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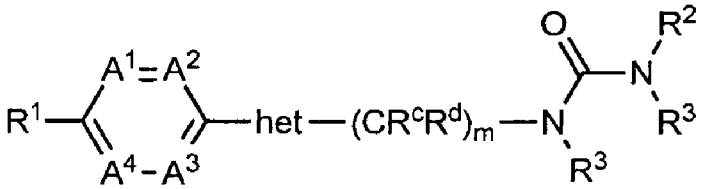
(54) Title: HETEROCYCLIC COMPOUNDS AS HEDGEHOG SIGNALING PATHWAY INHIBITORS



(I)

(57) Abstract: This invention relates to novel compounds of formula I. The compounds of the invention are hedgehog pathway antagonists. Specifically, the compounds of the invention are useful as Smoothened (SMO) inhibitors. The invention also contemplates the use of the compounds for treating conditions treatable by the inhibition of the Hedgehog pathway and SMO, for example cancer.

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 Smoothened (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 expression 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 to possess effective Hedgehog signalling pathway inhibitors and Smo inhibitors as effective treatments for various cancer types.

[0007] It is an aim of certain embodiments of this invention to provide new cancer treatments. In particular, it is an aim of certain embodiments of this invention to provide compounds which have comparable activity to existing cancer treatments, ideally better activity. Certain embodiments of the invention also aim to provide improved solubility compared to prior art compounds and existing therapies. It is particularly attractive for certain compounds of the invention to provide better activity and better solubility over known compounds.

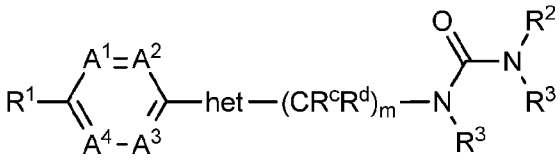
[0008] It is an aim of certain embodiments of this invention to provide compounds which exhibit reduced cytotoxicity relative to prior art compounds and existing therapies.

[0009] Another aim of certain embodiments of this invention is to provide compounds having a convenient pharmacokinetic profile and a suitable duration of action following dosing. A further aim of certain embodiments of this invention is to provide compounds in which the metabolised fragment or fragments of the drug after absorption are GRAS (Generally Regarded As Safe).

[0010] Certain embodiments of the present invention satisfy some or all of the above aims.

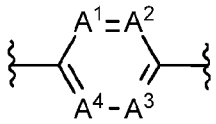
[0011] In accordance with the present invention there is provided compounds as disclosed below. Furthermore, the invention provides compounds capable of inhibiting the Hedgehog signalling pathway, specifically Smoothened (Smo) and the use of these compounds in inhibiting the Hedgehog signalling pathway and Smo. In accordance with the invention there is provided a method of treating conditions modulated by Smo. The invention provides compounds for use in treating a condition which is modulated by Smo.

[0012] In a first aspect of the invention there is provided a compound according to formula (I) and pharmaceutically acceptable salts and solvates thereof:



(I)

wherein



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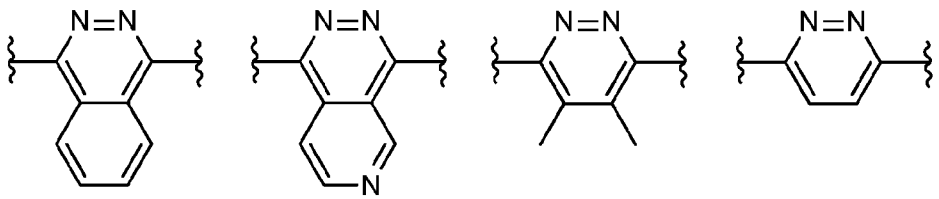

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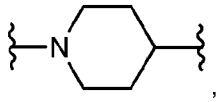


R^1 is substituted or unsubstituted pyrazolyl,

R^2 is substituted or unsubstituted phenyl, toluenyl and pyridinyl,

R^3 is H, methyl or $-C(O)CF_3$,

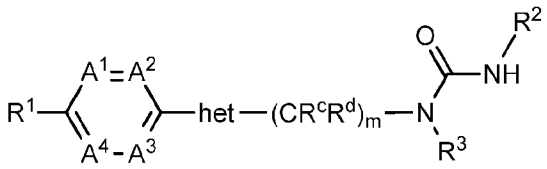
R^c and R^d are independently selected from H, halo, $-OR^a$, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} acyl, C_{3-7} cycloalkyl, and C_{3-7} halocycloalkyl, and

m is 0 or 1,

wherein 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, -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 $C(O)OR^a$; and

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.

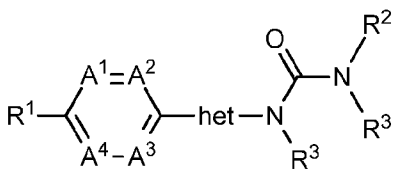
[0013] In an embodiment the compound of formula (**I**) is a compound according to formula (**Ia**):



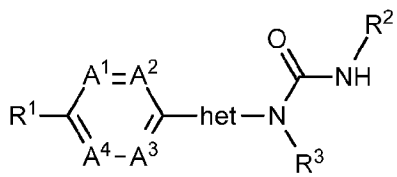
(**Ia**)

[0014] In an embodiment m is 0.

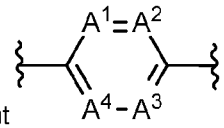
[0015] Thus, there is provided a compound of formula (**II**) and in particular a compound of formula (**IIa**):

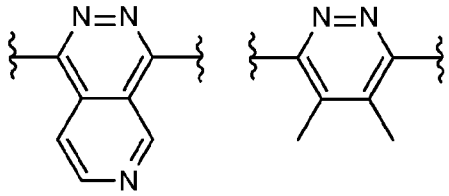


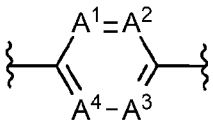
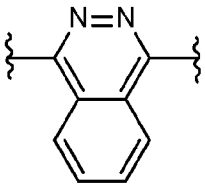
(**II**)

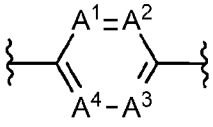
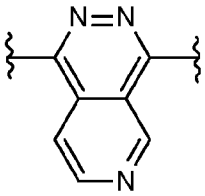


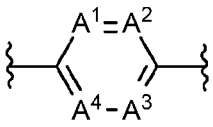
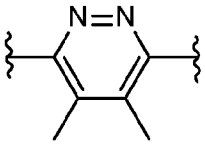
(**IIa**)

[0016] In an embodiment  is selected from:

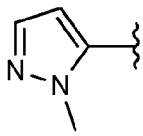


[0017] In an embodiment  is  .

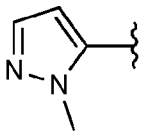
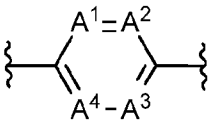
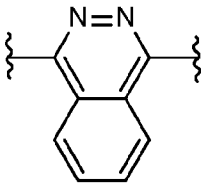
[0018] In an embodiment  is  .

[0019] In an embodiment  is  .

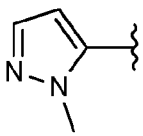
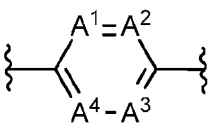
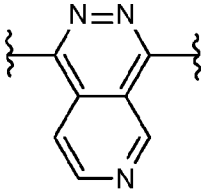
[0020] In an embodiment R^1 is:

 .

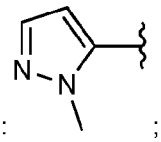
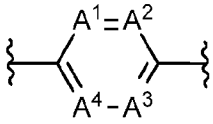
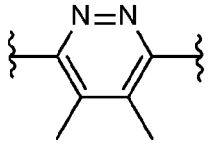
[0021] In an embodiment:

R^1 is:  ; and  is  .

[0022] In an embodiment:

R^1 is:  ; and  is  .

[0023] In an embodiment:

R^1 is:  ; and  is  .

[0024] In an embodiment R^2 may be substituted or unsubstituted phenyl. In an embodiment R^2 may be substituted or unsubstituted toluenyl. In an embodiment R^2 may be substituted or unsubstituted pyridinyl.

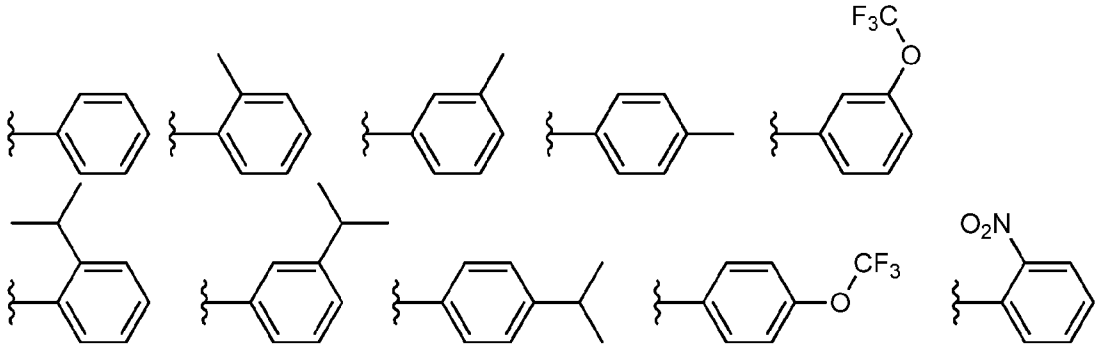
[0025] In embodiments where R^2 is substituted, R^2 may be substituted by 1 to 5 substituents, optionally 1, 2 or 3 substituents, independently selected at each occurrence from the group comprising halo, $-OR^a$, $-NO_2$, C_{1-6} alkyl, C_{1-6} haloalkyl, $-C(OR^a)R^aR^b$, $-SC_{1-4}$ alkyl, $-C(O)R_aR_b$, $-N(CO)R_a$, and -CN.

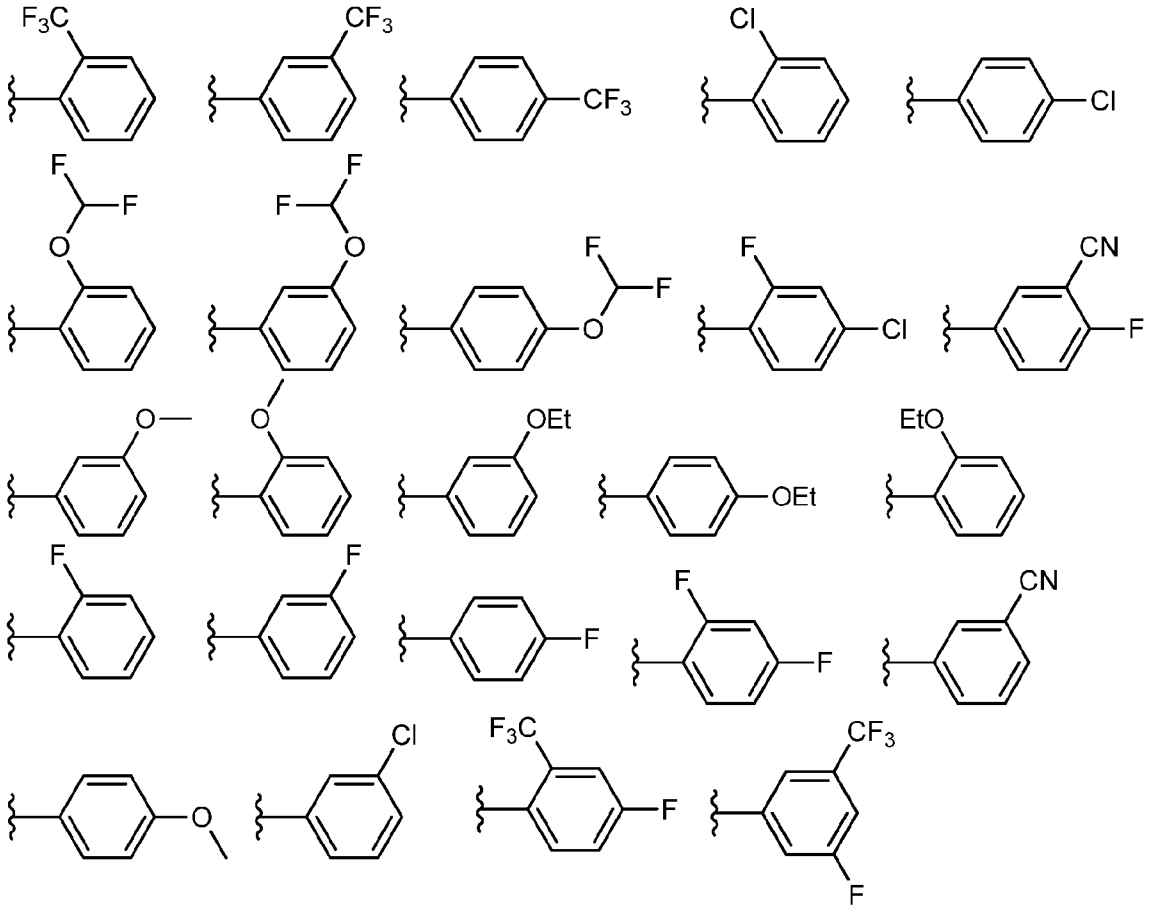
[0026] In embodiments where R^2 is substituted, R^2 may be substituted by 1 or 2 substituents independently selected at each occurrence from the group comprising halo (optionally fluoro or chloro), $-NO_2$, $-OC_{1-4}$ haloalkyl (optionally $-OCF_3$), C_{1-6} alkyl (optionally methyl, ethyl, *iso*-propyl or *tert*-butyl), C_{1-6} haloalkyl (optionally trifluormethyl), $-C(OH)(C_{1-6}$ alkyl)C_{1-6} alkyl, $-SC_{1-4}$ alkyl (optionally –SMe), $-SO_2C_{1-4}$ alkyl (optionally $–SO_2Me$), acyl (optionally –C(O)OMe) and -CN. For example, the substituents may be selected from fluoro, chloro, $-NO_2$, $-OCF_3$, $-OCF_2H$, -OMe, -OEt, -SMe, -SEt, $-SO_2Me$, methyl, ethyl, *iso*-propyl, *tert*-butyl, trifluoromethyl, -C(O)OMe, $-C(OH)(CH_3)CH_3$, $-C(OH)(CH_3)CH_2CH_3$ and -CN.

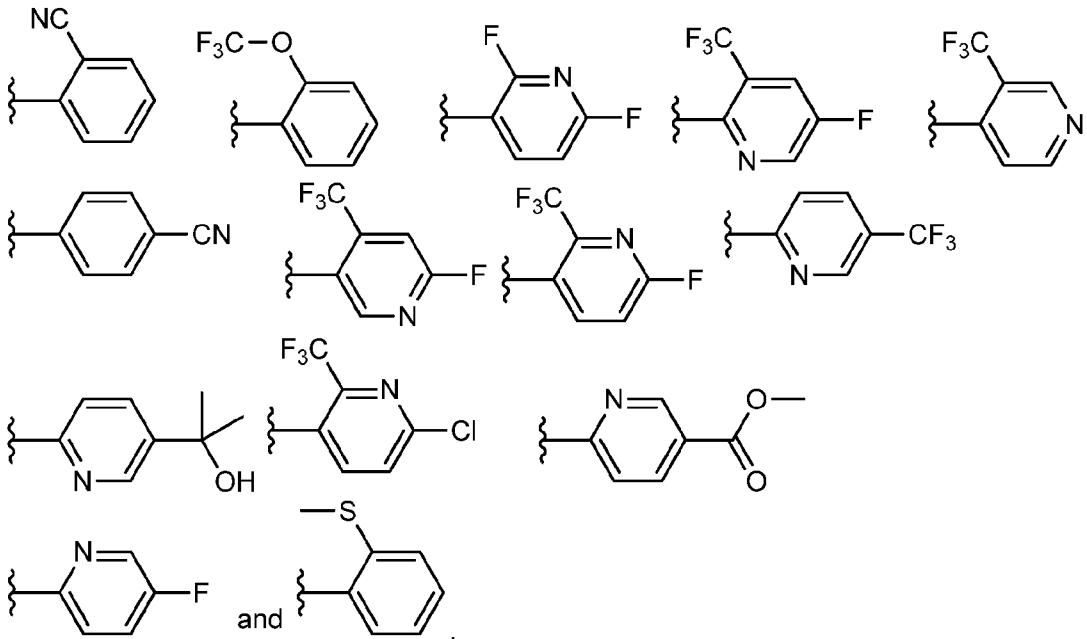
[0027] In embodiments where R^2 is substituted, R^2 may be substituted by 1 or 2 substituents independently selected at each occurrence from the group comprising halo, $-NO_2$, $-OC_{1-4}$ haloalkyl, C_{1-6} alkyl, C_{1-6} haloalkyl, $-C(OH)(C_{1-6}$ alkyl)C_{1-6} alkyl, $-SC_{1-4}$ alkyl and -CN. For example, the substituents may be selected from fluoro, chloro, $-NO_2$, $-OCF_3$, $-OCF_2H$, -OMe, -OEt, -SMe, -SEt, methyl, ethyl, trifluoromethyl, $-C(OH)(CH_3)CH_3$, $-C(OH)(CH_3)CH_2CH_3$ and -CN.

[0028] In an embodiment R^2 is substituted by trifluoromethyl. In an alternative embodiment R^2 is substituted by $–OCF_3$. In an embodiment R^2 is substituted by $-C(OH)(CH_3)CH_3$. In an embodiment R^2 is substituted by methyl. In an embodiment R^2 is substituted by fluoro. In an embodiment R^2 is substituted by chloro. In an embodiment R^2 is substituted by –CN. In an embodiment R^2 is substituted by fluoro and trifluoromethyl. In an embodiment R^2 is substituted by fluoro and $-OCF_3$. In an embodiment R^2 is substituted by fluoro and methyl.

[0029] R^2 may be represented by:



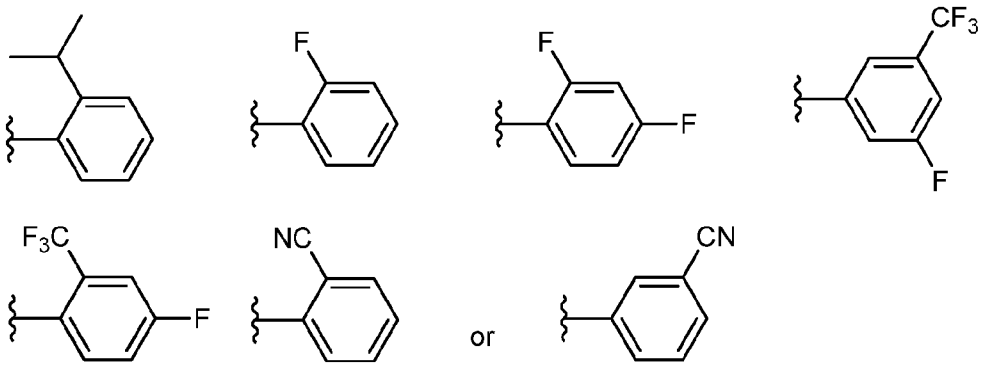




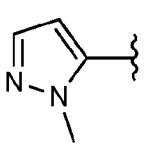
and

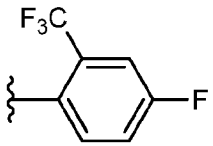
.

[0030] In a preferred embodiment R^2 is



[0031] In an embodiment:



R^1 is: ; and R^2 is  .

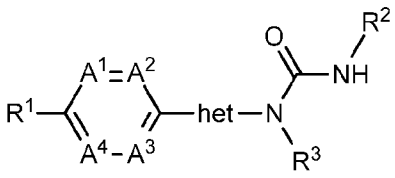
[0032] In an embodiment R^3 is H or substituted or unsubstituted C_{1-4} alkyl or substituted or unsubstituted C_{1-4} haloalkyl. R^3 may be H, methyl or $-C(O)CF_3$. Preferably, R^3 is H or methyl. Optionally, R^3 may be H. Optionally, R^3 may be methyl. In an embodiment where the compound contains two R^3 groups one R^3 may be methyl and the other R^3 may be H, or both R^3 groups may be H.

[0033] When a group is substituted, the group may contain 1 to 5 substituents independently selected at each occurrence from the group comprising: halo, $-OR^a$, $-SR^a$, $-NR^aR^b$, NO_2, -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 $C(O)OR^a$.

[0034] In an embodiment R^a and R^b are independently selected at each occurrence from: hydrogen, C_{1-4} alkyl and C_{1-4} haloalkyl. In an embodiment all occurrences of R^a and R^b are hydrogen.

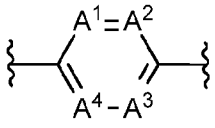
[0035] In an embodiment R^c and R^d are independently selected from: H, C_{1-4} alkyl and C_{1-4} haloalkyl.

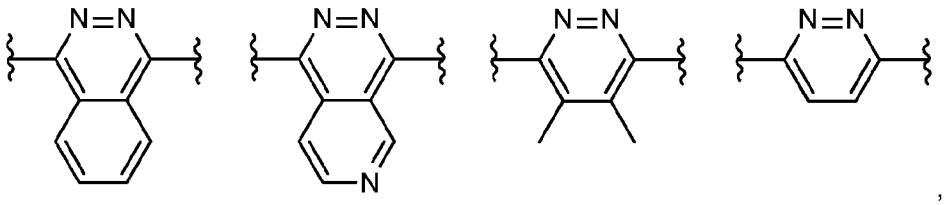
[0036] The invention provides compounds according to formula (**IIa**):



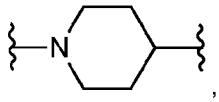
(**IIa**)

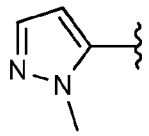
wherein,

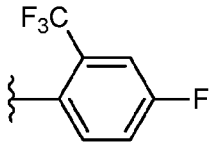
 is selected from:



het is:



R^1 is substituted or unsubstituted pyrazolyl, preferably 

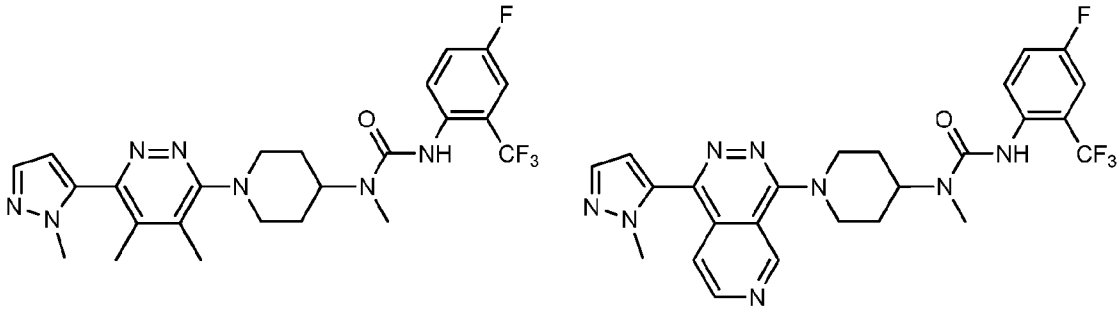
R^2 is substituted or unsubstituted phenyl, preferably 

R^3 is H or methyl, preferably methyl

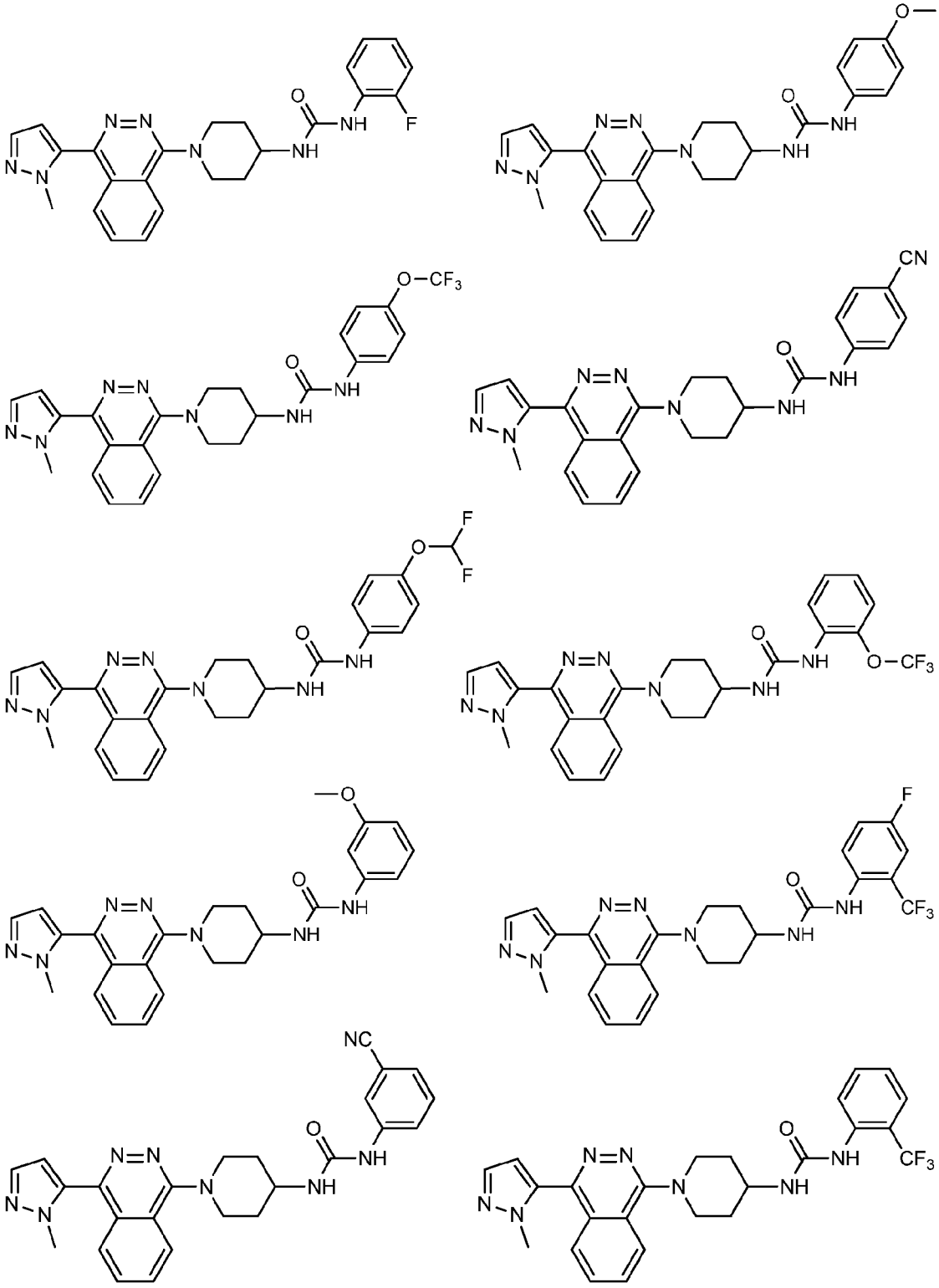
wherein when a group is substituted, the group contains 1 to 5 substituents independently selected at each occurrence from the group comprising: halo, $-OR^a$, $-SR^a$, $-NR^aR^b$, NO_2, =O, -CN, acyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-8} cycloalkyl, $-SO_2R^a$, and SO_3R^a , $-C(OR^a)R^aR^b$, $-C(O)R^a$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

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.

[0037] In an embodiment the compound of formula (I) is compound shown below:



[0038] Compounds of the invention include:



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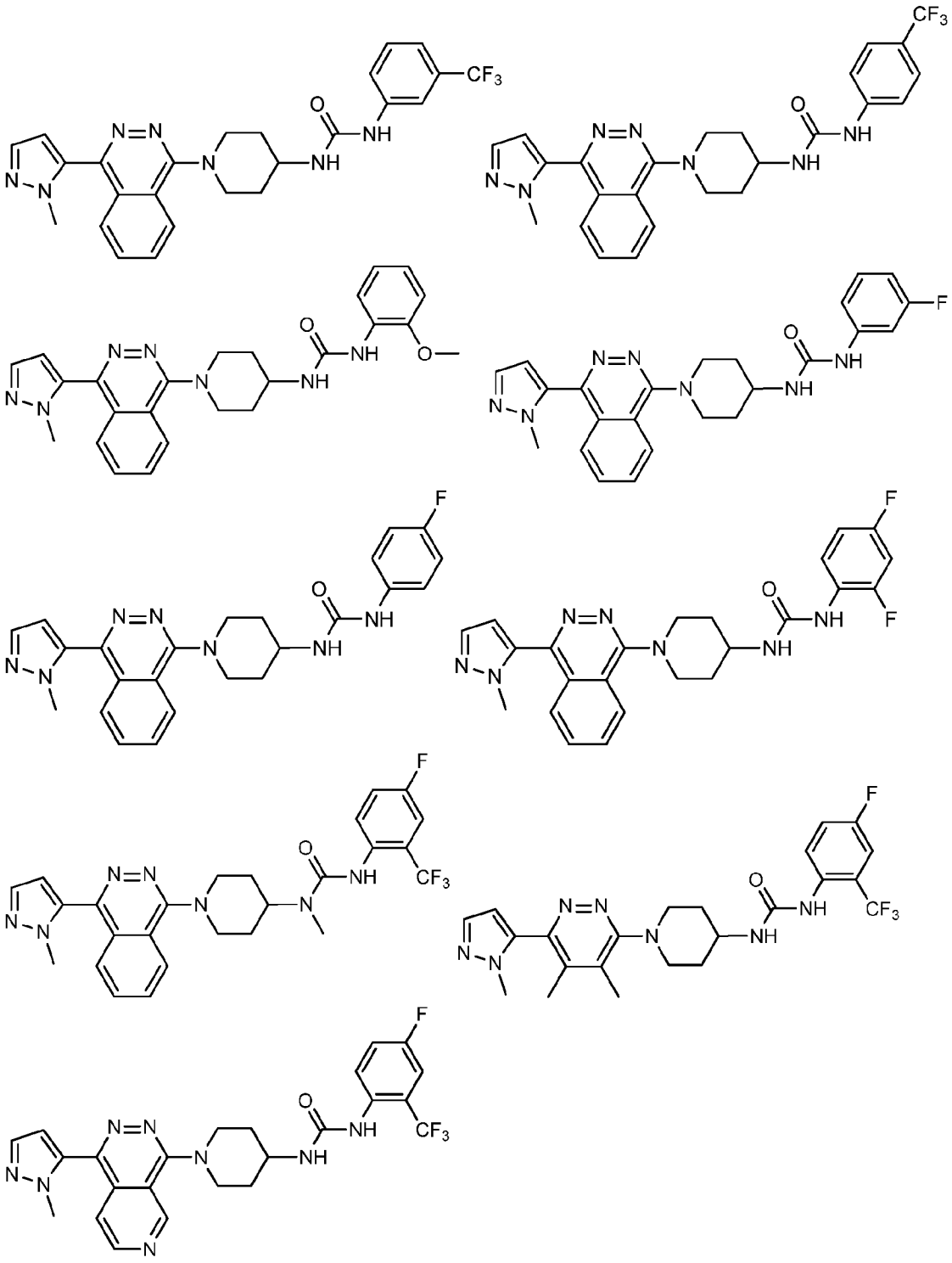
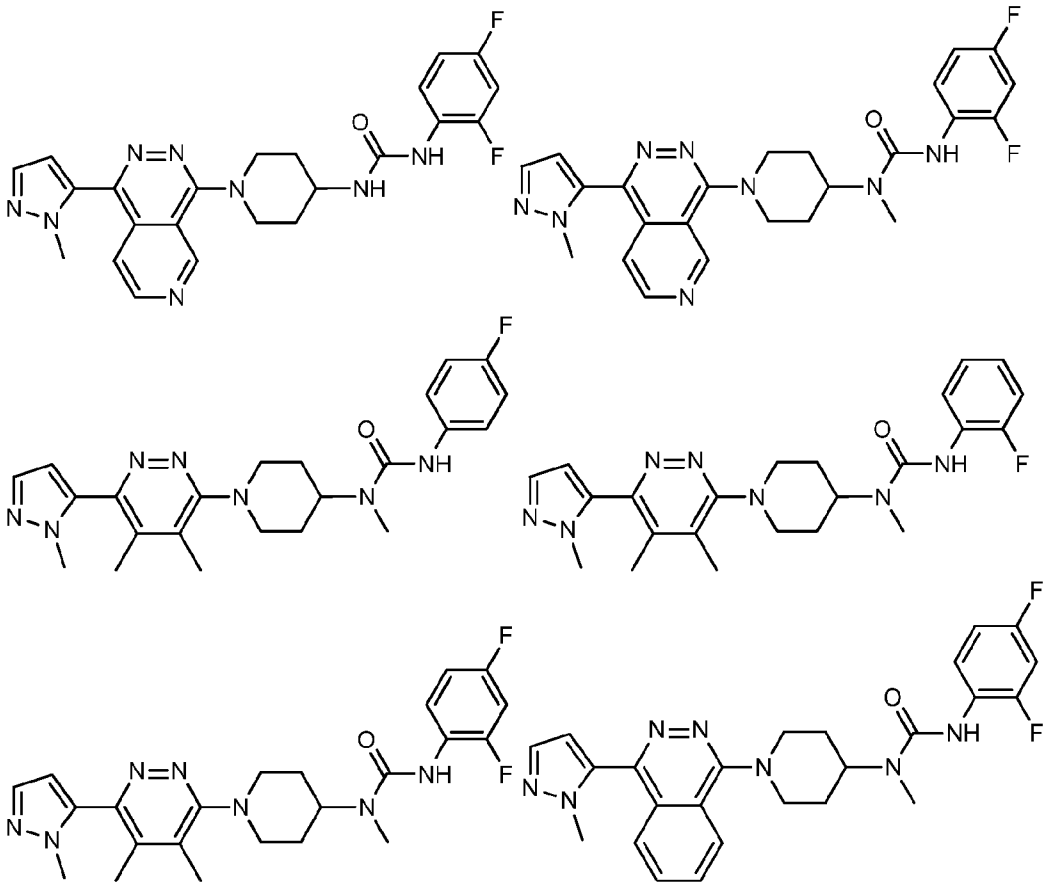


[0039] Compounds of the invention also include:



[0040] In another aspect of the invention there is provided a compound of formula (**I**) for use as a medicament.

[0041] In another aspect, a compound of formula (**I**) 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 formula (**I**) may be for use in the treatment of a condition treatable by the inhibition of the Hedgehog signalling pathway.

[0042] In addition the compounds of the present invention are for use in a method of treatment of a condition which is modulated by Smoothened (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 compound of formula (**I**) may be for use in the treatment of a condition treatable by the inhibition of Smo.

[0043] In embodiments the condition treatable by the inhibition of the Hedgehog signalling pathway or Smo may be selected from: cancer, sarcoma, carcinoma, blastoma, lymphoma, leukemia and haematological malignancies.

[0044] 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 expression of Smo, including various cancers, for example, solid tumours. In embodiments the condition treatable by the inhibition of the Hedgehog signalling pathway or 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.

[0045] In embodiments the preferred condition 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, 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, cervical cancer, ovarian cancer, skin cancer, renal cell carcinoma, gastric cancer and biliary tract cancer.

[0046] Conditions also treatable by the inhibition of the Hedgehog signalling pathway or Smo may be selected from inhibiting stem cell production, inhibiting stem cell renewal, inhibiting and/or modulating stem cell differentiation, benign prostatic hyperplasia, psoriasis and osteoporosis. The conditions treatable by the inhibition of the Hedgehog signalling pathway or Smo may be selected from inhibiting stem cell production, inhibiting stem cell renewal and inhibiting and/or modulating stem cell differentiation

[0047] In embodiments, a compound of the invention may be for use in the treatment of: cancer, sarcoma, carcinoma, blastoma, lymphoma, leukemia and haematological malignancies.

[0048] In embodiments, a compound of the invention may be for use in the treatment of: cancer, 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, 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.

[0049] A compound of the invention may be for use in the treatment of: inhibiting stem cell production, inhibiting stem cell renewal, inhibiting and/or modulating stem cell differentiation, benign prostatic hyperplasia, psoriasis and osteoporosis.

[0050] 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 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.

[0051] 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.

[0052] 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 compound of the invention, to a patient in need thereof.

[0053] 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.

[0054] The invention provides a method of treating a condition selected from: cancer, sarcoma, carcinoma, blastoma, lymphoma, leukemia and haematological malignancies, wherein the method comprises administering a therapeutic amount of a compound of the invention, to a patient in need thereof.

[0055] The invention also provides a method of treating a condition selected from: cancer, 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.

[0056] 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.

[0057] 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 formula (I), to a patient in need thereof.

[0058] In another aspect of the invention there is provided a pharmaceutical composition, wherein the composition comprises a compound of the invention and pharmaceutically acceptable excipients. 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 formula (I).

[0059] 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.

[0060] In an aspect of the invention there is provided a method of treatment of a condition selected from cancer, sarcoma, carcinoma, blastoma, lymphoma and leukemia 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 to a patient in need thereof.

[0061] In an embodiment the method of treatment may further comprise administering the compound of formula (I) to the patient topically. In an embodiment the method of treatment may further comprise administering the compound of formula (I) to the patient by any route of administration other than topically, for example by oral 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 enemas; or by inhalation in the form of an aerosol.

[0062] In an embodiment the compound of formula (I) may be topically administered. In an embodiment the compound of formula (I) may be administered by any route other than topically, for example orally in the form of tablets, capsules, syrups, powders or granules; or parenterally in the

form of a sterile solution, suspension or emulsion for injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion); or rectally in the form of suppositories or enemas; or by inhalation in the form of an aerosol.

DETAILED DESCRIPTION

[0063] 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.

[0064] 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 chlorine.

[0065] The term "C_{1-6} 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, "C_{1-4} alkyl" refers to a linear or branched hydrocarbon chain containing 1, 2, 3 or 4 carbon atoms and "C_{1-14} 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 substituents. Possible substituents are described below. Substiuents for the alkyl group may be halogen, e.g. fluorine, chlorine, bromine and iodine, OH, C_{1-6} alkoxy.

[0066] The term "C_{1-6} 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, 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, C_{1-6} alkoxy.

[0067] The term "C_{1-6} 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, "C_{1-4} haloalkyl" refers to a linear or branched hydrocarbon chain containing 1, 2, 3 or 4 carbon atoms and "C_{1-14} 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 present at any position on the hydrocarbon chain. For example, C_{1-6} haloalkyl may refer to chloromethyl, flouromethyl, 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.

[0068] The term "C_{2-6} 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 "C_{2-6} alkenyl" may be ethenyl, propenyl, butenyl, butadienyl, pentenyl, pentadienyl, hexenyl and hexadienyl.

[0069] The term "C_{2-6} alkynyl" refers to a branded 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 "C_{2-6} alkynyl" may be ethynyl, propynyl, butynyl, pentynyl and hexynyl.

[0070] The term "C_{1-6} heteroalkyl" refers to a branded 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 C_{1-6} heteroalkyl may be bonded to the rest of the molecule through a carbon or a heteroatom. For example, the "C_{1-6} heteroalkyl" may be C_{1-6} *N*-alkyl, C_{1-6} *N,N*-alkyl, or C_{1-6} *O*-alkyl.

[0071] 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 C_{3-8} cycloalkyl or C_{5-6} aryl.

[0072] 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 C_{3-8} heterocycloalkyl, C_{5-6} heteroaryl. For example, the heterocyclic group may be: oxirane, aziridine, azetidine, oxetane, tetrahydrofuran, pyrrolidine, imidazolidine, succinimide, pyrazolidine, oxazolidine, isoxazolidine, thiazolidine, isothiazolidine, piperidine, morpholine, thiomorpholine, piperazine, and tetrahydropyran.

[0073] The term "C_{3-8} cycloalkyl" refers to a saturated hydrocarbon ring system containing 3, 4, 5, 6, 7 or 8 carbon atoms. For example, the "C_{3-8} cycloalkyl" may be cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

[0074] The term "C_{3-8} 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

"C_{3-8} cycloalkyl" may be cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclopentadienyl, cyclohexenyl, cyclohexadienly, cycloheptenyl, cycloheptadiene, cyclooctenyl and cycloatadienyl.

[0075] The term "C_{3-8} heterocycloalkyl" refers to a saturated hydrocarbon ring system containing 3, 4, 5, 6, 7 or 8 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. The "C_{3-8} heterocycloalkyl" may be bonded to the rest of the molecule through any carbon atom or heteroatom. The "C_{3-8} 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 "C_{3-8} heterocycloalkyl" may be oxirane, aziridine, azetidine, oxetane, tetrahydrofuran, pyrrolidine, imidazolidine, succinimide, pyrazolidine, oxazolidine, isoxazolidine, thiazolidine, isothiazolidine, piperidine, morpholine, thiomorpholine, piperazine, and tetrahydropyran.

[0076] The term "C_{3-8} heterocycloalkenyl" refers to an unsaturated hydrocarbon ring system, containing 3, 4, 5, 6, 7 or 8 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. The "C_{3-8} heterocycloalkenyl" may be bonded to the rest of the molecule through any carbon atom or heteroatom. The "C_{3-8} heterocycloalkenyl" 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 "C_{3-8} heterocycloalkyl" may be tetrahydropyridine, dihydropyran, dihydrofuran, pyrroline.

[0077] 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 system are in the same plane. For example, the "aryl" may be phenyl and napthyl. The aryl system itself may be substituted with other groups.

[0078] 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 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.

[0079] The term "alkaryl" refers to an aryl group, as defined above, bonded to a C_{1-4} alkyl, where the C_{1-4} alkyl group provides attachment to the remainder of the molecule.

[0080] The term "alkheteroaryl" refers to a heteroaryl group, as defined above, bonded to a C_{1-4} alkyl, where the alkyl group provides attachment to the remainder of the molecule.

[0081] The term "halogen" herein includes reference to F, Cl, Br and I. Halogen may be Cl. Halogen may be F.

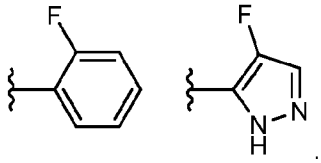
[0082] A bond terminating in a " ~ " represents that the bond is connected to another atom that is not shown in the structure. A bond terminating inside a cyclic structure and not terminating at an atom of the ring structure represents that the bond may be connected to any of the atoms in the ring structure where allowed by valency.

[0083] Throughout the specification A^1, A^2, A^3 and A^4 may collectively be referred to as "A groups". One of the "A groups" may generally be described as an "A group". The unsaturated ring containing A^1, A^2, A^3 and A^4 may be referred to as the "A ring".

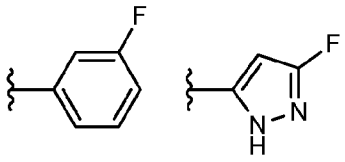
[0084] Where a moiety is substituted, it may be substituted at any point on the moiety where chemically possible and consistent with atomic valency requirements. The moiety may be substituted by one or more substitutuents, e.g. 1, 2, 3 or 4 substituents; optionally there are 1 or 2 substituents on a 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^9, amidino, guanidino, hydroxyguanidino, formamidino, isothioureido, ureido, mercapto, C(O)H, acyl, acyloxy, carboxy, sulfo, sulfamoyl, carbamoyl, cyano, azo, nitro, halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{3-8} cycloalkyl, C_{2-6} alkenyl, C_{2-6} 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 C_{4-8} ring along with the atoms of the moiety on which the substituents are substituted, wherein the C_{4-8} 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.

[0085] 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 inappropriate effort which substitutions are chemically possible and which are not.

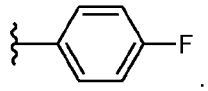
[0086] Ortho, meta and para substitution are well understood terms in the art. For the absence of doubt, "ortho" substitution is substitiution at a location adjacent to the position of attachment to the rest of the molecule, for example the two groups below are ortho substituted by fluorine:



[0087] "Meta" substitution is substitiution on the second atom away from the atom where the group is attached to the rest of the molecule, for example the two groups below are meta substituted by fluorine:



[0088] "Para" substitution is substitiution on the second atom away from the atom where the group is attached to the rest of the molecule, for example the group below is para substituted by fluorine:



[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, C_{1-6} alkyl, C_{3-8} cycloalkyl, phenyl, benzyl or phenethyl group, eg R is H or C_{1-3} 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] The invention contemplates pharmaceutically acceptable salts of the compounds of formula (**I**). These may include the acid addition and base salts of the compounds.

[0091] 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.

[0092] 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).

[0093] Preferably the salt is an acid addition salt. The salts may be formate or hydrochloride.

[0094] Pharmaceutically acceptable salts of compounds of formula (**I**) may be prepared by one or more of three methods:

(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.

[0095] 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.

[0096] 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.

[0097] 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 Haleblian (August 1975).

[0098] Hereinafter all references to compounds of any formula include references to salts, solvates and complexes thereof and to solvates and complexes of salts thereof.

[0099] 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.

[00100] Before purification, 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.

[00101] 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.

[00102] 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 crystallization or chromatography.

[00103] The method of treatment or the compound for use in the treatment of cancer, 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.

[00104] The method of treatment or the compound for use in the treatment of cancer, 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 (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, methotrexate, pemetrexed, cytosine arabinoside, 6-mercaptopurine riboside, leucovarin, UFT, doxifluridine, carmoflur, cytarabine, enocitabine 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, 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 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, lasofoxifeneand iodoxyfene), 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 5α-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; pemtumomab; and toll-like receptor modulators for example TLR-7 or TLR-9 agonists; and

(viii) cytotoxic agents for example fludaribine (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, fluclorolone, flumethasone, flunisolide, fluocinolone, fluocinolone acetonide, 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 acetonide, 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.

[00105] 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 employ the compounds of this invention within a therapeutically effective dosage range described hereinbefore and the other pharmaceutically-active agent within its approved dosage range.

[00106] 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.

[00107] In an embiment 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.

[00108] 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.

[00109] In an embodiment the condition is a condition modulated by Smo.

[00110] 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.

[00111] 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.

[00112] 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.

[00113] The condition modulated by the Hedgehog signalling pathway or Smo described above may be cancer, sarcoma, carcinoma, blastoma, lymphoma and leukemia. More specifically the condition modulated by BTK 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.

[00114] Conditions also treatable by the inhibition of the Hedgehog signalling pathway or Smo may be selected from inhibiting stem cell production, inhibiting stem cell renewal, inhibiting and/or modulating stem cell differentiation, benign prostatic hyperplasia, psoriasis and osteoporosis.

[00115] 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 (µg/kg) to 100 milligrams per kilogram body weight (mg/kg).

[00116] 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.

[00117] 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.

[00118] 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 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.

[00119] For oral administration the compounds of the invention may be admixed with an adjuvant 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 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.

[00120] 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

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 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.

[00121] For intravenous (parenteral) administration the compounds of the invention may be administered as a sterile aqueous or oily solution.

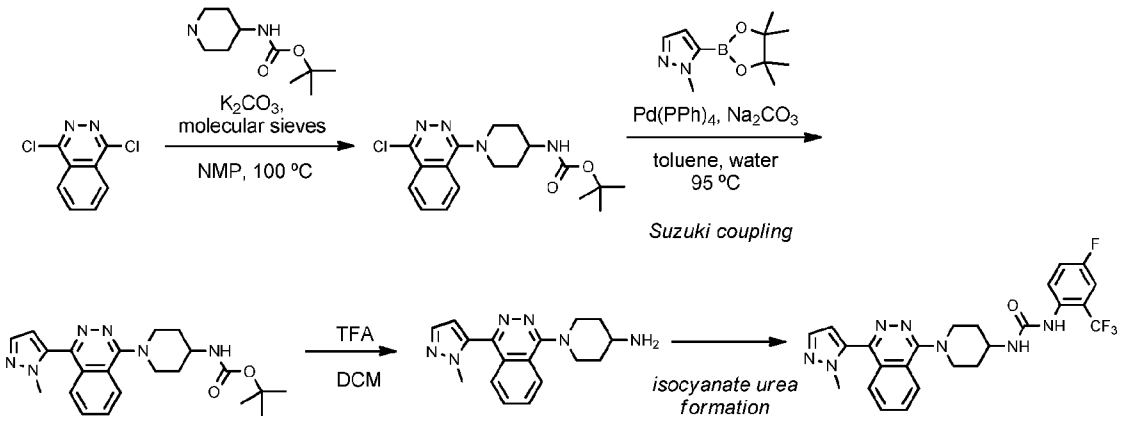
[00122] The size of the dose for therapeutic purposes of compounds of the invention will naturally vary according to the nature and severity of the conditions, the age and sex of the animal or patient and the route of administration, according to well-known principles of medicine.

[00123] 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 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

[00124] As used herein the following terms have the meanings given: "Boc" refers to tert-butoxycarbonyl; "CV" refers to column volume, "DCM" refers to dichloromethane; "DIPEA" refers to N,N-Diisopropylethylamine; "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.

[00125] The compounds of the invention may be synthesised by analogy with the following reaction route.



[00126] 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 before or after the urea formation etc.. Protecting groups may be present or absent as necessary. For example a nitrogen atom may be protected or unprotected.

[00127] 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 2µL aliquot was injected onto a guard column (0.2µm x 2 mm filters) and UPLC column (C18, 50 x 2.1 mm, < 2µm) in sequence maintained at 40°C. The samples were eluted at a flow rate of 0.6mL/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

[00128] NMR was also used to characterise final compounds. NMR spectra were obtained on a Bruker AVIII 400 Nanobay with 5mm BBFO probe. Optionally, compound Rf values on silica thin layer chromatography (TLC) plates were measured.

[00129] 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.

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

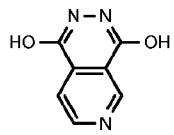
Table 2

[00130] 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.

[00131] Certain starting materials in the synthesis of compounds of formula (**I**) can be produced by the following procedures:

[00132] Procedure A

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



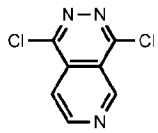
Pyridine-3,4-dicarboxylic acid (3.10g, 18.6mmol) and acetic anhydride (7.0mL, 74.2mmol) were added to a 50mL round bottomed flask and heated to reflux at 140°C. The white suspension turned into a black solution. The reaction was heated at this temperature for 3 hours. The reaction was cooled and the acetic anhydride was taken off by rotary evaporation to afford crude 3,4-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 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%).

^{1}H 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 (s(br),1H) .

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

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



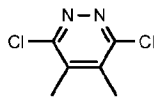
Pyrido[3,4-*d*]pyridazine-1,4-diol (1.83g, 11.2mmol) and phosphorus oxychloride (8.4mL, 89.7mmol) were added to a round bottomed flask. To this was added DIPEA (2.0mL, 11.2mmol) slowly. The suspension was then heated for 1 hour at 100°C. The reaction turned into a brown solution. The phosphorus oxychloride was then removed by rotary evaporator. The resulting brown residue was dissolved in DCM and added dropwise to a mixture of ice and saturated $NaHCO_3$ solution (aq). Saturated $NaHCO_3$ 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). The organic layers were combined and dried ($MgSO_4$) and then concentrated *in vacuo* to afford 1,4-dichloropyrido[3,4-*d*]pyridazine (1.74g, 8.7mmol, 77.6%).

^{1}H NMR (400MHz, $CDCl_3$) 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 200.0/202.0 $[M+H]^+$.

Similarly prepared was:

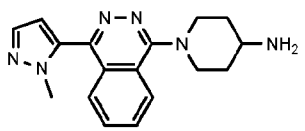
3,6-Dichloro-4,5-dimethyl-pyridazine



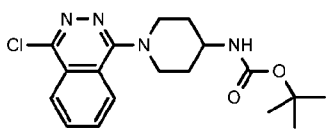
^{1}H NMR (400MHz, $CDCl_3$) δ/ppm: 2.46 (s, 6H).

[00133] Procedure B

Preparation of **1-[4-(2-methylpyrazol-3-yl)phthalazin-1-yl]piperidin-4-amine** and related compounds, intermediates in the synthesis of compounds of formula (**I**).



***tert*-Butyl *N*-[1-(4-chlorophthalazin-1-yl)-4-piperidyl]carbamate**



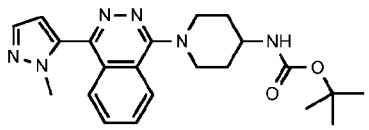
1,4-Dichlorophthalazine (4.80g, 24.1mmol) and 4-Boc-aminopiperidine (5.00g, 25.0mmol) were combined in NMP at room temperature and potassium carbonate (3.67g, 26.5mmol) was added followed by activated molecular sieves. Then the reaction was heated to 100°C overnight. The reaction was cooled to room temperature and poured over ice water, creating an off white semi-

solid precipitate. The products were extracted into ethyl acetate (x3) and then back washed with more water. The combined organics were washed with brine, dried ($MgSO_4$) and then concentrated *in vacuo* to afford *tert*-butyl *N*-[1-(4-chlorophthalazin-1-yl)-4-piperidyl]carbamate (7.08 g 19.5mmol, 80%) as an off white/fawn coloured amorphous solid.

^1H NMR (400MHz, $CDCl_3$) δ/ppm: 8.27-8.22 (m, 1H), 8.06-8.01 (m,1H), 7.94-7.88 (m,2H), 4.59 (s(br), 1H), 3.87 (m(br), 2H), 3.79 (s(br), 1H), 3.25 (m(br), 2H), 2.2-2.13 (m, 2H), 1.80-1.68 (m, 2H), 1.49 (s, 9H).

MS Method 1: RT: 3.94min, ES^+ m/z 363.3 $[M+H]^+$

tert-Butyl _N_-[1-[4-(2-methylpyrazol-3-yl)phthalazin-1-yl]-4-piperidyl]carbamate

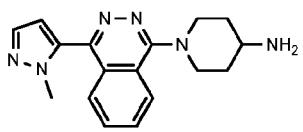


tert-Butyl *N*-[1-(4-chlorophthalazin-1-yl)-4-piperidyl]carbamate (2.0g, 5.5mmol) was dissolved in toluene (45mL) (required heating) and a solution of catalyst generated from triphenylphosphine (0.52g, 2.0mmol) and palladium acetate (112mg, 0.5mmol) in toluene (5mL) and ethanol (15mL) was added. 1-Methyl-1*H*-pyrazole-5-boronic acid, pinacolester (1.67g, 8.0mmol) was then added followed by water (15mL) and the sodium carbonate (1.75g 16.5mmol). The solution was de-gassed under vacuum and purged with nitrogen three times before heating to 95°C overnight. LCMS confirmed the presence of the desired product hence the reaction was cooled to room temperature and diluted with ethyl acetate and water. The organic and aqueous layers were separated and the organic layer washed with brine, dried ($MgSO_4$) and then concentrated *in vacuo* to afford a dark brown oil/gum. Purification by silica flash chromatography using 10% 3M NH_3/MeOH: 30% ethyl acetate: 60% heptane afforded *tert*-butyl *N*-[1-[4-(2-methylpyrazol-3-yl)phthalazin-1-yl]-4-piperidyl]carbamate (1.99 g 4.87mmol, 88%) as an off-white solid.

^1H NMR (400MHz, $CDCl_3$) δ/ppm: 8.11-8.06 (m,2H), 7.90-7.81 (m,2H), 7.67 (d, *J* 1.9Hz, 1H), 6.60 (d, *J* 1.9Hz, 1H), 4.61 (s (br), 1H), 4.07 (s, 3H), 4.00 (m(br), 2H), 3.82 (s(br), 1H), 3.32 (m(br), 2H), 2.24-2.17 (m, 2H), 1.84-1.73 (m, 2H), 1.50 (s, 9H).

MS Method 1: RT: 3.65min, ES^+ m/z 409.4 $[M+H]^+$

1-[4-(2-Methylpyrazol-3-yl)phthalazin-1-yl]piperidin-4-amine



A solution containing *tert*-butyl *N*-[1-[4-(2-methylpyrazol-3-yl)phthalazin-1-yl]-4-piperidyl]carbamate (6.0g, 14.7mmol) and trifluoroacetic acid (12.6mL, 176mmol) in DCM (40mL) was stirred overnight. The reaction mixture was concentrated *in vacuo*. The crude material was purified by SCX with MeOH washings followed by 2M NH_3 in MeOH to elute the product. The resulting solution was

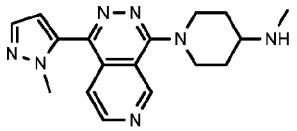
concentrated under reduced pressure to afford 1-[4-(2-methylpyrazol-3-yl)phthalazin-1-yl]piperidin-4-amine (2.82g,9.1mmol, 62% yield) as an oil.

^{1}H NMR (400MHz, $CDCl_3$) δ/ppm: 8.11-8.02 (m, 2H), 7.88-7.78 (m, 2H), 7.65 (d, *J* 1.9Hz, 1H), 6.58 (d, *J* 1.9Hz, 1H), 4.04 (s, 3H), 4.00 (m(br), 2H), 3.22 (m(br), 2H), 3.02 (tt, *J* 10.5hz, 4.2Hz 1H), 2.10-2.01 (m, 2H), 1.77-1.67 (m, 2H).

MS Method 2: RT: 0.91min. m/z 309.2 $[M+H]^+$

Similarly prepared was:

***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, 150mmol) , NMP (50mL) and heated to 100°C with stirring 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 (1.1g, 2.9mmol, 5.8%, 98% purity). Further mixed fractions of lower purity were also obtained.

^{1}H 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 (m(br), 2H), 3.29 (t, *J*12.5Hz, 2H), 2.83 (s, 3H), 2.11-1.97 (m, 2H), 1.90-1.81 (m, 2H), 1.50 (s, 9H).

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

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-1*H*-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 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 a gradient from 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%)

^{1}H NMR (400MHz, $CDCl_3$) 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).

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

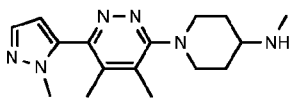
To a round bottomed flask was added *tert*-butyl *N*-methyl-*N*-[1-[1-(2-methylpyrazol-3-yl)pyrido[3,4-d]pyridazin-4-yl]-4-piperidyl]carbamate (1.50g, 3.54mmol) and trifluoroacetic acid (4.mL, 52mmol) and stirred at room temprature for 2 hours. The reaction was concentrated *in vacuo* and the resulting 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%).

^{1}H NMR (400MHz, $CDCl_3$) 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).

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 Na_2CO_3 aq. (50 mL). The organic layer was washed with 1M Na_2CO_3 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 actetate. 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).

^{1}H NMR (400MHz, $CDCl_3$) □/ppm: 4.34-3.84 (m, 2H), 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 (30mL, 16.91mmol) and a solution of potassium hydrophosphate (5.9g, 33.8mmol in 15mL water) was added, The vessels were sealed, the reaction

degassed with nitrogen by bubbling through the reaction mixture 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 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%).

^{1}H NMR (400MHz, $CDCl_3$) 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 (m(br), 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 $[M+H]^+$

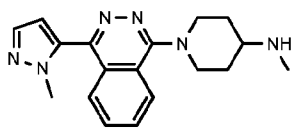
Trifluoroacetic acid (3.0mL, 39.2mmol) was added dropwise to a stirring solution of *tert*-butyl *N*-[1-[4,5-dimethyl-6-(2-methylpyrazol-3-yl)pyridazin-3-yl]-4-piperidyl]-*N*-methyl-carbamate (2.0g, 4.99mmol) in DCM (30mL) at room temperature and the reaction was stirred for 2 h. Further TFA (0.8 mL) was added and the reaction was stirred overnight. The mixture was concentrated *in vacuo* 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 NH_3 / 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) .

^{1}H NMR (400MHz, $CDCl_3$) 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), 3H), 3.03 (t, *J*12.2Hz, 2H), 2.61 (tt, *J*10.5Hz, 4.3Hz, 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:

_N_-Methyl-1-[4-(2-methylpyrazol-3-yl)phthalazin-1-yl]piperidin-4-amine



^{1}H NMR (400MHz, $CDCl_3$) δ/ppm: 8.10 (d, *J* 8.1Hz, 1H), 8.08 (d, *J* 8.1Hz, 1H), 7.90-7.80 (m, 2H), 7.67 (d, *J* 1.9Hz, 1H), 6.60 (d, *J* 1.9Hz, 1H), 4.07 (s, 3H), 4.07-4.01 (m(br), 2H), 3.28-3.20 (m(br), 2H), 2.73 (tt, *J* 10.5Hz, 3.9Hz, 1H), 2.55 (s, 3H), 2.20-2.13 (m, 2H), 1.78-1.67 (m, 2H).

tert-Butyl 4-[[4-fluoro-2-(trifluoromethyl)phenyl]methyl-methyl-amino]piperidine-1-carboxylate (1.15g, 2.95mmol) and trifluoroacetic acid (4.5mL, 58.9mmol) were combined and stirred at room temperature for 4 hours. The solution turned from to clear to light pink. The reaction was concentrated *in vacuo* and the resulting pink oil was dissolved in methanol and loaded onto a methanol primed SCX cartridge and washed with methanol (x3 column volumes) and triethylamine in methanol (x3 column volumes). The triethylamine wash was then concentrated *in vacuo* to afford N-[[4-fluoro-2-(trifluoromethyl)phenyl]methyl]-N-methyl-piperidin-4-amine (750mg, 2.6mmol, 88%).

^{1}H NMR (400MHz, $CDCl_3$) δ/ppm: 7.84 (dd, *J* 8.5Hz, 5.8Hz 1H), (dd, *J* 5.8Hz, 2.7Hz 1H), 7.22 (td, *J* 8.5Hz, 2.7Hz, 1H), 3.73 (s(br), 2H), 3.24-3.18 (m(br), 2H), 2.85 (s(br), 1H), 2.63 (td, *J*12.2Hz, 2.4Hz, 2H), 2.56 (tt, *J* 11.5Hz, 3.6Hz, 1H), 2.22 (s, 3H), 1.89-1.82 (m(br), 2H), 1.56 (qd, *J* 12.1Hz, 3.9Hz, 2H)

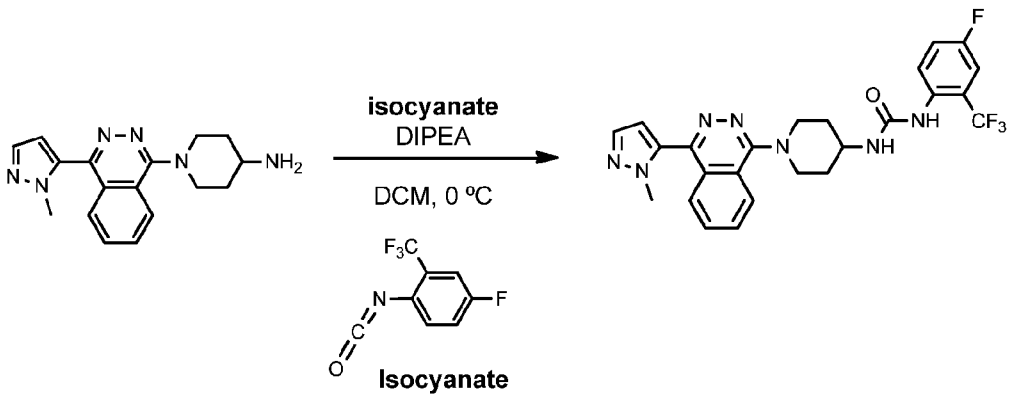
MS Method 2: RT: 0.73min, m/z 291.3 $[M+H]^+$

[00134] Compounds produced in the Procedures described above may take part in reactions to produce compounds of the invention, such as those exemplified below.

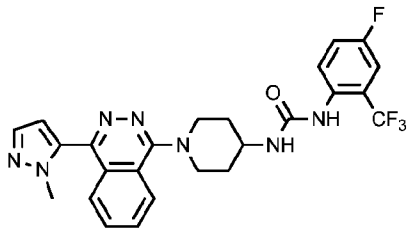
[00135] Example 1

[00136] Compounds of formula (**I**) can be prepared by the General Method A, shown below. General Method A may be carried out using compounds prepared by Procedure B as starting materials or another appropriate method for producing the starting materials may be used.

[00137] General Method A



1-[4-fluoro-2-(trifluoromethyl)phenyl]-3-[1-[4-(2-methylpyrazol-3-yl)phthalazin-1-yl]-4-piperidyl]urea



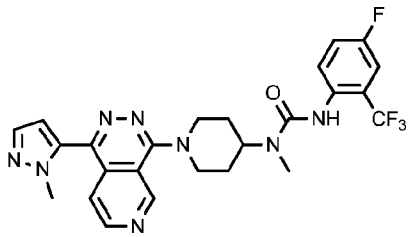
In dried glassware DIPEA (0.06mL, 0.34mmol), DCM (1mL) and 1-[4-(2-methylpyrazol-3-yl)phthalazin-1-yl]piperidin-4-amine (0.05mL, 0.23mmol) were combined. The suspension was cooled to 0°C and to this was added 4-fluoro-2-(trifluoromethyl)phenyl isocyanate (0.04mL, 0.2500mmol) dropwise. The reaction was stirred at 0°C and then stirred overnight at room temperature. An off-white precipitate formed. The reaction was filtered and the solid was washed with DCM. The white solid was then dried in the vacuum oven overnight to afford 1-[4-fluoro-2-(trifluoromethyl)phenyl]-3-[1-[4-(2-methylpyrazol-3-yl)phthalazin-1-yl]-4-piperidyl]urea (57.7mg, 0.11mmol, 50%).

^{1}H NMR (400MHz,DMSO-d6) δ/ppm: 8.19 (d, *J* 8.2Hz, 1H), 8.05-7.92 (m, 4H), 7.80 (s, 1H), 7.66 (d, *J* 1.9Hz, 1H), 7.55-7.47 (m, 2H), 7.15 (d, *J* 7.5Hz, 1H), 6.69 (d, *J* 1.9Hz, 1H), 3.89-3.82 (m(br), 3H), 3.87 (s, 3H), 3.34-3.26 (m, 2H), 2.14-2.06 (m, 2H), 1.82-1.71 (m, 2H).

MS Method 2: RT: 1.48 min, m/z 514.3 $[M+H]^+$

Similarly prepared was:

3-[4-Fluoro-2-(trifluoromethyl)phenyl]-1-methyl-1-[1-[1-(2-methylpyrazol-3-yl)pyrido[3,4-d]pyridazin-4-yl]-4-piperidyl]urea.



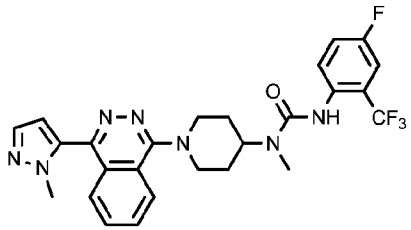
To a solution of *N*-methyl-1-[1-(2-methylpyrazol-3-yl)pyrido[3,4-*d*]pyridazin-4-yl]piperidin-4-amine (947mg, 2.93mmol) and *N,N*-diisopropylethylamine (0.76mL, 4.39mmol) in DCM (30mL) (dried over 4Å MS) was added 4-fluoro-2-(trifluoromethyl)phenyl isocyanate (0.42mL, 2.93mmol) dropwise at 0°C. The reaction was stirred at this temperature for 30min and then stirred at room temperature for 4 hours. The reaction was quenched with saturated aqueous. sodium bicarbonate and diluted with DCM , The mixture was passed through a phase separator and the aqueous layer was re-extracted several times with DCM, the organic layers were combined and concentrated *in vacuo*. The resulting residue was purified by silica flash chromatography using 0% methanol in ethyl acetate with a gradient increasing to 20% methanol in ethyl acetate to afford 3-[4-fluoro-2-(trifluoromethyl)phenyl]-1-methyl-1-[1-[1-(2-methylpyrazol-3-yl)pyrido[3,4-d]pyridazin-4-yl]-4-piperidyl]urea (920mg,1.74mmol, 59.5% yield) as a yellow solid. The product was then dried in the vacuum oven for 4 days.

^{1}H NMR (400MHz, $CDCl_3$) δ/ppm: 9.53 (s, 1H), 8.95 (d, *J*5.7Hz, 1H), 8.11 (dd, *J*9.0Hz, 5.0Hz, 1H), 7.86 (d, *J*5.7Hz, 1H), 7.68 (d, *J*1.9Hz, 1H), 7.33-7.23 (m, 2H), 6.73 (s, 1H), 6.61 (d, *J*1.9Hz, 1H), 4.66-4.55 (m, 1H), 4.39-4.31 (m(br), 2H), 4.11 (s, 3H), 3.47-3.37 (m, 2H), 2.99 (s, 3H), 2.16-2.04 (m, 2H), 1.99-1.92 (m, 2H).

MS Method 1: RT: 3.41 min, m/z 529.4 $[M+H]^+$

And similarly prepared was:

3-[4-Fluoro-2-(trifluoromethyl)phenyl]-1-methyl-1-[1-[4-(2-methylpyrazol-3-yl)phthalazin-1-yl]-4-piperidyl]urea

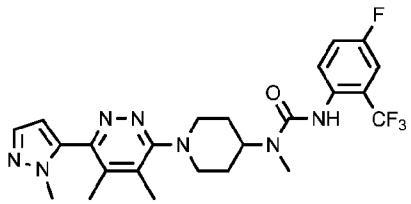


^{1}H NMR (400MHz, $CDCl_3$) δ/ppm: 8.17-8.07 (m, 3H), 7.92-7.82, (m, 2H), 7.68 (d, *J*1.9Hz, 1H), 7.34-7.25 (m, 2H), 6.76 (s, 1H), 6.61 (d, *J*1.9Hz, 1H),4.61-4.51 (m, 1H), 4.24-4.16 (m(br), 2H), 4.08 (s, 3H), 3.40-3.30 (t, *J* 12.5Hz, 2H), 3.02 (s, 3H), 2.20-2.08 (m, 2H), 1.98-1.91 (m, 2H).

MS Method 1: RT: 3.47min, m/z 528.3 $[M+H]^+$

And similarly prepared was:

1-[1-[4,5-Dimethyl-6-(2-methylpyrazol-3-yl)pyridazin-3-yl]-4-piperidyl]-3-[4-fluoro-2-(trifluoromethyl)phenyl]-1-methyl-urea.



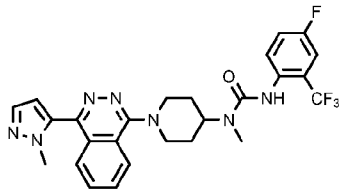
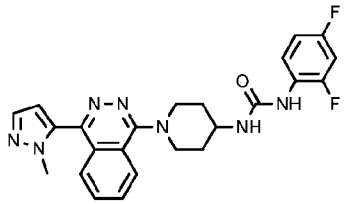
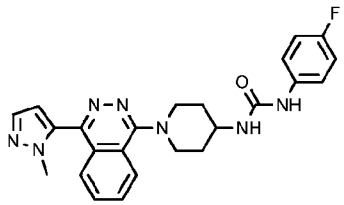
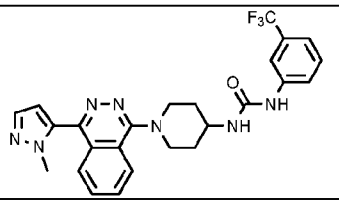
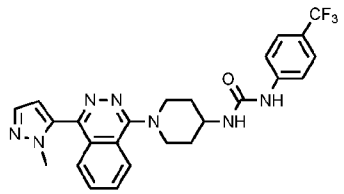
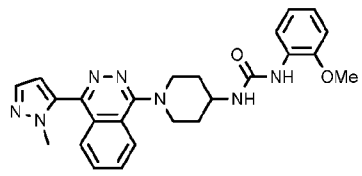
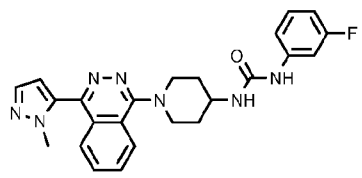
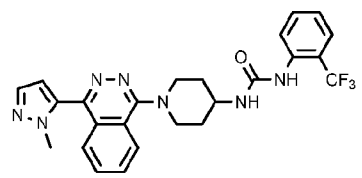
^{1}H NMR (400MHz, $CDCl_3$) δ/ppm: 8.15-8.09 (m, 1H), 7.57 (d, *J*2.0Hz, 1H), 7.31-7.21 (m, 2H), 6.72 (s, 1H), 6.36 (d, *J*2.0Hz, 1H), 4.48-4.37 (m, 1H), 3.93 (s, 3H), 3.74-3.67 (m(br), 2H), 3.16 (t, *J*12.8Hz, 2H), 2.96 (s, 3H), 2.30 (s, 3H), 2.23 (s, 3H), 2.03-1.91 (m, 2H), 1.90-1.83 (m, 2H).

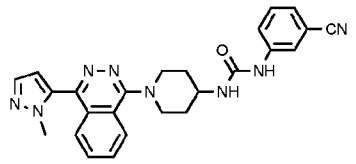
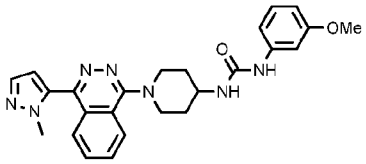
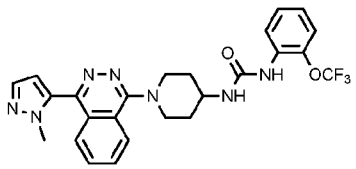
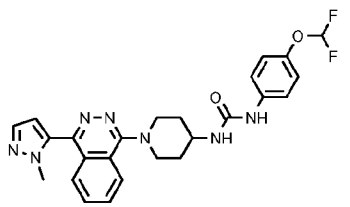
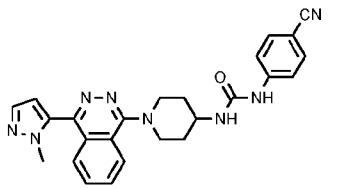
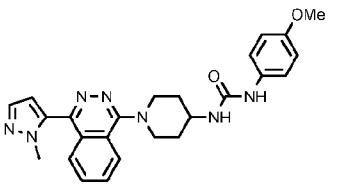
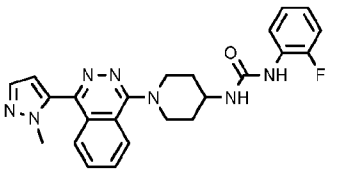
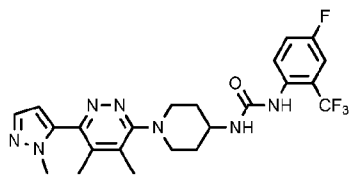
MS Method 1: RT: 3.63min, m/z 506.3 $[M+H]^+$

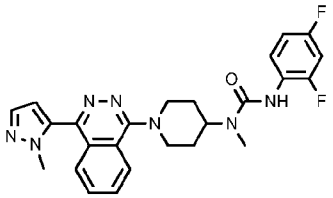
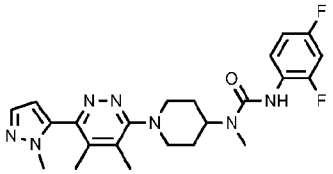
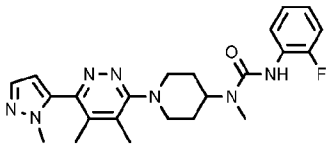
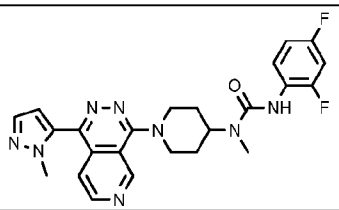
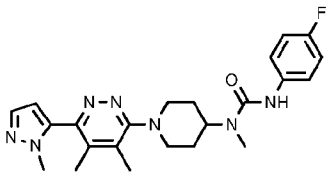
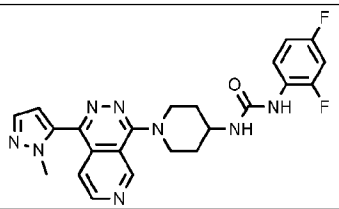
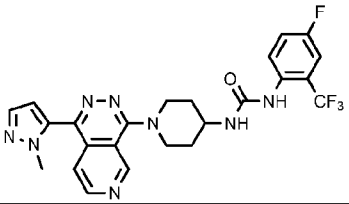
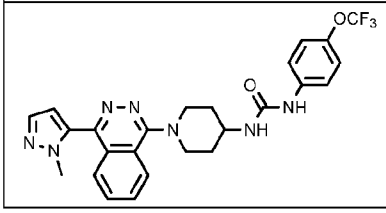
[00138] The compounds shown below in **Table 3** were similarly prepared by varying the isocyanate used in General Method A.

Table 3

Structure	Name	LCMS RT	m/z MIM

Structure	Name	LCMS RT	m/z MIM
	3-[4-fluoro-2-(trifluoromethyl)phenyl]-1-methyl-1-[1-[4-(2-methylpyrazol-3-yl)phthalazin-1-yl]-4-piperidyl]urea	1.52min (Method 2)	528.3 $[M+H]^+$
	1-(2,4-difluorophenyl)-3-[1-[4-(2-methylpyrazol-3-yl)phthalazin-1-yl]-4-piperidyl]urea	1.37min (Method 2)	464.3 $[M+H]^+$
	1-(4-fluorophenyl)-3-[1-[4-(2-methylpyrazol-3-yl)phthalazin-1-yl]-4-piperidyl]urea	1.33min (Method 2)	446.3 $[M+H]^+$
	1-[1-[4-(2-methylpyrazol-3-yl)phthalazin-1-yl]-4-piperidyl]-3-[3-(trifluoromethyl)phenyl]urea	1.53min (Method 2)	496.3 $[M+H]^+$
	1-[1-[4-(2-methylpyrazol-3-yl)phthalazin-1-yl]-4-piperidyl]-3-[4-(trifluoromethyl)phenyl]urea	1.54min (Method 2)	497.1 $[M+H]^+$
	1-(2-methoxyphenyl)-3-[1-[4-(2-methylpyrazol-3-yl)phthalazin-1-yl]-4-piperidyl]urea	1.37min (Method 2)	458.3 $[M+H]^+$
	1-(3-fluorophenyl)-3-[1-[4-(2-methylpyrazol-3-yl)phthalazin-1-yl]-4-piperidyl]urea	1.37min (Method 2)	446.3 $[M+H]^+$
	1-[1-[4-(2-methylpyrazol-3-yl)phthalazin-1-yl]-4-piperidyl]-3-[2-(trifluoromethyl)phenyl]urea	1.46min (Method 2)	496.3 $[M+H]^+$

Structure	Name	LCMS RT	m/z MIM
	1-(3-cyanophenyl)-3-[1-[4-(2-methylpyrazol-3-yl)phthalazin-1-yl]-4-piperidyl]urea	1.33min (Method 2)	453.3 $[M+H]^+$
	1-(3-methoxyphenyl)-3-[1-[4-(2-methylpyrazol-3-yl)phthalazin-1-yl]-4-piperidyl]urea	1.33min (Method 2)	458.2 $[M+H]^+$
	1-[1-[4-(2-methylpyrazol-3-yl)phthalazin-1-yl]-4-piperidyl]-3-[2-(trifluoromethoxy)phenyl]urea	1.54min (Method 2)	512.4 $[M+H]^+$
	1-[4-(difluoromethoxy)phenyl]-3-[1-[4-(2-methylpyrazol-3-yl)phthalazin-1-yl]-4-piperidyl]urea	1.41min (Method 2)	494.3 $[M+H]^+$
	1-(4-cyanophenyl)-3-[1-[4-(2-methylpyrazol-3-yl)phthalazin-1-yl]-4-piperidyl]urea	1.32min (Method 2)	453.2 $[M+H]^+$
	1-(4-methoxyphenyl)-3-[1-[4-(2-methylpyrazol-3-yl)phthalazin-1-yl]-4-piperidyl]urea	1.29min (Method 2)	458.3 $[M+H]^+$
	1-(2-fluorophenyl)-3-[1-[4-(2-methylpyrazol-3-yl)phthalazin-1-yl]-4-piperidyl]urea	1.35min (Method 2)	446.3 $[M+H]^+$
	1-[1-[4,5-dimethyl-6-(2-methylpyrazol-3-yl)pyridazin-3-yl]-4-piperidyl]-3-[4-fluoro-2-(trifluoromethyl)phenyl]urea	3.56min (Method 1)	492.4 $[M+H]^+$

Structure	Name	LCMS RT	m/z MIM
	3-(2,4-difluorophenyl)-1-methyl-1-[1-[4-(2-methylpyrazol-3-yl)phthalazin-1-yl]-4-piperidyl]urea	3.16min (Method 1)	478.4 $[M+H]^+$
	3-(2,4-difluorophenyl)-1-[1-[4,5-dimethyl-6-(2-methylpyrazol-3-yl)pyridazin-3-yl]-4-piperidyl]-1-methyl-urea	3.31min (Method 1)	456.4 $[M+H]^+$
	1-[1-[4,5-dimethyl-6-(2-methylpyrazol-3-yl)pyridazin-3-yl]-4-piperidyl]-3-(2-fluorophenyl)-1-methyl-urea	3.28min (Method 1)	438.4 $[M+H]^+$
	3-(2,4-difluorophenyl)-1-methyl-1-[1-[1-(2-methylpyrazol-3-yl)pyrido[3,4-d]pyridazin-4-yl]-4-piperidyl]urea	3.07min (Method 1)	479.4 $[M+H]^+$
	1-[1-[4,5-dimethyl-6-(2-methylpyrazol-3-yl)pyridazin-3-yl]-4-piperidyl]-3-(4-fluorophenyl)-1-methyl-urea	3.29min (Method 1)	438.4 $[M+H]^+$
	1-(2,4-difluorophenyl)-3-[1-[1-(2-methylpyrazol-3-yl)pyrido[3,4-d]pyridazin-4-yl]-4-piperidyl]urea	3.11min (Method 1)	465.4 $[M+H]^+$
	1-[4-fluoro-2-(trifluoromethyl)phenyl]-3-[1-[1-(2-methylpyrazol-3-yl)pyrido[3,4-d]pyridazin-4-yl]-4-piperidyl]urea	3.37min (Method 1)	515.4 $[M+H]^+$
	1-[1-[4-(2-methylpyrazol-3-yl)phthalazin-1-yl]-4-piperidyl]-3-[4-(trifluoromethoxy)phenyl]urea	1.56min (Method 2)	512.3 $[M+H]^+$

[00139] In cases where the isocyanate is not readily commercially available it can be prepared in situ via various methods known to those skilled in the art.

[00140] Example 2

[00141] *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 12 below.

[00142] 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% CO_2. 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.

[00143] 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% CO_2.

[00144] 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.

[00145] 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% CO_2. 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% CO_2.

[00146] 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).

[00147] The results of the *in vitro* biological evaluation for certain compounds of the invention are given in the table 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 200 nM to 2 µM. The category "++" refers to

compounds with an IC50 of 10 nM to 200 nM. The category "+++" refers to compounds with an IC50 of <10 nM.

ID No.	Compound	Category
1	3-[4-fluoro-2-(trifluoromethyl)phenyl]-1-methyl-1-[1-[4-(2-methylpyrazol-3-yl)phthalazin-1-yl]-4-piperidyl]urea	+++
2	1-(2,4-difluorophenyl)-3-[1-[4-(2-methylpyrazol-3-yl)phthalazin-1-yl]-4-piperidyl]urea	+++
3	1-(4-fluorophenyl)-3-[1-[4-(2-methylpyrazol-3-yl)phthalazin-1-yl]-4-piperidyl]urea	+++
4	1-[1-[4-(2-methylpyrazol-3-yl)phthalazin-1-yl]-4-piperidyl]-3-[3-(trifluoromethyl)phenyl]urea	+++
5	1-[1-[4-(2-methylpyrazol-3-yl)phthalazin-1-yl]-4-piperidyl]-3-[4-(trifluoromethyl)phenyl]urea	+++
6	1-(2-methoxyphenyl)-3-[1-[4-(2-methylpyrazol-3-yl)phthalazin-1-yl]-4-piperidyl]urea	+++
7	1-(3-fluorophenyl)-3-[1-[4-(2-methylpyrazol-3-yl)phthalazin-1-yl]-4-piperidyl]urea	+++
8	1-[1-[4-(2-methylpyrazol-3-yl)phthalazin-1-yl]-4-piperidyl]-3-[2-(trifluoromethyl)phenyl]urea	+++
9	1-(3-cyanophenyl)-3-[1-[4-(2-methylpyrazol-3-yl)phthalazin-1-yl]-4-piperidyl]urea	+++
10	1-[4-fluoro-2-(trifluoromethyl)phenyl]-3-[1-[4-(2-methylpyrazol-3-yl)phthalazin-1-yl]-4-piperidyl]urea	+++
11	1-(3-methoxyphenyl)-3-[1-[4-(2-methylpyrazol-3-yl)phthalazin-1-yl]-4-piperidyl]urea	+++
12	1-[1-[4-(2-methylpyrazol-3-yl)phthalazin-1-yl]-4-piperidyl]-3-[2-(trifluoromethoxy)phenyl]urea	+++
13	1-[4-(difluoromethoxy)phenyl]-3-[1-[4-(2-methylpyrazol-3-yl)phthalazin-1-yl]-4-piperidyl]urea	+++
14	1-(4-cyanophenyl)-3-[1-[4-(2-methylpyrazol-3-yl)phthalazin-1-yl]-4-piperidyl]urea	+++
15	1-(4-methoxyphenyl)-3-[1-[4-(2-methylpyrazol-3-yl)phthalazin-1-yl]-4-piperidyl]urea	++
16	1-(2-fluorophenyl)-3-[1-[4-(2-methylpyrazol-3-yl)phthalazin-1-yl]-4-piperidyl]urea	+++

[00148] Further results of the *in vitro* biological evaluation for certain compounds of the invention are given in the table 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 200 nM to 2 μM. The category "**" refers to compounds with an IC50 of 10 nM to 200 nM. The category "***" refers to compounds with an IC50 of <10 nM.

[00149]

ID No.s	Compound	Gli luc IC50 nM
17	1-[1-[4,5-dimethyl-6-(2-methylpyrazol-3-yl)pyridazin-3-yl]-4-piperidyl]-3-[4-fluoro-2-(trifluoromethyl)phenyl]urea	**
18	1-(2,4-difluorophenyl)-3-[1-[1-(2-methylpyrazol-3-yl)pyrido[3,4-d]pyridazin-4-yl]-4-piperidyl]urea	**
19	1-[4-fluoro-2-(trifluoromethyl)phenyl]-3-[1-[1-(2-methylpyrazol-3-yl)pyrido[3,4-d]pyridazin-4-yl]-4-piperidyl]urea	***
20	3-(2,4-difluorophenyl)-1-methyl-1-[1-[1-(2-methylpyrazol-3-yl)pyrido[3,4-d]pyridazin-4-yl]-4-piperidyl]urea	**
21	3-[4-fluoro-2-(trifluoromethyl)phenyl]-1-methyl-1-[1-[1-(2-methylpyrazol-3-yl)pyrido[3,4-d]pyridazin-4-yl]-4-piperidyl]urea	***
22	1-[1-[4,5-dimethyl-6-(2-methylpyrazol-3-yl)pyridazin-3-yl]-4-piperidyl]-3-(4-fluorophenyl)-1-methyl-urea	*
23	1-[1-[4,5-dimethyl-6-(2-methylpyrazol-3-yl)pyridazin-3-yl]-4-piperidyl]-3-(2-fluorophenyl)-1-methyl-urea	**
24	3-(2,4-difluorophenyl)-1-[1-[4,5-dimethyl-6-(2-methylpyrazol-3-yl)pyridazin-3-yl]-4-piperidyl]-1-methyl-urea	*
25	1-[1-[4,5-dimethyl-6-(2-methylpyrazol-3-yl)pyridazin-3-yl]-4-piperidyl]-3-[4-fluoro-2-(trifluoromethyl)phenyl]-1-methyl-urea	***
26	1-[1-[4-(2-methylpyrazol-3-yl)phthalazin-1-yl]-4-piperidyl]-3-[4-(trifluoromethoxy)phenyl]urea	***
27	3-(2,4-difluorophenyl)-1-methyl-1-[1-[4-(2-methylpyrazol-3-yl)phthalazin-1-yl]-4-piperidyl]urea	***

[00150] Examples of compounds of the invention with values for their IC50 are given in the table below.

ID No.	Compound	Gli Luc nM
1	3-[4-fluoro-2-(trifluoromethyl)phenyl]-1-methyl-1-[1-[4-(2-methylpyrazol-3-yl)phthalazin-1-yl]-4-piperidyl]urea	0.05
2	1-(2,4-difluorophenyl)-3-[1-[4-(2-methylpyrazol-3-yl)phthalazin-1-yl]-4-piperidyl]urea	0.99

3	1-(4-fluorophenyl)-3-[1-[4-(2-methylpyrazol-3-yl)phthalazin-1-yl]-4-piperidyl]urea	1.33
5	1-[1-[4-(2-methylpyrazol-3-yl)phthalazin-1-yl]-4-piperidyl]-3-[4-(trifluoromethyl)phenyl]urea	0.71
10	1-[4-fluoro-2-(trifluoromethyl)phenyl]-3-[1-[4-(2-methylpyrazol-3-yl)phthalazin-1-yl]-4-piperidyl]urea	0.66
21	3-[4-fluoro-2-(trifluoromethyl)phenyl]-1-methyl-1-[1-[1-(2-methylpyrazol-3-yl)pyrido[3,4-d]pyridazin-4-yl]-4-piperidyl]urea	1.25
25	1-[1-[4,5-dimethyl-6-(2-methylpyrazol-3-yl)pyridazin-3-yl]-4-piperidyl]-3-[4-fluoro-2-(trifluoromethyl)phenyl]-1-methyl-urea	5.12

[00151] Aqueous solubility evaluation of compounds of the invention was carried out using the procedures detailed below.

[00152] Kinetic Solubility

[00153] 6 µL of 10 mM DMSO are added to 294 µL of pH 7.4 phosphate buffer (0.1 M) in a 96 well filter plate (Millipore). The concentration of DMSO in the sample is 2% *v/v* and the maximum kinetic solubility attainable is 200 µM. A standard plate is prepared in a similar way by adding 14 µL of 10 mM DMSO to 686 µL of DMSO in a 1.5 mL 96 well plate. Both plates are shaken at room temperature for 2 h. At the end of this period the contents of the sample plate are filtered by positive pressure. The concentrations of the compounds in the supernatants are measured by HPLC-UV detection against single point calibration standards. For example 3-[4-fluoro-2-(trifluoromethyl)phenyl]-1-methyl-1-[1-[1-(2-methylpyrazol-3-yl)pyrido[3,4-d]pyridazin-4-yl]-4-piperidyl]urea had a solubility of 100.4mg/L (n of 3) or 190uM (n of 3).

[00154] Thermodynamic Solubility with Centrifugation

[00155] 0.5 mg of compound is weighed into a 1 mL glass vial (QMX). These vials fit into a 96 well plate designed to hold them. 0.5 mL of pH 7.4 phosphate buffer (0.1 M) is dispensed with a multichannel pipettor to each of the vials. The plate with vials is then shaken at 800 rpm for 24 h at room temperature. At the end of this period, the supernatants are centrifuged two consecutive times at 3000 rpm. A standard plate is prepared by pipetting 25 µL of 10 mM DMSO stock in a 475 µL of DMSO to give 500 µM standards. The concentration of the supernatants is measured by detection against single point calibration standards. For example 3-[4-fluoro-2-(trifluoromethyl)phenyl]-1-methyl-1-[1-[1-(2-methylpyrazol-3-yl)pyrido[3,4-d]pyridazin-4-yl]-4-piperidyl]urea had a solubility of 360.3mg/L (n of 3) or 677uM (n of 3).

[00156] It can be seen from the above data that in addition to good IC50 values the compounds of the invention also possess good kinetic and thermodynamic solubility. This provides a further benefit when the compounds are used in therapy.

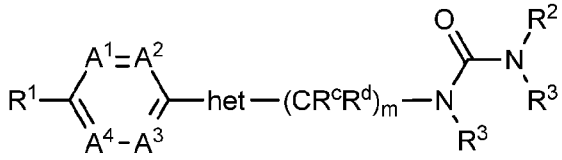
[00157] Throughout the description and claims of this specification, the words "comprise" and "contain" and variations of them mean "including but not limited to", and they are not intended to (and do not) exclude other moieties, additives, components, integers or steps. Throughout the description and 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.

[00158] 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 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 steps are mutually exclusive. The invention is not restricted to the details of any foregoing embodiments. 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.

[00159] 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 inspection with this specification, and the contents of all such papers and documents are incorporated herein by reference.

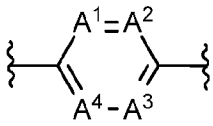
CLAIMS

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



(**I**)

wherein



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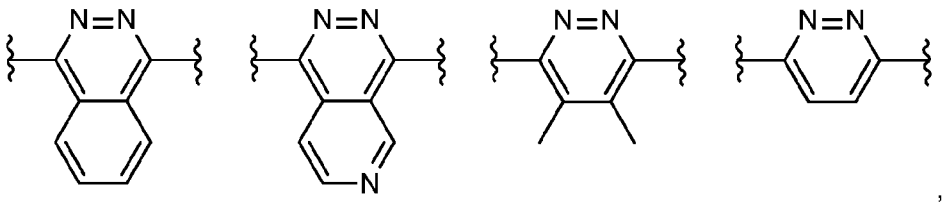

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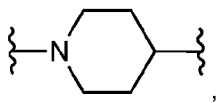


,

R^1 is substituted or unsubstituted pyrazolyl,

R^2 is substituted or unsubstituted phenyl, toluenyl and pyridinyl,

R^3 is H, methyl or $-C(O)CF_3$,

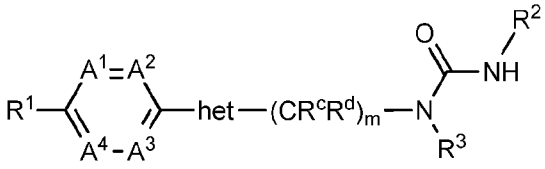
R^c and R^d are independently selected from H, halo, $-OR^a$, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} acyl, C_{3-7} cycloalkyl, and C_{3-7} halocycloalkyl, and

m is 0 or 1,

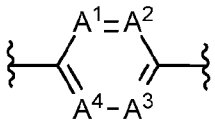
wherein when a group is substituted, the group contains 1 to 5 substituents independently selected at each occurrence from the group comprising: halo, $-OR^a$, $-SR^a$, $-NR^aR^b$, NO_2, -CN, acyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-8} cycloalkyl, $-SO_2R^a$, and SO_3R^a , $-C(OR^a)R^aR^b$, $-C(O)R^a$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

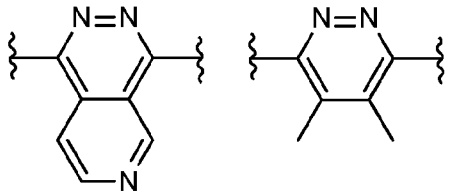
R^a and R^b are independently selected at each occurrence from: H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} acyl, C_{3-7} cycloalkyl, and C_{3-7} halocycloalkyl.

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



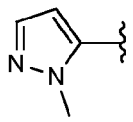
(**Ia**)

3. A compound of claim 1 or claim 2, wherein  is selected from:



4. A compound of any preceding claim, wherein m is 0.

5. A compound of any preceding claim wherein R^1 is:

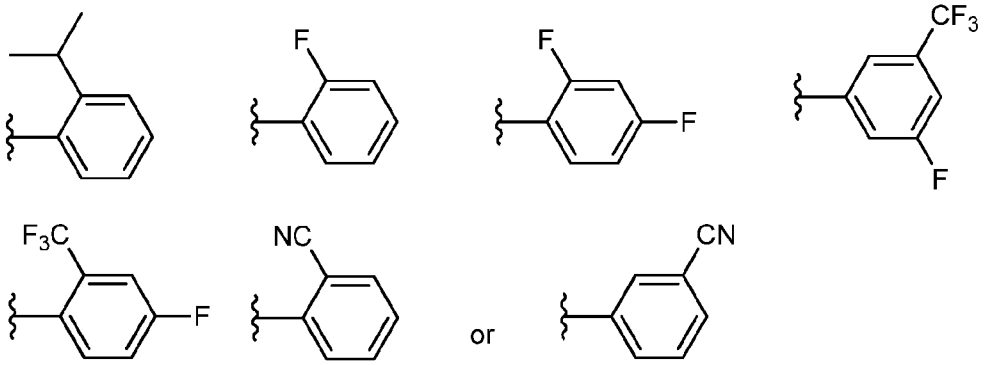


.

6. A compound of any preceding claim, wherein R^2 is substituted by 1 or 2 substituents independently selected at each occurrence from the group comprising halo, $-NO_2$, $-OC_{1-4}$ haloalkyl, C_{1-6} alkyl, C_{1-6} haloalkyl, $-C(OH)(C_{1-6}\text{ alkyl})C_{1-6}$ alkyl, $-SC_{1-4}$ alkyl and –CN.

7. A compound of claim 6 wherein R^2 is substituted by: trifluoromethyl; $-OCF_3$; $-C(OH)(CH_3)CH_3$; methyl; fluoro; chloro; –CN; fluoro and trifluoromethyl; fluoro and $-OCF_3$; or fluoro and methyl.

8. A compound of claim 7 wherein R^2 is selected from:

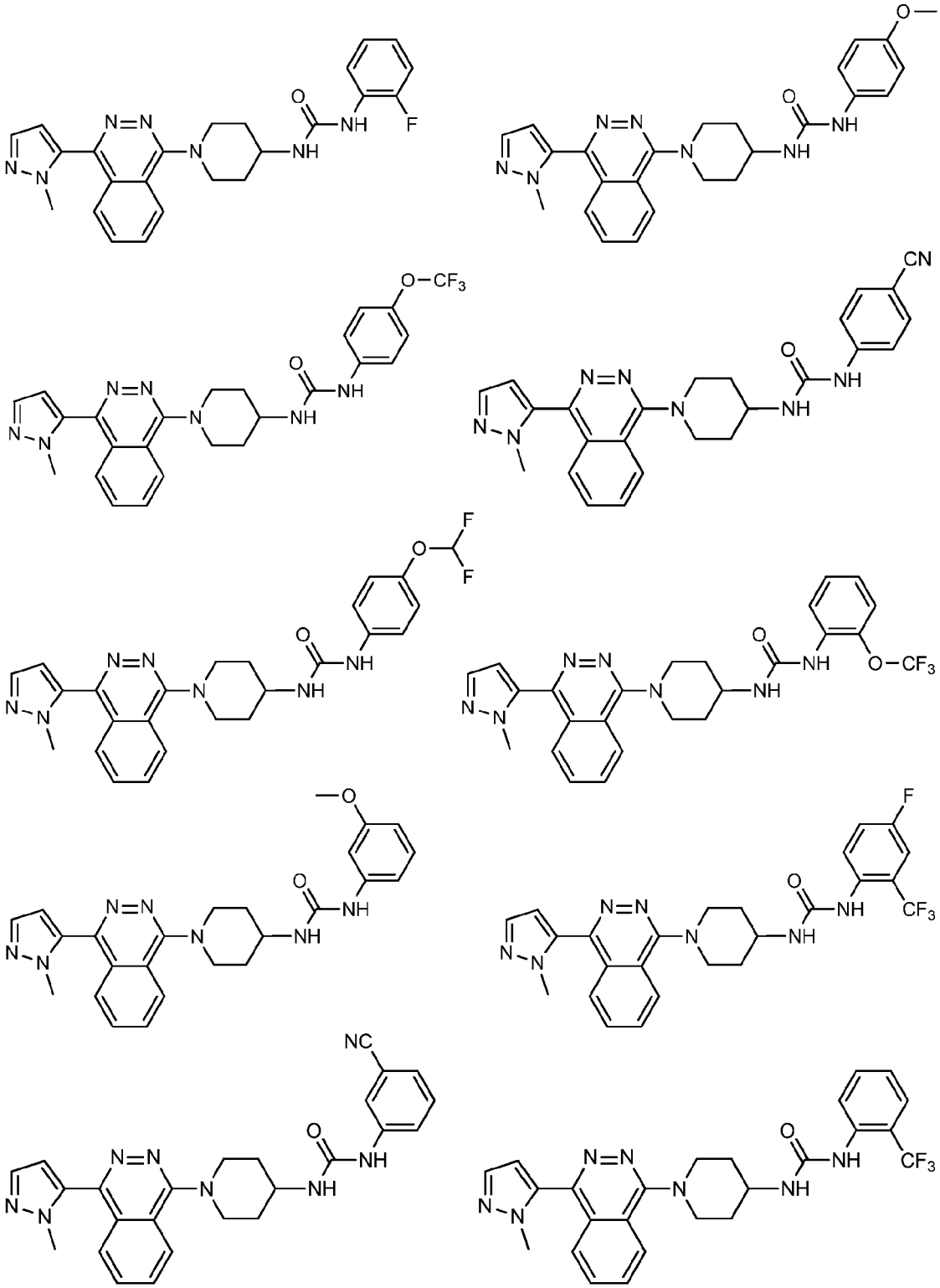


9. A compound of any preceding claim, wherein R^3 is H or methyl.

10. A compound of any preceding claim, wherein all occurrences of R^a and R^b are hydrogen.

11. A compound of any preceding claim, wherein all occurrences of R^c and R^d are hydrogen.

12. A compound of claim 1 wherein the compound of formula (I) is selected from



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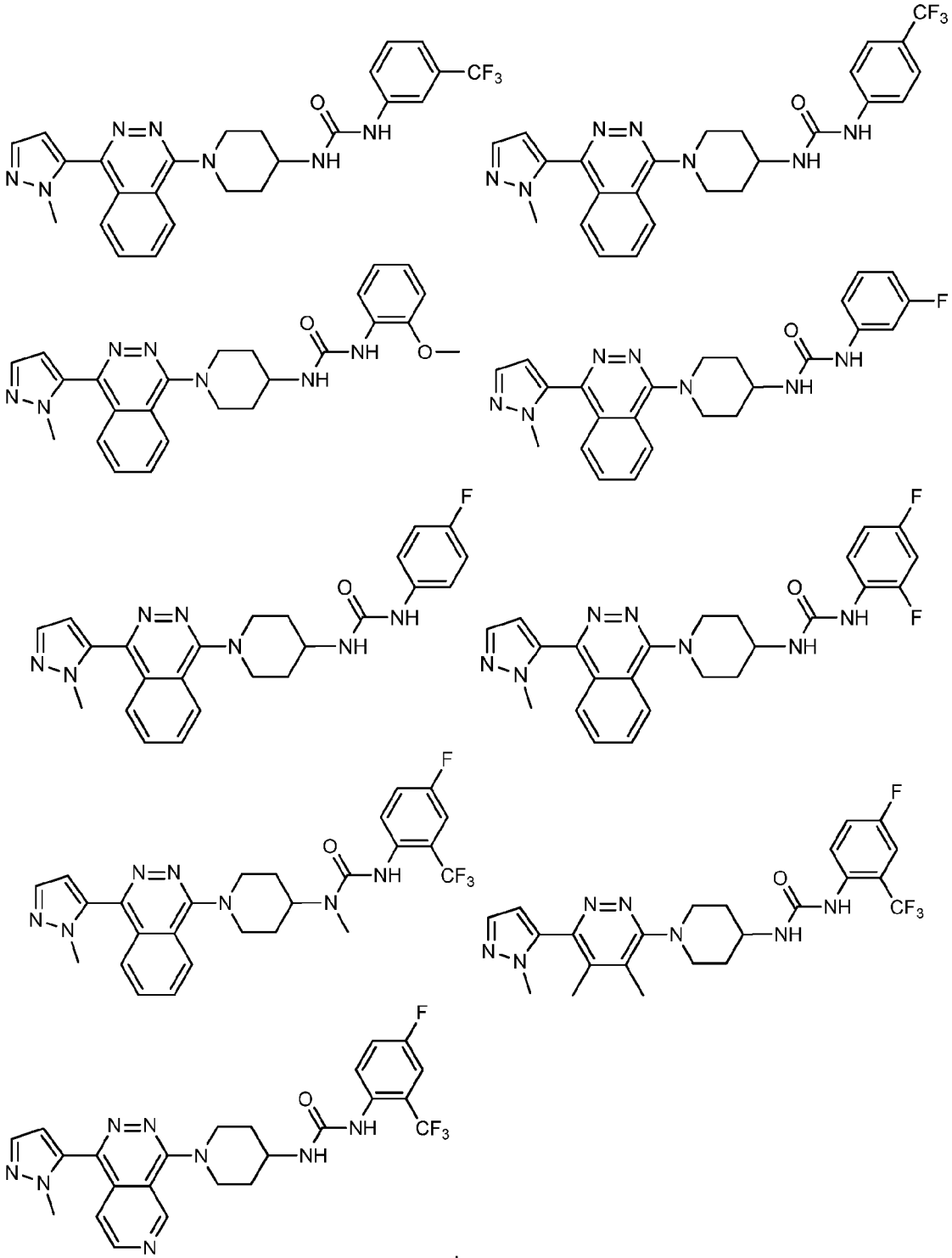
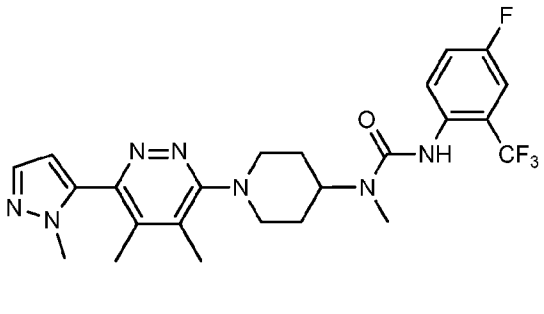
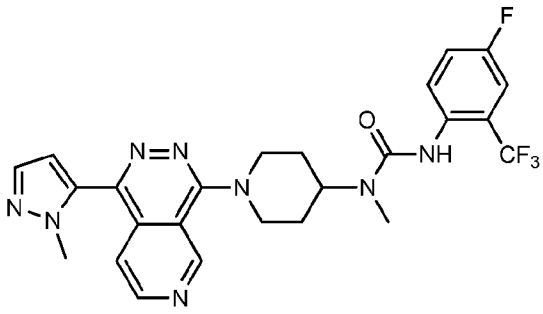
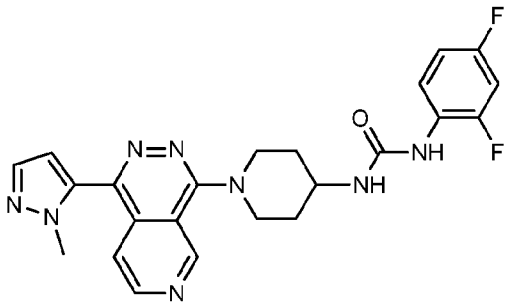


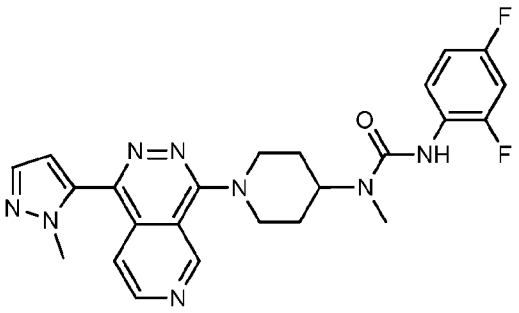
13. A compound of claim 1, wherein the compound is selected from:

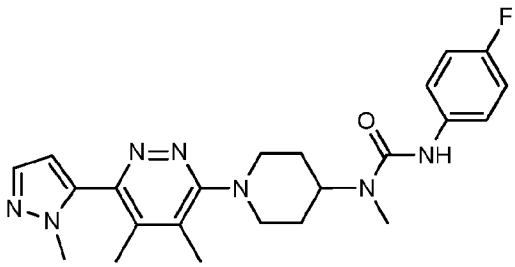


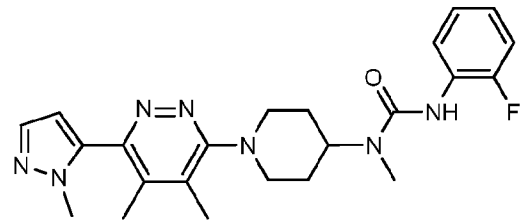


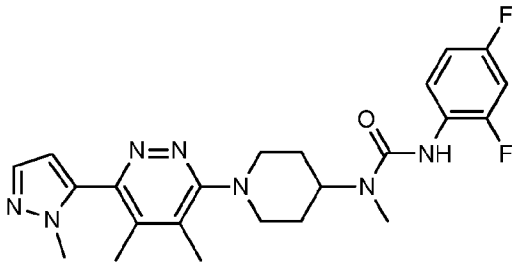
14. A compound of claim 1, wherein the compound is selected from

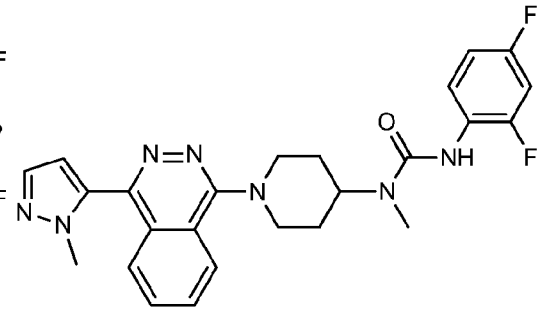












15. A compound of any preceding claim for use as a medicament.

16. A compound of any of claims 1 to 14 for use in a method of treatment of a condition which is modulated by the Hedgehog signalling pathway.

17. A compound of claim 16, wherein the condition which is modulated by the Hedgehog signalling pathway is cancer, sarcoma, carcinoma, blastoma, lymphoma and leukemia.

18. A compound of claim 16 or claim 17, wherein the condition which is modulated by the Hedgehog signalling pathway is 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.

19. A compound of any of claims 1 to 14 for use in a method of treatment wherein the treatment comprises inhibiting stem cell production, inhibiting stem cell renewal, and/or inhibiting and/or modulating stem cell differentiation.

20. A compound of any of claims 1 to 14 for use simultaneously, sequentially or separately with an additional anti-tumour agent, in a method of treatment of cancer, sarcoma, carcinoma, blastoma, lymphoma and leukemia.

21. A compound of claim 20 wherein the treatment may be of conditions treatable by the inhibition of the Hedgehog signalling pathway 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.

22. A pharmaceutical composition, wherein the composition comprises a compound of any of claims 1 to 14 and pharmaceutically acceptable excipients.

23. A pharmaceutical composition of claim 22 wherein the composition is a combination product and comprises an additional pharmaceutically active agent.

24. 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 any of claims 1 to 14, to a patient in need thereof.

25. A method of treatment of claim 24 wherein the condition which is modulated by the Hedgehog pathway is selected from: cancer, 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.

26. A method of treatment of claim 24 or claim 25 wherein the condition is 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.

27. A method of inhibiting stem cell production, inhibiting stem cell renewal, and/or inhibiting and/or modulating stem cell differentiation, wherein the method comprises administering a therapeutic amount of a compound of any of claims 1 to 14, to a patient in need thereof.

28. A method of treatment of a condition selected from cancer, sarcoma, carcinoma, blastoma, lymphoma and leukemia comprising administering a therapeutically effective amount of a compound of any of claims 1 to 14, or a pharmaceutically acceptable salt thereof simultaneously, sequentially or separately with an additional anti-tumour agent to a patient in need thereof.

29. A method of providing a combination product, wherein the method comprises providing a compound of any of claims 1 to 14 simultaneously, sequentially or separately with an anti-tumour agent.

30. Use of a compound of any of claims 1 to 14 in combination with an anti-tumour agent.

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2014/051622

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/14 C07D471/04 A61K31/501 A61K31/502 A61P35/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2010/147917 A1 (LILLY CO ELI [US]; HIPSKIND PHILIP ARTHUR [US]; PATEL BHARVIN KUMAR [U) 23 December 2010 (2010-12-23)	1-11, 15-30
A	claim 1	12-14

X	WO 2010/007120 A1 (NOVARTIS AG [CH]; HE FENG [CN]; PEUKERT STEFAN [US]; MILLER-MOSLIN KAR) 21 January 2010 (2010-01-21)	1-11, 15-30
A	claims 1, 18	12-14

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 June 2014	09/07/2014

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Brandstetter, T

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2014/051622

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Information on patent family members

International application No
PCT/GB2014/051622

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		WO 2010007120 A1	21-01-2010