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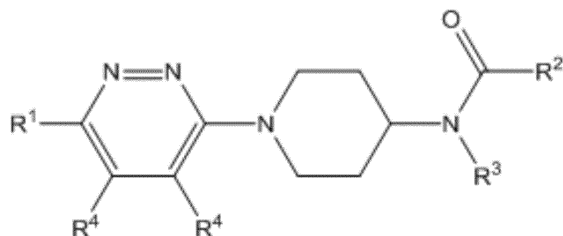
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WO 2010/147917 A1 WO 2010/056620 A1
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(54) Title of the Invention: **Compounds**
Abstract Title: **Pyridazine compounds as hedgehog pathway inhibitors**

(57)



(I)

Compounds of formula (I) or a pharmaceutically acceptable salt or solvate thereof wherein R¹, R² and R³ are as herein defined; R⁴ is a substituent as herein defined or both R⁴ groups form a ring together with the carbon atoms to which they are attached to form a fused bicyclic ring containing from 8 to 12 atoms which may be saturated or unsaturated provided that when R¹ is a substituted or unsubstituted pyrazolyl then R⁴ is not H and where both adjacent R⁴ groups form a ring with the atoms to which they are attached the adjacent R⁴ groups do not form an unsaturated carbocyclic ring with 6 carbon atoms; when R¹ is a substituted or unsubstituted C₆₋₁₀aryl then R⁴ is not H or methyl and where both adjacent R⁴ groups form a ring with the atoms to which they are attached the adjacent R⁴ groups do not form an unsaturated carbocyclic ring with 6 carbon atoms; and when R¹ is a substituted or unsubstituted pyridyl then R⁴ is not methyl. The compound 4-fluoro-N-[[1-[4-(2-methylpyrazol-3-yl)phthalazin-1-yl]pyrrolidin-3-yl]methyl]-2-(trifluoromethyl)benzamide is also provided. The compounds of formula (I) are useful as inhibitors in the hedgehog signalling pathway, particularly Smoothed (Smo) in the treatment of cancer.



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Compounds

[0001] This invention relates to compounds. More specifically, the invention relates to compounds useful as inhibitors of the Hedgehog signalling pathway. Specifically, inhibitors of Smoothed (Smo) are contemplated by the invention. In addition the invention contemplates processes to prepare the compounds and uses of the compounds.

[0002] The Hedgehog signalling pathway plays a key role in embryonic cells and is one of the key regulators of animal development. Malfunction of the Hedgehog signalling pathway during embryonic development can lead to abnormalities in the structure of bodily organs and the structure of the skeleton. Later in life, the Hedgehog signalling pathway has a role in regulating adult stem cells in the maintenance and the regeneration of tissue by directing cell differentiation and proliferation. Abnormalities in the Hedgehog signalling pathway have been shown to result in certain conditions, for example cancer.

[0003] There are three Hedgehog proteins (Hh) associated with the Hedgehog signalling pathway, Sonic Hedgehog (Shh), Indian Hedgehog (Ihh) and Desert Hedgehog (Dhh). The Hedgehog proteins bind to the Patched-1 receptor. The Patched-1 receptor inhibits Smo activity and upon binding of a Hedgehog protein with Patched-1 this inhibition is alleviated, leading to activation of the GLI transcription factors Gli1, Gli2 and Gli3 which are involved in cell fate determination and proliferation.

[0004] Aberrant activation of the hedgehog pathway has been implicated in patients suffering from a range of cancers, for example Basal cell carcinoma, pancreatic cancer, medulloblastoma, small cell lung cancer and prostate cancer. Moreover, it has been suggested that aberrant hedgehog signalling may contribute to the regulation of cancer stem cells.

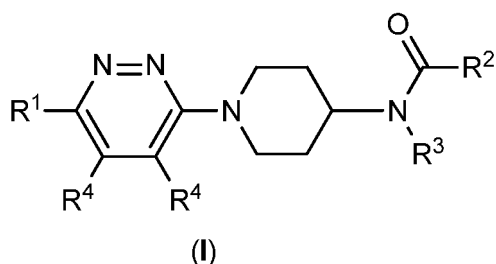
[0005] In January 2012 Genentech was given FDA approval for Vismodegib for the treatment of basal-cell carcinoma. This was approval of the first Hedgehog signalling pathway inhibitor. Vismodegib is being studied in the clinic for the treatment of a range of other cancers including colorectal cancer, small-cell lung cancer, stomach cancer, pancreatic cancer, medulloblastoma and chondrosarcoma. Recently, WO 2010/147917 disclosed Hedgehog pathway inhibitors for the treatment of various cancers. In addition Novartis Oncology have completed Phase II clinical trials for the treatment of Basal Cell Carcinomas on LDE225, a Smo receptor inhibitor. Thus, it is clear that inhibition of aberrant Hedgehog pathway signalling and Smo activation has emerged as an attractive target for anticancer therapy.

[0006] Inhibiting the Hedgehog signalling pathway with small molecules has become an important target for clinicians to treat clinically significant cancers, such as solid tumours, through the reversal or control of aberrant cell growth. However, there is still a need for further Hedgehog signalling pathway inhibitors and Smo inhibitors as effective treatments for various cancer types.

[0007] In accordance with the present invention there is provided compounds as disclosed below. Furthermore, the invention provides compounds capable of inhibiting the Hedgehog

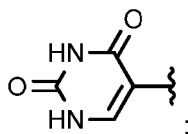
signalling pathway, specifically Smoothed (Smo) and the use of these compounds in inhibiting the Hedgehog signalling pathway and Smo. In accordance with the invention there is provided a method of treating conditions modulated by the Hedgehog signalling pathway, specifically Smo. The invention provides compounds for use in treating a condition which is modulated by the Hedgehog signalling pathway, specifically Smo.

[0008] In a first aspect of the invention there is provided a compound according to formula (I) and pharmaceutically acceptable salts and solvates thereof:



wherein

- 10 R¹ is selected from substituted or unsubstituted: C₆₋₁₀ aryl, pyrazolyl, pyridinyl, thiophenyl, oxazolyl, isoxazolyl, piperazinyl, -O-phenyl, -NH(CH₂)₂NMe₂, or



- 15 R² is represented by -CR⁵R⁶R⁷, wherein R⁵, R⁶ and R⁷ are independently selected at each occurrence from H and substituted or unsubstituted: C₁₋₁₄ alkyl, C₁₋₁₄ haloalkyl, carbocyclic, and heterocyclic,

or R² is selected from substituted or unsubstituted: C₁₋₁₄ alkyl, C₁₋₁₄ haloalkyl, carbocyclic, and heterocyclic;

- 20 R³ is selected from H, substituted or unsubstituted C₁₋₄ alkyl, C₁₋₄ haloalkyl or C₃₋₆ cycloalkyl;

- each R⁴ is independently selected from H, halo, C₁₋₆ alkyl, C₁₋₆ haloalkyl, -OR^a, -SH, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, C₃₋₈ cycloalkenyl, aryl, heterocyclic, -NR^aR^b, -CN, acyl, -C(O)R^a, -C(O)OR^a, -SO₂R^a, and -SO₃R^a, or wherein both of the R⁴ groups form a ring together with the carbon atoms to which they are attached thereby forming a fused bicyclic ring system containing from 8 to 12 atoms, wherein the ring formed by both R⁴ groups is a saturated or unsaturated carbocyclic ring with 4, 5, 6, 7, or 8 carbon atoms or a saturated or unsaturated heterocyclic ring with 4, 5, 6, 7, or 8 atoms containing 1, 2 or 3 heteroatoms;

R^a and R^b are independently selected at each occurrence from: H, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ acyl, C₃₋₇ cycloalkyl, and C₃₋₇ halocycloalkyl; and

- 5 when a group is substituted, the group contains 1 to 5 substituents independently selected at each occurrence from the group comprising: halo, -OR^a, -SR^a, -NR^aR^b, NO₂, =O, -CN, acyl, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₈ cycloalkyl, -SO₂R^a, and SO₃R^a, -C(OR^a)R^aR^b, -C(O)R^a and C(O)OR^a;

provided that:

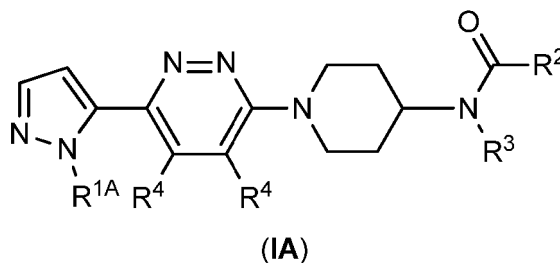
- 10 when R¹ is substituted or unsubstituted pyrazolyl then R⁴ is not H and where both adjacent R⁴ groups form a ring with the atoms to which they are attached the adjacent R⁴ groups do not form an unsaturated carbocyclic ring with 6 carbon atoms;

when R¹ is substituted or unsubstituted C₆₋₁₀ aryl then R⁴ is not H or methyl and where both adjacent R⁴ groups form a ring with the atoms to which they are attached the adjacent R⁴ groups do not form an unsaturated carbocyclic ring with 6 carbon atoms; and

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when R¹ is substituted or unsubstituted pyridyl then R⁴ is not methyl.

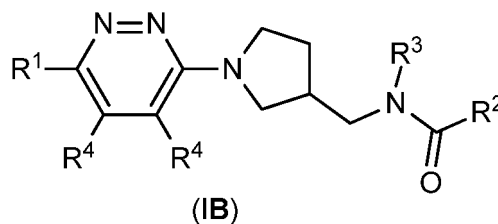
[0009] In an embodiment the compound of formula (I) is a compound according to formula (IA):



wherein

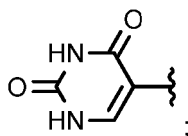
- 20 R^{1A} is selected from H, C₁₋₆ alkyl, or C₃₋₆ cycloalkyl.

[0010] In a second aspect of the invention there is provided a compound according to formula (IB) and pharmaceutically acceptable salts and solvates thereof:



wherein

- 25 R¹ is selected from substituted or unsubstituted: C₆₋₁₀ aryl, pyrazolyl, pyridinyl, thiophenyl, oxazolyl, isoxazolyl, piperazinyl, -O-phenyl, -NH(CH₂)₂NMe₂, or



5 R^2 is represented by $-CR^5R^6R^7$, wherein R^5 , R^6 and R^7 are independently selected at each occurrence from H and substituted or unsubstituted: C_{1-14} alkyl, C_{1-14} haloalkyl, carbocyclic, and heterocyclic,

or R^2 is selected from substituted or unsubstituted: C_{1-14} alkyl, C_{1-14} haloalkyl, carbocyclic, and heterocyclic;

10 R^3 is selected from H, substituted or unsubstituted C_{1-4} alkyl, C_{1-4} haloalkyl or C_{3-6} cycloalkyl;

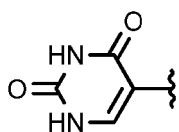
15 each R^4 is independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, $-OR^a$, $-SH$, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, aryl, heterocyclic, $-NR^aR^b$, $-CN$, acyl, $-C(O)R^a$, $-C(O)OR^a$, $-SO_2R^a$, and $-SO_3R^a$, or wherein both of the R^4 groups form a ring together with the carbon atoms to which they are attached thereby forming a fused bicyclic ring system containing from 8 to 12 atoms, wherein the ring formed by both R^4 groups is a saturated or unsaturated carbocyclic ring with 4, 5, 6, 7, or 8 carbon atoms or a saturated or unsaturated heterocyclic ring with 4, 5, 6, 7, or 8 atoms containing 1, 2 or 3 heteroatoms;

20 R^a and R^b are independently selected at each occurrence from: H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} acyl, C_{3-7} cycloalkyl, and C_{3-7} halocycloalkyl; and

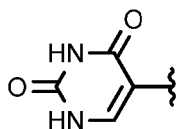
when a group is substituted, the group contains 1 to 5 substituents independently selected at each occurrence from the group comprising: halo, $-OR^a$, $-SR^a$, $-NR^aR^b$, NO_2 , $=O$, $-CN$, acyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-8} cycloalkyl, $-SO_2R^a$, and SO_3R^a , $-C(OR^a)R^aR^b$, $-C(O)R^a$ and $C(O)OR^a$.

25 **[0011]** In an embodiment, there is provided a compound of formula (IB), wherein R^1 is substituted or unsubstituted pyrazolyl, preferably methyl pyrazolyl.

[0012] In an embodiment R^1 is selected from substituted or unsubstituted: pyrazolyl, thiophenyl, oxazolyl, isoxazolyl, piperazinyl, $-O$ -phenyl, $-NH(CH_2)_2NMe_2$, or



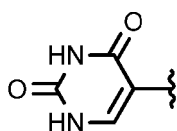
30 **[0013]** In an embodiment R^1 is selected from substituted or unsubstituted: thiophenyl, oxazolyl, isoxazolyl, piperazinyl, $-O$ -phenyl, $-NH(CH_2)_2NMe_2$, or



[0014] In an embodiment, R¹ is substituted or unsubstituted pyrazolyl, preferably methyl pyrazolyl.

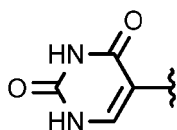
[0015] In embodiments R⁴ is as defined elsewhere herein, provided that R⁴ is not H or methyl and where both adjacent R⁴ groups form a ring with the atoms to which they are attached the adjacent R⁴ groups do not form an unsaturated carbocyclic ring with 6 carbon atoms.

[0016] In embodiments R¹ is selected from substituted or unsubstituted: C₆₋₁₀ aryl, pyrazolyl, pyridinyl, thiophenyl, oxazolyl, isoxazolyl, piperazinyl, -O-phenyl, -NH(CH₂)₂NMe₂, or



and R⁴ is selected from: C₂₋₆ alkyl, C₁₋₆ haloalkyl, aryl and heterocyclic, or both adjacent R⁴ groups form a ring with the atoms to which they are attached thereby forming a fused bicyclic ring system of 8 to 12 atoms, wherein the ring formed by the two R⁴ groups is a saturated or unsaturated carbocyclic ring with 4, 5, 7 or 8 carbon atoms or a saturated or unsaturated heterocyclic ring with 4, 5, 6, 7 or 8 atoms containing 1, 2 or 3 heteroatoms.

[0017] In embodiments R¹ is selected from substituted or unsubstituted: C₆₋₁₀ aryl, pyrazolyl, pyridinyl, thiophenyl, oxazolyl, isoxazolyl, piperazinyl, -O-phenyl, -NH(CH₂)₂NMe₂, or




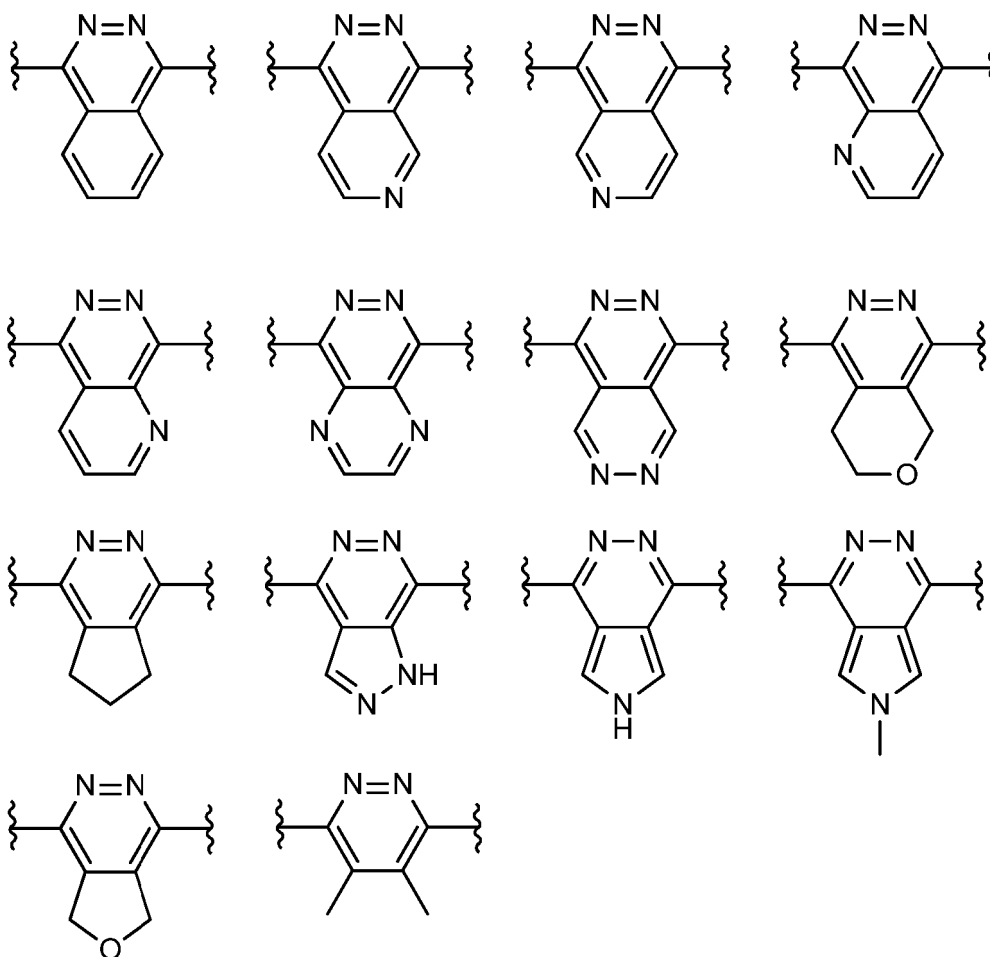
and both R⁴ groups are C₂₋₆ alkyl or both form a ring together with the atoms to which they are attached thereby forming a fused bicyclic ring system of 8 to 12 atoms, wherein the ring formed by the two R⁴ groups is a saturated or unsaturated carbocyclic ring with 4, 5, 7 or 8 carbon atoms or a saturated or unsaturated heterocyclic ring with 4, 5, 6, 7 or 8 atoms or a saturated or unsaturated heterocyclic ring with 4, 5, 6, 7 or 8 atoms containing 1, 2 or 3 heteroatoms.

[0018] In embodiments R⁴ is selected from: C₂₋₆ alkyl, C₁₋₆ haloalkyl, aryl and heterocyclic, or both adjacent R⁴ groups form a ring with the atoms to which they are attached thereby forming a fused bicyclic ring system of 8 to 12 atoms, wherein the ring formed by the two R⁴ groups is a saturated or unsaturated carbocyclic ring with 4, 5, 7 or 8 carbon atoms or a saturated or unsaturated heterocyclic ring with 4, 5, 6, 7 or 8 atoms containing 1, 2 or 3 heteroatoms.

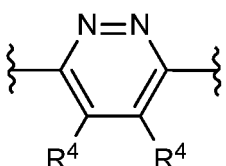
[0019] In embodiments both R⁴ groups are C₂₋₆ alkyl or both form a ring together with the atoms to which they are attached thereby forming a fused bicyclic ring system of 8 to 12 atoms, wherein the ring formed by the two R⁴ groups is a saturated or unsaturated carbocyclic ring with 4, 5, 7 or 8 carbon atoms or a saturated or unsaturated heterocyclic ring with 4, 5, 6, 7 or 8 atoms or a

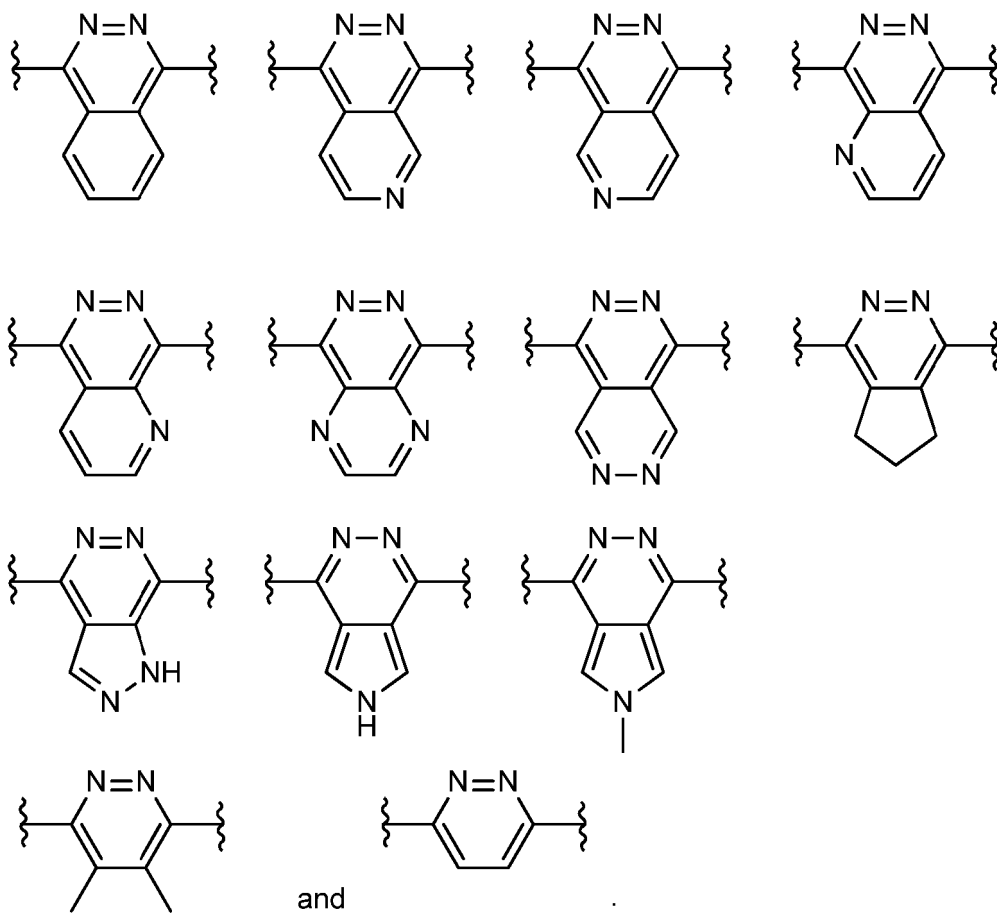
saturated or unsaturated heterocyclic ring with 4, 5, 6, 7 or 8 atoms containing 1, 2 or 3 heteroatoms.

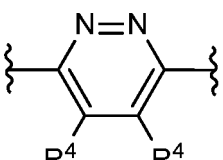
[0020] In embodiments  is selected from:

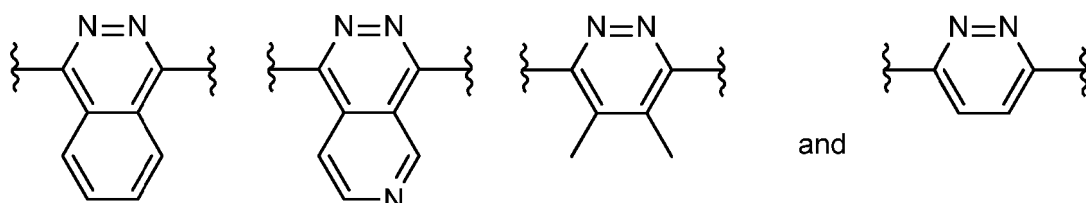



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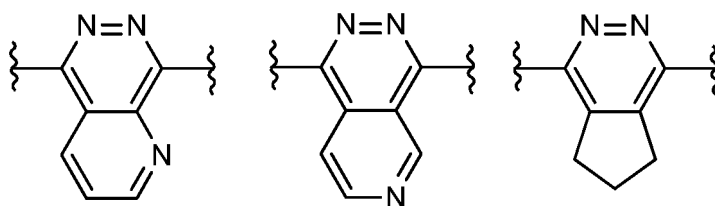
[0021] In embodiments  is selected from:

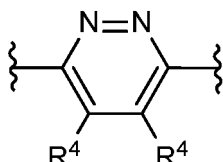


[0022] In an embodiment  is selected from:

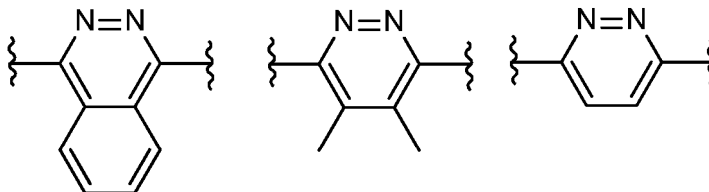


5 [0023] In an embodiment  is selected from:

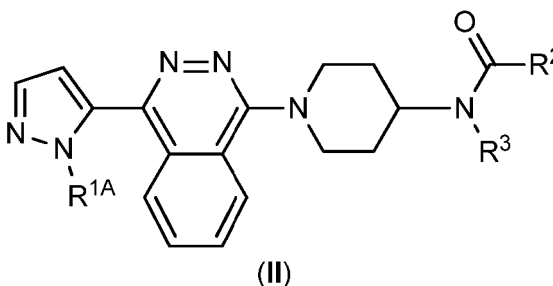




[0024] In an embodiment is not:

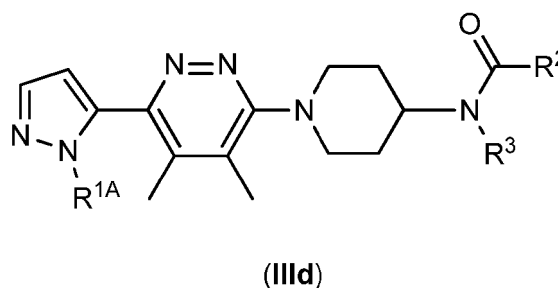
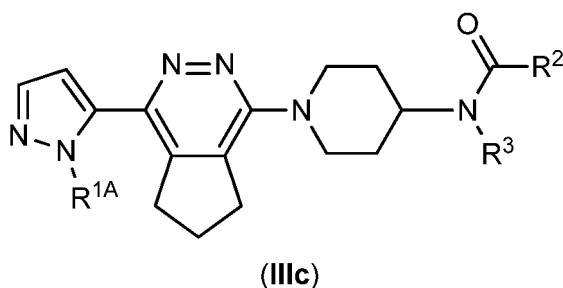
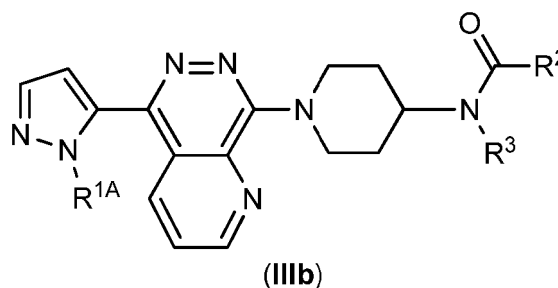
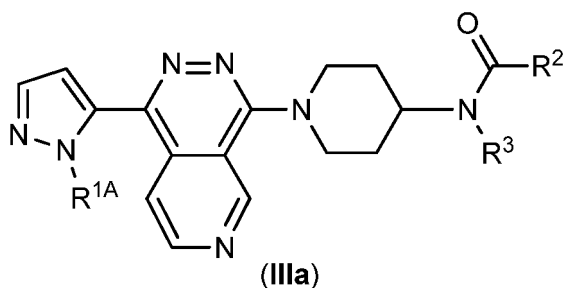


[0025] In an embodiment the compound of formula (I) is a compound according to formula (II) and pharmaceutically acceptable salts and solvates thereof:



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[0026] In an embodiment the compound of formula (I) is a compound according to formulae (IIIa), (IIIb), (IIIc) and (IIId) and pharmaceutically acceptable salts and solvates thereof:

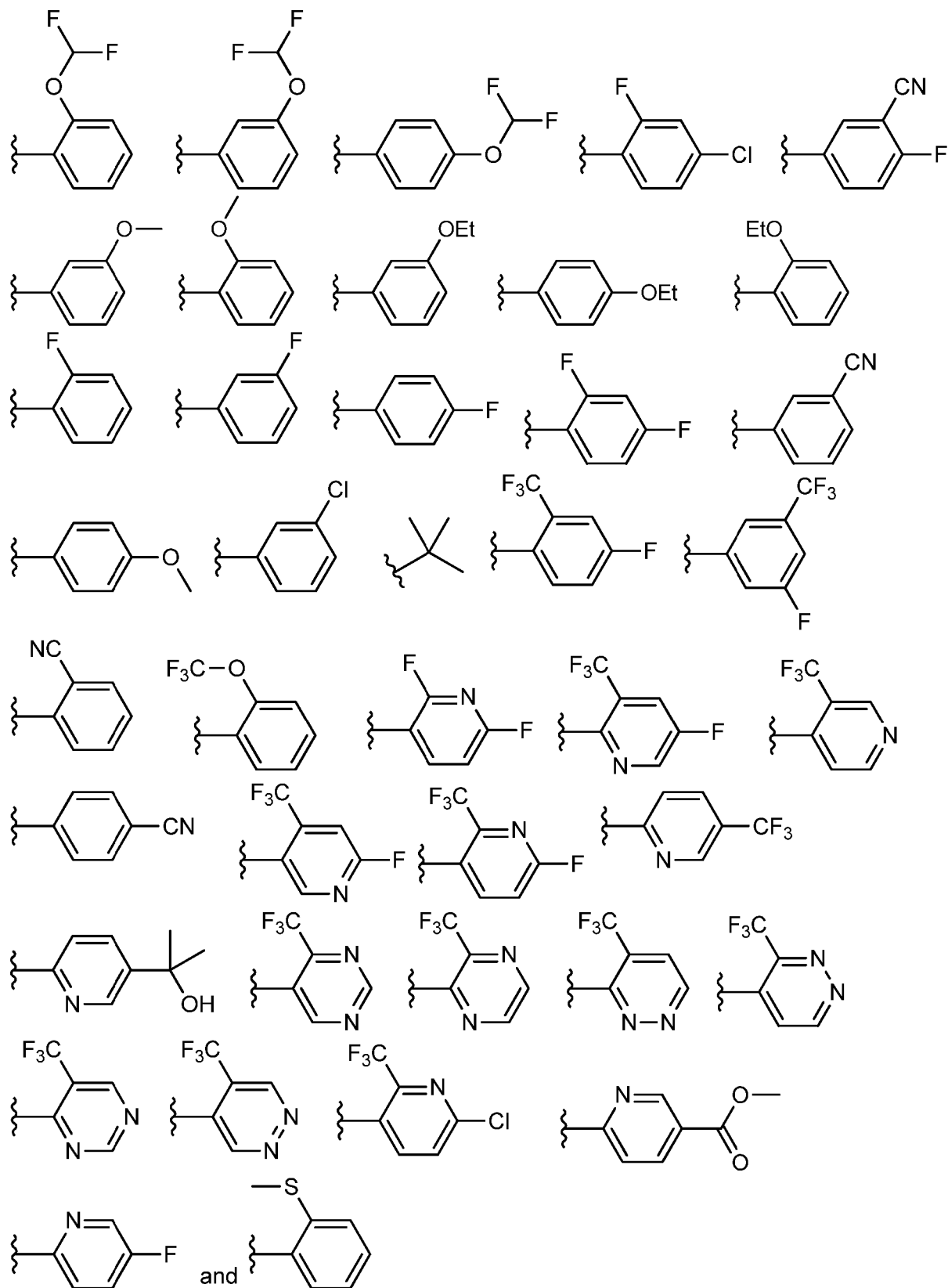


10 [0027] In embodiments R^{1A} is H, methyl, ethyl trifluoromethyl or cyclopropyl, preferably methyl.

[0028] In an embodiment R^2 is represented by $-CR^5R^6R^7$, wherein R^5 , R^6 and R^7 are independently selected at each occurrence from H and substituted or unsubstituted: C_{1-14} alkyl, C_{1-14} haloalkyl, carbocyclic, and heterocyclic. The carbocyclic and heterocyclic moieties may be

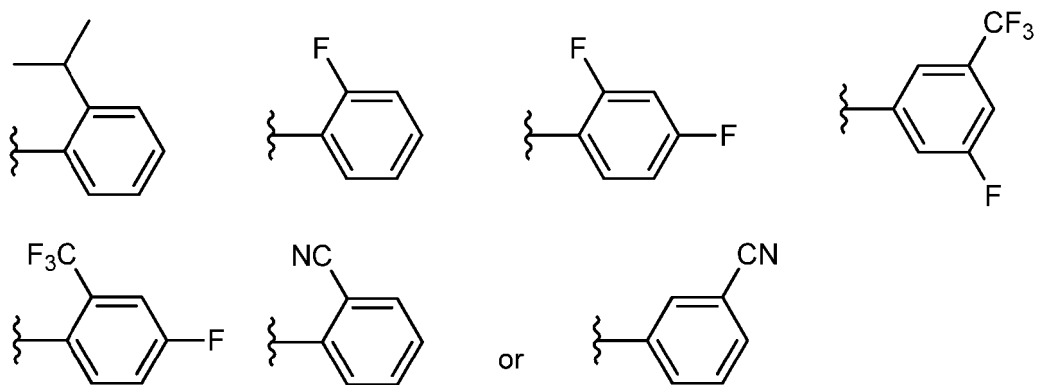
monocyclic or fused polycyclic ring systems, for example bicyclic fused ring systems. Optionally, carbocyclic may be cycloalkyl and aryl and heterocyclic may be heterocycloalkyl and heteroaryl. Further optionally carbocyclic may be C₃₋₈ cycloalkyl and C₅₋₆ aryl and heterocyclic may be C₃₋₈ heterocycloalkyl and C₅₋₆ heteroaryl.

- 5 **[0029]** In an embodiment R² is represented by -CR⁵R⁶R⁷, wherein R⁵, R⁶ and R⁷ are independently selected at each occurrence from H and substituted or unsubstituted: C₁₋₁₄ alkyl, C₁₋₁₄ haloalkyl, C₃₋₈ cycloalkyl, C₃₋₈ heterocycloalkyl, phenyl, toluenyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyrrolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, and isothiazolyl.
- 10 **[0030]** In an embodiment R⁵, R⁶ and R⁷ are independently selected at each occurrence from H and substituted or unsubstituted: C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₈ cycloalkyl, C₃₋₈ heterocycloalkyl, phenyl, toluenyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyrrolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, and isothiazolyl.
- [0031]** In an embodiment R⁵, R⁶ and R⁷ are independently selected at each occurrence from H and substituted or unsubstituted: C₁₋₁₄ alkyl (optionally C₁₋₆ alkyl), C₁₋₁₄ haloalkyl (optionally C₁₋₆ haloalkyl), C₃₋₈ cycloalkyl, phenyl, toluenyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyrrolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, and isothiazolyl.
- 15 **[0032]** In an embodiment two of R⁵, R⁶ and R⁷ are the same and the third is selected independently. In an alternative embodiment R⁵, R⁶ and R⁷ are all the same.
- 20 **[0033]** In an embodiment R⁵, R⁶ and R⁷ are all one of the groups selected from: methyl, trifluoromethyl, cyclohexanyl and phenyl.
- [0034]** In an embodiment R² is selected from substituted or unsubstituted: C₁₋₁₄ alkyl, C₁₋₁₄ haloalkyl, carbocyclic, and heterocyclic. The carbocyclic and heterocyclic moieties may be monocyclic or fused polycyclic ring systems, for example bicyclic fused ring systems. Optionally, carbocyclic may be cycloalkyl and aryl and heterocyclic may be heterocycloalkyl and heteroaryl. Further optionally carbocyclic may be C₃₋₈ cycloalkyl and C₅₋₆ aryl and heterocyclic may be C₃₋₈ heterocycloalkyl and C₅₋₆ heteroaryl. In an embodiment carbocyclic may be C₃₋₈ cycloalkyl and C₆ aryl and heterocyclic may be C₃₋₈ heterocycloalkyl and C₆ heteroaryl
- 25 **[0035]** In embodiments where R² is C₅₋₆ aryl and C₅₋₆ heteroaryl the ring of the C₅₋₆ aryl and C₅₋₆ heteroaryl may be ortho and/or meta and/or para substituted. In embodiments where R² is C₅₋₆ aryl and C₅₋₆ heteroaryl the ring may be ortho substituted. In embodiments where R² is C₅₋₆ aryl and C₅₋₆ heteroaryl the ring may be meta substituted. In embodiments where R² is C₆ aryl and C₆ heteroaryl the 6 membered ring may be para substituted. In embodiments where R² is C₆ aryl and C₆ heteroaryl the 6 membered ring may be ortho and para substituted. In embodiments where R² is C₅₋₆ aryl and C₅₋₆ heteroaryl the 6 membered ring may be di-meta substituted.
- 30 **[0036]** In an embodiment R² is selected from substituted or unsubstituted: C₁₋₁₄ alkyl, C₁₋₁₄ haloalkyl, C₃₋₈ cycloalkyl, C₃₋₈ heterocycloalkyl, phenyl, toluenyl, pyridinyl, pyridazinyl, pyrimidinyl,
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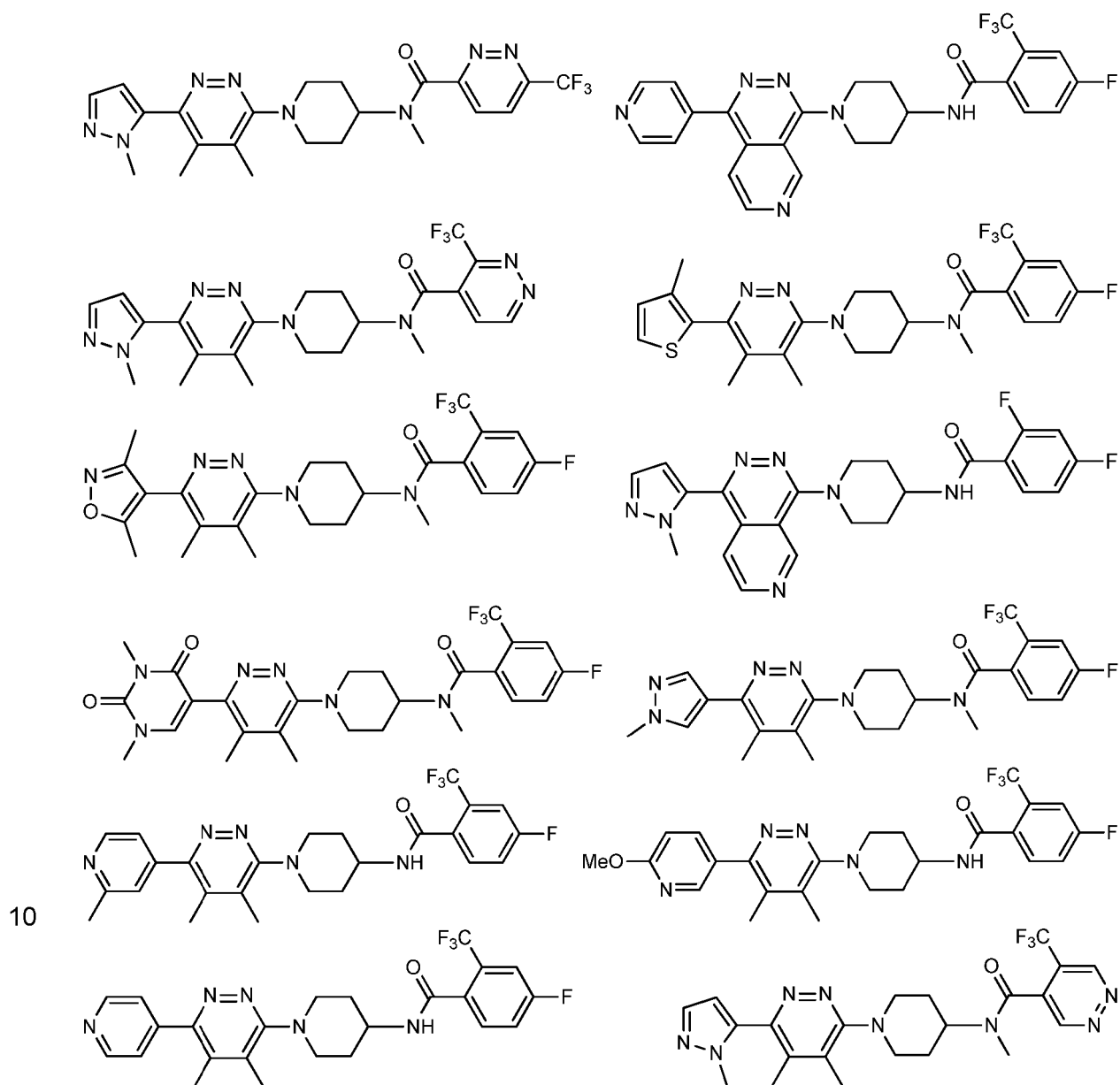
10 [0042] In a preferred embodiment R^2 is

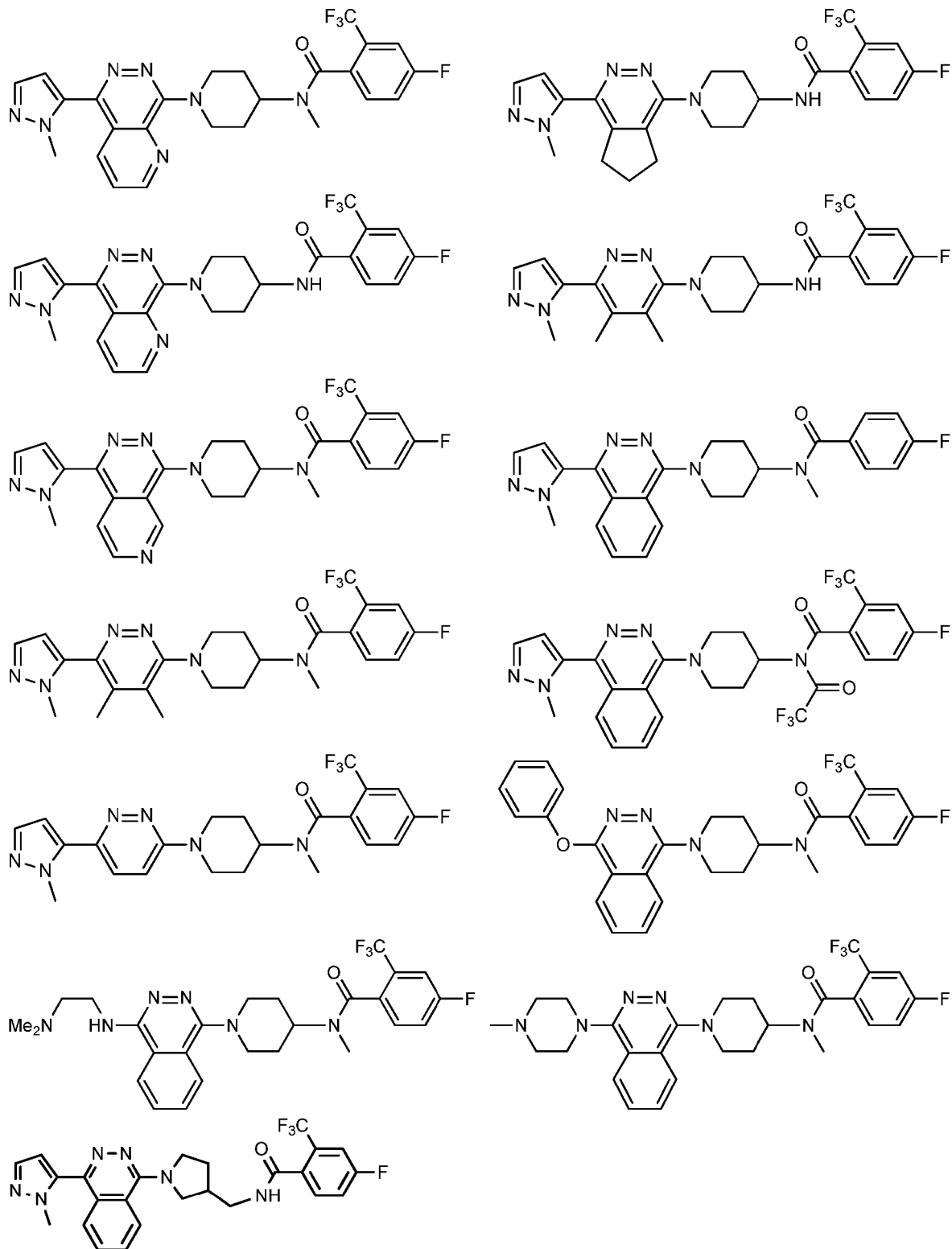


[0043] In an embodiment R^3 is H or substituted or unsubstituted C_{1-4} alkyl or substituted or unsubstituted C_{1-4} haloalkyl. Preferably, R^3 is H, methyl or $-C(O)CF_3$.

[0044] In an embodiment all occurrences of R^a and R^b are hydrogen.

5 **[0045]** Compounds of the invention include:





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[0046] In another aspect of the invention there is provided a compound of the invention for use as a medicament.

[0047] In another aspect, a compound of the invention is for use in a method of treatment of a condition which is modulated by the Hedgehog signalling pathway. Usually conditions that are

modulated by the Hedgehog signalling pathway are conditions that would be treated by the inhibition of the Hedgehog signalling pathway using a compound of the present invention. A compound of the invention may be for use in the treatment of a condition treatable by the inhibition of the Hedgehog signalling pathway.

5 **[0048]** In addition the compounds of the present invention are for use in a method of treatment of a condition which is modulated by Smoothed (Smo), a receptor in the Hedgehog signalling pathway. Therefore, in a related aspect a compound of formula (I) is for use in the treatment of a condition which is modulated by Smo. Usually conditions that are modulated by Smo are conditions that would be treated by the inhibition of Smo using a compound of the present invention. A
10 compound of the invention may be for use in the treatment of a condition treatable by the inhibition of Smo.

[0049] Inhibition of the Hedgehog signalling pathway and Smo is a novel approach for treating many different human diseases associated with the inappropriate activation of the Hedgehog signalling pathway and aberrant activation of Smo, including various cancers, for example, solid
15 tumours. In embodiments the condition treatable by the inhibition of the Hedgehog signalling pathway or Smo may be selected from: cancer, for example sarcoma, carcinoma, blastoma, lymphoma and leukemia. Specific conditions treatable by the inhibition of the Hedgehog signalling pathway or Smo may be selected from: basal cell carcinoma, medulloblastoma, rhabdomyosarcoma, chondrosarcoma, melanoma, small-cell lung cancer, non-small-cell lung
20 cancer, B-cell lymphoma, multiple myeloma, brain cancer, esophagus cancer, breast cancer, ovarian cancer, stomach cancer, colorectal cancer, liver cancer, kidney cancer, head and neck cancer, mesothelioma, soft tissue sarcomas, bone sarcomas, testicular cancer, prostate cancer, pancreatic cancer, bone cancer, bone metastasis, acute leukemia, chronic leukemia, glioma, hodgkin's disease, cutaneous melanoma, bladder cancer, endocrine system cancer, parathyroid
25 gland cancer, thyroid gland cancer, cervical cancer, endometrium cancer, ovarian cancer, skin cancer, renal cell carcinoma, pituitary adenoma, spinal axis tumours, uterine cancer, gastric cancer and biliary tract cancer.

[0050] In embodiments the preferred condition treatable by the inhibition of the hedgehog signalling pathway or Smo may be selected from: basal cell carcinoma, medulloblastoma,
30 rhabdomyosarcoma, chondrosarcoma, melanoma, small-cell lung cancer, non-small-cell lung cancer, B-cell lymphoma, brain cancer, esophagus cancer, breast cancer, ovarian cancer, stomach cancer, colorectal cancer, liver cancer, kidney cancer, head and neck cancer, soft tissue sarcomas, bone sarcomas, testicular cancer, prostate cancer, pancreatic cancer, bone cancer, bone metastasis, acute leukemia, glioma, bladder cancer, parathyroid gland cancer, thyroid gland cancer,
35 cervical cancer, ovarian cancer, skin cancer, renal cell carcinoma, gastric cancer and biliary tract cancer.

[0051] Conditions also treatable by the inhibition of the Hedgehog signalling pathway or Smo may be selected from benign prostatic hyperplasia, psoriasis and osteoporosis.

[0052] In an embodiment the compounds of the invention are for use in inhibiting stem cell production, inhibiting stem cell renewal and inhibiting and/or modulating stem cell differentiation. In an embodiment the stem cells are cancer stem cells which may also be referred to as tumorigenic stem cells or stem cell like tumorigenic cells.

5 **[0053]** In embodiments, a compound of the invention may be for use in the treatment of: cancer, for example sarcoma, carcinoma, blastoma, lymphoma and leukemia. The compound of the invention may be for use in the treatment of specific conditions selected from: basal cell carcinoma, medulloblastoma, rhabdomyosarcoma, chondrosarcoma, melanoma, small-cell lung cancer, non-small-cell lung cancer, B-cell lymphoma, multiple myeloma, brain cancer, esophagus cancer,
10 breast cancer, ovarian cancer, stomach cancer, colorectal cancer, liver cancer, kidney cancer, head and neck cancer, mesothelioma, soft tissue sarcomas, bone sarcomas, testicular cancer, prostate cancer, pancreatic cancer, bone cancer, bone metastasis, acute leukemia, chronic leukemia, glioma, bladder cancer, endocrine system cancer, parathyroid gland cancer, thyroid gland cancer, cervical cancer, endometrium cancer, ovarian cancer, skin cancer, renal cell carcinoma, pituitary
15 adenoma, spinal axis tumours, uterine cancer, gastric cancer and biliary tract cancer.

[0054] A compound of the invention may be for use in the treatment of: benign prostatic hyperplasia, psoriasis and osteoporosis.

[0055] The compounds of the present invention may be for use in a method of treatment wherein the treatment comprises inhibiting stem cell production, inhibiting stem cell renewal and/or inhibiting
20 and/or modulating stem cell differentiation. In an embodiment the compounds of the present invention may be for use in a method of treatment wherein the treatment comprises inhibiting stem cell renewal and/or stem cell production and the condition being treated is selected from any of the conditions mentioned above. In the above embodiments the stem cells may be cancer stem cells which may also be referred to as tumorigenic stem cells or stem cell like tumorigenic cells.

25 **[0056]** In an aspect of the invention there is provided a method of treatment of a condition which is modulated by Hedgehog signalling pathway, wherein the method comprises administering a therapeutic amount of a compound of the invention, to a patient in need thereof.

[0057] In an embodiment of the invention there is provided a method of treatment of a condition which is modulated by Smo, wherein the method comprises administering a therapeutic amount of a
30 compound of the invention, to a patient in need thereof.

[0058] The method of treatment may be a method of treating a condition treatable by the inhibition of the Hedgehog signalling pathway. Furthermore, the method of treatment may be a method of treating a condition treatable by the inhibition of Smo.

35 **[0059]** The invention also provides a method of treating a condition selected from: cancer, for example sarcoma, carcinoma, blastoma, lymphoma and leukemia, wherein the method comprises administering a therapeutic amount of a compound of the invention, to a patient in need thereof.

The invention also provides a method of treating a specific condition selected from: basal cell carcinoma, medulloblastoma, rhabdomyosarcoma, chondrosarcoma, melanoma, small-cell lung cancer, non-small-cell lung cancer, B-cell lymphoma, multiple myeloma, brain cancer, esophagus cancer, breast cancer, ovarian cancer, stomach cancer, colorectal cancer, liver cancer, kidney cancer, head and neck cancer, mesothelioma, soft tissue sarcomas, bone sarcomas, testicular cancer, prostate cancer, pancreatic cancer, bone cancer, bone metastasis, acute leukemia, chronic leukemia, glioma, bladder cancer, endocrine system cancer, parathyroid gland cancer, thyroid gland cancer, cervical cancer, endometrium cancer, ovarian cancer, skin cancer, renal cell carcinoma, pituitary adenoma, spinal axis tumours, uterine cancer, gastric cancer and biliary tract cancer, wherein the method comprises administering a therapeutic amount of a compound of formula (I), to a patient in need thereof.

[0060] The invention also provides a method of treating a condition selected from: inhibiting stem cell production, inhibiting stem cell renewal, inhibiting and/or modulating stem cell differentiation, benign prostatic hyperplasia, psoriasis and osteoporosis wherein the method comprises administering a therapeutic amount of a compound of the invention, to a patient in need thereof.

[0061] In an aspect of the invention there is provided a method of inhibiting stem cell renewal and/or stem cell production, wherein the method comprises administering a therapeutic amount of a compound of the invention, to a patient in need thereof. The stem cells may be cancer stem cells which may also be referred to as tumorigenic stem cells or stem cell like tumorigenic cells.

[0062] In another aspect of the invention there is provided a pharmaceutical composition, comprising a compound of the invention and a pharmaceutically acceptable excipient. The pharmaceutical composition may be used in the treatment of the diseases mentioned above. The method of treatment mentioned above may comprise administering a pharmaceutical composition of the invention instead of the compound of the invention.

[0063] In an embodiment the pharmaceutical composition may be a combination product comprising an additional pharmaceutically active agent. The additional pharmaceutically active agent may be an anti-tumor agent, as described below.

[0064] In an aspect of the invention there is provided a method of treatment of a condition selected from cancer, for example sarcoma, carcinoma, blastoma, lymphoma and leukemia comprising administering a therapeutically effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof simultaneously, sequentially or separately with an additional anti-tumour agent to a patient in need thereof.

[0065] In an aspect there is provided the use of a compound of formula (I) in the manufacture of a medicament for use in the treatment of a condition modulated by the Hedgehog pathway, for example a condition selected from cancer, for example sarcoma, carcinoma, blastoma, lymphoma

and leukemia. Optionally, the condition to be treated can be selected from any of those conditions mentioned above.

[0066] The embodiments described above may be applied individually, or in any combination of one another, and independently, to the compounds of the invention.

5 DETAILED DESCRIPTION

[0067] Given below are definitions of terms used in this application. Any term not defined herein takes the normal meaning as the skilled person would understand the term.

[0068] The term "halo" refers to one of the halogens, group 17 of the periodic table. In particular the term refers to fluorine, chlorine, bromine and iodine. Preferably, the term refers to fluorine or
10 chlorine.

[0069] The term "C₁₋₆ alkyl" refers to a linear or branched hydrocarbon chain containing 1, 2, 3, 4, 5 or 6 carbon atoms, for example methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, tert-butyl, n-pentyl and n-hexyl. Similarly, "C₁₋₄ alkyl" refers to a linear or branched hydrocarbon chain containing 1, 2, 3 or 4 carbon atoms, "C₁₋₃ alkyl" refers to a linear or branched hydrocarbon chain
15 containing 1, 2 or 3 carbon atoms and "C₁₋₁₄ alkyl" refers to a linear or branched hydrocarbon chain containing 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 or 14 carbon atoms. Alkylene groups may likewise be linear or branched and may have two places of attachment to the remainder of the molecule. Furthermore, an alkylene group may, for example, correspond to one of those alkyl groups listed in this paragraph. The alkyl and alkylene groups may be unsubstituted or substituted by one or more
20 substituents. Possible substituents are described below. Substituents for the alkyl group may be halogen, e.g. fluorine, chlorine, bromine and iodine, OH, C₁₋₆ alkoxy.

[0070] The term "C₁₋₆ alkoxy" refers to an alkyl group which is attached to a molecule via oxygen. This includes moieties where the alkyl part may be linear or branched and may contain 1, 2, 3, 4, 5 or 6 carbon atoms, for example methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, tert-butyl,
25 n-pentyl and n-hexyl. Therefore, the alkoxy group may be methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, sec-butoxy, tert-butoxy, n-pentoxy and n-hexoxy. The alkyl part of the alkoxy group may be unsubstituted or substituted by one or more substituents. Possible substituents are described below. Substituents for the alkyl group may be halogen, e.g. fluorine, chlorine, bromine and iodine, OH, C₁₋₆ alkoxy.

[0071] The term "C₁₋₆ haloalkyl" refers to a hydrocarbon chain substituted with at least one halogen atom independently chosen at each occurrence, for example fluorine, chlorine, bromine and iodine. Similarly, "C₁₋₄ haloalkyl" refers to a linear or branched hydrocarbon chain containing 1, 2, 3 or 4 carbon atoms and "C₁₋₁₄ haloalkyl" refers to a linear or branched hydrocarbon chain containing 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 or 14 carbon atoms. The halogen atom may be
30 present at any position on the hydrocarbon chain. For example, C₁₋₆ haloalkyl may refer to chloromethyl, fluoromethyl, trifluoromethyl, chloroethyl e.g. 1-chloromethyl and 2-chloroethyl,

trichloroethyl e.g. 1,2,2-trichloroethyl, 2,2,2-trichloroethyl, fluoroethyl e.g. 1-fluoromethyl and 2-fluoroethyl, trifluoroethyl e.g. 1,2,2-trifluoroethyl and 2,2,2-trifluoroethyl, chloropropyl, trichloropropyl, fluoropropyl, trifluoropropyl.

[0072] The term “C₂₋₆ alkenyl” refers to a branched or linear hydrocarbon chain containing at least one double bond and having 2, 3, 4, 5 or 6 carbon atoms. The double bond(s) may be present as the *E* or *Z* isomer. The double bond may be at any possible position of the hydrocarbon chain. For example, the “C₂₋₆ alkenyl” may be ethenyl, propenyl, butenyl, butadienyl, pentenyl, pentadienyl, hexenyl and hexadienyl.

[0073] The term “C₂₋₆ alkynyl” refers to a branched or linear hydrocarbon chain containing at least one triple bond and having 2, 3, 4, 5 or 6 carbon atoms. The triple bond may be at any possible position of the hydrocarbon chain. For example, the “C₂₋₆ alkynyl” may be ethynyl, propynyl, butynyl, pentynyl and hexynyl.

[0074] The term “C₁₋₆ heteroalkyl” refers to a branched or linear hydrocarbon chain containing 1, 2, 3, 4, 5, or 6 carbon atoms and at least one heteroatom selected from N, O and S positioned between any carbon in the chain or at an end of the chain. For example, the hydrocarbon chain may contain one or two heteroatoms. The C₁₋₆ heteroalkyl may be bonded to the rest of the molecule through a carbon or a heteroatom. For example, the “C₁₋₆ heteroalkyl” may be C₁₋₆ *N*-alkyl, C₁₋₆ *N,N*-alkyl, or C₁₋₆ *O*-alkyl.

[0075] The term “carbocyclic” refers to a saturated or unsaturated carbon containing ring system. A “carbocyclic” system may be monocyclic or a fused polycyclic ring system, for example, bicyclic or tricyclic. A “carbocyclic” moiety may contain from 3 to 14 carbon atoms, for example, 3 to 8 carbon atoms in a monocyclic system and 7 to 14 carbon atoms in a polycyclic system. “Carbocyclic” encompasses cycloalkyl moieties, cycloalkenyl moieties, aryl ring systems and fused ring systems including an aromatic portion. “Carbocyclic” may be C₃₋₈ cycloalkyl or C₆₋₁₀ aryl.

[0076] The term “heterocyclic” refers to a saturated or unsaturated ring system containing at least one heteroatom selected from N, O or S. A “heterocyclic” system may contain 1, 2, 3 or 4 heteroatoms, for example 1 or 2. A “heterocyclic” system may be monocyclic or a fused polycyclic ring system, for example, bicyclic or tricyclic. A “heterocyclic” moiety may contain from 3 to 14 carbon atoms, for example, 3 to 8 carbon atoms in a monocyclic system and 7 to 14 carbon atoms in a polycyclic system. “Heterocyclic” encompasses heterocycloalkyl moieties, heterocycloalkenyl moieties and heteroaromatic moieties. “Heterocyclic” groups may be C₃₋₈ heterocycloalkyl, C₅₋₆ heteroaryl. For example, the heterocyclic group may be: oxirane, aziridine, azetidione, oxetane, tetrahydrofuran, pyrrolidine, imidazolidine, succinimide, pyrazolidine, oxazolidine, isoxazolidine, thiazolidine, isothiazolidine, piperidine, morpholine, thiomorpholine, piperazine, and tetrahydropyran.

[0077] The term “C₃₋₁₄ cycloalkyl” refers to a saturated hydrocarbon ring system containing 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 or 14 carbon atoms. Similarly, “C₃₋₈ cycloalkyl” refers to a saturated


hydrocarbon ring system containing 3, 4, 5, 6, 7 or 8 carbon atoms and "C₅₋₇ cycloalkyl" refers to a saturated hydrocarbon ring system containing 5, 6 or 7 carbon atoms. For example, the "C₃₋₈ cycloalkyl" may be cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl. The term "C₃₋₇ halocycloalkyl" is a "cycloalkyl" ring having at least one halogen substituted thereon,
 5 independently selected at each occurrence. For example, the halogen may be fluorine, chlorine, bromine or iodine.

[0078] The term "C₃₋₈ cycloalkenyl" refers to an unsaturated hydrocarbon ring system containing 3, 4, 5, 6, 7 or 8 carbon atoms. The ring may contain more than one double bond. For example, the "C₃₋₈ cycloalkyl" may be cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclopentadienyl, cyclohexenyl,
 10 cyclohexadienyl, cycloheptenyl, cycloheptadiene, cyclooctenyl and cyclooctadienyl.

[0079] The term "C₃₋₁₄ heterocycloalkyl" refers to a saturated hydrocarbon ring system containing 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 or 14 carbon atoms and at least one heteroatom within the ring selected from N, O and S. For example there may be 1, 2 or 3 heteroatoms, optionally 1 or 2. Similarly, "C₃₋₈ heterocycloalkyl" refers to a saturated hydrocarbon ring system containing 3, 4, 5, 6,
 15 7 or 8 carbon atoms and "C₅₋₇ heterocycloalkyl" refers to a saturated hydrocarbon ring system containing 5, 6 or 7 carbon atoms. The "C₃₋₈ heterocycloalkyl" may be bonded to the rest of the molecule through any carbon atom or heteroatom. The "C₃₋₈ heterocycloalkyl" may have one or more, e.g. one or two, bonds to the rest of the molecule: these bonds may be through any of the atoms in the ring. For example, the "C₃₋₈ heterocycloalkyl" may be oxirane, aziridine, azetidine,
 20 oxetane, tetrahydrofuran, pyrrolidine, imidazolidine, succinimide, pyrazolidine, oxazolidine, isoxazolidine, thiazolidine, isothiazolidine, piperidine, morpholine, thiomorpholine, piperazine, and tetrahydropyran.

[0080] The term "C₃₋₁₄ heterocycloalkyl" refers to an unsaturated hydrocarbon ring system containing 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 or 14 carbon atoms and at least one heteroatom within
 25 the ring selected from N, O and S. For example there may be 1, 2 or 3 heteroatoms, optionally 1 or 2. Similarly, "C₃₋₈ heterocycloalkyl" refers to an unsaturated hydrocarbon ring system containing 3, 4, 5, 6, 7 or 8 carbon atoms and "C₅₋₇ heterocycloalkyl" refers to an unsaturated hydrocarbon ring system containing 5, 6 or 7 carbon atoms. The "C₃₋₈ heterocycloalkenyl" may be bonded to the rest of the molecule through any carbon atom or heteroatom. The "C₃₋₈ heterocycloalkenyl" may have
 30 one or more, e.g. one or two, bonds to the rest of the molecule: these bonds may be through any of the atoms in the ring. For example, the "C₃₋₈ heterocycloalkyl" may be tetrahydropyridine, dihydropyran, dihydrofuran, pyrroline.

[0081] The term "aryl" refers to an aromatic hydrocarbon ring system. The ring system has 4n + 2 electrons in a conjugated π system within a ring where all atoms contributing to the conjugated π
 35 system are in the same plane. The aryl group may be C₆₋₁₄ aryl, optionally C₆₋₁₀ aryl or C₆ aryl, wherein a C₆₋₁₄ aryl is a ring system with 6, 7, 8, 9, 10, 11, 12, 13 or 14 ring carbons within a single ring or within a fused ring system. For example, the "aryl" may be phenyl and naphthyl. The aryl system itself may be substituted with other groups.

- [0082]** The term “heteroaryl” refers to an aromatic hydrocarbon ring system with at least one heteroatom within a single ring or within a fused ring system, selected from O, N and S. The heteroaryl group may be C₅₋₁₄ heteroaryl, optionally C₅₋₁₀ heteroaryl or C₅₋₆ heteroaryl, wherein a C₅₋₁₄ heteroaryl is a ring system with 5, 6, 7, 8, 9, 10, 11, 12, 13 or 14 ring atoms with at least one heteroatom within a single ring or within a fused ring system, selected from O, N and S, for example there may be 1, 2 or 3 heteroatoms, optionally 1 or 2. The ring or ring system has 4n +2 electrons in a conjugated π system where all atoms contributing to the conjugated π system are in the same plane. For example, the “heteroaryl” may be imidazole, thiene, furane, thianthrene, pyrrol, benzimidazole, pyrazole, pyrazine, pyridine, pyrimidine and indole.
- 5
- [0083]** The term “alkaryl” refers to an aryl group, as defined above, bonded to a C₁₋₄ alkyl, where the C₁₋₄ alkyl group provides attachment to the remainder of the molecule.
- 10
- [0084]** The term “alkheteroaryl” refers to a heteroaryl group, as defined above, bonded to a C₁₋₄ alkyl, where the alkyl group provides attachment to the remainder of the molecule.
- [0085]** The term “halogen” herein includes reference to F, Cl, Br and I. Halogen may be Cl.
- 15 Halogen may be F.
- [0086]** A bond terminating in a “” represents that the bond is connected to another atom that is not shown. A bond terminating inside a cyclic structure and not terminating at an atom of the ring structure represents that the bond may be connected to any of the atoms in the ring structure where allowed by valency.
- 20
- [0087]** Where a moiety is substituted, it may be substituted at any point on the moiety where chemically possible and consistent with atomic valency requirements. The moiety may be substituted by one or more substituents, e.g. 1, 2, 3 or 4 substituents; optionally there are 1 or 2 substituents on a group. Where there are two or more substituents, the substituents may be the same or different. The substituent(s) may be selected from: OH, NHR^a, amidino, guanidino, hydroxyguanidino, formamidino, isothioureido, ureido, mercapto, C(O)H, acyl, acyloxy, carboxy, sulfo, sulfamoyl, carbamoyl, cyano, azo, nitro, halo, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkyl, C₃₋₈ cycloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, heteroaryl or alkaryl. Where the group to be substituted is an alkyl group the substituent may be =O. Where the moiety is substituted with two or more substituents and two of the substituents are adjacent the adjacent substituents may form a C₄₋₈ ring along with the atoms of the moiety on which the substituents are substituted, wherein the C₄₋₈ ring is a saturated or unsaturated hydrocarbon ring with 4, 5, 6, 7, or 8 carbon atoms or a saturated or unsaturated hydrocarbon ring with 4, 5, 6, 7, or 8 carbon atoms and 1, 2 or 3 heteroatoms.
- 25
- 30
- [0088]** Substituents are only present at positions where they are chemically possible, the person skilled in the art being able to decide (either experimentally or theoretically) without undue effort which substitutions are chemically possible and which are not.
- 35

[0089] By "acyl" is meant an organic radical derived from, for example, an organic acid by the removal of the hydroxyl group, e.g. a radical having the formula R-C(O)-, where R may be selected from H, C₁₋₆ alkyl, C₃₋₈ cycloalkyl, phenyl, benzyl or phenethyl group, eg R is H or C₁₋₃ alkyl. In one embodiment acyl is alkyl-carbonyl. Examples of acyl groups include, but are not limited to, formyl, acetyl, propionyl and butyryl. A particular acyl group is acetyl.

[0090] All stereoisomers of the compounds of the invention are contemplated. The compounds of the invention may be present as a single stereoisomer or may be mixtures of stereoisomers, for example racemic mixtures, and other enantiomeric mixtures, and diastereomeric mixtures. Where the mixture is a mixture of enantiomers the enantiomeric excess may be any of those disclosed above. Where the compound is a single stereoisomer the compound may still contain other diastereoisomers or enantiomers as impurities. Hence a single stereoisomer does not necessarily have an enantiomeric excess (e.e.) or diastereomeric excess (d.e.) of 100% but could have an e.e. or d.e. of about at least 85%.

[0091] The invention contemplates pharmaceutically acceptable salts of the compounds of formula (I). These may include the acid addition and base salts of the compounds. In addition the invention contemplates solvates of the compounds. These may be hydrates or other solvated forms of the compound.

[0092] Suitable acid addition salts are formed from acids which form non-toxic salts. Examples include the acetate, aspartate, benzoate, besylate, bicarbonate/carbonate, bisulphate/sulphate, borate, camsylate, citrate, edisylate, esylate, formate, fumarate, gluceptate, gluconate, glucuronate, hexafluorophosphate, hibenzate, hydrochloride/chloride, hydrobromide/bromide, hydroiodide/iodide, isethionate, lactate, malate, maleate, malonate, mesylate, methylsulphate, naphthylate, 1,5-naphthalenedisulfonate, 2-napsylate, nicotinate, nitrate, orotate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, saccharate, stearate, succinate, tartrate, tosylate and trifluoroacetate salts.

[0093] Suitable base salts are formed from bases which form non-toxic salts. Examples include the aluminium, arginine, benzathine, calcium, choline, diethylamine, diolamine, glycine, lysine, magnesium, meglumine, olamine, potassium, sodium, tromethamine and zinc salts. Hemisalts of acids and bases may also be formed, for example, hemisulphate and hemicalcium salts. For a review on suitable salts, see "Handbook of Pharmaceutical Salts: Properties, Selection, and Use" by Stahl and Wermuth (Wiley-VCH, Weinheim, Germany, 2002).

[0094] Preferably the salt is an acid addition salt. The salts may be formate or hydrochloride.

[0095] For example, pharmaceutically acceptable salts of compounds of formula (I) may be prepared:

(i) by reacting the compound of formula (I) with the desired acid or base;

- (ii) by removing an acid- or base-labile protecting group from a suitable precursor of the compound of formula (I) or by ring-opening a suitable cyclic precursor, for example, a lactone or lactam, using the desired acid or base; or
- (iii) by converting one salt of the compound of formula (I) to another by reaction with an appropriate acid or base or by means of a suitable ion exchange column.

[0096] All three reactions are typically carried out in solution. The resulting salt may precipitate out and be collected by filtration or may be recovered by evaporation of the solvent. The degree of ionisation in the resulting salt may vary from completely ionised to almost non-ionised.

[0097] The compounds of the invention may exist in both unsolvated and solvated forms. The term 'solvate' is used herein to describe a molecular complex comprising the compound of the invention and a stoichiometric amount of one or more pharmaceutically acceptable solvent molecules, for example, ethanol. The term 'hydrate' is employed when said solvent is water.

[0098] Included within the scope of the invention are complexes such as clathrates, drug-host inclusion complexes wherein, in contrast to the aforementioned solvates, the drug and host are present in stoichiometric or non-stoichiometric amounts. Also included are complexes of the drug containing two or more organic and/or inorganic components which may be in stoichiometric or non-stoichiometric amounts. The resulting complexes may be ionised, partially ionised, or non-ionised. For a review of such complexes, see J Pharm Sci, 64 (8), 1269-1288 by Halebian (August 1975).

[0099] Hereinafter all references to compounds of any formula include references to salts, solvates and complexes thereof and to solvates and complexes of salts thereof.

[00100] The compounds of the invention include compounds of a number of formula as herein defined, including all polymorphs and crystal habits thereof, prodrugs and isomers thereof (including optical, geometric and tautomeric isomers) as hereinafter defined and isotopically-labeled compounds of the invention.

[00101] The compounds of the present invention may exist as a mixture of enantiomers depending on the synthetic procedure used. The enantiomers can be separated by conventional techniques known in the art. Thus the invention covers individual enantiomers as well as mixtures thereof.

[00102] For some of the steps of the process of preparation of the compounds of formula (I), it may be necessary to protect potential reactive functions that are not wished to react, and to cleave said protecting groups in consequence. In such a case, any compatible protecting radical can be used. In particular methods of protection and deprotection such as those described by T.W. GREENE (Protective Groups in Organic Synthesis, A. Wiley- Interscience Publication, 1981) or by P. J. Kocienski (Protecting groups, Georg Thieme Verlag, 1994), can be used. All of the above reactions and the preparations of novel starting materials used in the preceding methods are conventional and appropriate reagents and reaction conditions for their performance or preparation

as well as procedures for isolating the desired products will be well-known to those skilled in the art with reference to literature precedents and the examples and preparations hereto.

[00103] Also, the compounds of the present invention as well as intermediates for the preparation thereof can be purified according to various well-known methods, such as for example
5 crystallization or chromatography.

[00104] The method of treatment or the compound of the invention may be applied as a sole therapy or be a combination therapy with an additional active agent. Optionally, the additional active agent may be an anti-tumour agent selected from the list below.

[00105] The method of treatment or the compound for use in the treatment of cancer, for example
10 sarcoma, carcinoma, blastoma, lymphoma and leukemia as defined hereinbefore may be applied as a sole therapy or be a combination therapy with an additional active agent. Optionally, the additional active agent may be an anti-tumour agent selected from the list below.

[00106] The method of treatment or the compound for use in the treatment of cancer, for example
15 sarcoma, carcinoma, blastoma, lymphoma and leukemia may involve, in addition to the compound of the invention, conventional surgery or radiotherapy or chemotherapy. Such chemotherapy may include one or more of the following specific anti-tumour agents listed below or anti-tumour agents from one or more of the categories of listed below:-

(i) antiproliferative/antineoplastic drugs and combinations thereof, such as alkylating agents
20 (for example cis-platin, oxaliplatin, carboplatin, cyclophosphamide, nitrogen mustard, bendamustin, melphalan, chlorambucil, busulphan, capecitabine, temozolamide, ifosamide, mitobronitol, carboquone, thiotepa, ranimustine, nimustine, AMD-473, altretamine, AP-5280, apaziquone, brostallicin, carmustine, estramustine, fotemustine, gulfosfamide, KW-2170, mafosfamide, mitolactol, etaplatin, lobaplatin, nedaplatin, strrplatin and nitrosoureas); antimetabolites (for example gemcitabine and antifolates such as fluoropyrimidines like 5-fluorouracil and tegafur, raltitrexed,
25 methotrexate, pemetrexed, cytosine arabinoside, 6-mercaptopurine riboside, leucovarin, UFT, doxifluridine, carmoflur, cytarabine, encitabine S-1, 5-azacitidine, cepecitabine, clofarabine, decitabine, eflornithine, ethynlcytidine, TS-1, nelarabine, nolatrexed, ocosfate, pelitrexol, triapine, trimetrexate, vidarabine, and hydroxyurea); antibiotics (for example anthracyclines like adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin,
30 mithramycin, aclarubicin, actinomycin D, amrubicin, annamycin, elsamitrucin, galarubicin, nemorubicin, neocarzinostatin, peplomycin, piarubicin, rebeccamycin, stimalamer, streptozocin, valrubicin and zinostatin); antimitotic agents (for example vinca alkaloids like vincristine, vinblastine, vindesine and vinorelbine and taxoids like taxol, docetaxol (Taxotere), and paclitaxel and polokinase inhibitors); proteasome inhibitors, for example carfilzomib and bortezomib; interferon
35 therapy; and topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, aclarubicin, amonafide, belotecan, 10-hydroxycamptothecin, 9-aminocamptothecin, diflomotecan, edotecarin, exatecan, gimatecan, lurtotecan, pirarubicin, pixantrone, rubitecan,

sobuzoxane, SN-38, tafluposide, amsacrine, topotecan, mitoxantrone and camptothecin) and adjuvants used in combination with these therapies, for example folinic acid;

- (ii) cytostatic agents such as antioestrogens (for example tamoxifen, fulvestrant, toremifene, raloxifene, droloxifene, lasofoxifene and idoxifyfene), antiandrogens (for example bicalutamide, mifepristone, flutamide, nilutamide, casodex and cyproterone acetate), LHRH antagonists or LHRH agonists (for example goserelin, leuprorelin and buserelin), progestogens (for example megestrol acetate), aromatase inhibitors (for example as anastrozole, letrozole, vorazole and exemestane) and inhibitors of 5 α -reductase such as finasteride;
- (iii) anti-invasion agents, for example dasatinib and bosutinib (SKI-606), and metalloproteinase inhibitors, inhibitors of urokinase plasminogen activator receptor function or antibodies to Heparanase;
- (iv) inhibitors of growth factor function: for example such inhibitors include growth factor antibodies and growth factor receptor antibodies, for example the anti-erbB2 antibody trastuzumab [Herceptin™], the anti-EGFR antibody panitumumab, the anti-erbB1 antibody cetuximab, tyrosine kinase inhibitors, for example inhibitors of the epidermal growth factor family (for example EGFR family tyrosine kinase inhibitors such as gefitinib, erlotinib and 6-acrylamido-*N*-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)-quinazolin-4-amine (CI 1033), erbB2 tyrosine kinase inhibitors such as lapatinib); ErbB2 inhibitors (for example GW-28297, Herceptin, 2C4, pertuzumab, TAK-165, GW-572016, AR-209, and 2B-1); inhibitors of the hepatocyte growth factor family; inhibitors of the insulin growth factor family; modulators of protein regulators of cell apoptosis (for example Bcl-2 inhibitors); inhibitors of the platelet-derived growth factor family such as imatinib and/or nilotinib (AMN107); inhibitors of serine/threonine kinases (for example Ras/Raf signalling inhibitors such as farnesyl transferase inhibitors, for example sorafenib, tipifarnib and lonafarnib), inhibitors of cell signalling through MEK and/or AKT kinases, c-kit inhibitors, abl kinase inhibitors, PI3 kinase inhibitors, Plt3 kinase inhibitors, CSF-1R kinase inhibitors, IGF receptor, kinase inhibitors; aurora kinase inhibitors and cyclin dependent kinase inhibitors such as CDK2 and/or CDK4 inhibitors;
- (v) antiangiogenic agents such as those which inhibit the effects of vascular endothelial growth factor, [for example the anti-vascular endothelial cell growth factor antibody bevacizumab (Avastin™); COXII inhibitors (for example Arcoxia (etoricoxib), Bextra (valdecoxib), Celebrex (celecoxib), Paracoxib Vioxx (rofecoxib)); MMP inhibitors (for example MMP-2 inhibitors, MMP-9 inhibitors, AG-3340, RO 32-3555, and RS 13-0830); thalidomide; lenalidomide; and for example, a VEGF receptor (for example SU-11248, SU-5416, SU-6668, and angiozyme) tyrosine kinase inhibitor (such as vandetanib, vatalanib, sunitinib, axitinib and pazopanib); acitretin; fenretinide; zoledronic acid; angiostatin; aplidine; cilengtide; A-4; endostatin; halofuginome; rebimastat; removab; revlimid; squalamine; ukrain; and vitaxincombretastatin;
- (vi) gene therapy approaches, including for example approaches to replace aberrant genes such as aberrant p53 or aberrant BRCA1 or BRCA2;

- (vii) immunotherapy approaches, including for example antibody therapy such as alemtuzumab, rituximab, ibritumomab tiuxetan (Zevalin®) and ofatumumab; interferons such as interferon α ; interleukins such as IL-2 (aldesleukin); interleukin inhibitors for example IRAK4 inhibitors; cancer vaccines including prophylactic and treatment vaccines such as HPV vaccines, for example Gardasil, Cervarix, Oncophage and Sipuleucel-T (Provenge); interferons, such as interferon alpha, interferon alpha-2a, interferon alpha-2b, interferon beta, interferon gamma-1a, and interferon gamma-n; PF3512676; Filgrastim (Neupogen); lentinan; sizofilan; TheraCys; ubenimex; WF-10; BAM-002; dacarbazine; daclizumab; denileukin; gemtuzumab; ozogamicin; imiquimod; lenograstim; melanoma vaccine (Corixa); molgramostim; OncoVAX- CL; sargramostim; tasonermin; tecleukin; thymalasin; tositumomab; Virulizin; Z-100; epratuzumab; mitumomab; oregovomab; pentumomab; and toll-like receptor modulators for example TLR-7 or TLR-9 agonists; and
- (viii) cytotoxic agents for example fludarabine (fludara), cladribine, pentostatin (Nipent™), edotecarin, SU-11248, paclitaxel, Erbitux, and irinotecan;
- (ix) steroids such as corticosteroids, including glucocorticoids and mineralocorticoids, for example aclometasone, aclometasone dipropionate, aldosterone, amcinonide, beclomethasone, beclomethasone dipropionate, betamethasone, betamethasone dipropionate, betamethasone sodium phosphate, betamethasone valerate, budesonide, clobetasone, clobetasone butyrate, clobetasol propionate, cloprednol, cortisone, cortisone acetate, cortivazol, deoxycortone, desonide, desoximetasone, dexamethasone, dexamethasone sodium phosphate, dexamethasone isonicotinate, difluorocortolone, flucorolone, flumethasone, flunisolide, fluocinolone, fluocinolone acetone, fluocinonide, fluocortin butyl, fluorocortisone, fluorocortolone, fluocortolone caproate, fluocortolone pivalate, fluorometholone, fluprednidene, fluprednidene acetate, flurandrenolone, fluticasone, fluticasone propionate, halcinonide, hydrocortisone, hydrocortisone acetate, hydrocortisone butyrate, hydrocortisone aceponate, hydrocortisone buteprate, hydrocortisone valerate, icomethasone, icomethasone enbutate, meprednisone, methylprednisolone, mometasone paramethasone, mometasone furoate monohydrate, prednicarbate, prednisolone, prednisone, tixocortol, tixocortol pivalate, triamcinolone, triamcinolone acetone, triamcinolone alcohol and their respective pharmaceutically acceptable derivatives. A combination of steroids may be used, for example a combination of two or more steroids mentioned in this paragraph;
- (x) targeted therapies, for example PI3Kd inhibitors, for example idelalisib and perifosine;
- (xi) and additional active agents such as estramustine phosphate, fludarabine phosphate, farnesyl transferase inhibitors, PDGFr, streptozocin, strontium-89, suramin, hormonal therapies (for example Lupron, doxercalciferol, fadrozole, formestane and trelstar), supportive care products (for example, Filgrastim (Neupogen), ondansetron (Zofran), Fragmin, Procrit, Aloxi and Emend), biological response modifiers (e.g. Krestin, lentinan, sizofiran, picibanil and ubenimex), alitretinoin, ampligen, atrasenten, bexarotene, bosentan, calcitriol, exisulind, fotemustine, ibandronic acid, miltefosine, l-asparaginase, procarbazine, dacarbazine, hydroxycarbamide, pegaspargase, tazarotne, TLK-286, Velcade, Tarceva, tretinoin.

- [00107]** The combination therapies defined above may be achieved by way of the simultaneous, sequential or separate dosing of the individual components of the treatment. Such combination products may employ the compounds of this invention within a therapeutically effective dosage range and the other pharmaceutically-active agent within its approved dosage range.
- 5 **[00108]** According to a further aspect of the invention there is provided a pharmaceutical product comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof as defined hereinbefore and an additional active agent for the treatment of a condition which is modulated by the Hedgehog signalling pathway. The additional active agent may be an anti-tumour agent as defined hereinbefore.
- 10 **[00109]** In an embodiment there is provided a pharmaceutical product comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof as defined hereinbefore and an additional active agent for the treatment of a condition which is modulated by Smo. The additional active agent may be an anti-tumour agent as defined hereinbefore.
- 15 **[00110]** According to a further aspect of the invention there is provided a method of treatment of a condition modulated by the Hedgehog signalling pathway comprising administering a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof simultaneously, sequentially or separately with an additional anti-tumour agent, as defined hereinbefore, to a patient in need thereof.
- [00111]** In an embodiment the condition is a condition modulated by Smo.
- 20 **[00112]** According to a further aspect of the invention there is provided a compound of formula (I), or a pharmaceutically acceptable salt thereof for use simultaneously, sequentially or separately with an additional anti-tumour agent as defined hereinbefore, in the treatment of a condition modulated by the Hedgehog signalling pathway. In an embodiment the condition is a condition modulated by Smo. The condition may be any condition described in this specification.
- 25 **[00113]** According to another aspect of the invention there is provided a use of the compound of formula (I) in combination with an anti-tumour agent as hereinbefore described. The compound of formula (I) may be used simultaneously, sequentially or separately with the additional anti-tumour agent. The use may be in a single combination product comprising the compound of formula (I) and the anti-tumour agent.
- 30 **[00114]** According to a further aspect there is provided a method of providing a combination product, wherein the method comprises providing a compound of formula (I) simultaneously, sequentially or separately with an anti-tumour agent, as defined hereinbefore. The method may comprise combining the compound of formula (I) and the anti-tumour agent in a single dosage form. Alternatively the method may comprise providing the anti-tumour agent as separate dosage forms.
- 35 **[00115]** The condition modulated by the Hedgehog signalling pathway or Smo described above may be cancer, for example sarcoma, carcinoma, blastoma, lymphoma and leukemia. More specifically the condition modulated by Smo may be selected from: cancer, sarcoma, carcinoma, blastoma, lymphoma and leukemia. Specific conditions treatable by the inhibition of the Hedgehog

signalling pathway or Smo may be selected from: basal cell carcinoma, medulloblastoma, rhabdomyosarcoma, chondrosarcoma, melanoma, small-cell lung cancer, non-small-cell lung cancer, B-cell lymphoma, multiple myeloma, brain cancer, esophagus cancer, breast cancer, ovarian cancer, stomach cancer, colorectal cancer, liver cancer, kidney cancer, head and neck cancer, mesothelioma, soft tissue sarcomas, bone sarcomas, testicular cancer, prostate cancer, pancreatic cancer, bone cancer, bone metastasis, acute leukemia, chronic leukemia, glioma, hodgkin's disease, cutaneous melanoma, bladder cancer, endocrine system cancer, parathyroid gland cancer, thyroid gland cancer, cervical cancer, endometrium cancer, ovarian cancer, skin cancer, renal cell carcinoma, pituitary adenoma, spinal axis tumours, uterine cancer, gastric cancer and biliary tract cancer.

[00116] Conditions also treatable by the inhibition of the Hedgehog signalling pathway or Smo may be selected benign prostatic hyperplasia, psoriasis and osteoporosis.

[00117] The condition modulated by the Hedgehog signalling pathway or Smo described above may be modulated by inhibiting stem cell production, inhibiting stem cell renewal, and/or modulating stem cell differentiation. In the above embodiments the stem cells may be cancer stem cells which may also be referred to as tumorigenic stem cells or stem cell like tumorigenic cells.

[00118] Compounds of the invention may exist in a single crystal form or in a mixture of crystal forms or they may be amorphous. Thus, compounds of the invention intended for pharmaceutical use may be administered as crystalline or amorphous products. They may be obtained, for example, as solid plugs, powders, or films by methods such as precipitation, crystallization, freeze drying, or spray drying, or evaporative drying. Microwave or radio frequency drying may be used for this purpose.

[00119] For the above-mentioned compounds of the invention the dosage administered will, of course, vary with the compound employed, the mode of administration, the treatment desired and the disorder indicated. For example, if the compound of the invention is administered orally, then the daily dosage of the compound of the invention may be in the range from 0.01 micrograms per kilogram body weight ($\mu\text{g}/\text{kg}$) to 100 milligrams per kilogram body weight (mg/kg).

[00120] A compound of the invention, or pharmaceutically acceptable salt thereof, may be used on their own but will generally be administered in the form of a pharmaceutical composition in which the compounds of the invention, or pharmaceutically acceptable salt thereof, is in association with a pharmaceutically acceptable adjuvant, diluent or carrier. Conventional procedures for the selection and preparation of suitable pharmaceutical formulations are described in, for example, "Pharmaceuticals - The Science of Dosage Form Designs", M. E. Aulton, Churchill Livingstone, 1988.

[00121] Depending on the mode of administration of the compounds of the invention, the pharmaceutical composition which is used to administer the compounds of the invention will preferably comprise from 0.05 to 99 %w (per cent by weight) compounds of the invention, more preferably from 0.05 to 80 %w compounds of the invention, still more preferably from 0.10 to 70 %w

compounds of the invention, and even more preferably from 0.10 to 50 %w compounds of the invention, all percentages by weight being based on total composition.

[00122] The pharmaceutical compositions may be administered topically (e.g. to the skin) in the form, e.g., of creams, gels, lotions, solutions, suspensions, or systemically, e.g. by oral
5 administration in the form of tablets, capsules, syrups, powders or granules; or by parenteral administration in the form of a sterile solution, suspension or emulsion for injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion); by rectal administration in the form of suppositories; or by inhalation in the form of an aerosol.

[00123] For oral administration the compounds of the invention may be admixed with an adjuvant
10 or a carrier, for example, lactose, saccharose, sorbitol, mannitol; a starch, for example, potato starch, corn starch or amylopectin; a cellulose derivative; a binder, for example, gelatine or polyvinylpyrrolidone; and/or a lubricant, for example, magnesium stearate, calcium stearate, polyethylene glycol, a wax, paraffin, and the like, and then compressed into tablets. If coated tablets are required, the cores, prepared as described above, may be coated with a concentrated sugar
15 solution which may contain, for example, gum arabic, gelatine, talcum and titanium dioxide. Alternatively, the tablet may be coated with a suitable polymer dissolved in a readily volatile organic solvent.

[00124] For the preparation of soft gelatine capsules, the compounds of the invention may be admixed with, for example, a vegetable oil or polyethylene glycol. Hard gelatine capsules may
20 contain granules of the compound using either the above-mentioned excipients for tablets. Also liquid or semisolid formulations of the compound of the invention may be filled into hard gelatine capsules. Liquid preparations for oral application may be in the form of syrups or suspensions, for example, solutions containing the compound of the invention, the balance being sugar and a mixture of ethanol, water, glycerol and propylene glycol. Optionally such liquid preparations may
25 contain colouring agents, flavouring agents, sweetening agents (such as saccharine), preservative agents and/or carboxymethylcellulose as a thickening agent or other excipients known to those skilled in art.

[00125] For intravenous (parenteral) administration the compounds of the invention may be administered as a sterile aqueous or oily solution.

[00126] The size of the dose for therapeutic purposes of compounds of the invention will naturally
30 vary according to the nature and severity of the conditions, the age and sex of the animal or patient and the route of administration, according to well known principles of medicine.

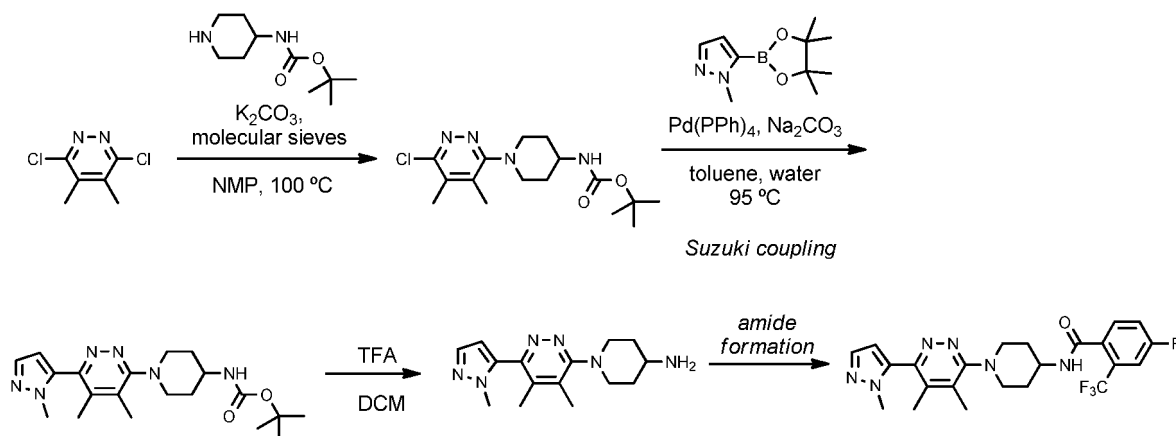
[00127] Dosage levels, dose frequency, and treatment durations of compounds of the invention are expected to differ depending on the formulation and clinical indication, age, and co-morbid
35 medical conditions of the patient. The standard duration of treatment with compounds of the invention is expected to vary between one and seven days for most clinical indications. It may be necessary to extend the duration of treatment beyond seven days in instances of recurrent

infections or infections associated with tissues or implanted materials to which there is poor blood supply including bones/joints, respiratory tract, endocardium, and dental tissues.

EXAMPLES AND SYNTHESIS

[00128] As used herein the following terms have the meanings given: “Boc” refers to tert-butoxycarbonyl; BOP refers to (Benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate; “CV” refers to column volumes, “DCM” refers to dichloromethane; “DIPEA” refers to N,N-Diisopropylethylamine; DME refers to Dimethoxyethane “LCMS” refers to liquid chromatography/mass spectrometry; “MIM” refers to monoisotopic mass; “min” refers to minutes; “NMP” refers to N-methylpyrrolidinone; “TLC” refers to thin layer chromatography; “Rf” refers to Retention factor; “RT” refers to retention time; “SCX” refers to strong cation exchange; “TFA” refers to trifluoroacetic acid; “THF” refers to tetrahydrofuran; and “TBME” refers to tert-Butyl methyl ether.

[00129] The compounds of the invention may be synthesised by analogy with the following reaction route.



[00130] The steps within the route shown above may be performed in the order shown above or in a different order. For example, as the skilled person would appreciate, the Suzuki coupling could be carried out after the substitution reaction or after the amide bond formation etc. Protecting groups may be present or absent as necessary. For example a nitrogen atom may be protected or unprotected.

[00131] Solvents, reagents and starting materials were purchased from commercial vendors and used as received unless otherwise described. All reactions were performed at room temperature unless otherwise stated. Compound identity and purity confirmations were performed by LCMS UV using a Waters Acquity SQ Detector 2 (ACQ-SQD2#LCA081). The diode array detector wavelength was 254nm and the MS was in positive and negative electrospray mode (m/z : 150-800). A $2\mu\text{L}$ aliquot was injected onto a guard column ($0.2\mu\text{m} \times 2\text{ mm}$ filters) and UPLC column (C18, $50 \times 2.1\text{ mm}$, $< 2\mu\text{m}$) in sequence maintained at $40\text{ }^\circ\text{C}$. The samples were eluted at a flow rate of 0.6 mL/min with a mobile phase system composed of A (0.1% (v/v) Formic Acid in Water) and B (0.1% (v/v) Formic Acid in Acetonitrile) according to the gradients outlined in **Table 1** below. Retention times RT are reported in minutes.

Method 1		
Time (min)	%A	%B
0	95	5
1.1	95	5
6.1	5	95
7	5	95
7.5	95	5
8	95	5
Method 2		
Time (min)	%A	%B
0	95	5
0.3	95	5
2	5	95
2.6	95	5
3	95	5

Table 1

[00132] NMR was also used to characterise final compounds. NMR spectra were obtained on a Bruker AVIII 400 Nanobay with 5mm BBFO probe. Optionally, compound R_f values on silica thin layer chromatography (TLC) plates were measured.

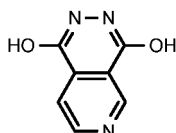
- 5 **[00133]** Compound purification was performed by flash column chromatography on silica or by preparative LCMS. LCMS purification was performed using a Waters 3100 Mass detector in positive and negative electrospray mode (*m/z*: 150-800) with a Waters 2489 UV/Vis detector. Samples were eluted at a flow rate of 20mL/min on a XBridge™ prep C18 5μM OBD 19x100mm column with a mobile phase system composed of A (0.1% (v/v) Formic Acid in Water) and B (0.1% (v/v) Formic Acid in Acetonitrile) according to the gradient outlined in **Table 2** below.
- 10

Time (min)	%A	%B
0	90	10
1.5	90	10
11.7	5	95
13.7	5	95
14	90	90
15	90	90

Table 2

[00134] Chemical names in this document were generated using mol2nam - Structure to Name Conversion by OpenEye Scientific Software. Starting materials were purchased from commercial sources or synthesised according to literature procedures.

- 15 **[00135]** Certain starting materials in the synthesis of compounds of formula (I) can be produced by the following procedures:

[00136] Procedure A**Pyrido[3,4-*d*]pyridazine-1,4-diol**

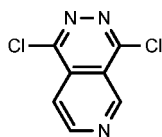
Pyridine-3,4-dicarboxylic acid (3.10g, 18.6mmol) and acetic anhydride (7.0mL, 74.2mmol) were added to a 50mL round bottomed flask and heated to reflux at 140°C. The white suspension turned into a black solution. The reaction was heated at this temperature for 3 hours. The reaction was cooled and the acetic anhydride was taken off by rotary evaporation to afford crude 3,4-
 5 pyridinedicarboxylic anhydride (2.68g, 18.0mmol, 97%) as brown crystals which was taken onto the next step without further purification.

To a round bottomed flask were added 3,4-pyridinedicarboxylic anhydride (690mg, 4.6mmol) and acetic acid (8.9mL). To this was added hydrazine hydrate (1.6mL, 18.5mmol) dropwise with ice bath cooling. The yellow suspension was refluxed at 100°C overnight. Analytical LCMS indicated
 10 formation of product and the reaction was cooled. The resultant cream solid was filtered and washed with water. The product was then dried by rotary evaporation to afford pyrido[3,4-d]pyridazine-1,4-diol (600mg, 3.7mmol, 79.5%).

¹H NMR (400MHz, d6 DMSO) δ/ppm: 11.9 (s(br), 2H), 9.34 (s(br), 1H), 9.03 (d, *J* 5.3Hz, 1H), 7.90 (d, *J* 5.3Hz, 1H) .

15 MS Method 2: RT: 0.54min, ES⁺ m/z 164.0 [M+H]⁺.

1,4-Dichloropyrido[3,4-*d*]pyridazine



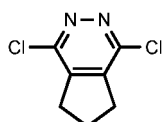
Pyrido[3,4-*d*]pyridazine-1,4-diol (1.83g, 11.2mmol) and phosphorus oxychloride (8.4mL, 89.7mmol) were added to a round bottomed flask. To this was added DIPEA (2.0mL, 11.2mmol) slowly. The
 20 suspension was then heated for 1 hour at 100°C. The reaction turned into a brown solution. The phosphorus oxychloride was then removed by rotary evaporator. The resulting brown residue was dissolved in DCM and added dropwise to a mixture of ice and saturated NaHCO₃ solution (aq). Saturated NaHCO₃ solution (aq) was added until the aqueous layer was neutral. The organic and aqueous layers were separated and the aqueous layer was further extracted with DCM (500mL).
 25 The organic layers were combined and dried (MgSO₄) and then concentrated *in vacuo* to afford 1,4-dichloropyrido[3,4-*d*]pyridazine (1.74g, 8.7mmol, 77.6%).

¹H NMR (400MHz, CDCl₃) δ/ppm: 9.78 (d, *J* 0.9Hz, 1H), 9.27 (d, *J* 5.7Hz, 1H), 8.09 (dd, *J* 5.7Hz, 0.9Hz, 1H).

MS Method 2: RT: 1.16min, ES⁺ m/z 200.0 [M+H]⁺.

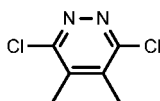
30 Similarly prepared were:

1,4-Dichloro-6,7-dihydro-5*H*-cyclopenta[*d*]pyridazine



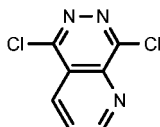
^1H NMR (400MHz, CDCl_3) δ /ppm: 3.13 (t, J 7.8Hz, 2H), 2.27 (m, J 7.8Hz, 4H).

3,6-Dichloro-4,5-dimethyl-pyridazine



^1H NMR (400MHz, CDCl_3) δ /ppm: 2.46 (s, 6H).

5 5,8-dichloropyrido[2,3-d]pyridazine

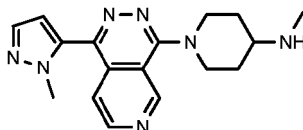


^1H NMR (400MHz, CDCl_3) δ /ppm: 9.41 (dd, J 4.3, 1.7Hz, 1H), 8.64 (dd, J 8.4, 1.7Hz, 1H), 8.02 (dd, J 8.4, 4.3Hz, 1H).

MS Method 2: RT: 1.15min, ES^+ m/z 200.0[M+H] $^+$.

10 [00137] Procedure B

***N*-Methyl-1-[1-(2-methylpyrazol-3-yl)pyrido[3,4-d]pyridazin-4-yl]piperidin-4-amine**



To a round bottomed flask were added *tert*-butyl piperidin-4-ylmethylcarbamate (0.29mL, 55mmol) ,
 1,4-dichloropyrido[3,4-*d*]pyridazine (13.48mL, 50mmol) , *N,N*-diisopropylethylamine (26mL,
 15 150mmol) , NMP (50mL) and heated to 100°C for 1 hour. The reaction was diluted with EtOAc and
 washed with water (5x100mL). The organic layer was dried over sodium sulphate, filtered and
 concentrated *in vacuo*. The resulting residue was purified by silica flash chromatography using 30%
 EtOAc in heptane using a slow isocratic elution and concentrated *in vacuo* to afford the major
 regioisomer *tert*-butyl *N*-[1-(1-chloropyrido[3,4-*d*]pyridazin-4-yl)-4-piperidyl]-*N*-methyl-carbamate
 20 (1.1g, 2.9mmol, 5.8%, 98% purity). Further mixed fractions of lower purity were also obtained.

^1H NMR (400MHz, CDCl_3) δ /ppm: 9.46 (s, 1H), 9.03 (d, J 5.6Hz, 1H), 7.94 (d, J 5.6Hz, 1H), 4.33
 (m(br), 1H), 4.22-4.12 (d, J 14.6Hz, 2H), 3.29 (t, J 12.5Hz, 2H), 2.83 (s, 3H), 2.11-1.97 (m, 2H), 1.90-
 1.81 (d, J 11.7Hz, 2H), 1.50 (s, 9H).

MS Method 2: RT: 1.73min. m/z 378.9[M+H] $^+$

25 Split between 2x 10-20mL microwave vials was added *tert*-butyl *N*-[1-(1-chloropyrido[3,4-
d]pyridazin-4-yl)-4-piperidyl]-*N*-methyl-carbamate (2.03g, 5.38mmol), toluene (12mL), ethanol
 (8mL), water (4mL), 1-methyl-1H-pyrazole-5-boronic acid, pinacolester (1.57g, 7.53mmol) and
 sodium carbonate (1.09g, 10.8mmol. The mixture was purged with nitrogen for 10 minutes. To the
 reaction vials was then added Palladium (0) tetrakis(triphenylphosphine) (935mg, 0.81mmol) and
 30 the vials were immediately capped and heated in the microwave for 1 hour at 150°C. The contents

of the vials were combined and diluted with EtOAc and partitioned with water. The organic layer was washed with 3x50 mL of water. The organic layer was dried over sodium sulphate, filtered and then concentrated to give a brown oil. The resulting residue was then purified by silica flash chromatography using 0% EtOAc in heptane to 90% ethyl acetate in heptane followed by a slow isocratic elution at 90% ethyl acetate in heptane to afford *tert*-butyl *N*-methyl-*N*-[1-[1-(2-methylpyrazol-3-yl)pyrido[3,4-*d*]pyridazin-4-yl]-4-piperidyl]carbamate (1.50g, 3.54mmol, 65.9%)

¹H NMR (400MHz, CDCl₃) δ/ppm: 9.54 (s, 1H), 8.96 (d, *J*5.7Hz, 1H), 7.87 (d, *J*5.7Hz, 1H), 7.69 (d, *J*2.0Hz, 1H), 6.63 (d, *J*2.0Hz, 1H), 4.49-4.27 (m(br), 3H), 4.12 (s, 3H), 3.38 (t, *J*12.5Hz, 2H), 2.85 (s, 3H), 2.15-2.01 (m, 2H), 1.95-1.87 (m, 2H), 1.57 (s, 3H).

10 MS Method 2: RT: 1.55min. *m/z* 424.4 [M+H]⁺

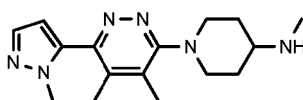
To a round bottomed flask was added *tert*-butyl *N*-methyl-*N*-[1-[1-(2-methylpyrazol-3-yl)pyrido[3,4-*d*]pyridazin-4-yl]-4-piperidyl]carbamate (1.50g, 3.54mmol) and trifluoroacetic acid (4. mL, 52mmol) and stirred at room temperature for 2 hours. The reaction was concentrated *in vacuo* and the resulting red oil was purified by SCX with MeOH washings followed by 2M NH₃ in MeOH to elute the product. The resulting solution was concentrated under reduced pressure to afford *N*-methyl-1-[1-(2-methylpyrazol-3-yl)pyrido[3,4-*d*]pyridazin-4-yl]piperidin-4-amine (947mg, 2.93mmol, 82.7%).

¹H NMR (400MHz, CDCl₃) δ/ppm: 9.53 (d, *J*0.9Hz, 1H), 8.95 (d, *J*5.7Hz, 1H), 7.85 (dd, *J*5.7Hz, 0.9Hz, 1H), 7.69 (d, *J*2.0Hz, 1H), 6.62 (d, *J*2.0Hz, 1H), 4.26-4.18 (m, 2H), 4.11 (s, 3H), 3.42-3.34 (m, 2H), 2.77 (tt, *J* 10.1hz, 4.0Hz, 1H), 2.55 (s, 3H), 2.23-2.14 (m, 2H), 1.79-1.67 (m, 2H).

20 MS Method 2: RT: 0.87min. *m/z* 324.2[M+H]⁺

And similarly prepared was:

1-[4,5-dimethyl-6-(2-methylpyrazol-3-yl)pyridazin-3-yl]-*N*-methyl-piperidin-4-amine



tert-Butyl piperidin-4-ylmethylcarbamate (3.81g, 17.8mmol), 3,6-dichloro-4,5-dimethyl-pyridazine (3.0g, 17.0mmol), NMP (14mL) and *N,N*-Diisopropylethylamine (4.43mL, 25.4mmol) were added to a round bottom flask and heated to 150 °C for 5 h. The mixture was partitioned between EtOAc (100 mL) and 1M Na₂CO₃ aq. (50 mL). The organic layer was washed with 1M Na₂CO₃ aq. (50mL), water (2 x 70mL), brine (70 mL), before passage through a hydrophobic frit and concentrated *in vacuo* to give an orange/brown solid. The crude material was purified by silica flash chromatography using 0% EtOAc in heptane with triethylamine 1% with a gradient increasing to 30% ethyl acetate. Fractions containing product were combined and concentrated *in vacuo* to afford *tert*-butyl *N*-[1-(6-chloro-4,5-dimethyl-pyridazin-3-yl)-4-piperidyl]-*N*-methyl-carbamate (1.8g, 5.1mmol, 30% yield).

¹H NMR (400MHz, CDCl₃) δ/ppm: 4.34-3.84 (m, 1H), 3.56-3.47 (m(br), 2H), 3.00 (t(br), *J*12.0Hz, 2H), 2.78 (s, 3H), 2.31 (s, 3H), 2.25 (s, 3H), 1.93-1.80 (m, 2H), 1.78-1.71 (m(br), 2H), 1.47 (s, 9H).

MS Method 2: RT: 1.88 min, m/z 355.9 [M+H]⁺

The reaction was carried out in 3 x 20mL microwave tubes: 1-methyl-1*H*-pyrazole-5-boronic acid, pinacolester (5.28g, 25.4mmol), *tert*-butyl *N*-[1-(6-chloro-4,5-dimethyl-pyridazin-3-yl)-4-piperidyl]-*N*-methyl-carbamate (6.0g, 16.9mmol), palladium(0) tetrakis(triphenylphosphine) (0.98g, 0.85mmol) were combined in 1,2-dimethoxyethane (30.mL, 16.91mmol) and a solution of potassium hydrophosphate (5.9g, 33.8mmol in 15mL water) was added, The vessels were sealed, the reaction mixture degassed with nitrogen and heated to 120°C in the microwave for 2hrs. Further 1-methyl-1*H*-pyrazole-5-boronic acid, pinacolester (2.14g, 12.7mmol), palladium(0) tetrakis(triphenylphosphine) (0.49g, 0.425mmol) and potassium hydrophosphate (2.85g, 16.9mmol in 7.5mL water) were added and the vessels were resealed, the reaction mixture was again degassed with nitrogen and heated to 120°C in the microwave for 2hrs. The reaction was cooled to room temperature, the organic and aqueous layers were separated and the aqueous layer was extracted with ethyl acetate (x3). The organic layers were combined, dried over brine and sodium sulphate. Filtered and evaporated *in vacuo* to a dark brown gum. . The crude material was purified by silica flash chromatography using 100% heptane with a gradient to 40% ethyl acetate in heptane then an isocratic flow of 40% ethyl acetate in heptane for 4 column volumes before increasing the gradient to 100% ethyl acetate. Fractions containing the product were combined and evaporated *in vacuo* to afford *tert*-butyl *N*-[1-[4,5-dimethyl-6-(2-methylpyrazol-3-yl)pyridazin-3-yl]-4-piperidyl]-*N*-methyl-carbamate (5.2g, 13mmol, 76.8%)

¹H NMR (400MHz, CDCl₃) δ/ppm: 7.56 (d, *J*1.9Hz, 1H), 6.35 (d, *J*1.9Hz, 1H), 4.36-3.93 (m(br), 1H), 3.92 (s, 3H), 3.68-3.61 (d, *J*12.8Hz, 2H), 3.09 (t, *J*12.1Hz, 2H), 2.81 (s, 3H), 2.28 (s, 3H), 2.22 (s, 3H), 1.97-1.85 (m, 2H), 1.83-1.76 (m(br),2H), 1.49 (s, 9H).

MS Method 2: RT: 1.66 min, m/z 401.3 [M+H]⁺

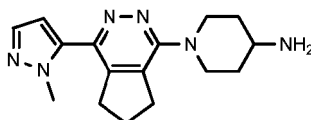
Trifluoroacetic acid (3.0mL, 39.2mmol) was added dropwise to a stirring solution of *tert*-butyl *N*-[1-[4,5-dimethyl-6-(2-methylpyrazol-3-yl)pyridazin-3-yl]-4-piperidyl]-*N*-methyl-carbamate (2.0g, 4.99mmol) in DCM (30mL) at room temperature and the reaction was stirred for 2 h. Further TFA (0.8 mL) was added and the reaction was stirred overnight. The mixture was concentrated *in vacuo* and then the resulting residue was loaded onto a primed SCX-2 cartridge, which was eluted with methanol (5 CV) to remove impurities and then 1M NH₃ / MeOH (2CV) to isolate the product. The latter fraction was concentrated *in vacuo* to afford an orange oil that solidified on standing, 1-[4,5-dimethyl-6-(2-methylpyrazol-3-yl)pyridazin-3-yl]-*N*-methyl-piperidin-4-amine (1.12g,3.73mmol, 74.7% yield) .

¹H NMR (400MHz, CDCl₃) δ/ppm: 7.56 (d, *J*1.9Hz, 1H), 6.35 (d, *J*1.9Hz, 1H),3.91 (s, 3H), 3.61-3.54 (m(br), 2H), 3.03 (t, *J*12.2Hz, 2H), 2.67-2.56 (m, 1H), 2.50 (s, 3H), 2.27 (s, 3H), 2.21 (s, 3H), 2.09-2.02 (m(br), 2H), 1.61-1.49 (m, 2H).

MS Method 2: RT: 0.92 min, m/z 301.2 [M+H]⁺

And similarly prepared were:

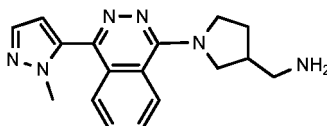
1-[1-(2-Methylpyrazol-3-yl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyridazin-4-yl]piperidin-4-amine



^1H NMR (400MHz, MeOD) δ /ppm: 7.56 (d, J 2.0Hz, 1H), 6.55 (d, 1H), 4.14-4.08 (m(br), 2H), 4.02 (s, 3H), 3.11-3.02 (m, 4H), 3.00-2.92 (m, 3H), 2.17-2.10 (m, 2H), 2.03-1.96 (m, 2H), 1.59-1.48 (m, 2H).

MS Method 2: RT: 0.89min m/z 299.3 $[\text{M}+\text{H}]^+$

5 **racemic [1-[4-(2-methylpyrazol-3-yl)phthalazin-1-yl]pyrrolidin-3-yl]methanamine**

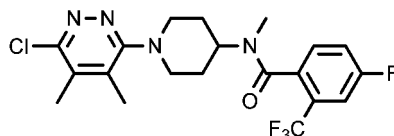


^1H NMR (400MHz, MeOD) δ /ppm: 8.53-8.49 (m, 1H), 7.95-7.81 (m, 3H), 7.69 (d, J 2.0Hz, 1H), 6.63 (d, J 2.0Hz, 1H), 4.17-4.00 (m, 3H), 3.88 (s, 3H), 3.83-3.76 (dd, J 10.8Hz, 8.0Hz, 1H), 2.87 (d, J 7.0Hz, 2H), 2.58-2.46 (m, 1H), 2.33-2.25 (m, 1H), 1.91-1.80 (m, 1H).

10 MS Method 2: RT: 0.60min m/z 309.2 $[\text{M}+\text{H}]^+$

[00138] Procedure C

[00139] *N*-[1-(6-chloro-4,5-dimethyl-pyridazin-3-yl)-4-piperidyl]-4-fluoro-*N*-methyl-2-(trifluoromethyl)benzamide



15 **[00140]** *tert*-Butyl 4-(methylamino)piperidine-1-carboxylate (0.4mL, 1.8mmol) was dissolved in anhydrous THF (12.5mL) under nitrogen atmosphere and triethylamine (0.52mL, 2.7mmol) was added followed by dropwise addition of 4-fluoro-2-(trifluoromethyl)benzoyl chloride (0.28mL, 1.8mmol). The reaction was left stirring at room temperature overnight. The reaction was quenched by the addition of water and extracted into EtOAc (x2). The combined organic layers were dried

20 (MgSO_4) and concentrated *in vacuo* to afford the crude *tert*-butyl 4-[[4-fluoro-2-(trifluoromethyl)benzoyl]-methyl-amino]piperidine-1-carboxylate (702mg, 1.75mmol, 95% yield) as a white solid.

[00141] The crude *tert*-butyl 4-[[4-fluoro-2-(trifluoromethyl)benzoyl]-methyl-amino]piperidine-1-carboxylate was dissolved in DCM (5mL) and TFA (2mL) was added. The reaction was stirred at

25 room temperature for 2h then concentrated *in vacuo*. Purification by SCX with MeOH washings followed by 2M NH_3 in MeOH to elute the product afforded a crude solid. Purification by silica flash chromatography using 10% 2M NH_3 in MeOH: DCM with a gradient increasing to 40% 2M NH_3 in MeOH afforded 4-fluoro-*N*-methyl-*N*-(4-piperidyl)-2-(trifluoromethyl)benzamide (369mg, 1.2mmol, 66%) as a white solid.

[00142] ¹H NMR (400MHz, CDCl₃) δ/ppm (2:1 mixture of rotamers): Rotamer 1: 7.37-7.46 (m, 1H), 7.27-7.32 (m, 2H), 4.62-4.72 (m, 1H), 3.12-3.21 (m, 2H), 2.72-2.83 (m, 2H), 2.65 (s, 3H), 1.47-1.80 (m, 4H). Rotamer 2: 7.37-7.46 (m, 1H), 7.27-7.32 (m, 2H), 3.12-3.21 (m, 1H), 3.02-3.10 (m, 2H), 3.01 (s, 3H), 2.26-2.41 (m, 2H), 1.47-1.80 (m, 4H).

5 **[00143]** MS Method 2: RT: 0.94min, m/z 305.1 [M+H]⁺

[00144] The 4-fluoro-*N*-methyl-*N*-(4-piperidyl)-2-(trifluoromethyl)benzamide (1.72g, 5.65mmol) prepared above was combined with 3,6-dichloro-4,5-dimethyl-pyridazine (1.0g, 5.65mmol), triethylamine (1.18mL, 8.47mmol in NMP (5mL) , and the reaction was heated at reflux (150°C) for 22 hours. The reaction mixture was then diluted in EtOAc (100mL), and extracted with water
10 (5x50mL) and brine (50mL). The organic layer was then dried over sodium sulfate, filtered and evaporated *in vacuo* to afford an oil. The crude material was purified by silica flash chromatography using 100% heptane with a gradient to 100% ethyl acetate in heptane. The desired fractions were combined and evaporated *in vacuo* to afford *N*-[1-(6-chloro-4,5-dimethyl-pyridazin-3-yl)-4-piperidyl]-4-fluoro-*N*-methyl-2-(trifluoromethyl)benzamide (793mg, 1.78mmol, 31.6% yield).

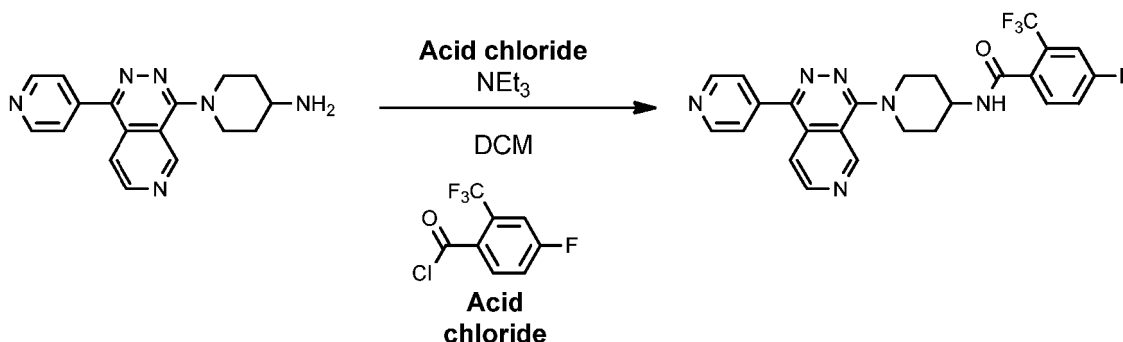
15 **[00145]** ¹H NMR (400MHz, CDCl₃) δ/ppm (2:1 mixture of rotamers): Rotamer 1: 7.44-7.38 (m, 1H), 7.37-7.27 (m, 2H), 4.67-4.86 (m, 1H), 3.61-3.71 (m, 1H), 3.08-3.22 (m, 2H), 2.69 (s, 3H), 2.33 (s, 3H), 2.27 (s, 3H), 1.96-2.11 (m, 2H), 1.81-1.93 (m, 2H). Rotamer 2: 7.44-7.38 (m, 1H), 7.37-7.27 (m, 2H), 3.38-3.48 (m, 2H), 3.06 (s, 3H), 2.66-2.77 (m, 1H), 2.31 (s, 3H), 2.23 (s, 3H), 1.96-2.11 (m, 1H), 1.81-1.93 (m, 1H), 1.72-1.80 (m, 1H), 1.61-1.70 (m, 1H).

20 **[00146]** MS Method 2: RT: 1.82min, m/z 445.3 [M+H]⁺

[00147] Compounds produced in the Procedures described above may take part in reactions to produce compounds of the invention, such as those exemplified below.

General Method A

25 **4-Fluoro-*N*-[1-[1-(4-pyridyl)pyrido[3,4-d]pyridazin-4-yl]-4-piperidyl]-2-(trifluoromethyl)benzamide**



To a round bottomed flask was added 1-[1-(4-pyridyl)pyrido[3,4-d]pyridazin-4-yl]piperidin-4-amine (80.mg, 0.26mmol) , DCM (1mL) , triethylamine (0.07mL, 0.5200mmol) , 4-fluoro-2-(trifluoromethyl)benzoyl chloride (0.04mL, 0.2900mmol) and the reaction was then stirred overnight
30 at room temperature. A purple precipitate formed. The reaction was partitioned between water and

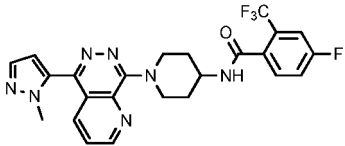
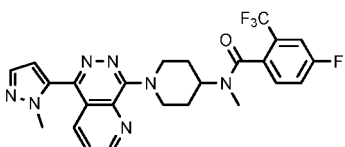
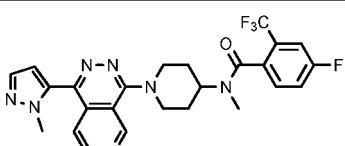
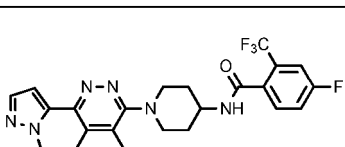
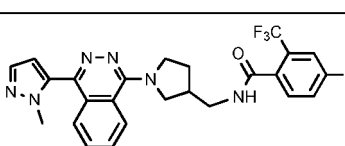
DCM, the organic layer was obtained through a phase separator and the aqueous layer was extracted with DCM several times. The organic layers were combined and concentrated and the resulting residue was purified by ZIP cartridge by eluting with 0-20%MeOH in EtOAc. The product was then taken up in a mixture of 90% acetonitrile and water and filtered. The solid was dried overnight in the vacuum oven to afford the product 4-fluoro-*N*-[1-[1-(4-pyridyl)pyrido[3,4-*d*]pyridazin-4-yl]-4-piperidyl]-2-(trifluoromethyl)benzamide (4.1mg, 0.0083mmol, 3.1627% yield) as a white solid.

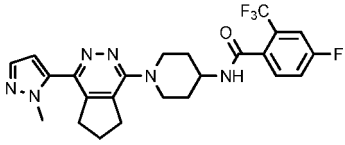
¹H NMR (400MHz, MeOD) δ /ppm: 9.58 (s, 1H), 8.97 (d, *J*5.8Hz, 1H), 8.81 (d, *J*6.1Hz, 1H), 8.81 (d, *J*2.9Hz, 1H), 7.88 (d, *J*5.8Hz, 1H), 7.84 (d, *J*6.1Hz, 1H), 7.84 (d, *J*2.9Hz, 1H), 7.65 (dd, *J*8.5, 5.4Hz, 1H), 7.58 (dd, *J*9.2, 2.5Hz, 1H), 7.50 (td, *J*8.5, 2.5Hz, 1H), 5.00-4.91 (m, 1H), 4.31-4.23 (m, 2H), 4.56-4.48 (m, 2H), 2.89-2.22 (m, 2H), 2.03-2.91 (m, 2H).

MS Method 1: RT:2.83min *m/z* 497.4 [M+H]⁺

[00148] The compounds shown below in **Table 3** were similarly prepared by varying the acid chloride shown in the reaction scheme for General Method A:

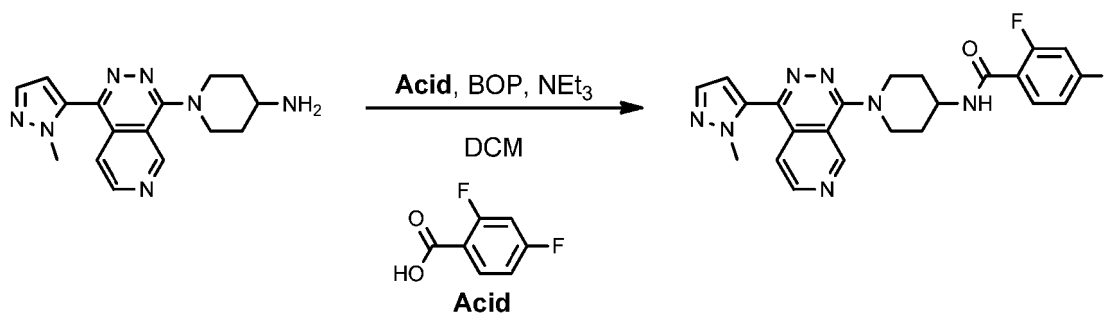
15 **Table 3**

COMPOUND	COMPOUND NAME	LCMS RT	<i>m/z</i> MIM
	4-fluoro- <i>N</i> -[1-[5-(2-methylpyrazol-3-yl)pyrido[2,3- <i>d</i>]pyridazin-8-yl]-4-piperidyl]-2-(trifluoromethyl)benzamide	1.38min (Method 2)	500.3 [M+H] ⁺
	4-fluoro- <i>N</i> -methyl- <i>N</i> -[1-[5-(2-methylpyrazol-3-yl)pyrido[2,3- <i>d</i>]pyridazin-8-yl]-4-piperidyl]-2-(trifluoromethyl)benzamide	1.48min (Method 2)	514.3 [M+H] ⁺
	4-fluoro- <i>N</i> -methyl- <i>N</i> -[1-[1-(2-methylpyrazol-3-yl)pyrido[3,4- <i>d</i>]pyridazin-4-yl]-4-piperidyl]-2-(trifluoromethyl)benzamide	1.52min (Method 2)	514.4 [M+H] ⁺
	<i>N</i> -[1-[4,5-dimethyl-6-(2-methylpyrazol-3-yl)pyridazin-3-yl]-4-piperidyl]-4-fluoro-2-(trifluoromethyl)benzamide	1.49min (Method 2)	477.5 [M+H] ⁺
	4-fluoro- <i>N</i> -[[1-[4-(2-methylpyrazol-3-yl)phthalazin-1-yl]pyrrolidin-3-yl]methyl]-2-(trifluoromethyl)benzamide	1.24min (Method 2)	499.3 [M+H] ⁺

COMPOUND	COMPOUND NAME	LCMS RT	m/z MIM
	4-fluoro-N-[1-[1-(2-methylpyrazol-3-yl)-6,7-dihydro-5H-cyclopenta[d]pyridazin-4-yl]-4-piperidyl]-2-(trifluoromethyl)benzamide	3.23min (Method 1)	489.4 [M+H] ⁺

General Method B

2,4-diFluoro-N-[1-[1-(2-methylpyrazol-3-yl)pyrido[3,4-d]pyridazin-4-yl]-4-piperidyl]benzamide



5 To a round bottomed flask were added 1-[1-(2-methylpyrazol-3-yl)pyrido[3,4-d]pyridazin-4-yl]piperidin-4-amine (80.mg, 0.26mmol) , BOP (229mg, 0.52mmol) , 2,4-difluorobenzoic acid (45mg, 0.28mmol) , and triethylamine (0.07mL, 0.52mmol) in DCM. The reaction was stirred at room temperature overnight. The reaction was diluted with DCM and partitioned with water. The organic layer was obtained through a phase separator. The resulting residue was purified by column chromatography using 0-20% MeOH in EtOAc and the fractions containing the product were concentrated *in vacuo*. The residue was taken up in 90% MeCN in water and further water was added to precipitate the product. The solid was obtained through vacuum filtration and dried in a vacuum oven overnight to afford 2,4-difluoro-N-[1-[1-(2-methylpyrazol-3-yl)pyrido[3,4-d]pyridazin-4-yl]-4-piperidyl]benzamide (22.1mg,0.049mmol, 19% yield)

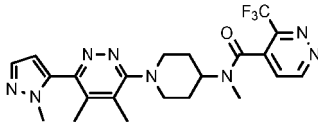
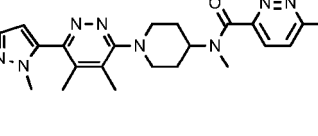
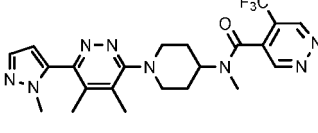
15 ¹H NMR (400MHz, DMSO-d₆) δ/ppm: 9.51 (s, 1H), 8.99 (d, J_{5.7}Hz, 1H), 8.45 (d, J_{7.6}Hz, 1H), 7.77 (dd, J_{5.7}, 0.8Hz, 1H), 7.72-7.65 (m, 2H), 7.40-7.33 (m, 1H), 7.18 (td, J_{8.5}, 2.4Hz, 1H), 6.75 (d, J_{1.9}Hz, 1H), 4.20-4.11 (m, 2H), 3.92 (s, 3H), 3.47-3.38 (m, 2H), 2.11-2.03 (m, 2H), 1.94-1.83 (m, 2H).

MS Method 1: RT:3.06min m/z 450.4 [M+H]⁺

20 **[00149]** The compounds shown below in **Table 4** were similarly prepared by varying the acid chloride shown in the reaction scheme for General Method B:

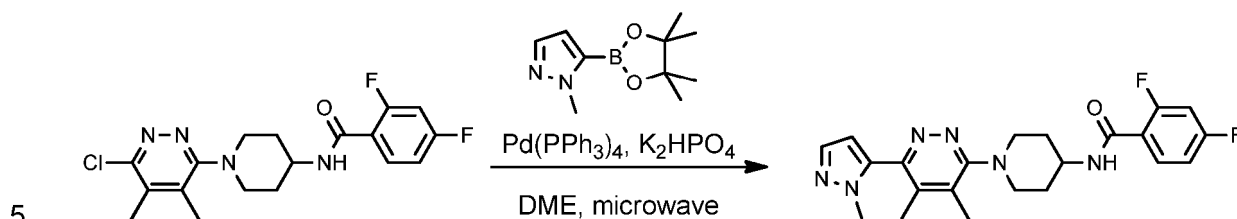
Table 4

COMPOUND	COMPOUND NAME	LCMS RT	m/z MIM
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COMPOUND	COMPOUND NAME	LCMS RT	m/z MIM
	<i>N</i> -[1-[4,5-dimethyl-6-(2-methylpyrazol-3-yl)pyridazin-3-yl]-4-piperidyl]- <i>N</i> -methyl-3-(trifluoromethyl)pyridazine-4-carboxamide	3.13min (Method 1)	475.4 [M+H] ⁺
	<i>N</i> -[1-[4,5-dimethyl-6-(2-methylpyrazol-3-yl)pyridazin-3-yl]-4-piperidyl]- <i>N</i> -methyl-6-(trifluoromethyl)pyridazine-3-carboxamide	3.25min (Method 1)	475.4 [M+H] ⁺
	<i>N</i> -[1-[4,5-dimethyl-6-(2-methylpyrazol-3-yl)pyridazin-3-yl]-4-piperidyl]- <i>N</i> -methyl-5-(trifluoromethyl)pyridazine-4-carboxamide	3.08min (Method 1)	475.4 [M+H] ⁺

General Method C

N-[1-[4,5-dimethyl-6-(2-methylpyrazol-3-yl)pyridazin-3-yl]-4-piperidyl]-4-fluoro-*N*-methyl-2-(trifluoromethyl)benzamide



1-methyl-1*H*-pyrazole-5-boronic acid, pinacolester (200mg, 0.96mmol), *N*-[1-(6-chloro-4,5-dimethylpyridazin-3-yl)-4-piperidyl]-4-fluoro-*N*-methyl-2-(trifluoromethyl)benzamide (286mg, 0.64mmol) and dipotassium hydrogen phosphate (224mg, 1.29mmol) were dissolved in DME (2.5mL, degassed by bubbling N₂(g) through it for 30mins) and water (0.6mL), then the solution was further degassed for 5mins. Tetrakis(triphenylphosphine)palladium(0) (74mg, 0.060mmol) was added in one portion and the solution was heated to 120 °C for 40mins in the microwave. Further 1-methyl-1*H*-pyrazole-5-boronic acid, pinacolester (30mg, 0.15mmol), dipotassium hydrogen phosphate (35mg, 0.20mmol) and tetrakis(triphenylphosphine)palladium(0) (10mg, 0.008mmol) were added and the reaction heated for a further 40mins at 120 °C in the microwave. The reaction mixture was partitioned between EtOAc (50mL) and water (20mL). The organic layer was washed with water (10mL), brine (10mL), dried over Na₂SO₄, filtered and evaporated under reduced pressure to give the crude product as a red gum. The resulting residue was purified by column chromatography using 0-100% MeOH in DCM. Fractions containing the product were concentrated *in vacuo* to afford an amber gum. Further purification by preparative LCMS afforded several fractions in which the product co-eluted with triphenylphosphine oxide bi-product. Fractions were analysed individually and only those containing pure product were combined to afford *N*-[1-[4,5-dimethyl-6-(2-methylpyrazol-3-

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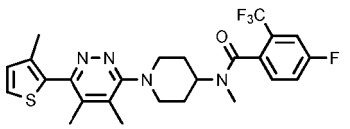
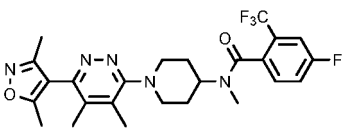
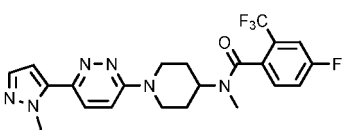
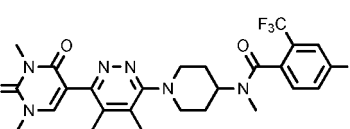
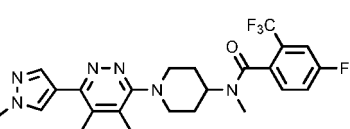
yl)pyridazin-3-yl]-4-piperidyl]-4-fluoro-*N*-methyl-2-(trifluoromethyl)benzamide (27mg, 0.05mmol, 8.4%).

¹H NMR (400MHz, CDCl₃) δ/ppm (2:1 mixture of rotamers): Rotamer 1: 7.59-7.60 (d, *J*2.0Hz, 1H), 7.42-7.50 (m, 1H), 7.31-7.40 (m, 2H), 6.38-6.39 (d, *J*2.0Hz, 1H), 4.82-4.92 (m, 1H), 3.95 (s, 3H), 3.77-3.87 (m, 1H), 3.67-3.75 (m, 1H), 3.15-3.32 (m, 2H), 2.75 (s, 3H), 2.33 (s, 3H), 2.25 (s, 3H), 2.02-2.18 (m, 2H), 1.87-2.01 (m, 2H). Rotamer 2: 7.57-7.58 (d, *J*2.0Hz, 1H), 7.42-7.50 (m, 1H), 7.31-7.40 (m, 2H), 6.36-6.37 (d, *J*2.0Hz, 1H), 3.91 (s, 3H), 3.52-3.64 (m, 2H), 3.33-3.44 (m, 1H), 3.10 (s, 3H), 2.77-2.87 (m, 2H), 2.83 (s, 3H), 2.24 (s, 3H), 1.87-2.01 (m, 2H), 1.79-1.87 (m, 1H), 1.67-1.74 (m, 1H).

10 MS Method 1: RT:3.71min m/z 491.3 [M+H]⁺

[00150] The compounds shown below in **Table 5** were similarly prepared by varying the acid chloride shown in the reaction scheme for General Method B:

Table 5

COMPOUND	COMPOUND NAME	LCMS RT	m/z MIM
	<i>N</i> -[1-[4,5-dimethyl-6-(3-methyl-2-thienyl)pyridazin-3-yl]-4-piperidyl]-4-fluoro- <i>N</i> -methyl-2-(trifluoromethyl)benzamide	4.19min (Method 1)	507.4 [M+H] ⁺
	<i>N</i> -[1-[6-(3,5-dimethylisoxazol-4-yl)-4,5-dimethyl-pyridazin-3-yl]-4-piperidyl]-4-fluoro- <i>N</i> -methyl-2-(trifluoromethyl)benzamide	3.83min (Method 1)	506.4 [M+H] ⁺
	4-fluoro- <i>N</i> -methyl- <i>N</i> -[1-[6-(2-methylpyrazol-3-yl)pyridazin-3-yl]-4-piperidyl]-2-(trifluoromethyl)benzamide	3.52min (Method 1)	463.3 [M+H] ⁺
	<i>N</i> -[1-[6-(1,3-dimethyl-2,4-dioxypyrimidin-5-yl)-4,5-dimethylpyridazin-3-yl]-4-piperidyl]-4-fluoro- <i>N</i> -methyl-2-(trifluoromethyl)benzamide	1.48min (Method 2)	549.4 [M+H] ⁺
	<i>N</i> -[1-[4,5-dimethyl-6-(1-methylpyrazol-4-yl)pyridazin-3-yl]-4-piperidyl]-4-fluoro- <i>N</i> -methyl-2-(trifluoromethyl)benzamide	1.41min (Method 2)	491.4 [M+H] ⁺

15 **[00151] In Vitro Biological Evaluation**

[00152] *In vitro* biological evaluation of compounds of the invention was carried out using the procedure detailed below. The procedure provides activity data for the compounds of the invention

against the Hedgehog signalling pathway. The activity is represented as IC₅₀ values in Table 6 below.

5 **[00153]** The Gli-reporter NIH3T3 cell line (BPS Biosciences) was grown according to the suppliers recommendations. Briefly, cells were maintained in growth medium (DMEM supplemented with 10% calf serum, 1% Penicillin/Streptomycin, and 500 g/mL of Geneticin) and grown at 37°C, 5% CO₂. In order to passage cells they were first rinsed with phosphate buffered saline before the addition of 0.05% Trypsin/EDTA. Fresh growth media was added and the cells were transferred to a centrifuge tube, spun and resuspended at an appropriate cell density.

10 **[00154]** Gli-reporter NIH-3T3 cells were seeded at 20,000 cells/well into 96 well, poly-D-lysine coated white clear bottomed full area TC plates in growth media (without geneticin). Three wells were left with just media as cell free controls. Cells were then incubated for 24 hours at 37°C in a 5% CO₂.

15 **[00155]** Serial dilutions of the test compounds were prepared in 100% DMSO. 10µl of compound or DMSO from each well was pipetted into a sterile, 0.5ml deep well conical bottomed 96 well plate (intermediate plate). 190µl of warmed assay media (Opti-MEM supplemented with 0.5% calf serum, 1% non-essential amino acids, 1mM sodium pyruvate, 10mM HEPES, 1% penicillin/Streptomycin) was then added to each well and mixed five times at 180µl by electronic pipette to ensure homogeneity of the compound solution. This 1:20 dilution gives a top concentration of 50µM in 5% DMSO, 95% assay media. 10µl was pipetted from each well of the intermediate plate into a second deep well sterile plate. 490µl of warm assay media was then added to each well and mixed five times at 300µl. This gives a final top concentration of 1µM in 0.1% DMSO.

25 **[00156]** After the 24 hour incubation, media was carefully removed by pipette and replaced with 45µl of compound dilutions in triplicate. This was incubated for one hour at 37°C in a 5% CO₂. After an hour, 5µl 10µg/mL recombinant mouse sonic hedgehog (R&D Systems) was added to each well and the plates were incubated for a further 24 hours at 37°C, 5% CO₂.

[00157] After 24 hours, plates were removed from the incubator and left to acclimatise to room temperature for 20 minutes. 50µl of OneGLO assay reagent (Promega) was then added to each well and the plates gently shaken for a further 30 minutes. Plates were then read for luminescence on the EnVision plate reader (PerkinElmer).

30 **[00158]** The results of the *in vitro* biological data for certain compounds of the invention are given in Table 6 below. The table shows the Hedgehog pathway inhibition activity of each compound characterised based on the IC₅₀ value of the compound as “+”, “++” and “+++”. The category “+” refers to compounds with an IC₅₀ of >500 nM. The category “++” refers to compounds with an IC₅₀ of 10 nM to 500 nM. The category “+++” refers to compounds with an IC₅₀ of <10 nM.

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Table 6

ID No.	Compound Name	Category
1	N-[1-[4,5-dimethyl-6-(2-methylpyrazol-3-yl)pyridazin-3-yl]-4-piperidyl]-N-methyl-6-(trifluoromethyl)pyridazine-3-carboxamide	+
2	4-fluoro-N-[1-[1-(4-pyridyl)pyrido[3,4-d]pyridazin-4-yl]-4-piperidyl]-2-(trifluoromethyl)benzamide	+++
3	N-[1-[4,5-dimethyl-6-(2-methylpyrazol-3-yl)pyridazin-3-yl]-4-piperidyl]-N-methyl-3-(trifluoromethyl)pyridazine-4-carboxamide	+++
4	N-[1-[6-(3,5-dimethylisoxazol-4-yl)-4,5-dimethyl-pyridazin-3-yl]-4-piperidyl]-4-fluoro-N-methyl-2-(trifluoromethyl)benzamide	++
5	N-[1-[4,5-dimethyl-6-(3-methyl-2-thienyl)pyridazin-3-yl]-4-piperidyl]-4-fluoro-N-methyl-2-(trifluoromethyl)benzamide	++
6	2,4-difluoro-N-[1-[1-(2-methylpyrazol-3-yl)pyrido[3,4-d]pyridazin-4-yl]-4-piperidyl]benzamide	++
7	N-[1-[6-(1,3-dimethyl-2,4-dioxo-pyrimidin-5-yl)-4,5-dimethyl-pyridazin-3-yl]-4-piperidyl]-4-fluoro-N-methyl-2-(trifluoromethyl)benzamide	+
8	N-[1-[4,5-dimethyl-6-(1-methylpyrazol-4-yl)pyridazin-3-yl]-4-piperidyl]-4-fluoro-N-methyl-2-(trifluoromethyl)benzamide	++
9	N-[1-[4,5-dimethyl-6-(2-methylpyrazol-3-yl)pyridazin-3-yl]-4-piperidyl]-N-methyl-5-(trifluoromethyl)pyridazine-4-carboxamide	+++
10	4-fluoro-N-methyl-N-[1-[5-(2-methylpyrazol-3-yl)pyrido[2,3-d]pyridazin-8-yl]-4-piperidyl]-2-(trifluoromethyl)benzamide	+++
11	4-fluoro-N-[1-[1-(2-methylpyrazol-3-yl)-6,7-dihydro-5H-cyclopenta[d]pyridazin-4-yl]-4-piperidyl]-2-(trifluoromethyl)benzamide	+++
12	4-fluoro-N-[1-[5-(2-methylpyrazol-3-yl)pyrido[2,3-d]pyridazin-8-yl]-4-piperidyl]-2-(trifluoromethyl)benzamide	+++
13	4-fluoro-N-[[1-[4-(2-methylpyrazol-3-yl)phthalazin-1-yl]pyrrolidin-3-yl]methyl]-2-(trifluoromethyl)benzamide	+++
14	N-[1-[4,5-dimethyl-6-(2-methylpyrazol-3-yl)pyridazin-3-yl]-4-piperidyl]-4-fluoro-2-(trifluoromethyl)benzamide	+++
15	4-fluoro-N-methyl-N-[1-[1-(2-methylpyrazol-3-yl)pyrido[3,4-d]pyridazin-4-yl]-4-piperidyl]-2-(trifluoromethyl)benzamide	+++
16	N-[1-[4,5-dimethyl-6-(2-methylpyrazol-3-yl)pyridazin-3-yl]-4-piperidyl]-4-fluoro-N-methyl-2-(trifluoromethyl)benzamide	+++
17	4-fluoro-N-methyl-N-[1-[6-(2-methylpyrazol-3-yl)pyridazin-3-yl]-4-piperidyl]-2-(trifluoromethyl)benzamide	++

[00159] Examples of compounds of the invention with values for their IC₅₀ are given in Table 7, below.

Table 7

ID No.	Compound	IC ₅₀
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3	N-[1-[4,5-dimethyl-6-(2-methylpyrazol-3-yl)pyridazin-3-yl]-4-piperidyl]-N-methyl-3-(trifluoromethyl)pyridazine-4-carboxamide	9.4
10	4-fluoro-N-methyl-N-[1-[5-(2-methylpyrazol-3-yl)pyrido[2,3-d]pyridazin-8-yl]-4-piperidyl]-2-(trifluoromethyl)benzamide	0.4
11	4-fluoro-N-[1-[1-(2-methylpyrazol-3-yl)-6,7-dihydro-5H-cyclopenta[d]pyridazin-4-yl]-4-piperidyl]-2-(trifluoromethyl)benzamide	0.5
12	4-fluoro-N-[1-[5-(2-methylpyrazol-3-yl)pyrido[2,3-d]pyridazin-8-yl]-4-piperidyl]-2-(trifluoromethyl)benzamide	4.2

[00160] Throughout the description and claims of this specification, the words “comprise” and “contain” and variations of them mean “including but not limited to”, and they are not intended to (and do not) exclude other moieties, additives, components, integers or steps. Throughout the

5 description and claims of this specification, the singular encompasses the plural unless the context otherwise requires. In particular, where the indefinite article is used, the specification is to be understood as contemplating plurality as well as singularity, unless the context requires otherwise.

[00161] Features, integers, characteristics, compounds, chemical moieties or groups described in conjunction with a particular aspect, embodiment or example of the invention are to be understood

10 to be applicable to any other aspect, embodiment or example described herein unless incompatible therewith. All of the features disclosed in this specification (including any accompanying claims, abstract and drawings), and/or all of the steps of any method or process so disclosed, may be combined in any combination, except combinations where at least some of such features and/or

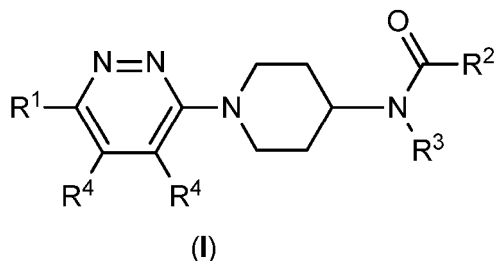
15 embodiments. The invention is not restricted to the details of any foregoing steps are mutually exclusive. The invention extends to any novel one, or any novel combination, of the features disclosed in this specification (including any accompanying claims, abstract and drawings), or to any novel one, or any novel combination, of the steps of any method or process so disclosed.

[00162] The reader's attention is directed to all papers and documents which are filed concurrently with or previous to this specification in connection with this application and which are open to public

20 inspection with this specification, and the contents of all such papers and documents are incorporated herein by reference.

CLAIMS

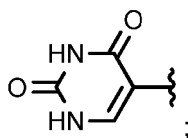
1. A compound according to formula (I) and pharmaceutically acceptable salts and solvates thereof:



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wherein

R¹ is selected from substituted or unsubstituted: C₆₋₁₀ aryl, pyrazolyl, pyridinyl, thiophenyl, oxazolyl, isoxazolyl, piperazinyl, -O-phenyl, -NH(CH₂)₂NMe₂, or



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R² is represented by -CR⁵R⁶R⁷, wherein R⁵, R⁶ and R⁷ are independently selected at each occurrence from H and substituted or unsubstituted: C₁₋₁₄ alkyl, C₁₋₁₄ haloalkyl, carbocyclic, and heterocyclic,

or R² is selected from substituted or unsubstituted: C₁₋₁₄ alkyl, C₁₋₁₄ haloalkyl, carbocyclic, and heterocyclic;

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R³ is selected from H, substituted or unsubstituted C₁₋₄ alkyl, C₁₋₄ haloalkyl or C₃₋₆ cycloalkyl;

each R⁴ is independently selected from H, halo, C₁₋₆ alkyl, C₁₋₆ haloalkyl, -OR^a, -SH, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, C₃₋₈ cycloalkenyl, aryl, heterocyclic, -NR^aR^b, -CN, acyl, -C(O)R^a, -C(O)OR^a, -SO₂R^a, and -SO₃R^a, or wherein both of the R⁴ groups form a ring together with the carbon atoms to which they are attached thereby forming a fused bicyclic ring system containing from 8 to 12 atoms, wherein the ring formed by both R⁴ groups is a saturated or unsaturated carbocyclic ring with 4, 5, 6, 7, or 8 carbon atoms or a saturated or unsaturated heterocyclic ring with 4, 5, 6, 7, or 8 atoms containing 1, 2 or 3 heteroatoms;

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R^a and R^b are independently selected at each occurrence from: H, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ acyl, C₃₋₇ cycloalkyl, and C₃₋₇ halocycloalkyl; and

- when a group is substituted, the group contains 1 to 5 substituents independently selected at each occurrence from the group comprising: halo, -OR^a, -SR^a, -NR^aR^b, NO₂, =O, -CN, acyl, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₈ cycloalkyl, -SO₂R^a, and SO₃R^a, -C(OR^a)R^aR^b, -C(O)R^a and C(O)OR^a;

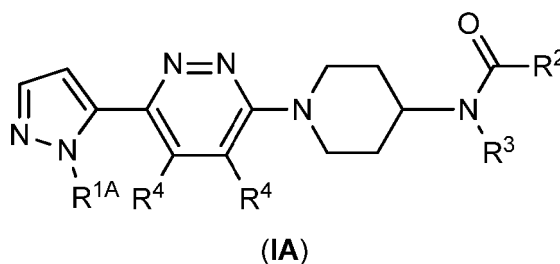
provided that:

- when R¹ is substituted or unsubstituted pyrazolyl then R⁴ is not H and where both adjacent R⁴ groups form a ring with the atoms to which they are attached the adjacent R⁴ groups do not form an unsaturated carbocyclic ring with 6 carbon atoms;

when R¹ is substituted or unsubstituted C₆₋₁₀ aryl then R⁴ is not H or methyl and where both adjacent R⁴ groups form a ring with the atoms to which they are attached the adjacent R⁴ groups do not form an unsaturated carbocyclic ring with 6 carbon atoms; and

- when R¹ is substituted or unsubstituted pyridyl then R⁴ is not methyl.

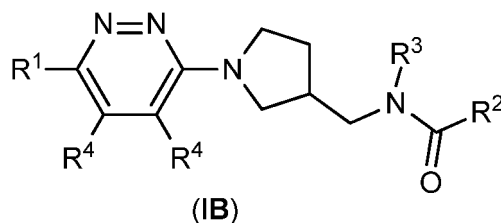
2. A compound of claim 1, wherein the compound is a compound according to formula (IA):



wherein

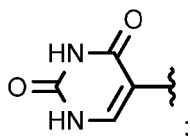
R^{1A} is selected from H, C₁₋₆ alkyl, or C₃₋₆ cycloalkyl.

3. A compound according to formula (IB) and pharmaceutically acceptable salts and solvates thereof:



wherein

- R¹ is selected from substituted or unsubstituted: C₆₋₁₀ aryl, pyrazolyl, pyridinyl, thiophenyl, oxazolyl, isoxazolyl, piperazinyl, -O-phenyl, -NH(CH₂)₂NMe₂, or



5 R² is represented by -CR⁵R⁶R⁷, wherein R⁵, R⁶ and R⁷ are independently selected at each occurrence from H and substituted or unsubstituted: C₁₋₁₄ alkyl, C₁₋₁₄ haloalkyl, carbocyclic, and heterocyclic;

or R² is selected from substituted or unsubstituted: C₁₋₁₄ alkyl, C₁₋₁₄ haloalkyl, carbocyclic, and heterocyclic;

10 R³ is selected from H, substituted or unsubstituted C₁₋₄ alkyl, C₁₋₄ haloalkyl or C₃₋₆ cycloalkyl;

15 each R⁴ is independently selected from H, halo, C₁₋₆ alkyl, C₁₋₆ haloalkyl, -OR^a, -SH, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, C₃₋₈ cycloalkenyl, aryl, heterocyclic, -NR^aR^b, -CN, acyl, -C(O)R^a, -C(O)OR^a, -SO₂R^a, and -SO₃R^a, or wherein both of the R⁴ groups form a ring together with the carbon atoms to which they are attached thereby forming a fused bicyclic ring system containing from 8 to 12 atoms, wherein the ring formed by both R⁴ groups is a saturated or unsaturated carbocyclic ring with 4, 5, 6, 7, or 8 carbon atoms or a saturated or unsaturated heterocyclic ring with 4, 5, 6, 7, or 8 atoms containing 1, 2 or 3 heteroatoms;

20 R^a and R^b are independently selected at each occurrence from: H, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ acyl, C₃₋₇ cycloalkyl, and C₃₋₇ halocycloalkyl; and

when a group is substituted, the group contains 1 to 5 substituents independently selected at each occurrence from the group comprising: halo, -OR^a, -SR^a, -NR^aR^b, NO₂, =O, -CN, acyl, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₈ cycloalkyl, -SO₂R^a, and SO₃R^a, -C(OR^a)R^aR^b, -C(O)R^a and C(O)OR^a.

25 4. A compound of claim 3, wherein R¹ is substituted or unsubstituted pyrazolyl, preferably methyl pyrazolyl.



Application No: GB1412660.1

Examiner: Dr Natalie Cole

Claims searched: 1-4

Date of search: 9 March 2015

Patents Act 1977: Search Report under Section 17

Documents considered to be relevant:

Category	Relevant to claims	Identity of document and passage or figure of particular relevance
A	-	WO2010/147917 A1 (ELI LILLY AND COMPANY) See whole document especially abstract, generic formula within page 2 lines 1-7 and examples
A	-	WO2009/134574 A2 (ELI LILLY AND COMPANY) See whole document especially abstract, generic formula within page 1 line 27-page 2 line 8 and examples
A	-	WO2010/056620 A1 (ELI LILLY AND COMPANY) See whole document especially abstract, generic formula within page 2 lines 1-6
A	-	WO2010/056588 A1 (ELI LILLY AND COMPANY) See whole document especially abstract, generic formula within page 2 lines 1-14 and examples

Categories:

X Document indicating lack of novelty or inventive step	A Document indicating technological background and/or state of the art.
Y Document indicating lack of inventive step if combined with one or more other documents of same category.	P Document published on or after the declared priority date but before the filing date of this invention.
& Member of the same patent family	E Patent document published on or after, but with priority date earlier than, the filing date of this application.

Field of Search:

Search of GB, EP, WO & US patent documents classified in the following areas of the UKC^X :

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Worldwide search of patent documents classified in the following areas of the IPC

C07D

The following online and other databases have been used in the preparation of this search report

CAS ONLINE, EPODOC, WPI



International Classification:

Subclass	Subgroup	Valid From
C07D	0401/14	01/01/2006
A61K	0031/501	01/01/2006
A61K	0031/502	01/01/2006
A61K	0031/5025	01/01/2006
A61K	0031/513	01/01/2006
A61P	0035/00	01/01/2006
C07D	0403/14	01/01/2006
C07D	0409/14	01/01/2006
C07D	0413/14	01/01/2006
C07D	0487/04	01/01/2006