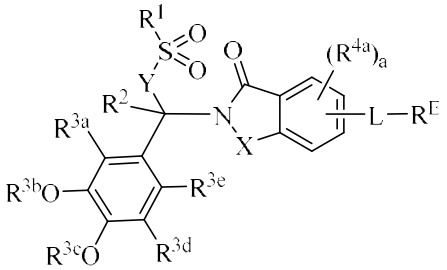
Claims

1. A compound of Formula (I):



(I)

or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein:

L is a linker;

X is $–CH_2–$ or –C(O)–;

Y is C_{1-6} alkylene or C_{3-10} cycloalkylene;

R^E is an E3 ubiquitin ligase binding moiety;

R^1 is (i) C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl; or (ii) $–OR^{1a}$ or $–NR^{1b}R^{1c}$;

R^2 is hydrogen or deuterium;

R^{3a}, R^{3d}, and R^{3e} are each independently (i) hydrogen, deuterium, cyano, halo, or nitro; (ii) C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl; or (iii) $–C(O)R^{1a}$, $–C(O)OR^{1a}$, $–C(O)NR^{1b}R^{1c}$, $–C(O)SR^{1a}$, $–C(NR^{1a})NR^{1b}R^{1c}$, $–C(S)R^{1a}$, $–C(S)OR^{1a}$, $–C(S)NR^{1b}R^{1c}$, $–OR^{1a}$, $–OC(O)R^{1a}$, $–OC(O)OR^{1a}$, $–OC(O)NR^{1b}R^{1c}$, $–OC(O)SR^{1a}$, $–OC(NR^{1a})NR^{1b}R^{1c}$, $–OC(S)R^{1a}$, $–OC(S)OR^{1a}$, $–OC(S)NR^{1b}R^{1c}$, $–OS(O)R^{1a}$, $–OS(O)_2R^{1a}$, $–OS(O)NR^{1b}R^{1c}$, $–OS(O)_2NR^{1b}R^{1c}$, $–NR^{1b}R^{1c}$, $–NR^{1a}C(O)R^{1d}$, $–NR^{1a}C(O)OR^{1d}$, $–NR^{1a}C(O)NR^{1b}R^{1c}$, $–NR^{1a}C(O)SR^{1d}$, $–NR^{1a}C(NR^{1d})NR^{1b}R^{1c}$, $–NR^{1a}C(S)R^{1d}$, $–NR^{1a}C(S)OR^{1d}$, $–NR^{1a}C(S)NR^{1b}R^{1c}$, $–NR^{1a}S(O)R^{1d}$, $–NR^{1a}S(O)_2R^{1d}$, $–NR^{1a}S(O)NR^{1b}R^{1c}$, $–NR^{1a}S(O)_2NR^{1b}R^{1c}$, $–SR^{1a}$, $–S(O)R^{1a}$, $–S(O)_2R^{1a}$, $–S(O)NR^{1b}R^{1c}$, or $–S(O)_2NR^{1b}R^{1c}$;

R^{3b} and R^{3c} are each independently C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl;

each R^{4a} is independently (i) deuterium, cyano, halo, or nitro; (ii) C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl; or (iii) $–C(O)R^{1a}$, $–C(O)OR^{1a}$, $–C(O)NR^{1b}R^{1c}$, $–C(O)SR^{1a}$, $–C(NR^{1a})NR^{1b}R^{1c}$, $–C(S)R^{1a}$, $–C(S)OR^{1a}$, $–C(S)NR^{1b}R^{1c}$, $–OR^{1a}$, $–OC(O)R^{1a}$, $–OC(O)OR^{1a}$, $–OC(O)NR^{1b}R^{1c}$, $–OC(O)SR^{1a}$, $–OC(NR^{1a})NR^{1b}R^{1c}$, $–OC(S)R^{1a}$, $–OC(S)OR^{1a}$, $–OC(S)NR^{1b}R^{1c}$, $–OS(O)R^{1a}$, $–OS(O)_2R^{1a}$, $–OS(O)NR^{1b}R^{1c}$, $–OS(O)_2NR^{1b}R^{1c}$, $–NR^{1b}R^{1c}$, $–NR^{1a}C(O)R^{1d}$, $–NR^{1a}C(O)OR^{1d}$, $–NR^{1a}C(O)NR^{1b}R^{1c}$, $–NR^{1a}C(O)SR^{1d}$, $–NR^{1a}C(NR^{1d})NR^{1b}R^{1c}$, $–NR^{1a}C(S)R^{1d}$, $–NR^{1a}C(S)OR^{1d}$, $–NR^{1a}C(S)NR^{1b}R^{1c}$, $–NR^{1a}S(O)R^{1d}$, $–NR^{1a}S(O)_2R^{1d}$, $–NR^{1a}S(O)NR^{1b}R^{1c}$, $–NR^{1a}S(O)_2NR^{1b}R^{1c}$, $–SR^{1a}$, $–S(O)R^{1a}$, $–S(O)_2R^{1a}$, $–S(O)NR^{1b}R^{1c}$, or $–S(O)_2NR^{1b}R^{1c}$; and R^4 is hydrogen or R^{4a};

each R^{1a}, R^{1b}, R^{1c}, and R^{1d} is independently hydrogen, deuterium, C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl; and

a is an integer of 0, 1, 2, 3, or 4;

wherein each alkyl, alkylene, heteroalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylene, aryl, aralkyl, heteroaryl, and heterocyclyl is optionally substituted with one or more~~, in one embodiment, one, two, three, or four,~~ substituents Q, wherein each Q is independently selected from: (a) deuterium, cyano, halo, imino, nitro, and oxo; (b) C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, and heterocyclyl, each of which is further optionally substituted with one or more~~, in one embodiment, one, two, three, or four,~~ substituents Q^a; and (c) $–C(O)R^a$, $–C(O)OR^a$, $–C(O)NR^bR^c$, $–C(O)SR^a$, $–C(NR^a)NR^bR^c$, $–C(S)R^a$, $–C(S)OR^a$, $–C(S)NR^bR^c$, $–OR^a$, $–OC(O)R^a$, $–OC(O)OR^a$, $–OC(O)NR^bR^c$, $–OC(O)SR^a$, $–OC(NR^a)NR^bR^c$, $–OC(S)R^a$, $–OC(S)OR^a$, $–OC(S)NR^bR^c$, $–OP(O)(OR^a)OR^d$, $–OS(O)R^a$, $–OS(O)_2R^a$, $–OS(O)NR^bR^c$, $–OS(O)_2NR^bR^c$, $–NR^bR^c$, $–NR^aC(O)R^d$, $–NR^aC(O)OR^d$, $–NR^aC(O)NR^bR^c$, $–NR^aC(O)SR^d$, $–NR^aC(NR^d)NR^bR^c$, $–NR^aC(S)R^d$, $–NR^aC(S)OR^d$, $–NR^aC(S)NR^bR^c$, $–NR^aS(O)R^d$, $–NR^aS(O)_2R^d$, $–NR^aS(O)NR^bR^c$, $–NR^aS(O)_2NR^bR^c$, $–SR^a$, $–S(O)R^a$, $–S(O)_2R^a$, $–S(O)NR^bR^c$, and $–S(O)_2NR^bR^c$, wherein each R^a, R^b, R^c, and R^d is independently (i) hydrogen or deuterium; (ii) C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl, each of which is optionally substituted with one or more~~, in one embodiment, one, two, three, or four,~~

substituents Q^a; or (iii) R^b and R^c together with the N atom to which they are attached form heterocyclyl, optionally substituted with one or more~~, in one embodiment, one, two, three, or four,~~ substituents Q^a;

wherein each Q^a is independently selected from: (a) deuterium, cyano, halo, nitro, imino, and oxo; (b) C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, and heterocyclyl; and (c) $–C(O)R^e$, $–C(O)OR^e$, $–C(O)NR^fR^g$, $–C(O)SR^e$, $–C(NR^e)NR^fR^g$, $–C(S)R^e$, $–C(S)OR^e$, $–C(S)NR^fR^g$, $–OR^e$, $–OC(O)R^e$, $–OC(O)OR^e$, $–OC(O)NR^fR^g$, $–OC(O)SR^e$, $–OC(NR^e)NR^fR^g$, $–OC(S)R^e$, $–OC(S)OR^e$, $–OC(S)NR^fR^g$, $–OP(O)(OR^f)OR^g$, $–OS(O)R^e$, $–OS(O)_2R^e$, $–OS(O)NR^fR^g$, $–OS(O)_2NR^fR^g$, $–NR^fR^g$, $–NR^eC(O)R^h$, $–NR^eC(O)OR^f$, $–NR^eC(O)NR^fR^g$, $–NR^eC(O)SR^f$, $–NR^eC(NR^h)NR^fR^g$, $–NR^eC(S)R^h$, $–NR^eC(S)OR^f$, $–NR^eC(S)NR^fR^g$, $–NR^eS(O)R^h$, $–NR^eS(O)_2R^h$, $–NR^eS(O)NR^fR^g$, $–NR^eS(O)_2NR^fR^g$, $–SR^e$, $–S(O)R^e$, $–S(O)_2R^e$, $–S(O)NR^fR^g$, and $–S(O)_2NR^fR^g$; wherein each R^e, R^f, R^g, and R^h is independently (i) hydrogen or deuterium; (ii) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl; or (iii) R^f and R^g together with the N atom to which they are attached form heterocyclyl.

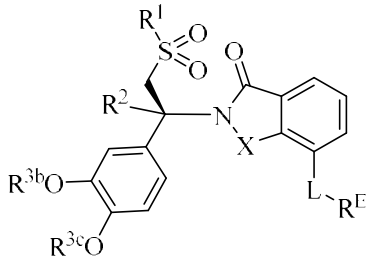
2. The compound of claim 1, wherein Y is C_{1-6} alkylene, optionally substituted with one or more substituents Q~~.~~;

~~3. The compound of claim 1 or 2, wherein~~ and/or R^{3a} is hydrogen~~.~~;

~~4. The compound of any one of claims 1 to 3, wherein~~ and/or R^{3d} is hydrogen~~.~~;

~~5. The compound of any one of claims 1 to 4, wherein~~ and/or R^{3e} is hydrogen.

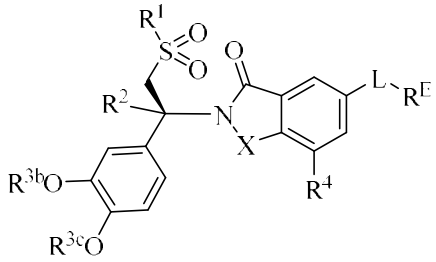
~~6~~3. The compound of ~~any one of claims 1 to 5~~ claims 1 or 2, having the structure of Formula (IV):



(IV)

or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof~~.~~; or

~~7. The compound of any one of claims 1 to 5,~~ having the structure of Formula (VI):



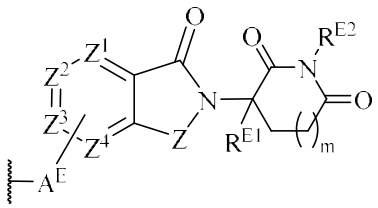
(VI)

or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

~~8~~4. The compound of any one of claims 1 to ~~7~~3, wherein R^E is a moiety of a cereblon (CRBN) E3 ligand, an inhibitors-of-apoptosis protein (IAP) E3 ligand, a mouse double minute 2 homolog (MDM2) E3 ligand, or a von Hippel-Lindau (VHL) E3 ligand.

~~9. The compound of any one of claims 1 to 8, wherein R^E is a moiety of a cereblon (CRBN) E3 ligand.~~

~~10~~5. The compound of any one of claims 1 to ~~9~~4, wherein R^E is a moiety having the structure of Formula (EC-I):



(EC-I)

or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; wherein:

A^E is a bond, –O–, –N(R^{1b})–, –S–, C_{1-6} alkylene, C_{1-6} heteroalkylene, C_{2-6} alkenylene, C_{2-6} heteroalkenylene, C_{2-6} alkynylene, C_{2-6} heteroalkynylene, C_{3-10} cycloalkylene, C_{6-14} arylene, C_{7-15} aralkylene, heteroarylene, heterocyclylene, C_{1-6} heteroalkylene-C_{6-14} arylene, or C_{2-6} alkynylene-heterocyclylene;

Z is $–CH_2–$ or –C(O)–;

one of Z^1, Z^2, Z^3, and Z^4 is –C= and the remaining three of Z^1, Z^2, Z^3, and Z^4 are each independently –C(R^{E5})=; or Z^1 is a bond, one of Z^2, Z^3, and Z^4 is –C=, and the remaining two of Z^2, Z^3, and Z^4 are each independently –C(R^{E5})= or –S–;

m is an integer of 0, 1, or 2;

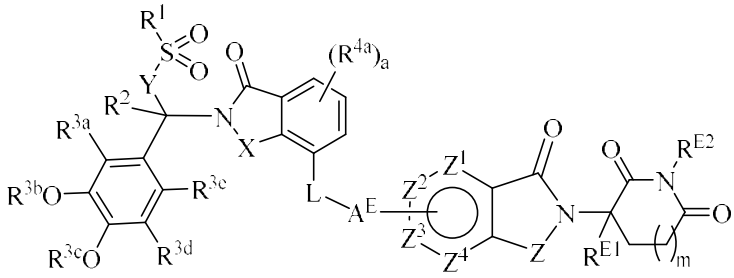
R^{E1} is hydrogen, deuterium, halo, or C_{1-6} alkyl;

R^{E2} is hydrogen or C_{1-6} alkyl; and

each R^{E4} is independently (i) deuterium, cyano, halo, or nitro; (ii) C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl; or (iii) –C(O)R^{1a}, –C(O)OR^{1a}, –C(O)N$R^{1b}R^{1c}$, –C(O)SR^{1a}, –C(NR^{1a})N$R^{1b}R^{1c}$, –C(S)R^{1a}, –C(S)OR^{1a}, –C(S)N$R^{1b}R^{1c}$, –OR^{1a}, –OC(O)R^{1a}, –OC(O)OR^{1a}, –OC(O)N$R^{1b}R^{1c}$, –OC(O)SR^{1a}, –OC(NR^{1a})N$R^{1b}R^{1c}$, –OC(S)R^{1a}, –OC(S)OR^{1a}, –OC(S)N$R^{1b}R^{1c}$, –OS(O)R^{1a}, –$OS(O)_2R^{1a}$, –OS(O)N$R^{1b}R^{1c}$, –$OS(O)_2$N$R^{1b}R^{1c}$, –N$R^{1b}R^{1c}$, –NR^{1a}C(O)R^{1d}, –NR^{1a}C(O)OR^{1d}, –NR^{1a}C(O)N$R^{1b}R^{1c}$, –NR^{1a}C(O)SR^{1d}, –NR^{1a}C(NR^{1d})N$R^{1b}R^{1c}$, –NR^{1a}C(S)R^{1d}, –NR^{1a}C(S)OR^{1d}, –NR^{1a}C(S)N$R^{1b}R^{1c}$, –NR^{1a}S(O)R^{1d}, –N$R^{1a}$$S(O)_2R^{1d}$, –N$R^{1a}$S(O)N$R^{1b}R^{1c}$, –N$R^{1a}$$S(O)_2NR^{1b}R^{1c}$, –S$R^{1a}$, –S(O)$R^{1a}$, –$S(O)_2R^{1a}$, –S(O)N$R^{1b}R^{1c}$, or –$S(O)_2NR^{1b}R^{1c}$; and each R^{E5} is independently hydrogen or R^{E4};

wherein each alkyl, alkylene, heteroalkyl, heteroalkylene, alkenyl, alkenylene, heteroalkenylene, alkynyl, alkynylene, heteroalkynylene, cycloalkyl, cycloalkylene, aryl, arylene, aralkyl, aralkylene, heteroaryl, heteroarylene, heterocyclyl, and heterocyclylene is optionally substituted with one or more~~, in one embodiment, one, two, three, or four,~~ substituents Q.

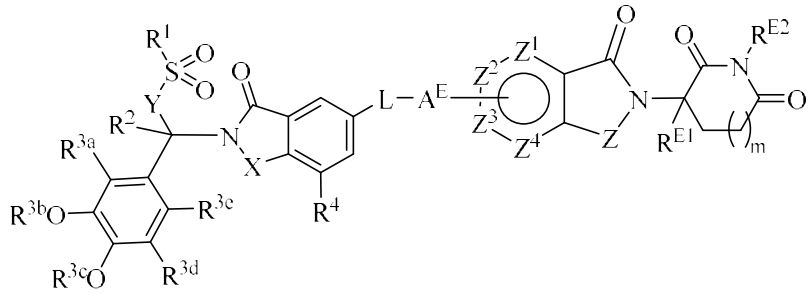
~~11~~6. The compound of claim ~~10~~5, having the structure of Formula (IX):



(IX)

or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof~~.~~; or

having the structure of Formula (XV):



(XV)

or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

~~12~~7. The compound of claim ~~10~~ 5 or ~~11~~6, wherein m is an integer of 1~~.~~; and/or

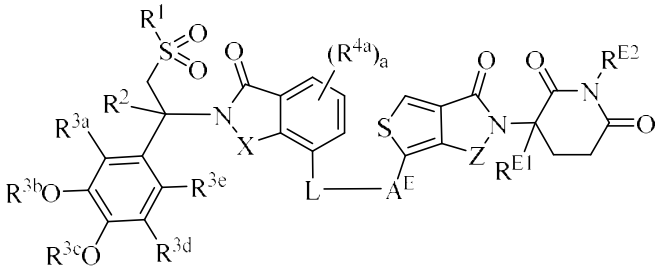
~~13. The compound of any one of claims 10 to 12,~~ wherein Z^1 is a bond~~.~~; and/or

~~14. The compound of any one of claims 10 to 13,~~ wherein Z^2 is S~~.~~; or

~~15. The compound of any one of claims 10 to 13, wherein~~ Z^3 is S~~.~~; or

~~16. The compound of any one of claims 10 to 13, wherein~~ Z^4 is S.

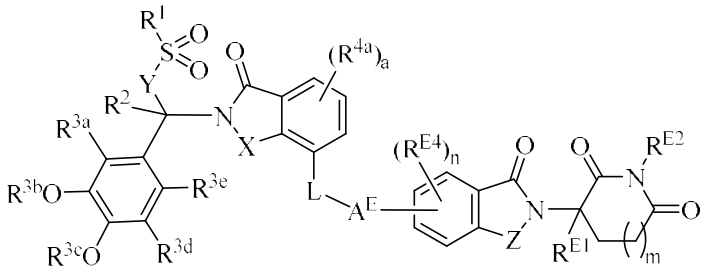
~~17~~8. The compound of claim ~~11~~ 6 or ~~15~~7, having the structure of Formula (X):



(X)

or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof~~.~~; or

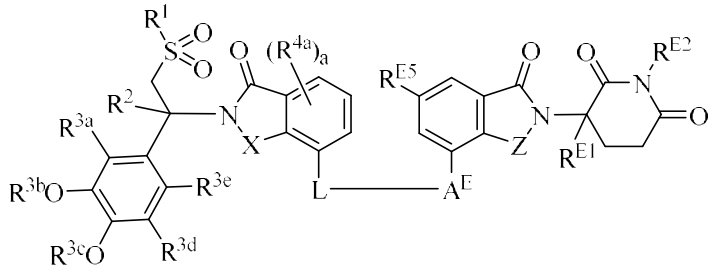
~~18. The compound of claim 11,~~ having the structure of Formula (XXI):



(XXI)

or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof~~.~~; or

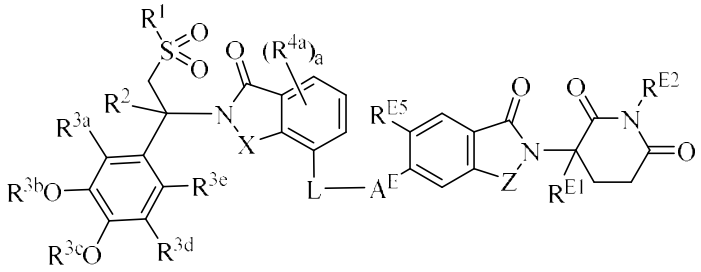
~~19. The compound of claim 11 or 18,~~ having the structure of Formula (XXII):



(XXII)

or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof~~.~~; optionally wherein R^{E5} is hydrogen, halo, or fluoro; or

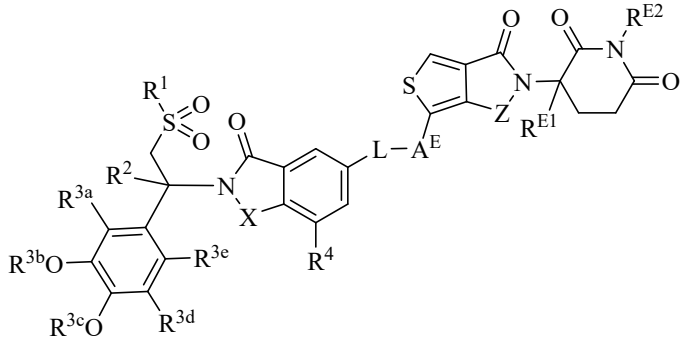
~~20. The compound of claim 11 or 18,~~ having the structure of Formula (XXVII):



(XXVII)

or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof~~.~~; optionally wherein R^{E5} is hydrogen, halo, or fluoro; or

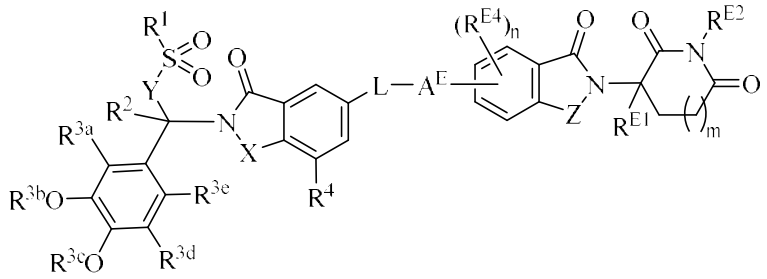
having the structure of Formula (XVI):



(XVI)

or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; or

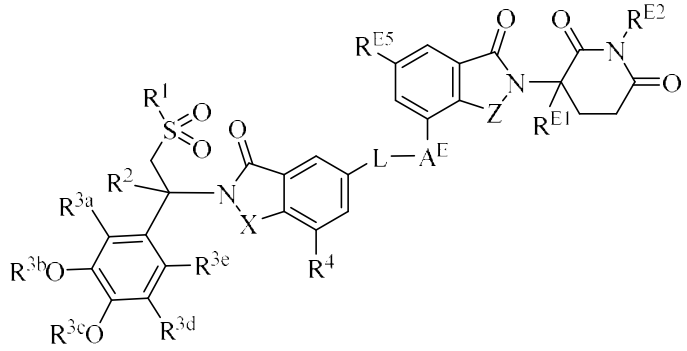
having the structure of Formula (XXXII):



(XXXII)

or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; or

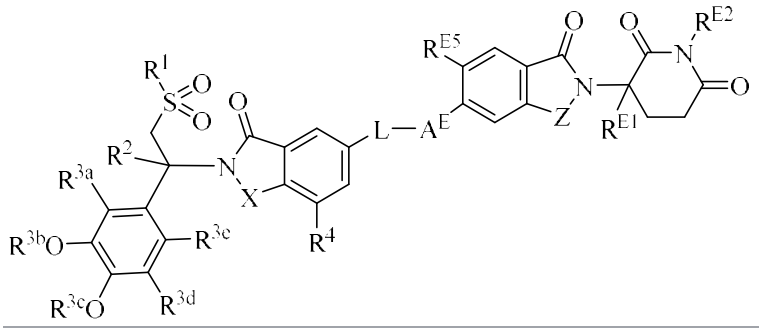
having the structure of Formula (XXXIII):



(XXXIII)

or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; optionally wherein R^{E5} is hydrogen, halo, or fluoro; or

having the structure of Formula (XXXVIII):



(XXXVIII)

or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; optionally wherein R^{E5} is hydrogen, halo, or fluoro.

~~219~~. The compound of any one of claims ~~1~~ 5 to ~~208~~, wherein X is $–CH_2–$~~.~~; or

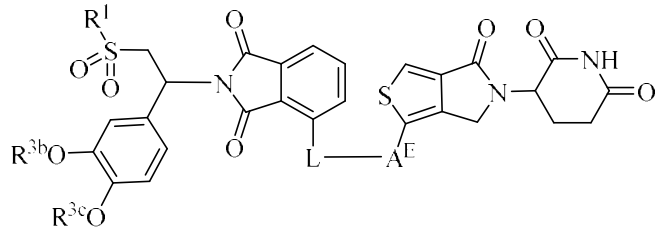
~~22. The compound of any one of claims 1 to 20,~~ wherein X is –C(O)–~~.~~; and/or

~~23. The compound of any one of claims 1 to 22,~~ wherein R^2 is hydrogen~~.~~; and/or

~~24. The compound of any one of claims 10 to 23,~~ wherein Z is $–CH_2–$~~.~~; or

~~25. The compound of any one of claims 10 to 23,~~ wherein Z is –C(O)–.

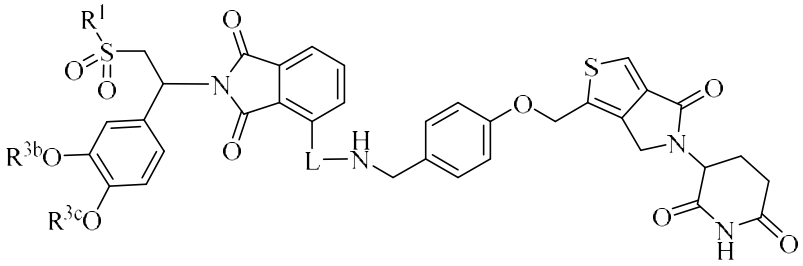
~~2610~~. The compound of claim ~~178~~, having the structure of Formula (XI):



(XI)

or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof~~.~~; or

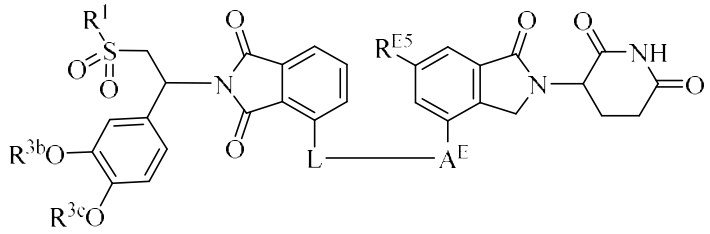
~~27. The compound of claim 26,~~ having the structure of Formula (XIII):



(XIII)

or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof~~.~~; or

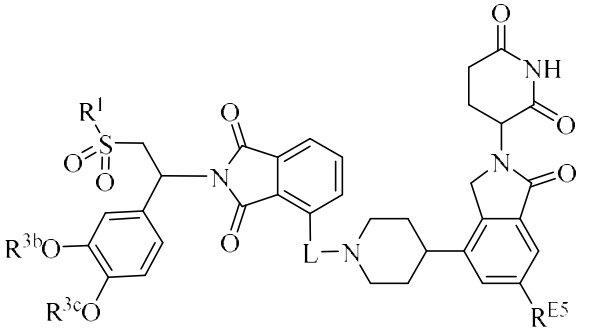
~~28. The compound of claim 18 or 19,~~ having the structure of Formula (XXIII):



(XXIII)

or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof~~.~~; optionally wherein R^{E5} is hydrogen, halo, or fluoro; or

~~29. The compound of claim 28,~~ having the structure of Formula (XXV):

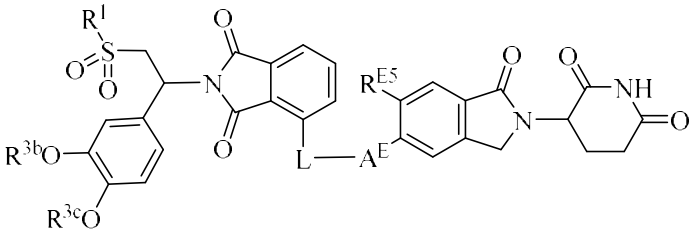


(XXV)

or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof~~.~~; optionally wherein R^{E5}

is hydrogen, halo, or fluoro; or

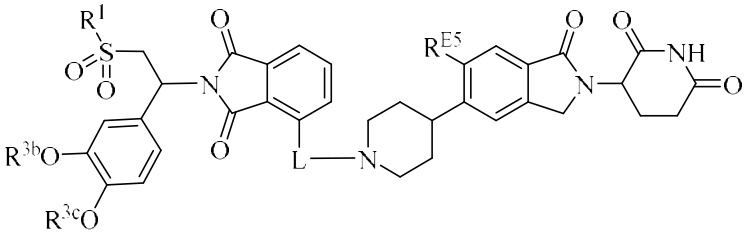
30. The compound of claim 18 or 20, having the structure of Formula (XXVIII):



(XXVIII)

or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.; optionally wherein R^{E5} is hydrogen, halo, or fluoro; or

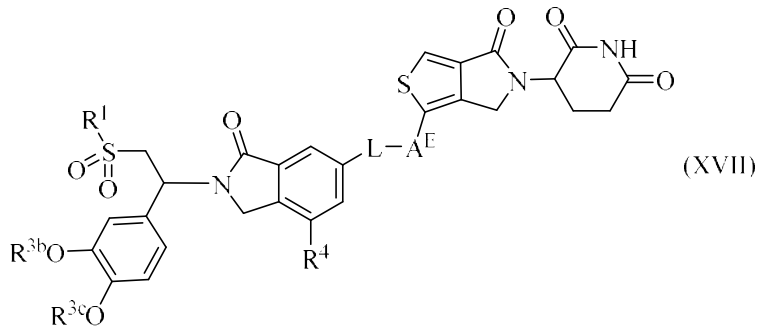
31. The compound of claim 30, having the structure of Formula (XXX):



(XXX)

or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.; optionally wherein R^{E5} is hydrogen, halo, or fluoro; or

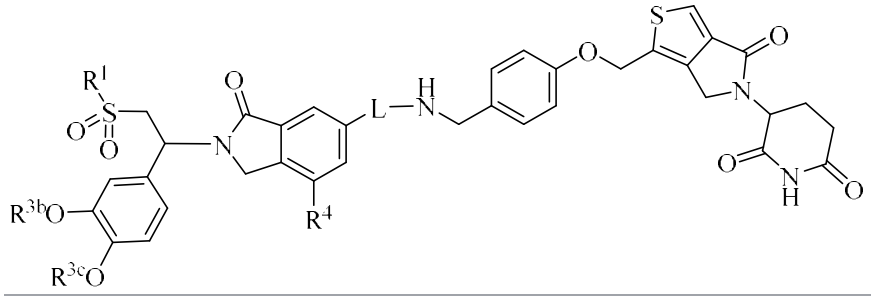
having the structure of Formula (XVII):



(XVII)

or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; or

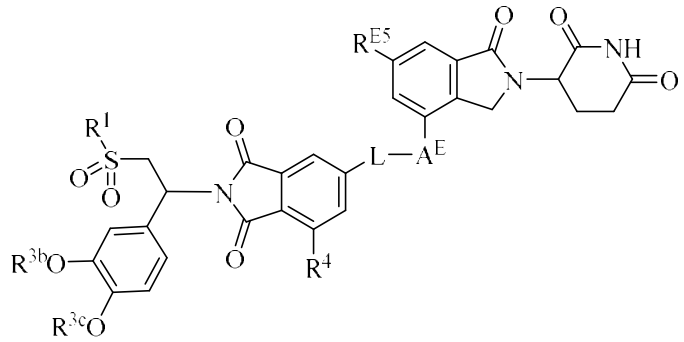
having the structure of Formula (XIX):



(XIX)

or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; or

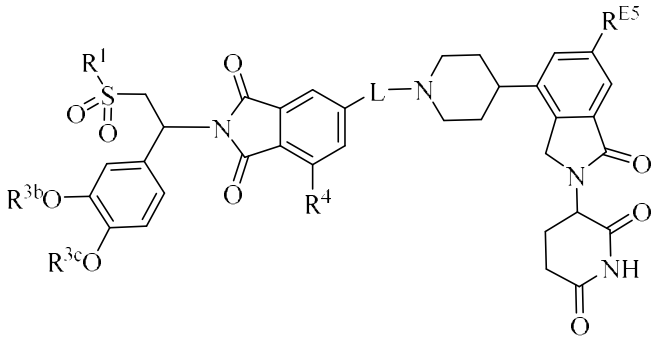
having the structure of Formula (XXXIV):



(XXXIV)

or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; optionally wherein R^{E5} is hydrogen, halo, or fluoro; or

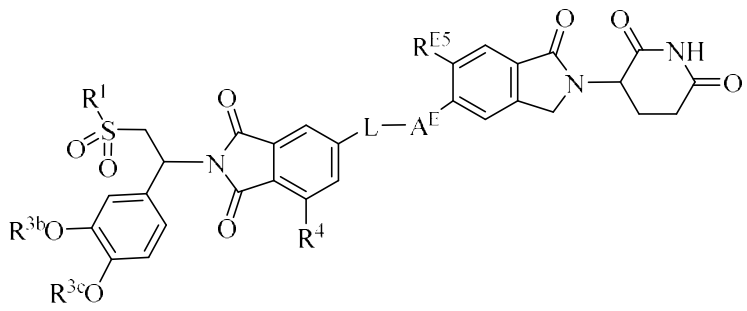
having the structure of Formula (XXXVI):



(XXXVI)

or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; optionally wherein R^{E5} is hydrogen, halo, or fluoro; or

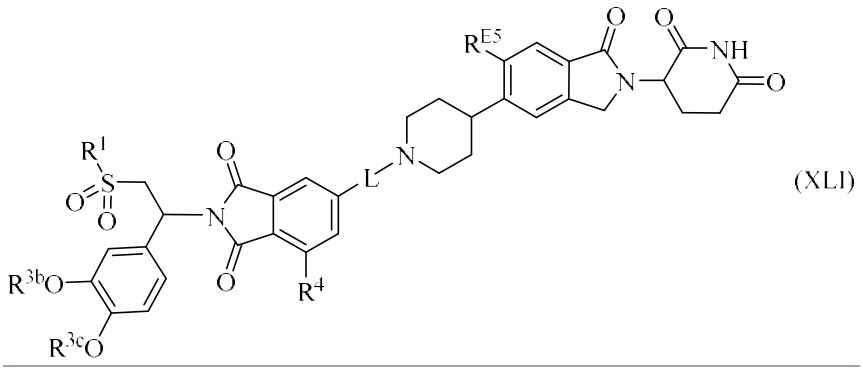
having the structure of Formula (XXXIX):



(XXXIX)

or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; optionally wherein R^{E5} is hydrogen, halo, or fluoro; or

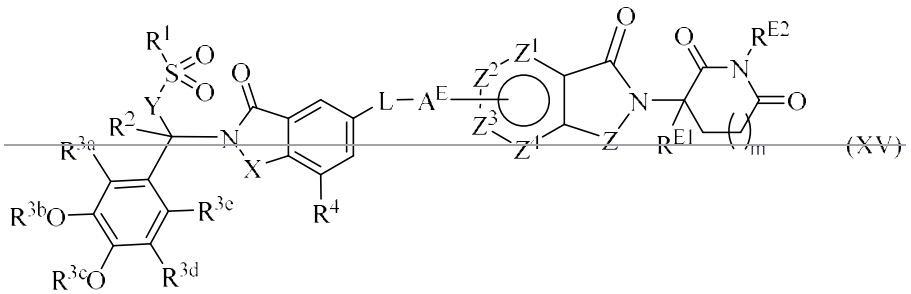
having the structure of Formula (XLI):



(XLI)

or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; optionally wherein R^{E5} is hydrogen, halo, or fluoro.

~~32. The compound of claim 10, having the structure of Formula (XV):~~



(XV)

~~or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.~~

~~33. The compound of claim 32, wherein m is an integer of 1.~~

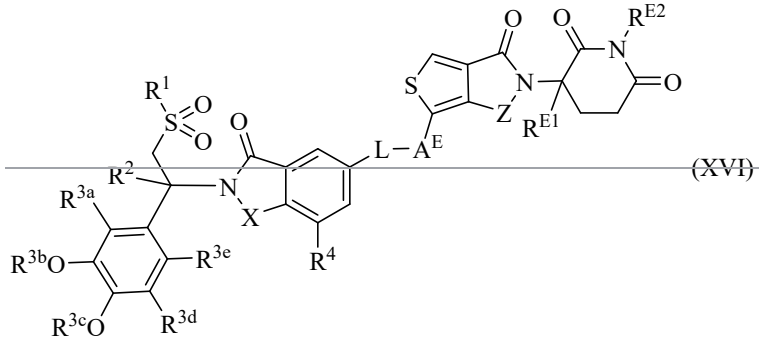
~~34. The compound of claim 32 or 33, wherein Z^1 is a bond.~~

~~35. The compound of any one of claims 32 to 34, wherein Z^2 is S.~~

~~36. The compound of any one of claims 32 to 34, wherein Z^3 is S.~~

~~37. The compound of any one of claims 32 to 34, wherein Z^4 is S.~~

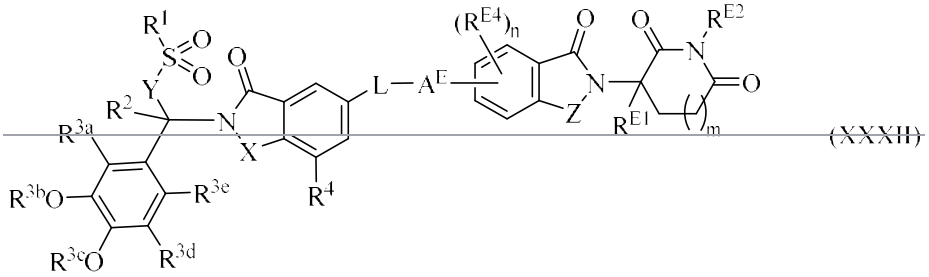
38. The compound of claim 32 or 36, having the structure of Formula (XVI):



(XVI)

or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

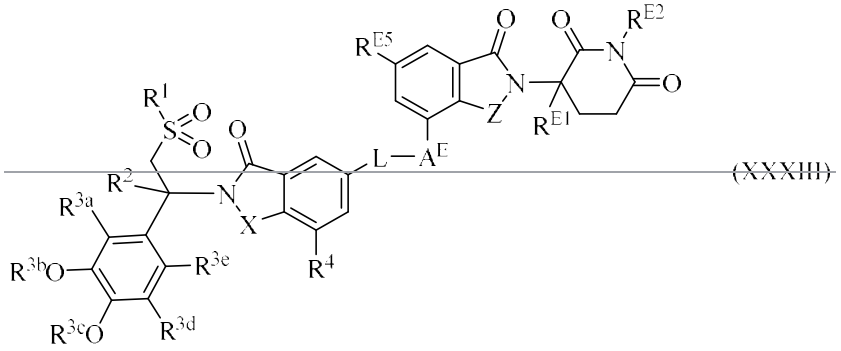
39. The compound of claim 32, having the structure of Formula (XXXII):



(XXXII)

or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

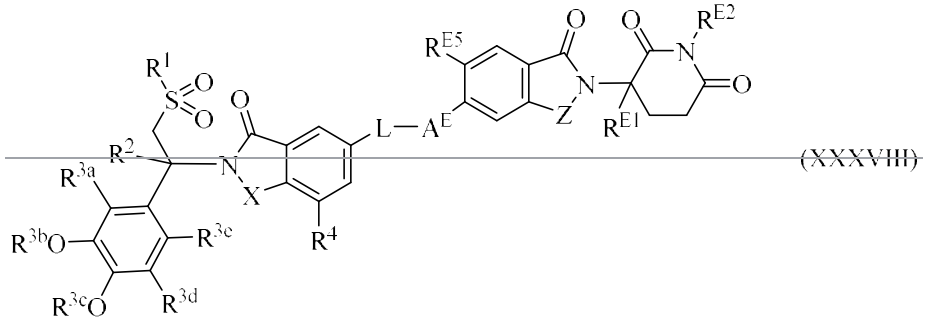
40. The compound of claim 32 or 39, having the structure of Formula (XXXIII):



(XXXIII)

or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

41. The compound of claim 32 or 39, having the structure of Formula (XXXVIII):



(XXXVIII)

or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

42. The compound of any one of claims 32 to 41, wherein X is $-CH_2-$.

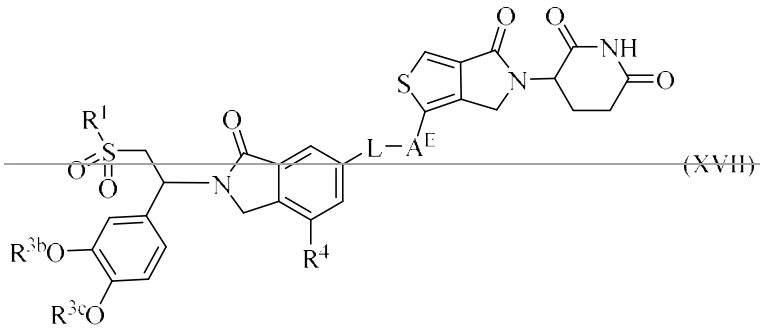
43. The compound of any one of claims 32 to 41, wherein X is $-C(O)-$.

44. The compound of any one of claims 32 to 43, wherein R^2 is hydrogen.

45. The compound of any one of claims 32 to 44, wherein Z is $-CH_2-$.

46. The compound of any one of claims 32 to 44, wherein Z is $-C(O)-$.

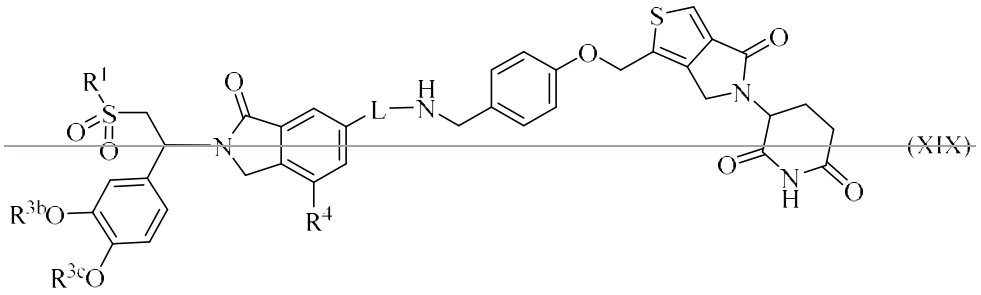
47. The compound of claim 32 or 38, having the structure of Formula (XVII):



(XVII)

or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

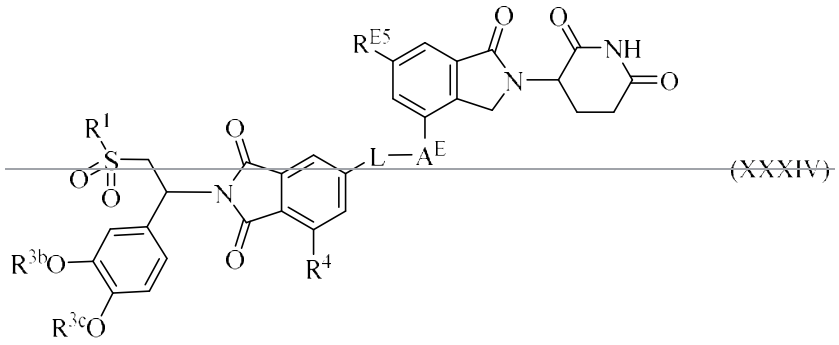
48. The compound of claim 47, having the structure of Formula (XIX):



(XIX)

or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

49. The compound of claim 39 or 40, having the structure of Formula (XXXIV):

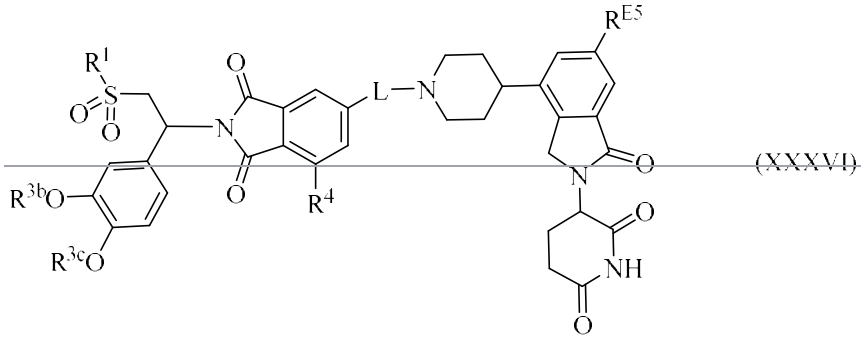


(XXXIV)

or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more

diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

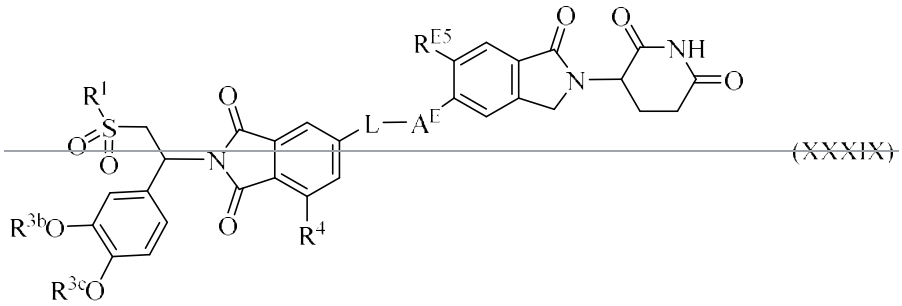
50. The compound of claim 49, having the structure of Formula (XXXVI):



(XXXVI)

or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

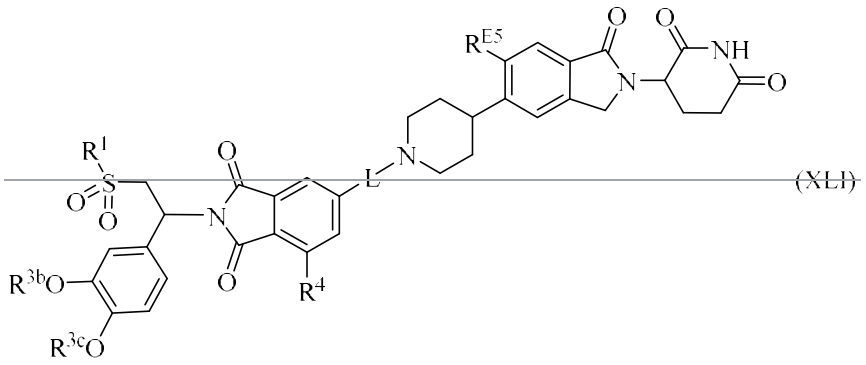
51. The compound of claim 39 or 41, having the structure of Formula (XXXIX):



(XXXIX)

or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

52. The compound of claim 51, having the structure of Formula (XLI):



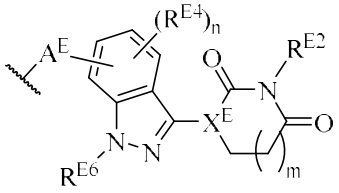
(XLI)

or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

53. The compound of any one of claims 19 to 25, 28 to 31, 40 to 46, and 52, wherein R^{E5} is hydrogen or halo.

54. The compound of claim 53, wherein R^{E5} is hydrogen or fluoro.

5511. The compound of any one of claims 1 to 94, wherein R^E is a moiety having the structure of Formula (EC-XXVIII):



(EC-XXVIII)

or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or wherein:

A^E is a bond, $-O-$, $-N(R^{1b})-$, $-S-$, C_{1-6} alkylene, C_{1-6} heteroalkylene, C_{2-6} alkenylene, C_{2-6} heteroalkenylene, C_{2-6} alkynylene, C_{2-6} heteroalkynylene, C_{3-10} cycloalkylene, C_{6-14} arylene, C_{7-15} aralkylene, heteroarylene, heterocyclylene, C_{1-6} heteroalkylene-C_{6-14} arylene, or C_{2-6} alkynylene-heterocyclylene;

X^E is $C(R^{E1})$ or N;

m is an integer of 0, 1, or 2;

~~n is an integer of 0, 1, 2, or 3;~~

~~R^{E1} is hydrogen, deuterium, halo, or C_{1-6} alkyl;~~

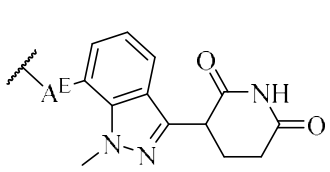
~~R^{E2} is hydrogen or C_{1-6} alkyl;~~

~~each R^{E4} is independently (i) deuterium, cyano, halo, or nitro; (ii) C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl; or (iii) $-C(O)R^{1a}$, $-C(O)OR^{1a}$, $-C(O)NR^{1b}R^{1c}$, $-C(O)SR^{1a}$, $-C(NR^{1a})NR^{1b}R^{1c}$, $-C(S)R^{1a}$, $-C(S)OR^{1a}$, $-C(S)NR^{1b}R^{1c}$, $-OR^{1a}$, $-OC(O)R^{1a}$, $-OC(O)OR^{1a}$, $-OC(O)NR^{1b}R^{1c}$, $-OC(O)SR^{1a}$, $-OC(NR^{1a})NR^{1b}R^{1c}$, $-OC(S)R^{1a}$, $-OC(S)OR^{1a}$, $-OC(S)NR^{1b}R^{1c}$, $-OS(O)R^{1a}$, $-OS(O)_2R^{1a}$, $-OS(O)NR^{1b}R^{1c}$, $-OS(O)_2NR^{1b}R^{1c}$, $-NR^{1b}R^{1c}$, $-NR^{1a}C(O)R^{1d}$, $-NR^{1a}C(O)OR^{1d}$, $-NR^{1a}C(O)NR^{1b}R^{1c}$, $-NR^{1a}C(O)SR^{1d}$, $-NR^{1a}C(NR^{1d})NR^{1b}R^{1c}$, $-NR^{1a}C(S)R^{1d}$, $-NR^{1a}C(S)OR^{1d}$, $-NR^{1a}C(S)NR^{1b}R^{1c}$, $-NR^{1a}S(O)R^{1d}$, $-NR^{1a}S(O)_2R^{1d}$, $-NR^{1a}S(O)NR^{1b}R^{1c}$, $-NR^{1a}S(O)_2NR^{1b}R^{1c}$, $-SR^{1a}$, $-S(O)R^{1a}$, $-S(O)_2R^{1a}$, $-S(O)NR^{1b}R^{1c}$, or $-S(O)_2NR^{1b}R^{1c}$; and each R^{E5} is independently hydrogen or R^{E4}; and~~

~~R^{E6} is (i) hydrogen; (ii) C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl; or (iii) $-C(O)R^{1a}$, $-C(O)OR^{1a}$, $-C(O)NR^{1b}R^{1c}$, $-C(O)SR^{1a}$, $-C(NR^{1a})NR^{1b}R^{1c}$, $-C(S)R^{1a}$, $-C(S)OR^{1a}$, $-C(S)NR^{1b}R^{1c}$, $-OR^{1a}$, $-OC(O)R^{1a}$, $-OC(O)OR^{1a}$, $-OC(O)NR^{1b}R^{1c}$, $-OC(O)SR^{1a}$, $-OC(NR^{1a})NR^{1b}R^{1c}$, $-OC(S)R^{1a}$, $-OC(S)OR^{1a}$, $-OC(S)NR^{1b}R^{1c}$, $-OS(O)R^{1a}$, $-OS(O)_2R^{1a}$, $-OS(O)NR^{1b}R^{1c}$, $-OS(O)_2NR^{1b}R^{1c}$, $-NR^{1b}R^{1c}$, $-NR^{1a}C(O)R^{1d}$, $-NR^{1a}C(O)OR^{1d}$, $-NR^{1a}C(O)NR^{1b}R^{1c}$, $-NR^{1a}C(O)SR^{1d}$, $-NR^{1a}C(NR^{1d})NR^{1b}R^{1c}$, $-NR^{1a}C(S)R^{1d}$, $-NR^{1a}C(S)OR^{1d}$, $-NR^{1a}C(S)NR^{1b}R^{1c}$, $-NR^{1a}S(O)R^{1d}$, $-NR^{1a}S(O)_2R^{1d}$, $-NR^{1a}S(O)NR^{1b}R^{1c}$, $-NR^{1a}S(O)_2NR^{1b}R^{1c}$, $-S(O)R^{1a}$, $-S(O)_2R^{1a}$, $-S(O)NR^{1b}R^{1c}$, or $-S(O)_2NR^{1b}R^{1c}$;~~

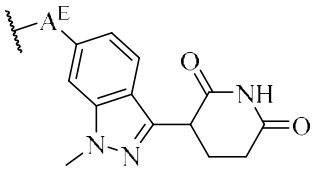
~~wherein each alkyl, alkylene, heteroalkyl, heteroalkylene, alkenyl, alkenylene, heteroalkenylene, alkynyl, alkynylene, heteroalkynylene, cycloalkyl, cycloalkylene, aryl, arylene, aralkyl, aralkylene, heteroaryl, heteroarylene, heterocyclyl, and heterocyclylene is optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q.~~

~~56. The compound of any one of claims 1 to 9 and 55,~~ wherein R^E is a moiety having the structure of:



EC-28

or

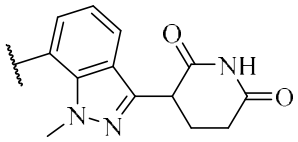


EC-29

;

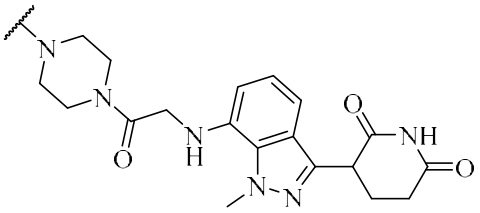
or an enantiomer, a mixture of enantiomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof.; or

57. The compound of any one of claims 1 to 9, 55, and 56, wherein R^E is a moiety having the structure of:



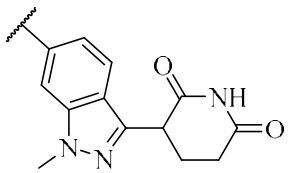
EC-30

,



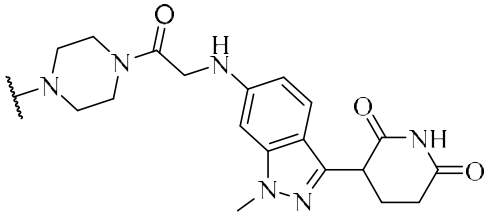
EC-31

,



EC-32

, or

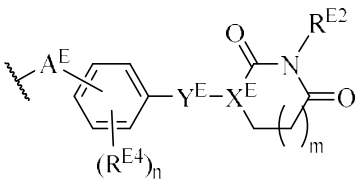


EC-33

;

or an enantiomer, a mixture of enantiomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof.; or

58. The compound of any one of claims 1 to 9, wherein R^E is a moiety having the structure of Formula (EC-XXXV):



(EC-XXXV)

or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more

diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or wherein:

A^E is a bond, -O-, -N(R^{1b})-, -S-, C_{1-6} alkylene, C_{1-6} heteroalkylene, C_{2-6} alkenylene, C_{2-6} heteroalkenylene, C_{2-6} alkynylene, C_{2-6} heteroalkynylene, C_{3-10} cycloalkylene, C_{6-14} arylene, C_{7-15} aralkylene, heteroarylene, heterocyclylene, C_{1-6} heteroalkylene-C_{6-14} arylene, or C_{2-6} alkynylene-heterocyclylene;

X^E is C(R^{E1}) or N;

Y^E is a bond, C_{1-6} alkylene, -O-, -S-, -S(O)-, -S(O_2)-, or -N(R^{E7})-;

m is an integer of 0, 1, or 2;

n is an integer of 0, 1, 2, or 3;

R^{E1} is hydrogen, deuterium, halo, or C_{1-6} alkyl;

R^{E2} is hydrogen or C_{1-6} alkyl;

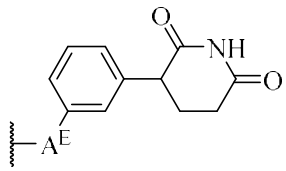
each R^{E4} is independently (i) deuterium, cyano, halo, or nitro; (ii) C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl; or (iii) -C(O)R^{1a}, -C(O)OR^{1a}, -C(O)N$R^{1b}R^{1c}$, -C(O)SR^{1a}, -C(NR^{1a})N$R^{1b}R^{1c}$, -C(S)R^{1a}, -C(S)OR^{1a}, -C(S)N$R^{1b}R^{1c}$, -OR^{1a}, -OC(O)R^{1a}, -OC(O)OR^{1a}, -OC(O)N$R^{1b}R^{1c}$, -OC(O)SR^{1a}, -OC(NR^{1a})N$R^{1b}R^{1c}$, -OC(S)R^{1a}, -OC(S)OR^{1a}, -OC(S)N$R^{1b}R^{1c}$, -OS(O)R^{1a}, -O$S(O)_2R^{1a}$, -OS(O)N$R^{1b}R^{1c}$, -O$S(O)_2$N$R^{1b}R^{1c}$, -N$R^{1b}R^{1c}$, -NR^{1a}C(O)R^{1d}, -NR^{1a}C(O)OR^{1d}, -NR^{1a}C(O)N$R^{1b}R^{1c}$, -NR^{1a}C(O)SR^{1d}, -NR^{1a}C(NR^{1d})N$R^{1b}R^{1c}$, -NR^{1a}C(S)R^{1d}, -NR^{1a}C(S)OR^{1d}, -NR^{1a}C(S)N$R^{1b}R^{1c}$, -NR^{1a}S(O)R^{1d}, -N$R^{1a}S(O)_2R^{1d}$, -NR^{1a}S(O)N$R^{1b}R^{1c}$, -N$R^{1a}S(O)_2$N$R^{1b}R^{1c}$, -SR^{1a}, -S(O)R^{1a}, -S$(O)_2R^{1a}$, -S(O)N$R^{1b}R^{1c}$, or -S$(O)_2$N$R^{1b}R^{1c}$; and each R^{E5} is independently hydrogen or R^{E4}; and

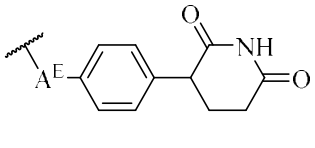
R^{E7} is hydrogen or C_{1-6} alkyl;

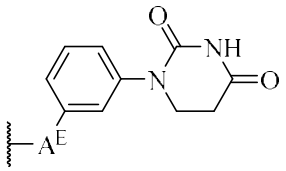
wherein each alkyl, alkylene, heteroalkyl, heteroalkylene, alkenyl, alkenylene, heteroalkenylene, alkynyl, alkynylene, heteroalkynylene, cycloalkyl, cycloalkylene, aryl, arylene, aralkyl, aralkylene, heteroaryl, heteroarylene, heterocyclyl, and heterocyclylene is optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q.

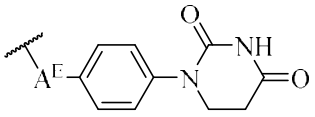
59. The compound of any one of claims 1 to 9 and 58, wherein R^E is a moiety having

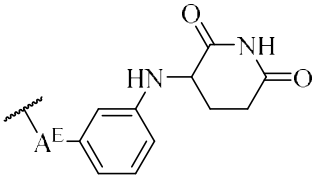
the structure of:

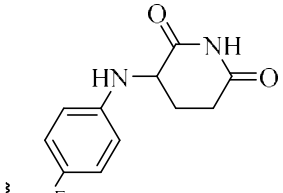

EC-34 ,


EC-35 ,


EC-36 ,

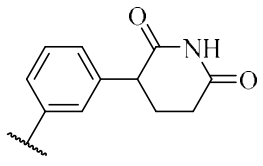

EC-37 ,

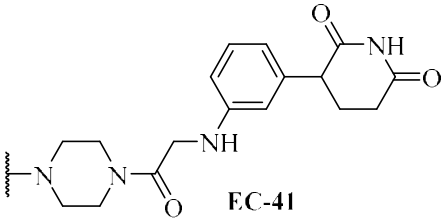

EC-38 , or

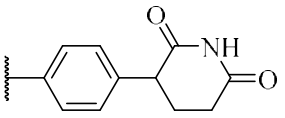

EC-39 ;

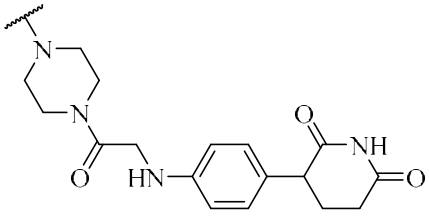
or an enantiomer, a mixture of enantiomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof~~;~~ or

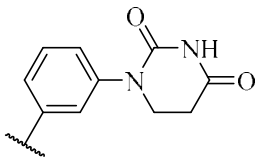
~~60. The compound of any one of claims 1 to 9, 58, and 59,~~ wherein R^E is a moiety having the structure of:

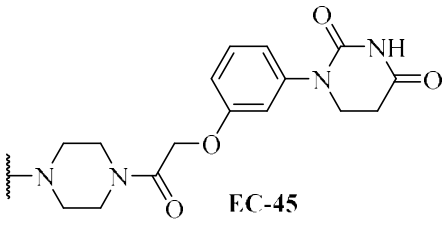

EC-40 ,

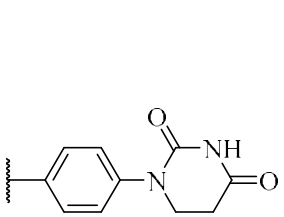

EC-41 ,


EC-42 ,

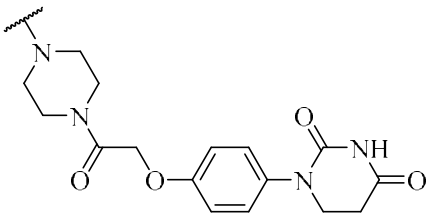

EC-43 ,


EC-44 ,

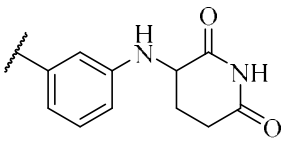

EC-45 ,



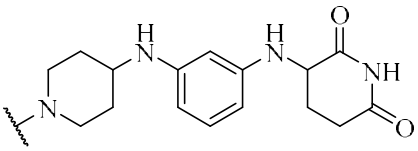
EC-46 ,



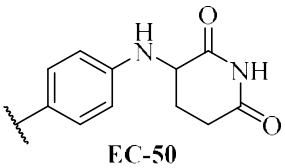
EC-47 ,



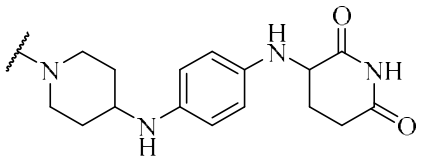
EC-48 ,



EC-49 ,



EC-50 , or



EC-51 ;

or an enantiomer, a mixture of enantiomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof;

wherein:

A^E is a bond, –O–, –N(R^{1b})–, –S–, C_{1-6} alkylene, C_{1-6} heteroalkylene, C_{2-6} alkenylene, C_{2-6} heteroalkenylene, C_{2-6} alkynylene, C_{2-6} heteroalkynylene, C_{3-10} cycloalkylene, C_{6-14} arylene, C_{7-15} aralkylene, heteroarylene, heterocyclylene, C_{1-6} heteroalkylene-C_{6-14} arylene, or C_{2-6} alkynylene-heterocyclylene;

X^E is C(R^{E1}) or N;

Y^E is a bond, C_{1-6} alkylene, –O–, –S–, –S(O)–, –S(O_2)–, or –N(R^{E7})–;

m is an integer of 0, 1, or 2;

n is an integer of 0, 1, 2, or 3;

R^{E1} is hydrogen, deuterium, halo, or C_{1-6} alkyl;

R^{E2} is hydrogen or C_{1-6} alkyl;

each R^{E4} is independently (i) deuterium, cyano, halo, or nitro; (ii) C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl; or (iii) –C(O)R^{1a}, –C(O)OR^{1a}, –C(O)N$R^{1b}R^{1c}$, –C(O)SR^{1a}, –C(NR^{1a})N$R^{1b}R^{1c}$, –C(S)R^{1a}, –C(S)OR^{1a}, –C(S)N$R^{1b}R^{1c}$, –OR^{1a}, –OC(O)R^{1a}, –OC(O)OR^{1a}, –OC(O)N$R^{1b}R^{1c}$, –OC(O)SR^{1a}, –OC(NR^{1a})N$R^{1b}R^{1c}$, –OC(S)R^{1a}, –OC(S)OR^{1a}, –OC(S)N$R^{1b}R^{1c}$, –OS(O)R^{1a}, –OS(O_2)R^{1a}, –OS(O)N$R^{1b}R^{1c}$, –OS(O_2)N$R^{1b}R^{1c}$, –N$R^{1b}R^{1c}$, –NR^{1a}C(O)R^{1d}, –NR^{1a}C(O)OR^{1d}, –NR^{1a}C(O)N$R^{1b}R^{1c}$, –NR^{1a}C(O)SR^{1d}, –NR^{1a}C(NR^{1d})N$R^{1b}R^{1c}$, –NR^{1a}C(S)R^{1d}, –NR^{1a}C(S)OR^{1d},

–$NR^{1a}C(S)NR^{1b}R^{1c}$, –$NR^{1a}S(O)R^{1d}$, –$NR^{1a}S(O)_2R^{1d}$, –$NR^{1a}S(O)NR^{1b}R^{1c}$, –$NR^{1a}S(O)_2NR^{1b}R^{1c}$, –$SR^{1a}$, –$S(O)R^{1a}$, –$S(O)_2R^{1a}$, –$S(O)NR^{1b}R^{1c}$, or –$S(O)_2NR^{1b}R^{1c}$; and each R^{E5} is independently hydrogen or R^{E4};

R^{E6} is (i) hydrogen; (ii) C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl; or (iii) –$C(O)R^{1a}$, –$C(O)OR^{1a}$, –$C(O)NR^{1b}R^{1c}$, –$C(O)SR^{1a}$, –$C(NR^{1a})NR^{1b}R^{1c}$, –$C(S)R^{1a}$, –$C(S)OR^{1a}$, –$C(S)NR^{1b}R^{1c}$, –OR^{1a}, –$OC(O)R^{1a}$, –$OC(O)OR^{1a}$, –$OC(O)NR^{1b}R^{1c}$, –$OC(O)SR^{1a}$, –$OC(NR^{1a})NR^{1b}R^{1c}$, –$OC(S)R^{1a}$, –$OC(S)OR^{1a}$, –$OC(S)NR^{1b}R^{1c}$, –$OS(O)R^{1a}$, –$OS(O)_2R^{1a}$, –$OS(O)NR^{1b}R^{1c}$, –$OS(O)_2NR^{1b}R^{1c}$, –$NR^{1b}R^{1c}$, –$NR^{1a}C(O)R^{1d}$, –$NR^{1a}C(O)OR^{1d}$, –$NR^{1a}C(O)NR^{1b}R^{1c}$, –$NR^{1a}C(O)SR^{1d}$, –$NR^{1a}C(NR^{1d})NR^{1b}R^{1c}$, –$NR^{1a}C(S)R^{1d}$, –$NR^{1a}C(S)OR^{1d}$, –$NR^{1a}C(S)NR^{1b}R^{1c}$, –$NR^{1a}S(O)R^{1d}$, –$NR^{1a}S(O)_2R^{1d}$, –$NR^{1a}S(O)NR^{1b}R^{1c}$, –$NR^{1a}S(O)_2NR^{1b}R^{1c}$, –$S(O)R^{1a}$, –$S(O)_2R^{1a}$, –$S(O)NR^{1b}R^{1c}$, or –$S(O)_2NR^{1b}R^{1c}$; and

R^{E7} is hydrogen or C_{1-6} alkyl;

wherein each alkyl, alkylene, heteroalkyl, heteroalkylene, alkenyl, alkenylene, heteroalkenylene, alkynyl, alkynylene, heteroalkynylene, cycloalkyl, cycloalkylene, aryl, arylene, aralkyl, aralkylene, heteroaryl, heteroarylene, heterocyclyl, and heterocyclylene is optionally substituted with one or more substituents Q.

~~61~~12. The compound of any one of claims 1 to ~~60~~11, wherein R^1 is C_{1-6} alkyl or C_{3-7} cycloalkyl, each optionally substituted with one or more substituents Q~~.~~; or

~~62. The compound of any one of claims 1 to 61,~~ wherein R^1 is C_{1-6} alkyl, optionally substituted with one or more substituents Q~~.~~; or

~~63. The compound of any one of claims 1 to 62,~~ wherein R^1 is methyl~~.~~; and/or

~~64. The compound of any one of claims 1 to 63,~~ wherein R^{3b} is C_{1-6} alkyl or C_{3-7} cycloalkyl, each optionally substituted with one or more substituents Q~~.~~; or

~~65. The compound of any one of claims 1 to 64,~~ wherein R^{3b} is C_{1-6} alkyl, optionally substituted with one or more substituents Q~~.~~; or

66. The compound of any one of claims 1 to 65, wherein R^{3b} is ethyl.; and/or

67. The compound of any one of claims 1 to 66, wherein R^{3c} is C_{1-6} alkyl or C_{3-7} cycloalkyl, each optionally substituted with one or more substituents Q.; or

68. The compound of any one of claims 1 to 67, wherein R^{3c} is C_{1-6} alkyl, optionally substituted with one or more substituents Q.; or

69. The compound of any one of claims 1 to 68, wherein R^{3c} is methyl.

7013. The compound of any one of claims 7 5 to 10 and 32 to 6912, wherein R^4 is hydrogen or $–NR^{1a}C(O)R^{1d}$.; or

71. The compound of claim 70, wherein R^4 is $–NHC(O)$-C_{1-6} alkyl.; or

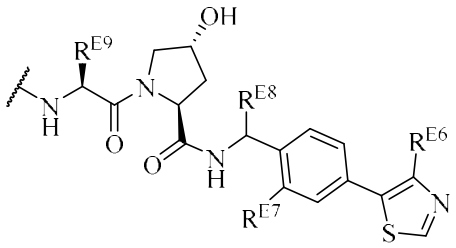
72. The compound of claim 70 or 71, wherein R^4 is $–NHC(O)CH_3$; and/or.

73. The compound of any one of claims 11 to 56, 58, 59, and 61 to 72, wherein A^E is a bond, –O–, –NH–, ethynediyl, piperidindiyl, piperazindiyl, (phendiyl)oxymethanediyl, or (piperidindiyl)ethynediyl.; or

74. The compound of any one of claims 11 to 56, 58, 59, and 61 to 73, wherein A^E is a bond, –NH–, piperidin-1,4-diyl, piperaz-1,4-diyl, (phen-1,4-diyl)oxymethanediyl, or (piperidin-1,4-diyl)ethynediyl.

75. The compound of any one of claims 1 to 8, wherein R^E is a moiety of a von Hippel-Lindau (VHL) E3 ligand.

7614. The compound of any one of claims 1 to 8 and 754, wherein R^E has the structure of Formula (EV-I):



(EV-I)

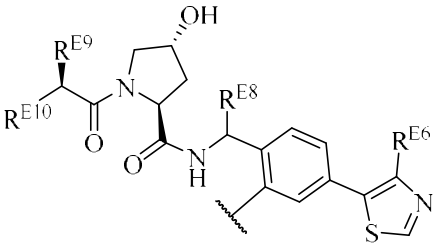
or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or ~~wherein:~~

~~R^{E6}, R^{E8}, and R^{E9} are each independently hydrogen, deuterium, C_{1-6} alkyl, or C_{3-10} cycloalkyl; and~~

~~R^{E7} is hydrogen, deuterium, halo, hydroxyl, $-OC_{1-6}$ alkyl, or $-OC_{3-10}$ cycloalkyl;~~

~~wherein each alkyl and cycloalkyl is optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q.~~

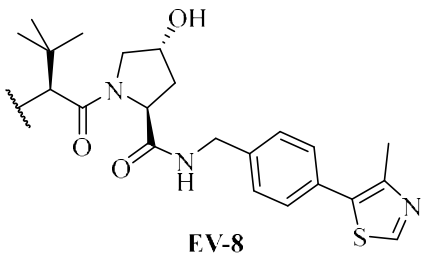
wherein R^E has the structure of Formula (EV-III):

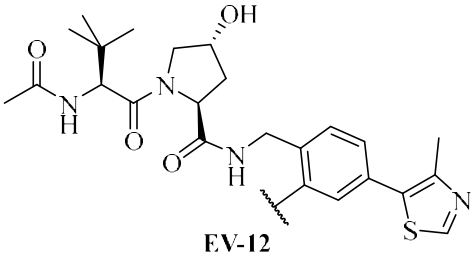


(EV-III)

or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or

wherein R^E is a moiety having the structure of:



EV-8, or 

EV-12;

wherein:

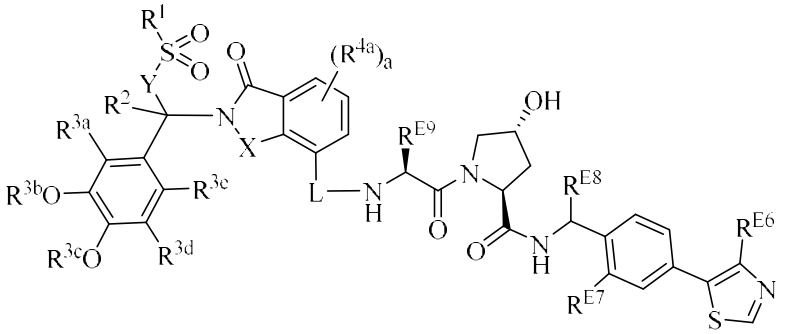
R^{E6}, R^{E8}, and R^{E9} are each independently hydrogen, deuterium, C_{1-6} alkyl, or C_{3-10} cycloalkyl;

R^{E7} is hydrogen, deuterium, halo, hydroxyl, $–OC_{1-6}$ alkyl, or $–OC_{3-10}$ cycloalkyl; and

R^{E10} is $–NHC(O)C_{1-6}$ alkyl, $–NHC(O)C_{3-10}$ cycloalkyl, or heterocyclyl;

wherein each alkyl, cycloalkyl, and heterocyclyl is optionally substituted with one or more substituents Q.

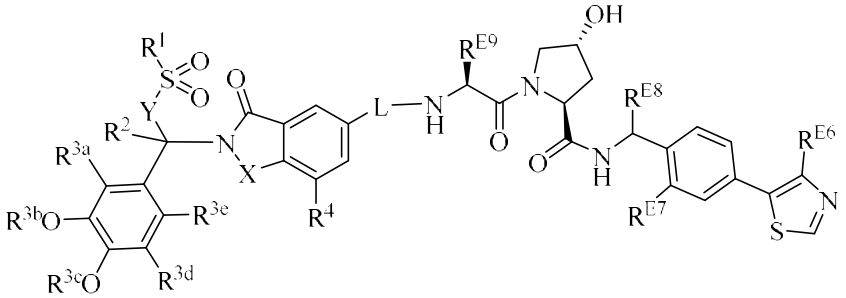
~~77~~15. The compound of claim ~~76~~14, having the structure of Formula (XLIII):



(XLIII)

or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof.~~;~~ or

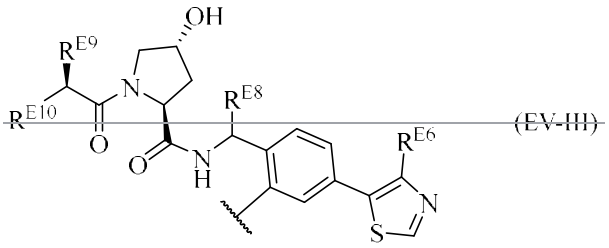
~~78. The compound of claim 76,~~ having the structure of Formula (XLV):



(XLV)

or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof.

~~79. The compound of claim 76, having the structure of Formula (EV-III):~~



(EV-III)

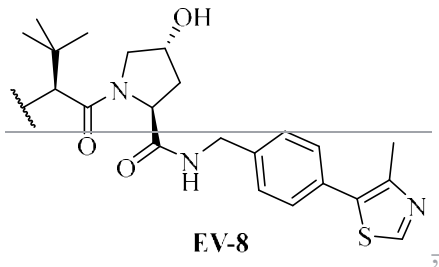
or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; wherein:

R^{E6}, R^{E8}, and R^{E9} are each independently hydrogen, deuterium, C_{1-6} alkyl, or C_{3-10} cycloalkyl; and

R^{E10} is $-NHC(O)C_{1-6}$ alkyl, $-NHC(O)C_{3-10}$ cycloalkyl, or heterocyclyl;

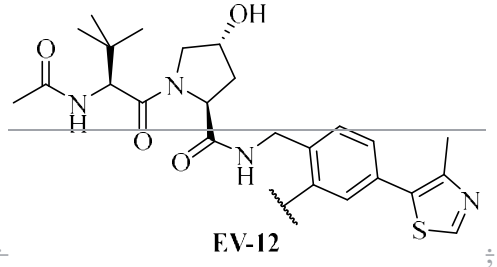
wherein each alkyl, cycloalkyl, and heterocyclyl is optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q.

80. The compound of any one of claims 1 to 8 and 75, wherein R^E is a moiety having the structure of:



EV-8

, or



EV-12

;

or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof.

8116. The compound of any one of claims 1 to 8015, wherein L is C_{1-20} alkylene, C_{1-20} heteroalkylene, C_{2-20} alkenylene, C_{2-20} heteroalkenylene, C_{2-20} alkynylene, C_{2-20} heteroalkynylene, C_{3-10} cycloalkylene, C_{6-14} arylene, heteroarylene, or heterocyclylene, each of which is optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q.; or

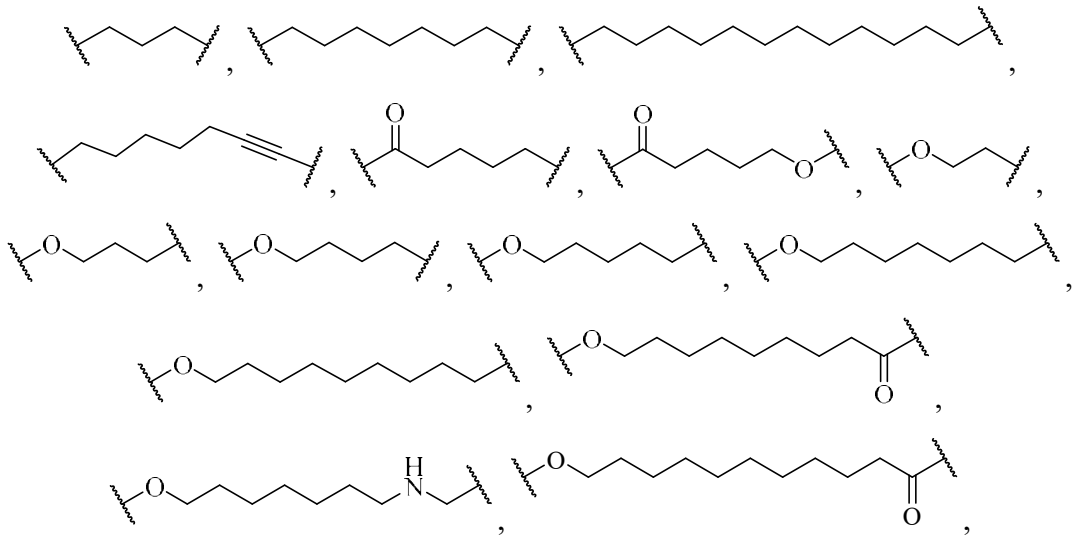
82. The compound of any one of claims 1 to 81, wherein L is C_{1-20} alkylene, C_{1-20}

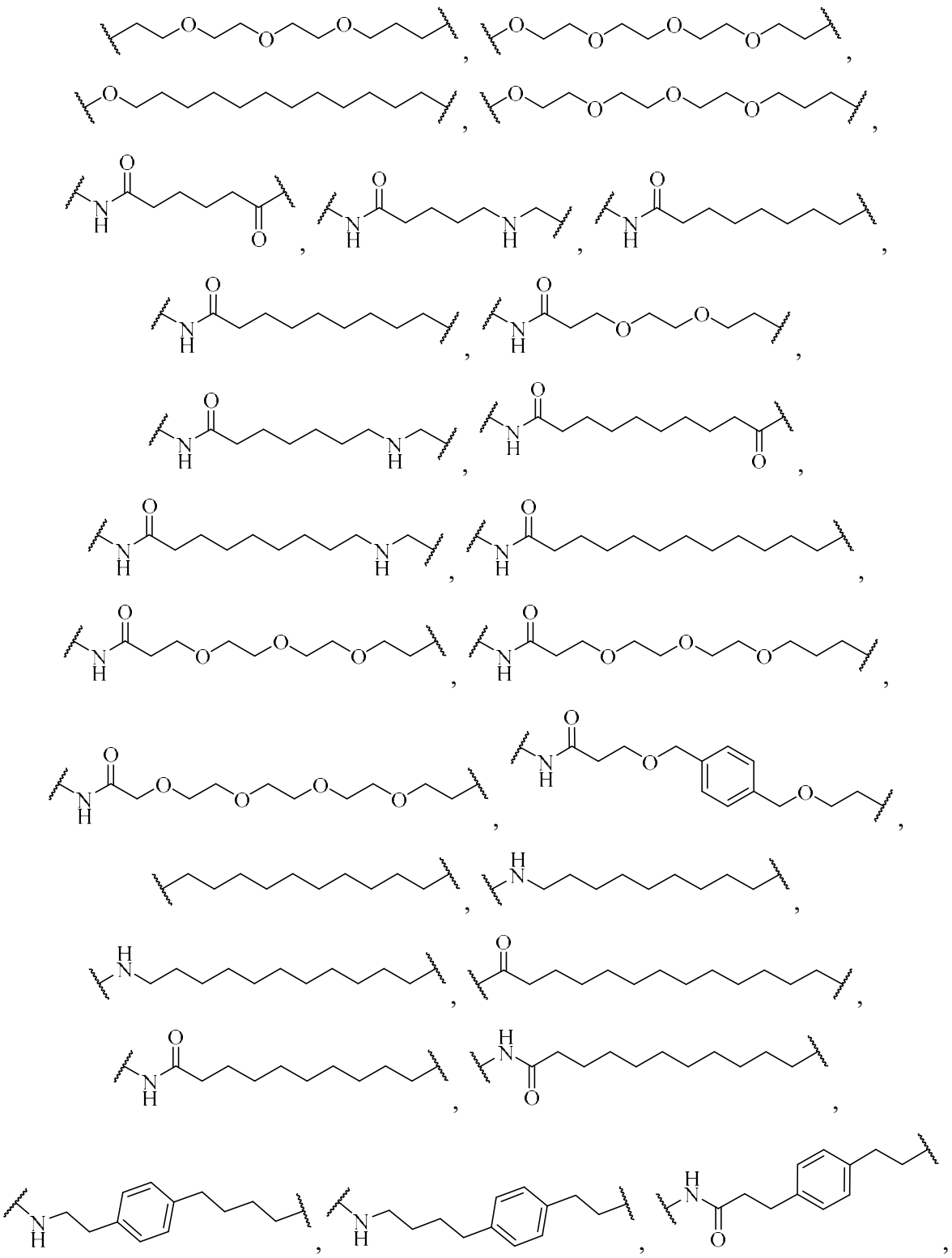
heteroalkylene, C_{2-20} alkynylene, or C_{2-20} heteroalkynylene, each of which is optionally substituted with one or more~~, in one embodiment, one, two, three, or four,~~ substituents Q~~.~~; or

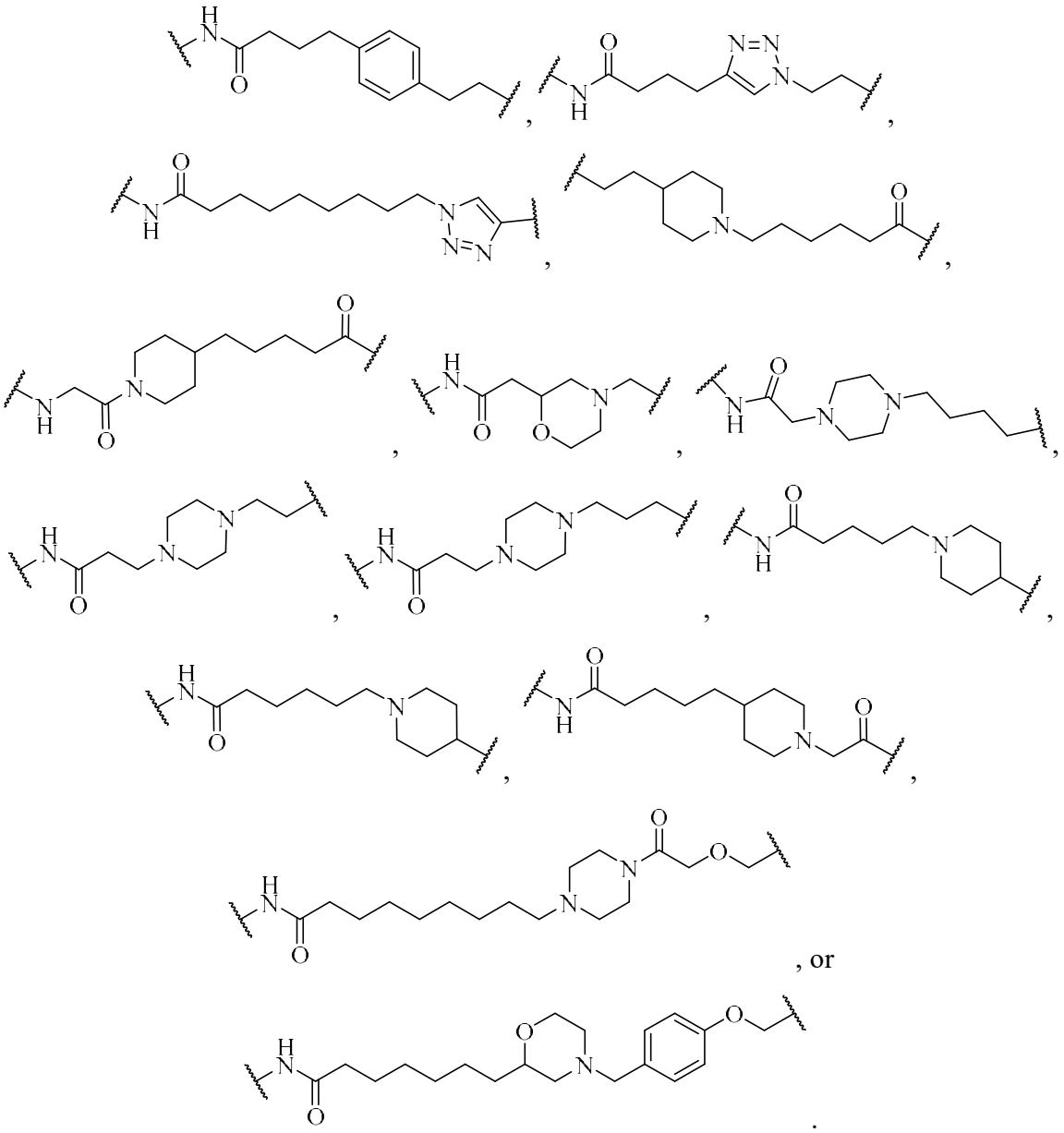
~~83. The compound of any one of claims 1 to 80,~~ wherein L is C_{1-20} alkylene, C_{1-20} heteroalkylene, C_{2-20} alkenylene, C_{2-20} heteroalkenylene, C_{2-20} alkynylene, or C_{2-20} heteroalkynylene, where one or more methylene groups are each independently replaced by a divalent group, and each divalent group is independently C_{3-10} cycloalkylene, C_{6-14} arylene, heteroarylene, or heterocyclylene; and wherein the alkylene, heteroalkylene, alkenylene, heteroalkenylene, alkynylene, heteroalkynylene, cycloalkylene, arylene, heteroarylene, and heterocyclylene are each optionally substituted with one or more~~, in one embodiment, one, two, three, or four,~~ substituents Q~~.~~; or

~~84. The compound of claim 83,~~ wherein L is C_{1-20} alkylene or C_{1-20} heteroalkylene, where one or more methylene groups are each independently replaced by a divalent group, and each divalent group is independently C_{3-10} cycloalkylene, C_{6-14} arylene, heteroarylene, or heterocyclylene; and wherein the alkylene, cycloalkylene, arylene, heteroarylene, and heterocyclylene are each optionally substituted with one or more~~, in one embodiment, one, two, three, or four,~~ substituents Q~~.~~; or

~~85. The compound of any one of claims 1 to 80,~~ wherein L is:







, or

.

8617. ~~The compound of claim 1, wherein the compound is~~A compound of:

N-(6-(7-(4-(2-(2,6-dioxopiperidin-3-yl)-6-fluoro-1-oxoisoindolin-4-yl)piperidin-1-yl)heptyl)-2-((*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl)-1,3-dioxoisoindolin-4-yl)acetamide **A1**;

N-(6-(7-(4-(2-(2,6-dioxopiperidin-3-yl)-6-fluoro-1-oxoisoindolin-4-yl)piperidin-1-yl)hept-1-yn-1-yl)-2-((*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl)-1,3-dioxo-

isoindolin-4-yl)acetamide **A2**;

N-(6-(5-(4-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)ethynyl)piperidin-1-yl)-5-oxopentyl)-2-((*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl)-1,3-dioxo-isoindolin-4-yl)acetamide **A3**;

14-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-*N*-(2-((*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl)-1,3-dioxoisoindolin-4-yl)-3,6,9,12-tetraoxa-tetradecan-1-amide **A4**;

N-(6-(3-(4-(2-(2,6-dioxopiperidin-3-yl)-6-fluoro-1-oxoisoindolin-4-yl)piperidin-1-yl)propyl)-2-((*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl)-1,3-dioxo-isoindolin-4-yl)acetamide **A5**;

12-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-*N*-(2-((*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl)-1,3-dioxoisoindolin-4-yl)dodecanamide **A6**;

9-(4-(2-(2,6-dioxopiperidin-3-yl)-6-fluoro-1-oxoisoindolin-5-yl)piperidin-1-yl)-*N*-(2-((*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl)-1,3-dioxoisoindolin-4-yl)-nonanamide **A7**;

N-(6-(7-(1-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)piperidin-4-yl)-heptyl)-2-((*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl)-1,3-dioxoisoindolin-4-yl)acetamide **A8**;

3-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)-ethoxy)-*N*-(2-((*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl)-1,3-dioxoisoindolin-4-yl)propanamide **A9**;

3-(2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)-ethoxy)ethoxy)-*N*-(2-((*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl)-1,3-dioxo-isoindolin-4-yl)propanamide **A10**;

3-((4-((2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)-methyl)benzyl)oxy)-*N*-(2-((*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl)-1,3-dioxoisoindolin-4-yl)propanamide **A11**;

9-((4-((5-(2,6-dioxopiperidin-3-yl)-4-oxo-5,6-dihydro-4*H*-thieno[3,4-*c*]pyrrol-1-yl)methoxy)benzyl)amino)-*N*-(2-((*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl)-

1,3-dioxoisoindolin-4-yl)nonanamide **A12**;

9-(4-(2-(2,6-dioxopiperidin-3-yl)-6-fluoro-1-oxoisoindolin-4-yl)piperidin-1-yl)-*N*-(2-((*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl)-1,3-dioxoisoindolin-4-yl)-nonanamide **A13**;

N-(6-(12-(4-(2-(2,6-dioxopiperidin-3-yl)-6-fluoro-1-oxoisoindolin-4-yl)piperidin-1-yl)dodecyl)-2-((*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl)-1,3-dioxo-isoindolin-4-yl)acetamide **A14**;

9-{1-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl]-piperidin-4-yl}-*N*-{2-[(1*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-methanesulfonylethyl]-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl}nonanamide **A15**;

9-({[4-({[2-(2,6-dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1*H*-isoindol-4-yl]oxy}-methyl)phenyl]methyl}amino)-*N*-{2-[(1*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-methanesulfonyl-ethyl]-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl}nonanamide **A16**;

N-[7-(12-{4-[2-(2,6-dioxopiperidin-3-yl)-6-fluoro-1-oxo-2,3-dihydro-1*H*-isoindol-4-yl]piperidin-1-yl}dodecyl)-2-[(1*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-methane-sulfonylethyl]-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl]acetamide **A17**;

4-amino-7-(12-{4-[2-(2,6-Dioxopiperidin-3-yl)-6-fluoro-1-oxo-2,3-dihydro-1*H*-isoindol-4-yl]piperidin-1-yl}dodecyl)-2-[(1*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-methane-sulfonylethyl]-2,3-dihydro-1*H*-isoindole-1,3-dione **A18**;

10-{4-[2-(2,6-dioxopiperidin-3-yl)-6-fluoro-1-oxo-2,3-dihydro-1*H*-isoindol-5-yl]piperidin-1-yl}-*N*-{2-[(1*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-methanesulfonylethyl]-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl}decanamide **A19**;

9-(4-{2-[2-(2,6-dioxopiperidin-3-yl)-6-fluoro-1-oxo-2,3-dihydro-1*H*-isoindol-5-yl]ethynyl}piperidin-1-yl)-*N*-{2-[(1*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-methanesulfonylethyl]-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl}nonanamide **A20**;

9-{4-[2-(2,6-dioxopiperidin-3-yl)-6-fluoro-1-oxo-2,3-dihydro-1*H*-isoindol-5-yl]piperidin-1-yl}-*N*-{2-[(1*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-methanesulfonylethyl]-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl}nonanamide **A21**;

8-{4-[2-(2,6-dioxopiperidin-3-yl)-6-fluoro-1-oxo-2,3-dihydro-1*H*-isoindol-5-

yl]piperidin-1-yl}-*N*-{2-[(1*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-methanesulfonylethyl]-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl}octanamide **A22**;

9-{4-[2-(2,6-dioxopiperidin-3-yl)-6-fluoro-1-oxo-2,3-dihydro-1*H*-isoindol-5-yl]-1*H*-1,2,3-triazol-1-yl}-*N*-{2-[(1*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-methanesulfonylethyl]-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl}nonanamide **A23**;

4-[1-(2-{4-[2-(2,6-dioxopiperidin-3-yl)-6-fluoro-1-oxo-2,3-dihydro-1*H*-isoindol-5-yl]piperidin-1-yl}ethyl)-1*H*-1,2,3-triazol-4-yl]-*N*-{2-[(1*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-methanesulfonylethyl]-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl}butanamide **A24**;

4-[(9-{4-[2-(2,6-dioxopiperidin-3-yl)-6-fluoro-1-oxo-2,3-dihydro-1*H*-isoindol-5-yl]piperidin-1-yl}nonyl)amino]-2-[(1*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-methanesulfonylethyl]-2,3-dihydro-1*H*-isoindole-1,3-dione **A25**;

9-{4-[2-(2,6-dioxopiperidin-3-yl)-1-oxo-2,3-dihydro-1*H*-isoindol-5-yl]piperidin-1-yl}-*N*-{2-[(1*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-methanesulfonylethyl]-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl}nonanamide **A26**;

4-(10-{4-[2-(2,6-dioxopiperidin-3-yl)-6-fluoro-1-oxo-2,3-dihydro-1*H*-isoindol-5-yl]piperidin-1-yl}decyl)-2-[(1*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-methanesulfonylethyl]-2,3-dihydro-1*H*-isoindole-1,3-dione **A27**;

2-[4-(4-{4-[2-(2,6-dioxopiperidin-3-yl)-6-fluoro-1-oxo-2,3-dihydro-1*H*-isoindol-5-yl]piperidin-1-yl}butyl)piperazin-1-yl]-*N*-{2-[(1*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-methanesulfonylethyl]-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl}acetamide **A28**;

6-{4-[2-(2,6-dioxopiperidin-3-yl)-6-fluoro-1-oxo-2,3-dihydro-1*H*-isoindol-5-yl]-[1,4'-bipiperidin]-1'-yl}-*N*-{2-[(1*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-methanesulfonylethyl]-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl}hexanamide **A29**;

5-{4-[2-(2,6-dioxopiperidin-3-yl)-6-fluoro-1-oxo-2,3-dihydro-1*H*-isoindol-5-yl]-[1,4'-bipiperidin]-1'-yl}-*N*-{2-[(1*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-methanesulfonylethyl]-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl}pentanamide **A30**;

3-[4-(3-{4-[2-(2,6-dioxopiperidin-3-yl)-6-fluoro-1-oxo-2,3-dihydro-1*H*-isoindol-5-yl]piperidin-1-yl}propyl)piperazin-1-yl]-*N*-{2-[(1*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-methanesulfonylethyl]-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl}propanamide **A31**;

8-(4-(2-(2,6-dioxopiperidin-3-yl)-6-fluoro-1-oxoisoindolin-4-yl)piperidin-1-yl)-*N*-(2-((*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl)-1,3-dioxoisoindolin-4-yl)-octanamide **A32**;

3-(2-(2-(3-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)amino)propoxy)-ethoxy)ethoxy)-*N*-(2-((*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl)-1,3-dioxo-isoindolin-4-yl)propanamide **A33**;

N-(6-(2-(2-(2-(3-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)amino)-propoxy)-ethoxy)ethoxy)ethyl)-2-((*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl)-1,3-dioxoisoindolin-4-yl)acetamide **A34**;

6-(4-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)ethynyl)piperidin-1-yl)-*N*-(2-((*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl)-1,3-dioxoisoindolin-4-yl)-6-oxohexanamide **A35**;

8-(4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)piperidin-1-yl)-*N*-(2-((*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl)-1,3-dioxoisoindolin-4-yl)octanamide **A36**;

N-(6-(7-(4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)piperidin-1-yl)-heptyl)-2-((*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl)-1,3-dioxoisoindolin-4-yl)acetamide **A37**;

7-((4-((5-((*S*)-2,6-dioxopiperidin-3-yl)-4-oxo-5,6-dihydro-4*H*-thieno[3,4-*c*]pyrrol-1-yl)-methoxy)benzyl)amino)-*N*-(2-((*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)-ethyl)-1,3-dioxoisoindolin-4-yl)heptanamide **A38**;

5-((4-((5-(2,6-dioxopiperidin-3-yl)-4-oxo-5,6-dihydro-4*H*-thieno[3,4-*c*]pyrrol-1-yl)methoxy)benzyl)amino)-*N*-(2-((*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl)-1,3-dioxoisoindolin-4-yl)pentanamide **A39**;

2-{4-[(4-{[5-(2,6-dioxopiperidin-3-yl)-4-oxo-4*H*,5*H*,6*H*-thieno[3,4-*c*]pyrrol-1-yl]methoxy}phenyl)methyl]morpholin-2-yl}-*N*-{2-[(1*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-methanesulfonylethyl]-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl}acetamide **A40**;

3-[2-(2-{[(4-{[5-(2,6-dioxopiperidin-3-yl)-4-oxo-4*H*,5*H*,6*H*-thieno[3,4-*c*]pyrrol-1-yl]methoxy}phenyl)methyl]amino}ethoxy)ethoxy]-*N*-{2-[(1*S*)-1-(3-ethoxy-4-methoxyphenyl)-

2-methanesulfonylethyl]-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl}propanamide **A41**;

4-[4-(2-{[(4-{[5-(2,6-Dioxopiperidin-3-yl)-4-oxo-4*H*,5*H*,6*H*-thieno[3,4-*c*]pyrrol-1-yl]methoxy}phenyl)methyl]amino}ethyl)phenyl]-*N*-{2-[(1*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-methanesulfonylethyl]-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl}butanamide **A42**;

11-{[(4-{[5-(2,6-dioxopiperidin-3-yl)-4-oxo-4*H*,5*H*,6*H*-thieno[3,4-*c*]pyrrol-1-yl]methoxy}phenyl)methyl]amino}-*N*-{2-[(1*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-methanesulfonylethyl]-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl}undecanamide **A43**;

4-[(9-{[(4-{[5-(2,6-dioxopiperidin-3-yl)-4-oxo-4*H*,5*H*,6*H*-thieno[3,4-*c*]pyrrol-1-yl]methoxy}phenyl)methyl]amino}nonyl)amino]-2-[(1*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-methanesulfonylethyl]-2,3-dihydro-1*H*-isoindole-1,3-dione **A44**;

4-[4-(2-{[(4-{[5-(2,6-dioxopiperidin-3-yl)-4-oxo-4*H*,5*H*,6*H*-thieno[3,4-*c*]pyrrol-1-yl]methoxy}phenyl)methyl]amino}ethyl)piperazin-1-yl]-*N*-{2-[(1*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-methanesulfonylethyl]-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl}butanamide **A45**;

11-{[(4-{[5-(2,6-dioxopiperidin-3-yl)-4-oxo-4*H*,5*H*,6*H*-thieno[3,4-*c*]pyrrol-1-yl]-methoxy}phenyl)methyl](methyl)amino}-*N*-{2-[(1*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-methanesulfonylethyl]-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl}undecanamide **A46**;

8-(4-(2-(2,6-dioxopiperidin-3-yl)-6-fluoro-1-oxoisoindolin-4-yl)piperidin-1-yl)-*N*-(2-((*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl)-1,3-dioxoisoindolin-4-yl)octanamide **A47**;

4-[1-(2-{[(4-{[5-(2,6-dioxopiperidin-3-yl)-4-oxo-4*H*,5*H*,6*H*-thieno[3,4-*c*]pyrrol-1-yl]methoxy}phenyl)methyl]amino}ethyl)-1*H*-1,2,3-triazol-4-yl]-*N*-{2-[(1*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-methanesulfonylethyl]-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl}butanamide **A48**;

4-(10-{[(4-{[5-(2,6-dioxopiperidin-3-yl)-4-oxo-4*H*,5*H*,6*H*-thieno[3,4-*c*]pyrrol-1-yl]methoxy}phenyl)methyl]amino}decyl)-2-[(1*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-methanesulfonylethyl]-2,3-dihydro-1*H*-isoindole-1,3-dione **A49**;

4-[(9-{[(4-{[5-(2,6-dioxopiperidin-3-yl)-4-oxo-4*H*,5*H*,6*H*-thieno[3,4-*c*]pyrrol-1-yl]methoxy}phenyl)methyl]amino}nonyl)oxy]-2-[(1*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-methanesulfonylethyl]-2,3-dihydro-1*H*-isoindole-1,3-dione **A50**;

4-({2-[4-(4-{[(4-{[5-(2,6-dioxopiperidin-3-yl)-4-oxo-4*H*,5*H*,6*H*-thieno[3,4-*c*]-pyrrol-1-yl]methoxy}phenyl)methyl]amino}butyl)phenyl]ethyl}amino)-2-[(1*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-methanesulfonylethyl]-2,3-dihydro-1*H*-isoindole-1,3-dione **A51**;

4-[(11-{[(4-{[5-(2,6-dioxopiperidin-3-yl)-4-oxo-4*H*,5*H*,6*H*-thieno[3,4-*c*]pyrrol-1-yl]methoxy}phenyl)methyl]amino}undecyl)amino]-2-[(1*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-methanesulfonylethyl]-2,3-dihydro-1*H*-isoindole-1,3-dione **A52**;

4-({4-[4-(2-{[(4-{[5-(2,6-dioxopiperidin-3-yl)-4-oxo-4*H*,5*H*,6*H*-thieno[3,4-*c*]-pyrrol-1-yl]methoxy}phenyl)methyl]amino}ethyl)phenyl]butyl}amino)-2-[(1*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-methanesulfonylethyl]-2,3-dihydro-1*H*-isoindole-1,3-dione **A53**;

9-[4-(2-{[5-(2,6-dioxopiperidin-3-yl)-4-oxo-4*H*,5*H*,6*H*-thieno[3,4-*c*]pyrrol-1-yl]methoxy}acetyl)piperazin-1-yl]-*N*-{2-[(1*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-methane-sulfonylethyl]-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl}nonanamide **A54**;

4-[4-(2-{[(4-{[5-(2,6-dioxopiperidin-3-yl)-4-oxo-4*H*,5*H*,6*H*-thieno[3,4-*c*]pyrrol-1-yl]methoxy}phenyl)methyl](methyl)amino}ethyl)phenyl]-*N*-{2-[(1*S*)-1-(3-ethoxy-4-methoxy-phenyl)-2-methanesulfonylethyl]-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl}butanamide **A55**;

11-(4-{[5-(2,6-dioxopiperidin-3-yl)-4-oxo-4*H*,5*H*,6*H*-thieno[3,4-*c*]pyrrol-1-yl]methoxy}phenyl)-*N*-{2-[(1*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-methanesulfonylethyl]-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl}undecanamide **A56**;

11-(4-{[5-(2,6-dioxopiperidin-3-yl)-4-oxo-4*H*,5*H*,6*H*-thieno[3,4-*c*]pyrrol-1-yl]methoxy}phenyl)-*N*-{2-[(1*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-methanesulfonylethyl]-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl}undecanamide **A57**;

8-(4-((5-(2,6-dioxopiperidin-3-yl)-4-oxo-5,6-dihydro-4*H*-thieno[3,4-*c*]pyrrol-1-yl)methoxy)phenyl)-*N*-(2-((*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl)-1,3-dioxoisoindolin-4-yl)octanamide **A58**;

N-(6-(7-(4-((5-(2,6-dioxopiperidin-3-yl)-4-oxo-5,6-dihydro-4*H*-thieno[3,4-*c*]pyrrol-1-yl)methoxy)phenyl)heptyl)-2-((*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl)-1,3-dioxoisoindolin-4-yl)acetamide **A59**;

N^{1}-(2-((*S*)-1-(3-Ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl)-1,3-dioxo-isoindolin-4-yl)-N^{10}-((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)-

pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)decanediamide **A60**;

(2*S*,4*R*)-1-[(2*S*)-2-(13-{7-acetamido-2-[(1*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-methanesulfonylethyl]-1,3-dioxo-2,3-dihydro-1*H*-isoindol-5-yl}tridecanamido)-3,3-dimethylbutanoyl]-4-hydroxy-*N*-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide **A61**;

(2*S*,4*R*)-1-[(2*S*)-2-(11-{2-[(1*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-methanesulfonylethyl]-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl}undecanamido)-3,3-dimethylbutanoyl]-4-hydroxy-*N*-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide **A62**;

(2*S*,4*R*)-1-[(2*S*)-2-(2-{4-[4-({2-[(1*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-methanesulfonylethyl]-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl}carbamoyl)butyl]piperazin-1-yl}acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-*N*-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}-pyrrolidine-2-carboxamide **A63**;

N-{2-[(1*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-methanesulfonylethyl]-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl}-*N*′-[(2*S*)-1-[(2*S*,4*R*)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]dodecanediamide **A64**;

(2*S*,4*R*)-1-[(2*S*)-2-{[9-({2-[(1*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-methanesulfonylethyl]-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl}carbamoyl)nonyl]amino}-3,3-dimethylbutanoyl]-4-hydroxy-*N*-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide **A65**;

(2*S*,4*R*)-1-[(2*S*)-2-(5-{4-[2-({2-[(1*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-methanesulfonylethyl]-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl}amino)acetyl]piperazin-1-yl}pentanamido)-3,3-dimethylbutanoyl]-4-hydroxy-*N*-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}-pyrrolidine-2-carboxamide **A66**;

N-{2-[(1*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-methanesulfonylethyl]-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl}-*N*′-[(2*S*)-1-[(2*S*,4*R*)-4-hydroxy-2-({[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]octanediamide **A67**;

(2*S*,4*R*)-1-[(2*S*)-2-(2-{4-[4-({2-[(1*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-methanesulfonylethyl]-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl}carbamoyl)butyl]piperidin-1-yl}acet-

amido)-3,3-dimethylbutanoyl]-4-hydroxy-*N*-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}-pyrrolidine-2-carboxamide **A68**;

(2*S*,4*R*)-1-[(2*S*)-2-{[10-({2-[(1*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-methanesulfonylethyl]-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl}amino)decyl]amino}-3,3-dimethylbutanoyl]-4-hydroxy-*N*-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide **A69**;

(2*S*,4*R*)-1-[(2*S*)-2-{6-[4-(2-{2-[(1*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-methanesulfonylethyl]-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl}ethyl)piperidin-1-yl]hexanamido}-3,3-dimethylbutanoyl]-4-hydroxy-*N*-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide **A70**;

(2*S*,4*R*)-1-[(2*S*)-2-(5-{1-[2-({2-[(1*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-methanesulfonylethyl]-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl}amino)acetyl]piperidin-4-yl}pentanamido)-3,3-dimethylbutanoyl]-4-hydroxy-*N*-{[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl}-pyrrolidine-2-carboxamide **A71**;

(2*S*,4*R*)-1-((*S*)-2-((8-((2-((*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)-ethyl)-1,3-dioxoisoindolin-4-yl)amino)-8-oxooctyl)amino)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide **A72**;

(2*S*,4*R*)-1-((*S*)-2-((7-(7-acetamido-2-((*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl)-1,3-dioxoisoindolin-5-yl)heptyl)amino)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide **A73**;

(2*S*,4*R*)-1-[(2*S*)-2-acetamido-3,3-dimethylbutanoyl]-*N*-[(2-{[8-({2-[(1*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-methanesulfonylethyl]-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl}-carbamoyl)octyl]oxy}-4-(4-methyl-1,3-thiazol-5-yl)phenyl)methyl]-4-hydroxypyrrolidine-2-carboxamide **A74**;

(2*S*,4*R*)-1-[(2*S*)-2-acetamido-3,3-dimethylbutanoyl]-*N*-[(2-{[10-({2-[(1*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-methanesulfonylethyl]-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl}-carbamoyl)decyl]oxy}-4-(4-methyl-1,3-thiazol-5-yl)phenyl)methyl]-4-hydroxypyrrolidine-2-carboxamide **A75**;

(2*S*,4*R*)-1-[(2*S*)-2-acetamido-3,3-dimethylbutanoyl]-*N*-[(2-{[6-({2-[(1*S*)-1-(3-

ethoxy-4-methoxyphenyl)-2-methanesulfonylethyl]-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl}-carbamoyl)hexyl]oxy}-4-(4-methyl-1,3-thiazol-5-yl)phenyl)methyl]-4-hydroxypyrrolidine-2-carboxamide **A76**;

8-[4-({[3-(2,6-dioxopiperidin-3-yl)-1-methyl-1*H*-indazol-6-yl]carbamoyl}-methyl)piperazin-1-yl]-*N*-{2-[(1*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-methanesulfonylethyl]-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl}octanamide **A77**;

6-[4-({[3-(2,6-dioxopiperidin-3-yl)-1-methyl-1*H*-indazol-6-yl]carbamoyl}-methyl)piperazin-1-yl]-*N*-{2-[(1*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-methanesulfonylethyl]-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl}hexanamide **A78**;

10-[4-({[3-(2,6-dioxopiperidin-3-yl)-1-methyl-1*H*-indazol-6-yl]carbamoyl}-methyl)piperazin-1-yl]-*N*-{2-[(1*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-methanesulfonylethyl]-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl}decanamide **A79**;

8-[4-({[3-(2,6-dioxopiperidin-3-yl)-1-methyl-1*H*-indazol-7-yl]carbamoyl}-methyl)piperazin-1-yl]-*N*-{2-[(1*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-methanesulfonylethyl]-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl}octanamide **A80**;

10-[4-({[3-(2,6-dioxopiperidin-3-yl)-1-methyl-1*H*-indazol-7-yl]carbamoyl}-methyl)piperazin-1-yl]-*N*-{2-[(1*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-methanesulfonylethyl]-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl}decanamide **A81**;

6-[4-({[3-(2,6-dioxopiperidin-3-yl)-1-methyl-1*H*-indazol-7-yl]carbamoyl}-methyl)piperazin-1-yl]-*N*-{2-[(1*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-methanesulfonylethyl]-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl}hexanamide **A82**;

6-[4-({[4-(2,6-dioxopiperidin-3-yl)phenyl]carbamoyl}methyl)piperazin-1-yl]-*N*-{2-[(1*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-methanesulfonylethyl]-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl}hexanamide **A83**;

8-[4-({[4-(2,6-dioxopiperidin-3-yl)phenyl]carbamoyl}methyl)piperazin-1-yl]-*N*-{2-[(1*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-methanesulfonylethyl]-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl}octanamide **A84**;

8-[4-({[3-(2,6-dioxopiperidin-3-yl)phenyl]carbamoyl}methyl)piperazin-1-yl]-*N*-{2-[(1*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-methanesulfonylethyl]-1,3-dioxo-2,3-dihydro-1*H*-

isoindol-4-yl}octanamide **A85**;

10-[4-({[4-(2,6-dioxopiperidin-3-yl)phenyl]carbamoyl}methyl)piperazin-1-yl]-*N*-{2-[(1*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-methanesulfonylethyl]-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl}decanamide **A86**;

6-[4-({[3-(2,6-dioxopiperidin-3-yl)phenyl]carbamoyl}methyl)piperazin-1-yl]-*N*-{2-[(1*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-methanesulfonylethyl]-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl}hexanamide **A87**;

10-[4-({[3-(2,6-dioxopiperidin-3-yl)phenyl]carbamoyl}methyl)piperazin-1-yl]-*N*-{2-[(1*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-methanesulfonylethyl]-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl}decanamide **A88**;

N-{6-[12-({3-[(2,6-dioxopiperidin-3-yl)amino]phenyl}amino)dodecyl]-2-[(1*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-methanesulfonylethyl]-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl}acetamide **A89**;

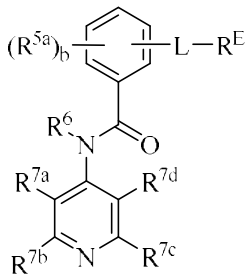
4-amino-6-[12-({3-[(2,6-dioxopiperidin-3-yl)amino]phenyl}amino)dodecyl]-2-[(1*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-methanesulfonylethyl]-2,3-dihydro-1*H*-isoindole-1,3-dione **A90**;

9-({3-[(2,6-dioxopiperidin-3-yl)amino]phenyl}amino)-*N*-{2-[(1*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-methanesulfonylethyl]-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl}nonanamide **A91**; or

6-{4-[({3-[(2,6-dioxopiperidin-3-yl)amino]phenyl}carbamoyl)methyl]piperazin-1-yl}-*N*-{2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-methanesulfonylethyl]-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl}hexanamide **A92**;

or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

~~87~~18. A compound of Formula (IA):



(IA)

or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein:

L is a linker;

R^E is an E3 ubiquitin ligase binding moiety;

each R^{5a} is independently (i) deuterium, cyano, halo, or nitro; (ii) C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl; or (iii) $–C(O)R^{1a}$, $–C(O)OR^{1a}$, $–C(O)NR^{1b}R^{1c}$, $–C(O)SR^{1a}$, $–C(NR^{1a})NR^{1b}R^{1c}$, $–C(S)R^{1a}$, $–C(S)OR^{1a}$, $–C(S)NR^{1b}R^{1c}$, $–OR^{1a}$, $–OC(O)R^{1a}$, $–OC(O)OR^{1a}$, $–OC(O)NR^{1b}R^{1c}$, $–OC(O)SR^{1a}$, $–OC(NR^{1a})NR^{1b}R^{1c}$, $–OC(S)R^{1a}$, $–OC(S)OR^{1a}$, $–OC(S)NR^{1b}R^{1c}$, $–OS(O)R^{1a}$, $–OS(O)_2R^{1a}$, $–OS(O)NR^{1b}R^{1c}$, $–OS(O)_2NR^{1b}R^{1c}$, $–NR^{1b}R^{1c}$, $–NR^{1a}C(O)R^{1d}$, $–NR^{1a}C(O)OR^{1d}$, $–NR^{1a}C(O)NR^{1b}R^{1c}$, $–NR^{1a}C(O)SR^{1d}$, $–NR^{1a}C(NR^{1d})NR^{1b}R^{1c}$, $–NR^{1a}C(S)R^{1d}$, $–NR^{1a}C(S)OR^{1d}$, $–NR^{1a}C(S)NR^{1b}R^{1c}$, $–NR^{1a}S(O)R^{1d}$, $–NR^{1a}S(O)_2R^{1d}$, $–NR^{1a}S(O)NR^{1b}R^{1c}$, $–NR^{1a}S(O)_2NR^{1b}R^{1c}$, $–SR^{1a}$, $–S(O)R^{1a}$, $–S(O)_2R^{1a}$, $–S(O)NR^{1b}R^{1c}$, or $–S(O)_2NR^{1b}R^{1c}$; and R^5 is hydrogen or R^{5a};

R^6 is hydrogen, C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl;

R^{7a}, R^{7b}, R^{7c}, and R^{7d} are each independently (i) hydrogen, deuterium, cyano, halo, or nitro; (ii) C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl; or (iii) $–C(O)R^{1a}$, $–C(O)OR^{1a}$, $–C(O)NR^{1b}R^{1c}$, $–C(O)SR^{1a}$, $–C(NR^{1a})NR^{1b}R^{1c}$, $–C(S)R^{1a}$, $–C(S)OR^{1a}$, $–C(S)NR^{1b}R^{1c}$, $–OR^{1a}$, $–OC(O)R^{1a}$, $–OC(O)OR^{1a}$, $–OC(O)NR^{1b}R^{1c}$, $–OC(O)SR^{1a}$, $–OC(NR^{1a})NR^{1b}R^{1c}$, $–OC(S)R^{1a}$, $–OC(S)OR^{1a}$, $–OC(S)NR^{1b}R^{1c}$, $–OS(O)R^{1a}$, $–OS(O)_2R^{1a}$, $–OS(O)NR^{1b}R^{1c}$, $–OS(O)_2NR^{1b}R^{1c}$, $–NR^{1b}R^{1c}$, $–NR^{1a}C(O)R^{1d}$, $–NR^{1a}C(O)OR^{1d}$, $–NR^{1a}C(O)NR^{1b}R^{1c}$, $–NR^{1a}C(O)SR^{1d}$, $–NR^{1a}C(NR^{1d})NR^{1b}R^{1c}$, $–NR^{1a}C(S)R^{1d}$, $–NR^{1a}C(S)OR^{1d}$, $–NR^{1a}C(S)NR^{1b}R^{1c}$, $–NR^{1a}S(O)R^{1d}$, $–NR^{1a}S(O)_2R^{1d}$,

$–NR^{1a}S(O)NR^{1b}R^{1c}$, $–NR^{1a}S(O)_2NR^{1b}R^{1c}$, $–SR^{1a}$, $–S(O)R^{1a}$, $–S(O)_2R^{1a}$, $–S(O)NR^{1b}R^{1c}$, or $–S(O)_2NR^{1b}R^{1c}$;

each R^{1a}, R^{1b}, R^{1c}, and R^{1d} is independently hydrogen, deuterium, C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl; and

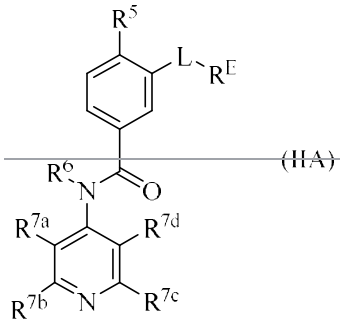
b is an integer of 0, 1, 2, 3, or 4;

wherein each alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heteroaryl, and heterocyclyl is optionally substituted with one or more~~, in one embodiment, one, two, three, or four,~~ substituents Q, wherein each Q is independently selected from: (a) deuterium, cyano, halo, imino, nitro, and oxo; (b) C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, and heterocyclyl, each of which is further optionally substituted with one or more~~, in one embodiment, one, two, three, or four,~~ substituents Q^a; and (c) $–C(O)R^a$, $–C(O)OR^a$, $–C(O)NR^bR^c$, $–C(O)SR^a$, $–C(NR^a)NR^bR^c$, $–C(S)R^a$, $–C(S)OR^a$, $–C(S)NR^bR^c$, $–OR^a$, $–OC(O)R^a$, $–OC(O)OR^a$, $–OC(O)NR^bR^c$, $–OC(O)SR^a$, $–OC(NR^a)NR^bR^c$, $–OC(S)R^a$, $–OC(S)OR^a$, $–OC(S)NR^bR^c$, $–OP(O)(OR^a)OR^d$, $–OS(O)R^a$, $–OS(O)_2R^a$, $–OS(O)NR^bR^c$, $–OS(O)_2NR^bR^c$, $–NR^bR^c$, $–NR^aC(O)R^d$, $–NR^aC(O)OR^d$, $–NR^aC(O)NR^bR^c$, $–NR^aC(O)SR^d$, $–NR^aC(NR^d)NR^bR^c$, $–NR^aC(S)R^d$, $–NR^aC(S)OR^d$, $–NR^aC(S)NR^bR^c$, $–NR^aS(O)R^d$, $–NR^aS(O)_2R^d$, $–NR^aS(O)NR^bR^c$, $–NR^aS(O)_2NR^bR^c$, $–SR^a$, $–S(O)R^a$, $–S(O)_2R^a$, $–S(O)NR^bR^c$, and $–S(O)_2NR^bR^c$, wherein each R^a, R^b, R^c, and R^d is independently (i) hydrogen or deuterium; (ii) C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl, each of which is optionally substituted with one or more~~, in one embodiment, one, two, three, or four,~~ substituents Q^a; or (iii) R^b and R^c together with the N atom to which they are attached form heterocyclyl, optionally substituted with one or more~~, in one embodiment, one, two, three, or four,~~ substituents Q^a;

wherein each Q^a is independently selected from: (a) deuterium, cyano, halo, nitro, imino, and oxo; (b) C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, and heterocyclyl; and (c) $–C(O)R^e$, $–C(O)OR^e$, $–C(O)NR^fR^g$, $–C(O)SR^e$, $–C(NR^e)NR^fR^g$, $–C(S)R^e$, $–C(S)OR^e$, $–C(S)NR^fR^g$, $–OR^e$, $–OC(O)R^e$, $–OC(O)OR^e$, $–OC(O)NR^fR^g$, $–OC(O)SR^e$, $–OC(NR^e)NR^fR^g$, $–OC(S)R^e$, $–OC(S)OR^e$, $–OC(S)NR^fR^g$,

$–OP(O)(OR^f)OR^g$, $–OS(O)R^e$, $–OS(O)_2R^e$, $–OS(O)NR^fR^g$, $–OS(O)_2NR^fR^g$, $–NR^fR^g$, $–NR^eC(O)R^h$, $–NR^eC(O)OR^f$, $–NR^eC(O)NR^fR^g$, $–NR^eC(O)SR^f$, $–NR^eC(NR^h)NR^fR^g$, $–NR^eC(S)R^h$, $–NR^eC(S)OR^f$, $–NR^eC(S)NR^fR^g$, $–NR^eS(O)R^h$, $–NR^eS(O)_2R^h$, $–NR^eS(O)NR^fR^g$, $–NR^eS(O)_2NR^fR^g$, $–SR^e$, $–S(O)R^e$, $–S(O)_2R^e$, $–S(O)NR^fR^g$, and $–S(O)_2NR^fR^g$; wherein each R^e, R^f, R^g, and R^h is independently (i) hydrogen or deuterium; (ii) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl; or (iii) R^f and R^g together with the N atom to which they are attached form heterocyclyl.

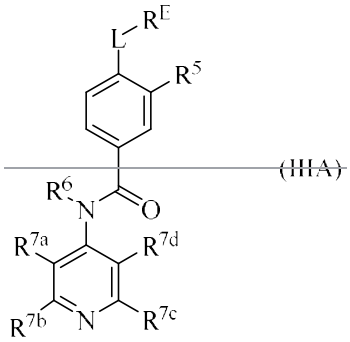
~~88. The compound of claims 87, having the structure of Formula (IIA):~~



~~(IIA)~~

~~or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.~~

~~89. The compound of claims 87, having the structure of Formula (IIIA):~~

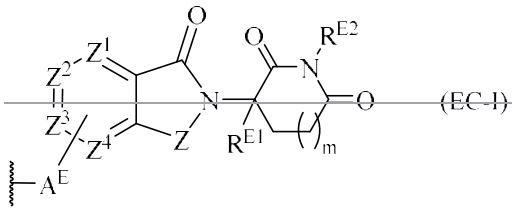


~~(IIIA)~~

~~or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.~~

90. The compound of any one of claims 87 to 89, wherein R^E is a moiety of a cereblon (CRBN) E3 ligand.

91. The compound of any one of claims 87 to 90, wherein R^E is a moiety having the structure of Formula (EC-I):



(EC-I)

or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; wherein:

A^E is a bond, -O-, -N(R^{1b})-, -S-, C_{1-6} alkylene, C_{1-6} heteroalkylene, C_{2-6} alkenylene, C_{2-6} heteroalkenylene, C_{2-6} alkynylene, C_{2-6} heteroalkynylene, C_{3-10} cycloalkylene, C_{6-14} arylene, C_{7-15} aralkylene, heteroarylene, heterocyclylene, C_{1-6} heteroalkylene-C_{6-14} arylene, or C_{2-6} alkynylene-heterocyclylene;

Z is CH_2 or C(O);

one of Z^1, Z^2, Z^3, and Z^4 is -C= and the remaining three of Z^1, Z^2, Z^3, and Z^4 are each independently -C(R^{E5})=; or Z^1 is a bond, one of Z^2, Z^3, and Z^4 is -C=, and the remaining two of Z^2, Z^3, and Z^4 are each independently -C(R^{E5})= or -S-;

m is an integer of 0, 1, or 2;

R^{E1} is hydrogen, deuterium, halo, or C_{1-6} alkyl;

R^{E2} is hydrogen or C_{1-6} alkyl; and

each R^{E4} is independently (i) deuterium, cyano, halo, or nitro; (ii) C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl; or (iii) $C(O)R^{1a}$, $C(O)OR^{1a}$, $C(O)NR^{1b}R^{1c}$, $C(O)SR^{1a}$, $C(NR^{1a})NR^{1b}R^{1c}$, $C(S)R^{1a}$, $C(S)OR^{1a}$, $C(S)NR^{1b}R^{1c}$, OR^{1a}, $OC(O)R^{1a}$, $OC(O)OR^{1a}$, $OC(O)NR^{1b}R^{1c}$, $OC(O)SR^{1a}$, $OC(NR^{1a})NR^{1b}R^{1c}$, $OC(S)R^{1a}$, $OC(S)OR^{1a}$, $OC(S)NR^{1b}R^{1c}$, $OS(O)R^{1a}$, $OS(O)_2R^{1a}$, $OS(O)NR^{1b}R^{1c}$, $OS(O)_2NR^{1b}R^{1c}$, $NR^{1b}R^{1c}$, $NR^{1a}C(O)R^{1d}$, $NR^{1a}C(O)OR^{1d}$,

~~$-NR^{1a}C(O)NR^{1b}R^{1c}$, $-NR^{1a}C(O)SR^{1d}$, $-NR^{1a}C(NR^{1d})NR^{1b}R^{1c}$, $-NR^{1a}C(S)R^{1d}$, $-NR^{1a}C(S)OR^{1d}$, $-NR^{1a}C(S)NR^{1b}R^{1c}$, $-NR^{1a}S(O)R^{1d}$, $-NR^{1a}S(O)_2R^{1d}$, $-NR^{1a}S(O)NR^{1b}R^{1c}$, $-NR^{1a}S(O)_2NR^{1b}R^{1c}$, $-SR^{1a}$, $-S(O)R^{1a}$, $-S(O)_2R^{1a}$, $-S(O)NR^{1b}R^{1c}$, or $-S(O)_2NR^{1b}R^{1c}$; and R^{E5} is hydrogen or R^{E4};~~

~~wherein each alkyl, alkylene, heteroalkyl, heteroalkylene, alkenyl, alkenylene, heteroalkenylene, alkynyl, alkynylene, heteroalkynylene, cycloalkyl, cycloalkylene, aryl, arylene, aralkyl, aralkylene, heteroaryl, heteroarylene, heterocyclyl, and heterocyclylene is optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q.~~

~~92. The compound of claim 91, wherein m is an integer of 1.~~

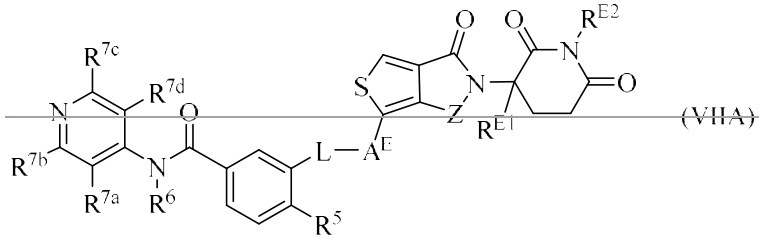
~~93. The compound of claims 91 or 92, wherein Z^1 is a bond.~~

~~94. The compound of any one of claims 91 to 93, wherein Z^2 is S.~~

~~95. The compound of any one of claims 91 to 93, wherein Z^3 is S.~~

~~96. The compound of any one of claims 91 to 93, wherein Z^4 is S.~~

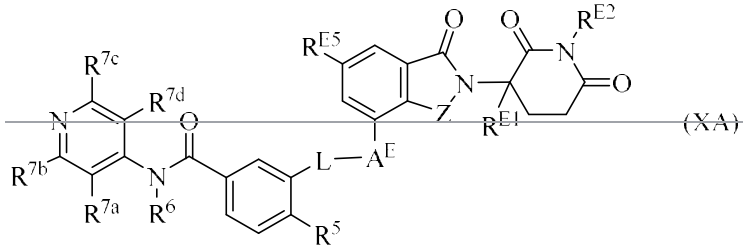
~~97. The compound of claim 91 or 95, having the structure of Formula (VIIA):~~



~~(VIIA)~~

~~or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.~~

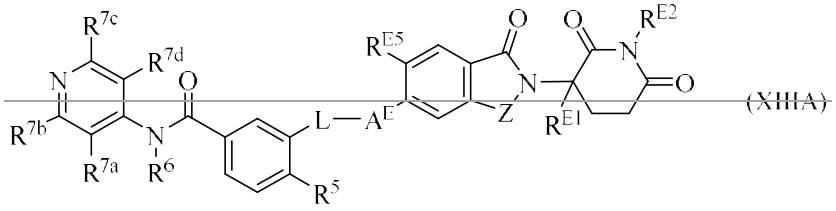
~~98. The compound of claim 91, having the structure of Formula (XA):~~



(XA)

~~or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.~~

~~99. The compound of claim 91, having the structure of Formula (XIIIA):~~



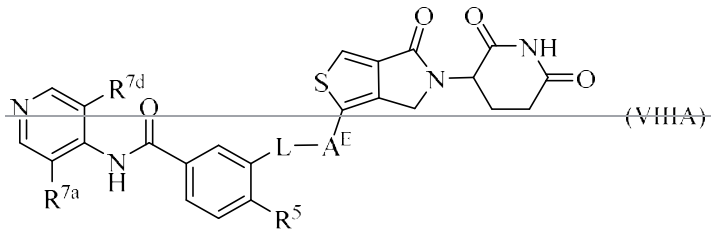
(XIIIA)

~~or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.~~

~~100. The compound of any one of claims 91 to 99, wherein Z is $-CH_2-$.~~

~~101. The compound of any one of claims 91 to 99, wherein Z is $-C(O)-$.~~

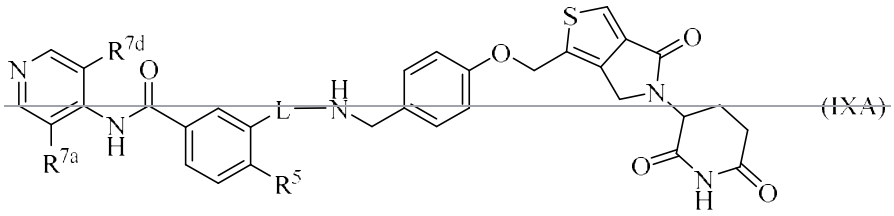
~~102. The compound of claim 97, having the structure of Formula (VIIIA):~~



(VIIIA)

~~or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.~~

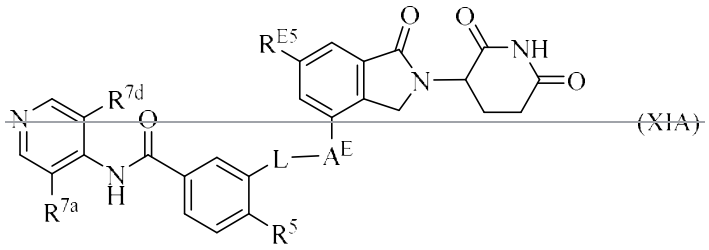
103. The compound of claim 102, having the structure of Formula (IXA):



(IXA)

or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

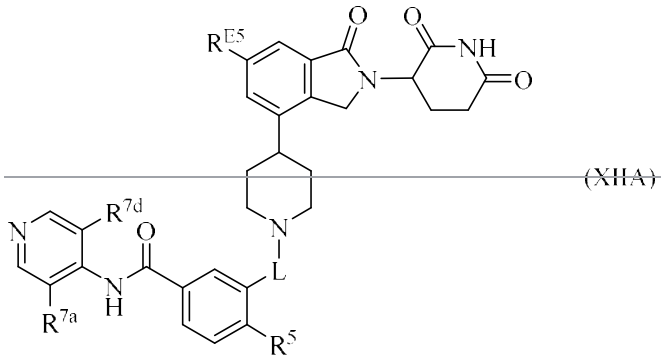
104. The compound of claim 98, having the structure of Formula (XIA):



(XIA)

or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

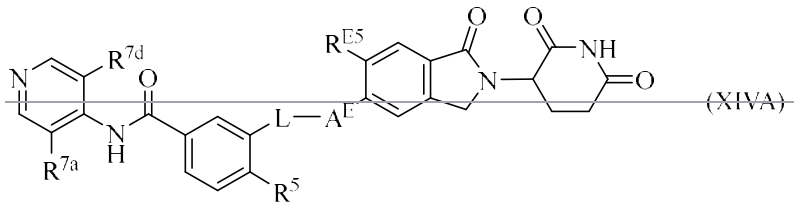
105. The compound of claim 104, having the structure of Formula (XIIA):



(XIIA)

or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

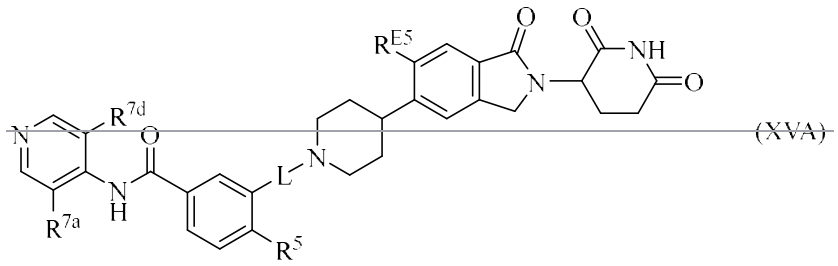
106. The compound of claim 99, having the structure of Formula (XIVA):



(XIVA)

or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

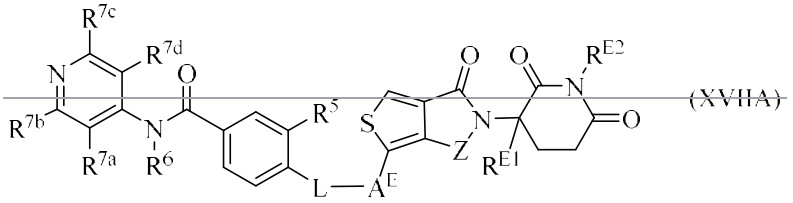
107. The compound of claim 106, having the structure of Formula (XVA):



(XVA)

or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

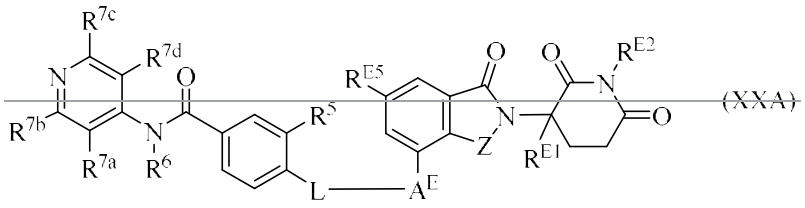
108. The compound of claim 91, having the structure of Formula (XVIIA):



(XVIIA)

or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

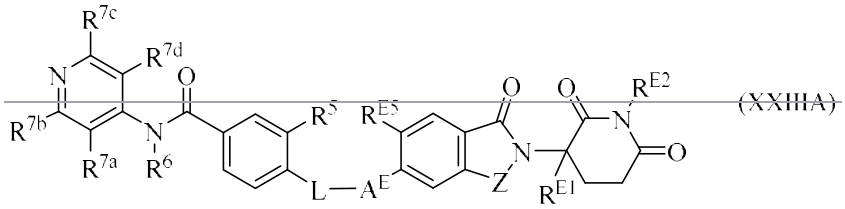
109. The compound of claim 91, having the structure of Formula (XXA):



(XXA)

or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

110. The compound of claim 91, having the structure of Formula (XXIIIA):



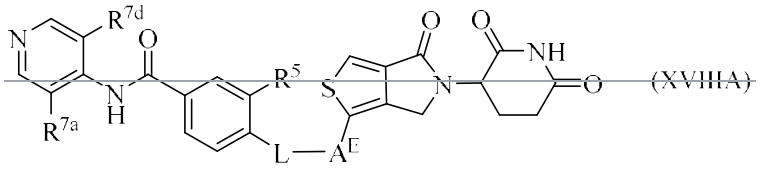
(XXIIIA)

or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

111. The compound of any one of claims 108 to 110, wherein Z is $-CH_2-$.

112. The compound of any one of claims 108 to 110, wherein Z is $-C(O)-$.

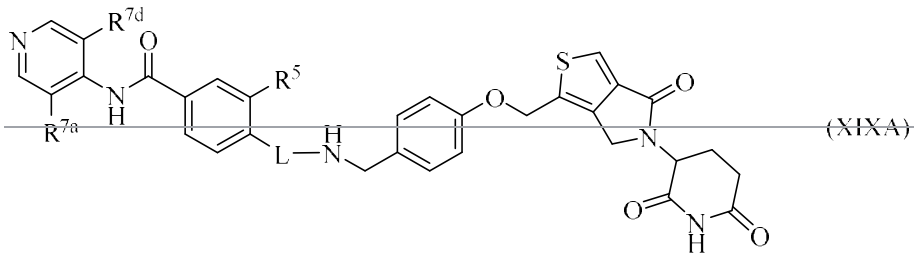
113. The compound of claim 108, having the structure of Formula (XVIIIA):



(XVIIIA)

or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

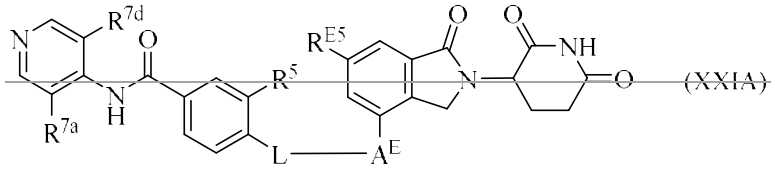
114. The compound of claim 113, having the structure of Formula (XIXA):



(XIXA)

or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

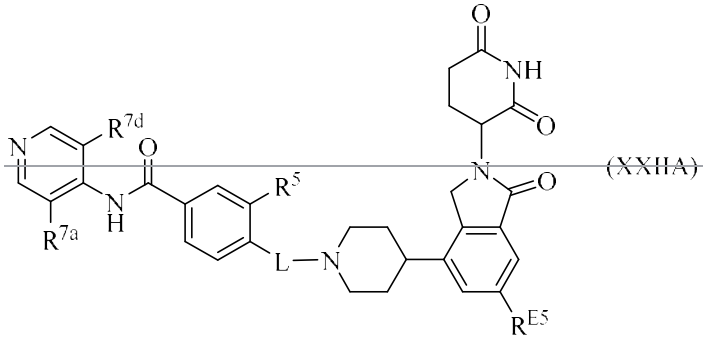
115. The compound of claim 109, having the structure of Formula (XXIA):



(XXIA)

or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

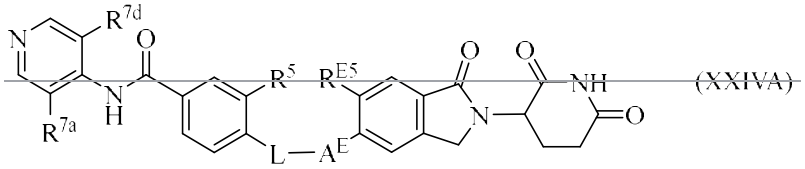
116. The compound of claim 115, having the structure of Formula (XXIIA):



(XXIIA)

or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

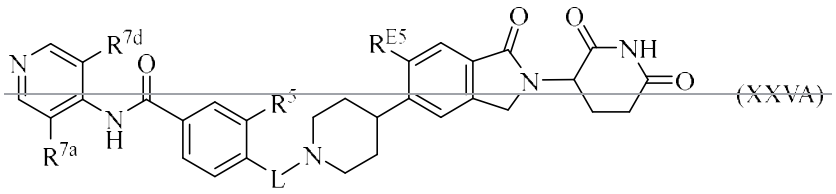
117. The compound of claim 110, having the structure of Formula (XXIVA):



(XXIVA)

or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

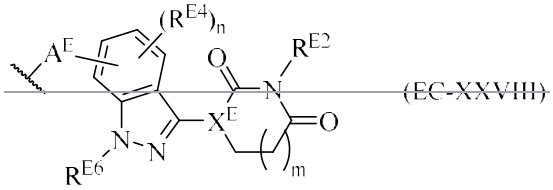
118. The compound of claim 117, having the structure of Formula (XXVA):



(XXVA)

or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

119. The compound of any one of claims 87 to 90, wherein R^E is a moiety having the structure of Formula (EC-XXVIII):



(EC-XXVIII)

or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; wherein:

A^E is a bond, -O-, -N(R^{1b})-, -S-, C_{1-6} alkylene, C_{1-6} heteroalkylene, C_{2-6} alkenylene, C_{2-6} heteroalkenylene, C_{2-6} alkynylene, C_{2-6} heteroalkynylene, C_{3-10} cycloalkylene, C_{6-14} arylene, C_{7-15} aralkylene, heteroarylene, heterocyclylene, C_{1-6} heteroalkylene-C_{6-14} arylene, or C_{2-6} alkynylene-heterocyclylene;

X^E is C(R^{E1}) or N;

m is an integer of 0, 1, or 2;

n is an integer of 0, 1, 2, or 3;

R^{E1} is hydrogen, deuterium, halo, or C_{1-6} alkyl;

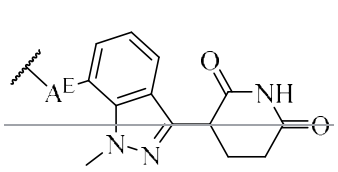
R^{E2} is hydrogen or C_{1-6} alkyl;

each R^{E4} is independently (i) deuterium, cyano, halo, or nitro; (ii) C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl; or (iii) $C(O)R^{1a}$, $C(O)OR^{1a}$, $C(O)NR^{1b}R^{1c}$, $C(O)SR^{1a}$, $C(NR^{1a})NR^{1b}R^{1c}$, $C(S)R^{1a}$, $C(S)OR^{1a}$, $C(S)NR^{1b}R^{1c}$, OR^{1a}, $OC(O)R^{1a}$, $OC(O)OR^{1a}$, $OC(O)NR^{1b}R^{1c}$, $OC(O)SR^{1a}$, $OC(NR^{1a})NR^{1b}R^{1c}$, $OC(S)R^{1a}$, $OC(S)OR^{1a}$, $OC(S)NR^{1b}R^{1c}$, $OS(O)R^{1a}$, $OS(O)_2R^{1a}$, $OS(O)NR^{1b}R^{1c}$, $OS(O)_2NR^{1b}R^{1c}$, $NR^{1b}R^{1c}$, $NR^{1a}C(O)R^{1d}$, $NR^{1a}C(O)OR^{1d}$, $NR^{1a}C(O)NR^{1b}R^{1c}$, $NR^{1a}C(O)SR^{1d}$, $NR^{1a}C(NR^{1d})NR^{1b}R^{1c}$, $NR^{1a}C(S)R^{1d}$, $NR^{1a}C(S)OR^{1d}$, $NR^{1a}C(S)NR^{1b}R^{1c}$, $NR^{1a}S(O)R^{1d}$, $NR^{1a}S(O)_2R^{1d}$, $NR^{1a}S(O)NR^{1b}R^{1c}$, $NR^{1a}S(O)_2NR^{1b}R^{1c}$, SR^{1a}, $S(O)R^{1a}$, $S(O)_2R^{1a}$, $S(O)NR^{1b}R^{1c}$, or $S(O)_2NR^{1b}R^{1c}$; and each R^{E5} is independently hydrogen or R^{E4}; and

R^{E6} is (i) hydrogen; (ii) C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl; or (iii) $C(O)R^{1a}$, $C(O)OR^{1a}$, $C(O)NR^{1b}R^{1c}$, $C(O)SR^{1a}$, $C(NR^{1a})NR^{1b}R^{1c}$, $C(S)R^{1a}$, $C(S)OR^{1a}$, $C(S)NR^{1b}R^{1c}$, OR^{1a}, $OC(O)R^{1a}$, $OC(O)OR^{1a}$, $OC(O)NR^{1b}R^{1c}$, $OC(O)SR^{1a}$, $OC(NR^{1a})NR^{1b}R^{1c}$, $OC(S)R^{1a}$, $OC(S)OR^{1a}$, $OC(S)NR^{1b}R^{1c}$, $OS(O)R^{1a}$, $OS(O)_2R^{1a}$, $OS(O)NR^{1b}R^{1c}$, $OS(O)_2NR^{1b}R^{1c}$, $NR^{1b}R^{1c}$, $NR^{1a}C(O)R^{1d}$, $NR^{1a}C(O)OR^{1d}$, $NR^{1a}C(O)NR^{1b}R^{1c}$, $NR^{1a}C(O)SR^{1d}$, $NR^{1a}C(NR^{1d})NR^{1b}R^{1c}$, $NR^{1a}C(S)R^{1d}$, $NR^{1a}C(S)OR^{1d}$, $NR^{1a}C(S)NR^{1b}R^{1c}$, $NR^{1a}S(O)R^{1d}$, $NR^{1a}S(O)_2R^{1d}$, $NR^{1a}S(O)NR^{1b}R^{1c}$, $NR^{1a}S(O)_2NR^{1b}R^{1c}$, $S(O)R^{1a}$, $S(O)_2R^{1a}$, $S(O)NR^{1b}R^{1c}$, or $S(O)_2NR^{1b}R^{1c}$;

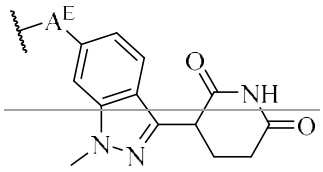
wherein each alkyl, alkylene, heteroalkyl, heteroalkylene, alkenyl, alkenylene, heteroalkenylene, alkynyl, alkynylene, heteroalkynylene, cycloalkyl, cycloalkylene, aryl, arylene, aralkyl, aralkylene, heteroaryl, heteroarylene, heterocyclyl, and heterocyclylene is optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q.

120. The compound of claim 119, wherein R^{E} is a moiety having the structure of:



EC-28

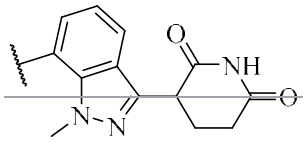
or



EC-29 ;

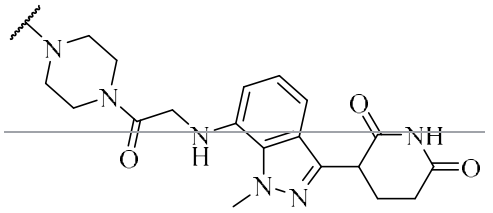
or an enantiomer, a mixture of enantiomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof.

121. The compound of claim 119 or 120, wherein R^E is a moiety having the structure of:

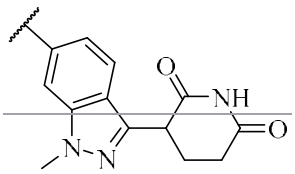


EC-30

,

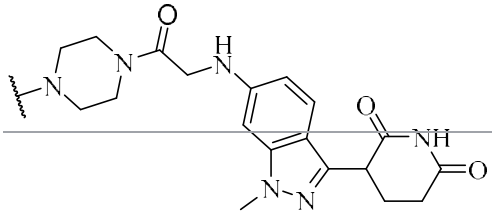


EC-31 ;



EC-32

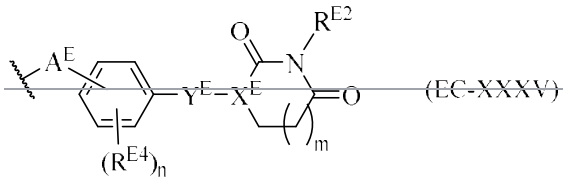
, or



EC-33 ;

or an enantiomer, a mixture of enantiomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof.

122. The compound of any one of claims 87 to 90, wherein R^E is a moiety having the structure of Formula (EC-XXXV):



(EC-XXXV)

or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more

diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; wherein:

A^E is a bond, –O–, –N(R^{1b})–, –S–, C_{1-6} alkylene, C_{1-6} heteroalkylene, C_{2-6} alkenylene, C_{2-6} heteroalkenylene, C_{2-6} alkynylene, C_{2-6} heteroalkynylene, C_{3-10} cycloalkylene, C_{6-14} arylene, C_{7-15} aralkylene, heteroarylene, heterocyclylene, C_{1-6} heteroalkylene-C_{6-14} arylene, or C_{2-6} alkynylene-heterocyclylene;

X^E is C(R^{E1}) or N;

Y^E is a bond, C_{1-6} alkylene, –O–, –S–, –S(O)–, –S(O_2)–, or –N(R^{E7})–;

m is an integer of 0, 1, or 2;

n is an integer of 0, 1, 2, or 3;

R^{E1} is hydrogen, deuterium, halo, or C_{1-6} alkyl;

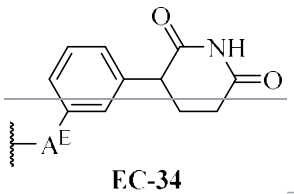
R^{E2} is hydrogen or C_{1-6} alkyl;

each R^{E4} is independently (i) deuterium, cyano, halo, or nitro; (ii) C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl; or (iii) –C(O)R^{1a}, –C(O)OR^{1a}, –C(O)N$R^{1b}R^{1c}$, –C(O)SR^{1a}, –C(NR^{1a})N$R^{1b}R^{1c}$, –C(S)R^{1a}, –C(S)OR^{1a}, –C(S)N$R^{1b}R^{1c}$, –OR^{1a}, –OC(O)R^{1a}, –OC(O)OR^{1a}, –OC(O)N$R^{1b}R^{1c}$, –OC(O)SR^{1a}, –OC(NR^{1a})N$R^{1b}R^{1c}$, –OC(S)R^{1a}, –OC(S)OR^{1a}, –OC(S)N$R^{1b}R^{1c}$, –OS(O)R^{1a}, –OS(O_2)R^{1a}, –OS(O)N$R^{1b}R^{1c}$, –OS(O_2)N$R^{1b}R^{1c}$, –N$R^{1b}R^{1c}$, –NR^{1a}C(O)R^{1d}, –NR^{1a}C(O)OR^{1d}, –NR^{1a}C(O)N$R^{1b}R^{1c}$, –NR^{1a}C(O)SR^{1d}, –NR^{1a}C(NR^{1d})N$R^{1b}R^{1c}$, –NR^{1a}C(S)R^{1d}, –NR^{1a}C(S)OR^{1d}, –NR^{1a}C(S)N$R^{1b}R^{1c}$, –NR^{1a}S(O)R^{1d}, –NR^{1a}S(O_2)R^{1d}, –NR^{1a}S(O)N$R^{1b}R^{1c}$, –NR^{1a}S(O_2)N$R^{1b}R^{1c}$, –SR^{1a}, –S(O)R^{1a}, –S(O_2)R^{1a}, –S(O)N$R^{1b}R^{1c}$, or –S(O_2)N$R^{1b}R^{1c}$; and each R^{E5} is independently hydrogen or R^{E4}; and

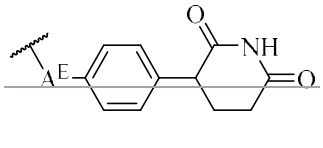
R^{E7} is hydrogen or C_{1-6} alkyl;

wherein each alkyl, alkylene, heteroalkyl, heteroalkylene, alkenyl, alkenylene, heteroalkenylene, alkynyl, alkynylene, heteroalkynylene, cycloalkyl, cycloalkylene, aryl, arylene, aralkyl, aralkylene, heteroaryl, heteroarylene, heterocyclyl, and heterocyclylene is optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q.

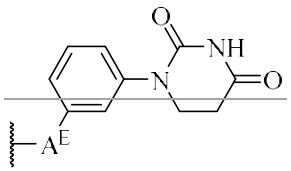
123. The compound of claim 122, wherein R^E is a moiety having the structure of:



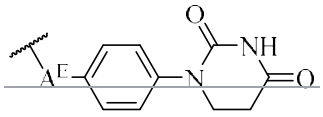
EC-34 ,



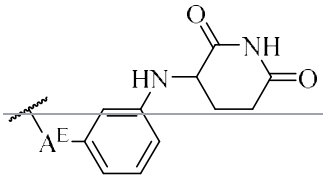
EC-35 ,



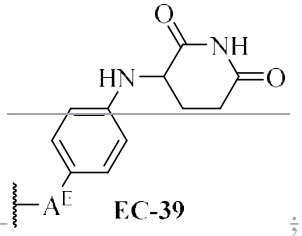
EC-36 ,



EC-37 ,



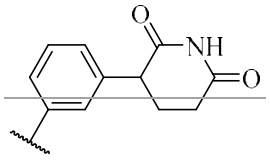
EC-38 , or



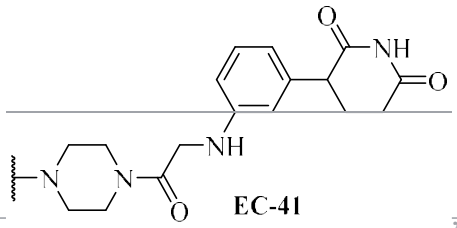
EC-39 ;

or an enantiomer, a mixture of enantiomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof.

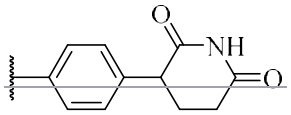
124. The compound of claim 121 or 122, wherein R^E is a moiety having the structure of:



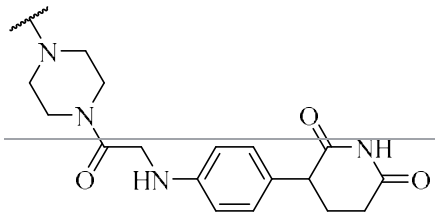
EC-40 ,



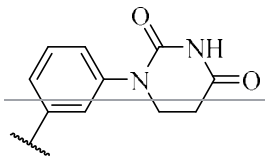
EC-41 ,



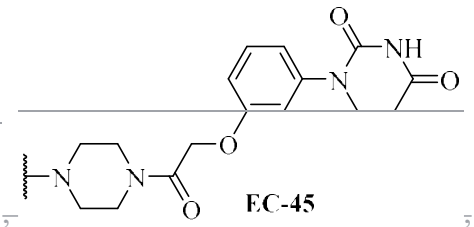
EC-42 ,



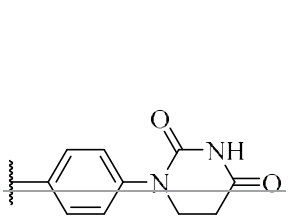
EC-43 ;



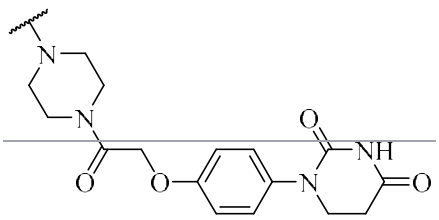
EC-44 ,



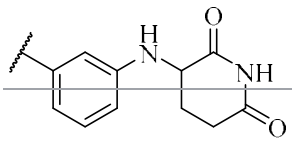
EC-45 ;



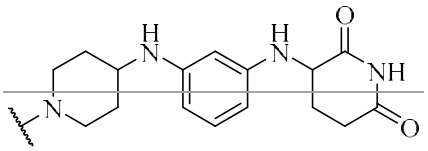
EC-46 ,



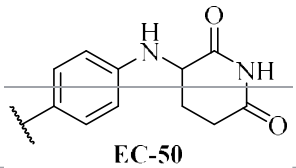
EC-47 ,



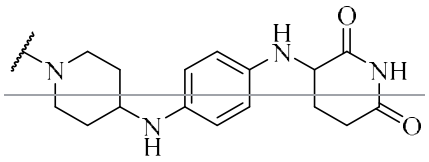
EC-48 ,



EC-49 ,



EC-50 , or



EC-51 ;

or an enantiomer, a mixture of enantiomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof.

125. The compound of any one of claims 87 to 124, wherein R^5 is (i) hydrogen or deuterium; (ii) C_{1-6} alkyl, optionally substituted with one or more substituents Q; or (iii) $-OR^{1a}$.

126. The compound of any one of claims 87 to 125, wherein R^5 is $-OR^{1a}$.

127. The compound of any one of claims 87 to 126, wherein R^5 is methoxy, difluoromethoxy, trifluoromethoxy, ethoxy, or cyclopropylmethoxy.

128. The compound of any one of claims 87 to 127, wherein R^{7a} is hydrogen or halo.

129. The compound of claim 128, wherein R^{7a} is chloro.

130. The compound of any one of claims 87 to 129, wherein R^{7d} is hydrogen or halo.

131. The compound of claim 130, wherein R^{7d} is chloro.

132. The compound of any one of claims 98 to 101, 104 to 107, 109 to 112, 115 to 118, and 125 to 131, wherein R^{E5} is hydrogen or halo.

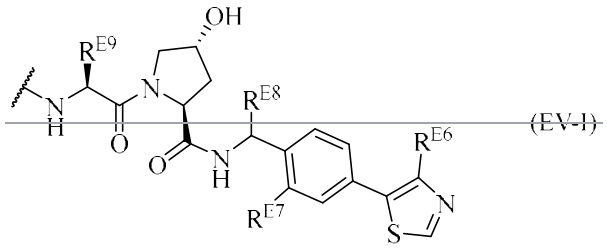
133. The compound of claim 132, wherein R^{E5} is hydrogen or fluoro.

134. The compound of any one of claims 91 to 133, wherein A^E is a bond, -O-, -NH-, ethynediyl, piperidindiyl, piperazindiyl, (phendiyl)oxymethanediyl, or (piperidindiyl)ethynediyl.

135. The compound of any one of claims 91 to 134, wherein A^E is a bond, -NH-, piperidin-1,4-diyl, piperaz-1,4-diyl, (phen-1,4-diyl)oxymethanediyl, or (piperidin-1,4-diyl)ethynediyl.

136. The compound of any one of claims 87 to 89, wherein R^E is a moiety of a von Hippel-Lindau (VHL) E3 ligand.

137. The compound of any one of claims 87 to 89 and 136, wherein R^E has the structure of Formula (EV-I):



(EV-I)

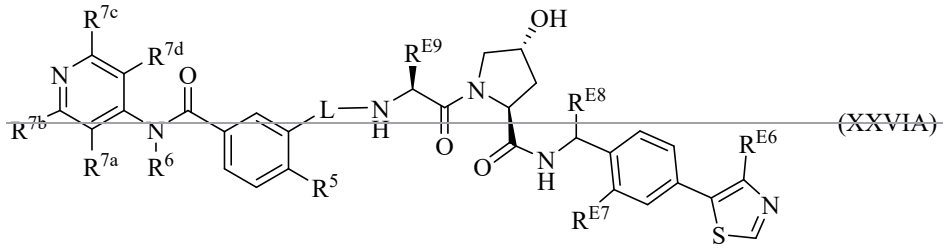
or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; wherein:

R^{E6}, R^{E8}, and R^{E9} are each independently hydrogen, deuterium, C_{1-6} alkyl, or C_{3-10} cycloalkyl; and

R^{E7} is hydrogen, deuterium, halo, hydroxyl, $-OC_{1-6}$ alkyl, or $-OC_{3-10}$ cycloalkyl;

wherein each alkyl and cycloalkyl is optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q.

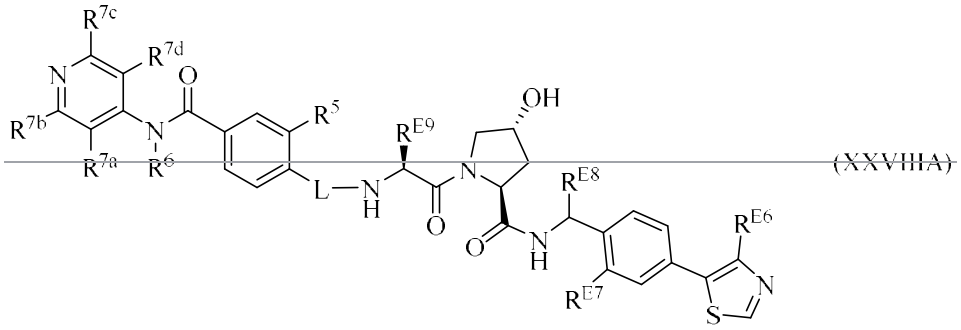
138. The compound of claim 137, having the structure of Formula (XXVIA):



(XXVIA)

~~or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof.~~

~~139. The compound of claim 138, having the structure of Formula (XXVIIIA):~~



(XXVIIIA)

~~or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof.~~

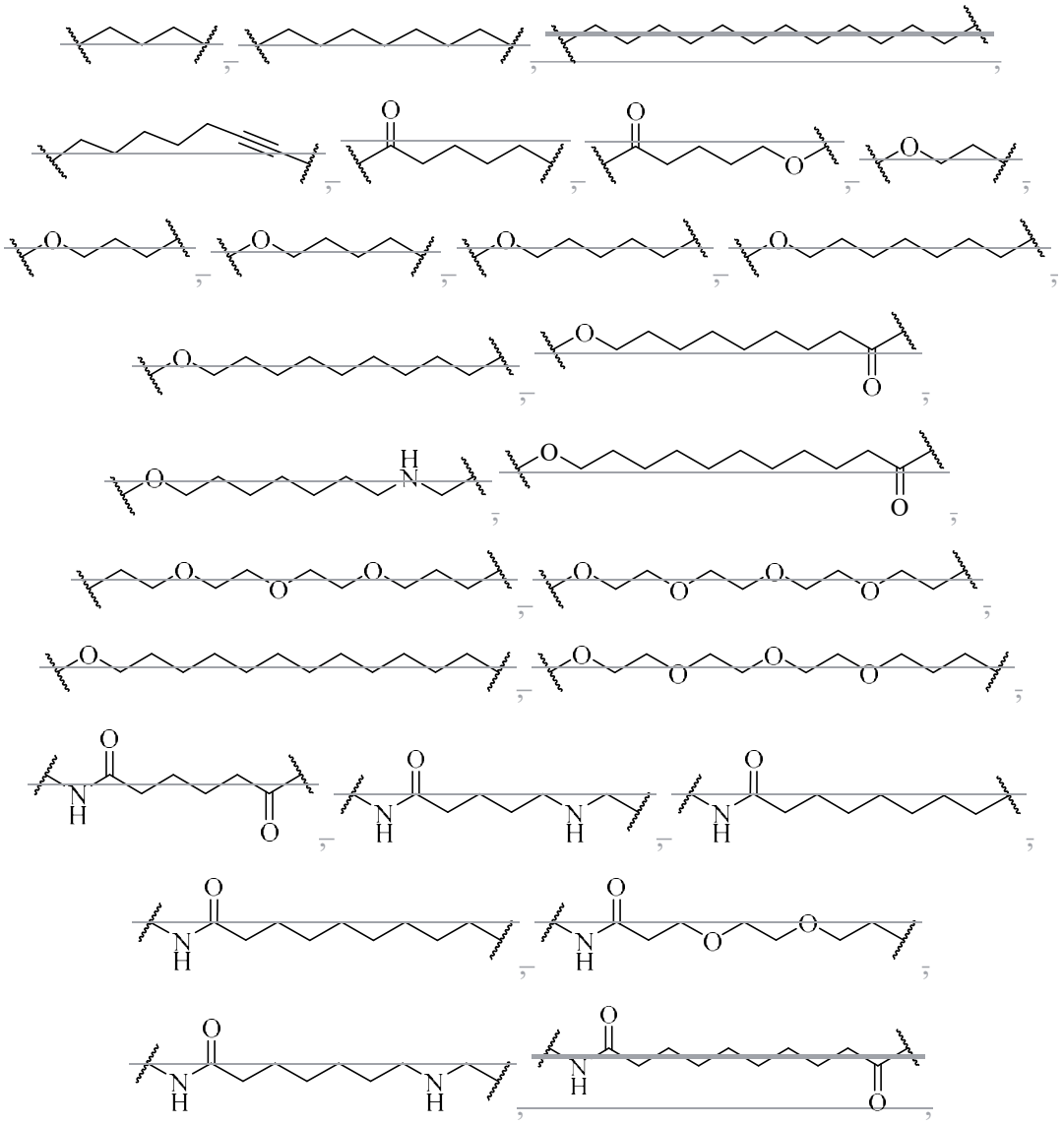
~~140. The compound of any one of claims 87 to 139, wherein L is C_{1-20} alkylene, C_{1-20} heteroalkylene, C_{2-20} alkenylene, C_{2-20} heteroalkenylene, C_{2-20} alkynylene, C_{2-20} heteroalkynylene, C_{3-10} cycloalkylene, C_{6-14} arylene, heteroarylene, or heterocyclylene, each of which is optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q.~~

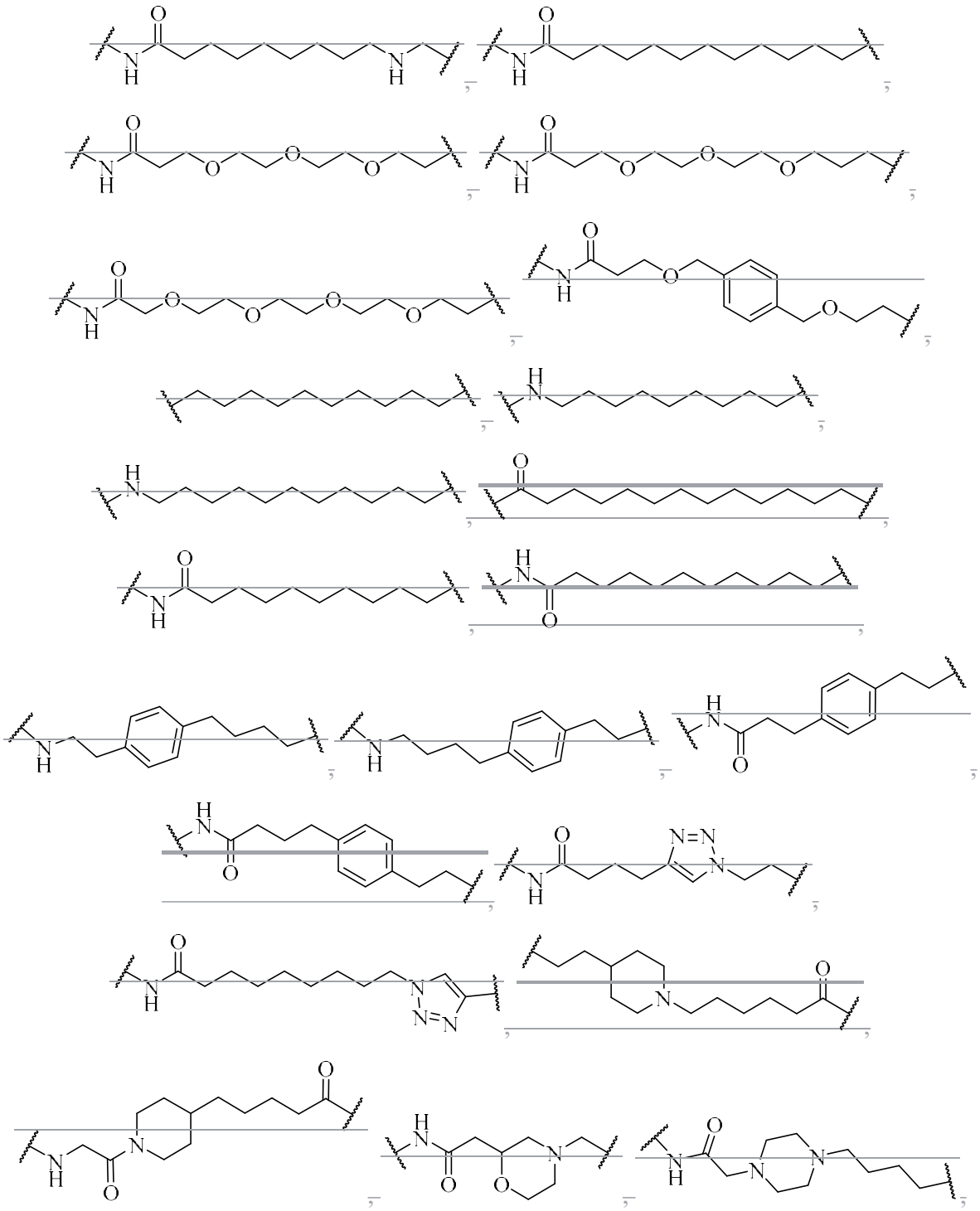
~~141. The compound of claim 140, wherein L is C_{1-20} alkylene, C_{1-20} heteroalkylene, C_{2-20} alkynylene, or C_{2-20} heteroalkynylene, each of which is optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q.~~

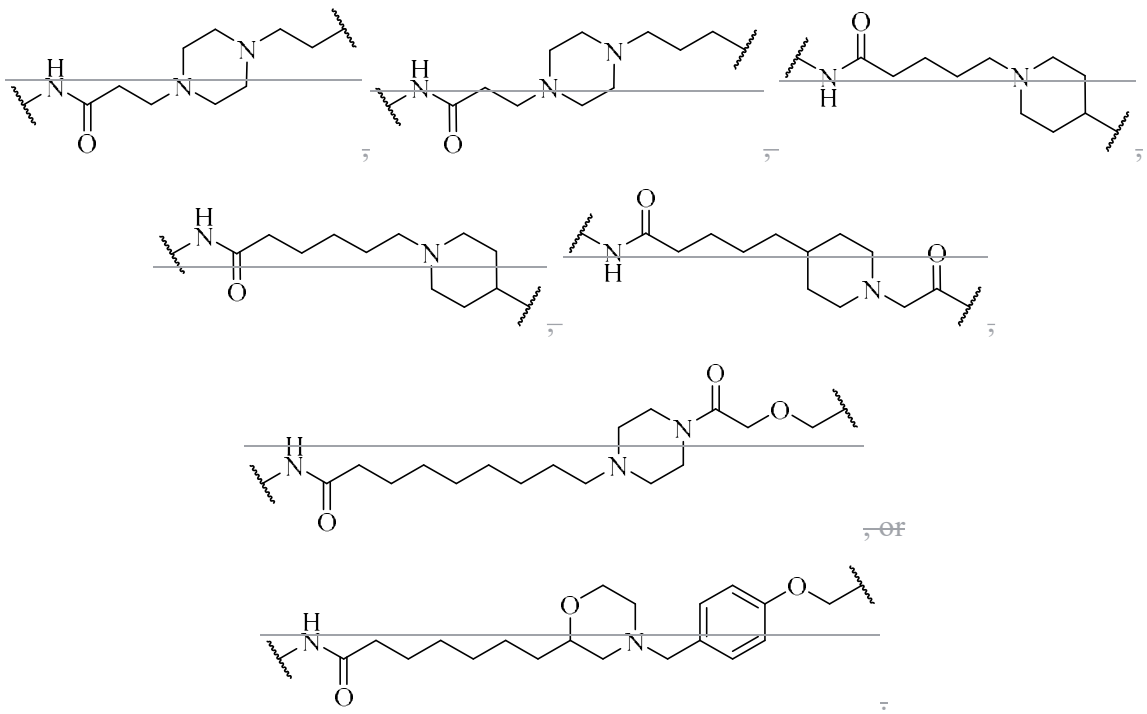
~~142. The compound of any one of claims 87 to 139, wherein L is C_{1-20} alkylene, C_{1-20} heteroalkylene, C_{2-20} alkenylene, C_{2-20} heteroalkenylene, C_{2-20} alkynylene, or C_{2-20} heteroalkynylene, where one or more methylene groups are each independently replaced by a divalent group, and each divalent group is independently C_{3-10} cycloalkylene, C_{6-14} arylene, heteroarylene, or heterocyclylene; and wherein the alkylene, heteroalkylene, alkenylene, heteroalkenylene, alkynylene, heteroalkynylene, cycloalkylene, arylene, heteroarylene, and heterocyclylene are each optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q.~~

143. The compound of claim 142, wherein L is C_{1-20} alkylene or C_{1-20} heteroalkylene, where one or more methylene groups are each independently replaced by a divalent group, and each divalent group is independently C_{3-10} cycloalkylene, C_{6-14} arylene, heteroarylene, or heterocyclylene; and wherein the alkylene, cycloalkylene, arylene, heteroarylene, and heterocyclylene are each optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q.

144. The compound of any one of claims 87 to 139, wherein L is:







145. The compound of claim 87, wherein the compound is:

N-(3,5-dichloropyridin-4-yl)-4-(difluoromethoxy)-3-((7-(4-(2-(2,6-dioxopiperidin-3-yl)-6-fluoro-1-oxoisoindolin-4-yl)piperidin-1-yl)heptyl)oxy)benzamide **B1**;

N-(3,5-dichloropyridin-4-yl)-4-(difluoromethoxy)-3-((5-(4-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)ethynyl)piperidin-1-yl)-5-oxopentyl)oxy)benzamide **B2**;

N-(3,5-dichloropyridin-4-yl)-4-(difluoromethoxy)-3-((7-(4-(2-(2,6-dioxopiperidin-3-yl)-6-fluoro-1-oxoisoindolin-5-yl)piperidin-1-yl)heptyl)oxy)benzamide **B3**;

N-(3,5-dichloropyridin-4-yl)-4-(difluoromethoxy)-3-((9-(4-(2-(2,6-dioxopiperidin-3-yl)-6-fluoro-1-oxoisoindolin-4-yl)piperidin-1-yl)nonyl)oxy)benzamide **B4**;

N-(3,5-dichloropyridin-4-yl)-4-(difluoromethoxy)-3-((5-(4-(2-(2,6-dioxopiperidin-3-yl)-6-fluoro-1-oxoisoindolin-4-yl)piperidin-1-yl)pentyl)oxy)benzamide **B5**;

N-(3,5-dichloropyridin-4-yl)-4-(difluoromethoxy)-3-((7-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)heptyl)oxy)benzamide **B6**;

N-(3,5-dichloropyridin-4-yl)-4-(difluoromethoxy)-3-((12-(4-(2-(2,6-dioxopiperidin-3-yl)-6-fluoro-1-oxoisoindolin-4-yl)piperidin-1-yl)dodecyl)oxy)benzamide **B7**;

N-(3,5-dichloropyridin-4-yl)-3-(difluoromethoxy)-4-(2-(2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)ethoxy)ethoxy)benzamide **B8**;

3-(cyclopropylmethoxy)-*N*-(3,5-dichloropyridin-4-yl)-4-(2-(2-(2-(3-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)amino)propoxy)ethoxy)ethoxy)ethoxy)benzamide **B9**;

3-(cyclopropylmethoxy)-*N*-(3,5-dichloropyridin-4-yl)-4-((7-(4-(2-(2,6-dioxopiperidin-3-yl)-6-fluoro-1-oxoisoindolin-4-yl)piperidin-1-yl)heptyl)oxy)benzamide **B10**;

N-(3,5-dichloropyridin-4-yl)-4-(difluoromethoxy)-3-(3-(4-(2-(2,6-dioxopiperidin-3-yl)-6-fluoro-1-oxoisoindolin-4-yl)piperidin-1-yl)propoxy)benzamide **B11**;

3-(cyclopropylmethoxy)-*N*-(3,5-dichloropyridin-4-yl)-4-((9-(4-(2-(2,6-dioxopiperidin-3-yl)-6-fluoro-1-oxoisoindolin-4-yl)piperidin-1-yl)nonyl)oxy)benzamide **B12**;

3-((9-(4-(2-(1-acetamido-1-oxopropan-2-yl)-6-fluoro-1-oxoisoindolin-4-yl)-piperidin-1-yl)nonyl)oxy)-*N*-(3,5-dichloropyridin-4-yl)-4-(difluoromethoxy)benzamide **B13**;

N-(3,5-dichloropyridin-4-yl)-4-(difluoromethoxy)-3-((7-(1-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)piperidin-4-yl)heptyl)oxy)benzamide **B14**;

N-(3,5-dichloropyridin-4-yl)-4-(difluoromethoxy)-3-(2-{4-[2-(2,6-dioxopiperidin-3-yl)-6-fluoro-1-oxo-2,3-dihydro-1*H*-isoindol-5-yl]piperidin-1-yl}ethoxy)benzamide **B15**;

N-(3,5-dichloropyridin-4-yl)-4-(difluoromethoxy)-3-(2-(2-(2-(3-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)amino)propoxy)ethoxy)ethoxy)ethoxy)benzamide **B16**;

N-(3,5-dichloropyridin-4-yl)-4-(difluoromethoxy)-3-((7-(4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)piperidin-1-yl)heptyl)oxy)benzamide **B17**;

N-(3,5-dichloropyridin-4-yl)-4-(difluoromethoxy)-3-((7-((4-((5-(2,6-dioxopiperidin-3-yl)-4-oxo-5,6-dihydro-4*H*-thieno[3,4-*c*]pyrrol-1-yl)methoxy)benzyl)amino)heptyl)-oxy)benzamide **B18**;

N-(3,5-dichloropyridin-4-yl)-4-(difluoromethoxy)-3-((7-(4-((5-(2,6-dioxopiperidin-3-yl)-4-oxo-5,6-dihydro-4*H*-thieno[3,4-*c*]pyrrol-1-yl)methoxy)phenyl)heptyl)oxy)-benzamide **B19**;

(2*S*,4*R*)-1-((*S*)-2-(9-(5-((3,5-dichloropyridin-4-yl)carbamoyl)-2-(difluoromethoxy)phenoxy)nonanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-

yl)benzyl)pyrrolidine-2-carboxamide **B20**;

(2*S*,4*R*)-1-((*S*)-2-(11-(5-((3,5-dichloropyridin-4-yl)carbamoyl)-2-(difluoromethoxy)phenoxy)undecanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide **B21**;

(2*S*,4*R*)-1-((*S*)-2-(9-(2-(cyclopropylmethoxy)-5-((3,5-dichloropyridin-4-yl)carbamoyl)phenoxy)nonanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide **B22**;

(2*S*,4*R*)-1-((*S*)-2-((7-(5-((3,5-dichloropyridin-4-yl)carbamoyl)-2-(difluoromethoxy)-phenoxy)heptyl)amino)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)-pyrrolidine-2-carboxamide **B23**;

N-(3,5-dichloropyridin-4-yl)-4-(difluoromethoxy)-3-(2-(4-(2-((3-((2,6-dioxopiperidin-3-yl)amino)phenyl)amino)-2-oxoethyl)piperazin-1-yl)ethoxy)benzamide **B24**; or

N-(3,5-dichloropyridin-4-yl)-4-(difluoromethoxy)-3-(4-(4-(2-((3-((2,6-dioxopiperidin-3-yl)amino)phenyl)amino)-2-oxoethyl)piperazin-1-yl)butoxy)benzamide **B25**;

or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

1461519. A pharmaceutical composition comprising a compound of any one of claims 1 to 1451518, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

1472020. The compound of any one of claims 1 to 18 for use in a A method of for treating, preventing, or ameliorating one or more symptoms of a disease, disorder, or condition mediated by a PDE4 in a subject, comprising administering to the subject in need thereof a therapeutically effective amount of a compound of any one of claims 1 to 145.

148. The method of claim 147, wherein the disease, disorder, or condition associated with a PDE4 is an inflammatory disease.

149. A method of treating, preventing, or ameliorating one or more symptoms of or an

inflammatory disease; ~~in a subject, comprising administering to the subject in need thereof a therapeutically effective amount of a compound of any one of claims 1 to 145.~~

~~150. The method of claim 148 or 149,~~ optionally wherein the inflammatory disease is arthritis, ankylosing spondylitis, osteoarthritis, rheumatoid arthritis, Behcet's disease, inflammatory bowel disease, psoriasis, psoriatic arthritis, atopic dermatitis, or contact dermatitis, chronic or obstructive pulmonary disease (COPD).

~~151. The method of any one of claims 147 to 150, wherein the compound is administered orally or topically.~~

~~152. The method of any one of claims 147 to 151, wherein the subject is a human.~~

~~153. A method of inhibiting the activity of a PDE4, comprising contacting the PDE4 with an effective amount of a compound of any one of claims 1 to 145.~~

~~154. A method of inducing degradation of a PDE4, comprising contacting the PDE4 with an effective amount of a compound of any one of claims 1 to 145.~~

~~155. The method of claim 153 or 154, wherein the PDE4 is PDE4D.~~