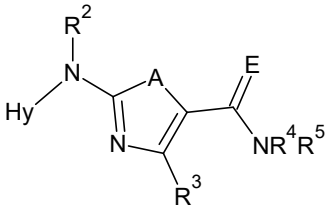
CLAIMS

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



(Ia),

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

wherein:

Hy is a heteroaryl or heterocyclyl which is optionally substituted with one or more independently selected R^{1e};

each R^{1e} is independently selected from the group consisting of R^{1a}, R^{1b}, R^{1c} and R^{1d};

each of R^{1a} and R^{1d} is independently 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 a 5-membered monocyclic heteroaryl which contains at least one S ring atom and which is 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 $-XC(=X)XR^{11}$, wherein each of the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, and heteroaryl groups is optionally substituted with one or more independently selected R^{30}, wherein at least one of R^7 is F and/or at least one of R^7 is substituted with one or more F atoms;

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;

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.

2. The compound of claim 1, wherein at least one of R^7 is F and/or at least one of R^7 is selected from the group consisting of C_{1-3}alkyl, $-O(C_{1-3}$alkyl), $-NH(C_{1-3}$alkyl) or $-N(C_{1-3}$alkyl$)_2$, wherein the alkyl group of C_{1-3}alkyl, $-NH(C_{1-3}$alkyl), and $-O(C_{1-3}$alkyl) and at least one of the alkyl groups of $-N(C_{1-3}$alkyl$)_2$ is substituted with one or more F atoms.

3. The compound of claim 1 or 2, wherein at least one of R^7 is F and/or at least one of R^7 is C_{1-3}alkyl, wherein the alkyl group of C_{1-3}alkyl is substituted with one or more F atoms; and/or,

wherein at least one of R^7 is F and/or at least one of R^7 is selected from the group consisting of $-CH_2F$, $-CHF_2$, and $-CF_3$, preferably selected from the group consisting of $-CH_2F$ and $-CHF_2$; and/or

wherein one R^7 is attached to the C ring atom at position 2 relative to the ring atom by which R^6 is bound to the remainder of the compound, preferably wherein said R^7 is F and/or said R^7 is substituted with one or more F atoms; and/or

wherein one R^7 is attached to the C ring atom at position 5 relative to the ring atom by which R^6 is bound to the remainder of the compound, preferably wherein said R^7 is F and/or said R^7 is substituted with one or more F atoms.

4. The compound of any one of claims 1 to 3, wherein R^6 is selected from the group consisting of thienyl, thiazolyl, and thiadiazolyl, each of which is substituted with one or more independently selected R^7; and/or,

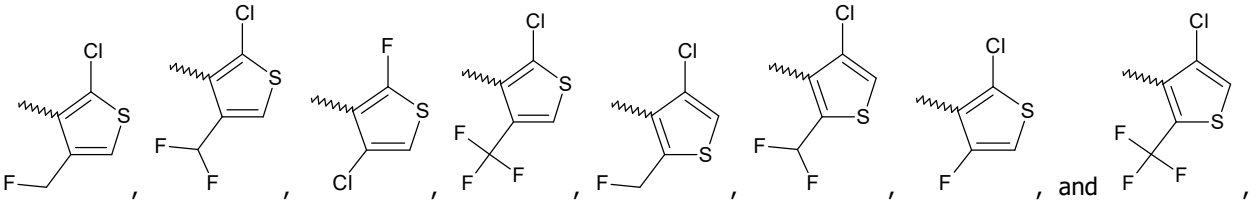
wherein R^6 is selected from the group consisting of thienyl and thiazolyl, each of which is substituted with one or more independently selected R^7

5. The compound of any one of claims 1 to 4, wherein R^6 is thienyl which is substituted with one or more independently selected R^7.

6. The compound of any one of claims 1 to 5, wherein the ring atom of R^6 by which R^6 is bound to the remainder of the compound is a C atom; and/or

wherein the S ring atom of R^6 is not adjacent to the ring atom by which R^6 is bound to the remainder of the compound.

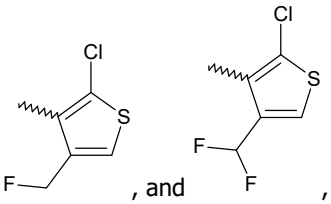
7. The compound of any one of claims 1 to 6, wherein R^6 is selected from the group consisting of



, and ,

wherein ~~~ represents the bond by which R^6 is bound to the remainder of the compound; and/or,

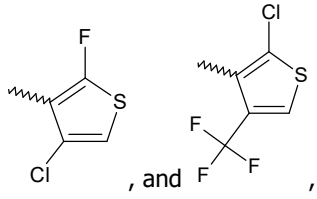
wherein R^6 is selected from the group consisting of



, and ,

wherein ~~~ represents the bond by which R^6 is bound to the remainder of the compound; or

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.

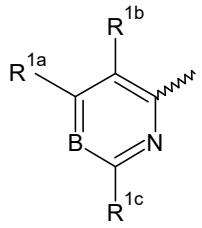
8. The compound of any one of claims 1 to 7, wherein L is a bond; E is O; and/or A is selected from the group consisting of S, O, NH, N(C_{1-6} alkyl), and C(C_{1-6} alkyl)$_2$.

9. The compound of any one of claims 1 to 8, wherein L is a bond; E is O; and A is S.

10. The compound of any one of claims 1 to 9, wherein Hy is selected from the group consisting of a 5- to 6-membered monocyclic heteroaryl, a 5- to 6-membered monocyclic heterocyclyl, a 9- to 10-membered bicyclic

heteroaryl, and a 8- to 10-membered bicyclic heterocyclyl, each of which is optionally substituted with one or more independently selected R^{1e}.

11. The compound of any one of claims 1 to 10, wherein Hy is:



wherein ~~~~ represents the bond by which Hy is bound to the remainder of the compound; R^{1a}, R^{1b}, and R^{1c} are as defined inclaim 1; and B is N or CR^{1d}.

12. The compound of any one of claims 1 to 11, 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, piperidinyl, hexahydropyrimidinyl, hexahydropyridazinyl, morpholinyl, 1,2-oxazinanyl, 1,3-oxazinanyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, diazepanyl, oxazepanyl, azaspirononanyl, diazaspirononanyl, azaspirodecanyl, diazaspirodecanyl, azaspiroundecanyl, and diazaspiroundecanyl, wherein each of the piperazinyl, piperidinyl, hexahydropyrimidinyl, hexahydropyridazinyl, morpholinyl, 1,2-oxazinanyl, 1,3-oxazinanyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, diazepanyl, oxazepanyl, azaspirononyl, diazaspirononyl, azaspirodecyl, diazaspirodecyl, azaspiroundecyl, and diazaspiroundecyl groups is optionally substituted with one or two independently selected R^{30}, wherein the one or two independently selected R^{30} optionally substituting R^{1a} are independently selected from the group consisting of methyl, ethyl, -OH, =O, -OCH_3, -SCH_3, cyclopropyl, 2-hydroxyethyl, 2-(N,N-dimethylamino)ethyl, 2-(N,N-dimethylamino)ethoxy, 2-(methoxy)ethoxy, 2-aminoethyl, 2-(N-methylamino)ethyl, 2-(methoxy)ethyl, 4-methylpiperazinyl, -C(=O)(C_{1-3} alkyl), -NHC(=O)(C_{1-3} alkyl), -N(C_{1-3} alkyl)C(=O)(C_{1-3} alkyl), -NHS(O)$_2$(C_{1-3} alkyl), -N(C_{1-3} alkyl)S(O)$_2$(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.

13. The compound of any one of claims 1 to 12, wherein R^{1a} is non-symmetrical; optionally,

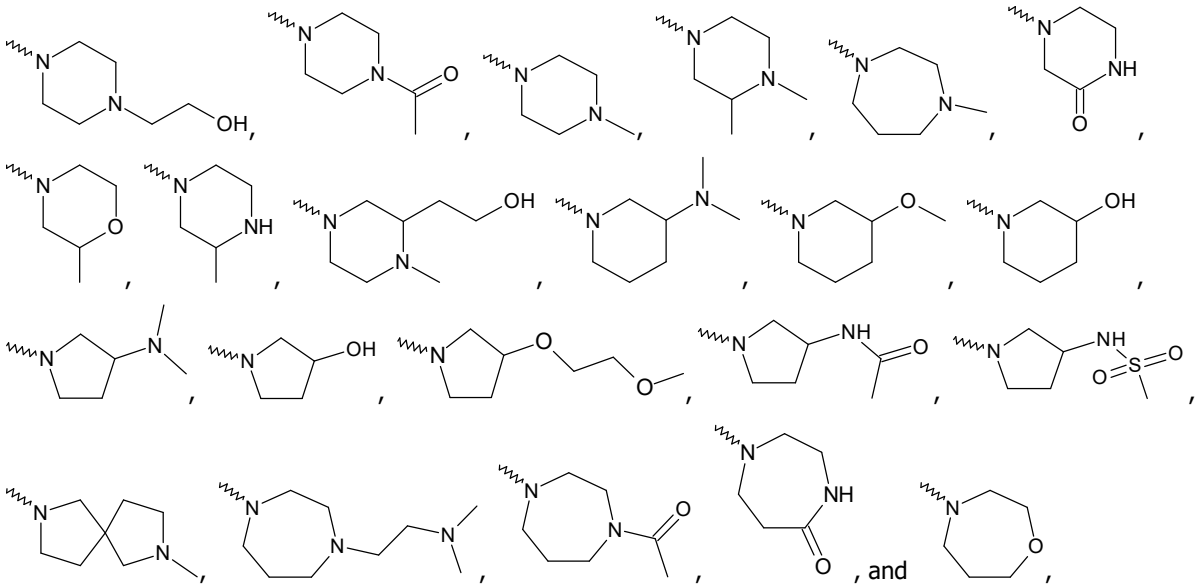
wherein R^{1a} is selected from the group consisting of 3,4-dimethylpiperazinyl, 4-methyl-1,4-diazepan-1-yl, 3-oxopiperazin-1-yl, 2-methylmorpholin-4-yl, 3-methylpiperazin-1-yl, 3-(2-hydroxyethyl)piperazin-1-yl, 3-(2-hydroxyethyl)-4-methylpiperazin-1-yl, 3-(dimethylamino)piperidin-1-yl, 3-(methoxy)piperidin-1-yl, 3-(hydroxy)piperidin-1-yl, 3-(dimethylamino)pyrrolidin-1-yl, 3-(hydroxy)pyrrolidin-1-yl, 3-(2-methoxyethoxy)pyrrolidin-1-yl, 3-(acetylamino)pyrrolidin-1-yl, 3-(methylsulfonylamino)pyrrolidin-1-yl, 7-methyl-2,7-diazaspiro[4.4]non-2-yl, 4-[2-(dimethylamino)ethyl]-1,4-diazepan-1-yl, 4-(acetyl)-1,4-diazepan-1-yl, 5-oxo-1,4-diazepan-1-yl, and 1,4-oxazepan-4-yl.

14. The compound of any one of claims 1 to 13, wherein the atom of R^{1a} by which R^{1a} is bound to the remainder of the compound is an atom other than C, preferably is an N atom; optionally,

wherein R^{1a} is selected from the group consisting of heterocyclyl, heteroaryl, -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})$_2$, -XC(=X)R^{11}, and -XC(=X)XR^{11}, wherein each of the heterocyclyl and heteroaryl groups is bound to the remainder of the compound via an atom other than C and is optionally substituted with one or more independently selected R^{30}; and/or

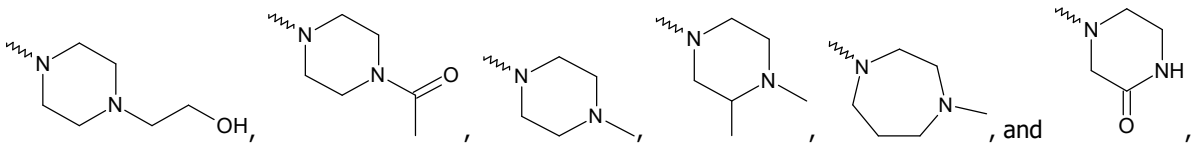
wherein R^{1a} is heterocyclyl which contains at least one N ring atom and which is bound to the remainder of the compound via an N ring atom.

15. The compound of claim 14, wherein R^{1a} is selected from the group consisting of:



wherein ~~~ represents the bond by which R^{1a} is bound to the remainder of the compound; optionally,

wherein R^{1a} is selected from the group consisting of:



wherein ~~~ represents the bond by which R^{1a} is bound to the remainder of the compound.

16. The compound of any one of claims 1 to 15, wherein R^{1b} is methyl, ethyl, propyl, or isopropyl, preferably methyl; and R^{1c} is H.

17. The compound of any one of claims 1 to 16, wherein B is N.

18. The compound of any one of claims 1 to 17, wherein R^{1b} is H; R^{1c} is methyl; B is N; and R^3 is H.

19. The compound of claim 11, 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 11-membered heterocyclyl, preferably a heterocyclyl that is bound to the remainder of the compound via an atom other than C, wherein the 3- to 11-membered heterocyclyl group is optionally substituted with one or two independently selected R^{30}, wherein the one or two independently selected R^{30} optionally substituting R^{1a} are independently selected from the group consisting of methyl, ethyl, -OH, =O, -OCH_3, -SCH_3, cyclopropyl, 2-hydroxyethyl, 2-(N,N-dimethylamino)ethyl, 2-(N,N-dimethylamino)ethoxy, 2-(methoxy)ethoxy, 2-aminoethyl, 2-(N-methylamino)ethyl, 2-(methoxy)ethyl, 4-methylpiperazinyl, -C(=O)(C_{1-3} alkyl), -NHC(=O)(C_{1-3} alkyl), -N(C_{1-3} alkyl)C(=O)(C_{1-3} alkyl), -NHS(O)$_2$(C_{1-3} alkyl), -N(C_{1-3} alkyl)S(O)$_2$(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; and

(B') at least one of R^{1b} and R^{1c} is selected from the group consisting of H, methyl, ethyl, propyl, isopropyl, -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 independently selected from the group consisting of H, methyl, ethyl, propyl, isopropyl, -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, preferably wherein one of R^{1b} and R^{1c} is H; and the other of R^{1b} and R^{1c} is methyl, ethyl, propyl, isopropyl, or phenyl, more preferably the other of R^{1b} and R^{1c} is methyl; and

(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 three 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, preferably wherein R^3 is H; and

(D') at least one of R^7 is F and/or at least one of R^7 is selected from the group consisting of C_{1-3}alkyl, $-O(C_{1-3}$alkyl), $-NH(C_{1-3}$alkyl) or $-N(C_{1-3}$alkyl)$_2$, wherein the alkyl group of C_{1-3}alkyl, $-NH(C_{1-3}$alkyl), and $-O(C_{1-3}$alkyl) and at least one of the alkyl groups of $-N(C_{1-3}$alkyl)$_2$ is substituted with one or more F atoms;

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

(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)$_2$, preferably wherein B is N; and

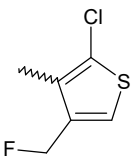
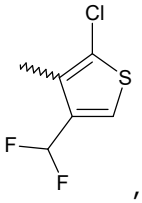
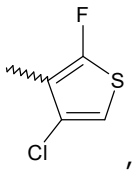
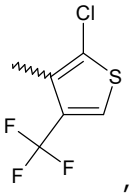
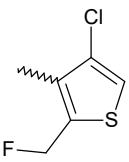
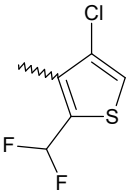
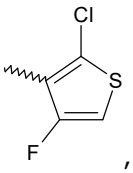
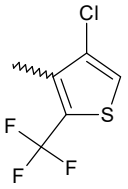
(G') E is O or S, preferably O.

20. The compound of claim 19, wherein one R^7 is selected from the group consisting of $-CH_2F$, $-CHF_2$, and $-CF_3$, preferably selected from the group consisting of $-CH_2F$ and $-CHF_2$.

21. The compound of claim 19 or 20, wherein one R^7 is selected from the group consisting of $-CH_2F$, $-CHF_2$, and $-CF_3$, preferably selected from the group consisting of $-CH_2F$ and $-CHF_2$, and one R^7 is Cl.

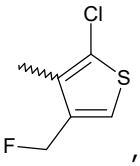
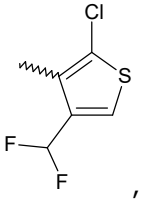
22. The compound of claim 19, wherein one R^7 is F and one R^7 is Cl.

23. The compound of claim 19, 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; or

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.

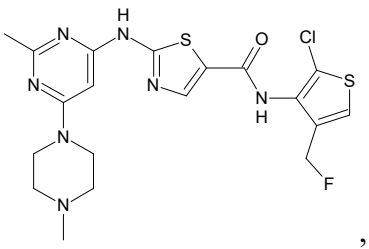
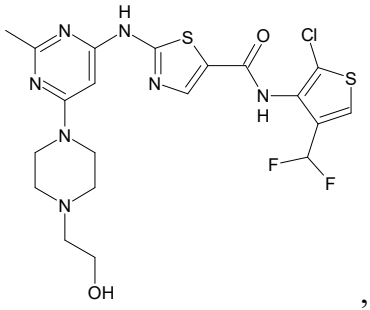
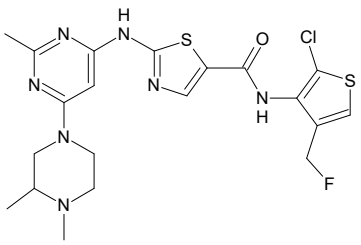
24. The compound of any one of claims 19 to 23, wherein R^{1a} is selected from the group consisting of 4-(2-hydroxyethyl)piperazinyl, 4-methylpiperazinyl, 3,4-dimethylpiperazinyl, 4-methyl-1,4-diazepan-1-yl, 3-oxopiperazin-1-yl, 2-methylmorpholin-4-yl, 3-methylpiperazin-1-yl, 3-(2-hydroxyethyl)piperazin-1-yl, 3-(2-hydroxyethyl)-4-methylpiperazin-1-yl, 3-(dimethylamino)piperidin-1-yl, 3-(methoxy)piperidin-1-yl, 3-(hydroxy)piperidin-1-yl, 3-(dimethylamino)pyrrolidin-1-yl, 3-(hydroxy)pyrrolidin-1-yl, 3-(2-methoxyethoxy)pyrrolidin-1-yl, 3-(acetylamino)pyrrolidin-1-yl, 3-(methylsulfonylamino)pyrrolidin-1-yl, 7-methyl-2,7-diazaspiro[4.4]non-2-yl, 4-[2-(dimethylamino)ethyl]-1,4-diazepan-1-yl, 4-(acetyl)-1,4-diazepan-1-yl, 5-oxo-1,4-diazepan-1-yl, and 1,4-oxazepan-4-yl.

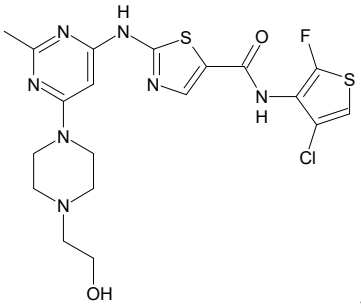
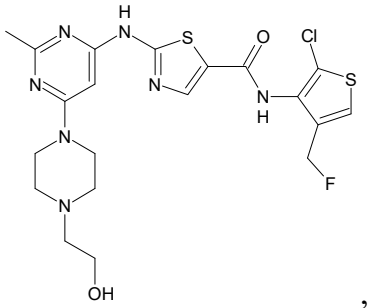
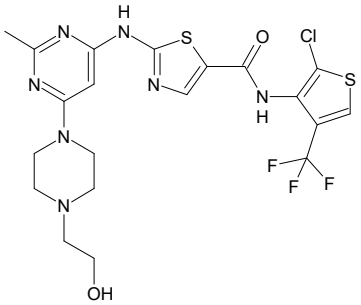
25. The compound of any one of claims 19 to 24, wherein R^{1a} is non-symmetrical.

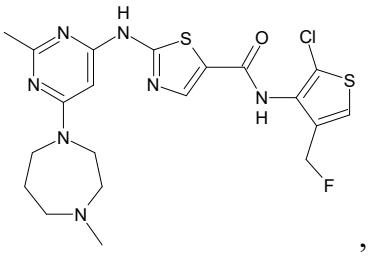
26. The compound of any one of claims 19 to 25, wherein the atom of R^{1a} by which R^{1a} is bound to the remainder of the compound is an atom other than C, preferably is an N atom.

27. The compound of any one of claims 19 to 26, wherein R^{1b} is H; R^{1c} is methyl; A is S; B is N; E is O; and R^3 is H.

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

 ,  ,  ,

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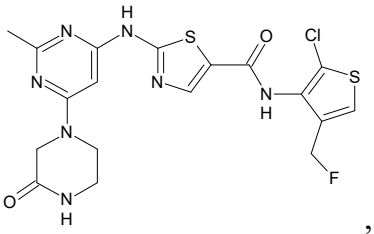
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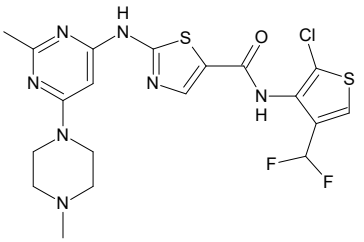
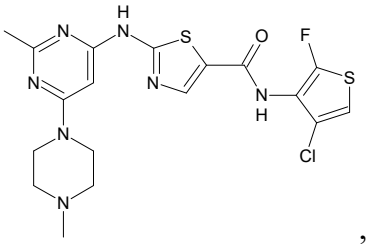
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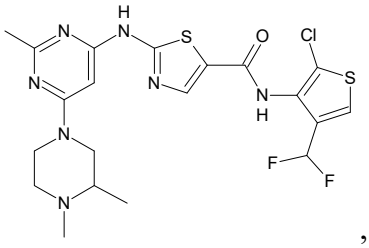
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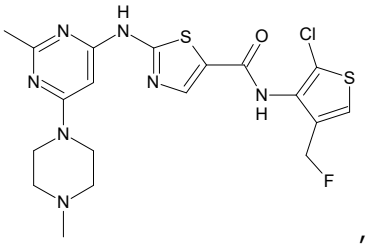
and solvates, salts, N-oxides, complexes, polymorphs, crystalline forms, racemic mixtures, diastereomers, enantiomers, tautomers, conformers, isotopically labeled forms, prodrugs, and combinations thereof.

29. The compound of any one of claims 1 to 28, wherein the compound is selected from the group consisting of: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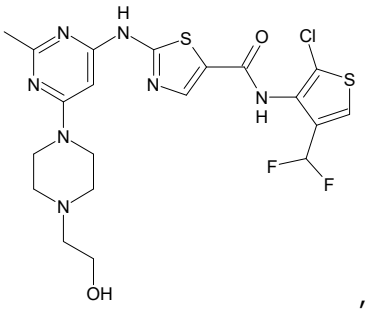
and solvates, salts, N-oxides, complexes, polymorphs, crystalline forms, tautomers, conformers, isotopically labeled forms, prodrugs, and combinations thereof; or

wherein the compound is selected from the group consisting of: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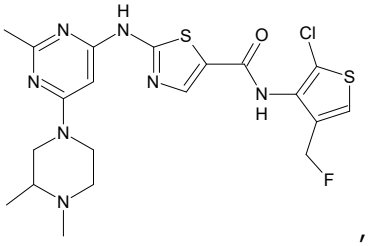
and solvates, salts, N-oxides, complexes, polymorphs, crystalline forms, tautomers, conformers, isotopically labeled forms, prodrugs, and combinations thereof; or

wherein the compound is selected from the group consisting of: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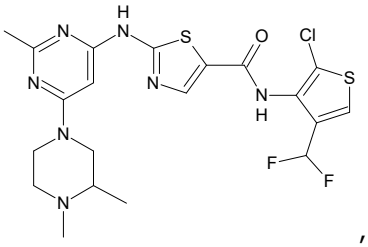
and solvates, salts, N-oxides, complexes, polymorphs, crystalline forms, racemic mixtures, diastereomers, enantiomers, tautomers, conformers, isotopically labeled forms, prodrugs, and combinations thereof; or

wherein the compound is selected from the group consisting of: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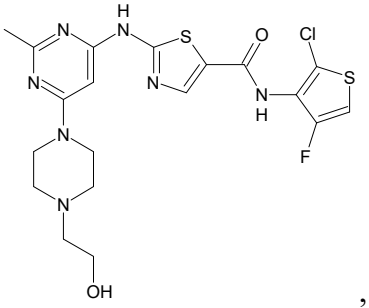
and solvates, salts, N-oxides, complexes, polymorphs, crystalline forms, racemic mixtures, diastereomers, enantiomers, tautomers, conformers, isotopically labeled forms, prodrugs, and combinations thereof.

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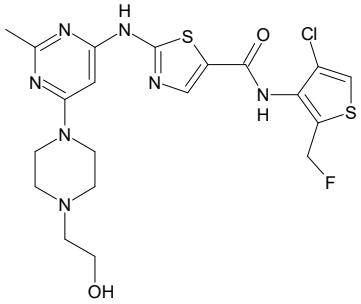
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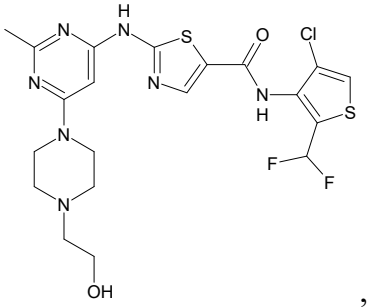
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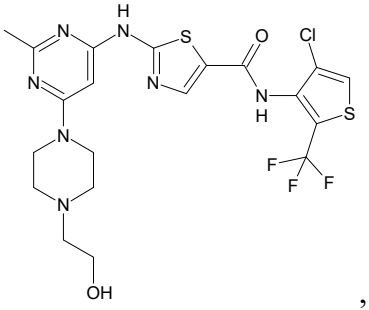
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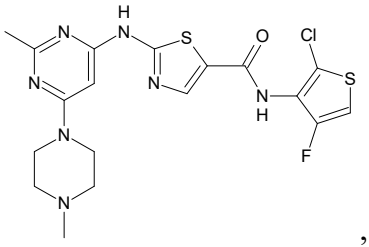
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and solvates, salts, N-oxides, complexes, polymorphs, crystalline forms, tautomers, conformers, isotopically labeled forms, prodrugs, and combinations thereof.

31. The compound of any one of claims 1 to 30, wherein the compound is in substantially pure form, in particular in greater than about 90%, 95%, 98% or 99% pure form.

32. **A pharmaceutical composition** comprising the compound of any one of claims 1 to 31, and optionally further comprising a pharmaceutically acceptable excipient; optionally,

wherein the pharmaceutical composition is formulated for oral administration; and/or

wherein the pharmaceutical composition is in unit dose form.

33. The compound of any one of claims 1 to 31, or the pharmaceutical composition of claim 32, for use as a medicament.

34. Use of **a compound** of any one of claims 1 to 31 **or a pharmaceutical composition** of claim 32, in the manufacture of a medicament for use in a treatment of a proliferative disorder in a subject.

35. The use of claim 34, wherein the proliferative disorder is a cancer or tumour; optionally, where the cancer is a solid tumour.

36. The use of claim 34 or 35, wherein an immune checkpoint inhibitor is to also be administered to the subject.

37. The use of any one of claims 34 to 36, wherein cells involved with the proliferative disorder in the subject are to be exposed to: (i) TNF, a TNF variant, and/or an agonist of TNFR12 or TNFR1-signalling; and (ii) the compound or pharmaceutical composition; optionally:

wherein the amount of TNF exposed to cells involved with the proliferative disorder in the subject is increased; and/or

wherein: (i) TNF, a TNF variant or an agonist of TNFR1 or TNFR2-signalling is to be 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 to be 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; and/or

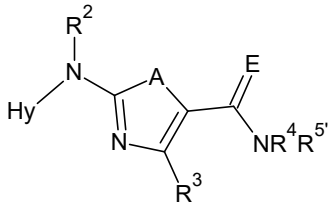
wherein the exposure of the cells involved with the proliferative disorder to TNF is induced by a pharmaceutical, therapeutic or other procedure that increases the amount of TNF in the plasma of the subject and/or in the environment of such cells.

38. The use of claims 34 to 37, wherein the compound or the pharmaceutical composition it to be administered two times daily (*bis in die*; BID).

39. Use of **a compound**, **or of a pharmaceutical composition** , in a manufacture of a medicament for use in a treatment of a proliferative disorder in a subject, **wherein the compound is selected from the following compounds (a) to (c)**, and the pharmaceutical composition comprises such a compound and, optionally, a pharmaceutically acceptable excipient:

(a) a compound of any one of claims 1 to 31; and

(b) a compound having the following formula:



(Ib),

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

wherein:

Hy, R^2, R^3, A, E, and R^4 are as defined in claim 1;

$R^{5'}$ is -L-$R^{6'}$;

L is a bond;

$R^{6'}$ is a 5- or 6-membered heteroaryl which is optionally substituted with one or more independently selected $R^{7'}$;

$R^{7'}$ is independently selected from the group consisting of R^7, 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}; and

R^{11}, R^{12}, R^{13}, X, and R^{30} are as defined in claim 1,

optionally, with the proviso that

(I) when A is S; R^3 is H; E is O; and $R^{6'}$ is 1-[2,4-bis(trifluoromethyl)benzyl]-1H-pyrazol-4-yl; then Hy is not 2-pyridyl;

(II) when Hy is 1-{(2E)-4-[(2-methoxyethyl)amino]-1-oxo-2-buten-1-yl}piperidine-4-yl; R^3 is H; A is O; E is O; then $R^{6'}$ is not 5-methyl-pyridin-2-yl;

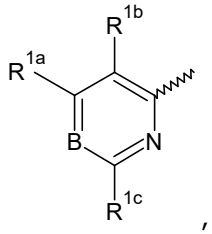
(III) when R^3 is trifluoromethyl; A is O; E is O; and

(i) $R^{6'}$ is 6-{4-[(2-fluorophenyl)carbamoyl]piperazin-1-yl}pyridine-3-yl; then Hy is not 1-(phenylmethyl)-piperidine-4-yl, 1-(phenylmethyl)pyrrolidine-3-yl, or tetrahydro-2H-pyran-4-yl; or

(ii) Hy is 1-(phenylmethyl)piperidine-4-yl; then $R^{6'}$ is not 6-(3-{[(2-fluorophenyl)carbamoyl]amino}-pyrrolidin-1-yl)pyridine-3-yl or 6-({1-[(2-fluorophenyl)carbamoyl]piperidin-4-yl}amino)pyridine-3-yl; or

(iii) Hy is 1-(phenylmethyl)pyrrolidine-3-yl; then $R^{6'}$ is not 6-({(3S)-1-[(2-fluorophenyl)carbamoyl]-pyrrolidin-3-yl}amino)pyridine-3-yl or 6-({(3R)-1-[(2-fluorophenyl)carbamoyl]pyrrolidin-3-yl}-amino)pyridine-3-yl; and/or

(IV) when Hy is



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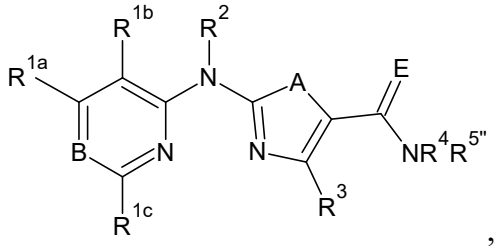
and

(1) 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; and A is S; then $R^{6'}$ is not 4-chloro-2-methylpyridin-3-yl;

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

(c) a compound having the following formula (Ic):



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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}, R^{1b}, R^{1c}, R^2, R^3, A, E, and R^4 are as defined in claim 1;

B is N or CR^{1d}, wherein R^{1d} is as defined in claim 1;

$R^{5"}$ is -L-$R^{6"}$;

L is as defined in claim 1;

$R^{6"}$ 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 R^7, 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}; and

R^{11}, R^{12}, R^{13}, X, and R^{30} are as defined in claim 1,

optionally, with the proviso

(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/or

(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;

(6) when A is S; R^3 is H; E is O; L is a bond; $R^{6''}$ is 1-[2,4-bis(trifluoromethyl)benzyl]-1H-pyrazol-4-yl; R^{1a} is H, R^{1b} is H, R^{1c} is H; and B is CR^{1d}; then R^{1d} is not H; and

wherein the proliferative disorder is selected from one or more of (α) to (γ):

(α) a proliferative disorder characterised by, or cells involved with the proliferative disorder characterised by, the presence of myocyte enhancer factor 2C (MEF2C) protein, such as of phosphorylated MEF2C protein and/or of MEF2C protein as an active transcription factor; preferably wherein the proliferative disorder is further characterised by, or cells involved with the proliferative disorder characterised by, the presence of phosphorylated histone deacetylase 4 (HDAC4) protein, such as of HDAC4 protein phosphorylated by SIK3; and/or

(β) a proliferative disorder characterised by, or cells involved with the proliferative disorder characterised by,: (i) the presence of a human chromosomal translocation at 11q23; (ii) the presence of a rearrangement of the lysine methyltransferase 2A (*KMT2A*) gene; (iii) the presence of an KMT2A fusion oncoprotein; and/or (iv) the presence of a mutation in the K-RAS proto-oncogene GTPase (*KRAS*) gene and/or in the RUNX family transcription factor 1 (*RUNX1*) gene; and/or

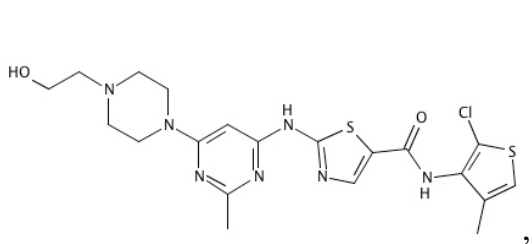
(γ) a mixed phenotype acute leukaemia (MPAL).

40. The use of claim 39:

wherein the compound is a compound as defined in (b) of claim 19 and $R^{6'}$ is a 5-membered monocyclic heteroaryl 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 $R^{7'}$; or

wherein the compound is a compound as defined in (c) of claim 19 and $R^{6''}$ is a 5- or 6-membered heteroaryl which contains at least one S ring atom and which is optionally substituted with one two or three independently selected $R^{7'}$.

41. The use of claim 39 or 40, wherein the compound is selected from the group consisting of: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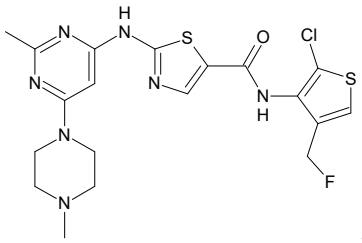
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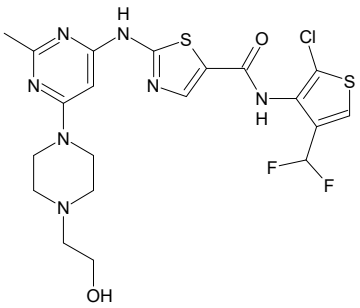
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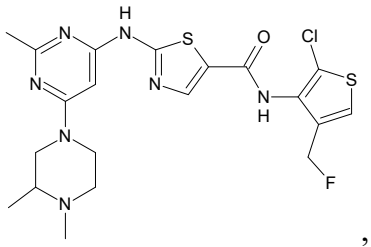
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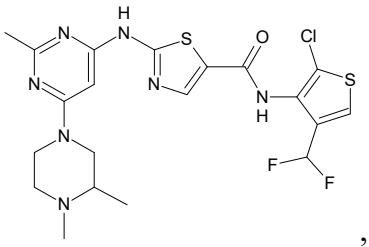
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and solvates, salts, N-oxides, complexes, polymorphs, crystalline forms, racemic mixtures, diastereomers, enantiomers, tautomers, conformers, isotopically labeled forms, prodrugs, and combinations thereof.

42. **A method for determining** that a subject suffering from a proliferative disorder is suitable for treatment with a compound or pharmaceutical composition as described in any one of claims 40 to 42, the method comprising, determining in a biological sample that has been obtained from said subject, and preferable that comprises cells involved with the proliferative disorder:

(X) the presence of MEF2C protein, such as of phosphorylated MEF2C protein and/or of MEF2C protein as an active transcription factor; preferably wherein the proliferative disorder is further characterised by the presence of phosphorylated HDAC4 protein, such as of HDAC4 protein phosphorylated by SIK3; and/or

(Y) (i) the presence of a human chromosomal translocation at 11q23; (ii) the presence of a rearrangement of the *KMT2A* gene; (iii) the presence of an KMT2A fusion oncoprotein; and/or (iv) the presence of a mutation in the *KRAS* gene and/or in the *RUNX1* gene,

wherein, the presence of said protein, translocation, rearrangement, oncoprotein and or mutation in the biological sample indicates that the subject is suitable for treatment with the compound or pharmaceutical composition.

43. The use of any one of claims 39 to 41, or the method of claim 42, wherein the proliferative disorder is characterised by, or cells involved with the proliferative disorder characterised by,: (i) the presence of a human chromosomal translocation at 11q23; (ii) the presence of a rearrangement of the *KMT2A* gene; and/or (iii) the presence of an KMT2A fusion oncoprotein, preferably wherein:

(a) the human chromosome translocation is one selected from the group consisting of: t(4,11), t(9,11), t(11,19), t(10,11) and t(6,11); and/or

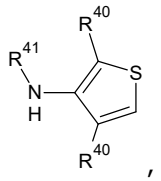
(b) the rearrangement of the *KMT2A* gene comprises, or the KMT2A fusion oncoprotein is expressed from a rearrangement that comprises, a fusion of the *KMT2A* gene with a translocation partner gene selected from the group consisting of: *AF4*, *AF9*, *ENL*, *AF10*, *ELL* and *AF6*.

44. The use of any one of claims 39 to 41 and 43, or the method of claim 42 or 43, wherein the proliferative disorder is: (i) a myeloma, preferably multiple myeloma; or (ii) a leukaemia, preferably an acute myeloid leukaemia (AML) or an acute lymphoblastic leukaemia (ALL), more preferably T cell acute lymphoblastic leukaemia (T-ALL), an MLL-AML or an MLL-ALL.

45. The use of any one of claims 39 to 41, 43 and 44, or the method of any one of claims 42 to 44, wherein the subject is a subject carrying a *KMT2A* rearrangement (*KMT2A-r*); preferably wherein such subject is a patient suffering from a *KMT2A-r* leukaemia.

46. The method of claim 42, wherein a compound or pharmaceutical composition as defined in any one of claims 40 to 42 is to be administered to a subject where the presence of, or an amount of, said protein, translocation, oncoprotein and or mutation is determined in a biological sample that had been obtained from said subject.

47. **An intermediate** selected from a compound having formula (Id):



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and solvates, salts, complexes, polymorphs, crystalline forms, racemic mixtures, diastereomers, enantiomers, tautomers, conformers, isotopically labeled forms, and combinations thereof,

wherein:

one of R^{40} is F or is selected from the group consisting of $C_{1\text{-}3}$alkyl, -O($C_{1\text{-}2}$alkyl), -NH($C_{1\text{-}2}$alkyl) and -N($C_{1\text{-}2}$alkyl)$_2$, wherein the alkyl group of $C_{1\text{-}3}$alkyl, -O($C_{1\text{-}2}$alkyl), and -NH($C_{1\text{-}2}$alkyl) and at least one of the alkyl groups of -N($C_{1\text{-}2}$alkyl)$_2$ is substituted with one, two, or three F atoms, and the other R^{40} is selected from the group consisting of halogen, -Me, -OMe, -Et and -OEt; and

R^{41} is selected from the group consisting of H and an amino protecting group,

with the proviso that

(1) the intermediate is not 2-bromo-4-(trifluoromethyl)thiophen-3-amine;

(2) when the R^{40} attached to the C ring atom at position 4 of the thienyl ring is -Me, and the other R^{40} is -CHF_2, then R^{41} is not (1-propylpiperidin-2-yl)carbonyl; and

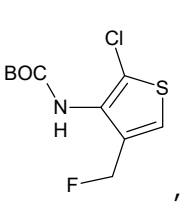
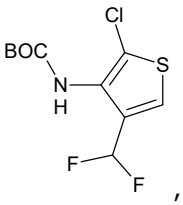
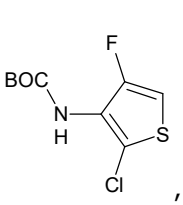
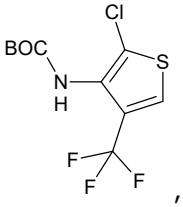
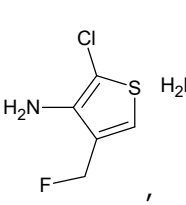
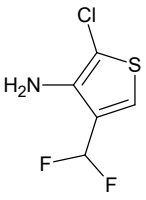
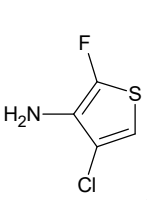
(3) when the R^{40} attached to the C ring atom at position 4 of the thienyl ring is -Me, and the other R^{40} is F, then R^{41} is not 4,5-dihydro-1*H*-imidazol-2-yl.

48. The intermediate of claim 47, wherein one R^{40} is selected from the group consisting of F, -CH_2F, -CHF_2, and -CF_3, and the other R^{40} is selected from the group consisting of halogen, -Me, -OMe, -Et and -OEt, more preferably selected from the group consisting of Cl, Br, F, and -Me; and/or

wherein one R^{40} is selected from the group consisting of F, -CH_2F, -CHF_2, and -CF_3, preferably selected from the group consisting of -CH_2F and -CHF_2, and the other R^{40}, optionally the R^{40} bound to the C ring atom adjacent to the S ring atom, is Cl.

49. The intermediate of claim 47 or 48, wherein the amino protecting group is selected from the group consisting of tert-butyloxycarbonyl (BOC), 9-fluorenylmethoxycarbonyl (FMOC), benzyloxycarbonyl (Cbz), p-methoxybenzylcarbonyl (MOZ), acetyl (Ac), trifluoroacetyl, benzoyl (Bz), benzyl (Bn), p-methoxybenzyl (PMB), 3,4-dimethoxyphenyl (DMPM), p-methoxyphenyl (PMP), 2,2,2-trichloroethoxycarbonyl (Troc), triphenylmethyl (trityl; Tr), toluenesulfonyl (tosyl; Ts), *para*-bromophenylsulfonyl (brosyl), 4-nitrobenzenesulfonyl (nosyl), and 2-nitrophenylsulfenyl (Nps).

50. The intermediate of any one of claims 47 to 49, wherein the intermediate is selected from the group consisting of: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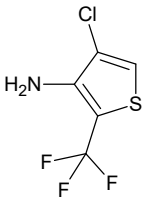
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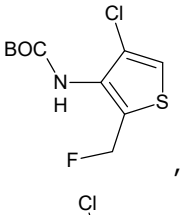
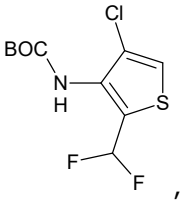
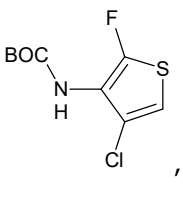
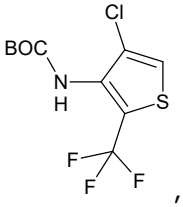
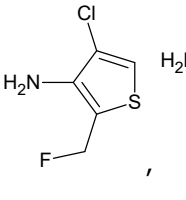
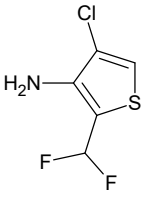
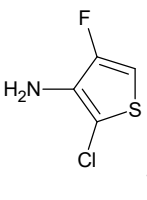
and solvates, salts, complexes, polymorphs, crystalline forms, tautomers, conformers, isotopically labeled forms, and combinations thereof; or

wherein the intermediate is selected from the group consisting of: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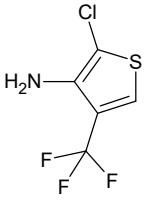
,

and solvates, salts, complexes, polymorphs, crystalline forms, tautomers, conformers, isotopically labeled forms, and combinations thereof.

51. **A method of manufacturing a compound** comprising an amide moiety, the method comprising the step of reacting the intermediate of claim 47 or 48 with a corresponding carboxylic acid, and, optionally, removing the amino protecting group; optionally,

wherein the compound is a kinase inhibitor, in particular an inhibitor of one or more protein kinases selected from the list consisting of: SIK (preferably SIK3), CSFR1, ABL, SRC, HCK, PDGFR and KIT; preferably selected from the list consisting of: SIK3, ABL/BCR-ABL, HCK and CSF1R kinases.

52. **A method of preparing a compound** of claim 31, comprising the steps:

- providing a compound of any one of claims 1 to 30 in admixture with one or more impurities; and
- removing at least a fraction of the impurities from the admixture.

53. **A method of manufacturing a pharmaceutical composition** comprising the step of formulating a compound of any one of claims 1 to 31 together with a pharmaceutically acceptable excipient.

54. **A method of manufacturing a pharmaceutical composition** comprising the step of formulating a compound of any one of claims 1 to 29 together with a pharmaceutically acceptable excipient; or

comprising:

- practicing, or having practiced, the method of claim 51 to manufacture a compound; and
- formulating the manufactured compound together with a pharmaceutically acceptable excipient.

55. **A method of preparing a pharmaceutical package**, comprising the steps:

- inserting into packaging a pharmaceutical composition of claim 32 (preferably in finished pharmaceutical form), thereby forming a package containing the pharmaceutical composition; and optionally,
- inserting into the package a leaflet describing prescribing information for the pharmaceutical composition.

56. **A pharmaceutical package** containing a pharmaceutical composition of claim 32; preferably, wherein the pharmaceutical composition is in finished pharmaceutical form.