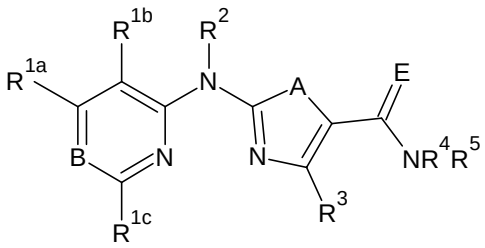
CLAIMS

1. A compound selected from the group consisting of a kinase inhibitor of the formula:



(I)

and solvates, salts, N-oxides, complexes, polymorphs, crystalline forms, racemic mixtures, diastereomers, enantiomers, tautomers, conformers, isotopically labeled forms, prodrugs, and combinations thereof;

wherein:

R^{1a} is selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, halogen, -CN, azido, $-NO_2$, $-OR^{11}$, $-N(R^{12})(R^{13})$, $-N(R^{11})(OR^{11})$, $-S(O)_{0-2}R^{11}$, $-S(O)_{1-2}OR^{11}$, $-OS(O)_{1-2}R^{11}$, $-OS(O)_{1-2}OR^{11}$, $-S(O)_{1-2}N(R^{12})(R^{13})$, $-OS(O)_{1-2}N(R^{12})(R^{13})$, $-N(R^{11})S(O)_{1-2}R^{11}$, $-NR^{11}S(O)_{1-2}OR^{11}$, $-NR^{11}S(O)_{1-2}N(R^{12})(R^{13})$, $-P(O)(OR^{11})_2$, $-OP(O)(OR^{11})_2$, $-C(=X)R^{11}$, $-C(=X)XR^{11}$, $-XC(=X)R^{11}$, and $-XC(=X)XR^{11}$, wherein each of the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, and heteroaryl groups is optionally substituted with one or more independently selected R^{30};

each of R^{1b} and R^{1c} is independently selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{6-10} aryl, 3- to 7-membered heteroaryl, 3- to 7-membered heterocyclyl, $-O(CH_2)_{0-2}$(C_{3-7} cycloalkyl), $-O(CH_2)_{0-2}$(C_{6-10} aryl), $-O(CH_2)_{0-2}$(3- to 7-membered heteroaryl), $-O(CH_2)_{0-2}$(3- to 7-membered heterocyclyl), $-NH(CH_2)_{0-2}$(C_{3-7} cycloalkyl), $-NH(CH_2)_{0-2}$(C_{6-10} aryl), $-NH(CH_2)_{0-2}$(3- to 7-membered heteroaryl), $-NH(CH_2)_{0-2}$(3- to 7-membered heterocyclyl), halogen, $-CF_3$, -CN, azido, $-NO_2$, -OH, $-O(C_{1-6}$ alkyl), $-OCF_3$, $-S(C_{1-6}$ alkyl), $-NH_2$, $-NH(C_{1-6}$ alkyl), $-N(C_{1-6}$ alkyl)$_2$, $-NHS(O)_2(C_{1-6}$ alkyl), $-S(O)_2NH_{2-z}(C_{1-6}$ alkyl)$_z$, $-C(=O)(C_{1-6}$ alkyl), -C(=O)OH, $-C(=O)O(C_{1-6}$ alkyl), $-C(=O)NH_{2-z}(C_{1-6}$ alkyl)$_z$, $-NHC(=O)(C_{1-6}$ alkyl), $-NHC(=NH)NH_{z-2}(C_{1-6}$ alkyl)$_z$, and $-N(C_{1-6}$ alkyl)$C(=NH)NH_{2-z}(C_{1-6}$ alkyl)$_z$, wherein z is 0, 1, or 2 and each of the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{6-10} aryl, 3- to 7-membered heteroaryl, and 3- to 7-membered heterocyclyl groups is optionally substituted with one, two, or three moieties independently selected from the group consisting of -OH, methyl, ethyl, $-OCH_3$, $-SCH_3$, and $-NH_{2-z}(CH_3)_z$;

R^2 is H;

R^3 is selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, halogen, -CN, azido, $-NO_2$, $-OR^{11}$, $-N(R^{12})(R^{13})$, $-N(R^{11})(OR^{11})$, $-S(O)_{0-2}R^{11}$, $-S(O)_{1-2}OR^{11}$, $-OS(O)_{1-2}R^{11}$, $-OS(O)_{1-2}OR^{11}$, $-S(O)_{1-2}N(R^{12})(R^{13})$, $-OS(O)_{1-2}N(R^{12})(R^{13})$, $-N(R^{11})S(O)_{1-2}R^{11}$, $-NR^{11}S(O)_{1-2}OR^{11}$, $-NR^{11}S(O)_{1-2}N(R^{12})(R^{13})$, $-P(O)(OR^{11})_2$, $-OP(O)(OR^{11})_2$, $-C(=X)R^{11}$, $-C(=X)XR^{11}$, $-XC(=X)R^{11}$, and $-XC(=X)XR^{11}$, wherein each of the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, and heteroaryl groups is optionally substituted with one or more independently selected R^{30};

R^4 is H;

R^5 is -L-R^6;

L is selected from the group consisting of a bond, C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, and $-(CH_2)_m$-[Y-$(CH_2)_n]_o$-, wherein m is an integer between 1 and 6, n is an integer between 0 and 3, o is an integer between 1 and 3, wherein if n is 0 then o is 1; Y is independently selected from O, S, and $-N(R^{13})$-; and each of the C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, $-(CH_2)_m$-, and $-(CH_2)_n$- groups is optionally substituted with one or two independently selected R^{30};

R^6 is heteroaryl or heterocyclyl each of which is optionally substituted with one or more independently selected R^7;

R^7 is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, halogen, -CN, azido, $-NO_2$, $-OR^{11}$, $-N(R^{12})(R^{13})$, $-N(R^{11})(OR^{11})$, $-S(O)_{0-2}R^{11}$, $-S(O)_{1-2}OR^{11}$, $-OS(O)_{1-2}R^{11}$, $-OS(O)_{1-2}OR^{11}$, $-S(O)_{1-2}N(R^{12})(R^{13})$, $-OS(O)_{1-2}N(R^{12})(R^{13})$, $-N(R^{11})S(O)_{1-2}R^{11}$, $-NR^{11}S(O)_{1-2}OR^{11}$, $-NR^{11}S(O)_{1-2}N(R^{12})(R^{13})$, $-P(O)(OR^{11})_2$, $-OP(O)(OR^{11})_2$, $-C(=X)R^{11}$, $-C(=X)XR^{11}$, $-XC(=X)R^{11}$, and $-XC(=X)XR^{11}$, and/or any two R^7 which are bound to the same atom of R^6 being a heterocyclyl group may join together to form =O, wherein each of the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, and heteroaryl groups is optionally substituted with one or more independently selected R^{30};

A is selected from the group consisting of S, O, NR^8, and $C(R^9)_2$;

R^8 is selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, and heteroaryl, wherein each of the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, and heteroaryl groups is optionally substituted with one or more independently selected R^{30};

R^9 is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, halogen, -CN, azido, $-NO_2$, $-OR^{11}$, $-N(R^{12})(R^{13})$, $-S(O)_{0-2}R^{11}$, $-S(O)_{1-2}OR^{11}$, $-OS(O)_{1-2}R^{11}$, $-OS(O)_{1-2}OR^{11}$, $-S(O)_{1-2}N(R^{12})(R^{13})$, $-OS(O)_{1-2}N(R^{12})(R^{13})$, $-N(R^{11})S(O)_{1-2}R^{11}$, $-NR^{11}S(O)_{1-2}OR^{11}$, $-NR^{11}S(O)_{1-2}N(R^{12})(R^{13})$, $-C(=X)R^{11}$, $-C(=X)XR^{11}$, $-XC(=X)R^{11}$, and $-XC(=X)XR^{11}$, wherein each of the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, and heteroaryl groups is optionally substituted with one or more independently selected R^{30};

X is independently selected from the group consisting of O, S, and $N(R^{14})$;

E is O or S;

B is N or CR^{1d};

R^{1d} is selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, halogen, -CN, azido, $-NO_2$, $-OR^{11}$, $-N(R^{12})(R^{13})$, $-N(R^{11})(OR^{11})$, $-S(O)_{0-2}R^{11}$, $-S(O)_{1-2}OR^{11}$, $-OS(O)_{1-2}R^{11}$, $-OS(O)_{1-2}OR^{11}$, $-S(O)_{1-2}N(R^{12})(R^{13})$, $-OS(O)_{1-2}N(R^{12})(R^{13})$, $-N(R^{11})S(O)_{1-2}R^{11}$, $-NR^{11}S(O)_{1-2}OR^{11}$, $-NR^{11}S(O)_{1-2}N(R^{12})(R^{13})$, $-P(O)(OR^{11})_2$, $-OP(O)(OR^{11})_2$, $-C(=X)R^{11}$, $-C(=X)XR^{11}$, $-XC(=X)R^{11}$, and $-XC(=X)XR^{11}$, wherein each of the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, and heteroaryl groups is optionally substituted with one or more independently selected R^{30};

R^{11} is independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl, wherein each of the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl groups is optionally substituted with one or more independently selected R^{30};

each of R^{12} and R^{13} is independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl, or R^{12} and R^{13} may join together with the nitrogen atom to which they are attached to form the group $-N=CR^{15}R^{16}$, wherein each of the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl groups is optionally substituted with one or more independently selected R^{30};

R^{14} is independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, and $-OR^{11}$, wherein each of the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl groups is optionally substituted with one or more independently selected R^{30};

each of R^{15} and R^{16} is independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, and $-NH_yR^{20}{}_{2-y}$, or R^{15} and R^{16} may join together with the atom to which they are attached to form a ring which is optionally substituted with one or more independently selected R^{30}, wherein each of the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl groups is optionally substituted with one or more independently selected R^{30};

y is an integer from 0 to 2;

R^{20} is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl, wherein each of the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl groups is optionally substituted with one or more independently selected R^{30}; and

R^{30} is a 1st level substituent and is, in each case, independently selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, heterocyclyl, halogen, -CN, azido, $-NO_2$, $-OR^{71}$, $-N(R^{72})(R^{73})$, $-S(O)_{0-2}R^{71}$, $-S(O)_{1-2}OR^{71}$, $-OS(O)_{1-2}R^{71}$, $-OS(O)_{1-2}OR^{71}$, $-S(O)_{1-2}N(R^{72})(R^{73})$, $-OS(O)_{1-2}N(R^{72})(R^{73})$, $-N(R^{71})S(O)_{1-2}R^{71}$, $-NR^{71}S(O)_{1-2}OR^{71}$, $-NR^{71}S(O)_{1-2}N(R^{72})(R^{73})$, $-OP(O)(OR^{71})_2$, $-C(=X^1)R^{71}$, $-C(=X^1)X^1R^{71}$, $-X^1C(=X^1)R^{71}$, and $-X^1C(=X^1)X^1R^{71}$, and/or any two R^{30} which are bound to the same carbon atom of a cycloalkyl or heterocyclyl group may join together to form $=X^1$, wherein each of the alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, and heterocyclyl groups being a 1st level substituent is optionally substituted by one or more 2nd level substituents, wherein said 2nd level substituent is, in each case, independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 14-membered aryl, 3- to 14-membered heteroaryl, 3- to 14-membered cycloalkyl, 3- to 14-membered heterocyclyl, halogen, $-CF_3$, -CN, azido, $-NO_2$, $-OR^{81}$, $-N(R^{82})(R^{83})$, $-S(O)_{0-2}R^{81}$, $-S(O)_{1-2}OR^{81}$, $-OS(O)_{1-2}R^{81}$, $-OS(O)_{1-2}OR^{81}$, $-S(O)_{1-2}N(R^{82})(R^{83})$, $-OS(O)_{1-2}N(R^{82})(R^{83})$, $-N(R^{81})S(O)_{1-2}R^{81}$, $-NR^{81}S(O)_{1-2}OR^{81}$, $-NR^{81}S(O)_{1-2}N(R^{82})(R^{83})$, $-OP(O)(OR^{81})_2$, $-C(=X^2)R^{81}$, $-C(=X^2)X^2R^{81}$, $-X^2C(=X^2)R^{81}$, and $-X^2C(=X^2)X^2R^{81}$, and/or any two 2nd level substituents which are bound to the same carbon atom of a cycloalkyl or heterocyclyl group being a 1st level substituent may join together to form $=X^2$, wherein each of the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 14-membered aryl, 3- to 14-membered heteroaryl, 3- to 14-membered cycloalkyl, 3- to 14-membered heterocyclyl groups being a 2nd level substituent is optionally substituted with one or more 3rd level substituents, wherein said 3rd level substituent is, in each case, independently selected from the group consisting of C_{1-3} alkyl, halogen, $-CF_3$, -CN, azido, $-NO_2$, -OH, $-O(C_{1-3}$ alkyl), $-OCF_3$, $-S(C_{1-3}$ alkyl), $-NH_2$, $-NH(C_{1-3}$ alkyl), $-N(C_{1-3}$ alkyl$)_2$, $-NHS(O)_2(C_{1-3}$ alkyl), $-S(O)_2NH_{2-z}(C_{1-3}$ alkyl$)_z$, -C(=O)OH, $-C(=O)O(C_{1-3}$ alkyl), $-C(=O)NH_{2-z}(C_{1-3}$ alkyl$)_z$, $-NHC(=O)(C_{1-3}$ alkyl), $-NHC(=NH)NH_{z-2}(C_{1-3}$ alkyl$)_z$, and $-N(C_{1-3}$ alkyl$)C(=NH)NH_{2-z}(C_{1-3}$ alkyl$)_z$, wherein each z is independently 0, 1, or 2 and each C_{1-3} alkyl is independently methyl, ethyl, propyl or isopropyl, and/or any two 3rd level substituents which are bound to the same carbon atom of a 3- to 14-membered cycloalkyl or heterocyclyl group being a 2nd level substituent may join together to form =O, =S, =NH, or $=N(C_{1-3}$ alkyl);

wherein

each of R^{71}, R^{72}, and R^{73} is independently selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 7-membered cycloalkyl, 5- or 6-membered aryl, 5- or 6-membered heteroaryl, and 3- to 7-membered heterocyclyl, wherein each of the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 7-membered cycloalkyl, 5- or 6-membered aryl, 5- or 6-membered heteroaryl, and 3- to 7-membered heterocyclyl groups is optionally substituted with one, two or three substituents independently selected from the group consisting of C_{1-3} alkyl, halogen, $-CF_3$, -CN, azido, $-NO_2$, -OH, $-O(C_{1-3}$ alkyl), $-OCF_3$, =O, $-S(C_{1-3}$ alkyl), $-NH_2$, $-NH(C_{1-3}$ alkyl), $-N(C_{1-3}$ alkyl$)_2$, $-NHS(O)_2(C_{1-3}$ alkyl), $-S(O)_2NH_{2-z}(C_{1-3}$ alkyl$)_z$, $-C(=O)(C_{1-3}$ alkyl), -C(=O)OH, $-C(=O)O(C_{1-3}$ alkyl), $-C(=O)NH_{2-z}(C_{1-3}$ alkyl$)_z$, $-NHC(=O)(C_{1-3}$ alkyl), $-NHC(=NH)NH_{z-2}(C_{1-3}$ alkyl$)_z$, and $-N(C_{1-3}$ alkyl$)C(=NH)NH_{2-z}(C_{1-3}$ alkyl$)_z$, wherein each z is independently 0, 1, or 2 and each C_{1-3} alkyl is independently methyl, ethyl, propyl or isopropyl;

each of R^{81}, R^{82}, and R^{83} is independently selected from the group consisting of H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, 3- to 6-membered cycloalkyl, 5- or 6-membered aryl, 5- or 6-membered heteroaryl, and 3- to 6-membered heterocyclyl, wherein each of the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, 3- to 6-membered cycloalkyl, 5- or 6-membered aryl, 5- or 6-membered heteroaryl, and 3- to 6-membered heterocyclyl groups is optionally substituted with one, two or three substituents independently selected from the group consisting of C_{1-3} alkyl, halogen, $-CF_3$, -CN, azido, $-NO_2$, -OH, $-O(C_{1-3}$ alkyl), $-OCF_3$, =O, $-S(C_{1-3}$ alkyl), $-NH_2$, $-NH(C_{1-3}$ alkyl), $-N(C_{1-3}$ alkyl$)_2$, $-NHS(O)_2(C_{1-3}$ alkyl), $-S(O)_2NH_{2-z}(C_{1-3}$ alkyl$)_z$, $-C(=O)(C_{1-3}$ alkyl), -C(=O)OH, $-C(=O)O(C_{1-3}$ alkyl), $-C(=O)NH_{2-z}(C_{1-3}$ alkyl$)_z$, $-NHC(=O)(C_{1-3}$ alkyl), $-NHC(=NH)NH_{z-2}(C_{1-3}$ alkyl$)_z$, and $-N(C_{1-3}$ alkyl$)C(=NH)NH_{2-z}(C_{1-3}$ alkyl$)_z$, wherein each z is independently 0, 1, or 2 and each C_{1-3} alkyl is independently methyl, ethyl, propyl or isopropyl; and

each of X^1 and X^2 is independently selected from O, S, and $N(R^{84})$, wherein R^{84} is H or C_{1-3} alkyl;

with the proviso that

(1) when R^{1a} is 4-(2-hydroxyethyl)piperazin-1-yl or Cl; R^{1b} is H; R^{1c} is methyl; B is N; E is O; R^3 is H; A is S; and L is a bond; then R^6 is not 4-chloro-2-methylpyridin-3-yl*;*

(2) when R^{1a} is methoxy; R^{1b} is H; R^{1c} is methoxy; B is N; E is O; R^3 is H; A is S; and L is a bond; then R^6 is not 2,2-difluoro-5H-1,3-dioxolo[4,5-f]benzimidazol-6-yl;

(3) when R^3 is H; A is S; L is a bond; R^6 is 1-methyl-4-piperidinyl; R^{1b} is H; B is N; E is O; and

(i) R^{1a} is methyl; then R^{1c} is not N-tert-butoxycarbonylpiperidin-4-yl; or

(ii) R^{1c} is methyl; then R^{1a} is not N-tert-butoxycarbonylpiperidin-4-yl or N-tert-butoxycarbonylpiperidin-3-yl;

(4) when E is O; B is CR^{1d} and R^{1d} is either H, F, Cl or Br, then R^{1a} is not H; and

(5) when R^{1a} is methyl; each of R^{1b} and R^{1c} is H; B is CH; E is O; A is S; and R^3 is methyl; then R^5 is not 1,3-benzodioxol-5-ylmethyl, 2-furanylmethyl, 1,3-benzodioxol-5-yl, 2-(2-thienyl)ethyl, 2-(4-morpholinyl)ethyl, 2-(2-pyridinyl)ethyl, 2-pyridinylmethyl, or tetrahydro-2-furanylmethyl.

2. The compound of claim 1, wherein R^6 is a mono- or bicyclic heteroaryl or a mono- or bicyclic heterocyclyl, each of which is optionally substituted with one, two, or three independently selected R^7; preferably wherein R^6 is a 5- to 6-membered monocyclic heteroaryl optionally substituted with one, two, or three independently selected R^7.

3. The compound of claim 1 or 2, wherein R^6 is a 5-membered monocyclic heteroaryl which contains at least one ring heteroatom selected from the group consisting of N, O, and S and which is optionally substituted with one, two, or three independently selected R^7.

4. The compound of claim 1 or 2, wherein R^6 is a 5- or 6-membered monocyclic heteroaryl which contains at least one S ring atom and which is optionally substituted with one, two, or three independently selected R^7, preferably wherein R^6 is thienyl optionally substituted with one, two, or three independently selected R^7.

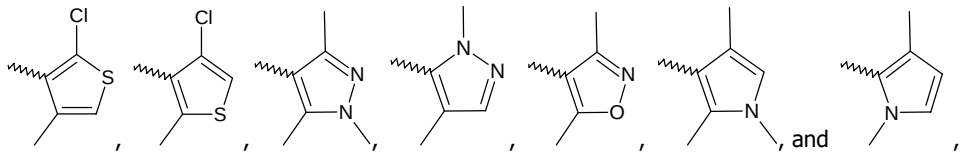
5. The compound of any one of claims 1 to 4, wherein R^7 is independently selected from the group consisting of $C_{1\text{-}3}$ alkyl, halogen, -CN, -O($C_{1\text{-}3}$ alkyl), -NH($C_{1\text{-}3}$ alkyl), and -N($C_{1\text{-}3}$ alkyl)$_2$, and/or any two R^7 which are bound to the same atom of R^6 being a heterocyclyl group may join together to form =O, wherein each of the $C_{1\text{-}3}$ alkyl groups is optionally substituted with one or more independently selected R^{30}; preferably

wherein R^7 is independently selected from the group consisting of halogen and $C_{1\text{-}2}$ alkyl, wherein the $C_{1\text{-}2}$ alkyl groups is optionally substituted with one, two, or three independently selected R^{30}, more preferably

wherein R^7 is independently selected from the group consisting of Cl, Br, and methyl.

6. The compound of any one of claims 1 to 5, wherein one R^7 group is bound to a ring atom of R^6 at position 2 relative to the ring atom by which R^6 is bound to the remainder of the compound.

7. The compound of any one of claims 1 to 3, wherein R^6 is selected from the group consisting of



, and ,

wherein ∿∿∿ represents the bond by which R^6 is bound to the remainder of the compound.

8. The compound of any one of claims 1 to 7, wherein L is selected from the group consisting of a bond; C_1 alkylene, optionally substituted with one R^{30}; C_2 alkylene (in particular 1,2-ethylene or 1,1-ethylene), optionally substituted with one R^{30}; C_3 alkylene (in particular trimethylene), optionally substituted with one R^{30}; C_4 alkylene (in particular tetramethylene or 2,4-butandiyl), optionally substituted with one R^{30}; -$(CH_2)_m$O-; and -$(CH_2)_m$NH-, wherein

m is 1, 2, or 3; preferably wherein L is a bond.

9. The compound of any one of claims 1 to 8, wherein R^{1a} is selected from the group consisting of alkyl, -O(alkyl), -S(alkyl), -NH(alkyl), -N(alkyl)$_2$, and heterocyclyl, wherein each of the alkyl and heterocyclyl groups is optionally substituted with one or more independently selected R^{30}.

10. The compound of claim 9, wherein the one or more independently selected R^{30} optionally substituting R^{1a} are selected from (i) C_{1-3} alkyl, phenyl, thiazolidinyl, halogen, -NH_2, -$NHS(O)_2(C_{1-3}$ alkyl), -$NHC(=O)(C_{1-3}$ alkyl), and -$NHC(=NH)NH_{z-2}(C_{1-3}$ alkyl)$_z$, wherein z is 0, 1, or 2 and each C_{1-3} alkyl is independently methyl, ethyl, propyl or isopropyl; (ii) methyl, ethyl, propyl, isopropyl, phenyl, =O, and =S; or (iii) methyl, ethyl, propyl, isopropyl, halogen, and -CF_3.

11. The compound of any one of claims 1 to 9, wherein R^{1a} is selected from the group consisting of -O(alkyl), -S(alkyl), -NH(alkyl), -N(alkyl)$_2$, and heterocyclyl, wherein each of the alkyl and heterocyclyl groups is optionally substituted with one or more independently selected $R^{30;}$ or

wherein R^{1a} is selected from the group consisting of C_{1-3} alkyl, -O(C_{1-3} alkyl), -S(C_{1-3} alkyl), -NH(C_{1-3} alkyl), piperazinyl, morpholinyl, piperidinyl, and pyrrolidinyl, wherein each of the piperazinyl, morpholinyl, piperidinyl, and pyrrolidinyl groups is optionally substituted with one or two moieties independently selected from the group consisting of methyl, ethyl, -OH, -OCH_3, -SCH_3, cyclopropyl, 2-hydroxyethyl, 2-(N,N-dimethylamino)ethyl, 2-(N,N-dimethylamino)ethoxy, 2-aminoethyl, 2-(N-methylamino)ethyl, 2-(methoxy)ethyl, 4-methylpiperazinyl, -C(=O)(C_{1-3} alkyl), -$(CH_2)_{1-3}$COOH, and -$NH_{2-z}(CH_3)_z$, wherein z is 0, 1, or 2; and each of the C_{1-3} alkyl groups is optionally substituted with one or two moieties independently selected from the group consisting of -OH, -OCH_3, -SCH_3, cyclopropyl, piperazinyl, 4-methyl-piperazinyl, 4-(2-hydroxyethyl)piperazinyl, 2-(N,N-dimethylamino)ethoxy, and -$NH_{2-z}(CH_3)_z$, wherein z is 0, 1, or 2; or

wherein R^{1a} is selected from the group consisting of -NH(C_{1-3} alkyl), piperazinyl, piperidinyl, and pyrrolidinyl, wherein the piperazinyl group is optionally substituted with one or two moieties independently selected from the group consisting of 2-hydroxyethyl, methyl, -CH_2COOH, and -C(=O)CH_3; the piperidinyl group is optionally substituted with one or two moieties independently selected from the group consisting of -NH_2 and 4-methylpiperazinyl; the pyrrolidinyl is optionally substituted with one or two -OH; and each of the C_{1-3} alkyl groups is optionally substituted with one or two moieties independently selected from the group consisting of -OH, -OCH_3, and -$NH_{2-z}(CH_3)_z$, wherein z is 0, 1, or 2.

12. The compound of any one of claims 1 to 9 and 11, wherein R^{1a} is selected from the group consisting of 4-(2-hydroxyethyl)piperazinyl, 4-methylpiperazinyl, 4-acetylpiperazinyl, and (2-hydroxyethyl)amino.

13. The compound of any one of claims 1 to 12, wherein at least one of R^{1b} and R^{1c} is selected from the group consisting of H, methyl, ethyl, -OH, -OCH_3, -SCH_3, cyclopropyl, 2-hydroxyethyl, 2-(N,N-dimethylamino)ethyl, 2-(N,N-dimethylamino)ethoxy, 2-aminoethyl, 2-(N-methylamino)ethyl, 2-(methoxy)ethyl, -$NH_{2-z}(CH_3)_z$, and phenyl, wherein z is 0, 1, or 2; preferably wherein R^{1b} is H; and R^{1c} is methyl, ethyl, propyl, isopropyl, or phenyl, preferably methyl.

14. The compound of any one of claims 1 to 13, wherein A is S, O, or N$(CH_3)_2$, preferably wherein A is S.

15. The compound of any one of claims 1 to 14, wherein B is N or CR^{1d}, wherein R^{1d} is selected from the group consisting of C_{1-3} alkyl, halogen, -O(C_{1-3} alkyl), -S(C_{1-3} alkyl), -NH(C_{1-3} alkyl), and -N(C_{1-3} alkyl)$_2$, wherein each of the C_{1-3} alkyl groups is optionally substituted with one or two moieties independently selected from the group consisting of halogen, -OH, -OCH_3, -SCH, and -$NH_{2-z}(CH_3)_z$, wherein z is 0, 1, or 2, preferably wherein B is N.

16. The compound of any one of claims 1 to 15, wherein E is O.

17. The compound of any one of claims 1 to 16, wherein R^3 is selected from the group consisting of H, methyl, ethyl, propyl, isopropyl, phenyl, and halogen; preferably wherein R^3 is H.

18. The compound of claim 1, wherein:

L is a bond; and

(A) R^{1a} is selected from the group consisting of alkyl, -O(alkyl), -S(alkyl), -NH(alkyl), -N(alkyl)$_2$, and heterocyclyl, wherein each of the alkyl and heterocyclyl groups is optionally substituted with one or more independently selected R^{30}, wherein, preferably, each R^{30} is independently (i) C_{1-3} alkyl, phenyl, thiazolidinyl, halogen, -NH_2, -$NHS(O)_2$(C_{1-3} alkyl), -NHC(=O)(C_{1-3} alkyl), and -NHC(=NH)NH_{z-2}(C_{1-3} alkyl)$_z$, wherein z is 0, 1, or 2 and each C_{1-3} alkyl is independently methyl, ethyl, propyl or isopropyl; (ii) methyl, ethyl, propyl, isopropyl, phenyl, =O, and =S; or (iii) methyl, ethyl, propyl, isopropyl, halogen, and -CF_3;

(B) each of R^{1b} and R^{1c} is independently selected from the group consisting of H, methyl, ethyl, -OH, -OCH_3, -SCH_3, cyclopropyl, 2-hydroxyethyl, 2-(N,N-dimethylamino)ethyl, 2-(N,N-dimethylamino)ethoxy, 2-aminoethyl, 2-(N-methylamino)ethyl, 2-(methoxy)ethyl, -NH_{2-z}(CH_3)$_z$, phenyl, pyridinyl, pyrazolyl, phenoxy, pyridinyloxy, imidazolylamino, and tetrahydrofuranylmethoxy, wherein z is 0, 1, or 2; and each of the phenyl, pyridinyl, pyrazolyl, phenoxy, pyridinyloxy, imidazolylamino, and tetrahydrofuranylmethoxy groups is optionally substituted with one, two or three moieties independently selected from methyl, ethyl, -OH, -OCH_3, -SCH_3, cyclopropyl, 2-hydroxyethyl, 2-(N,N-dimethylamino)ethyl, 2-(N,N-dimethylamino)ethoxy, 2-aminoethyl, 2-(N-methylamino)ethyl, 2-(methoxy)ethyl, and -NH_{2-z}(CH_3)$_z$, wherein z is 0, 1, or 2;

(C) R^3 is selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, phenyl, halogen, -CN, azido, -NO_2, -O(C_{1-6} alkyl), -OCF_3, -S(C_{1-6} alkyl), -NH_2, -NH(C_{1-6} alkyl), -N(C_{1-6} alkyl)$_2$, -$NHS(O)_2$(C_{1-6} alkyl), -$S(O)_2NH_{2-z}$(C_{1-6} alkyl)$_z$, -C(=O)(C_{1-6} alkyl), -C(=O)OH, -C(=O)O(C_{1-6} alkyl), -C(=O)NH_{2-z}(C_{1-6} alkyl)$_z$, -NHC(=O)(C_{1-6} alkyl), -NHC(=NH)NH_{z-2}(C_{1-6} alkyl)$_z$, and -N(C_{1-6} alkyl)C(=NH)NH_{2-z}(C_{1-6} alkyl)$_z$, wherein z is 0, 1, or 2 and wherein each of the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, and phenyl groups is optionally substituted with one or more independently selected R^{30};

(D) R^6 is a 3- to 10-membered heteroaryl or a 3- to 10-membered heterocyclyl, each of which is optionally substituted with one, two, or three independently selected R^7;

(E) A is selected from the group consisting of S, O, NH, N(C_{1-6} alkyl), and C(C_{1-6} alkyl)$_2$;

(F) B is N or CR^{1d}, wherein R^{1d} is selected from the group consisting of C_{1-3} alkyl, halogen, -O(C_{1-3} alkyl), -S(C_{1-3} alkyl), -NH(C_{1-3} alkyl), and -N(C_{1-3} alkyl)$_2$, wherein each of the C_{1-3} alkyl groups is optionally substituted with one or two moieties independently selected from the group consisting of halogen, -OH, -OCH_3, -SCH, and -NH_{2-z}(CH_3)$_z$, wherein z is 0, 1, or 2; and/or

(G) E is O or S, preferably O.

19. The compound of claim 1, wherein:

L is a bond; and

(A') R^{1a} is selected from the group consisting of C_{1-3} alkyl, -O(C_{1-3} alkyl), -S(C_{1-3} alkyl), -NH(C_{1-3} alkyl), -N(C_{1-3} alkyl)$_2$, and 3- to 7-membered heterocyclyl, wherein the 3- to 7-membered heterocyclyl group is optionally substituted with one or two moieties independently selected from the group consisting of methyl, ethyl, -OH, -OCH_3, -SCH_3, cyclopropyl, 2-hydroxyethyl, 2-(N,N-dimethylamino)ethyl, 2-(N,N-dimethylamino)ethoxy, 2-aminoethyl, 2-(N-methylamino)ethyl, 2-(methoxy)ethyl, 4-methylpiperazinyl, -C(=O)(C_{1-3} alkyl), -$(CH_2)_{1-3}$COOH, and -NH_{2-z}(CH_3)$_z$, wherein z is 0, 1, or 2; and each of the C_{1-3} alkyl

groups is optionally substituted with one or two moieties independently selected from the group consisting of -OH, $-OCH_3$, $-SCH_3$, cyclopropyl, piperazinyl, 4-methyl-piperazinyl, 4-(2-hydroxyethyl)piperazinyl, 2-(N,N-dimethylamino)ethoxy, and $-NH_{2-z}(CH_3)_z$, wherein z is 0, 1, or 2;

(B') at least one of R^{1b} and R^{1c} is selected from the group consisting of H, methyl, ethyl, -OH, $-OCH_3$, $-SCH_3$, cyclopropyl, 2-hydroxyethyl, 2-(N,N-dimethylamino)ethyl, 2-(N,N-dimethylamino)ethoxy, 2-aminoethyl, 2-(N-methylamino)ethyl, 2-(methoxy)ethyl, $-NH_{2-z}(CH_3)_z$, and phenyl, wherein z is 0, 1, or 2, and the other of R^{1b} and R^{1c} is as defined above under (B) in claim 18;

(C') R^3 is selected from the group consisting of H, C_{1-4} alkyl, C_{3-6} cycloalkyl, phenyl, halogen, -CN, $-O(C_{1-4}$ alkyl), $-OCF_3$, $-S(C_{1-4}$ alkyl), $-NH_2$, $-NH(C_{1-4}$ alkyl), $-N(C_{1-4}$ alkyl$)_2$, $-C(=O)(C_{1-4}$ alkyl), $-C(=O)OH$, $-C(=O)O(C_{1-4}$ alkyl), $-C(=O)NH_{2-z}(C_{1-4}$ alkyl$)_z$, $-NHC(=O)(C_{1-4}$ alkyl), $-NHC(=NH)NH_{z-2}(C_{1-4}$ alkyl$)_z$, and $-N(C_{1-4}$ alkyl$)C(=NH)NH_{2-z}(C_{1-4}$ alkyl$)_z$, wherein the phenyl group is optionally substituted with one, two or groups independently selected from the group consisting of halogen, methyl, isopropyl, -CN, $-CF_3$, $-OCF_3$, -OH, $-NH_2$, $-NH(C_{1-3}$ alkyl), $-N(C_{1-3}$ alkyl$)_2$, $-NHC(=O)(C_{1-3}$ alkyl), $-C(=O)NH_{2-z}(C_{1-3}$ alkyl$)_z$, $-(CH_2)_{1-3}NH_2$, $-(CH_2)_{1-3}NH(C_{1-3}$ alkyl), $-(CH_2)_{1-3}N(C_{1-3}$ alkyl$)_2$, $-(CH_2)_{1-3}OH$, and $-(CH_2)_{1-3}O(C_{1-3}$ alkyl); and wherein z is 0, 1, or 2;

(D') R^6 is a 3- to 10-membered heteroaryl containing at least one ring heteroatom selected from the group consisting of N, O, and S or a 3- to 10-membered heterocyclyl containing at least one ring heteroatom selected from the group consisting of N, O, and S, each of which is optionally substituted with one, two, or three independently selected R^7, preferably R^6 is a mono- or bicyclic heteroaryl or a mono- or bicyclic heterocyclyl, each of which is optionally substituted with one, two, or three independently selected R^7;

(E') A is S, O, or $N(CH_3)_2$;

(F') B is N or CR^{1d}, wherein R^{1d} is selected from the group consisting of C_{1-3} alkyl, halogen, $-O(C_{1-3}$ alkyl), $-S(C_{1-3}$ alkyl), $-NH(C_{1-3}$ alkyl), and $-N(C_{1-3}$ alkyl$)_2$; and/or

(G') E is O or S, preferably O.

20. The compound of claim 18 or 19, wherein R^6 is a 5-membered monocyclic heteroaryl which contains at least one ring heteroatom selected from the group consisting of N, O, and S and which is optionally substituted with one, two, or three independently selected R^7.

21. The compound of claim 18 or 19, wherein R^6 is a 5- or 6-membered monocyclic heteroaryl which contains at least one S ring atom and which is optionally substituted with one, two, or three independently selected R^7; preferably wherein R^6 is thienyl optionally substituted with one, two, or three independently selected R^7.

22. The compound of any one of claims 18 to 21, wherein R^7 is independently selected from the group consisting of C_{1-3} alkyl, halogen, -CN, $-O(C_{1-3}$ alkyl), $-NH(C_{1-3}$ alkyl), and $-N(C_{1-3}$ alkyl$)_2$, and/or any two R^7 which are bound to the same atom of R^6 being a heterocyclyl group may join together to form =O, wherein each of the C_{1-3} alkyl groups is optionally substituted with one or more independently selected R^{30}.

23. The compound of any one of claims 18 to 22, wherein R^7 is independently selected from the group consisting of halogen and C_{1-2} alkyl, wherein the C_{1-2} alkyl groups is optionally substituted with one, two, or three independently selected R^{30}, preferably wherein R^7 is independently selected from the group consisting of Cl, Br, and methyl.

24. The compound of any one of claims 18 to 23, wherein R^{1a} is selected from the group consisting of $-NH(C_{1-3}$ alkyl), piperazinyl, piperidinyl, and pyrrolidinyl, wherein the piperazinyl group is optionally substituted with one or two moieties independently selected from the group consisting of 2-hydroxyethyl, methyl, $-CH_2COOH$, and $-C(=O)CH_3$; the piperidinyl group is optionally substituted with one or two moieties independently selected from the

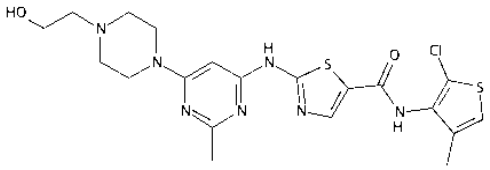
group consisting of -NH_2 and 4-methylpiperazinyl; the pyrrolidinyl is optionally substituted with one or two -OH; and each of the C_{1-3} alkyl groups is optionally substituted with one or two moieties independently selected from the group consisting of -OH, -OCH_3, and -$NH_{2-z}(CH_3)_z$, wherein z is 0, 1, or 2; preferably wherein R^{1a} is selected from the group consisting of 4-(2-hydroxyethyl)piperazinyl, 4-methylpiperazinyl, 4-acetylpiperazinyl, and (2-hydroxyethyl)amino.

25. The compound of any one of claims 18 to 24, wherein R^{1b} is H; and R^{1c} is methyl, ethyl, propyl, isopropyl, or phenyl, preferably methyl.

26. The compound of any one of claims 18 to 25, wherein A is S, B is N and/or E is O.

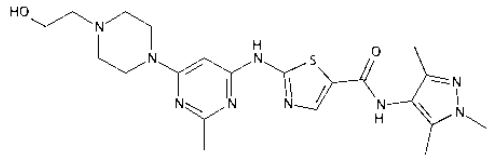
27. The compound of any one of claims 18 to 26, wherein R^3 is selected from the group consisting of H, methyl, ethyl, propyl, isopropyl, phenyl, and halogen, preferably wherein R^3 is H.

28. The compound of any one of claims 1 to 27, selected from the group consisting of:



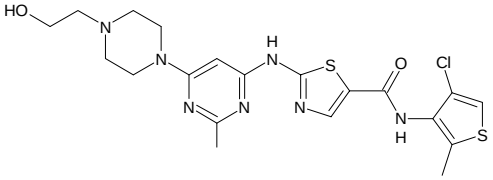
and solvates, salts, N-oxides, complexes, polymorphs, crystalline forms, tautomers, conformers, isotopically labeled forms, prodrugs, and combinations thereof.

29. The compound of any one of claims 1 to 20 and 22 to 27, selected from the group consisting of:



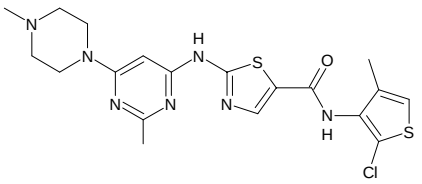
and solvates, salts, N-oxides, complexes, polymorphs, crystalline forms, tautomers, conformers, isotopically labeled forms, prodrugs, and combinations thereof.

30. The compound of any one of claims 1 to 27, selected from the group consisting of:



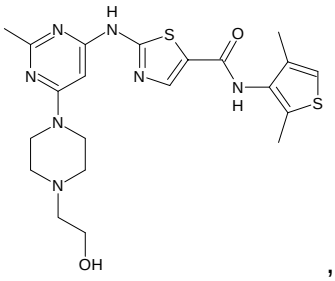
and solvates, salts, N-oxides, complexes, polymorphs, crystalline forms, tautomers, conformers, isotopically labeled forms, prodrugs, and combinations thereof.

31. The compound of any one of claims 1 to 27, selected from the group consisting of:



and solvates, salts, N-oxides, complexes, polymorphs, crystalline forms, tautomers, conformers, isotopically labeled forms, prodrugs, and combinations thereof.

32. The compound of any one of claims 1 to 27, selected from the group consisting of: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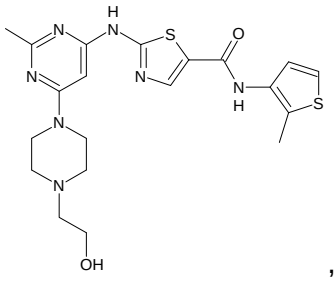
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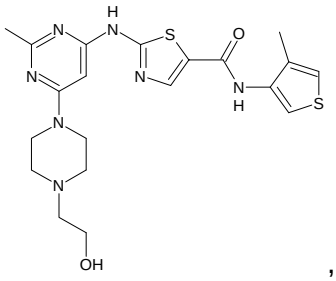
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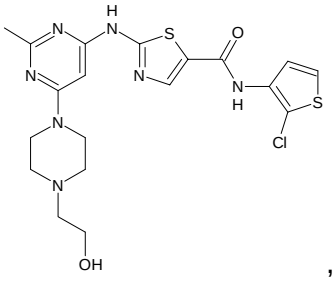
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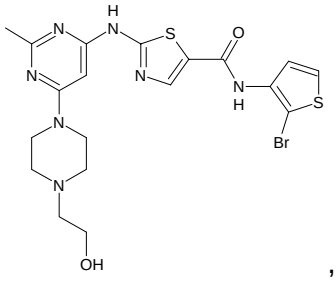
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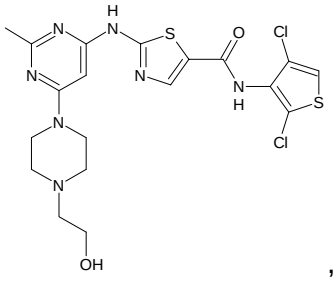
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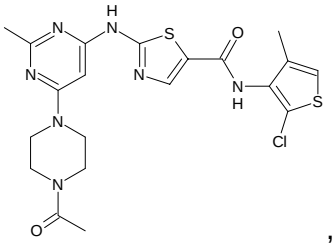
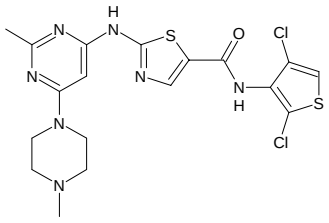
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and solvates, salts, N-oxides, complexes, polymorphs, crystalline forms, tautomers, conformers, isotopically labeled forms, prodrugs, and combinations thereof.

33. The compound of any one of claims 1 to 29 in substantially pure form, in particular in greater than about 90%, 95%, 98% or 99% pure form.

34. A pharmaceutical composition comprising the compound of any one of claims 1 to 29 or 33, and optionally further comprising a pharmaceutically acceptable excipient.

35. The pharmaceutical composition of claim 34 in unit dose form and/or formulated for oral administration.

36. The compound of any one of claims 1 to 29 and 33, or the pharmaceutical composition of 34 or 35, for use in therapy.

37. Use of a compound or a pharmaceutical composition in the manufacture of a medicament for treating a disease, disorder or condition in an individual, comprising administering to the individual the compound, or the pharmaceutical composition, wherein the compound is a compound of any one of claims 1 to 29 and 33, or the pharmaceutical composition is a pharmaceutical composition of claim 34, optionally wherein the disease, (disorder) or condition is associated with a kinase.

38. Use of a compound or a pharmaceutical composition in the manufacture of a medicament for treating a proliferative disorder in a subject, the treatment comprising administering the compound or the pharmaceutical composition to the subject,
wherein, the compound is a compound of any one of claims 1 to 29 and 33, or the pharmaceutical composition is a pharmaceutical composition of claim 34, optionally wherein (i) the proliferative disorder has progressed on standard therapy in the subject; or (ii) the subject is unable to receive standard therapy..

39. The use of claim 38, wherein the proliferative disorder is a cancer or tumour, preferably wherein the cancer

is a solid tumour.

40. The compound or pharmaceutical composition for use of claim 36 and the use of claim 38 or 39, wherein treatment involves inhibiting SIK3 and/or wherein the treatment further comprises administration of an immune checkpoint inhibitor.

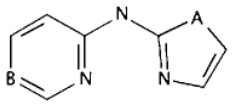
41. The use of any one of claims 38 to 40, wherein the treatment involves sensitising cells involved with the proliferative disorder to a cell-mediated immune response, preferably wherein the compound or pharmaceutical composition is administered to the subject to sensitise cells involved with the proliferative disorder to killing induced by TNF.

42. The use of any one of claims 38 to 41, the treatment comprising exposing cells involved with the proliferative disorder in the subject to: (i) TNF, a TNF variant, and/or an agonist of TNFR12 or TNFR1-signalling; and (ii) the compound or pharmaceutical composition, preferably the amount of TNF exposed to cells involved with the proliferative disorder in the subject is increased.

43. The use of claim 42, wherein: (i) TNF, a TNF variant or an agonist of TNFR1 or TNFR2-signalling is administered to the subject; (ii) an agent that is capable of inducing or induces the exposure of the cells involved with the proliferative disorder to TNF, a TNF variant or an agonist of TNFR1- or TNFR2-signalling, is administered to the subject; or (iii) the exposure of the cells involved with the proliferative disorder to TNF is induced by a pharmaceutical, therapeutic or other procedure that increases the amount of TNF in the plasma of the subject and/or in the environment of such cells.

44. The use of claim 42 or 43, wherein the exposure of the cells involved with the proliferative disorder to TNF is induced by a pharmaceutical, therapeutic or other procedure that increases the amount of TNF in the plasma of the subject and/or in the environment of such cells.

45. A use of an intermediate to prepare a compound of any one of claims 1 to 29, wherein the intermediate comprises a substructure of R^6 or R^{1a}, or comprises the following substructure:



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wherein, R^6, R^{1a}, A and B are as defined in any one of claims 1 to 29.

46. The use of an intermediate of claim 45, wherein the intermediate is selected from the list consisting of:

- 4-chloro-2-methylpyridin-3-amine;
- 2,4-dimethylpyridin-3-amine;
- 3-methylpyridin-2-amine;
- 4-bromo-2-methylpyridin-3-amine;
- 3-chloro-5-methylpyridin-4-amine;
- 3,5-dimethylpyridin-4-amine;
- 2-methylpyridin-3-amine;
- 2-chloro-4-methylthiophen-3-amine;
- 1,3,5-trimethyl-1H-pyrazol-4-amine;
- 3,5-dimethylisoxazol-4-amine;
- quinuclidine-3-amine; and
- 2-ethyl-4-methylpyridin-3-amine.

47. An intermediate selected from the group consisting of a compound having a structure of formula (I) as defined in any one of claims 1 to 29, wherein R^{1a} is a leaving group, such as a halogen, preferably Cl.

48. A method of preparing a compound of claim 33, comprising the steps:

- providing a compound of any one of claims 1 to 29 in admixture with one or more impurities; and
- removing at least a fraction of the impurities from the admixture.

49. A pharmaceutical package containing a pharmaceutical composition of claim 34 or 35; preferably, wherein the pharmaceutical composition is in finished pharmaceutical form.

50. A method of delivering a pharmaceutical composition of claim 34 or 35, or a pharmaceutical package of claim 49, from a first location to a second location, comprising the steps:

- receiving at a first location a request from a second location for the delivery of an amount of the pharmaceutical composition or the pharmaceutical package; and
- delivering at least a portion of (preferably, all of) the requested amount of the pharmaceutical composition or the pharmaceutical package from the first location to the second location in one or more deliveries,

wherein first location and the second location are separated by a distance of greater than about 10m, and one or more of the deliveries is/are transported for at least part of the distance between the first location to the second location by wheeled transporters.