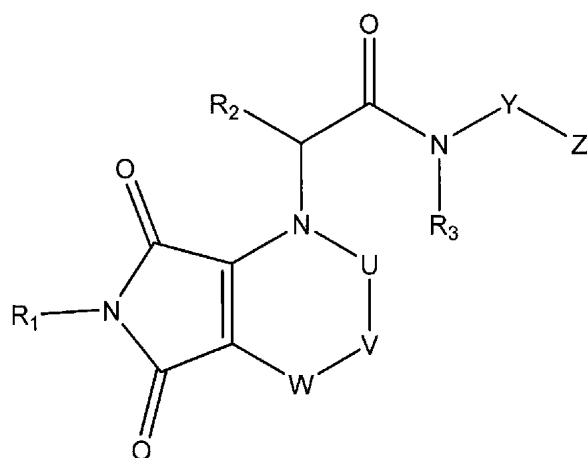


sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like.

[0056] Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like.

Summary

[0057] There is provided a compound of formula (I),



(I)

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

[0058] R_1 represents alkyl which is optionally substituted by one or more substituents each independently selected from C_{1-6} alkoxy; carbocyclyl which is optionally substituted by 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; or $-alkylaryl$;

[0059] R_2 represents H; or alkyl;

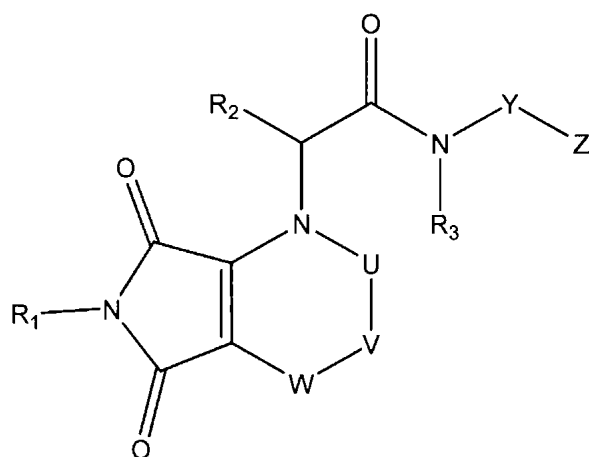
[0060] R_3 represents H; or alkyl;

[0061] U, V and W each represent $-(CH_2)-$; or U and V together represent $-CH=CH-$ and W represents $C=O$;

[0062] 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

[0063] Z 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.

[0063a] In an aspect, there is provided a compound of formula (I)



(I)

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

R₁ represents optionally substituted alkyl, wherein optional substituents include one or more substituents each independently selected from C₁₋₆alkoxy; optionally substituted carbocyclyl, wherein optional substituents include one or more substituents each independently selected from C₁₋₆alkyl, C₁₋₆alkoxy, C₁₋₆haloalkyl, C₁₋₆haloalkoxy and halo; or -alkylaryl;

R₂ represents H; or alkyl;

R₃ represents H; or alkyl;

U, V and W represent -(CH₂)-; or U and V together represent -CH=CH- and W represents C=O;

Y represents aryl or heteroaryl, each independently being optionally substituted by one or more groups independently selected from monovalent or multivalent; and

Z represents aryl or heteroaryl, each independently being optionally substituted by one or more groups independently selected from monovalent or multivalent.

[0063b] In another aspect, there is provided a compound as defined in any one of examples 1 to 158.

[0063c] In another aspect, there is provided a compound as defined in any one of examples 1 to 158, wherein compounds having an IC₅₀ against HEK293-STF3A cells of 10 micromolar or more are excluded.

[0063d] In another aspect, there is provided a compound as defined above for use as a medicament.

[0063e] 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.

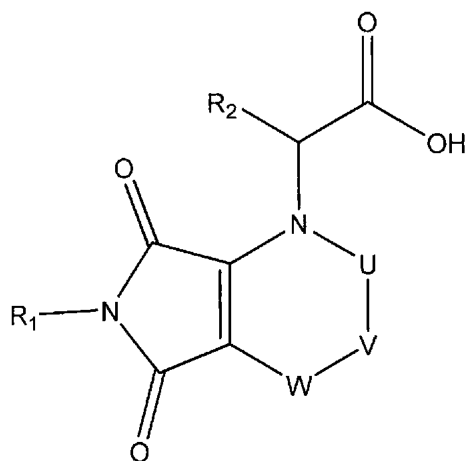
[0063f] In another aspect, there is provided the compound as defined above for use in modulation of the WNT pathway.

[0063g] In another aspect, there is provided a method of modulating WNT activity comprising exposing a WNT protein or a WNT receptor to a compound as defined above, with the proviso that the method is not a method of treatment of the human or animal body by therapy.

[0063h] In another aspect, there is provided the compound as defined above for use in the treatment of a disease or condition associated with WNT pathway activity.

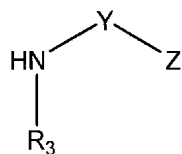
[0063i] In another aspect, there is provided the use of a compound as defined above in the manufacture of a medicament for the treatment of a disease or condition associated with WNT pathway activity.

[0063] In another aspect, there is provided a process for preparation of a compound as defined above or a protected derivative thereof, which process comprises reaction of a compound of formula (II)



(II)

or a protected derivative thereof, wherein R_1 , R_2 , U, V and W are as defined above, with a compound of formula (III)



(III)

or a protected derivative thereof wherein R_3 , Y and Z are as defined above.

Brief Description of Drawings

[0064] Figure 1: A bar chart illustrating inhibition of the activity of mammalian porcupine by the two compounds, Compound 13 and 43.

[0065] Figure 2: A graph illustrating efficacy of Compound 43 on the MMTV-Wnt1 mouse model.

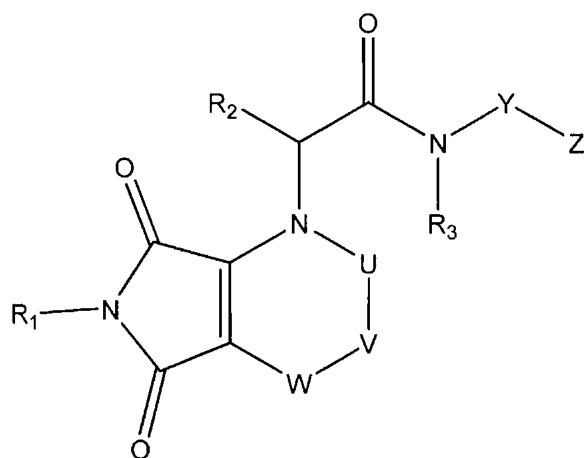
[0066] Figure 3: A graph illustrating efficacy of Compound 52 on the MMTV-Wnt1 mouse model.

[0067] Figure 4: Images illustrating inhibition of Palmitoylation of Wnt3a by Compound 43.

[0068] Figures 5 to 7: Images and graphs showing results of the Soft Agar Assay. Figure 5 shows the results for Cell line AsPC-1 treated with Compound 43. Figure 6 shows the results for Cell line HPAF-II treated with Compound 43. Figure 7 shows the results for Cell line CFPAC-1 treated with Compound 43.

CLAIMS

1. A compound of formula (I)



(I)

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

R₁ represents optionally substituted alkyl, wherein optional substituents include one or more substituents each independently selected from C₁₋₆alkoxy; optionally substituted carbocyclyl, wherein optional substituents include one or more substituents each independently selected from C₁₋₆alkyl, C₁₋₆alkoxy, C₁₋₆haloalkyl, C₁₋₆haloalkoxy and halo; or -alkylaryl;

R₂ represents H; or alkyl;

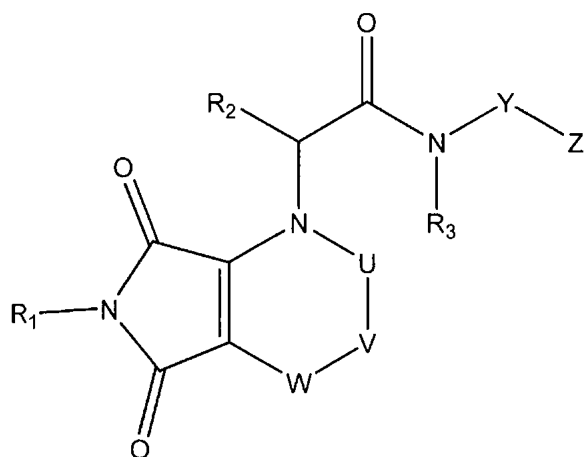
R₃ represents H; or alkyl;

U, V and W represent -(CH₂)-; or U and V together represent -CH=CH- and W represents C=O;

Y represents aryl or heteroaryl, each independently being optionally substituted by one or more groups independently selected from monovalent or multivalent; and

Z represents aryl or heteroaryl, each independently being optionally substituted by one or more groups independently selected from monovalent or multivalent.

2. A compound of formula (I) according to claim 1



(I)

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

R₁ represents alkyl which is optionally substituted by one or more substituents each independently selected from C₁₋₆alkoxy; 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 -alkylaryl;

R₂ represents H; or alkyl;

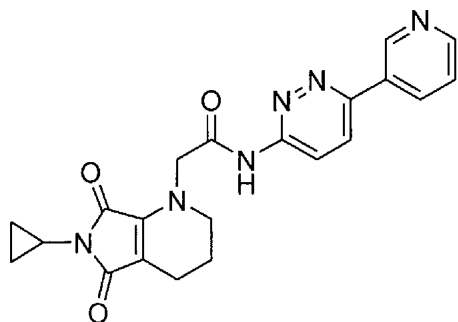
R₃ represents H; or alkyl;

U, V and W each represent -(CH₂)-; or U and V together represent -CH=CH- and W represents C=O;

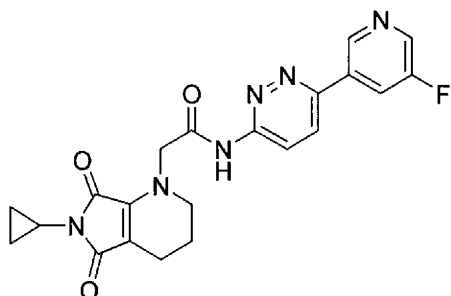
Y represents aryl or heteroaryl, each independently being optionally substituted by one or more groups independently selected from monovalent or multivalent; and

Z represents aryl or heteroaryl, each independently being optionally substituted by one or more groups independently selected from monovalent or multivalent.

yl)acetamide:



26. A compound as defined by claim 1 or claim 2, wherein the compound is 2-(6-cyclopropyl-5,7-dioxo-2,3,4,5,6,7-hexahydro-1H-pyrrolo[3,4-b]pyridin-1-yl)-N-(6-(5-fluoropyridin-3-yl)pyridazin-3-yl)acetamide:



27. A compound as defined in any one of examples 1 to 158, wherein compounds having an IC_{50} against HEK293-STF3A cells of 10 micromolar or more are excluded.

28. A compound according to any one of claims 1 to 27 for use as a medicament.

29. The compound of any one of claims 1 to 28 having an IC_{50} against HEK293-STF3A cells of less than about 10 micromolar.

30. A pharmaceutical composition comprising a compound according to any one of claims 1 to 29 in combination with one or more therapeutically acceptable adjuvants, diluents or carriers.

31. The compound of any one of claims 1 to 29 for use in modulation of the WNT pathway.

32. A method of modulating WNT activity comprising exposing a WNT protein or a WNT receptor to a compound according to any one of claims 1 to 29, with the proviso that the method is not a method of treatment of the human or animal body by therapy.

33. The compound of any one of claims 1 to 29 for use in the treatment of a disease or condition associated with WNT pathway activity.
34. Use of a compound according to any one of claims 1 to 29 in the manufacture of a medicament for the treatment of a disease or condition associated with WNT pathway activity.
35. The compound of claim 33 or use of claim 34 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.
36. The compound or use of claim 35 wherein the cancer is a cancer characterised by high WNT activity.
37. The compound or use of claim 35 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, 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.
38. A process for preparation of a compound according to any one of claims 1 to 29 or a protected derivative thereof, which process comprises reaction of a compound of formula (II)