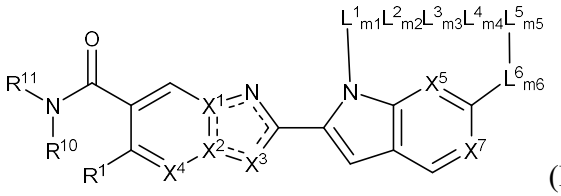
What is claimed is:

1. A compound of Formula (I):



(I)

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein:

X^1 and X^2 are C or N;

X^3 is N-R^3 or C-R^3; provided that two of X^1, X^2, and X^3 are C; where each dashed line represents an optional bond to complete valency requirements of each X^1, X^2 and X^3;

X^4 is N or C-R^2;

X^5 is N or CR^6;

X^7 is N or CR^7;

R^1 is hydrogen, halo, -CN, -OR^{12}, -N(R^{12})$_2$, -SR^{12}, -$C_{1\text{-}8}$ alkyl optionally substituted with 1 to 3 Z^1, $C_{3\text{-}6}$ cycloalkyl optionally substituted with 1 to 3 Z^1, or 4-6 membered heterocyclyl optionally substituted with 1 to 3 Z^1;

R^2 is hydrogen, halo, -CN, -OR^{12}, -N(R^{12})$_2$, -SR^{12}, -$C_{1\text{-}8}$ alkyl optionally substituted with 1 to 3 Z^2, $C_{3\text{-}6}$ cycloalkyl optionally substituted with 1 to 3 Z^2, or 4-6 membered heterocyclyl optionally substituted with 1 to 3 Z^2;

when X^3 is N-R^3, R^3 is hydrogen, $C_{1\text{-}8}$ alkyl optionally substituted with 1 to 3 Z^3, $C_{3\text{-}10}$ alkenyl optionally substituted with 1 to 3 Z^3, $C_{3\text{-}10}$ alkynyl optionally substituted with 1 to 3 Z^3, $C_{3\text{-}10}$ cycloalkyl optionally substituted with 1 to 3 Z^3, or 4-10 membered heterocyclyl optionally substituted with 1 to 3 Z^3; and

when X^3 is C-R^3; R^3 is hydrogen, halo, -CN, -OR^{12}, -N(R^{12})$_2$, -SR^{12}, $C_{1\text{-}8}$ alkyl optionally substituted with 1 to 3 Z^3, $C_{2\text{-}10}$ alkenyl optionally substituted with 1 to 3 Z^3, $C_{2\text{-}10}$ alkynyl optionally substituted with 1 to 3 Z^3, $C_{3\text{-}10}$ cycloalkyl optionally substituted with 1 to 3 Z^3, or 4-10 membered heterocyclyl optionally substituted with 1 to 3 Z^3; or

when R^2 is -C_{1-8} alkyl, -OR^{12}, or -$N(R^{12})_2$, and R^3 is C_{1-8} alkyl, then R^2 and R^3 may be taken together with the atoms to which they are attached to form an optionally substituted 6 to 8 membered ring;

R^6 is hydrogen, halo, -CN, -OR^{12}, -C_{1-8} alkyl optionally substituted with 1 to 3 Z^6, C_{3-6} cycloalkyl optionally substituted with 1 to 3 Z^6, or 4-6 membered heterocyclyl optionally substituted with 1 to 3 Z^6;

R^7 is hydrogen, halo, -CN, -OR^{12}, -C_{1-8} alkyl optionally substituted with 1 to 3 Z^7, C_{3-6} cycloalkyl optionally substituted with 1 to 3 Z^7, or 4-6 membered heterocyclyl optionally substituted with 1 to 3 Z^7;

L^1, L^2, L^3, L^4, L^5, and L^6 are each independently:

C_{1-10} alkylene, optionally substituted with 1 to 3 Z^8;

C_{2-10} alkenylene, optionally substituted with 1 to 3 Z^8;

C_{2-10} alkynylene, optionally substituted with 1 to 3 Z^8;

2-6 membered heteroalkylene, optionally substituted with 1 to 3 Z^8;

C_3-C_{10} cycloalkylene, optionally substituted with 1 to 3 Z^8;

4-10 membered heterocyclene, optionally substituted with 1 to 3 Z^8;

C_{6-10} arylene, optionally substituted with 1 to 3 Z^8;

5-10 membered heteroarylene, optionally substituted with 1 to 3 Z^8; or

-O-, -$N(R^8)$-, -S-, -C(O)-, -C(O)O-, -C(O)$N(R^8)$-, -SO-, -SO_2-, -$SO_2N(R^8)$-,-$N(R^8)$C(O)O-, -OC(O)O-, -$N(R^8)$C(O)$N(R^8)$-, -$N(R^8)S(O)_2N(R^8)$-, -$N(R^8)$C(N-CN)-, -S(O)(NR^8)-, or -S(O)$(NR^8)N(R^8)$-; and

m1, m2, m3, m4, m5, and m6 are each independently 0 or 1;

provided that $L^1{}_{m1}$, $L^2{}_{m2}$, $L^3{}_{m3}$, $L^4{}_{m4}$, $L^5{}_{m5}$, and $L^6{}_{m6}$ taken together with the four consecutive atoms between which they are attached form an optionally substituted 11 to 20 membered macrocyclic ring;

each R^8 and R^9 is independently hydrogen, C_{1-8} alkyl optionally substituted with 1 to 3 Z^{1b}, C_{2-8} alkenyl optionally substituted with 1 to 3 Z^{1b}, C_{2-8} alkynyl optionally substituted with 1 to 3 Z^{1b}, C_{3-10} cycloalkyl optionally substituted with 1 to 3 Z^{1b}, 4-10 membered heterocyclyl optionally substituted with 1 to 3 Z^{1b}, C_{6-10} aryl optionally substituted with 1 to 3 Z^{1b}, or 5-10 membered heteroaryl optionally substituted with 1 to 3 Z^{1b};

R^{10} is hydrogen, -C_{1-8} alkyl optionally substituted with 1 to 3 Z^{10}, or C_{3-6} cycloalkyl optionally substituted with 1 to 3 Z^{10};

R^{11} is hydrogen, -C_{1-8} alkyl optionally substituted with 1 to 4 Z^{11}, -C_{3-8} cycloalkyl optionally substituted with 1 to 4 Z^{11}, or 4-12-membered heterocyclyl optionally substituted with 1 to 4 Z^{11}; or

R^{10} and R^{11} are taken together with nitrogen to which they are attached to form a 4-12-membered heterocyclyl optionally substituted with 1 to 4 Z^{11};

each R^{12} and R^{13} are independently hydrogen, C_{1-8} alkyl optionally substituted with 1 to 3 Z^{1b}, C_{2-8} alkenyl optionally substituted with 1 to 3 Z^{1b}, C_{2-8} alkynyl optionally substituted with 1 to 3 Z^{1b}, C_{3-10} cycloalkyl optionally substituted with 1 to 3 Z^{1b}, 4-10 membered heterocyclyl optionally substituted with 1 to 3 Z^{1b}, C_{6-10} aryl optionally substituted with 1 to 3 Z^{1b}, or 5-10 membered heteroaryl optionally substituted with 1 to 3 Z^{1b};

each Z^1, Z^2, Z^3, Z^6, Z^7, and Z^8 is independently oxo, halo, -NO_2, -N_3, -CN, C_{1-8} alkyl optionally substituted by 1 to 3 Z^{1a}, C_{2-8} alkenyl optionally substituted by 1 to 3 Z^{1a}, C_{2-8} alkynyl optionally substituted by 1 to 3 Z^{1a}, C_{3-8} cycloalkyl optionally substituted by 1 to 3 Z^{1a}, 6-10 membered aryl optionally substituted by 1 to 3 Z^{1a}, 4-10 membered heterocyclyl optionally substituted by 1 to 3 Z^{1a}, 5-10 membered heteroaryl optionally substituted with 1 to 3 Z^{1a}, -OR^9, -$C(O)R^9$, -$C(O)OR^9$, -$C(O)N(R^9)_2$, -$N(R^9)_2$, -$N(R^9)_3^+$, -$N(R^9)C(O)R^9$, -$N(R^9)C(O)OR^9$, -$N(R^9)C(O)N(R^9)_2$, -$N(R^9)S(O)_2(R^9)$, -$NR^9S(O)_2N(R^9)_2$, -$NR^9S(O)_2O(R^9)$, -$NS(O)(R^9)_2$, -$OC(O)R^9$, -$OC(O)OR^9$, -$OC(O)N(R^9)_2$, -$Si(R^9)_3$, -SR^9, -$S(O)R^9$, -SF_5, -$S(O)(NR^9)R^9$, -$S(NR^9)(NR^9)R^9$, -$S(O)(NR^9)N(R^9)_2$, -$S(O)(NCN)R^9$, -$S(O)_2R^9$, -$S(O)_2N(R^9)_2$, -$C(O)N(R^9)S(O)_2R^9$, or -$S(O)_2N(R^9)C(O)R^9$, wherein each Z^2, Z^3, Z^6, Z^7, and Z^8 is independently optionally substituted with 1 to 3 Z^{1a};

each Z^{1a} is independently oxo, halo, -NO_2, -N_3, -CN, C_{1-8} alkyl optionally substituted by 1 to 3 Z^{1b}, C_{2-8} alkenyl optionally substituted by 1 to 3 Z^{1b}, C_{2-8} alkynyl optionally substituted by 1 to 3 Z^{1b}, C_{3-8} cycloalkyl optionally substituted by 1 to 3 Z^{1b}, 6-10 membered aryl optionally substituted by 1 to 3 Z^{1b}, 4-10 membered heterocyclyl optionally substituted by 1 to 3 Z^{1b}, 5-10 membered heteroaryl optionally substituted with 1 to 3 Z^{1b}, -OR^{13}, -$C(O)R^{13}$, -$C(O)OR^{13}$, -$C(O)N(R^{13})_2$, -$N(R^{13})_2$, -$N(R^{13})_3^+$, -$N(R^{13})C(O)R^{13}$, -$N(R^{13})C(O)OR^{13}$, -$N(R^{13})C(O)N(R^{13})_2$, -$N(R^{13})S(O)_2(R^{13})$, -$NR^{13}S(O)_2N(R^{13})_2$, -$NR^{13}S(O)_2O(R^{13})$, -$NS(O)(R^{13})_2$, -$OC(O)R^{13}$, -$OC(O)OR^{13}$, -$OC(O)N(R^{13})_2$, -$Si(R^{13})_3$, -SR^{13}, -$S(O)R^{13}$, -SF_5, -$S(O)(NR^{13})R^{13}$, -$S(NR^{13})(NR^{13})R^{13}$, -$S(O)(NR^{13})N(R^{13})_2$, -$S(O)(NCN)R^{13}$, -$S(O)_2R^{13}$, -$S(O)_2N(R^{13})_2$, -$C(O)N(R^{13})S(O)_2R^{13}$, or -$S(O)_2N(R^{13})C(O)R^{13}$;

each Z^{10} and Z^{11} is independently selected from oxo, halo, -CN, C_{1-8} alkyl optionally substituted by 1 to 3 Z^{1b}, C_{3-8} cycloalkyl optionally substituted by 1 to 3 Z^{1b}, aryl optionally substituted by 1 to 3 Z^{1b}, 4-10 membered heterocyclyl optionally substituted by 1 to 3 Z^{1b}, 5-10 membered heteroaryl optionally substituted with 1 to 3 Z^{1b}, $-OR^{13}$, $-C(O)R^{13}$, $-C(O)OR^{13}$, $-C(O)N(R^{13})_2$, $-N(R^{13})_2$, $-N(R^{13})_3^+$, $-N(R^{13})C(O)R^{13}$, $-N(R^{13})C(O)OR^{13}$, $-N(R^{13})C(O)N(R^{13})_2$, $-OC(O)R^{13}$, $-OC(O)OR^{13}$, $-OC(O)-N(R^{13})_2$, and $-S-R^{13}$; and

each Z^{1b} is independently oxo, hydroxy, halo, $-NO_2$, $-N_3$, -CN, C_{1-9} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-15} cycloalkyl, C_{1-8} haloalkyl, aryl, heteroaryl, heterocyclyl, $-O(C_{1-9}$ alkyl), $-O(C_{2-6}$ alkenyl), $-O(C_{2-6}$ alkynyl), $-O(C_{3-15}$ cycloalkyl), $-O(C_{1-8}$ haloalkyl), -O(aryl), -O(heteroaryl), -O(heterocyclyl), -OC(O) (C_{1-9} alkyl), $-OC(O)(C_{2-6}$ alkenyl), $-OC(O)(C_{2-6}$ alkenyl), $-OC(O)(C_{2-6}$ alkynyl), $-OC(O)(C_{3-15}$ cycloalkyl), $-OC(O)(C_{1-8}$ haloalkyl), -OC(O)(aryl), -OC(O)(heteroaryl), -OC(O)(heterocyclyl), $-NH_2$, $-NH(C_{1-9}$ alkyl), $-NH(C_{2-6}$ alkenyl), $-NH(C_{2-6}$ alkynyl), $-NH(C_{3-15}$ cycloalkyl), $-NH(C_{1-8}$ haloalkyl), -NH(aryl), -NH(heteroaryl), -NH(heterocyclyl), $-N(C_{1-9}$ alkyl)$_2$, $-N(C_{3-15}$ cycloalkyl)$_2$, $-N(C_{2-6}$ alkenyl)$_2$, $-N(C_{2-6}$ alkynyl)$_2$, $-N(C_{3-15}$ cycloalkyl)$_2$, $-N(C_{1-8}$ haloalkyl)$_2$, $-N(aryl)_2$, $-N(heteroaryl)_2$, $-N(heterocyclyl)_2$, $-N(C_{1-9}$ alkyl)(C_{3-15} cycloalkyl), $-N(C_{1-9}$ alkyl)(C_{2-6} alkenyl), $-N(C_{1-9}$ alkyl)(C_{2-6} alkynyl), $-N(C_{1-9}$ alkyl)(C_{1-8} haloalkyl), $-N(C_{1-9}$ alkyl)(aryl), $-N(C_{1-9}$ alkyl)(heteroaryl), $-N(C_{1-9}$ alkyl)(heterocyclyl), $-C(O)(C_{1-9}$ alkyl), $-C(O)(C_{2-6}$ alkenyl), $-C(O)(C_{2-6}$ alkynyl), $-C(O)(C_{3-15}$ cycloalkyl), $-C(O)(C_{1-8}$ haloalkyl), -C(O)(aryl), -C(O)(heteroaryl), -C(O)(heterocyclyl), $-C(O)O(C_{1-9}$ alkyl), $-C(O)O(C_{2-6}$ alkenyl), $-C(O)O(C_{2-6}$ alkynyl), $-C(O)O(C_{3-15}$ cycloalkyl), $-C(O)O(C_{1-8}$ haloalkyl), -C(O)O(aryl), -C(O)O(heteroaryl), -C(O)O(heterocyclyl), $-C(O)NH_2$, $-C(O)NH(C_{1-9}$ alkyl), $-C(O)NH(C_{2-6}$ alkenyl), $-C(O)NH(C_{2-6}$ alkynyl), $-C(O)NH(C_{3-15}$ cycloalkyl), $-C(O)NH(C_{1-8}$ haloalkyl), -C(O)NH(aryl), -C(O)NH(heteroaryl), -C(O)NH(heterocyclyl), $-C(O)N(C_{1-9}$ alkyl)$_2$, $-C(O)N(C_{3-15}$ cycloalkyl)$_2$, $-C(O)N(C_{2-6}$ alkenyl)$_2$, $-C(O)N(C_{2-6}$ alkynyl)$_2$, $-C(O)N(C_{1-8}$ haloalkyl)$_2$, $-C(O)N(aryl)_2$, $-C(O)N(heteroaryl)_2$, $-C(O)N(heterocyclyl)_2$, $-NHC(O)(C_{1-9}$ alkyl), $-NHC(O)(C_{2-6}$ alkenyl), $-NHC(O)(C_{2-6}$ alkynyl), $-NHC(O)(C_{3-15}$ cycloalkyl), $-NHC(O)(C_{1-8}$ haloalkyl), -NHC(O)(aryl), -NHC(O)(heteroaryl), -NHC(O)(heterocyclyl), $-NHC(O)O(C_{1-9}$ alkyl), $-NHC(O)O(C_{2-6}$ alkenyl), $-NHC(O)O(C_{2-6}$ alkynyl), $-NHC(O)O(C_{3-15}$ cycloalkyl), $-NHC(O)O(C_{1-8}$ haloalkyl), -NHC(O)O(aryl), -NHC(O)O(heteroaryl), -NHC(O)O(heterocyclyl), $-NHC(O)NH(C_{1-9}$ alkyl), $-NHC(O)NH(C_{2-6}$ alkenyl), $-NHC(O)NH(C_{2-6}$ alkynyl), $-NHC(O)NH(C_{3-15}$ cycloalkyl), $-NHC(O)NH(C_{1-8}$ haloalkyl), -NHC(O)NH(aryl), -NHC(O)NH(heteroaryl), -NHC(O)NH(heterocyclyl), -SH, $-S(C_{1-9}$ alkyl), $-S(C_{2-6}$ alkenyl), $-S(C_{2-6}$ alkynyl), $-S(C_{3-15}$ cycloalkyl), $-S(C_{1-8}$ haloalkyl), -S(aryl), -S(heteroaryl), -S(heterocyclyl), $-NHS(O)(C_{1-9}$ alkyl), -

$N(C_{1-9}$ alkyl)($S(O)(C_{1-9}$ alkyl), $-S(O)N(C_{1-9}$ alkyl)$_2$, $-S(O)(C_{1-9}$ alkyl), $-S(O)(NH)(C_{1-9}$ alkyl), $-S(O)(C_{2-6}$ alkenyl), $-S(O)(C_{2-6}$ alkynyl), $-S(O)(C_{3-15}$ cycloalkyl), $-S(O)(C_{1-8}$ haloalkyl), -S(O)(aryl), -S(O)(heteroaryl), -S(O)(heterocyclyl), $-S(O)_2(C_{1-9}$ alkyl), $-S(O)_2(C_{2-6}$ alkenyl), $-S(O)_2(C_{2-6}$ alkynyl), $-S(O)_2(C_{3-15}$ cycloalkyl), $-S(O)_2(C_{1-8}$ haloalkyl), $-S(O)_2$(aryl), $-S(O)_2$(heteroaryl), $-S(O)_2$(heterocyclyl), $-S(O)_2NH(C_{1-9}$ alkyl), or $-S(O)_2N(C_{1-9}$ alkyl)$_2$;

wherein any alkyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl of Z^{1b} is optionally substituted with one or more halo, C_{1-9} alkyl, C_{1-8} haloalkyl, -OH, $-NH_2$, $-NH(C_{1-9}$ alkyl), $-NH(C_{3-15}$ cycloalkyl), $-NH(C_{1-8}$ haloalkyl), -NH(aryl), -NH(heteroaryl), -NH(heterocyclyl), $-N(C_{1-9}$ alkyl)$_2$, $-N(C_{3-15}$ cycloalkyl)$_2$, $-NHC(O)(C_{3-15}$ cycloalkyl), $-NHC(O)(C_{1-8}$ haloalkyl), -NHC(O)(aryl), -NHC(O)(heteroaryl), -NHC(O)(heterocyclyl), $-NHC(O)O(C_{1-9}$ alkyl), $-NHC(O)O(C_{2-6}$ alkynyl), $-NHC(O)O(C_{3-15}$ cycloalkyl), $-NHC(O)O(C_{1-8}$ haloalkyl), -NHC(O)O(aryl), -NHC(O)O(heteroaryl), -NHC(O)O(heterocyclyl), $-NHC(O)NH(C_{1-9}$ alkyl), $-S(O)(NH)(C_{1-9}$ alkyl), $-S(O)_2(C_{1-9}$ alkyl), $-S(O)_2(C_{3-15}$ cycloalkyl), $-S(O)_2(C_{1-8}$ haloalkyl), $-S(O)_2$(aryl), $-S(O)_2$(heteroaryl), $-S(O)_2$(heterocyclyl), $-S(O)_2NH(C_{1-9}$ alkyl), $-S(O)_2N(C_{1-9}$ alkyl)$_2$, $-O(C_{3-15}$ cycloalkyl), $-O(C_{1-8}$ haloalkyl), -O(aryl), -O(heteroaryl), -O(heterocyclyl), or $-O(C_{1-9}$ alkyl).

2. The compound of claim 1, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein

R^1 is hydrogen, fluoro, chloro, -CN, $-OR^{12}$, $-C_{1-6}$ alkyl, or C_{3-5} cycloalkyl;

X^1 and X^2 are each C;

X^3 is N-R^3, and R^3 is hydrogen, C_{1-6} alkyl optionally substituted with 1 to 3 Z^3, C_{3-6} alkenyl optionally substituted with 1 to 3 Z^3, C_{3-6} alkynyl optionally substituted with 1 to 3 Z^3, C_{3-6} cycloalkyl optionally substituted with 1 to 3 Z^3, or 4-6 membered heterocyclyl optionally substituted with 1 to 3 Z^3;

X^4 is C-R^2, wherein R^2 is hydrogen, -F, -Cl, $-CH_3$, $-CF_3$, $-CHF_2$, cyclopropyl, $-OCH_3$, -O-ethyl, -O-propyl, -O-isopropyl, -O-cyclopropyl, $-OCF_3$, or $-OCHF_2$; and

X^5 is N.

~~3. The compound of claim 1 or 2, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein R^1 is hydrogen, fluoro, chloro, $-CH_3$, or $-OCH_3$.~~

4. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein R^1 is hydrogen.

5. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein R^1 is fluoro.

6. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein R^2 is hydrogen, fluoro, chloro, $-OR^{12}$, $-N(R^{12})_2$, $-C_{1-5}$ alkyl optionally substituted with 1 to 3 halo, or C_{3-5} cycloalkyl.

7. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein R^2 is hydrogen, -F, -Cl, $-CH_3$, $-CF_3$, $-CHF_2$, cyclopropyl, $-OCH_3$, -O-ethyl, -O-propyl, -O-isopropyl, -O-cyclopropyl, $-OCF_3$, or $-OCHF_2$.

8. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein R^2 is fluoro.

9. The compound of any one of claims 1-7, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein R^2 is $-OCH_3$.

10. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein X^3 is C-R^3 and R^3 is hydrogen, fluoro, chloro, -CN, $-OR^{12}$, $-N(R^{12})_2$, C_{1-6} alkyl optionally substituted with 1 to 3 Z^3, C_{2-6} alkenyl optionally substituted with 1 to 3 Z^3, C_{2-6} alkynyl optionally substituted with 1 to 3 Z^3, or C_{3-6} cycloalkyl optionally substituted with 1 to 3 Z^3.

11. The compound of claim 10, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein R^3 is hydrogen, C_{1-6} alkyl optionally substituted with 1 to 3 Z^3, C_{2-6} alkenyl optionally substituted with 1 to 3 Z^3, C_{2-6} alkynyl optionally substituted with 1 to 3 Z^3, or C_{3-6} cycloalkyl optionally substituted with 1 to 3 Z^3.

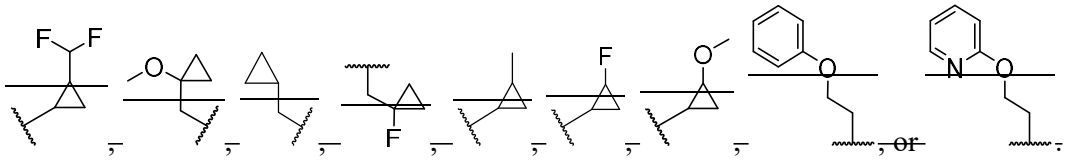
12. The compound of claim 10, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein R^3 is hydrogen, $-CH_3$, $-C_2H_5$, or cyclopropyl.

13. The compound of any one of claims 1-9, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein X^3 is N-R^3, and R^3

is hydrogen, C_{1-6} alkyl optionally substituted with 1 to 3 Z^3, C_{3-6} alkenyl optionally substituted with 1 to 3 Z^3, C_{3-6} alkynyl optionally substituted with 1 to 3 Z^3, C_{3-6} cycloalkyl optionally substituted with 1 to 3 Z^3, or 4-6 membered heterocyclyl optionally substituted with 1 to 3 Z^3.

14. The compound of claim 13, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein R^3 is C_{1-6} alkyl optionally substituted with 1 to 3 Z^3, or C_{3-6} cycloalkyl optionally substituted with 1 to 3 Z^3.

15. The compound of claim 13, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein R^3 is $-CH_3$, $-C_2H_5$, $-CH_2CHF_2$, $-CH_2CF_3$, $-CH_2CH_2OCH_3$, $-CH_2CH(CH_3)OCH_3$, $-CH_2CH_2OCH(CH_3)_2$, $-CH_2C(CH_3)_3$, $-CH_2CH_2OCH_2CH_3$, $-CH_2CH_2CN$, $-CH_2CH_2CONH_2$, $-CH_2CH(CH_3)OCH_3$, cyclopropyl, cyclobutyl,



, or .

16. The compound of claim 13, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein R^3 is $-CH_3$.

17. The compound of claim 13, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein R^3 is cyclopropyl.

18. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein X^4 is N.

19. The compound of any one of claims 1-17, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein X^4 is C-R^2.

20. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein X^5 is C-R^6.

21. The compound of any one of claims 1-19, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein X^5 is N.

22. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein X^7 is C-R^7.

~~23. The compound of any one of claims 1-20 and 22, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein R^6 is hydrogen, fluoro, chloro, -CN, -CF_3, -CHF_2, -OR^{12}, C_{1-5} alkyl, or C_{3-5} cycloalkyl.~~

~~24. The compound of any one of claims 1-20 and 22, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein R^6 is hydrogen, fluoro, chloro, -CH_3, -OCH_3, or cyclopropyl.~~

~~25. The compound of any one of claims 1-20 and 22, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein R^6 is hydrogen or fluoro,~~

~~26. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein R^7 is hydrogen, fluoro, chloro, -CN, -CF_3, -CHF_2, -OR^{12}, C_{1-3} alkyl, or C_{3-5} cycloalkyl.~~

~~27. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein R^7 is hydrogen, fluoro, chloro, -CH_3, -OCH_3, or cyclopropyl.~~

~~28. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein R^7 is hydrogen.~~

~~29. The compound of any one of claims 1-27, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein R^7 is fluoro.~~

~~30~~3. The compound of ~~any one of the preceding~~ claims 1 or 2, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein L^1, L^2, L^3, L^4, L^5, and L^6 are each independently:

C_{1-10} alkylene optionally substituted with 1 to 2 Z^8;

C_{2-10} alkenylene optionally substituted with 1 to 2 Z^8;

C_{2-10} alkynylene optionally substituted with 1 to 2 Z^8;

2 to 6 membered heteroalkylene having 1 to 2 heteroatoms selected from O and N and optionally substituted with 1 to 2 Z^8;

C_3-C_{10} cycloalkylene optionally substituted with 1 to 2 Z^8;

4-8 membered heterocyclene having 1 to 2 heteroatoms selected from O and N and optionally substituted with 1 to 2 Z^8;

C_{6-10} arylene optionally substituted with 1 to 3 Z^8;

5-10 membered heteroarylene having 1 to 3 heteroatoms selected from O, N, and S and optionally substituted with 1 to 3 Z^8; or

-O-, -N(R^8)-, -C(O)-, -C(O)O-, -C(O)N(R^8)-, -SO_2N(R^8)-, -SO_2-, -N(R^8)C(O)O-, -OC(O)O-, or -N(R^8)C(O)N(R^8); and

m1, m2, m3, m4, m5, and m6 are each independently 0 or 1;

provided that L^1_{m1}, L^2_{m2}, L^3_{m3}, L^4_{m4}, L^5_{m5}, and L^6_{m6} taken together with the four consecutive atoms between which they are attached form an optionally substituted 11 to 20 membered macrocyclic ring.

~~31. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein L^1_{m1}, L^2_{m2}, L^3_{m3}, L^4_{m4}, L^5_{m5}, and L^6_{m6} taken together with the four consecutive atoms between which they are attached form an optionally substituted 12-16 membered macrocyclic ring.~~

~~32~~4. The compound of any one of ~~the preceding~~ claims 1-3, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein R^{10} is hydrogen or -CH_3, and R^{11} is hydrogen, C_{1-6} alkyl optionally substituted with 1 to 3 Z^{11}, C_{3-6} cycloalkyl optionally substituted with 1 to 3 Z^{11}, or 4-12 membered heterocyclyl optionally substituted with 1 to 3 Z^{11}; or R^{10} and R^{11} taken together with the nitrogen to which they are attached form a 4-10 membered heterocyclyl optionally substituted with 1 to 3 Z^{11}.

~~33. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein R^{10} is hydrogen or -CH_3, and R^{11} is 4-12 membered heterocyclyl optionally substituted with 1 to 3 Z^{11}.~~

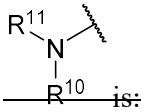
~~34. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein R^{10} is hydrogen, and R^{11} is 5-10 membered heterocyclyl optionally substituted with 1 to 3 substituents selected from the group consisting of -CH_3, -CF_3, fluoro, -OH, -NH_2, -COOH, and -OCH_3.~~

~~35. The compound of claim 34, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein R^{11} is pyrrolidinyl or piperidinyl, wherein pyrrolidinyl or piperidinyl may be monocyclic or part of a bicyclic system, and~~

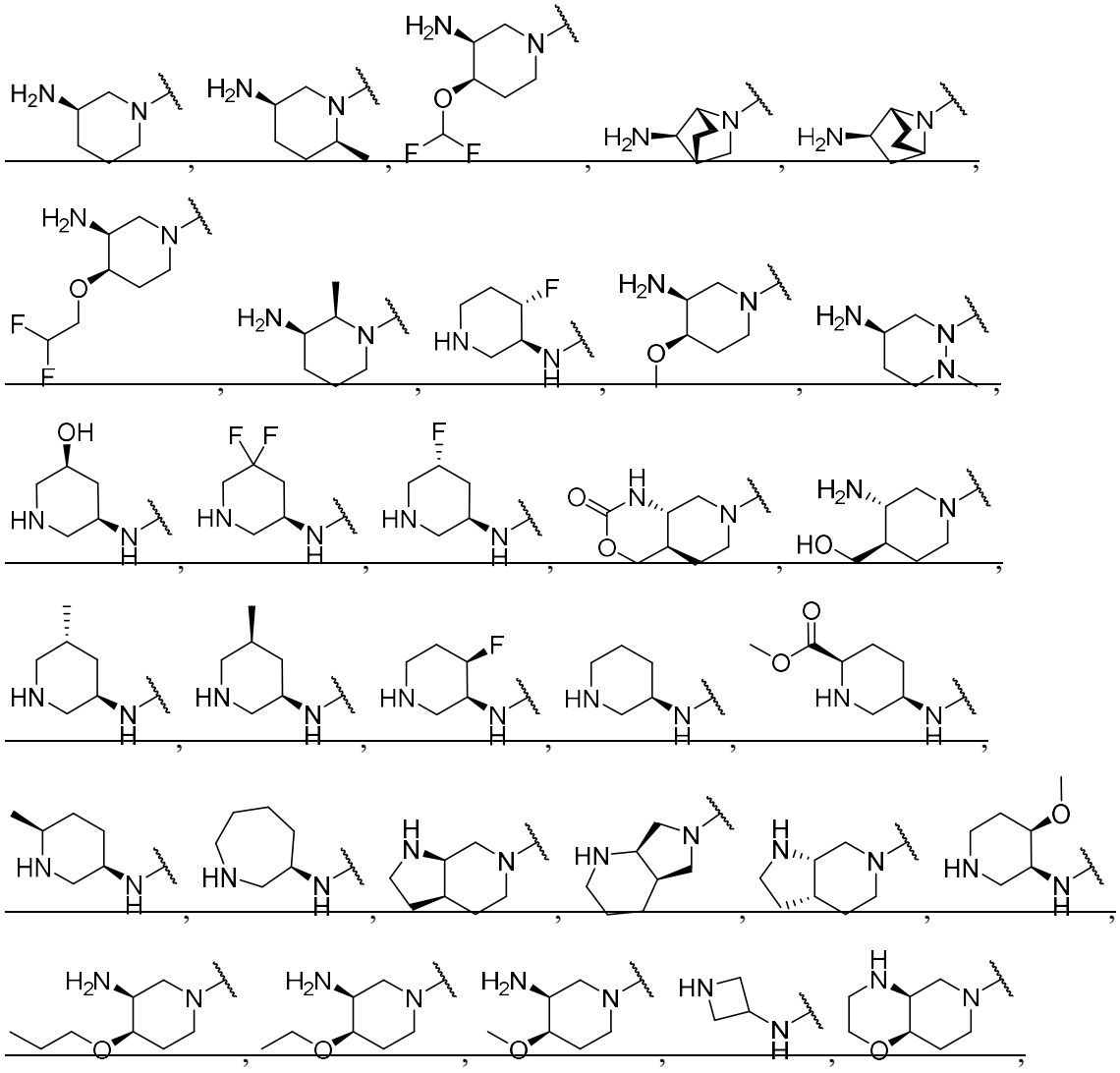
~~may be optionally substituted with 1 to 3 substituents selected from the group consisting of $-CH_3$, $-CF_3$, fluoro, -OH, -COOH, and $-OCH_3$.~~

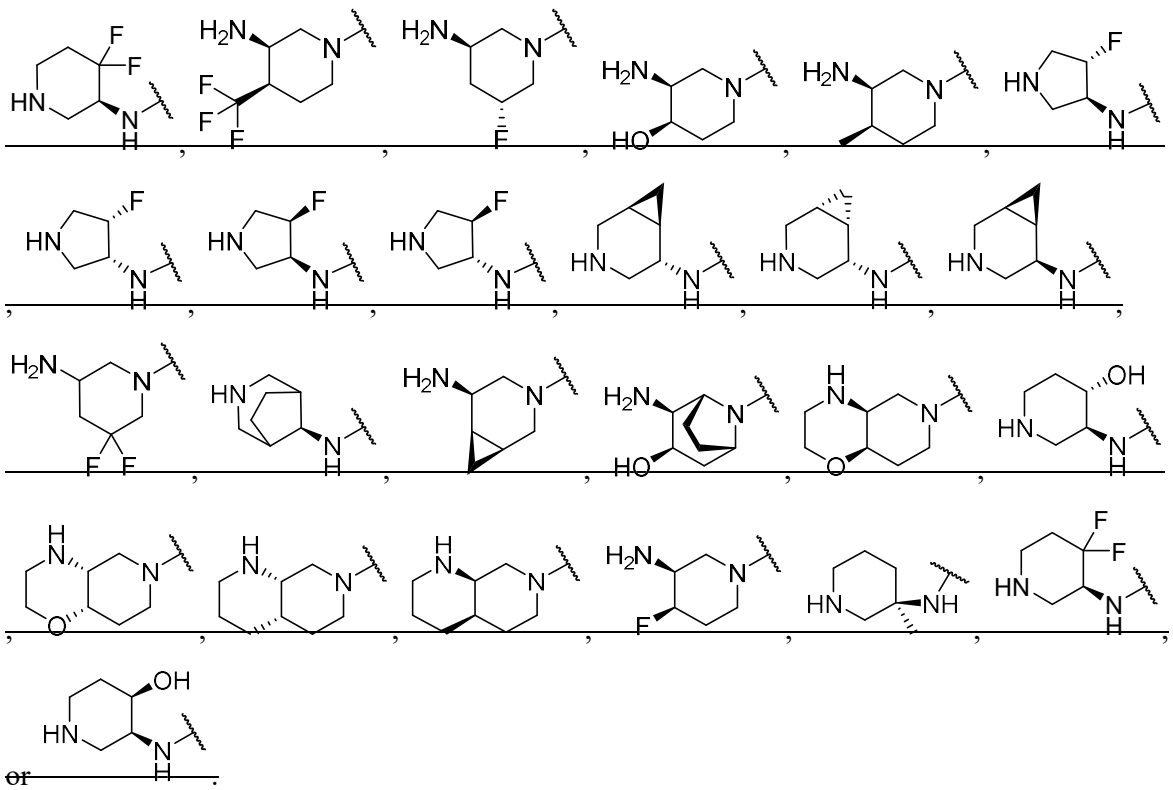
~~36. The compound of any one of claims 1-32, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein R^{10} and R^{11} taken together with the nitrogen to which they are attached to form a 4-10 membered heterocyclyl optionally substituted with 1 to 3 Z^{11}.~~

~~37. The compound of any one of claims 1-32, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein the moiety~~



~~is:~~





38. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein each R^{12} and R^{13} is independently hydrogen, C_{1-6} alkyl optionally substituted with 1 to 3 Z^{1b}, C_{3-6} cycloalkyl optionally substituted with 1 to 3 Z^{1b}, 4-6 membered heterocyclyl having 1 to 2 heteroatoms selected from O and N optionally substituted with 1 to 3 Z^{1b}, C_{6-10} aryl optionally substituted with 1 to 3 Z^{1b}, or 5-6 membered heteroaryl optionally substituted with 1 to 3 Z^{1b}.

39. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein each R^{12} and R^{13} is independently hydrogen, $-CH_3$, ethyl, isopropyl, cyclopropyl, cyclobutyl, tert-butyl, $-CH_2$-cyclopropyl, fluorocyclopropyl, $-CHF_2$, $-CF_3$, $-CH_2CF_3$, or $-CH_2CHF_2$.

40. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein each Z^1, Z^2, Z^3, Z^6, Z^7, and Z^8 is independently halo, oxo, -CN, C_{1-6} alkyl optionally substituted by 1 to 3 Z^{1a}, C_{3-6} cycloalkyl optionally substituted with 1 to 3 Z^{1a}, 4-6 membered heterocyclyl having 1 to 2 heteroatoms selected from O and N that is optionally substituted by 1 to 3 Z^{1a}, 5-6 membered heteroaryl having 1 to 4 heteroatoms selected from O and N and

optionally substituted with 1 to 3 Z^{1a}, -OR^9, -$N(R^9)_2$, -$C(O)R^9$, -$N(R^9)C(O)R^9$, -$N(R^9)C(O)OR^9$, -$N(R^9)S(O)_2R^9$, -$OC(O)R^9$, -$OC(O)OR^9$, -$OC(O)N(R^9)_2$, or -$S(O)_2R^9$.

41. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein each Z^1, Z^2, Z^3, Z^6, Z^7, and Z^8 is independently oxo, hydroxy, fluoro, chloro, -CN, -CH_3, ethyl, isopropyl, tert-butyl, -CF_3, -CHF_2, cyclopropyl, cyclobutyl, -OCH_3, -O-ethyl, -O-isopropyl, -O-cyclopropyl, -OCF_3, -OCF_2H, -C(O)-alkyl, -C(O)-cycloalkyl, -C(O)-aryl, -C(O)-heteroaryl, or -NH_2.

42. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein each Z^{1a} is independently halo, -CN, C_{1-6} alkyl optionally substituted by 1 to 3 Z^{1b}, C_{3-6} cycloalkyl optionally substituted by 1 to 3 Z^{1b}, 6 membered aryl optionally substituted by 1 to 3 Z^{1b}, 4-6 membered heterocyclyl having 1 to 2 heteroatoms selected from O or N that is optionally substituted by 1 to 3 Z^{1b}, 5-6 membered heteroaryl having 1 to 2 heteroatoms selected from O and N and optionally substituted with 1 to 3 Z^{1b}, -OR^{13}, -$N(R^{13})_2$, -$C(O)R^{13}$, -$N(R^{13})C(O)R^{13}$, -$N(R^{13})C(O)OR^{13}$, -$N(R^{13})S(O)_2R^{13}$, -$OC(O)R^{13}$, -$OC(O)OR^{13}$, -$OC(O)N(R^{13})_2$, or -$S(O)_2R^{13}$.

43. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein each Z^{1a} is independently halo, -CH_3, cyclopropyl, or -OCH_3.

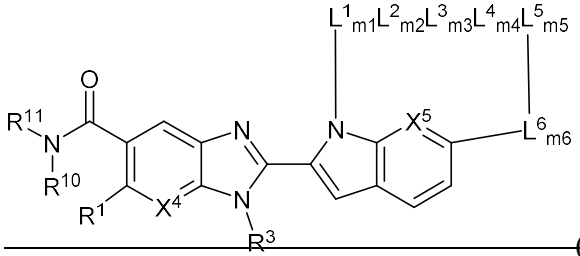
44. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein each Z^{1b} is independently hydroxy, halo, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, aryl, heteroaryl, heterocyclyl, or -O(C_{1-6} alkyl).

45. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein each Z^{10} and Z^{11} is independently fluoro, chloro, -CN, C_{1-6} alkyl optionally substituted with 1 to 3 Z^{1b}, C_{3-6} cycloalkyl optionally substituted with 1 to 3 Z^{1b}, -OR^{13}, -$C(O)R^{13}$, -$OC(O)R^{13}$, -$OC(O)OR^{13}$, -$OC(O)N(R^{13})_2$, -$N(R^{13})C(O)R^{13}$, -$N(R^{13})C(O)OR^{13}$, or -$N(R^{13})_2$.

46. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein each Z^{10} and

~~Z^{11} is independently fluoro, chloro, -CN, -OH, -OCH_3, -$OCHF_2$, -OCF_3, -CH_3, -CHF_2, -CF_3, -CH_2OH, -CH_2OCH_3, or -NH_2.~~

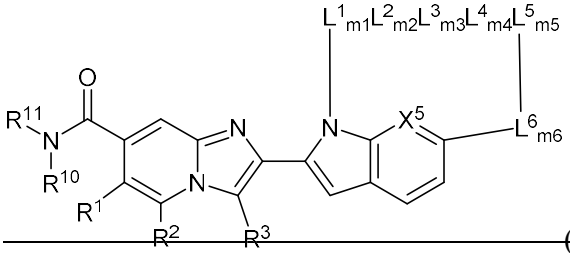
~~47. The compound of any one of claims 1-9, 13-19, 21, and 30-46, represented by Formula (Ia):~~



~~(Ia)~~

~~or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof.~~

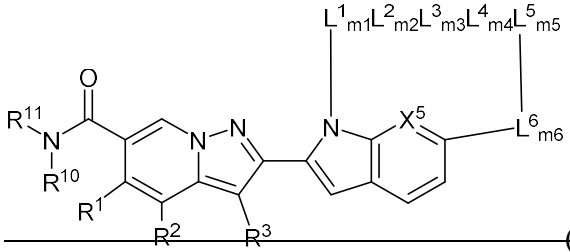
~~48. The compound of any one of claims 1-12, 21, and 30-46, represented by Formula (Ib):~~



~~(Ib)~~

~~or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof.~~

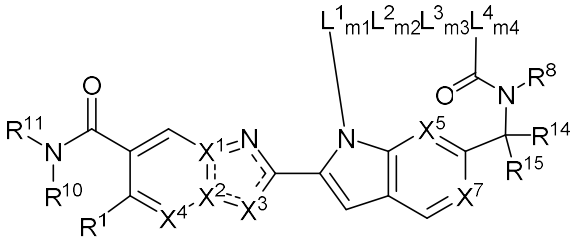
~~49. The compound of any one of claims 1-12, 21, and 30-46, represented by Formula (Ic):~~



~~(Ic)~~

~~or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof.~~

~~50~~5. The compound of any one of claims 1-~~49~~, represented by Formula (Id):



(Id)

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein:

R^{14} is hydrogen, C_{1-8} alkyl optionally substituted with 1-3 Z^{1a}, C_{3-8} cycloalkyl optionally substituted with 1-3 Z^{1a}, C_{4-6} heterocyclyl having 1-3 heteroatoms selected from O, N, and S, optionally substituted with 1-3 Z^{1a}; and

R^{15} is hydrogen, C_{1-8} alkyl optionally substituted with 1-3 Z^{1a}, C_{3-8} cycloalkyl optionally substituted with 1-3 Z^{1a}, C_{4-6} heterocyclyl having 1-3 heteroatoms selected from O, N, and S, optionally substituted with 1-3 Z^{1a};

or R^{14} and R^{15} can be taken together with the carbon to which they are attached to form a 3-6 membered cycloalkyl that is optionally substituted with 1 to 3 Z^{1a} or 4-6 membered heterocyclyl containing 1-2 heteroatoms independently selected from O, N, or S that is optionally substituted with 1-3 Z^{1a}.

~~51. The compound of any one of claims 1-50, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein:~~

~~L^1 is C_{1-10} alkylene, optionally substituted with 1 to 3 substituents selected from the group consisting of halo, $-OCH_3$, and 5-6 membered heteroaryl optionally substituted with halo;~~

~~L^2 is C_3-C_{10} cycloalkylene or C_{2-10} alkenylene, wherein C_3-C_{10} cycloalkylene or C_{2-10} alkenylene is optionally substituted with 1 to 3 substituents selected from the group consisting of halo, and C_{1-5} alkyl optionally substituted with halo;~~

~~L^3 is $-O-$ or $-O-C_{1-6}$ alkylene;~~

~~L^4 is C_{1-10} alkylene optionally substituted with 1 to 3 Z^8, 4-10 membered heterocyclene optionally substituted with 1 to 3 Z^8, C_3-C_{10} cycloalkylene optionally substituted with 1 to 3 Z^8, 5-10 membered heteroarylene optionally substituted with 1 to 3 Z^8, or C_6-$_{10}$ arylene optionally substituted with 1 to 3 Z^8; and~~

~~m1 is 1.~~

52. The compound of claim 51, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein:

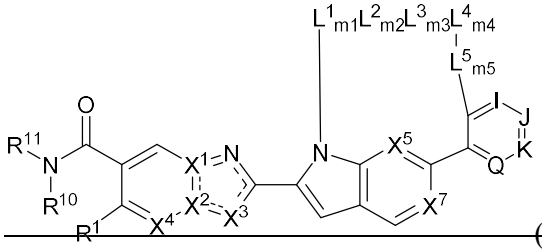
L^3 is -O-;

L^4 is C_{1-5} alkylene;

m3 is 1; and

m4 is 1.

53. The compound of any one of claims 1-49, represented by Formula (Ie):

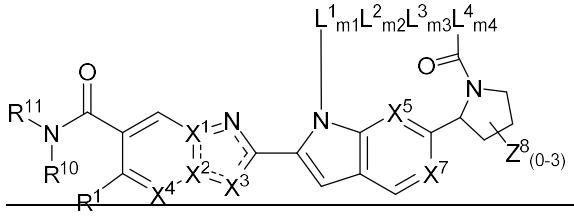


(Ie)

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein:

I, J, K, and Q are each independently N, CH, or C-Z^8 provided that at least two of I, J, K, and Q are CH or C-Z^8.

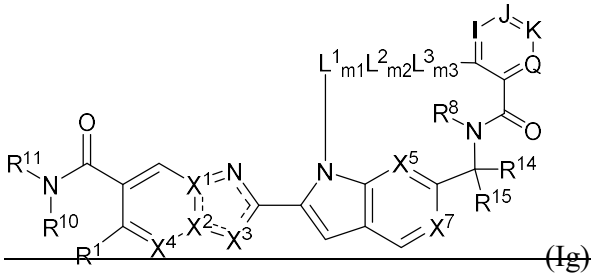
54. The compound of any one of claims 1-49, represented by Formula (If):



(If)

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof.

55. The compound of any one of claims 1-49, represented by Formula (Ig):



(Ig)

~~or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein:~~

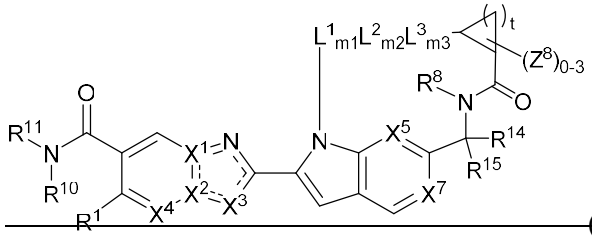
~~R^{14} is hydrogen, C_{1-8} alkyl optionally substituted with 1-3 Z^{1a}, C_{3-8} cycloalkyl optionally substituted with 1-3 Z^{1a}, C_{4-6} heterocyclyl having 1-3 heteroatoms selected from O, N, and S, optionally substituted with 1-3 Z^{1a}; and~~

~~R^{15} is hydrogen, C_{1-8} alkyl optionally substituted with 1-3 Z^{1a}, C_{3-8} cycloalkyl optionally substituted with 1-3 Z^{1a}, C_{4-6} heterocyclyl having 1-3 heteroatoms selected from O, N, and S, optionally substituted with 1-3 Z^{1a};~~

~~or R^{14} and R^{15} can be taken together with the carbon to which they are attached to form a 3-6 membered cycloalkyl that is optionally substituted with 1 to 3 Z^{1a} or 4-6 membered heterocyclyl containing 1-2 heteroatoms independently selected from O, N, or S that is optionally substituted with 1-3 Z^{1a};~~

~~I, J, K, and Q are each independently N, CH, or C-Z^{8} provided that at least two of I, J, K, and Q are CH, or C-Z^{8}.~~

~~56. The compound of any one of claims 1-49, represented by Formula (Ih):~~



~~(Ih)~~

~~or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein:~~

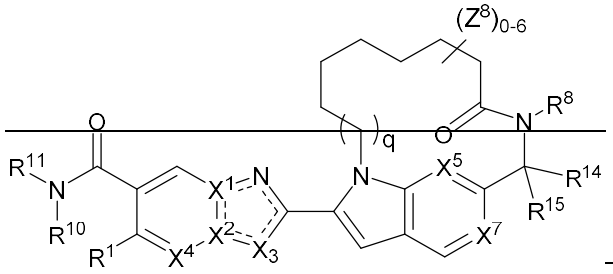
~~R^{14} is hydrogen, C_{1-8} alkyl optionally substituted with 1-3 Z^{1a}, C_{3-8} cycloalkyl optionally substituted with 1-3 Z^{1a}, C_{4-6} heterocyclyl having 1-3 heteroatoms selected from O, N, and S, optionally substituted with 1-3 Z^{1a};~~

~~R^{15} is hydrogen, C_{1-8} alkyl optionally substituted with 1-3 Z^{1a}, C_{3-8} cycloalkyl optionally substituted with 1-3 Z^{1a}, C_{4-6} heterocyclyl having 1-3 heteroatoms selected from O, N, and S, optionally substituted with 1-3 Z^{1a};~~

~~or R^{14} and R^{15} can be taken together with the carbon to which they are attached to form a 3-6 membered cycloalkyl that is optionally substituted with 1 to 3 Z^{1a} or 4-6 membered heterocyclyl containing 1-2 heteroatoms independently selected from O, N, and S that is optionally substituted with 1-3 Z^{1a}; and~~

t is 1, 2, 3, or 4.

57. The compound of any one of claims 1-49, Formula (Ii):



(Ii)

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein:

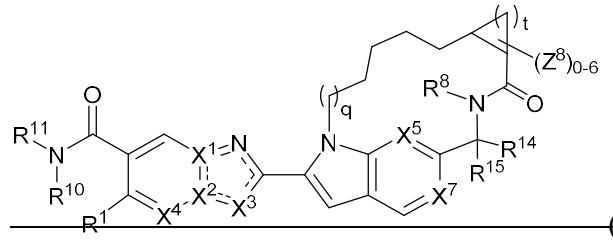
R^{14} is hydrogen, C_{1-8} alkyl optionally substituted with 1-3 Z^{1a}, C_{3-8} cycloalkyl optionally substituted with 1-3 Z^{1a}, C_{4-6} heterocyclyl having 1-3 heteroatoms selected from O, N, and S, optionally substituted with 1-3 Z^{1a}; and

R^{15} is hydrogen, C_{1-8} alkyl optionally substituted with 1-3 Z^{1a}, C_{3-8} cycloalkyl optionally substituted with 1-3 Z^{1a}, C_{4-6} heterocyclyl having 1-3 heteroatoms selected from O, N, and S, optionally substituted with 1-3 Z^{1a};

or R^{14} and R^{15} can be taken together with the carbon to which they are attached to form a 3-6 membered cycloalkyl that is optionally substituted with 1 to 3 Z^{1a} or 4-6 membered heterocyclyl containing 1-2 heteroatoms independently selected from O, N, and S that is optionally substituted with 1-3 Z^{1a};

q is 0, 1 or 2.

58. The compound of any one of claims 1-49, represented by Formula (Ij):



(Ij)

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein:

R^{14} is hydrogen, C_{1-8} alkyl optionally substituted with 1-3 Z^{1a}, C_{3-8} cycloalkyl optionally substituted with 1-3 Z^{1a}, C_{4-6} heterocyclyl having 1-3 heteroatoms selected from O, N, and S, optionally substituted with 1-3 Z^{1a}; and

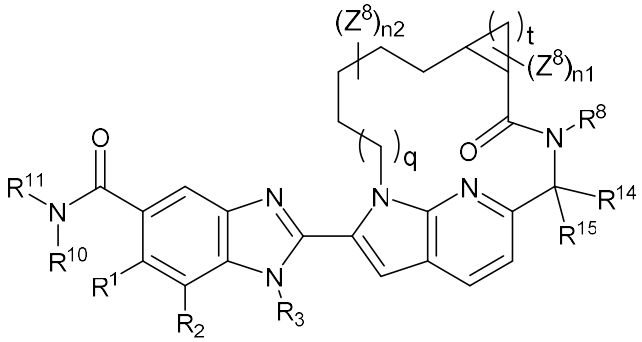
~~R^{15} is hydrogen, C_{1-8} alkyl optionally substituted with 1-3 Z^{1a}, C_{3-8} cycloalkyl optionally substituted with 1-3 Z^{1a}, C_{4-6} heterocyclyl having 1-3 heteroatoms selected from O, N, and S, optionally substituted with 1-3 Z^{1a};~~

~~or R^{14} and R^{15} can be taken together with the carbon to which they are attached to form a 3-6 membered cycloalkyl that is optionally substituted with 1 to 3 Z^{1a} or 4-6 membered heterocyclyl containing 1-2 heteroatoms independently selected from O, N, and S that is optionally substituted with 1-3 Z^{1a};~~

~~t is 1, 2, 3, or 4;~~

~~q is 0, 1 or 2.~~

~~59~~6. The compound of any one of claims 1-~~9, 13-19, and 30-46~~5, ~~-~~represented by Formula (Ij-1):



(Ij-1)

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein:

R^{14} and R^{15} are each independently hydrogen, C_{1-8} alkyl optionally substituted with 1-2 Z^{1a}, C_{3-8} cycloalkyl optionally substituted with 1-2 Z^{1a}, C_{4-6} heterocyclyl having 1-3 heteroatoms selected from O, N, and S, optionally substituted with 1-2 Z^{1a};

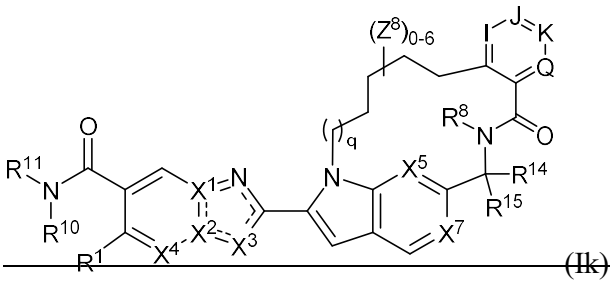
t is 1, 2, 3, or 4;

q is 0, 1 or 2;

n1 is 0, 1, or 2; and

n2 is 0, 1, 2, or 3.

~~60. The compound of any one of claims 1-49, represented by Formula (Ik):~~



~~(Ik)~~

~~or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein:~~

~~I, J, K, and Q are each independently N, CH, or C-Z^8 provided that at least two of I, J, K, and Q are CH, or C-Z^8;~~

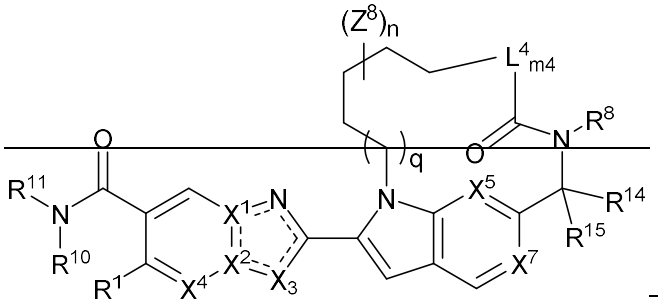
~~q is 0, 1 or 2;~~

~~R^{14} is hydrogen, C_{1-8} alkyl optionally substituted with 1-3 Z^{1a}, C_{3-8} cycloalkyl optionally substituted with 1-3 Z^{1a}, C_{4-6} heterocyclyl having 1-3 heteroatoms selected from O, N, and S, optionally substituted with 1-3 Z^{1a}; and~~

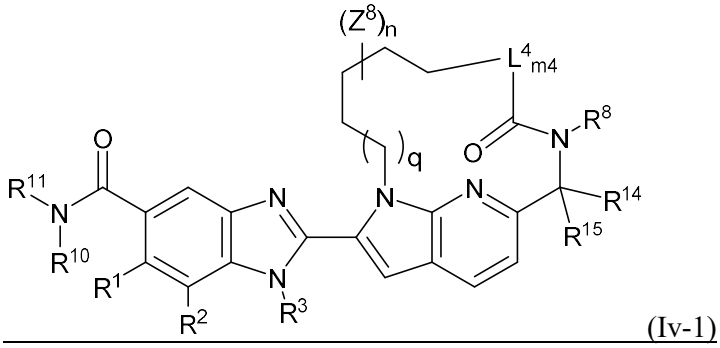
~~R^{15} is hydrogen, C_{1-8} alkyl optionally substituted with 1-3 Z^{1a}, C_{3-8} cycloalkyl optionally substituted with 1-3 Z^{1a}, C_{4-6} heterocyclyl having 1-3 heteroatoms selected from O, N, and S, optionally substituted with 1-3 Z^{1a};~~

~~or R^{14} and R^{15} can be taken together with the carbon to which they are attached to form a 3-6 membered cycloalkyl that is optionally substituted with 1 to 3 Z^{1a} or 4-6 membered heterocyclyl containing 1-2 heteroatoms independently selected from O, N, and S that is optionally substituted with 1-3 Z^{1a}.~~

~~61~~7. The compound of any one of claims 1-~~49~~6, represented by Formula (Iv-1):



~~(Iv)~~



(Iv-1)

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein:

L^4 is methylene optionally substituted with 1 to 2 Z^8, C_{3-6} cycloalkylene optionally substituted with 1 to 2 Z^8, 4-10 membered heterocyclene optionally substituted with 1 to 2 Z^8, 6-10 membered arylene optionally substituted with 1 to 2 Z^8, or 5-10 membered heteroarylene optionally substituted with 1 to 2 Z^8;

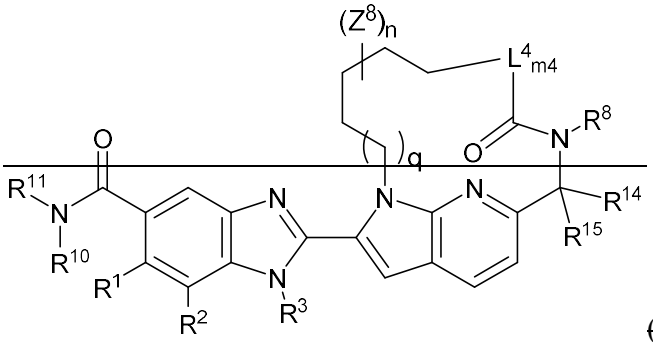
m4 is 1;

q is 0, 1 or 2;

n is 0, 1, 2, 3, or 4; and

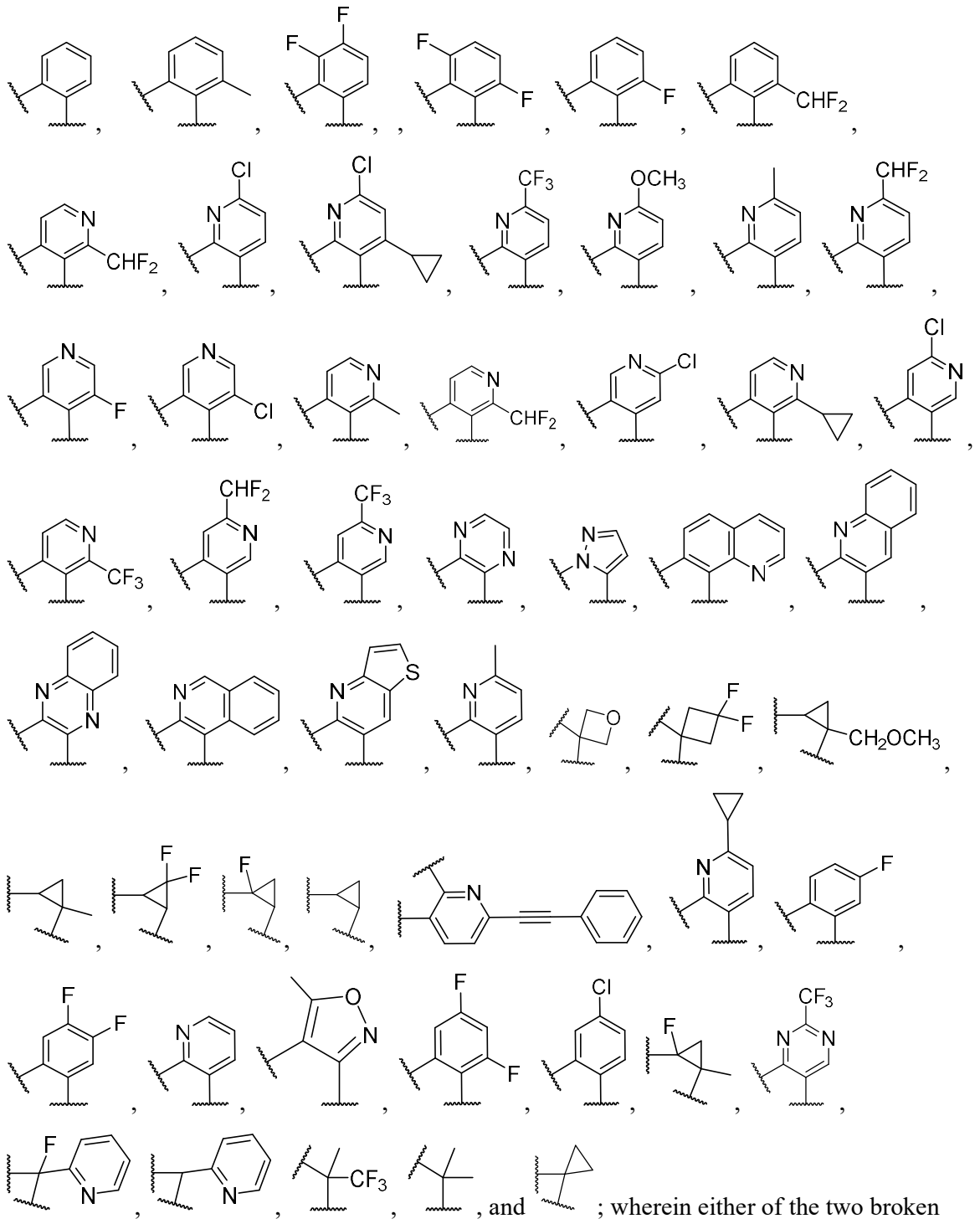
R^{14} and R^{15} are each independently hydrogen, C_{1-8} alkyl optionally substituted with 1-3 Z^{1a}, C_{3-8} cycloalkyl optionally substituted with 1-3 Z^{1a}, C_{4-6} heterocyclyl having 1-3 heteroatoms selected from O, N, and S, optionally substituted with 1-3 Z^{1a}.

~~62. The compound of claim 61, represented by Formula (Iv-1):~~

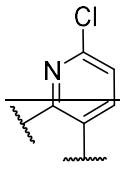


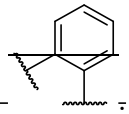
~~(Iv-1).~~

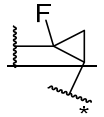
~~63~~8. The compound of claim ~~61 or 62~~7, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein L^4 is selected from the group consisting of:

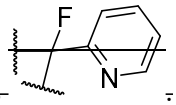


; wherein either of the two broken bonds may be attached to -CO- in -CO-NR^8-.

64. The compound of claim 61 or 62, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein L^4 is , wherein the broken bond with * is attached to -CO- of $-NR^8-CO-$.

65. The compound of claim 61 or 62, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein L^4 is .

66. The compound of claim 61 or 62, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein L^4 is , wherein the broken bond with * is attached to -CO- of $-NR^8-CO-$.

67. The compound of claim 61 or 62, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein L^4 is .

68. The compound of claim 55 or 60, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein at least two of I, J, K, and Q are C-H, C-Cl, C-F, C-OCH_3, C-CH_3, C-cyclopropyl, C-CH_2F, or C-CF_3.

69. The compound of any one of claims 50-52 and 55-68, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein R^{14} is methyl, and R^{15} is hydrogen.

70. The compound of any one of claims 1-52 and 55-69, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein R^8 is hydrogen.

71. The compound of any one of claims 1-70, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein each Z^8 is independently halo, C_{1-5} alkyl, -O(C_{1-5} alkyl), C_{3-6} cycloalkyl, 6-10 membered aryl, or 5-10 membered heteroaryl, wherein C_{1-5} alkyl, -O(C_{1-5} alkyl), C_{3-6} cycloalkyl, 6-10 membered aryl, or 5-10 membered heteroaryl, is optionally substituted with 1 to 2 halo or -O(C_{1-5} alkyl).

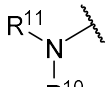
~~72. The compound of any one of claims 1-70, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein each Z_8 is independently -CF_3, -CHF_2, -OCH_3, -$OCHF_2$, -OCF_3, fluoro, chloro, cyclopropyl, or -CH_3 optionally substituted with -OCH_3.~~

~~73. The compound of any one of claims 1-70, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein each Z^8 is independently fluoro, chloro, cyclopropyl, or -CH_3.~~

~~74. The compound of any one of claims 1-70, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein Z^8 is fluoro.~~

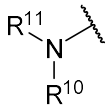
~~75. The compound of any one of claims 61-74, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein n is 0, 1, or 2.~~

~~76. The compound of any one of claims 1-32 and 38-75, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof , wherein the moiety~~



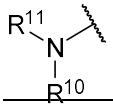
~~is a 5-10 membered heterocyclyl optionally substituted with 1 to 3 substituents selected from the group consisting of oxo, -OR^{13}, -$N(R^{13})_2$, fluoro, chloro, and C_{1-5} alkyl optionally substituted with 1 to 3 Z^{1b}.~~

~~77~~9. The compound of any one of claims 1-~~32 and 38-75~~8, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof , wherein the moiety



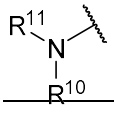
is a 5-8 membered heterocyclyl optionally substituted with 1 to 3 substituents selected from the group consisting of -NH_2, -NH(C_{1-5} alkyl), -OH, fluoro, C_{1-5} alkyl, and -O(C_{1-5} alkyl), wherein C_{1-5} alkyl or -O(C_{1-5} alkyl) may be optionally substituted with fluoro, -O(C_{1-5} alkyl), or -OH.

~~78. The compound of any one of claims 1-32 and 38-77, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein the moiety~~



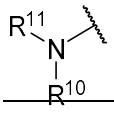
~~is a 5-8 membered monocyclic heterocyclyl.~~

~~79. The compound of any one of claims 1-32 and 38-77, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein the moiety~~



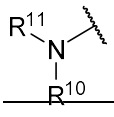
~~is a 5-8 membered bridged bicyclic heterocyclyl.~~

~~80. The compound of any one of claims 1-32 and 38-77, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein the moiety~~



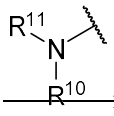
~~is a 5-8 membered fused bicyclic heterocyclyl.~~

~~81. The compound of any one of claims 1-32 and 38-77, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein the moiety~~



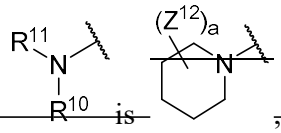
~~is a 5-8 membered spiro bicyclic heterocyclyl.~~

~~82. The compound of any one of claims 1-32, 38-76, and 79, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein the moiety~~

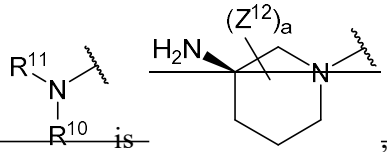


~~is a bridged bicyclic piperidyl or pyrrolidinyl, wherein piperidyl or pyrrolidinyl is optionally substituted with one to three substituents selected from the group consisting of $-NH_2$, $-NH(C_{1-5}$ alkyl), -OH, fluoro, and C_{1-5} alkyl or $-O(C_{1-5}$ alkyl) optionally substituted with fluoro, $-O(C_{1-5}$ alkyl), or -OH.~~

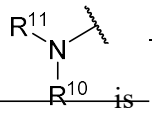
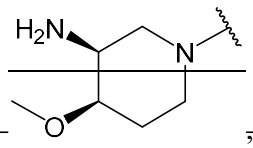
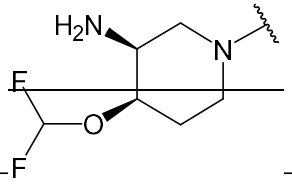
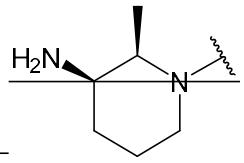
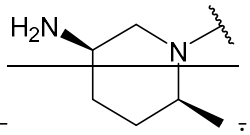
~~83. The compound of claim any one of claims 1-32 and 38-76, and 78, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof,~~

~~wherein the moiety~~  ~~, wherein each Z^{12} is independently $-NH_2$, fluoro, -OH, C_{1-6} alkyl, or $-OCH_3$ optionally substituted with F; a is 1, 2, or 3.~~

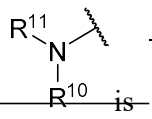
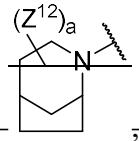
~~84. The compound of any one of claims 1-32, 38-76, 78, and 83, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof,~~

wherein the moiety  is , wherein each Z^{12} is independently -F, -OH, C_{1-6} alkyl, or $-OCH_3$ optionally substituted with F; a is 0, 1, or 2.

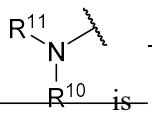
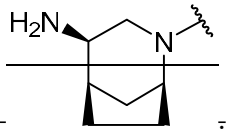
85. The compound of any one of claims 1-32, 38-76, 78, 83, and 84, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof,

wherein the moiety  is , , , or .

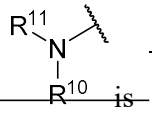
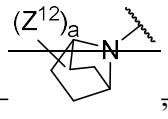
86. The compound of any one of claims 1-32, 38-76, 79, and 82, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof,

wherein the moiety  is , wherein each Z^{12} is independently $-NH_2$, F, or $-OCH_3$ optionally substituted with F; a is 1, 2, or 3.

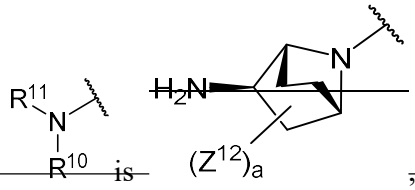
87. The compound of claim 86 or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein at least one Z^{12} is $-NH_2$.

88. The compound of any one of claims 1-32, 38-76, 79, 82, 86, and 87, or a pharmaceutically acceptable salt thereof, wherein the moiety  is .

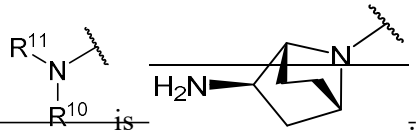
89. The compound of any one of claims 1-32, 38-76, 79, and 82, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof,

wherein the moiety  is , wherein each Z^{12} is independently $-NH_2$, fluoro, -OH, or $-OCH_3$ optionally substituted with F; and a is 1, 2, or 3.

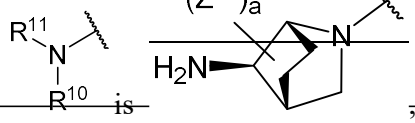
~~90. The compound of any one of claims 1-32, 38-76, 79, 82, and 89, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof,~~

~~wherein the moiety~~  ~~is~~ ~~, wherein each Z^{12} is independently fluoro, -OH, or -OCH_3 optionally substituted with F; and a is 0, 1, or 2.~~

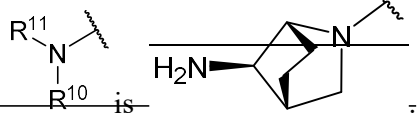
~~91. The compound of any one of claims 1-32, 38-76, 79, 82, 89, and 90, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof,~~

~~wherein the moiety~~  ~~is~~ ~~.~~

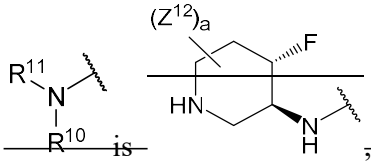
~~92. The compound of any one of claims 1-32, 38-76, 79, and 82, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof,~~

~~wherein the moiety~~  ~~is~~ ~~, wherein each Z^{12} is independently fluoro, -OH, or -OCH_3 optionally substituted with F; and a is 0, 1, or 2.~~

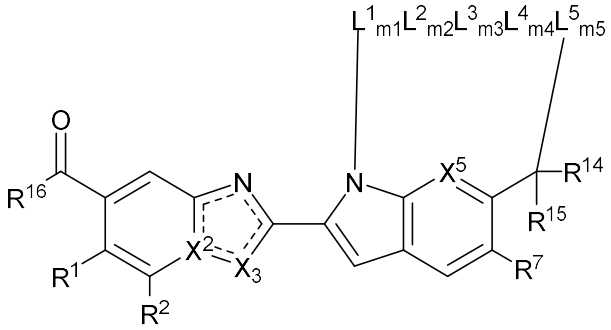
~~93. The compound of any one of claims 1-32, 38-76, 79, 82, and 92, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof,~~

~~wherein the moiety~~  ~~is~~ ~~.~~

~~94. The compound of any one of claims 1-33 and 38-75, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein the moiety~~

 ~~is~~ ~~, wherein each Z^{12} is independently fluoro, -CH_3, -CF_3, -CHF_2, or -OCH_3 optionally substituted with fluoro; and a is 0, 1, or 2.~~

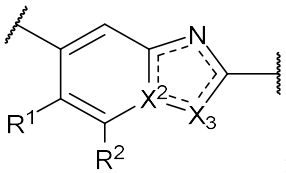
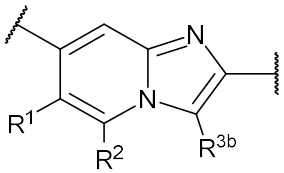
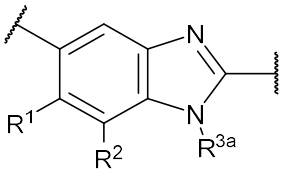
~~95~~10. A compound of Formula (Iu):



(Iu),

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof,

wherein

the moiety  is  or ;

R^1 is hydrogen or fluoro;

R^2 is hydrogen, $-OCH_3$, $-CH_3$, fluoro, chloro, $-OCHF_2$, or $-OCF_3$;

R^{3a} is $-CH_3$, $-CH_2CH_3$, $-CH_2$-cyclopropyl, $-CH_2CHF_2$, $-CH_2CH_2OCH_3$, or cyclopropyl optionally substituted with 1 to 3 fluoro or $-CHF_2$;

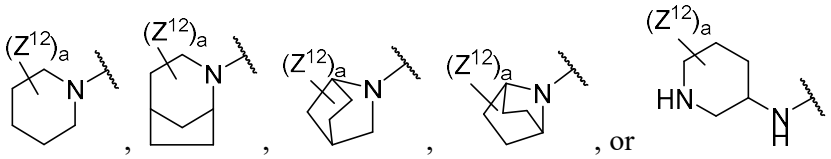
R^{3b} is $-CH_3$ or cyclopropyl;

X^5 is CH, N, or CF;

R^7 is hydrogen or fluoro;

R^{14} and R^{15} are each independently hydrogen, C_{1-6} alkyl, cyclopropyl, or $-CF_3$; or R^{14} and R^{15} taken together with the carbon to which they are attached form a C_{3-6} cycloalkyl;

R^{16} is



; each Z^{12} is independently -NH_2, fluoro, -OH, C_{1-6} alkyl optionally substituted with 1 to 3 fluoro, or -OCH_3 optionally substituted with 1 to 3 fluoro; a is 1, 2, or 3;

L^1 is C_{1-10} alkylene optionally substituted with 1 to 3 Z^8;

L^2 is C_3-C_6 cycloalkylene optionally substituted with 1 to 3 Z^8, or C_{2-6} alkenylene optionally substituted with 1 to 3 Z^8;

L^3 is -O-, -O-C_{1-8} alkylene optionally substituted with 1 to 3 Z^8, or C_{1-8} alkylene optionally substituted with 1 to 3 Z^8;

L^4 is C_{1-10} alkylene optionally substituted with 1 to 3 Z^8, 4-10 membered heterocyclene optionally substituted with 1 to 3 Z^8, C_3-C_{10} cycloalkylene optionally substituted with 1 to 3 Z^8, 5-10 membered heteroarylene optionally substituted with 1 to 3 Z^8, or C_{6-10} arylene optionally substituted with 1 to 3 Z^8;

each Z^8 is independently halo, -CN, C_{1-8} alkyl optionally substituted with 1 to 3 Z^{1a}, C_{2-8} alkenyl optionally substituted with 1 to 3 Z^{1a}, C_{2-8} alkynyl optionally substituted with 1 to 3 Z^{1a}, C_{3-8} cycloalkyl optionally substituted with 1 to 3 Z^{1a}, 6-10 membered aryl optionally substituted with 1 to 3 Z^{1a}, 4-10 membered heterocyclyl optionally substituted with 1 to 3 Z^{1a}, 5-10 membered heteroaryl optionally substituted with 1 to 3 Z^{1a}, -OR^9, -C(O)R^9, or -C(O)OR^9;

each Z^{1a} is independently halo, -CN, C_{1-8} alkyl optionally substituted with 1 to 3 Z^{1b}, C_{2-8} alkenyl optionally substituted with 1 to 3 Z^{1b}, or C_{2-8} alkynyl optionally substituted with 1 to 3 Z^{1b};

C_{3-8} cycloalkyl optionally substituted with 1 to 3 Z^{1b}, 6-10 membered aryl optionally substituted with 1 to 3 Z^{1b}, 4-10 membered heterocyclyl optionally substituted with 1 to 3 Z^{1b}, 5-10 membered heteroaryl optionally substituted with 1 to 3 Z^{1b}, -OR^{13}, -C(O)R^{13}, or -C(O)OR^{13};

each Z^{1b} is independently hydroxy, halo, -CN, C_{1-9} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-15} cycloalkyl, C_{1-8} haloalkyl, 6-10 membered aryl, 5-10 membered heteroaryl, 4-10 membered heterocyclyl, -O(C_{1-9} alkyl), -O(C_{3-15} cycloalkyl), -O(C_{1-8} haloalkyl), -C(O)O(C_{1-9} alkyl), -C(O)O(C_{3-15} cycloalkyl), or -C(O)O(C_{1-8} haloalkyl);

each R^9 and R^{13} are independently hydrogen, C_{1-8} alkyl optionally substituted with 1 to 3 Z^{1b}, C_{2-8} alkenyl optionally substituted with 1 to 3 Z^{1b}, C_{2-8} alkynyl optionally substituted with 1 to 3 Z^{1b}, C_{3-10} cycloalkyl optionally substituted with 1 to 3 Z^{1b}, 4-10 membered heterocyclyl

optionally substituted with 1 to 3 Z^{1b}, C_{6-10} aryl optionally substituted with 1 to 3 Z^{1b}, or 5-10 membered heteroaryl optionally substituted with 1 to 3 Z^{1b};

L^5 is -NHCO-, -N(CH_3)CO-, or -N($COCH_3$)-;

m1 is 1;

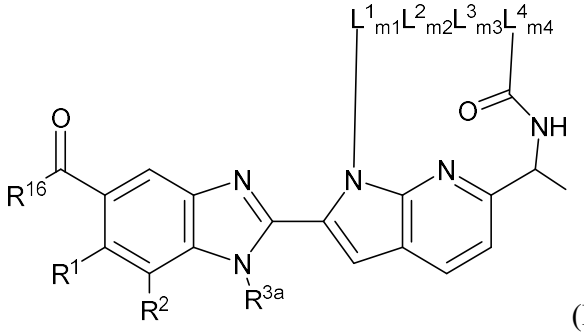
m2 is 0 or 1;

m3 is 0 or 1;

m4 is 0 or 1; and

m5 is 1.

~~96~~11. The compound of claim ~~95~~10, represented by Formula (Iu-1)



(Iu-1)

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof.

~~97~~12. The compound of claim ~~95 or 96~~10 or 11, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein

L^1 is C_{1-10} alkylene optionally substituted with 1 to 3 halo;

L^2 is C_3-C_6 cycloalkylene optionally substituted with 1 to 3 halo, or C_{2-6} alkenylene optionally substituted with 1 to 3 halo;

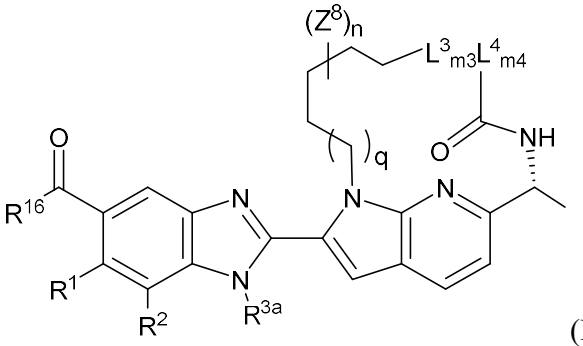
L^3 is -O-, -O-C_{1-8} alkylene optionally substituted with 1 to 3 halo, or C_{1-8} alkylene optionally substituted with 1 to 3 halo;

L^4 is C_{1-6} alkylene optionally substituted with 1 to 3 Z^{8a}, 5-10 membered nitrogen-containing heteroarylene optionally substituted with 1 to 3 Z^{8b}, C_{6-10} arylene optionally substituted with 1 to 3 Z^{8b}, or C_3-C_6 cycloalkylene optionally substituted with 1 to 3 Z^{8b};

each Z^{8a} is independently halo, or 5-10 membered heteroaryl optionally substituted with 1-2 halo; and

each Z^{8b} is independently halo, C_{1-6} alkyl, C_{1-6} haloalkyl, -O(C_{1-6} alkyl), -O(C_{1-6} haloalkyl), -O(C_{3-6} cycloalkyl), cyclopropyl, or phenylethynyl.

~~98~~13. The compound of any one of claims ~~95-97~~10-12, represented by formula (Iu-2)



(Iu-2)

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein

L^3 is -O-;

m3 is 0 or 1;

m4 is 1;

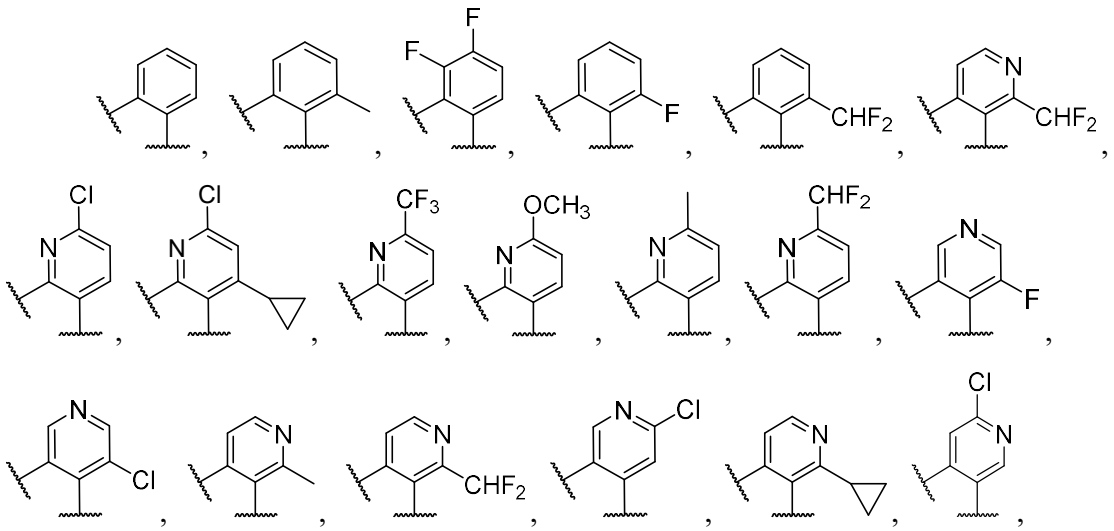
Z^8 is fluoro;

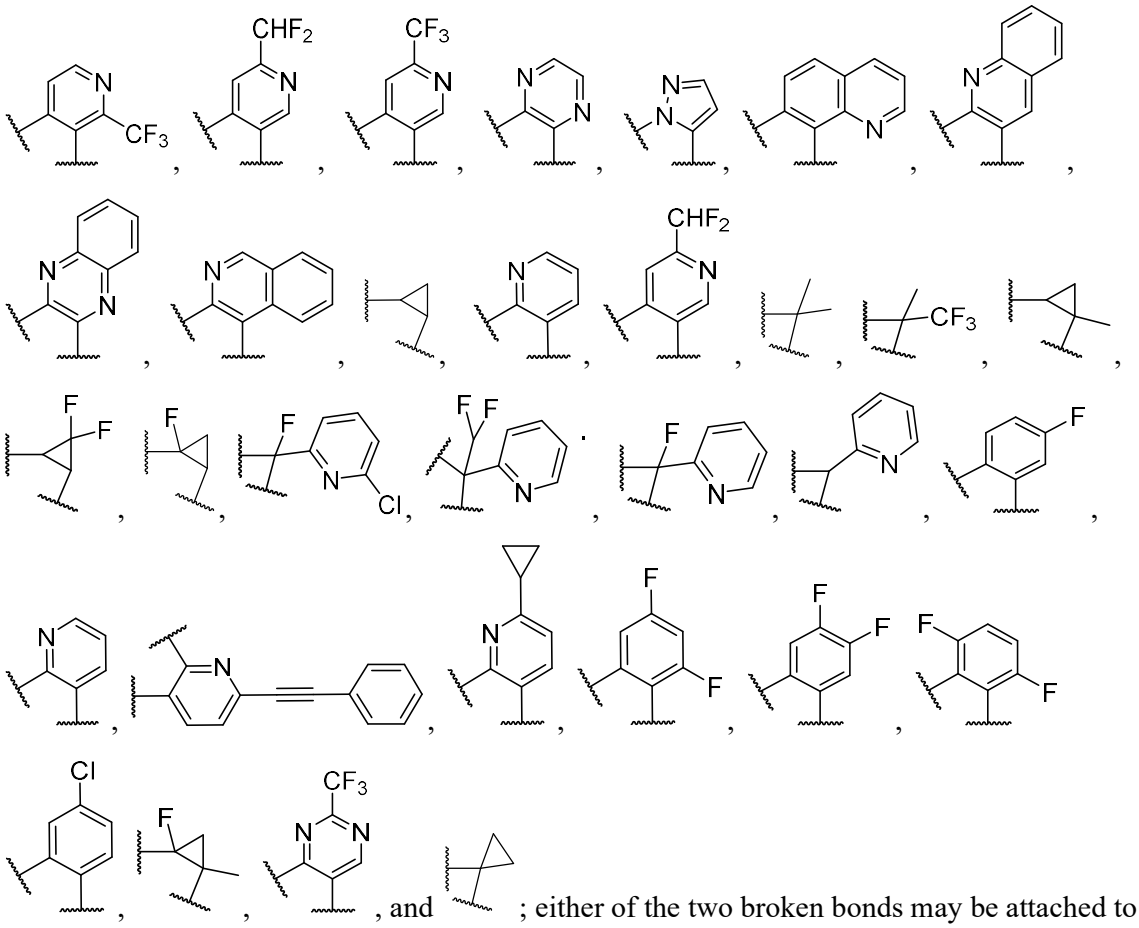
n is 0, 1, 2, or 3; and

q is 0, 1, or 2.

~~99~~14. The compound of any one of claims ~~95-98~~10-13, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein

L^4 is selected from the group consisting of



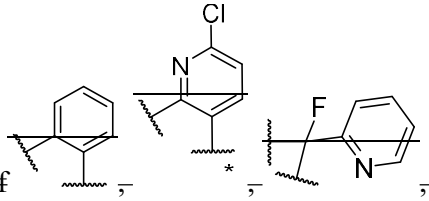
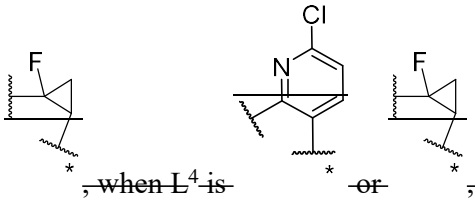


; either of the two broken bonds may be attached to L^5, or -CO- in -CO-NH-;

~~100. The compound of claim 98 or 99, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein~~

~~m3 is 0;~~

~~q is 1 or 2; and~~

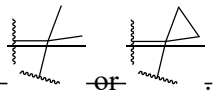
~~L^4 is selected from the group consisting of~~  ~~, and~~  ~~, when L^4 is~~ ~~or~~ ~~, the broken bond with * is attached to -CO- of -CO-NH-.~~

~~101. The compound of claim 98 or 99, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein~~

~~m3 is 1;~~

~~n is 0 or 2;~~

~~q is 1 or 2; and~~

~~L^4 is~~  ~~or~~ ~~.~~

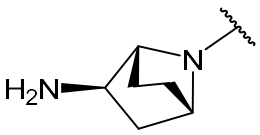
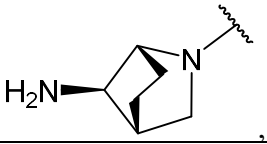
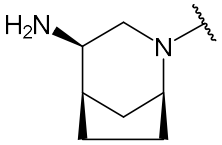
~~102. The compound of any one of claims 95-101, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein at least one Z^{12} is $-NH_2$.~~

~~103~~15. The compound of any one of claims ~~95-102~~10-14, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein

R^1 is hydrogen;

R^2 is fluoro, hydrogen or $-OCH_3$;

R^{3a} is $-CH_3$ or cyclopropyl; and

R^{16} is , , or .

~~104. The compound of any one of claims 95-103, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein R^2 is fluoro.~~

~~105. The compound of any one of claims 95-103, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein R^2 is hydrogen.~~

~~106. The compound of any one of claims 95-103, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein R^2 is $-OCH_3$.~~

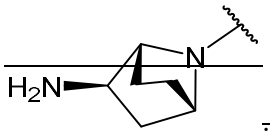
~~107. The compound of any one of claims 95-106, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein R^{3a} is $-CH_3$.~~

~~108. The compound of any one of claims 95-106, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein R^{3a} is cyclopropyl.~~

~~109. The compound of any one of claims 95-98 and 102-108, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein L^4 is C_{1-6}~~

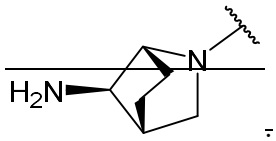
~~alkylene, optionally substituted with 1 to 3 substituents selected from the group consisting of halo, and pyridyl optionally substituted with 1-2 halo.~~

~~110. The compound of any one of claims 95-109, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein R^{16} is~~



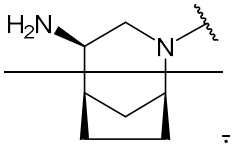
~~.~~

~~111. The compound of any one of claims 95-109, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein R^{16} is~~



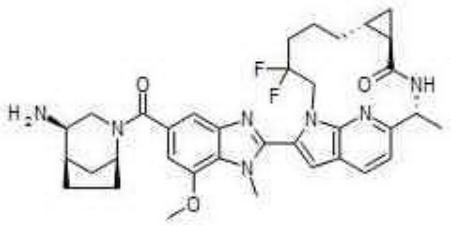
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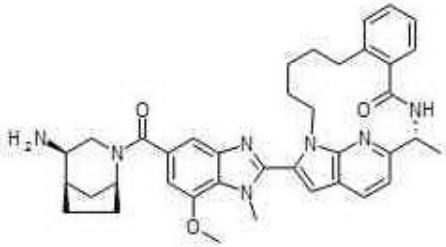
~~112. The compound of any one of claims 95-109, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, wherein R^{16} is~~

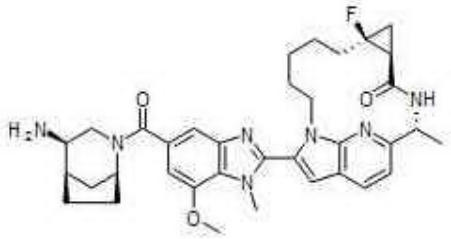
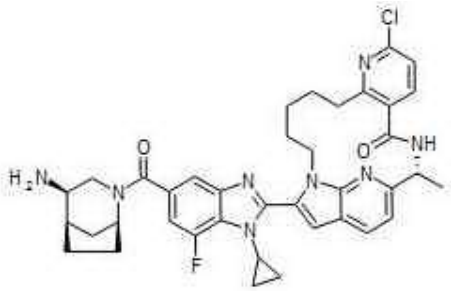


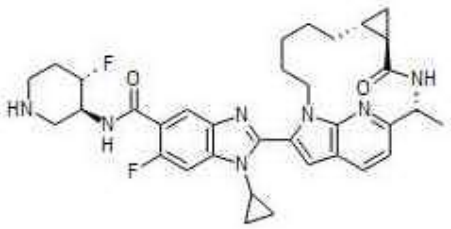
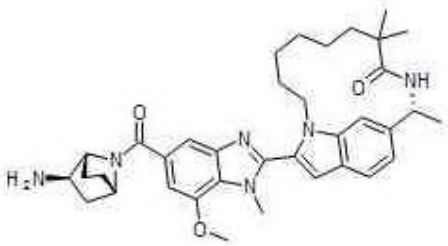
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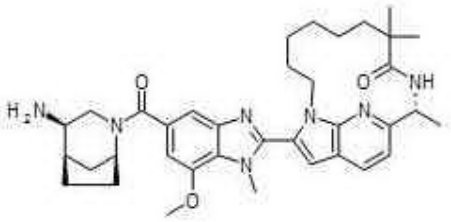
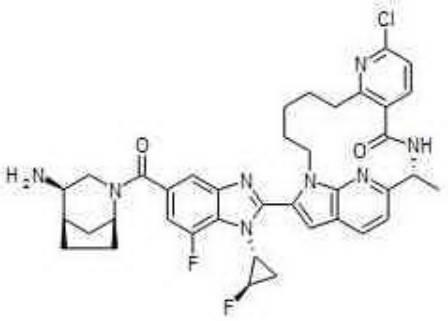
~~113~~16. A compound which is:

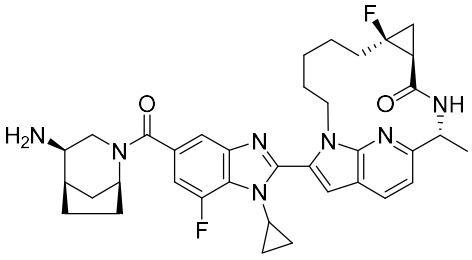
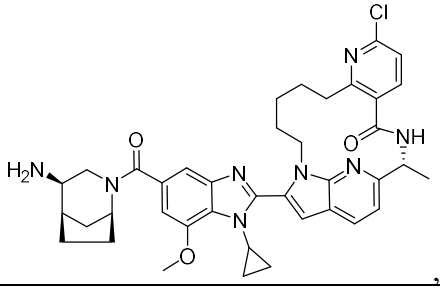


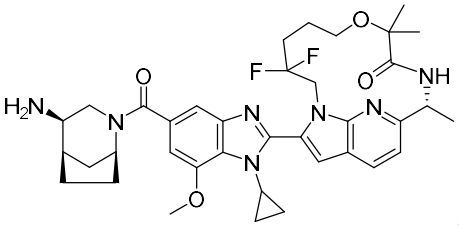
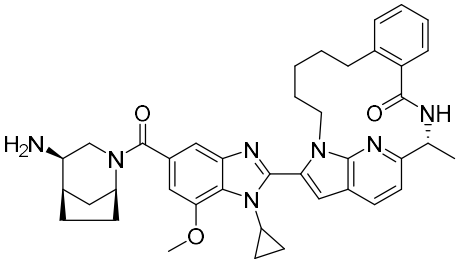
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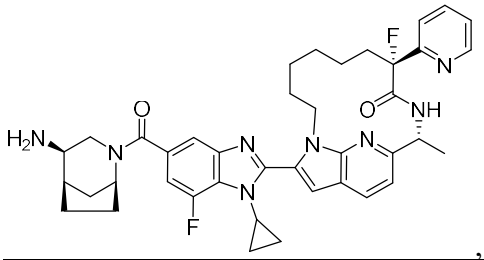
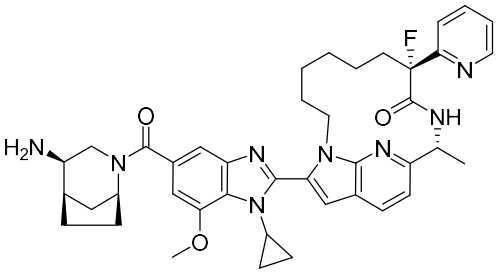
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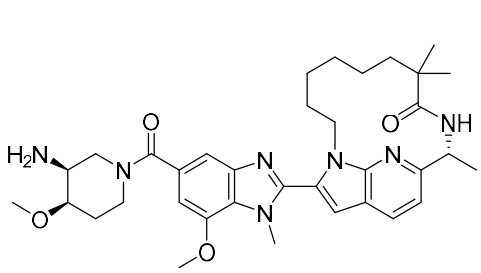
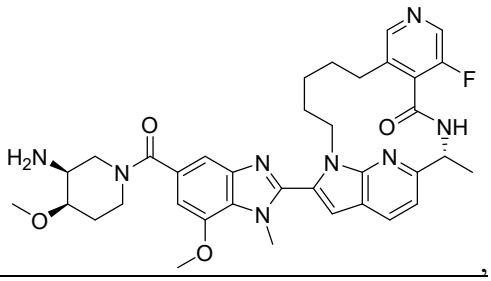

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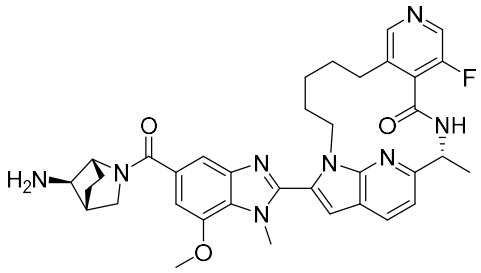
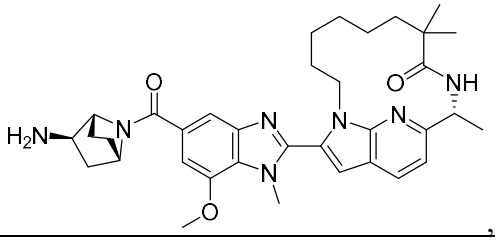

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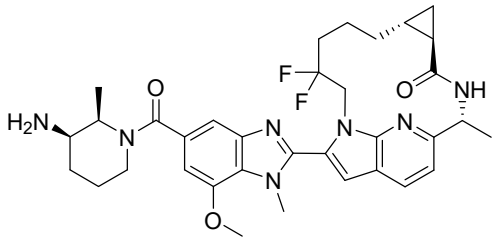
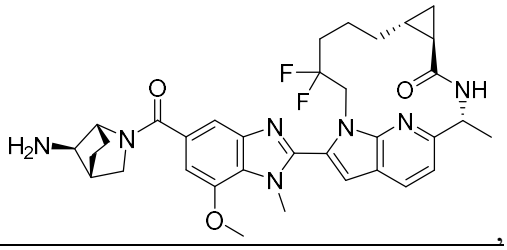

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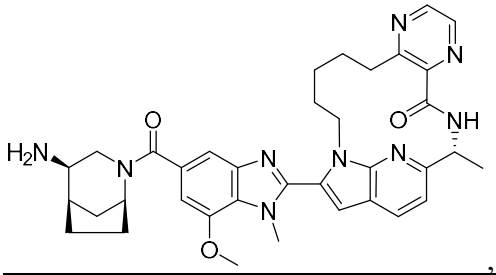

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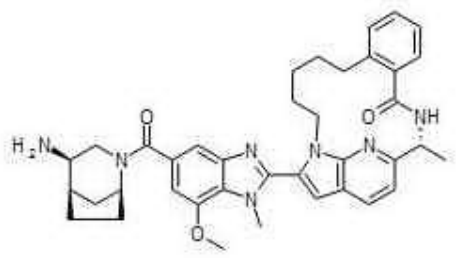
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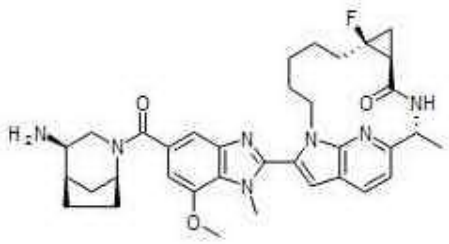
, or

or a pharmaceutically acceptable salt thereof.

~~114. A compound which is:~~

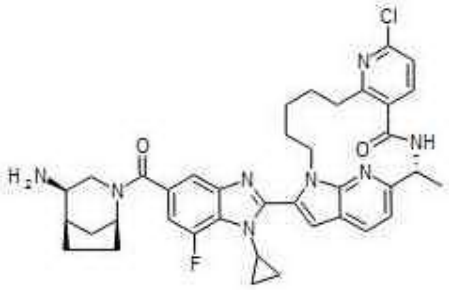
~~, or a pharmaceutically acceptable salt thereof.~~

~~115. A compound which is:~~



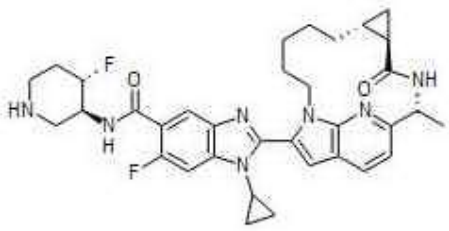
~~, or a pharmaceutically acceptable salt thereof.~~

~~116. A compound which is:~~



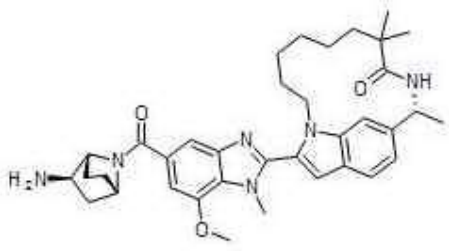
~~, or a pharmaceutically acceptable salt thereof.~~

~~117. A compound which is:~~



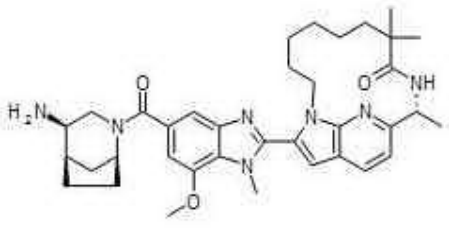
~~, or a pharmaceutically acceptable salt thereof.~~

~~118. A compound which is:~~



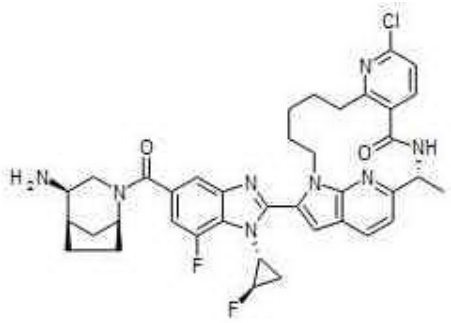
~~, or a pharmaceutically acceptable salt thereof.~~

~~119. A compound which is:~~



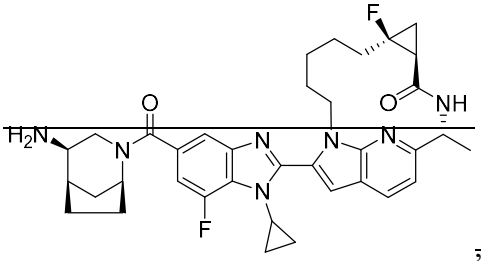
~~, or a pharmaceutically acceptable salt thereof.~~

~~120. A compound which is:~~



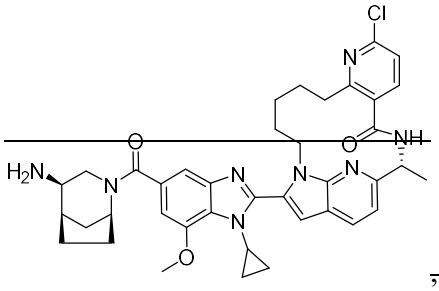
~~, or a pharmaceutically acceptable salt thereof.~~

~~121. A compound which is~~



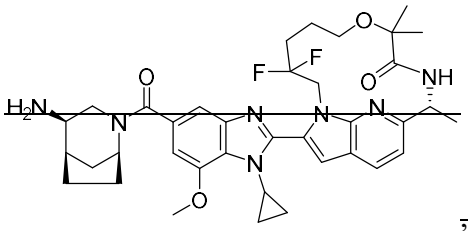
~~, or a pharmaceutically acceptable salt thereof.~~

~~122. A compound which is~~



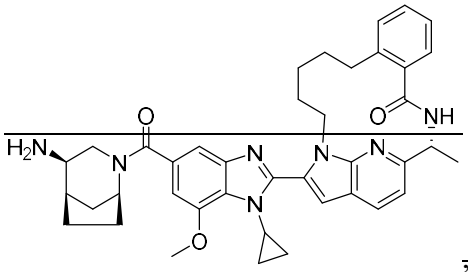
~~, or a pharmaceutically acceptable salt thereof.~~

~~123. A compound which is~~



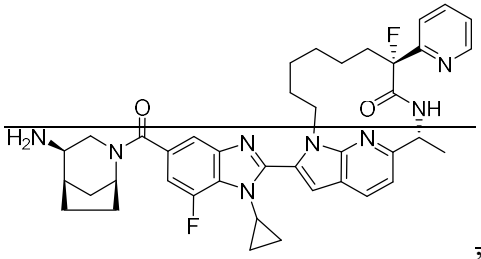
~~, or a pharmaceutically acceptable salt thereof.~~

~~124. A compound which is~~



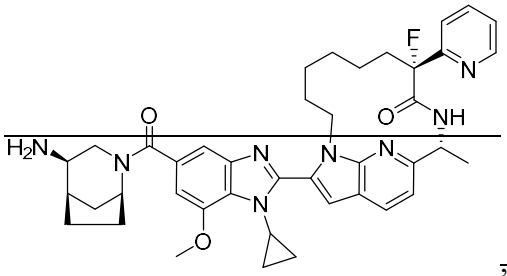
~~, or a pharmaceutically acceptable salt thereof.~~

~~125. A compound which is~~



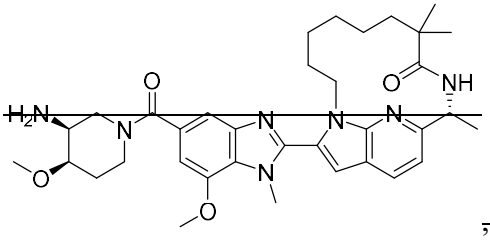
~~, or a pharmaceutically acceptable salt thereof.~~

~~126. A compound which is~~



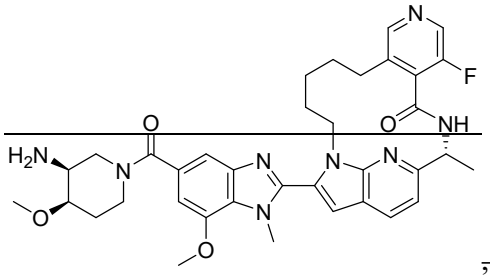
~~, or a pharmaceutically acceptable salt thereof.~~

~~127. A compound which is~~



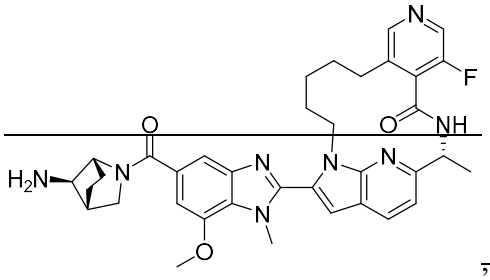
~~, or a pharmaceutically acceptable salt thereof.~~

~~128. A compound which is~~



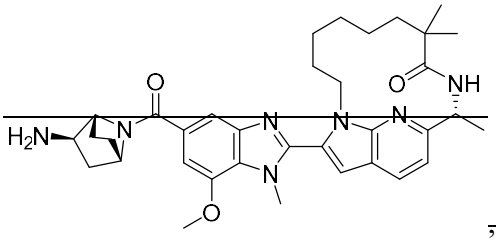
~~, or a pharmaceutically acceptable salt thereof.~~

~~129. A compound which is~~



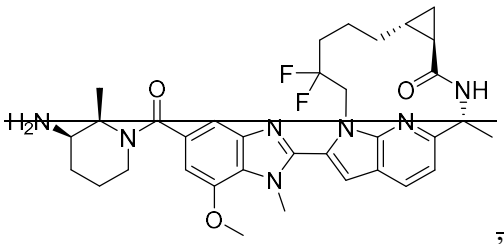
~~, or a pharmaceutically acceptable salt thereof.~~

~~130. A compound which is~~



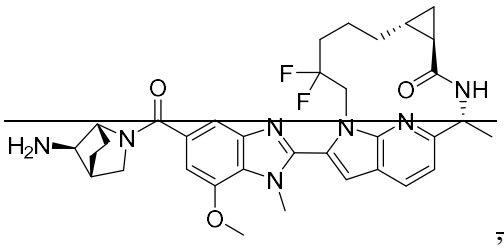
~~, or a pharmaceutically acceptable salt thereof.~~

~~131. A compound which is~~



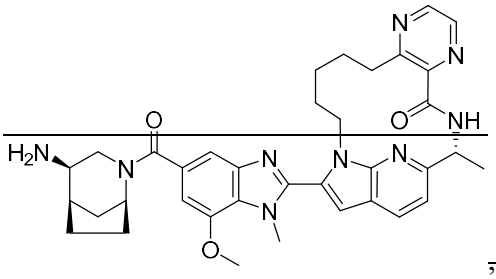
~~, or a pharmaceutically acceptable salt thereof.~~

~~132. A compound which is~~



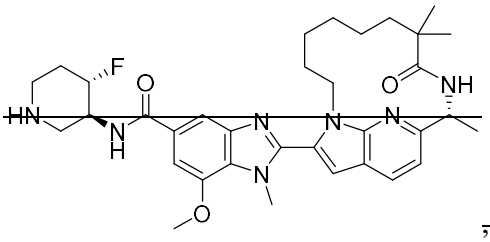
~~, or a pharmaceutically acceptable salt thereof.~~

~~133. A compound which is~~



~~, or a pharmaceutically acceptable salt thereof.~~

~~134. A compound which is~~



~~, or a pharmaceutically acceptable salt thereof.~~

~~135~~17. A compound as shown in Table 1 or Table 1A, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof.

~~136. A compound as shown in Table 1, or a pharmaceutically acceptable salt thereof.~~

~~137. A compound as shown in Table 1.~~

~~138. A compound as shown in Table 1A, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof.~~

~~139. A compound as shown in Table 1A, or a pharmaceutically acceptable salt thereof.~~

~~140. A compound as shown in Table 1A.~~

~~141~~18. The use of~~A~~ a pharmaceutical composition comprising a compound according to any one of claims 1-17 ~~-140~~ or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, and at least one pharmaceutically acceptable excipient for the manufacture of a medicament.

~~142. The pharmaceutical composition of claim 141, further comprising at least one additional therapeutic agent.~~

~~143. The pharmaceutical composition of claim 142, wherein the additional therapeutic agent is a Janus kinase inhibitor.~~

~~144. The pharmaceutical composition of claim 143, wherein the additional therapeutic agent is filgotinib, tofacitinib, baricitinib, or upadacitinib.~~

~~145. A method for inhibiting peptidylarginine deiminase type 4 (PAD4), comprising administering a therapeutically effective amount of a compound of any one of claims 1-140 or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, or a composition of any one of claims 141-144, to a patient in need thereof.~~

~~146. A method of treating a disease or disorder mediated by peptidylarginine deiminase type 4 (PAD4), comprising administering a therapeutically effective amount of a compound of any one of claims 1-140 or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, or a composition of any one of claims 141-144, to a patient in need thereof.~~

~~147. The method of claim 146, wherein the disease or disorder is acute lymphocytic leukemia, ankylosing spondylitis, cancer, chronic lymphocytic leukemia, colitis, lupus, systemic lupus erythematosus, cutaneous lupus erythematosus, rheumatoid arthritis, multiple sclerosis, or ulcerative colitis.~~

~~148~~19. ~~A method~~The use ~~pharmaceutical composition~~ of claim 18 wherein, the medicament is used for treating inflammatory bowel disease, acute lymphocytic leukemia, ankylosing spondylitis, cancer, chronic lymphocytic leukemia, colitis, lupus, systemic lupus erythematosus, cutaneous lupus erythematosus, rheumatoid arthritis, multiple sclerosis, or ulcerative colitis~~, comprising administering a therapeutically effective amount of a compound of any one of claims 1-140 or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, or a composition of any one of claims 141-144, to a patient in need thereof~~.

~~149. A method for treating anti-neutrophil cytoplasm antibodies (ANCA) vasculitis, antiphospholipid syndrome, psoriasis, lung inflammatory diseases, interstitial lung disease (ILD), idiopathic pulmonary fibrosis (IPF), acute lung injury (ALI), acute respiratory distress syndrome (ARDS), chronic obstructive pulmonary disease (COPD), cystic fibrosis (CF), or COVID-19 ARDS comprising administering a therapeutically effective amount of a compound of any one of claims 1-140 or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, or a composition of any one of claims 141-144, to a patient in need thereof.~~

~~150. A compound according to any one of claims 1-140 or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, for use in therapy.~~

~~151~~20. A compound according to any one of claims 1-~~140~~ 17 or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, for use in the manufacture of a medicament for treating rheumatoid arthritis.

~~152. A compound according to any one of claims 1-140 or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, and at least one additional therapeutic agent selected from the group consisting of filgotinib, tofacitinib, baricitinib, and upadacitinib for use in the manufacture of a medicament for treating rheumatoid arthritis.~~

~~153. A kit for treating rheumatoid arthritis or a disease or condition that is amenable to treatment by inhibiting peptidylarginine deiminase type 4 (PAD4) in a patient in need thereof, comprising:~~

~~a) a compound according to any of claims 1-140, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof;~~

~~b) an additional therapeutic agent; and optionally~~

~~c) a label or instructions for use.~~