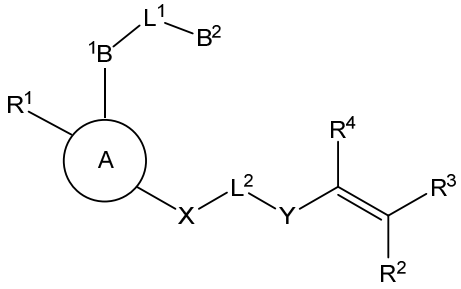
CLAIMS

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, $C_{1\text{-}12}$alkyl, $–C_{2\text{-}12}$alkenyl, $–C_{2\text{-}12}$alkynyl, D, $–CD_3$, $–OCD_3$, halo, –CN, –oxo, $–CF_3$, $–OCF_3$, $–OCHF_2$, $–NO_2$, $–B(OH)_2$, –P(O), $–P(O)C_{1\text{-}3}$ alkyl, $–PO(OR^{11})_2$, $–PO(OR^{11})R^{12}$, $C_{3\text{-}12}$cycloalkyl–, $C_{3\text{-}12}$cycloalkyl–$C_{1\text{-}12}$alkylene–, $C_{3\text{-}12}$heterocycloalkyl–, $C_{3\text{-}12}$heterocycloalkyl–$C_{1\text{-}12}$alkylene–, aryl–, aryl–$C_{1\text{-}12}$alkylene–, aryl–$C_{3\text{-}12}$cycloalkylene–, aryl–$C_{3\text{-}12}$heterocycloalkylene–, heteroaryl–, heteroaryl–$C_{1\text{-}12}$alkylene–, heteroaryl–$C_{3\text{-}12}$cycloalkylene–, heteroaryl–$C_{3\text{-}12}$heterocycloalkylene–, $–OR^{11}$, $–C_{1\text{-}6}$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.