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(54) Titre : DERIVES D'OXAZOLINE THERAPEUTIQUEMENT ACTIFS
(54) Title: THERAPEUTICALLY ACTIVE OXAZOLINE DERIVATIVES

(57) Abrégé/Abstract:

Compounds of formula (I) i.e. monocyclic or bicyclic diamine-substituted thieno[2,3-d]pyrimidine and isothiazolo[5,4-d]pyrimidine derivatives substituted by an optionally substituted oxazolin-2-yl moiety, are beneficial in the treatment and/or prevention of various human ailments, including inflammatory, autoimmune and oncological disorders; viral diseases; and organ and cell transplant rejection.

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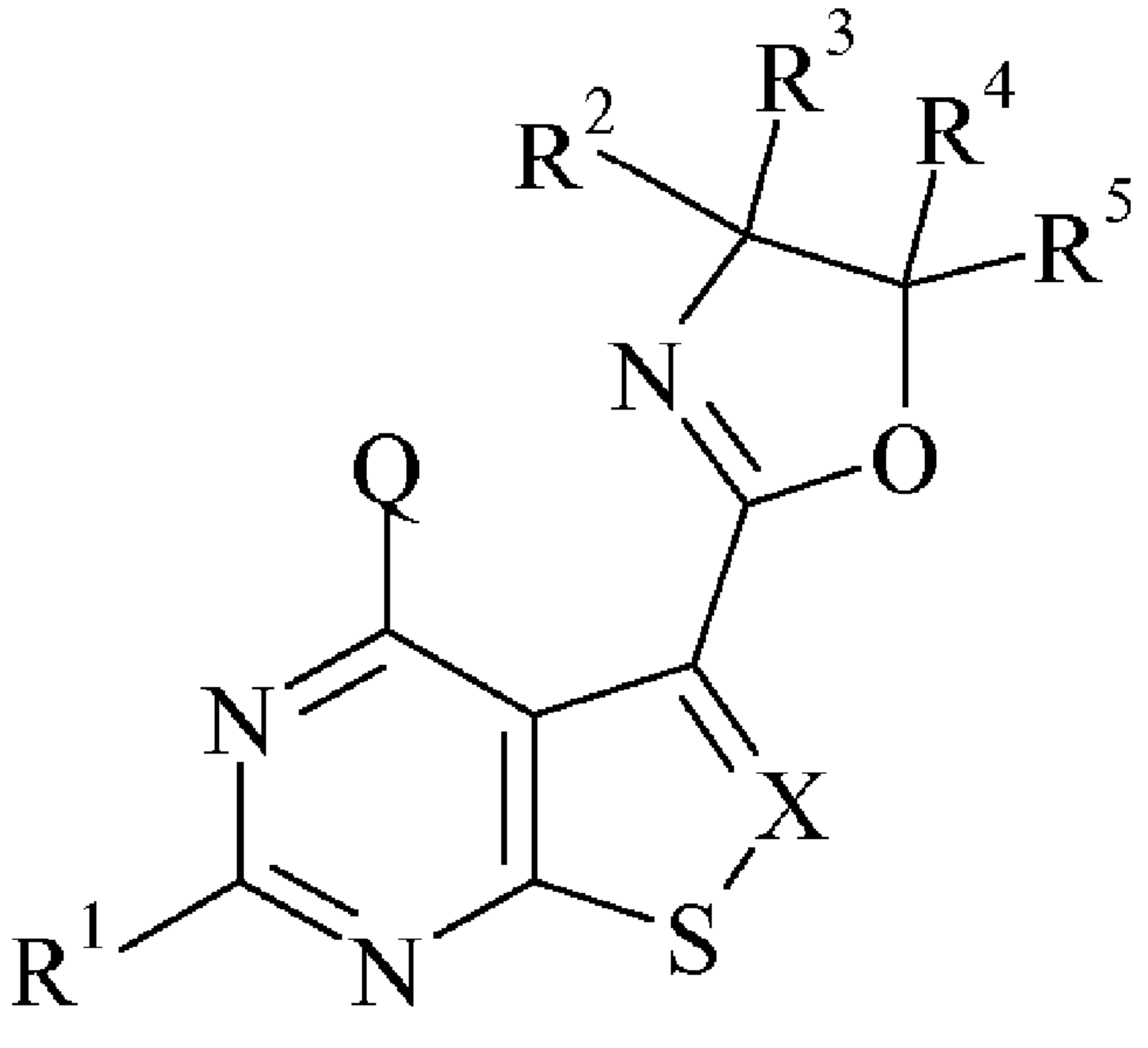

(I)

(57) Abstract: Compounds of formula (I) i.e. monocyclic or bicyclic diamine-substituted thieno[2,3-d]pyrimidine and isothiazolo[5,4-d]pyrimidine derivatives substituted by an optionally substituted oxazolin-2-yl moiety, are beneficial in the treatment and/or prevention of various human ailments, including inflammatory, autoimmune and oncological disorders; viral diseases; and organ and cell transplant rejection.

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THERAPEUTICALLY ACTIVE OXAZOLINE DERIVATIVES

The present invention relates to a class of oxazoline derivatives, and to their use in therapy. These compounds are of benefit as pharmaceutical agents, especially in the treatment of adverse inflammatory, autoimmune and oncological disorders, in the treatment of viral diseases, and in the management of organ and cell transplant rejection.

In addition, the compounds in accordance with the present invention may be beneficial as pharmacological standards for use in the development of new biological tests and in the search for new pharmacological agents. Thus, the compounds of this invention may be useful as radioligands in assays for detecting pharmacologically active compounds.

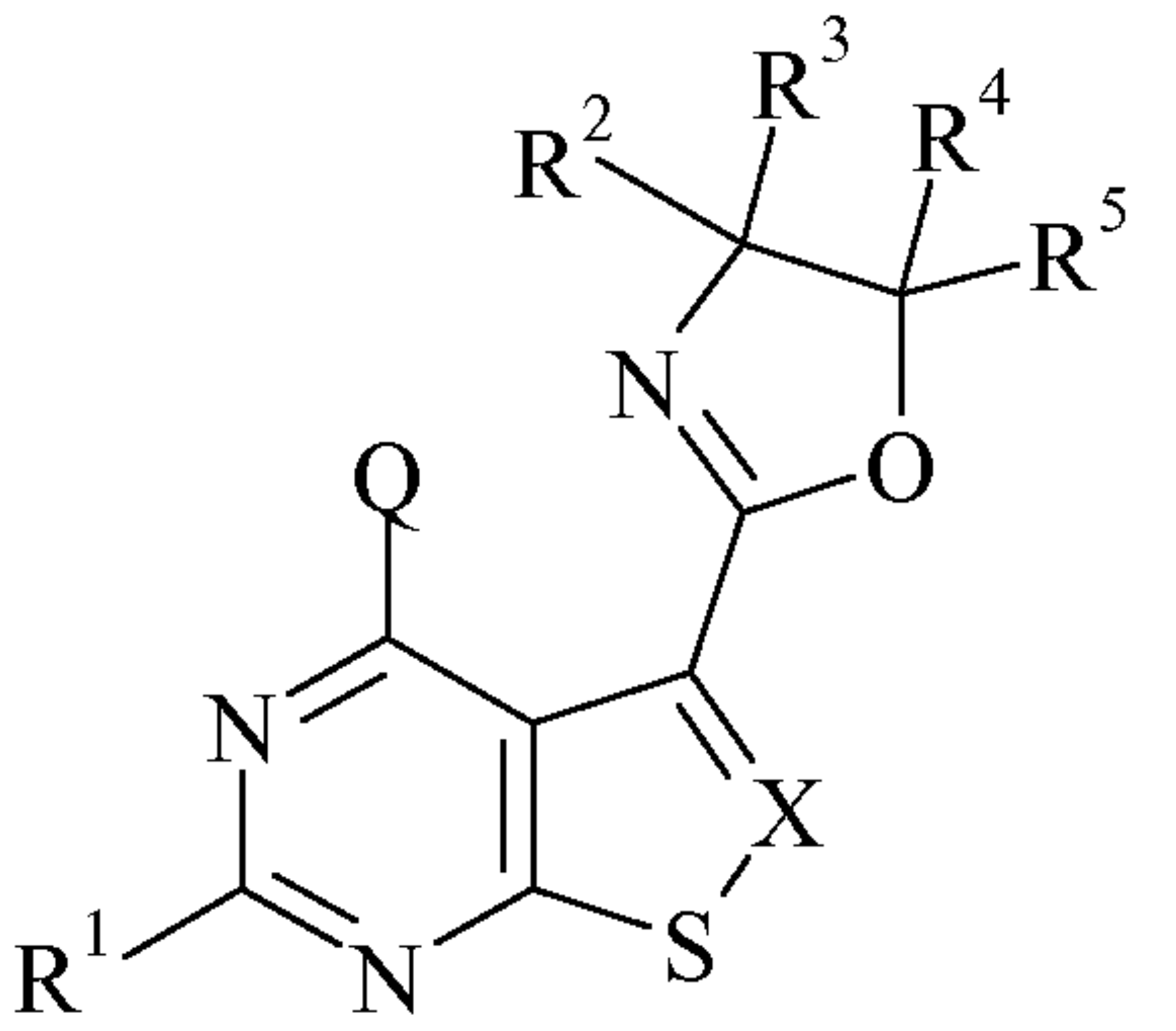
WO 2010/103130 describes a family of oxazolo[5,4-*d*]pyrimidine, thiazolo[5,4-*d*]-pyrimidine, thieno[2,3-*d*]pyrimidine and purine derivatives that are active in a range of assays, including the Mixed Lymphocyte Reaction (MLR) test, and are stated to be effective for the treatment of immune and auto-immune disorders, and organ and cell transplant rejection. WO 2011/147753 discloses the same family of compounds as having significant antiviral activity. Furthermore, WO 2012/035423 discloses the same family of compounds as having significant anticancer activity.

Copending international patent application PCT/GB2012/051992, published on 21 February 2013 as WO 2013/024291, describes a family of monocyclic or bicyclic diamine-substituted thieno[2,3-*d*]pyrimidine and isothiazolo[5,4-*d*]pyrimidine derivatives that are stated to be of benefit as pharmaceutical agents, especially in the treatment of adverse inflammatory, autoimmune and oncological disorders, in the treatment of viral diseases, and in the management of organ and cell transplant rejection.

None of the prior art available to date, however, discloses or suggests the precise structural class of oxazoline derivatives as provided by the present invention.

The compounds in accordance with the present invention are active as inhibitors when subjected to the Mixed Lymphocyte Reaction (MLR) test. The MLR test is predictive of immunosuppression or immunomodulation. Thus, when subjected to the MLR test, the compounds of the present invention display an IC_{50} value of 10 μM or less, generally of 5 μM or less, usually of 2 μM or less, typically of 1 μM or less, suitably of 500 nM or less, ideally of 100 nM or less, and preferably of 20 nM or less (the skilled person will appreciate that a *lower* IC_{50} figure denotes a *more active* compound).

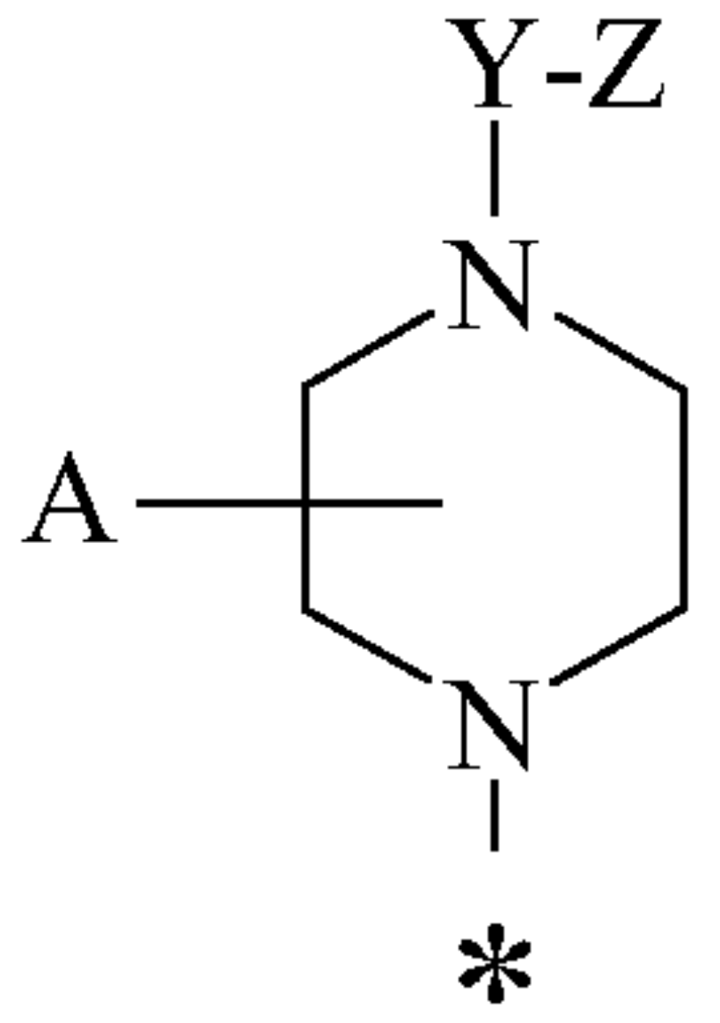
The present invention provides a compound of formula (I) or an *N*-oxide thereof, or a pharmaceutically acceptable salt or solvate thereof:



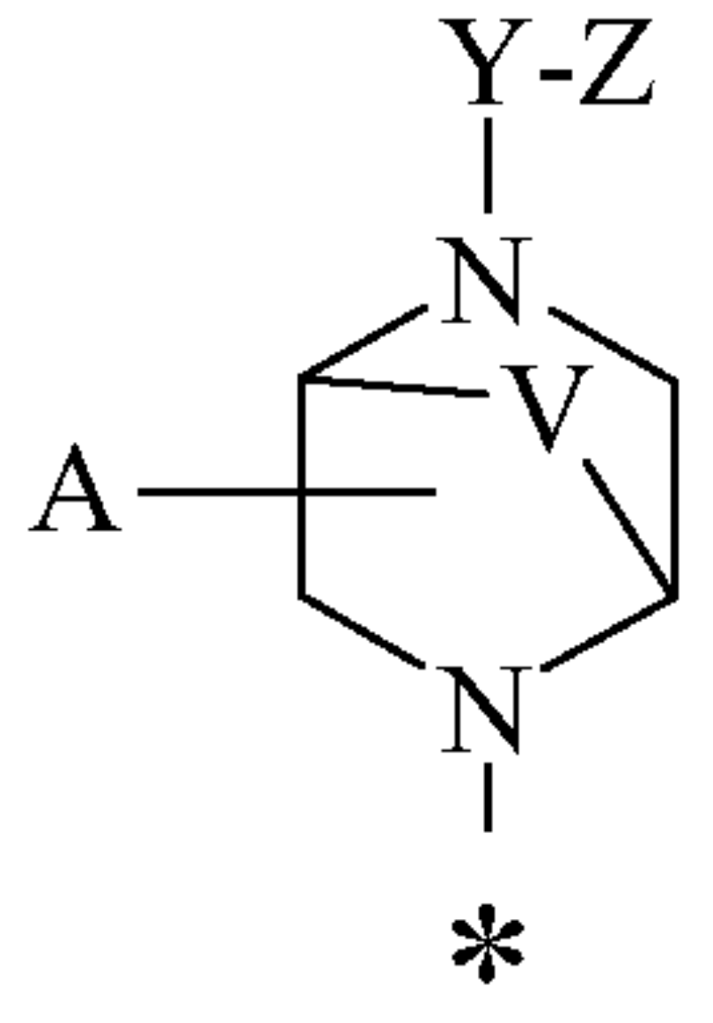
(I)

wherein

Q represents a group of formula (Qa) or (Qb):



(Qa)



(Qb)

in which the asterisk (*) represents the point of attachment to the remainder of the molecule;

V represents $-CH_2-$, $-C(CH_3)_2-$, $-CH_2CH_2-$ or $-CH_2CH_2CH_2-$;

X represents C-R^6 or N;

Y represents a covalent bond, or a linker group selected from -C(O)-, -S(O)-, $-S(O)_2-$, -C(O)O-, -C(O)N(R^7)- and $-S(O)_2N(R^7)-$;

Z represents hydrogen; or Z represents C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl-(C_{1-6})alkyl, aryl, aryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl, heteroaryl or heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted by one or more substituents;

A represents hydrogen or trifluoromethyl; or A represents C_{1-6} alkyl, optionally substituted by one or more substituents independently selected from halogen, $-OR^a$, $-S(O)R^a$ and $-NR^bR^c$;

R^1 represents hydrogen, halogen, cyano, nitro, hydroxy, trifluoromethyl, trifluoromethoxy, $-OR^a$, $-SR^a$, $-SOR^a$, $-SO_2R^a$, $-NR^bR^c$, $-CH_2NR^bR^c$, $-NR^cCOR^d$, $-CH_2NR^cCOR^d$, $-NR^cCO_2R^d$, $-NHCONR^bR^c$, $-NR^cSO_2R^e$, $-N(SO_2R^e)_2$, $-NHSO_2NR^bR^c$, $-COR^d$, $-CO_2R^d$, $-CONR^bR^c$, $-CON(OR^a)R^b$ or $-SO_2NR^bR^c$; or R^1 represents C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl(C_{1-6})alkyl, aryl, aryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl, heteroaryl or heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted by one or more substituents;

R^2 represents hydrogen or C_{1-6} alkyl; and

R^3 represents hydrogen; or R^3 represents C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl(C_{1-6})alkyl, aryl, aryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl, heteroaryl or heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted by one or more substituents; or

R^2 and R^3, when taken together with the carbon atom to which they are both attached, represent C_{3-7} cycloalkyl or C_{3-7} heterocycloalkyl, either of which groups may be optionally substituted by one or more substituents;

R^4 represents hydrogen or C_{1-6} alkyl; and

R^5 represents hydrogen; or R^5 represents C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl(C_{1-6})alkyl, aryl, aryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl, heteroaryl or heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted by one or more substituents; or

R^4 and R^5, when taken together with the carbon atom to which they are both attached, represent C_{3-7} cycloalkyl or C_{3-7} heterocycloalkyl, either of which groups may be optionally substituted by one or more substituents;

R^6 and R^7 independently represent hydrogen; or C_{1-6} alkyl, optionally substituted by one or more substituents independently selected from $-OR^a$ and $-NR^bR^c$;

R^a represents hydrogen; or R^a represents C_{1-6} alkyl, aryl, aryl(C_{1-6})alkyl, heteroaryl or heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted by one or more substituents;

R^b and R^c independently represent hydrogen or trifluoromethyl; or C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl(C_{1-6})alkyl, aryl, aryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl, C_{3-7}

heterocycloalkyl(C_{1-6})alkyl, heteroaryl or heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted by one or more substituents; or

R^b and R^c, when taken together with the nitrogen atom to which they are both attached, represent azetidin-1-yl, pyrrolidin-1-yl, oxazolidin-3-yl, isoxazolidin-2-yl, thiazolidin-3-yl, isothiazolidin-2-yl, piperidin-1-yl, morpholin-4-yl, thiomorpholin-4-yl, piperazin-1-yl, homopiperidin-1-yl, homomorpholin-4-yl or homopiperazin-1-yl, any of which groups may be optionally substituted by one or more substituents;

R^d represents hydrogen; or C_{1-6} alkyl, C_{3-7} cycloalkyl, aryl, C_{3-7} heterocycloalkyl or heteroaryl, any of which groups may be optionally substituted by one or more substituents; and

R^e represents C_{1-6} alkyl, aryl or heteroaryl, any of which groups may be optionally substituted by one or more substituents.

Where any of the groups in the compounds of formula (I) above is stated to be optionally substituted, this group may be unsubstituted, or substituted by one or more substituents. Typically, such groups will be unsubstituted, or substituted by one or two substituents.

For use in medicine, the salts of the compounds of formula (I) will be pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds of the invention or of their pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound of the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulphuric acid, methanesulphonic acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, citric acid, tartaric acid or phosphoric acid. Furthermore, where the compounds of the invention carry an acidic moiety, e.g. carboxy, suitable pharmaceutically acceptable salts thereof may include alkali metal salts, e.g. sodium or potassium salts; alkaline earth metal salts, e.g. calcium or magnesium salts; and salts formed with suitable organic ligands, e.g. quaternary ammonium salts.

The present invention includes within its scope solvates of the compounds of formula (I) above. Such solvates may be formed with common organic solvents, e.g. hydrocarbon solvents such as benzene or toluene; chlorinated solvents such as chloroform or dichloromethane; alcoholic solvents such as methanol, ethanol or isopropanol; ethereal solvents such as diethyl ether or tetrahydrofuran; or ester solvents such as ethyl acetate.

Alternatively, the solvates of the compounds of formula (I) may be formed with water, in which case they will be hydrates.

Suitable alkyl groups which may be present on the compounds of the invention include straight-chained and branched C_{1-6} alkyl groups, for example C_{1-4} alkyl groups. Typical examples include methyl and ethyl groups, and straight-chained or branched propyl, butyl, pentyl and hexyl groups. Particular alkyl groups include methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *sec*-butyl, isobutyl, *tert*-butyl, 2,2-dimethylpropyl and 3-methylbutyl. Derived expressions such as "C_{1-6} alkoxy", "C_{1-6} alkylthio", "C_{1-6} alkylsulphonyl" and "C_{1-6} alkylamino" are to be construed accordingly.

Specific C_{3-7} cycloalkyl groups, which may comprise benzo-fused analogues thereof, include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 1,2,3,4-tetrahydronaphthyl and cycloheptyl.

Suitable aryl groups include phenyl and naphthyl, preferably phenyl.

Suitable aryl(C_{1-6})alkyl groups include benzyl, phenylethyl, phenylpropyl, phenylbutyl and naphthylmethyl.

Suitable heterocycloalkyl groups, which may comprise benzo-fused analogues thereof, include azetidinyl, tetrahydrofuranyl, dihydrobenzofuranyl, pyrrolidinyl, indolinyl, thiazolidinyl, imidazolidinyl, tetrahydropyranyl, chromanyl, piperidinyl, 1,2,3,4-tetrahydroquinolinyl, 1,2,3,4-tetrahydroisoquinolinyl, piperazinyl, 1,2,3,4-tetrahydroquinoxalinyl, homopiperazinyl, morpholinyl, benzoxazinyl and thiomorpholinyl.

Suitable heteroaryl groups include furyl, benzofuryl, dibenzofuryl, thienyl, benzothienyl, dibenzothienyl, pyrrolyl, indolyl, pyrrolo[2,3-*b*]pyridinyl, pyrrolo[3,2-*c*]pyridinyl, pyrazolyl, pyrazolo[1,5-*a*]pyridinyl, pyrazolo[3,4-*d*]pyrimidinyl, indazolyl, oxazolyl, benzoxazolyl, isoxazolyl, thiazolyl, benzothiazolyl, isothiazolyl, imidazolyl, benzimidazolyl, imidazo[1,2-*a*]pyridinyl, imidazo[4,5-*b*]pyridinyl, purinyl, imidazo[1,2-*a*]pyrimidinyl, imidazo[1,2-*a*]pyrazinyl, oxadiazolyl, thiadiazolyl, triazolyl, benzotriazolyl, tetrazolyl, pyridinyl, quinolinyl, isoquinolinyl, naphthyridinyl, pyridazinyl, cinnolinyl, phthalazinyl, pyrimidinyl, quinazolinyl, pyrazinyl, quinoxalinyl, pteridinyl, triazinyl and chromenyl groups.

The term "halogen" as used herein is intended to include fluorine, chlorine, bromine and iodine atoms, typically fluorine, chlorine or bromine.

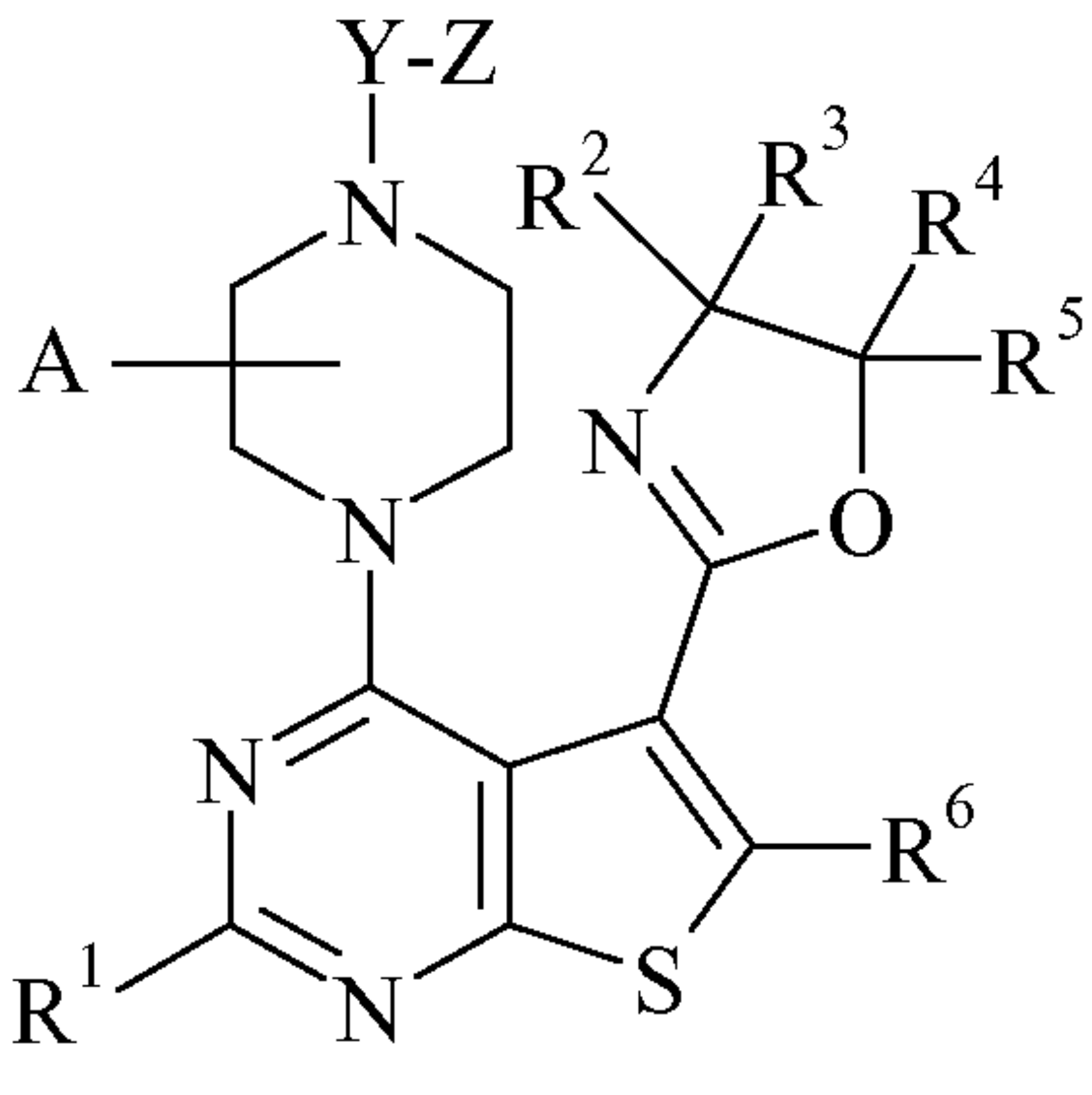
Where the compounds of formula (I) have one or more asymmetric centres, they may accordingly exist as enantiomers. Where the compounds of the invention possess two or more asymmetric centres, they may additionally exist as diastereomers. The invention is to be understood to extend to all such enantiomers and diastereomers, and to mixtures thereof in any proportion, including racemates. Formula (I) and the formulae depicted hereinafter are intended to represent all individual stereoisomers and all possible mixtures thereof, unless stated or shown otherwise. In addition, compounds of formula (I) may exist as tautomers, for example keto ($CH_2C=O$)↔enol ($CH=CHOH$) tautomers or amide ($NHC=O$)↔hydroxyimine ($N=COH$) tautomers. Formula (I) and the formulae depicted hereinafter are intended to represent all individual tautomers and all possible mixtures thereof, unless stated or shown otherwise.

It is to be understood that each individual atom present in formula (I), or in the formulae depicted hereinafter, may in fact be present in the form of any of its naturally occurring isotopes, with the most abundant isotope(s) being preferred. Thus, by way of example, each individual hydrogen atom present in formula (I), or in the formulae depicted hereinafter, may be present as a ^{1}H, ^{2}H (deuterium) or ^{3}H (tritium) atom, preferably ^{1}H. Similarly, by way of example, each individual carbon atom present in formula (I), or in the formulae depicted hereinafter, may be present as a ^{12}C, ^{13}C or ^{14}C atom, preferably ^{12}C.

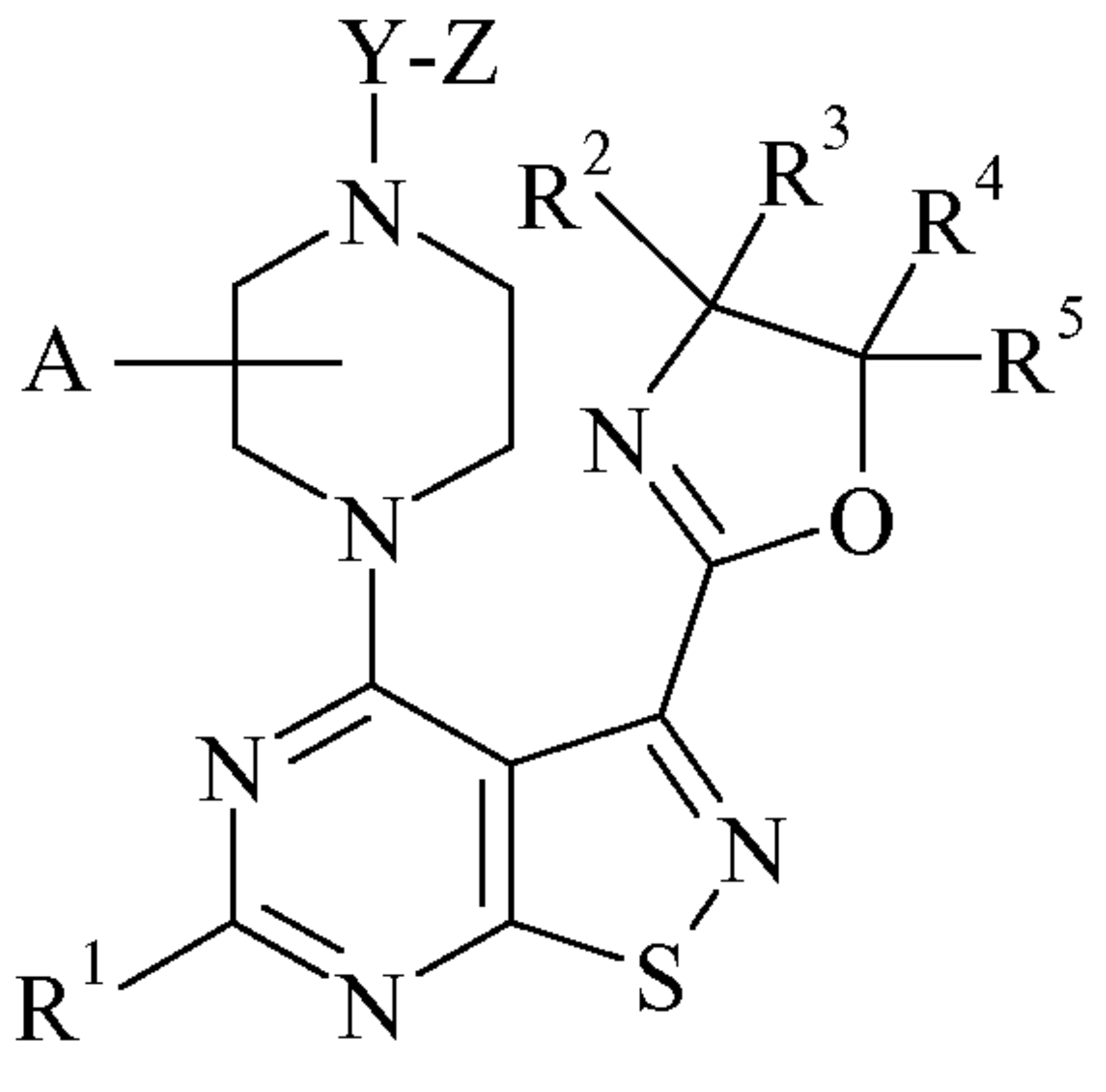
In a particular embodiment, Q represents a group of formula (Qa) as defined above. In another embodiment, Q represents a group of formula (Qb) as defined above.

In one embodiment, X represents C-R^6. In another embodiment, X represents N.

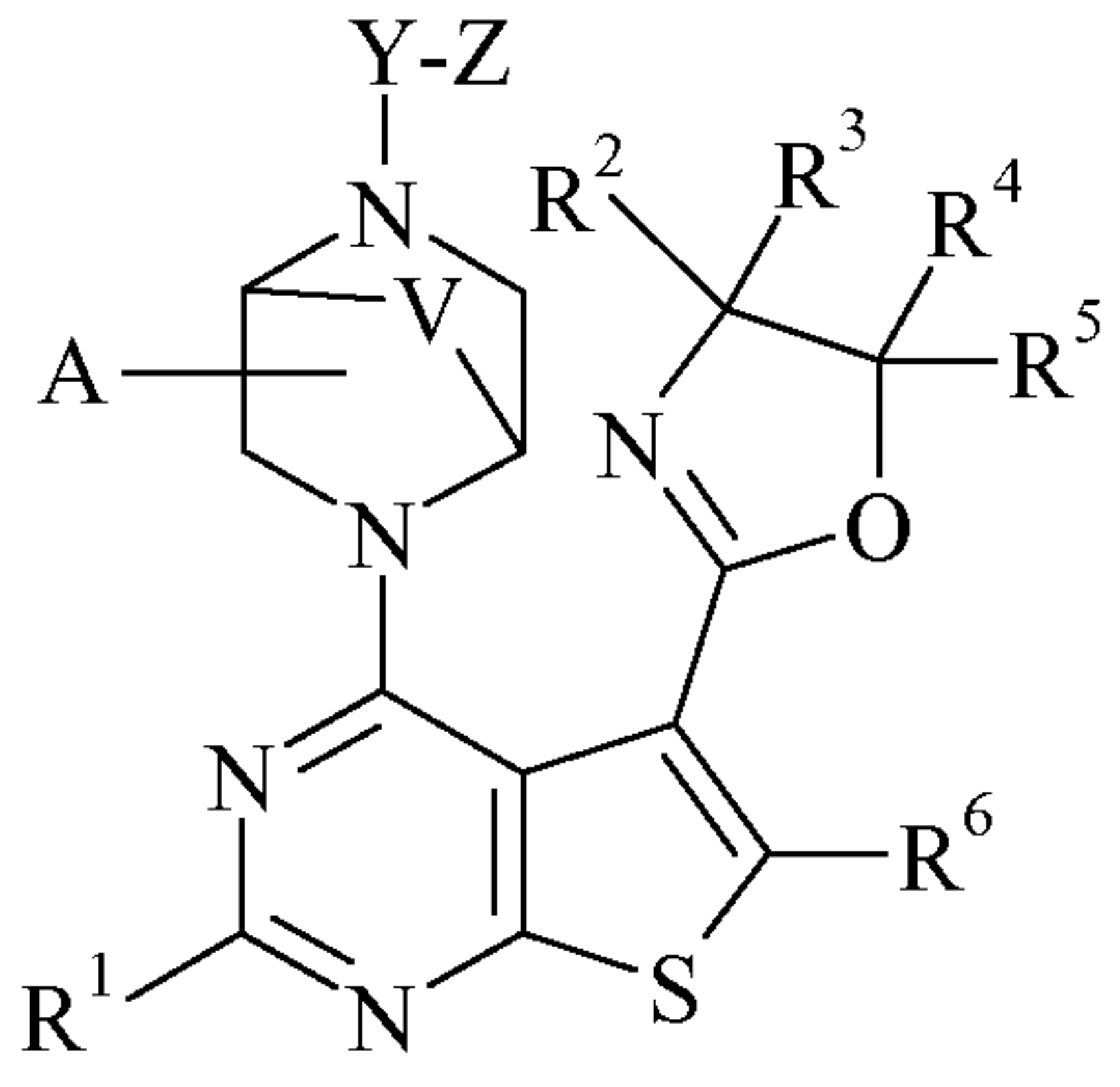
Particular sub-classes of compounds in accordance with the present invention are represented by the compounds of formula (IA), (IB), (IC) and (ID):



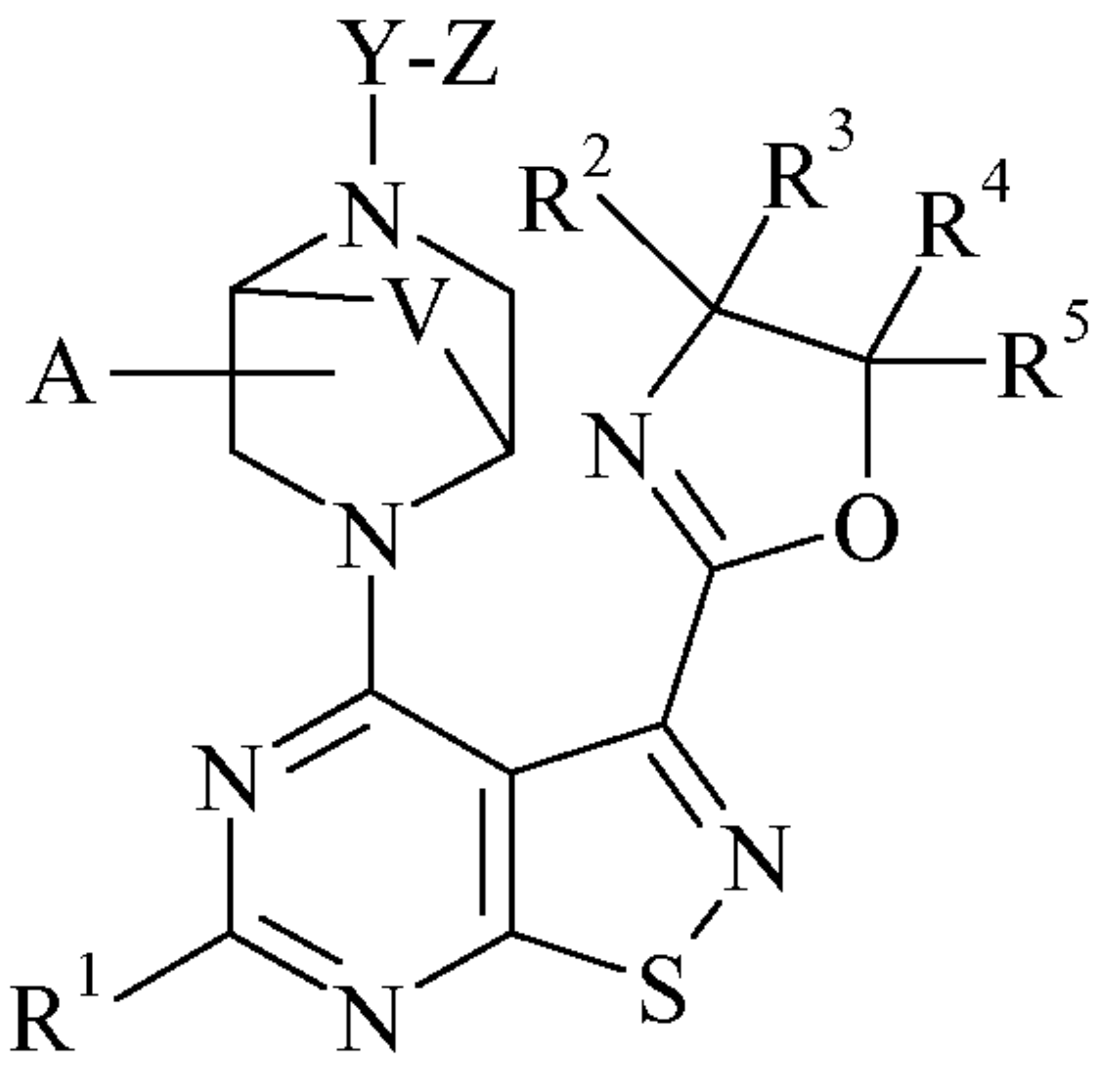
(IA)



(IB)



(IC)

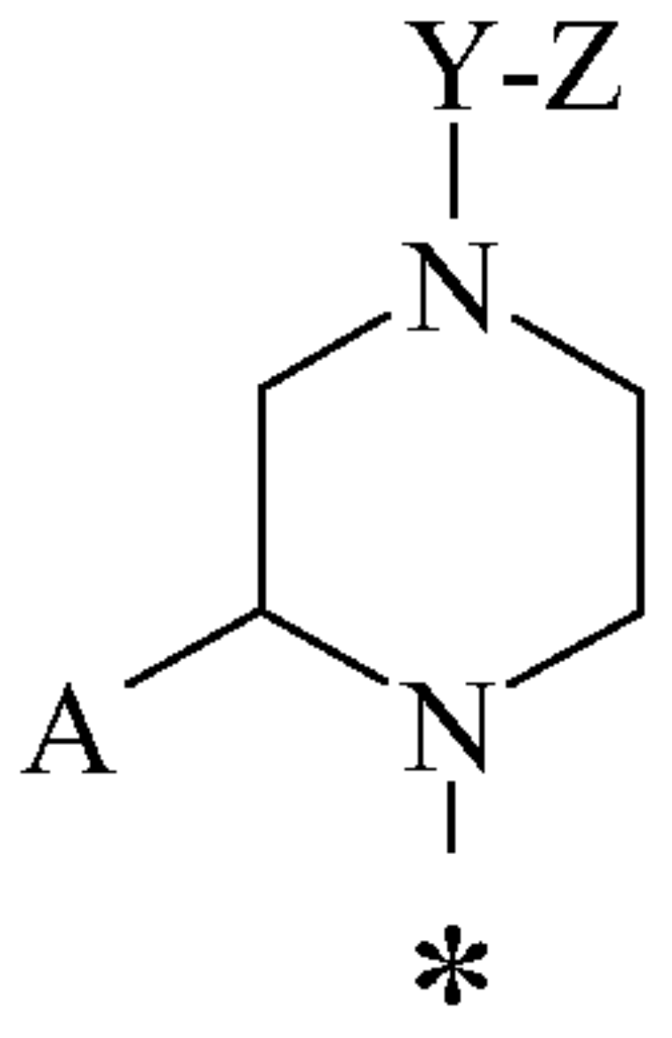


(ID)

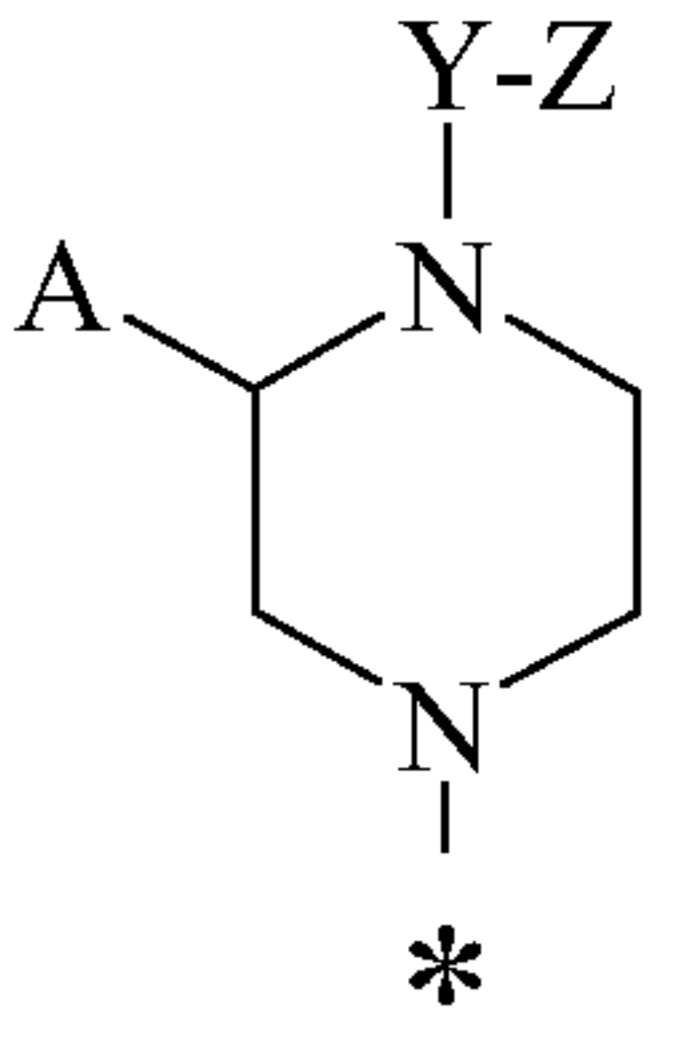
wherein V, Y, Z, A, R^1, R^2, R^3, R^4, R^5 and R^6 are as defined above.

A favoured sub-class of compounds in accordance with the present invention is represented by the compounds of formula (IA) as defined above.

Where Q represents a group of formula (Qa) as defined above, this may be a group of formula (Qa-1) or (Qa-2):



(Qa-1)



(Qa-2)

in which the asterisk (*) represents the point of attachment to the remainder of the molecule; and

Y, Z and A are as defined above.

In a first embodiment, Q represents a group of formula (Qa-1) as defined above.

In a second embodiment, Q represents a group of formula (Qa-2) as defined above.

In a particular embodiment, V represents $-CH_2-$ or $-C(CH_3)_2-$. In a first aspect of that embodiment, V represents $-CH_2-$. In a second aspect of that embodiment, V represents $-C(CH_3)_2-$. Where V represents $-CH_2-$ or $-C(CH_3)_2-$, the bicyclic moiety containing the integer V is a 2,5-diazabicyclo[2.2.1]heptane ring system.

In another embodiment, V represents $-CH_2CH_2-$. Where V represents $-CH_2CH_2-$, the bicyclic moiety containing the integer V is a 2,5-diazabicyclo[2.2.2]octane ring system.

In a further embodiment, V represents $-CH_2CH_2CH_2-$. Where V represents $-CH_2CH_2CH_2-$, the bicyclic moiety containing the integer V is a 6,8-diazabicyclo[3.2.2]-nonane ring system.

Typically, Y represents a covalent bond, or a linker group selected from -C(O)-, $-S(O)_2-$, -C(O)O-, $-C(O)N(R^7)-$ and $-S(O)_2N(R^7)-$;

Suitably, Y represents a covalent bond, or a linker group selected from -C(O)- and $-C(O)N(R^7)-$.

Suitable values of Y include -C(O)-, -S(O)-, $-S(O)_2-$, -C(O)O-, $-C(O)N(R^7)-$ and $-S(O)_2N(R^7)-$.

Particular values of Y include -C(O)-, $-S(O)_2-$, -C(O)O-, $-C(O)N(R^7)-$ and $-S(O)_2N(R^7)-$.

Selected values of Y include -C(O)- and $-C(O)N(R^7)-$.

In a first embodiment, Y represents a covalent bond. In a second embodiment, Y represents -C(O)-. In a third embodiment, Y represents -S(O)-. In a fourth embodiment, Y represents $-S(O)_2-$. In a fifth embodiment, Y represents -C(O)O-. In a sixth embodiment, Y represents $-C(O)N(R^7)-$. In a seventh embodiment, Y represents $-S(O)_2N(R^7)-$.

In one aspect, Z represents hydrogen. In an alternative aspect, Z represents C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl(C_{1-6})alkyl, aryl, aryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl, heteroaryl or heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted by one or more substituents.

Suitably, Z represents aryl, C_{3-7} heterocycloalkyl or heteroaryl, any of which groups may be optionally substituted by one or more substituents.

In a first embodiment, Z represents hydrogen. In a second embodiment, Z represents C_{1-6} alkyl, which group may be optionally substituted by one or more substituents. In a third embodiment, Z represents C_{3-7} cycloalkyl, which group may be optionally substituted by one or more substituents. In a fourth embodiment, Z represents C_{3-7} cycloalkyl(C_{1-6})alkyl, which group may be optionally substituted by one or more substituents. In a fifth embodiment, Z represents aryl, which group may be optionally substituted by one or more substituents. In a sixth embodiment, Z represents aryl(C_{1-6})-

alkyl, which group may be optionally substituted by one or more substituents. In a seventh embodiment, Z represents C_{3-7} heterocycloalkyl, which group may be optionally substituted by one or more substituents. In an eighth embodiment, Z represents C_{3-7} heterocycloalkyl(C_{1-6})alkyl, which group may be optionally substituted by one or more substituents. In a ninth embodiment, Z represents heteroaryl, which group may be optionally substituted by one or more substituents. In a tenth embodiment, Z represents heteroaryl(C_{1-6})alkyl, which group may be optionally substituted by one or more substituents.

Selected values of Z include hydrogen; and methyl, cyclopropyl, 1,2,3,4-tetrahydronaphthyl, cyclopentylethyl, phenyl, benzyl, phenylethyl, phenylpropyl, phenylbutyl, pyrrolidinyl, indolinyl, piperidinyl, 1,2,3,4-tetrahydroisoquinolinyl, piperazinylmethyl, morpholinylmethyl, piperazinylethyl, morpholinylethyl, thienyl, indolyl, pyrazolyl, indazolyl, imidazolyl, benzimidazolyl, imidazo[1,2-*a*]pyridinyl, pyridinyl, quinolinyl, isoquinolinyl, pyrazinyl, quinoxalinyl, thienylmethyl, pyridinylmethyl, furylethyl, indolylethyl, imidazolylethyl, benzimidazolylethyl or pyridinylethyl, any of which groups may be optionally substituted by one or more substituents.

Suitable values of Z include phenyl, indolinyl, thienyl and indolyl, any of which groups may be optionally substituted by one or more substituents.

In a particular embodiment, Z is other than hydrogen.

In one embodiment, Z is unsubstituted. In another embodiment, Z is substituted by one or more substituents, typically by one or two substituents. In one aspect of that embodiment, Z is monosubstituted. In another aspect of that embodiment, Z is disubstituted.

Typical examples of optional substituents on Z include one or more substituents independently selected from halogen, cyano, nitro, C_{1-6} alkyl, trifluoromethyl, aryl, (C_{1-6})alkyl(C_{3-7})heterocycloalkyl, (C_{3-7})heterocycloalkyl(C_{1-6})alkyl, hydroxy, hydroxy-(C_{1-6})alkyl, oxo, C_{1-6} alkoxy, difluoromethoxy, trifluoromethoxy, (C_{1-3})alkylenedioxy, (C_{1-6})alkoxyaryl, aryloxy, haloaryloxy, (C_{1-6})alkoxyaryloxy, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, amino, C_{1-6} alkylamino, di(C_{1-6})alkylamino, arylamino, C_{2-6} alkylcarbonylamino, C_{2-6} alkoxycarbonylamino, *N*-[(C_{2-6})alkoxycarbonyl]-*N*-[(C_{1-6})-alkyl]amino, C_{1-6} alkylsulfonylamino, formyl, C_{2-6} alkylcarbonyl, C_{3-6} cycloalkyl-carbonyl, C_{3-6} heterocycloalkylcarbonyl, carboxy, C_{2-6} alkoxycarbonyl, aminocarbonyl,

C_{1-6} alkylaminocarbonyl, di(C_{1-6})alkylaminocarbonyl, aminosulfonyl, C_{1-6} alkylaminosulfonyl and di(C_{1-6})alkylaminosulfonyl.

Suitable examples of optional substituents on Z include one or more substituents independently selected from halogen, cyano, C_{1-6} alkyl, C_{1-6} alkoxy, difluoromethoxy, C_{2-6} alkylcarbonyl and C_{2-6} alkoxycarbonyl.

Typical examples of specific substituents on Z include fluoro, chloro, bromo, iodo, cyano, nitro, methyl, isopropyl, trifluoromethyl, phenyl, methylpiperazinyl, piperidinylmethyl, morpholinylmethyl, hydroxy, hydroxymethyl, oxo, methoxy, ethoxy, difluoromethoxy, trifluoromethoxy, methylenedioxy, methoxyphenyl, phenoxy, chlorophenoxy, methoxyphenoxy, methylthio, methylsulfinyl, methylsulfonyl, amino, methylamino, *tert*-butylamino, dimethylamino, phenylamino, acetylamino, methoxycarbonylamino, *N*-(*tert*-butoxycarbonyl)-*N*-(methyl)amino, methylsulfonylamino, formyl, acetyl, cyclopropylcarbonyl, azetidinylcarbonyl, pyrrolidinylcarbonyl, piperidinylcarbonyl, piperazinylcarbonyl, morpholinylcarbonyl, carboxy, methoxycarbonyl, ethoxycarbonyl, *tert*-butoxycarbonyl, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, aminosulfonyl, methylaminosulfonyl and dimethylaminosulfonyl.

Suitable examples of specific substituents on Z include fluoro, iodo, cyano, methyl, methoxy, difluoromethoxy, acetyl and ethoxycarbonyl.

Assorted values of Z include hydrogen, methyl, phenoxymethyl, chlorophenoxymethyl, methoxyphenoxymethyl, dimethylaminomethyl, cyclopropyl, phenylcyclopropyl, methoxyphenylcyclopropyl, 1,2,3,4-tetrahydronaphthyl, cyclopentylethyl, phenyl, fluorophenyl, difluorophenyl, chlorophenyl, (fluoro)(iodo)phenyl, cyanophenyl, methylphenyl, isopropylphenyl, methylpiperazinylphenyl, piperidinylmethylphenyl, morpholinylmethylphenyl, methoxyphenyl, (chloro)(methoxy)phenyl, (methoxy)(methyl)phenyl, dimethoxyphenyl, ethoxyphenyl, difluoromethoxyphenyl, trifluoromethoxyphenyl, methylenedioxyphenyl, dimethylaminophenyl, acetylphenyl, ethoxycarbonylphenyl, benzyl, methylbenzyl, methoxybenzyl, dimethoxybenzyl, methylaminobenzyl, dimethylaminobenzyl, *N*-(*tert*-butoxycarbonyl)-*N*-(methyl)aminobenzyl, phenylethyl, fluorophenylethyl, methylphenylethyl, hydroxyphenylethyl, methoxyphenylethyl, (chloro)(methoxy)phenylethyl, phenylpropyl, phenylbutyl, methylpyrrolidinyl, methylindolinyl, *tert*-butoxycarbonylpiperidinyl, 1,2,3,4-tetrahydroisoquinolinyl, *tert*-butoxycarbonyl-1,2,3,4-tetrahydroisoquinolinyl, methylpiperazinylmethyl, morpholinylmethyl, methylpiperazinylethyl, morpholinylethyl, thienyl, indolyl, methylindolyl, pyrazolyl, methylpyrazolyl, indazolyl, methylimidazolyl, benzimidazolyl, imidazo[1,2-*a*]pyridinyl, pyridinyl, hydroxymethylpyridinyl, quinolinyl, isoquinolinyl, pyrazinyl, quinoxalinyl, thienylmethyl, pyridinylmethyl, furylethyl, indolylethyl, methylimidazolylethyl, benzimidazolylethyl and pyridinylethyl.

Particular values of Z include (fluoro)(iodo)phenyl, cyanophenyl, methylphenyl, methoxyphenyl, (methoxy)(methyl)phenyl, difluoromethoxyphenyl, acetylphenyl, ethoxycarbonylphenyl, methylindolinyl, thienyl and methylindolyl.

One selected value of Z is methoxyphenyl, especially 4-methoxyphenyl.

Another selected value of Z is (methoxy)(methyl)phenyl, especially 4-methoxy-2-methylphenyl.

Suitably, A represents hydrogen or trifluoromethyl; or A represents C_{1-6} alkyl, optionally substituted by $-OR^a$.

Appositely, A represents hydrogen; or A represents C_{1-6} alkyl, optionally substituted by $-OR^a$.

Illustrative values of A include hydrogen, methyl, hydroxymethyl and trifluoromethyl.

Selected values of A include hydrogen, methyl and hydroxymethyl.

In a particular embodiment, A represents hydrogen. In another embodiment, A represents trifluoromethyl. In a further embodiment, A represents C_{1-6} alkyl, optionally substituted by one or more substituents independently selected from halogen, $-OR^a$, $-S(O)R^a$ and $-NR^bR^c$. In a first aspect of that embodiment, A represents unsubstituted C_{1-6} alkyl, especially methyl. In a second aspect of that embodiment, A represents C_{1-6} alkyl monosubstituted by halogen, $-OR^a$, $-S(O)R^a$ or $-NR^bR^c$. In a third aspect of that embodiment, A represents C_{1-6} alkyl substituted by two substituents independently selected from halogen, $-OR^a$, $-S(O)R^a$ and $-NR^bR^c$. In a particular feature of the second aspect, A represents C_{1-6} alkyl monosubstituted by $-OR^a$, e.g. hydroxymethyl.

Generally, R^1 represents hydrogen, halogen, cyano, nitro, hydroxy, trifluoromethyl, trifluoromethoxy, $-OR^a$, $-SR^a$, $-SOR^a$, $-SO_2R^a$, $-NR^bR^c$, $-CH_2NR^bR^c$, $-NR^cCOR^d$, $-CH_2NR^cCOR^d$, $-NR^cCO_2R^d$, $-NHCONR^bR^c$, $-NR^cSO_2R^e$, $-N(SO_2R^e)_2$, $-NHSO_2NR^bR^c$, $-COR^d$, $-CO_2R^d$, $-CONR^bR^c$, $-CON(OR^a)R^b$ or $-SO_2NR^bR^c$; or R^1 represents C_{1-6} alkyl, aryl, aryl(C_{1-6})alkyl, heteroaryl or heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted by one or more substituents.

Suitably, R^1 represents hydrogen, halogen, cyano, nitro, hydroxy, trifluoromethyl, trifluoromethoxy, $-OR^a$, $-SO_2R^a$, $-NR^bR^c$, $-CH_2NR^bR^c$, $-NR^cCOR^d$, $-CH_2NR^cCOR^d$, $-NR^cCO_2R^d$, $-NHCONR^bR^c$, $-NR^cSO_2R^e$, $-NHSO_2NR^bR^c$, $-COR^d$, $-CO_2R^d$, $-CONR^bR^c$, $-CON(OR^a)R^b$ or $-SO_2NR^bR^c$; or R^1 represents C_{1-6} alkyl, aryl or heteroaryl, any of which groups may be optionally substituted by one or more substituents.

Typically, R^1 represents hydrogen, $-NR^bR^c$ or $-NR^cCOR^d$; or R^1 represents C_{1-6} alkyl, which group may be optionally substituted by one or more substituents.

Suitable values of R^1 include hydrogen and $-NR^bR^c$.

In one embodiment, R^1 represents hydrogen. In another embodiment, R^1 represents $-NR^bR^c$. In a further embodiment, R^1 represents $-NR^cCOR^d$. In an additional embodiment, R^1 represents optionally substituted C_{1-6} alkyl. In one aspect of that embodiment, R^1 represents optionally substituted methyl.

Examples of typical substituents on R^1 include one or more substituents independently selected from halogen, cyano, nitro, C_{1-6} alkyl, trifluoromethyl, aryl(C_{1-6})alkyl, hydroxy, C_{1-6} alkoxy, difluoromethoxy, trifluoromethoxy, aryloxy, C_{1-4} alkylenedioxy, C_{1-6} alkoxy(C_{1-6})alkyl, C_{1-6} alkylthio, C_{1-6} alkylsulphonyl, oxo, amino, C_{1-6} alkylamino, di(C_{1-6})alkylamino, C_{2-6} alkylcarbonylamino, C_{2-6} alkoxycarbonylamino, aryl(C_{1-6})alkoxycarbonylamino, C_{1-6} alkylaminocarbonylamino, arylaminocarbonylamino, C_{1-6} alkylsulphonylamino, formyl, C_{2-6} alkylcarbonyl, carboxy, C_{2-6} alkoxycarbonyl, aminocarbonyl, C_{1-6} alkylaminocarbonyl, di(C_{1-6})alkylaminocarbonyl, aminosulphonyl, C_{1-6} alkylaminosulphonyl and di(C_{1-6})alkylaminosulphonyl.

Specific examples of typical substituents on R^1 include one or more substituents independently selected from fluoro, chloro, bromo, cyano, nitro, methyl, ethyl, *tert*-butyl, trifluoromethyl, benzyl, hydroxy, methoxy, difluoromethoxy, trifluoromethoxy, phenoxy, methylenedioxy, ethylenedioxy, methoxymethyl, methylthio, methylsulphonyl, oxo, amino, methylamino, dimethylamino, acetylamino, methoxycarbonylamino, ethoxycarbonylamino, benzyloxycarbonylamino, ethylaminocarbonylamino, butylaminocarbonylamino, phenylaminocarbonylamino, methylsulphonylamino, formyl, acetyl, carboxy, methoxycarbonyl, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, aminosulphonyl, methylaminosulphonyl and dimethylaminosulphonyl.

Typical values of R^2 include hydrogen, methyl and ethyl. In one embodiment, R^2 is hydrogen. In another embodiment, R^2 is C_{1-6} alkyl, especially methyl.

Suitably, R^3 represents hydrogen; or R^3 represents C_{1-6} alkyl, C_{3-7} cycloalkyl or aryl, any of which groups may be optionally substituted by one or more substituents.

Examples of typical substituents on R^3 include halogen, cyano, nitro, C_{1-6} alkyl, trifluoromethyl, hydroxy, C_{1-6} alkoxy, difluoromethoxy, trifluoromethoxy, aryloxy, C_{1-6} alkylthio, C_{1-6} alkylsulphonyl, amino, C_{1-6} alkylamino, di(C_{1-6})alkylamino, C_{2-6} alkylcarbonylamino, C_{2-6} alkoxycarbonylamino, C_{1-6} alkylsulphonylamino, formyl, C_{2-6} alkylcarbonyl, carboxy, C_{2-6} alkoxycarbonyl, aminocarbonyl, C_{1-6} alkylaminocarbonyl, di(C_{1-6})alkylaminocarbonyl, aminosulphonyl, C_{1-6} alkylaminosulphonyl and di(C_{1-6})alkylaminosulphonyl; especially halogen, C_{1-6} alkoxy or C_{1-6} alkylthio.

Examples of particular substituents on R^3 include fluoro, chloro, bromo, cyano, nitro, methyl, trifluoromethyl, hydroxy, methoxy, difluoromethoxy, trifluoromethoxy, phenoxy, methylthio, methylsulphonyl, amino, methylamino, dimethylamino, acetylamino, methoxycarbonylamino, methylsulphonylamino, formyl, acetyl, carboxy, methoxycarbonyl, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, aminosulphonyl, methylaminosulphonyl and dimethylaminosulphonyl; especially chloro, methoxy or methylthio.

Typical values of R^3 include hydrogen, methyl, *n*-propyl, isopropyl, isobutyl, cyclohexyl and phenyl. Particular values of R^3 include hydrogen and methyl.

In one embodiment, R^3 is hydrogen. In another embodiment, R^3 is C_{1-6} alkyl, especially methyl.

Alternatively, R^2 and R^3 may together form an optionally substituted spiro linkage. Thus, R^2 and R^3, when taken together with the carbon atom to which they are both attached, may represent C_{3-7} cycloalkyl or C_{3-7} heterocycloalkyl, either of which groups may be unsubstituted, or substituted by one or more, typically by one or two, substituents. In this context, R^2 and R^3, when taken together with the carbon atom to which they are both attached, may suitably represent an optionally substituted cyclopentyl, cyclohexyl, pyrrolidine or piperidine ring.

Typical values of R^4 include hydrogen, methyl and ethyl. In one embodiment, R^4 is hydrogen. In another embodiment, R^4 is C_{1-6} alkyl, especially methyl.

Suitably, R^5 represents hydrogen; or R^5 represents C_{1-6} alkyl, C_{3-7} cycloalkyl or aryl, any of which groups may be optionally substituted by one or more substituents.

Examples of typical substituents on R^5 include halogen, cyano, nitro, C_{1-6} alkyl, trifluoromethyl, hydroxy, C_{1-6} alkoxy, difluoromethoxy, trifluoromethoxy, aryloxy, C_{1-6}

alkylthio, C_{1-6} alkylsulphonyl, amino, C_{1-6} alkylamino, di(C_{1-6})alkylamino, C_{2-6} alkylcarbonylamino, C_{2-6} alkoxycarbonylamino, C_{1-6} alkylsulphonylamino, formyl, C_{2-6} alkylcarbonyl, carboxy, C_{2-6} alkoxycarbonyl, aminocarbonyl, C_{1-6} alkylaminocarbonyl, di(C_{1-6})alkylaminocarbonyl, aminosulphonyl, C_{1-6} alkylaminosulphonyl and di(C_{1-6})alkylaminosulphonyl; especially halogen, C_{1-6} alkoxy or C_{1-6} alkylthio.

Examples of particular substituents on R^5 include fluoro, chloro, bromo, cyano, nitro, methyl, trifluoromethyl, hydroxy, methoxy, difluoromethoxy, trifluoromethoxy, phenoxy, methylthio, methylsulphonyl, amino, methylamino, dimethylamino, acetylamino, methoxycarbonylamino, methylsulphonylamino, formyl, acetyl, carboxy, methoxycarbonyl, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, aminosulphonyl, methylaminosulphonyl and dimethylaminosulphonyl; especially chloro, methoxy or methylthio.

Typical values of R^5 include hydrogen, methyl, *n*-propyl, isopropyl, isobutyl, cyclohexyl and phenyl. Particular values of R^5 include hydrogen and methyl.

In one embodiment, R^5 is hydrogen. In another embodiment, R^5 is C_{1-6} alkyl, especially methyl.

Alternatively, R^4 and R^5 may together form an optionally substituted spiro linkage. Thus, R^4 and R^5, when taken together with the carbon atom to which they are both attached, may represent C_{3-7} cycloalkyl or C_{3-7} heterocycloalkyl, either of which groups may be unsubstituted, or substituted by one or more, typically by one or two, substituents. In this context, R^4 and R^5, when taken together with the carbon atom to which they are both attached, may suitably represent an optionally substituted cyclopentyl, cyclohexyl, pyrrolidine or piperidine ring, typically an optionally substituted cyclopentyl ring.

Suitably, R^6 represents hydrogen or C_{1-6} alkyl.

Suitable values of R^6 include hydrogen and methyl.

In one embodiment, R^6 represents hydrogen. In another embodiment, R^6 represents C_{1-6} alkyl, optionally substituted by one or more substituents independently selected from $-OR^a$ and $-NR^bR^c$. In one aspect of that embodiment, R^6 represents unsubstituted C_{1-6} alkyl, especially methyl. In another aspect of that embodiment, R^6 represents C_{1-6} alkyl monosubstituted by $-OR^a$ or $-NR^bR^c$. In a further aspect of that embodiment, R^6 represents C_{1-6} alkyl substituted by two substituents independently selected from $-OR^a$ and $-NR^bR^c$.

Suitably, R^7 represents hydrogen or C_{1-6} alkyl.

Suitable values of R^7 include hydrogen and methyl.

In one embodiment, R^7 represents hydrogen. In another embodiment, R^7 represents C_{1-6} alkyl, optionally substituted by one or more substituents independently selected from $-OR^a$ and $-NR^bR^c$. In one aspect of that embodiment, R^7 represents unsubstituted C_{1-6} alkyl, especially methyl. In another aspect of that embodiment, R^7 represents C_{1-6} alkyl monosubstituted by $-OR^a$ or $-NR^bR^c$. In a further aspect of that embodiment, R^7 represents C_{1-6} alkyl substituted by two substituents independently selected from $-OR^a$ and $-NR^bR^c$.

Typical examples of suitable substituents on R^a, R^b, R^c, R^d or R^e, or on the heterocyclic moiety $-NR^bR^c$, include halogen, C_{1-6} alkyl, C_{1-6} alkoxy, difluoromethoxy, trifluoromethoxy, C_{1-6} alkoxy(C_{1-6})alkyl, C_{1-6} alkylthio, C_{1-6} alkylsulphinyl, C_{1-6} alkylsulphonyl, hydroxy, hydroxy(C_{1-6})alkyl, amino(C_{1-6})alkyl, cyano, trifluoromethyl, oxo, C_{2-6} alkylcarbonyl, carboxy, C_{2-6} alkoxycarbonyl, C_{2-6} alkylcarbonyloxy, amino, C_{1-6} alkylamino, di(C_{1-6})alkylamino, phenylamino, pyridinylamino, C_{2-6} alkylcarbonylamino, C_{2-6} alkylcarbonylamino(C_{1-6})alkyl, C_{2-6} alkoxycarbonylamino, C_{1-6} alkylsulphonylamino, aminocarbonyl, C_{1-6} alkylaminocarbonyl and di(C_{1-6})alkylaminocarbonyl.

Typical examples of specific substituents on R^a, R^b, R^c, R^d or R^e, or on the heterocyclic moiety $-NR^bR^c$, include fluoro, chloro, bromo, methyl, ethyl, isopropyl, methoxy, isopropoxy, difluoromethoxy, trifluoromethoxy, methoxymethyl, methylthio, ethylthio, methylsulphinyl, methylsulphonyl, hydroxy, hydroxymethyl, hydroxyethyl, aminomethyl, cyano, trifluoromethyl, oxo, acetyl, carboxy, methoxycarbonyl, ethoxycarbonyl, *tert*-butoxycarbonyl, acetoxy, amino, methylamino, ethylamino, dimethylamino, phenylamino, pyridinylamino, acetylamino, acetylaminomethyl, *tert*-butoxycarbonylamino, methylsulphonylamino, aminocarbonyl, methylaminocarbonyl and dimethylaminocarbonyl.

Illustratively, R^a represents hydrogen; or R^a represents C_{1-6} alkyl, aryl(C_{1-6})alkyl or heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted by one or more substituents.

Typically, R^a represents C_{1-6} alkyl, aryl, aryl(C_{1-6})alkyl, heteroaryl or heteroaryl-(C_{1-6})alkyl, any of which groups may be optionally substituted by one or more substituents.

Suitably, R^a represents C_{1-6} alkyl, aryl(C_{1-6})alkyl or heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted by one or more substituents.

Appositely, R^a represents hydrogen; or R^a represents C_{1-6} alkyl, which group may be optionally substituted by one or more substituents.

Particular values of R^a include hydrogen; and methyl, ethyl, benzyl and isoindolylpropyl, any of which groups may be optionally substituted by one or more substituents.

Selected values of R^a include methyl, ethyl, benzyl and isoindolylpropyl, any of which groups may be optionally substituted by one or more substituents.

Selected examples of suitable substituents on R^a include C_{1-6} alkoxy and oxo.

Selected examples of specific substituents on R^a include methoxy and oxo.

In one embodiment, R^a represents hydrogen. In another embodiment, R^a represents optionally substituted C_{1-6} alkyl. In one aspect of that embodiment, R^a ideally represents unsubstituted C_{1-6} alkyl, especially methyl. In another aspect of that embodiment, R^a ideally represents substituted C_{1-6} alkyl, e.g. methoxyethyl. In another embodiment, R^a represents optionally substituted aryl. In one aspect of that embodiment, R^a represents unsubstituted aryl, especially phenyl. In another aspect of that embodiment, R^a represents monosubstituted aryl, especially methylphenyl. In another embodiment, R^a represents optionally substituted aryl(C_{1-6})alkyl, ideally unsubstituted aryl(C_{1-6})alkyl, especially benzyl. In a further embodiment, R^a represents optionally substituted heteroaryl. In a further embodiment, R^a represents optionally substituted heteroaryl(C_{1-6})alkyl, e.g. dioxoisoindolylpropyl.

Specific values of R^a include methyl, methoxyethyl, benzyl and dioxoisoindolyl-propyl.

Generally, R^a represents hydrogen or C_{1-6} alkyl.

Individual values of R^a include hydrogen and methyl.

In a particular aspect, R^b represents hydrogen or trifluoromethyl; or R^b represents C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl(C_{1-6})alkyl, aryl, aryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl, heteroaryl or heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted by one or more substituents.

Selected values of R^b include hydrogen; and C_{1-6} alkyl, aryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl or C_{3-7} heterocycloalkyl(C_{1-6})alkyl, any of which groups may be optionally substituted by one or more substituents.

Appositely, R^b represents hydrogen; or R^b represents C_{1-6} alkyl, which group may be optionally substituted by one or more substituents.

Typical values of R^b include hydrogen and C_{1-6} alkyl.

Illustratively, R^b represents hydrogen or trifluoromethyl; or methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, 2-methylpropyl, *tert*-butyl, pentyl, hexyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, phenyl, benzyl, phenylethyl, azetidinyl, tetrahydrofuryl, tetrahydrothienyl, pyrrolidinyl, piperidinyl, homopiperidinyl, morpholinyl, azetidinylmethyl, tetrahydrofurylmethyl, pyrrolidinylmethyl, pyrrolidinylethyl, pyrrolidinylpropyl, thiazolidinylmethyl, imidazolidinylethyl, piperidinylmethyl, piperidinylethyl, tetrahydroquinolinylmethyl, piperazinylpropyl, morpholinylmethyl, morpholinylethyl, morpholinylpropyl, pyridinyl, indolylmethyl, pyrazolylmethyl, pyrazolylethyl, imidazolylmethyl, imidazolylethyl, benzimidazolylmethyl, triazolylmethyl, pyridinylmethyl or pyridinylethyl, any of which groups may be optionally substituted by one or more substituents.

Representative values of R^b include hydrogen; and methyl, ethyl, *n*-propyl, *tert*-butyl, benzyl, pyrrolidinyl or morpholinylpropyl, any of which groups may be optionally substituted by one or more substituents.

Selected examples of suitable substituents on R^b include C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylsulphinyl, C_{1-6} alkylsulphonyl, hydroxy, cyano, C_{2-6} alkoxycarbonyl, di-(C_{1-6})alkylamino and C_{2-6} alkoxycarbonylamino.

Selected examples of specific substituents on R^b include methoxy, methylthio, methylsulphinyl, methylsulphonyl, hydroxy, cyano, *tert*-butoxycarbonyl, dimethylamino and *tert*-butoxycarbonylamino.

A particular optional substituent on R^b is hydroxy.

Specific values of R^b include hydrogen, methyl, methoxyethyl, methylthioethyl, methylsulphinylethyl, methylsulphonylethyl, hydroxyethyl, cyanoethyl, dimethylaminoethyl, *tert*-butoxycarbonylaminoethyl, dihydroxypropyl, 1,1-dimethyl-2-hydroxyethyl, benzyl, pyrrolidinyl, *tert*-butoxycarbonylpyrrolidinyl and morpholinylpropyl.

In one embodiment, R^b represents hydrogen. In another embodiment, R^b represents C_{1-6} alkyl, especially methyl. In a further embodiment, R^b represents hydroxy(C_{1-6})alkyl, especially 1,1-dimethyl-2-hydroxyethyl.

Particular values of R^b include hydrogen, methyl and 1,1-dimethyl-2-hydroxyethyl.

Selected values of R^c include hydrogen; and C_{1-6} alkyl, C_{3-7} cycloalkyl or C_{3-7} heterocycloalkyl, any of which groups may be optionally substituted by one or more substituents.

In a particular aspect, R^c represents hydrogen, C_{1-6} alkyl or C_{3-7} cycloalkyl.

Representative values of R^c include hydrogen; and methyl, cyclobutyl, cyclopentyl, cyclohexyl, tetrahydropyranyl or piperidinyl, any of which groups may be optionally substituted by one or more substituents.

Selected examples of suitable substituents on R^c include C_{2-6} alkylcarbonyl and C_{2-6} alkoxycarbonyl.

Selected examples of specific substituents on R^c include acetyl and *tert*-butoxycarbonyl.

Specific values of R^c include hydrogen, methyl, cyclobutyl, cyclopentyl, cyclohexyl, tetrahydropyranyl, acetylpiperidinyl and *tert*-butoxycarbonylpiperidinyl.

Suitably, R^c represents hydrogen or C_{1-6} alkyl. In one embodiment, R^c is hydrogen. In another embodiment, R^c represents C_{1-6} alkyl, especially methyl or ethyl, particularly methyl. In a further embodiment, R^c represents C_{3-7} cycloalkyl, e.g. cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

Alternatively, the moiety $-NR^bR^c$ may suitably represent azetidin-1-yl, pyrrolidin-1-yl, oxazolidin-3-yl, isoxazolidin-2-yl, thiazolidin-3-yl, isothiazolidin-2-yl, piperidin-1-yl, morpholin-4-yl, thiomorpholin-4-yl, piperazin-1-yl, homopiperidin-1-yl, homomorpholin-4-yl or homopiperazin-1-yl, any of which groups may be optionally substituted by one or more substituents.

Selected examples of suitable substituents on the heterocyclic moiety $-NR^bR^c$ include C_{1-6} alkyl, C_{1-6} alkylsulphonyl, hydroxy, hydroxy(C_{1-6})alkyl, amino(C_{1-6})alkyl, cyano, oxo, C_{2-6} alkylcarbonyl, carboxy, C_{2-6} alkoxycarbonyl, amino, C_{2-6} alkylcarbonylamino, C_{2-6} alkylcarbonylamino(C_{1-6})alkyl, C_{2-6} alkoxycarbonylamino, C_{1-6} alkylsulphonylamino and aminocarbonyl.

Selected examples of specific substituents on the heterocyclic moiety $-NR^bR^c$ include methyl, methylsulphonyl, hydroxy, hydroxymethyl, aminomethyl, cyano, oxo, acetyl, carboxy, ethoxycarbonyl, amino, acetylamino, acetylaminomethyl, *tert*-butoxycarbonylamino, methylsulphonylamino and aminocarbonyl.

Specific values of the moiety $-NR^bR^c$ include azetidin-1-yl, hydroxyazetidin-1-yl, hydroxymethylazetidin-1-yl, (hydroxy)(hydroxymethyl)azetidin-1-yl, aminomethyl-azetidin-1-yl, cyanoazetidin-1-yl, carboxyazetidin-1-yl, aminoazetidin-1-yl, aminocarbonylazetidin-1-yl, pyrrolidin-1-yl, aminomethylpyrrolidin-1-yl, oxopyrrolidin-1-yl, acetylaminomethylpyrrolidin-1-yl, *tert*-butoxycarbonylaminopyrrolidin-1-yl, oxo-oxazolidin-3-yl, hydroxyisoxazolidin-2-yl, thiazolidin-3-yl, oxothiazolidin-3-yl, dioxo-isothiazolidin-2-yl, piperidin-1-yl, hydroxypiperidin-1-yl, hydroxymethylpiperidin-1-yl, aminopiperidin-1-yl, acetylaminopiperidin-1-yl, *tert*-butoxycarbonylaminopiperidin-1-yl, methylsulphonylaminopiperidin-1-yl, morpholin-4-yl, piperazin-1-yl, methylpiperazin-1-yl, methylsulphonylpiperazin-1-yl, oxopiperazin-1-yl, acetylpiperazin-1-yl, ethoxycarbonylpiperazin-1-yl and oxohomopiperazin-1-yl.

Suitably, R^d represents hydrogen; or C_{1-6} alkyl, aryl or heteroaryl, any of which groups may be optionally substituted by one or more substituents.

Selected examples of suitable values for R^d include hydrogen, methyl, ethyl, isopropyl, 2-methylpropyl, *tert*-butyl, cyclopropyl, cyclobutyl, phenyl, thiazolidinyl, thienyl, imidazolyl and thiazolyl, any of which groups may be optionally substituted by one or more substituents.

Selected examples of suitable substituents on R^d include halogen, C_{1-6} alkyl, C_{1-6} alkoxy, oxo, C_{2-6} alkylcarbonyloxy and di(C_{1-6})alkylamino.

Selected examples of particular substituents on R^d include fluoro, methyl, methoxy, oxo, acetoxy and dimethylamino.

In one embodiment, R^d represents hydrogen. In another embodiment, R^d represents optionally substituted C_{1-6} alkyl. In one aspect of that embodiment, R^d ideally represents unsubstituted C_{1-6} alkyl, e.g. methyl, ethyl, isopropyl, 2-methylpropyl or *tert*-butyl, especially methyl or ethyl. In another aspect of that embodiment, R^d ideally represents substituted C_{1-6} alkyl, e.g. substituted methyl or substituted ethyl, including acetoxymethyl, dimethylaminomethyl and trifluoroethyl. In another embodiment, R^d represents optionally substituted aryl. In one aspect of that embodiment, R^d represents unsubstituted aryl, especially phenyl. In another aspect of that embodiment, R^d represents monosubstituted aryl, especially methylphenyl. In a further aspect of that embodiment, R^d represents disubstituted aryl, e.g. dimethoxyphenyl. In a further embodiment, R^d represents optionally substituted heteroaryl, e.g. thienyl, chlorothienyl, methylthienyl, methylimidazolyl or thiazolyl. In another embodiment, R^d represents optionally substituted C_{3-7} cycloalkyl, e.g. cyclopropyl or cyclobutyl. In a further embodiment, R^d

represents optionally substituted C_{3-7} heterocycloalkyl, e.g. thiazolidinyl or oxo-thiazolidinyl.

Selected examples of specific values for R^d include hydrogen, methyl, ethyl, acetoxymethyl, dimethylaminomethyl, ethyl, trifluoroethyl, isopropyl, 2-methylpropyl, *tert*-butyl, cyclopropyl, cyclobutyl, phenyl, dimethoxyphenyl, thiazolidinyl, oxothiazolidinyl, thienyl, chlorothienyl, methylthienyl, methylimidazolyl and thiazolyl.

Generally, R^d represents hydrogen or C_{1-6} alkyl.

Apposite values of R^d include hydrogen and ethyl.

A particular value of R^d is ethyl.

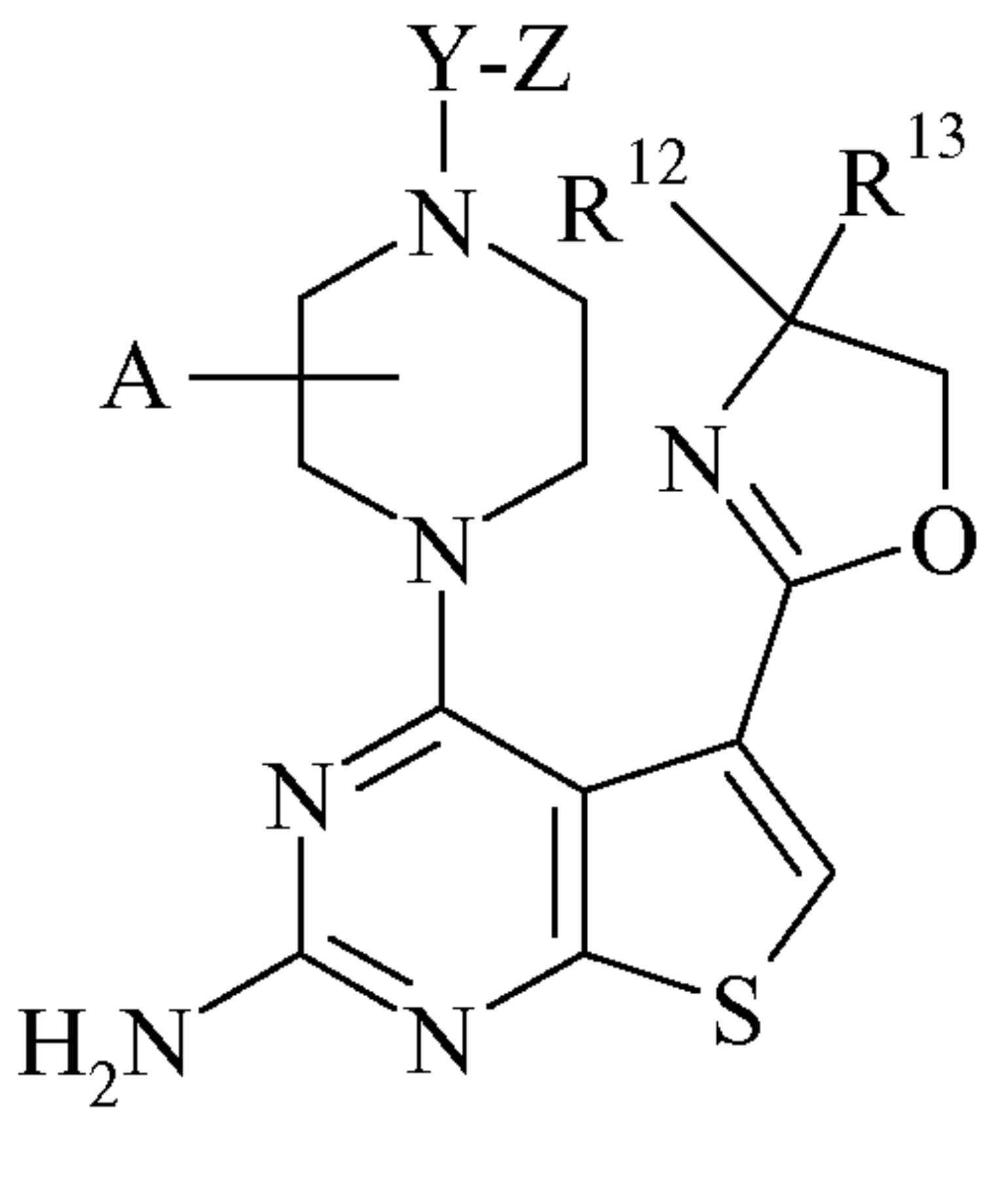
Suitably, R^e represents C_{1-6} alkyl or aryl, either of which groups may be optionally substituted by one or more substituents.

Selected examples of suitable substituents on R^e include C_{1-6} alkyl, especially methyl.

In one embodiment, R^e represents optionally substituted C_{1-6} alkyl, ideally unsubstituted C_{1-6} alkyl, e.g. methyl or propyl, especially methyl. In another embodiment, R^e represents optionally substituted aryl. In one aspect of that embodiment, R^e represents unsubstituted aryl, especially phenyl. In another aspect of that embodiment, R^e represents monosubstituted aryl, especially methylphenyl. In a further embodiment, R^e represents optionally substituted heteroaryl.

Selected values of R^e include methyl, propyl and methylphenyl.

One sub-class of compounds according to the invention is represented by the compounds of formula (IIA), and pharmaceutically acceptable salts and solvates thereof:



(IIA)

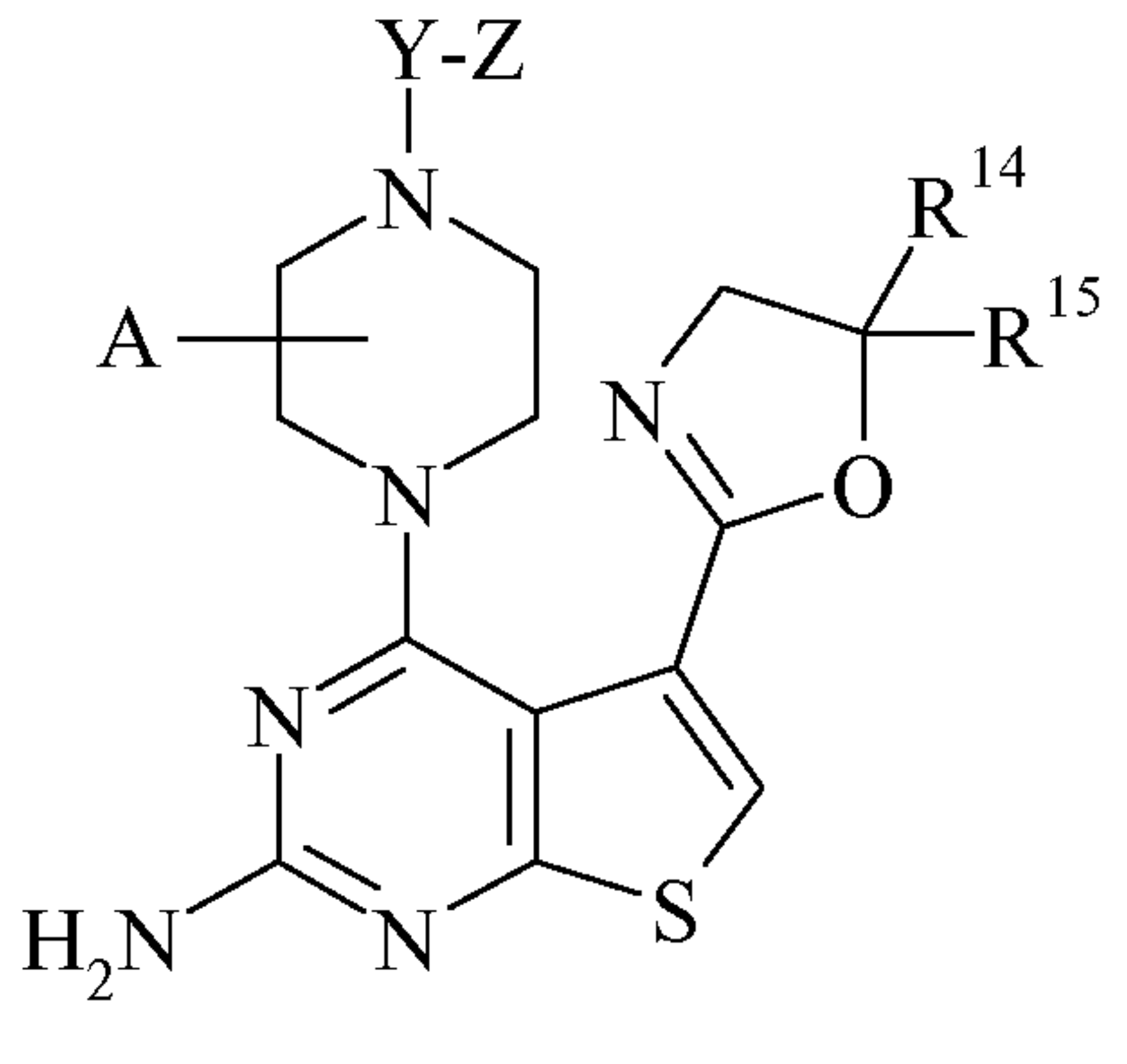
wherein Y, Z and A are as defined above; and

R^{12} and R^{13} independently represent hydrogen or C_{1-6} alkyl.

In one embodiment, R^{12} represents hydrogen. In another embodiment, R^{12} represents C_{1-6} alkyl. In one aspect of that embodiment, R^{12} represents methyl.

In one embodiment, R^{13} represents hydrogen. In another embodiment, R^{13} represents C_{1-6} alkyl. In one aspect of that embodiment, R^{13} represents methyl.

Another sub-class of compounds according to the invention is represented by the compounds of formula (IIB), and pharmaceutically acceptable salts and solvates thereof:



(IIB)

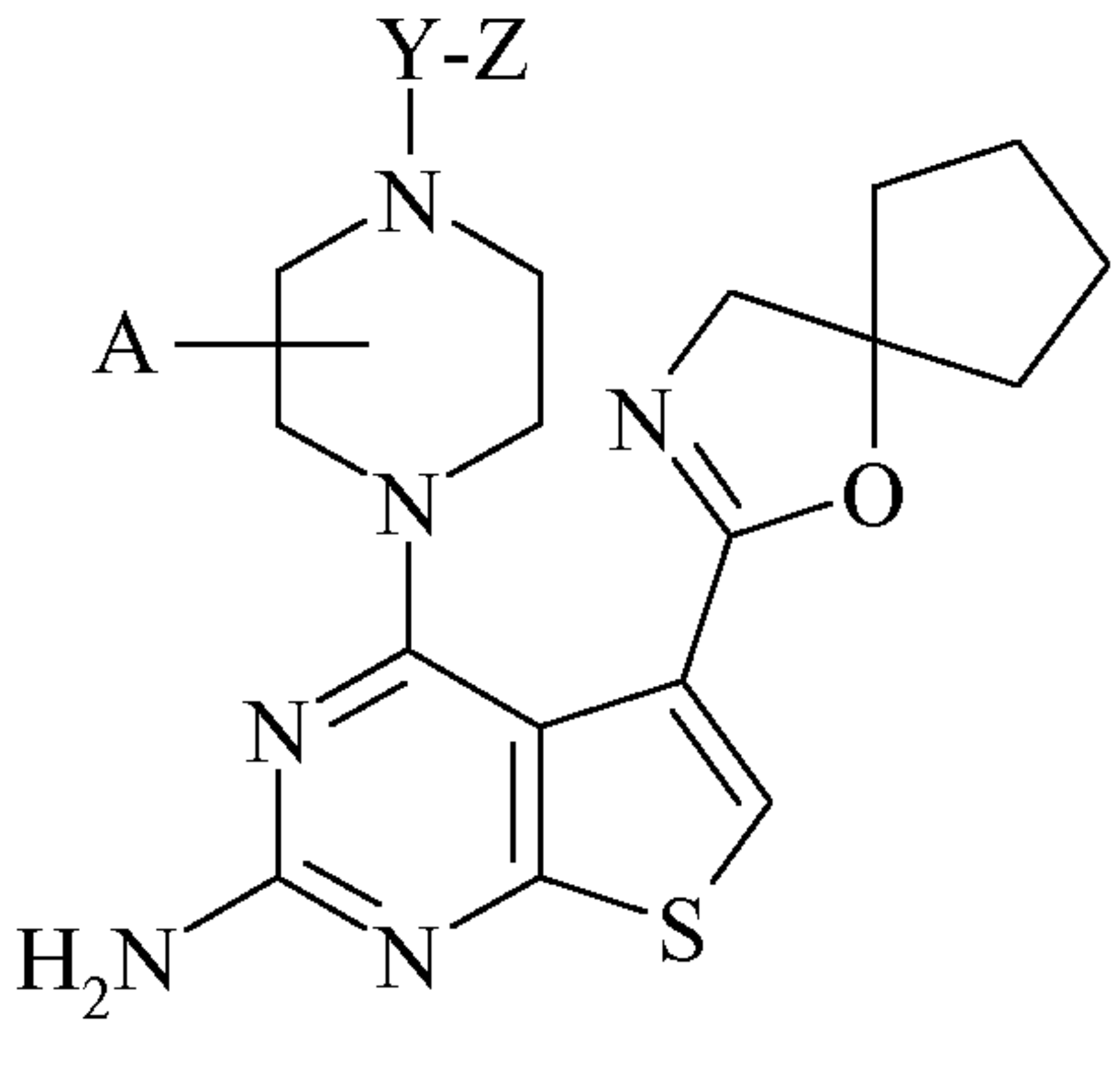
wherein Y, Z and A are as defined above; and

R^{14} and R^{15} independently represent hydrogen or C_{1-6} alkyl.

In one embodiment, R^{14} represents hydrogen. In another embodiment, R^{14} represents C_{1-6} alkyl. In one aspect of that embodiment, R^{14} represents methyl. In another aspect of that embodiment, R^{14} represents isopropyl.

In one embodiment, R^{15} represents hydrogen. In another embodiment, R^{15} represents C_{1-6} alkyl. In one aspect of that embodiment, R^{15} represents methyl.

Another sub-class of compounds according to the invention is represented by the compounds of formula (IIC), and pharmaceutically acceptable salts and solvates thereof:



(IIC)

wherein Y, Z and A are as defined above.

Specific novel compounds in accordance with the present invention include each of the compounds whose preparation is described in the accompanying Examples, and pharmaceutically acceptable salts and solvates thereof.

The compounds in accordance with the present invention are beneficial in the treatment and/or prevention of various human ailments. These include inflammatory, autoimmune and oncological disorders; viral diseases; and organ and cell transplant rejection.

Inflammatory and autoimmune disorders include systemic autoimmune disorders, autoimmune endocrine disorders and organ-specific autoimmune disorders. Systemic autoimmune disorders include systemic lupus erythematosus (SLE), psoriasis, vasculitis, polymyositis, scleroderma, multiple sclerosis, ankylosing spondylitis, rheumatoid arthritis and Sjögren’s syndrome. Autoimmune endocrine disorders include thyroiditis. Organ-specific autoimmune disorders include Addison’s disease, haemolytic or pernicious anaemia, glomerulonephritis (including Goodpasture’s syndrome), Graves’ disease, idiopathic thrombocytopenic purpura, insulin-dependent diabetes mellitus, juvenile diabetes, uveitis, inflammatory bowel disease (including Crohn’s disease and ulcerative colitis), pemphigus, atopic dermatitis, autoimmune hepatitis, primary biliary cirrhosis, autoimmune pneumonitis, autoimmune carditis, myasthenia gravis and spontaneous infertility.

Oncological disorders, which may be acute or chronic, include proliferative disorders, especially cancer, in animals, including mammals, especially humans. Particular categories of cancer include haematological malignancy (including leukaemia and lymphoma) and non-haematological malignancy (including solid tumour cancer, sarcoma, meningioma, glioblastoma multiforme, neuroblastoma, melanoma, gastric carcinoma and renal cell carcinoma). Chronic leukaemia may be myeloid or lymphoid. Varieties of leukaemia include lymphoblastic T cell leukaemia, chronic myelogenous leukaemia (CML), chronic lymphocytic/lymphoid leukaemia (CLL), hairy-cell leukaemia, acute lymphoblastic leukaemia (ALL), acute myelogenous leukaemia (AML), myelodysplastic syndrome, chronic neutrophilic leukaemia, acute lymphoblastic T cell leukaemia, plasmacytoma, immunoblastic large cell leukaemia, mantle cell leukaemia, multiple myeloma, acute megakaryoblastic leukaemia, acute megakaryocytic leukaemia, promyelocytic leukaemia and erythroleukaemia. Varieties of lymphoma include malignant lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, lymphoblastic T cell lymphoma, Burkitt's lymphoma, follicular lymphoma, MALT1 lymphoma and marginal zone lymphoma. Varieties of non-haematological malignancy include cancer of the prostate, lung, breast, rectum, colon, lymph node, bladder, kidney, pancreas, liver, ovary, uterus, cervix, brain, skin, bone, stomach and muscle.

Viral diseases include infections caused by various families of virus, including the *Retroviridae*, *Flaviviridae*, *Picornaviridae*. Various genera within the *Retroviridae* family include *Alpharetrovirus*, *Betaretrovirus*, *Gammaretrovirus*, *Deltaretrovirus*, *Epsilonretrovirus*, *Lentivirus* and *Spumavirus*. Members of the *Lentivirus* genus include human immunodeficiency virus 1 (HIV-1) and human immunodeficiency virus 2 (HIV-2). Various genera within the *Flaviviridae* family include *Flavivirus*, *Pestivirus*, *Hepacivirus* and *Hepatitis G Virus*. Members of the *Flavivirus* genus include Dengue fever virus, yellow fever virus, West Nile encephalitis virus and Japanese encephalitis virus. Members of the *Pestivirus* genus include bovine viral diarrhoea virus (BVDV), classical swine fever virus and border disease virus 2 (BDV-2). Members of the *Hepacivirus* genus include hepatitis C virus (HCV). Members of the *Hepatitis G Virus* genus include hepatitis G virus. Various genera within the *Picornaviridae* family include *Aphthovirus*, *Avihepatovirus*, *Cardiovirus*, *Enterovirus*, *Erbovirus*, *Hepatovirus*, *Kobuvirus*, *Parechovirus*, *Sapelovirus*, *Senecavirus*, *Teschovirus* and *Tremovirus*. Members of the *Enterovirus* genus include poliovirus, coxsackie A virus, coxsackie B virus and rhinovirus.

Organ transplant rejection includes the rejection of transplanted or grafted organs or cells (both allografts and xenografts), including graft-versus-host reaction disease. The term "organ" as used herein means all organs or parts of organs in mammals, particularly humans, including kidney, lung, bone marrow, hair, cornea, eye (vitreous), heart, heart valve, liver, pancreas, blood vessel, skin, muscle, bone, intestine and stomach. The term "rejection" as used herein means all reactions of the recipient body or the transplanted organ which ultimately lead to cell or tissue death in the transplanted organ, or adversely affect the functional ability and viability of the transplanted organ or the recipient. In particular, this means acute and chronic rejection reactions.

Cell transplant rejection includes the rejection of cell transplants and xeno-transplantation. The major hurdle for xenotransplantation is that even before the T lymphocytes (responsible for the rejection of allografts) are activated, the innate immune system (especially T-independent B lymphocytes and macrophages) is activated. This provokes two types of severe and early acute rejection, referred to as hyperacute rejection and vascular rejection respectively. Conventional immunosuppressant drugs, including cyclosporine A, are ineffective in xenotransplantation. The compounds in accordance with the present invention are not liable to this drawback. The ability of the compounds of this invention to suppress T-independent xeno-antibody production as well as macrophage activation may be demonstrated by their ability to prevent xenograft rejection in athymic, T-deficient mice receiving xenogenic hamster-heart grafts.

The present invention also provides a pharmaceutical composition which comprises a compound in accordance with the invention as described above, or a pharmaceutically acceptable salt or solvate thereof, in association with one or more pharmaceutically acceptable carriers.

Pharmaceutical compositions according to the invention may take a form suitable for oral, buccal, parenteral, nasal, topical, ophthalmic or rectal administration, or a form suitable for administration by inhalation or insufflation.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets, lozenges or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methyl cellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogenphosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents, emulsifying agents, non-aqueous vehicles or preservatives. The preparations may also contain buffer salts, flavouring agents, colouring agents or sweetening agents, as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

For buccal administration, the compositions may take the form of tablets or lozenges formulated in conventional manner.

The compounds of formula (I) may be formulated for parenteral administration by injection, e.g. by bolus injection or infusion. Formulations for injection may be presented in unit dosage form, e.g. in glass ampoules or multi-dose containers, e.g. glass vials. The compositions for injection may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising, preserving and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

In addition to the formulations described above, the compounds of formula (I) may also be formulated as a depot preparation. Such long-acting formulations may be administered by implantation or by intramuscular injection.

For nasal administration or administration by inhalation, the compounds according to the present invention may be conveniently delivered in the form of an aerosol spray presentation for pressurised packs or a nebuliser, with the use of a suitable propellant, e.g. dichlorodifluoromethane, fluorotrichloromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas or mixture of gases.

The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack or dispensing device may be accompanied by instructions for administration.

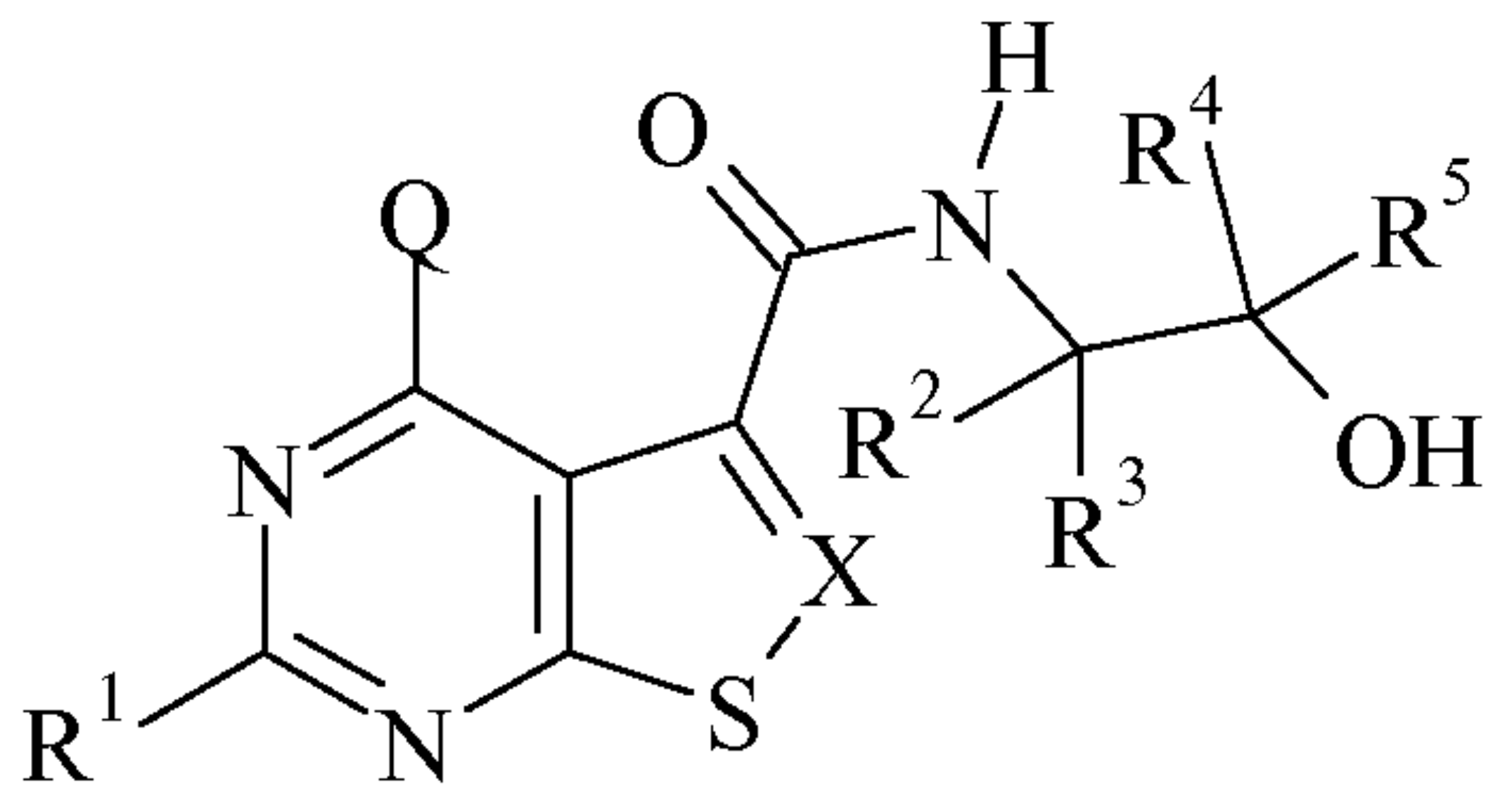
For topical administration the compounds of use in the present invention may be conveniently formulated in a suitable ointment containing the active component suspended or dissolved in one or more pharmaceutically acceptable carriers. Particular carriers include, for example, mineral oil, liquid petroleum, propylene glycol, polyoxyethylene, polyoxypropylene, emulsifying wax and water. Alternatively, the compounds of use in the present invention may be formulated in a suitable lotion containing the active component suspended or dissolved in one or more pharmaceutically acceptable carriers. Particular carriers include, for example, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, benzyl alcohol, 2-octyldodecanol and water.

For ophthalmic administration the compounds of use in the present invention may be conveniently formulated as micronized suspensions in isotonic, pH-adjusted sterile saline, either with or without a preservative such as a bactericidal or fungicidal agent, for example phenylmercuric nitrate, benzylalkonium chloride or chlorhexidine acetate. Alternatively, for ophthalmic administration compounds may be formulated in an ointment such as petrolatum.

For rectal administration the compounds of use in the present invention may be conveniently formulated as suppositories. These can be prepared by mixing the active component with a suitable non-irritating excipient which is solid at room temperature but liquid at rectal temperature and so will melt in the rectum to release the active component. Such materials include, for example, cocoa butter, beeswax and polyethylene glycols.

The quantity of a compound of use in the invention required for the prophylaxis or treatment of a particular condition will vary depending on the compound chosen and the condition of the patient to be treated. In general, however, daily dosages may range from around 10 ng/kg to 1000 mg/kg, typically from 100 ng/kg to 100 mg/kg, e.g. around 0.01 mg/kg to 40 mg/kg body weight, for oral or buccal administration, from around 10 ng/kg to 50 mg/kg body weight for parenteral administration, and from around 0.05 mg to around 1000 mg, e.g. from around 0.5 mg to around 1000 mg, for nasal administration or administration by inhalation or insufflation.

The compounds of formula (I) above may be prepared by a process which comprises cyclising a compound of formula (III):



(III)

wherein Q, X, R^1, R^2, R^3, R^4 and R^5 are as defined above.

The cyclisation may be effected by treating compound (III) with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) and triphenylphosphine, in which case the reaction is conveniently performed at ambient temperature in a suitable solvent or mixture of solvents. Such solvent or solvents may typically be selected as appropriate from a chlorinated solvent such as dichloromethane, and a dipolar aprotic solvent such as *N*,*N*-dimethylformamide.

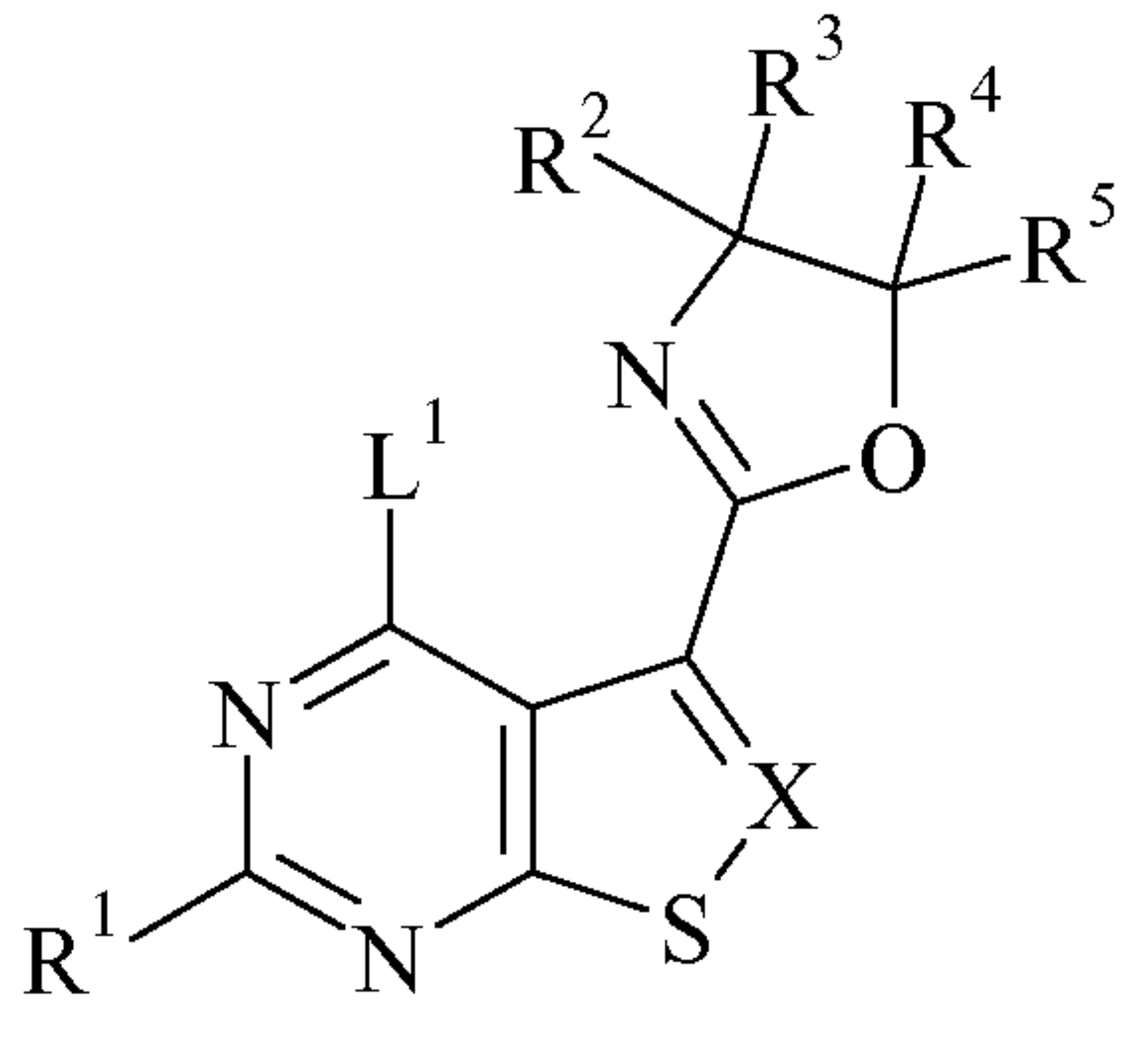
Alternatively, the cyclisation may be effected by treating compound (III) with (methoxycarbonylsulfamoyl)triethylammonium hydroxide (Burgess reagent), in which case the reaction is conveniently performed at ambient temperature in a suitable solvent, e.g. a dipolar aprotic solvent such as *N*,*N*-dimethylformamide.

Alternatively, the cyclisation may be effected by a two-step procedure which comprises: (i) reacting compound (III) with a halogenating agent; and (ii) reacting the material thereby obtained with a base.

The halogenating agent of use in step (i) of the above procedure may suitably be thionyl chloride, in which case the process is conveniently effected at an elevated temperature. Alternatively, the halogenating agent may suitably be (diethylamino)sulfur trifluoride (DAST), in which case the process is conveniently effected at a temperature in the region of -78°C. Step (i) may be conveniently performed in a suitable solvent, typically a chlorinated solvent such as dichloromethane.

The base of use in step (ii) of the above procedure may suitably be an alkali metal hydroxide, e.g. sodium hyroxide, in which case the process is conveniently effected at an elevated temperature in a suitable solvent, typically a C_{1-4} alkanol such as methanol. Alternatively, the base may suitably be an alkali metal carbonate, e.g. potassium carbonate, in which case the process is conveniently effected at ambient temperature in a suitable solvent, typically a chlorinated solvent such as dichloromethane.

Alternatively, the compounds of formula (I) above may be prepared by a process which comprises reacting a compound of formula Q-H with a compound of formula (IV):



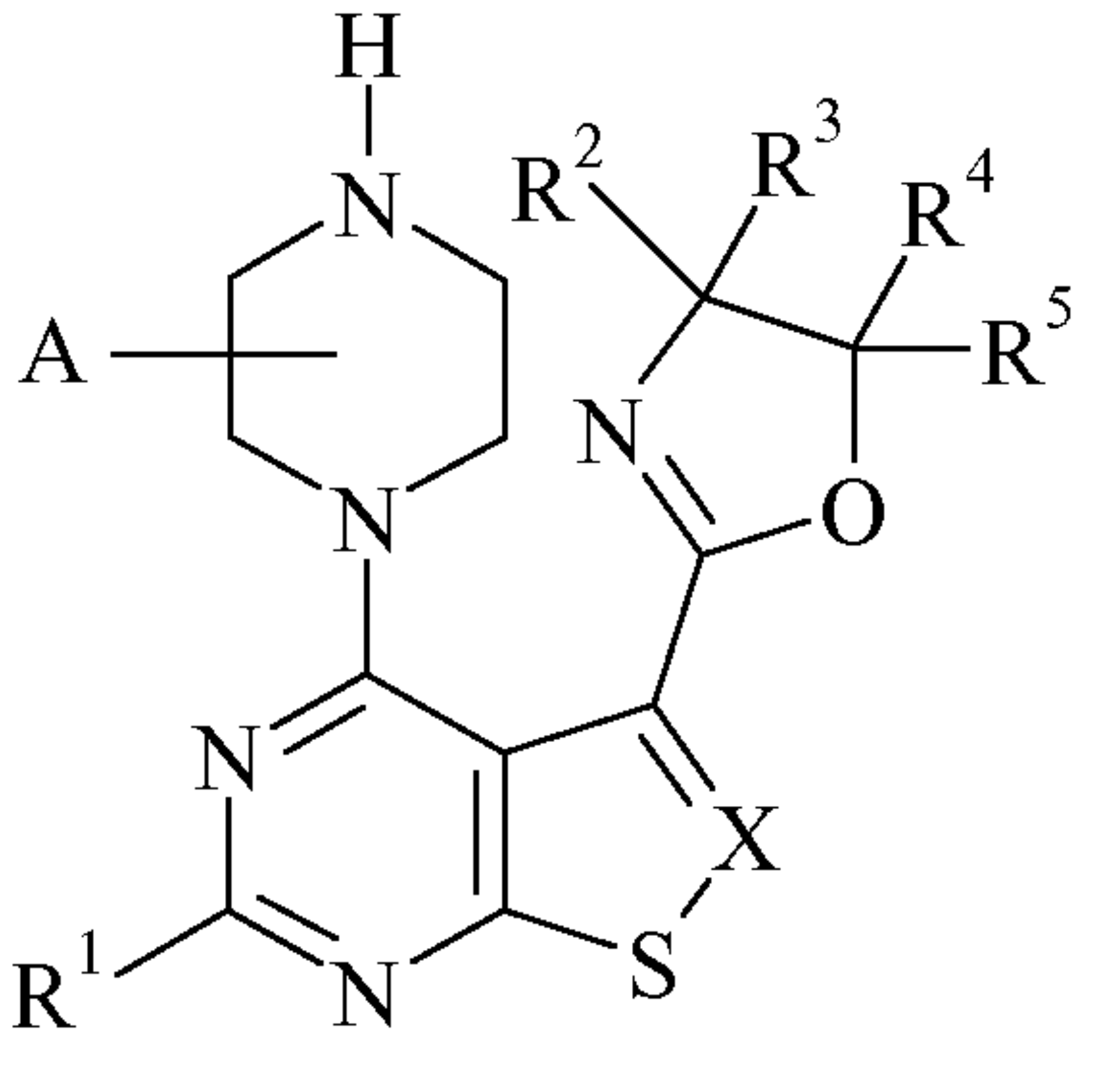
(IV)

wherein Q, X, R^1, R^2, R^3, R^4 and R^5 are as defined above, and L^1 represents a suitable leaving group.

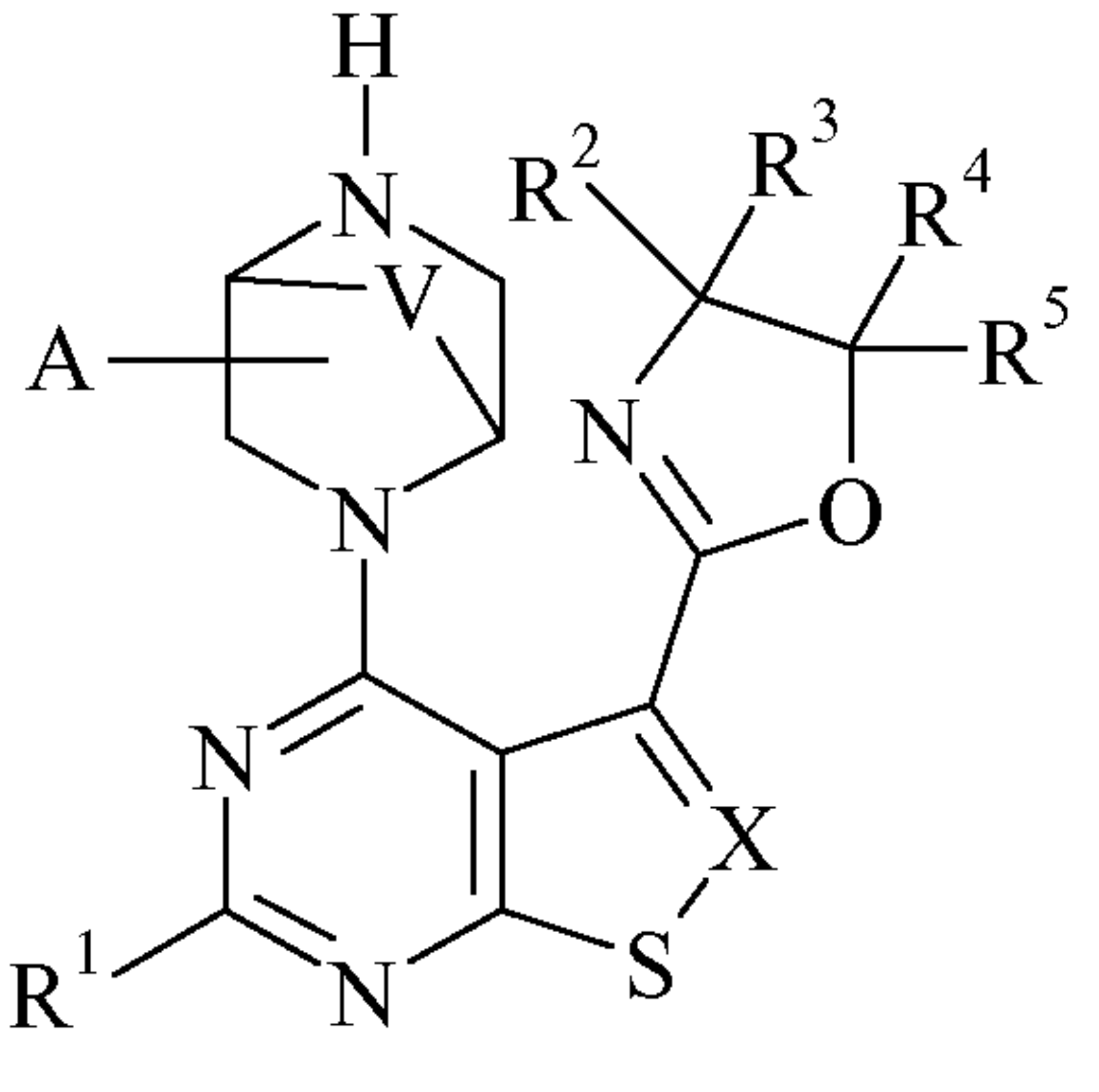
The leaving group L^1 is typically a halogen atom, e.g. chloro.

The reaction is conveniently effected at ambient temperature in a suitable solvent, e.g. a chlorinated solvent such as dichloromethane.

In an alternative procedure, the compounds of formula (I) above wherein Y represents -C(O)-, -S(O)$_2$- or -C(O)O- may be prepared by a process which comprises reacting a compound of formula L^2-C(O)-Z, L^2-S(O)$_2$-Z or L^2-C(O)O-Z respectively with a compound of formula (VA) or (VB):



(VA)



(VB)

wherein V, X, Z, A, R^1, R^2, R^3, R^4 and R^5 are as defined above, and L^2 represents a suitable leaving group.

The leaving group L^2 is typically a halogen atom, e.g. chloro.

The reaction is conveniently effected at ambient temperature in a suitable solvent, e.g. an ethereal solvent such as 1,4-dioxane, typically in the presence of a base. A suitable base for use in the reaction may be an organic base such as *N*,*N*-diisopropylethylamine, or an inorganic base such as potassium carbonate.

Alternatively, the leaving group L^2 may be 2-methyl-3-(trifluoromethylsulfonyl)-1*H*-imidazol-3-ium-1-yl, in which case the reaction may conveniently be effected at ambient temperature in an organic solvent such as acetonitrile.

In a variant procedure, the compounds of formula (I) above wherein Y represents -C(O)- may be prepared by a process which comprises reacting a compound of formula (VA) or (VB) as defined above with a compound of formula $Z\text{-}CO_2H$.

The reaction is conveniently effected at ambient temperature in a suitable solvent, e.g. a dipolar aprotic solvent such as *N*,*N*-dimethylformamide, typically in the presence of a coupling agent and a base. A suitable coupling agent for use in the reaction may be *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N'*,*N'*-tetramethyluronium hexafluorophosphate (HATU). A suitable base for use in the reaction may be an organic base such as *N*,*N*-diisopropylethylamine.

In another procedure, the compounds of formula (I) above wherein Y represents -C(O)NH- may be prepared by a process which comprises reacting a compound of formula (VA) or (VB) as defined above with an isocyanate derivative of formula Z-N=C=O, wherein Z is as defined above.

The reaction is conveniently effected at ambient temperature in a suitable solvent or mixture of solvents. Such solvent or solvents may typically be selected as appropriate from an ethereal solvent such as 1,4-dioxane or tetrahydrofuran, a chlorinated solvent such as dichloromethane, a nitrile-containing solvent such as acetonitrile, and a dipolar aprotic solvent such as *N*,*N*-dimethylformamide. The reaction may optionally be performed in the presence of a base, e.g. an organic base such as diisopropylamine, *N*,*N*-diisopropylethylamine or triethylamine.

In a further procedure, the compounds of formula (I) above wherein Y represents $-S(O)_2NH-$ may be prepared by a two-step process which comprises: (i) reacting a compound of formula (VA) or (VB) as defined above with methyl trifluoromethanesulfonate; and (ii) reacting the material thereby obtained with a compound of formula $Z\text{-}NH_2$, wherein Z is as defined above.

Step (i) of the above process is conveniently effected at a temperature in the region of 0°C in a suitable solvent, typically a chlorinated solvent such as dichloromethane. Step

(ii) is conveniently effected at an elevated temperature in a suitable solvent, e.g. a nitrile-containing solvent such as acetonitrile.

In a further procedure, the compounds of formula (I) above wherein Y represents a covalent bond, and Z represents optionally substituted C_{1-6} alkyl, optionally substituted C_{3-7} cycloalkyl(C_{1-6})alkyl, optionally substituted aryl(C_{1-6})alkyl, optionally substituted C_{3-7} heterocycloalkyl(C_{1-6})alkyl or optionally substituted heteroaryl(C_{1-6})alkyl, may be prepared by a process which comprises reacting a compound of formula (VA) or (VB) as defined above with a compound of formula Z^1-L^3 wherein Z^1 represents C_{1-6} alkyl, C_{3-7} cycloalkyl(C_{1-6})alkyl, aryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl or heteroaryl(C_{1-6})-alkyl, any of which groups may be optionally substituted by one or more substituents, and L^3 represents a suitable leaving group.

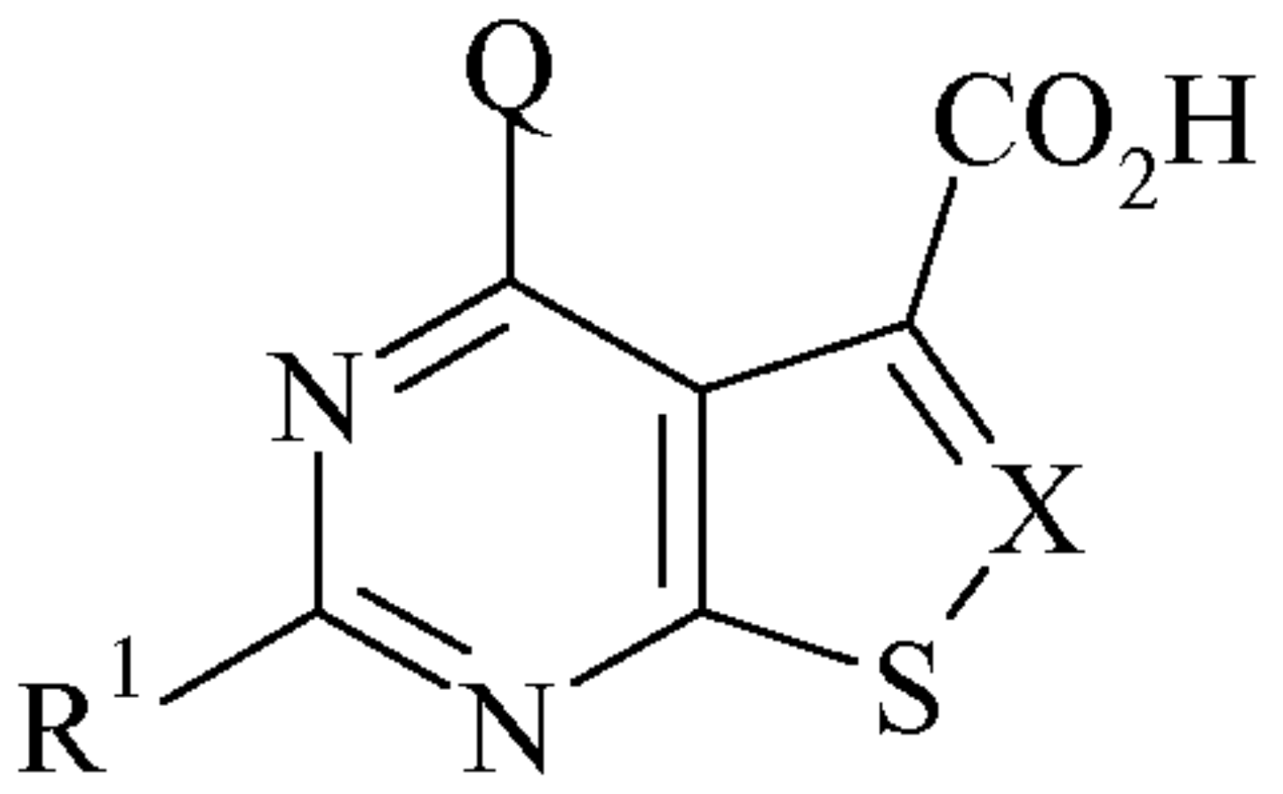
The leaving group L^3 is typically a halogen atom.

The reaction is conveniently effected at ambient temperature in a suitable solvent, e.g. a dipolar aprotic solvent such as *N*,*N*-dimethylformamide, or a chlorinated solvent such as dichloromethane, typically in the presence of a base. A suitable base for use in the reaction may be an organic base such as triethylamine, or an inorganic base such as caesium carbonate.

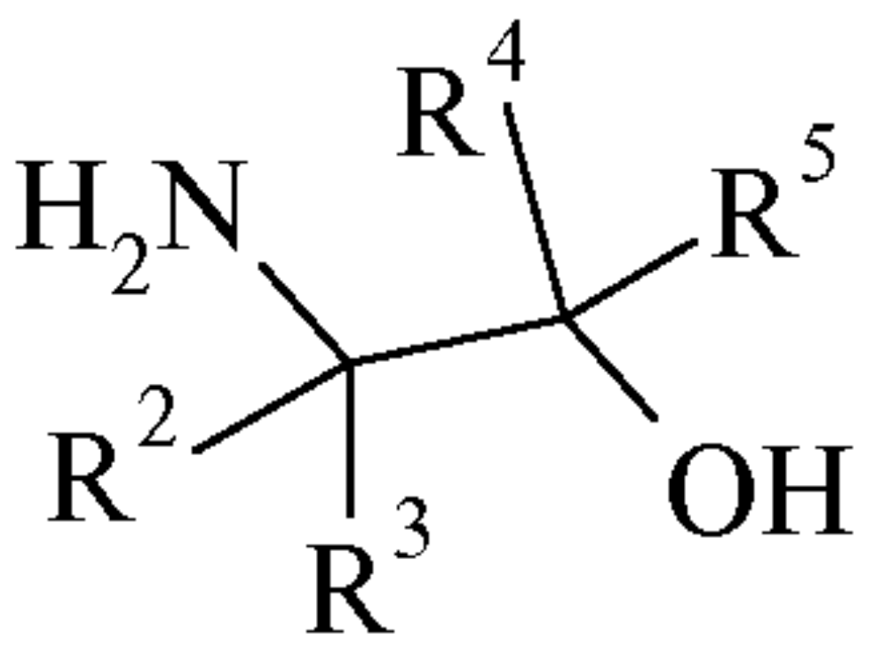
In a variant procedure, the compounds of formula (I) above wherein Y represents a covalent bond, and Z represents optionally substituted C_{1-6} alkyl, optionally substituted C_{3-7} cycloalkyl(C_{1-6})alkyl, optionally substituted aryl(C_{1-6})alkyl, optionally substituted C_{3-7} heterocycloalkyl(C_{1-6})alkyl or optionally substituted heteroaryl(C_{1-6})alkyl, may be prepared by a two-step process which comprises: (i) reacting a compound of formula (VA) or (VB) as defined above with a compound of formula Z^2-CHO, wherein Z^2-CH_2- corresponds to a group of formula Z^1- as defined above; and (ii) reacting the material thereby obtained with a reducing agent.

Steps (i) and (ii) of the above process are conveniently effected at ambient temperature in a suitable solvent, e.g. a C_{1-4} alkanol such as methanol. Step (i) is typically performed in the presence of a base, e.g. an organic base such as triethylamine. The reducing agent for use in step (ii) may suitably be an alkali metal borohydride such as sodium borohydride.

The intermediates of formula (III) above may be prepared by reacting a compound of formula (VI) with a compound of formula (VII):



(VI)

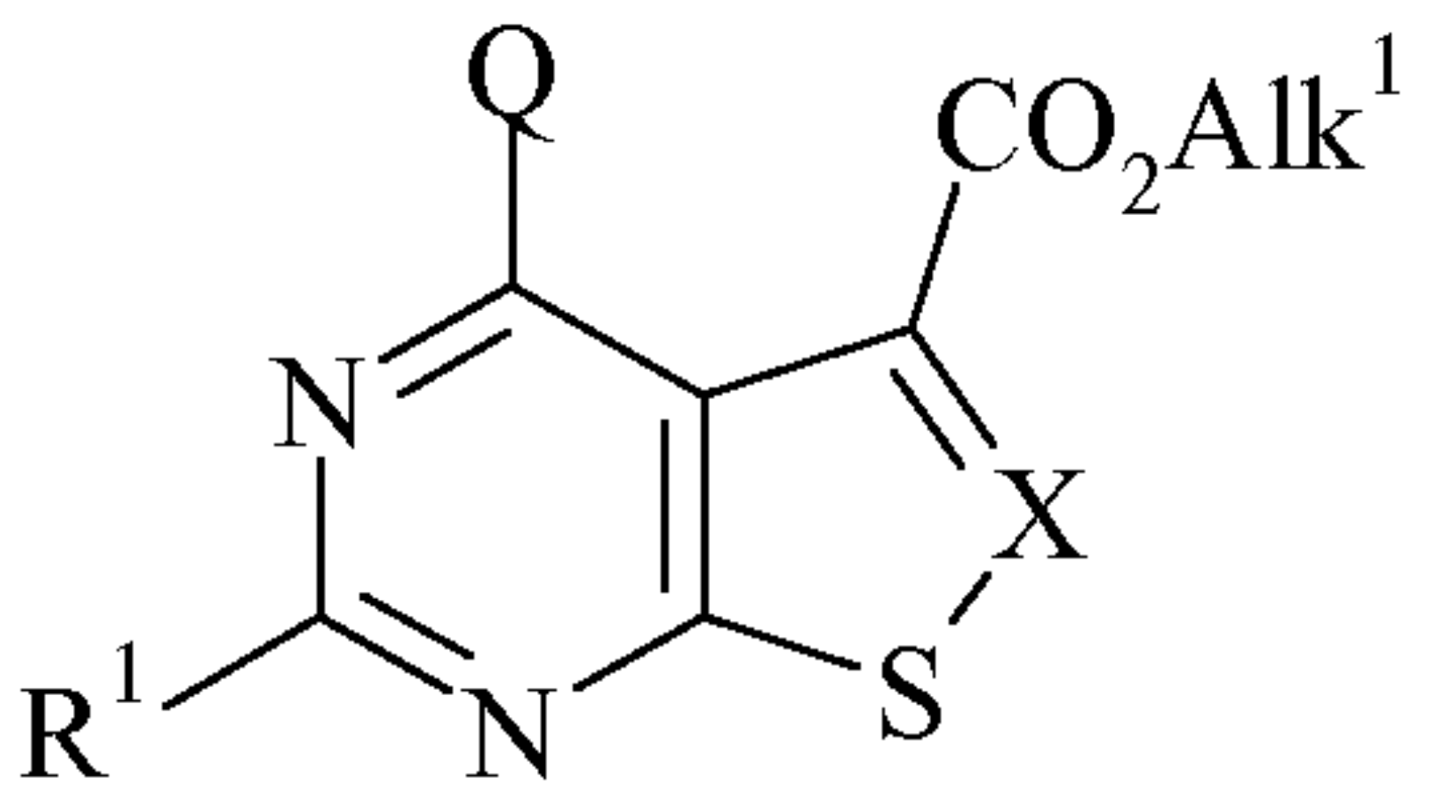


(VII)

wherein Q, X, R^1, R^2, R^3, R^4 and R^5 are as defined above.

The reaction is conveniently effected at ambient temperature in a suitable solvent, e.g. a dipolar aprotic solvent such as *N*,*N*-dimethylformamide, typically in the presence of a coupling agent and a base. A suitable coupling agent for use in the reaction may be HATU. Alternatively, the coupling agent may be 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC), in which case it will be conveniently utilised in the presence of an additive such as 1-hydroxybenzotriazole hydrate (HOBT). A suitable base for use in the reaction may be an organic base such as *N*,*N*-diisopropylethylamine.

The intermediates of formula (VI) above may be prepared by reacting a compound of formula (VIII):

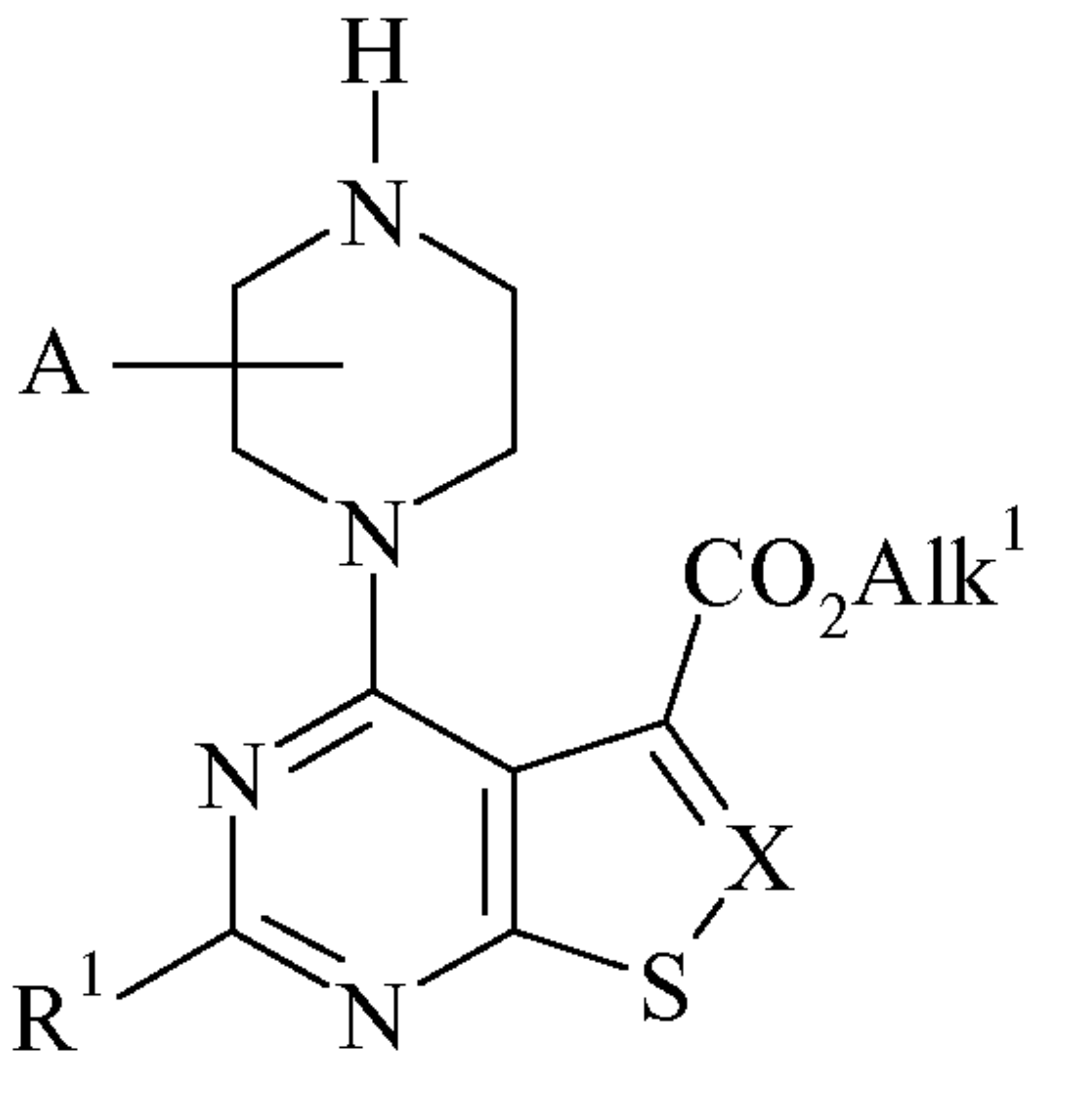


(VIII)

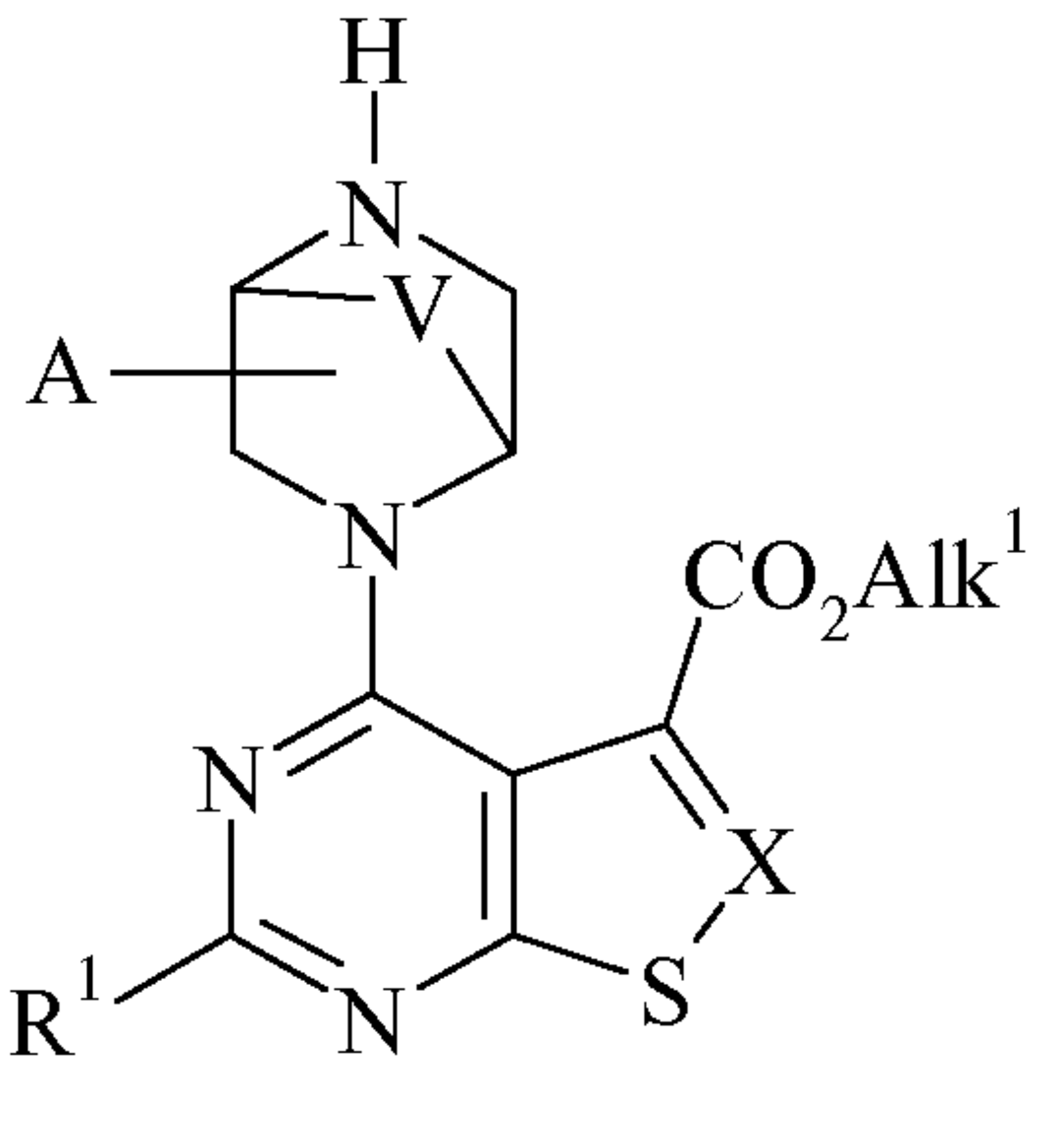
wherein Q, X and R^1 are as defined above, and Alk^1 represents a C_{1-6} alkyl group, e.g. ethyl; with a base.

The base of use in the above reaction may suitably be an alkali metal hydroxide, e.g. sodium hydroxide. The reaction is conveniently effected at an elevated temperature in a suitable solvent or mixture of solvents. Such solvent or solvents may typically be selected as appropriate from an ethereal solvent such as tetrahydrofuran, and a C_{1-4} alkanol such as ethanol.

The intermediates of formula (VIII) above may be prepared by attaching the -Y-Z moiety to a compound of formula (IXA) or (IXB):



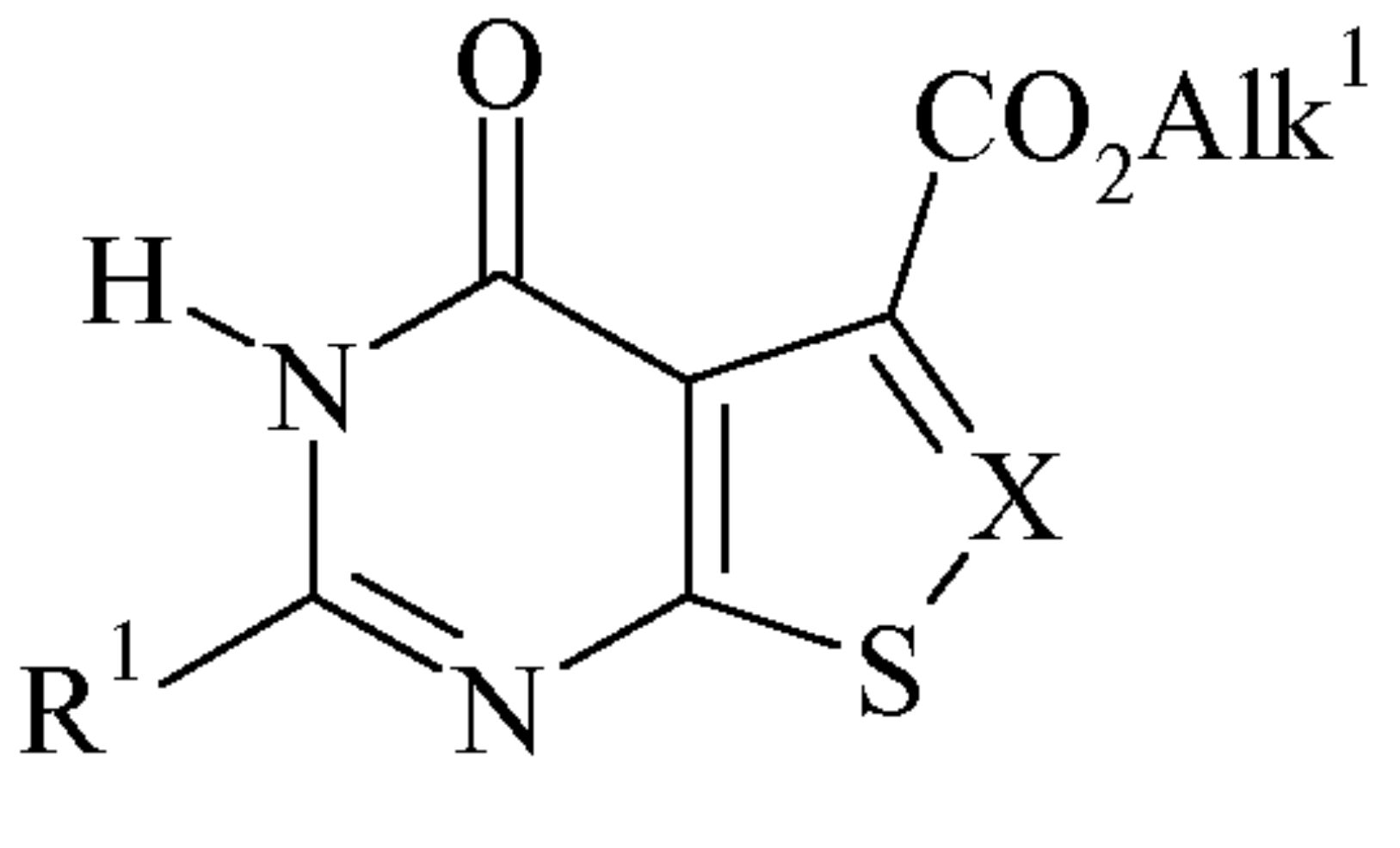
(IXA)



(IXB)

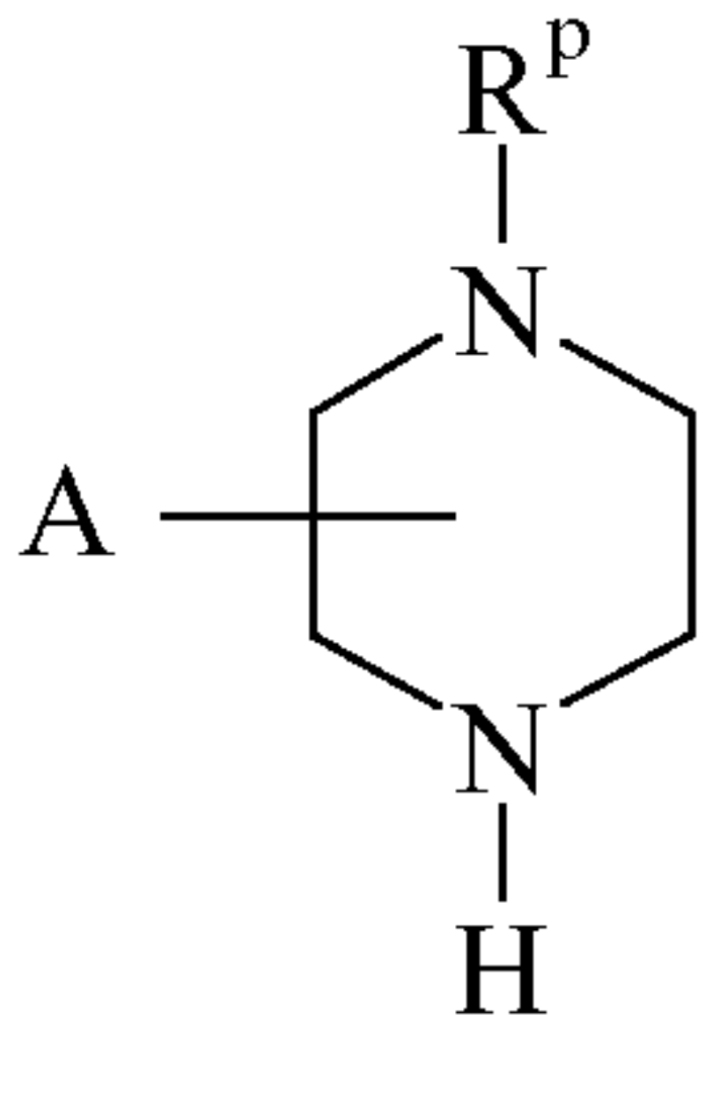
wherein V, X, Y, Z, A, R^1 and Alk^1 are as defined above; under conditions analogous to those described above for the attachment of the -Y-Z moiety to a compound of formula (VA) or (VB).

The intermediates of formula (IXA) and (IXB) above may be prepared by reacting a compound of formula (X):

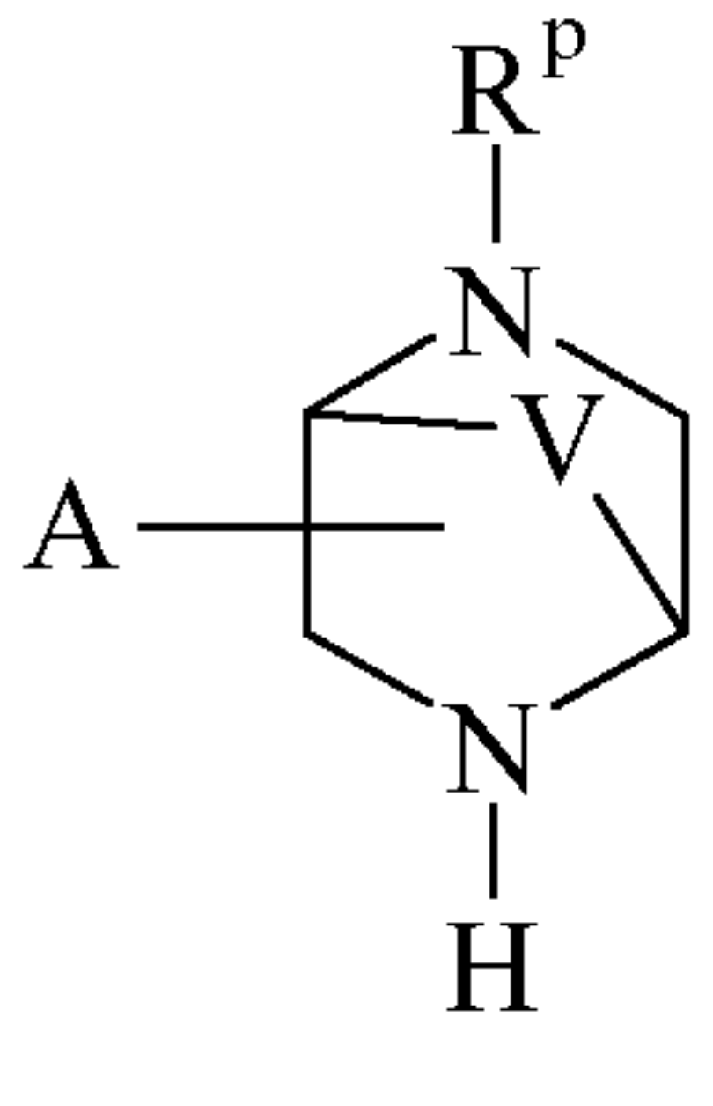


(X)

wherein X, R^1 and Alk^1 are as defined above; with a compound of formula (XIA) or (XIB):



(XIA)



(XIB)

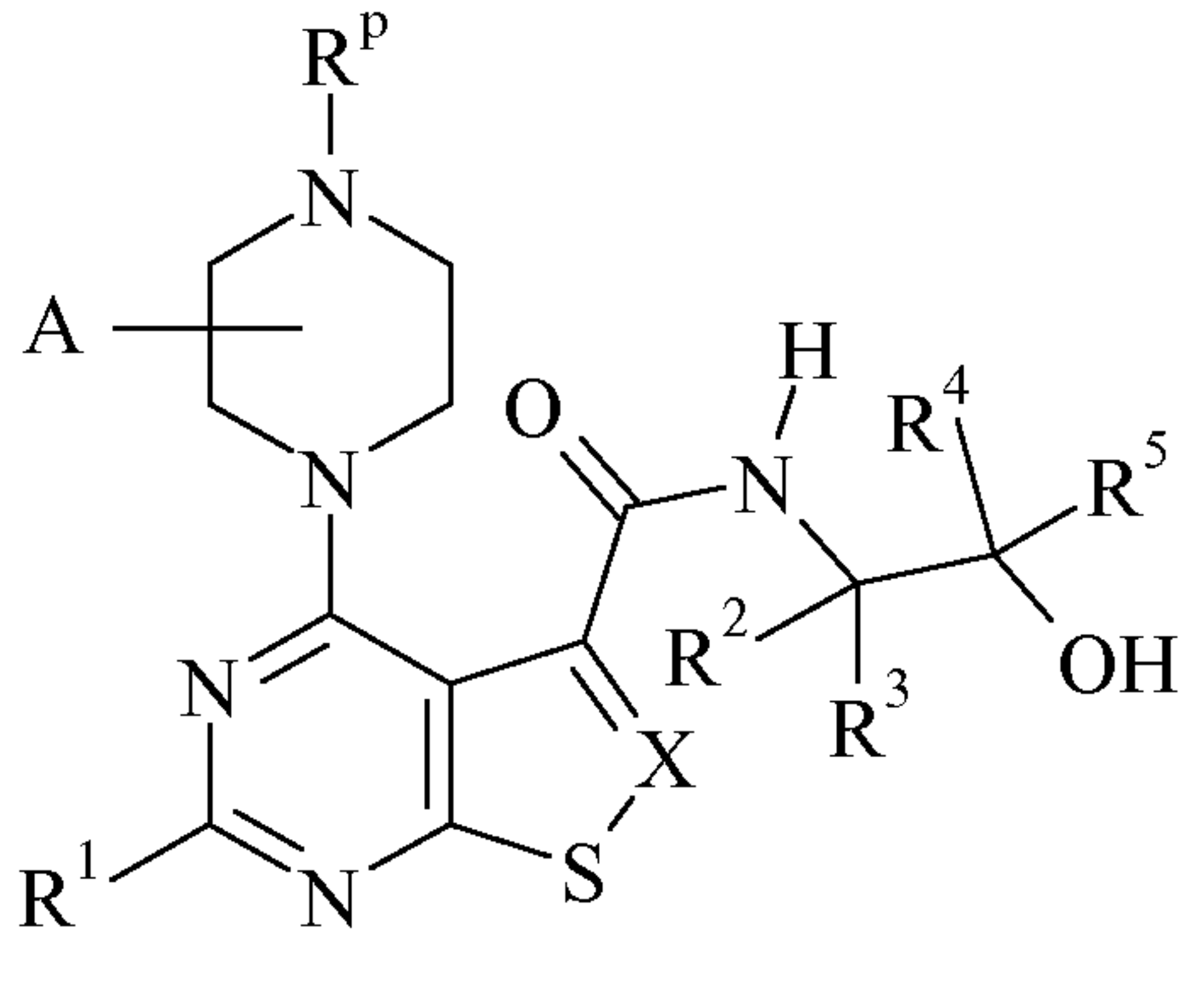
wherein V and A are as defined above, and R^p represents hydrogen or an *N*-protecting group; followed, as necessary, by removal of the *N*-protecting group R^p.

The *N*-protecting group R^p is typically *tert*-butoxycarbonyl (BOC).

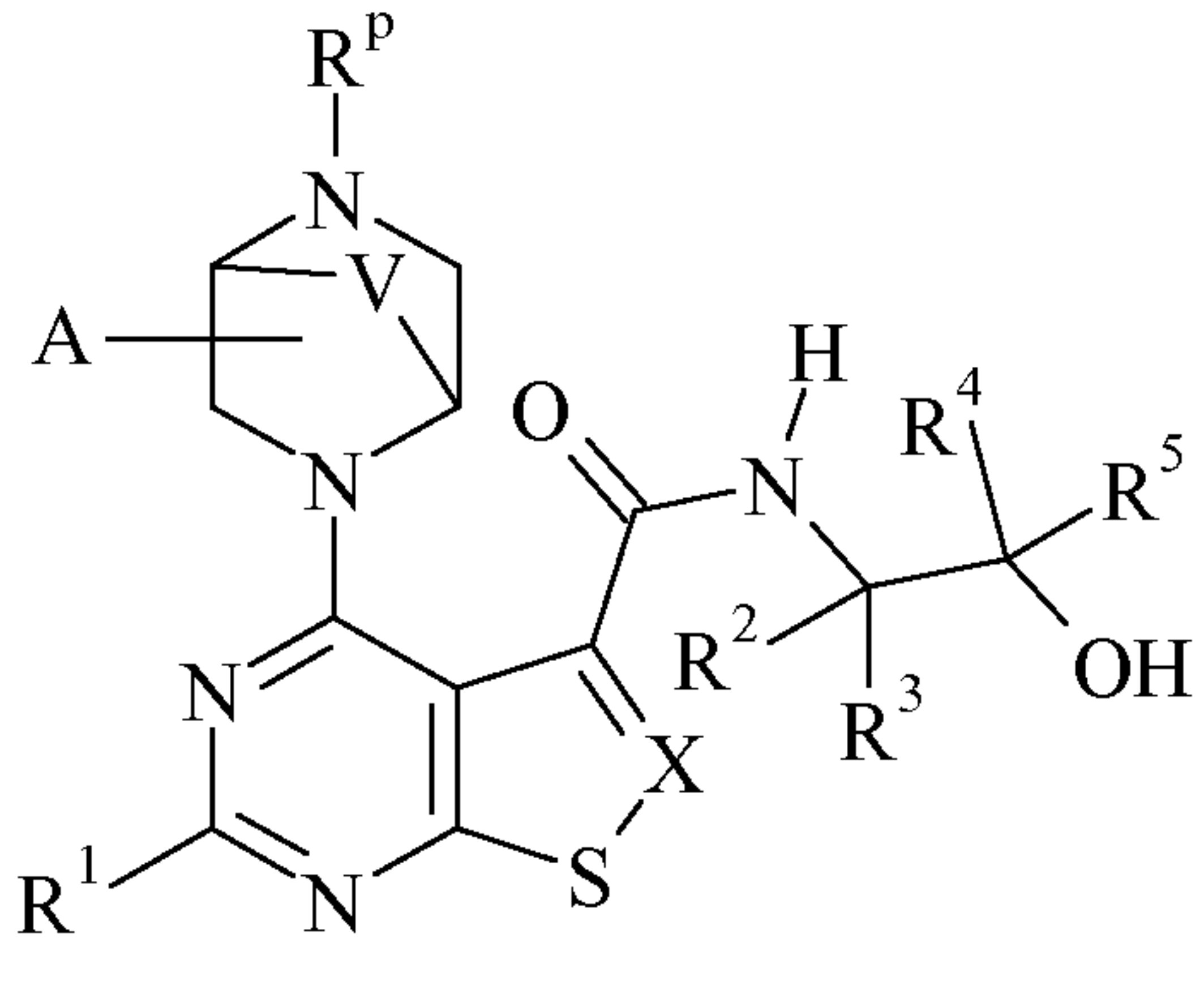
The reaction between compound (X) and compound (XIA) or (XIB) is conveniently accomplished at a suitable temperature (ambient or elevated) in a solvent such as acetonitrile or *N*,*N*-dimethylformamide, ideally in the presence of a coupling agent such as benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP) or (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PyBOP), and a base, e.g. an organic base such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).

Where the *N*-protecting group R^p is BOC, subsequent removal of the BOC group may typically be accomplished by treatment with an acid, e.g. a mineral acid such as hydrochloric acid, or an organic acid such as trifluoroacetic acid.

The intermediates of formula (VA) and (VB) above may be prepared by cyclising a compound of formula (XIIA) or (XIIB):



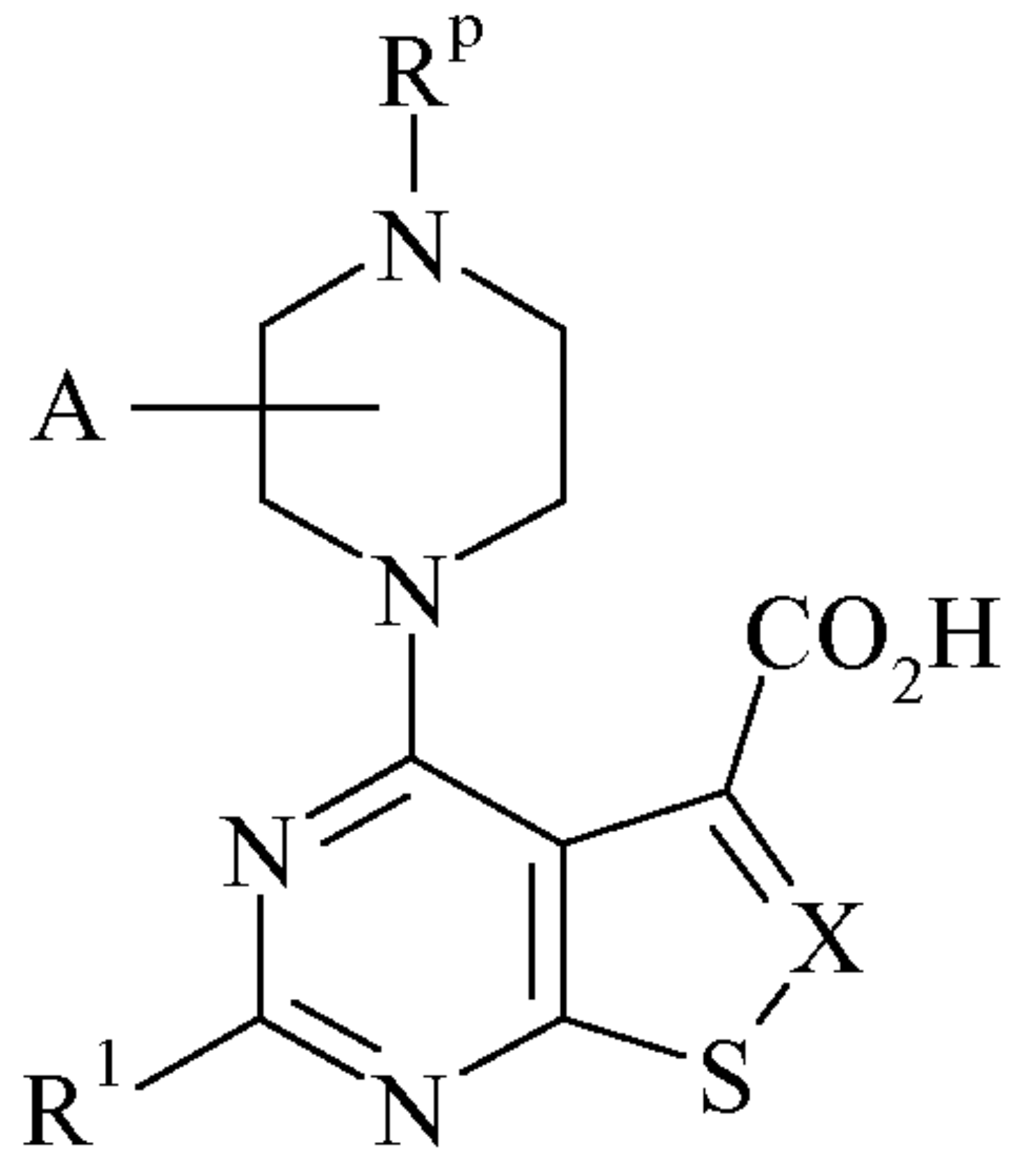
(XIIA)



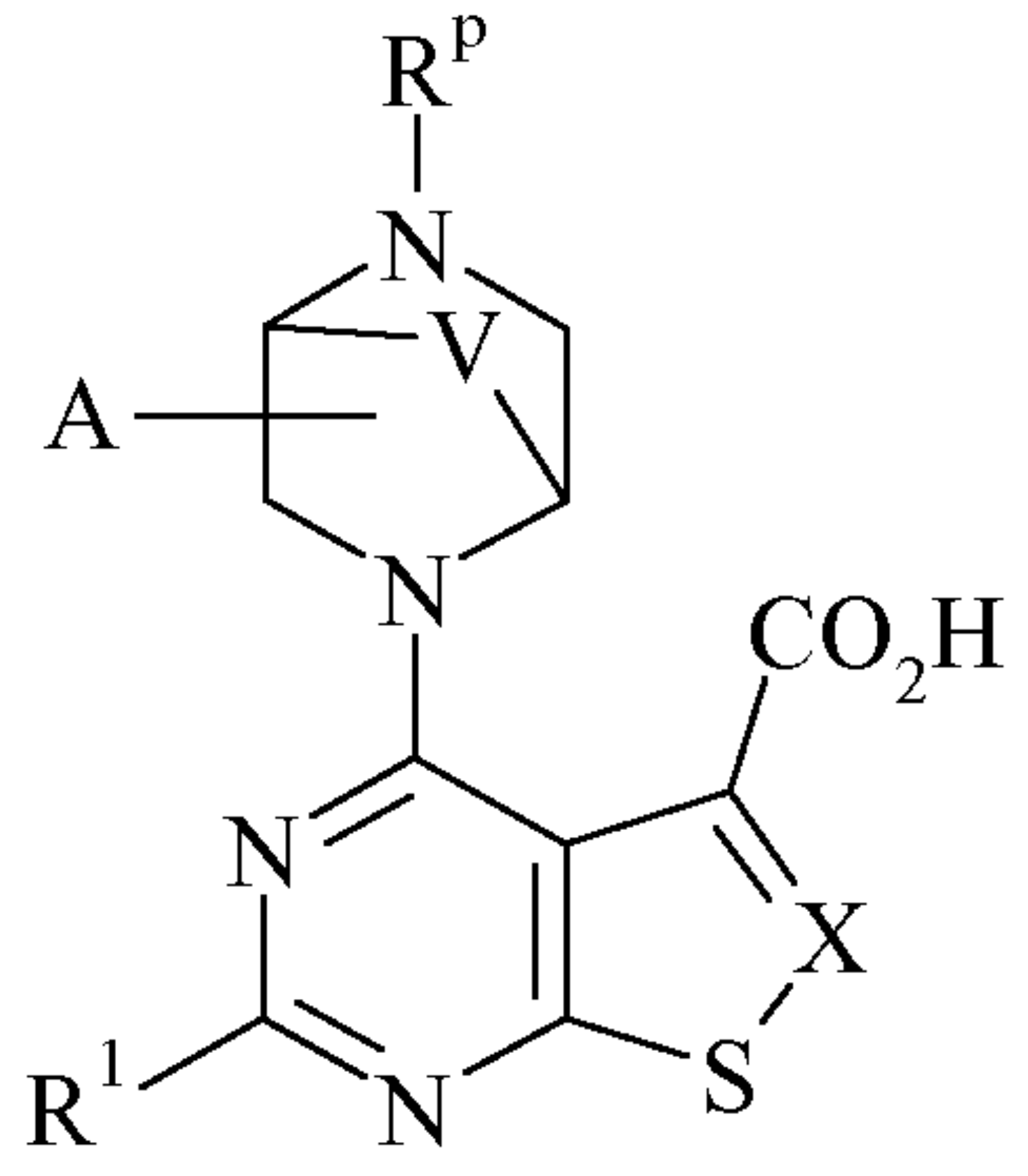
(XIIB)

wherein V, X, A, R^1, R^2, R^3, R^4, R^5 and R^p are as defined above; under conditions analogous to those described above for the cyclisation of compound (III); followed, as necessary, by removal of the *N*-protecting group R^p, under conditions analogous to those described above.

The intermediates of formula (XIIA) and (XIIB) above may be prepared by reacting a compound of formula (VII) as defined above with a compound of formula (XIIIA) or (XIIIB):



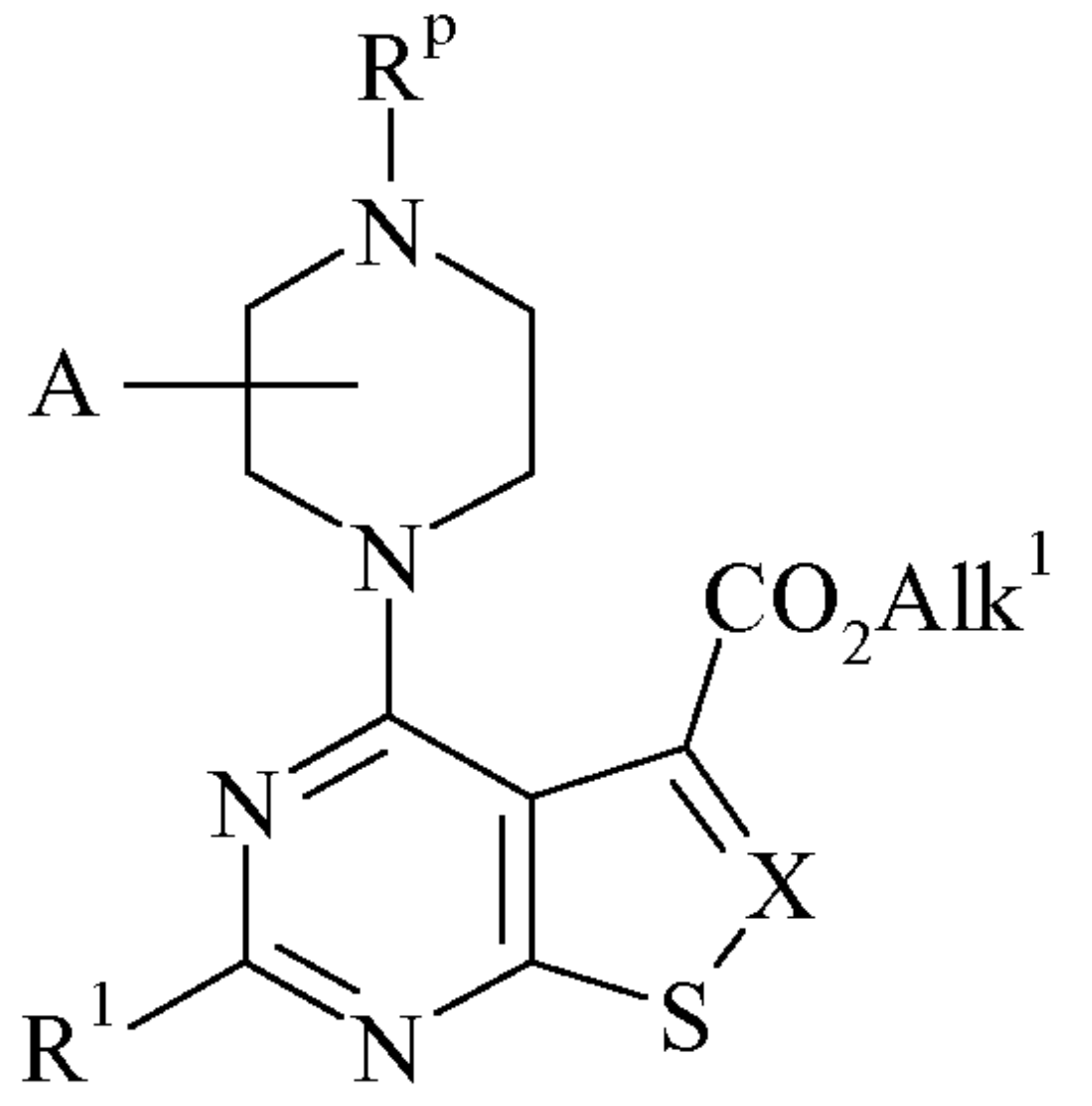
(XIIIA)



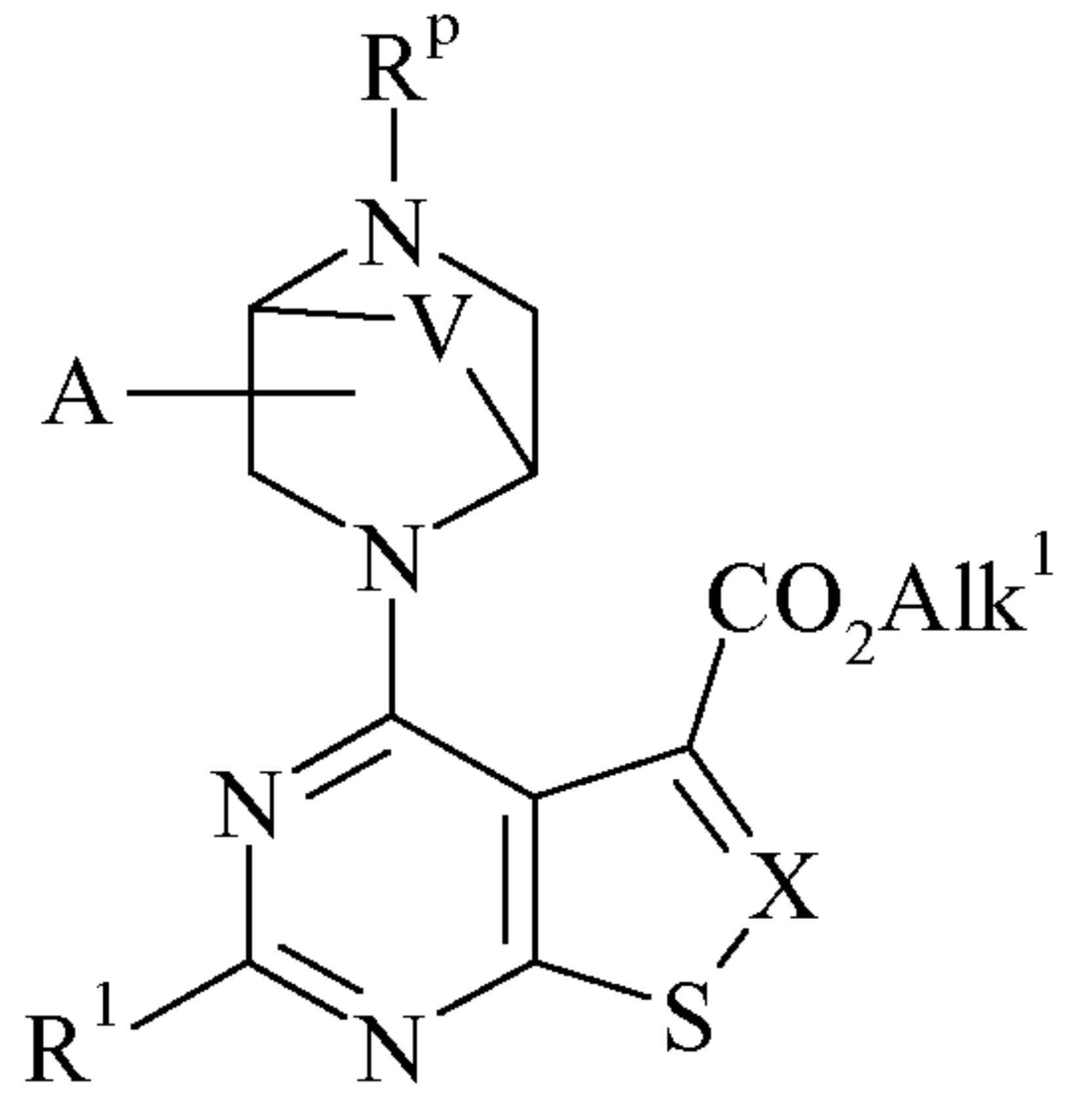
(XIIIB)

wherein V, X, A, R^1 and R^p are as defined above; under conditions analogous to those described above for the reaction between compounds (VI) and (VII).

The intermediates of formula (XIIIA) and (XIIIB) above may be prepared by reacting a compound of formula (XIVA) or (XIVB):



(XIVA)

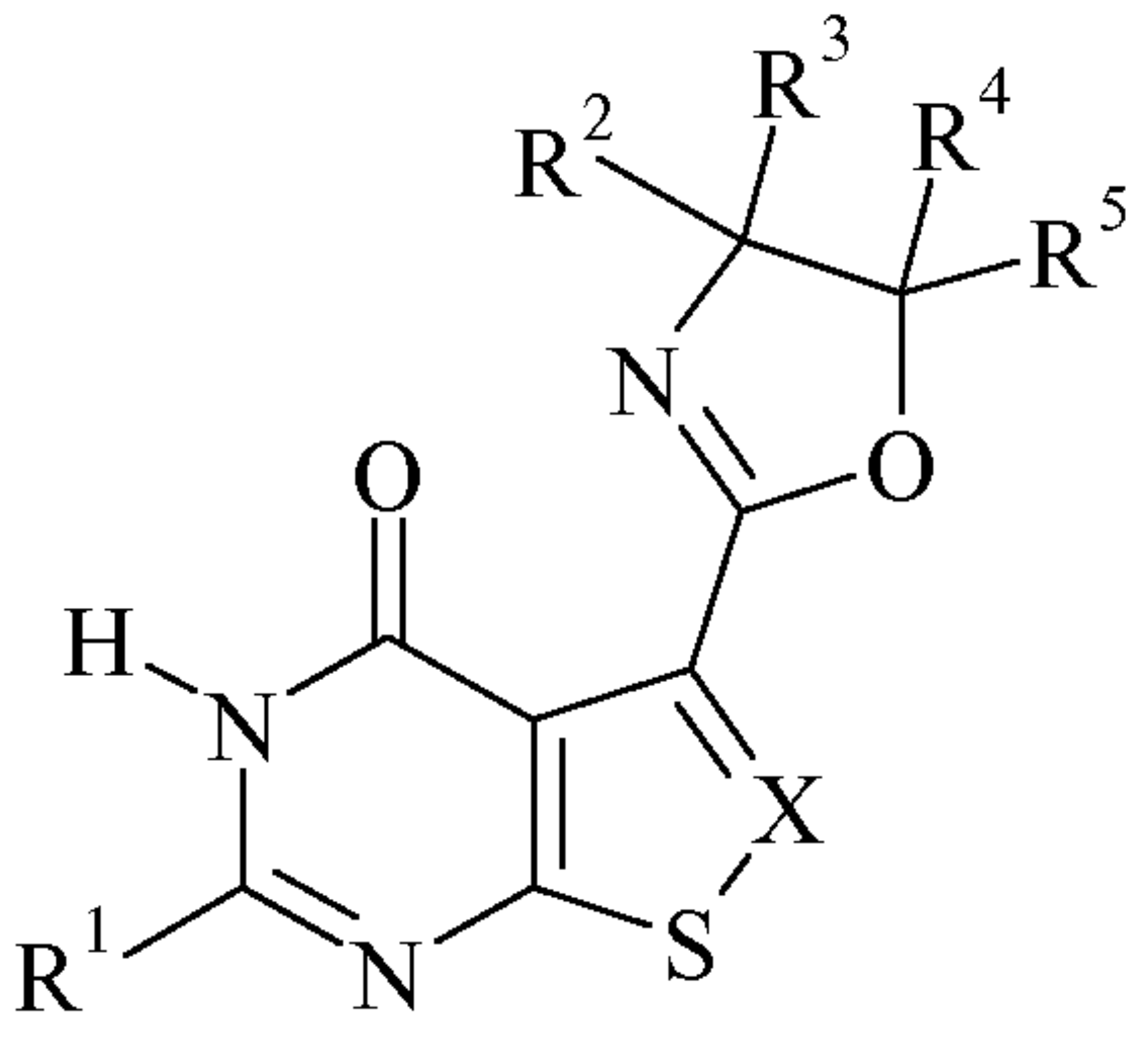


(XIVB)

wherein V, X, A, R^1, R^p and Alk^1 are as defined above; with a base; under conditions analogous to those described above for the conversion of compound (VIII) into compound (VI).

The intermediates of formula (XIVA) and (XIVB) above may be prepared by reacting a compound of formula (X) with a compound of formula (XIA) or (XIB) as described above.

The intermediates of formula (IV) above wherein L^1 represents a halogen atom may be prepared by treating a compound of formula (XV):



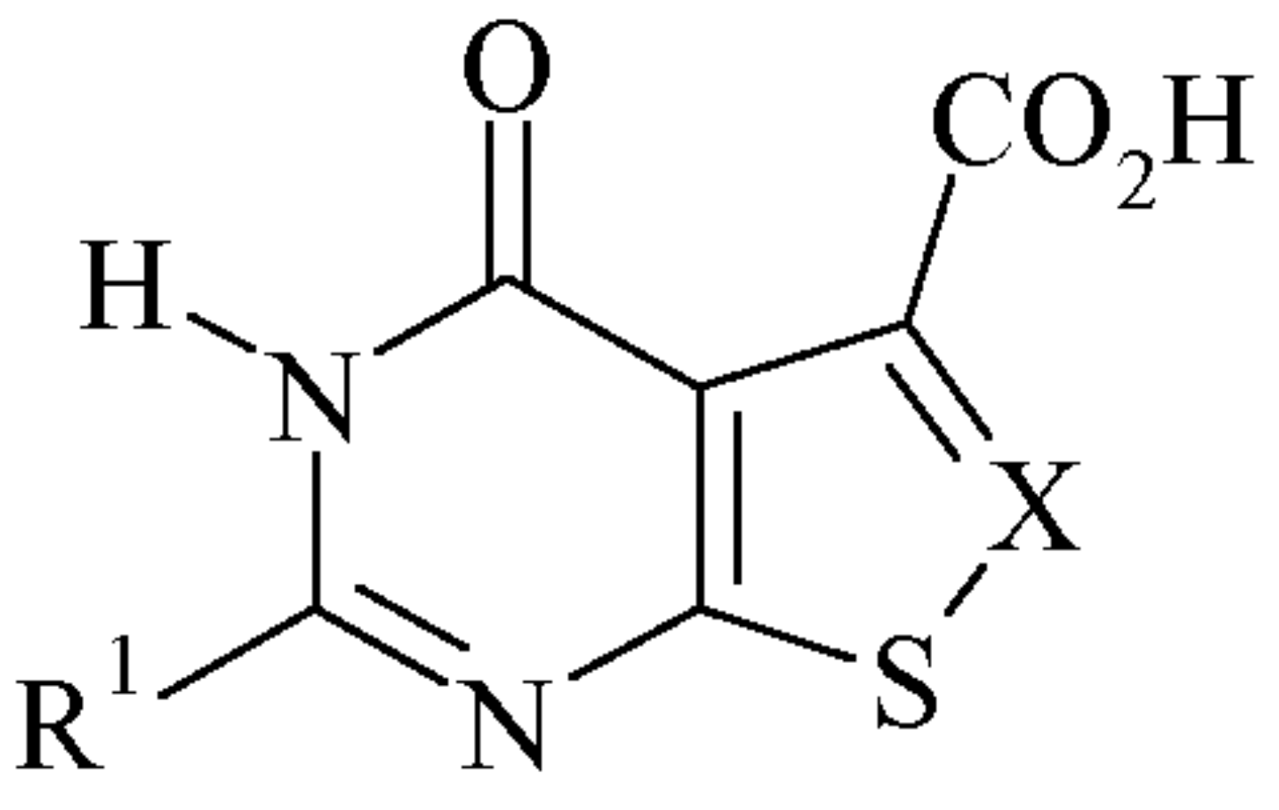
(XV)

wherein X, R^1, R^2, R^3, R^4 and R^5 are as defined above; with a halogenating agent.

Where L^1 in the compounds of formula (IV) is chloro, the halogenating agent employed in the above reaction will be a chlorinating reagent. A suitable chlorinating agent is phosphorus oxychloride.

The reaction is conveniently effected by contacting the reagents at an elevated temperature.

The intermediates of formula (XV) above may be prepared by reacting a compound of formula (VII) as defined above with a compound of formula (XVI):



(XVI)

wherein X and R^1 are as defined above; under conditions analogous to those described above for the reaction between compounds (VI) and (VII).

The intermediates of formula (XVI) above may be prepared by reacting a compound of formula (X) as defined above with a base, under conditions analogous to those described above for the conversion of compound (VIII) into compound (VI).

Depending upon the substitution pattern around the ring system, the compounds of formula (X), (XV) and (XVI) as depicted above may exist predominantly as the hydroxyimine tautomer.

As will be appreciated, the intermediates of formula (VA) and (VB) correspond to compounds in accordance with the present invention wherein Y represents a covalent bond and Z is hydrogen. Similarly, the intermediates of formula (XIA) and (XIB) wherein R^p is hydrogen correspond to intermediates of formula Q-H wherein Y represents a covalent bond and Z is hydrogen. Furthermore, the intermediates of formula (IXA) and (IXB) correspond to intermediates of formula (XIVA) and (XIVB) wherein R^p is hydrogen.

Where they are not commercially available, the starting materials of formula (VII), (X), (XIA) and (XIB) may be prepared by methods analogous to those described in the accompanying Examples, or by standard methods well known from the art.

It will be understood that any compound of formula (I) initially obtained from any of the above processes may, where appropriate, subsequently be elaborated into a further compound of formula (I) by techniques known from the art.

Where a mixture of products is obtained from any of the processes described above for the preparation of compounds according to the invention, the desired product can be separated therefrom at an appropriate stage by conventional methods such as preparative HPLC; or column chromatography utilising, for example, silica and/or alumina in conjunction with an appropriate solvent system.

Where the above-described processes for the preparation of the compounds according to the invention give rise to mixtures of stereoisomers, these isomers may be separated by conventional techniques. In particular, where it is desired to obtain a particular enantiomer of a compound of formula (I) this may be produced from a corresponding mixture of enantiomers using any suitable conventional procedure for resolving enantiomers. Thus, for example, diastereomeric derivatives, e.g. salts, may be produced by reaction of a mixture of enantiomers of formula (I), e.g. a racemate, and an appropriate chiral compound, e.g. a chiral base. The diastereomers may then be separated by any convenient means, for example by crystallisation, and the desired enantiomer recovered, e.g. by treatment with an acid in the instance where the diastereomer is a salt. In another resolution process a racemate of formula (I) may be separated using chiral HPLC. Moreover, if desired, a particular enantiomer may be obtained by using an appropriate chiral intermediate in one of the processes described above. Alternatively, a particular enantiomer may be obtained by performing an enantiomer-specific enzymatic biotransformation, e.g. an ester hydrolysis using an esterase, and then purifying only the enantiomerically pure hydrolysed acid from the unreacted ester antipode.

Chromatography, recrystallisation and other conventional separation procedures may also be used with intermediates or final products where it is desired to obtain a particular geometric isomer of the invention.

During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in *Protective Groups in Organic Chemistry*, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene & P.G.M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, 3rd edition, 1999. The protecting groups may be removed at any convenient subsequent stage utilising methods known from the art.

The following Examples illustrate the preparation of compounds according to the invention.

The compounds in accordance with this invention are potent inhibitors when measured in the MLR test described below.

The Mixed Lymphocyte Reaction (MLR) Test

Human peripheral blood mononuclear cells (PBMCs) were isolated from buffy coats, obtained from healthy blood donors by Ficoll (Lymphoprep, Axis-Shield PoC AS, Oslo, Norway) density-gradient centrifugation. The cells at the Ficoll-plasma interface were washed three times and used as “Responder” cells. RPMI 1788 (ATCC, N° CCL-156) cells were treated with mitomycin C (Kyowa, Nycomed, Brussels, Belgium) and used as “Stimulator” cells. Responder cells (0.12 x 106), Stimulator cells (0.045 x 106) and compounds (in different concentrations) were cocultured for 6 days in RPMI 1640 medium (BioWhittaker, Lonza, Belgium) supplemented with 10% fetal calf serum, 100 U/ml Geneticin (Gibco, LifeTechnologies, UK). Cells were cultured in triplicate in flat-bottomed 96-well microtiter tissue culture plates (TTP, Switzerland). After 5 days, cells were pulsed with 1 μCi of methyl-^{3}H thymidine (MP Biomedicals, USA), harvested 18 h later on glass filter paper and counted. Proliferation values were expressed as counts per minute (cpm), and converted to % inhibition with respect to a blank MLR test (identical but without added compound). The IC_{50} was determined from a graph with at least four points, each derived from the mean of 2 experiments. The IC_{50} value represents the lowest concentration of test compound (expressed in μM) that resulted in a 50% inhibition of the MLR.

The compounds of the accompanying Examples were all found to generate IC_{50} values in the MLR test of 10 μM or better.

EXAMPLES

Abbreviations

THF: tetrahydrofuran
DMF: *N*,*N*-dimethylformamide
MeOH: methanol
DCM: dichloromethane
EtOH: ethanol
EtOAc: ethyl acetate
DMSO: dimethylsulfoxide
DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene
DIPEA: *N*,*N*-diisopropylethylamine
HOBT: 1-hydroxybenzotriazole hydrate
DAST: (diethylamino)sulfur trifluoride
MeCN: acetonitrile
Et_2O: diethyl ether
PPh_3: triphenylphosphine
DDQ: 2,3-dichloro-5,6-dicyano-*p*-benzoquinone
Burgess reagent: (methoxycarbonylsulfamoyl)triethylammonium hydroxide
HATU: *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N'*,*N'*-tetramethyluronium hexafluorophosphate
PyBOP: (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate
EDC: 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
h: hour
br: broad
MS: Mass Spectrometry
M: mass
HPLC: High Performance Liquid Chromatography
LCMS: Liquid Chromatography Mass Spectrometry
RT: retention time

Analytical Methods

Unless stated otherwise, the products were analysed using *Analytical Method 2*.

Method 1: *Preparative HPLC (Waters UV Prep System)*

The reverse phase separation was carried out on a Waters X-Bridge, C18, 30 x 150 mm, 10 μm silica particle for both the low and high pH methods.

Injection Volume	100-1000 μL
UV data	230 to 400 nm, Resolution 1.2 nm
Flow Rate	50 mL/min

pH 3 Method:

Solvent A1	10 mM ammonium formate in water + 0.1% formic acid
Solvent B1	acetonitrile + 5% Solvent A1 + 0.1% formic acid

pH 10 Method:

Solvent A2	10 mM ammonium bicarbonate in water + 0.1% ammonia solution
Solvent B2	acetonitrile + 5% Solvent A2 + 0.1% ammonia solution

Analytical Method 2*: *LCMS (pH 10)

Column	Waters X-Bridge, 20 x 2.1 mm, 2.5 µL
Injection Volume	1-5 µL
UV data	230 to 400 nm, Peak Width 0.1 s
Column Temperature	40°C
Flow Rate	1.0 mL/min
Split to MS	~0.05 mL/min
Split to DAD and ELSD	~0.95 mL/min

High pH (approximately pH 9.5):

Solvent A2	10 mM ammonium bicarbonate in water + 0.1% ammonia solution
Solvent B2	acetonitrile + 5% Solvent A2 + 0.1% ammonia solution

Analytical Method 3*: *LCMS (pH 10)

Column	Waters X-Bridge, 20 x 2.1 mm, 2.5 µL
Column ID	E-AC-3/11/COL/035
Mobile Phase A:	10 mM ammonium formate in water + 0.1% ammonia
Mobile Phase B:	acetonitrile + 5% Solvent A + 0.1% ammonia
Injection Volume	5.0 µL
Flow Rate	1.00 mL/minute

INTERMEDIATE 1

Diethyl 2-aminothiophene-3,4-dicarboxylate

To a solution of ethyl pyruvate (1.8 mL, 16 mmol), ethyl cyanoacetate (2.4 mL, 22.4 mmol) and triethylamine (2.7 mL, 19.2 mmol) in DMF (8.0 mL) was added sulfur (564 mg, 17.6 mmol; finely ground using a mortar). The suspension was heated at 60°C for 5 h. The solvents were removed *in vacuo* and the slurry was dissolved in EtOAc. The organic solution was extracted successively with brine, saturated aqueous sodium bicarbonate solution, brine, hydrogen chloride (1*N*) and again brine. The organic fraction was dried over magnesium sulfate after which the solvent was removed *in vacuo*. The crude residue was purified by silica gel flash chromatography, the mobile phase being a mixture of heptane and EtOAc (in a ratio gradually ranging from 20% to 30% EtOAc in heptane), yielding the *title compound* (1.8 g) as a yellow powder. ^{13}C NMR δ (75 MHz, $CDCl_3$) 164.78, 164.30, 162.54, 132.57, 110.81, 104.64, 60.87, 59.83, 13.88, 13.84. MS (*m/z*) 244 $[M+H]^+$.

INTERMEDIATE 2

2-Amino-5-(ethoxycarbonyl)thieno[2,3-*d*]pyrimidin-4(1*H*)-one

A mixture of *Intermediate 1* (1.0 g, 4.1 mmol), chloroformamidine hydrochloride (1.2 g, 10.3 mmol) and dimethylsulfone (1.9 g, 20.5 mmol) was heated at 135°C for 45 minutes. Water was added and the mixture was cooled down to room temperature. An aqueous ammonia solution was added to adjust the solution to pH 9. The precipitate was filtered off, yielding the *title compound* (0.78 g) as a white powder. ^{13}C NMR δ (75 MHz, $CDCl_3$) 169.24, 163.33, 157.02, 153.90, 129.29, 120.85, 112.43, 60.73, 14.15. MS (*m/z*) 240 $[M+H]^+$.

INTERMEDIATE 3

2-Amino-4-[4-(*tert*-butoxycarbonyl)piperazin-1-yl]thieno[2,3-*d*]pyrimidine-5-carboxylic acid ethyl ester

DBU (12.1 mL, 79.3 mmol) was added to *Intermediate 2* (12.6 g, 52.7 mmol), stirring in acetonitrile (500 mL). After stirring for 5 minutes, PyBOP (36.4 g, 68.5 mmol) was added, followed by *tert*-butyl piperazine-1-carboxylate (29.4 g, 158 mmol). The reaction mixture was then stirred at room temperature for 12 h, after which time LCMS analysis confirmed disappearance of starting materials. The solid that had formed in the flask was removed by filtration. The filtrate was concentrated *in vacuo* and the crude residue was purified by column chromatography, eluting with 20-50% EtOAc/hexanes. The *title compound* (9.5 g) was isolated as a pale solid. δ_H (DMSO-d_6, 300 MHz) 7.77 (1H, s), 6.49 (2H, br s), 4.26 (2H, q, *J* 7.1 Hz), 3.36 (8H, s), 1.41 (9H, s), 1.29 (3H, t, *J* 7.1 Hz). MS (*m/z*) 408 $[M+H]^+$.

INTERMEDIATE 4 (GENERAL METHOD 1)

2-Amino-4-(piperazin-1-yl)thieno[2,3-*d*]pyrimidine-5-carboxylic acid ethyl ester, hydrochloric acid salt

Intermediate 3 (9.5 g) was dissolved in the minimum amount of methanol and HCl (4M in 1,4-dioxane, 20 mL) was added. The reaction mixture was stirred for 1 h, then concentrated *in vacuo*, to give the *title compound* (quantitative) as a white solid. LCMS (pH 10) RT 0.99 minutes; MS (*m/z*) 308 $[M+H]^+$.

INTERMEDIATE 5 (GENERAL METHOD 2)

2-Amino-4-[4-(*tert*-butoxycarbonyl)piperazin-1-yl]thieno[2,3-*d*]pyrimidine-5-carboxylic acid

To a solution of *Intermediate 3* (450 mg, 1.1 mol) in EtOH:THF (1:1, 10 mL) was added aqueous NaOH solution (2M, 10 mL). The reaction mixture was heated to 50°C overnight and on completion (by LCMS monitoring) the solvents were removed *in vacuo*. The residue was re-dissolved in water, then the solution was adjusted to pH 6 by addition of HCl (2M). The resulting precipitate was filtered and dried on a sinter for 12 h, to give the *title compound* (380 mg) as a white solid. LCMS (pH 10) RT 0.89 minutes; MS (*m/z*) 380 $[M+H]^+$.

INTERMEDIATE 6 (GENERAL METHOD 3)

4-[2-Amino-5-(2-hydroxy-1,1-dimethylethylcarbamoyl)thieno[2,3-*d*]pyrimidin-4-yl]-piperazine-1-carboxylic acid *tert*-butyl ester

DIPEA (690 µL, 3.97 mmol) was added to a stirred solution of *Intermediate 5* (0.5 g, 1.32 mmol), 2-amino-2-methylpropan-1-ol (140 mg, 1.5 mmol) and HATU (0.75 g, 1.97 mol) in DMF (4 mL). After 15 minutes, the mixture was partitioned between EtOAc and brine. The organic layer was washed with brine, then dried and recrystallised from Et_2O. The crystals were filtered, then washed with Et_2O and dried on a sinter, to give the *title compound* (0.59 g) as a cream solid. LCMS (pH 10) RT 1.22 minutes; MS (*m*/*z*) 451 $[M+H]^+$.

INTERMEDIATE 7

4-[2-Amino-5-(4,4-dimethyl-5*H*-oxazol-2-yl)thieno[2,3-*d*]pyrimidin-4-yl]piperazine-1-carboxylic acid *tert*-butyl ester

To a solution of *Intermediate 6* (0.54 g, 1.2 mmol), stirring in DMF (6 mL) at 0°C, was added Burgess reagent (0.4 g, 1.68 mmol). The reaction mixture was stirred at room temperature overnight, after which time LCMS analysis showed near completion. A further aliquot of Burgess reagent (0.14 g) was added, and the reaction mixture was stirred for a further 24 h, after which time LCMS analysis showed full conversion to product. The reaction mixture was partitioned between EtOAc and brine. The organic layer was washed with brine, then dried and concentrated *in vacuo*. The crude residue was purified by column chromatography, eluting with EtOAc/hexane (5:2), followed by recrystallisation from Et_2O. The resulting crystals were collected by filtration and dried on a sinter, to give the *title compound* (0.17 g) as a white solid. LCMS (pH 10) RT 1.37 minutes; MS (*m*/*z*) 433 $[M+H]^+$.

INTERMEDIATE 8

5-(4,4-Dimethyl-5*H*-oxazol-2-yl)-4-(piperazin-1-yl)thieno[2,3-*d*]pyrimidin-2-ylamine

Prepared from *Intermediate 7* via *General Method 1*, to give the *title compound* (quantitative) as a white solid. LCMS (pH 10) RT 0.89 minutes; MS (*m*/*z*) 333 $[M+H]^+$.

INTERMEDIATE 9 (GENERAL METHOD 4)

2-Amino-4-[4-(4-methoxy-2-methylphenylcarbamoyl)piperazin-1-yl]thieno[2,3-*d*]-pyrimidine-5-carboxylic acid ethyl ester

To *Intermediate 4* (4 g, 0.01 mol), stirring in DMF (150 mL), were added 4-methoxy-2-methylphenyl isocyanate (1.5 mL, 0.01 mol) and DIPEA (2 mL, 0.02 mol). The reaction mixture was stirred at room temperature for 15 minutes, then concentrated *in vacuo*. An aliquot was purified by preparative HPLC, to give the *title compound* (75 mg) as a white solid; the crude residue was utilised in subsequent steps without further purification. δ_H (DMSO-d$_6$, 400 MHz) 8.00 (1H, br s), 7.78 (1H, s), 7.03 (1H, d, *J* 8.6 Hz), 6.77 (1H, m), 6.69 (1H, dd, *J* 8.4, 2.9 Hz), 6.51 (2H, br s), 4.29 (2H, q, *J* 7.1 Hz), 3.72 (3H, s), 3.54-3.44 (8H, br m), 2.13 (3H, s), 1.31 (3H, t, *J* 7.1 Hz). LCMS (pH 10) RT 1.90 minutes; MS (*m*/*z*) 471 $[M+H]^+$.

INTERMEDIATE 10

2-Amino-4-[4-(4-methoxy-2-methylphenylcarbamoyl)piperazin-1-yl]thieno[2,3-*d*]-pyrimidine-5-carboxylic acid

Prepared from *Intermediate 9* (3 g, 6.4 mmol) via *General Method 2* to give the *title compound* (2 g) as a white solid. MS (*m*/*z*) 433 $[M+H]^+$.

INTERMEDIATE 11

2-Amino-4-[4-(4-methoxyphenylcarbamoyl)piperazin-1-yl]thieno[2,3-*d*]pyrimidine-5-carboxylic acid ethyl ester

Prepared from *Intermediate 4* and 4-methoxyphenylisocyanate via *General Method 4* to give the *title compound* as a white solid. ^{13}C NMR δ (75 MHz, CD$_3$OD) 171.65, 162.60, 160.54, 159.64, 155.32, 154.73, 133.60, 127.71, 124.13, 121.41 (2C), 113.30 (2C), 106.19, 60.79, 54.73, 47.93 (2C), 43.38 (2C), 13.73. LCMS (pH 10) RT 1.91 minutes; MS (*m*/*z*) 457 $[M+H]^+$.

INTERMEDIATE 12

2-Amino-4-[4-(4-methoxyphenylcarbamoyl)piperazin-1-yl]thieno[2,3-*d*]pyrimidine-5-carboxylic acid

Prepared from *Intermediate 11* via *General Method 2* to give the *title compound* (63%) as a white solid. LCMS (pH 10) RT 0.48 minutes; MS (*m/z*) 429 $[M+H]^+$.

INTERMEDIATES 13 TO 22 (GENERAL METHOD 5)

To a solution of *Intermediate 10* or *Intermediate 12* (0.70 mmol) in DMF (2 mL) was added the appropriate hydroxy-substituted amine (0.84 mmol), followed by HATU (1.05 mmol) and DIPEA (1.05 mmol). The reaction mixture was stirred at room temperature for 12 h. The reaction mixture was then diluted with water and extracted with EtOAc. The organic layer was separated, dried over anhydrous sodium sulphate and concentrated *in vacuo*. The crude residue was purified by column chromatography (0-10% MeOH:DCM) to afford the *title compound*.

Intermediate	Compound Name	LCMS	
		RT	(M^+)
13	2-Amino-4-[4-(4-methoxyphenylcarbamoyl)piperazin-1-yl]thieno[2,3-*d*]pyrimidine-5-carboxylic acid (2-hydroxy-ethyl)amide	1.08	472.1
14	2-Amino-4-[4-(4-methoxy-2-methylphenylcarbamoyl)-piperazin-1-yl]thieno[2,3-*d*]pyrimidine-5-carboxylic acid (2-hydroxyethyl)amide	1.42	486.1
15	2-Amino-4-[4-(4-methoxyphenylcarbamoyl)piperazin-1-yl]thieno[2,3-*d*]pyrimidine-5-carboxylic acid (1-hydroxy-cyclopentylmethyl)amide	1.56	526.1
16	2-Amino-4-[4-(4-methoxy-2-methylphenylcarbamoyl)-piperazin-1-yl]thieno[2,3-*d*]pyrimidine-5-carboxylic acid (1-hydroxycyclopentylmethyl)amide	1.58	540.2
17	2-Amino-4-[4-(4-methoxyphenylcarbamoyl)piperazin-1-yl]thieno[2,3-*d*]pyrimidine-5-carboxylic acid (2-hydroxy-propyl)amide	1.05	486.1

18	2-Amino-4-[4-(4-methoxy-2-methylphenylcarbamoyl)-piperazin-1-yl]thieno[2,3-*d*]pyrimidine-5-carboxylic acid (2-hydroxypropyl)amide	1.50	500.1
19	2-Amino-4-[4-(4-methoxyphenylcarbamoyl)piperazin-1-yl]thieno[2,3-*d*]pyrimidine-5-carboxylic acid (2-hydroxy-3-methylbutyl)amide	1.36	514.1
20	2-Amino-4-[4-(4-methoxy-2-methylphenylcarbamoyl)-piperazin-1-yl]thieno[2,3-*d*]pyrimidine-5-carboxylic acid (2-hydroxy-3-methylbutyl)amide	1.72	528.1
21	2-Amino-4-[4-(4-methoxy-2-methylphenylcarbamoyl)-piperazin-1-yl]thieno[2,3-*d*]pyrimidine-5-carboxylic acid (2-hydroxy-1-methylethyl)amide	1.47	500.1
22	2-Amino-4-[4-(4-methoxyphenylcarbamoyl)piperazin-1-yl]thieno[2,3-*d*]pyrimidine-5-carboxylic acid (2-hydroxy-1-methylethyl)amide	1.10	486.0

INTERMEDIATE 23

2-Amino-4-[4-(4-methoxy-2-methylphenylcarbamoyl)piperazin-1-yl]thieno[2,3-*d*]-pyrimidine-5-carboxylic acid (2-hydroxy-1,1-dimethylethyl)amide

To a solution of *Intermediate 10* (0.2 g, 0.45 mmol) in DMF (15 mL) were added 2-amino-2-methylpropan-1-ol (68 µL, 1.13 mmol), HOBT (76 mg, 0.50 mmol), EDC (95 mg, 0.50 mmol) and DIPEA (313 µL, 1.80 mmol). The reaction mixture was stirred at room temperature overnight, then concentrated *in vacuo*. The crude material was purified by column chromatography, eluting with 0-10% MeOH/EtOAc, to give the *title compound* (135 mg) as a white solid. δ_H (DMSO-d$_6$, 400 MHz) 8.00 (1H, s), 7.67 (1H, s), 7.36 (1H, s), 7.03 (1H, d, *J* 8.6 Hz), 6.77 (1H, m), 6.69 (1H, dd, *J* 8.6, 2.9 Hz), 6.40 (2H, br s), 4.89 (1H, t, *J* 5.8 Hz), 3.72 (3H, s), 3.48 (8H, br m), 3.31 (6H, s), 2.12 (2H, s), 1.31 (3H, s). LCMS (pH 10) RT 1.28 minutes; MS (*m/z*) 514 $[M+H]^+$.

EXAMPLE 1

4-[2-Amino-5-(4,4-dimethyl-5*H*-oxazol-2-yl)thieno[2,3-*d*]pyrimidin-4-yl]piperazine-1-carboxylic acid (4-methoxy-2-methylphenyl)amide

DDQ (33 mg, 0.15 mmol) and PPh_3 (38 mg, 0.15 mmol) were stirred in DCM (10 mL) in an oven-dried flask for 3 minutes, followed by the addition of *Intermediate 23* (50 mg, 0.09 mmol). A yellow precipitate formed and a few drops of DMF were added to aid solubility. The reaction mixture was left to stir overnight. The reaction failed to reach completion, but the *title compound* (11 mg) was isolated as a white solid by preparative HPLC (*Analytical Method 1*). δ_H (DMSO-d_6, 400 MHz) 7.99 (1H, br s), 7.55 (1H, br s), 7.03 (1H, br d, *J* 8.3 Hz), 6.77 (1H, br s), 6.70 (1H, br d, *J* 7.1 Hz), 6.44 (2H, br s), 4.10 (2H, br s), 3.72 (3H, br s), 3.52 (4H, br m), 3.46 (4H, br m), 2.12 (3H, br s), 1.31 (6H, br s). LCMS (pH 10) RT 2.26 minutes; MS (*m/z*) 496 $[M+H]^+$.

EXAMPLES 2 TO 11 (GENERAL METHOD 6)

The appropriate isocyanate (1.5 equiv., 0.12 mmol) was added to a reaction tube. A solution of *Intermediate 8* (300 mg) in DMF (10 mL) and DIPEA (0.28 mL) was prepared and an aliquot of this solution (1 mL) was added to the tube. The tube was covered with parafilm and stirred overnight at room temperature. The reaction mixture was analysed by LCMS, then filtered through an acrodisk into a HPLC submission vial, washing with DMF (0.2 mL) into a second vial. The reaction mixture was purified using *Analytical Method 1*. The product fraction was evaporated, then transferred in MeCN/ water to a submission vial and freeze-dried, to give the *title compound* as a white solid.

Example	Compound Name	LCMS		
		Method	RT	(M^+)
2	4-[2-Amino-5-(4,4-dimethyl-5*H*-oxazol-2-yl)thieno-[2,3-*d*]pyrimidin-4-yl]-*N*-(4-methoxyphenyl)-piperazine-1-carboxamide	2	1.68	482.8
3	4-[2-Amino-5-(4,4-dimethyl-5*H*-oxazol-2-yl)thieno-[2,3-*d*]pyrimidin-4-yl]-*N*-(2-fluoro-4-iodophenyl)-piperazine-1-carboxamide	2	2.10	596.6

4	4-[2-Amino-5-(4,4-dimethyl-5*H*-oxazol-2-yl)thieno-[2,3-*d*]pyrimidin-4-yl]-*N*-(2-cyanophenyl)piperazine-1-carboxamide	2	1.74	477.8
5	Ethyl 4-({4-[2-amino-5-(4,4-dimethyl-5*H*-oxazol-2-yl)thieno[2,3-*d*]pyrimidin-4-yl]piperazine-1-carbonyl}amino)benzoate	2	1.96	524.8
6	*N*-(4-Acetylphenyl)-4-[2-amino-5-(4,4-dimethyl-5*H*-oxazol-2-yl)thieno[2,3-*d*]pyrimidin-4-yl]piperazine-1-carboxamide	2	1.66	494.8
7	4-[2-Amino-5-(4,4-dimethyl-5*H*-oxazol-2-yl)thieno-[2,3-*d*]pyrimidin-4-yl]-*N*-(*p*-tolyl)piperazine-1-carboxamide	2	1.86	466.8
8	4-[2-Amino-5-(4,4-dimethyl-5*H*-oxazol-2-yl)thieno-[2,3-*d*]pyrimidin-4-yl]-*N*-[4-(difluoromethoxy)-phenyl]piperazine-1-carboxamide	2	1.93	518.8
9	4-[2-Amino-5-(4,4-dimethyl-5*H*-oxazol-2-yl)thieno-[2,3-*d*]pyrimidin-4-yl]-*N*-(thien-3-yl)piperazine-1-carboxamide	2	1.66	458.6
10	4-[2-Amino-5-(4,4-dimethyl-5*H*-oxazol-2-yl)thieno-[2,3-*d*]pyrimidin-4-yl]-*N*-(1-methylindolin-5-yl)-piperazine-1-carboxamide	2	1.72	507.6
11	4-[2-Amino-5-(4,4-dimethyl-5*H*-oxazol-2-yl)thieno-[2,3-*d*]pyrimidin-4-yl]-*N*-(1-methylindol-5-yl)-piperazine-1-carboxamide	2	1.79	505.8

GENERAL METHOD 7

To a solution of the appropriate hydroxy-substituted amide *Intermediate* (0.53 mmol) in DCM (5 mL) was added thionyl chloride (1.32 mmol) and the reaction mixture was heated at 70°C for 2 h. The reaction mixture was then neutralized using saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted into DCM, dried over anhydrous sodium sulphate and concentrated *in vacuo*. To the crude residue were added methanol (5 mL) and NaOH (0.49 mmol) and the reaction mixture was stirred at 50°C for 1 h. The reaction mixture was then concentrated and purified by column chromatography (silica 100-200 mesh, 5-10 % MeOH in DCM) to afford the *title compound*.

GENERAL METHOD 8

To a solution of the appropriate hydroxy-substituted amide *Intermediate* (0.47 mmol) in DCM (3 mL) at -78°C was added DAST (2.38 mmol), and the reaction mixture was stirred at -78°C for 2 h. Solid K_2CO_3 (2.61 mmol) was added, and the reaction mixture was stirred at room temperature for 20 minutes. The reaction mixture was then diluted with water and extracted with DCM. The organic layer was dried over anhydrous sodium sulphate and concentrated *in vacuo*. The crude material was purified by column chromatography (100-200 mesh, 5-10% MeOH in DCM) to afford the *title compound*.

EXAMPLES 12 TO 21

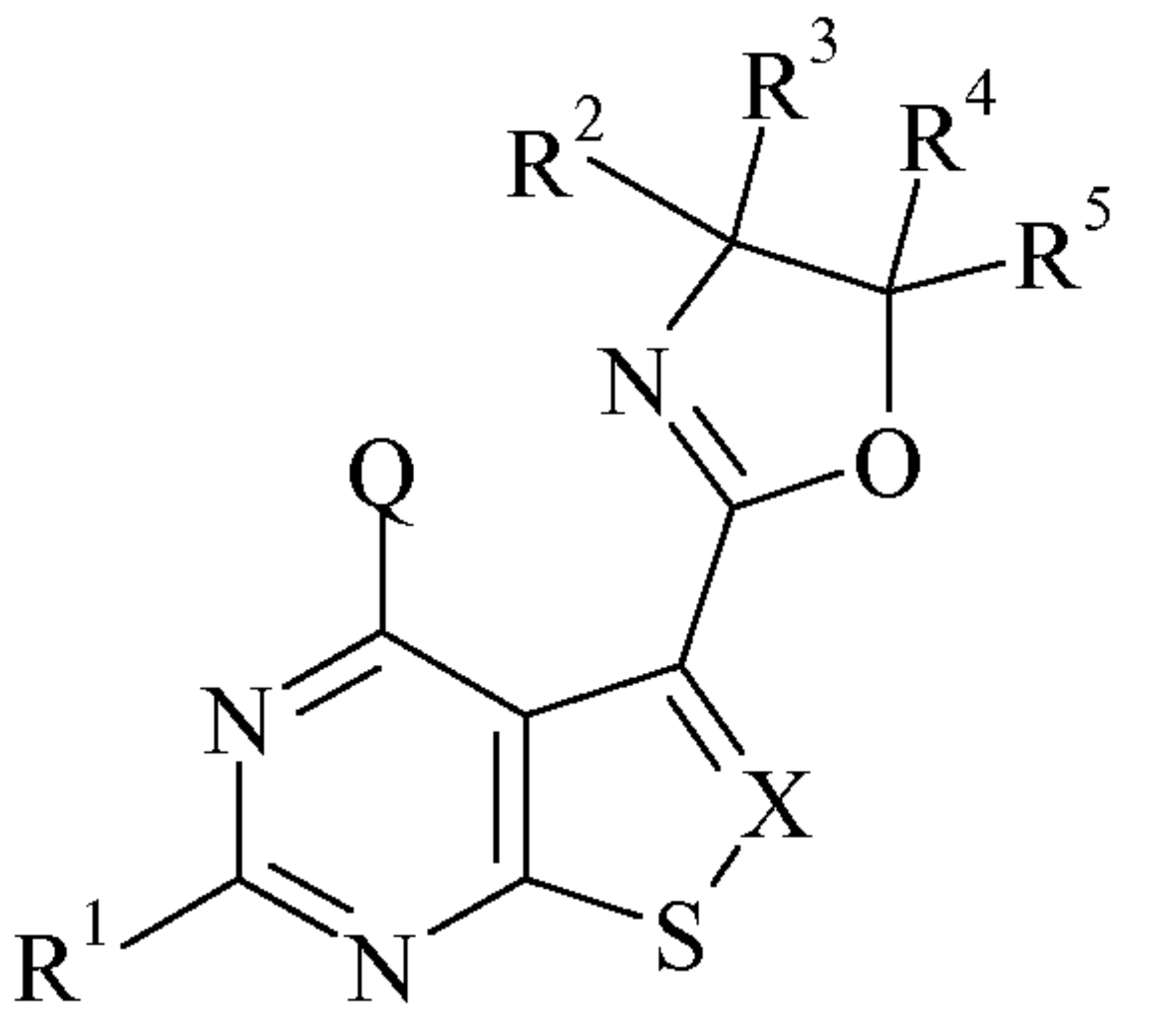
The following compounds were prepared via the indicated *General Method*.

Example	**Compound Name**	**General Method**	**LCMS**	
			Method	**(M^+)**
12	4-[2-Amino-5-(4,5-dihydrooxazol-2-yl)thieno-[2,3-*d*]pyrimidin-4-yl]-*N*-(4-methoxyphenyl)-piperazine-1-carboxamide	7	3	454.2
13	4-[2-Amino-5-(4,5-dihydrooxazol-2-yl)thieno-[2,3-*d*]pyrimidin-4-yl]-*N*-(4-methoxy-2-methyl-phenyl)piperazine-1-carboxamide	7	3	468.2
14	4-[2-Amino-5-(4-oxa-2-azaspiro[4.4]non-2-en-3-yl)thieno[2,3-*d*]pyrimidin-4-yl]-*N*-(4-methoxy-phenyl)piperazine-1-carboxamide	8	3	508.2
15	4-[2-Amino-5-(4-oxa-2-azaspiro[4.4]non-2-en-3-yl)thieno[2,3-*d*]pyrimidin-4-yl]-*N*-(4-methoxy-2-methylphenyl)piperazine-1-carboxamide	8	3	522.1
16	4-[2-Amino-5-(5-methyl-4,5-dihydrooxazol-2-yl)thieno[2,3-*d*]pyrimidin-4-yl]-*N*-(4-methoxy-phenyl)piperazine-1-carboxamide	7	3	468.1
17	4-[2-Amino-5-(5-methyl-4,5-dihydrooxazol-2-yl)thieno[2,3-*d*]pyrimidin-4-yl]-*N*-(4-methoxy-2-	7	3	482.2

	methylphenyl)piperazine-1-carboxamide			
18	4-[2-Amino-5-(5-isopropyl-4,5-dihydrooxazol-2-yl)thieno[2,3-*d*]pyrimidin-4-yl]-*N*-(4-methoxy-phenyl)piperazine-1-carboxamide	7	3	496.2
19	4-[2-Amino-5-(5-isopropyl-4,5-dihydrooxazol-2-yl)thieno[2,3-*d*]pyrimidin-4-yl]-*N*-(4-methoxy-2-methylphenyl)piperazine-1-carboxamide	7	3	510.3
20	4-[2-Amino-5-(4-methyl-4,5-dihydrooxazol-2-yl)thieno[2,3-*d*]pyrimidin-4-yl]-*N*-(4-methoxy-2-methylphenyl)piperazine-1-carboxamide	7	3	482.2
21	4-[2-Amino-5-(4-methyl-4,5-dihydrooxazol-2-yl)thieno[2,3-*d*]pyrimidin-4-yl]-*N*-(4-methoxy-phenyl)piperazine-1-carboxamide	7	3	468.1

Claims:

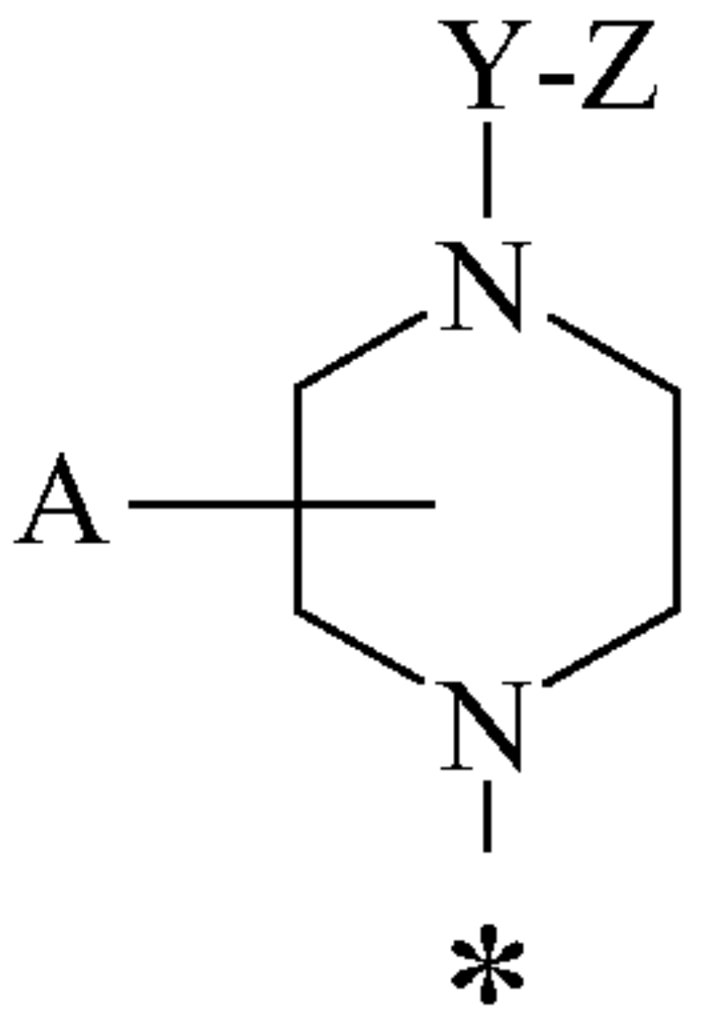
1. A compound of formula (I) or an *N*-oxide thereof, or a pharmaceutically acceptable salt or solvate thereof:



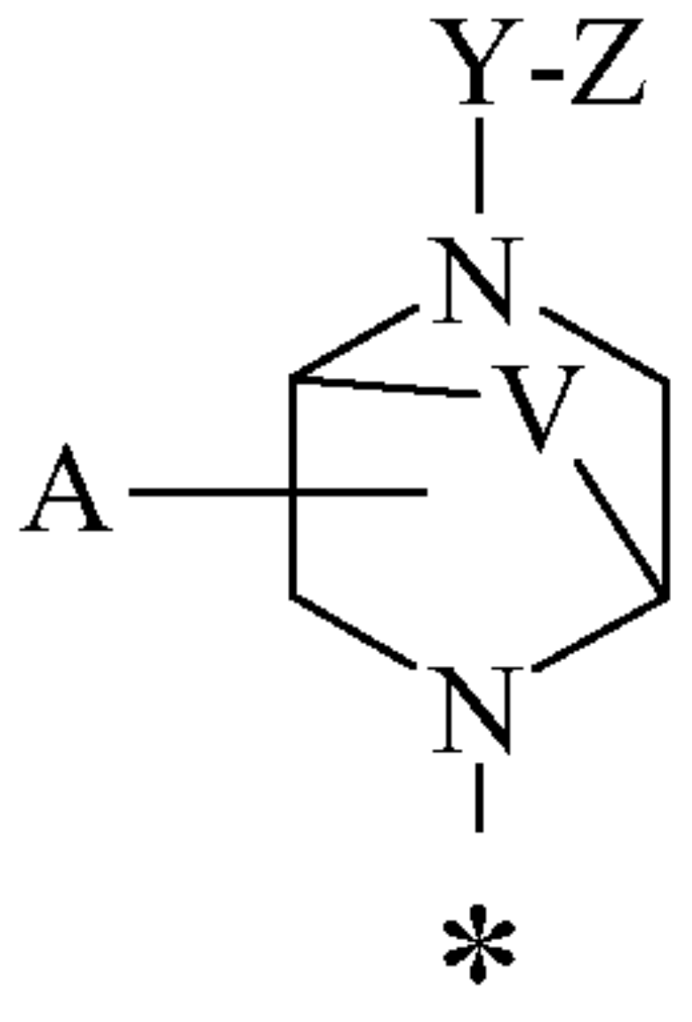
(I)

wherein

Q represents a group of formula (Qa) or (Qb):



(Qa)



(Qb)

in which the asterisk (*) represents the point of attachment to the remainder of the molecule;

V represents $-CH_2-$, $-C(CH_3)_2-$, $-CH_2CH_2-$ or $-CH_2CH_2CH_2-$;

X represents C-R^6 or N;

Y represents a covalent bond, or a linker group selected from -C(O)-, -S(O)-, $-S(O)_2-$, -C(O)O-, -C(O)N(R^7)- and $-S(O)_2N(R^7)-$;

Z represents hydrogen; or Z represents C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl-(C_{1-6})alkyl, aryl, aryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl, heteroaryl or heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted by one or more substituents;

A represents hydrogen or trifluoromethyl; or A represents C_{1-6} alkyl, optionally substituted by one or more substituents independently selected from halogen, $-OR^a$, $-S(O)R^a$ and $-NR^bR^c$;

R^1 represents hydrogen, halogen, cyano, nitro, hydroxy, trifluoromethyl, trifluoromethoxy, $-OR^a$, $-SR^a$, $-SOR^a$, $-SO_2R^a$, $-NR^bR^c$, $-CH_2NR^bR^c$, $-NR^cCOR^d$, $-CH_2NR^cCOR^d$, $-NR^cCO_2R^d$, $-NHCONR^bR^c$, $-NR^cSO_2R^e$, $-N(SO_2R^e)_2$, $-NHSO_2NR^bR^c$, $-COR^d$, $-CO_2R^d$, $-CONR^bR^c$, $-CON(OR^a)R^b$ or $-SO_2NR^bR^c$; or R^1 represents C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl(C_{1-6})alkyl, aryl, aryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl, heteroaryl or heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted by one or more substituents;

R^2 represents hydrogen or C_{1-6} alkyl; and

R^3 represents hydrogen; or R^3 represents C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl(C_{1-6})alkyl, aryl, aryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl, heteroaryl or heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted by one or more substituents; or

R^2 and R^3, when taken together with the carbon atom to which they are both attached, represent C_{3-7} cycloalkyl or C_{3-7} heterocycloalkyl, either of which groups may be optionally substituted by one or more substituents;

R^4 represents hydrogen or C_{1-6} alkyl; and

R^5 represents hydrogen; or R^5 represents C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl(C_{1-6})alkyl, aryl, aryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl, heteroaryl or heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted by one or more substituents; or

R^4 and R^5, when taken together with the carbon atom to which they are both attached, represent C_{3-7} cycloalkyl or C_{3-7} heterocycloalkyl, either of which groups may be optionally substituted by one or more substituents;

R^6 and R^7 independently represent hydrogen; or C_{1-6} alkyl, optionally substituted by one or more substituents independently selected from $-OR^a$ and $-NR^bR^c$;

R^a represents hydrogen; or R^a represents C_{1-6} alkyl, aryl, aryl(C_{1-6})alkyl, heteroaryl or heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted by one or more substituents;

R^b and R^c independently represent hydrogen or trifluoromethyl; or C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl(C_{1-6})alkyl, aryl, aryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl, C_{3-7}

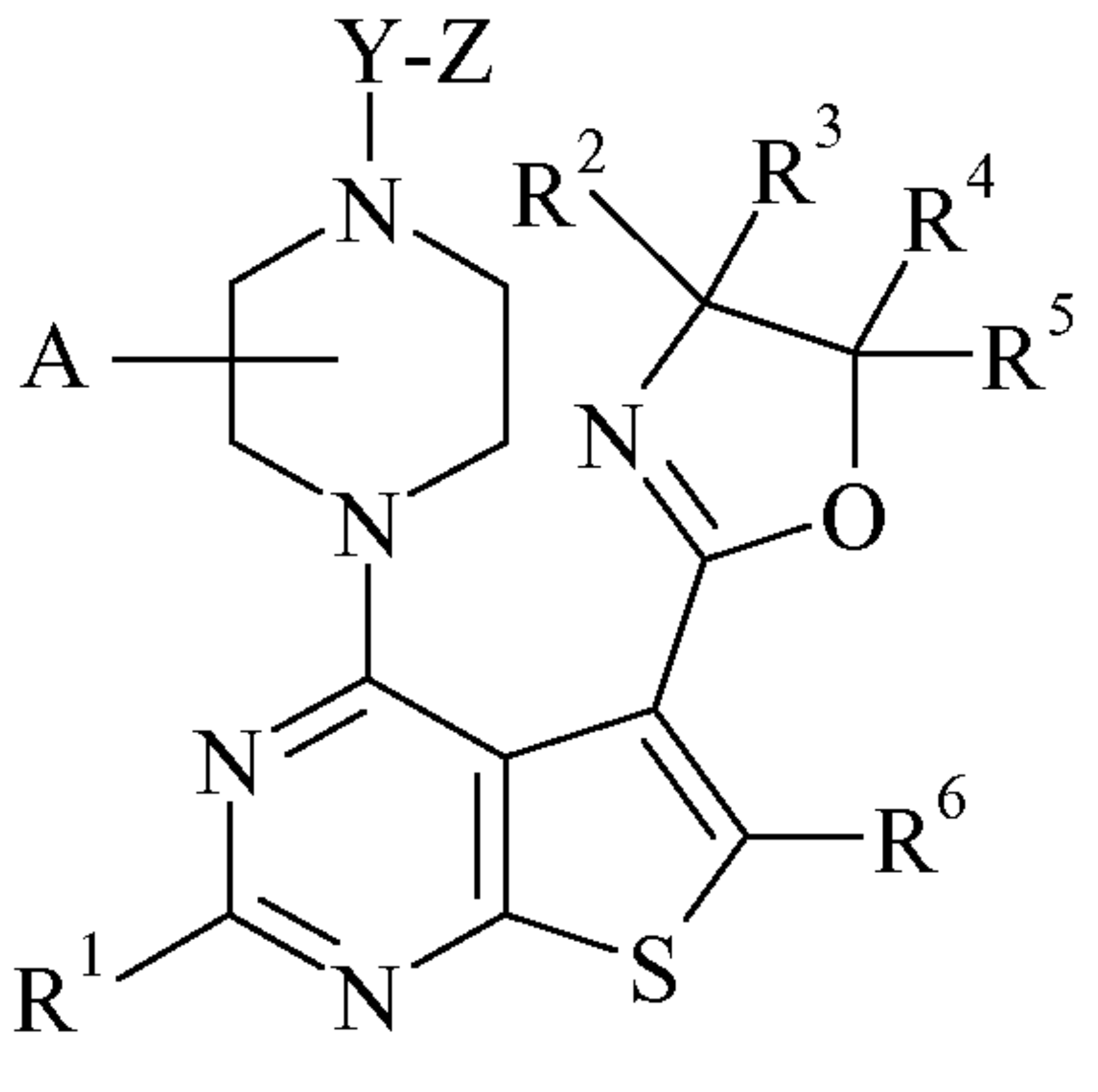
heterocycloalkyl(C_{1-6})alkyl, heteroaryl or heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted by one or more substituents; or

R^b and R^c, when taken together with the nitrogen atom to which they are both attached, represent azetidin-1-yl, pyrrolidin-1-yl, oxazolidin-3-yl, isoxazolidin-2-yl, thiazolidin-3-yl, isothiazolidin-2-yl, piperidin-1-yl, morpholin-4-yl, thiomorpholin-4-yl, piperazin-1-yl, homopiperidin-1-yl, homomorpholin-4-yl or homopiperazin-1-yl, any of which groups may be optionally substituted by one or more substituents;

R^d represents hydrogen; or C_{1-6} alkyl, C_{3-7} cycloalkyl, aryl, C_{3-7} heterocycloalkyl or heteroaryl, any of which groups may be optionally substituted by one or more substituents; and

R^e represents C_{1-6} alkyl, aryl or heteroaryl, any of which groups may be optionally substituted by one or more substituents.

2. A compound as claimed in claim 1 represented by formula (IA), or a pharmaceutically acceptable salt or solvate thereof:



(IA)

wherein Y, Z, A, R^1, R^2, R^3, R^4, R^5 and R^6 are as defined in claim 1.

3. A compound as claimed in claim 1 or claim 2 wherein R^1 represents hydrogen or $-NR^bR^c$, in which R^b and R^c are as defined in claim 1.

4. A compound as claimed in any one of the preceding claims wherein

R^2 represents hydrogen or C_{1-6} alkyl; and

R^3 represents hydrogen or C_{1-6} alkyl; or

R^2 and R^3, when taken together with the carbon atom to which they are both attached, represent C_{3-7} cycloalkyl or C_{3-7} heterocycloalkyl.

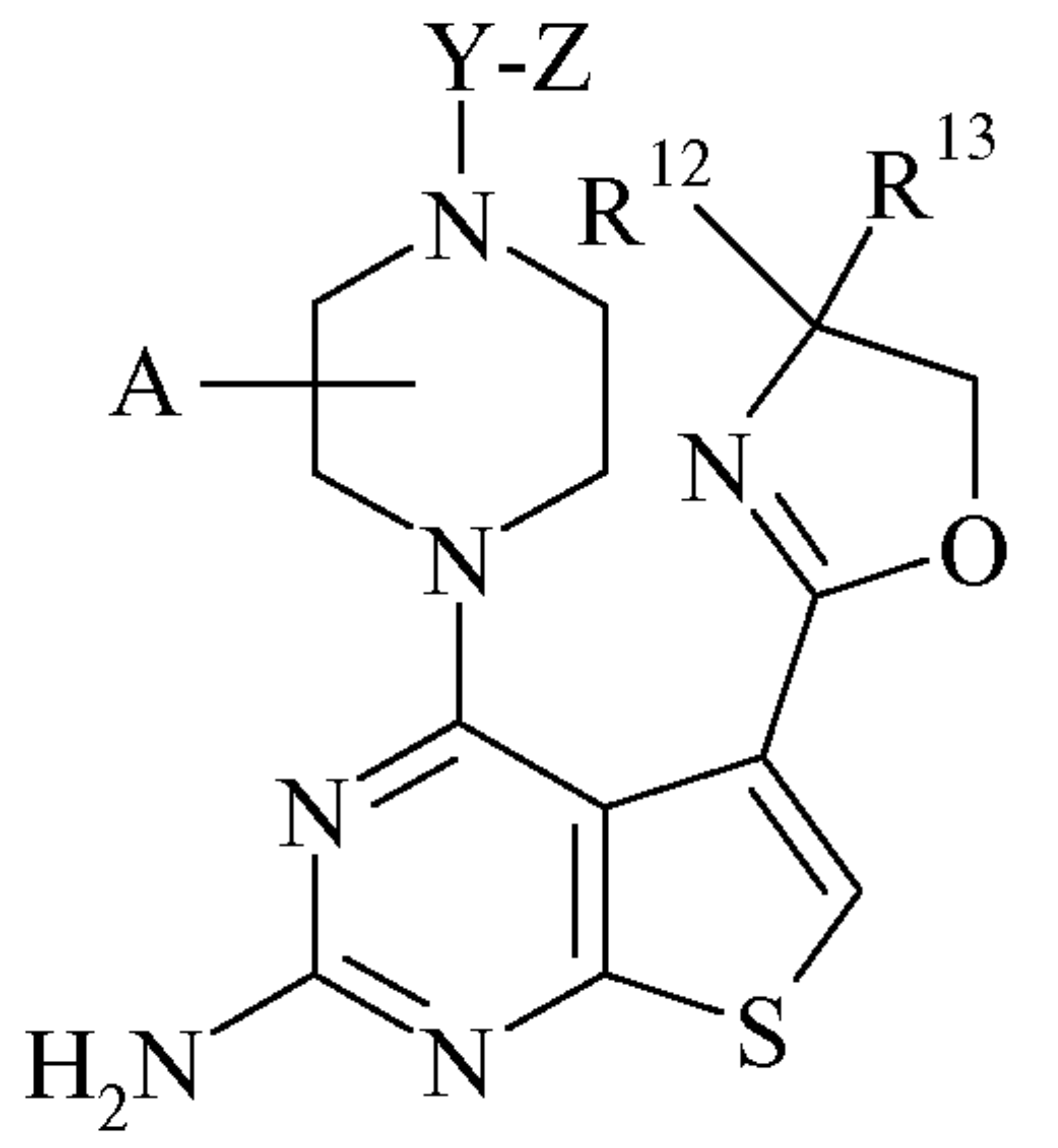
5. A compound as claimed in any one of the preceding claims wherein

R^4 represents hydrogen or C_{1-6} alkyl; and

R^5 represents hydrogen or C_{1-6} alkyl; or

R^4 and R^5, when taken together with the carbon atom to which they are both attached, represent C_{3-7} cycloalkyl or C_{3-7} heterocycloalkyl.

6. A compound as claimed in any one of the preceding claims represented by formula (IIA), or a pharmaceutically acceptable salt or solvate thereof:

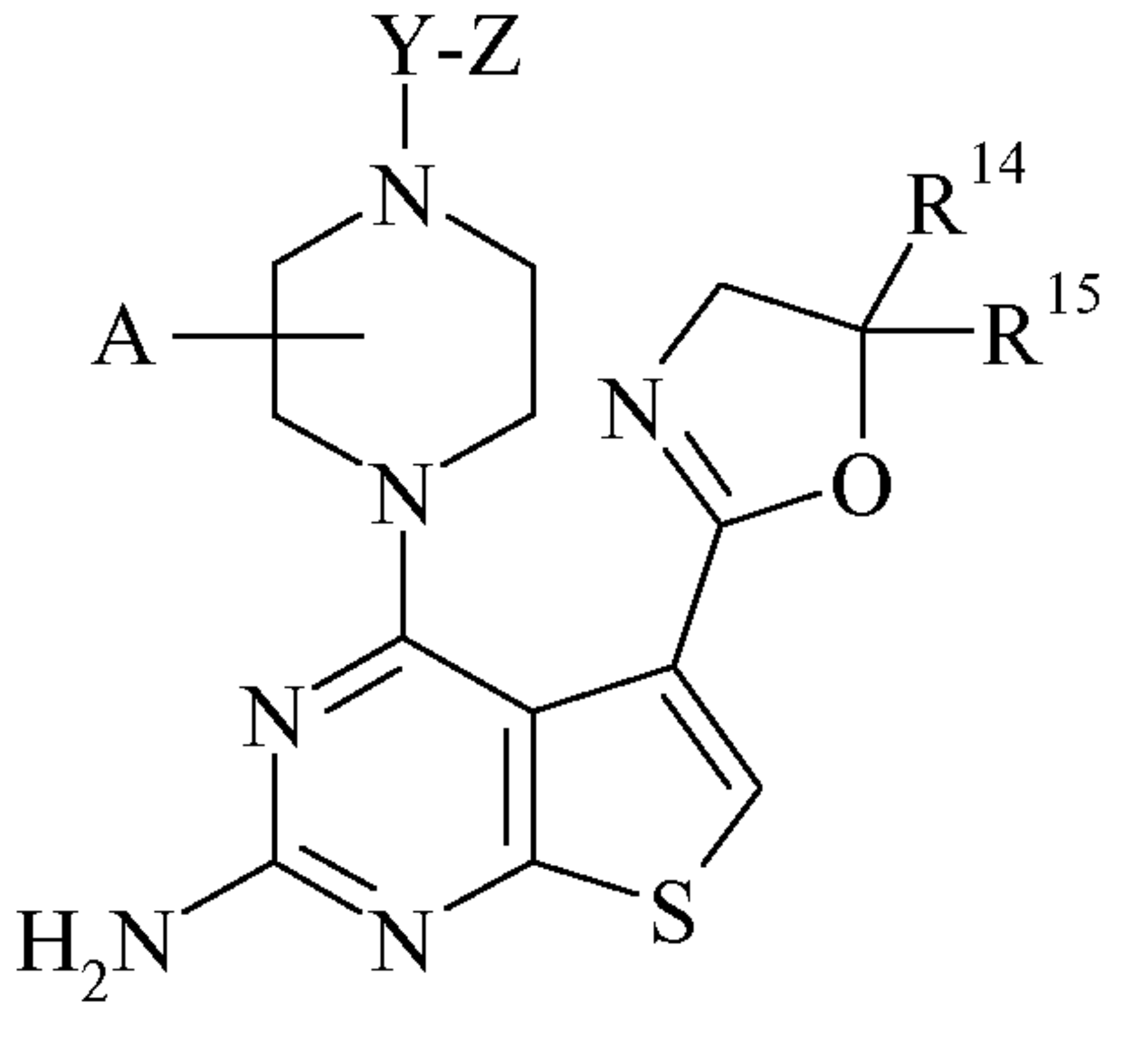


(IIA)

wherein Y, Z and A are as defined in claim 1; and

R^{12} and R^{13} independently represent hydrogen or C_{1-6} alkyl.

7. A compound as claimed in any one of claims 1 to 5 represented by formula (IIB), or a pharmaceutically acceptable salt or solvate thereof:

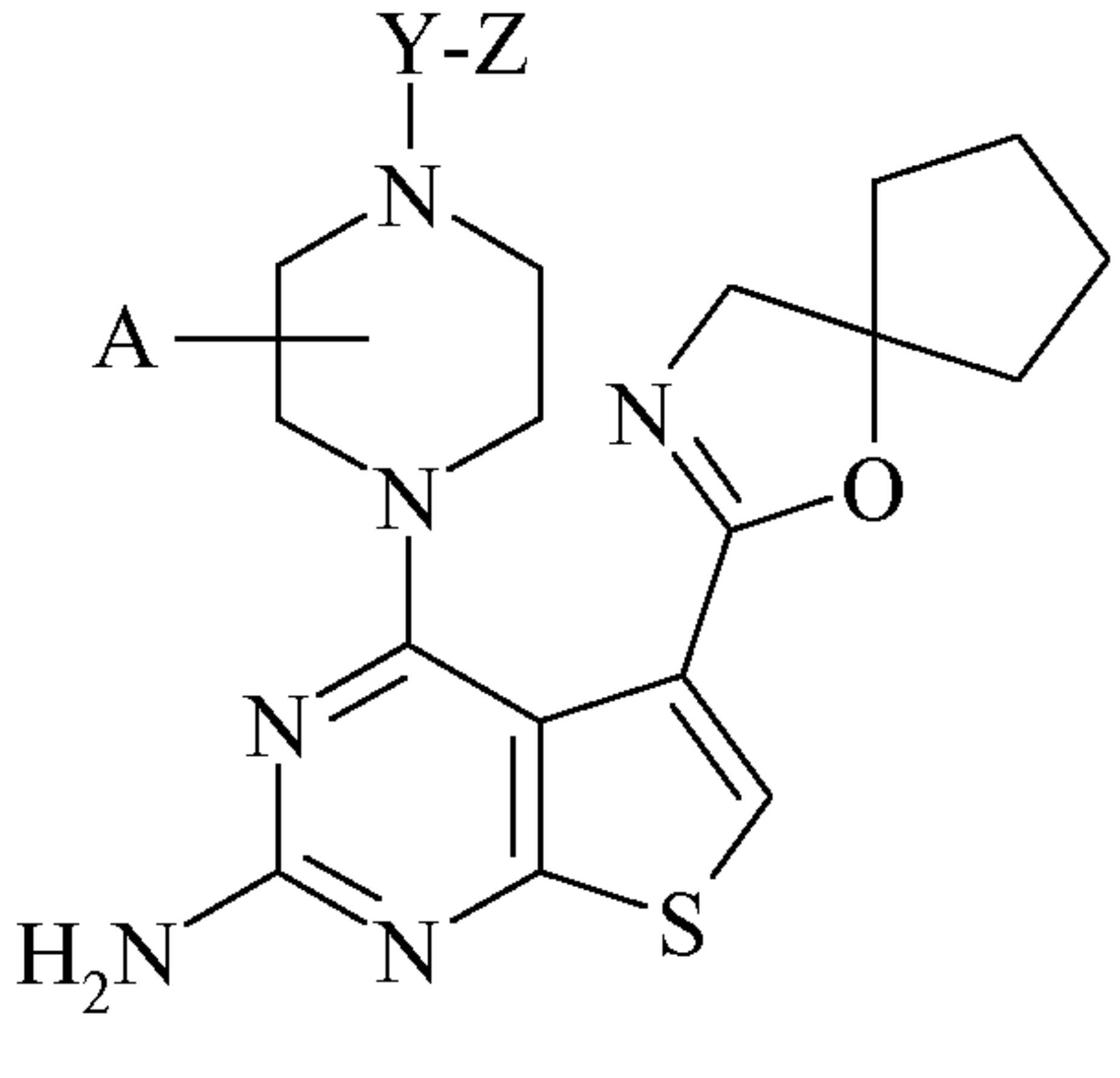


(IIB)

wherein Y, Z and A are as defined in claim 1; and

R^{14} and R^{15} independently represent hydrogen or C_{1-6} alkyl.

8. A compound as claimed in any one of claims 1 to 5 represented by formula (IIC), or a pharmaceutically acceptable salt or solvate thereof:



(IIC)

wherein Y, Z and A are as defined in claim 1.

9. A compound as claimed in any one of the preceding claims wherein Y represents $-C(O)N(R^7)-$, in which R^7 is as defined in claim 1.

10. A compound as claimed in any one of the preceding claims wherein Z represents aryl, C_{3-7} heterocycloalkyl or heteroaryl, any of which groups may be optionally substituted by one or two substituents independently selected from halogen,

cyano, C_{1-6} alkyl, C_{1-6} alkoxy, difluoromethoxy, C_{2-6} alkylcarbonyl and C_{2-6} alkoxycarbonyl.

11. A compound as claimed in any one of the preceding claims wherein A represents hydrogen; or A represents C_{1-6} alkyl, optionally substituted by $-OR^a$, in which R^a is as defined in claim 1.

12. A compound as claimed in claim 1 as herein specifically disclosed in any one of the Examples.

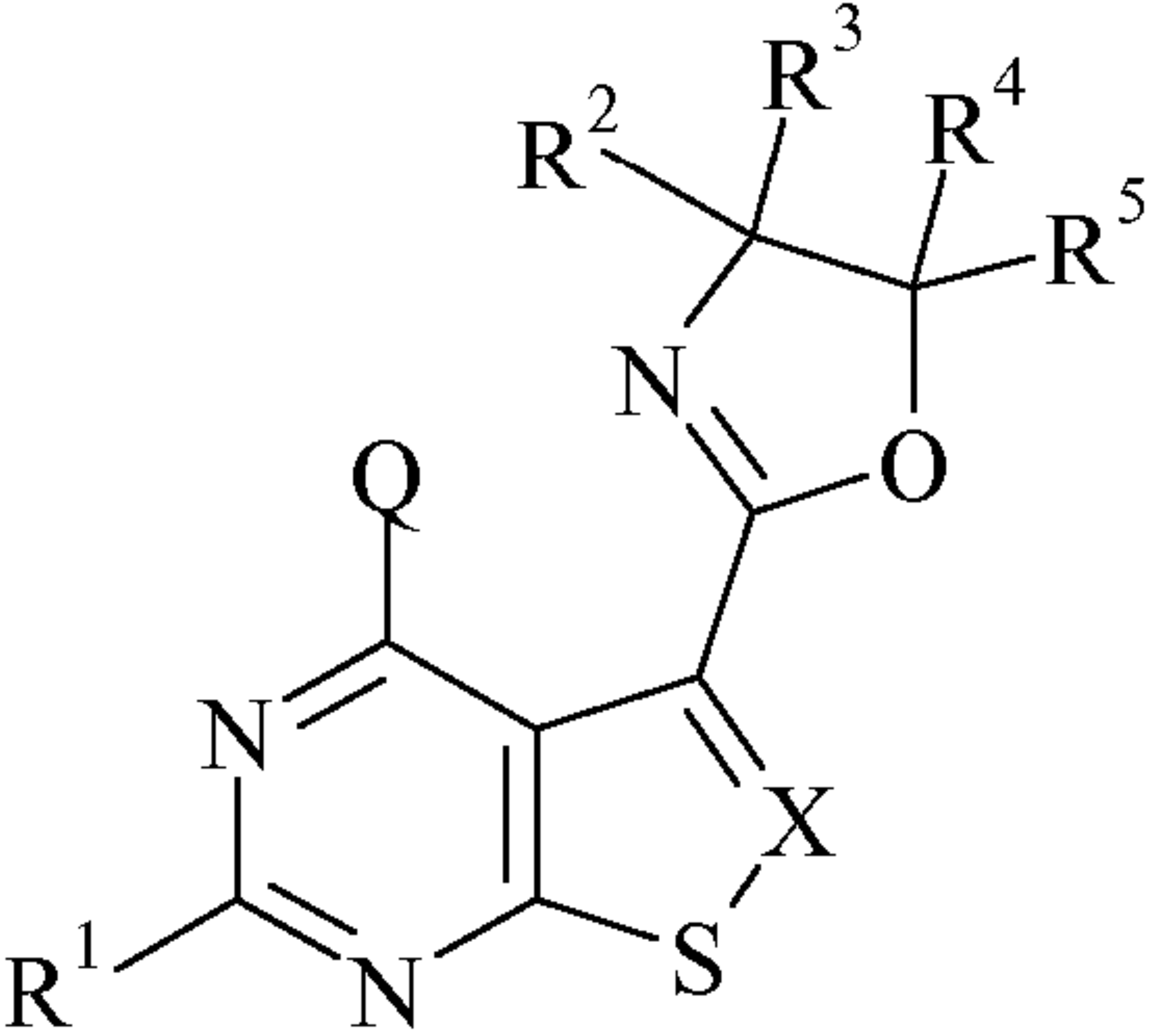
13. A compound of formula (I) as defined in claim 1 or an *N*-oxide thereof, or a pharmaceutically acceptable salt or solvate thereof, for use in therapy.

14. A compound of formula (I) as defined in claim 1 or an *N*-oxide thereof, or a pharmaceutically acceptable salt or solvate thereof, for use in the treatment and/or prevention of an inflammatory, autoimmune or oncological disorder; a viral disease; or organ or cell transplant rejection.

15. A pharmaceutical composition comprising a compound of formula (I) as defined in claim 1 or an *N*-oxide thereof, or a pharmaceutically acceptable salt or solvate thereof, in association with a pharmaceutically acceptable carrier.

16. The use of a compound of formula (I) as defined in claim 1 or an *N*-oxide thereof, or a pharmaceutically acceptable salt or solvate thereof, for the manufacture of a medicament for the treatment and/or prevention of an inflammatory, autoimmune or oncological disorder; a viral disease; or organ or cell transplant rejection.

17. A method for the treatment and/or prevention of an inflammatory, autoimmune or oncological disorder, a viral disease, or organ or cell transplant rejection, which comprises administering to a patient in need of such treatment an effective amount of a compound of formula (I) as defined in claim 1 or an *N*-oxide thereof, or a pharmaceutically acceptable salt or solvate thereof.



(I)