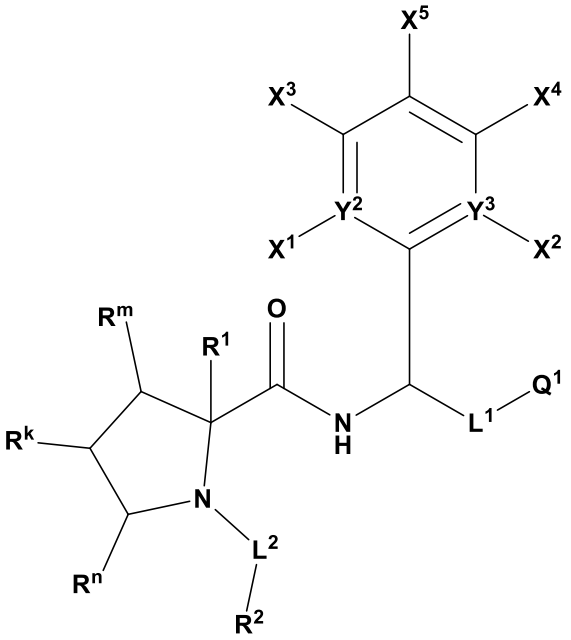
[0005] The reliance on high levels of glycogen by clear cell cancers has recently emerged as a novel therapeutic target. Ewing sarcoma (ES), clear cell renal cell carcinoma (ccRCC), glycogen rich clear cell carcinoma breast cancer (GRCC), acute myeloid leukemia (AML), and nonsmall-cell lung carcinoma (NSCLC) are all examples of cancers histopathologically defined by PAS+ abnormally high levels of cellular glycogen. Elevated transcriptional levels of GYS1 have been significantly correlated with poor disease outcomes in NSCLC (Giatromanolaki A, et al. Expression of enzymes related to glucose metabolism in non-small cell lung cancer and prognosis. Experimental Lung Research, vol. 43, no. 4-5, 2017) and AML (Falantes JF, et al. Overexpression of GYS1, MIF, and MYC is associated with adverse outcome and poor response to azacitidine in myelodysplastic syndromes and acute myeloid leukemia. Clinical Lymphoma, Myeloma & Leukemia, vol. 15, no. 4, 2015). Lentiviral knockdown of GYS1 in cultured myeloid leukemia cells potently inhibited in vitro cancer cell growth and in vivo tumorigenesis (Bhanot H, et al. Pathological glycogenesis through glycogen synthase I and suppression of excessive AMP kinase activity in myeloid leukemia cells. Leukemia, vol. 29, no. 7, 2015). Genetic knock-down of GYS1 in ccRCC cell models both suppresses tumor growth in vivo and increases the synthetic lethality of sunitinub (Chen S, et al. GYS1 induces glycogen accumulation and promotes tumor progression via the NF-kB pathway in clear cell renal carcinoma. Theranostics, vol. 10, no. 20, 2020).

[0006] Reduction of GYS1 enzyme activity and reduced cellular stores of glycogen in preclinical models of Pompe disease, APBD, LD, AML, ccRCC, and NSCLC all provide compelling evidence of the potential therapeutic benefit of inhibiting glycogen synthesis. It is the aim of this invention to inhibit glycogen synthase enzyme activity resulting in reduction of tissue glycogen stores with therapeutic benefit to patients suffering the consequences of accumulated cellular glycogen.

BRIEF SUMMARY

[0006a] In an aspect of the present disclosure, there is provided a compound of formula (I’):



(I'),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein:

Y^2 and Y^3 are each C, or

one of Y^2 and Y^3 is N and the other of Y^2 and Y^3 is C;

X^1 and X^2 are each independently H, C_{1-6}alkyl, or C_{1-6}alkoxy;

X^3 and X^4 are each independently H, halo, C_{1-6}alkyl, C_{1-6}alkoxy, or 5-20 membered heteroaryl, wherein the C_{1-6}alkyl of X^3 and X^4 is optionally substituted with one of more halo;

X^5 is H, C_{1-6}alkyl, C_{1-6}alkoxy, or C_{3-10}cycloalkyl;

either

(1) L^1 is absent; and

Q^1 is selected from (i) to (iv):

(i) phenyl, wherein the phenyl of Q^1 is substituted with one or more halo, C_{1-6}alkyl, C_{2-6}alkenyl, -NH_2, -NH-C(O)-(C_{1-6}alkyl), -NH-C(O)-(3-15 membered heterocyclyl), C_{3-10}cycloalkyl, or 5-20 membered heteroaryl, wherein

the C_{1-6}alkyl is optionally substituted with one or more halo, -NH-C(O)-NH(C_{1-6}alkyl), -NH-C(O)-C_{1-6}alkyl, or -NH-C(O)-C_{1-6}alkoxy,

the C_{3-10}cycloalkyl is optionally substituted with one or more halo or C_{1-6}alkyl, and

the 5-20 membered heteroaryl is optionally substituted with one or more C_{1-6}alkyl,

(ii) 3-15 membered heterocyclyl, wherein the 3-15 membered heterocyclyl of Q^1 is optionally substituted with one or more oxo, or C_{1-6}alkyl,

(iii) 5-20 membered heteroaryl, wherein the 5-20 membered heteroaryl of Q^1 is optionally substituted with one or more halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{1-6}alkoxy, -NH_2, or C_{3-10}cycloalkyl, wherein,

the C_{1-6}alkyl is optionally substituted with one or more halo, and

the C_{3-10}cycloalkyl is optionally substituted with one or more halo or C_{1-6}alkyl, and

(iv) C_{3-10}cycloalkyl;

or

(2) L^1 is -CH_2-; and

Q^1 is C_{3-10}cycloalkyl;

L^2 is -C(O)- or -$S(O)_2$-

R^1 is H or C_{1-6}alkyl;

R^k is halo, -OH, -NH_2, or -NH-C(O)C_{1-6}alkyl;

R^m is H, -OH, or C_{1-6}alkyl;

R^n is H, C_{1-6}alkyl, or C_{3-10}cycloalkyl or R^n taken together with the carbon atom to which it is attached forms C_{3-5} cycloalkyl;

or R^k is taken together with either R^m or R^n, and the atoms to which they are attached, to form cyclopropyl; and

R^2 is selected from (i) to (vii):

(i) C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^2 is optionally substituted with one or more R^a, wherein R^a is:

(a) -OH,

(b) cyano,

(c) C_{2-6}alkynyl,

(d) C_{6-20}aryl, wherein the C_{6-20}aryl of R^a is optionally substituted with one or more halo, cyano, C_{1-6}alkoxy, or -NH-C(O)-C_{1-6}alkyl,

(e) 3-15 membered heterocyclyl, wherein the 3-15 membered heterocyclyl of R^a is optionally substituted with one or more R^c, wherein

R^c is halo, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, -C(O)-C_{1-6}alkyl, or -C(O)-C_{1-6}alkoxy, wherein

the C_{1-6}alkyl of R^c is optionally substituted with one or more halo or C_{2-6}alkynyl, and

the -C(O)-C_{1-6}alkoxy of R^c is optionally substituted with one or more halo,

(f) -N(R^c)(R^d), wherein R^c and R^d of -N(R^c)(R^d) are, independently of each other, H, C_{1-6}alkyl,
-C(O)-C_{1-6}alkyl, -C(O)-C_{1-6}alkoxy, -C(O)-NH_2, -C(O)-NH(C_{1-6}alkyl), -C(O)-N(C_{1-6}alkyl)$_2$, -C(O)-(3-15 membered heterocyclyl), -CH_2-C(O)-NH_2, 3-15 membered heterocyclyl, or 5-20 membered heteroaryl, wherein

the C_{1-6}alkyl of R^c or R^d is optionally substituted with one or more -C(O)-NH_2,

the -C(O)-C_{1-6}alkyl of R^c or R^d is optionally substituted with one or more halo,

the 3-15 membered heterocyclyl and the 5-20 membered heteroaryl of R^c or R^d are independently optionally substituted with one or more C_{1-6}alkyl,

the -C(O)-(3-15 membered heterocyclyl) of R^c or R^d is optionally substituted with one or more halo, -C(O)-C_{1-6}alkoxy, or C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more halo, C_{1-6}alkoxy, or C_{3-10}cycloalkyl, and

the C_{1-6}alkyl of the -C(O)-N(C_{1-6}alkyl)$_2$ of R^c or R^d are, independently of each other, optionally substituted with one or more halo or C_{6-20}aryl,

(g) -O-R^e, wherein R^e is C_{1-6}alkyl, C_{6-20}aryl, -C(O)-(3-15 membered heterocyclyl), -C(O)-N-(C_{1-6}alkyl)$_2$, or 5-20 membered heteroaryl, wherein

the C_{1-6}alkyl of R^e is optionally substituted with one or more C_{1-6}alkoxy, wherein the C_{1-6}alkoxy is optionally substituted with one or more C_{2-6}alkynyl,

the C_{6-20}aryl of R^e is optionally substituted with one or more C_{1-6}alkyl, and

the -C(O)-(3-15 membered heterocyclyl) of R^e is optionally substituted with one or more C_{1-6}alkyl, C_{1-6}alkoxy, or -C(O)-C_{1-6}alkoxy, wherein the C_{1-6}alkyl is optionally substituted with one or more halo, C_{1-6}alkoxy, or C_{3-10}cycloalkyl,

(h) -C(O)-R^e, wherein R^e is -NH_2, -OH, or 3-15 membered heterocyclyl, or

(i) -$S(O)_2$-R^f, wherein R^f is C_{1-6}alkyl or 3-15 membered heterocyclyl,

provided that, when R^2 is unsubstituted methyl, then either

(1) Q^1 is 5-20 membered heteroaryl, wherein the 5-20 membered heteroaryl of Q^1 is optionally substituted with one or more halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{1-6}alkoxy, -NH_2, C_{3-10}cycloalkyl, or -OH, and wherein Q^1 is not unsubstituted pyridyl, or

(2) Q^1 is phenyl, wherein the phenyl of Q^1 is substituted with

(i) at least one C_{3-6}alkyl, wherein the at least one C_{3-6}alkyl is optionally substituted with one or more halo, or

(ii) at least one C_{3-10}cycloalkyl, wherein the at least one C_{3-10}cycloalkyl is optionally substituted with one or more halo or C_{1-6}alkyl, or

(iii) at least one 5-20 membered heteroaryl, wherein the at least one 5-20 membered heteroaryl is optionally substituted with one or more C_{1-6}alkyl,

(ii) C_{3-10}cycloalkyl, wherein the C_{3-10}cycloalkyl of R^2 is optionally substituted with one or more R^q, wherein R^q is 5-20 membered heteroaryl or C_{6-20}aryl, wherein the C_{6-20}aryl of R^q is optionally substituted with one or more C_{1-6}alkoxy,

(iii) 3-15 membered heterocyclyl, wherein the 3-15 membered heterocyclyl of R^2 is optionally substituted with one or more halo, oxo, C_{1-6}alkyl, -C(O)-C_{1-6}alkyl, or 5-20 membered heteroaryl,

(iv) 5-20 membered heteroaryl or -(C_{1-4}alkyl)(5-20 membered heteroaryl), wherein the C_{1-4} alkyl is optionally substituted with one or more or more –OH, halo, -NH_2, -NH(C_{1-6}alkyl), -N(C_{1-6}alkyl)$_2$, and wherein the 5-20 membered heteroaryl is optionally substituted with one or more R^s, wherein

R^s is halo, C_{1-6}alkyl, C_{1-6}alkoxy, -NH_2, -NH(C_{1-6}alkyl), -N(C_{1-6}alkyl)$_2$, -NH-C(O)-C_{1-6}alkyl, C_{6-20}aryl, C_{3-10}cycloalkyl, 3-15 membered heterocyclyl, 5-20 membered heteroaryl, or -C(O)-C_{1-6}alkoxy, wherein

the C_{1-6}alkyl of R^s is optionally substituted with one or more halo, C_{1-6}alkoxy, -NH_2, -NH(C_{1-6}alkyl), -N(C_{1-6}alkyl)$_2$, -NH-C(O)C_{1-6}alkyl, or -NH-C(O)-C_{1-6}alkoxy, and

the 3-15-membered heterocyclyl of R^s is optionally substituted with one or more halo or -C(O)-C_{1-6}alkoxy,

(v) -N(R^g)(R^h), wherein R^g and R^h are independently H or C_{1-6}alkyl,

(vi) -C(O)-R^j, wherein R^j is C_{3-10}cycloalkyl, -NH(C_{1-6}alkyl), -N(C_{1-6}alkyl)$_2$, or -NH(5-20 membered heteroaryl), and

(vii) C_{6-20}aryl, wherein the C_{6-20}aryl of R^2 is optionally substituted with one or more 5-20 membered heteroaryl or -O-R^p, wherein R^p is 3-15 membered heterocyclyl, wherein the 3-15 membered heterocyclyl of R^p is optionally substituted with one or more -C(O)-C_{1-6}alkyl.

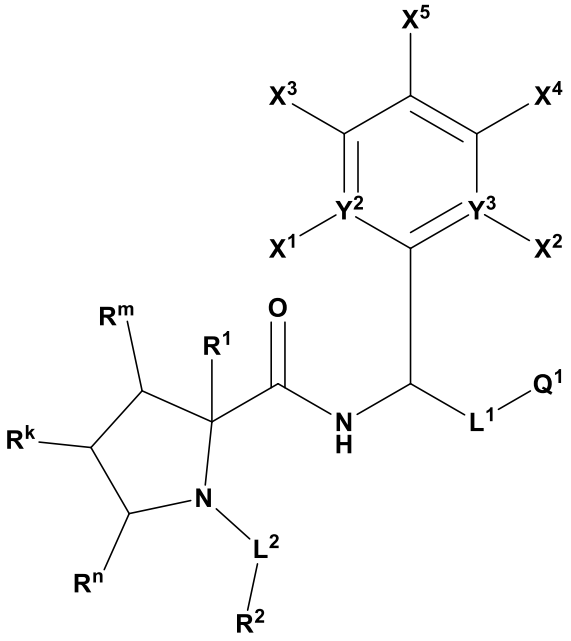
[0006b] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising (i) a compound disclosed herein, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and (ii) one or more pharmaceutically acceptable excipients.

[0006c] In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or a pharmaceutical composition disclosed herein, in the manufacture of a medicament for treating a GYS1-mediated disease, disorder, or condition in an individual in need thereof.

[0006d] In another aspect of the present disclosure, there is provided a kit, comprising (i) a compound disclosed herein, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or a pharmaceutical composition disclosed herein, and (ii) instructions for use in treating an GYS1-mediated disease, disorder, or condition in an individual in need thereof.

[0006e] In a further aspect of the present disclosure, there is provided a compound disclosed herein, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or a pharmaceutical composition disclosed herein, for use in therapy.

[0007] In one example, provided herein is a compound of formula (I')



(I'),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein:

Y^2 and Y^3 are each C, or

one of Y^2 and Y^3 is N and the other of Y^2 and Y^3 is C;

X^1 and X^2 are each independently H, C_{1-6}alkyl, or C_{1-6}alkoxy;

X^3 and X^4 are each independently H, halo, C_{1-6}alkyl, C_{1-6}alkoxy, or 5-20 membered heteroaryl, wherein the C_{1-6}alkyl of X^3 and X^4 is optionally substituted with one of more halo;

X^5 is H, C_{1-6}alkyl, C_{1-6}alkoxy, or C_{3-10}cycloalkyl;

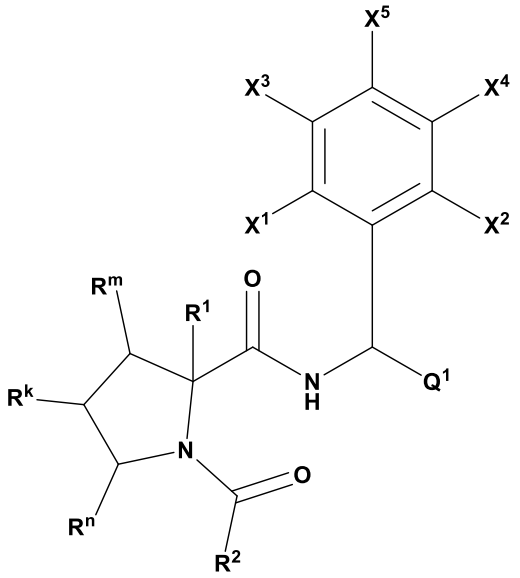
either

(1) L^1 is absent; and

Q^1 is selected from (i) to (iv):

(vii) C_{6-20}aryl, wherein the C_{6-20}aryl of R^2 is optionally substituted with one or more 5-20 membered heteroaryl or -O-R^p, wherein R^p is 3-15 membered heterocyclyl, wherein the 3-15 membered heterocyclyl of R^p is optionally substituted with one or more -C(O)-C_{1-6}alkyl.

[0008] In one example, provided herein is a compound of formula (I):



(I),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein:

X^1 and X^2 are each independently H, C_{1-6}alkyl, or C_{1-6}alkoxy;

X^3 and X^4 are each independently H, halo, C_{1-6}alkyl, C_{1-6}alkoxy, or 5-20 membered heteroaryl;

X^5 is H, C_{1-6}alkyl, C_{1-6}alkoxy, or C_{3-10}cycloalkyl;

Q^1 is selected from (i) to (iii):

(i) phenyl, wherein the phenyl of Q^1 is substituted with one or more halo, C_{1-6}alkyl, C_{2-6}alkenyl, -NH_2, -NH-C(O)-(C_{1-6}alkyl), -NH-C(O)-(3-15 membered heterocyclyl), or C_{3-10}cycloalkyl, wherein

the C_{1-6}alkyl is optionally substituted with one or more halo, and

(iii) 3-15 membered heterocyclyl, wherein the 3-15 membered heterocyclyl of R^2 is optionally substituted with one or more halo, oxo, C_{1-6}alkyl, -C(O)-C_{1-6}alkyl, or 5-20 membered heteroaryl,

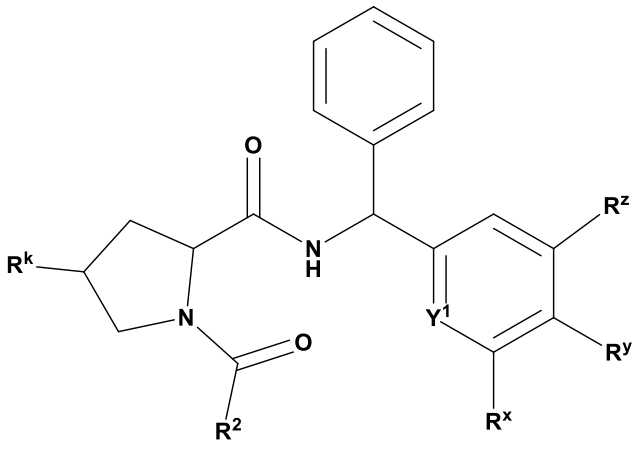
(iv) 5-20 membered heteroaryl, wherein the 5-20 membered heteroaryl of R^2 is optionally substituted with one or more R^s, wherein R^s is C_{1-6}alkyl, C_{1-6}alkoxy, -NH-C(O)-C_{1-6}alkyl, C_{6-20}aryl, or 5-20 membered heteroaryl, wherein the C_{1-6}alkyl of R^s is optionally substituted with one or more C_{1-6}alkoxy,

(v) -N(R^g)(R^h), wherein R^g and R^h are independently H or C_{1-6}alkyl,

(vi) -C(O)-R^j, wherein R^j is C_{3-10}cycloalkyl, -NH(C_{1-6}alkyl), -N(C_{1-6}alkyl)$_2$, or -NH(5-20 membered heteroaryl), and

(vii) C_{6-20}aryl, wherein the C_{6-20}aryl of R^2 is optionally substituted with one or more 5-20 membered heteroaryl or -O-R^p, wherein R^p is 3-15 membered heterocyclyl, wherein the 3-15 membered heterocyclyl of R^p is optionally substituted with one or more -C(O)-C_{1-6}alkyl.

[0009] In one example, provided herein is a compound of formula (I-A):

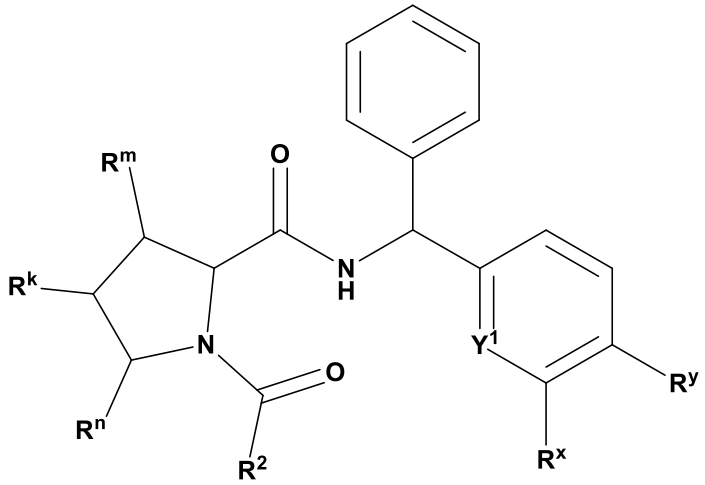


(I-A),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein Y^1, R^2, R^k, R^x, R^y, and R^z are as defined elsewhere herein. In another

variation, Y^1, R^2, R^k, R^x, R^y, and R^z of formula (I-A) are as defined for a compound of formula (I') , or formula (I) elsewhere herein, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or example thereof.

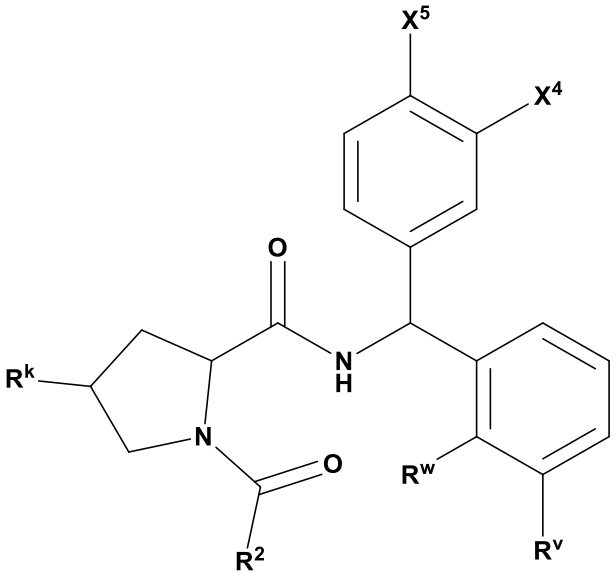
[0010] In one example, provided herein is a compound of formula (I-B):



(I-B),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein Y^1, R^2, R^k, R^m, R^n, R^x, and R^y are as defined elsewhere herein. In another variation, Y^1, R^2, R^k, R^m, R^n, R^x, and R^y of formula (I-B) are as defined for a compound of formula (I'), or formula (I) elsewhere herein, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or example thereof.

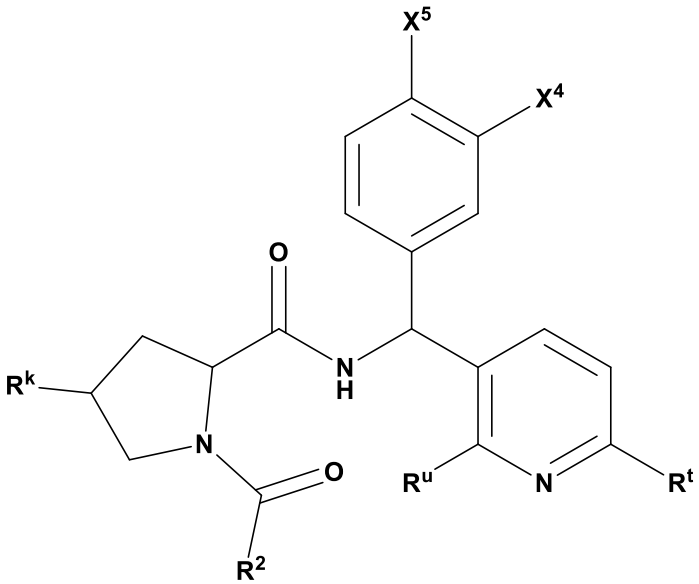
[0011] In one example, provided herein is a compound of formula (I-C):



(I-C),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein X^4, X^5, R^2, R^k, R^v, and R^w are as defined elsewhere herein. In another variation, X^4, X^5, R^2, R^k, R^v, and R^w of formula (I-C) are as defined for a compound of formula (I') , or formula (I) elsewhere herein, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or example thereof.

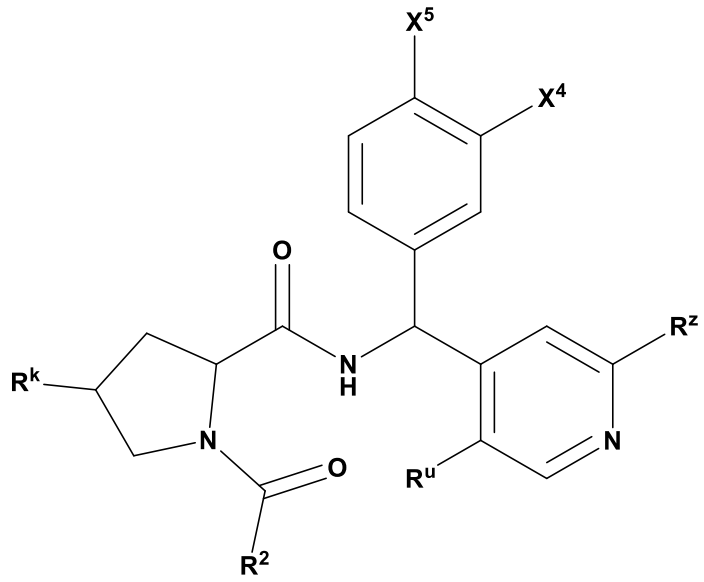
[0012] In one example, provided herein is a compound of formula (I-D):



(I-D),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein X^4, X^5, R^2, R^k, R^u, and R^t are as defined elsewhere herein. In another variation, X^4, X^5, R^2, R^k, R^u, and R^t of formula (I-D) are as defined for a compound of formula (I'), or formula (I) elsewhere herein, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or example thereof.

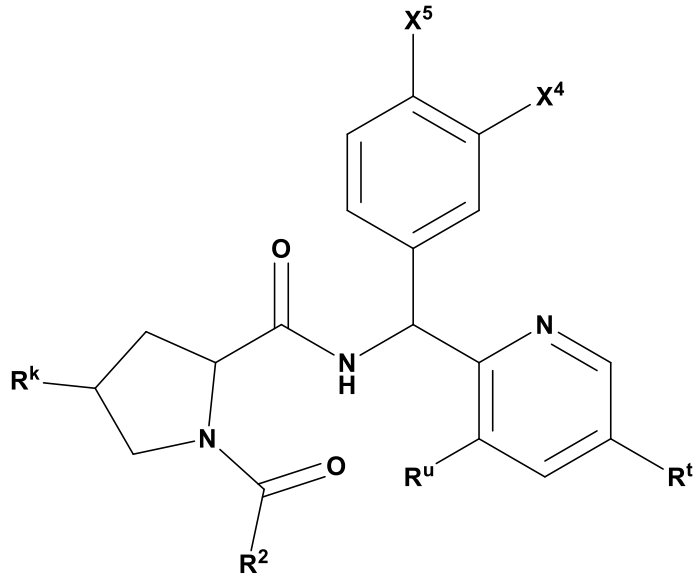
[0013] In one example, provided is a compound of formula (I'), wherein the compound is a compound of formula (I-D1):



(I-D1),

wherein X^4, X^5, R^2, R^k, R^u, and R^z of formula (I-D1) are as defined for a compound of formula (I') elsewhere herein, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or example thereof.

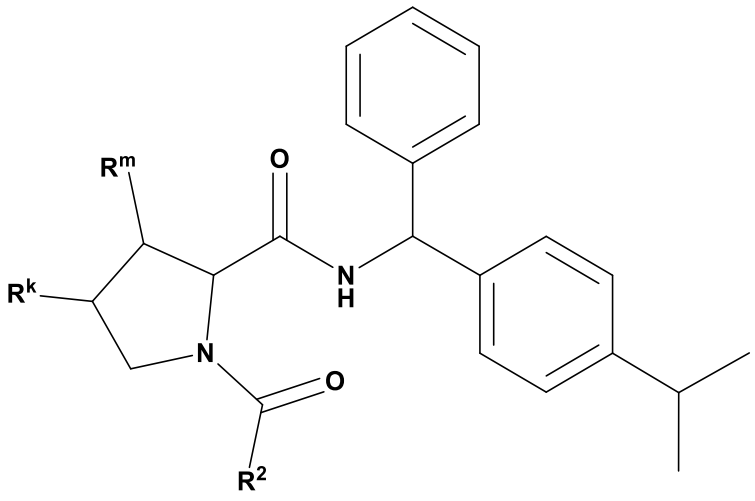
[0014] In one example, provided is a compound of formula (I'),, wherein the compound is a compound of formula (I-D1):



(I-D2),

wherein X^4, X^5, R^2, R^k, R^t, and R^u of formula (I-D2) are as defined for a compound of formula (I') elsewhere herein, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or example thereof.

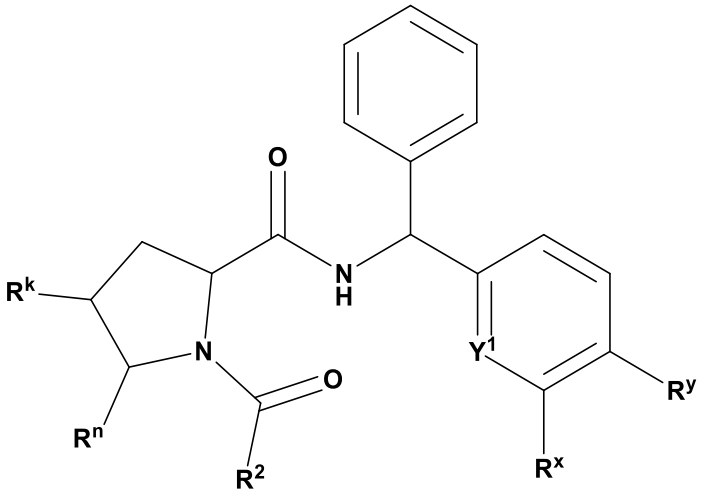
[0015] In one example, provided herein is a compound of formula (I-E):



(I-E),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2, R^k, and R^m are as defined elsewhere herein. In another variation, R^2, R^k, and R^m of formula (I-E) are as defined for a compound of formula (I'), or formula (I) elsewhere herein, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or example thereof.

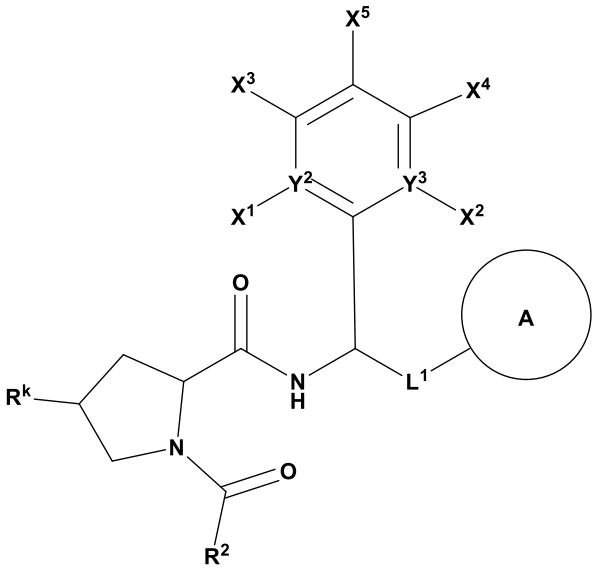
[0016] In one example, provided herein is a compound of formula (I-F):



(I-F),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein Y^1, R^2, R^k, R^n, R^x, and R^y are as defined elsewhere herein. In another variation, R^2, R^k, and R^m of formula (I-F) are as defined for a compound of formula (I'), or formula (I) elsewhere herein, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or example thereof.

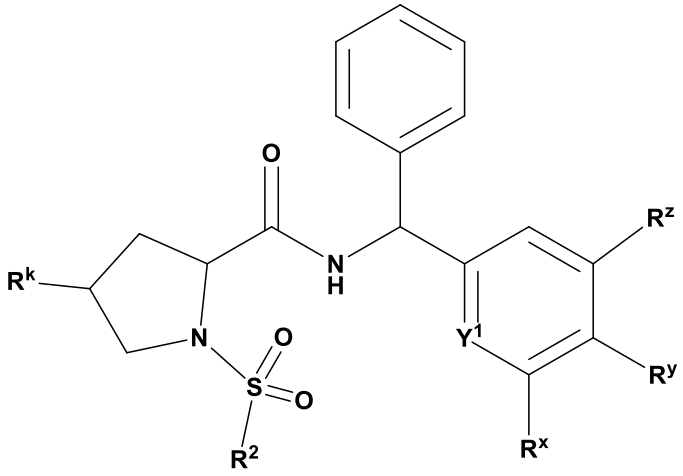
[0017] In one example, provided herein is a compound of formula (I') wherein the compound is of the formula (I-G):



(I-G),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein ring A, L^1, Y^2, Y^3, R^2, R^k, X^1, X^2, X^3, X^4, and X^5 are as defined elsewhere herein.

[0018] In one example, provided herein is a compound of formula (I') wherein the compound is of the formula (I-H):



(I-H),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein Y^1, R^2, R^k, R^n, R^x, and R^y are as defined elsewhere herein.

[0019] In one example, provided herein is a pharmaceutical composition, comprising (i) a compound of formula (I), or any variation or example thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and (ii) one or more pharmaceutically acceptable excipients. In another variation, provided herein is a pharmaceutical composition, comprising (i) a compound of formula (I'), or any variation or example thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and (ii) one or more pharmaceutically acceptable excipients.

[0020] In one example, provided herein is a method of modulating GYS1 in a cell, comprising exposing the cell to (i) a composition comprising an effective amount of a compound of formula (I), or any variation or example thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or (ii) a pharmaceutical composition, comprising a compound of formula (I), or any variation or example thereof, or a

stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and one or more pharmaceutically acceptable excipients. In another variation, provided herein is a method of modulating GYS1 in a cell, comprising exposing the cell to (i) a composition comprising an effective amount of a compound of formula (I'), or any variation or example thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or (ii) a pharmaceutical composition, comprising a compound of formula (I'), or any variation or example thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and one or more pharmaceutically acceptable excipients.

[0021] In one example, provided herein is a method of inhibiting GYS1 in a cell, comprising exposing the cell to (i) a composition comprising an effective amount of a compound of formula (I), or any variation or example thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or (ii) a pharmaceutical composition, comprising a compound of formula (I), or any variation or example thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and one or more pharmaceutically acceptable excipients. In another variation, provided herein is a method of inhibiting GYS1 in a cell, comprising exposing the cell to (i) a composition comprising an effective amount of a compound of formula (I'), or any variation or example thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or (ii) a pharmaceutical composition, comprising a compound of formula (I'), or any variation or example thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and one or more pharmaceutically acceptable excipients.

[0022] In one example, provided herein is a method of reducing tissue glycogen stores in an individual in need thereof, comprising administering to the individual an effective amount of (i) a GYS1 inhibitor, or (ii) a pharmaceutical composition comprising a GYS1 inhibitor and one or more pharmaceutically acceptable excipients. In some examples, the GYS1 inhibitor is selective for GYS1 over GYS2. In some examples, the GYS1 inhibitor is greater than 500 or 1,000 or 1,500 or 1,700-fold selective for GYS1 over GYS2. In some examples, the GYS1 inhibitor is a small molecule.

[0023] In one example, provided herein is a method of reducing tissue glycogen stores in an individual in need thereof, comprising administering to the individual an effective amount

of (i) a composition comprising an effective amount of a compound of formula (I), or any variation or example thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or (ii) a pharmaceutical composition, comprising a compound of formula (I), or any variation or example thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and one or more pharmaceutically acceptable excipients. In another variation, provided herein is a method of reducing tissue glycogen stores in an individual in need thereof, comprising administering to the individual an effective amount of (i) a composition comprising an effective amount of a compound of formula (I'), or any variation or example thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or (ii) a pharmaceutical composition, comprising a compound of formula (I'), or any variation or example thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and one or more pharmaceutically acceptable excipients.

[0024] In one example, provided herein is a method of modulating GYS1 in a cell of an an individual in need thereof, comprising administering to the individual an effective amount of (i) a composition comprising an effective amount of a compound of formula (I), or formula (I') or any variation or example thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or (ii) a pharmaceutical composition, comprising a compound of formula (I), or any variation or example thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and one or more pharmaceutically acceptable excipients.

[0025] In one example, provided herein is a method of treating a GYS1-mediated disease, disorder, or condition in an individual in need thereof, comprising subjecting the individual to glycogen substrate reduction therapy. In some examples, the glycogen substrate reduction therapy comprises administration of a GYS1 inhibitor. In some examples, the GYS1 inhibitor is a small molecule. In some examples, the GYS1 inhibitor is selective for GYS1 over GYS2. In some examples, the GYS1 inhibitor is greater than 500 or 1,000 or 1,500 or 1,700-fold selective for GYS1 over GYS2.

[0026] In one example, provided herein is a method of treating a GYS1-mediated disease, disorder, or condition in an individual in need thereof, comprising administering to the

individual an effective amount of (i) a composition comprising an effective amount of a compound of formula (I), or any variation or example thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or (ii) a pharmaceutical composition, comprising a compound of formula (I), or any variation or example thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and one or more pharmaceutically acceptable excipients. In another variation, provided herein is a method of treating a GYS1-mediated disease, disorder, or condition in an individual in need thereof, comprising administering to the individual an effective amount of (i) a composition comprising an effective amount of a compound of formula (I'), or any variation or example thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or (ii) a pharmaceutical composition, comprising a compound of formula (I'), or any variation or example thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and one or more pharmaceutically acceptable excipients.

[0027] In one example, provided herein is a method of treating a glycogen storage disease, disorder, or condition in an individual in need thereof, comprising subjecting the individual to glycogen substrate reduction therapy. In some examples, the glycogen substrate reduction therapy comprises administration of a GYS1 inhibitor. In some examples, the GYS1 inhibitor is a small molecule. In some examples, the GYS1 inhibitor is selective for GYS1 over GYS2. In some examples, the GYS1 inhibitor is greater than 500 or 1,000 or 1,500 or 1,700-fold selective for GYS1 over GYS2.

[0028] In one example, provided herein is a kit, comprising (i) a composition comprising an effective amount of a compound of formula (I), or any variation or example thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or a pharmaceutical composition, comprising a compound of formula (I), or any variation or example thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and one or more pharmaceutically acceptable excipients, and (ii) instructions for use in treating an GYS1-mediated disease, disorder, or condition in an individual in need thereof. In another variation, provided herein is a kit, comprising (i) a composition comprising an effective amount of a compound of formula (I'), or any variation or example thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt

of any of the foregoing, or a pharmaceutical composition, comprising a compound of formula (I'), or any variation or example thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and one or more pharmaceutically acceptable excipients, and (ii) instructions for use in treating an GYS1-mediated disease, disorder, or condition in an individual in need thereof.

[0029] In some example, provided herein are methods of preparing a compound of formula (I) or (I'), or any example or variation thereof, such as a compound of formula (I), (I-A), (I-A1), (I-A2), (I-A3), (I-A4), (I-B), (I-B1), (I-B2), (I-C), (I-D), (I-D1), (I-D2), (I-E), (I-F), (I-G), or (I-H) or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

BRIEF DESCRIPTION OF THE DRAWINGS

[0030] FIG. **1** depicts the pathway in which PPP1R3A Loss of Function (LoF) leads to reduction in muscle glycogen.

[0031] FIGS. **2A** and **2B** depict the association between PPP1R3A protein truncating variant (PTV) and left ventricular ejection (LVEF) (%) and left ventricle wall thickness (mm) in UK Biobank.

[0032] FIGS. **2C** and **2D** depict the association between PPP1R3A protein truncating variant (PTV) and exercise output (watts) and max heart rate (HR) exercise (bpm) in UK Biobank.

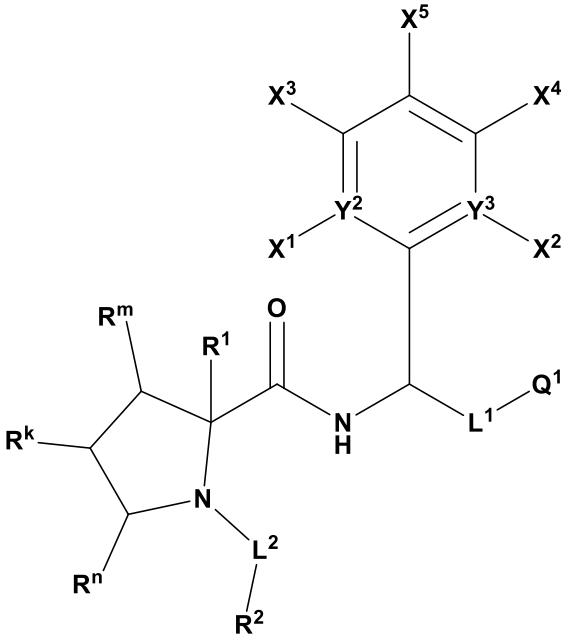
[0033] FIGS. **2E** and **2F** depict the association between PPP1R3A protein truncating variant (PTV) and PQ interval (ms) and QRS duration (ms) in UK Biobank.

[0034] FIGS. **2G** and **2H** depict the association between PPP1R3A protein truncating variant (PTV) and QT interval (ms) and serum glucose (mmol/L) in UK Biobank.

CLAIMS

What is claimed is:

1. A compound of formula (I'):



(I'),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein:

Y^2 and Y^3 are each C, or

one of Y^2 and Y^3 is N and the other of Y^2 and Y^3 is C;

X^1 and X^2 are each independently H, C_{1-6}alkyl, or C_{1-6}alkoxy;

X^3 and X^4 are each independently H, halo, C_{1-6}alkyl, C_{1-6}alkoxy, or 5-20 membered heteroaryl, wherein the C_{1-6}alkyl of X^3 and X^4 is optionally substituted with one of more halo;

X^5 is H, C_{1-6}alkyl, C_{1-6}alkoxy, or C_{3-10}cycloalkyl;

either

(1) L^1 is absent; and

Q^1 is selected from (i) to (iv):

(i) phenyl, wherein the phenyl of Q^1 is substituted with one or more halo, C_{1-6}alkyl, C_{2-6}alkenyl, -NH_2, -NH-C(O)-(C_{1-6}alkyl), -NH-C(O)-(3-15 membered heterocyclyl), C_{3-10}cycloalkyl, or 5-20 membered heteroaryl, wherein

the C_{1-6}alkyl is optionally substituted with one or more halo, -NH-C(O)-NH(C_{1-6}alkyl), -NH-C(O)-C_{1-6}alkyl, or -NH-C(O)-C_{1-6}alkoxy,

the C_{3-10}cycloalkyl is optionally substituted with one or more halo or C_{1-6}alkyl, and

the 5-20 membered heteroaryl is optionally substituted with one or more C_{1-6}alkyl,

(ii) 3-15 membered heterocyclyl, wherein the 3-15 membered heterocyclyl of Q^1 is optionally substituted with one or more oxo, or C_{1-6}alkyl,

(iii) 5-20 membered heteroaryl, wherein the 5-20 membered heteroaryl of Q^1 is optionally substituted with one or more halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{1-6}alkoxy, -NH_2, or C_{3-10}cycloalkyl, wherein,

the C_{1-6}alkyl is optionally substituted with one or more halo, and

the C_{3-10}cycloalkyl is optionally substituted with one or more halo or C_{1-6}alkyl, and

(iv) C_{3-10}cycloalkyl;

or

(2) L^1 is -CH_2-; and

Q^1 is C_{3-10}cycloalkyl;

L^2 is -C(O)- or -$S(O)_2$-

R^1 is H or C_{1-6}alkyl;

R^k is halo, -OH, -NH_2, or -NH-C(O)C_{1-6}alkyl;

R^m is H, -OH, or C_{1-6}alkyl;

R^n is H, C_{1-6}alkyl, or C_{3-10}cycloalkyl or R^n taken together with the carbon atom to which it is attached forms C_{3-5} cycloalkyl;

or R^k is taken together with either R^m or R^n, and the atoms to which they are attached, to form cyclopropyl; and

R^2 is selected from (i) to (vii):

(i) C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^2 is optionally substituted with one or more R^a, wherein R^a is:

(a) -OH,

(b) cyano,

(c) C_{2-6}alkynyl,

(d) C_{6-20}aryl, wherein the C_{6-20}aryl of R^a is optionally substituted with one or more halo, cyano, C_{1-6}alkoxy, or -NH-C(O)-C_{1-6}alkyl,

(e) 3-15 membered heterocyclyl, wherein the 3-15 membered heterocyclyl of R^a is optionally substituted with one or more R^c, wherein

R^c is halo, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, -C(O)-C_{1-6}alkyl, or -C(O)-C_{1-6}alkoxy, wherein

the C_{1-6}alkyl of R^c is optionally substituted with one or more halo or C_{2-6}alkynyl, and

the -C(O)-C_{1-6}alkoxy of R^c is optionally substituted with one or more halo,

(f) -N(R^c)(R^d), wherein R^c and R^d of -N(R^c)(R^d) are, independently of each other, H, C_{1-6}alkyl,
-C(O)-C_{1-6}alkyl, -C(O)-C_{1-6}alkoxy, -C(O)-NH_2, -C(O)-NH(C_{1-6}alkyl), -C(O)-N(C_{1-6}alkyl)$_2$, -C(O)-(3-15 membered heterocyclyl), -CH_2-C(O)-NH_2, 3-15 membered heterocyclyl, or 5-20 membered heteroaryl, wherein

the C_{1-6}alkyl of R^c or R^d is optionally substituted with one or more -C(O)-NH_2,

the -C(O)-C_{1-6}alkyl of R^c or R^d is optionally substituted with one or more halo,

the 3-15 membered heterocyclyl and the 5-20 membered heteroaryl of R^c or R^d are independently optionally substituted with one or more C_{1-6}alkyl,

the -C(O)-(3-15 membered heterocyclyl) of R^c or R^d is optionally substituted with one or more halo, -C(O)-C_{1-6}alkoxy, or C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more halo, C_{1-6}alkoxy, or C_{3-10}cycloalkyl, and

the C_{1-6}alkyl of the -C(O)-N(C_{1-6}alkyl)$_2$ of R^c or R^d are, independently of each other, optionally substituted with one or more halo or C_{6-20}aryl,

(g) -O-R^e, wherein R^e is C_{1-6}alkyl, C_{6-20}aryl, -C(O)-(3-15 membered heterocyclyl), -C(O)-N-(C_{1-6}alkyl)$_2$, or 5-20 membered heteroaryl, wherein

the C_{1-6}alkyl of R^e is optionally substituted with one or more C_{1-6}alkoxy, wherein the C_{1-6}alkoxy is optionally substituted with one or more C_{2-6}alkynyl,

the C_{6-20}aryl of R^e is optionally substituted with one or more C_{1-6}alkyl, and

the -C(O)-(3-15 membered heterocyclyl) of R^e is optionally substituted with one or more C_{1-6}alkyl, C_{1-6}alkoxy, or -C(O)-C_{1-6}alkoxy, wherein the C_{1-6}alkyl is optionally substituted with one or more halo, C_{1-6}alkoxy, or C_{3-10}cycloalkyl,

(h) -C(O)-R^e, wherein R^e is -NH_2, -OH, or 3-15 membered heterocyclyl, or

(i) -$S(O)_2$-R^f, wherein R^f is C_{1-6}alkyl or 3-15 membered heterocyclyl,

provided that, when R^2 is unsubstituted methyl, then either

(1) Q^1 is 5-20 membered heteroaryl, wherein the 5-20 membered heteroaryl of Q^1 is optionally substituted with one or more halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{1-6}alkoxy, -NH_2, C_{3-10}cycloalkyl, or -OH, and wherein Q^1 is not unsubstituted pyridyl, or

(2) Q^1 is phenyl, wherein the phenyl of Q^1 is substituted with

(i) at least one C_{3-6}alkyl, wherein the at least one C_{3-6}alkyl is optionally substituted with one or more halo, or

(ii) at least one C_{3-10}cycloalkyl, wherein the at least one C_{3-10}cycloalkyl is optionally substituted with one or more halo or C_{1-6}alkyl, or

(iii) at least one 5-20 membered heteroaryl, wherein the at least one 5-20 membered heteroaryl is optionally substituted with one or more C_{1-6}alkyl,

(ii) C_{3-10}cycloalkyl, wherein the C_{3-10}cycloalkyl of R^2 is optionally substituted with one or more R^q, wherein R^q is 5-20 membered heteroaryl or C_{6-20}aryl, wherein the C_{6-20}aryl of R^q is optionally substituted with one or more C_{1-6}alkoxy,

(iii) 3-15 membered heterocyclyl, wherein the 3-15 membered heterocyclyl of R^2 is optionally substituted with one or more halo, oxo, C_{1-6}alkyl, -C(O)-C_{1-6}alkyl, or 5-20 membered heteroaryl,

(iv) 5-20 membered heteroaryl or -(C_{1-4}alkyl)(5-20 membered heteroaryl), wherein the C_{1-4} alkyl is optionally substituted with one or more or more –OH, halo, -NH_2, -NH(C_{1-6}alkyl), -N(C_{1-6}alkyl)$_2$, and wherein the 5-20 membered heteroaryl is optionally substituted with one or more R^s, wherein

R^s is halo, C_{1-6}alkyl, C_{1-6}alkoxy, -NH_2, -NH(C_{1-6}alkyl), -N(C_{1-6}alkyl)$_2$, -NH-C(O)-C_{1-6}alkyl, C_{6-20}aryl, C_{3-10}cycloalkyl, 3-15 membered heterocyclyl, 5-20 membered heteroaryl, or -C(O)-C_{1-6}alkoxy, wherein

the C_{1-6}alkyl of R^s is optionally substituted with one or more halo, C_{1-6}alkoxy, -NH_2, -NH(C_{1-6}alkyl), -N(C_{1-6}alkyl)$_2$, -NH-C(O)C_{1-6}alkyl, or -NH-C(O)-C_{1-6}alkoxy, and

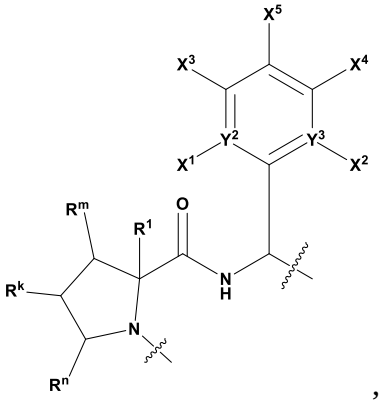
the 3-15-membered heterocyclyl of R^s is optionally substituted with one or more halo or -C(O)-C_{1-6}alkoxy,

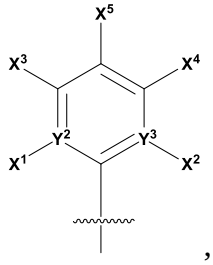
(v) -N(R^g)(R^h), wherein R^g and R^h are independently H or C_{1-6}alkyl,

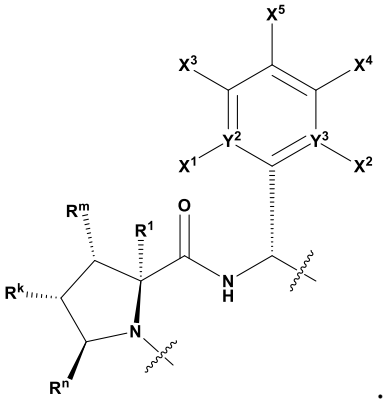
(vi) -C(O)-R^j, wherein R^j is C_{3-10}cycloalkyl, -NH(C_{1-6}alkyl), -N(C_{1-6}alkyl)$_2$, or -NH(5-20 membered heteroaryl), and

(vii) C_{6-20}aryl, wherein the C_{6-20}aryl of R^2 is optionally substituted with one or more 5-20 membered heteroaryl or -O-R^p, wherein R^p is 3-15 membered heterocyclyl, wherein the 3-15 membered heterocyclyl of R^p is optionally substituted with one or more -C(O)-C_{1-6}alkyl.

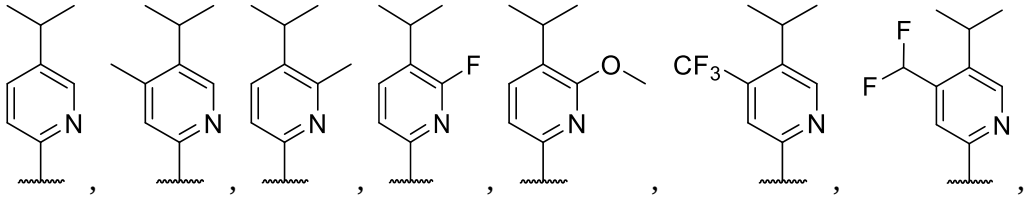
2. The compound of claim 1, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein the moiety represented by

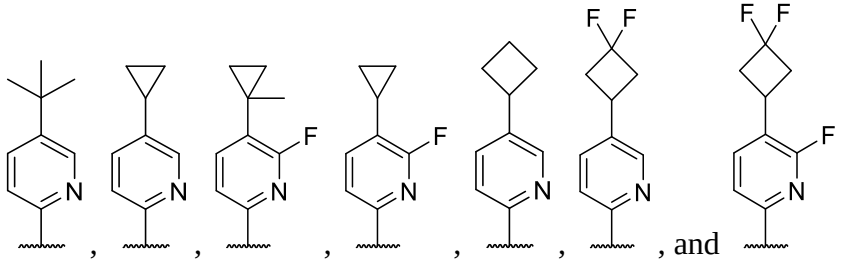


, with carbon atoms bearing moieties 

, R^k, R^m, R^n, and R^1, has a stereochemical configuration of the formula: 

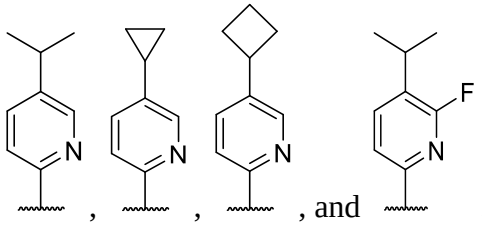
.

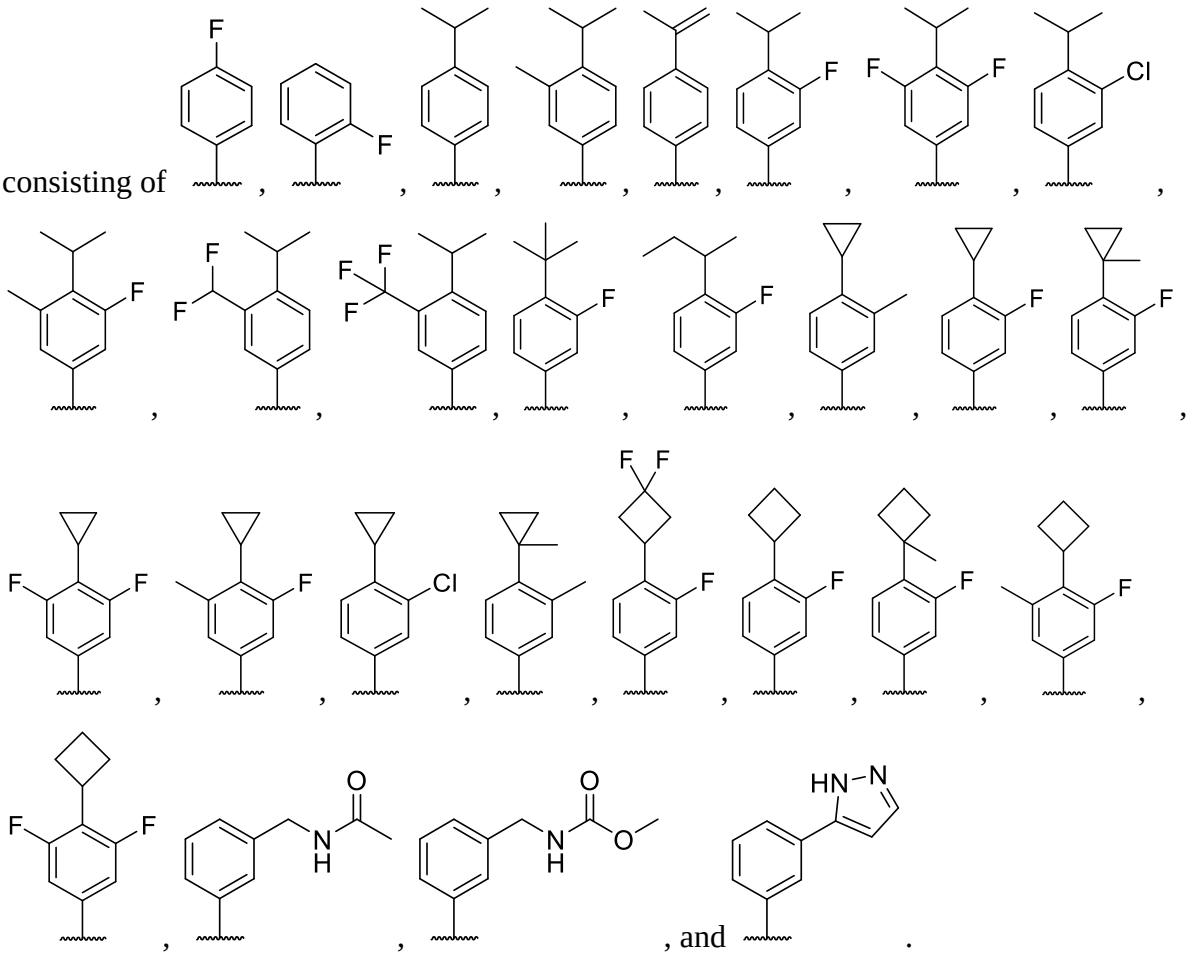
3. The compound of claim 1 or 2, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein Q^1 is selected from the group consisting of 

, 

, and

.

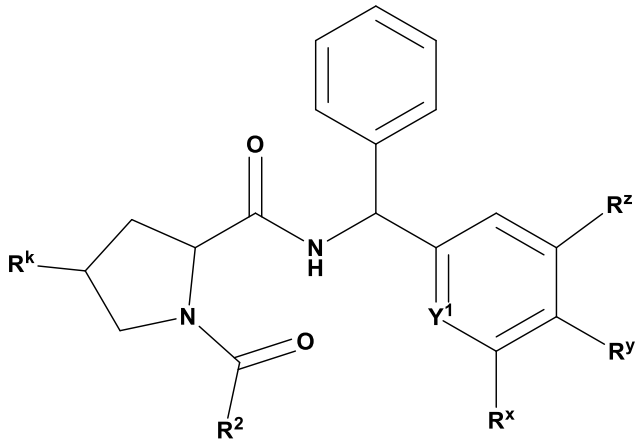
4. The compound of any one of claims 1-3, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein Q^1 is selected from the group consisting of  .

5. The compound of claim 1 or 2, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein Q^1 is selected from the group consisting of  .

6. The compound of any one of claims 1-5, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^m is H, R^n is H, and R^k is halo, -OH, $-NH_2$, or $-NH\text{-}C(O)C_{1\text{-}6}$alkyl.

7. The compound of any one of claims 1, 2, 4, and 5, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^k is taken together with either R^m or R^n, and the atoms to which they are attached, to form cyclopropyl.

8. The compound of claim 1, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein the compound is of formula (I-A):



(I-A),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein

Y^1 is CH or N;

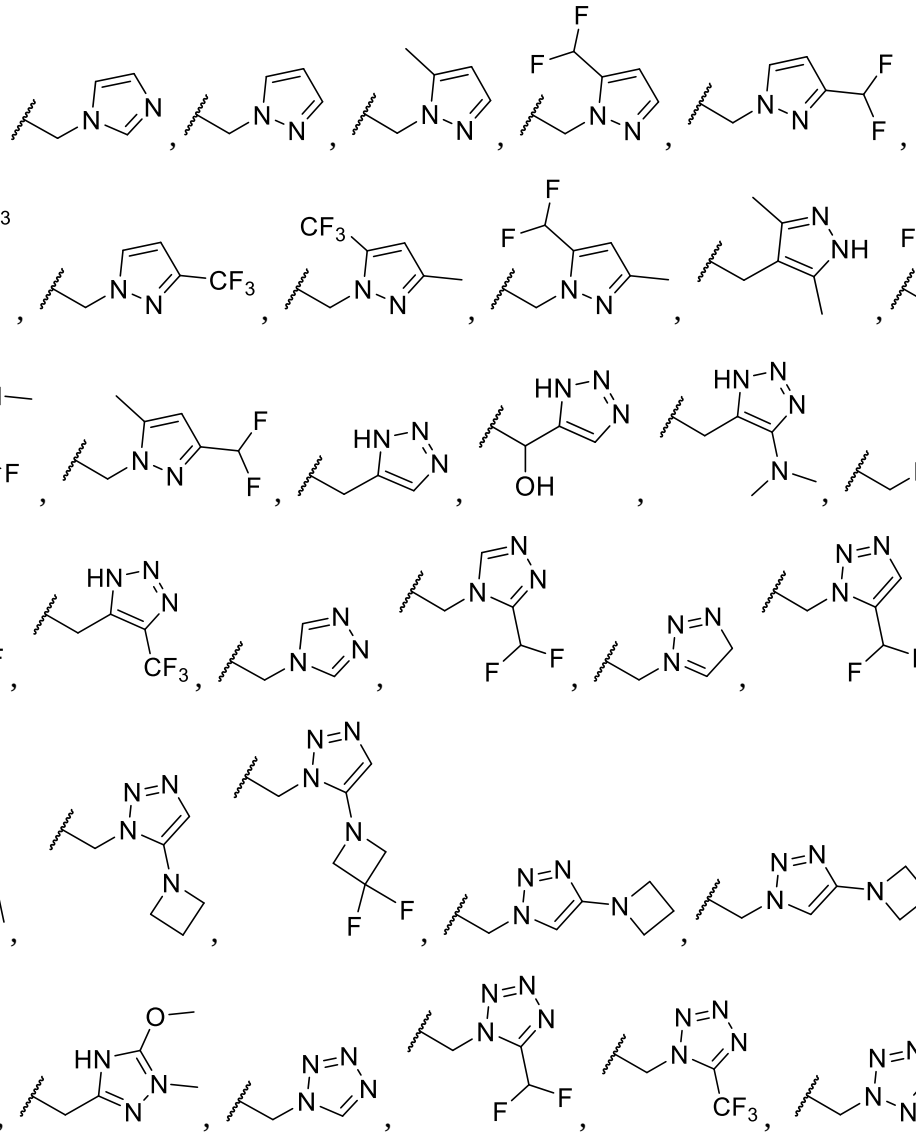
R^x and R^z are independently H, halo, C_{1-6}alkyl, or $-NH_2$, wherein, when Y^1 is CH, the C_{1-6}alkyl of R^x or R^z may be optionally substituted with one or more halo; and

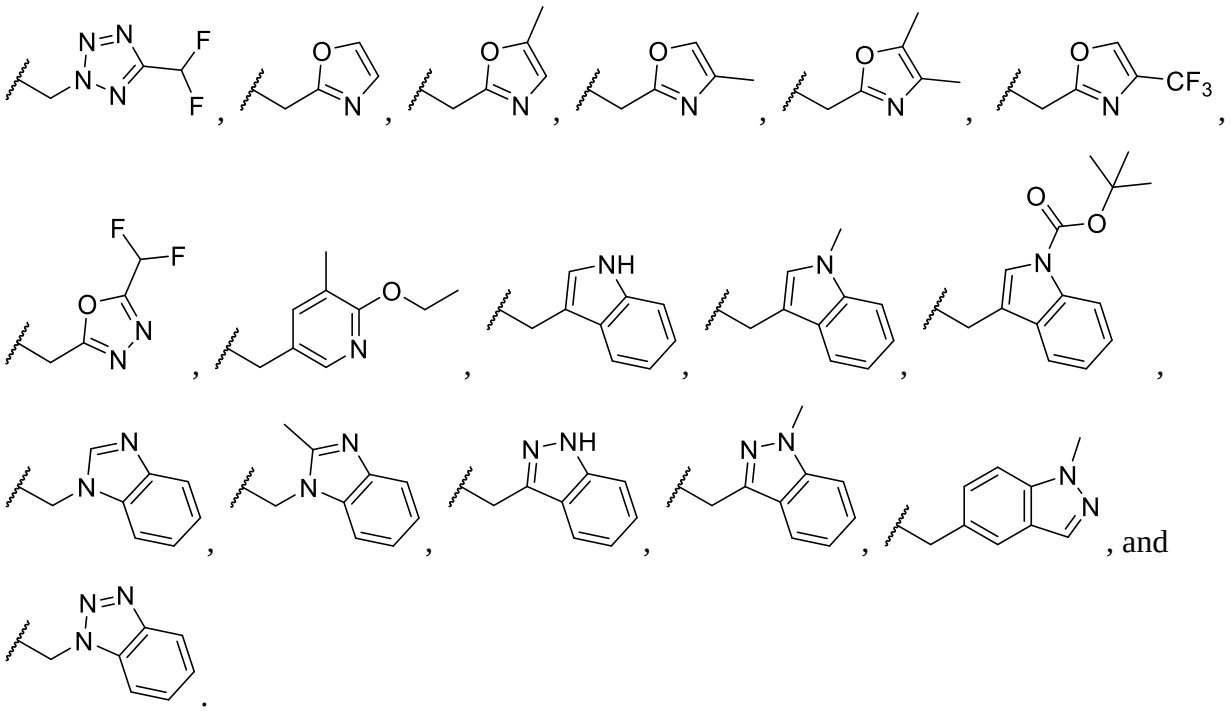
R^y is (i) C_{1-6}alkyl, or (ii) C_{3-10}cycloalkyl, wherein the C_{3-10}cycloalkyl is optionally substituted with one or more halo or C_{1-6}alkyl.

9. The compound of claim 1 or claim 8, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^x is H, fluoro, or methyl, and R^y is (i) isopropyl, or (ii) C_{3-4}cycloalkyl, wherein the C_{3-4}cycloalkyl is optionally substituted with one or more fluoro or methyl.

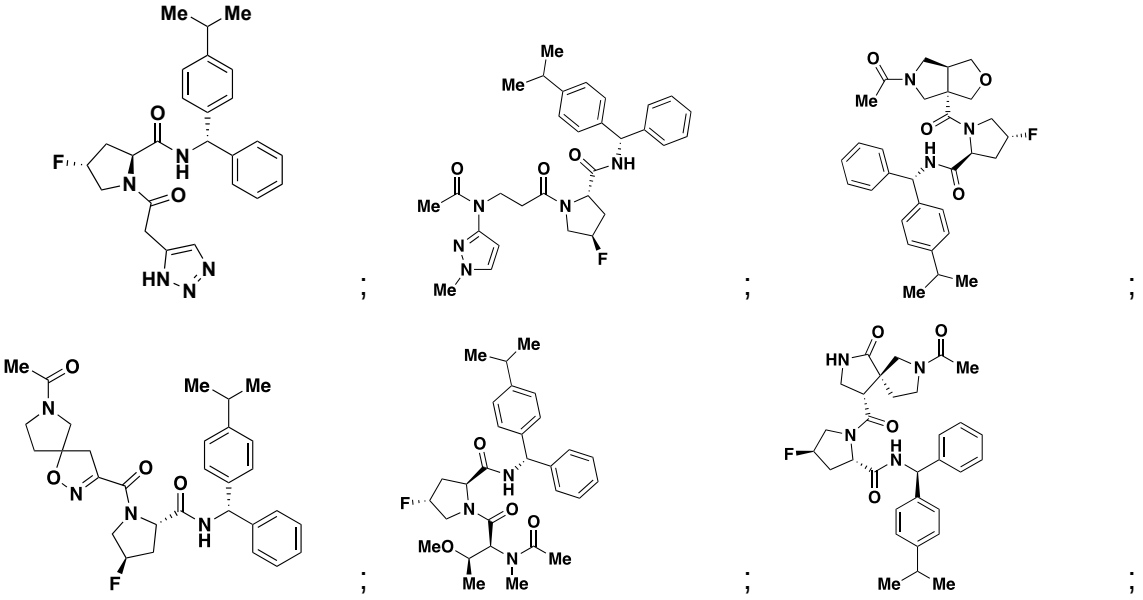
10. The compound of any one of claims 1, 8, and 9 or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^k is halo.

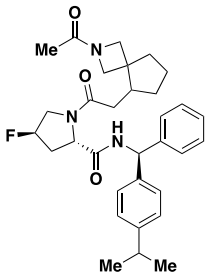
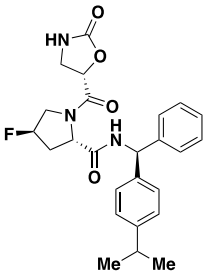
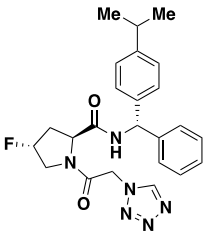
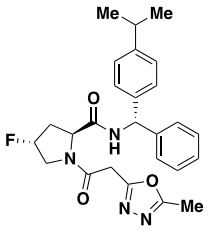
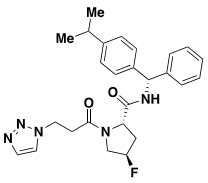
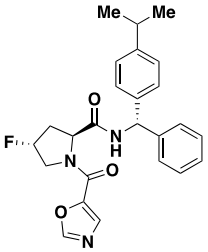
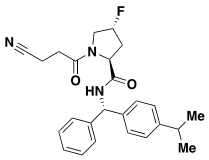
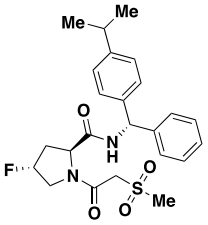
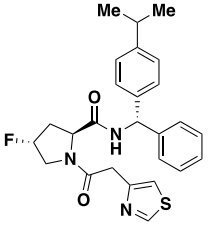
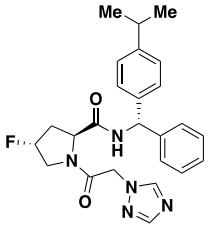
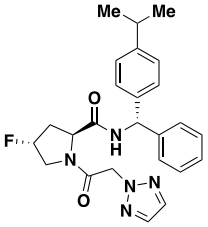
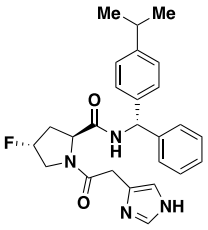
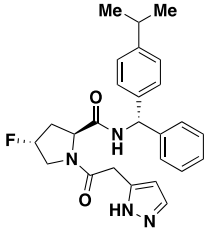
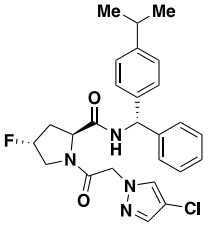
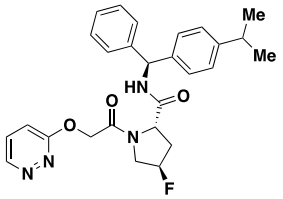
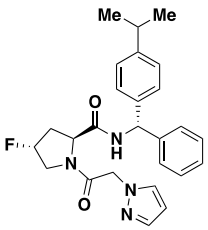
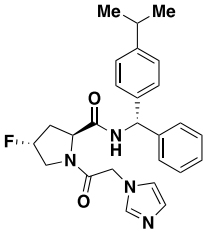
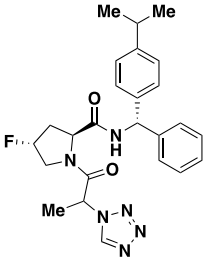
11. The compound of any one of claims 1 and 8-10, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is 5-20 membered heteroaryl or -(C_{1-4}alkyl)(5-20 membered heteroaryl), wherein the C_{1-4} alkyl is optionally substituted with one or more or more –OH, halo, -NH_2, -NH(C_{1-6}alkyl), -N(C_{1-6}alkyl)$_2$, and wherein the 5-20 membered heteroaryl is optionally substituted with one or more R^s.

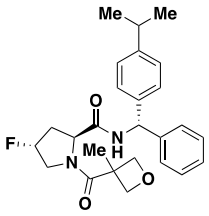
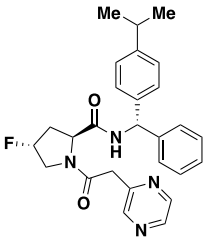
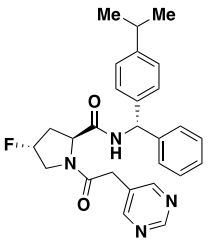
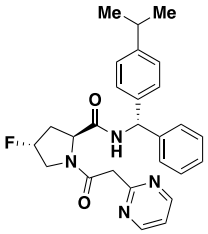
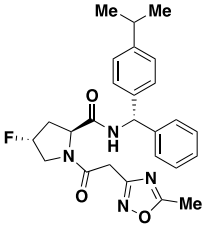
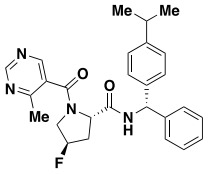
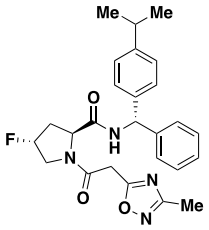
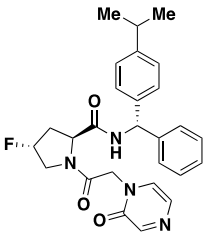
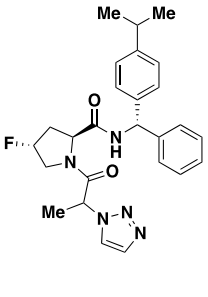
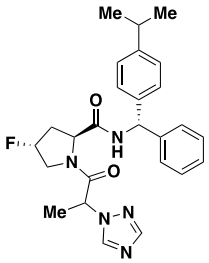
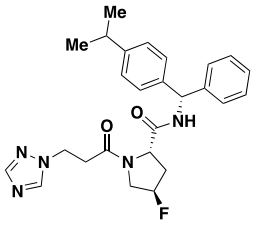
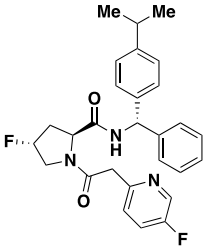
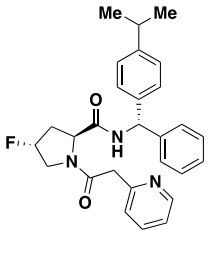
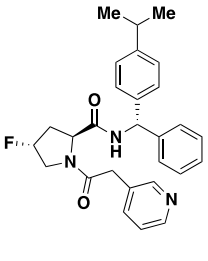
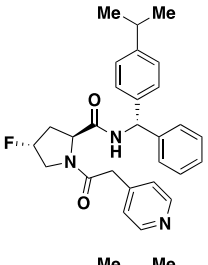
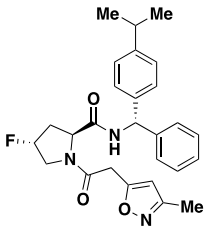
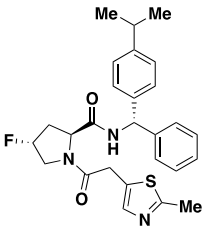
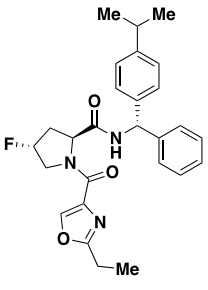
12. The compound of any one of claims 1 and 8-11, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is selected from the group consisting of 

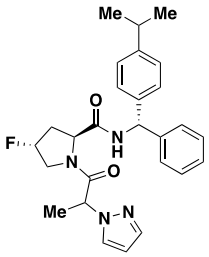
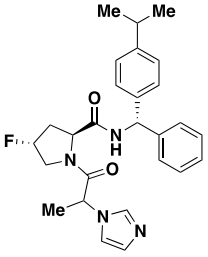
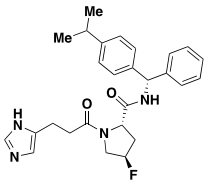
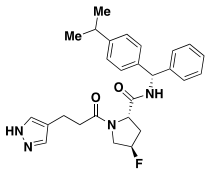
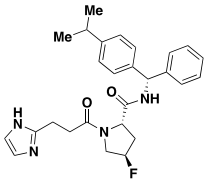
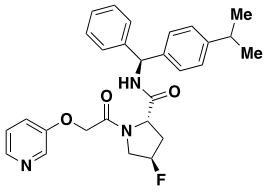
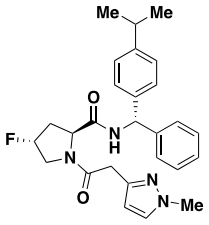
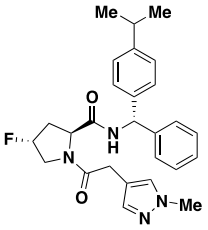
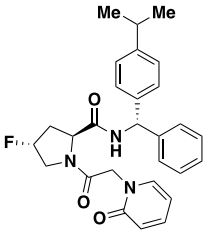
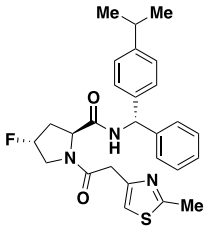
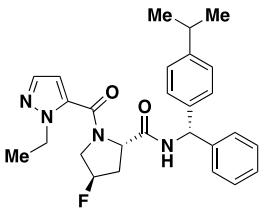
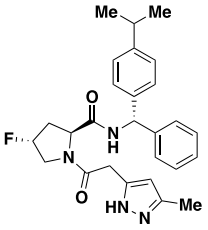
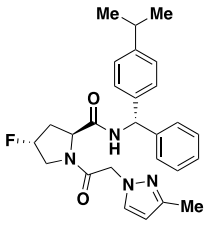
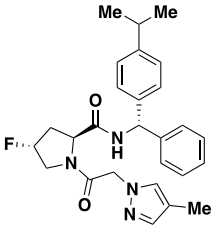
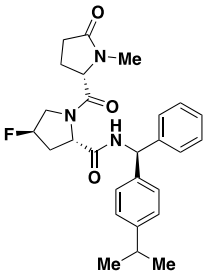
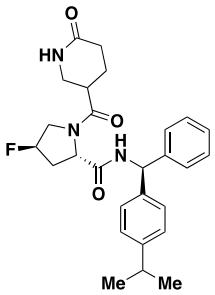
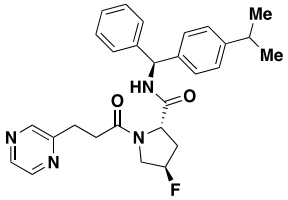
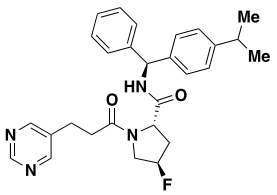
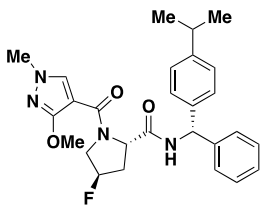
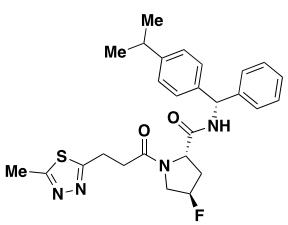
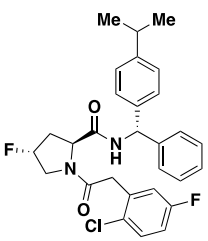


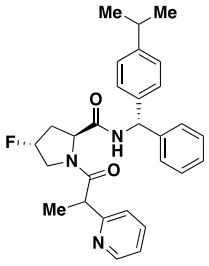
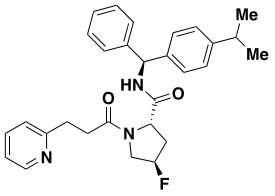
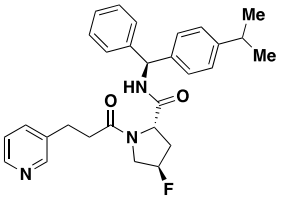
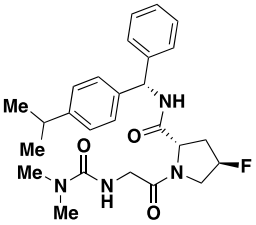
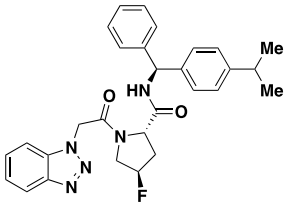
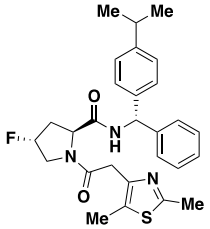
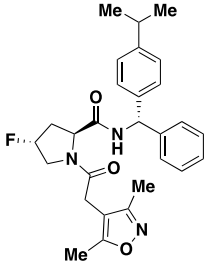
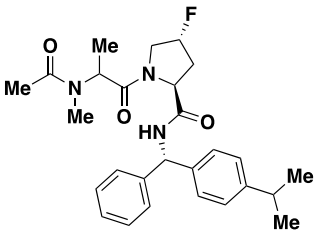
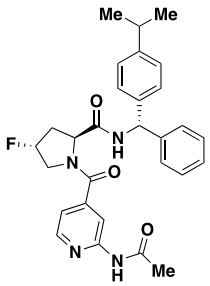
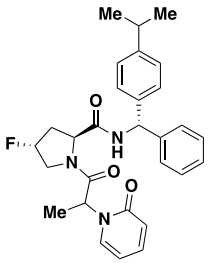
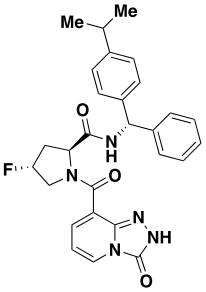
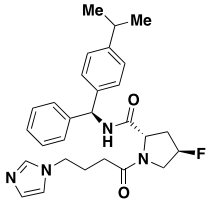
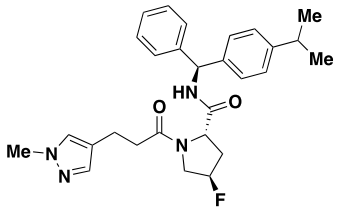
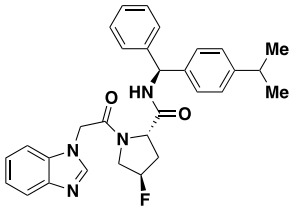
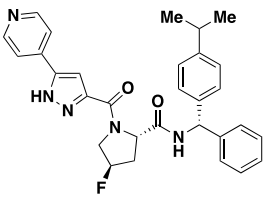
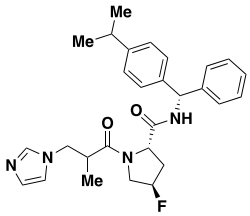
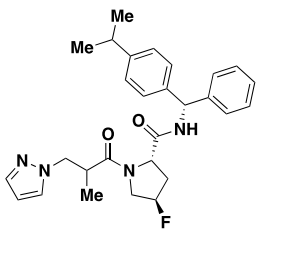
13. The compound of claim 1, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein the compound, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, is selected from the group consisting of



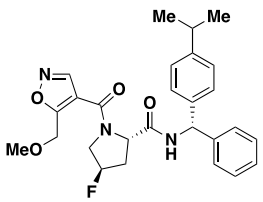
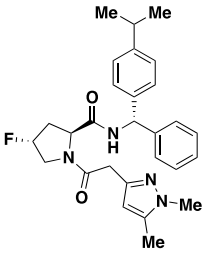
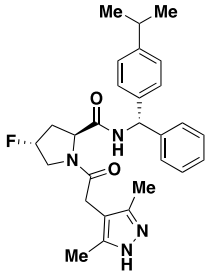
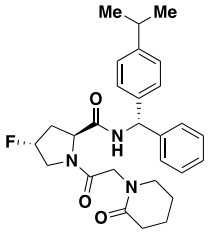
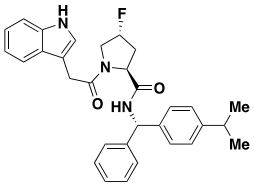
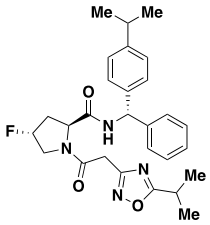
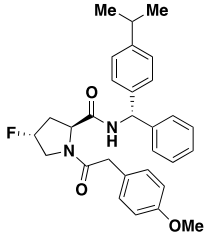
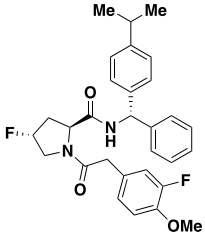
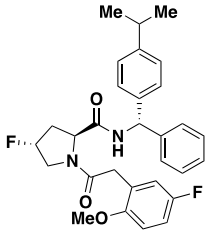
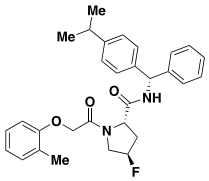
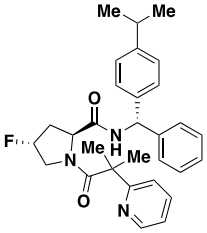
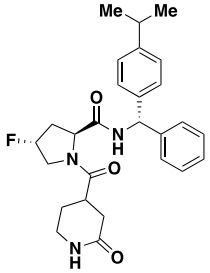
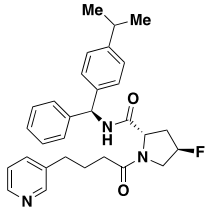
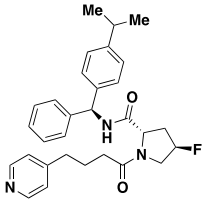
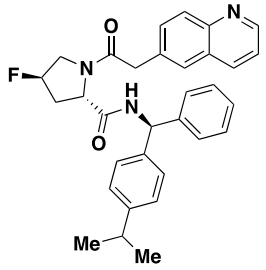
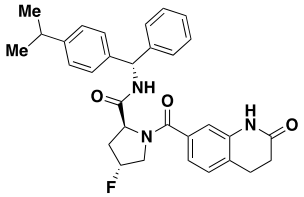
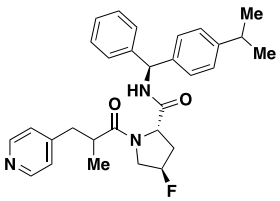
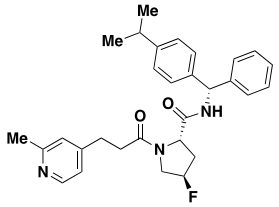

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

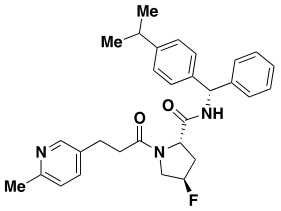
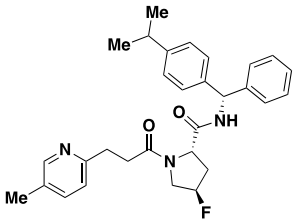
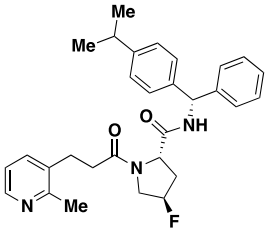
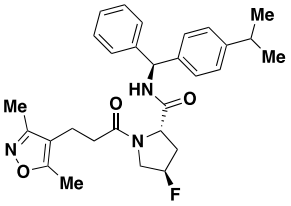
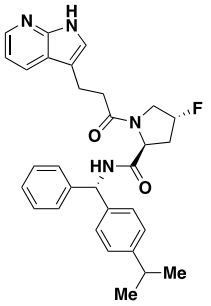
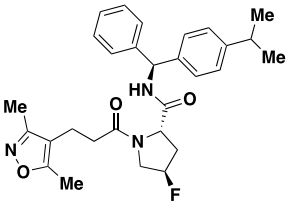
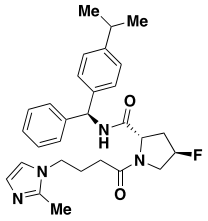
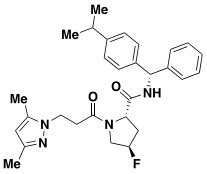
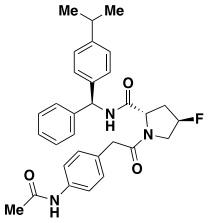
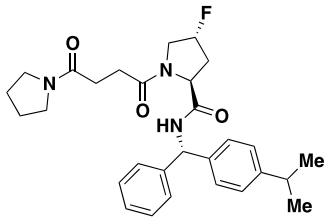
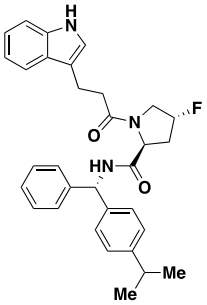
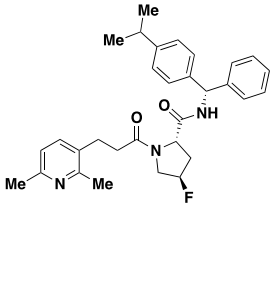
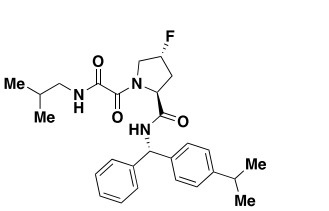
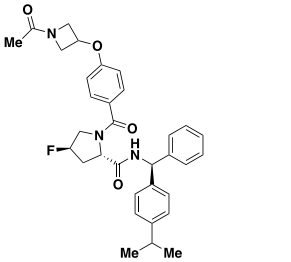

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;


;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;


;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

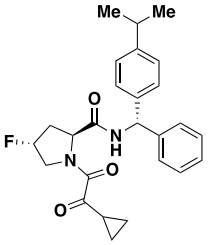
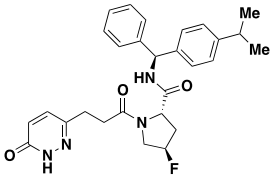
;

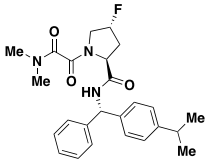
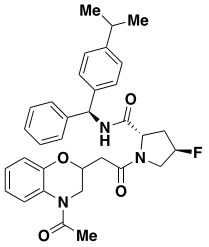
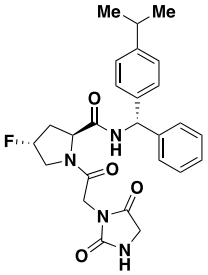

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

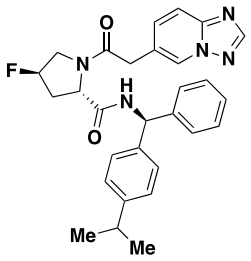
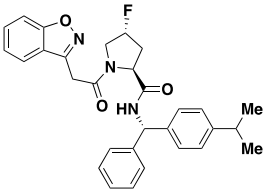
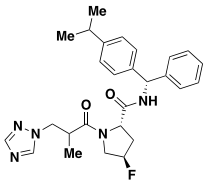

;

;

;

;

;

;

;

;

;

;

;

;

;

;

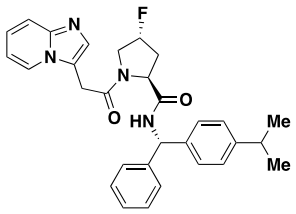
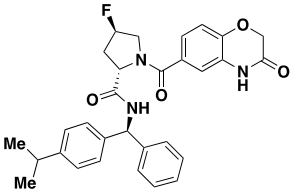
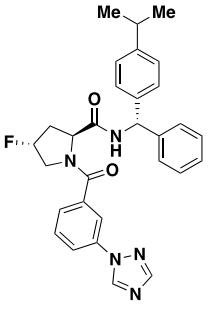
;

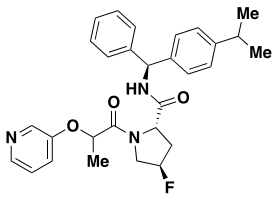
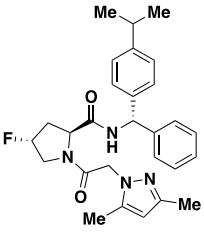
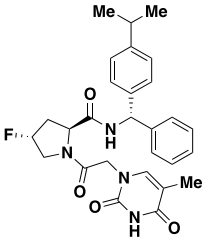
;

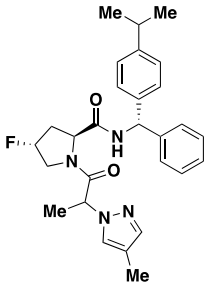
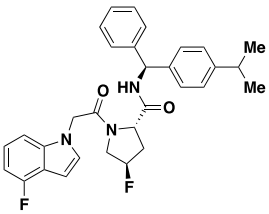
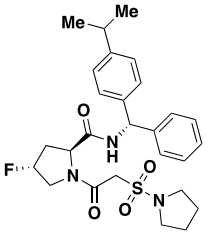
;

;

;

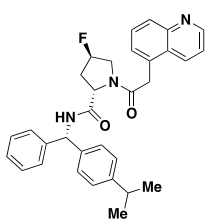
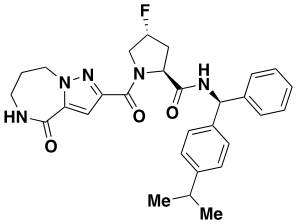
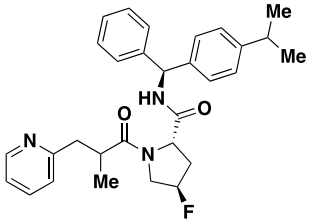

;

;

;

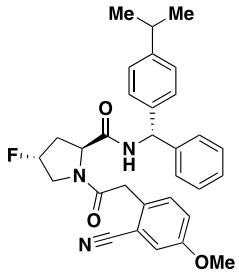
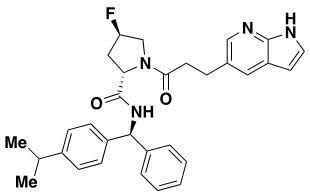
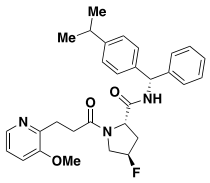

;

;

;

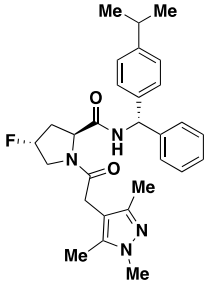
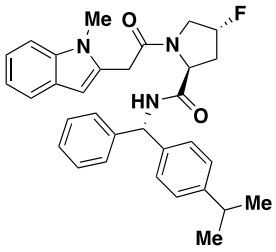
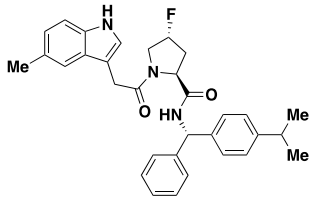

;

;

;

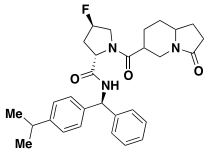
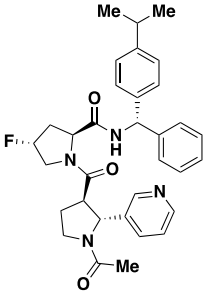
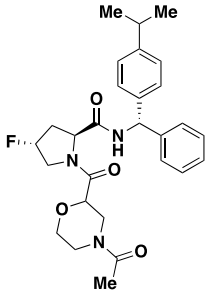

;

;

;

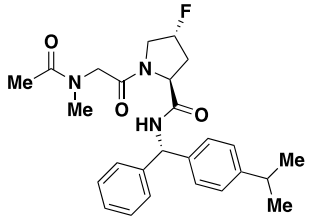
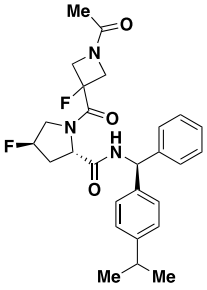
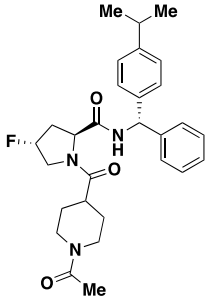

;

;

;

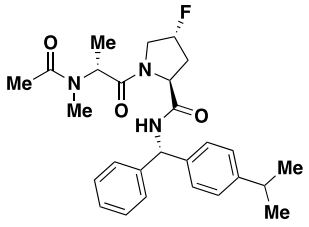
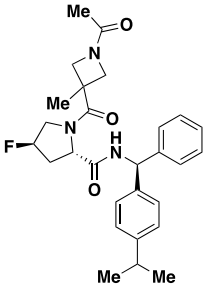
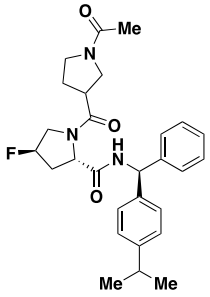

;

;

;

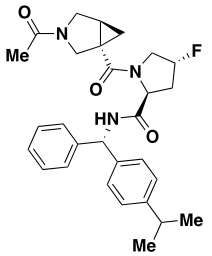
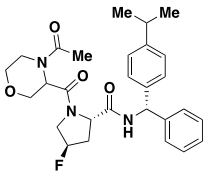
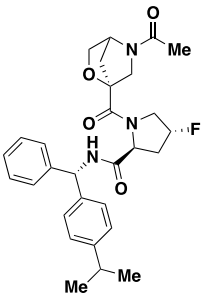
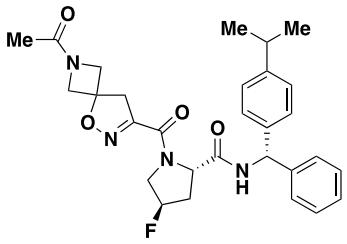
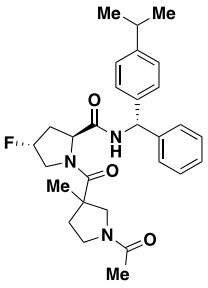
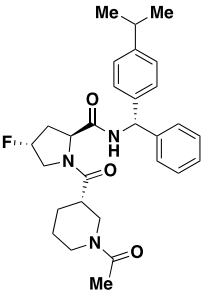
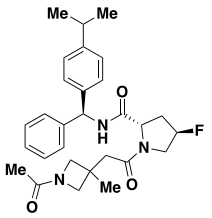
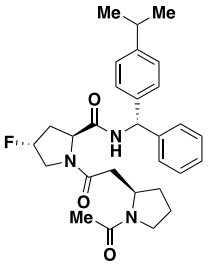
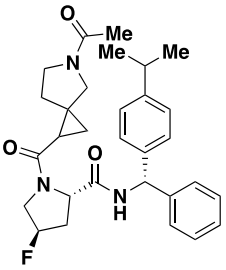
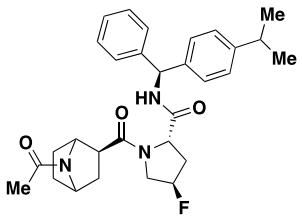
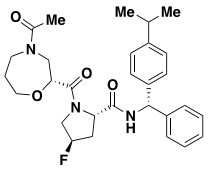
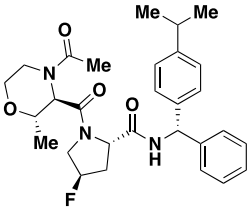
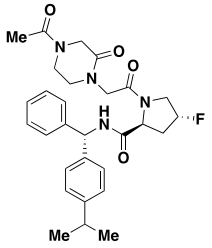
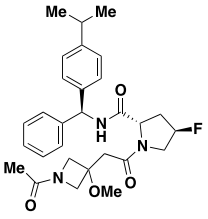
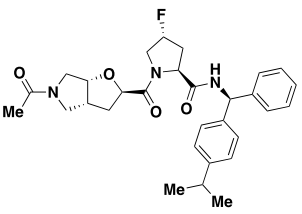
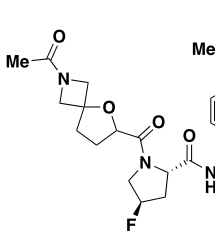
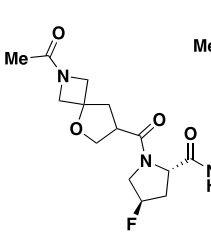
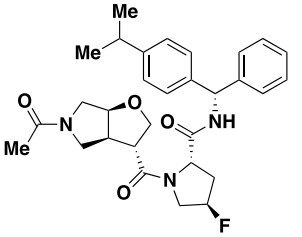

;

;

;

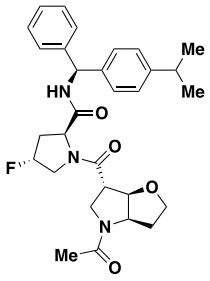
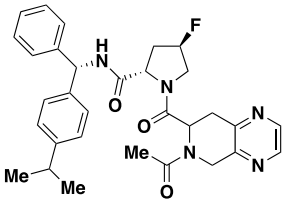
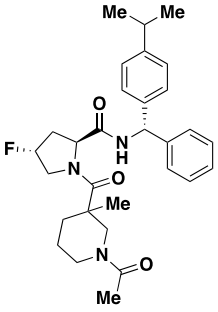
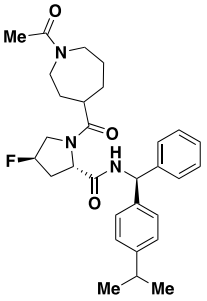
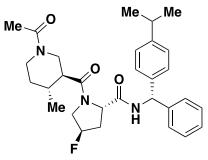
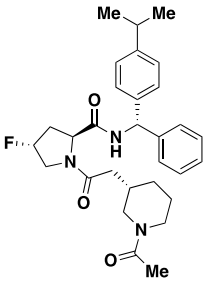
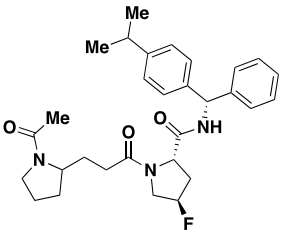
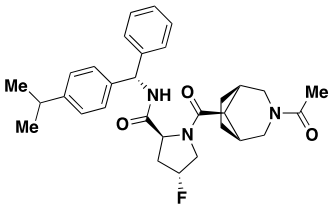
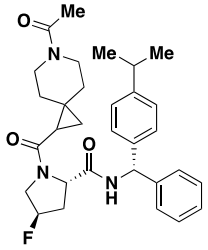
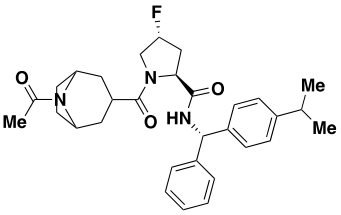
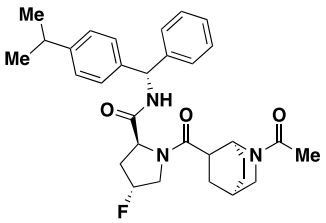
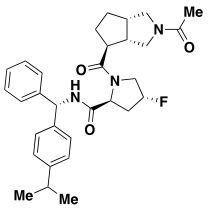
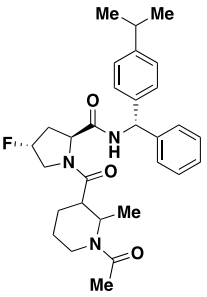
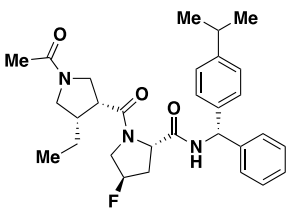
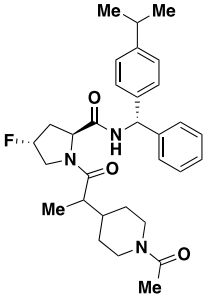
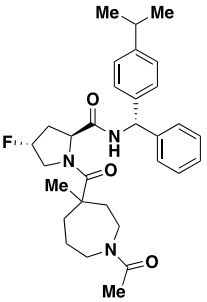
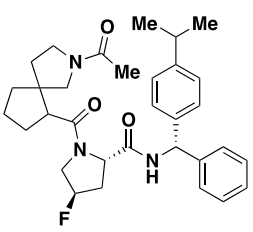
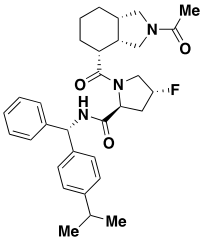

;

;

;

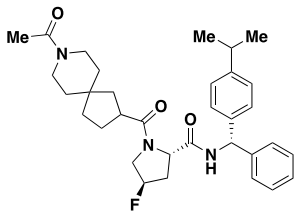
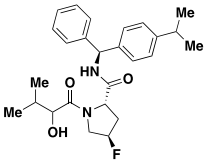
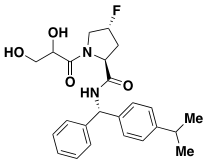
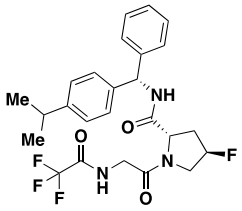
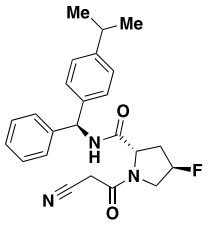
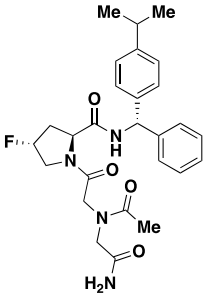
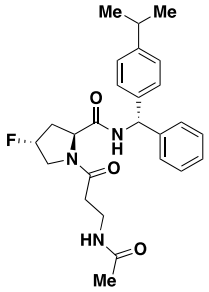
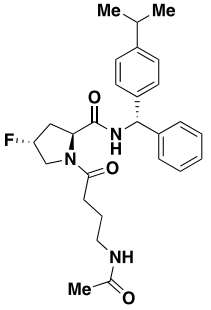
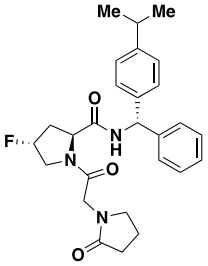
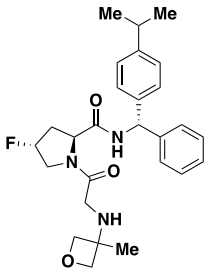
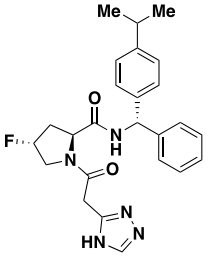
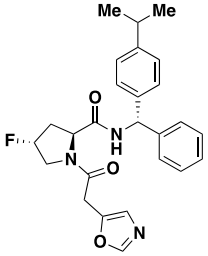
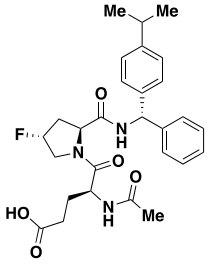
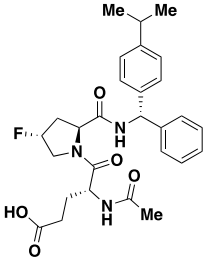
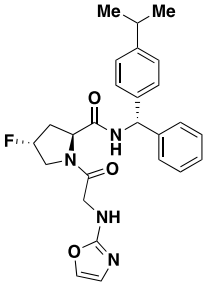
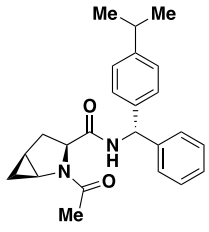
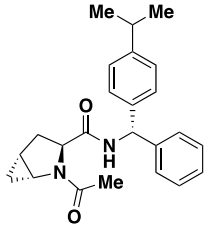
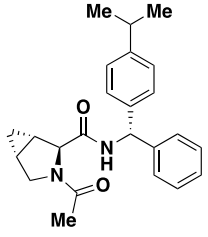

;

;

;

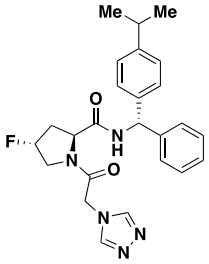
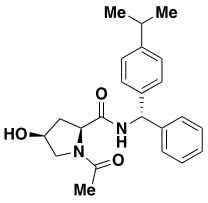
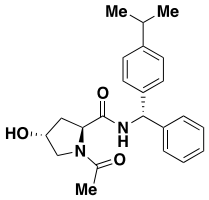
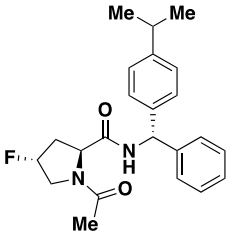
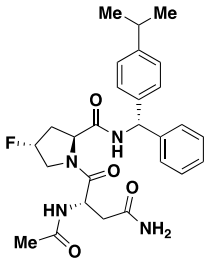
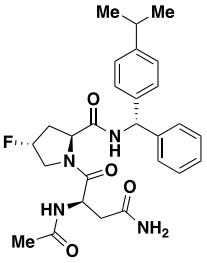
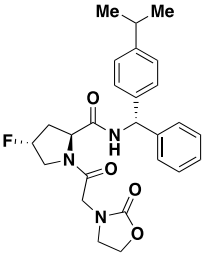
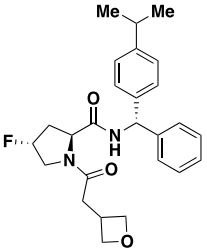
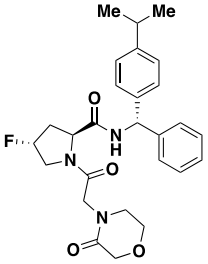
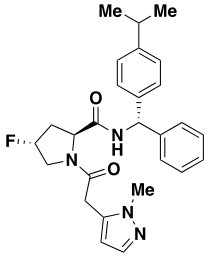
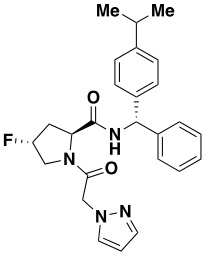
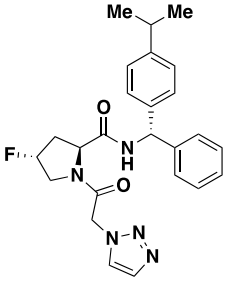
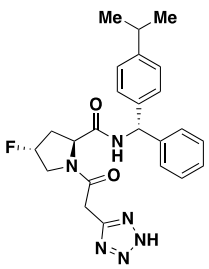
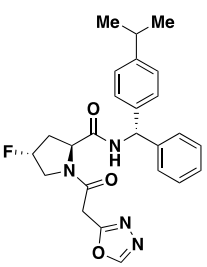
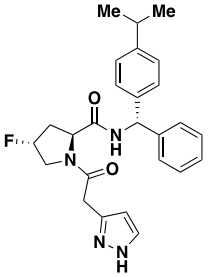

;

;

;

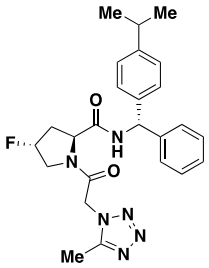
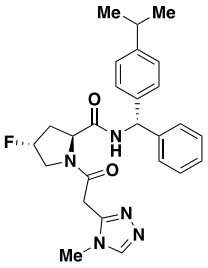
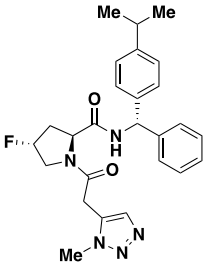
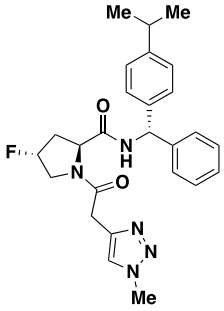
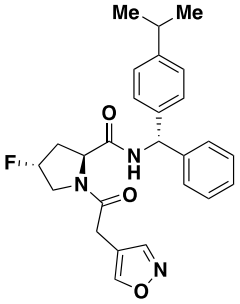
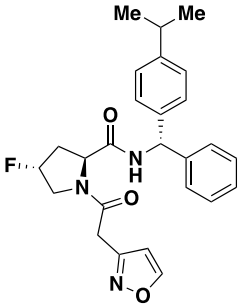
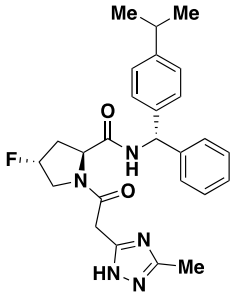
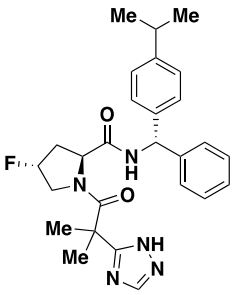
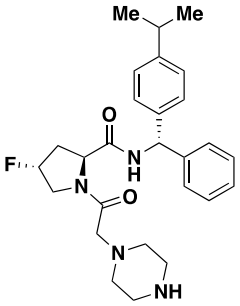
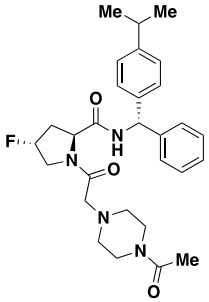
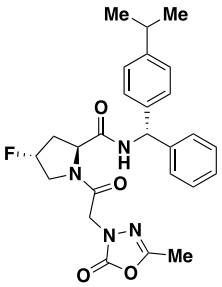
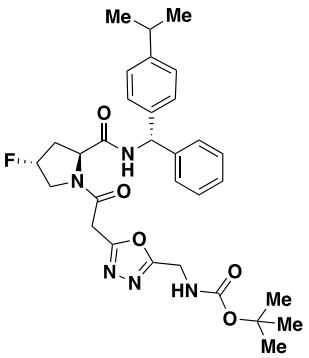
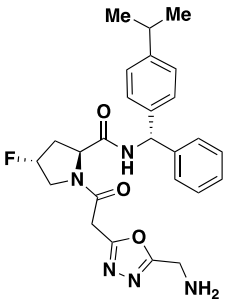
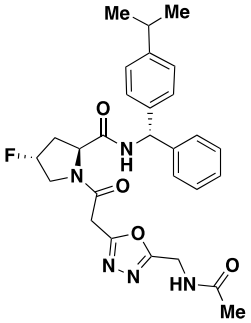
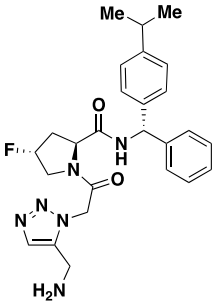

;

;

;

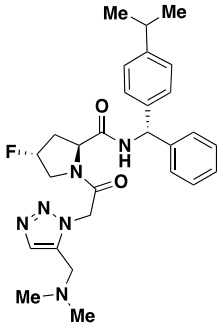
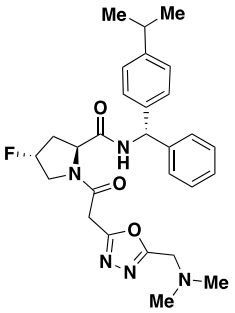
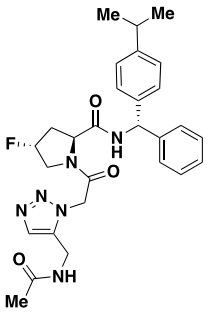

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

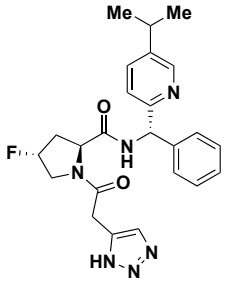
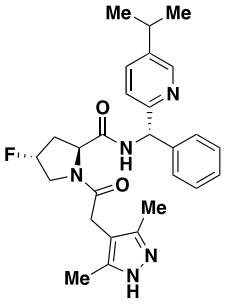

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

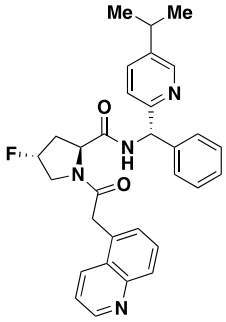
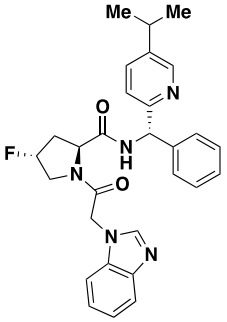
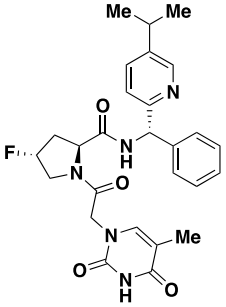

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

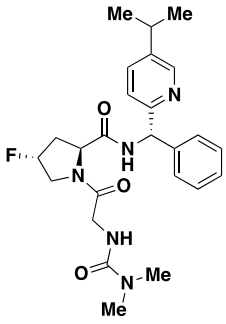
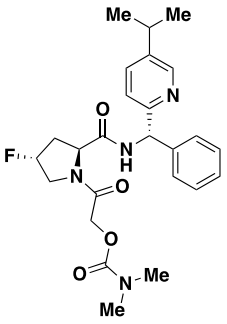
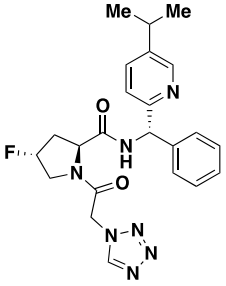

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

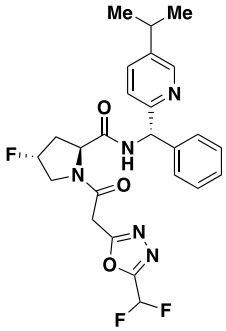
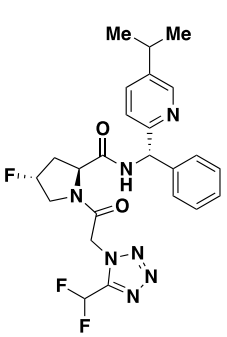
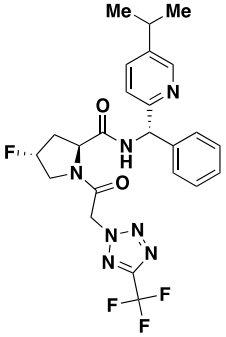

Me
Me
O
F
N
H
O
N
N
N
N
Me
;

Me
Me
O
F
N
H
O
N
N
N
Me
;

Me
Me
O
F
N
H
O
N
N
N
Me
;

Me
Me
O
F
N
H
O
N
N
N
Me
;

Me
Me
O
F
N
H
O
N
O
;

Me
Me
O
F
N
H
O
N
O
;

Me
Me
O
F
N
H
O
N
HN
N
Me
;

Me
Me
O
F
N
H
O
Me
Me
NH
N
;

Me
Me
O
F
N
H
O
N
NH
;

Me
Me
O
F
N
H
O
N
N
Me
O
;

Me
Me
O
F
N
H
O
N
N
Me
O
O
;

Me
Me
O
F
N
H
O
O
N
N
HN
O
Me
Me
Me
;

Me
Me
O
F
N
H
O
O
N
N
NH2
;

Me
Me
O
F
N
H
O
O
N
N
HN
O
Me
;

Me
Me
O
F
N
H
O
N
N
N
H2N
;

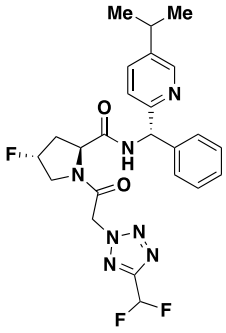
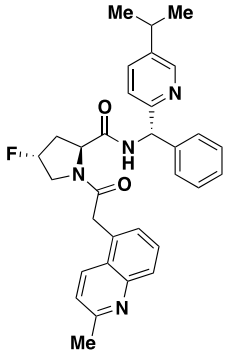
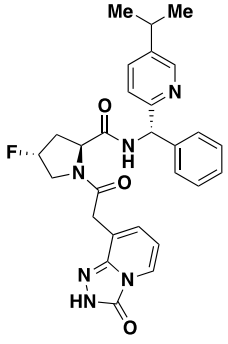
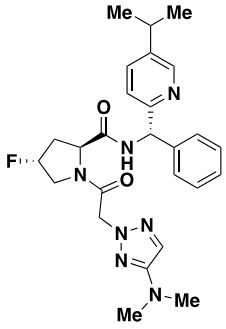
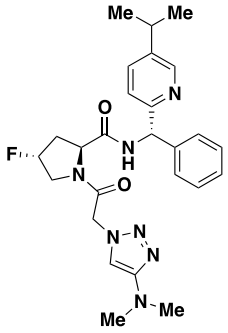
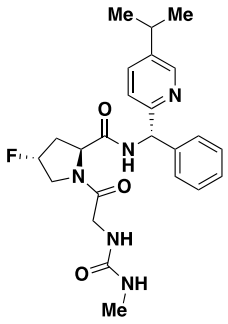
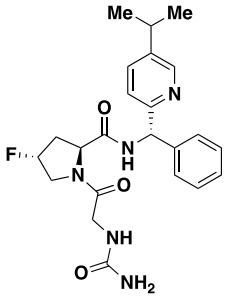
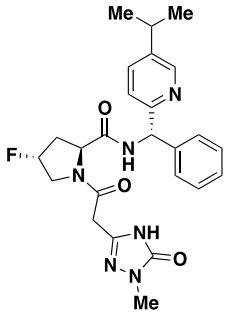
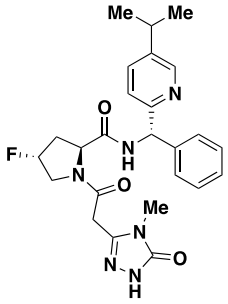
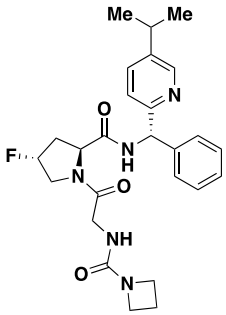
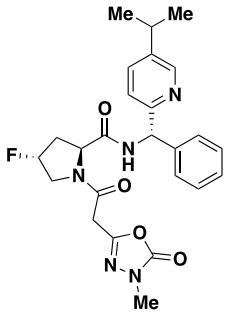
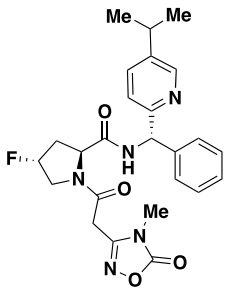
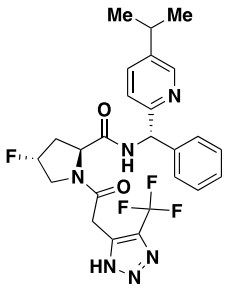
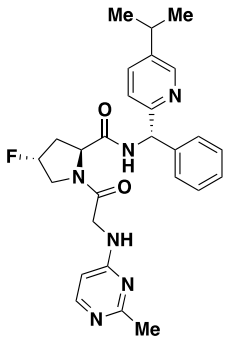
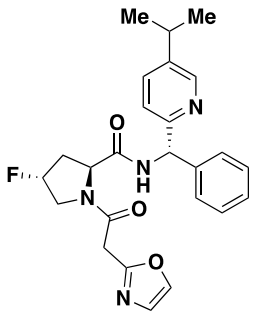

;

;

;

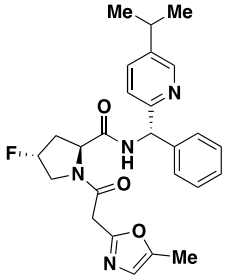
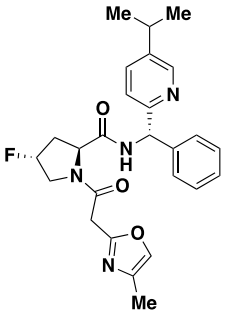
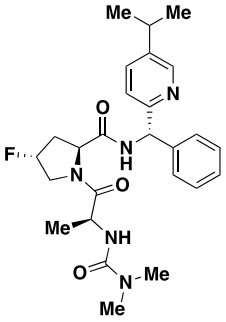
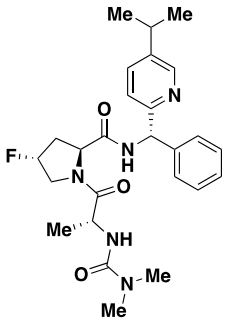
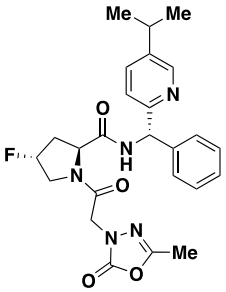
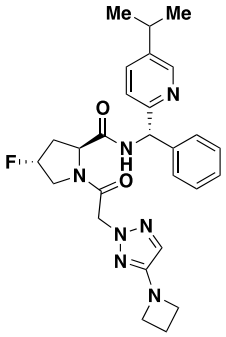
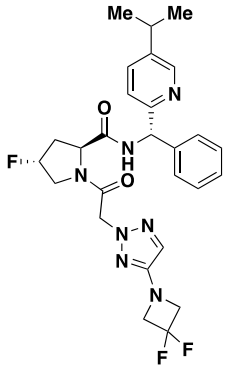
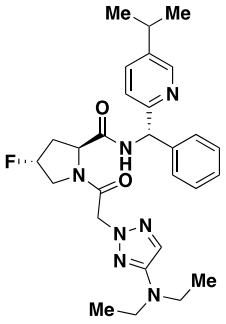
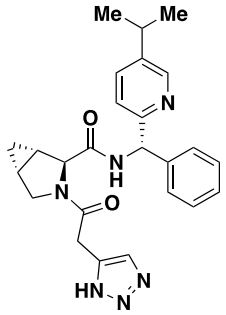
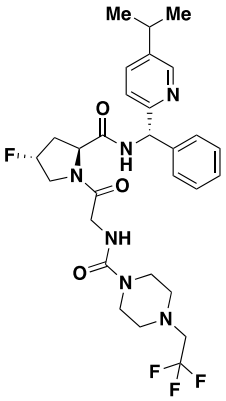
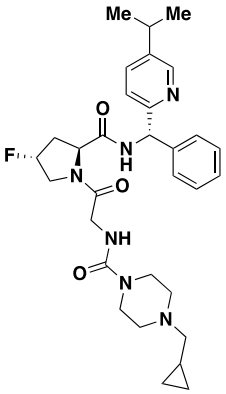

;

;

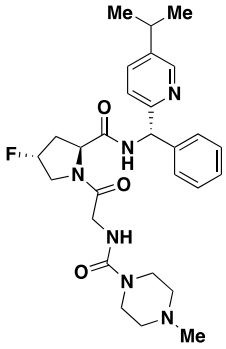
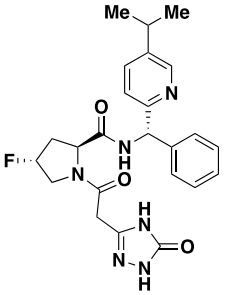
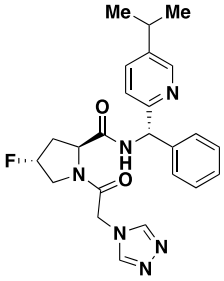
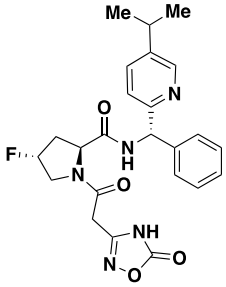
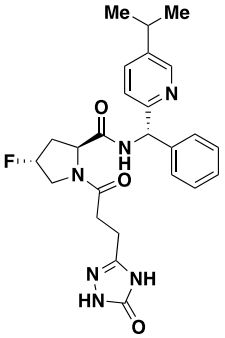
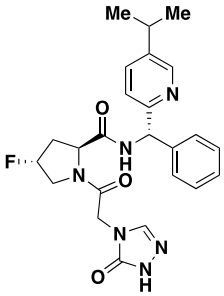
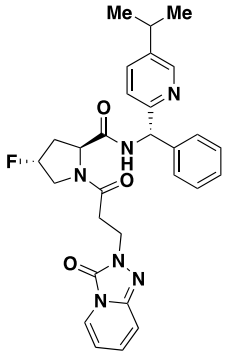
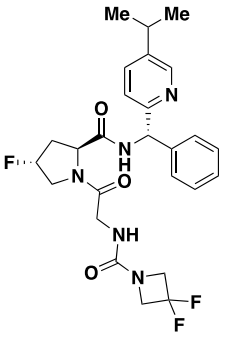
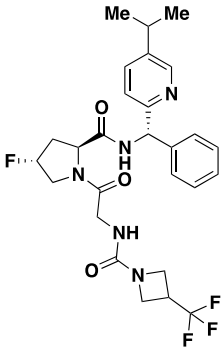
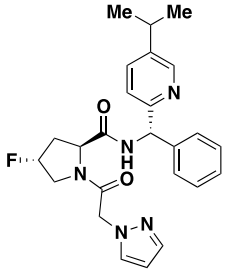
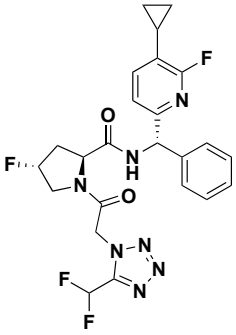
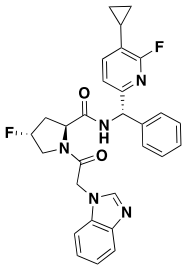
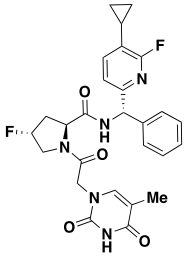
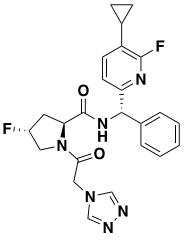
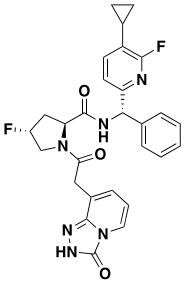

;

;

;

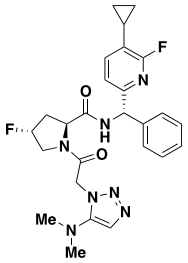
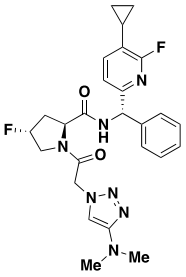
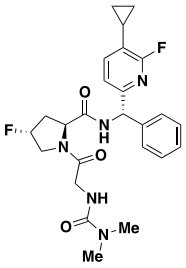

;

;

;

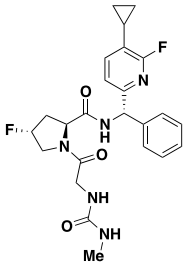
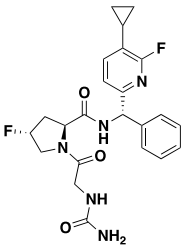
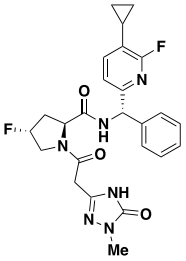

;

;

;

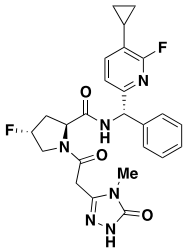
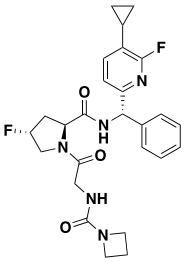
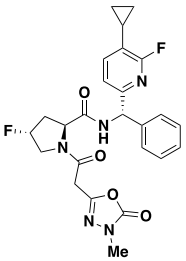

Me
Me
N
O
F
N
H
N
O
N
N
N
F
F
;

Me
Me
N
O
F
N
H
N
O
N
Me
;

Me
Me
N
O
F
N
H
N
O
N
HN
N
O
;

Me
Me
N
O
F
N
H
N
O
N
N
N
Me
Me
;

Me
Me
N
O
F
N
H
N
O
N
N
N
Me
Me
;

Me
Me
N
O
F
N
H
N
O
NH
O
NH
Me
;

Me
Me
N
O
F
N
H
N
O
NH
O
NH2
;

Me
Me
N
O
F
N
H
N
O
NH
N
N
O
Me
;

Me
Me
N
O
F
N
H
N
O
Me
N
N
O
H
;

Me
Me
N
O
F
N
H
N
O
NH
O
N
;

Me
Me
N
O
F
N
H
N
O
O
N
N
Me
;

Me
Me
N
O
F
N
H
N
O
Me
N
N
O
O
;

Me
Me
N
O
F
N
H
N
O
F
F
F
HN
N
N
;

Me
Me
N
O
F
N
H
N
O
NH
N
N
Me
;

Me
Me
N
O
F
N
H
N
O
O
N
;

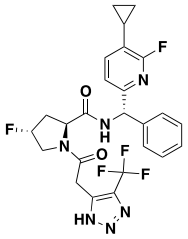
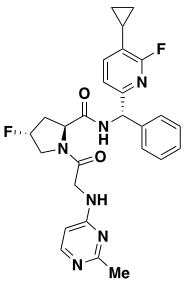
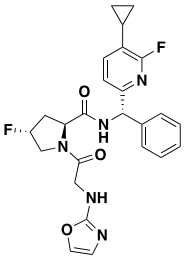

;

;

;

;

;

;

;

;

;

;

;

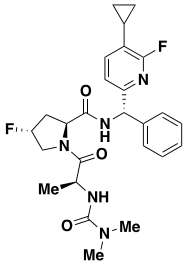
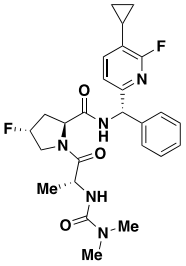
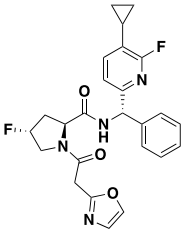

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

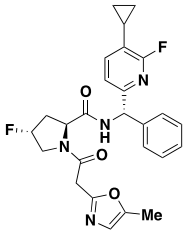
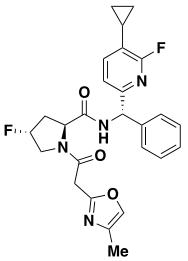
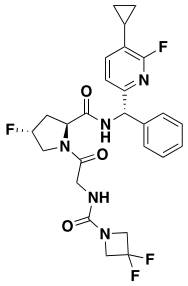

;

;

;

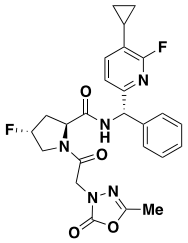
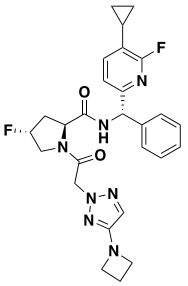
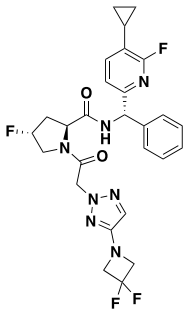

;

;

;

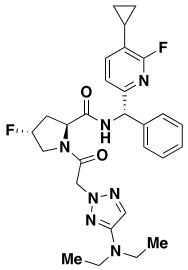
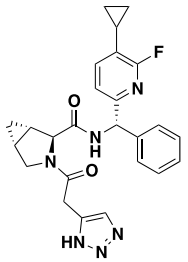

;

;

;

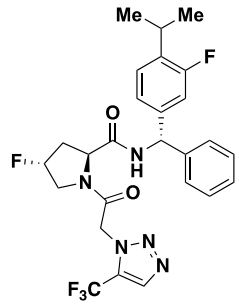
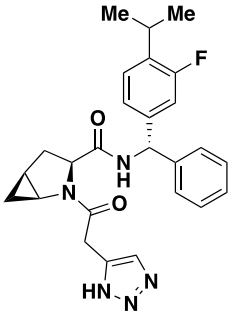

;

;

;

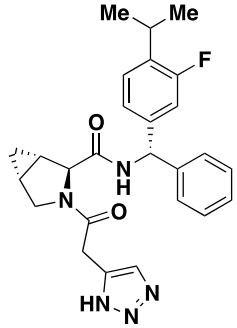
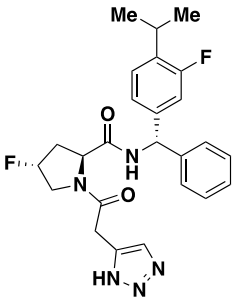
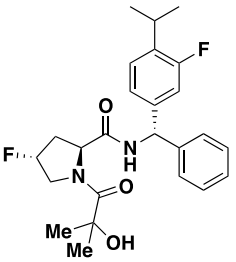

;

;

;

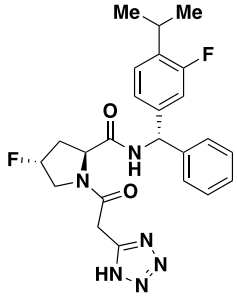
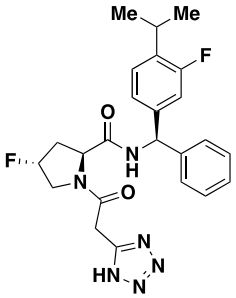
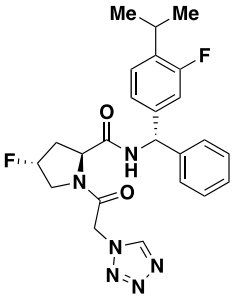
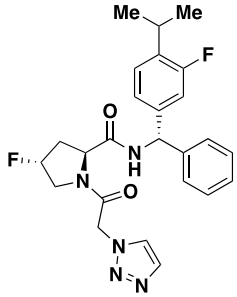
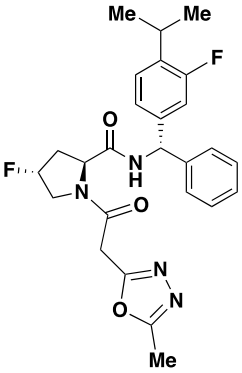
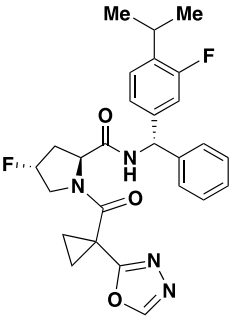
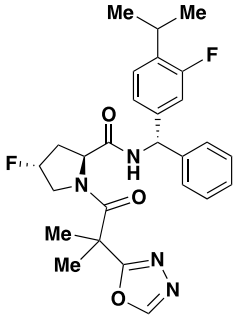
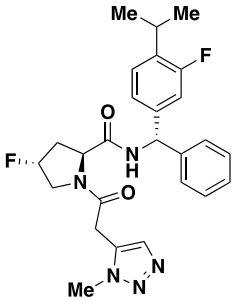
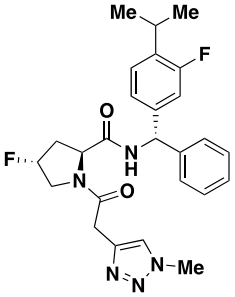
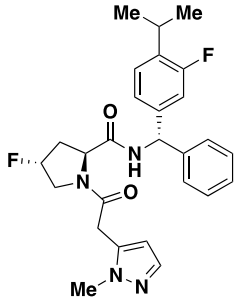
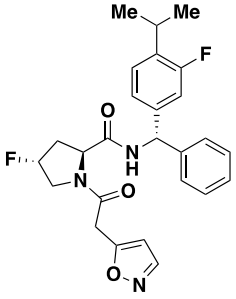
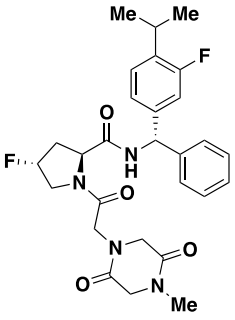
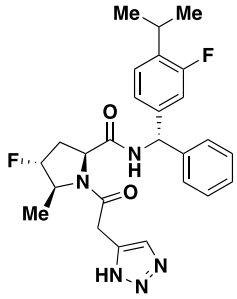

;

;

;

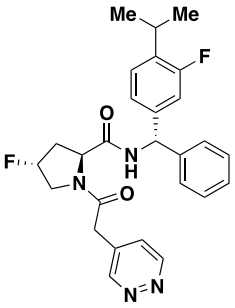

;

;

;


;

;


;

;

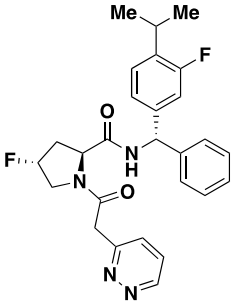
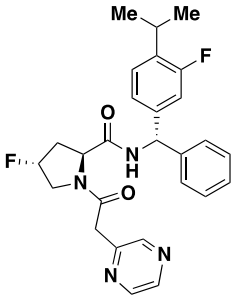
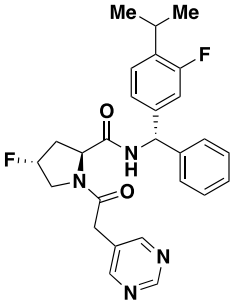
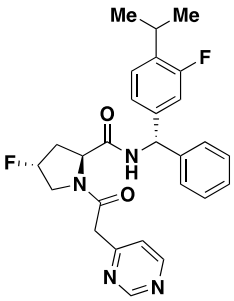
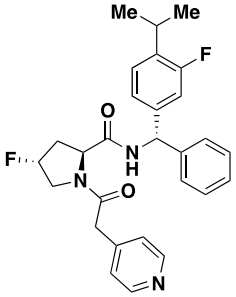
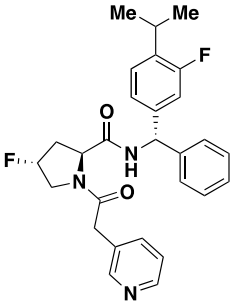
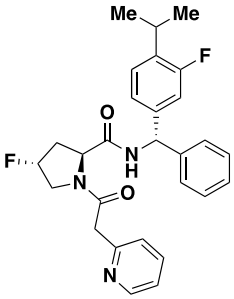
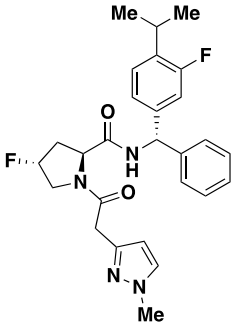
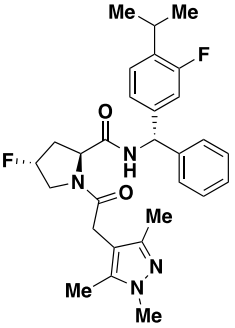
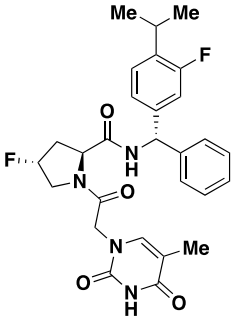
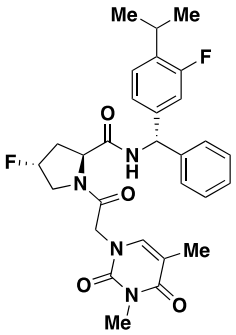
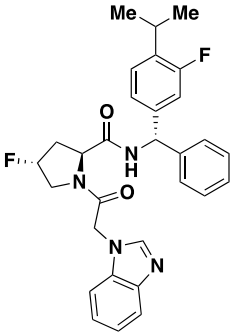
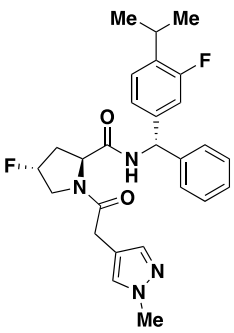
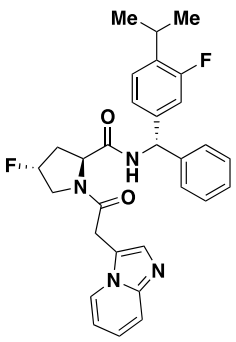
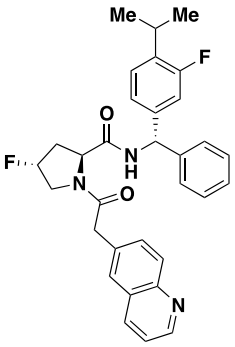

;

;

;

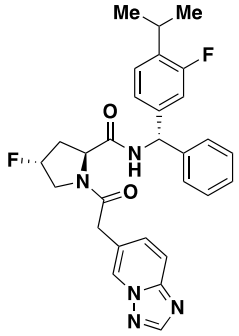
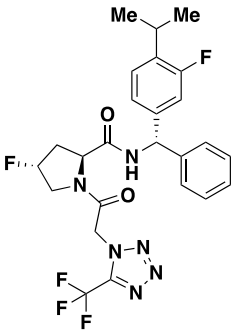
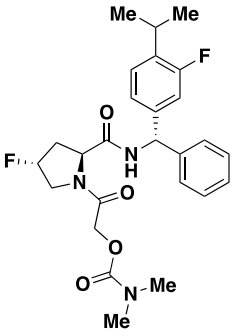
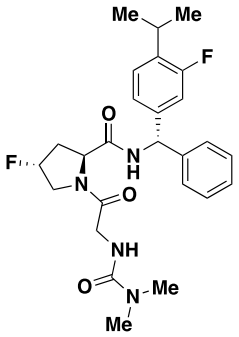
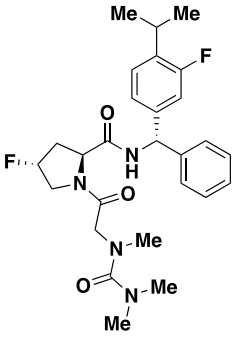
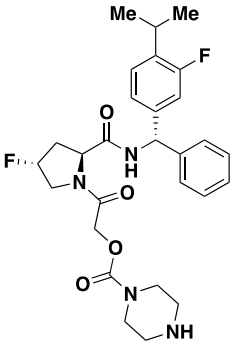
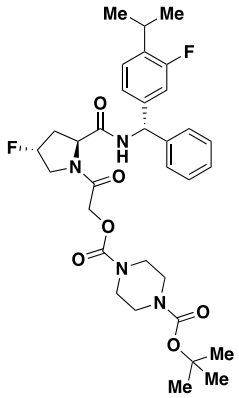
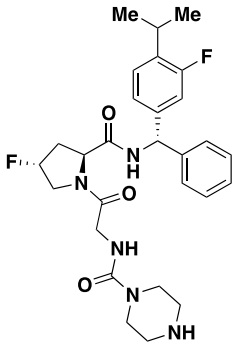
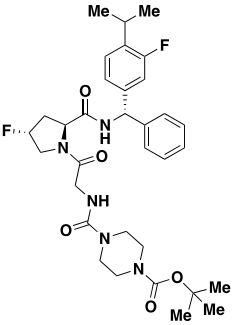
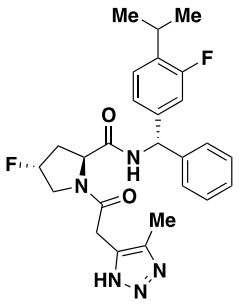
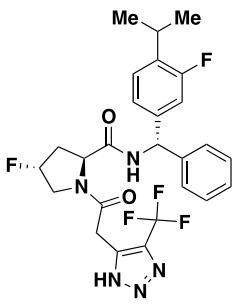
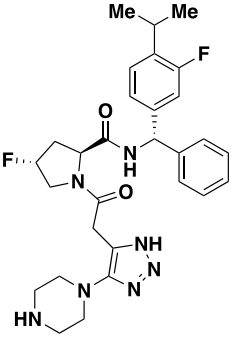

;

;

;

;

;

;

;

;

;

;

;

;

;

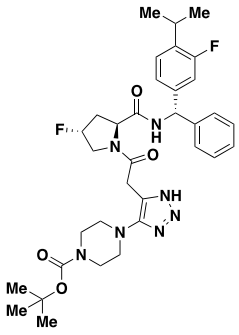
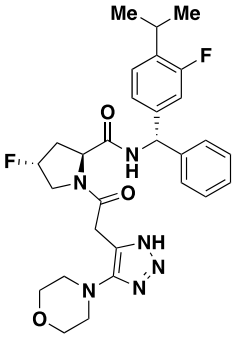
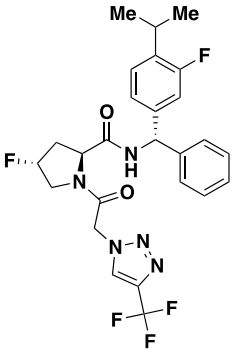
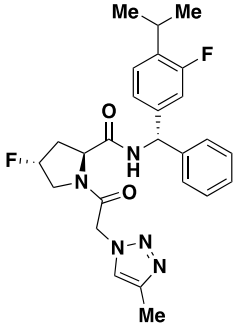
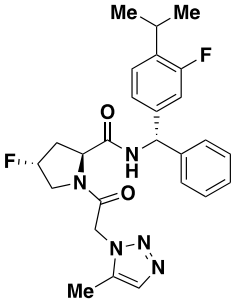
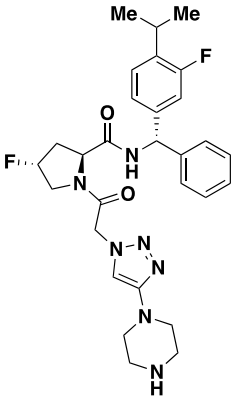
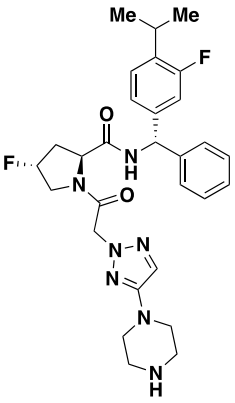
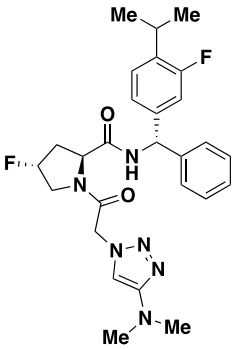
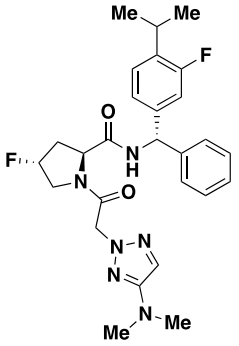
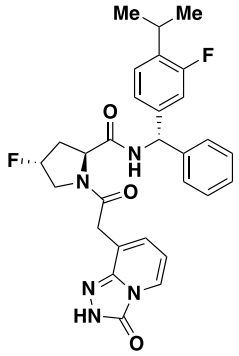
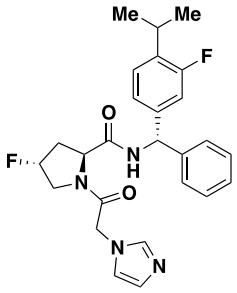
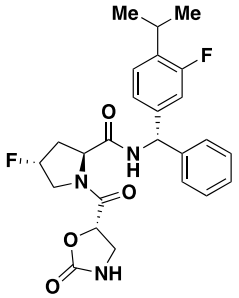
;

;

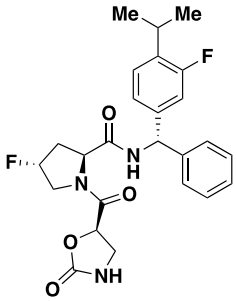
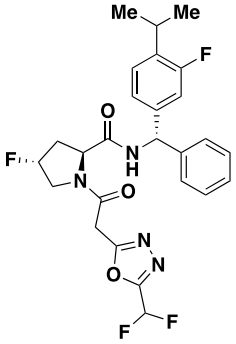
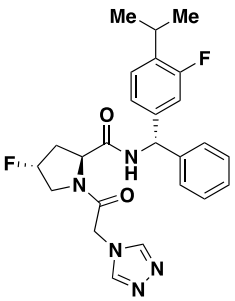
;

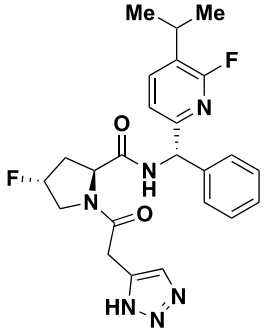
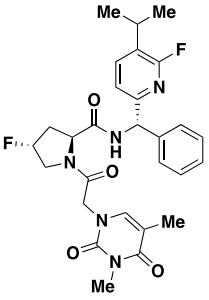
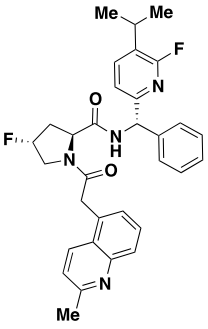
;

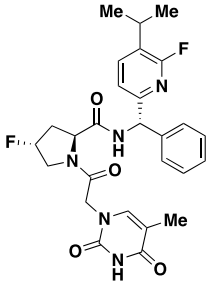
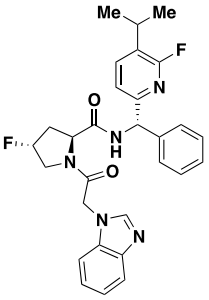
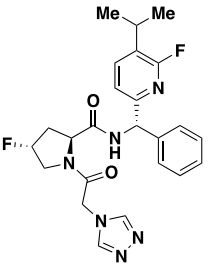

Me
Me
F
O
F
N
H
N
O
N
N
;

Me
Me
F
O
F
N
H
N
O
N
N
;

Me
Me
F
O
F
N
H
N
O
N
N
;

Me
Me
F
O
F
N
H
N
O
N
N
;

Me
Me
F
O
F
N
H
N
O
N
;

Me
Me
F
O
F
N
H
N
O
N
;

Me
Me
F
O
F
N
H
N
O
N
;

Me
Me
F
O
F
N
H
N
O
N
N
Me
;

Me
Me
F
O
F
N
H
N
O
Me
N
Me
N
Me
;

Me
Me
F
O
F
N
H
N
O
N
Me
O
N
H
O
;

Me
Me
F
O
F
N
H
N
O
N
Me
O
N
Me
O
;

Me
Me
F
O
F
N
H
N
O
N
N
;

Me
Me
F
O
F
N
H
N
O
N
N
Me
;

Me
Me
F
O
F
N
H
N
O
N
N
;

Me
Me
F
O
F
N
H
N
O
N
;

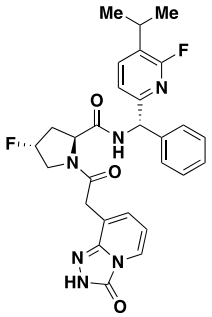
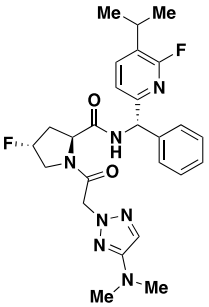
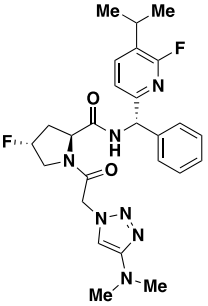

;

;

;

;

;

;

;

;

;

;

;

;

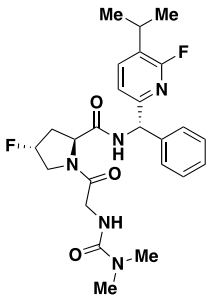
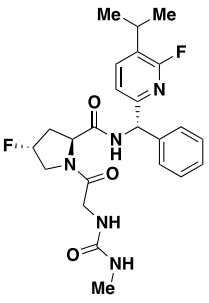
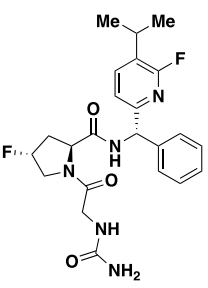

;

;

;

;

;

;

;

;

;

;

;

;

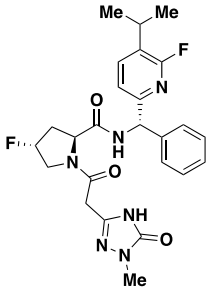
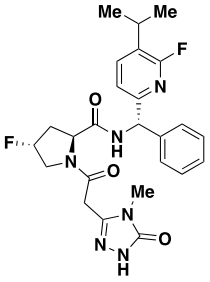
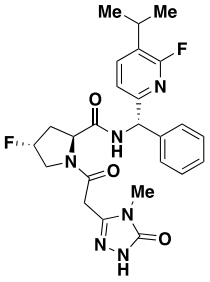
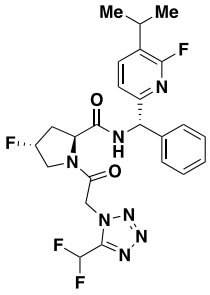
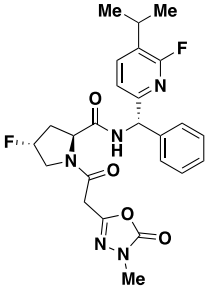
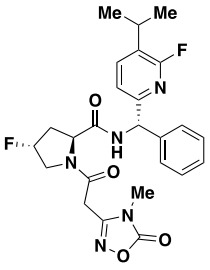
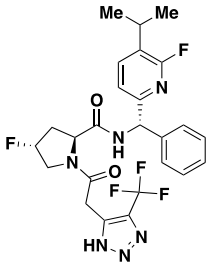
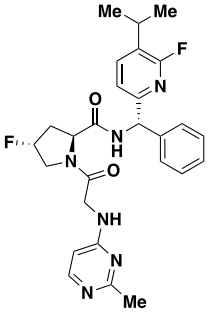
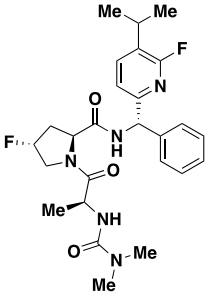
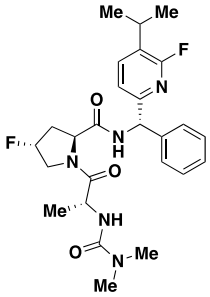
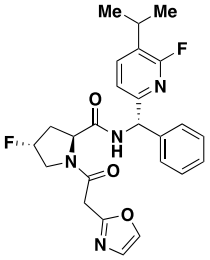
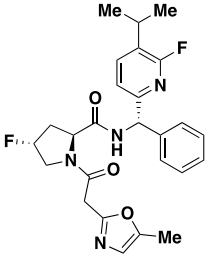
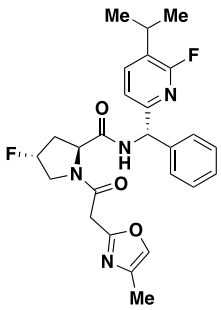
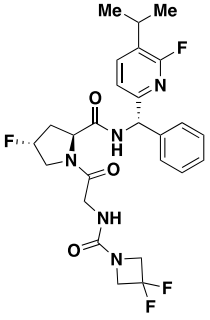
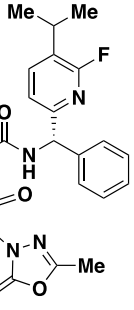

;

;

;

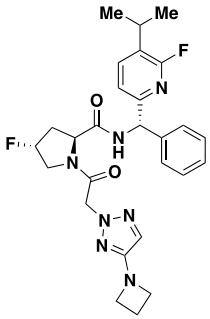
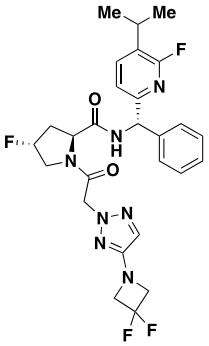
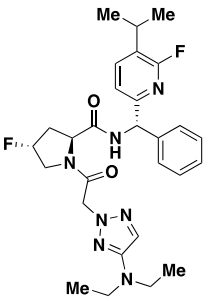
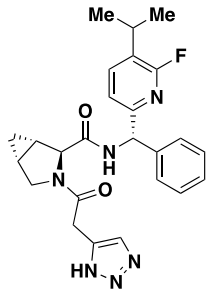
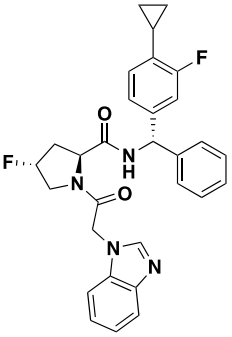
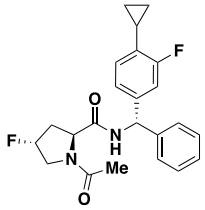
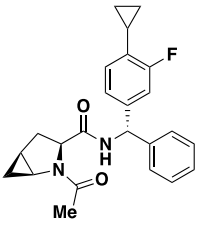
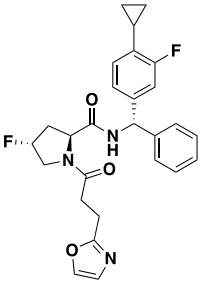
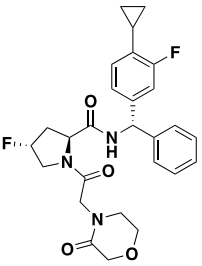
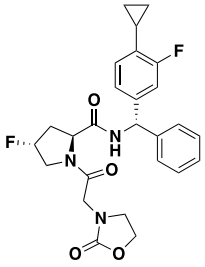
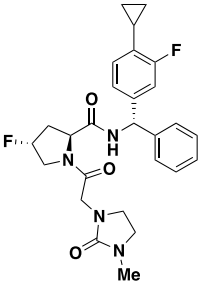
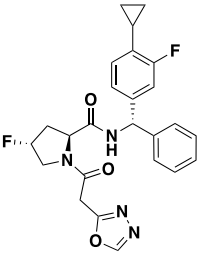

;

;

;

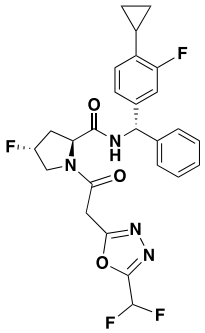
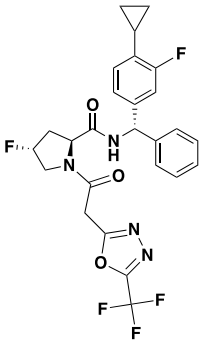
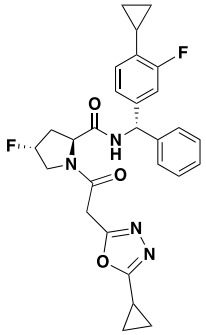
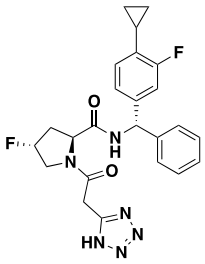
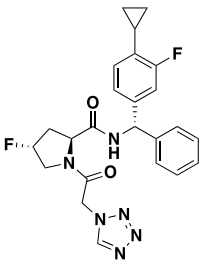
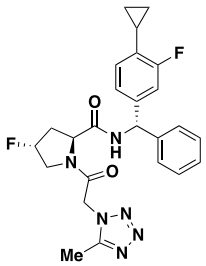
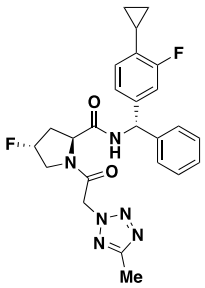
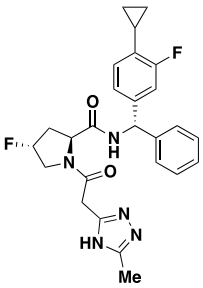
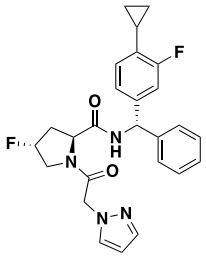
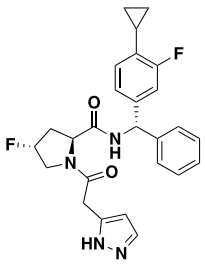
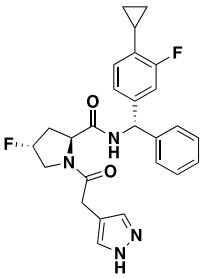
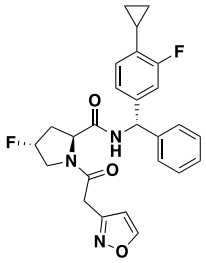
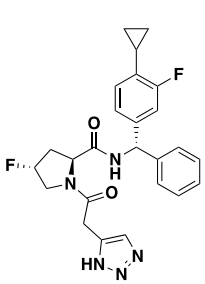
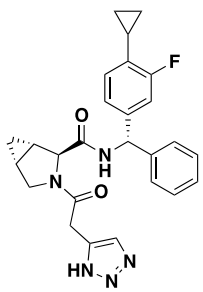
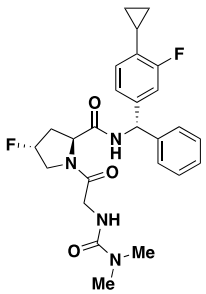

;

;

;

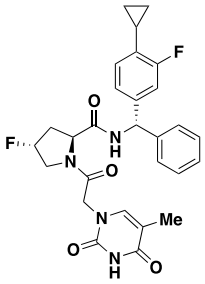
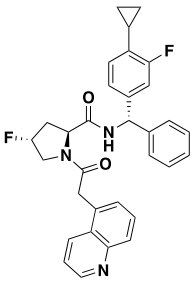
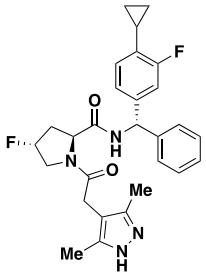
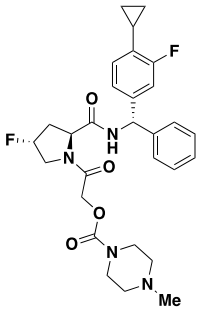
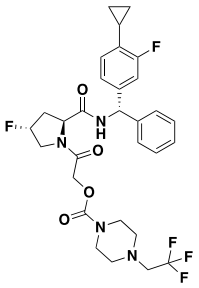
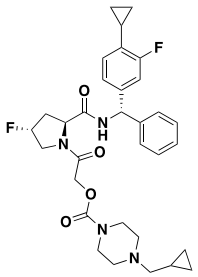
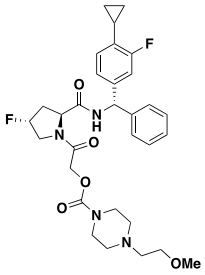
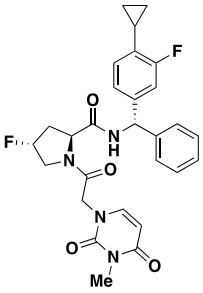
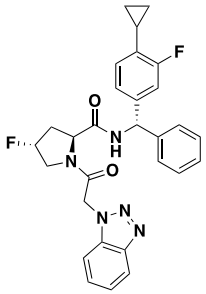
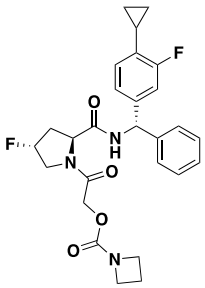
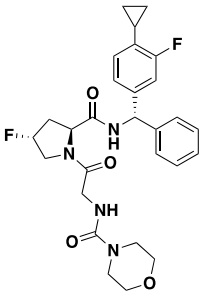
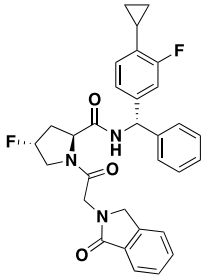
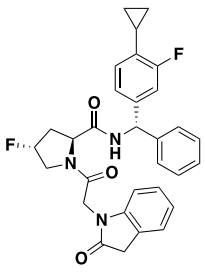
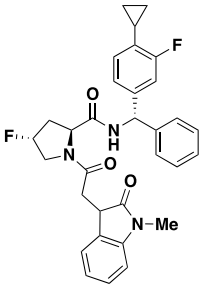
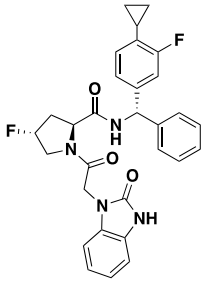

;

;

;

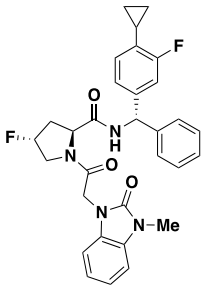
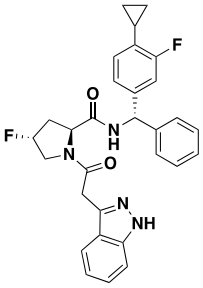
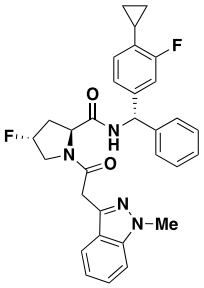
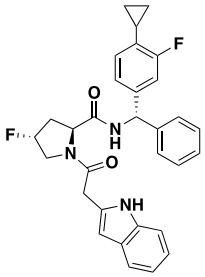
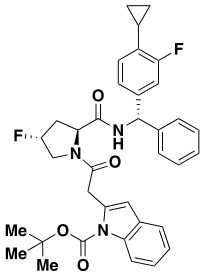
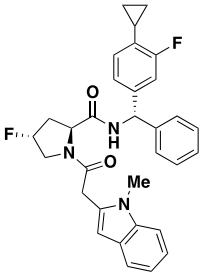
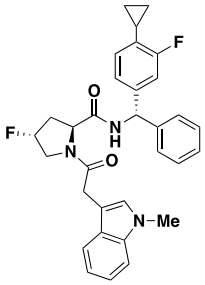
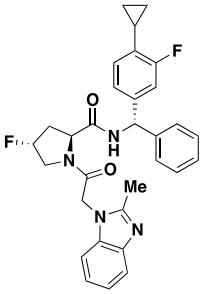
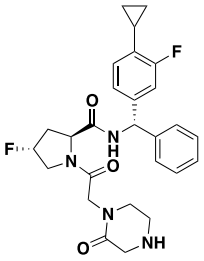
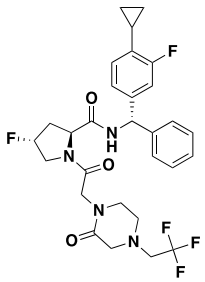
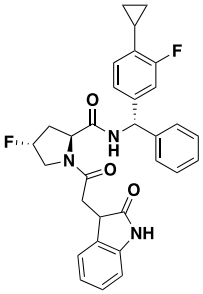
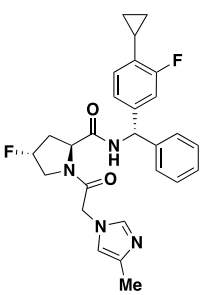
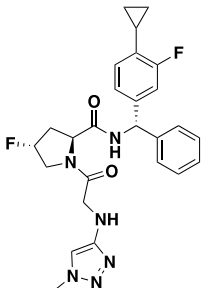
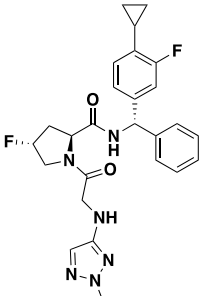
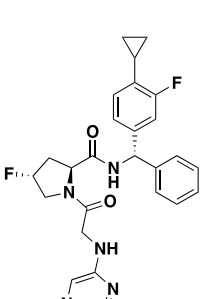

;

;

;


;

;

;

;

;

;

;

;

;

;

;

;

;

;

;


;

;

;

;

;

;

;

;

;

;

;

;


;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

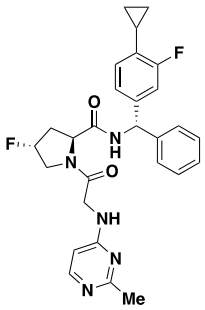
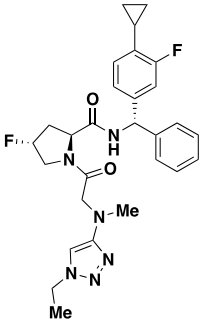
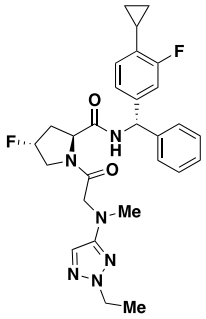
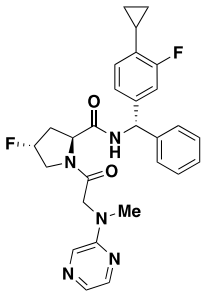
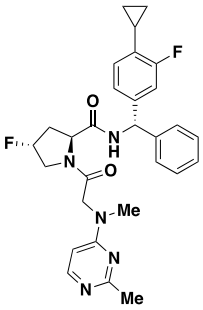
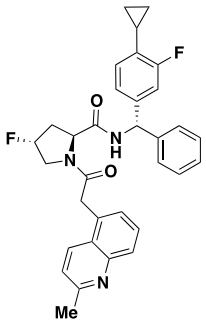
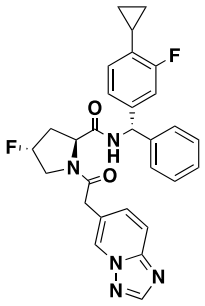
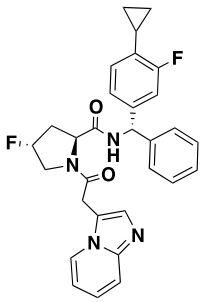
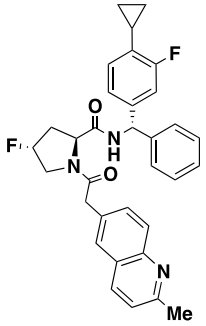
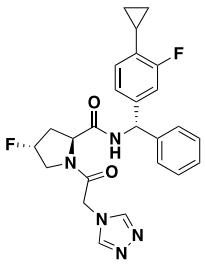
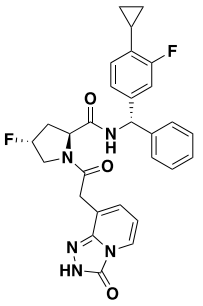
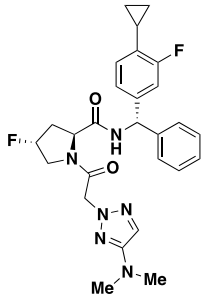
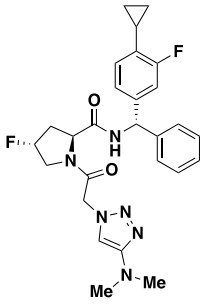
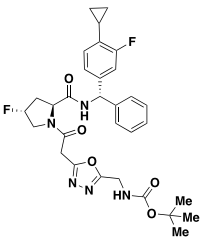
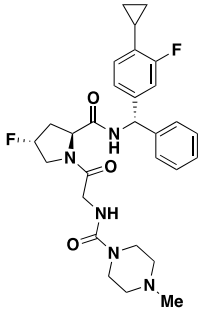

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

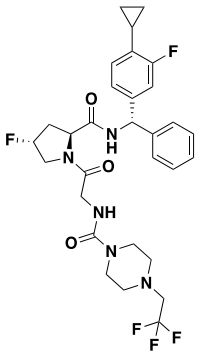
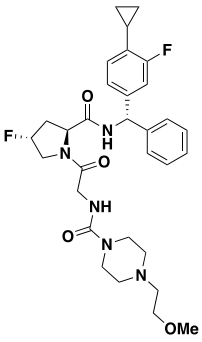
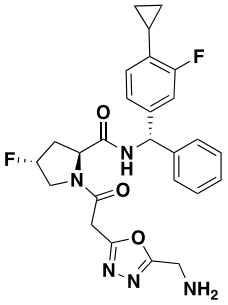

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

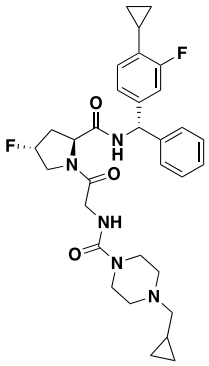
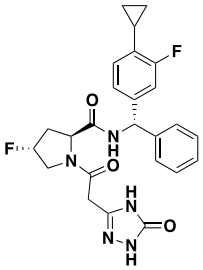
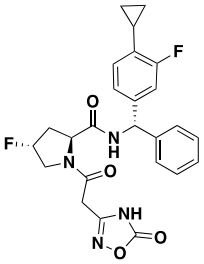
;

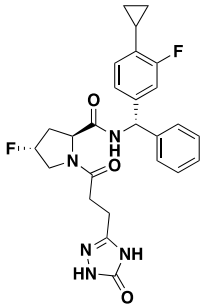
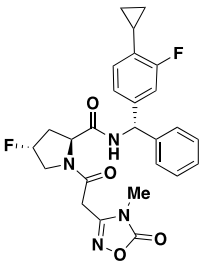
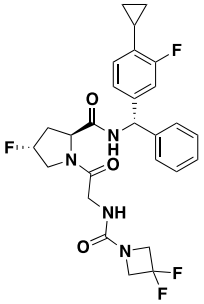
;

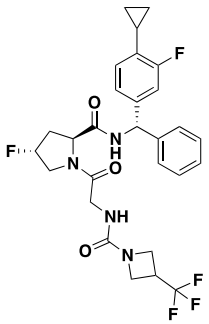
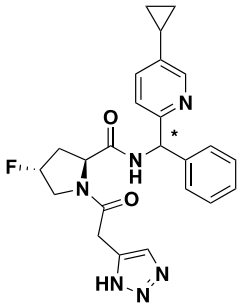
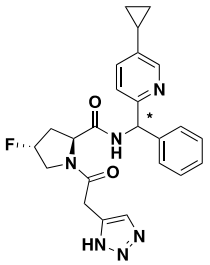
;

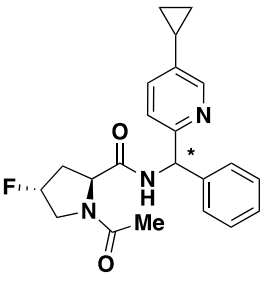
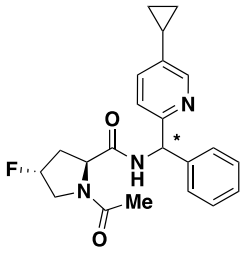
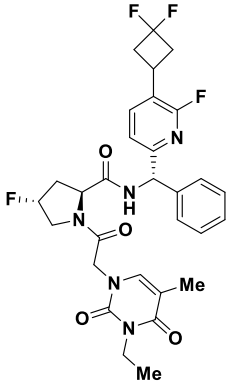

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

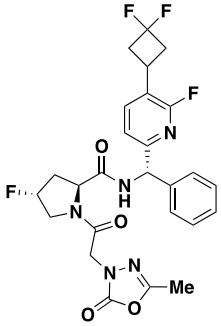
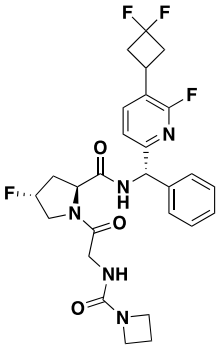
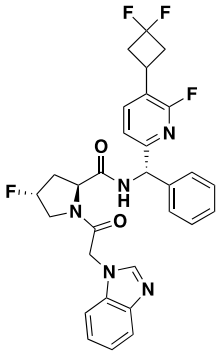
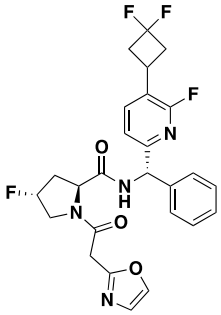
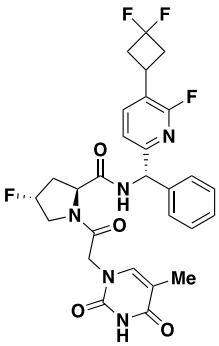
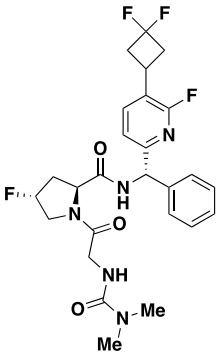
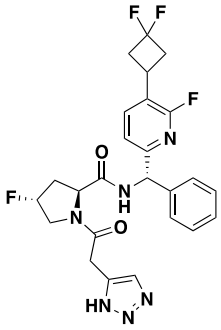
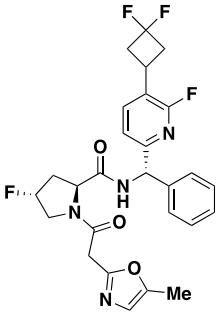
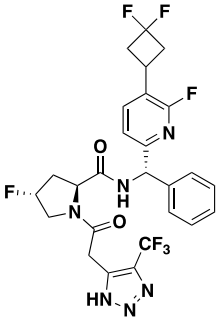
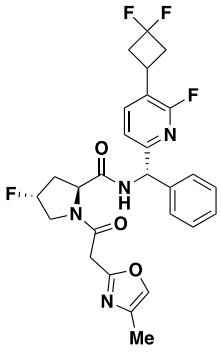
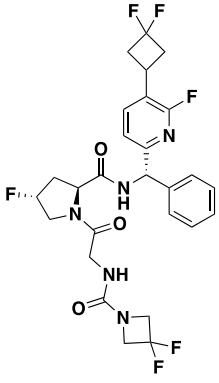
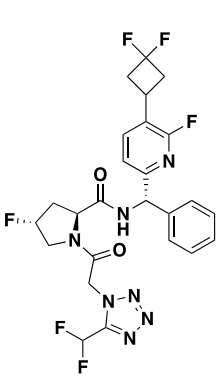

;

;

;

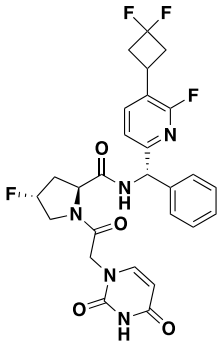
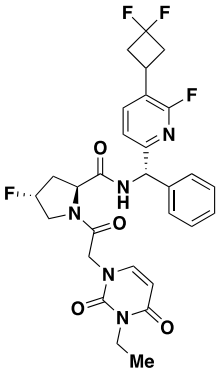
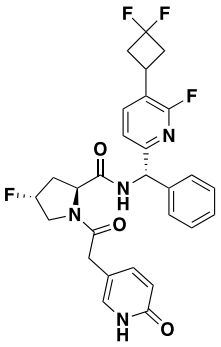

;

;

;

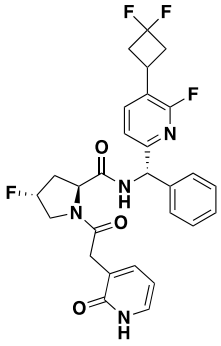
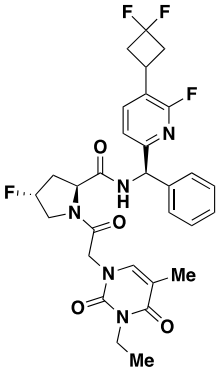
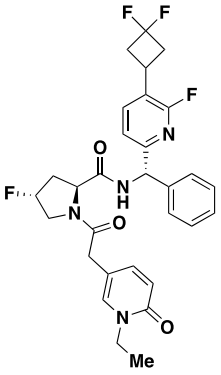

;

;

;

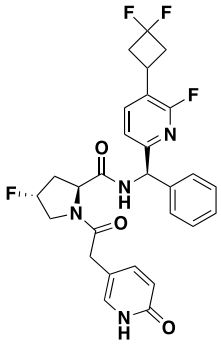
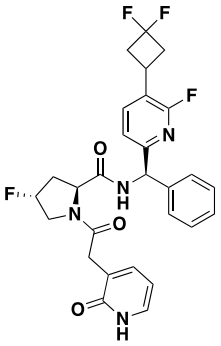
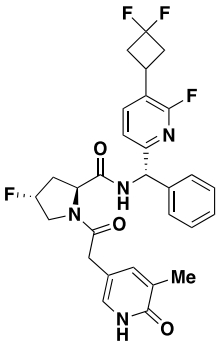

;

;

;

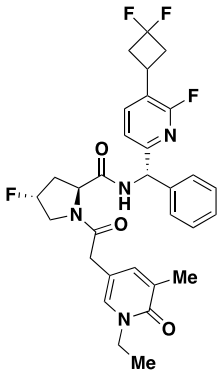
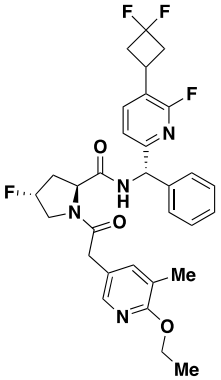
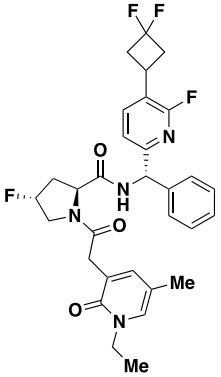

;

;

;

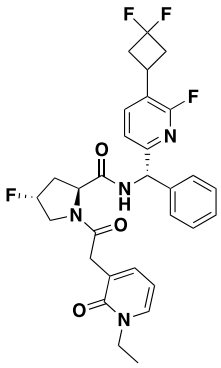
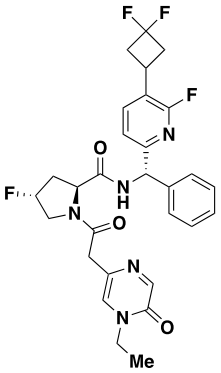
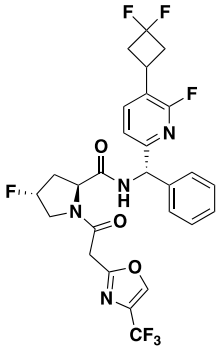
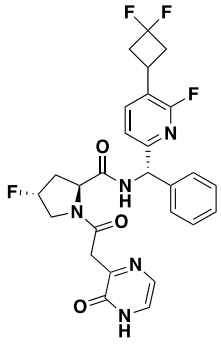
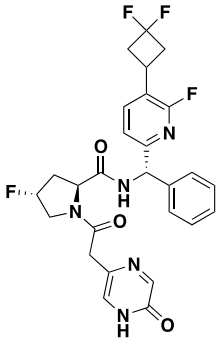
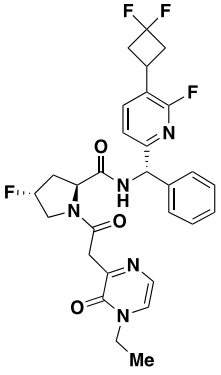
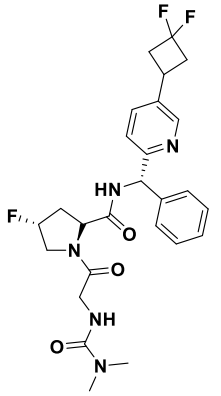
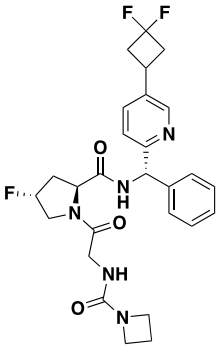
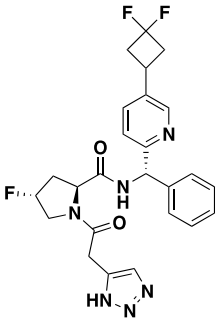
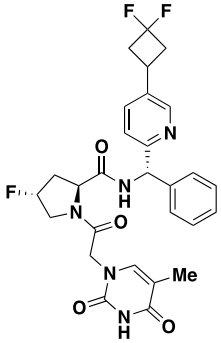
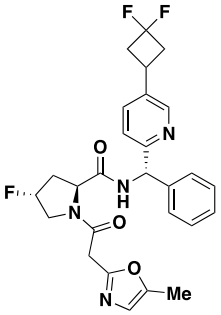
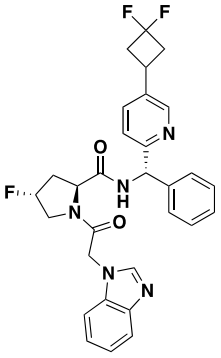

;

;

;

;

;

;

;

;

;

;

;

;

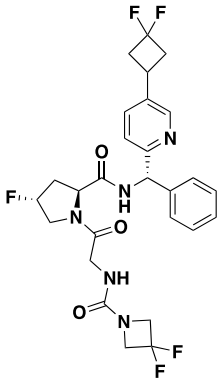
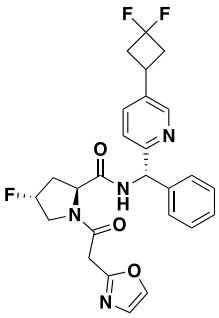
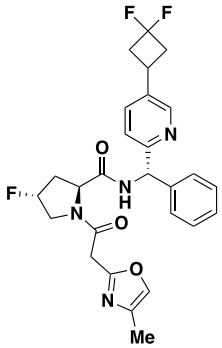
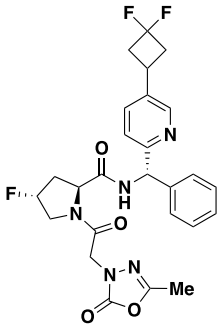
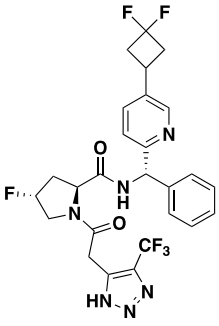
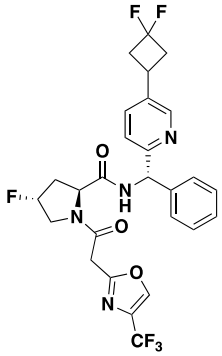
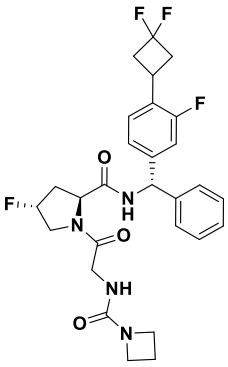
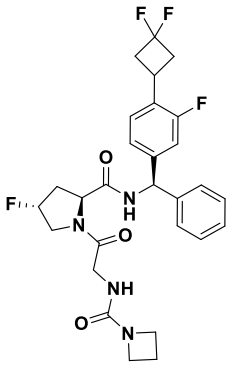
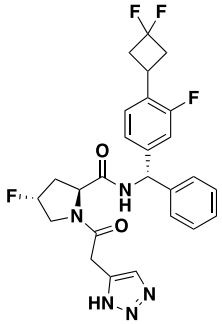
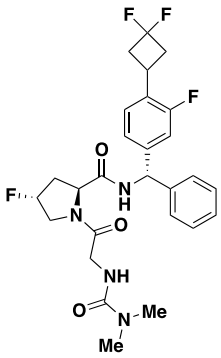
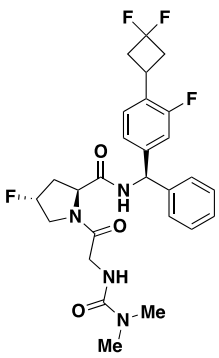
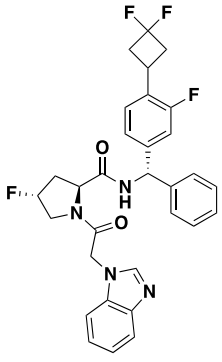

;

;

;

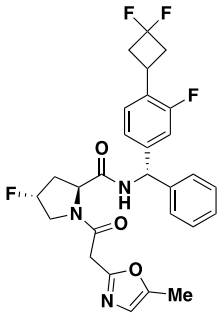
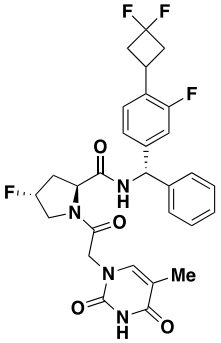
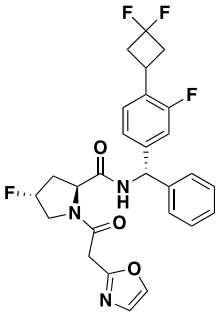
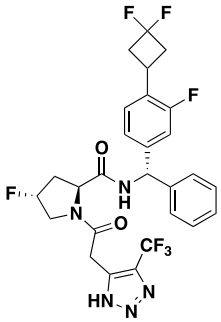
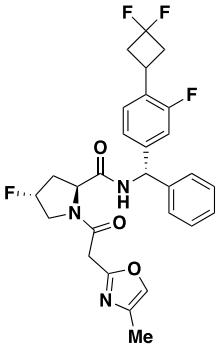
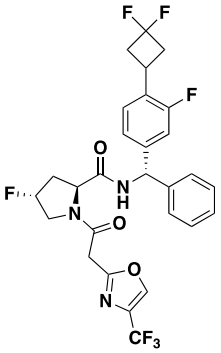
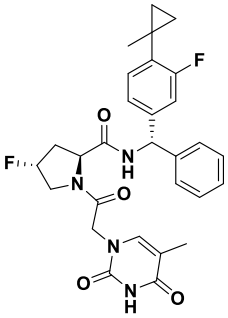
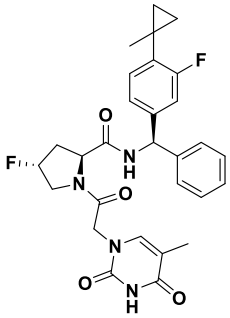
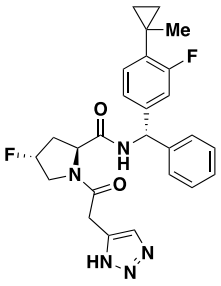
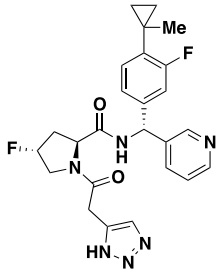
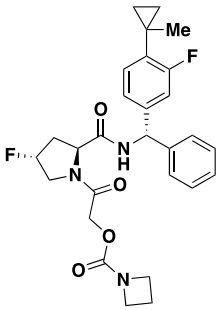
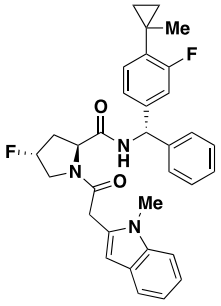
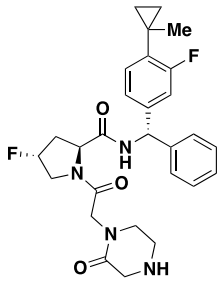
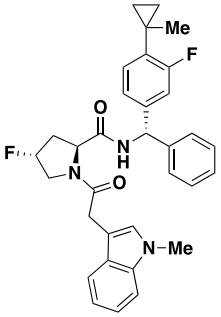
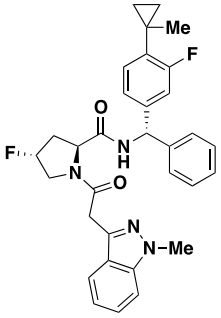

;

;

;

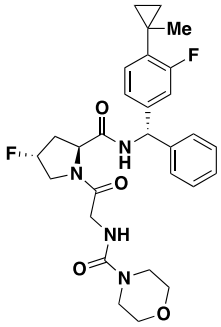
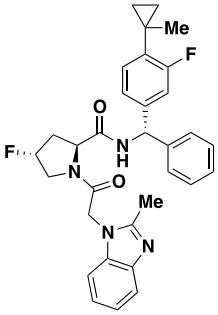
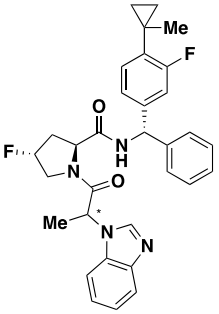
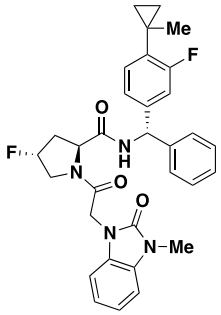
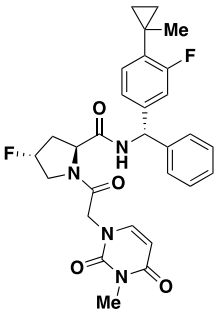
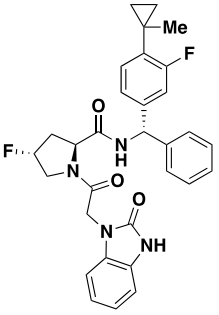
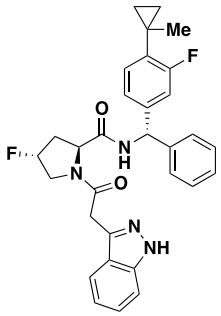
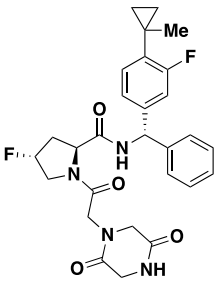
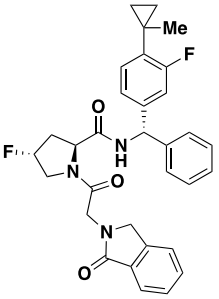
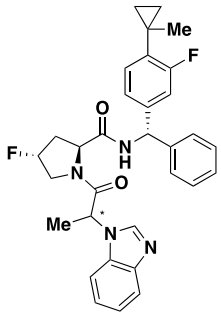
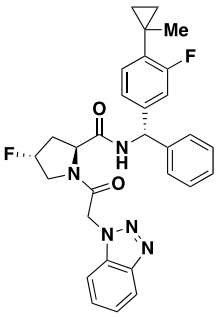
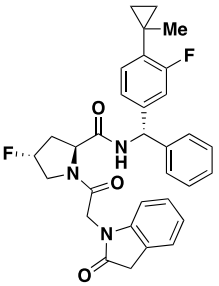
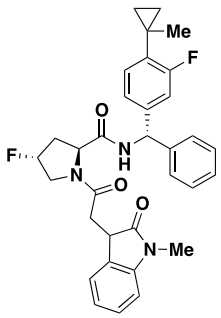
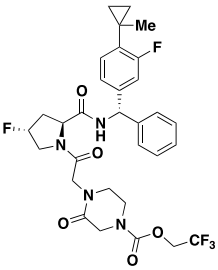
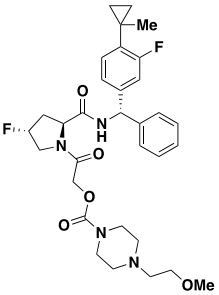

;

;

;

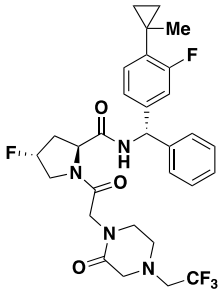
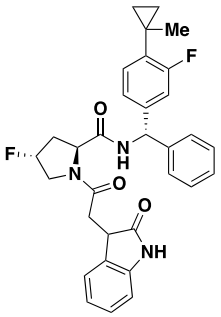
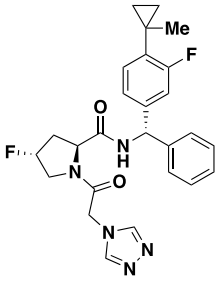
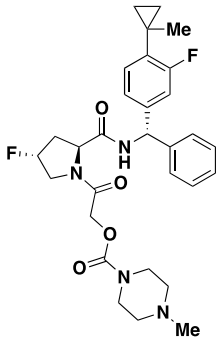
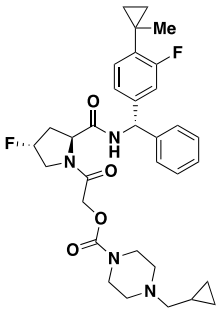
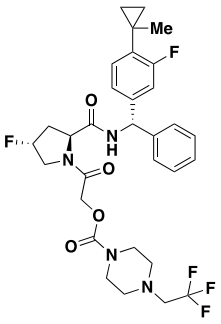
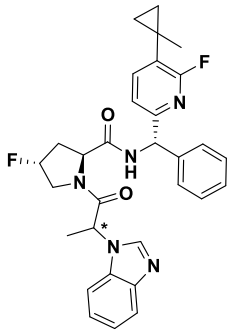
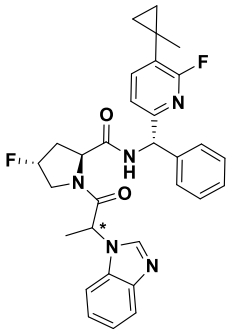
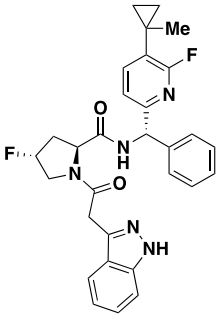
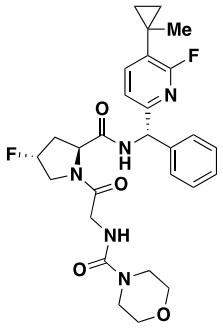
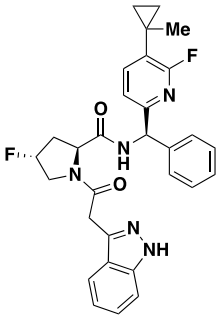
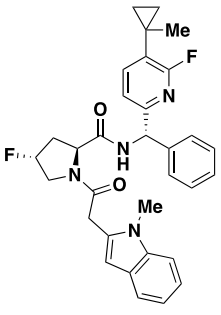
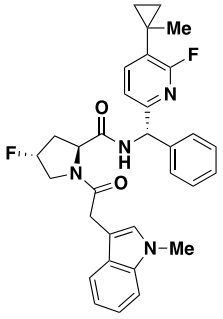
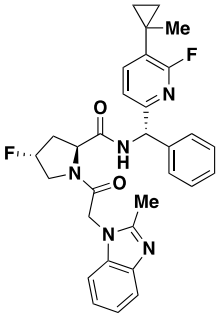
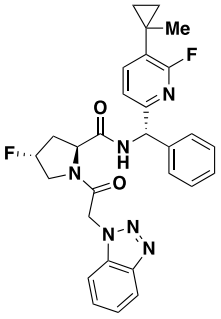

;

;

;

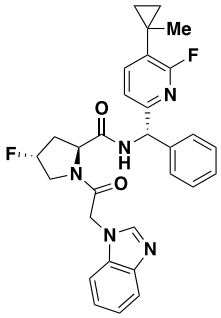
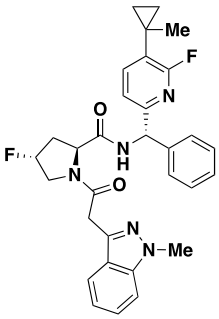
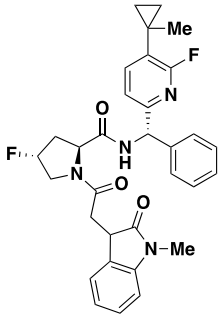
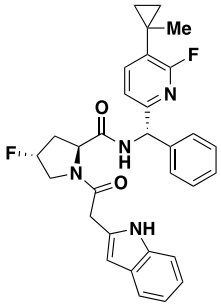
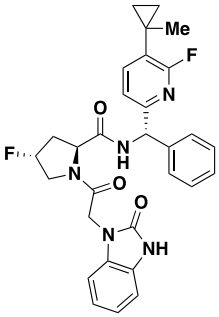
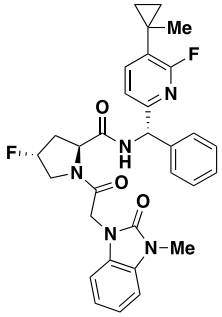
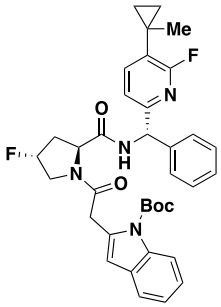
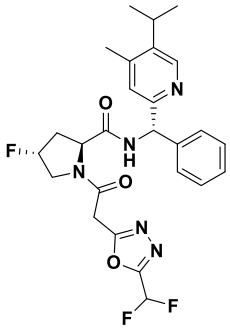
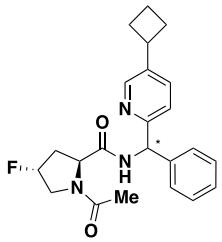
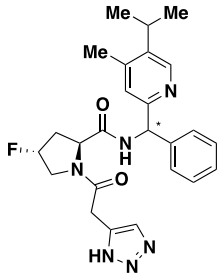
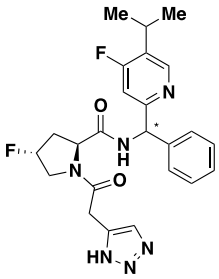
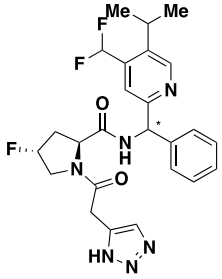
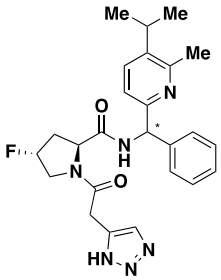
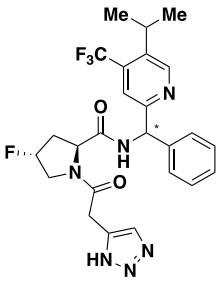
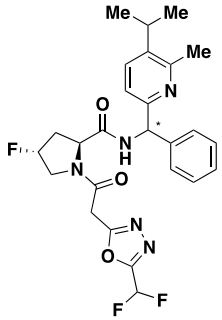

;

;

;

;

;

;

;

;

;

;

;

;

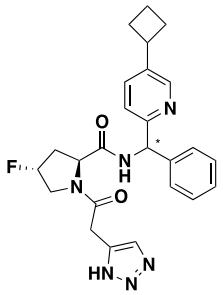
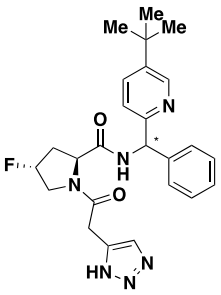
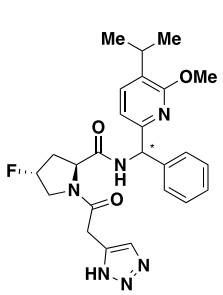
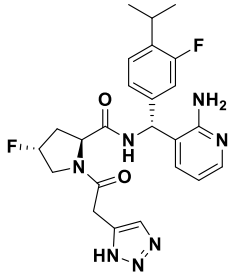
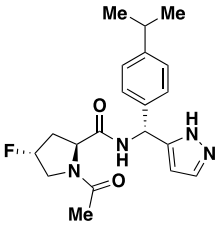
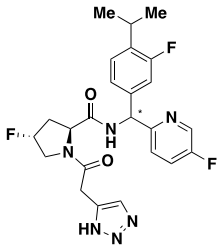
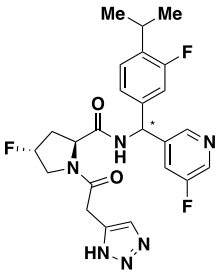
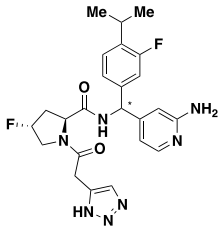
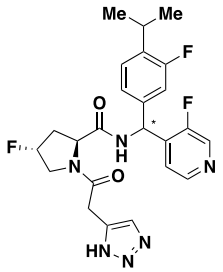
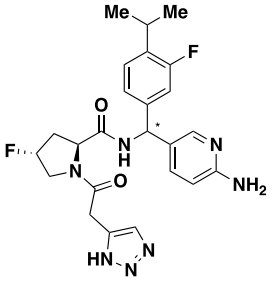
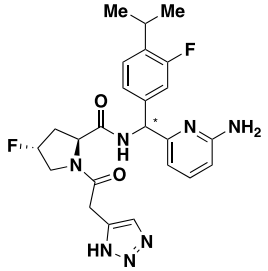
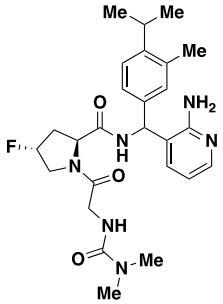
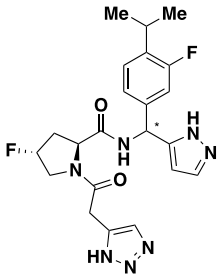
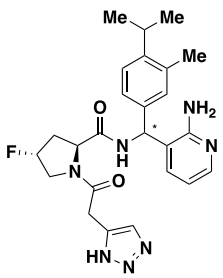
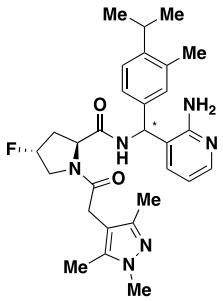
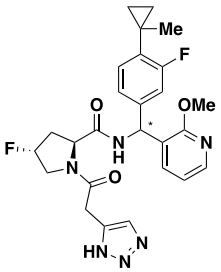
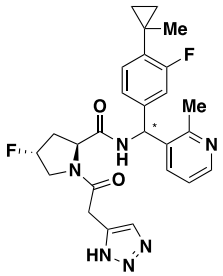

;

;

;

;

;

;

;

;

;

;

;

;

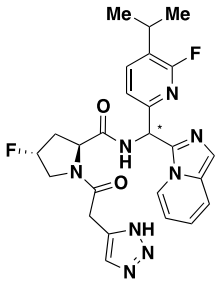
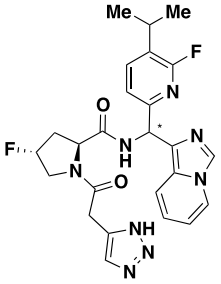
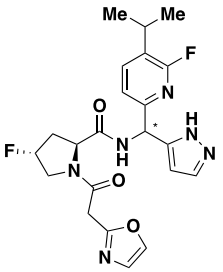
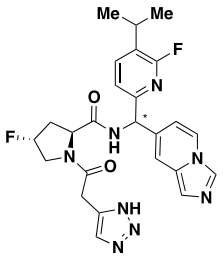
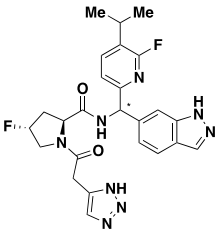
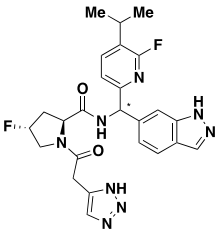
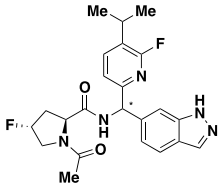
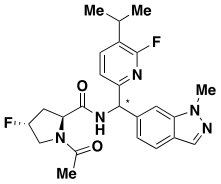
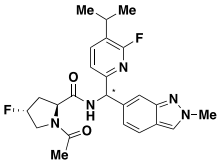
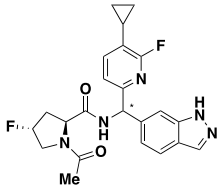
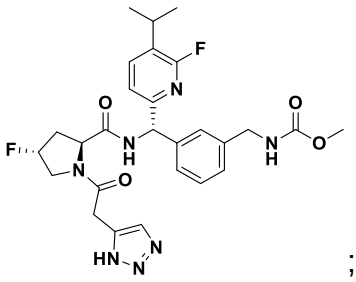
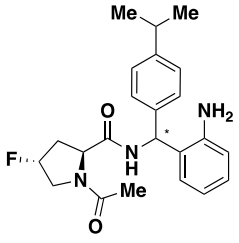
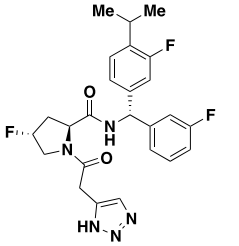

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

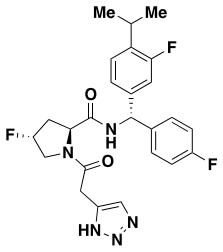
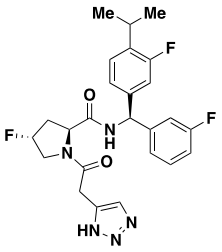

Me
F
F
O
N
H
N
O
NH
O
N
O
;

Me
F
F
O
N
H
N
O
Me
N
N
;

Me
F
F
O
N
H
N
O
Me
*
N
N
;

Me
F
F
O
N
H
N
O
O
N
N–Me
;

Me
F
F
O
N
H
N
O
N
O
O
N
Me
;

Me
F
F
O
N
H
N
O
O
N
NH
;

Me
F
F
O
N
H
N
O
N
NH
;

Me
F
F
O
N
H
N
O
N
O
O
NH
;

Me
F
F
O
N
H
N
O
N
O
;

Me
F
F
O
N
H
N
O
Me
*
N
N
;

Me
F
F
O
N
H
N
O
N
N
N
;

Me
F
F
O
N
H
N
O
N
O
;

Me
F
F
O
N
H
N
O
O
N–Me
;

Me
F
F
O
N
H
N
O
O
N
O
O
CF3
;

Me
F
F
O
N
H
N
O
O
O
N
N
OMe
;

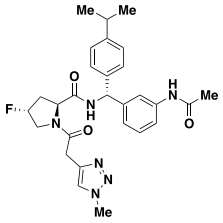
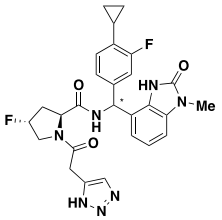
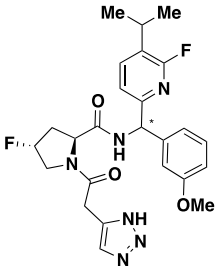

Me
F
F
O
N
H
N
O
O
N
O
N
CF3
;

Me
F
F
O
N
H
N
O
O
NH
;

Me
F
F
O
N
H
N
O
N
N
N
;

Me
F
F
O
N
H
N
O
O
O
N
N
Me
;

Me
F
F
O
N
H
N
O
O
O
N
;

Me
F
F
O
N
H
N
O
O
O
N
N
F
F
F
;

F
F
O
N
H
N
O
*
N
N
;

F
F
O
N
H
N
O
*
N
N
;

Me
F
F
O
N
H
N
O
N
NH
;

Me
F
F
O
N
H
N
O
NH
O
N
O
;

Me
F
F
O
N
H
N
O
N
NH
;

Me
F
F
O
N
H
N
O
Me
N
;

Me
F
F
O
N
H
N
O
N–Me
;

Me
F
F
O
N
H
N
O
Me
N
;

Me
F
F
O
N
H
N
O
N
N
N
;

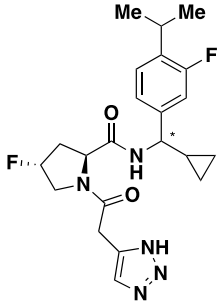
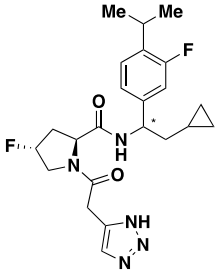
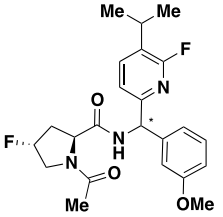

Me
F
N
O
N
H
F
N
O
N
N
;

Me
F
N
O
N
H
F
N
O
N
N
N–Me
;

Me
F
N
O
N
H
F
N
O
O
N–Me
;

Me
F
N
O
N
H
F
N
O
NH
;

Me
F
N
O
N
H
F
N
O
O
NH
;

Me
F
N
O
N
H
F
N
O
O
N–Me
;

Me
F
N
O
N
H
F
N
O
Boc
N
;

N
O
N
H
F
N
O
N
N
O
F
F
;

N
O
N
H
F
N
Me
O
;

Me
Me
Me
N
O
N
H
F
N
O
HN
N
N
;

Me
Me
F
N
O
N
H
F
N
O
HN
N
N
;

Me
Me
F
F
N
O
N
H
F
N
O
HN
N
N
;

Me
Me
Me
N
O
N
H
F
N
O
HN
N
N
;

Me
Me
F3C
N
O
N
H
F
N
O
HN
N
N
;

Me
Me
Me
N
O
N
H
F
N
O
N
O
F
F
;

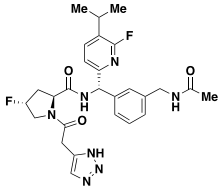
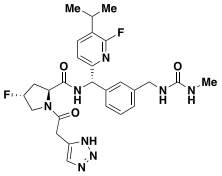
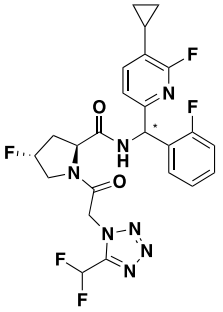

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

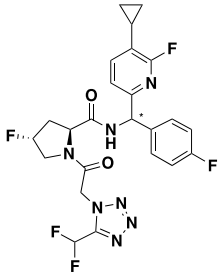
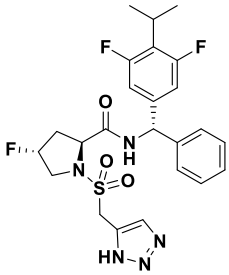
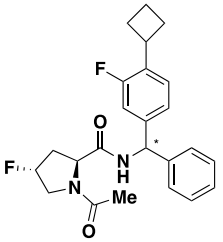

;

;

;

;

;

;

;

;

;

;

;

;

;

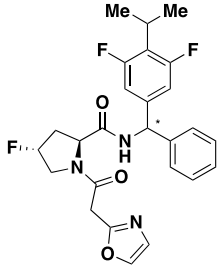
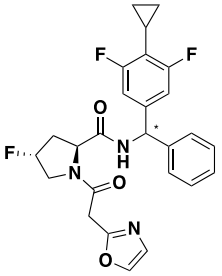
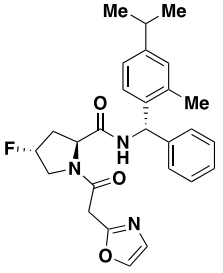

;

;

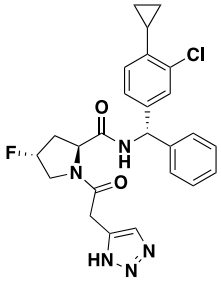
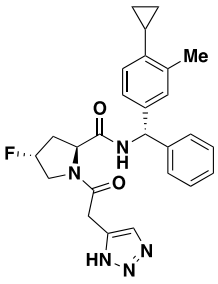
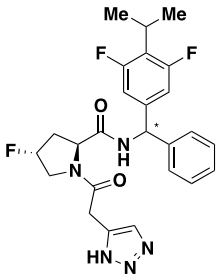
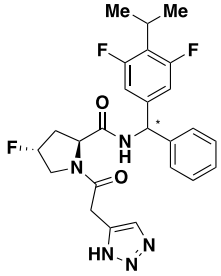
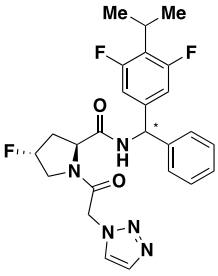
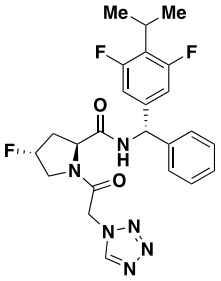
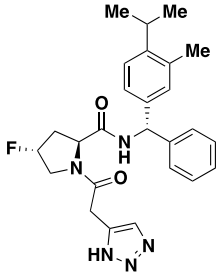
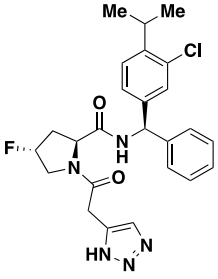
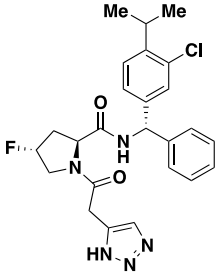
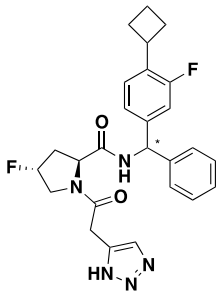
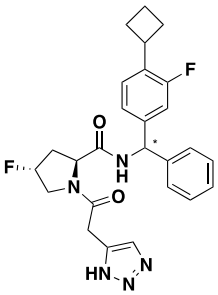
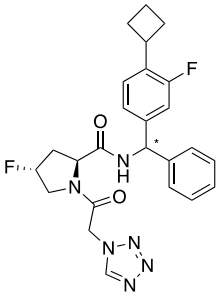
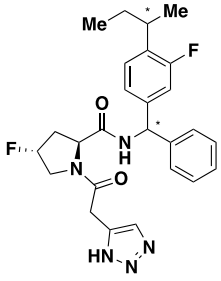
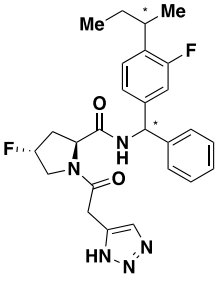
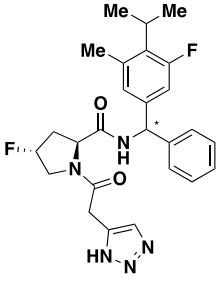
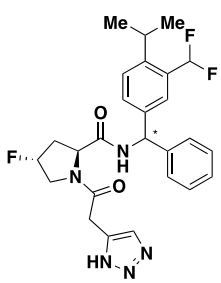
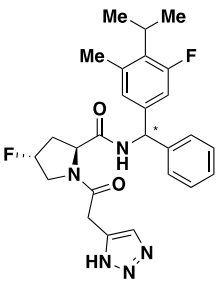
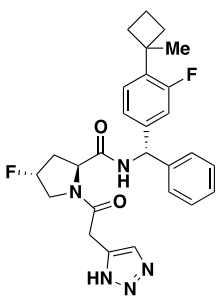

;

;

;

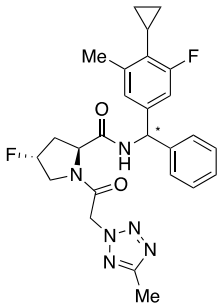
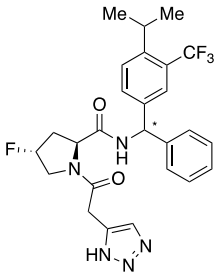
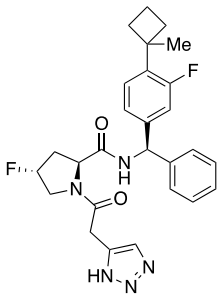
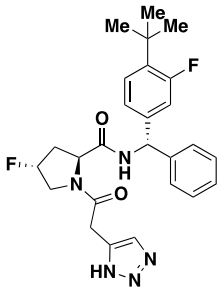
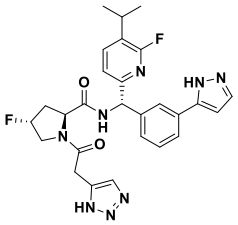
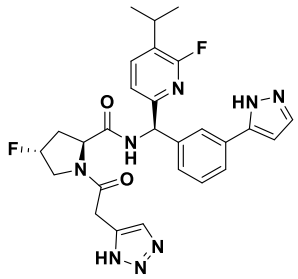
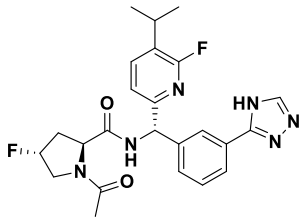
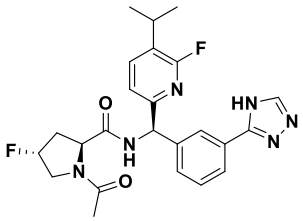
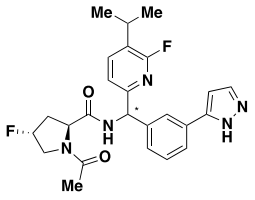
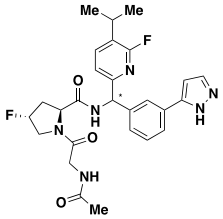
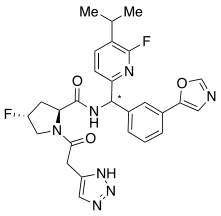
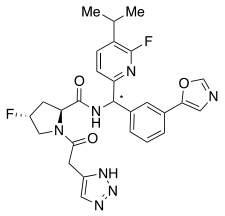
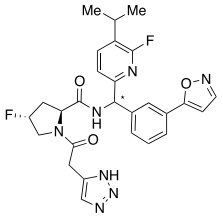
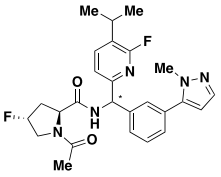
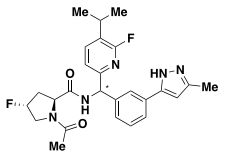
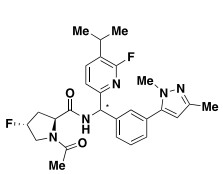
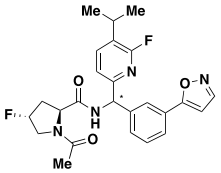

;

;

;

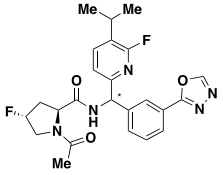
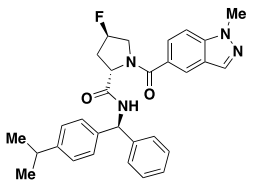

;

;

;

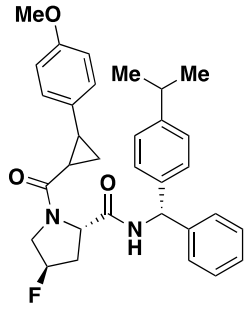
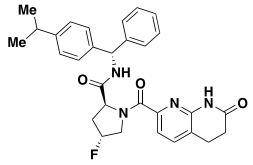
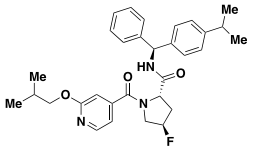
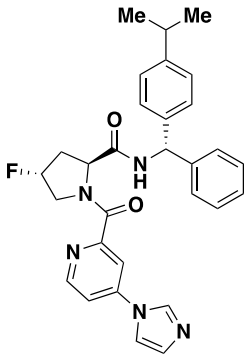
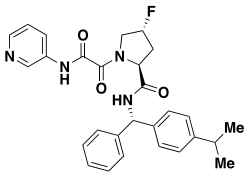
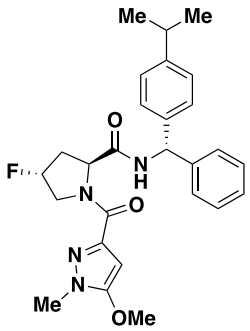
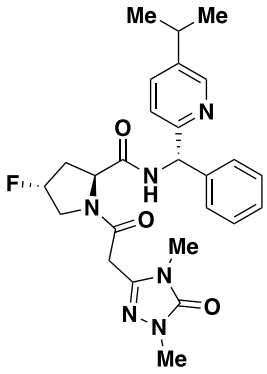
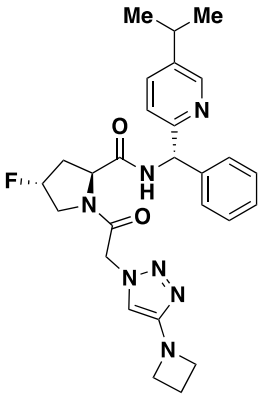
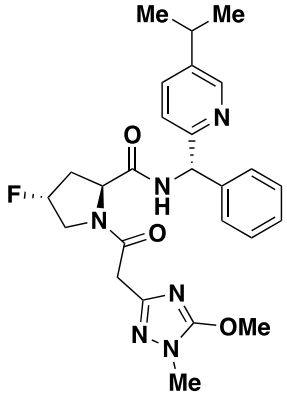
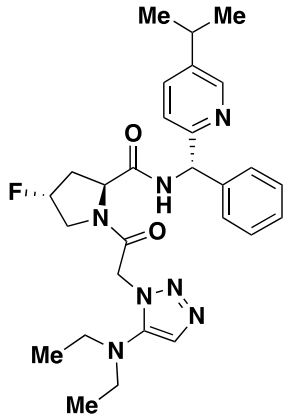
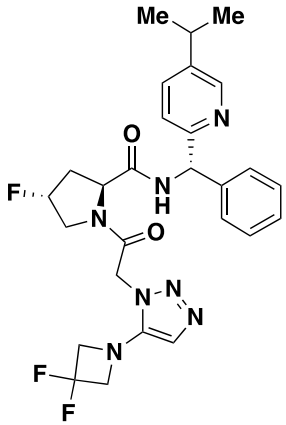
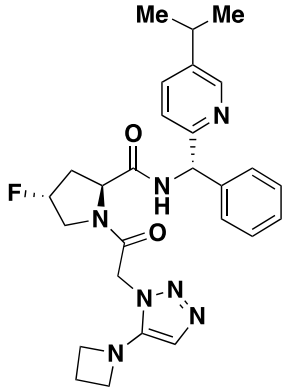

;

;

;

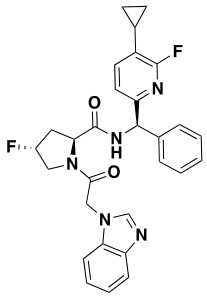
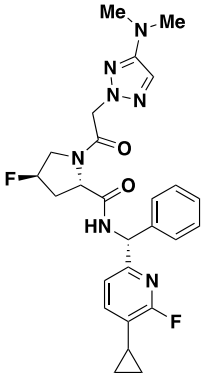
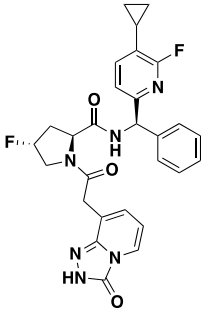
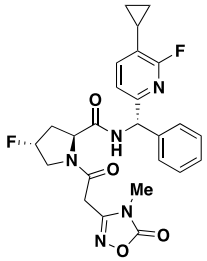
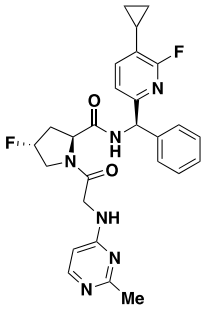
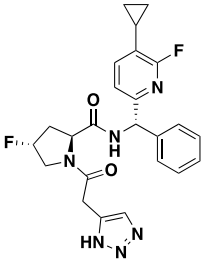
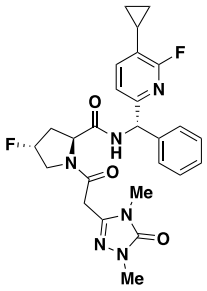
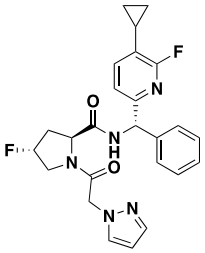
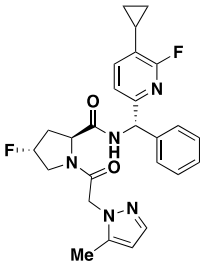
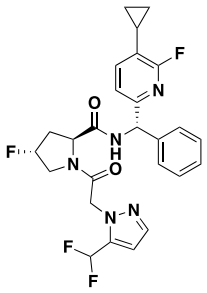
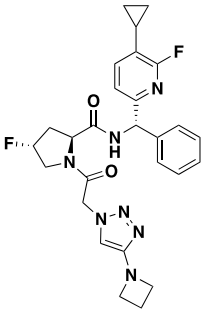
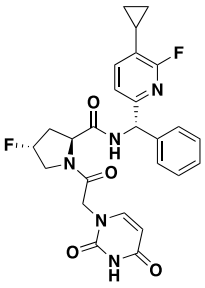
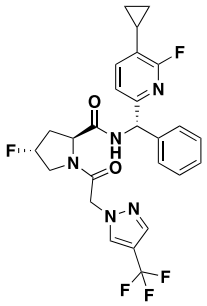
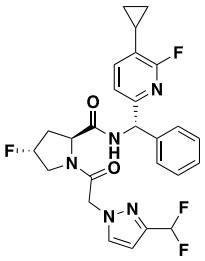
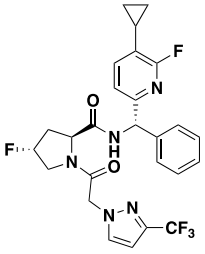

;

;

;

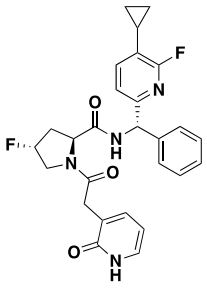
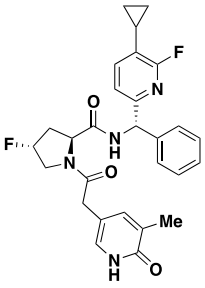
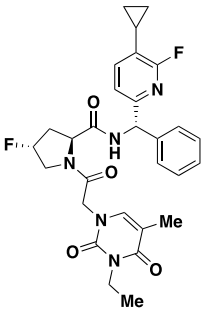

Cl
O
F
N
H
O
HN
N
N
;

Me
O
F
N
H
O
HN
N
N
;

Me
Me
F
F
O
F
N
H
O
HN
N
N
;

Me
Me
F
F
O
F
N
H
O
HN
N
N
;

Me
Me
F
F
O
F
N
H
O
N
N
N
;

Me
Me
F
F
O
F
N
H
O
N
N
N
;

Me
Me
Me
O
F
N
H
O
HN
N
N
;

Me
Me
Cl
O
F
N
H
O
HN
N
N
;

Me
Me
Cl
O
F
N
H
O
HN
N
N
;

F
O
F
N
H
O
HN
N
N
;

F
O
F
N
H
O
HN
N
N
;

F
O
F
N
H
O
N
N
N
;

Me
Me
F
O
F
N
H
O
HN
N
N
;

Me
Me
F
O
F
N
H
O
HN
N
N
;

Me
Me
Me
F
O
F
N
H
O
HN
N
N
;

Me
Me
F
F
O
F
N
H
O
HN
N
N
;

Me
Me
Me
F
O
F
N
H
O
HN
N
N
;

Me
F
O
F
N
H
O
HN
N
N
;

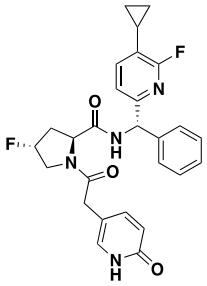
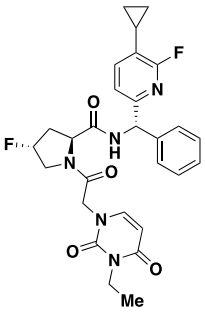
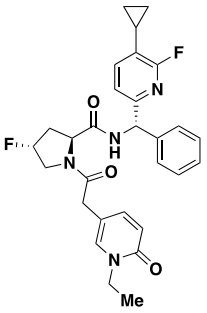

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

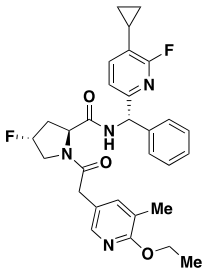
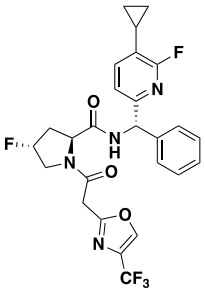
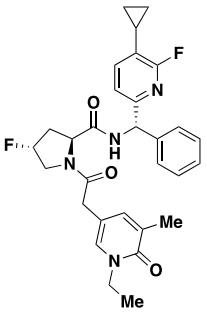
;

;

;

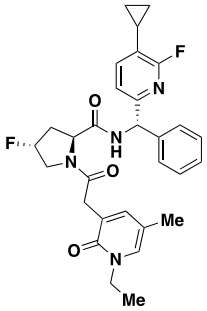
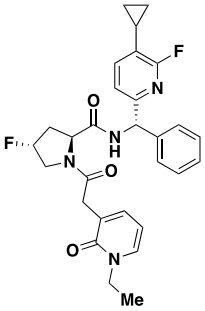
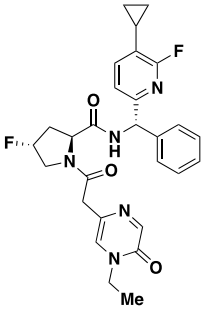

MeO
Me
Me
O
O
N
N
H
F
;

Me
Me
NH
O
O
N
N
H
O
F
;

Me
Me
HN
O
Me
O
O
N
N
F
;

Me
Me
O
F
N
H
N
O
N
N
N
;

F
N
O
N
H
O
N
O
HN
Me
Me
;

Me
Me
O
F
N
H
N
O
N
N
Me
OMe
;

Me
Me
N
O
F
N
H
N
O
Me
N
N
N
Me
;

Me
Me
N
O
F
N
H
N
O
N
N
N
N
;

Me
Me
N
O
F
N
H
N
O
N
N
OMe
N
Me
;

Me
Me
N
O
F
N
H
N
O
N
N
N
Me
N
Me
;

Me
Me
N
O
F
N
H
N
O
N
N
N
F
N
F
;

Me
Me
N
O
F
N
H
N
O
N
N
N
N
;

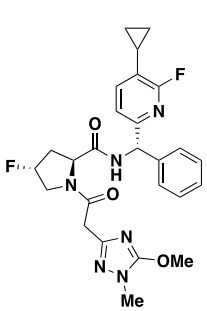
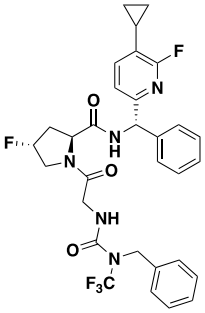
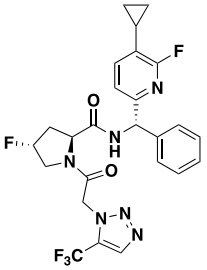

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

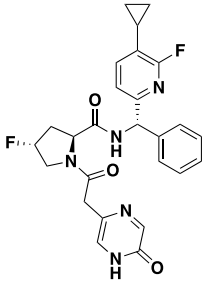
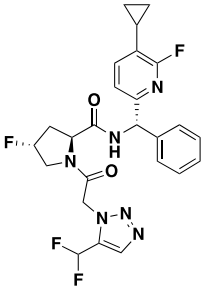
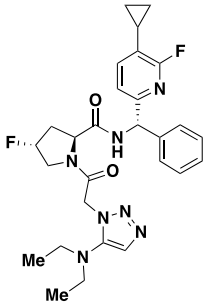
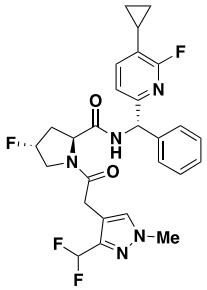
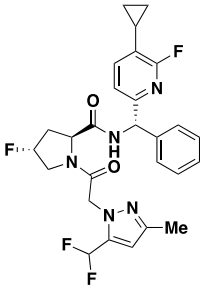
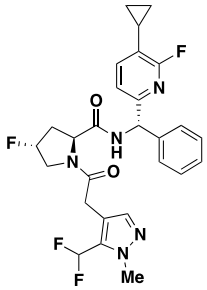
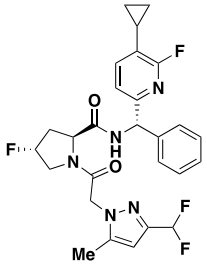
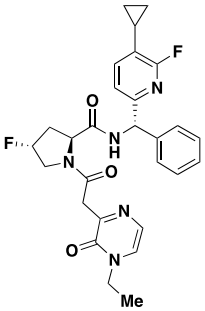
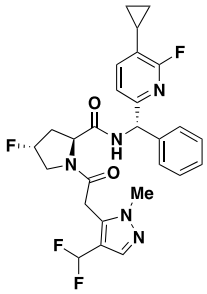
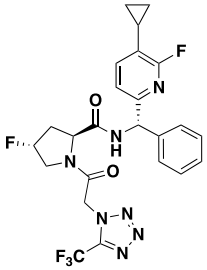
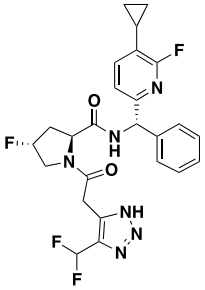
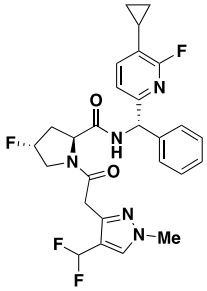
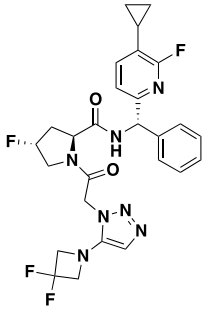
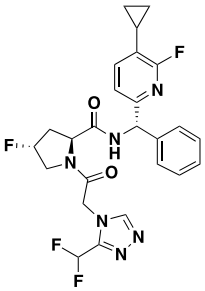
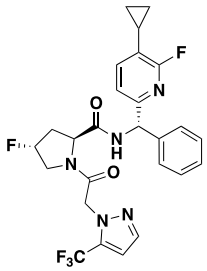

;

;

;

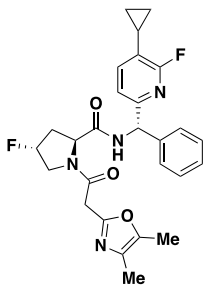
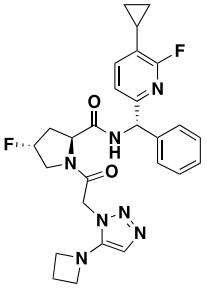
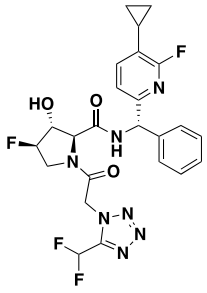
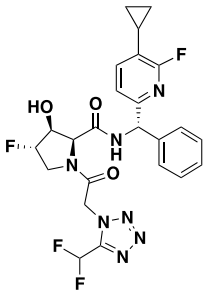
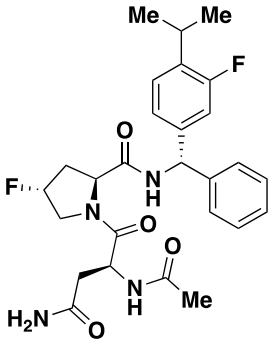
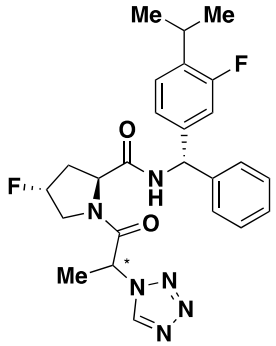
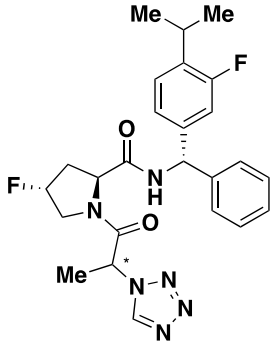
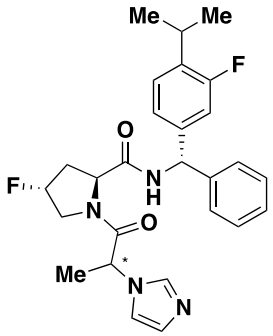
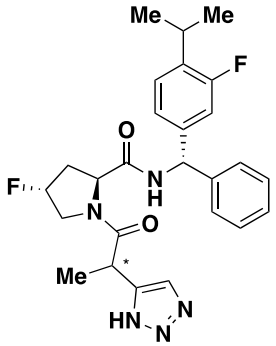
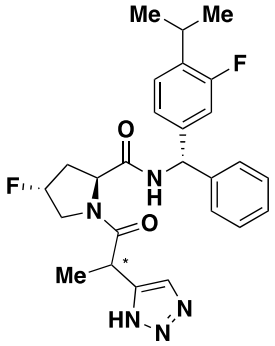
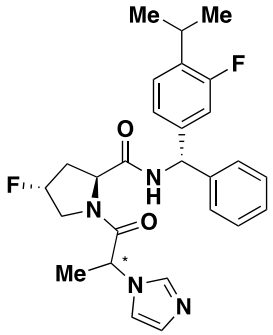
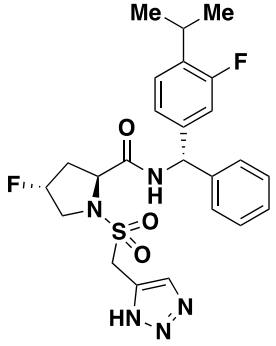
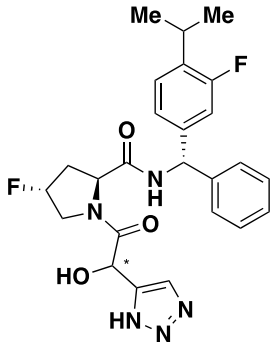
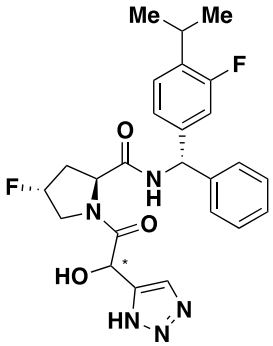
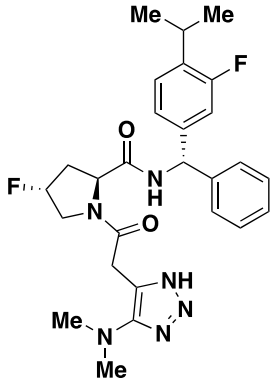

;

;

;

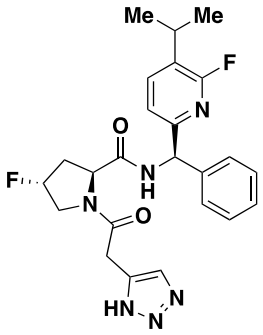
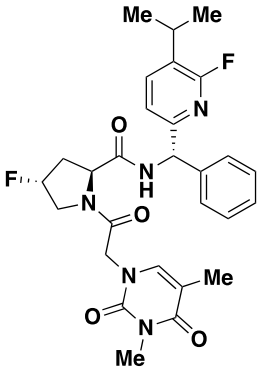
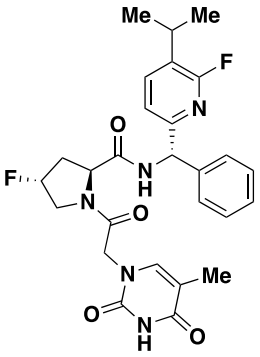
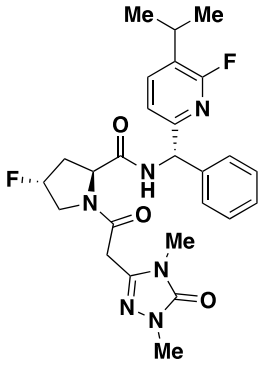
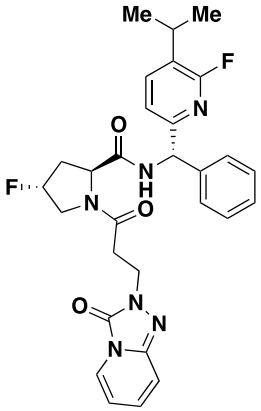
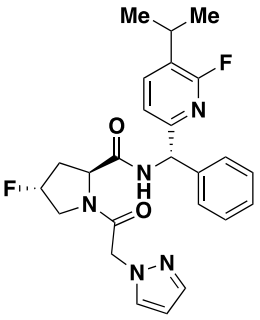
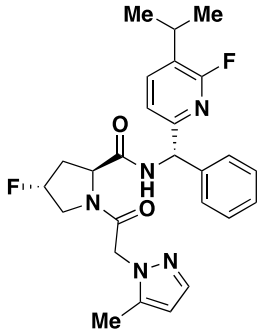
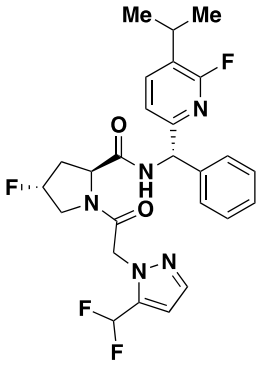
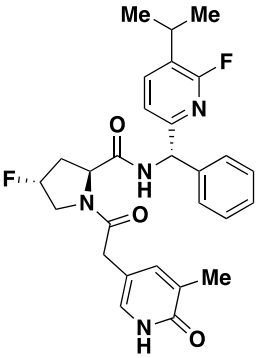
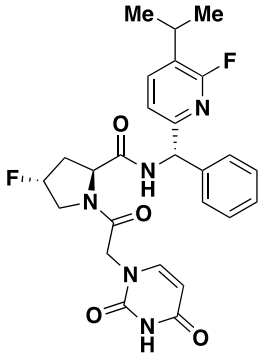
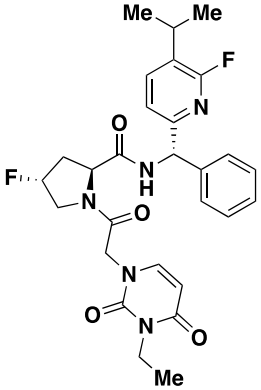
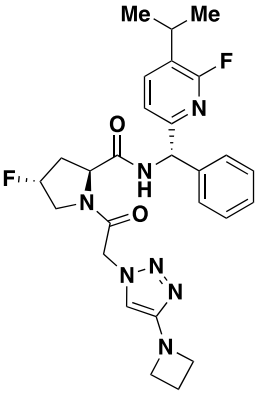

;

;

;

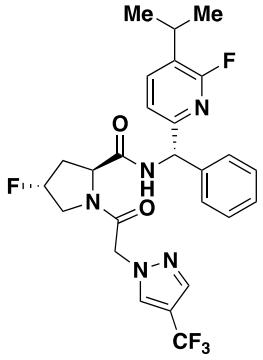
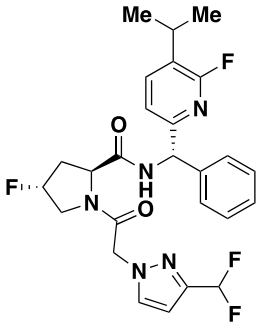
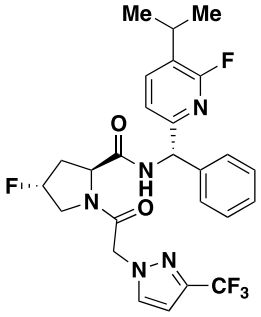
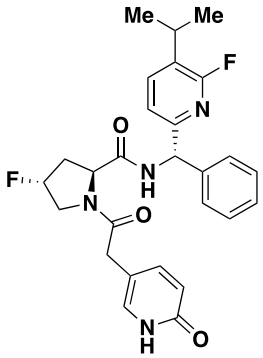
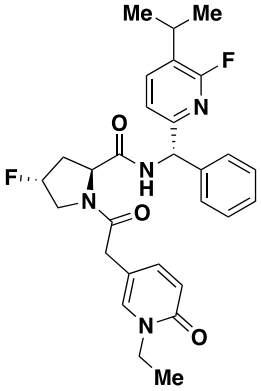
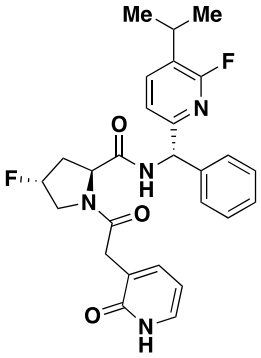
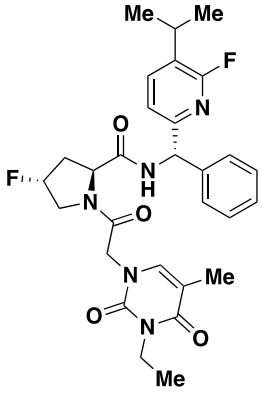
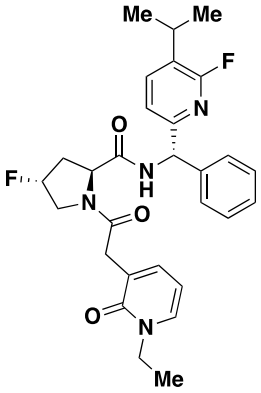
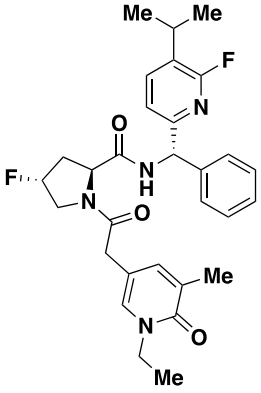
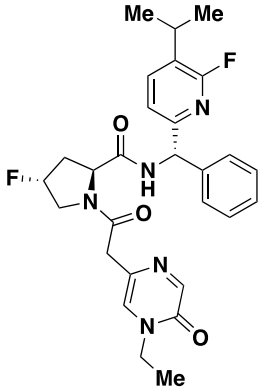
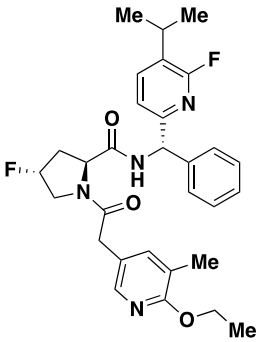
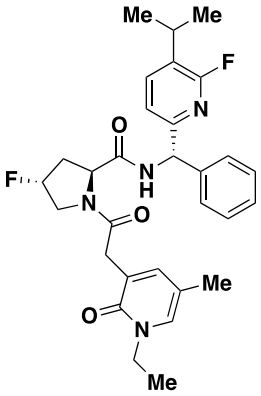

;

;

;

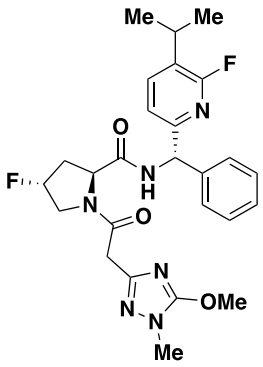
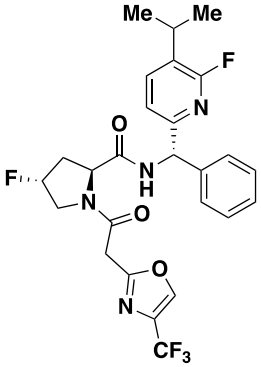
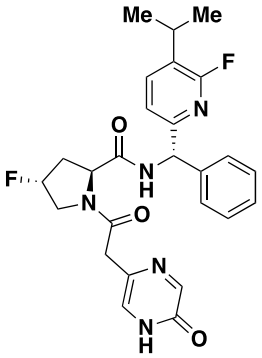
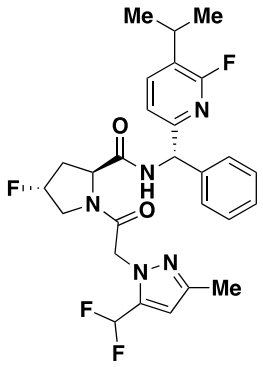
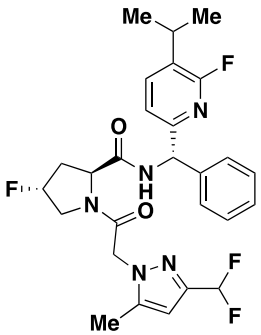
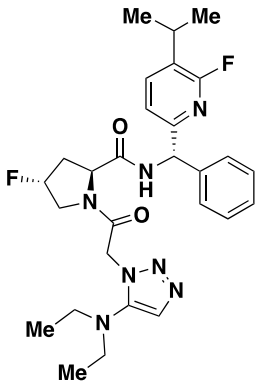
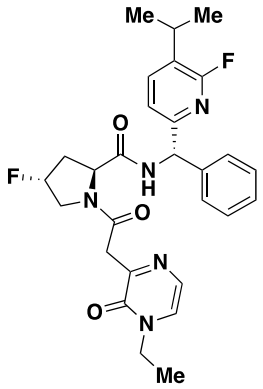
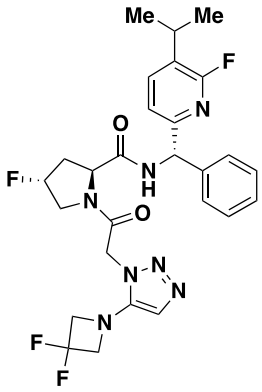
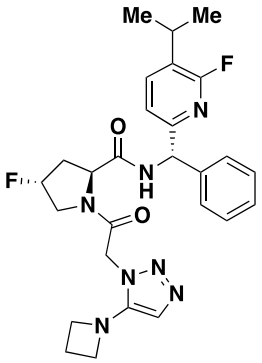
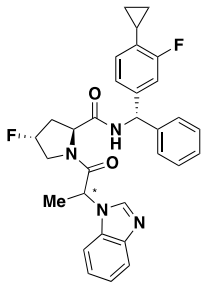
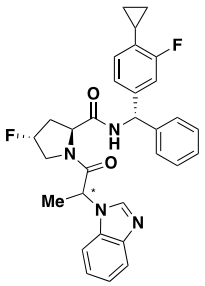

;

;

;


;

;

;

;

;

;

;

;

;

;

;

;

;

;

;


F
N
O
N
H
F
N
O
O
N
O
Me
Me
;

F
N
O
N
H
F
N
O
N
N
N
N
;

HO
F
N
O
N
H
F
N
O
N
N
N
F
F
;

F
N
HO
O
F
N
H
N
O
N
N
N
F
F
;

Me
Me
F
O
F
N
H
N
O
O
N
H
Me
H2N
O
;

Me
Me
F
O
F
N
H
N
O
Me
*
N
N
N
N
;

Me
Me
F
O
F
N
H
N
O
Me
*
N
N
N
N
;

Me
Me
F
O
F
N
H
N
O
Me
*
N
N
;

Me
Me
F
O
F
N
H
N
O
Me
*
HN
N
N
;

Me
Me
F
O
F
N
H
N
O
Me
*
HN
N
N
;

Me
Me
F
O
F
N
H
N
O
Me
*
N
N
;

Me
Me
F
O
F
N
H
N
O
S
O
O
HN
N
N
;

Me
Me
F
O
F
N
H
N
O
HO
*
HN
N
N
;

Me
Me
F
O
F
N
H
N
O
HO
*
HN
N
N
;

Me
Me
F
O
F
N
H
N
O
NH
N
N
Me
N
Me
;


;

;

;

;

;

;

;

;

;

;

;

;


Me
Me
F
N
O
N
H
F
N
O
N
N
CF3
;

Me
Me
F
N
O
N
H
F
N
O
N
N
F
F
;

Me
Me
F
N
O
N
H
F
N
O
N
N
CF3
;

Me
Me
F
N
O
N
H
F
N
O
N
H
O
;

Me
Me
F
N
O
N
H
F
N
O
N
O
Me
;

Me
Me
F
N
O
N
H
F
N
O
O
N
H
;

Me
Me
F
N
O
N
H
F
N
O
N
Me
O
N
O
Me
;

Me
Me
F
N
O
N
H
F
N
O
O
N
Me
;

Me
Me
F
N
O
N
H
F
N
O
Me
N
O
Me
;

Me
Me
F
N
O
N
H
F
N
O
N
N
O
Me
;

Me
Me
F
N
O
N
H
F
N
O
Me
N
O
Me
;

Me
Me
F
N
O
N
H
F
N
O
Me
O
N
Me
;


;

;

;

;

;

;

;

;

;

;

;

and a pharmaceutically acceptable salt of any of the foregoing.

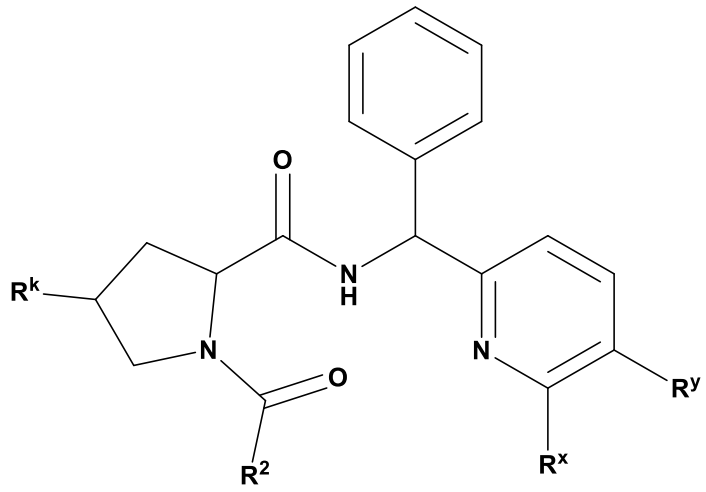
14. A pharmaceutical composition comprising (i) a compound of any one of claims 1-13, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and (ii) one or more pharmaceutically acceptable excipients.

15. Use of a compound of any one of claims 1-13, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or a pharmaceutical composition of claim 14, in the manufacture of a medicament for treating a GYS1-mediated disease, disorder, or condition in an individual in need thereof.

16. The use according to claim 15, wherein the disease, disorder, or condition is Pompe disease.

17. A kit, comprising (i) a compound of any one of claims 1-13, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or a pharmaceutical composition of claim 14, and (ii) instructions for use in treating an GYS1-mediated disease, disorder, or condition in an individual in need thereof.

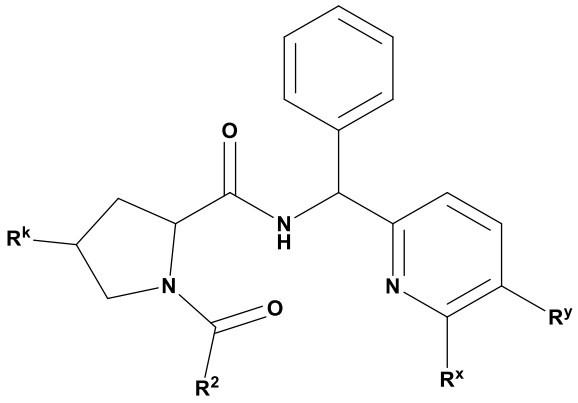
18. The compound of claim 1, wherein the compound is a compound of formula (I-A3):



(I-A3),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^x is H, halo, C_{1-6}alkyl, or -NH_2, wherein the C_{1-6}alkyl is optionally substituted with one or more halo.

19. The use according to claim 16, wherein the compound is a compound of formula (I-A3):



(I-A3),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^x is H, halo, C_{1-6}alkyl, or -NH_2, wherein the C_{1-6}alkyl is optionally substituted with one or more halo.

20. A compound of any one of claims 1-13, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or a pharmaceutical composition of claim 14, for use in therapy.