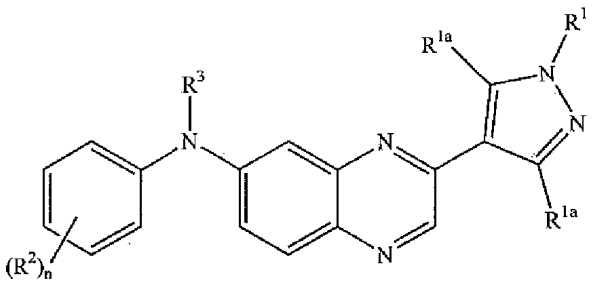
PYRAZOLYL QUINOXALINE KINASE INHIBITORS

FIELD OF THE INVENTION

The invention relates to new quinoxaline derivative compounds, to pharmaceutical compositions comprising said compounds, to processes for the preparation of said compounds and to the use of said compounds in the treatment of diseases, e.g. cancer.

SUMMARY

In one aspect, there is provided a compound of formula (I):



(I)

including any tautomeric or stereochemically isomeric form thereof, wherein

n represents an integer equal to 0, 1, 2, 3 or 4;

R^1 represents hydrogen, C_{1-6}alkyl, C_{2-4}alkenyl, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl, hydroxyhaloC_{1-6}alkyl, cyanoC_{1-4}alkyl, C_{1-6}alkoxyC_{1-6}alkyl wherein each C_{1-6}alkyl may optionally be substituted with one or two hydroxyl groups, C_{1-6}alkyl substituted with $-NR^4R^5$, C_{1-6}alkyl substituted with $-C(=O)-NR^4R^5$, $-S(=O)_2-C_{1-6}$alkyl, $-S(=O)_2-$haloC_{1-6}alkyl, $-S(=O)_2-NR^{14}R^{15}$, C_{1-6}alkyl substituted with $-S(=O)_2-C_{1-6}$alkyl, C_{1-6}alkyl substituted with $-S(=O)_2-$haloC_{1-6}alkyl, C_{1-6}alkyl substituted with $-S(=O)_2-NR^{14}R^{15}$, C_{1-6}alkyl substituted with $-NH-S(=O)_2-C_{1-6}$alkyl, C_{1-6}alkyl substituted with $-NH-S(=O)_2-$haloC_{1-6}alkyl, C_{1-6}alkyl substituted with $-NR^{12}-S(=O)_2-NR^{14}R^{15}$, R^6, C_{1-6}alkyl substituted with R^6, C_{1-6}alkyl substituted with $-C(=O)-R^6$, hydroxyC_{1-6}alkyl substituted with R^6, C_{1-6}alkyl substituted with $-Si(CH_3)_3$, C_{1-6}alkyl substituted with $-P(=O)(OH)_2$ or C_{1-6}alkyl substituted with $-P(=O)(OC_{1-6}alkyl)_2$;

each R^{1a} is independently selected from hydrogen, C_{1-4}alkyl, hydroxyC_{1-4}alkyl, C_{1-4}alkyl substituted with amino or mono- or di(C_{1-4}alkyl)amino or -NH(C_{3-6}cycloalkyl), cyanoC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, and C_{1-4}alkyl substituted with one or more fluoro atoms;

two hydroxyl groups, R^6, C_{1-6}alkyl substituted with R^6, -C(=O)-R^6, -C(=O)-C_{1-6}alkyl, –C(=O)-hydroxyC_{1-6}alkyl, -C(=O)-haloC_{1-6}alkyl,-C(=O)-hydroxyhaloC_{1-6}alkyl, C_{1-6}alkyl substituted with –$Si(CH_3)_3$, –$S(=O)_2$-C_{1-6}alkyl, –$S(=O)_2$-haloC_{1-6}alkyl, -$S(=O)_2$-$NR^{14}R^{15}$, C_{1-6}alkyl substituted with -$S(=O)_2$-C_{1-6}alkyl, C_{1-6}alkyl substituted with -$S(=O)_2$-haloC_{1-6}alkyl, C_{1-6}alkyl substituted with –$S(=O)_2$-$NR^{14}R^{15}$, C_{1-6}alkyl substituted with –NH-$S(=O)_2$-C_{1-6}alkyl, C_{1-6}alkyl substituted with –NH-$S(=O)_2$-haloC_{1-6}alkyl or C_{1-6}alkyl substituted with –NH-$S(=O)_2$-$NR^{14}R^{15}$;

R^{12} represents hydrogen or C_{1-4}alkyl optionally substituted with C_{1-4}alkoxy;

R^{13} represents C_{3-8}cycloalkyl or a saturated 4 to 6-membered monocyclic heterocyclyl containing at least one heteroatom selected from N, O or S, wherein said C_{3-8}cycloalkyl or monocyclic heterocyclyl is optionally substituted with 1, 2 or 3 substituents each independently selected from halogen, hydroxyl, C_{1-6}alkyl, -C(=O)-C_{1-6}alkyl, C_{1-6}alkoxy, or -$NR^{14}R^{15}$;

R^{14} and R^{15} each independently represent hydrogen, or haloC_{1-4}alkyl, or C_{1-4}alkyl optionally substituted with a substituent selected from hydroxyl, C_{1-4}alkoxy, amino or mono-or di(C_{1-4}alkyl)amino;

R^{16} represents hydroxyl, halogen, cyano, C_{1-4}alkyl, C_{1-4}alkoxy, -$NR^{14}R^{15}$ or –C(=O)$NR^{14}R^{15}$;

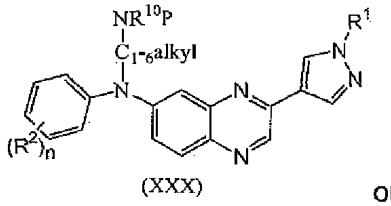
the *N*-oxides thereof, the pharmaceutically acceptable salts thereof or the solvates thereof.

In another aspect, there is provided a combination of a compound as defined herein with one or more anticancer agents.

In another aspect, there is provided a product containing as first active ingredient a compound as defined herein and as further active ingredient one or more anticancer agent, as a combined preparation for simultaneous, separate or sequential use in the treatment of patients suffering from cancer.

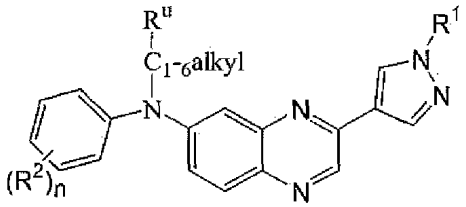
In another aspect, there is provided a process for the preparation of a compound of formula (I) as defined herein, which process comprises:

(i) deprotecting a compound of formula (XXX) wherein P represents a –C(=O)-O-$C(CH_3)_3$ protective group, in the presence of an acid selected from HCl or trifluoroacetic acid,



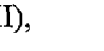
(XXX) or

(ii) the reaction of a compound of the formula (IX) or (IX'):



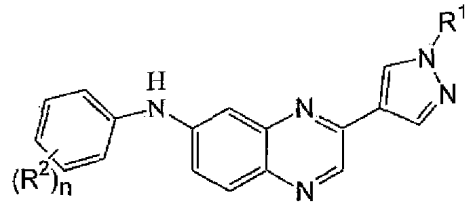
(IX) : R^u is -O-S(=O)$_2$-CH_3

(IX') : R^u is Cl

or a protected form thereof, with an appropriately substituted amine or a reactive derivative thereofselected from $NHR^{10}R^{11}$ (X), $NHR^{10}P$ (X-a) wherein P represents a –C(=O)-O-C(CH_3)$_3$ protective group, or a suitable nitrogen containing ring within the definition of R^9 :  (XXI),

in the presence of a base selected from triethylamine, K_2CO_3, Na_2CO_3 and sodium hydride, and/or in the presence or absence of a solvent selected from acetonitrile, tetrahydrofuran, dioxane, N,N-dimethylformamide, 1-methyl-pyrrolidinone, dimethylacetamide and an alcohol; or

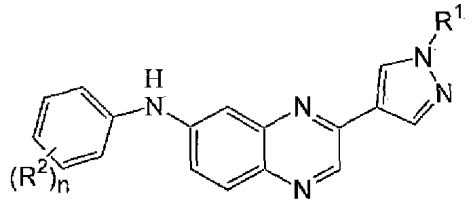
(iii) the reaction of a compound of the formula (VI):



(VI)

or a protected form thereof, with a compound of formula W_6-C_{1-6}alkyl-$NR^{10}P$ wherein P represents a –C(=O)-O-C(CH_3)$_3$ protective group and W_6 represents a leaving group selected from halo and –O-S(=O)$_2$-CH_3, in the presence of sodium hydride, and a solvent selected from N,N-dimethylformamide and N,N-dimethylacetamide, followed by removing P and optionally removing any further protecting group present; or

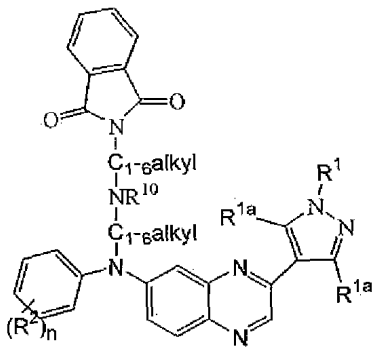
(iv) the reaction of a compound of the formula (VI):



(VI)

or a protected form thereof, with a compound of formula W_6-C_{1-6}alkyl-NHR^{10} wherein W_6 represents a leaving group selected from halo and –O-S(=O)$_2$-CH_3, in the presence of sodium hydride, and a solvent selected from N,N-dimethylformamide and N,N-dimethylacetamide; or

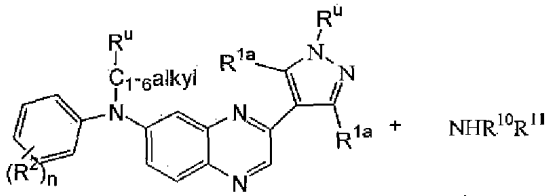
(v) the reaction of a compound of formula (XXXVI)



(XXXVI)

with hydrazine in the presence of an alcohol; or

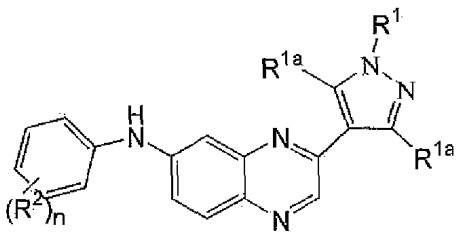
(vi) the reaction of a compound of formula (IX-1) wherein R^u represents –O-S(=O)$_2$-CH_3,



(IX-1)

with an intermediate of formula (X) in the presence acetonitrile; or

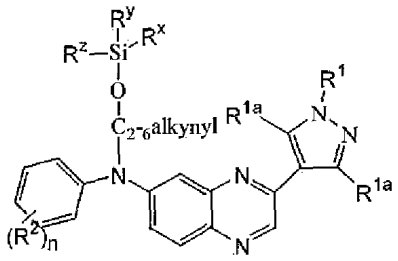
(vii) the reaction of a compound of formula (VI)



(VI)

with an intermediate of formula W_{11}-R^{3b} wherein R^{3b} represents optionally substituted C_{2-6}alkynyl and W_{11} represents a leaving group selected from halo and –O-S(=O)$_2$-CH_3, in the presence of sodium hydride and N,N-dimethylformamide; or

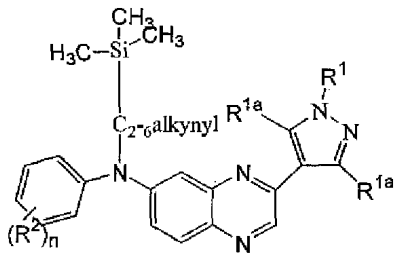
(viii) the reaction of a compound of formula (VIII') wherein R^x and R^y represent C_{1-4}alkyl, and R^z represent C_{1-4}alkyl or phenyl,



(VIII')

with trifluoroacetic acid, in the presence of tetrahydrofuran; or

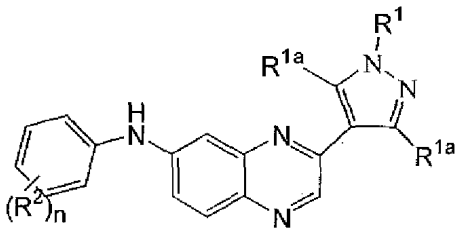
(ix) deprotecting a compound of formula (XXXXII)



(XXXXII)

in the presence of K_2CO_3 and an alcohol; or

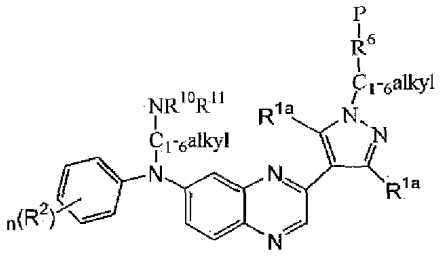
(x) the reaction of a compound of formula (VI)



(VI)

with di(C_{1-6}alkyl)vinylphosphonate in the presence of tri-N-butylphosphine and acetonitrile; or

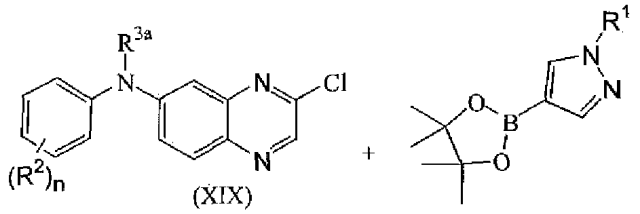
(xi) deprotecting a compound of formula (XXXXI) wherein P represents a –O-C(=O)-C_{1-6}alkyl protective group



(XXXXI)

in the presence of K_2CO_3 and an alcohol; or

(xii) the reaction of a compound of formula (XIX) wherein R^{3a} represents optionally substituted C_{1-6}alkyl with a compound of formula (III)

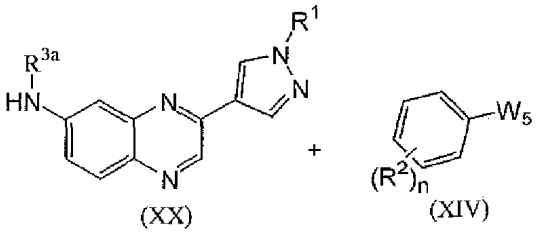


(XIX)

(III)

in the presence of a catalyst selected from tetrakis(triphenyl)phosphine palladium and $Pd_2(dba)_3$ (tris(dibenzylideneacetone) dipalladium (0)); 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl;a base selected from Na_2CO_3 and K_3PO_4; and a solvent selected from ethylene glycol dimethylether, dioxane and water; or

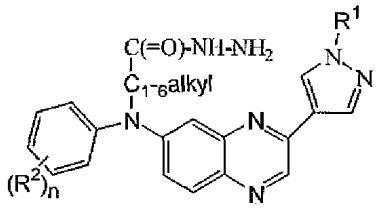
(xiii) the reaction of a compound of formula (XX) wherein R^{3a} represents optionally substituted C_{1-6}alkyl, with a compound of formula (XIV) wherein W_5 represents halo



(XX) (XIV)

in the presence of a catalyst selected from palladium (II) acetate and $Pd_2(dba)_3$ (tris(dibenzylidene acetone) dipalladium (0)); a ligand selected from 2-dicyclohexylphosphino-tris-isopropyl-biphenyl and 1,1'-[1,1'-binaphthalene]-2,2'-diylbis[1,1-diphenylphosphine]; sodium tert-butoxide; and ethylene glycol dimethylether; or

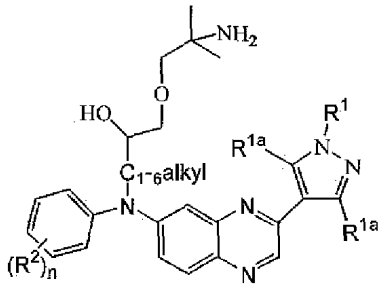
(xiv) the reaction of a compound of formula (XXXI)



(XXXI)

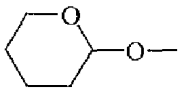
with W_8-CN, wherein W_8 represents halo, in the presence of $NaHCO_3$ and a solvent selected from water and dioxane; or

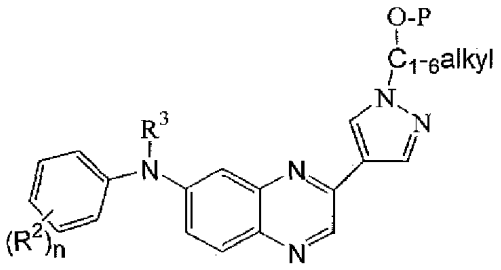
(xv) the reaction of a compound of formula (XXXV)



(XXXV)

with a base selected from *N,N*-diisopropylethylamine and triethylamine in the presence of an alcohol; or

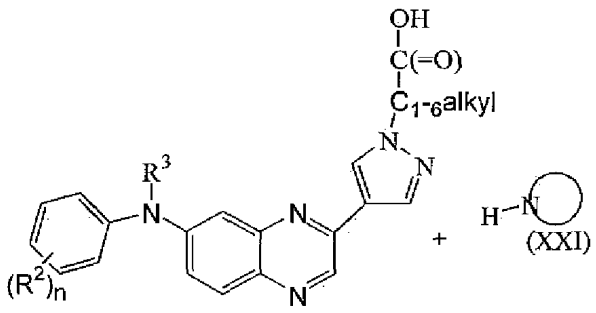
(xvi) deprotecting a compound of formula (XXVI) wherein P represents a protective group selected from –O-Si(CH3)2(C(CH3)3) and ,



(XXVI)

in the presence of an acid selected from HCl and trifluoroacetic acid, or tetrabutyl ammonium fluoride, and a solvent selected from an alcohol and tetrahydrofuran; or

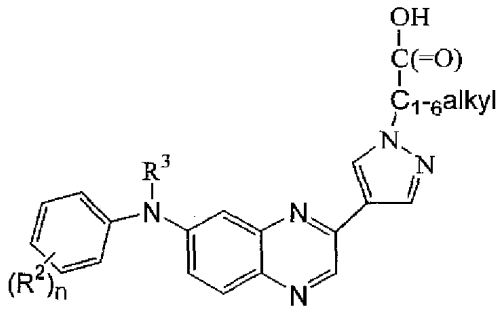
(xvii) the reaction of a compound of formula (XXIX) with a compound of formula (XXI)



(XXIX)

in the presence of peptide coupling reagents selected from 1-hydroxy-benzotriazole and 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide HCl; or

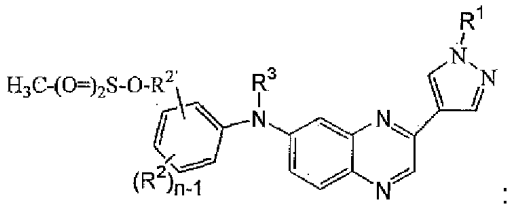
(xviii) the reaction of a compound of formula (XXIX)



(XXIX)

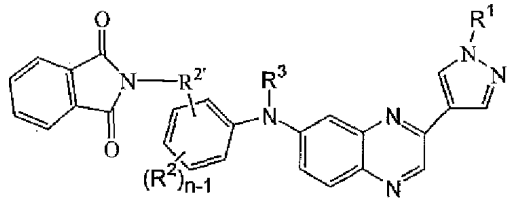
with NHR^4R^5 in the presence of peptide coupling reagents selected from 1-hydroxybenzotriazole and 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide HCl and triethylamine, and dichloromethane; or

(xix) reacting the below compound



with NHR^7R^8 in the presence of K_2CO_3 and tetrahydrofuran; or

(xx) deprotecting the below compound



in the presence of hydrazine monohydrate and an alcohol;

wherein R^1, R^{1a}, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11} and n are as defined herein; and optionally thereafter converting one compound of the formula (I) into another compound of the formula (I).

In another aspect, there is provided a pharmaceutical composition comprising a compound of formula (I) as defined herein.

In another aspect, there is provided a compound as defined herein for use in therapy.

In another aspect, there is provided a compound as defined herein for use in the prophylaxis or treatment of a disease state or condition selected from multiple myeloma, myeloproliferative disorders, endometrial cancer, prostate cancer, bladder cancer, lung cancer, ovarian cancer, breast cancer, gastric cancer, colorectal cancer, and oral squamous cell carcinoma.

In another aspect, there is provided a compound as defined herein for use in the prophylaxis or treatment of cancer.

In another aspect, there is provided use of a compound as defined herein for the manufacture of a medicament for the prophylaxis or treatment of cancer.

In another aspect, there is provided use of a compound as defined herein for the manufacture of a medicament for the prophylaxis or treatment of a carcinoma wherein the carcinoma is a carcinoma of the bladder, breast, colon, kidney, epidermis, liver, lung, oesophagus, head and neck, gall bladder, ovary, pancreas, stomach, gastrointestinal (also known as gastric) cancer, cervix, endometrium, thyroid, prostate, or skin, a hematopoietic tumour of lymphoid lineage; a hematopoietic tumour of myeloid lineage; multiple myeloma; thyroid follicular cancer; a tumour of mesenchymal origin; a tumour of the central or peripheral nervous system; melanoma; seminoma; teratocarcinoma; osteosarcoma; xeroderma pigmentosum; keratoctanthoma; thyroid follicular cancer; or Kaposi's sarcoma.

In another aspect, there is provided a compound as defined herein for use in the treatment of cancer wherein said compound is used in combination with one or more anticancer agents.

In another aspect, there is provided a compound as defined herein use in the treatment of cancer wherein said compound is used in combination with one or more anticancer agents and wherein the one or more anticancer agents comprises a kinase inhibitor.

WO2006/092430, WO2008/003702, WO01/68047, WO2005/007099, WO2004/098494, WO2009/141386, WO 2004/030635, WO 2008/141065, WO 2011/026579, WO 2011/028947 and WO 00/42026 which each disclose a series of heterocyclyl derivatives.

DETAILED DESCRIPTION OF THE INVENTION

Unless the context indicates otherwise, references to formula (I) in all sections of this document (including the uses, methods and other aspects of the invention) include references to all other sub-formula (e.g. I', I'', I''', I^0, $I^{0'}$, $I^{0''}$, $I^{0'''}$), sub-groups, preferences, embodiments and examples as defined herein.

The prefix "C_{x-y}" (where x and y are integers) as used herein refers to the number of carbon atoms in a given group. Thus, a C_{1-6}alkyl group contains from 1 to 6 carbon

optionally be substituted with one or two hydroxyl groups, C_{1-6}alkyl substituted with -NR^4R^5, C_{1-6}alkyl substituted with –C(=O)-NR^4R^5, –$S(=O)_2$-C_{1-6}alkyl, –$S(=O)_2$-$NR^{14}R^{15}$, C_{1-6}alkyl substituted with -$S(=O)_2$-C_{1-6}alkyl, C_{1-6}alkyl substituted with -NH-$S(=O)_2$-C_{1-6}alkyl, R^6, C_{1-6}alkyl substituted with R^6, C_{1-6}alkyl substituted with –C(=O)-R^6, hydroxyC_{1-6}alkyl substituted with R^6, or C_{1-6}alkyl substituted with –$Si(CH_3)_3$; wherein each R^{1a} is hydrogen; wherein R^{10} and R^{11} each independently represent hydrogen, C_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkyl substituted with –$NR^{14}R^{15}$, C_{1-6}alkyl substituted with –C(=O)-$NR^{14}R^{15}$, haloC_{1-6}alkyl, hydroxyC_{1-6}alkyl, hydroxyhaloC_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl wherein each C_{1-6}alkyl may optionally be substituted with one or two hydroxyl groups, R^6, C_{1-6}alkyl substituted with R^6, -C(=O)-R^6, -C(=O)-C_{1-6}alkyl, –C(=O)-hydroxyC_{1-6}alkyl, -C(=O)-haloC_{1-6}alkyl,-C(=O)-hydroxyhaloC_{1-6}alkyl, C_{1-6}alkyl substituted with –$Si(CH_3)_3$, –$S(=O)_2$-C_{1-6}alkyl, –$S(=O)_2$-haloC_{1-6}alkyl, -$S(=O)_2$-$NR^{14}R^{15}$, C_{1-6}alkyl substituted with -$S(=O)_2$-C_{1-6}alkyl, C_{1-6}alkyl substituted with -$S(=O)_2$-haloC_{1-6}alkyl, C_{1-6}alkyl substituted with –$S(=O)_2$-$NR^{14}R^{15}$, C_{1-6}alkyl substituted with –NH-$S(=O)_2$-C_{1-6}alkyl, C_{1-6}alkyl substituted with –NH-$S(=O)_2$-haloC_{1-6}alkyl or C_{1-6}alkyl substituted with –NH-$S(=O)_2$-$NR^{14}R^{15}$.

3. A compound according to claim 1 wherein each R^{1a} is hydrogen.

4. A compound according to any one of the preceding claims wherein R^1 represents C_{1-6}alkyl.

5. A compound according to any one of the preceding claims wherein R^1 represents CH_3- or CD_3-.

6. A compound according to any one of the preceding claims wherein R^2 is independently selected from halogen, cyano, C_{1-4}alkyl, C_{2-4}alkenyl, C_{1-4}alkoxy, hydroxyC_{1-4}alkyl, hydroxyC_{1-4}alkoxy, haloC_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl, R^{13}, C_{1-4}alkoxy substituted with R^{13}, -C(=O)-R^{13}, C_{1-4}alkyl substituted with NR^7R^8, C_{1-4}alkoxy substituted with NR^7R^8, -NR^7R^8 and -C(=O)-NR^7R^8.

7. A compound according to claim 6 wherein R^2 represents C_{1-4}alkoxy.