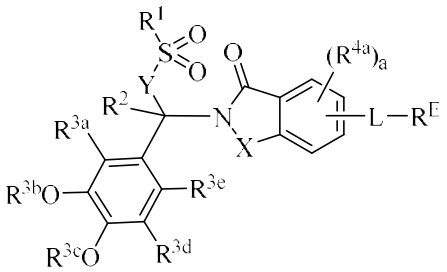
Claims

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 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 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

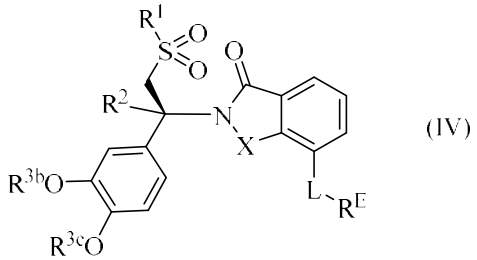
of which is optionally substituted with one or more substituents Q^a; or (iii) R^b and R^c together with the N atom to which they are attached form heterocyclyl, optionally substituted with one or more substituents Q^a;

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; and/or R^{3a} is hydrogen; and/or R^{3d} is hydrogen; and/or R^{3e} is hydrogen.

3. The compound of claims 1 or 2,

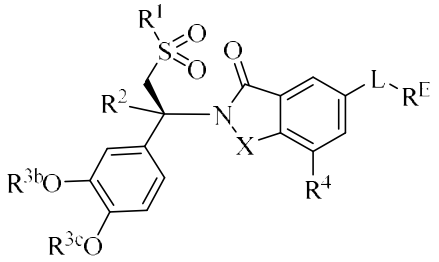
having the structure of Formula (IV):



(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

having the structure of Formula (VI):

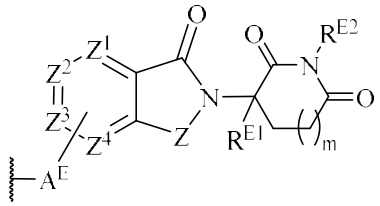


(VI)

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.

4. The compound of any one of claims 1 to 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.

5. The compound of any one of claims 1 to 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;

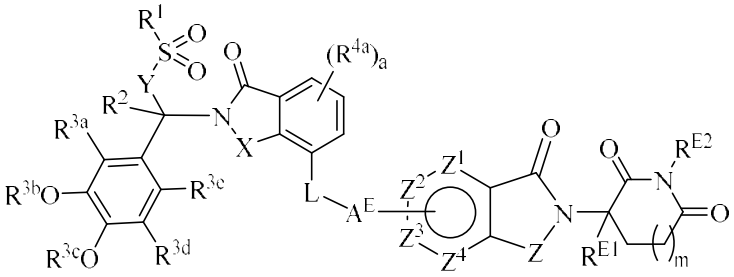
R^{E2} is hydrogen or C_{1-6} alkyl; and

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

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.

6. The compound of claim 5,

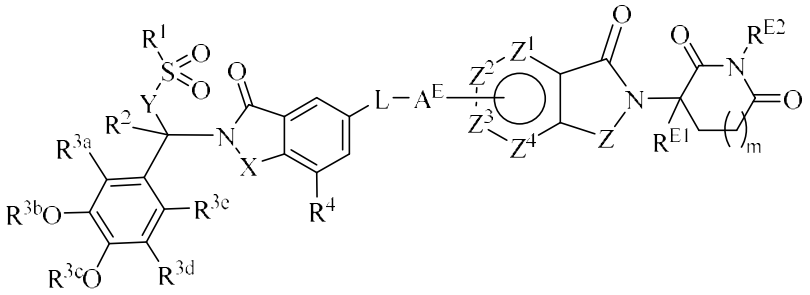
having the structure of Formula (IX):



(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.

7. The compound of claim 5 or 6,

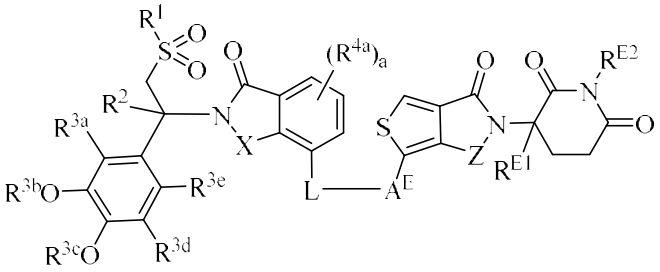
wherein m is an integer of 1; and/or

wherein Z^1 is a bond; and/or

wherein Z^2 is S; or Z^3 is S; or Z^4 is S.

8. The compound of claim 6 or 7,

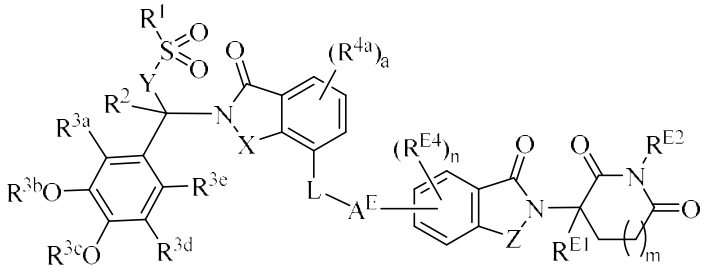
having the structure of Formula (X):



(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

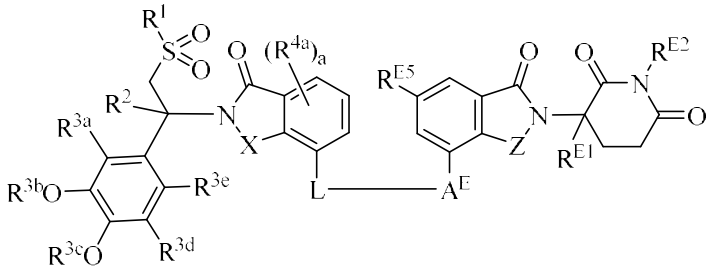
having the structure of Formula (XXI):



(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

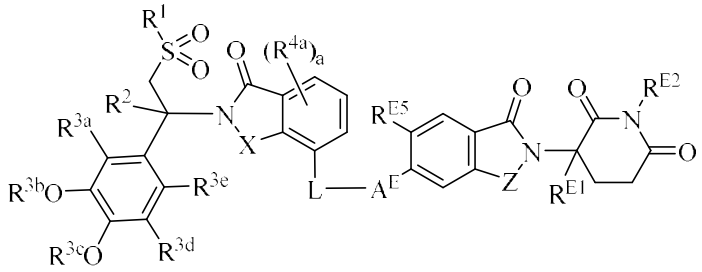
having the structure of Formula (XXII):



(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

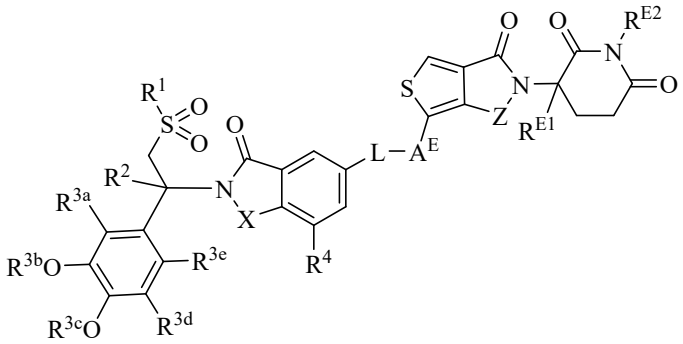
having the structure of Formula (XXVII):



(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

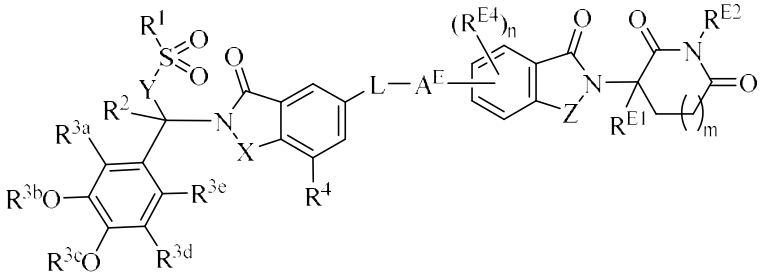
having the structure of Formula (XVI):



(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

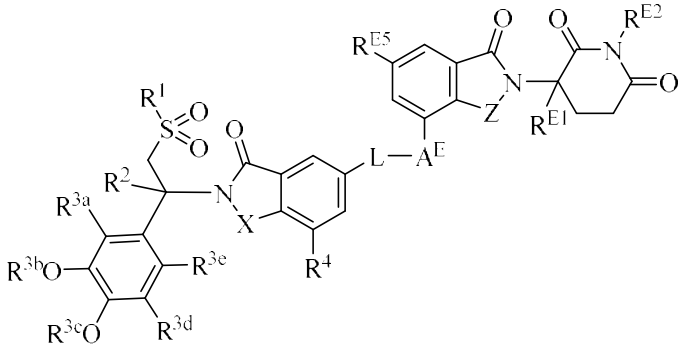
having the structure of Formula (XXXII):



(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

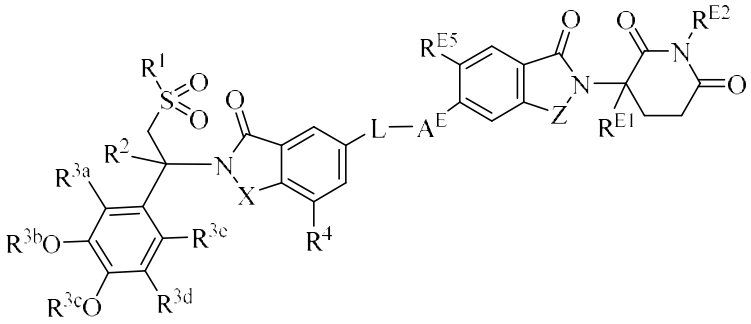
having the structure of Formula (XXXIII):



(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.

9. The compound of any one of claims 5 to 8,

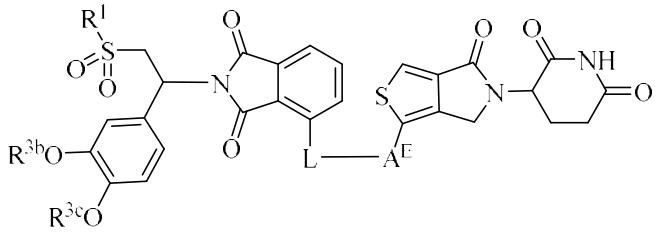
wherein X is $–CH_2–$; or wherein X is –C(O)–; and/or

wherein R^2 is hydrogen; and/or

wherein Z is $–CH_2–$; or wherein Z is –C(O)–.

10. The compound of claim 8,

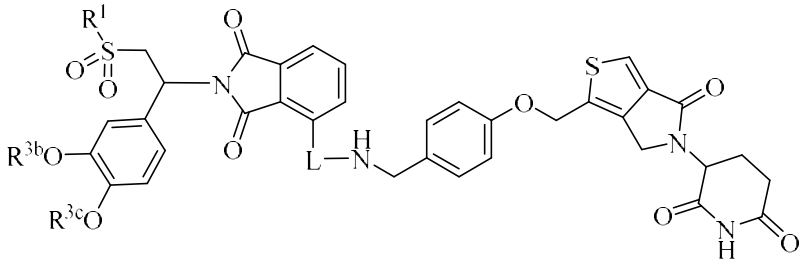
having the structure of Formula (XI):



(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

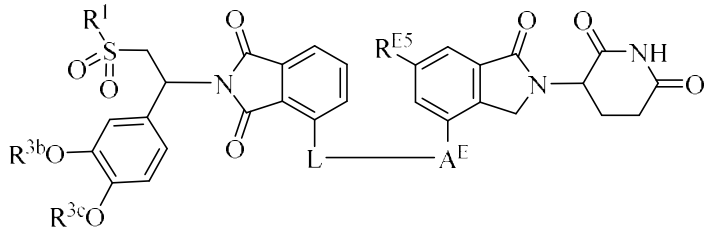
having the structure of Formula (XIII):



(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

having the structure of Formula (XXIII):

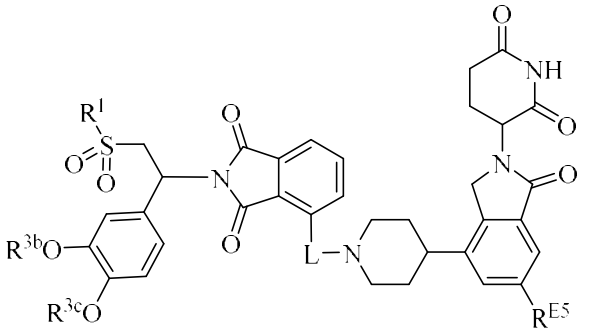


(XXIII)

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

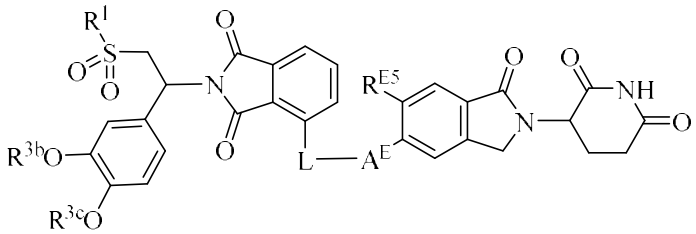
having the structure of Formula (XXV):



(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

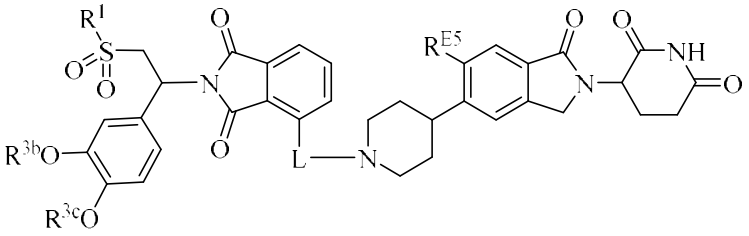
having the structure of Formula (XXVIII):



(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

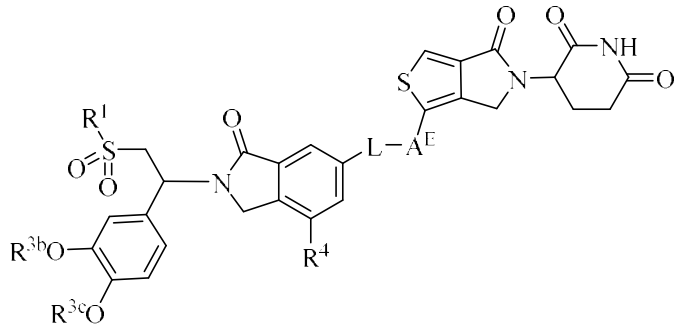
having the structure of Formula (XXX):



(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

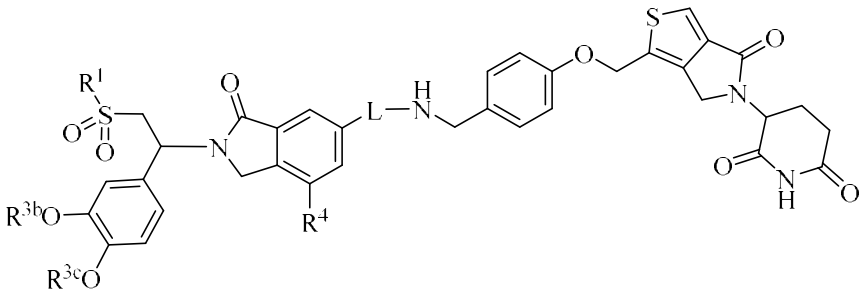
having the structure of Formula (XVII):



(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

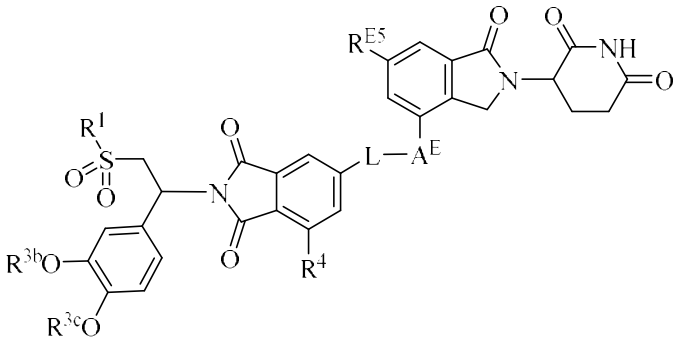
having the structure of Formula (XIX):



(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

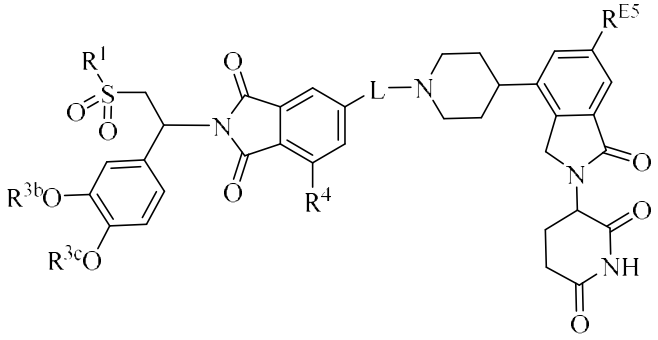
having the structure of Formula (XXXIV):



(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

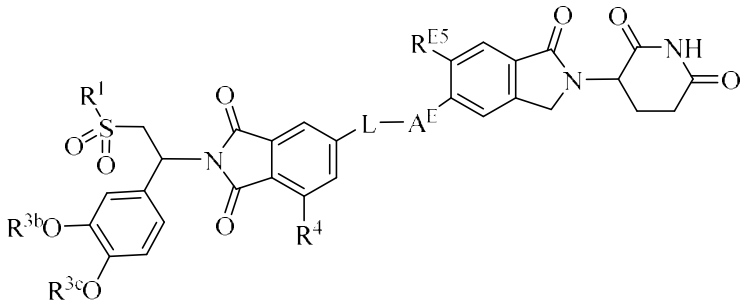
having the structure of Formula (XXXVI):



(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

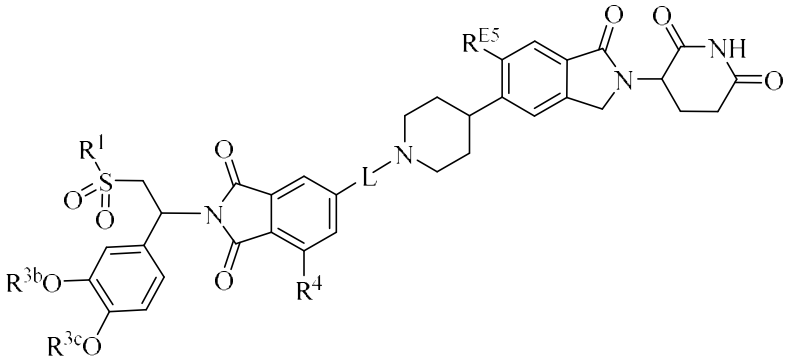
having the structure of Formula (XXXIX):



(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):

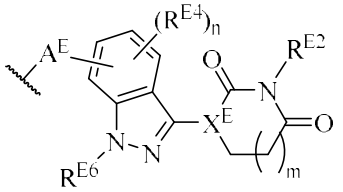


(XLI)

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.

11. The compound of any one of claims 1 to 4,

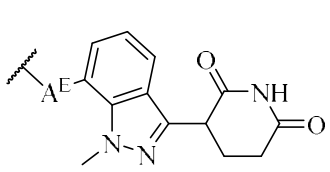
wherein R^{E} is a moiety having the structure of Formula (EC-XXVIII):



(EC-XXVIII)

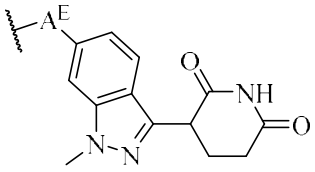
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or

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



EC-28

or

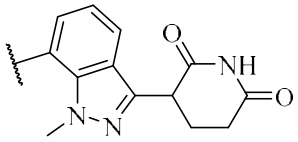


EC-29

;

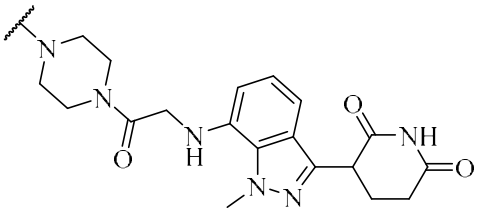
or an enantiomer, a mixture of enantiomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or

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



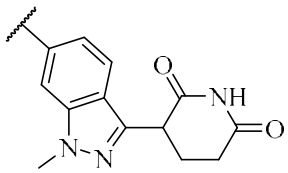
EC-30

,



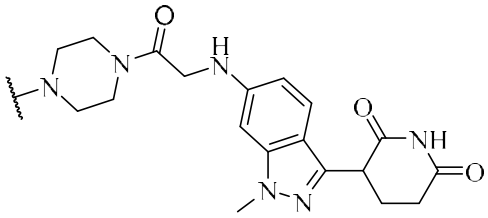
EC-31

,



EC-32

, or

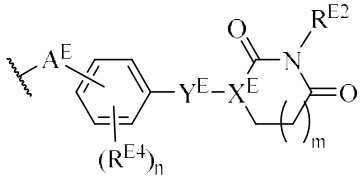


EC-33

;

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

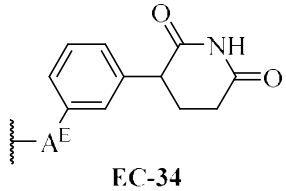
wherein R^E is a moiety having the structure of Formula (EC-XXXV):

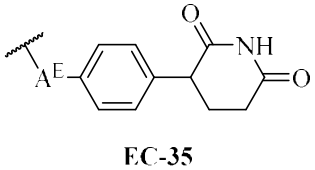


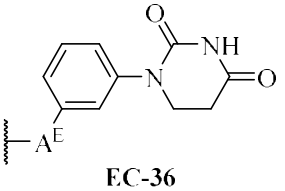
(EC-XXXV)

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

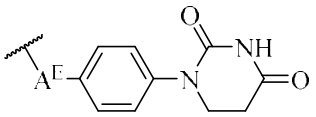
wherein R^E is a moiety having the structure of:

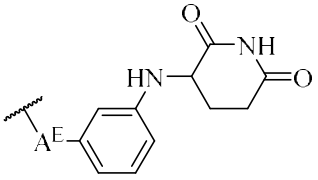


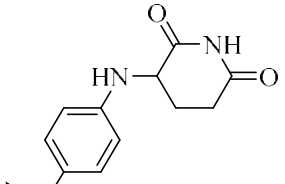
EC-34, 

EC-35, 

EC-36,



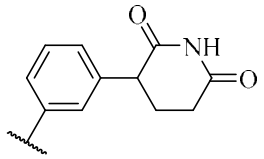
EC-37, 

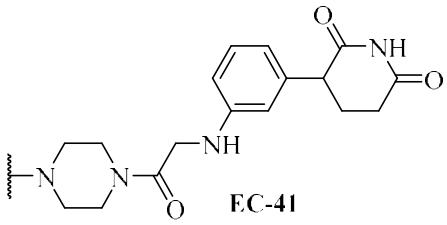
EC-38, or 

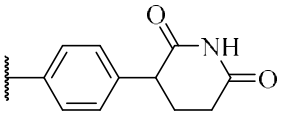
EC-39;

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

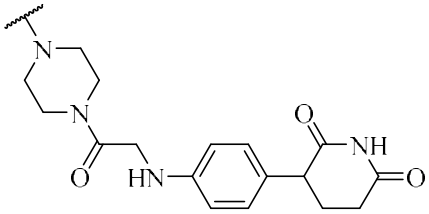
wherein R^E is a moiety having the structure of:

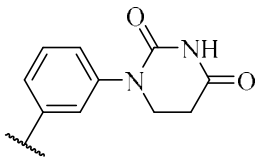


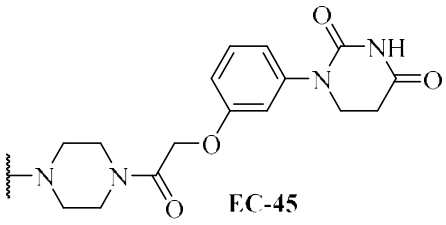
EC-40, 

EC-41, 

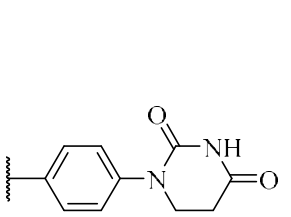
EC-42,



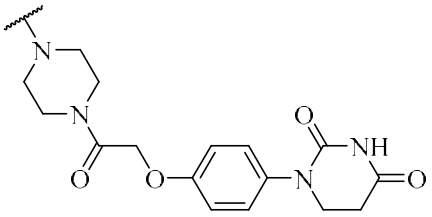
EC-43, 

EC-44, 

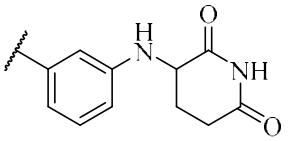
EC-45,



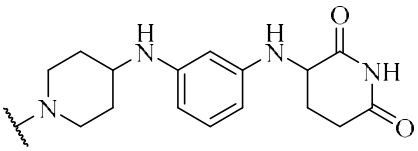
EC-46 ,



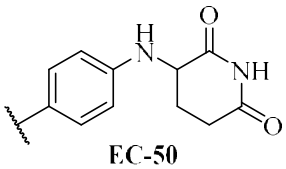
EC-47 ,



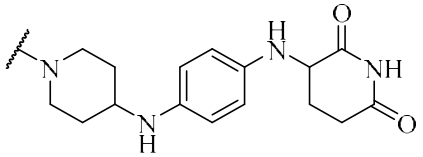
EC-48 ,



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},

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

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.

12. The compound of any one of claims 1 to 11,

wherein R^1 is C_{1-6} alkyl or C_{3-7} cycloalkyl, each optionally substituted with one or more substituents Q; or wherein R^1 is C_{1-6} alkyl, optionally substituted with one or more substituents Q; or wherein R^1 is methyl; and/or

wherein R^{3b} is C_{1-6} alkyl or C_{3-7} cycloalkyl, each optionally substituted with one or more substituents Q; or wherein R^{3b} is C_{1-6} alkyl, optionally substituted with one or more substituents Q; or wherein R^{3b} is ethyl; and/or

wherein R^{3c} is C_{1-6} alkyl or C_{3-7} cycloalkyl, each optionally substituted with one or more substituents Q; or wherein R^{3c} is C_{1-6} alkyl, optionally substituted with one or more substituents Q; or wherein R^{3c} is methyl.

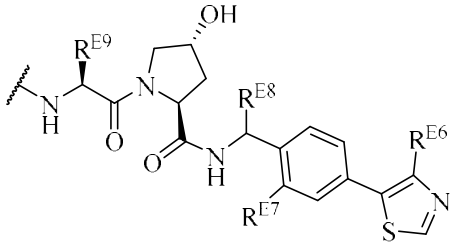
13. The compound of any one of claims 5 to 12,

wherein R^4 is hydrogen or $–NR^{1a}C(O)R^{1d}$; or wherein R^4 is $–NHC(O)\text{-}C_{1\text{-}6}$ alkyl; or wherein R^4 is $–NHC(O)CH_3$; and/or

wherein A^E is a bond, –O–, –NH–, ethynediyl, piperidindiyl, piperazindiyl, (phendiyl)oxymethanediyl, or (piperidindiyl)ethynediyl; or 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.

14. The compound of any one of claims 1 to 4,

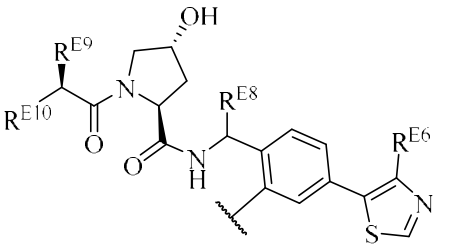
wherein R^E has the structure of Formula (EV-I):



(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

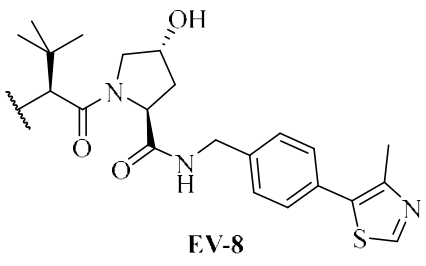
wherein R^E has the structure of Formula (EV-III):



(EV-III)

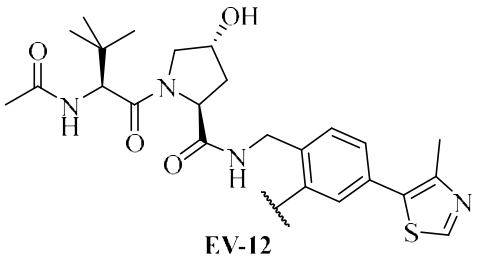
or a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or

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;

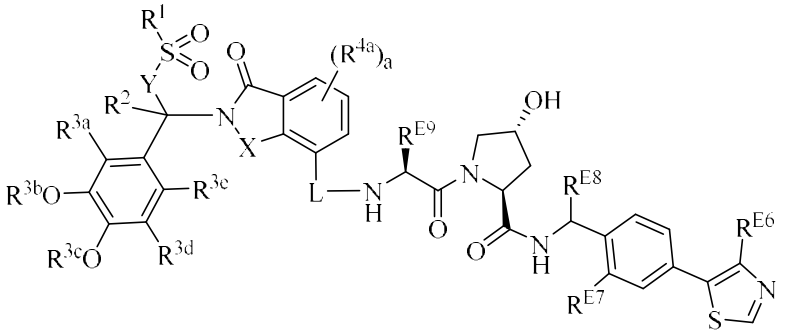
R^{E7} is hydrogen, deuterium, halo, hydroxyl, $–OC_{1-6}$ alkyl, or $–OC_{3-10}$ cycloalkyl; and

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.

15. The compound of claim 14,

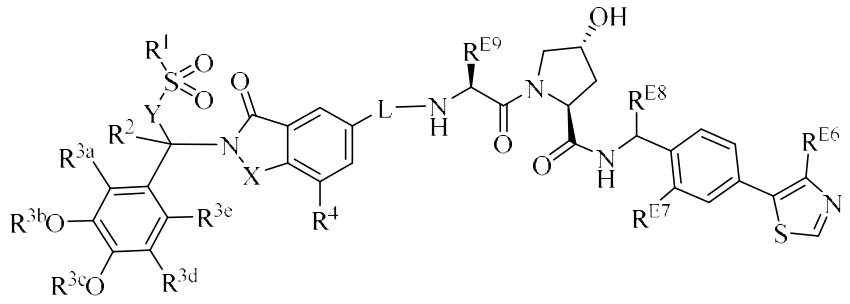
having the structure of Formula (XLIII):



(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

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.

16. The compound of any one of claims 1 to 15,

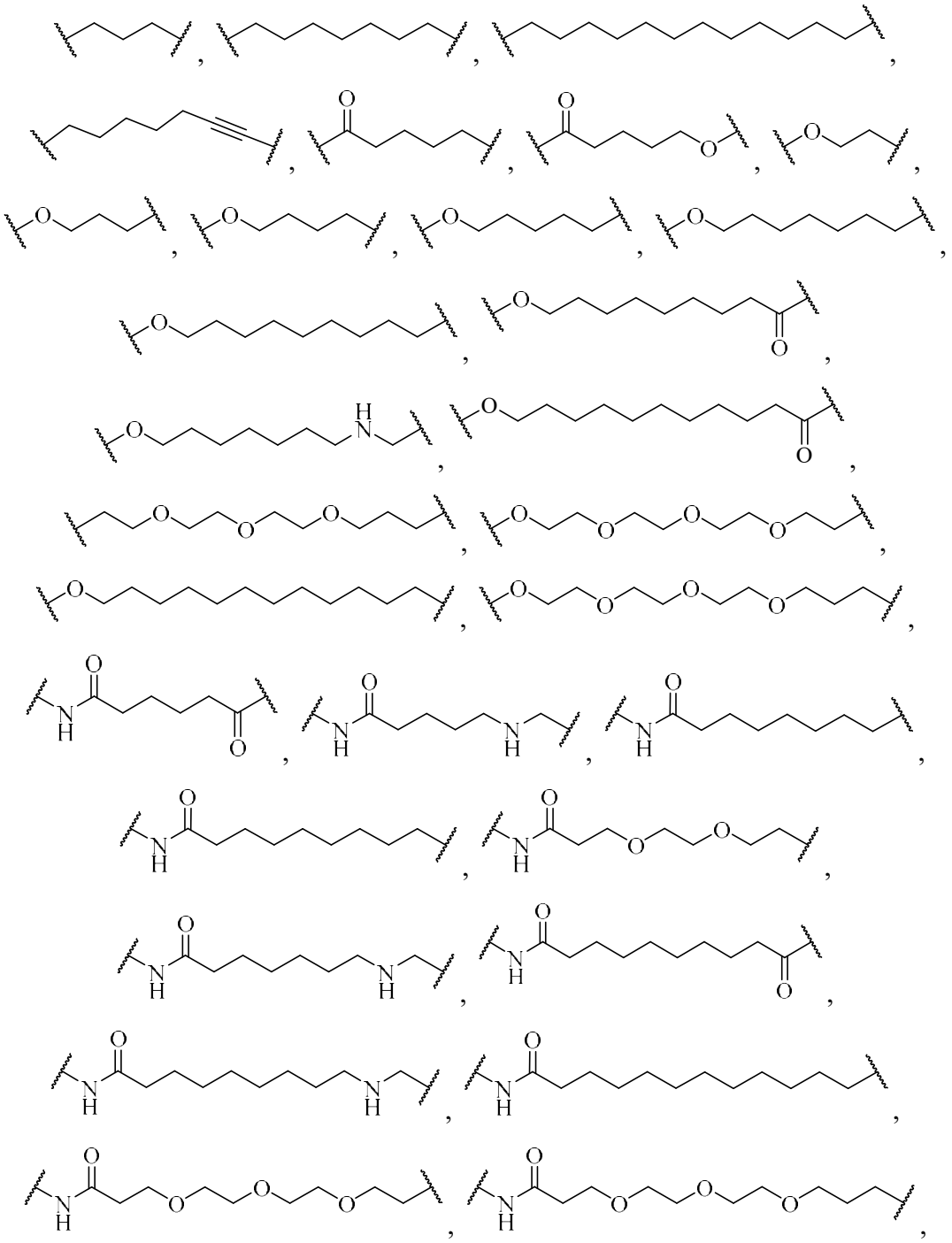
wherein L is C_{1-20} alkylene, C_{1-20} heteroalkylene, C_{2-20} alkenylene, C_{2-20} heteroalkenylene, C_{2-20} alkynylene, C_{2-20} heteroalkynylene, C_{3-10} cycloalkylene, C_{6-14} arylene, heteroarylene, or heterocyclylene, each of which is optionally substituted with one or more substituents Q; or

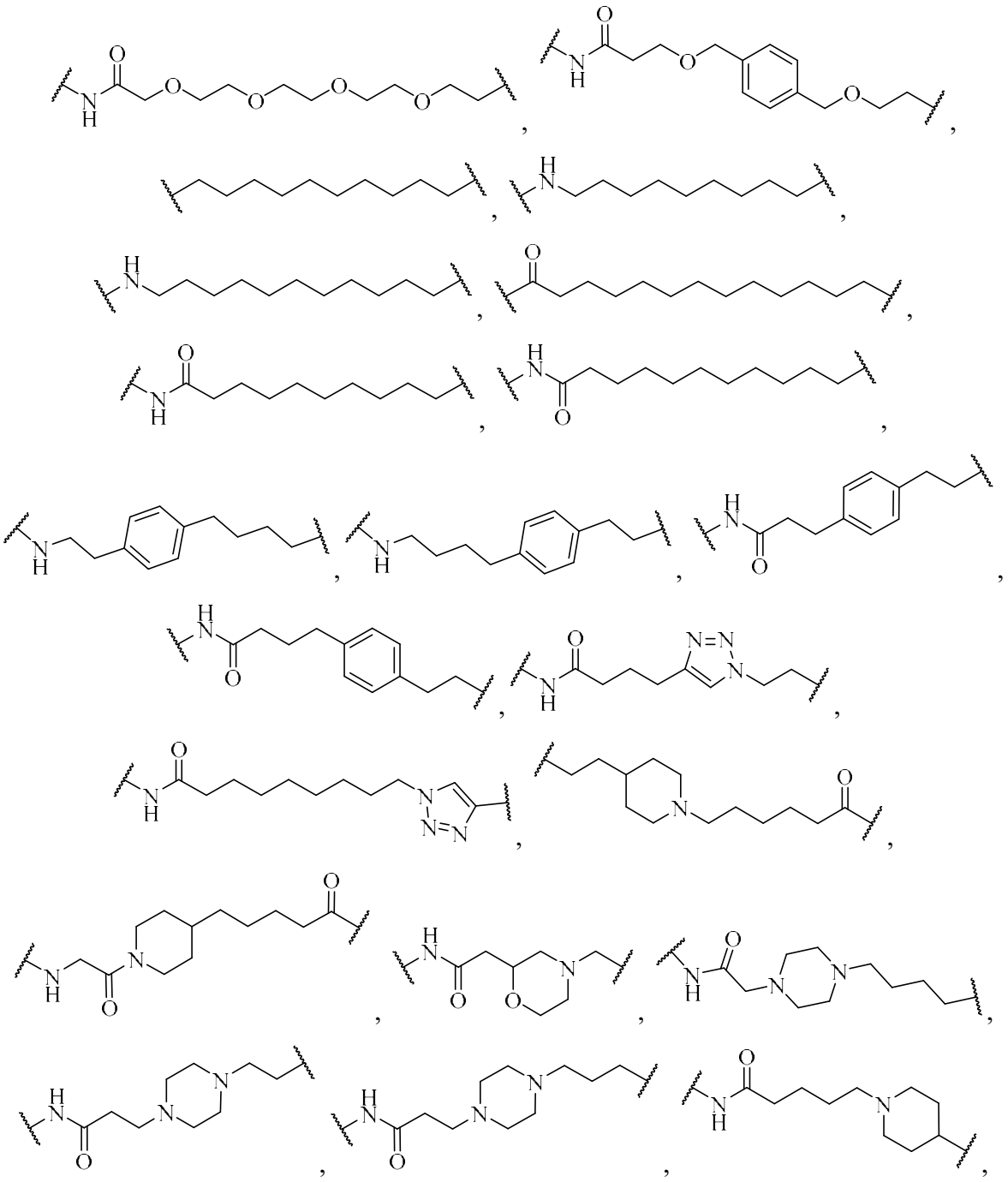
wherein L is C_{1-20} alkylene, C_{1-20} heteroalkylene, C_{2-20} alkynylene, or C_{2-20} heteroalkynylene, each of which is optionally substituted with one or more substituents Q; or

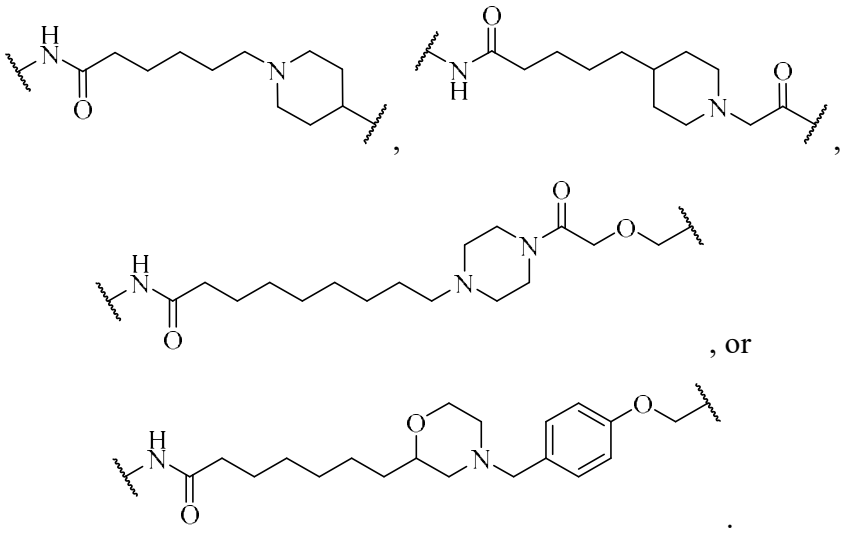
wherein L is C_{1-20} alkylene, C_{1-20} heteroalkylene, C_{2-20} alkenylene, C_{2-20} heteroalkenylene, C_{2-20} alkynylene, or C_{2-20} heteroalkynylene, where one or more methylene groups are each independently replaced by a divalent group, and each divalent group is independently C_{3-10} cycloalkylene, 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 substituents Q; or

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 substituents Q; or

wherein L is:







17. 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-methanesulfonylethyl]-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-methanesulfonylethyl]-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-methane-sulfonylethyl]-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-methoxy-

phenyl)-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-methane-sulfonylethyl]-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-methoxyphenyl)-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-dimethyl-butanoyl]-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-methane-sulfonylethyl]-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-methane-sulfonylethyl]-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl}carbamoyl)butyl]piperazin-1-yl}acet-amido)-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}acetamido)-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}pentan-

amido)-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**;

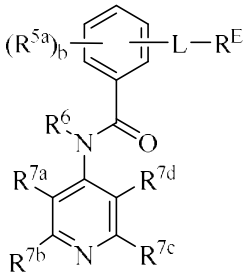
4-amino-6-[12-({3-[(2,6-dioxopiperidin-3-yl)amino]phenyl}amino)dodecyl]-2-[(1*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-methanesulfonylethyl]-2,3-dihydro-1*H*-isoindole-1,3-dione **A90**;

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.

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)$_2$R^{1a}, –OS(O)NR^{1b}R^{1c}, –OS(O)$_2$NR^{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)$_2$R^{1d}, –NR^{1a}S(O)NR^{1b}R^{1c}, –NR^{1a}S(O)$_2$NR^{1b}R^{1c}, –SR^{1a}, –S(O)R^{1a}, –S(O)$_2$R^{1a}, –S(O)NR^{1b}R^{1c}, or –S(O)$_2$NR^{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)$_2$R^{1a}, –OS(O)NR^{1b}R^{1c}, –OS(O)$_2$NR^{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)$_2$R^{1d}, –NR^{1a}S(O)NR^{1b}R^{1c}, –NR^{1a}S(O)$_2$NR^{1b}R^{1c}, –SR^{1a}, –S(O)R^{1a}, –S(O)$_2$R^{1a}, –S(O)NR^{1b}R^{1c}, or –S(O)$_2$NR^{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 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 substituents Q^a; and (c) –C(O)R^a, –C(O)OR^a, –C(O)NR^{b}R^c, –C(O)SR^a, –C(NR^a)NR^{b}R^c, –C(S)R^a, –C(S)OR^a, –C(S)NR^{b}R^c, –OR^a, –OC(O)R^a, –OC(O)OR^a, –OC(O)NR^{b}R^c, –OC(O)SR^a, –OC(NR^a)NR^{b}R^c, –OC(S)R^a, –OC(S)OR^a, –OC(S)NR^{b}R^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 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 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.

19. A pharmaceutical composition comprising a compound of any one of claims 1 to 18, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

20. The compound of any one of claims 1 to 18 for use in a method for treating, preventing, or ameliorating one or more symptoms of a disease, disorder, or condition mediated by a PDE4 or an inflammatory disease; 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).