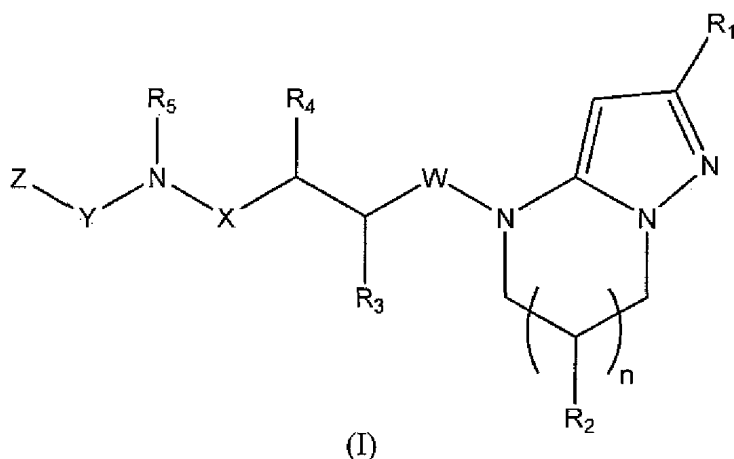


sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like.

[0057] Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like.

Summary

[0058] In the disclosure, there is provided a compound of formula (I),



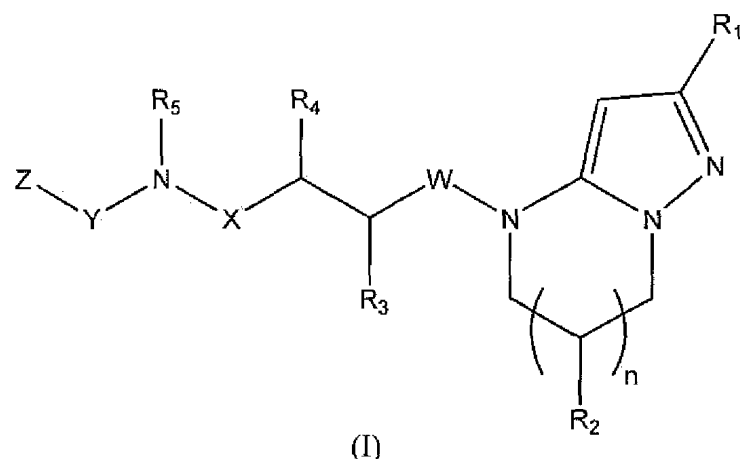
or a pharmaceutically acceptable salt, solvate or polymorph thereof, including all tautomers and stereoisomers thereof wherein:

[0059] R_1 represents H; optionally substituted alkyl (wherein optional substituents include one or more substituents each independently selected from C_{1-6} alkoxy, NH_2 , $-NHC_{1-3}$ alkyl and $-N(C_{1-3}alkyl)_2$; $-C(O)Oalkyl$; haloalkyl; haloalkoxy; or $-alkylaryl$;

[0060] each R_2 independently represents H; optionally substituted alkyl (wherein optional substituents include one or more substituents each independently selected from C_{1-6} alkoxy, NH_2 , $-NHC_{1-3}$ alkyl and $-N(C_{1-3}alkyl)_2$; $-alkylaryl$; optionally substituted carbocyclyl (wherein optional substituents include one or more substituents each independently selected from $C_{1-6}alkyl$, $C_{1-6}alkoxy$, $C_{1-6}haloalkyl$, $C_{1-6}haloalkoxy$ and halo); optionally substituted heterocyclyl (wherein optional substituents include one or more substituents each independently selected from $C_{1-6}alkyl$, $C_{1-6}alkoxy$, $-C(O)OC_{1-6}alkyl$, $-C(O)C_{1-6}alkyl$ and $-C(O)NHC_{1-6}alkyl$); $-NHalkyl$; $-N(alkyl)_2$; amino; hydroxyl; alkoxy or halo;

[0061] n represents 0, 1 or 2;

[0067a] In an aspect, there is provided a compound of formula (I),



or a pharmaceutically acceptable salt, solvate or polymorph thereof, including all tautomers and stereoisomers thereof wherein:

[0067b] R_1 represents H; alkyl, optionally substituted with one or more substituents each independently selected from C_{1-6} alkoxy, NH_2 , $-NHC_{1-3}$ alkyl and $-N(C_{1-3}alkyl)_2$; $-C(O)Oalkyl$; haloalkyl; haloalkoxy; or $-alkylaryl$;

[0067c] each R_2 independently represents H; alkyl, optionally substituted with one or more substituents each independently selected from C_{1-6} alkoxy, NH_2 , $-NHC_{1-3}$ alkyl and $-N(C_{1-3}alkyl)_2$; $-alkylaryl$; carbocyclyl, optionally substituted with one or more substituents each independently selected from C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy and halo; heterocyclyl, optionally substituted with one or more substituents each independently selected from C_{1-6} alkyl, C_{1-6} alkoxy, $-C(O)OC_{1-6}alkyl$, $-C(O)C_{1-6}alkyl$ and $-C(O)NHC_{1-6}alkyl$; $-NHalkyl$; $-N(alkyl)_2$; amino; hydroxyl; alkoxy; or halo;

[0067d] n represents 0, 1 or 2;

[0067e] R_3 represents H or alkyl;

[0067f] R_4 represents H or alkyl;

[0067g] R_5 represents H or alkyl;

[0067h] W and X each independently represent $C=O$; $C=S$; or CH_2 ;

[0067i] Y represents monocyclic aryl or 6-membered monocyclic heteroaryl; said aryl or heteroaryl being optionally substituted by one or more groups each independently selected from alkyl, alkenyl, alkynyl, haloalkyl, -alkoxy, cycloalkyl, alkenyloxy-, alkynyloxy-, alkoxyalkyl-, nitro, halogen, cyano, hydroxyl, oxo, -C(O)-alkyl, C(O)OH, -C(O)Oalkyl, -OC(O)alkyl, -NH₂, -NHalkyl, -N(alkyl)₂, -C(O)NH₂, -C(O)NH(alkyl), -NHC(O)alkyl, -C(NH)NH₂, thioalkyl, -SO₂alkyl, -SOalkyl, -SO₂cycloalkyl and -SOcycloalkyl; and

[0067j] Z represents monocyclic aryl or monocyclic heteroaryl; said aryl or heteroaryl being optionally substituted by one or more groups each independently selected from alkyl, alkenyl, alkynyl, haloalkyl, -alkoxy, cycloalkyl, alkenyloxy-, alkynyloxy-, alkoxyalkyl-, nitro, halogen, cyano, hydroxyl, oxo, -C(O)-alkyl, C(O)OH, -C(O)Oalkyl, -OC(O)alkyl, -NH₂, -NHalkyl, -N(alkyl)₂, -C(O)NH₂, -C(O)NH(alkyl), -NHC(O)alkyl, -C(NH)NH₂, thioalkyl, -SO₂alkyl, -SOalkyl, -SO₂cycloalkyl and -SOcycloalkyl.

[0076] Y represents aryl; heteroaryl; carbocyclyl which is optionally substituted by one or more substituents each independently selected from C₁₋₆alkyl, C₁₋₆alkoxy, C₁₋₆haloalkyl, C₁₋₆haloalkoxy and halo; or heterocyclyl which is optionally substituted by one or more substituents each independently selected from C₁₋₆alkyl, C₁₋₆alkoxy, -C(O)OC₁₋₆alkyl, -C(O)C₁₋₆alkyl and -C(O)NHC₁₋₆alkyl; and

[0077] Z represents alkyl which is optionally substituted by one or more substituents each independently selected from C₁₋₆alkoxy, NH₂, -NHC₁₋₃alkyl and -N(C₁₋₃alkyl)₂; aryl; heteroaryl; -alkylaryl; -alkylheteroaryl; carbocyclyl which is optionally substituted by one or more substituents each independently selected from C₁₋₆alkyl, C₁₋₆alkoxy, C₁₋₆haloalkyl, C₁₋₆haloalkoxy and halo; heterocyclyl which is optionally substituted by one or more substituents each independently selected from C₁₋₆alkyl, C₁₋₆alkoxy, -C(O)OC₁₋₆alkyl, -C(O)C₁₋₆alkyl and -C(O)NHC₁₋₆alkyl; -alkylcarbocyclyl wherein carbocyclyl is optionally substituted by one or more substituents each independently selected from C₁₋₆alkyl, C₁₋₆alkoxy, C₁₋₆haloalkoxy and halo; -alkylheterocyclyl wherein heterocyclyl is optionally substituted by one or more substituents each independently selected from C₁₋₆alkyl, -C(O)OC₁₋₆alkyl, -C(O)C₁₋₆alkyl and -C(O)NHC₁₋₆alkyl; -arylcarbocyclyl wherein carbocyclyl is optionally substituted by one or more substituents each independently selected from C₁₋₆alkyl, C₁₋₆alkoxy, C₁₋₆haloalkoxy and halo; or -arylheterocyclyl wherein heterocyclyl is optionally substituted by one or more substituents each independently selected from C₁₋₆alkyl, -C(O)OC₁₋₆alkyl, -C(O)C₁₋₆alkyl and -C(O)NHC₁₋₆alkyl.

[0077a] In another aspect, there is provided a compound as defined above for use as a medicament.

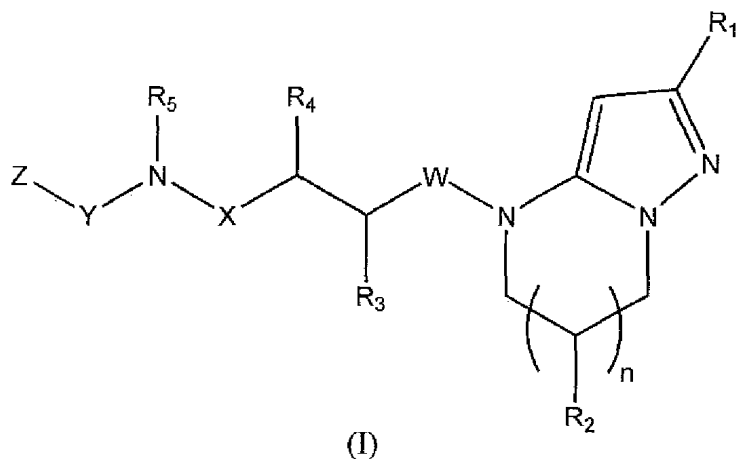
[0077b] In another aspect, there is provided a pharmaceutical composition comprising a compound as defined above in combination with one or more therapeutically acceptable adjuvants, diluters or carriers.

[0077c] In another aspect, there is provided the compound as defined above for use in modulation of the WNT pathway.

[0077d] In the disclosure, there is provided a method of modulating WNT activity comprising exposing a WNT protein or a WNT receptor to a compound as defined above.

CLAIMS

1. A compound of formula (I),



or a pharmaceutically acceptable salt, solvate or polymorph thereof, including all tautomers and stereoisomers thereof wherein:

R_1 represents H; alkyl, optionally substituted with one or more substituents each independently selected from C_{1-6} alkoxy, NH_2 , $-NHC_{1-3}$ alkyl and $-N(C_{1-3}alkyl)_2$; $-C(O)Oalkyl$; haloalkyl; haloalkoxy; or $-alkylaryl$;

each R_2 independently represents H; alkyl, optionally substituted with one or more substituents each independently selected from C_{1-6} alkoxy, NH_2 , $-NHC_{1-3}$ alkyl and $-N(C_{1-3}alkyl)_2$; $-alkylaryl$; carbocyclyl, optionally substituted with one or more substituents each independently selected from C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy and halo; heterocyclyl, optionally substituted with one or more substituents each independently selected from C_{1-6} alkyl, C_{1-6} alkoxy, $-C(O)OC_{1-6}alkyl$, $-C(O)C_{1-6}alkyl$ and $-C(O)NHC_{1-6}alkyl$; $-NHalkyl$; $-N(alkyl)_2$; amino; hydroxyl; alkoxy; or halo;

n represents 0, 1 or 2;

R_3 represents H or alkyl;

R_4 represents H or alkyl;

W and X each independently represent C=O; C=S; or CH₂;

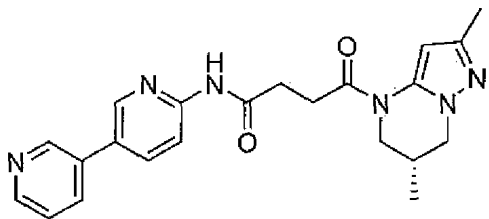
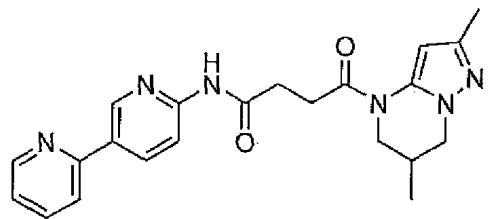
Y represents monocyclic aryl or 6-membered monocyclic heteroaryl; said aryl or heteroaryl being optionally substituted by one or more groups each independently selected from alkyl, alkenyl, alkynyl, haloalkyl, -alkoxy, cycloalkyl, alkenyloxy-, alkynyloxy-, alkoxyalkyl-, nitro, halogen, cyano, hydroxyl, oxo, -C(O)-alkyl, C(O)OH, -C(O)Oalkyl, -OC(O)alkyl, -NH₂, -NHalkyl, -N(alkyl)₂, -C(O)NH₂, -C(O)NH(alkyl), -NHC(O)alkyl, -C(NH)NH₂, thioalkyl, -SO₂alkyl, -SOalkyl, -SO₂cycloalkyl and -SOcycloalkyl; and

Z represents monocyclic aryl or monocyclic heteroaryl; said aryl or heteroaryl being optionally substituted by one or more groups each independently selected from alkyl, alkenyl, alkynyl, haloalkyl, -alkoxy, cycloalkyl, alkenyloxy-, alkynyloxy-, alkoxyalkyl-, nitro, halogen, cyano, hydroxyl, oxo, -C(O)-alkyl, C(O)OH, -C(O)Oalkyl, -OC(O)alkyl, -NH₂, -NHalkyl, -N(alkyl)₂, -C(O)NH₂, -C(O)NH(alkyl), -NHC(O)alkyl, -C(NH)NH₂, thioalkyl, -SO₂alkyl, -SOalkyl, -SO₂cycloalkyl and -SOcycloalkyl.

2. A compound according to claim 1 wherein R₁ represents H, methyl, ethyl, -C(O)OMe, CF₃ or OMe.
3. A compound according to claim 1 or claim 2 wherein R₁ represents methyl.
4. A compound according to any one of claims 1 to 3 wherein each R₂ independently represents H or alkyl.
5. A compound according to any one of claims 1 to 4 wherein each R₂ represents H.
6. A compound according to any one of claims 1 to 5 wherein n represents 1.
7. A compound according to any one of claims 1 to 6 wherein R₃ represents H.
8. A compound according to any one of claims 1 to 7 wherein R₄ represents H.
9. A compound according to any one of claims 1 to 8 wherein R₅ represents H.
10. A compound according to any one of claims 1 to 9 wherein W and X each represent C=O.
11. A compound according to any one of claims 1 to 10 wherein Y represents monocyclic heteroaryl comprising one, two or three ring heteroatoms including one or two nitrogen atoms; said heteroaryl being optionally substituted by one or more groups each independently selected from alkyl, alkenyl, alkynyl, haloalkyl, -alkoxy, cycloalkyl, alkenyloxy-, alkynyloxy-, alkoxyalkyl-, nitro, halogen, cyano, hydroxyl, oxo, -C(O)-alkyl, C(O)OH, -C(O)Oalkyl, -OC(O)alkyl, -NH₂, -NHalkyl, -N(alkyl)₂, -C(O)NH₂, -C(O)NH(alkyl), -NHC(O)alkyl, -C(NH)NH₂, thioalkyl, -SO₂alkyl, -SOalkyl, -SO₂cycloalkyl and -SOcycloalkyl.
12. A compound according to any one of claims 1 to 10 wherein Y represents phenyl, optionally substituted by one or more groups each independently selected from alkyl, alkenyl, alkynyl, haloalkyl, -alkoxy, cycloalkyl, alkenyloxy-, alkynyloxy-, alkoxyalkyl-, nitro, halogen, cyano, hydroxyl, oxo, -C(O)-alkyl, C(O)OH, -C(O)Oalkyl, -OC(O)alkyl, -NH₂, -NHalkyl, -N(alkyl)₂, -C(O)NH₂, -C(O)NH(alkyl), -NHC(O)alkyl, -C(NH)NH₂, thioalkyl, -SO₂alkyl, -SOalkyl, -SO₂cycloalkyl and -SOcycloalkyl.

13. A compound according to any one of claims 1 to 12 wherein Y is substituted by one or more substituents each independently selected from C₁₋₆ alkyl, C₁₋₆alkoxy, halo and C₁₋₆haloalkyl.
14. A compound according to any one of claims 1 to 13 wherein Y is monosubstituted.
15. A compound according to any one of claims 1 to 12 wherein Y is unsubstituted.
16. A compound according to claim 1, which is one of the following compounds:

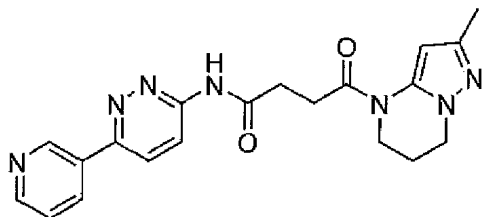
Cpd ID	Structure	IUPAC Name
14		4-(2-methyl-6,7-dihydropyrazolo[1,5-a]pyrimidin-4(5H)-yl)-4-oxo-N-(4'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)butanamide
24		4-(2-methyl-6,7-dihydropyrazolo[1,5-a]pyrimidin-4(5H)-yl)-N-(4-(oxazol-5-yl)phenyl)-4-oxobutanamide
25		4-(2-methyl-6,7-dihydropyrazolo[1,5-a]pyrimidin-4(5H)-yl)-N-(4-(oxazol-5-yl)phenyl)-4-oxobutanamide
26		4-(2-methyl-6,7-dihydropyrazolo[1,5-a]pyrimidin-4(5H)-yl)-4-oxo-N-(5-(thiazol-2-yl)pyridin-2-yl)butanamide
27		N-(4-(1H-imidazol-1-yl)phenyl)-4-(2-methyl-6,7-dihydropyrazolo[1,5-a]pyrimidin-4(5H)-yl)-4-oxobutanamide

Cpd ID	Structure	IUPAC Name
170		(R)-N-([3,3'-bipyridin]-6-yl)-4-(2,6-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrimidin-4(5H)-yl)-4-oxobutanamide
171		N-([2,3'-bipyridin]-6'-yl)-4-(2,6-dimethyl-6,7-dihydropyrazolo[1,5-a]pyrimidin-4(5H)-yl)-4-oxobutanamide

or a pharmaceutically acceptable salt, solvate or polymorph thereof, including all tautomers and stereoisomers thereof.

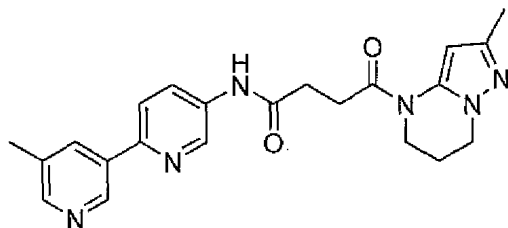
17. A compound according to claim 16, wherein compounds having an IC_{50} against STF3A cells of 10 micromolar or more are excluded.

18. The compound of claim 1 which is 4-(2-methyl-6,7-dihydropyrazolo[1,5-a]pyrimidin-4(5H)-yl)-4-oxo-N-(6-(pyridin-3-yl)pyridazin-3-yl)butanamide:



or a pharmaceutically acceptable salt, solvate or polymorph thereof, including all tautomers and stereoisomers thereof

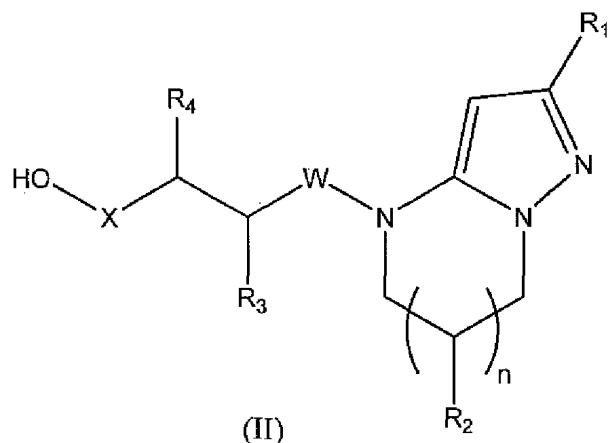
19. The compound of claim 1 which is N-(5'-methyl-2,3'-bipyridin-5-yl)-4-(2-methyl-6,7-dihydropyrazolo[1,5-a]pyrimidin-4(5H)-yl)-4-oxobutanamide:



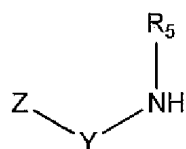
. or a pharmaceutically acceptable salt, solvate or polymorph thereof, including all tautomers and stereoisomers thereof

20. A compound according to any one of claims 1 to 19 for use as a medicament.
21. The compound of any one of claims 1 to 20 having an IC_{50} against HEK293-STF3A cells of less than about 10 micromolar.
22. A pharmaceutical composition comprising a compound according to any one of claims 1 to 21 in combination with one or more therapeutically acceptable adjuvants, diluents or carriers.
23. The compound of any one of claims 1 to 21 for use in modulation of the WNT pathway.
24. The compound of any one of claims 1 to 21 for use in the treatment of a disease or condition associated with WNT pathway activity.

25. Use of a compound according to any one of claims 1 to 21 in the manufacture of a medicament for the treatment of a disease or condition associated with WNT pathway activity.
26. The compound of claim 24 or use of claim 25 wherein the disease or condition is selected from the group consisting of cancers, fibrotic diseases, metabolic diseases, degenerative diseases, rheumatoid arthritis, psoriasis and myocardial infarction.
27. The compound, or use of claim 26 wherein the disease or condition is cervical cancer, colon cancer, breast cancer, bladder cancer, head and neck cancer, gastric cancer, lung cancer, ovarian cancer, prostate cancer, thyroid cancer, non-small-cell lung cancer, chronic lymphocytic leukemia, mesothelioma, melanoma, pancreatic adenocarcinoma, basal cell carcinoma, osteosarcoma, hepatocellular carcinoma, Wilm's tumor, medulloblastoma, pulmonary fibrosis, liver fibrosis, skin fibrosis, renal fibrosis, or diabetic retinopathy.
28. A compound according to any one of claims 1 to 21 for use in diagnosis.
29. A process for preparation of a compound according to any one of claims 1 to 21, wherein W and X each represent C=O, which process comprises reaction of a compound of formula (II)



wherein R_1 , R_2 , R_2 , n , R_3 and R_4 are as defined in any one of claims 1 to 21, with a compound of formula (III)



(III)

or a protected derivative thereof, wherein R_5 , Y and Z are as defined any one of claims 1 to 21.

30. A process for preparation of a compound according to any one of claims 1 to 9, wherein W and X each represent CH_2 , which process comprises conversion of the W and X groups of compounds of formula (I) from $\text{C}=\text{O}$ groups into CH_2 groups.

31. A process for preparation of a compound according to any one of claims 1 to 9, wherein W and X each represent $\text{C}=\text{S}$, which process comprises conversion of the W and X groups of compounds of formula (I) from $\text{C}=\text{O}$ groups into $\text{C}=\text{S}$ groups.