yl)ethyl)amino)benzonitrile

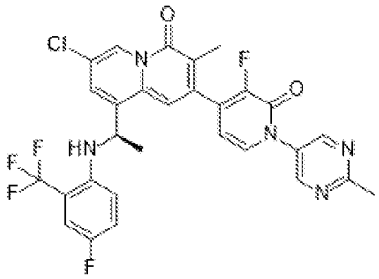
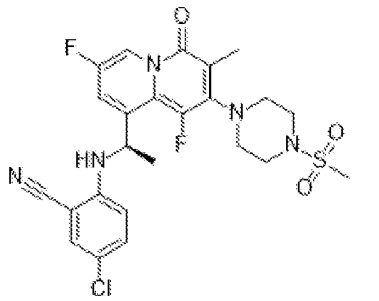
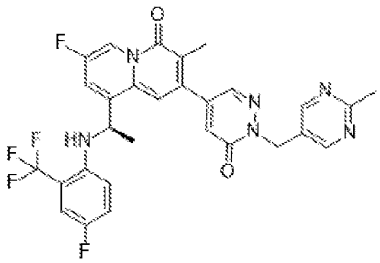
 $C_{29}H_{21}Cl_3N_6O_3$	48	(R)-2-(3-chloro-1-methyl-2-oxo-1,2-dihydropyridin-4-yl)-5-(7-chloro-9-(1-((4-chloro-2-cyanophenyl)amino)ethyl)-3-methyl-4-oxo-4H-quinolizin-2-yl)pyrimidine 1-oxide
 $C_{26}H_{30}N_6O_3S$	49	(R)-9-(1-(cinnolin-8-ylamino)ethyl)-3,7-dimethyl-2-(4-(methylsulfonyl)piperazin-1-yl)-4H-quinolizin-4-one
 $C_{29}H_{22}ClF_4N_5O_2$	50	(R)-3-(5-(9-(1-((4-chloro-2-(trifluoromethyl)phenyl)amino)ethyl)-7-fluoro-3-methyl-4-oxo-4H-quinolizin-2-yl)pyrimidin-2-yl)-2-methylpyridine 1-oxide

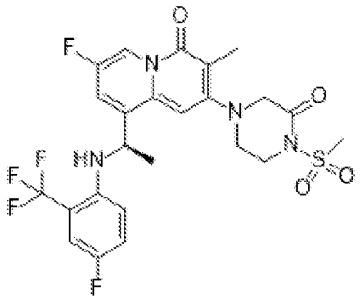
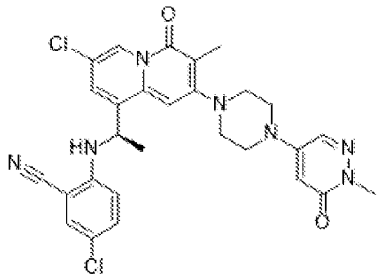
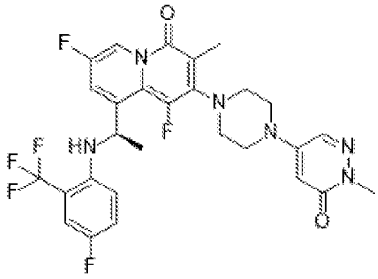
 $C_{26}H_{30}ClN_5O_3S$	51	5-chloro-2-(((R)-1-(3,7-dimethyl-2-((R)-2-methyl-4-(methylsulfonyl)piperazin-1-yl)-4-oxo-4H-quinolizin-9-yl)ethyl)amino)benzonitrile
 $C_{26}H_{30}ClN_5O_3S$	52	5-chloro-2-(((R)-1-(3,7-dimethyl-2-((S)-2-methyl-4-(methylsulfonyl)piperazin-1-yl)-4-oxo-4H-quinolizin-9-yl)ethyl)amino)benzonitrile
 $C_{27}H_{28}F_6N_4O_3S$	53	(R)-2-(4-(1,1-dioxidoisothiazolidin-2-yl)piperidin-1-yl)-1,7-difluoro-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3-methyl-4H-quinolizin-4-one

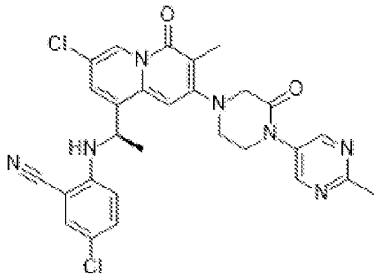
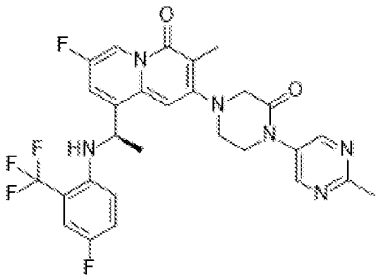
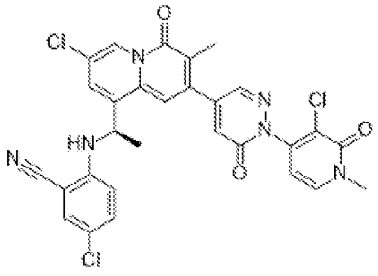
 $C_{26}H_{28}ClF_2N_7O_3S$	54	(R)-7-chloro-1-fluoro-9-(1-((4-fluoro-2-(4-methyl-1H-1,2,3-triazol-1-yl)phenyl)amino)ethyl)-3-methyl-2-(4-(methylsulfonyl)piperazin-1-yl)-4H-quinolizin-4-one
 $C_{27}H_{29}ClF_2N_6O_3S$	55	(R)-7-chloro-9-(1-((4-fluoro-2-(3-fluoro-1-methyl-1H-pyrazol-4-yl)phenyl)amino)ethyl)-3-methyl-2-(4-(methylsulfonyl)piperazin-1-yl)-4H-quinolizin-4-one
 $C_{26}H_{29}ClF_4N_6O_3S$	56	(R)-7-chloro-2-(4-((3-fluoroazetidin-1-yl)sulfonyl)piperazin-1-yl)-3-methyl-9-(1-((6-methyl-2-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-4H-quinolizin-4-one

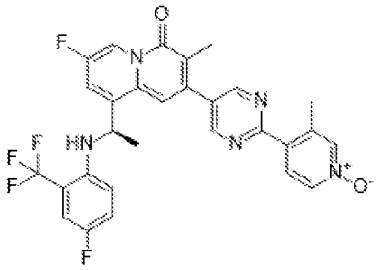
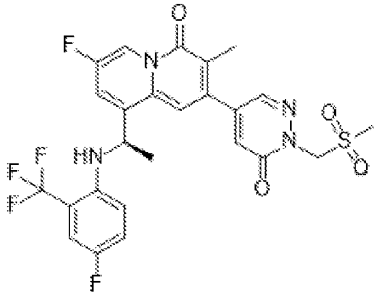
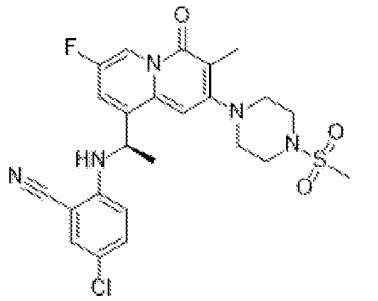
 $C_{26}H_{26}ClFN_4O_3S$	57	(R)-5-chloro-2-((1-(2-(2,2-dioxido-2-thia-7-azaspiro[3.5]nonan-7-yl)-7-fluoro-3-methyl-4-oxo-4H-quinolizin-9-yl)ethyl)amino)benzonitrile
 $C_{26}H_{30}N_8O_3S$	58	(R)-3,7-dimethyl-2-(4-(methylsulfonyl)piperazin-1-yl)-9-(1-(quinazolin-8-ylamino)ethyl)-4H-quinolizin-4-one
 $C_{29}H_{24}ClF_2N_5O_4S$	59	(R)-7-chloro-2-(3-fluoro-1-(2-methylpyrimidin-5-yl)-2-oxo-1,2-dihydropyridin-4-yl)-9-(1-((4-fluoro-2-(methylsulfonyl)phenyl)amino)ethyl)-3-methyl-4H-quinolizin-4-one

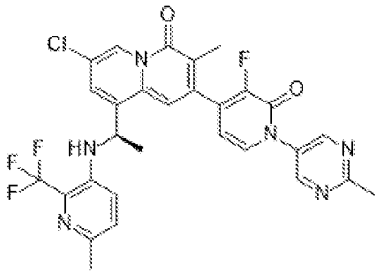
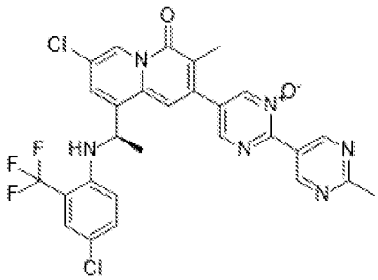
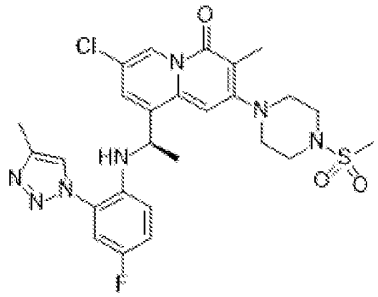
 $C_{27}H_{29}F_5N_4O_3S$	60	(R)-2-(4-(1,1-dioxidoisothiazolidin-2-yl)piperidin-1-yl)-7-fluoro-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3-methyl-4H-quinolizin-4-one
 $C_{25}H_{26}Cl_2FN_5O_3S$	61	(R)-5-chloro-2-((1-(7-chloro-1-fluoro-3-methyl-2-(4-(methylsulfonyl)-1,4-diazepan-1-yl)-4-oxo-4H-quinolizin-9-yl)ethyl)amino)benzonitrile
 $C_{30}H_{24}ClFN_6O_2$	62	(R)-5-chloro-2-((1-(2-(3-fluoro-1-(2-methylpyrimidin-5-yl)-2-oxo-1,2-dihydropyridin-4-yl)-3,7-dimethyl-4-oxo-4H-quinolizin-9-yl)ethyl)amino)benzonitrile

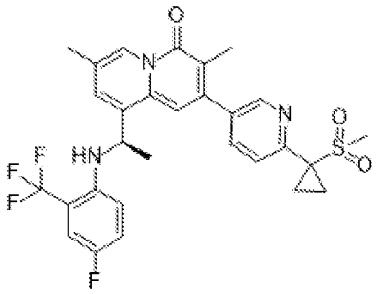
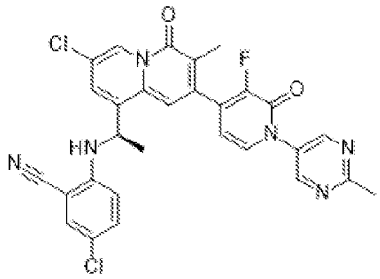
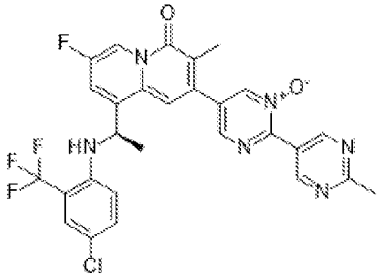
 $C_{29}H_{21}ClF_5N_5O_2$	63	(R)-7-chloro-2-(3-fluoro-1-(2-methylpyrimidin-5-yl)-2-oxo-1,2-dihydropyridin-4-yl)-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3-methyl-4H-quinolizin-4-one
 $C_{24}H_{24}ClF_2N_5O_3S$	64	(R)-5-chloro-2-((1-(1,7-difluoro-3-methyl-2-(4-(methylsulfonyl)piperazin-1-yl)-4-oxo-4H-quinolizin-9-yl)ethyl)amino)benzonitrile
 $C_{29}H_{23}F_5N_6O_2$	65	(R)-7-fluoro-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3-methyl-2-(1-((2-methylpyrimidin-5-yl)methyl)-6-oxo-1,6-dihydropyridazin-4-yl)-4H-quinolizin-4-one

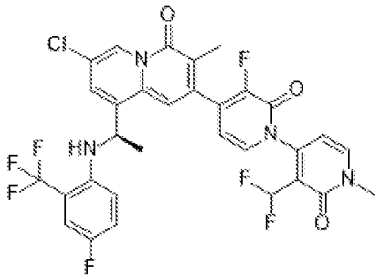
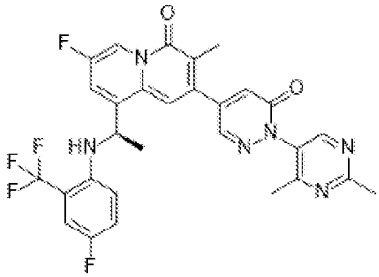
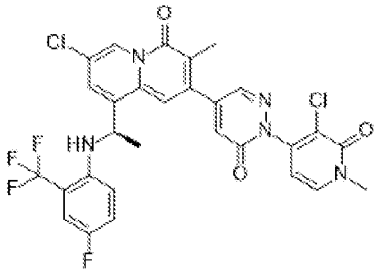
 $C_{24}H_{23}F_5N_4O_4S$	66	(R)-7-fluoro-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3-methyl-2-(4-(methylsulfonyl)-3-oxopiperazin-1-yl)-4H-quinolizin-4-one
 $C_{28}H_{27}Cl_2N_7O_2$	67	(R)-5-chloro-2-((1-(7-chloro-3-methyl-2-(4-(1-methyl-6-oxo-1,6-dihydropyridazin-4-yl)piperazin-1-yl)-4-oxo-4H-quinolizin-9-yl)ethyl)amino)benzonitrile
 $C_{28}H_{26}F_6N_6O_2$	68	(R)-1,7-difluoro-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3-methyl-2-(4-(1-methyl-6-oxo-1,6-dihydropyridazin-4-yl)piperazin-1-yl)-4H-quinolizin-4-one

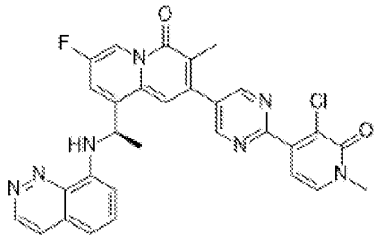
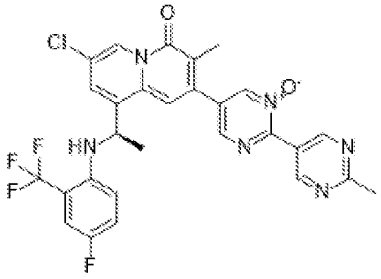
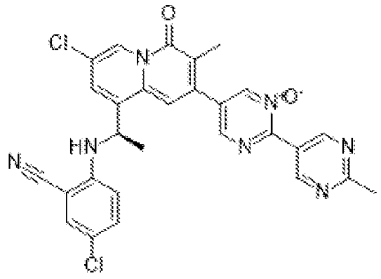
 $C_{28}H_{25}Cl_2N_7O_2$	69	(R)-5-chloro-2-((1-(7-chloro-3-methyl-2-(4-(2-methylpyrimidin-5-yl)-3-oxopiperazin-1-yl)-4-oxo-4H-quinolizin-9-yl)ethyl)amino)benzonitrile
 $C_{28}H_{25}F_5N_6O_2$	70	(R)-7-fluoro-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3-methyl-2-(4-(2-methylpyrimidin-5-yl)-3-oxopiperazin-1-yl)-4H-quinolizin-4-one
 $C_{29}H_{21}Cl_3N_6O_3$	71	(R)-5-chloro-2-((1-(7-chloro-2-(1-(3-chloro-1-methyl-2-oxo-1,2-dihydropyridin-4-yl)-6-oxo-1,6-dihydropyridazin-4-yl)-3-methyl-4-oxo-4H-quinolizin-9-yl)ethyl)amino)benzonitrile

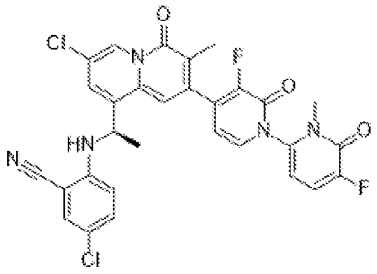
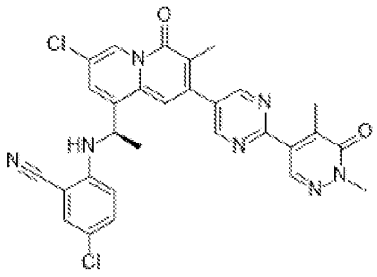
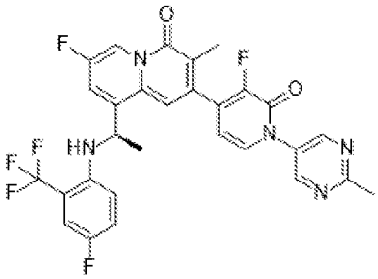
 $C_{29}H_{22}F_5N_5O_2$	72	(R)-4-(5-(7-fluoro-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3-methyl-4-oxo-4H-quinolizin-2-yl)pyrimidin-2-yl)-3-methylpyridine 1-oxide
 $C_{25}H_{21}F_5N_4O_4S$	73	(R)-7-fluoro-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3-methyl-2-(1-((methylsulfonyl)methyl)-6-oxo-1,6-dihydropyridazin-4-yl)-4H-quinolizin-4-one
 $C_{24}H_{25}ClFN_5O_3S$	74	(R)-5-chloro-2-((1-(7-fluoro-3-methyl-2-(4-(methylsulfonyl)piperazin-1-yl)-4-oxo-4H-quinolizin-9-yl)ethyl)amino)benzonitrile

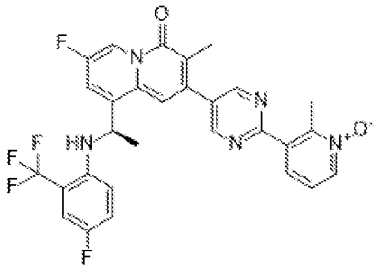
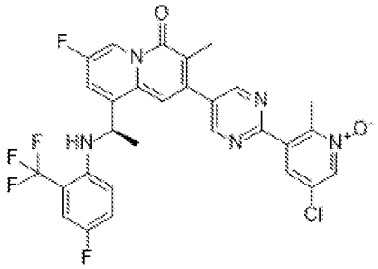
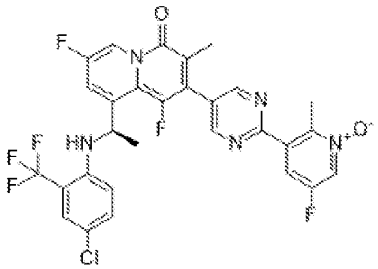
 $C_{29}H_{23}ClF_4N_6O_2$	75	(R)-7-chloro-2-(3-fluoro-1-(2-methylpyrimidin-5-yl)-2-oxo-1,2-dihydropyridin-4-yl)-3-methyl-9-(1-((6-methyl-2-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-4H-quinolizin-4-one
 $C_{28}H_{21}Cl_2F_3N_6O_2$	76	(R)-5-(7-chloro-9-(1-((4-chloro-2-(trifluoromethyl)phenyl)amino)ethyl)-3-methyl-4-oxo-4H-quinolizin-2-yl)-2'-methyl-[2,5'-bipyrimidine] 1-oxide
 $C_{26}H_{29}ClFN_7O_3S$	77	(R)-7-chloro-9-(1-((4-fluoro-2-(4-methyl-1H-1,2,3-triazol-1-yl)phenyl)amino)ethyl)-3-methyl-2-(4-(methylsulfonyl)piperazin-1-yl)-4H-quinolizin-4-one

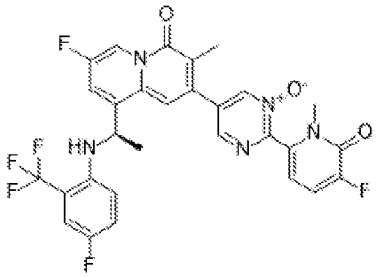
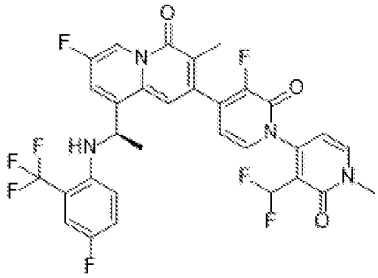
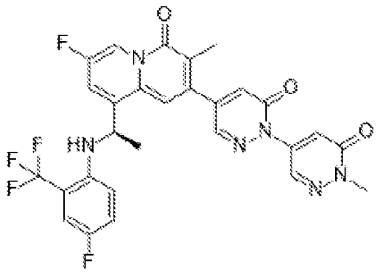
 $C_{29}H_{27}F_4N_3O_3S$	78	(R)-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3,7-dimethyl-2-(6-(1-(methylsulfonyl)cyclopropyl)pyridin-3-yl)-4H-quinolizin-4-one
 $C_{29}H_{21}Cl_2FN_6O_2$	79	(R)-5-chloro-2-((1-(7-chloro-2-(3-fluoro-1-(2-methylpyrimidin-5-yl)-2-oxo-1,2-dihydropyridin-4-yl)-3-methyl-4-oxo-4H-quinolizin-9-yl)ethyl)amino)benzonitrile
 $C_{28}H_{21}ClF_4N_6O_2$	80	(R)-5-(9-(1-((4-chloro-2-(trifluoromethyl)phenyl)amino)ethyl)-7-fluoro-3-methyl-4-oxo-4H-quinolizin-2-yl)-2'-methyl-[2,5'-bipyrimidine] 1-oxide

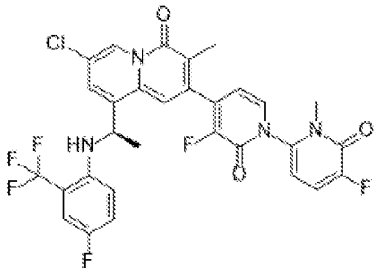
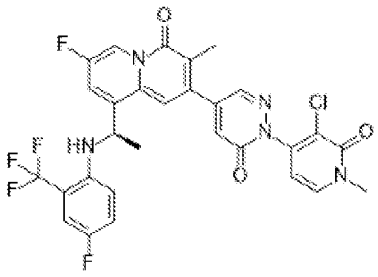
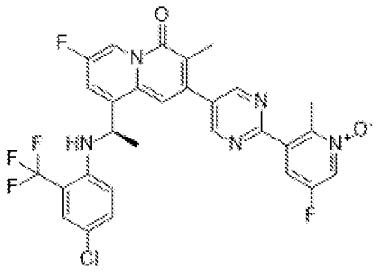
 $C_{31}H_{22}ClF_7N_4O_3$	81	(R)-4-(7-chloro-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3-methyl-4-oxo-4H-quinolizin-2-yl)-3'-(difluoromethyl)-3-fluoro-1'-methyl-2H-[1,4'-bipyridine]-2,2'(1'H)-dione
 $C_{29}H_{23}F_5N_6O_2$	82	(R)-2-(1-(2,4-dimethylpyrimidin-5-yl)-6-oxo-1,6-dihydropyridazin-4-yl)-7-fluoro-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3-methyl-4H-quinolizin-4-one
 $C_{29}H_{21}Cl_2F_4N_5O_3$	83	(R)-7-chloro-2-(1-(3-chloro-1-methyl-2-oxo-1,2-dihydropyridin-4-yl)-6-oxo-1,6-dihydropyridazin-4-yl)-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3-methyl-4H-quinolizin-4-one

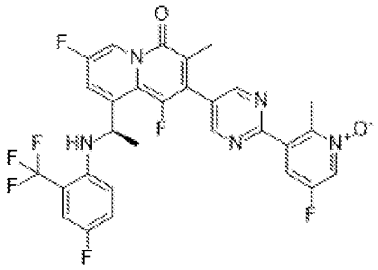
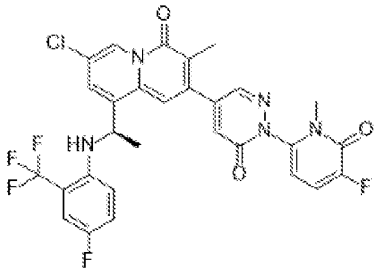
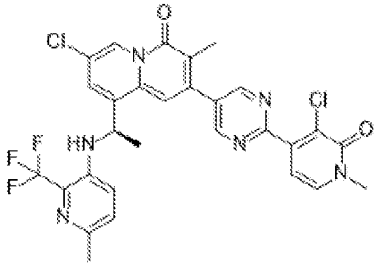
 $C_{30}H_{23}ClFN_7O_2$	84	(R)-2-(2-(3-chloro-1-methyl-2-oxo-1,2-dihydropyridin-4-yl)pyrimidin-5-yl)-9-(1-(cinnolin-8-ylamino)ethyl)-7-fluoro-3-methyl-4H-quinolizin-4-one
 $C_{28}H_{21}ClF_4N_6O_2$	85	(R)-5-(7-chloro-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3-methyl-4-oxo-4H-quinolizin-2-yl)-2'-methyl-[2,5'-bipyrimidine] 1-oxide
 $C_{28}H_{21}Cl_2N_7O_2$	86	(R)-5-(7-chloro-9-(1-((4-chloro-2-cyanophenyl)amino)ethyl)-3-methyl-4-oxo-4H-quinolizin-2-yl)-2'-methyl-[2,5'-bipyrimidine] 1-oxide

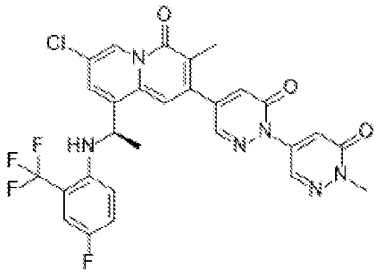
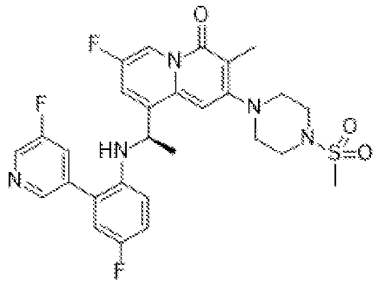
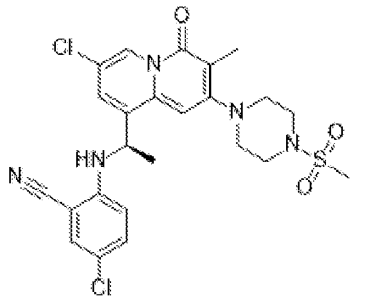
 $C_{30}H_{21}Cl_2F_2N_5O_3$	87	(R)-5-chloro-2-((1-(7-chloro-2-(3,5'-difluoro-1'-methyl-2,6'-dioxo-1',6'-dihydro-2H-[1,2'-bipyridin]-4-yl)-3-methyl-4-oxo-4H-quinolizin-9-yl)ethyl)amino)benzonitrile
 $C_{29}H_{23}Cl_2N_7O_2$	88	(R)-5-chloro-2-((1-(7-chloro-2-(2-(1,5-dimethyl-6-oxo-1,6-dihydropyridazin-4-yl)pyrimidin-5-yl)-3-methyl-4-oxo-4H-quinolizin-9-yl)ethyl)amino)benzonitrile
 $C_{29}H_{21}F_6N_5O_2$	89	(R)-7-fluoro-2-(3-fluoro-1-(2-methylpyrimidin-5-yl)-2-oxo-1,2-dihydropyridin-4-yl)-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3-methyl-4H-quinolizin-4-one

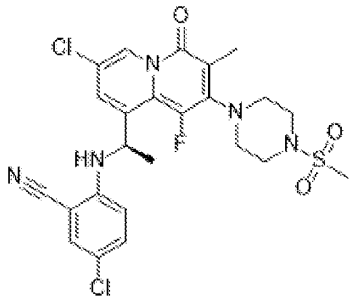
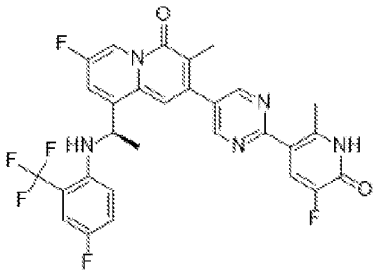
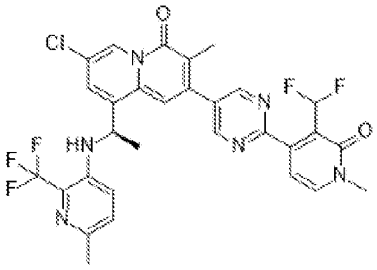
 $C_{29}H_{22}F_5N_5O_2$	90	(R)-3-(5-(7-fluoro-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3-methyl-4-oxo-4H-quinolizin-2-yl)pyrimidin-2-yl)-2-methylpyridine 1-oxide
 $C_{29}H_{21}ClF_5N_5O_2$	91	(R)-5-chloro-3-(5-(7-fluoro-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3-methyl-4-oxo-4H-quinolizin-2-yl)pyrimidin-2-yl)-2-methylpyridine 1-oxide
 $C_{29}H_{20}ClF_6N_5O_2$	92	(R)-3-(5-(9-(1-((4-chloro-2-(trifluoromethyl)phenyl)amino)ethyl)-1,7-difluoro-3-methyl-4-oxo-4H-quinolizin-2-yl)pyrimidin-2-yl)-5-fluoro-2-methylpyridine 1-oxide

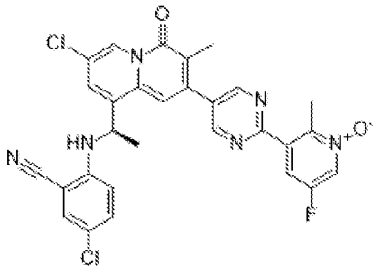
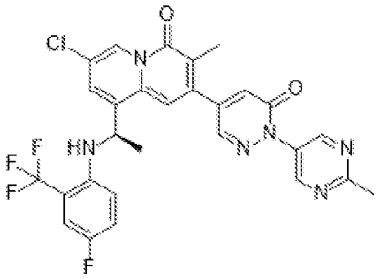
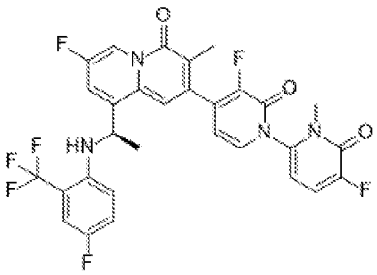
 $C_{29}H_{21}F_6N_5O_3$	93	(R)-2-(5-fluoro-1-methyl-6-oxo-1,6-dihydropyridin-2-yl)-5-(7-fluoro-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3-methyl-4-oxo-4H-quinolizin-2-yl)pyrimidine 1-oxide
 $C_{31}H_{22}F_8N_4O_3$	94	(R)-3'-(difluoromethyl)-3-fluoro-4-(7-fluoro-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3-methyl-4-oxo-4H-quinolizin-2-yl)-1'-methyl-2H-[1,4'-bipyridine]-2,2'(1'H)-dione
 $C_{28}H_{21}F_5N_6O_3$	95	(R)-4-(7-fluoro-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3-methyl-4-oxo-4H-quinolizin-2-yl)-1'-methyl-6H-[1,4'-bipyridazine]-6,6'(1'H)-dione

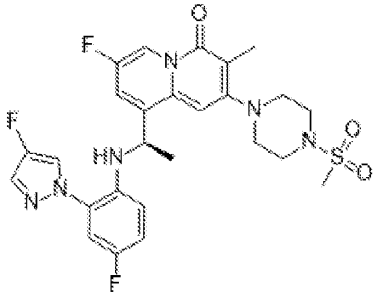
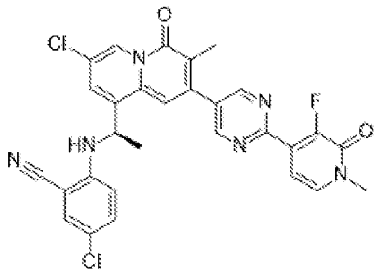
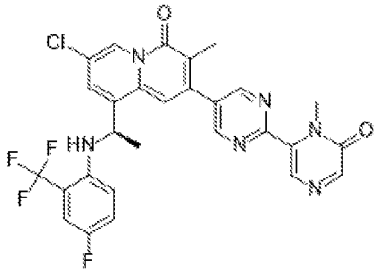
 $C_{30}H_{21}ClF_6N_4O_3$	96	(R)-4-(7-chloro-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3-methyl-4-oxo-4H-quinolizin-2-yl)-3,5'-difluoro-1'-methyl-2H-[1,2'-bipyridine]-2,6'(1'H)-dione
 $C_{29}H_{21}ClF_5N_5O_3$	97	(R)-2-(1-(3-chloro-1-methyl-2-oxo-1,2-dihydropyridin-4-yl)-6-oxo-1,6-dihydropyridazin-4-yl)-7-fluoro-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3-methyl-4H-quinolizin-4-one
 $C_{29}H_{21}ClF_5N_5O_2$	98	(R)-3-(5-(9-(1-((4-chloro-2-(trifluoromethyl)phenyl)amino)ethyl)-7-fluoro-3-methyl-4-oxo-4H-quinolizin-2-yl)pyrimidin-2-yl)-5-fluoro-2-methylpyridine 1-oxide

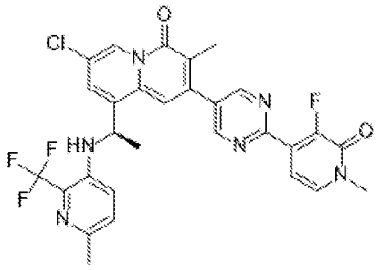
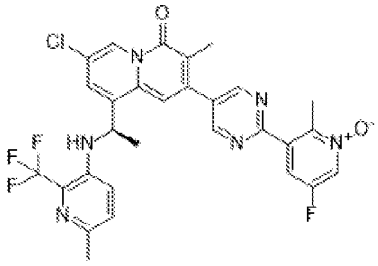
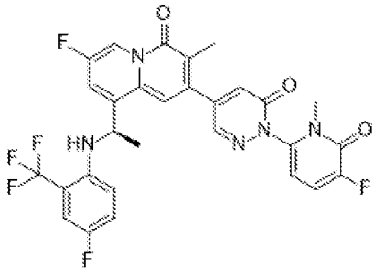
 $C_{29}H_{20}F_7N_5O_2$	99	(R)-3-(5-(1,7-difluoro-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3-methyl-4-oxo-4H-quinolizin-2-yl)pyrimidin-2-yl)-5-fluoro-2-methylpyridine 1-oxide
 $C_{29}H_{21}ClF_5N_5O_3$	100	(R)-7-chloro-2-(1-(5-fluoro-1-methyl-6-oxo-1,6-dihydropyridin-2-yl)-6-oxo-1,6-dihydropyridazin-4-yl)-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3-methyl-4H-quinolizin-4-one
 $C_{29}H_{23}Cl_2F_3N_6O_2$	101	(R)-7-chloro-2-(2-(3-chloro-1-methyl-2-oxo-1,2-dihydropyridin-4-yl)pyrimidin-5-yl)-3-methyl-9-(1-((6-methyl-2-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-4H-quinolizin-4-one

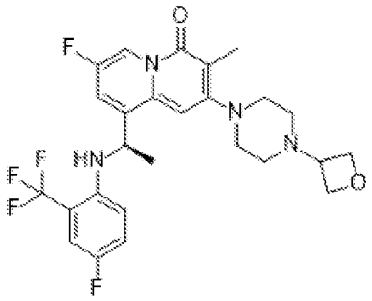
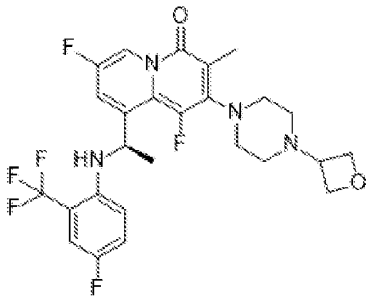
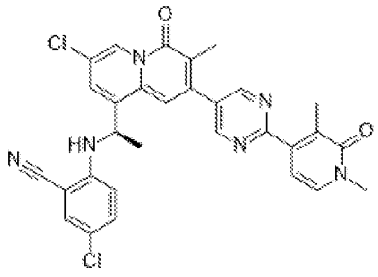
 $C_{28}H_{21}ClF_4N_6O_3$	102	(R)-4-(7-chloro-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3-methyl-4-oxo-4H-quinolizin-2-yl)-1'-methyl-6H-[1,4'-bipyridazine]-6,6'(1'H)-dione
 $C_{28}H_{28}F_3N_5O_3S$	103	(R)-7-fluoro-9-(1-((4-fluoro-2-(5-fluoropyridin-3-yl)phenyl)amino)ethyl)-3-methyl-2-(4-(methylsulfonyl)piperazin-1-yl)-4H-quinolizin-4-one
 $C_{24}H_{25}Cl_2N_5O_3S$	104	(R)-5-chloro-2-((1-(7-chloro-3-methyl-2-(4-(methylsulfonyl)piperazin-1-yl)-4-oxo-4H-quinolizin-9-yl)ethyl)amino)benzonitrile

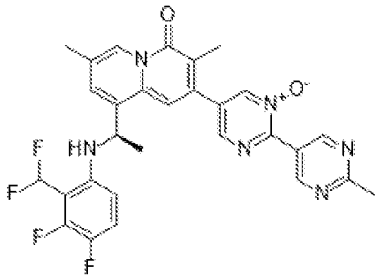
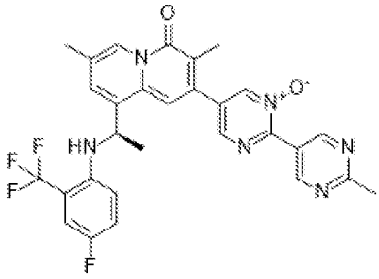
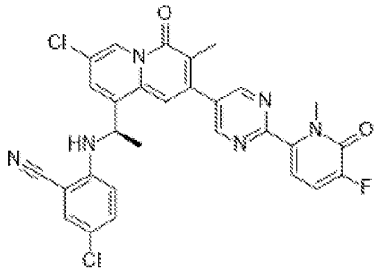
 $C_{24}H_{24}Cl_2FN_5O_3S$	105	(R)-5-chloro-2-((1-(7-chloro-1-fluoro-3-methyl-2-(4-(methylsulfonyl)piperazin-1-yl)-4-oxo-4H-quinolizin-9-yl)ethyl)amino)benzonitrile
 $C_{29}H_{21}F_6N_5O_2$	106	(R)-7-fluoro-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-2-(2-(5-fluoro-2-methyl-6-oxo-1,6-dihydropyridin-3-yl)pyrimidin-5-yl)-3-methyl-4H-quinolizin-4-one
 $C_{30}H_{24}ClF_5N_6O_2$	107	(R)-7-chloro-2-(2-(3-(difluoromethyl)-1-methyl-2-oxo-1,2-dihydropyridin-4-yl)pyrimidin-5-yl)-3-methyl-9-(1-((6-methyl-2-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-4H-quinolizin-4-one

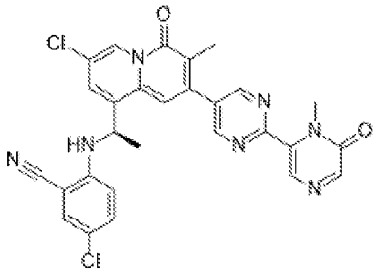
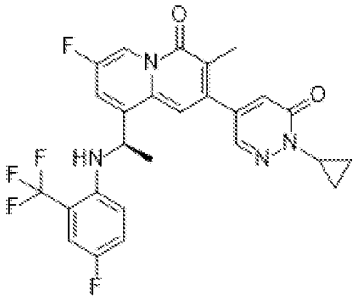
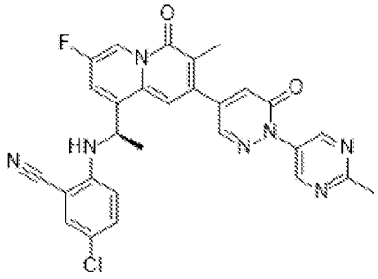
 $C_{29}H_{21}Cl_2FN_6O_2$	108	(R)-3-(5-(7-chloro-9-(1-((4-chloro-2-cyanophenyl)amino)ethyl)-3-methyl-4-oxo-4H-quinolizin-2-yl)pyrimidin-2-yl)-5-fluoro-2-methylpyridine 1-oxide
 $C_{28}H_{21}ClF_4N_6O_2$	109	(R)-7-chloro-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3-methyl-2-(1-(2-methylpyrimidin-5-yl)-6-oxo-1,6-dihydropyridazin-4-yl)-4H-quinolizin-4-one
 $C_{30}H_{21}F_7N_4O_3$	110	(R)-3,5'-difluoro-4-(7-fluoro-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3-methyl-4-oxo-4H-quinolizin-2-yl)-1'-methyl-2H-[1,2'-bipyridine]-2,6'(1'H)-dione

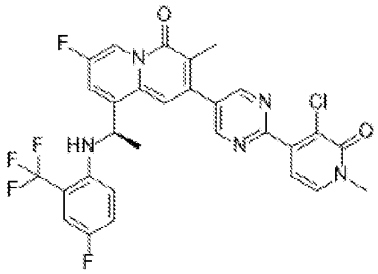
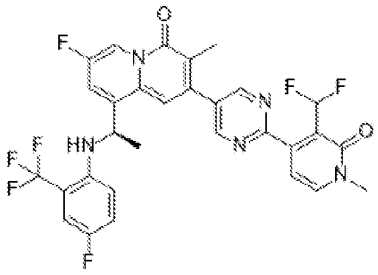
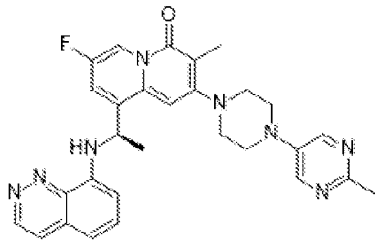
 $C_{26}H_{27}F_3N_6O_3S$	111	(R)-7-fluoro-9-(1-((4-fluoro-2-(4-fluoro-1H-pyrazol-1-yl)phenyl)amino)ethyl)-3-methyl-2-(4-(methylsulfonyl)piperazin-1-yl)-4H-quinolizin-4-one
 $C_{29}H_{21}Cl_2FN_6O_2$	112	(R)-5-chloro-2-((1-(7-chloro-2-(2-(3-fluoro-1-methyl-2-oxo-1,2-dihydropyridin-4-yl)pyrimidin-5-yl)-3-methyl-4-oxo-4H-quinolizin-9-yl)ethyl)amino)benzonitrile
 $C_{28}H_{21}ClF_4N_6O_2$	113	(R)-7-chloro-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3-methyl-2-(2-(1-methyl-6-oxo-1,6-dihydropyrazin-2-yl)pyrimidin-5-yl)-4H-quinolizin-4-one

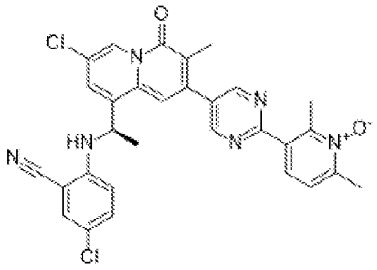
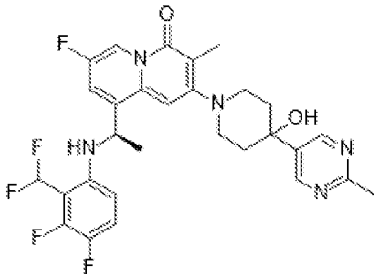
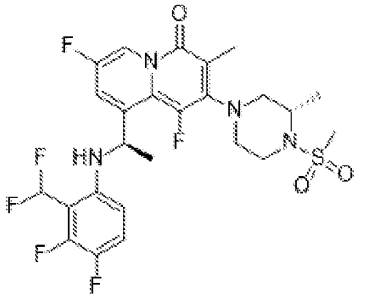
 $C_{29}H_{23}ClF_4N_6O_2$	114	(R)-7-chloro-2-(2-(3-fluoro-1-methyl-2-oxo-1,2-dihydropyridin-4-yl)pyrimidin-5-yl)-3-methyl-9-(1-((6-methyl-2-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-4H-quinolizin-4-one
 $C_{29}H_{23}ClF_4N_6O_2$	115	(R)-3-(5-(7-chloro-3-methyl-9-(1-((6-methyl-2-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-4-oxo-4H-quinolizin-2-yl)pyrimidin-2-yl)-5-fluoro-2-methylpyridine 1-oxide
 $C_{29}H_{21}F_6N_5O_3$	116	(R)-7-fluoro-2-(1-(5-fluoro-1-methyl-6-oxo-1,6-dihydropyridin-2-yl)-6-oxo-1,6-dihydropyridazin-4-yl)-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3-methyl-4H-quinolizin-4-one

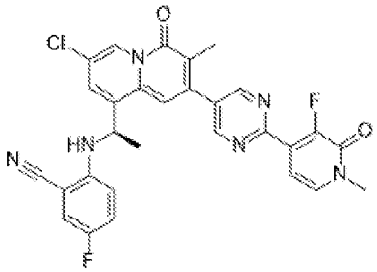
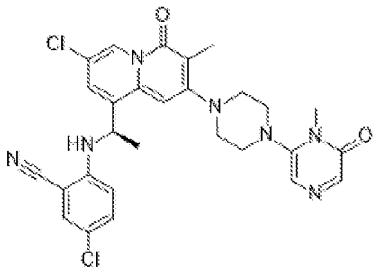
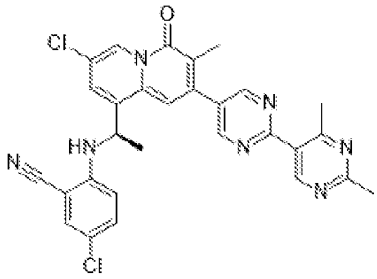
 $C_{26}H_{27}F_5N_4O_2$	117	(R)-7-fluoro-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3-methyl-2-(4-(oxetan-3-yl)piperazin-1-yl)-4H-quinolizin-4-one
 $C_{26}H_{26}F_6N_4O_2$	118	(R)-1,7-difluoro-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3-methyl-2-(4-(oxetan-3-yl)piperazin-1-yl)-4H-quinolizin-4-one
 $C_{30}H_{24}Cl_2N_6O_2$	119	(R)-5-chloro-2-((1-(7-chloro-2-(2-(1,3-dimethyl-2-oxo-1,2-dihydropyridin-4-yl)pyrimidin-5-yl)-3-methyl-4-oxo-4H-quinolizin-9-yl)ethyl)amino)benzonitrile

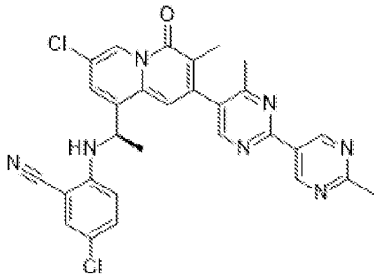
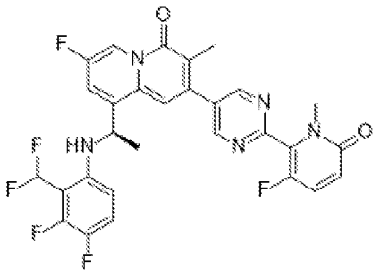
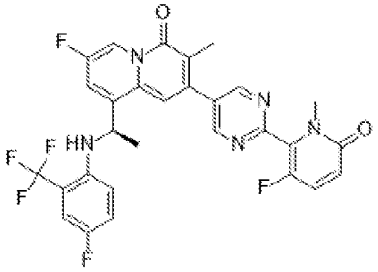
 $C_{29}H_{24}F_4N_6O_2$	120	(R)-5-(9-(1-((2-(difluoromethyl)-3,4-difluorophenyl)amino)ethyl)-3,7-dimethyl-4-oxo-4H-quinolizin-2-yl)-2'-methyl-[2,5'-bipyrimidine] 1-oxide
 $C_{29}H_{24}F_4N_6O_2$	121	(R)-5-(9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3,7-dimethyl-4-oxo-4H-quinolizin-2-yl)-2'-methyl-[2,5'-bipyrimidine] 1-oxide
 $C_{29}H_{21}Cl_2FN_6O_2$	122	(R)-5-chloro-2-((1-(7-chloro-2-(2-(5-fluoro-1-methyl-6-oxo-1,6-dihydropyridin-2-yl)pyrimidin-5-yl)-3-methyl-4-oxo-4H-quinolizin-9-yl)ethyl)amino)benzonitrile

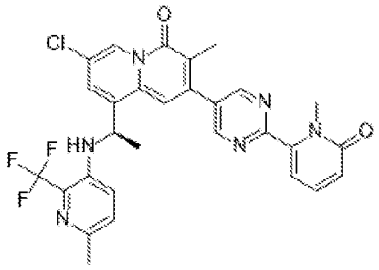
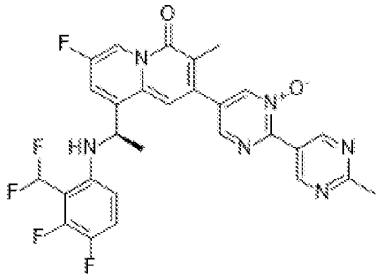
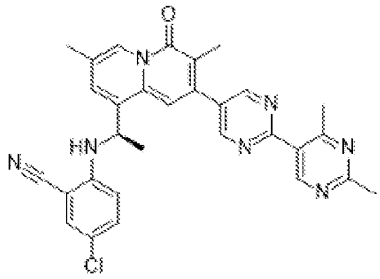
 $C_{28}H_{21}Cl_2N_7O_2$	123	(R)-5-chloro-2-((1-(7-chloro-3-methyl-2-(2-(1-methyl-6-oxo-1,6-dihydropyrazin-2-yl)pyrimidin-5-yl)-4-oxo-4H-quinolizin-9-yl)ethyl)amino)benzonitrile
 $C_{26}H_{21}F_5N_4O_2$	124	(R)-2-(1-cyclopropyl-6-oxo-1,6-dihydropyridazin-4-yl)-7-fluoro-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3-methyl-4H-quinolizin-4-one
 $C_{28}H_{21}ClFN_7O_2$	125	(R)-5-chloro-2-((1-(7-fluoro-3-methyl-2-(1-(2-methylpyrimidin-5-yl)-6-oxo-1,6-dihydropyridazin-4-yl)-4-oxo-4H-quinolizin-9-yl)ethyl)amino)benzonitrile

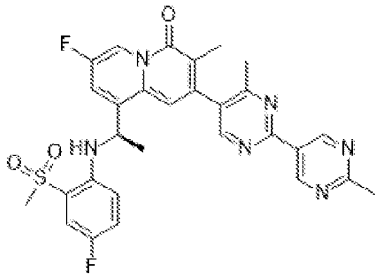
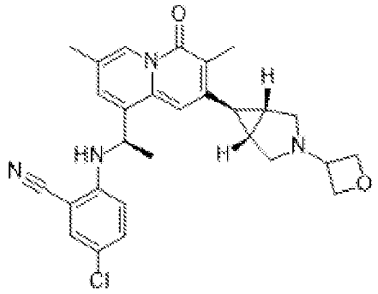
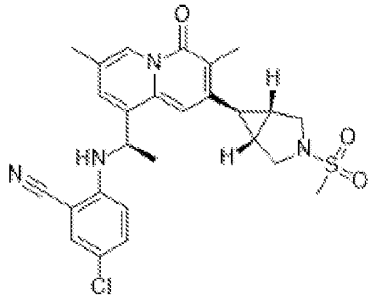
 $C_{29}H_{21}ClF_5N_5O_2$	126	(R)-2-(2-(3-chloro-1-methyl-2-oxo-1,2-dihydropyridin-4-yl)pyrimidin-5-yl)-7-fluoro-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3-methyl-4H-quinolizin-4-one
 $C_{30}H_{22}F_7N_5O_2$	127	(R)-2-(2-(3-(difluoromethyl)-1-methyl-2-oxo-1,2-dihydropyridin-4-yl)pyrimidin-5-yl)-7-fluoro-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3-methyl-4H-quinolizin-4-one
 $C_{29}H_{29}FN_8O$	128	(R)-9-(1-(cinnolin-8-ylamino)ethyl)-7-fluoro-3-methyl-2-(4-(2-methylpyrimidin-5-yl)piperazin-1-yl)-4H-quinolizin-4-one

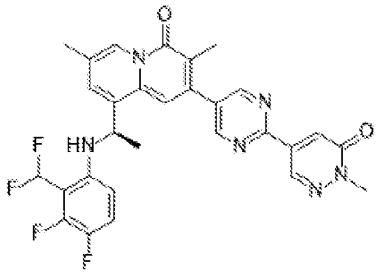
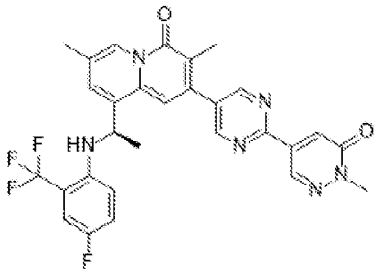
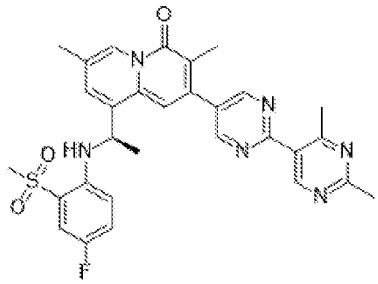
 $C_{30}H_{24}Cl_2N_6O_2$	129	(R)-3-(5-(7-chloro-9-(1-((4-chloro-2-cyanophenyl)amino)ethyl)-3-methyl-4-oxo-4H-quinolizin-2-yl)pyrimidin-2-yl)-2,6-dimethylpyridine 1-oxide
 $C_{29}H_{28}F_5N_5O_2$	130	(R)-9-(1-((2-(difluoromethyl)-3,4-difluorophenyl)amino)ethyl)-7-fluoro-2-(4-hydroxy-4-(2-methylpyrimidin-5-yl)piperidin-1-yl)-3-methyl-4H-quinolizin-4-one
 $C_{25}H_{26}F_6N_4O_3S$	131	9-((R)-1-((2-(difluoromethyl)-3,4-difluorophenyl)amino)ethyl)-1,7-difluoro-3-methyl-2-((S)-3-methyl-4-(methylsulfonyl)piperazin-1-yl)-4H-quinolizin-4-one

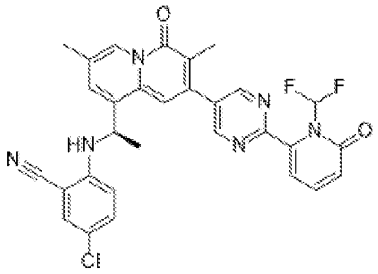
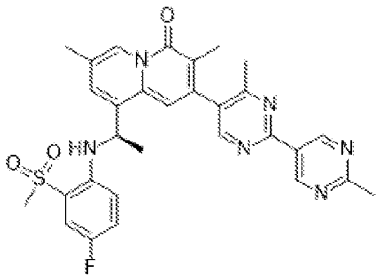
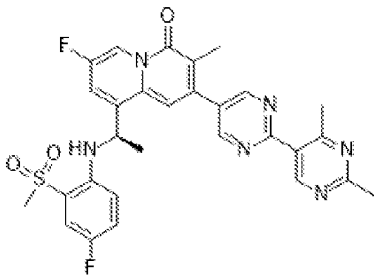
 $C_{29}H_{21}ClF_2N_6O_2$	132	(R)-2-((1-(7-chloro-2-(2-(3-fluoro-1-methyl-2-oxo-1,2-dihydropyridin-4-yl)pyrimidin-5-yl)-3-methyl-4-oxo-4H-quinolizin-9-yl)ethyl)amino)-5-fluorobenzonitrile
 $C_{28}H_{27}Cl_2N_7O_2$	133	(R)-5-chloro-2-((1-(7-chloro-3-methyl-2-(4-(1-methyl-6-oxo-1,6-dihydropyrazin-2-yl)piperazin-1-yl)-4-oxo-4H-quinolizin-9-yl)ethyl)amino)benzonitrile
 $C_{29}H_{23}Cl_2N_7O$	134	(R)-5-chloro-2-((1-(7-chloro-2-(2',4'-dimethyl-[2,5'-bipyrimidin]-5-yl)-3-methyl-4-oxo-4H-quinolizin-9-yl)ethyl)amino)benzonitrile

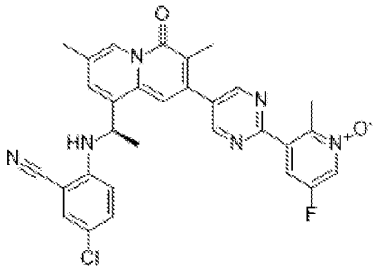
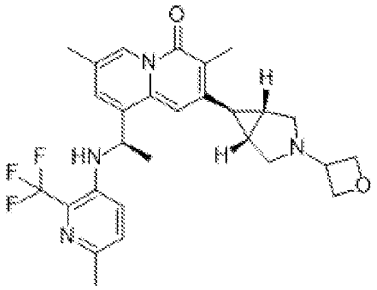
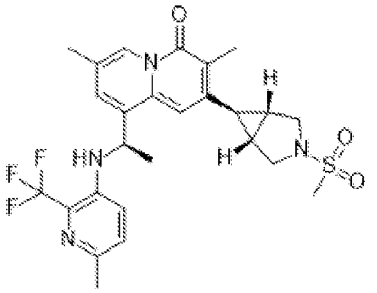
 $C_{29}H_{23}Cl_2N_7O$	135	(R)-5-chloro-2-((1-(7-chloro-2-(2',4-dimethyl-[2,5'-bipyrimidin]-5-yl)-3-methyl-4-oxo-4H-quinolizin-9-yl)ethyl)amino)benzonitrile
 $C_{29}H_{21}F_6N_5O_2$	136	(R)-9-(1-((2-(difluoromethyl)-3,4-difluorophenyl)amino)ethyl)-7-fluoro-2-(2-(3-fluoro-1-methyl-6-oxo-1,6-dihydropyridin-2-yl)pyrimidin-5-yl)-3-methyl-4H-quinolizin-4-one
 $C_{29}H_{21}F_6N_5O_2$	137	(R)-7-fluoro-2-(2-(3-fluoro-1-methyl-6-oxo-1,6-dihydropyridin-2-yl)pyrimidin-5-yl)-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3-methyl-4H-quinolizin-4-one

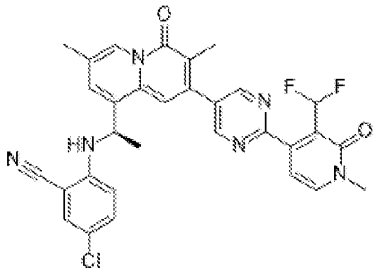
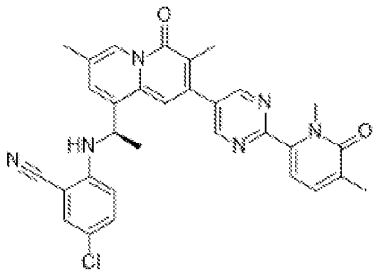
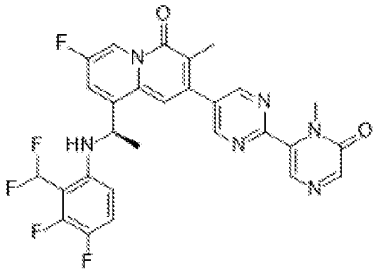
 $C_{29}H_{24}ClF_3N_6O_2$	138	(R)-7-chloro-3-methyl-9-(1-((6-methyl-2-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-2-(2-(1-methyl-6-oxo-1,6-dihydropyridin-2-yl)pyrimidin-5-yl)-4H-quinolizin-4-one
 $C_{28}H_{21}F_5N_6O_2$	139	(R)-5-(9-(1-((2-(difluoromethyl)-3,4-difluorophenyl)amino)ethyl)-7-fluoro-3-methyl-4-oxo-4H-quinolizin-2-yl)-2'-methyl-[2,5'-bipyrimidine] 1-oxide
 $C_{30}H_{26}ClN_7O$	140	(R)-5-chloro-2-((1-(2-(2',4'-dimethyl-[2,5'-bipyrimidin]-5-yl)-3,7-dimethyl-4-oxo-4H-quinolizin-9-yl)ethyl)amino)benzonitrile

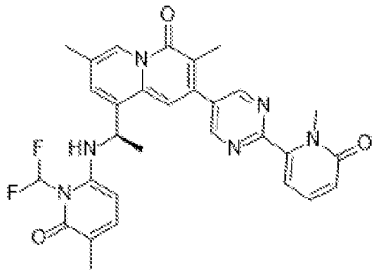
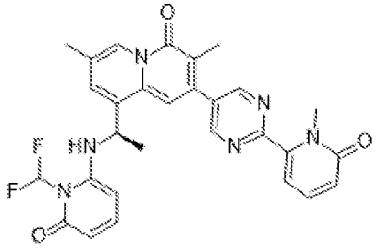
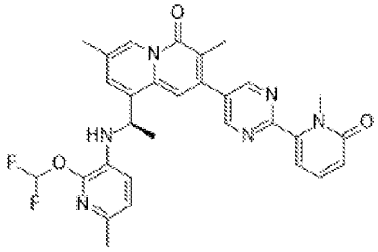
 $C_{29}H_{26}F_2N_6O_3S$	141	(R)-2-(2',4-dimethyl-[2,5'-bipyrimidin]-5-yl)-7-fluoro-9-(1-((4-fluoro-2-(methylsulfonyl)phenyl)amino)ethyl)-3-methyl-4H-quinolizin-4-one
 $C_{28}H_{29}ClN_4O_2$	142	5-chloro-2-(((R)-1-(3,7-dimethyl-2-((1R,5S,6s)-3-(oxetan-3-yl)-3-azabicyclo[3.1.0]hexan-6-yl)-4-oxo-4H-quinolizin-9-yl)ethyl)amino)benzonitrile
 $C_{26}H_{27}ClN_4O_3S$	143	5-chloro-2-(((R)-1-(3,7-dimethyl-2-((1R,5S,6s)-3-(methylsulfonyl)-3-azabicyclo[3.1.0]hexan-6-yl)-4-oxo-4H-quinolizin-9-yl)ethyl)amino)benzonitrile

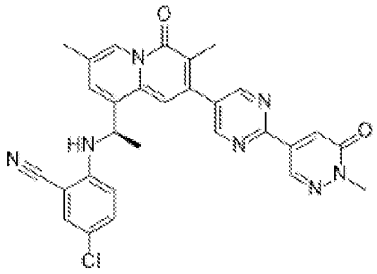
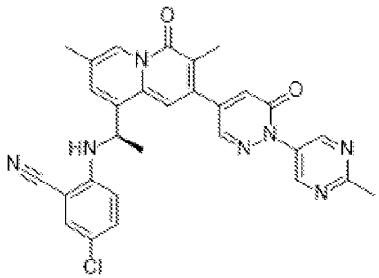
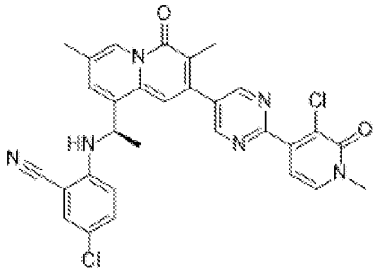
 $C_{29}H_{24}F_4N_6O_2$	144	(R)-9-(1-((2-(difluoromethyl)-3,4-difluorophenyl)amino)ethyl)-3,7-dimethyl-2-(2-(1-methyl-6-oxo-1,6-dihydropyridazin-4-yl)pyrimidin-5-yl)-4H-quinolizin-4-one
 $C_{29}H_{24}F_4N_6O_2$	145	(R)-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3,7-dimethyl-2-(2-(1-methyl-6-oxo-1,6-dihydropyridazin-4-yl)pyrimidin-5-yl)-4H-quinolizin-4-one
 $C_{30}H_{29}FN_6O_3S$	146	(R)-2-(2',4'-dimethyl-[2,5'-bipyrimidin]-5-yl)-9-(1-((4-fluoro-2-(methylsulfonyl)phenyl)amino)ethyl)-3,7-dimethyl-4H-quinolizin-4-one

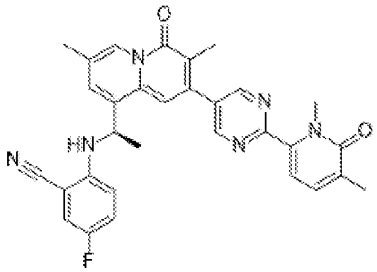
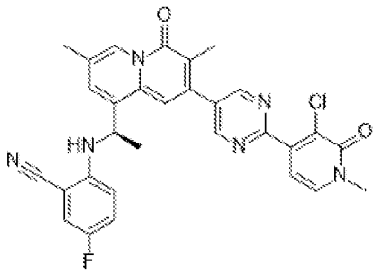
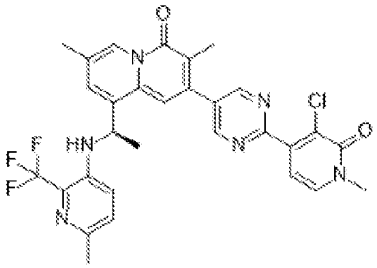
 $C_{30}H_{23}ClF_2N_6O_2$	147	(R)-5-chloro-2-((1-(2-(2-(1-(difluoromethyl)-6-oxo-1,6-dihydropyridin-2-yl)pyrimidin-5-yl)-3,7-dimethyl-4-oxo-4H-quinolizin-9-yl)ethyl)amino)benzonitrile
 $C_{30}H_{29}FN_6O_3S$	148	(R)-2-(2',4-dimethyl-[2,5'-bipyrimidin]-5-yl)-9-(1-((4-fluoro-2-(methylsulfonyl)phenyl)amino)ethyl)-3,7-dimethyl-4H-quinolizin-4-one
 $C_{29}H_{26}F_2N_6O_3S$	149	(R)-2-(2',4'-dimethyl-[2,5'-bipyrimidin]-5-yl)-7-fluoro-9-(1-((4-fluoro-2-(methylsulfonyl)phenyl)amino)ethyl)-3-methyl-4H-quinolizin-4-one

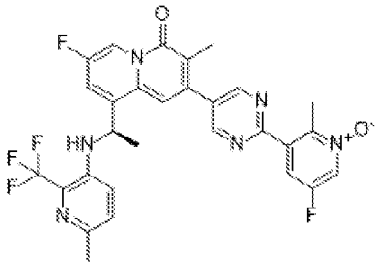
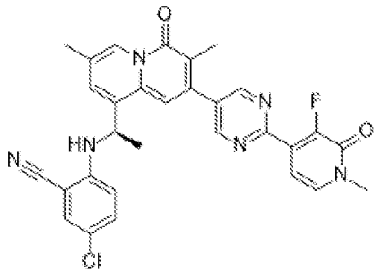
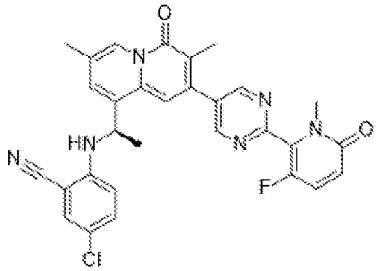
 $C_{30}H_{24}ClFN_6O_2$	150	(R)-3-(5-(9-(1-((4-chloro-2-cyanophenyl)amino)ethyl)-3,7-dimethyl-4-oxo-4H-quinolizin-2-yl)pyrimidin-2-yl)-5-fluoro-2-methylpyridine 1-oxide
 $C_{28}H_{31}F_3N_4O_2$	151	3,7-dimethyl-9-((R)-1-((6-methyl-2-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-2-((1R,5S,6s)-3-(oxetan-3-yl)-3-azabicyclo[3.1.0]hexan-6-yl)-4H-quinolizin-4-one
 $C_{26}H_{29}F_3N_4O_3S$	152	3,7-dimethyl-9-((R)-1-((6-methyl-2-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-2-((1R,5S,6s)-3-(methylsulfonyl)-3-azabicyclo[3.1.0]hexan-6-yl)-4H-quinolizin-4-one

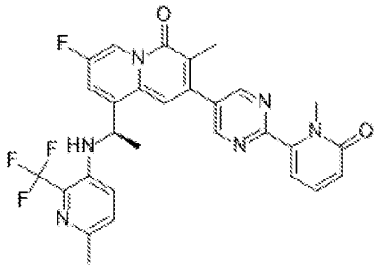
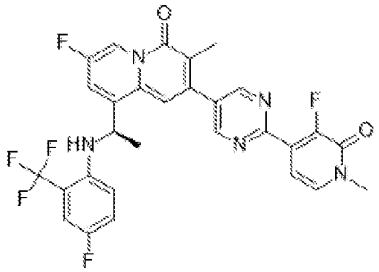
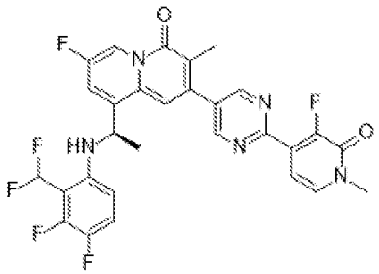
 $C_{31}H_{25}ClF_2N_6O_2$	153	(R)-5-chloro-2-((1-(2-(2-(3-(difluoromethyl)-1-methyl-2-oxo-1,2-dihydropyridin-4-yl)pyrimidin-5-yl)-3,7-dimethyl-4-oxo-4H-quinolizin-9-yl)ethyl)amino)benzonitrile
 $C_{31}H_{27}ClN_6O_2$	154	(R)-5-chloro-2-((1-(2-(2-(1,5-dimethyl-6-oxo-1,6-dihydropyridin-2-yl)pyrimidin-5-yl)-3,7-dimethyl-4-oxo-4H-quinolizin-9-yl)ethyl)amino)benzonitrile
 $C_{28}H_{21}F_5N_6O_2$	155	(R)-9-(1-((2-(difluoromethyl)-3,4-difluorophenyl)amino)ethyl)-7-fluoro-3-methyl-2-(2-(1-methyl-6-oxo-1,6-dihydropyrazin-2-yl)pyrimidin-5-yl)-4H-quinolizin-4-one

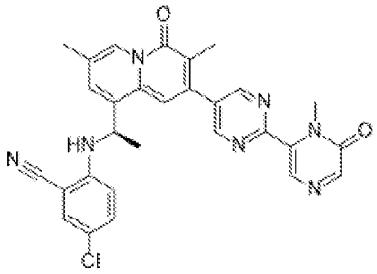
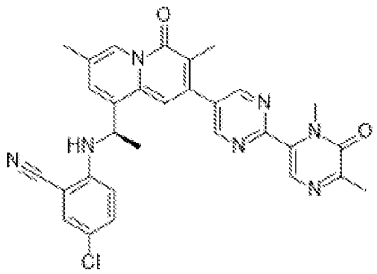
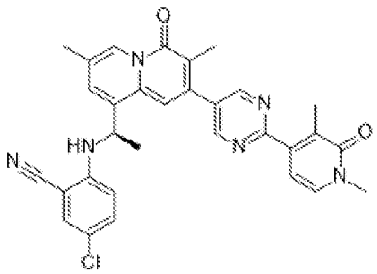
 $C_{30}H_{28}F_2N_6O_3$	156	(R)-9-(1-((1-(difluoromethyl)-5-methyl-6-oxo-1,6-dihydropyridin-2-yl)amino)ethyl)-3,7-dimethyl-2-(2-(1-methyl-6-oxo-1,6-dihydropyridin-2-yl)pyrimidin-5-yl)-4H-quinolizin-4-one
 $C_{29}H_{26}F_2N_6O_3$	157	(R)-9-(1-((1-(difluoromethyl)-6-oxo-1,6-dihydropyridin-2-yl)amino)ethyl)-3,7-dimethyl-2-(2-(1-methyl-6-oxo-1,6-dihydropyridin-2-yl)pyrimidin-5-yl)-4H-quinolizin-4-one
 $C_{30}H_{28}F_2N_6O_3$	158	(R)-9-(1-((2-(difluoromethoxy)-6-methylpyridin-3-yl)amino)ethyl)-3,7-dimethyl-2-(2-(1-methyl-6-oxo-1,6-dihydropyridin-2-yl)pyrimidin-5-yl)-4H-quinolizin-4-one

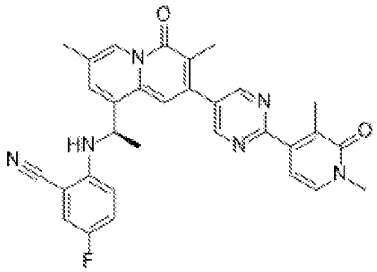
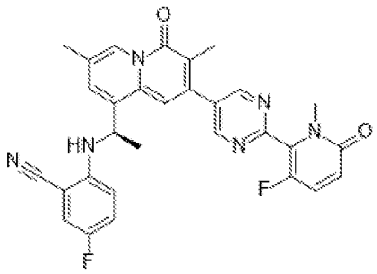
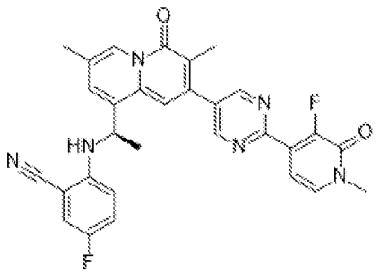
 $C_{29}H_{24}ClN_7O_2$	159	(R)-5-chloro-2-((1-(3,7-dimethyl-2-(2-(1-methyl-6-oxo-1,6-dihydropyridazin-4-yl)pyrimidin-5-yl)-4-oxo-4H-quinolizin-9-yl)ethyl)amino)benzonitrile
 $C_{29}H_{24}ClN_7O_2$	160	(R)-5-chloro-2-((1-(3,7-dimethyl-2-(1-(2-methylpyrimidin-5-yl)-6-oxo-1,6-dihydropyridazin-4-yl)-4-oxo-4H-quinolizin-9-yl)ethyl)amino)benzonitrile
 $C_{30}H_{24}Cl_2N_6O_2$	161	(R)-5-chloro-2-((1-(2-(2-(3-chloro-1-methyl-2-oxo-1,2-dihydropyridin-4-yl)pyrimidin-5-yl)-3,7-dimethyl-4-oxo-4H-quinolizin-9-yl)ethyl)amino)benzonitrile

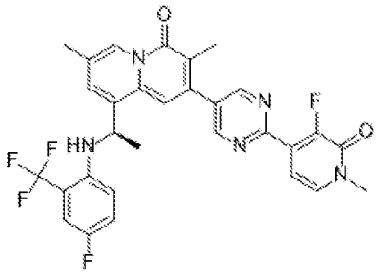
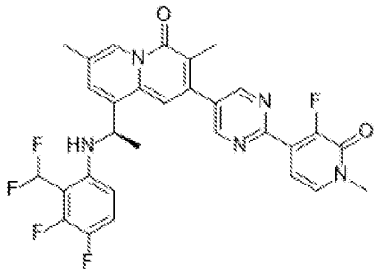
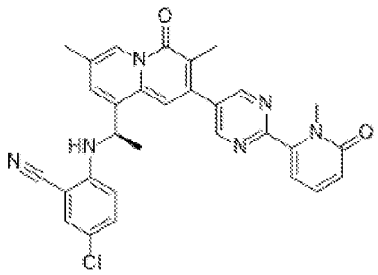
 $C_{31}H_{27}FN_6O_2$	162	(R)-2-((1-(2-(2-(1,5-dimethyl-6-oxo-1,6-dihydropyridin-2-yl)pyrimidin-5-yl)-3,7-dimethyl-4-oxo-4H-quinolizin-9-yl)ethyl)amino)-5-fluorobenzonitrile
 $C_{30}H_{24}ClFN_6O_2$	163	(R)-2-((1-(2-(2-(3-chloro-1-methyl-2-oxo-1,2-dihydropyridin-4-yl)pyrimidin-5-yl)-3,7-dimethyl-4-oxo-4H-quinolizin-9-yl)ethyl)amino)-5-fluorobenzonitrile
 $C_{30}H_{26}ClF_3N_6O_2$	164	(R)-2-(2-(3-chloro-1-methyl-2-oxo-1,2-dihydropyridin-4-yl)pyrimidin-5-yl)-3,7-dimethyl-9-(1-((6-methyl-2-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-4H-quinolizin-4-one

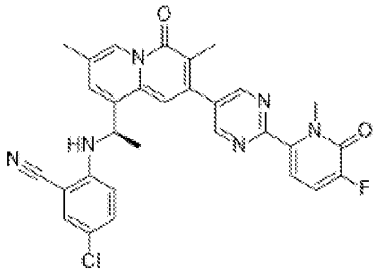
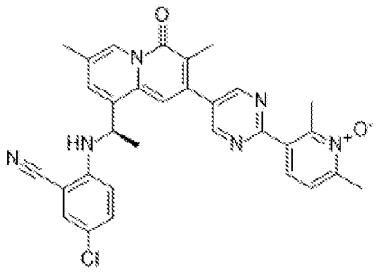
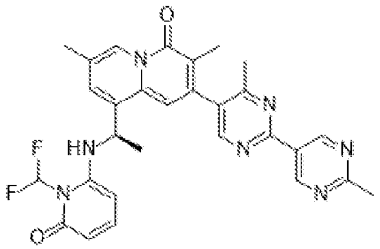
 $C_{29}H_{23}F_5N_6O_2$	165	(R)-5-fluoro-3-(5-(7-fluoro-3-methyl-9-(1-((6-methyl-2-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-4-oxo-4H-quinolizin-2-yl)pyrimidin-2-yl)-2-methylpyridine 1-oxide
 $C_{30}H_{24}ClFN_6O_2$	166	(R)-5-chloro-2-((1-(2-(2-(3-fluoro-1-methyl-2-oxo-1,2-dihydropyridin-4-yl)pyrimidin-5-yl)-3,7-dimethyl-4-oxo-4H-quinolizin-9-yl)ethyl)amino)benzonitrile
 $C_{30}H_{24}ClFN_6O_2$	167	(R)-5-chloro-2-((1-(2-(2-(3-fluoro-1-methyl-6-oxo-1,6-dihydropyridin-2-yl)pyrimidin-5-yl)-3,7-dimethyl-4-oxo-4H-quinolizin-9-yl)ethyl)amino)benzonitrile

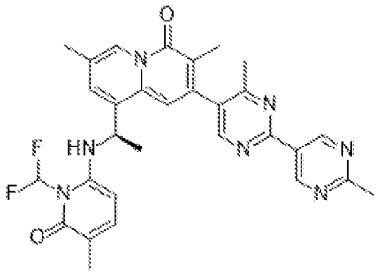
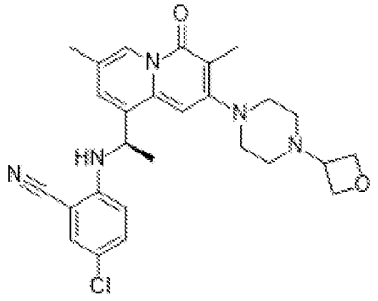
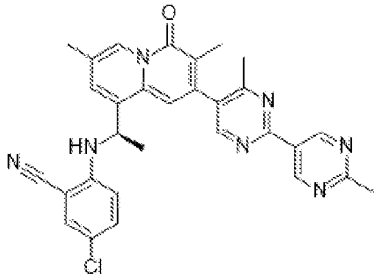
 $C_{29}H_{24}F_4N_6O_2$	168	(R)-7-fluoro-3-methyl-9-(1-((6-methyl-2-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-2-(2-(1-methyl-6-oxo-1,6-dihydropyridin-2-yl)pyrimidin-5-yl)-4H-quinolizin-4-one
 $C_{29}H_{21}F_6N_5O_2$	169	(R)-7-fluoro-2-(2-(3-fluoro-1-methyl-2-oxo-1,2-dihydropyridin-4-yl)pyrimidin-5-yl)-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3-methyl-4H-quinolizin-4-one
 $C_{29}H_{21}F_6N_5O_2$	170	(R)-9-(1-((2-(difluoromethyl)-3,4-difluorophenyl)amino)ethyl)-7-fluoro-2-(2-(3-fluoro-1-methyl-2-oxo-1,2-dihydropyridin-4-yl)pyrimidin-5-yl)-3-methyl-4H-quinolizin-4-one

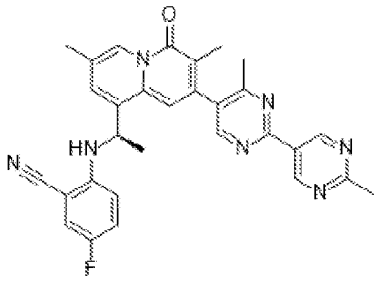
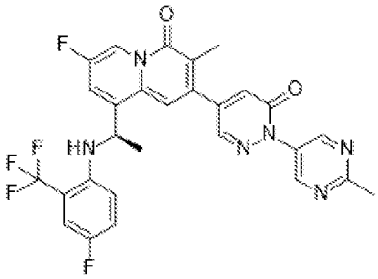
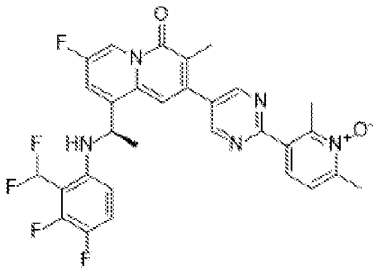
 $C_{29}H_{24}ClN_7O_2$	171	(R)-5-chloro-2-((1-(3,7-dimethyl-2-(2-(1-methyl-6-oxo-1,6-dihydropyrazin-2-yl)pyrimidin-5-yl)-4-oxo-4H-quinolizin-9-yl)ethyl)amino)benzonitrile
 $C_{30}H_{26}ClN_7O_2$	172	(R)-5-chloro-2-((1-(2-(2-(1,5-dimethyl-6-oxo-1,6-dihydropyrazin-2-yl)pyrimidin-5-yl)-3,7-dimethyl-4-oxo-4H-quinolizin-9-yl)ethyl)amino)benzonitrile
 $C_{31}H_{27}ClN_6O_2$	173	(R)-5-chloro-2-((1-(2-(2-(1,3-dimethyl-2-oxo-1,2-dihydropyridin-4-yl)pyrimidin-5-yl)-3,7-dimethyl-4-oxo-4H-quinolizin-9-yl)ethyl)amino)benzonitrile

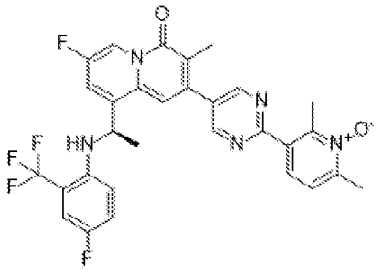
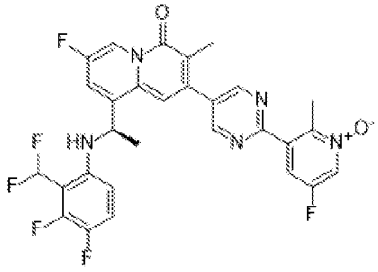
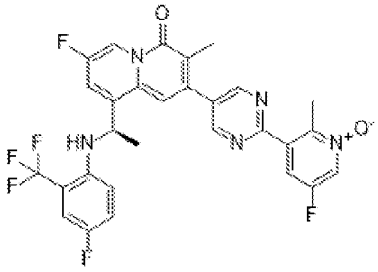
 $C_{31}H_{27}FN_6O_2$	174	(R)-2-((1-(2-(2-(1,3-dimethyl-2-oxo-1,2-dihydropyridin-4-yl)pyrimidin-5-yl)-3,7-dimethyl-4-oxo-4H-quinolizin-9-yl)ethyl)amino)-5-fluorobenzonitrile
 $C_{30}H_{24}F_2N_6O_2$	175	(R)-5-fluoro-2-((1-(2-(2-(3-fluoro-1-methyl-6-oxo-1,6-dihydropyridin-2-yl)pyrimidin-5-yl)-3,7-dimethyl-4-oxo-4H-quinolizin-9-yl)ethyl)amino)benzonitrile
 $C_{30}H_{24}F_2N_6O_2$	176	(R)-5-fluoro-2-((1-(2-(2-(3-fluoro-1-methyl-2-oxo-1,2-dihydropyridin-4-yl)pyrimidin-5-yl)-3,7-dimethyl-4-oxo-4H-quinolizin-9-yl)ethyl)amino)benzonitrile

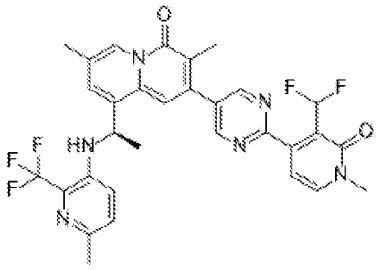
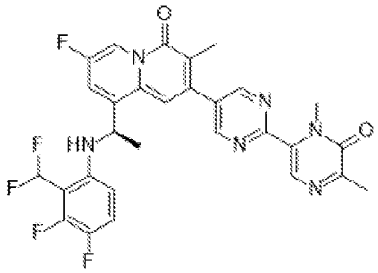
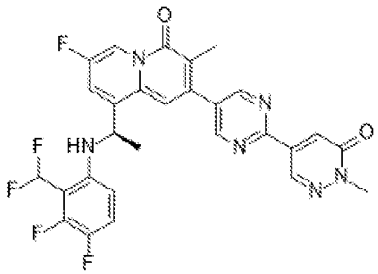
 $C_{30}H_{24}F_5N_5O_2$	177	(R)-2-(2-(3-fluoro-1-methyl-2-oxo-1,2-dihydropyridin-4-yl)pyrimidin-5-yl)-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3,7-dimethyl-4H-quinolizin-4-one
 $C_{30}H_{24}F_5N_5O_2$	178	(R)-9-(1-((2-(difluoromethyl)-3,4-difluorophenyl)amino)ethyl)-2-(2-(3-fluoro-1-methyl-2-oxo-1,2-dihydropyridin-4-yl)pyrimidin-5-yl)-3,7-dimethyl-4H-quinolizin-4-one
 $C_{30}H_{25}ClN_6O_2$	179	(R)-5-chloro-2-((1-(3,7-dimethyl-2-(2-(1-methyl-6-oxo-1,6-dihydropyridin-2-yl)pyrimidin-5-yl)-4-oxo-4H-quinolizin-9-yl)ethyl)amino)benzonitrile

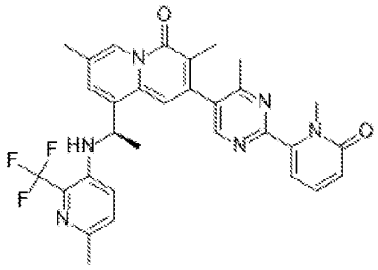
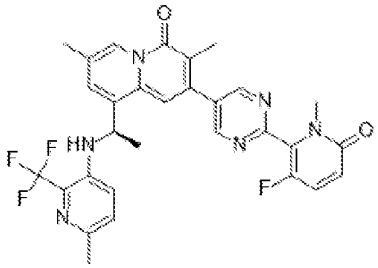
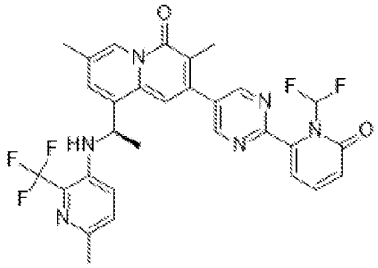
 $C_{30}H_{24}ClFN_6O_2$	180	(R)-5-chloro-2-((1-(2-(2-(5-fluoro-1-methyl-6-oxo-1,6-dihydropyridin-2-yl)pyrimidin-5-yl)-3,7-dimethyl-4-oxo-4H-quinolizin-9-yl)ethyl)amino)benzonitrile
 $C_{31}H_{27}ClN_6O_2$	181	(R)-3-(5-(9-(1-((4-chloro-2-cyanophenyl)amino)ethyl)-3,7-dimethyl-4-oxo-4H-quinolizin-2-yl)pyrimidin-2-yl)-2,6-dimethylpyridine 1-oxide
 $C_{29}H_{27}F_2N_7O_2$	182	(R)-9-(1-((1-(difluoromethyl)-6-oxo-1,6-dihydropyridin-2-yl)amino)ethyl)-2-(2',4-dimethyl-[2,5'-bipyrimidin]-5-yl)-3,7-dimethyl-4H-quinolizin-4-one

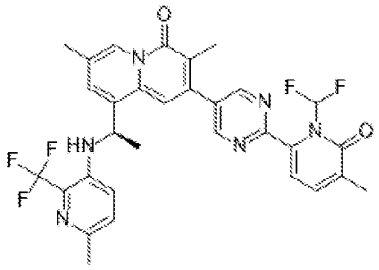
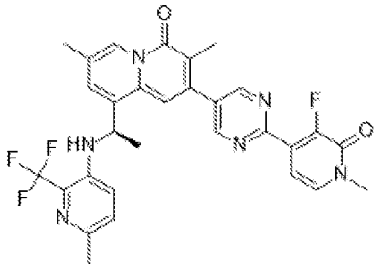
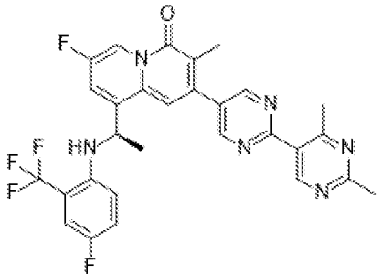
 $C_{30}H_{29}F_2N_7O_2$	183	(R)-9-(1-((1-(difluoromethyl)-5-methyl-6-oxo-1,6-dihydropyridin-2-yl)amino)ethyl)-2-(2',4-dimethyl-[2,5'-bipyrimidin]-5-yl)-3,7-dimethyl-4H-quinolizin-4-one
 $C_{27}H_{30}ClN_5O_2$	184	(R)-5-chloro-2-((1-(3,7-dimethyl-2-(4-(oxetan-3-yl)piperazin-1-yl)-4-oxo-4H-quinolizin-9-yl)ethyl)amino)benzonitrile
 $C_{30}H_{26}ClN_7O$	185	(R)-5-chloro-2-((1-(2-(2',4-dimethyl-[2,5'-bipyrimidin]-5-yl)-3,7-dimethyl-4-oxo-4H-quinolizin-9-yl)ethyl)amino)benzonitrile

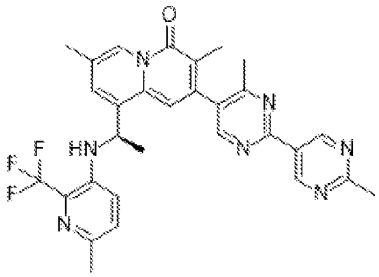
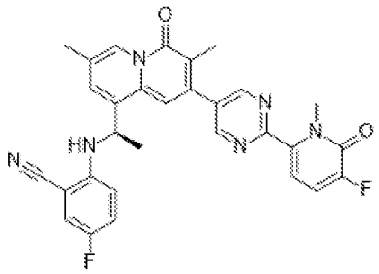
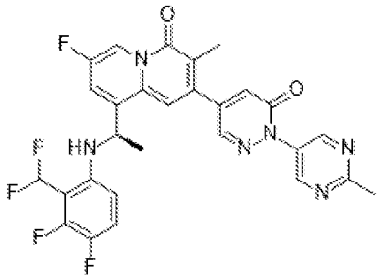
 $C_{30}H_{26}FN_7O$	186	(R)-2-((1-(2-(2',4-dimethyl-[2,5'-bipyrimidin]-5-yl)-3,7-dimethyl-4-oxo-4H-quinolizin-9-yl)ethyl)amino)-5-fluorobenzonitrile
 $C_{28}H_{21}F_5N_6O_2$	187	(R)-7-fluoro-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3-methyl-2-(1-(2-methylpyrimidin-5-yl)-6-oxo-1,6-dihydropyridazin-4-yl)-4H-quinolizin-4-one
 $C_{30}H_{24}F_5N_5O_2$	188	(R)-3-(5-(9-(1-((2-(difluoromethyl)-3,4-difluorophenyl)amino)ethyl)-7-fluoro-3-methyl-4-oxo-4H-quinolizin-2-yl)pyrimidin-2-yl)-2,6-dimethylpyridine 1-oxide

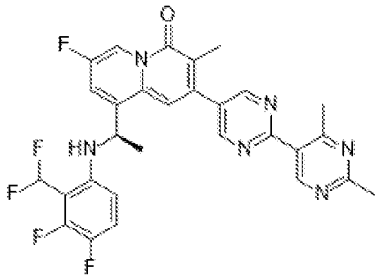
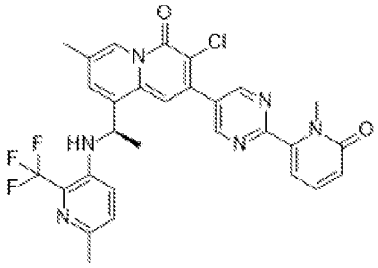
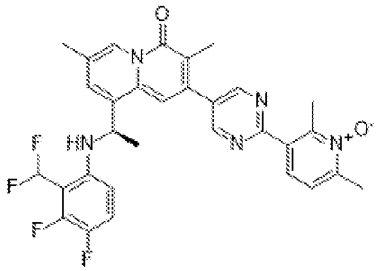
 $C_{30}H_{24}F_5N_5O_2$	189	(R)-3-(5-(7-fluoro-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3-methyl-4-oxo-4H-quinolizin-2-yl)pyrimidin-2-yl)-2,6-dimethylpyridine 1-oxide
 $C_{29}H_{21}F_6N_5O_2$	190	(R)-3-(5-(9-(1-((2-(difluoromethyl)-3,4-difluorophenyl)amino)ethyl)-7-fluoro-3-methyl-4-oxo-4H-quinolizin-2-yl)pyrimidin-2-yl)-5-fluoro-2-methylpyridine 1-oxide
 $C_{29}H_{21}F_6N_5O_2$	191	(R)-5-fluoro-3-(5-(7-fluoro-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3-methyl-4-oxo-4H-quinolizin-2-yl)pyrimidin-2-yl)-2-methylpyridine 1-oxide

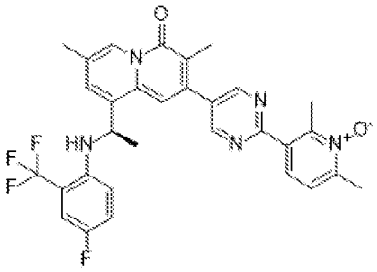
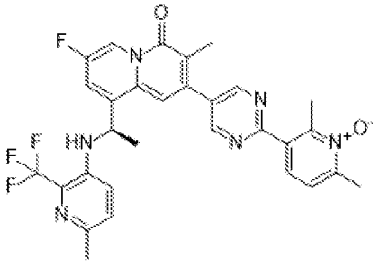
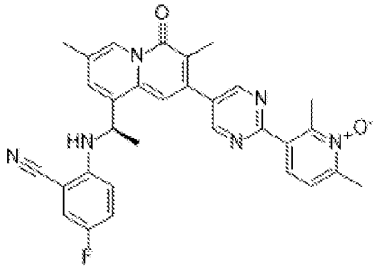
 $C_{31}H_{27}F_5N_6O_2$	192	(R)-2-(2-(3-(difluoromethyl)-1-methyl-2-oxo-1,2-dihydropyridin-4-yl)pyrimidin-5-yl)-3,7-dimethyl-9-(1-((6-methyl-2-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-4H-quinolizin-4-one
 $C_{29}H_{23}F_5N_6O_2$	193	(R)-9-(1-((2-(difluoromethyl)-3,4-difluorophenyl)amino)ethyl)-2-(2-(1,5-dimethyl-6-oxo-1,6-dihydropyrazin-2-yl)pyrimidin-5-yl)-7-fluoro-3-methyl-4H-quinolizin-4-one
 $C_{28}H_{21}F_5N_6O_2$	194	(R)-9-(1-((2-(difluoromethyl)-3,4-difluorophenyl)amino)ethyl)-7-fluoro-3-methyl-2-(2-(1-methyl-6-oxo-1,6-dihydropyridazin-4-yl)pyrimidin-5-yl)-4H-quinolizin-4-one

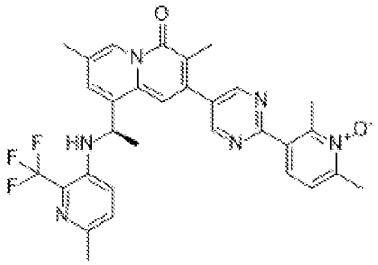
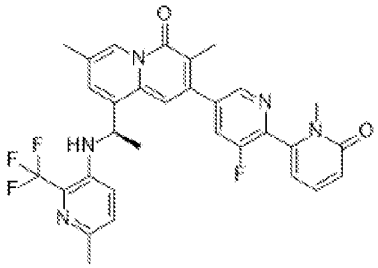
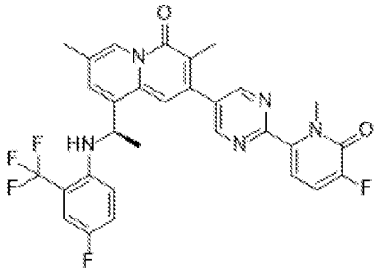
 $C_{31}H_{29}F_3N_6O_2$	195	(R)-3,7-dimethyl-2-(4-methyl-2-(1-methyl-6-oxo-1,6-dihydropyridin-2-yl)pyrimidin-5-yl)-9-(1-((6-methyl-2-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-4H-quinolizin-4-one
 $C_{30}H_{26}F_4N_6O_2$	196	(R)-2-(2-(3-fluoro-1-methyl-6-oxo-1,6-dihydropyridin-2-yl)pyrimidin-5-yl)-3,7-dimethyl-9-(1-((6-methyl-2-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-4H-quinolizin-4-one
 $C_{30}H_{25}F_5N_6O_2$	197	(R)-2-(2-(1-(difluoromethyl)-6-oxo-1,6-dihydropyridin-2-yl)pyrimidin-5-yl)-3,7-dimethyl-9-(1-((6-methyl-2-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-4H-quinolizin-4-one

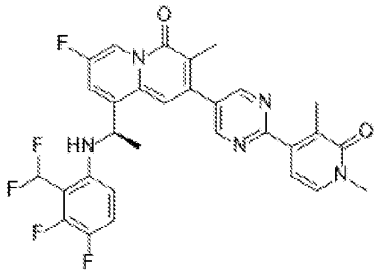
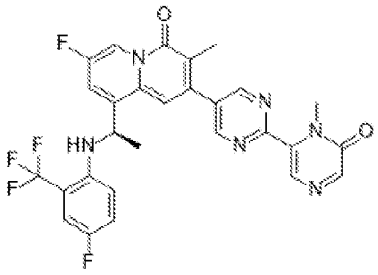
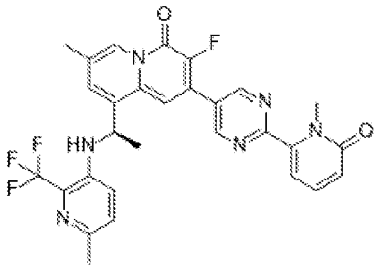
 $C_{31}H_{27}F_5N_6O_2$	198	(R)-2-(2-(1-(difluoromethyl)-5-methyl-6-oxo-1,6-dihydropyridin-2-yl)pyrimidin-5-yl)-3,7-dimethyl-9-(1-((6-methyl-2-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-4H-quinolizin-4-one
 $C_{30}H_{26}F_4N_6O_2$	199	(R)-2-(2-(3-fluoro-1-methyl-2-oxo-1,2-dihydropyridin-4-yl)pyrimidin-5-yl)-3,7-dimethyl-9-(1-((6-methyl-2-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-4H-quinolizin-4-one
 $C_{29}H_{23}F_5N_6O$	200	(R)-2-(2',4'-dimethyl-[2,5'-bipyrimidin]-5-yl)-7-fluoro-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3-methyl-4H-quinolizin-4-one

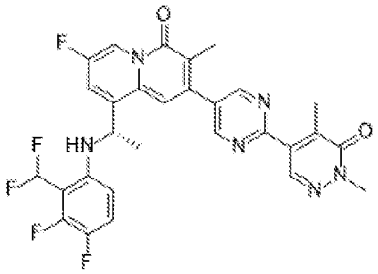
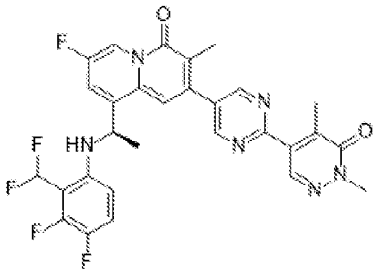
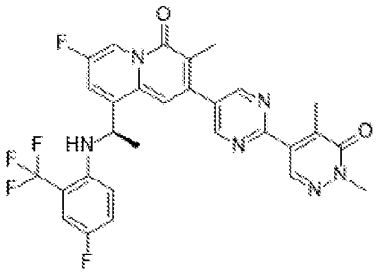
 $C_{30}H_{28}F_3N_7O$	201	(R)-2-(2',4-dimethyl-[2,5'-bipyrimidin]-5-yl)-3,7-dimethyl-9-(1-((6-methyl-2-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-4H-quinolizin-4-one
 $C_{30}H_{24}F_2N_6O_2$	202	(R)-5-fluoro-2-((1-(2-(2-(5-fluoro-1-methyl-6-oxo-1,6-dihydropyridin-2-yl)pyrimidin-5-yl)-3,7-dimethyl-4-oxo-4H-quinolizin-9-yl)ethyl)amino)benzonitrile
 $C_{28}H_{21}F_5N_6O_2$	203	(R)-9-(1-((2-(difluoromethyl)-3,4-difluorophenyl)amino)ethyl)-7-fluoro-3-methyl-2-(1-(2-methylpyrimidin-5-yl)-6-oxo-1,6-dihydropyridazin-4-yl)-4H-quinolizin-4-one

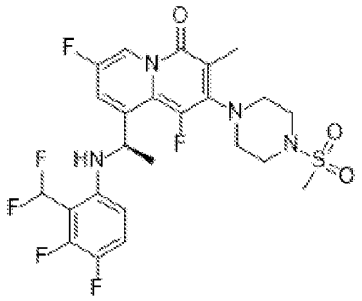
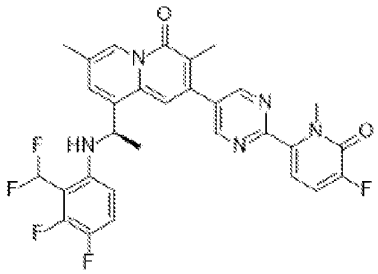
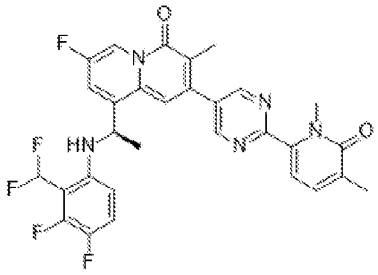
 $C_{29}H_{23}F_5N_6O$	204	(R)-9-(1-((2-(difluoromethyl)-3,4-difluorophenyl)amino)ethyl)-2-(2',4'-dimethyl-[2,5'-bipyrimidin]-5-yl)-7-fluoro-3-methyl-4H-quinolizin-4-one
 $C_{29}H_{24}ClF_3N_6O_2$	205	(R)-3-chloro-7-methyl-9-(1-((6-methyl-2-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-2-(2-(1-methyl-6-oxo-1,6-dihydropyridin-2-yl)pyrimidin-5-yl)-4H-quinolizin-4-one
 $C_{31}H_{27}F_4N_5O_2$	206	(R)-3-(5-(9-(1-((2-(difluoromethyl)-3,4-difluorophenyl)amino)ethyl)-3,7-dimethyl-4-oxo-4H-quinolizin-2-yl)pyrimidin-2-yl)-2,6-dimethylpyridine 1-oxide

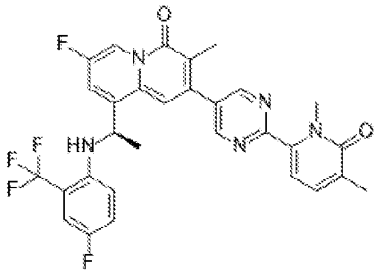
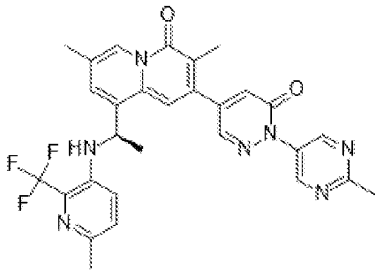
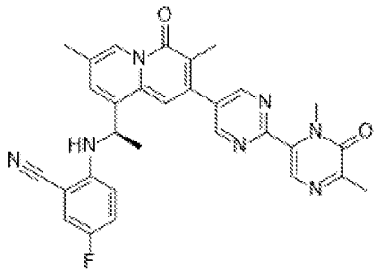
 $C_{31}H_{27}F_4N_5O_2$	207	(R)-3-(5-(9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3,7-dimethyl-4-oxo-4H-quinolizin-2-yl)pyrimidin-2-yl)-2,6-dimethylpyridine 1-oxide
 $C_{30}H_{26}F_4N_6O_2$	208	(R)-3-(5-(7-fluoro-3-methyl-9-(1-((6-methyl-2-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-4-oxo-4H-quinolizin-2-yl)pyrimidin-2-yl)-2,6-dimethylpyridine 1-oxide
 $C_{31}H_{27}FN_6O_2$	209	(R)-3-(5-(9-(1-((2-cyano-4-fluorophenyl)amino)ethyl)-3,7-dimethyl-4-oxo-4H-quinolizin-2-yl)pyrimidin-2-yl)-2,6-dimethylpyridine 1-oxide

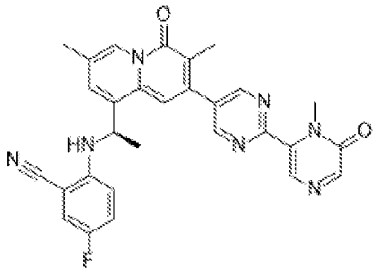
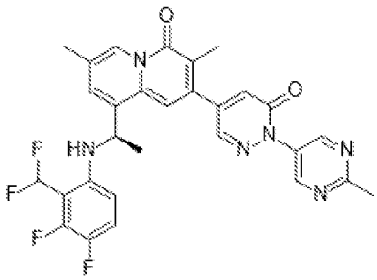
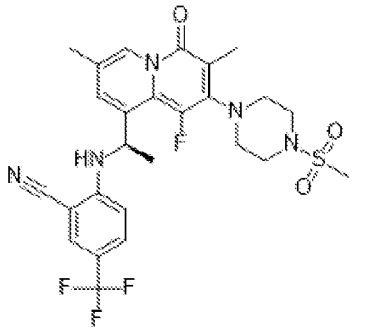
 $C_{31}H_{29}F_3N_6O_2$	210	(R)-3-(5-(3,7-dimethyl-9-(1-((6-methyl-2-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-4-oxo-4H-quinolizin-2-yl)pyrimidin-2-yl)-2,6-dimethylpyridine 1-oxide
 $C_{31}H_{27}F_4N_5O_2$	211	(R)-2-(3-fluoro-1'-methyl-6'-oxo-1',6'-dihydro-[2,2'-bipyridin]-5-yl)-3,7-dimethyl-9-(1-((6-methyl-2-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-4H-quinolizin-4-one
 $C_{30}H_{24}F_5N_5O_2$	212	(R)-2-(2-(5-fluoro-1-methyl-6-oxo-1,6-dihydropyridin-2-yl)pyrimidin-5-yl)-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3,7-dimethyl-4H-quinolizin-4-one

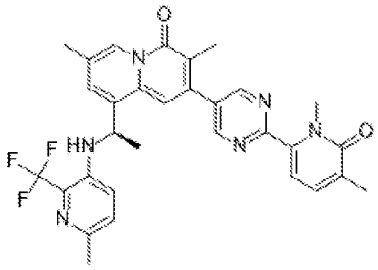
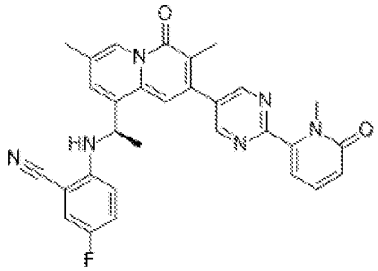
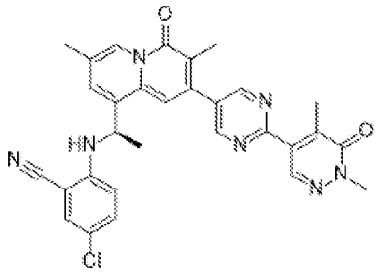
 $C_{30}H_{24}F_5N_5O_2$	213	(R)-9-(1-((2-(difluoromethyl)-3,4-difluorophenyl)amino)ethyl)-2-(2-(1,3-dimethyl-2-oxo-1,2-dihydropyridin-4-yl)pyrimidin-5-yl)-7-fluoro-3-methyl-4H-quinolizin-4-one
 $C_{28}H_{21}F_5N_6O_2$	214	(R)-7-fluoro-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3-methyl-2-(2-(1-methyl-6-oxo-1,6-dihydropyrazin-2-yl)pyrimidin-5-yl)-4H-quinolizin-4-one
 $C_{29}H_{24}F_4N_6O_2$	215	(R)-3-fluoro-7-methyl-9-(1-((6-methyl-2-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-2-(2-(1-methyl-6-oxo-1,6-dihydropyridin-2-yl)pyrimidin-5-yl)-4H-quinolizin-4-one

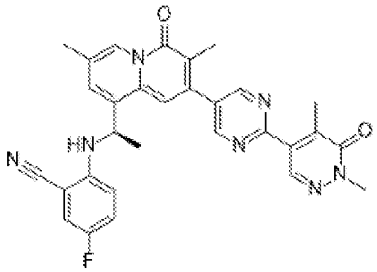
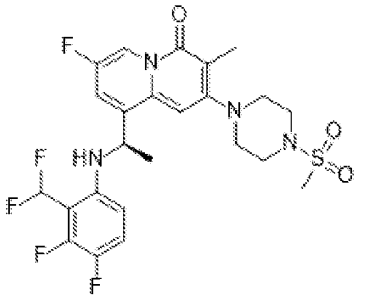
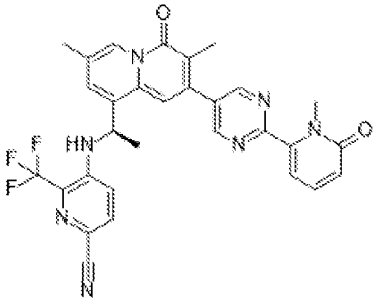
 $C_{29}H_{23}F_5N_6O_2$	216	(S)-9-(1-((2-(difluoromethyl)-3,4-difluorophenyl)amino)ethyl)-2-(2-(1,5-dimethyl-6-oxo-1,6-dihydropyridazin-4-yl)pyrimidin-5-yl)-7-fluoro-3-methyl-4H-quinolizin-4-one
 $C_{29}H_{23}F_5N_6O_2$	217	(R)-9-(1-((2-(difluoromethyl)-3,4-difluorophenyl)amino)ethyl)-2-(2-(1,5-dimethyl-6-oxo-1,6-dihydropyridazin-4-yl)pyrimidin-5-yl)-7-fluoro-3-methyl-4H-quinolizin-4-one
 $C_{29}H_{23}F_5N_6O_2$	218	(R)-2-(2-(1,5-dimethyl-6-oxo-1,6-dihydropyridazin-4-yl)pyrimidin-5-yl)-7-fluoro-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3-methyl-4H-quinolizin-4-one

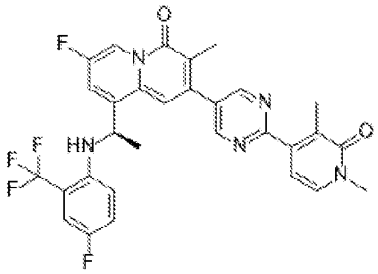
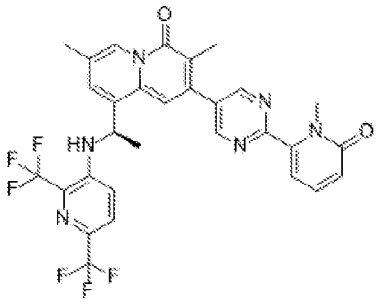
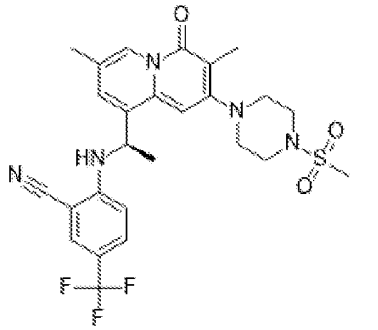
 $C_{24}H_{24}F_6N_4O_3S$	219	(R)-9-(1-((2-(difluoromethyl)-3,4-difluorophenyl)amino)ethyl)-1,7-difluoro-3-methyl-2-(4-(methylsulfonyl)piperazin-1-yl)-4H-quinolizin-4-one
 $C_{30}H_{24}F_5N_5O_2$	220	(R)-9-(1-((2-(difluoromethyl)-3,4-difluorophenyl)amino)ethyl)-2-(2-(5-fluoro-1-methyl-6-oxo-1,6-dihydropyridin-2-yl)pyrimidin-5-yl)-3,7-dimethyl-4H-quinolizin-4-one
 $C_{30}H_{24}F_5N_5O_2$	221	(R)-9-(1-((2-(difluoromethyl)-3,4-difluorophenyl)amino)ethyl)-2-(2-(1,5-dimethyl-6-oxo-1,6-dihydropyridin-2-yl)pyrimidin-5-yl)-7-fluoro-3-methyl-4H-quinolizin-4-one

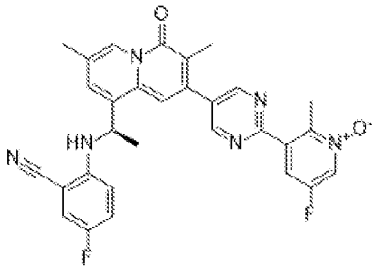
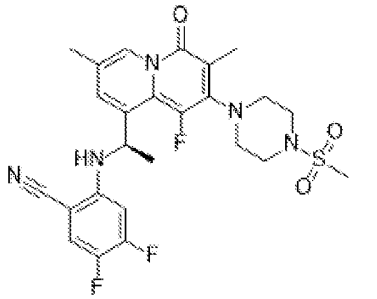
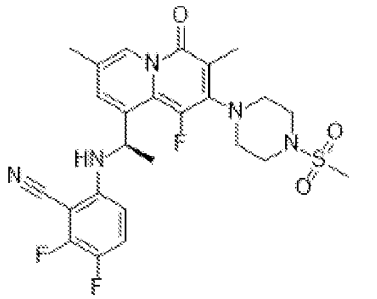
 $C_{30}H_{24}F_5N_5O_2$	222	(R)-2-(2-(1,5-dimethyl-6-oxo-1,6-dihydropyridin-2-yl)pyrimidin-5-yl)-7-fluoro-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3-methyl-4H-quinolizin-4-one
 $C_{29}H_{26}F_3N_7O_2$	223	(R)-3,7-dimethyl-9-(1-((6-methyl-2-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-2-(1-(2-methylpyrimidin-5-yl)-6-oxo-1,6-dihydropyridazin-4-yl)-4H-quinolizin-4-one
 $C_{30}H_{26}FN_7O_2$	224	(R)-2-((1-(2-(2-(1,5-dimethyl-6-oxo-1,6-dihydropyrazin-2-yl)pyrimidin-5-yl)-3,7-dimethyl-4-oxo-4H-quinolizin-9-yl)ethyl)amino)-5-fluorobenzonitrile

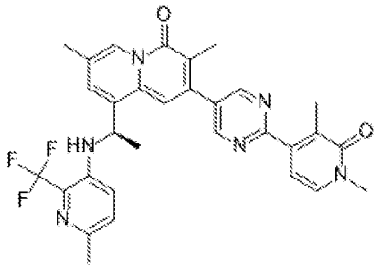
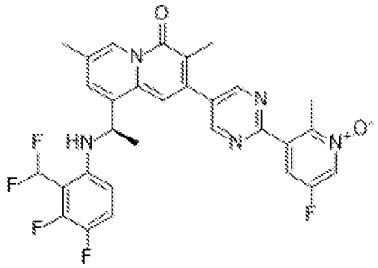
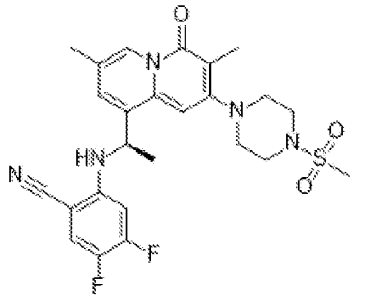
 $C_{29}H_{24}FN_7O_2$	225	(R)-2-((1-(3,7-dimethyl-2-(2-(1-methyl-6-oxo-1,6-dihydropyrazin-2-yl)pyrimidin-5-yl)-4-oxo-4H-quinolizin-9-yl)ethyl)amino)-5-fluorobenzonitrile
 $C_{29}H_{24}F_4N_6O_2$	226	(R)-9-(1-((2-(difluoromethyl)-3,4-difluorophenyl)amino)ethyl)-3,7-dimethyl-2-(1-(2-methylpyrimidin-5-yl)-6-oxo-1,6-dihydropyridazin-4-yl)-4H-quinolizin-4-one
 $C_{26}H_{27}F_4N_5O_3S$	227	(R)-2-((1-(1-fluoro-3,7-dimethyl-2-(4-(methylsulfonyl)piperazin-1-yl)-4-oxo-4H-quinolizin-9-yl)ethyl)amino)-5-(trifluoromethyl)benzonitrile

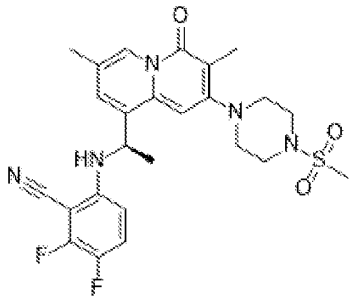
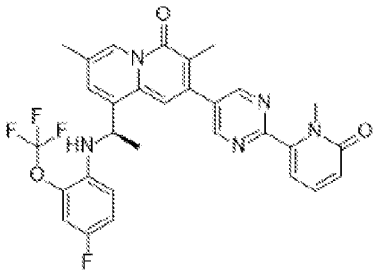
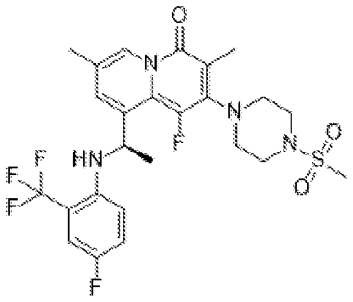
 $C_{31}H_{29}F_3N_6O_2$	228	(R)-2-(2-(1,5-dimethyl-6-oxo-1,6-dihydropyridin-2-yl)pyrimidin-5-yl)-3,7-dimethyl-9-(1-((6-methyl-2-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-4H-quinolizin-4-one
 $C_{30}H_{25}FN_6O_2$	229	(R)-2-((1-(3,7-dimethyl-2-(2-(1-methyl-6-oxo-1,6-dihydropyridin-2-yl)pyrimidin-5-yl)-4-oxo-4H-quinolizin-9-yl)ethyl)amino)-5-fluorobenzonitrile
 $C_{30}H_{26}ClN_7O_2$	230	(R)-5-chloro-2-((1-(2-(2-(1,5-dimethyl-6-oxo-1,6-dihydropyridazin-4-yl)pyrimidin-5-yl)-3,7-dimethyl-4-oxo-4H-quinolizin-9-yl)ethyl)amino)benzonitrile

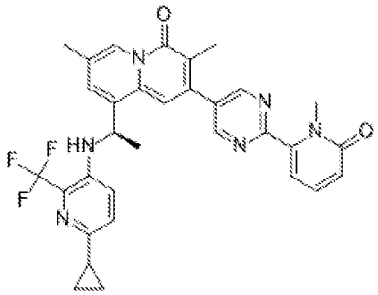
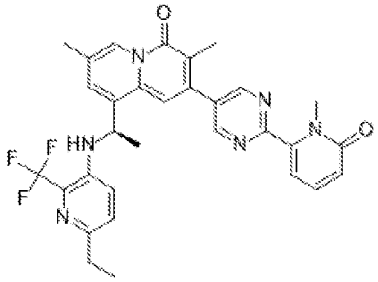
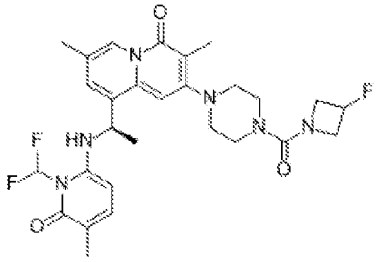
 $C_{30}H_{26}FN_7O_2$	231	(R)-2-((1-(2-(2-(1,5-dimethyl-6-oxo-1,6-dihydropyridazin-4-yl)pyrimidin-5-yl)-3,7-dimethyl-4-oxo-4H-quinolizin-9-yl)ethyl)amino)-5-fluorobenzonitrile
 $C_{24}H_{25}F_5N_4O_3S$	232	(R)-9-(1-((2-(difluoromethyl)-3,4-difluorophenyl)amino)ethyl)-7-fluoro-3-methyl-2-(4-(methylsulfonyl)piperazin-1-yl)-4H-quinolizin-4-one
 $C_{30}H_{24}F_3N_7O_2$	233	(R)-5-((1-(3,7-dimethyl-2-(2-(1-methyl-6-oxo-1,6-dihydropyridin-2-yl)pyrimidin-5-yl)-4-oxo-4H-quinolizin-9-yl)ethyl)amino)-6-(trifluoromethyl)picolinonitrile

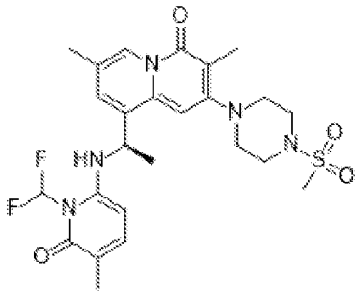
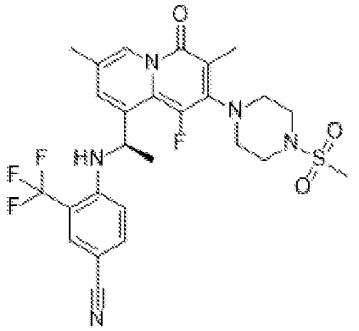
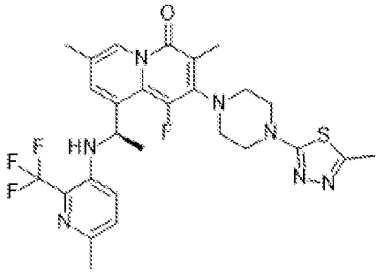
 $C_{30}H_{24}F_5N_5O_2$	234	(R)-2-(2-(1,3-dimethyl-2-oxo-1,2-dihydropyridin-4-yl)pyrimidin-5-yl)-7-fluoro-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3-methyl-4H-quinolizin-4-one
 $C_{30}H_{24}F_6N_6O_2$	235	(R)-9-(1-((2,6-bis(trifluoromethyl)pyridin-3-yl)amino)ethyl)-3,7-dimethyl-2-(2-(1-methyl-6-oxo-1,6-dihydropyridin-2-yl)pyrimidin-5-yl)-4H-quinolizin-4-one
 $C_{26}H_{28}F_3N_5O_3S$	236	(R)-2-((1-(3,7-dimethyl-2-(4-(methylsulfonyl)piperazin-1-yl)-4-oxo-4H-quinolizin-9-yl)ethyl)amino)-5-(trifluoromethyl)benzonitrile

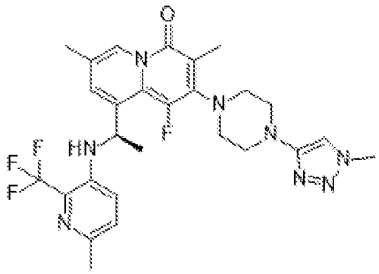
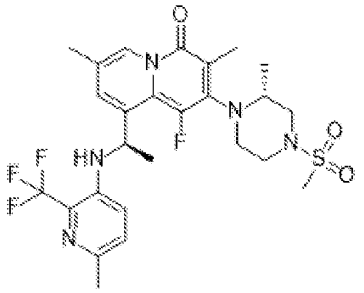
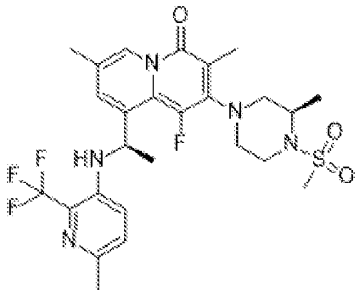
 $C_{30}H_{24}F_2N_6O_2$	237	(R)-3-(5-(9-(1-((2-cyano-4-fluorophenyl)amino)ethyl)-3,7-dimethyl-4-oxo-4H-quinolizin-2-yl)pyrimidin-2-yl)-5-fluoro-2-methylpyridine 1-oxide
 $C_{25}H_{26}F_3N_5O_3S$	238	(R)-4,5-difluoro-2-((1-(1-fluoro-3,7-dimethyl-2-(4-(methylsulfonyl)piperazin-1-yl)-4-oxo-4H-quinolizin-9-yl)ethyl)amino)benzonitrile
 $C_{25}H_{26}F_3N_5O_3S$	239	(R)-2,3-difluoro-6-((1-(1-fluoro-3,7-dimethyl-2-(4-(methylsulfonyl)piperazin-1-yl)-4-oxo-4H-quinolizin-9-yl)ethyl)amino)benzonitrile

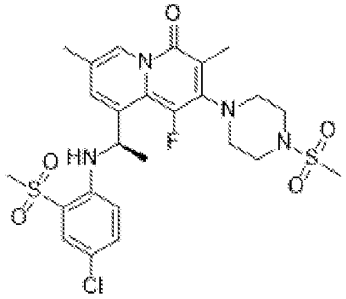
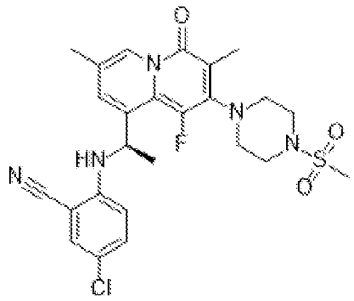
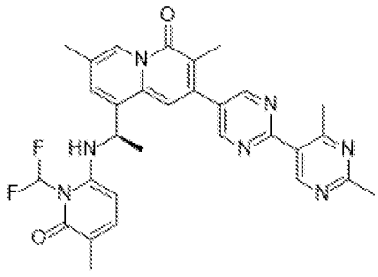
 $C_{31}H_{29}F_3N_6O_2$	240	(R)-2-(2-(1,3-dimethyl-2-oxo-1,2-dihydropyridin-4-yl)pyrimidin-5-yl)-3,7-dimethyl-9-(1-((6-methyl-2-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-4H-quinolizin-4-one
 $C_{30}H_{24}F_5N_5O_2$	241	(R)-3-(5-(9-(1-((2-(difluoromethyl)-3,4-difluorophenyl)amino)ethyl)-3,7-dimethyl-4-oxo-4H-quinolizin-2-yl)pyrimidin-2-yl)-5-fluoro-2-methylpyridine 1-oxide
 $C_{25}H_{27}F_2N_5O_3S$	242	(R)-2-((1-(3,7-dimethyl-2-(4-(methylsulfonyl)piperazin-1-yl)-4-oxo-4H-quinolizin-9-yl)ethyl)amino)-4,5-difluorobenzonitrile

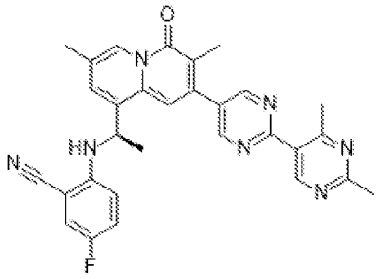
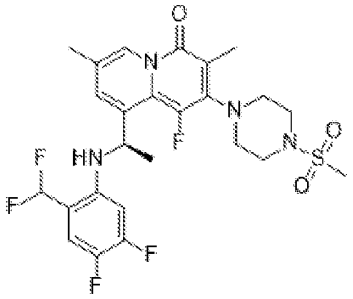
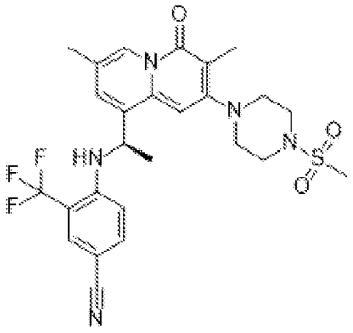
 $C_{25}H_{27}F_2N_5O_3S$	243	(R)-6-((1-(3,7-dimethyl-2-(4-(methylsulfonyl)piperazin-1-yl)-4-oxo-4H-quinolizin-9-yl)ethyl)amino)-2,3-difluorobenzonitrile
 $C_{30}H_{25}F_4N_5O_3$	244	(R)-9-(1-((4-fluoro-2-(trifluoromethoxy)phenyl)amino)ethyl)-3,7-dimethyl-2-(2-(1-methyl-6-oxo-1,6-dihydropyridin-2-yl)pyrimidin-5-yl)-4H-quinolizin-4-one
 $C_{25}H_{27}F_5N_4O_3S$	245	(R)-1-fluoro-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3,7-dimethyl-2-(4-(methylsulfonyl)piperazin-1-yl)-4H-quinolizin-4-one

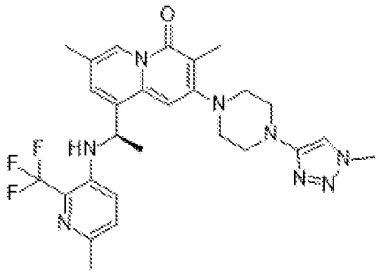
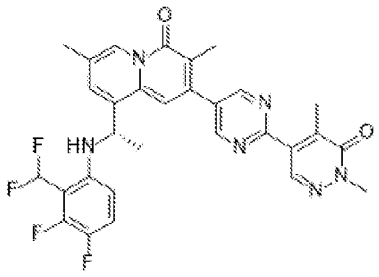
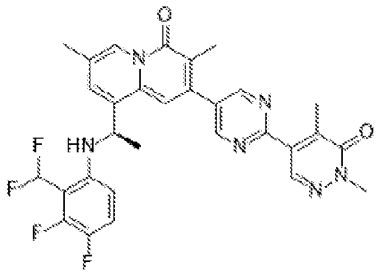
 $C_{32}H_{29}F_3N_6O_2$	246	(R)-9-(1-((6-cyclopropyl-2-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-3,7-dimethyl-2-(2-(1-methyl-6-oxo-1,6-dihydropyridin-2-yl)pyrimidin-5-yl)-4H-quinolizin-4-one
 $C_{31}H_{29}F_3N_6O_2$	247	(R)-9-(1-((6-ethyl-2-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-3,7-dimethyl-2-(2-(1-methyl-6-oxo-1,6-dihydropyridin-2-yl)pyrimidin-5-yl)-4H-quinolizin-4-one
 $C_{28}H_{33}F_3N_6O_3$	248	(R)-9-(1-((1-(difluoromethyl)-5-methyl-6-oxo-1,6-dihydropyridin-2-yl)amino)ethyl)-2-(4-(3-fluoroazetidine-1-carbonyl)piperazin-1-yl)-3,7-dimethyl-4H-quinolizin-4-one

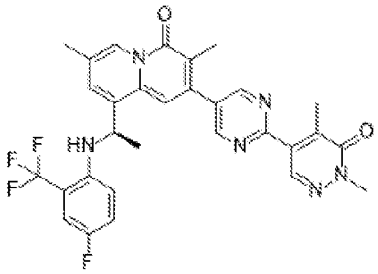
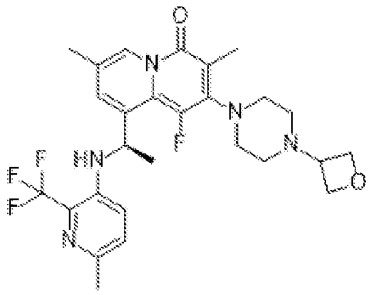
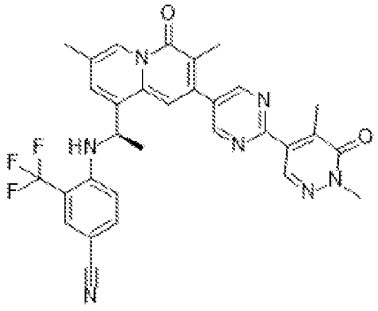
 $C_{25}H_{31}F_2N_5O_4S$	249	(R)-9-(1-((1-(difluoromethyl)-5-methyl-6-oxo-1,6-dihydropyridin-2-yl)amino)ethyl)-3,7-dimethyl-2-(4-(methylsulfonyl)piperazin-1-yl)-4H-quinolizin-4-one
 $C_{26}H_{27}F_4N_5O_3S$	250	(R)-4-((1-(1-fluoro-3,7-dimethyl-2-(4-(methylsulfonyl)piperazin-1-yl)-4-oxo-4H-quinolizin-9-yl)ethyl)amino)-3-(trifluoromethyl)benzonitrile
 $C_{27}H_{29}F_4N_7OS$	251	(R)-1-fluoro-3,7-dimethyl-2-(4-(5-methyl-1,3,4-thiadiazol-2-yl)piperazin-1-yl)-9-(1-((6-methyl-2-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-4H-quinolizin-4-one

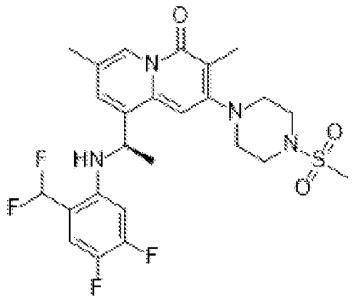
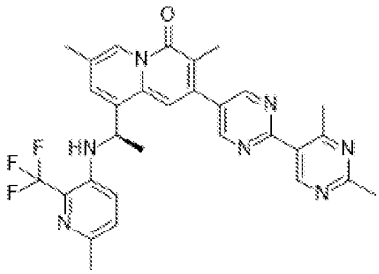
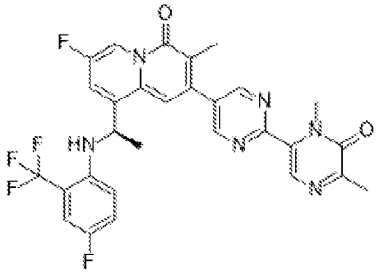
 $C_{27}H_{30}F_4N_8O$	252	(R)-1-fluoro-3,7-dimethyl-2-(4-(1-methyl-1H-1,2,3-triazol-4-yl)piperazin-1-yl)-9-(1-((6-methyl-2-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-4H-quinolizin-4-one
 $C_{26}H_{31}F_4N_5O_3S$	253	1-fluoro-3,7-dimethyl-9-((R)-1-((6-methyl-2-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-2-((R)-2-methyl-4-(methylsulfonyl)piperazin-1-yl)-4H-quinolizin-4-one
 $C_{26}H_{31}F_4N_5O_3S$	254	1-fluoro-3,7-dimethyl-9-((R)-1-((6-methyl-2-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-2-((R)-3-methyl-4-(methylsulfonyl)piperazin-1-yl)-4H-quinolizin-4-one

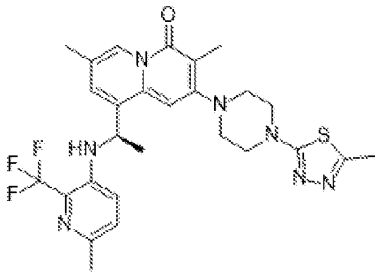
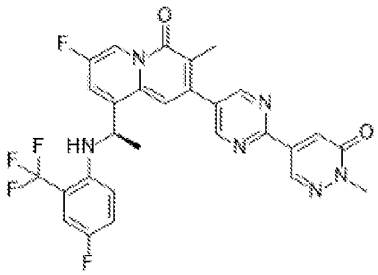
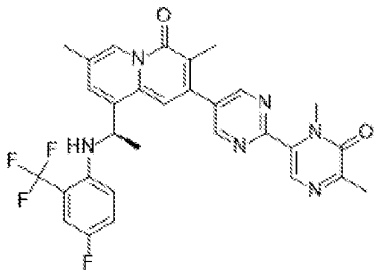
 $C_{25}H_{30}ClFN_4O_5S_2$	255	(R)-9-(1-((4-chloro-2-(methylsulfonyl)phenyl)amino)ethyl)-1-fluoro-3,7-dimethyl-2-(4-(methylsulfonyl)piperazin-1-yl)-4H-quinolizin-4-one
 $C_{25}H_{27}ClFN_5O_3S$	256	(R)-5-chloro-2-((1-(1-fluoro-3,7-dimethyl-2-(4-(methylsulfonyl)piperazin-1-yl)-4-oxo-4H-quinolizin-9-yl)ethyl)amino)benzonitrile
 $C_{30}H_{29}F_2N_7O_2$	257	(R)-9-(1-((1-(difluoromethyl)-5-methyl-6-oxo-1,6-dihydropyridin-2-yl)amino)ethyl)-2-(2',4'-dimethyl-[2,5'-bipyrimidin]-5-yl)-3,7-dimethyl-4H-quinolizin-4-one

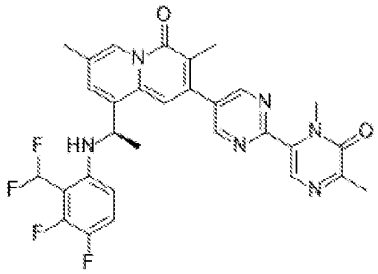
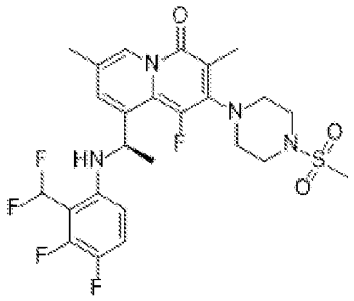
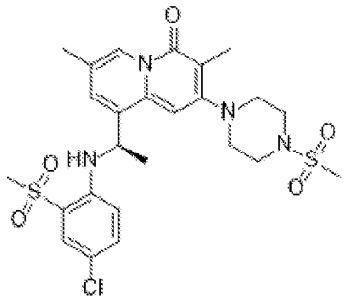
 $C_{30}H_{26}FN_7O$	258	(R)-2-((1-(2-(2',4'-dimethyl-[2,5'-bipyrimidin]-5-yl)-3,7-dimethyl-4-oxo-4H-quinolizin-9-yl)ethyl)amino)-5-fluorobenzonitrile
 $C_{25}H_{27}F_5N_4O_3S$	259	(R)-9-(1-((2-(difluoromethyl)-4,5-difluorophenyl)amino)ethyl)-1-fluoro-3,7-dimethyl-2-(4-(methylsulfonyl)piperazin-1-yl)-4H-quinolizin-4-one
 $C_{26}H_{28}F_3N_5O_3S$	260	(R)-4-((1-(3,7-dimethyl-2-(4-(methylsulfonyl)piperazin-1-yl)-4-oxo-4H-quinolizin-9-yl)ethyl)amino)-3-(trifluoromethyl)benzonitrile

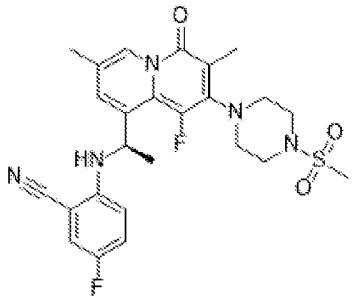
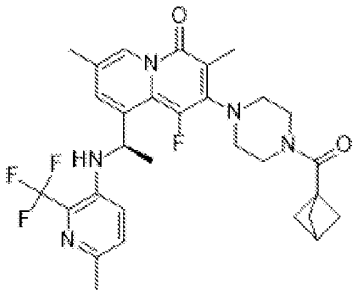
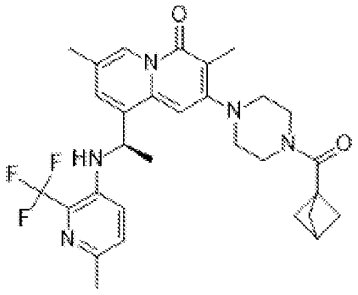
 $C_{27}H_{31}F_3N_8O$	261	(R)-3,7-dimethyl-2-(4-(1-methyl-1H-1,2,3-triazol-4-yl)piperazin-1-yl)-9-(1-((6-methyl-2-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-4H-quinolizin-4-one
 $C_{30}H_{26}F_4N_6O_2$	262	(S)-9-(1-((2-(difluoromethyl)-3,4-difluorophenyl)amino)ethyl)-2-(2-(1,5-dimethyl-6-oxo-1,6-dihydropyridazin-4-yl)pyrimidin-5-yl)-3,7-dimethyl-4H-quinolizin-4-one
 $C_{30}H_{26}F_4N_6O_2$	263	(R)-9-(1-((2-(difluoromethyl)-3,4-difluorophenyl)amino)ethyl)-2-(2-(1,5-dimethyl-6-oxo-1,6-dihydropyridazin-4-yl)pyrimidin-5-yl)-3,7-dimethyl-4H-quinolizin-4-one

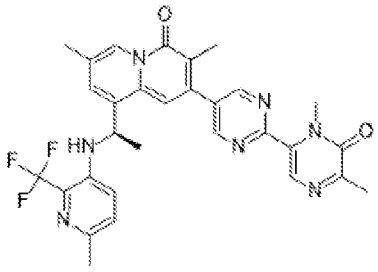
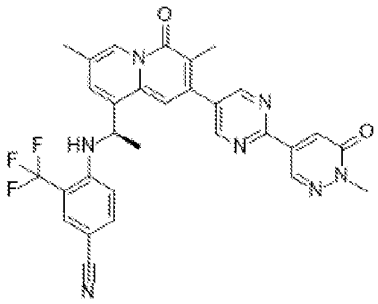
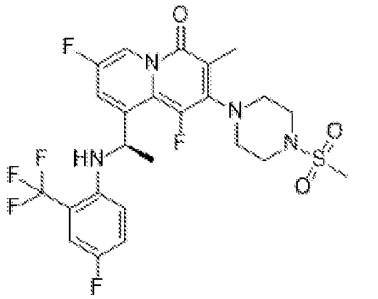
 $C_{30}H_{26}F_4N_6O_2$	264	(R)-2-(2-(1,5-dimethyl-6-oxo-1,6-dihydropyridazin-4-yl)pyrimidin-5-yl)-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3,7-dimethyl-4H-quinolizin-4-one
 $C_{27}H_{31}F_4N_5O_2$	265	(R)-1-fluoro-3,7-dimethyl-9-(1-((6-methyl-2-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-2-(4-(oxetan-3-yl)piperazin-1-yl)-4H-quinolizin-4-one
 $C_{31}H_{26}F_3N_7O_2$	266	(R)-4-((1-(2-(2-(1,5-dimethyl-6-oxo-1,6-dihydropyridazin-4-yl)pyrimidin-5-yl)-3,7-dimethyl-4-oxo-4H-quinolizin-9-yl)ethyl)amino)-3-(trifluoromethyl)benzonitrile

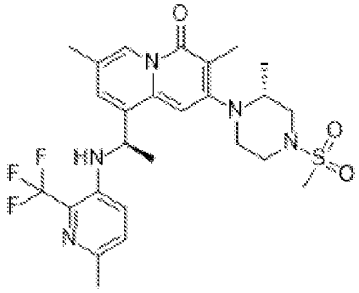
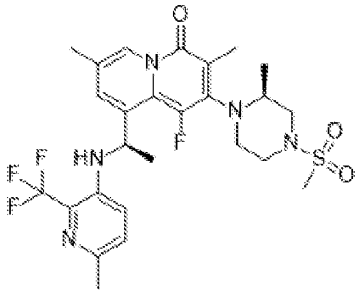
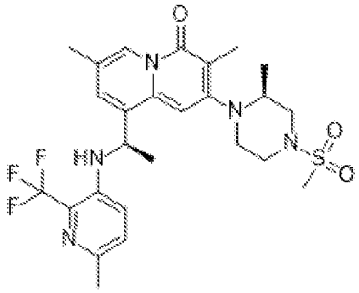
 $C_{25}H_{28}F_4N_4O_3S$	267	(R)-9-(1-((2-(difluoromethyl)-4,5-difluorophenyl)amino)ethyl)-3,7-dimethyl-2-(4-(methylsulfonyl)piperazin-1-yl)-4H-quinolizin-4-one
 $C_{30}H_{28}F_3N_7O$	268	(R)-2-(2',4'-dimethyl-[2,5'-bipyrimidin]-5-yl)-3,7-dimethyl-9-(1-((6-methyl-2-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-4H-quinolizin-4-one
 $C_{29}H_{23}F_5N_6O_2$	269	(R)-2-(2-(1,5-dimethyl-6-oxo-1,6-dihydropyrazin-2-yl)pyrimidin-5-yl)-7-fluoro-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3-methyl-4H-quinolizin-4-one

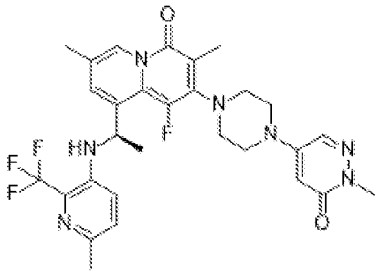
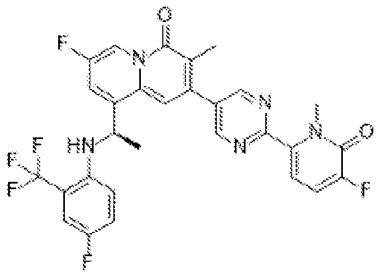
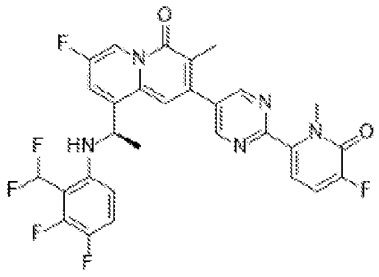
 $C_{27}H_{30}F_3N_7OS$	270	(R)-3,7-dimethyl-2-(4-(5-methyl-1,3,4-thiadiazol-2-yl)piperazin-1-yl)-9-(1-((6-methyl-2-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-4H-quinolizin-4-one
 $C_{28}H_{21}F_5N_6O_2$	271	(R)-7-fluoro-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3-methyl-2-(2-(1-methyl-6-oxo-1,6-dihydropyridazin-4-yl)pyrimidin-5-yl)-4H-quinolizin-4-one
 $C_{30}H_{26}F_4N_6O_2$	272	(R)-2-(2-(1,5-dimethyl-6-oxo-1,6-dihydropyrazin-2-yl)pyrimidin-5-yl)-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3,7-dimethyl-4H-quinolizin-4-one

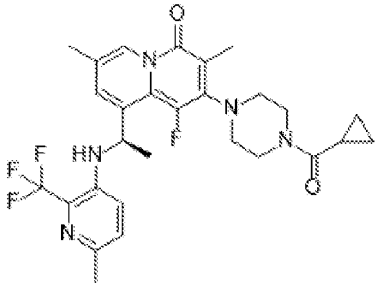
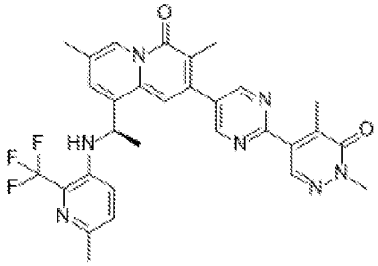
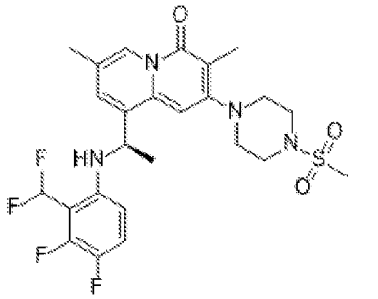
 $C_{30}H_{26}F_4N_6O_2$	273	(R)-9-(1-((2-(difluoromethyl)-3,4-difluorophenyl)amino)ethyl)-2-(2-(1,5-dimethyl-6-oxo-1,6-dihydropyrazin-2-yl)pyrimidin-5-yl)-3,7-dimethyl-4H-quinolizin-4-one
 $C_{25}H_{27}F_5N_4O_3S$	274	(R)-9-(1-((2-(difluoromethyl)-3,4-difluorophenyl)amino)ethyl)-1-fluoro-3,7-dimethyl-2-(4-(methylsulfonyl)piperazin-1-yl)-4H-quinolizin-4-one
 $C_{25}H_{31}ClN_4O_5S_2$	275	(R)-9-(1-((4-chloro-2-(methylsulfonyl)phenyl)amino)ethyl)-3,7-dimethyl-2-(4-(methylsulfonyl)piperazin-1-yl)-4H-quinolizin-4-one

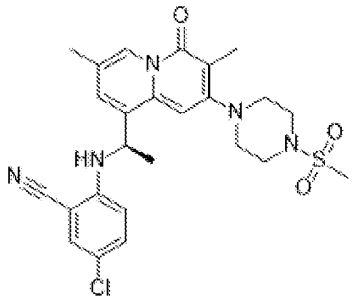
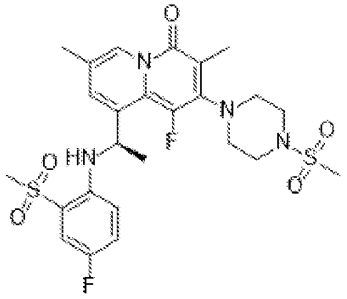
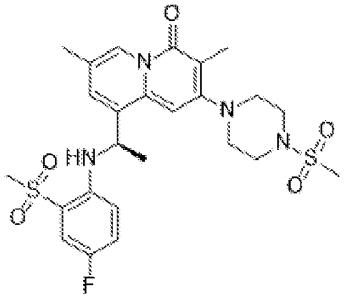
 $C_{25}H_{27}F_2N_5O_3S$	276	(R)-5-fluoro-2-((1-(1-fluoro-3,7-dimethyl-2-(4-(methylsulfonyl)piperazin-1-yl)-4-oxo-4H-quinolizin-9-yl)ethyl)amino)benzonitrile
 $C_{30}H_{33}F_4N_5O_2$	277	(R)-2-(4-(bicyclo[1.1.1]pentane-1-carbonyl)piperazin-1-yl)-1-fluoro-3,7-dimethyl-9-(1-((6-methyl-2-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-4H-quinolizin-4-one
 $C_{30}H_{34}F_3N_5O_2$	278	(R)-2-(4-(bicyclo[1.1.1]pentane-1-carbonyl)piperazin-1-yl)-3,7-dimethyl-9-(1-((6-methyl-2-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-4H-quinolizin-4-one

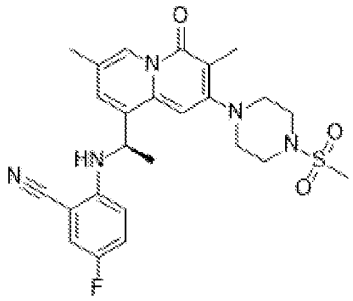
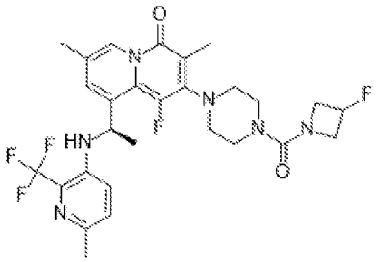
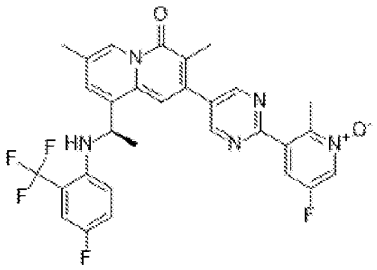
 $C_{30}H_{28}F_3N_7O_2$	279	(R)-2-(2-(1,5-dimethyl-6-oxo-1,6-dihydropyrazin-2-yl)pyrimidin-5-yl)-3,7-dimethyl-9-(1-((6-methyl-2-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-4H-quinolizin-4-one
 $C_{30}H_{24}F_3N_7O_2$	280	(R)-4-((1-(3,7-dimethyl-2-(2-(1-methyl-6-oxo-1,6-dihydropyridazin-4-yl)pyrimidin-5-yl)-4-oxo-4H-quinolizin-9-yl)ethyl)amino)-3-(trifluoromethyl)benzonitrile
 $C_{24}H_{24}F_6N_4O_3S$	281	(R)-1,7-difluoro-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3-methyl-2-(4-(methylsulfonyl)piperazin-1-yl)-4H-quinolizin-4-one

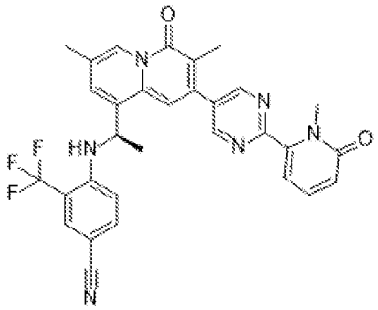
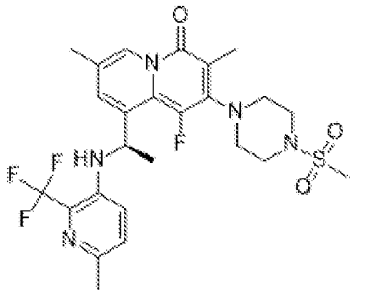
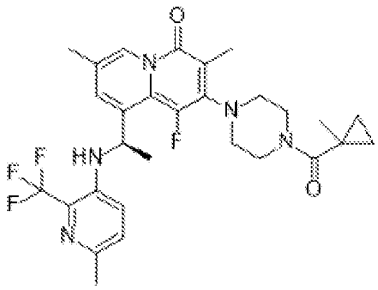
 $C_{26}H_{32}F_3N_5O_3S$	282	3,7-dimethyl-9-((R)-1-((6-methyl-2-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-2-((R)-2-methyl-4-(methylsulfonyl)piperazin-1-yl)-4H-quinolizin-4-one
 $C_{26}H_{31}F_4N_5O_3S$	283	1-fluoro-3,7-dimethyl-9-((R)-1-((6-methyl-2-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-2-((S)-2-methyl-4-(methylsulfonyl)piperazin-1-yl)-4H-quinolizin-4-one
 $C_{26}H_{32}F_3N_5O_3S$	284	3,7-dimethyl-9-((R)-1-((6-methyl-2-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-2-((S)-2-methyl-4-(methylsulfonyl)piperazin-1-yl)-4H-quinolizin-4-one

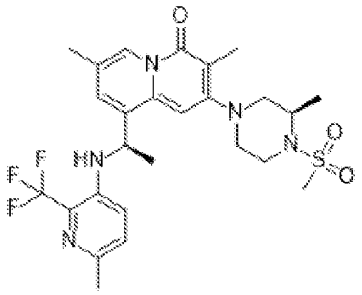
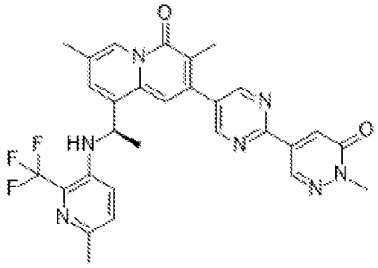
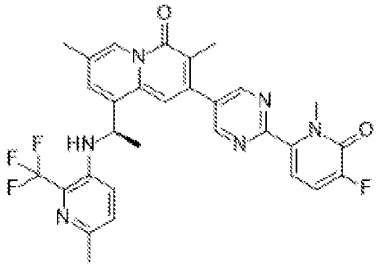
 $C_{29}H_{31}F_4N_7O_2$	285	(R)-1-fluoro-3,7-dimethyl-9-(1-((6-methyl-2-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-2-(4-(1-methyl-6-oxo-1,6-dihydropyridazin-4-yl)piperazin-1-yl)-4H-quinolizin-4-one
 $C_{29}H_{21}F_6N_5O_2$	286	(R)-7-fluoro-2-(2-(5-fluoro-1-methyl-6-oxo-1,6-dihydropyridin-2-yl)pyrimidin-5-yl)-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3-methyl-4H-quinolizin-4-one
 $C_{29}H_{21}F_6N_5O_2$	287	(R)-9-(1-((2-(difluoromethyl)-3,4-difluorophenyl)amino)ethyl)-7-fluoro-2-(2-(5-fluoro-1-methyl-6-oxo-1,6-dihydropyridin-2-yl)pyrimidin-5-yl)-3-methyl-4H-quinolizin-4-one

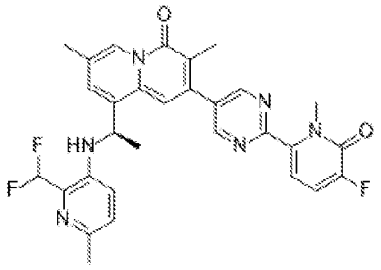
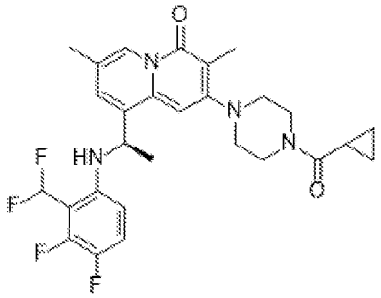
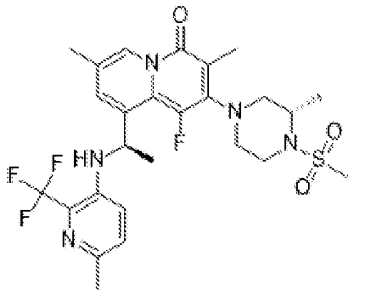
 $C_{28}H_{31}F_4N_5O_2$	288	(R)-2-(4-(cyclopropanecarbonyl)piperazin-1-yl)-1-fluoro-3,7-dimethyl-9-(1-((6-methyl-2-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-4H-quinolizin-4-one
 $C_{30}H_{28}F_3N_7O_2$	289	(R)-2-(2-(1,5-dimethyl-6-oxo-1,6-dihydropyridazin-4-yl)pyrimidin-5-yl)-3,7-dimethyl-9-(1-((6-methyl-2-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-4H-quinolizin-4-one
 $C_{25}H_{28}F_4N_4O_3S$	290	(R)-9-(1-((2-(difluoromethyl)-3,4-difluorophenyl)amino)ethyl)-3,7-dimethyl-2-(4-(methylsulfonyl)piperazin-1-yl)-4H-quinolizin-4-one

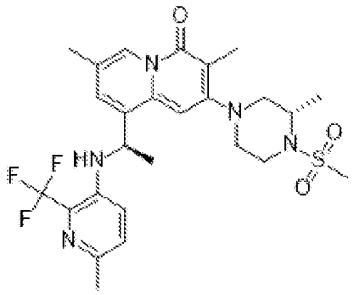
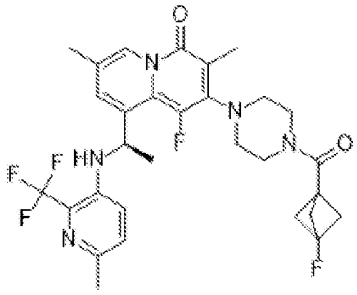
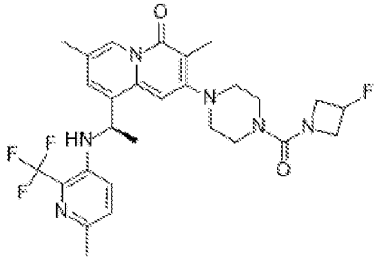
 $C_{25}H_{28}ClN_5O_3S$	291	(R)-5-chloro-2-((1-(3,7-dimethyl-2-(4-(methylsulfonyl)piperazin-1-yl)-4-oxo-4H-quinolizin-9-yl)ethyl)amino)benzonitrile
 $C_{25}H_{30}F_2N_4O_5S_2$	292	(R)-1-fluoro-9-(1-((4-fluoro-2-(methylsulfonyl)phenyl)amino)ethyl)-3,7-dimethyl-2-(4-(methylsulfonyl)piperazin-1-yl)-4H-quinolizin-4-one
 $C_{25}H_{31}FN_4O_5S_2$	293	(R)-9-(1-((4-fluoro-2-(methylsulfonyl)phenyl)amino)ethyl)-3,7-dimethyl-2-(4-(methylsulfonyl)piperazin-1-yl)-4H-quinolizin-4-one

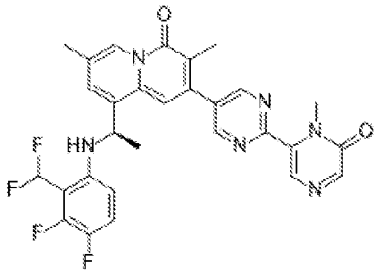
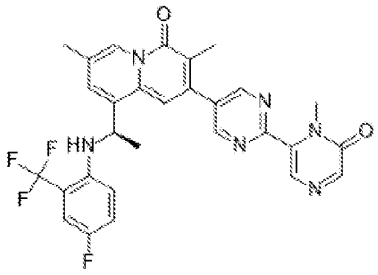
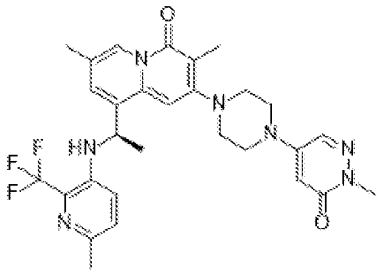
 $C_{25}H_{28}FN_5O_3S$	294	(R)-2-((1-(3,7-dimethyl-2-(4-(methylsulfonyl)piperazin-1-yl)-4-oxo-4H-quinolizin-9-yl)ethyl)amino)-5-fluorobenzonitrile
 $C_{28}H_{31}F_5N_6O_2$	295	(R)-1-fluoro-2-(4-(3-fluoroazetidine-1-carbonyl)piperazin-1-yl)-3,7-dimethyl-9-(1-((6-methyl-2-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-4H-quinolizin-4-one
 $C_{30}H_{24}F_5N_5O_2$	296	(R)-5-fluoro-3-(5-(9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3,7-dimethyl-4-oxo-4H-quinolizin-2-yl)pyrimidin-2-yl)-2-methylpyridine 1-oxide

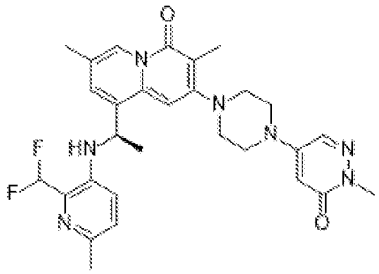
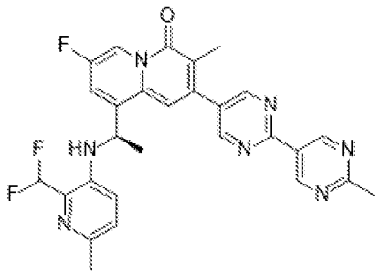
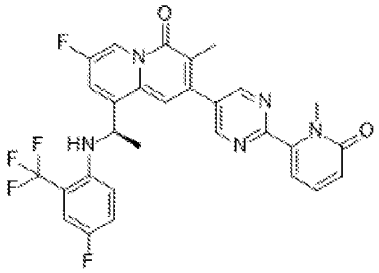
 $C_{31}H_{25}F_3N_6O_2$	297	(R)-4-((1-(3,7-dimethyl-2-(2-(1-methyl-6-oxo-1,6-dihydropyridin-2-yl)pyrimidin-5-yl)-4-oxo-4H-quinolizin-9-yl)ethyl)amino)-3-(trifluoromethyl)benzonitrile
 $C_{25}H_{29}F_4N_5O_3S$	298	(R)-1-fluoro-3,7-dimethyl-9-(1-((6-methyl-2-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-2-(4-(methylsulfonyl)piperazin-1-yl)-4H-quinolizin-4-one
 $C_{29}H_{33}F_4N_5O_2$	299	(R)-1-fluoro-3,7-dimethyl-9-(1-((6-methyl-2-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-2-(4-(1-methylcyclopropane-1-carbonyl)piperazin-1-yl)-4H-quinolizin-4-one

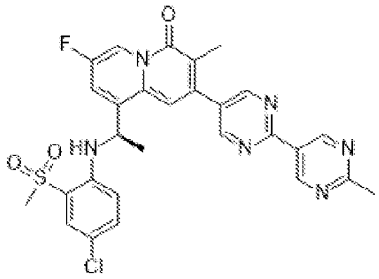
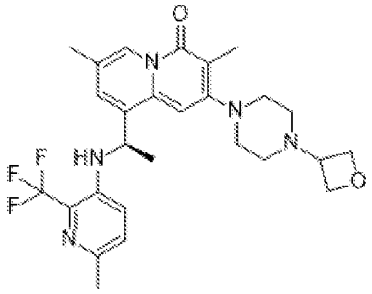
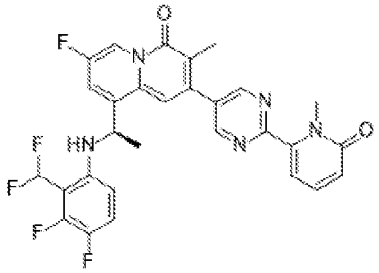
 $C_{26}H_{32}F_3N_5O_3S$	300	3,7-dimethyl-9-((R)-1-((6-methyl-2-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-2-((R)-3-methyl-4-(methylsulfonyl)piperazin-1-yl)-4H-quinolizin-4-one
 $C_{29}H_{26}F_3N_7O_2$	301	(R)-3,7-dimethyl-9-(1-((6-methyl-2-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-2-(2-(1-methyl-6-oxo-1,6-dihydropyridazin-4-yl)pyrimidin-5-yl)-4H-quinolizin-4-one
 $C_{30}H_{26}F_4N_6O_2$	302	(R)-2-(2-(5-fluoro-1-methyl-6-oxo-1,6-dihydropyridin-2-yl)pyrimidin-5-yl)-3,7-dimethyl-9-(1-((6-methyl-2-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-4H-quinolizin-4-one

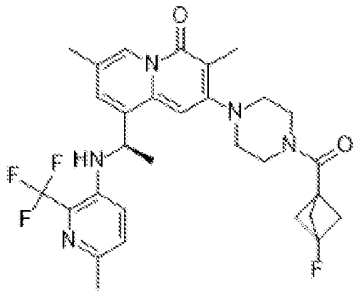
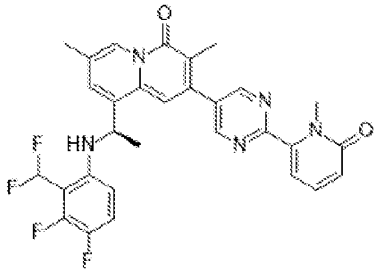
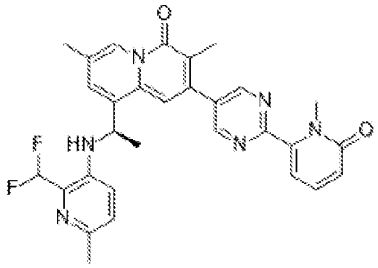
 $C_{30}H_{27}F_3N_6O_2$	303	(R)-9-(1-((2-(difluoromethyl)-6-methylpyridin-3-yl)amino)ethyl)-2-(2-(5-fluoro-1-methyl-6-oxo-1,6-dihydropyridin-2-yl)pyrimidin-5-yl)-3,7-dimethyl-4H-quinolizin-4-one
 $C_{28}H_{30}F_4N_4O_2$	304	(R)-2-(4-(cyclopropanecarbonyl)piperazin-1-yl)-9-(1-((2-(difluoromethyl)-3,4-difluorophenyl)amino)ethyl)-3,7-dimethyl-4H-quinolizin-4-one
 $C_{26}H_{31}F_4N_5O_3S$	305	1-fluoro-3,7-dimethyl-9-((R)-1-((6-methyl-2-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-2-((S)-3-methyl-4-(methylsulfonyl)piperazin-1-yl)-4H-quinolizin-4-one

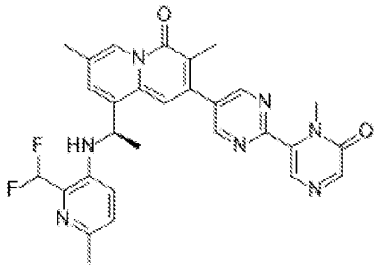
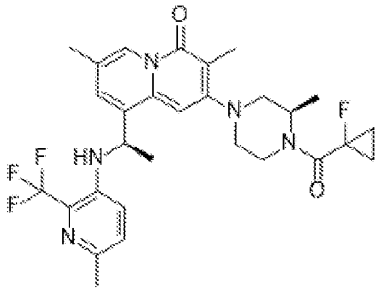
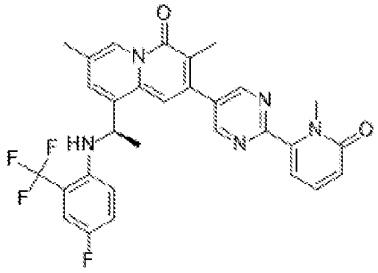
 $C_{26}H_{32}F_3N_5O_3S$	306	3,7-dimethyl-9-((R)-1-((6-methyl-2-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-2-((S)-3-methyl-4-(methylsulfonyl)piperazin-1-yl)-4H-quinolizin-4-one
 $C_{30}H_{32}F_5N_5O_2$	307	(R)-1-fluoro-2-(4-(3-fluorobicyclo[1.1.1]pentane-1-carbonyl)piperazin-1-yl)-3,7-dimethyl-9-(1-((6-methyl-2-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-4H-quinolizin-4-one
 $C_{28}H_{32}F_4N_6O_2$	308	(R)-2-(4-(3-fluoroazetidine-1-carbonyl)piperazin-1-yl)-3,7-dimethyl-9-(1-((6-methyl-2-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-4H-quinolizin-4-one

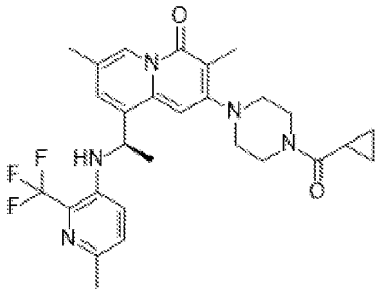
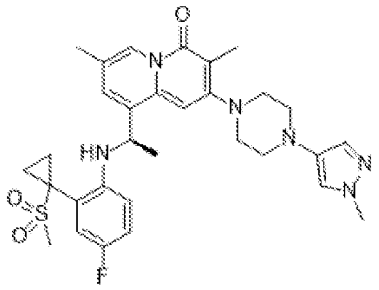
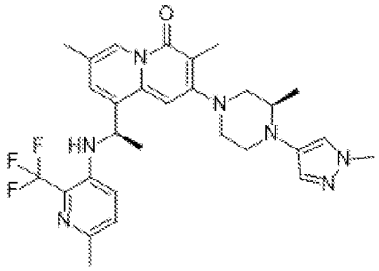
 $C_{29}H_{24}F_4N_6O_2$	309	(R)-9-(1-((2-(difluoromethyl)-3,4-difluorophenyl)amino)ethyl)-3,7-dimethyl-2-(2-(1-methyl-6-oxo-1,6-dihydropyrazin-2-yl)pyrimidin-5-yl)-4H-quinolizin-4-one
 $C_{29}H_{24}F_4N_6O_2$	310	(R)-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3,7-dimethyl-2-(2-(1-methyl-6-oxo-1,6-dihydropyrazin-2-yl)pyrimidin-5-yl)-4H-quinolizin-4-one
 $C_{29}H_{32}F_3N_7O_2$	311	(R)-3,7-dimethyl-9-(1-((6-methyl-2-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-2-(4-(1-methyl-6-oxo-1,6-dihydropyridazin-4-yl)piperazin-1-yl)-4H-quinolizin-4-one

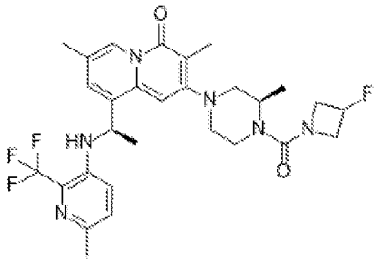
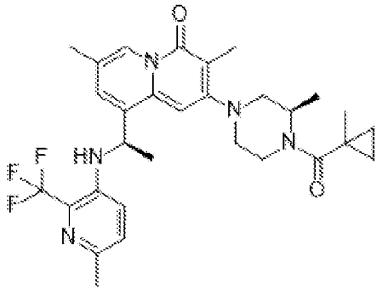
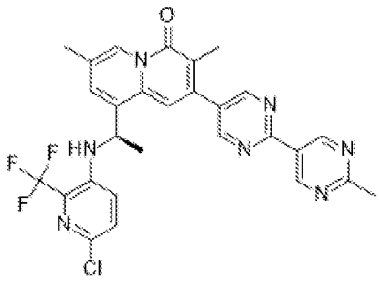
 $C_{29}H_{33}F_2N_7O_2$	312	(R)-9-(1-((2-(difluoromethyl)-6-methylpyridin-3-yl)amino)ethyl)-3,7-dimethyl-2-(4-(1-methyl-6-oxo-1,6-dihydropyridazin-4-yl)piperazin-1-yl)-4H-quinolizin-4-one
 $C_{28}H_{24}F_3N_7O$	313	(R)-9-(1-((2-(difluoromethyl)-6-methylpyridin-3-yl)amino)ethyl)-7-fluoro-3-methyl-2-(2'-methyl-[2,5'-bipyrimidin]-5-yl)-4H-quinolizin-4-one
 $C_{29}H_{22}F_5N_5O_2$	314	(R)-7-fluoro-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3-methyl-2-(2-(1-methyl-6-oxo-1,6-dihydropyridin-2-yl)pyrimidin-5-yl)-4H-quinolizin-4-one

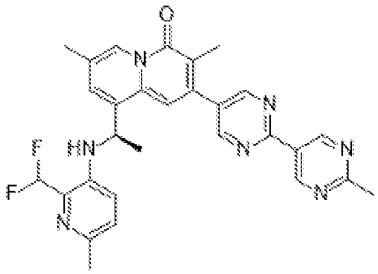
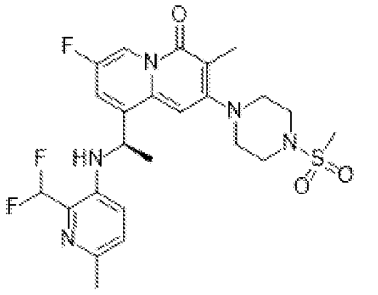
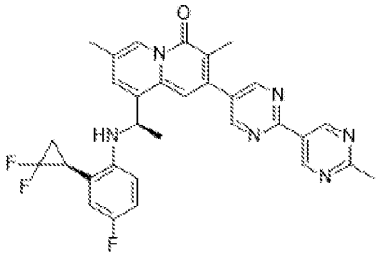
 $C_{28}H_{24}ClFN_6O_3S$	315	(R)-9-(1-((4-chloro-2-(methylsulfonyl)phenyl)amino)ethyl)-7-fluoro-3-methyl-2-(2'-methyl-[2,5'-bipyrimidin]-5-yl)-4H-quinolizin-4-one
 $C_{27}H_{32}F_3N_5O_2$	316	(R)-3,7-dimethyl-9-(1-((6-methyl-2-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-2-(4-(oxetan-3-yl)piperazin-1-yl)-4H-quinolizin-4-one
 $C_{29}H_{22}F_5N_5O_2$	317	(R)-9-(1-((2-(difluoromethyl)-3,4-difluorophenyl)amino)ethyl)-7-fluoro-3-methyl-2-(2-(1-methyl-6-oxo-1,6-dihydropyridin-2-yl)pyrimidin-5-yl)-4H-quinolizin-4-one

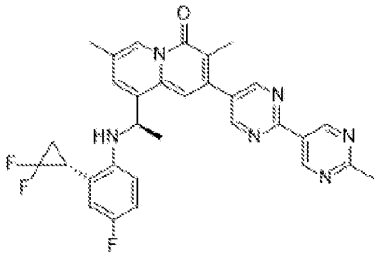
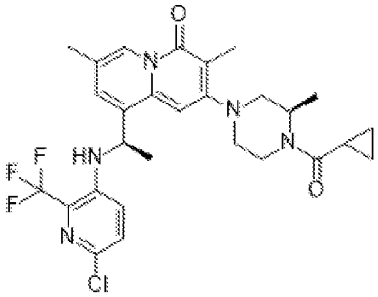
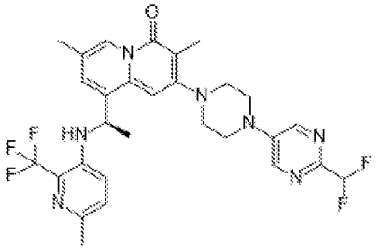
 $C_{30}H_{33}F_4N_5O_2$	318	(R)-2-(4-(3-fluorobicyclo[1.1.1]pentane-1-carbonyl)piperazin-1-yl)-3,7-dimethyl-9-(1-((6-methyl-2-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-4H-quinolizin-4-one
 $C_{30}H_{25}F_4N_5O_2$	319	(R)-9-(1-((2-(difluoromethyl)-3,4-difluorophenyl)amino)ethyl)-3,7-dimethyl-2-(2-(1-methyl-6-oxo-1,6-dihydropyridin-2-yl)pyrimidin-5-yl)-4H-quinolizin-4-one
 $C_{30}H_{28}F_2N_6O_2$	320	(R)-9-(1-((2-(difluoromethyl)-6-methylpyridin-3-yl)amino)ethyl)-3,7-dimethyl-2-(2-(1-methyl-6-oxo-1,6-dihydropyridin-2-yl)pyrimidin-5-yl)-4H-quinolizin-4-one

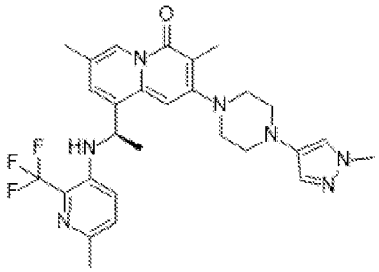
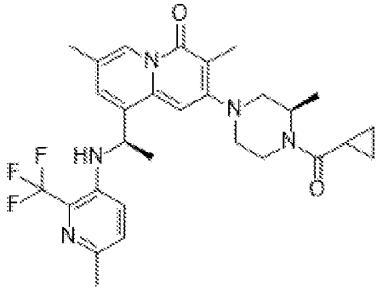
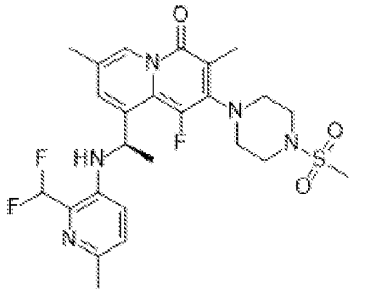
 $C_{29}H_{27}F_2N_7O_2$	321	(R)-9-(1-((2-(difluoromethyl)-6-methylpyridin-3-yl)amino)ethyl)-3,7-dimethyl-2-(2-(1-methyl-6-oxo-1,6-dihydropyrazin-2-yl)pyrimidin-5-yl)-4H-quinolizin-4-one
 $C_{29}H_{33}F_4N_5O_2$	322	2-((R)-4-(1-fluorocyclopropane-1-carbonyl)-3-methylpiperazin-1-yl)-3,7-dimethyl-9-((R)-1-((6-methyl-2-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-4H-quinolizin-4-one
 $C_{30}H_{25}F_4N_5O_2$	323	(R)-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3,7-dimethyl-2-(2-(1-methyl-6-oxo-1,6-dihydropyridin-2-yl)pyrimidin-5-yl)-4H-quinolizin-4-one

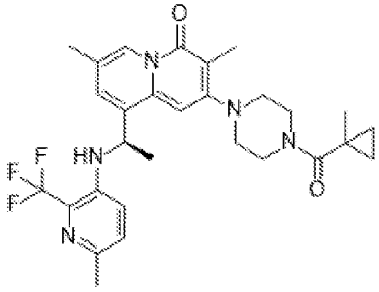
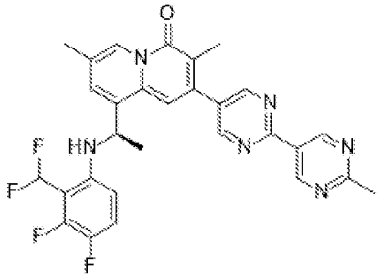
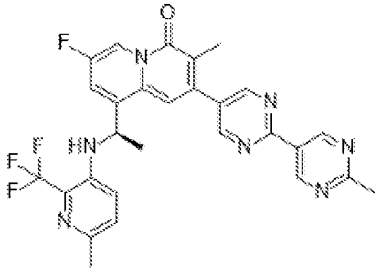
 $C_{28}H_{32}F_3N_5O_2$	324	(R)-2-(4-(cyclopropanecarbonyl)piperazin-1-yl)-3,7-dimethyl-9-(1-((6-methyl-2-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-4H-quinolizin-4-one
 $C_{31}H_{37}FN_6O_3S$	325	(R)-9-(1-((4-fluoro-2-(1-(methylsulfonyl)cyclopropyl)phenyl)amino)ethyl)-3,7-dimethyl-2-(4-(1-methyl-1H-pyrazol-4-yl)piperazin-1-yl)-4H-quinolizin-4-one
 $C_{29}H_{34}F_3N_7O$	326	3,7-dimethyl-9-((R)-1-((6-methyl-2-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-2-((R)-3-methyl-4-(1-methyl-1H-pyrazol-4-yl)piperazin-1-yl)-4H-quinolizin-4-one

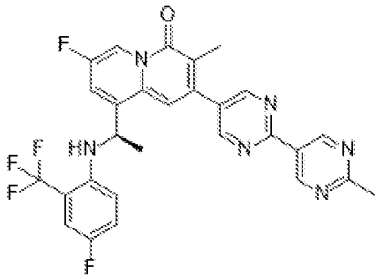
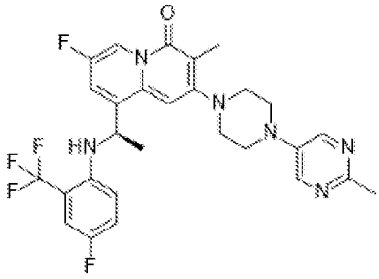
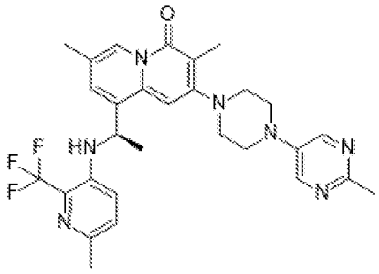
 $C_{29}H_{34}F_4N_6O_2$	327	2-((R)-4-(3-fluoroazetidine-1-carbonyl)-3-methylpiperazin-1-yl)-3,7-dimethyl-9-((R)-1-((6-methyl-2-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-4H-quinolizin-4-one
 $C_{30}H_{36}F_3N_5O_2$	328	3,7-dimethyl-9-((R)-1-((6-methyl-2-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-2-((R)-3-methyl-4-(1-methylcyclopropane-1-carbonyl)piperazin-1-yl)-4H-quinolizin-4-one
 $C_{28}H_{23}ClF_3N_7O$	329	(R)-9-(1-((6-chloro-2-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-3,7-dimethyl-2-(2'-methyl-[2,5'-bipyrimidin]-5-yl)-4H-quinolizin-4-one

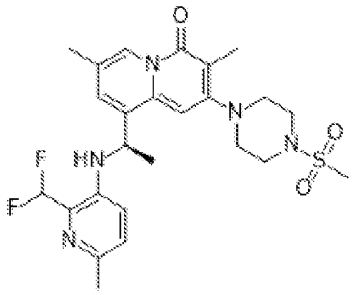
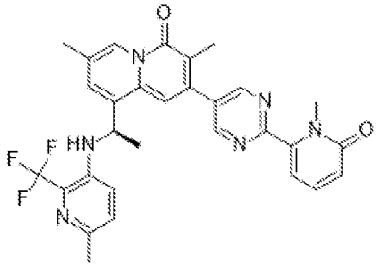
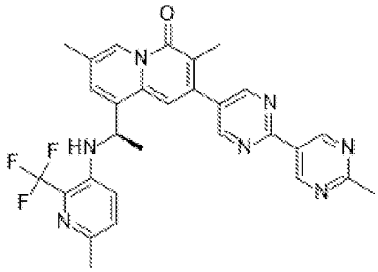
 $C_{29}H_{27}F_2N_7O$	330	(R)-9-(1-((2-(difluoromethyl)-6-methylpyridin-3-yl)amino)ethyl)-3,7-dimethyl-2-(2'-methyl-[2,5'-bipyrimidin]-5-yl)-4H-quinolizin-4-one
 $C_{24}H_{28}F_3N_5O_3S$	331	(R)-9-(1-((2-(difluoromethyl)-6-methylpyridin-3-yl)amino)ethyl)-7-fluoro-3-methyl-2-(4-(methylsulfonyl)piperazin-1-yl)-4H-quinolizin-4-one
 $C_{31}H_{27}F_3N_6O$	332	9-((R)-1-((2-((S)-2,2-difluorocyclopropyl)-4-fluorophenyl)amino)ethyl)-3,7-dimethyl-2-(2'-methyl-[2,5'-bipyrimidin]-5-yl)-4H-quinolizin-4-one

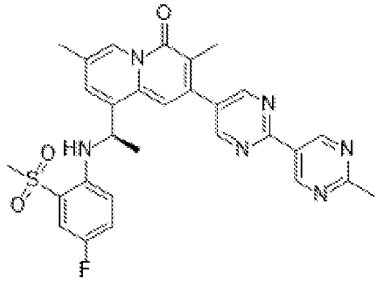
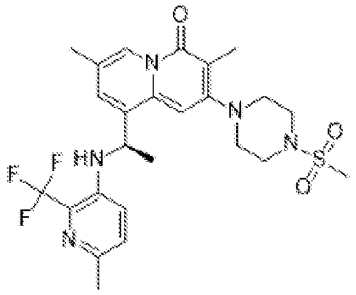
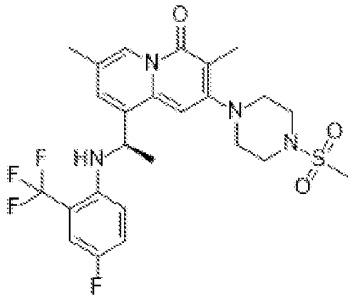
 $C_{31}H_{27}F_3N_6O$	333	9-((R)-1-((2-((R)-2,2-difluorocyclopropyl)-4-fluorophenyl)amino)ethyl)-3,7-dimethyl-2-(2'-methyl-[2,5'-bipyrimidin]-5-yl)-4H-quinolizin-4-one
 $C_{28}H_{31}ClF_3N_5O_2$	334	9-((R)-1-((6-chloro-2-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-2-((R)-4-(cyclopropanecarbonyl)-3-methylpiperazin-1-yl)-3,7-dimethyl-4H-quinolizin-4-one
 $C_{29}H_{30}F_5N_7O$	335	(R)-2-(4-(2-(difluoromethyl)pyrimidin-5-yl)piperazin-1-yl)-3,7-dimethyl-9-(1-((6-methyl-2-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-4H-quinolizin-4-one

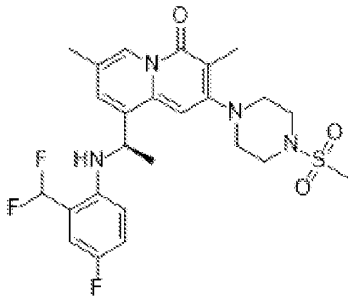
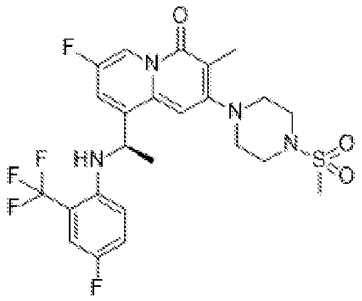
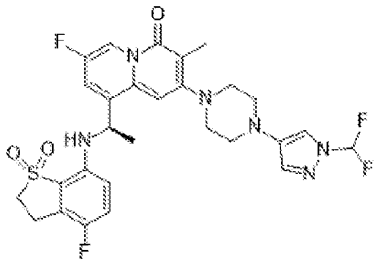
 $C_{28}H_{32}F_3N_7O$	336	(R)-3,7-dimethyl-2-(4-(1-methyl-1H-pyrazol-4-yl)piperazin-1-yl)-9-(1-((6-methyl-2-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-4H-quinolizin-4-one
 $C_{29}H_{34}F_3N_5O_2$	337	2-((R)-4-(cyclopropanecarbonyl)-3-methylpiperazin-1-yl)-3,7-dimethyl-9-((R)-1-((6-methyl-2-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-4H-quinolizin-4-one
 $C_{25}H_{30}F_3N_5O_3S$	338	(R)-9-(1-((2-(difluoromethyl)-6-methylpyridin-3-yl)amino)ethyl)-1-fluoro-3,7-dimethyl-2-(4-(methylsulfonyl)piperazin-1-yl)-4H-quinolizin-4-one

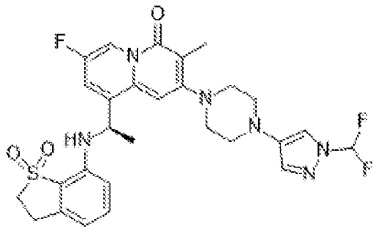
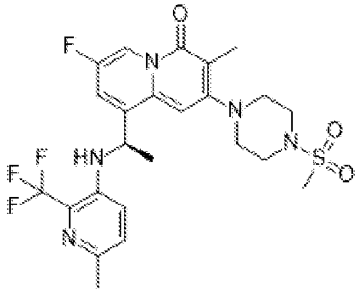
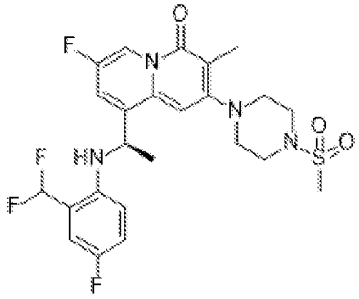
 $C_{29}H_{34}F_3N_5O_2$	339	(R)-3,7-dimethyl-9-(1-((6-methyl-2-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-2-(4-(1-methylcyclopropane-1-carbonyl)piperazin-1-yl)-4H-quinolizin-4-one
 $C_{29}H_{24}F_4N_6O$	340	(R)-9-(1-((2-(difluoromethyl)-3,4-difluorophenyl)amino)ethyl)-3,7-dimethyl-2-(2'-methyl-[2,5'-bipyrimidin]-5-yl)-4H-quinolizin-4-one
 $C_{28}H_{23}F_4N_7O$	341	(R)-7-fluoro-3-methyl-9-(1-((6-methyl-2-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-2-(2'-methyl-[2,5'-bipyrimidin]-5-yl)-4H-quinolizin-4-one

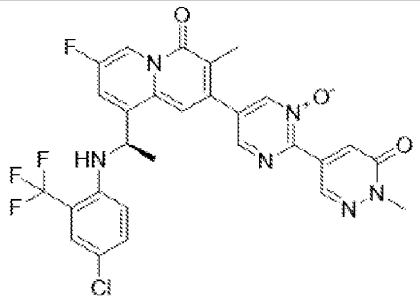
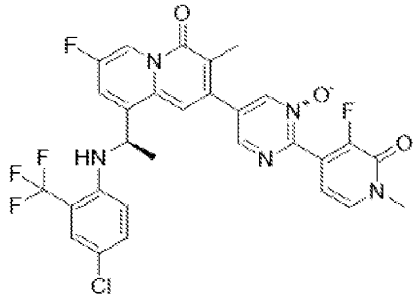
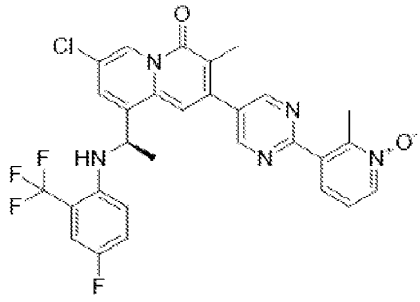
 $C_{28}H_{21}F_5N_6O$	342	(R)-7-fluoro-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3-methyl-2-(2'-methyl-[2,5'-bipyrimidin]-5-yl)-4H-quinolizin-4-one
 $C_{28}H_{27}F_5N_6O$	343	(R)-7-fluoro-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3-methyl-2-(4-(2-methylpyrimidin-5-yl)piperazin-1-yl)-4H-quinolizin-4-one
 $C_{29}H_{32}F_3N_7O$	344	(R)-3,7-dimethyl-9-(1-((6-methyl-2-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-2-(4-(2-methylpyrimidin-5-yl)piperazin-1-yl)-4H-quinolizin-4-one

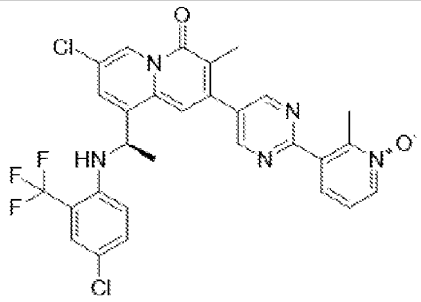
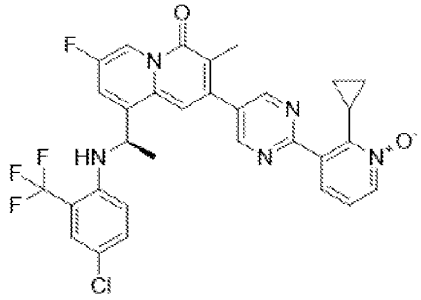
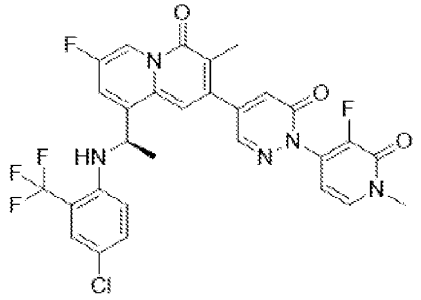
 $C_{25}H_{31}F_2N_5O_3S$	345	(R)-9-(1-((2-(difluoromethyl)-6-methylpyridin-3-yl)amino)ethyl)-3,7-dimethyl-2-(4-(methylsulfonyl)piperazin-1-yl)-4H-quinolizin-4-one
 $C_{30}H_{27}F_3N_6O_2$	346	(R)-3,7-dimethyl-9-(1-((6-methyl-2-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-2-(2-(1-methyl-6-oxo-1,6-dihydropyridin-2-yl)pyrimidin-5-yl)-4H-quinolizin-4-one
 $C_{29}H_{26}F_3N_7O$	347	(R)-3,7-dimethyl-9-(1-((6-methyl-2-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-2-(2'-methyl-[2,5'-bipyrimidin]-5-yl)-4H-quinolizin-4-one

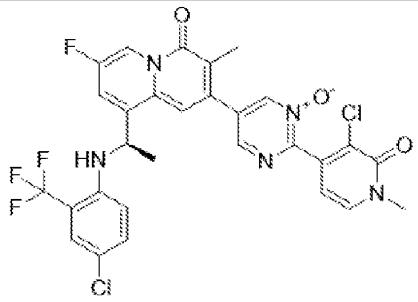
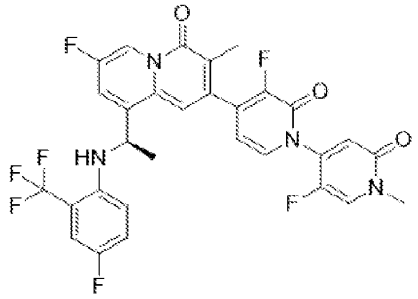
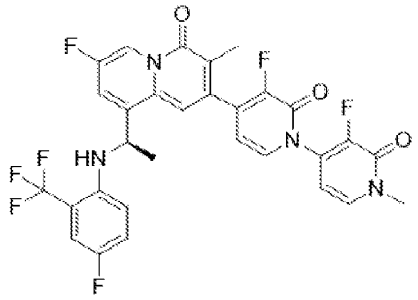
 $C_{29}H_{27}FN_6O_3S$	348	(R)-9-(1-((4-fluoro-2-(methylsulfonyl)phenyl)amino)ethyl)-3,7-dimethyl-2-(2'-methyl-[2,5'-bipyrimidin]-5-yl)-4H-quinolizin-4-one
 $C_{25}H_{30}F_3N_5O_3S$	349	(R)-3,7-dimethyl-9-(1-((6-methyl-2-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-2-(4-(methylsulfonyl)piperazin-1-yl)-4H-quinolizin-4-one
 $C_{25}H_{28}F_4N_4O_3S$	350	(R)-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3,7-dimethyl-2-(4-(methylsulfonyl)piperazin-1-yl)-4H-quinolizin-4-one

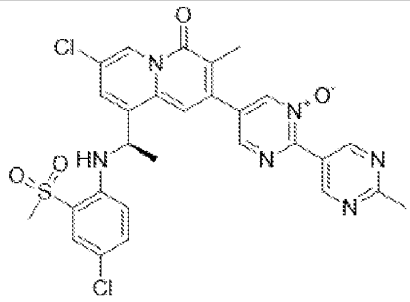
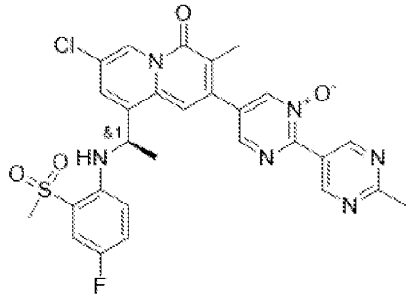
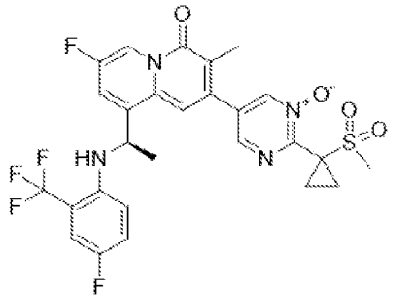
 $C_{25}H_{29}F_3N_4O_3S$	351	(R)-9-(1-((2-(difluoromethyl)-4-fluorophenyl)amino)ethyl)-3,7-dimethyl-2-(4-(methylsulfonyl)piperazin-1-yl)-4H-quinolizin-4-one
 $C_{24}H_{25}F_5N_4O_3S$	352	(R)-7-fluoro-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3-methyl-2-(4-(methylsulfonyl)piperazin-1-yl)-4H-quinolizin-4-one
 $C_{28}H_{28}F_4N_6O_3S$	353	(R)-2-(4-(1-(difluoromethyl)-1H-pyrazol-4-yl)piperazin-1-yl)-7-fluoro-9-(1-((4-fluoro-1,1-dioxido-2,3-dihydrobenzo[b]thiophen-7-yl)amino)ethyl)-3-methyl-4H-quinolizin-4-one

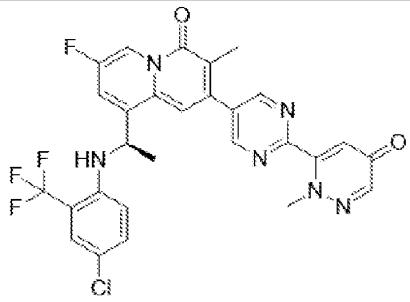
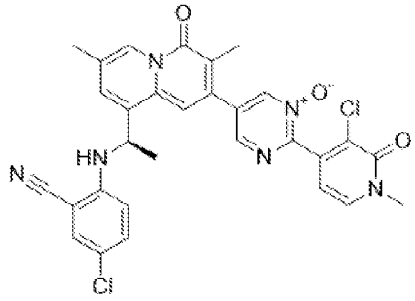
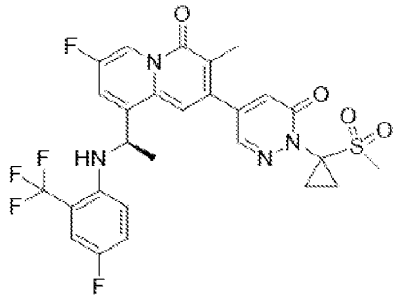
 $C_{28}H_{29}F_3N_6O_3S$	354	(R)-2-(4-(1-(difluoromethyl)-1H-pyrazol-4-yl)piperazin-1-yl)-9-(1-((1,1-dioxido-2,3-dihydrobenzo[b]thiophen-7-yl)amino)ethyl)-7-fluoro-3-methyl-4H-quinolizin-4-one
 $C_{24}H_{27}F_4N_5O_3S$	355	(R)-7-fluoro-3-methyl-9-(1-((6-methyl-2-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-2-(4-(methylsulfonyl)piperazin-1-yl)-4H-quinolizin-4-one
 $C_{24}H_{26}F_4N_4O_3S$	356	(R)-9-(1-((2-(difluoromethyl)-4-fluorophenyl)amino)ethyl)-7-fluoro-3-methyl-2-(4-(methylsulfonyl)piperazin-1-yl)-4H-quinolizin-4-one

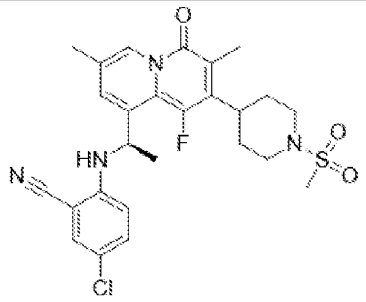
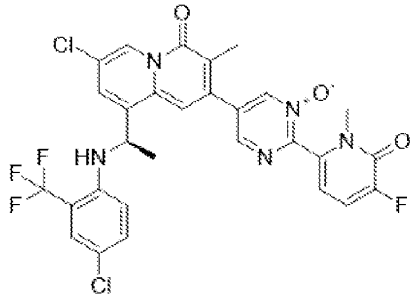
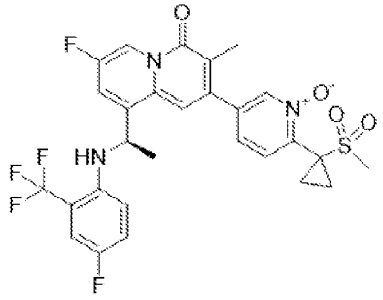
 $C_{28}H_{21}ClF_4N_6O_3$	358	(R)-5-(9-(1-((4-chloro-2-(trifluoromethyl)phenyl)amino)ethyl)-7-fluoro-3-methyl-4-oxo-4H-quinolizin-2-yl)-2-(1-methyl-6-oxo-1,6-dihydropyridazin-4-yl)pyrimidine 1-oxide
 $C_{29}H_{21}ClF_5N_5O_3$	359	(R)-5-(9-(1-((4-chloro-2-(trifluoromethyl)phenyl)amino)ethyl)-7-fluoro-3-methyl-4-oxo-4H-quinolizin-2-yl)-2-(3-fluoro-1-methyl-2-oxo-1,2-dihydropyridin-4-yl)pyrimidine 1-oxide
 $C_{29}H_{22}ClF_4N_5O_2$	360	(R)-3-(5-(7-chloro-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3-methyl-4-oxo-4H-quinolizin-2-yl)pyrimidin-2-yl)-2-methylpyridine 1-oxide

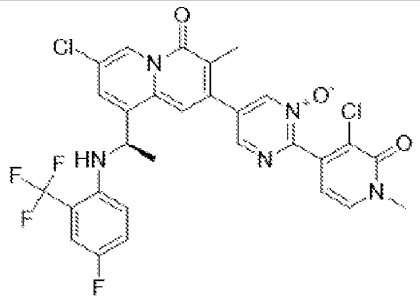
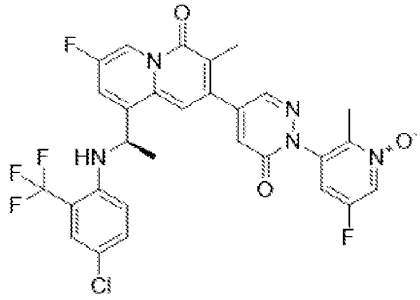
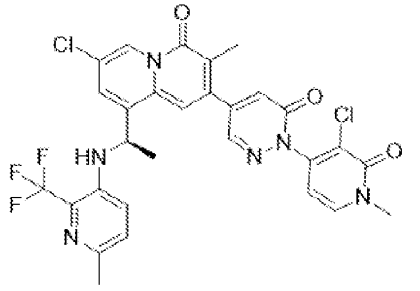
 $C_{29}H_{22}Cl_2F_3N_5O_2$	361	(R)-3-(5-(7-chloro-9-(1-((4-chloro-2-(trifluoromethyl)phenyl)amino)ethyl)-3-methyl-4-oxo-4H-quinolizin-2-yl)pyrimidin-2-yl)-2-methylpyridine 1-oxide
 $C_{31}H_{24}ClF_4N_5O_2$	362	(R)-3-(5-(9-(1-((4-chloro-2-(trifluoromethyl)phenyl)amino)ethyl)-7-fluoro-3-methyl-4-oxo-4H-quinolizin-2-yl)pyrimidin-2-yl)-2-cyclopropylpyridine 1-oxide
 $C_{29}H_{21}ClF_5N_5O_3$	363	(R)-9-(1-((4-chloro-2-(trifluoromethyl)phenyl)amino)ethyl)-7-fluoro-2-(1-(3-fluoro-1-methyl-2-oxo-1,2-dihydropyridin-4-yl)-6-oxo-1,6-dihydropyridazin-4-yl)-3-methyl-4H-quinolizin-4-one

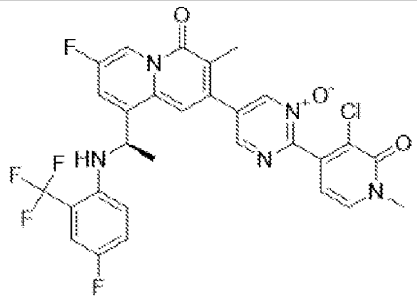
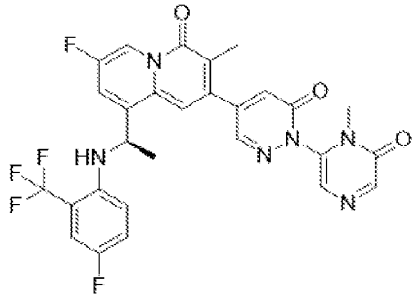
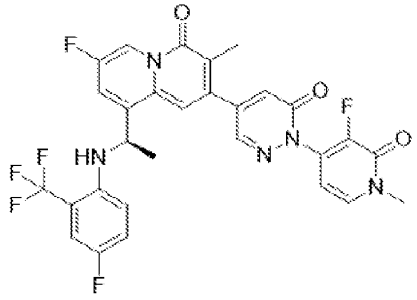
 $C_{29}H_{21}Cl_2F_4N_5O_3$	364	(R)-2-(3-chloro-1-methyl-2-oxo-1,2-dihydropyridin-4-yl)-5-(9-(1-((4-chloro-2-(trifluoromethyl)phenyl)amino)ethyl)-7-fluoro-3-methyl-4-oxo-4H-quinolizin-2-yl)pyrimidine 1-oxide
 $C_{30}H_{21}F_7N_4O_3$	365	(R)-3,5'-difluoro-4-(7-fluoro-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3-methyl-4-oxo-4H-quinolizin-2-yl)-1'-methyl-2H-[1,4'-bipyridine]-2,2'(1'H)-dione
 $C_{30}H_{21}F_7N_4O_3$	366	(R)-3,3'-difluoro-4-(7-fluoro-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3-methyl-4-oxo-4H-quinolizin-2-yl)-1'-methyl-2H-[1,4'-bipyridine]-2,2'(1'H)-dione

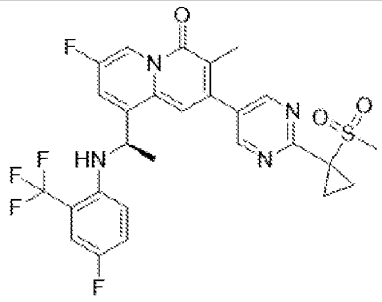
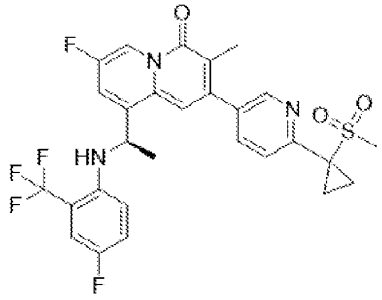
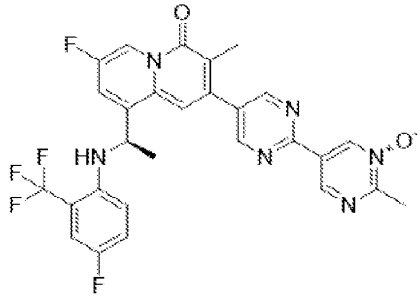
 $C_{28}H_{24}Cl_2N_5O_4S$	367	(R)-5-(7-chloro-9-(1-((4-chloro-2-(methylsulfonyl)phenyl)amino)ethyl)-3-methyl-4-oxo-4H-quinolizin-2-yl)-2'-methyl-[2,5'-bipyrimidine] 1-oxide
 $C_{28}H_{24}ClFN_6O_4S$	368	rac-(R)-5-(7-chloro-9-(1-((4-fluoro-2-(methylsulfonyl)phenyl)amino)ethyl)-3-methyl-4-oxo-4H-quinolizin-2-yl)-2'-methyl-[2,5'-bipyrimidine] 1-oxide
 $C_{27}H_{23}F_5N_4O_4S$	369	(R)-5-(7-fluoro-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3-methyl-4-oxo-4H-quinolizin-2-yl)-2-(1-(methylsulfonyl)cyclopropyl)pyrimidine 1-oxide

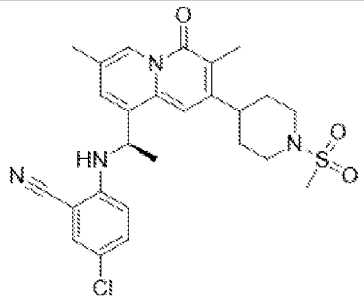
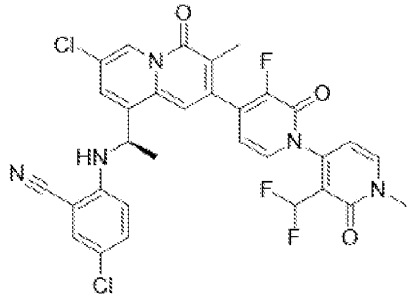
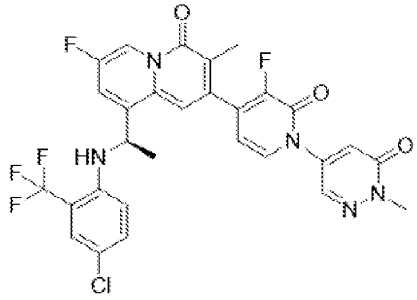
 $C_{28}H_{21}ClF_4N_6O_2$	370	(R)-9-(1-((4-chloro-2-(trifluoromethyl)phenyl)amino)ethyl)-7-fluoro-3-methyl-2-(2-(2-methyl-5-oxo-2,5-dihydropyridazin-3-yl)pyrimidin-5-yl)-4H-quinolizin-4-one
 $C_{30}H_{24}Cl_2N_6O_3$	371	(R)-2-(3-chloro-1-methyl-2-oxo-1,2-dihydropyridin-4-yl)-5-(9-(1-((4-chloro-2-cyanophenyl)amino)ethyl)-3,7-dimethyl-4-oxo-4H-quinolizin-2-yl)pyrimidine 1-oxide
 $C_{27}H_{23}F_5N_4O_4S$	372	(R)-7-fluoro-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3-methyl-2-(1-(1-(methylsulfonyl)cyclopropyl)-6-oxo-1,6-dihydropyridazin-4-yl)-4H-quinolizin-4-one

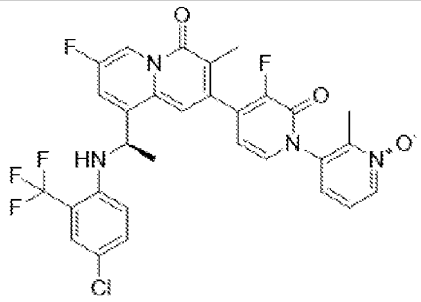
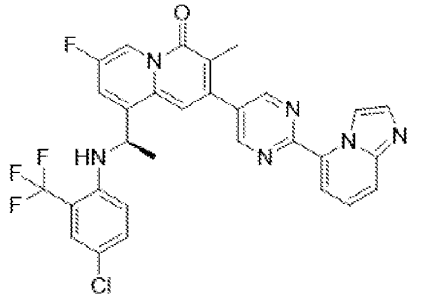
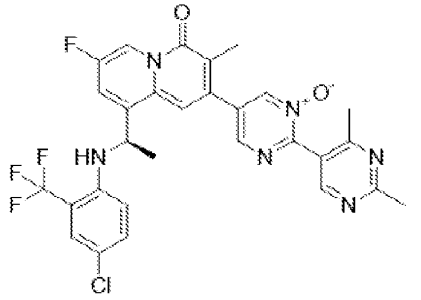
 $C_{26}H_{28}ClFN_4O_3S$	373	(R)-5-chloro-2-((1-(1-fluoro-3,7-dimethyl-2-(1-(methylsulfonyl)piperidin-4-yl)-4-oxo-4H-quinolizin-9-yl)ethyl)amino)benzonitrile
 $C_{29}H_{21}Cl_2F_4N_5O_3$	376	(R)-5-(7-chloro-9-(1-((4-chloro-2-(trifluoromethyl)phenyl)amino)ethyl)-3-methyl-4-oxo-4H-quinolizin-2-yl)-2-(5-fluoro-1-methyl-6-oxo-1,6-dihydropyridin-2-yl)pyrimidine 1-oxide
 $C_{28}H_{24}F_5N_3O_4S$	377	(R)-5-(7-fluoro-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3-methyl-4-oxo-4H-quinolizin-2-yl)-2-(1-(methylsulfonyl)cyclopropyl)pyridine 1-oxide

 $C_{29}H_{21}Cl_2F_4N_5O_3$	378	(R)-2-(3-chloro-1-methyl-2-oxo-1,2-dihydropyridin-4-yl)-5-(7-chloro-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3-methyl-4-oxo-4H-quinolizin-2-yl)pyrimidine 1-oxide
 $C_{29}H_{21}ClF_5N_5O_3$	379	(R)-3-(4-(9-(1-((4-chloro-2-(trifluoromethyl)phenyl)amino)ethyl)-7-fluoro-3-methyl-4-oxo-4H-quinolizin-2-yl)-6-oxopyridazin-1(6H)-yl)-5-fluoro-2-methylpyridine 1-oxide
 $C_{29}H_{23}Cl_2F_3N_6O_3$	380	(R)-7-chloro-2-(1-(3-chloro-1-methyl-2-oxo-1,2-dihydropyridin-4-yl)-6-oxo-1,6-dihydropyridazin-4-yl)-3-methyl-9-(1-((6-methyl-2-(trifluoromethyl)pyridin-3-yl)amino)ethyl)-4H-quinolizin-4-one

 $C_{29}H_{21}ClF_5N_5O_3$	381	(R)-2-(3-chloro-1-methyl-2-oxo-1,2-dihydropyridin-4-yl)-5-(7-fluoro-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3-methyl-4-oxo-4H-quinolizin-2-yl)pyrimidine 1-oxide
 $C_{28}H_{21}F_5N_6O_3$	382	(R)-7-fluoro-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3-methyl-2-(1-(1-methyl-6-oxo-1,6-dihydropyrazin-2-yl)-6-oxo-1,6-dihydropyridazin-4-yl)-4H-quinolizin-4-one
 $C_{29}H_{21}F_6N_5O_3$	383	(R)-7-fluoro-2-(1-(3-fluoro-1-methyl-2-oxo-1,2-dihydropyridin-4-yl)-6-oxo-1,6-dihydropyridazin-4-yl)-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3-methyl-4H-quinolizin-4-one

 $C_{27}H_{23}F_5N_4O_3S$	384	(R)-7-fluoro-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3-methyl-2-(2-(1-(methylsulfonyl)cyclopropyl)pyrimidin-5-yl)-4H-quinolizin-4-one
 $C_{28}H_{24}F_5N_3O_3S$	385	(R)-7-fluoro-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3-methyl-2-(6-(1-(methylsulfonyl)cyclopropyl)pyridin-3-yl)-4H-quinolizin-4-one
 $C_{28}H_{21}F_5N_6O_2$	386	(R)-5-(7-fluoro-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3-methyl-4-oxo-4H-quinolizin-2-yl)-2'-methyl-[2,5'-bipyrimidine] 1'-oxide

 $C_{26}H_{29}ClN_4O_3S$	387	(R)-5-chloro-2-((1-(3,7-dimethyl-2-(1-(methylsulfonyl)piperidin-4-yl)-4-oxo-4H-quinolizin-9-yl)ethyl)amino)benzonitrile
 $C_{31}H_{22}Cl_2F_3N_5O_3$	388	(R)-5-chloro-2-((1-(7-chloro-2-(3'-(difluoromethyl)-3-fluoro-1'-methyl-2,2'-dioxo-1',2'-dihydro-2H-[1,4'-bipyridin]-4-yl)-3-methyl-4-oxo-4H-quinolizin-9-yl)ethyl)amino)benzonitrile
 C29H21ClF5N5O3	389	(R)-9-(1-((4-chloro-2-(trifluoromethyl)phenyl)amino)ethyl)-7-fluoro-2-(3-fluoro-1-(1-methyl-6-oxo-1,6-dihydropyridazin-4-yl)-2-oxo-1,2-dihydropyridin-4-yl)-3-methyl-4H-quinolizin-4-one

 C30H22ClF5N4O3	392	(R)-4-(9-(1-((4-chloro-2-(trifluoromethyl)phenyl)amino)ethyl)-7-fluoro-3-methyl-4-oxo-4H-quinolizin-2-yl)-3-fluoro-2'-methyl-2-oxo-2H-[1,3'-bipyridine] 1'-oxide
 C30H21ClF4N6O	393	(R)-9-(1-((4-chloro-2-(trifluoromethyl)phenyl)amino)ethyl)-7-fluoro-2-(2-(imidazo[1,2-a]pyridin-5-yl)pyrimidin-5-yl)-3-methyl-4H-quinolizin-4-one
 C29H23ClF4N6O2	394	(R)-5-(9-(1-((4-chloro-2-(trifluoromethyl)phenyl)amino)ethyl)-7-fluoro-3-methyl-4-oxo-4H-quinolizin-2-yl)-2',4'-dimethyl-[2,5'-bipyrimidine] 1-oxide

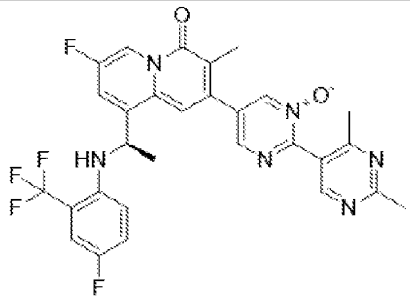
 C29H23F5N6O2	395	(R)-5-(7-fluoro-9-(1-((4-fluoro-2-(trifluoromethyl)phenyl)amino)ethyl)-3-methyl-4-oxo-4H-quinolizin-2-yl)-2',4'-dimethyl-[2,5'-bipyrimidine] 1-oxide

Table 2. NMR and LCMS data for Examples 12, 13, 17 and 29-395

Example	LCMS (m/z)	^{1}H NMR data (MHz, solvent, ppm)
12	ES+ 563.1 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.60 (s, 2H), 9.21 (s, 2H), 8.97 – 8.91 (m, 1H), 7.63 – 7.56 (m, 1H), 7.51 – 7.45 (m, 1H), 7.37 (s, 1H), 7.34 – 7.24 (m, 1H), 6.52 (d, J = 5.1 Hz, 1H), 6.48 – 6.40 (m, 1H), 5.31 – 5.24 (m, 1H), 3.38 (s, 3H), 2.76 (s, 3H), 2.28 (s, 3H), 1.62 (d, J = 6.5 Hz, 3H).
13	ES+ 535.2 [M+H]	^{1}H NMR (400 MHz, CD_3OD): δ 9.70 (s, 2H), 9.10 (s, 2H), 9.08 – 8.89 (m, 1H), 7.75 – 7.54 (m, 1H), 7.45 (s, 1H), 7.20 – 7.03 (m, 2H), 6.97 – 6.81 (m, 1H), 6.42 – 6.29 (m, 1H), 5.28 – 5.09 (m, 1H), 2.83 (s, 3H), 2.40 – 2.30 (m, 3H), 1.78 – 1.62 (m, 3H).
17	ES+ 531.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.60 (s, 2H), 9.19 (s, 2H), 8.82 (s, 1H), 7.52 – 7.22 (m, 3H), 7.21 – 7.14 (m, 1H), 7.08-6.98 (m, 1H), 6.38 – 6.30 (m, 1H), 5.84 (d, J = 6.2 Hz, 1H), 5.21 – 5.11 (m, 1H), 2.75 (s, 3H), 2.33 – 2.28 (m, 3H), 2.24 (s, 3H), 1.56 (d, J = 6.5 Hz, 3H).
29	ES+ 618.0 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.08 (d, J = 1.8 Hz, 1H), 8.93 – 8.92 (m, 1H), 8.65 (d, J = 1.8 Hz, 1H), 7.92 (d, J = 7.0 Hz, 1H), 7.56 – 7.54 (m, 1H), 7.44 – 7.41 (s, 1H), 7.39 – 7.36 (m, 1H), 7.23 – 7.20 (m, 1H), 6.54 – 6.45 (m, 2H), 5.64 (d, J = 6.5 Hz, 1H), 5.36 – 5.28 (m, 1H), 3.61 (s, 3H), 2.29 (s, 3H), 1.63 (d, J = 6.5 Hz, 3H).
30	ES+ 585.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.98 – 8.83 (m, 1H), 8.60 (s, 1H), 8.51 (s, 1H), 8.36 (d, J = 2.0 Hz, 1H), 7.58 – 7.49 (m, 1H), 7.42 – 7.30 (m, 3H), 7.28 – 7.16 (m, 1H), 6.53 – 6.41 (m, 1H), 5.64 (d, J = 6.4 Hz, 1H), 5.34 – 5.21 (m, 1H), 3.96 (s, 3H), 2.31 (s, 3H), 1.63 (d, J = 6.5 Hz, 3H).

31	ES+ 602.1 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.94 – 8.89 (m, 1H), 8.36 (d, J = 2.1 Hz, 1H), 7.81 – 7.74 (m, 1H), 7.58 – 7.51 (m, 1H), 7.41 – 7.33 (m, 3H), 7.25 – 7.16 (m, 1H), 6.53 – 6.44 (m, 2H), 5.63 (d, J = 6.4 Hz, 1H), 5.35 – 5.27 (m, 1H), 3.59 (s, 3H), 2.28 (s, 3H), 1.62 (d, J = 6.5 Hz, 3H).
32	ES+ 579.1 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.06 (s, 2H), 8.95 – 8.88 (m, 1H), 7.57 – 7.50 (m, 1H), 7.41 – 7.33 (m, 1H), 7.34 (s, 1H), 7.24 – 7.15 (m, 1H), 6.51 – 6.43 (m, 1H), 5.62 (d, J = 6.5 Hz, 1H), 5.31-5.28 (m, 1H), 3.50 (s, 3H), 2.23 (s, 3H), 1.94 – 1.73 (m, 4H), 1.60 (d, J = 6.5 Hz, 3H).
33	ES+ 578.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.94 – 8.87 (m, 1H), 8.79 – 8.74 (m, 1H), 8.08 – 8.01 (m, 1H), 7.83 – 7.76 (m, 1H), 7.54 – 7.56 (m, 1H), 7.40 – 7.33 (m, 1H), 7.26 – 7.15 (m, 2H), 6.52 – 6.44 (m, 1H), 5.62 – 5.56 (m, 1H), 5.33 – 5.25 (m, 1H), 3.14 (s, 3H), 2.20 (s, 3H), 1.80 – 1.72 (m, 2H), 1.63 – 1.57 (m, 3H), 1.57 – 1.50 (m, 2H).
34	ES+ 569.1 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.23 (s, 2H), 9.18 (s, 1H), 9.07 (s, 1H), 8.92 (d, J = 5.7 Hz, 1H), 7.55 (d, J = 8.4 Hz, 1H), 7.44 – 7.35 (m, 2H), 7.22 (d, J = 9.2 Hz, 1H), 6.53 – 6.45 (m, 1H), 5.63 (d, J = 6.4 Hz, 1H), 5.33 – 5.26 (m, 1H), 2.68 (s, 3H), 2.27 (s, 3H), 1.62 (d, J = 6.4 Hz, 3H).
35	ES+ 513.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.71 (s, 1H), 7.64 (d, J = 2.5 Hz, 1H), 7.39 – 7.32 (m, 2H), 6.92 (s, 1H), 6.73 (d, J = 6.8 Hz, 1H), 6.39 (d, J = 9.2 Hz, 1H), 5.29 – 5.26 (m, 1H), 3.75 – 3.68 (m, 2H), 3.03 – 2.96 (m, 1H), 2.96 – 2.85 (m, 5H), 2.32 – 2.16 (m, 6H), 1.97 – 1.90 (m, 2H), 1.89 – 1.78 (m, 2H), 1.58 (d, J = 6.6 Hz, 3H).
36	ES+ 640.0 [M+H]	^{1}H NMR (400 MHz, $CDCl_3$): δ 9.17 (s, 1H), 7.62 (d, J = 7.3 Hz, 1H), 7.47 (d, J = 2.4 Hz, 1H), 7.35 (s, 1H), 7.27 (s, 1H), 7.04 (s, 1H), 6.71 (s, 1H), 6.34 (d, J = 7.2 Hz, 1H), 6.23 (s, 1H), 6.19 – 6.11 (m, 1H),

		4.97 – 4.90 (m, 1H), 4.90 – 4.83 (m, 1H), 3.76 – 3.65 (m, 4H), 2.34 (s, 3H), 1.75 (d, J = 6.5 Hz, 3H).
37	ES+ 547.1 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.81 (s, 1H), 8.75 (d, J = 2.3 Hz, 1H), 8.06 – 7.99 (m, 1H), 7.78 (d, J = 8.1 Hz, 1H), 7.65 (d, J = 2.5 Hz, 1H), 7.46 (d, J = 1.7 Hz, 1H), 7.36 – 7.29 (m, 1H), 7.04 (s, 1H), 6.75 (d, J = 6.8 Hz, 1H), 6.38 (d, J = 9.2 Hz, 1H), 5.26 – 5.15 (m, 1H), 3.14 (s, 3H), 2.31 (d, J = 1.3 Hz, 3H), 2.17 (s, 3H), 1.78 – 1.71 (m, 2H), 1.58 (d, J = 6.5 Hz, 3H), 1.55 – 1.50 (m, 2H).
38	ES+ 574.1 [M+H]	^{1}H NMR (400 MHz, $CDCl_3$): δ 8.98 – 8.85 (m, 1H), 7.46 – 7.42 (m, 1H), 7.25 – 7.20 (m, 1H), 7.04 – 6.94 (m, 1H), 6.28 – 6.22 (m, 1H), 5.21 (d, J = 6.7 Hz, 1H), 4.60 – 4.55 (m, 1H), 4.05 – 4.00 (m, 4H), 3.36 – 3.21 (m, 4H), 2.38 (s, 3H), 2.20 – 2.05 (m, 4H), 1.64 (d, J = 6.4 Hz, 3H).
39	ES+ 556.1 [M+H]	^{1}H NMR (400 MHz, $CDCl_3$): δ 9.03 – 8.97 (m, 1H), 7.43 – 7.36 (m, 1H), 7.28 – 7.25 (m, 1H), 6.99 – 6.94 (m, 1H), 6.61 (s, 1H), 6.20 – 6.10 (m, 1H), 4.90 – 4.80 (m, 1H), 4.62 – 4.58 (m, 1H), 4.05 – 4.00 (m, 4H), 3.12 – 2.90 (m, 4H), 2.34 (s, 3H), 2.25 – 2.15 (m, 4H), 1.71 (d, J = 6.5 Hz, 3H).
40	ES+ 556.1 [M+H]	^{1}H NMR (400 MHz, $CDCl_3$): δ 9.16 (d, J = 1.6 Hz, 1H), 8.48 (d, J = 2.4 Hz, 1H), 7.85 – 7.75 (m, 1H), 7.56 (d, J = 8.4 Hz, 1H), 7.45 (d, J = 2.4 Hz, 1H), 7.31 (d, J = 1.2 Hz, 1H), 7.25 – 7.15 (m, 1H), 6.67 (s, 1H), 6.10 (d, J = 9.2 Hz, 1H), 4.91 (d, J = 4.0 Hz, 1H), 4.87 – 4.71 (m, 1H), 3.50 (s, 3H), 3.15 (s, 3H), 2.32 (s, 3H), 1.71 (d, J = 6.4 Hz, 3H).
41	ES+ 631.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.08 (d, J = 1.9 Hz, 1H), 8.96 (d, J = 2.0 Hz, 1H), 8.65 (d, J = 1.8 Hz, 1H), 7.92 (d, J = 7.0 Hz, 1H), 7.48 (d, J = 2.1 Hz, 1H), 7.37 (s, 1H), 7.19 (d, J = 8.6 Hz, 1H), 6.88 (d, J = 8.7 Hz, 1H), 6.51 (d, J = 6.9 Hz, 1H), 6.32 – 6.29 (m, 1H), 5.85 (d, J = 6.8

		Hz, 1H), 3.60 (s, 3H), 2.32 (s, 3H), 2.28 (s, 3H), 1.63 (d, J = 6.5 Hz, 3H).
42	ES+ 559.1 [M+H]	^{1}H NMR (400 MHz, $CDCl_3$): δ 9.14 – 8.94 (m, 1H), 8.84 (s, 2H), 7.45 (s, 1H), 7.42 – 7.33 (m, 1H), 7.28 – 7.25 (m, 1H), 7.24 – 7.14 (m, 1H), 6.73 (s, 1H), 6.35 – 6.20 (m, 1H), 6.13 (d, J = 9.2 Hz, 1H), 4.96 – 4.92 (m, 1H), 4.90 – 4.78 (m, 1H), 2.86 (s, 3H), 2.36 (s, 3H), 1.73 (d, J = 6.8 Hz, 3H).
43	ES+ 591.1 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.96 (d, J = 2.0 Hz, 1H), 8.36 (d, J = 2.1 Hz, 1H), 7.78 – 7.76 (m, 1H), 7.68 (d, J = 2.6 Hz, 1H), 7.60 (d, J = 2.1 Hz, 1H), 7.39 – 7.32 (m, 2H), 7.30 (s, 1H), 6.86 (d, J = 7.2 Hz, 1H), 6.51 – 6.47 (m, 1H), 6.40 (d, J = 9.1 Hz, 1H), 5.28 – 5.25 (m, 1H), 3.58 (s, 3H), 2.28 (s, 3H), 1.60 (d, J = 6.5 Hz, 3H).
44	ES+ 596.1 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.96 (d, J = 2.0 Hz, 1H), 8.76 (s, 1H), 8.36 (d, J = 2.0 Hz, 1H), 7.48 (d, J = 2.1 Hz, 1H), 7.37 (d, J = 2.1 Hz, 1H), 7.29 (s, 1H), 7.19 (d, J = 8.6 Hz, 1H), 6.88 (d, J = 8.7 Hz, 1H), 5.85 (d, J = 6.7 Hz, 1H), 5.37 – 5.19 (m, 1H), 2.70 (s, 3H), 2.37 (s, 3H), 2.33 – 2.28 (m, 6H), 1.63 (d, J = 6.6 Hz, 3H).
45	ES+ 595.1 [M+H]	^{1}H NMR (400 MHz, CD_3OD): δ 9.16 (s, 2H), 9.12 (d, J = 1.6 Hz, 1H), 8.29 (d, J = 2.0 Hz, 1H), 7.58 – 7.50 (m, 2H), 7.30 – 7.22 (m, 2H), 7.19 –7.11 (m, 1H), 6.62 (d, J = 6.4 Hz, 1H), 6.50 – 6.43 (m, 1H), 5.22 – 5.15 (m, 1H), 3.26 (s, 3H), 2.80 (s, 3H), 2.38 (s, 3H), 1.72 (d, J = 6.4 Hz, 3H).
46	ES+ 591.1 [M+H]	^{1}H NMR (400 MHz, $CDCl_3$): δ 9.18 (s, 1H), 8.57 (s, 1H), 8.41 (s, 1H), 7.48 – 7.40 (m, 2H), 7.23 – 7.15 (m, 2H), 6.72 (s, 1H), 6.43 (s, 1H), 6.10 (d, J = 7.6 Hz, 1H), 4.94 (s, 1H), 4.91 – 4.83 (s, 1H), 3.56 (s, 3H), 2.38 (s, 3H), 1.77 (d, J = 6.4 Hz, 3H).

47	ES+ 572.1 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.97 (s, 1H), 8.75 (s, 1H), 8.48 (s, 1H), 7.68 – 7.65 (m, 1H), 7.62 – 6.60 (m, 1H), 7.40 – 7.35 (m, 2H), 7.30 (s, 1H), 6.88 – 6.86 (m, 1H), 6.42 – 6.39 (m, 1H), 5.27 – 5.23 (m, 1H), 2.70 (s, 3H), 2.32 (s, 3H), 2.31 (s, 3H), 1.62 (d, J = 6.6 Hz, 3H).
48	ES+ 609.0 [M+H]	^{1}H NMR (400 MHz, CD_3OD): δ 9.13 (d, J = 1.6 Hz, 1H), 8.98 (d, J = 2.0 Hz, 1H), 8.71 (d, J = 2.0 Hz, 1H), 7.84 (d, J = 7.2 Hz, 1H), 7.57 (d, J = 2.0 Hz, 1H), 7.51 (d, J = 2.4 Hz, 1H), 7.34 – 7.24 (m, 2H), 6.60 (d, J = 3.2 Hz, 1H), 6.43 (d, J = 8.8 Hz, 1H), 5.27 – 5.20 (m, 1H), 3.74 (s, 3H), 2.38 (s, 3H), 1.72 (d, J = 6.4 Hz, 3H).
49	ES+ 507.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.31 (d, J = 5.9 Hz, 1H), 8.71 (s, 1H), 8.04 (d, J = 5.9 Hz, 1H), 7.79 (d, J = 6.8 Hz, 1H), 7.55 – 7.47 (m, 1H), 7.45 (d, J = 1.7 Hz, 1H), 7.08 (d, J = 8.1 Hz, 1H), 6.74 (s, 1H), 6.47 (d, J = 7.8 Hz, 1H), 5.34 – 5.26 (m, 1H), 3.33 – 3.26 (m, 4H), 3.19 – 3.15 (m, 4H), 2.96 (s, 3H), 2.20 (s, 3H), 2.16 (s, 3H), 1.76 (d, J = 6.6 Hz, 3H).
50	ES+ 584.1 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.23 (s, 2H), 8.96 – 8.90 (m, 1H), 8.48 (d, J = 6.5 Hz, 1H), 7.80 (d, J = 7.7 Hz, 1H), 7.57 – 7.45 (m, 3H), 7.40 (s, 1H), 7.37 – 7.33 (m, 1H), 6.51 (d, J = 9.1 Hz, 1H), 5.88 (d, J = 6.6 Hz, 1H), 5.38 – 5.30 (m, 1H), 2.65 (s, 3H), 2.29 (s, 3H), 1.64 (d, J = 6.5 Hz, 3H).
51	ES+ 528.2 [M+H]	^{1}H NMR (400 MHz, $CDCl_3$): δ 8.89 (s, 1H), 7.42 (d, J = 2.4 Hz, 1H), 7.26 – 7.17 (m, 2H), 6.52 (s, 1H), 6.13 (d, J = 9.2 Hz, 1H), 4.93 (d, J = 4.6 Hz, 1H), 4.87 - 4.80 (m, 1H), 3.69 – 3.55 (m, 2H), 3.50 – 3.44 (m, 2H), 3.38 – 3.33 (m, 1H), 3.20 – 3.05 (m, 2H), 2.87 (s, 3H), 2.34 (s, 3H), 2.31 (s, 3H), 1.69 (d, J = 6.4 Hz, 3H), 1.10 (d, J = 5.2 Hz, 3H).
52	ES+ 528.2 [M+H]	^{1}H NMR (400 MHz, $CDCl_3$): δ 8.89 (s, 1H), 7.41 (d, J = 2.0 Hz, 1H), 7.26 – 7.18 (m, 2H), 6.51 (s, 1H), 6.15 (d, J = 8.8 Hz, 1H), 4.95 - 4.90

		(m, 1H), 4.85 – 4.60 (m, 1H), 3.70 – 3.20 (m, 5H), 3.18 – 3.01 (m, 2H), 2.86 (s, 3H), 2.32 (s, 3H), 2.31 (s, 3H) 1.70 (d, J = 6.8 Hz, 3H),1.09 (d, J = 6.0 Hz, 3H).
53	ES+ 603.1 [M+H]	^{1}H NMR (400 MHz, CD_3OD): δ 8.88 – 8.87 (m, 1H), 7.48 – 7.46 (m, 1H), 7.31 – 7.29 (m, 1H), 7.11 – 7.09 (m, 1H), 6.91 (s, 1H), 6.48 – 6.45 (m, 1H), 5.16 – 5.14 (m, 1H), 3.60 – 3.52 (m, 3H), 3.43 – 3.39 (m, 4H), 3.24-3.21 (m, 2H), 2.45 – 2.33 (m, 5H), 2.05 – 2.03 (m, 4H), 1.72 – 1.70 (m, 3H).
54	ES+ 592.1 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.79 (s, 1H), 8.35 (s, 1H), 7.35 – 7.25 (m, 2H), 7.15 – 7.05 (m, 1H), 6.62 – 6.50 (m, 1H), 6.18 – 6.10 (m, 1H), 5.15 – 4.95 (m, 1H) 3.40 – 3.25 (m, 8H), 2.96 (s, 3H), 2.36 (s, 3H), 2.23 (s, 3H), 1.52 (d, J = 6.5 Hz, 3H).
55	ES+ 591.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.83 (d, J = 2.0 Hz, 1H), 8.03 (d, J = 2.2 Hz, 1H), 7.37 (s, 1H), 6.97 – 6.81 (m, 2H), 6.72 (s, 1H), 6.24 – 6.16 (m, 1H), 5.25 (d, J = 6.2 Hz, 1H), 4.96 (d, J = 6.6 Hz, 1H), 3.81 (s, 3H), 3.30 – 3.13 (m, 8H), 2.96 (s, 3H), 2.16 (s, 3H), 1.52 (d, J = 6.5 Hz, 3H).
56	ES+ 617.3 [M+H]	^{1}H NMR (400 MHz, CD_3OD): δ 8.97 (d, J = 2.4 Hz, 1H), 7.41 (d, J = 1.6 Hz, 1H), 7.18 (d, J = 8.8 Hz, 1H), 6.88 (d, J = 8.8 Hz, 1H), 6.79 (s, 1H), 5.44 – 5.33 (m, 1H), 5.32 – 5.22 (m, 1H), 5.20 – 5.08 (m, 1H), 4.26 – 4.14 (m, 2H), 4.13 – 3.97 (m, 2H), 3.58 – 3.35 (m, 4H), 3.30 – 3.05 (m, 4H), 2.41 (s, 3H), 2.27 (s, 3H), 1.71 (d, J = 6.4 Hz, 3H).
57	ES+ 529.0 [M+H]	^{1}H NMR (400 MHz, CD_3OD): δ 8.92 – 8.84 (m, 1H), 7.55 – 7.46 (m, 2H), 7.36 – 7.28 (m, 1H), 6.85 (s, 1H), 6.46 (d, J = 9.1 Hz, 1H), 5.24 – 5.13 (m, 1H), 4.03 (m, 4H), 3.18 – 3.09 (m, 4H), 2.27 (s, 3H), 2.14 – 2.07 (m, 4H), 1.73 (d, J = 6.7 Hz, 3H).

58	ES+ 507.1 [M+H]	^{1}H NMR (400 MHz, CD_3OD): δ 9.37 (s, 1H), 9.19 (s, 1H), 8.83 (s, 1H), 7.50 (d, J = 1.7 Hz, 1H), 7.46 – 7.44 (m, 1H), 7.29 – 7.24 (m, 1H), 6.86 (s, 1H), 6.68 – 6.60 (m, 1H), 5.30 – 5.25 (m, 1H), 3.45 – 3.35 (m, 4H), 3.25 – 3.20 (m, 4H), 2.92 (s, 3H), 2.33 – 2.21 (m, 6H), 1.82 (d, J = 6.6 Hz, 3H).
59	ES+ 612.1 [M+H]	^{1}H NMR (400 MHz, CD_3OD): δ 9.12 (d, J = 1.9 Hz, 1H), 8.95 (s, 2H), 7.71 – 7.69 (m, 1H), 7.56 – 7.51 (m, 2H), 7.23 (s, 1H), 7.19 – 7.12 (m, 1H), 6.61 (d, J = 5.3 Hz, 1H), 6.58 – 6.52 (m, 1H), 6.47 – 6.44 (m, 1H), 5.15 – 5.12 (m, 1H), 3.25 (s, 3H), 2.82 (s, 3H), 2.32 (s, 3H), 1.71 (d, J = 6.6 Hz, 3H).
60	ES+ 585.3 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.80 – 8.74 (m, 1H), 7.43 – 7.34 (m, 2H), 7.24 (s, 1H), 6.73 (s, 1H), 6.52 – 6.44 (m, 1H), 5.54 (d, J = 6.5 Hz, 1H), 5.21 – 5.13 (m, 1H), 3.47 – 3.37 (m, 3H), 3.25 – 3.17 (m, 2H), 2.99 – 2.84 (m, 2H), 2.97 – 2.83 (m, 2H), 2.30 – 2.18 (m, 2H), 2.15 (s, 3H), 1.91 – 1.83 (m, 4H), 1.62 (d, J = 6.5 Hz, 3H).
61	ES+ 566.1 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.79 (d, J = 2.0 Hz, 1H), 7.66 (d, J = 2.6 Hz, 1H), 7.39 – 7.31 (m, 2H), 6.81 (s, 1H), 6.52 (d, J = 9.1 Hz, 1H), 5.21 – 5.18 (m, 1H), 3.52 – 3.46 (m, 4H), 3.43 – 3.34 (m, 4H), 2.95 (s, 3H), 2.24 (s, 3H), 1.95 (d, J = 6.2 Hz, 2H), 1.59 (d, J = 6.4 Hz, 3H).
62	ES+ 555.1 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.95 (s, 2H), 8.82 (s, 1H), 7.91 – 7.78 (m, 1H), 7.66 (d, J = 2.6 Hz, 1H), 7.48 (d, J = 1.7 Hz, 1H), 7.42 – 7.28 (m, 1H), 7.05 (s, 1H), 6.77 (d, J = 6.7 Hz, 1H), 6.61 – 6.44 (m, 1H), 6.35 (d, J = 9.1 Hz, 1H), 5.29 – 4.91 (m, 1H), 2.74 (s, 3H), 2.34 – 2.30 (m, 3H), 2.21 – 2.16 (m, 3H), 1.59 (d, J = 6.5 Hz, 3H).
63	ES+ 602.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.97 – 8.93 (m, 3H), 7.88 – 7.80 (m, 1H), 7.44 (d, J = 2.1 Hz, 1H), 7.41 – 7.33 (m, 1H), 7.25 – 7.18 (m, 2H), 6.61 – 6.50 (m, 1H), 6.50 – 6.41 (m, 1H), 5.62 (d, J = 6.5

		Hz, 1H), 5.25 – 5.11 (m, 1H), 2.75 (s, 3H), 2.21 (d, J = 1.3 Hz, 3H), 1.60 (d, J = 6.5 Hz, 3H).
64	ES+ 536.1 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.82 – 8.69 (m, 1H), 7.67 (d, J = 2.6 Hz, 1H), 7.55 – 7.48 (m, 1H), 7.38 – 7.20 (m, 1H), 6.79 (d, J = 6.9 Hz, 1H), 6.50 (d, J = 9.2 Hz, 1H), 5.31 – 5.06 (m, 1H), 3.41 – 3.33 (m, 4H), 3.32 – 3.25 (m, 4H), 2.97 (s, 3H), 2.25 (s, 3H), 1.65 – 1.58 (m, 3H).
65	ES+ 583.1 [M+H]	^{1}H NMR (400 MHz, $CDCl_3$): 9.04 – 9.01 (m, 1H), 8.95 (s, 2H), 7.85 (d, J = 2.0 Hz, 1H), 7.51 – 7.44 (m, 1H), 7.28 – 7.23 (m, 1H), 7.05 – 6.85 (m, 2H), 6.64 (s, 1H), 6.15 – 5.95 (m, 1H), 5.42 (s, 2H), 4.83 – 4.81 (m, 1H), 4.62 (s, 1H), 2.85 (s, 3H), 2.32 (s, 3H), 1.67 (d, J = 6.8 Hz, 3H).
66	ES+ 559.1 [M+H]	^{1}H NMR (400 MHz, $CDCl_3$): δ 9.04 – 8.97 (m, 1H), 7.46 – 7.38 (m, 1H), 7.26 (d, J = 2.8 Hz, 1H), 6.95 (d, J = 8.1 Hz, 1H), 6.45 (s, 1H), 6.17 – 6.11 (m, 1H), 4.82 – 4.78 (m, 1H), 4.63 – 4.57 (m, 1H), 4.03 (s, 2H), 3.98 – 3.90 (m, 2H), 3.58 – 3.52 (m, 2H), 3.46 (s, 3H), 2.35 (s, 3H), 1.70 (d, J = 6.8 Hz, 3H).
67	ES+ 564.2 [M+H]	(400 MHz, CD_3OD): δ 9.00 (d, J = 2.0 Hz, 1H), 8.04 (d, J = 2.8 Hz, 1H), 7.52 (d, J = 2.8 Hz, 1H), 7.45 (d, J = 2.0 Hz, 1H), 7.37 – 7.22 (m, 1H), 6.82 (s, 1H), 6.48 (d, J = 7.2 Hz, 1H), 6.04 (d, J = 2.8 Hz, 1H), 5.29 – 5.04 (m, 1H), 3.70 (s, 3H), 3.68 – 3.55 (m, 4H), 3.32 – 3.28 (m, 4H), 2.32 (s, 3H), 1.73 (d, J = 6.4 Hz, 3H).
68	ES+ 593.2 [M+H]	^{1}H NMR (400 MHz, CD_3OD): δ 8.98 – 8.72 (m, 1H), 8.06 (d, J = 2.8 Hz, 1H), 7.61 – 7.45 (m, 1H), 7.45 – 7.22 (m, 1H), 7.19 – 6.95 (m, 1H), 6.64 – 6.37 (m, 1H), 6.05 (d, J = 2.8 Hz, 1H), 5.44 – 5.22 (m, 1H), 3.70 (s, 3H), 3.68 – 3.42 (m, 8H), 2.40 (s, 3H), 1.67 (d, J = 6.4 Hz, 3H).

69	ES+ 562.2 [M+H]	^{1}H NMR (400 MHz, $CDCl_3$): δ 9.14 (d, J = 2.0 Hz, 1H), 8.87 (s, 2H), 7.47 (d, J = 2.0 Hz, 1H), 7.34 (d, J = 2.0 Hz, 1H), 7.25 (d, J = 8.4 Hz, 1H), 6.44 (s, 1H), 6.15 (d, J = 8.7 Hz, 1H), 4.92 (s, 1H), 4.85 – 4.79 (m, 1H), 4.11 (s, 2H), 3.99 – 3.85 (m, 2H), 3.70 – 3.62 (m, 2H), 2.86 (s, 3H), 2.39 (s, 3H), 1.74 (d, J = 6.3 Hz, 3H).
70	ES+ 573.3 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.84 (s, 2H), 8.83 – 8.78 (m, 1H), 7.51 – 7.39 (m, 1H), 7.39 – 7.35 (m, 1H), 7.29 – 7.13 (m, 1H), 6.81 (s, 1H), 6.51 – 6.44 (m, 1H), 5.57 (d, J = 6.3 Hz, 1H), 5.29 – 5.19 (m, 1H), 4.26 – 4.04 (m, 2H), 4.01 – 3.92 (m, 2H), 3.70 – 3.55 (m, 2H), 2.65 (s, 3H), 2.25 (s, 3H), 1.63 (d, J = 6.5 Hz, 3H).
71	ES+ 607.1 [M+H]	^{1}H NMR (400 MHz, CD_3OD): δ 9.12 (d, J = 1.6 Hz, 1H), 8.27 (d, J = 2.0 Hz, 1H), 7.87 (d, J = 7.2 Hz, 1H), 7.65 – 7.43 (m, 2H), 7.36 – 7.18 (m, 3H), 6.62 (d, J = 7.2 Hz, 1H), 6.44 (d, J = 9.2 Hz, 1H), 5.34 – 5.05 (m, 1H), 3.73 (s, 3H), 2.37 (s, 3H), 1.72 (d, J = 6.8 Hz, 3H).
72	ES+ 568.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.19 (s, 2H), 8.99 – 8.82 (m, 1H), 8.35 (d, J = 1.9 Hz, 1H), 8.29 – 8.17 (m, 1H), 8.12 (d, J = 6.8 Hz, 1H), 7.68 – 7.47 (m, 1H), 7.38 – 7.35 (m, 2H), 7.24 – 7.07 (m, 1H), 6.68 – 6.42 (m, 1H), 5.63 (d, J = 6.4 Hz, 1H), 5.40 – 5.12 (m, 1H), 2.65 (s, 3H), 2.28 (s, 3H), 1.62 (d, J = 6.5 Hz, 3H).
73	ES+ 569.2 [M+H]	^{1}H NMR (400 MHz, CD_3OD): δ 9.16 – 8.91 (m, 1H), 8.18 (d, J = 2.0 Hz, 1H), 7.67 – 7.45 (m, 1H), 7.36 – 7.25 (m, 2H), 7.22 (d, J = 2.0 Hz, 1H), 7.13 – 6.98 (m, 1H), 6.55 – 6.35 (m, 1H), 5.66 (s, 2H), 5.32 – 5.08 (m, 2H), 3.20 (s, 3H), 2.34 (s, 3H), 1.70 (d, J = 6.8 Hz, 3H).
74	ES+ 518.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.84 – 8.67 (m, 1H), 7.67 (d, J = 2.5 Hz, 1H), 7.59 – 7.43 (m, 1H), 7.42 – 7.25 (m, 1H), 6.83 – 6.73 (m, 2H), 6.43 (d, J = 9.2 Hz, 1H), 5.30 – 5.07 (m, 1H), 3.33 – 3.29

		(m, 4H), 3.28 – 3.12 (m, 4H), 2.97 (s, 3H), 2.17 (s, 3H), 1.62 (d, J = 6.7 Hz, 3H).
75	ES+ 599.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.05 – 8.95 (m, 3H), 7.87 – 7.80 (m, 1H), 7.45 (d, J = 2.1 Hz, 1H), 7.23 – 7.16 (m, 2H), 6.85 (d, J = 8.7 Hz, 1H), 6.57 – 6.50 (m, 1H), 5.82 (d, J = 6.8 Hz, 1H), 5.25 – 5.18 (m, 1H), 2.75 (s, 3H), 2.32 (s, 3H), 2.21 (d, J = 1.3 Hz, 3H), 1.60 (d, J = 6.5 Hz, 3H).
76	ES+ 601.1 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.75 (s, 2H), 9.09 (s, 1H), 9.09 (s, 1H), 8.71 (d, J = 1.9 Hz, 1H), 7.50 – 7.45 (s, 1H), 7.44 – 7.41 (m, 1H), 7.39 – 7.33 (m, 2H), 6.51 – 6.48 (d, J = 6.7 Hz, 1H), 5.88 (d, J = 6.7 Hz, 1H), 5.26 (s, 1H), 2.75 (s, 3H), 2.30 (s, 3H), 1.62 (d, J = 6.5 Hz, 3H).
77	ES+ 574.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.82 (s, 1H), 8.35 (m, 1H), 7.40 – 7.30 (m, 2H), 7.15 – 7.05 (m, 1H), 6.75 (s, 1H), 6.55 – 6.50 (m, 1H), 6.20 – 6.10 (m, 1H), 5.17 – 5.15 (m, 1H), 3.15 – 3.13 (m, 8H), 2.96 (s, 3H), 2.38 (s, 3H), 2.17 (s, 3H), 1.62 (d, J = 6.5 Hz, 3H).
78	ES+ 574.1 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.81 (s, 1H), 8.79 – 8.73 (m, 1H), 8.07 – 8.00 (m, 1H), 7.82 – 7.74 (m, 1H), 7.39 – 7.31 (m, 2H), 7.23 – 7.14 (m, 1H), 7.07 (s, 1H), 6.50 – 6.40 (m, 1H), 5.45 (d, J = 6.3 Hz, 1H), 5.25 – 5.17 (m, 1H), 3.13 (s, 3H), 2.29 (d, J = 1.2 Hz, 3H), 2.17 (s, 3H), 1.78 – 1.71 (m, 2H), 1.60 – 1.49 (m, 5H).
79	ES+ 575.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.97 – 8.91 (m, 3H), 7.86 – 7.79 (m, 1H), 7.67 (d, J = 2.6 Hz, 1H), 7.56 (d, J = 2.0 Hz, 1H), 7.38 – 7.30 (m, 1H), 7.18 (s, 1H), 6.84 (d, J = 7.2 Hz, 1H), 6.56 – 6.48 (m, 1H), 6.37 (d, J = 9.2 Hz, 1H), 5.22 – 5.14 (m, 1H), 2.74 (s, 3H), 2.20 (s, 3H), 1.58 (d, J = 6.6 Hz, 3H).

80	ES+ 585.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.75 (s, 2H), 9.09 (d, J = 1.9 Hz, 1H), 8.95 – 8.88 (m, 1H), 8.71 (d, J = 1.9 Hz, 1H), 7.56 – 7.48 (m, 2H), 7.41 – 7.31 (m, 2H), 6.49 (d, J = 9.0 Hz, 1H), 5.87 (d, J = 6.7 Hz, 1H), 5.37 – 5.28 (m, 1H), 2.75 (s, 3H), 2.30 (s, 3H), 1.63 (d, J = 6.6 Hz, 3H).
81	ES+ 667.1 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.96 (d, J = 2.0 Hz, 1H), 8.17 (d, J = 7.2 Hz, 1H), 7.59 (d, J = 7.2 Hz, 1H), 7.45 (s, 1H), 7.41 – 7.34 (m, 1H), 7.20 (s, 1H), 6.90 (s, 1H), 6.49 – 6.41 (m, 3H), 5.61 (d, J = 6.4 Hz, 1H), 5.24 – 5.16 (m, 1H), 3.57 (s, 3H), 2.18 (s, 3H), 1.60 (d, J = 6.5 Hz, 3H).
82	ES+ 583.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.96 – 8.88 (m, 1H), 8.75 (s, 1H), 8.36 (d, J = 2.1 Hz, 1H), 7.59 – 7.50 (m, 1H), 7.41 – 7.33 (m, 3H), 7.25 – 7.16 (m, 1H), 6.52 – 6.43 (m, 1H), 5.63 (d, J = 6.4 Hz, 1H), 5.34 – 5.24 (m, 1H), 2.69 (s, 3H), 2.36 (s, 3H), 2.30 (s, 3H), 1.63 (d, J = 6.6 Hz, 3H).
83	ES+ 634.4 [M+H]	^{1}H NMR (400 MHz, $CDCl_3$): δ 9.18 (s, 1H), 8.00 (s, 1H), 7.52 – 7.35 (m, 2H), 7.27 – 7.21 (m, 1H), 7.10 (d, J = 2.0 Hz, 1H), 7.07 – 6.90 (m, 1H), 6.71 (s, 1H), 6.40 (d, J = 7.2 Hz, 1H), 6.19 – 6.13 (m, 1H), 4.86 – 4.83 (m, 1H), 4.61 (s, 1H), 3.71 (s, 3H), 2.40 (s, 3H), 1.71 (d, J = 6.4 Hz, 3H).
84	ES+ 568.2 [M+H]	^{1}H NMR (400 MHz, CD_3OD): δ 9.23 (d, J = 5.9 Hz, 1H), 9.14 (s, 2H), 9.10 – 9.00 (m, 1H), 8.04 (d, J = 6.0 Hz, 1H), 7.81 (d, J = 7.2 Hz, 1H), 7.78 – 7.68 (m, 1H), 7.57 – 7.50 (m, 1H), 7.50 – 7.45 (m, 1H), 7.14 (d, J = 6.8 Hz, 1H), 6.77 (d, J = 7.2 Hz, 1H), 6.49 (d, J = 7.6 Hz, 1H), 5.50 – 5.40 (m, 1H), 3.74 (s, 3H), 2.37 (s, 3H), 1.88 (d, J = 6.4 Hz, 3H).
85	ES+ 585.2 [M+H]	^{1}H NMR (400 MHz, $CDCl_3$): δ 10.09 (s, 2H), 9.20 (d, J = 2.0 Hz, 1H), 8.63 – 8.62 (m, 1H), 8.49 (d, J = 1.9 Hz, 1H), 7.48 (d, J = 2.0 Hz, 1H),

		7.27 (d, J = 2.8 Hz, 1H), 7.02 – 6.95 (m, 1H), 6.71 (s, 1H), 6.17 – 6.14 (m, 1H), 4.82 (d, J = 6.7 Hz, 1H), 4.61 (s, 1H), 2.99 (d, J = 2.0 Hz, 3H), 2.41 (s, 3H), 1.70 (d, J = 6.6 Hz, 3H).
86	ES+ 558.1 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.75 (s, 2H), 9.09 (d, J = 2.0 Hz, 1H), 8.97 (d, J = 2.0 Hz, 1H), 8.71 (d, J = 1.9 Hz, 1H), 7.68 (d, J = 2.6 Hz, 1H), 7.60 (d, J = 2.1 Hz, 1H), 7.38 – 7.30 (m, 2H), 6.87 (d, J = 7.2 Hz, 1H), 6.40 (d, J = 9.2 Hz, 1H), 5.26 – 5.23 (m, 1H), 2.75 (s, 3H), 2.30 (s, 3H), 1.61 (d, J = 6.5 Hz, 3H).
87	ES+ 608.0 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.95 (s, 1H), 7.68 – 7.55 (m, 4H), 7.34 (d, J = 9.5 Hz, 1H), 7.19 (s, 1H), 6.81 (d, J = 6.8 Hz, 1H), 6.55 – 6.51 (m, 2H), 6.37 (d, J = 9.1 Hz, 1H), 5.15 (s, 1H), 3.30 – 3.29 (m, 3H), 2.20 (s, 3H), 1.60 (d, J = 6.6 Hz, 3H).
88	ES+ 572.1 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.25 (s, 2H), 8.97 (s, 1H), 8.33 (s, 1H), 7.67 (d, J = 2.6 Hz, 1H), 7.59 (s, 1H), 7.38 – 7.30 (m, 2H), 6.86 (d, J = 7.2 Hz, 1H), 6.41 (d, J = 9.2 Hz, 1H), 5.30 – 5.20 (m, 1H), 3.75 (s, 3H), 2.46 (s, 3H), 2.27 (s, 3H), 1.60 (d, J = 6.5 Hz, 3H).
89	ES+ 586.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.95 (s, 2H), 8.93 – 8.88 (m, 1H), 7.86 – 7.80 (m, 1H), 7.56 – 7.49 (m, 1H), 7.41 – 7.33 (m, 1H), 7.26 (s, 1H), 7.24 – 7.15 (m, 1H), 6.58 – 6.50 (m, 1H), 6.48 – 6.40 (m, 1H), 5.61 (d, J = 6.4 Hz, 1H), 5.26 – 5.19 (m, 1H), 2.75 (s, 3H), 2.21 (s, 3H), 1.61 (d, J = 6.5 Hz, 3H).
90	ES+ 568.1 [M+H]	^{1}H NMR (400 MHz, $CDCl_3$): δ 9.12 – 9.05 (m, 1H), 9.01 (s, 2H), 8.56 (d, J = 6.3 Hz, 1H), 7.99 (d, J = 8.0 Hz, 1H), 7.52 – 7.45 (m, 1H), 7.42 – 7.35 (m, 1H), 7.31 – 7.24 (m, 1H), 7.00 – 6.91 (m, 1H), 6.80 (s, 1H), 6.20 – 6.12 (m, 1H), 4.93 – 4.86 (m, 1H), 4.65 (d, J = 3.2 Hz, 1H), 2.92 (s, 3H), 2.41 (s, 3H), 1.73 (d, J = 6.6 Hz, 3H).

91	ES+ 602.0 [M+H]	^{1}H NMR (400 MHz, $CDCl_3$): δ 9.16 – 9.07 (m, 1H), 9.01 (s, 2H), 8.61 (d, J = 2.0 Hz, 1H), 8.08 (d, J = 2.0 Hz, 1H), 7.53 – 7.46 (m, 1H), 7.32 – 7.24 (m, 1H), 7.01 – 6.92 (m, 1H), 6.78 (s, 1H), 6.19 – 6.12 (m, 1H), 4.92 – 4.85 (m, 1H), 4.64 (s, 1H), 2.90 (s, 3H), 2.40 (s, 3H), 1.74 (s, 3H).
92	ES+ 620.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.24 (s, 2H), 9.08 – 8.89 (m, 1H), 8.88 – 8.76 (m, 1H), 7.93 – 7.70 (m, 1H), 7.61 – 7.47 (m, 2H), 7.39 – 7.28 (m, 1H), 6.58 (d, J = 9.1 Hz, 1H), 5.84 (s, 1H), 5.36 – 5.18 (m, 1H), 2.60 (s, 3H), 2.22 (s, 3H), 1.71 – 1.58 (m, 3H).
93	ES+ 602.2 [M+H]	^{1}H NMR (400 MHz, CD_3OD): δ 9.11 – 9.02 (m, 1H), 9.00 (d, J = 2.0 Hz, 1H), 8.72 (d, J = 1.6 Hz, 1H), 7.65 – 7.57 (m, 1H), 7.56 – 7.46 (m, 1H), 7.39 (s, 1H), 7.35 – 7.24 (m, 1H), 7.13 – 6.99 (m, 1H), 6.79 – 6.56 (m, 1H), 6.55 – 6.40 (m, 1H), 5.36 – 5.10 (m, 1H), 3.59 (s, 3H), 2.41 (s, 3H), 1.72 (d, J = 6.4 Hz, 3H).
94	ES+ 651.1 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.95 – 8.88 (m, 1H), 8.17 (d, J = 7.2 Hz, 1H), 7.59 (d, J = 7.1 Hz, 1H), 7.56 – 7.49 (m, 1H), 7.41 – 7.34 (m, 1H), 7.26 – 7.16 (m, 2H), 6.91 (s, 1H), 6.50 – 6.41 (m, 3H), 5.63 – 5.57 (m, 1H), 5.27 – 5.19 (m, 1H), 3.57 (s, 3H), 2.19 (s, 3H), 1.61 (d, J = 6.5 Hz, 3H).
95	ES+ 585.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.97 – 8.88 (m, 1H), 8.46 – 8.33 (m, 2H), 7.58 – 7.48 (m, 1H), 7.42 (d, J = 2.4 Hz, 1H), 7.40 – 7.35 (m, 2H), 7.30 (s, 1H), 7.24 – 7.16 (m, 1H), 6.59 – 6.41 (m, 1H), 5.63 (d, J = 6.5 Hz, 1H), 5.37 – 5.18 (m, 1H), 3.71 (s, 3H), 2.28 (s, 3H), 1.61 (d, J = 6.6 Hz, 3H).
96	ES+ 635.1 [M+H]	^{1}H NMR (400 MHz, CD_3OD): δ 9.11 (d, J = 2.0 Hz, 1H), 7.70 – 7.58 (m, 1H), 7.56 – 7.42 (m, 2H), 7.33 – 7.24 (m, 2H), 7.12 – 7.02 (m,

		1H), 6.62 – 6.55 (m, 2H), 6.49 – 6.27 (m 1H), 5.22 – 5.04 (m, 1H), 3.48 (s, 3H), 2.32 (s, 3H), 1.70 (d, J = 6.5 Hz, 3H).
97	ES+ 618.2 [M+H]	^{1}H NMR (400 MHz, CD_3OD): δ 9.09 – 8.92 (m, 1H), 8.28 (d, J = 2.0 Hz, 1H), 7.87 (d, J = 7.6 Hz, 1H), 7.66 – 7.48 (m, 1H), 7.34 (s, 1H), 7.33 – 7.27 (m, 2H), 7.12 – 6.98 (m, 1H), 6.63 (d, J = 7.2 Hz, 1H), 6.50 – 6.40 (m, 1H), 5.33 – 5.21 (m, 1H), 5.20 – 5.08 (m, 1H), 3.73 (s, 3H), 2.38 (s, 3H), 1.72 (d, J = 6.4 Hz, 3H).
98	ES+ 602.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.25 (s, 2H), 8.99 – 8.92 (m, 1H), 8.85 – 8.78 (m, 1H), 7.82 – 7.75 (m, 1H), 7.60 – 7.45 (m, 2H), 7.43 – 7.33 (m, 2H), 6.51 (d, J = 9.1 Hz, 1H), 5.87 (d, J = 6.6 Hz, 1H), 5.39 – 5.28 (m, 1H), 2.62 (s, 3H), 2.29 (s, 3H), 1.64 (d, J = 6.5 Hz, 3H).
99	ES+ 604.1 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.24 (s, 2H), 9.00 – 8.94 (m, 1H), 8.85 – 8.78 (m, 1H), 7.86 – 7.78 (m, 1H), 7.55 (d, J = 8.6 Hz, 1H), 7.43 – 7.36 (m, 1H), 7.24 – 7.14 (m, 1H), 6.56 (s, 1H), 5.61 (d, J = 6.4 Hz, 1H), 5.27 – 5.18 (m, 1H), 2.60 (s, 3H), 2.21 (s, 3H), 1.63 (d, J = 6.4 Hz, 3H).
100	ES+ 618.1 [M+H]	^{1}H NMR (400 MHz, CD_3OD): δ 9.11 (d, J = 2.0 Hz, 1H), 8.29 (d, J = 2.0 Hz, 1H), 7.57 – 7.48 (m, 2H), 7.39 – 7.19 (m, 3H), 7.13 – 6.87 (m, 1H), 6.70 – 6.58 (m, 1H), 6.52 – 6.28 (m, 1H), 5.28 – 5.08 (m, 2H), 3.49 (s, 3H), 2.38 (s, 3H), 1.71 (d, J = 6.0 Hz, 3H).
101	ES+ 615.0 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.22 (s, 2H), 8.98 – 8.96 (m, 1H), 7.89 (d, J = 7.1 Hz, 1H), 7.49 – 7.46 (m, 1H), 7.35 (s, 1H), 7.19 (d, J = 8.6 Hz, 1H), 6.88 (d, J = 8.7 Hz, 1H), 6.61 (d, J = 7.0 Hz, 1H), 5.83 (d, J = 6.9 Hz, 1H), 5.34 – 5.26 (m, 1H), 3.60 (s, 3H), 2.31 (s, 3H), 2.25 (s, 3H), 1.61 (d, J = 6.6 Hz, 3H).
102	ES+ 601.0 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.96 (s, 1H), 8.44 – 8.36 (m, 2H), 7.47 (d, J = 2.1 Hz, 1H), 7.45 – 7.33 (m, 3H), 7.27 (s, 1H), 7.25 –

		7.17 (m, 1H), 6.52 – 6.44 (m, 1H), 5.64 (d, J = 6.6 Hz, 1H), 5.29 – 5.22 (m, 1H), 3.72 (s, 3H), 2.28 (s, 3H), 1.61 (d, J = 6.5 Hz, 3H).
103	ES+ 572.1 [M+H]	^{1}H NMR (400 MHz, $CDCl_3$): δ 9.17 – 8.98 (m, 1H), 8.70 (s, 1H), 8.60 (s, 1H), 7.90 (d, J = 8.4 Hz, 1H), 7.43 (d, J = 6.4 Hz, 1H), 7.00 – 6.82 (m, 2H), 6.55 (s, 1H), 6.25 – 6.09 (m, 1H), 4.83 – 4.71 (m, 1H), 3.55 – 3.44 (m, 4H), 3.31 – 3.20 (m, 4H), 2.90 (s, 3H), 2.34 (s, 3H), 1.62 (d, J = 6.4 Hz, 3H).
104	ES+ 534.1 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.83 (d, J = 2.1 Hz, 1H), 7.65 (d, J = 2.6 Hz, 1H), 7.44 (d, J = 2.1 Hz, 1H), 7.38 – 7.35 (m, 1H), 6.77 (d, J = 7.0 Hz, 1H), 6.70 (s, 1H), 6.44 (d, J = 9.1 Hz, 1H), 5.18 – 5.13 (m, 1H), 3.32 – 3.14 (m, 8H), 2.96 (s, 3H), 2.16 (s, 3H), 1.61 (d, J = 6.5 Hz, 3H).
105	ES+ 552.1 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.83 – 8.77 (m, 1H), 7.66 (d, J = 2.6 Hz, 1H), 7.39 (s, 1H), 7.43 – 7.31 (m, 1H), 6.80 (s, 1H), 6.50 (d, J = 9.2 Hz, 1H), 5.18 – 5.13 (m, 1H), 3.32 – 3.14 (m, 8H), 2.96 (s, 3H), 2.23 (s, 3H), 1.60 (d, 3H).
106	ES+ 586.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 12.52 – 12.34 (m, 1H), 9.07 (d, J = 1.0 Hz, 2H), 8.90 (d, J = 5.2 Hz, 1H), 8.15 (d, J = 12.5 Hz, 1H), 7.52 (d, J = 8.7 Hz, 1H), 7.34 (d, J = 18.0 Hz, 2H), 7.19 (s, 1H), 6.49 (s, 1H), 5.58 (d, J = 6.4 Hz, 1H), 5.29 (s, 1H), 2.72 (s, 3H), 2.26 (s, 3H), 1.61 (d, J = 6.5 Hz, 3H).
107	ES+ 631.0 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.21 (s, 2H), 8.97 (s, 1H), 8.07 (d, J = 7.0 Hz, 1H), 7.47 (d, J = 2.0 Hz, 1H), 7.31 (s, 1H), 7.29 – 6.97 (m, 2H), 6.88 (d, J = 8.4 Hz, 1H), 6.59 (d, J = 6.8 Hz, 1H), 5.84 (d, J = 6.9 Hz, 1H), 5.32 – 5.24 (m, 1H), 3.56 (s, 3H), 2.32 (s, 3H), 2.27 (s, 3H), 1.62 (d, J = 6.6 Hz, 3H).

108	ES+ 575.1 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.24 (s, 2H), 8.98 (d, J = 2.0 Hz, 1H), 8.84 – 8.77 (m, 1H), 7.80 – 7.74 (m, 1H), 7.69 – 7.66 (m, 1H), 7.60 – 7.50 (m, 1H), 7.39 – 7.35 (m, 1H), 7.33 (d, J = 6.0 Hz, 1H), 6.87 (d, J = 7.2 Hz, 1H), 6.42 (d, J = 9.2 Hz, 1H), 5.32 – 5.20 (m, 1H), 2.62 (s, 3H), 2.28 (s, 3H), 1.61 (d, J = 6.7 Hz, 3H).
109	ES+ 585.0 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.08 (s, 2H), 8.96 (d, J = 2.0 Hz, 1H), 8.40 (d, J = 2.1 Hz, 1H), 7.46 (d, J = 2.0 Hz, 1H), 7.39 – 7.35 (m, 2H), 7.28 (s, 1H), 7.23 – 7.18 (m, 1H), 6.50 – 6.42 (m, 1H), 5.64 (d, J = 6.6 Hz, 1H), 5.28 – 5.25 (m, 1H), 2.73 (s, 3H), 2.29 (s, 3H), 1.61 (d, J = 6.6 Hz, 3H).
110	ES+ 619.1 [M+H]	^{1}H NMR (400 MHz, CD_3OD): δ 9.08 – 8.84 (m, 1H), 7.75 – 7.56 (m, 2H), 7.55 – 7.42 (m, 1H), 7.36 – 7.26 (m, 2H), 7.11 – 7.02 (m, 1H), 6.71 – 6.47 (m, 2H), 6.44 – 6.28 (m, 1H), 5.17 (d, J = 8.0 Hz, 1H), 3.48 (s, 3H), 2.33 (d, J = 1.1 Hz, 3H), 1.83 – 1.62 (m, 3H).
111	ES+ 561.1 [M+H]	^{1}H NMR (400 MHz, $CDCl_3$): δ 8.99 – 8.97 (m, 1H), 7.71 – 7.69 (m, 2H), 7.44 – 7.41 (m, 1H), 6.98 – 6.95 (m, 1H), 6.83 – 6.78 (m, 1H), 6.57 (s, 2H), 6.19 – 6.15 (m, 1H), 4.83 – 4.78 (m, 1H), 3.50 – 3.47 (m, 4H), 3.28 –3.21 (m, 4H), 2.90 (s, 3H), 2.33 (s, 3H), 1.65 (d, J = 6.4 Hz, 3H).
112	ES+ 575.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.23 (s, 2H), 8.96 (d, J = 2.0 Hz, 1H), 7.74 – 7.64 (m, 2H), 7.59 (d, J = 2.0 Hz, 1H), 7.38 – 7.31 (m, 2H), 6.89 – 6.78 (m, 2H), 6.40 (d, J = 9.2 Hz, 1H), 5.30 – 5.22 (m, 1H), 3.57 (s, 3H), 2.26 (s, 3H), 1.59 (d, J = 6.6 Hz, 3H).
113	ES+ 585.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.24 (s, 2H), 8.97 (d, J = 2.1 Hz, 1H), 8.20 (s, 1H), 7.79 (s, 1H), 7.47 (d, J = 2.1 Hz, 1H), 7.39 – 7.34 (m, 1H), 7.33 (s, 1H), 7.20 – 7.18 (m, 1H), 6.55 – 6.51 (m, 1H), 5.60

		(d, J = 6.4 Hz, 1H), 5.27 – 5.23 (m, 1H), 3.62 (s, 3H), 2.27 (s, 3H), 1.61 (d, J = 6.5 Hz, 3H).
114	ES+ 599.1 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.22 (s, 2H), 8.95 (s, 1H), 7.70 (d, J = 7.6 Hz, 1H), 7.47 (s, 1H), 7.32 (s, 1H), 7.18 (d, J = 8.8 Hz, 1H), 6.88 (d, J = 8.8 Hz, 1H), 6.84 – 6.80 (m, 1H), 5.79 (d, J = 6.6 Hz, 1H), 5.31 – 5.22 (m, 1H), 3.58 (s, 3H), 2.31 (s, 3H), 2.26 (s, 3H), 1.61 (d, J = 6.5 Hz, 3H).
115	ES+ 599.2 [M+H]	^{1}H NMR (400 MHz, CD_3OD): δ 9.16 (s, 2H), 9.13 (d, J = 2.0 Hz, 1H), 8.75 – 8.59 (m, 1H), 8.10 – 7.88 (m, 1H), 7.52 (d, J = 1.6 Hz, 1H), 7.30 (s, 1H), 7.15 (d, J = 8.4 Hz, 1H), 6.85 (d, J = 8. Hz, 1H), 5.27 – 5.10 (m, 1H), 2.80 (s, 3H), 2.40 (s, 3H), 2.36 (s, 3H), 1.72 (d, J = 6.4 Hz, 3H).
116	ES+ 602.3 [M+H]	^{1}H NMR (400 MHz, CD_3OD): δ 9.03 (m, , 1H), 8.30 (d, J = 2.0 Hz, 1H), 7.64 – 7.55 (m, 1H), 7.53 – 7.46 (m, 1H), 7.37 – 7.26 (m, 3H), 7.13 – 7.00 (m, 1H), 6.69 – 6.51 (m, 1H), 6.50 – 6.31 (m, 1H), 5.30 – 5.14 (m, 1H), 3.49 (s, 3H), 2.40 (s, 3H), 1.72 (d, J = 6.6 Hz, 3H).
117	ES+ 523.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.80 – 8.73 (m, 1H), 7.43 – 7.32 (m, 2H), 7.27 – 7.19 (m, 1H), 6.73 (s, 1H), 6.55 – 6.48 (m, 1H), 5.50 (d, J = 6.3 Hz, 1H), 5.20 – 5.13 (m, 1H), 4.62 – 4.54 (m, 2H), 4.51 – 4.44 (m, 2H), 3.54 – 3.47 (m, 1H), 3.14 (m, 4H), 2.44 (m, 4H), 2.13 (s, 3H), 1.62 (d, J = 6.5 Hz, 3H).
118	ES+ 541.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.78 – 8.71 (m, 1H), 7.41 – 7.34 (m, 2H), 7.25 – 7.16 (m, 1H), 6.53 (s, 1H), 5.50 (s, 1H), 5.20 – 5.13 (m, 1H), 4.61 – 4.53 (m, 2H), 4.53 – 4.45 (m, 2H), 3.57 – 3.46 (m, 1H), 3.33 (d, J = 1.8 Hz, 4H), 2.43 (d, J = 5.5 Hz, 4H), 2.21 (s, 3H), 1.60 (d, J = 6.4 Hz, 3H).

119	ES+ 571.0 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.19 (s, 2H), 8.97 (d, J = 2.0 Hz, 1H), 7.72 – 7.66 (m, 2H), 7.59 (d, J = 2.1 Hz, 1H), 7.38 – 7.32 (m, 2H), 6.86 (d, J = 7.2 Hz, 1H), 6.62 (d, J = 7.1 Hz, 1H), 6.41 (d, J = 9.2 Hz, 1H), 5.30 – 5.25 (m, 1H), 3.52 (s, 3H), 2.27 (d, J = 1.6 Hz, 6H), 1.60 (d, J = 6.5 Hz, 3H).
120	ES+ 565.2 [M+H]	^{1}H NMR (400 MHz, $CDCl_3$): δ 10.21 (s, 2H), 9.01 (s, 1H), 8.64 (s, 1H), 8.52 (s, 1H), 7.44 (s, 1H), 7.30 – 7.05 (s, 1H), 7.00 – 6.90 (m, 1H), 6.68 (s, 1H), 5.86 – 5.82 (m, 1H), 5.07 – 5.02 (m, 1H), 4.86 – 4.82 (m, 1H), 3.07 (s, 3H), 2.41 – 2.34 (s, 6H), 1.69 (s, 3H).
121	ES+ 565.2 [M+H]	^{1}H NMR (400 MHz, $CDCl_3$): δ 10.34 (s, 2H), 9.01 (s, 1H), 8.66 (s, 1H), 8.54 (d, J = 1.7 Hz, 1H), 7.43 (s, 1H), 7.29 – 7.22 (m, 1H), 6.98 – 6.90 (m, 1H), 6.69 (s, 1H), 6.20 – 6.12 (m, 1H), 4.87 – 4.85 (m, 1H), 4.64 – 4.60 (m, 1H), 3.17 (s, 3H), 2.42 – 2.36 (m, 6H), 1.68 (s, 3H).
122	ES+ 575.3 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.20 (s, 2H), 8.97 (d, J = 2.0 Hz, 1H), 7.66 (d, J = 2.6 Hz, 1H), 7.61 – 7.51 (m, 2H), 7.38 – 7.31 (m, 1H), 7.30 (s, 1H), 6.82 (d, J = 7.2 Hz, 1H), 6.78 – 6.70 (m, 1H), 6.42 (d, J = 9.2 Hz, 1H), 5.29 – 5.21 (m, 1H), 3.65 (s, 3H), 2.27 (s, 3H), 1.61 (d, J = 6.5 Hz, 3H).
123	ES+ 558.1 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.25 (s, 2H), 8.97 (d, J = 2.0 Hz, 1H), 8.21 (s, 1H), 7.79 (s, 1H), 7.67 (d, J = 2.5 Hz, 1H), 7.60 (d, J = 2.1 Hz, 1H), 7.36 –7.32 (m, 1H), 7.32 (s, 1H), 6.86 (d, J = 7.2 Hz, 1H), 6.41 (d, J = 9.2 Hz, 1H), 5.27 – 5.23 (m, 1H), 3.62 (s, 3H), 2.28 (s, 3H), 1.60 (d, J = 6.6 Hz, 3H).
124	ES+ 516.9 [M+H]	^{1}H NMR (400 MHz, CD_3OD): δ 9.12 – 8.87 (m, 1H), 8.06 (d, J = 2.0 Hz, 1H), 7.71 – 7.48 (m, 1H), 7.33 – 7.28 (m, 1H), 7.24 (s, 1H), 7.09 (d, J = 2.0 Hz, 1H), 7.09 – 6.99 (m, 1H), 6.50 – 6.36 (m, 1H), 5.30 –

		5.06 (m, 1H), 4.28 – 4.09 (m, 1H), 2.31 (s, 3H), 1.69 (d, J = 6.4 Hz, 3H), 1.27 – 1.16 (m, 2H), 1.15 – 0.99 (m, 2H).
125	ES+ 542.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.08 (s, 2H), 8.95 – 8.89 (m, 1H), 8.40 (d, J = 2.1 Hz, 1H), 7.71 – 7.64 (m, 2H), 7.39 – 7.33 (m, 2H), 7.29 (s, 1H), 6.84 (d, J = 7.1 Hz, 1H), 6.39 (d, J = 9.2 Hz, 1H), 5.32 – 5.27 (m, 1H), 2.73 (s, 3H), 2.30 (s, 3H), 1.62 (d, J = 6.6 Hz, 3H).
126	ES+ 602.1 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.21 (s, 2H), 8.97 – 8.90 (m, 1H), 8.07 (d, J = 7.1 Hz, 1H), 7.59 – 7.51 (m, 1H), 7.41 – 7.34 (m, 2H), 7.28 – 7.13 (m, 1H), 6.60 (d, J = 7.0 Hz, 1H), 6.53 – 6.45 (m, 1H), 5.63 (d, J = 6.4 Hz, 1H), 5.34 – 5.26 (m, 1H), 3.56 (s, 3H), 2.27 (s, 3H), 1.63 (d, J = 6.5 Hz, 3H).
127	ES+ 618.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.21 (s, 2H), 8.97 – 8.90 (m, 1H), 8.07 (d, J = 7.1 Hz, 1H), 7.59 – 7.51 (m, 1H), 7.41 – 7.34 (m, 2H), 7.28 – 7.13 (m, 2H), 6.60 (d, J = 7.0 Hz, 1H), 6.53 – 6.45 (m, 1H), 5.63 (d, J = 6.4 Hz, 1H), 5.34 – 5.26 (m, 1H), 3.56 (s, 3H), 2.27 (s, 3H), 1.63 (d, J = 6.5 Hz, 3H).
128	ES+ 525.3 [M+H]	^{1}H NMR (400 MHz, $CDCl_3$): δ 9.26 (s, 1H), 9.01 (s, 1H), 8.47 (s, 2H), 7.86 (d, J = 6.0 Hz, 1H), 7.62 – 7.39 (m, 2H), 7.31 (d, J = 4.8 Hz, 1H), 7.08 (d, J = 8.0 Hz, 1H), 6.64 (s, 1H), 6.27 (d, J = 8.0 Hz, 1H), 5.28 – 4.95 (m, 1H), 3.49 – 3.43 (m, 4H), 3.36 – 3.30 (m, 4H), 2.78 (s, 3H), 2.39 (s, 3H), 1.87 (d, J = 6.4 Hz, 3H).
129	ES+ 571.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.21 (s, 2H), 9.01 – 8.94 (m, 1H), 7.73 (d, J = 8.2 Hz, 1H), 7.67 (d, J = 2.6 Hz, 1H), 7.61 – 7.52 (m, 2H), 7.38 – 7.30 (m, 2H), 6.86 (d, J = 7.1 Hz, 1H), 6.41 (d, J = 9.1 Hz, 1H), 5.26 – 5.24 (m, 1H), 2.68 (s, 3H), 2.47 (s, 3H), 2.28 (s, 3H), 1.60 (d, J = 6.5 Hz, 3H).

130	ES+ 574.3 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.85 (s, 2H), 8.81 – 8.74 (m, 1H), 7.79 –7.14 (m, 3H), 6.79 (s, 1H), 6.21 – 6.11 (m, 2H), 5.40 (s, 1H), 5.19 – 5.12 (m, 1H), 3.31 – 3.25 (m, 4H), 2.62 (s, 3H), 2.20 – 2.12 (m, 5H), 1.84 – 1.74 (m, 2H), 1.59 (d, J = 6.5 Hz, 3H).
131	ES+ 577.0 [M+H]	^{1}H NMR (400 MHz, $CDCl_3$): δ 8.91 – 8.90 (m, 1H), 7.42 – 7.40 (m, 1H), 7.30 – 6.93 (m, 2H), 6.02 – 5.94 (m, 1H), 5.20 (s, 1H), 5.01 (s, 1H), 4.26 – 4.19 (m, 1H), 3.69 – 3.65 (m, 2H), 3.53 – 3.50 (m, 1H), 3.38 – 3.30 (m, 1H), 3.24 (d, J = 12.0 Hz, 1H), 3.06 – 3.01 (m, 1H), 2.95 (s, 3H), 2.41 (s, 3H), 1.74 – 1.61 (m, 3H), 1.50 (d, J = 6.8 Hz, 3H).
132	ES+ 559.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.23 (d, J = 1.0 Hz, 2H), 8.96 (s, 1H), 7.73 – 7.67 (m, 1H), 7.62 – 7.48 (m, 2H), 7.34 (s, 1H), 7.26 – 7.18 (m, 1H), 6.85 – 6.80 (m, 1H), 6.64 (d, J = 7.0 Hz, 1H), 6.42 – 6.35 (m, 1H), 5.26 – 5.18 (m, 1H), 3.57 (s, 3H), 2.26 (s, 3H), 1.58 (d, J = 6.4 Hz, 3H).
133	ES+ 564.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.84 (s, 1H), 7.74 (s, 1H), 7.65 (d, J = 2.6 Hz, 1H), 7.44 (d, J = 2.1 Hz, 1H), 7.39 – 7.36 (m, 1H), 7.19 (s, 1H), 6.78 (d, J = 7.1 Hz, 1H), 6.72 (s, 1H), 6.46 (d, J = 9.2 Hz, 1H), 5.22 – 5.17 (m, 1H), 3.46 (s, 3H), 3.29 – 3.26 (m, 4H), 3.25 – 3.13 (m, 4H), 2.18 (s, 3H), 1.62 (d, J = 6.6 Hz, 3H).
134	ES+ 556.1 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.21 (d, J = 3.2 Hz, 3H), 8.97 (d, J = 2.0 Hz, 1H), 7.67 (d, J = 2.6 Hz, 1H), 7.59 (d, J = 2.1 Hz, 1H), 7.39 – 7.31 (m, 1H), 7.32 (s, 1H), 6.86 (d, J = 7.2 Hz, 1H), 6.41 (d, J = 9.1 Hz, 1H), 5.31 – 5.23 (m, 1H), 2.83 (s, 3H), 2.68 (s, 3H), 2.28 (s, 3H), 1.60 (d, J = 6.6 Hz, 3H).
135	ES+ 556.3 [M+H]	^{1}H NMR (400 MHz, $CDCl_3$): δ 9.66 (s, 2H), 9.17 (d, J = 2.0 Hz, 1H), 8.60 (d, J = 7.6 Hz, 1H), 7.46 – 7.42 (m, 1H), 7.35 (s, 1H), 7.24 – 7.16 (m, 1H), 6.57 (d, J = 9.1 Hz, 1H), 6.09 (d, J = 9.0 Hz, 1H), 4.90

		(d, J = 4.4 Hz, 1H), 4.81 – 4.74 (m, 1H), 2.86 (s, 3H), 2.49 (d, J = 7.4 Hz, 3H), 2.17 (d, J = 1.5 Hz, 3H), 1.73 – 1.65 (m, 3H).
136	ES+ 586.1 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.28 (s, 2H), 8.94 – 8.93 (m, 1H), 7.78 – 7.76 (m, 1H), 7.74 – 7.22 (m, 4H), 6.69 – 6.67 (m, 1H), 6.24 (d, J = 6.2 Hz, 1H), 6.12 (d, J = 9.4 Hz, 1H), 5.28 – 5.20 (m, 1H), 3.34 – 3.28 (m, 3H), 2.26 (s, 3H), 1.59 (d, J = 6.5 Hz, 3H).
137	ES+ 586.1 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.28 (s, 2H), 8.94 – 8.92 (m, 1H), 7.79 – 7.77 (m, 1H), 7.63 – 7.55 (m, 1H), 7.43 (s, 1H), 7.38 – 7.35 (m, 1H), 7.21 – 7.18 (m, 1H), 6.69 – 6.67 (m, 1H), 6.49 – 6.47 (m, 1H), 5.63 – 5.62 (m, 1H) , 5.32 – 5.29 (m, 1H), 3.36 – 3.28 (m, 3H), 2.26 (s, 3H), 1.63 (d, 3H).
138	ES+ 581.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.21 (s, 2H), 8.96 (d, J = 2.0 Hz, 1H), 7.61 – 7.54 (m, 1H), 7.47 (d, J = 2.0 Hz, 1H), 7.31 (s, 1H), 7.18 (d, J = 8.7 Hz, 1H), 6.88 (d, J = 8.7 Hz, 1H), 6.71 – 6.65 (m, 1H), 6.63 – 6.59 (m, 1H), 5.79 (d, J = 6.6 Hz, 1H), 5.31 – 5.22 (m, 1H), 3.53 (s, 3H), 2.31 (s, 3H), 2.27 (s, 3H), 1.62 (d, J = 6.6 Hz, 3H).
139	ES+ 569.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.76 (s, 2H), 9.09 (d, J = 1.9 Hz, 1H), 8.94 – 8.91 (m, 1H), 8.71 (d, J = 1.9 Hz, 1H), 7.62 – 7.56 (m, 1H), 7.44 (d, J = 46.6 Hz, 2H), 7.27 (d, J = 9.6 Hz, 1H), 6.26 (d, J = 6.2 Hz, 1H), 6.12 (d, J = 9.4 Hz, 1H), 5.24 – 5.21 (m, 1H), 2.76 (s, 3H), 2.30 (s, 3H), 1.59 (d, J = 6.5 Hz, 3H).
140	ES+ 536.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.22 – 9.18 (s, 3H), 8.84 (s, 1H), 7.66 (d, J = 2.6 Hz, 1H), 7.50 (d, J = 1.7 Hz, 1H), 7.41 – 7.29 (m, 1H), 7.20 (s, 1H), 6.78 (d, J = 6.8 Hz, 1H), 6.40 (d, J = 9.2 Hz, 1H), 5.35 – 5.03 (m, 1H), 2.83 (s, 3H), 2.69 (s, 3H), 2.33 (s, 3H), 2.26 (s, 3H), 1.60 (d, J = 6.5 Hz, 3H).

141	ES+ 577.1 [M+H]	^{1}H NMR (400 MHz, CD_3OD): δ 9.68 (s, 2H), 9.06 – 9.04 (m, 1H), 8.78 (d, J = 7.1 Hz, 1H), 7.61 – 7.58 (m, 1H), 7.56 – 7.52 (m, 1H), 7.27 (s, 1H), 7.23 – 7.11 (m, 1H), 6.46 (d, J = 4.1 Hz, 1H), 6.44 (d, J = 4.0 Hz, 1H), 5.22 – 5.02 (m, 1H), 3.26 (d, J = 2.8 Hz, 3H), 2.83 (s, 3H), 2.55 (d, J = 10.0 Hz, 3H), 2.18 (d, J = 1.5 Hz, 3H), 1.74 – 1.68 (m, 3H).
142	ES+ 489.0 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.69 (s, 1H), 7.65 (d, J = 2.6 Hz, 1H), 7.36 – 7.30 (m, 1H), 7.32 (d, J = 1.7 Hz, 1H), 6.70 (d, J = 6.8 Hz, 1H), 6.46 (s, 1H), 6.40 (d, J = 9.2 Hz, 1H), 5.16 – 5.10 (m, 1H), 4.58 – 4.55 (m, 2H), 4.50 – 4.45 (m, 2H), 3.78 – 3.75 (m, 1H), 3.14 – 3.10 (m, 2H), 2.46 – 2.40 (m, 2H), 2.38 – 2.35 (m, 1H), 2.30 (s, 3H), 2.25 (d, J = 1.3 Hz, 3H), 2.01 – 1.99 (m, 1H), 1.94 – 1.90 (m, 1H), 1.56 (d, J = 6.6 Hz, 3H).
143	ES+ 511.1 [M+H]	^{1}H NMR (400 MHz, CD_3OD): δ 8.84 (s, 1H), 7.50 (d, J = 2.6 Hz, 1H), 7.43 (d, J = 1.6 Hz, 1H), 7.28 – 7.25 (m, 1H), 6.75 (s, 1H), 6.43 (d, J = 9.1 Hz, 1H), 5.19 – 5.10 (m, 1H), 3.75 – 3.70 (m, 2H), 3.59 – 3.51 (m, 2H), 2.97 (s, 3H), 2.44 (s, 3H), 2.34 (d, J = 1.2 Hz, 3H), 2.24 – 2.20 (m, 1H), 2.19 – 2.11 (m, 2H), 1.70 (d, J = 6.7 Hz, 3H).
144	ES+ 565.3 [M+H]	^{1}H NMR (400 MHz, $CDCl_3$): δ 8.99 (s, 1H), 8.96 (s, 2H), 8.81 (d, J = 2.0 Hz, 1H), 8.02 (d, J = 2.0 Hz, 1H), 7.39 (s, 1H), 7.23 – 6.82 (m, 2H), 6.68 (s, 1H), 5.90 – 5.65 (m, 1H), 4.90 – 4.72 (m, 1H), 3.90 (s, 3H), 2.36 (s, 3H), 2.35 (s, 3H), 1.68 (d, J = 6.4 Hz, 3H).
145	ES+ 565.2 [M+H]	^{1}H NMR (400 MHz, $CDCl_3$): δ 9.01 (s, 1H), 8.98 (s, 2H), 8.83 (d, J = 2.0 Hz, 1H), 8.04 (d, J = 2.0 Hz, 1H), 7.39 (s, 1H), 7.29 – 7.22 (m, 1H), 6.99 – 6.89 (m, 1H), 6.70 (s, 1H), 6.22 – 6.08 (m, 1H), 4.90 – 4.81 (m, 1H), 4.62 (s, 1H), 3.92 (s, 3H), 2.37 (s, 6H), 1.69 (d, J = 6.4 Hz, 3H).

146	ES+ 573.3 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.24 – 9.20 (m, 3H), 8.84 (s, 1H), 7.48 – 7.44 (m, 1H), 7.41 (d, J = 1.7 Hz, 1H), 7.32 – 7.25 (m, 1H), 7.21 (s, 1H), 6.51 (d, J = 5.5 Hz, 1H), 6.48 – 6.43 (m, 1H), 5.28 – 5.20 (m, 1H), 3.33 (s, 3H), 2.83 (s, 3H), 2.68 (s, 3H), 2.32 (d, J = 1.4 Hz, 3H), 2.26 (s, 3H), 1.60 (d, J = 6.4 Hz, 3H).
147	ES+ 573.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.18 (s, 2H), 8.83 (s, 1H), 7.73 – 7.62 (m, 3H), 7.56 – 7.47 (m, 1H), 7.37 – 7.29 (m, 1H), 7.18 (s, 1H), 6.82 – 6.75 (m, 2H), 6.70 (d, J = 9.3 Hz, 1H), 6.38 (d, J = 9.2 Hz, 1H), 5.27 – 5.19 (m, 1H), 2.34 – 2.30 (m, 3H), 2.23 (s, 3H), 1.60 (d, J = 6.5 Hz, 3H).
148	ES+ 573.2 [M+H]	^{1}H NMR (400 MHz, CD_3OD): δ 9.68 (s, 2H), 8.98 (s, 1H), 8.76 (d, J = 7.7 Hz, 1H), 7.55 – 7.47 (m, 2H), 7.19 – 7.09 (m, 2H), 6.50 – 6.41 (m, 1H), 5.19 – 5.09 (m, 1H), 3.23 (d, J = 3.6 Hz, 3H), 2.82 (s, 3H), 2.54 (d, J = 9.8 Hz, 3H), 2.42 – 2.36 (m, 3H), 2.16 (s, 3H), 1.72 – 1.64 (m, 3H).
149	ES+ 577.1 [M+H]	^{1}H NMR (400 MHz, CD_3OD): δ 9.28 (s, 1H), 9.13 (s, 2H), 9.07 – 9.00 (m, 1H), 7.63 – 7.57 (m, 1H), 7.56 – 7.50 (m, 1H), 7.35 (s, 1H), 7.20 – 7.11 (m, 1H), 6.51 – 6.43 (m, 1H), 5.26 – 5.18 (m, 1H), 3.26 (s, 3H), 2.92 (s, 3H), 2.77 (s, 3H), 2.37 (s, 3H), 1.73 (d, J = 6.6 Hz, 3H).
150	ES+ 555.2 [M+H]	^{1}H NMR (400 MHz, CD_3OD): δ 9.14 (s, 2H), 8.97 (s, 1H), 8.66 – 8.65 (m, 1H), 8.04 – 8.01 (m, 1H), 7.55 (d, J = 1.7 Hz, 1H), 7.49 (d, J = 2.5 Hz, 1H), 7.27 – 7.22 (m, 2H), 6.43 (d, J = 9.1 Hz, 1H), 5.26 – 5.21 (m, 1H), 2.80 – 2.77 (m, 3H), 2.41 (d, J = 1.3 Hz, 3H), 2.35 (s, 3H), 1.72 (d, J = 6.7 Hz, 3H).
151	ES+ 513.1 [M+H]	^{1}H NMR (400 MHz, $CDCl_3$): δ 8.89 (s, 1H), 7.19 (d, J = 1.7 Hz, 1H), 6.99 (d, J = 8.5 Hz, 1H), 6.50 (d, J = 8.6 Hz, 1H), 6.37 (s, 1H), 4.84 – 4.69 (m, 6H), 4.01 (s, 1H), 3.40 (s, 2H), 2.75 (s, 2H), 2.71 (s, 1H),

		2.49 (s, 3H), 2.45(s, 3H), 2.29 (s, 3H), 1.91 (d, J = 16.0 Hz, 2H), 1.68 (d, J = 6.5 Hz, 3H).
152	ES+ 535.1 [M+H]	^{1}H NMR (400 MHz, $CDCl_3$): δ 8.90 (s, 1H), 7.22 (d, J = 1.7 Hz, 1H), 7.00 (d, J = 8.5 Hz, 1H), 6.50 (d, J = 8.5 Hz, 1H), 6.39 (s, 1H), 4.85 – 4.78 (m, 1H), 4.72 (s, 1H), 3.89 – 3.81 (m, 2H), 3.56 – 3.48 (m, 2H), 2.93 (s, 3H), 2.46 (s, 3H), 2.45 (s, 3H), 2.30 (s, 3H), 2.28 – 2.23 (m, 1H), 2.06 – 1.91 (m, 2H), 1.68 (d, J = 8.0 Hz, 3H).
153	ES+ 587.1 [M+H]	^{1}H NMR (400 MHz, $CDCl_3$): δ 9.00 (d, J = 12.2 Hz, 2H), 7.75 – 7.65 (m, 1H), 7.58 (d, J = 6.6 Hz, 1H), 7.51 (s, 1H), 7.45 (d, J = 2.0 Hz, 1H), 7.35 (s, 1H), 7.20 – 7.15 (m, 1H), 7.03 (s, 1H), 6.70 (s, 1H), 6.65 – 6.60 (m, 1H), 6.15 (s, 1H), 4.96 – 4.91 (m, 1H), 3.69 (s, 3H), 2.38 (d, J = 8.3 Hz, 6H), 1.73 (s, 3H).
154	ES+ 551.0 [M+H]	^{1}H NMR (400 MHz, $CDCl_3$): δ 9.01 (s, 1H), 8.96 (s, 2H), 7.45 (d, J = 2.5 Hz, 1H), 7.40 – 7.32 (m, 2H), 7.24 – 7.16 (m, 1H), 6.74 (d, J = 7.0 Hz, 1H), 6.66 (s, 1H), 6.15 (d, J = 9.0 Hz, 1H), 4.96 (d, J = 4.6 Hz, 1H), 4.93 – 4.86 (m, 1H), 3.77 (s, 3H), 2.44 – 2.36 (m, 6H), 2.31 – 2.18 (m, 3H), 1.74 (d, J = 6.6 Hz, 3H).
155	ES+ 569.2 [M+H]	^{1}H NMR (400 MHz, CD_3OD): δ 9.15 (s, 2H), 9.08 – 8.98 (m, 1H), 8.24 (s, 1H), 7.94 (s, 1H), 7.65 – 7.55 (m, 1H), 7.40 – 6.97 (m, 3H), 6.12 (d, J = 9.2 Hz, 1H), 5.27 – 5.12 (m, 1H), 3.79 (s, 3H), 2.37 (s, 3H), 1.70 (d, J = 6.8 Hz, 3H).
156	ES+ 559.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.19 (s, 2H), 8.86 (s, 1H), 8.41 – 7.89 (m, 1H), 7.75 – 7.51 (m, 1H), 7.47 (d, J = 1.7 Hz, 1H), 7.19 (s, 1H), 7.12 – 7.05 (m, 1H), 6.79 – 6.65 (m, 1H), 6.64 – 6.48 (m, 1H), 6.25 (d, J = 6.0 Hz, 1H), 5.40 – 5.03 (m, 1H), 4.98 (d, J = 8.0 Hz, 1H), 3.53 (s, 3H), 2.36 (d, J = 1.2 Hz, 3H), 2.25 (s, 3H), 1.83 – 1.78 (m, 3H), 1.60 (d, J = 6.6 Hz, 3H).

157	ES+ 545.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.19 (s, 2H), 8.86 (s, 1H), 8.16 (s, 1H), 7.59 – 7.55 (m, 1H), 7.48 (d, J = 1.7 Hz, 1H), 7.23 – 7.15 (m, 2H), 6.70 – 6.66 (m, 1H), 6.64 – 6.60 (m, 1H), 6.55 – 6.48 (d, J = 4.0 Hz, 1H), 5.63 (d, J = 9.0 Hz, 1H), 5.23 – 5.18 (m, 1H), 5.06 (d, J = 8.0 Hz, 1H), 3.53 (s, 3H), 2.36 (d, J = 1.2 Hz, 3H), 2.25 (s, 3H), 1.61 (d, J = 6.7 Hz, 3H).
158	ES+ 559.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.20 (s, 2H), 8.83 (s, 1H), 7.88 – 7.56 (m, 2H), 7.52 – 7.43 (m, 1H), 7.22 (s, 1H), 6.74 (d, J = 8.0 Hz, 1H), 6.69 – 6.67 (m, 1H), 6.63 – 6.60 (m, 1H), 6.56 (d, J = 8.0 Hz, 1H), 5.87 (d, J = 7.1 Hz, 1H), 5.14 – 5.08 (m, 1H), 3.53 (s, 3H), 2.31 (d, J = 1.2 Hz, 3H), 2.25 (s, 3H), 2.22 (s, 3H), 1.58 (d, J = 6.5 Hz, 3H).
159	ES+ 538.1 [M+H]	^{1}H NMR (400 MHz, CD_3OD): δ 9.12 (s, 2H), 8.97 (s, 1 H), 8.93 (d, J = 2.0 Hz, 1H), 7.98 (d, J = 2.0 Hz, 1H), 7.55 (s, 1H), 7.49 (d, J = 2.8 Hz, 1H), 7.30 – 7.23 (m, 1H), 7.21 (s, 1H), 6.42 (d, J = 9.2 Hz, 1H), 5.28 – 5.18 (m, 1H), 3.89 (s, 3H), 2.41 (s, 3H), 2.33 (s, 3H), 1.72 (d, J = 6.8 Hz, 3H).
160	ES+ 538.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.07 (s, 2H), 8.83 (s, 1H), 8.39 (d, J = 2.1 Hz, 1H), 7.66 (d, J = 2.6 Hz, 1H), 7.50 (d, J = 1.7 Hz, 1H), 7.36 – 7.31 (m, 2H), 7.13 (s, 1H), 6.37 (d, J = 9.2 Hz, 1H), 5.21 (d, J = 6.7 Hz, 1H), 2.72 (s, 3H), 2.32 (d, J = 1.3 Hz, 3H), 2.27 (s, 3H), 1.59 (d, J = 6.5 Hz, 3H).
161	ES+ 571.1 [M+H]	^{1}H NMR (400 MHz, $CDCl_3$): δ 9.01 (s, 3H), 7.45 (d, J = 2.0 Hz, 1H), 7.41 (d, J = 7.2 Hz, 1H), 7.34 (s, 1H), 7.23 – 7.18 (m, 1H), 6.71 – 6.65 (m, 2H), 6.14 (d, J = 9.2 Hz, 1H), 5.01 – 4.83 (m, 2H), 3.73 (s, 3H), 2.39 (s, 6H), 1.74 (d, J = 6.4 Hz, 3H).
162	ES+ 535.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.18 (s, 2H), 8.85 – 8.80 (m, 1H), 7.54 – 7.44 (m, 3H), 7.26 – 7.17 (m, 2H), 6.66 (d, J = 7.0 Hz, 1H), 6.54 (d, J = 6.8 Hz, 1H), 6.41 – 6.34 (m, 1H), 5.25 – 5.14 (m, 1H),

		3.57 (s, 3H), 2.32 (d, J = 1.3 Hz, 3H), 2.25 (s, 3H), 2.18 – 2.05 (m, 3H), 1.59 (d, J = 6.5 Hz, 3H).
163	ES+ 555.3 [M+H]	^{1}H NMR (400 MHz, $CDCl_3$): δ 9.14 (s, 2H), 8.97 (s, 1H), 7.81 (d, J = 7.2 Hz, 1H), 7.52 – 7.36 (m, 2H), 7.25 – 7.13 (m, 1H), 7.12 – 6.99 (m, 1H), 6.76 (d, J = 6.8 Hz, 1H), 6.50 – 6.40 (m, 1H), 5.26 – 5.18 (m, 2H), 3.73 (s, 3H), 2.41 (s, 3H), 2.36 (s, 3H), 1.72 (d, J = 6.4 Hz, 3H).
164	ES+ 595.1 [M+H]	^{1}H NMR (400 MHz, $CDCl_3$): δ 9.02 (s, 2H), 9.00 (s, 1H), 7.42 (d, J = 6.8 Hz, 1H), 7.36 (s, 1H), 7.03 – 6.98 (m, 1H), 6.73 – 6.65 (m, 2H), 6.52 (d, J = 8.4 Hz, 1H), 4.97 – 4.68 (m, 2H), 3.73 (s, 3H), 2.46 (s, 3H), 2.39 (s, 3H), 2.37 (s, 3H), 1.72 (d, J = 6.4 Hz, 3H).
165	ES+ 583.1 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.25 (s, 2H), 8.94 – 8.92 (m, 1H), 8.82 – 8.80 (m, 1H), 7.80 – 7.77 (m, 1H), 7.58 – 7.55 (m, 1H), 7.38 (s, 1H), 7.19 (d, J = 8.6 Hz, 1H), 6.87 (d, J = 8.7 Hz, 1H), 5.83 (d, J = 6.7 Hz, 1H), 5.33 – 5.30 (m, 1H), 2.62 (s, 3H), 2.30 (d, J = 13.0 Hz, 6H), 1.63 (d, J = 6.5 Hz, 3H).
166	ES+ 555.1 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.22 (s, 2H), 8.83 (s, 1H), 7.74 – 7.67 (m, 1H), 7.65 (d, J = 2.6 Hz, 1H), 7.50 (s, 1H), 7.35 – 7.29 (m, 1H), 7.22 (s, 1H), 6.86 – 6.75 (m, 2H), 6.37 (d, J = 9.2 Hz, 1H), 5.21 (d, J = 6.8 Hz, 1H), 3.57 (s, 3H), 2.32 (d, J = 1.2 Hz, 3H), 2.24 (s, 3H), 1.59 (d, J = 6.5 Hz, 3H).
167	ES+ 555.1 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.27 (s, 2H), 8.84 (s, 1H), 7.81 – 7.72 (m, 1H), 7.65 (d, J = 2.6 Hz, 1H), 7.51 (d, J = 1.7 Hz, 1H), 7.37 – 7.29 (m, 1H), 7.25 (s, 1H), 6.79 (d, J = 6.8 Hz, 1H), 6.72 – 6.63 (m, 1H), 6.38 (d, J = 9.2 Hz, 1H), 5.28 – 5.20 (m, 1H), 3.28 (s, 3H), 2.32 (d, J = 1.4 Hz, 3H), 2.24 (s, 3H), 1.61 (d, J = 6.6 Hz, 3H).

168	ES+ 565.1 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.21 (s, 2H), 8.92 – 8.90 (m, 1H), 7.59 – 7.57 (m, 2H), 7.36 (s, 1H), 7.18 (d, J = 8.4 Hz, 1H), 6.87 (d, J = 8.7 Hz, 1H), 6.68 – 6.66 (m, 1H), 6.62 – 6.59 (m, 1H), 5.79 (d, J = 6.6 Hz, 1H), 5.31 – 5.28 (m, 1H), 3.53 (s, 3H), 2.30 – 2.27 (m, 6H), 1.63 (d, J = 6.5 Hz, 3H).
169	ES+ 586.1 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.23 (s, 2H), 8.94 – 8.89 (m, 1H), 7.74 – 7.67 (m, 1H), 7.58 – 7.51 (m, 1H), 7.43 – 7.33 (m, 2H), 7.25 – 7.15 (m, 1H), 6.87 – 6.79 (m, 1H), 6.50 – 6.42 (m, 1H), 5.63 (d, J = 6.5 Hz, 1H), 5.34 – 5.26 (m, 1H), 3.58 (s, 3H), 2.26 (s, 3H), 1.61 (d, J = 6.5 Hz, 3H).
170	ES+ 586.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.23 (s, 2H), 8.94 – 8.89 (m, 1H), 7.71 (d, J = 5.9 Hz, 1H), 7.61 – 7.55 (m, 1H), 7.49 – 7.34 (m, 2H), 7.26 (d, J = 9.7 Hz, 1H), 6.86 – 6.80 (m, 1H), 6.25 (d, J = 6.2 Hz, 1H), 6.11 (d, J = 9.3 Hz, 1H), 5.24 (d, J = 6.4 Hz, 1H), 3.58 (s, 3H), 2.26 (s, 3H), 1.57 (d, J = 6.5 Hz, 3H).
171	ES= 538.2 [M+H]	^{1}H NMR (400 MHz, CD3CN) δ 9.03 (s, 2H), 8.88 (s, 1H), 8.12 (s, 1H), 7.74 (s, 1H), 7.51 (d, J = 2.6 Hz, 1H), 7.44 (s, 1H), 7.22 –7.19 (m, 1H), 6.90 (s, 1H), 6.32 (d, J = 9.0 Hz, 1H), 5.42 (d, J = 5.6 Hz, 1H), 5.18 – 4.79 (m, 1H), 3.63 (s, 3H), 2.32 (s, 3H), 2.28 (s, 3H), 1.65 (d, J = 6.6 Hz, 3H).
172	ES+ 552.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.21 (s, 2H), 8.83 (s, 1H), 7.70 – 7.63 (m, 2H), 7.50 (s, 1H), 7.35 –7.32 (m, 1H), 7.20 (s, 1H), 6.79 (d, J = 6.7 Hz, 1H), 6.38 (d, J = 9.1 Hz, 1H), 5.25 – 5.18 (m, 1H), 3.64 (s, 3H), 2.41 (s, 3H), 2.32 (s, 3H), 2.25 (s, 3H), 1.59 (d, J = 6.5 Hz, 3H).
173	ES+ 551.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.17 (s, 2H), 8.83 (s, 1H), 7.69 (d, J = 7.1 Hz, 1H), 7.65 (d, J = 2.6 Hz, 1H), 7.49 (s, 1H), 7.36 – 7.30 (m, 1H), 7.20 (s, 1H), 6.77 (d, J = 6.8 Hz, 1H), 6.62 (d, J = 7.1 Hz, 1H),

		6.39 (d, J = 9.2 Hz, 1H), 5.26 – 5.19 (m, 1H), 3.52 (s, 3H), 2.32 (d, J = 1.2 Hz, 3H), 2.25 (d, J = 9.2 Hz, 6H), 1.59 (d, J = 6.6 Hz, 3H).
174	ES+ 535.3 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.17 (s, 2H), 8.83 (s, 1H), 7.69 (d, J = 7.0 Hz, 1H), 7.53 – 7.46 (m, 2H), 7.26 – 7.16 (m, 2H), 6.61 (d, J = 7.1 Hz, 1H), 6.53 (d, J = 6.8 Hz, 1H), 6. 42 – 6.33 (m, 1H), 5.24 – 5.16 (m, 1H), 3.52 (s, 3H), 2.32 (d, J = 1.3 Hz, 3H), 2.26 (s, 3H), 2.24 (s, 3H), 1.59 (d, J = 6.6 Hz, 3H).
175	ES+ 539.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.27 (s, 2H), 8.84 (s, 1H), 7.81 – 7.72 (m, 1H), 7.55 – 7.47 (m, 2H), 7.26 (s, 1H), 7.25– 7.17 (m, 1H), 6.71 – 6.63 (m, 1H), 6.56 (d, J = 6.7 Hz, 1H), 6.41 – 6.33 (m, 1H), 5.24 – 5.15 (m, 1H), 3.28 (s, 3H), 2.32 (d, J = 1.3 Hz, 3H), 2.24 (s, 3H), 1.60 (d, J = 6.5 Hz, 3H).
176	ES+ 539.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.21 (s, 2H), 8.83 (s, 1H), 7.74 – 7.67 (m, 1H), 7.54 – 7.46 (m, 2H), 7.26 – 7.16 (m, 2H) 6.86 – 6.79 (m, 1H), 6.54 (d, J = 6.7 Hz, 1H), 6.41 – 6.33 (m, 1H), 5.23 – 5.14 (m, 1H), 3.58 (s, 3H), 2.32 (d, J = 1.2 Hz, 3H), 2.24 (s, 3H), 1.58 (d, J = 6.6 Hz, 3H).
177	ES+ 582.1 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.22 (s, 2H), 8.83 (s, 1H), 7.74 – 7.67 (m, 1H), 7.42 – 7.31 (m, 2H), 7.27 – 7.14 (m, 2H), 6.86 – 6.79 (m, 1H), 6.50 – 6.42 (m, 1H), 5.50 (d, J = 6.2 Hz, 1H), 5.27 – 5.20 (m, 1H), 3.58 (s, 3H), 2.30 (d, J = 1.3 Hz, 3H), 2.24 (s, 3H), 1.59 (d, J = 6.5 Hz, 3H).
178	ES+ 582.3 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.21 (s, 2H), 8.83 (s, 1H), 7.74 – 7.67 (m, 1H), 7.63 – 7.38 (m, 2H), 7.37 – 7.20 (m, 2H), 6.86 – 6.80 (m, 1H), 6.18 (d, J = 6.2 Hz, 1H), 6.11 (d, J = 9.4 Hz, 1H), 5.21 – 5.13 (m, 1H), 3.58 (s, 3H), 2.31 (d, J = 1.2 Hz, 3H), 2.24 (s, 3H), 1.55 (d, J = 6.5 Hz, 3H).

179	ES+ 537.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.20 (s, 2H), 8.84 (s, 1H), 7.65 (d, J = 2.6 Hz, 1H), 7.60 – 7.56 (m, 1H), 7.50 (d, J = 1.6 Hz, 1H), 7.36 – 7.33 (m, 1H), 7.21 (s, 1H), 6.78 (d, J = 6.7 Hz, 1H), 6.71 – 6.62 (m, 1H), 6.61 – 6.51 (m, 1H), 6.39 (d, J = 9.2 Hz, 1H), 5.33 – 5.05 (m, 1H), 3.53 (s, 3H), 2.33 (s, 3H), 2.25 (s, 3H), 1.61 (d, J = 6.5 Hz, 3H).
180	ES+ 555.1 [M+H]	^{1}H NMR (400 MHz, $CDCl_3$): δ 9.01 (s, 1H), 8.96 (s, 2H), 7.45 (d, J = 2.5 Hz, 1H), 7.35 (d, J = 1.7 Hz, 1H), 7.29 – 7.16 (m, 2H), 6.83 – 6.75 (m, 1H), 6.66 (s, 1H), 6.15 (d, J = 9.0 Hz, 1H), 4.98 (d, J = 4.7 Hz, 1H), 4.95 – 4.85 (m, 1H), 3.83 (s, 3H), 2.42 – 2.35 (m, 6H), 1.74 (d, J = 6.6 Hz, 3H).
181	ES+ 551.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.20 (s, 2H), 8.84 (s, 1H), 7.73 (d, J = 8.4 Hz, 1H), 7.66 (d, J = 2.4 Hz, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.50 (d, J = 1.6 Hz, 1H), 7.41 – 7.29 (m, 1H), 7.21 (s, 1H), 6.78 (d, J = 6.8 Hz, 1H), 6.40 (d, J = 9.2 Hz, 1H), 5.34 – 5.11 (m, 1H), 2.69 (s, 3H), 2.48 (s, 3H), 2.33 (s, 3H), 2.26 (s, 3H), 1.60 (d, J = 6.8 Hz, 3H).
182	ES+ 544.2 [M+H]	^{1}H NMR (400 MHz, CD_3OD): δ 9.68 (s, 2H), 9.00 (s, 1H), 8.75 (d, J = 7.7 Hz, 1H), 8.36 – 8.10 (m, 1H), 7.56 (d, J = 5.9 Hz, 1H), 7.26 – 7.21 (m, 1H), 7.11 (d, J = 2.2 Hz, 1H), 5.77 – 5.74 (m, 1H), 5.19 – 5.15 (m, 2H), 2.83 (s, 3H), 2.54 – 2.44 (m, 6H), 2.16 (d, J = 1.3 Hz, 3H), 1.72 – 1.69 (m, 3H).
183	ES+ 558.2 [M+H]	^{1}H NMR (400 MHz, CD_3OD): δ 9.68 (s, 2H), 8.99 (s, 1H), 8.74 (d, J = 5.5 Hz, 1H), 8.39 – 8.09 (m, 1H), 7.59 – 7.52 (m, 1H), 7.10 (d, J = 7.5 Hz, 2H), 5.11 – 5.04 (m, 2H), 2.82 (s, 3H), 2.57 – 2.44 (m, 6H), 2.16 (d, J = 1.3 Hz, 3H), 1.91 (d, J = 3.1 Hz, 3H), 1.72 – 1.64 (m, 3H).
184	ES+ 492.2 [M+H]	^{1}H NMR (400 MHz, $CDCl_3$): δ 8.90 (s, 1H), 7.44 (d, J = 2.5 Hz, 1H), 7.25 – 7.18 (m, 2H), 6.42 (s, 1H), 6.18 (d, J = 9.0 Hz, 1H), 4.94 (d, J = 4.9 Hz, 1H), 4.88 – 4.79 (m, 1H), 4.75 (d, J = 6.5 Hz, 4H), 3.74 – 3.66

		(m, 1H), 3.27 – 3.20 (m, J = 4.7 Hz, 4H), 2.65 (m, 4H), 2.33 – 2.27 (m, 6H), 1.71 (d, J = 6.6 Hz, 3H).
185	ES+ 536.1 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.58 (s, 2H), 8.83 (d, J = 4.8, 2H), 7.64 – 7.63 (m, 1H), 7.49 (d, J = 9.6 Hz, 1H), 7.33 – 7.30 (m, 1H), 7.10 (d, J = 7.2 Hz, 1H), 6.80 – 6.73 (m, 1H), 6.38 – 6.34 (m, 1H), 5.14 – 5.11 (m, 1H), 2.75 (s, 3H), 2.46 (s, 3H), 2.33 (s, 3H), 2.05 (s, 3H), 1.57 – 1.54 (m, 3H).
186	ES+ 520.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.58 (s, 2H), 8.86 – 8.80 (m, 2H), 7.54 – 7.45 (m, 2H), 7.24 – 7.21 (m, 1H), 7.11 (d, J = 6.4 Hz, 1H), 6.53 (d, J = 6.8 Hz, 1H), 6.41 – 6.37 (m, 1H), 5.12 – 5.10 (m, 1H), 2.75 (s, 3H), 2.46 (s, 3H), 2.33 (s, 3H), 2.05 (s, 3H), 1.56 – 1.54 (d, J = 6.4, 3H).
187	ES+ 569.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.08 (s, 2H), 8.94 – 8.92 (m, 1H), 8.40 (d, J = 2.1 Hz, 1H), 7.55 – 7.53 (m, 1H), 7.44 – 7.31 (m, 3H), 7.24 – 7.18 (m, 1H), 6.50 – 6.47 (m, 1H), 5.63 (d, J = 6.4 Hz, 1H), 5.32 – 5.28 (m, 1H), 2.73 (s, 3H), 2.30 (s, 3H), 1.62 (d, J = 6.5 Hz, 3H).
188	ES+ 582.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.20 (s, 2H), 8.96 – 8.89 (m, 1H), 7.73 (d, J = 8.1 Hz, 1H), 7.63 – 7.53 (m, 3H), 7.36 (d, J = 10.1 Hz, 1H), 7.32 – 7.21 (m, 1H), 6.25 (d, J = 6.2 Hz, 1H), 6.13 (d, J = 9.6 Hz, 1H), 5.28 – 5.20 (m, 1H), 2.68 (s, 3H), 2.50 – 2.45 (m, 3H), 2.28 (s, 3H), 1.58 (d, J = 6.5 Hz, 3H).
189	ES+ 582.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.21 (s, 2H), 8.96 – 8.89 (m, 1H), 7.73 (d, J = 8.1 Hz, 1H), 7.60 – 7.51 (m, 2H), 7.42 – 7.33 (m, 2H), 7.25 – 7.16 (m, 1H), 6.53 – 6.45 (m, 1H), 5.63 (d, J = 6.5 Hz, 1H), 5.36 – 5.26 (m, 1H), 2.68 (s, 3H), 2.50 – 2.46 (m, 3H), 2.28 (s, 3H), 1.62 (d, J = 6.5 Hz, 3H).

190	ES+ 586.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.24 (s, 2H), 8.93 – 8.91 (m, 1H), 8.81 – 8.80 (m, 1H), 7.78 – 7.76 (m, 1H), 7.63 – 7.54 (m, 1H), 7.48 – 7.36 (m, 2H), 7.27 – 7.22 (m, 1H), 6.25 (d, J = 6.2 Hz, 1H), 6.16 – 6.09 (m, 1H), 5.24 – 5.21 (m, 1H), 2.61 (d, J = 1.1 Hz, 3H), 2.27 (s, 3H), 1.58 (d, J = 6.6 Hz, 3H).
191	ES+ 586.3 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.25 (s, 2H), 8.93 – 8.92 (m, 1H), 8.81 – 8.80 (m, 1H), 7.78 – 7.56 (m, 1H), 7.55 – 7.53 (m, 1H), 7.42 – 7.34 (m, 2H), 7.21 – 7.19 (m, 1H), 6.49 – 6.47 (m, 1H), 5.63 (d, J = 6.4 Hz, 1H), 5.31 – 5.29 (m, 1H), 2.62 (s, 3H), 2.28 (s, 3H), 1.63 (d, J = 6.5 Hz, 3H).
192	ES+ 611.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.20 (s, 2H), 8.83 (s, 1H), 8.07 (d, J = 7.0 Hz, 1H), 7.41 (d, J = 1.7 Hz, 1H), 7.22 – 7.11 (m, 3H), 6.85 (d, J = 8.7 Hz, 1H), 6.60 (d, J = 7.0 Hz, 1H), 5.70 (d, J = 6.5 Hz, 1H), 5.28 – 5.20 (m, 1H), 3.56 (s, 3H), 2.30 (s, 6H), 2.25 (s, 3H), 1.64 – 1.58 (m, 3H).
193	ES+ 583.2 [M+H]	^{1}H NMR (400 MHz, CD_3OD): δ 9.14 (s, 2H), 9.08 – 8.95 (m, 1H), 7.82 (s, 1H), 7.65 – 7.50 (m, 1H), 7.45 – 7.03 (m, 3H), 6.18 – 6.09 (m, 1H), 5.32 – 5.12 (m, 1H), 3.79 (s, 3H), 2.53 (s, 3H), 2.37 (s, 3H), 1.70 (d, J = 6.4 Hz, 3H).
194	ES+ 569.2 [M+H]	^{1}H NMR (400 MHz, $CDCl_3$): δ 9.12 – 9.05 (m, 1H), 8.98 (s, 2H), 8.83 (d, J = 2.0 Hz, 1H), 8.04 (d, J = 2.1 Hz, 1H), 7.58 – 7.40 (m, 1H), 7.26 – 7.22 (m, 1H), 7.05 – 6.90 (m, 1H), 6.76 (s, 1H), 5.86 – 5.82 (m, 1H), 5.10 – 5.05 (m, 1H), 4.88 – 4.83 (m, 1H), 3.92 (s, 3H), 2.38 (s, 3H), 1.71 (d, J = 6.4 Hz, 3H).
195	ES+ 575.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.89 – 8.80 (m, 2H), 7.57 – 7.53 (m, 1H), 7.39 (s, 1H), 7.20 – 7.11 (m, 2H), 6.84 – 6.81 (m, 1H), 6.66 – 6.56 (m, 2H), 5.70 (d, J = 6.5 Hz, 1H), 5.20 – 5.05 (m, 1H), 3.50 (d,

		J = 2.1 Hz, 3H), 2.45 (d, J = 11.0 Hz, 3H), 2.33 – 2.30 (m, 6H), 2.05 (d, J = 3.6 Hz, 3H), 1.58 (d, J = 6.8, 2.8 Hz, 3H).
196	ES+ 579.3 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.27 (s, 2H), 8.83 (s, 1H), 7.78 – 7.76 (m, 1H), 7.42 (d, J = 1.7 Hz, 1H), 7.26 (s, 1H), 7.16 (d, J = 8.6 Hz, 1H), 6.84 (d, J = 8.6 Hz, 1H), 6.69 – 6.66 (m, 1H), 5.70 (d, J = 6.5 Hz, 1H), 5.27 – 5.23 (m, 1H), 3.31 – 3.28 (m, 3H), 2.32 – 2.26 (m, 6H), 2.24 (s, 3H), 1.61 (d, J = 6.5 Hz, 3H).
197	ES+ 597.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.19 (s, 2H), 8.82 (s, 1H), 7.87 – 7.51 (m, 2H), 7.40 (d, J = 1.7 Hz, 1H), 7.19 (s, 1H), 7.16 (d, J = 8.7 Hz, 1H), 6.84 (d, J = 8.7 Hz, 1H), 6.81-6.77 (m, 1H), 6.72-6.67 (m, 1H), 5.70 (d, J = 6.6 Hz, 1H), 5.29 – 5.21 (m, 1H), 2.33 (s, 3H), 2.31 (s, 3H), 2.23 (s, 3H), 1.60 (d, J = 6.5 Hz, 3H).
198	ES+ 611.3 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.16 (s, 2H), 8.82 (s, 1H), 7.86 – 7.57 (m, 1H), 7.56 (d, J = 1.5 Hz, 1H), 7.40 (d, J = 1.7 Hz, 1H), 7.18 (s, 1H), 7.16 (d, J = 8.7 Hz, 1H), 6.84 (d, J = 8.7 Hz, 1H), 6.77 (d, J = 6.9 Hz, 1H), 5.69 (d, J = 6.6 Hz, 1H), 5.29 – 5.21 (m, 1H), 2.30 (s, 3H), 2.29 (s, 3H), 2.23 (s, 3H), 2.12 (d, J = 1.2 Hz, 3H), 1.60 (d, J = 6.5 Hz, 3H).
199	ES+ 579.3 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.22 (s, 2H), 8.82 (s, 1H), 7.74 – 7.67 (m, 1H), 7.41 (d, J = 1.7 Hz, 1H), 7.23 (s, 1H), 7.16 (d, J = 8.7 Hz, 1H), 6.88 – 6.79 (m, 2H), 5.70 (d, J = 6.5 Hz, 1H), 5.30 – 5.20 (m, 1H), 3.58 (s, 3H), 2.31 (s, 3H), 2.29 (s, 3H), 2.24 (s, 3H), 1.60 (d, J = 6.6 Hz, 3H).
200	ES+ 567.1 [M+H]	^{1}H NMR (400 MHz, CD_3OD): δ 9.28 (s, 1H), 9.13 (s, 2H), 9.06 – 9.01 (m, 1H), 7.61 – 7.54 (m, 1H), 7.36 (s, 1H), 7.33 – 7.26 (m, 1H), 7.11 – 7.02 (m, 1H), 6.50 – 6.41 (m, 1H), 5.28 – 5.16 (m, 1H), 2.93 (s, 3H), 2.77 (s, 3H), 2.37 (s, 3H), 1.72 (d, J = 6.6 Hz, 3H).

201	ES+ 560.1 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.58 (s, 2H), 8.87 – 8.80 (m, 2H), 7.44 (d, J = 1.6 Hz, 1H), 7.21 – 7.10 (m, 2H), 6.84 – 6.81 (m, 1H), 5.68 (d, J = 6.5 Hz, 1H), 5.14 – 5.12 (m, 1H), 2.75 (s, 3H), 2.47 (s, 3H), 2.34 (s, 6H), 2.05 (s 3H), 1.58 (d, J = 6.4, 3H).
202	ES+ 539.1 [M+H]	^{1}H NMR (400 MHz, $CDCl_3$): δ 9.01 (s, 1H), 8.97 (s, 2H), 7.38 (s, 1H), 7.31 – 7.17 (m, 2H), 7.06 – 6.96 (m, 1H), 6.82 – 6.75 (m, 1H), 6.67 (s, 1H), 6.19 – 6.11 (m, 1H), 4.92 – 4.83 (m, 2H), 3.83 (s, 3H), 2.40 (s, 3H), 2.38 (s, 3H), 1.74 (d, J = 4.0 Hz, 3H).
203	ES+ 569.2 [M+H]	^{1}H NMR (400 MHz, CD_3OD): δ 9.17 (s, 2H), 9.05 – 9.01 (m, 1H), 8.29 (d, J = 2.1 Hz, 1H), 7.63 – 7.60 (m, 1H), 7.31 – 7.05 (m, 4H), 6.12 (d, J = 9.5 Hz, 1H), 5.22 – 5.16 (m, 1H), 2.81 (s, 3H), 2.39 (s, 3H), 1.70 (d, J = 6.6 Hz, 3H).
204	ES+ 567.1 [M+H]	^{1}H NMR (400 MHz, CD_3OD): δ 9.28 (s, 1H), 9.13 (s, 2H), 9.07 – 9.00 (m, 1H), 7.63 – 7.55 (m, 1H), 7.36 – 7.04 (m, 3H), 6.17 – 6.09 (m, 1H), 5.25 – 5.15 (m, 1H), 2.93 (s, 3H), 2.77 (s, 3H), 2.37 (s, 3H), 1.70 (d, J = 6.6 Hz, 3H).
205	ES+ 581.2 [M+H]	^{1}H NMR (400 MHz, CD_3OD): δ 9.24 (s, 2H), 9.02 (s, 1H), 7.69 (d, J = 7.1 Hz, 1H), 7.66 (d, J = 7.1 Hz, 1H), 7.40 (s, 1H), 7.12 (d, J = 8.6 Hz, 1H), 6.93 – 6.81 (m, 2H), 6.76 – 6.70 (m, 1H), 5.25 – 5.20 (m, 1H), 3.70 (s, 3H), 2.42 (s, 3H), 2.38 (s, 3H), 1.72 (d, J = 6.6 Hz, 3H).
206	ES+ 578.3 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.19 (s, 2H), 8.83 (s, 1H), 7.73 (d, J = 8.0 Hz, 1H), 7.65 – 7.48 (m, 2H), 7.43 – 7.34 (m, 1H), 7.32 – 7.15 (m, 2H), 6.28 – 6.17 (m, 2H), 5.27 – 5.09 (m, 1H), 2.68 (s, 3H), 2.48 (s, 3H), 2.32 (s, 3H), 2.25 (s, 3H), 1.56 (d, J = 6.4 Hz, 3H).
207	ES+ 578.3 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.20 (s, 2H), 8.83 (s, 1H), 7.73 (d, J = 8.4 Hz, 1H), 7.56 (d, J = 8.4 Hz, 1H), 7.41 (d, J = 1.6 Hz, 1H), 7.38 – 7.31 (m, 1H), 7.24 (s, 1H), 7.23 – 7.12 (m, 1H), 6.55 – 6.37 (m, 1H),

		5.49 (d, J = 6.3 Hz, 1H), 5.35 – 5.09 (m, 1H), 2.68 (s, 3H), 2.48 (s, 3H), 2.30 (s, 3H), 2.26 (s, 3H), 1.60 (d, J = 6.8 Hz, 3H).
208	ES+ 579.1 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.21 (s, 2H), 8.95 – 8.88 (m, 1H), 7.73 (d, J = 8.1 Hz, 1H), 7.60 – 7.52 (m, 2H), 7.38 (s, 1H), 7.18 (d, J = 8.6 Hz, 1H), 6.87 (d, J = 8.7 Hz, 1H), 5.83 (d, J = 6.7 Hz, 1H), 5.35 – 5.27 (m, 1H), 2.69 (s, 3H), 2.51 – 2.45 (m, 3H), 2.33 - 2.26 (m, 6H), 1.63 (d, J = 6.5 Hz, 3H).
209	ES+ 535.3 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.20 (s, 2H), 8.84 (s, 1H), 7.73 (d, J = 8.0 Hz, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.52 – 7.48 (m, 2H), 7.30 – 7.16 (m, 2H), 6.55 (d, J = 6.4 Hz, 1H), 6.47 – 6.28 (m, 1H), 5.31 – 5.08 (m, 1H), 2.69 (s, 3H), 2.48 (s, 3H), 2.33 (s, 3H), 2.26 (s, 3H), 1.59 (d, J = 6.4 Hz, 3H).
210	ES+ 575.3 [M+H]	^{1}H NMR (400 MHz, $CDCl_3$): δ 9.10 – 8.95 (m, 3H), 8.04 (s, 1H), 7.43 (d, J = 8.4 Hz, 1H), 7.36 (s, 1H), 7.00 (d, J = 8.4 Hz, 1H), 6.71 (s, 1H), 6.53 (d, J = 8.8 Hz, 1H), 4.95 – 4.82 (m, 1H), 4.76 (s, 1H), 3.01 (s, 3H), 2.76 (s, 3H), 2.46 (s, 3H), 2.39 (s, 3H), 2.37 (s, 3H), 1.72 (d, J = 6.4 Hz, 3H).
211	ES+ 578.2 [M+H]	^{1}H NMR (400 MHz, CD_3OD): δ 8.95 (s, 1H), 8.82 – 8.60 (m, 1H), 8.09 – 8.00 (m, 1H), 7.71 – 7.59 (m, 1H), 7.51 (d, J = 1.6 Hz, 1H), 7.22 (s, 1H), 7.12 (d, J = 8.6 Hz, 1H), 6.82 (d, J = 8.6 Hz, 1H), 6.81 – 6.71 (m, 1H), 6.69 – 6.58 (m, 1H), 5.33 – 5.09 (m, 1H), 3.52 – 3.47 (m, 3H), 2.41 – 2.35 (m, 6H), 2.33 (s, 3H), 1.70 (d, J = 6.7 Hz, 3H).
212	ES+ 582.1 [M+H]	^{1}H NMR (400 MHz, $CDCl_3$): δ 9.01 (s, 1H), 8.97 (s, 2H), 7.40 (s, 1H), 7.31 – 7.20 (m, 2H), 6.98 – 6.89 (m, 1H), 6.82 – 6.74 (m, 1H), 6.71 (s, 1H), 6.22 – 6.15 (m, 1H), 4.92 – 4.82 (m, 1H), 4.65 – 4.59 (m, 1H), 3.83 (s, 3H), 2.38 (s, 6H), 1.70 (d, J = 8.0 Hz, 3H).

213	ES+ 582.2 [M+H]	^{1}H NMR (400 MHz, CD_3OD): δ 9.11 (s, 2H), 9.05 – 9.03 (m, 1H), 7.66 (d, J = 7.2 Hz, 1H), 7.58 (d, J = 8.3, 2.5 Hz, 1H), 7.36 – 7.24 (m, 2H), 7.12 – 7.05 (m, 1H), 6.81 (d, J = 7.1 Hz, 1H), 6.12 (d, J = 9.3 Hz, 1H), 5.20 (d, J = 6.6 Hz, 1H), 3.68 (s, 3H), 2.36 (d, J = 1.9 Hz, 6H), 1.70 (d, J = 6.7 Hz, 3H).
214	ES+ 569.1 [M+H]	^{1}H NMR (400 MHz, $CDCl_3$): δ 9.15 – 9.03 (m, 1H), 9.01 (s, 2H), 8.33 (s, 1H), 7.94 (s, 1H), 7.58 – 7.40 (m, 1H), 7.01 – 6.91 (m, 1H), 6.78 (s, 1H), 6.27 – 6.09 (m, 1H), 4.91 – 4.86 (m, 1H), 4.69 – 4.60 (m, 1H), 3.82 (s, 3H), 2.40 (s, 3H), 1.74 (d, J = 6.4 Hz, 3H).
215	ES+ 565.1 [M+H]	^{1}H NMR (400 MHz, CD_3OD): δ 9.39 – 9.35 (m, 2H), 8.96 (s, 1H), 7.72 – 7.64 (m, 1H), 7.58 – 7.56 (m, 1H), 7.43 (d, J = 6.1 Hz, 1H), 7.12 (d, J = 8.6 Hz, 1H), 6.95 – 6.88 (m, 1H), 6.86 (d, J = 8.6 Hz, 1H), 6.80 – 6.73 (m, 1H), 5.36 – 5.27 (m, 1H), 3.70 (s, 3H), 2.43 – 2.36 (m, 6H), 1.74 (d, J = 6.7 Hz, 3H).
216	ES+ 583.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.26 (s, 2H), 8.94 – 8.92 (m, 1H), 8.34 (s, 1H), 7.60 – 7.37 (m, 3H), 7.27 (d, J = 9.5 Hz, 1H), 6.25 (d, J = 6.2 Hz, 1H), 6.13 (d, J = 9.4 Hz, 1H), 5.25 – 5.22 (m, 1H), 3.76 (s, 3H), 2.47 (s, 3H), 2.28 (s, 3H), 1.58 (d, J = 6.5 Hz, 3H).
217	ES+ 583.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.26 (s, 2H), 8.94 – 8.92 (m, 1H), 8.34 (s, 1H), 7.61 – 7.37 (m, 3H), 7.29 – 7.22 (m, 1H), 6.25 (d, J = 6.2 Hz, 1H), 6.13 (d, J = 9.5 Hz, 1H), 5.23 (d, J = 6.5 Hz, 1H), 3.76 (s, 3H), 2.47 (s, 3H), 2.28 (s, 3H), 1.58 (d, J = 6.5 Hz, 3H).
218	ES+ 583.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.26 (s, 2H), 8.94 – 8.92 (m, 1H), 8.34 (s, 1H), 7.55 – 7.53 (m, 1H), 7.40 – 7.36 (m, 2H), 7.22 – 7.19 (m, 1H), 6.50 – 6.47 (m, 1H), 5.63 (d, J = 6.5 Hz, 1H), 5.33 – 5.23 (m, 1H), 3.75 (s, 3H), 2.46 (s, 3H), 2.28 (s, 3H), 1.61 (d, J = 6.5 Hz, 3H).

219	ES+ 563.1 [M+H]	^{1}H NMR (400 MHz, $CDCl_3$): δ 8.96 – 8.90 (m, 1H), 7.47 – 7.40 (m, 1H), 7.13 – 6.95 (m, 2H), 5.97 (d, J = 8.9 Hz, 1H), 5.24 – 5.16 (m, 1H), 5.03 (s, 1H), 3.50 – 3.35 (m, 8H), 2.90 (s, 3H), 2.38 (s, 3H), 1.63 (d, J = 6.4 Hz, 3H).
220	ES+ 582.1 [M+H]	^{1}H NMR (400 MHz, $CDCl_3$): δ 9.01 (s, 1H), 8.97 (s, 2H), 7.42 (s, 1H), 7.27 – 7.21 (m, 1H), 7.11 (s, 1H), 7.00 – 6.90 (m, 1H), 6.82 – 6.75 (m, 1H), 6.71 (s, 1H), 5.94 – 5.79 (m, 1H), 5.22 – 4.95 (m, 1H), 4.91 – 4.77 (m, 1H), 3.83 (s, 3H), 2.39 (s, 3H), 2.38 (s, 3H), 1.70 (d, J = 4.0 Hz, 3H).
221	ES+ 582.3 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.19 (s, 2H), 8.96 – 8.92 (m, 1H), 7.63 – 7.34 (m, 4H), 7.30 – 7.23 (m, 1H), 6.67 (d, J = 7.0 Hz, 1H), 6.25 (d, J = 6.2 Hz, 1H), 6.13 (d, J = 9.4 Hz, 1H), 5.28 – 5.22 (m, 1H), 3.59 (s, 3H), 2.28 (s, 3H), 2.12 (d, J = 1.2 Hz, 3H), 1.59 (d, J = 6.5 Hz, 3H).
222	ES+ 582.1 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.20 (s, 2H), 8.94 – 8.92 (m, 1H), 7.56 – 7.53 (m, 1H), 7.49 – 7.47 (m, 1H), 7.38 (d, J = 10.3 Hz, 2H), 7.30 – 7.13 (m, 1H), 6.68 (d, J = 7.0 Hz, 1H), 6.51 – 6.47 (m, 1H), 5.63 (d, J = 6.5 Hz, 1H), 5.32 – 5.48 (m, 1H), 3.59 (s, 3H), 2.28 (s, 3H), 2.12 (s, 3H), 1.63 (d, J = 6.6 Hz, 3H).
223	ES+ 562.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.07 (d, J = 1.1 Hz, 2H), 8.82 (s, 1H), 8.42 – 8.38 (m, 1H), 7.43 – 7.33 (m, 2H), 7.20 – 7.13 (m, 2H), 6.83 (d, J = 8.7 Hz, 1H), 5.70 (d, J = 6.4 Hz, 1H), 5.27 – 5.20 (m, 1H), 2.72 (s, 3H), 2.32 – 2.25 (m, 9H), 1.60 (d, J = 6.5 Hz, 3H).
224	ES+ 536.3 [M+H]	^{1}H NMR (400 MHz, CD_3CN): δ 9.02 (s, 2H), 8.88 (s, 1H), 7.65 (s, 1H), 7.45 (s, 1H), 7.30 – 7.27 (m, 1H), 7.06 – 7.01 (m, 1H), 6.93 (s, 1H), 6.34 – 6.30 (m, 1H), 5.28 (d, J = 5.6 Hz, 1H), 5.13 – 4.99 (m, 1H),

		3.64 (s, 3H), 2.43 (s, 3H), 2.32 (d, J = 1.3 Hz, 3H), 2.28 (s, 3H), 1.64 (d, J = 6.6 Hz, 3H).
225	ES+ 522.2 [M+H]	^{1}H NMR (400 MHz, CD_3CN): δ 9.04 (s, 2H), 8.88 (s, 1H), 8.11 (s, 1H), 7.74 (s, 1H), 7.45 (d, J = 1.7 Hz, 1H), 7.29 – 7.27 (m, 1H), 7.06 – 7.01 (m, 1H), 6.92 (s, 1H), 6.34 – 6.30 (m, 1H), 5.26 (d, J = 5.6 Hz, 1H), 5.05 – 4.98 (m, 1H), 3.63 (s, 3H), 2.31 (d, J = 1.3 Hz, 3H), 2.27 (s, 3H), 1.64 (d, J = 6.7 Hz, 3H).
226	ES+ 565.3 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.07 (d, J = 1.5 Hz, 2H), 8.82 (s, 1H), 8.41 – 8.36 (m, 1H), 7. 64 – 7.47 (m, 1H), 7.42 – 7.32 (m, 2H), 7.30 – 7.19 (m, 1H), 7.14 (s, 1H), 6.18 (d, J = 6.1 Hz, 1H), 6.10 (d, J = 9.4 Hz, 1H), 5.20 – 5.11 (m, 1H), 2.72 (d, J = 1.6 Hz, 3H), 2.33 (s, 3H), 2.24 (s, 3H), 1.56 (d, J = 6.4 Hz, 3H).
227	ES+ 566.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.67 (s, 1H), 7.94 (d, J = 2.1 Hz, 1H), 7.61 (d, J = 9.7 Hz, 1H), 7.38 (s, 1H), 7.19 (s, 1H), 6.62 (d, J = 9.2 Hz, 1H), 5.38 – 5.21 (m, 1H), 3.32 – 3.24 (m, 8H), 2.96 (s, 3H), 2.26 – 2.19 (m, 6H), 1.62 (d, J = 6.4 Hz, 3H).
228	ES+ 575.3 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.11 (s, 2H), 8.82 (s, 1H), 7.63 – 7.52 (m, 2H), 7.46 (s, 1H), 7.24 (s, 1H), 7.17 (d, J = 8.5 Hz, 1H), 6.89 (d, J = 8.7 Hz, 1H), 6.74 (d, J = 7.2 Hz, 1H), 5.21 (d, J = 7.1 Hz, 1H), 3.58 (s, 3H), 2.31 – 2.28 (m, 6H), 2.25 (s, 3H), 2.15 (s, 3H), 1.63 (d, J = 6.5 Hz, 3H).
229	ES+ 521.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.20 (s, 2H), 8.84 (s, 1H), 7.66 – 7.53 (m, 1H), 7.54 – 7.47 (m, 2H), 7.27 – 7.12 (m, 2H), 6.71 – 6.68 (m, 1H), 6.67 – 6.58 (m, 1H), 6.55 (d, J = 6.7 Hz, 1H), 6.44 – 6.27 (m, 1H), 5.39 – 5.03 (m, 1H), 3.53 (s, 3H), 2.35 – 2.30 (m, 3H), 2.25 (s, 3H), 1.60 (d, J = 6.5 Hz, 3H).

230	ES+ 552.3 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.24 (s, 2H), 8.83 (s, 1H), 8.34 (s, 1H), 7.65 (d, J = 2.6 Hz, 1H), 7.50 (d, J = 1.7 Hz, 1H), 7.36 – 7.32 (m, 1H), 7.20 (s, 1H), 6.78 (d, J = 6.8 Hz, 1H), 6.39 (d, J = 9.2 Hz, 1H), 5.25 – 5.20 (m, 1H), 3.75 (s, 3H), 2.46 (s, 3H), 2.32 (d, J = 1.4 Hz, 3H), 2.25 (s, 3H), 1.59 (d, J = 6.6 Hz, 3H).
231	ES+ 536.3 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.24 (s, 2H), 8.83 (s, 1H), 8.33 (s, 1H), 7.54 – 7.48 (m, 2H), 7.25 – 7.18 (m, 2H), 6.55 (d, J = 6.8 Hz, 1H), 6.38 – 6.34 (m, 1H), 5.21 – 5.17 (m, 1H), 3.75 (s, 3H), 2.46 (s, 3H), 2.34 – 2.30 (m, 3H), 2.25 (s, 3H), 1.58 (d, J = 6.5 Hz, 3H).
232	ES+ 545.1 [M+H]	^{1}H NMR (400 MHz, $CDCl_3$): δ 9.03 – 8.96 (s, 1H), 7.43 – 7.36 (m, 1H), 7.13 – 6.92 (m, 2H), 6.53 (s, 1H), 5.87 – 5.79 (m, 1H), 5.05 (d, J = 4.0 Hz, 1H), 4.86 – 4.75 (m, 1H), 3.52 – 3.45 (m, 4H), 3.30 – 3.19 (m, 4H), 2.90 (s, 3H), 2.33 (s, 3H), 1.70 (d, J = 6.5 Hz, 3H).
233	ES+ 572.1 [M+H]	^{1}H NMR (400 MHz, CD_3OD): δ 9.14 (s, 2H), 8.97 (s, 1H), 7.72 – 7.62 (m, 2H), 7.50 (d, J = 1.6 Hz, 1H), 7.23 (s, 1H), 6.95 (d, J = 8.9 Hz, 1H), 6.92 – 6.86 (m, 1H), 6.80 – 6.73 (m, 1H), 5.35 – 5.26 (m, 1H), 3.71 (s, 3H), 2.42 – 2.34 (m, 6H), 1.76 (d, J = 6.7 Hz, 3H).
234	ES+ 582.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.19 (s, 2H), 8.92 (d, J = 4.5 Hz, 1H), 7.70 (d, J = 7.1 Hz, 1H), 7.54 (d, J = 7.5 Hz, 1H), 7.43 – 7.31 (m, 2H), 7.21-7.19 (m, 1H), 6.62 (d, J = 7.1 Hz, 1H), 6.51 – 6.47 (m, 1H), 5.63 (d, J = 6.6 Hz, 1H), 5.41 – 5.22 (m, 1H), 3.52 (s, 3H), 2.27 (s, 6H), 1.62 (d, J = 6.5 Hz, 3H).
235	ES+ 615.1 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.22 (s, 2H), 8.85 (s, 1H), 7.80 (d, J = 8.9 Hz, 1H), 7.69 – 7.50 (m, 1H), 7.45 (d, J = 1.6 Hz, 1H), 7.23 (s, 1H), 7.06 (d, J = 9.0 Hz, 1H), 6.79 – 6.61 (m, 2H), 6.60 – 6.51 (m, 1H), 5.58 – 5.13 (m, 1H), 3.36 (s, 3H), 2.32 (d, J = 1.3 Hz, 3H), 2.26 (s, 3H), 1.67 (d, J = 6.5 Hz, 3H).

236	ES+ 548.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.70 (s, 1H), 7.94 (d, J = 2.2 Hz, 1H), 7.67 – 7.60 (m, 1H), 7.39 (d, J = 1.7 Hz, 1H), 7.22 (d, J = 6.8 Hz, 1H), 6.60 (s, 1H), 6.57 (d, J = 9.1 Hz, 1H), 5.27 – 5.19 (m, 1H), 3.31 – 3.26 (m, 4H), 3.18 – 3.10 (m, 4H), 2.95 (d, J = 1.1 Hz, 3H), 2.25 (d, J = 1.3 Hz, 3H), 2.14 (s, 3H), 1.63 (d, J = 6.6 Hz, 3H).
237	ES+ 539.1 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.23 (s, 2H), 8.86 – 8.77 (m, 2H), 7.81-7.74 (m, 1H), 7.54 – 7.46 (m, 2H), 7.26 – 7.17 (m, 2H), 6.55 (d, J = 6.8 Hz, 1H), 6.41 – 6.33 (m, 1H), 5.24 – 5.15 (m, 1H), 2.60 (s, 3H), 2.34 – 2.31 (m, 3H), 2.25 (s, 3H), 1.59 (d, J = 6.6 Hz, 3H).
238	ES+ 534.3 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.67 (s, 1H), 7.82 – 7.77 (m, 1H), 7.33 (d, J = 1.7 Hz, 1H), 6.73 (s, 1H), 6.51 – 6.48 (m, 1H), 5.17 – 5.14 (m, 1H), 3.31 – 3.24 (m, 8H), 2.96 (s, 3H), 2.23 (s, 3H), 2.20 (s, 3H), 1.59 (d, J = 6.6 Hz, 3H).
239	ES+ 534.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.67 (s, 1H), 7.46 – 7.41 (m, 1H), 7.37 (s, 1H), 6.90 (s, 1H), 6.25 (d, J = 9.5 Hz, 1H), 5.21 – 5.18 (m, 1H), 3.31 – 3.24 (m, 8H), 2.96 (s, 3H), 2.25 (s, 3H), 2.19 (s, 3H), 1.58 (d, J = 6.5 Hz, 3H).
240	ES+ 575.3 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.18 (s, 2H), 8.82 (s, 1H), 7.70 (d, J = 7.1 Hz, 1H), 7.40 (s, 1H), 7.22 (s, 1H), 7.17 (d, J = 8.7 Hz, 1H), 6.86 (d, J = 8.6 Hz, 1H), 6.62 (d, J = 7.0 Hz, 1H), 5.70 – 5.68 (m, 1H), 5.26 – 5.23 (m, 1H), 3.52 (s, 3H), 2.32 – 2.22 (m, 12H), 1.60 (d, J = 6.5 Hz, 3H).
241	ES+ 582.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.22 (s, 2H), 8.86 – 8.77 (m, 2H), 7.82 – 7.74 (m, 1H), 7.64 – 7.36 (m, 2H), 7.24 (d, J = 21.5 Hz, 2H), 6.19 (d, J = 6.2 Hz, 1H), 6.11 (d, J = 8.8 Hz, 1H), 5.22 – 5.12 (m, 1H), 2.61 (s, 3H), 2.32 (d, J = 1.3 Hz, 3H), 2.25 (s, 3H), 1.56 (d, J = 6.5 Hz, 3H).

242	ES+ 516.3 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.70 (s, 1H), 7.84 – 7.79 (m, 1H), 7.37 (d, J = 1.7 Hz, 1H), 6.80 – 6.78 (m, 1H), 6.60 (s, 1H), 6.54 – 6.51 (m, 1H), 5.13 – 5.10 (m, 1H), 3.40 – 3.32 (m, 4H), 3.32 – 3.16 (m, 4H), 2.96 (s, 3H), 2.27 (d, J = 1.3 Hz, 3H), 2.14 (s, 3H), 1.59 (d, J = 6.5 Hz, 3H).
243	ES+ 516.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.69 (s, 1H), 7.50 – 7.42 (m, 1H), 7.37 (d, J = 1.8 Hz, 1H), 6.92 (d, J = 6.7 Hz, 1H), 6.62 (s, 1H), 6.24 – 6.12 (m, 1H), 5.15 – 5.10 (m, 1H), 3.32 – 3.27 (m, 4H), 3.22 – 3.14 (m, 4H), 2.96 (s, 3H), 2.25 (d, J = 1.2 Hz, 3H), 2.14 (s, 3H), 1.59 (d, J = 6.6 Hz, 3H).
244	ES+ 580.0 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.20 (s, 2H), 8.83 (s, 1H), 7.62 – 7.54 (m, 1H), 7.41 (d, J = 1.7 Hz, 1H), 7.24 (s, 1H), 7.22 – 7.14 (m, 1H), 6.98 – 6.88 (m, 1H), 6.71 – 6.65 (m, 1H), 6.65 – 6.58 (m, 1H), 6.42 – 6.34 (m, 1H), 6.18 (d, J = 6.9 Hz, 1H), 5.20 – 5.08 (m, 1H), 3.53 (s, 3H), 2.30 (d, J = 1.3 Hz, 3H), 2.25 (s, 3H), 1.57 (d, J = 6.6 Hz, 3H).
245	ES+ 559.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.67 (s, 1H), 7.38 – 7.37 (m, 1H), 7.36 – 7.30 (m, 1H), 7.22 – 7.18 (m, 1H), 6.49 – 6.48 (m, 1H), 5.41 (s, 1H), 5.18 – 5.15 (m, 1H), 3.32 – 3.27 (m, 8H), 2.97 (s, 3H), 2.23 – 2.19 (m, 6H), 1.59 – 1.57 (m, 3H).
246	ES+ 587.2 [M+H]	^{1}H NMR (400 MHz, CD_3OD): δ 9.13 (s, 2H), 8.96 (s, 1H), 7.72 – 7.64 (m, 1H), 7.53 (d, J = 1.7 Hz, 1H), 7.26 (s, 1H), 7.06 (d, J = 8.7 Hz, 1H), 6.93 – 6.86 (m, 1H), 6.80 – 6.73 (m, 2H), 5.23 – 5.13 (m, 1H), 3.71 (s, 3H), 2.41 – 2.33 (m, 6H), 1.99 – 1.88 (m, 1H), 1.70 (d, J = 6.6 Hz, 3H), 1.02 – 0.66 (m, 4H).
247	ES+ 575.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.21 (s, 2H), 8.83 (s, 1H), 7.70 – 7.50 (m, 1H), 7.44 (d, J = 1.7 Hz, 1H), 7.25 – 7.17 (m, 2H), 6.87 (d, J = 8.7 Hz, 1H), 6.77 – 6.63 (m, 1H), 6.62 – 6.50 (m, 1H), 5.85 – 5.59

		(m, 1H), 5.38 – 5.03 (m, 1H), 3.54 (s, 3H), 2.65 – 2.52 (m, 2H), 2.34 – 2.18 (m, 6H), 1.61 (d, J = 6.5 Hz, 3H), 1.19 – 1.01 (m, 3H).
248	ES+ 559.3 [M+H]	^{1}H NMR (400 MHz, CD_3OD): δ 8.84 (s, 1H), 8.42 – 7.97 (m, 1H), 7.46 (d, J = 0.8 Hz, 1H), 7.29 – 7.10 (m, 1H), 6.70 (s, 1H), 5.54 – 5.23 (m, 1H), 5.17 (d, J = 8.0 Hz, 1H), 5.14 – 5.02 (m, 1H), 4.47 – 4.28 (m, 2H), 4.25 – 4.06 (m, 2H), 3.62 – 3.45 (m, 4H), 3.21 – 2.93 (m, 4H), 2.37 (s, 3H), 2.29 (s, 3H), 1.94 (s, 3H), 1.71 (d, J = 6.4 Hz, 3H).
249	ES+ 536.3 [M+H]	^{1}H NMR (400 MHz, CD_3OD): δ 8.84 (s, 1H), 8.50 – 8.03 (m, 1H), 7.47 (s, 1H), 7.16 (d, J = 8.0, 1H), 6.72 (s, 1H), 5.18 (d, J = 8.0 Hz, 1H), 5.16 – 5.05 (m, 1H), 3.50 – 3.41 (m, 4H), 3.32 – 3.16 (m, 4H), 2.93 (s, 3H), 2.37 (s, 3H), 2.29 (s, 3H), 1.94 (s, 3H), 1.72 (d, J = 6.4 Hz, 3H).
250	ES+ 566.1 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.69 (s, 1H), 7.98 – 7.96 (m, 1H), 7.71 – 7.68 (m, 1H), 7.24 (d, J = 9.8 Hz, 1H), 6.64 (d, J = 9.2 Hz, 1H), 6.36 (s, 1H), 5.31 – 5.29 (m, 1H), 3.34 – 3.28 (m, 4H), 3.35 – 3.25 (m, 4H), 2.97 (s, 3H), 2.26 – 2.22 (m, 6H), 1.64 (d, J = 6.4 Hz, 3H).
251	ES+ 576.2 M+H]	^{1}H NMR (400 MHz, $CDCl_3$): δ 8.82 (s, 1H), 7.27 (s, 1H), 7.02 (d, J = 8.4 Hz, 1H), 6.64 (d, J = 8.4 Hz, 1H), 5.20 – 5.17 (m, 1H), 4.70 – 4.65 (m, 1H), 3.70 – 3.65 (m, 4H), 3.50 – 3.25 (m, 4H), 2.64 (s, 3H), 2.46 (s, 3H), 2.39 (s, 3H), 2.25 (s, 3H), 1.63 (d, J = 6.4 Hz, 3H).
252	ES+ 559.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.69 – 8.65 (m, 1H), 7.51 (s, 1H), 7.28 (s, 1H), 7.19 (d, J = 8.6 Hz, 1H), 6.89 (d, J = 8.7 Hz, 1H), 5.60 (s, 1H), 5.19 – 5.16 (m, 1H), 3.96 (s, 3H), 3.39 – 3.35 (m, 4H), 3.25 – 3.19 (m, 4H), 2.32 (s, 3H), 2.24 (s, 3H), 2.19 (d, J = 1.3 Hz, 3H), 1.63 – 1.57 (m, 3H).

253	ES+ 570.2 [M+H]	^{1}H NMR (400 MHz, $CDCl_3$): δ 8.85 (s, 1H), 7.28 – 7.27 (s, 1H), 7.05 (d, J = 8.5 Hz, 1H), 6.69 (d, J = 8.6 Hz, 1H), 5.26 – 5.21 (m, 1H), 4.69 (s, 1H), 3.70 – 3.68 (m, 3H), 3.40 – 3.35 (m, 1H), 3.17 – 3.13 (m, 2H), 2.89 (s, 3H), 2.58 – 2.72 (m, 1H), 2.47 (m, 3H), 2.41 (s, 3H), 2.27 (s, 3H), 1.61 (d, J = 6.3 Hz, 3H), 1.02 (s, 3H).
254	ES+ 570.2 [M+H]	^{1}H NMR (400 MHz, $CDCl_3$): δ 8.83 (s, 1H), 7.30 – 7.19 (m, 1H), 7.02 (d, J = 8.5 Hz, 1H), 6.63 (d, J = 8.6 Hz, 1H), 5.21 – 5.17 (m, 1H), 4.69 (s, 1H), 4.26 – 4.22 (m, 1H), 3.75 – 3.63 (m, 2H), 3.59 – 3.48 (m, 1H), 3.44 – 3.34 (m, 1H), 3.27 – 3.19 (m, 1H), 3.15 – 3.08 (m, 1H), 2.96 (s, 3H), 2.46 (s, 3H), 2.41 (s, 3H), 2.25 (s, 3H), 1.64 (d, J = 6.4 Hz, 3H), 1.52 (d, J = 6.8 Hz, 3H).
255	ES+ 585.1 [M+H]	^{1}H NMR (400 MHz, CD_3CN): δ 8.72 (s, 1H), 7.68 (d, J = 2.6 Hz, 1H), 7.28 – 7.26 (m, 2H), 6.64 (s, 1H), 6.48 (d, J = 8.9 Hz, 1H), 5.23 (d, J = 6.2 Hz, 1H), 3.50 – 3.20 (m, 8H), 3.16 (s, 3H), 2.84 (s, 3H), 2.27 (s, 3H), 2.19 (d, J = 1.2 Hz,3H), 1.61 (d, J = 6.2 Hz, 3H).
256	ES+ 532.7 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.73 – 8.62 (m, 1H), 7.64 (d, J = 2.6 Hz, 1H), 7.41 – 7.28 (m, 2H), 6.73 (s, 1H), 6.46 (d, J = 9.2 Hz, 1H), 5.29 – 5.13 (m, 1H), 3.34 – 3.25 (m, 8H), 2.97 (s, 3H), 2.26 – 2.17 (m, 6H), 1.58 (d, J = 6.4 Hz, 3H).
257	ES+ 558.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.21 (s, 1H), 9.19 (s, 2H), 8.85 (s, 1H), 8.34 – 8.03 (m, 1H), 7.47 (s, 1H), 7.18 (s, 1H), 7.08 (d, J = 8.0, 1H), 6.26 – 6.22 (m, 1H), 5.18 – 5.16 (m, 1H), 5.05 – 4.92 (m, 1H), 2.83 (s, 3H), 2.69 (s, 3H), 2.36 (s, 3H), 2.26 (s, 3H), 1.86 (s, 3H), 1.60 (d, J = 6.4, 3H).
258	ES+ 520.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.22 – 9.18 (m, 3H), 8.84 (s, 1H), 7.51 – 7.49 (m, 2H), 7.22 – 7.20 (m, 2H), 6.54 (d, J = 6.8 Hz, 1H),

		6.40 – 6.37 (m, 1H), 5.21 – 5.19 (m, 1H), 2.83 (s, 3H), 2.69 (s, 3H), 2.33 (s, 3H), 2.26 (s, 3H), 1.62 (d, J = 6.8, 3H).
259	ES+ 559.2 [M+H]	^{1}H NMR (400 MHz, CD_3OD): δ 8.84 – 8.79 (m, 1H), 7.46 (s, 1H), 7.41 – 7.27 (m, 1H), 7.03 – 6.78 (m, 1H), 6.30 – 6.17(m, 1H), 5.30 – 5.19 (m, 1H), 3.49 – 3.41 (m, 8H), 2.94 (s, 3H), 2.36 (s, 3H), 2.29 (d, J = 1.3 Hz, 3H), 1.66 – 1.56 (m, 3H).
260	ES+ 548.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.70 (s, 1H), 7.94 (d, J = 2.0 Hz, 1H), 7.73 – 7.71 (m, 1H), 7.26 (d, J = 1.7 Hz, 1H), 6.62 – 6.60 (m, 1H), 6.42 (d, J = 6.7 Hz, 1H), 5.37 – 5.16 (m, 1H), 3.28 (d, J = 4.9 Hz, 4H), 3.17 – 3.15 (m, 4H), 2.96 (s, 3H), 2.24 (d, J = 1.2 Hz, 3H), 2.15 (s, 3H), 1.64 (d, J = 6.5 Hz, 3H).
261	ES+ 541.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.69 (s, 1H), 7.52 (s, 1H), 7.27 (d, J = 1.8 Hz, 1H), 7.21 (d, J = 8.6 Hz, 1H), 6.87 (d, J = 8.7 Hz, 1H), 6.63 (s, 1H), 5.61 (d, J = 6.5 Hz, 1H), 5.16 – 5.14 (m, 1H), 3.96 (s, 3H), 3.29 – 3.25 (m, 4H), 3.20 – 3.18 (m, 4H), 2.31 (s, 3H), 2.23 (s, 3H), 2.16 (s, 3H), 1.61 (d, J = 6.5 Hz, 3H).
262	ES+ 579.2 [M+H]	^{1}H NMR (400 MHz, CD_3OD): δ 9.14 (s, 2H), 8.96 (s, 1H), 8.45 (s, 1H), 7.55 (d, J = 1.7 Hz, 1H), 7.42 – 7.04 (m, 3H), 6.12 (d, J = 9.6 Hz, 1H), 5.16 – 5.13 (m, 1H), 3.87 (s, 3H), 2.56 (s, 3H), 2.40 (d, J = 1.3 Hz, 3H), 2.34 (s, 3H), 1.68 (d, J = 6.6 Hz, 3H).
263	ES+ 579.2 [M+H]	^{1}H NMR (400 MHz, CD_3OD): δ 9.15 (s, 2H), 8.97 (s, 1H), 8.46 (s, 1H), 7.55 (s, 1H), 7.31 – 7.17 (m, 2H), 7.11 – 7.05 (m, 1H), 6.12 (d, J = 9.4 Hz, 1H), 5.19 – 5.14 (m, 1H), 3.88 (s, 3H), 2.57 (s, 3H), 2.40 (s, 3H), 2.35 (s, 3H), 1.69 – 1.63 (m, 3H).
264	ES+ 579.2 [M+H]	^{1}H NMR (400 MHz, CD_3OD): δ 9.14 (s, 2H), 8.96 (s, 1H), 8.45 (s, 1H), 7.54 (d, J = 1.7 Hz, 1H), 7.27 (d, J = 9.2 Hz, 2H), 7.06 – 7.01 (m, 1H),

		6.45 – 6.42 (m, 1H), 5.20 – 5.10 (m, 2H), 3.87 (s, 3H), 2.56 (s, 3H), 2.39 (d, J = 1.3 Hz, 3H), 2.34 (s, 3H), 1.69 (d, J = 6.6 Hz, 3H).
265	ES+ 534.3 [M+H]	^{1}H NMR (400 MHz, $CDCl_3$): δ 8.82 (s, 1H), 7.24 (s, 1H), 7.03 (d, J = 8.5 Hz, 1H), 6.67 (d, J = 8.5 Hz, 1H), 5.26 – 5.16 (m, 1H), 4.78 – 4.66 (m, 5H), 3.68 – 3.58 (m, 1H), 3.40 – 3.30 (m, 4H), 2.55 – 2.52 (m, 4H), 2.46 (s, 3H), 2.35 (s, 3H), 2.24 (s, 3H), 1.63 (d, J = 6.4 Hz, 3H).
266	ES+ 586.3 [M+H]	^{1}H NMR (400 MHz, CD_3OD): δ 9.15 (s, 2H), 8.98 (s, 1H), 8.46 (s, 1H), 7.86 (s, 1H), 7.57 (d, J = 8.7 Hz, 1H), 7.49 (s, 1H), 7.23 (s, 1H), 6.58 (d, J = 8.9 Hz, 1H), 5.33 (d, J = 6.9 Hz, 1H), 3.88 (s, 3H), 2.57 (s, 3H), 2.40 (s, 3H), 2.35 (s, 3H), 1.75 (d, J = 6.7 Hz, 3H).
267	ES+ 541.1 [M+H]	^{1}H NMR (400 MHz, CD_3OD): δ 8.83 (d, J = 2.0 Hz, 1H), 7.43 (d, J = 1.7 Hz, 1H), 7.35 – 7.25 (m, 1H), 7.20 – 6.95 (m, 1H), 6.87 – 6.77 (m, 1H), 6.31 – 6.21 (m, 1H), 5.11 – 4.99 (m, 1H), 3.49 – 3.40 (m, 4H), 3.32 – 3.22 (m, 4H), 2.94 (s, 3H), 2.36 – 2.28 (m, 6H), 1.67 (d, J = 6.7 Hz, 3H).
268	ES+ 560.1 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.21 – 9.15 (m, 3H), 8.83 (s, 1H), 7.41 (s, 1H), 7.22 (s, 1H), 7.17 (d, J = 8.4 Hz, 1H), 6.86 (d, J = 8.8 Hz, 1H), 5.70 (d, J = 6.4 Hz, 1H), 5.27 – 5.24 (m, 1H), 2.83 (s, 3H), 2.69 (s, 3H), 2.33 – 2.24 (m, 9H), 1.61 (d, J = 6.4, 3H).
269	ES+ 583.3 [M+H]	^{1}H NMR (400 MHz, CD_3OD): δ 9.14 (s, 2H), 9.06 – 9.02 (m, 1H), 7.82 (s, 1H), 7.61 – 7.56 (m, 1H), 7.36 (s, 1H), 7.33 – 7.28 (m, 1H), 7.09 – 7.04 (m, 1H), 6.47 – 6.43 (m, 1H), 5.24 – 5.18 (m, 2H), 3.79 (s, 3H), 2.53 (s, 3H), 2.37 (s, 3H), 1.71 (d, J = 6.4 Hz, 3H).
270	ES+ 558.3 [M+H]	^{1}H NMR (400 MHz, $CDCl_3$): δ 8.89 (s, 1H), 7.27 (s, 1H), 7.00 (d, J = 8.4 Hz, 1H), 6.49 (d, J = 8.4 Hz, 1H), 6.42 (s, 1H), 4.84 – 4.76 (m, 1H), 4.74 – 4.71 (m, 1H), 3.90 – 3.60 (m, 4H), 3.40 – 3.10 (m, 4H),

		2.62 (s, 3H), 2.48 (s, 3H), 2.35 (s, 3H), 2.29 (s, 3H), 1.69 (d, J = 6.4 Hz, 3H).
271	ES+ 569.1 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.26 (s, 2H), 8.93-8.91 (m, 1H), 8.77 (d, J = 2.1 Hz, 1H), 7.76 (d, J = 2.1 Hz, 1H), 7.56 – 7.53 (m, 1H), 7.44 – 7.31 (m, 2H), 7.22 – 7.18 (m, 1H), 6.59 – 6.42 (m, 1H), 5.63 (d, J = 6.4 Hz, 1H), 5.39 – 5.20 (m, 1H), 3.76 (s, 3H), 2.26 (s, 3H), 1.61 (d, J = 6.5 Hz, 3H).
272	ES+ 579.2 [M+H]	^{1}H NMR (400 MHz, CD_3CN): δ 9.01 (s, 2H), 8.86 (s, 1H), 7.64 (s, 1H), 7.39 (d, J = 1.8 Hz, 1H), 7.30 – 7.27 (m, 1H), 7.05 – 6.89 (m, 2H), 6.41 – 6.37 (m, 1H), 5.06 – 5.00 (m, 1H), 4.91 (d, J = 5.4 Hz, 1H), 3.64 (s, 3H), 2.42 (s, 3H), 2.29 (d, J = 1.2 Hz, 3H), 2.27 (s, 3H), 1.62 (d, J = 6.6 Hz, 3H).
273	ES+ 579.3 [M+H]	^{1}H NMR (400 MHz, CD_3CN): δ 9.01 (s, 2H), 8.87 (s, 1H), 7.65 (s, 1H), 7.39 (s, 1H), 7.30 – 7.15 (m, 1H), 7.04 – 6.98 (m, 1H), 6.93 (s, 1H), 6.07 (d, J = 9.4 Hz, 1H), 5.20 (s, 1H), 5.04 – 4.95 (m, 1H), 3.64 (s, 3H), 2.43 (s, 3H), 2.31 (d, J = 1.3 Hz, 3H), 2.27 (s, 3H), 1.60 (d, J = 6.6 Hz, 3H).
274	ES+ 559.1 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.67 (s, 1H), 7.63 – 7.33 (m, 1H), 7.31 – 7.20 (m, 2H), 6.17 – 6.08 (m, 2H), 5.15 – 5.06 (m, 1H), 3.35 – 3.22 (m, 8H), 2.96 (d, J = 2.6 Hz, 3H), 2.25 – 2.18 (m, 6H), 1.55 (d, J = 6.3 Hz, 3H).
275	ES+ 567.1 [M+H]	^{1}H NMR (400 MHz, CD_3CN): δ 8.76 (s, 1H), 7.68 (d, J = 2.6 Hz, 1H), 7.30 – 7.23 (m, 2H), 6.63 (d, J = 5.5 Hz, 1H), 6.52 (s, 1H), 6.42 (d, J = 9.0 Hz, 1H), 5.00 – 4.97 (m, 1H), 3.37 – 3.34 (m, 4H), 3.19 – 3.17 (m, 4H), 3.14 (s, 3H), 2.84 (s, 3H), 2.24 (d, J = 1.2 Hz, 3H), 2.20 (s, 3H), 1.64 (d, J = 6.6 Hz, 3H).

276	ES+ 516.1 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.67 (d, J = 1.5 Hz, 1H), 7.53 – 7.45 (m, 1H), 7.38 (s, 1H), 7.27 – 7.17 (m, 1H), 6.49 (s, 1H), 6.47 – 6.41 (m, 1H), 5.24 – 5.12 (m, 1H), 3.39 – 3.33 (m, 4H), 3.30 – 3.23 (m, 4H), 2.96 (s, 3H), 2.25 – 2.18 (m, 6H), 1.58 (d, J = 6.4 Hz, 3H).
277	ES+ 572.3 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.66 (s, 1H), 7.28 (s, 1H), 7.18 (d, J = 8.6 Hz, 1H), 6.87 (d, J = 8.7 Hz, 1H), 5.61 (s, 1H), 5.20 – 5.10 (m, 1H), 3.75 – 3.58 (m, 4H), 3.25 – 3.15 (m, 4H), 2.48 (s, 1H), 2.31 (s, 3H), 2.22 (s, 3H), 2.18 (d, J = 1.3 Hz, 3H), 2.12 (s, 6H), 1.58 (d, J = 6.4 Hz, 3H).
278	ES+ 554.3 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.68 (s, 1H), 7.27 (d, J = 1.8 Hz, 1H), 7.19 (d, J = 8.7 Hz, 1H), 6.84 (d, J = 8.7 Hz, 1H), 6.60 (s, 1H), 5.61 (d, J = 6.6 Hz, 1H), 5.17 – 5.08 (m, 1H), 3.76 – 3.60 (m, 4H), 3.05 – 2.95 (m, 4H), 2.48 (s, 1H), 2.30 (s, 3H), 2.22 (d, J = 1.2 Hz, 3H), 2.15 (s, 3H), 2.11 (s, 6H), 1.59 (d, J = 6.5 Hz, 3H).
279	ES+ 576.3 [M+H]	^{1}H NMR (400 MHz, CD_3CN): δ 9.02 (s, 2H), 8.86 (s, 1H), 7.65 (s, 1H), 7.39 (d, J = 1.8 Hz, 1H), 7.04 (d, J = 8.6 Hz, 1H), 6.93 (s, 1H), 6.72 (d, J = 8.6 Hz, 1H), 5.15 – 5.01 (m, 1H), 3.64 (s, 3H), 2.42 (s, 3H), 2.33 (s, 3H), 2.29 (d, J = 1.3 Hz, 3H), 2.27 (s, 3H), 1.62 (d, J = 5.9 Hz, 3H).
280	ES+ 572.3 [M+H]	(400 MHz, CD_3OD): δ 9.12 (s, 2H), 8.97 (s, 1H), 8.95 – 8.88 (m, 1H), 7.99 (s, 1H), 7.86 (s, 1H), 7.56 (d, J = 8.8, 1H), 7.49 (s, 1H), 7.21 (s, 1H), 6.58 (d, J = 8.8 Hz, 1H), 5.39 – 5.22 (m, 1H), 3.89 (s, 3H), 2.40 (s, 3H), 2.33 (s, 3H), 1.74 (d, J = 6.8 Hz, 3H).
281	ES+ 563.1 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.78 – 8.77 (m, 1H), 7.40 – 7.37 (m, 2H), 7.26 – 7.17 (m, 1H), 6.58 – 6.51 (m, 1H), 5.55 (d, J = 6.0 Hz, 1H), 5.19 – 5.15 (m, 1H), 3.40 – 3.25 (m, 8H), 2.97 (d, J = 1.0 Hz, 3H), 2.26 (s, 3H), 1.62 (d, J = 6.4 Hz, 3H).

282	ES+ 552.3 [M+H]	^{1}H NMR (400 MHz, $CDCl_3$): δ 8.90 (s, 1H), 7.23 (s, 1H), 7.00 (d, J = 8.4 Hz, 1H), 6.51 (d, J = 8.4 Hz, 2H), 4.81 – 4.74 (m, 1H), 4.73 – 4.66 (m, 1H), 3.60 – 3.53 (m, 2H), 3.51 – 3.42 (m, 2H), 3.37 – 3.33 (m, 1H), 3.13 – 3.10 (m, 1H), 3.07 – 2.99 (m, 1H), 2.86 (s, 3H), 2.44 (s, 3H), 2.35 (s, 3H), 2.31 (s, 3H), 1.67 (d, J = 6.4, 3H), 1.12 – 1.00 (m, 3H).
283	ES+ 570.3 [M+H]	^{1}H NMR (400 MHz, CD_3OD): δ 8.83 (s, 1H), 7.48 (s, 1H), 7.16 (d, J = 8.8 Hz, 1H), 6.89 (d, J = 8.0 Hz, 1H), 5.43 – 5.22 (m, 1H), 3.75 – 3.52 (m, 3H), 3.32 – 3.13 (m, 3H), 3.02 – 2.76 (m, 4H), 2.40 (s, 3H), 2.39 (s, 3H), 2.30 (s, 3H), 1.68 (d, J = 6.0 Hz, 3H), 1.10 (d, J = 5.6 Hz, 3H).
284	ES+ 552.3 [M+H]	^{1}H NMR (400 MHz, CD_3OD): δ 8.83 (s, 1H), 7.44 (s, 1H), 7.18 (d, J = 8.8 Hz, 1H), 6.93 (d, J = 8.8 Hz, 1H), 6.83 (s, 1H), 5.21 – 5.01 (m, 1H), 3.73 – 3.56 (m, 1H), 3.52 – 3.43 (m, 2H), 3.42 – 3.37 (m, 1H), 3.31 – 3.25 (m, 1H), 3.24 – 3.18 (m, 1H), 3.08 – 2.97 (m, 1H), 2.92 (s, 3H), 2.40 (s, 3H), 2.34 (s, 3H), 2.30 (s, 3H), 1.71 (d, J = 6.4 Hz, 3H), 1.06 (d, J = 6.4 Hz, 3H).
285	ES+ 586.3 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.67 (s, 1H), 8.03 (d, J = 2.9 Hz, 1H), 7.29 (s, 1H), 7.18 (d, J = 8.6 Hz, 1H), 6.88 (d, J = 8.7 Hz, 1H), 5.95 (d, J = 2.8 Hz, 1H), 5.61 (s, 1H), 5.17 – 5.15 (m, 1H), 3.60 – 3.52 (m, 4H), 3.51 – 3.32 (m, 7H), 2.28 (s, 3H), 2.25 (s, 3H) 2.19 (s, 3H), 1.59 (d, J = 6.4 Hz, 3H).
286	ES+ 586.1 [M+H]	^{1}H NMR (400 MHz, CD_3OD): δ 9.13 (s, 2H), 9.01 – 9.95 (m, 1H), 7.58 – 7.50 (m, 1H), 7.49 – 7.40 (m, 1H), 7.37 (s, 1H), 7.29 – 7.20 (m, 1H), 7.05 – 6.95 (m, 1H), 6.91 – 9.86 (m, 1H), 6.45 – 6.40 (m, 1H), 5.22 – 5.12 (m, 1H), 3.79 (d, J = 1.9 Hz, 3H), 2.35 (d, J = 2.4 Hz, 3H), 1.72 – 1.70 (m, 3H).
287	ES+ 586.3 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.21 (s, 2H), 8.92 – 8.89 (m, 1H), 7.63 – 7.46 (m, 3H), 7.38 – 7.21 (m, 2H), 6.74 – 6.70 (m, 1H), 6.25

		(d, J = 6.2 Hz, 1H), 6.12 (d, J = 9.7 Hz, 1H), 5.23 – 5.20 (m, 1H), 3.65 (s, 3H), 2.27 (s, 3H), 1.58 (d, J = 6.5 Hz, 3H).
288	ES+ 546.2 [M+H]	^{1}H NMR (400 MHz, CD_3OD): δ 8.79 (d, J = 0.8, 1H), 7.44 (s, 1H), 7.15 (d, J = 8.8 Hz, 1H), 6.82 – 6.93 (m, 1H), 5.40 – 5.21 (m, 1H), 4.10 – 3.70 (m, 4H), 3.43 – 3.31 (m, 4H), 2.39 (s, 3H), 2.38 (s, 3H), 2.27 (s, 3H), 2.10 – 2.00 (m, 1H), 1.66 (d, J = 6.0 Hz, 3H), 0.99 - 0.93 (m, 4H).
289	ES+ 576.3 [M+H]	^{1}H NMR (400 MHz, CD_3OD): δ 9.15 (s, 2H), 8.97 (s, 1H), 8.46 (s, 1H), 7.53 (d, J = 1.6 Hz, 1H), 7.25 (s, 1H), 7.12 (d, J = 8.6 Hz, 1H), 6.82 (d, J = 8.6 Hz, 1H), 5.22 – 5.18 (m, 1H), 3.88 (s, 3H), 2.57 (s, 3H), 2.44 – 2.32 (m, 9H), 1.71 (d, J = 6.6 Hz, 3H).
290	ES+ 541.1 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.69 (s, 1H), 7.65 – 7.45 (m, 1H), 7.37 – 7.22 (m, 2H), 6.63 (s, 1H), 6.12 (d, J = 6.4 Hz, 2H), 5.08 – 4.99 (m, 1H), 3.30 – 3.26 (m, 4H), 3.24 – 3.11 (m, 4H), 2.96 (s, 3H), 2.24 (d, J = 1.2 Hz, 3H), 2.15 (s, 3H), 1.56 (d, J = 6.5 Hz, 3H).
291	ES+ 514.5 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.81 – 8.55 (m, 1H), 7.65 (d, J = 2.6, 1H), 7.41 – 7.32 (m, 2H), 6.72 (d, J = 6.7 Hz, 1H), 6.61 (s, 1H), 6.41 (d, J = 9.2 Hz, 1H), 5.20 – 5.04 (m, 1H), 3.31 – 3.25 (m, 4H), 3.23 – 3.12 (m, 4H), 2.96 (s, 3H), 2.25 (d, J = 1.3 Hz, 3H), 2.14 (s, 3H), 1.60 (d, J = 6.6 Hz, 3H).
292	ES+ 569.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_5): δ 8.68 – 8.64 (m, 1H), 7.46 – 7.43 (m, 1H), 7.30 – 7.25 (m, 2H), 6.47 (s, 2H), 5.19 – 5.12 (m, 1H), 3.34 – 3.28 (m, 11H), 2.96 (s, 3H), 2.23 (s, 3H), 2.20 (s, 3H), 1.59 (d, J = 6.3 Hz, 3H).
293	ES+ 551.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.72– 8.69 (m, 1H), 7.48– 7.43 (m, 1H), 7.37 – 7.27 (m, 2H), 6.62 (s, 1H), 6.51 – 6.42 (m, 2H), 5.18–

		5.10 (m, 1H), 3.32– 3.27 (m, 7H), 3.23 – 3.13 (m, 4H), 2.96 (s, 3H), 2.24 (d, J = 1.3 Hz, 3H), 2.15 (s, 3H), 1.60 (d, J = 6.5 Hz, 3H).
294	ES+ 498.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.69 (s, 1H), 7.54 – 7.45 (m, 1H), 7.37 (d, J = 1.8 Hz, 1H), 7.30 – 7.19 (m, 1H), 6.64 (s, 1H), 6.48 (d, J = 6.7 Hz, 1H), 6.44 – 6.36 (m, 1H), 5.13 – 5.05 (m, 1H), 3.29 (d, J = 4.9 Hz, 4H), 3.24 – 3.12 (m, 4H), 2.96 (s, 3H), 2.24 (d, J = 1.2 Hz, 3H), 2.15 (s, 3H), 1.59 (d, J = 6.5 Hz, 3H).
295	ES+ 579.3 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.73 – 8.54 (m, 1H), 7.27 (s, 1H), 7.18 (d, J = 8.6 Hz, 1H), 6.87 (d, J = 8.8 Hz, 1H), 5.60 (s, 1H), 5.47 – 5.26 (m, 1H), 5.22 – 5.06 (m, 1H), 4.34 – 4.18 (m, 2H), 4.07 – 3.93 (m, 2H), 3.46 – 3.36 (m, 4H), 3.23 – 3.20 (m, 4H), 2.31 (s, 3H), 2.21 (s, 3H), 2.18 (d, J = 1.3 Hz, 3H), 1.59 (d, J = 6.5 Hz, 3H).
296	ES+ 582.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.23 (s, 2H), 8.86 – 8.77 (m, 2H), 7.82 – 7.74 (m, 1H), 7.41 (d, J = 1.7 Hz, 1H), 7.38 – 7.31 (m, 1H), 7.26 – 7.15 (m, 2H), 6.51 – 6.43 (m, 1H), 5.50 (d, J = 6.2 Hz, 1H), 5.28 – 5.18 (m, 1H), 2.61 (s, 3H), 2.31 (d, J = 1.2 Hz, 3H), 2.25 (s, 3H), 1.60 (d, J = 6.5 Hz, 3H).
297	ES+ 571.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.03 (s, 2H), 8.86 (s, 1H), 7.82 – 7.74 (m, 1H), 7.55 – 7.45 (m, 2H), 7.33 (s, 1H), 6.90 (s, 1H), 6.65 – 6.59 (m, 2H), 6.55 – 6.50 (m, 1H), 5.65 – 5.55 (m, 1H), 5.28 – 5.18 (m, 1H), 2.61 (s, 3H), 2.31 (d, J = 1.2 Hz, 3H), 2.25 (s, 3H), 1.60 (d, J = 6.5 Hz, 3H).
298	ES+ 556.0 [M+H]	^{1}H NMR (400 MHz, CD_3OD): δ 8.80 (s, 1H), 7.44 (s, 1H), 7.15 (d, J = 8.6 Hz, 1H), 6.88 (d, J = 8.7 Hz, 1H), 5.46 – 5.23 (m, 1H), 3.57 – 3.35 (m, 8H), 2.94 (s, 3H), 2.50 – 2.33 (m, 6H), 2.30 – 2.12 (m, 3H), 1.79 – 1.53 (m, 3H).

299	ES+ 560.0 [M+H]	^{1}H NMR (400 MHz, CD_3OD): δ 8.98 – 8.66 (m, 1H), 7.57 – 7.39 (m, 1H), 7.15 (d, J = 8.6 Hz, 1H), 6.88 (d, J = 8.7 Hz, 1H), 5.44 – 5.25 (m, 1H), 3.88 (m, 4H), 3.37 (m, 4H), 2.48 – 2.34 (m, 6H), 2.32 – 2.10 (m, 3H), 1.75 – 1.57 (m, 3H), 1.38 (s, 3H), 1.11 – 0.89 (m, 2H), 0.83 – 0.51 (m, 2H).
300	ES+ 552.2 [M+H]	^{1}H NMR (400 MHz, CD_3OD): δ 8.82 (s, 1H), 7.41 (d, J = 1.7 Hz, 1H), 7.16 (d, J = 8.6 Hz, 1H), 6.86 (d, J = 8.7 Hz, 1H), 6.74 (s, 1H), 5.28 (d, J = 5.7 Hz, 1H), 5.11 – 4.86 (m, 1H), 4.23 – 4.17 (m, 1H), 3.69 – 3.59 (m, 1H), 3.56 – 3.49 (m, 1H), 3.44 – 3.36 (m, 1H), 3.33 – 3.25 (m, 1H), 3.08 – 3.06 (m, 1H), 3.00 (s, 3H), 2.92 – 2.81 (m, 1H), 2.39 (s, 3H), 2.34 – 2.29 (m, 6H), 1.71 (d, J = 6.6 Hz, 3H), 1.52 (d, J = 6.8 Hz, 3H).
301	ES+ 562.3 [M+H]	^{1}H NMR (400 MHz, CD_3OD): δ 9.13 (s, 2H), 9.03 – 8.86 (m, 2H), 7.98 (d, J = 2.0 Hz, 1H), 7.52 (s, 1H), 7.23 (s, 1H), 7.12 (d, J = 8.8 Hz, 1H), 6.82 (d, J = 8.8 Hz, 1H), 5.34 (d, J = 5.6 Hz, 1H), 5.28 – 5.12 (m, 1H), 3.89 (s, 3H), 2.38 (s, 3H), 2.37 (s, 3H), 2.33 (s, 3H), 1.71 (d, J = 6.4 Hz, 3H).
302	ES+ 579.3 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.21 (s, 2H), 8.83 (s, 1H), 7.57 – 7.50 (m, 1H), 7.41 (d, J = 1.7 Hz, 1H), 7.21 (s, 1H), 7.17 (d, J = 8.6 Hz, 1H), 6.84 (d, J = 8.7 Hz, 1H), 6.74 – 6.70 (m, 1H), 5.70 (d, J = 6.6 Hz, 1H), 5.24 – 5.20 (m, 1H), 3.65 (s, 3H), 2.34 – 2.30 (m, 6H), 2.25 (s, 3H), 1.61 (d, J = 6.5 Hz, 3H).
303	ES+ 561.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.20 (s, 2H), 8.82 (s, 1H), 7.57 – 7.50 (m, 1H), 7.43 – 7.16 (m, 3H), 7.09 – 6.95 (m, 1H), 6.78 – 6.69 (m, 2H), 5.88 (d, J = 6.6 Hz, 1H), 5.19 – 5.10 (m, 1H), 3.65 (s, 3H), 2.33 (s, 3H), 2.29 (s, 3H), 2.25 (s, 3H), 1.58 (d, J = 6.5 Hz, 3H).
304	ES+ 531.2 [M+H]	^{1}H NMR (400 MHz, CD_3OD): δ 8.81 (s, 1H), 7.43 (d, J = 1.2 Hz, 1H), 7.36 – 7.02 (m, 2H), 6.78 (s, 1H), 6.18 – 6.10 (m, 1H), 5.12 – 5.00

		(m, 1H), 4.10 – 3.90 (m, 2H), 3.88 – 3.79 (m, 2H), 3.32 – 3.09 (m, 4H), 2.33 (s, 3H), 2.31 (s, 3H), 2.10 – 2.00 (m, 1H), 1.67 (d, J = 6.8 Hz, 3H), 0.95 – 0.83 (m, 4H).
305	ES+ 570.3 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.71 – 8.61 (m, 1H), 7.27 (s, 1H), 7.19 (d, J = 8.6 Hz, 1H), 6.88 (d, J = 8.6 Hz, 1H), 5.59 (s, 1H), 5.22 – 5.15 (m, 1H), 4.11 – 3.98 (m, 1H), 3.57 – 3.39 (m, 4H), 3.21 – 3.10 (m, 2H), 3.02 (s, 3H), 2.32 (s, 3H), 2.26 (s, 3H), 2.18 (d, J = 1.3 Hz, 3H), 1.61 – 1.55 (m, 3H), 1.36 (d, J = 6.7 Hz, 3H).
306	ES+ 552.3 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.68 (s, 1H), 7.28 (d, J = 1.7 Hz, 1H), 7.20 (d, J = 8.6 Hz, 1H), 6.85 (d, J = 8.7 Hz, 1H), 6.59 (s, 1H), 5.62 (d, J = 6.5 Hz, 1H), 5.20 – 5.10 (m, 1H), 4.06 (d, J = 7.2 Hz, 1H), 3.53 (d, J = 13.1 Hz, 1H), 3.41 (d, J = 11.9 Hz, 1H), 3.29 (s, 1H), 3.20 (d, J = 12.2 Hz, 1H), 3.05 – 3.00 (m, 1H), 3.00 (s, 3H), 2.88 – 2.83 (m, 1H), 2.31 (s, 3H), 2.22 (d, J = 1.2 Hz, 3H), 2.17 (s, 3H), 1.60 (d, J = 6.5 Hz, 3H), 1.40 (d, J = 6.7 Hz, 3H).
307	ES+ 590.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.66 (s, 1H), 7.28 (s, 1H), 7.17 (d, J = 8.6 Hz, 1H), 6.86 (d, J = 8.5 Hz, 1H), 5.61 (s, 1H), 5.17 – 5.13 (m, 1H), 3.70 – 3.60 (m, 4H), 3.25 – 3.15 (m, 4H), 2.42 (d, J = 2.5 Hz, 6H), 2.31 (s, 3H), 2.22 (s, 3H), 2.18 (s, 3H), 1.58 (d, J = 6.3 Hz, 3H).
308	ES+ 561.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.72 – 8.62 (m, 1H), 7.26 (d, J = 1.8 Hz, 1H), 7.19 (d, J = 8.6 Hz, 1H), 6.84 (d, J = 8.7 Hz, 1H), 6.59 (s, 1H), 5.61 (d, J = 6.5 Hz, 1H), 5.48 – 5.24 (m, 1H), 5.19 – 5.02 (m, 1H), 4.34 – 4.15 (m, 2H), 4.08 – 3.91 (m, 2H), 3.49 – 3.37 (m, 4H), 3.11 – 2.94 (m, 4H), 2.30 (s, 3H), 2.22 (d, J = 1.2 Hz , 3H), 2.14 (s, 3H), 1.59 (d, J = 6.5 Hz, 3H).
309	ES+ 565.3 [M+H]	^{1}H NMR (400 MHz, CD_3CN): δ 9.04 (s, 2H), 8.87 (s, 1H), 8.12 (s, 1H), 7.74 (s, 1H), 7.40 (d, J = 1.6 Hz, 1H), 7.32 – 7.15 (m, 1H), 7.03 (d, J = 9.5 Hz, 1H), 6.93 (s, 1H), 6.11 – 6.04 (m, 1H), 5.19 (s, 1H), 5.03 –

		4.97 (m, 1H), 3.63 (s, 3H), 2.31 (d, J = 1.2 Hz, 3H), 2.27 (s, 3H), 1.61 (d, J = 6.7 Hz, 3H).
310	ES+ 565.2 [M+H]	^{1}H NMR (400 MHz, CD_3CN): δ 9.04 (s, 2H), 8.88 (s, 1H), 8.12 (s, 1H), 7.74 (s, 1H), 7.39 (d, J = 1.5 Hz, 1H), 7.30 – 7.27 (m, 1H), 7.03 – 6.98 (m, 1H), 6.94 (s, 1H), 6.40 – 6.37 (m, 1H), 5.04 – 4.99 (m, 1H), 4.90 (d, J = 5.3 Hz, 1H), 3.63 (s, 3H), 2.30 (d, J = 1.2 Hz, 3H), 2.28 (s, 3H), 1.62 (d, J = 6.6 Hz, 3H).
311	ES+ 568.3 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.70 – 8.69 (m, 1H), 8.04 (d, J = 2.9 Hz, 1H), 7.27 (d, J = 1.7 Hz, 1H), 7.19 (d, J = 8.6 Hz, 1H), 6.84 (d, J = 8.7 Hz, 1H), 6.63 (s, 1H), 5.95 (d, J = 2.8 Hz, 1H), 5.62 (d, J = 6.5 Hz, 1H), 5.15 – 5.14 (m, 1H), 3.54 – 3.50 (m, 4H), 3.50 – 3.40 (m, 4H), 3.32 (s, 3H), 2.31 (s, 3H), 2.24 (s, 3H), 2.18 (s, 3H), 1.60 (d, J = 6.5 Hz, 3H).
312	ES+ 550.3 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.69 (s, 1H), 8.04 (d, J = 2.9 Hz, 1H), 7.26 (d, J = 4.1 Hz, 1H), 7.06 (d, J = 8.1 Hz, 2H), 6.72 (d, J = 8.6 Hz, 1H), 6.64 (s, 1H), 5.95 (d, J = 2.9 Hz, 1H), 5.81 (d, J = 6.3 Hz, 1H), 5.13 – 5.06 (m, 1H), 3.60 – 3.50 (m, 7H), 3.23 – 3.14 (m, 4H), 2.29 (s, 3H), 2.22 (s, 3H), 2.17 (s, 3H), 1.58 (d, J = 6.5 Hz, 3H).
313	ES+ 532.1 [M+H]	^{1}H NMR (400 MHz, CD_3OD): δ 9.70 (s, 2H), 9.09 – 9.01 (m, 3H), 7.59 – 7.57 (m, 1H), 7.33 (s, 1H), 7.07 (d, J = 8.4 Hz, 1H), 6.87 (s, 1H), 6.81 – 6.71 (m, 1H), 5.22 – 5.21 (m, 1H), 2.83 (s, 3H), 2.38 (s, 3H), 2.36 (s, 3H), 1.72 (d, J = 6.8, 3H).
314	ES+ 568.2 [M+H]	^{1}H NMR (400 MHz, CD_3OD): δ 9.14 (s, 2H), 9.05 – 9.03 (m, 1H), 7.70 – 7.66 (m, 1H), 7.60 – 7.57 (m, 1H), 7.37 (s, 1H), 7.31 – 7.28 (m, 1H), 7.09 – 7.02 (m, 1H), 6.91 – 6.89 (m, 1H), 6.78 – 6.75 (m, 1H), 6.45 – 6.43 (m, 1H), 5.24 – 5.19 (m, 1H), 3.71 (s, 3H), 2.37 (s, 3H), 1.72 (d, J = 6.4 Hz, 3H).

315	ES+ 579.1 [M+H]	^{1}H NMR (400 MHz, CD_3OD): δ 9.70 (s, 2H), 9.11 (s, 2H), 9.08 – 9.01 (m, 1H), 7.75 (d, J = 2.6 Hz, 1H), 7.63 – 7.55 (m, 1H), 7.37 – 7.30 (m, 1H), 6.81 (d, J = 5.4 Hz, 1H), 6.47 (d, J = 8.9 Hz, 1H), 5.29 – 5.22 (m, 1H), 3.29 – 3.22 (m, 3H), 2.83 (s, 3H), 2.37 (s, 3H), 1.74 (d, J = 6.6 Hz, 3H).
316	ES+ 516.2 [M+H]	^{1}H NMR (400 MHz, $CDCl_3$): δ 8.89 (s, 1H), 7.23 (s, 1H), 7.01 (d, J = 8.3 Hz, 1H), 6.54 (d, J = 8.6 Hz, 1H), 6.46 (s, 1H), 4.97 – 4.66 (m, 6H), 3.70 (s, 1H), 3.27 (m, 4H), 2.66 (m, 4H), 2.46 (s, 3H), 2.32 – 2.27 (m, 6H), 1.69 (d, J = 8.0 Hz, 3H).
317	ES+ 568.3 [M+H]	^{1}H NMR (400 MHz, CD_3OD): δ 9.14 (s, 2H), 9.04 – 9.02 (m, 1H), 7.70 – 7.66 (m, 1H), 7.60 – 7.58 (m, 1H), 7.38 – 7.24 (m, 1H), 7.11 – 7.05 (m, 1H), , 6.91 – 6.89 (m, 1H), 6.78 – 6.75 (m, 1H), 6.14 – 6.08 (m, 1H), 5.21 – 5.17 (m, 1H), 3.70 (s, 3H), 2.36 (s, 3H), 1.70 (d, J = 6.6 Hz, 3H).
318	ES+ 572.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.68 (d, J = 1.7 Hz, 1H), 7.27 (d, J = 1.8 Hz, 1H), 7.19 (d, J = 8.6 Hz, 1H), 6.84 (d, J = 8.7 Hz, 1H), 6.59 (s, 1H), 5.61 (d, J = 6.4 Hz, 1H), 5.13 – 5.10 (m, 1H), 3.68 – 3.65 (m, 4H), 3.11 – 2.94 (m, 4H), 2.42 (d, J = 2.4 Hz, 6H), 2.31 (d, J = 1.5 Hz, 3H), 2.22 (d, J = 1.4 Hz, 3H), 2.15 (d, J = 1.4 Hz, 3H), 1.59 (d, J = 6.4 Hz, 3H).
319	ES+ 564.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.20 (s, 2H), 8.83 (s, 1H), 7.65 – 7.46 (m, 2H), 7.42 – 7.36 (m, 1H), 7.32 – 7.20 (m, 2H), 6.70 – 6.65 (m, 1H), 6.64 – 6.59 (m ,1H), 6.20 (d, J = 6.1 Hz, 1H), 6.10 (d, J = 9.3 Hz, 1H), 5.20 – 5.11 (m, 1H), 3.53 (s, 3H), 2.32 (d, J = 1.2 Hz, 3H), 2.25 (s, 3H), 1.56 (d, J = 6.5 Hz, 3H).
320	ES+ 543.3 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.20 (s, 2H), 8.82 (s, 1H), 7.61 – 7.55 (m, 1H), 7.40 (d, J = 1.7 Hz, 1H), 7.34 – 7.14 (m, 2H), 7.13 – 6.96 (m, 1H), 6.77 – 6.55 (m, 3H), 5.87 (d, J = 6.4 Hz, 1H), 5.23 –

		5.15 (m, 1H), 3.53 (s, 3H), 2.32 – 2.27 (m, 6H), 2.25 (s, 3H), 1.58 (d, J = 6.5 Hz, 3H).
321	ES+ 544.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.25 (s, 2H), 8.82 (s, 1H), 8.21 (s, 1H), 7.79 (s, 1H), 7.40 (d, J = 1.7 Hz, 1H), 7.35 – 7.06 (m, 2H), 7.03 (d, J = 8.5 Hz, 1H), 6.72 (d, J = 8.6 Hz, 1H), 5.88 (d, J = 6.4 Hz, 1H), 5.21 – 5.18 (m, 1H), 3.62 (s, 3H), 2.32 – 2.27 (m, 6H), 2.25 (s, 3H), 1.58 (d, J = 6.5 Hz, 3H).
322	ES+ 560.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.69 (d, J = 2.1 Hz, 1H), 7.26 (d, J = 1.7 Hz, 1H), 7.19 (d, J = 8.6 Hz, 1H), 6.85 (d, J = 8.7 Hz, 1H), 6.60 (s, 1H), 5.61 (d, J = 6.5 Hz, 1H), 5.14 – 5.11 (m, 1H), 4.58 (s, 1H), 4.19 (d, J = 13.2 Hz, 1H), 3.36 (d, J = 11.6 Hz, 2H), 3.29 (d, J = 12.5 Hz, 1H), 3.01 – 2.80 (m, 2H), 2.30 (s, 3H), 2.25 – 2.18 (m, 6H), 1.59 (d, J = 6.5 Hz, 3H), 1.42 (s, 3H), 1.37 – 1.05 (m, 4H).
323	ES+ 564.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.20 (s, 2H), 8.83 (d, J = 2.0 Hz, 1H), 7.60 – 7.57 (m, 1H), 7.41 (d, J = 1.7 Hz, 1H), 7.37 – 7.34 (m, 1H), 7.23 (s, 1H), 7.22 – 7.18 (m, 1H), 6.70 – 6.57 (m, 1H), 6.63 – 6.58 (m, 1H), 6.45 – 6.43 (m, 1H), 5.50 (d, J = 6.3 Hz, 1H), 5.30 – 5.20 (m, 1H), 3.53 (s, 3H), 2.30 (d, J = 1.3 Hz, 3H), 2.25 (s, 3H), 1.60 (d, J = 6.5 Hz, 3H).
324	ES+ 528.2 [M+H]	^{1}H NMR (400 MHz, CD_3OD): δ 8.82 (s, 1H), 7.40 (d, J = 1.2 Hz, 1H), 7.14 (d, J = 8.4 Hz, 1H), 6.85 (d, J = 8.8 Hz, 1H), 6.77 (s, 1H), 5.16 – 5.07 (m, 1H), 3.93 – 3.75 (m, 4H), 3.27 – 3.00 (m, 2H), 2.38 (s, 3H), 2.32 (s, 6H), 2.10 – 2.00 (m, 1H), 1.70 (d, J = 6.4, 3H), 1.01 – 0.81 (m, 4H).
325	ES+ 593.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.70 (s, 1H), 7.43 – 7.28 (m, 3H), 7.20 (s, 1H), 6.97 (s, 1H), 6.65 (s, 1H), 6.19 (s, 1H), 5.36 – 5.28 (m, 1H), 4.95 (s, 1H), 3.75 (s, 3H), 3.21 – 3.03 (m, 11H), 2.22 (d, J = 17.3

		Hz, 3H), 2.16 (s, 3H), 2.05 – 1.95 (m, 1H), 1.80 – 1.70 (m, 1H), 1.57 (d, J = 6.4 Hz, 3H), 1.30 – 1.15 (m, 2H).
326	ES+ 554.3 [M+H]	^{1}H NMR (400 MHz, CD_3OD): δ 8.82 (s, 1H), 7.45 – 7.39 (m, 2H), 7.33 (d, J = 0.9 Hz, 1H), 7.17 (d, J = 8.6 Hz, 1H), 6.89 (d, J = 8.7 Hz, 1H), 6.78 (s, 1H), 5.13 (d, J = 6.6 Hz, 1H), 3.86 (s, 3H), 3.36 (d, J = 5.2 Hz, 2H), 3.29 – 3.20 (m, 3H), 3.18 – 3.11 (m, 1H), 3.06 – 3.00 (m, 1H), 2.39 (s, 3H), 2.34 – 2.30 (m, 6H), 1.72 (d, J = 6.6 Hz, 3H), 1.15 (d, J = 6.3 Hz, 3H).
327	ES+ 575.2 [M+H]	^{1}H NMR (400 MHz, CD_3OD): δ 8.82 (s, 1H), 7.41 (d, J = 1.7 Hz, 1H), 7.16 (d, J = 8.6 Hz, 1H), 6.85 (d, J = 8.6 Hz, 1H), 6.74 (s, 1H), 5.51 – 5.21 (m, 2H), 5.17 – 5.02 (m, 1H), 4.49 – 4.28 (m, 2H), 4.23 (s, 1H), 4.19 – 4.00 (m, 2H), 3.91 – 3.67 (m, 1H), 3.52 – 3.43 (m, 1H), 3.42 – 3.36 (m, 1H), 3.30 – 3.27 (m, 1H), 3.08 – 2.94 (m, 1H), 2.91 – 2.78 (m, 1H), 2.39 (s, 3H), 2.35 – 2.24 (m, 5H), 1.71 (d, J = 6.6 Hz, 3H), 1.47 (d, 3H).
328	ES+ 556.3 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.70 – 8.67 (m, 1H), 7.26 (d, J = 1.7 Hz, 1H), 7.19 (d, J = 8.6 Hz, 1H), 6.85 (d, J = 8.7 Hz, 1H), 6.58 (s, 1H), 5.60 (d, J = 6.5 Hz, 1H), 5.16 – 5.08 (m, 1H), 4.60 – 4.50 (m, 1H), 4.25 – 4.20 (m, 1H), 3.50 – 3.30 (m, 1H), 3.30 – 3.20 (m, 2H), 2.90 – 2.70 (m, 2H), 2.30 (s, 3H), 2.25 (s, 3H), 2.17 (s, 3H), 1.59 (d, J = 6.5 Hz, 3H), 1.34 (d, J = 6.0 Hz, 3H), 1.26 (s, 3H), 0.88 – 0.75 (m, 2H), 0.63 – 0.42 (m, 2H).
329	ES+ 566.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.59 – 9.57 (m, 2H), 9.19 (s, 2H), 8.82 (s, 1H), 7.46 – 7.41 (m, 2H), 7.19 (s, 1H), 7.00 – 6.97 (m, 1H), 6.20 – 6.19 (m, 1H), 5.29 – 5.26 (m, 1H), 2.75 (s, 3H), 2.50 – 2.31 (m, 3H), 2.25 (s, 3H), 1.62 – 1.61 (m, 3H).
330	ES+ 528.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.60 (s, 2H), 9.19 (s, 2H), 8.82 (s, 1H), 7.41 (d, J = 1.7 Hz, 1H), 7.24 – 6.98 (m, 3H), 6.74 (d, J = 8.6 Hz,

		1H), 5.87 (d, J = 6.4 Hz, 1H), 5.22 – 5.18 (m, 1H), 2.76 (s, 3H), 2.38 – 2.09 (m, 9H), 1.58 (d, J = 6.5 Hz, 3H).
331	ES+ 524.1 [M+H]	^{1}H NMR (400 MHz, CD_3OD): δ 8.89 – 8.88 (m, 1H), 7.50 – 7.47 (m, 1H), 7.10 (d, J = 8.5 Hz, 1H), 6.99 – 6.72 (m, 3H), 5.18 – 5.14 (m, 1H), 3.45 – 3.43 (m, 4H), 3.28 – 3.25 (m, 4H), 2.94 (s, 3H), 2.39 (s, 3H), 2.31 (s, 3H), 1.72 (d, J = 6.6 Hz, 3H).
332	ES+ 557.3 [M+H]	^{1}H NMR (400 MHz, CD_3OD): δ 9.70 (s, 2H), 9.09 (s, 2H), 8.96 (s, 1H), 7.60 (s, 1H), 7.25 (s, 1H), 6.90 – 6.88 (m, 1H), 6.71 – 6.68 (m, 1H), 6.21 – 6.19 (m, 1H), 5.12 – 4.86 (m, 1H), 3.67 – 3.60 (m, 1H), 2.92 – 2.89 (m, 1H), 2.83 (s, 3H), 2.39 – 2.33 (m, 6H), 2.00 – 1.99 (m, 1H), 1.73 – 1.68 (m, 4H).
333	ES+ 557.3 [M+H]	^{1}H NMR (400 MHz, CD_3OD): δ 9.70 (s, 2H), 9.08 (s, 2H), 8.97 (s, 1H), 7.60 (d, J = 1.7 Hz, 1H), 7.24 (s, 1H), 6.89 – 6.87 (m, 1H), 6.72 – 6.69 (m, 1H), 6.20 – 6.18 (m, 1H), 5.08 – 5.07 (m, 1H), 3.66 (d, J = 2.8 Hz, 1H), 2.92 – 2.88 (m, 1H), 2.83 (s, 3H), 2.40 (d, J = 1.3 Hz, 3H), 2.35 (s, 3H), 2.02 – 1.73 (m, 1H), 1.73 – 1.68 (m, 4H).
334	ES+ 562.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.69 (s, 1H), 7.45 (d, J = 8.9 Hz, 1H), 7.26 (d, J = 1.7 Hz, 1H), 6.98 (d, J = 9.0 Hz, 1H), 6.57 (s, 1H), 6.12 (d, J = 6.6 Hz, 1H), 5.19 – 5.16 (m, 1H), 4.75 – 4.55 (m, 1H), 4.33 – 4.18 (m, 1H), 3.65 – 3.42 (m, 1H), 3.41-3.23 (m, 1H), 3.01 – 2.77 (m, 3H), 2.26 – 2.12 (m, 6H), 2.02 – 2.00 (m, 1H), 1.61 (d, J = 6.6 Hz, 3H), 1.50 – 1.20 (m, 3H), 0.83 – 0.68 (m, 4H).
335	ES+ 588.2 [M+H]	^{1}H NMR (400 MHz, CD_3OD): δ 8.84 (s, 1H), 8.62 (s, 2H), 7.43 (s, 1H), 7.16 (d, J = 8.4 Hz, 1H), 6.89 – 6.82 (m, 2H), 6.82 – 6.49 (m, 1H), 5.28 – 5.02 (m, 1H), 3.78 – 3.58 (m, 4H), 3.43 – 3.36 (m, 4H), 2.39 (s, 3H), 2.34 (s, 3H), 2.33 (s, 3H), 1.72 (d, J = 6.8 Hz, 3H).

336	ES+ 540.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.69 (s, 1H), 7.32 (s, 1H), 7.27 (d, J = 1.6 Hz, 1H), 7.21 – 7.09 (m, 2H), 6.88 (d, J = 8.7 Hz, 1H), 6.62 (s, 1H), 5.60 (d, J = 6.6 Hz, 1H), 5.15 – 5.12 (m, 1H), 3.76 (s, 3H), 3.19 – 3.17 (m, 4H), 3.02 – 3.01 (m, 4H), 2.32 (s, 3H), 2.23 (d, J = 1.2 Hz, 3H), 2.15 (s, 3H), 1.62 (d, J = 6.5 Hz, 3H).
337	ES+ 542.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.69 (s, 1H), 7.27 (s, 1H), 7.20 (d, J = 8.6 Hz, 1H), 6.86 (d, J = 8.6 Hz, 1H), 6.60 (s, 1H), 5.60 (d, J = 6.5 Hz, 1H), 5.25 – 5.03 (m, 1H), 4.65 (s, 1H), 4.26 (s, 1H), 3.56 (s, 1H), 3.26 – 2.62 (m, 4H), 2.31 (s, 3H), 2.23 (s, 3H), 2.18 – 2.06 (m, 3H), 2.04 – 1.95 (m, 1H), 1.60 (d, J = 6.5 Hz, 3H), 1.50 – 1.14 (m, 3H), 0.91 – 0.67 (m, 4H).
338	ES+ 538.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.66 (d, J = 1.8 Hz, 1H), 7.30 (m, 1H), 7.19 (s, 1H), 7.05 (d, J = 8.4 Hz, 1H), 6.74 (s, 1H), 5.80 (s, 1H), 5.15 – 5.11 (m, 1H), 3.40 – 3.20 (m, 8H), 2.96 (s, 3H), 2.30 (s, 3H), 2.23 (s, 3H), 2.18 (d, J = 1.3 Hz, 3H), 1.57 (d, J = 6.3 Hz, 3H).
339	ES+ 542.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.68 (s, 1H), 7.27 (d, J = 1.8 Hz, 1H), 7.19 (d, J = 8.6 Hz, 1H), 6.85 (d, J = 8.7 Hz, 1H), 6.60 (s, 1H), 5.61 (d, J = 6.5 Hz, 1H), 5.16 – 5.08 (m, 1H), 3.65 – 3.55 (m, 4H), 3.09 – 2.99 (m, 4H), 2.30 (s, 3H), 2.22 (d, J = 1.3 Hz, 3H), 2.16 (s, 3H), 1.59 (d, J = 6.5 Hz, 3H), 1.27 (s, 3H), 0.86 – 0.79 (m, 2H), 0.61 – 0.54 (m, 2H).
340	ES+ 549.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.59 (s, 2H), 9.18 (s, 2H), 8.82 (s, 1H), 7.62 – 7.36 (m, 2H), 7.26 – 7.21 (m, 2H), 6.18 – 6.17 (m, 1H), 6.12 – 6.10 (m, 1H), 5.17 – 5.14 (m, 1H), 2.75 (s, 3H), 2.31 – 2.28 (m, 3H), 2.24 (s, 3H), 1.56 – 1.55 (m, 3H).
341	ES+ 550.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.61 (s, 2H), 9.21 (s, 2H), 8.99 – 8.82 (m, 1H), 7.67 – 7.43 (m, 1H), 7.37 (s, 1H), 7.19 (d, J = 8.6 Hz, 1H), 6.88 (d, J = 8.7 Hz, 1H), 5.98 – 5.72 (m, 1H), 5.41 – 5.18 (m,

		1H), 2.76 (s, 3H), 2.33 – 2.31 (m, 3H), 2.29 – 2.25 (m, 3H), 1.63 (d, J = 6.6 Hz, 3H).
342	ES+ 553.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.61 (s, 2H), 9.21 (s, 2H), 8.99 – 8.79 (m 1H), 7.78 – 7.43 (m, 1H), 7.42 – 7.34 (m, 2H), 7.29 – 7.11 (m, 1H), 6.61 – 6.33 (m, 1H), 5.71 – 5.54 (m, 1H), 5.38 – 5.20 (m, 1H), 2.76 (s, 3H), 2.28 (s, 3H), 1.62 (d, J = 6.5 Hz, 3H).
343	ES+ 559.2 [M+H]	^{1}H NMR (400 MHz, CD_3OD): δ 8.94 – 8.88 (m, 1H), 8.5-8.44 (m, 3H), 7.52 – 7.45 (m, 1H), 7.33 – 7.26 (m, 1H), 7.14 – 7.05 (m, 1H), 6.92 (s, 1H), 6.51 – 6.43 (m, 1H), 5.22 – 5.12 (m, 1H), 3.53 – 3.46 (m, 4H), 3.44 – 3.34 (m, 4H), 2.62 (s, 3H), 2.34 (s, 3H), 1.72 (d, J = 6.6 Hz, 3H).
344	ES+ 552.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.70 (s, 1H), 8.47 (s, 2H), 7.28 (d, J = 1.9 Hz, 1H), 7.20 (d, J = 8.6 Hz, 1H), 6.87 (d, J = 8.7 Hz, 1H), 6.65 (s, 1H), 5.68 – 5.48 (m, 1H), 5.20 – 5.02 (m 1H), 3.48 – 3.33 (m, 4H), 3.29 – 3.13 (m, 4H), 2.52 (s, 3H), 2.31 (s, 3H), 2.22 – 2.19 (m, 3H) 2.18 (s, 3H), 1.62 (d, J = 6.5 Hz, 3H).
345	ES+ 520.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.68 (s, 1H), 7.36 – 7.00 (m, 3H), 6.75 (d, J = 8.6 Hz, 1H), 6.62 (s, 1H), 5.80 (d, J = 6.4 Hz, 1H), 5.10 – 5.06 (m, 1H), 3.30 – 3.25 (m, 4H), 3.21 – 3.12 (m, 4H), 2.96 (s, 3H), 2.29 (s, 3H), 2.22 (d, J = 1.2 Hz, 3H), 2.14 (s, 3H), 1.58 (d, J = 6.5 Hz, 3H).
346	ES+ 561.3 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.21 (s, 2H), 8.82 (d, 1H), 7.61 – 7.54 (m, 1H), 7.43 – 7.39 (m, 1H), 7.22 (s, 1H), 7.19 – 7.15 (m, 1H), 6.86 – 6.82 (m, 1H), 6.71 – 6.66 (m, 1H), 6.63 – 6.59 (m, 1H), 5.72 – 5.68 (m, 1H), 5.28 – 5.20 (m, 1H), 3.53 (s, 3H), 2.32 – 2.28 (m, 6H), 2.25 (s, 3H), 1.61 (d, 3H).

347	ES+ 546.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.60 (s, 2H), 9.19 (s, 2H), 8.82 (s, 1H), 7.41 (d, J = 1.7 Hz, 1H), 7.21 (s, 1H), 7.17 (d, J = 8.6 Hz, 1H), 6.85 (d, J = 8.7 Hz, 1H), 5.70 (d, J = 6.5 Hz, 1H), 5.28 – 5.20 (m, 1H), 2.75 (s, 3H), 2.31 (s, 3H), 2.28 (s, 3H), 2.25 (s, 3H), 1.60 (d, J = 6.5 Hz, 3H).
348	ES+ 559.0 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.59 (s, 2H), 9.20 (s, 2H), 8.84 (s, 1H), 7.50 – 7.46 (m, 1H), 7.41 (d, J = 1.7 Hz, 1H), 7.33 – 7.24 (m, 1H), 7.21 (s, 1H), 6.51 (d, J = 5.5 Hz, 1H), 6.48 – 6.42 (m, 1H), 5.27 – 5.20 (m, 1H), 3.35 (s, 3H), 2.75 (s, 3H), 2.32 (d, J = 1.3 Hz, 3H), 2.25 (s, 3H), 1.59 (d, J = 6.4 Hz, 3H).
349	ES+ 538.1 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.68 (s, 1H), 7.28 (d, J = 1.7 Hz, 1H), 7.20 (d, J = 8.7 Hz, 1H), 6.86 (d, J = 8.7 Hz, 1H), 6.61 (s, 1H), 5.63 (d, J = 6.5 Hz, 1H), 5.15 – 5.12 (m, 1H), 3.28 (d, J = 4.8 Hz, 4H), 3.18 – 3.15 (m, 4H), 2.96 (s, 3H), 2.31 (s, 3H), 2.22 (d, J = 1.2 Hz, 3H), 2.14 (s, 3H), 1.60 (d, J = 6.6 Hz, 3H).
350	ES+ 541.1 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.69 (s, 1H), 7.37 – 7.34 (m, 1H), 7.28 (s, 1H), 7.26 – 7.18 (m, 1H), 6.64 (s, 1H), 6.48 – 6.44 (m, 1H), 5.42 (d, J = 6.2 Hz, 1H), 5.14 – 5.10 (m, 1H), 3.32 – 3.28 (m, 4H), 3.22 – 3.11 (m, 4H), 2.96 (s, 3H), 2.23 (s, 3H), 2.15 (s, 3H), 1.60 (d, J = 6.4 Hz, 3H).
351	ES+ 523.1 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.69 (s, 1H), 7.54 – 7.24 (m, 2H), 7.25 – 7.15 (m, 1H), 7.08 – 7.03 (m, 1H), 6.65 (s, 1H), 6.35 – 6.32 (m, 1H), 5.80 (d, J = 6.1 Hz, 1H), 5.07 – 5.02 (m, 1H), 3.31 – 3.29 (m, 4H), 3.23 – 3.14 (m, 4H), 2.96 (s, 3H), 2.23 (d, J = 1.3 Hz, 3H), 2.15 (s, 3H), 1.57 (d, J = 6.5 Hz, 3H).
352	ES+ 545.1 [M+H]	^{1}H NMR (400 MHz, DMSO-d_5): δ 8.79 – 8.78 (m, 1H), 7.43 – 7.40 (m, 2H), 7.25 – 7.20 (m, 1H), 6.78 (s, 1H), 6.49 – 6.46 (m, 1H), 5.56

		(d, J = 6.4 Hz, 1H), 5.22 – 5.20 (m, 1H), 3.33 – 3.13 (m, 8H), 2.97 (s, 3H), 2.18 (s, 3H), 1.62 (d, J = 6.5 Hz, 3H).
353	ES+ 605.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.79-8.77 (m, 1H), 7.94 – 7.49 (m, 3H), 7.44 – 7.41 (m, 1H), 7.24 – 7.22 (m, 1H), 6.79 (s, 1H), 6.48 – 6.45 (m, 1H), 5.62 (d, J = 6.9 Hz, 1H), 5.40 – 5.24 (m, 1H), 3.69 – 3.65 (m, 2H), 3.29 – 3.18 (m, 6H), 3.14 (d, J = 4.8 Hz, 4H), 2.17 (s, 3H), 1.62 (d, J = 6.5 Hz, 3H).
354	ES+ 587.2 [M+H]	^{1}H NMR (400 MHz, CD_3OD): δ 8.93 – 8.86 (m, 1H), 7.68 – 7.60 (m, 2H), 7.59 – 7.48 (m, 1H), 7.38 – 7.26 (m, 2H), 6.92 (s, 1H), 6.72 (d, J = 7.5 Hz, 1H), 6.42 (d, J = 8.2 Hz, 1H), 5.31 – 5.23 (m, 1H), 3.60 – 3.52 (m, 2H), 3.37 – 3.33 (m, 1H), 3.32 – 3.27 (m, 5H), 3.24 – 3.17 (m, 4H), 2.31 (s, 3H), 1.74 (d, J = 6.7 Hz, 3H).
355	ES+ 542.1 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.78 – 8.76 (m, 1H), 7.43 – 7.41 (m, 1H), 7.21 (d, J = 8.6 Hz, 1H), 6.88 (d, J = 8.6 Hz, 1H), 6.75 (s, 1H), 5.75 (d, J = 6.7 Hz, 1H), 5.25 – 5.17 (m, 1H), 3.32 – 3.20 (m, 8H), 2.94 (d, J = 16.9 Hz, 3H), 2.32 (s, 3H), 2.17 (s, 3H), 1.62 (d, J = 6.5 Hz, 3H).
356	ES+ 527.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.78 – 8.75 (m, 1H), 7.44 – 7.16 (m, 3H), 7.11 – 7.02 (m, 1H), 6.79 (s, 1H), 6.35 – 6.32 (m, 1H), 5.86 (d, J = 6.2 Hz, 1H), 5.18 – 5.10 (m, 1H), 3.32 – 3.14 (m, 8H), 2.97 (s, 3H), 2.17 (s, 3H), 1.58 (d, J = 6.5 Hz, 3H).
358	ES+ 601.2 [M+H]	^{1}H NMR (400 MHz, $CDCl_3$): δ 9.13 – 9.00 (m, 1H), 8.79 (d, J = 2.2 Hz, 1H), 8.65 – 8.51 (m, 2H), 8.48 (d, J = 1.9 Hz, 1H), 7.55 – 7.38 (m, 2H), 7.19 – 7.11 (m, 1H), 6.73 (s, 1H), 6.11 (d, J = 8.9 Hz, 1H), 4.87 – 4.81 (m, 1H), 4.76 (bs, 1H), 3.90 (s, 3H), 2.41 (s, 3H), 1.72 (d, J = 6.6 Hz, 3H).

359	ES+ 618.8 [M+H]	^{1}H NMR (400 MHz, CD_3OD): δ 9.04 – 9.03 (m, 1H), 8.99 – 8.98 (d, J = 1.8 Hz, 1H), 8.71 – 8.70 (d, J = 1.9 Hz, 1H), 7.67 – 7.65 (m, 1H), 7.58 – 7.55 (m, 1H), 7.49 – 7.48 (d, J = 2.5 Hz, 1H), 7.37 (s, 1H), 7.26 – 7.23 (m, 1H), 6.66 – 6.62 (m, 1H), 6.44 – 6.41 (d, J = 9.0 Hz, 1H), 5.39 – 5.37 (d, J = 5.4 Hz, 1H), 5.24 – 5.23 (m, 1H), 3.73 (s, 3H), 2.39 (s, 3H), 1.72 – 7.71 (d, J = 6.6 Hz, 3H).
360	ES+ 584.1 [M+H]	^{1}H NMR (400 MHz, CD_3OD): δ 9.14 – 9.12 (m, 3H), 8.56 – 8.54 (d, J = 6.1 Hz, 1H), 8.15 – 8.13 (m, 1H), 7.60 – 7.57 (m, 1H), 7.53 – 7.52 (d, J = 2.1 Hz, 1H), 7.30 – 7.27 (m, 2H), 7.10 – 7.04 (m, 1H), 6.47 – 6.44 (m, 1H), 5.21 – 5.16 (m, 1H), 2.84 (s, 3H), 2.37 (s, 3H), 1.70 (d, J = 6.5 Hz, 3H).
361	ES+ 600.1 [M+H]	^{1}H NMR (400 MHz, CD_3OD): δ 9.14 – 9.12 (m, 3H), 8.56 – 8.54 (d, J = 6.3 Hz, 1H), 8.15 – 8.13 (m, 1H), 7.59 – 7.57 (m, 1H), 7.50 – 7.48 (m, 2H), 7.30 (s, 1H), 7.28 – 7.24 (m, 1H), 6.46 (d, J = 9.0 Hz, 1H), 5.22 – 5.20 (m, 1H), 2.84 (s, 3H), 2.36 (s, 3H), 1.71 (d, J = 6.6 Hz, 3H).
362	ES+ 610.1 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.21 – 9.15 (m, 2H), 8.99 – 8.90 (m, 1H), 8.40 – 8.35 (m, 1H), 7.62 – 7.56 (m, 2H), 7.55 – 7.49 (m, 1H), 7.46 – 7.42 (m, 1H), 7.40 – 7.31 (m, 2H), 6.52 (d, J = 9.2 Hz, 1H), 5.86 (d, J = 6.4 Hz, 1H), 5.41 – 5.30 (m, 1H), 2.27 (s, 3H), 2.16 – 2.01 (m, 1H), 1.64 (d, J = 6.4 Hz, 3H), 0.91 – 0.80 (m, 2H), 0.49 – 0.35 (m, 2H).
363	ES+ 618.1 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.92 (d, J = 3.2 Hz, 1H), 8.36 (d, J = 2.0 Hz, 1H), 7.78 – 7.76 (m, 1H), 7.57 – 7.48 (m, 2H), 7.39 – 7.32 (m, 3H), 6.54 – 6.46 (m, 2H), 5.87 (d, J = 6.6 Hz, 1H), 5.38 – 5.30 (m, 1H), 3.59 (s, 3H), 2.28 (s, 3H), 1.63 (d, J = 6.5 Hz, 3H).
364	ES+ 634.1 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.09 (d, J = 1.9 Hz, 1H), 8.94 – 8.91 (m, 1H), 8.65 (d, J = 1.9 Hz, 1H), 7.92 (d, J = 7.0 Hz, 1H), 7.53 – 7.38

		(m, 4H), 6.52 – 6.48 (m, 2H), 5.88 (d, J = 6.7 Hz, 1H), 5.38 – 5.34 (m, 1H), 3.61 (s, 3H), 2.29 (s, 3H), 1.64 (d, J = 6.6 Hz, 3H).
365	ES+ 619.1 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.93 – 8.86 (m, 1H), 8.28 – 8.21 (m, 1H), 7.76 – 7.71 (m, 1H), 7.55 – 7.50 (m, 1H), 7.40 – 7.31 (m, 1H), 7.30 (s, 1H), 7.26 –7.15 (m, 1H), 6.80 – 6.71 (m, 1H), 6.55 – 6.40 (m, 2H), 5.68 – 5.58 (m, 1H), 5.28 – 5.20 (m, 1H), 3.48 (s, 3H), 2.19 (s, 3H), 1.59 (d, J = 6.4 Hz, 3H).
366	ES+ 619.1 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.95 – 8.86 (m, 1H), 7.85 – 7.75 (m, 1H), 7.73 – 7.69 (m, 1H), 7.56 – 7.49 (m, 1H), 7.40 – 7.34 (m, 1H), 7.32 (s, 1H), 7.26 –7.15 (m, 1H), 6.61 – 6.38(m, 3H), 5.71 – 5.58 (m, 1H), 5.29 – 5.20 (m, 1H), 3.59 (s, 3H), 2.19 (s, 3H), 1.59 (d, J = 6.4 Hz, 3H).
367	ES+ 611.1 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.75 (s, 2H), 9.10 (d, J = 1.9 Hz, 1H), 8.98 (d, J = 2.0 Hz, 1H), 8.71 (d, J = 1.9 Hz, 1H), 7.64 (d, J = 2.6 Hz, 1H), 7.47 (d, J = 2.0 Hz, 1H), 7.45 – 7.38 (m, 1H), 7.32 (s, 1H), 6.68 (d, J = 5.5 Hz, 1H), 6.46 (d, J = 9.0 Hz, 1H), 5.30 – 5.23 (m, 1H), 3.39 (s, 3H), 2.75 (s, 3H), 2.30 (s, 3H), 1.63 (d, J = 6.5 Hz, 3H).
368	ES+ 595.1 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.75 (s, 2H), 9.10 (d, J = 1.9 Hz, 1H), 8.98 (d, J = 2.0 Hz, 1H), 8.71 (d, J = 1.9 Hz, 1H), 7.51 – 7.44 (m, 1H), 7.47 (s, 1H), 7.35 – 7.25 (m, 2H), 6.56 – 6.41 (m, 2H), 5.28 – 5.20 (m, 1H), 3.38 (s, 3H), 2.75 (s, 3H), 2.30 (s, 3H), 1.62 (d, J = 6.6 Hz, 3H).
369	ES+ 595.0 [M+H]	^{1}H NMR (400 MHz, CD_3OD): δ 9.05 – 8.98 (m, 1H), 8.86 (d, J = 2.0 Hz, 1H), 8.58 (d, J = 2.0 Hz, 1H), 7.59 – 7.57 (m, 1H), 7.35 – 7.25 (m, 2H), 7.09 – 7.00 (m, 1H), 6.43 – 6.40 (m, 1H), 5.20 (m, J = 6.4 Hz, 1H), 3.31 (s, 3H), 2.34 (s, 3H), 2.05 – 1.97 (m, 2H), 1.83 – 1.73 (m, 2H), 1.70 (d, J = 6.6 Hz, 3H).

370	ES+ 585.1 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.29 (s, 2H), 8.94 – 8.92 (m, 1H), 7.95 (d, J = 3.1 Hz, 1H), 7.57 – 7.48 (m, 2H), 7.41 – 7.31 (m, 2H), 6.76 (d, J = 3.1 Hz, 1H), 6.49 (d, J = 9.0 Hz, 1H), 5.87 (d, J = 6.6 Hz, 1H), 5.33 – 5.30 (m, 1H), 4.01 (s, 3H), 2.28 (s, 3H), 1.63 (d, J = 6.6 Hz, 3H).
371	ES+ 587.1 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.06 (d, J = 1.8 Hz, 1H), 8.83 (s, 1H), 8.63 (d, J = 1.8 Hz, 1H), 7.91 (d, J = 7.0 Hz, 1H), 7.66 (d, J = 2.6 Hz, 1H), 7.51 (d, J = 1.7 Hz, 1H), 7.36 – 7.29 (m, 1H), 7.24 (s, 1H), 6.79 (d, J = 6.8 Hz, 1H), 6.50 (d, J = 6.9 Hz, 1H), 6.37 (d, J = 9.2 Hz, 1H), 5.28 – 5.20 (m, 1H), 3.60 (s, 3H), 2.32 (s, 3H), 2.26 (s, 3H), 1.60 (d, J = 6.5 Hz, 3H).
372	ES+ 595.1 [M+H]	^{1}H NMR (400 MHz, CD_3OD): δ 9.06 – 8.95 (m, 1H), 8.16 (d, J = 2.4 Hz, 1H), 7.68 – 7.52 (m, 1H), 7.39 – 7.21 (m, 2H), 7.15 (d, J = 2.4 Hz, 1H), 7.10 – 6.98 (m, 1H), 6.50 – 6.36 (m, 1H), 5.22 – 5.18 (m, 1H), 4.60 (s, 1H), 3.16 (s, 3H), 2.34 (s, 3H), 2.17 – 2.04 (m, 2H), 1.88 – 1.76 (m, 2H), 1.70 (d, J = 6.4 Hz, 3H).
373	ES+ 531.2 [M+H]	^{1}H NMR (400 MHz, $CDCl_3$): δ 8.86 (s, 1H), 7.45 (d, J = 2.5 Hz, 1H), 7.26 – 7.21 (m, 2H), 6.27 (d, J = 9.1 Hz, 1H), 5.28 (s, 1H), 4.91 (s, 1H), 4.05 (d, J = 11.9 Hz, 2H), 3.21 – 3.13 (m, 1H), 2.88 (s, 3H), 2.84 – 2.76 (m, 2H), 2.47 (s, 3H), 2.39 (d, J = 8.6 Hz, 2H), 2.29 (s, 3H), 1.95 – 1.86 (m, 2H), 1.65 (d, J = 6.4 Hz, 3H).
376	ES+ 634.1 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.13 (d, J = 1.9 Hz, 1H), 8.98 (d, J = 2.0 Hz, 1H), 8.69 (d, J = 1.8 Hz, 1H), 7.60 – 7.56 (m, 1H), 7.51 (d, J = 2.6 Hz, 1H), 7.46 (d, J = 2.1 Hz, 1H), 7.36 (d, J = 10.9 Hz, 2H), 6.56 – 6.53 (m, 1H), 6.49 (d, J = 9.0 Hz, 1H), 5.89 (d, J = 6.6 Hz, 1H), 5.29 – 5.23 (m, 1H), 3.42 (s, 3H), 2.32 (s, 3H), 1.64 (d, J = 6.5 Hz, 3H).
377	ES+ 594.0 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.99 – 8.82 (m, 1H), 8.58 (d, J = 1.6 Hz, 1H), 7.76 (d, J = 8.1 Hz, 1H), 7.64 – 7.42 (m, 2H), 7.41 – 7.30

		(m, 1H), 7.28 (s, 1H), 7.24 – 7.15 (m, 1H), 6.59 – 6.28 (m, 1H), 5.60 (d, J = 6.4 Hz, 1H), 5.43 – 5.19 (m, 1H), 3.20 (s, 3H), 2.21 (s, 3H), 1.98 – 1.78 (m, 2H), 1.60 (d, J = 6.5 Hz, 3H), 1.55 – 1.47 (m, 2H).
378	ES+ 634.1 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.08 (d, J = 1.0 Hz, 1H), 8.97 (d, J = 1.6 Hz, 1H), 8.67 (d, J = 1.6 Hz, 1H), 7.92 (d, J = 6.8 Hz, 1H), 7.48 (d, J = 1.6 Hz, 1H), 7.42 – 7.34 (m, 2H), 7.26 – 7.16 (m, 1H), 6.53 – 6.45 (m, 2H), 5.67 – 5.61 (m, 1H), 5.33 – 5.25 (m, 1H), 3.60 (s, 3H), 2.28 (s, 3H), 1.62 (d, J = 6.4 Hz, 3H).
379	ES+ 618.1 [M+H]	^{1}H NMR (400 MHz, CD_3OD): δ 9.06 – 9.01 (m, 1H), 8.73 – 8.66 (m, 1H), 8.29 (d, J = 2.0 Hz, 1H), 7.78 – 7.70 (m, 1H), 7.62 – 7.52 (m, 1H), 7.49 (d, J = 2.4 Hz, 1H), 7.33 (s, 1H), 7.30 (s, 1H), 7.29 – 7.20 (m, 1H), 6.45 (d, J = 8.8 Hz, 1H), 5.26 – 5.17 (m, 1H), 2.40 (s, 3H), 2.37 (s, 3H), 1.73 (d, J = 6.8 Hz, 3H).
380	ES+ 631.1 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.96 (d, J = 2.0 Hz, 1H), 8.34 (d, J = 2.0 Hz, 1H), 7.97 (d, J = 7.2 Hz, 1H), 7.48 (d, J = 2.1 Hz, 1H), 7.35 (d, J = 2.0 Hz, 1H), 7.29 (s, 1H), 7.19 (d, J = 8.6 Hz, 1H), 6.88 (d, J = 8.7 Hz, 1H), 6.58 (d, J = 7.2 Hz, 1H), 5.83 (d, J = 6.9 Hz, 1H), 5.35 – 5.27 (m, 1H), 3.61 (s, 3H), 2.32 (s, 3H), 2.27 (s, 3H), 1.62 (d, J = 6.5 Hz, 3H).
381	ES+ 618.0 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.08 (d, J = 1.8 Hz, 1H), 8.93 – 8.92 (m, 1H), 8.65 (d, J = 1.8 Hz, 1H), 7.92 (d, J = 7.0 Hz, 1H), 7.56 – 7.54 (m, 1H), 7.44 – 7.41 (s, 1H), 7.39 – 7.36 (m, 1H), 7.23 – 7.20 (m, 1H), 6.54 – 6.45 (m, 2H), 5.64 (d, J = 6.5 Hz, 1H), 5.36 – 5.28 (m, 1H), 3.61 (s, 3H), 2.29 (s, 3H), 1.63 (d, J = 6.5 Hz, 3H).
382	ES+ 585.1 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.01 – 8.89 (m, 1H), 8.60 (s, 1H), 8.51 (s, 1H), 8.36 (d, J = 2.0 Hz, 1H), 7.71 – 7.47 (m, 1H), 7.44 – 7.33 (m, 3H), 7.27 – 7.13 (m, 1H), 6.60 – 6.33 (m, 1H), 5.64 (d, J =

		6.4 Hz, 1H), 5.41 – 5.25 (m, 1H), 3.96 (s, 3H), 2.31 (s, 3H), 1.63 (d, J = 6.5 Hz, 3H).
383	ES+ 602.1 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.95 – 8.88 (m, 1H), 8.36 (d, J = 2.1 Hz, 1H), 7.81 – 7.74 (m, 1H), 7.58 – 7.51 (m, 1H), 7.41 – 7.33 (m, 3H), 7.25 – 7.15 (m, 1H), 6.53 – 6.44 (m, 2H), 5.63 (d, J = 6.4 Hz, 1H), 5.35 – 5.27 (m, 1H), 3.59 (s, 3H), 2.28 (s, 3H), 1.62 (d, J = 6.5 Hz, 3H).
384	ES+ 579.1 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.06 (s, 2H), 8.91 – 8.90 (m, 1H), 7.55 –7.52 (m, 1H), 7.41 – 7.34 (m, 2H), 7.20 –7.18 (m, 1H), 6.49 – 6.45 (m, 1H), 5.62 (d, J = 6.5 Hz, 1H), 5.30 (m, 1H), 3.50 (s, 3H), 2.23 (s, 3H), 1.94 – 1.85 (m, 2H), 1.85 – 1.73 (m, 2H), 1.60 (d, J = 6.5 Hz, 3H).
385	ES+ 578.1 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.93 – 8.87 (m, 1H), 8.77 (d, J = 2.0 Hz, 1H), 8.08 – 8.01 (m, 1H), 7.80 (d, J = 8.0 Hz, 1H), 7.53 - 7.46 (m, 1H), 7.40 - 7.33 (m, 1H), 7.26 – 7.15 (m, 2H), 6.51 – 6.43 (m, 1H), 5.59 (d, J = 5.6 Hz, 1H), 5.33 – 5.25 (m, 1H), 3.14 (s, 3H), 2.20 (s, 3H), 1.80 – 1.72 (m, 2H), 1.60 (d, J = 6.8 Hz, 3H), 1.57 – 1.50 (m, 2H).
386	ES+ 569.1 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.23 – 9.18 (m, 3H), 9.07 (s, 1H), 8.92 (d, J = 5.7 Hz, 1H), 7.55 (d, J = 8.4 Hz, 1H), 7.38 (d, J = 12.0 Hz, 2H), 7.22 (d, J = 9.2 Hz, 1H), 6.53 – 6.45 (m, 1H), 5.63 (d, J = 6.4 Hz, 1H), 5.33 – 5.26 (m, 1H), 2.68 (s, 3H), 2.27 (s, 3H), 1.62 (d, J = 6.4 Hz, 3H).
387	ES+ 513.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.71 (s, 1H), 7.64 (d, J = 2.5 Hz, 1H), 7.39 – 7.32 (m, 2H), 6.92 (s, 1H), 6.73 (d, J = 6.8 Hz, 1H), 6.39 (d, J = 9.2 Hz, 1H), 5.29 – 5.26 (m, 1H), 3.74 – 3.67 (m, 2H), 3.03 – 2.96 (m, 1H), 2.94 – 2.86 (m, 5H), 2.32 – 2.16 (m, 6H), 1.97 – 1.90 (m, 2H), 1.87 – 1.83 (ms, 2H), 1.58 (d, J = 6.6 Hz, 3H).

388	ES+ 640.0 [M+H]	^{1}H NMR (400 MHz, $CDCl_3$): δ 9.16 (s, 1H), 7.62 (d, J = 7.3 Hz, 1H), 7.47 (d, J = 2.4 Hz, 1H), 7.54 – 7.28 (m, 2H), 7.21 – 7.16 (m, 1H), 7.06 – 7.00 (m, 1H), 6.89 (s, 1H), 6.34 (d, J = 7.2 Hz, 1H), 6.23 (s, 1H), 6.19 – 6.11 (m, 1H), 4.93 (s, 1H), 4.86 (s, 1H), 3.68 (s, 3H), 2.34 (s, 3H), 1.75 (d, J = 6.5 Hz, 3H).
389	ES+ 618.2 [M+H]	^{1}H NMR (400 MHz, $CDCl_3$): δ 9.08 – 9.02 (m, 1H), 8.16 (d, J = 2.5 Hz, 1H), 7.51 (d, J = 2.5 Hz, 1H), 7.44 – 7.37 (m, 1H), 7.27 – 7.21 (m, 1H), 7.21 – 7.14 (m, 1H), 7.00 (d, J = 2.5 Hz, 1H), 6.76 (s, 1H), 6.38 – 6.30 (m, 1H), 6.14 (d, J = 8.8 Hz, 1H), 4.86 (s, 1H), 4.75 (s, 1H), 3.89 (s, 3H), 2.37 (s, 3H), 1.72 (d, J = 6.4 Hz, 3H).
392	ES+ 617.1 [M+H]	^{1}H NMR (400 MHz, $CDCl_3$): δ 9.06 – 9.02 (m, 1H), 8.60 – 8.40 (m, 1H), 7.51 (d, J = 2.5 Hz, 1H), 7.46 – 7.36 (m, 3H), 7.21 – 7.15 (m, 2H), 6.79 (s, 1H), 6.32 – 6.25 (m, 1H), 6.20 – 6.10 (m, 1H), 4.88 (d, J = 6.9 Hz, 1H), 4.76 (s, 1H), 2.50 (s, 3H), 2.35 (s, 3H), 1.73 (d, J = 6.6 Hz, 3H).
393	ES+ 593.2 [M+H]	^{1}H NMR (400 MHz, $CDCl_3$): δ 9.72 (s, 1H), 9.11 (s, 3H), 8.73 (d, J = 7.4 Hz, 1H), 8.53 (d, J = 8.9 Hz, 1H), 7.96 (d, J = 1.9 Hz, 1H), 7.88 – 7.70 (m, 1H), 7.55 – 7.44 (m, 2H), 7.18 – 7.12 (m, 1H), 6.80 (s, 1H), 6.17 (d, J = 8.8 Hz, 1H), 4.95 – 4.88 (m, 1H), 4.76 (s, 1H), 2.42 (s, 3H), 1.75 (d, J = 6.6 Hz, 3H).
394	ES+ 599.1 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.09 (d, J = 1.9 Hz, 1H), 8.93 – 8.92 (m, 1H), 8.86 (s, 1H), 8.67 (d, J = 1.9 Hz, 1H), 7.58 – 7.48 (m, 2H), 7.48 – 7.32 (m, 2H), 6.50 (d, J = 9.1 Hz, 1H), 5.88 (d, J = 6.5 Hz, 1H), 5.34 – 5.29 (m, 1H), 2.69 (s, 3H), 2.48 (s, 3H), 2.32 (s, 3H), 1.65 (d, J = 6.5 Hz, 3H).
395	ES+ 583.2 [M+H]	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.09 (d, J = 1.9 Hz, 1H), 8.93 – 8.92 (m, 1H), 8.86 (s, 1H), 8.67 (d, J = 1.7 Hz, 1H), 7.56 – 7.54 (m, 1H), 7.41 – 7.37 (m, 2H), 7.23 – 7.19 (m, 1H), 6.49 – 6.46 (m, 1H), 5.65

		(d, J = 6.4 Hz, 1H), 5.31 – 5.28 (m, 1H), 2.69 (s, 3H), 2.49 (s, 3H), 2.32 (s, 3H), 1.64 (d, J = 6.5 Hz, 3H).

Assays and Compound Testing

[000362] In vitro cell proliferation: Determination of EC50 values for inhibition of proliferation in T-47D cells expressing mutant PI3Kα (H1047R) mutation and SK-BR-3 cells expressing WT PI3Kα.

[000363] T-47D or SK-BR-3 cells were trypsinized, resuspended in culture media and seeded onto assay ready plates. T-47D culture media consisted of RPMI, 10% FBS and Insulin (0.2 units/mL). SK-BR-3 culture media consisted of McCoys 5a and 10% FBS. Cells were seeded at a density of 1,500 cells/well and dispensed in 50 µL onto 384 well assay ready plates (Corning, 89089-790). Assay ready plates had previously been stamped with 10-point dilutions of compounds of interest, as well as controls. The Echo655 is used to stamp plates at 40 nL of compound or DMSO. Cells were grown for 72 hours at 37 ° Celsius and 5% CO_2. After 72 hours, cells were equilibrated at room temperature for 15 minutes. 30 uL of CellTiter-Glo reagent is added to the plate, which is then shaken for 30 minutes at temperature at 300-500 rpm. Cells are then read on an Envision plate reader. The percentage of inhibition of proliferation was calculated using the following formula: %Inhibition = 100 x (Lum_D – Lum_{Sample}) / (Lum_D –Lum_{Inh}), where D is obtained from cells treated with 0.1% DMSO only; Inh is obtained from cells treated with 10 uM Alpelisib. The effective concentration achieving 50% inhibition of proliferation (EC50) is calculated by fitting the Curve using Xlfit (v5.3.1.3), equation 201: Y = Bottom + (Top - Bottom)/(1 + 10^((LogEC50 - X)*HillSlope)).

Reagent table

Reagent	Vendor	Cat No.
Cell Titer Glo 2.0 Assay 500 mL	Promega	G9243

Corning 384-well Low Flange Black Flat Bottom Polystyrene TC-treated Microplates, 10 per Bag, with Lid, Sterile SKU: 3571	Corning	89089-790
PBS	Solarbio	P1020
Trypan blue solution 0.4%	Fisher	T10282
Fetal Bovine Serum Australia origin	Sigma	82051-458
Gibco RPMI 1640 Medium	Fisher	11875093
Gibco McCoy's 5A (modified) Medium, HEPES	Fisher	12330031
DMEM, high glucose, HEPES, no phenol red	Fisher	21063045
Insulin, human recombinant, zinc solution	Fisher	12585-014

[000364] For EC50 values shown in Table 3, "A" refers to EC50 < 100 nM; "B" refers to 100 nM < EC50 < 300 nM; "C" refers to 300 nM < EC50 < 1 μM; "D" refers to 1 μM < EC50 < 3 μM; "E" refers to 3 μM < EC50 < 10 μM; "F" refers to EC50 ≥ 10 μM.

Table 3. Cellular proliferation data

Example	**Avg T-47D EC50**	**Avg SK-BR-3 EC50**
1	C	E
2	A	C
3	F	F
12	A	D

13	A	D
17	A	C
21	A	C
22	A	D
23	A	B
24	A	D
25	A	D
26	A	E
27	B	D
28	A	D
29	A	D
30	A	D
31	A	D
32	C	F
33	B	E
34	A	D
35	A	D
36	B	E
37	B	E

38	A	D
39	A	D
40	C	D
41	B	E
42	B	E
43	B	D
44	A	D
45	A	D
46	C	F
47	A	D
48	A	D
49	B	F
50	A	D
51	A	D
52	A	E
53	A	D
54	A	C
55	A	B
56	A	C

57	A	D
58	C	E
59	A	D
60	A	E
61	A	D
62	A	C
63	A	C
64	A	E
65	C	E
66	D	F
67	A	B
68	A	C
69	A	D
70	A	C
71	A	C
72	A	E
73	B	E
74	B	E
75	A	C

76	A	C
77	A	C
78	A	D
79	A	D
80	A	E
81	A	D
82	A	C
83	A	C
84	B	F
85	A	C
86	A	D
87	B	E
88	A	D
89	A	D
90	A	E
91	A	D
92	A	D
93	B	E
94	A	D

95	A	C
96	A	D
97	A	C
98	A	D
99	A	C
100	A	C
101	A	C
102	A	C
103	A	C
104	A	C
105	A	D
106	A	E
107	A	C
108	A	C
109	A	C
110	B	E
111	A	D
112	C	E
113	A	D

114	B	E
115	A	D
116	A	D
117	B	E
118	A	D
119	B	E
120	A	D
121	A	C
122	B	D
123	B	D
124	C	E
125	A	D
126	A	C
127	A	C
128	A	E
129	B	D
130	A	C
131	A	C
132	B	E

133	A	C
134	A	D
135	B	D
136	A	D
137	A	D
138	A	E
139	A	E
140	A	C
141	B	F
142	A	D
143	C	E
144	A	C
145	A	C
146	A	C
147	A	C
148	A	D
149	A	D
150	A	C
151	A	D

152	B	E
153	B	E
154	B	D
155	B	D
156	A	D
157	A	E
158	B	E
159	A	C
160	A	C
161	A	C
162	A	C
163	A	C
164	A	C
165	B	E
166	A	C
167	A	D
168	B	F
169	A	D
170	A	D

171	A	D
172	A	D
173	A	C
174	A	C
175	A	D
176	A	D
177	A	C
178	A	D
179	A	D
180	A	D
181	A	D
182	B	E
183	A	D
184	A	E
185	A	D
186	A	E
187	A	D
188	A	D
189	A	D

190	A	D
191	A	D
192	A	C
193	A	D
194	A	D
195	A	E
196	A	D
197	A	C
198	A	C
199	A	D
200	A	D
201	A	D
202	A	D
203	A	D
204	A	D
205	A	D
206	A	C
207	A	C
208	A	D

209	A	D
210	A	C
211	A	D
212	A	C
213	A	D
214	A	D
215	C	F
216	C	E
217	A	C
218	A	B
219	A	D
220	A	C
221	A	D
222	A	D
223	A	B
224	A	D
225	A	D
226	A	C
227	A	E

228	A	D
229	A	D
230	A	C
231	A	C
232	A	D
233	C	E
234	A	D
235	B	E
236	B	E
237	A	D
238	A	E
239	A	D
240	A	C
241	A	C
242	C	F
243	B	D
244	A	D
245	A	D
246	C	F

247	A	D
248	A	D
249	A	D
250	B	D
251	A	C
252	A	D
253	A	D
254	B	E
255	A	B
256	A	C
257	A	D
258	A	D
259	A	E
260	B	E
261	A	D
262	C	F
263	A	C
264	A	C
265	A	D

266	A	C
267	B	E
268	A	D
269	A	D
270	A	C
271	A	D
272	A	C
273	A	C
274	A	C
275	A	C
276	A	D
277	A	D
278	A	D
279	A	C
280	A	C
281	A	E
282	A	D
283	A	D
284	A	E

285	A	C
286	A	D
287	A	D
288	A	C
289	A	C
290	A	C
291	A	D
292	A	C
293	A	C
294	A	D
295	A	D
296	A	C
297	B	E
298	A	D
299	A	D
300	A	D
301	A	C
302	A	D
303	A	D

304	A	C
305	A	C
306	A	C
307	A	D
308	A	D
309	A	C
310	A	C
311	A	C
312	A	C
313	B	E
314	A	D
315	A	D
316	A	E
317	A	E
318	A	D
319	A	D
320	A	E
321	A	E
322	A	D

323	A	C
324	A	D
325	A	E
326	A	D
327	A	D
328	A	D
329	A	D
330	A	E
331	C	F
332	A	C
333	A	D
334	A	C
335	A	C
336	A	D
337	A	D
338	A	E
339	A	E
340	A	C
341	B	F

342	A	D
343	A	C
344	A	C
345	B	E
346	A	E
347	A	D
348	A	C
349	A	D
350	A	C
351	A	D
352	A	D
353	B	E
354	C	F
355	B	E
356	A	E
358	A	D
359	B	E
360	A	D
361	A	C

362	A	C
363	A	D
364	A	D
365	B	E
366	B	F
367	A	D
368	A	D
369	C	F
370	B	D
371	A	C
372	C	F
373	A	C
376	A	D
377	C	F
378	A	C
379	A	D
380	A	C
381	A	D
382	A	D

383	A	D
384	C	F
385	B	E
386	A	D
387	A	D
388	B	E
389	A	C
392	A	E
393	C	F
394	A	D
395	A	D

[000365] In vitro cell pAKT: determination of IC50 values for inhibition of phosphorylation of AKT (pAKT) in the following cell lines: SK-BR-3 cells expressing WT PI3Kα, T-47D cells expressing mutant PI3Kα (H1047R), MCF-7 cells expressing mutant PI3Kα (E545K), BT-483 cells expressing mutant PI3Kα (E542K), EFM-19 cells expressing mutant PI3Kα (H1047L), and MFE-280 cells expressing mutant PI3Kα (H1047Y).

[000366] Cells, grown in culture media (specified below), were harvested, resuspended in assay media (specified below), and seeded onto assay ready plates. Cells were seeded at a density as outlined below and dispensed in 12.5 µL onto 384-well assay ready plates (Perkin Elmer, 6008238). Assay ready plates had previously been stamped with 10-point dilutions of compounds of interest, as well as controls. The Echo655 was used to stamp plates at 12.5 nL of compound or DMSO. Cells, in assay ready plates, were grown for 6 hours at 37°C and 5% CO_2. After 6 hours, 4 µL of lysis buffer reagent were added to the plate, which was then centrifuged

for 1 minute at 1000 rpm. Then the plate was incubated at room temperature for 30 minutes. After 30 minutes, 4 µL of antibody mix containing Eu cryptate, d2 cryptate, and detection buffer were added to the plate. The plate was centrifuged for 1 minute at 1000 rpm and then incubated overnight at room temperature with lid, protected from light. The plate was read on an BMG-PHERAstar FSX plate reader using the HTRF protocol. The percentage of inhibition of AKT phosphorylation was calculated using the following formula: % Inhibition = 100 x (pAKTHC – pAKTSample) / (pAKTHC –pAKTLC), where pAKTHC is obtained from cells treated with 0.2% DMSO only, pAKTLC is obtained from cells treated with 10 µM alpelisib, and pAKTSample referring to the well for which % inhibition is being calculated. The IC50 (concentration achieving 50% inhibition of pAKT) is calculated by fitting the curve using Xlfit (v5.3.1.3), equation 201: Y = Bottom + (Top - Bottom)/(1 + 10^((LogIC50 - X)*HillSlope)).

[000367] SK-BR-3 culture media consisted of McCoy's 5a and 10% FBS, and assay media consisted of DMEM (no phenol red) + 10% FBS. T-47D culture media consisted of RPMI, 10% FBS and insulin (0.2 U/mL), and assay media consisted of RPMI 1640 (no phenol red) + 10% FBS + 0.2 U/ml insulin. MCF-7 culture media consisted of EMEM + 10% FBS, and assay media consisted of DMEM (no phenol red) + 10% FBS. BT-483 culture media consisted of RPMI 1640 + 20% FBS + 10 µg/ml insulin, and assay media consisted of DMEM (no phenol red) + 10% FBS. EFM-19 culture media consisted of RPMI 1640 + 10% FBS , and assay media consisted of DMEM (no phenol red) + 10% FBS. MFE-280 culture media consisted of MEM + 10% FBS, and assay media consisted of DMEM (no phenol red) + 10% FBS.

[000368] Cell density for dispensing into assay ready plates as follows: SK-BR-3 at 5,000 cells/well, T-47D at 5,000 cells/well, MCF-7 at 5,000 cells/well, BT-483 at 5,000 cells/well, EFM-19 at 5,000 cells/well, MFE-280 at 10,000 cells/well.

Reagent table

Reagent	Vendor	Cat No.
Gibco RPMI 1640 Medium, no phenol red	Fisher	11835030
Gibco RPMI 1640 Medium	Fisher	11875093
McCoy's 5A (Modified) Medium, HEPES	Fisher	12330031

DMEM, high glucose, HEPES, no phenol red	Fisher	21063045
Gibco Trypsin-EDTA (0.5%), no phenol red	Fisher	15400054
Eagle's Minimum Essential Medium	ATCC	30-2003
MEM Medium	Gibco	42360032
PBS	Solarbio	P1020
Trypan blue solution 0.4%	Fisher	T10282
Fetal Bovine Serum Australia origin	Gibco	10099141C
ProxiPlate-384 Plus, White, TC treated, Case of 160	Perkin Elmer	6008238
Insulin	Aladin	I189675
Trypsin-EDTA	SolarBio	T1300
Phospho-AKT1/2/3 (Ser473) cellular HTRF kit	Revvity	64AKSPEY
T-47D Cells	ATCC	HTB-133
SK-BR-3 Cells	ATCC	HTB-30
MCF-7 Cells	ATCC	HTB-22
BT-483 Cells	ATCC	HTB-121
EFM-19 Cells	Cobioer	CBP60363
MFE-280 Cells	ECACC	98050131

[000369] For IC50 values shown in Table 4, "A" refers to IC50 < 100 nM; "B" refers to 100 nM < IC50 < 300 nM; "C" refers to 300 nM < IC50 < 1 μM; "D" refers to 1 μM < IC50 < 3 μM; "E" refers to 3 μM < IC50 < 10 μM; "F" refers to IC50 ≥ 10 μM.

Table 4. Cellular pAKT data

Example	Avg T-47D IC50	Avg SK-BR-3 IC50	Avg MCF-7 IC50	Avg BT-483 IC50	Avg EFM-19 IC50	Avg MFE-280 IC50
1	C	F	–	–	–	–
2	A	B	A	A	A	A
3	E	F	–	–	–	–
12	A	C	A	A	A	A
13	A	C	–	–	–	–
17	A	B	–	–	–	–
21	A	B	–	–	–	–
22	A	C	A	A	A	A
23	A	A	A	A	A	A
24	A	C	B	B	A	–
25	A	B	A	–	–	–
26	A	C	B	B	A	A
27	A	C	B	–	–	–
28	A	C	A	A	A	A

29	A	C	A	–	–	–
30	A	C	A	–	–	–
31	A	C	A	B	A	A
32	B	E	D	–	–	–
33	A	D	B	–	–	–
34	A	D	B	–	–	–
35	A	B	A	–	–	–
36	A	D	A	B	–	–
37	A	E	B	–	–	–
38	A	C	B	–	–	–
39	A	D	B	–	–	–
40	B	E	B	–	–	–
41	A	C	B	–	–	–
42	A	D	B	–	–	–
43	A	C	B	–	–	–
44	A	C	B	–	–	–
45	A	B	A	–	–	–
46	B	E	C	–	–	–
47	A	C	A	–	–	–

48	A	C	A	A	A	A
49	A	E	C	–	–	–
50	A	C	A	B	A	A
51	A	C	A	B	A	A
52	A	D	A	B	B	A
53	A	D	B	–	–	–
54	A	B	A	–	–	–
55	A	B	A	–	–	–
56	A	C	A	–	–	–
57	A	D	B	–	–	–
58	B	E	C	–	–	–
59	A	B	A	B	A	A
60	A	C	A	A	A	A
61	A	C	A	–	–	–
62	A	B	A	–	–	–
63	A	B	A	–	–	–
64	A	C	A	–	–	–
65	B	E	C	–	–	–
66	C	F	C	–	–	–

67	A	B	A	–	–	–
68	A	B	A	–	–	–
69	A	B	A	–	–	–
70	A	B	A	–	–	–
71	A	B	A	–	–	–
72	A	D	B	–	–	–
73	A	D	C	–	–	–
74	A	D	B	–	–	–
75	A	C	A	–	–	–
76	A	B	A	–	–	–
77	A	B	A	–	–	–
78	A	B	A	–	–	–
79	A	C	A	–	–	–
80	A	C	A	B	A	A
81	A	C	A	–	–	–
82	A	B	A	–	–	–
83	A	B	A	–	–	–
84	A	E	C	–	–	–
85	A	B	A	A	A	A

86	A	C	B	A	A	A
87	A	E	–	–	–	–
88	A	B	–	–	–	–
89	A	C	A	A	A	A
90	A	C	A	B	A	A
91	A	C	A	B	A	A
92	A	C	A	–	–	–
93	A	D	B	B	B	A
94	A	C	A	–	–	–
95	A	B	A	A	A	A
96	A	C	A	–	–	–
97	A	B	A	A	A	A
98	A	C	A	A	A	A
99	A	C	A	–	–	–
100	A	B	A	–	–	–
101	A	B	–	–	–	–
102	A	B	A	–	–	–
103	A	B	–	–	–	–
104	A	C	–	–	–	–

105	A	C	A	–	–	–
106	A	C	–	–	–	–
107	A	C	B	–	–	–
108	A	C	A	–	–	–
109	A	B	–	–	–	–
110	A	D	–	–	–	–
111	A	B	A	A	A	–
112	A	C	–	–	–	–
113	A	C	A	–	–	–
114	A	C	B	–	–	–
115	A	C	A	B	A	–
116	A	C	B	–	–	–
117	A	D	–	–	–	–
118	A	D	–	–	–	–
119	A	C	B	–	–	–
120	A	B	–	–	–	–
121	A	B	–	–	–	–
122	A	C	–	–	–	–
123	A	C	B	B	B	–

124	B	E	–	–	–	–
125	A	C	A	–	–	–
126	A	B	–	–	–	–
127	A	B	A	A	A	A
128	A	D	–	–	–	–
129	A	D	–	–	–	–
130	A	B	–	–	–	–
131	A	B	–	–	–	–
132	A	C	–	–	–	–
133	A	B	–	–	–	–
134	A	C	–	–	–	–
135	A	C	–	–	–	–
136	A	C	–	–	–	–
137	A	C	–	–	–	–
138	A	C	B	B	A	–
139	A	C	–	–	–	–
140	A	B	A	A	A	A
141	A	D	–	–	–	–
142	A	B	–	–	–	–

143	A	D	–	–	–	–
144	A	B	–	–	–	–
145	A	B	–	–	–	–
146	A	B	–	–	–	–
147	A	B	–	–	–	–
148	A	C	–	–	–	–
149	A	C	–	–	–	–
150	A	B	A	A	A	–
151	A	C	–	–	–	–
152	A	D	–	–	–	–
153	A	D	B	–	–	–
154	A	D	–	–	–	–
155	A	C	–	–	–	–
156	A	C	–	–	–	–
157	A	D	–	–	–	–
158	A	D	–	–	–	–
159	A	B	–	–	–	–
160	A	B	–	–	–	–
161	A	B	A	A	A	–

162	A	B	A	A	A	A
163	A	A	–	–	–	–
164	A	B	–	–	–	–
165	A	D	–	–	–	–
166	A	C	A	A	A	A
167	A	C	–	–	–	–
168	B	E	–	–	–	–
169	A	C	–	–	–	–
170	A	C	–	–	–	–
171	A	B	A	A	A	A
172	A	C	–	–	–	–
173	A	C	B	C	A	A
174	A	B	–	–	–	–
175	A	C	–	–	–	–
176	A	C	A	B	A	A
177	A	B	–	–	–	–
178	A	B	–	–	–	–
179	A	C	–	–	–	–
180	A	B	A	A	A	A

181	A	C	–	–	–	–
182	A	D	–	–	–	–
183	A	C	–	–	–	–
184	A	C	–	–	–	–
185	A	C	B	–	–	–
186	A	C	–	–	–	–
187	A	B	A	A	A	A
188	A	B	–	–	–	–
189	A	B	–	–	–	–
190	A	B	A	A	A	–
191	A	C	A	B	A	A
192	A	B	A	B	A	–
193	A	C	–	–	–	–
194	A	B	A	A	A	A
195	A	D	–	–	–	–
196	A	C	–	–	–	–
197	A	B	–	–	–	–
198	A	B	A	A	A	A
199	A	C	B	B	A	A

200	A	C	A	A	A	A
201	A	C	–	–	–	–
202	A	B	–	–	–	–
203	A	B	–	–	–	–
204	A	C	–	–	–	–
205	A	C	–	–	–	–
206	A	B	–	–	–	–
207	A	A	–	–	–	–
208	A	D	–	–	–	–
209	A	B	–	–	–	–
210	A	B	–	–	–	–
211	A	C	A	A	A	A
212	A	B	–	–	–	–
213	A	B	–	–	–	–
214	A	C	A	B	A	–
215	C	E	–	–	–	–
216	C	D	–	–	–	–
217	A	B	–	–	–	–
218	A	B	–	–	–	–

219	A	C	A	A	A	A
220	A	B	–	–	–	–
221	A	B	–	–	–	–
222	A	B	–	–	–	–
223	A	B	–	–	–	–
224	A	B	A	A	A	A
225	A	C	A	A	A	–
226	A	A	–	–	–	–
227	A	D	–	–	–	–
228	A	C	A	A	A	A
229	A	C	–	–	–	–
230	A	B	–	–	–	–
231	A	B	A	A	A	A
232	A	C	–	–	–	–
233	C	E	–	–	–	–
234	A	B	A	A	A	A
235	A	C	–	–	–	–
236	B	E	–	–	–	–
237	A	B	A	A	A	–

238	A	C	–	–	–	–
239	A	C	–	–	–	–
240	A	B	–	–	–	–
241	A	A	–	–	–	–
242	A	D	–	–	–	–
243	A	C	–	–	–	–
244	A	B	A	A	A	A
245	A	B	–	–	–	–
246	A	D	–	–	–	–
247	A	C	–	–	–	–
248	A	C	–	–	–	–
249	A	C	–	–	–	–
250	A	C	–	–	–	–
251	A	B	–	–	–	–
252	A	B	–	–	–	–
253	A	C	–	–	–	–
254	A	C	–	–	–	–
255	A	B	–	–	–	–
256	A	B	A	A	A	A

257	A	C	–	–	–	–
258	A	B	A	A	A	A
259	A	C	–	–	–	–
260	A	C	–	–	–	–
261	A	C	–	–	–	–
262	C	E	–	–	–	–
263	A	B	–	–	–	–
264	A	B	–	–	–	–
265	A	C	–	–	–	–
266	A	B	–	–	–	–
267	A	D	–	–	–	–
268	A	C	–	–	–	–
269	A	C	–	–	–	–
270	A	A	A	A	A	A
271	A	C	A	B	A	A
272	A	B	–	–	–	–
273	A	B	–	–	–	–
274	A	B	–	–	–	–
275	A	B	A	A	A	A

276	A	B	–	–	–	–
277	A	C	–	–	–	–
278	A	C	–	–	–	–
279	A	B	–	–	–	–
280	A	C	A	B	A	A
281	A	D	–	–	–	–
282	A	C	–	–	–	–
283	A	C	–	–	–	–
284	A	C	–	–	–	–
285	A	B	–	–	–	–
286	A	C	–	–	–	–
287	A	C	–	–	–	–
288	A	B	–	–	–	–
289	A	B	–	–	–	–
290	A	B	–	–	–	–
291	A	B	–	–	–	–
292	A	B	–	–	–	–
293	A	B	–	–	–	–
294	A	C	–	–	–	–

295	A	C	–	–	–	–
296	A	A	A	A	A	–
297	A	D	–	–	–	–
298	A	C	A	–	–	–
299	A	C	–	–	–	–
300	A	C	–	–	–	–
301	A	B	–	–	A	A
302	A	B	–	–	–	–
303	A	C	–	–	–	–
304	A	B	–	–	–	–
305	A	B	–	–	–	–
306	A	B	A	B	A	A
307	A	C	–	–	A	A
308	A	C	–	–	–	–
309	A	A	–	–	–	–
310	A	B	A	A	A	A
311	A	B	A	A	A	A
312	A	B	–	–	–	–
313	A	D	–	–	–	–

314	A	C	–	–	–	–
315	A	B	A	A	A	–
316	A	C	–	–	–	–
317	A	C	A	A	A	A
318	A	C	B	B	A	A
319	A	B	–	–	–	–
320	A	C	–	–	–	–
321	A	C	–	–	–	–
322	A	C	–	–	–	–
323	A	B	–	–	–	–
324	A	C	–	–	–	–
325	A	C	–	–	–	–
326	A	C	–	–	–	–
327	A	C	A	A	A	A
328	A	C	–	–	–	–
329	A	C	–	–	–	–
330	A	C	A	B	A	A
331	A	D	–	–	–	–
332	A	B	–	–	–	–

333	A	C	B	B	A	A
334	A	B	–	–	–	–
335	A	B	A	B	A	A
336	A	C	–	–	–	–
337	A	C	–	–	–	–
338	A	C	–	–	–	–
339	A	C	–	–	–	–
340	A	B	–	–	–	–
341	A	D	–	–	–	–
342	A	C	A	A	A	–
343	A	B	–	–	–	–
344	A	B	–	–	–	–
345	A	C	–	–	–	–
346	A	C	A	B	A	A
347	A	B	–	–	–	–
348	A	B	A	A	A	A
349	A	C	A	B	A	A
350	A	B	A	A	A	A
351	A	B	A	A	A	A

352	A	C	A	A	A	A
353	A	D	–	–	–	–
354	B	F	–	–	–	–
355	A	D	–	–	–	–
356	A	D	A	A	A	A
358	A	C	A	–	–	–
359	A	D	B	–	–	–
360	A	B	A	–	–	–
361	A	B	A	–	–	–
362	A	B	A	–	–	–
363	A	C	A	–	–	–
364	A	C	A	–	–	–
365	A	D	B	–	–	–
366	A	D	B	–	–	–
367	A	C	A	–	–	–
368	A	C	B	–	–	–
369	C	F	D	–	–	–
370	A	D	B	–	–	–
371	A	B	A	–	–	–

372	A	E	C	–	–	–
373	A	B	A	–	–	–
376	A	C	A	A	A	A
377	B	E	C	–	–	–
378	A	B	A	–	–	–
379	A	B	A	–	–	–
380	A	B	A	–	–	–
381	A	C	A	A	A	A
382	A	C	A	–	–	–
383	A	C	A	A	A	A
384	B	E	D	–	–	–
385	A	D	B	–	–	–
386	A	D	B	–	–	–
387	A	B	A	–	–	–
388	A	D	B	–	–	–
389	A	C	A	–	–	–
392	A	D	B	–	–	–
393	B	F	C	–	–	–
394	A	C	A	–	–	–

395	A	C	B	–	–	–

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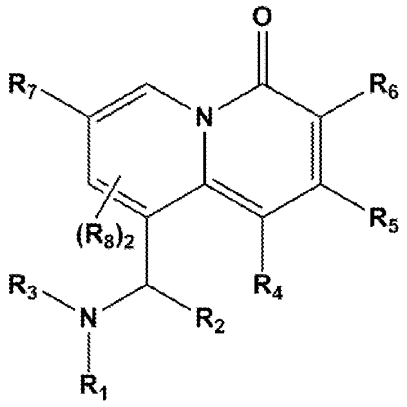
IN THE CLAIMS

1. A compound of Formula (1)



(1)

or a solvate, enantiomer, diastereomer, tautomer, polymorph or isotope-labeled compound thereof, or a pharmaceutically acceptable salt thereof,

wherein:

R_1 is aryl, heteroaryl or heterocyclyl, where each of the aryl, heteroaryl and heterocyclyl is unsubstituted or substituted, with the proviso that when R_1 is aryl or heteroaryl, a carboxylic acid or ester thereof is not a substituent at a position ortho to the point of attachment of the aryl or heteroaryl ring to the nitrogen atom of N-R_3;

R_2 is H, C_1-C_4 alkyl, C_3-C_7 cycloalkyl, CF_3, CFH_2 or CF_2H, where the C_1-C_4 alkyl and C_3-C_7 cycloalkyl is unsubstituted or substituted, and where R_2 is not H, the carbon atom attached to R_2 is a chiral center and exists as a (R)- and (S)-racemic mixture or as either the (R)- or (S)- enantiomer;

R_3 is H or C_1-C_4 alkyl, where the C_1-C_4 alkyl is unsubstituted or substituted;

R_4 is H, F, Cl, C_1-C_4 alkyl, C_3-C_7 cycloalkyl, CN, CF_3, OCF_3, CFH_2 or CF_2H, where the C_1-C_4 alkyl and C_3-C_7 cycloalkyl is unsubstituted or substituted;

R_6 is H, F, Cl, C_1-C_4 alkyl, C_3-C_7 cycloalkyl, heteroaryl, CF_3, CFH_2 or CF_2H, where each of the C_1-C_4 alkyl, C_3-C_7 cycloalkyl and heteroaryl is unsubstituted or substituted;

R_7 is H, F, Cl, C_1-C_4 alkyl, C_3-C_7 cycloalkyl, CN, CF_3, OCF_3, CFH_2 or CF_2H, where the C_1-C_4 alkyl and C_3-C_7 cycloalkyl is unsubstituted or substituted;

each R_8 is independently H, F, Cl, C_1-C_4 alkyl, C_3-C_7 cycloalkyl, CN, CF_3, OCF_3, CFH_2 or CF_2H, where the C_1-C_4 alkyl and C_3-C_7 cycloalkyl is unsubstituted or substituted;

R_5 is

halogen;

-O-L_1-L_2-L_3-L_4-L_5-L_6-L_7-R_9;

-S-L_1-L_2-L_3-L_4-L_5-L_6-L_7-R_9;

-S(O)-L_1-L_2-L_3-L_5-L_6-L_7-R_9;

-$S(O)_2$-L_1-L_2-L_3-L_5-L_6-L_7-R_9;

-(NR_{10})-L_1-L_2-L_3-L_4-L_5-L_6-L_7-R_9; or

-L_8-L_9-L_{10}-L_{11}-L_{12}-R_{14},

wherein:

each of L_1, L_2, L_3, L_6 and L_7 is independently (CHR_{11}), (CHR_{11}-O), (CHR_{11}-S), (C_3-C_7 cycloalkyl), $(CH_2)_{1-4}$ or a bond;

L_4 is C=O, C=S or a bond;

L_5 is NR_{10}, S, O or a bond;

R_9 is H, C(=O)R_{12}, C(=O)$NR_{12}R_{13}$, $NR_{12}R_{13}$, C(=O)OR_{12}, C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl, where each of the C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl is unsubstituted or substituted; or alternatively when NR_{10} is present, R_9 and R_{10} together with the attached nitrogen atom may form a substituted or unsubstituted ring;

each of R_{10} and R_{11} is independently H or C_1-C_4 alkyl (such as CH_3, CH_2CH_3 or $CH(CH_3)_2$), where the C_1-C_4 alkyl is unsubstituted or substituted;

each of R_{12} and R_{13} is independently H, C_1-C_6 alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl, where each of the C_1-C_6 alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl is unsubstituted or substituted; or alternatively, R_{12} and R_{13} together with the attached nitrogen atom may form a substituted or unsubstituted ring;

L_8 is (CHR_{15}), (CHR_{15}-O), (CHR_{15}-S), (CHR_{15}-NR_{16}), C=O, C=S or a bond;

L_9 is C_3-C_7 cycloalkyl that is optionally part of a bridged, fused or spiro ring system, $C(R_{15})=C(R_{15})$, C≡C or a bond;

L_{10} is independently (CHR_{15}), O, S, (NCR_{15}), N(C=O) or a bond;

L_{11} is (CHR_{15}), C=O, C=S or a bond;

L_{12} is H, (C_3-C_7 cycloalkyl), heterocyclyl, aryl, heteroaryl or a bond, where each of the C_3-C_7 cycloalkyl, heterocyclyl, aryl or heteroaryl is unsubstituted or substituted, and the C_3-C_7 cycloalkyl and/or heterocyclyl is optionally part of a bridged, fused or spiro ring system;

R_{14} is H, $CR_{15}R_{16}R_{17}$, OR_{17}, SR_{17}, $NR_{16}R_{17}$, C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl, where each of the C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl is unsubstituted or substituted,

each of R_{15} and R_{16} is independently H or C_1-C_3 alkyl; and

each R_{17} is independently H, C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl, where each of the C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl is unsubstituted or substituted; or alternatively, R_{16} and R_{17} together with the attached nitrogen atom may form a substituted or unsubstituted ring;

with the proviso that when R_5 is -L_8-L_9-L_{10}-L_{11}-L_{12}-R_{14}, at least one of L_8, L_9, L_{10}, L_{11}, L_{12} and R_{14} is a carbon-containing moiety and R_5 is directly attached to the core structure by a carbon atom;

or R_5 is

a non-aromatic N-linked heterocyclic ring 

, where the heterocyclic ring is substituted or unsubstituted, optionally contains one or more additional ring atoms selected from N, O, Si and S, and is optionally part of a bridged, fused or spiro ring system. In particular embodiments, the N-linked heterocyclyl ring is a substituted or unsubstituted azetidine, pyrrolidine, imidazoline, imidazolidine, piperazine, morpholine, thiomorpholine, piperidine, indoline, tetrahydroquinoline, decahydroquinoline, 2-oxa-7-azaspiro[3.5]nonane, 1, 4-dioxa-7-azaspiro[4.4]nonane or 2-azaadamantane.

2. The compound according to claim 1 or a solvate, enantiomer, diastereomer, tautomer, polymorph or isotope-labeled compound, or a pharmaceutically acceptable salt thereof, wherein R_5 is $-(NR_{10})-L_1-L_2-L_3-L_4-L_5-L_6-L_7-R_9$, where L_1 to L_7, R_9 and R_{10} are as defined.

3. The compound according to claim 1 or a solvate, enantiomer, diastereomer, tautomer, polymorph or isotope-labeled compound, or a pharmaceutically acceptable salt thereof, wherein R_5 is $-O-L_1-L_2-L_3-L_4-L_5-L_6-L_7-R_9$, where L_1 to L_7 and R_9 are as defined.

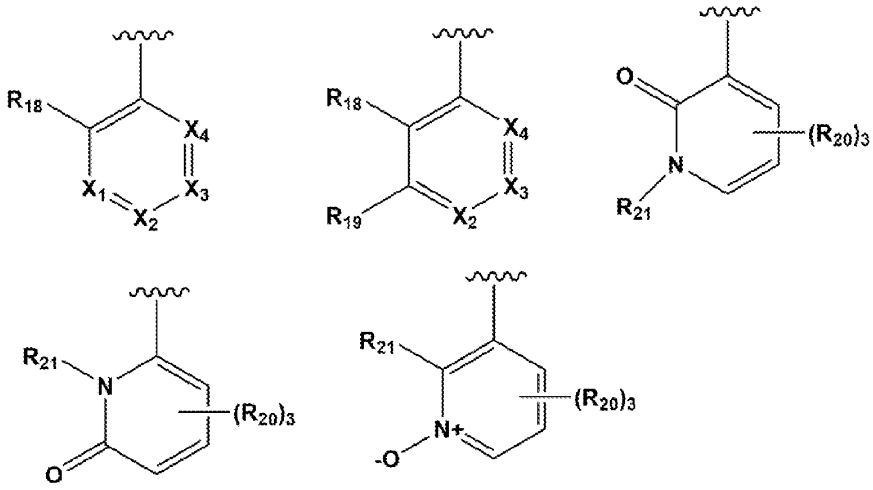
4. The compound according to claim 1 or a solvate, enantiomer, diastereomer, tautomer, polymorph or isotope-labeled compound, or a pharmaceutically acceptable salt thereof, wherein R_5 is $-S-L_1-L_2-L_3-L_4-L_5-L_6-L_7-R_9$; $-S(O)-L_1-L_2-L_3-L_5-L_6-L_7-R_9$; or $-S(O)_2-L_1-L_2-L_3-L_5-L_6-L_7-R_9$, where L_1 to L_7 and R_9 are as defined.

5. The compound according to claim 1 or a solvate, enantiomer, diastereomer, tautomer, polymorph or isotope-labeled compound, or a pharmaceutically acceptable salt thereof, wherein R_5 is $-L_8-L_9-L_{10}-L_{11}-L_{12}-R_{14}$, where L_8 to L_{12} and R_{14} are as defined.

6. The compound according to claim 1 or a solvate, enantiomer, diastereomer, tautomer, polymorph or isotope-labeled compound, or a pharmaceutically acceptable salt thereof, wherein R_5 is a non-aromatic N-linked heterocyclyl ring 

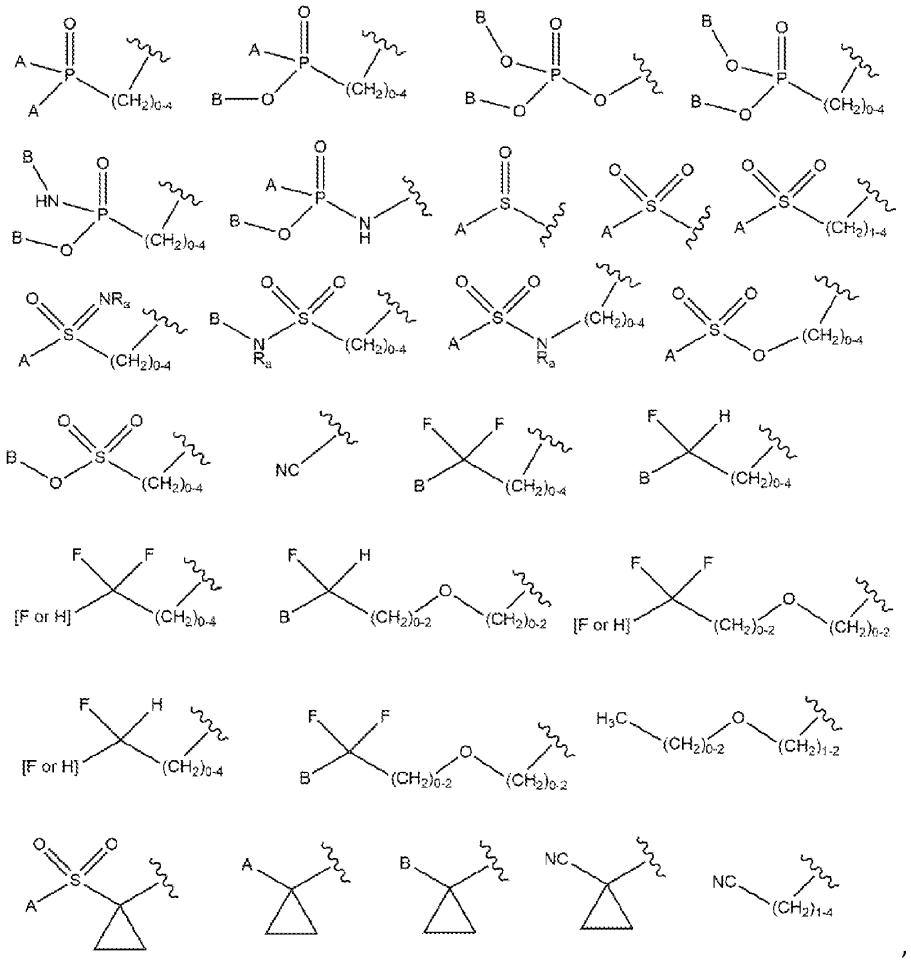
, where the heterocyclyl ring is substituted or unsubstituted, optionally contains one or more additional ring atoms selected from N, O, Si and S, and is optionally part of a bridged, fused or spiro ring system.

7. The compound according to claim 1 or a solvate, enantiomer, diastereomer, tautomer, polymorph or isotope-labeled compound, or a pharmaceutically acceptable salt thereof, wherein R_1 is selected from



wherein:

R_{18} is a substituted or unsubstituted 5- or 6-membered nitrogen-containing heteroaryl ring or R_{18} is selected from the following:



where each A is independently C_1-C_4 alkyl, fluoroalkyl, C_3-C_7 cycloalkyl, $N(R_a)_2$, $(CH_2)_{0-5}$-NR_a-C(O)-C_3-C_7 cycloalkyl, $(CH_2)_{1-5}$-O-C_1-C_3 cycloalkyl, $(CH_2)_{1-5}$-O-$(CH_2)_{1-5}$-C_1-C_3 fluoroalkyl, $(CH_2)_{0-5}$-aryl, $(CH_2)_{0-5}$-heteroaryl, $(CH_2)_{0-5}$-heterocyclyl, $(CH_2)_{0-5}$-NR_a-$(CH_2)_{0-5}$-heteroaryl or $(CH_2)_{0-5}$-NR_a-$(CH_2)_{1-5}$-N-heterocyclyl, where the alkyl, fluoroalkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl are substituted or unsubstituted, or alternatively, A and A together with the attached -P(=O)- moiety may form a substituted or unsubstituted heterocyclyl ring;

each B is independently H, C_1-C_4 alkyl, C_3-C_7 cycloalkyl, $(CH_2)_{1-5}$-NR_a-C(O)-C_3-C_7 cycloalkyl, $(CH_2)_{0-5}$-aryl, $(CH_2)_{0-5}$-heteroaryl, $(CH_2)_{0-5}$-heterocyclyl, $(CH_2)_{1-5}$-NR_a-$(CH_2)_{0-5}$-heteroaryl or $(CH_2)_{1-5}$-NR_a-$(CH_2)_{2-5}$-N-heterocyclyl, O-C_{1-5}-alkyl, O-C_{0-5}-cycloalkyl, O-C_{0-5}-heterocyclyl, where the alkyl, cycloalkyl, aryl,

heteroaryl and heterocyclyl are substituted or unsubstituted, or alternatively, B and B together with the attached -[O or NH]-P(=O)-O- moiety may form a substituted or unsubstituted heterocyclyl ring, or alternatively, A and B together with the attached -P(=O)-O- moiety may form a substituted or unsubstituted heterocyclyl ring;

each R_a is independently H, C_1-C_4 alkyl, C(O)C_1-C_3 alkyl or C(O)-$(CH_2)_{1-5}$-O-C_1-C_3 alkyl, where the alkyl is substituted or unsubstituted, or alternatively, R_a and A together with the attached -$S(=O)_2$- moiety may form a substituted or unsubstituted heterocyclic ring, or

R_{18} and R_{19} together form a substituted or unsubstituted heterocyclic ring (such as a 5- or 6-membered heterocyclic ring) containing one or more sulfur atoms (which includes the sulfoxide (SO) and sulfone (SO_2) forms), nitrogen atoms (which includes the oxidized forms) and oxygen atoms;

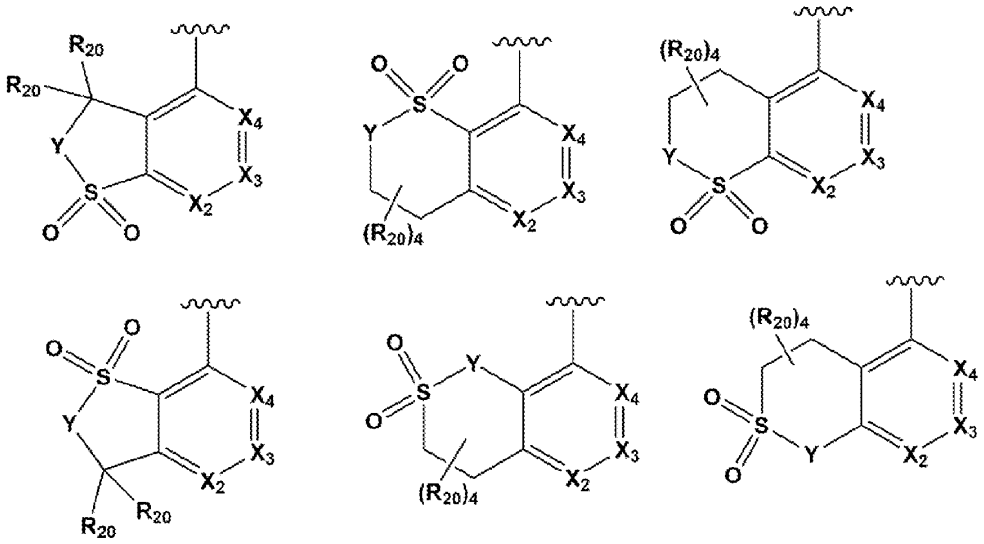
R_{19} is H, C_1-C_4 alkyl, C_3-C_7 cycloalkyl, halogen, CN, CF_3, OCF_3, CFH_2 or CF_2H, where the alkyl and cycloalkyl is substituted or unsubstituted, or R_{19} and R_{18} together form a heterocyclic ring;

each R_{20} is independently H, C_1-C_4 alkyl, C_3-C_7 cycloalkyl, halogen, CN, CF_3, OCF_3, CFH_2 or CF_2H, where the alkyl and cycloalkyl is substituted or unsubstituted;

R_{21} is H, C_1-C_4 alkyl, C_3-C_7 cycloalkyl, CF_3, CFH_2 or CF_2H, where the alkyl and cycloalkyl is substituted or unsubstituted; and

each X_1, X_2, X_3 and X_4 is independently CH, N or substituted C.

8. The compound according to claim 7 or a solvate, enantiomer, diastereomer, tautomer, polymorph or isotope-labeled compound, or a pharmaceutically acceptable salt thereof, wherein R_1 is selected from

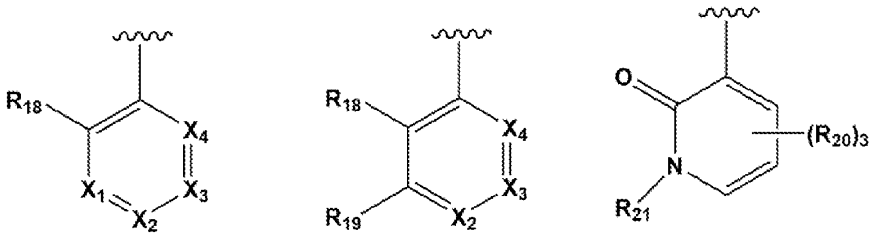


wherein:

Y is O, NR_{21} or $C(R_4)_2$; and

X_2, X_3, X_4 and each R_4, R_{20} and R_{21} are defined as in claim 7.

9. The compound according to claim 7 or a solvate, enantiomer, diastereomer, tautomer, polymorph or isotope-labeled compound, or a pharmaceutically acceptable salt thereof, wherein R_1 is selected from

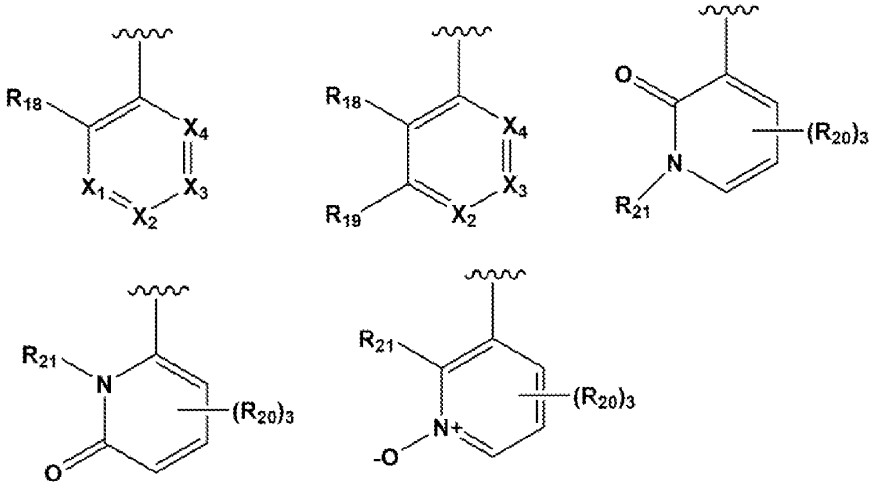


where R_{18}, R_{19}, R_{20}, R_{21}, X_1, X_2, X_3 and X_4 are as defined in claim 7.

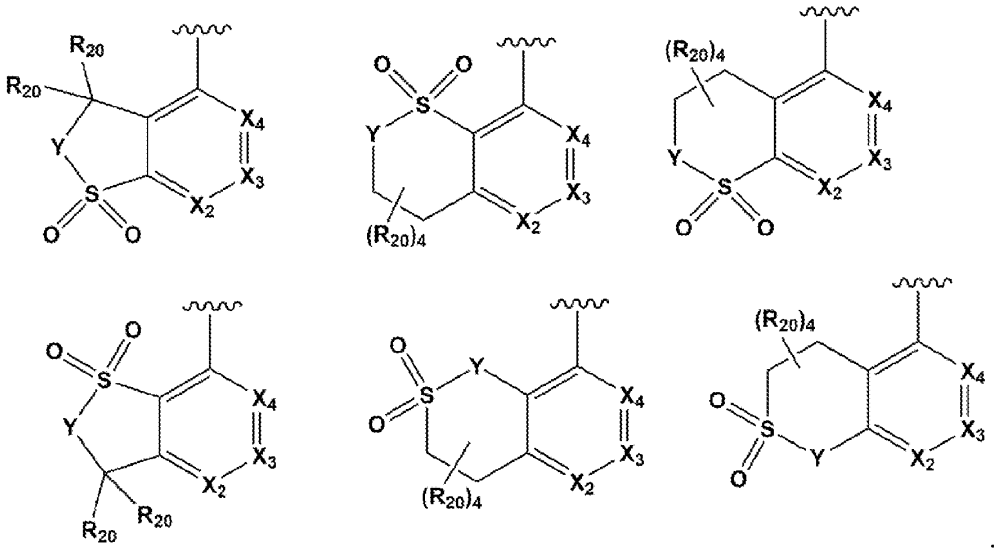
10. The compound according to claim 1 or claim 7 or a solvate, enantiomer, diastereomer, tautomer, polymorph or isotope-labeled compound, or a pharmaceutically acceptable salt thereof, wherein R_2 is CH_3 or CH_2F.

11. The compound according to claim 1 or claim 7 or a solvate, enantiomer, diastereomer, tautomer, polymorph or isotope-labeled compound, or a pharmaceutically acceptable salt thereof, wherein R_3 is H.

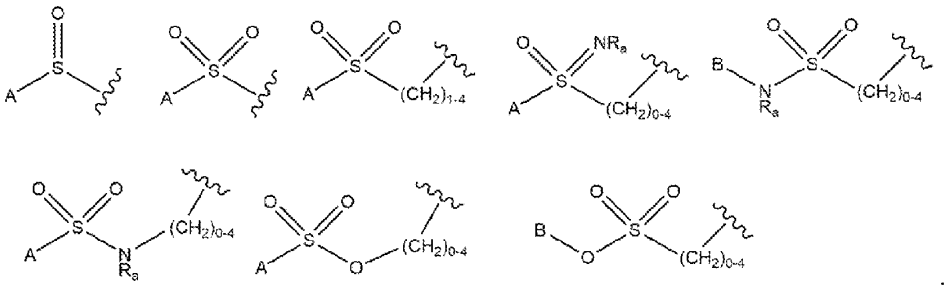
12. The compound according to claim 7 or a solvate, enantiomer, diastereomer, tautomer, polymorph or isotope-labeled compound, or a pharmaceutically acceptable salt thereof, wherein R_2 is CH_3 or CH_2F, R_3 is H and R_1 is selected from



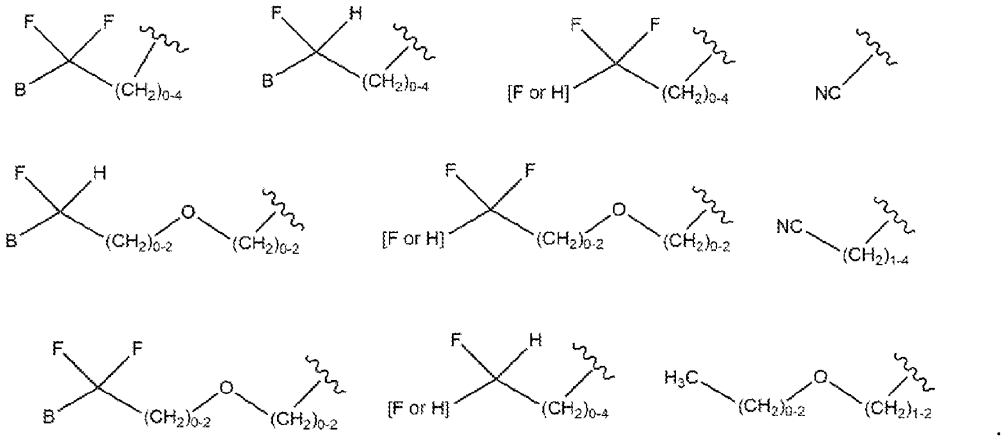
13. The compound according to claim 7 or a solvate, enantiomer, diastereomer, tautomer, polymorph or isotope-labeled compound, or a pharmaceutically acceptable salt thereof, wherein R_2 is CH_3 or CH_2F, R_3 is H and R_1 is selected from



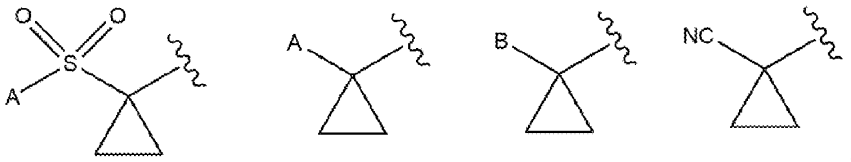
14. The compound according to claim 7 or a solvate, enantiomer, diastereomer, tautomer, polymorph or isotope-labeled compound, or a pharmaceutically acceptable salt thereof, wherein R_{18} is selected from



15. The compound according to claim 7 or a solvate, enantiomer, diastereomer, tautomer, polymorph or isotope-labeled compound, or a pharmaceutically acceptable salt thereof, wherein R_{18} is selected from



16. The compound according to claim 7 or a solvate, enantiomer, diastereomer, tautomer, polymorph or isotope-labeled compound, or a pharmaceutically acceptable salt thereof, wherein R_{18} is selected from

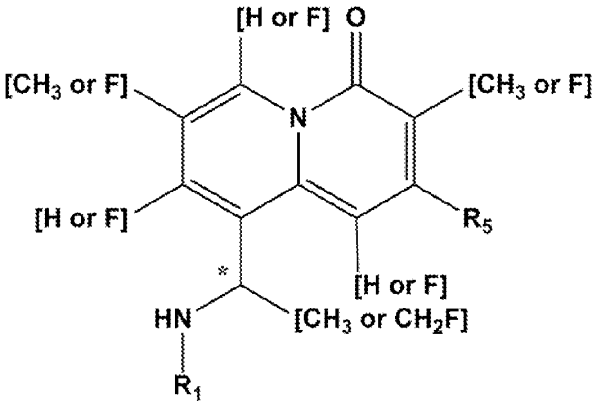


17. The compound according to claim 1 or claim 7 or a solvate, enantiomer, diastereomer, tautomer, polymorph or isotope-labeled compound, or a pharmaceutically acceptable salt thereof, wherein R_2 is CH_3 or CH_2F, R_3 is H and R_5 is -S-L_1-L_2-L_3-L_4-L_5-L_6-L_7-R_9.

18. The compound according to claim 1 or claim 7 or a solvate, enantiomer, diastereomer, tautomer, polymorph or isotope-labeled compound, or a pharmaceutically acceptable salt thereof, wherein R_2 is CH_3 or CH_2F, R_3 is H and R_5 is -(NR_{10})-L_1-L_2-L_3-L_4-L_5-L_6-L_7-R_9.

19. The compound according to claim 1 or claim 7 or a solvate, enantiomer, diastereomer, tautomer, polymorph or isotope-labeled compound, or a pharmaceutically acceptable salt thereof, wherein R_2 is CH_3 or CH_2F, R_3 is H and R_5 is -L_8-L_9-L_{10}-L_{11}-L_{12}-R_{14}.

20. The compound according to claim 1 or a solvate, enantiomer, diastereomer, tautomer, polymorph or isotope-labeled compound, or a pharmaceutically acceptable salt thereof, wherein the compound of Formula (1) is a compound of Formula (2)



(2)

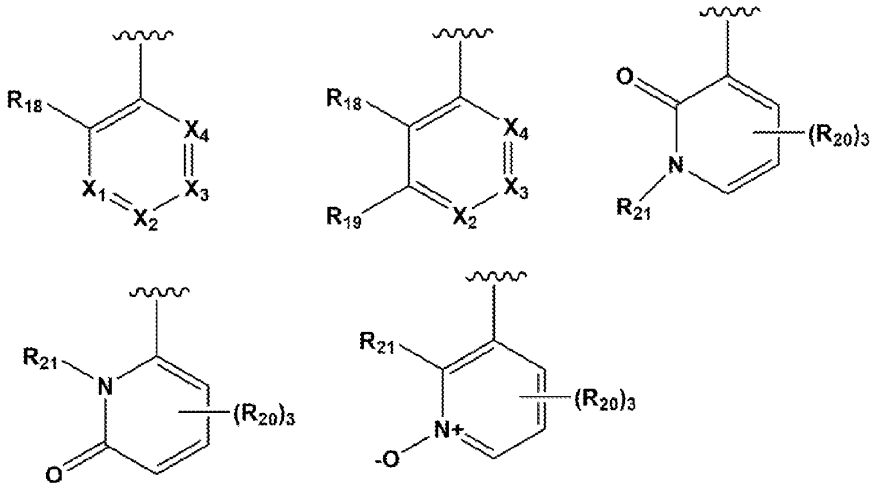
or a solvate, enantiomer, diastereomer, tautomer, polymorph or isotope-labeled compound, or a pharmaceutically acceptable salt thereof,

wherein:

R_1 and R_5 are defined as for the compound of Formula (1), and

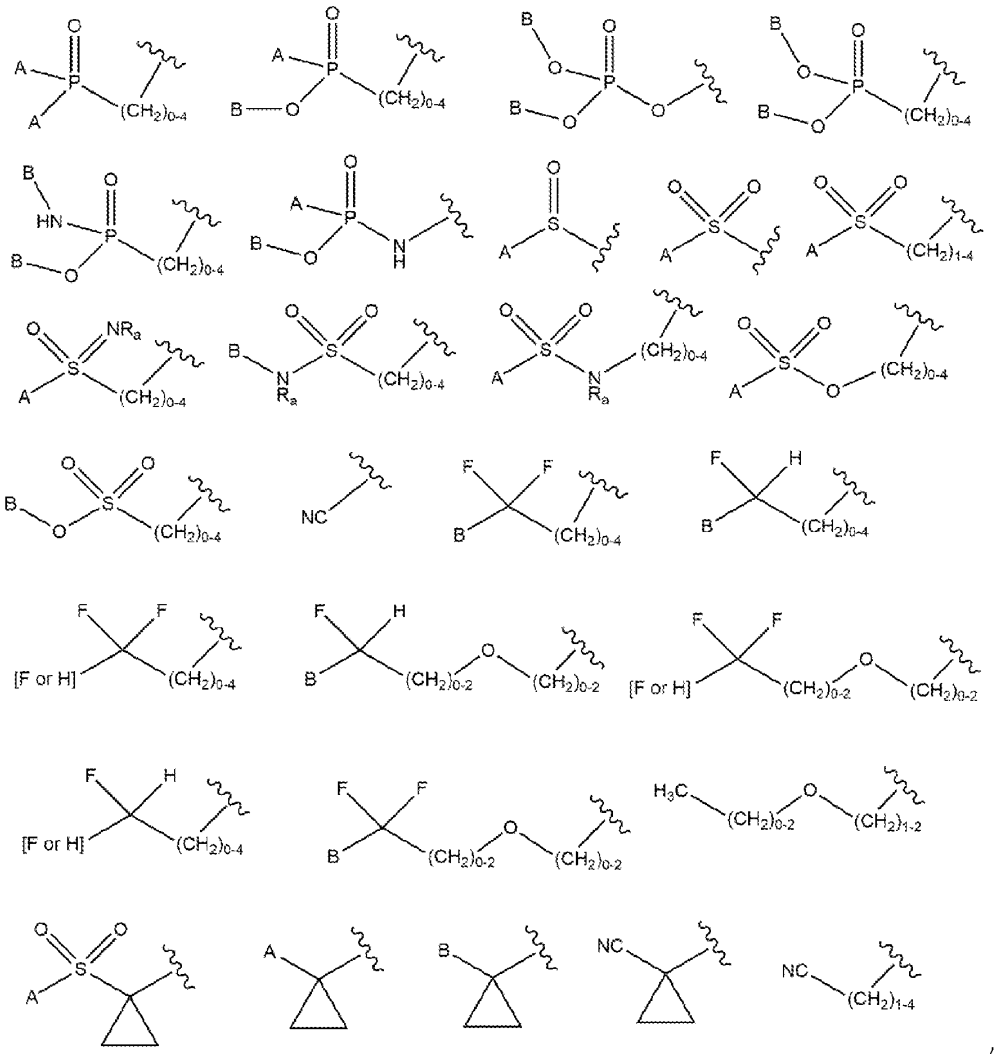
the carbon marked with * is a chiral center and exists as a (R)- and (S)-racemic mixture or as either the (R)- or (S)- enantiomer.

21. The compound according to claim 20 or a solvate, enantiomer, diastereomer, tautomer, polymorph or isotope-labeled compound, or a pharmaceutically acceptable salt thereof, wherein R_1 is selected from



wherein:

R_{18} is selected from the following:



where each A is independently C_1-C_4 alkyl, fluoroalkyl, C_3-C_7 cycloalkyl, $N(R_a)_2$, $(CH_2)_{0-5}$-NR_a-C(O)-C_3-C_7 cycloalkyl, $(CH_2)_{1-5}$-O-C_1-C_3 cycloalkyl, $(CH_2)_{1-5}$-O-$(CH_2)_{1-5}$-C_1-C_3 fluoroalkyl, $(CH_2)_{0-5}$-aryl, $(CH_2)_{0-5}$-heteroaryl, $(CH_2)_{0-5}$-heterocyclyl, $(CH_2)_{0-5}$-NR_a-$(CH_2)_{0-5}$-heteroaryl or $(CH_2)_{0-5}$-NR_a-$(CH_2)_{1-5}$-N-heterocyclyl, where the alkyl, fluoroalkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl are substituted or unsubstituted, or alternatively, A and A together with the attached -P(=O)- moiety may form a substituted or unsubstituted heterocyclyl ring;

each B is independently H, C_1-C_4 alkyl, C_3-C_7 cycloalkyl, $(CH_2)_{1-5}$-NR_a-C(O)-C_3-C_7 cycloalkyl, $(CH_2)_{0-5}$-aryl, $(CH_2)_{0-5}$-heteroaryl, $(CH_2)_{0-5}$-heterocyclyl, $(CH_2)_{1-5}$-NR_a-$(CH_2)_{0-5}$-heteroaryl or $(CH_2)_{1-5}$-NR_a-$(CH_2)_{2-5}$-N-heterocyclyl, O-C_{1-5}-alkyl, O-C_{0-5}-cycloalkyl, O-C_{0-5}-heterocyclyl, where the alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl are substituted or unsubstituted, or alternatively, B and B together with the attached -[O or NH]-P(=O)-O- moiety may form a substituted or unsubstituted heterocyclyl ring, or alternatively, A and B together with the attached -P(=O)-O- moiety may form a substituted or unsubstituted heterocyclyl ring;

each R_a is independently H, C_1-C_4 alkyl, C(O)C_1-C_3 alkyl or C(O)-$(CH_2)_{1-5}$-O-C_1-C_3 alkyl, where the alkyl is substituted or unsubstituted, or alternatively, R_a and A together with the attached -$S(=O)_2$- moiety may form a substituted or unsubstituted heterocyclic ring, or

R_{18} and R_{19} together form a substituted or unsubstituted heterocyclic ring (such as a 5- or 6-membered heterocyclic ring) containing one or more sulfur atoms (which includes the sulfoxide (SO) and sulfone (SO_2) forms), nitrogen atoms (which includes the oxidized forms) and oxygen atoms;

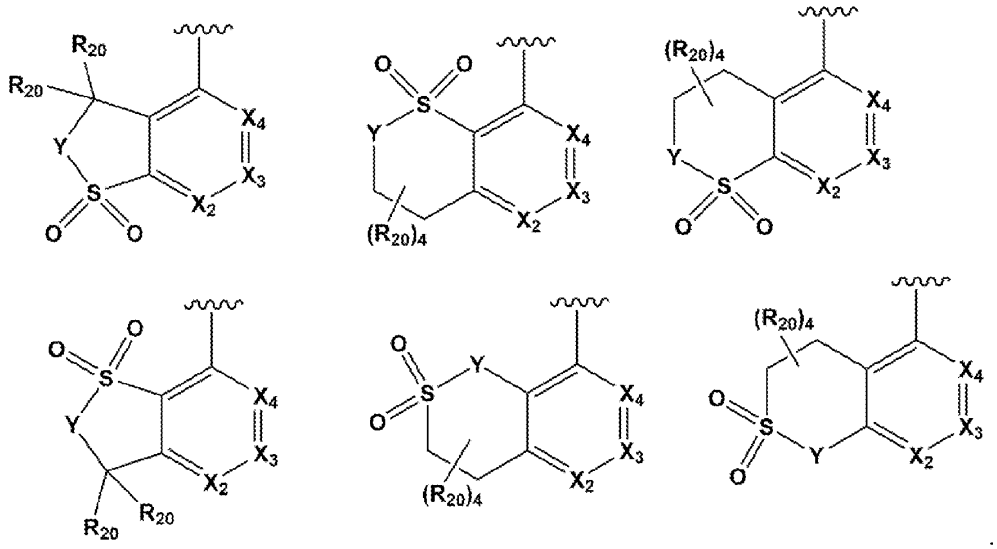
R_{19} is H, C_1-C_4 alkyl, C_3-C_7 cycloalkyl, halogen, CN, CF_3, OCF_3, CFH_2 or CF_2H, where the alkyl and cycloalkyl is substituted or unsubstituted, or R_{19} and R_{18} together form a heterocyclic ring;

each R_{20} is independently H, C_1-C_4 alkyl, C_3-C_7 cycloalkyl, halogen, CN, CF_3, OCF_3, CFH_2 or CF_2H, where the alkyl and cycloalkyl is substituted or unsubstituted;

R_{21} is H, C_1-C_4 alkyl, C_3-C_7 cycloalkyl, CF_3, CFH_2 or CF_2H, where the alkyl and cycloalkyl is substituted or unsubstituted; and

each X_1, X_2, X_3 and X_4 is independently CH, N or substituted C.

22. The compound according to claim 20 or a solvate, enantiomer, diastereomer, tautomer, polymorph or isotope-labeled compound, or a pharmaceutically acceptable salt thereof, wherein R_1 is selected from



23. A pharmaceutical composition comprising the compound of any one of claims 1 to 22 or a solvate, enantiomer, diastereomer, tautomer, polymorph or isotope-labeled compound, or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

24. The pharmaceutical composition according to claim 23, further comprising one or more anti-cancer agents.

25. The pharmaceutical composition according to claim 24, wherein the one or more anti-cancer agents are selected from the group consisting of cyclophosphamide, dacarbazine, cisplatin, methotrexate, mercaptopurine, thioguanine, fluorouracil, cytarabine, vinblastine, paclitaxel, doxorubicin, bleomycin, mitomycin, prednisone, tamoxifen, flutamide, asparaginase, rituximab, trastuzumab, imatinib, retinoic acid, amifostine, camptothecin, topotecan, thalidomide, lenalidomide, a CDK inhibitor and a proteasome inhibitor.

26. A method of treating a disease in which PI3K activity is implicated in a subject in need of such treatment, the method comprising administering to the subject a therapeutically effective amount of the compound of any one of claims 1 to 22 or a solvate, enantiomer, diastereomer, tautomer, polymorph or isotope-labeled compound, or a pharmaceutically acceptable salt thereof.

27. The method of claim 26, wherein the disease is cancer.

28. The method of claim 26, wherein the disease is congenital lipomatous overgrowth, vascular malformations, epidermal naevi, scoliosis/skeletal and spinal syndrome (CLOVES), mosaic tissue overgrowth syndromes, venous malformations and brain malformations associated with severe epilepsy or PIK3CA-related overgrowth syndrome (PROS).

29. The method of claim 26, wherein the disease is a cancer bearing a PI3Kα H1047R mutation.