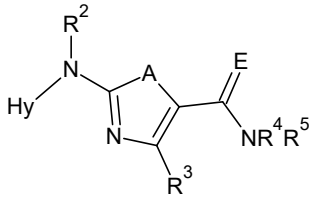
## CLAIMS

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

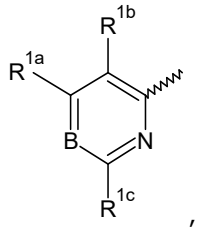


(Ia),

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

wherein:

**Hy** is:



,

wherein ^WWW^ represents the bond by which Hy is bound to the remainder of the compound;

**B** is N;

**$R^{1a}$** is selected from the group consisting of piperazinyl, piperidinyl, morpholinyl, pyrrolidinyl, diazepanyl, oxazepanyl, and diazaspirononyl, wherein each of the piperazinyl, piperidinyl, morpholinyl, pyrrolidinyl, diazepanyl, oxazepanyl, and diazaspirononyl 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, -OH, =O, $-OCH_3$, 2-hydroxyethyl, 2-(N,N-dimethylamino)ethyl, 2-(methoxy)ethoxy, $-C(=O)(C_{1-3}$ alkyl), $-NHC(=O)(C_{1-3}$ alkyl), $-NHS(O)_2(C_{1-3}$ alkyl), and $-NH_{2-z}(CH_3)_z$, wherein z is 0, 1, or 2; and wherein, the atom of $R^{1a}$ by which $R^{1a}$ is bound to the remainder of the compound is an N atom;

***either*: $R^{1b}$** is H; and **$R^{1c}$** is methyl, ethyl, propyl, isopropyl, or phenyl; ***or* $R^{1b}$** is methyl, ethyl, propyl, or isopropyl; and **$R^{1c}$** is H;

**$R^2$** is H;

**$R^3$** is selected from the group consisting of H, methyl, ethyl, propyl, isopropyl, phenyl, and halogen;

**$R^4$** is H;

**$R^5$** is $-L-R^6$;

**L** is a bond;

**$R^6$** is a thienyl which is substituted with two $R^7$ which differ from each other;

***either*: one $R^7$** is selected from the group consisting of $-CH_2F$, $-CHF_2$, and $-CF_3$, and **one $R^7$** is selected from the group consisting of halogen, $-CH_3$, $-CH_2$(hal), $-CH$(hal)$_2$, and $-C$(hal)$_3$; ***or* one $R^7$** is F and **one $R^7$** is selected from the group consisting of halogen, $-CH_3$, $-CH_2$(hal), $-CH$(hal)$_2$, and $-C$(hal)$_3$;

**A** is S; and

**E** is O.

2. The compound of claim 1,

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

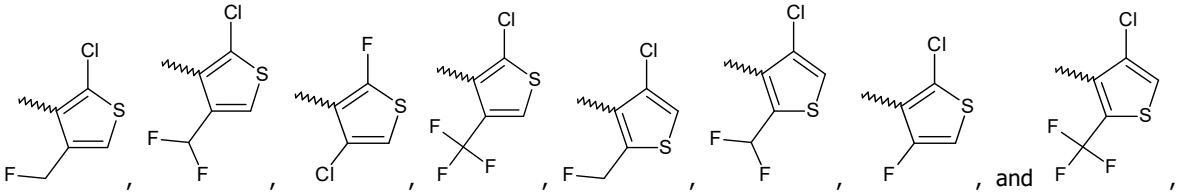
wherein one $R^7$ is attached to the C ring atom at position 5 relative to the ring atom by which $R^6$ is bound to the remainder of the compound, preferably wherein said $R^7$ is F and/or said $R^7$ is substituted with one or more F atoms.

3. The compound of claims 1 or 2, wherein *either*: one $R^7$ is selected from the group consisting of $CH_2F$, $-CHF_2$, and $-CF_3$, and one $R^7$ is Cl; *or* one $R^7$ is F and one $R^7$ is Cl.

4. The compound of any one of claims 1 to 3, 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

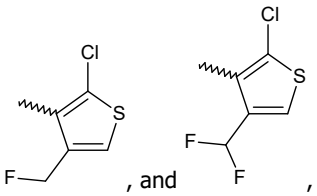
wherein the S ring atom of $R^6$ is not adjacent to the ring atom by which $R^6$ is bound to the remainder of the compound.

5. The compound of any one of claims 1 to 4, wherein $R^6$ is selected from the group consisting of



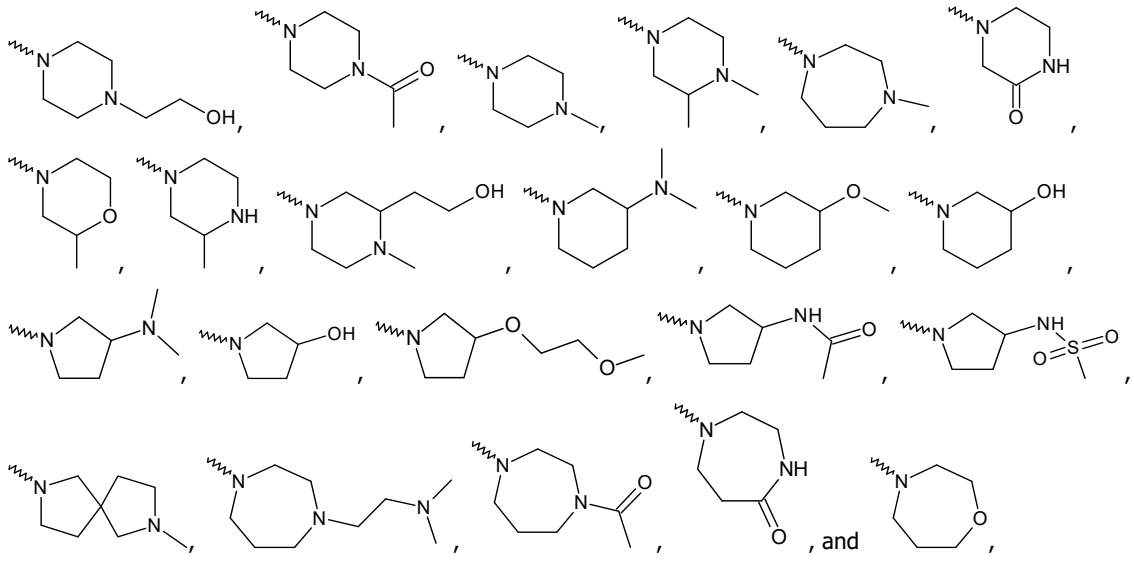

wherein ~~~~ represents the bond by which $R^6$ is bound to the remainder of the compound.

6. The compound of any one of claims 1 to 5, wherein $R^6$ is selected from the group consisting of



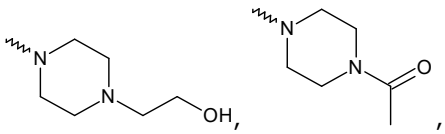
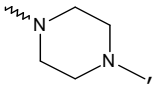
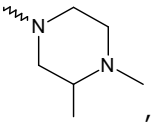
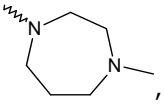
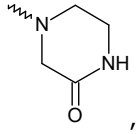

wherein ~~~~ represents the bond by which $R^6$ is bound to the remainder of the compound.

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




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

8. The compound of any one of claims 1 to 7, wherein $R^{1a}$ is selected from the group consisting of:


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

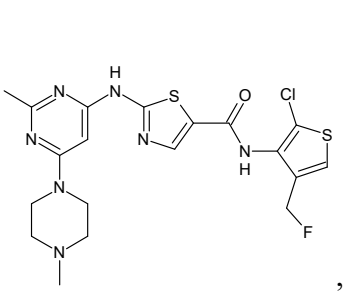
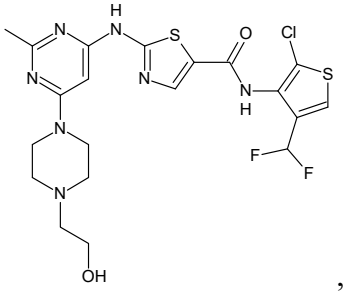
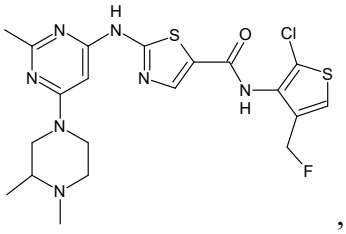
9. The compound of any one of claims 1 to 8, wherein $R^{1b}$ is H, and $R^{1c}$ is methyl.

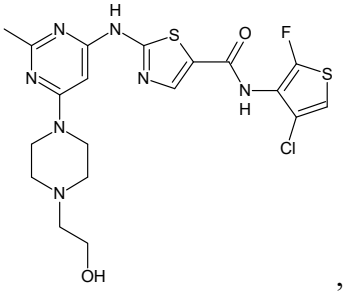
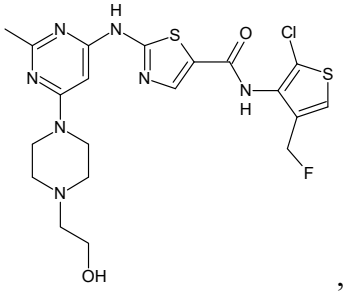
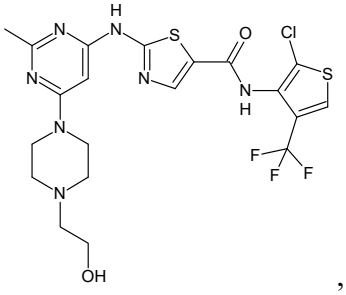
10. The compound of any one of claims 1 to 8, wherein $R^{1b}$ is methyl; and $R^{1c}$ is H.

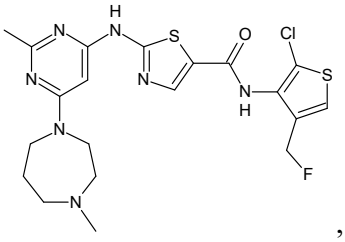
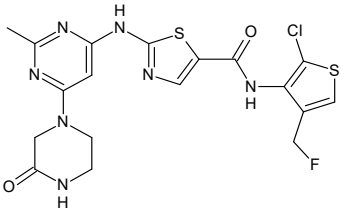
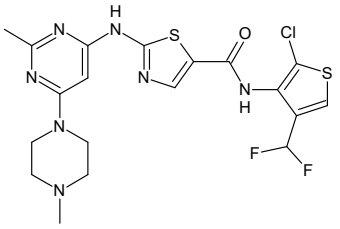
11. The compound of any one of claims 1 to 10, wherein $R^3$ is H.

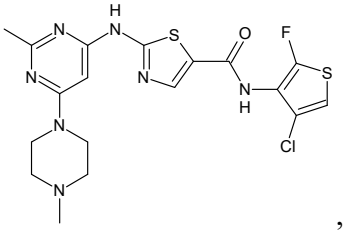
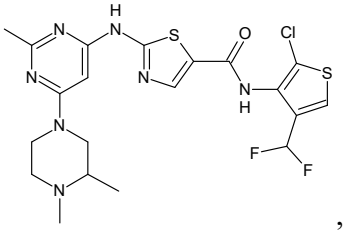
12. The compound of any one of claims 1 to 11, wherein $R^{1b}$ is H; $R^{1c}$ is methyl; and $R^3$ is H.

13. The compound of any one of claims 1 to 12, wherein the compound is selected from the group consisting of:


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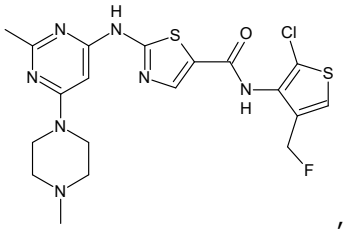

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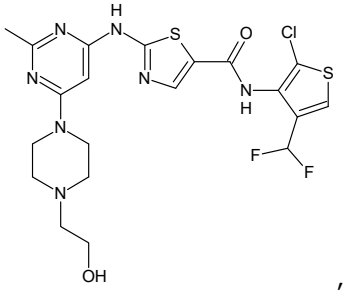
and solvates, salts, N-oxides, complexes, polymorphs, crystalline forms, racemic mixtures, diastereomers, enantiomers, tautomers, conformers, isotopically labeled forms, and combinations thereof.

14. The compound of any one of claims 1 to 12, wherein the compound is selected from the group consisting of:


,

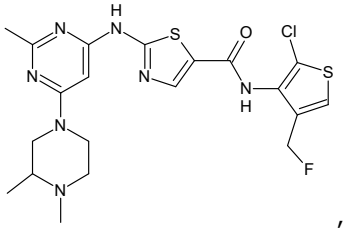
and solvates, salts, N-oxides, complexes, polymorphs, crystalline forms, tautomers, conformers, isotopically labeled forms, and combinations thereof.

15. The compound of any one of claims 1 to 12, wherein the compound is selected from the group consisting of:


,

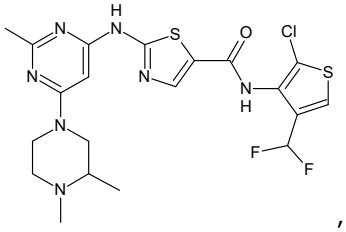
and solvates, salts, N-oxides, complexes, polymorphs, crystalline forms, tautomers, conformers, isotopically labeled forms, and combinations thereof.

16. The compound of any one of claims 1 to 12, wherein the compound is selected from the group consisting of:


,

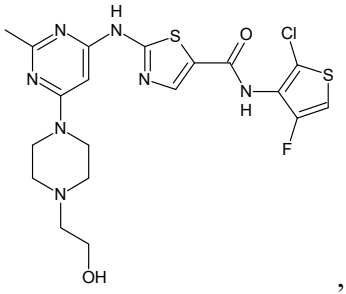
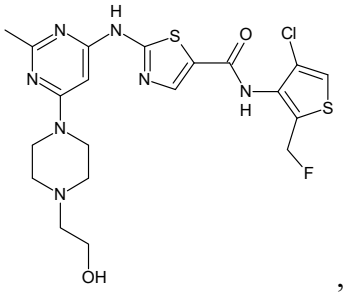
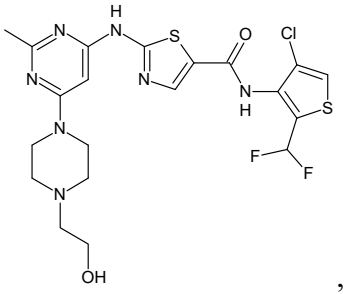
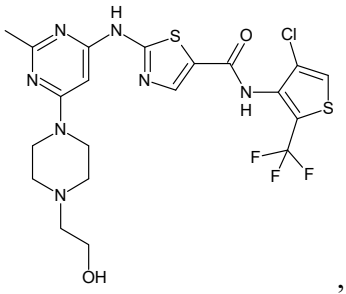
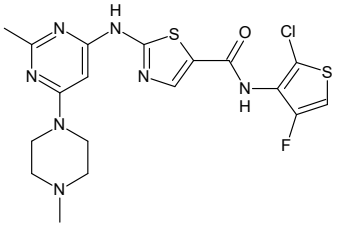
and solvates, salts, N-oxides, complexes, polymorphs, crystalline forms, racemic mixtures, diastereomers, enantiomers, tautomers, conformers, isotopically labeled forms, and combinations thereof.

17. The compound of any one of claims 1 to 12, wherein the compound is selected from the group consisting of:


,

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

18. The compound of any one of claims 1 to 12, wherein the compound is selected from the group consisting of:

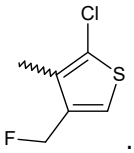

,

,

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, and

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

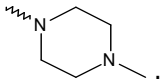
19. The compound of any one of claims 1 to 18, wherein the compound is in substantially pure form, in particular in greater than about 90%, 95%, 98% or 99% pure form.

20. The compound of any one of claims 1 to 18, wherein the compound is selected from the group consisting of a kinase inhibitor of formula (Ia), and solvates and pharmaceutically acceptable salts thereof.

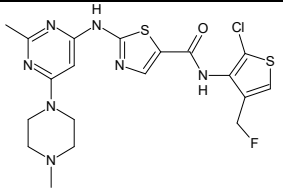
21. The compound of claim 6, wherein $R^6$ is:


.

22. The compound of claim 8, wherein $R^{1a}$ is:


.

23. **A compound** consisting of a kinase inhibitor, wherein the compound is:

| | | |
|---|---|---|
| E9 |  | *N*-(2-chloro-4-(fluoromethyl)thiophen-3-yl)-2-((2-methyl-6-(4-methylpiperazin-1-yl)pyrimidin-4-yl)amino)thiazole-5-carboxamide |

24. **A solvate** of the compound of claim 23.

25. **A salt** of the compound of claim 23.

26. The salt of claim 25, wherein the salt is a pharmaceutically acceptable salt.

27. **A pharmaceutical composition** comprising the compound of 23, the solvate of claim 24 or the salt of claim 26, and further comprising a pharmaceutically acceptable excipient.

28. **A pharmaceutical composition** comprising the compound of any one of claims 1 to 19, and 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.

29. The compound of any one of claims 1 to 19, or the pharmaceutical composition of claim 32, for use as a medicament.

30. Use of **a compound** of any one of claims 1 to 19 **or a pharmaceutical composition** of claim 28, in the manufacture of a medicament for use in a treatment of a proliferative disorder in a subject, preferably wherein the proliferative disorder is selected from the group consisting of: cancer, atherosclerosis, rheumatoid arthritis, idiopathic pulmonary fibrosis and cirrhosis of the liver.

31. The use of claim 30, wherein the proliferative disorder is a cancer or tumour.

32. The use of claim 31, where the cancer is a solid tumour.

33. The use of any one of claims 30 to 32, wherein an immune checkpoint inhibitor is to also be administered to the subject.

34. The use of any one of claims 30 to 33, 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 TNFR2 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.

35. The use of any one of claims 30 to 34, 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.

36. The use of any one of claims 30 to 35, wherein the compound or the pharmaceutical composition is to be administered two times daily (*bis in die*; BID).

37. 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** a compound of any one of claims 1 to 19, and the pharmaceutical composition comprises such a compound and, a pharmaceutically acceptable excipient, and

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

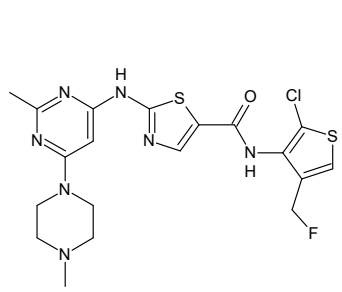
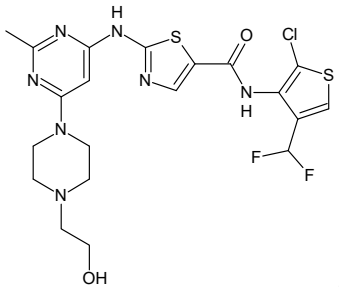
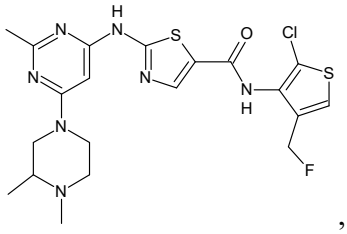
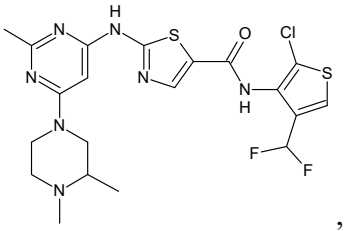
**(α)** a proliferative disorder characterised by, or cells involved with the proliferative disorder characterised by, the presence of myocyte enhancer factor 2C (MEF2C) protein, such as of phosphorylated MEF2C protein and/or of MEF2C protein as an active transcription factor; preferably wherein the 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).

38. The use of claim 37, 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, and combinations thereof.

39. The use of claim 37 or 38, 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

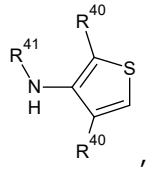
(b) the rearrangement of the *KMT2A* gene comprises, or the KMT2A fusion oncoprotein is expressed from a rearrangement that comprises, a fusion of the *KMT2A* gene with a translocation partner gene selected from the group consisting of: *AF4*, *AF9*, *ENL*, *AF10*, *ELL* and *AF6*.

40. The use of any one of claims 37 to 39, 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.

41. The use of any one of claims 37 to 40,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.

42. The use of any one of claims 30 to 41, wherein the subject is a human subject.

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



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 selected from the group consisting of F, $-CH_2F$, $-CHF_2$, and $-CF_3$, and the other $R^{40}$ is halogen; 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.

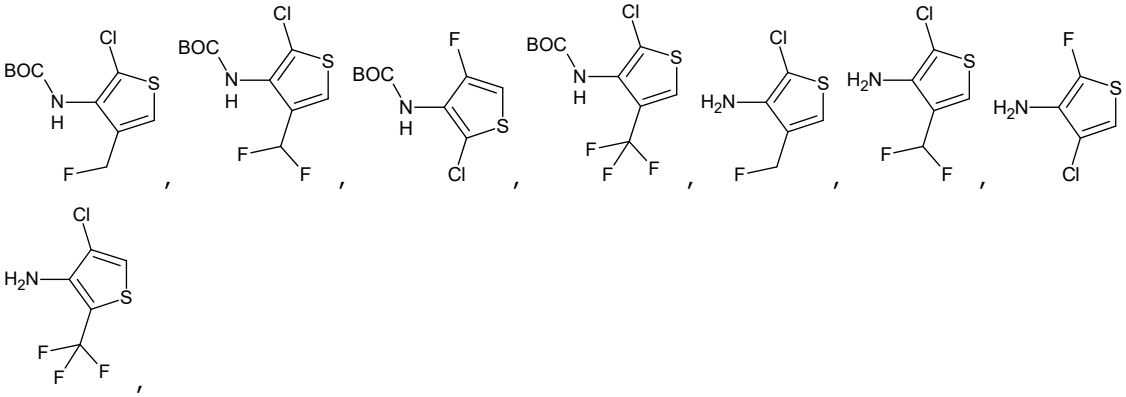
44. The intermediate of claim 43,

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

45. The intermediate of claim 44, wherein one $R^{40}$ is 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.

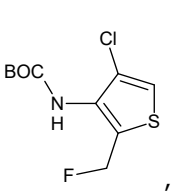
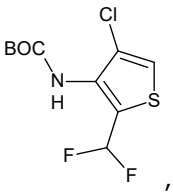
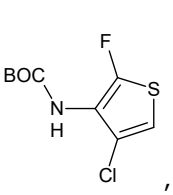
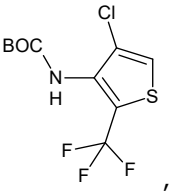
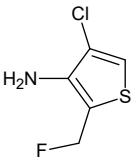
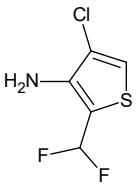
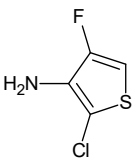
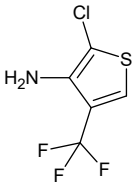
46. The intermediate of any one of claims 43 to 45, wherein the amino protecting group is selected from the group consisting of tert-butyloxycarbonyl (BOC), 9-fluorenylmethoxycarbonyl (FMOC), benzyloxycarbonyl (Cbz), p-methoxybenzylcarbonyl (MOZ), acetyl (Ac), trifluoroacetyl, benzoyl (Bz), benzyl (Bn), 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).

47. The intermediate of any one of claims 43 to 46, wherein the intermediate is selected from the group consisting of:



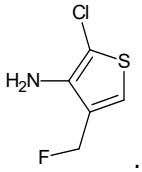
and solvates, salts, complexes, polymorphs, crystalline forms, tautomers, conformers, isotopically labeled forms, and combinations thereof.

48. The intermediate of any one of claims 43 to 46, 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.

49. The intermediate of claim 47, wherein the intermediate is a compound having the formula:


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50. A solvate of the intermediate of claim 49.

51. A salt of the intermediate of claim 49.

52. The salt of claim 51 that is 2-chloro-4-(fluoromethyl)thiophen-3-amine hydrochloride.

53. **A method of manufacturing a compound** comprising an amide moiety, the method comprising the step of reacting the intermediate of any one of claims 43 to 45 with a corresponding carboxylic acid, and when $R^{41}$ is an amino protecting group, 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.

54. **A method of preparing a compound** of claim 19, comprising the steps:

- providing a compound of any one of claims 1 to 18 in admixture with one or more impurities; and
- removing at least a fraction of the impurities from the admixture.

55. **A method of manufacturing a pharmaceutical composition** comprising the step of formulating a compound of any one of claims 1 to 19 together with a pharmaceutically acceptable excipient.

56. **A method of manufacturing a pharmaceutical composition** comprising the step of formulating a compound of any one of claims 1 to 17 together with a pharmaceutically acceptable excipient; or

comprising:

- practicing, or having practiced, the method of claim 53 to manufacture a compound; and
- formulating the manufactured compound together with a pharmaceutically acceptable excipient.

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

- inserting into packaging a pharmaceutical composition of claim 28 (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.

58. **A pharmaceutical package** containing a pharmaceutical composition of claim 28; preferably, wherein the pharmaceutical composition is in finished pharmaceutical form.