(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
8 January 2015 (08.01.2015)

WIPO | PCT

(10) International Publication Number
WO 2015/001348 A1

(51) International Patent Classification:
C07D 403/14 (2006.01) *A61K 31/5025* (2006.01)
C07D 471/04 (2006.01) *A61P 35/00* (2006.01)
A61K 31/502 (2006.01)

(21) International Application Number:
PCT/GB2014/052029

(22) International Filing Date:
3 July 2014 (03.07.2014)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
1311953.2 3 July 2013 (03.07.2013) GB

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *of inventorship (Rule 4.17(iv))*

Published:

— *with international search report (Art. 21(3))*

WO 2015/001348 A1

(54) Title: PYRIDAZINE DERIVATIVES AS HEDGEHOG PATHWAY INHIBITORS

(57) Abstract: This invention relates to novel compounds. The compounds of the invention are hedgehog pathway agonists. Specifically, the compounds of the invention are useful as Smoothened (SMO) agonists. 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.

PYRIDAZINE DERIVATIVES AS HEDGEHOG PATHWAY INHIBITORS

[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.

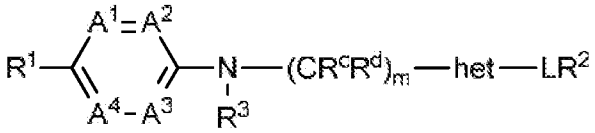
[0004] Aberrant activation of the hedgehog pathway has been implicated in patients suffering from a range of cancers, for example Basal cell carcinoma, pancreatic cancer, medulloblastoma, small cell lung cancer and prostate cancer. Moreover, it has been suggested that aberrant hedgehog signalling may 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 activation has emerged as an attractive target for anticancer therapy.

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

[0007] In accordance with the present invention there is provided compounds as disclosed below. Furthermore, the invention provides compounds capable of inhibiting the Hedgehog signalling pathway, specifically 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 the Hedgehog signalling pathway, specifically Smo. The invention provides compounds for use in treating a condition which is modulated by the Hedgehog signalling pathway, specifically Smo.

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



(I)

"het" is selected from substituted or unsubstituted: pyrolidinylene, piperidinylene and azepanylene;

or "het" represents a substituted or unsubstituted heteroalkylene chain in which the heteroatom present in a C_{1-6} alkylene chain is nitrogen and wherein the nitrogen atom is substituted by hydrogen or C_{1-4} alkyl;

at least one of A^1, A^2, A^3 and A^4 is N and the remaining A^1, A^2, A^3 and A^4 are each independently selected from CR^4 or N;

wherein R^4 is selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, $-OR^a$, $-CR^cR^dOR^a$, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, $-NR^aR^b$, -CN, $-C(O)R^a$, $-C(O)OR^a$ and $-C(O)NR^aR^b$, and two adjacent R^4 groups may form a ring with the carbon atom to which they are attached forming a fused bicyclic ring system of 8 to 12 atoms, wherein the ring formed by the two R^4 groups is a saturated or unsaturated carbocyclic ring with 4, 5, 6, 7, or 8 carbon atoms or a saturated or unsaturated heterocyclic ring with 4, 5, 6, 7, or 8 atoms containing 1, 2 or 3 heteroatoms;

L is selected from either a substituted or unsubstituted C_{1-3} alkylene chain which is saturated or unsaturated and which may also optionally contain, where chemically possible, 1 N, O, or S atoms in the chain which are independently chosen at each occurrence;

or L is selected from a bond, $-C(O)-$, $-C(NR^a)-$, $-C(O)O-$, $-C(O)NR^a-$, $-C(NR^a)NR^a-$, and $-SO_2-$;

R^1 is selected from substituted or unsubstituted: heterocycloalkyl, -O-heterocycloalkyl, $-NR^a$-heterocycloalkyl, $-CR^cR^d$-heterocycloalkyl, heterocycloalkenyl, -O-heterocycloalkenyl, $-NR^a$-heterocycloalkenyl, $-CR^cR^d$-heterocycloalkenyl, aryl, -O-aryl, $-NR^a$-aryl, $-CR^cR^d$-aryl, heteroaryl, -O-heteroaryl, $-NR^a$-heteroaryl, and $-CR^cR^d$-heteroaryl;

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

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

R^3 is selected from H, substituted or unsubstituted C_{1-4} alkyl, C_{1-4} haloalkyl, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted C_{3-8} cycloalkenyl, substituted or unsubstituted aryl, and substituted or unsubstituted heterocyclic;

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;

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;

m is 0, 1 or 2; and

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

[0009] In certain embodiments of the invention there is provided a compound according to formula (**I**) and pharmaceutically acceptable salts and solvates thereof:

"het" is selected from substituted or unsubstituted: pyrolidinylene, piperidinylene and azepanylene;

or "het" represents a substituted or unsubstituted heteroalkylene chain in which the heteroatom present in a C_{1-6} alkylene chain is nitrogen and wherein the nitrogen atom is substituted by hydrogen or C_{1-4} alkyl;

at least one of A^1, A^2, A^3 and A^4 is N and the remaining A^1, A^2, A^3 and A^4 are each independently selected from CR^4 or N;

wherein R^4 is selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, $-OR^a$, $-CR^cR^dOR^a$, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, $-NR^aR^b$, -CN, $-C(O)R^a$, $-C(O)OR^a$ and $-C(O)NR^aR^b$, and two adjacent R^4 groups may form a ring with the carbon atom to which they are attached forming a fused bicyclic ring system of 8 to 12 atoms, wherein the ring formed by the two R^4 groups is a

saturated or unsaturated carbocyclic ring with 4, 5, 6, 7, or 8 carbon atoms or a saturated or unsaturated heterocyclic ring with 4, 5, 6, 7, or 8 atoms containing 1, 2 or 3 heteroatoms;

L is selected from either a substituted or unsubstituted C_{1-3} alkylene chain which is saturated or unsaturated and which may also optionally contain, where chemically possible, 1 N, O, or S atoms in the chain which are independently chosen at each occurrence;

or L is selected from a bond, -C(O)-, -C(NR^a)-, -C(O)O-, -C(O)NR^a-, -C(NR^a)NR^a-, and -SO_2-;

R^1 is selected from substituted or unsubstituted: heterocycloalkyl, -O-heterocycloalkyl, -NR^a-heterocycloalkyl, -CR^cR^d-heterocycloalkyl, heterocycloalkenyl, -O-heterocycloalkenyl, -NR^a-heterocycloalkenyl, -CR^cR^d-heterocycloalkenyl, aryl, -O-aryl, -NR^a-aryl, -CR^cR^d-aryl, heteroaryl, -O-heteroaryl, -NR^a-heteroaryl, and -CR^cR^d-heteroaryl;

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

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

R^3 is selected from substituted or unsubstituted C_{1-14} alkyl, C_{1-14} haloalkyl, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted C_{3-8} cycloalkenyl, substituted or unsubstituted aryl, and substituted or unsubstituted heterocyclic;

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;

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;

m is 0, 1 or 2; and

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

[0010] In certain embodiments, the compounds of formula (**I**) are as described above in paragraph [0008] or [0009] with the proviso that when:

two adjacent R^4 groups form a ring with the carbon atom to which they are attached and the ring formed by the two R^4 groups and those carbon atoms is a benzene ring; and

L is C_{1-3} alkylene chain which is saturated or unsaturated;

then R^1 is selected from substituted or unsubstituted: aryl or heteroaryl, preferably substituted or unsubstituted heteroaryl (and optionally R^1 is selected from substituted or unsubstituted: pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, oxadiazolyl, isoxazolyl, triazolyl, tetrazolyl, thiazolyl, isothiazolyl, furanyl, pyridinyl, pyridazinyl, pyrazinyl and pyrimidinyl; preferably substituted or unsubstituted pyrazolyl).

[0011] In certain embodiments, the compounds of formula (**I**) are as described above in paragraph [0008] or [0009] with the proviso when:

two adjacent R^4 groups form a ring with the carbon atom to which they are attached and the ring formed by the two R^4 groups and those carbon atoms is a benzene ring;

then R^1 is selected from substituted or unsubstituted: aryl or heteroaryl, preferably substituted or unsubstituted heteroaryl (and optionally R^1 is selected from substituted or unsubstituted: pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, oxadiazolyl, isoxazolyl, triazolyl, tetrazolyl, thiazolyl, isothiazolyl, furanyl, pyridinyl, pyridazinyl, pyrazinyl and pyrimidinyl; preferably substituted or unsubstituted pyrazolyl).

[0012] In certain embodiments, the compounds of formula (**I**) are as described above in paragraph [0008] or [0009] with the proviso that R^1 is aryl and heteroaryl (optionally R^1 is selected from substituted or unsubstituted: pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, oxadiazolyl, isoxazolyl, triazolyl, tetrazolyl, thiazolyl, isothiazolyl, furanyl, pyridinyl, pyridazinyl, pyrazinyl and pyrimidinyl) when L is selected from either a substituted or unsubstituted C_{1-3} alkylene chain. Thus, in these embodiments, R^1 is not selected from substituted or unsubstituted: heterocycloalkyl, -O-heterocycloalkyl, -NR^a-heterocycloalkyl, -CR^cR^d-heterocycloalkyl, heterocycloalkenyl, -O-heterocycloalkenyl, -NR^a-heterocycloalkenyl, -CR^cR^d-heterocycloalkenyl, -O-aryl, -NR^a-aryl, -CR^cR^d-aryl, -O-heteroaryl, -NR^a-heteroaryl, and -CR^cR^d-heteroaryl, when L is selected from either a substituted or unsubstituted C_{1-3} alkylene chain.

[0013] In certain embodiments of the compounds of Formula (I) as described in any of the preceding paragraphs, R^4 is selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, -OR^a, -$CR^cR^dOR^a$, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, -NR^aR^b, -CN, -$C(O)R^a$, -$C(O)OR^a$ and –$C(O)NR^aR^b$, and two adjacent R^4 groups may form a ring with the carbon atom to which they are attached forming a fused bicyclic ring system of 8 to 12 atoms, wherein the ring formed by the two R^4 groups is a saturated or unsaturated carbocyclic ring with 4, 5, 6, 7, or 8 carbon atoms or a saturated or unsaturated heterocyclic ring with 4, 5, 6, 7, or 8 atoms containing 1, 2 or 3 heteroatoms;

L is an unsubstituted C_{1-3} alkylene chain which is saturated or unsaturated;

or L is selected from a bond, -C(O)-, -$C(NR^a)$-, -C(O)O-, -$C(O)NR^a$-, -$C(NR^a)NR^a$-, and -SO_2-;

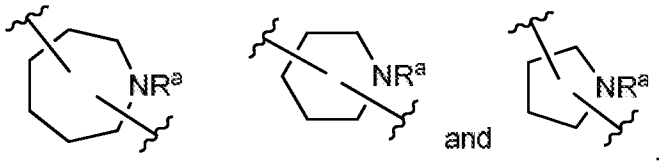
R^1 is selected from substituted or unsubstituted: aryl and heteroaryl (optionally R^1 is selected from substituted or unsubstituted: pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, oxadiazolyl, isoxazolyl, triazolyl, tetrazolyl, thiazolyl, isothiazolyl, furanyl, pyridinyl, pyridazinyl, pyrazinyl and pyrimidinyl);

and m is 0 or 1.

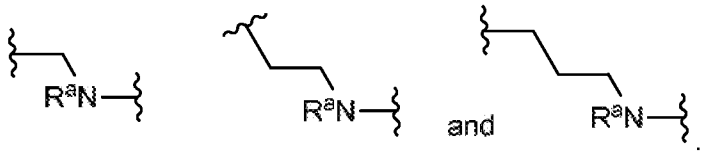
[0014] In all embodiments “het” may be selected from substituted or unsubstituted pyrolidinylene, substituted or unsubstituted piperidinylene, and substituted or unsubstituted azepanylene.

[0015] In an embodiment "het" is selected from substituted or unsubstituted: pyrolidinylene, piperidinylene and azepanylene. In an alternative embodiment "het" represents a substituted or unsubstituted heteroalkylene chain in which the heteroatom present in a C_{1-6} alkylene chain is nitrogen and wherein the nitrogen atom is substituted by hydrogen or C_{1-4} alkyl.

[0016] In an embodiment "het" is represented by groups selected from substituted or unsubstituted:

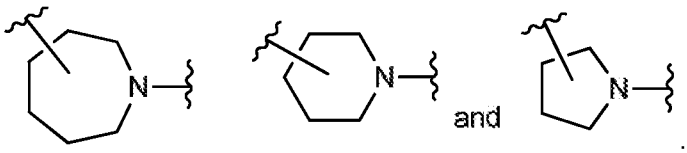


[0017] In an alternative embodiment "het" is selected from substituted or unsubstituted:

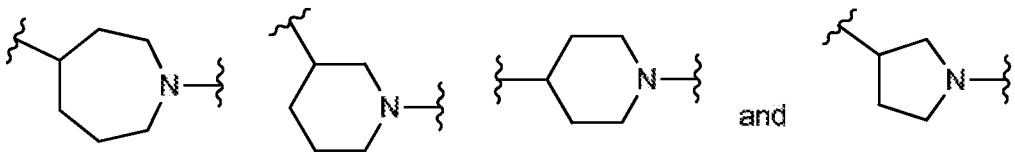


[0018] In embodiments "het" and -$(CR^cR^d)_m$- are attached to each other via a carbon atom of "het". In embodiments "het" and L are attached to each other via a nitrogen atom of "het". In embodiments "het" and -$(CR^cR^d)_m$- are attached to each other via a carbon atom of "het" and "het" and L are attached to each other via a nitrogen atom of "het". When m = 0 and there is no -$(CR^cR^d)_m$- then "het" is bonded to –$N(R^3)$-, instead of -$(CR^cR^d)_m$-, via a carbon atom of "het".

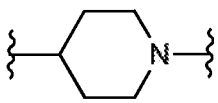
[0019] In embodiments "het" is selected from substituted or unsubstituted:



[0020] In an embodiment "het" is selected from substituted or unsubstituted:

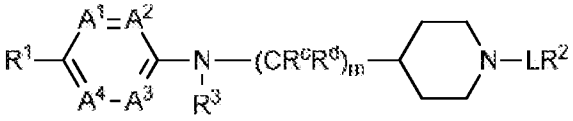


[0021] Preferably "het" is substituted or unsubstituted:



[0022] In embodiments "het" is unsubstituted. In alternative embodiments "het" is substituted with 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 , -$C(O)R^a$ and $C(O)OR^a$.

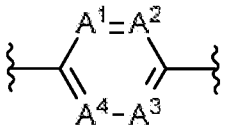
[0023] In an embodiment the compound of formula (**I**) is a compound according to formula (**II**):

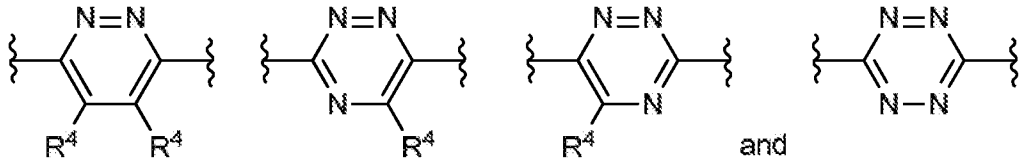


(**II**)

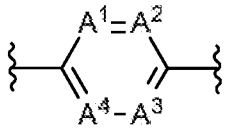
[0024] In embodiments one of A^1, A^2, A^3 and A^4 is N and the remaining A^1, A^2, A^3 and A^4 are each independently selected from N or CR^4. Optionally, one of A^1, A^2, A^3 and A^4 is N, two of the remaining A^1, A^2, A^3 and A^4 are each CR^4 and the remaining A^1, A^2, A^3 and A^4 is selected from N or CR^4. In embodiments at least two of A^1, A^2, A^3 and A^4 are N and the remaining A^1, A^2, A^3 and A^4 are each independently selected from N or CR^4. Optionally, two of A^1, A^2, A^3 and A^4 are N and two of A^1, A^2, A^3 and A^4 are CR^4.

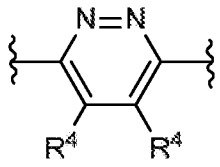
[0025]

[0026] In embodiments  is selected from:



and .

[0027] In an embodiment  is:



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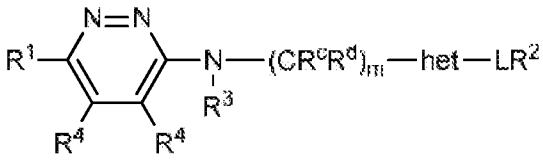
[0028] In an embodiment the compound of formula (**I**) is a compound according to formula (**III**):



(**III**)

[0029] In an embodiment the compound of formula (**I**) is a compound according to formula (**III**):

wherein R^4 is selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, $-OR^a$, $-CR^cR^dOR^a$, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, $-NR^aR^b$, -CN, $-C(O)R^a$, $-C(O)OR^a$ and $-C(O)NR^aR^b$, and

two adjacent R^4 groups may form a ring with the carbon atom to which they are attached forming a fused bicyclic ring system of 8 to 12 atoms, wherein the ring formed by the two R^4 groups is a saturated or unsaturated carbocyclic ring with 4, 5, 6, 7, or 8 carbon atoms or a saturated or unsaturated heterocyclic ring with 4, 5, 6, 7, or 8 atoms containing 1, 2 or 3 heteroatoms.

[0030] In an embodiment the compound of formula (**I**) is a compound according to formula (**III**):

wherein R^4 is selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, $-OR^a$, $-CR^cR^dOR^a$, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, $-NR^aR^b$, -CN, $-C(O)R^a$, $-C(O)OR^a$ and $-C(O)NR^aR^b$, and two adjacent R^4 groups may form a ring with the carbon atom to which they are attached forming a fused bicyclic ring system of 8 to 12 atoms, wherein the ring formed by the two R^4 groups is a saturated or unsaturated carbocyclic ring with 4, 5, 6, 7, or 8 carbon atoms or a saturated or unsaturated heterocyclic ring with 4, 5, 6, 7, or 8 atoms containing 1, 2 or 3 heteroatoms; and

m is 0 or 1.

[0031] In an embodiment the compound of formula (**I**) is a compound according to formula (**III**):

wherein R^4 is selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, $-OR^a$, $-CR^cR^dOR^a$, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, $-NR^aR^b$, -CN, $-C(O)R^a$, $-C(O)OR^a$ and $-C(O)NR^aR^b$, and two adjacent R^4 groups may form a ring with the carbon atoms to which they are attached the ring being a saturated or unsaturated carbocyclic ring with 4, 5, 6, 7, or 8 carbon atoms or a saturated or unsaturated heterocyclic ring with 4, 5, 6, 7, or 8 atoms containing 1, 2 or 3 heteroatoms; and

m is 0 or 1;

with the proviso that when:

two adjacent R^4 groups form a ring with the carbon atom to which they are attached and the ring formed by the two R^4 groups and those carbon atoms is a benzene ring, and

L is C_{1-3} alkylene chain which is saturated or unsaturated

then R^1 is selected from substituted or unsubstituted: aryl or heteroaryl, preferably substituted or unsubstituted heteroaryl (and optionally R^1 is selected from substituted or unsubstituted: pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, oxadiazolyl, isoxazolyl, triazolyl, tetrazolyl, thiazolyl, isothiazolyl, furanyl, pyridinyl, pyridazinyl, pyrazinyl and pyrimidinyl; preferably substituted or unsubstituted pyrazolyl).

[0032] In an embodiment the compound of formula (**I**) is a compound according to formula (**III**):

wherein R^4 is selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, $-OR^a$, $-CR^cR^dOR^a$, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, $-NR^aR^b$, -CN, $-C(O)R^a$, $-C(O)OR^a$ and $-C(O)NR^aR^b$, and two adjacent R^4 groups may form a ring with the carbon atoms to which they are attached the ring being a saturated or unsaturated carbocyclic ring with 4, 5, 6, 7, or 8 carbon atoms or a saturated or unsaturated heterocyclic ring with 4, 5, 6, 7, or 8 atoms containing 1, 2 or 3 heteroatoms; and

m is 0 or 1;

with the proviso that when two adjacent R^4 groups form a ring with the carbon atom to which they are attached and the ring formed by the two R^4 groups and those carbon atoms is a benzene ring, then R^1 is selected from substituted or unsubstituted: aryl or heteroaryl, preferably substituted or unsubstituted heteroaryl (and optionally R^1 is selected from substituted or unsubstituted: pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, oxadiazolyl, isoxazolyl, triazolyl, tetrazolyl, thiazolyl, isothiazolyl, furanyl, pyridinyl, pyridazinyl, pyrazinyl and pyrimidinyl; preferably substituted or unsubstituted pyrazolyl).

[0033] In an embodiment the compound of formula (**I**) is a compound according to formula (**III**):

wherein R^4 is selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, $-OR^a$, $-CR^cR^dOR^a$, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, $-NR^aR^b$, -CN, $-C(O)R^a$, $-C(O)OR^a$ and $-C(O)NR^aR^b$, and two adjacent R^4 groups may form a ring with the carbon atoms to which they are attached the ring being a saturated or unsaturated carbocyclic ring with 4, 5, 6, 7, or 8 carbon atoms or a saturated or unsaturated heterocyclic ring with 4, 5, 6, 7, or 8 atoms containing 1, 2 or 3 heteroatoms; and

m is 0 or 1;

with the proviso that when two adjacent R^4 groups form a ring with the carbon atom to which they are attached and the ring formed by the two R^4 groups and those carbon atoms is a benzene ring, then L is not C_{1-3} alkylene chain which is saturated or unsaturated.

[0034] In an embodiment the compound of formula (**I**) is a compound according to formula (**III**):

wherein R^4 is selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, $-OR^a$, $-CR^cR^dOR^a$, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, $-NR^aR^b$, -CN, $-C(O)R^a$, $-C(O)OR^a$ and $-C(O)NR^aR^b$, and two adjacent R^4 groups may form a ring with the carbon atoms to which they are attached the ring being a saturated or unsaturated carbocyclic ring with 4, 5, 6, 7, or 8 carbon atoms or a saturated or unsaturated heterocyclic ring with 4, 5, 6, 7, or 8 atoms containing 1, 2 or 3 heteroatoms; and

m is 0 or 1;

with the proviso that when L is selected from either a substituted or unsubstituted C_{1-3} alkylene chain, then R^1 is selected from substituted or unsubstituted: aryl or heteroaryl, preferably substituted or unsubstituted heteroaryl (and optionally R^1 is selected from substituted or unsubstituted: pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, oxadiazolyl, isoxazolyl, triazolyl, tetrazolyl, thiazolyl, isothiazolyl, furanyl, pyridinyl, pyridazinyl, pyrazinyl and pyrimidinyl; preferably substituted or unsubstituted pyrazolyl).

[0035] In an embodiment the compound of formula (**I**) is a compound according to formula (**III**):

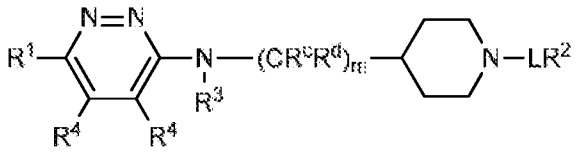
wherein R^4 is selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, $-OR^a$, $-CR^cR^dOR^a$, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, $-NR^aR^b$, -CN, $-C(O)R^a$, $-C(O)OR^a$ and $-C(O)NR^aR^b$, and two adjacent R^4 groups may form a ring with the carbon atoms to which they are attached the ring being a saturated or unsaturated carbocyclic ring with 4, 5, 6, 7, or 8 carbon atoms or a saturated or unsaturated heterocyclic ring with 4, 5, 6, 7, or 8 atoms containing 1, 2 or 3 heteroatoms;

R^1 is selected from substituted or unsubstituted: aryl or heteroaryl, preferably substituted or unsubstituted heteroaryl (and optionally R^1 is selected from substituted or unsubstituted: pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, oxadiazolyl, isoxazolyl, triazolyl, tetrazolyl, thiazolyl, isothiazolyl, furanyl, pyridinyl, pyridazinyl, pyrazinyl and pyrimidinyl; preferably substituted or unsubstituted pyrazolyl); and

m is 0 or 1.

[0036] Preferably, the R^4 groups of compounds of formula (**III**) are both C_{1-6} alkyl or both form a ring with the atom to which the R^4 groups are attached forming a fused bicyclic ring system of 8 to 12 atoms, (preferably 9 or 10 atoms) wherein the ring formed by the two R^4 groups is a saturated or unsaturated carbocyclic ring with 4, 5, 6, 7 or 8 carbon atoms (preferably 5 or 6 atoms) or a saturated or unsaturated heterocyclic ring with 4, 5, 6, 7 or 8 atoms (preferably 5 or 6 atoms) containing 1, 2 or 3 heteroatoms (e.g. 1 or 2 heteroatoms). Preferably, the heteroatom may be nitrogen.

[0037] In an embodiment the compound of formula (**I**) is a compound according to formula (**IV**):

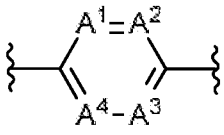


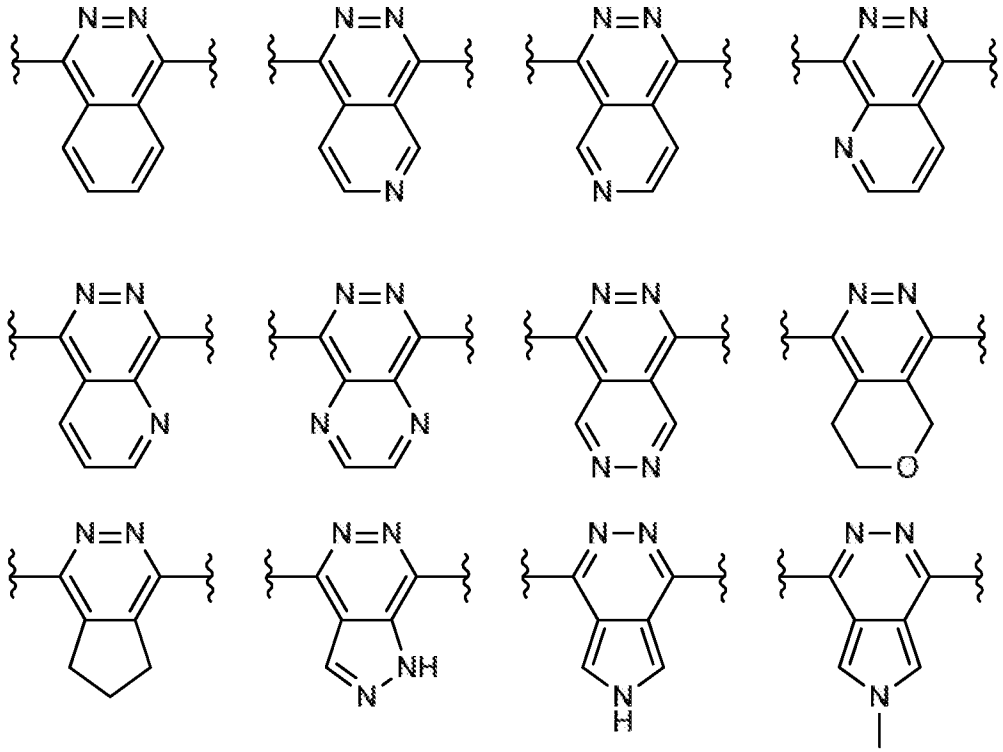
(**IV**)

[0038] In embodiments R^4 is selected from: C_{1-6} alkyl, C_{1-6} haloalkyl, $-CR^cR^dOR^a$, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, $-NR^aR^b$, -CN, $-C(O)R^a$, $-C(O)OR^a$ and $-C(O)NR^aR^b$, and two adjacent R^4 groups may form a ring with the atom to which the R^4 groups are attached forming a fused bicyclic ring system of 8 to 12 atoms, wherein the ring formed by the two R^4 groups is a saturated or unsaturated carbocyclic ring with 4, 5, 6, 7 or 8 carbon atoms or a saturated or unsaturated heterocyclic ring with 4, 5, 6, 7 or 8 atoms containing 1, 2 or 3 heteroatoms (e.g. 1 or 2 heteroatoms).

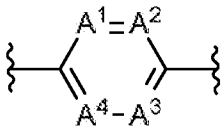
[0039] In embodiments two adjacent R^4 groups are both C_{1-6} alkyl or both form a ring with the atom to which the R^4 groups are attached forming a fused bicyclic ring system of 8 to 12 atoms, wherein the ring formed by the two R^4 groups is a saturated or unsaturated carbocyclic ring with 4, 5, 6, 7 or 8 carbon atoms or a saturated or unsaturated heterocyclic ring with 4, 5, 6, 7 or 8 atoms containing 1, 2 or 3 heteroatoms (e.g. 1 or 2 heteroatoms).

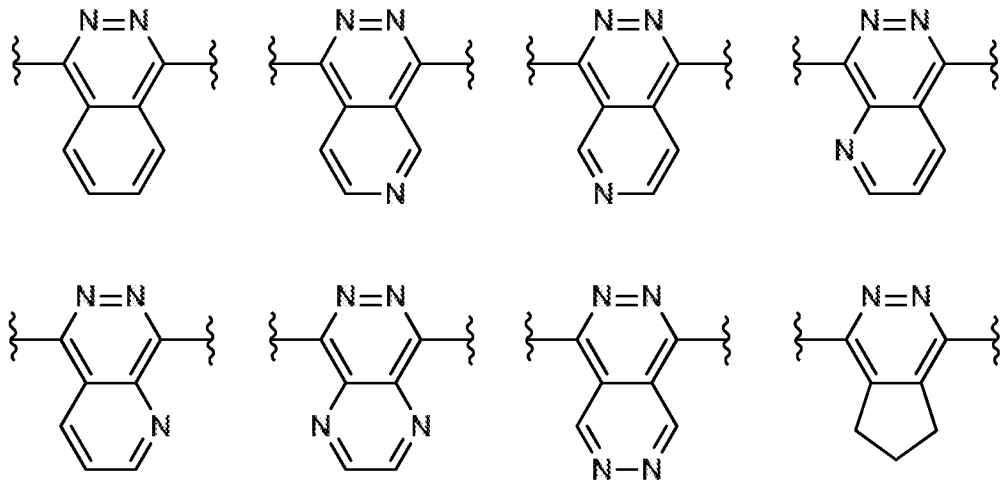
[0040] In embodiments two adjacent R^4 groups are both methyl or both form a ring with the atom to which the R^4 groups are attached forming a fused bicyclic ring system of 9 or 10 atoms, wherein the ring formed by the two R^4 groups is a saturated or unsaturated carbocyclic ring with 5 or 6 carbon atoms or a saturated or unsaturated heterocyclic ring with 6 atoms containing 1 or 2 heteroatoms.

[0041] In embodiments  is selected from:



and .

[0042] In embodiments  is selected from:



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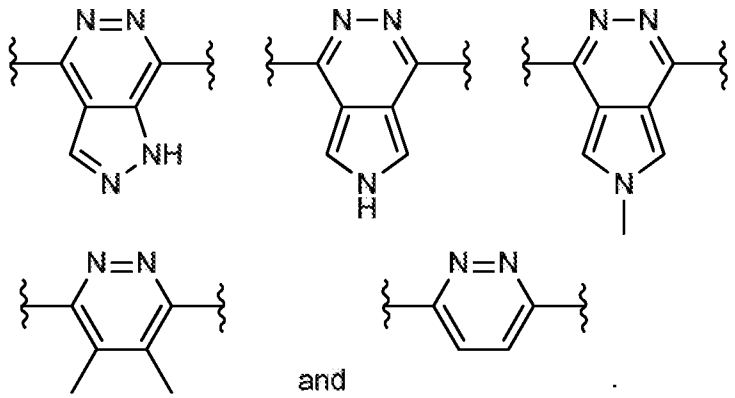
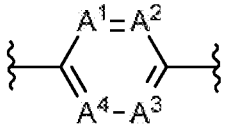
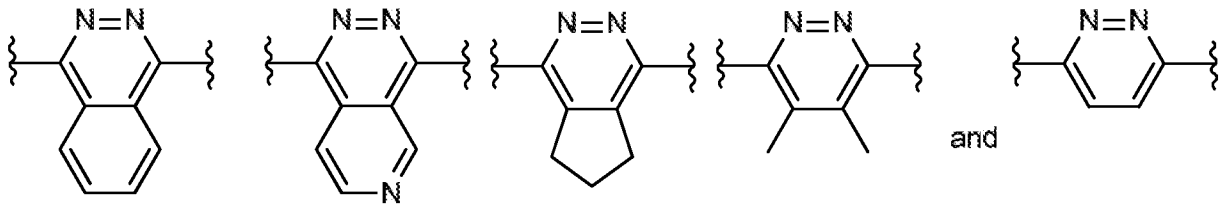


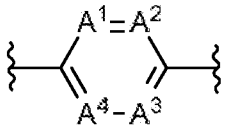
and .



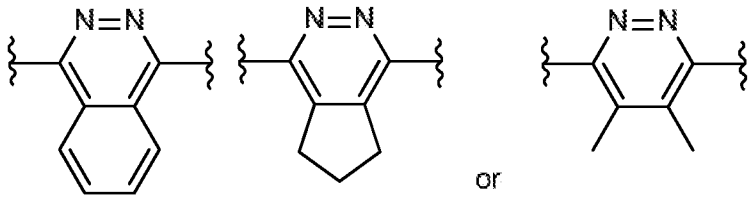
[0043] In an embodiment is selected from:



and .

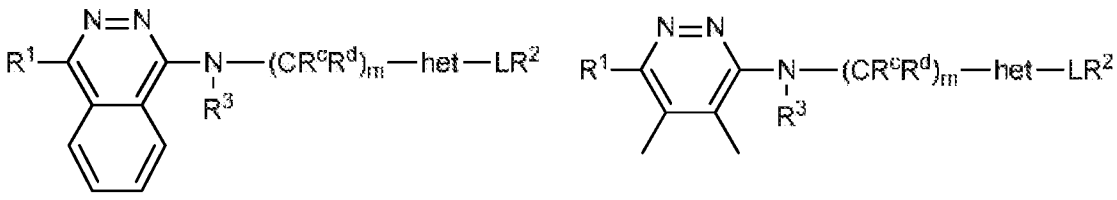


[0044] In an embodiment is

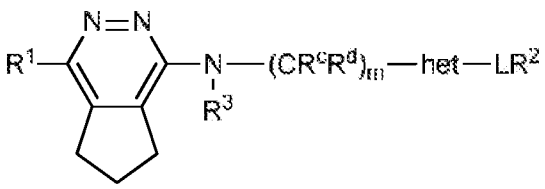


or .

[0045] In an embodiment the compound of formula (**I**) is a compound according to formula (**Va**), formula (**Vb**) or formula (**Vc**):

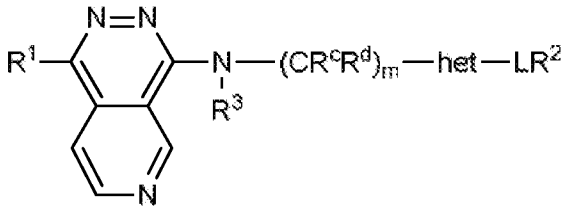


(**Va**) (**Vb**)



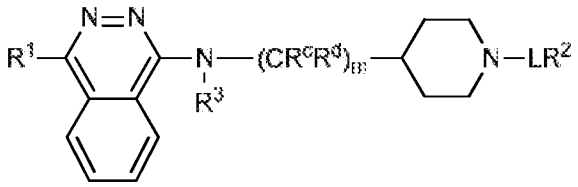
(**Vc**)

[0046] In addition the compound of formula (**I**) may be a compound according to formula (**Vd**):

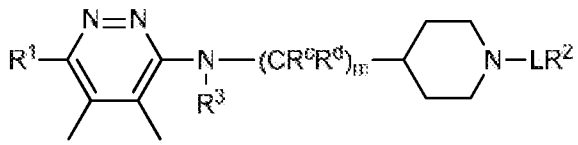


(Vd)

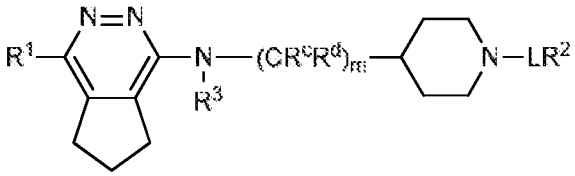
[0047] In an embodiment the compound of formula (**I**) is a compound according to formula (**VIa**), formula (**VIb**) or formula (**VIc**):



(VIa)

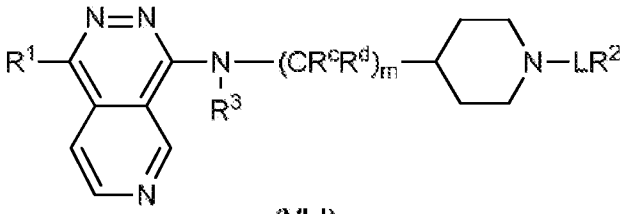


(VIb)



(VIc)

[0048] In addition the compound of formula (**I**) may be a compound according to formula (**VId**):



(VId)

[0049] In embodiments L is selected from a substituted or unsubstituted saturated C_{1-3} alkylene chain which may also contain where chemically possible 1 N, O or S atoms in the chain which are independently chosen at each occurrence, or L is selected from a bond, -C(O)-, -C(NR^a)-, -C(O)O-, -C(O)NR^a-, C(NR^a)NR^a- and –SO_2-.

[0050] There are provided compounds where L is selected from a bond, -C(O)-, -C(NR^a)-, -C(O)O-, -C(O)NR^a-, -C(NR^a)NR^a-, and -SO_2-.

[0051] In embodiments L is selected from a bond, -CR^cR^d-, -$CR^cR^dCR^cR^d$-, -C(O)-, -C(O)NR^a- and -SO_2-. Optionally, R^c and R^d are independently selected at each occurrence from H and C_{1-4} alkyl and R^3 is selected from H and C_{1-4} alkyl. In an alternative embodiment L is selected from a bond, -C(O)-, -C(O)NR^a- and -SO_2-.

[0052] In embodiments L is selected from a bond, -CH_2-, -CH_2CH_2-, -$CH(CH_3)$-, -C(NH)-, -C(O)NH-, -$C(O)N(CH_3)$- and -SO_2-. In an embodiment L is -CH_2- or -C(O)NH-. In an alternative embodiment, L is selected from a bond, -C(O)-, -C(NH)-, -C(O)NH-, -$C(O)N(CH_3)$- and -SO_2-.

[0053] In an embodiment R^1 is selected from unsubstituted heterocycloalkyl, unsubstituted heterocycloalkenyl, and the following substituted or unsubstituted groups: -O-heterocycloalkyl, -NR^a-heterocycloalkyl, -CR^cR^d-heterocycloalkyl, -O-heterocycloalkenyl, -NR^a-heterocycloalkenyl, -CR^cR^d-heterocycloalkenyl, aryl, -O-aryl, -NR^a-aryl, -CR^cR^d-aryl, heteroaryl, -O-heteroaryl, -NR^a-heteroaryl, and -CR^cR^d-heteroaryl. Optionally, heterocycloalkyl is C_{3-14} heterocycloalkyl (e.g. C_{3-8} heterocycloalkyl or C_{5-7} heterocycloalkyl), heterocycloalkenyl is C_{3-14} heterocycloalkenyl (e.g. C_{3-8} heterocycloalkenyl or C_{5-7} heterocycloalkenyl), aryl is C_{6-14} aryl (e.g. C_{6-10} aryl or C_6 aryl) and heteroaryl is C_{5-14} heteroaryl (e.g. C_{5-10} heteroaryl or C_{5-6} heteroaryl).

[0054] In certain embodiments R^1 is not heterocycloalkyl or heterocycloalkenyl.

[0055] In an embodiment R^1 is selected from substituted or unsubstituted: -O-heterocycloalkyl, -NR^a-heterocycloalkyl, -CR^cR^d-heterocycloalkyl, -O-heterocycloalkenyl, -NR^a-heterocycloalkenyl, -CR^cR^d-heterocycloalkenyl, aryl, -O-aryl, -NR^a-aryl, -CR^cR^d-aryl, heteroaryl, -O-heteroaryl, -NR^a-heteroaryl, and -CR^cR^d-heteroaryl.

[0056] In an embodiment the heterocycloalkyl group and the heterocycloalkenyl group of R^1 is not a group where the only heteroatoms are 1 or 2 nitrogen atoms. For example, in this embodiment the heterocycloalkyl group and the heterocycloalkenyl group of R^1 still encompass groups where both N and O heteroatoms are present but not groups where only N is present. In an embodiment the heterocycloalkyl group of R^1 is not piperidine, piperazine, piperidinone, or piperazinone. In an embodiment the heterocycloalkenyl group of R^1 is not tetrahydropyridine.

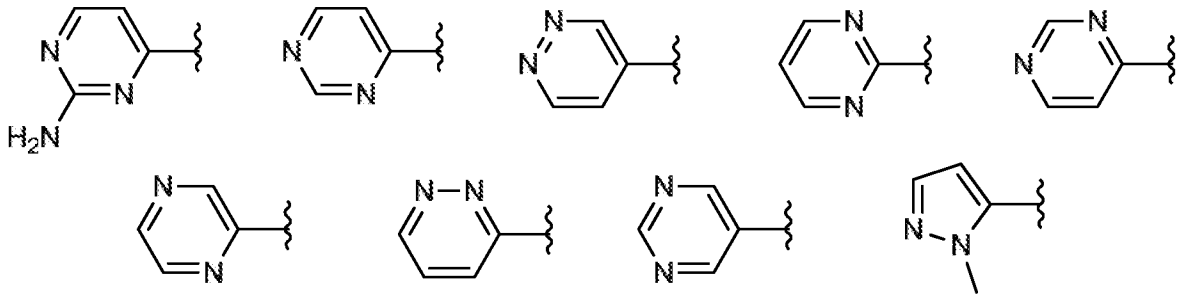
[0057] In embodiments R^1 is selected from unsubstituted heterocycloalkyl, unsubstituted heterocycloalkenyl and substituted or unsubstituted: -O-heterocycloalkyl, -NR^a-heterocycloalkyl, -CR^cR^d-heterocycloalkyl, -O-heterocycloalkenyl, -NR^a-heterocycloalkenyl, -CR^cR^d-heterocycloalkenyl, aryl, -O-aryl, -NR^a-aryl, -CR^cR^d-aryl, heteroaryl, -O-heteroaryl, -NR^a-heteroaryl, and -CR^cR^d-heteroaryl. Optionally, heterocycloalkyl is C_{3-14} heterocycloalkyl (e.g. C_{3-8} heterocycloalkyl or C_{5-7} heterocycloalkyl), heterocycloalkenyl is C_{3-14} heterocycloalkenyl (e.g. C_{3-8} heterocycloalkenyl or C_{5-7} heterocycloalkenyl), aryl is C_{6-14} aryl (e.g. C_{6-10} aryl or C_6 aryl) and heteroaryl is C_{5-14} heteroaryl (e.g. C_{5-10} heteroaryl or C_{5-6} heteroaryl).

[0058] In embodiments R^1 is selected from substituted or unsubstituted: heteroaryl, -O-heteroaryl, -NR^a-heteroaryl, and -CR^cR^d-heteroaryl. Optionally, heteroaryl is C_{5-14} heteroaryl (e.g. C_{5-10} heteroaryl or C_{5-6} heteroaryl). Optionally heteroaryl is selected from: pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, oxadiazolyl, isoxazolyl, triazolyl, tetrazolyl, thiazolyl, isothiazolyl, furanyl, pyridinyl, pyridazinyl, pyrazinyl and pyrimidinyl.

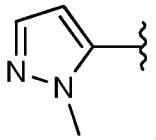
[0059] In an embodiment R^1 is substituted or unsubstituted heteroaryl. Preferably, R^1 is substituted or unsubstituted C_{5-14} heteroaryl (e.g. C_{5-10} heteroaryl or C_{5-6} heteroaryl). Optionally, the heteroatom is nitrogen.

[0060] In an embodiment R^1 is selected from substituted or unsubstituted: pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, oxadiazolyl, isoxazolyl, triazolyl, tetrazolyl, thiazolyl, isothiazolyl, furanyl, pyridinyl, pyridazinyl, pyrazinyl and pyrimidinyl. In an embodiment the substituted or unsubstituted C_{5-6} heteroaryl of R^1 may be substituted or unsubstituted: pyrazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, imidazolyl or tetrazolyl. Preferably, R^1 is substituted or unsubstituted pyrimidinyl, pyrazolyl, isoxazolyl and triazolyl. Preferably, R^1 is substituted or unsubstituted pyrazolyl.

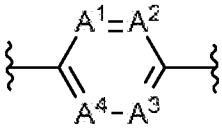
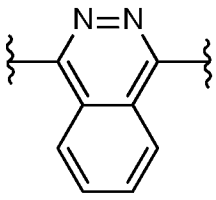
[0061] R^1 may be selected from:

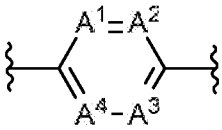
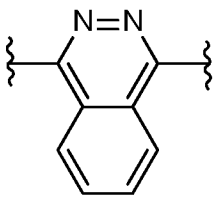


[0062] In an embodiment R^1 is:



.

[0063] In an embodiment A^1, A^2, A^3, A^4 and R^1 are each as defined above with the exception that when  is  , R^1 is substituted or unsubstituted aryl or heteroaryl. Preferably, R^1 is substituted or unsubstituted C_{5-14} heteroaryl (e.g. C_{5-10} heteroaryl or C_{5-6} heteroaryl). Optionally, the heteroatom is nitrogen. Heteroaryl may be selected from substituted or unsubstituted: pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, oxadiazolyl, isoxazolyl, triazolyl, tetrazolyl, thiazolyl, isothiazolyl, furanyl, pyridinyl, pyridazinyl, pyrazinyl and pyrimidinyl. Heteroaryl may be substituted or unsubstituted: pyrazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, imidazolyl or tetrazolyl. Preferably, heteroaryl may be substituted or unsubstituted pyrimidinyl, pyrazolyl, isoxazolyl and triazolyl. Preferably, heteroaryl may be substituted or unsubstituted pyrazolyl.

[0064] In an embodiment A^1, A^2, A^3, A^4 and R^1 are each as defined above with the exception that when  is  , R^1 is substituted or unsubstituted pyrazolyl.

[0065] In an embodiment R^2 is represented by $-CR^5R^6R^7$, wherein R^5, R^6 and R^7 are independently selected at each occurrence from H and substituted or unsubstituted: C_{1-14} alkyl, C_{1-14} haloalkyl, carbocyclic, and heterocyclic. The carbocyclic and heterocyclic moieties may be monocyclic or fused polycyclic ring systems, for example bicyclic fused ring systems. Optionally, carbocyclic may be cycloalkyl and aryl and heterocyclic may be heterocycloalkyl and heteroaryl. Further optionally carbocyclic may be C_{3-14} cycloalkyl (e.g. C_{3-8} cycloalkyl or C_{5-7} cycloalkyl) and C_{6-14} aryl (e.g. C_{6-10} aryl or C_6 aryl) and heterocyclic may be C_{3-14} heterocycloalkyl (e.g. C_{3-8} heterocycloalkyl or C_{5-7} heterocycloalkyl) and C_{5-14} heteroaryl (e.g. C_{5-10} heteroaryl or C_{5-6} heteroaryl).

[0066] In an embodiment R^2 is represented by $-CR^5R^6R^7$, wherein R^5, R^6 and R^7 are independently selected at each occurrence from H and substituted or unsubstituted: C_{1-14} alkyl (optionally C_{1-6} alkyl), C_{1-14} haloalkyl (optionally C_{1-6} haloalkyl), cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, oxirane, aziridine, azetidine, oxetane, tetrahydrofuran, pyrrolidine, imidazolidine, succinimide, pyrazolidine, oxazolidine, isoxazolidine, thiazolidine, isothiazolidine, piperidine, morpholine, thiomorpholine, piperazine, tetrahydropyran, phenyl, toluenyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyrrolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, and isothiazolyl.

[0067] In an embodiment two of R^5, R^6 and R^7 are the same and the third is selected independently. In an alternative embodiment R^5, R^6 and R^7 are all the same.

[0068] In an embodiment R^5, R^6 and R^7 are all one of the groups selected from: methyl, trifluoromethyl, cyclohexanyl and phenyl.

[0069] In an embodiment R^2 is selected from substituted or unsubstituted: C_{1-14} alkyl, C_{1-14} haloalkyl, carbocyclic, and heterocyclic. In a preferred embodiment R^2 is selected from substituted or unsubstituted: carbocyclic, and heterocyclic. The carbocyclic and heterocyclic moieties may be monocyclic or fused polycyclic ring systems, for example bicyclic fused ring systems. Optionally, carbocyclic may be cycloalkyl and aryl and heterocyclic may be heterocycloalkyl and heteroaryl. Further optionally carbocyclic may be C_{3-14} cycloalkyl (e.g. C_{3-8} cycloalkyl or C_{5-7} cycloalkyl) and C_{6-14} aryl (e.g. C_{6-10} aryl or C_6 aryl) and heterocyclic may be C_{3-14} heterocycloalkyl (e.g. C_{3-8} heterocycloalkyl or C_{5-7} heterocycloalkyl) and C_{5-14} heteroaryl (e.g. C_{5-10} heteroaryl or C_{5-6} heteroaryl).

[0070] In an embodiment R^2 is selected from substituted or unsubstituted: C_{1-14} alkyl (optionally C_{1-6} alkyl), C_{1-14} haloalkyl (optionally C_{1-6} haloalkyl), cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, oxirane, aziridine, azetidine, oxetane, tetrahydrofuran, pyrrolidine, imidazolidine, succinimide, pyrazolidine, oxazolidine, isoxazolidine, thiazolidine, isothiazolidine, piperidine, morpholine, thiomorpholine, piperazine, tetrahydropyran, phenyl, toluenyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyrrolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, and isothiazolyl.

[0071] In an embodiment R^2 may be selected from substituted or unsubstituted: phenyl, toluenyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyrrolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, and isothiazolyl. Preferably, R^2 is substituted or unsubstituted phenyl, toluenyl or pyridinyl.

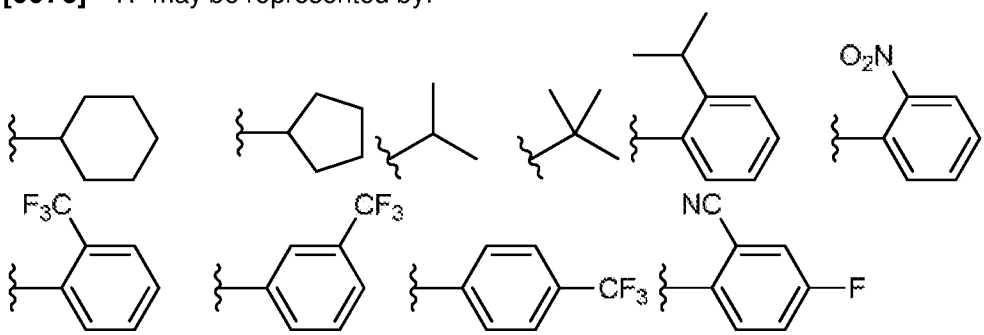
[0072] In an embodiment R^2 may be selected from substituted or unsubstituted: *tert*-butyl, isopropyl, cyclopentyl, phenyl, toluenyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyrrolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, and isothiazolyl. Preferably, R^2 may be selected from substituted or unsubstituted: phenyl, toluenyl, pyridinyl, pyridazinyl, oxazolyl, *tert*-butyl, isopropyl, and cyclopentyl.

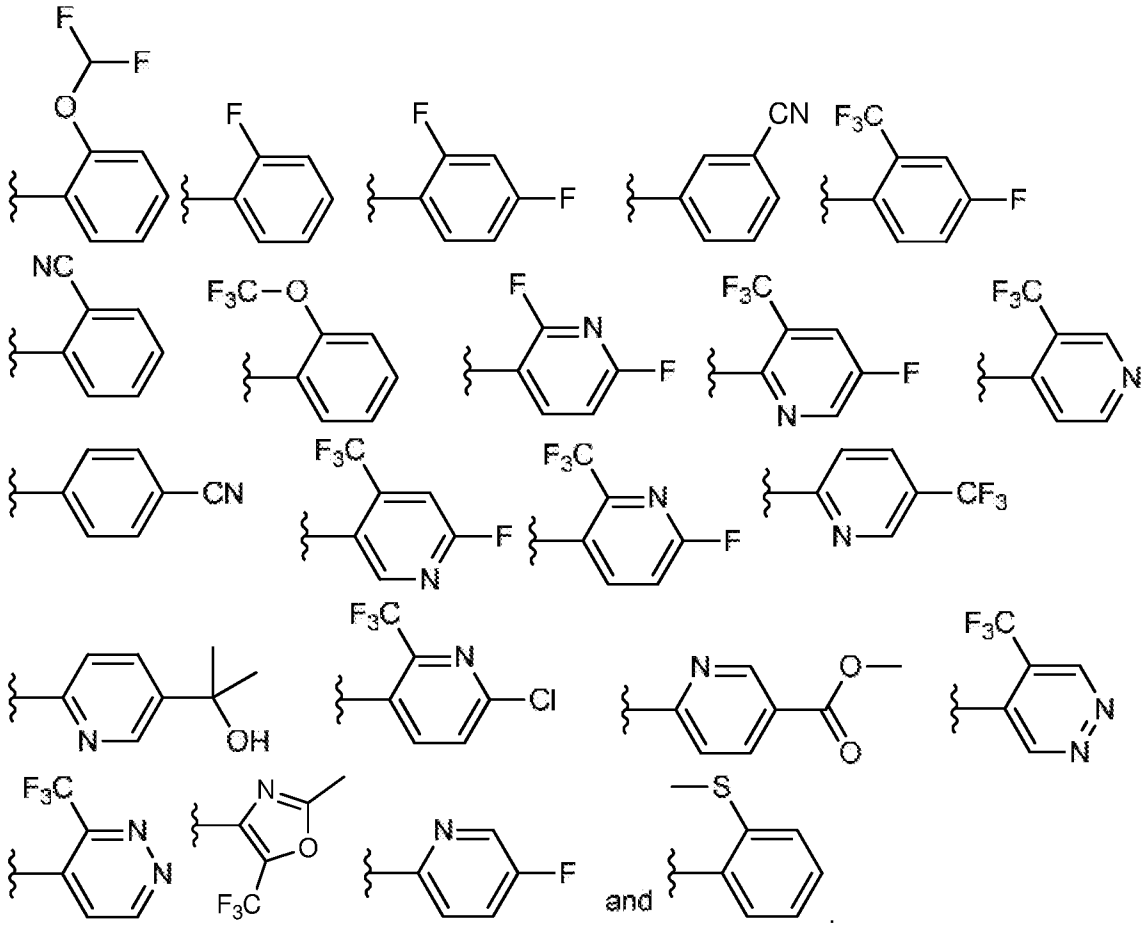
[0073] In embodiments where R^2 is substituted, R^2 may be substituted by 1 to 5 substituents, optionally 1, 2 or 3 substituents, independently selected at each occurrence from the group comprising halo, $-OR^a$, $-NO_2$, C_{1-6} alkyl, C_{1-6} haloalkyl, $-C(OR^a)R^aR^b$, $-SC_{1-4}$ alkyl, $-C(O)R_aR_b$, $-N(CO)R_a$, and -CN. In embodiments where R^2 is a cyclic group, for example a cycloalkyl, heterocycloalkyl, aryl or heteroaryl group, the group may be substituted at the ortho position, meta position, para position or a combination of these positions. In embodiments where R^2 is a cyclic group the ring may be ortho substituted. In embodiments where R^2 is a cyclic group the ring may be meta substituted. In embodiments where R^2 is a cyclic group the ring may be para substituted. In embodiments where R^2 is a cyclic group the ring may be ortho and para substituted. In embodiments where R^2 is a cyclic group the ring may be di-meta substituted.

[0074] 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, $-C(OH)(C_{1-6}\text{ alkyl})C_{1-6}$ 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.

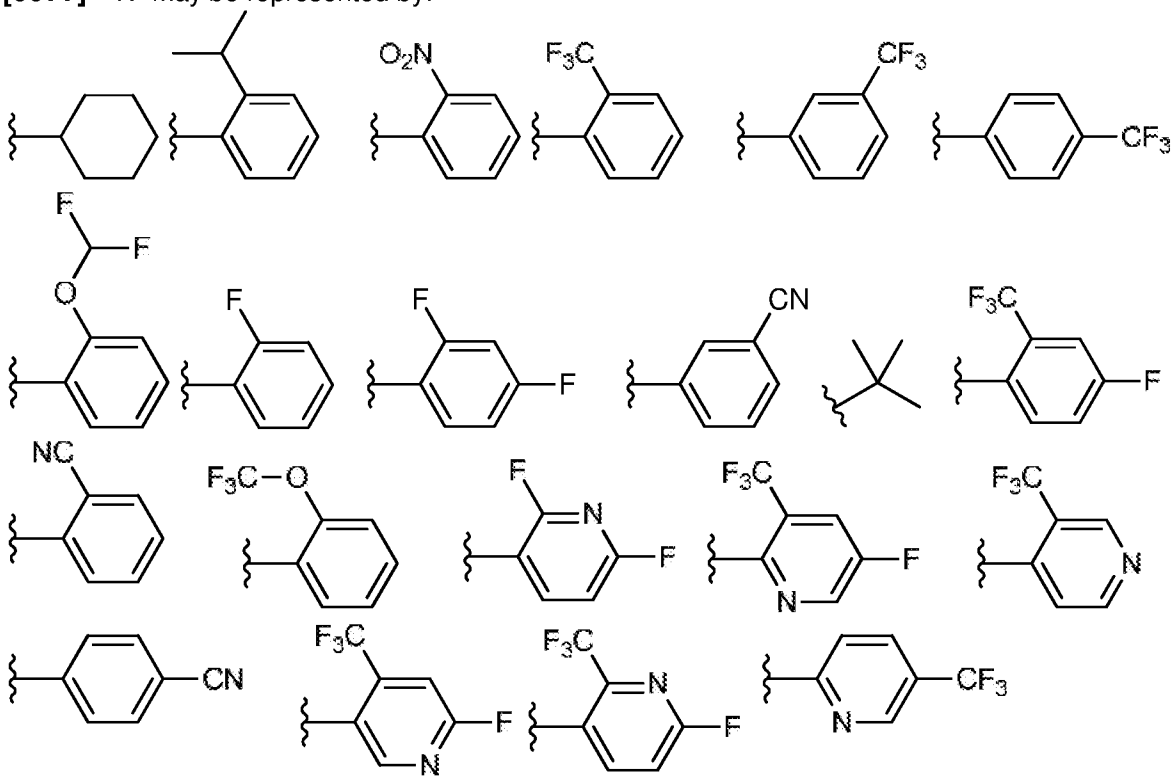
[0075] In an embodiment R^2 is substituted by trifluoromethyl. In an alternative embodiment R^2 is substituted by $-OCF_3$. In an embodiment R^2 is substituted by $-C(OH)(CH_3)CH_3$. In an embodiment R^2 is substituted by methyl. In an embodiment R^2 is substituted by fluoro. In an embodiment R^2 is 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.

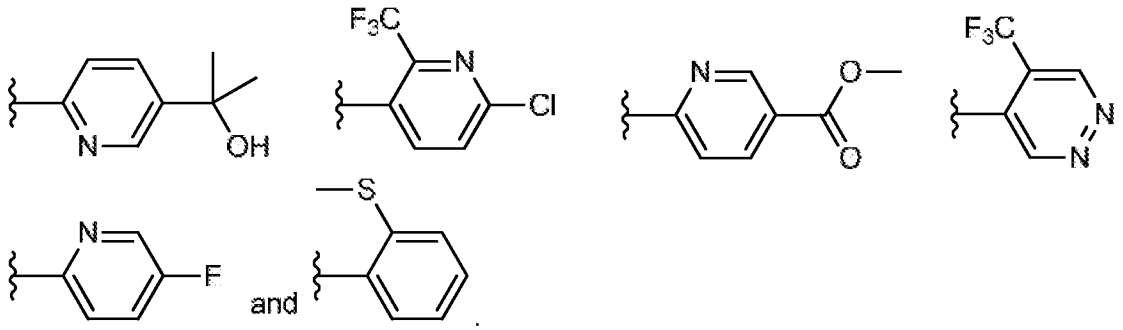
[0076] R^2 may be represented by:





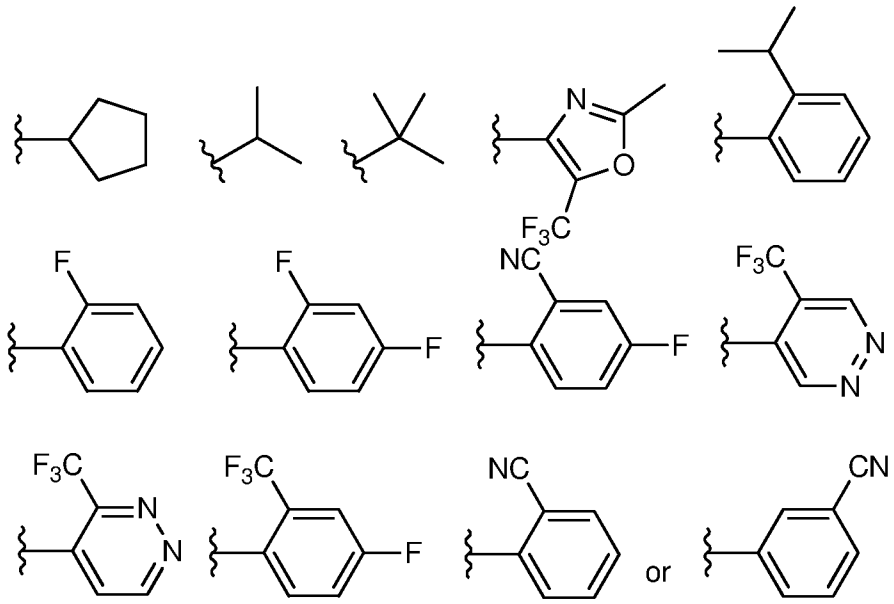
[0077] R^2 may be represented by:



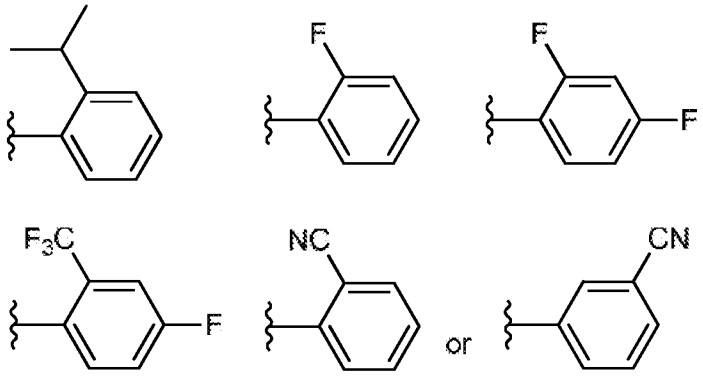


[0078] R^2 may alternatively be represented by:

[0079] In an embodiment R^2 is



[0080] In a preferred embodiment R^2 is



[0081] R^3 may be selected from: H, substituted or unsubstituted C_{1-4} alkyl, C_{1-4} haloalkyl, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted C_{3-8} cycloalkenyl, substituted or unsubstituted aryl, and substituted or unsubstituted heterocyclic.

[0082] R^3 may be selected from: substituted or unsubstituted C_{1-4} alkyl, C_{1-4} haloalkyl, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted C_{3-8} cycloalkenyl, substituted or unsubstituted aryl, and substituted or unsubstituted heterocyclic.

[0083] In an embodiment R^3 is H, substituted or unsubstituted C_{1-4} alkyl or substituted or unsubstituted C_{1-4} haloalkyl. Preferably, R^3 is H methyl, ethyl or $-C(O)CF_3$.

[0084] In an embodiment R^3 is substituted or unsubstituted C_{1-4} alkyl or substituted or unsubstituted C_{1-4} haloalkyl. Preferably, R^3 is methyl, ethyl or $-C(O)CF_3$.

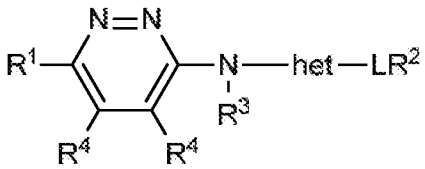
[0085] In an embodiment R^3 and L are as described herein except that when R^3 is H, L is selected from a bond, $-C(O)-$, $-C(NR^a)-$, $-C(O)O-$, $-C(O)NR^a-$, $-C(NR^a)NR^a-$, and $-SO_2-$. Thus, when R^3 is H, L is not selected from either a substituted or unsubstituted C_{1-3} alkylene chain which is saturated or unsaturated and which may also optionally contain, where chemically possible, 1 N, O, or S atoms in the chain which are independently chosen at each occurrence. In particular, when R^3 is H, L is not an unsubstituted C_{1-3} alkylene chain which is saturated or unsaturated.

[0086] In an embodiment all occurrences of R^a and R^b are hydrogen.

[0087] In an embodiment all occurrences of R^c and R^d are hydrogen.

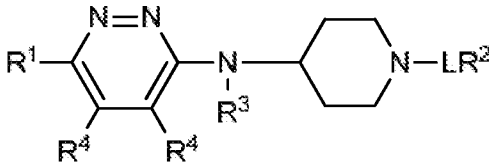
[0088] In an embodiment m is 0 or 1. Preferably, m is 0.

[0089] In embodiments the compound of formula (**I**) is a compound according to formula (**VII**):



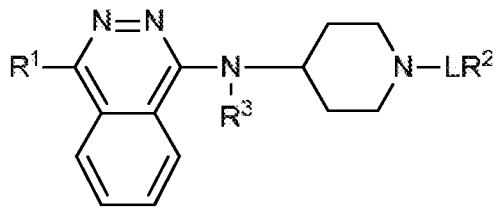
(VII)

[0090] In embodiments the compound of formula (**I**) is a compound according to formula (**VIII**):

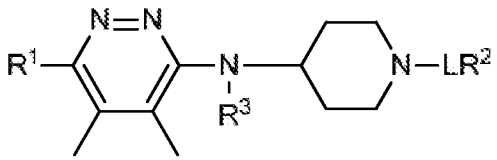


(VIII)

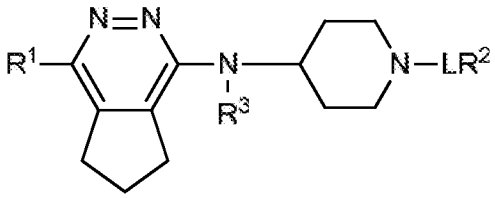
[0091] In embodiments, the compound of formula (**I**) is a compound according to formula (**IXa**), (**IXb**) or formula (**IXc**):



(IXa)

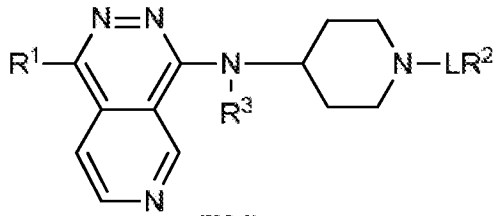


(IXb)



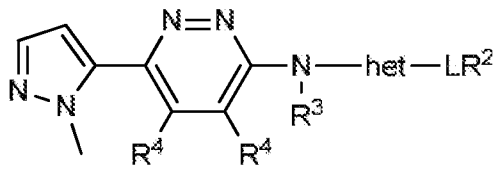
(IXc)

[0092] In addition the compound of formula (**I**) may be a compound according to formula (**IXd**):



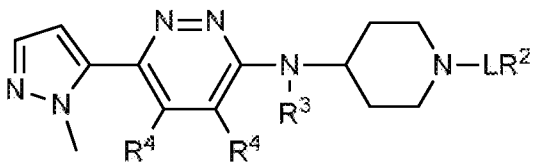
(IXd)

[0093] In an embodiment, the compound of formula (**I**) is a compound according to formula (**X**):



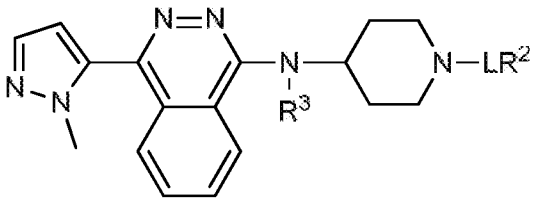
(X)

[0094] In an embodiment, the compound of formula (**I**) is a compound according to formula (**XI**):

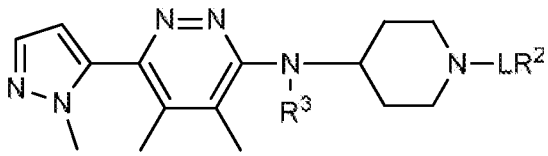


(XI)

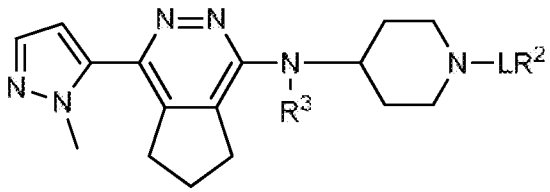
[0095] In an embodiment, the compound of formula (**I**) is a compound according to formula (**XIIa**), formula (**XIIb**) or formula (**XIIc**):



(XIIa)

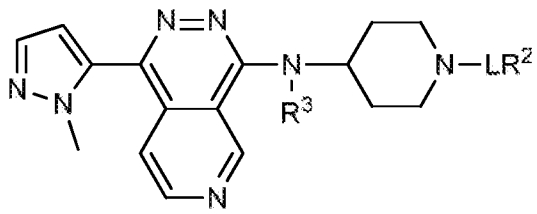


(XIIb)



(XIIc)

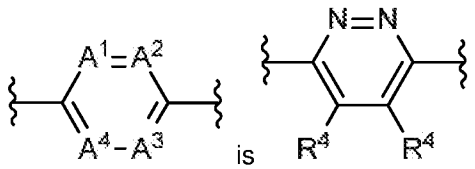
[0096] In addition the compound of formula (**I**) may be a compound according to formula (**XIId**):



(XIId)

[0097] In certain embodiments of the compound according to formula (**I**):

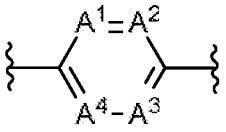
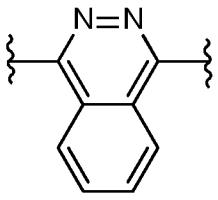
"het" is selected from substituted or unsubstituted: pyrolidinylene, piperidinylene and azepanylene;



wherein two adjacent R^4 groups are both C_{1-6} alkyl or both form a ring with the atom to which the R^4 groups are attached forming a fused bicyclic ring system of 8 to 12 atoms (preferably 9 or 10 atoms), wherein the ring formed by the two R^4 groups is a saturated or unsaturated carbocyclic ring with 4, 5, 6, 7 or 8 carbon atoms (preferably 5 to 6 carbon atoms) or a saturated or unsaturated heterocyclic ring with 4, 5, 6, 7 or 8 atoms (preferably 6 atoms) containing 1, 2 or 3 heteroatoms (e.g. 1 or 2 heteroatoms);

L is an unsubstituted C_{1-3} alkylene chain which is saturated or unsaturated;

or L is selected from a bond, -C(O)-, -C(NR^a)-, -C(O)O-, -C(O)NR^a-, -C(NR^a)NR^a-, and -SO_2-,

with the proviso that when  is  , L is selected from a bond, -C(O)-, -C(NR^a)-, -C(O)O-, -C(O)NR^a-, -C(NR^a)NR^a-, and -SO$_2$-

R^1 is selected from substituted or unsubstituted: aryl and heteroaryl;

R^2 is selected from substituted or unsubstituted: carbocyclic and heterocyclic;

R^3 is selected from H, substituted or unsubstituted C$_{1-4}$ alkyl and C$_{1-4}$ haloalkyl;

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;

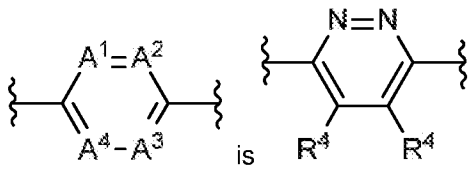
R^c and R^d are independently selected from H, halo, -OR^a, C$_{1-4}$ alkyl, C$_{1-4}$ haloalkyl, C$_{1-4}$ acyl, C$_{3-7}$ cycloalkyl, and C$_{3-7}$ halocycloalkyl;

m is 0 or 1; and

when a group is substituted, the group contains 1 to 5 substituents independently selected at each occurrence from the group comprising: halo, -OR^a, - SR^a, -NR^{a}R^b, NO$_2$, =O, -CN, acyl, C$_{1-6}$ alkyl, C$_{1-6}$ haloalkyl, C$_{3-8}$ cycloalkyl, -SO$_2$R^a, and SO$_3$R^a , -C(OR^a)R^{a}R^b, -C(O)R^a, -C(O)OR^a and -C(O)NR^{a}R^b.

[0098] In certain embodiments of the compound according to formula (I):

"het" is selected from substituted or unsubstituted: pyrolidinylene, piperidinylene and azepanylene;



wherein R^4 is selected from halo, C$_{1-6}$ alkyl, C$_{1-6}$ haloalkyl, -OR^a, -CR^{c}R^{d}OR^a, C$_{2-6}$ alkenyl, C$_{2-6}$ alkynyl, C$_{3-8}$ cycloalkyl, C$_{3-8}$ cycloalkenyl, -NR^{a}R^b, -CN, -C(O)R^a, -C(O)OR^a and –C(O)NR^{a}R^b, and two adjacent R^4 groups may form a ring with the carbon atom to which they are attached forming a fused bicyclic ring system of 8 to 12 atoms, wherein the ring formed by the two R^4 groups is a saturated or unsaturated carbocyclic ring with 4, 5, 6, 7, or 8 carbon atoms or a saturated or unsaturated heterocyclic ring with 4, 5, 6, 7, or 8 atoms containing 1, 2 or 3 heteroatoms,

optionally two adjacent R^4 groups are both C$_{1-6}$ alkyl or both form a ring with the atom to which the R^4 groups are attached forming a fused bicyclic ring system of 8 to 12 atoms (preferably 9 or 10 atoms), wherein the ring formed by the two R^4 groups is a saturated or unsaturated carbocyclic ring with 4, 5, 6, 7 or 8 carbon atoms (preferably 5 to 6 carbon atoms) or a saturated or unsaturated heterocyclic ring with 4, 5, 6, 7 or 8 atoms (preferably 6 atoms) containing 1, 2 or 3 heteroatoms (e.g. 1 or 2 heteroatoms);

L is selected from either a substituted or unsubstituted C_{1-3} alkylene chain which is saturated or unsaturated and which may also optionally contain, where chemically possible, 1 N, O, or S atoms in the chain which are independently chosen at each occurrence;

or L is selected from a bond, -C(O)-, -C(NR^a)-, -C(O)O-, -C(O)NR^a-, -C(NR^a)NR^a-, and -SO_2-;

R^1 is selected from substituted or unsubstituted pyrazolyl;

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

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

R^3 is selected from H, substituted or unsubstituted C_{1-4} alkyl, C_{1-4} haloalkyl, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted C_{3-8} cycloalkenyl, substituted or unsubstituted aryl, and substituted or unsubstituted heterocyclic;

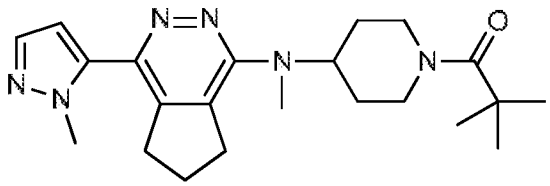
R^a and R^b are independently selected at each occurrence from: H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} acyl, C_{3-7} cycloalkyl, and C_{3-7} halocycloalkyl;

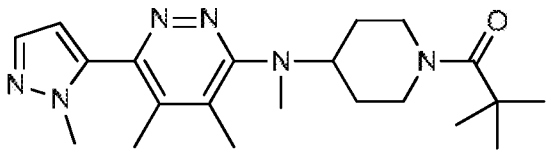
R^c and R^d are independently selected from H, halo, -OR^a, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} acyl, C_{3-7} cycloalkyl, and C_{3-7} halocycloalkyl;

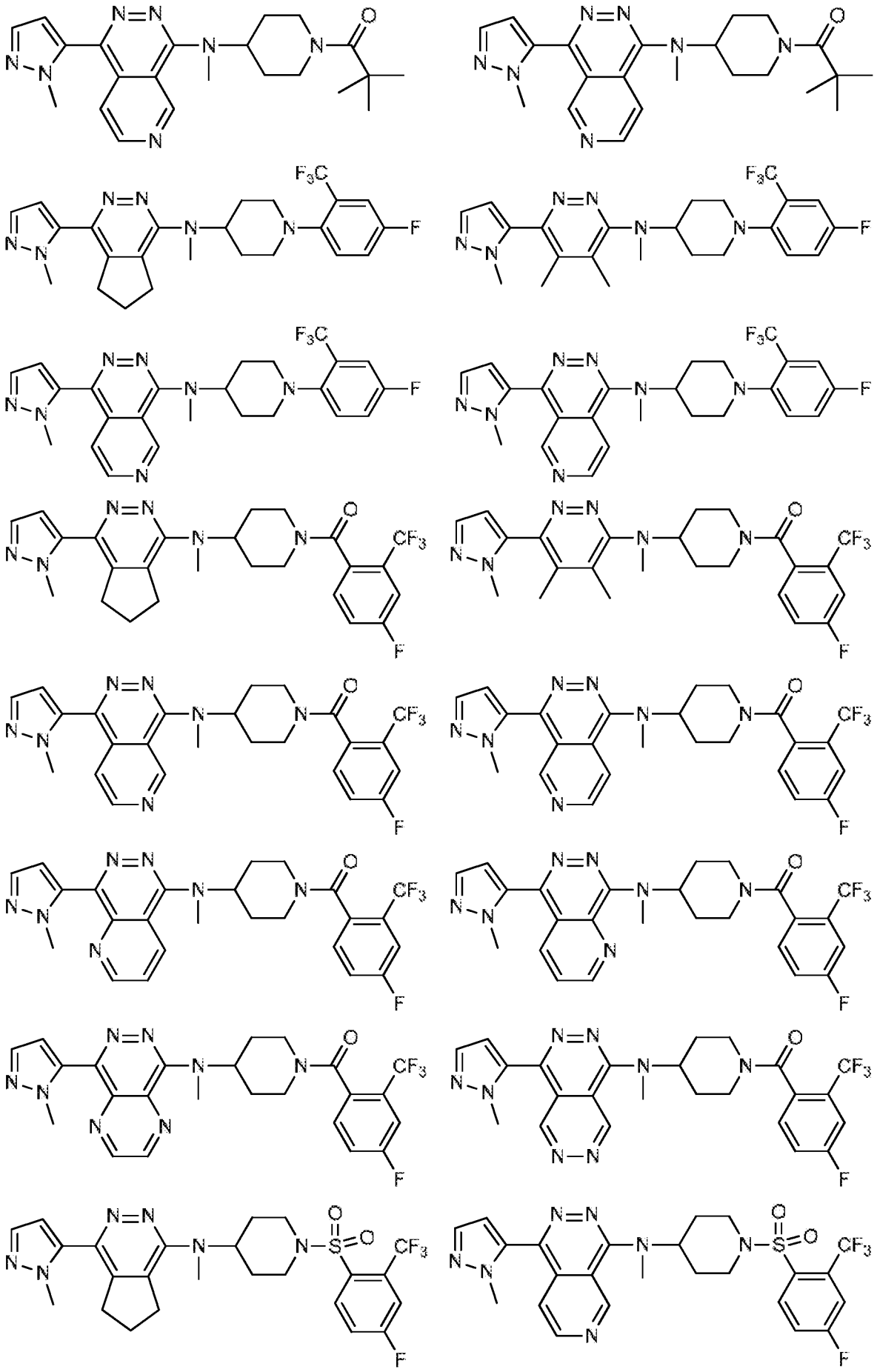
m is 0, 1 or 2; and

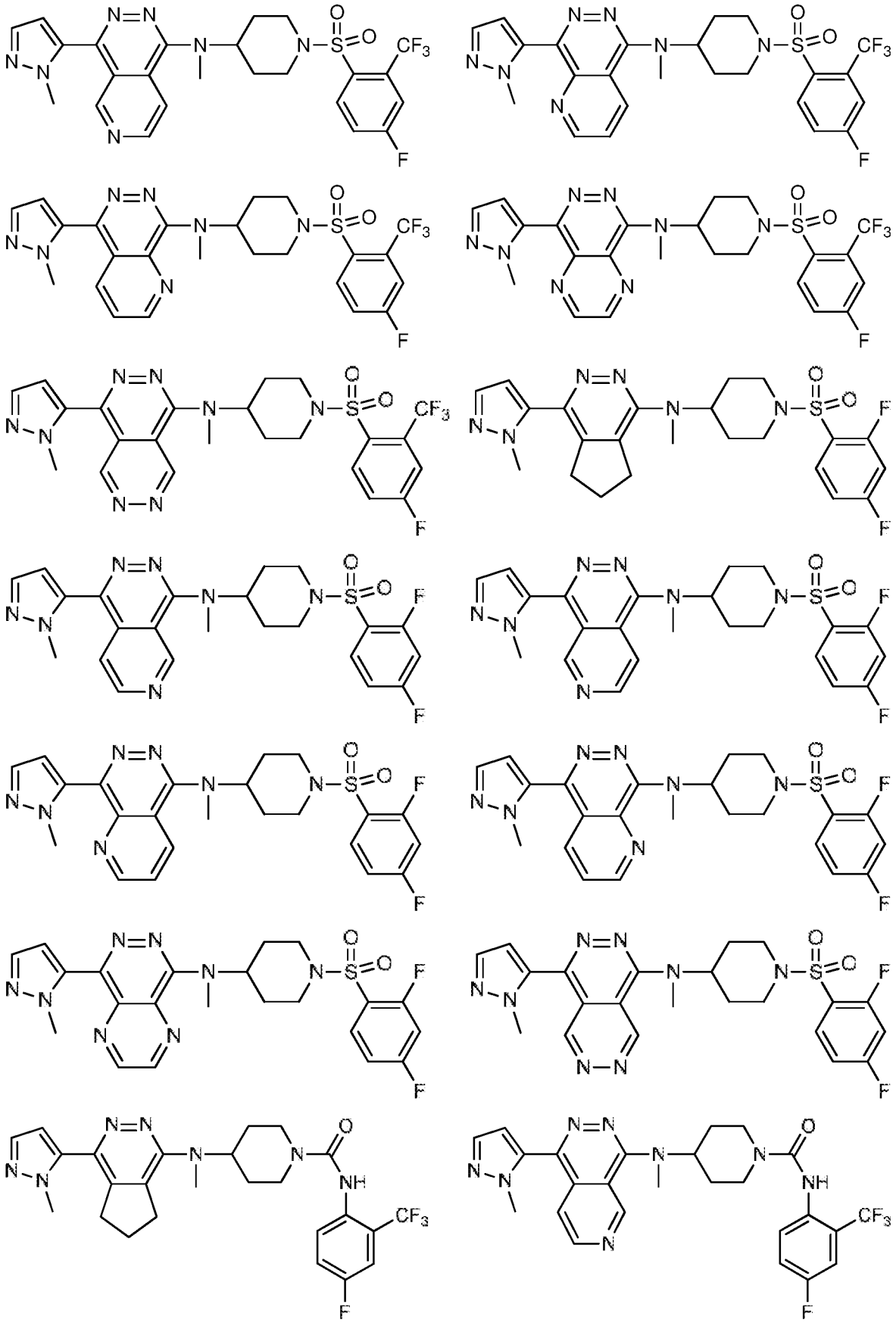
when a group is substituted, the group contains 1 to 5 substituents independently selected at each occurrence from the group comprising: halo, -OR^a, - SR^a, -NR^aR^b, NO_2, =O, -CN, acyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-8} cycloalkyl, -SO_2R^a, and SO_3R^a , -C(OR^a)R^aR^b, -C(O)R^a, -C(O)OR^a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

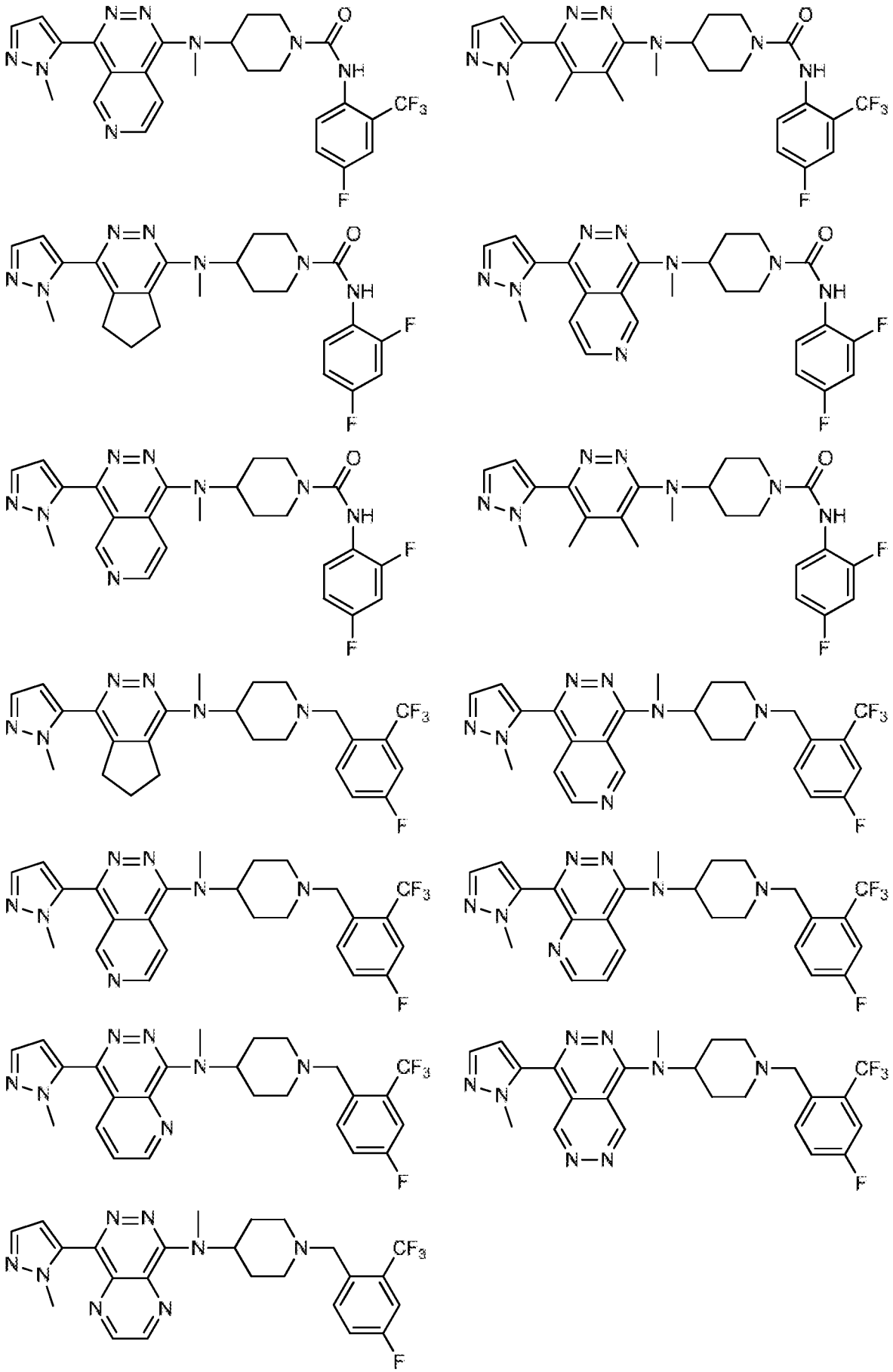
[0099] Compounds of formula (**I**) include:



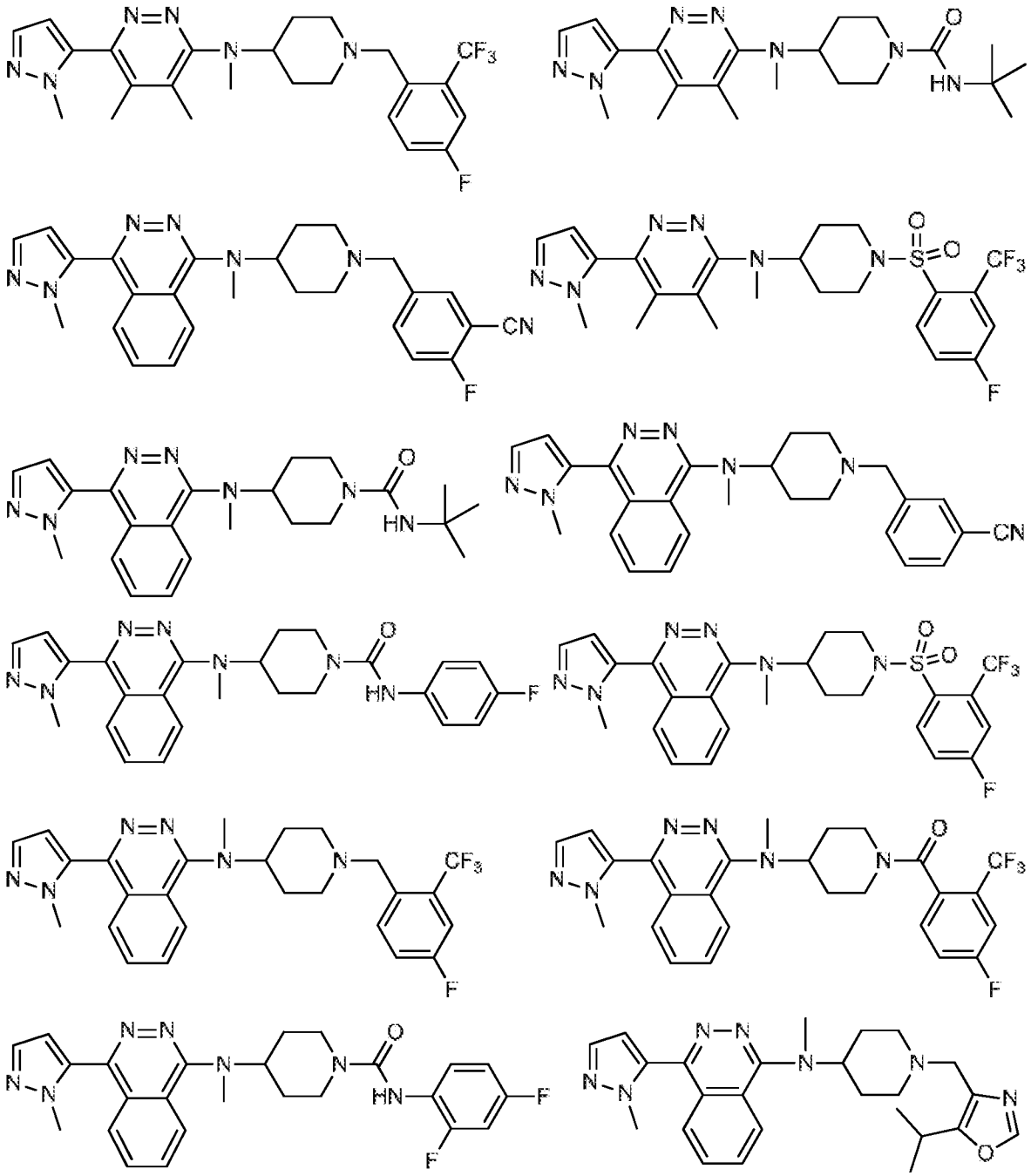




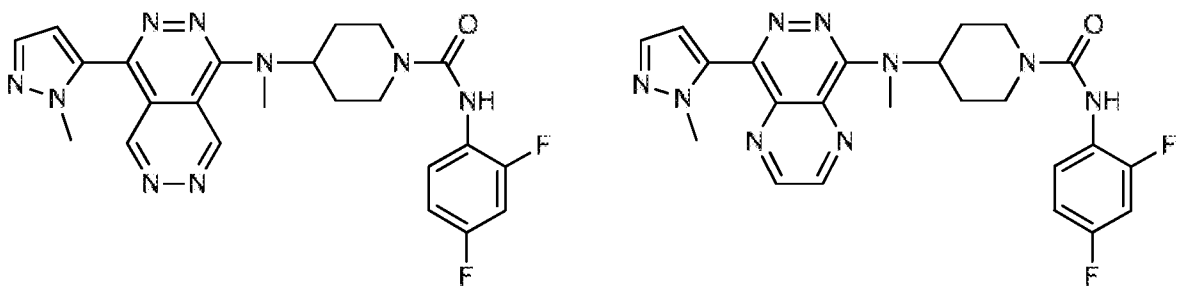


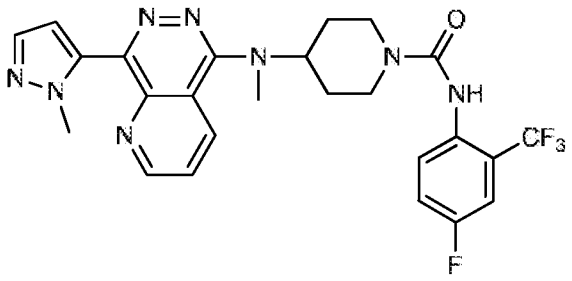
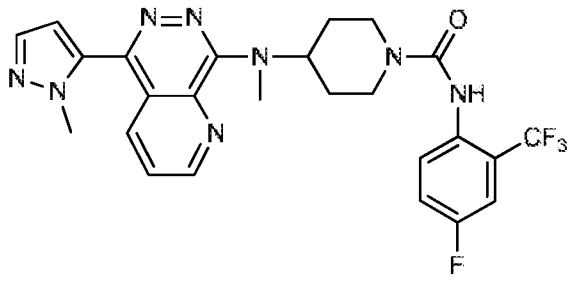
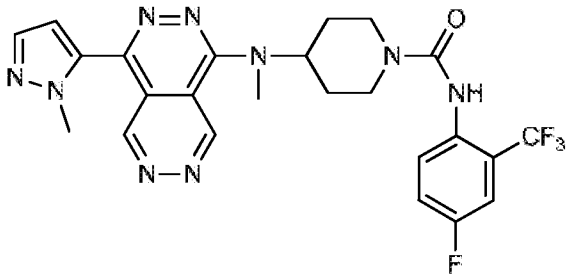
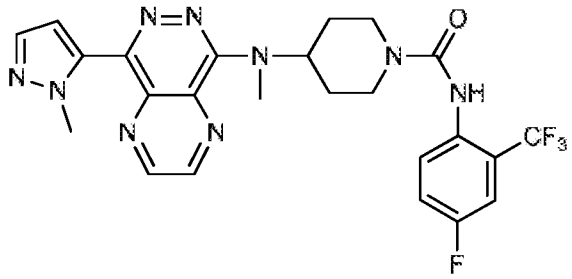


[00100] Compounds also contemplated by the invention that are particularly preferred are:

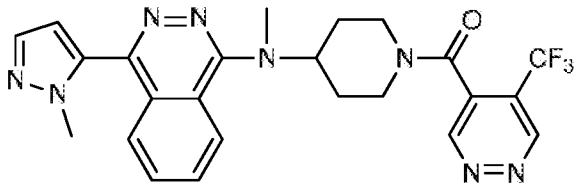
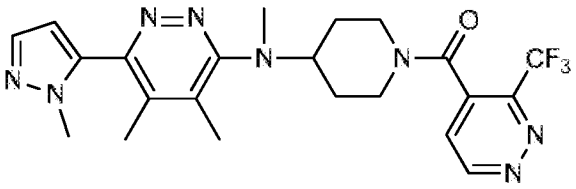
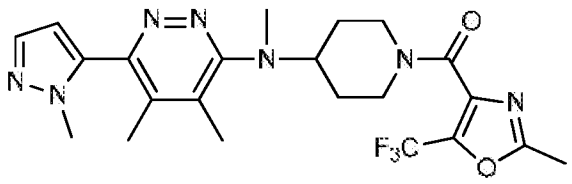
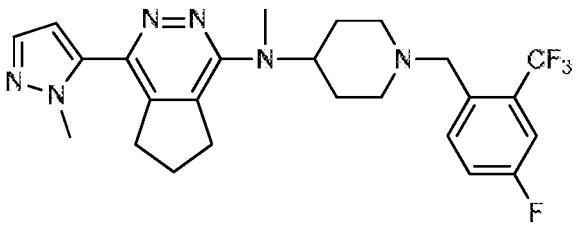
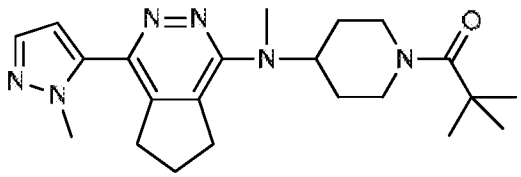
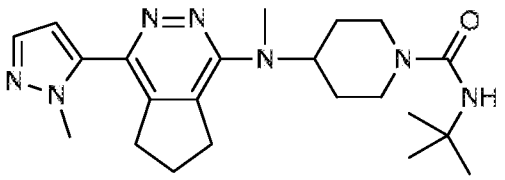
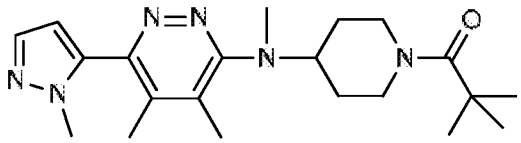
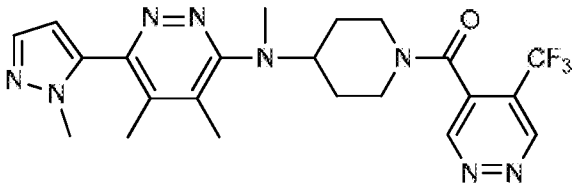
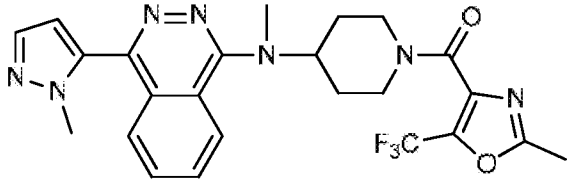
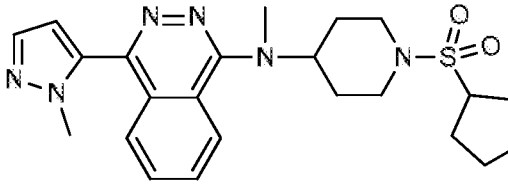


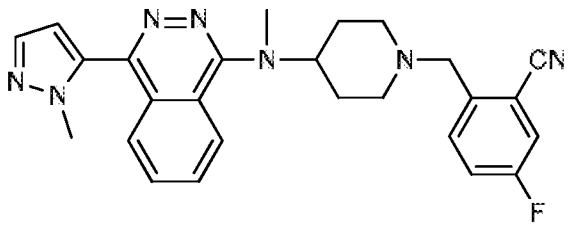
[00101] Compounds of the invention also contemplated are:

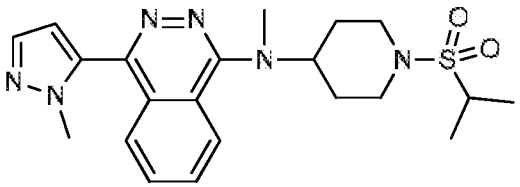


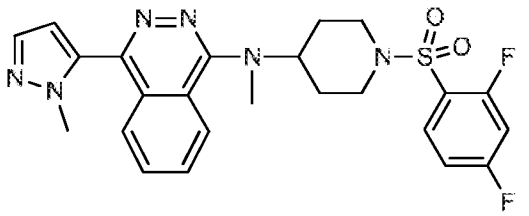





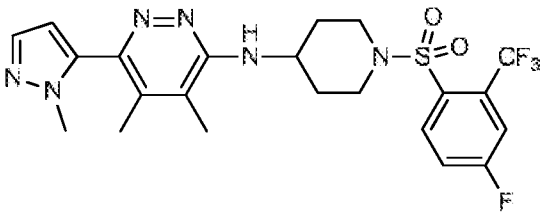
[00102] Compounds also contemplated by the invention that are preferred are:

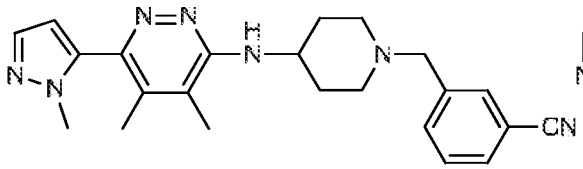











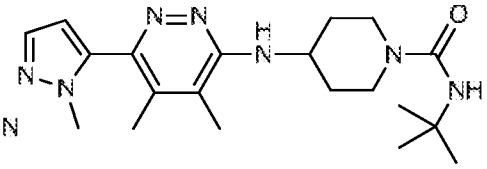


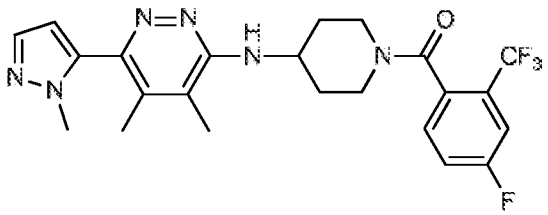


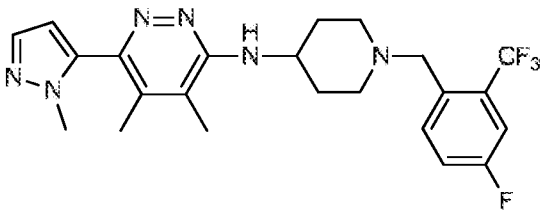


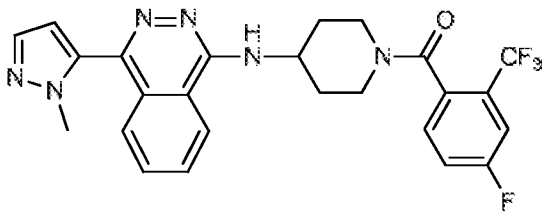


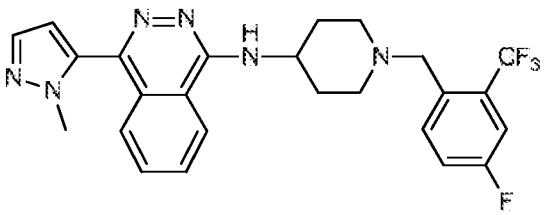


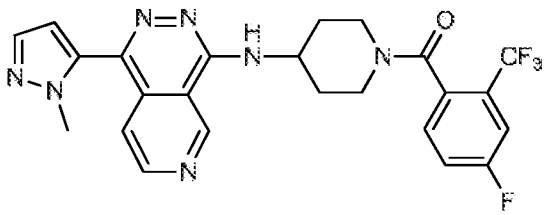


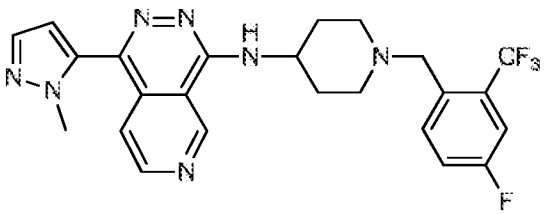


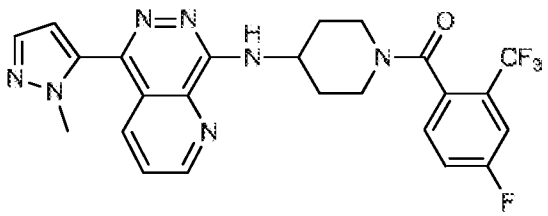


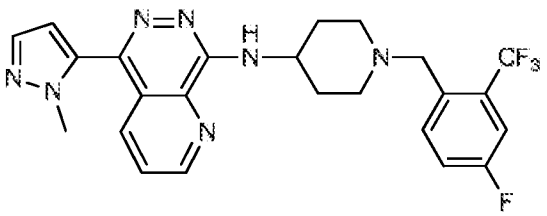


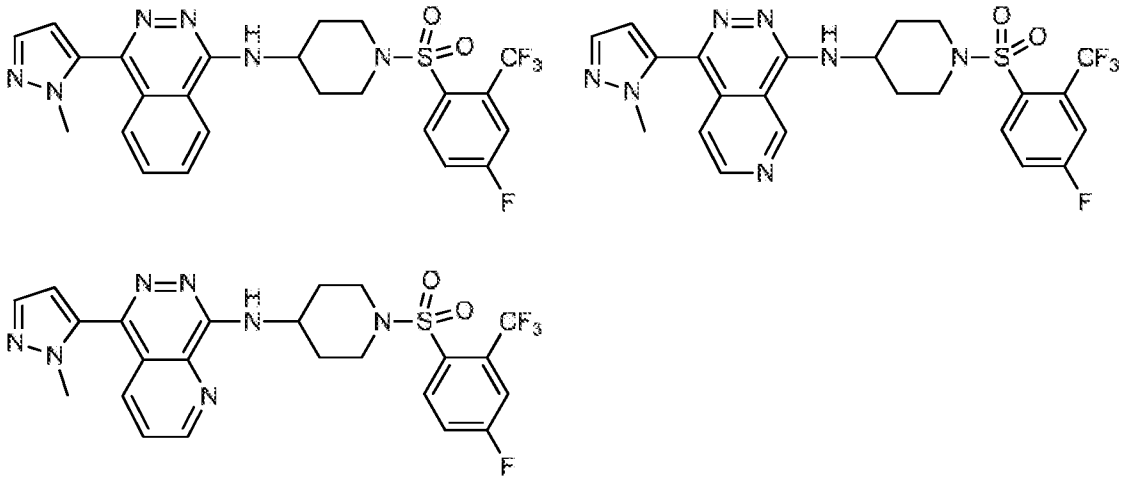












[00103] In another aspect of the invention there is provided a compound of the invention for use as a medicament.

[00104] In another aspect, a compound of the invention is for use in a method of treatment of a condition which is modulated by the Hedgehog signalling pathway. Usually conditions that are modulated by the Hedgehog signalling pathway are conditions that would be treated by the inhibition of the Hedgehog signalling pathway using a compound of the present invention. A compound of the invention may be for use in the treatment of a condition treatable by the inhibition of the Hedgehog signalling pathway.

[00105] 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 the invention may be for use in the treatment of a condition treatable by the inhibition of Smo.

[00106] Inhibition of the Hedgehog signalling pathway and Smo is a novel approach for treating many different human diseases associated with the inappropriate activation of the Hedgehog signalling pathway and aberrant activation of Smo, including various cancers, for example, solid 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.

[00107] 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.

[00108] 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

[00109] 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.

[00110] 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.

[00111] 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.

[00112] 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.

[00113] 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.

[00114] 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.

[00115] 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.

[00116] 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.

[00117] In an aspect of the invention there is provided a method of inhibiting stem cell renewal and/or stem cell production, wherein the method comprises administering a therapeutic amount of a compound of the invention, to a patient in need thereof.

[00118] 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 the invention.

[00119] 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.

[00120] 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 the invention, or a pharmaceutically acceptable salt thereof simultaneously, sequentially or separately with an additional anti-tumour agent to a patient in need thereof.

[00121] In an aspect there is provided the use of a compound of formula (**I**) in the manufacture of a medicament for use in the treatment of a condition modulated by the Hedgehog pathway, for example a condition selected from cancer, sarcoma, carcinoma, blastoma, lymphoma and leukemia. Optionally, the condition to be treated can be selected from any of those conditions mentioned above.

[00122] The embodiments described above may be applied individually, or in any combination of one another, and independently, to the compounds of the invention.

DETAILED DESCRIPTION

[00123] 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.

[00124] 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.

[00125] 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, "C_{1-3} alkyl" refers to a linear or branched hydrocarbon chain containing 1, 2 or 3 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.

[00126] 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.

[00127] 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.

[00128] 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.

[00129] 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.

[00130] 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.

[00131] 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_{6-10} aryl.

[00132] 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.

[00133] The term "C_{3-14} cycloalkyl" refers to a saturated hydrocarbon ring system containing 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 or 14 carbon atoms. Similarly,"C_{3-8} cycloalkyl" refers to a saturated hydrocarbon ring system containing 3, 4, 5, 6, 7 or 8 carbon atoms and "C_{5-7} cycloalkyl" refers to a saturated hydrocarbon ring system containing 5, 6 or 7 carbon atoms. For example, the "C_{3-8} cycloalkyl" may be cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl. The term "C_{3-7} halocycloalkyl" is a "cycloalkyl" ring having at least one halogen substituted thereon, independently selected at each occurrence. For example, the halogen may be fluorine, chlorine, bromine or iodine.

[00134] 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.

[00135] The term "C_{3-14} heterocycloalkyl" refers to a saturated hydrocarbon ring system containing 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 or 14 carbon atoms and at least one heteroatom within the ring selected from N, O and S. For example there may be 1, 2 or 3 heteroatoms, optionally 1 or 2. Similarly,"C_{3-8} heterocycloalkyl" refers to a saturated hydrocarbon ring system containing 3, 4, 5, 6, 7 or 8 carbon atoms and "C_{5-7} heterocycloalkyl" refers to a saturated hydrocarbon ring system containing 5, 6 or 7 carbon atoms. 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.

[00136] The term "C_{3-14} heterocycloalkyl" refers to an unsaturated hydrocarbon ring system containing 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 or 14 carbon atoms and at least one heteroatom within the ring selected from N, O and S. For example there may be 1, 2 or 3 heteroatoms, optionally 1 or 2. Similarly,"C_{3-8} heterocycloalkyl" refers to an unsaturated hydrocarbon ring system containing 3, 4, 5, 6, 7 or 8 carbon atoms and "C_{5-7} heterocycloalkyl" refers to an unsaturated hydrocarbon ring system containing 5, 6 or 7 carbon atoms. 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.

[00137] The term "aryl" refers to an aromatic hydrocarbon ring system. The ring system has 4n +2 electrons in a conjugated system within a ring where all atoms contributing to the conjugated system are in the same plane. The aryl group may be C_{6-14} aryl, optionally C_{6-10} aryl or C_6 aryl, wherein a C_{6-14} aryl is a ring system with 6, 7, 8, 9, 10, 11, 12, 13 or 14 ring carbons within a single ring or within a fused ring system. For example, the "aryl" may be phenyl and napthyl. The aryl system itself may be substituted with other groups.

[00138] The term "heteroaryl" refers to an aromatic hydrocarbon ring system with at least one heteroatom within a single ring or within a fused ring system, selected from O, N and S. The heteroaryl group may be C_{5-14} heteroaryl, optionally C_{5-10} heteroaryl or C_{5-6} heteroaryl, wherein a C_{5-14} heteroaryl is a ring system with 5, 6, 7, 8, 9, 10, 11, 12, 13 or 14 ring atoms with at least one heteroatom within a single ring or within a fused ring system, selected from O, N and S, for example there may be 1, 2 or 3 heteroatoms, optionally 1 or 2. The ring or ring system has 4n +2 electrons in a conjugated system where all atoms contributing to the conjugated system are in the same plane. For example, the "heteroaryl" may be imidazole, thiene, furane, thianthrene, pyrrol, benzimidazole, pyrazole, pyrazine, pyridine, pyrimidine and indole.

[00139] 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.

[00140] 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.

[00141] The term "halogen" herein includes reference to F, Cl, Br and I. Halogen may be Cl. Halogen may be F.

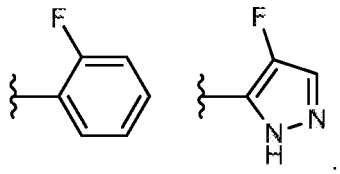
[00142] A bond terminating in a "  " represents that the bond is connected to another atom that is not shown. A bond terminating inside a cyclic structure and not terminating at an atom of the ring structure represents that the bond may be connected to any of the atoms in the ring structure where allowed by valency.

[00143] 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".

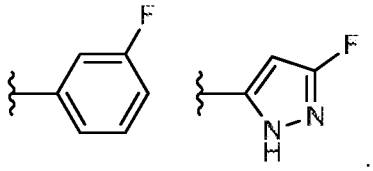
[00144] Where a moiety is substituted, it may be substituted at any point on the moiety where chemically possible and consistent with atomic valency requirements. The moiety may be substituted by one or more substitutuents, e.g. 1, 2, 3 or 4 substituents; optionally there are 1 or 2 substituents on a 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^a, 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.

[00145] 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.

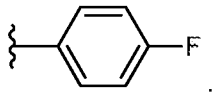
[00146] Ortho, meta and para substitution are well understood terms in the art. For the absence of doubt, "ortho" substitution is substitiution at a location adjacent to the position of attachment to the rest of the molecule, for example the two groups below are ortho substituted by fluorine:



[00147] "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:



[00148] "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:



[00149] 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.

[00150] The invention contemplates pharmaceutically acceptable salts of the compounds of formula (**I**). These may include the acid addition and base salts of the compounds.

[00151] 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.

[00152] 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).

[00153] Preferably the salt is an acid addition salt. The salts may be formate or hydrochloride.

[00154] 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.

[00155] 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.

[00156] 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.

[00157] 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).

[00158] Hereinafter all references to compounds of any formula include references to salts, solvates and complexes thereof and to solvates and complexes of salts thereof.

[00159] 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.

[00160] 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.

[00161] 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.

[00162] 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.

[00163] 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. Optionally, the additional active agent may be an anti-tumour agent selected from the list below.

[00164] 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 ; 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.

[00165] The combination therapies defined above may be achieved by way of the simultaneous, sequential or separate dosing of the individual components of the treatment. Such combination products may employ the compounds of this invention within a therapeutically effective dosage range and the other pharmaceutically-active agent within its approved dosage range.

[00166] 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.

[00167] In an embodiment there is provided a pharmaceutical product comprising a compound of formula (**I**), or a pharmaceutically acceptable salt thereof as defined hereinbefore and an additional

active agent for the treatment of a condition which is modulated by Smo. The additional active agent may be an anti-tumour agent as defined hereinbefore.

[00168] 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.

[00169] In an embodiment the condition is a condition modulated by Smo.

[00170] According to a further aspect of the invention there is provided a compound of formula (**I**), or a pharmaceutically acceptable salt thereof for use simultaneously, sequentially or separately with an additional anti-tumour agent as defined hereinbefore, in the treatment of a condition modulated by the Hedgehog signalling pathway. In an embodiment the condition is a condition modulated by Smo. The condition may be any condition described in this specification.

[00171] 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.

[00172] 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.

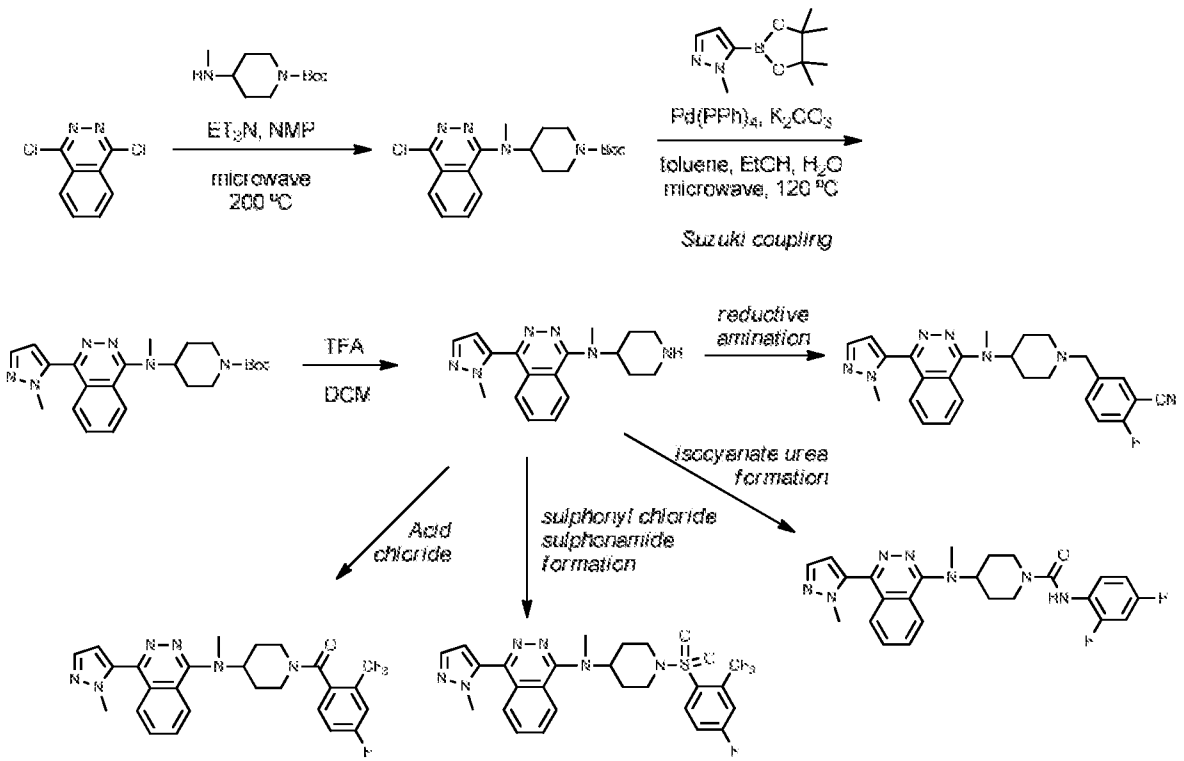
[00173] The condition modulated by the Hedgehog signalling pathway or Smo described above may be cancer, sarcoma, carcinoma, blastoma, lymphoma and leukemia. More specifically the condition modulated by BTK may be selected from: cancer, sarcoma, carcinoma, blastoma, lymphoma and leukemia. Specific conditions 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.

[00174] 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.

EXAMPLES AND SYNTHESIS

[00175] As used herein the following terms have the meanings given: "atm" refers to atmosphere; "Boc" refers to tert-butoxycarbonyl; "BOP" refers to (Benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate; "DCM" refers to dichloromethane; "DIPEA" refers to N,N-Diisopropylethylamine; "DMF" refers to N,N-dimethylformamide; "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.

[00176] The compounds of the invention may be synthesised by analogy with the following reaction route.



[00177] The steps within the route shown above may be performed in the order shown above or in a different order. For example, as the skilled person would appreciate, the Suzuki coupling could be carried out after the reductive amination 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.

[00178] 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 2mm filters) and UPLC column (C18, 50 x 2.1mm, < 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

[00179] 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.

[00180] 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

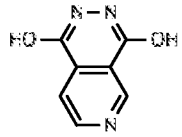
Table 2

[00181] 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.

[00182] Certain starting materials in the synthesis of compounds of formula (**I**) can be produced by the following procedures:

[00183] Procedure A

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



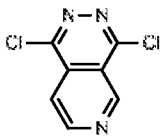
Pyridine-3,4-dicarboxylic acid (3.10g, 18.6mmol) and acetic anhydride (7.0mL, 74.2mmol) were heated to reflux at 140°C. The white suspension turned into a black solution. The reaction was heated at this temperature for 3 hours. The reaction was cooled and concentrated *in vacuo* to afford crude 3,4-pyridinedicarboxylic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

3,4-Pyridinedicarboxylic anhydride (690mg, 4.6mmol) and acetic acid (8.9mL) were combined. 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 concentrated *in vacuo* to afford pyrido[3,4-d]pyridazine-1,4-diol (600mg, 3.7mmol, 80%)

^{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



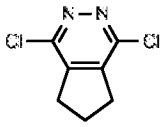
Pyrido[3,4-d]pyridazine-1,4-diol (1.83g, 11.2mmol) and phosphorus oxychloride (8.4mL, 89.7mmol) were added to a round bottomed flask. To this was added DIPEA (2.0mL, 11.2mmol) slowly. The suspension was then heated for 1 hour at 100°C. The reaction turned into a brown solution. The phosphorus oxychloride 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, 78%).

^{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 [M+H]$^+$

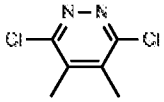
Similarly prepared were:

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



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

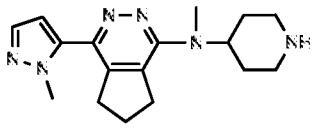
3,6-Dichloro-4,5-dimethyl-pyridazine



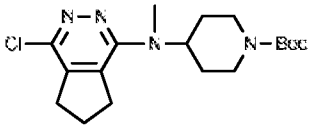
^{1}H NMR (400MHz, $CDCl_3$) δ/ppm: 2.46 (s, 6H).

[00184] Procedure B

Preparation of **N-Methyl-1-(2-methylpyrazol-3-yl)-N-(4-piperidyl)-6,7-dihydro-5H-cyclopenta[d]pyridazin-4-amine** and related compounds, intermediates in the synthesis of compounds of formula (**I**).



tert-Butyl 4-[(4-chloro-6,7-dihydro-5H-cyclopenta[d]pyridazin-1-yl)-methyl-amino]piperidine-1-carboxylate

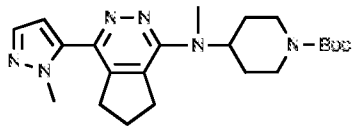


1,4-Dichloro-6,7-dihydro-5*H*-cyclopenta[d]pyridazine (2.0g, 10.6mmol) and N-Boc-4-methylaminopiperidine (2.3mL, 10.6mmol) were placed in a microwave vial which was sealed and purged with nitrogen. Triethylamine (1.8mL, 12.7mmol) and anhydrous NMP (14mL) were then added and the mixture heated using microwave irradiation at 200°C for 4 hours. The reaction mixture was diluted with EtOAc (200mL) and water (100mL) and the two phases were separated. The aqueous phase was extracted with EtOAc and the organic layers combined and washed with water (6 x 100mL), dried over sodium sulfate and concentrated *in vacuo*. The crude product was purified by silica flash column chromatography eluting with 0% ethyl acetate in heptane with a gradient to 80% ethyl acetate to afford 970mg of recovered starting material and the desired product *tert*-butyl 4-[(4-chloro-6,7-dihydro-5*H*-cyclopenta[d]pyridazin-1-yl)-methyl-amino]piperidine-1-carboxylate (441mg, 1.2mmol, 11%)

^{1}H NMR (400MHz, $CDCl_3$) δ/ppm: 4.34-4.17 (m, 3H), 3.11 (t, *J* 7.5Hz, 2H), 2.98 (s, 3H), 2.95 (t, *J* 7.5Hz, 2H), 2.87-2.74 (m, 2H), 2.18-2.11 (m, 2H), 1.83-1.69 (m, 4H), 1.49 (s, 9H).

MS Method 2: RT: 1.78min, ES^+ m/z 367.2 $[M+H]^+$

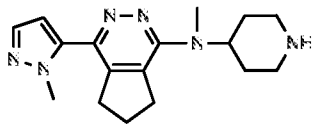
tert-Butyl 4-[methyl-[1-(2-methylpyrazol-3-yl)-6,7-dihydro-5H-cyclopenta[d]pyridazin-4-yl]amino]piperidine-1-carboxylate



tert-Butyl 4-[(4-chloro-6,7-dihydro-5H-cyclopenta[d]pyridazin-1-yl)-methyl-amino]piperidine-1-carboxylate (627.8mg, 1.71mmol), 1-methyl-1H-pyrazole-5-boronic acid, pinacol ester (0.71g, 3.42mmol) and potassium carbonate (0.47g, 3.42mmol) were combined in toluene (9mL), ethanol (3mL) and water (3mL) and the mixture was degassed. Palladium (0) tetrakis(triphenylphosphine) (0.1g, 0.090mmol) was quickly added and the vial capped and heated using microwave irradiation at 120°C for 1 hour. LCMS analysis showed the reaction had not gone to completion. Further 1-methyl-1H-pyrazole-5-boronic acid, pinacol ester (0.36g, 1.7mmol), potassium carbonate (0.24g, 1.7mmol) and palladium (0) tetrakis(triphenylphosphine) (0.1g, 0.09mmol) were added and the reaction heated using microwave irradiation at 120°C for 1 hour. The reaction mixture was diluted with water and extracted with DCM. The organic layer was washed with water (x3), dried over sodium sulfate, filtered and concentrated in vacuo. The crude product was purified by silica flash column chromatography eluting with 20% ethyl acetate in heptane with a gradient to 100% ethyl acetate to afford tert-butyl 4-[methyl-[1-(2-methylpyrazol-3-yl)-6,7-dihydro-5H-cyclopenta[d]pyridazin-4-yl]amino]piperidine-1-carboxylate (545mg,1.32mmol, 77% yield) as a yellow orange oil which was used immediately in the next step.

MS Method 2: RT: 1.45min, ES^+ m/z 413.3 $[M+H]^+$

N-methyl-1-(2-methylpyrazol-3-yl)-N-(4-piperidyl)-6,7-dihydro-5H-cyclopenta[d]pyridazin-4-amine



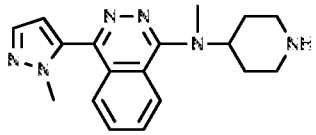
A solution containing *tert*-butyl 4-[methyl-[1-(2-methylpyrazol-3-yl)-6,7-dihydro-5*H*-cyclopenta[d]pyridazin-4-yl]amino]piperidine-1-carboxylate (544.6mg, 1.32mmol) and trifluoroacetic acid (1.13mL, 15.8mmol) in DCM (4mL) was prepared and stirred overnight. The reaction mixture was concentrated *in vacuo* before being loaded onto an SCX cartridge, washed with methanol and eluted using 2M ammonia in methanol. Concentration *in vacuo* afforded *N*-methyl-1-(2-methylpyrazol-3-yl)-*N*-(4-piperidyl)-6,7-dihydro-5*H*-cyclopenta[d]pyridazin-4-amine (285mg,0.91mmol, 69% yield) as an oil.

^{1}H NMR (400MHz, MeOD) δ/ppm: 7.57 (d, *J*2.1Hz, 1H), 6.55 (d, *J* 2.1Hz, 1H), 4.27-4.18 (tt, *J*11.5Hz, 4.0Hz, 1H), 4.01 (s, 3H), 3.21-3.16 (m, 4H), 3.10 (s, 3H), 2.96 (t, *J*7.5Hz, 2H), 2.77-2.70 (td, *J*12.4Hz, 2.8Hz, 2H), 2.18-2.10 (m, *J*7.5Hz, 2H), 1.96-1.91 (dd, *J*11.9Hz, 4.1Hz, 1H), 1.90-1.85 (dd, *J*12.2Hz, 4.1Hz, 1H) 1.85-1.78 (m, 2H).

MS Method 2: RT: 0.90min, ES$^+$ m/z 313.3 $[M+H]^+$

Similarly prepared were:

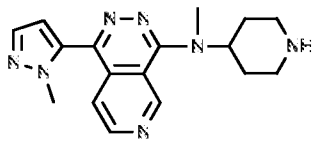
N-Methyl-4-(2-methylpyrazol-3-yl)-N-(4-piperidyl)phthalazin-1-amine



^{1}H NMR (CDCl3, 400 MHz) /ppm: 8.10 (d, J = 7.5 Hz, 1H), 8.03 (d, J = 7.5 Hz, 1H), 7.83 (m, 2H), 7.67 (d, J = 2.0 Hz, 1H), 6.59 (d, J = 2.0 Hz, 1H), 4.06 (m, 5H), 3.24 (m, 5H), 2.71 (m, 2H), 2.01 (m, 4H).

MS Method 2: RT: 0.93min, ES$^+$ m/z 323.3 $[M+H]^+$

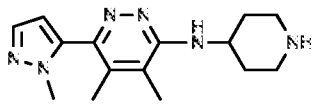
N-methyl-1-(2-methylpyrazol-3-yl)-N-(4-piperidyl)pyrido[3,4-d]pyridazin-4-amine



^{1}H NMR (CDCl3, 400 MHz) /ppm:9.52 (d, *J*0.8Hz, 1H), 8.91 (d, *J*5.7Hz, 1H), 7.81 (dd, *J*5.7,0.8Hz, 1H), 7.68 (d, *J*2.0Hz, 1H), 6.59 (d, *J*2.0Hz, 1H), 4.45-4.36 (m, 1H), 4.10 (s, 3H), 3.34 (s, 3H), 3.30-3.24 (m, 2H), 2.80-2.75 (m, 2H), 2.09-1.97 (m, 4H).

MS Method 2: RT: 0.93min, ES$^+$ m/z 324.3 $[M+H]^+$

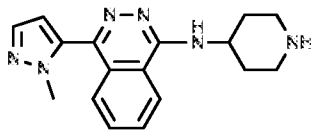
4,5-dimethyl-6-(2-methylpyrazol-3-yl)-N-(4-piperidyl)pyridazin-3-amine



^{1}H NMR (MeOD, 400 MHz) /ppm:7.58 (d, *J*2.0Hz, 1H),6.43 (d, *J*2.0Hz, 1H), 4.25 (tt, *J*11.1Hz, 4.0Hz, 1H), 3.77 (s, 3H), 3.19-3.13 (m, 2H), 2.79 (td, *J*12.5, 2.4Hz, 2H), 2.19 (s, 3H), 2.15 (s, 3H), 2.18-2.10 (m, 2H), 1.60 (qd, *J*12.1, 4.0Hz, 2H).

MS Method 2: RT: 0.79min, ES$^+$ m/z 287.3 $[M+H]^+$

4-(2-methylpyrazol-3-yl)-N-(4-piperidyl)phthalazin-1-amine

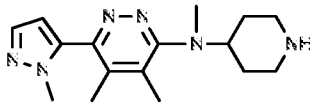


^{1}H NMR ($CDCl_3$, 400 MHz) /ppm: 7.99-7.78 (m, 4H), 7.65 (d, *J*1.9Hz, 1H), 6.54 (d, *J*1.9Hz, 1H), 5.45 (d, *J*7.3Hz, 1H), 4.68-4.57 (m, 1H), 4.01 (s, 3H), 3.32-3.25 (m, 2H), 2.94 (td, *J*21.5, 2.3, 2H), 2.40-2.31 (m, 2H), 1.75-1.63 (m, 2H).

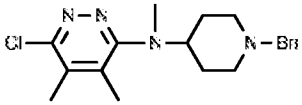
MS Method 2: RT: 0.81min, ES^+ m/z 309.2 $[M+H]^+$

[00185] Procedure C

[00186] Preparation of **N,4,5-trimethyl-6-(2-methylpyrazol-3-yl)-N-(4-piperidyl)pyridazin-3-amine** and related compounds, intermediates in the synthesis of compounds of formula (**I**)..



N-(1-benzyl-4-piperidyl)-6-chloro-N,4,5-trimethyl-pyridazin-3-amine

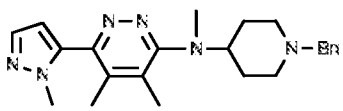


1-Benzyl-N-methyl-piperidin-4-amine (0.9mL, 4.1mmol), 3,6-dichloro-4,5-dimethyl-pyridazine (1.g, 5.65mmol) and DIPEA (1.08mL, 6.21mmol) were dissolved in NMP (2.5mL) and heated to 150 °C under microwave irradiation for 10hrs. The resulting solution was partitioned between EtOAc (50mL) and water (50mL). The phases were separated and the water re-extracted with EtOAc (50mL). The combined organics were washed with brine (3 x 50mL), dried (Na_2SO_4) and concentrated to afford a brown oil. Purification by silica flash chromatography eluting with 20% EtOAc in heptane with a gradient to 80% ethyl acetate afforded *N*-(1-benzyl-4-piperidyl)-6-chloro-*N*,4,5-trimethyl-pyridazin-3-amine (1.0g, 2.90mmol, 51% yield) as a colourless oil which crystalised on standing at room temperature.

MS Method 2: RT: 1.18min, ES^+ m/z 345.3 $[M+H]^+$

^{1}H NMR (400MHz, $CDCl_3$) δ/ppm: 7.34-7.25 (m, 5H), 3.52 (s, 2H), 3.26-3.18 (tt, *J* 11.2Hz, 3.9Hz, 1H), 3.00-2.94 (m, 2H), 2.85 (s, 3H), 2.34 (s, 3H), 2.25 (s, 3H), 2.05-1.87 (m, 4H), 1.79-1.72 (m, 2H).

N-(1-benzyl-4-piperidyl)-N,4,5-trimethyl-6-(2-methylpyrazol-3-yl)pyridazin-3-amine

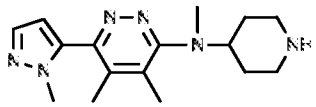


N-(1-Benzyl-4-piperidyl)-6-chloro-*N*,4,5-trimethyl-pyridazin-3-amine (500mg, 1.45mmol) and potassium carbonate (401mg, 2.9mmol) were added to toluene (1.5mL), ethanol (1mL) and water (0.50mL) and degassed by purging with nitrogen for 10min. Palladium (0)

tetrakis(triphenylphosphine) (252mg, 0.22mmol) and 1-methyl-1H-pyrazole-5-boronic acid, pinacolester (452mg, 2.17mmol) were then added, the vial sealed and heated by microwave irradiation at 150°C for 55 mins. The reaction mixture was poured into EtOAc (25mL) and water (25mL) and the phases were separated. The aqueous layer was re-extracted with EtOAc (2x25 mL) and the combined organic layers washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford brown semi-solid. The residue was taken up in methanol and purified through a 5g SCX cartridge with methanol washings followed by 0.7M ammonia in methanol solution to elute the product. Concentration *in vacuo* afforded N-(1-benzyl-4-piperidyl)-N,4,5-trimethyl-6-(2-methylpyrazol-3-yl)pyridazin-3-amine (500mg,1.28mmol, 88% yield) as a pale yellow oil which was used immediately in the next step.

MS Method 2: RT: 1.10min, ES^+ m/z 391.3 $[M+H]^+$

N,4,5-trimethyl-6-(2-methylpyrazol-3-yl)-N-(4-piperidyl)pyridazin-3-amine



N-(1-benzyl-4-piperidyl)-*N*,4,5-trimethyl-6-(2-methylpyrazol-3-yl)pyridazin-3-amine (490.mg, 1.25mmol) was dissolved in methanol (10mL) and hydrogenated over 10% palladium on carbon (20mg, 0.06mmol) under 1atm hydrogen. The reaction was stirred for 72h at room temperature. The reaction was purged with nitrogen to replace the hydrogen, filtered through celite and concentrated to afford the crude as a brown oil. The residue was taken up in methanol and purified through a 5g SCX cartridge with methanol washings followed by 0.7M ammonia in methanol solution to elute the product. Concentration *in vacuo* afforded *N*,4,5-trimethyl-6-(2-methylpyrazol-3-yl)-*N*-(4-piperidyl)pyridazin-3-amine as a pale yellow oil (385mg,1.28mmol, quantitative)

^1H NMR (400MHz, $CDCl_3$) δ/ppm: 7.58 (d, *J*1.9Hz, 1H), 6.37 (d, *J*1.9Hz, 1H), 3.95 (s, 3H), 3.50-3.42 (m, 1H), 3.23-3.16 (m, 2H), 2.96 (s, 3H), 2.72-2.63 (m, 2H), 2.29 (s, 3H), 2.24 (s, 3H), 1.89-1.79 (m, 4H).

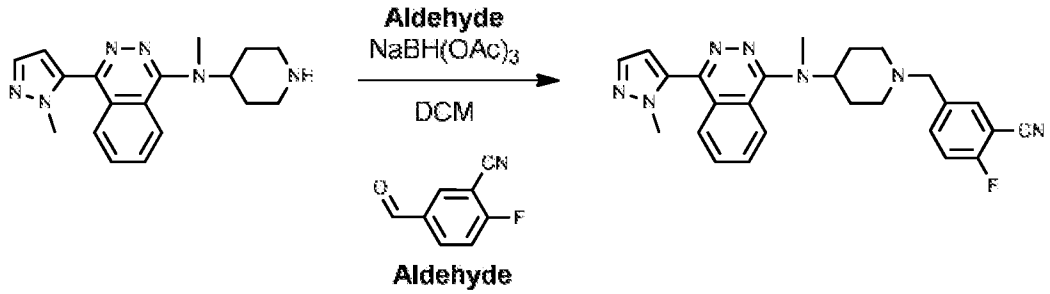
MS Method 2: RT: 0.96 min, m/z 301.3 $[M+H]^+$

[00187] Compounds produced in the Procedures described above may take part in reactions to produce compounds of the invention, for example those exemplified below.

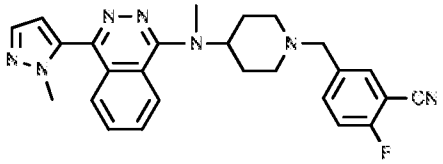
[00188] Example 1

[00189] Compounds of formula (I) can be prepared by General Method A, shown below. General Method A may be carried out using the compound prepared by Procedure B or C or another appropriate method for producing the compound.

General Method A



2-fluoro-5-[[4-[methyl-[4-(2-methylpyrazol-3-yl)phthalazin-1-yl]amino]-1-piperidyl]methyl]benzonitrile



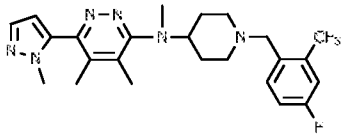
N-Methyl-4-(2-methylpyrazol-3-yl)-*N*-(4-piperidyl)phthalazin-1-amine (50.0mg, 0.16mmol) and 2-fluoro-5-formylbenzonitrile (27.8mg, 0.19mmol) were dissolved in DCM (10mL) in a 100mL round-bottomed flask. The reaction was stirred for 15min and sodium triacetoxyborohydride (66mg, 0.31mmol) was added and the reaction stirred overnight. LC-MS analysis indicated that the reaction was not complete. 2-fluoro-5-formylbenzonitrile (28mg, 0.19 mmol) and sodium triacetoxyborohydride (33mg, 0.16mmol) were added to the flask and the reaction stirred overnight. LC-MS indicated that the reaction was complete. The reaction mixture diluted with saturated sodium bicarbonate solution (50mL) and extracted with DCM (3 × 20mL). The combined organic layers were combined, dried (Na_2SO_4), and the solvent removed *in vacuo* to afford the crude material which was purified by preparative LCMS to afford the formate salt of 2-fluoro-5-[[4-[methyl-[4-(2-methylpyrazol-3-yl)phthalazin-1-yl]amino]-1-piperidyl]methyl]benzonitrile (24.5 mg, 0.05 mmol, 35%) as a yellow solid.

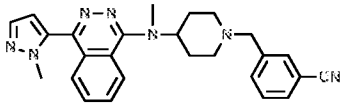
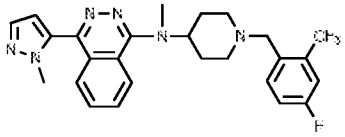
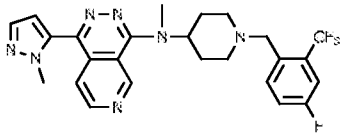
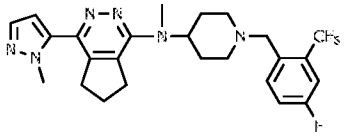
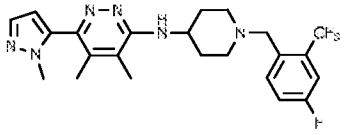
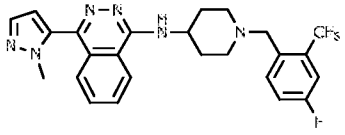
^{1}H NMR ($CDCl_3$, 400 MHz) /ppm: 8.23 (s, 1H), 8.10 (d, *J* = 7.5 Hz, 1H), 8.03 (d, *J* = 7.5 Hz, 1H), 7.88-7.80 (m, 2H), 7.69-7.61 (m, 3H), 7.22 (t, *J* = 8.5 Hz, 1H), 6.59 (d, *J* = 2.0 Hz, 1H), 4.19-4.10 (m, 1H), 4.05 (s, 3H), 3.63 (s, 2H), 3.22 (s, 3H), 3.11-3.05 (m, 3H), 2.30-2.04 (m, 6H).

MS Method 1: RT: 2.61 min, m/z 456.4 $[M+H]^+$

[00190] The compounds shown below in **Table 3** were similarly prepared by varying the aldehyde shown in the reaction scheme for General Method A:

Table 3

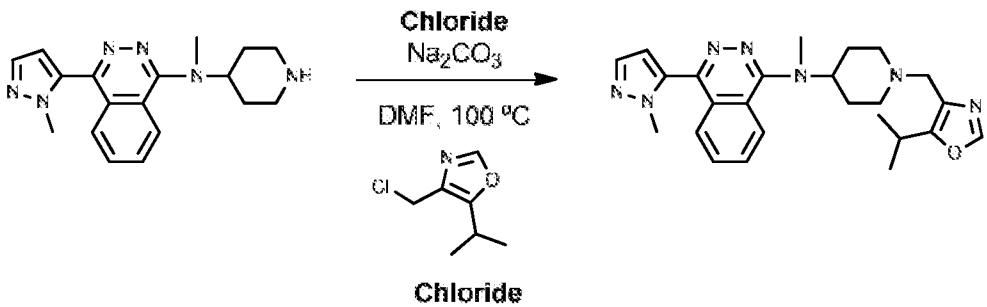
Structure	Compound Name	LCMS RT	m/z MIM
	*N*-[1-[[4-fluoro-2-(trifluoromethyl)phenyl]methyl]-4-piperidyl]-*N*,4,5-trimethyl-6-(2-methylpyrazol-3-yl)pyridazin-3-amine	2.91min (Method 1)	477.4 $[M+H]^+$

Structure	Compound Name	LCMS RT	m/z MIM
	3-[[4-[methyl-[4-(2-methylpyrazol-3-yl)phthalazin-1-yl]amino]-1-piperidyl]methyl]benzonitrile	2.48min (Method 1)	438.4 $[M+H]^+$
	*N*-[1-[[4-fluoro-2-(trifluoromethyl)phenyl]methyl]-4-piperidyl]-*N*-methyl-4-(2-methylpyrazol-3-yl)phthalazin-1-amine	1.29min (Method 2)	499.3 $[M+H]^+$
	*N*-[1-[[4-fluoro-2-(trifluoromethyl)phenyl]methyl]-4-piperidyl]-*N*-methyl-1-(2-methylpyrazol-3-yl)pyrido[3,4-*d*]pyridazin-4-amine	1.21min (Method 2)	500.4 $[M+H]^+$
	*N*-[1-[[4-fluoro-2-(trifluoromethyl)phenyl]methyl]-4-piperidyl]-*N*-methyl-1-(2-methylpyrazol-3-yl)-6,7-dihydro-5H-cyclopenta[*d*]pyridazin-4-amine	2.88min (Method 1)	489.4 $[M+H]^+$
	*N*-[1-[[4-fluoro-2-(trifluoromethyl)phenyl]methyl]-4-piperidyl]-4,5-dimethyl-6-(2-methylpyrazol-3-yl)pyridazin-3-amine	1.12min (Method 2)	463.3 $[M+H]^+$
	*N*-[1-[[4-fluoro-2-(trifluoromethyl)phenyl]methyl]-4-piperidyl]-4-(2-methylpyrazol-3-yl)phthalazin-1-amine	1.10min (Method 2)	485.2 $[M+H]^+$

[00191] Example 2

[00192] Compounds of formula (I) can be prepared by General Method B, shown below. General Method B may be carried out using the compound prepared by Procedure B or another appropriate method for producing the compound.

General Method B



N-[1-[(5-isopropyloxazol-4-yl)methyl]-4-piperidyl]-N-methyl-4-(2-methylpyrazol-3-yl)phthalazin-1-amine

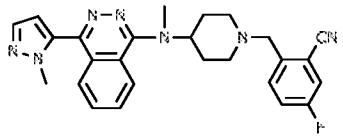
N-Methyl-4-(2-methylpyrazol-3-yl)-N-(4-piperidyl)phthalazin-1-amine (50mg, 0.16mmol) was dissolved in DMF (5mL), to which was added 4-(chloromethyl)-5-isopropyl-oxazole (37mg, 0.23mmol) and sodium carbonate (33mg, 0.31mmol). The reaction was heated at 100ºC overnight before cooling to room temperature. The reaction was diluted with ethyl acetate (30mL) and washed with water (4 x 50mL). The aqueous layer was re-extracted with *n*-butanol (10mL). The organic layers were combined, dried (Na_2SO_4) and concentrated *in vacuo*, to afford 90 mg of crude product. The crude product was purified by preparative LCMS. The sample obtained was further purified by SCX with methanol washings and elution with 1M ammonia in methanol. Further purification by silica flash chromatography with 0% methanol in DCM with a gradient to 10% methanol afforded a sample which was further purified by SCX with methanol washings and elution with 1M ammonia in methanol to afford *N*-[1-[(5-isopropyloxazol-4-yl)methyl]-4-piperidyl]-*N*-methyl-4-(2-methylpyrazol-3-yl)phthalazin-1-amine (11.2mg,0.025mmol, 16% yield).

^{1}H NMR ($CDCl_3$, 400 MHz) /ppm: 8.11-8.08 (m, 1H), 8.03-8.00 (m, 1H), 7.88-7.78 (m, 2H), 7.75 (s, 1H), 7.66 (d, *J*2.0Hz, 1H), 6.58 (d, *J*2.0Hz, 1H), 4.05 (s, 3H), 4.07-4.04 (m(br), 1H), 3.56 (s(br), 2H), 3.19 (s, 3H), 3.21-3.10 (m, 3H), 2.35-1.99 (m, 6H), 1.28 (d, *J*7.0Hz, 6H).

MS Method 1: RT: 2.60min, m/z 446.4 $[M+H]^+$

Similarly prepared was:

5-fluoro-2-[[4-[methyl-[4-(2-methylpyrazol-3-yl)phthalazin-1-yl]amino]-1-piperidyl]methyl]benzonitrile



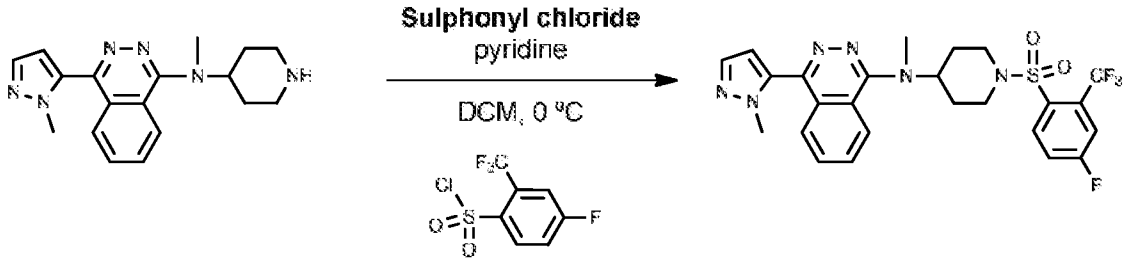
^{1}H NMR (400MHz, $CDCl_3$) δ/ppm: 7.99 (d, *J*7.9Hz, 1H), 7.94, (d, *J*7.7Hz, 1H), 7.74 (m, 2H), 7.58 (d, *J*1.9Hz, 1H), 7.50 (dd, *J*8.5, 5.4Hz, 1H), 7.28 (dd, *J*7.9, 2.6Hz, 1H), 7.22 (dt, *J*8.3, 2.9Hz, 1H), 6.50 (d, *J*1.9Hz, 1H), 3.97 (s, 3H), 3.93 (tt, *J*11.5, 3.8Hz, 1H), 3.61 (s, 2H), 3.11 (s, 3H), 2.92 (d, *J*11.6Hz, 2H), 2.03 (m, 6H)

MS Method 1: RT: 2.58min, m/z 456.4 $[M+H]^+$

[00193] Example 3

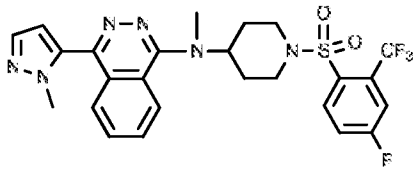
[00194] Compounds of formula (I) can be prepared by General Method C, shown below. General Method C may be carried out using the compound prepared by Procedure B or C or another appropriate method for producing the compound.

General Method C



Sulphonyl chloride

N-[1-[4-fluoro-2-(trifluoromethyl)phenyl]sulfonyl-4-piperidyl]-N-methyl-4-(2-methylpyrazol-3-yl)phthalazin-1-amine



N-Methyl-4-(2-methylpyrazol-3-yl)-*N*-(4-piperidyl)phthalazin-1-amine (43mg, 0.13mmol) and pyridine (0.3mL, 3.71mmol) were taken up in DCM and cooled to 0°C then 4-fluoro-2-(trifluoromethyl)benzenesulfonyl chloride (132mg, 0.50mmol) was added. The mixture was slowly allowed to warm to room temperature then stirred at this temperature for 7 hours. LCMS analysis indicated no product was present. The reaction mixture was left to stand overnight. 4-fluoro-2-(trifluoromethyl)benzenesulfonyl chloride (100mg, 0.38mmol) and pyridine (0.2 mL) were added and the mixture was heated to 40°C for 6 hours. The reaction was cooled to room temperature and the reaction mixture was washed with water (10mL) and brine (10 mL). The organics were collected, dried (Na_2SO_4) and concentrated *in vacuo* to afford a brown oil. The crude material was purified by preparative LCMS to afford *N*-[1-[4-fluoro-2-(trifluoromethyl)phenyl]sulfonyl-4-piperidyl]-*N*-methyl-4-(2-methylpyrazol-3-yl)phthalazin-1-amine (4.7mg, 8.6μmol, 6.4% yield)

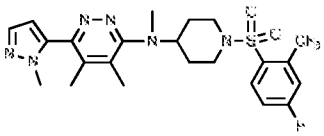
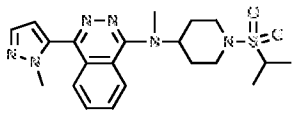
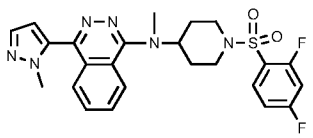
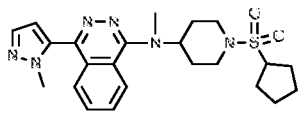
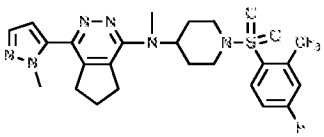
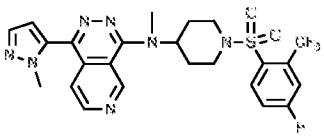
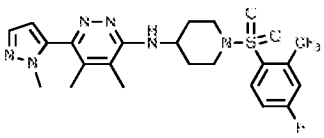
^{1}H NMR ($CDCl_3$, 400 MHz) /ppm: 8.24-8.20 (dd, *J*8.9Jz, 5.2Hz, 1H), 8.10-8.08 (m, 1H), 8.05-8.02 (m, 1H), 7.88-7.80 (m, 2H), 7.67 (d, *J*1.9Hz, 1H), 7.63 (dd, *J* 8.9Hz, 2.8Hz, 1H), 7.44-7.39 (m, 1H), 6.58 (d, *J*1.9Hz, 1H), 4.29-4.21 (m, 1H), 4.05 (s, 3H), 4.01-3.95 (m, 2H), 3.20 (s, 3H), 2.93-2.84 (td, *J*12.4Hz, 2.7Hz, 2H), 2.20-2.04 (m, 4H)

MS Method 1: RT: 3.82 min, m/z 549.2 $[M+H]^+$

[00195] The compounds shown below in **Table 4** were similarly prepared by varying the sulphonyl chloride shown in the reaction scheme for General Method C:

Table 4

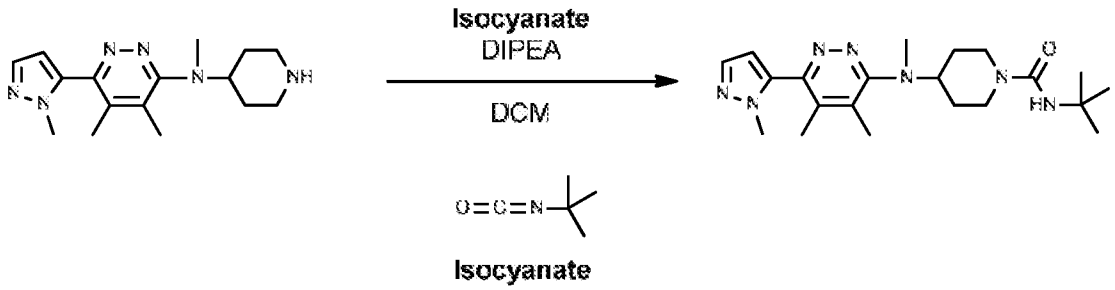
Structure	Compound Name	LCMS RT	m/z MIM

Structure	Compound Name	LCMS RT	m/z MIM
	*N*-[1-[4-fluoro-2-(trifluoromethyl)phenyl]sulfonyl-4-piperidyl]-*N*,4,5-trimethyl-6-(2-methylpyrazol-3-yl)pyridazin-3-amine	4.05min (Method 1)	527.3 $[M+H]^+$
	*N*-(1-isopropylsulfonyl-4-piperidyl)-*N*-methyl-4-(2-methylpyrazol-3-yl)phthalazin-1-amine	2.89min (Method 1)	429.4 $[M+H]^+$
	*N*-[1-(2,4-difluorophenyl)sulfonyl-4-piperidyl]-*N*-methyl-4-(2-methylpyrazol-3-yl)phthalazin-1-amine	3.51min (Method 1)	499.3 $[M+H]^+$
	*N*-(1-cyclopentylsulfonyl-4-piperidyl)-*N*-methyl-4-(2-methylpyrazol-3-yl)phthalazin-1-amine	3.19min (Method 1)	455.4 $[M+H]^+$
	*N*-[1-[4-fluoro-2-(trifluoromethyl)phenyl]sulfonyl-4-piperidyl]-*N*-methyl-1-(2-methylpyrazol-3-yl)-6,7-dihydro-5H-cyclopenta[*d*]pyridazin-4-amine	3.74min (Method 1)	539.3 $[M+H]^+$
	*N*-[1-[4-fluoro-2-(trifluoromethyl)phenyl]sulfonyl-4-piperidyl]-*N*-methyl-1-(2-methylpyrazol-3-yl)pyrido[3,4-d]pyridazin-4-amine	1.63min (Method 2)	550.3 $[M+H]^+$
	*N*-[1-[4-fluoro-2-(trifluoromethyl)phenyl]sulfonyl-4-piperidyl]-4,5-dimethyl-6-(2-methylpyrazol-3-yl)pyridazin-3-amine	1.47min (Method 2)	513.2 $[M+H]^+$

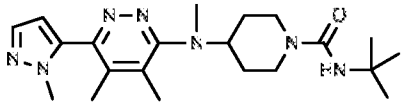
[00196] Example 4

[00197] Compounds of formula (I) can be prepared by General Method D, shown below. General Method D may be carried out using the compound prepared by Procedure B or C or another appropriate method for producing the compound.

General Method D



N-tert-butyl-4-[[4,5-dimethyl-6-(2-methylpyrazol-3-yl)pyridazin-3-yl]-methyl-amino]piperidine-1-carboxamide



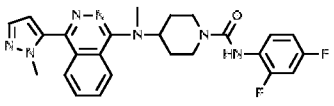
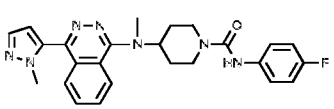
N,4,5-Trimethyl-6-(2-methylpyrazol-3-yl)-*N*-(4-piperidyl)pyridazin-3-amine (100mg, 0.33mmol) was dissolved in DCM (2mL) and DIPEA (0.12mL, 0.67mmol). The reaction was stirred at room temperature under nitrogen, *tert*-butyl isocyanate (0.04mL, 0.33mmol) was added in one portion and the reaction was stirred overnight. Water (20mL) and DCM (20mL) were added and the aqueous and organic layers were separated through a phase separator. Concentration *in vacuo* afforded a crude oil which was purified by flash column chromatography using 5% methanol in ethyl acetate with a gradient increasing to 30% MeOH to afford N-tert-butyl-4-[[4,5-dimethyl-6-(2-methylpyrazol-3-yl)pyridazin-3-yl]-methyl-amino]piperidine-1-carboxamide (95mg,0.21mmol, 64% yield).

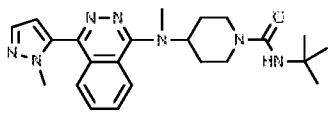
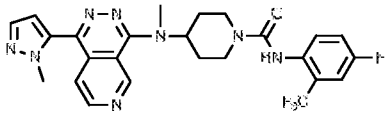
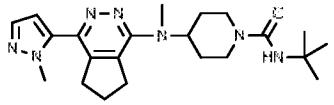
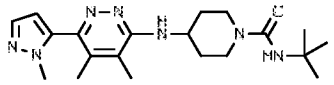
^{1}H NMR ($CDCl_3$, 400 MHz) /ppm: 7.58 (d, *J*1.9Hz, 1H), 6.37 (d, *J*1.9Hz, 1H), 4.36 (s, 1H), 4.02-3.95 (m, 2H), 3.94 (s, 3H), 3.68-3.59 (tt, *J*11.3Hz, 3.9Hz, 1H), 2.89 (s, 3H), 2.86-2.78 (m, 2H), 2.29 (s, 3H), 2.24 (s, 3H), 1.95-1.88 (m, 2H), 1.88-1.76 (qd, *J*12.1Hz, 4.0Hz, 2H), 1.38 (s, 9H).

MS Method 1: RT: 3.12min, m/z 400.4 $[M+H]^+$

[00198] The compounds shown below in **Table 5** were similarly prepared by varying the sulphonyl chloride shown in the reaction scheme for General Method C:

Table 5

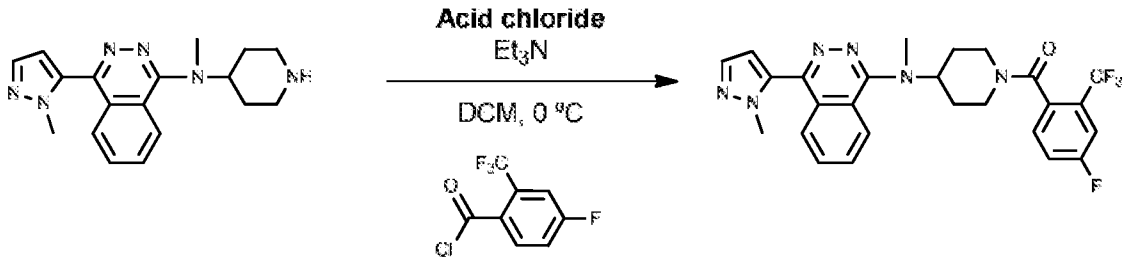
Structure	Compound Name	LCMS RT	m/z MIM
	*N*-(2,4-difluorophenyl)-4-[methyl-[4-(2-methylpyrazol-3-yl)phthalazin-1-yl]amino]piperidine-1-carboxamide	2.98min (Method 1)	478.3 $[M+H]^+$
	*N*-(4-fluorophenyl)-4-[methyl-[4-(2-methylpyrazol-3-yl)phthalazin-1-yl]amino]piperidine-1-carboxamide	2.99min (Method 1)	460.3 $[M+H]^+$

Structure	Compound Name	LCMS RT	m/z MIM
	*N*-tert-butyl-4-[methyl-[4-(2-methylpyrazol-3-yl)phthalazin-1-yl]amino]piperidine-1-carboxamide	2.82min (Method 1)	422.4 $[M+H]^+$
	*N*-[4-fluoro-2-(trifluoromethyl)phenyl]-4-[methyl-[1-(2-methylpyrazol-3-yl)pyrido[3,4-d]pyridazin-4-yl]amino]piperidine-1-carboxamide	3.30min (Method 1)	529.4 $[M+H]^+$
	*N*-tert-butyl-4-[methyl-[1-(2-methylpyrazol-3-yl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyridazin-4-yl]amino]piperidine-1-carboxamide	2.79min (Method 1)	412.4 $[M+H]^+$
	*N*-tert-butyl-4-[[4,5-dimethyl-6-(2-methylpyrazol-3-yl)pyridazin-3-yl]amino]piperidine-1-carboxamide	1.12min (Method 2)	386.3 $[M+H]^+$

[00199] Example 5

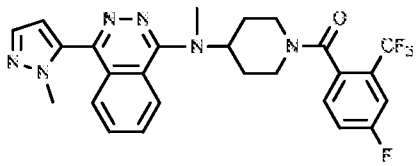
[00200] Compounds of formula (I) can be prepared by General Method E, shown below. General Method E may be carried out using the compound prepared by Procedure B or another appropriate method for producing the compound.

General Method E



Acid chloride

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

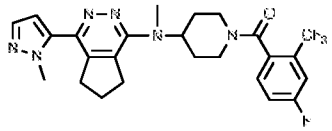
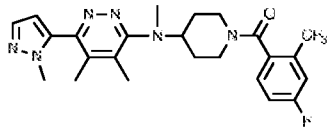
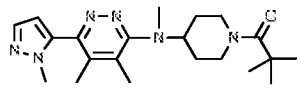
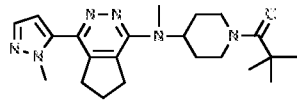
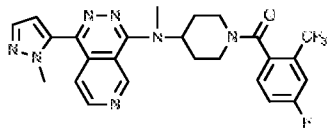


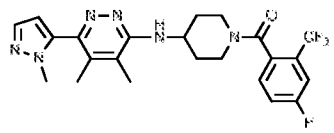
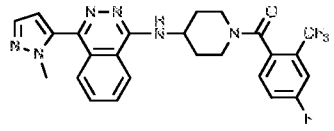
To a solution of *N*-methyl-4-(2-methylpyrazol-3-yl)-N-(4-piperidyl)phthalazin-1-amine (477 mg, 1.48 mmol) in DCM (8mL) was added triethylamine (0.41mL, 2.96mmol). The solution was cooled to 0°C before 4-fluoro-2-(trifluoromethyl)benzoyl chloride (0.25mL, 1.63mmol) was slowly added dropwise. The solution was stirred for 5min before allowing to warm to room temperature and left to stir for 2 hours. LCMS indicated that the starting material had been consumed so the solution was diluted with DCM (15mL) and partitioned with water (20mL) before being passed through a phase separator. The organic layer was concentrated *in vacuo* and the resulting oil was purified using silica flash column chromatography using 0% methanol in DCM with a gradient to 5% methanol to afford the crude product. 100mg of this material was further purified by preparative LCMS to afford [4-fluoro-2-(trifluoromethyl)phenyl]-[4-[methyl-[4-(2-methylpyrazol-3-yl)phthalazin-1-yl]amino]-1-piperidyl]methanone (10.2mg, 0.020mmol, 1.3%)

MS Method 2: RT: 1.49 min, m/z 513.5 $[M+H]^+$

^{1}H NMR (400 MHz, MeOD) /ppm: 8.30-8.26 (d(br), *J*8.2Hz, 1H), 8.03-7.93 (m, 3H), 7.71 (d, *J*2.0Hz, 1H), 7.71-7.49 (m, 3H), 6.68 (d, *J*2.0Hz, 1H), 4.86-4.79 (m, 1H), 4.40-4.29 (m, 1H), 3.50 (s, 3H), 3.46-3.39 (m, 1H), 3.29-3.12 (m, 1H), 3.24 (s, 1.5H, rotamer), 3.19 (s, 1.5H, rotamer), 2.95-2.85 (m, 1H), 2.24-1.86 (m, 4H).

Table 6

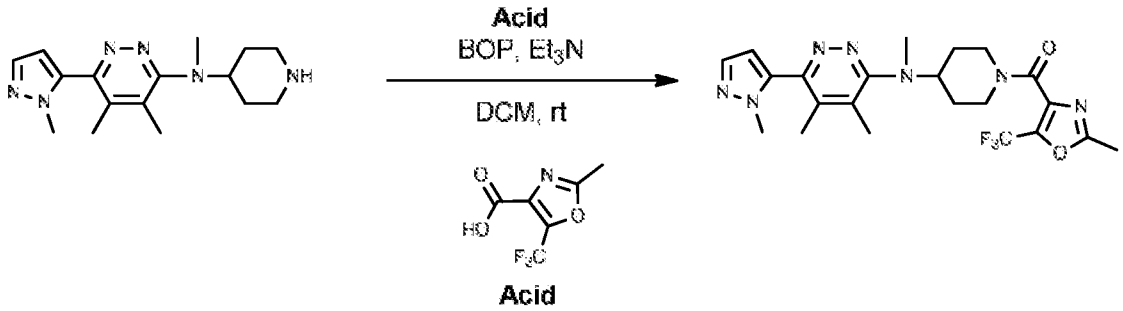
Structure	Compound Name	LCMS RT	m/z MIM
	[4-fluoro-2-(trifluoromethyl)phenyl]-[4-[methyl-[1-(2-methylpyrazol-3-yl)-6,7-dihydro-5*H*-cyclopenta[d]pyridazin-4-yl]amino]-1-piperidyl]methanone	3.35min (Method 1)	503.4 $[M+H]^+$
	[4-[[4,5-dimethyl-6-(2-methylpyrazol-3-yl)pyridazin-3-yl]-methyl-amino]-1-piperidyl]-[4-fluoro-2-(trifluoromethyl)phenyl]methanone	3.63min (Method 1)	491.4 $[M+H]^+$
	1-[4-[[4,5-dimethyl-6-(2-methylpyrazol-3-yl)pyridazin-3-yl]-methyl-amino]-1-piperidyl]-2,2-dimethyl-propan-1-one	3.23min (Method 1)	385.4 $[M+H]^+$
	2,2-dimethyl-1-[4-[methyl-[1-(2-methylpyrazol-3-yl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyridazin-4-yl]amino]-1-piperidyl]propan-1-one	2.90min (Method 1)	397.4 $[M+H]^+$
	[4-fluoro-2-(trifluoromethyl)phenyl]-[4-[methyl-[1-(2-methylpyrazol-3-yl)pyrido[3,4-d]pyridazin-4-yl]amino]-1-piperidyl]methanone	1.48min (Method 2)	514.3 $[M+H]^+$

Structure	Compound Name	LCMS RT	m/z MIM
	[4-[[4,5-dimethyl-6-(2-methylpyrazol-3-yl)pyridazin-3-yl]amino]-1-piperidyl]-[4-fluoro-2-(trifluoromethyl)phenyl]methanone	1.30min (Method 2)	477.3 $[M+H]^+$
	[4-fluoro-2-(trifluoromethyl)phenyl]-[4-[[4-(2-methylpyrazol-3-yl)phthalazin-1-yl]amino]-1-piperidyl]methanone	1.28min (Method 2	499.2 $[M+H]^+$

[00201] Example 6

[00202] Compounds of formula (I) can be prepared by General Method F, shown below. General Method F may be carried out using the compound prepared by Procedure B or another appropriate method for producing the compound.

General Method F



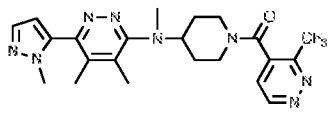
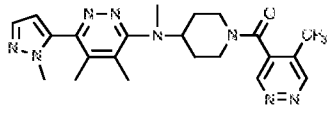
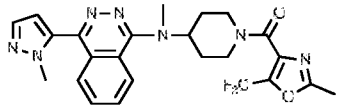
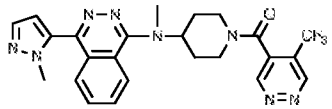
[4-[[4,5-Dimethyl-6-(2-methylpyrazol-3-yl)pyridazin-3-yl]-methyl-amino]-1-piperidyl]-[2-methyl-5-(trifluoromethyl)oxazol-4-yl]methanone

To a round bottomed flask were added *N*,4,5-trimethyl-6-(2-methylpyrazol-3-yl)-*N*-(4-piperidyl)pyridazin-3-amine (130mg, 0.43mmol), BOP (210mg, 0.48mmol), 2-methyl-5-(trifluoromethyl)oxazole-4-carboxylic acid (93mg, 0.48mmol) and triethylamine (88mg, 0.87mmol) in DCM. The reaction was stirred at RT overnight. The reaction was then partitioned between water and DCM. The organic layer was obtained through a phase separator. The aqueous layer was extracted with DCM (3x10mL). The organic layers were combined and concentrated *in vacuo*. The resulting residue purified by flash silica chromatography using 0-20% MeOH in EtOAc Further purification was performed by preparative LCMS to afford .[4-[[4,5-dimethyl-6-(2-methylpyrazol-3-yl)pyridazin-3-yl]-methyl-amino]-1-piperidyl]-[2-methyl-5-(trifluoromethyl)oxazol-4-yl]methanone (6mg,0.013mmol, 2.9% yield).

MS Method 2: RT: 1.47 min, m/z 478.4 $[M+H]^+$

^{1}H NMR (400 MHz, MeOD) /ppm: 7.61 (d, *J*2.0Hz, 1H), 6.50 (d, *J*2.0Hz, 1H),4.72-4.64 (m, 1H), 3.92-3.77 (m, 2H), 3.80 (s, 3H), 3.29-3.20 (m, 1H), 2.98 (td, *J*12.8, 3.0Hz, 1H),2.93 (s, 3H), 2.59 (s, 3H), 2.39 (s, 3H), 2.23 (s, 3H), 2.07-2.00 (m, 1H), 1.97-1.84 (m, 3H).

Table 7

Structure	Compound Name	LCMS RT	m/z MIM
	[4-[[4,5-dimethyl-6-(2-methylpyrazol-3-yl)pyridazin-3-yl]-methyl-amino]-1-piperidyl]-[3-(trifluoromethyl)pyridazin-4-yl]methanone	1.38min (Method 2)	475.4 $[M+H]^+$
	[4-[[4,5-dimethyl-6-(2-methylpyrazol-3-yl)pyridazin-3-yl]-methyl-amino]-1-piperidyl]-[5-(trifluoromethyl)pyridazin-4-yl]methanone	3.05min (Method 1)	475.4 $[M+H]^+$
	[4-[methyl-[4-(2-methylpyrazol-3-yl)phthalazin-1-yl]amino]-1-piperidyl]-[2-methyl-5-(trifluoromethyl)oxazol-4-yl]methanone	3.14min (Method 1)	500.4 $[M+H]^+$
	[4-[methyl-[4-(2-methylpyrazol-3-yl)phthalazin-1-yl]amino]-1-piperidyl]-[5-(trifluoromethyl)pyridazin-4-yl]methanone	2.91min (Method 1)	497.4 $[M+H]^+$

[00203] Example 7

[00204] *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 reported as IC50 values.

[00205] 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.

[00206] 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.

[00207] Serial dilutions of the test compounds were prepared in 100% DMSO. 10 l of compound or DMSO from each well was pipetted into a sterile, 0.5ml deep well conical bottomed 96 well plate

(intermediate plate). 190 l 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 180 l by electronic pipette to ensure homogeneity of the compound solution. This 1:20 dilution gives a top concentration of 50 M in 5% DMSO, 95% assay media. 10 l was pipetted from each well of the intermediate plate into a second deep well sterile plate. 490 l of warm assay media was then added to each well and mixed five times at 300 l. This gives a final top concentration of 1 M in 0.1% DMSO.

[00208] After the 24 hour incubation, media was carefully removed by pipette and replaced with 45 l of compound dilutions in triplicate. This was incubated for one hour at 37°C in a 5% CO_2. After an hour, 5 l 10 g/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.

[00209] After 24 hours, plates were removed from the incubator and left to acclimatise to room temperature for 20 minutes. 50 l 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).

[00210] The results of the *in vitro* biological data 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 75 nM to 1500 nM. The category "++" refers to compounds with an IC50 of 15 nM to 75 nM. The category "+++" refers to compounds with an IC50 of <15 nM. The category "-" refers to a compound with a IC50 value of >6uM.

ID No.	Compound	Category
1	N-tert-butyl-4-[methyl-[4-(2-methylpyrazol-3-yl)phthalazin-1-yl]amino]piperidine-1-carboxamide	++
2	3-[[4-[methyl-[4-(2-methylpyrazol-3-yl)phthalazin-1-yl]amino]-1-piperidyl]methyl]benzonitrile	+
3	N-(4-fluorophenyl)-4-[methyl-[4-(2-methylpyrazol-3-yl)phthalazin-1-yl]amino]piperidine-1-carboxamide	+
4	N-(2,4-difluorophenyl)-4-[methyl-[4-(2-methylpyrazol-3-yl)phthalazin-1-yl]amino]piperidine-1-carboxamide	++
5	N-[1-[4-fluoro-2-(trifluoromethyl)phenyl]sulfonyl-4-piperidyl]-N-methyl-4-(2-methylpyrazol-3-yl)phthalazin-1-amine	+++
6	[4-fluoro-2-(trifluoromethyl)phenyl]-[4-[methyl-[4-(2-methylpyrazol-3-yl)phthalazin-1-yl]amino]-1-piperidyl]methanone	+++
7	N-[1-[[4-fluoro-2-(trifluoromethyl)phenyl]methyl]-4-piperidyl]-N-methyl-4-(2-methylpyrazol-3-yl)phthalazin-1-amine	+++

8	[4-[methyl-[4-(2-methylpyrazol-3-yl)phthalazin-1-yl]amino]-1-piperidyl]-[5-(trifluoromethyl)pyridazin-4-yl]methanone	++
9	N-[4-fluoro-2-(trifluoromethyl)phenyl]-4-[methyl-[1-(2-methylpyrazol-3-yl)pyrido[3,4-d]pyridazin-4-yl]amino]piperidine-1-carboxamide	+++
10	[4-[[4,5-dimethyl-6-(2-methylpyrazol-3-yl)pyridazin-3-yl]-methyl-amino]-1-piperidyl]-[3-(trifluoromethyl)pyridazin-4-yl]methanone	++
11	[4-[[4,5-dimethyl-6-(2-methylpyrazol-3-yl)pyridazin-3-yl]-methyl-amino]-1-piperidyl]-[2-methyl-5-(trifluoromethyl)oxazol-4-yl]methanone	+
12	N-[1-[[4-fluoro-2-(trifluoromethyl)phenyl]methyl]-4-piperidyl]-N-methyl-1-(2-methylpyrazol-3-yl)-6,7-dihydro-5H-cyclopenta[d]pyridazin-4-amine	+
13	N-[1-[4-fluoro-2-(trifluoromethyl)phenyl]sulfonyl-4-piperidyl]-N-methyl-1-(2-methylpyrazol-3-yl)pyrido[3,4-d]pyridazin-4-amine	+++
14	2,2-dimethyl-1-[4-[methyl-[1-(2-methylpyrazol-3-yl)-6,7-dihydro-5H-cyclopenta[d]pyridazin-4-yl]amino]-1-piperidyl]propan-1-one	+
15	N-[1-[4-fluoro-2-(trifluoromethyl)phenyl]sulfonyl-4-piperidyl]-N-methyl-1-(2-methylpyrazol-3-yl)-6,7-dihydro-5H-cyclopenta[d]pyridazin-4-amine	+++
16	N-tert-butyl-4-[methyl-[1-(2-methylpyrazol-3-yl)-6,7-dihydro-5H-cyclopenta[d]pyridazin-4-yl]amino]piperidine-1-carboxamide	++
17	[4-[[4,5-dimethyl-6-(2-methylpyrazol-3-yl)pyridazin-3-yl]-methyl-amino]-1-piperidyl]-[4-fluoro-2-(trifluoromethyl)phenyl]methanone	++
18	1-[4-[[4,5-dimethyl-6-(2-methylpyrazol-3-yl)pyridazin-3-yl]-methyl-amino]-1-piperidyl]-2,2-dimethyl-propan-1-one	+
19	[4-fluoro-2-(trifluoromethyl)phenyl]-[4-[methyl-[1-(2-methylpyrazol-3-yl)-6,7-dihydro-5H-cyclopenta[d]pyridazin-4-yl]amino]-1-piperidyl]methanone	+++
20	[4-fluoro-2-(trifluoromethyl)phenyl]-[4-[methyl-[1-(2-methylpyrazol-3-yl)pyrido[3,4-d]pyridazin-4-yl]amino]-1-piperidyl]methanone	++
21	[4-[[4,5-dimethyl-6-(2-methylpyrazol-3-yl)pyridazin-3-yl]-methyl-amino]-1-piperidyl]-[5-(trifluoromethyl)pyridazin-4-yl]methanone	++
22	[4-[methyl-[4-(2-methylpyrazol-3-yl)phthalazin-1-yl]amino]-1-piperidyl]-[2-methyl-5-(trifluoromethyl)oxazol-4-yl]methanone	+
23	N-(1-cyclopentylsulfonyl-4-piperidyl)-N-methyl-4-(2-methylpyrazol-3-yl)phthalazin-1-amine	+++
24	N-(1-isopropylsulfonyl-4-piperidyl)-N-methyl-4-(2-methylpyrazol-3-yl)phthalazin-1-amine	++
25	5-fluoro-2-[[4-[methyl-[4-(2-methylpyrazol-3-yl)phthalazin-1-yl]amino]-1-piperidyl]methyl]benzonitrile	++

26	N-[1-(2,4-difluorophenyl)sulfonyl-4-piperidyl]-N-methyl-4-(2-methylpyrazol-3-yl)phthalazin-1-amine	++
27	N-[1-[[4-fluoro-2-(trifluoromethyl)phenyl]methyl]-4-piperidyl]-N,4,5-trimethyl-6-(2-methylpyrazol-3-yl)pyridazin-3-amine	+
28	N-[1-[4-fluoro-2-(trifluoromethyl)phenyl]sulfonyl-4-piperidyl]-4,5-dimethyl-6-(2-methylpyrazol-3-yl)pyridazin-3-amine	+++
29	N-tert-butyl-4-[[4,5-dimethyl-6-(2-methylpyrazol-3-yl)pyridazin-3-yl]amino]piperidine-1-carboxamide	+
30	[4-[[4,5-dimethyl-6-(2-methylpyrazol-3-yl)pyridazin-3-yl]amino]-1-piperidyl]-[4-fluoro-2-(trifluoromethyl)phenyl]methanone	+
31	N-[1-[[4-fluoro-2-(trifluoromethyl)phenyl]methyl]-4-piperidyl]-4,5-dimethyl-6-(2-methylpyrazol-3-yl)pyridazin-3-amine	++
32	[4-fluoro-2-(trifluoromethyl)phenyl]-[4-[[4-(2-methylpyrazol-3-yl)phthalazin-1-yl]amino]-1-piperidyl]methanone	+
33	N-[1-[[4-fluoro-2-(trifluoromethyl)phenyl]methyl]-4-piperidyl]-4-(2-methylpyrazol-3-yl)phthalazin-1-amine	+
34	3-[[4-[[4,5-dimethyl-6-(2-methylpyrazol-3-yl)pyridazin-3-yl]amino]-1-piperidyl]methyl]benzonitrile	-

[00211] Examples of compounds of the invention with values for their IC50 are given in the table below.

ID No.	Compound	Gli Luc nM
5	N-[1-[4-fluoro-2-(trifluoromethyl)phenyl]sulfonyl-4-piperidyl]-N-methyl-4-(2-methylpyrazol-3-yl)phthalazin-1-amine	0.71
6	[4-fluoro-2-(trifluoromethyl)phenyl]-[4-[methyl-[4-(2-methylpyrazol-3-yl)phthalazin-1-yl]amino]-1-piperidyl]methanone	4.87
13	N-[1-[4-fluoro-2-(trifluoromethyl)phenyl]sulfonyl-4-piperidyl]-N-methyl-1-(2-methylpyrazol-3-yl)pyrido[3,4-d]pyridazin-4-amine	0.35
19	[4-fluoro-2-(trifluoromethyl)phenyl]-[4-[methyl-[1-(2-methylpyrazol-3-yl)-6,7-dihydro-5H-cyclopenta[d]pyridazin-4-yl]amino]-1-piperidyl]methanone	5.92
28	N-[1-[4-fluoro-2-(trifluoromethyl)phenyl]sulfonyl-4-piperidyl]-4,5-dimethyl-6-(2-methylpyrazol-3-yl)pyridazin-3-amine	0.45

[00212] 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

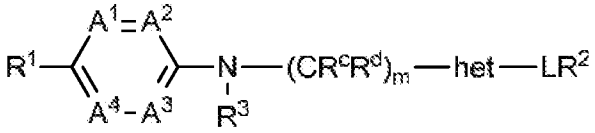
description and claims of this specification, the singular encompasses the plural unless the context otherwise requires. In particular, where the indefinite article is used, the specification is to be understood as contemplating plurality as well as singularity, unless the context requires otherwise.

[00213] 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.

[00214] 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)

"het" is selected from substituted or unsubstituted: pyrolidinylene, piperidinylene and azepanylene;

or "het" represents a substituted or unsubstituted heteroalkylene chain in which the heteroatom present in a C_{1-6} alkylene chain is nitrogen and wherein the nitrogen atom is substituted by hydrogen or C_{1-4} alkyl;

at least one of A^1, A^2, A^3 and A^4 is N and the remaining A^1, A^2, A^3 and A^4 are each independently selected from CR^4 or N;

wherein R^4 is selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, $-OR^a$, $-CR^cR^dOR^a$, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, $-NR^aR^b$, -CN, $-C(O)R^a$, $-C(O)OR^a$ and $-C(O)NR^aR^b$, and two adjacent R^4 groups may form a ring with the carbon atom to which they are attached forming a fused bicyclic ring system of 8 to 12 atoms, wherein the ring formed by the two R^4 groups is a saturated or unsaturated carbocyclic ring with 4, 5, 6, 7, or 8 carbon atoms or a saturated or unsaturated heterocyclic ring with 4, 5, 6, 7, or 8 atoms containing 1, 2 or 3 heteroatoms;

L is selected from either a substituted or unsubstituted C_{1-3} alkylene chain which is saturated or unsaturated and which may also optionally contain, where chemically possible, 1 N, O, or S atoms in the chain which are independently chosen at each occurrence;

or L is selected from a bond, $-C(O)-$, $-C(NR^a)-$, $-C(O)O-$, $-C(O)NR^a-$, $-C(NR^a)NR^a-$, and $-SO_2-$;

R^1 is selected from substituted or unsubstituted: heterocycloalkyl, -O-heterocycloalkyl, $-NR^a$-heterocycloalkyl, $-CR^cR^d$-heterocycloalkyl, heterocycloalkenyl, -O-heterocycloalkenyl, $-NR^a$-heterocycloalkenyl, $-CR^cR^d$-heterocycloalkenyl, aryl, -O-aryl, $-NR^a$-aryl, $-CR^cR^d$-aryl, heteroaryl, -O-heteroaryl, $-NR^a$-heteroaryl, and $-CR^cR^d$-heteroaryl;

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

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

R^3 is selected from H, substituted or unsubstituted C_{1-4} alkyl, C_{1-4} haloalkyl, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted C_{3-8} cycloalkenyl, substituted or unsubstituted aryl, and substituted or unsubstituted heterocyclic;

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;

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;

m is 0, 1 or 2; and

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

2. The compound of claim 1, wherein R^3 is selected from substituted or unsubstituted C_{1-14} alkyl, C_{1-14} haloalkyl, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted C_{3-8} cycloalkenyl, substituted or unsubstituted aryl, and substituted or unsubstituted heterocyclic.

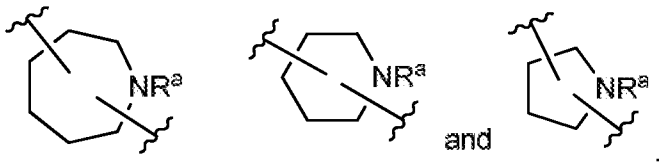
3. The compound of claim 1 or claim 2, provided that when:

two adjacent R^4 groups form a ring with the carbon atom to which they are attached and the ring formed by the two R^4 groups and those carbon atoms is a benzene ring; and

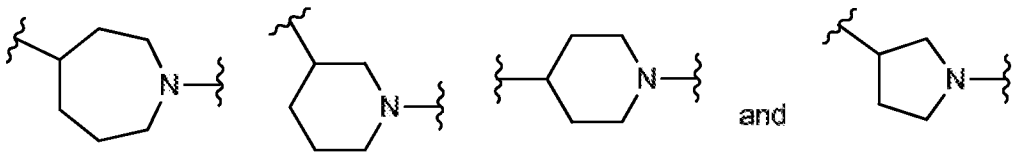
L is C_{1-3} alkylene chain which is saturated or unsaturated;

then R^1 is selected from substituted or unsubstituted: aryl or heteroaryl, optionally wherein R^1 is selected from substituted or unsubstituted: pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, oxadiazolyl, isoxazolyl, triazolyl, tetrazolyl, thiazolyl, isothiazolyl, furanyl, pyridinyl, pyridazinyl, pyrazinyl and pyrimidinyl; preferably substituted or unsubstituted pyrazolyl.

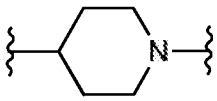
4. The compound of any preceding claim, wherein “het” is represented by groups selected from substituted or unsubstituted:



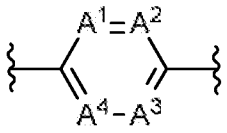
5. The compound of any preceding claim, wherein "het" is selected from substituted or unsubstituted:



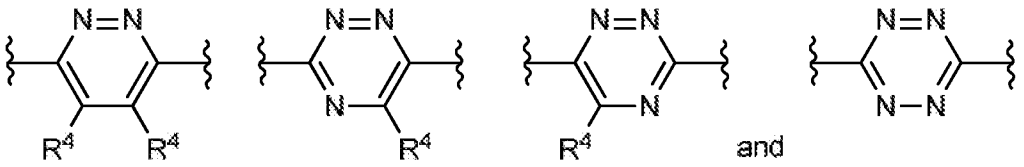
6. The compound of claim 5, wherein "het" is substituted or unsubstituted:

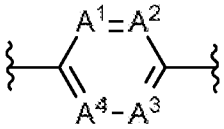


7. The compound of any preceding claim, wherein one of A^1, A^2, A^3 and A^4 is N and the remaining A^1, A^2, A^3 and A^4 are each independently selected from N or CR^4.

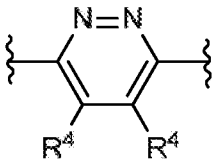
8. The compound of any preceding claim, wherein 

is selected from:

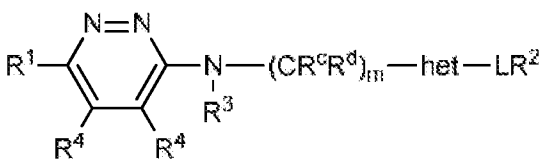


9. The compound of claim 8, wherein 

is:



10. The compound of any preceding claim, wherein the compound of formula (**I**) is a compound according to formula (**III**):



(**III**)

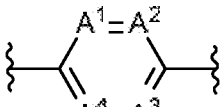
11. The compound of any preceding claim, wherein R^4 is selected from: C_{1-6} alkyl, C_{1-6} haloalkyl, $-CR^cR^dOR^a$, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, $-NR^aR^b$, -CN, $-C(O)R^a$, $-C(O)OR^a$ and $-C(O)NR^aR^b$, and two adjacent R^4 groups may form a ring with the atom to which the R^4 groups are attached forming a fused bicyclic ring system of 8 to 12 atoms, wherein the ring formed by the two R^4 groups is a saturated or unsaturated carbocyclic ring with 4, 5, 6, 7 or 8 carbon atoms or a saturated or unsaturated heterocyclic ring with 4, 5, 6, 7 or 8 atoms containing 1, 2 or 3 heteroatoms.

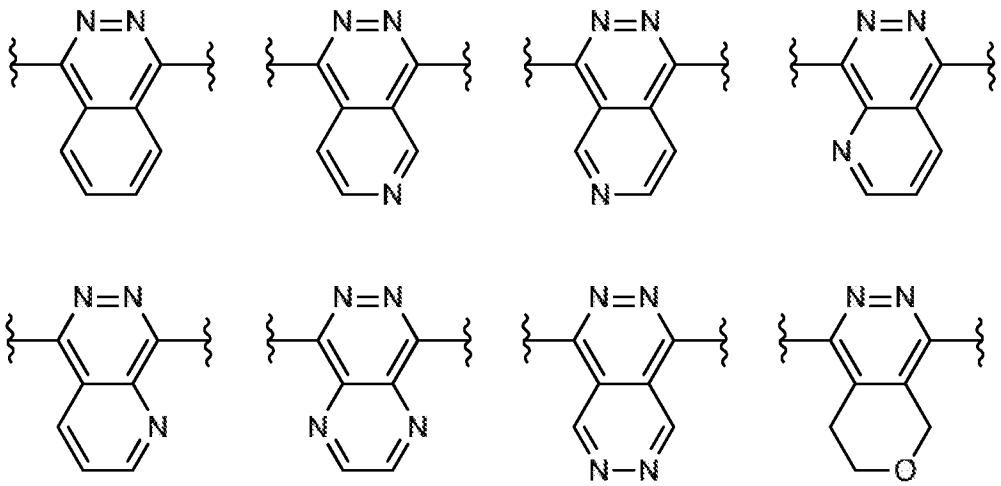
12. The compound of claim 11, wherein the two adjacent R^4 groups are both C_{1-6} alkyl or both form a ring with the atom to which the R^4 groups are attached forming a fused bicyclic ring system of 8 to 12 atoms, wherein the ring formed by the two R^4 groups is a saturated or unsaturated carbocyclic ring with 4, 5, 6, 7 or 8 carbon atoms or a saturated or unsaturated heterocyclic ring with 4, 5, 6, 7 or 8 atoms or a saturated or unsaturated heterocyclic ring with 4, 5, 6, 7 or 8 atoms containing 1, 2 or 3 heteroatoms.

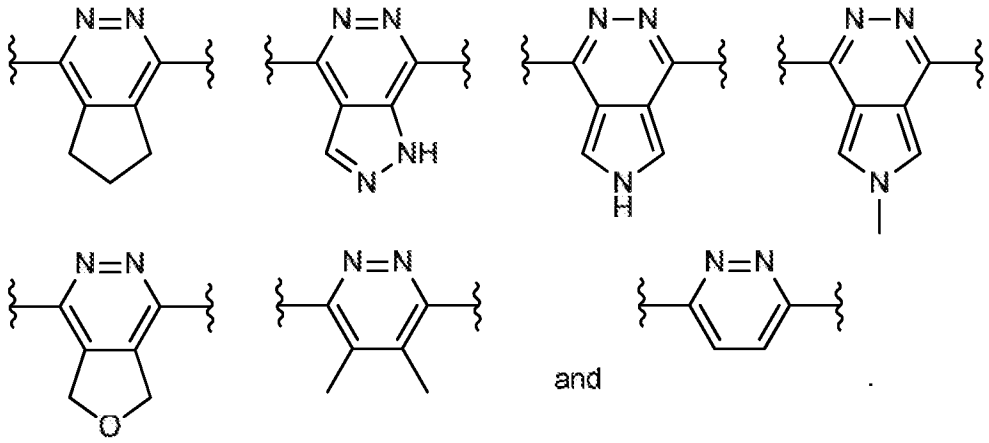
13. The compound of claim 10, wherein R^4 is selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, $-OR^a$, $-CR^cR^dOR^a$, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, $-NR^aR^b$, -CN, $-C(O)R^a$, $-C(O)OR^a$ and $-C(O)NR^aR^b$, and two adjacent R^4 groups may form a ring with the carbon atoms to which they are attached the ring being a saturated or unsaturated carbocyclic ring with 4, 5, 6, 7, or 8 carbon atoms or a saturated or unsaturated heterocyclic ring with 4, 5, 6, 7, or 8 atoms containing 1, 2 or 3 heteroatoms;

R^1 is selected from substituted or unsubstituted: aryl or heteroaryl, preferably substituted or unsubstituted heteroaryl (and optionally R^1 is selected from substituted or unsubstituted: pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, oxadiazolyl, isoxazolyl, triazolyl, tetrazolyl, thiazolyl, isothiazolyl, furanyl, pyridinyl, pyridazinyl, pyrazinyl and pyrimidinyl; preferably substituted or unsubstituted pyrazolyl); and

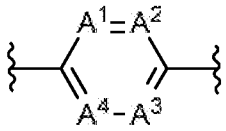
m is 0 or 1.

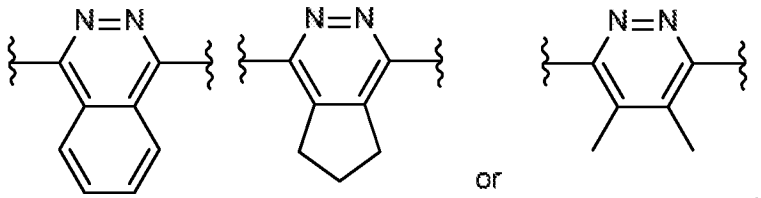
14. The compound of claim 9, wherein  is selected from:





and .

15. The compound of claim 14, wherein  is



or .

16. The compound of any preceding claim, wherein L is selected from a bond, $-CR^cR^d-$, $-CR^cR^dCR^cR^d-$, $-C(O)-$, $-C(O)NR^a-$ and $-SO_2-$.

17. The compound of claim 16, wherein L is selected from a bond, $-CH_2-$, $-CH_2CH_2-$, $-CH(CH_3)-$, $-C(NH)-$, $-C(O)NH-$, $-C(O)N(CH_3)-$ and $-SO_2-$.

18. The compound of any of claims 1 to 12 and 14 to 17, wherein R^1 is selected from unsubstituted heterocycloalkyl, unsubstituted heterocycloalkenyl and substituted or unsubstituted: -O-heterocycloalkyl, $-NR^a$-heterocycloalkyl, $-CR^cR^d$-heterocycloalkyl, -O-heterocycloalkenyl, $-NR^a$-heterocycloalkenyl, $-CR^cR^d$-heterocycloalkenyl, aryl, -O-aryl, $-NR^a$-aryl, $-CR^cR^d$-aryl, heteroaryl, -O-heteroaryl, $-NR^a$-heteroaryl, and $-CR^cR^d$-heteroaryl.

19. The compound of any preceding claim wherein R^1 is not heterocycloalkyl or heterocycloalkenyl.

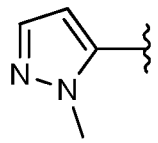
20. The compound of any of claims 1 to 12 and 14 to 19, wherein R^1 is selected from substituted or unsubstituted: C_{6-14} aryl, -O-C_{6-14} aryl, $-NR^a$-C_{6-14} aryl, $-CR^cR^d$-C_{6-14} aryl, C_{5-14} heteroaryl, -O-C_{5-14} heteroaryl, $-NR^a$-C_{5-14} heteroaryl, and $-CR^cR^d$-C_{5-14} heteroaryl.

21. The compound of any of claims 1 to 12 and 14 to 19, wherein R^1 is selected from substituted or unsubstituted: heteroaryl, -O-heteroaryl, $-NR^a$-heteroaryl, and $-CR^cR^d$-heteroaryl.

22. The compound of claim 21, wherein heteroaryl is selected from: pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, oxadiazolyl, isoxazolyl, triazolyl, tetrazolyl, thiazolyl, isothiazolyl, furanyl, pyridinyl, pyridazinyl, pyrazinyl and pyrimidinyl.

23. The compound of any of claims 1 to 12 and 14 to 21, wherein R^1 is selected from substituted or unsubstituted: pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, oxadiazolyl, isoxazolyl, triazolyl, tetrazolyl, thiazolyl, isothiazolyl, furanyl, pyridinyl, pyridazinyl, pyrazinyl and pyrimidinyl.

24. The compound of any preceding claim wherein R^1 is:



25. The compound of any preceding claim, wherein R^2 is represented by $-CR^5R^6R^7$, wherein R^5, R^6 and R^7 are independently selected at each occurrence from H and substituted or unsubstituted: C_{1-14} alkyl, C_{1-14} haloalkyl, cycloalkyl, aryl, heterocycloalkyl and heteroaryl

or R^2 is selected from substituted or unsubstituted: C_{1-14} alkyl, C_{1-14} haloalkyl, cycloalkyl, aryl, heterocycloalkyl and heteroaryl.

26. The compound of any preceding claim, wherein R^2 is represented by $-CR^5R^6R^7$, wherein R^5, R^6 and R^7 are independently selected at each occurrence from H and substituted or unsubstituted: C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-8} cycloalkyl, C_{6-10} aryl, C_{3-8} heterocycloalkyl and C_{5-10} heteroaryl

or R^2 is selected from substituted or unsubstituted: C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-8} cycloalkyl, C_{6-10} aryl, C_{3-8} heterocycloalkyl and C_{5-10} heteroaryl.

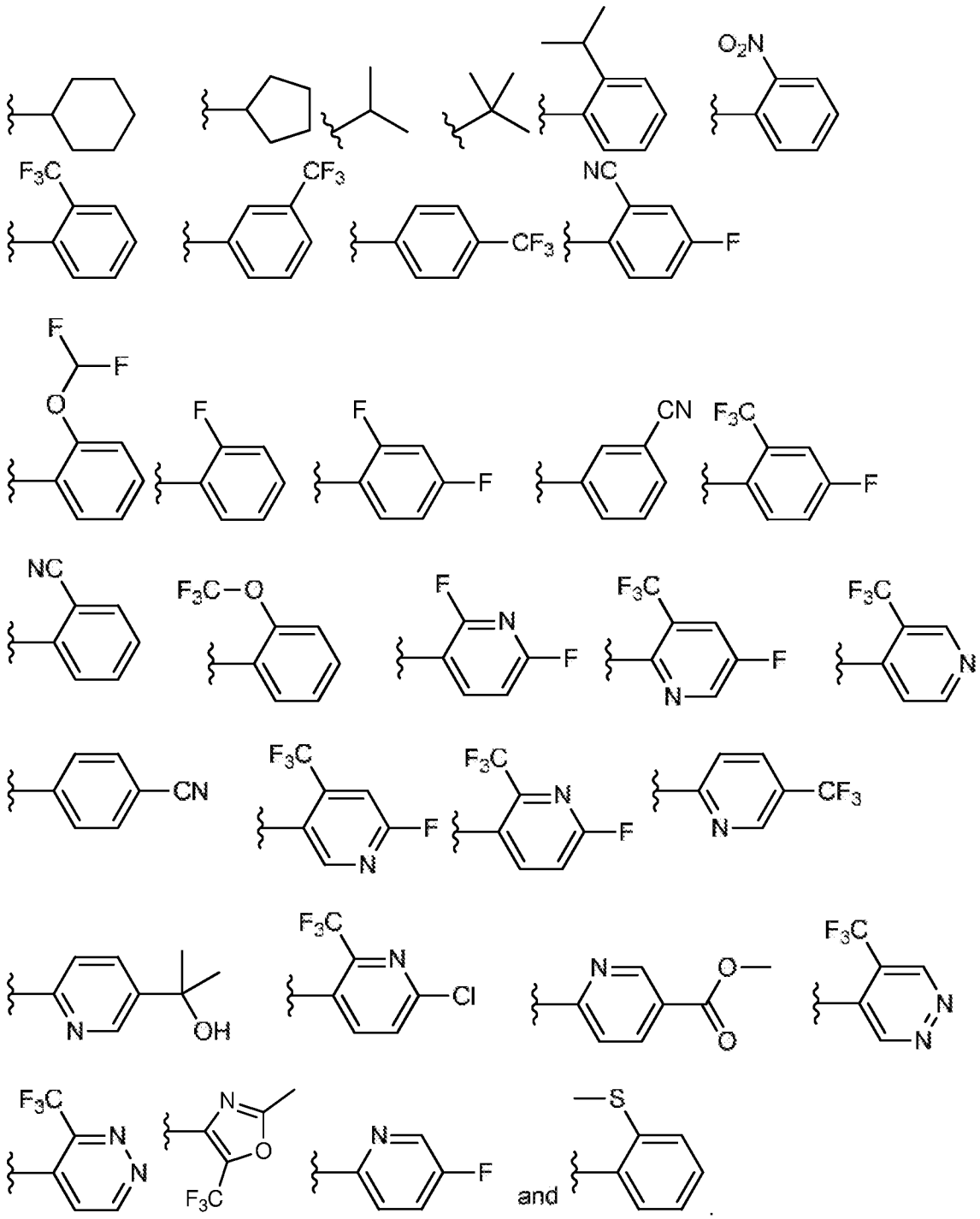
27. The compound of any preceding claim, wherein R^5, R^6 and R^7 are independently selected at each occurrence from H and substituted or unsubstituted: methyl, ethyl, propyl, butyl, pentyl, hexyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, oxirane, aziridine, azetidine, oxetane, tetrahydrofuran, pyrrolidine, imidazolidine, succinimide, pyrazolidine, oxazolidine, isoxazolidine, thiazolidine, isothiazolidine, piperidine, morpholine, thiomorpholine, piperazine, tetrahydropyran, phenyl, toluenyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyrrolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, and isothiazolyl.

28. The compound of claim 27, wherein R^5, R^6 and R^7 are all one of the groups selected from: methyl, trifluoromethyl, cyclohexanyl and phenyl

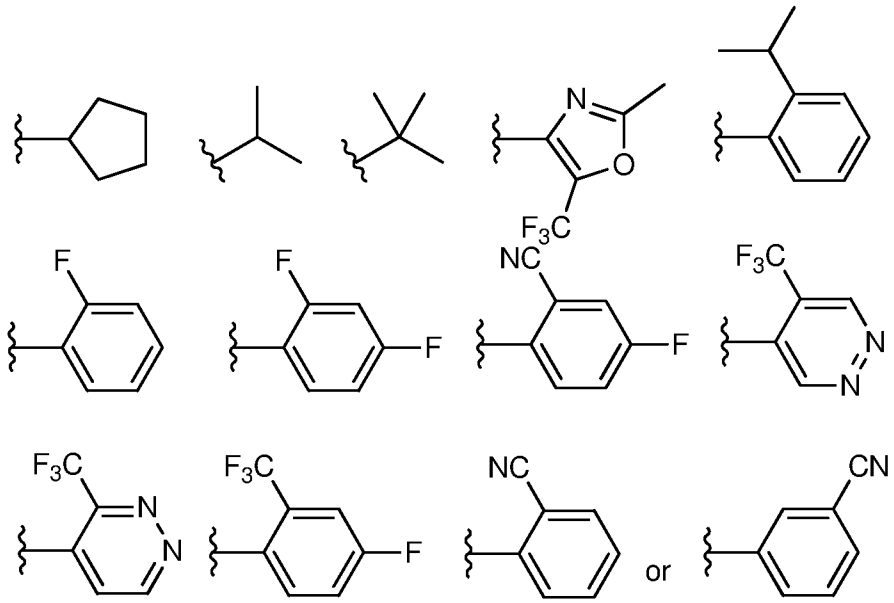
29. The compound of any of claims 1 to 25 wherein R^2 is selected from substituted or unsubstituted: methyl, ethyl, propyl, butyl, pentyl, hexyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, oxirane, aziridine, azetidine, oxetane, tetrahydrofuran, pyrrolidine, imidazolidine, succinimide, pyrazolidine, oxazolidine, isoxazolidine, thiazolidine, isothiazolidine, piperidine, morpholine, thiomorpholine, piperazine, tetrahydropyran, phenyl, toluenyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyrrolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, and isothiazolyl.

30. The compound of claim 29, wherein R^2 is substituted or unsubstituted: phenyl, toluenyl, pyridinyl, pyridazinyl, oxazolyl, *tert*-butyl, isopropyl, and cyclopentyl.

31. The compound of claim 30, wherein R^2 is represented by:



32. The compound of claim 31 wherein, R^2 is



33. The compound of any preceding claim, wherein R^3 is H, substituted or unsubstituted C_{1-4} alkyl or substituted or unsubstituted C_{1-4} haloalkyl.

34. The compound of claim 33, wherein R^3 is methyl, ethyl or $-C(O)CF_3$.

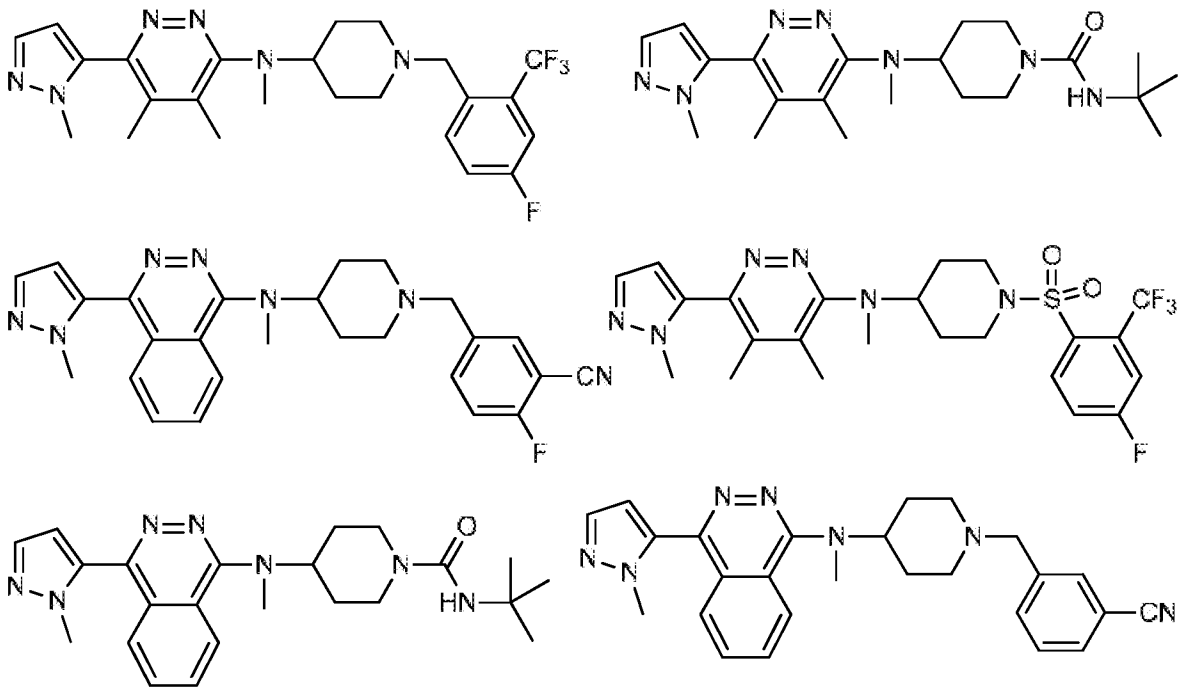
35. The compound of any preceding claim, wherein R^a and R^b are hydrogen.

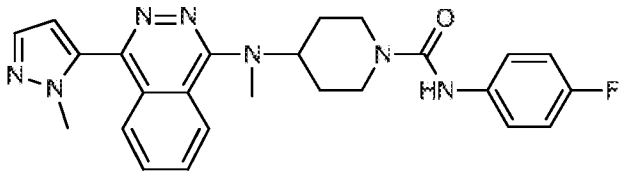
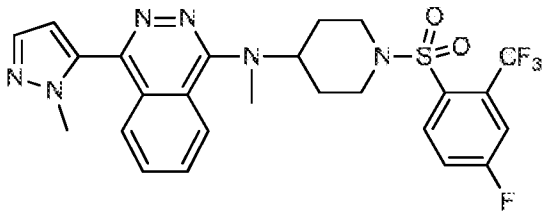
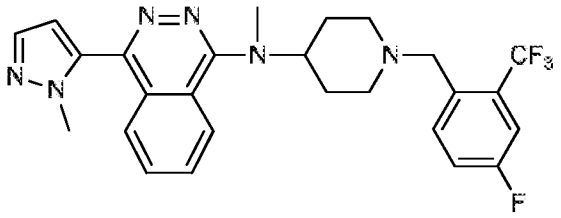
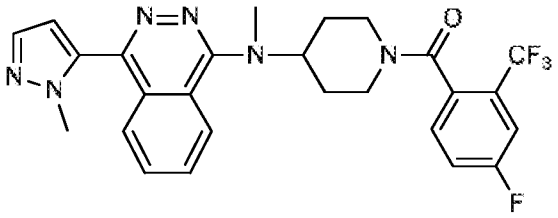
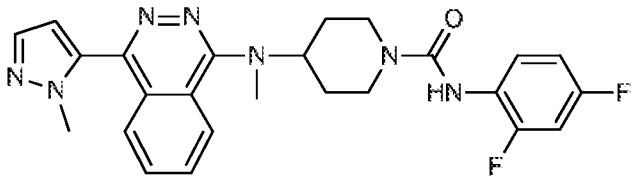
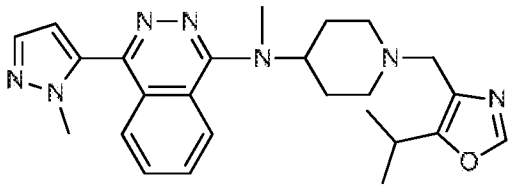
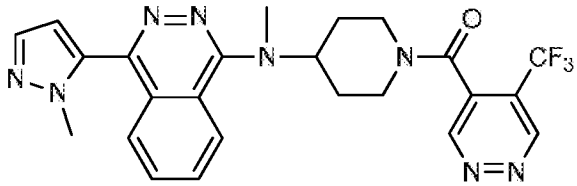
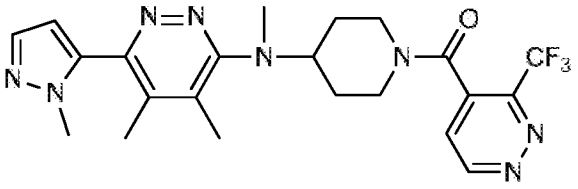
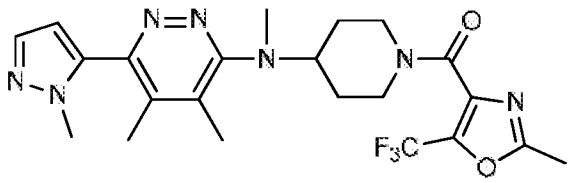
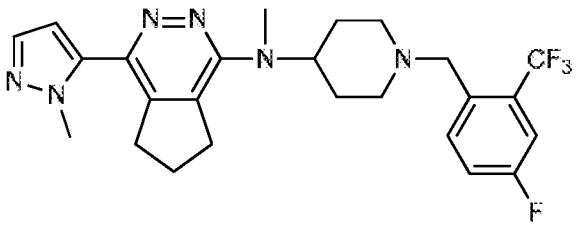
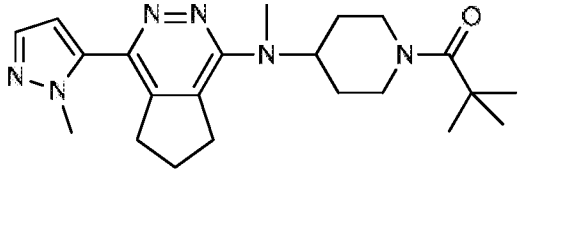
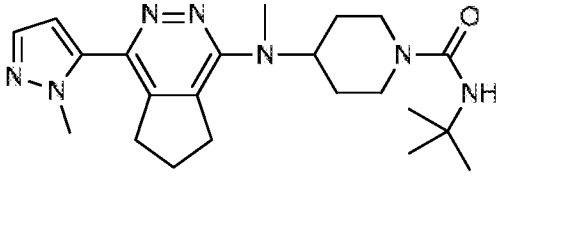
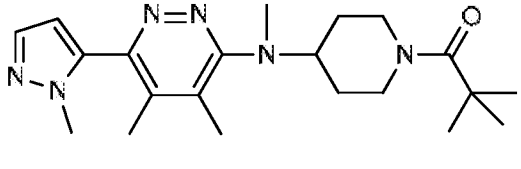
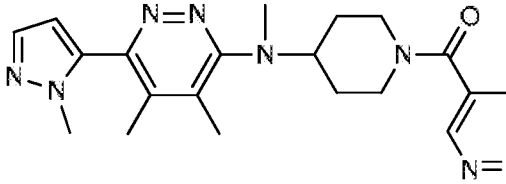
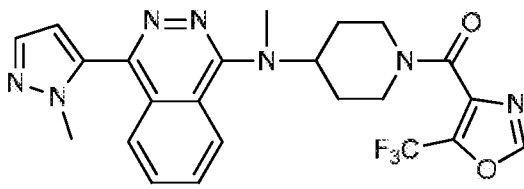
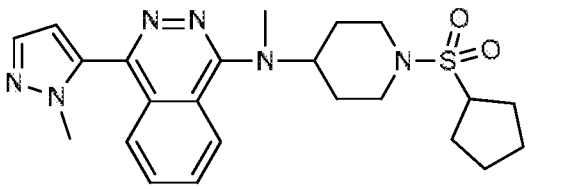
36. The compound of any preceding claim, wherein R^c and R^d are hydrogen.

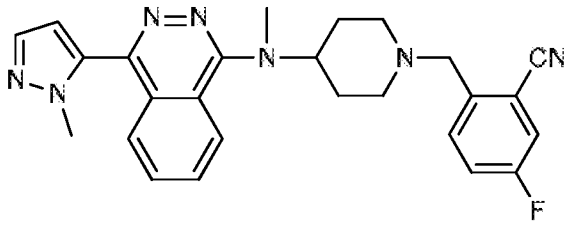
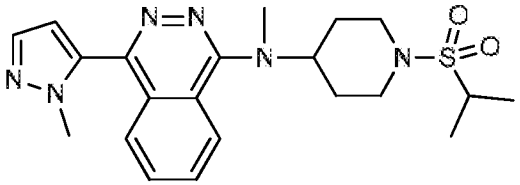
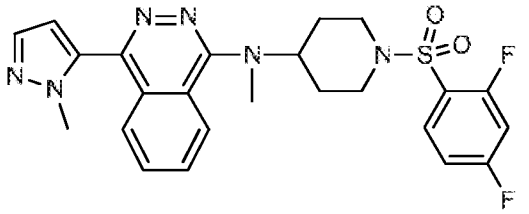
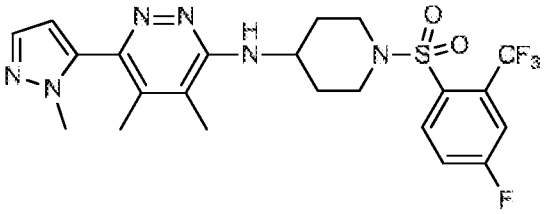
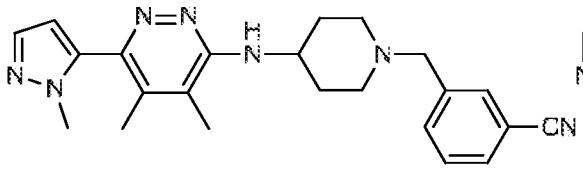
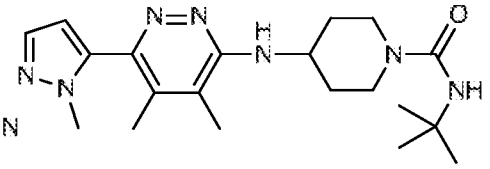
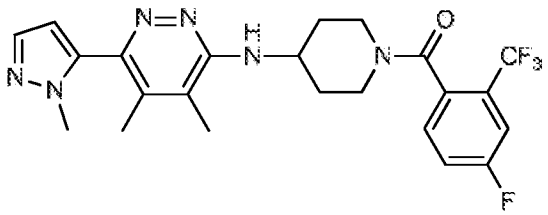
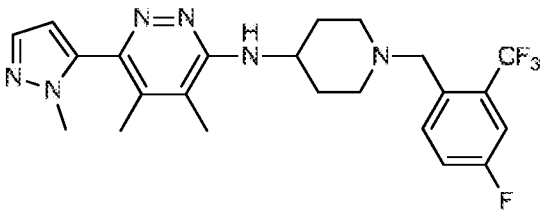
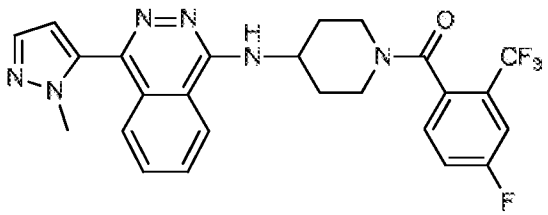
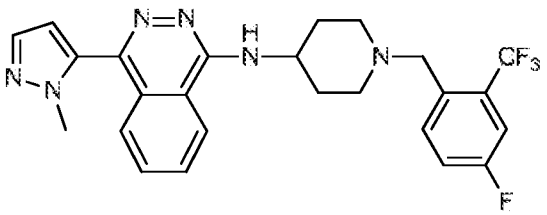
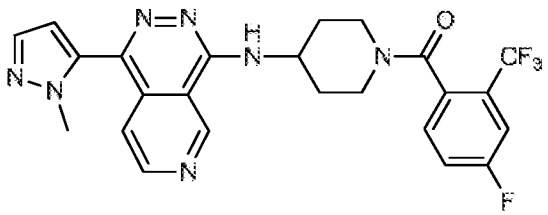
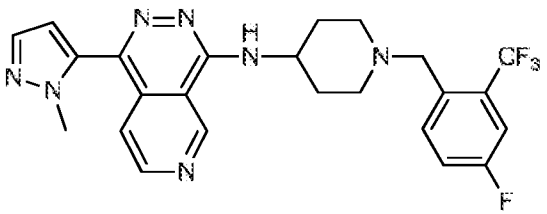
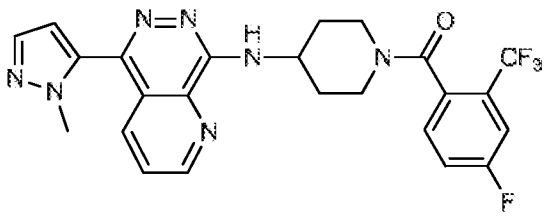
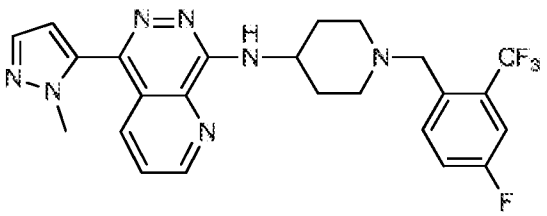
37. The compound of any preceding claim, wherein m is 0 or 1.

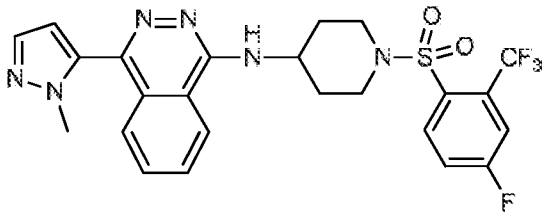
38. The compound of claim 33 wherein m is 0.

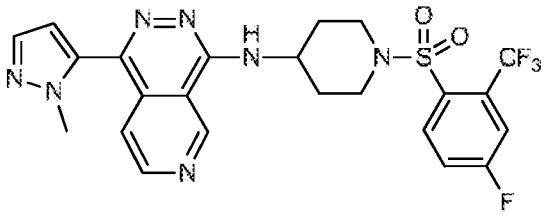
39. The compound of claim 1, wherein the compound of formula (**I**) is selected from:

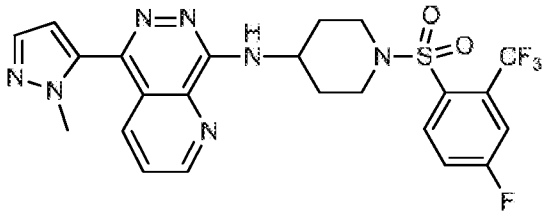








40. A compound of any preceding claim for use as a medicament.

41. A compound of any of claims 1 to 39 for use in a method of treatment of a condition which is modulated by the Hedgehog signalling pathway.

42. A compound of claim 41, wherein the condition which is modulated by the Hedgehog signalling pathway is cancer, sarcoma, carcinoma, blastoma, lymphoma and leukemia.

43. A compound of claim 41 or claim 42, 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.

44. A compound of any of claims 1 to 39 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.

45. A compound of any of claims 1 to 39 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.

46. A compound of claim 45 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.

47. A pharmaceutical composition, wherein the composition comprises a compound of any of claims 1 to 39 and pharmaceutically acceptable excipients.

48. A pharmaceutical composition of claim 47 wherein the composition is a combination product and comprises an additional pharmaceutically active agent.

49. 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 39, to a patient in need thereof.

50. A method of treatment of claim 49 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.

51. A method of treatment of claim 49 or claim 50 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.

52. 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 39, to a patient in need thereof.

53. 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 39, or a pharmaceutically acceptable salt thereof simultaneously, sequentially or separately with an additional anti-tumour agent to a patient in need thereof.

54. A method of providing a combination product, wherein the method comprises providing a compound of any of claims 1 to 39 simultaneously, sequentially or separately with an anti-tumour agent.

55. Use of a compound of any of claims 1 to 39 in combination with an anti-tumour agent.

56. Use of a compound of any of claims 1 to 39 in the manufacture of a medicament for use in the treatment of a condition modulated by the Hedgehog pathway.

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2014/052029

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D403/14 C07D471/04 A61K31/502 A61K31/5025 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 A61K A61P

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 98/58929 A1 (JANSSEN PHARMACEUTICA NV [BE]; STOKBROEKX RAYMOND ANTOINE [BE]; CEUSTE) 30 December 1998 (1998-12-30) Abstract; claims; page 10, lines 9-17; examples e.g. page 18, table F.1. ----- -/--	1,2, 7-10,14, 16-19, 21,25, 26, 29-31, 34,37, 38,40-56

[X] Further documents are listed in the continuation of Box C.

[X] 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

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"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
1 August 2014	20/08/2014

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	Weisbrod, Thomas

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Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2008/145681 A2 (BOEHRINGER INGELHEIM INT [DE]; EBEL HEINER [DE]; PETERS STEFAN [DE]; H) 4 December 2008 (2008-12-04) Abstract; claims; page 50, paragraph 2; page 41, example 43, page 43, example 65, page 46, examples 83, 84.	1,5-10, 14, 16-20, 25-27, 29,31, 33,37, 38,40-56
X	WO 2007/127475 A2 (UNIV NORTHWESTERN [US]; WATTERSON MARTIN [US]; VAN ELDIK LINDA [US]; H) 8 November 2007 (2007-11-08) Abstract; claims; table 1: page 94, compound 91, page 96, compound 122, page 97, compounds 123 and 125, page 98, compound 149, page 100, compound 189, page 102, compounds 199 and 205.	1,5-10, 14, 16-20, 25-27, 29,30, 33, 36-38,40
X	WO 2007/130383 A2 (NEUROMEDIX INC [CA]; WATTERSON MARTIN [US]; VAN ELDIK LINDA [US]; HU W) 15 November 2007 (2007-11-15) Abstract; claims; examples e.g. page 115: compound 91, page 117: compound 122, page 118: compounds 123 and 125, page 119: compound 149, page 121: compound 189, page 123: compounds 199 and 205.	1,5-10, 14, 16-20, 25-27, 29,30, 33, 36-38,40
X	WO 2007/003604 A2 (NOVO NORDISK AS [DK]; HOHLWEG ROLF [DK]; ANDERSEN KNUD ERIK [DK]; SOER) 11 January 2007 (2007-01-11) Abstract; claims; page 41, lines 6-10; pages 81-82: examples 31, 32; page 82: example 35.	1,5-10, 14, 16-20, 25-27, 29,33, 37,38, 40-56

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CONTRERAS ET AL.: "Aminopyridazines as acetylcholinesterase inhibitors", J. MED. CHEM., vol. 42, no. 4, 25 February 1999 (1999-02-25), pages 730-741, XP002353008, ISSN: 0022-2623, DOI: 10.1021/JM981101Z Title; abstract; page 736, table 4: compounds 3s to 3y.	1,5-10, 14, 16-20, 25-27, 29,30, 33,37, 38,40
X	CONTRERAS ET AL.: "Design, synthesis, and structure-activity relationships of a series of 3-[2-(1-benzylpiperidin-4-yl)ethylamino]py ridazine derivatives as acetylcholinesterase inhibitors", J. MED. CHEM., vol. 44, no. 17, 16 August 2001 (2001-08-16), pages 2707-2718, XP002353010, ISSN: 0022-2623, DOI: 10.1021/JM001088U Title; abstract; compounds of tables 1, 3, and 4.	1,3, 5-12, 14-20, 25-27, 29,30, 33,36,40
X	US 2008/064697 A1 (CHRIST ANDREAS D [CH] ET AL) 13 March 2008 (2008-03-13) Abstract; claims; paragraph [0390]; examples e.g. pages 36-37: examples 24-27, 29-32, 34, 35, 37-39.	1,5-7, 16-18, 25-27, 29,30, 33,37, 38,40
X	EP 1 988 077 A1 (SHIONOGI & CO [JP]) 5 November 2008 (2008-11-05) Abstract; page 1, paragraph [0001]; claims; page 90, example I-60.	1,5-7, 16-23, 25,26, 29-31, 33,37, 38,40
X	DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 14 September 2011 (2011-09-14), XP002728063, CAS Registry Numbers: 1332219-62-1, 1332151-10-6.	1,5, 8-10,14, 16-19, 21-23, 25-27, 29,30, 33,37,38

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 4 November 2011 (2011-11-04), XP002728064, CAS Registry Numbers: 1340956-75-3, 1340906-37-7, 1340819-10-4, 1340771-98-3. -----	1,3, 5-10, 14-19, 21-23, 25-27, 29,30, 33,37,38
X	FR 2 868 780 A1 (SANOFI SYNTHELABO [FR]) 14 October 2005 (2005-10-14) Page 18, lines 20-22; claims 1; page 17, compound no. 16. -----	1,3, 5-10, 14-19, 21, 25-27, 29,30, 33,37, 38,40
A	WO 97/26258 A1 (JANSSEN PHARMACEUTICA NV [BE]; STOKBROEKX RAYMOND ANTOINE [BE]; AA MAR) 24 July 1997 (1997-07-24) Abstract; claims; examples. -----	1-3,5-56
A	WO 2010/147917 A1 (LILLY CO ELI [US]; HIPSKIND PHILIP ARTHUR [US]; PATEL BHARVIN KUMAR [U) 23 December 2010 (2010-12-23) cited in the application Abstract; claims; examples. -----	1-3,5-56

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2014/052029

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9858929 A1	30-12-1998	AR 013124 A1	13-12-2000
		AT 235489 T	15-04-2003
		AU 732129 B2	12-04-2001
		AU 8853798 A	04-01-1999
		BR 9810321 A	05-09-2000
		CA 2294551 A1	30-12-1998
		CN 1261364 A	26-07-2000
		CZ 9904508 A3	16-08-2000
		DE 69812623 D1	30-04-2003
		DE 69812623 T2	19-02-2004
		DK 0991649 T3	21-07-2003
		EE 9900591 A	15-08-2000
		ES 2195374 T3	01-12-2003
		HU 0004457 A2	28-02-2002
		ID 23443 A	20-04-2000
		IL 133652 A	10-04-2003
		NO 996391 A	22-12-1999
		NZ 501649 A	26-10-2001
		PL 337657 A1	28-08-2000
		PT 991649 E	29-08-2003
		SK 176999 A3	12-09-2000
		TR 9902955 T2	21-06-2000
		TW 455588 B	21-09-2001
		US 6265407 B1	24-07-2001
		US 2001046999 A1	29-11-2001
		WO 9858929 A1	30-12-1998
WO 2008145681 A2	04-12-2008	AR 066799 A1	16-09-2009
		CA 2687931 A1	04-12-2008
		EP 2155689 A2	24-02-2010
		JP 2010528089 A	19-08-2010
		TW 200904434 A	01-02-2009
		US 2010204209 A1	12-08-2010
		WO 2008145681 A2	04-12-2008
WO 2007127475 A2	08-11-2007	NONE	
WO 2007130383 A2	15-11-2007	NONE	
WO 2007003604 A2	11-01-2007	AT 536344 T	15-12-2011
		AU 2006264966 A1	11-01-2007
		BR PI0613564 A2	18-01-2011
		CA 2614116 A1	11-01-2007
		CN 103110635 A	22-05-2013
		EP 1902028 A2	26-03-2008
		EP 2233470 A1	29-09-2010
		EP 2386554 A1	16-11-2011
		ES 2375929 T3	07-03-2012
		JP 5121707 B2	16-01-2013
		JP 2009500372 A	08-01-2009
		KR 20080032069 A	14-04-2008
		RU 2011142654 A	27-04-2013
		US 2009312309 A1	17-12-2009
		US 2012232078 A1	13-09-2012
		WO 2007003604 A2	11-01-2007
US 2008064697 A1	13-03-2008	AU 2007296692 A1	20-03-2008
		BR PI0716428 A2	11-03-2014

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		CA 2662099 A1	20-03-2008
		CN 101511817 A	19-08-2009
		EP 2066658 A1	10-06-2009
		JP 4948604 B2	06-06-2012
		JP 2010502758 A	28-01-2010
		KR 20090052390 A	25-05-2009
		US 2008064697 A1	13-03-2008
		WO 2008031735 A1	20-03-2008
EP 1988077 A1	05-11-2008	EP 1988077 A1	05-11-2008
		EP 2520567 A2	07-11-2012
		TW 200800182 A	01-01-2008
		US 2009062261 A1	05-03-2009
		US 2011172415 A1	14-07-2011
		WO 2007099828 A1	07-09-2007
FR 2868780 A1	14-10-2005	AR 049543 A1	16-08-2006
		AT 372998 T	15-09-2007
		AU 2005235766 A1	03-11-2005
		BR PI0509910 A	18-09-2007
		CA 2562100 A1	03-11-2005
		CN 1953972 A	25-04-2007
		DE 602005002470 T2	12-06-2008
		DO P2005000062 A	15-10-2006
		EP 1737840 A1	03-01-2007
		FR 2868780 A1	14-10-2005
		GT 200500089 A	31-10-2005
		JP 4918477 B2	18-04-2012
		JP 2007532611 A	15-11-2007
		KR 20070007361 A	15-01-2007
		MA 28575 B1	02-05-2007
		PE 03362006 A1	15-05-2006
		SV 2005002083 A	01-12-2005
		US 2007099895 A1	03-05-2007
		UY 28855 A1	30-11-2005
		WO 2005103033 A1	03-11-2005
WO 9726258 A1	24-07-1997	AT 203534 T	15-08-2001
		AU 717744 B2	30-03-2000
		AU 1443997 A	11-08-1997
		CA 2237273 A1	24-07-1997
		CN 1208415 A	17-02-1999
		DE 69705819 D1	30-08-2001
		DE 69705819 T2	11-04-2002
		DK 0876366 T3	05-11-2001
		EP 0876366 A2	11-11-1998
		ES 2162235 T3	16-12-2001
		GR 3036900 T3	31-01-2002
		IL 124461 A	26-07-2000
		JP 4169368 B2	22-10-2008
		JP 2000503014 A	14-03-2000
		KR 100443893 B1	15-10-2004
		MY 117098 A	31-05-2004
		NO 982037 A	15-09-1998
		NZ 326354 A	28-05-1999
		PT 876366 E	30-01-2002
		SI 876366 T1	31-12-2001
		TW 480256 B	21-03-2002

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2014/052029

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		US 5985878 A	16-11-1999
		WO 9726258 A1	24-07-1997
		ZA 9700288 A	14-07-1998
WO 2010147917 A1	23-12-2010	AR 077014 A1	27-07-2011
		AU 2010260244 A1	19-01-2012
		CA 2764542 A1	23-12-2010
		CN 102459233 A	16-05-2012
		CO 6480932 A2	16-07-2012
		CR 20110658 A	20-02-2012
		DK 2443104 T3	06-05-2013
		DO P2011000386 A	29-02-2012
		EA 201270049 A1	30-05-2012
		EC SP11011541 A	31-01-2012
		EP 2443104 A1	25-04-2012
		ES 2409054 T3	24-06-2013
		HK 1164872 A1	19-09-2013
		HN 2011003139 A	29-07-2013
		HR P20130408 T1	30-06-2013
		JP 2012530705 A	06-12-2012
		KR 20120024783 A	14-03-2012
		MA 33363 B1	01-06-2012
		NZ 596882 A	30-08-2013
		PE 10502012 A1	09-08-2012
		PT 2443104 E	07-05-2013
		SG 177289 A1	28-02-2012
		SI 2443104 T1	31-07-2013
		TW 201113268 A	16-04-2011
		US 2010324048 A1	23-12-2010
		US 2012316174 A1	13-12-2012
		WO 2010147917 A1	23-12-2010

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Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 4(completely); 1-3, 5-38, 40-56(partially)
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

Continuation of Box II.2

Claims Nos.: 4(completely); 1-3, 5-38, 40-56(partially)

The claims 1-38 and 40-56 relate to an extremely large number of possible compounds (I). Support and disclosure in the sense of Articles 6 and 5 PCT is to be found however for only a very small proportion of the compounds (I) wherein R1 = 2-methylpyrazol-3-yl, A1 = A2 = N, m = 0, and het is piperidin-1,4-diyl in the direction drawn in claim 6. In addition, the initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claims may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, the search has been limited in as far as the claims relate to compounds of the formula (I) wherein R1 is a monocyclic heteroaryl group, A1 and A2 both are N, m is the integer 0, het is pyrrolidine-diyl, piperidine-diyl or azepane-diyl, and L-R2 is attached to the ring nitrogen atom of het. This corresponds to a partial search of the claims 1-3, 5-38, and 40-56; no search for claim 4; and a full search of claim 39.