SAM-competitive PRMT5 inhibitor (Kruykov et al., 2016; Marjon et al., 2016 and Markarov et al., 2016).

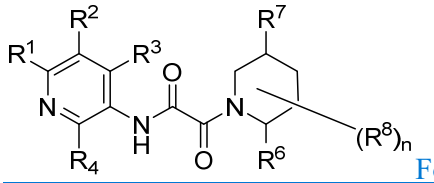
[0003] PRMT5 is a type II arginine methyltransferase that regulates essential cellular functions, including the regulation of cell cycle progression, apoptosis and the DNA-damage response, by symmetrically dimethylating proteins involved in transcription and signaling (Koh, Bezzi and Guccione *Curr Mol Bio Rep* 2015 and Wu et al *Nat Rev Drug Discovery* 2021). However, data from genome-wide genetic perturbation screens using shRNA has revealed a selective requirement for PRMT5 activity in *MTAP*-deleted cancer cell lines (Kruykov et al., 2016; Marjon et al., 2016 and Markarov et al., 2016). The accumulation of MTA caused by *MTAP*-deletion in these cell lines partially inhibits PRMT5, rendering those cells selectively sensitive to additional PRMT5 inhibition.

[0004] PRMT5 inhibitors have been developed, yet they do not demonstrate selectivity for MTAP-deleted cancer cell lines. This lack of selectivity can be explained by the mechanisms of action of the inhibitors, as they are either SAM-uncompetitive or SAM-competitive inhibitors and therefore, MTAP-agnostic (Kruykov et al., 2016; Marjon et al., 2016 and Markarov et al., 2016) However, if a PRMT5 inhibitor were developed that leverages the accumulation of MTA by binding in an MTA-uncompetitive, non-competitive or mixed mode manner or in a MTA-cooperative binding manner, it could demonstrate selectivity for MTAP-deleted tumor cells.

Summary ~~of the Invention~~

[0004a] In one aspect of the present disclosure, there is provided a compound of Formula (I) or a pharmaceutically acceptable salt thereof;

wherein:



Formula (I),

each R^1 is independently selected from H, –D, halo, –CN, –C_1–C_6 alkyl, –C_1–C_6 heteroalkyl, –C_1–C_6 haloalkyl, –C_3–C_9 cycloalkyl, 3-10 membered heterocyclyl, heterocyclylalkyl, heteroarylalkyl, arylalkyl, cycloalkylalkyl, –OR^{a1}, –$N(R^{a1})_2$, –$C(=O)R^{a1}$, –$C(=O)OR^{a1}$, –$NR^{a1}C(=O)R^{a1}$, –$NR^{a1}C(=O)OR^{a1}$, –$C(=O)N(R^{a1})_2$, –$OC(=O)N(R^{a1})_2$,-$S(=O)R^{a1}$, –$S(=O)_2R^{a1}$, –SR^{a1}, –$S(=O)(=NR^{a1})R^{a1}$, –$NR^{a1}S(=O)_2R^{a1}$ and –$S(=O)_2N(R^{a1})_2$;

each R^2 is independently selected from halo, –CN, –C_1–C_6 alkyl, –C_1–C_6 heteroalkyl, –C_1–C_6 haloalkyl, –C_1–C_6 haloalkoxy, –C_3–C_9 cycloalkyl, 3-10 membered heterocyclyl, heterocyclylalkyl, heteroarylalkyl, arylalkyl, cycloalkylalkyl, –OR^{a2}, –$N(R^{a2})_2$, –$C(=O)R^{a2}$, –$C(=O)OR^{a2}$, –$NR^{a2}C(=O)R^{a2}$, –$NR^{a2}C(=O)OR^{a2}$, –$C(=O)N(R^{a2})_2$, –$C(=O)N(OR^{a2})(R^{a2})$, –$OC(=O)N(R^{a2})_2$,-$S(=O)R^{a2}$, –$S(=O)_2R^{a2}$, –SR^{a2}, –$S(=O)(=NR^{a2})R^{a2}$, –$NR^{a2}S(=O)_2R^{a2}$ and –$S(=O)_2N(R^{a2})_2$;

each R^3 is independently selected from H, –D, halo, –CN, –C_1–C_6 alkyl, –C_1–C_6 heteroalkyl, –C_1–C_6 haloalkyl, –C_3–C_9 cycloalkyl, 3-10 membered heterocyclyl, heterocyclylalkyl, heteroarylalkyl, arylalkyl, cycloalkylalkyl, –OR^{a3}, –$N(R^{a3})_2$, –$C(=O)R^{a3}$, –$C(=O)OR^{a3}$, –$NR^{a3}C(=O)R^{a3}$, –$NR^{a3}C(=O)OR^{a3}$, –$C(=O)N(R^{a3})_2$, –$OC(=O)N(R^{a3})_2$,-$S(=O)R^{a3}$, –$S(=O)_2R^{a3}$, –SR^{a3}, –$S(=O)(=NR^{a3})R^{a3}$, –$NR^{a3}S(=O)_2R^{a3}$ and –$S(=O)_2N(R^{a3})_2$;

each R^4 is independently selected from H, –D, halo, –CN, –C_1–C_6 alkyl, –C_1–C_6 heteroalkyl, –C_1–C_6 haloalkyl, –C_3–C_9 cycloalkyl, 3-10 membered heterocyclyl, heterocyclylalkyl, heteroarylalkyl, arylalkyl, cycloalkylalkyl, –OR^{a4}, –$N(R^{a4})_2$, –$C(=O)R^{a4}$, –$C(=O)OR^{a4}$, –$NR^{a4}C(=O)R^{a4}$, –$NR^{a4}C(=O)OR^{a4}$, –$C(=O)N(R^{a4})_2$, –$OC(=O)N(R^{a4})_2$, –$S(=O)R^{a4}$, –$S(=O)_2R^{a4}$, –SR^{a4}, –$S(=O)(=NR^{a4})R^{a4}$, –$NR^{a4}S(=O)_2R^{a4}$ and –$S(=O)_2N(R^{a4})_2$;

each R^6 is independently absent or selected from H, –D, halo, –CN, –C_1–C_6 alkyl, –C_1–C_6 heteroalkyl, –C_1–C_6 haloalkyl, –C_3–C_{10} carbocyclyl, 3-10 membered heterocyclyl, heterocyclylalkyl, C_6–C_{10} aryl, 5-10 member heteroaryl, heteroarylalkyl, arylalkyl, cycloalkylalkyl, –OR^{a6}, –$N(R^{a6})_2$, –$C(=O)R^{a6}$, –$C(=O)OR^{a6}$, –$NR^{a6}C(=O)R^{a6}$, –$NR^{a6}C(=O)OR^{a6}$, –$C(=O)N(R^{a6})_2$, –$OC(=O)N(R^{a6})_2$,-$S(=O)R^{a6}$, –$S(=O)_2R^{a6}$, –SR^{a6}, –$S(=O)(=NR^{a6})R^{a6}$, –$NR^{a6}S(=O)_2R^{a6}$ and –$S(=O)_2N(R^{a6})_2$, wherein each alkyl, carbocyclyl, heterocyclyl, cycloalkylalkyl, heterocyclylalkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl is optionally substituted at any available position;

each R^7 is independently absent or selected from H, –D, halo, –CN, –C_1–C_6 alkyl, –C_1–C_6 hydroxyalkyl, –C_1–C_6 haloalkyl, –C_3–C_9 cycloalkyl, 3-10 membered heterocyclyl, 5-6-membered monocyclic heteroaryl, heterocyclylalkyl, heteroarylalkyl, arylalkyl, cycloalkylalkyl, –OR^{a7}, –$N(R^{a7})_2$, –$C(=O)R^{a7}$, –$C(=O)OR^{a7}$, –$NR^{a7}C(=O)R^{a7}$, –$NR^{a7}C(=O)OR^{a7}$, –$C(=O)N(R^{a7})_2$, –$OC(=O)N(R^{a7})_2$,-$S(=O)R^{a7}$, –$S(=O)_2R^{a7}$, –SR^{a7}, –$S(=O)(=NR^{a7})R^{a7}$, –$NR^{a7}S(=O)_2R^{a7}$ and –$S(=O)_2N(R^{a7})_2$;

each R^8 is independently selected from H, –D, =O, halo, –CN, –C_1–C_6 alkyl, –C_1–C_6 heteroalkyl, –C_1–C_6 haloalkyl, –C_3–C_9 cycloalkyl, 3-10 membered heterocyclyl, heterocyclylalkyl, heteroarylalkyl, arylalkyl, cycloalkylalkyl, –OR^{a8}, –$N(R^{a8})_2$, –$C(=O)R^{a8}$, –

$C(=O)OR^{a8}$, $–NR^{a8}C(=O)R^{a8}$, $–NR^{a8}C(=O)OR^{a8}$, $–CH_2C(=O)N(R^{a8})_2$ – $C(=O)N(R^{a8})_2$, $–OC(=O)N(R^{a8})_2$, $–CH_2C(=O)N(R^{a8})_2$,-$S(=O)R^{a8}$, $–S(=O)_2R^{a8}$, $–SR^{a8}$, $–S(=O)(=NR^{a8})R^{a8}$, $–NR^{a8}S(=O)_2R^{a8}$ and $–S(=O)_2N(R^{a8})_2$ wherein two instances of R^8 together with the atom or atoms to which they are attached can be taken together to form a 3-10 member cycloalkyl or heterocyclyl ring;

each R^{a1}, R^{a2}, R^{a3}, R^{a4}, R^{a6}, R^{a7} and R^{a8} is independently selected from H, C_1–C_6 alkyl, –C_1–C_6 heteroalkyl, C_3–C_9 cycloalkyl, 3-7 membered heterocyclyl, cycloalkylalkyl, heterocyclylalkyl, aryl, 5-6 membered heteroaryl, arylalkyl and heteroarylalkyl wherein each alkyl, cycloalkyl, heterocyclyl, cycloalkylalkyl, heterocyclylalkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl is optionally substituted at any available position ; and

n is 0, 1, 2 or 3

provided that:

(i) when R^1 is H, R^2 is not halo, –OPr, $–N(CH_3)_2$ or $–CF_3$;

(ii) when R^1 is OR^{a1}, R^2 is not $–OR^{a2}$;

(iii) when R^1 is H and R^2 is $–CH_3$, R^8 groups cannot be taken together to form a ring and R^6 is not absent or H, and is not thiazolyl, furanyl or pyrrolyl;

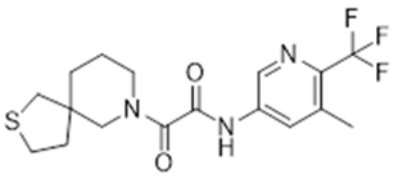
(iv) when R^2 is Me, R^1 is not piperidine

(v) the compound is not:

A. 5-(2-(5-methyl-2-(p-tolyl)piperidin-1-yl)-2-oxoacetamido)nicotinamide or any of its enantiomers or diastereomers;

B. 2-(2-(4-(2H-tetrazol-5-yl)phenyl)-5-methylpiperidin-1-yl)-N-(5,6-dimethylpyridin-3-yl)-2-oxoacetamide or any of its enantiomers or diastereomers;

C. 2-cyano-5-(2-(5-methyl-2-phenylpiperidin-1-yl)-2-oxoacetamido)nicotinamide or any of its enantiomers or diastereomers; or

D. N-(5-methyl-6-(trifluoromethyl)pyridin-3-yl)-2-oxo-2-(2-thia-7-azaspiro[4.5]decan-7-yl)acetamide  or any of its enantiomers or diastereomers.

[0004b] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound disclosed herein, or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

[0004c] In a further aspect of the present disclosure, there is provided a compound disclosed herein or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable composition disclosed herein, for use in treating an MTAP-deficient and/or an MTA-accumulating disease in a subject in need thereof.

[0004d] In another aspect of the present disclosure, there is provided a compound disclosed herein for use in treating a cancer in a subject, wherein:

a) the level of MTAP and/or MTA in a test sample obtained from said subject is assessed, wherein the MTA level can be assessed directly or indirectly;

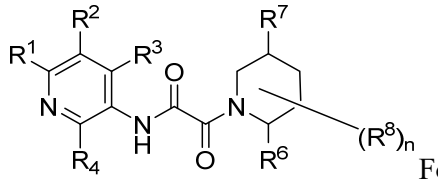
b) the test sample is compared with a reference, wherein MTAP deficiency and/or MTA accumulation in said test sample compared to the reference indicates the cancer in said subject will respond to therapeutic treatment with a PRMT5 inhibitor; and

c) the compound is to be administered to the subject identified in step b).

[0004e] In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating an MTAP-deficient and/or an MTA-accumulating disease in a subject in need thereof.

[0005] In one ~~aspect~~example of the ~~invention~~disclosure, provided is a compound of Formula (I) or a pharmaceutically acceptable salt thereof;

wherein:

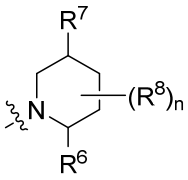


Formula (I),

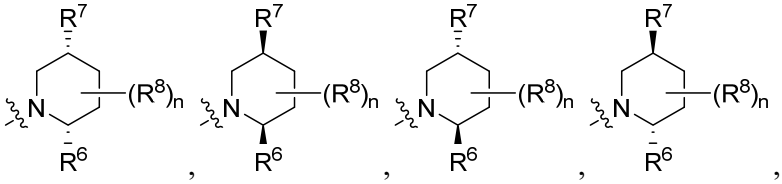
each R^1 is independently selected from H, –D, halo, –CN, –C_1–C_6 alkyl, –C_1–C_6 heteroalkyl, –C_1–C_6 haloalkyl, –C_3–C_9 cycloalkyl, 3-10 membered heterocyclyl, heterocyclylalkyl, heteroarylalkyl, arylalkyl, cycloalkylalkyl, –OR^{a1}, –$N(R^{a1})_2$, –$C(=O)R^{a1}$, –$C(=O)OR^{a1}$, –$NR^{a1}C(=O)R^{a1}$, –$NR^{a1}C(=O)OR^{a1}$, –$C(=O)N(R^{a1})_2$, –$OC(=O)N(R^{a1})_2$,-$S(=O)R^{a1}$, –$S(=O)_2R^{a1}$, –SR^{a1}, –$S(=O)(=NR^{a1})R^{a1}$, –$NR^{a1}S(=O)_2R^{a1}$ and –$S(=O)_2N(R^{a1})_2$;

[0006] In certain ~~embodiment~~examples, R^6 and R^7 are not H and are in a *trans* relative configuration. In some ~~embodiment~~examples, R^6 and R^7 are not H and are in a *cis* relative configuration.

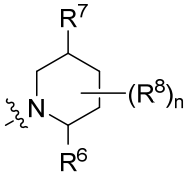
[0007] In some ~~embodiment~~examples of Formula (I), the moiety represented as



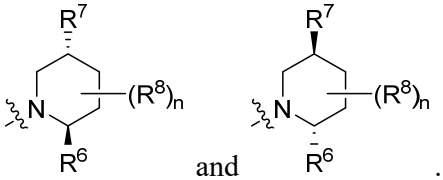
is selected from:



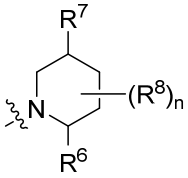
[0008] In some ~~embodiment~~examples of Formula (I) the moiety represented as



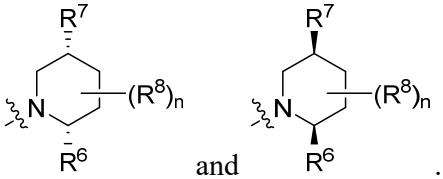
is selected from:



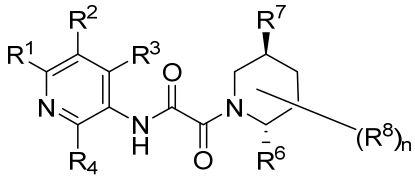
[0009] In other ~~embodiment~~examples of Formula (I), the moiety represented as



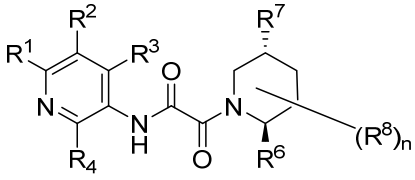
is selected from:



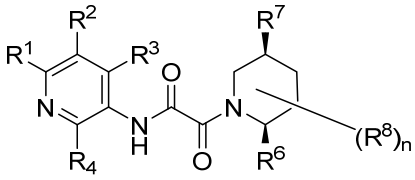
[0010] In some ~~embodiment~~examples, the compound is of Formula (Ia)

 Formula (Ia).

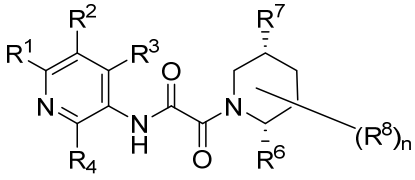
[0011] In other ~~embodiment~~examples, the compound is of Formula (Ib)

 Formula (Ib).

[0012] In some ~~embodiment~~examples, the compound is of Formula (Ic)

 Formula (Ic).

[0013] In other ~~embodiment~~examples, the compound is of Formula (Id)

 Formula (Id).

[0014] In some ~~embodiment~~examples of Formula (I), (Ia), (Ib), (Ic) and (Id), each R^8 is independently selected from H, –D, =O, halo, –CN, –C_1–C_6 alkyl, –C_1–C_6 heteroalkyl, –C_1–C_6 haloalkyl, –C_3–C_9 cycloalkyl, 3-10 membered heterocyclyl, heterocyclylalkyl, heteroarylalkyl, arylalkyl, cycloalkylalkyl, –OR^{a8}, –$N(R^{a8})_2$, –$C(=O)R^{a8}$, –$C(=O)OR^{a8}$, –$NR^{a8}C(=O)R^{a8}$, –$NR^{a8}C(=O)OR^{a8}$, –$CH_2C(=O)N(R^{a8})_2$ –$C(=O)N(R^{a8})_2$, –$OC(=O)N(R^{a8})_2$, –$CH_2C(=O)N(R^{a8})_2$, -$S(=O)R^{a8}$, –$S(=O)_2R^{a8}$, –SR^{a8}, –$S(=O)(=NR^{a8})R^{a8}$, –$NR^{a8}S(=O)_2R^{a8}$ and –$S(=O)_2N(R^{a8})_2$.

[0015] In some ~~embodiment~~examples of Formula (I), (Ia), (Ib), (Ic) and (Id), R^1 is selected from H, halo, –CN, –C_1–C_6 alkyl, –C_1–C_6 heteroalkyl, –C_1–C_6 haloalkyl, –C_3–C_9 cycloalkyl, 3-10 membered heterocyclyl, –OR^{a1}, –$N(R^{a1})_2$, –$C(=O)R^{a1}$, –$C(=O)OR^{a1}$, –$NR^{a1}C(=O)R^{a1}$, –$NR^{a1}C(=O)OR^{a1}$, –$C(=O)N(R^{a1})_2$ and –$OC(=O)N(R^{a1})_2$. In some ~~embodiment~~examples, R^1 is selected from H, halo, –CN, –C_1–C_6 alkyl, –C_1–C_6 haloalkyl, –OR^{a1} and –$N(R^{a1})_2$. In some ~~embodiment~~examples, R^1 is selected from H, –C_1–C_6 alkyl, –C_1–C_6 haloalkyl, –OR^{a1} and –$N(R^{a1})_2$.

In further ~~embodiment~~examples, each R^{a1} is independently selected from H, –C_1–C_6 alkyl (*e.g.*, –Me, –Et, –Pr, –^{i}Pr,–^{n}Bu, –^{t}Bu, –*sec*-Bu, –*iso*-Bu) and –C_1–C_6 haloalkyl (*e.g.*, –CHF_2, –CF_3).

[0016] In certain ~~embodiment~~examples of Formula (I), (Ia), (Ib), (Ic) and (Id), R^1 is selected from H, –C_1–C_6 alkyl (*e.g.*, –Me, –Et, –Pr, –^{i}Pr,–^{n}Bu, –^{t}Bu, –*sec*-Bu, –*iso*-Bu), –C_1–C_6 alkyl (*e.g.*, –CF_3, –CHF_2), –OH, –O–(C_1–C_6 alkyl) (*e.g.*, –OMe, –OEt), –O–(C_1–C_6 haloalkyl) (*e.g.*, –OCF_3, –$OCHF_2$), –NH_2, –NH–(C_1–C_6 alkyl) (*e.g.*, –NHMe) and –N–(C_1–C_6 alkyl)$_2$ (*e.g*, NMe_2). In some ~~embodiment~~examples, R^1 is selected from H, –Me, –Et, –CHF_2, –OMe, –OEt, –$OCHF_2$, –OCF_3, –OH and –NH_2. In further ~~embodiment~~examples, R^1 is selected from H, –Et, –OMe, –OEt, –$OCHF_2$, –OCF_3 and –OH. In certain ~~embodiment~~examples, R^1 is selected from H and –OMe. In some ~~embodiment~~examples, R^1 is H. In other ~~embodiment~~examples, R^1 is –OMe.

[0017] In certain ~~embodiment~~examples, R^1 is selected from H, –Me, –CHF_2 and –NH_2. In further ~~embodiment~~examples, R^1 is selected from –Me and –NH_2. In certain ~~embodiment~~examples, R^1 is –Me. In other ~~embodiment~~examples, R^1 is –NH_2.

[0018] In some ~~embodiment~~examples of Formula (I), (Ia), (Ib), (Ic) and (Id), R^2 is selected from halo, –CN, –C_1–C_6 alkyl, –C_1–C_6 heteroalkyl, –C_1–C_6 haloalkyl, –C_1–C_6 haloalkoxy, –C_3–C_9 cycloalkyl (*e.g.*, cyclopropyl), 3-10 membered heterocyclyl (*e.g.*, oxetanyl, tetrahydrofuranyl), –OR^{a2}, –$N(R^{a2})_2$, –$C(=O)R^{a2}$, –$C(=O)OR^{a2}$, –$NR^{a2}C(=O)R^{a2}$, –$NR^{a2}C(=O)OR^{a2}$, –$C(=O)N(R^{a2})_2$, –$C(=O)N(OR^{a2})(R^{a2})$ and –$OC(=O)N(R^{a2})_2$. In further ~~embodiment~~examples, R^2 is selected from halo, –CN, –C_1–C_6 alkyl, –C_1–C_6 haloalkyl, –C_1–C_6 haloalkoxy, –C_3–C_9 cycloalkyl (*e.g.*, cyclopropyl), 3-6 membered heterocyclyl (*e.g.*, oxetanyl, tetrahydrofuranyl), –OR^{a2}, –$N(R^{a2})_2$, –$C(=O)N(OR^{a2})(R^{a2})$, –$C(=O)R^{a2}$ and –$C(=O)N(R^{a2})_2$. In certain ~~embodiment~~examples, R^2 is selected from halo, –C_1–C_6 alkyl, –C_1–C_6 haloalkyl, –C_1–C_6 haloalkoxy, –C_3–C_9 cycloalkyl (*e.g.*, cyclopropyl), 3-6 membered heterocyclyl (*e.g.*, oxetanyl, tetrahydrofuranyl), –OR^{a2}, –$C(=O)R^{a2}$ and –$C(=O)N(R^{a2})_2$. In some ~~embodiment~~examples, R^2 is selected from halo, –C_1–C_6 alkyl, –C_3–C_9 cycloalkyl (*e.g.*, cyclopropyl), 3-6 membered heterocyclyl (*e.g.*, oxetanyl, tetrahydrofuranyl), –C_1–C_6 haloalkyl, –C_1–C_6 haloalkoxy, –OR^{a2}, and –$C(=O)N(R^{a2})_2$. In further ~~embodiment~~examples, each R^{a2} is independently selected from H and –C_1–C_6 alkyl (*e.g.*, –Me, –Et, –Pr, –^{i}Pr,–^{n}Bu, –^{t}Bu, –*sec*-Bu, –*iso*-Bu). In certain ~~embodiment~~examples, R^2 is selected from halo (*e.g.*, –Cl), –C_1–C_6 alkyl (*e.g.*, –Me, –Et, –Pr, –^{i}Pr,–^{n}Bu, –^{t}Bu, –*sec*-Bu, –*iso*-Bu), –C_1–C_6 haloalkyl (*e.g.*, –CF_3, CHF_2), –C_3–C_9 cycloalkyl (*e.g.*, cyclopropyl), 3-6 membered heterocyclyl (*e.g.*, oxetanyl, tetrahydrofuranyl), –C_1–C_6 haloalkoxy (*e.g.*, –OCF_3, –$OCHF_2$), –OMe, –C(=O)H, –C(=O)NHOH, and –$C(=O)NH_2$. In further ~~embodiment~~examples, R^2 is selected from –Cl, –Me, –Et,

–^{i}Pr, –CF_3, CHF_2, –$OCHF_2$, –OCF_3, cyclopropyl, –C(=O)NHOH, –C(=O)H and –$C(=O)NH_2$. In certain ~~embodiment~~examples, R^2 is selected from –$C(=O)NH_2$ and –C(=O)H. In some ~~embodiment~~examples, R^2 is –$C(=O)NH_2$. In certain ~~embodiment~~examples, R^2 is selected from –Cl, –Me, –Et, –^{i}Pr, –CF_3, –CHF_2, –$OCHF_2$, –OCF_3, oxetan-3-yl, tetrahydrofuran-3-yl, and cyclopropyl. In further ~~embodiment~~examples, R^2 is selected from cyclopropyl, –Me and –Et.

[0019] In some ~~embodiment~~examples, R^1 is selected from H, –OMe, –OEt,–OCF_3, –$OCHF_2$, –CHF_2, –Me, –Et, –OH and –NH_2 and R^2 is selected from –Cl, –Me, –Et, –^{i}Pr, –CF_3, –CHF_2, –$OCHF_2$, –OCF_3, cyclopropyl, –$C(=O)NH_2$, and –C(=O)H, provided that when R^2 is –Me, R^1 is NH_2. In some ~~embodiment~~examples, R^1 is selected from H, –CHF_2, –Me and –NH_2 and R^2 is selected from –Cl, –Me, –Et, –CF_3, –CHF_2, –$OCHF_2$ and cyclopropyl, provided that when R^2 is –Me, R^1 is NH_2. In certain ~~embodiment~~examples, R^1 is selected from –NH_2 and –Me and R^2 is selected from –Me, and –Et. In further ~~embodiment~~examples, R^1 is –NH_2 and R^2 is selected from cyclopropyl, –Me, and –Et.

In some ~~embodiment~~examples R^1 is selected from H, –OMe, –OEt,–OCF_3, –$OCHF_2$, –Et and –OH and R^2 is selected from –$C(=O)NH_2$ and –C(=O)H. In further ~~embodiment~~examples, R^1 is selected from H and –OMe and R^2 is –$C(=O)NH_2$.

[0020] In some ~~embodiment~~examples of Formula (I), (Ia), (Ib), (Ic) and (Id), R^3 is selected from H, halo, –CN, –C_1–C_6 alkyl, –C_1–C_6 heteroalkyl, –C_1–C_6 haloalkyl, –C_3–C_9 cycloalkyl, 3-10 membered heterocyclyl, –OR^{a3}, –$N(R^{a3})_2$, –$C(=O)R^{a3}$, –$C(=O)OR^{a3}$, –$NR^{a3}C(=O)R^{a3}$, –$NR^{a3}C(=O)OR^{a3}$, –$C(=O)N(R^{a3})_2$ and –$OC(=O)N(R^{a3})_2$. In some ~~embodiment~~examples, R^3 is selected from H, halo, –CN, –C_1–C_6 alkyl, –C_1–C_6 haloalkyl and –$N(R^{a3})_2$. In further ~~embodiment~~examples, R^{a3} is selected from H and C_1–C_6 alkyl (*e.g.*, –Me, –Et, –Pr, –^{i}Pr,–^{n}Bu, –^{t}Bu, –*sec*-Bu, –*iso*-Bu). In certain ~~embodiment~~examples, R^3 is selected from –C_1–C_6 alkyl (*e.g.*, –Me, –Et, –Pr, –^{i}Pr,–^{n}Bu, –^{t}Bu, –*sec*-Bu, –*iso*-Bu), –OH, –O–(C_1–C_6 alkyl) (*e.g.*, –OMe), –NH_2, –NH–(C_1–C_6 alkyl) (*e.g.*, –NHMe) and –N–(C_1–C_6 alkyl)$_2$ (*e.g*, NMe_2). In further ~~embodiment~~examples, R^3 is selected from H, –Me and –NH_2. In certain ~~embodiment~~examples, R^3 is selected from H and –Me. In further ~~embodiment~~examples, R^3 is –Me.

[0021] In some ~~embodiment~~examples of Formula (I), (Ia), (Ib), (Ic) and (Id), R^4 is selected from H, halo, –CN, –C_1–C_6 alkyl, –C_1–C_6 heteroalkyl, –C_1–C_6 haloalkyl, –C_3–C_9 cycloalkyl, 3-10 membered heterocyclyl, –OR^{a4}, –$N(R^{a4})_2$, –$C(=O)R^{a4}$, –$C(=O)OR^{a4}$, –$NR^{a4}C(=O)R^{a4}$, –$NR^{a4}C(=O)OR^{a4}$, –$C(=O)N(R^{a4})_2$ and –$OC(=O)N(R^{a4})_2$. In some ~~embodiment~~examples, R^4 is selected from H, halo, –CN, –C_1–C_6 alkyl, –C_1–C_6 haloalkyl and –$N(R^{a4})_2$. In further ~~embodiment~~examples,

each R^{a4} is independently selected from H and –C_1–C_6 alkyl (*e.g.*, –Me, –Et, –Pr, –^{i}Pr,–^{n}Bu, –^{t}Bu, –*sec*-Bu, –*iso*-Bu). In certain ~~embodiment~~examples, R^4 is selected from –C_1–C_6 alkyl (*e.g.*, –Me, –Et, –Pr, –^{i}Pr,–nBu, –^{t}Bu, –*sec*-Bu, –*iso*-Bu), –OH, –O–(C_1–C_6 alkyl) (*e.g.*, –OMe), –NH_2, –NH–(C_1–C_6 alkyl) (*e.g.*, –NHMe) and –N–(C_1–C_6 alkyl)$_2$ (*e.g*, NMe_2). In further ~~embodiment~~examples, R^4 is H.

[0022] In some ~~embodiment~~examples of Formula (I), (Ia), (Ib), (Ic) and (Id), each R^6 is independently selected from H, –D, halo, –CN, –C_1–C_6 alkyl, –C_1–C_6 heteroalkyl, –C_1–C_6 haloalkyl, –C_3–C_{10} carbocyclyl, 3-10 membered heterocyclyl, heterocyclylalkyl, C_6–C_{10} aryl, 5-10 member heteroaryl, heteroarylalkyl, arylalkyl, cycloalkylalkyl, –OR^{a6}, –$N(R^{a6})_2$, –$C(=O)R^{a6}$, –$C(=O)OR^{a6}$, –$NR^{a6}C(=O)R^{a6}$, –$NR^{a6}C(=O)OR^{a6}$, –$C(=O)N(R^{a6})_2$, –$OC(=O)N(R^{a6})_2$,-$S(=O)R^{a6}$, –$S(=O)_2R^{a6}$, –SR^{a6}, –$S(=O)(=NR^{a6})R^{a6}$, –$NR^{a6}S(=O)_2R^{a6}$ and –$S(=O)_2N(R^{a6})_2$, wherein each alkyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, cycloalkylalkyl, heterocyclylalkyl, arylalkyl and heteroarylalkyl is substituted at any available position with 0, 1, 2 or 3 instances of R^{10}, wherein:

each R^{10} is independently selected from –D, =O, –CN, halo, –C_1–C_6 alkyl, –C_1–C_6 heteroalkyl, –C_1–C_6 haloalkyl, –C_3–C_9 cycloalkyl, 3-10 membered heterocyclyl, C_6–C_{10} aryl, 5-10 membered heteroaryl, cycloalkylalkyl, heterocyclylalkyl, arylalkyl, heteroarylalkyl, heterocyclylalkoxy, –OR^{b10}, –$N(R^{b10})_2$, –$C(=O)R^{b10}$, –$C(=O)OR^{b10}$, –$NR^{b10}C(=O)R^{b10}$, –$NR^{b10}C(=O)OR^{b10}$, –$C(=O)N(R^{b10})_2$, –$OC(=O)R^{b10}$, –$OC(=O)N(R^{b10})_2$,-$S(=O)R^{b10}$, –$S(=O)_2R^{b10}$, –SR^{b10}, –$S(=O)(=NR^{b10})R^{b10}$, –$NR^{b10}S(=O)_2R^{b10}$ and –$S(=O)_2N(R^{b10})_2$, wherein each alkyl, cycloalkyl, heteroalkyl, heterocyclyl, aryl, heteroaryl, cycloalkylalkyl, heterocyclylalkyl, heterocyclylalkoxy, arylalkyl and heteroarylalkyl of R^{10} is optionally substituted (*e.g.*, substituted with 0, 1, 2 or 3 instances of –Me, –OH, C(=O)Me, –C(=O)NHMe, –NH_2, –NHC(=O)Me or a combination thereof);

each R^{b10} is independently H; –C_1–C_6 alkyl; –C_1–C_6 haloalkyl; –C_1–C_6 heteroalkyl substituted with 0 or 1 instance of =O; C_3–C_9 cycloalkyl; or 3-10 member heterocyclyl substituted with 0 or 1 instances of =O, –Me or a combination thereof.

[0023] In some ~~embodiment~~examples of Formula (I), (Ia), (Ib), (Ic) and (Id), each R^6 is independently selected from –D, halo, –CN, –C_1–C_6 alkyl, –C_1–C_6 heteroalkyl, –C_1–C_6 haloalkyl, –C_3–C_{10} carbocyclyl, 3-10 membered heterocyclyl, heterocyclylalkyl, C_6–C_{10} aryl, 5-10 member heteroaryl, heteroarylalkyl, arylalkyl, cycloalkylalkyl, –OR^{a6}, –$N(R^{a6})_2$, –$C(=O)R^{a6}$, –$C(=O)OR^{a6}$, –$NR^{a6}C(=O)R^{a6}$, –$NR^{a6}C(=O)OR^{a6}$, –$C(=O)N(R^{a6})_2$, –$OC(=O)N(R^{a6})_2$,-$S(=O)R^{a6}$, –$S(=O)_2R^{a6}$, –SR^{a6}, –$S(=O)(=NR^{a6})R^{a6}$, –$NR^{a6}S(=O)_2R^{a6}$ and –

$S(=O)_2N(R^{a6})_2$, wherein each alkyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, cycloalkylalkyl, heterocyclylalkyl, arylalkyl and heteroarylalkyl is substituted at any available position with 0, 1, 2 or 3 instances of R^{10}, wherein:

each R^{10} is independently selected from –D, =O, –CN, halo, $–C_1–C_6$ alkyl, $–C_1–C_6$ heteroalkyl, $–C_1–C_6$ haloalkyl, $–C_3–C_9$ cycloalkyl, 3-10 membered heterocyclyl, $C_6–C_{10}$ aryl, 5-10 membered heteroaryl, cycloalkylalkyl, heterocyclylalkyl, arylalkyl, heteroarylalkyl, heterocyclylalkoxy, $–OR^{b10}$, $–N(R^{b10})_2$, $–C(=O)R^{b10}$, $–C(=O)OR^{b10}$, $–NR^{b10}C(=O)R^{b10}$, $–NR^{b10}C(=O)OR^{b10}$, $–C(=O)N(R^{b10})_2$, $–OC(=O)R^{b10}$, $–OC(=O)N(R^{b10})_2$,-$S(=O)R^{b10}$, $–S(=O)_2R^{b10}$, $–SR^{b10}$, $–S(=O)(=NR^{b10})R^{b10}$, $–NR^{b10}S(=O)_2R^{b10}$ and $–S(=O)_2N(R^{b10})_2$, wherein each alkyl, cycloalkyl, heteroalkyl, heterocyclyl, aryl, heteroaryl, cycloalkylalkyl, heterocyclylalkyl, heterocyclylalkoxy, arylalkyl and heteroarylalkyl of R^{10} is optionally substituted (*e.g.*, substituted with 0, 1, 2 or 3 instances of –Me, –OH, C(=O)Me, –C(=O)NHMe, $–NH_2$, –NHC(=O)Me or a combination thereof);

each R^{b10} is independently H; $–C_1–C_6$ alkyl; $–C_1–C_6$ haloalkyl; $–C_1–C_6$ heteroalkyl substituted with 0 or 1 instance of =O; $C_3–C_9$ cycloalkyl; or 3-10 member heterocyclyl substituted with 0 or 1 instances of =O, –Me or a combination thereof.

[0024] In some ~~embodiment~~examples of Formula (I), (Ia), (Ib), (Ic) and (Id), each R^6 is independently selected from H, halo, –CN, $–C_1–C_6$ alkyl, $–C_1–C_6$ heteroalkyl, $–C_1–C_6$ haloalkyl, $–C_3–C_{10}$ carbocyclyl, 3-10 membered heterocyclyl, heterocyclylalkyl, $C_6–C_{10}$ aryl, 5-10 member heteroaryl, heteroarylalkyl, arylalkyl, cycloalkylalkyl, $–OR^{a6}$, $–N(R^{a6})_2$, $–C(=O)R^{a6}$, $–C(=O)OR^{a6}$, $–NR^{a6}C(=O)R^{a6}$, $–NR^{a6}C(=O)OR^{a6}$, $–C(=O)N(R^{a6})_2$, $–OC(=O)N(R^{a6})_2$,-$S(=O)R^{a6}$, $–S(=O)_2R^{a6}$, $–SR^{a6}$, $–S(=O)(=NR^{a6})R^{a6}$, $–NR^{a6}S(=O)_2R^{a6}$ and $–S(=O)_2N(R^{a6})_2$, wherein each alkyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, cycloalkylalkyl, heterocyclylalkyl, arylalkyl and heteroarylalkyl is substituted at any available position with 0, 1, 2 or 3 instances of R^{10}, wherein:

each R^{10} is independently selected from –D, =O, –CN, halo, $–C_1–C_6$ alkyl, $–C_1–C_6$ heteroalkyl, $–C_1–C_6$ haloalkyl, $–C_3–C_9$ cycloalkyl, 3-10 membered heterocyclyl, $C_6–C_{10}$ aryl, 5-10 membered heteroaryl, cycloalkylalkyl, heterocyclylalkyl, arylalkyl, heteroarylalkyl, heterocyclylalkoxy, $–OR^{b10}$, $–N(R^{b10})_2$, $–C(=O)R^{b10}$, $–C(=O)OR^{b10}$, $–NR^{b10}C(=O)R^{b10}$, $–NR^{b10}C(=O)OR^{b10}$, $–C(=O)N(R^{b10})_2$, $–OC(=O)R^{b10}$, $–OC(=O)N(R^{b10})_2$,-$S(=O)R^{b10}$, $–S(=O)_2R^{b10}$, $–SR^{b10}$, $–S(=O)(=NR^{b10})R^{b10}$, $–NR^{b10}S(=O)_2R^{b10}$ and $–S(=O)_2N(R^{b10})_2$, wherein each alkyl, cycloalkyl, heteroalkyl, heterocyclyl, aryl, heteroaryl, cycloalkylalkyl, heterocyclylalkyl, heterocyclylalkoxy, arylalkyl and heteroarylalkyl of R^{10} is optionally

substituted (*e.g.*, substituted with 0, 1, 2 or 3 instances of –Me, –OH, C(=O)Me, –C(=O)NHMe, $–NH_2$, –NHC(=O)Me or a combination thereof);

each R^{b10} is independently H; $–C_1–C_6$ alkyl; $–C_1–C_6$ haloalkyl; $–C_1–C_6$ heteroalkyl substituted with 0 or 1 instance of =O; $C_3–C_9$ cycloalkyl; or 3-10 member heterocyclyl substituted with 0 or 1 instances of =O, –Me or a combination thereof.

[0025] In some ~~embodiment~~examples, each R^{a6} is independently selected from H and $–C_1–C_6$ alkyl (*e.g.*, –Me, –Et, –Pr, $–^i$Pr,$–^n$Bu, $–^t$Bu, –*sec*-Bu, –*iso*-Bu).

In some ~~embodiment~~examples of Formula (I), (Ia), (Ib), (Ic) and (Id), each R^6 is independently selected from H, $–C_1–C_6$ alkyl, $–C_1–C_6$ heteroalkyl, $–C_1–C_6$ haloalkyl, $–C_3–C_{10}$ carbocyclyl, 3-10 membered heterocyclyl, heterocyclylalkyl, $C_6–C_{10}$ aryl, 5-10 member heteroaryl, heteroarylalkyl, arylalkyl and cycloalkylalkyl, wherein each alkyl, cycloalkyl, heterocyclyl, cycloalkylalkyl, heterocyclylalkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl is optionally substituted at any available position.

[0026] In some ~~embodiment~~examples, each R^6 is independently selected from $–C_1–C_6$ alkyl, $–C_1–C_6$ heteroalkyl, $–C_1–C_6$ haloalkyl, $–C_3–C_{10}$ carbocyclyl, 3-10 membered heterocyclyl, heterocyclylalkyl, $C_6–C_{10}$ aryl, 5-10 member heteroaryl, heteroarylalkyl, arylalkyl and cycloalkylalkyl, wherein each alkyl, cycloalkyl, heterocyclyl, cycloalkylalkyl, heterocyclylalkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl is optionally substituted at any available position.

In some ~~embodiment~~examples, each R^6 is independently selected from H, $–C_1–C_6$ alkyl, $–C_1–C_6$ heteroalkyl, $–C_1–C_6$ haloalkyl, $–C_3–C_{10}$ carbocyclyl, 3-10 membered heterocyclyl, heterocyclylalkyl, $C_6–C_{10}$ aryl, 5-10 member heteroaryl, heteroarylalkyl, arylalkyl and cycloalkylalkyl, wherein each alkyl, cycloalkyl, heterocyclyl, cycloalkylalkyl, heterocyclylalkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl is substituted at any available position with 0, 1, 2 or 3 instances of R^{10} wherein:

each R^{10} is independently selected from –D, =O, –CN, halo, $–C_1–C_6$ alkyl, $–C_1–C_6$ heteroalkyl, $–C_1–C_6$ haloalkyl, $–C_3–C_9$ cycloalkyl, 3-10 membered heterocyclyl, $C_6–C_{10}$ aryl, 5-10 membered heteroaryl, cycloalkylalkyl, arylalkyl, heteroarylalkyl, heterocyclylalkoxy, heterocyclylalkyl, $–OR^{b10}$, $–N(R^{b10})_2$, $–C(=O)R^{b10}$, $–C(=O)OR^{b10}$, $–NR^{b10}C(=O)R^{b10}$, $–NR^{b10}C(=O)OR^{b10}$, $–C(=O)N(R^{b10})_2$, $–OC(=O)R^{b10}$, $–OC(=O)N(R^{b10})_2$,-$S(=O)R^{b10}$, $–S(=O)_2R^{b10}$, $–SR^{b10}$, $–S(=O)(=NR^{b10})R^{b10}$, $–NR^{b10}S(=O)_2R^{b10}$ and-$S(=O)_2N(R^{b10})_2$, wherein each alkyl, cycloalkyl, heteroalkyl, heterocyclyl, aryl, heteroaryl, cycloalkylalkyl, heterocyclylalkyl, arylalkyl and heteroarylalkyl of R^{10} is optionally substituted (*e.g.*, with 0,

1, 2, 3, 4, or 5 instances of –Me, –Et, –^{i}Pr, cyclopropyl, oxetan-3-yl, –OH, =O, –F, –OMe, –CH_2CH_2F, –CH_2CHF_2, –$CH_2CH_2CF_3$, –C(=O)Me, –$N(Me)_2$, –$CH_2N(CH_3)_2$, –$CH_2N(CH_3)CH_2CH_3$, –N(^{i}Pr)(Et), –N(^{i}Pr)(Me), –$N(Et)_2$, –$N(CH_3)(Et)$, –NHC(=O)Me, or a combination thereof); and

each R^{b10} is independently selected from H; –C_1–C_6 alkyl; –C_1–C_6 haloalkyl; –C_1–C_6 heteroalkyl substituted with 0 or 1 instance of =O; C_3–C_9 cycloalkyl; and a 3-10 member heterocyclyl substituted with 0 or 1 instances of =O, –Me or a combination thereof.

[0027] In some ~~embodiment~~examples of Formula (I), (Ia), (Ib), (Ic) and (Id), each R^6 is independently selected from H, –C_1–C_6 alkyl, –C_1–C_6 heteroalkyl, –C_1–C_6 haloalkyl, –C_3–C_{10} carbocyclyl, 3-10 membered heterocyclyl, heterocyclylalkyl, C_6–C_{10} aryl, 5-10 member heteroaryl, heteroarylalkyl, arylalkyl and cycloalkylalkyl, wherein each alkyl, cycloalkyl, heterocyclyl, cycloalkylalkyl, heterocyclylalkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl is optionally substituted at any available position. In certain ~~embodiment~~examples, each R^6 is independently selected from H, –C_1–C_6 alkyl, –C_1–C_6 heteroalkyl, –C_1–C_6 haloalkyl, –C_3–C_{10} carbocyclyl, 3-10 membered heterocyclyl, heterocyclylalkyl, C_6–C_{10} aryl, 5-10 member heteroaryl, heteroarylalkyl, arylalkyl and cycloalkylalkyl, wherein each alkyl, cycloalkyl, heterocyclyl, cycloalkylalkyl, heterocyclylalkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl is substituted at any available position with 0, 1, 2 or 3 instances of R^{10} wherein:

each R^{10} is independently selected from –D, =O, –CN, halo, –C_1–C_6 alkyl, –C_1–C_6 heteroalkyl, –C_1–C_6 haloalkyl, –C_3–C_9 cycloalkyl, 3-10 membered heterocyclyl, C_6–C_{10} aryl, 5-10 membered heteroaryl, cycloalkylalkyl, arylalkyl, heteroarylalkyl, heterocyclylalkoxy, heterocyclylalkyl, –OR^{b10}, –$N(R^{b10})_2$, –C(=O)R^{b10}, –C(=O)OR^{b10}, –$NR^{b10}C(=O)R^{b10}$, –$NR^{b10}C(=O)OR^{b10}$, –C(=O)$N(R^{b10})_2$, –OC(=O)R^{b10}, –OC(=O)$N(R^{b10})_2$,-S(=O)R^{b10}, –$S(=O)_2R^{b10}$, –SR^{b10}, –S(=O)(=NR^{b10})R^{b10}, –$NR^{b10}S(=O)_2R^{b10}$ and-$S(=O)_2N(R^{b10})_2$, wherein each alkyl, cycloalkyl, heteroalkyl, heterocyclyl, aryl, heteroaryl, cycloalkylalkyl, heterocyclylalkyl, arylalkyl and heteroarylalkyl of R^{10} is optionally substituted (*e.g.*, with 0, 1, 2, 3, 4, or 5 instances of –Me, –Et, –^{i}Pr, cyclopropyl, oxetan-3-yl, –OH, =O, –F, –OMe, –CH_2CH_2F, –CH_2CHF_2, –$CH_2CH_2CF_3$, –C(=O)Me, –$N(Me)_2$, –$CH_2N(CH_3)_2$, –$CH_2N(CH_3)CH_2CH_3$, –N(^{i}Pr)(Et), –N(^{i}Pr)(Me), –$N(Et)_2$, –$N(CH_3)(Et)$, –NHC(=O)Me, or a combination thereof); and

each R^{b10} is independently selected from H; –C_1–C_6 alkyl; –C_1–C_6 haloalkyl; –C_1–C_6 heteroalkyl substituted with 0 or 1 instance of =O; C_3–C_9 cycloalkyl; and a 3-10 member heterocyclyl substituted with 0 or 1 instances of =O, –Me or a combination thereof.

In some ~~embodiment~~examples, each R^6 is independently selected from H, –C_1–C_6 alkyl (*e.g.*, –Me, –Et, –Pr, –^{i}Pr, -^{i}Bu, *sec*-Bu, –^{t}Bu), –C_3–C_{10} monocyclic or bicyclic carbocyclyl (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, bicyclo[1.1.1]pentan-yl, 4,5,6,7-tetrahydro-1H-indazolyl, spiro[3.3]heptanyl), 3-10 membered mono or bicyclic heterocyclyl (*e.g.*, oxetanyl, azepanyl, piperidinyl, pyrorolidinyl, tetrahydrofuranyl, tetrahydropyranyl, 1,2-dihydropyridinyl, morpholinyl, isoindolinyl), C_6–C_{10} mono or bicyclic aryl (*e.g.*, phenyl, naphthyl, 1,2,3,4-tetrahydronaphthalenyl, 2,3-dihydro-1H-indenyl, 1,2,3,4 tetrahydroquinolinyl, 1,2 dihydroquinolinyl, 1,2-dihydroisoquinolinyl, 1,2,3,4 tetrahydroisoquinolinyl, chromanyl, indolinyl, 3,4-dihydro-2H-benzo[b][1,4]oxazinyl, 2,3-dihydrobenzofuranyl, benzo[*d*][1,3] dioxolyl, 2,3-dihydro-1H-benzo[d]imidazolyl), 5-6 member monocyclic heteroaryl (*e.g.*, thiophenyl, thiazolyl, pyrazolyl, imidazolyl, oxazolyl, pyridinyl, pyrimidinyl), 8-10 member bicyclic heteroaryl (*e.g.*, benzo[d]isothiazolyl, indolyl, benzofuranyl, 1H-indazolyl, 2H-indazolyl, benzo[b]thiophenyl, quinolinyl, 1,5-naphthyridinyl, 1,2-dihydro-1,5-naphthyridinyl, 1,2,3,4-tetrahydro-1,8-naphthyridinyl, isoquinolinyl, benzo[*d*]imidazolyl, benzo[*d*]thiazolyl, benzo[*d*]oxazolyl, [1,2,4]triazolo[4,3-*a*]pyridinyl, imidazo[1,2-*a*]pyridinyl, imidazo[1,5-*a*]pyridinyl, 1H-pyrazolo[4,3-*b*]pyridinyl), 1H-pyrazolo[3,4-b]pyridinyl, 1H-thieno[2,3-c]pyrazolyl, 1H-thieno[3,2-c]pyrazolyl, thiazolo[5,4-b]pyridinyl) wherein each alkyl, carbocyclyl, heterocyclyl, aryl and heteroaryl is optionally substituted (*e.g.*, substituted with 0, 1, 2 or 3 instances of R^{10}).In some ~~embodiment~~examples, each R^6 is independently selected from –C_1–C_6 alkyl (*e.g.*, –Me, –Et, –Pr, –^{i}Pr, -^{i}Bu, *sec*-Bu, –^{t}Bu), –C_3–C_{10} monocyclic or bicyclic carbocyclyl (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, bicyclo[1.1.1]pentan-yl, 4,5,6,7-tetrahydro-1H-indazolyl, spiro[3.3]heptanyl), 3-10 membered mono or bicyclic heterocyclyl (*e.g.*, oxetanyl, azepanyl, piperidinyl, pyrorolidinyl, tetrahydrofuranyl, tetrahydropyranyl, 1,2-dihydropyridinyl, morpholinyl, isoindolinyl), C_6–C_{10} mono or bicyclic aryl (*e.g.*, phenyl, naphthyl, 1,2,3,4-tetrahydronaphthalenyl, 2,3-dihydro-1H-indenyl, 1,2,3,4 tetrahydroquinolinyl, 1,2 dihydroquinolinyl, 1,2-dihydroisoquinolinyl, 1,2,3,4 tetrahydroisoquinolinyl, chromanyl, indolinyl, isoindolinyl, 3,4-dihydro-2H-benzo[b][1,4]oxazinyl, 2,3-dihydrobenzofuranyl, benzo[*d*][1,3] dioxolyl, 2,3-dihydro-1H-benzo[d]imidazolyl), 5-6 member monocyclic heteroaryl (*e.g.*, thiophenyl, thiazolyl,

pyrazolyl, imidazolyl, oxazolyl, pyridinyl, pyrimidinyl), 8-10 member bicyclic heteroaryl (*e.g.*, benzo[d]isothiazolyl, indolyl, benzofuranyl, 1H-indazolyl, 2H-indazolyl, benzo[b]thiophenyl, quinolinyl, 1,5-naphthyridinyl, 1,2-dihydro-1,5-naphthyridinyl, 1,2,3,4-tetrahydro-1,8-naphthyridinyl, isoquinolinyl, benzo[*d*]imidazolyl, benzo[*d*]thiazolyl, benzo[*d*]oxazolyl, [1,2,4]triazolo[4,3-*a*]pyridinyl, imidazo[1,2-*a*]pyridinyl, imidazo[1,5-*a*]pyridinyl, 1H-pyrazolo[4,3-*b*]pyridinyl), 1H-pyrazolo[3,4-b]pyridinyl, 1H-thieno[2,3-c]pyrazolyl, 1H-thieno[3,2-c]pyrazolyl, thiazolo[5,4-b]pyridinyl) wherein each alkyl, carbocyclyl, heterocyclyl, aryl and heteroaryl is optionally substituted (*e.g.*, substituted with 0, 1, 2 or 3 instances of R^{10}).

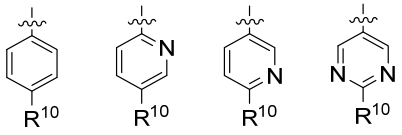
In certain ~~embodiment~~examples, each R^6 is an 8-10 member bicyclic heteroaryl (*e.g.*, indolyl, benzofuranyl, 1H-indazolyl, 2H-indazolyl, benzo[b]thiophenyl, quinolinyl, 1,5-naphthyridinyl, 1,2-dihydro-1,5-naphthyridinyl, 1,2,3,4-tetrahydro-1,8-naphthyridinyl, imidazo[1,2-a]pyridinyl, imidazo[1,5-a]pyridinyl, isoquinolinyl, benzo[*d*]imidazolyl, benzo[*d*]thiazolyl, benzo[d]isothiazolyl, benzo[*d*]oxazolyl, [1,2,4]triazolo[4,3-*a*]pyridinyl, imidazo[1,2-*a*]pyridinyl, 1H-pyrazolo[4,3-*b*]pyridinyl),1H- pyrazolo[3,4-b]pyridinyl, 1H-thieno[2,3-c]pyrazolyl, 1H-thieno[3,2-c]pyrazolyl, thiazolo[5,4-b]pyridinyl, 1,2,3,4-tetrahydro-1,8-naphthyridinyl) wherein the bicyclic heteroaryl is optionally substituted (*e.g.*, substituted with 0, 1, 2 or 3 instances of R^{10}).In some ~~embodiment~~examples, each R^6 is independently selected from H, –Me, –^{i}Pr, -^{i}Bu, *sec*-Bu, cyclobutyl, cyclopentyl, cyclohexyl, bicyclo[1.1.1]pentan-1-yl, spiro[3.3]heptan-2-yl, 4,5,6,7-tetrahydro-1H-indazol-6-yl, piperidin-4-yl, piperidin-3-yl, pyrrolidin-3-yl, 1,2-dihydropyridin-4-yl, phenyl, naphthalen-2-yl, 1,2,3,4-tetrahydroquinolin-6-yl, 1,2,3,4-tetrahydronaphthalen-6-yl, chroman-6-yl, 1,5-naphthyridin-6-yl, 1,2,3,4-tetrahydro-1,8-naphthyridin-6-yl, 2,3-dihydro-1H-inden-5-yl, indolin-5-yl, indolin-4-yl, 2,3-dihydro-1H-benzo[d]imidazol-5-yl, 2,3-dihydrobenzofuran-5-yl, 2,3-dihydrobenzofuran-6-yl, benzo[*d*][1,3] dioxol-5-yl], isoindolin-5-yl, isoindolin-6-yl, 3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl, 1,2-dihydroquinolin-6-yl, 1,2-dihydroisoquinolin-7-yl, thiophen-2-yl, thiophen-3-yl, thiazol-2-yl, thiazol-4-yl, thiazol-5-yl, pyrazol-1-yl, pyrazol-5-yl, pyrazol-3-yl, pyrazol-4-yl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyrimidin-5-yl, indol-4-yl, indol-5-yl, benzofuran-5-yl, benzofuran-6-yl, 1*H* indazol-5-yl, 1*H* indazol-4-yl, 2H-indazol-6-yl, 2H-indazol-5-yl, benzo[*b*]thiophen-3-yl, benzo[*b*]thiophen-5-yl, quinolin-6-yl, quinoline-3-yl, isoquinolin-6-yl, benzo[*d*]imidazo-5-yl, 1H-benzo[d]imidazol-4-yl, benzo[*d*]thiazol-5-yl, benzo[d]thiazol-6-yl, benzo[d]thiazol-4-yl, benzo[d]isothiazol-5-yl, benzo[*d*]oxazol-4-yl, benzo[*d*]oxazol-5-yl, [1,2,4]triazolo[4,3-*a*]pyridin-6-yl, imidazo[1,2-

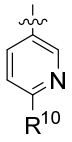
a]pyridin-6-yl, imidazo[1,2-a]pyridin-7-yl, imidazo[1,5-a]pyridin-6-yl, pyrazolo[4,3-*b*]pyridin-6-yl, 1H-pyrazolo[3,4-b]pyridin-5-yl, 1H-pyrazolo[3,4-b]pyridin-5-yl, 1H-pyrazolo[4,3-b]pyridin-5-yl, 1H-pyrazolo[4,3-b]pyridin-6-yl, 1H-thieno[2,3-c]pyrazol-5-yl, 1H-thieno[3,2-c]pyrazol-5-yl, thiazolo[5,4-b]pyridin-6-yl), each optionally substituted (*e.g.*, substituted with 0, 1, 2 or 3 instances of R^{10}).

In some ~~embodiment~~examples, each R^6 is independently selected from –Me, –^{i}Pr, -^{i}Bu, *sec*-Bu, cyclobutyl, cyclopentyl, cyclohexyl, bicyclo[1.1.1]pentan-1-yl, spiro[3.3]heptan-2-yl, 4,5,6,7-tetrahydro-1H-indazol-6-yl, piperidin-4-yl, piperidin-3-yl, pyrrolidin-3-yl, 1,2-dihydropyridin-4-yl, phenyl, naphthalen-2-yl, 1,2,3,4 tetrahydroquinolin-6-yl, 1,2,3,4-tetrahydronaphthalen-6-yl, chroman-6-yl, 1,5-naphthyridin-6-yl, 1,2,3,4-tetrahydro-1,8-naphthyridin-6-yl, 2,3-dihydro-1H-inden-5-yl, indolin-5-yl, indolin-4-yl, 2,3-dihydro-1H-benzo[d]imidazol-5-yl, 2,3-dihydrobenzofuran-5-yl, 2,3-dihydrobenzofuran-6-yl, benzo[*d*][1,3] dioxol-5-yl], isoindolin-5-yl, isoindolin-6-yl, 3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl, 1,2-dihydroquinolin-6-yl, 1,2-dihydroisoquinolin-7-yl, thiophen-2-yl, thiophen-3-yl, thiazol-2-yl, thiazol-4-yl, thiazol-5-yl, pyrazol-1-yl, pyrazol-5-yl, pyrazol-3-yl, pyrazol-4-yl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyrimidin-5-yl, indol-4-yl, indol-5-yl, benzofuran-5-yl, benzofuran-6-yl, 1*H* indazol-5-yl, 1*H* indazol-4-yl, 2H-indazol-6-yl, 2H-indazol-5-yl, benzo[*b*]thiophen-3-yl, benzo[*b*]thiophen-5-yl, quinolin-6-yl, quinoline-3-yl, isoquinolin-6-yl, benzo[*d*]imidazo-5-yl, 1H-benzo[d]imidazol-4-yl, benzo[*d*]thiazol-5-yl, benzo[d]thiazol-6-yl, benzo[*d*]thiazol-4-yl, benzo[*d*]isothiazol-5-yl, benzo[*d*]oxazol-4-yl, benzo[*d*]oxazol-5-yl, [1,2,4]triazolo[4,3-*a*]pyridin-6-yl, imidazo[1,2-*a*]pyridin-6-yl, imidazo[1,2-*a*]pyridin-7-yl, imidazo[1,5-a]pyridin-6-yl, pyrazolo[4,3-*b*]pyridin-6-yl, 1H-pyrazolo[3,4-b]pyridin-5-yl, 1H-pyrazolo[3,4-b]pyridin-5-yl, 1H-pyrazolo[4,3-b]pyridin-5-yl, 1H-pyrazolo[4,3-b]pyridin-6-yl, 1H-thieno[2,3-c]pyrazol-5-yl, 1H-thieno[3,2-c]pyrazol-5-yl, thiazolo[5,4-b]pyridin-6-yl), each optionally substituted (*e.g.*, substituted with 0, 1, 2 or 3 instances of R^{10}).

[0028] In some ~~embodiment~~examples, R^6 is selected from optionally substituted phenyl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, and pyrimidin-5-yl (*e.g.*, substituted with 0, 1, 2 or 3 instances of R^{10}). In some ~~embodiment~~examples, R^6 is selected from phenyl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyrimidin-5-yl and phenyl substituted with one instance of R^{10}.

[0029] In some ~~embodiment~~examples, R^6 is selected from:



. In further ~~embodiment~~examples, R^6 is 

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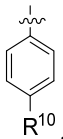
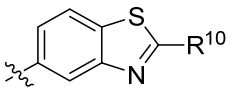
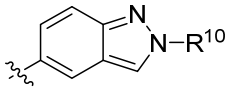
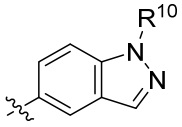
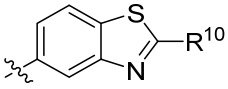
[0030] In some ~~embodiment~~examples, R^6 is optionally substituted phenyl (*e.g.*, substituted with 0, 1, 2 or 3 instances of R^{10}). In certain ~~embodiment~~examples, R^6 is 

.
In some ~~embodiment~~examples, R^6 is selected from optionally substituted bicyclic heteroaryl (*e.g.*, substituted with 0, 1, 2 or 3 instances of R^{10}). In further ~~embodiment~~examples, R^6 is selected from optionally substituted 1*H*-indazol-5-yl, 2*H*-indazol-5-yl, benzo[d]isothiazol-5-yl, benzo[d]thiazol-5-yl, benzo[b]thiophen-5-yl, benzo[*d*]oxazol-4-yl, benzo[*d*]oxazol-5-yl, quinoline-7-yl, 1H-thieno[2,3-c]pyrazol-5-yl, imidazo[1,2-a]pyridin-7-yl, and imidazo[1,5-a]pyridin-6-yl, (*e.g.*, substituted with 0, 1, 2 or 3 instances of R^{10}).

[0031] In some ~~embodiment~~examples, R^6 is 

, 

, or 

. In further ~~embodiment~~examples, 

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[0032] In certain ~~embodiment~~examples of the ~~invention~~disclosure, R^{10} is independently selected from –D, =O, halo (e.g., F, Cl, Br), –CN, –C1–C6 alkyl (e.g., –Me, –Et, –Pr, –iPr, –sec–Bu, –tBu, CH2(CH3)(iPr)), –C1–C6 heteroalkyl (e.g., –CH(CH3)(NMe2), –CH2CH2N(Me)(oxetan-3-yl)), –CH2CH(CH3)(NMe2), –CH2OH, –CH(OH)(CH3), –C(OH)(CH3)2, –CH2NH2), –C1–C6 haloalkyl (e.g., –CHF2, –CH2CF3, –CF3), –C3–C9 cycloalkyl (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl), 3-10 membered heterocyclyl (e.g.,tetrahydrofuranyl, tetrahydropyranyl, oxetanyl, morpholinyl, pyrolidinyl, piperidinyl, piperidin-2-onyl, piperazinyl, piperazin-2-only, azetidinyl, decahydro-1,6-naphthyridinyl, 2-azaspiro[3.3]heptanyl, 5-oxa-2,8-diazaspiro[3.5]nonanyl, 8-azabicyclo[3.2.1]octanyl, 2-azabicyclo[2.2.2]octanyl, 3-azabicyclo[3.2.0]heptanyl, 3-azabicyclo[3.1.1]heptanyl, 3-azabicyclo[3.1.0]hexanyl, 2-azabicyclo[2.1.1]hexanyl, 1-azabicyclo[2.2.1]heptanyl, 3-azabicyclo[3.2.0]heptanyl, 2,9-diazaspiro[5.5]undecanyl, bicyclo[1.1.1]pentanyl, octahydrocyclopenta[c]pyrrolyl, decahydro-1,6-naphthyridinyl, octahydro-1H-pyrrolo[3,4-c]pyridinyl, decahydro-2,7-naphthyridinyl, 2,9-diazaspiro[5.5]undecanyl), 5-10 membered

heteroaryl (e.g., pyridinyl, imidazo[1,2-a]pyridinyl, imidazolyl, pyrazolyl, thiazolyl, thiophenyl), cycloalkylalkyl (e.g. –CH2-cyclopropyl), heterocyclylalkyl (e.g., –CH2-morpholinyl, –(CH2)2-pyrolidinyl –(CH2)2-pyrolidinyl –CH2-imidazolyl, –CH2-pyrazolyl, –CH2-1,2,4-triazolyl, –CH2-morpholinyl, –(CH2)2-morpholinyl), heterocyclylalkoxy (e.g., –O-(CH2)2-pyrolidinyl, –O-CH2-piperidinyl, –O-CH2-oxetanyl, –O-CH2-tetrahydrofuranyl, –O-CH2-tetrahydropyranyl), heteroarylalkyl (e.g., –CH2-triazolyl, –CH2-imidazolyl, –CH2-pyrazolyl), –ORb10 (e.g., –OH, –OMe, OEt, –O-tetrahydrofuranyl, –O-tetrahydropyran-4-yl, –OCF3, –OCHF2), –N(Rb10)2, (e.g., –NH2, –NHRb10, –NHMe, –NMe2, –NHCH2CF3, –NH-oxetan-3-yl, –NH-(N-Me-2-oxo-pyrolidin-3-yl), –NRb10C(=O)Rb10 (e.g., –NHC(=O)Me), –C(=O)N(Rb10)2, (e.g., –C(=O)NH2, C(=O)NHMe), –OC(=O)Rb10 (e.g., –OC(=O)Me), –S(=O)Rb10 (e.g., –SO2Me), –NRb10S(=O)2Rb10 (e.g., NHSO2Me) and –S(=O)2N(Rb10)2 (e.g., SO2NH2, SO2NHMe), wherein each alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, cycloalkylalkyl, heterocyclylalkyl, arylalkyl and heteroarylalkyl is optionally substituted (e.g., with 0, 1, 2, 3, 4, or 5 instances of –Me, –Et, –iPr, cyclopropyl, oxetan-3-yl, –OH, =O, –F, –OMe, –CH2CH2F, –CH2CHF2, –CH2CH2CF3, –C(=O)Me, –N(Me)2, –CH2N(CH3)2, –CH2N(CH3)CH2CH3, –N(iPr)(Et), –N(iPr)(Me), –N(Et)2, –N(CH3)(Et), –NHC(=O)Me, or a combination thereof); and wherein:

each R^{b10} is independently selected from H, –C_1–C_6 alkyl, (*e.g.*, –Me, –Et, –Pr, –^{i}Pr, –*sec*-Bu, –^{t}Bu), –C_1–C_6 haloalkyl (*e.g.*, –CF_3, –CHF_2, –CH_2CF_3), –C_1–C_6 heteroalkyl substituted with 0 or 1 instances of =O (*e.g.*, –$CH_2CH_2NMe_2$, –$CH_2C(=O)NMe_2$, –$CH(CH_3)CH_2NMe_2$, –$CH(CH_3)C(=O)NMe_2$), C_3–C_9 cycloalkyl and 3-10 member heterocyclyl (*e.g.* tetrahydrofuran-3-yl, tetrahydropyran-4-yl, oxetan-3-yl, N-Me-2-oxo-pyrolidin-3-yl, piperidin-4-yl) substituted with 0 or 1 instances of =O, –Me or a combination thereof.

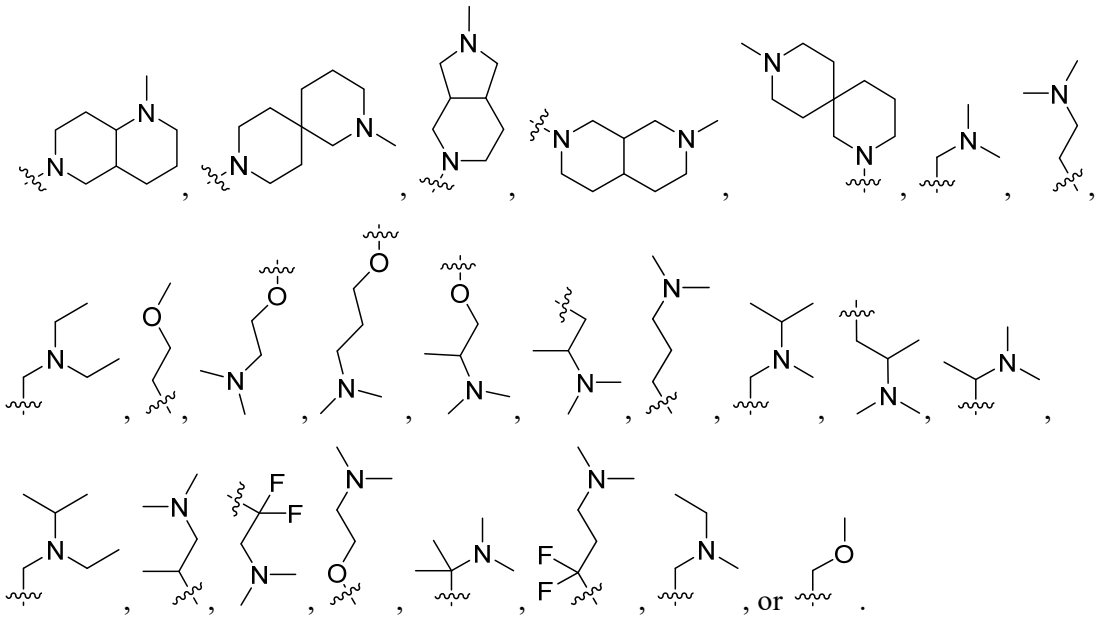
In certain ~~embodiment~~examples, each R^{b10} is independently selected from H, –Me, –Et, –Pr, –^{i}Pr, –*sec*-Bu, –^{t}Bu, –CF_3, –CHF_2, –CH_2CF_3, –$CH_2CH_2NMe_2$, –$CH_2C(=O)NMe_2$, –$CH(CH_3)CH_2NMe_2$, –$CH(CH_3)C(=O)NMe_2$), tetrahydrofuran-3-yl, tetrahydropyran-4-yl, oxetan-4-yl and N-Me-2-oxo-pyrolidin-3-yl.

[0033] In some ~~embodiment~~examples, each R^{10} is independently selected from the group consisting of –D, =O, –OH, –F, –Cl, –Br, –CN, –Me, –Et, –Pr, –^{i}Pr, –*sec*-Bu, –^{t}Bu, –OMe, –OEt, –CHF_2, –CH_2CF_3, –CF_3, –OCF_3, –$OCHF_2$, –CH_2OH, –$CH(OH)(CH_3)$, –CH_2OMe, –$C(OH)(CH_3)_2$, –CH_2NH_2, –$CH(CH_3)(NMe_2)$, –$CH_2CH(CH_3)(NMe_2)$, –$CH_2(CH_3)(^{i}Pr)$, –NH_2, –NHMe, –$NHCH_2CF_3$, –NMe_2, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, thiazol-2-yl, thiazol-5-yl, thiophen-2-yl, tetrahydrofuran-3-yl, tetrahydropyran-

4-yl, oxetan-3-yl, morpholin-2-yl, –CH_2-morpholin-4-yl, –$(CH_2)_2$-morpholin-4-yl, imidazol-2-yl, 1H-pyrazol-5-yl, 1H-imidazol-4-yl, imidazo[1,2-a]pyridin-7-yl, pyrolidin-1-yl, pyrolidin-3-yl, piperidin-4-yl, piperidin-3-yl, piperidin-2-one-4-yl, piperazin-4-yl, piperazin-4-yl, piperazin-2-on-5-yl pyridine-4-yl, pyridine-3-yl, pyrazol-1-yl, pyrazol-3-yl, pyrazol-4-yl, pyrazol-5-yl, 1H-pyrazol-5-yl, azetidin-3-yl, –$(CH_2)_2$-pyrolidin-1-yl –$(CH_2)_2$-pyrolidin-2-yl –CH_2-imidazol-1-yl, –CH_2-pyrazol-1-yl, –CH_2-1,2,4-triazol-1-yl, –CH_2-cyclopropyl, –$O(CH_2)_2NMe_2$, –O-tetrahydrofuran-3-yl, –O-tetrahydropyran-4-yl, –O-(N-Me-2-oxo-pyrolidin-3-yl), –O-$(CH_2)_2$-pyrolidin-2-yl –O-CH_2-piperidin-4-yl –O-CH_2-oxetan-3-yl, –NCH_3-piperidin-4-yl –NH-oxetan-3-yl, –NH-(N-Me-2-oxo-pyrolidin-3-yl), decahydro-1,6-naphthyridin-6-yl, 2-azaspiro[3.3]heptan-6-yl, 5-oxa-2,8-diazaspiro[3.5]nonan-8-yl, 8-azabicyclo[3.2.1]octan-3-yl, 2-azabicyclo[2.2.2]octan-4-yl, 3-azabicyclo[3.2.0]heptan-6-yl, 3-azabicyclo[3.1.1]heptan-1-yl, 3-azabicyclo[3.1.0]hexan-6-yl, 1-azabicyclo[2.2.1]heptan-4-yl, 3-azabicyclo[3.2.0]heptan-6-yl, 2-azabicyclo[2.1.1]hexan-4-yl, 2,9-diazaspiro[5.5]undecane-9-yl, bicyclo[1.1.1]pentan-2-yl, octahydrocyclopenta[c]pyrrol-5-yl, decahydro-1,6-naphthyridin-6-yl, octahydro-1H-pyrrolo[3,4-c]pyridine-5-yl, decahydro-2,7-naphthyridin-2-yl, 2,9-diazaspiro[5.5]undecan-2-yl, –NHC(=O)Me, –$NHCH_2C(=O)NMe_2$, –$NHCH(CH_3)C(=O)NMe_2$, –$C(=O)NH_2$, C(=O)NHMe, –OC(=O)Me, –SO_2Me, –$NHSO_2Me$,– SO_2NH_2 and –SO_2NHMe, wherein each –OMe, –OEt, –Me, –Et, –Pr, –^{i}Pr, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, tetrahydrofuran-3-yl, oxetan-3-yl, pyrolidin-1-yl, pyrolidin-3-yl, piperidin-4-yl, piperidin-3-yl, piperidin-2-one-4-yl piperazin-4-yl, pyrazol-1-yl, pyrazol-3-yl, pyrazol-4-yl, pyrazol-5-yl, thiazol-2-yl, thiophen-2-yl, –CH_2-cyclopropyl, –CH_2-morpholin-4-yl, –$(CH_2)_2$-morpholin-4-yl, –morpholin-2-yl, –$(CH_2)_2$-pyrolidin-1-yl, –CH_2-1,2,4-triazol-1-yl –CH_2-imidazol-1-yl, imidazol-2-yl,–CH_2-pyrazol-1-yl, –OCH_2-piperidin-4-yl, azetidin-3-yl, 2-azaspiro[3.3]heptan-6-yl, 2-methyl-5-oxa-2,8-diazaspiro[3.5]nonan-8-yl, 8-azabicyclo[3.2.1]octan-3-yl, and decahydro-1,6-naphthyridin-6-yl; and wherein

each R^{10} can be independently substituted with 0, 1, 2, 3, 4, or 5 instances of –Me, –Et, –^{i}Pr, cyclopropyl, oxetan-3-yl, –OH, =O, –F, –OMe, –CH_2CH_2F, –CH_2CHF_2, –$CH_2CH_2CF_3$, –C(=O)Me, –$N(Me)_2$, –$CH_2N(CH_3)_2$, –$CH_2N(CH_3)CH_2CH_3$, –N(^{i}Pr)(Et), –N(^{i}Pr)(Me), –$N(Et)_2$, –$N(CH_3)(Et)$, –NHC(=O)Me, or a combination thereof.

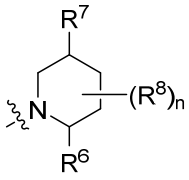
[0034] In some ~~embodiment~~example$s$, R^{10} is optionally substituted 3-6 membered monocyclic heteterocyclyl or optionally substituted 6-10 membered bicyclic heteterocyclyl. In further ~~embodiment~~example$s$, R^{10} is –D, –Cl, –F, –Me, –CH_2-OH,



[0035] In some ~~embodiment~~examples of Formula (I), (Ia), (Ib), (Ic) and (Id), each R^7 is independently selected from H, halo (*e.g.*, F, Cl), –CN, –C_1–C_6 alkyl (*e.g.*, –Me, –Et, –Pr, –^{i}Pr, –*sec*-Bu, –^{t}Bu), 5-membered heteroaryl (*e.g.*, pyrazolyl), –C_1–C_6 haloalkyl (*e.g.*, –CF_3, –CHF_2, –CH_2CF_3), –C_1–C_6 hydroxyalkyl (*e.g.*, –CH_2OH), –C_3–C_9 cycloalkyl (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl), –OR^{a7} (*e.g.*, –OH, –OMe, –$OCHF_2$), –$N(R^{a7})_2$ and –$C(=O)N(R^{a7})_2$ (*e.g.*, –$C(=O)NH_2$, –C(=O)NHMe). In further ~~embodiment~~examples, each R^{a7} is independently selected from H and –C_1–C_6 alkyl (*e.g.*, –Me, –Et, –Pr, –^{i}Pr,–^{n}Bu, –^{t}Bu, –*sec*-Bu, –*iso*-Bu). In some ~~embodiment~~examples, each R^7 is independently selected from H and methyl. In certain ~~embodiment~~examples, each R^7 is H. In other ~~embodiment~~examples, each R^7 is methyl.

[0036] In some ~~embodiment~~examples of Formula (I), (Ia), (Ib), (Ic) and (Id), each R^8 is independently selected from H, –D, halo (*e.g.*, –F, –Cl), –CN, –C_1–C_6 alkyl (*e.g.*, –Me, –Et, –Pr, –^{i}Pr, –*sec*-Bu, –^{t}Bu), arylalkyl, (*e.g.*, benzyl), –$C(=O)R^{a8}$ (*e.g.*, –C(=O)Me, –C(=O)Et,–C(=O)Pr, –C(=O)^{i}Pr), –$N(R^{a8})_2$ (*e.g.*, –NHMe, NH_2, NMe_2), –$NR^{a8}C(=O)R^{a8}$ (*e.g.*, –NHC(=O)Me), –$CH_2C(=O)N(R^{a8})_2$ (*e.g.*, –$CH_2C(=O)NH_2$) and –OR^{a8} (*e.g.*, –OH, –OMe, –O^{i}Pr, –OCF_3). In further ~~embodiment~~examples, each R^{a8} is independently selected from H, –CF_3,and –C_1–C_6 alkyl (*e.g.*, –Me, –Et, –Pr, –^{i}Pr,–^{n}Bu, –^{t}Bu, –*sec*-Bu, –*iso*-Bu). In some ~~embodiment~~examples, each R^8 is independently selected from H, –D, –F, –Me, –Et, –CN, –OMe, –O^{i}Pr, –OFC_3, benzyl, –NHC(=O)Me, –NMe_2, –$CH_2C(=O)NH_2$, –C(=O)^{i}Pr and –OH. In certain ~~embodiment~~examples, each R^8 is independently selected from H, –D, –F, –Me, –Et and –CN. In further ~~embodiment~~examples, each R^8 is independently selected from H, –D, –F and –Me.

[0037] In some ~~embodiment~~examples of Formula (I), (Ia), (Ib), (Ic) and (Id), n is 0. In other ~~embodiment~~examples, n is 1. In certain ~~embodiment~~examples, n is 2. In other ~~embodiment~~examples, n is 3. In some ~~embodiment~~examples of Formula (I), (Ia), (Ib), (Ic) and (Id), the moiety represented as



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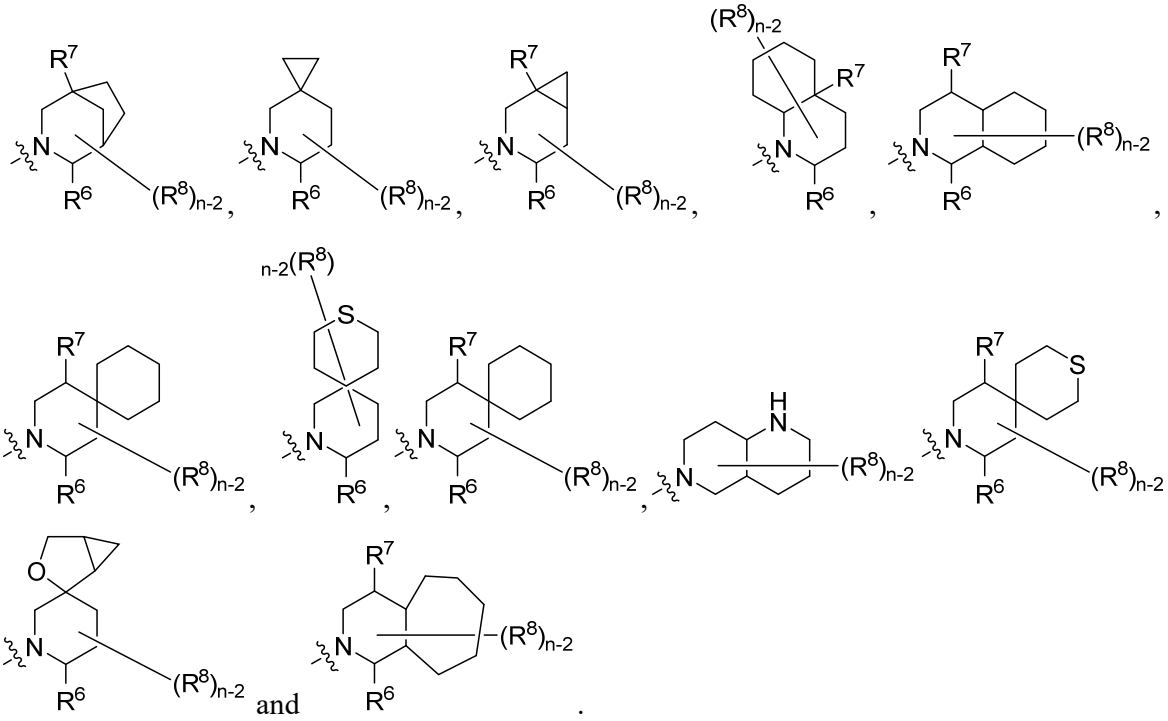
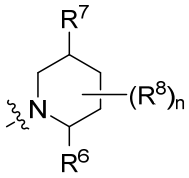


[0038] In some ~~embodiment~~examples of Formula (I), (Ia), (Ib), (Ic) and (Id), the moiety represented as



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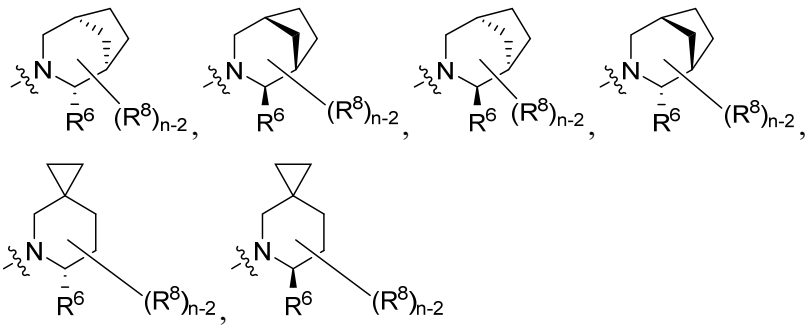
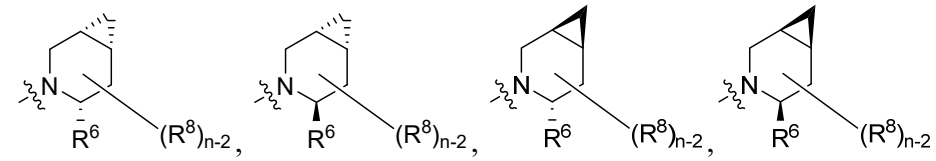
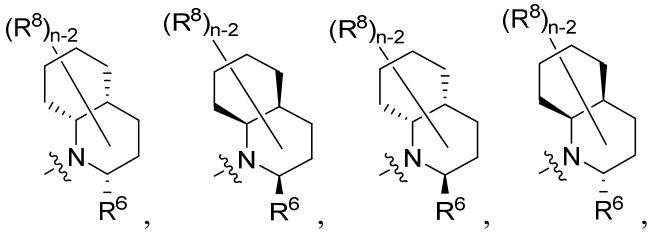
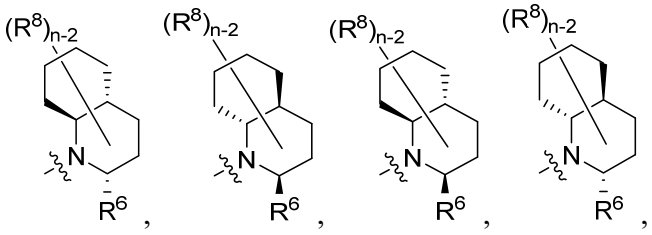
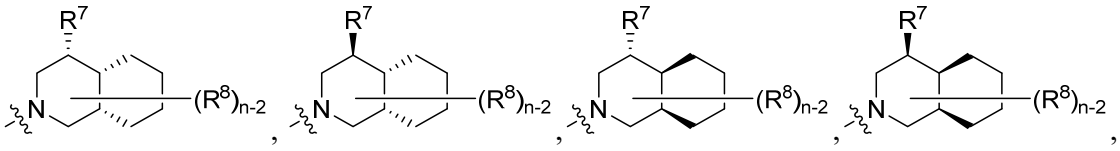
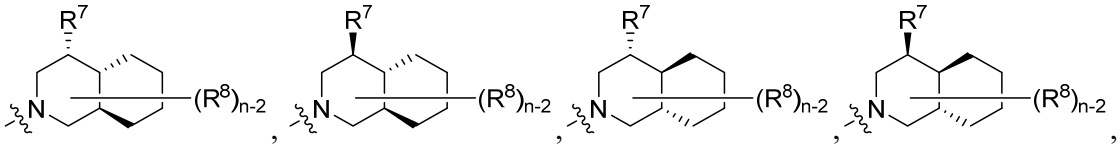
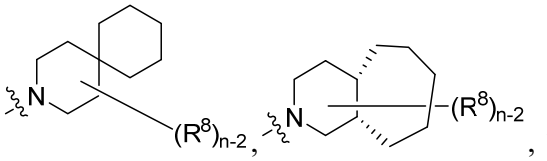
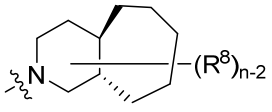








and


[0039] In some of the above ~~embodiment~~examples wherein the piperidine is part of a larger ring, n is 2. In some ~~embodiment~~examples, each R^6 and R^7 is independently selected from H and $–CH_3$. In further ~~embodiment~~examples, R^6 is H. In other ~~embodiment~~examples, R^6 is $–CH_3$. In certain ~~embodiment~~examples, R^7 is H. In certain ~~embodiment~~examples, R^7 is $–CH_3$.

[0040] In some ~~embodiment~~examples, the compounds of Formula (I), (Ia), (Ib), (Ic) and (Id) are selected from Table 1.

[0041] In one ~~aspect~~example, provided is a pharmaceutical composition comprising a compound of Formula (I), (Ia), (Ib), (Ic) and (Id) as defined herein and a pharmaceutically acceptable

carrier. In some ~~embodiment~~examples, the pharmaceutical composition further comprises a second therapeutic agent.

[0042] In one ~~aspect~~example, provided is a method of treating an MTAP-deficient and/or an MTA-accumulating disease in a subject in need thereof by administering to the subject a therapeutically effective amount of a c or a pharmaceutically acceptable composition thereof. In some ~~embodiment~~examples, the compound or composition is administered in combination with a second therapeutic agent.

[0043] In some ~~embodiment~~examples, the disease is a proliferating disease. In one ~~embodiment~~example, the disease is an MTAP-deficient and/or MTA-accumulating cancer. In certain ~~embodiment~~examples, the cancer is glioblastoma, malignant peripheral nerve sheath tumors (MPNST), esophageal cancer (*e.g.*, esophageal squamous cell carcinoma or esophageal adenocarcinoma), bladder cancer (*e.g.*, bladder urothelial carcinoma), pancreatic cancer (*e.g.*, pancreatic adenocarcinoma), mesothelioma, melanoma, non-small cell lung cancer (NSCLC; *e.g.*, lung squamous or lung adenocarcinoma), astrocytoma, undifferentiated pleiomorphic sarcoma, diffuse large B-cell lymphoma (DLBCL), leukemia, head and neck cancer, stomach adenocarcinoma, myxofibrosarcoma, cholangiosarcoma, cancer of the brain, stomach, kidney, breast, endometrium, urinary tract, liver, soft tissue, pleura and large intestine or sarcoma.

[0044] In one ~~aspect~~example, provided is a method of treating a cancer in a subject in need thereof comprising the steps of:

a) assessing the level of MTAP and/or MTA in a test sample obtained from said subject, wherein the MTA level can be assessed directly (*e.g.*, by ELISA or LC-MS/MS) or indirectly (*e.g.*, by SDMA-modified protein ELISA or IHC, or by RNA splicing);

b) comparing the test sample with a reference, wherein MTAP deficiency and/or MTA accumulation in said test sample compared to the reference indicates the cancer in said subject will respond to therapeutic treatment with a PRMT5 inhibitor; and

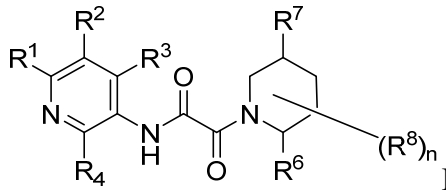
c) administering a therapeutically effective amount of a compound of Formula (I), (Ia), (Ib), (Ic) and (Id) as defined herein or a pharmaceutical composition thereof to the subject identified in step b).

Brief description of the drawings

[0045] FIG. 1. Frequency of MTAP homozygous deletion in cell lines representing exemplary cancers according to The Cancer Genome Atlas (TCGA).

Claims

1. A compound of Formula (I) or a pharmaceutically acceptable salt thereof; wherein:



Formula (I),

each R^1 is independently selected from H, –D, halo, –CN, –C_1–C_6 alkyl, –C_1–C_6 heteroalkyl, –C_1–C_6 haloalkyl, –C_3–C_9 cycloalkyl, 3-10 membered heterocyclyl, heterocyclylalkyl, heteroarylalkyl, arylalkyl, cycloalkylalkyl, –OR^{a1}, –$N(R^{a1})_2$, –$C(=O)R^{a1}$, –$C(=O)OR^{a1}$, –$NR^{a1}C(=O)R^{a1}$, –$NR^{a1}C(=O)OR^{a1}$, –$C(=O)N(R^{a1})_2$, –$OC(=O)N(R^{a1})_2$,-$S(=O)R^{a1}$, –$S(=O)_2R^{a1}$, –SR^{a1}, –$S(=O)(=NR^{a1})R^{a1}$, –$NR^{a1}S(=O)_2R^{a1}$ and –$S(=O)_2N(R^{a1})_2$;

each R^2 is independently selected from halo, –CN, –C_1–C_6 alkyl, –C_1–C_6 heteroalkyl, –C_1–C_6 haloalkyl, –C_1–C_6 haloalkoxy, –C_3–C_9 cycloalkyl, 3-10 membered heterocyclyl, heterocyclylalkyl, heteroarylalkyl, arylalkyl, cycloalkylalkyl, –OR^{a2}, –$N(R^{a2})_2$, –$C(=O)R^{a2}$, –$C(=O)OR^{a2}$, –$NR^{a2}C(=O)R^{a2}$, –$NR^{a2}C(=O)OR^{a2}$, –$C(=O)N(R^{a2})_2$, –$C(=O)N(OR^{a2})(R^{a2})$, –$OC(=O)N(R^{a2})_2$,-$S(=O)R^{a2}$, –$S(=O)_2R^{a2}$, –SR^{a2}, –$S(=O)(=NR^{a2})R^{a2}$, –$NR^{a2}S(=O)_2R^{a2}$ and –$S(=O)_2N(R^{a2})_2$;

each R^3 is independently selected from H, –D, halo, –CN, –C_1–C_6 alkyl, –C_1–C_6 heteroalkyl, –C_1–C_6 haloalkyl, –C_3–C_9 cycloalkyl, 3-10 membered heterocyclyl, heterocyclylalkyl, heteroarylalkyl, arylalkyl, cycloalkylalkyl, –OR^{a3}, –$N(R^{a3})_2$, –$C(=O)R^{a3}$, –$C(=O)OR^{a3}$, –$NR^{a3}C(=O)R^{a3}$, –$NR^{a3}C(=O)OR^{a3}$, –$C(=O)N(R^{a3})_2$, –$OC(=O)N(R^{a3})_2$,-$S(=O)R^{a3}$, –$S(=O)_2R^{a3}$, –SR^{a3}, –$S(=O)(=NR^{a3})R^{a3}$, –$NR^{a3}S(=O)_2R^{a3}$ and –$S(=O)_2N(R^{a3})_2$;

each R^4 is independently selected from H, –D, halo, –CN, –C_1–C_6 alkyl, –C_1–C_6 heteroalkyl, –C_1–C_6 haloalkyl, –C_3–C_9 cycloalkyl, 3-10 membered heterocyclyl, heterocyclylalkyl, heteroarylalkyl, arylalkyl, cycloalkylalkyl, –OR^{a4}, –$N(R^{a4})_2$, –$C(=O)R^{a4}$, –$C(=O)OR^{a4}$, –$NR^{a4}C(=O)R^{a4}$, –$NR^{a4}C(=O)OR^{a4}$, –$C(=O)N(R^{a4})_2$, –$OC(=O)N(R^{a4})_2$, –$S(=O)R^{a4}$, –$S(=O)_2R^{a4}$, –SR^{a4}, –$S(=O)(=NR^{a4})R^{a4}$, –$NR^{a4}S(=O)_2R^{a4}$ and –$S(=O)_2N(R^{a4})_2$;

each R^6 is independently absent or selected from H, –D, halo, –CN, –C_1–C_6 alkyl, –C_1–C_6 heteroalkyl, –C_1–C_6 haloalkyl, –C_3–C_{10} carbocyclyl, 3-10 membered heterocyclyl, heterocyclylalkyl, C_6–C_{10} aryl, 5-10 member heteroaryl, heteroarylalkyl, arylalkyl, cycloalkylalkyl, –OR^{a6}, –$N(R^{a6})_2$, –$C(=O)R^{a6}$, –$C(=O)OR^{a6}$, –$NR^{a6}C(=O)R^{a6}$, –$NR^{a6}C(=O)OR^{a6}$, –$C(=O)N(R^{a6})_2$, –$OC(=O)N(R^{a6})_2$,-$S(=O)R^{a6}$, –$S(=O)_2R^{a6}$, –SR^{a6}, –$S(=O)(=NR^{a6})R^{a6}$, –$NR^{a6}S(=O)_2R^{a6}$ and –$S(=O)_2N(R^{a6})_2$, wherein each alkyl, carbocyclyl, heterocyclyl, cycloalkylalkyl, heterocyclylalkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl is optionally substituted at any available position;

each R^7 is independently absent or selected from H, –D, halo, –CN, –C_1–C_6 alkyl, –C_1–C_6 hydroxyalkyl, –C_1–C_6 haloalkyl, –C_3–C_9 cycloalkyl, 3-10 membered heterocyclyl, 5-6-membered monocyclic heteroaryl, heterocyclylalkyl, heteroarylalkyl, arylalkyl, cycloalkylalkyl, –OR^{a7}, –$N(R^{a7})_2$, –$C(=O)R^{a7}$, –$C(=O)OR^{a7}$, –$NR^{a7}C(=O)R^{a7}$, –$NR^{a7}C(=O)OR^{a7}$, –$C(=O)N(R^{a7})_2$, –$OC(=O)N(R^{a7})_2$,-$S(=O)R^{a7}$, –$S(=O)_2R^{a7}$, –SR^{a7}, –$S(=O)(=NR^{a7})R^{a7}$, –$NR^{a7}S(=O)_2R^{a7}$ and –$S(=O)_2N(R^{a7})_2$;

each R^8 is independently selected from H, –D, =O, halo, –CN, –C_1–C_6 alkyl, –C_1–C_6 heteroalkyl, –C_1–C_6 haloalkyl, –C_3–C_9 cycloalkyl, 3-10 membered heterocyclyl, heterocyclylalkyl, heteroarylalkyl, arylalkyl, cycloalkylalkyl, –OR^{a8}, –$N(R^{a8})_2$, –$C(=O)R^{a8}$, –$C(=O)OR^{a8}$, –$NR^{a8}C(=O)R^{a8}$, –$NR^{a8}C(=O)OR^{a8}$, –$CH_2C(=O)N(R^{a8})_2$ –$C(=O)N(R^{a8})_2$, –$OC(=O)N(R^{a8})_2$, –$CH_2C(=O)N(R^{a8})_2$,-$S(=O)R^{a8}$, –$S(=O)_2R^{a8}$, –SR^{a8}, –$S(=O)(=NR^{a8})R^{a8}$, –$NR^{a8}S(=O)_2R^{a8}$ and –$S(=O)_2N(R^{a8})_2$ wherein two instances of R^8 together with the atom or atoms to which they are attached can be taken together to form a 3-10 member cycloalkyl or heterocyclyl ring; ~~(*e.g.*, a ring that together with the piperidine ring of Structure I can form a bridged, fused or spiro bicyclic heterocyclic ring)~~

each R^{a1}, R^{a2}, R^{a3}, R^{a4}, R^{a6}, R^{a7} and R^{a8} is independently selected from H, C_1–C_6 alkyl, –C_1–C_6 heteroalkyl, C_3–C_9 cycloalkyl, 3-7 membered heterocyclyl, cycloalkylalkyl, heterocyclylalkyl, aryl, 5-6 membered heteroaryl, arylalkyl and heteroarylalkyl wherein each alkyl, cycloalkyl, heterocyclyl, cycloalkylalkyl, heterocyclylalkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl is optionally substituted at any available position ~~(*e.g.*, substituted with 0, 1, 2 or 3 instances of R^9, wherein each R^9 is independently selected from =O, halo, –CN, –C_1–C_6 alkyl, –C_1–C_6 heteroalkyl, –C_1–C_6 haloalkyl, –C_3–C_9 cycloalkyl, 3-10 membered heterocyclyl, C_6–C_{10} aryl, 5-10 membered heteroaryl, cycloalkylalkyl, heterocyclylalkyl, arylalkyl, heteroarylalkyl, –~~

~~OR^b, $N(R^b)_2$, $C(=O)R^b$, $C(=O)OR^b$, $NR^bC(=O)R^b$, $NR^bC(=O)OR^b$, $C(=O)N(R^b)_2$, $OC(=O)N(R^b)_2$, $S(=O)R^b$, $S(=O)_2R^b$, SR^b, $S(=O)(=NR^b)R^b$, $NR^bS(=O)_2R^b$ and $S(=O)_2N(R^b)_2$, wherein each R^b is independently selected from H, C_1–C_6 alkyl (*e.g.*, Me, Et, Pr, ^{i}Pr, ^{n}Bu, ^{t}Bu, *sec*-Bu, *iso*-Bu)), and C_3–C_9 cycloalkyl (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl);~~ and

n is 0, 1, 2 or 3

provided that:

(i) when R^1 is H, R^2 is not halo, –OPr, $–N(CH_3)_2$ or $–CF_3$;

(ii) when R^1 is OR^{a1}, R^2 is not $–OR^{a2}$;

(iii) when R^1 is H and R^2 is $–CH_3$, R^8 groups cannot be taken together to form a ring and R^6 is not absent or H, and is not thiazolyl, furanyl or pyrrolyl;

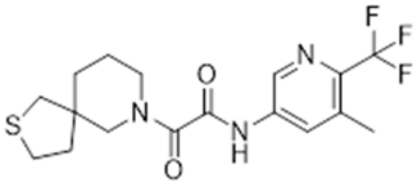
(iv) when R^2 is Me, R^1 is not ~~optionally substituted~~ piperidine

(v) the compound is not:

A. 5-(2-(5-methyl-2-(p-tolyl)piperidin-1-yl)-2-oxoacetamido)nicotinamide or any of its enantiomers or diastereomers;

B. 2-(2-(4-(2H-tetrazol-5-yl)phenyl)-5-methylpiperidin-1-yl)-N-(5,6-dimethylpyridin-3-yl)-2-oxoacetamide or any of its enantiomers or diastereomers;

C. 2-cyano-5-(2-(5-methyl-2-phenylpiperidin-1-yl)-2-oxoacetamido)nicotinamide or any of its enantiomers or diastereomers; or~~.~~

D. N-(5-methyl-6-(trifluoromethyl)pyridin-3-yl)-2-oxo-2-(2-thia-7-azaspiro[4.5]decan-7-yl)acetamide  or any of its enantiomers or diastereomers.

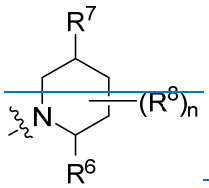
2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein each R^{a1}, R^{a2}, R^{a3}, R^{a4}, R^{a6}, R^{a7} and R^{a8} is independently selected from H, C_1–C_6 alkyl, $–C_1$–C_6 heteroalkyl, C_3–C_9 cycloalkyl, 3-7 membered heterocyclyl, cycloalkylalkyl, heterocyclylalkyl, aryl, 5-6 membered heteroaryl, arylalkyl and heteroarylalkyl wherein each alkyl, cycloalkyl, heterocyclyl, cycloalkylalkyl, heterocyclylalkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl is

independently substituted with 0, 1, 2 or 3 instances of R^9, wherein each R^9 is independently selected from =O, halo, –CN, –C_1–C_6 alkyl, –C_1–C_6 heteroalkyl, –C_1–C_6 haloalkyl, –C_3–C_9 cycloalkyl, 3-10 membered heterocyclyl, C_6–C_{10} aryl, 5-10 membered heteroaryl, cycloalkylalkyl, heterocyclylalkyl, arylalkyl, heteroarylalkyl, –OR^b, –$N(R^b)_2$, –$C(=O)R^b$, –$C(=O)OR^b$, –$NR^bC(=O)R^b$, –$NR^bC(=O)OR^b$, –$C(=O)N(R^b)_2$, –$OC(=O)N(R^b)_2$,-$S(=O)R^b$, –$S(=O)_2R^b$, –SR^b, –$S(=O)(=NR^b)R^b$, –$NR^bS(=O)_2R^b$ and –$S(=O)_2N(R^b)_2$, wherein each R^b is independently selected from H, –C_1–C_6 alkyl, and C_3–C_9 cycloalkyl.

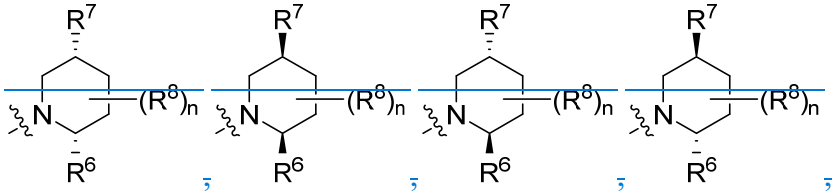
~~2. The compound of claim 1 wherein R^6 and R^7 are not H and are in a *trans* relative configuration.~~

~~3. The compound of claim 1 wherein R^6 and R^7 are not H and are in a *cis* relative configuration.~~

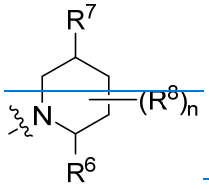
~~4. The compound of any one of claims 1 to 3 wherein the moiety represented as~~



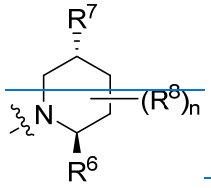
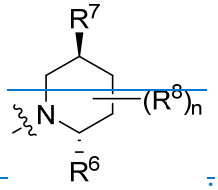
~~is selected from:~~



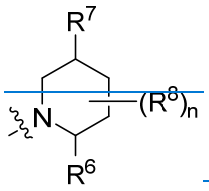
~~5. The compound of any one of claims 1, 2 and 4 wherein the moiety represented as~~

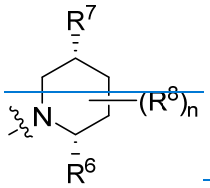
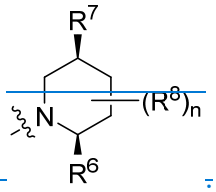


~~is selected from:~~

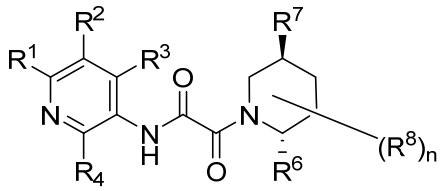


~~and~~ .

~~6. The compound of any one of claims 1, 3 and 4 wherein the moiety represented as~~

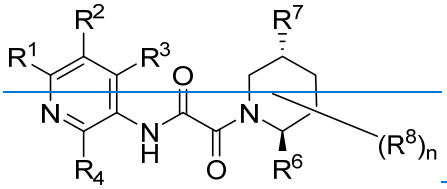

~~is selected from:~~



~~and~~ .

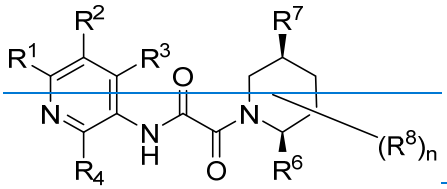
~~7.~~3. The~~A~~ compound of claim ~~5~~1 or 2, or a pharmaceutically acceptable salt thereof, wherein the compound is of Formula (Ia)


Formula (Ia).

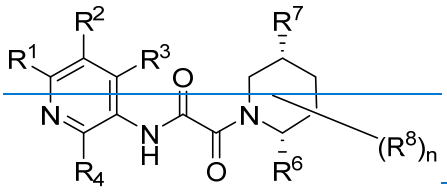
~~8. A compound of claim 5, wherein the compound is of Formula (Ib)~~


~~Formula (Ib).~~

~~9. A compound of claim 6, wherein the compound is of Formula (Ic)~~


~~Formula (Ic).~~

~~10. A compound of claim 6, wherein the compound is of Formula (Id)~~



~~Formula (Id).~~

~~11.~~4. The compound of any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof,~~10~~ wherein each R^8 is independently selected from H, –D, =O, halo, –CN, –C_1–C_6 alkyl, –C_1–C_6 heteroalkyl, –C_1–C_6 haloalkyl, –C_3–C_9 cycloalkyl, 3-10 membered heterocyclyl, heterocyclylalkyl, heteroarylalkyl, arylalkyl, cycloalkylalkyl, –OR^{a8}, –$N(R^{a8})_2$, –$C(=O)R^{a8}$, –$C(=O)OR^{a8}$, –$NR^{a8}C(=O)R^{a8}$, –$NR^{a8}C(=O)OR^{a8}$, –$CH_2C(=O)N(R^{a8})_2$ –$C(=O)N(R^{a8})_2$, –$OC(=O)N(R^{a8})_2$, –$CH_2C(=O)N(R^{a8})_2$, -$S(=O)R^{a8}$, –$S(=O)_2R^{a8}$, –SR^{a8}, –$S(=O)(=NR^{a8})R^{a8}$, –$NR^{a8}S(=O)_2R^{a8}$ and –$S(=O)_2N(R^{a8})_2$.

~~12.~~5. The~~A~~ compound of any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof,~~11~~ wherein R^1 is selected from H, halo, –CN, –C_1–C_6 alkyl, –C_1–C_6 heteroalkyl, –C_1–C_6 haloalkyl, –C_3–C_9 cycloalkyl, 3-10 membered heterocyclyl, –OR^{a1}, –$N(R^{a1})_2$, –$C(=O)R^{a1}$, –$C(=O)OR^{a1}$, –$NR^{a1}C(=O)R^{a1}$, –$NR^{a1}C(=O)OR^{a1}$, –$C(=O)N(R^{a1})_2$ and –$OC(=O)N(R^{a1})_2$.

~~13. A compound of any one of claims 1 to 12 wherein R^1 is selected from H, halo, –CN, –C_1–C_6 alkyl, –C_1–C_6 haloalkyl, OR^{a1} and $N(R^{a1})_2$.~~

~~14.~~6. The~~A~~ compound of any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof,~~13~~ wherein R^1 is selected from H, –C_1–C_6 alkyl, –C_1–C_6 haloalkyl, –OR^{a1} and –$N(R^{a1})_2$.

~~15.~~7. The~~A~~ compound of any one of claims 1 to 6,~~14~~ or a pharmaceutically acceptable salt thereof, wherein each R^{a1} is independently selected from H, –C_1–C_6 alkyl ~~(*e.g.*, Me, Et, Pr, ^{i}Pr, ^{n}Bu, ^{t}Bu, *sec*-Bu, *iso*-Bu)~~ and –C_1–C_6 haloalkyl. ~~(*e.g.*, CHF_2, CF_3).~~

~~16. A compound of any one of claims 1 to 15 wherein R^1 is selected from H, C_1-C_6 alkyl (*e.g.*, Me, Et, Pr, ^{i}Pr, ^{n}Bu, ^{t}Bu, *sec*-Bu, *iso*-Bu), C_1-C_6 haloalkyl (*e.g.*, CF_3, CHF_2), OH, O (C_1-C_6 alkyl) (*e.g.*, OMe, OEt), O (C_1-C_6 haloalkyl) (*e.g.*, OCF_3, $OCHF_2$), NH_2, NH (C_1-C_6 alkyl) (*e.g.*, NHMe) and N (C_1-C_6 alkyl)$_2$ (*e.g*, NMe_2).~~

~~17.~~8. The ~~A~~ compound of any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof,~~16~~ wherein R^1 is selected from H, –Me, –Et, $–CHF_2$, –OMe, –OEt, $–OCHF_2$, $–OCF_3$, –OH and $–NH_2$.

~~18. A compound of any one of claims 1 to 16 wherein R^1 is selected from H, Et, OMe, OEt, $OCHF_2$, OCF_3 and OH.~~

~~19. A compound of any one of claims 1 to 16 wherein R^1 is selected from H and OMe.~~

~~20. A compound of any one of claims 1 to 16 wherein R^1 is H.~~

~~21. A compound of any one of claims 1 to 16 wherein R^1 is OMe.~~

~~22. A compound of any one of claims 1 to 16 wherein R^1 is selected from H, Me, CHF_2 and NH_2.~~

~~23.~~9. The~~A~~ compound of any one of claims 1 to 4,~~16~~ or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from –Me and $–NH_2$.

~~24. A compound of any one of claims 1 to 16 wherein R^1 is Me.~~

~~25.~~10. The~~A~~ compound of any one of claims 1 to 4,~~16~~ or a pharmaceutically acceptable salt thereof, wherein R^1 is $–NH_2$.

~~26. A compound of any one of claims 1 to 25 wherein R^2 is selected from halo, CN, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_3-C_9 cycloalkyl (*e.g.*, cyclopropyl), 3-6 membered heterocyclyl (*e.g.*, oxetanyl, tetrahydrofuranyl), OR^{a2}, $N(R^{a2})_2$, $C(=O)R^{a2}$, $C(=O)OR^{a2}$, $NR^{a2}C(=O)R^{a2}$, $NR^{a2}C(=O)OR^{a2}$, $C(=O)N(R^{a2})_2$, $OC(=O)N(R^{a2})_2$.~~

~~27.~~11. The~~A~~ compound of any one of claims 1 to 10,~~26~~ or a pharmaceutically acceptable salt thereof, wherein R^2 is selected from halo, –CN, –C_1–C_6 alkyl, –C_1–C_6 haloalkyl, –C_1–C_6 haloalkoxy, –C_3–C_9 cycloalkyl, ~~(*e.g.*, cyclopropyl),~~ 3-6 membered heterocyclyl, ~~(*e.g.*, oxetanyl, tetrahydrofuranyl),~~ –OR^{a2}, –$N(R^{a2})_2$, –$C(=O)R^{a2}$, –$C(=O)N(OR^{a2})(R^{a2})$, and –$C(=O)N(R^{a2})_2$.

~~28. A compound of any one of claims 1 to 27 wherein R^2 is selected from halo, C_1–C_6 alkyl, C_1–C_6 haloalkyl, C_1–C_6 haloalkoxy, C_3–C_9 cycloalkyl (*e.g.*, cyclopropyl), 3–6 membered heterocyclyl (*e.g.*, oxetanyl, tetrahydrofuranyl), OR^{a2}, $C(=O)N(OR^{a2})(R^{a2})$, $C(=O)R^{a2}$ and $C(=O)N(R^{a2})_2$.~~

~~29. A compound of any one of claims 1 to 28 wherein R^2 is selected from halo, C_1–C_6 alkyl, C_3–C_9 cycloalkyl (*e.g.*, cyclopropyl), C_1–C_6 haloalkoxy, 3–6 membered heterocyclyl (*e.g.*, oxetanyl, tetrahydrofuranyl), C_1–C_6 haloalkyl, OR^{a2}, and $C(=O)N(R^{a2})_2$.~~

~~30.~~12. The~~A~~ compound of any one of claims 1 to 11,~~29~~ or a pharmaceutically acceptable salt thereof, wherein each R^{a2} is independently selected from H and –C_1–C_6 alkyl ~~(*e.g.*, Me, Et, Pr, ^{i}Pr, ^{n}Bu, ^{t}Bu, *sec*-Bu, *iso*-Bu)~~.

~~31.~~13. The~~A~~ compound of any one of claims 1 to 10,~~30~~ or a pharmaceutically acceptable salt thereof, wherein R^2 is selected from halo ~~(*e.g.*, Cl)~~, –C_1–C_6 alkyl ~~(*e.g.*, Me, Et, Pr, ^{i}Pr, ^{n}Bu, ^{t}Bu, *sec*-Bu, *iso*-Bu)~~, –C_1–C_6 haloalkyl ~~(*e.g.*, CF_3, CHF_2)~~, –C_1–C_6 haloalkoxy ~~(*e.g.*, OCH_2F, OCF_3)~~, –C_3–C_9 cycloalkyl ~~(*e.g.*, cyclopropyl)~~, 3-6 membered heterocyclyl ~~(*e.g.*, oxetanyl, tetrahydrofuranyl)~~, –C_1–C_6 haloalkoxy, ~~(*e.g.*, OCF_3, $OCHF_2$),~~ –OMe, –C(=O)H, –C(=O)NHOH, and –$C(=O)NH_2$.

~~32.~~14. The~~A~~ compound of any one of claims 1 to 10,~~26~~ or a pharmaceutically acceptable salt thereof, wherein R^2 is selected from –Cl, –Me, –Et, –^{i}Pr, –CF_3, –CHF_2, –$OCHF_2$, –OCF_3, cyclopropyl, oxetan-3-yl, tetrahydrofuran-3-yl, –OMe, –C(=O)H, –C(=O)NHOH, and –$C(=O)NH_2$.

~~33. A compound of any one of claims 1 to 26 wherein R^2 is selected from –C(=O)NH_2 and –C(=O)H.~~

~~34. A compound of any one of claims 1 to 26 wherein R^2 is –C(=O)NH_2.~~

~~35. A compound of any one of 1 to 26 wherein R^2 is selected from –Cl, –Me, –Et, –^{i}Pr, –CF_3, –CHF_2, –$OCHF_2$, –OCF_3, oxetan-3-yl, tetrahydrofuran-3-yl, and cyclopropyl.~~

~~36.~~15. The~~A~~ compound of any one of claims 1 to 10,~~35~~ or a pharmaceutically acceptable salt thereof, wherein R^2 is selected from cyclopropyl, –Me, and –Et.

~~37.~~16. The~~A~~ compound of any one of claims 1 to 4,~~11~~ or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from H, –OMe, –OEt, –OCF_3, –$OCHF_2$, –CHF_2, –Me, –Et, –OH and –NH_2 and R^2 is selected from –Cl, –Me, –Et, –^{i}Pr, –CF_3, –CHF_2, –$OCHF_2$, –OCF_3, cyclopropyl, –C(=O)NH_2, and –C(=O)H, provided that when R^2 is –Me, R^1 is NH_2.

~~38.~~17. The~~A~~ compound of any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof,~~11~~ wherein R^1 is selected from H, –CHF_2, –Me and –NH_2 and R^2 is selected from –Cl, –Me, –Et, –CF_3, –CHF_2, –$OCHF_2$ and cyclopropyl, provided that when R^2 is –Me, R^1 is NH_2.

~~39. A compound of any one of claims 1 to 11 wherein R^1 is selected from –NH_2 and –Me and R^2 is selected from cyclopropyl, –Me, and –Et.~~

~~40.~~18. The~~A~~ compound of claim 17~~39~~, or a pharmaceutically acceptable salt thereof, wherein R^1 is –NH_2 and R^2 is selected from cyclopropyl, –Me or –Et.

~~41.~~19. The~~A~~ compound of any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof,~~37~~ wherein R^1 is selected from H, –OMe, –OEt,–OCF_3, –$OCHF_2$, –Et and –OH and R^2 is selected from –C(=O)NH_2 and –C(=O)H.

~~42.~~20. The~~A~~ compound of claim 19, or a pharmaceutically acceptable salt thereof,~~41~~ wherein R^1 is selected from H and –OMe and R^2 is –C(=O)NH_2.

~~43.~~21. The~~A~~ compound of any one of claims 1 to 20, or a pharmaceutically acceptable salt thereof,~~42~~ wherein R^3 is selected from H, halo, –CN, –C_1–C_6 alkyl, –C_1–C_6 heteroalkyl, –C_1–C_6 haloalkyl, –C_3–C_9 cycloalkyl, 3-10 membered heterocyclyl, –OR^{a3}, –$N(R^{a3})_2$, –$C(=O)R^{a3}$, –$C(=O)OR^{a3}$, –$NR^{a3}C(=O)R^{a3}$, –$NR^{a3}C(=O)OR^{a3}$, –$C(=O)N(R^{a3})_2$ and –$OC(=O)N(R^{a3})_2$.

~~44. The compound of any one of claims 1 to 43 wherein R^3 is selected from H, halo, CN, C_1–C_6 alkyl, C_1–C_6 haloalkyl and $N(R^{a3})_2$.~~

~~45. The compound of any one of claims 1 to 44 wherein R^{a3} is selected from H and C_1–C_6 alkyl (*e.g.*, Me, Et, Pr, ^{i}Pr, ^{n}Bu, ^{t}Bu, *sec*-Bu, *iso*-Bu).~~

~~46. The compound of any one of claims 1 to 45 wherein R^3 is selected from C_1–C_6 alkyl (*e.g.*, Me, Et, Pr, ^{i}Pr, ^{n}Bu, ^{t}Bu, *sec*-Bu, *iso*-Bu), OH, O (C_1–C_6 alkyl) (*e.g.*, OMe), NH_2, NH (C_1–C_6 alkyl) (*e.g.*, NHMe) and N (C_1–C_6 alkyl)$_2$ (*e.g*, NMe_2).~~

~~47.~~22. The compound of any one of claims 1 to 20,~~46~~ or a pharmaceutically acceptable salt thereof, wherein R^3 is selected from H, –Me and –NH_2.

~~48. The compound of any one of claims 1 to 47 wherein R^3 is selected from H and Me.~~

~~49. The compound of any one of claims 1 to 48 wherein R^3 is Me.~~

~~50.~~23. The~~A~~ compound of any one of claims 1 to 22,~~49~~ or a pharmaceutically acceptable salt thereof, wherein R^4 is selected from H, halo, –CN, –C_1–C_6 alkyl, –C_1–C_6 heteroalkyl, –C_1–C_6 haloalkyl, –C_3–C_9 cycloalkyl, 3-10 membered heterocyclyl, –OR^{a4}, –$N(R^{a4})_2$, –$C(=O)R^{a4}$, –$C(=O)OR^{a4}$, –$NR^{a4}C(=O)R^{a4}$, –$NR^{a4}C(=O)OR^{a4}$, –$C(=O)N(R^{a4})_2$ and –$OC(=O)N(R^{a4})_2$.

~~51. The compound of any one of claims 1 to 50 wherein R^4 is selected from H, halo, CN, C_1–C_6 alkyl, C_1–C_6 haloalkyl and $N(R^{a4})_2$.~~

~~52. The compound of any one of claims 1 to 51 wherein each R^{a4} is independently selected from H and C_1–C_6 alkyl (*e.g.*, Me, Et, Pr, ^{i}Pr, ^{n}Bu, ^{t}Bu, *sec*-Bu, *iso*-Bu).~~

~~53. The compound of any one of claims 1 to 52 wherein R^4 is selected from C_1–C_6 alkyl (*e.g.*, Me, Et, Pr, ^{i}Pr, nBu, ^{t}Bu, *sec*-Bu, *iso*-Bu), OH, O (C_1–C_6 alkyl) (*e.g.*, OMe), NH_2, NH (C_1–C_6 alkyl) (*e.g.*, NHMe) and N (C_1–C_6 alkyl)$_2$ (*e.g*, NMe_2).~~

~~54.~~24. The compound of any one of claims 1 to 22,~~53~~ or a pharmaceutically acceptable salt thereof, wherein R^4 is H.

~~55. The compound of any one of claims 1 to 54 wherein each R^6 is independently selected from D, halo, CN, C_1–C_6 alkyl, C_1–C_6 heteroalkyl, C_1–C_6 haloalkyl, C_3–C_{10} carbocyclyl, 3-10 membered heterocyclyl, heterocyclylalkyl, C_6–C_{10} aryl, 5-10 member heteroaryl, heteroarylalkyl, arylalkyl, cycloalkylalkyl, OR^{a6}, $N(R^{a6})_2$, $C(=O)R^{a6}$, $C(=O)OR^{a6}$, $NR^{a6}C(=O)R^{a6}$, $NR^{a6}C(=O)OR^{a6}$, $C(=O)N(R^{a6})_2$, $OC(=O)N(R^{a6})_2$, $S(=O)R^{a6}$, $S(=O)_2R^{a6}$, SR^{a6}, $S(=O)(=NR^{a6})R^{a6}$, $NR^{a6}S(=O)_2R^{a6}$ and $S(=O)_2N(R^{a6})_2$, wherein each alkyl, carbocyclyl, heterocyclyl, cycloalkylalkyl, heterocyclylalkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl is optionally substituted at any available position.~~

~~56.~~25. The compound of any one of claims 1 to 24,~~54~~ or a pharmaceutically acceptable salt thereof, wherein each R^6 is independently selected from H, halo, –CN, –C_1–C_6 alkyl, –C_1–C_6 heteroalkyl, –C_1–C_6 haloalkyl, –C_3–C_{10} carbocyclyl, 3-10 membered heterocyclyl, heterocyclylalkyl, C_6–C_{10} aryl, 5-10 member heteroaryl, heteroarylalkyl, arylalkyl, cycloalkylalkyl, $–OR^{a6}$, $–N(R^{a6})_2$, $–C(=O)R^{a6}$, $–C(=O)OR^{a6}$, $–NR^{a6}C(=O)R^{a6}$, $–NR^{a6}C(=O)OR^{a6}$, $–C(=O)N(R^{a6})_2$, $–OC(=O)N(R^{a6})_2$,-$S(=O)R^{a6}$, $–S(=O)_2R^{a6}$, $–SR^{a6}$, $–S(=O)(=NR^{a6})R^{a6}$, $–NR^{a6}S(=O)_2R^{a6}$ and $–S(=O)_2N(R^{a6})_2$, wherein each alkyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, cycloalkylalkyl, heterocyclylalkyl, arylalkyl and heteroarylalkyl is substituted at any available position with 0, 1, 2 or 3 instances of R^{10}, wherein:

each R^{10} is independently selected from –D, =O, –CN, halo, –C_1–C_6 alkyl, –C_1–C_6 heteroalkyl, –C_1–C_6 haloalkyl, –C_3–C_9 cycloalkyl, 3-10 membered heterocyclyl, C_6–C_{10} aryl, 5-10 membered heteroaryl, cycloalkylalkyl, heterocyclylalkyl, arylalkyl, heteroarylalkyl,

heterocyclylalkoxy, $–OR^{b10}$, $–N(R^{b10})_2$, $–C(=O)R^{b10}$, $–C(=O)OR^{b10}$, $–NR^{b10}C(=O)R^{b10}$, $–NR^{b10}C(=O)OR^{b10}$, $–C(=O)N(R^{b10})_2$, $–OC(=O)R^{b10}$, $–OC(=O)N(R^{b10})_2$,-$S(=O)R^{b10}$, $–S(=O)_2R^{b10}$, $–SR^{b10}$, $–S(=O)(=NR^{b10})R^{b10}$, $–NR^{b10}S(=O)_2R^{b10}$ and $–S(=O)_2N(R^{b10})_2$, wherein each alkyl, cycloalkyl, heteroalkyl, heterocyclyl, aryl, heteroaryl, cycloalkylalkyl, heterocyclylalkyl, heterocyclylalkoxy, arylalkyl and heteroarylalkyl of R^{10} is optionally substituted at any available position; and wherein:

each R^{b10} is independently H; $–C_1–C_6$ alkyl; $–C_1–C_6$ haloalkyl; $–C_1–C_6$ heteroalkyl substituted with 0 or 1 instance of =O; $C_3–C_9$ cycloalkyl; or 3-10 member heterocyclyl substituted with 0 or 1 instances of =O, –Me or a combination thereof.

~~57.~~26. The compound of any one of claims 1 to 24, or a pharmaceutically acceptable salt thereof,~~54~~ wherein each R^6 is independently selected from halo, –CN, $–C_1–C_6$ alkyl, $–C_1–C_6$ heteroalkyl, $–C_1–C_6$ haloalkyl, $–C_3–C_{10}$ carbocyclyl, 3-10 membered heterocyclyl, heterocyclylalkyl, $C_6–C_{10}$ aryl, 5-10 member heteroaryl, heteroarylalkyl, arylalkyl, cycloalkylalkyl, $–OR^{a6}$, $–N(R^{a6})_2$, $–C(=O)R^{a6}$, $–C(=O)OR^{a6}$, $–NR^{a6}C(=O)R^{a6}$, $–NR^{a6}C(=O)OR^{a6}$, $–C(=O)N(R^{a6})_2$, $–OC(=O)N(R^{a6})_2$,-$S(=O)R^{a6}$, $–S(=O)_2R^{a6}$, $–SR^{a6}$, $–S(=O)(=NR^{a6})R^{a6}$, $–NR^{a6}S(=O)_2R^{a6}$ and $–S(=O)_2N(R^{a6})_2$, wherein each alkyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, cycloalkylalkyl, heterocyclylalkyl, arylalkyl and heteroarylalkyl is substituted at any available position with 0, 1, 2 or 3 instances of R^{10}, wherein:

each R^{10} is independently selected from –D, =O, –CN, halo, $–C_1–C_6$ alkyl, $–C_1–C_6$ heteroalkyl, $–C_1–C_6$ haloalkyl, $–C_3–C_9$ cycloalkyl, 3-10 membered heterocyclyl, $C_6–C_{10}$ aryl, 5-10 membered heteroaryl, cycloalkylalkyl, heterocyclylalkyl, arylalkyl, heteroarylalkyl, heterocyclylalkoxy, $–OR^{b10}$, $–N(R^{b10})_2$, $–C(=O)R^{b10}$, $–C(=O)OR^{b10}$, $–NR^{b10}C(=O)R^{b10}$, $–NR^{b10}C(=O)OR^{b10}$, $–C(=O)N(R^{b10})_2$, $–OC(=O)R^{b10}$, $–OC(=O)N(R^{b10})_2$,-$S(=O)R^{b10}$, $–S(=O)_2R^{b10}$, $–SR^{b10}$, $–S(=O)(=NR^{b10})R^{b10}$, $–NR^{b10}S(=O)_2R^{b10}$ and $–S(=O)_2N(R^{b10})_2$, wherein each alkyl, cycloalkyl, heteroalkyl, heterocyclyl, aryl, heteroaryl, cycloalkylalkyl, heterocyclylalkyl, heterocyclylalkoxy, arylalkyl and heteroarylalkyl of R^{10} is optionally substituted at any available position~~, (*e.g.*, with 0, 1, 2, 3, 4, or 5 instances of Me, Et, ^{i}Pr, cyclopropyl, oxetan-3-yl, OH, =O, F, OMe, CH_2CH_2F, CH_2CHF_2, $CH_2CH_2CF_3$, C(=O)Me, $N(Me)_2$, $CH_2N(CH_3)_2$, $CH_2N(CH_3)CH_2CH_3$, $N(^i$Pr)(Et), $N(^i$Pr)(Me), $N(Et)_2$, $N(CH_3)(Et)$, NHC(=O)Me, or a combination thereof),~~ and wherein:

each R^{b10} is independently H; –C_1–C_6 alkyl; –C_1–C_6 haloalkyl; –C_1–C_6 heteroalkyl substituted with 0 or 1 instance of =O; C_3–C_9 cycloalkyl; or 3-10 member heterocyclyl substituted with 0 or 1 instances of =O, –Me or a combination thereof.

~~58.~~27. ~~The A~~ compound of any one of claims 1 to 26, or a pharmaceutically acceptable salt thereof,~~58~~ wherein each R^{a6} is independently selected from H and –C_1–C_6 alkyl. ~~(*e.g.*, Me, Et, Pr, ^{i}Pr, ^{n}Bu, ^{t}Bu, *sec*-Bu, *iso*-Bu).~~

~~59. The compound of any one of claims 1 to 54 wherein each R^6 is independently selected from H, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, C_1-C_6 haloalkyl, C_3-C_{10} carbocyclyl, 3-10 membered heterocyclyl, heterocyclylalkyl, C_6-C_{10} aryl, 5-10 member heteroaryl, heteroarylalkyl, arylalkyl and cycloalkylalkyl, wherein each alkyl, cycloalkyl, heterocyclyl, cycloalkylalkyl, heterocyclylalkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl is optionally substituted at any available position.~~

~~60. The compound of any one of claims 1 to 54 wherein each R^6 is independently selected from C_1-C_6 alkyl, C_1-C_6 heteroalkyl, C_1-C_6 haloalkyl, C_3-C_{10} carbocyclyl, 3-10 membered heterocyclyl, heterocyclylalkyl, C_6-C_{10} aryl, 5-10 member heteroaryl, heteroarylalkyl, arylalkyl and cycloalkylalkyl, wherein each alkyl, cycloalkyl, heterocyclyl, cycloalkylalkyl, heterocyclylalkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl is optionally substituted at any available position.~~

~~61. The compound of any one of claims 1 to 54 wherein each R^6 is independently selected from H, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, C_1-C_6 haloalkyl, C_3-C_{10} carbocyclyl, 3-10 membered heterocyclyl, heterocyclylalkyl, C_6-C_{10} aryl, 5-10 member heteroaryl, heteroarylalkyl, arylalkyl and cycloalkylalkyl, wherein each alkyl, cycloalkyl, heterocyclyl, cycloalkylalkyl, heterocyclylalkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl is substituted at any available position with 0, 1, 2 or 3 instances of R^{10} wherein:~~

~~each R^{10} is independently selected from D, =O, CN, halo, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, C_1-C_6 haloalkyl, C_3-C_9 cycloalkyl, 3-10 membered heterocyclyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, cycloalkylalkyl, arylalkyl, heteroarylalkyl, heterocyclylalkoxy, heterocyclylalkyl, OR^{b10}, $N(R^{b10})_2$, $C(=O)R^{b10}$, $C(=O)OR^{b10}$, $NR^{b10}C(=O)R^{b10}$,~~

~~$NR^{b10}C(=O)OR^{b10}$, $C(=O)N(R^{b10})_2$, $OC(=O)R^{b10}$, $OC(=O)N(R^{b10})_2$, $S(=O)R^{b10}$, $S(=O)_2R^{b10}$, SR^{b10}, $S(=O)(=NR^{b10})R^{b10}$, $NR^{b10}S(=O)_2R^{b10}$ and $S(=O)_2N(R^{b10})_2$, wherein each alkyl, cycloalkyl, heteroalkyl, heterocyclyl, aryl, heteroaryl, cycloalkylalkyl, heterocyclylalkyl, arylalkyl and heteroarylalkyl of R^{10} is optionally substituted (*e.g.*, with 0, 1, 2, 3, 4, or 5 instances of Me, Et, ^{i}Pr, cyclopropyl, oxetan-3-yl, OH, =O, F, OMe, CH_2CH_2F, CH_2CHF_2, $CH_2CH_2CF_3$, C(=O)Me, $N(Me)_2$, $CH_2N(CH_3)_2$, $CH_2N(CH_3)CH_2CH_3$, $N(^i Pr)(Et)$, $N(^i Pr)(Me)$, $N(Et)_2$, $N(CH_3)(Et)$, NHC(=O)Me, or a combination thereof), and wherein:~~

~~each R^{b10} is independently selected from H; C_1-C_6 alkyl; C_1-C_6 haloalkyl; C_1-C_6 heteroalkyl substituted with 0 or 1 instance of =O; C_3-C_9 cycloalkyl; and a 3-10 member heterocyclyl substituted with 0 or 1 instances of =O, Me or a combination thereof.~~

~~62. The compound of any one of claims 1 to 54 wherein each R^6 is independently selected from C_1-C_6 alkyl, C_1-C_6 heteroalkyl, C_1-C_6 haloalkyl, C_3-C_{10} carbocyclyl, 3-10 membered heterocyclyl, heterocyclylalkyl, C_6-C_{10} aryl, 5-10 member heteroaryl, heteroarylalkyl, arylalkyl and cycloalkylalkyl, wherein each alkyl, cycloalkyl, heterocyclyl, cycloalkylalkyl, heterocyclylalkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl is substituted at any available position with 0, 1, 2 or 3 instances of R^{10} wherein:~~

~~each R^{10} is independently selected from D, =O, CN, halo, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, C_1-C_6 haloalkyl, C_3-C_9 cycloalkyl, 3-10 membered heterocyclyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, cycloalkylalkyl, arylalkyl, heteroarylalkyl, heterocyclylalkyl, heterocyclylalkoxy, OR^{b10}, $N(R^{b10})_2$, $C(=O)R^{b10}$, $C(=O)OR^{b10}$, $NR^{b10}C(=O)R^{b10}$, $NR^{b10}C(=O)OR^{b10}$, $C(=O)N(R^{b10})_2$, $OC(=O)R^{b10}$, $OC(=O)N(R^{b10})_2$, $S(=O)R^{b10}$, $S(=O)_2R^{b10}$, SR^{b10}, $S(=O)(=NR^{b10})R^{b10}$, $NR^{b10}S(=O)_2R^{b10}$ and $S(=O)_2N(R^{b10})_2$, wherein each alkyl, cycloalkyl, heteroalkyl, heterocyclyl, heterocyclylalkoxy, aryl, heteroaryl, cycloalkylalkyl, heterocyclylalkyl, arylalkyl and heteroarylalkyl of R^{10} is optionally substituted (*e.g.*, substituted with 0, 1, 2, 3, 4, or 5 instances of Me, Et, ^{i}Pr, cyclopropyl, oxetan-3-yl, OH, =O, F, OMe, CH_2CH_2F, CH_2CHF_2, $CH_2CH_2CF_3$, C(=O)Me, $N(Me)_2$, $CH_2N(CH_3)_2$, $CH_2N(CH_3)CH_2CH_3$, $N(^i Pr)(Et)$, $N(^i Pr)(Me)$, $N(Et)_2$, $N(CH_3)(Et)$, NHC(=O)Me, or a combination thereof)); and~~

~~each R^{b10} is independently selected from H; C_1–C_6 alkyl; C_1–C_6 haloalkyl; C_1–C_6 heteroalkyl substituted with 0 or 1 instance of =O; C_3–C_9 cycloalkyl; and a 3-10 member heterocyclyl substituted with 0 or 1 instances of =O, Me or a combination thereof.~~

~~63.~~28. The compound of any one of claims 25~~1~~ to 27,~~54~~ or a pharmaceutically acceptable salt thereof, wherein each R^6 is independently selected from H, –C_1–C_6 alkyl ~~(*e.g.*, Me, Et, Pr, ^{i}Pr, ^{i}Bu, *sec*-Bu, ^{t}Bu)~~, –C_3–C_{10} monocyclic or bicyclic carbocyclyl ~~(*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, bicyclo[1.1.1]pentan-yl, 4,5,6,7-tetrahydro-1H-indazolyl, spiro[3.3]heptanyl)~~, 3-10 membered mono or bicyclic heterocyclyl ~~(*e.g.*, oxetanyl, azepanyl, piperidinyl, pyrorolidinyl, tetrahydrofuranyl, tetrahydropyranyl, 1,2-dihydropyridinyl, morpholinyl)~~, C_6–C_{10} mono or bicyclic aryl ~~(*e.g.*, phenyl, naphthyl, 1,2,3,4-tetrahydronaphthalenyl, 2,3-dihydro-1H-indenyl, 1,2,3,4 tetrahydroquinolinyl, 1,2 dihydroquinolinyl, 1,2-dihydroisoquinolinyl, 1,2,3,4 tetrahydroisoquinolinyl, chromanyl, indolinyl, isoindolinyl, 3,4-dihydro-2H-benzo[b][1,4]oxazinyl, 2,3-dihydrobenzofuranyl, benzo[*d*][1,3] dioxolyl, 2,3-dihydro-1H-benzo[d]imidazolyl)~~, 5-6 member monocyclic heteroaryl ~~(*e.g.*, thiophenyl, thiazolyl, pyrazolyl, imidazolyl, oxazolyl, pyridinyl, pyrimidinyl)~~, 8-10 member bicyclic heteroaryl ~~(*e.g.*, benzo[d]isothiazolyl, indolyl, benzofuranyl, 1H-indazolyl, 2H-indazolyl, benzo[b]thiophenyl, quinolinyl, 1,5-naphthyridinyl, 1,2-dihydro-1,5-naphthyridinyl, 1,2,3,4-tetrahydro-1,8-naphthyridinyl, isoquinolinyl, benzo[*d*]imidazolyl, benzo[*d*]thiazolyl, benzo[*d*]oxazolyl, [1,2,4]triazolo[4,3-*a*]pyridinyl, imidazo[1,2-*a*]pyridinyl, imidazo[1,5-*a*]pyridinyl, 1H-pyrazolo[4,3-*b*]pyridinyl), 1H-pyrazolo[3,4-b]pyridinyl, 1H-thieno[2,3-c]pyrazolyl, 1H-thieno[3,2-c]pyrazolyl, thiazolo[5,4-b]pyridinyl)~~ wherein each alkyl, carbocyclyl, heterocyclyl, aryl and heteroaryl~~-~~ is ~~optionally substituted (*e.g.*,~~ substituted with 0, 1, 2 or 3 instances of R^{10}~~)~~.

~~64. The compound of any one of claims 1 to 54 wherein each R^6 is independently selected from C_1–C_6 alkyl (*e.g.*, Me, Et, Pr, ^{i}Pr, ^{i}Bu, *sec*-Bu, ^{t}Bu), C_3–C_{10} monocyclic or bicyclic carbocyclyl (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, bicyclo[1.1.1]pentan-yl, 4,5,6,7-tetrahydro-1H-indazolyl, spiro[3.3]heptanyl), 3-10 membered mono or bicyclic heterocyclyl (*e.g.*, oxetanyl, azepanyl, piperidinyl, pyrorolidinyl, tetrahydrofuranyl, tetrahydropyranyl, 1,2-dihydropyridinyl, morpholinyl), C_6–C_{10} mono or~~

~~bicyclic aryl (*e.g.*, phenyl, naphthyl, 1,2,3,4-tetrahydronaphthalenyl, 2,3-dihydro-1H-indenyl, 1,2,3,4 tetrahydroquinolinyl, 1,2 dihydroquinolinyl, 1,2-dihydroisoquinolinyl, 1,2,3,4 tetrahydroisoquinolinyl, chromanyl, indolinyl, isoindolinyl, 3,4-dihydro-2H-benzo[b][1,4]oxazinyl, 2,3-dihydrobenzofuranyl, benzo[*d*][1,3] dioxolyl, 2,3-dihydro-1H-benzo[d]imidazolyl), 5-6 member monocyclic heteroaryl (*e.g.*, thiophenyl, thiazolyl, pyrazolyl, imidazolyl, oxazolyl, pyridinyl, pyrimidinyl), 8-10 member bicyclic heteroaryl (*e.g.*, benzo[d]isothiazolyl, indolyl, benzofuranyl, 1H-indazolyl, 2H-indazolyl, benzo[b]thiophenyl, quinolinyl, 1,5-naphthyridinyl, 1,2-dihydro-1,5-naphthyridinyl, 1,2,3,4-tetrahydro-1,8-naphthyridinyl, isoquinolinyl, benzo[*d*]imidazolyl, benzo[*d*]thiazolyl, benzo[*d*]oxazolyl, [1,2,4]triazolo[4,3-*a*]pyridinyl, imidazo[1,2-*a*]pyridinyl, imidazo[1,5-*a*]pyridinyl, 1H-pyrazolo[4,3-*b*]pyridinyl), 1H- pyrazolo[3,4-b]pyridinyl, 1H-thieno[2,3-c]pyrazolyl, 1H-thieno[3,2-c]pyrazolyl, thiazolo[5,4-b]pyridinyl) wherein each alkyl, carbocyclyl, heterocyclyl, aryl and heteroaryl is optionally substituted (*e.g.*, substituted with 0, 1, 2 or 3 instances of R^{10}).~~

~~65. The compound of claim 63 wherein R^6 is an 8-10 member bicyclic heteroaryl (*e.g.*, indolyl, benzofuranyl, 1H-indazolyl, 2H-indazolyl, benzo[b]thiophenyl, quinolinyl, 1,5-naphthyridinyl, 1,2-dihydro-1,5-naphthyridinyl, 1,2,3,4-tetrahydro-1,8-naphthyridinyl, imidazo[1,2-a]pyridinyl, imidazo[1,5-a]pyridinyl, isoquinolinyl, benzo[*d*]imidazolyl, benzo[*d*]thiazolyl, benzo[d]isothiazolyl, benzo[*d*]oxazolyl, [1,2,4]triazolo[4,3-*a*]pyridinyl, imidazo[1,2-*a*]pyridinyl, 1H-pyrazolo[4,3-*b*]pyridinyl),1H- pyrazolo[3,4-b]pyridinyl, 1H-thieno[2,3-c]pyrazolyl, 1H-thieno[3,2-c]pyrazolyl, thiazolo[5,4-b]pyridinyl, 1,2,3,4-tetrahydro-1,8-naphthyridinyl) wherein the bicyclic heteroaryl is optionally substituted (*e.g.*, substituted with 0, 1, 2 or 3 instances of R^{10}).~~

~~66. The compound of any one of claims 1 to 54 wherein each R^6 is independently selected from H, Me, ^{i}Pr, ^{i}Bu, *sec*-Bu, cyclobutyl, cyclopentyl, cyclohexyl, bicyclo[1.1.1]pentan-1-yl, spiro[3.3]heptan-2-yl, 4,5,6,7-tetrahydro-1H-indazol-6-yl, piperidin-4-yl, piperidin-3-yl, pyrrolidin-3-yl, 1,2-dihydropyridin-4-yl, phenyl, naphthalen-2-yl, 1,2,3,4-tetrahydroquinolin-6-yl, 1,2,3,4-tetrahydronaphthalen-6-yl, chroman-6-yl, 1,5-naphthyridin-6-yl, 1,2,3,4-tetrahydro-1,8-naphthyridin-6-yl, 2,3-dihydro-1H-inden-5-yl, indolin-5-yl, indolin-4-yl, 2,3-dihydro-1H-benzo[d]imidazol-5-yl, 2,3-dihydrobenzofuran-5-yl, 2,3-dihydrobenzofuran-6-yl, benzo[*d*][1,3] dioxol-5-yl], isoindolin-5-yl, isoindolin-6-yl, 3,4-dihydro-2H-~~

~~benzo[b][1,4]oxazin-7-yl, 1,2-dihydroquinolin-6-yl, 1,2-dihydroisoquinolin-7-yl, thiophen-2-yl, thiophen-3-yl, thiazol-2-yl, thiazol-4-yl, thiazol-5-yl, pyrazol-1-yl, pyrazol-5-yl, pyrazol-3-yl, pyrazol-4-yl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyrimidin-5-yl, indol-4-yl, indol-5-yl, benzofuran-5-yl, benzofuran-6-yl, 1*H* indazol-5-yl, 1*H* indazol-4-yl, 2H-indazol-6-yl, 2H-indazol-5-yl, benzo[*b*]thiophen-3-yl, benzo[*b*]thiophen-5-yl, quinolin-6-yl, quinoline-3-yl, isoquinolin-6-yl, benzo[*d*]imidazo-5-yl, 1H-benzo[d]imidazol-4-yl, benzo[*d*]thiazol-5-yl, benzo[d]thiazol-6-yl, benzo[d]thiazol-4-yl, benzo[d]isothiazol-5-yl, benzo[*d*]oxazol-4-yl, benzo[*d*]oxazol-5-yl, [1,2,4]triazolo[4,3-*a*]pyridin-6-yl, imidazo[1,2-*a*]pyridin-6-yl, imidazo[1,2-a]pyridin-7-yl, imidazo[1,5-a]pyridin-6-yl, pyrazolo[4,3-*b*]pyridin-6-yl, 1H-pyrazolo[3,4-b]pyridin-5-yl, 1H-pyrazolo[3,4-b]pyridin-5-yl, 1H-pyrazolo[4,3-b]pyridin-5-yl, 1H-pyrazolo[4,3-b]pyridin-6-yl, 1H-thieno[2,3-c]pyrazol-5-yl, 1H-thieno[3,2-c]pyrazol-5-yl, thiazolo[5,4-b]pyridin-6-yl), each optionally substituted (*e.g.*, substituted with 0, 1, 2 or 3 instances of R^{10}).~~

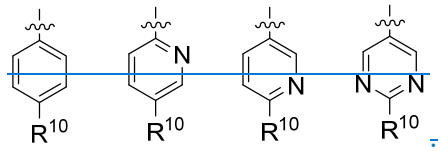
~~67.~~29. The compound of any one of claims 25~~1~~ to 27,~~54~~ or a pharmaceutically acceptable salt thereof, wherein each R^6 is independently selected from~~-~~ –Me, –^{i}Pr, -^{i}Bu, *sec*-Bu, cyclobutyl, cyclopentyl, cyclohexyl, bicyclo[1.1.1]pentan-1-yl, spiro[3.3]heptan-2-yl, 4,5,6,7-tetrahydro-1H-indazol-6-yl, piperidin-4-yl, piperidin-3-yl, pyrrolidin-3-yl, 1,2-dihydropyridin-4-yl, phenyl, naphthalen-2-yl, 1,2,3,4 tetrahydroquinolin-6-yl, 1,2,3,4-tetrahydronaphthalen-6-yl, chroman-6-yl, 1,5-naphthyridin-6-yl, 1,2,3,4-tetrahydro-1,8-naphthyridin-6-yl, 2,3-dihydro-1H-inden-5-yl, indolin-5-yl, indolin-4-yl, 2,3-dihydro-1H-benzo[d]imidazol-5-yl, 2,3-dihydrobenzofuran-5-yl, 2,3-dihydrobenzofuran-6-yl, benzo[*d*][1,3] dioxol-5-yl], isoindolin-5-yl, isoindolin-6-yl, 3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl, 1,2-dihydroquinolin-6-yl, 1,2-dihydroisoquinolin-7-yl, thiophen-2-yl, thiophen-3-yl, thiazol-2-yl, thiazol-4-yl, thiazol-5-yl, pyrazol-1-yl, pyrazol-5-yl, pyrazol-3-yl, pyrazol-4-yl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyrimidin-5-yl, indol-4-yl, indol-5-yl, benzofuran-5-yl, benzofuran-6-yl, 1*H* indazol-5-yl, 1*H* indazol-4-yl, 2H-indazol-6-yl, 2H-indazol-5-yl, benzo[*b*]thiophen-3-yl, benzo[*b*]thiophen-5-yl, quinolin-6-yl, quinoline-3-yl, isoquinolin-6-yl, -benzo[*d*]imidazo-5-yl, 1H-benzo[d]imidazol-4-yl, benzo[*d*]thiazol-5-yl, benzo[d]thiazol-6-yl, benzo[*d*]thiazol-4-yl, benzo[*d*]isothiazol-5-yl, benzo[*d*]oxazol-4-yl, benzo[*d*]oxazol-5-yl, [1,2,4]triazolo[4,3-*a*]pyridin-6-yl, imidazo[1,2-

a]pyridin-6-yl, imidazo[1,2-*a*]pyridin-7-yl, imidazo[1,5-a]pyridin-6-yl, pyrazolo[4,3-*b*]pyridin-6-yl, 1H-pyrazolo[3,4-b]pyridin-5-yl, 1H-pyrazolo[3,4-b]pyridin-5-yl, 1H-pyrazolo[4,3-b]pyridin-5-yl, 1H-pyrazolo[4,3-b]pyridin-6-yl, -1H-thieno[2,3-c]pyrazol-5-yl, 1H-thieno[3,2-c]pyrazol-5-yl, thiazolo[5,4-b]pyridin-6-yl), each ~~optionally substituted (*e.g.*,~~ substituted with 0, 1, 2 or 3 instances of R^{10}~~)~~.

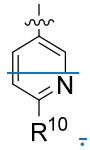
~~68.~~30. The compound of any one of claims 25~~1~~ to 27~~67~~, or a pharmaceutically acceptable salt thereof, wherein R^6 is selected from ~~optionally substituted~~ phenyl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl~~,~~ and pyrimidin-5-yl and phenyl ~~(*e.g.*~~, each substituted with 0, 1, 2 or 3 instances of R^{10}~~)~~.

~~69.~~31. The compound of claim 30, or a pharmaceutically acceptable salt thereof,~~68,~~ wherein R^6 is selected from phenyl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, and pyrimidin-5-yl substituted with one instance of R^{10}.

~~70. The compound of claim 68, wherein R^6 is selected from:~~

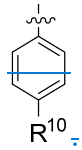


~~71. The compound of claim 68, wherein R^6 is~~



~~72. The compound of any one of claims 1 to 67 wherein R^6 is optionally substituted phenyl (*e.g.*, substituted with 0, 1, 2 or 3 instances of R^{10}).~~

~~73. The compound of claim 72 wherein R^6 is~~

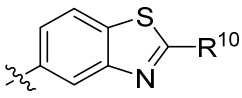
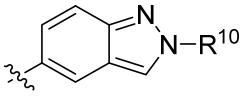
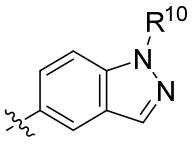


~~74. The compound of any one of claims 1 to 67, wherein R^6 is selected from optionally substituted bicyclic heteroaryl (*e.g.*, substituted with 0, 1, 2 or 3 instances of R^{10}).~~

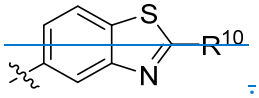
~~75.~~32. The compound of claim ~~74~~29, or a pharmaceutically acceptable salt thereof, wherein R^6 is selected from ~~optionally substituted~~ 1*H*-indazol-5-yl, 2*H*-indazol-5-yl, benzo[d]isothiazol-5-yl, benzo[d]thiazol-5-yl, benzo[b]thiophen-5-yl, benzo[*d*]oxazol-4-yl, benzo[*d*]oxazol-5-yl, quinoline-7-yl, 1H-thieno[2,3-c]pyrazol-5-yl, imidazo[1,2-a]pyridin-7-yl, and imidazo[1,5-a]pyridin-6-yl~~, (*e.g.,* substituted with 0, 1, 2 or 3 instances of R^{10})~~.

33. The compound of claim 32, or a pharmaceutically acceptable salt thereof, wherein R^6 is benzo[d]thiazol-5-yl substituted with 0, 1, 2 or 3 instances of R^{10}.

~~76.~~34. The compound of claim 32, or a pharmaceutically acceptable salt thereof~~75~~, wherein

R^6 is  ,  , or  .

~~77. The compound of claim 76, wherein R^6 is~~



~~.~~

~~78.~~35. The compound of any one of claims 25-34, or a pharmaceutically acceptable salt thereof,~~1 to 77~~ wherein each R^{10} is independently selected from –D, =O, halo, ~~(*e.g.*, F, Cl, Br),~~ –CN, –C_1–C_6 alkyl, ~~(*e.g.*, Me, Et, Pr, ^{i}Pr, *sec* Bu, ^{t}Bu, $CH_2(CH_3)(^i$Pr)),~~ –C_1–C_6 heteroalkyl, ~~(*e.g.*, CH(CH$_3$)(NMe$_2$), CH$_2$CH$_2$N(Me)(oxetan-3-yl)), CH$_2$CH(CH$_3$)(NMe$_2$), CH$_2$OH, CH(OH)(CH$_3$), C(OH)(CH$_3$)$_2$, . CH$_2$NH$_2$),~~ –C_1–C_6 haloalkyl, ~~(*e.g.*, CHF$_2$, CH$_2$CF$_3$, CF$_3$),~~ –C_3–C_9 cycloalkyl, ~~(*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl),~~ 3-10 membered heterocyclyl, ~~(*e.g.*,tetrahydrofuranyl, tetrahydropyranyl, oxetanyl, morpholinyl, pyrolidinyl, piperidinyl, piperidin-2-onyl, piperazinyl, piperazin-2-only, azetidinyl, decahydro-1,6-naphthyridinyl, 2-azaspiro[3.3]heptanyl, 5-oxa-2,8-diazaspiro[3.5]nonanyl, 8-azabicyclo[3.2.1]octanyl, 2-azabicyclo[2.2.2]octanyl, 3-azabicyclo[3.2.0]heptanyl, 3-azabicyclo[3.1.1]heptanyl, 3-azabicyclo[3.1.0]hexanyl, 2-azabicyclo[2.1.1]hexanyl, 1-azabicyclo[2.2.1]heptanyl, 3-azabicyclo[3.2.0]heptanyl, 2,9-diazaspiro[5.5]undecanyl, bicyclo[1.1.1]pentanyl,~~

~~octahydrocyclopenta[c]pyrrolyl, decahydro-1,6-naphthyridinyl, octahydro-1H-pyrrolo[3,4-c]pyridinyl, decahydro-2,7-naphthyridinyl, 2,9-diazaspiro[5.5]undecanyl),~~ 5-10 membered heteroaryl, ~~(*e.g.*, pyridinyl, imidazo[1,2-a]pyridinyl, imidazolyl, pyrazolyl, thiazolyl, thiophenyl), cycloalkylalkyl (*e.g.*, CH_2-cyclopropyl),~~ heterocyclylalkyl, ~~(*e.g.*, CH_2-morpholinyl, $(CH_2)_2$-pyrolidinyl, $(CH_2)_2$-pyrolidinyl, CH_2-imidazolyl, CH_2-pyrazolyl, CH_2-1,2,4-triazolyl, CH_2-morpholinyl, $(CH_2)_2$-morpholinyl),~~ heterocyclylalkoxy, ~~(e.g., O-$(CH_2)_2$-pyrolidinyl, O-CH_2-piperidinyl, O-CH_2-oxetanyl, O-CH_2-tetrahydrofuranyl, O-CH_2-tetrahydropyranyl),~~ heteroarylalkyl, ~~(*e.g.*, CH_2-triazolyl, CH_2-imidazolyl, CH_2-pyrazolyl),~~ $–OR^{b10}$, ~~(*e.g.*, OH, OMe, OEt, O-tetrahydrofuranyl, O-tetrahydropyran-4-yl, $–OCF_3$, $–OCHF_2$),~~ $–N(R^{b10})_2$, ~~(*e.g.*, NH_2, NHR^{b10}, NHMe, NMe_2, $NHCH_2CF_3$, NH-oxetan-3-yl, NH-(N-Me-2-oxo-pyrolidin-3-yl),~~ $–NR^{b10}C(=O)R^{b10}$, ~~(*e.g.*, NHC(=O)Me),~~ $–C(=O)N(R^{b10})_2$, ~~(*e.g.*, $C(=O)NH_2$, C(=O)NHMe),~~ $–OC(=O)R^{b10}$, ~~(*e.g.*, OC(=O)Me),~~ $–S(=O)R^{b10}$, ~~(*e.g.*, SO_2Me),~~ $–NR^{b10}S(=O)_2R^{b10}$ ~~(*e.g.*, $NHSO_2$Me)~~ and $–S(=O)_2N(R^{b10})_2$, ~~(*e.g.*, SO_2NH_2, SO_2NHMe),~~ wherein each alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, cycloalkylalkyl, heterocyclylalkyl, arylalkyl and heteroarylalkyl is ~~optionally~~ substituted ~~(*e.g.*,~~ with 0, 1, 2, 3, 4, or 5 instances of –Me, –Et, $–^iPr$, cyclopropyl, oxetan-3-yl, –OH, =O, –F, ~~–~~ –OMe, $–CH_2CH_2F$, $–CH_2CHF_2$, $–CH_2CH_2CF_3$, ~~–~~C(=O)Me, $–N(Me)_2$, $–CH_2N(CH_3)_2$, $–CH_2N(CH_3)CH_2CH_3$, $–N(^iPr)(Et)$, $–N(^iPr)(Me)$, $–N(Et)_2$, $–N(CH_3)(Et)$, –NHC(=O)Me, or a combination thereof, ~~),~~ and wherein:

each R^{b10} is independently selected from H, $–C_1$–C_6 alkyl, ~~(*e.g.*, Me, Et, Pr, ^{i}Pr, *sec*-Bu, ^{t}Bu),~~ $–C_1$–C_6 haloalkyl, ~~(*e.g.*, CF_3, CHF_2, CH_2CF_3),~~ $–C_1$–C_6 heteroalkyl substituted with 0 or 1 instances of =O, ~~(*e.g.*, $CH_2CH_2NMe_2$, $CH_2C(=O)NMe_2$, $CH(CH_3)CH_2NMe_2$, $CH(CH_3)C(=O)NMe_2$),~~ C_3–C_9 cycloalkyl, and 3-10 member heterocyclyl ~~(*e.g.* tetrahydrofuran-3-yl, tetrahydropyran-4-yl, oxetan-3-yl, N-Me-2-oxo-pyrolidin-3-yl, piperidine-4-yl)~~ substituted with 0 or 1 instances of =O, –Me or a combination thereof.

~~79~~36. The compound of any one of claims 25-35 or a pharmaceutically acceptable salt thereof, ~~1 to 78~~ wherein each R^{b10} is independently selected from H, –Me, –Et, –Pr, $–^iPr$, *–sec*-Bu, $–^t$Bu, $–CF_3$, $–CHF_2$, $–CH_2CF_3$, $–CH_2CH_2NMe_2$, $–CH_2C(=O)NMe_2$, $–CH(CH_3)CH_2NMe_2$, –

$CH(CH_3)C(=O)NMe_2$), tetrahydrofuran-3-yl, tetrahydropyran-4-yl, oxetan-4-yl, N-Me-2-oxo-pyrolidin-3-yl, and piperidine-4-yl.

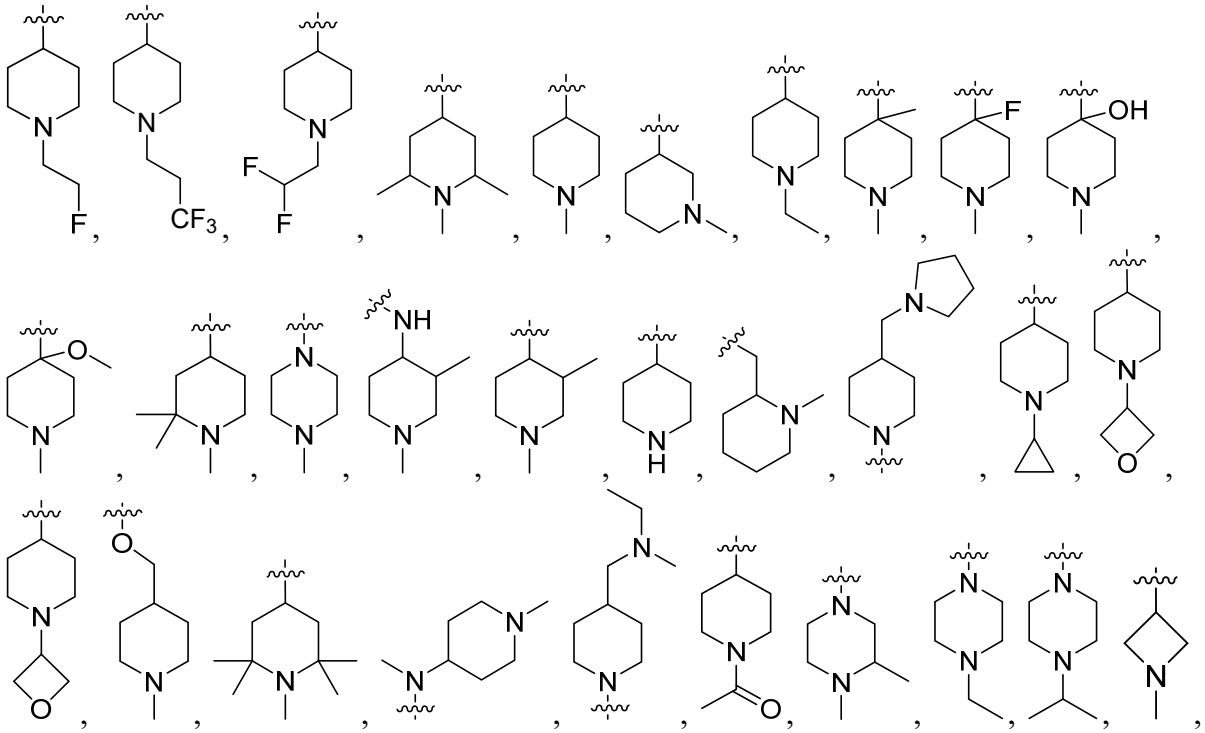
~~80~~37. The compound of any one of claims 25-35, or a pharmaceutically acceptable salt thereof,~~1 to 75~~ wherein each R^{10} is independently selected from the group consisting of: –D, =O, –OH, –F, –Cl, –Br, –CN, –Me, –Et, –Pr, –^{i}Pr, –*sec*-Bu, –^{t}Bu, –OMe, –OEt, $–CHF_2$, $–CH_2CF_3$, $–CF_3$, $–OCF_3$, $–OCHF_2$, $–CH_2OH$, $–CH(OH)(CH_3)$, $–CH_2OMe$, $–C(OH)(CH_3)_2$, $–CH_2NH_2$, $–CH(CH_3)(NMe_2)$, $–CH_2CH(CH_3)(NMe_2)$, $–CH_2(CH_3)(^iPr)$, $–NH_2$, –NHMe, $–NHCH_2CF_3$, $–NMe_2$, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, thiazol-2-yl, thiazol-5-yl, thiophen-2-yl, tetrahydrofuran-3-yl, tetrahydropyran-4-yl, oxetan-3-yl, morpholin-2-yl, $–CH_2$-morpholin-4-yl, $–(CH_2)_2$-morpholin-4-yl, imidazol-2-yl, 1H-pyrazol-5-yl, 1H-imidazol-4-yl, imidazo[1,2-a]pyridin-7-yl, pyrrolidin~~pyrolidin~~-1-yl, pyrrolidin~~pyrolidin~~-3-yl, piperidin-4-yl, piperidin-3-yl, piperidin-2-one-4-yl, piperazin-4-yl, piperazin-4-yl, piperazin-2-on-5-yl pyridine-4-yl, pyridine-3-yl, pyrazol-1-yl, pyrazol-3-yl, pyrazol-4-yl, pyrazol-5-yl, 1H-pyrazol-5-yl, azetidin-3-yl, $–(CH_2)_2$-pyrolidin-1-yl $–(CH_2)_2$-pyrolidin-2-yl $–CH_2$-imidazol-1-yl, $–CH_2$-pyrazol-1-yl, $–CH_2$-1,2,4-triazol-1-yl, $–CH_2$-cyclopropyl, $–O(CH_2)_2NMe_2$, –O-tetrahydrofuran-3-yl, –O-tetrahydropyran-4-yl, –O-(N-Me-2-oxo-pyrrolidin~~pyrolidin~~-3-yl), $–O-(CH_2)_2$-pyrrolidin~~pyrolidin~~-2-yl, $–O-CH_2$-piperidin-4-yl, $–O-CH_2$-oxetan-3-yl $–NCH_3-CH_2$-piperidin-4-yl, –NH-oxetan-3-yl, –NH-(N-Me-2-oxo-pyrolidin-3-yl), decahydro-1,6-naphthyridin-6-yl, 2-azaspiro[3.3]heptan-6-yl, 5-oxa-2,8-diazaspiro[3.5]nonan-8-yl, 8-azabicyclo[3.2.1]octan-3-yl, 2-azabicyclo[2.2.2]octan-4-yl, 3-azabicyclo[3.2.0]heptan-6-yl, 3-azabicyclo[3.1.1]heptan-1-yl, 3-azabicyclo[3.1.0]hexan-6-yl, 1-azabicyclo[2.2.1]heptan-4-yl, 3-azabicyclo[3.2.0]heptan-6-yl, 2-azabicyclo[2.1.1]hexan-4-yl, 2,9-diazaspiro[5.5]undecane-9-yl, bicyclo[1.1.1]pentan-2-yl, octahydrocyclopenta[c]pyrrol-5-yl, decahydro-1,6-naphthyridin-6-yl, octahydro-1H-pyrrolo[3,4-c]pyridine-5-yl, decahydro-2,7-naphthyridin-2-yl, 2,9-diazaspiro[5.5]undecan-2-yl, $–NHC(=O)Me$, $–NHCH_2C(=O)NMe_2$, $–NHCH(CH_3)C(=O)NMe_2$, $–C(=O)NH_2$, C(=O)NHMe, –OC(=O)Me, $–SO_2Me$, $–NHSO_2Me$,– SO_2NH_2 and $–SO_2NHMe$, wherein each –OMe, –OEt, –Me, –Et, –Pr, –^{i}Pr, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, tetrahydrofuran-3-yl, oxetan-3-yl, pyrolidin-1-yl, pyrolidin-3-yl, piperidin-4-yl, piperidin-3-yl, piperidin-2-one-4-yl piperazin-4-yl, pyrazol-1-yl, pyrazol-3-yl, pyrazol-4-yl, pyrazol-5-yl, thiazol-2-yl, thiophen-2-yl, $–CH_2$-cyclopropyl, $–CH_2$-morpholin-4-yl, $–(CH_2)_2$-

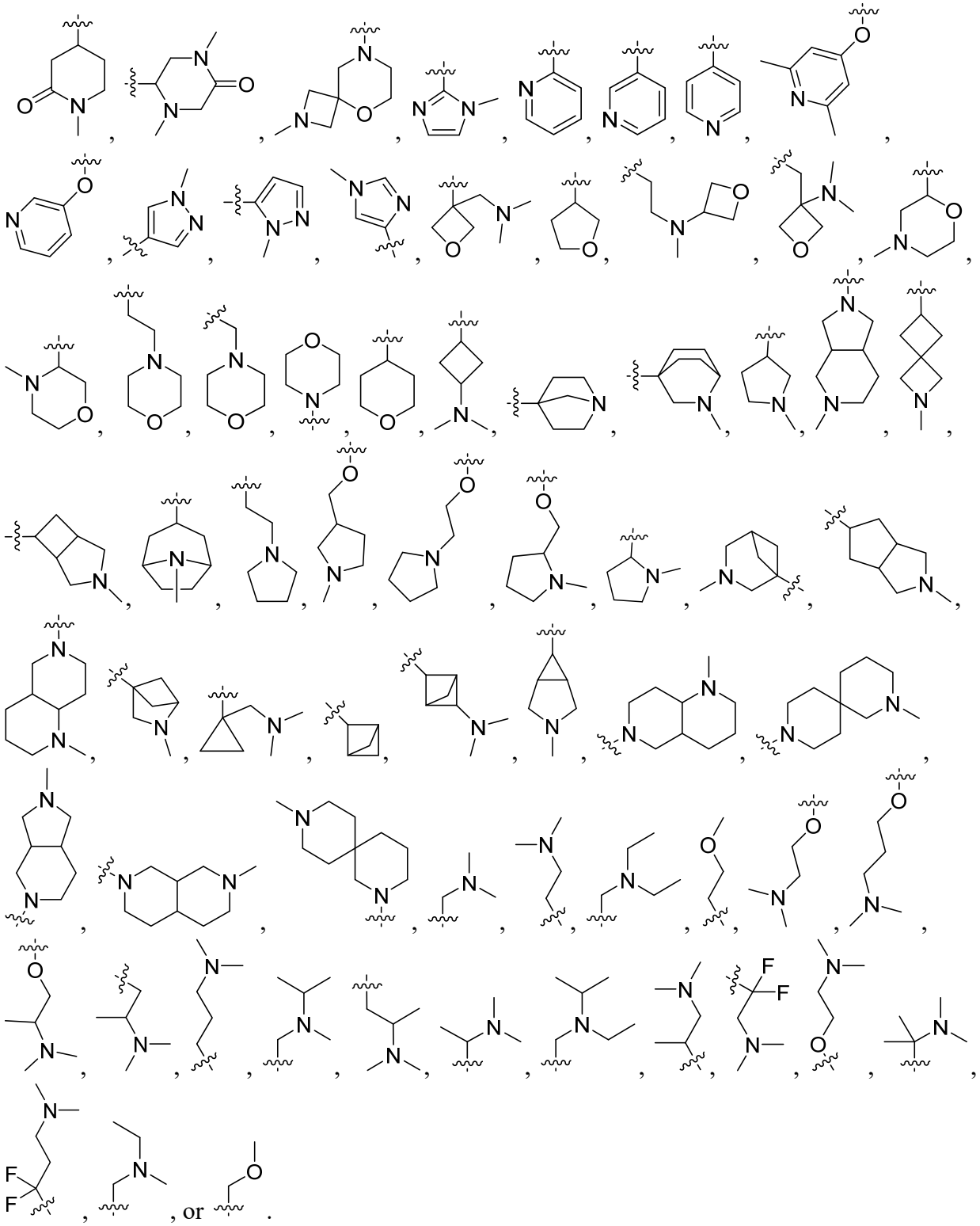
morpholin-4-yl, –morpholin-2-yl, –$(CH_2)_2$-pyrolidin-1-yl, –CH_2-1,2,4-triazol-1-yl –CH_2-imidazol-1-yl, imidazol-2-yl,–CH_2-pyrazol-1-yl, –OCH_2-piperidin-4-yl, azetidin-3-yl, 2-azaspiro[3.3]heptan-6-yl, 2-methyl-5-oxa-2,8-diazaspiro[3.5]nonan-8-yl, 8-azabicyclo[3.2.1]octan-3-yl, and decahydro-1,6-naphthyridin-6-yl; and wherein

each R^{10} can be independently substituted with 0, 1, 2, 3, 4, or 5 instances of –Me, –Et, –^{i}Pr, cyclopropyl, oxetan-3-yl, –OH, =O, –F, –OMe, $–CH_2CH_2F$, $–CH_2CHF_2$, $–CH_2CH_2CF_3$, –C(=O)Me, $–N(Me)_2$, $–CH_2N(CH_3)_2$, $–CH_2N(CH_3)CH_2CH_3$, –N(^{i}Pr)(Et), –N(^{i}Pr)(Me), $–N(Et)_2$, $–N(CH_3)(Et)$, –NHC(=O)Me, or a combination thereof.

~~81~~38. The compound of any one of claims 25-35, or a pharmaceutically acceptable salt thereof~~claim 1 to 67~~, wherein R^{10} is optionally substituted 3-6 membered monocyclic heterocyclyl~~heteterocyclyl~~ or optionally substituted 6-10 membered bicyclic heterocyclyl.~~heteterocyclyl.~~

~~82~~39. The compound of any one of claims 25-35, or a pharmaceutically acceptable salt thereof~~claim 80~~, wherein R^{10} is –D, –Cl, –F, –Me, $–CH_2$-OH,





4083. The compound of any one of claims 1 to 39, or a pharmaceutically acceptable salt thereof, ~~82~~ wherein each R^7 is independently selected from H, halo, ~~(*e.g.*, F, Cl),~~ –CN, –C_1–C_6

alkyl, ~~(*e.g.*, Me, Et, Pr, ^{i}Pr, *sec*-Bu, ^{t}Bu),~~ 5-membered heteroaryl, ~~(*e.g.*, pyrazolyl),~~ –C$_1$–C$_6$ haloalkyl, ~~(*e.g.*, CF_3, CHF_2, CH_2CF_3),~~ –C$_1$–C$_6$ hydroxyalkyl, ~~(*e.g.*, CH_2OH),~~ –C$_3$–C$_9$ cycloalkyl, ~~(*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl),~~ –OR^{a7}, ~~(*e.g.*, OH, OMe, $OCHF_2$),~~ –N(R^{a7})$_2$ and –C(=O)N(R^{a7})$_2$. ~~(*e.g.*, $C(=O)NH_2$, C(=O)NHMe).~~

~~84. The compound of any one of claims 1 to 82 wherein each R^{a7} is independently selected from H and C$_1$–C$_6$ alkyl (*e.g.*, Me, Et, Pr, ^{i}Pr, ^{n}Bu, ^{t}Bu, *sec*-Bu, *iso*-Bu).~~

41~~85~~. The compound of any one of claims 1 to 39,~~84~~ or a pharmaceutically acceptable salt thereof, wherein each R^7 is independently selected from H and methyl.

42~~86~~. The compound of any one of claims 1 to 39, or a pharmaceutically acceptable salt thereof,~~84~~ wherein each R^7 is H.

43~~87~~. The compound of any one of claims 1 to 39, or a pharmaceutically acceptable salt thereof,~~84~~ wherein each R^7 is methyl.

44~~88~~. The compound of any one of claims 1 to 43, or a pharmaceutically acceptable salt thereof,~~87~~ wherein each R^8 is independently selected from H, –D, halo, ~~(*e.g.*, F, Cl),~~ –CN, –C$_1$–C$_6$ alkyl, ~~(*e.g.*, Me, Et, Pr, ^{i}Pr, *sec*-Bu, ^{t}Bu),~~ –C$_1$–C$_6$ haloalkoxy, ~~(*e.g.*, OCF_3),~~ arylalkyl, ~~(*e.g.*, benzyl),~~ –C(=O)R^{a8}, ~~(*e.g.*, C(=O)Me, C(=O)Et, C(=O)Pr, C(=O)^{i}Pr),~~ –N(R^{a8})$_2$, ~~(*e.g.*, NHMe, NH_2, NMe_2),~~ –NR^{a8}C(=O)R^{a8}, ~~(*e.g.*, NHC(=O)Me),~~ –CH_2C(=O)N(R^{a8})$_2$ ~~(*e.g.*, $CH_2C(=O)NH_2$)~~ and –OR^{a8} ~~(*e.g.*, OH, OMe, O^{i}Pr)~~.

~~89. The compound of any one of claims 1 to 88, wherein each R^{a8} is independently selected from H, CF_3 and C$_1$–C$_6$ alkyl, (*e.g.*, Me, Et, Pr, ^{i}Pr, ^{n}Bu, ^{t}Bu, *sec*-Bu, *iso*-Bu).~~

~~90. The compound of any one of claims 1 to 89, wherein each R^8 is independently selected from H, D, F, Me, Et, *sec*-Bu, CN, OMe, O^{i}Pr, OCF_3, benzyl, NHC(=O)Me, NMe_2, $CH_2C(=O)NH_2$, C(=O)^{i}Pr and OH.~~

4591. The compound of any one of claims 1 to 43, or a pharmaceutically acceptable salt thereof89, wherein each R^8 is independently selected from H, –D, –F, –Me, –Et and –CN.

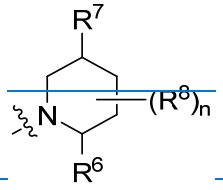
92. The compound of any one of claims 1 to 89, wherein each R^8 is independently selected from H, D, F and Me.

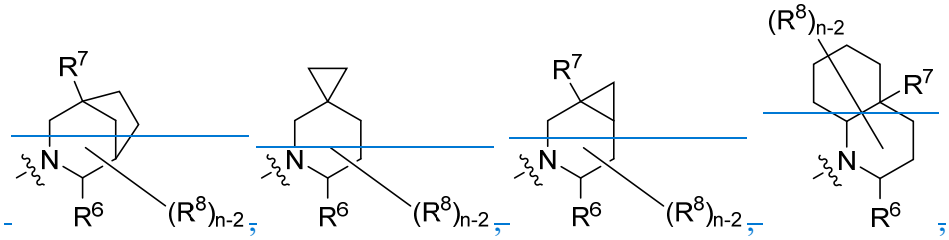
4693. The compound of any one of claims 1 to 4592, or a pharmaceutically acceptable salt thereof, wherein n is 0.

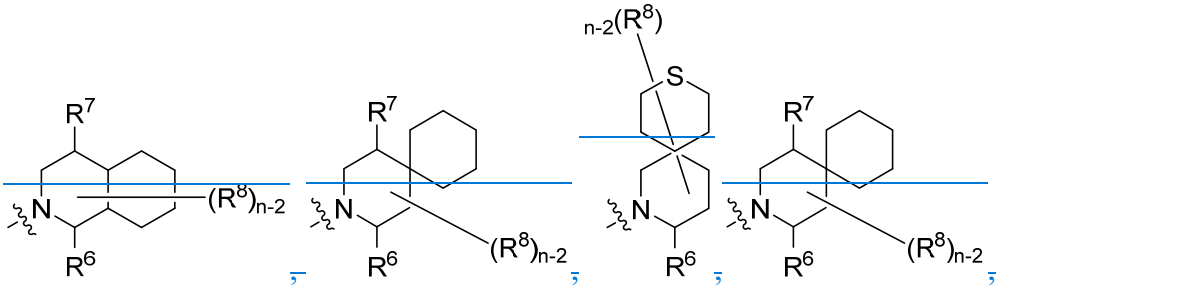
94. The compound of any one of claims 1 to 92 wherein n is 1.

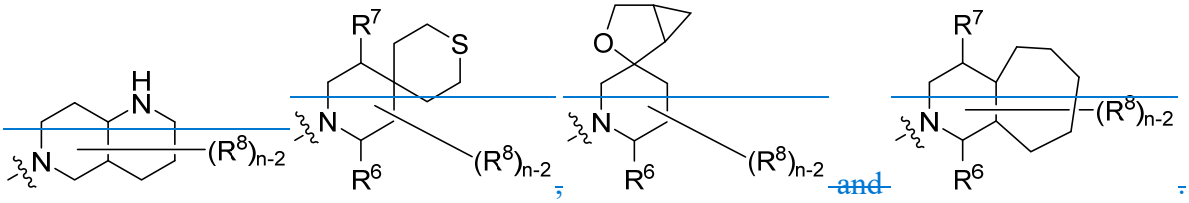
95. The compound of any one of claims 1 to 92 wherein n is 2.

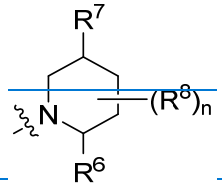
96. The compound of any one of claims 1 to 92 wherein n is 3.

97. The compound of any one of claims 1, 12 to 92 and 95 to 96 wherein the moiety represented as  is selected from:

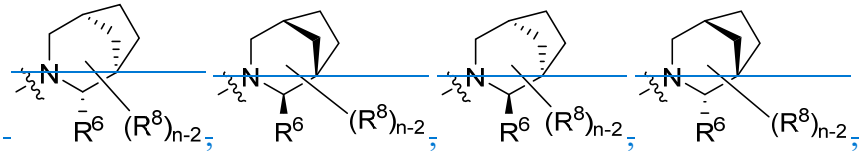


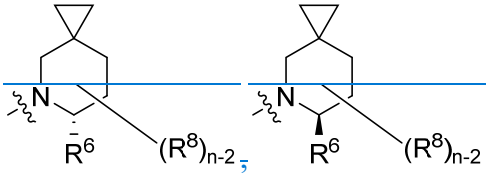


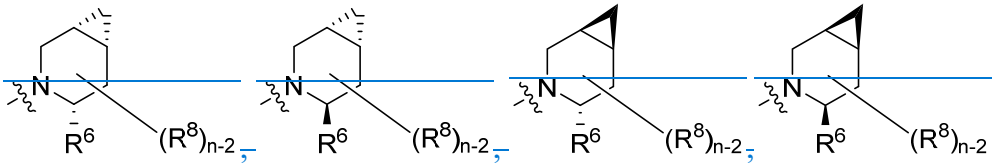


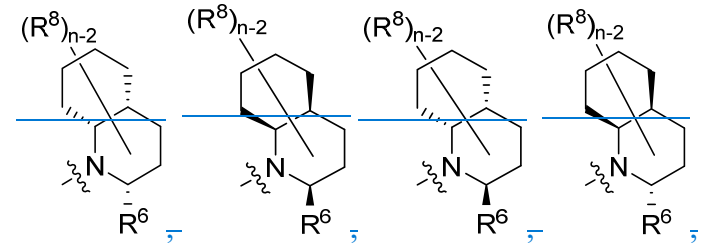


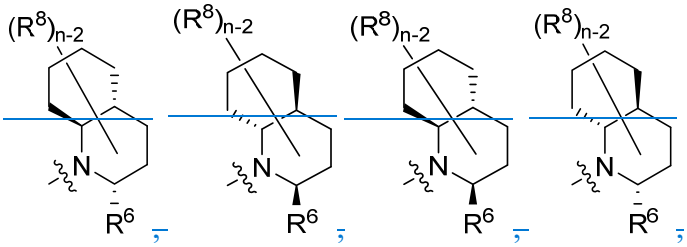
~~98. The compound of claim 97 wherein the moiety represented as~~ ~~is selected from:~~

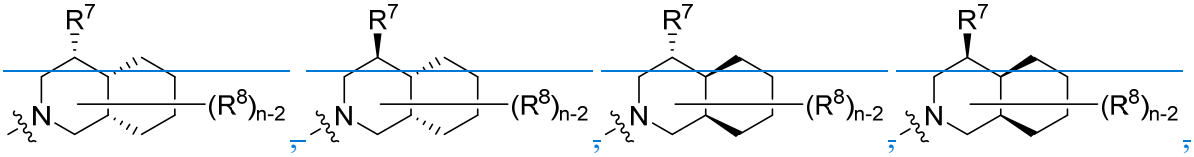


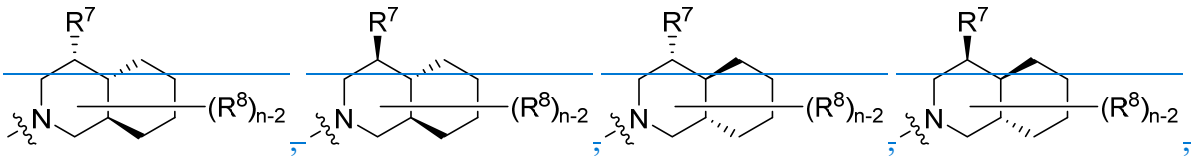


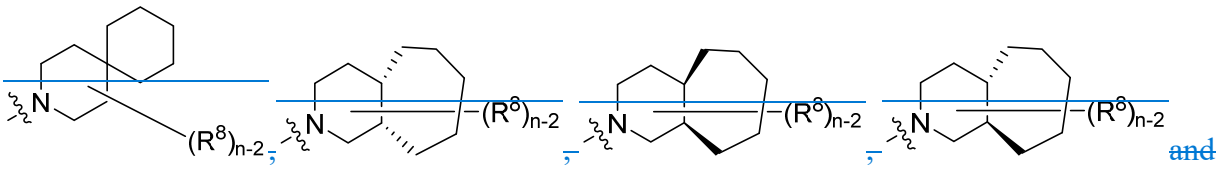


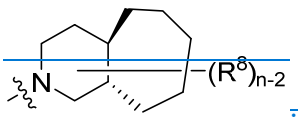












and

99. The compound of claim 97 to 98 wherein n is 2.

100. The compound of any one of claims 97 to 98 wherein each R^6 and R^7 is independently selected from H and CH_3.

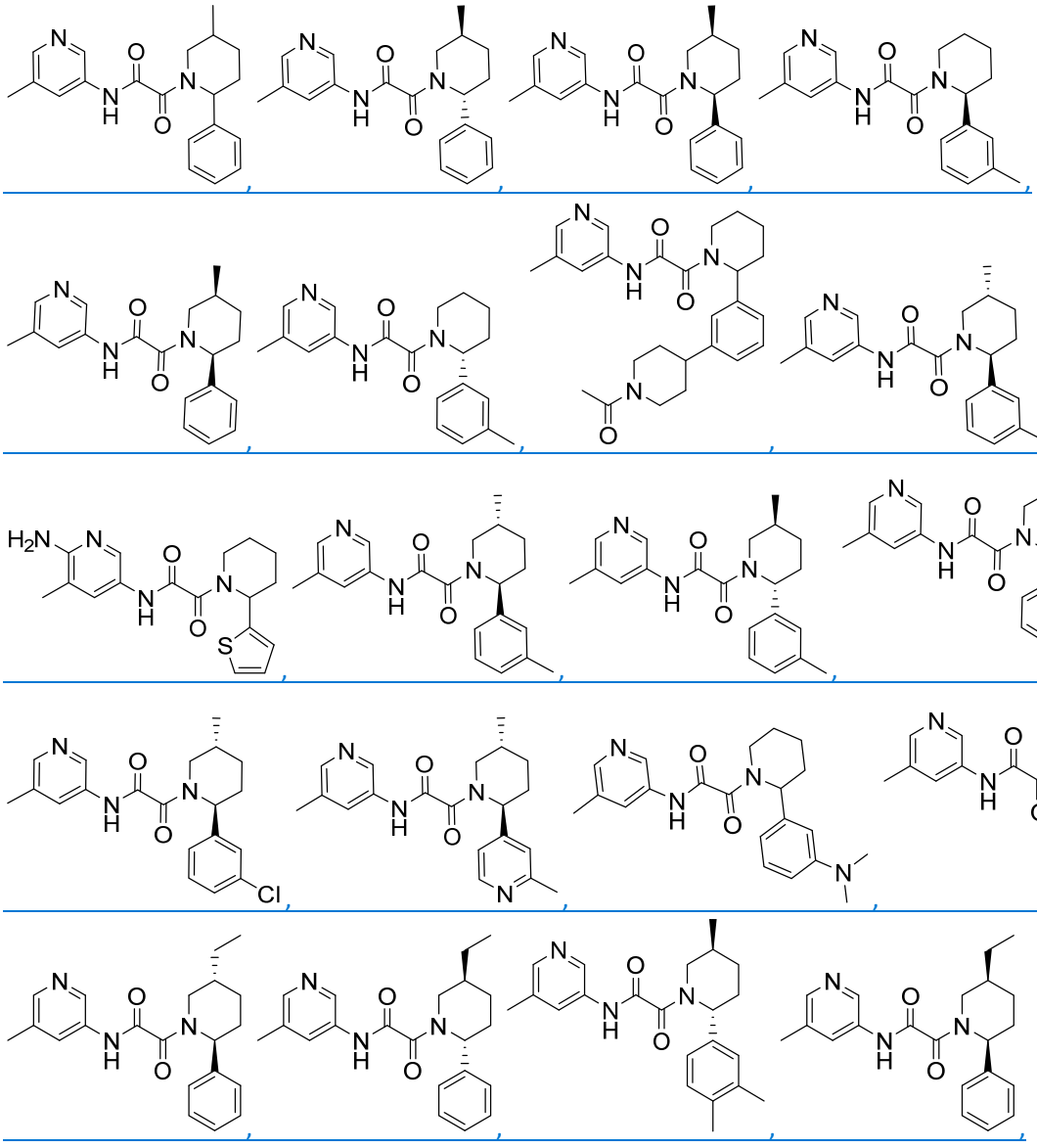
101. The compound of any one of claims 97 to 98 wherein R^6 is H.

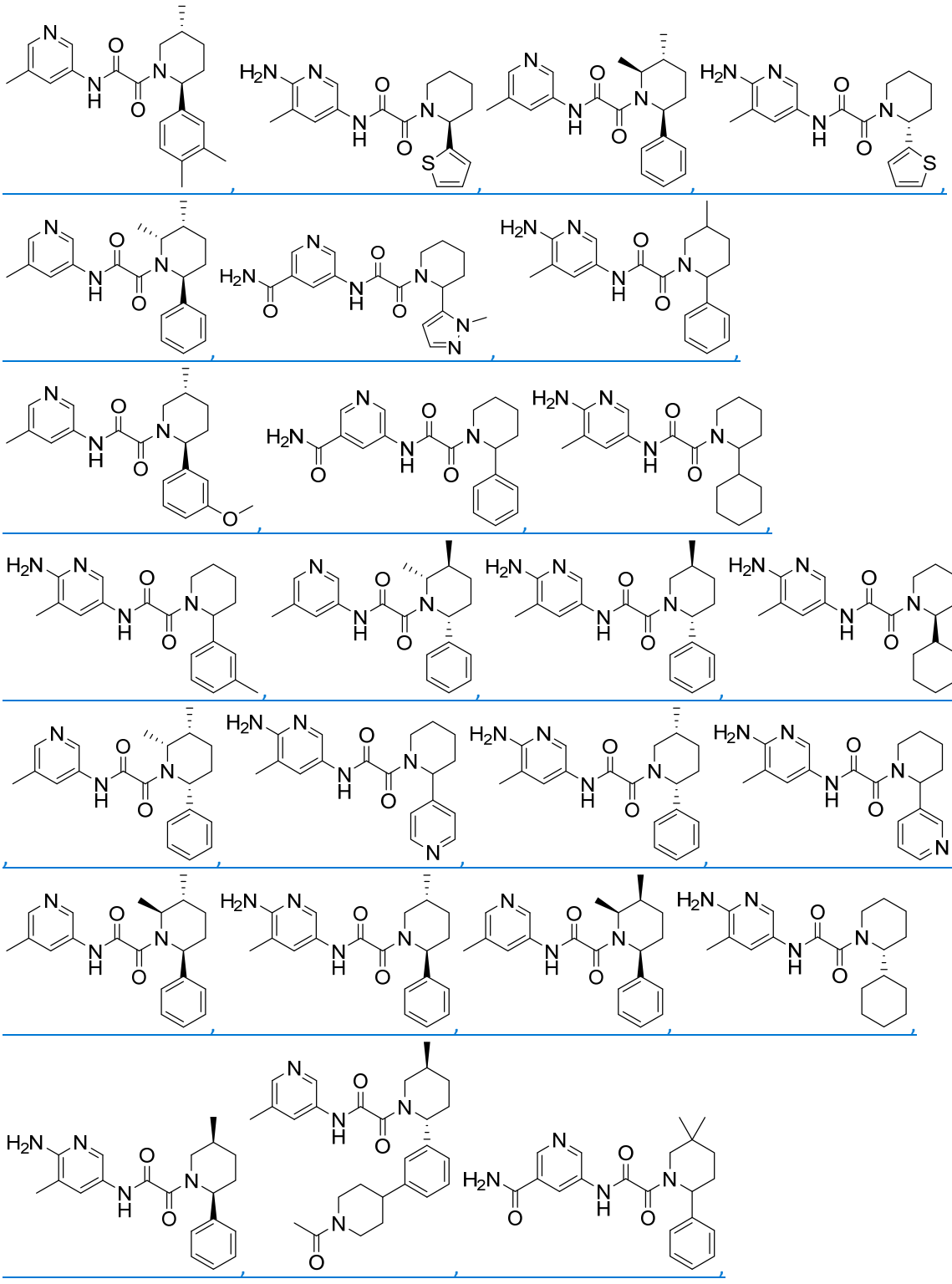
102. The compound of any one of claims 97 to 98 wherein R^6 is CH_3.

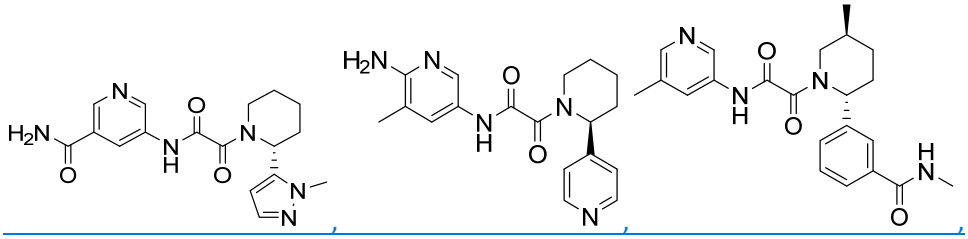
~~103. The compound of any one of claims 97 to 101 wherein R^7 is H.~~

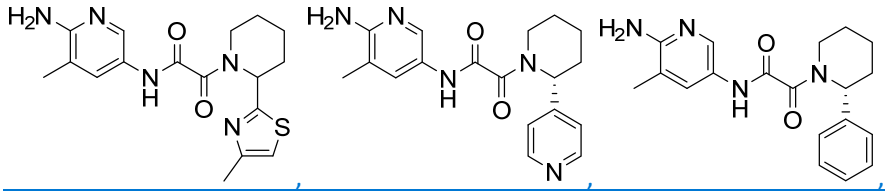
~~104. The compound of any one of claims 97 to 101 wherein R^7 is CH_3.~~

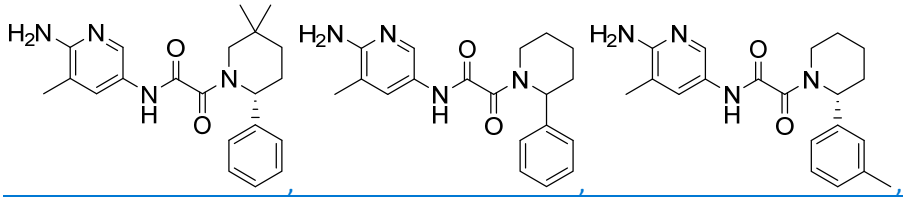
47~~105~~. The compound of any one of claims 1 to 46,~~104~~ or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of: ~~Table 1.~~

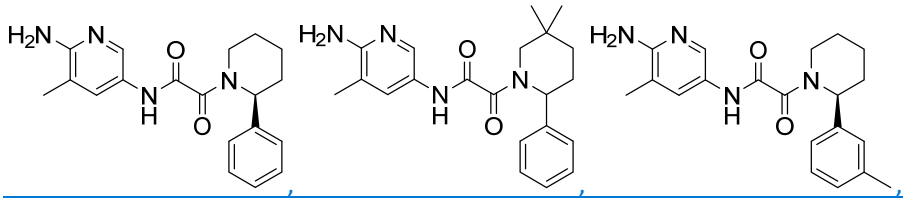


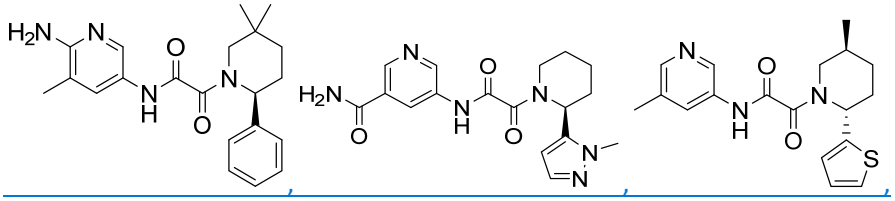


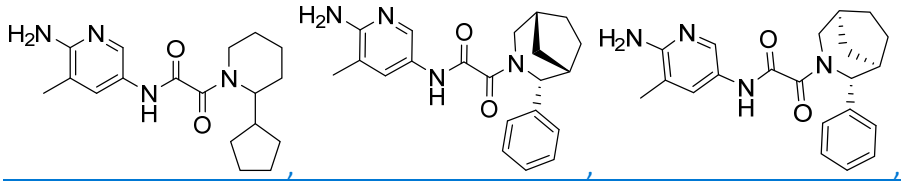


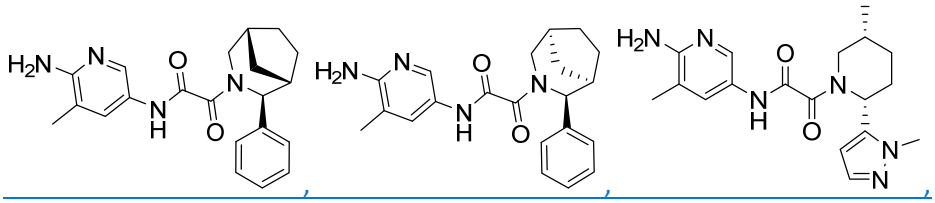


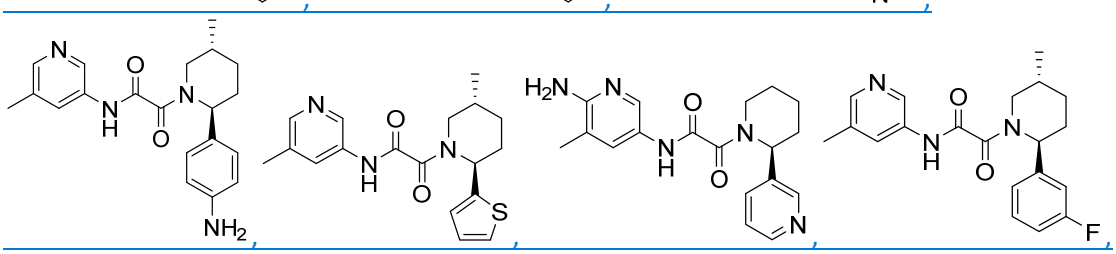


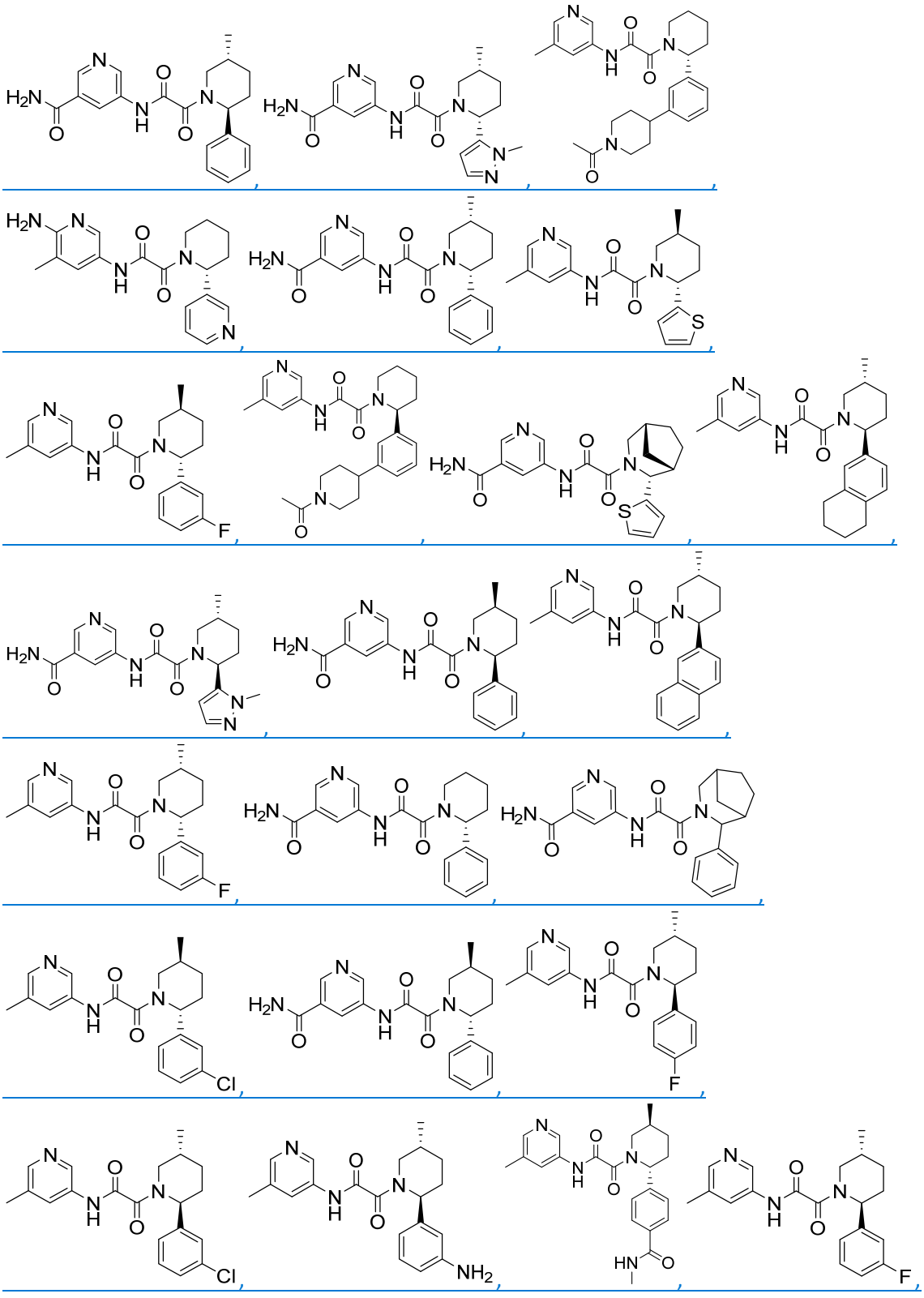


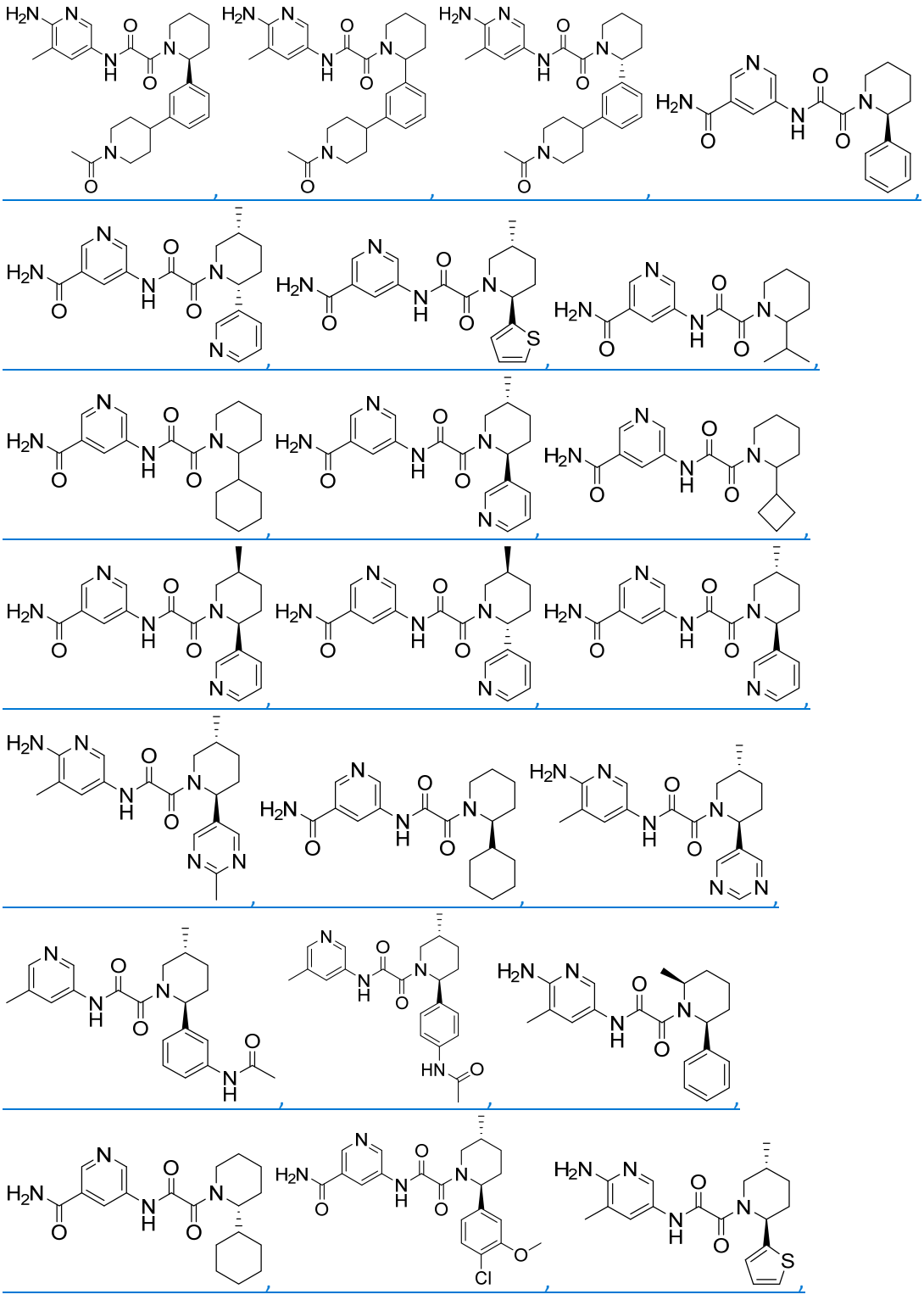


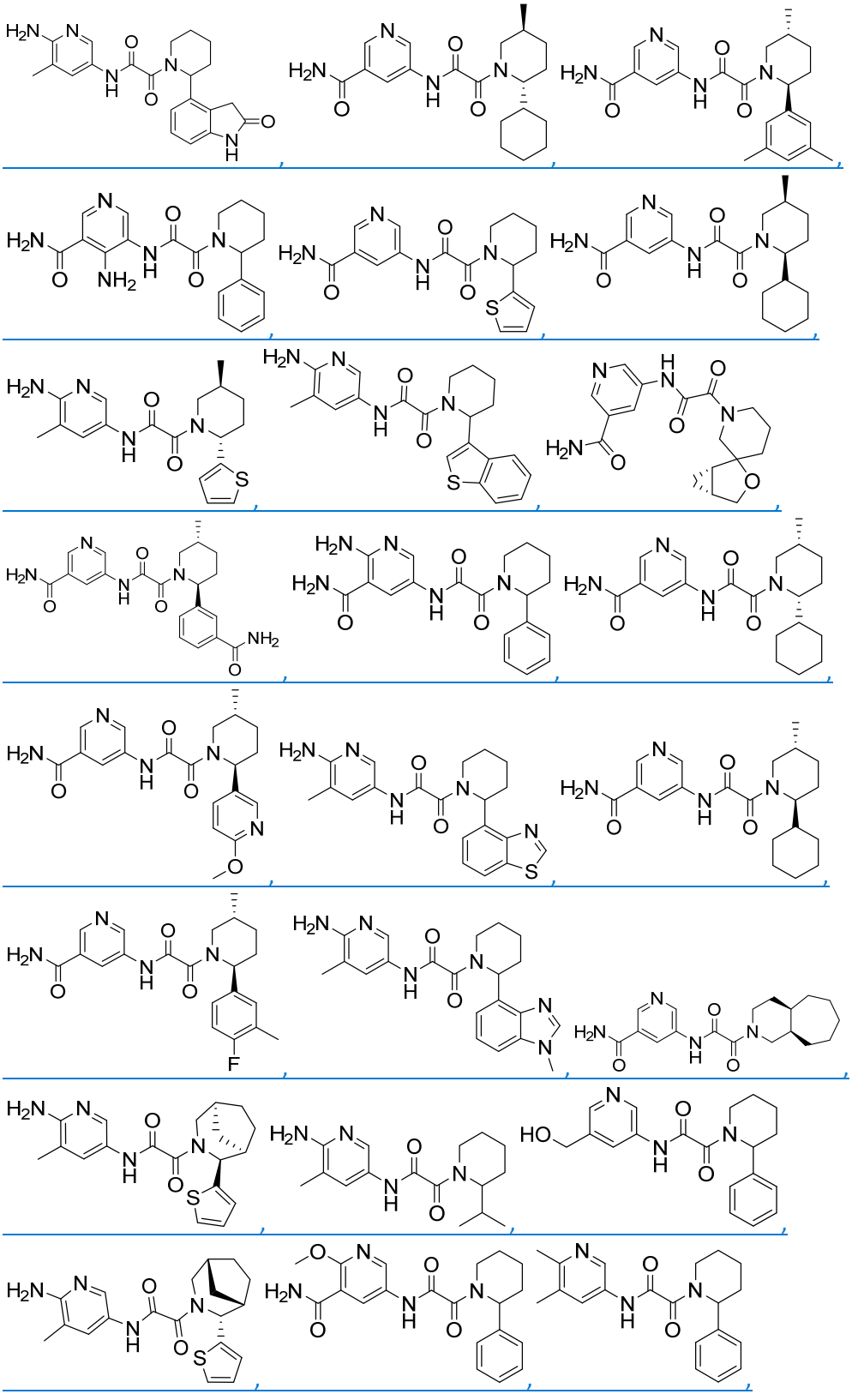


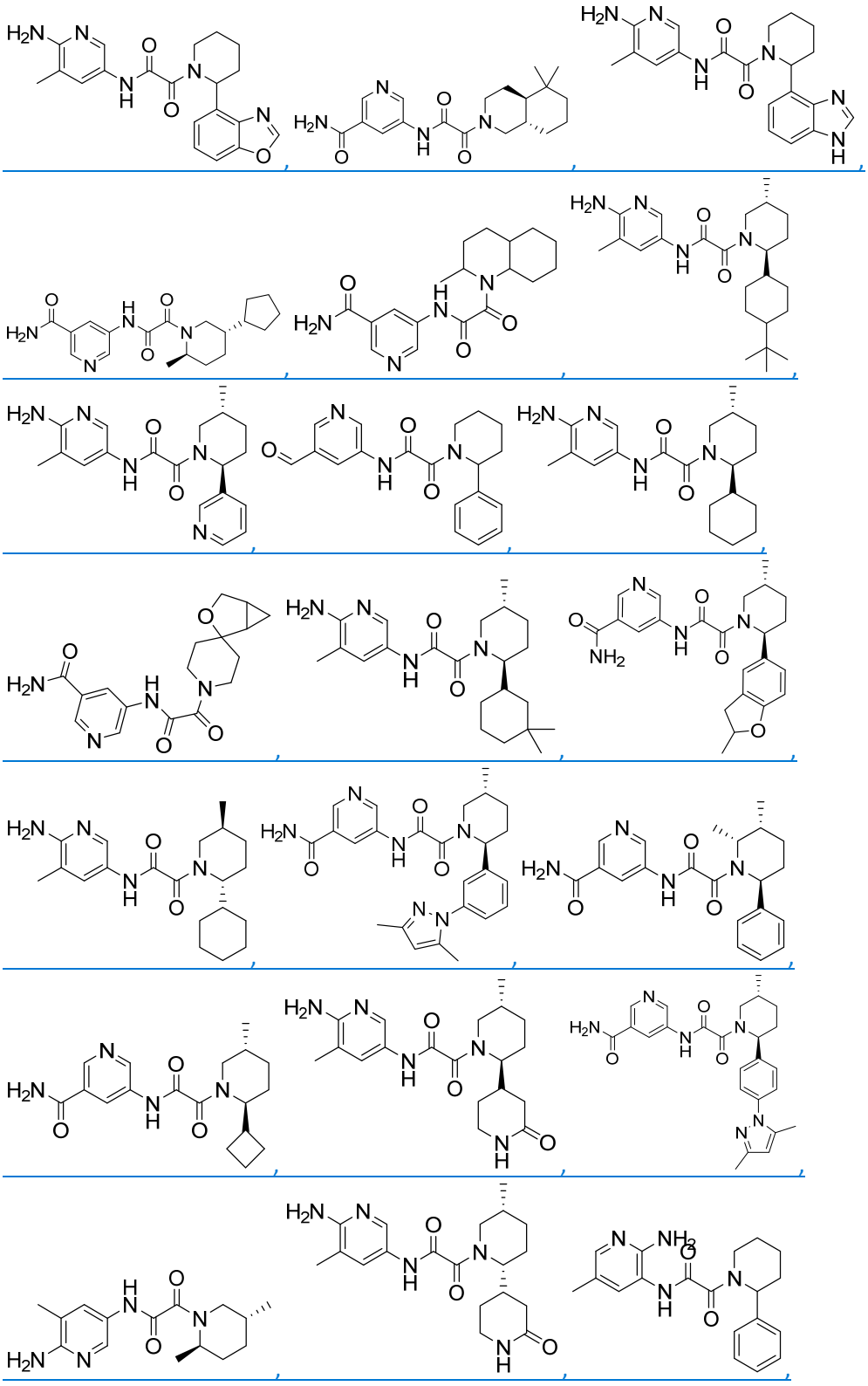


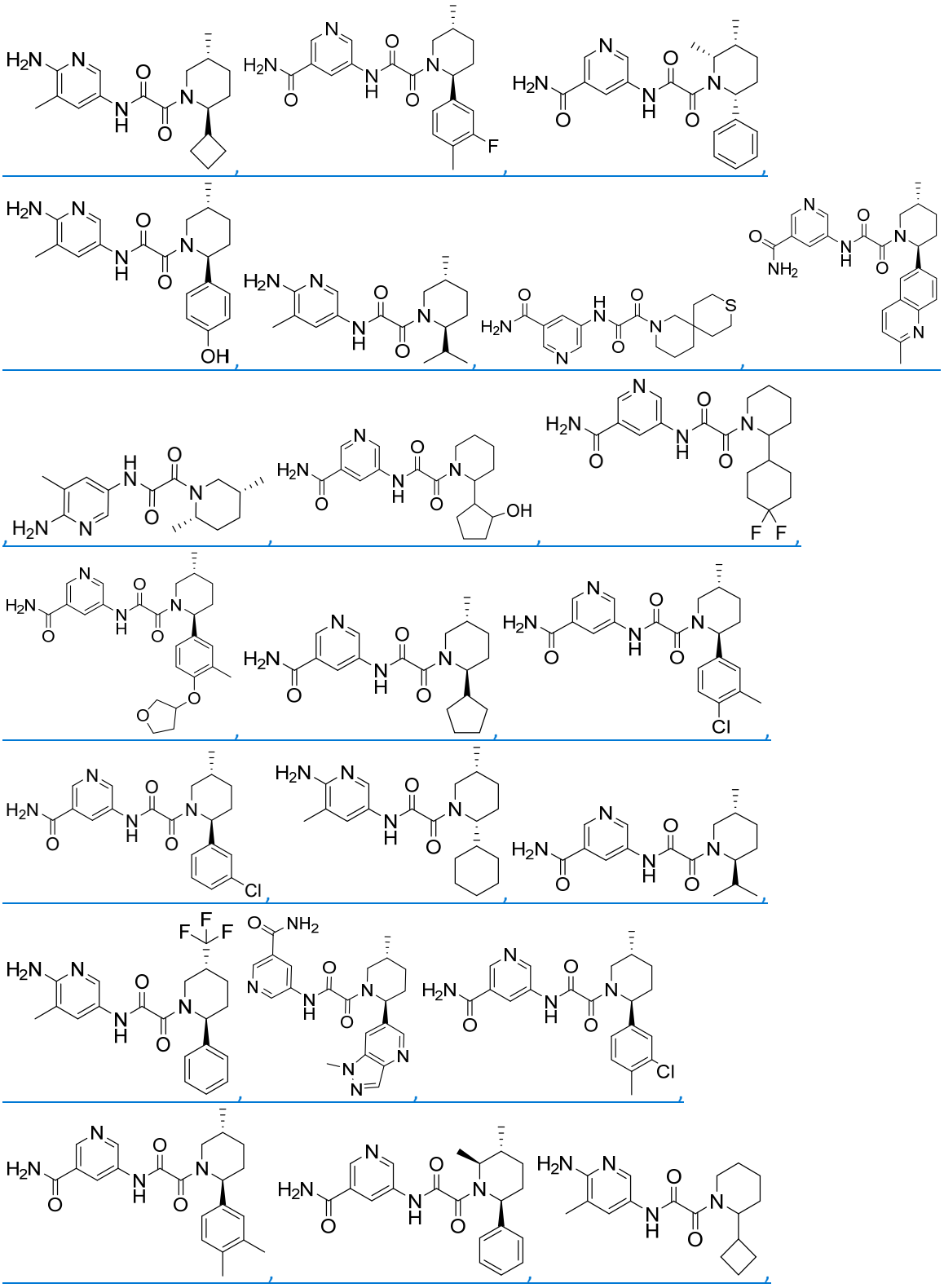


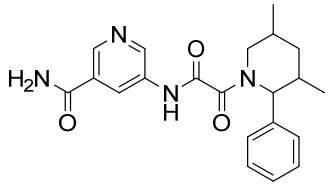
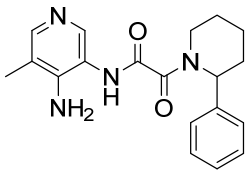
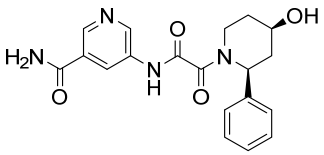
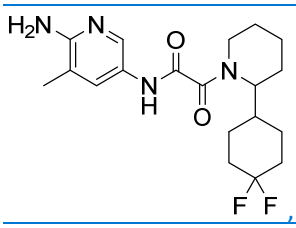
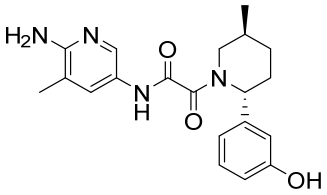
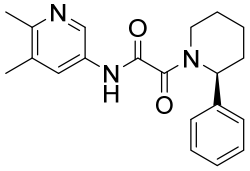
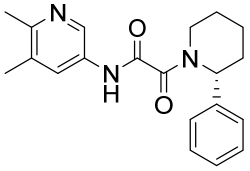
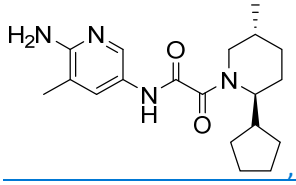
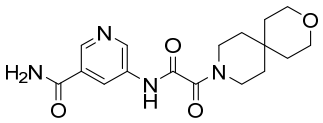
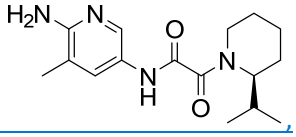
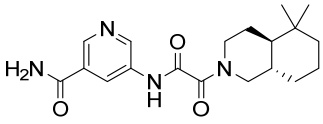
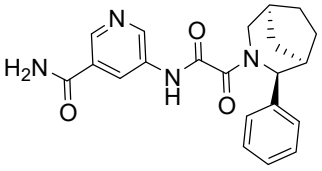
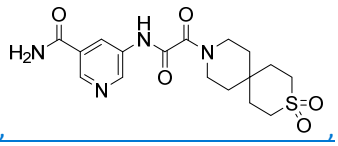
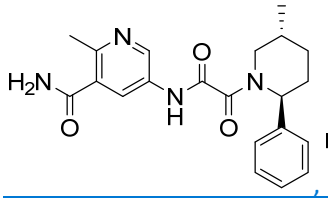
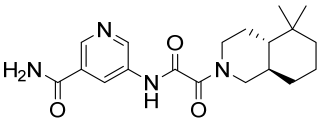
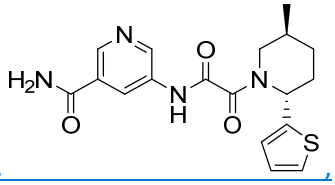
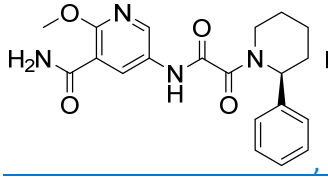
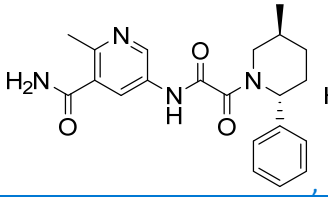


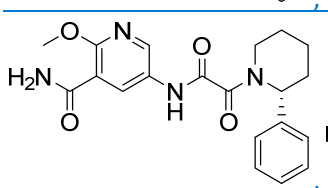
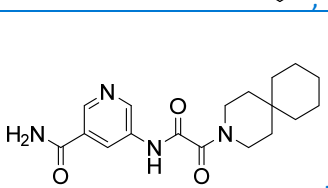
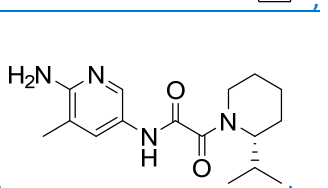
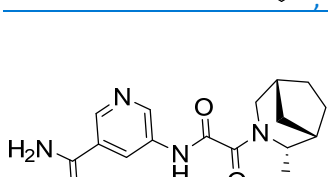
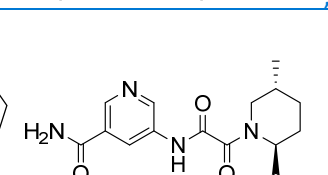
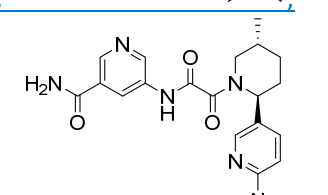
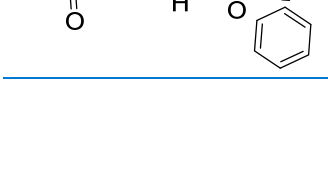
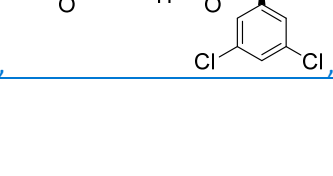
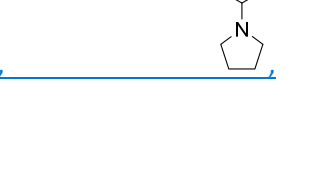


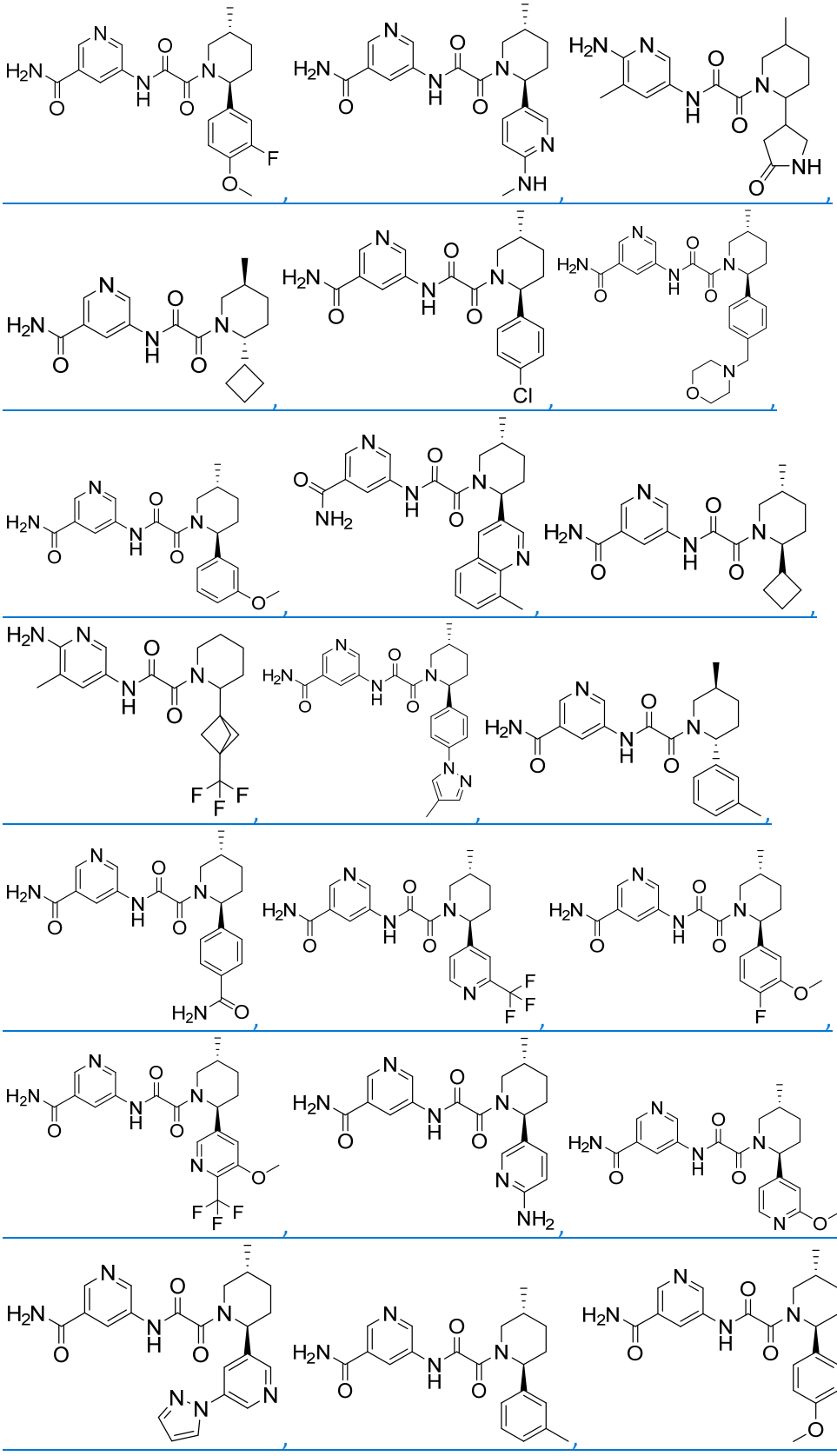


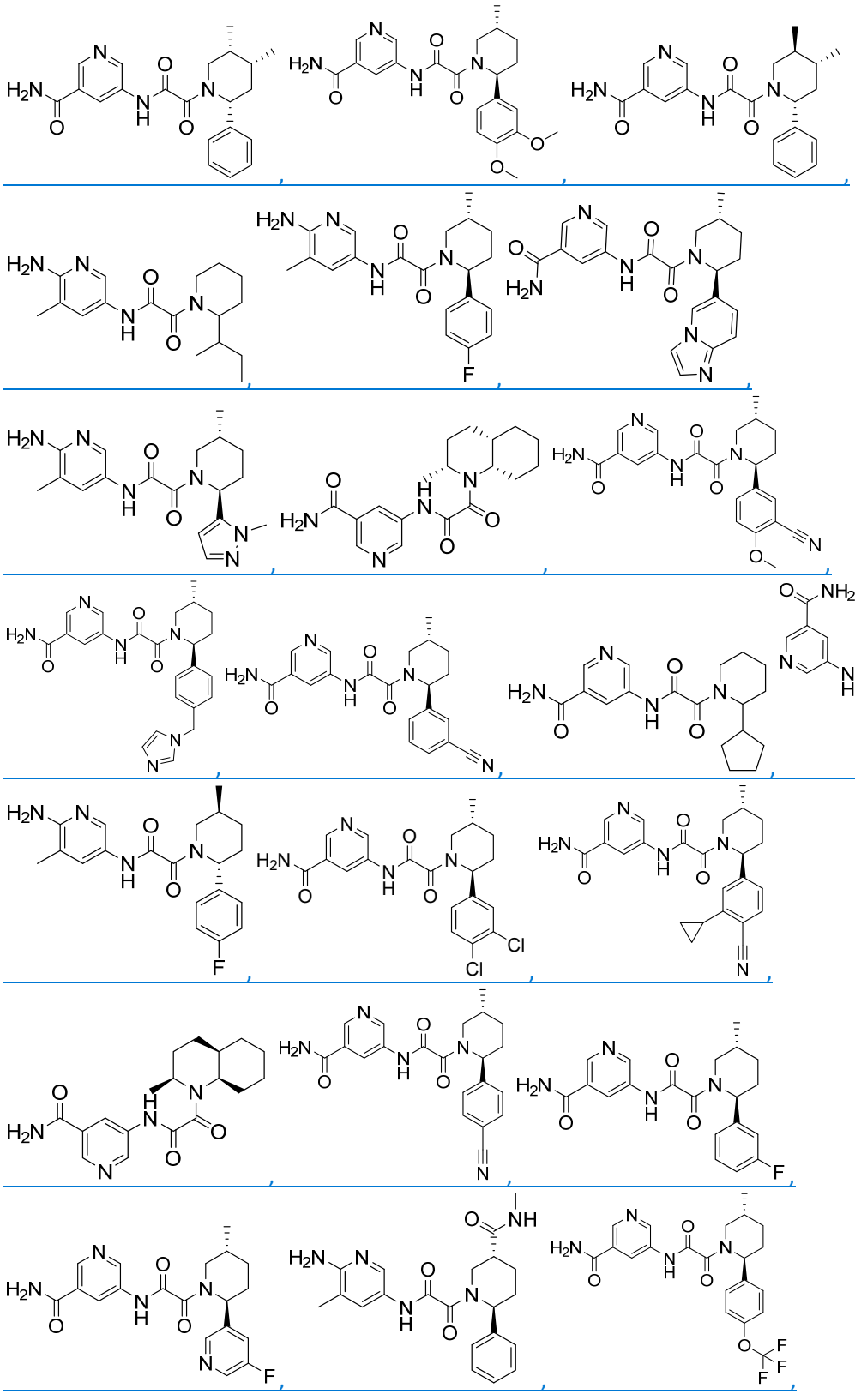


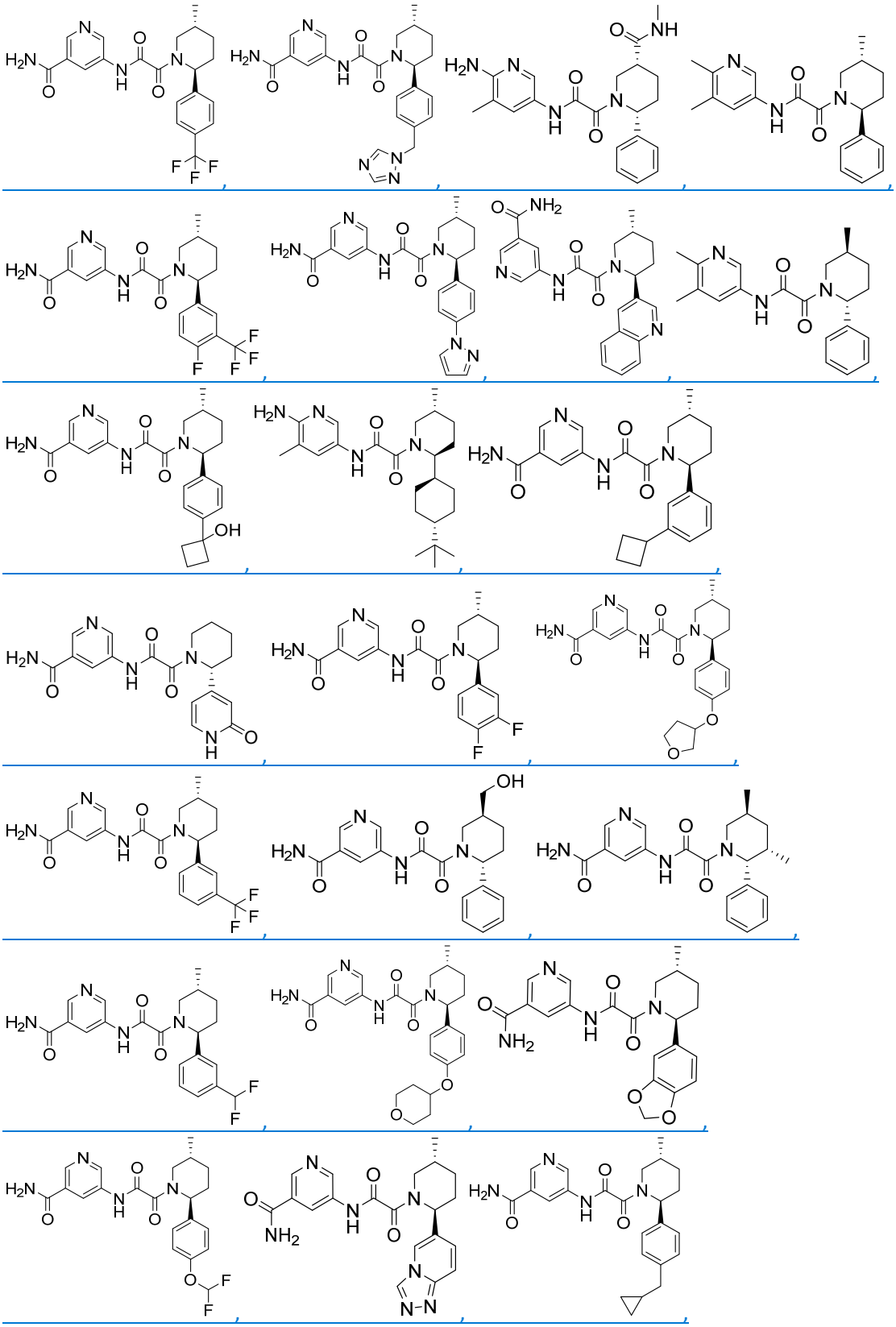


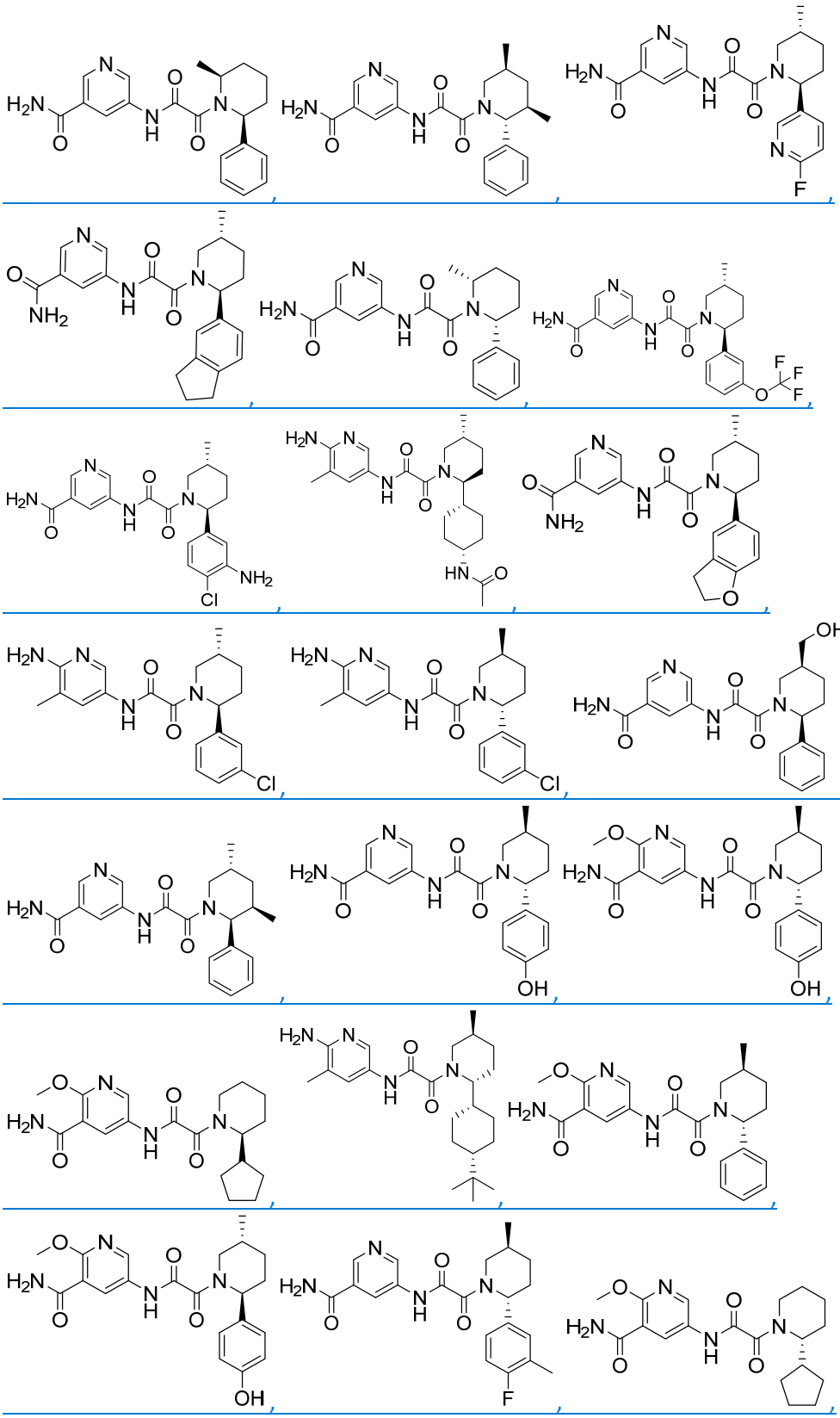



















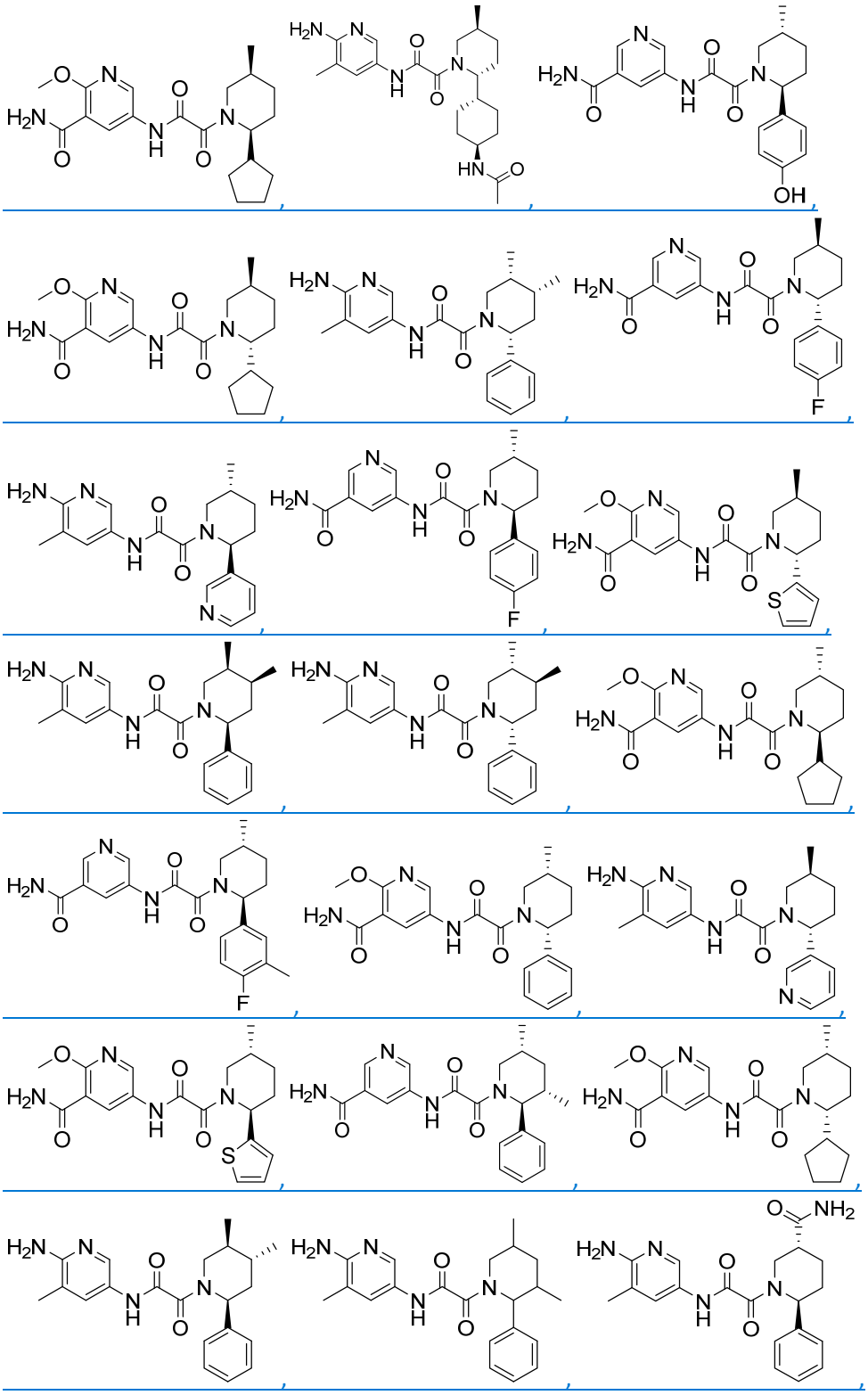










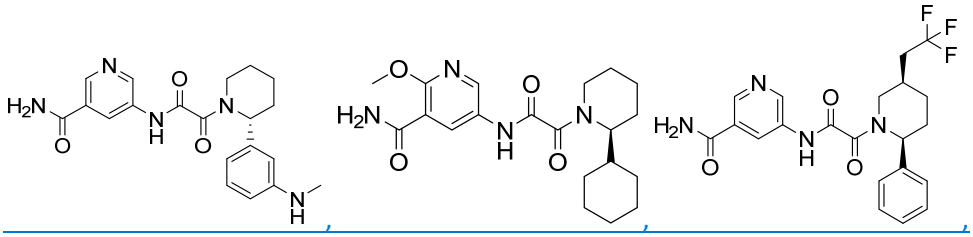


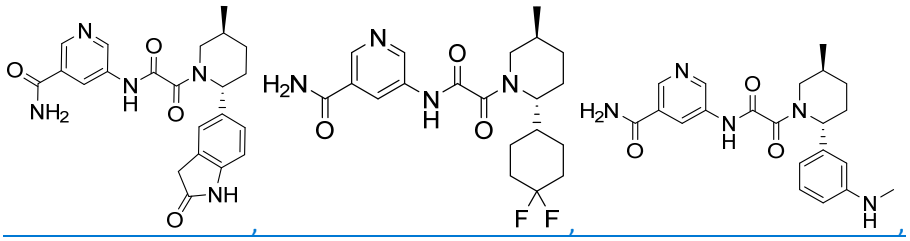


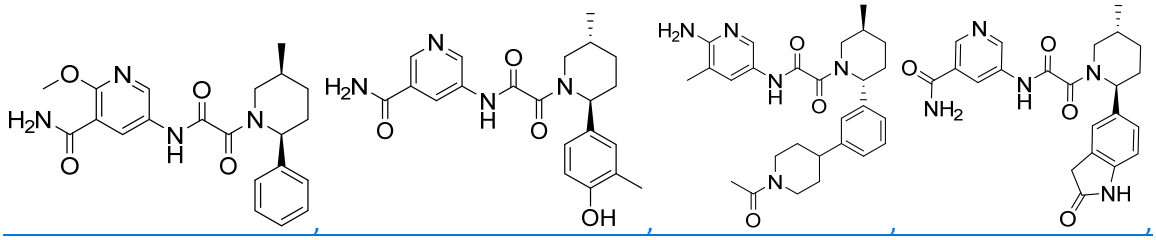


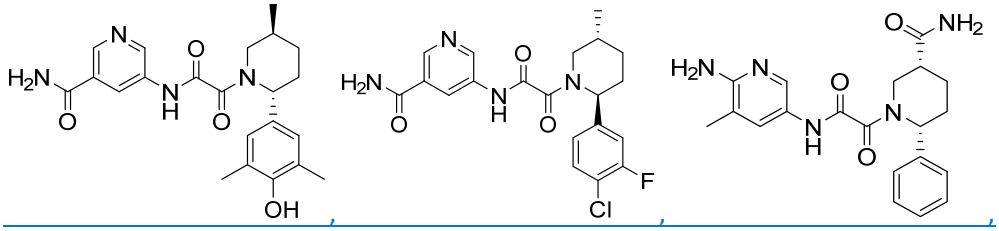


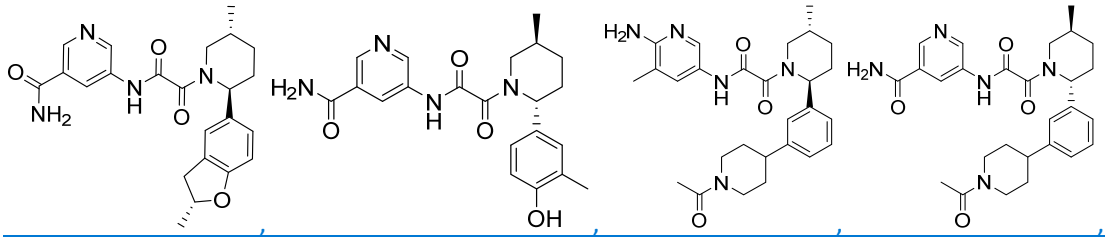


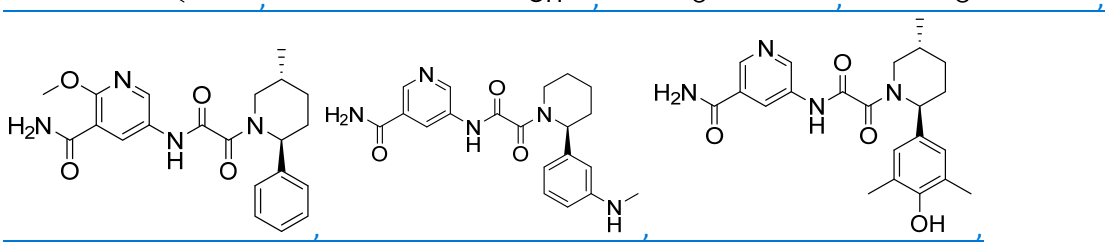


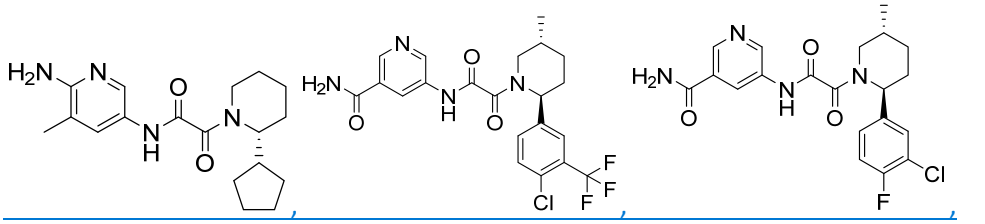


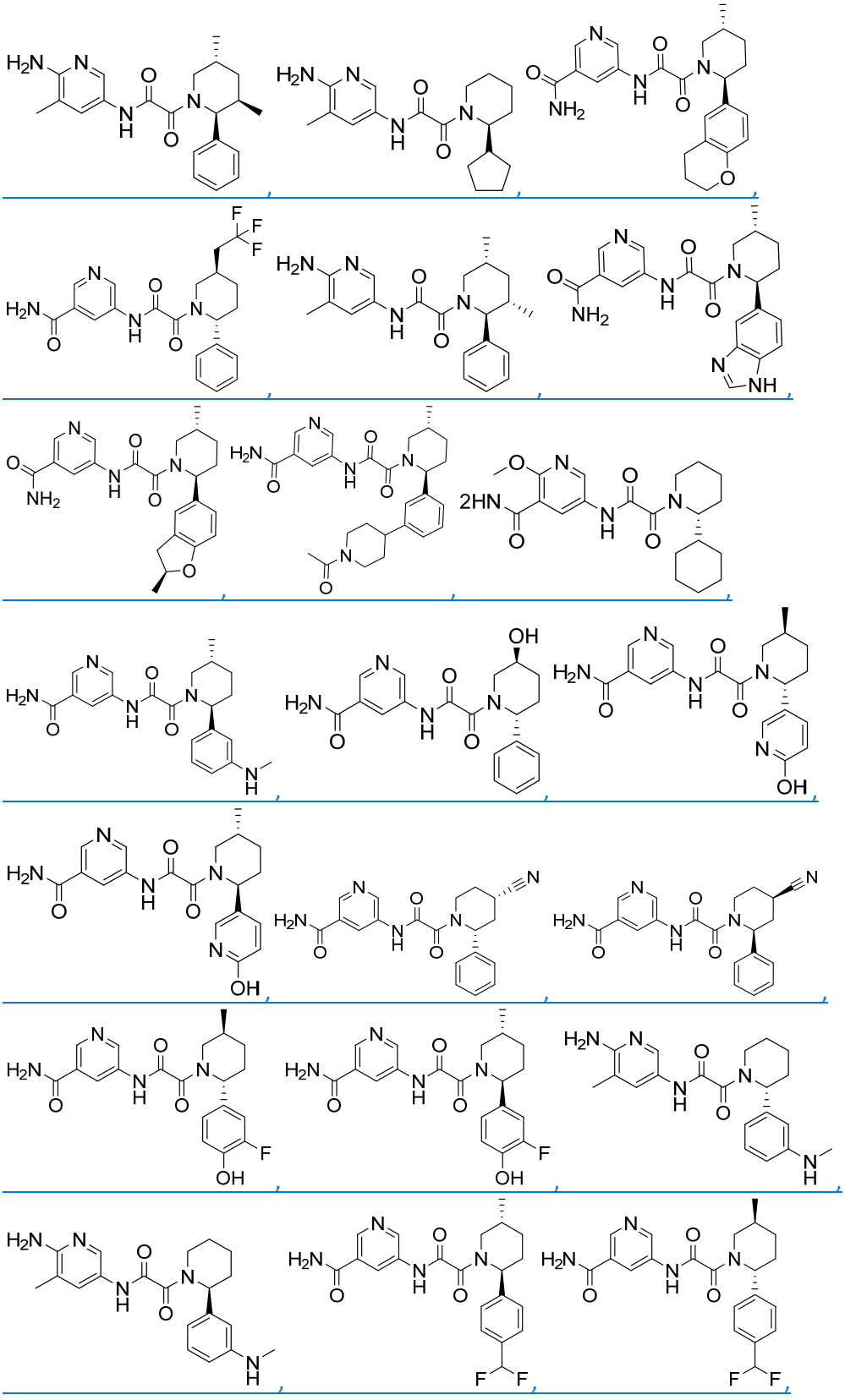


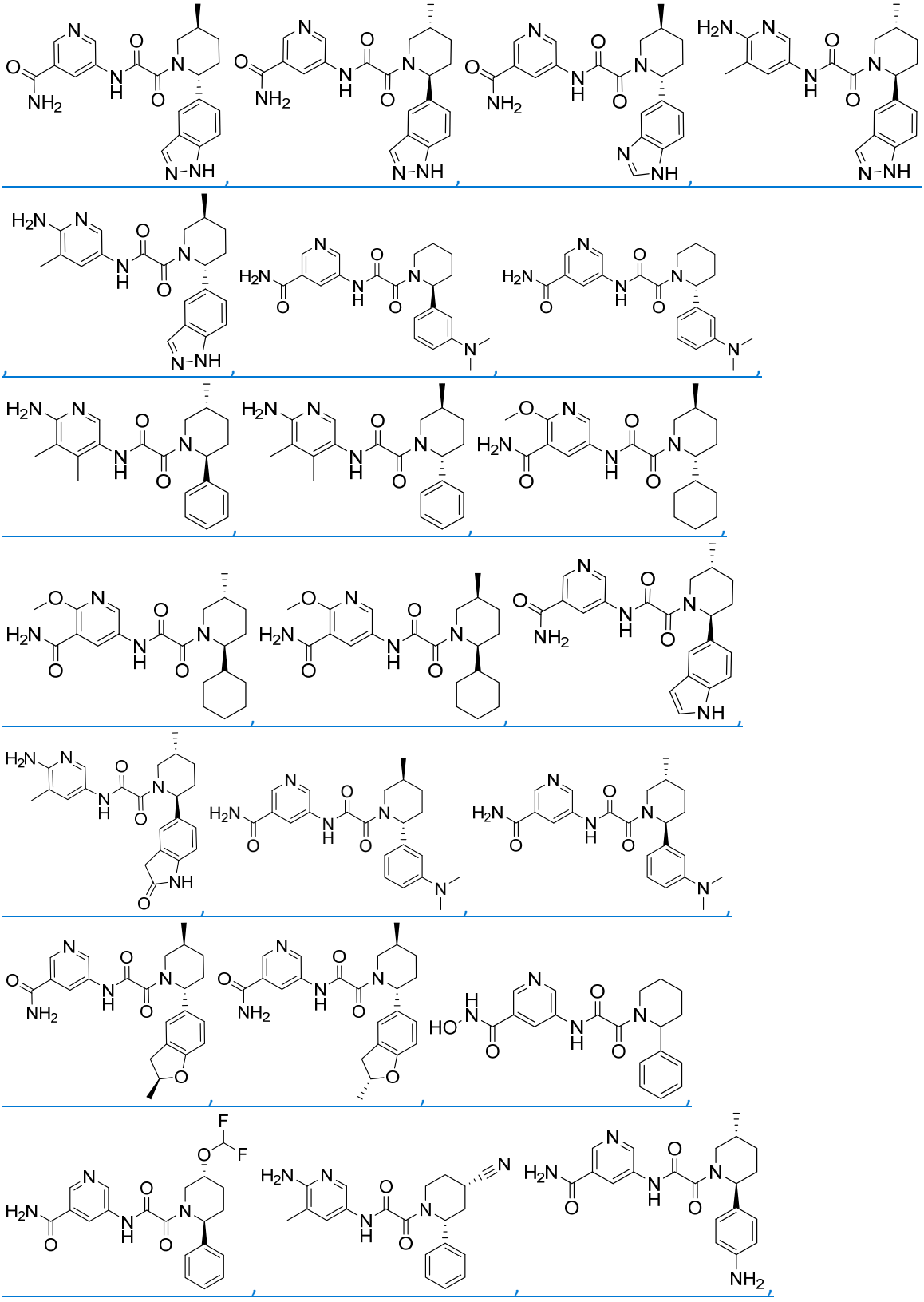


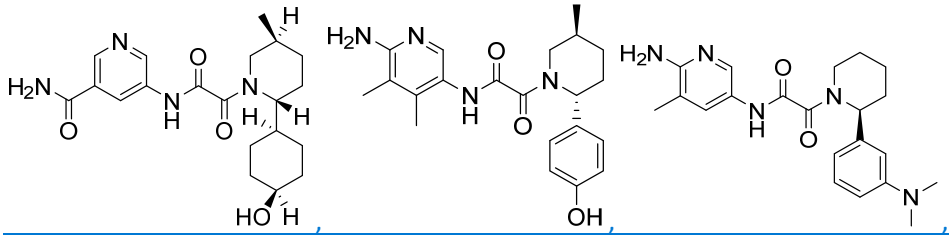
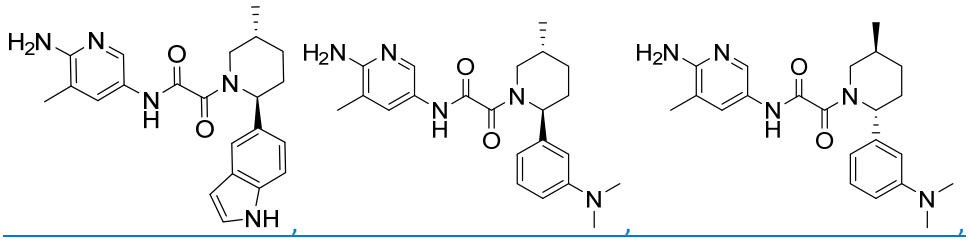
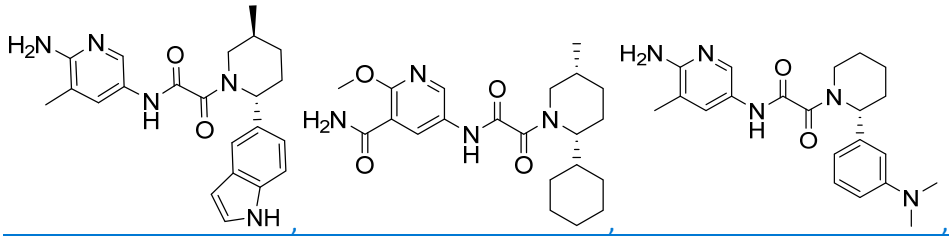
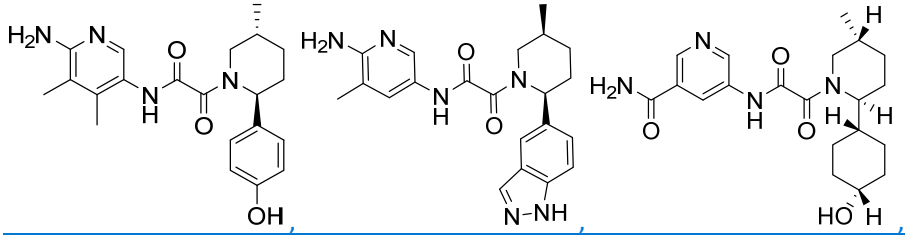
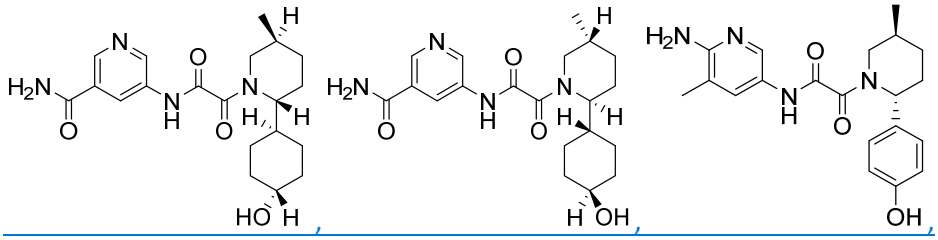
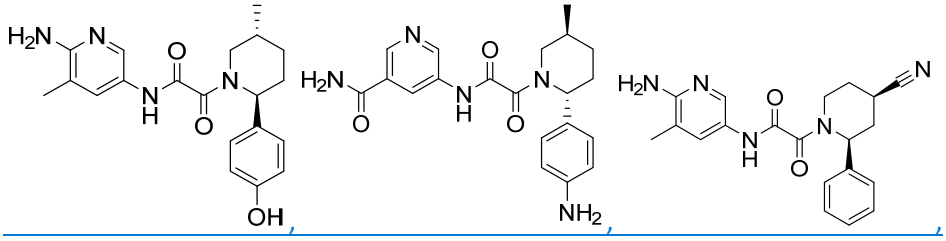
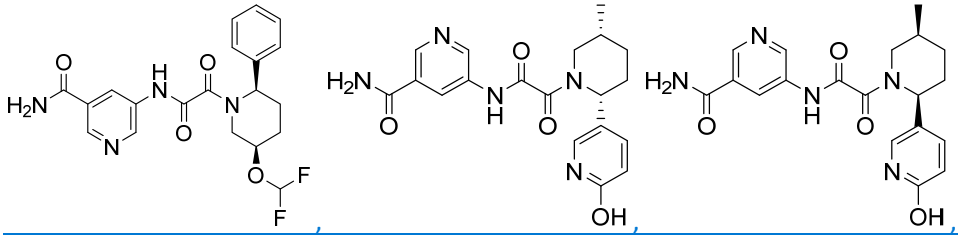


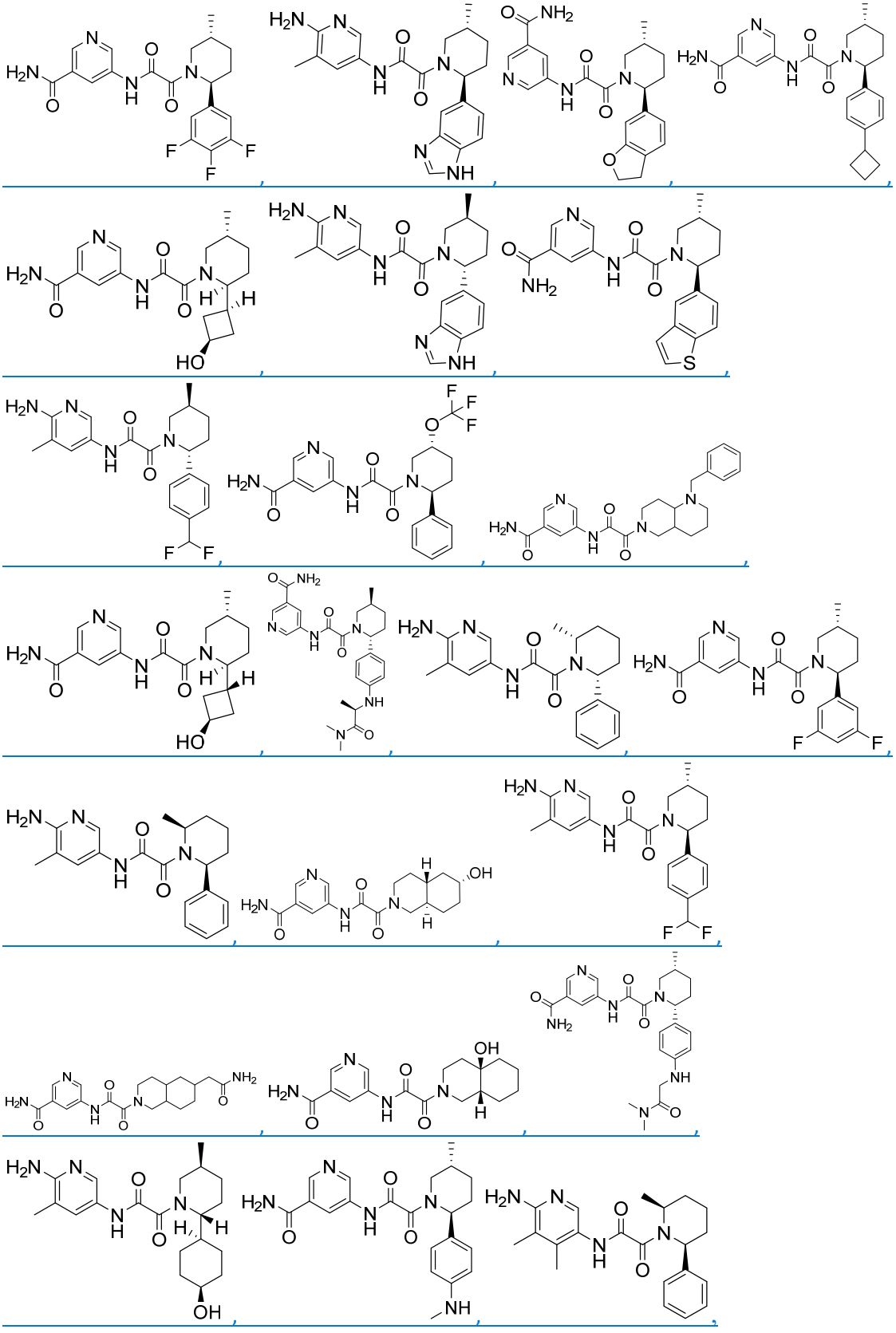


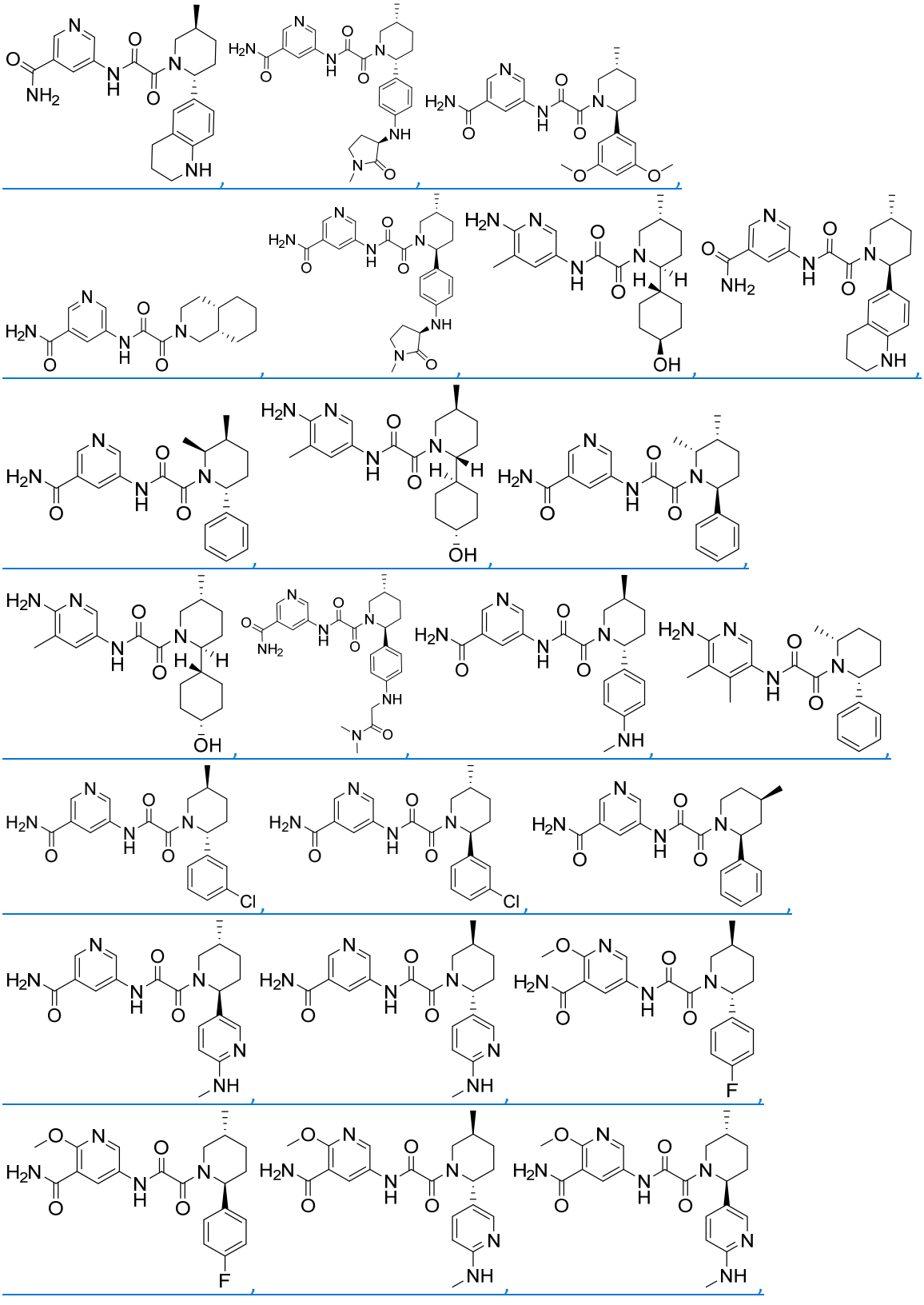


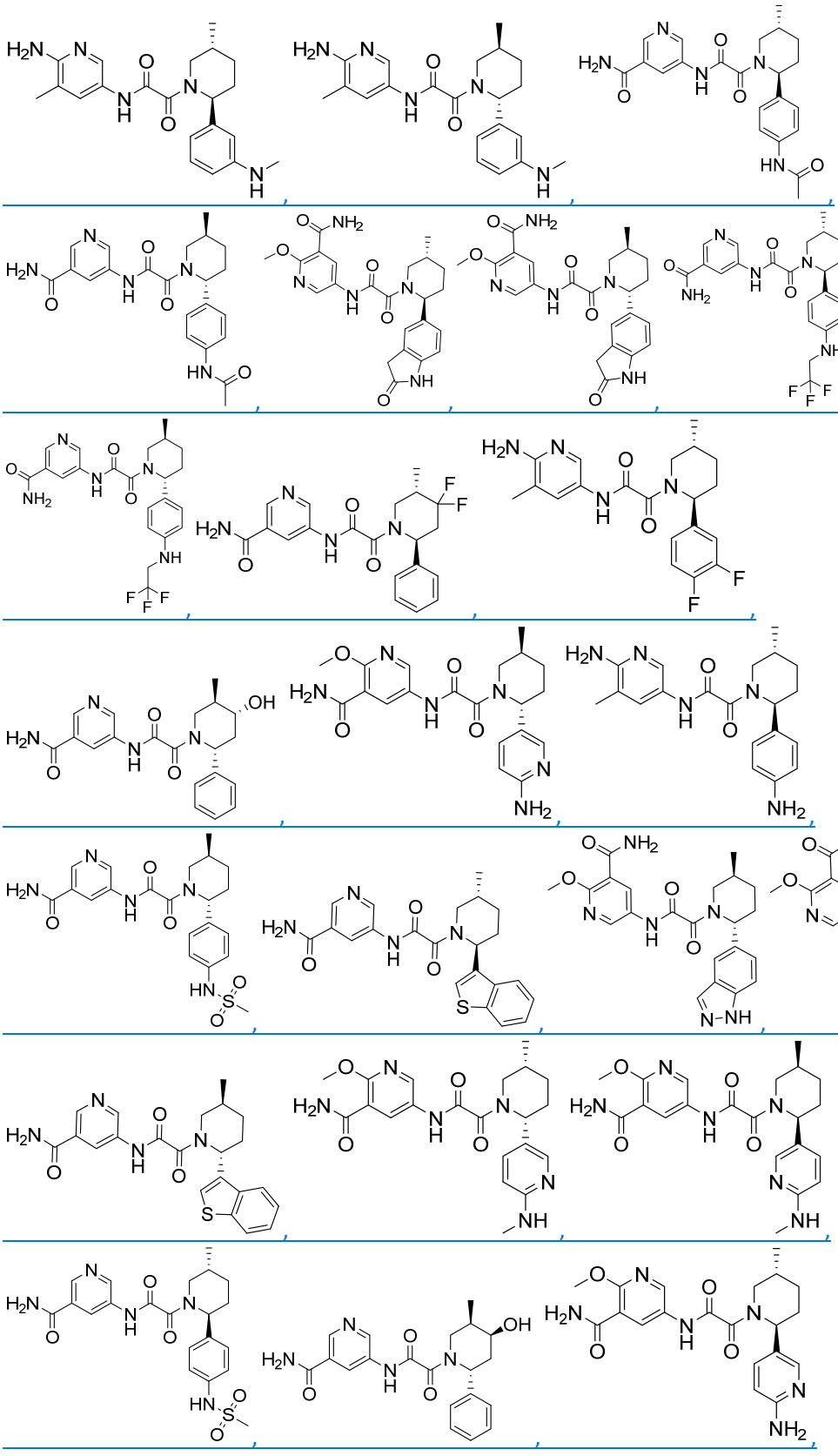


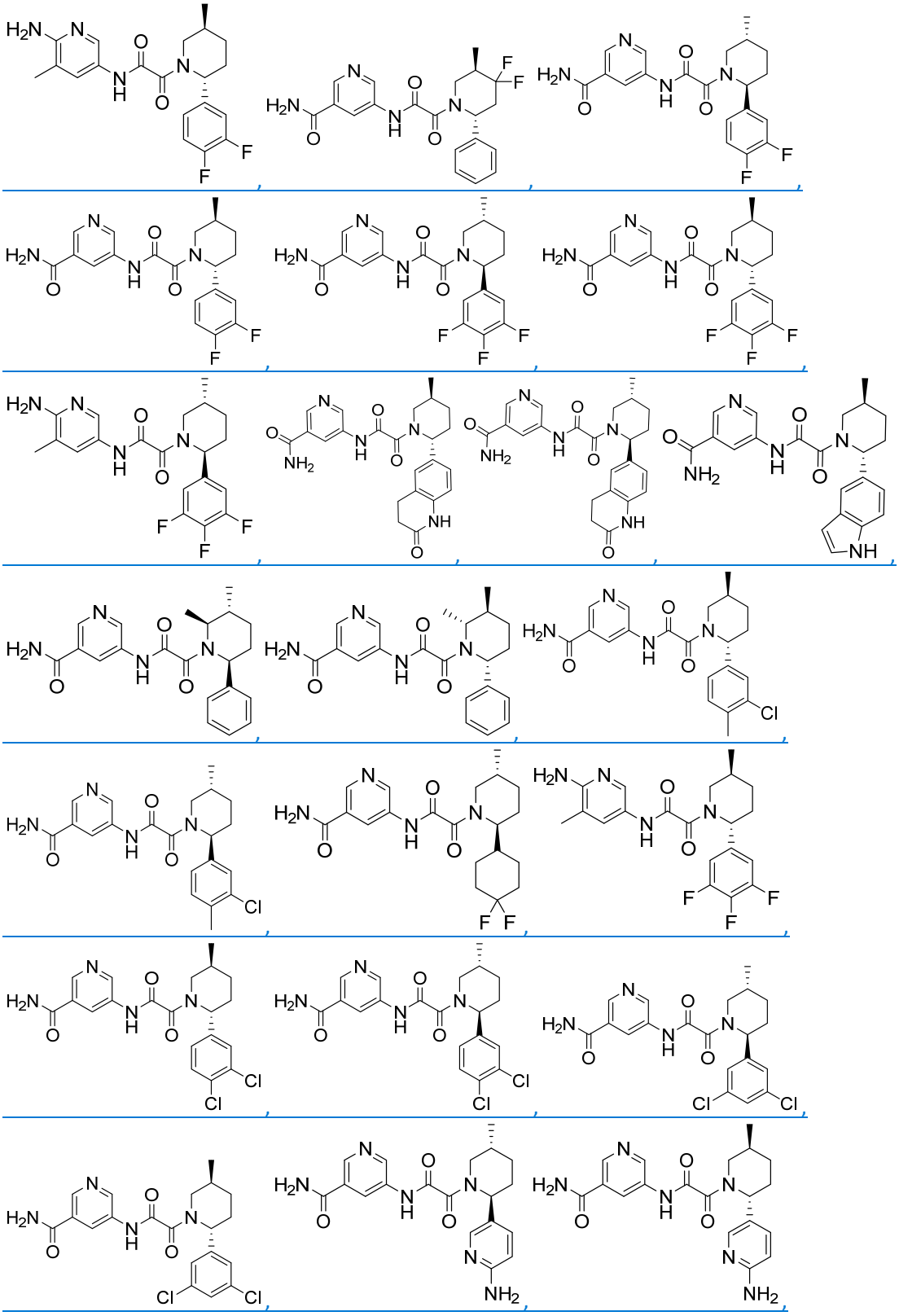


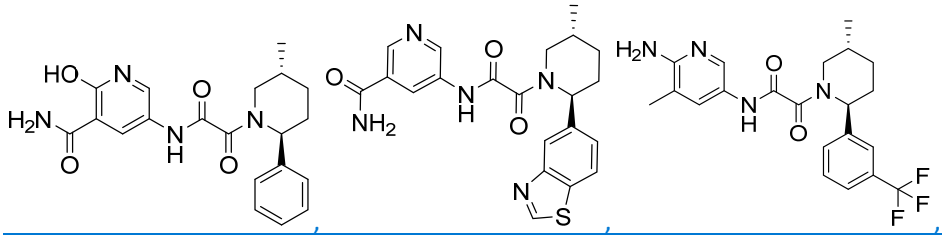
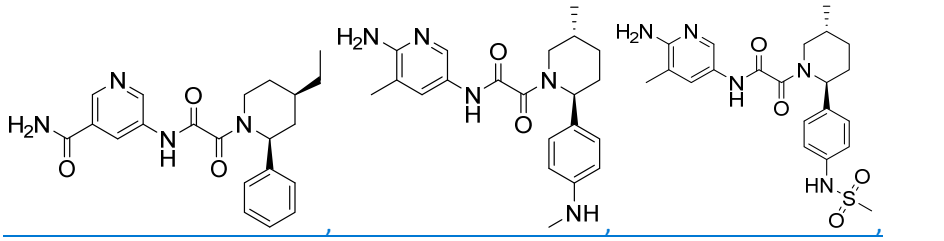
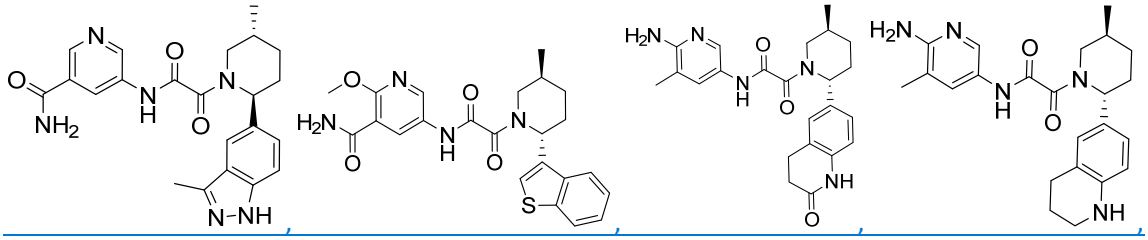
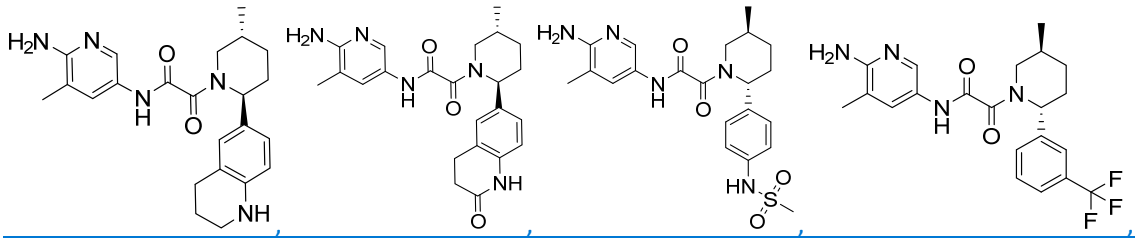
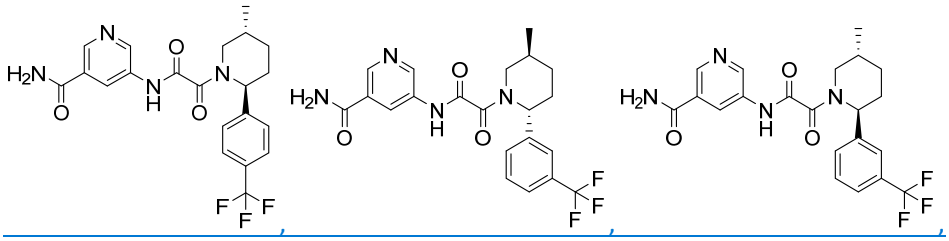
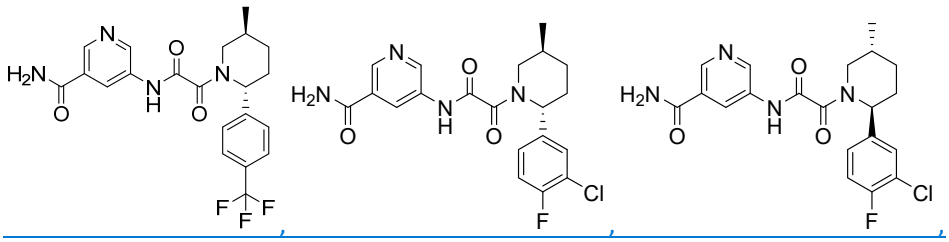
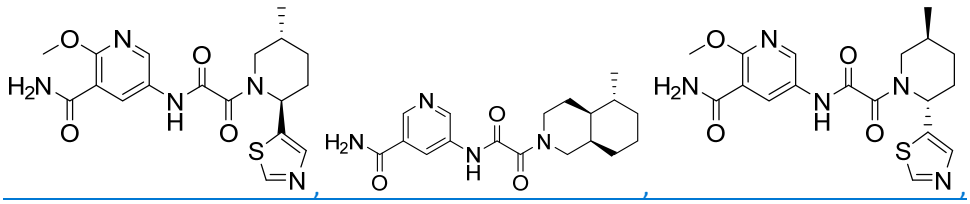








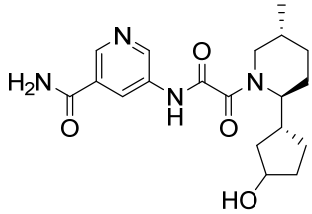
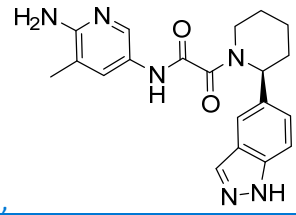
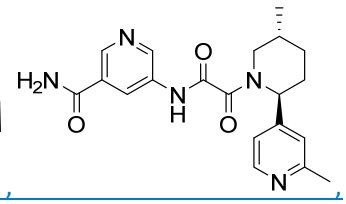


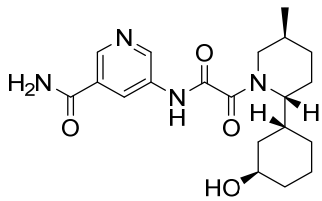
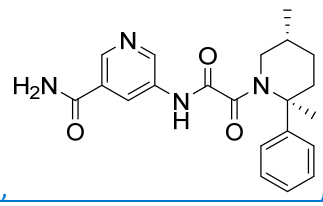
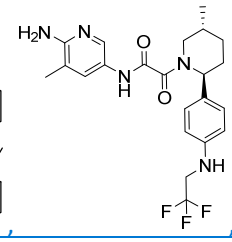
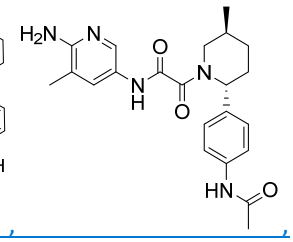


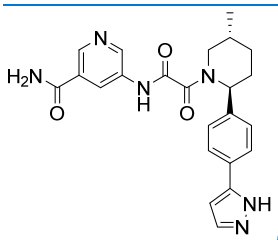
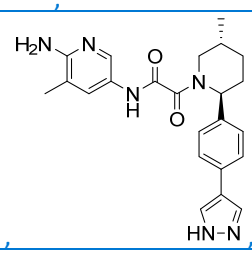
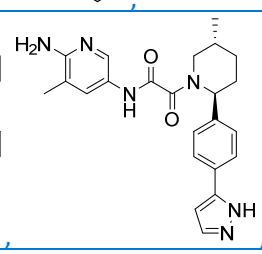
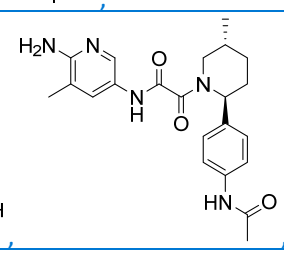


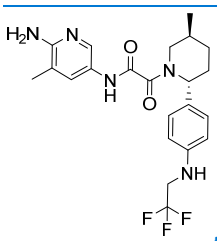
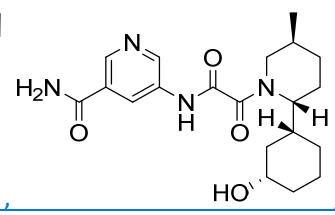
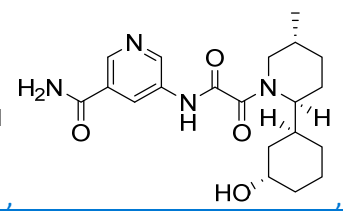


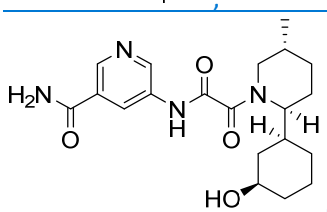
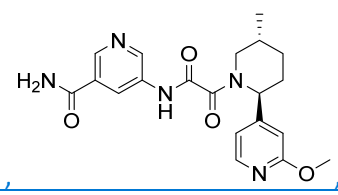
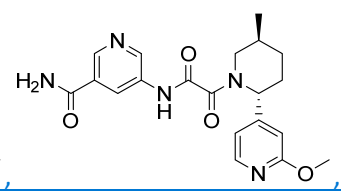








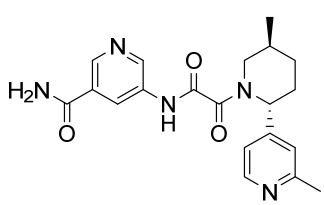
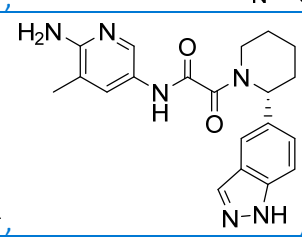
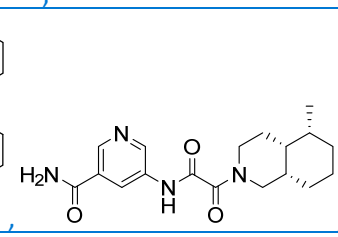




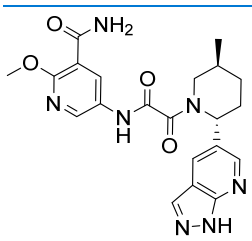
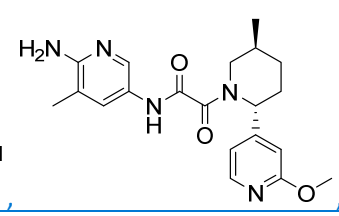
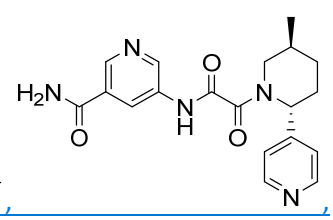





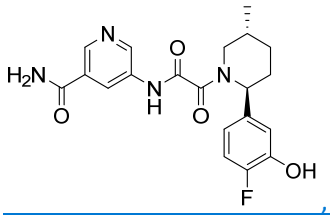
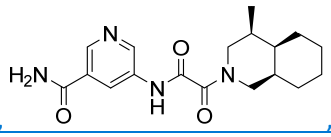
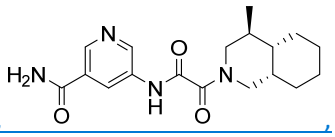
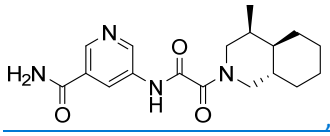
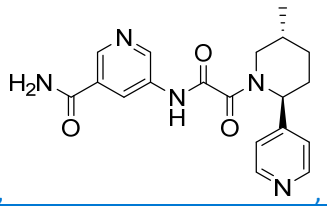
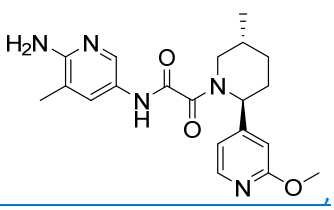
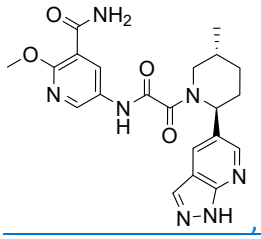
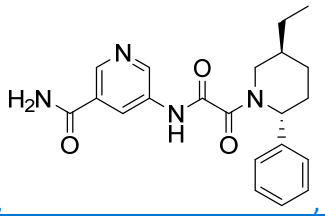
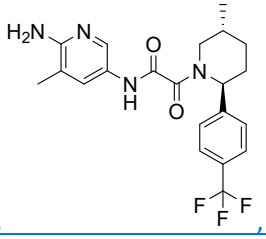
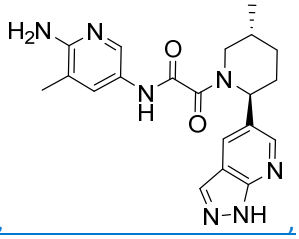
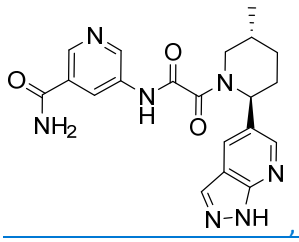
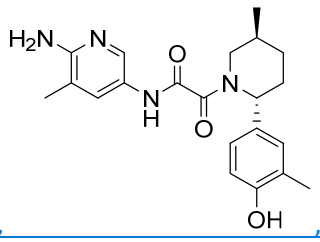
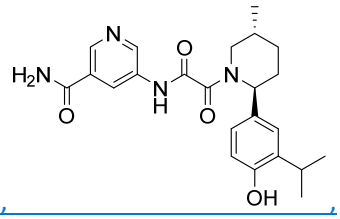
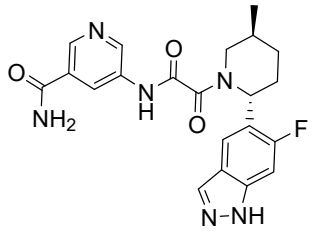
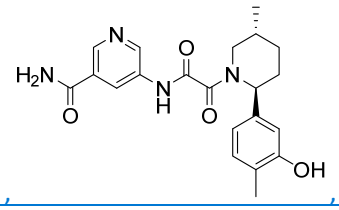
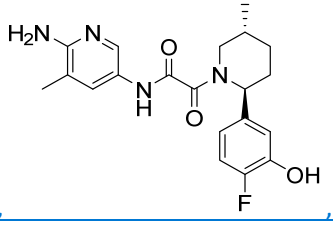
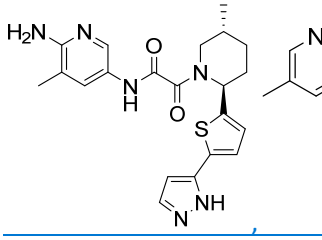
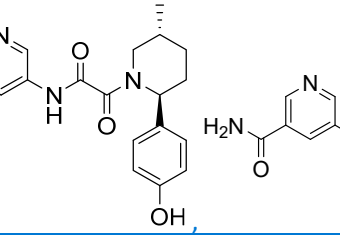
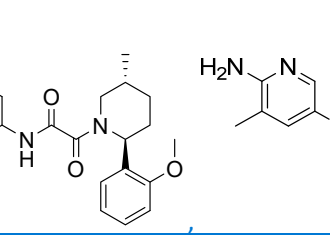
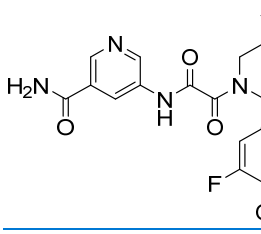
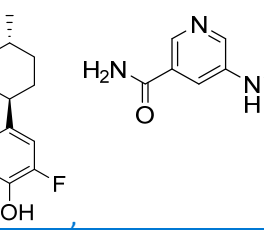
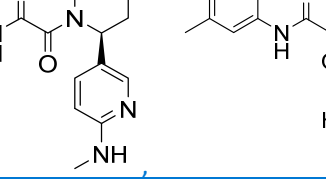
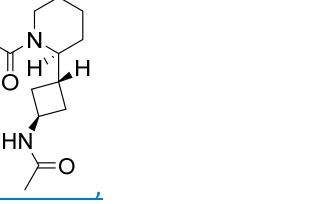





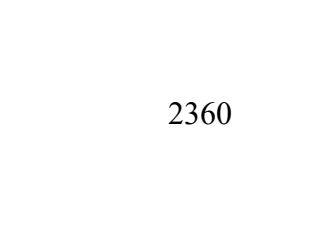




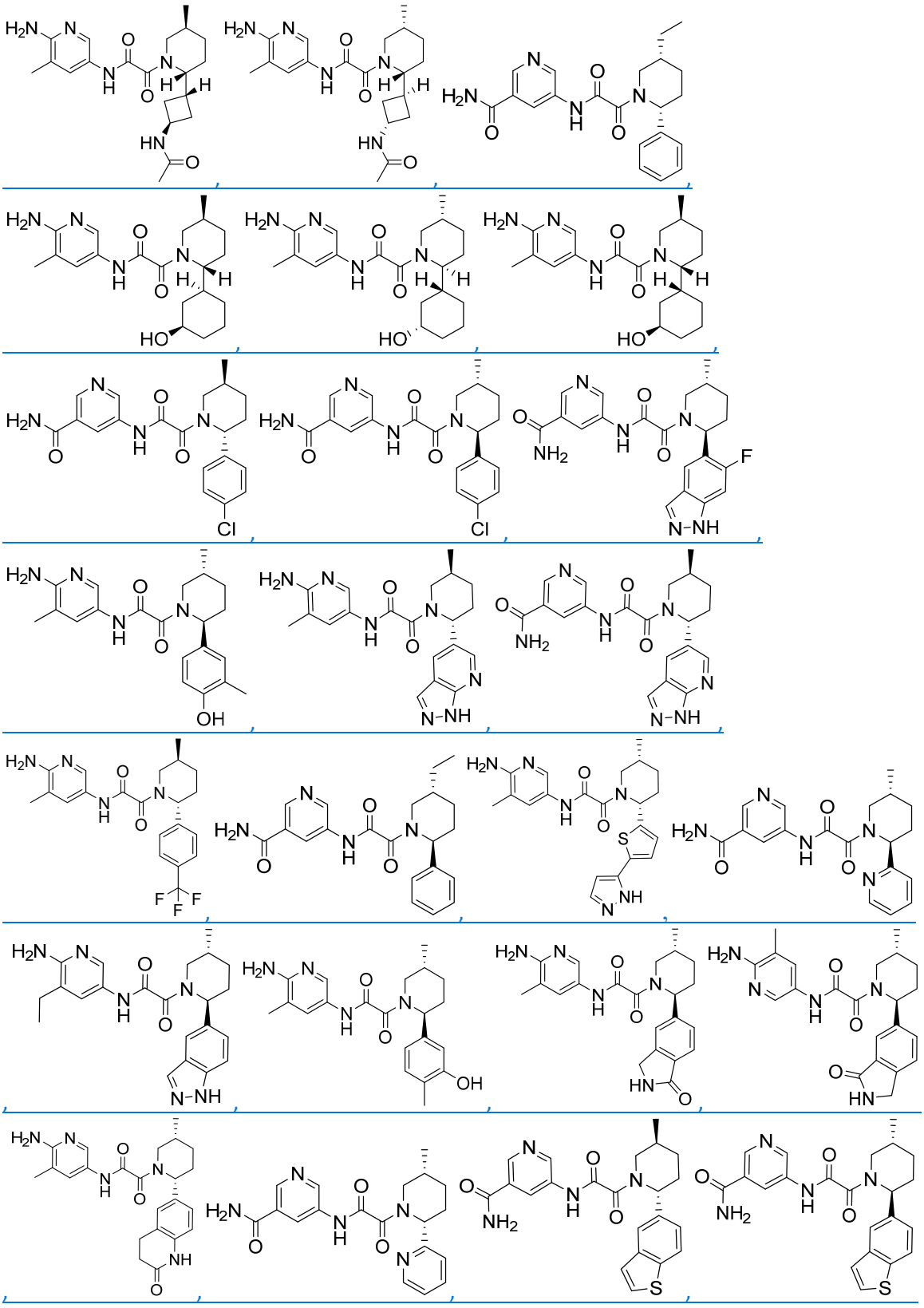




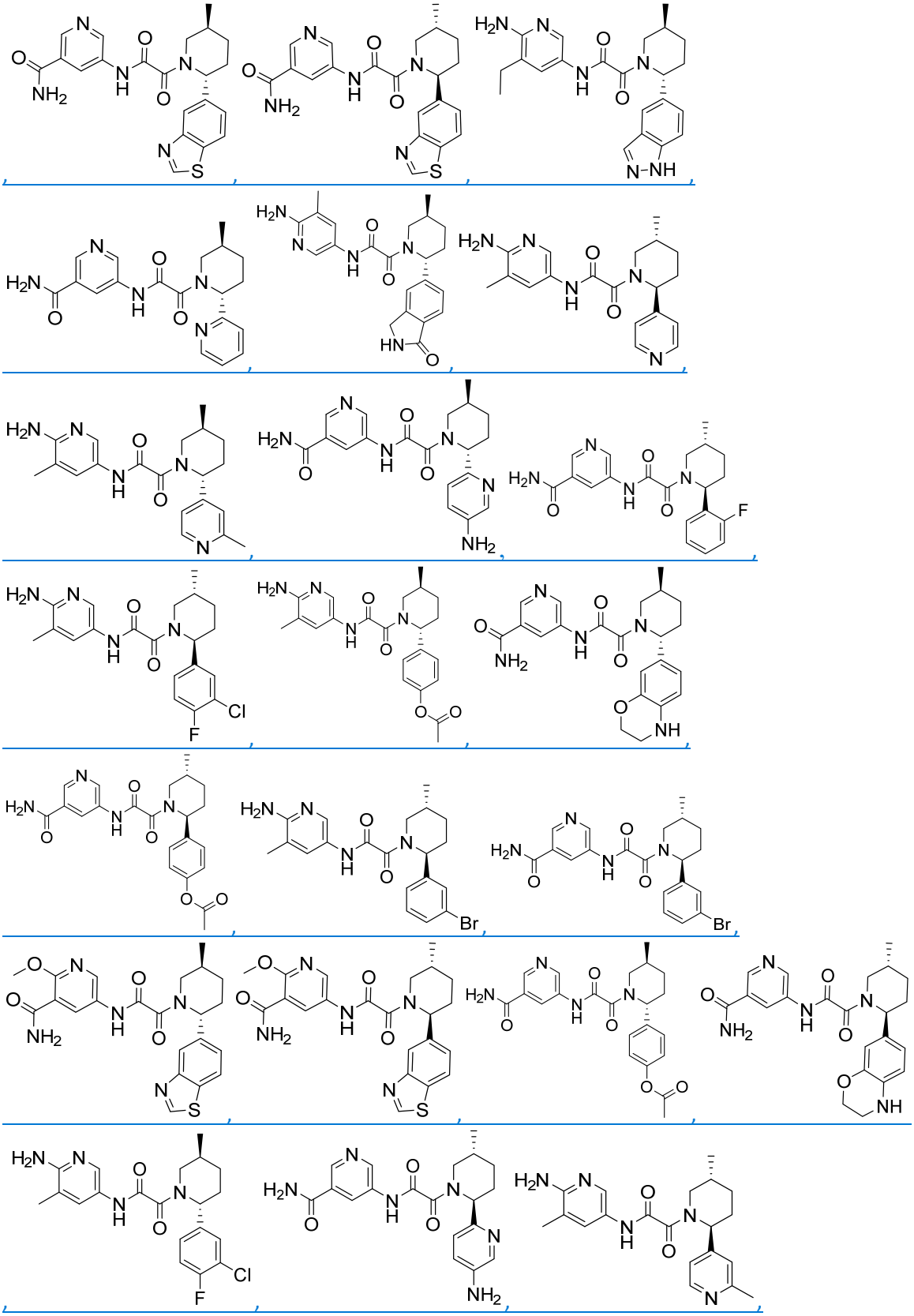




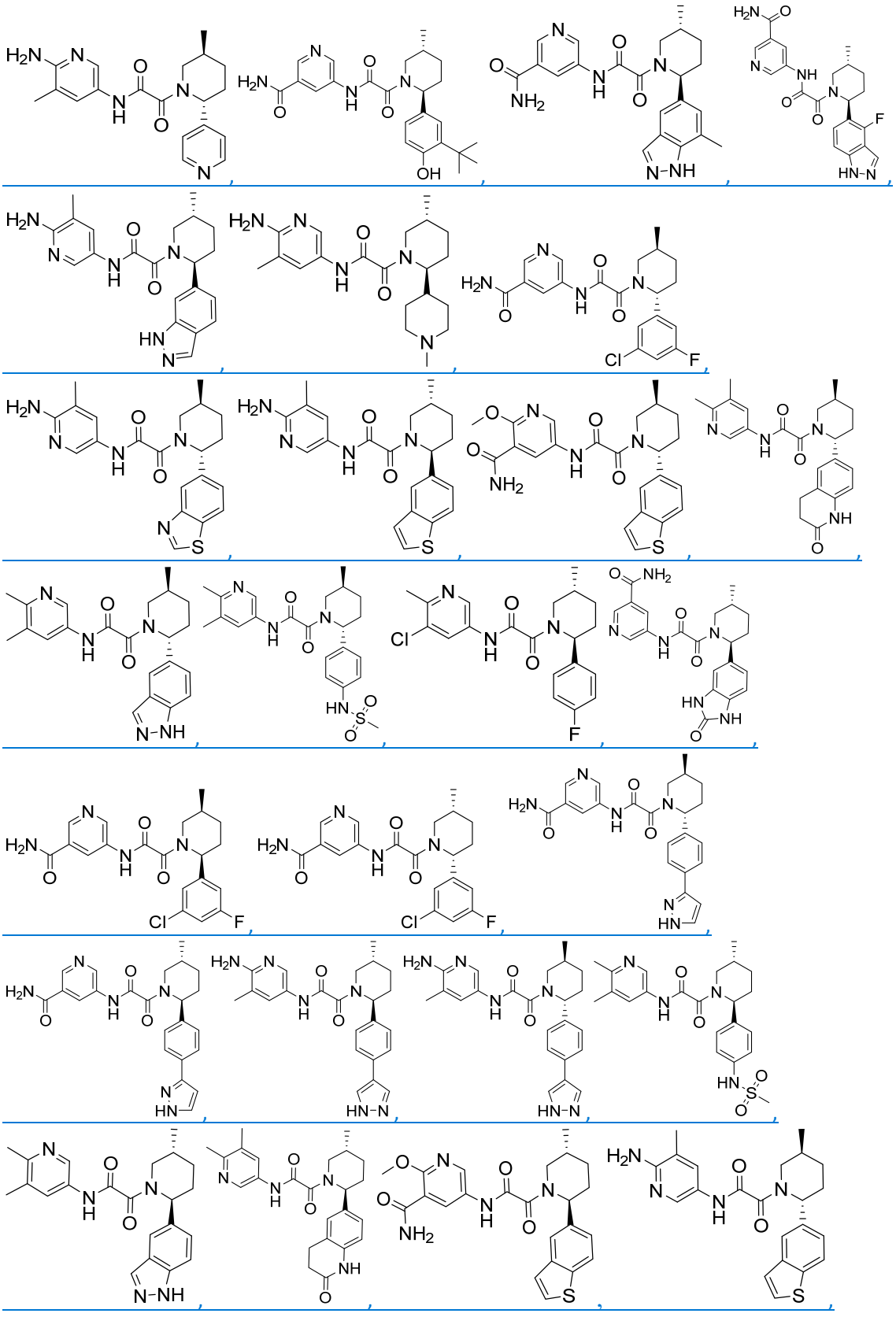




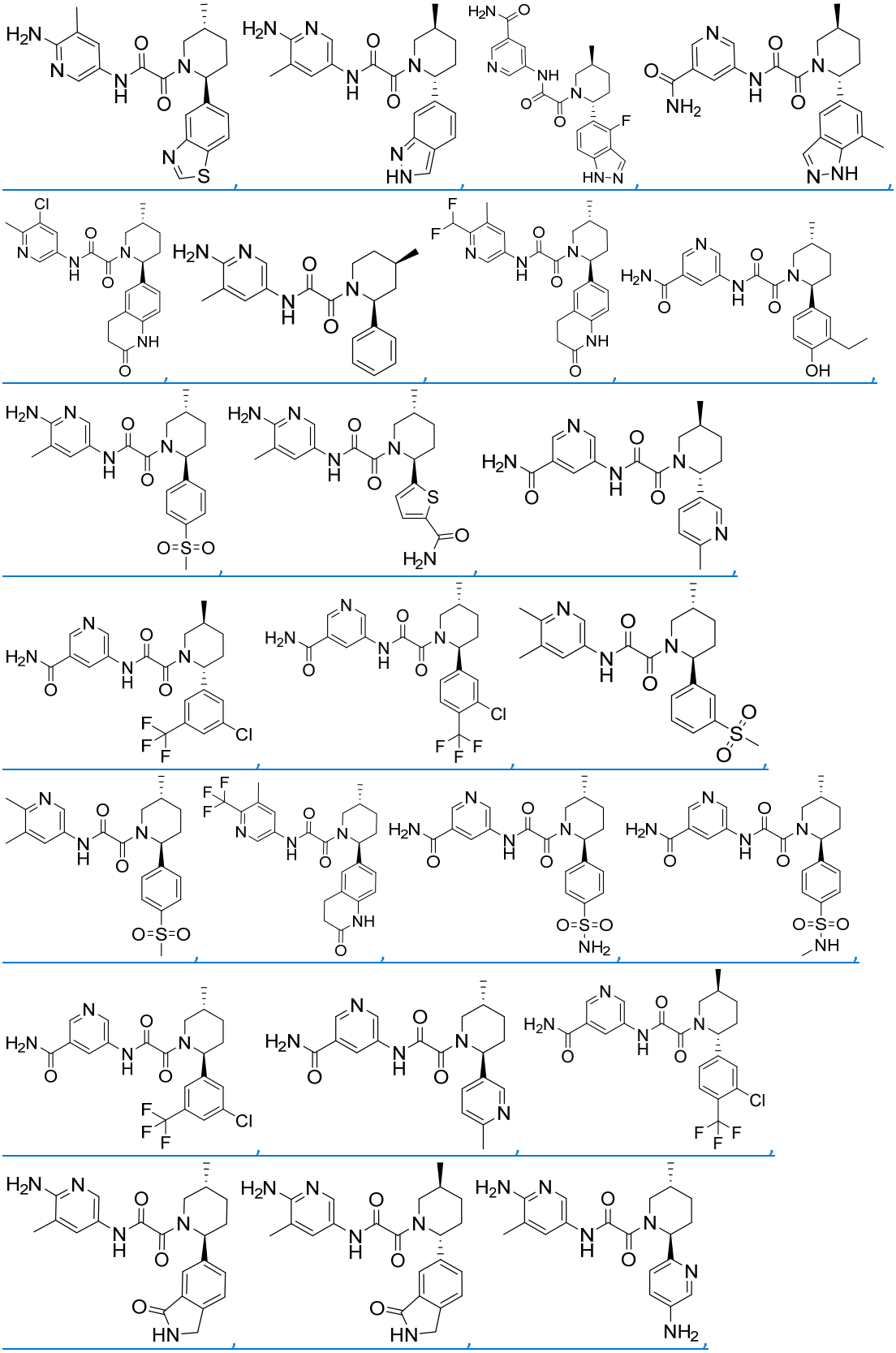
























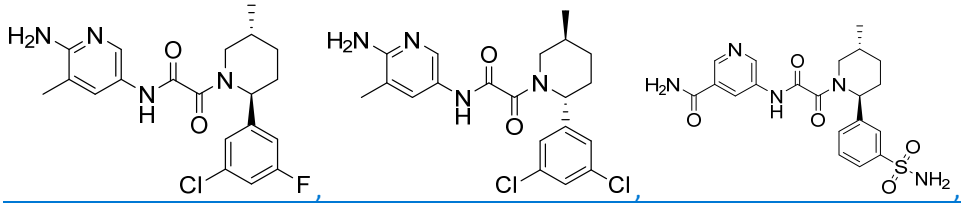
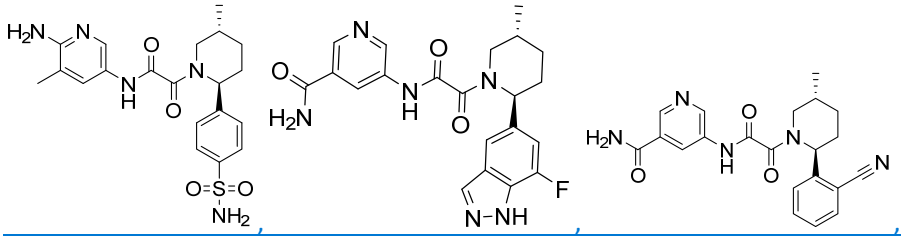
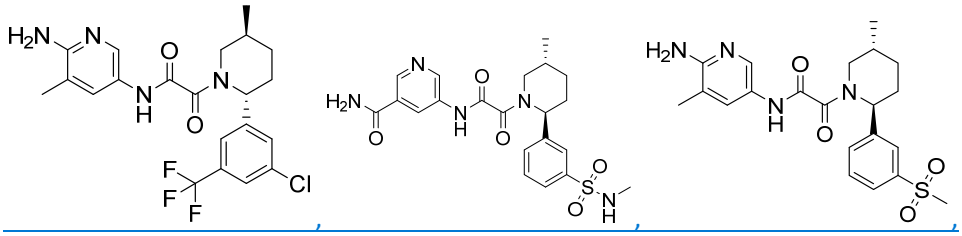
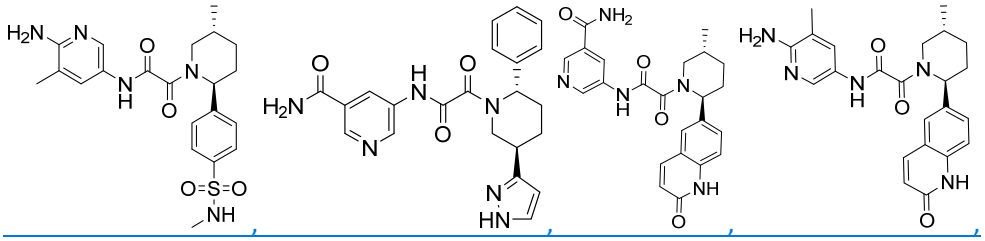
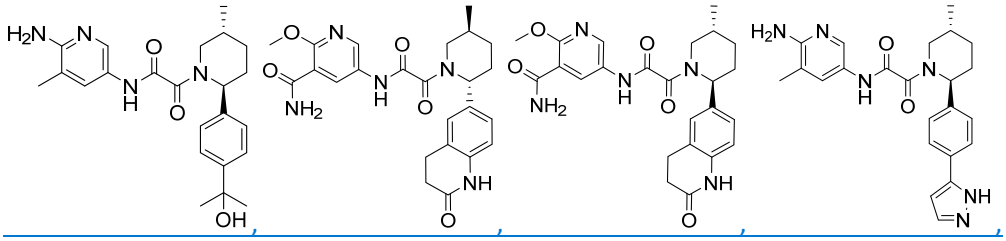
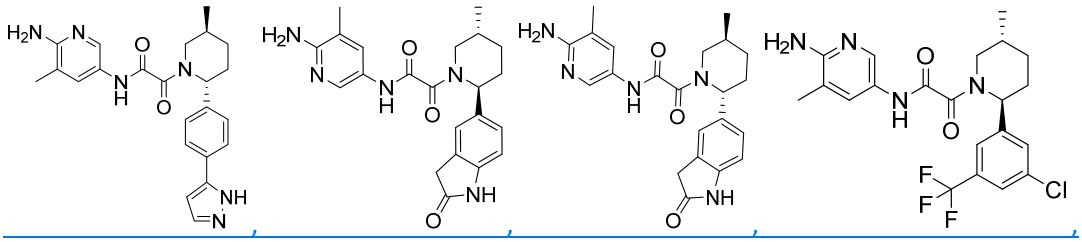
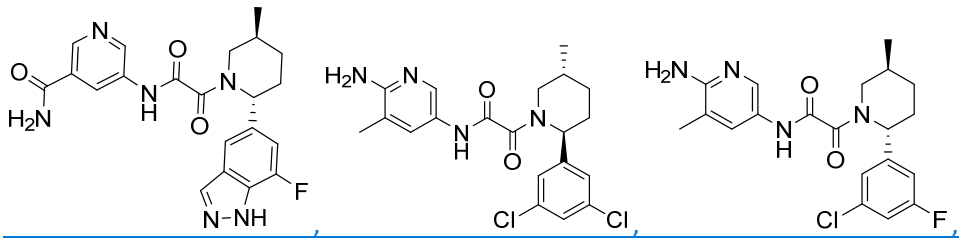


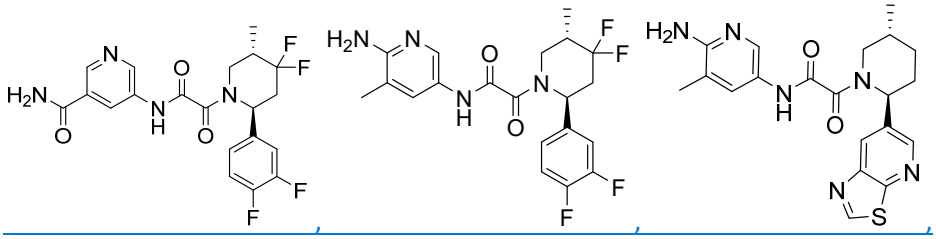
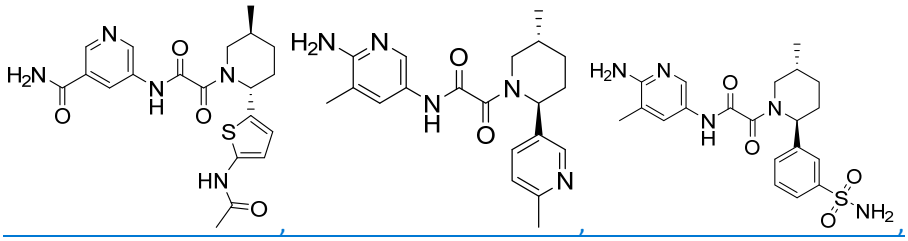
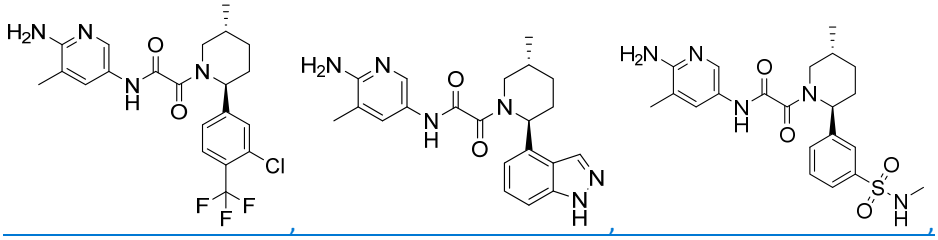
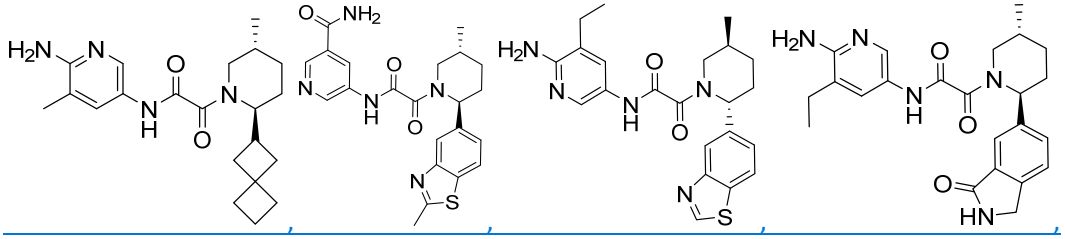
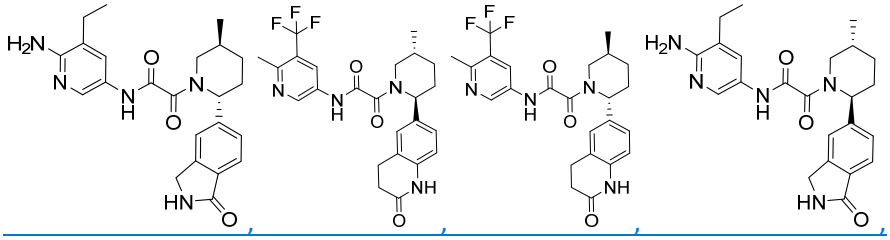
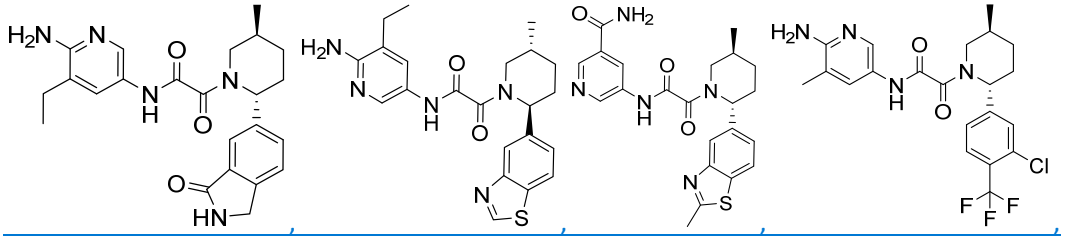
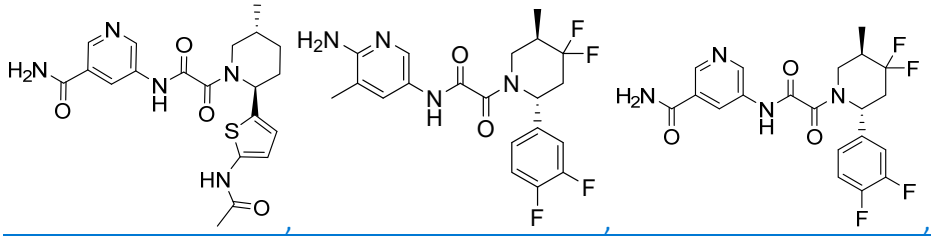


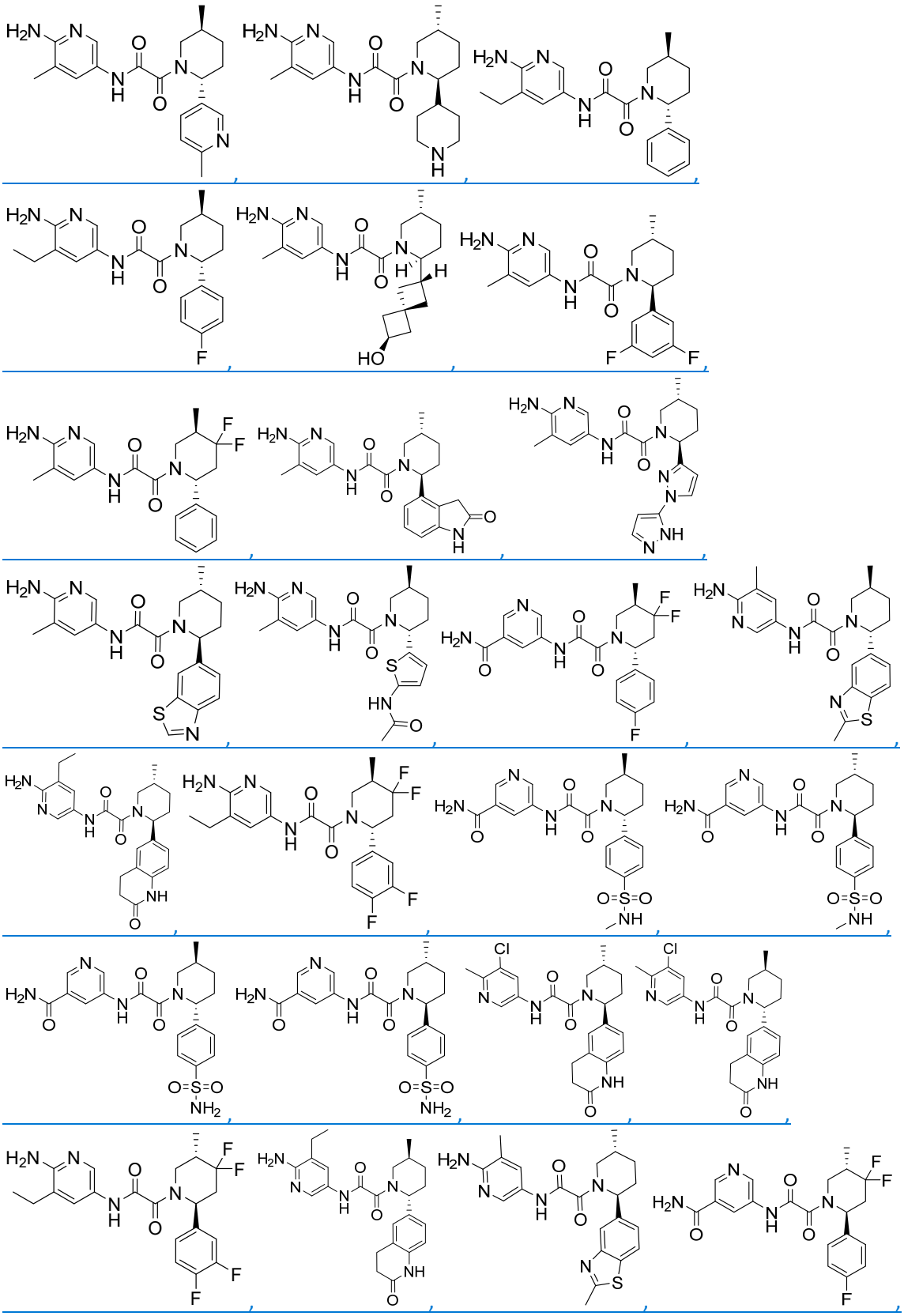


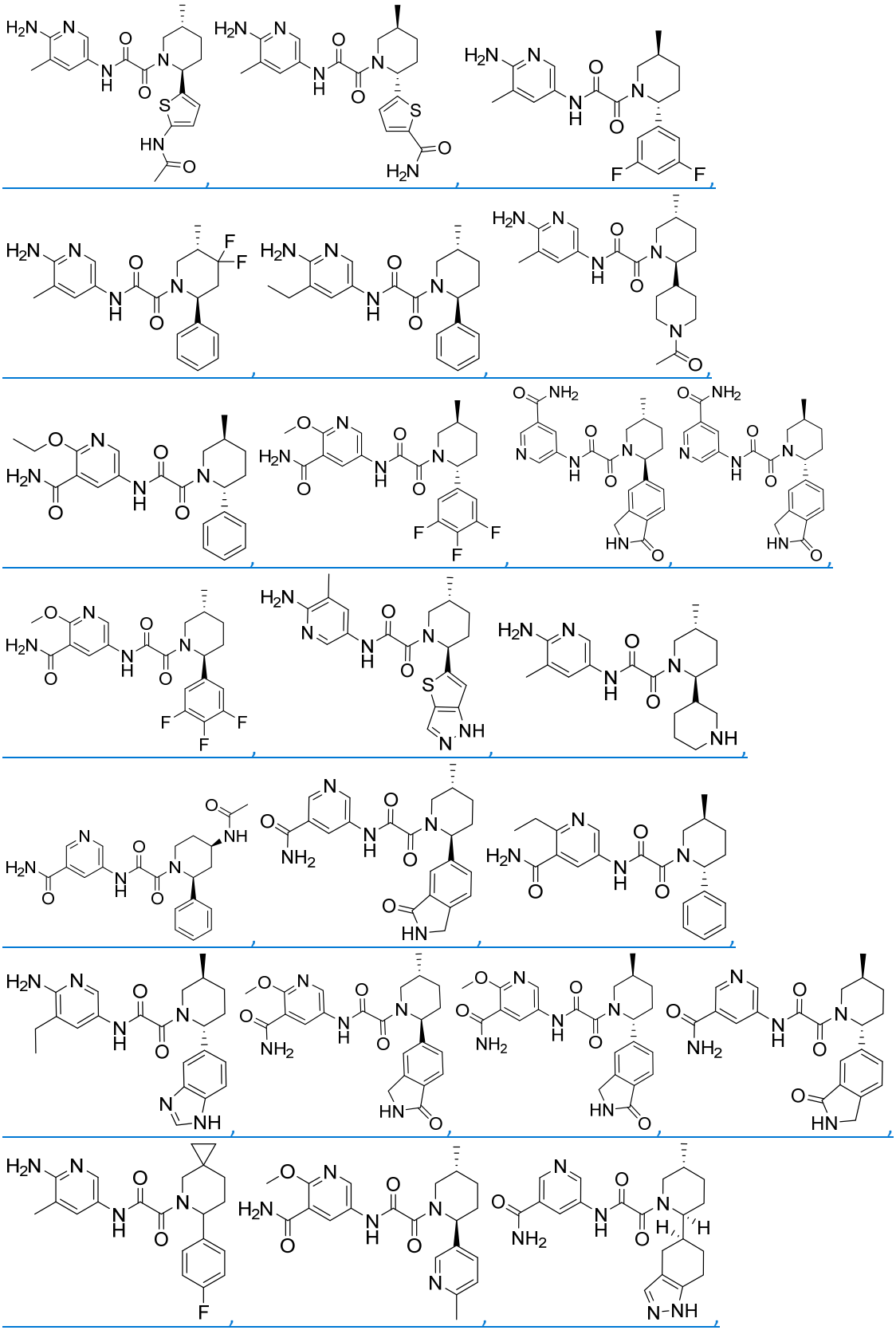


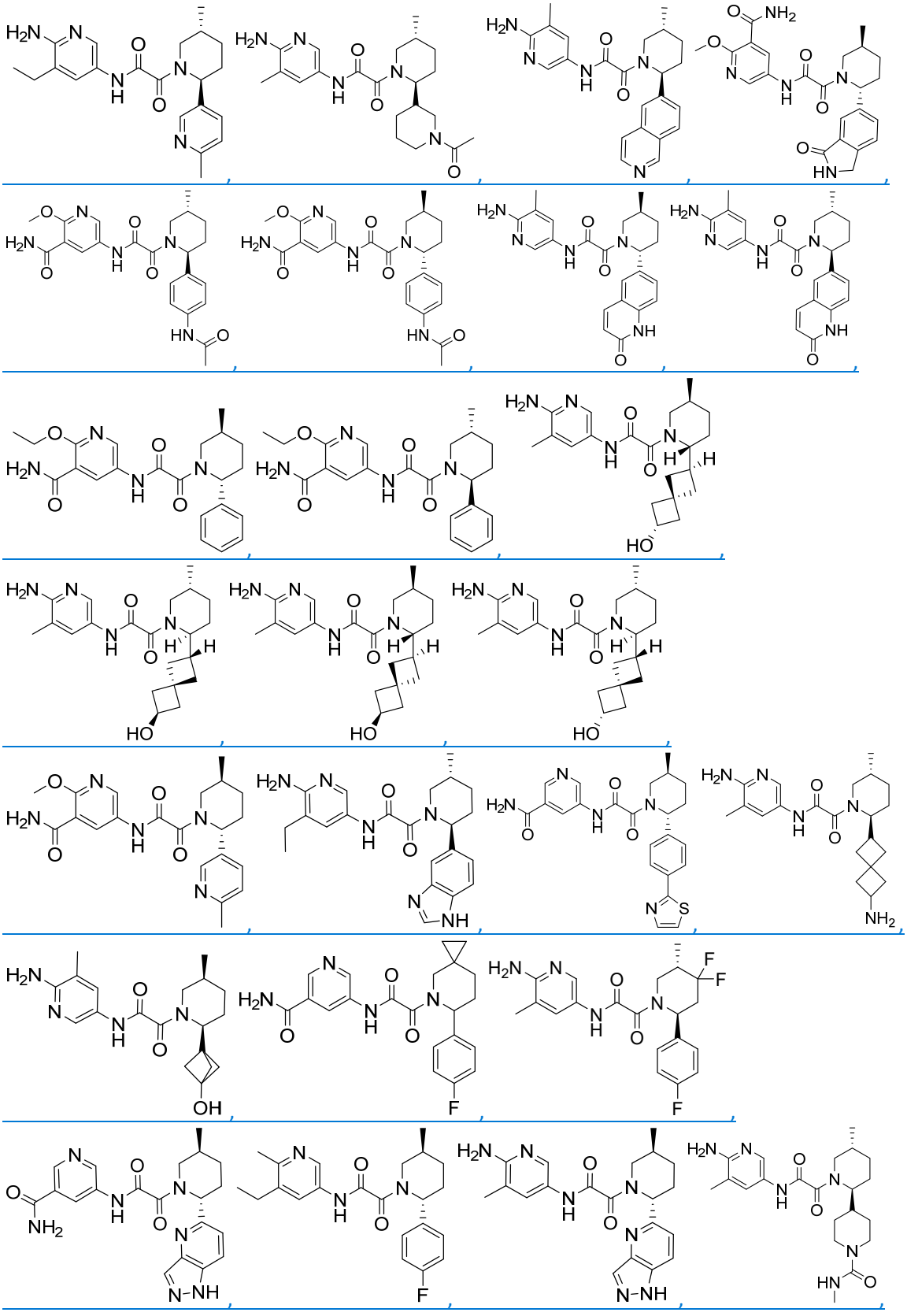


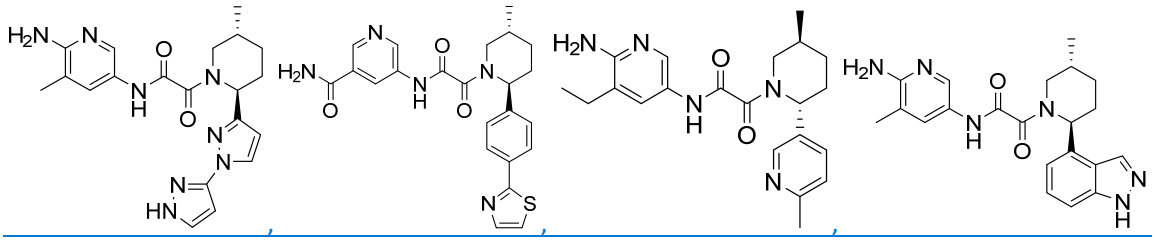








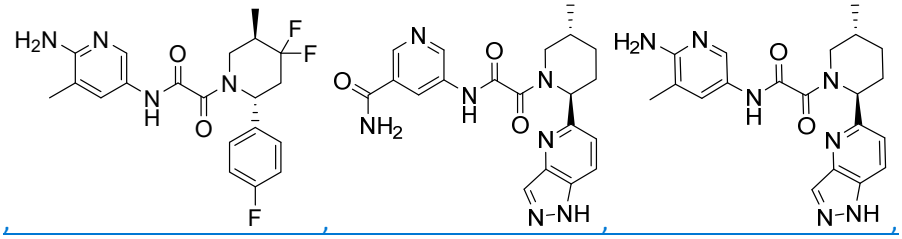








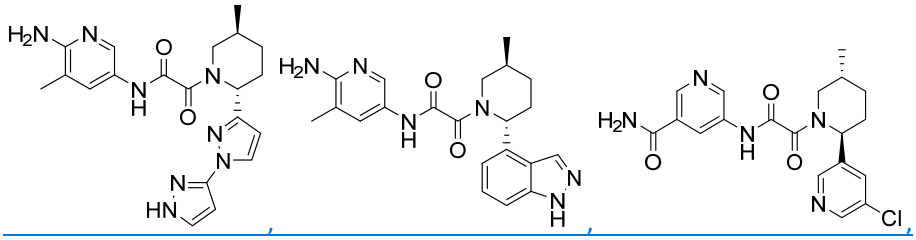


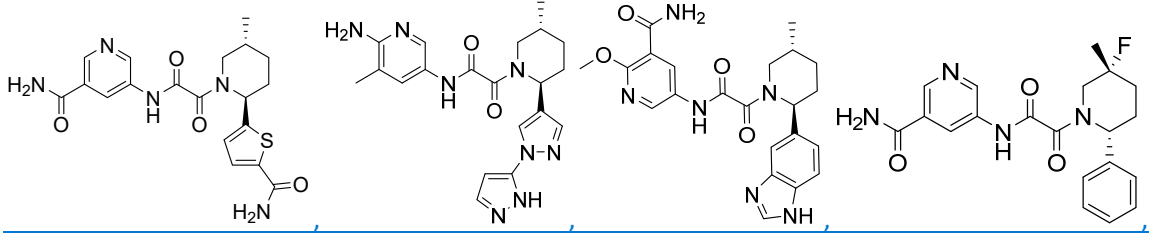


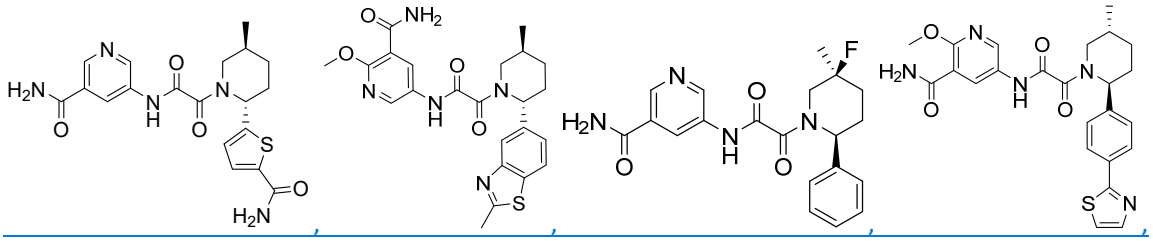


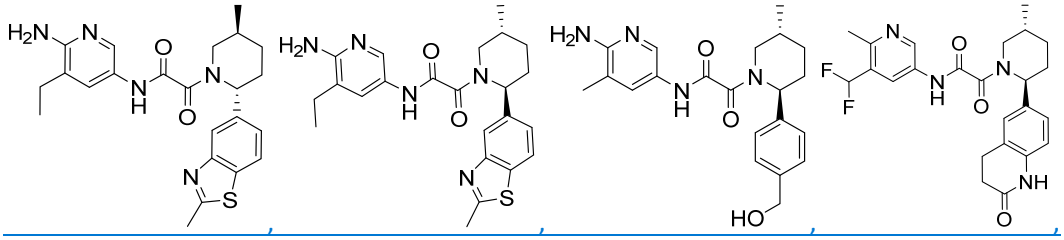


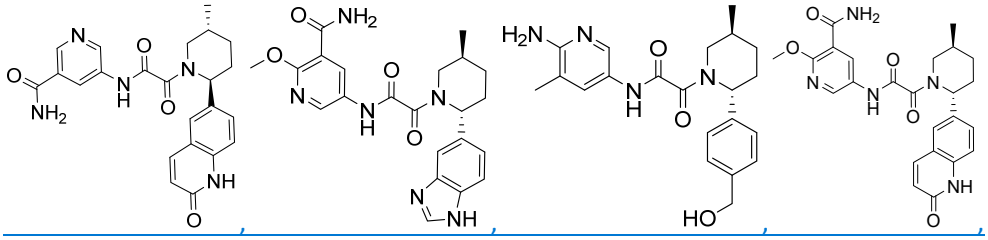


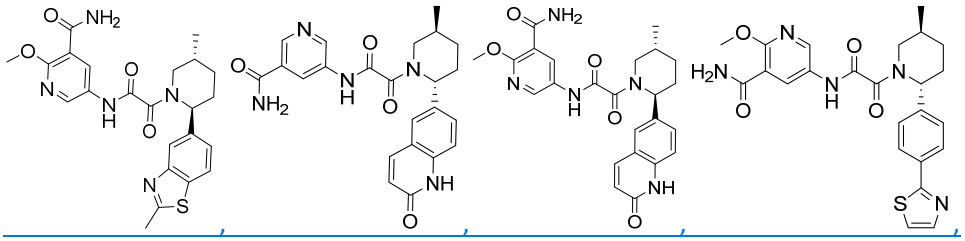


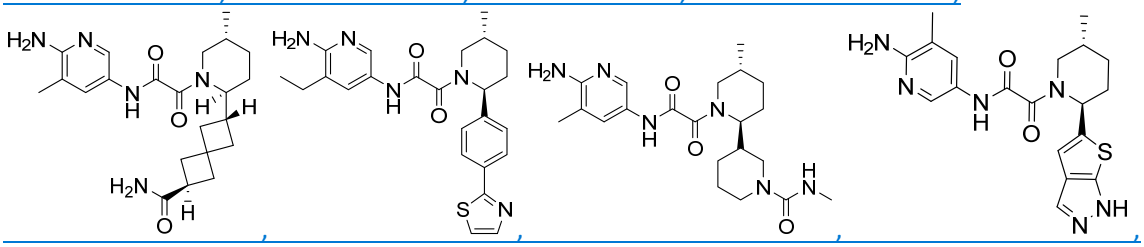


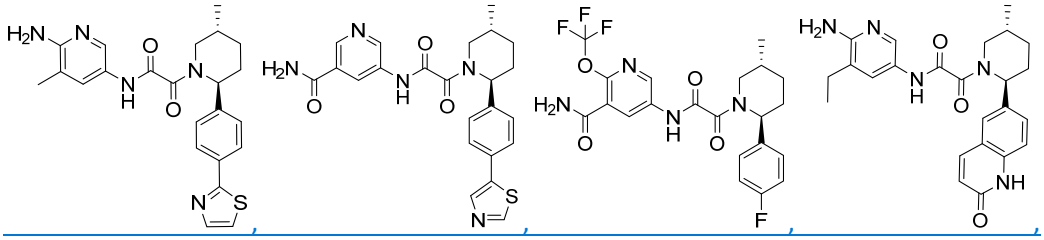


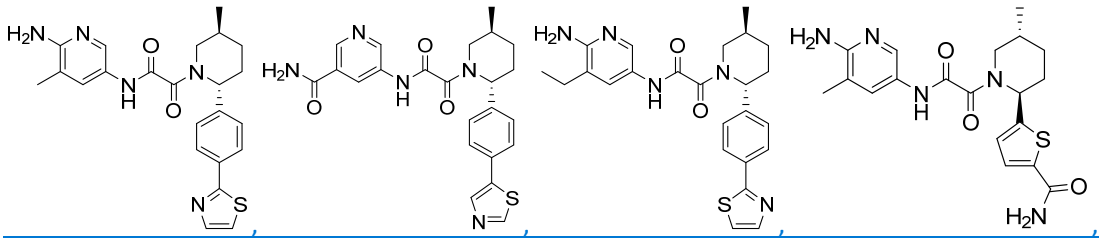


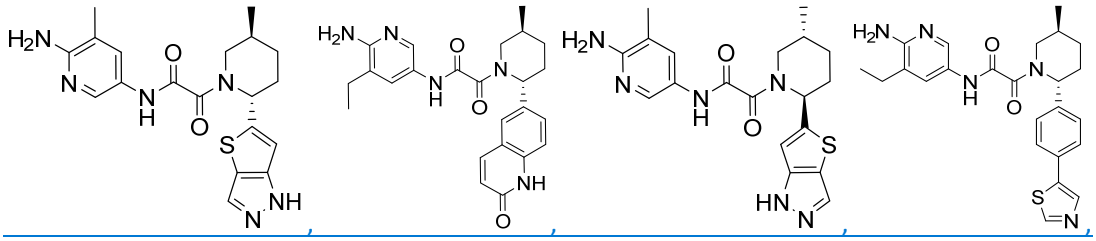


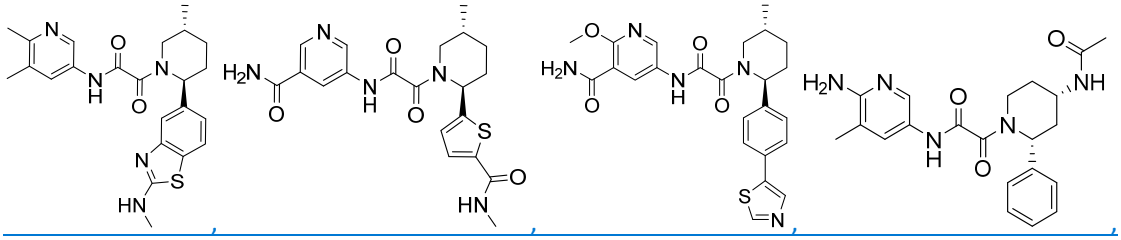


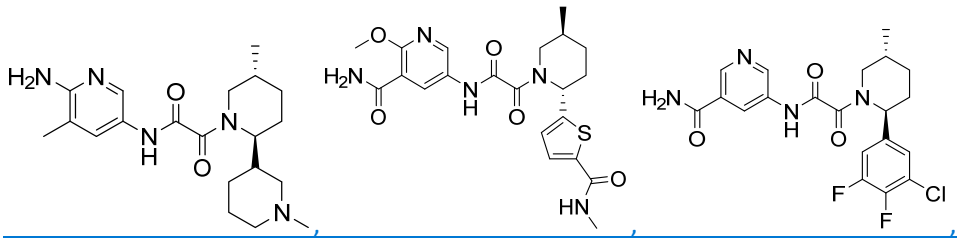


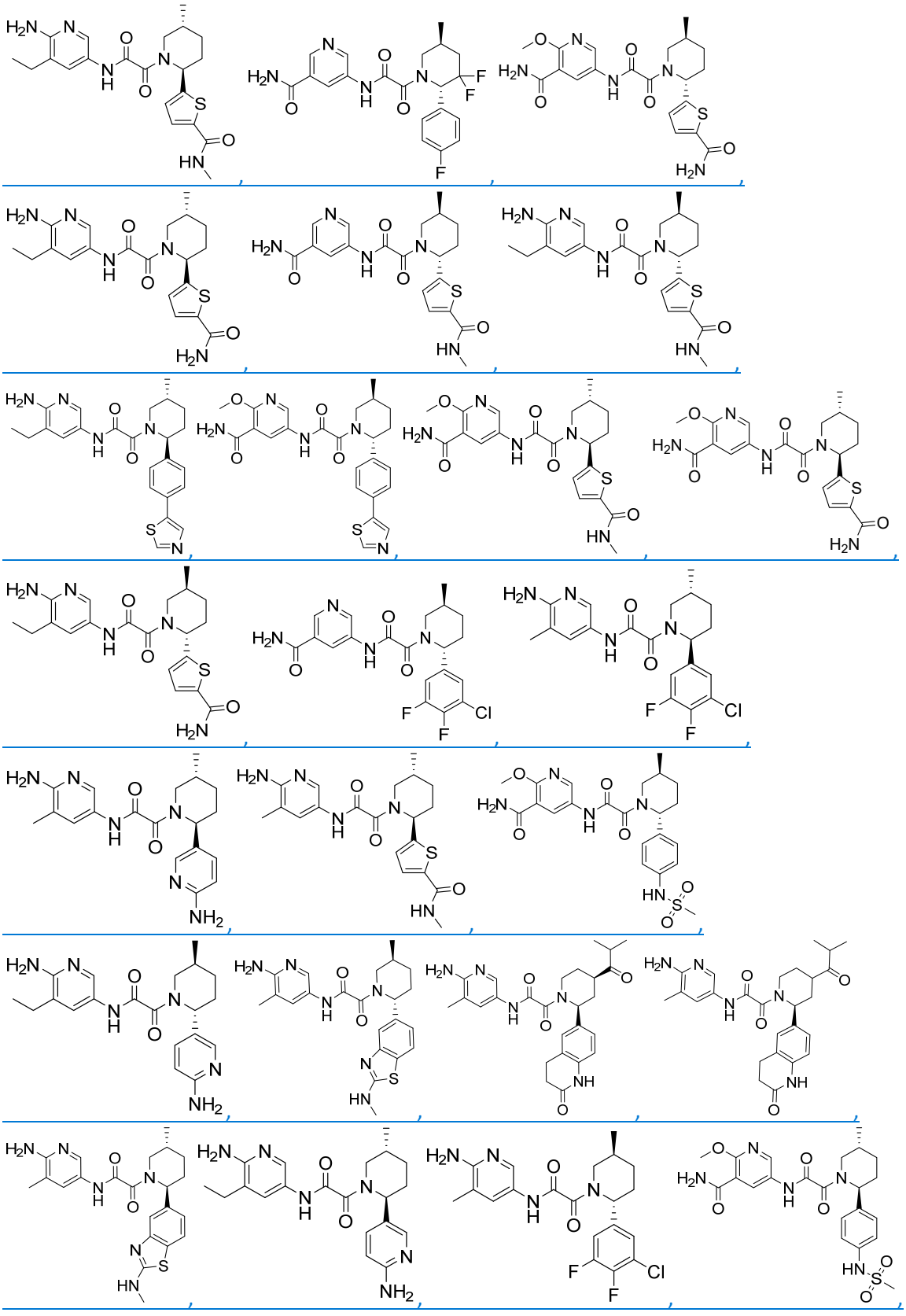


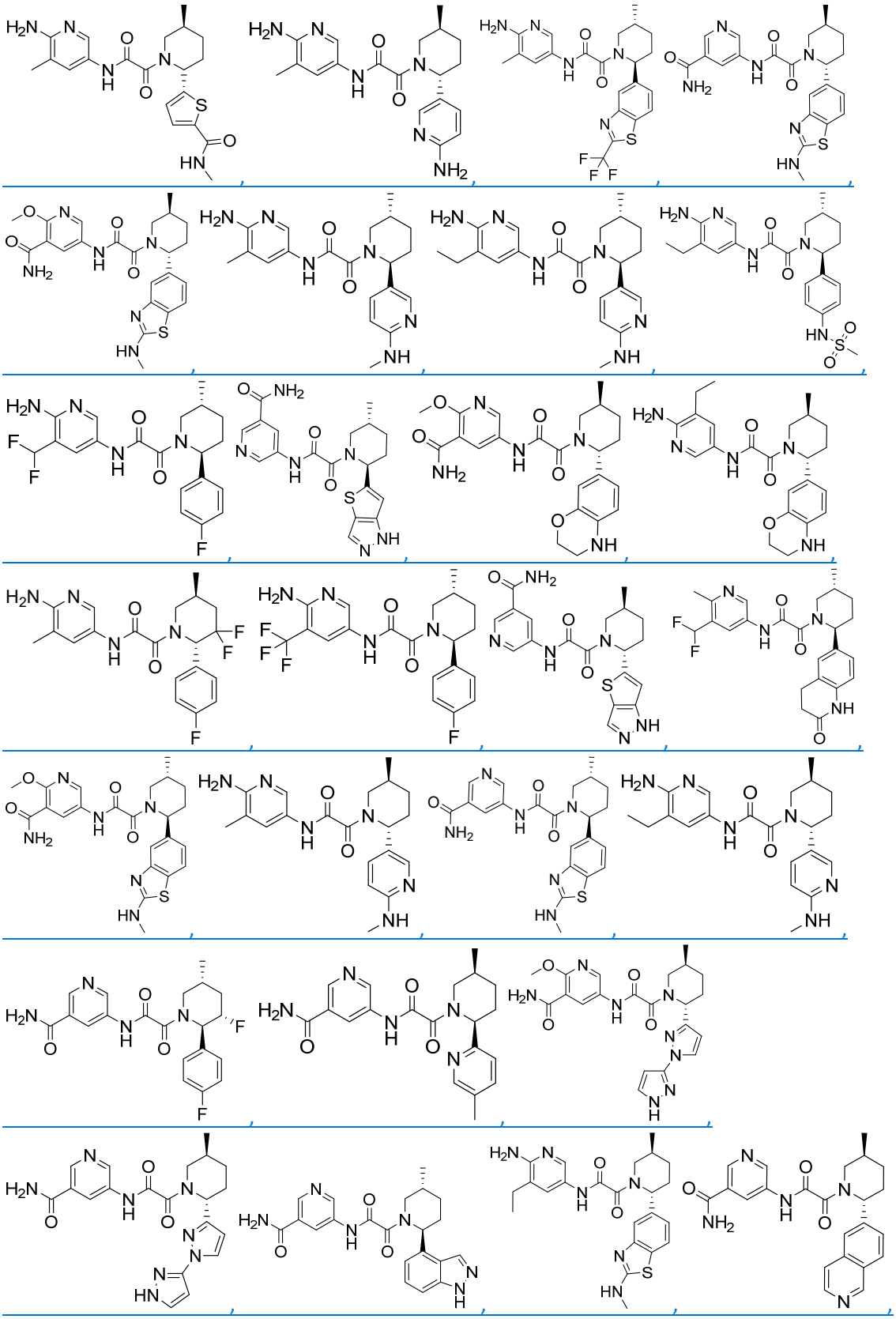


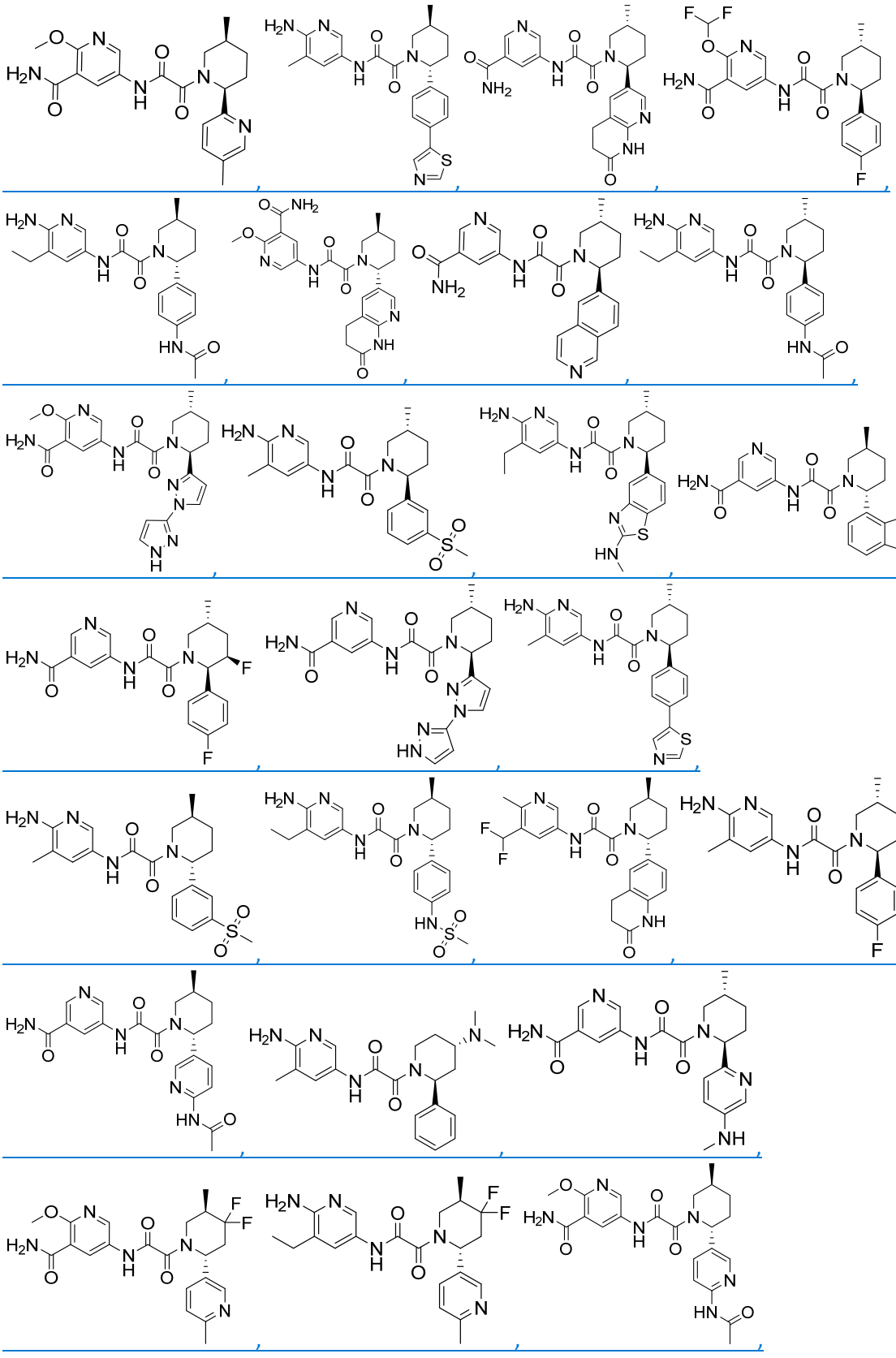


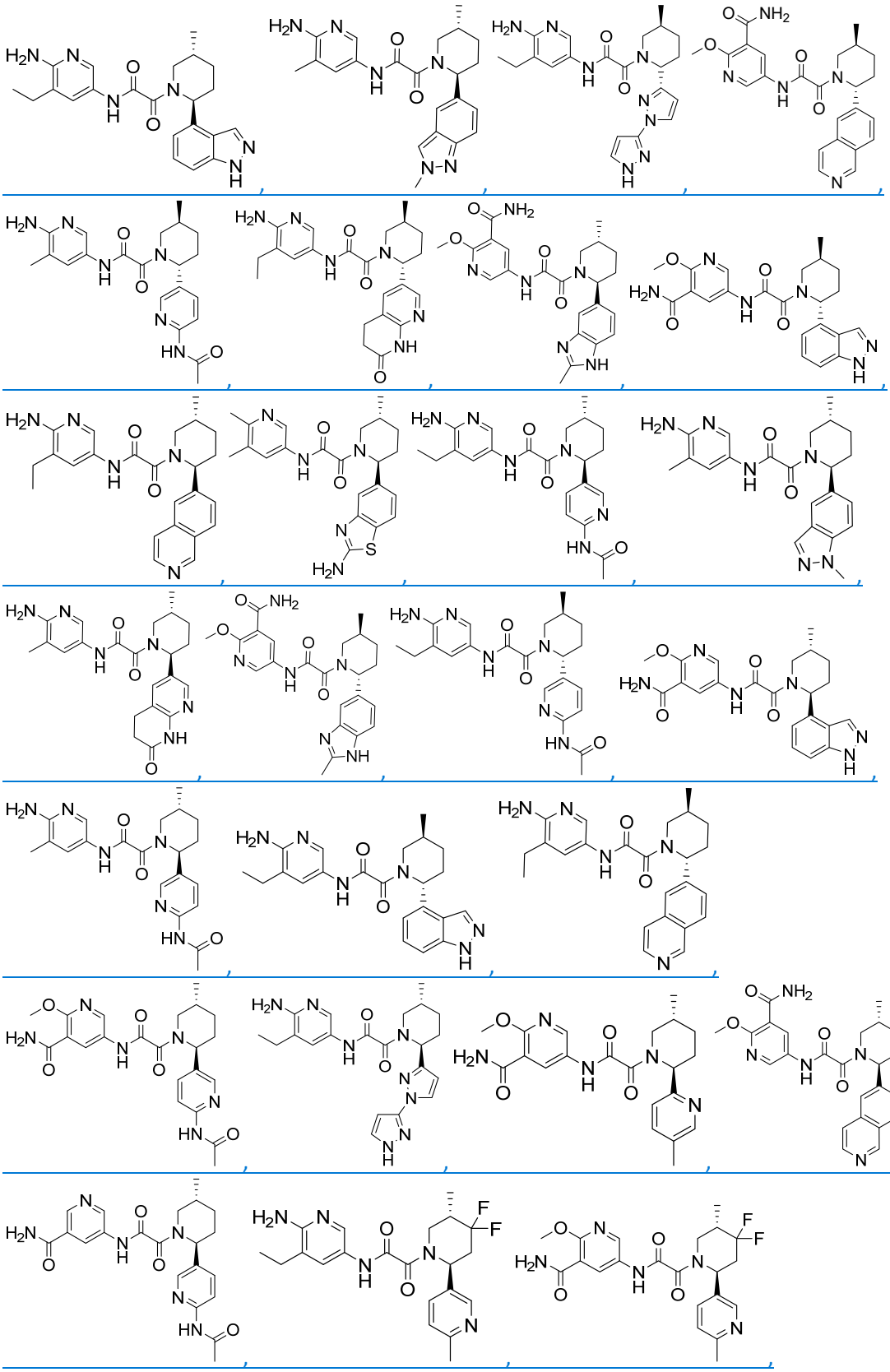


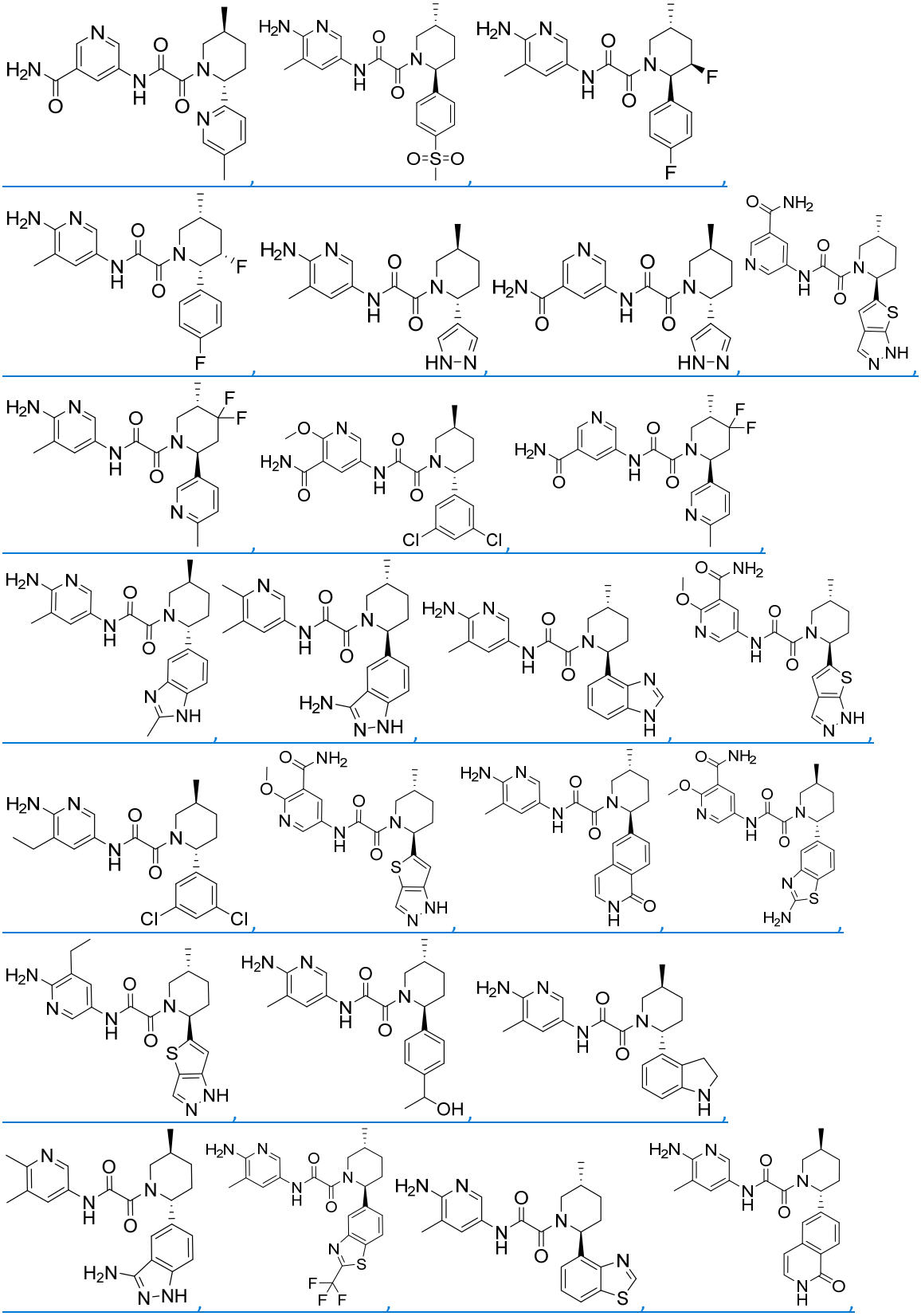


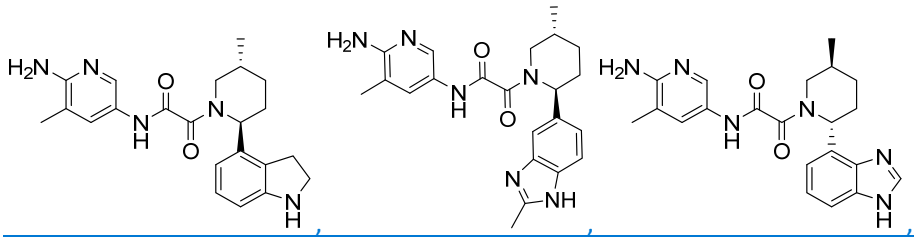


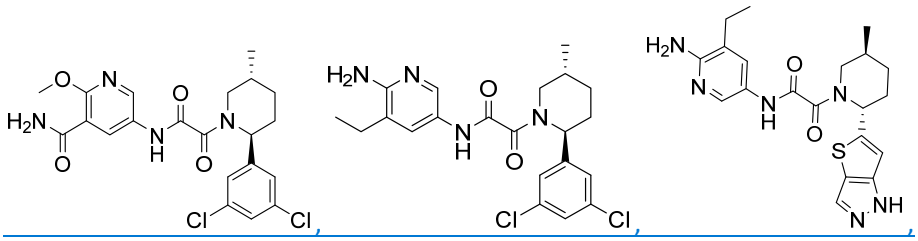


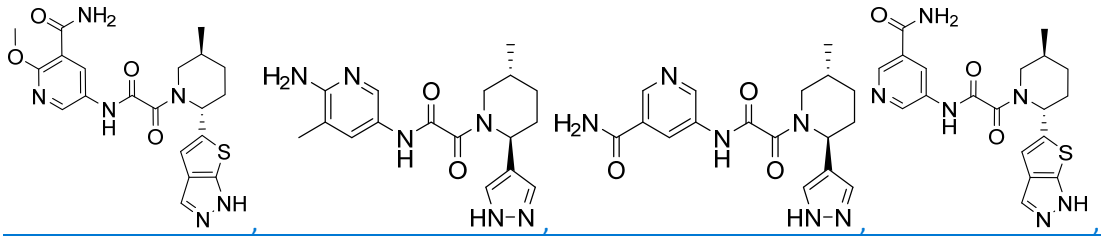


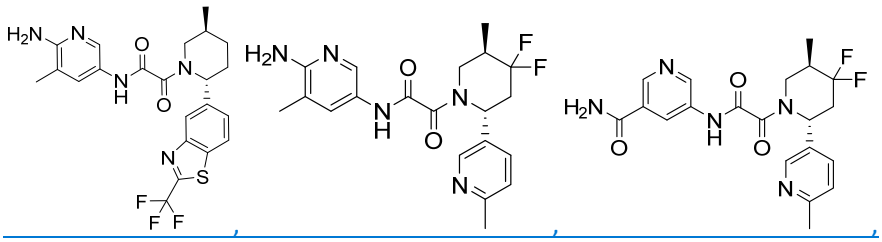


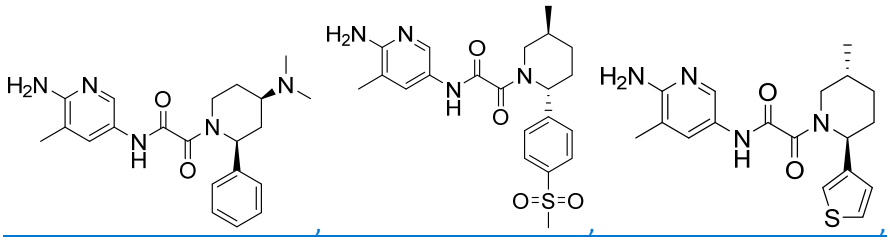


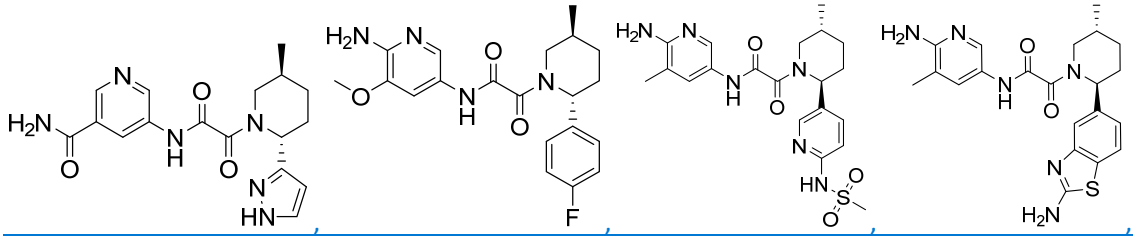


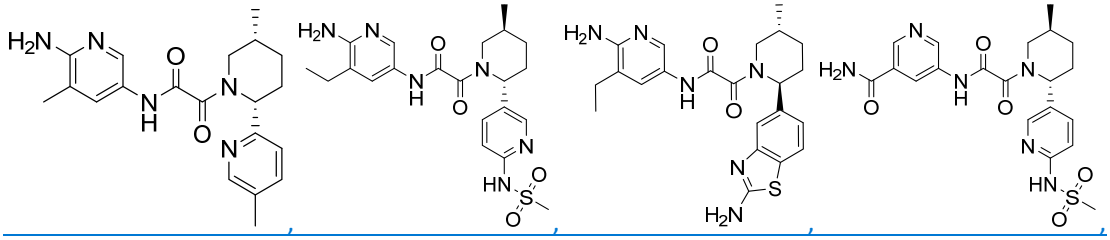


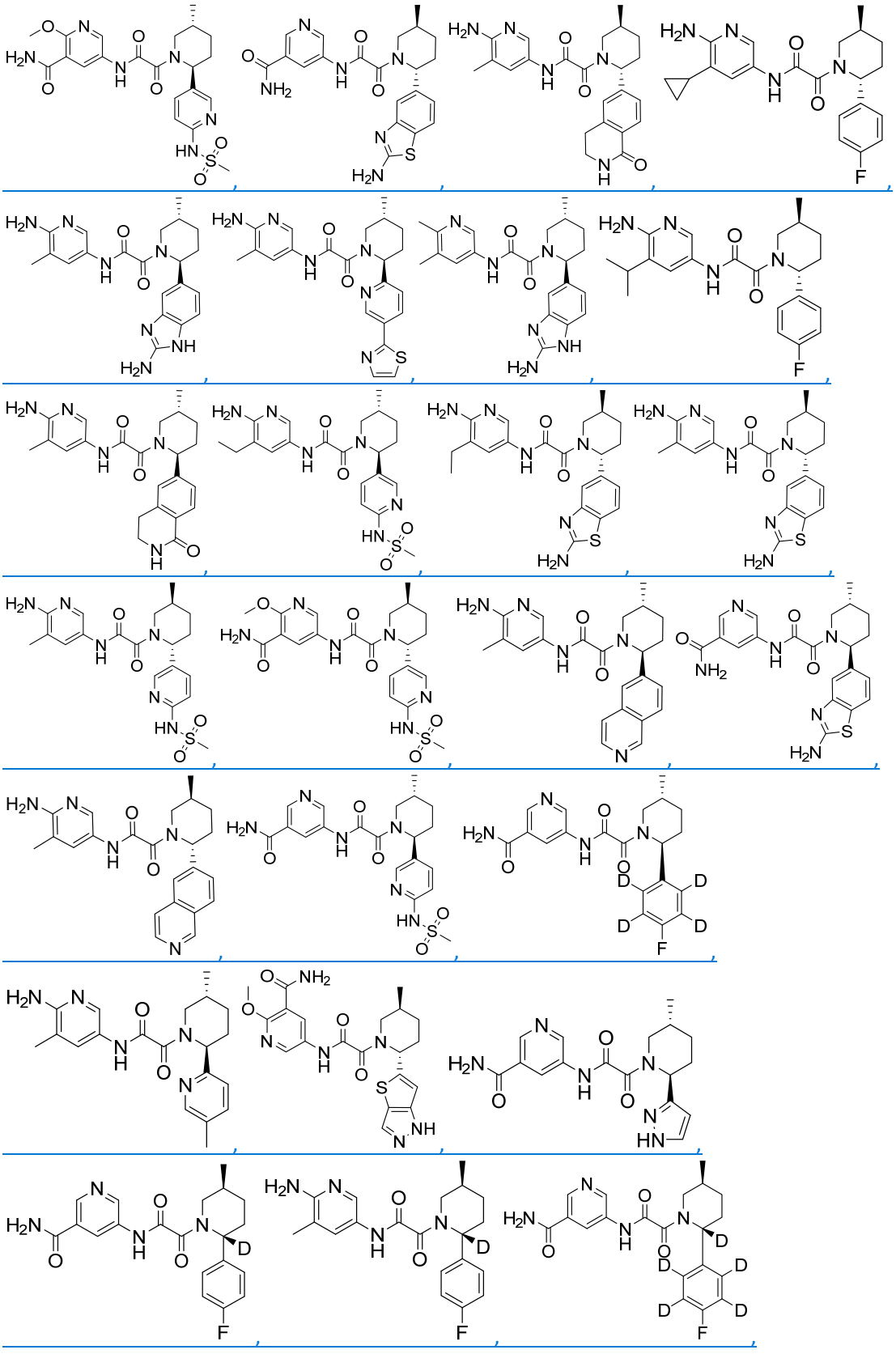


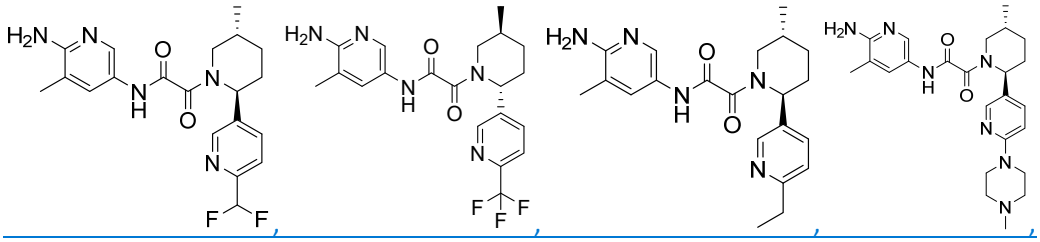


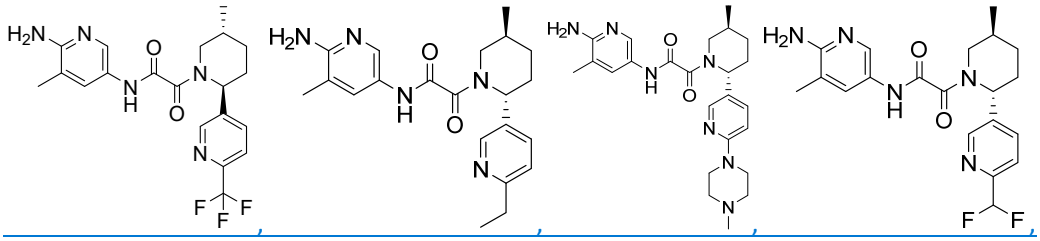


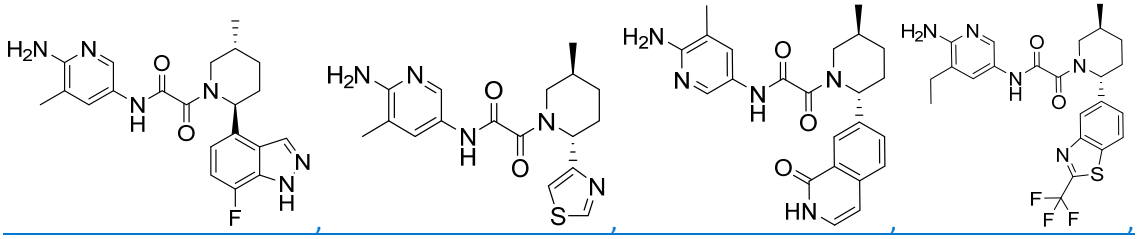


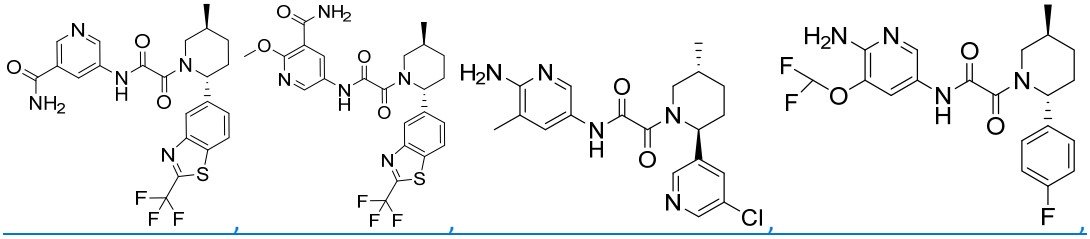


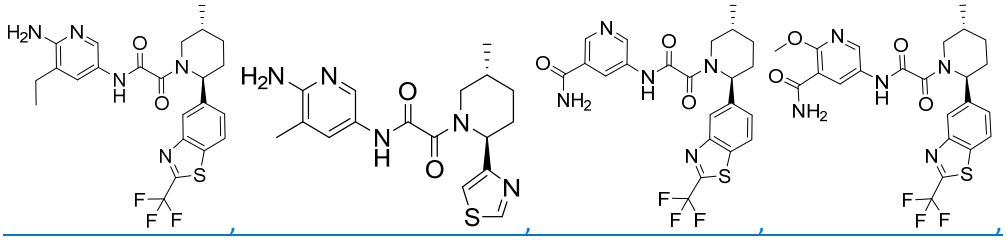


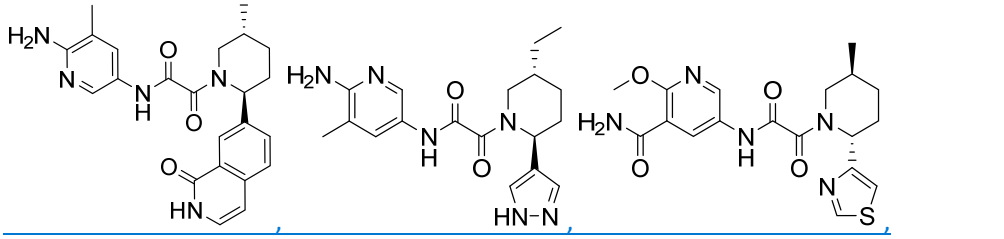


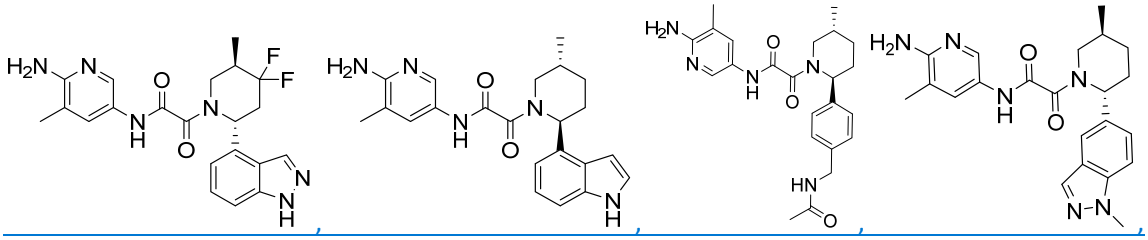


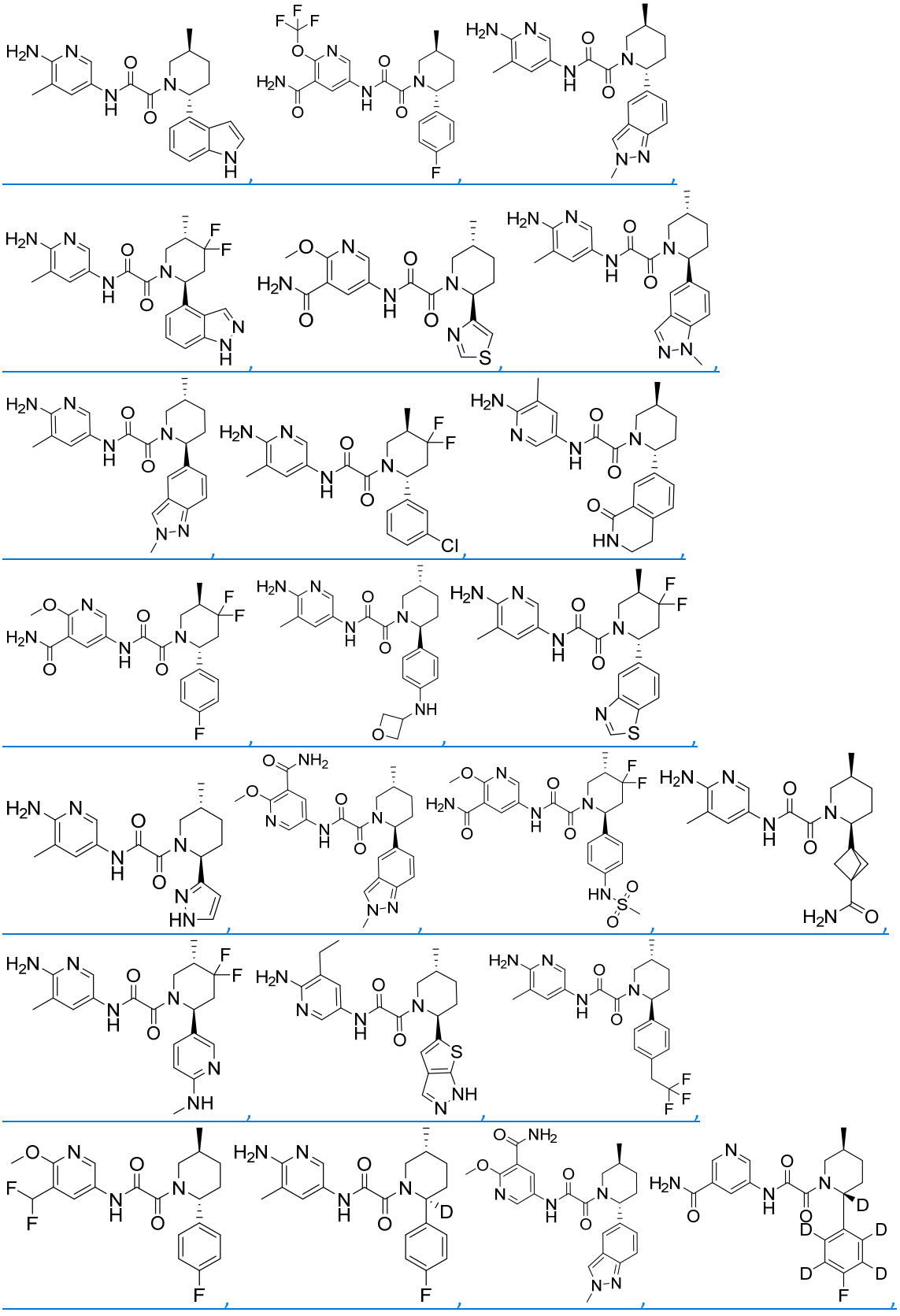


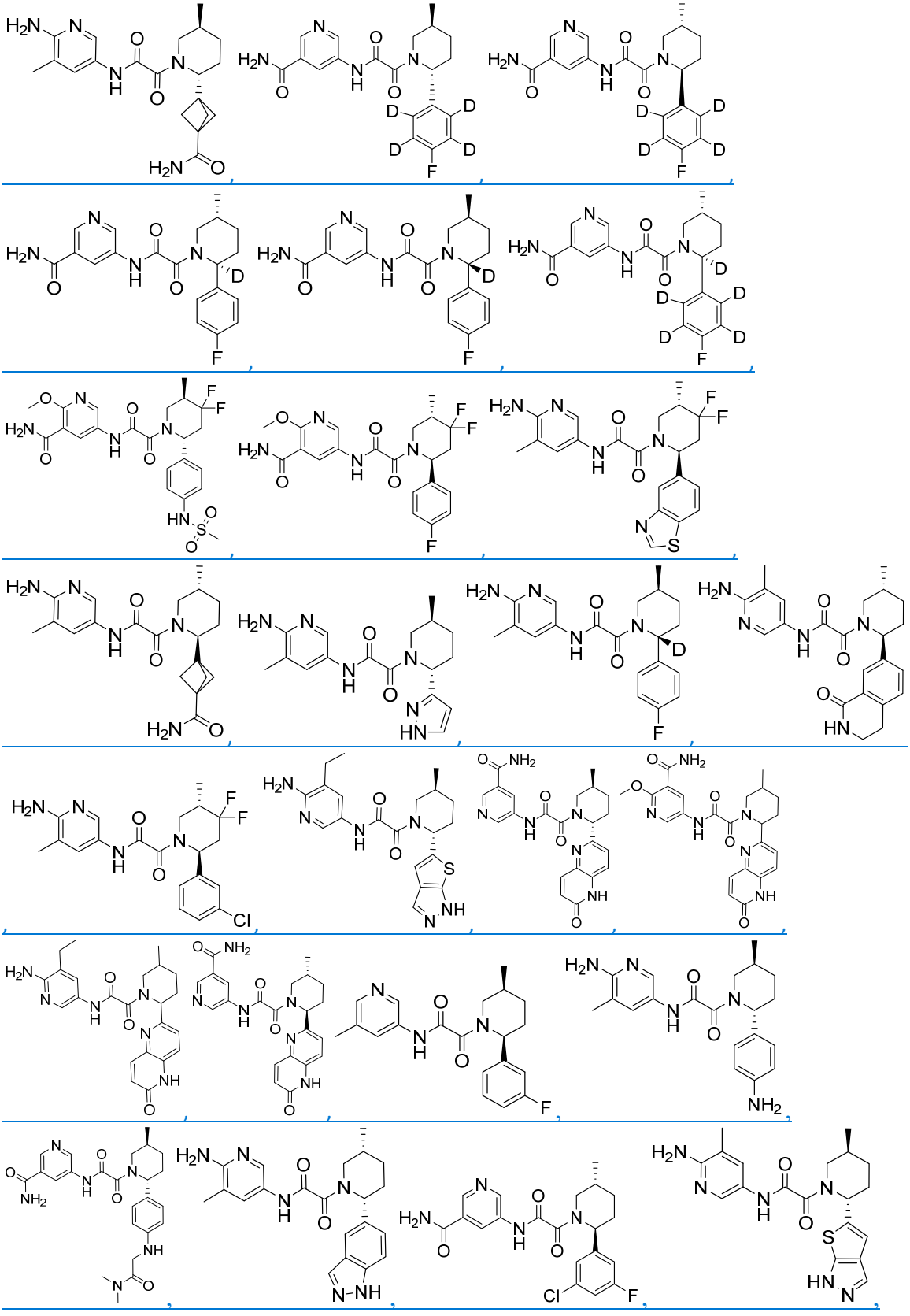


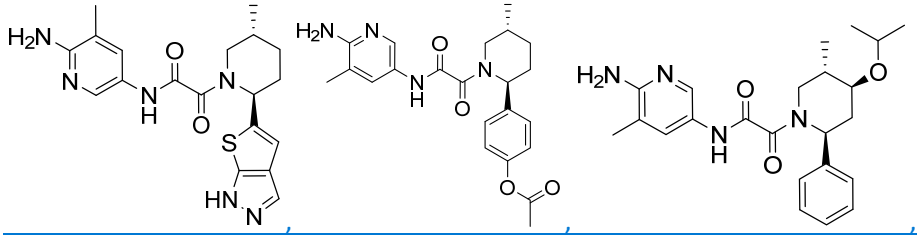


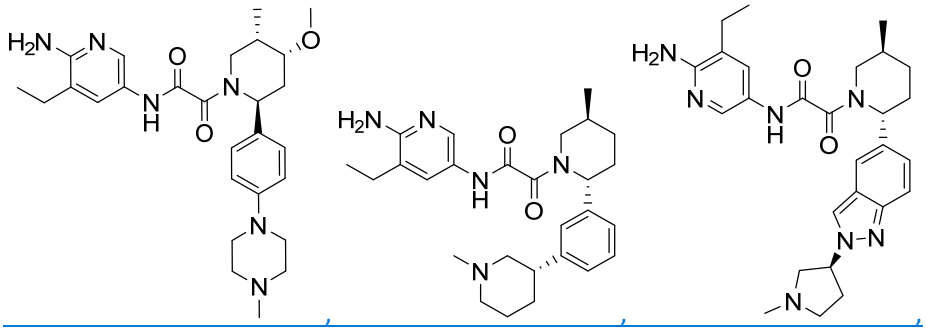


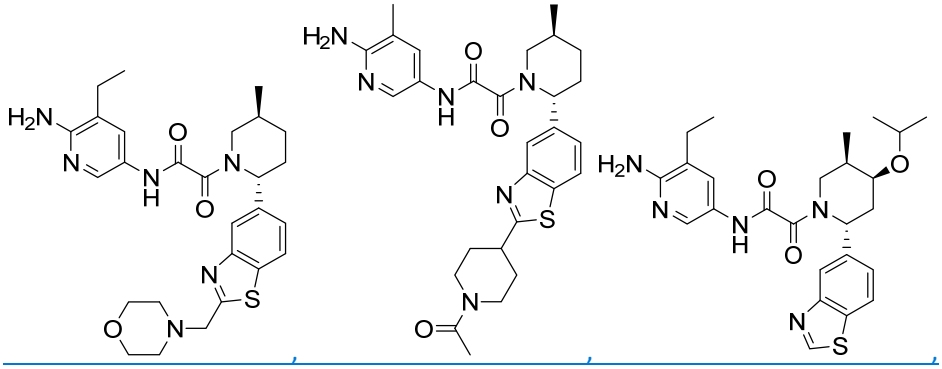


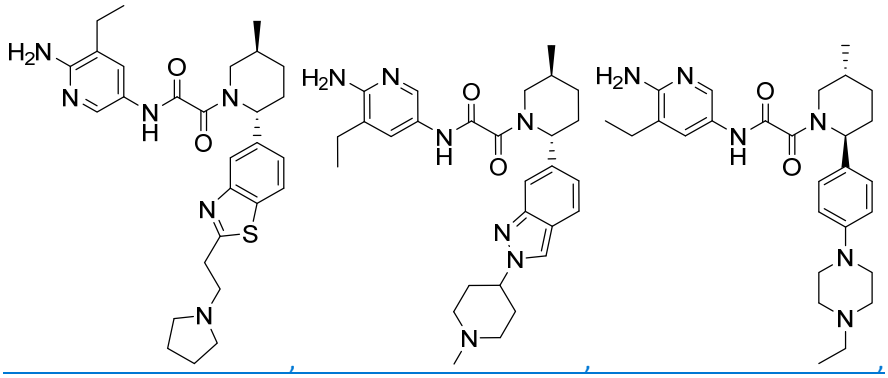


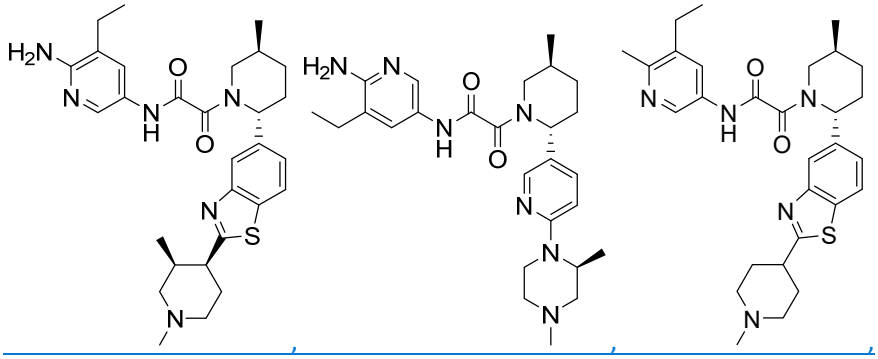


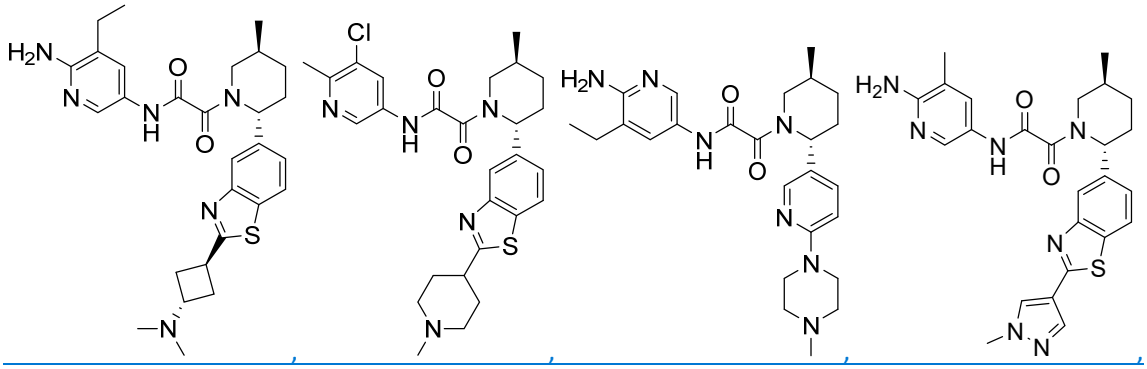


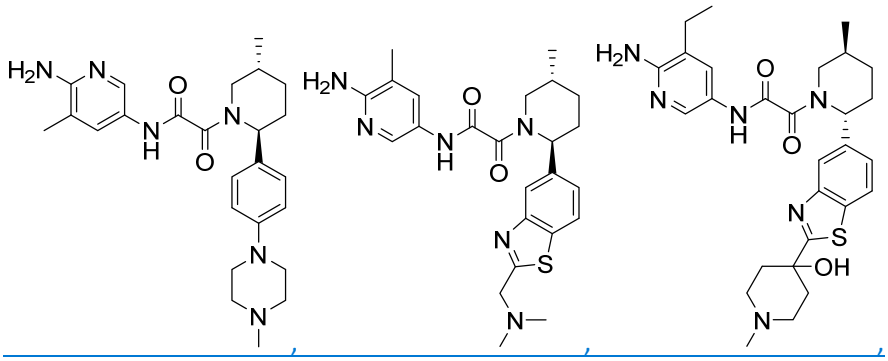


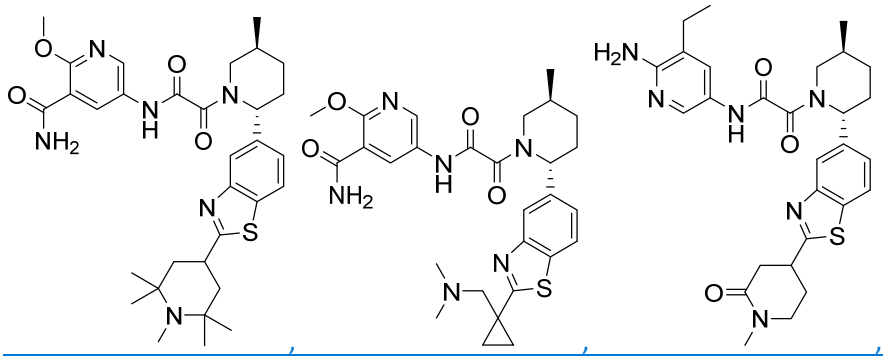


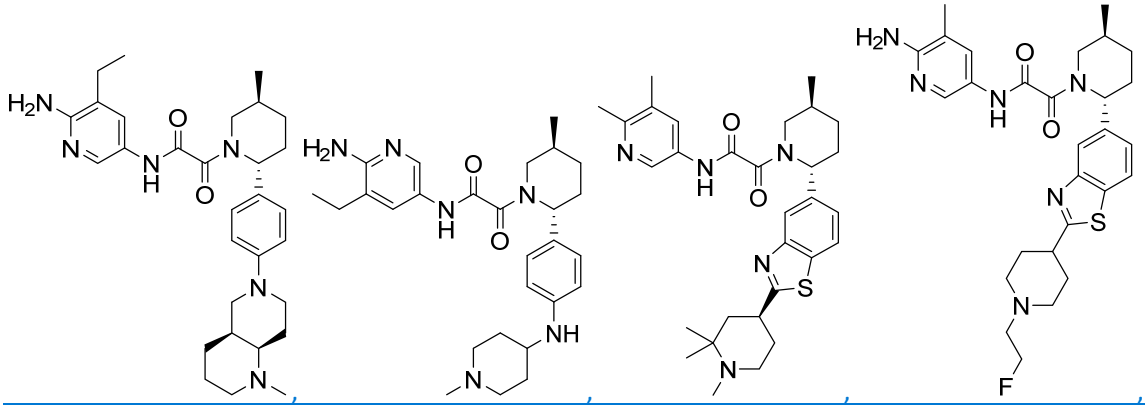


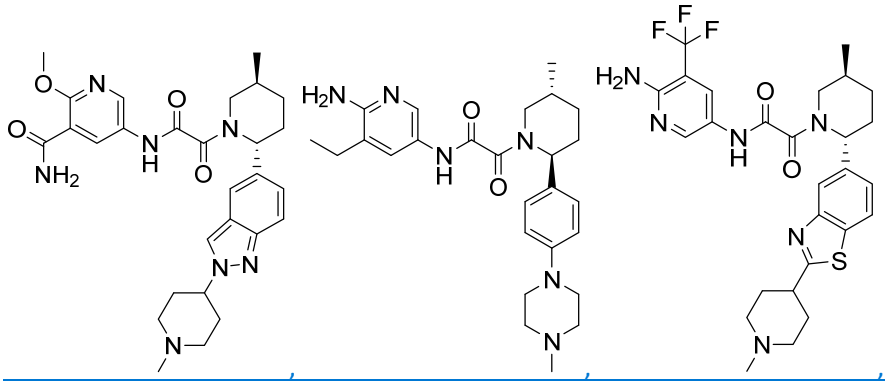


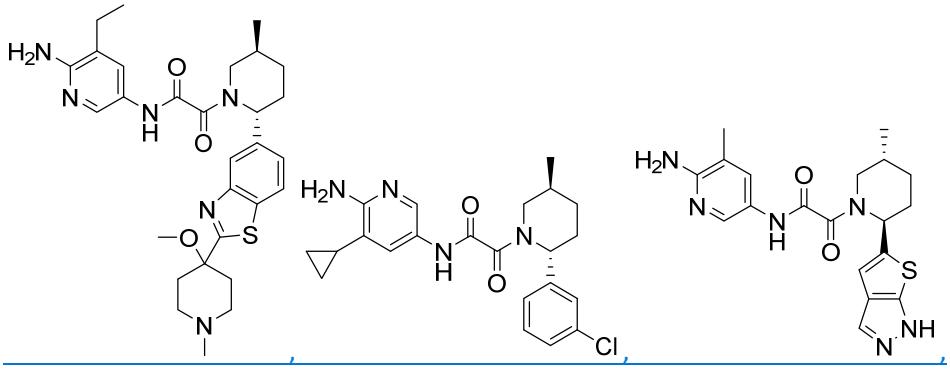


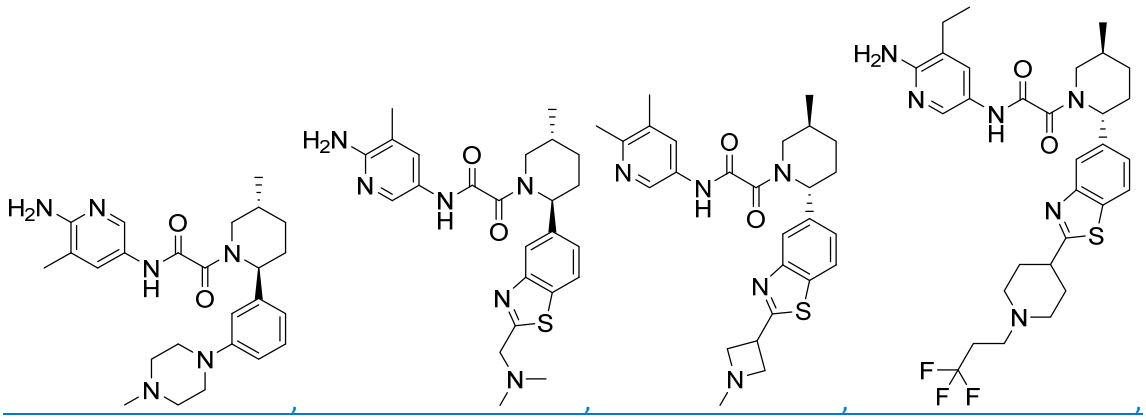


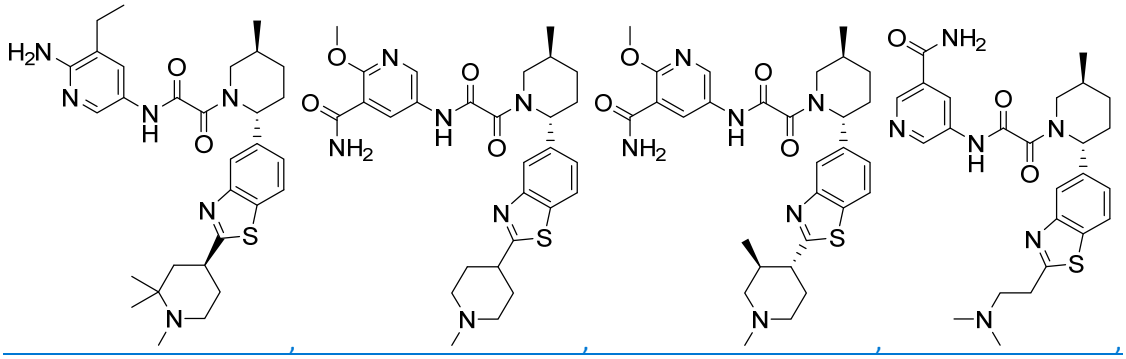


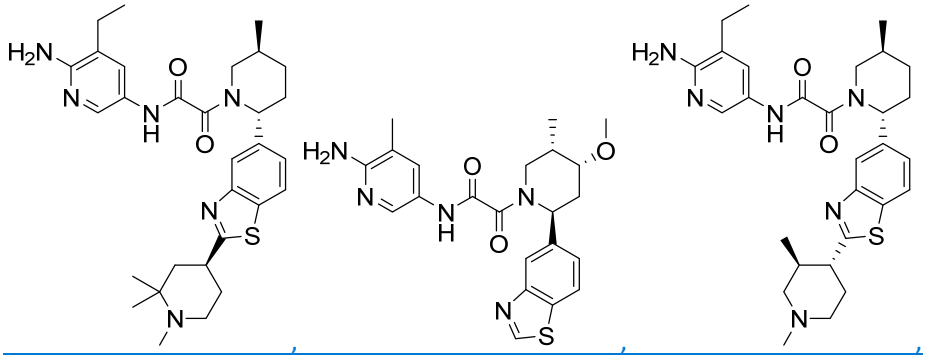


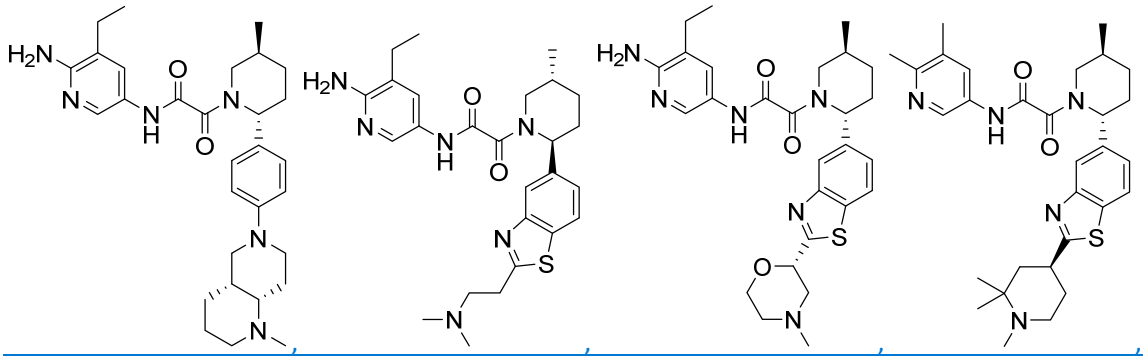


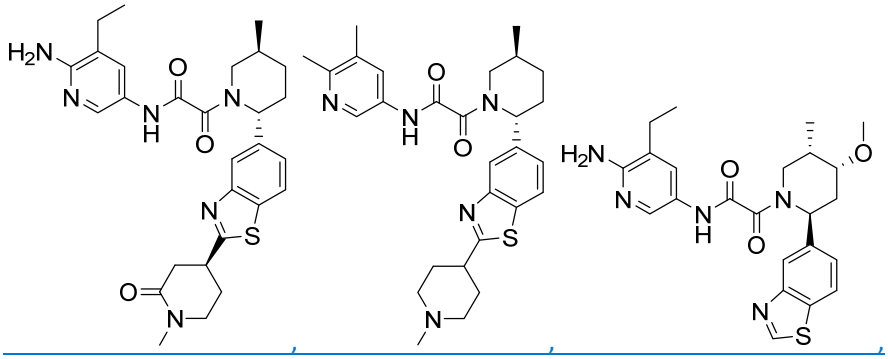


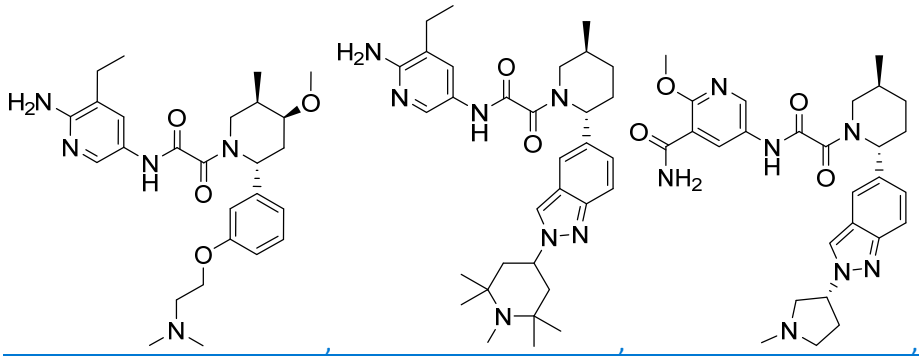


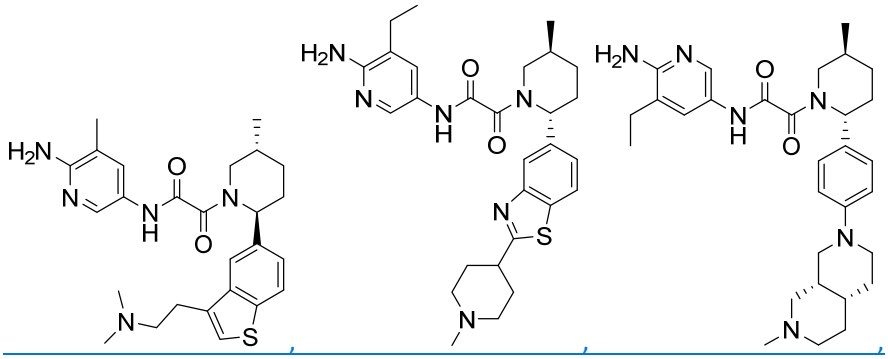


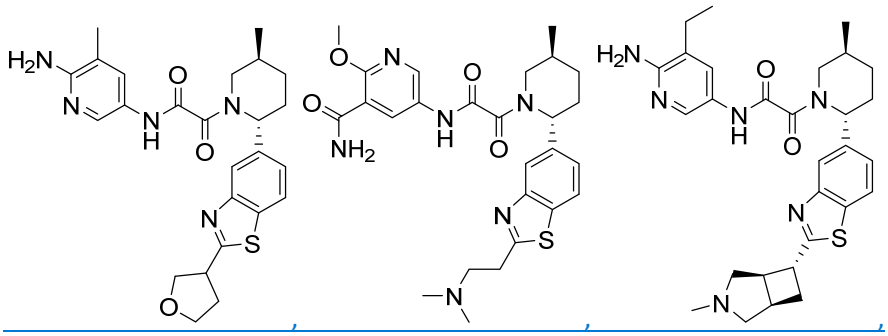


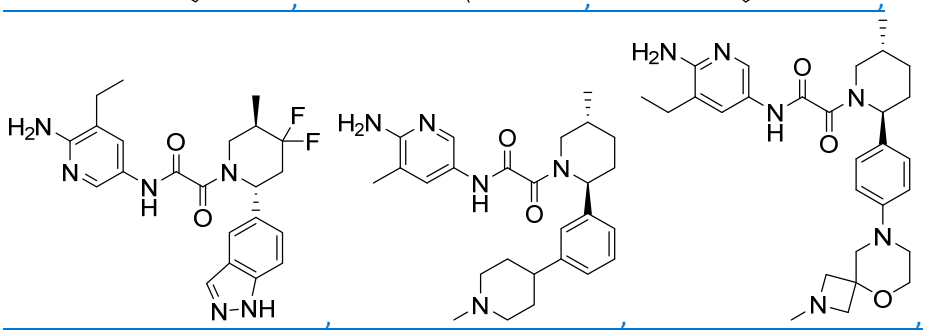


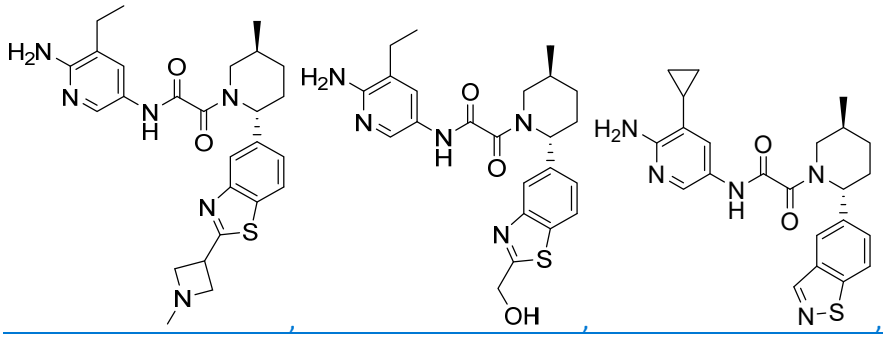


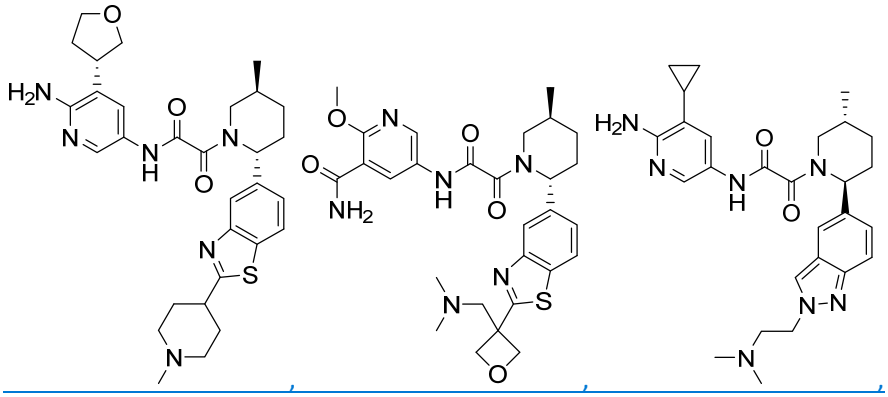


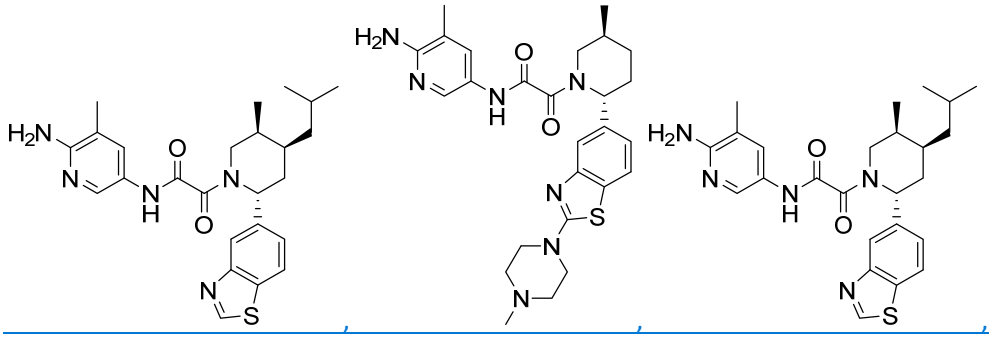


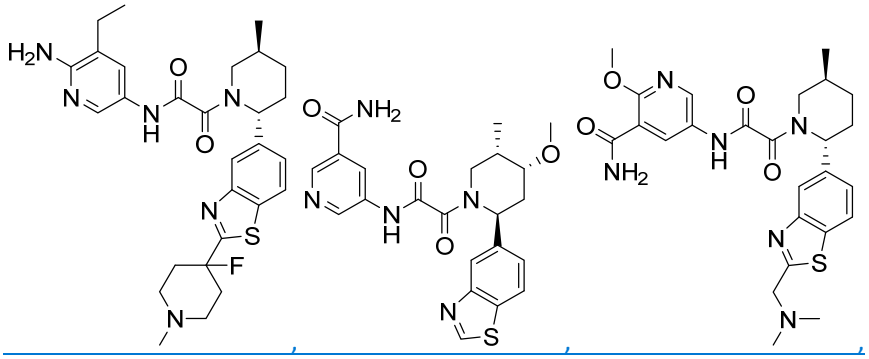


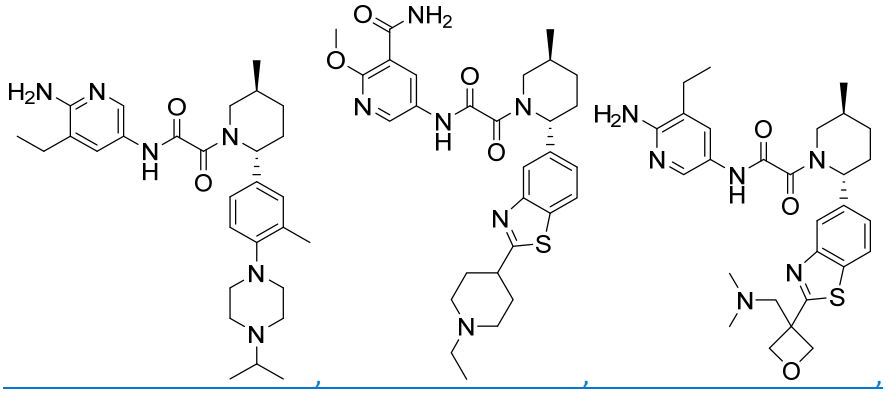


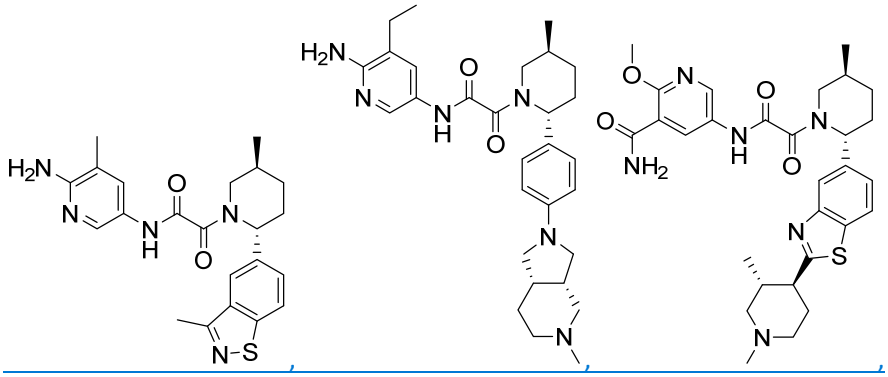


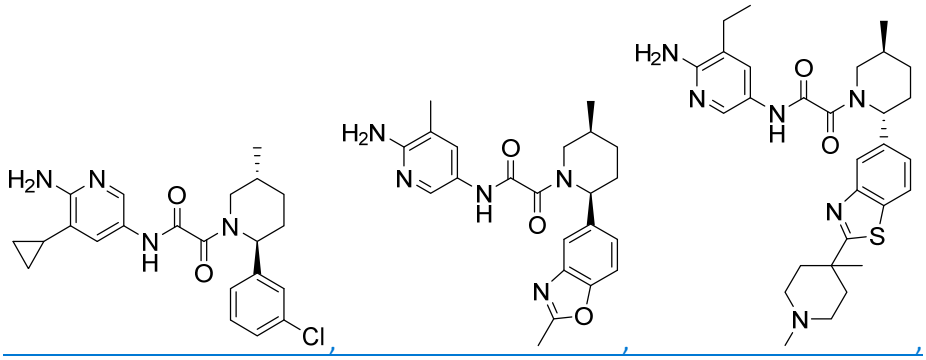


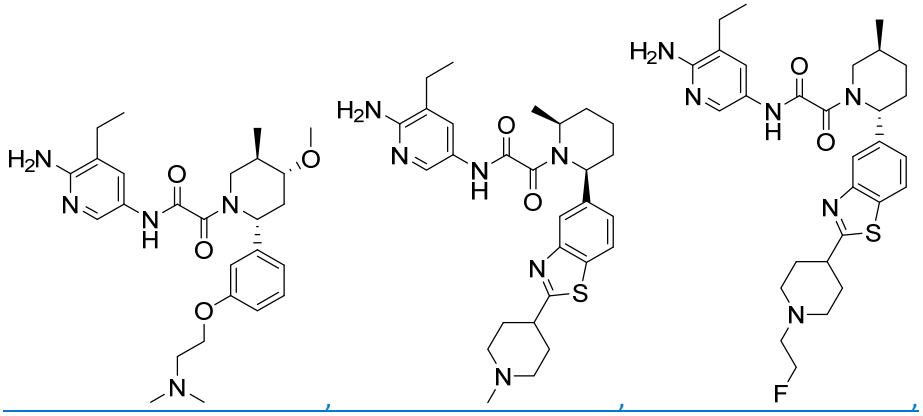


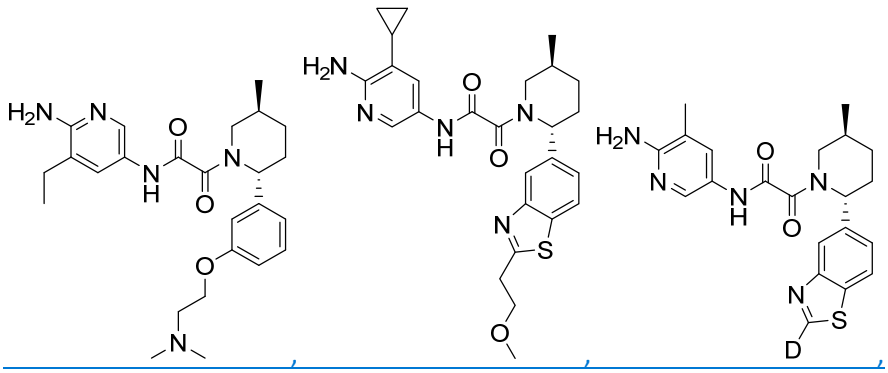


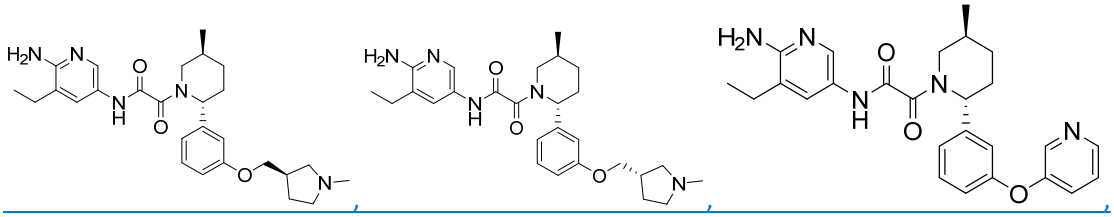


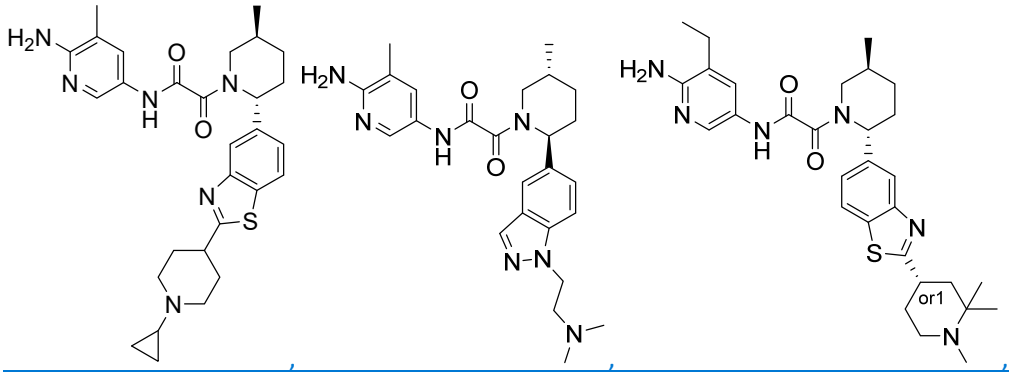


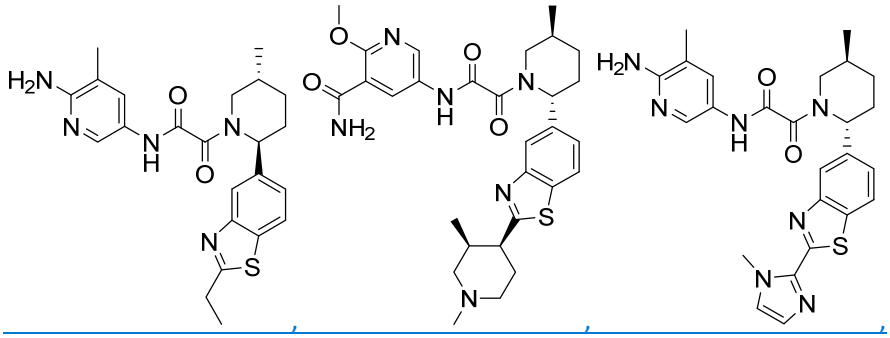


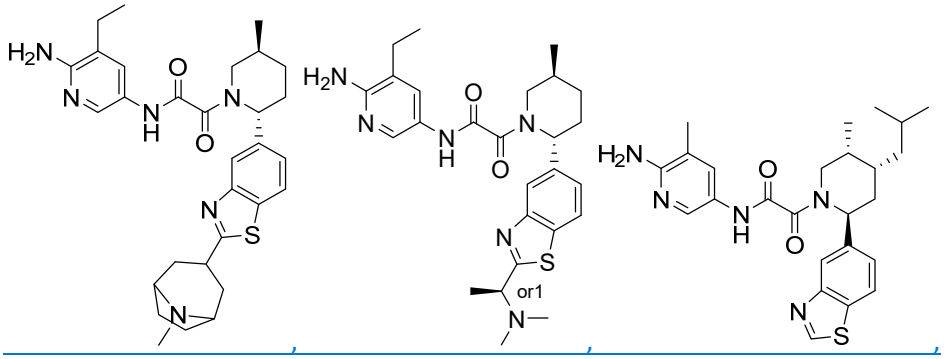


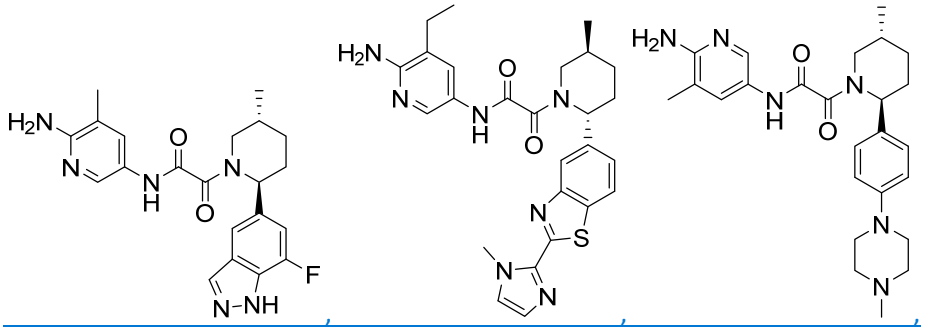


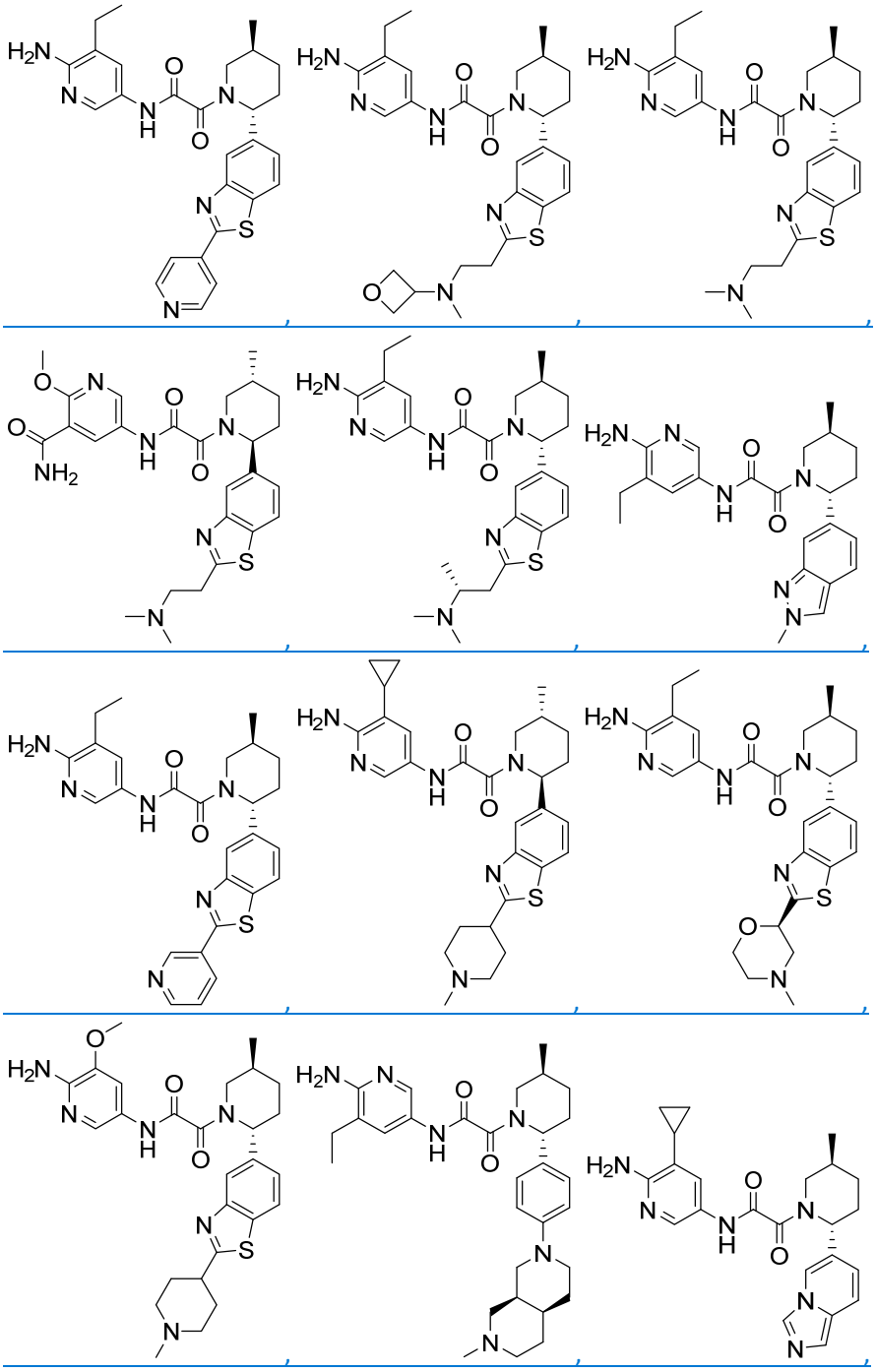


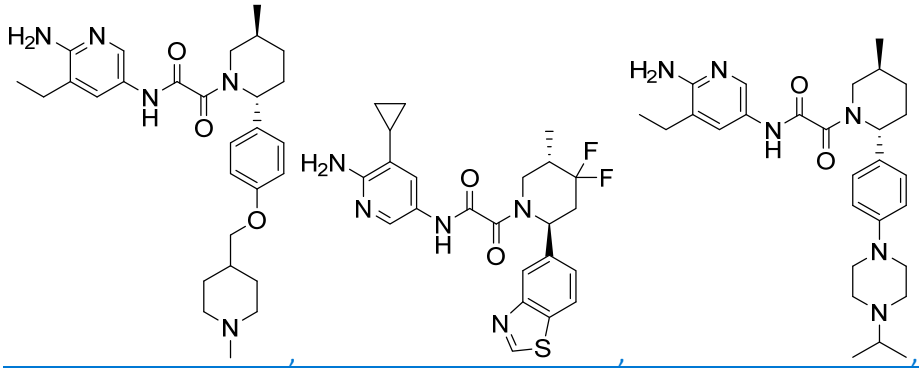


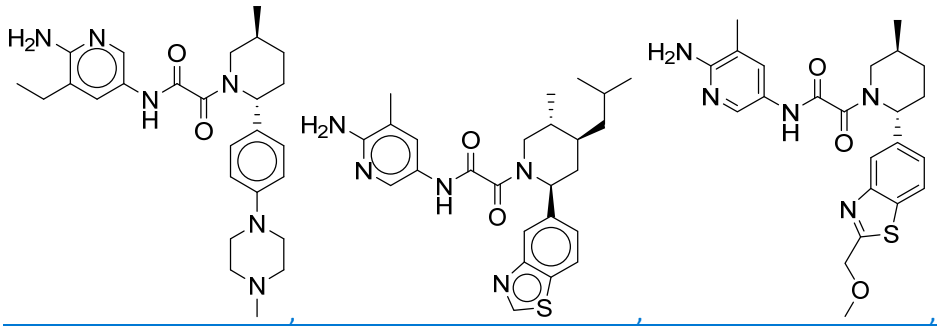


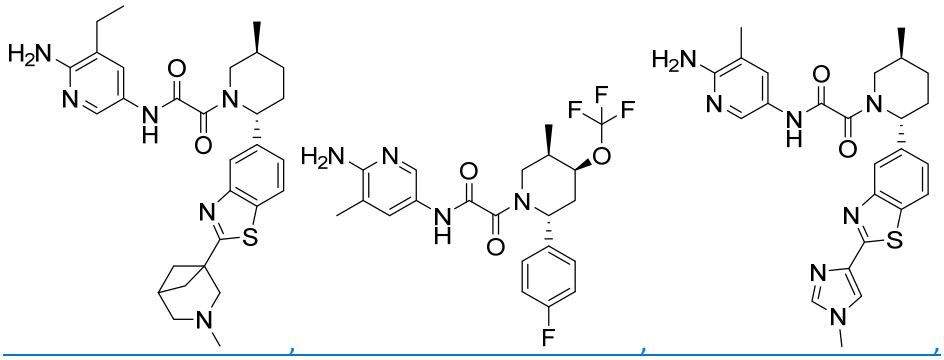


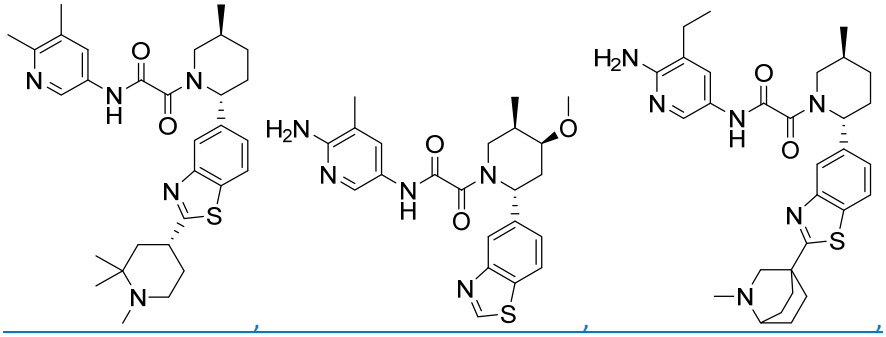


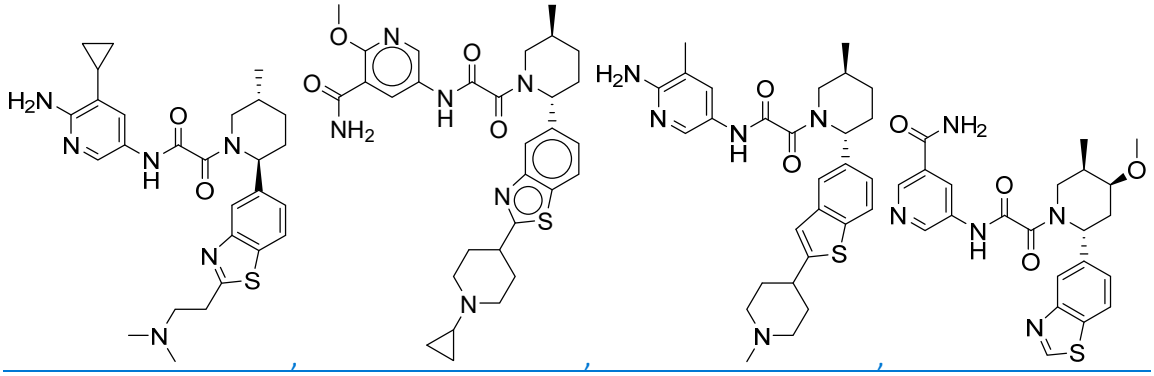


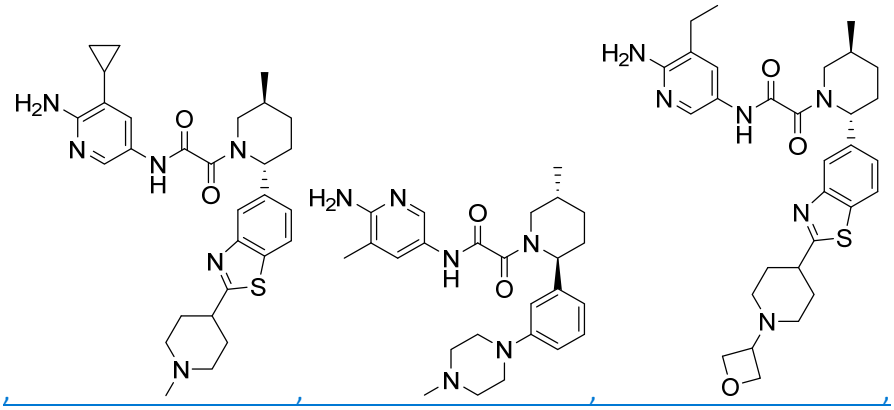


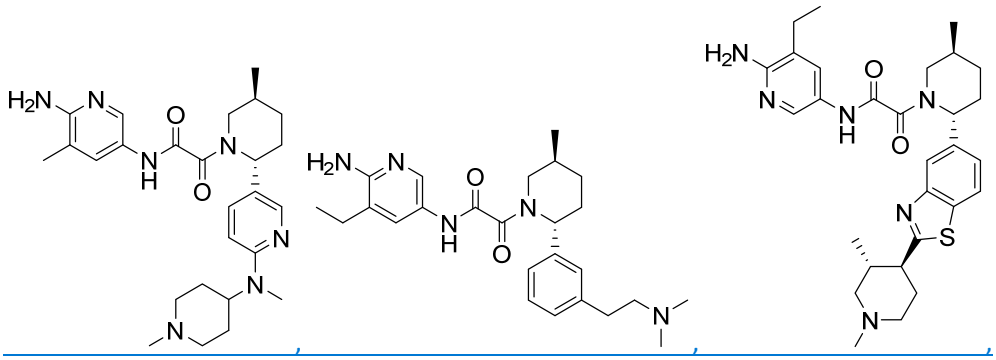


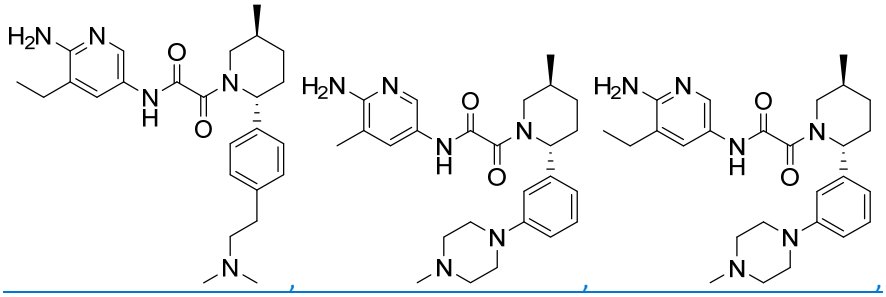


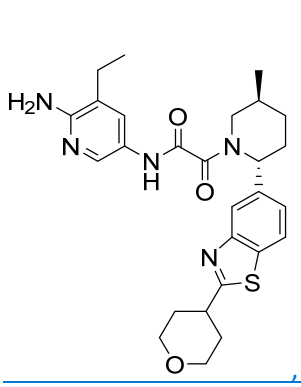
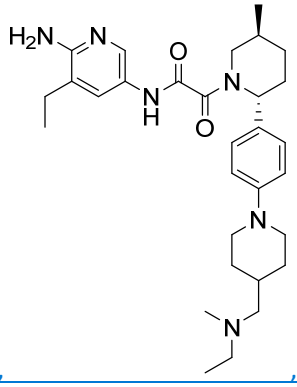
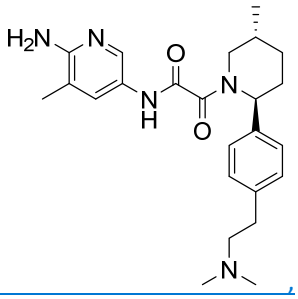
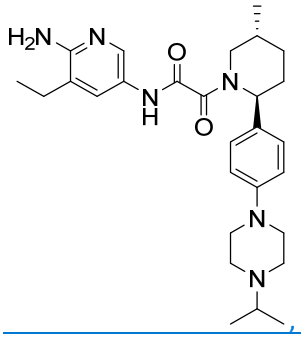
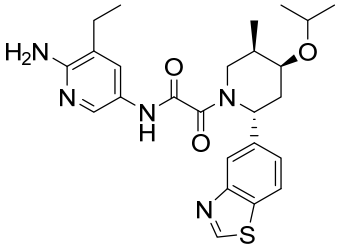
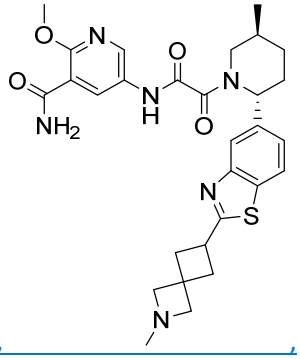
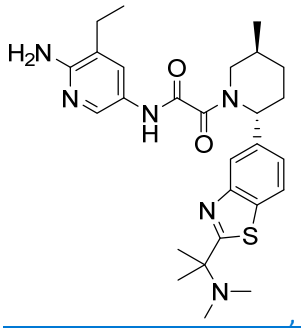
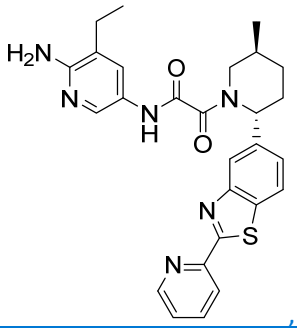
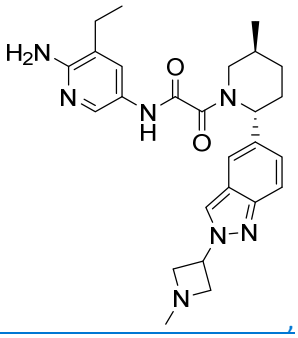
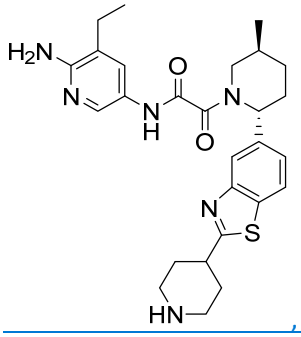
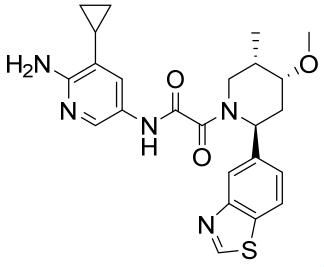
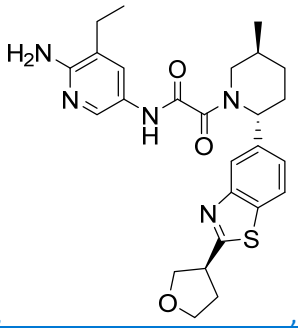


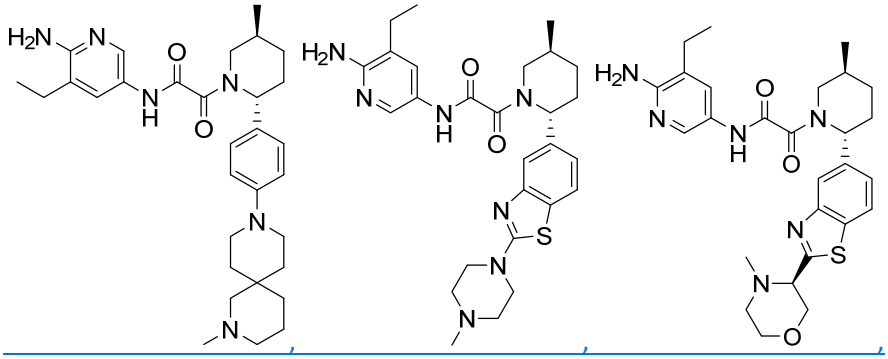


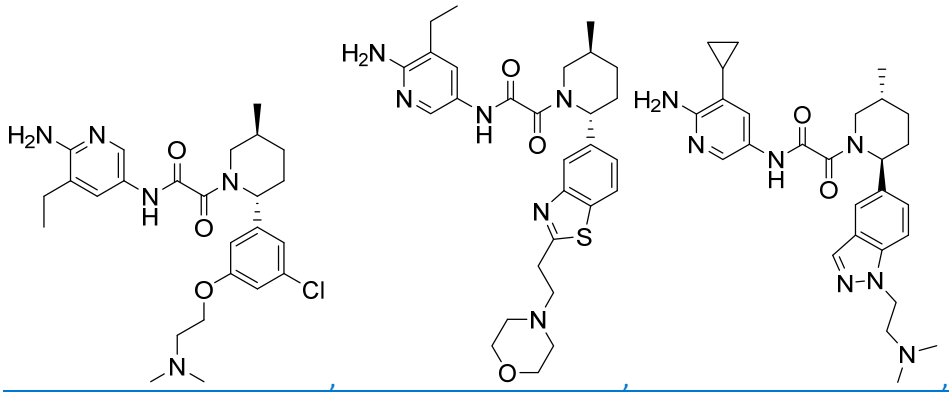


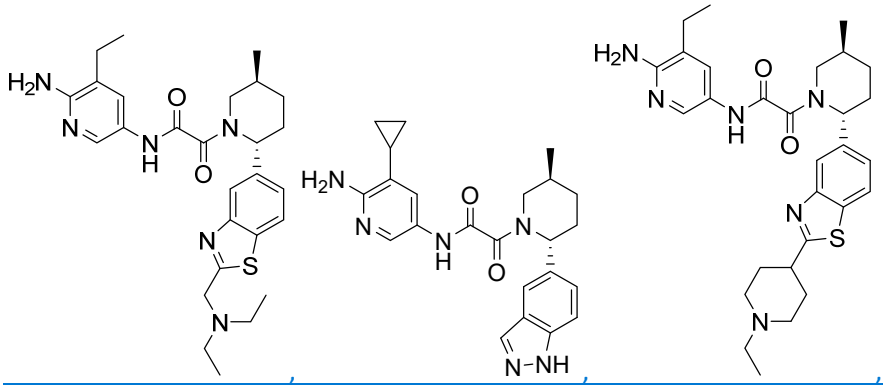


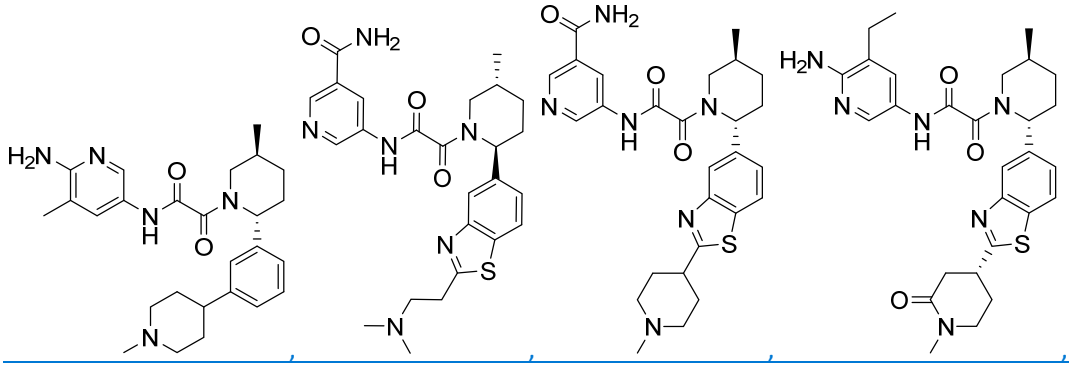


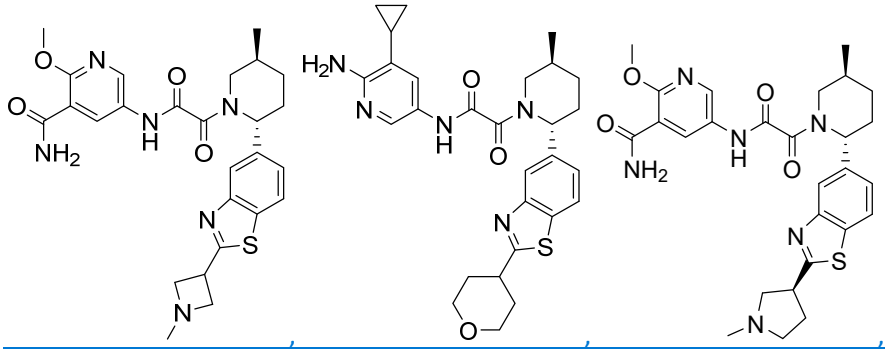













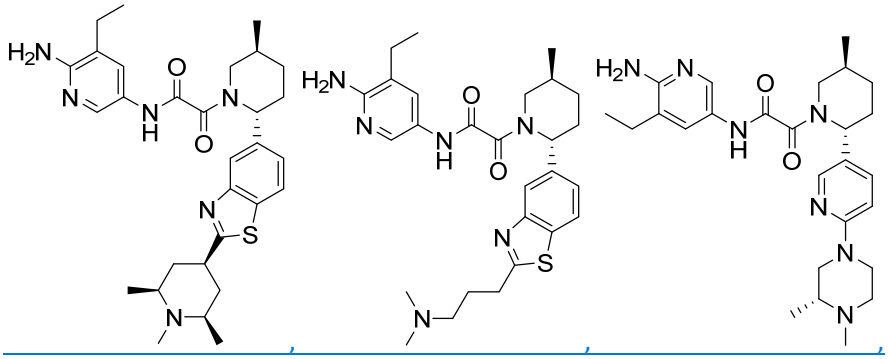


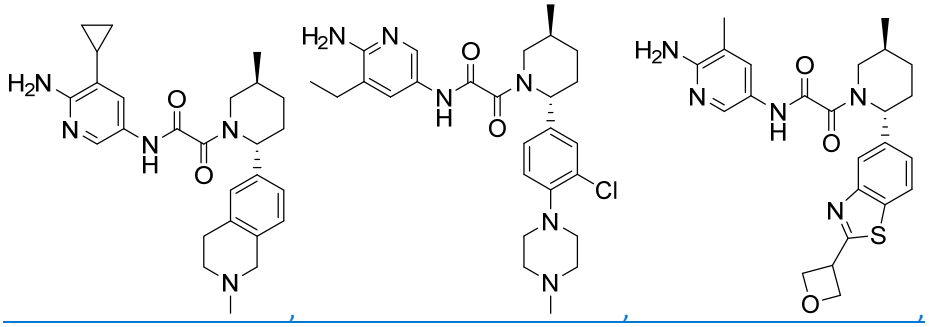


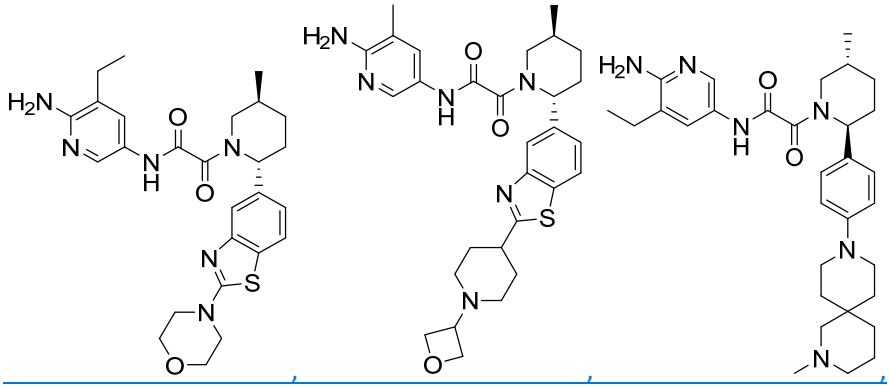


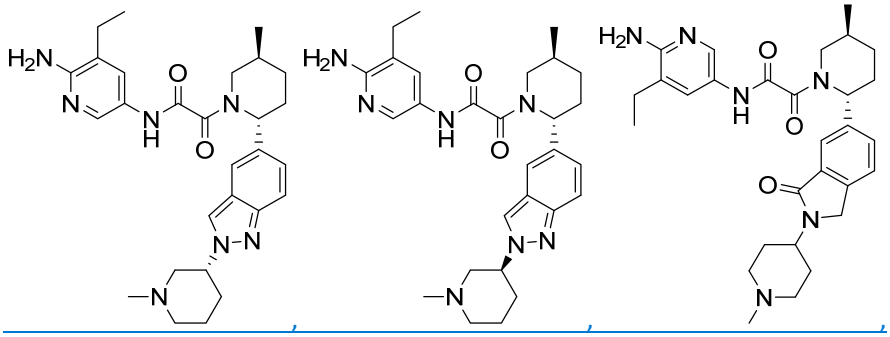


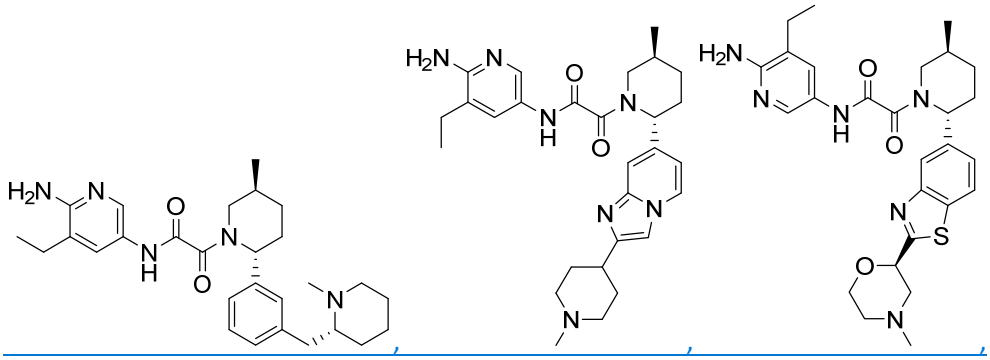


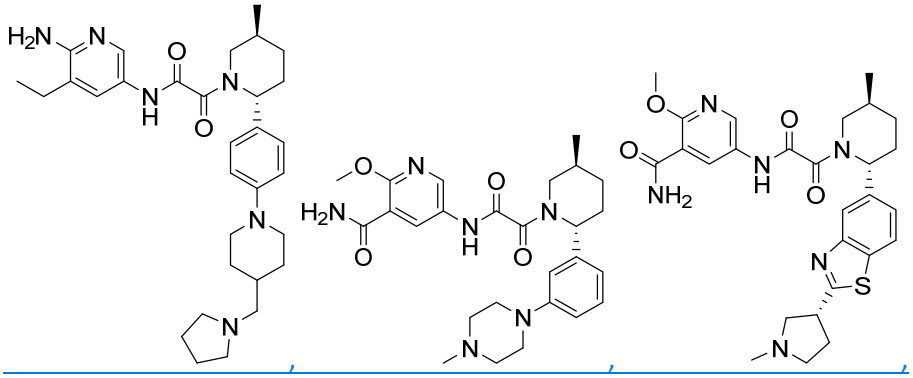


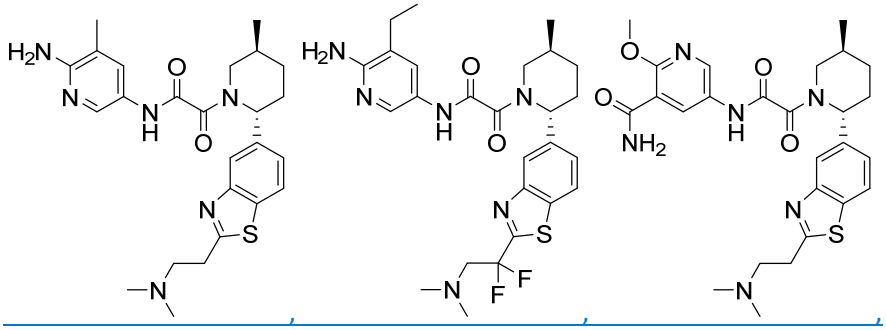


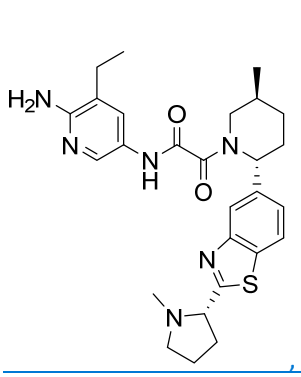
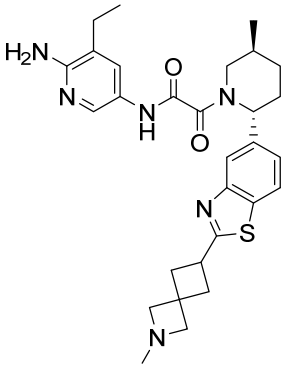
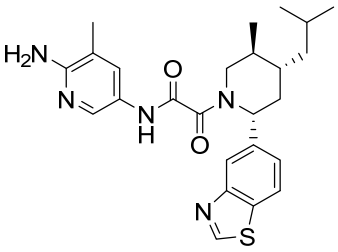
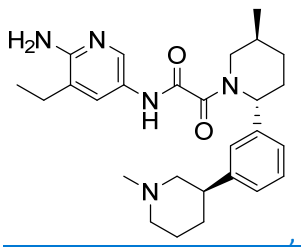
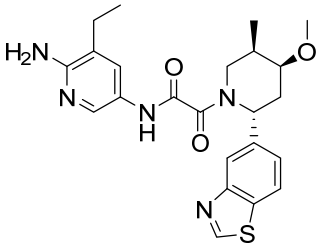
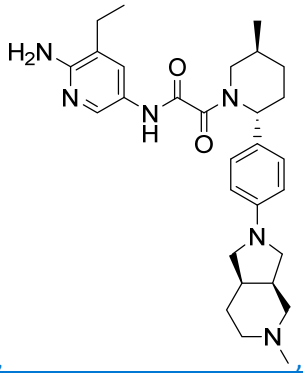
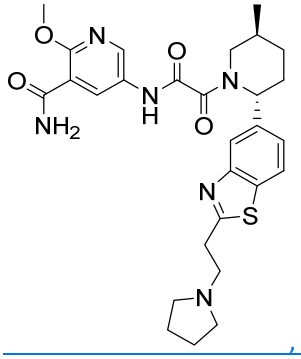
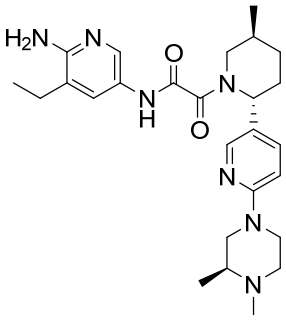
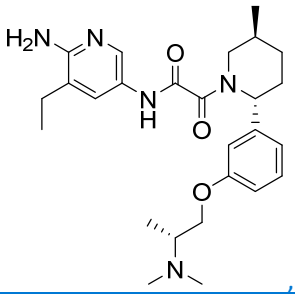
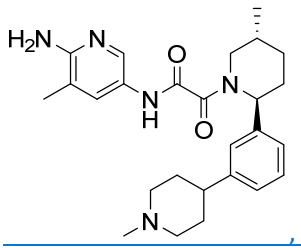
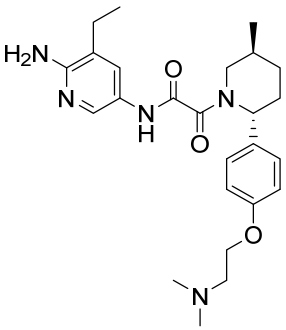
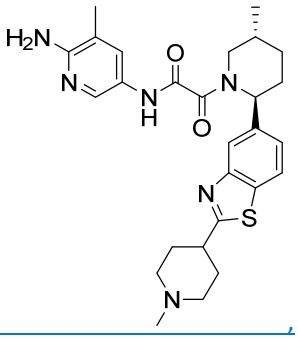


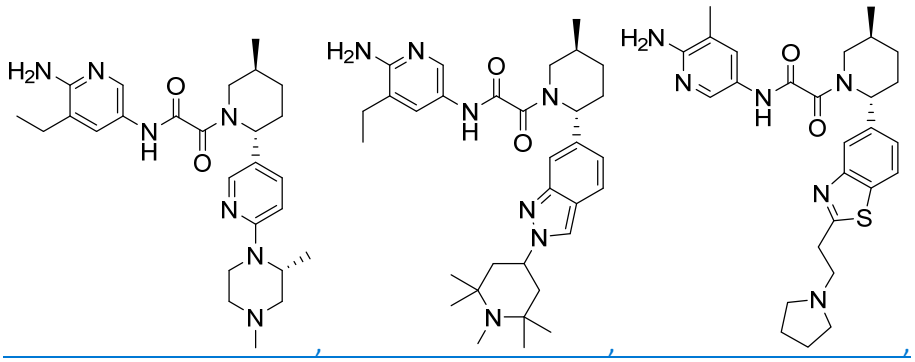


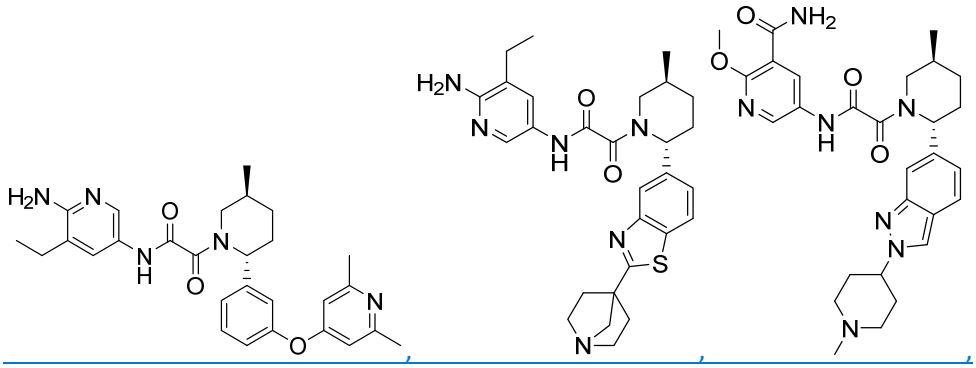


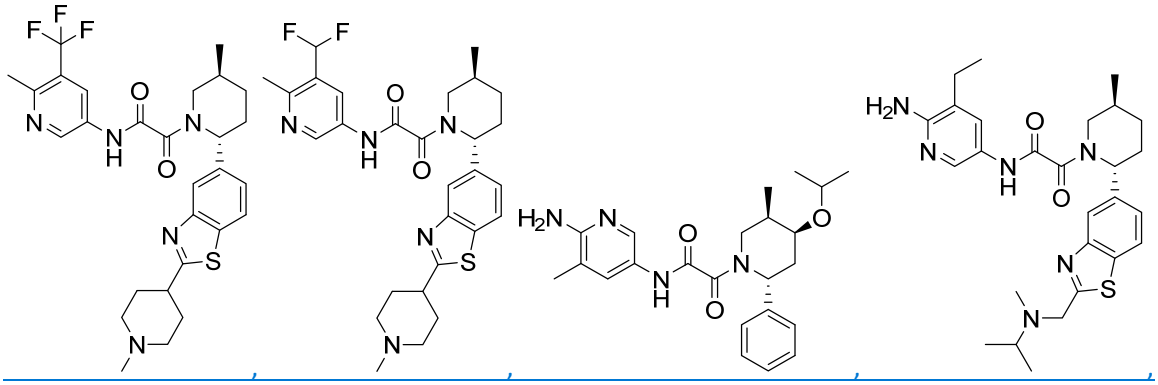


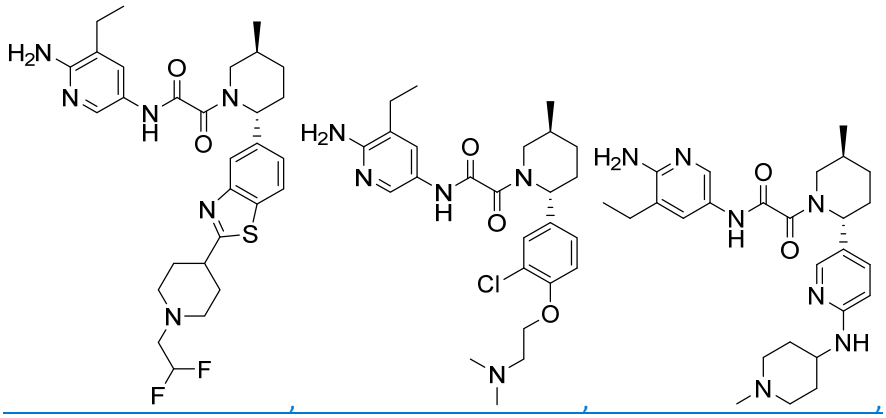


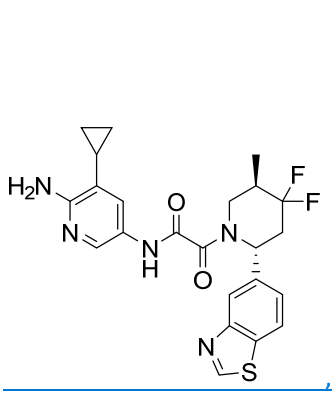
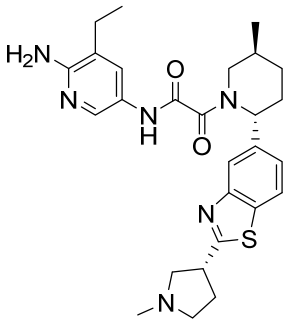
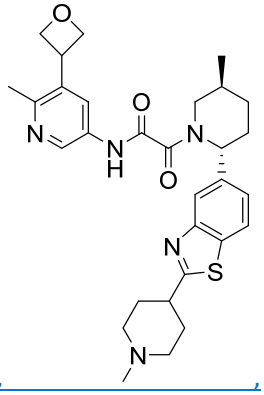
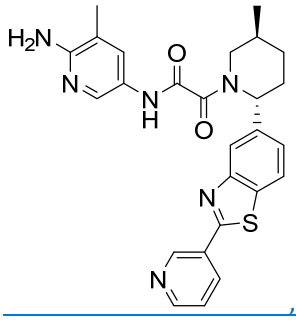
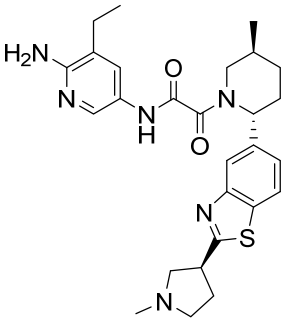
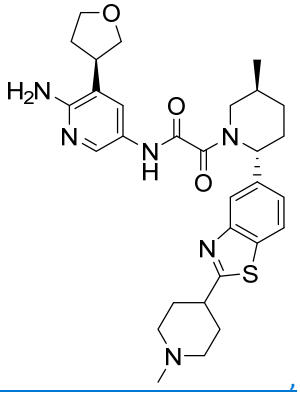
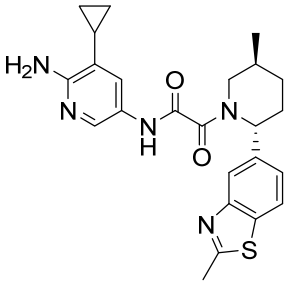
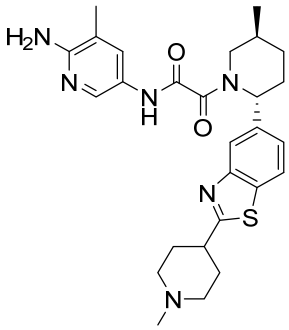
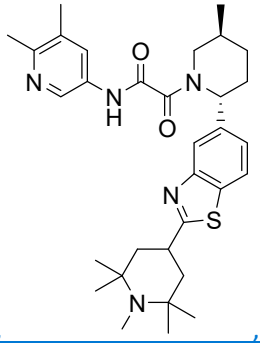
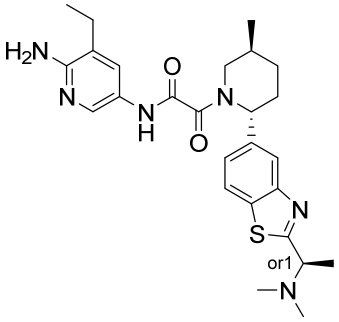
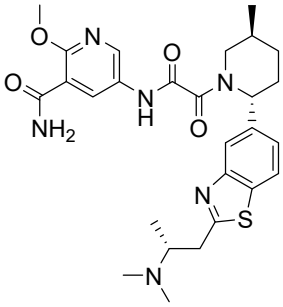
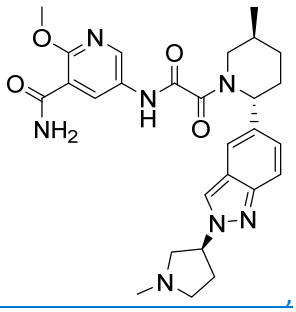













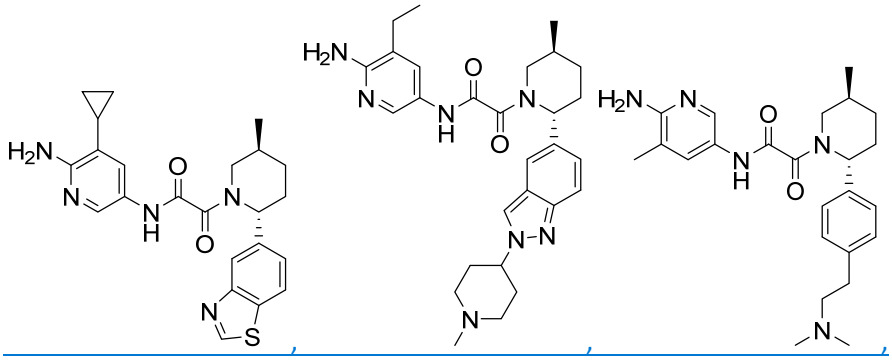


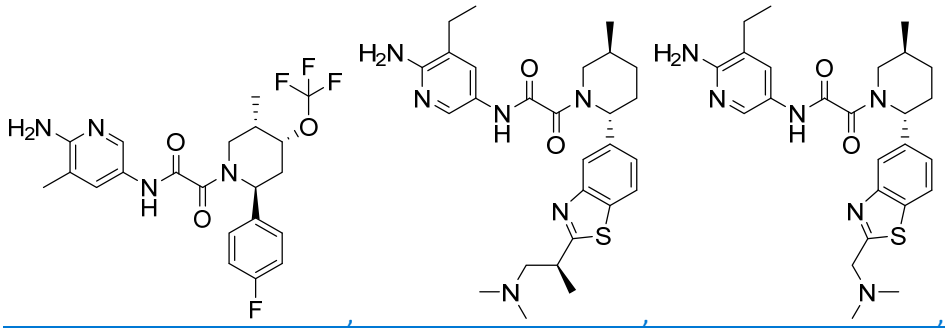


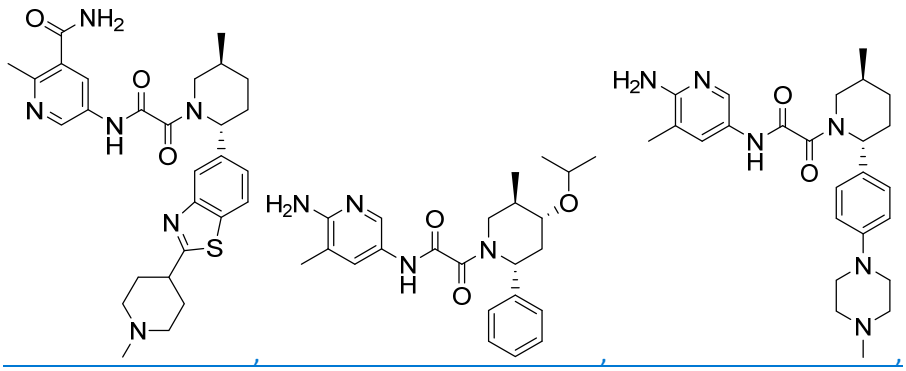


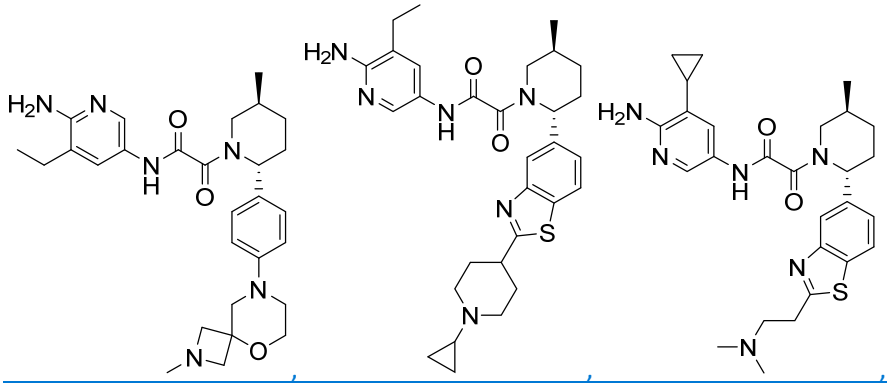


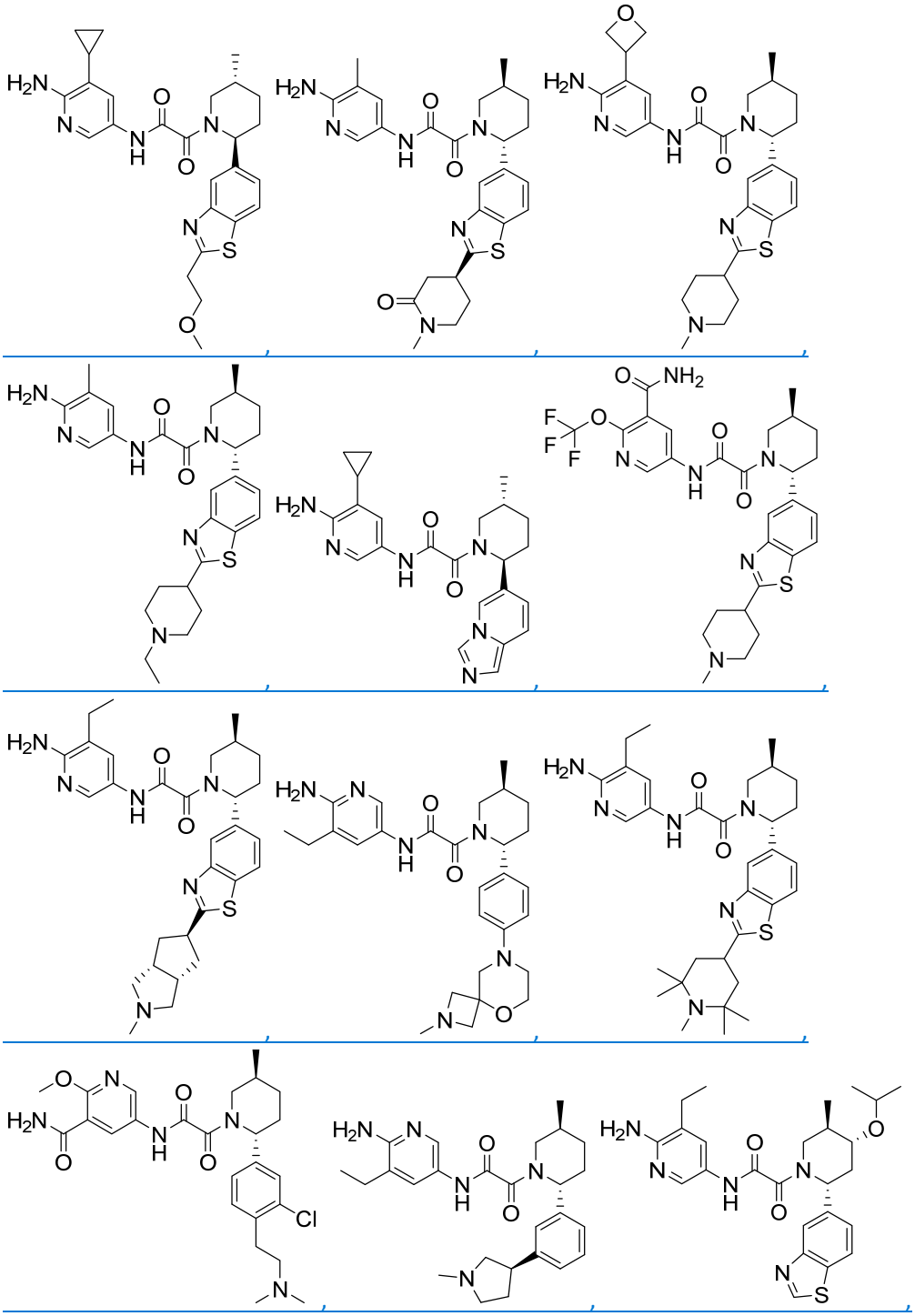













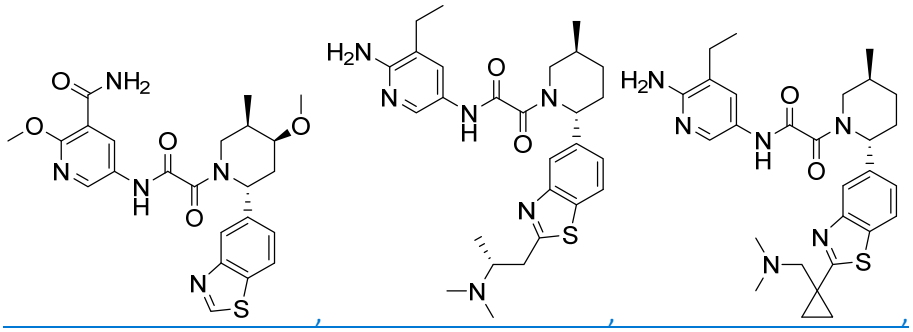


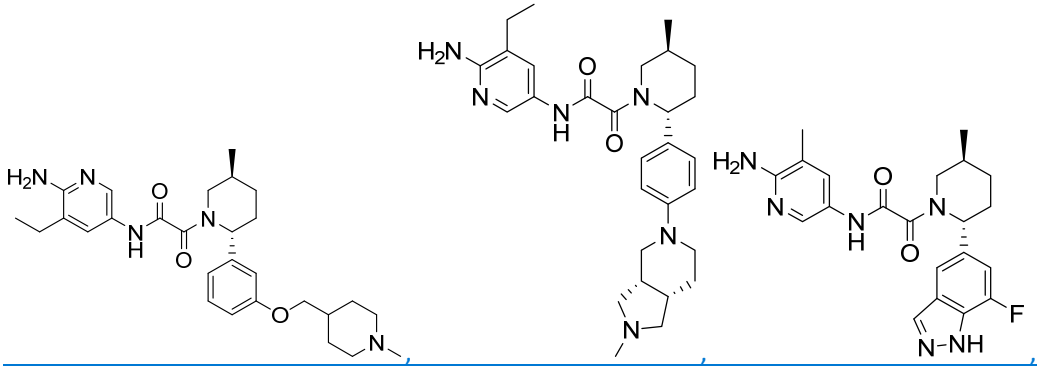


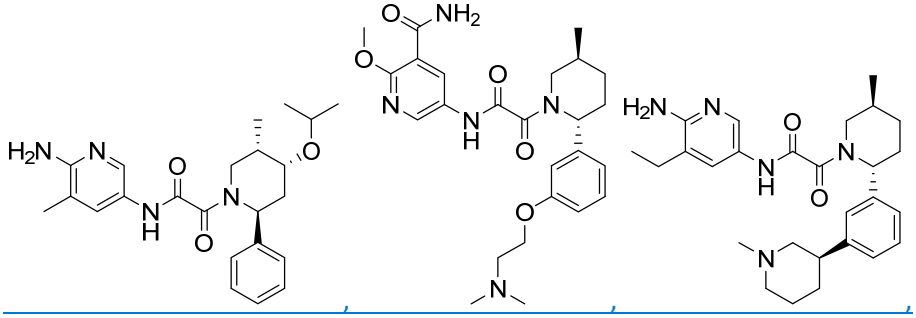


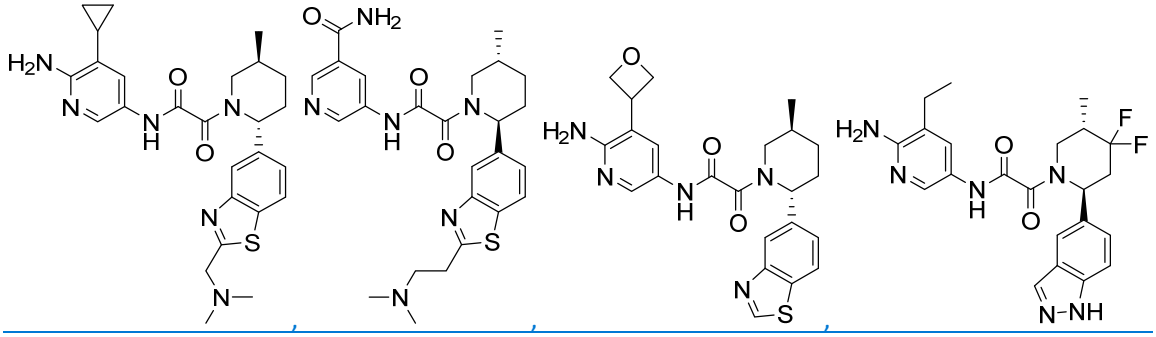


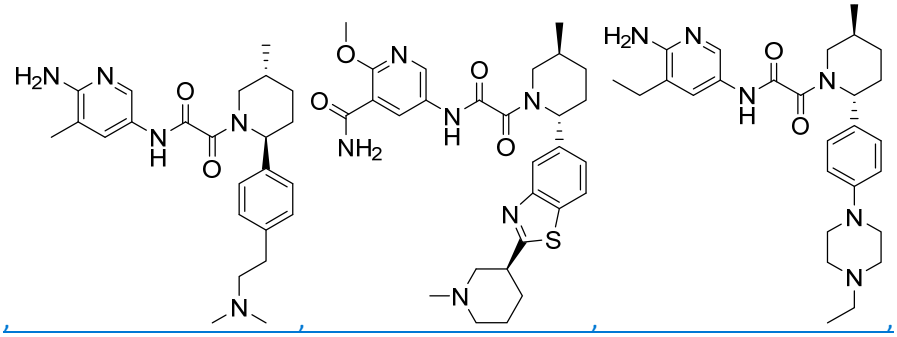


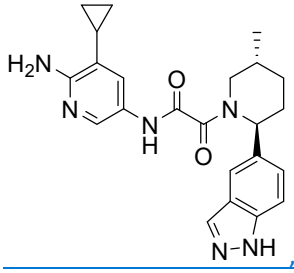
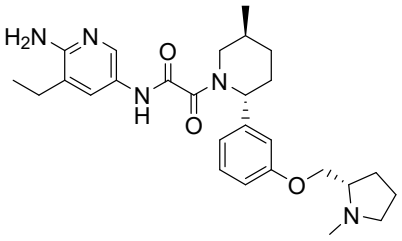
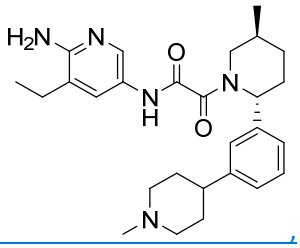
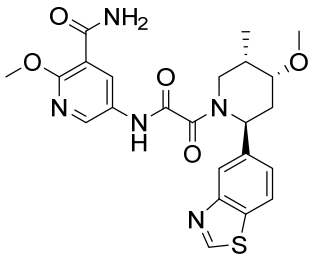
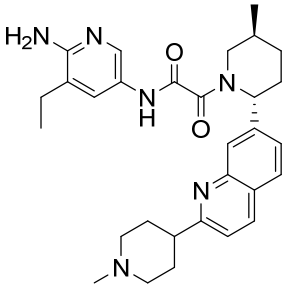
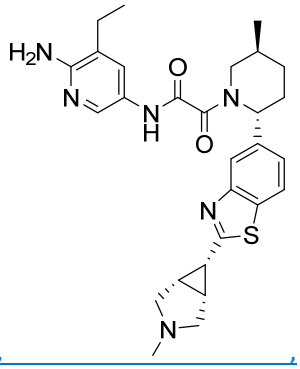
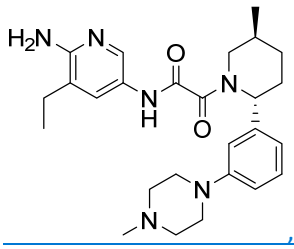
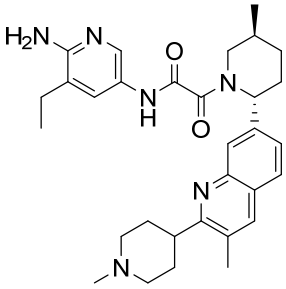
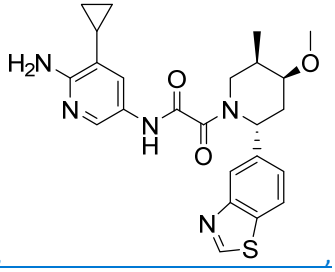
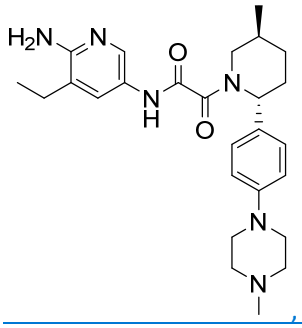
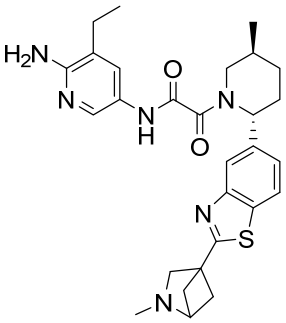
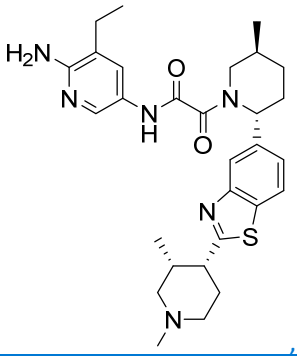
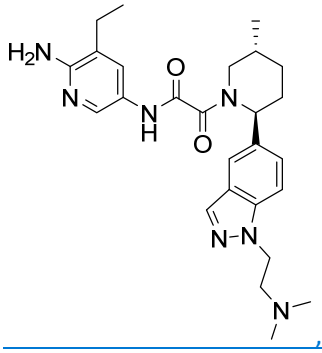
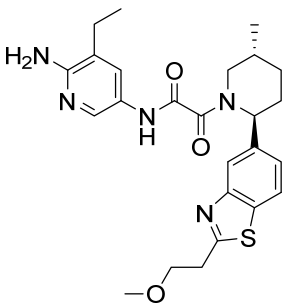
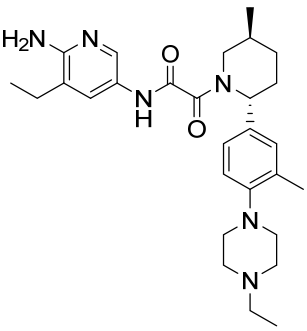


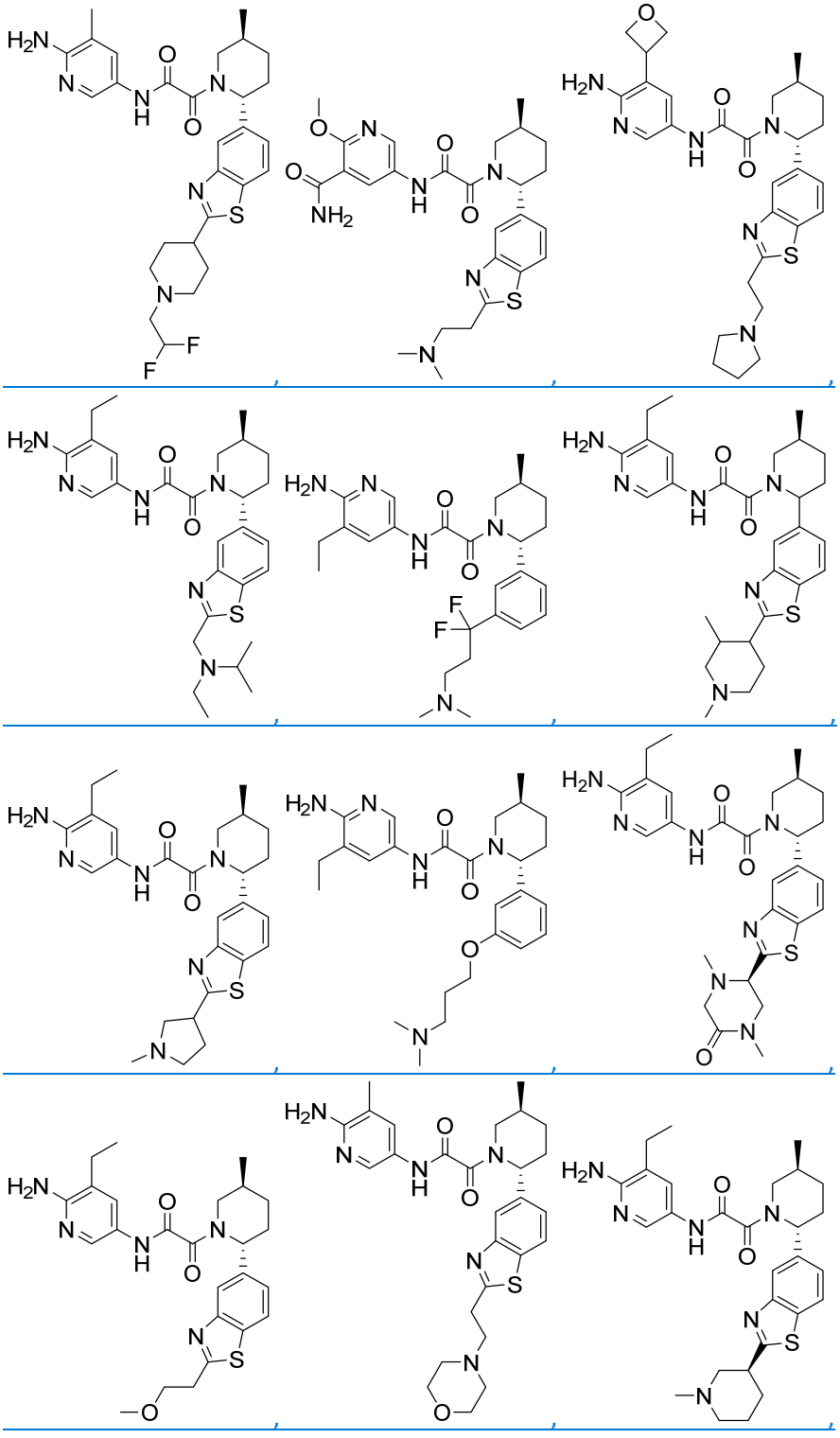


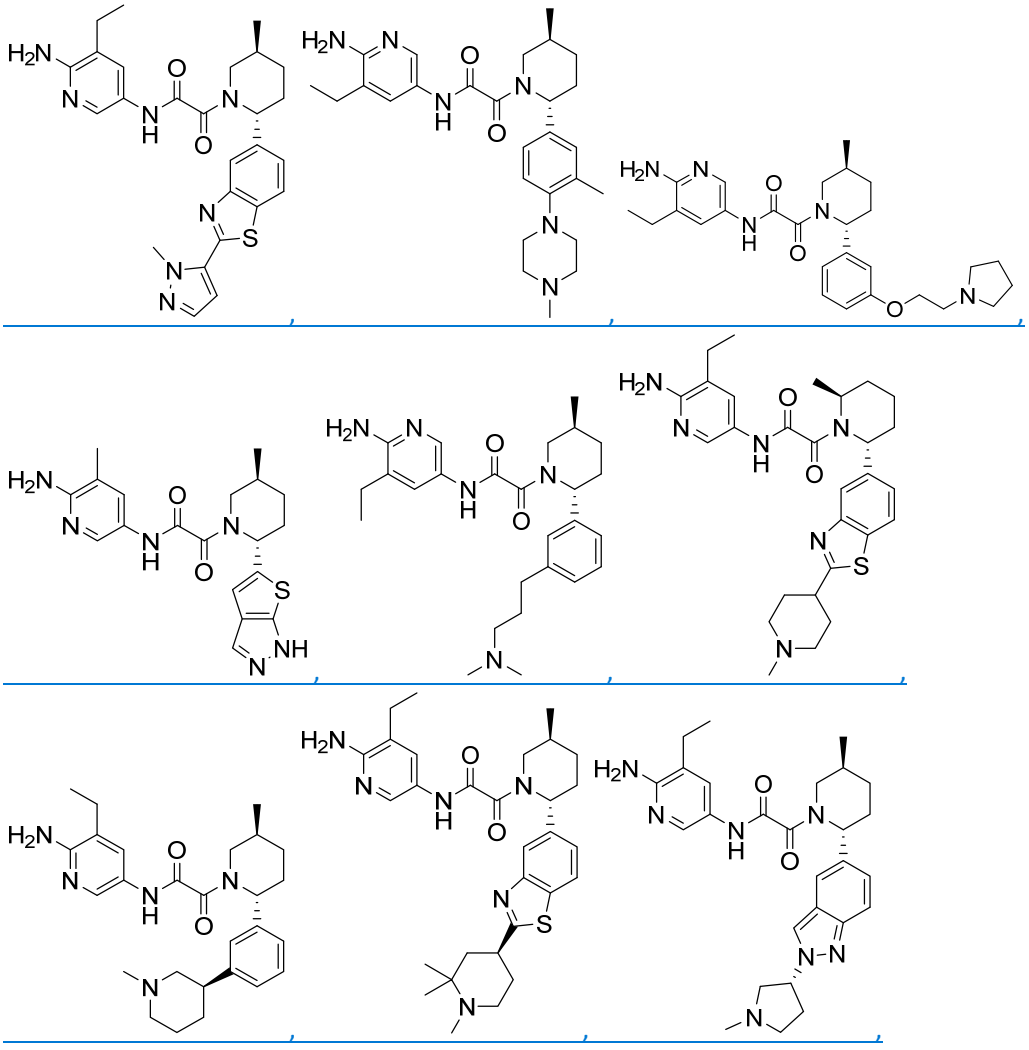


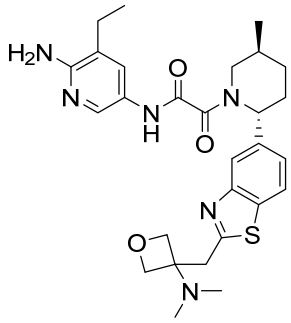
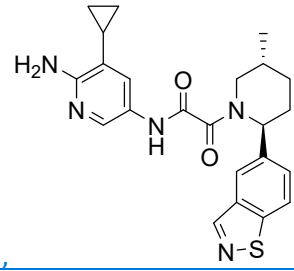
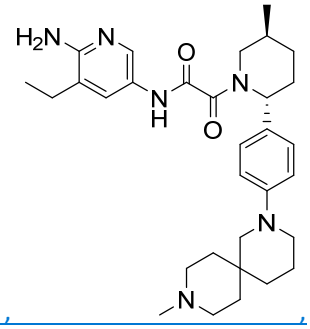


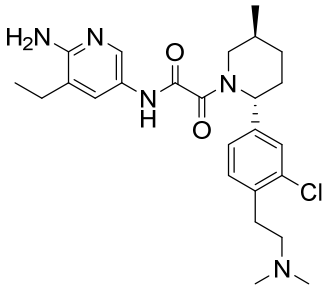
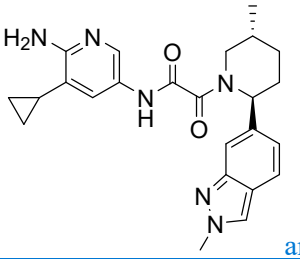
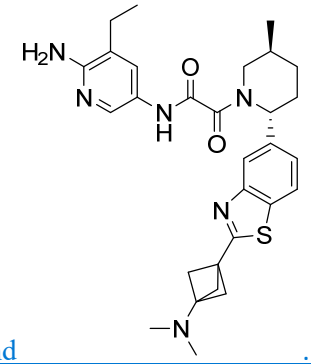


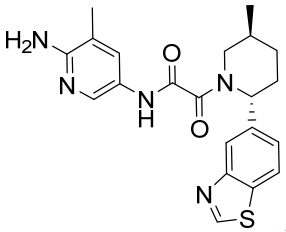
















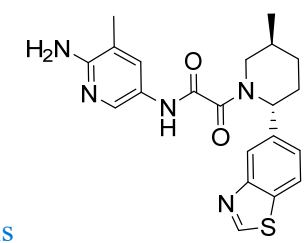


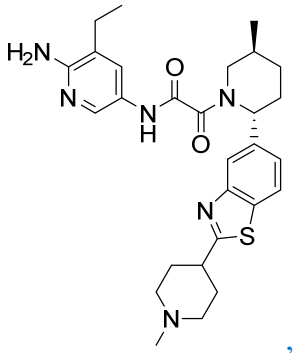


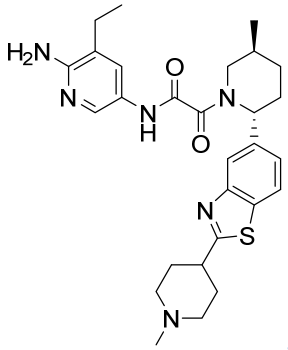
 ,  ,  ,

 ,  and  .

48. The compound of claim 47, wherein the compound is  , or a pharmaceutically acceptable salt thereof.

49. The compound of claim 47, wherein the compound is  .

50. The compound of claim 47, wherein the compound is  , or a pharmaceutically acceptable salt thereof.

51. The compound of claim 47, wherein the compound is  .

52~~106~~. A pharmaceutical composition comprising a compound of any one of claims 1 to 51, or a pharmaceutically acceptable salt thereof~~105~~ and a pharmaceutically acceptable carrier.

53~~107~~. The pharmaceutical composition of claim 52~~106~~, further comprising a second therapeutic agent.

54~~108~~. A compound of any one of claims 1 to 51 or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable composition of claim 52, for use in~~A method of~~ treating an MTAP-deficient and/or an MTA-accumulating disease in a subject in need thereof ~~by administering to the subject a therapeutically effective amount of a compound of any one of claims 1 to 99 or a pharmaceutically acceptable composition of claim 100~~.

55~~109~~. The compound, salt, or composition for use~~method~~ of claim 54~~108~~, wherein the compound, salt, or composition is to be administered in combination with a second therapeutic agent.

~~110.A method of treating an MTAP-deficient and/or an MTA-accumulating disease in a subject in need thereof by administering to the subject a therapeutically effective amount of a pharmaceutically acceptable composition of claim 107.~~

56~~111~~. The compound, salt, or composition for use~~method~~ of ~~any one of~~ claim~~s~~ 54 or 55,~~108 to 110~~ wherein the disease is a proliferating disease.

57~~112~~. The compound, salt, or composition for use~~method~~ of claim 56~~111~~ wherein the disease is an MTAP-deficient and/or MTA-accumulating cancer.

58~~113~~. The compound, salt, or composition for use~~method~~ of claim 57~~112~~, wherein the cancer is glioblastoma, malignant peripheral nerve sheath tumors (MPNST), esophageal cancer, ~~(*e.g.*, esophageal squamous cell carcinoma or esophageal adenocarcinoma),~~ bladder cancer, ~~(*e.g.*, bladder urothelial carcinoma),~~ pancreatic cancer, ~~(*e.g.*, pancreatic adenocarcinoma),~~ mesothelioma, melanoma, non-small cell lung cancer, ~~(NSCLC; *e.g.*, lung squamous or lung adenocarcinoma),~~ astrocytoma, undifferentiated pleiomorphic sarcoma, diffuse large B-cell lymphoma (DLBCL), leukemia, head and neck cancer, stomach adenocarcinoma, myxofibrosarcoma, cholangiosarcoma, brain cancer ~~of the brain~~, stomach cancer, kidney cancer, breast cancer, endometrium cancer, urinary tract cancer, liver cancer, soft tissue cancer, pleura cancer,~~and~~ large intestine cancer or a sarcoma.

59. The compound, salt, or composition for use of claim 57, wherein the cancer is glioblastoma, malignant peripheral nerve sheath tumors (MPNST), esophageal squamous cell carcinoma, esophageal adenocarcinoma, bladder urothelial carcinoma, pancreatic adenocarcinoma, mesothelioma, melanoma, lung squamous cancer, lung adenocarcinoma, astrocytoma, undifferentiated pleiomorphic sarcoma, diffuse large B-cell lymphoma (DLBCL), leukemia, head and neck cancer, stomach adenocarcinoma, myxofibrosarcoma, cholangiosarcoma, brain cancer, stomach cancer, kidney cancer, breast cancer, endometrium cancer, urinary tract cancer, liver cancer, soft tissue cancer, pleura cancer and large intestine cancer or a sarcoma.

60~~114~~. A compound of any one of claims 1 to 51, for use in ~~method of~~ treating a cancer in a subject ~~in need thereof~~, wherein ~~comprising the steps of~~:

a) ~~assessing~~ the level of MTAP and/or MTA in a test sample obtained from said subject is assessed, wherein the MTA level can be assessed directly or indirectly;~~(*e.g.*, by ELISA or LC-MS/MS) or indirectly (*e.g.*, by SDMA-modified protein ELISA or IHC, or by RNA splicing);~~

b) ~~comparing~~ the test sample is compared with a reference, wherein MTAP deficiency and/or MTA accumulation in said test sample compared to the reference indicates the cancer in said subject will respond to therapeutic treatment with a PRMT5 inhibitor; and

c) ~~administering a therapeutically effective amount of~~ athe compound ~~of any one of claims 1 to 99 or composition of claim 100 or 101~~ is to be administered to the subject identified in step b).

61. Use of a compound of any one of claims 1 to 51, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating an MTAP-deficient and/or an MTA-accumulating disease in a subject in need thereof.

62. The use according to claim 61, wherein the medicament is configured to be administered in combination with a second therapeutic agent.

63. The use according to claim 61 or 62, wherein the disease is a proliferating disease.

64. The use according to claim 63, wherein the disease is an MTAP-deficient and/or MTA-accumulating cancer.

65. The use according to claim 64, wherein the cancer is glioblastoma, malignant peripheral nerve sheath tumors (MPNST), esophageal cancer, bladder cancer, pancreatic cancer, mesothelioma, melanoma, non-small cell lung cancer, astrocytoma, undifferentiated pleiomorphic sarcoma, diffuse large B-cell lymphoma (DLBCL), leukemia, head and neck cancer, stomach adenocarcinoma, myxofibrosarcoma, cholangiosarcoma, brain cancer, stomach cancer, kidney cancer, breast cancer, endometrium cancer, urinary tract cancer, liver cancer, soft tissue cancer, pleura cancer, large intestine cancer or a sarcoma.

66. The use according to claim 64, wherein the cancer is glioblastoma, malignant peripheral nerve sheath tumors (MPNST), esophageal squamous cell carcinoma, esophageal adenocarcinoma, bladder urothelial carcinoma, pancreatic adenocarcinoma, mesothelioma, melanoma, lung squamous cancer, lung adenocarcinoma, astrocytoma, undifferentiated pleiomorphic sarcoma, diffuse large B-cell lymphoma (DLBCL), leukemia, head and neck cancer, stomach adenocarcinoma, myxofibrosarcoma, cholangiosarcoma, brain cancer, stomach cancer, kidney cancer, breast cancer, endometrium cancer, urinary tract cancer, liver cancer, soft tissue cancer, pleura cancer, large intestine cancer or a sarcoma.