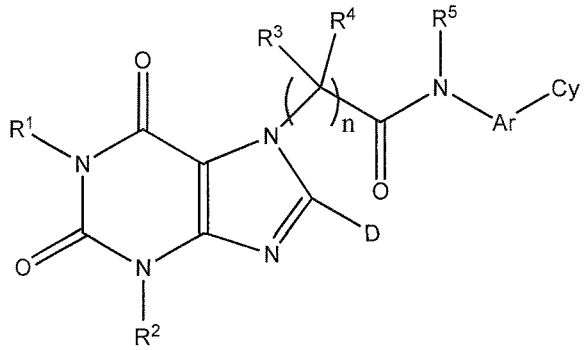
play a role in severe fibrotic diseases, such as pulmonary fibrosis, liver fibrosis, skin fibrosis and renal fibrosis.

[0008] Dysregulation of Wnt/β-catenin signalling contributes also to the development of diabetic retinopathy by inducing retinal inflammation, vascular leakage, and neovascularization. The binding of Wnt proteins to plasma membrane receptors on mesenchymal cells induces the differentiation of these cells into the osteoblast lineage and thereby supports bone formation. Wnts are also key signalling proteins in joint remodeling processes. Active Wnt signalling contributes to osteophyte formation and might have an essential role in the anabolic pattern of joint remodeling that is observed in ankylosing spondylitis and osteoarthritis. In contrast, blockade of Wnt signalling facilitates bone erosion and contributes to catabolic joint remodeling, a process that is observed in rheumatoid arthritis.

[0009] There is therefore a need for compounds that modulate or inhibit Wnt activity so as to treat diseases associated with Wnt activity.

Summary ~~of Invention~~

[00010] ~~In a first aspect of the invention t~~There is provided a compound of structure (I) for use in, or when used in, modulating Wnt activity,



(I)

wherein:

R^1, R^2, R^3, R^4 and R^5 are each, independently, H or an alkyl group;

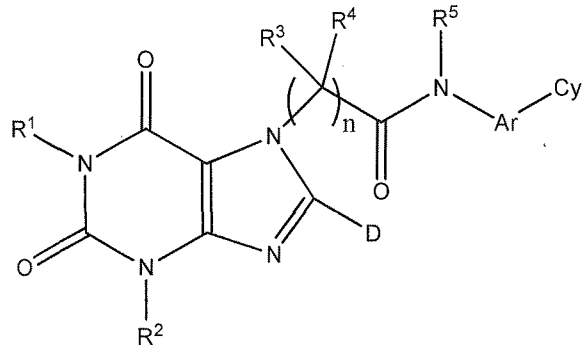
D is selected from the group consisting of H, halogen, alkyl, cycloalkyl, aryl, and dialkylamino, each (other than H and halogen) being optionally substituted;

Ar is an aryl or heteroaryl group, each being optionally substituted;

Cy is an aryl, heteroaryl or a saturated ring containing at least one heteroatom, each being optionally substituted; and

n is an integer from 1 to 3.

[00010a] In an aspect, there is provided a compound having structure (I)



(I)

wherein:

R^1, R^2, R^3, R^4 and R^5 are each, independently, H or an alkyl group;

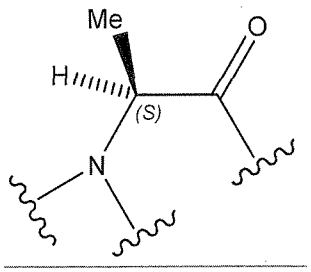
D is selected from the group consisting of H, halogen, alkyl, cycloalkyl, aryl, and dialkylamino, each (other than H and halogen) being optionally substituted;

Ar is a 6-membered heteroaryl ring having 1 or 2 nitrogen atoms having no substituents other than Cy and the amide nitrogen atom, these being in a 1,4-relationship on said ring; and

Cy is an aryl, heteroaryl or a saturated ring containing at least one heteroatom, each being optionally substituted; and

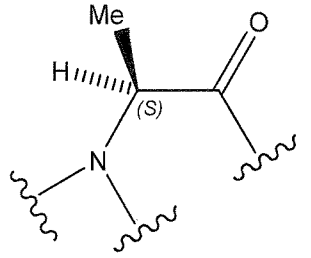
n is an integer from 1 to 3

wherein, if n=1 and one of R^3 and R^4 is methyl and the other is H, the stereochemistry of the compound is as shown in partial structure (II):



(II).

[00011] In some embodiments, if n=1 and one of R^3 and R^4 is methyl and the other is H, the stereochemistry of the compound is as shown in partial structure (II)



(II).

In some particular embodiments, n=1 and one of R^3 and R^4 is methyl and the other is H and the stereochemistry of the compound is as shown in partial structure (II).

[00012] Any one or more of the following groups a) to e), and/or any one or more individual compounds within any one or more of said groups, optionally all thereof, may be excluded from the scope of the first aspect. Notwithstanding any such exclusions, the compounds referred to hereinafter as compound 5 and compound 86 may be explicitly included within the scope of the first aspect.

a) Any one or more of the compounds described in WO2010/036821 A1;

b) Any one or more compounds of the formula shown below,

[00023] The compound may not modulate, or may not inhibit, TRPA1. It may not inhibit TRPA1 at an IC_{50} of < 5 micromolar or at an IC_{50} of < 10 micromolar.

[00024] The ~~first aspect~~above embodiment also includes all enantiomers and diastereomers of the compound, as well as salts of the compounds. Suitable salts include pharmaceutically and/or veterinarially acceptable salts, for example the hydrochloride salts. The free bases of the compounds are also encompassed.

[00025] In ~~a second aspect of the invention~~an embodiment, there is provided use of a compound as defined ~~in the first aspect~~above for modulating, optionally inhibiting, Wnt activity and/or porcupine activity. There is also provided a method of modulating, optionally inhibiting, Wnt activity (e.g. Wnt secretion) and/or porcupine activity comprising exposing cells, or a Wnt protein or a Wnt receptor, to a compound as defined ~~in the first aspect~~above. The cells may be cells that over-express Wnt protein. The method may be an *in vitro* method or it may be an *in vivo* method. Without wishing to be bound by theory, the inventors hypothesise that the compounds defined ~~in the first aspect~~above inhibit the secretion of Wnt proteins. The compounds ~~of the invention~~as defined above are capable of inhibiting porcupine, which is essential and specific for the palmitoylation of Wnt proteins before secretion. Thus in an embodiment there is provided a method of inhibiting, Wnt secretion in a cell, said method comprising exposing said cell to a compound as defined ~~in the first aspect~~above. In another embodiment there there is provided a method of inhibiting Wnt secretion in a cell which over-expresses Wnt protein, said method comprising exposing said cell to a compound as defined ~~in the first aspect~~above.

[00026] In another embodiment, ~~third aspect of the invention~~ there is provided use of a compound as defined ~~in the first aspect~~above for treatment of a disease or condition associated with Wnt pathway activity. The Wnt pathway activity may be excessive activity. This ~~aspect~~ embodiment also includes a method for treating said disease or condition, comprising administering to a subject in need thereof a therapeutically effective amount of the compound. The subject may be a human or may be a non-human, e.g. a non-human mammal or other non-human animal.

[00027] The disease or condition may be selected from the group consisting of cancer, fibrosis, stem cell and diabetic retinopathy. The cancer may be a cancer characterised by abnormal, optionally high, Wnt activity.

[00028] In a ~~fourth aspect of the invention~~another embodiment there is provided use of a compound as defined ~~in the first aspect~~above for the manufacture of a medicament for the treatment of a disease or condition associated with abnormal, optionally high, Wnt pathway activity. The disease or condition may be selected from the group consisting of cancer, fibrosis, stem cell and diabetic retinopathy, rheumatoid arthritis, psoriasis and myocardial infarction. There is also provided a composition or medicament for the treatment of such a disease or condition, said composition or medicament comprising a compound as defined ~~in the first aspect~~above together with one or more pharmaceutically acceptable carriers, diluents or adjuvants.

[00029] The disease or condition may be a cancer, such as cervical, colon, breast, bladder, head and neck, gastric, lung, ovarian, prostate, thyroid, non-small-cell lung, as well as chronic lymphocytic leukemia, mesothelioma, melanoma, pancreatic adenocarcinoma, basal cell carcinoma, osteosarcoma, hepatocellular carcinoma, Wilm's tumour or medulloblastoma. The disease or condition may be a severe fibrotic disease, such as pulmonary fibrosis, liver fibrosis, skin fibrosis or renal fibrosis. It may be a degenerative disease. It may be a metabolic disease such as diabetic retinopathy.

[00029a] In another aspect, there is provided the use of a compound as defined above in the manufacture of a medicament for the treatment of a disease or condition associated with Wnt pathway activity, said disease or condition being selected from the group consisting of cancer, such as cervical, colon, breast, bladder, head and neck, gastric, lung, ovarian, prostate, thyroid, non-small-cell lung, as well as chronic lymphocytic leukemia, mesothelioma, melanoma, pancreatic adenocarcinoma, basal cell carcinoma, osteosarcoma, hepatocellular carcinoma, Wilm's tumor or medulloblastoma, or a fibrotic disease, such as pulmonary fibrosis, liver fibrosis, skin fibrosis or renal fibrosis, or a degenerative disease, or a metabolic disease such as diabetic retinopathy.

[00030] In an embodiment, ~~fifth aspect of the invention~~ there is provided a compound as defined ~~in the first aspect~~above for use in therapy.

[0030a] In another aspect, there is provided the use of a compound as defined above in diagnosis.

[00031] In ~~a sixth~~another aspect, ~~of the invention~~ there is provided a pharmaceutical composition comprising a compound ~~according to the first aspect~~as defined above together with one or more pharmaceutically acceptable carriers, diluents or adjuvants.

[00032] In ~~a seventh~~another aspect, ~~of the invention~~ there is provided an anhydrous form of the free base of 2-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7H-purin-7-yl)-N-(6-phenylpyridazin-3-yl)acetamide. There is also provided a pharmaceutical composition comprising said anhydrous free base, a method of treating or preventing a proliferative disorder comprising administering a therapeutically effective amount of said anhydrous free base to a subject in need thereof and use of said anhydrous free base either in the treatment of a proliferative disorder or in the manufacture of a medicament for the treatment of a proliferative disorder.

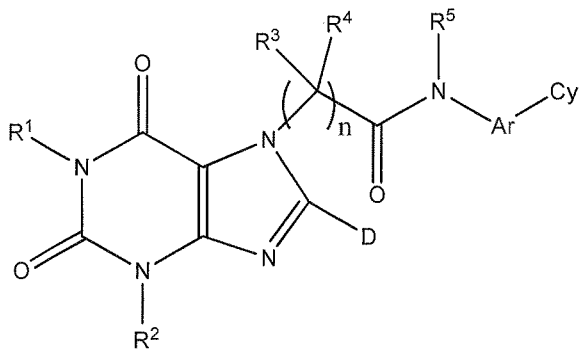
[00032a] In another aspect, there is provided a pharmaceutical composition comprising an anhydrous free base as defined above.

[00032b] In another aspect, there is provided a use of an anhydrous free base as defined above in the manufacture of a medicament for the treatment of a proliferative disorder regulated by the Wnt pathway.

Brief Description of Drawings

CLAIMS

1. A compound ~~for use in modulation of the Wnt pathway, said compound~~ having structure (I)



(I)

wherein:

R^1, R^2, R^3, R^4 and R^5 are each, independently, H or an alkyl group;

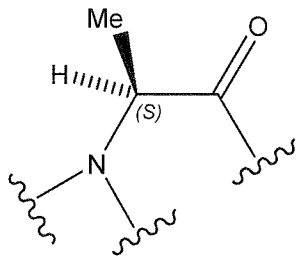
D is selected from the group consisting of H, halogen, alkyl, cycloalkyl, aryl, and dialkylamino, each (other than H and halogen) being optionally substituted;

Ar is ~~an aryl or heteroaryl group, optionally substituted~~ a 6-membered heteroaryl ring having 1 or 2 nitrogen atoms having no substituents other than Cy and the amide nitrogen atom, these being in a 1,4-relationship on said ring; and

Cy is an aryl, heteroaryl or a saturated ring containing at least one heteroatom, each being optionally substituted; and

n is an integer from 1 to 3

wherein, if n=1 and one of R^3 and R^4 is methyl and the other is H, the stereochemistry of the compound is as shown in partial structure (II):



(II).

2. The compound of claim 1 wherein R^1 and R^2 are the same.

3. The compound of claim 1 or claim 2 wherein R^1 and R^2 are both methyl.

4. The compound of claim 1 or claim 2 wherein R^1 and R^2 are both ethyl.

~~5. The compound of any one of claims 1 to 4 wherein if Ar is a 6-membered ring it is 1,4-disubstituted and if it is a 5-membered ring it is 1,3-disubstituted.~~

~~6. The compound of any one of claims 1 to 5 wherein Ar is a disubstituted benzene ring, a disubstituted thiophene ring or a disubstituted nitrogen heterocycle having between 1 and 4 nitrogen atoms.~~

~~7.~~5. The compound of any one of claims 1 to ~~6~~ 4 wherein Cy is a 5 or 6 membered aromatic ring having between 0 and 2 nitrogen atoms, 0 or 1 sulfur atoms and 0 or 1 oxygen atoms.

~~8.~~6. The compound of any one of claims 1 to ~~7~~ 5 wherein Cy is piperazine, substituted on both nitrogen atoms.

~~9.~~7. The compound of any one of claims 1 to ~~8~~ 6 wherein n is 1.

~~10.~~8. The compound of any one of claims 1 to ~~8~~ 7 wherein n is 2 or 3.

~~11.~~9. The compound of any one of claims 1 to ~~10~~ 8 wherein D is H.

~~12.~~10. The compound of any one of claims 1 to ~~11~~ 9 wherein R^1 and R^2 are both methyl, R^3, R^4, R^5 and D are all H and n is 1.

~~13. The compound of claim 12 wherein Ar is 1,4-phenylene and Cy is thiophene-3-yl.~~

~~14.~~11. The compound of any one of claims 1 to ~~8~~10 or 13 in which D is methyl, cyclopropyl, trifluoromethyl, phenyl, dimethylamino, morpholin-N-yl, thiophene-3-yl or bromo.

~~15. The compound of any one of claims 1 to 10, 13 or 14 in which D is not H and Ar is 1,4-phenylene and Cy is thiophene-3-yl.~~

~~16. The compound of claim 10 wherein Ar is 1,4-phenylene and Cy is thiophene-3-yl or thiazole-2-yl.~~

~~17.~~12. The compound of any one of claims 1 to ~~16~~11 wherein R^3 and R^4 are either both H or both methyl.

~~18.~~13. The compound of any one of claims 1 to ~~16~~11 wherein one of R^3 and R^4 is H and the other is methyl or ethyl.

~~19. The compound of any one of claims 1 to 18 wherein R^3 and R^4 are not both H, and Ar is 1,4-phenylene or Cy is phenyl or at least one of Ar and Cy is thiazole-2-yl.~~

~~20.~~14. The compound of any one of claims 1 to ~~19~~13 wherein R^5 is H.

~~21. The compound of any one of claims 1 to 20 wherein Ar is 1,4-phenylene and Cy is thiophene-3-yl or thiazole-2-yl.~~

~~22. The compound of claim 21 wherein Ar is 1,4-phenylene and Cy is thiophene-3-yl.~~

~~23.~~15. The compound of claim 1 in which R^1 and R^2 are both Me, D is H, n is 1 and R^3 and R^4 are both H.

~~24. The compound of claim 23 wherein if Ar is 1,4-phenylene, Cy is not thiophene-3-yl.~~

~~25. The compound of claim 23 wherein either R^1 and R^2 are not both methyl, or D is not H, or n is not 1, or R^3 and R^4 are not both H and Ar is 1,4-phenylene and Cy is thiophene-3-yl or thiazole-2-yl.~~

~~26. The compound of claim 25 wherein Cy is thiophene-3-yl.~~

~~27. The compound of any one of claims 1 to 26 wherein Ar and Cy are not both optionally substituted phenyl rings.~~

~~28. The compound of any one of claims 1 to 27 wherein, if Ar is 1,4-phenylene or 2,5-pyridyl, Cy has no more than 1 ring nitrogen atom.~~

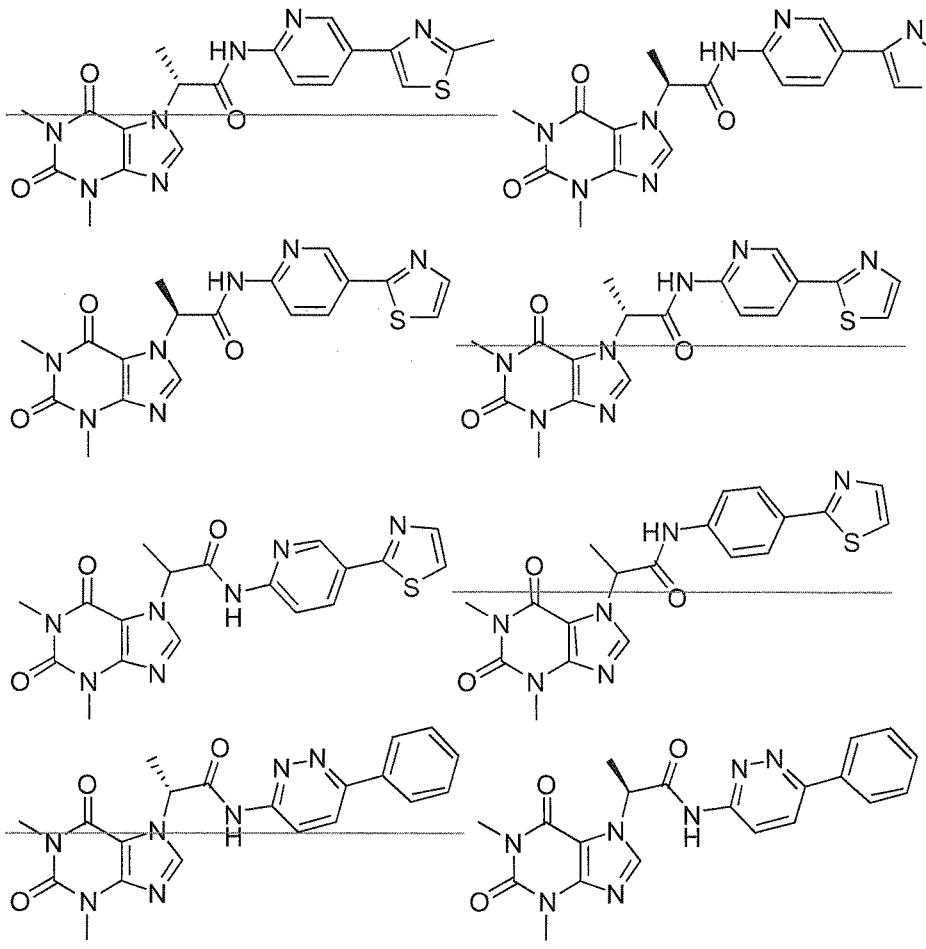
~~29. The compound of any one of claims 1 to 28 wherein, if Ar is a 5-membered ring, it is not oxazolediyl.~~

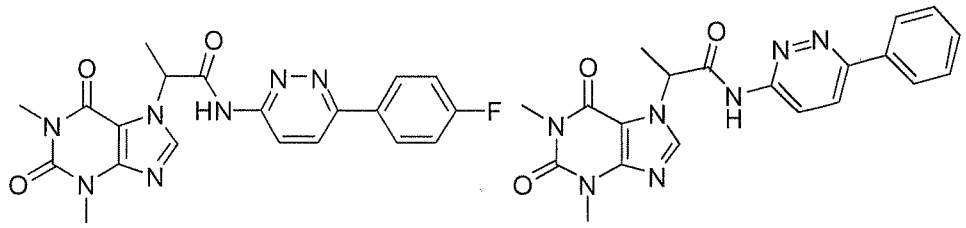
~~30. The compound of claim 29 wherein, if Ar is a 5-membered ring, it is thiophenediyl, optionally thiophene-2,4-diyl.~~

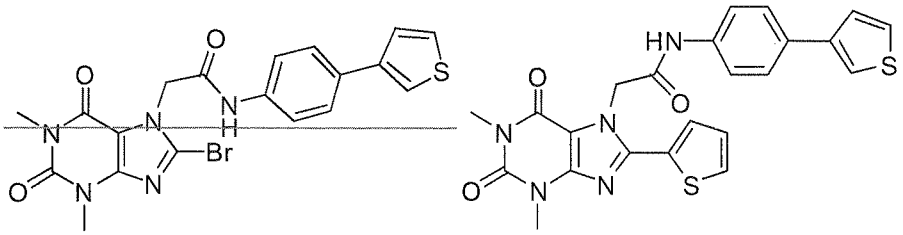
~~31.~~16. The compound of any one of claims 1 to ~~30~~ 15 having IC_{50} against STF3A of less than 10 micromolar, optionally less than 5 micromolar.

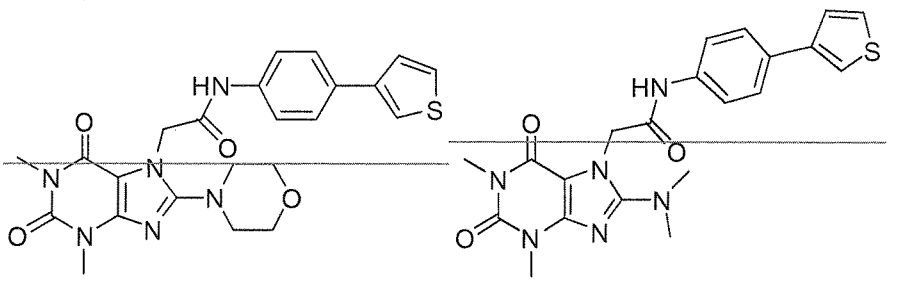
~~32.~~17. The compound of any one of claims 1 to ~~31~~ 16 which does not inhibit TRPA1 at an IC_{50} of 10 micromolar, optionally 5 micromolar.

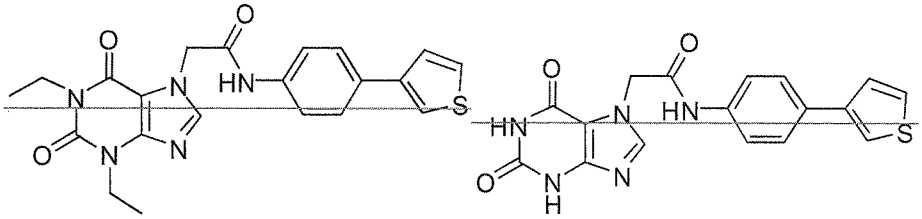
~~33.~~18. The compound of ~~any one of~~ claims ~~1 to 32~~ which is one of the following:

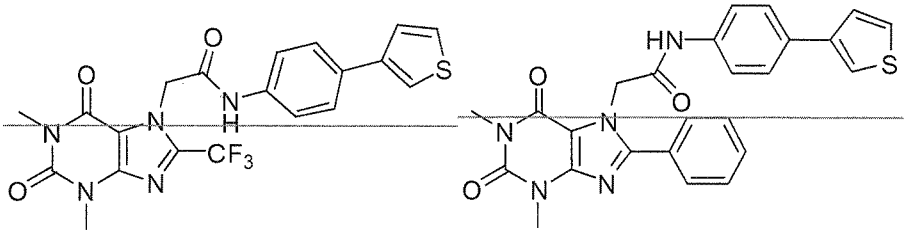


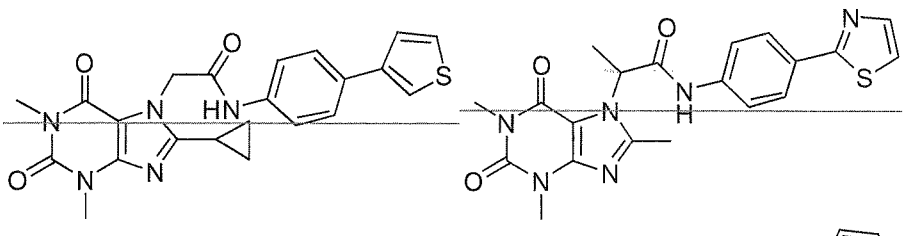


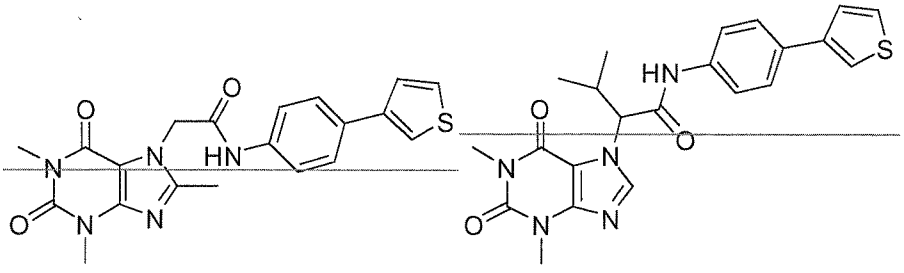


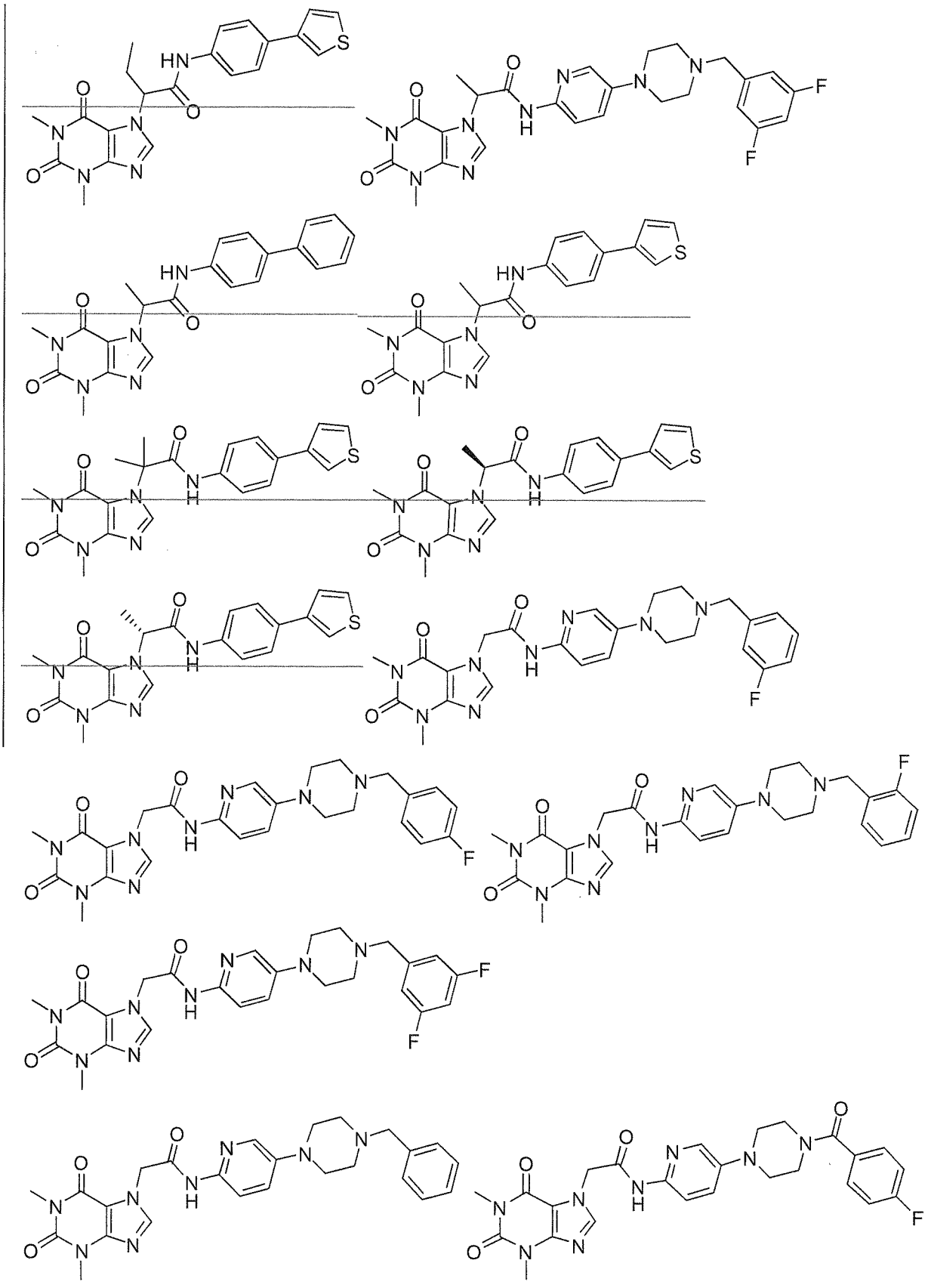


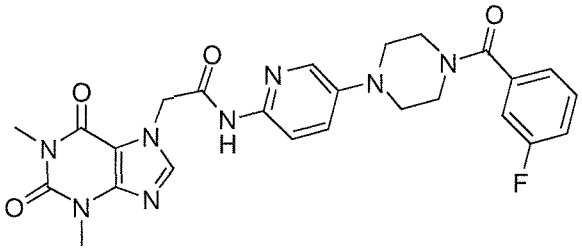


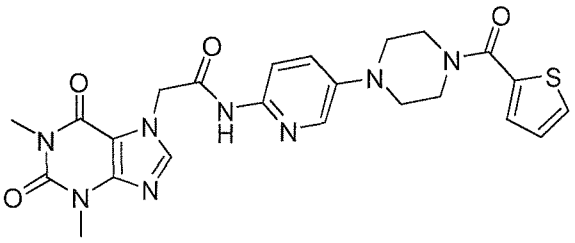


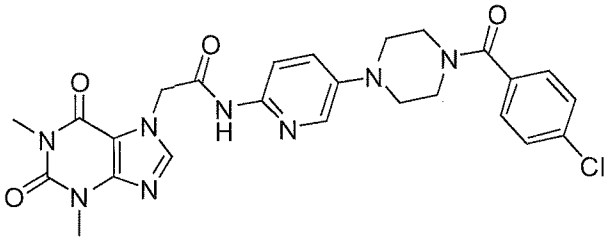


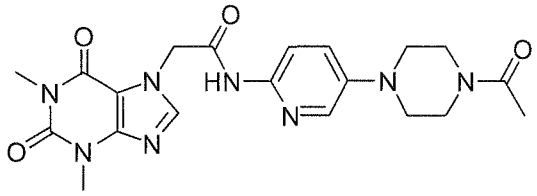


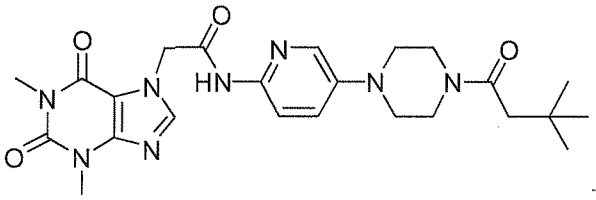


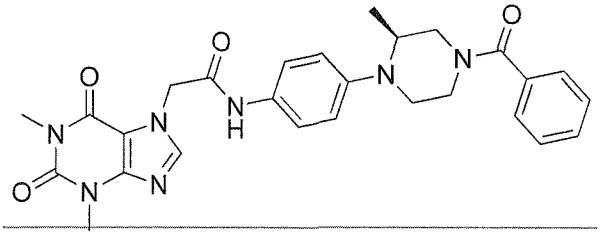


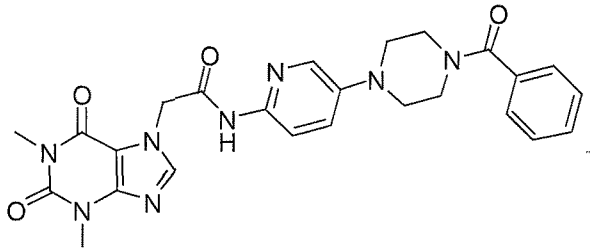


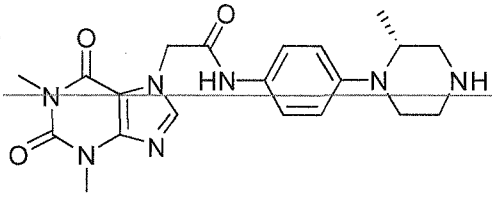


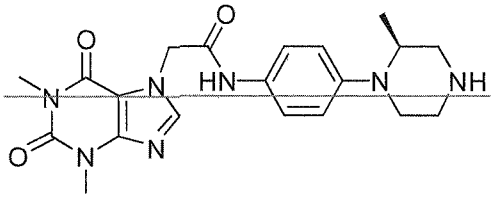


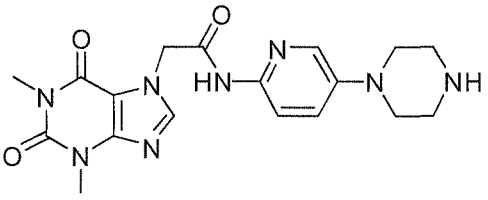


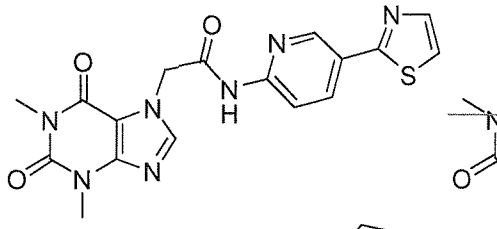


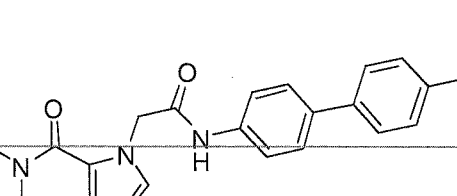


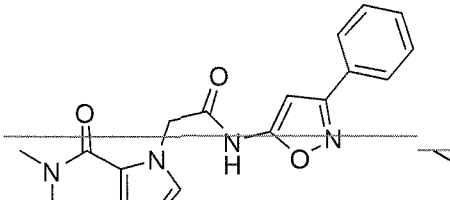




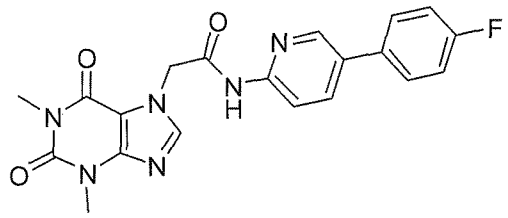


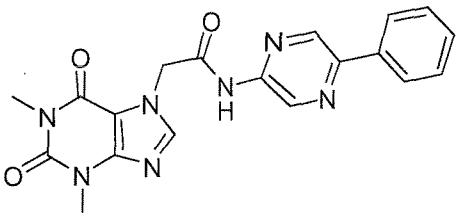


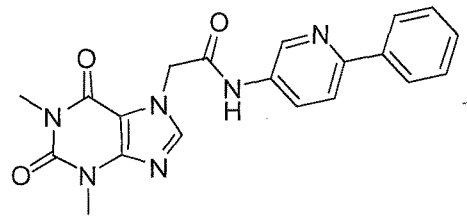


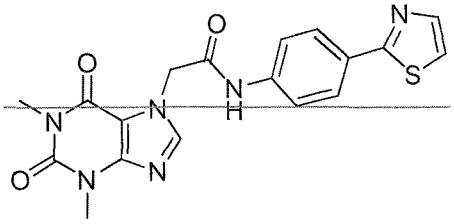


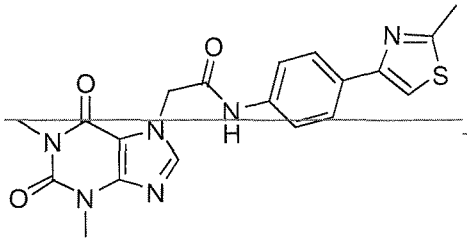


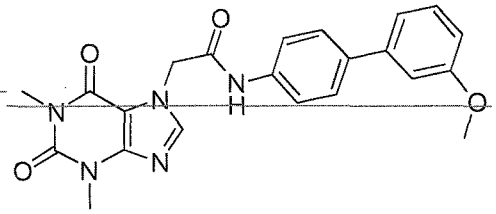


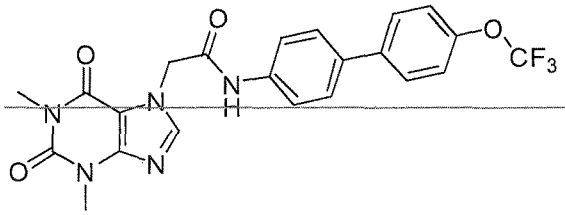


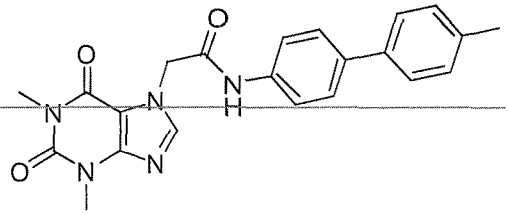


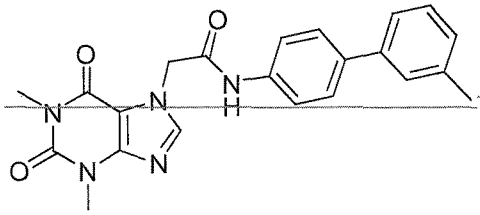


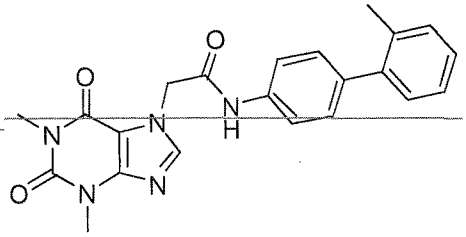


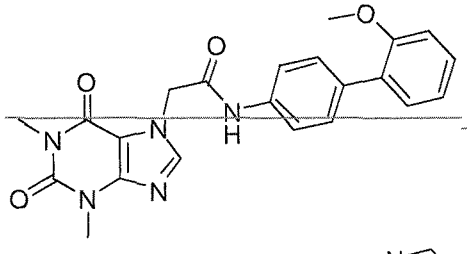


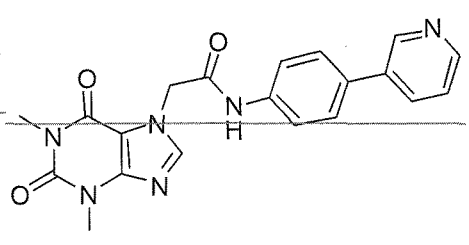


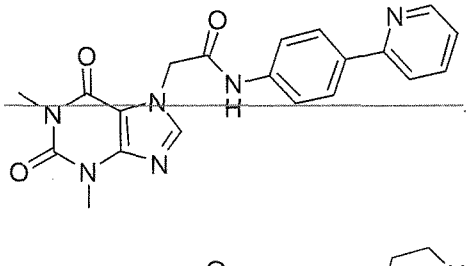


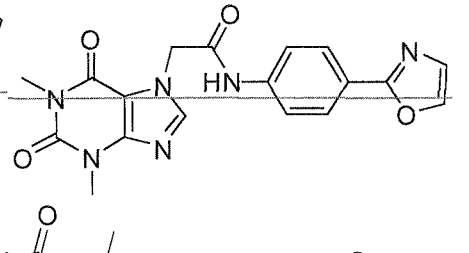


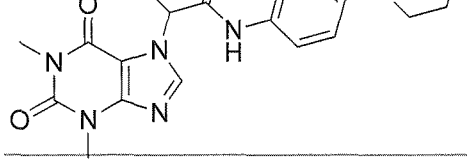


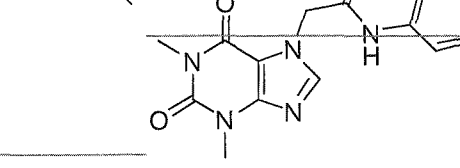


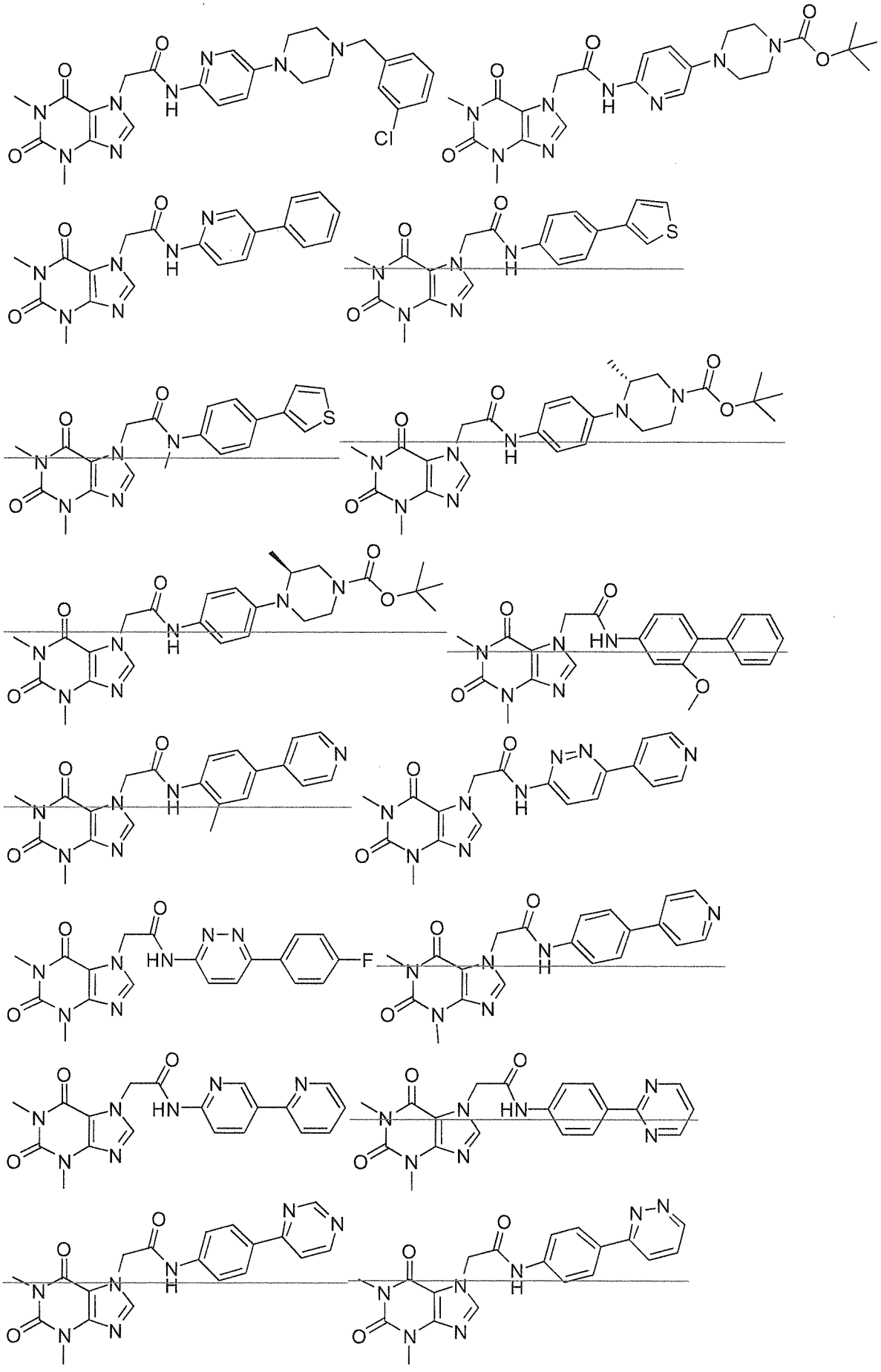


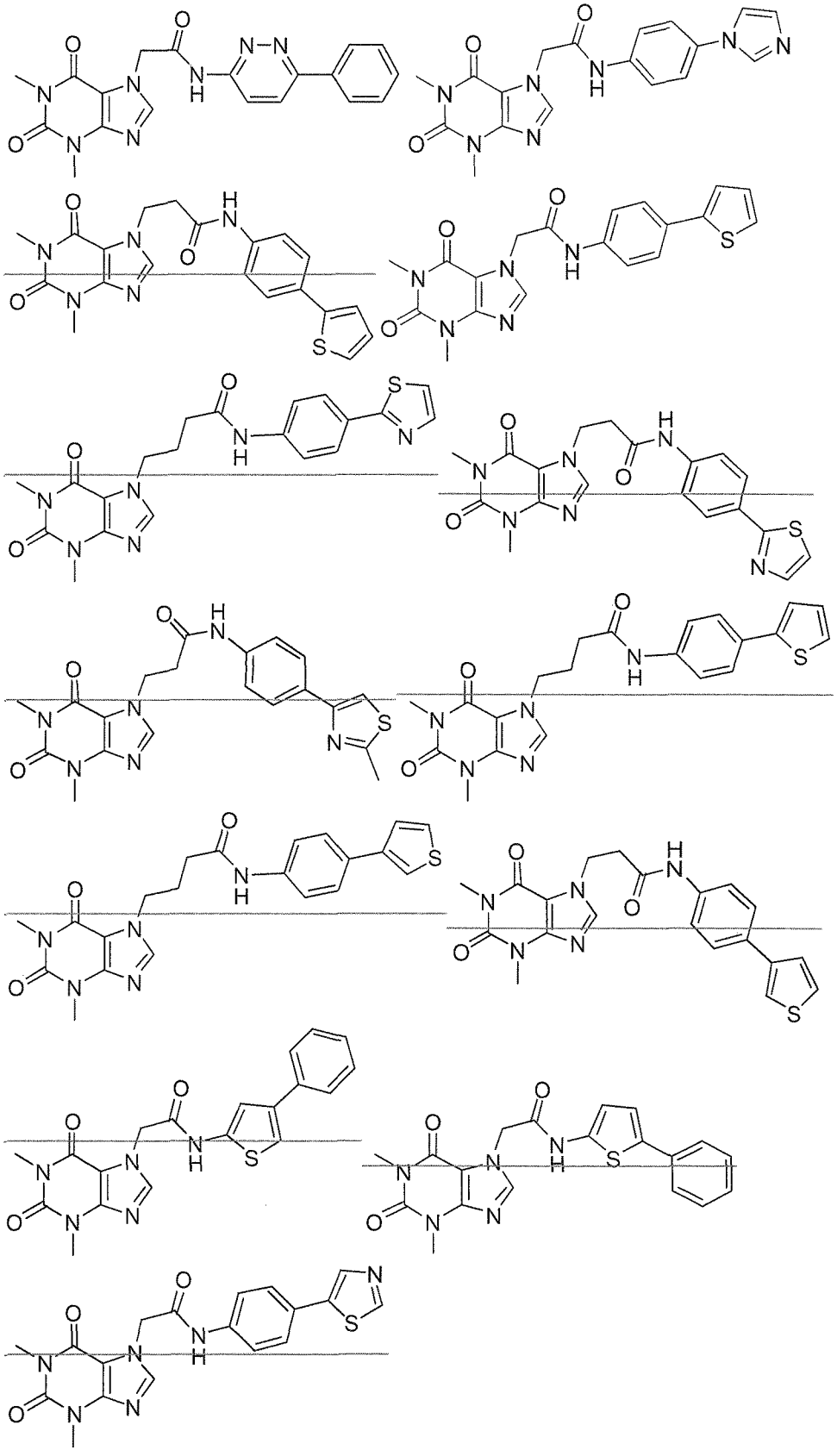












~~34. The compound of any one of claims 1 to 33 which is not any one of the following compounds:~~

2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(4-(pyridazin-3-yl)phenyl)acetamide,

2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(3-methyl biphenyl-4-yl)acetamide,

2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(2'-methoxy-biphenyl-4-yl)acetamide,

2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(2'-methyl biphenyl-4-yl)acetamide,

2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(3-phenyl isoxazol-5-yl)acetamide,

2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(5-(piperazin-1-yl)pyridin-2-yl)acetamide,

(S)-2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(4-(2-methyl piperazin-1-yl)phenyl)acetamide,

(R)-2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(4-(2-methyl piperazin-1-yl)phenyl)acetamide,

(R)-2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(4-(thiophen-3-yl)phenyl)propanamide,

N-(biphenyl-4-yl)-2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-3-methylbutanamide,

2-(2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(4-(thiophen-3-yl)phenyl) acetamide,

(R)-2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(4-(thiophen-3-yl)phenyl)propanamide and

~~(R)-2-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7H-purin-7-yl)-N-(5-(thiazol-2-yl)pyridin-2-yl)propanamide.~~

~~35. The compound of claim 34 which is not any one of the following compounds:~~

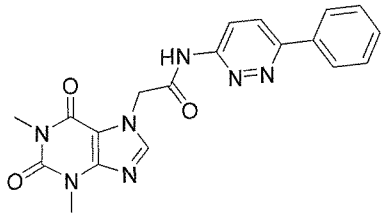
~~2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(4-(pyrimidin-2-yl)phenyl)acetamide,~~

~~2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(6-(pyridin-4-yl)pyridazin-3-yl)acetamide,~~

~~2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(5-(4-(2-fluorobenzyl)piperazin-1-yl)pyridin-2-yl)acetamide and~~

~~(R)-2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(5-(2-methyl thiazol-4-yl)pyridin-2-yl)propanamide.~~

~~36.~~19. The compound of claim 1 which is:



~~37.~~20. The compound of any one of claims 1 to ~~36~~19 for use in the treatment of a disease or condition associated with Wnt pathway activity.

~~38.~~21. The compound of claim ~~37~~20 wherein the disease or condition is a cancer, such as cervical, colon, breast, bladder, head and neck, gastric, lung, ovarian, prostate, thyroid, non-small-cell lung, as well as chronic lymphocytic leukemia, mesothelioma, melanoma, pancreatic adenocarcinoma, basal cell carcinoma, osteosarcoma, hepatocellular carcinoma, Wilm's tumor or medulloblastoma, or a fibrotic disease, such as pulmonary fibrosis, liver

fibrosis, skin fibrosis or renal fibrosis, or a degenerative disease, or a metabolic disease such as diabetic retinopathy.

~~39. The compound of any one of claims 1 to 36 for use in the modulation of Wnt secretion and/or porcupine activity comprising exposing cells to the compound as described above.~~

~~40.~~ Use of a compound according to any one of claims 1 to ~~36~~ 19 in the manufacture of a medicament for the treatment of a disease or condition associated with Wnt pathway activity.

~~41.~~ 22. ~~The use of claim 40 wherein the~~ said disease or condition being~~is~~ selected from the group consisting of cancer, such as cervical, colon, breast, bladder, head and neck, gastric, lung, ovarian, prostate, thyroid, non-small-cell lung, as well as chronic lymphocytic leukemia, mesothelioma, melanoma, pancreatic adenocarcinoma, basal cell carcinoma, osteosarcoma, hepatocellular carcinoma, Wilm's tumor or medulloblastoma, or a fibrotic disease, such as pulmonary fibrosis, liver fibrosis, skin fibrosis or renal fibrosis, or a degenerative disease, or a metabolic disease such as diabetic retinopathy.

42.23. The use of claim 41-22 wherein the disease or condition is selected from the group consisting of cancer, fibrosis, stem cell and diabetic retinopathy, rheumatoid arthritis, psoriasis and myocardial infarction.

43.24. The use of claim 2241 or claim 42-23 wherein the cancer is characterised by high Wnt activity or a fibrotic disease or a degenerative disease.

44.25. Use of a compound according to any one of claims 1 to 36-19 in diagnosis.

45.26. A pharmaceutical composition comprising a compound according to any one of claims 1 to 36-19 together with one or more pharmaceutically acceptable carriers, diluents or adjuvants.

46.27. An anhydrous form of the free base of 2-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7H-purin-7-yl)-N-(6-phenylpyridazin-3-yl)acetamide.

47.28. The anhydrous form of claim 46-27 which is a non-hydrated single polymorph.

48.29. The anhydrous form of claim 46-27 or claim 47-28 which is crystalline.

49.30. The anhydrous form of claim 48-29 which shows on X-ray diffraction a peak on the 2theta scale at 22.2°±0.5°.

50.31. The anhydrous form of claim 48-29 or claim 49-30 which shows on X-ray diffraction peaks on the 2theta scale at 5.5°±0.5° and 14.2°±0.5°.

51.32. The anhydrous form of any one of claims 48-29 to 50-31 which shows on X-ray diffraction at least four peaks on the 2theta scale selected from the group consisting of 5.5°±0.5° and 12.5°±0.5°, 14.2°±0.5°, 16.7°±0.5°, 17.7°±0.5°, 18.8°±0.5°, 22.4°±0.5°, 24.2°±0.5° and 31.7°±0.5°.

52.33. The anhydrous form of any one of claims 48-29 to 51-32 which shows on X-ray diffraction peaks on the 2theta scale of and 5.5°±0.5° and 12.5°±0.5°, 14.2°±0.5°, 16.7°±0.5°, 17.7°±0.5°, 18.0°±0.5°, 18.8°±0.5°, 19.6°±0.5°, 20.6°±0.5°, 22.4°±0.5°, 24.2°±0.5°, 24.4°±0.5°, 25.0°±0.5°, 27.0°±0.5°, 27.6°±0.5°, 29.8°±0.5°, 31.7°±0.5° and 32.2°±0.5°.

~~53.~~34. A pharmaceutical composition comprising an anhydrous free base according to any one of claims ~~46~~ 27 to ~~52~~33.

~~54.~~35. Use of an anhydrous free base according to any one of claims ~~46~~ 27 to ~~52~~ 33 in the manufacture of a medicament for the treatment of a proliferative disorder regulated by the Wnt pathway.

~~55.~~36. Use according to claim ~~54~~35 wherein the proliferative disorder is cancer.