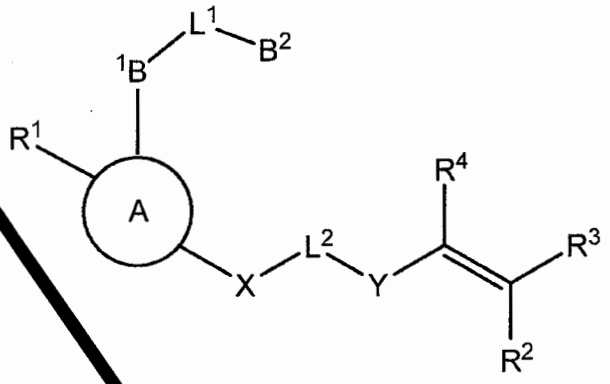
CLAIMS

1. A compound according to Formula I:



I

wherein:

A is selected from C_{3-12}cycloalkyl, C_{3-12}heterocycloalkyl, C_{3-12}aryl, or C_{3-12}heteroaryl, any of which is optionally substituted with G^1 substituents;

B^1 is selected from C_{3-12}cycloalkyl–C_{0-12}alkyl–, C_{3-12}heterocycloalkyl–C_{0-12}alkyl–, aryl–C_{0-12}alkyl–, aryl–C_{3-12}cycloalkyl–, aryl–C_{3-12}heterocycloalkyl–, heteroaryl–C_{0-12}alkyl–, heteroaryl–C_{3-12}cycloalkyl–, or heteroaryl–C_{3-12}heterocycloalkyl–, any of which is optionally substituted with G^2 substituents;

B^2 is selected from C_{0-12}alkyl, C_{3-12}cycloalkyl–C_{0-12}alkyl–, C_{3-12}heterocycloalkyl–C_{0-12}alkyl–, aryl–C_{0-12}alkyl–, aryl–C_{3-12}cycloalkyl–, aryl–C_{3-12}heterocycloalkyl–, heteroaryl–C_{0-12}alkyl–, heteroaryl–C_{3-12}cycloalkyl–, or heteroaryl–C_{3-12}heterocycloalkyl–, any of which is optionally substituted with G^3 substituents;

L^1 is selected from $-C_{0-2}$alkyl–, $-CR^5R^6-$, $-C_{0-3}$alkyl$(R^5)(OH)-$, –C(O)–, $-CH_2O-$, $-OCH_2-$, $-CF_2-$, $-SCR^5R^6-$, $-CR^5R^6S-$, $-N(R^5)-$, $-N(R^5)C(O)-$, $-C(O)N(R^5)-$, $-N(R^5)C(O)N(R^6)-$, –O–, –S–, $-S(O)_{m1}-$, $-N(R^5)S(O)_{m1}-$, or $-S(O)_{m1}N(R^5)-$;

L^2 is selected from $-C_{0-4}$alkyl–, –C(O)–, $-N(R^7)-$, $-N(R^7)C(O)-$, or $-N(R^7)S(O)_{m2}-$;

X is selected from C_{3-12}cycloalkyl–C_{0-12}alkyl–, C_{3-12}heterocycloalkyl–C_{0-12}alkyl–, aryl–C_{0-12}alkyl–, aryl–C_{3-12}cycloalkyl–, aryl–C_{3-12}heterocycloalkyl–, heteroaryl–C_{0-12}alkyl–, heteroaryl–C_{3-12}cycloalkyl–, or heteroaryl–C_{3-12}heterocycloalkyl–, any of which is optionally substituted with G^4 substituents;

Y is selected from –C(O)–, $-N(R^8)-$, $-N(R^8)C(O)-$, $-S(O)_{m3}-$, or $-N(R^8)S(O)_{m3}-$;

R^1 is selected from $-C(O)R^9$, $-C(O)NR^9R^{10}$, $-C(O)OR^9$, C_{1-4}alkynyl, OR^9, $S(O)_{m4}R^9R^{10}$, or $-CN$;

R^2, R^3, and R^4 are each independently selected from C_{0-12}alkyl, –CN, halo, C_{3-12}cycloalkyl–C_{0-12}alkyl–, C_{3-12}heterocycloalkyl–C_{0-12}alkyl–, aryl–C_{0-12}alkyl–, aryl–C_{3-12}cycloalkyl–, aryl–C_{3-12}heterocycloalkyl–, heteroaryl–C_{0-12}alkyl–, heteroaryl–C_{3-12}cycloalkyl–, or heteroaryl–C_{3-12}heterocycloalkyl–, any of which is optionally substituted with G^5 substituents;

R^5, R^6, R^7, R^8, R^9 and R^{10} are each independently selected from C_{0-12}alkyl, C_{3-12}cycloalkyl–C_{0-12}alkyl–, C_{3-12}heterocycloalkyl–C_{0-12}alkyl–, aryl–C_{0-12}alkyl–, aryl–C_{3-12}cycloalkyl–, aryl–C_{3-12}heterocycloalkyl–, heteroaryl–C_{0-12}alkyl–, heteroaryl–C_{3-12}cycloalkyl–, or heteroaryl–C_{3-12}heterocycloalkyl–, any of which is optionally substituted with G^6 substituents;

G^1, G^2, G^3, G^4, G^5, and G^6 are each independently selected from one or more of C_{0-12}alkyl, $-C_{2-12}$alkenyl, $-C_{2-12}$alkynyl, D, $-CD_3$, $-OCD_3$, halo, –CN, –oxo–, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-NO_2$, $-B(OH)_2$, $-P(O)C_{0-3}$ alkyl, $-PO(OR^{11})_2$, $-PO(OR^{11})R^{12}$, C_{3-12}cycloalkyl–C_{0-12}alkyl–, C_{3-12}heterocycloalkyl–C_{0-12}alkyl–, aryl–C_{0-12}alkyl–, aryl–C_{3-12}cycloalkyl–, aryl–C_{3-12}heterocycloalkyl–, heteroaryl–C_{0-12}alkyl–, heteroaryl–C_{3-12}cycloalkyl–, heteroaryl–C_{3-12}heterocycloalkyl–, $-C_{0-6}$alkylOR^{11},$-OC(O)NR^{11}R^{12}$, $-C(O)OR^{11}$, $-C(O)NR^{11}R^{12}$, $-C(O)R^{11}$, $-NR^{11}R^{12}$, $-NR^{11}C(O)R^{12}$, $-NR^{13}C(O)NR^{11}R^{12}$, $-S(O)_{m5}R^{11}$, and $-NR^{11}S(O)_{m5}R^{12}$, any of which is optionally substituted with independently selected Q^1 substituents;

Q^1 is selected from one or more of C_{0-12}alkyl–, $-C_{2-12}$alkenyl, $-C_{2-12}$alkynyl, D, halo, –CN, $-CD_3$, $-OCD_3$, –oxo–, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-NO_2$, $-B(OH)_2$, $-PO(OR^{14})_2$, $-PO(OR^{14})R^{15}$, $NR^{14}R^{15}$, $-C(O)NR^{14}OH$, $-C_{0-6}$alkylOR^{14}, aryl–C_{0-12}alkyl–, heteroaryl–C_{0-12}alkyl–, C_{3-12}cycloalkyl–C_{0-12}alkyl–, C_{3-12}heterocycloalkyl–C_{0-12}alkyl–, aryl–C_{3-12}cycloalkyl–, heteroaryl–C_{3-12}cycloalkyl–, C_{3-12}heterocycloalkyl–C_{3-12}cycloalkyl–, C_{3-12}cycloalkyl–C_{3-12}cycloalkyl–, C_{3-12}heterocycloalkyl–C_{3-12}heterocycloalkyl–, aryl–C_{3-12}heterocycloalkyl–, heteroaryl–C_{3-12}heterocycloalkyl–, $-C(O)$-$C(O)NR^{14}R^{15}$, $-C(O)$-$C(O)OR^{14}$, $-OC(O)R^{14}$, $-NR^{14}C(O)R^{15}$, $-NR^{14}S(O)_{m6}R^{15}$, $-(CR^{15}R^{16})_{n1}C(O)R^{14}$, $-(CR^{15}R^{16})_{n1}C(O)OR^{14}$, $-(CR^{15}R^{16})_{n1}C(O)NR^{14}R^{17}$, $-(CR^{15}R^{16})_{n1}S(O)_{m6}NR^{14}R^{17}$, $-(CR^{15}R^{16})_{n1}NR^{14}R^{17}$, $-(CR^{15}R^{16})_{n1}OR^{14}$, $-(CR^{15}R^{16})_{n1}S(O)_{m6}R^{14}$, $-NR^{16}C(O)NR^{14}R^{15}$, and $-NR^{16}S(O)_{m6}NR^{14}R^{15}$, any of which is optionally substituted with independently selected E^1 substituents;

E^1 is selected from one or more of C_{0-12}alkyl–, –C_{2-12}alkenyl, –C_{2-12}alkynyl, D, halo, –CN, –oxo–, $-CD_3$, $-OCD_3$, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-NO_2$, $-B(OH)_2$, $-PO(OR^{18})_2$, $-PO(OR^{18})R^{19}$, $-C(O)NR^{18}OH$, $-C(O)NR^{18}R^{19}$, $-C_{0-12}alkylOR^{18}$, aryl–C_{0-12}alkyl–, heteroaryl–C_{0-12}alkyl–, C_{3-12}cycloalkyl–C_{0-12}alkyl–, C_{3-12}heterocycloalkyl–C_{0-12}alkyl–, aryl–C_{0-12}cycloalkyl–, heteroaryl–C_{3-12}cycloalkyl–, C_{3-12}heterocycloalkyl–C_{3-12}cycloalkyl–, C_{3-12}cycloalkyl–C_{3-12}cycloalkyl–, C_{3-12}heterocycloalkyl–C_{3-12}heterocycloalkyl–, aryl–C_{3-12}heterocycloalkyl–, heteroaryl–C_{3-12}heterocycloalkyl–, $-C(O)$-$C(O)NR^{18}R^{19}$, $-C_{0-12}alkylC(O)OR^{18}$, $-C(O)$-$C(O)OR^{18}$, $-OC(O)R^{18}$, $-NR^{18}C(O)R^{19}$, $-NR^{18}C(O)OR^{19}$, $-NR^{18}S(O)_{m7}R^{19}$, $-(CR^{19}R^{20})_{n2}C(O)R^{18}$, $-(CR^{19}R^{20})_{n2}C(O)OR^{18}$, $-(CR^{19}R^{20})_{n2}C(O)NR^{18}R^{21}$, $-(CR^{19}R^{20})_{n2}S(O)_{m7}NR^{18}R^{21}$, $-(CR^{19}R^{20})_{n2}NR^{18}R^{21}$, $-(CR^{19}R^{20})_{n2}OR^{18}$, $-(CR^{19}R^{20})_{n2}S(O)_{m7}R^{18}$, $-NR^{20}C(O)NR^{18}R^{19}$, and $-NR^{20}S(O)_{m7}NR^{18}R^{19}$ substituents;

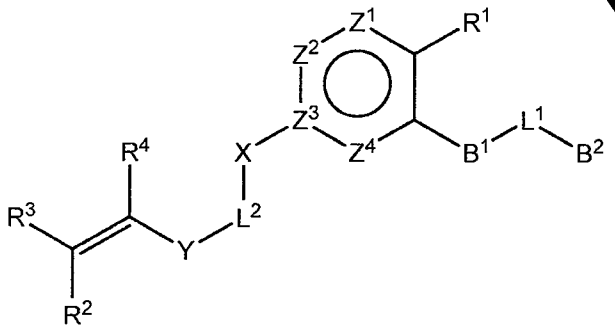
R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, and R^{21} are each independently selected from H, C_{1-6}alkyl–, C_{3-8}cycloalkyl–C_{0-6}alkyl–, C_{3-8}heterocycloalkyl–C_{0-6}alkyl–, aryl–C_{0-6}alkyl–, aryl–C_{3-8}cycloalkyl–, aryl–C_{3-8}heterocycloalkyl–, heteroaryl–C_{1-6}alkyl–, heteroaryl–C_{3-8}cycloalkyl–, or heteroaryl–C_{3-8}heterocycloalkyl–;

R^3 and R^4 are taken together with the carbon atoms to which they are attached to form a 3-12 membered partially saturated or unsaturated ring, wherein said ring optionally includes one or more additional heteroatoms selected from O, N, or $S(O)_{m8}$;

m1, m2, m3, m4, m5, m6, m7, m8, n1, and n2 are each independently selected from 0, 1, or 2;

or a pharmaceutically acceptable salt, solvate or a prodrug thereof.

2. The compound or salt of any one of the preceding claims, which is represented by Formula Ia:



Ia

wherein:

B^1 is selected from C_{3-12}cycloalkyl–C_{0-12}alkyl–, C_{3-12}heterocycloalkyl–C_{0-12}alkyl–, aryl–C_{0-12}alkyl–, aryl–C_{3-12}cycloalkyl–, aryl–C_{3-12}heterocycloalkyl–, heteroaryl–C_{0-12}alkyl–, heteroaryl–C_{3-12}cycloalkyl–, or heteroaryl–C_{3-12}heterocycloalkyl–, any of which is optionally substituted with G^2 substituents;

B^2 is selected from C_{0-12}alkyl, C_{3-12}cycloalkyl–C_{0-12}alkyl–, C_{3-12}heterocycloalkyl–C_{0-12}alkyl–, aryl–C_{0-12}alkyl–, aryl–C_{3-12}cycloalkyl–, aryl–C_{3-12}heterocycloalkyl–, heteroaryl–C_{0-12}alkyl–, heteroaryl–C_{3-12}cycloalkyl–, or heteroaryl–C_{3-12}heterocycloalkyl–, any of which is optionally substituted with G^3 substituents;

L^1 is selected from –C_{0-3}alkyl–, $–CR^5R^6–$, $–C_{0-3}alkyl(R^5)(OH)–$, –C(O)–, $–CH_2O–$, $–OCH_2–$, $–CF_2–$, $–SCR^5R^6–$, $–CR^5R^6S–$, $–N(R^5)–$, $–N(R^5)C(O)–$, $–C(O)N(R^5)–$, $–N(R^5)C(O)N(R^6)–$, –O–, –S–, $–S(O)_{m1}–$, $–N(R^5)S(O)_{m1}–$, or $–S(O)_{m1}N(R^5)–$;

L^2 is selected from –C_{0-4}alkyl–, –C(O)–, $–N(R^7)–$, $–N(R^7)C(O)–$, or $–N(R^7)S(O)_{m2}–$;

X is selected from C_{3-12}cycloalkyl–C_{0-12}alkyl–, C_{3-12}heterocycloalkyl–C_{0-12}alkyl–, aryl–C_{0-12}alkyl–, aryl–C_{3-12}cycloalkyl–, aryl–C_{3-12}heterocycloalkyl–, heteroaryl–C_{0-12}alkyl–, heteroaryl–C_{3-12}cycloalkyl–, or heteroaryl–C_{3-12}heterocycloalkyl–, any of which is optionally substituted with G^4 substituents;

Y is selected from –C(O)–, $–N(R^8)–$, $–N(R^8)C(O)–$, $–S(O)_{m3}–$, or $–N(R^8)S(O)_{m3}–$;

Z^1 is $(CR^a)_{0-1}$;

Z^2 is selected from CR^b, NR^b, O, or S;

Z^3 is selected from C or N;

Z^4 is selected from CR^c, NR^c, O, or S;

R^1 is selected from $–C(O)R^9$, $–C(O)NR^9R^{10}$, $–C(O)OR^9$, C_{1-4}alkynyl, OR^9, $S(O)_{m4}R^9R^{10}$, or –CN;

R^2, R^3, R^4, R^a, R^b, and R^c are each independently selected from C_{0-12}alkyl, –CN, halo, C_{3-12}cycloalkyl–C_{0-12}alkyl–, C_{3-12}heterocycloalkyl–C_{0-12}alkyl–, aryl–C_{0-12}alkyl–, aryl–C_{3-12}cycloalkyl–, aryl–C_{3-12}heterocycloalkyl–, heteroaryl–C_{0-12}alkyl–, heteroaryl–C_{3-12}cycloalkyl–, or heteroaryl–C_{3-12}heterocycloalkyl–, any of which is optionally substituted with G^5 substituents;

R^5, R^6, R^7, R^8, R^9, and R^{10} are each independently selected from C_{0-12}alkyl, C_{3-12}cycloalkyl–C_{0-12}alkyl–, C_{3-12}heterocycloalkyl–C_{0-12}alkyl–, aryl–C_{0-12}alkyl–, aryl–C_{3-12}

$_{12}$cycloalkyl–, aryl–C_{3-12}heterocycloalkyl–, heteroaryl–C_{0-12}alkyl–, heteroaryl–C_{3-12}cycloalkyl–, or heteroaryl–C_{3-12}heterocycloalkyl–, any of which is optionally substituted with G^6 substituents;

G^1, G^2, G^3, G^4, G^5, and G^6 are each independently selected from one or more of C_{0-12}alkyl, –C_{2-12}alkenyl, –C_{2-12}alkynyl, D, –CD_3, –OCD_3, halo, –CN, –oxo–, –CF_3, –OCF_3, –$OCHF_2$, –NO_2, –$B(OH)_2$, –$P(O)C_{0-3}$ alkyl, –$PO(OR^{11})_2$, –$PO(OR^{11})R^{12}$, C_{3-12}cycloalkyl–C_{0-12}alkyl–, C_{3-12}heterocycloalkyl–C_{0-12}alkyl–, aryl–C_{0-12}alkyl–, aryl–C_{3-12}cycloalkyl–, aryl–C_{3-12}heterocycloalkyl–, heteroaryl–C_{0-12}alkyl–, heteroaryl–C_{3-12}cycloalkyl–, heteroaryl–C_{3-12}heterocycloalkyl–, –C_{0-6}alkylOR^{11},–OC(O)NR^{11}R^{12}, –C(O)OR^{11}, –C(O)NR^{11}R^{12}, –C(O)R^{11}, –NR^{11}R^{12}, –NR^{11}C(O)R^{12}, –NR^{13}C(O)NR^{11}R^{12}, –S(O)$_{m5}$R^{11}, and –NR^{11}S(O)$_{m5}$R^{12}, any of which is optionally substituted with independently selected Q^1 substituents;

Q^1 is selected from one or more of C_{0-12}alkyl–, –C_{2-12}alkenyl, –C_{2-12}alkynyl, D, halo, –CN, –CD_3, –OCD_3, –oxo–, –CF_3, –OCF_3, –$OCHF_2$, –NO_2, –$B(OH)_2$, –$PO(OR^{14})_2$, –$PO(OR^{14})R^{15}$, $NR^{14}R^{15}$, –C(O)NR^{14}OH, –C_{0-6}alkylOR^{14}, C_{0-12}alkyl–, aryl–C_{0-12}alkyl–, heteroaryl–C_{0-12}alkyl–, C_{3-12}cycloalkyl–C_{0-12}alkyl–, C_{3-12}heterocycloalkyl–C_{0-12}alkyl–, aryl–C_{0-12}cycloalkyl–, heteroaryl–C_{3-12}cycloalkyl–, C_{3-12}heterocycloalkyl–C_{3-12}cycloalkyl–, C_{3-12}cycloalkyl–C_{3-12}cycloalkyl–, C_{3-12}heterocycloalkyl–C_{3-12}heterocycloalkyl–, aryl–C_{3-12}heterocycloalkyl–, heteroaryl–C_{3-12}heterocycloalkyl–, –C(O)-C(O)NR^{14}R^{15}, –C(O)-C(O)OR^{14}, –OC(O)R^{14}, –NR^{14}C(O)R^{15}, –NR^{14}S(O)$_{m6}$R^{15}, –(CR^{15}R^{16})$_{n1}$C(O)R^{14}, –(CR^{15}R^{16})$_{n1}$C(O)OR^{14}, –(CR^{15}R^{16})$_{n1}$C(O)NR^{14}R^{17}, –(CR^{15}R^{16})$_{n1}$S(O)$_{m6}$NR^{14}R^{17}, –(CR^{15}R^{16})$_{n1}$NR^{14}R^{17}, –(CR^{15}R^{16})$_{n1}$OR^{14}, –(CR^{15}R^{16})$_{n1}$S(O)$_{m6}$R^{14}, –NR^{16}C(O)NR^{14}R^{15}, and –NR^{16}S(O)$_{m6}$NR^{14}R^{15}, any of which is optionally substituted with independently selected E^1 substituents;

E^1 is selected from one or more of C_{0-12}alkyl–, –C_{2-12}alkenyl, –C_{2-12}alkynyl, D, halo, –CN, –oxo–, –CD_3, –OCD_3, –CF_3, –OCF_3, –$OCHF_2$, –NO_2, –$B(OH)_2$, –$PO(OR^{18})_2$, –$PO(OR^{18})R^{19}$, –C(O)NR^{18}OH, –C(O)NR^{18}R^{19}, –C_{0-12}alkylOR^{18}, aryl–C_{0-12}alkyl–, heteroaryl–C_{0-12}alkyl–, C_{3-12}cycloalkyl–C_{0-12}alkyl–, C_{3-12}heterocycloalkyl–C_{0-12}alkyl–, aryl–C_{0-12}cycloalkyl–, heteroaryl–C_{3-12}cycloalkyl–, C_{3-12}heterocycloalkyl–C_{3-12}cycloalkyl–, C_{3-12}cycloalkyl–C_{3-12}cycloalkyl–, C_{3-12}heterocycloalkyl–C_{3-12}heterocycloalkyl–, aryl–C_{3-12}heterocycloalkyl–, heteroaryl–C_{3-12}heterocycloalkyl–, –C(O)-C(O)NR^{18}R^{19}, –C_{0-12}alkylC(O)OR^{18}, –C(O)-C(O)OR^{18}, –OC(O)R^{18}, –NR^{18}C(O)R^{19}, –NR^{18}C(O)OR^{19}, –NR^{18}S(O)$_{m7}$R^{19}, –(CR^{19}R^{20})$_{n2}$C(O)R^{18}, –(CR^{19}R^{20})$_{n2}$C(O)OR^{18}, –(CR^{19}R^{20})$_{n2}$C(O)NR^{18}R^{21}, –

$(CR^{19}R^{20})_{n2}S(O)_{m7}NR^{18}R^{21}$, $-(CR^{19}R^{20})_{n2}NR^{18}R^{21}$, $-(CR^{19}R^{20})_{n2}OR^{18}$, $-(CR^{19}R^{20})_{n2}S(O)_{m7}R^{18}$, $-NR^{20}C(O)NR^{18}R^{19}$, and $-NR^{20}S(O)_{m7}NR^{18}R^{19}$ substituents;

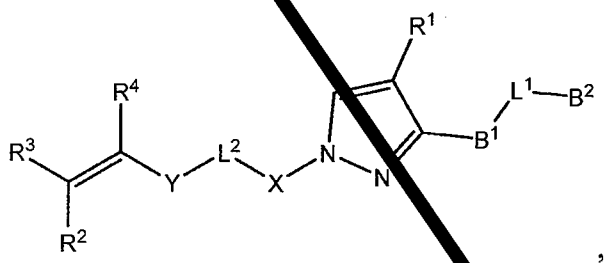
R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, and R^{21} are each independently selected from H, C_{1-6}alkyl–, C_{3-8}cycloalkyl–C_{0-6}alkyl–, C_{3-8}heterocycloalkyl–C_{0-6}alkyl–, aryl–C_{0-6}alkyl–, aryl–C_{3-8}cycloalkyl–, aryl–C_{3-8}heterocycloalkyl–, heteroaryl–C_{1-6}alkyl–, heteroaryl–C_{3-8}cycloalkyl–, or heteroaryl–C_{3-8}heterocycloalkyl–;

R^3 and R^4 are taken together with the carbon atoms to which they are attached to form a 3-12 membered partially saturated or unsaturated ring, wherein said ring optionally includes one or more additional heteroatoms selected from O, N, or $S(O)_{m8}$;

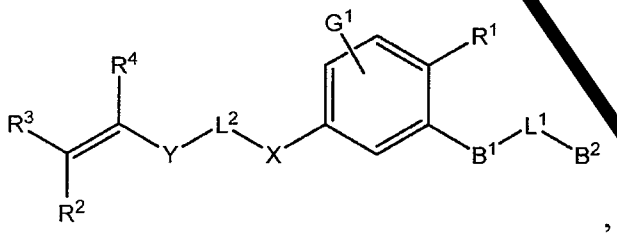
m1, m2, m3, m4, m5, m6, m7, m8, n1, and n2 are each independently selected from 0, 1, or 2;

or a pharmaceutically acceptable salt, solvate or a prodrug thereof.

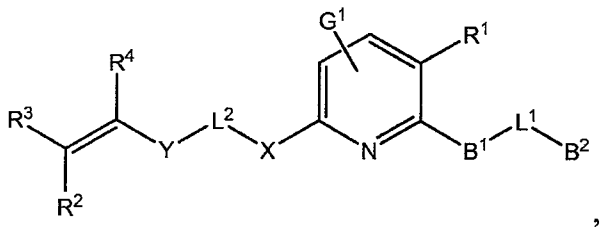
3. The compound or salt of any one of the preceding claims, wherein the compound of Formula I is selected from one of Formulas Ib-Ii:



Ib

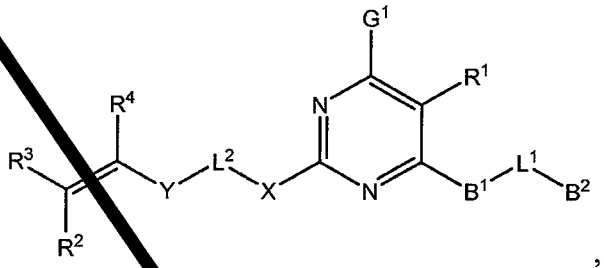


Ic



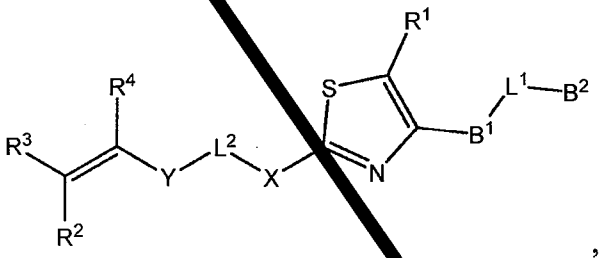
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Id



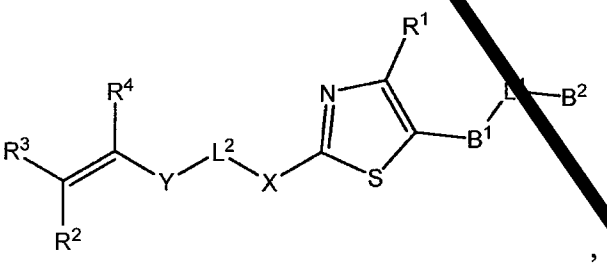
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Ie



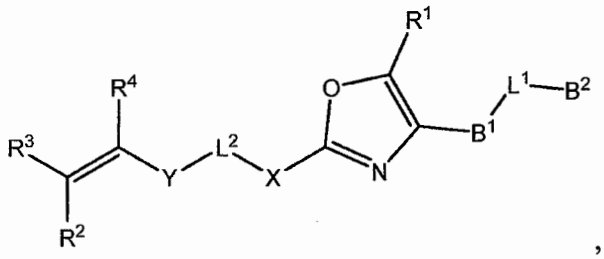
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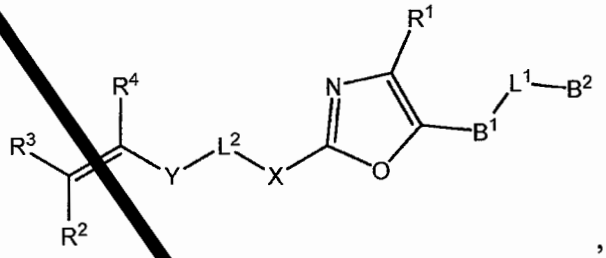
,

Ig



, or

Ih



,

Ii

wherein:

B^1 is selected from C_{3-12}cycloalkyl–C_{0-12}alkyl–, C_{3-12}heterocycloalkyl–C_{0-12}alkyl–, aryl–C_{0-12}alkyl–, aryl–C_{3-12}cycloalkyl–, aryl–C_{3-12}heterocycloalkyl–, heteroaryl–C_{0-12}alkyl–, heteroaryl–C_{3-12}cycloalkyl–, or heteroaryl–C_{3-12}heterocycloalkyl–, any of which is optionally substituted with G^2 substituents;

B^2 is selected from C_{0-12}alkyl, C_{3-12}cycloalkyl–C_{0-12}alkyl–, C_{3-12}heterocycloalkyl–C_{0-12}alkyl–, aryl–C_{0-12}alkyl–, aryl–C_{3-12}cycloalkyl–, aryl–C_{3-12}heterocycloalkyl–, heteroaryl–C_{0-12}alkyl–, heteroaryl–C_{3-12}cycloalkyl–, or heteroaryl–C_{3-12}heterocycloalkyl–, any of which is optionally substituted with G^3 substituents;

L^1 is selected from –C_{0-2}alkyl–, –CR^5R^6–, –C_{0-3}alkyl(R^5)(OH)–, –C(O)–, –CH_2O–, –OCH_2–, –CF_2–, –SCR^5R^6–, –CR^5R^6S–, –$N(R^5)$–, –$N(R^5)C(O)$–, –$C(O)N(R^5)$–, –$N(R^5)C(O)N(R^6)$–, –O–, –S–, –$S(O)_{m1}$–, –$N(R^5)S(O)_{m1}$–, or –$S(O)_{m1}N(R^5)$–;

L^2 is selected from –C_{0-4}alkyl–, –C(O)–, –$N(R^7)$–, –$N(R^7)C(O)$–, or –$N(R^7)S(O)_{m2}$–;

X is selected from C_{3-12}cycloalkyl–C_{0-12}alkyl–, C_{3-12}heterocycloalkyl–C_{0-12}alkyl–, aryl–C_{0-12}alkyl–, aryl–C_{3-12}cycloalkyl–, aryl–C_{3-12}heterocycloalkyl–, heteroaryl–C_{0-12}alkyl–, heteroaryl–C_{3-12}cycloalkyl–, or heteroaryl–C_{3-12}heterocycloalkyl–, any of which is optionally substituted with G^4 substituents;

Y is selected from –C(O)–, –$N(R^8)$–, –$N(R^8)C(O)$–, –$S(O)_{m3}$–, or –$N(R^8)S(O)_{m3}$–;

R^1 is selected from $-C(O)R^9$, $-C(O)NR^9R^{10}$, $-C(O)OR^9$, C_{1-4}alkynyl, OR^9, $S(O)_{m4}R^9R^{10}$, or $-CN$;

R^2, R^3, and R^4 are each independently selected from C_{0-12}alkyl, –CN, halo, C_{3-12}cycloalkyl–C_{0-12}alkyl–, C_{3-12}heterocycloalkyl–C_{0-12}alkyl–, aryl–C_{0-12}alkyl–, aryl–C_{3-12}cycloalkyl–, aryl–C_{3-12}heterocycloalkyl–, heteroaryl–C_{0-12}alkyl–, heteroaryl–C_{3-12}cycloalkyl–, or heteroaryl–C_{3-12}heterocycloalkyl–, any of which is optionally substituted with G^5 substituents;

R^5, R^6, R^7, R^8, R^9 and R^{10} are each independently selected from C_{0-12}alkyl, C_{3-12}cycloalkyl–C_{0-12}alkyl–, C_{3-12}heterocycloalkyl–C_{0-12}alkyl–, aryl–C_{0-12}alkyl–, aryl–C_{3-12}cycloalkyl–, aryl–C_{3-12}heterocycloalkyl–, heteroaryl–C_{0-12}alkyl–, heteroaryl–C_{3-12}cycloalkyl–, or heteroaryl–C_{3-12}heterocycloalkyl–, any of which is optionally substituted with G^6 substituents;

G^1, G^2, G^3, G^4, G^5, and G^6 are each independently selected from one or more of C_{0-12}alkyl, –C_{2-12}alkenyl, –C_{2-12}alkynyl, D, $-CD_3$, $-OCD_3$, halo, –CN, –oxo–, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-NO_2$, $-B(OH)_2$, $-P(O)C_{0-3}$ alkyl, $-PO(OR^{11})_2$, $-PO(OR^{11})R^{12}$, C_{3-12}cycloalkyl–C_{0-12}alkyl–, C_{3-12}heterocycloalkyl–C_{0-12}alkyl–, aryl–C_{0-12}alkyl–, aryl–C_{3-12}cycloalkyl–, aryl–C_{3-12}heterocycloalkyl–, heteroaryl–C_{0-12}alkyl–, heteroaryl–C_{3-12}cycloalkyl–, heteroaryl–C_{3-12}heterocycloalkyl–, $-C_{0-6}$alkylOR^{11},$-OC(O)NR^{11}R^{12}$, $-C(O)OR^{11}$, $-C(O)NR^{11}R^{12}$, $-C(O)R^{11}$, $-NR^{11}R^{12}$, $-NR^{11}C(O)R^{12}$, $-NR^{13}C(O)NR^{11}R^{12}$, $-S(O)_{m5}R^{11}$, and $-NR^{11}S(O)_{m5}R^{12}$, any of which is optionally substituted with independently selected Q^1 substituents;

Q^1 is selected from one or more of C_{0-12}alkyl–, –C_{2-12}alkenyl, –C_{2-12}alkynyl, D, halo, –CN, $-CD_3$, $-OCD_3$, –oxo–, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-NO_2$, $-B(OH)_2$, $-PO(OR^{14})_2$, $-PO(OR^{14})R^{15}$, $NR^{14}R^{15}$, $-C(O)NR^{14}OH$, $-C_{0-6}$alkylOR^{14}, aryl–C_{0-12}alkyl–, heteroaryl–C_{0-12}alkyl–, C_{3-12}cycloalkyl–C_{0-12}alkyl–, C_{3-12}heterocycloalkyl–C_{0-12}alkyl–, aryl–C_{3-12}cycloalkyl–, heteroaryl–C_{3-12}cycloalkyl–, C_{3-12}heterocycloalkyl–C_{3-12}cycloalkyl–, C_{3-12}cycloalkyl–C_{3-12}cycloalkyl–, C_{3-12}heterocycloalkyl–C_{3-12}heterocycloalkyl–, aryl–C_{3-12}heterocycloalkyl–, heteroaryl–C_{3-12}heterocycloalkyl–, $-C(O)$-$C(O)NR^{14}R^{15}$, $-C(O)$-$C(O)OR^{14}$, $-OC(O)R^{14}$, $-NR^{14}C(O)R^{15}$, $-NR^{14}S(O)_{m6}R^{15}$, $-(CR^{15}R^{16})_{n1}C(O)R^{14}$, $-(CR^{15}R^{16})_{n1}C(O)OR^{14}$, $-(CR^{15}R^{16})_{n1}C(O)NR^{14}R^{17}$, $-(CR^{15}R^{16})_{n1}S(O)_{m6}NR^{14}R^{17}$, $-(CR^{15}R^{16})_{n1}NR^{14}R^{17}$, $-(CR^{15}R^{16})_{n1}OR^{14}$, $-(CR^{15}R^{16})_{n1}S(O)_{m6}R^{14}$, $-NR^{16}C(O)NR^{14}R^{15}$, and $-NR^{16}S(O)_{m6}NR^{14}R^{15}$, any of which is optionally substituted with independently selected E^1 substituents;

E^1 is selected from one or more of C_{0-12}alkyl–, –C_{2-12}alkenyl, –C_{2-12}alkynyl, D, halo, –CN, –oxo–, $-CD_3$, $-OCD_3$, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-NO_2$, $-B(OH)_2$, $-PO(OR^{18})_2$, $-PO(OR^{18})R^{19}$, $-C(O)NR^{18}OH$, $-C(O)NR^{18}R^{19}$, $-C_{0-12}alkylOR^{18}$, aryl–C_{0-12}alkyl–, heteroaryl–C_{0-12}alkyl–, C_{3-12}cycloalkyl–C_{0-12}alkyl–, C_{3-12}heterocycloalkyl–C_{0-12}alkyl–, aryl–C_{0-12}cycloalkyl–, heteroaryl–C_{3-12}cycloalkyl–, C_{3-12}heterocycloalkyl–C_{3-12}cycloalkyl–, C_{3-12}cycloalkyl–C_{3-12}cycloalkyl–, C_{3-12}heterocycloalkyl–C_{3-12}heterocycloalkyl–, aryl–C_{3-12}heterocycloalkyl–, heteroaryl–C_{3-12}heterocycloalkyl–, –C(O)-$C(O)NR^{18}R^{19}$, $-C_{0-12}alkylC(O)OR^{18}$, –C(O)-$C(O)OR^{18}$, $-OC(O)R^{18}$, $-NR^{18}C(O)R^{19}$, $-NR^{18}C(O)OR^{19}$, $-NR^{18}S(O)_{m7}R^{19}$, $-(CR^{19}R^{20})_{n2}C(O)R^{18}$, $-(CR^{19}R^{20})_{n2}C(O)OR^{18}$, $-(CR^{19}R^{20})_{n2}C(O)NR^{18}R^{21}$, $-(CR^{19}R^{20})_{n2}S(O)_{m7}NR^{18}R^{21}$, $-(CR^{19}R^{20})_{n2}NR^{18}R^{21}$, $-(CR^{19}R^{20})_{n2}OR^{18}$, $-(CR^{19}R^{20})_{n2}S(O)_{m7}R^{18}$, $-NR^{20}C(O)NR^{18}R^{19}$, and $-NR^{20}S(O)_{m7}NR^{18}R^{19}$ substituents;

R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, and R^{21} are each independently selected from H, C_{1-6}alkyl–, C_{3-8}cycloalkyl–C_{0-6}alkyl–, C_{3-8}heterocycloalkyl–C_{0-6}alkyl–, aryl–C_{0-6}alkyl–, aryl–C_{3-8}cycloalkyl–, aryl–C_{3-8}heterocycloalkyl–, heteroaryl–C_{1-6}alkyl–, heteroaryl–C_{3-8}cycloalkyl–, or heteroaryl–C_{3-8}heterocycloalkyl–;

R^3 and R^4 are taken together with the carbon atoms to which they are attached to form a 3-12 membered partially saturated or unsaturated ring, wherein said ring optionally includes one or more additional heteroatoms selected from O, N, or $S(O)_{m8}$;

m1, m2, m3, m4, m5, m6, m7, m8, n1, and n2 are each independently selected from 0, 1, or 2;

or a pharmaceutically acceptable salt, solvate or a prodrug thereof.

4. The compound or salt of any one of the preceding claims, wherein B^1 is selected from C_{4-8}cycloalkyl–C_{0-12}alkyl–, C_{4-8}heterocycloalkyl–C_{0-12}alkyl–, C_{4-8}aryl–C_{0-12}alkyl–, or C_{4-8}heteroaryl–C_{0-12}alkyl–, any of which is optionally substituted with G^2 substituents.

5. The compound or salt of any one of the preceding claims, wherein B^2 is selected from C_{4-8}cycloalkyl–C_{0-12}alkyl–, C_{4-8}heterocycloalkyl–C_{0-12}alkyl–, C_{4-8}aryl–C_{0-12}alkyl–, or C_{4-8}heteroaryl–C_{0-12}alkyl–, any of which is optionally substituted with G^3 substituents.

6. The compound or salt of any one of the preceding claims, wherein L^1 is selected from –C_{0-2}alkyl–, –CR^5R^6–, –C_{0-3}alkyl(R^5)(OH)–, –C(O)–, –CH_2O–, –OCH_2–, –CF_2–, –N(R^5)–, –N(R^5)C(O)–, –C(O)N(R^5)–, –O–, or –S(O)$_{m1}$–.

7. The compound or salt of any one of the preceding claims, wherein L^1 is selected from –C_{0-2}alkyl–, –CR^5R^6–, –C_{1-2}alkyl(R^5)(OH)–, –C(O)–, –CF_2–, –N(R^5)–, –N(R^5)C(O)–, –C(O)N(R^5)–, –O–, or –S(O)$_{m1}$–.

8. The compound or salt of any one of the preceding claims, wherein L^2 is selected from –C_{0-2}alkyl–, –C(O)–, or –N(R^7)–.

9. The compound or salt of any one of the preceding claims, wherein X is selected from C_{4-8}cycloalkyl–C_{0-12}alkyl–, C_{4-8}heterocycloalkyl–C_{0-12}alkyl–, C_{4-8}aryl–C_{0-12}alkyl–, or C_{4-8}heteroaryl–C_{0-12}alkyl–.

10. The compound or salt of any one of the preceding claims, wherein Y is selected from –C(O)–, –N(R^8)–, –N(R^8)C(O)–, or –S(O)$_{m3}$–.

11. The compound or salt of any one of the preceding claims, wherein R^1 is selected from –C(O)NR^9R^{10}, –C(O)OR^9, C_{1-4}alkynyl, or –CN.

12. The compound or salt of any one of the preceding claims, wherein R^2, R^3, and R^4 are each independently selected from C_{0-12}alkyl, –CN, halo, C_{3-6}cycloalkyl–C_{0-12}alkyl–, or C_{3-6}heterocycloalkyl–C_{0-12}alkyl–, any of which is optionally substituted with G^5 substituents.

13. The compound or salt of any one of the preceding claims, wherein G^1, G^2, G^3, G^4, G^5, and G^6 are each independently selected from one to three of C_{0-12}alkyl, –C_{2-12}alkenyl, –C_{2-12}alkynyl, D, –CD_3, –OCD_3, halo, –CN, –oxo–, –CF_3, –OCF_3, –$OCHF_2$, –NO_2, –B(OH)$_2$, –P(O)C_{0-3} alkyl, –PO(OR^{11})$_2$, –PO(OR^{11})R^{12}, C_{3-12}cycloalkyl–C_{0-12}alkyl–, C_{3-12}heterocycloalkyl–C_{0-12}alkyl–, aryl–C_{0-12}alkyl–, aryl–C_{3-12}cycloalkyl–, aryl–C_{3-12}heterocycloalkyl–, heteroaryl–C_{0-12}alkyl–, heteroaryl–C_{3-12}cycloalkyl–, heteroaryl–C_{3-12}heterocycloalkyl–, –C_{0-6}alkylOR^{11},–

$OC(O)NR^{11}R^{12}$, $-C(O)OR^{11}$, $-C(O)NR^{11}R^{12}$, $-C(O)R^{11}$, $-NR^{11}R^{12}$, $-NR^{11}C(O)R^{12}$, $-NR^{13}C(O)NR^{11}R^{12}$, $-S(O)_{m5}R^{11}$, and $-NR^{11}S(O)_{m5}R^{12}$, any of which is optionally substituted with independently selected Q^1 substituents.

14. The compound or salt of any one of the preceding claims, wherein G^1, G^2, G^3, G^4, G^5, and G^6 are each independently selected from one to two of C_{0-12}alkyl, $-C_{2-12}$alkenyl, $-C_{2-12}$alkynyl, D, $-CD_3$, $-OCD_3$, halo, –CN, –oxo–, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-NO_2$, $-B(OH)_2$, $-P(O)C_{0-3}$ alkyl, $-PO(OR^{11})_2$, $-PO(OR^{11})R^{12}$, C_{3-12}cycloalkyl–C_{0-12}alkyl–, C_{3-12}heterocycloalkyl–C_{0-12}alkyl–, aryl–C_{0-12}alkyl–, aryl–C_{3-12}cycloalkyl–, aryl–C_{3-12}heterocycloalkyl–, heteroaryl–C_{0-12}alkyl–, heteroaryl–C_{3-12}cycloalkyl–, heteroaryl–C_{3-12}heterocycloalkyl–, $-C_{0-6}$alkylOR^{11},$-OC(O)NR^{11}R^{12}$, $-C(O)OR^{11}$, $-C(O)NR^{11}R^{12}$, $-C(O)R^{11}$, $-NR^{11}R^{12}$, $-NR^{11}C(O)R^{12}$, $-NR^{13}C(O)NR^{11}R^{12}$, $-S(O)_{m5}R^{11}$, and $-NR^{11}S(O)_{m5}R^{12}$, any of which is optionally substituted with independently selected Q^1 substituents.

15. A pharmaceutical composition comprising the compound or salt of any one of the compounds of Formula I, formulated with or without one or more pharmaceutical carriers.

16. A method for the treatment of at least one of cancer, chronic inflammation, and autoimmune disease mediated at least in part by BTK comprising administering to a subject in need thereof a therapeutically effective amount of a compound or salt of the compound of Formula I.

17. A method of treating cancer, chronic inflammation, or autoimmune disease in a mammal comprising administering a therapeutically effective amount of a compound according to any one of the preceding claims, or a pharmaceutically acceptable salt thereof, to the mammal in need thereof.

18. A method of irreversibly inhibiting tyrosine kinases, the method comprising administering to a patient a therapeutically effective amount of a tyrosine kinase inhibitor comprising a compound according to any one of the preceding claims.

19. A method of irreversibly inhibiting BTK, the method comprising administering to a patient a therapeutically effective amount of a BTK inhibitor comprising a compound according to any one of the preceding claims.

20. A compound selected from one or more of:

6-(3-acrylamidophenyl)-2-(4-phenoxyphenyl)nicotinamide;

2-(4-phenoxyphenyl)-6-(piperidin-4-yl)nicotinamide;

6-(1-acryloylpiperidin-4-yl)-2-(4-phenoxyphenyl)nicotinamide;

2-(4-phenoxyphenyl)-6-(piperazin-1-yl)nicotinamide;

6-(4-acryloylpiperazin-1-yl)-2-(4-phenoxyphenyl)nicotinamide;

6-(1-acryloylpyrrolidin-3-yl)-2-(4-phenoxyphenyl)nicotinamide;

6-(4-acrylamidophenyl)-2-(4-phenoxyphenyl)nicotinamide;

6-(1-acryloylpiperidin-3-yl)-2-(4-phenoxyphenyl)nicotinamide;

6-(4-acrylamidopiperidin-1-yl)-2-(4-phenoxyphenyl)nicotinamide;

6-(3-acrylamidopyrrolidin-1-yl)-2-(4-phenoxyphenyl)nicotinamide;

1-(1-acryloylpiperidin-3-yl)-3-(4-phenoxyphenyl)-1H-pyrazole-4-carboxamide;

1-(1-acryloylpiperidin-4-yl)-3-(4-phenoxyphenyl)-1H-pyrazole-4-carboxamide;

1-(1-acryloylpyrrolidin-3-yl)-3-(4-phenoxyphenyl)-1H-pyrazole-4-carboxamide;

1-(azetidin-3-yl)-3-(4-phenoxyphenyl)-1H-pyrazole-4-carboxamide;

1-(1-acryloylazetidin-3-yl)-3-(4-phenoxyphenyl)-1H-pyrazole-4-carboxamide;

1-(4-acrylamidophenyl)-3-(4-phenoxyphenyl)-1H-pyrazole-4-carboxamide;

1-(3-aminophenyl)-3-(4-phenoxyphenyl)-1H-pyrazole-4-carboxamide;

1-(3-acrylamidophenyl)-3-(4-phenoxyphenyl)-1H-pyrazole-4-carboxamide;

(S)-1-(1-acryloylpyrrolidin-3-yl)-3-(4-phenoxyphenyl)-1H-pyrazole-4-carboxamide;

(R)-1-(1-acryloylpyrrolidin-3-yl)-3-(4-phenoxyphenyl)-1H-pyrazole-4-carboxamide;

2-(1-acryloylpiperidin-4-yl)-4-(4-phenoxyphenyl)pyrimidine-5-carboxamide;

2-(1-acryloylpyrrolidin-3-yl)-4-(4-phenoxyphenyl)pyrimidine-5-carboxamide;

6-(1-acryloylpyrrolidin-3-yl)-2-(4-phenoxyphenyl)pyridine-3-carboxamide;

6-(1-acryloylpiperidin-4-yl)-2-(4-phenoxyphenyl)pyridine-3-carbonitrile

(E)-6-(4-(4-(dimethylamino)but-2-enoyl)piperazin-1-yl)-2-(4-phenoxyphenyl)nicotinamide;

6-(4-acryloylpiperazin-1-yl)-2-(4-phenoxyphenyl)pyridine-3-carboxylic acid

6-(4-acryloylpiperazin-1-yl)-2-(4-(4-cyanophenoxy)phenyl)nicotinamide;

6-(4-acryloylpiperazin-1-yl)-2-(4-(cyclohexyloxy)phenyl)nicotinamide;

6-(4-acryloylpiperazin-1-yl)-2-(3-methoxy-4-methylphenyl)nicotinamide;

6-(4-acryloylpiperazin-1-yl)-2-(4-fluoro-3-methoxyphenyl)nicotinamide;

6-(4-acryloylpiperazin-1-yl)-6'-phenoxy-2,3'-bipyridine-3-carboxamide;

6-(4-acryloylpiperazin-1-yl)-2-(4-(pyridin-2-yloxy)phenyl)nicotinamide;

6-(4-acryloylpiperazin-1-yl)-2-(4-chlorophenyl)nicotinamide;

1-(1-(4-(dimethylamino)but-2-enoyl)pyrrolidin-3-yl)-3-(4-phenoxyphenyl)-1H-pyrazole-4-carboxamide;

6-(4-acryloylpiperazin-1-yl)-2-(4-(3-fluorophenoxy)phenyl)nicotinamide;

6-(4-acryloylpiperazin-1-yl)-2-(3-fluoro-4-phenoxyphenyl)nicotinamide;

6-(4-acryloylpiperazin-1-yl)-2-(4-(4-fluorophenoxy)phenyl)nicotinamide;

6-(4-acryloylpiperazin-1-yl)-2-(4-(2-fluorophenoxy)phenyl)nicotinamide;

6-(4-acryloylpiperazin-1-yl)-2-(2-fluoro-4-phenoxyphenyl)nicotinamide;

2-(1-acryloylpiperidin-3-yl)-4-(4-phenoxyphenyl)thiazole-5-carboxamide;

2-(1-acryloylpyrrolidin-3-yl)-4-(4-phenoxyphenyl)thiazole-5-carboxamide;

2-(1-acryloylpiperidin-3-yl)-4-(4-phenoxyphenyl)oxazole-5-carboxamide;

2-(1-acryloylpyrrolidin-3-yl)-4-(4-phenoxyphenyl)oxazole-5-carboxamide;

2-(1-acryloylpyrrolidin-3-yl)-5-(4-phenoxyphenyl)thiazole-4-carboxamide;

2-(1-acryloylpiperidin-3-yl)-5-(4-phenoxyphenyl)thiazole-4-carboxamide;

2-(1-acryloylpiperidin-4-yl)-4-(4-phenoxyphenyl)oxazole-5-carboxamide;

2-(4-acryloylpiperazin-1-yl)-N-methyl-4-(4-phenoxyphenyl)thiazole-5-carboxamide;

2-(1-acryloylpyrrolidin-3-yl)-5-(4-phenoxyphenyl)oxazole-4-carboxamide;

2-(1-acryloylpiperidin-4-yl)-5-(4-phenoxyphenyl)thiazole-4-carboxamide;

2-(4-acryloylpiperazin-1-yl)-4-(4-phenoxyphenyl)thiazole-5-carboxamide;

2-(1-acryloylpiperidin-4-yl)-4-(4-phenoxyphenyl)thiazole-5-carboxamide;

(E)-1-(1-(2-cyano-3-cyclopropylacryloyl)azetidin-3-yl)-3-(4-phenoxyphenyl)-1H-pyrazole-4-carboxamide;

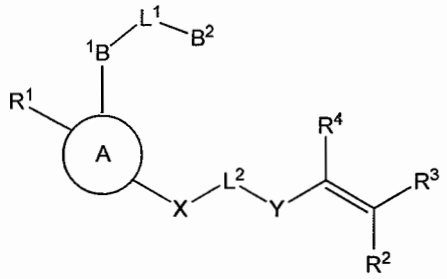
1-cyclopentyl-5-(4-phenoxyphenyl)-1H-pyrazole-4-carboxamide;

2-(1-acryloylpiperidin-3-yl)-5-(4-phenoxyphenyl)oxazole-4-carboxamide;

5-(1-acryloylpiperidin-4-yl)-4'-phenoxybiphenyl-2-carboxamide;
5-(1-acryloylpiperidin-4-yl)-1-(4-phenoxyphenyl)-1H-pyrazole-3-carboxamide;
5-(4-acryloylpiperazin-1-yl)-4'-phenoxybiphenyl-2-carboxamide;
6-(1-acryloylpiperidin-4-yl)-2-(4-(hydroxy(phenyl)methyl)phenyl)nicotinamide;
(E)-1-(1-(2-cyanobut-2-enoyl)azetidin-3-yl)-3-(4-phenoxyphenyl)-1H-pyrazole-4-carboxamide;
6-(4-acryloylpiperazin-1-yl)-2-(4-((4,4-difluorocyclohexyl)oxy)phenyl)nicotinamide;
6-(1-acryloylpiperidin-4-yl)-2-(4-(phenylcarbamoyl)phenyl)nicotinamide;
6-cyclohexyl-2-(4-phenoxyphenyl)nicotinamide;
2-(4-phenoxyphenyl)-6-(4-(vinylsulfonyl)piperazin-1-yl)nicotinamide;
2-(4-phenoxyphenyl)-6-(4-(vinylsulfonyl)piperidin-4-yl)nicotinamide;
1-(1-acryloylpiperidin-3-yl)-3-(4-(phenylcarbamoyl)phenyl)-1H-pyrazole-4-carboxamide;
1-(1-acryloylpiperidin-3-yl)-3-(4-((4-(trifluoromethyl)pyridin-2-yl)carbamoyl)phenyl)-1H-pyrazole-4-carboxamide;
6-(4-acrylamidophenyl)-2-(4-(phenylcarbamoyl)phenyl) nicotinamide;
6-(4-acrylamidophenyl)-2-(4-((4-(trifluoromethyl)pyridin-2-yl)carbamoyl)phenyl) nicotinamide;
1-(1-acryloylpiperidin-3-yl)-3-(4-(hydroxy(phenyl)methyl)phenyl)-1H-pyrazole-4-carboxamide;
1-(1-acryloylpiperidin-3-yl)-3-(4-(methyl(phenyl)amino)phenyl)-1H-pyrazole-4-carboxamide;
6-(4-acrylamidophenyl)-2-(4-(1-hydroxy-1-phenylethyl)phenyl)nicotinamide;
6-(4-acrylamidophenyl)-2-(4-(difluoro(phenyl)methyl)phenyl)nicotinamide;
1-(1-acryloylpiperidin-3-yl)-3-(4-(phenylsulfonyl)phenyl)-1H-pyrazole-4-carboxamide;
6-(4-acrylamidophenyl)-2-(4-(phenylsulfonyl)phenyl) nicotinamide;
or a pharmaceutically acceptable salt thereof.

CLAIMS

1. A compound according to Formula I:



I

wherein:

A is a ring selected from pyridyl ring, pyrazolyl ring, thiazolyl ring, oxazolyl ring and phenyl ring, any of which is optionally substituted with G^1 substituents;

B^1 is selected from aryl– and heteroaryl–, any of which is optionally substituted with G^2 substituents;

B^2 is selected from H, C_{1-12}alkyl, C_{3-12}cycloalkyl–, C_{3-12}cycloalkyl–C_{1-12}alkyl–, aryl–, aryl-C_{1-12}alkyl– and heteroaryl-, any of which is optionally substituted with G^3 substituents;

L^1 is selected from a bond, –C_{1-2}alkylene–, -$C(R^5)(OH)$–, -C_{1-2}alkylene-$C(R^5)(OH)$-, –CH_2O–, –CF_2–, –$N(R^5)$–, –$N(R^5)C(O)$–, –$C(O)N(R^5)$–, –O– or –$S(O)_{m1}$–;

L^2 is a bond;

X is a ring selected from piperidinyl ring, piperazinyl ring, pyrrolidinyl ring, azetidinyl ring, and phenyl ring, any of which is optionally substituted with G^4 substituents;

Y is selected from –C(O)–, –$N(R^8)C(O)$–, –$S(O)_{m3}$–, or –$N(R^8)S(O)_{m3}$–;

R^1 is -$C(O)NH_2$;

R^2, R^3, and R^4 are each independently selected from H, C_{1-12}alkyl, –CN, halo, C_{3-12}cycloalkyl–, and C_{3-12}cycloalkyl–C_{1-12}alkylene–, any of which is optionally substituted with G^5 substituents;

R^5, R^6, R^7, R^8, R^9, and R^{10} are each independently selected from H, C_{1-12}alkyl, C_{3-12}cycloalkyl–, C_{3-12}cycloalkyl–C_{1-12}alkylene–, C_{3-12}heterocycloalkyl–, C_{3-12}heterocycloalkyl–C_{1-12}alkylene–, aryl–, aryl – C_{1-12}alkylene–, aryl–C_{3-12}cycloalkylene–, aryl–C_{3-12}heterocycloalkylene–,

heteroaryl–, heteroaryl–C_{1-12}alkylene–, heteroaryl–C_{3-12}cycloalkylene–, or heteroaryl–C_{3-12}heterocycloalkylene–, any of which is optionally substituted with G^6 substituents;

G^1, G^2, G^3, G^4, G^5, and G^6 are each independently selected from one or more of H, C_{1-12}alkyl, –C_{2-12}alkenyl, –C_{2-12}alkynyl, D, –CD_3, –OCD_3, halo, –CN, –oxo, –CF_3, –OCF_3, –$OCHF_2$, –NO_2, –$B(OH)_2$, –P(O), -P(O)C_{1-3} alkyl, –$PO(OR^{11})_2$, –$PO(OR^{11})R^{12}$, C_{3-12}cycloalkyl–, C_{3-12}cycloalkyl–C_{1-12}alkylene–, C_{3-12}heterocycloalkyl–, C_{3-12}heterocycloalkyl–C_{1-12}alkylene–, aryl–, aryl – C_{1-12}alkylene–, aryl–C_{3-12}cycloalkylene–, aryl–C_{3-12}heterocycloalkylene–, heteroaryl–, heteroaryl–C_{1-12}alkylene–, heteroaryl–C_{3-12}cycloalkylene–, heteroaryl–C_{3-12}heterocycloalkylene–, -OR^{11}-, –C_{1-6}alkylene-OR^{11}, –$OC(O)NR^{11}R^{12}$, –$C(O)OR^{11}$, –$C(O)NR^{11}R^{12}$, –$C(O)R^{11}$, –$NR^{11}R^{12}$, –$NR^{11}C(O)R^{12}$, –$NR^{13}C(O)NR^{11}R^{12}$, –$S(O)_{m5}R^{11}$, and –$NR^{11}S(O)_{m5}R^{12}$, any of which is optionally substituted with independently selected Q^1 substituents;

Q^1 is selected from one or more of H, C_{1-12}alkyl–, –C_{2-12}alkenyl, –C_{2-12}alkynyl, D, halo, –CN, –CD_3, –OCD_3, –oxo-, –CF_3, –OCF_3, –$OCHF_2$, –NO_2, –$B(OH)_2$, –$PO(OR^{14})_2$, –$PO(OR^{14})R^{15}$, $NR^{14}R^{15}$, –$C(O)NR^{14}OH$, -OR^{14}, –C_{1-6}alkyleneOR^{14}, aryl–, aryl–C_{1-12}alkylene–, heteroaryl–, heteroaryl–C_{1-12}alkylene–, C_{3-12}cycloalkyl–, C_{3-12}cycloalkyl–C_{1-12}alkylene–, C_{3-12}heterocycloalkyl–, C_{3-12}heterocycloalkyl–C_{1-12}alkylene–, aryl–C_{3-12}cycloalkylene–, heteroaryl–C_{3-12}cycloalkylene–, C_{3-12}heterocycloalkyl–C_{3-12}cycloalkylene–, C_{3-12}cycloalkyl–C_{3-12}cycloalkylene–, C_{3-12}heterocycloalkyl–C_{3-12}heterocycloalkylene–, aryl–C_{3-12}heterocycloalkylene-, heteroaryl–C_{3-12}heterocycloalkylene–, –C(O)-$C(O)NR^{14}R^{15}$, –C(O)-$C(O)OR^{14}$, –$OC(O)R^{14}$, –$NR^{14}C(O)R^{15}$, –$NR^{14}S(O)_{m6}R^{15}$, –$(CR^{15}R^{16})_{n1}C(O)R^{14}$, –$(CR^{15}R^{16})_{n1}C(O)OR^{14}$, –$(CR^{15}R^{16})_{n1}C(O)NR^{14}R^{17}$, –$(CR^{15}R^{16})_{n1}S(O)_{m6}NR^{14}R^{17}$, –$(CR^{15}R^{16})_{n1}NR^{14}R^{17}$, –$(CR^{15}R^{16})_{n1}OR^{14}$, –$(CR^{15}R^{16})_{n1}S(O)_{m6}R^{14}$, –$NR^{16}C(O)NR^{14}R^{15}$, and –$NR^{16}S(O)_{m6}NR^{14}R^{15}$, any of which is optionally substituted with independently selected E^1 substituents;

E^1 is selected from one or more of H, C_{1-12}alkyl–, –C_{2-12}alkenyl, –C_{2-12}alkynyl, D, halo, –CN, –oxo, –CD_3, –OCD_3, –CF_3, –OCF_3, –$OCHF_2$, –NO_2, –$B(OH)_2$, –$PO(OR^{18})_2$, –$PO(OR^{18})R^{19}$, –$C(O)NR^{18}OH$, –$C(O)NR^{18}R^{19}$, -OR^{18}, –C_{1-12}alkylOR^{18}, aryl–, aryl–C_{1-12}alkylene–, heteroaryl–, heteroaryl–C_{1-12}alkylene–, C_{3-12}cycloalkyl–, C_{3-12}cycloalkyl–C_{1-12}alkylene–, C_{3-12}heterocycloalkyl–, C_{3-12}heterocycloalkyl–C_{1-12}alkylene–, aryl–, aryl – C_{1-12}cycloalkylene–, heteroaryl–C_{3-12}cycloalkylene–, C_{3-12}heterocycloalkyl–C_{3-12}cycloalkylene–, C_{3-12}cycloalkyl–C_{3-12}cycloalkylene–,

C_{3-12}heterocycloalkyl–C_{3-12}heterocycloalkylene–, aryl–C_{3-12}heterocycloalkylene–, heteroaryl–C_{3-12}heterocycloalkylene–, –C(O)-C(O)$NR^{18}R^{19}$, –C(O)OR^{18}, –C_{1-12}alkyleneC(O)OR^{18}, –C(O)-C(O)OR^{18}, –OC(O)R^{18}, –NR^{18}C(O)R^{19}, –NR^{18}C(O)OR^{19}, –$NR^{18}S(O)_{m7}R^{19}$, –$(CR^{19}R^{20})_{n2}$C(O)R^{18}, –$(CR^{19}R^{20})_{n2}$C(O)OR^{18}, –$(CR^{19}R^{20})_{n2}$C(O)$NR^{18}R^{21}$, –$(CR^{19}R^{20})_{n2}S(O)_{m7}NR^{18}R^{21}$, –$(CR^{19}R^{20})_{n2}NR^{18}R^{21}$, –$(CR^{19}R^{20})_{n2}OR^{18}$, –$(CR^{19}R^{20})_{n2}S(O)_{m7}R^{18}$, –$NR^{20}$C(O)$NR^{18}R^{19}$, and –$NR^{20}S(O)_{m7}NR^{18}R^{19}$ substituents;

R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, and R^{21} are each independently selected from H, C_{1-6}alkyl–, C_{3-8}cycloalkyl–, C_{3-8}cycloalkyl–C_{1-6}alkylene–, C_{3-8}heterocycloalkyl–, C_{3-8}heterocycloalkyl–C_{1-6}alkylene–, aryl–, aryl–C_{1-6}alkylene–, aryl–C_{3-8}cycloalkylene–, aryl–C_{3-8}heterocycloalkylene–, heteroaryl–C_{1-6}alkylene–, heteroaryl–C_{3-8}cycloalkylene–, or heteroaryl–C_{3-8}heterocycloalkylene–;

R^3 and R^4 can be taken together with the carbon atoms to which they are attached to form a 3-12 membered partially unsaturated or unsaturated ring, wherein said ring optionally includes one or more additional heteroatoms selected from O, N, or $S(O)_{m8}$;

m1, m2, m3, m4, m5, m6, m7, m8, n1, and n2 are each independently selected from 0, 1, or 2;

or a pharmaceutically acceptable salt or solvate thereof.

2. The compound of claim 1, wherein L^1 is selected from a bond, –C_{1-2}alkylene–, –$C(R^5)$(OH)–, –$C(R^5)$(OH)CH_2–, –C(O)–, –CF_2–, –$N(R^5)$–, –$N(R^5)$C(O)–, –C(O)$N(R^5)$–, –O–, or –$S(O)_{m1}$–, or a pharmaceutically acceptable salt or solvate thereof.

3. The compound of claim 1, wherein G^1, G^2, G^3, G^4, G^5, and G^6 are each independently selected from one to three of H, C_{1-12}alkyl, –C_{2-12}alkenyl, –C_{2-12}alkynyl, D, –CD_3, –OCD_3, halo, –CN, –oxo, –CF_3, –OCF_3, –$OCHF_2$, –NO_2, –$B(OH)_2$, –P(O), –P(O)C_{1-3} alkyl, –$PO(OR^{11})_2$, –$PO(OR^{11})R^{12}$, C_{3-12}cycloalkyl–, C_{3-12}cycloalkyl–C_{1-12}alkylene–, C_{3-12}heterocycloalkyl–, C_{3-12}heterocycloalkyl–C_{1-12}alkylene–, aryl–, aryl-C_{1-12}alkylene–, aryl–C_{3-12}cycloalkylene–, aryl–C_{3-12}heterocycloalkylene–, heteroaryl–, heteroaryl–C_{1-12}alkylene–, heteroaryl–C_{3-12}cycloalkylene–, heteroaryl–C_{3-12}heterocycloalkylene–, –OR^{11}, –C_{1-6}alkylene-OR^{11}, –OC(O)$NR^{11}R^{12}$, –C(O)OR^{11}, –

$C(O)NR^{11}R^{12}$, $-C(O)R^{11}$, $-NR^{11}R^{12}$, $-NR^{11}C(O)R^{12}$, $-NR^{13}C(O)NR^{11}R^{12}$, $-S(O)_{m5}R^{11}$, and $-NR^{11}S(O)_{m5}R^{12}$, any of which is optionally substituted with independently selected Q^1 substituents, or a pharmaceutically acceptable salt or solvate thereof.

4. The compound of claim 1, wherein G^1, G^2, G^3, G^4, G^5, and G^6 are each independently selected from one to two of H, C_{1-12}alkyl, $-C_{2-12}$alkenyl, $-C_{2-12}$alkynyl, D, $-CD_3$, $-OCD_3$, halo, $-CN$, $-$oxo, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-NO_2$, $-B(OH)_2$, $-P(O)$, $-P(O)C_{1-3}$ alkyl, $-PO(OR^{11})_2$, $-PO(OR^{11})R^{12}$, C_{3-12}cycloalkyl–, C_{3-12}cycloalkyl–C_{1-12}alkylene–, C_{3-12}heterocycloalkyl–, C_{3-12}heterocycloalkyl–C_{1-12}alkylene–, aryl–, aryl–C_{1-12}alkylene–, aryl–C_{3-12}cycloalkylene–, aryl–C_{3-12}heterocycloalkylene–, heteroaryl–, heteroaryl–C_{1-12}alkylene–, heteroaryl–C_{3-12}cycloalkylene–, heteroaryl–C_{3-12}heterocycloalkylene–, $-OR^{11}$, $-C_{1-6}$alkylene-OR^{11},$-OC(O)NR^{11}R^{12}$, $-C(O)OR^{11}$, $-C(O)NR^{11}R^{12}$, $-C(O)R^{11}$, $-NR^{11}R^{12}$, $-NR^{11}C(O)R^{12}$, $-NR^{13}C(O)NR^{11}R^{12}$, $-S(O)_{m5}R^{11}$, and $-NR^{11}S(O)_{m5}R^{12}$, any of which is optionally substituted with independently selected Q^1 substituents, or a pharmaceutically acceptable salt or solvate thereof.

5. A pharmaceutical composition comprising the compound according to any one of the preceding claims, formulated with or without one or more pharmaceutical carriers.

6. Use of a compound according to claim 1 or a pharmaceutically acceptable salt or solvate thereof in the manufacture of a medicament for the treatment of at least one of cancer, chronic inflammation, and autoimmune disease mediated at least in part by BTK.

7. Use of a compound according to claim 1 or a pharmaceutically acceptable salt or solvate thereof in the manufacture of a medicament for the treatment of cancer, chronic inflammation, or autoimmune disease in a mammal.

8. Use of a compound according to claim 1 or a pharmaceutically acceptable salt or solvate thereof in the manufacture of a medicament for the irreversible inhibition of tyrosine kinases.

9. Use of a compound according to claim 1 or a pharmaceutically acceptable salt or solvate thereof in the manufacture of a medicament for the irreversible inhibition of BTK.

10. A compound selected from one or more of:

6-(3-acrylamidophenyl)-2-(4-phenoxyphenyl)nicotinamide;

2-(4-phenoxyphenyl)-6-(piperidin-4-yl)nicotinamide;

6-(1-acryloylpiperidin-4-yl)-2-(4-phenoxyphenyl)nicotinamide;

2-(4-phenoxyphenyl)-6-(piperazin-1-yl)nicotinamide;

6-(4-acryloylpiperazin-1-yl)-2-(4-phenoxyphenyl)nicotinamide;

6-(1-acryloylpyrrolidin-3-yl)-2-(4-phenoxyphenyl)nicotinamide;

6-(4-acrylamidophenyl)-2-(4-phenoxyphenyl)nicotinamide;

6-(1-acryloylpiperidin-3-yl)-2-(4-phenoxyphenyl)nicotinamide;

6-(4-acrylamidopiperidin-1-yl)-2-(4-phenoxyphenyl)nicotinamide;

6-(3-acrylamidopyrrolidin-1-yl)-2-(4-phenoxyphenyl)nicotinamide;

1-(1-acryloylpiperidin-3-yl)-3-(4-phenoxyphenyl)-1H-pyrazole-4-carboxamide;

1-(1-acryloylpiperidin-4-yl)-3-(4-phenoxyphenyl)-1H-pyrazole-4-carboxamide;

1-(azetidin-3-yl)-3-(4-phenoxyphenyl)-1H-pyrazole-4-carboxamide;

1-(1-acryloylazetidin-3-yl)-3-(4-phenoxyphenyl)-1H-pyrazole-4-carboxamide;

1-(4-acrylamidophenyl)-3-(4-phenoxyphenyl)-1H-pyrazole-4-carboxamide;

1-(3-aminophenyl)-3-(4-phenoxyphenyl)-1H-pyrazole-4-carboxamide;

1-(3-acrylamidophenyl)-3-(4-phenoxyphenyl)-1H-pyrazole-4-carboxamide;

(S)-1-(1-acryloylpyrrolidin-3-yl)-3-(4-phenoxyphenyl)-1H-pyrazole-4-carboxamide;

(R)-1-(1-acryloylpyrrolidin-3-yl)-3-(4-phenoxyphenyl)-1H-pyrazole-4-carboxamide;

6-(1-acryloylpyrrolidin-3-yl)-2-(4-phenoxyphenyl)pyridine-3-carboxamide;

(E)-6-(4-(4-(dimethylamino)but-2-enoyl)piperazin-1-yl)-2-(4-phenoxyphenyl)nicotinamide;

6-(4-acryloylpiperazin-1-yl)-2-(4-(4-cyanophenoxy)phenyl)nicotinamide;

6-(4-acryloylpiperazin-1-yl)-2-(4-(cyclohexyloxy)phenyl)nicotinamide;

6-(4-acryloylpiperazin-1-yl)-2-(3-methoxy-4-methylphenyl)nicotinamide;

6-(4-acryloylpiperazin-1-yl)-2-(4-fluoro-3-methoxyphenyl)nicotinamide;

6-(4-acryloylpiperazin-1-yl)-6'-phenoxy-2,3'-bipyridine-3-carboxamide;

6-(4-acryloylpiperazin-1-yl)-2-(4-(pyridin-2-yloxy)phenyl)nicotinamide;

6-(4-acryloylpiperazin-1-yl)-2-(4-chlorophenyl)nicotinamide;

1-(1-(4-(dimethylamino)but-2-enoyl)pyrrolidin-3-yl)-3-(4-phenoxyphenyl)-1H-pyrazole-4-carboxamide;

6-(4-acryloylpiperazin-1-yl)-2-(4-(3-fluorophenoxy)phenyl)nicotinamide;

6-(4-acryloylpiperazin-1-yl)-2-(3-fluoro-4-phenoxyphenyl)nicotinamide;

6-(4-acryloylpiperazin-1-yl)-2-(4-(4-fluorophenoxy)phenyl)nicotinamide;

6-(4-acryloylpiperazin-1-yl)-2-(4-(2-fluorophenoxy)phenyl)nicotinamide;

6-(4-acryloylpiperazin-1-yl)-2-(2-fluoro-4-phenoxyphenyl)nicotinamide;

2-(1-acryloylpiperidin-3-yl)-4-(4-phenoxyphenyl)thiazole-5-carboxamide;

2-(1-acryloylpyrrolidin-3-yl)-4-(4-phenoxyphenyl)thiazole-5-carboxamide;

2-(1-acryloylpiperidin-3-yl)-4-(4-phenoxyphenyl)oxazole-5-carboxamide;

2-(1-acryloylpyrrolidin-3-yl)-4-(4-phenoxyphenyl)oxazole-5-carboxamide;

2-(1-acryloylpyrrolidin-3-yl)-5-(4-phenoxyphenyl)thiazole-4-carboxamide;

2-(1-acryloylpiperidin-3-yl)-5-(4-phenoxyphenyl)thiazole-4-carboxamide;

2-(1-acryloylpiperidin-4-yl)-4-(4-phenoxyphenyl)oxazole-5-carboxamide;

2-(4-acryloylpiperazin-1-yl)-N-methyl-4-(4-phenoxyphenyl)thiazole-5-carboxamide;

2-(1-acryloylpyrrolidin-3-yl)-5-(4-phenoxyphenyl)oxazole-4-carboxamide;

2-(1-acryloylpiperidin-4-yl)-5-(4-phenoxyphenyl)thiazole-4-carboxamide;

2-(4-acryloylpiperazin-1-yl)-4-(4-phenoxyphenyl)thiazole-5-carboxamide;

2-(1-acryloylpiperidin-4-yl)-4-(4-phenoxyphenyl)thiazole-5-carboxamide;

(E)-1-(1-(2-cyano-3-cyclopropylacryloyl)azetidin-3-yl)-3-(4-phenoxyphenyl)-1H-pyrazole-4-carboxamide;

1-cyclopentyl-5-(4-phenoxyphenyl)-1H-pyrazole-4-carboxamide;

2-(1-acryloylpiperidin-3-yl)-5-(4-phenoxyphenyl)oxazole-4-carboxamide;

5-(1-acryloylpiperidin-4-yl)-4'-phenoxybiphenyl-2-carboxamide;

5-(1-acryloylpiperidin-4-yl)-1-(4-phenoxyphenyl)-1H-pyrazole-3-carboxamide;

5-(4-acryloylpiperazin-1-yl)-4'-phenoxybiphenyl-2-carboxamide;

6-(1-acryloylpiperidin-4-yl)-2-(4-(hydroxy(phenyl)methyl)phenyl)nicotinamide;

(E)-1-(1-(2-cyanobut-2-enoyl)azetidin-3-yl)-3-(4-phenoxyphenyl)-1H-pyrazole-4-carboxamide;

6-(4-acryloylpiperazin-1-yl)-2-(4-((4,4-difluorocyclohexyl)oxy)phenyl)nicotinamide;

6-(1-acryloylpiperidin-4-yl)-2-(4-(phenylcarbamoyl)phenyl)nicotinamide;

6-cyclohexyl-2-(4-phenoxyphenyl)nicotinamide;

2-(4-phenoxyphenyl)-6-(4-(vinylsulfonyl)piperazin-1-yl)nicotinamide;

2-(4-phenoxyphenyl)-6-(1-(vinylsulfonyl)piperidin-4-yl)nicotinamide;

1-(1-acryloylpiperidin-3-yl)-3-(4-(phenylcarbamoyl)phenyl)-1H-pyrazole-4-carboxamide;

1-(1-acryloylpiperidin-3-yl)-3-(4-((4-(trifluoromethyl)pyridin-2-yl)carbamoyl)phenyl)-1H-pyrazole-4-carboxamide;

6-(4-acrylamidophenyl)-2-(4-(phenylcarbamoyl)phenyl) nicotinamide;

6-(4-acrylamidophenyl)-2-(4-((4-(trifluoromethyl)pyridin-2-yl)carbamoyl)phenyl) nicotinamide;

1-(1-acryloylpiperidin-3-yl)-3-(4-(hydroxy(phenyl)methyl)phenyl)-1H-pyrazole-4-carboxamide;

1-(1-acryloylpiperidin-3-yl)-3-(4-(methyl(phenyl)amino)phenyl)-1H-pyrazole-4-carboxamide;

6-(4-acrylamidophenyl)-2-(4-(1-hydroxy-1-phenylethyl)phenyl)nicotinamide;

6-(4-acrylamidophenyl)-2-(4-(difluoro(phenyl)methyl)phenyl)nicotinamide;

1-(1-acryloylpiperidin-3-yl)-3-(4-(phenylsulfonyl)phenyl)-1H-pyrazole-4-carboxamide;

6-(4-acrylamidophenyl)-2-(4-(phenylsulfonyl)phenyl) nicotinamide;

or a pharmaceutically acceptable salt or solvate thereof.