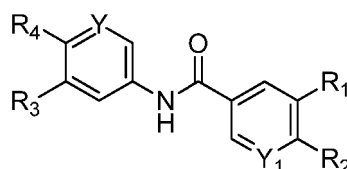


[00524] It is understood that the Examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims.

CLAIMS

We Claim:

1. The compound of claim 1 of formula (I):



(I)

in which:

R₁ is pyrazolyl; wherein said pyrazolyl is unsubstituted or substituted with 1 to 2 R₆ groups;

R₂ is pyrrolidinyl; wherein said pyrrolidinyl is substituted with one R₇ group;

R₃ is selected from hydrogen and halo;

R₄ is selected from -SF₅ and -Y₂-CF₂-Y₃;

R₆ at each occurrence is independently selected from hydrogen, hydroxy, methyl, methoxy, cyano, trifluoromethyl, hydroxy-methyl, halo, amino, fluoro-ethyl, ethyl and cyclopropyl;

R₇ is selected from hydroxy, methyl, halo, methoxy, hydroxy-methyl, amino, methyl-amino, amino-methyl, trifluoromethyl, 2-hydroxypropan-2-yl, methyl-carbonyl-amino, dimethyl-amino, 2-amino-3-methylbutanoyl)oxy, carboxy, methoxy-carbonyl, phosphonooxy, cyano and amino-carbonyl;

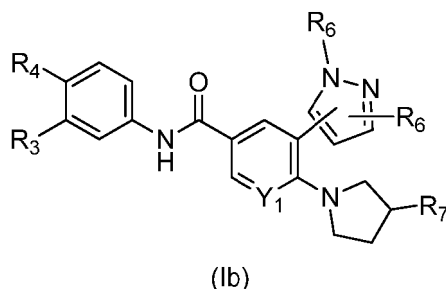
Y is selected from CH and N;

Y₁ is selected from CH and N;

Y₂ is selected from CF₂, O and S(O)₀₋₂; and

Y₃ is selected from hydrogen, chloro, fluoro, methyl, difluoromethyl and trifluoromethyl; or the pharmaceutically acceptable salts thereof.

2. The compound of claim 1 of formula (Ib):



in which:

R_3 is selected from hydrogen and halo;

R_4 is selected from $-SF_5$ and $-Y_2-CF_2-Y_3$;

R_6 when linked to a nitrogen of the pyrazolyl ring is selected from hydrogen, methyl, hydroxy-ethyl, fluoro-ethyl, ethyl and cyclopropyl; and R_6 when linked to a carbon atom of the pyrazolyl ring is selected from hydrogen, hydroxy, methyl, methoxy, cyano, trifluoromethyl, hydroxy-methyl, halo, amino, fluoro-ethyl, ethyl and cyclopropyl;

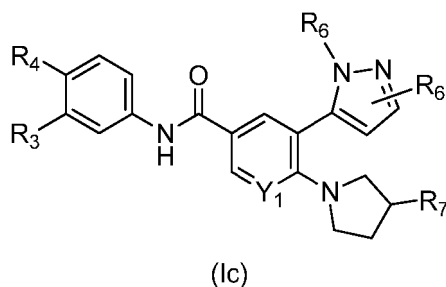
R_7 is selected from hydroxy, methyl, halo, methoxy, hydroxy-methyl, amino, methyl-amino, amino-methyl, trifluoromethyl, 2-hydroxypropan-2-yl, methyl-carbonyl-amino, dimethyl-amino, 2-amino-3-methylbutanoyl)oxy, carboxy, methoxy-carbonyl, phosphonooxy, cyano and amino-carbonyl;

Y_1 is selected from CH and N;

Y_2 is selected from CF_2 , O and $S(O)_{0-2}$;

Y_3 is selected from hydrogen, fluoro, chloro, methyl, difluoromethyl and trifluoromethyl; or the pharmaceutically acceptable salts thereof.

3. The compound of claim 2 of formula (Ic):



in which:

R₃ is selected from hydrogen and halo;

R₄ is selected from -SF₅ and -Y₂-CF₂-Y₃;

R₆ when linked to a nitrogen of the pyrazolyl ring is selected from hydrogen, methyl, hydroxy-ethyl, fluoro-ethyl, ethyl and cyclopropyl; and R₆ when linked to a carbon atom of the pyrazolyl ring is selected from hydrogen, hydroxy, methyl, methoxy, cyano, trifluoromethyl, hydroxy-methyl, halo, amino, fluoro-ethyl, ethyl and cyclopropyl;

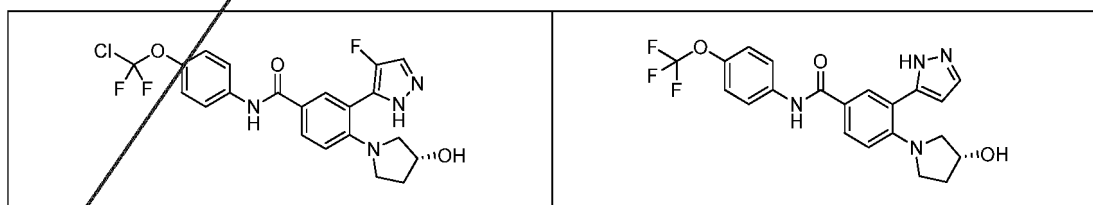
R₇ is selected from hydroxy, methyl, halo, methoxy, hydroxy-methyl, amino, methyl-amino, amino-methyl, trifluoromethyl, 2-hydroxypropan-2-yl, methyl-carbonyl-amino, dimethyl-amino, 2-amino-3-methylbutanoyloxy, carboxy, methoxy-carbonyl, phosphonoxy, cyano and amino-carbonyl;

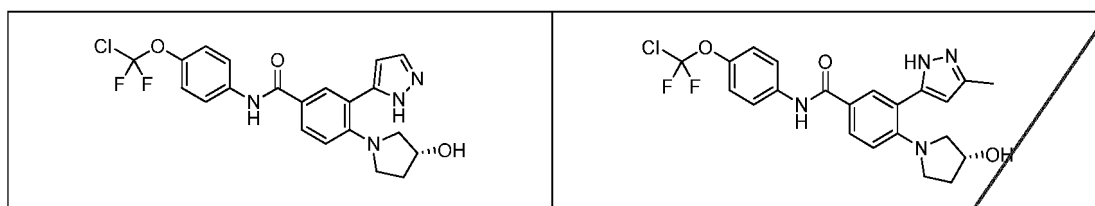
Y₁ is selected from CH and N;

Y₂ is selected from CF₂, O and S(O)₀₋₂;

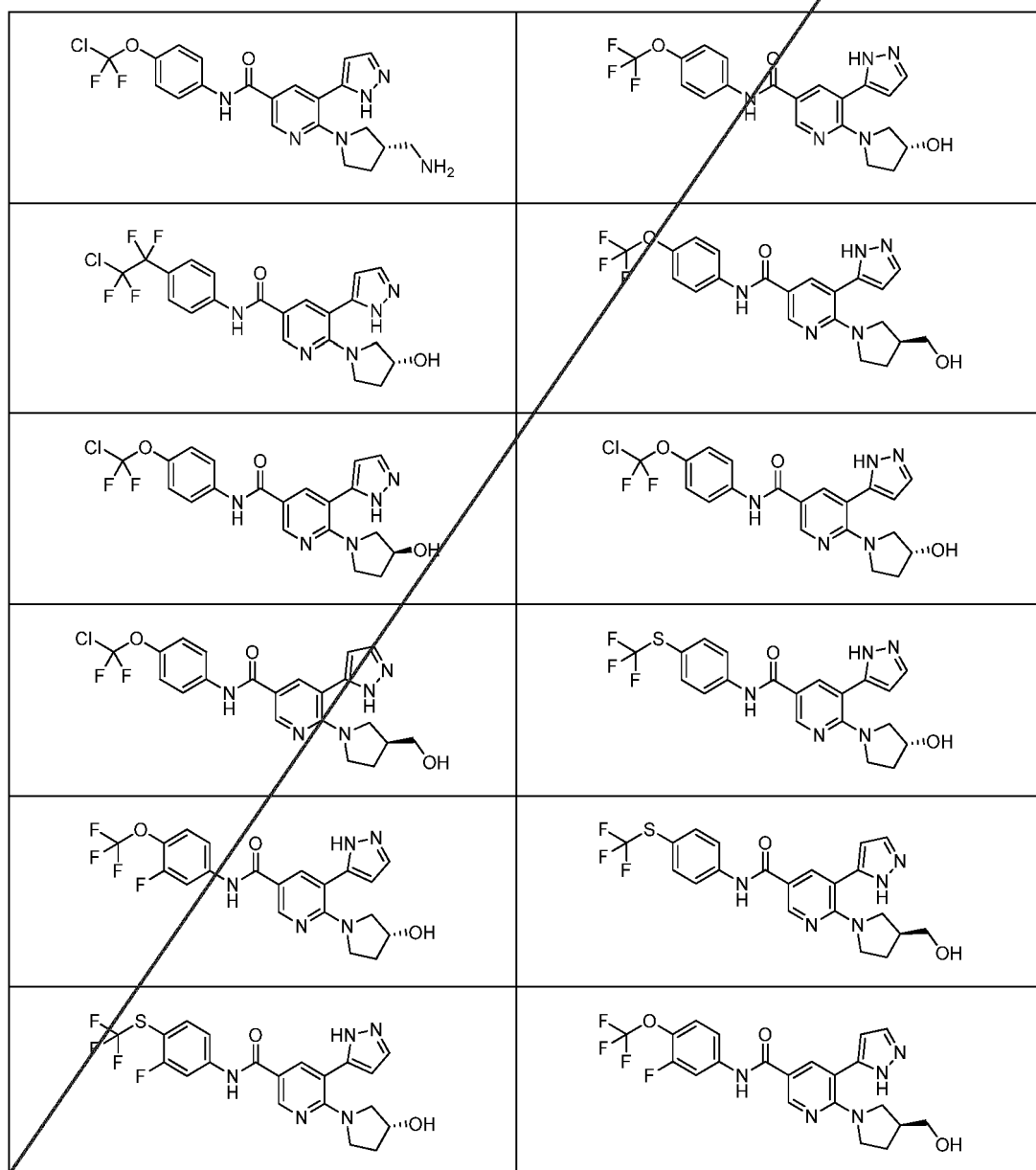
Y₃ is selected from hydrogen, fluoro, chloro, methyl, difluoromethyl and trifluoromethyl; or the pharmaceutically acceptable salts thereof.

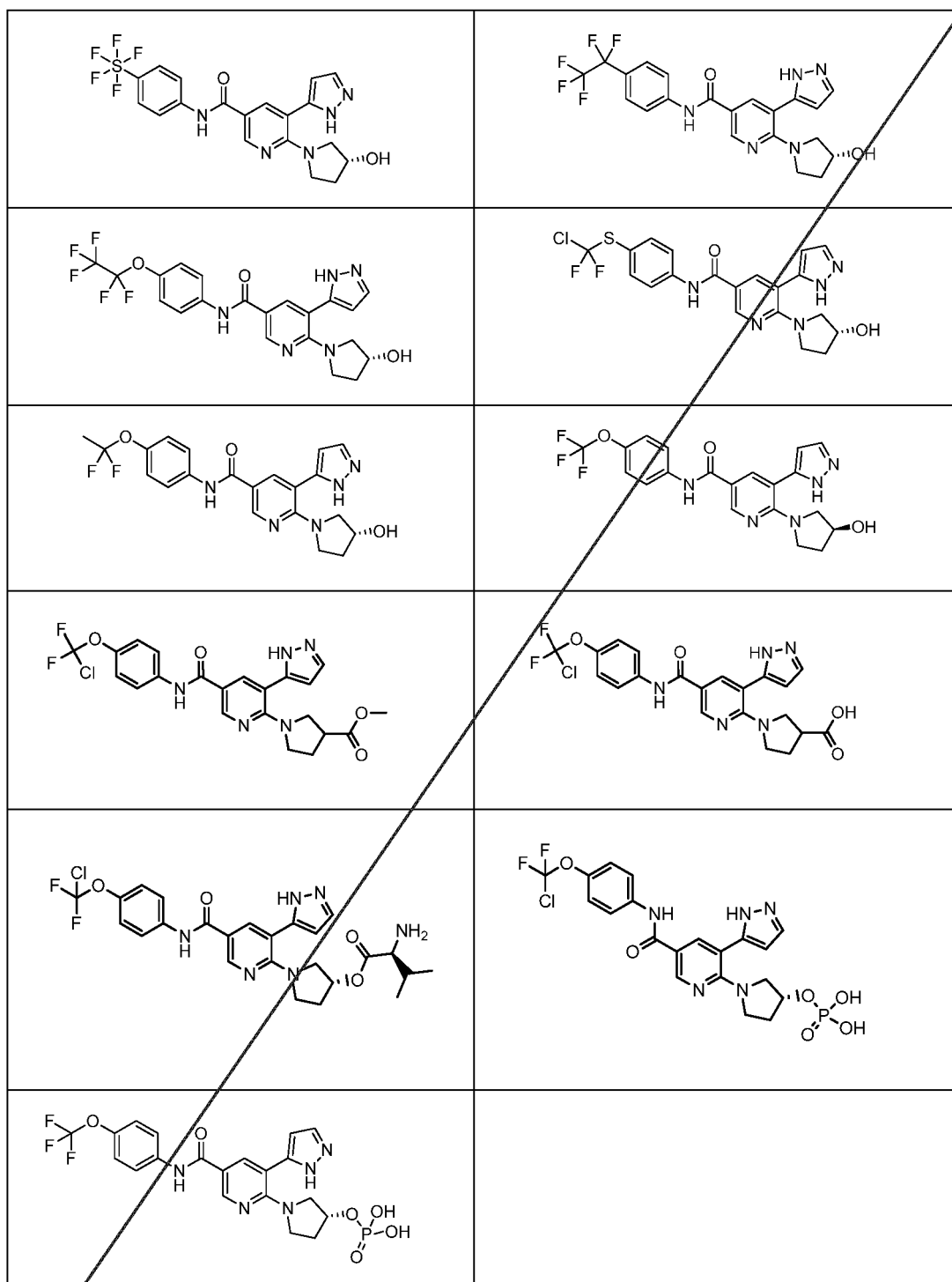
4. The compound of claim 3, or a pharmaceutically acceptable salt thereof, selected from:



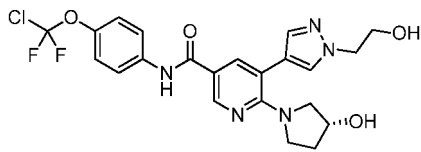
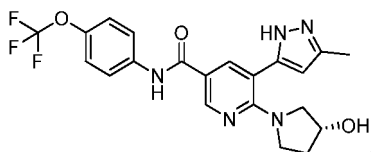
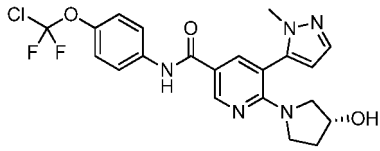
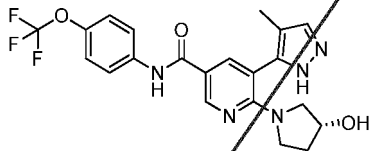
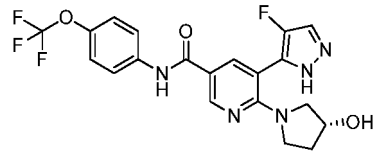
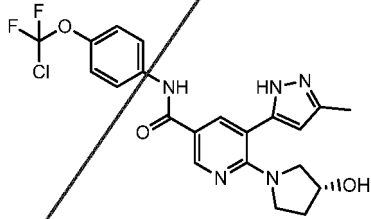
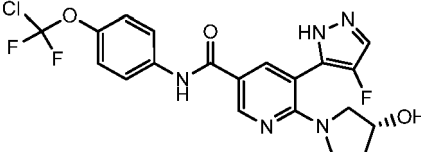
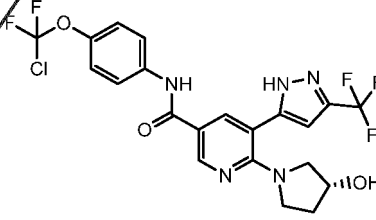
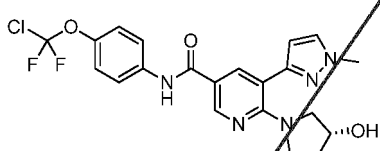
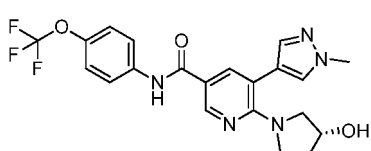
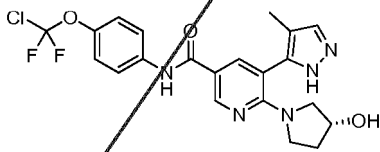
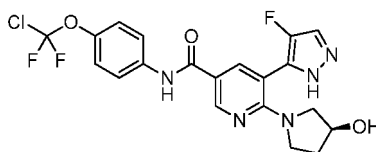


5. The compound of claim 3, or a pharmaceutically acceptable salt thereof, selected from:

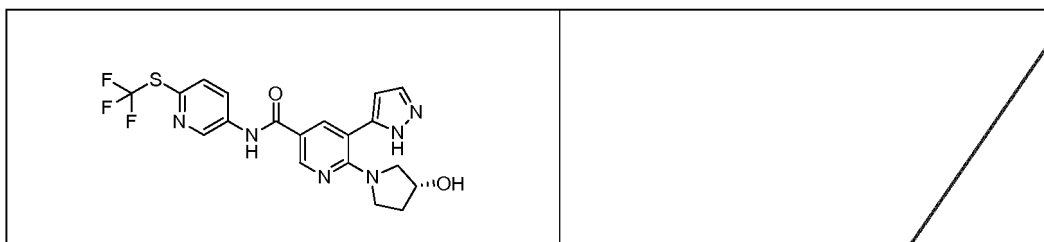




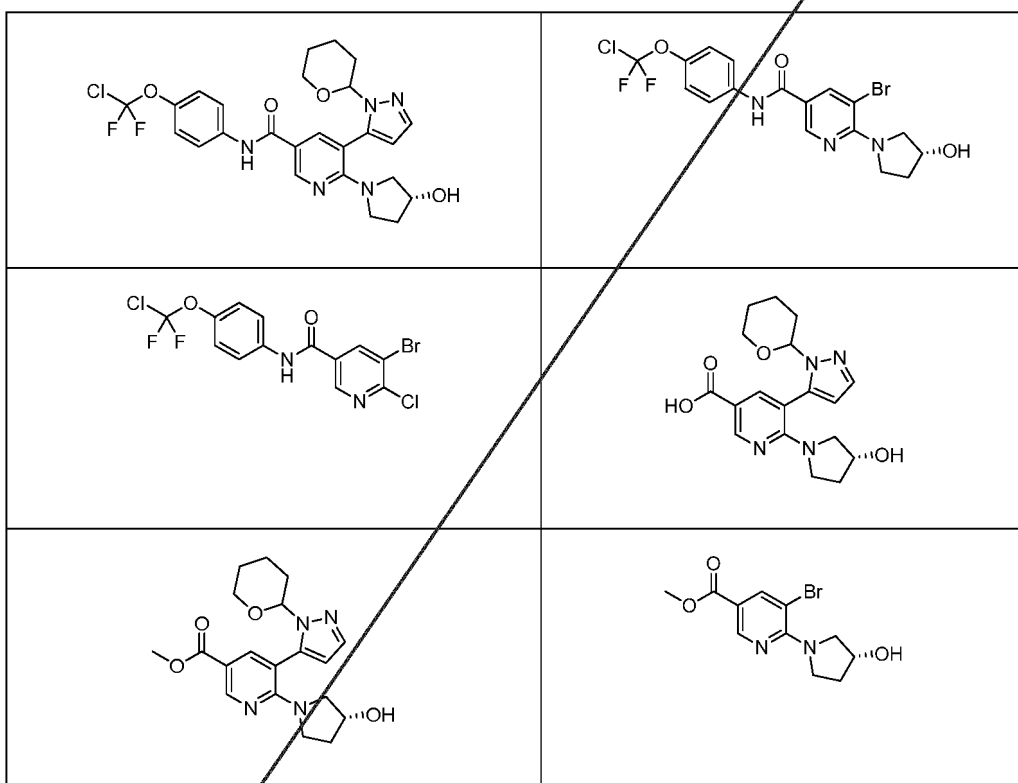
6. The compound of claim 3, or a pharmaceutically acceptable salt thereof, selected from:

7. The compound of claim 1, or a pharmaceutically acceptable salt thereof, that is:



8. A compound selected from:



9. The compound of claim 1 that is (R)-N-(4-(chlorodifluoromethoxy)phenyl)-6-(3-hydroxypyrrolidin-1-yl)-5-(1H-pyrazol-5-yl)nicotinamide or a pharmaceutically acceptable salt thereof.

10. A pharmaceutical composition comprising an amorphous dispersion of (R)-N-(4-(chlorodifluoromethoxy)phenyl)-6-(3-hydroxypyrrolidin-1-yl)-5-(1H-pyrazol-5-yl)nicotinamide and 1 to 2 excipients selected from PVP VA64 and Pharmacoat 603.

11. The composition of claim 10, wherein the percentage of Pharmacoat 603 is in the range of 30% to 45%, the percentage of PVP VA64 is in the range of 30% to 45% and the percentage of (R)-N-(4-(chlorodifluoromethoxy)phenyl)-6-(3-hydroxypyrrolidin-1-yl)-5-(1H-pyrazol-5-yl)nicotinamide is in the range of 20% to 30%.

12. The composition of claim 11, wherein the percentage of Pharmacoat 603 is 37.5%, the percentage of PVP VA64 is 37.5% and the percentage of (R)-N-(4-(chlorodifluoromethoxy)phenyl)-6-(3-hydroxypyrrolidin-1-yl)-5-(1H-pyrazol-5-yl)nicotinamide is 25%.

13. A method for treating a patient having a leukemia selected from chronic myeloid leukemia (CML) and acute lymphoblastic leukemia (ALL) comprising administering to said patient a therapeutically effective amount of (R)-N-(4-(chlorodifluoromethoxy)phenyl)-6-(3-hydroxypyrrolidin-1-yl)-5-(1H-pyrazol-5-yl)nicotinamide or a pharmaceutically acceptable salt thereof and optionally a sequential or simultaneous administration of a therapeutically effective amount of a compound selected from imatinib, nilotinib, dasatinib, bosutinib, ponatinib and bafetinib.

14. The method of claim 13 comprising administering to said patient a therapeutically effective amount of (R)-N-(4-(chlorodifluoromethoxy)phenyl)-6-(3-hydroxypyrrolidin-1-yl)-5-(1H-pyrazol-5-yl)nicotinamide or a pharmaceutically acceptable salt thereof.

15. The method of claim 13 comprising a sequential administration of a therapeutically effective amount of a compound of (R)-N-(4-(chlorodifluoromethoxy)phenyl)-6-(3-hydroxypyrrolidin-1-yl)-5-(1H-pyrazol-5-yl)nicotinamide or a pharmaceutically acceptable salt thereof and a

sequential administration of a therapeutically effective amount of a compound selected from imatinib, nilotinib, dasatinib, bosutinib, ponatinib and bafetinib.

16. The method of claim 13 comprising administering to said patient a therapeutically effective amount of (R)-N-(4-(chlorodifluoromethoxy)phenyl)-6-(3-hydroxypyrrolidin-1-yl)-5-(1H-pyrazol-5-yl)nicotinamide or a pharmaceutically acceptable salt thereof and a simultaneous administration of a therapeutically effective amount of a compound selected from imatinib, nilotinib, dasatinib, bosutinib, ponatinib and bafetinib.

17. The method of claim 16 wherein (R)-N-(4-(chlorodifluoromethoxy)phenyl)-6-(3-hydroxypyrrolidin-1-yl)-5-(1H-pyrazol-5-yl)nicotinamide is dosed in the range of 90-130 mg/kg.

18. The method of claim 17 wherein nilotinib is dosed at 10-50 mg/kg.

19. The method of claim 18 wherein imatinib is dosed at 50-200 mg/kg.

20. A compound of formula (I), or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 9 for use in the treatment of cancer.

21. A compound of formula (I), or a pharmaceutically acceptable salt thereof, for use according to claim 20, wherein the cancer is leukemia selected from chronic myeloid leukemia and acute lymphoblastic leukemia.

22. A compound of formula (I), or a pharmaceutically acceptable salt thereof, for use according to claim 20 or claim 21, together with an additional compound selected from imatinib, nilotinib, dasatinib, bosutinib, ponatinib and bafetinib.

23. A compound of formula (I), or a pharmaceutically acceptable salt thereof, for use according to claim 22 in sequential or simultaneous administration with said additional compound wherein said additional compound is nilotinib.

24. A compound of formula (I), or a pharmaceutically acceptable salt thereof, for use according to any one of claims 20 to 23 wherein the compound is (R)-N-(4-(chlorodifluoromethoxy)phenyl)-6-(3-hydroxypyrrolidin-1-yl)-5-(1H-pyrazol-5-yl)nicotinamide or a pharmaceutically acceptable salt thereof.

25. Use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of cancer.

26. Use according to claim 25 wherein the cancer is leukemia selected from chronic myeloid leukemia and acute lymphoblastic leukemia.

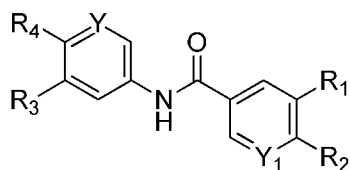
[00524] It is understood that the Examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims.

[00525] The reference in this specification to any prior publication (or information derived from it), or to any matter which is known, is not, and should not be taken as an acknowledgment or admission or any form of suggestion that that prior publication (or information derived from it) or known matter forms part of the common general knowledge in the field of endeavour to which this specification relates.

[00526] Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. The compound of claim 1 of formula (I):



(I)

in which:

R₁ is pyrazolyl; wherein said pyrazolyl is unsubstituted or substituted with 1 to 2 R₆ groups;

R₂ is pyrrolidinyl; wherein said pyrrolidinyl is substituted with one R₇ group;

R₃ is selected from hydrogen and halo;

R₄ is selected from -SF₅ and -Y₂-CF₂-Y₃;

R₆ at each occurrence is independently selected from hydrogen, hydroxy, methyl, methoxy, cyano, trifluoromethyl, hydroxy-methyl, halo, amino, fluoro-ethyl, ethyl and cyclopropyl;

R₇ is selected from hydroxy, methyl, halo, methoxy, hydroxy-methyl, amino, methyl-amino, amino-methyl, trifluoromethyl, 2-hydroxypropan-2-yl, methyl-carbonyl-amino, dimethyl-amino, 2-amino-3-methylbutanoyl)oxy, carboxy, methoxy-carbonyl, phosphonooxy, cyano and amino-carbonyl;

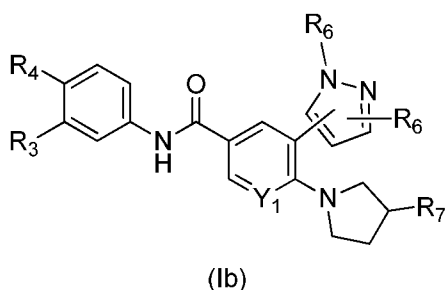
Y is selected from CH and N;

Y₁ is selected from CH and N;

Y₂ is selected from CF₂, O and S(O)₀₋₂; and

Y₃ is selected from hydrogen, chloro, fluoro, methyl, difluoromethyl and trifluoromethyl; or the pharmaceutically acceptable salts thereof.

2. The compound of claim 1 of formula (Ib):



in which:

R_3 is selected from hydrogen and halo;

R₄ is selected from -SF₅ and -Y₂-CF₂-Y₃;

R₆ when linked to a nitrogen of the pyrazolyl ring is selected from hydrogen, methyl, hydroxy-ethyl, fluoro-ethyl, ethyl and cyclopropyl; and **R₆** when linked to a carbon atom of the pyrazolyl ring is selected from hydrogen, hydroxy, methyl, methoxy, cyano, trifluoromethyl, hydroxy-methyl, halo, amino, fluoro-ethyl, ethyl and cyclopropyl;

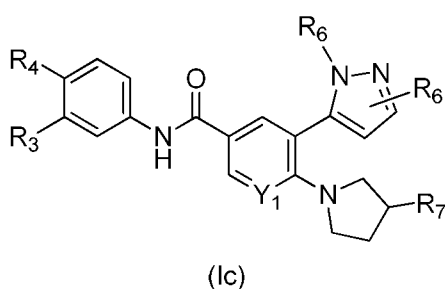
R₇ is selected from hydroxy, methyl, halo, methoxy, hydroxy-methyl, amino, methyl-amino, amino-methyl, trifluoromethyl, 2-hydroxypropan-2-yl, methyl-carbonyl-amino, dimethyl-amino, 2-amino-3-methylbutanoyl)oxy, carboxy, methoxy-carbonyl, phosphonooxy, cyano and amino-carbonyl;

Y_1 is selected from CH and N;

Y_2 is selected from CF_2 , O and $S(O)_{0-2}$;

Y₃ is selected from hydrogen, fluoro, chloro, methyl, difluoromethyl and trifluoromethyl; or the pharmaceutically acceptable salts thereof.

3. The compound of claim 2 of formula (Ic):



in which:

R₃ is selected from hydrogen and halo;

R₄ is selected from -SF₅ and -Y₂-CF₂-Y₃;

R₆ when linked to a nitrogen of the pyrazolyl ring is selected from hydrogen, methyl, hydroxy-ethyl, fluoro-ethyl, ethyl and cyclopropyl; and R₆ when linked to a carbon atom of the pyrazolyl ring is selected from hydrogen, hydroxy, methyl, methoxy, cyano, trifluoromethyl, hydroxy-methyl, halo, amino, fluoro-ethyl, ethyl and cyclopropyl;

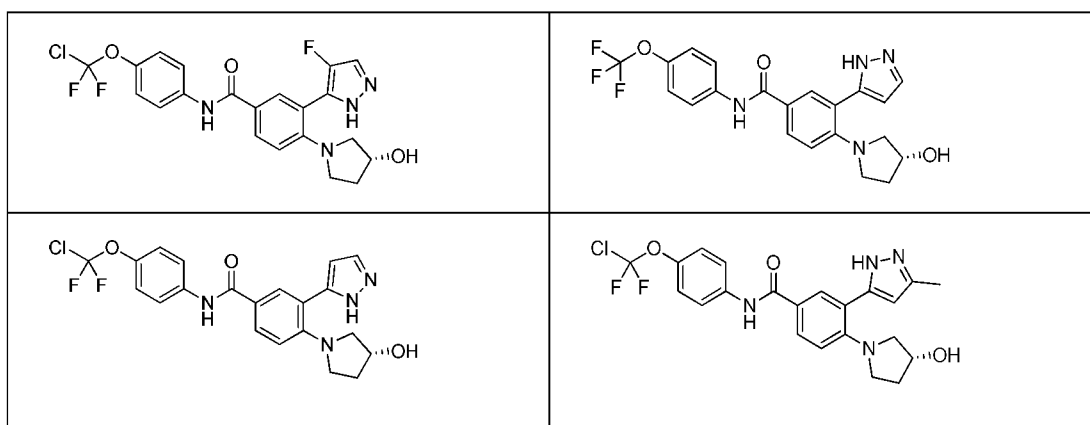
R₇ is selected from hydroxy, methyl, halo, methoxy, hydroxy-methyl, amino, methyl-amino, amino-methyl, trifluoromethyl, 2-hydroxypropan-2-yl, methyl-carbonyl-amino, dimethyl-amino, 2-amino-3-methylbutanoyl)oxy, carboxy, methoxy-carbonyl, phosphonooxy, cyano and amino-carbonyl;

Y₁ is selected from CH and N;

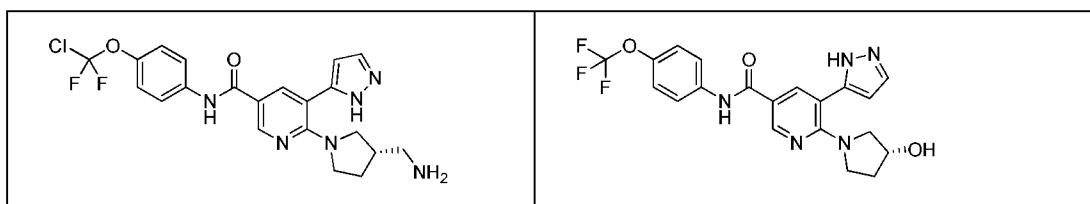
Y₂ is selected from CF₂, O and S(O)₀₋₂;

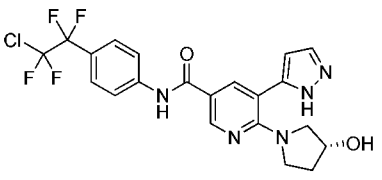
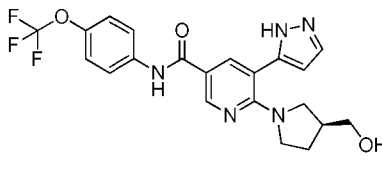
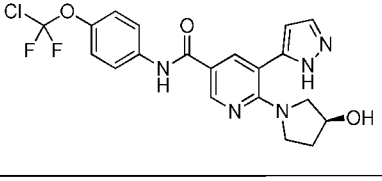
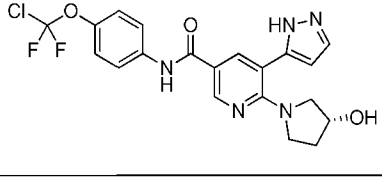
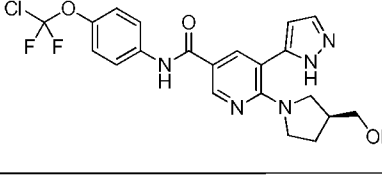
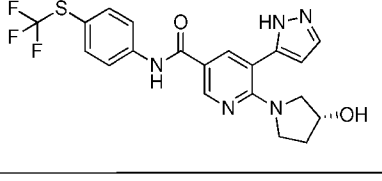
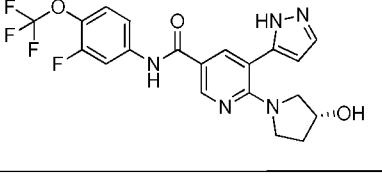
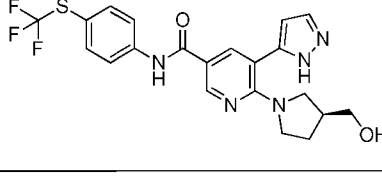
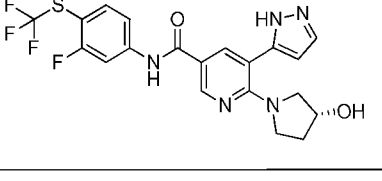
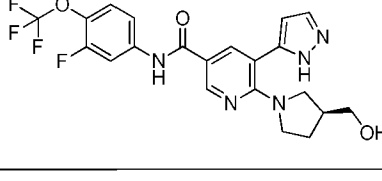
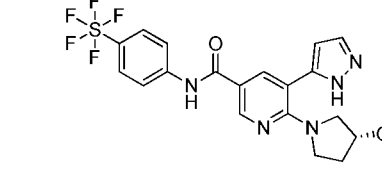
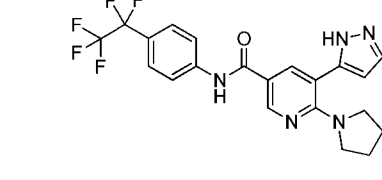
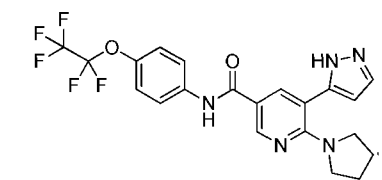
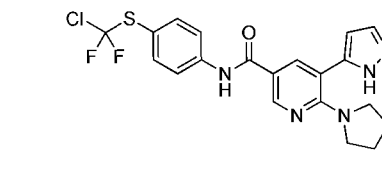
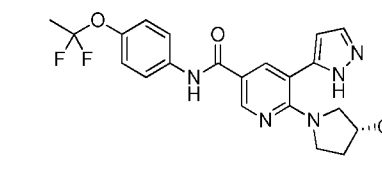
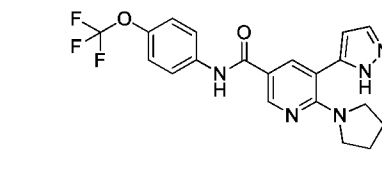
Y₃ is selected from hydrogen, fluoro, chloro, methyl, difluoromethyl and trifluoromethyl; or the pharmaceutically acceptable salts thereof.

4. The compound of claim 3, or a pharmaceutically acceptable salt thereof, selected from:

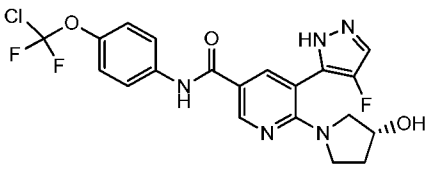
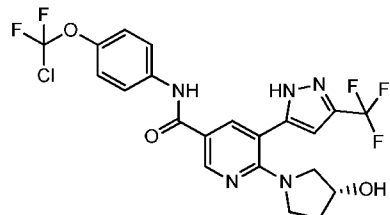
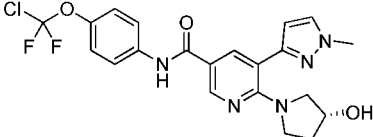
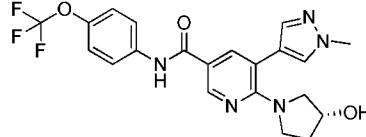
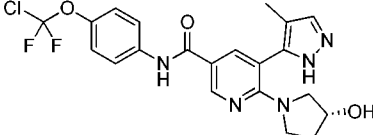
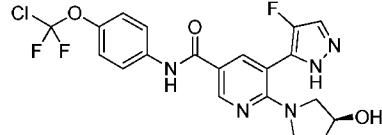


5. The compound of claim 3, or a pharmaceutically acceptable salt thereof, selected from:

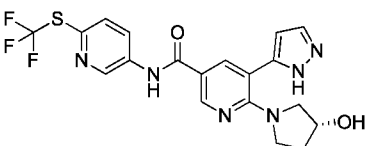


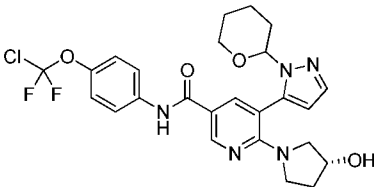
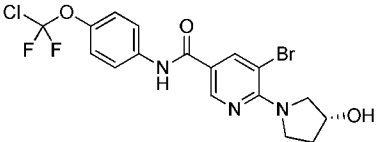
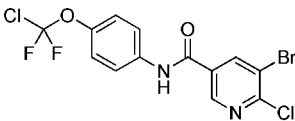
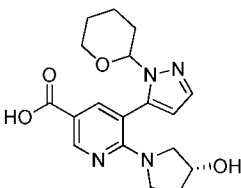
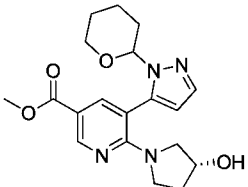
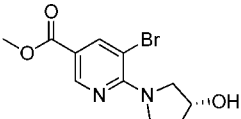
6. The compound of claim 2, or a pharmaceutically acceptable salt thereof, selected from:

7. The compound of claim 1, or a pharmaceutically acceptable salt thereof, that is:

	
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8. A compound selected from:

9. The compound of claim 1 that is (R)-N-(4-(chlorodifluoromethoxy)phenyl)-6-(3-hydroxypyrrolidin-1-yl)-5-(1H-pyrazol-5-yl)nicotinamide or a pharmaceutically acceptable salt thereof.

10. A pharmaceutical composition comprising an amorphous dispersion of (R)-N-(4-(chlorodifluoromethoxy)phenyl)-6-(3-hydroxypyrrolidin-1-yl)-5-(1H-pyrazol-5-yl)nicotinamide and 1 to 2 excipients selected from PVP VA64 and Pharmacoat 603.

11. The composition of claim 10, wherein the percentage of Pharmacoat 603 is in the range of 30% to 45%, the percentage of PVP VA64 is in the range of 30% to 45% and the percentage of (R)-N-(4-(chlorodifluoromethoxy)phenyl)-6-(3-hydroxypyrrolidin-1-yl)-5-(1H-pyrazol-5-yl)nicotinamide is in the range of 20% to 30%.

12. The composition of claim 11, wherein the percentage of Pharmacoat 603 is 37.5%, the percentage of PVP VA64 is 37.5% and the percentage of (R)-N-(4-(chlorodifluoromethoxy)phenyl)-6-(3-hydroxypyrrolidin-1-yl)-5-(1H-pyrazol-5-yl)nicotinamide is 25%.

13. A compound of formula (I), or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 9 for use in the treatment of cancer.

14. Use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 9 in the manufacture of a medicament for the treatment of a leukemia selected from chronic myeloid leukemia and acute lymphoblastic leukemia.

15. Use according to claim 14, wherein the medicament is formulated to be administered together with an additional compound selected from imatinib, nilotinib, dasatinib, bosutinib, ponatinib and bafetinib.

16. Use according to claim 15 wherein the medicament is formulated to be administered in sequential or simultaneous administration with said additional compound wherein said additional compound is nilotinib.

17. Use according to any one of claims 14 to 16 wherein the compound of formula (I) is (R)-N-(4-(chlorodifluoromethoxy)phenyl)-6-(3-hydroxypyrrolidin-1-yl)-5-(1H-pyrazol-5-yl)nicotinamide or a pharmaceutically acceptable salt thereof.